

## PROTOCOL TITLE

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

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## **RANDOMIZED CLINICAL TRIAL ON LYMPHADENECTOMY IN UROTHELIAL CARCINOMA IN THE RENAL PELVIS AND URETER**

### **Background:**

Two out of three tumours in the upper urinary tract are located in the renal pelvis [1]. Muscle-invasive urothelial carcinoma is probably more common among tumours in the upper urinary tract compared to tumours in the urinary bladder. Thus, muscle-invasive tumours represent approximately 45 % of renal pelvic tumours [2,3] compared to 25 % of tumours 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, 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 (tumour size, preoperative urinary cytology, lymph node enlargement on CT, PET-CT positivity) and postoperative risk factors for lymph node metastases (stage, grade, tumour diameter, presence of necrosis in the tumour (none; <10%; >10% of total tumour 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 received mapped lymphadenectomy in conjugation 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 – 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.

*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 ureteral 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 and two fractions on the left side according to Dissection template (Appendix 1). Renal hilar nodes are included in fraction 1 and 3, respectively.

*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:**

1. Age above 18 years

2. Locally advanced high grade urothelial carcinoma in the renal pelvis or upper 2/3 of the ureter (Clinical stage > T1)
3. Patient with ECOG performance score of 2 and less.
4. Able to give informed consent

**Exclusion criteria:**

1. Clinical suspicion of non-muscle invasive UUTUC
2. Metastatic urothelial carcinoma for the renal pelvis or upper 2/3 of the ureter
3. Inability to understand written consent forms or give consent

**Recruitment:**

The project will be reported to the regional ethical committee. The patients will be informed about the project and a written consent from the patient will be obtained.

**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 January 2016 and 366 patients will be included in the project, when this number of patients included successfully to the study. The study will be terminated.

**Place to perform the project:** Department of Urology, Roskilde Hospital; Department of Urology Herlev Hospital; Department of Urology, Aarhus University Hospital; Department of Urology, Aalborg University Hospital; Department of Urology, Odense University Hospital; and Department of Urology, Hospital of West Jutland.

**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 will be arranged according to vancouver rules.

**Ethics:** The study will be reported to the Regional Ethical Committee of Region Sjælland.

Data will be reported to Region Sjælland data control agency ”Region Sjælland paraplygodkendelse fra Datatilsynet”, as well as clinical trials database.

Act on processing of personal data will be observed.

**Data:** Data will be collected with share point data program. Data will be stored secure in Region Sjælland server and in anonymous form in PC with access only to the project’s involved persons and 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:** We will apply funds to support project charges. We will apply to research account at Department of Urology/Roskilde hospital/ region Sjaelland.

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

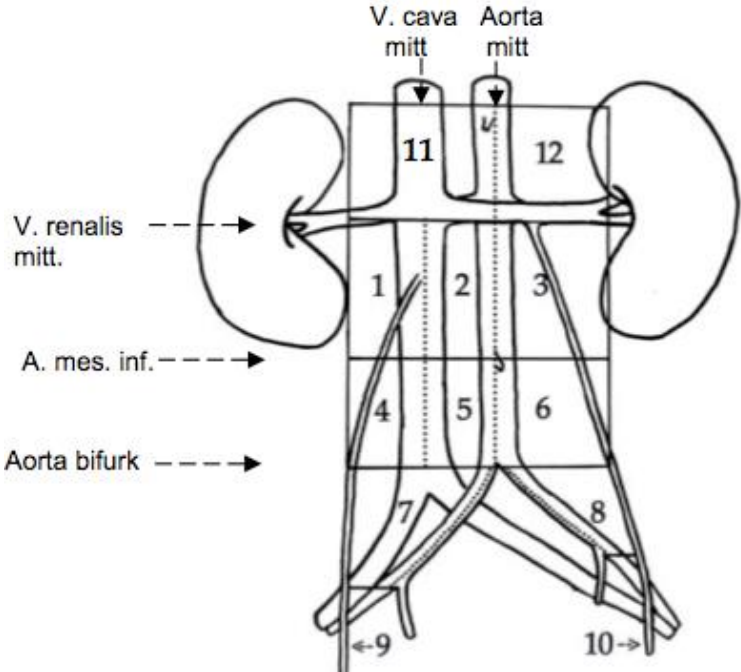
**Budget:**

Salary to one nurse conjugated to project for one month per year per department

28.000 kr. X 5 years X 5 department

I alt 700.000 kr.

Appendix 1.



Right side: 11, 1, 2, 4, 5  
 Left side: 12, 3, 6

## References

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