Lymph Node Dissection in Renal Cancer and Upper Tract Urothelial Cancer

Pieter J. le Roux

Lymph Node Dissection in Renal Cell Carcinoma

Introduction

The role of lymph node dissection (LND) in the treatment of renal cell carcinoma (RCC) is controversial. LND is accepted as the most reliable staging procedure to detect lymph node involvement but any therapeutic benefit remains unproven. Many urological surgeons have abandoned routine LND at time of nephrectomy due to a lack of proven benefit in cancer control and the increased use of laparoscopic surgery which makes LND a challenging and time consuming exercise. Robotic assisted surgery enables minimally invasive LND comparable to what can be achieved with open surgery. The widespread application of cross-sectional imaging has led to stage migration with increased diagnosis of early stage, low risk disease, where the incidence of nodal spread is negligible and where LND has no therapeutic or staging benefit. A subset of high risk patients may benefit from LND.

Guidelines

The 2019 update of the EAU guidelines in the management of renal cancer advises against LND in patients with clinically negative nodes [1]. The guidelines state that LND was not associated with reduced risk of distant metastases, cancer specific mortality or all-cause mortality. LND also did not improve oncological outcomes for patients at high risk of nodal involvement. LND can be considered for staging

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purposes. Resection of visibly enlarged nodes on preoperative imaging and palpable nodes found at time of surgery is recommended where this is technically feasible.

Evidence

The only published prospective randomised trial of nephrectomy with and without LND enrolled 772 patients with clinically node negative disease. Patients were randomised to nephrectomy alone versus nephrectomy plus regional lymphadenectomy [2]. EORTC 30881 did not show any benefit in cancer control for patients treated with LND and nephrectomy but the majority of patients in the trial had low-stage tumours with a very low risk of nodal involvement where LND was unlikely to be beneficial. Precise information regarding the template used for LND and the number of nodes removed were lacking and the number of high risk patients was too small to assess the benefit of LND. The trial could not answer the question of where and to what extent LND should be performed. It is possible that these results may not be applicable to all RCC patients.

EORTC 30881 included only cT1-3N0M0 cases according to the 1978 TNM classification. Today 70% of the cases enrolled in this trial would be classified as cT1abN0M0. The trial provides level one evidence that LND has no therapeutic benefit in low risk patients. In addition the risk of occult nodal metastases is so low that LND also has no staging role in these patients. This is in keeping with the findings of numerous retrospective series as shown in Table 1 [3–5].

Some observational studies have reported a survival benefit for LND with radical nephrectomy and it has been argued that a more extensive dissection might confer a survival advantage [6]. In subsets of patients with clinically isolated N1M0 disease long term survival has been observed after LND [7–11]. However several modern observational studies have failed to demonstrate a survival benefit with LND in both non-metastatic and metastatic settings [4, 12, 13]. Bhindi et al. conducted a systematic review and meta-analysis of 51 unique studies and reported that the current literature does not support a therapeutic benefit for LND in either M0 or M1 renal carcinoma. The authors note that high-risk M0 patients warrant further study since a subset of patients with isolated nodal metastases experience long term survival after surgical resection [14].

Blute et al. proposed a protocol for LND based on metastatic risk. In a series of 1652 patients undergoing radical nephrectomy for clinical M0 clear cell RCC 93% were pN0 and 7% were node positive. Multivariable analysis demonstrated that the presence of nuclear Grade 3 or 4, presence of sarcomatoid components, tumour size more than or equal to 10 cm, tumour stage pT3 or pT4, and presence of coagulative tumour necrosis were independent predictors of regional lymph node involvement at time of nephrectomy [15]. Crispin et al. presented similar data with stage, grade, coagulative necrosis and sarcomatoid differentiation being strong predictors of lymph node involvement, and proposed that patients with larger masses might benefit from LND, at least for staging purposes. The likelihood of lymph node

Table 1 Papers published in the last 20 years assessing the effect of LND on survival

References	Study design	Number of patients	Patients included	LND definition and extension[a]	Measured outcomes	Effect of LND
Feuerstein et al.	Retrospective, single institution, controlled for confounders	524	≥7 cm TanyNanyMany	Mixed, non-standardized	Overall survival	No survival difference
Feuerstein et al.	Retrospective, single institution	258	M1	Mixed, non-standardized 0–3 nodes (30%) 4–7 (21%) ≥8 (49%)	Overall survival	No survival difference
Capitanio et al.	Retrospective, single institution, controlled for confounders	1983	TanyNanyMany	Mixed, non-standardized: No LND (56%) Hilar LND (18%): 3.1 (3) Side-specific LND (15%): 10 (8) Extended LND (9%): 15 (13)	Cancer-specific survival; Metastatic progression	Protective effect in increasing the number of nodes removed in patients with pT2a–pT2b or pT3c–pT4 or tumour size >10 cm or when sarcomatoid features were found
Bekema et al.	Systematic review, post hoc analyses of a prospective randomized	645 + 213[b]	TanyNanyMany cT3N0M0[b]	Mixed, non-standardized, unknown number of nodes removed	Cancer-specific survival; other causes survival	No robust evidence to suggest superior oncologic outcomes
Capitanio et al.	Retrospective, single institution, controlled for confounders	44	pT4	Extended: 12 (8)	Cancer-specific survival	Protective effect in increasing the number of nodes removed

(continued)

Table 1 (continued)

References	Study design	Number of patients	Patients included	LND definition and extension[a]	Measured outcomes	Effect of LND
Whitson et al.	Retrospective, population based cohort, controlled for confounders	9586	TanyNanyMany	Mixed, non-standardized, unknown number of nodes removed	Cancer-specific survival	Increased disease-specific survival with extent of lymphadenectomy in pN1 cases
Blom et al.	Prospective randomized	732	T1-3N0M0	Limited, non-standardized, unknown number of nodes removed	Cancer-specific survival; other causes survival	No benefit in terms of survival for patients treated with LND
Vasselli et al.	Retrospective, single institution	154	M1	Non-standardized, unknown number of nodes removed	Overall survival	Indirect low evidence suggesting a potential effect of LND in preparation of adjuvant interleukin regimen
Schafhauser et al.	Retrospective, single institution	1035	T1-4NanyM0	No LND (29%) Removal of lymphadenopathy only (19%): 6 Systematic LND (51%): 18	Overall survival	Patients treated with systematic lymphadenectomy had the least favorable tumor stage but better survival relative to patients not treated with LND

[a]Mean (median) number of nodes removed when available
[b]Systematic review with post hoc analyses of level 1b evidence

involvement increased with the number of risk factors involved [16]. Neither of these studies assessed the impact of LND on survival.

Capitanio et al. evaluated whether the number of lymph nodes removed may affect cancer-specific survival or progression free survival in specific scenarios. After a mean follow up of 7 years the number of nodes removed showed an independent protective effect in patients with larger tumours [9]. Feuerstein et al. did not find a reduction in overall or recurrence free survival in patients with tumours more than or equal to 7 cm whether they underwent LND or not [4]. A subanalysis of the prospective EORTC trial looking at clinical T3 tumours only reported a 15% overall survival benefit at 5 years for the patients who underwent LND and nephrectomy versus nephrectomy alone [17].

More often than not lymph node involvement signifies metastatic disease whether this is visible on imaging at the time or not. There is considerable argument for lymph node involvement to be reclassified as such.

Anatomical Considerations and Surgical Templates

The lymphatic drainage of the kidneys is highly variable. The retroperitoneal lymph nodes are an extensive network of lymphatics between the first and fifth lumbar vertebrae. These nodes serve as the primary landing sites for renal lymph and have unpredictable interconnections before reaching the thoracic duct. The efferent lymphatic vessels from the right kidney drain into the paracaval, precaval, retrocaval and interaortocaval nodes. From the left kidney efferent lymphatic vessels drain into the para-aortic, preaortic, retroaortic and interaortocaval nodes [16]. On both sides posterior lymphatic vessels can pass through the crus of the diaphragm and connect with the thoracic duct without passing through any lymph nodes.

Crispin et al. reported on 169 consecutive high risk patients who underwent LND at the time of radical nephrectomy in a single institution. Of these 169 patients 64 (38%) had lymph node metastases. All patients with nodal metastases had involvement of the primary lymphatic landing sites for each kidney. Of the 64 patients with nodal involvement 29 (45%) had no metastases identified in the perihilar lymph nodes. No patient with a right sided tumour had involvement of the para-aortic nodes without involvement of the other retroperitoneal nodes and no patient with a left-sided tumour had involvement of the paracaval nodes without involvement of the para-aortic or interaortocaval nodes [16].

There is no prospective study comparing limited versus extended LND in RCC for positive node detection, cancer control or surgical safety. There are no validated agreed templates for LND in RCC and most studies delineate only the presence or absence of a surgeon-related LND. Even EORTC 30881 could not inform to what extent LND should be performed since information regarding the location and number of lymph nodes removed were lacking [2]. Based on anatomical studies and indirect evidence Capitanio et al. propose for the right kidney the removal of paracaval, retrocaval and precaval nodes from the adrenal vein to the level of the inferior

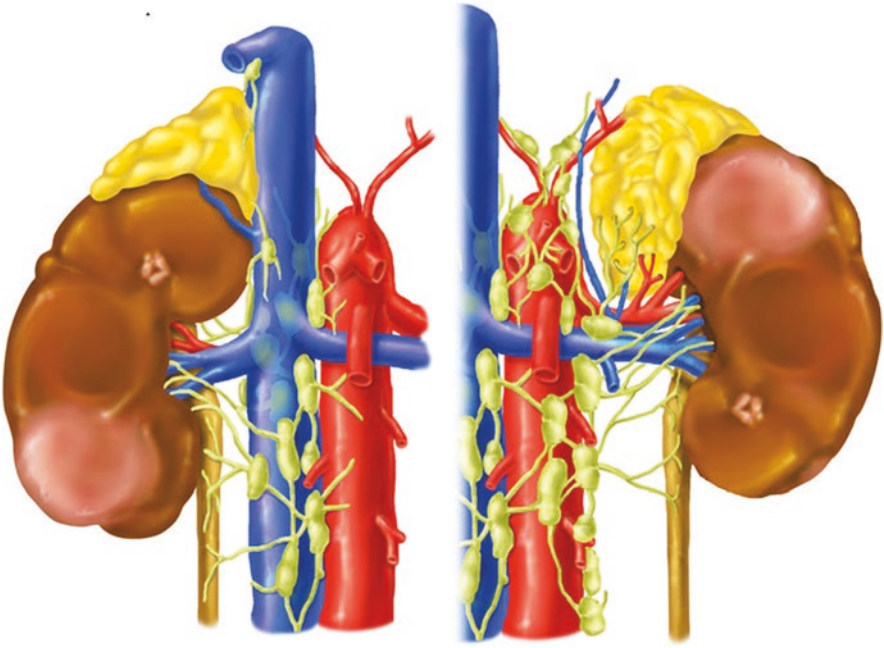

Fig. 1 LND might include, on the right side, para-, retro- and precaval nodes from the adrenal vein to the level of the inferior mesenteric artery. On the left, para-aortic and preaortic nodes from the crus of the diaphragm to the inferior mesenteric artery should be removed. Interaortocaval nodes should be removed as well when extended LND is sought. With permission from: Capitanio U, Leibivich BC (2017) The rationale and the role of lymph node dissection in renal cell carcinoma. World J Urol 35:497–506

mesenteric artery. For the left side the para-aortic and pre-aortic nodes from the level of the crus of the diaphragm to the inferior mesenteric artery should be removed. The interaortocaval nodes should also be removed for both left and right sided tumours if an extended LND is sought [10]. (See Fig. 1).

Salvage Lymph Node Dissection

Isolated regional lymphadenopathy during the follow up after surgery for RCC presents a dilemma due to lack of data in support of observation versus resection or systemic therapy. Retroperitoneal nodal recurrences are usually associated with systemic progression and distant metastases. In this scenario surgery is seldom indicated and patients are treated with systemic therapy if appropriate. If lymph node involvement appears to be truly isolated and this is confirmed by a trial of time, then salvage LND is indicated in selected patients if technically feasible. Similar to the concept of surgical resection of a solitary metastases this may delay disease progression and defer the start time of systemic therapy in some patients.

Imaging

Clinical node status is based on cross sectional imaging with CT or MRI and palpation at the time of surgery. Cross sectional imaging is not able to detect small metastases in nodes of normal shape or size. Studer et al. showed that histologically positive nodes were found in only 42% of patients with enlarged nodes at preoperative CT, with a false negative rate of 4.1% [18]. Abnormally enlarged nodes may be due to RCC metastases, reactive change, sarcoidosis or other malignancy such as lymphoma. Radiological features such as nodal size, contrast uptake, lack of hilar fat and restricted diffusion on MRI may increase sensitivity and specificity of cross sectional imaging. Lymph nodes more than 2 cm in diameter are more likely to be metastatic. Positron emission tomography (PET) CT with fluorine- 18 fluorodeoxyglucose (FDG) is seldom helpful.

Sentinel node biopsy has been proposed for RCC but is hampered by the extremely variable pattern of renal lymphatic drainage. Bex et al. investigated the feasibility of intratumoural injection with a radioisotope labelled nanocolloid (Technesium 99) on the day before surgery and intra-operative scintigraphy with the use of a gamma camera. Six of 8 patients demonstrated sentinel nodes on scintigraphy [19].

Molecular and Genetic Markers

Molecular and genetic markers have the potential to replace clinical characteristics and cross sectional imaging in determining which patients if any might benefit from LND. Turajlic et al. analysed 575 primary and 335 metastatic biopsies in a landmark study of matched primary and metastatic biopsies in 100 clear cell renal cell carcinoma (ccRCC) cases. Metastatic competence was heavily influenced by chromosome complexity with chromosome 9p loss a highly selected event driving metastases and ccRCC related mortality. Distinct patterns of metastatic spread were observed, including rapid progression to multiple sites seeded by primary tumours of monoclonal structure. Lymph node metastases were characterised by poor prognosis and very frequent 9p loss (21 of 22 cases) indicating that lymphatic and haematogenous spread require comparable metastatic competence [20]. These findings are consistent with the frequent presentation of lymph node metastases with visceral metastases and lack of proof of therapeutic benefit of LND in RCC.

Lymph Node Dissection in Upper Tract Urothelial Carcinoma

Upper tract urothelial carcinoma (UTUC) is a rare malignancy with a poor prognosis comprising 5–10% of urothelial malignancies. Lymph node dissection (LND) in the surgical management of muscle invasive urothelial carcinoma of the bladder is

well-established but the role of LND in UTUC is controversial due to a lack of high quality evidence. The potential lymphatic drainage covers a wide area and is dependent on the laterality, the site, and the extent of the disease. Templates for LND in UTUC are not universally defined or validated. LND provides the most accurate staging tool for UTUC. The existing data consists mainly of retrospective level 3 evidence indicating improved staging and potential improved survival for some patients, particularly those with muscle invasive or locally advanced disease. Despite this the uptake of LND in UTUC by urological surgeons remain low outside of a specialist centres [21].

The EAU guidelines for treatment of UTUC updated in 2017 state that LND is not required for pTa and pT1 disease due to the low incidence of nodal involvement in superficial disease, with lymph node involvement of 2.2% for T1 versus 16% for T2–4 tumours [22]. The likelihood of lymph node involvement is directly related to T stage and likely to be under reported in retrospective data. It is often not possible to accurately stage patients pre-operatively with imaging and limited tissue biopsies provided by ureterorenoscopy. The guidelines state that it is not possible to standardise the indications or templates for LND.

The lymphatic drainage varies greatly for the renal pelvis and the different segments of the ureter. The potential wide area for LND could contribute to an unacceptable increase in perioperative morbidity. Matin et al., following on from the work of Kondo et al., performed a mapping study of lymph node metastases in UTUC [23, 24]. Matin et al. showed that upward migration of lymphatic metastases from UTUC of the distal ureter to the paracaval and para-aortic regions and downward migration from mid ureter to the iliac nodes were common events. Templates for LND in UTUC as proposed by Kondo et al. and Matin et al. are illustrated in Fig. 2.

Standardised dissection templates based on tumour location may improve lymph node yield and need to be evaluated for safety and potential clinical benefit, preferable in multi-centre prospective trials. Until such data and accompanying guidelines are available the utilisation of LND in UTUC will remain highly variable and at the discretion of local units and surgeons.

Key Points

- Lymphatic drainage from the kidneys is highly variable
- No role for LND in low risk localised disease
- LND can provide valuable staging information in intermediate and high risk cases
- Lymph node involvement usually signifies metastatic disease and carries a poor prognosis
- Some high risk patients may benefit from LND

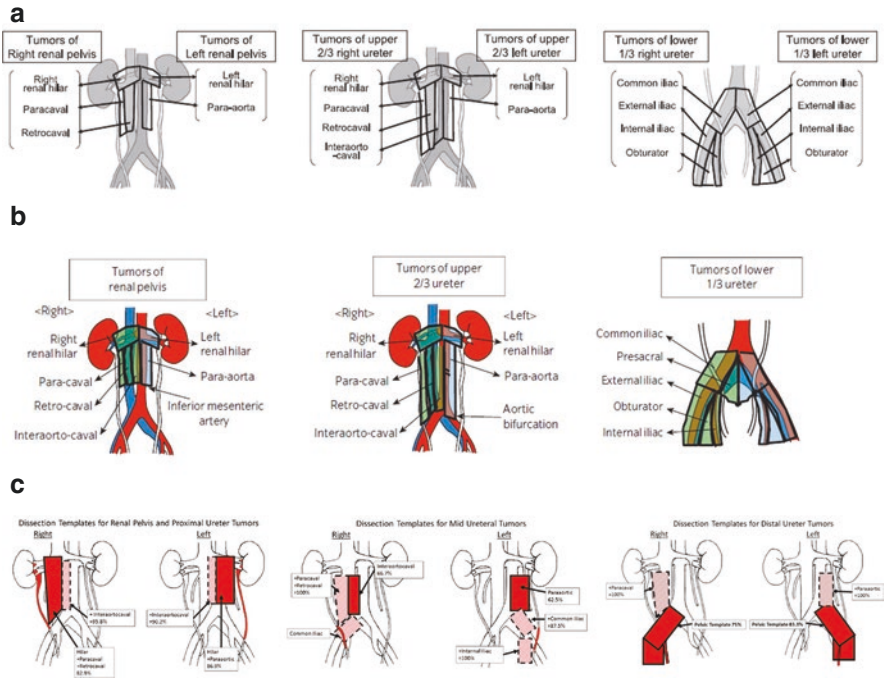

Fig. 2 Comparison of lymph node dissection templates according to tumor location between Kondo et al. (**a**, **b**) and Matin et al. (**c**). With permission from: Seisen T, Shariat SF, Cussenot O, Peyronnet B, Renard-Penna R, Colin P et al. (2017) Contemporary role of lymph node dissection at the time of radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol 35: 535–548

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