

Clinical protocol

**LYMPHADENECTOMY IN UROTHELIAL CARCINOMA IN THE RENAL PELVIS
AND URETER**

**- A RANDOMIZED INTERNATIONAL CLINICAL TRIAL ON LYMPHADENECTOMY
IN UROTHELIAL CARCINOMA IN THE RENAL PELVIS AND URETER**

Principal investigators

Nessn H. Azawi, MB.Ch.B.
Department of Urology
Kogevej 7-13
4000 Roskilde
Tel: +45 47 32 35 95
E-mail: nesa@regionsjaelland.dk

Jørgen Bjerggaard Jensen, MD, DMSc
Professor, Consultant in Urology
Chairman of the Danish Bladder Cancer
Group
Department of Urology
Aarhus University Hospital and Hospital of
West Jutland
Tel: +45 78 45 26 17
E-mail: jb@skejby.net

Sub investigators:

<u>Bjarne Kromann-Andersen, MD</u> Herlev University Hospital, Denmark	<u>Prof. Lars Lund, MD</u> Odense University Hospital, Denmark
<u>Helle Handler Petersen, MD</u> Aalborg University Hospital, Denmark	<u>Per Bagi, MD</u> Rigshospital, Denmark
<u>Prof. Paolo Gontero, MD</u> Molinette Hospital, Torino. Italy	<u>Ryuta Tanimoto, MD</u> Okayama University Hospital. Japan
<u>Prof. Louis Kavoussi, MD</u> The Arthur Smith Institute for Urology. New York, USA	<u>Giuseppe Simone MD, PhD</u> Regina Elena National Cancer Institute. Rome. Italy
<u>Prof. Ghulam Nabi, MD</u> University of Dundee. Scotland, United Kingdom	<u>Shekhar Biyani, MD</u> St James's University Hospital. West Yorkshire. Unit- ed Kingdom
<u>Prof. Simon Horenblas, MD, PhD., FEBU</u> Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital. Amsterdam. The Netherlands	<u>Philippe E Spiess, MD</u> Moffitt cancer centre, Tampa. Florida. USA
<u>Prof. Kees Hendricksen, MD, PhD, FEBU</u> The Netherlands Cancer Institute , Amster- dam, The Netherlands	<u>Prof. Manfred Wirth, MD</u> University Hospital Carl Gustav Carus, Dresden. Germany

Background:

Two out of three tumors in the upper urinary tract are located in the renal pelvis [1]. Muscle-invasive urothelial carcinoma is probably more common among tumors in the upper urinary tract compared to tumors in the urinary bladder. Thus, muscle-invasive tumors represent approximately 45 % of renal pelvic tumors [2,3] compared to 25 % of tumors within the urinary bladder. As in the bladder, lymph node metastases are rare in non-muscle invasive disease. Information regarding indications, extent and possible curative potential is currently lacking for lymphadenectomy in conjunction with nephroureterectomy for urothelial carcinoma in the upper urinary tract (UUTUC). There are, however, retrospective series with survival data for patients with lymph node metastasis that report long term survival after surgery as monotherapy [4] with similar survival proportions as in bladder cancer with lymph node metastases after radical cystectomy. A retrospective study from Tokyo [5] was expanded to the only available prospective study, where 68 patients with UUTUC were submitted to template-based lymphadenectomy [6]. Another retrospective study by the same Japanese group showed that 5-year cancer-specific and recurrence-free survival was significantly higher in the complete lymphadenectomy group than in the incomplete lymphadenectomy or without lymphadenectomy groups [7]. Tanaka N et al. reported recurrence rate after nephroureterectomy without lymphadenectomy at 1 and 3 years were 18.9 and 29.8 %, respectively [8].

Hypothesis: Complete lymphadenectomy during nephroureterectomy because of invasive urothelial carcinoma may reduce the incidence of lymph nodes metastasis, local recurrence, and distant metastasis and improve the cancer survival rate.

Purpose: To evaluate the influence of complete lymphadenectomy on recurrence and cancer specific survival rate compared to limited or no lymphadenectomy.

Primary endpoint/analysis: Recurrence free survival at five-year postoperative.

Secondary endpoints: Incidence of lymph node metastases, local recurrence and/or distant metastasis, cancer specific and overall survival at one, three and five-year postoperative. Complications rate according to Clavien classification within the first thirty days postoperatively [9].

Another endpoint/analysis: Multivariate analysis of possible preoperative risk factors for lymph node metastases (tumor size, preoperative urinary cytology, lymph node enlargement on CT, PET-CT positive) and postoperative risk factors for lymph node metastases (stage, grade, tumor diameter, presence of necrosis in the tumor (none; <10%; >10% of total tumor area), number of lymph nodes excised).

Design: Prospectively randomized to template based lymphadenectomy or not, in patients with clinically muscle-invasive UUTUC in the renal pelvis or upper 2/3 of the ureter. One to one, controlled clinical trial. Patients will be randomly allocated into two groups, 183 patients in each group. Group A will be scheduled to receive routine standard open or robot assisted nephroureterectomy without lymphadenectomy except for clinically enlarged. Group B will be scheduled to receive mapped lymphadenectomy in conjunction with nephroureterectomy.

Preoperative investigations:

CT-urography
CT or FDG-PET/CT of thorax and abdomen

Surgery:

Open or robot-assisted radical nephroureterectomy according to department standard.

Procedure:

Robot /laparoscopic – assisted nephroureterectomy:

A 12-mm camera port is placed at the level of the umbilicus and lateral; this port is moved farther laterally in morbidly obese patients to allow for the instruments to reach the target organs. Three 8-mm robotic trocars are placed under direct vision and a 12-mm assistant port is placed in the midline a 5-8 cm above the umbilicus. If needed, another 5-mm assistant port is similarly placed below the umbilicus. The assistant ports might be moved to the other side of the midline, especially in thin patients, to allow minimum distance between the trocars. For right-sided tumors, an additional 5-mm port is placed in the midline just below the xiphoid process for liver retraction. Placement of the trocars can be changed according to surgeon preference. The same placement of the trocars recommended for laparoscopic technique.

Nephrectomy:

After reflecting the colon medially, the ureter is identified off of the lower pole of the kidney. Careful attention is paid to keeping the peri-ureteric tissue with the ureter in order to allow an adequate margin in the event of urethral invasion by the malignancy. Once the ureter is identified, a 10mm Hem-o-lok clip (Teleflex Medical; Research Triangle Park, NC) is placed around the ureter to prevent tumor from traveling down the ureter during manipulation. The ureter is swept upward off of the psoas muscle and followed superiorly to the renal hilum. The renal artery and vein dissect free and ligate individually with a 10mm Hem-o-lok clip, two pieces central. Once the perinephric attachments are free, dissection carries on along the ureter as distal as possible toward the iliac vessels.

Lymphadenectomy (intervention group only):

Lymphadenectomy performs in four fractions on the right side (1, 2, 4, 5) and two fractions on the left side (3, 6) according to Dissection template (Appendix 1). Renal hilar nodes are included in fraction 1 and 3, respectively. Lymph nodes located posterior to the aorta and vena cava are not included in the template.

Excision of distal ureter with bladder cuff:

After completion of nephrectomy with or without lymphadenectomy, the ureter is dissected down to the ureterovesical junction. Retrograde filling of the bladder may be performed at this stage in order to better identify the ureterovesical junction. A 1-cm cuff of bladder is carefully excised around the ureteric orifice, and the specimen is then placed in the Endocatch bag. The specimen removed through 7 – 10 cm incision in the inguinal region.

Open nephroureterectomy:

Radical nephroureterectomy may be performed through a long midline incision or through a subcostal plus Gibson, lower midline, or Pfannenstiel incision. Alternatively, through a single

thoracoabdominal incision. Then the same surgical technique as performed in robot – assisted nephroureterectomy.

Inclusion criteria:

- Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up.
- Age \geq 18 years
- Eastern Cooperative Oncology Group (ECOG) status of 0-2.

All patients needs at least one criteria of A and one of B

A. Histological defined UTUC: Histologically confirmed diagnosis of predominantly urothelial carcinoma of the upper urinary tract.

1. Positive biopsy for high grade tumor
2. Selective upper tract positive cytology
3. Micturition positive cytology (if there is no bladder cancer simultaneously)

B. Radiological defined UTUC: Patients with UTUC cT2-T4, N0- M0 (TNM classification): Criteria must to be defined by radiologists.

Pelvic or calyx tumor

1. Absence of fat between pelvis and kidney
2. Evidence of parenchymal invasion
3. Growing of tumor out of the renal pelvis
4. Tumor $>$ 1 cm

Upper 2/3 of ureter

1. Growing of the tumor out of the ureter
2. Dilation grade 3-4
3. Tumor $>$ 1 cm

Exclusion criteria:

- Clinical suspicion of non-muscle invasive UTUC
- Metastatic urothelial carcinoma for the renal pelvis or upper 2/3 of the ureter
- Radiological positive lymph nodes in the retroperitoneal region

Risks and complications

Lymph edema in the form of swelling of the legs in 23%, lympho-cystic in the form of accumulation of lymph liquid in operation's region, thrombosis (blood clotting) and neighboring organ injury.

Information from patient records: We will review the medical records to collect further information about tumor size and types, urine cytology test, the number and size of lymph node by scans, blood samples taken in connection with the operation and subsequent follow-up, complications associated with surgery.

Statistic power:

Five years estimated recurrence free rate in patients undergoing complete lymphadenectomy is 65% and without lymphadenectomy 50%. With a sample power of 80% and alpha error of 0.05, the number of patients needed per group is 183 patients and thus 366 in all. The calculation performed using SAS statistic program.

Results: The reading of results will be collected and analyzed with SAS software program. Correlation and multiple regressions analyses will be used to describe the relation of results. Kaplan – Meier will be used to estimate the survival rate.

Projects schedule The study will start at September 2016 and 366 patients will be included in the project, when this number of patients included successfully to the study. The study will be expected to end inclusion by the end of September 2021 and will be terminated five years after inclusion of the last patient.

Publication: Nessn H. Azawi is responsible for conception and design, acquisition, analysis and interpretation of data. Negative as well positive results will be published in international journals where Nessn H. Azawi will be the first author and Jørgen Bjerggaard Jensen as last author. Other authors, such as the sub investigators, will be arranged according to Vancouver rules.

Ethical considerations:

Muscle-invasive urethelial carcinoma is probably more common in the upper urinary tract. Presence of metastatic disease to lymph nodes at the time of surgery is not rare and associated with poor survival. The only prospective study describe this matter was with small number of patients, but they provide significant increase in the survival associated with lymphadenectomy in conjugated with nephroureterectomy [6]. Recurrences of the disease after nephroureterectomy without lymphadenectomy occur more frequently within the first three years and can be due to metastasis to the lymph nodes, which mislaid on the primary diagnosis. Removing lymph nodes in patients with high-risk urethelial carcinoma can improve recurrence free survival by 15%, which is significant improvement if we compare this benefit to the number of complications associated with lymphadenectomy reported in the previous studies. These complications reported during the initial experiences with this technique and there is possible improvement in the learning curve.

The study will be carried out in accordance with the the ICH GCP Guidelines. The study will be reported to the National Ethical Committee and the Data Protection Agency in each country participating.

In Denmark the study will be reported to the Danish Health Authority, the National Ethical Committee of Region Zealand, and to the Danish Data Protection Agency.

The investigators and sub investigators are obligated to provide a curriculum vitae before initiating the study.

Informed Consent: Investigators and sub investigators are responsible for ensuring that all subjects voluntarily confirm their willingness to participate in the study. The subjects must be fully informed about the purpose of the study, both in oral and in written form. The subjects must be informed about potential risk factors related to the surgical procedure, and other relevant issues regarding participating in the study. Investigators and sub investigators must allow the necessary time for the subject and the assessor to inquire the details about the study.

Informed consent is documented in accordance with the ICH GCP Guidelines.

Data Handling: Data will be reported by all participating parties - investigators and sub investigators. The responsibility for reporting data on each subject in the electronic Case Report Form (eCRF) lies with the investigators and sub investigators. Only the investigators are authorized to make data changes.

Data are reported to eCRF in the REDCap system. REDCap is considered a secure web application for building and managing online surveys and databases.

The eCRF is stored on a secured server in the Region of Southern Denmark, with a backup disk placed in a locked cabinet. Data will be stored for 10 years after end of the study after which the data will be deleted. Danish law on personal data observation will be met.

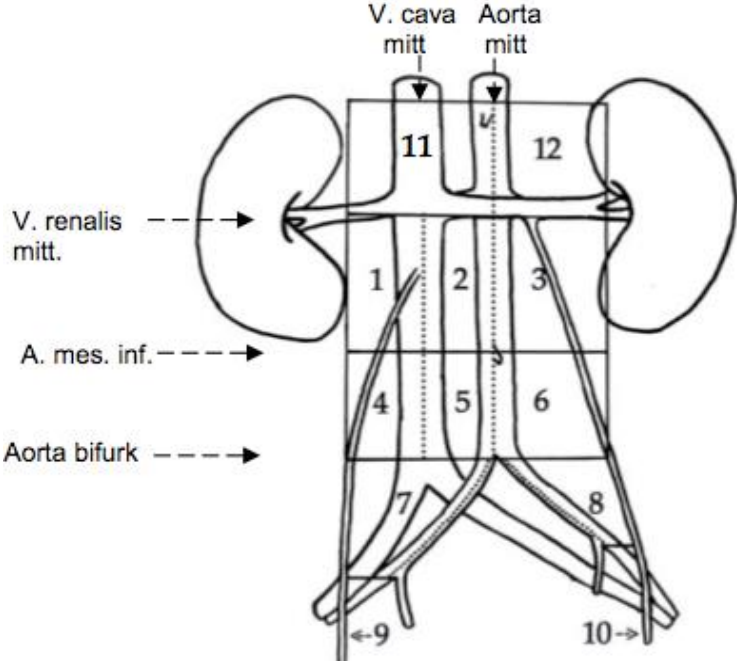
Economy: Fund applications will be developed in order to support the study costs.

There are no economic interests in the results of the study. There will be no connection between the investigators and the donors.

Budget

Start up fee		7.000 EUR
PhD salary		220.000 EUR
Patient recruitment Fee (250 EUR per enrolled patient)	250 EUR x 366	91.500 EUR
Coordinating Project nurse		85.000 EUR
Travel Reimbursement*		27.000 EUR
Conference fee		10.000 EUR
Budget in total		440.500 EUR

Appendix 1.



Right side: 1, 2, 4, 5
Left side: 3, 6

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