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PII: S0090-4295(19)30390-5
DOI: https://doi.org/10.1016/j.urology.2019.04.026
Reference: URL 21572

To appear in: *Urology*

Please cite this article as: Teele Kuusk , Oscar Brouwer , Niels Graafland , Kees Hendricksen , Maarten Donswijk , Axel Bex , Sentinel-lymph node biopsy in renal tumours- surgical technique and safety, *Urology* (2019), doi: https://doi.org/10.1016/j.urology.2019.04.026

Sentinel-lymph node biopsy in renal tumours- surgical technique and safety

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ABSTRACT

Objective: To understand uncertainties and knowledge gaps regarding lymphatic drainage in renal tumours, we performed two prospective studies to demonstrate regional lymph node (LN) drainage with sentinel lymph node (SN) imaging and biopsy. Here, we report the technique and perioperative safety of retroperitoneal SN dissection with different surgical approaches.

Methods: 73 patients from the two trials were included in the analysis. Patients had cT1-2N0M0 renal tumours (</=10 cm) and underwent nephrectomy (46/63%) or

partial nephrectomy (27/37%) with SN dissection after intraoperative detection with a γ-probe, and locoregional LND. Twenty-nine of 73 patients had open surgery, 27/73 laparoscopic and 17/73 robot-assisted laparoscopic (partial)nephrectomy. Surgery time, intraoperative adverse events (AE) according to CTCAE 5.0, and postoperative AE according to Clavien-Dindo (CD) were retrospectively assessed.

Results: There were no grade ≥3 intraoperative CTCAE 5.0 AEs. Postoperative AE rate was 16.4% of which 7 (9.6%) were CD grade 1-2 and 5 (6.8%) were 3a grade complications. There were no statistically significant differences between presence of AE, CD grade and surgical modality (p=0.27 and p=0.13, respectively). Blood loss was a median of 550 ml (IQR 200-900ml) and 225 (IQR 42-751ml) for partial nephrectomy (PN) and radical nephrectomy, respectively. Length of the procedure was 170 min (IQR 149-184min), 155 min (IQR 130-177min) 180 min (IQR 162-202min) in open, laparoscopic and robot-assisted procedures, respectively.

Conclusions: The addition of retroperitoneal SN dissection combined with locoregional LND during (partial)nephrectomy is surgically safe. Complication rate is low and does not differ between surgical approaches.

KEYWORDS: Lymphoscintigraphy; Morbidity; Nephrectomy; Renal cell carcinoma; SPECT/CT; Sentinel lymph node

Acknowledgements: We are grateful for Antoni Van Leeuwenhoek Netherlands Cancer Institute team members for their contribution to the study.

Introduction

Decreased morbidity compared to full template lymph node dissection (LND) and locating the first lymphatic landing sites are the key elements of lymph node mapping and biopsy [1]. Sentinel lymph node biopsy (SLNB) has been studied with promising results in different urological cancers with the longest history and indication established in penile cancer [2]. Even though SLNB is experimental in renal cancer, it has shown to identify lymphatic drainage from renal tumours [3,4] and may gain importance for improved staging of high-risk tumours eligible for adjuvant immunotherapy trials as well as for translational studies of early metastasis and immune response. The feasibility of sentinel lymph node detection in renal cancer has previously been published, however the surgical safety of retroperitoneal SLNB has not been reported [5,6,7]. Furthermore, there is lacking comprehensive description of the surgical procedure. Our study combined SLNB with locoregional retroperitoneal LND, therefore surgical morbidity could be expected to be the same or even higher than in partial(nephrectomies) with LND alone. The aim of this study was to analyze intra- and postoperative adverse events of SLNB combined with locoregional non-SN LND and describe the procedure in detail.

Patients and methods

We performed a prospective single center feasibility and phase 2 imaging study of sentinel lymph node (SN) detection and biopsy to investigate the pattern of lymphatic drainage and a rate of LN metastases in renal tumours. The studies were conducted after institutional ethics board approval between 2008 and 2017 (N06SNR and N08SNR; registered under NL26406.031.08 at www.ccmo.nl). All patients signed an

informed consent form. Inclusion criteria were cT1-2 renal tumors ≤10 cm of any subtype, clinically and radiologically non-metastatic disease (cN0M0), age ≥18 years, life expectancy >3 months, WHO performance status 0-1 and no prior systemic therapy.

The procedure of SLNB was performed as described earlier [3,7]. Briefly, one day prior to surgery, 225MBq of ^{99m}Tc-nanocolloid (Nanocoll©; GE Healthcare, Eindhoven, Netherlands) in a volume of 0.4 ml was injected into the tumour percutaneously by ultrasound guidance. After 20 minutes and 2-4 hours planar lymphoscintigraphy of the thorax and abdomen was performed, followed by combined SPECT and low dose CT (SymbiaT, Siemens, Erlangen, Germany) of the site of interest. The following day, resection of the primary tumour and the SN was performed. Surgical approach (open, transperitoneal laparoscopic, robot-assisted) was decided per case depending on the primary tumour. At surgery, SN(s) were located by preoperative SPECT/CT images and detected intraoperatively with a γ-probe (Neoprobe, Johnson&Johnson Medical, Hamburg, Germany) in combination with a mobile γ-camera (Sentinella, S102,GEM imaging, Valencia, Spain) (figure 1,2). After SN excision, the surgical area was scanned using the mobile γ-camera to verify complete SN removal. For ethical reasons, only SNs accessible through the chosen surgical approach were removed. Additionally, non-SNs within the locoregional retroperitoneal LND area were resected to study the false-negative rate. Harvested SNs and non-SNs were measured *ex vivo* with both γ-probe and-camera. Surgery time, intraoperative adverse events (AE) according to CTCA 5.0 and blood loss were documented on surgical and anesthesia reports. Postoperative 30-day and the 90-day morbidity and mortality and AEs were collected from the patient files. All the procedures were performed by an experienced uro-oncology surgeon (A.B.).

Intraoperative surgical technique of sentinel lymph node procedure

The renal tumour was removed by open transperitoneal, transperitoneal laparoscopic and robot-assisted laparoscopic (da Vinci S(i) Surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) approaches as partial or radical nephrectomy was decided on per case based on individual tumor location and complexity. Independent of the surgical approach, the procedure of SLNB took place after mobilization of the kidney. First, the γ-probe was used to detect the SN(s) in the anatomical location assessed on SPECT/CT. For the laparoscopic (robot assisted) approach, the laparoscopic probe was inserted through the assistant port or any other of convenience (figure 1 A and B). In open surgery, in case of activity with a γ-probe, we re-confirmed the location of the SNs with a mobile γ-camera *in vivo* (figure 1 C and D). With the laparoscopic approach, the camera was used *ex vivo* only. LN which showed any activity with one or the other SN detection methods were harvested and radionuclide activity was re-confirmed with a γ-probe and camera *ex vivo*. Subsequently, excision of non-SNs was performed in accordance with the suggested LND template: in the right side hilar, pre-para-retrocaval and interaortocaval nodes and from left side hilar, pre-para-aortal and interaortocaval nodes cranially from the crus of diaphragm and distally to the bifurcation of the aorta. Hemostasis and lymph leakage was controlled by bipolar cautery/dissector or metallic clips.

Statistical analysis

Statistical analysis was performed using descriptive statistics reporting continues variables with medians and IQRs and categorical variables with proportions. Characteristics of patients and procedures were compared between patients who did

and did not develop AE using Fisher's exact, Chi-Square or Mann-Whitney U test. All tests were two-sided and p value ≤0.05 was considered statistically significant. Data was analyzed using SPSS version 22 (IBM, Chicago, IL, USA).

Results

Seventy-three patients with a median age of 59 years (IQR 52-65) were included in the final analysis (table 1), from which 45 patients (61.6%) had SN detection either with SPECT/CT or intraoperatively with a γ-probe, the remaining patients had locoregional LND. Median size of the tumours was 6 cm (IQR 4.9-8 cm) and more than half of the cases 43(58.9%) had high RENAL complexity score. The majority underwent nephrectomy 46 (62.8%) and laparoscopic surgery outweighed the other surgical approaches. Median operating time was 170 minutes (IQR 149-187) and median blood loss was 300 ml (IQR 100-752). The highest rate of blood loss occurred with open surgery, median 865 ml (IQR 600-1505ml), laparoscopic 50 (IQR 0-200ml) and robot-assisted laparoscopic 250 ml (IQR 151-575ml). Length of the procedure was 170 min (IQR 149-184min), 155 min (IQR 130-177min) 180 min (IQR 162-202min) for open, laparoscopic and robot-assisted procedure, respectively. This includes the additional time for SN detection and regional LND which was a median of 30 minutes (IQR 12-52 min) and did not statistically differ between the surgical approaches. Except blood loss, no intraoperative complications occurred. Blood loss was unrelated to SN and LND. Median follow-up was 52 months (IQR 13-72 months). Postoperative AE rate was 16.4% (12/73) from which 7 (9.6%) were Clavien-Dindo grade 1-2 and 5 (6.8%) were grade 3a complications (3 with open surgery and 2 with robot-assisted) (table 2). The majority (10/12) of the complications occurred within 30 days after the operation. Only 1 of these AE was linked to SLNB or LND (lymph fluid collection after open RN). Open partial nephrectomies had the highest number

of AE, however the approach (open vs laparoscopic vs robot-assisted) and technique (partial vs nephrectomy) were not associated with having CD complications or not p=0.13 and p=0.14, respectively. Complications were not associated with the number of harvested SNs (p=0.22) nor with the number of non-SNs removed during the LND (p=0.73). Intraoperative detection with SPECT/CT visualization did not differ significantly between surgical approaches (p=0.42).

Discussion

In this study, we explored the surgical safety of retroperitoneal SLNB in renal tumours. We showed that the procedure performed either as open, laparoscopic or robot assisted approach has no additional intraoperative complications and has acceptable long-term perioperative morbidity. Our single-center results suggest that SLNB in renal tumours has a perioperative AE rate that is comparable or even less than the reported morbidity with LND and nephrectomy [8,9].

To our knowledge, there are no prior studies reporting perioperative AEs following a technique of retroperitoneal SLNB in renal tumours using different surgical approaches. Sherif et al studied feasibility of SLNB in renal cancer in 13 patients who underwent nephrectomy but did not report on long-term morbidity nor details of the SLNB procedure [5].

In renal cancer locoregional LND is challenging due to approximation of large blood vessels. Despite that, data on LND in renal cancer suggest that there is no significant additional impact on complications compared to no LND in patients who underwent a nephrectomy (26% vs 22%, respectively) whereas lymph fluid drainage was reported in 2.4% and 3.9%, respectively [8]. Furthermore, a previously published meta-

analysis reported a perioperative complication rate with nephrectomy and LND in 17-26% [9], whereas our AE rate was 16.4% without any intraoperative complication directly linked to SLNB, demonstrating safety and minimal morbidity of the procedure. Regarding intraoperative blood loss and surgery time, there are great variations in different publications. In retrospective series mean blood loss has been 856-1301 ml for open nephrectomy and LND with a mean surgery time of 178 min [9,10], whereas in the laparoscopic setting, 150 ml and 217 min were reported, respectively [11]. In our series, mean surgery time was 173 min, with mean blood loss of 1286 ml, which was 166 min and 142 ml for the laparoscopic approach, respectively. Generally, SN procedure with LND is 10-50 minutes longer than (partial) nephrectomy with LND alone. The duration of robot-assisted laparoscopic operations was the longest, however this was predominantly due to the majority of patients having a partial rather than total nephrectomy. In addition, the study period coincided with the beginning of learning curve for RAPN in our institute.

One of the main reasons for SN mapping and biopsy is to detect the first draining lymph nodes and to reduce the morbidity of extended LND without diminishing oncological outcome. Owing to a lack of evidence that LND provides oncological advantage in renal cancer [8], LND is not part of a standard nephrectomy. However, abandoning LND in renal cancer entirely is controversial. Lymph node metastases are the third most common metastatic sites [12] and are associated with an extremely poor outcome [9,13]. Finding better therapeutic options for these patients is critical and multiple adjuvant studies are ongoing. For this reason, evaluating the presence of occult lymph node metastatic disease in high risk renal cancer is gaining importance for staging purposes as lymphonodular involvement is part of the inclusion criteria in novel adjuvant immunotherapy and combination therapy trials.

Furthermore, it has been shown that there is a subgroup of patients who survive longer when occult lymph node metastases are removed early [9,13].

Instead of performing extended LND which detects only a small number of occult lymph nodes (4-8%), it may be convenient to use SLNB instead. Nevertheless, we do not have a comparative study between SLNB and extended LND in renal cancer. SLNB could theoretically save procedural time and would also guide the surgeon to the first lymphatic landing sites for performing SPECT/CT guided selected LND for staging rather than removing all retroperitoneal locoregional lymph nodes around the aorta and caval vein. Furthermore, due to aberrant lymphatic drainage in renal tumours (35%), SNLB [3] can be used for mapping and directing LND. The new technique adaptation and performance is feasible in expert hands and SLNB could be used in trials where staging is needed [14]. For further lymphatic drainage trials in high risk renal cancer patients, it is of importance to demonstrate that perioperative AE and long term morbidity following SLNB is not exceeding renal surgery without LND.

Our study is not without limitation. It is retrospective and lacks a group for comparison. Also the low number of patients per surgical approach limits the interpretation of the findings.

Conclusions

The results suggest long-term safety and low morbidity of retroperitoneal SLNB for renal tumours patients who undergo (partial) nephrectomy and LND.

Funding

None

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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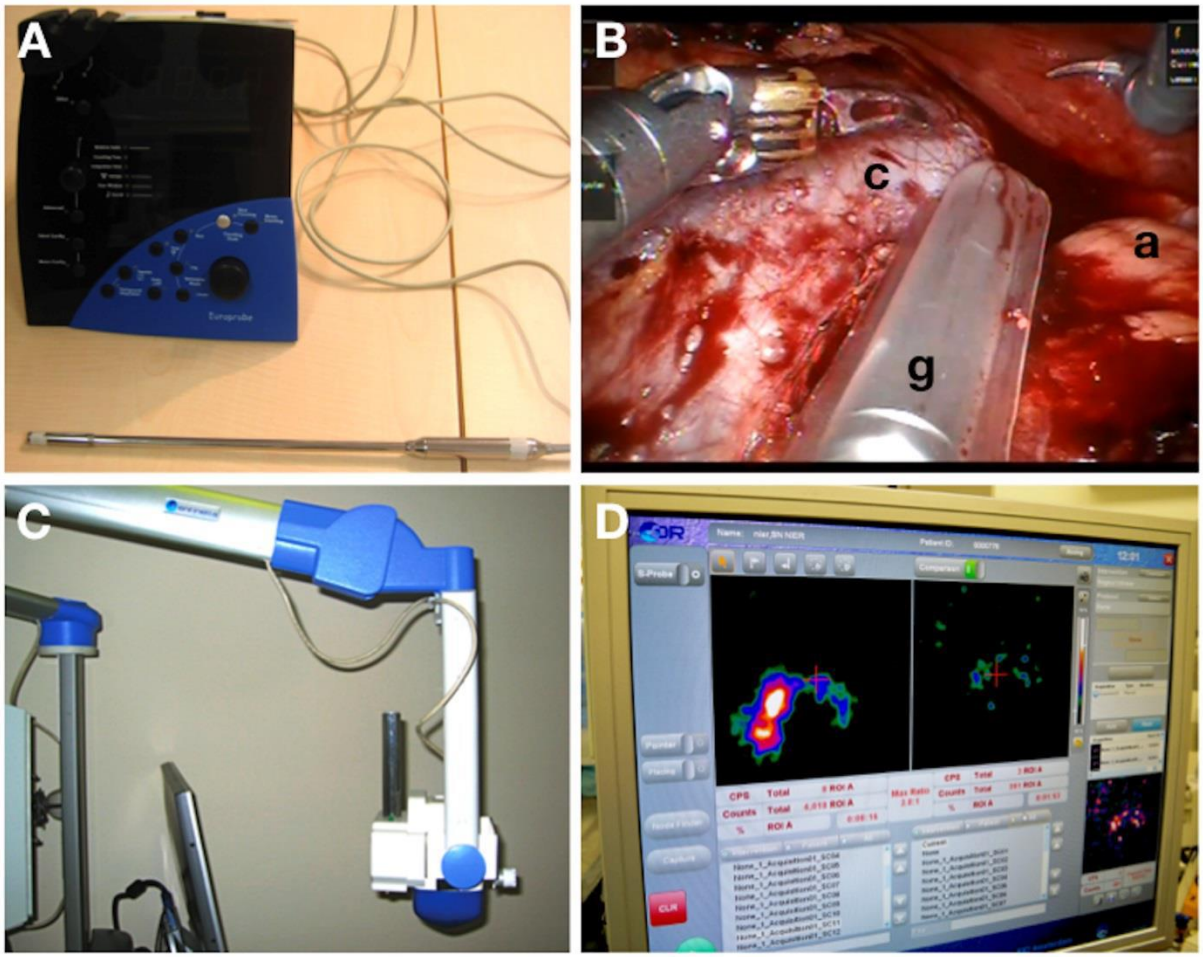

Figure 1 A. γ-probe tool B. γ-probe detecting interaortocaval SN intraoperatively c (caval vein) a (aorta) g (γ-probe) C. Sentinella mobile γ-camera D. Sentinella mobile γ-camera monitor image showing detection of SN

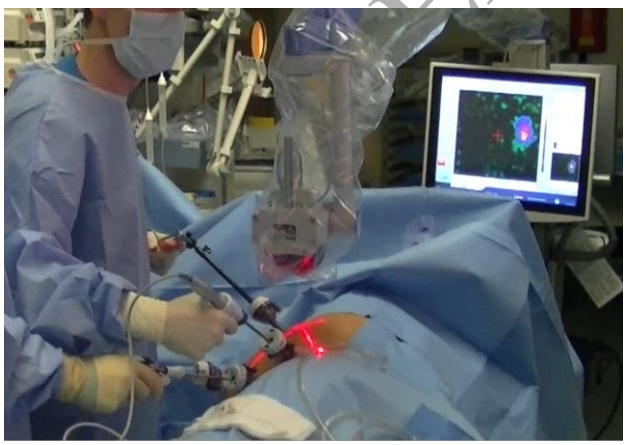

Figure 2 Sentinel lymph node detection with a γ-camera during laparoscopic surgical procedure.

Table 1. Patient and tumor characteristics

Number of patients	73
Age (median, IQR)	59 (52-65)
BMI (median, IQR)	26.4 (24.1-30.9)
Tumour size in cm (median, IQR)	6 (4.9-8)
pT stage	
T1a	11 (15.1%)
T1b	43 (58.9%)
T2a	8 (11.0%)
T2b	3 (4.1%)
T3a	8 (11.0%)
pN stage	
N0	65 (89.0%)
N1	2 (2.7%)
Nx	6 (8.2%)
Right side	36 (49.3%)
Left side	37 (50.7%)
Upper pole	15 (20.5%)
Intermedial pole	31(42.5%)
Lower pole	27 (37.0%)
Histology	
Clear cell RCC	52 (71.2%)
Papillary type 1 RCC	7 (9.6%)
Papillary type 2 RCC	4 (5.5%)
Chromophobe RCC	5 (6.8%)
Oncocytoma	3 (4.1%)
Solitary fibrous tumor	1 (1.4%)
Leibovich score in ccRCC	
Low	28(38.4%)
Intermediate	22(30.1%)
High	8(11.0%)
RENAL score	
Low	12 (16.4%)
Moderate	18 (24.7%)
High	43 (58.9%)
Surgical type	
Open, radical nephrectomy	18 (24.6%)
Open, partial nephrectomy	11 (15.0%)
Laparoscopic, radical nephrectomy	27 (36.9%)
Robot-assisted, laparoscopic radical nephrectomy	1 (1.3%)
Robot-assisted, laparoscopic partial nephrectomy	16 (21.9%)
Overall complication rate	12 (16.4%)
Clavien Dindo grade 1	2 (2.7%)

Clavien Dindo grade 2	5 (6.8%)
Clavien Dindo grade 3a	5 (6.8%)
Blood loss (median, IQR)	300 ml (100-750)
Operating time (median, IQR)	170 min (149-187)

Legend: IQR interquartile range

Table 2. Patients with complications

Patient nr	CD grade	Age	Gender	Side	Tumour (cm)	pT stage	RENAL score	Surgery	Complication	Treatment	PO day
1	2	63	Male	R	4.0	1b	Low	RAPN	DVT	Anticoagulants	39
2	3a	63	Male	L	5.6	1b	High	RAPN	Bladder clot retention	Transurethral evacuation	26
3	3a	39	Female	L	5.7	1b	Mod	RAPN	AVF	Endovascular Coiling	13
4	2	47	Male	R	3.5	1a	Mod	RAPN	Pneumonia	AB	3
5	2	74	Female	L	7.0	1b	High	Lap RN	AF	Medication	5
6	1	56	Male	R	6.0	3a	Mod	Open RN	Wound infection	Topical dressings	7
7	3a	72	Female	R	4.8	1b	High	Open RN	Subcutaneous lymph fluid collection	Drainage	3
8	1	55	Female	R	5.0	1b	High	Open PN	Wound infection	Topical dressings	5
9	3a	59	Female	L	5.5	1b	High	Open RN	Wound hernia	Surgical repair	60
10	3	54	Female	L	3.5	1a	Low	Open PN	Urine leakage	Double-J stent	5
11	2	67	Male	R	6.5	1b	High	Open RN	Pneumonia	AB	4
12	2	77	Female	R	8.0	3a	High	Open RN	Pneumonia	AB	6

PO post-operative; DVT deep vein thrombosis; R right; L left; Mod Moderate; AVF arteriovenous fistula; AF artrial fibrillation; AB antibiotics; RN radical nephrectomy; PN partial nephrectomy; Lap laparoscopic; RALPN robotic-assisted laparoscopic partial nephrectomy