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Currie, Claire; Stewart, Sharon

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The relationship of apparent diffusion coefficient values of renal cell carcinoma before and after cryotherapy ablation

C. Currie*, S. Stewart

Glasgow Caledonian University. Govan Mbeki, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA, Scotland, UK

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ABSTRACT

Introduction: The diagnosis of renal cell carcinoma (RCC) is increasing due to incidental findings with more frequent use of cross-sectional imaging. Therefore improvements to diagnostic and follow up imaging techniques is necessary. MRI diffusion weighted imaging (DWI) is a recognised method of measuring the diffusion of water within lesions using the apparent diffusion coefficient (ADC), and may have a role in monitoring the efficacy of cryotherapy ablation of RCC.

Methods: A retrospective cohort study of 50 patients was approved to investigate if the ADC value can determine the success of cryotherapy ablation treatment for RCC. DWI was performed at a single centre using 1.5 T MRI before and after cryotherapy ablation to the RCC. The control group was considered as the unaffected kidney. The ADC value of the RCC tumour and normal kidney tissue prior to and after cryotherapy ablation was measured, and compared to the result of the MRI.

Results: A statistically significant change in the ADC values was observed, pre ablation ($1.562 \times 10 mm^2$/sec) to the post ablation ($1.126 \times 10^3 mm^2$/sec), $p < 0.0005$. There was no statistical significance in any of the other outcomes measured.

Conclusion: Although a change of ADC value occurred this is likely due to cryotherapy ablation causing coagulative necrosis at the site, and does not determine the success of the cryotherapy ablation. This can be considered a feasibility study for future research.

Implications for practice: DWI is a quick addition to routine protocols, does not require intravenous gadolinium based contrast agent, and provides qualitative and quantitative data. Further research is required to establish the role of ADC for treatment monitoring.

Introduction

The diagnosis of renal cell carcinoma (RCC) is increasing due to incidentally finding renal lesions with computerised tomography (CT), ultrasound (USS) and magnetic resonance imaging (MRI).[1] Information Services Division[2] rank kidney cancer as the 8th most common cancer within Scotland, within this 90% of cases are RCC[3]; which are further classified into five histological subtypes: clear cell (most common subtype at a 70%–85% incidence), papillary (7%–15% incidence), chromophobe (5–10% incidence) and collecting duct carcinoma (rare).[1,4] Diagnosis of RCC is by a variety of laboratory tests followed up with USS and CT, whereas MRI is not the examination of choice but may be used where CT contrast is contraindicated and to stage local spread.[1] MRI offers a non-invasive tool for pre surgical imaging of renal tumours,[5] and where ablation is the treatment of choice a renal biopsy is also required for confirmation and classification.[6]

Diffusion weighted imaging (DWI) used to monitor oncological treatment response is an advancing area which shows much promise[7]; this is non-invasive, does not require intravenous contrast agent, does not use ionising radiation and can be quickly acquired as part of routine MRI scanning. The apparent diffusion coefficient (ADC) is a quantitative measurement which is calculated post acquisition of the DWI sequence with at least two different b-values; using post processing tools an ADC map is produced, where each pixel contains an ADC value.[8] The resultant map signals are mostly opposite to those seen on the DWI[9] (Fig. 1.). A region of interest (ROI) can then be drawn onto the map to give a quantitative measurement. Promising uses for DWI and ADC

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* Corresponding author.
E-mail address: Claire.Currie@gcu.ac.uk (C. Currie).
(C. Currie)

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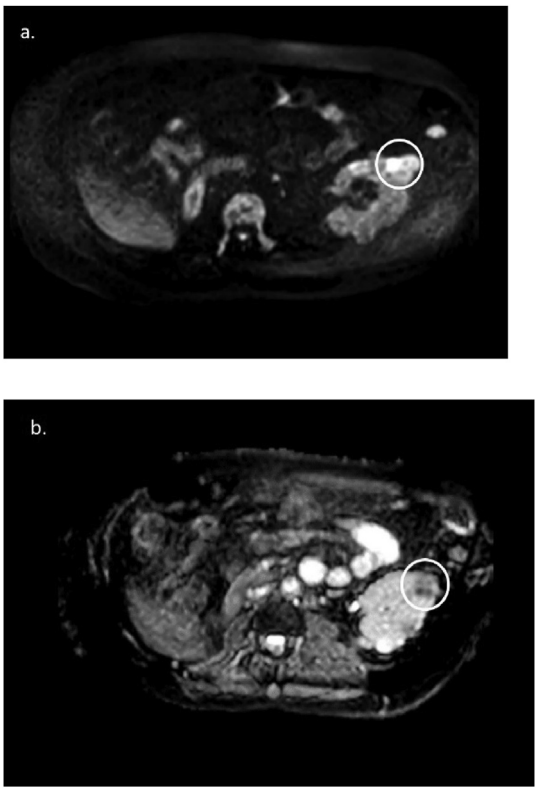

Figure 1. Renal cell carcinoma of left kidney, (a) hyperintense on DWI, (b) hypointense on ADC.

include characterisation of tumour type, response to drug treatments or radiotherapy, establishing treatment changes versus tumour, establishing lymph node invasion and possibly predicting the outcome of a treatment pathway.[7]

Nephron sparing surgery, such as cryotherapy ablation is becoming increasingly used for treating small renal lesions, and as treatment methods develop the requirement for non-invasive methods of characterising and surveillance of RCC is needed.[10] In addition, establishing methods to differentiate renal tumours is as important in the assessment of treatment response and evaluation of likely response to treatment.[11] It appears that research in the field of RCC and DWI focuses on characterisation of renal lesion and the sub types of RCC,[10–15] rather than disease follow up and monitoring; there is perhaps a lack of research due to preference to use CT to follow up treatment, or perhaps there was no requirement for follow up scans as the treatment of choice for all studies reviewed was surgical nephrectomy.

Bharwani[16] examined the use of ADC measurements as an indication of response to the drug Sunitinib (Sutent®), which is commonly used to treat RCC, their result showed a significant change in ADC measurement after the therapy. Tumours demonstrated low ADC values prior to Sunitab, and an increased ADC value after due to apoptosis.[16] Although there are several differences with their study design and this study it was likely that ablation therapy may also cause a change in ADC value. To measure the diffusion of water within the lesion using the ADC is therefore of interest before and after the cryotherapy ablation. Review of previous literature found no research in the combined field of RCC, cryotherapy ablation and DWI, therefore this research asked if ADC value can be used to determine the success of cryotherapy ablation treatment for RCC. The hypothesis was: the ADC value of RCC tumour will be affected by cryotherapy ablation to the tumour site. The expectation is a decrease in ADC value may be caused by treatments which targets the vasculature of a tumour, as opposed to the more usual finding of a significant rise in ADC values after treatments such as chemotherapy or radiotherapy.[17] Further aims considered the ADC value of the RCC and normal kidney before ablation to compare to previous literature, and discuss the benefit or shortfall of ADC to monitor treatment response of RCC to cryotherapy ablation compared to the routine MRI protocol.

Methods

Advice was sought from the Health Board's Research and Development Team and as retrospective and part of routine care, the project was deemed to be service evaluation. Caldicott approval and University School ethical approval was granted (HLS/NCH/15/33). Data was anonymised and securely stored on password protected hospital network and picture archiving and communication system (PACS). Research data is confidential. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

A retrospective cohort study design was used, with analysis of the ADC values on a sample purposively identified from the radiology information system (RIS). The inclusion criteria were RCC treated with cryotherapy ablation, imaging acquired on the same centre scanner both before and after cryotherapy, and no cryotherapy to the same kidney previously. The exclusion criteria were images with susceptibility artefact, images degraded by motion artefact, at ADC measurement stage RCC with large cystic components were excluded, MRI data which was irretrievable from PACS, duplicates on database, or tumour not identified by researcher on MR images.

All sequences including DWI were routinely acquired and not for the purposes of research. MRI was performed at a single centre using a Philips Ingenia 1.5 T MRI scanner with standard sequences including dynamic contrast enhancement (DCE), echo planar imaging DWI, free breath, and multiple signal acquisition technique, b-values of 0, 400 and 800 s/mm^2 (Table 1). The ADC map was automatically produced at the time of acquisition. The control group was considered as an ADC value of the unaffected kidney both before and after ablation. The MR imaging included the two full examinations; one prior to ablation and the first post ablation, which were retrieved from the PACS to the MRI workstation. All examinations were retrieved prior to analysis, using Philips MR Workspace – Extended MR workspace 2.6.3.4 2012. Measurements were performed by the researcher – a Radiographer with over 15 years MRI experience, blinded to the result of the routine MRI when performing the ADC measurement, all MRI sequences were accessed. A standardised procedure to measure the ADC value was used; the RCC was identified on the T2 weighted transverse images or DCE, and DW images as an area of different intensity within the kidney. The ROI was drawn within the border of the RCC on a single ADC image, to include the largest homogenous area possible (Fig. 2a, b, c). There were no set limitations on the size of the ROI as all tumours measured differing sizes, the ROI size was documented. The same size ROI was also placed in the corresponding area on the opposite kidney for the normal tissue measurement.

Subsequent to measuring ADC, clinical details were retrieved from the RIS and the Hospital Information System. The data collected was: sex, age, days between ablation and follow up MRI, the size of the tumour and location, laterality of the tumour, the histopathology and result of routine follow up MRI. The result of the routine follow up MRI was considered as the standard of reference of success of the ablation, and necessary to address comparability of routine MRI sequences against changes in ADC. The reference standard for satisfactory ablation was distinguished as a non-enhancing rim of the ablation zone and no increase in size.

Table 1
Routine Kidney MRI sequences and parameters.

Sequence name	Survey	BTFE	DWI	T1 in/out phase	T2 TSE multivane	eTHRIVE
Scan Plane	multiplane	coronal	Transverse	Transverse	Transverse	Transverse
Sequence type	BFFE	BTFE	Spin echo EPI	TSE	TSE	FFE 3D
Matrix	224 × 256	272 × 253	132 × 114	308 × 206	350 × 350	200 × 176
Reconstructed voxel (mm)	20.01 × 1.76 × 10	1.46 × 1.47 × 6.5	3 × 3 × 5	1.3 × 1.7 × 5.5	1 × 1 × 5	2 × 2 × 2
Number of slices	24	15	35	28	35	115
Slice thickness (mm)	10	6.5	5	5.5	5	2
TR (ms)		1.72	shortest 1385	104	1846	3.9
TE (ms)		3.4	64	2.3 & 4.6	100	1.82
Number of signal averages	1	1	8	1	1	1
Parallel imaging/P reduction	no	no	SENSE P reduction 2	SENSE P reduction 2	no	P reduction 2 S reduction 1.3
Phase direction	3 directions	RL	AP	AP	AP	AP
Breathing technique	breath hold	breath hold	free breath	breath hold x 2	respiratory triggered	breath hold
Fat suppression	no	no	SPIR	no	no	yes
B values	NA	NA	0,400,800	NA	NA	NA
Dynamic	NA	NA	NA	NA	NA	Pre,0,40, 141 s
Scan time	15 s	16 s	3.57 min	22 s	approx. 4.12 min	16.7 s each
Additional sequence info			3 Packages			
			EPI factor 57			2D bolus tracking
			WFS (pix/BW Hz) 7.578/28.7			
			BW in EP freq. dir (Hz) 2067.9			
			gradient overplus	Gradient mode	max	

Persistent enhancement was indicative of residual disease, however, at the first follow up MRI equivocal changes such as inflammation and haemorrhage may be evident. All scans were reported by the same consultant radiologist who performed the ablation.

Statistical analysis was performed using IBM SPSS Statistics version 22. Kolmogorov–Smirnov test was used to assess distribution. To answer the aims and sub aims the tests used were a paired sample t-test, independent t-test, Kappa Measure of Agreement, Spearman Rho and Kruskal–Wallis test, which regard significance at $P < 0.05$. Furthermore, data was split into the subgroups of clear cell RCC, papillary RCC and chromophobe RCC. Intra-observer agreement was performed, whereby the researcher conducted the ADC measurement collection again after six weeks, to reduce the chance of recall.

Results

Fifty participants were retrospectively identified, eight were excluded as the MRI data was irretrievable from PACS to the MRI workstation, five exclusions for tumours identified as being cystic and or necrotic at the analysis stage, one tumour could not be identified on the imaging by the researcher; one patient had been inadvertently duplicated on the database and a further patient was excluded as the images were undiagnostic due to susceptibility

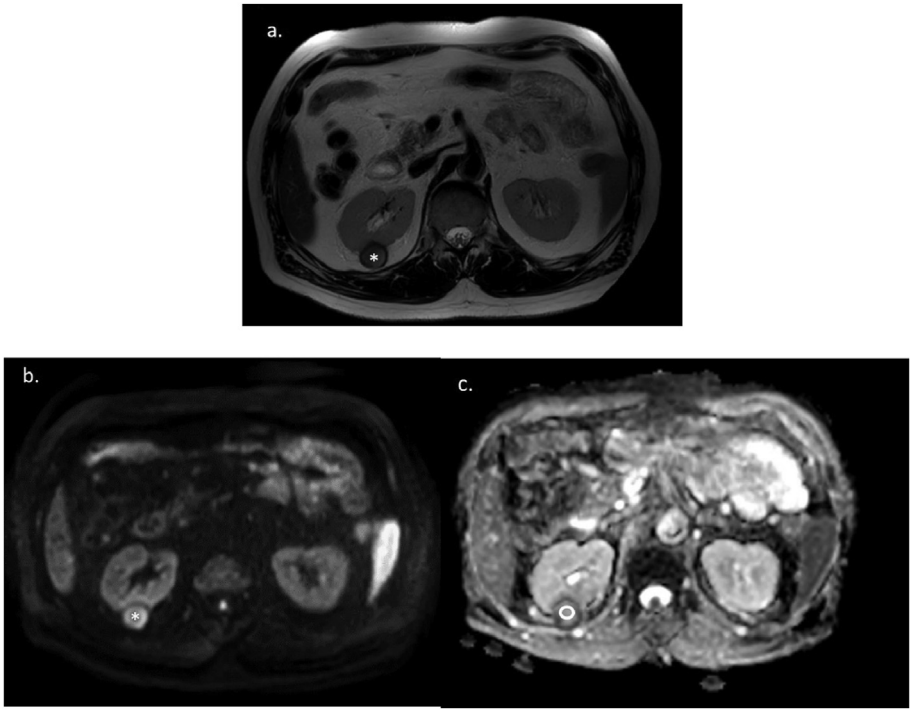

Figure 2. Renal cell carcinoma post cryotherapy ablation, a. * identification of lesion on T2W image, b. * lesion on DWI b800, c. ROI identified in centre of lesion on ADC.

Table 2
Summary of patient demographics, clinical and pathological characteristics.

Subject details		Total
Total included participants		34
Sex	Male	24 (70%)
	Female	10 (30%)
Age (years)	Mean	69 (range 49–80, SD = 21.9)
Histology (subtype RCC)	Clear cell	21 (62%)
	Papillary	1 (2%)
	Chromophobe	6 (18%)
	Unknown histology	6 (18%)
Laterality of tumour	Right kidney	22 (65%)
	Left kidney	12 (35%)
Diameter of tumour (mm)	Mean	30 (range 20–55)
ROI of pre cryotherapy ablation measurement (mm^2)	Maximum	235.8
	Minimum	40.4
	Mean	120.3
ROI of post cryotherapy ablation measurement (mm^2)	Maximum	232
	Minimum	48.6
	Mean	115.9
Time from cryotherapy ablation to follow up MRI (days)	Maximum	170
	Minimum	44
	Mean	104
Routine MRI follow up result	Satisfactory ablation	24 (70%)
	Residual disease	3 (9%)
	Inflammatory changes	6 (18%)
	Haemorrhage	1 (3%)

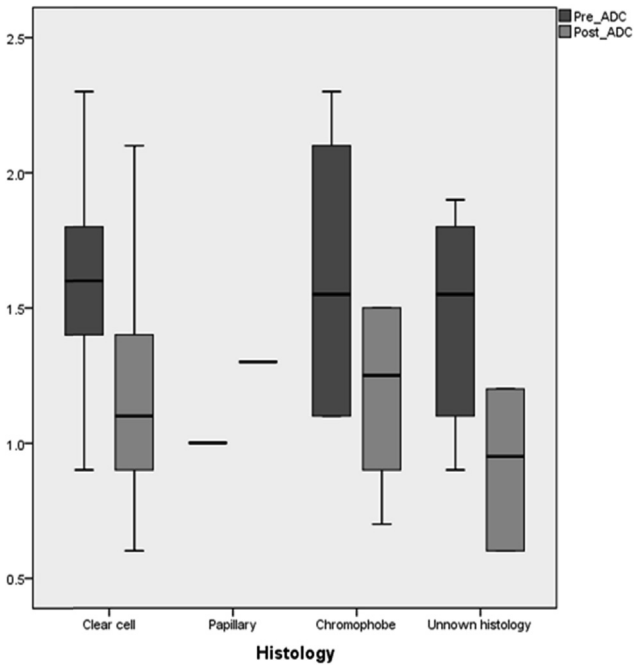

Figure 3. Pre cryotherapy ablation ADC value against post cryotherapy ablation ADC value ($\times 10^3 mm^2$/sec) of affected kidney.

artefact from an implant. Therefore, the sample analysed was 34 (Table 2). There was a statistically significant decrease in the ADC values from ADC pre ablation ($1.562 \times 10^3 mm^2$/sec, SD = 0.39) to the ADC post ablation ($1.126 \times 10^3 mm^2$/sec) $P < 0.0005$ (two tailed). The mean decrease in ADC value was $0.453 \times 10^3 mm^2$/sec with a 95% confidence interval ranging from $0.248 \times 10^3 mm^2$/sec to $0.6223 \times 10^3 mm^2$/sec. There was a significant difference between the pre ADC and post ADC with clear cell RCC but not chromophobe or histology unknown (Fig. 3). Caution is given that even with significant difference there may be other reason why this occurred,[18] although to aid in this the control group of the unaffected kidney shows no significant change in ADC measurement. The mean ADC value for normal kidney tissue in the opposite kidney was $2.038 \times 10^3 mm^2$/sec ±0.954.

Independent-samples t-test was conducted to compare the difference in ADC value between pre and post ablation and satisfactory ablation, or residual disease, inflammatory changes or haemorrhage, based on the routine follow up MRI. There was no significant difference between the ADC value difference for the satisfactory ablation group and the residual disease, inflammatory changes or haemorrhage group $P = 0.2$ (two-tailed). The magnitude of the difference in the means for the sample (mean difference = 0.26, 95% CI: −0.14 to 0.67) was small to moderate (eta squared 0.05). Therefore only 5% of the variance in the ADC values was explained by satisfactory ablation or not. Additionally, there was no relationship between the difference in the before and after ablation ADC values, and the number of days between the cryotherapy ablation and the follow up MRI scan ($p = 0.095$).

Kappa Measure of Agreement was performed finding fair intra observer reliability between measuring the ADC values on two separate occasions. Intra observer reliability measurement of Kappa for the pre cryotherapy ablation ADC values were 0.39, for the post cryotherapy ablation was 0.42 and for normal kidney tissue was 0.3.

Discussion

The research aimed to use DWI and ADC to detect tumour response to cryotherapy ablation, the result indicates a significant overall decrease in ADC value between the pre cryotherapy ablation and the post cryotherapy ablation with a large effect size. This decrease in ADC value may be as the treatment targets the vasculature of a tumour.[19] The pathophysiological process of cryotherapy ablation suggests the treatment causes direct tissue destruction by failure of cell metabolism and changes to the vasculature.[20] The cryotherapy employs an ice ball of minus 140°, which enters the extracellular space and creates a hyperosmotic environment causing the cells to shrink and damage the membranes. Ice crystals form within the cell and then as they thaw, the crystals fuse into larger ice crystals which draw the water back into the cell and cause the cell membrane to rupture, causing coagulative necrosis.[20] Considering this against the basic principle of DWI it can be concluded that these complex changes cause the changes in the restriction of water and thus change the ADC value. However, as all RCC tumours showed changes in ADC value it is impossible to say whether the process of cryotherapy ablation has resulted in satisfactorily curing the tumour of whether the process alone caused the change.

Overall, there was no significant difference between the change in ADC value for the satisfactory ablation group or residual disease, therefore, the conclusion to the research question is ADC value has not determined the success of cryotherapy ablation for RCC. The change of ADC value will occur due to treatment direct to the disease site, or cannot be explained without further research or increasing sample size. It would perhaps be more pragmatic to optimise an ADC histogram technique; whereby ADC measurements of ROIs in different slices are summated to deduce voxel by voxel ADC values.[21] Van Oostenbrugge[22] sought to discriminate between benign renal lesion, oncocytoma and RCC using a whole tumour ADC histogram parameters. Their two ROIs covered the entire tumour volume and healthy renal cortex, finding that ADC standard deviation and entropy were statistically different between oncocytoma and RCC. The small ROI used in this study has limitations, such as the variability of placement, and do not demonstrate the full histopathologic features in the tumour or adjacent tissues.

Previous studies, researching ADC values of RCC focus on pre-treatment[10–15] use different methods in acquiring the DWI

sequence, different b-values and perform the scans on different models of scanners, hence the research presented here did not reproduce any of the past study designs. However, the ADC values acquired before ablation can be compared. Of the reviewed literature three presented a mean ADC value for normal kidney tissue greater than 2.0×10^{-3}mm^{-2}s[5,12,14]; in concurrence the presented research. Normal kidney tissue demonstrated a higher ADC value than RCC; this is to be expected as the water has free random motion. Most other studies and this research found clear cell RCC to have the next highest ADC value or equal to chromophobe RCC[10, 11, 12,13,14,15]. Donati[23] pointed to significant differences in ADC results between vendors. With three major vendors available, and numerous models and specifications available it has been impossible for studies to rigorously replicate other studies. Future studies should clearly establish average ADC values of normal and RCC subtypes for the study protocol in advance.

The use of DWI for quantitative and qualitative assessment should continue to be of particular interest for this patient group who are susceptible to poor kidney function and limited use of intravenous gadolinium contrast agents is prudent, hence further research in this field is justified. The methods of this study should be revised to include the peripheral zone of the ablation field to allow for investigation of local tumour progression. Also, it was not practical to have two subject groups; ideally a control group of patients with RCC on active surveillance would be followed to ascertain whether a change in ADC is due to the cryotherapy ablation or by chance. The use of DWI within the routine kidneys protocol should not be discontinued. DWI is a quick addition to the routine protocol, does not require intravenous gadolinium contrast agent, and provides qualitative information from the DW image and quantitative information with the ADC map.[23] Additionally, continued use of the DWI sequence should allow further collection of retrospective data, or ethical approval should be sought for a prospective study.

Limitations: In concurrence with the literature reviewed the research is limited by its retrospective methodology and limited full medical history; indeed, histology results of six participants could not be determined. The sample is small, risking overly representing subgroups within the sample population,[24] occurring here with the rarer subtypes of papillary RCC and chromophobe RCC. The purposive sampling method has also resulted in selection bias, whereby the results are now only generalisable to a small subgroup of RCC patients, with small non metastatic RCC only. The analysis did not control for sex or age, however, the sample is representative of the population with a higher incidence in men and increasing incidence in older age groups.[2] The research is also limited by being conducted by a single researcher; a collaborative approach with radiologists and physicists would seek to increase validity of the methodology. Ideally inter-observer reliability would have been preferable, but due to restraints only intra observer reliability was performed with fair to moderate agreement was reported.

Conclusion

The research was an original study and as such can be considered a feasibility study for future research in this current trend in MR imaging. In summary the ADC value of RCC tumour was affected by cryotherapy ablation to the tumour site. Although a change in ADC value occurred between the pre and the post cryotherapy ablation there was no statistical significance in this change against the result of the routine MRI follow up. It is therefore concluded that the change of ADC value will occur due to treatment direct to the disease site, or for reasons which cannot be explained. There were similarities between the mean ADC values of RCC and normal kidney and the reviewed literature, thus showing some promise of using this as a tool to subtype RCC without biopsy. Future studies should optimise an ADC histogram technique.

Conflict of interest statement

None

Acknowledgments

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