World Journal of Urology (2019) 37:1623–1629
https://doi.org/10.1007/s00345-018-2573-3

ORIGINAL ARTICLE

The side and the location of the primary tumor does not affect the probability of lymph node invasion in patients with renal cell carcinoma

Alessandro Nini[1,2] · Alessandro Larcher[1,2] · Walter Cazzaniga[1,2] · Paolo Dell'Oglio[1,2] · Francesco Cianflone[1,2] · Fabio Muttin[1,2] · Francesco Ripa[1,2] · Andrea Salonia[1,2] · Alberto Briganti[1,2] · Francesco Montorsi[1,2] · Roberto Bertini[1,2] · Umberto Capitanio[1,2]

Received: 11 August 2018 / Accepted: 20 November 2018 / Published online: 24 November 2018

Abstract

Purpose To evaluate the role of side and location of the primary renal cell carcinoma (RCC) on the risk of lymph node invasion (LNI) and/or nodal progression (NP) during follow-up.

Materials and methods We evaluated 2485 patients with unilateral RCC, surgically treated in a single tertiary care referral center. Outcomes were LNI at surgery and/or NP during follow-up. We studied if RCC side (left vs. right) and location (upper vs. middle vs. hilar vs. lower area vs. more than one area) affected the probability of LNI and/or NP at follow-up.

Results Overall, 43 and 15% of patients underwent lymph node dissection and had LNI at surgery, respectively. During follow-up, 2.2% of patients had NP. Higher rates of LNI and NP were observed for patients with primary tumor located in more than one anatomical kidney area relative to patients with tumor in a single area (upper 11% vs. middle 10% vs. hilar 0%, vs. lower 12% vs. more than one area 26%, $p < 0.01$). cM1, cN1, pT2/pT3/pT4 disease and Fuhrman grade 3/4 were independent predictors of the study outcome (all $p \leq 0.01$). Neither the RCC side nor the location reached the independent predictor status (all $p > 0.1$).

Conclusions Patients with single-side and more than one anatomical kidney area affected by RCC have higher rate of LNI at surgery and/or NP at follow-up. Neither side nor location of primary RCC tumor is related to the risk of harboring LNI at surgery and/or developing NP at follow-up.

Keywords Lymph node invasion · Metastases · Kidney cancer · Renal cancer

Introduction

Over the last decades, a trend towards lower rate of lymph node dissection (LND) in renal cell carcinoma was observed due to lack of proven cancer control, widespread increase of minimally invasive surgery and stage migration [1, 2]. However, accurate nodal staging does maintain a key role for prognosis, follow-up schedule and, potentially, for consideration of adjuvant therapy [3–5].

Cadaveric dissection and sentinel-node studies [6–9] demonstrated wide heterogeneity of retroperitoneal lymphatic drainage originating from kidney. In cadaveric dye studies, beyond the intrarenal crossing systems between hilar and intraparenchymatous drainage, it has been described that efferent kidney lymphatic system may reach either retroperitoneal nodal landing sites or the thoracic duct, thus connecting directly with supraclavicular and mediastinal nodes [6]. Sentinel-node studies have indeed confirmed aberrant and unpredictable lymphatic spread with additional nodal invasion outside the respective locoregional retroperitoneal template in up to 35% cases (14/40) [9].

However, to the best of our knowledge, no study has ever addressed the issue whether the tumor side (right vs. left) and tumor location (upper vs. middle vs. hilar vs. lower area

✉ Umberto Capitanio
umbertocapitanio@gmail.com

1 Unit of Urology, University Vita-Salute San Raffaele, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

2 Renal Cancer Unit, Division of Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

vs. more than one kidney area) may be associated with the risk of lymph node invasion (LNI) at final pathology and/or nodal progression (NP) at follow-up.

Materials and methods

Patient population

After institutional review board approval, we identified 2485 patients with sporadic, unilateral RCC surgically treated at a single tertiary care referral center between 1987 and 2016. Comprehensive clinical, surgical, pathologic and follow-up data of patients were collected and entered into a prospectively maintained database. The decision to perform LND was customarily taken by the treating urologist and was based on the presence of cT2 disease and above, lymphadenopathies and/or palpable lymph nodes during surgery.

Clinical and pathologic evaluation

Dedicated genitourinary pathologists examined all surgical specimens. TNM stages and Fuhrman grades were assigned according to 8th American Joint Committee on Cancer classification [10] and to the World Health Organization/International Society of Urological Pathology classification) [11]. Patients treated before the introduction of the most updated classification were reclassified. Clinical tumor size definition was based on pre-surgery imaging and was defined as the greatest tumor diameter in cm. Patients were staged preoperatively with CT or MRI of the abdomen. A clinically positive node was defined as the presence of at least one radiologically detected lymphadenopathy (> 10 mm) in the retroperitoneal lymphatic area at preoperative staging imaging.

Template for lymph node dissection

The LND procedure consisted of excising the fibrofatty tissue along anatomically defined areas (interaortocaval, pre-/para-aortic, pre-/paracaval). Specifically, the interaortocaval region extended from the midline of the inferior vena cava to the midline of the aorta, the para-aortic region extended from the midline of the aorta to the left ureter, and the right precaval and paracaval nodal regions extended from the midline of the inferior vena cava to the right ureter. When an extended LND was sought, lymph nodes were collected according to the above-cited anatomical classification from the crus of the diaphragm to the aortic (left) or caval (right) bifurcation. Fat tissue containing lymph nodes from different anatomical regions were sent in separate containers and fixed in 10% buffered formalin.

Outcomes and covariates

The primary outcome of the study was the presence of lymph node invasion (LNI) at final pathology and/or the presence of nodal progression (NP) during follow-up period. Covariates consisted of age, gender, tumor side (right vs. left), tumor location (upper vs. middle vs. hilar vs. lower area vs. more than one kidney area), the presence of symptoms at diagnosis, clinical metastatic status (cM0 vs. cM1), clinical nodal status (cN0 vs. cN1), pathological T stage (pT1 vs. pT2 vs. pT3/pT4), pathological N stage (pN*x*/pN0 vs. pN1), Fuhrman grade (G3–G4 vs. G1–G2) [11], pathological tumor size, number of removed and positive lymph nodes. Subgroup analyses on the overall population and after exclusion of pT1a RCC according to LND extent (no vs. regional vs. extended LND) were then performed to evaluate LNI and/or NP or only NP after stratification for the location of the tumor (superior vs. middle vs. hilar vs. inferior vs. multiple) and the side (left vs. right).

Statistical analyses

Statistical analyses consisted of two steps. First, means, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables on the study population, respectively. Independent *t* test and Pearsons' Chi square test were used to compare means and proportions. Second, multivariable logistic regression analyses were used to assess the independent predictors of the risk of LNI at surgery and/or NP at follow-up. All statistical tests were performed using SPSS version 22 (IBM Corp., Somers, NY, USA). All tests were two-sided with a significance level set at p value < 0.05.

Results

Patients were treated with no LND ($n = 1424$, 57%) or regional LND (hilar LND plus, on the right side, pre-retrocaval nodes or, on the left side, para-aortic nodes, $n = 789$, 33%) or extended LND (regional plus interaortocaval nodes, $n = 244$, 10%). Clinicopathologic features are summarized in Table 1. The prevalence of LNI was 7% (159/2485 patients) and 15% (159/1061 patients) in the overall and LND groups, respectively. In patients treated with radical nephrectomy (RN), the prevalence of LNI was 10% (158/1555 patients) and 0.1% (1/930 patients) in the partial nephrectomy (PN) group, respectively. When considering only patients who underwent LND ($n = 1061$; 43%), the LNI rates were 18% and 12% in patients with right and left RCC, respectively ($p = 0.02$). After stratification according to RCC location,

Table 1 Descriptive statistics of the overall population

	Overall population
Gender, *n* (%)	
Male	1788 (72%)
Female	697 (28%)
Mean age, years (median IQR)	60 (62, 52–70)
Symptoms, *n* (%)	
No symptoms	1591 (64%)
Local and/or sistemic symptoms	894 (36%)
Clinical T stage, *n* (%)	
cT1	1778 (71%)
cT2	452 (18%)
cT3	238 (10%)
cT4	16 (1%)
Clinical N stage, *n* (%)	
cN0	2113 (85%)
cN1	372 (15%)
Clinical M stage, *n* (%)	
cM0	2206 (89%)
cM1	279 (11%)
Tumour side, *n* (%)	
Left	1199 (48%)
Right	1286 (52%)
Tumour location, *n* (%)	
Upper area	666 (27%)
Middle area	654 (26%)
Hilar area	26 (1%)
Lower area	640 (26%)
More than one area	470 (19%)
Missing	30 (1%)
Type of surgical technique	
Open	2081 (84%)
Minimally invasive	404 (16%)
Type of kidney surgery	
Partial nephrectomy	930 (37%)
Radical nephrectomy	1555 (63%)
Histology type, *n* (%)	
Clear cell carcinoma	1978 (80%)
Chromophobe	136 (5%)
Papillary type I	172 (7%)
Papillary type II	147 (6%)
Other	52 (2%)
Pathologic T stage, *n* (%)	
pT1a–b	1557 (63%)
pT2a–b	257 (10%)
pT3a–b–c	620 (25%)
pT4	51 (2%)
Pathologic N stage, *n* (%)	
pN*x*/pN0	2326 (93%)
pN1	159 (7%)
Lymph node progression during follow-up	
Present	213 (9%)
Absent	2272 (91%)
Pathologic Fuhrman grade, *n* (%)	
G1	270 (11%)
G2	1470 (59%)
G3	611 (25%)
G4	134 (5%)
Mean pathologic dimension, cm (median, IQR)	5.6 (5.3–7.5)
Lymphovascular invasion, *n* (%)	
Yes	298 (12%)
No	2187 (88%)
Necrosis, *n* (%)	
Yes	951 (38%)
No	1534 (62%)

LNI rates were 11, 10, 0, 12 and 26% for upper, middle, hilar, lower area and more than one kidney area, respectively ($p < 0.01$). When considering only patients with single locations, no statistically significant difference was observed ($p = 0.3$).

The median number of removed lymph nodes (LNs) was 6 (IQR 3-10). The median numbers of LNs removed were 5 and 12 in patients undergoing regional and extended LND, respectively ($p < 0.01$). After stratification for RCC side, LNI at surgery was 15% and 8% for upper area, 11% and 9% for middle area, 14% and 10% for lower area, 0% and 0% for hilar area and 29% and 23% for more than one kidney area, in right and left RCC, respectively (Fig. 1, all $p < 0.01$).

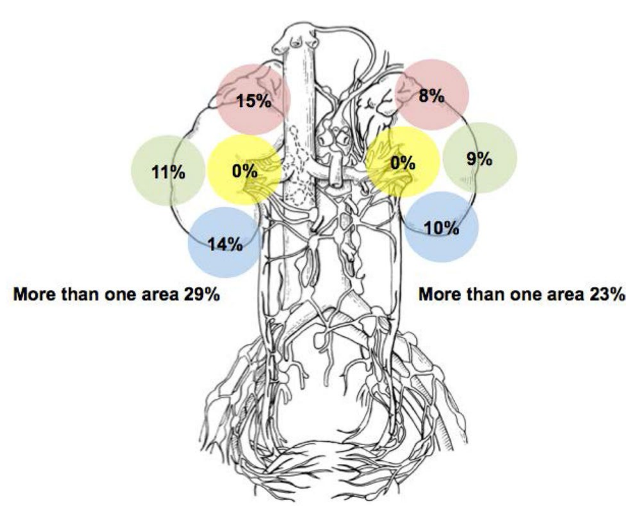

Fig. 1 Lymph node invasion rates at surgery in 1061 patients undergoing non-standardized LND at a tertiary care center after stratification for side and location of RCC (all $p < 0.01$). For each area, proportions are expressed as the number of patients with pN1 disease at surgery over the number of patients undergoing LND

When considering only patients with single locations, no statistically significant difference was observed (right RCC $p = 0.5$; left RCC $p = 0.7$).

The median follow-up period for uncensored cases was 60 months. During the study period, the rate of NP was 2.2%. After stratification for RCC side, LNI at surgery and NP at follow-up was 8% and 8% for superior area, 5% and 4% for middle area, 8% and 7% for lower area, 8% and 0% for hilar area and 19% and 16% for more than one area, in right and left RCC, respectively (all $p < 0.01$, Fig. 2). When considering only patients with single involved area, no statistically significant difference was observed (right RCC $p = 0.4$; left RCC $p = 0.1$). In subgroup analyses on the overall population according to LND extent (namely no vs. regional vs. extended LND), patients not receiving LND with more than one kidney area had a higher proportion of LNI and/or NP or only NP compared to other groups (2.6%, $p = 0.004$, Tables 2, 3, 4, 5). Higher but not statistically significant proportions of LNI and/or NP were always registered for patients with multiple RCC locations also in case of regional LND (17.8%, $p = 0.08$) and extended LND (48.9%, $p = 0.1$) in comparison to patients with single RCC locations. When focusing only

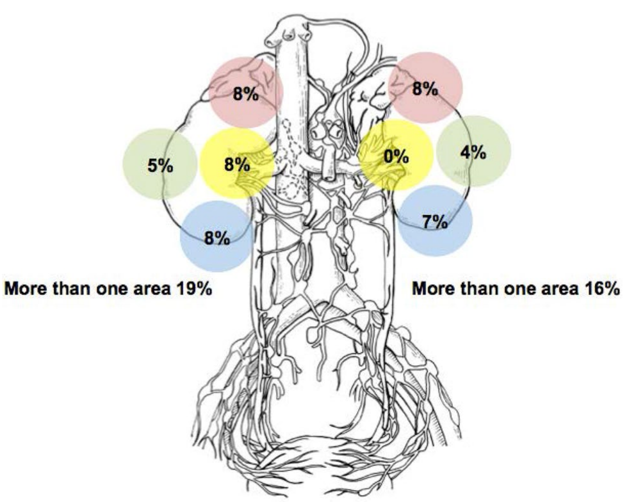

Fig. 2 Lymph node invasion rates at surgery in 1061 patients undergoing non-standardized LND at a tertiary care center after stratification for side and location of RCC (all $p < 0.01$). For each area, proportions are expressed as the number of patients with pN1 disease at surgery and/or nodal progression at follow-up over the number of patients surgically treated for RCC

Table 3 Subgroup analyses according to LND extent for LNI and/or NP after stratification for the side of the tumor

	Left (%)	Right (%)	p value
No LND	0.7	0.7	0.9
Regional LND	13.3	14.5	0.6
Extended LND	33.3	41.6	0.2

on NP, patients with superior and inferior RCC locations had higher but not statistically significant proportions in comparison to other groups, 5.3% and 7.9% for regional LND ($p = 0.07$) and 9.2% and 9.4% for extended LND ($p = 0.6$). No statistically significant difference was seen when patients were stratified according to RCC side (all $p \geq 0.2$).

Additionally, after excluding T1a RCC patients (Tables 6, 7, 8, 9), in case of no LND, patients with multiple RCC locations (5.1%) had higher proportions of LNI and/or NP compared to single RCC locations ($p = 0.01$). In case of regional LND, higher proportions of LNI and /or NP were registered for patients with single inferior RCC location (19.4%) and multiple locations (18.9%) although not statistically significant ($p = 0.1$). While for patients undergoing extended LND, higher rates were registered for multiple RCC locations (48.4%) and superior single RCC location (40.4%, $p = 0.2$). No statistically significant difference was seen when patients were stratified according to RCC side (all $p \geq 0.2$). When focusing only on NP, patients with superior and inferior RCC locations had higher but not statistically significant proportions in comparison to other groups, 6% and 9% for regional LND ($p = 0.08$) and 8.8% and 10% for extended LND ($p = 0.7$). No statistically significant difference was seen when patients were stratified according to RCC side (all $p \geq 0.3$).

In multivariable analyses on the overall population, clinical metastatic status (cM1), clinical nodal status (cN1), pT2 and pT3/pT4 disease, Fuhrman grade 3/4 were independent predictors of LNI at surgery and/or NP at follow-up (all $p \leq 0.01$; Table 10), after adjusting for all the potential confounders. Conversely, neither the side (right vs. left), nor the location of RCC (upper vs. middle vs. hilar vs. lower area vs. more than one area) reached the independent predictor status (all $p > 0.1$; Table 10).

Table 2 Subgroup analyses according to LND extent for LNI and/or NP after stratification for the location of the tumor

	Superior (%)	Middle (%)	Hilar (%)	Inferior (%)	Multiple (%)	p value
No LND	0.3	0.2	0	0	2.6	0.004
Regional LND	10.5	11.8	5	17	17.8	0.08
Extended LND	37	30	0	29.7	48.9	0.1

Table 4 Subgroup analyses according to LND extent for NP after stratification for the location of the tumor

	Superior (%)	Middle (%)	Hilar (%)	Inferior (%)	Multiple (%)	*p* value
No LND	0.3	0.2	0	0	2.6	0.004
Regional LND	5.3	2.8	5	7.9	2.1	0.07
Extended LND	9.2	5	0	9.4	4.4	0.6

Table 5 Subgroup analyses according to LND extent for NP after stratification for the side of the tumor

	Left (%)	Right (%)	*p* value
No LND	0	0.2	0.2
Regional LND	3.9	5.5	0.6
Extended LND	7.4	6.8	0.8

Table 6 Subgroup analyses after exclusion of pT1a RCC according to LND extent for LNI and/or NP after stratification for the location of the tumor

	Superior (%)	Middle (%)	Hilar (%)	Inferior (%)	Multiple (%)	*p* value
No LND	2.8	0.7	0	0	5.1	0.01
Regional LND	11.9	15.2	5.6	19.4	18.9	0.1
Extended LND	40.4	37.5	0	31.7	48.4	0.2

Discussion

Patients with nodal involvement in RCC have a eightfold greater chance of cancer-specific mortality compared to pN0 counterparts [12, 13] and this has an independent prognostic value even in patient with metastatic RCC [14]. Published retrospective studies [2] have indeed failed to reach an agreement on the topic. Moreover, the EORTC 30881 [15] did not demonstrate any benefit in terms of cancer control, although today, roughly 70% of that study population would have been classified as cT1a-bN0M0. Moreover, the LNI rate in cT1–T2N0M0 RCC patients is actually low (namely 2.2%) [16]. On the other hand, a sub-analysis of the EORTC 30811 study, focusing only on cT3 tumors, showed a 15% overall survival benefit at 5 years for LND recipients [17]. Regardless of the effect of LND on cancer-specific survival, LND does maintain its key role in terms of staging and following prognostication for RCC patients. The majority of studies on the subject have indeed identified worse prognosis for nodal positive RCC patients, both in M0 and M1 settings [18]. For that reason, pathologic nodal assessment is of importance to tailor closer post-operative surveillance scheme or consideration of enrolment into adjuvant therapy trials [3]. Since nobody, to the best of our knowledge, has previously questioned the impact of RCC anatomical side and location, and therefore, the nodal spreading potential on the base of lymphatic drainage, on LNI at surgery and/or NP risk, we could observe that the rate of harboring nodal

Table 7 Subgroup analyses after exclusion of pT1a RCC according to LND extent for LNI and/or NP after stratification for the side of the tumor

	Left (%)	Right (%)	*p* value
No LND	1.8	1.8	0.9
Regional LND	15.4	16.4	0.7
Extended LND	36	43.3	0.2

Table 9 Subgroup analyses after exclusion of pT1a RCC according to LND extent for NP after stratification for the side of the tumor

	Left (%)	Right (%)	*p* value
No LND	0	0.6	0.5
Regional LND	4.5	6.3	0.3
Extended LND	8	6.7	0.7

Table 8 Subgroup analyses after exclusion of pT1a RCC according to LND extent for NP after stratification for the location of the tumor

	Superior (%)	Middle (%)	Hilar (%)	Inferior (%)	Multiple (%)	*p* value
No LND	0.6	0.7	0	0	0	0.6
Regional LND	6	3.8	5.6	9	2.3	0.08
Extended LND	8.8	6.3	0	10	4.4	0.7

Table 10 Multivariable logistic regression analysis predicting nodal invasion at surgery and/or nodal progression at follow-up

	OR	95% CI	*p* value
Age	1	0.9–1	0.3
cM status (cM1 vs. cM0)	2.2	1.5–3.2	< 0.01
cN status (cN1 vs. cN0)	4.3	3–6.2	< 0.01
Pathologic diameter	1.1	1–1.1	< 0.01
Fuhrman grade (G3–G4 vs. G1–G2)	3.7	2.4–5.7	< 0.01
pT stage			
pT1	–	–	Ref.
pT2	2.7	1.2–5.7	0.01
pT3/4	5.4	2.9–9.9	< 0.01
RCC location			
Upper area	–	–	Ref.
Middle area	0.9	0.5–1.7	0.8
Hilar area	0.3	0–2.6	0.3
Lower area	1	0.6–1.7	0.9
More than one area	0.8	0.4–1.2	0.3
Right vs. left kidney tumour	1.3	0.9–1.8	0.2

disease at surgery is not dissimilar after stratification for side of RCC. However when stratifying patients for RCC location (upper vs. middle vs. hilar vs. lower area vs. more than one area) and then considering only patients with single locations (upper vs. middle vs. hilar vs. lower area), it appears that imbalances in proportions of patients with LNI at surgery and/or NP are exclusively due to patients with single-side RCC with more than one area affected in the overall population. In fact, patient with multiple location single-side RCC had higher proportions of LNI and/or NP in case of no LND ($p = 0.004$) and, although not statistically significant, also in regional ($p = 0.08$) and extended LND ($p = 0.1$) in comparison to patients with single-location single-side RCC. On the contrary, this was not confirmed when analyzing patients with only NP, since in this case, patients with superior or inferior location RCC, either after regional or extended LND, were more prone to recur in lymph nodes after surgery, although this was not statistically significant. To avoid potential confounding factors coming from a population with low nodal metastatic potential, T1a patients were excluded in the subsequent subgroup analysis. Nevertheless, the proportion of LNI and/or NP was higher for patients with multiple-location RCCs not receiving LND ($p = 0.01$) and after extended LND ($p = 0.2$), in comparison to other groups. As evaluated in the overall population, the rate of NP was higher for patients with superior and inferior single-side RCC either after regional and extended LND, although not statistically significant. These observation may be explained by considering that the intrarenal lymphatic system originates from the superficial network under the fibrous capsule and drains directly to the hilum or connects to the deeper cortical lymph capillaries, which after collecting fluid from the connective tissue, travel in the renal sinus along blood vessels to the hilum [19, 20]. However, this system could branch off into the paracaval/para-aortal and the interaortocaval lymph nodes, but, as demonstrated by pioneering cadaveric and sentinel-node studies [6–9, 21–23], extreme variations in drainage among RCC patients could be observed, even with aberrant firstly draining thoracic nodes. Second, when considering the overall population (patients undergoing LND and not) and the risk of LNI at surgery and/or NP at follow-up, neither the side nor the location of RCC reached the status of independent predictors. As expected, prognostic factors were represented by clinical metastatic status, clinical nodal status, pT2 and pT3/pT4 disease, and Fuhrman grade 3/4. These findings are in line with previous studies on the same topic [2, 18].

Despite several strengths, our analyses are not devoid of limitations, mainly due to its retrospective and non-comparative nature. First, patients underwent a LND with different template extensions according to tumor characteristics and to preference of the surgeon. Second, any RCC histology was considered for the present analyses and this could have created an uneven population, due to different metastatic potential of each histologic type. Third, over the years, many aspects, as for the administration and type of recommended adjuvant treatment, have been changing in the oncosurgical management of patients with RCC and nodal involvement. On the other hand, to the best of our knowledge, this is the first study evaluating the risk of LNI and NP at follow-up, after stratification for the RCC side and location.

Conclusions

In patients with RCC, single-side tumors with involvement of more than one area, tend to have higher rates of nodal involvement relative to patients with single-area RCC location. However, neither the side (left vs. right) nor the location (upper vs. middle vs. hilar vs. inferior area) of the primary RCC tumor is related to the risk of harboring LNI at surgery and/or developing NP at follow-up.

Authors' contribution NA: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. LA: Protocol/project development, Data analysis. DP: Protocol/project development. CF: Data collection or management. MF: Data collection or management. RF: Data collection or management. CW: Data analysis. SA: Supervision. BA: Supervision. MF: Supervision. BR: Protocol/project development, Data collection or management, Manuscript writing/editing, Supervision. CU: Protocol/project development, Data collection or management, Manuscript writing/editing, Supervision.

Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

Ethical approval For this type of study, formal consent is not required.

References

1. Kates M, Lavery HJ, Brajtbord J et al (2012) Decreasing rates of lymph node dissection during radical nephrectomy for renal cell carcinoma. Ann Surg Oncol 19:2693–2699. https://doi.org/10.1245/s10434-012-2330-6
2. Capitanio U, Leibovich BC (2017) The rationale and the role of lymph node dissection in renal cell carcinoma. World J Urol 35:497–506. https://doi.org/10.1007/s00345-016-1886-3
3. Ravaud A, Motzer RJ, Pandha HS et al (2016) Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 375:2246–2254. https://doi.org/10.1056/NEJMoa1611406
4. Capitanio U, Montorsi F (2016) Renal cancer. Lancet 387:894–906. https://doi.org/10.1016/S0140-6736(15)00046-X
5. Bex A (2016) Follow-up for renal cell carcinoma: absence of evidence and beyond. Eur Urol Focus 1:282–283. https://doi.org/10.1016/j.euf.2015.07.006
6. Karmali RJ, Suami H, Wood CG, Karam JA (2014) Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int 114:806–817. https://doi.org/10.1111/bju.12814
7. Bex A, Vermeeren L, Meinhardt W et al (2011) Intraoperative sentinel node identification and sampling in clinically node-negative renal cell carcinoma: initial experience in 20 patients. World J Urol 29:793–799. https://doi.org/10.1007/s00345-010-0615-6
8. Sherif AM, Eriksson E, Thörn M et al (2012) Sentinel node detection in renal cell carcinoma. A feasibility study for detection of tumour-draining lymph nodes. BJU Int 109:1134–1139. https://doi.org/10.1111/j.1464-410X.2011.10444.x
9. Kuusk T, De Bruijn R, Brouwer RO et al (2017) Lymphatic drainage from renal tumors in vivo: a prospective sentinel node study using SPECT/CT imaging. J Urol. https://doi.org/10.1016/j.juro.2017.11.112
10. Paner GP, Stadler WM, Hansel DE et al (2018) Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. Eur Urol. https://doi.org/10.1016/j.eururo.2017.12.018
11. Delahunt B, Cheville JC, Martignoni G et al (2013) The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol:1490–1504
12. Blute ML, Leibovich BC, Cheville JC et al (2004) A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. J Urol 172:465–469. https://doi.org/10.1097/01.ju.0000129815.91927.85
13. Capitanio U, Jeldres C, Patard J-J et al (2009) Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. BJU Int 103:33–37. https://doi.org/10.1111/j.1464-410X.2008.08014.x
14. Lughezzani G, Capitanio U, Jeldres C et al (2009) Prognostic significance of lymph node invasion in patients with metastatic renal cell carcinoma: a population-based perspective. Cancer 115:5680–5687. https://doi.org/10.1002/cncr.24682
15. Blom JHM, Van Poppel H, Maréchal JM et al (2009) Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol 55:28–34. https://doi.org/10.1016/j.eururo.2008.09.052
16. Dell'Oglio P, Larcher A, Muttin F et al (2017) Lymph node dissection should not be dismissed in case of localized renal cell carcinoma in the presence of larger diseases. Urol Oncol 35:662.e9–662.e15. https://doi.org/10.1016/j.urolonc.2017.07.010
17. Bekema HJ, MacLennan S, Imamura M et al (2013) Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. Eur Urol 64:799–810. https://doi.org/10.1016/j.eururo.2013.04.033
18. Bhindi B, Wallis CJD, Boorjian SA et al (2018) The role of lymph node dissection in the management of renal cell carcinoma: a systematic review and meta-analysis. BJU Int. https://doi.org/10.1111/bju.14127
19. Delamere G, Poirier P, Cunéo B (1904) The lymphatics. Ann Surg 39:1040–1044. https://doi.org/10.1097/00000658-190406000-00014
20. Clodius L (2006) M. Földi, E. Földi, S. Kubik (eds) Textbook of lymphology (in German), 6th edn. Elsevier, Munich, 2005. ISBN 3-437-45322-X, US\$ 95.00. Eur J Plastic Surg 28:537–538. https://doi.org/10.1007/s00238-005-0024-z
21. Brouwer OR, Noe A, Olmos RAV, Bex A (2013) Lymphatic drainage from renal cell carcinoma along the thoracic duct visualized with SPECT/CT. Lymphat Res Biol 11:233–238. https://doi.org/10.1089/lrb.2013.0017
22. Hultén L, Rosencrantz M, Seeman T et al (1969) Occurrence and localization of lymph node metastases in renal carcinoma. A lymphographic and histopathological investigation in connection with nephrectomy. Scand J Urol Nephrol 3:129–133
23. Johnsen JA, Hellsten S (1997) Lymphatogenous spread of renal cell carcinoma: an autopsy study. J Urol 157:450–453