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

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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45429

Source
ToetsingOnline

Brief title
Lymphadenectomy in urothelial carcinoma in the renal pelvis and ureter

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Ureteric disorders
- Renal and urinary tract therapeutic procedures

Synonym
cancer of the renal pelvis and ureter, upper tract urothelial carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Zealand University Hospital
Source(s) of monetary or material Support: Door de initiatiefnemers uit Denemarken wordt nog gezocht naar potentiële fondsen voor de uitvoering van de studie;deze zijn er vooralsnog niet. Buiten het wetenschappelijk belang;heeft deelname voor ons geen financieel belang

Intervention

Keyword: lymphadenectomy, renal pelvis, ureter, urothelial carcinoma

Outcome measures

Primary outcome

Primary endpoint/analysis:

Recurrence free survival at five-year postoperative.

Secondary outcome

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).

Study description

Background summary

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 uri-nary 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].

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4 Lughezzani G, Jeldres C, Isbarn H, Shariat SF, Sun M, Pharand D et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology 2010: 75(1):118-124.
5 Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K. Primary site and incidence of lymph node metastases in urothelial carcinoma of upper

urinary tract. Urology 2007: 69(2):265-269.
6 Kondo T, Hara I, Takagi T, Kodama Y, Hashimoto Y, Kobayashi H et al. Template-based lymphadenectomy in urothelial carcinoma of the renal pelvis: a prospective study. Int J Urol 2014: 21(5):453-459.
7 Kondo T, Hara I, Takagi T, Kodama Y, Hashimoto Y, Kobayashi H et al. Possible role of template-based lymphadenectomy in reducing the risk of regional node recurrence after nephroureterectomy in patients with renal pelvic cancer. Jpn J Clin Oncol 2014: 44(12):1233-1238.
8 Tanaka N, Kikuchi E, Kanao K, Matsumoto K, Kobayashi H, Ide H et al. Metastatic behavior of upper tract urothelial carcinoma after radical nephroureterectomy: association with primary tumor location. Ann Surg Oncol 2014: 21(3):1038-1045.
9 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004: 240(2):205-213.

Study objective

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.

Study 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, that will undergo nephro-ureterectomy. 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 conjugation with nephroureterectomy.

Intervention

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.

Study burden and risks

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 neighbor-ing organ injury.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-written informed consent
-age >17 years
-Eastern Cooperative Oncology Group (ECOG) performance status 0-2;All patients need at

least one criterium of A and one of B.
A. Histological defined upper tract urothelial carcinoma (UTUC): histologically confirmed diagnosis of predominantly urothelial carcinoma of the upper 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 be defined by radiologists;Pelvic of calyx tumor:
1. Absence of fat between pelvis and kidney
2. Evidence of parenchymal invasion
3. Growing of tumour out of the renal pelvis
4. Tumor >1 cm;Upper 2/3 of ureter:
1. growing of the tumour 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

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-07-2017
Enrollment:	20

Type:	Actual

Ethics review

Approved WMO Date:	06-06-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT02607709
CCMO	NL60507.031.17