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Role of diffusion-weighted MRI for prediction of regional lymph node positivity in radiologically organ-confined renal tumour: a prospective study

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Abstract

Background: Lymph node metastasis is one of the major factors that decide the prognosis of renal cell carcinoma. Presently, lymphadenectomy is only accepted as the most precise and dependable staging method to detect lymph node invasion; still, its therapeutic value for renal cell carcinoma is controversial. Diffusion-weighted magnetic resonance imaging along with its apparent diffusion coefficient value has already shown great value as a non-invasive modality to detect early microstructural changes in various human tumours. The present study is done to know the role of DWMRI in determining regional lymph node positivity in radiologically organ-confined renal cell carcinoma.

Methods: In this prospective study, we measured the ADC value of renal mass and regional lymph node in patient of RCC. ADC value < 1.25 is taken as cut-off to determine lymph node involvement. A malignant lymph node was confirmed by histopathology postoperatively. After that, we analysed the data retrospectively and studied the association between cut-off ADC value and lymph node positivity.

Results: Total 44 patients of RCC were evaluated in the study. Out of 44 patients, lymph node was found to be malignant on histopathology in 25 (56.8%) patients, and of these, 23 patients had ADC value < 1.25. This association was statistically significant ($p < 0.05$). The findings of DW MRI were accurate in 72.7% of patients with sensitivity of 63.1%, specificity of 80% and positive predictive value of 70.5%.

Conclusions: Lymph node with ADC value $< 1.25 \times 10^{-3}$ mm^2/s has higher probabilities of harbouring malignant cell, so ADC value of DWMRI can be used as a sensitive and specific parameter to differentiate malignant lymph node from benign lymph node. However, our futuristic observation needs to be validated by multi-institutional large sample cohort.

Keywords: Renal cell carcinoma (RCC), Magnetic resonance imaging (MRI), Diffusion-weighted magnetic resonance imaging (DWMRI), Apparent diffusion coefficient (ADC)

1 Background

Renal cell carcinoma accounts for 2–3% of all adult malignant neoplasms [1] and most common soft tissue mass and accounts for 85% of all malignant masses of the kidney. The behaviour of RCC depends upon its subtype, staging and Fuhrman grade. Precise prediction of the subtype and stage may be helpful for planning

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appropriate surgical modality namely radical nephrectomy, adrenal sparing nephrectomy or nephron-sparing nephrectomy. Renal cell carcinoma metastasizes by both blood and lymphatic routes. Regional lymphadenectomy has been proposed as a method of improving the results of surgical therapy [2]. Lymph node dissection has resulted in the detection of nodal metastasis in 7.5–22.5% of patients, who have no other evidence of metastatic disease and there is little doubt about the value of regional lymph node dissection as a staging procedure [3]. Lymph nodal involvement is one of the major factors influencing the prognosis of RCC. However, the therapeutic value of lymphadenectomy for renal cell carcinoma is still controversial [4]. Moreover, there is no biomarker to predict which patient harbours malignancy in regional nodes requiring lymph node dissection.

Currently, CT scan and standard MRI are used for evaluation of patients with RCC to determine tumour localization, size, tumour thrombus extent and lymph node metastasis. Nazim et al. conducted a study to determine the accuracy of multidetector CT scan in staging of RCC and they found, the specificity of CT for detecting nodal was 82% [5].

According to Sphan et al., the sensitivity of colour duplex sonography in detection of RCC and lymph node metastasis is comparable to that of CT with being advantage of lower exposure to radiation and less expensive [6].

A pilot study presented by Guimaraes AR demonstrated that use of lymphotropic nanoparticle-enhanced MRI for assessing lymph node in renal cell cancer has high sensitivity (100%) and specificity (95.7%) [7].

In recent past years, various studies have been done to evaluate the accuracy of DWMRI in determining the regional lymph node spread in different malignancies like cervical, uterine, breast, prostate, penis, cervical and uterine cancer. According to these studies, the DWMRI has higher sensitivity and specificity in determining lymph node positivity in comparison to other diagnostic modalities like USG, CT scan and standard MRI [8–13].

With this background, this study is designed to verify the role of DWMRI (apparent diffusion coefficient—ADC value) in determining regional lymph node positivity in patient with radiologically organ-confined renal tumour.

2 Methods

This prospective study was conducted between April 2018 and October 2019 in the Department of Urology and Renal Transplant, Gauhati Medical College & Hospital, Guwahati, Assam, India after obtaining approval from institutional Ethical committee. A written informed consent was taken from all patients.

2.1 Case definition

Among genitourinary cancer, RCC has highest mortality rate because early clinical symptoms of RCC are non-specific and diverse. Only 10% of RCC present with classic triad of haematuria, pain and flank mass. More than 40% of patients have no symptom at the time of presentation. More than 60% of RCC are incidental finding [14].

2.2 Radiological staging of RCC (TNM staging 8th) [15]

- T–T1
  - T1a: tumour confined to kidney, < 4 cm
  - T1b: tumour confined to kidney, > 4 cm but < 7 cm
- T2: limited to kidney > 7 cm
  - T2a: tumour confined to kidney, > 7 cm but not > 10 cm
  - T2b: tumour confined to kidney, > 10 cm
- T3: tumour extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota's fascia
  - T3a: tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond the Gerota's fascia
  - T3b: spread to infra diaphragmatic IVC
  - T3c: spread to supra diaphragmatic IVC or invades the wall of the IVC
- T4: involves ipsilateral adrenal gland or invades beyond Gerota's fascia

N

- N0: no nodal involvement
- N1: metastatic involvement of regional lymph node(s)

M

- M0: no distant metastases
- M1: distant metastases

Stage groupings

- Stage I: T1 N0 M0

- Stage II: T2 N0 M0
- Stage III: T3 or N1 with M0
- Stage IV: T4 or M1

2.3 Inclusion criteria

All patients who presented with presumed diagnosis of organ-confined solid renal neoplasm by imaging like ultrasound and CT scan.

2.4 Exclusion criteria

1. Patients with locally advanced (T4) and metastatic (M1) renal tumour.
2. Patients who were unfit for MRI.

A total of 44 consecutive patients were enrolled in the study. All patients were examined with DWMRI for renal tumour and regional lymph node. After work-up, patients were treated with radical nephrectomy and regional lymphadenectomy. After regional lymphadenectomy, all obtained lymph nodes were described in terms of number, size of largest node and any gross feature and submitted for histology. Lymph nodes were fixed overnight in Carnoy's solution before sectioning. Multiple sections were taken if size of lymph node was less than 5 mm and in large lymph node grossly involved by tumour only one section was submitted for examination and remaining node was saved for resampling if necessary. Any correlation between the findings of ADC value of lymph node and histopathological findings of dissected lymph node were analysed.

MRI was performed with the patient in the supine position, using a 1.5 T MR scanner equipped with an 8-channel phased array body coil for the signals. The following routine sequences were acquired: transverse breath-hold T1-weighted in-phase and opposed-phase sequences, transverse and coronal breath-hold T2-weighted sequence and transverse 3D fat-suppressed T1-weighted interpolated spoiled gradient echo (volumetric interpolated breath-hold examination [VIBE]) sequence. Before the administration of gadolinium, a single shot echo planar DWI sequence was acquired.

The ADC was manually calculated by setting a region of interest (ROI) within the tumour image. In our study, ROI was to assess the ADC value of regional lymph node either less than 1 cm or more than 1 cm in size. In our study, we analysed the ADC value of renal mass, regional lymph node, histopathology of renal mass and lymph node positivity. Finally, we assessed the correlation of ADC value of lymph node with lymph node positivity for malignant cell.

The association between variables was assessed using Chi-square/Fisher exact and *t* test. ROC analysis was performed to predict the cut-off ADC value of regional lymph node. A p value of < 0.05 was considered significant. All these statistical analyses were done using SPSS version 21.0.

3 Results and observation

A total 44 patients were included in this study. Age groups ranged from 30 to 84 years with a mean age of 56.4 years. The largest numbers of patients were in the age group of 50–59 (14, 31.8%). 32 patients (72.2%) were males (mean age 58.59 ± 11.5), while 12 patients (27.9%) were females (mean age 50.58 ± 13.2) and male:female ratio was 2.66:1.

The best cut-off value to detect lymph node positivity based on lymph node ADC value is 1.25. DWI of lymph node showed an area under the ROC curve (AUC) of 0.716, standard error (SE) − 0.080; 95% confidence interval (CI)—(0.558–0.873) on right side (Table 1 and Fig. 1).

Cut-off ADC value of lymph node < 1.25 was found in 20 patients out of 25 patients with malignant lymph nodes and cut-off ADC value < 1.25 was found in 7 patients out of 19 patients with negative lymph nodes (Table 2 and Fig. 2).

Table 2 shows that out of 25 patients with malignant lymph nodes, 14 patients had lymph node < 1 cm in size (11 patients with < 1.25 ADC value and 3 patients with > 1.25 ADC value) and 11 patients had lymph node > 1 cm in size (9 patients with < 1.25 ADC value and 2 patients with > 1.25 ADC value). In study population, ADC value of lymph node < 1.25 was found in 20 patients out of 25 patients with malignant lymph nodes, 14 patients had normal-sized lymph nodes, when these variables were significantly associated, difference was observed ($p = < 0.05$). We also noticed that of 19 patients with negative lymph nodes, 18 patients had lymph node < 1 cm in size (6 patients with < 1.25 ADC value and 12 patients with > 1.25 ADC value) and 1 patient had lymph node > 1 cm in size (< 1.25 ADC value) hence no significant difference was observed ($p = 0.179$) (Table 2 and Fig. 3).

Table 1 ROC curve based on lymph node ADC value

Area	SE[a]	Asymptotic sig[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
.716	.080	.015	.558	.873

Area under the curve

Test result variable(s): node

[a] Under the nonparametric assumption

[b] Null hypothesis: true area = 0.5

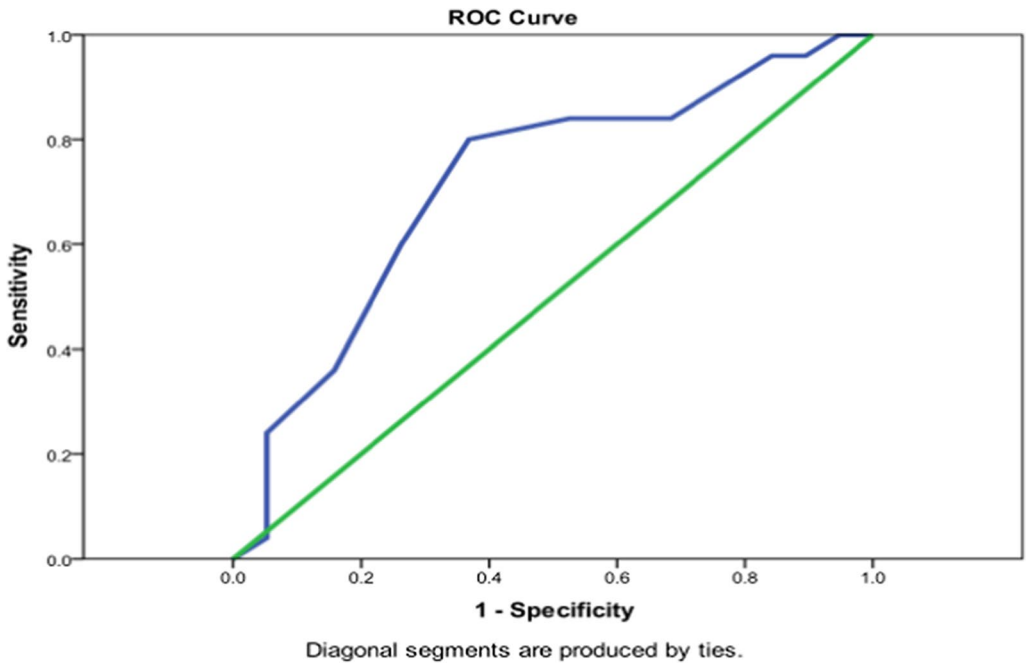

Fig. 1 ROC curve based on lymph node ADC value

Table 2 Relationship of lymph node cut-off ADC value and size of lymph node with lymph node positivity

Lymph node	Node size	ADC < 1.25	ADC > 1.25	Total
Negative	< 1	6	12	18
	> 1	1	0	1
	Total	7	12	19
Positive	< 1	11	3	14
	> 1	9	2	11
	Total	20	5	25

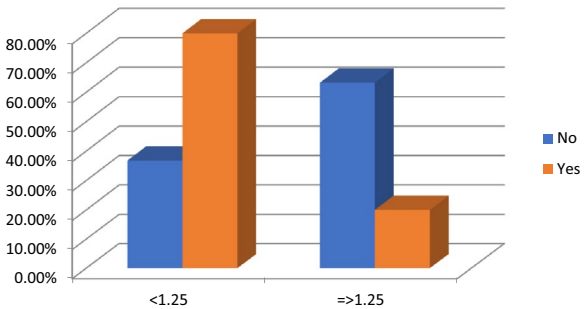

Fig. 2 Relationship of lymph node positivity and lymph node cut-off ADC value

Figure 4 shows the T2 weighted MRI films of 64-year-old female with clear cell RCC of right kidney (stage 2A, grade 2) at different levels. In this patient, ADC value of regional lymph node was 1.04×10^{-3}mm^2/s.

Figure 5a shows intraoperative picture taken during retroperitoneal lymph node dissection of same patient showing bare major blood vessels after removing lymph nodes. Figure 5b shows histopathological picture of lymph node removed during surgery showing malignant involvement.

In the present study, ADC value of 1.25×10^{-3}mm^2/s was used as a cut-off for differentiating benign from malignant lymph nodes, the results were found to be accurate in 72.7% of patients with sensitivity of 63.1%, specificity of 80% and positive predictive value of 70.5% (Table 3).

4 Discussion

Clear cell carcinoma is the most common subtype; accounting for approximately 70% of RCCs and in our study, incidence of clear cell carcinoma was 63.6% [16]. Papillary renal carcinomas, the second most common subtype, comprise 10% to 15% of RCCs and in our study, it was 15.9% [17].

MRI is considered a useful tool for imaging solid renal mass and equivocal lesions and also for post-treatment follow-up [18]. DWMRI is widely used in almost all discipline tumour detection, tumour characterization and the evaluation of treatment response in patients with cancer [19]. A quantitative analysis of ADC can be used

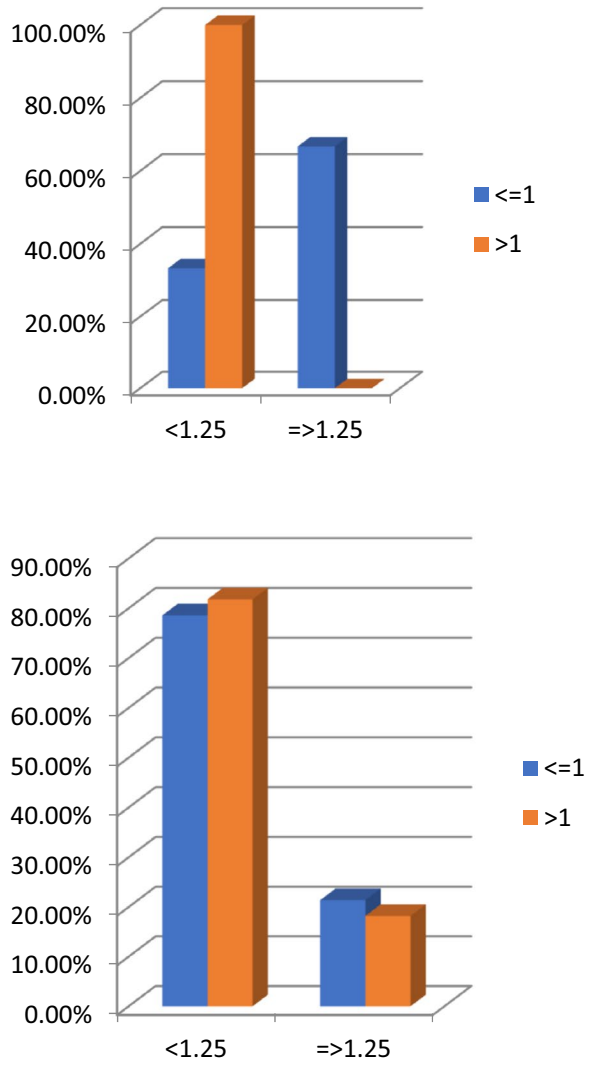

Fig. 3 Relationship of lymph node cut-off ADC value and size of lymph node with lymph node positivity

to characterize tumours and assess response to treatment [20, 21]. DWI evaluates the Brownian movement of water molecules at microscopic level, which is related to tissue microstructure, cell membrane integrity and cellularity [22].

Altering the gradient amplitude, duration and time interval *(b-value, measured in seconds per square millimetre)* between paired diffusion gradients alters the sensitivity to the degree of water motion [19, 23]. There are three principle applications of DWI for renal imaging. First, low *b*-value DW images can replace fat-saturation T2-weighted images, decreasing total examination time. Second, the long *b*-value DW images may improve renal lesion detection. And last, DWI-derived parameter (i.e. ADC values) could potentially characterize renal lesions [24]. By performing DWI using different b-values, quantitative analysis, namely, the calculation of apparent diffusion coefficient (ADC) values, is possible and the ADC values can be displayed as a parametric map (ADC map) [19]. The gradients are characterized by their b-values, which express the amount of diffusion weighting [25, 26]. Restricted water diffusion demonstrates high signal intensity on DWI and lower ADC values on ADC map [19, 23]. Malignant tissues have increased cellularity with decreased extracellular space, resulting in restriction of water diffusion and thus leading to higher signal intensity on DWI and lower ADC value.

Liu B et al. conducted a meta-analysis to compare diagnostic performance of non-invasive modalities like CT, MRI, PET with 2-FDG and DWMRI for detecting metastatic lymph node in patients with cervical cancer. Among the 4 non-invasive modalities, DWI-MRI was found to have the highest sensitivity [8].

The role of DWI and ADC values in distinguishing benign and malignant lymph nodes is limited because cellular tissues such as lymph nodes have high signal intensity on DWI regardless of their biologic behaviour [27]. There is still considerable overlap in ADC values and lymph node evaluation in clinical practice, that mandate to rely on conventional features such as shape, size and growth patterns [28].

On cross-sectional imaging, a normal lymph node usually measures < 1 cm in diameter, has a smooth, well-defined border, shows homogeneous density or signal intensity and tends to have an oval or cigar shape. Metastatic disease can change the shape of the node by infiltrating nodal tissue and expanding the nodal capsule. Thus, rounded rather than oval nodes are suspicious to harbour malignancy [29].

Lin G et al. studied the DWI for detection of pelvic lymph node metastasis in patients with cervical and uterine cancers. They analysed that the relative ADC values between tumour and nodes were significantly lower in metastatic than in benign nodes (0.06 vs. 0.21×10^{-3} mm^{-2}/s, $p < 0.001$; cut-off value 0.10×10^{-3} mm^2/s). They concluded that the combination of size and relative ADC values is useful in detecting pelvic lymph node metastasis in patients with cervical and uterine cancers [9].

Kim et al. observed that the ADC values were significantly lower in the metastatic lymph nodes than in the non-metastatic lymph nodes of cervical cancer patients. The ADC was significantly lower in the metastatic lymph nodes (0.7651×10^{-3} $mm^2/s \pm 0.1137$) than in the non-metastatic lymph nodes ($1.0021 \times 10^{-3} mm^2/s \pm 0.1859$; $p < 0.001$). Measurement of ADC values may be useful, especially for detection of small metastatic lymph nodes

compared with the limited sensitivity of CT and conventional MRI [30].

Luo N et al. studied on apparent diffusion coefficient ratio between axillary lymph node with primary tumour to detect nodal metastasis in 36 patients of breast cancers. They found that the mean ADC value of metastatic lymph nodes was significantly lower than those of benign lymph nodes (0.787×10^{-3} mm^2/s $\pm$ 0.145 versus $1.043 \times \times 10^{-3}$ mm^2/s $\pm$ 0.257; $p < 0.05$) [10].

Hasanzadeh F et al. also conducted a study on diagnostic value of diffusion-weighted magnetic resonance imaging in evaluation of metastatic axillary lymph nodes in a sample of Iranian women with breast cancer. They found that the mean ADC value of metastatic axillary lymph nodes was $0.824 \pm 0.103 \times 10^{-3}$ mm^2/s and of non-metastatic axillary lymph nodes was $1.098 \pm 0.23 \times 10^{-3}$ mm^2/s. There was statistical difference in mean ADC values between metastatic and non-metastatic axillary lymph nodes (p value < 0.001) [11].

Vallini V et al. conducted a study on carcinoma prostate to evaluate the usefulness of diffusion-weighted imaging (DWI) in patients with prostate cancer candidate to radical prostatectomy and extended pelvic lymph node dissection in 26 patients with pathologically proven prostate cancer. They observed mean fitted ADC values as $0.79 \pm 0.14 \times 10^{-3}$ mm^2/s for metastatic lymph nodes and $1.13 \pm 0.29 \times 10^{-3}$ mm^2/s in non-metastatic ones ($p < 0.0001$) [12].

In the present study, out of total 44 cases lymph nodes were found positive on histopathology, in 25 (56.8%) patients with lymph node mean ADC value of

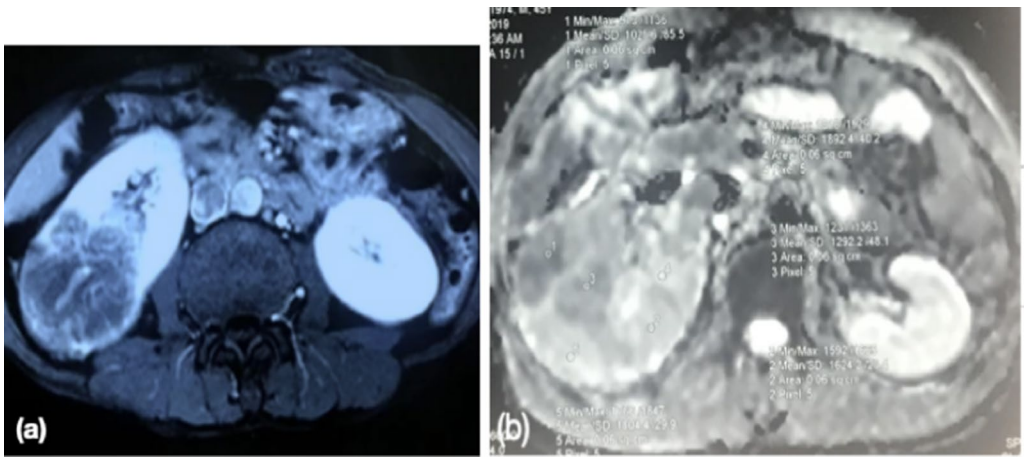

Fig. 4 **a** Transverse section of T2 weighted MRI depicts lower and mid polar right renal mass (T2bN1M0) and **b** transverse section of DW MRI (ADC map) of right renal mass (lymph node ADC value 1.04×10^{-3} mm^2/s)

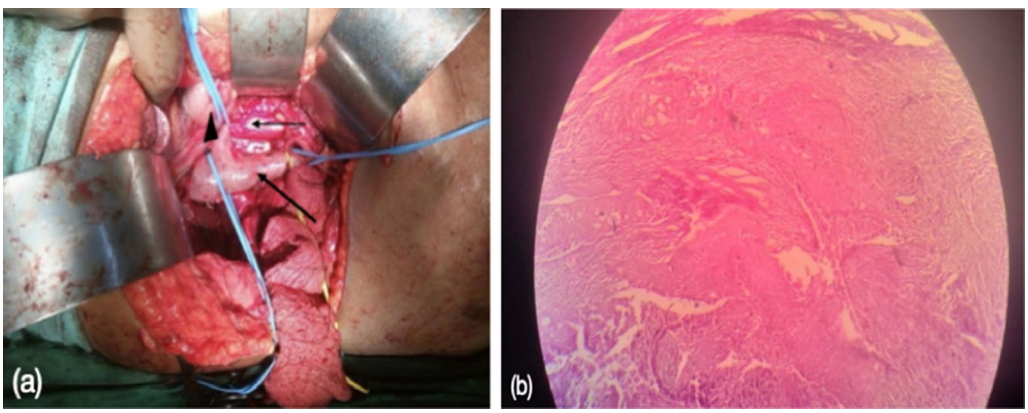

Fig. 5 **a** Bare major vessels after standard retroperitoneal lymph node dissection in case of right renal mass (T2bN1M0, lymph node ADC value 1.04×10^{-3}mm^2/s, thick arrow—inferior vena cava, thin arrow—aorta and arrow head—left renal vein) and **b** H&E staining of lymph node

Table 3 Validity of DWMRI in RCC patients

Statistics	Value (%)	95% CI
Sensitivity	63.1	38.3–83.7
Specificity	80.0	59.3–93.1
Positive predictive value	70.5	50.4–84.9
Negative predictive value	74.0	60.5–84.1
Accuracy	72.7	57.2–85.0

$1.16 \pm 0.26 \times 10^{-3}$ mm^2/s. We found that lymph nodes with lower ADC value and ADC value below the cut-off (1.25×10^{-3} mm^2/s) have higher probabilities harbouring cancerous cells ($p = 0.05$). Similar results were observed by Lin G et al., Kim et al., Luo et al., Hasanzadeh et al. and Vallini et al. studies [9–12, 30].

Si J et al. performed a study in 25 patients oral squamous cell carcinoma and compared the mean ADC value of 30 histo-pathologically proved reactive lymph nodes and 21 histo-pathologically proved metastatic lymph nodes. Their result showed significant difference between mean ADC values of reactive lymph node (1.037 ± 0.149) and metastatic lymph node (0.702 ± 0.197) [31].

He XU et al. analysed that the ADC value in positive lymph nodes was significantly lower than that with negative lymph nodes [SMD = 1.02, 95% confidence interval (CI) = 0.54–1.50, $p < 0.001$] in 687 cases with cervical tumour [32].

Barua et al. studied the primary penile tumour characteristics with DWMRI and its correlations with inguinal LN status and tumour positivity in LN dissection specimen within normal-sized LNs. In their study, primary tumour ADC ranged from 0.65×10^{-3} to 1.2×10^{-3} mm^2/s (mean: $0.87 \times 10^{-3} \pm 0.11 \times 10^{-3}$ mm^2/s). The mean ADC values for grade 1, grade 2 and grade 3 tumour were 0.89×10^{-3}, $0.82 \times 10^{-3}$and 0.80×10^{-3} mm^2/s, respectively. The ADC value of $< 0.95 \times 10^{-3}$ mm^2/s was positively correlated with pathological LN presence within normal-sized LN with mean ADC value of $0.87 \times 10^{-3} \pm 0.11 \times 10^{-3}$ mm^2/s. The mean ADC value for higher-grade and -stage tumour was low. They conclude that the ADC value of primary tumour can help in prediction of LN metastasis in carcinoma penis with clinically and radiologically normal groin [13].

According to Studer et al., enlarged (> 1 cm) nodes are not necessarily metastatic but may be reactive, i.e. false positive (58%) which may be more common in necrotic tumours or tumours that involve the renal vein [33]. In our study, also 2 patients had lymph node > 1 cm in size that was benign on histopathology.

In the present study, when an ADC value of 1.25×10^{-3} mm^2/s was taken as a cut-off for differentiating between benign and malignant lymph nodes, the results were accurate in 72.7% of patients with sensitivity of 63.1%, specificity of 80% and positive predictive value of 70.5%.

Basara et al. conducted a study on carcinoma breast in female. They found that mean ADC values were 1.00×10^{-3} mm^2/s for the malignant and 1.39×10^{-3} mm^2/s for the benign lymph nodes. The ADC values of malignant lymph nodes were significantly lower than the benign ones ($p = 0.001$). When 1.22×10^{-3} mm^2/s was accepted as the cut-off ADC value, a sensitivity of 75.6% and a specificity of 71.1% were detected [34].

Lee et al. studied the 22 patients with head and neck cancer and found mean ADC values as 1.086 ± 0.222 10 3 mm^2/s for benign lymph nodes and 0.705 ± 0.118 10 3 mm^2/s for malignant lymph nodes (p 0.0001). When an ADC value of 0.851 10 3 mm^2/s was used as a threshold value for differentiating benign from malignant lymph nodes, the best results were obtained with an accuracy of 91.0%, sensitivity of 91.3% and specificity of 91.1% [35].

In the study population, we also found that, out of total 44 cases lymph nodes were found malignant on histopathology, in 25 (56.8%) patients with mean renal tumour ADC value of $0.89 \pm 0.18 \times 10^{-3}$ mm^2/s ($p = 0.05$). It was evident that primary renal tumour with lower ADC value has higher chances of harbouring malignant lymph nodes.

There is paucity of study comparing the ADC value of regional lymph node and its predictive value of foretelling malignant lymph node among genitourinary cancer. Although histological subtypes are being described based on renal tumour ADC values. Possibilities of harbouring malignant nodes in renal tumour were not studied in detail. Our study is probably the first in this direction to predict lymph node positivity in patients with radiologically organ-confined RCC.

In our study, while correlating the ADC value to that of lymph node positivity, it was observed that those lymph nodes with low ADC value and below cut-off ADC value were found to harbour malignant cell and are considered for standard lymph node dissection.

5 Conclusions

Renal cell carcinoma is the most lethal among all the Urological cancer. Prognosis of renal cell carcinoma is dependent on various factors, like capsular invasion, necrosis, calcification within the tumour, subtypes of RCC and regional lymph node metastasis. However, performing a standard lymph node dissection along with tumour extirpation in patients with organ-confined RCC is still a subject of debate and there is paucity of consensus in these scenarios about feasibility and benefits of lymph node dissection. Moreover, there hardly exists any biomarker to predict the malignancy harbouring lymph

nodes in patients with organ-confined RCC. There is paucity of study comparing the ADC value of regional lymph node and its predictive value of foretelling malignant lymph node among genitourinary cancer. Our study is probably the first in this direction to predict lymph node positivity in patients with radiologically organ-confined RCC, who may otherwise be a suitable candidate for lymph node dissection during tumour extirpative surgery.

In our study, while correlating the ADC value to that of lymph node positivity, it was observed that those lymph nodes with low ADC value (lymph node mean ADC value of $1.16 \pm 0.26 \times 10^{-3}$ mm^2/s) and below cut-off ADC value (1.25) were found to harbour malignant cell and considered suitable for standard lymph node dissection. Further, long-term multi-institutional studies with larger sample size are required for validation of role of DWI ADC value in predicting positive regional lymph node in patients with RCC.

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Nil.

Author contributions
AG is the main investigator, conceptualized the study, collected the data and wrote the paper. SB is the main investigator and contributed to design of the study. RT is the co-investigator and analysed and interpreted the data. PB, DS and MP acquired and analysed the data. VS contributed to revision and overall editing. All authors have read and approved the manuscript.

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Availability of data and materials
The datasets used and analysed during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by Institutional ethics Committee of Gauhati Medical College and Hospital with letter number MC/190/2007/Pt-11/51. A written informed consent was taken from all patients.

Consent for publication
Consent was taken from patients during their enrolment into the study.

Competing interests
The authors have no competing interest to declare.

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