Asian Journal of Urology 9 (2022) 215—226

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Review

Potential benefit of lymph node dissection during radical nephrectomy for kidney cancer: A review and critical analysis of current literature

Michele Marchioni [a,*], Daniele Amparore [b], Igino Andrea Magli [a], Riccardo Bertolo [c], Umberto Carbonara [d], Selcuk Erdem [e], Alexandre Ingels [f], Constantijn H.J. Muselaers [g], Onder Kara [h], Marco Mascitti [a], Tobias Klatte [i], Maximilian Kriegmair [j], Nicola Pavan [k], Eduard Roussel [l], Angela Pecoraro [b], Laura Marandino [m], Riccardo Campi [n], Luigi Schips [a], on behalf of the European Association of Urology (EAU) Young Academic Urologists (YAU) Renal Cancer group

[a] *Department of Urology, SS Annunziata Hospital, "G. D'Annunzio" University of Chieti, Chieti, Italy*
[b] *Division of Urology, Department of Oncology, School of Medicine, San Luigi Hospital, University of Turin, Orbassano, Turin, Italy*
[c] *Department of Urology, San Carlo Di Nancy Hospital, Rome, Italy*
[d] *Department of Emergency and Organ Transplantation-Urology, Andrology and Kidney Transplantation Unit, University of Bari, Bari, Italy*
[e] *Division of Urologic Oncology, Department of Urology, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey*
[f] *Department of Urology, University Hospital Henri Mondor, APHP, Créteil, France*
[g] *Department of Urology, Radboud University Medical Center, Nijmegen, the Netherlands*
[h] *Department of Urology, Kocaeli University School of Medicine, Kocaeli, Turkey*
[i] *Department of Urology, Royal Bournemouth Hospital, Bournemouth, UK*
[j] *Department of Urology, University Medical Centre Mannheim, Mannheim, Germany*
[k] *Urology Clinic, Department of Medical, Surgical and Health Science, University of Trieste, Trieste, Italy*
[l] *Department of Urology, University Hospitals Leuven, Leuven, Belgium*
[m] *Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

* Corresponding author.
E-mail address: mic.marchioni@gmail.com (M. Marchioni).
Peer review under responsibility of Tongji University.

https://doi.org/10.1016/j.ajur.2022.03.007

[n] *Unit of Urological Robotic Surgery and Renal Transplantation, University of Florence, Careggi Hospital, Florence, Italy*

Received 8 December 2021; received in revised form 20 February 2022; accepted 22 March 2022
Available online 27 May 2022

KEYWORDS
Renal cell carcinoma;
Lymph node dissection;
Radical nephrectomy;
Salvage lymph node dissection

Abstract *Objective:* The role of lymph node dissection (LND) is still controversial in patients with renal cell carcinoma undergoing surgery. We aimed to provide a comprehensive review of the literature about the effect of LND on survival, prognosis, surgical outcomes, as well as patient selection and available LND templates.
Methods: Recent literature (from January 2011 to December 2021) was assessed through PubMed and MEDLINE databases. A narrative review of most relevant articles was provided.
Results: The frequencies in which LNDs are being carried out are decreasing due to an increase in minimally invasive and nephron sparing surgery. Moreover, randomized clinical trials and meta-analyses failed to show any survival advantage of LND versus no LND. However, retrospective studies suggest a survival benefit of LND in high-risk patients (bulky tumors, T3-4 stage, and cN1 patients). Moreover, extended LND might provide important staging information, which could be of interest for adjuvant treatment planning.
Conclusion: No level 1 evidence of any survival advantage deriving from LND is currently available in literature. Thus, the role of LND is limited to staging purposes. However, low grade evidence suggests a possible role of LND in high-risk patients. Randomized clinical trials are warranted to corroborate these findings.

1. Introduction

Several factors might predict progression during follow-up in patients with renal cell carcinoma (RCC) [1]. The presence of lymph-nodal metastases is a strong predictor of worse prognosis, either in locally advanced or even metastatic disease [2,3]. Therefore, lymph node dissection (LND) to surgically remove nodal metastases at the time of nephrectomy would be expected to be associated with a survival benefit.

Although LND is an established step during surgical treatment of urological [4—6] and non-urological malignancies [7,8], its role at the time of RCC surgery is not well defined [9]. Indeed, current European Association of Urology guidelines do not recommend the routine use of LND but reserve it for patients with clinically positive nodes [10].

This recommendation is based on results of several studies, including a randomized clinical trial that failed to show any survival benefit in patients who underwent a LND at the time of surgery for RCC [9,11]. Historical reviews of the literature pointed out the lack of evidence favoring LND at the time of nephrectomy when the overall population was examined [12]. However, there are also contradictory findings reporting a survival benefit in specific subgroups of patients undergoing LND [13]. These findings have been also corroborated by a recent meta-analysis, in which those with advanced RCC were examined [14]. In addition, LND might provide key information about lymph node status that standard imaging techniques are unable to provide [15].

Because of these contradictory findings, we aimed to perform an updated literature review about the topic. We focused on the potential role of LND relative to survival; templates for LND carried out were resumed. Finally, an overview of available tools aiding patient selection was provided.

2. Methods

A review of the literature was performed searching the PubMed and MEDLINE databases for articles published within the last 10 years (from January 2011 to December 2021) on core clinical journals in English language. The peer-review process was performed by two authors (Carbonara U and Pecoraro A) and supervised by Mascitti M. Search terms included "renal cell carcinoma" or "renal cancer" in combination with "lymph node dissection" or "lymphadenectomy". The references within chosen articles were also screened.

A structured data extraction was performed within an Excel® (Microsoft, Redmond, WA, USA) sheet including year of publication, first author, country of residence, main study's feature, number of patients included, main pathological characteristics of patients included, primary outcomes, and main findings.

A critical analysis of included studies has been included in a narrative format after consensus of all authors was obtained. The primary aim was to evaluate the impact of LND at the time of RCC surgery on oncological outcomes (overall survival [OS], cancer-specific survival, and recurrence-free survival). The secondary aim was to give an overview of the templates to perform LND and the tools to identify patients who might benefit most from undergoing LND.

3. Results

The main characteristics of selected studies were resumed in Table 1.

3.1. LND in non-metastatic RCC

Several non-randomized studies have shown no clinical benefit of LND at the time of radical nephrectomy in patients diagnosed with seemingly non-metastatic disease [16—22]. On the other hand, others reported a survival benefit in specific subgroups of patients [13,23,24]. Unfortunately, available studies were characterized by high inter-study heterogeneity with important differences in

Table 1 Main patients' characteristics of included studies.

Reference	Study design	Patient, *n* (no LND/LND)	Primary endpoint	Tumor stage, (*n*, no LND/LND)
Localized				
Gershman et al. 2017, [16]	Monocentric retrospective	1797 (1191/606)	CSM and ACM	-pT1a (340/36); pT1b (352/84); pT2a (152/81); pT2b (65/66); pT3a (210/218); pT3b (41/91); pT3c (11/13); pT4 (9/16) Missing (12)
Farber et al. 2019, [21]	Monocentric retrospective	19 500 (9750/9750)	OS	-pT1 (3327/3120); pT2 (2838/3294); pT3 (3328/3048); pT4 (257/288)
Feuerstein et al. 2014, [22]	Monocentric retrospective	524 (190/334)	5-year RFS and 5-year OS	-pT2 (84/95); pT3 (101/227); pT4 (5/12); -pN0 (0/308); pN1 (0/26)
Gershman et al. 2018, [20]	Multicentric retrospective	2437 (1398/1039)	CSM and ACM	-pT1a (299/195); pT1b (401/301); pT2a (182/136); p T2b (96/71); pT3a (321/253); pT3b (64/54); pT3c (23/18); pT4 (12/11); -cN1 (47/47)
Advanced and metastatic				
Tilki et al. 2018, [27]	Multicentric retrospective	1978 (952/1026)	CSS	-pNx 952 (NA); pN0 803 (NA); pN1 223 (NA)
Faiena et al. 2018, [28]	Monocentric retrospective	1780 (514/1266)	OS	-pT1-2 (41/101); pT3a (263/656); pT3b-c (78/255); pT4 (59/212); pTx (73/42); -pN0 (NA/163); pN1 (NA/1036); pNx (514/41); Missing (0/26)
Chipollini et al. 2018, [31]	Multicentric retrospective	293 (106/187)	CSS	-pT3a 84 (NA); pT3b 137 (NA); pT3c 34 (NA); pT4 38 (NA);

(*continued on next page*)

Table 1 (*continued*)

Reference	Study design	Patient, *n* (no LND/LND)	Primary endpoint	Tumor stage, (*n*, no LND/LND)
				-pN0 68 (NA); pN1 119 (NA); pNx 106 (NA)
Capitanio et al. 2012, [13]	Multicentric retrospective	1983 (1109/874)	CSS	-pT1a 760 (NA); pT1b 487 (NA); pT2a 152 (NA); pT2b 68 (NA); pT3a 375 (NA); pT3b 61 (NA); pT3c 38 (NA); pT4 42 (NA); -pN0 754 (NA) pN1 120 (NA); pNx 1109 (NA)
Marchioni et al. 2018, [17]	Monocentric retrospective	25 357 (19 057/6300)	CSS	-pT2 (8268/2275); pT3 (10 789/4025)
Feuerstein et al. 2014, [29]	Monocentric retrospective	258 (81/177)	OS	-pT1 (25/11); pT2 (5/19); ≥pT3 (51/147)
Gershman et al. 2017, [30]	Monocentric retrospective	305 (117/188)	CSM and ACM	-pT1a 3 (1/2); pT1b 26 (12/14); pT2a 31 (15/16); pT2b 22 (10/12); pT3a 143 (53/90); pT3b 40 (12/28); pT3c 10 (3/7); pT4 28 (10/18) Missing (2)
Salvage				
Barboza et al. 2020, [33]	Monocentric retrospective	19 (0/19)	RFS and CSS	-pT1/pT2 6 (NA); pT3 10 (NA); pT4 1 (NA); Unknown 2 (NA) -pN0 4 (NA); pN1 4 (NA); pNx 9 (NA); Unknown 2 (NA)
Russell et al. 2015, [34]	Monocentric retrospective	50 (0/50)	RFS and CSS	-pT1a 4 (NA); pT1b 6 (NA); pT2a 7 (NA); pT2b 3 (NA); pT3a 25 (NA); pT3b 5 (NA); -pN0/Nx 35 (NA); pN1 15 (NA)

OS, overall survival; CSS, cancer-specific survival; RFS, recurrence-free survival; LND, lymph node dissection; NA, not available; CSM, cancer-specific mortality; ACM, all-cause mortality.

terms of study population (*i.e.*, inclusion criteria, template used, and number of nodes removed) and results that sometimes were controversial. The most interesting examples were the analyses by Whitson et al. [24] and Sun et al. [19] who tested the effect of LND in the same cohort and reached opposite conclusions. Both researchers relied on the Surveillance, Epidemiology, and End Results (SEER) database, including patients diagnosed with RCC between 1998 and 2008. Primary outcome was cancer-specific mortality (CSM). The main difference between the two studies was caused by the differences in the missing data management. The paper from Whitson et al. [24] relied on multiple imputation to correct for missing information regarding tumor grade [24]. Sun et al. [19] instead replied to this methodology and tried out other two alternative ways to manage missing data; namely, they excluded patients with missing data and included patients with missing grade as a subgroup category defined "Gx". As a result, both studies reached a statistically significant protective effect of increased extent of LND when missing data were handled with multiple imputation [19,24]. Whitson et al. [24] showed hazard ratio (HR) of 0.8 (95% confidence interval [CI]: 0.7–1.0; $p=0.04$). Similarly, Sun et al. [19] reached almost identical results with HR of 0.82 (95% CI: 0.68–0.99, $p=0.04$). However, such results were not confirmed when missing data were censored (HR: 0.83, 95% CI: 0.66–1.05, $p=0.100$) or used with a missing indicator (HR: 0.82, 95% CI: 0.68–1.01, $p=0.05$) [19]. Looking to 95% CIs, the benefit extent of LND may be as great as a 34% reduction in CSM. Moreover, with the three methodologies CIs almost completely overlap, suggesting a possible benefit of more extended LND [25].

Marchioni et al. [17] also performed an analysis of the SEER database focusing on patients diagnosed as pT2-3 after radical nephrectomy (2001–2013) [17]. In multivariable models, LND did not influence CSM. Similarly, the LND extent did not decrease CSM (HR: 0.94; $p=0.300$) [17]. However, in patients with positive nodes more extended LND exerted a protective effect on CSM (HR: 0.98, $p=0.007$) [17]. Such results corroborated those of previous studies on the same dataset [17,19,24].

Other analyses were conducted on population-based registry; specifically Farber et al. [21] analyzed data within the National Cancer Database. Their analyses failed to show any significant improvement in OS in patients who did versus those who did not undergo LND (median OS 34.7 *vs*. 34.9 months, $p=0.980$) [21]. Moreover, authors could not find any OS benefit in those with clinically positive lymph nodes undergoing LND ($p=0.900$) [21]. These results were in line with those of single center and multicenter studies that also found no survival advantage in patients who had LND versus those who did not [16,20,22].

Taken together, these results suggested lack of a clinical benefit of LND over no LND in patients with non-metastatic RCC. On the other hand, some of the analyses also showed that a more extended LND might exert a clinical meaningful survival benefit in specific subgroups of patients [17,24]. These considerations could be corroborated by the results of other studies. Wei et al. [23] evaluated the LND effect on a total of 5532 pN0M0 RCC patients. In multivariable models, a less extensive LND defined as <2 nodes removed, showed a detrimental effect on OS in pT3 patients (HR: 1.442, $p=0.0032$) but not in pT1 and pT2 subgroups. Interestingly, the beneficial effect of more extended LND was not confirmed when CSM was evaluated [23]. Capitanio et al. [13] reported similar findings in patients with pT4 tumors. In multivariable models, the risk of dying from RCC decreased with 8% for each lymph node removed. Another study from the same research group also showed a survival benefit of more extended LND in specific subgroups of patients. In multivariable models, the number of nodes removed was associated with better prognosis in pT2a-b and pT3c-4 RCC patients (HR: 0.91 and 0.89, respectively; $p=0.008$ and $p<0.001$, respectively) [26]. Moreover, more extended LNDs were significantly associated with a reduced CSM in patients with bulky tumors (size >10 cm) and in those with sarcomatoid features [26]. However, it is noteworthy that almost 12% of the entire cohort were patients with a M1 status [26]. In addition, Tilki et al. [27] evaluated oncological outcomes of patients undergoing LND within the International Renal Cell Carcinoma-Venous Thrombus Consortium and showed that presence of lymph node metastasis, the number of positive nodes, and the lymph nodes density were independently associated with CSM. Interestingly, although the number of positive nodes was a strong predictor of survival, the number of removed nodes was not [27].

3.2. LND in metastatic RCC

Over the years, it has been hypothesized that LND might result in a survival benefit in patients with metastatic RCC. Several authors tested this hypothesis in different registries. Faiena et al. [28] evaluated the effect of LND at the time of cytoreductive nephrectomy in patients with cN1 nodal status [28]. Authors reported a worse OS in patients who underwent LND compared to those who did not (10.8 *vs*. 12.6 months, $p<0.001$), but this difference could be the effect of case selection. However, even though the lymph node yield was associated with a 3% increase of survival for each node removed, LND was still not associated with a better OS in cN1 patients in multivariable models [28]. In addition, when limited and extended LND were compared, no statistically significant differences were found in terms of OS [28].

These findings corroborated those of Feuerstein et al. [29] who performed a similar analysis in a cohort of 258 patients who underwent cytoreductive nephrectomy. Sixty-nine percent of the patients in this cohort underwent a LND, and positive nodes were found in 33% of the patients. No statistically significant differences were found in terms of OS and the number of nodes resected was no predictor of survival. These results were confirmed by other studies that also could not show any therapeutic benefit of LND at the time of cytoreductive nephrectomy [30,31].

3.3. Salvage LND

The role of surgery for the treatment of RCC local recurrence is well established [32]. However, the role of LND in patients with nodal only recurrences is more controversial. Salvage LND was investigated in two studies among those included in our research [33,34]. Barboza et al. [33] evaluated the outcomes of salvage LND in 19 patients treated between 2011 and 2018. After salvage LND, 42.1% of patients had no signs of disease at the last follow-up. Among those who relapsed, 45.5% were subjected to further resection of abdominal lesions. The 3- and 5-year cancer-specific survival were 81.5% and 61.1%, respectively [33]. Similar results were reported by Russell et al. [34] who showed a median progression-free survival after LND of 19.5 months, and 3- and 5-year progression-free survival of 40.5% and 35.4%, respectively. Taken together, these results suggested that salvage LND can be considered in RCC patients who presented with isolated nodal recurrence. Selection of patients who could be candidate to salvage LND might be based on the primary tumor histology. Recent analyses showed more frequent nodal metastases in papillary RCC than in clear cell RCC; thus

LND in these patients might have the larger beneficial effect [35]. Indeed, a recent analysis of the RECUR database also showed that recurrence sites vary based on the primary histology. Nodal recurrences were more frequent for those who harbored papillary RCC. However, it is worthy of note that nodal spread was not limited to regional nodes, but extended also to mediastinal and retroperitoneal nodes [36]. These results were corroborated by Rosiello et al. [37] that showed an increased risk of lymph node involvement in those with a diagnosis of papillary, sarcomatoid, and collecting duct histology compared to clear cell RCC. The latter suggested a limited effectiveness of regional LND in these patients.

3.4. Evidence from randomized clinical trials and meta-analyses

The only randomized clinical trial investigating the role of LND in RCC patients was sponsored by the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group (EORTC 30881) [11]. This trial included 383 versus 389 patients randomly assigned to radical nephrectomy with or without complete LND [11]. The final analysis showed no differences in terms of complication rate between the two groups [11]. Among those who underwent LND, more than 97% were node negative. In addition, no significant differences were found in terms of OS, time to progression of disease, or progression-free survival between the two groups [11]. However, the main limitation of this study stood on the low proportion of high-risk patients included (cT3 patients represented approximately 30% of the entire cohort) and subsequently the low number of patients with positive nodes [11]. Instead, a subgroup analysis focused on cT3 patients showed a non-statistically significant 15% survival advantage favoring LND versus no LND [38].

This potential survival advantage was not confirmed in a recent subgroup analysis of the Adjuvant Sorafenib and Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial that enrolled high-risk RCC patients [39]. Within the ASSURE trial, LND was performed in cN+ disease or at surgeons' discretion. In total, 36.1% of patients underwent LND. There was no OS benefit for LND compared to no LND (HR: 1.14, $p=0.200$) [39]. No difference in surgical complication rates were found according to LND performed [39].

A recent meta-analysis also investigated the possible role of LND in different patients setting [40]. In the final analysis, seven studies were included. Authors showed no OS benefit in patients with M0 (HR: 1.02; 95% CI: 0.92—1.12), M1 (HR: 1.04, 95% CI: 0.83—1.29), or M0-1 disease (HR: 1.00, 95% CI: 0.92—1.09) [40]. The overall quality of included studies was scored low. An evident benefit was not found, even in those M0 at highest risk [40]. However, a durable cancer-specific survival was highlighted in pN1M0 patients, corroborating the indication to perform LND in presence of clearly detectable nodal metastases. Authors also examined the importance of LND yields, concluding that more extended LND does not provide a survival benefit, but still extended LND represents the best tool to correcting classify nodal status [40].

These results, in the overall population, were corroborated by another meta-analysis by Luo et al. [14] who found no survival benefit of LND in patients with pT1-4NxM0 (pooled HR: 0.93; 95%CI: 0.78—1.11). However, when locally advanced tumors only were considered, authors found a survival advantage for LND patients (pooled HR: 0.73; 95% CI: 0.60—0.90).

3.5. LND templates

As previously stated, the role of LND in RCC patients remains controversial, with different studies showing negative, positive, or no effect, also based on baseline patients' characteristics [41]. One of the most controversial aspects regarding this subject is which template should be used, as several different templates have been proposed.

Proposed LND templates are based on the evolving knowledge about the lymphatic drainage of kidney. A schematic and complete review of current understanding about this complex system has been provided by Karmali and colleagues [42]. The authors distinguished an anterior and posterior efferent route that varies per kidney side. It was noteworthy that these routes have numerous connections which can vary a lot. For the right kidney, the principal nodes involved are the precaval, paracaval, interaortocaval, and retrocaval nodes, while on the left kidney, the involved nodes are the preaortic, paraaortic, and retroaortic ones [42]. However, we should be aware that retroperitoneal lymphatic system is an extensive network extended between the first and the fifth lumbar vertebrae with an intricate web of connections [42].

Crispen et al. [43] also evaluated location of lymph node metastases based on the side of primary tumor. Authors showed that 45% of patients with retroperitoneal nodal metastases had no involvement at perihilar lymph nodes. Moreover, authors also showed that about 20% of right-sided tumors spread to paraaortic nodes, while 7% of left-sided tumors spread to paracaval nodes. However, all these patients had involvement of paracaval (for right side tumors) or paraaortic nodes (for left side tumors) [43].

Based on anatomical knowledge about kidney lymphatic drainage, several templates have been developed. Previously proposed templates were resumed in Fig. 1. On this regard, Campi et al. [41] proposed a comprehensive review of the available literature on the topic, pointing out the relatively low quality of the included studies, assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. On the right-sided tumors, usually hilar, paracaval, and precaval nodes were more frequently retrieved. For the left-sided tumors, hilar, pre-aortic, and para-aortic nodes were usually resected. In both sides, the cranio-caudal extension of the LND is often limited to the diaphragm crus and the aortic bifurcation [41]. However, more extended templates have also been proposed [41]. More specifically, on right-sided tumors also interaortocaval, retrocaval, common iliac nodes, and even pre-aortic or paraaortic nodes were included. Similarly, for left-sided tumors, some authors also reported such extended LND template, although at a lower frequency [41]. Suggested templates were resumed in Fig. 1.

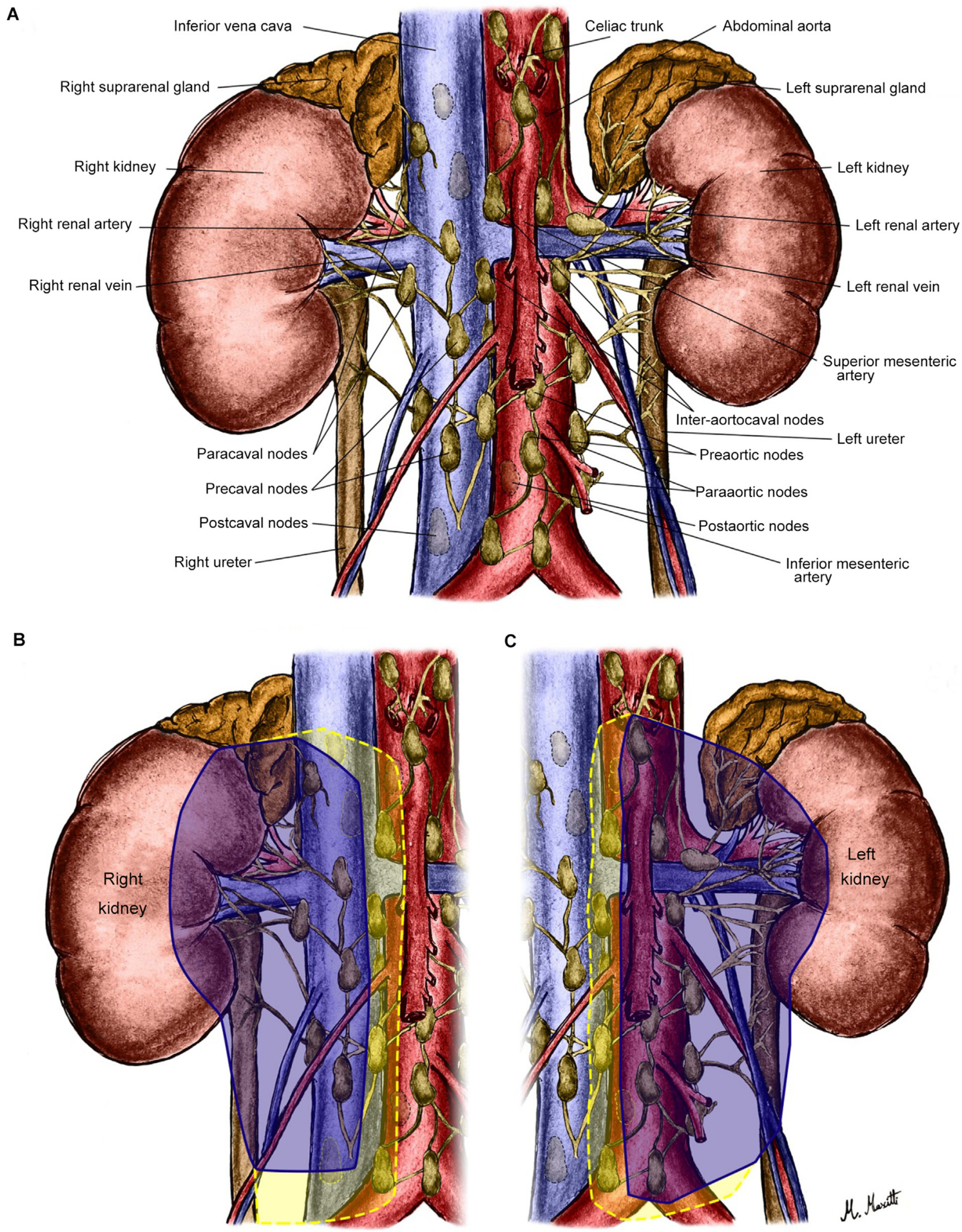

Figure 1 Schematic representation of mainly used lymph node dissection templates. (A) Schematic representation of main kidney lymphatic drainage. In blue are the most common lymphatic stations involved in standard lymph node dissection for the right (B) and left kidney (C). In yellow are lymphatic stations involved in extended lymph node dissection for the right (B) and left (C) kidney.

3.6. Patient selection

Patients' selection for LND at the time of surgery remains a cornerstone when planning renal surgery. Indeed, a recent review of the literature by Capitanio and Leibovich [9] showed that lymph node invasion rates might varies from 4% to 40% based on different series. However, it is of note that LND indication and extension were non-standardized in most of the cases in these studies [9]. As we already discussed, the importance of LND templates remains crucial. Alongside with the correct template, it is fundamental to choose the best candidate to LND. Current European Association of Urology guidelines limit recommendation for LND to patients with clinical suspicious lymph nodes [10], but such definition might underestimate the real need for LND and limit its role in diagnosis.

Results from ASSURE trials did not show a survival advantage of LND versus no LND in patients at highest risk [39]. However, the definition of high risk in the trial was based only on clinical characteristics. Indeed, the study included patients with pT1b high grade (G3-G4) tumors that could be fully resected. Nodal status could be either cN0 or N+ [44]. More recent analyses have shown that the probability to have nodal invasion is also based on the primary histology of resected tumors, and that the prevalence of nodal metastases is higher in papillary renal cancer [36]. Instead, in the ASSURE trial only 7%–8% of patients harbored a papillary tumor, while up to 80% were diagnosed with a clear cell RCC [39].

Several nomograms have been developed to warrant the best candidate selection for LND. Li et al. [45] proposed a nomogram including clinical nodal and tumor stage, preoperative symptoms, age at surgery, and lymphocyte percent. Their nomogram showed a good accuracy (C-index: 0.824). Similarly, Hutterer et al. [46] proposed a nomogram including age at diagnosis, preoperative symptoms, and tumor size. The nomogram was externally validated and showed also fair accuracy (area under the curve: 78.4%) [46]. Another nomogram has been proposed by Babaian et al. [47], which included performance status, clinical nodal stage, preoperative symptoms, and lactate dehydrogenase blood levels. Authors reported a good accuracy too (C-index: 0.89). Differently from previously cited authors, Capitanio et al. [48] also included patients with metastases while developing their nomogram. In their model, authors also included the clinical tumor and nodal stage as well as the tumor size along to metastatic status. They reported also a fair accuracy (area under the curve: 86.9%). At the time of LND planning, one of the most important predictor of node metastases is the clinical nodal status at imaging. Gershman et al. [49] showed that the most important predictors of pN1 disease were the maximum node short axis diameter and radiographic perinephric and/or sinus fat invasion in multivariable models, after having taken into account several clinical features. Taking together, these results suggest the importance of preoperative imaging when LND must be planned.

That said, the number of patients treated with LND who did not show lymph node metastases is still too high. The use of new biomarkers might be helpful to further improve the selection process. As shown in previous analyses, the use of molecular markers might improve lymph node invasion detection, even if only minimal LND is performed based on specific clinical, pathological, and molecular profile [50,51]. For instance, Kroeger et al. [50] showed in a retrospective analysis, which included 502 localized RCC patients with or without lymphatic spreading, that low carbonic anhydrase IX and high epithelial vascular endothelial growth factor receptor 2 protein expression were associated with higher risk of lymphatic spread. Conversely, loss of chromosome 3p was associated with a lower risk. Such associations remained statistically significant even after adjustment for important clinical covariates namely, stage, smoking history, tumor grade, and performance status [50]. The use of integrated models might improve the accuracy of currently available tools in order to detect preoperatively patients at highest risk who might benefit of LND or more extensive follow-up.

More recently other tissue, plasmatic, and urinary biomarkers have been studied to better stratify patients at highest risk of recurrence after RCC surgery [52]. In this field, the use of micro-RNA (miRNA) has shown an interesting and promising area of research that could be implemented in routine clinical practice introducing prognostic models which encompass also miRNAs expression [53,54]. The miRNAs are endogenous non-coding small RNAs playing as gene regulators. The miRNAs could be detected in tissue specimen (from the final pathology or biopsies) and in body fluids (such as blood and urine) [54]. A growing body of literature results have shown an association between specific miRNAs expression and tumor stage [55]. Modern techniques allow miRNAs identification in body fluids, which are easier to collect than a tumor specimen, with higher repeatability than tissue miRNAs [55]. In the next future, a specific miRNAs signature could be useful to identify patients at highest risk of nodal metastases or nodal progression. In these patients, as suggested above, LND could be more beneficial or allow a more accurate staging, resulting in a positive net benefit derived from the procedure. To the best of our knowledge, no study exploring specifically the association between miRNAs expression and nodal status has been published. Indeed, this is an unexplored field, and more efforts are needed to improve our knowledge and to standardize procedures in order to obtain reliable results [56].

4. Discussion

Literature results strongly suggested not to perform LND in the majority of RCC patients since association with a clinical benefit is far from proven [11]. In addition, even in metastatic patients, the percentage of patients with positive nodes remains below 50% [29]. Studies showed that the prevalence of lymph node invasion could drop to 6.1% when considering all stages, and only about 4% of patients might experience progression of such lymph node progression. In this light, patient selection becomes fundamental to reduce possible harm and improve the quality of care.

Although LND is not recommended for most RCC patients, some patients, generally with clinical positive nodes, are those who might benefit from LND [26]. Unfortunately, few evidence-based recommendations could be given to the extent of LND and node yield. It might suggested that LND should be extended in order to improve its diagnostic accuracy and to provide important clinical information, which should be reserved to patients at high risk of nodal metastases [48]. Larger tumors, over 7 cm, are at higher risk of lymph node invasion, as previously demonstrated by Dell'Oglio et al. [57]. Authors concluded that LND should not be dismissed in these groups of patients. However, it should be noted that the prevalence of positive nodes was still low (2.2%) [57]. Capitanio et al. [48] showed that a model including clinical tumor stage, clinical nodal status, the presence of metastasis, and clinical tumor size could safely predict the presence of lymph node metastases with an overall accuracy of about 87%.

However, decreasing rate of LND performance over time has been shown [58,59]. Such decrease could be related to two important aspects highlighted in the current review of the literature, namely high heterogeneity regarding LND templates and uncertain beneficial effect of LND on survival [16,30]. A recent analysis showed a gradual decline in LND performed since the 1990s. This decrease was quantified as 21.5% per year from 2008 to 2011 [58]. Similar results have been shown within the SEER registry [59]. Kates et al. [59] reported a gradual decline in LND beginning in 1988 with acceleration after 1997. In the European series, the period between 1998 and 2005 was characterized by the lowest LND rates. Overall the decline was quantified as of 63% among localized tumors. More specifically, within the SEER database the proportion of LNDs declined in pT2 patients, but remained stable in the pT3 patients who underwent radical nephrectomy between 2001 and 2013 [17].

Reasons for the observed reduction in the number of LNDs performed could be various. Alongside with the lack of survival advantage [17,58], the spread of minimally invasive procedures [60] might also have played a role. Indeed, patients who underwent open surgery have almost twice the probability to undergo concomitant LND (odds ratio for LND performance in open *vs*. minimally invasive surgery: 1.75, $p<0.0001$) [58]. Moreover, nephron sparing surgery has become more popular over the years, even for larger renal masses [61—64]. The use of partial nephrectomy is also associated with lower LND rates. More specifically, LND are performed five times more frequent in patients who undergo radical nephrectomy than in patients in which a partial nephrectomy is performed [58].

Summarizing, LND is performed much more rarely than in the past, probably due to the absence of an evident survival benefit. Lack of evidence strongly supporting LND performance limits its role at the time of nephrectomy during daily clinical practice. However, it still represents the best staging approach in high-risk RCC patients. Therefore, we could assist to a decline in staging quality. Consequently, we might misdiagnose patients at high-risk as low-risk. These patients, who might be candidate for clinical trials on adjuvant systemic therapies [65], might lose a treatment opportunity. It is worthy of note that previous studies highlighted a correlation between number of nodes removed and the percentage of nodal involvement in addition to an higher staging accuracy when more extended LNDs were performed [15]. On the other hand, other researches showed a survival benefit in node positive patients who underwent more extended LND [17]. However, the median number of nodes removed at the time of LND was generally lower than desirable in several series [17,39]. Taking together, available evidence suggests suboptimal LND quality. Further improvement might derive from the use of novel technologies in the field of sentinel nodes, novel minimally invasive approaches, or augmented reality [66,67]. As we have seen in other application of renal surgery, such as minimally invasive approaches or augmented reality [68,69], new technological improvement might improve the accuracy of nodal staging and confer a clinical benefit. To the best of our knowledge, no large cohort study investigating the use of such technologies for LND in RCC patients has been reported, although robotic retroperitoneal LND has been performed for large complex renal masses allowing to retrieve more than 30 nodes [70]. Similarly, robotic retroperitoneal LND has been performed for other malignancies, such as testicular cancer, with good results in terms of number of nodes removed [71], proving the feasibility and efficacy of this approach.

In conclusion, LND could not be recommended at the time of nephrectomy in absence of high-risk nodal metastases to date.

Future studies should focus on the possible impact of new predictive tools and surgical techniques, which might allow a better patient stratification and a more extensive LND as it has been reported for other aspects of kidney surgery [72—74]. On the other hand, patients should be carefully consulted about the risk of nodal metastases and on the opportunity to perform a surgery that might not have any effect on survival. Previous studies have already shown the importance of patients' prospective and patients' selection in order to improve treatment adherence and outcomes [75,76].

Our review is not devoid of limitations, firstly because of its narrative nature. We did not provide any quantitative synthesis of collected data. Moreover, our non-systematic literature review relied only on one dataset and only English language studies were collected. It might be possible that the current review represents a partial and biased view of currently available evidence on this topic because of its non-systematic nature.

5. Conclusion

LND at the time of radical nephrectomy does not result any survival advantage in most RCC cases. Its role should be limited to patients presenting with suspected lymph nodes.

Author contributions

Study concept and design: Michele Marchioni, Riccardo Campi.
Data acquisition: Igino Andrea Magli, Marco Mascitti, Daniele Amparore.
Drafting of manuscript: Michele Marchioni, Daniele Amparore, Igino Andrea Magli, Riccardo Bertolo, Umberto Carbonara, Selcuk Erdem, Alexandre Ingels, Constantijn H.J. Muselaers, Onder Kara, Marco Mascitti, Tobias Klatte, Maximilian Kriegmair, Nicola Pavan, Eduard Roussel, Angela Pecoraro, Laura Marandino, Riccardo Campi, Luigi Schips.
Critical revision of the manuscript: Riccardo Berotlo, Riccardo Campi.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Perri D, Palumbo C, Billia M, Umari P, Zacchero M, D'Agate D, et al. Assessment of predictors of renal cell carcinoma progression after nephrectomy at short and intermediate term follow-up and implication on surveillance protocols. Minerva Urol Nephrol 2021. https://doi.org/10.23736/S2724-6051.21.04322-6.

[2] Bandini M, Smith A, Zaffuto E, Pompe RS, Marchioni M, Capitanio U, et al. Effect of pathological high-risk features on cancer-specific mortality in non-metastatic clear cell renal cell carcinoma: a tool for optimizing patient selection for adjuvant therapy. World J Urol 2018;36:51—7.

[3] 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;115:5680—7.

[4] Nakagawa T. Lymph node dissection for bladder cancer: current standards and the latest evidence. Int J Urol Off J Jpn Urol Assoc 2021;28:7—15.

[5] Preisser F, Nazzani S, Bandini M, Marchioni M, Tian Z, Montorsi F, et al. Increasing rate of lymph node invasion in patients with prostate cancer treated with radical prostatectomy and lymph node dissection. Urol Oncol Semin Orig Investig 2018;36:365.e1—7. https://doi.org/10.1016/j.urolonc.2018.05.019.

[6] Bandini M, Preisser F, Nazzani S, Marchioni M, Tian Z, Fossati N, et al. Contemporary trends and survival outcomes after aborted radical prostatectomy in lymph node metastatic prostate cancer patients. Eur Urol Focus 2019;5:381—8.

[7] Pesce C, Morrow M. The need for lymph node dissection in nonmetastatic breast cancer. Annu Rev Med 2013;64:119—29.

[8] Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation—technical notes and outcome. Colorectal Dis 2009;11:354—64; discussion 364—5.

[9] Capitanio U, Leibovich BC. The rationale and the role of lymph node dissection in renal cell carcinoma. World J Urol 2017;35:497—506.

[10] 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;67:913—24.

[11] Blom JHM, 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;55:28—34.

[12] John NT, Blum KA, Hakimi AA. Role of lymph node dissection in renal cell cancer. Urol Oncol Semin Orig Investig 2019;37:187—92.

[13] Capitanio U, Matloob R, Suardi N, Abdollah F, Castiglione F, Di Trapani D, et al. The extent of lymphadenectomy does affect cancer specific survival in pathologically confirmed T4 renal cell carcinoma. Urol J 2012;79:109—15.

[14] Luo X, Li JX, Liu YT, Zou G, Yao WX, Qing GQ, et al. Influence of lymph node dissection in patients undergoing radical nephrectomy for non-metastatic renal cell carcinoma: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2019;23:6079—90.

[15] Terrone C, Guercio S, De Luca S, Poggio M, Castelli E, Scoffone C, et al. The number of lymph nodes examined and staging accuracy in renal cell carcinoma. BJU Int 2003;91:37—40.

[16] 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;71:560—7.

[17] Marchioni M, Bandini M, Pompe RS, Martel T, Tian Z, Shariat SF, et al. The impact of lymph node dissection and positive lymph nodes on cancer-specific mortality in contemporary pT(2-3) non-metastatic renal cell carcinoma treated with radical nephrectomy. BJU Int 2018;121:383—92.

[18] Lee HW, Jeon HG, Jeong BC, Seo SI, Jeon SS, Choi HY, et al. Diagnostic and prognostic significance of radiologic node-positive renal cell carcinoma in the absence of distant metastases: a retrospective analysis of patients undergoing nephrectomy and lymph node dissection. J Kor Med Sci 2015;30:1321. https://doi.org/10.3346/jkms.2015.30.9.1321.

[19] Sun M, Trinh Q-D, Bianchi M, Hansen J, Abdollah F, Tian Z, et al. Extent of lymphadenectomy does not improve the survival of patients with renal cell carcinoma and nodal metastases: biases associated with the handling of missing data. BJU Int 2014;113:36—42.

[20] Gershman B, Thompson RH, Boorjian SA, Larcher A, Capitanio U, Montorsi F, et al. Radical nephrectomy with or without lymph node dissection for high risk nonmetastatic renal cell carcinoma: a multi-institutional analysis. J Urol 2018;199:1143—8.

[21] Farber NJ, Rivera-Núñez Z, Kim S, Shinder B, Radadia K, Sterling J, et al. Trends and outcomes of lymphadenectomy for nonmetastatic renal cell carcinoma: a propensity score-weighted analysis of the National Cancer Database. Urol Oncol Semin Orig Investig 2019;37:26—32.

[22] Feuerstein MA, Kent M, Bazzi WM, Bernstein M, Russo P. Analysis of lymph node dissection in patients with ≥7-cm renal tumors. World J Urol 2014;32:1531—6.

[23] Wei Y, Wang M, Jin Y, Zhou C, Lyu J. Extent of lymph node dissection improves overall survival in pT3N0 non-metastatic renal cell carcinoma patients treated with radical nephrectomy: a propensity score-based analysis. World J Urol 2020;38:1579—85.

[24] Whitson JM, Harris CR, Reese AC, Meng MV. Lymphadenectomy improves survival of patients with renal cell carcinoma and nodal metastases. J Urol 2011;185:1615—20.

[25] Whitson JM, Meng M. Extent of lymphadenectomy does not improve the survival of patients with renal cell carcinoma and nodal metastases: biases associated with the handling of missing data. BJU Int 2014;113:2—3.

[26] Capitanio U, Suardi N, Matloob R, Roscigno M, Abdollah F, Di Trapani E, 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): effect of LND extent on RCC-specific survival and metastatic progression. BJU Int 2014;114:210—5.

[27] Tilki D, Chandrasekar T, Capitanio U, Ciancio G, Daneshmand S, Gontero P, et al. Impact of lymph node dissection at the time of radical nephrectomy with tumor thrombectomy on oncological outcomes: results from the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC). Urol Oncol Semin Orig Investig 2018;36:79.e11—7. https://doi.org/10.1016/j.urolonc.2017.10.008.

[28] Faiena I, Salmasi A, Lenis AT, Donin NM, Johnson DC, Bachour K, et al. Overall survival in patients with metastatic renal cell carcinoma and clinical N1 disease undergoing cytoreductive nephrectomy and lymph node dissection. Urol Oncol Semin Orig Investig 2018;36:79.e19—26. https://doi.org/10.1016/j.urolonc.2017.10.009.

[29] Feuerstein MA, Kent M, Bernstein M, Russo P. Lymph node dissection during cytoreductive nephrectomy: a retrospective analysis. Int J Urol 2014;21:874—9.

[30] Gershman B, Thompson RH, Moreira DM, Boorjian SA, Lohse CM, Costello BA, et al. Lymph node dissection is not associated with improved survival among patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma: a propensity score based analysis. J Urol 2017;197: 574—9.
[31] Chipollini J, Abel EJ, Peyton CC, Boulware DC, Karam JA, Margulis V, et al. Pathologic predictors of survival during lymph node dissection for metastatic renal-cell carcinoma: results from a multicenter collaboration. Clin Genitourin Cancer 2018;16:e443—50. https://doi.org/10.1016/j.clgc.2017.10.004.
[32] Marchioni M, Sountoulides P, Furlan M, Mir MC, Aretano L, Rubio-Briones J, et al. Management of local recurrence after radical nephrectomy: surgical removal with or without systemic treatment is still the gold standard. Results from a multicenter international cohort. Int Urol Nephrol 2021;53: 2273—80.
[33] Barboza MP, Speir RW, Boris RS, Calaway AC, Cary C, Foster RS, et al. Understanding the role of salvage lymphadenectomy in node only recurrences after nephrectomy for renal cell carcinoma. Urol Oncol Semin Orig Investig 2020;38: 739.e1—8. https://doi.org/10.1016/j.urolonc.2020.06.006.
[34] Russell CM, Lue K, Fisher J, Kassouf W, Schwaab T, Sexton WJ, et al. Oncological control associated with surgical resection of isolated retroperitoneal lymph node recurrence of renal cell carcinoma. BJU Int 2016;117:e60—6. https://doi.org/10.1111/bju.13212.
[35] Dudani S, de Velasco G, Wells JC, Gan CL, Donskov F, Porta C, et al. Evaluation of clear cell, papillary, and chromophobe renal cell carcinoma metastasis sites and association with survival. JAMA Netw Open 2021;4:e2021869. https://doi.org/10.1001/jamanetworkopen.2020.21869.
[36] Abu-Ghanem Y, Powles T, Capitanio U, Beisland C, Järvinen P, Stewart GD, et al. The impact of histological subtype on the incidence, timing, and patterns of recurrence in patients with renal cell carcinoma after surgery—results from RECUR consortium. Eur Urol Oncol 2020. https://doi.org/10.1016/-j.euo.2020.09.005. S2588931120301656.
[37] Rosiello G, Palumbo C, Knipper S, Pecoraro A, Luzzago S, Tian Z, et al. Histotype predicts the rate of lymph node invasion at nephrectomy in patients with nonmetastatic renal cell carcinoma. Urol Oncol Semin Orig Investig 2020;38:537—44.
[38] Bekema HJ, MacLennan S, Imamura M, Lam TBL, Stewart F, Scott N, et al. Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. Eur Urol 2013;64:799—810.
[39] Ristau BT, Manola J, Haas NB, Heng DYC, Messing EM, Wood CG, 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.
[40] Bhindi B, Wallis CJD, Boorjian SA, Thompson RH, Farrell A, Kim SP, 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.
[41] Campi R, Sessa F, Di Maida F, Greco I, Mari A, Takáčová T, et al. Templates of lymph node dissection for renal cell carcinoma: a systematic review of the literature. Front Surg 2018;5:76. https://doi.org/10.3389/fsurg.2018.00076.
[42] Karmali RJ, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int 2014;114: 806—17.
[43] 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;59:18—23.
[44] Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, 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 Lond Engl 2016;387:2008—16.
[45] Li P, Peng C, Xie Y, Wang L, Gu L, Wu S, et al. A Novel Preoperative Nomogram for predicting lymph node invasion in renal cell carcinoma patients without metastasis. Cancer Manag Res 2019;11:9961—7.
[46] Hutterer GC, Patard J-J, Perrotte P, Ionescu C, de La Taille A, Salomon L, et al. Patients with renal cell carcinoma nodal metastases can be accurately identified: external validation of a new nomogram. Int J Cancer 2007;121:2556—61.
[47] Babaian KN, Kim DY, Kenney PA, Wood CG, Wong J, Sanchez C, et al. Preoperative predictors of pathological lymph node metastasis in patients with renal cell carcinoma undergoing retroperitoneal lymph node dissection. J Urol 2015;193: 1101—7.
[48] Capitanio U, Abdollah F, Matloob R, Suardi N, Castiglione F, Di Trapani E, et al. When to perform lymph node dissection in patients with renal cell carcinoma: a novel approach to the preoperative assessment of risk of lymph node invasion at surgery and of lymph node progression during follow-up. BJU Int 2013;112:e59—66. https://doi.org/10.1111/bju.12125.
[49] Gershman B, Takahashi N, Moreira DM, Thompson RH, Boorjian SA, Lohse CM, et al. Radiographic size of retroperitoneal lymph nodes predicts pathological nodal involvement for patients with renal cell carcinoma: development of a risk prediction model. BJU Int 2016;118:742—9.
[50] Kroeger N, Seligson DB, Klatte T, Rampersaud EN, Birkhäuser FD, Rao PN, et al. Clinical, molecular, and genetic correlates of lymphatic spread in clear cell renal cell carcinoma. Eur Urol 2012;61:888—95.
[51] Gao L, Zhao H, Zhang D, Zhou C, Wang H, Ren C, et al. Role of APLP2 in the prognosis and clinicopathology of renal cell carcinoma. Oncol Lett 2018. https://doi.org/10.3892/ol.2018.9577.
[52] Marchioni M, Rivas JG, Autran A, Socarras M, Albisinni S, Ferro M, et al. Biomarkers for renal cell carcinoma recurrence: state of the art. Curr Urol Rep 2021;22:31. https://doi.org/10.1007/s11934-021-01050-0.
[53] Fasanella D, Antonaci A, Esperto F, Scarpa RM, Ferro M, Schips L, et al. Potential prognostic value of miRNAs as biomarker for progression and recurrence after nephrectomy in renal cell carcinoma: a literature review. Diagnosis (Berl) 2021;9:157—65.
[54] Oto J, Herranz R, Plana E, Sánchez-González JV, Pérez-Ardavín J, Hervás D, et al. Identification of miR-20a-5p as robust normalizer for urine microRNA studies in renal cell carcinoma and a profile of dysregulated microRNAs. Int J Mol Sci 2021;22:7913. https://doi.org/10.3390/ijms22157913.
[55] Shi L, Wang M, Li H, You P. MicroRNAs in body fluids: a more promising biomarker for clear cell renal cell carcinoma. Cancer Manag Res 2021;13:7663—75.
[56] Oto J, Plana E, Sánchez-González JV, García-Olaverri J, Fernández-Pardo Á, España F, et al. Urinary microRNAs: looking for a new tool in diagnosis, prognosis, and monitoring of renal cancer. Curr Urol Rep 2020;21:11. https://doi.org/10.1007/s11934-020-0962-9.
[57] Dell'Oglio P, Larcher A, Muttin F, Di Trapani E, Trevisani F, Ripa F, et al. Lymph node dissection should not be dismissed in case of localized renal cell carcinoma in the presence of larger diseases. Urol Oncol Semin Orig Investig 2017;35: 662.e9—15. https://doi.org/10.1016/j.urolonc.2017.07.010.
[58] Capitanio U, Stewart GD, Larcher A, Ouzaid I, Akdogan B, Roscigno M, et al. European temporal trends in the use of lymph node dissection in patients with renal cancer. Eur J Surg Oncol 2017;43:2184—92.

[59] Kates M, Lavery HJ, Brajtbord J, Samadi D, Palese MA. Decreasing rates of lymph node dissection during radical nephrectomy for renal cell carcinoma. Ann Surg Oncol 2012;19: 2693—9.
[60] Marchioni M, Nazzani S, Preisser F, Bandini M, Tian Z, Kapoor A, et al. The effect of institution teaching status on perioperative outcomes after robotic partial or radical nephrectomy. J Endourol 2018;32:621—9.
[61] Amparore D, Pecoraro A, Piramide F, Checcucci E, Cillis SDE, Volpi G, et al. Comparison between minimally-invasive partial and radical nephrectomy for the treatment of clinical T2 renal masses: results of a 10-year study in a tertiary care center. Minerva Urol Nephrol 2021;73:509—17.
[62] Carbonara U, Simone G, Capitanio U, Minervini A, Fiori C, Larcher A, et al. Robot-assisted partial nephrectomy: 7-year outcomes. Minerva Urol Nephrol 2021;73:540—3.
[63] Bertolo R, Autorino R, Simone G, Derweesh I, Garisto JD, Minervini A, et al. Outcomes of robot-assisted partial nephrectomy for clinical T2 renal tumors: a multicenter analysis (ROSULA Collaborative Group). Eur Urol 2018;74:226—32.
[64] Bradshaw AW, Autorino R, Simone G, Yang B, Uzzo RG, Porpiglia F, et al. Robotic partial nephrectomy *vs.* minimally invasive radical nephrectomy for clinical T2a renal mass: a propensity score-matched comparison from the ROSULA (Robotic Surgery for Large Renal Mass) Collaborative Group. BJU Int 2020;126:114—23.
[65] Capogrosso P, Larcher A, Nini A, Muttin F, Cianflone F, Ripa F, et al. The critical role of lymph node dissection in selecting high-risk nonmetastatic renal cancer candidates for adjuvant therapy after nephrectomy. Urol Oncol Semin Orig Investig 2019;37:293.e25—30. https://doi.org/10.1016/j.urolonc.2019.01.009.
[66] Kuusk T, Brouwer O, Graafland N, Hendricksen K, Donswijk M, Bex A. Sentinel lymph node biopsy in renal tumors: surgical technique and safety. Urology 2019;130:186—90.
[67] Hartana CA, Kinn J, Rosenblatt R, Anania S, Alamdari F, Glise H, et al. Detection of micrometastases by flow cytometry in sentinel lymph nodes from patients with renal tumours. Br J Cancer 2016;115:957—66.
[68] Checcucci E, Amparore D, Pecoraro A, Peretti D, Aimar R, Cillis SDE, et al. 3D mixed reality holograms for preoperative surgical planning of nephron-sparing surgery: evaluation of surgeons' perception. Minerva Urol Nephrol 2021;73: 367—75.
[69] Vuong N-S, Ferriere J-M, Michiels C, Calen L, Tesi L, Capon G, et al. Robot-assisted versus open surgery for radical nephrectomy with level 1-2 vena cava tumor thrombectomy: a French monocenter experience (UroCCR study #73). Minerva Urol Nephrol 2021;73:498—508.
[70] Bratslavsky G, Cheng JS. Robotic-assisted radical nephrectomy with retrohepatic vena caval tumor thrombectomy (Level III) combined with extended retroperitoneal lymph node dissection. Urology 2015;86:1235—40.
[71] Afferi L, Baumeister P, Fankhauser C, Mordasini L, Moschini M, Aschwanden F, et al. Nerve-sparing robot-assisted retroperitoneal lymph node dissection: the monoblock technique. Eur Urol Open Sci 2021;32:1—7.
[72] Introini C, Di Domenico A, Ennas M, Campodonico F, Brusasco C, Benelli A. Functional and oncological outcomes of 3D clampless sutureless laparoscopic partial nephrectomy for renal tumors with low nephrometry score. Minerva Urol Nephrol 2020;72:723—8.
[73] Brassetti A, Anceschi U, Bertolo R, Ferriero M, Tuderti G, Costantini M, et al. Comprehensive long-term assessment of outcomes following robot-assisted partial nephrectomy for renal cell carcinoma: the ROMe's achievement and its predicting nomogram. Minerva Urol Nefrol 2020;72:482—9.
[74] Bianchi L, Schiavina R, Borghesi M, Chessa F, Casablanca C, Angiolini A, et al. Which patients with clinical localized renal mass would achieve the trifecta after partial nephrectomy? The impact of surgical technique. Minerva Urol Nephrol 2020; 72:339—49.
[75] Campi R, Sessa F, Corti F, Carrion DM, Mari A, Amparore D, et al. Triggers for delayed intervention in patients with small renal masses undergoing active surveillance: a systematic review. Minerva Urol Nephrol 2020;72:389—407.
[76] Marchioni M, Cheaib JG, Takagi T, Pavan N, Antonelli A, Everaerts W, et al. Active surveillance for small renal masses in elderly patients does not increase overall mortality rates compared to primary intervention: a propensity score weighted analysis. Minerva Urol Nephrol 2021;73: 781—8.