Aus der Urologie und Kinderurologie-Klinik,

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The role of lymph node dissection in kidney cancer

surgery for staging and therapy

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Abstract

Background

Controversies on the therapeutic efficacy of lymph node dissection (LND) at time of radical nephrectomy (RN) for renal cell carcinoma (RCC) patients have not yet been solved, due to a limited knowledge of nodal dissemination patterns, thus licensing the use of unstandardized LND templates among institutions and causing post-operative patient risk-category misclassification. The aims of the thesis were I) to evaluate if the side and the location of RCC affected the probability of lymph nodal invasion (LNI) and/or nodal progression (NP) at follow-up, II) to describe nodal disease dissemination in clear cell RCC (ccRCC) patients and to assess the effect of the anatomical sites and the number of affected nodal areas on cancer specific mortality (CSM), III) to test the clinical usefulness of performing LND to stratify the risk of patients with RCC and select candidates for adjuvant treatment.

Methods

Core-data were represented by a prospectively collected database of 3,645 consecutive patients enrolled at a single tertiary Institution and submitted to surgery for RCC with comprehensive clinical, surgical, pathologic and follow-up data of patients. Regional LND consisted of hilar nodes plus, on the right side, pre-retro-caval nodes or, on the left side, para-aortic nodes. Extended LND consisted of regional LND plus interaortocaval nodes.

Results

Overall, 15% of patients underwent LND and were pN1 at surgery and 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 area relative to patients with tumor in a single area (p<0.01). Neither the RCC side nor the location reached the independent predictor status (all p>0.1). In the second study, among patients with one involved nodal site, 54 and 26% of patients were positive only in side-specific and interaortocaval station, respectively. Interaortocaval nodal positivity (HR 2.3, CI 95%: 1.3–3.9, p<0.01) represented an independent predictor of CSM. In the third study, LNI resulted as the most informative predictor of early progression (OR: 6.39; CI 95%: 3.26-12.54; p<0.0001). The accuracy was higher (p=0.008) for the model to predict early recurrence when implemented with pN (AUC: 0.76; CI95%: 0.71-0.80), as compared to the base model (AUC: 0.72; CI95%: 0.68-0.76). Patients with high-risk disease showed a large difference in the risk of progression according to pN-status (1-year risk: 58% for pN1; 31% for pN0; p<0.001).

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, but this was predicted neither by side nor by location of RCC. When ccRCC patients (about 90% of all RCC) harbour nodal disease, its spreading can occur at any

nodal station without involving the others. The presence of interoartocaval positive nodes does affect oncologic outcomes and therefore an extended LND template is advisable, when indicated. Moreover, performing LND at the time of RN improves risk stratification, resulting into clinical advantage for selecting high-risk patients for further treatment after surgery.

Introduction

The role of lymph node dissection (LND) in patients submitted to surgery for renal cell carcinoma (RCC) has been extensively investigated but, although accepted as a staging procedure, its therapeutic effect is still a matter of debate[1,2]

Since autoptic evaluations as well as sentinel node studies of pN1 disease dissemination in RCC patient ascertained unpredictable and extreme interindividual variability[3-5], the aim of the first study was to investigate[6] the role of anatomical side and location of the primary RCC, namely upper vs. middle vs. lower vs. hilar vs. more than one kidney area, on the risk of lymph node invasion (LNI) and/or nodal progression (NP) during follow-up.

Considering the weakness of Guidelines recommendations, as well as the conflicting results on survival from studies dealing with the topic of LND in kidney cancer, and taken into account the use of unstandardized LND templates among institutions and the inclusion of any kidney cancer histology, the aim of the second study[7] was to describe nodal disease dissemination in clear cell RCC (ccRCC) patients and to assess the effect of the anatomical sites and the number of nodal areas affected on cancer specific mortality (CSM).

Moreover, since LND could identify pN1 disease and thus high-risk patients, who may be candidates for adjuvant treatment, regardless of the other risk-factors (disease stage, Fuhrman grade and on the Eastern Cooperative Oncology Group Performance Status), the aim of the third study[8] was to test the clinical usefulness of performing LND to stratify the risk of patients with RCC and select candidates for systemic treatment after RN.

Material and methods

Core-data were represented by a prospectively collected database of 3,645 consecutive patients enrolled at a single tertiary Institution and submitted to surgery for renal cell carcinoma with comprehensive clinical, surgical, pathologic and follow-up data of patients.

In the first publication[6], "The side and the location of the primary tumor does not affect the probability of lymph node invasion in patients with renal cell carcinoma", namely 2485 patients with sporadic, unilateral RCC surgically treated at a single tertiary care referral center between 1987 and 2016 were identified. 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. Regional LND consisted of hilar nodes plus, on the right side, pre-retro-caval nodes or, on the left side, para-aortic nodes. Extended LND consisted of regional LND plus interaortocaval nodes. The primary outcome of the study was represented by the presence of lymph node invasion (LNI) at final pathology and/or the presence of nodal progression (NP) during follow-up period after stratification for tumor side and location.

In the second publication[7], "The effect of anatomical location of lymph node metastases on cancer specific survival in patients with clear cell renal cell carcinoma", data on 415 patients with sporadic, unilateral, ccRCC treated with open RN and eLND at two tertiary referral centers (1980-2012) were analysed. Outcomes of the study were represented by other cause mortality (OCM)- and cancer specific mortality (CSM)-free survival rate. Secondly, a description of the pattern of nodal cancer dissemination in pN1 patients was performed on the overall ccRCC population and after stratification according to the kidney tumour side (right vs. left). Finally, we assessed the CSM-free survival rate according to the pattern of nodal dissemination (lymph node site or number of lymph node areas involved).

In the third publication[8], "The critical role of lymph node dissection in selecting high-risk nonmetastatic renal cancer candidates for adjuvant therapy after nephrectomy", 861 patients with nonmetastatic ccRCC treated with RN at a single academic center from 1987 to 2016 were identified. The follow-up was based on clinical evaluation and chest-abdomen CT scans performed at 3 to 6 months and at 12 months after surgery over the first year, and annually thereafter. Additional imaging assessments were performed if the patient's symptoms raised clinical suspicion of relapse. Disease progression after surgery was defined as the evidence of retroperitoneal or distant recurrence demonstrable on imaging at least 1 month after treatment. A model including pT stage, disease grade and ECOG-PS was compared with the same model implemented with pN stage, in terms of the accuracy for predicting early disease progression after surgery, defined as relapse within 12 (±3) months post-treatment. The accuracy of the predictive models was assessed by area under the curve (AUC). The accuracy of the models and decision curves was corrected for overfitting using 10-fold cross-validation.

Results

In the first study[6], it was found that 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, either after stratification for the extent of LND (no LND vs. regional LND, namely, hilar LND plus, side specific pre/para-caval LND vs. extended LND, namely hilar LND plus side-specific, pre/paraaortic or pre/paracaval, and interaortocaval LND), or after exclusion of pT1a RCC. However, neither the side (left vs. right) nor the location (upper vs. middle vs. hilar vs. inferior area) of the primary RCC tumor represented independent predictors of the risk of harboring LNI at surgery and/or developing NP at follow-up. These figures suggested that anatomical location or side of the tumor are not reliable clinical parameters to identify patients who are at risk of nodal metastatic dissemination, but cM1 status, cN1 status, pT2 and pT3/pT4 disease, and Fuhrman grade 3/4.

In the second study[7], within the group of patients with one positive nodal area, in 54% of patients, nodal dissemination skipped the hilar nodal area, in line with what has been previously reported by EAU guidelines (35–45%)[9], while in 26% of cases, both the hilar and the side-specific areas were eluded. Instead, when looking at patients with two nodal areas involved, hilar nodal area was skipped in 54% of patients and side-specific area only in 4% of cases. Moreover, after stratification for the ccRCC side, in case of interaortocaval-only nodal positivity among patients with one positive nodal site, 10 out of 12 patients had right ccRCC. This discrepancy was also identified in case of patients with two positive nodal areas and interaortocaval nodal involvement: the majority of patients had right ccRCC (14 out of 15 patients). On Multivariable Cox regression analyses, when considering the location of nodal metastases, independent predictors of CSM were represented by pT3 (HR: 2.7; CI 95%: 1.5–5) and pT4 stage (HR: 6.1; CI 95%: 2.6–14.3), cM1 status (HR: 4.3; CI 95%: 3–6.2) and positive status of interaortocaval nodal area (HR: 2.3, CI 95%: 1.3–3.9), all $p \leq 0.01$. These figures suggest that hilar LND could not be representative for every patient to be properly pN staged and thereafter to tailor adjuvant treatment. Among patients with right ccRCC and single nodal positive site, approximately 60% would have been properly staged as pN1 only by hilar and side-specific template, 40% only by extended LND. Conversely, in left kidney tumors, 91% would have been properly staged as pN1 only by hilar and side-specific template, 9% only by extended LND, in line with previous results[10]. Moreover, cM1 disease, pT3-pT4 stage and positive interaortocaval nodal status and presence of any positive nodal area were independent predictors of CSM (all $p \leq 0.01$), thus suggesting that extended LND could properly stage patients and tailor adjuvant treatment in the ccRCC population.

In the third study[8], the accuracy and clinical usefulness of a logistic regression model predicting disease progression within 12 months after surgery including factors defining high-risk patients according to the S-TRAC trial [(pT3 and Grade≥2 and performance status score ≥1) or pT4] relative to the base model plus pN stage for the prediction of early progression after surgery were compared. Nodal invasion resulted the most informative predictor of early progression (odds ratio: 6.39; 95% confidence interval [CI]: 3.26, 12.54; P < 0.0001). The accuracy was higher (P = 0.008) for the model implemented

with pN (area under the curve: 0.76; 95% CI: 0.71, 0.80) as compared to the base model (area under the curve: 0.72; 95% CI: 0.68, 0.76). Performing LND to select patients for postoperative systemic treatment, resulted in a slightly higher net benefit as compared to a strategy defining risk on the base of factors other than pN. Patients with high-risk disease showed a large difference in the risk of progression according to pN-status (1-year risk: 58% [95% CI: 45, 72] for pN1; 31% [95% CI: 25, 38] for pN0; P < 0.001).

Discussion

      The current Guidelines of the European Association of Urology[9] suggest to offer an extended LND to patients with adverse clinical features, including a large diameter of the primary tumor (rating: weak), and in patients with cN1 disease only for staging purposes or local control (LE: 2b). Although the healthy nodal spreading pathways in kidney have been traced, autoptic evaluations as well as sentinel node studies of pN1 disease dissemination in patients with RCC ascertained unpredictable through extreme interindividual variability[3-5]. Indeed, renal lymphatic system follows the topography of renal vasculature[11]. From the right kidney, efferent lymphatic vessels running anterior to the renal vein (anterior bundles) can drain into paracaval, precaval, retrocaval and interaortocaval nodes. Retrocaval nodes are located close to the right crus of the diaphragm and connect with the thoracic duct. Lymphatics from the hilum running posterior to the renal vein but anterior to the pelvis of the kidney and the renal artery (intravascular bundles) are few in number. Their drainage is not well described. Lymphatic vessels travelling posterior to the renal artery (posterior bundles) drain to the paracaval, retrocaval and interaortocaval nodes. In some cases, posterior efferent lymphatic vessels have been observed curving superiorly through the right crus of the diaphragm and connecting directly to the thoracic duct without passing through any lymph nodes.

      From the left kidney, efferent lymphatic vessels running anterior to the renal vein can drain into the para-aortic and preaortic nodes. These vessels have also been observed to give off branches that run superiorly and connect with posterior draining efferent vessels. Intravascular bundles from the left kidney, like the right kidney, are few in number and not clearly described. Posterior efferent lymphatic vessels can drain to the para-aortic and retroaortic nodes. They can also curve superiorly through the left crus of the diaphragm and connect directly to the thoracic duct without passing through any lymph node. The retroperitoneal lymph nodes are an extensive network of lymphatics between the first and fifth lumbar vertebrae. They serve as the primary landing sites of renal lymph and have unpredictable interconnections before reaching the thoracic duct. In addition to draining the kidney, they also drain the sacrum, mesocolon, testicle, uterus, ovaries, adrenal glands, deep muscles of the dorsal region and the diaphragm[12]. Therefore the role of anatomical side and location of the primary RCC, namely upper vs. middle vs. lower vs. hilar vs. more than one kidney area, on the risk of lymph node invasion (LNI) and/or nodal progression (NP) during follow-up were investigated[6]. The first study did underline that lymph nodal invasion cannot be predicted by anatomical location or side of the tumor and identification of candidates for LND is mainly relying on disease features (cM1 status, cN1 status, pT2 and pT3/pT4 disease, and Fuhrman grade 3/4), due to unpredictable and extreme interindividual variability.

      Evidence on the oncologic advantage of LND in RCC patients are mainly derived from the only randomized trial on the topic, European Organization for Research and Treatment of Cancer (EORTC) 30881[13], and prospective studies included in a recent metanalysis examining the role of LND in RCC[1]. It was found that LND and its extent are not associated with improved survival in either M0 or M1 RCC patients, but pN1 status is associated with adverse prognosis in M0 and M1 RCC, without increasing

perioperative morbidity[1]. However, a re-analysis of the EORTC 30881 trial focusing on cT3 tumors, since roughly 70% of that study population would have been classified nowadays as cT1abN0M0, showed a 15% overall survival benefit at 5 years for LND recipients[14]. At the same time, the American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) Guidelines suggest to perform LND for staging and prognostic purposes, and recommend against routine LND in patients with clinically negative nodes[15,16]. The weakness of Guidelines recommendations, as well as conflicting results from studies dealing with the topic, is mainly linked to an unstandardized LND template/extent among institutions, stressing the anatomical unpredictability of nodal dissemination and the weighing of oncological benefits and the risk of surgical complications[17]. Moreover, each RCC histology subtype has different rates of LNI: the lowest rates are recorded for chromophobe (7%) and clear cell RCC (8.7%), while the highest for sarcomatoid (38.3%) and collecting duct RCC (71.4%)[18]. Therefore, in the second study[7], nodal disease dissemination in clear cell RCC (ccRCC) patients submitted to LND was described and the effect of the anatomical sites and the number of nodal areas on cancer specific mortality (CSM) was evaluated. It was found that at least, 40% of patients with right and 9% with left ccRCC would not been staged as pN1 by a LND limited to hilar and side-specific lymph nodes, mainly due to a nodal-station-skipping phenomenon of metastasis. Moreover positive interaortocaval nodal status represented an independent predictor of CSM. Therefore, it seems advisable to perform an extended LND involving hilar, side-specific (pre/paraaortic or pre/paracaval) and interaortocaval LND, since this would aid patient risk stratification and multimodality upfront treatment.

Since 30-35% of patients who undergo surgery for localized or locally advanced RCC will eventually develop recurrence (mostly in form of distant metastases), adjuvant treatment could reduce the risk of progression or cancer-related death. At the moment all tested adjuvant agents, except an autologous renal tumor cell vaccine and sunitinib, an inhibitor of the vascular endothelial growth factor receptor (VEGFR), sunitinib, have failed to show any benefit[19]. As far as sunitinib is concerned, the Food and Drug Administration approved the drug for this indication in 2017 due to a disease-free survival advantage over placebo as an adjuvant treatment after RN for high-risk renal cancer patients in the S-TRAC trial, whereas the European Medicines Agency did not[20]. The trial showed that patients treated with sunitinib had a 26% risk reduction of disease progression. Since the definition of high-risk disease was based on disease stage, Fuhrman grade and on the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and patients with pN1 disease were classified as high-risk regardless of all other risk factors; as such, performing LND at the time of surgery could allow to detect patients with nodal metastases who may otherwise not be selected for adjuvant treatments[21,22] on the solely base of T stage, disease grade and performance status. In this case nodal staging would greatly influence clinical practice; however, in the S-TRAC trial a LND was not routinely performed and not standardized, thus leaving the question unanswered. In the third study[8], it was demonstrated that performing LND at the time of nephrectomy improves risk stratification, resulting into a small but

nonnegligible clinical advantage for selecting high-risk patients for further treatment after surgery. If current adjuvant trials with immune checkpoint inhibition demonstrate a survival benefit over placebo, LND within these templates may regain an indication for proper risk and prognosis assessment and techniques to identify first landing sites of occult LN metastases may reduce the need for extensive templates. Indeed, implementation of the base model used to define high-risk patients in S-TRAC trial, showed a slightly increased accuracy and net benefit.

Bibliography

1. Bhindi B, Wallis CJD, Boorjian SA, et al. The role of lymph node dissection in the management of renal cell carcinoma: a systematic review and meta-analysis. BJU Int 2018;121(5):684–98.

2. Capitanio U, Montorsi F. Renal cancer. Lancet 2016;387(10021):894–906.

3. Johnsen JA, Hellsten S. Lymphatogenous spread of renal cell carcinoma: an autopsy study. J Urol 1997;157(2):450–3.

4. Kuusk T, De Bruijn R, Brouwer OR, et al. Lymphatic Drainage from Renal Tumors In Vivo: A Prospective Sentinel Node Study Using SPECT/CT Imaging. J Urol 2018;199(6):1426–32.

5. Sherif AM, Eriksson E, Thörn M, et al. Sentinel node detection in renal cell carcinoma. A feasibility study for detection of tumour-draining lymph nodes. BJU Int 2012;109(8):1134–9.

6. Nini A, Larcher A, Cazzaniga W, et al. The side and the location of the primary tumor does not affect the probability of lymph node invasion in patients with renal cell carcinoma. World J Urol 2019;37(8):1623–9.

7. Nini A, Larcher A, Cianflone F, et al. The Effect of Anatomical Location of Lymph Node Metastases on Cancer Specific Survival in Patients with Clear Cell Renal Cell Carcinoma. Front Surg 2018;5:26.

8. Capogrosso P, Larcher A, Nini A, et al. The critical role of lymph node dissection in selecting high-risk nonmetastatic renal cancer candidates for adjuvant therapy after nephrectomy. Urol Oncol 2019;37(4):293.e25–293.e30.

9. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67(5):913–24.

10. Crispen PL, Breau RH, Allmer C, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. Eur Urol 2011;59(1):18–23.

11. O'Morchoe CC, O'Morchoe PJ. The renal lymphatic system: a brief review. Contrib Nephrol 1988;68:230–7.

12. Karmali RJ, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int 2014;114(6):806–17.

13. Blom JHM, van Poppel H, Maréchal JM, et al. 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 2009;55(1):28–34.

14. Bekema HJ, MacLennan S, Imamura M, et al. Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. Eur Urol 2013;64(5):799–810.

15. Campbell S, Uzzo RG, Allaf ME, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J. Urol. 2017;198(3):520–9.

16. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney Cancer, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(6):804–34.

17. Campi R, Sessa F, Di Maida F, et al. Templates of Lymph Node Dissection for Renal Cell Carcinoma: A Systematic Review of the Literature. Front Surg 2018;5:76.

18. Rosiello G, Palumbo C, Knipper S, et al. Histotype predicts the rate of lymph node invasion at nephrectomy in patients with nonmetastatic renal cell carcinoma. Urol Oncol 2020;

19. Porta C, Cosmai L, Leibovich BC, Powles T, Gallieni M, Bex A. The adjuvant treatment of kidney cancer: a multidisciplinary outlook. Nat Rev Nephrol 2019;15(7):423–33.

20. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med 2016;375(23):2246–54.

21. Motzer RJ, Haas NB, Donskov F, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. J Clin Oncol 2017;35(35):3916–23.

22. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387(10032):2008–16.

Aknowledgements

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

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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

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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 (pNx/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%)

Table 1 (continued)

	Overall population
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 $p < 0.01$).
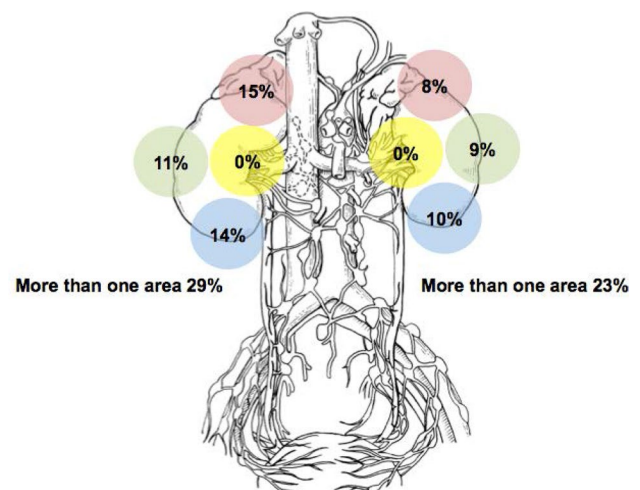

Fig. 1 Lymph node invasion rates at surgery in 1061 patients undergoing non-standardized LND at a tertiary care center after stratification for side and location of RCC (all $p < 0.01$). For each area, proportions are expressed as the number of patients with pN1 disease at surgery over the number of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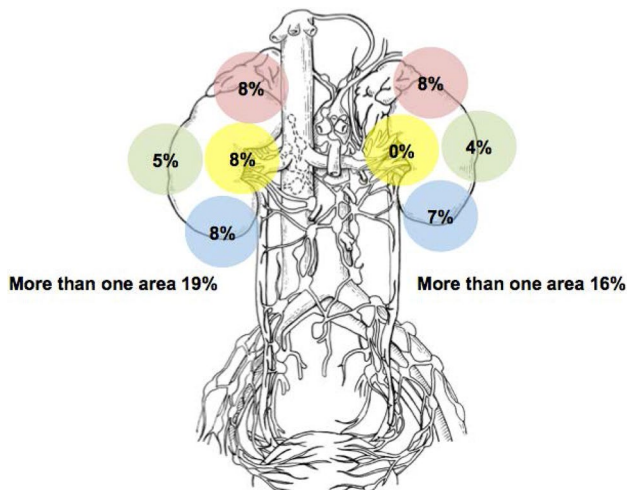

Fig. 2 Lymph node invasion rates at surgery in 1061 patients undergoing non-standardized LND at a tertiary care center after stratification for side and location of RCC (all $p < 0.01$). For each area, proportions are expressed as the number of patients with pN1 disease at surgery and/or nodal progression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

Compliance with ethical standards

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

The Effect of Anatomical Location of Lymph Node Metastases on Cancer Specific Survival in Patients with Clear Cell Renal Cell Carcinoma

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Background: Positive nodal status (pN1) is an independent predictor of survival in renal cell carcinoma (RCC) patients. However, no study to date has tested whether the location of lymph node (LN) metastases does affect oncologic outcomes in a population submitted to radical nephrectomy (RN) and extended lymph node dissection (eLND).

Objective: To describe nodal disease dissemination in clear cell RCC (ccRCC) patients and to assess the effect of the anatomical sites and the number of nodal areas affected on cancer specific mortality (CSM).

Design, setting and partecipants: The study included 415 patients who underwent RN and eLND, defined as the removal of hilar, side-specific (pre/paraaortic or pre/paracaval) and interaortocaval LNs for ccRCC, at two institutions.

Outcome measurement and statistical analysis: Descriptive statistics were used to depict nodal dissemination in pN1 patients, stratified according to nodal site and number of involved areas. Multivariable Cox regression analyses and Kaplan-Meier curves were used to explore the relationship between pN1 disease features and survival outcomes.

Results and limitations: Median number of removed LN was 14 (IQR 9–19); 23% of patients were pN1. Among patients with one involved nodal site, 54 and 26% of patients were positive only in side-specific and interaortocaval station, respectively. The most frequent nodal site was the interaortocaval and side-specific one, for right and left ccRCC, respectively. Interaortocaval nodal positivity (HR 2.3, CI 95%: 1.3–3.9, $p < 0.01$) represented an independent predictor of CSM.

Conclusions: When ccRCC patient harbour nodal disease, its spreading can occur at any nodal station without involving the others. The presence of interoartocaval positive nodes does affect oncologic outcomes.

Patient summary: Lymph node invasion in patients with clear cell renal cell carcinoma is not following a fixed anatomical pattern. An extended lymph node dissection, during treatment for primary kidney tumour, would aid patient risk stratification and multimodality upfront treatment.

Keywords: lymph node invasion, metastases, survival, kidney cancer, renal cancer

INTRODUCTION

Positive nodal status and number of positive nodes are independent predictors of survival in renal cell carcinoma (RCC) patients (1, 2). Moreover, the role of lymph node dissection (LND) for RCC staging is widely accepted in intermediate/high risk patients, although its effect on cancer control is limited, especially in low risk patients (3). Adequate nodal staging and subsequent prognosis assessment become even more important in the light of the recent data published in the setting of adjuvant therapy, follow-up and salvage therapy (4–6).

The natural history of patients with nodal metastases is already known. Recently, it has been reported a 12% metastasis-free survival at 5 years (7). However, no study evaluated if prognosis is affected by location of the nodal metastasis or by the number of areas affected by nodal disease. This appears of paramount importance, if we consider that nodal invasion is often considered a criterion to define a RCC patient as metastatic, especially among medical oncologists.

Cadaveric dissection and sentinel-node studies (8–10) demonstrated wide heterogeneity of retroperitoneal lymphatic vessels anatomy. In addition, RCC histologies have different distant spreading rates (11) and oncologic outcomes (12, 13). Therefore, a critical analysis of nodal involvement areas in RCC patients submitted to RN and extended LND (eLND) might provide additional information on the pattern of lymphatic dissemination and its impact on the natural history of the disease.

Under such premises, the aim of this study was to describe nodal disease dissemination in clear cell RCC (ccRCC) patients and to assess the effect of the anatomical sites and the number of nodal areas affected by disease on cancer specific mortality (CSM).

MATERIALS AND METHODS

Patient Population

After institutional ethic committee board approvals (IRCCS San Raffaele, Milan and Ospedale Maggiore della Carita´, Novara, Italy), we identified 2,884 patients with sporadic, unilateral, RCC treated with open radical nephrectomy (RN) between 1980 and 2012. Of these, 415 patients (14.4%) presented with clear cell RCC (ccRCC) histology and underwent RN plus eLND (San Raffaele 165/415, 40% and Novara 250/415, 60%), defined by a template including hilar, side-specific (pre/paraaortic or pre/paracaval) and interaortocaval nodal stations. All patients signed written informed consent to undergo surgery and to use clinical data in an anonymous fashion for scientific purposes. Nodal dissection template was shared between the Institutions, and ipsilateral template on the left side included nodes from the crus of the diaphragm to the inferior mesenteric artery, and on the right side, from the adrenal vein to the level of inferior mesenteric artery. Each nodal station was separately labelled and delivered to pathology (**Figure 1**).

The decision to perform LND was based on surgeon's discretion and inclusion criteria were represented by cT2 disease and above, tumor size >10 cm, lymphadenopathies and palpable lymph nodes during surgery.
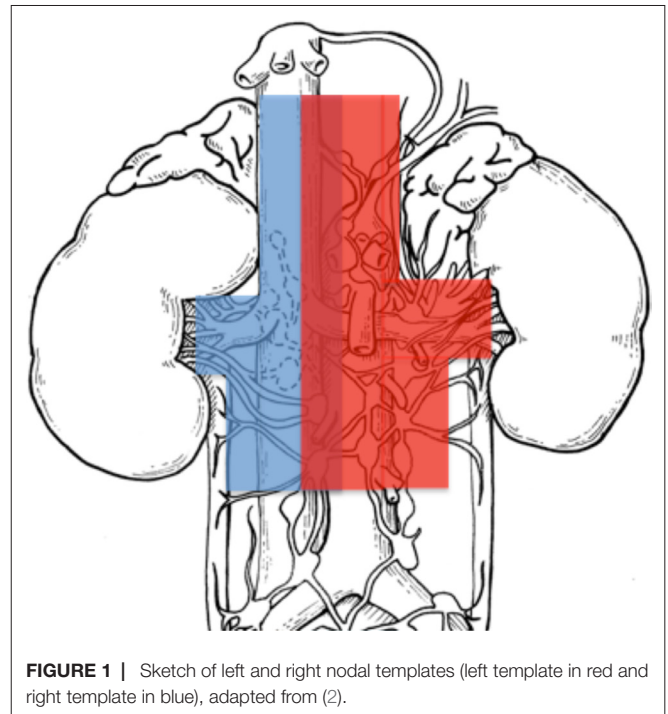

FIGURE 1 | Sketch of left and right nodal templates (left template in red and right template in blue), adapted from (2).

Outcomes

Outcomes were other cause mortality (OCM)- and cancer specific mortality (CSM)-free survival rate. Secondly, a description of the pattern of nodal cancer dissemination in pN1 patient was performed on the overall ccRCC population and after stratification according to the kidney tumour side (right vs. left). Finally, we assessed the CSM-free survival rate according to the pattern of nodal dissemination (lymph node site or number of lymph node areas involved).

Covariates

Covariates consisted of age, gender, tumour side (right vs. left), symptoms, clinical metastatic status (cM0 vs. cM1), pathological T stage (defined according to 7th American Joint Committee on Cancer classification) (14), pathological N stage, Fuhrman grade (according to the WHO/International Society of Urological Pathology classification) (15), tumour size, mean number of lymph nodes removed, number of positive lymph nodes, number of involved nodal sites, hilar, side-specific and interaortocaval nodal status.

Statistical Analyses

Statistical analyses, as well as reporting and interpretation of the results, consisted of three steps.

Firstly, means, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables on the study population, respectively. Kaplan-Meier analyses were used to assess OCM- and CSM-free survival rate at different time points, on the overall population and after stratification for pN status.

Secondly, among patients with pN1 disease, a description of anatomical nodal involvement, stratified according to the number of the involved nodal sites (1 vs. 2 vs. 3) was performed.

Thirdly, among patients with pN1 disease, Cox multivariable regression analysis was used to predict the risk of CSM. Predictors consisted of number of involved lymph node areas, age, pT stage, pathologic tumour size, Fuhrman grade, and cM status. In an additional set of Cox multivariable regression analysis predicting CSM, anatomical nodal involvement (hilar vs. side-specific vs. interaortocaval nodal invasion) was used instead of number of involved lymph node areas. All statistical tests were performed using RStudio graphical interface v.0.98 for R software environment v.3.0.2 (R Foundation, Vienna, Austria). All tests were two-sided with a significance level set at p value < 0.05.

RESULTS

Clinicopathologic features are summarized in **Table 1**. The median number of removed lymph nodes (LNs) was 14 (IQR 9–19) and the median number of positive LNs was 3 (IQR 2–8). Overall, 74 patients (18%) and 179 patients (43%) had systemic and local symptoms, respectively. Clinical M1 status was present in 112 patients (27%), pT3/pT4 disease was found in 260 patients (63%), while 199 (48%) had Fuhrman grade 3/4.
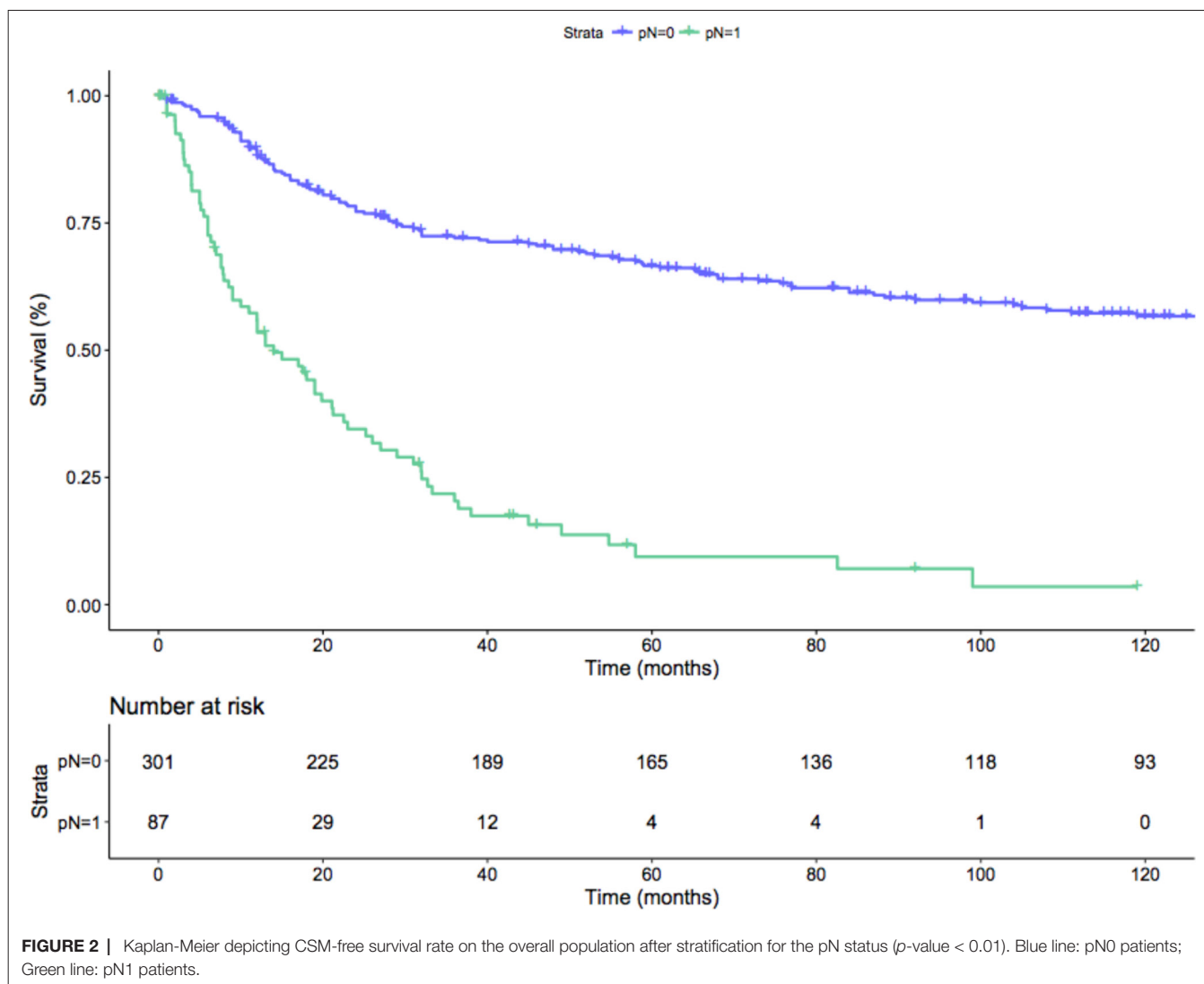
Median follow-up among survivors was 43.7 months, with an overall OCM- and CSM-free survival rate of 91 and 60%. The 1 year, 3 year and 5 year OCM- and CSM-free survival rates were 97%, 93%, 90% and 80%, 61%, 55%, respectively. When patients were stratified according to nodal status (namely, pN0 and pN1), pN0 patients had 1 year, 3 year and 5 year CSM-free survival rates of 89, 72 and 66%, conversely pN1 patients' CSM-free survival rates were 53, 20 and 9% (p < 0.01; **Figure 2**). Median time to CSM in pN0 cM0 patients was 30 months.

Locations of nodal metastases are summarized in **Figure 3** and **Table S1**. Overall, within the group of patients with one positive nodal area, in 54% of patients metastatic dissemination skipped the hilar nodal area, while in 26% of cases, both the hilar and the side-specific areas were eluded. Instead, when looking at patients with two nodal areas involved, hilar nodal area was skipped in 54% of patients and side-specific area only in 4% of cases. Moreover after stratification for the ccRCC side, in case of interaortocaval-only nodal positivity among patients with one positive nodal site, 10 out of 12 patients had right ccRCC. This discrepancy was also identified in case of patients with two positive nodal areas and interaortocaval nodal involvement: the majority of patients had right ccRCC (14 out of 15 patients).

On Multivariable Cox regression analyses, when considering the location of nodal metastases, independent predictors of CSM were represented by pT3 (HR: 2.7; CI 95%: 1.5–5) and pT4 stage (HR: 6.1; CI 95%: 2.6–14.3), cM1 status (HR: 4.3; CI 95%: 3–6.2) and positive status of interaortocaval nodal area (HR: 2.3, CI 95%: 1.3–3.9), all $p \leq 0.01$ (**Table 2**). Instead, when predicting CSM considering the number of positive nodal areas, independent predictors were pT3 (HR: 2.6; CI 95%: 1.4–4.8) and pT4 stage (HR: 4.2; CI 95%:1.9–9.6), pathologic tumour size (HR: 1.1; CI 95%: 1–1.1), cM1 status (HR: 4.2;

TABLE 1 | Descriptive statistics of 415 patients submitted to radical nephrectomy and extended LND with clear cell renal cell carcinoma.

Variable	Overall
Mean age (years; median, IQR)	57.6 (59, 55–66)
Gender	
Male	285 (68.7%)
Female	130 (31.3%)
Symptoms	
No symptoms	162 (39.0%)
Local symptoms	179 (43%)
Systemic symptoms	74 (18%)
Site of primary tumour	
Right	238 (57.3%)
Left	177 (42.7 %)
Decade of surgery	
1980–1989	108 (26%)
1990–1999	202 (48.7%)
2000–2009	80 (19.3%)
2010–2012	25 (6%)
Metastatic status at diagnosis	
cM0	303 (73%)
cM1	112 (27%)
Pathologic T stage	
T1a	26 (6.3%)
T1b	74 (17.8%)
T2a	43 (10.4%)
T2b	12 (2.9%)
T3a	100 (24.1%)
T3b	105 (25.3%)
T3c	28 (6.7%)
T4	27 (6.5%)
Pathologic N stage	
pN0	320 (77%)
pN1	95 (23%)
Fuhrman grade	
1	20 (4.8%)
2	174 (41.9%)
3	162 (39.0%)
4	37 (8.9%)
NA	22 (5.3%)
Mean pathologic tumour size (cm; median, IQR)	9 (8.5, 6–11.5)
Mean number of nodes removed (median, IQR)	15 (14, 9–19)
Mean number of negative nodes (median, IQR)	13 (12, 7–17)
Mean number of positive nodes (median, IQR)	5 (3, 2–8)
Hilar nodal status	
Negative	371 (89.4%)
Positive	44 (10.6%)
Side-specific (paraaortic/pre- or paracaval) nodal status	
Negative	342 (82.4%)
Positive	73 (17.6%)
Interaortocaval nodal status	
Negative	365 (88%)
Positive	50 (12%)
Number of nodal sites involved	
0	320 (77%)
1	46 (11.2%)
2	26 (6.3%)
3	23 (5.5%)
Mean time to last follow-up or death (months; median, IQR)	75.6 (43.7, 12.8–117)

FIGURE 2 | Kaplan-Meier depicting CSM-free survival rate on the overall population after stratification for the pN status (*p*-value < 0.01). Blue line: pN0 patients; Green line: pN1 patients.

CI 95%: 2.9–6) and presence of any number of nodal area involved (HR: 1.6–2.7; CI 95%: 1–5), all *p* < 0.05 (**Table 3**).
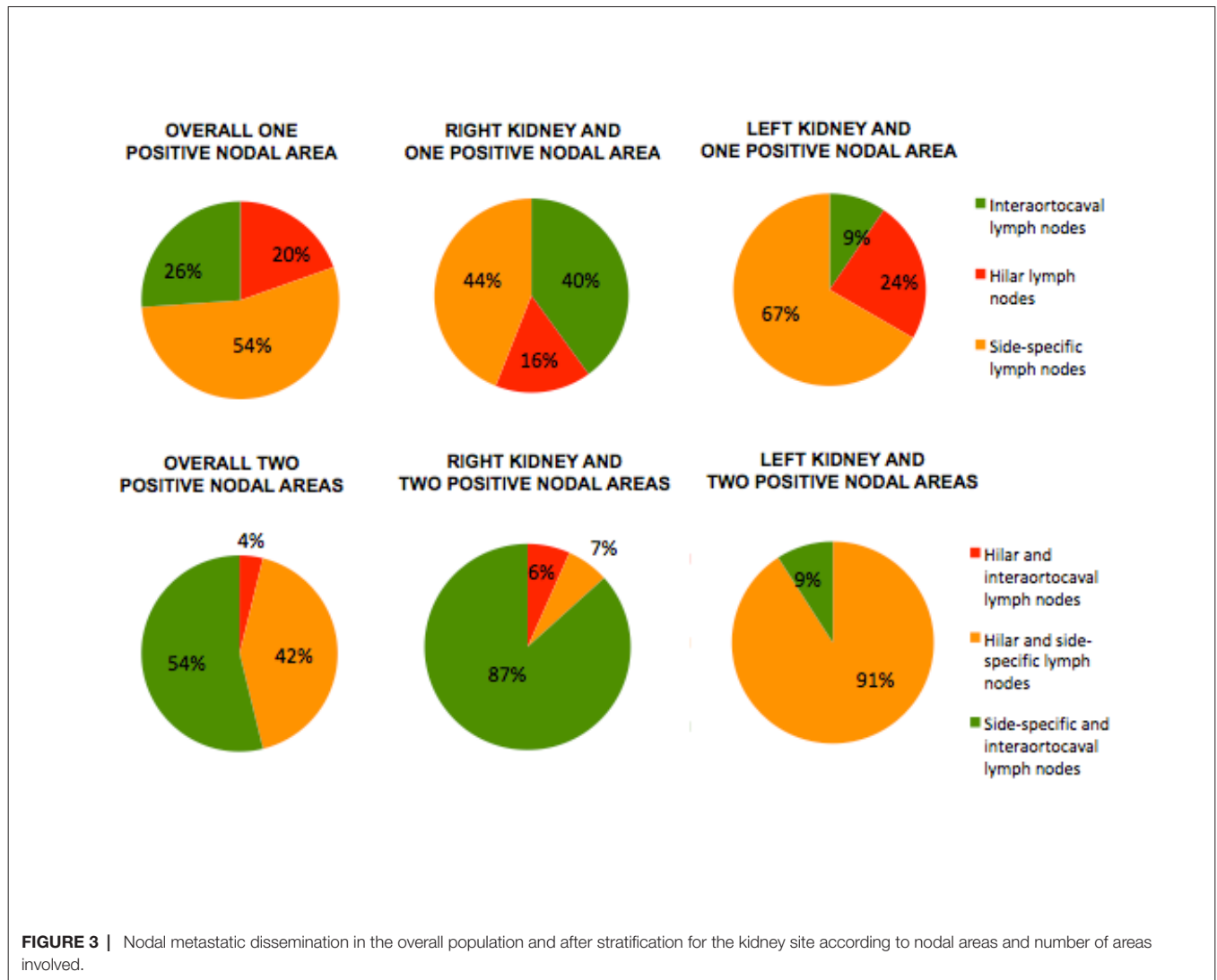
However when considering only pN1 patients, no difference was seen at Kaplan-Meier analysis in terms of CSM-free survival rate, after stratification of number of involved nodal areas (*p* = 0.5; **Figure 4**).

DISCUSSION

Patients with nodal involvement in RCC have an 7.8-fold greater chance of CSM compared to pN0 counterparts (16, 17) and this has an independent prognostic value even in patient with metastatic RCC (1). Published retrospective studies (18) have indeed failed to reach an agreement on the topic. Moreover, the EORTC 30881 (19) did not demonstrate any benefit in terms of cancer control. Nevertheless, today, roughly 70% of that study population would have been classified as cT1abN0M0. In this regards, a subanalysis focusing only on cT3 tumours, showed a 15% overall survival benefit at 5 years for LND

recipients (20). Therefore, EAU guidelines recognize the role of LND for cN1, although its extent remains controversial, and suggest an eLND for cN0 patients, only in presence of adverse clinical features (21). However, the picture appears even more complex, when considering that RCC histologies can differ in terms of distant spreading rates (11, 12) and oncologic outcomes (13).

Several observations of the current study are of importance. First, we described the oncologic outcomes of eLND in ccRCC patients. Cancer-specific mortality-free survival rates were worse for pN1 patients at any time point, compared to pN0 ones. According to Blute et al., among ccRCC patients, estimated CSM-free survival rates at 1-, 5- and 10 year follow-up were 95, 82 and 72.5% for pNx/pN0 patients and 52, 21 and 11% for pN +patients (16). Discrepancies with our results could be ascribed to inclusion of only cM0 ccRCC population and to omission of LND in some patients (42% of the overall population, data not shown for ccRCC histology). Moreover the study lacked of a definition for the extent of LND.

FIGURE 3 | Nodal metastatic dissemination in the overall population and after stratification for the kidney site according to nodal areas and number of areas involved.

Second, for 54% of pN1 patients, disease eluded hilar nodal site (when considering patients with one or two positive nodal stations), in line with what has been previously reported by EAU guidelines (35–45%) (21). Only among patients with one positive nodal station, in 26% of patients, cancer skipped the hilar and the side-specific nodal stations. When looking at any patient with positive interaortocaval nodal station, the majority of them (n = 27/36, 75%) showed a right ccRCC. Focusing on those patients, with interaortocaval-only positive location of nodal metastases, 10/12 (83%) had right ccRCC. This observation is

TABLE 2 | Cox Logistic Regression analysis predicting CSM considering the location of nodal metastases.

	UNIVARIABLE ANALYSES		MULTIVARIABLE ANALYSES	
VARIABLES	**HR (CI 95%)**	***p*-value**	**HR (CI 95%)**	***p*-value**
Positive hilar nodes	4.1 (2.7–6)	<0.01	1.0 (0.6–1.8)	0.8
Positive side-specific nodes	4.2 (3–5.8)	<0.01	1 (0.6–1.6)	0.9
Positive interaortocaval nodes	5 (3.4–7.3)	<0.01	2.3 (1.3–3.9)	<0.01
Age	1 (0.9–1)	0.9	1 (0.9–1)	0.2
pT stage pT2 vs. pT1	1.8 (0.9–3.5)	0.09	1.2 (0.6–2.5)	0.6
pT3 vs. pT1	5.6 (3.4–9.3)	<0.01	2.7 (1.5–5)	0.01
pT4 vs pT1	21.6 (11.4–40.8)	<0.01	6.1 (2.6–14.3)	<0.01
Pathologic tumour size	1.1 (1.1–1.2)	<0.01	1 (1–1.1)	<0.01
Fuhrman grade	2.9 (2.1–4)	<0.01	1.2 (0.9–1.8)	0.2
Clinical metastatic status	7.5 (5.5–10.2)	<0.01	4.3 (3–6.2)	<0.01

TABLE 3 | Cox Regression analysis predicting CSM considering the number of locations of nodal metastases.

VARIABLES	UNIVARIABLE ANALYSES		MULTIVARIABLE ANALYSES	
	HR (CI 95%)	*p*-value	HR (CI 95%)	*p*-value
Number of positive sites				
1 vs. 0	4.5 (3–6.7)	<0.01	1.6 (1–2.6)	<0.05
2 vs. 0	5.3 (3.3–8.7)	<0.01	1.7 (1–3)	<0.05
3 vs. 0	6.5 (3.7–11.4)	<0.01	2.7 (1.5–5)	<0.01
Age	1 (0.9–1)	0.9	1 (0.9–1)	0.2
pT stage				
pT2 vs. pT1	1.8 (0.9–3.5)	0.09	1.2 (0.5–2.4)	0.7
pT3 vs. pT1	5.6 (3.4–9.3)	<0.01	2.6 (1.4–4.8)	<0.01
pT4 vs. pT1	21.6 (11.4–40.8)	<0.01	4.2 (1.9–9.6)	<0.01
Pathologic tumour size	1.1 (1.1–1.2)	<0.01	1.1 (1–1.1)	<0.01
Fuhrman grade	2.9 (2.1–4)	<0.01	1.2 (0.9–1.8)	0.2
Clinical metastatic status	7.5 (5.5–10.2)	<0.01	4.2 (2.9–6)	<0.01

line with the studies investigating the role of sentinel LND (9, 10). In the first paper, 7/14 patients presented with interaortocaval nodal positivity: 3 of them had interoaortocaval and side-specific nodal positivity, 2 interaortocaval-only nodal positivity and 2 interaortocaval positivity and non-regional positivity; 6 of these patients had right kidney tumour. In the second, it was reported that right-sided tumour drained only to the paracaval nodes and left-sided tumours drained to the side-specific nodes.

It was formerly believed that RCC nodal drainage followed a fixed pattern, originating from the hilar region and branching off into the
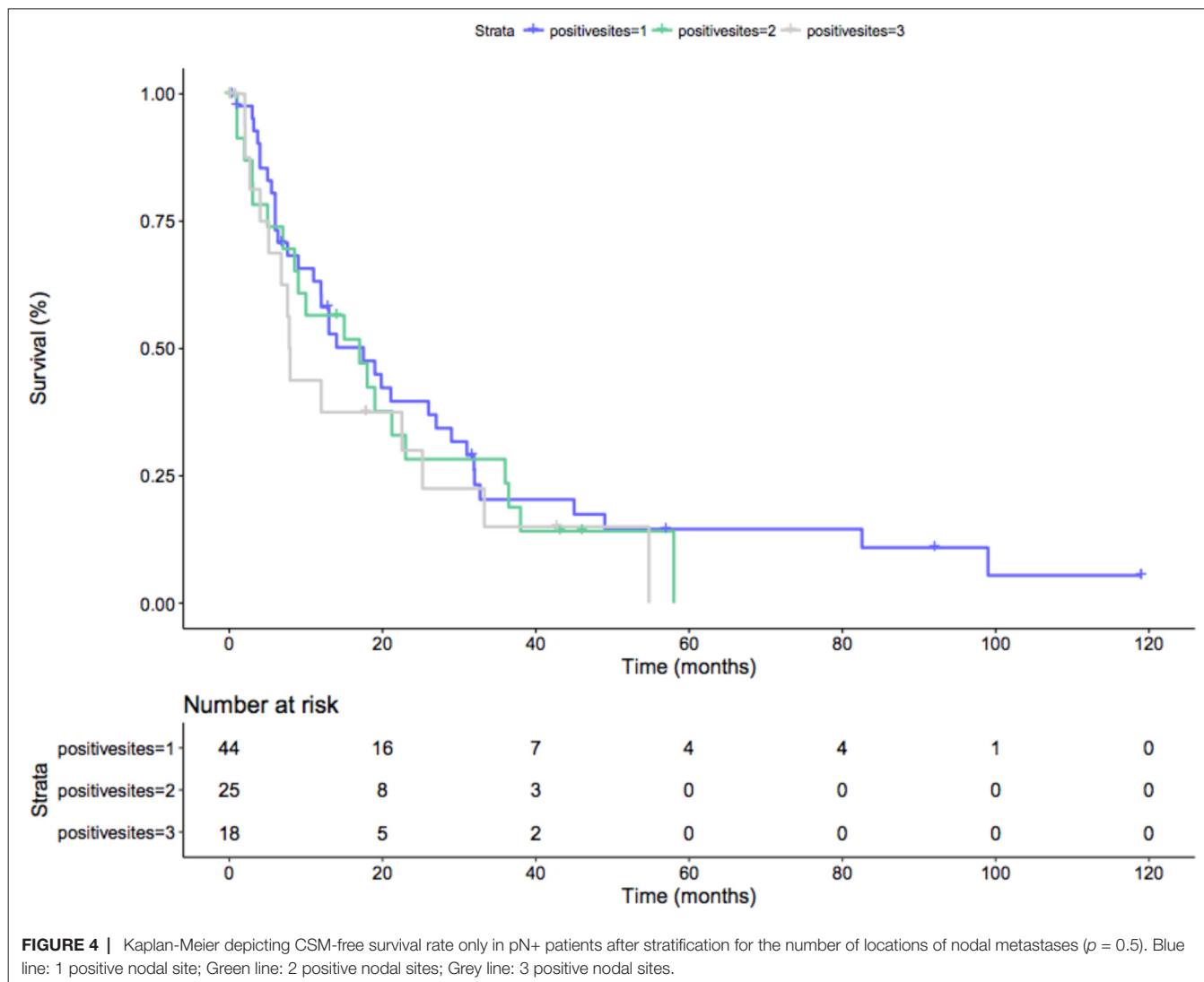

FIGURE 4 | Kaplan-Meier depicting CSM-free survival rate only in pN+ patients after stratification for the number of locations of nodal metastases (*p* = 0.5). Blue line: 1 positive nodal site; Green line: 2 positive nodal sites; Grey line: 3 positive nodal sites.

side-specific (paracaval/para-aortal) and the interaortocaval lymph nodes. Pioneering cadaveric and sentinel-node studies (8, 22–24) demonstrated extreme variations in drainage among RCC patients, even with aberrant firstly draining thoracic nodes. From the right kidney, efferent lymphatic vessels running anterior and posterior to the renal vein (anterior and posterior bundles) can drain into right side-specific and interaortocaval nodes. Retrocaval nodes connect with the thoracic duct but in some cases, efferent lymphatic vessels could reach the thoracic duct without passing through any lymph nodes. From the left kidney, efferent lymphatic vessels running anterior or posterior to the renal vein can drain into the left side-specific nodes. Posterior efferent lymphatic vessels could also connect directly to the thoracic duct without passing through any lymph node (8, 25, 26). These figures suggest that hilar LND could not be sufficient for every patient to be properly pN staged. Approximately, among patients with right ccRCC and single nodal positive site, 60% of them would have been properly staged as pN1 only by hilar and side-specific template, 40% only by eLND. Conversely, in left kidney tumours, 91% would have been properly staged as pN1 only by hilar and side-specific template, 9% only by eLND, in line with results from Crispen et al. (27).

Third, in an attempt to identify prognostic factors to aid patient risk stratification and multimodality upfront treatment, we found that cM1 disease, pT3-pT4 stage and positive interaortocaval nodal status and presence of any positive nodal area were independent predictors of CSM (all $p \leq 0.01$). Taking into account the study on preoperative lymphoscintigraphy by Bex et al. (9), where 2/4 patients with interaortocaval-only nodal involvement had non-regional nodal involvement too, and the study by Brouwer et al. (22), where 1/4 patients with early lymphatic drainage of the thoracic duct had no retroperitoneal nodal metastasis, it is possible to state that eLND nodal dissection seems to be of utmost importance to properly stage patients and to tailor adjuvant treatment in the ccRCC population.

Despite several strengths, our analyses are not devoid of limitations. First, our report is intrinsically limited by their retrospective and noncomparative nature. Second, we could not match data to a control group of patients with ccRCC, who were not submitted to eLND. Third, over the years, many aspects, as for the administration and type of recommended adjuvant treatment, have been changing in the onco-surgical management of patients with ccRCC and nodal involvement. Four, central radiology and pathology revision of patient features was not possible. On the other hand, problems like analyses on any RCC histology and unstandardized LND template were overcome. Moreover, median number of resected lymph nodes was 14, which is considered the threshold to consider adequate an eLND. Specifically, by considering all locations of nodal metastases, the pattern of ccRCC metastatitic spread before reaching the thoracic duct has been drawn.

CONCLUSION

At least, 40% of patients with right and 9% with left ccRCC would not been staged as pN1 by a LND limited to hilar and side-specific lymph nodes. Positive interaortocaval nodal status represented an independent predictor of CSM.

AUTHOR CONTRIBUTIONS

Conception and design of the work: UC, RB, CT, AV. Acquisition, analysis and interpretation of data: AN, AL, FR, FC, FT. Drafting the work: AN, AL, UC. Critical revision of the work for important intellectual content: UC, RB, CT, AV, FM, AS, AB.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fsurg.2018.00026/full#supplementary-material

REFERENCES

1. Lughezzani G, Capitanio U, Jeldres C, Isbarn H, Shariat SF, Arjane P, et al. Prognostic significance of lymph node invasion in patients with metastatic renal cell carcinoma: a population-based perspective. *Cancer* (2009) 115(24):5680–7. doi: 10.1002/cncr.24682
2. Capitanio U, Becker F, Blute ML, Mulders P, Patard JJ, Russo P, et al. Lymph node dissection in renal cell carcinoma. *Eur Urol* (2011) 60(6):1212–20. doi: 10.1016/j.eururo.2011.09.003
3. Gershman B, Thompson RH, Moreira DM, Boorjian SA, Tollefson MK, Lohse CM, et al. Radical nephrectomy with or without lymph node dissection for nonmetastatic renal cell carcinoma: a propensity score-based analysis. *Eur Urol* (2017) 71(4):560–7. doi: 10.1016/j.eururo.2016.09.019
4. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med* (2016) 375(23):2246–54. doi: 10.1056/NEJMoa1611406
5. Capitanio U, Montorsi F. Renal cancer. *Lancet* (2016) 387(10021):894–906. doi: 10.1016/S0140-6736(15)00046-X
6. Bex A. Follow-up for renal cell carcinoma: absence of evidence and beyond. *Eur Urol Focus* (2016) 1(3):282–3. doi: 10.1016/j.euf.2015.07.006
7. Gershman B, Moreira DM, Thompson RH, Boorjian SA, Lohse CM, Costello BA, et al. Renal cell carcinoma with isolated lymph node involvement: long-term natural history and predictors of oncologic outcomes following surgical resection. *Eur Urol* (2017) 72(2):300–6. doi: 10.1016/j.eururo.2016.12.027
8. Karmali RJ, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. *BJU Int* (2014) 114(6):806–17. doi: 10.1111/bju.12814
9. Bex A, Vermeeren L, Meinhardt W, Prevoo W, Horenblas S, Valdés Olmos RA. Intraoperative sentinel node identification and sampling in clinically node-negative renal cell carcinoma: initial experience in 20 patients. *World J Urol* (2011) 29(6):793–9. doi: 10.1007/s00345-010-0615-6
10. Sherif AM, Eriksson E, Thörn M, Vasko J, Riklund K, Ohberg L, et al. Sentinel node detection in renal cell carcinoma. A feasibility study for detection of tumour-draining lymph nodes. *BJU Int* (2012) 109(8):1134–9. doi: 10.1111/j.1464-410X.2011.10444.x
11. Renshaw AA, Richie JP. Subtypes of renal cell carcinoma. Different onset and sites of metastatic disease. *Am J Clin Pathol* (1999) 111(4):539–43. doi: 10.1093/ajcp/111.4.539
12. Mai KT, Landry DC, Robertson SJ, Commons AS, Burns BF, Thijssen A, et al. A comparative study of metastatic renal cell carcinoma with correlation

to subtype and primary tumor. *Pathol Res Pract* (2001) 197(10):671–5. doi: 10.1078/0344-0338-00144

13. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM, The UTM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol* (2016) 70(1):93–105. doi: 10.1016/j.eururo.2016.02.029

14. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* (2010) 17(6):1471–4. doi: 10.1245/s10434-010-0985-4

15. . Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* (2013) 37(10):1490–504. doi: 10.1097/PAS.0b013e318299f0fb

16. Blute ML, Leibovich BC, Cheville JC, Lohse CM, Zincke H. 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* (2004) 172(2):465–9. doi: 10.1097/01.ju. 0000129815.91927.85

17. Capitanio U, Jeldres C, Patard JJ, Perrotte P, Zini L, de La Taille A, et al. Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. *BJU Int* (2009) 103(1):33–7. doi: 10.1111/j.1464-410X.2008.08014.x

18. Capitanio U, Leibovich BC. The rationale and the role of lymph node dissection in renal cell carcinoma. *World J Urol* (2017) 35(4):497–506. doi: 10.1007/s00345-016-1886-3

19. Blom JH, van Poppel H, Maréchal JM, Jacqmin D, Schröder FH, de Prijck L, et al. 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* (2009) 55(1):28–34. doi: 10.1016/j.eururo.2008.09.052

20. Bekema HJ, Maclennan S, Imamura M, Lam TB, Stewart F, Scott N, et al. Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. *Eur Urol* (2013) 64(5):799–810. doi: 10.1016/j. eururo.2013.04.033

21. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* (2015) 67(5):913–24. doi: 10.1016/j.eururo.2015.01.005

22. Brouwer OR, Noe A, Olmos RA, Bex A. Lymphatic drainage from renal cell carcinoma along the thoracic duct visualized with SPECT/CT. *Lymphat Res Biol* (2013) 11(4):233–8. doi: 10.1089/lrb.2013.0017

23. Hultén L, Rosencrantz M, Seeman T, Wahlqvist L, Ahrén C. Occurrence and localization of lymph node metastases in renal carcinoma. A lymphographic and histopathological investigation in connection with nephrectomy. *Scand J Urol Nephrol* (1969) 3(2):129–33. doi: 10.3109/00365596909135393

24. Johnsen JA, Hellsten S. Lymphatogenous spread of renal cell carcinoma: an autopsy study. *J Urol* (1997) 157(2):450–3. doi: 10.1016/S0022-5347(01)65167-X

25. Assouad J, Riquet M, Berna P, Danel C. Intrapulmonary lymph node metastasis and renal cell carcinoma. *Eur J Cardiothorac Surg* (2007) 31(1):132–4. doi: 10.1016/j.ejcts.2006.10.025

26. Assouad J, Riquet M, Foucault C, Hidden G, Delmas V. Renal lymphatic drainage and thoracic duct connections: implications for cancer spread. *Lymphology* (2006) 39(1):26–32.

27. Crispen PL, Breau RH, Allmer C, Lohse CM, Cheville JC, Leibovich BC, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. *Eur Urol* (2011) 59(1):18–23. doi: 10.1016/j.eururo.2010.08.042

UROLOGIC
ONCOLOGY

Clinical-Kidney cancer

The critical role of lymph node dissection in selecting high-risk nonmetastatic renal cancer candidates for adjuvant therapy after nephrectomy

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Abstract

Background: The role of lymph node dissection (LND) during nephrectomy for renal cell carcinoma (RCC) is controversial. We looked at the clinical usefulness of performing LND to stratify the risk of patients with RCC and select candidates for systemic treatment after nephrectomy.

Materials and Methods: We identified 730 patients with nonmetastatic RCC treated with nephrectomy and LND at a single center. We compared the accuracy and clinical usefulness of a base model including factors defining high-risk patients according to the S-TRAC trial [(pT3 and Grade≥2 and performance status score ≥1) or pT4] relative to the base model plus pN stage for the prediction of early progression after surgery.

Results: LN invasion resulted the most informative predictor of early progression (odds ratio: 6.39; 95% confidence interval [CI]: 3.26, 12.54; $P < 0.0001$). The accuracy was higher ($P = 0.008$) for the model implemented with pN (area under the curve: 0.76; 95% CI: 0.71, 0.80) as compared to the base model (area under the curve: 0.72; 95% CI: 0.68, 0.76). Performing LND to select patients for postoperative systemic treatment, resulted in a slightly higher net benefit as compared to a strategy defining risk on the base of factors other than pN. Patients with high-risk disease showed a large difference in the risk of progression according to pN-status (1-year risk: 58% [95% CI: 45, 72] for pN1; 31% [95% CI: 25, 38] for pN0; $P < 0.001$).

Conclusions: Performing LND at the time of nephrectomy improves risk stratification, resulting into a small but nonnegligible clinical advantage for selecting high-risk patients for further treatment after surgery. Further trials should investigate whether high-risk pN1 patients would benefit from a different postoperative management. © 2019 Elsevier Inc. All rights reserved.

Keywords: Renal cancer; Lymph node dissection; Lymph node metastasis; Adjuvant therapy; Staging

1. Introduction

The role of lymph node dissection (LND) in the management of renal cell carcinoma (RCC) has been largely investigated and is still controversial [1,2].

Currently available evidence does not support a survival advantage for RCC patients treated with nephrectomy and LND. Indeed, a randomized trial and several retrospective studies have failed to prove higher disease-free and overall survival rates associated with LND [1,3−11]. However, the prognostic value of positive LNs is undeniable, with a number of previous studies demonstrating an increased cancer-specific and overall mortality for patients found with pN1 disease at the time of nephrectomy [12−16]. As such, the staging role of LND may be crucial for the management of patients with RCC: patients with nodal disease could be selected for a more intensive surveillance protocol; more

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importantly, they may be the optimal candidates for adjuvant systemic treatments after surgery.

The US Food and Drug Administration has recently approved sunitinib for the adjuvant treatment of patients at high risk of recurrent RCC following nephrectomy. The approval was based on the results of the S-TRAC trial testing the effect of adjuvant sunitinib in patients with high-risk nonmetastatic clear cell cancer [17]. Patients treated with sunitinib had a significantly longer median disease-free survival as compared to placebo. When stratifying the cohort according to disease characteristics, patients at higher risk for recurrence, defined on the base of disease stage, Fuhrman grade and on the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), harbored a 26% lower risk of disease progression associated with adjuvant treatment after surgery. Translating these results into clinical practice, we could argue that those patients are the ones who may greatly benefit from systemic therapy after nephrectomy, although other randomized trials did not confirm a survival advantage with adjuvant treatment [18,19]. Interestingly, patients with pN1 disease were classified as high risk regardless of all other risk factors [17]; as such, performing LND at the time of surgery could allow to detect patients with LN metastases who may otherwise not be selected for adjuvant treatments on the solely base of T stage, disease grade and PS. In this case LN staging would greatly influence clinical practice; however, in the S-TRAC trial a LND was not routinely performed and not standardized, thus leaving the question unanswered.

To evaluate the clinical advantage of performing LND to identify nonmetastatic high-risk patients who may benefit from systemic treatment after surgery, we tested if the addition of nodal staging in a model accounting for factors that were used to define high-risk disease in the S-TRAC trial would result in a higher accuracy for predicting early disease progression after surgery, in a cohort of patients treated with nephrectomy and LND at a single academic center.

2. Methods

After institution review board approval, we collected data from a cohort of 861 patients with nonmetastatic RCC who were treated with nephrectomy and LND from 1987 to 2016 at a single academic center.

All patients had histology-proven clear cell disease and were free of metastases at preoperative staging. Clinical and pathologic data, including the ECOG-PS score, pathologic stage (TNM classification) and Fuhrman grade were collected for each patient. Histological tumor necrosis was defined as the presence of any microscopic coagulative tumor necrosis. A sarcomatoid component was defined as a spindle cell malignancy with histological appearance of a sarcoma. No patient received either neoadjuvant or adjuvant therapy.

The LND procedure was performed based on the clinical judgment of each treating physician, according to preoperative patient and cancer characteristics and

intraoperative assessment by direct palpation. The procedure consisted of excising the fibro-fatty tissue along anatomically defined areas (hilar, interaortocaval, para-aortic, pre-, and retrocaval) as previously described [20].

The follow-up was based on clinical evaluation and chest-abdomen CT scans performed at 3 to 6 months and at 12 months after surgery over the first year, and annually thereafter. Additional imaging assessments were performed if the patient's symptoms raised clinical suspicion of relapse.

Disease progression after surgery was defined as the evidence of retroperitoneal or distant recurrence demonstrable on imaging at least 1 month after treatment; patients who did not experience relapse were censored at the date at the last follow-up.

Patients missing clinical or pathologic data (131 [15.8%]) relevant to the study outcome were excluded from the analysis.

2.1. Statistical analysis

The aim of the study was to test whether adding pN stage to a model including factors identifying patients at high risk of progression according to the criteria defined within the S-TRAC randomized clinical trial ([T3 disease and Fuhrman grade ≥ 2 and performance status score ≥ 1] or T4 disease) [17] would improve disease-risk stratification. Therefore, we compared a model including pT stage, disease grade and ECOG-PS with a same model implemented with pN stage, in terms of the accuracy for predicting early disease progression after surgery, defined as relapse within 12 (± 3) months post-treatment. We selected this outcome as a clinically reasonable indicator of patients who may deserve adjuvant treatment after surgery. Moreover, given that performing a LND in all cases would not represent the everyday clinical practice, we tested the accuracy of a third model mirroring a risk-based strategy to select patients for LND: we used a reliable and externally validated risk score [21,22] identifying patients with 2 or more risk factors for LN invasion (e.g., tumor size ≥ 10 cm; Fuhrman grade ≥ 3; pT ≥ 3; tumor necrosis; sarcomatoid component) as deserving LND. Those patients were included in the model considering the actual pN stage (e.g., N0 or N1), while those with less than 2 risk factors for positive LNs were considered as pNx/pN0 regardless of their pN status. Logistic regression analysis was used considering early disease progression as a binary outcome: patients were considered to have progressed if disease was evident at follow-up assessments within 12 months after surgery; likewise, patients were considered free from early progression if they had a last negative assessment at 12 months or at further follow-up, or if they relapsed after 12 months from surgery. Patients with a last negative follow-up before 9 months postsurgery ($n = 20$) and those with a recurrence after 15 months but without a previous negative assessment within the 12 (± 3) months window ($n = 6$) were excluded from the early progression outcome analysis. As a sensitivity analysis, we included all patients with follow-up data, using

the assessment closest to 1 year; moreover, we checked for the potential influence of year of surgery and of the number of LN removed by including these factors in the multivariable model.

The accuracy of the predictive models was assessed by area under the curve (AUC). We used decision curve analysis to evaluate the clinical consequences of model predictions by comparing net benefit, based on true positives and false positives, at various threshold probabilities of progression [23]. Because it is unlikely that a physician would submit a patient to adjuvant treatment if the probability of early progression was <5% or would avoid additional treatment for patients with a probability higher than 40%, we examined the range of threshold probabilities between 5% and 40%. The accuracy of the models and decision curves was corrected for overfitting using 10-fold cross-validation.

Finally, we used Kaplan-Meier analysis to estimate the risk of disease progression and overall mortality of high-risk patients with either pN0 or pN1 disease. Statistical analyses were conducted using Stata 15.0 (StataCorp, College Station, TX), with a 2-sided significance level set at $P < 0.05$.

3. Results

Table 1 reports the clinical and pathological characteristics of the entire cohort ($n = 730$). The majority of patients was treated with radical nephrectomy (95%). Lymph node metastases were found in 7% of cases; according to the S-TRAC trial definition, 257 (35%) patients would be categorized as high-risk; of them, 21% had pN1 disease. A total of 341 (47%) patients would deserve a LND according to a risk-based approach [21,22]. In our cohort, this approach showed a good accuracy (AUC: 0.70; 95% confidence interval [CI]: 0.64−0.75) with a sensitivity of 83.3% a specificity of 56.2% and a positive and negative predictive value of 13.2% and 97.7%, respectively.

At logistic regression analysis, pN stage was significantly associated with early disease progression when included in a model accounting for the other factors defining patients at high-risk (Table 2) both when considering pN stage as all patients would receive a LND (e.g., N0 vs. N1; odds ratio: 6.39; 95% CI: 3.26, 12.54; $P < 0.0001$) and when considering the pN status only for patients who would undergo a LND according to a risk-based approach (e.g., NX/0 vs. N1; odds ratio: 5.63; 95% CI: 2.72, 11.68); $P < 0.0001$). The predictive models implemented with pN stage showed a significantly higher accuracy ($P = 0.008$), with an AUC of 0.76 (95% CI: 0.71, 0.80) and 0.75 (95% CI: 0.71, 0.79) for model 2 and 3, respectively, as compared to 0.72 (95% CI: 0.68, 0.76) for the base model, after cross-validation.

Decision curve analysis shows the clinical benefit of using each model to select patients at high-risk of early progression who may benefit from systemic treatment postsurgery (Fig. 1). The models including pN stage showed a slightly higher net benefit, which looks prominent for threshold probabilities higher than 30%: if we accept a

Table 1
Clinical and pathological characteristics of the entire cohort ($n = 730$) of nonmetastatic RCC patients.

Age [yrs] Median(IQR)	60 (51, 69)
Number of LN removed Median(IQR)	6 (3,10)
ECOG-PS score	
0	228 (31%)
1	395 (54%)
2	101 (14%)
3	6 (1%)
Clinical node stage	
0	588 (81%)
1	142 (19%)
Fuhrman grade	
G1	86 (12%)
G2	354 (48%)
G3	225 (31%)
G4	65 (9%)
pN stage	
N0	676 (93%)
N1	54 (7%)
pT stage	
T1	290 (40%)
T2	118 (16%)
T3	305 (42%)
T4	17 (2%)
Histological tumor necrosis	358 (49%)
Histological sarcomatoid component	29 (4.0%)
Number of risk factors for LN invasion[a]	
0	228 (31%)
1	161 (22%)
2	130 (18%)
3	121 (17%)
4	81 (11%)
5	9 (1.2%)
Type of treatment	
RN	690 (95%)
PN	40 (5%)
Perioperative complications	156 (21%)
Clavien-Dindo	
1	19 (2.6%)
2	109 (15%)
3	23 (3.2%)
4	3 (0.4%)
5	2 (0.3%)
High-risk patients[b]	257 (35%)
pN0	203 (79%)
pN1	54 (21%)
Follow-up [mos] Median(IQR)	49 (13, 125)

ECOG-PS = Eastern Cooperative Oncology Group-Performance Status; LN = lymph nodes.

[a] Including: tumor size ≥10 cm; Fuhrman grade ≥3; pT ≥3; tumor necrosis; sarcomatoid component [21,22].

[b] Defined as pT3 and Fuhrman grade ≥2 and ECOG-PS≥1 or pT4 or pN1, as described in the S-TRAC [17].

threshold risk of progression ranging from 10% to 35%, a strategy accounting for pN status would allow to detect from 0.3% to 1.6% more patients at high risk eventually deserving adjuvant treatment, without any unnecessary treatment. Comparable results were observed when considering a strategy submitting to LND only patients at higher risk of LN invasion (Fig. 1).

Table 2
Logistic regression model predicting disease progression within 12 months; model 1 accounting for factors defining high-risk nonmetastatic patients regardless of pN stage; model 2 accounting for factors defining high risk patients including pN stage and assuming that all patients would receive lymph node dissection; model 3 including pN stage only for patients at high risk of positive nodes who would undergo lymph node dissection.

	Model 1			Model 2			Model 3		
	OR	95% CI	95% CI	OR	95% CI	*P* value	OR	95% CI	*P* value
pT stage pT1-2 vs. pT ≥3	5.56	3.61, 8.56	<0.0001	4.95	3.18, 7.71	<0.0001	4.70	3.02, 7.31	<0.0001
ECOG-PS score 0 vs. ≥1	1.34	0.87, 2.08	0.2	1.28	0.81, 2.02	0.3	1.29	0.82, 2.02	0.3
Fuhrman grade G1 vs. G ≥2	5.55	1.31, 23.47	0.02	5.09	1.20, 21.59	0.02	5.13	1.21, 21.71	0.02
pN stage 0/x vs. 1	–	–	–	6.39	3.26, 12.54	<0.0001	5.63	2.72, 11.68	<0.0001

ECOG-PS = Eastern Cooperative Oncology Group-Performance Status.

Moreover, high-risk nonmetastatic patients with pN1 disease showed significantly worse outcomes (Fig. 2), with a risk of disease progression at 1 year post-treatment of 58% (95% CI: 45, 72) as compared to 31% (95% CI: 25, 38) for high-risk patients with negative LNs (*P* = 0.0001; Table 3). Likewise, the estimated 1-year overall mortality risk was 33% (95% CI: 22, 48) and 13% (95% CI: 9, 18) for node-positive and node-negative nonmetastatic high-risk patients (*P* < 0.0001).

Same results were found at sensitivity analyses including all patients with at least 1 follow-up assessment but who were not evaluated within the eligible time frame; moreover, the number of LNs removed and the year of surgery were not independently associated with early progression
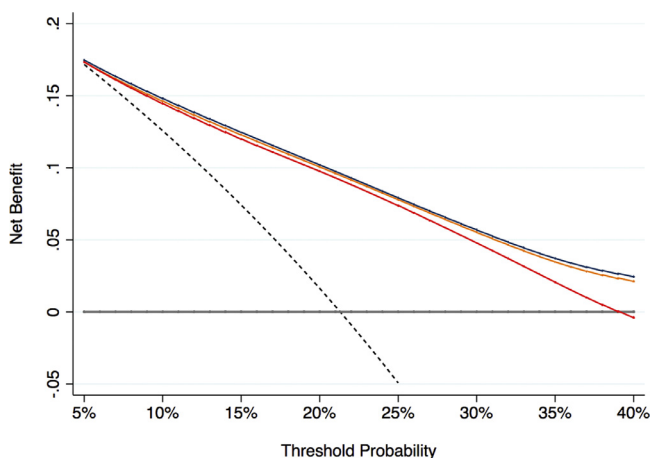

Fig. 1. Decision curve analysis assessing net benefit for prediction of disease progression within 12 months after surgery in high-risk nonmetastatic patients. The red line represents the net benefit of using a risk stratification model without lymph node status. The blue line represents the net benefit of using a risk stratification considering lymph node status and assuming that all patients would receive a lymph node dissection. The orange line represents the net benefit of using a risk stratification considering lymph node status only for patients who would receive a lymph node dissection according to the risk of lymph node invasion. The dashed line represents the "treat-all" strategy. The gray line represents the "treat−none" strategy. (Color version of figure is available online.)

when included in the multivariable logistic model (all *P* > 0.4; Supplementary Table 1).

4. Discussion

We looked at the clinical advantage of performing LND to better stratify the risk of postoperative progression of RCC and to identify patients at high-risk who may deserve additional treatments after surgery. Our interest was fueled by the recent findings of the S-TRAC trial suggesting that patients considered at high-risk of progression may benefit more from adjuvant systemic treatment [17]. Those patients were defined by local T-stage, disease grade and PS or by pN stage if LND was performed. Our results showed that the information on LN status allows for higher accuracy in the prediction of early progression after surgery. However, performing LND in each case to include pN stage in risk-stratification would allow to detect less than 2% more patients potentially deserving additional treatment, as compared to a strategy assessing patients-risk according to risk factors other than LN status. Similar results would be obtained when performing LND only in patients at higher risk of positive LNs according to a risk-stratification tool [21,22]. In light of these findings, the clinical advantage of performing a time-consuming and challenging procedure like retroperitoneal LND might be considered questionable. On the other hand, LND has shown low perioperative morbidity [5,24,25]: in a recently matched-cohort analysis, nephrectomy along with LND was associated with a comparable risk of Clavien grade ≥3 complications as compared to nephrectomy alone [24]. As such, even a slightly higher clinical benefit for detecting high-risk patients could justify performing LND for staging purpose, at least in those at higher risk for LN invasion.

Previous studies confirmed the independent prognostic significance of LN status in RCC patients [1,7,12−16]: in a large multicenter cohort of 3,507 patients, Capitanio et al. showed that pN1 disease was associated with a 3.2 times higher risk of cancer-specific mortality after adjusting for T
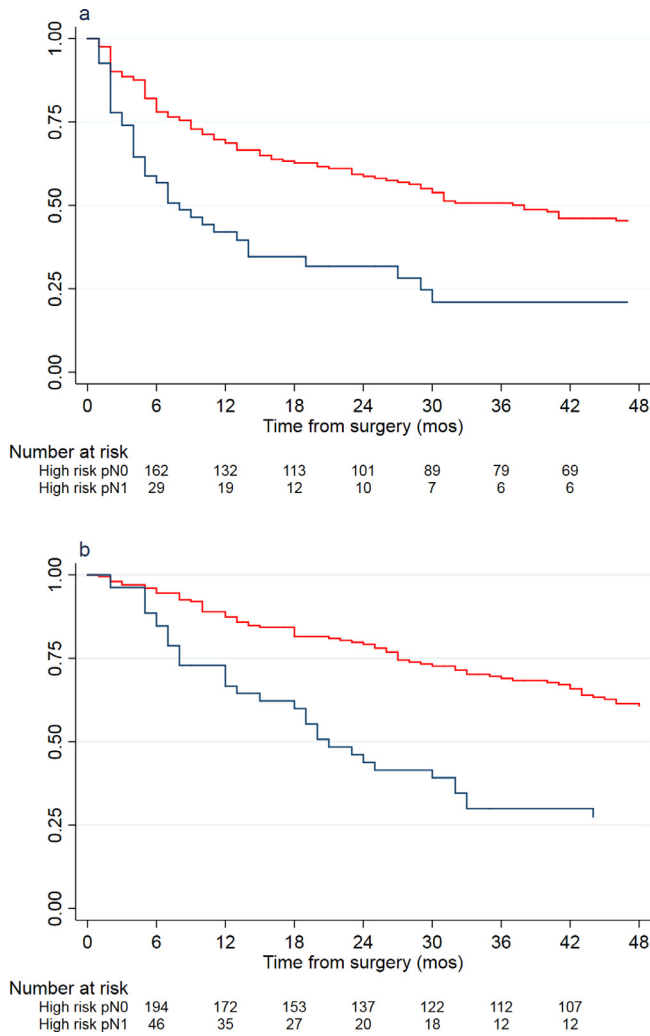
Fig. 2. Estimated probability of disease free survival (a) and overall survival (b); the red line represents high-risk nonmetastatic patients with pN0 disease; the blue line represents high-risk nonmetastatic patients with pN1 disease. The log-rank test indicate significant difference between groups ($P < 0.0001$). (Color version of figure is available online.)

stage and Fuhrman grade [12]; similarly, in a population-based cohort study, the percentage of positive nodes emerged as an independent predictor of post-treatment mortality when included in a model accounting for several clinical and pathological factors [13].

Patients with positive LNs have shown worse oncological outcomes in several series [1,7,26,27]. Gershman et al. recently analyzed the long-term survival of 138 patients with isolated LN involvement after nephrectomy [26]: the 5-year CSS and OS rate were only 26% and 25%, with a median time to development of metastases of 4.2 months. Similar data were reported in other series, with a postoperative 5-year CSS rate ranging from 22% to 39% for pN1 patients [1]. In line with these findings, we observed that even among patients with high-risk disease, those with LNs metastases showed about 2-fold higher probability of progression and overall mortality as compared with same risk node negative patients. These results, suggest that LND may be of particular value for high-risk nonmetastatic patients, by further stratifying disease risk and inform postoperative management. Indeed, we could argue that postoperative adjuvant treatment may lead to a greater survival advantage in high-risk patients with pN1 disease relative to pN0; at the same time, given the large difference observed in the risk of progression, patients with LN metastases may benefit from different therapeutic protocols as compared to high risk node negative patients. These findings call for further clinical trials, including large cohorts of patients properly staged for LN disease at the time of nephrectomy, aimed to better define the best candidates for additional treatments after surgery.

Our study has some limitations. As a retrospective analysis there is a risk of selection bias, which might have influenced the results. Indeed, by including only patients treated with LND, we could have selected those at higher risk of LN metastasis and therefore submitted to nephrectomy along with LND; indeed, the majority of patients received a radical nephrectomy, even for low stage disease. However, about 40% of patients included were staged as T1, thus suggesting that even lower risk patients received a LND. Moreover, we applied a validated risk score used to define patients at high risk of positive LNs who would deserve a LND: according to this score 53% of patients would not be submitted to LND. As such, our cohort could be considered as representative of the majority of patients commonly submitted to surgical treatment for RCC in clinical practice.

The number of LNs removed was not equal for every patient. Some of them could have received a suboptimal staging thus potentially altering the results. However, the number

Table 3
Estimated oncological outcomes of high risk nonmetastatic RCC patients treated with surgery, according to Kaplan-Meier analysis.

Risk of disease progression (95% CI)	High risk pN0	High risk pN1	P value
6 mos	22% (17, 28)	43% (31, 58)	0.0001
12 mos	31% (25, 38)	58% (45, 72)	
24 mos	41% (35, 49)	68% (55, 81)	
60 mos	59% (52, 67)	79% (64,90)	
Risk of overall mortality (95% CI)			
6 mos	5% (3, 10)	15% (8, 28)	<0.0001
12 mos	13% (9, 18)	33% (22, 48)	
24 mos	21% (16, 27)	56% (43, 71)	
60 mos	44% (37, 52)	80%(67, 90)	

of LNs removed was not significantly associated with the risk of early progression when included in the multivariable model.

Finally, considering the large time interval covered by our study, patients could have been treated differently in more recent years, eventually resulting in better outcomes. To control for this bias we checked for the influence of the year of surgery on the risk of disease progression without observing a significant correlation.

5. Conclusions

Our results suggest that performing LND at the time of nephrectomy for RCC would result in a small clinical advantage for selecting candidates to further treatment after surgery. However, LND allows to better define the risk of progression even among high-risk cases. Whether patients with high-risk nonmetastatic RCC may benefit from a different postoperative management according to LN status needs to be investigated in further clinical trials.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.009.

References

[1] Bhindi B, Wallis CJD, Boorjian SA, et al. The role of lymph node dissection in the management of renal cell carcinoma: a systematic review and meta-analysis. BJU Int 2018;121:684–98.
[2] Capitanio U, Montorsi F. Renal cancer. Lancet 2016;387:894–906.
[3] Blom JH, van Poppel H, Marechal JM, et al. 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 2009;55:28–34.
[4] Gershman B, Thompson RH, Moreira DM, et al. Radical nephrectomy with or without lymph node dissection for nonmetastatic renal cell carcinoma: a propensity score-based analysis. Eur Urol 2017;71:560–7.
[5] Ristau BT, Manola J, Haas NB, et al. Retroperitoneal Lymphadenectomy for high risk, nonmetastatic renal cell carcinoma: an analysis of the ASSURE (ECOG-ACRIN 2805) adjuvant trial. J Urol 2018;199:53–9.
[6] Gershman B, Thompson RH, Boorjian SA, et al. Radical nephrectomy with or without lymph node dissection for high risk nonmetastatic renal cell carcinoma: a multi-institutional analysis. J Urol 2017;199:1143–8.
[7] Sun M, Bianchi M, Hansen J, et al. Nodal involvement at nephrectomy is associated with worse survival: a stage-for-stage and grade-for-grade analysis. Int J Urol 2013;20:372–80.
[8] Feuerstein MA, Kent M, Bernstein M, et al. Lymph node dissection during cytoreductive nephrectomy: a retrospective analysis. Int J Urol 2014;21:874–9.
[9] Feuerstein MA, Kent M, Bazzi WM, et al. Analysis of lymph node dissection in patients with >/=7-cm renal tumors. World J Urol 2014;32:1531–6.
[10] Aziz A, May M, Zigeuner R, et al. Do young patients with renal cell carcinoma feature a distinct outcome after surgery? A comparative analysis of patient age based on the multinational CORONA database. J Urol 2014;191:310–5.
[11] Pantuck AJ, Zisman A, Dorey F, et al. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. J Urol 2003;169:2076–83.
[12] Capitanio U, Jeldres C, Patard JJ, et al. Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. BJU Int 2009;103:33–7.
[13] Trinh QD, Schmitges J, Bianchi M, et al. Node-positive renal cell carcinoma in the absence of distant metastases: predictors of cancer-specific mortality in a population-based cohort. BJU Int 2012;110:E21–7.
[14] Kwon T, Song C, Hong JH, et al. Reassessment of renal cell carcinoma lymph node staging: analysis of patterns of progression. Urology 2011;77:373–8.
[15] Lughezzani G, Capitanio U, Jeldres C, et al. Prognostic significance of lymph node invasion in patients with metastatic renal cell carcinoma: a population-based perspective. Cancer 2009;115:5680–7.
[16] Bazzi WM, Sjoberg DD, Feuerstein MA, et al. Long-term survival rates after resection for locally advanced kidney cancer: Memorial Sloan Kettering Cancer Center 1989 to 2012 experience. J Urol 2015;193:1911–6.
[17] Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 2016;375:2246–54.
[18] Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol 2017;35:3916–23.
[19] Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387:2008–16.
[20] Capitanio U, Suardi N, Matloob R, et al. Extent of lymph node dissection at nephrectomy affects cancer-specific survival and metastatic progression in specific sub-categories of patients with renal cell carcinoma (RCC). BJU Int 2014;114:210–5.
[21] Blute ML, Leibovich BC, Cheville JC, et al. 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 2004;172:465–9.
[22] Crispen PL, Breau RH, Allmer C, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. Eur Urol 2011;59:18–23.
[23] Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565–74.
[24] Gershman B, Moreira DM, Thompson RH, et al. Perioperative morbidity of lymph node dissection for renal cell carcinoma: a propensity score-based analysis. Eur Urol 2017. [Epub ahead of print].
[25] Chapman TN, Sharma S, Zhang S, et al. Laparoscopic lymph node dissection in clinically node-negative patients undergoing laparoscopic nephrectomy for renal carcinoma. Urology 2008;71:287–91.
[26] Gershman B, Moreira DM, Thompson RH, et al. Renal cell carcinoma with isolated lymph node involvement: long-term natural history and predictors of oncologic outcomes following surgical resection. Eur Urol 2017;72:300–6.
[27] Karakiewicz PI, Trinh QD, Bhojani N, et al. Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease: prognostic indicators of disease-specific survival. Eur Urol 2007;51:1616–24.

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