Assessing lymph node status in patients with kidney cancer

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Abstract: Accurate detection of lymph node involvement on pre-operative imaging in patients diagnosed with renal cell carcinoma (RCC) is critical for determination of disease stage, one of the most significant prognostic factors in RCC. The presence of lymph node involvement in RCC doubles a patient's risk of distant metastasis and significantly reduces their 5-year survival. Currently, lymph node involvement in patients with RCC is evaluated with numerous modalities, with rapid advancements occurring across these modalities. The purpose of this study was to evaluate the advantages and disadvantages of each modality and utilize sensitivities and specificities to determine the highest performing modalities for accurate lymph node involvement in renal cancer. A comprehensive computer-based literature search of full-length original research English language studies of human subjects with biopsy-proven RCC was performed to evaluate publications on the diagnostic performance of color Doppler sonography (CDS), magnetic resonance imaging (MRI), lymphotrophic nanoparticle enhanced MRI (LNMRI), multidetector-row computed tomography (MDCT), F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET), and PET/ CT for evaluation of lymph node status in kidney cancers in articles that were published prior to May 2018. Limited studies were available for evaluating CDS performance for determination of lymph node involvement in renal cancer. While CT is the most common modality for nodal staging, due to its availability and relatively low expense, it did not demonstrate the highest performance of the modalities examined for determination of lymph node status in patients with RCC. Of the modalities examined, MRI demonstrated the highest sensitivity (92-95.7%) for detection of lymph node involvement in RCC. Studies of lymph node involvement in RCC using both MRI and CT indicated that using the current diameter criteria (greater than 1 cm) for determination of positive lymph nodes should be re-evaluated as micro-metastases are frequently overlooked. Studies evaluating lymph node involvement with FDG-PET had the highest specificity (100%), indicating FDG-PET is the preferred modality for confirming lymph node involvement and extent of involvement. However, due to the low sensitivity of FDG-PET, clinicians should be skeptical of negative reports of lymph node involvement in RCC patients. Further studies examining determination of lymph node involvement in renal cancer across modalities are greatly needed, current literature suggests utilizing a combination of MRI and FDG-PET may offer the highest accuracy.

Keywords: Imaging; kidney cancer; metastatic lymph node; renal cell carcinoma (RCC)

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Introduction

Kidney cancer represents nearly 5% of all newly diagnosed cancers, resulting in 209,000 new cases and approximately 102,000 deaths annually worldwide (1). Renal cell carcinoma (RCC), arising from epithelial tissue, is the most common type of kidney cancer, responsible for 85% of all renal cancer and its incidence has been increasing (2,3). Due to its prevalence, our examination of lymph node involvement in renal neoplasms was limited to RCC. RCC is an umbrella term which includes multiple subtypes (i.e., clear cell, papillary types I and II, and chromophobe), which all differ in their aggression and ultimately treatment course (2,4). Currently, RCC is managed surgically, through partial nephrectomy or local ablative therapies, with the patients exhibiting lymph node infiltration additionally undergoing a regional lymphadenectomy (1,5). Furthermore, RCC frequently metastasizes, with 18% of patients presenting with metastases at diagnosis and 50% of patients developing metastases following surgical nephrectomy. Of the subtypes, clear cell RCC, the most common subtype, demonstrates the highest risk of metastases, with more than 90% of metastatic RCC being of the clear cell subtype (1,6).

RCC is currently staged using the Robson Classification and the TNM Classification from the International Union against Cancer (UICC). The TNM Classification is more specific than the Robeson Classification using preoperative imaging to determine invasion and metastasis (7). The classification systems are compared in *Table 1* (7,8). Determination of lymph node (LN) involvement, a poor prognostic factor, is critical to determining TNM classification, as it greatly influences long-term survival. The presence of LN involvement increases the incidence of distant metastasis by 50%. Moreover, patients without LN involvement (N0) have a 5-year estimated survival of greater than 50%, while patients with LN involvement (N1, N2) have an estimated 5-year survival of 5–38% (7,9-11).

Pre-operative imaging has the greatest influence on determining treatment course, as tumor diameter and disease stage are the most important prognostic factors in RCC (12). Accurate determination of LN involvement is therefore critical to patient treatment course, pre-surgical counseling, and surgical planning (7,12-14).

With rapid advancements in multiple imaging modalities used to visualize RCC (9), the purpose of this study was to evaluate the advantages and disadvantages of each modality and determine the best modality for accurate detection of LN involvement in renal cancer rather than focusing on LN staging.

Evidence acquisition

A comprehensive computer-based literature search of English language studies of human subjects was performed to evaluate publications on the diagnostic performance of ultrasound (US), magnetic resonance imaging (MRI), lymphotropic nanoparticle-enhanced MRI (LNMRI), multidetector-row computed tomography (MDCT), F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) and PET/CT to evaluate LN status in kidney cancers. Google Scholar and MEDLINE/PubMed were used to identify relevant literature. Our search keywords consisted of: ("kidney cancer" or "renal cancer" or "renal cell carcinoma" or "renal carcinoma") and ("lymph node" or "nodes" or "lymphatic drainage" or "lymph node metastasis" or "node metastasis" or "node infiltration" or "lymphatic involvement" or "nodal metastasis" or "lymph node staging" or "lymph node status" or "lymph node TNM" or "TNM staging" or "Robson classification") and ("ultrasound" or "US" or "Color Doppler sonography" or "CDS" or "lymph node imaging" or " CT scan" or "CAT" or "MRI" or "PET" or "PET/CT" or "positron-emission tomography" or "FDG" or "2-fluoro-2deoxy-D-glucose" or "FDG-PET" or "MR imaging" or "magnetic resonance imaging" or "LNMRI" or "lymphotropic MNP" or "lymphotropic nanoparticleenhanced MRI"). This extensive review article includes articles published from 1985 to May 2018.

Only studies using US, MDCT, MRI, LNMRI, FDG-PET and PET/CT to asses LN involvement in patients with biopsy-proven kidney cancer were included in the study. The exclusion criteria were non-English language studies and studies of non-human subjects. Furthermore, all case reports, meta-analysis, review articles, and abstracts were excluded from this study.

Author names, year of publication, number of patients, number of involved LNs, technical details of imaging studies, criteria for positive LN, interpreter(s) and evidence for reference standard were noted. Sensitivity (SN) and specificity (SP) for each article were noted. If these values were not reported, they were calculated by using false positive, false negative, true positive, and true negative values.

Evidence synthesis

After an extensive computer search, 150 relevant articles were selected. After reviewing the titles and abstracts of the studies, 59 articles were potentially eligible to be included in this study. All 59 articles were reviewed in full and 10 articles were selected according to our eligibility criteria for final analysis.

Color Doppler sonography (CDS)

Doppler sonography is widely available and frequently used for the detection of urologic disease (15). CDS is an inexpensive and non-invasive method to evaluate LN infiltration. However, the use of CDS is limited by poor imaging quality in patients with obesity or in instances when the study site is covered by bowel gas (9,16). Moreover, the quality of CDS is dependent on the physician's skill level. Our literature review only identified a single study examining LN involvement in RCC using CDS. This prospective study of 60 patients with RCC, detected 5 positive LN, later confirmed by histopathology report, providing a SN of 100% (*Table 2*) (16).

CT scan

CT scan is the most commonly used method for nodal staging due to its availability, low expense, and high accuracy (72–90%) (7,17). Advancements in CT technology

 Table 1 Correlation of Robson and TNM staging in renal cell carcinoma

Robson	TNM	Disease status
I	T1	Tumor limited to kidney (≤7 cm)
	T2	Tumor limited to kidney (>7 cm)
II	T3a	Tumor invades to renal vein or fat but not beyond Gerota's fascia
IIIA	T3b	Tumor extends to vena cava
IIIB	N1-N2	Tumor spreads to regional LN
IIIC	T3b, N1–N2	Tumor spreads to regional LN and veins
IVA	T4	Tumor invades beyond Gerota's fascia
IVB	M1	Distant metastases

LN, lymph node.

and the introduction of MDCT, with thin slice collimation and fast acquisition, provides an accurate representation of LN size and shape and the detailed anatomy surrounding organs (Figure 1) (12,18). On CT, a short axis diameter greater than 1 cm, shape and enhancement are the determining factors used to identify a positive LN (8,12,19-21). However, these criteria are one of the disadvantages of CT scans because micro-metastases in LN less than 1 cm may be overlooked. Moreover, in one study, 58% of patients with enlarged LN (>1 cm) had reactive hyperplasia, not positive LN (19). The reported SN and SP of conventional CT scan, ranged from 60-100% (median 83%) and 75–98.1% (median 88.5%) respectively (Table 3) (16,19,20,22,23). However, the SN and SP of MDCT ranged from 75-77% (median 76%) and 75-82% (median 78.5%), respectively (Table 3) (12,21).

MRI

MRI provides an excellent anatomical view due to high soft-tissue contrast resolution. However, in conventional MRI the only criteria used to identify positive LN's is the size (diameter greater than 1 cm) (Figure 2). Therefore, MRI cannot differentiate reactive enlarged LN from metastatic nodes or micro-metastases in nodes less than 1 cm (7,9,17). In recent years, use of lymphotropic nanoparticle-enhanced MRI (LNMRI), which uses lymphotropic magnetic nanoparticles (MNP) with the monocrystalline superparamagnetic iron core, has aided physicians in the detection of metastatic nodes through utilization of additional characteristics, such as heterogeneity, hyper-intensity, and single-intensity of LN. One LNMRI study reported that SN and SP for positive node detection were 100% and 95.7%, respectively (24). Comparatively, a conventional MRI study reported the SN and SP of 100% and 92%, respectively (Table 4) (23).

PET scan

FDG-PET is an established and commonly used imaging modality for cancer assessment. FDG-PET provides

Table 2 Sensitivity and specificity for metastatic lymph node detection in a published ultrasound study

Study	Year	No. of patients	Transducer type, frequency (MHZ)	Criteria for positive LN	Interpreter(s)	Reference standard	LN number	SN (%)	SP (%)
Saphn <i>et al.</i> (16)	2001	60	Convex probe, 3.5	-	One urologist	HP report	-	100	-

LN, lymph node; SN, sensitivity; SP, specificity; HP, histopathology.

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Figure 1 Twenty-six-year-old male with left renal cell cancer, papillary type II (arrow) and ipsilateral retroperitoneal enlarged lymph nodes (arrowheads) in the axial post contrast computed tomography (CT).

functional information rather than detailed anatomic features based on increased FDG tracer uptake within lesions, easily visualized due to the increased metabolic activity of most malignant lesions (25). Therefore, it can be a useful tool in evaluating metastatic lesions. However, inconsistencies in tumor uptake and lack of detailed anatomical views requires physicians to utilize conventional imaging modalities to accompany PET scans (Figure 2) (17,22,25,26). FDG-PET has a high SP in detection of distant metastases, but low SN (high false negativity) (25). In our search of the literature, we found three articles that reported the SN and SP of detecting metastatic LN using FDG-PET. In these articles, the SN ranged from 75 to 87% (median 77%) and a SP of 100% in patients with RCC (Table 5) (22,25,27).

Metastatic nodes

Presence of metastatic LN in patients with RCC is a poor prognostic factor and results in a lower 5-year survival (11). In addition, detection of positive LN is critical to the determination of treatment course and overall tumor stage. Clarification of the best imaging modality for the detection of metastatic nodes on pre-operative imaging is important to avoid missing patients with metastases or increasing the burden of unnecessary work-ups in patients lacking metastases. Detection of metastatic nodes is usually based on dimensional thresholds, with LNs less than 8-10 mm in diameter considered negative (28). In two studies in patients with bladder and prostate cancer, 25% of patients who had normal size LN were diagnosed with positive LNs during the surgery (29,30).

Lable 5 Sensitivity a.	nd specif.	Icity for me	tastatic lymph node	detection in seven pr	IDIIShed co	omputed tomography	v studies					
Study	Year	No. of patients	Detector rows × collimation (mm)	Intravenous contrast (dose)	Imaging plane	Section thickness (mm), gap (mm)	Criteria for positive LN	Interpreter(s)	Reference standard	LN number	SN (%)	SP (%)
Nazim <i>et al.</i> (12)	2010	88	– × 0.5	1	ı	-, 0.5	LN >1 cm	One investigator	HP report	39	77	82
Türkvatan <i>et al.</i> (21)	2008	37	16 × -	lodinated contrast (320 mgl/mL)	Axial	5, –	LN >1 cm	Two radiologists	HP report	57	75	75
Kang <i>et al.</i> (22)	2004	82	I	I	I	l Î	LN >1 cm in short axis	I	HP report	I	92.6	98.1
Spahn <i>et al.</i> (16)	2001	60	I	Yes (-)	I	10, –	I	One radiologist	HP report	I	100	I
Constantinides <i>et al.</i> (23)	1991	47	I	I	I	I	I	I	HP report	27	60	85
Studer <i>et al.</i> (19)	1990	163	I	I	Axial	ľ	LN >1 cm	I	HP report	I	78.2	82.1
Johnson <i>et al.</i> (20)	1987	97	I	Yes (–)	I	10, 10	LN >1 cm	I	HP report	I	83	88
LN, lymph node; SN	l, sensitiv	/ity; SP, sp(ecificity; HP, histopa	ithology.								

	No. of Patients	Field strength (T), coil type	Intravenous contrast (dose)	Sequence (s)	Imaging plane	Section thickness (mm), gap (mm)	Criteria for positive LN	llnterpreter(s)	Reference standard	LN number	SN (%)	SP (%)
Guimaraes 2008 et al. (24)	თ	1.5, phased array body coil	MNP (2.6 mg)	T1, T2, T2w	Axial, coronal	°. S	Node with: (I) heterogeneous signal intensity; (II) discrete area of hyper intensity; (III) peripheral decrease in signal intensity	Two radiologists	HP report	3	100	95.7
Constantinides 1991 <i>et al.</i> (23)	47	I	I	I	I	I	I	I	HP report	27	100	92

Tadayoni et al. Lymph node assessment in RCC patients

In our review article, we have noticed that there is just one study on CDS for assessing LN in patients with RCC. The SN (100%) was high; however, the SP was not reported. CT, routinely used for tumor staging, had lower SN (median 78.2%) and SP (median 83.5%) than two different studies on MRI, which had a reported SN of 100% and median SP of 93.9%. Additionally, between MRIs the SP of LNMRI was higher than conventional MRI with gadolinium. It appears that FDG-PET had the highest SP (100%) for detection of metastatic nodes; however, it presented with a sub-optimal SN (median 77%) optimal (12,16,19-25,27).

Future directions

Overall, our review indicated FDG-PET had the highest SP compared to other modalities. Thus, PET can be used to confirm metastatic LNs. However, due to the low SN (high false negativity) of this modality, physicians should be skeptical of FDG-PET reports that are LN negative in patients with RCC (22,25,27). On the other hand, MRI has a very high SN, allowing physicians to rely on negative results and use MRI to rule out LN involvement (23,24). Overall, we recommend these two methods can be combined as a hybrid PET/MRI modality for detecting metastatic LNs. The other advantage of this hybrid modality is providing both the detailed anatomy of MRI and functional information of PET.

As we mentioned before, the criteria for metastatic LN detection is a cut-off-point of 1cm in short axis diameter in CT-scan studies which is non-specific and can be seen in non-metastatic enlarged inflammatory LNs (12,16,19-22). Thus, establishing new RCC subtype-specific size cut-offs might be helpful to differentiate benign from metastatic LNs with higher accuracy.

Additionally, MRI had a high SN but lower SP for malignant LN detection (23,24). In a DWI-MRI study on patients with prostate cancer, the apparent diffusion coefficient (ADC) value was significantly lower in malignant LNs compared to benign LNs (P<0.0001). As a result, the ADC value was reported as a marker to discriminate benign from malignant LN in the patient with prostate cancer (31). To the best of our knowledge, there is no publication using DWI-MRI for LN differentiation on RCC patients. Thus, future studies can focus on DWI-MRI to increase the capability of MRI for positive LN detection in the patient with RCC.



Figure 2 Twenty-year-old male with medullary renal cell carcinoma (arrow) in lower pole of right kidney (A) and ipsilateral retroperitoneal T2-hyperintense enlarged lymph nodes (arrow) on axial T2-weighted magnetic resonance imaging (MRI) (B). Axial post contrast T1-weighted MRI shows the same lymph nodes (arrow) with the rim enhancement and central necrosis (C). Positron emission tomography scan shows the intense fludeoxyglucose (FDG) of the same lymph nodes (arrow) (D).

Table 5 Sensitivity and specificity for met studies	astatic lymph node detection in three published F-fluoro-2-deoxyglucose positron emission tomography
Time of	EDG does time

Study	Year	No. of patients	Time of fasting before scanning	FDG dose, time interval between agent administration and scanning	lmaging plane	Criteria for positive LN	Interpreter(s)	Reference standard(s)	LN number	SN (%)	SP (%)
Kang <i>et al.</i> (22) 2004)	90	_	–, 45 min	_	Increase in metabolic activity (inconsistent with inflammation)	Nuclear medicine physician	HP report	-	75	100
Majhail et al. (25) 2003	24	Over night	395.9 mBq, 45–60 min	_	Scored as positive or negative for each site of suspected metastases identified by CT/ MRI	Two Nuclear medicine physicians	HP report	11	77	100
Safaei <i>et al.</i> (27	2002	20	-	-, -	-	-	-	HP report	25	87	100

LN, lymph node; SN, sensitivity; SP, specificity; FDG, F-fluoro-2-deoxyglucose; CT, computed tomography; MRI, magnetic resonance imaging; HP, histopathology.

Conclusions

Pre-operative LN status in patients with RCC is traditionally evaluated using CT and MRI studies (28). However, our comprehensive review indicates that while MRI has the highest SN and is useful for evaluating the absence or presence of LN involvement, FDG-PET has the highest SP and is useful for confirming involvement and extent of disease. Utilization of a combination of modalities, the establishment of new cut-off points for LN involvement in CT and MRI, and use of new techniques, such as the incorporation of diffusion-weighted imaging (DWI), should improve our capability to accurately detect LN involvement in RCC patients. In conclusion, there is a capability to differentiate malignant from benign LNs in RCC patients with higher accuracy through the use of new techniques, a combination of modalities, or new cut off point interoperations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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