Fat-fraction provides classification and treatment response assessment of metastatic lymph nodes for patients with radio-recurrent prostate cancer

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Synopsis

Lesion size threshold is the most common imaging feature used to assess response to therapy. Size as an imaging feature has its limitations. Quantitative imaging biomarkers (QIBs) could identify subtle microstructural changes prior to morphological changes. In this study, we explored the use of novel whole-body MRI (WB-MRI) QIBs for nodal disease characterisation and treatment response monitoring in radio-recurrent prostate cancer (rPC). We showed signal fat fraction could discriminate between positive and negative nodes and that it can be used for response monitoring.

Introduction

Whole-body MRI (WB-MRI) offers the opportunity to provide a cost effective solution for cancer staging (1). However, attempts to use quantitative imaging biomarkers (QIBs), such as apparent-diffusion-coefficient ADC, for classification and response monitoring have met with limited success [2,3] and are rarely applied in the clinical arena. Lymph nodes are composed of a predominantly fatty hilum surrounded by a cellular rim [4]. Replacement of the fatty components of lymph node by cancer cells is commonly seen in patients with metastatic prostate cancer [5]. Recent studies in multiple myeloma have shown that mDixon signal fat-fraction (sFF) is a repeatable and useful QIB for classification and treatment response (6). In this study, we explored the value of sFF as a nodal status classifier and response marker in patients with radio-recurrent prostate cancer (rPCa).

Methods

Patients with suspicion of rPCa as per phoenix criteria (7) underwent prostate multi-parametric MRI, 18F-choline-PET-CT, 99mTc bone scan as routine imaging. For research purposes, a baseline 3T WB-MRI was performed (fig 1). Patients underwent treatment guided by routine imaging. All patients were re-imaged with follow-up WB-MRI at 1 year. Of 120 patients with 1-year follow-up WB-MRI, 40 were randomly selected for quantitative analysis. Up to10 anatomically distributed nodes were selected for analysis for each patient. sFF for each node was derived as previously described (8) : SIpre-contrast-F / (SIpre-contrast-F + SIpre-contrast-w). An enhanced-reference-standard (ERS) fig.2 was applied to each node (using a combination of choline PET-CT, nodal size change between baseline and follow-upWB-MRI (See Fig 3) and PSA kinetics .Nodes were classified as positive, negative or unknown based on the ERS. Baseline WB-MRI node size (short axis diameter)and sFF were compared between positive and negative using the Mann-Whitney test. Receiver-operating-characteristic (ROC)area-under-curve (AUC) calculated for assessment of sFF as a classifier of nodal disease status. Positive nodes were identified in 14/40 patients(fig 4). 13/14 patients were treated with androgen deprivation therapy (ADT). Patients were divided into responder and non-responder groups based on PSA PCWG-2 response criteria (9). Baseline and follow-up (post-treatment) sFF of nodes within these 13 patients was extracted. Baseline size and sFF, and percentage change in (delta)sFF after treatment were compared between responder and non-responder groups using the Mann-Whitney test. ROC analysis of (delta)sFF was performed.

Results

40 patients [median age 73 (range 65-85years) and median PSA 4.45 (range 0.24-28.3ug/L)] were identified. A total of 206 nodes across the 40 patients were analysed(per patient median number 4, range 1 to10). 75/206 were classified as unknown and excluded from sFF analysis. 30/131 were positive (short axis median size 0.8 cm, range 0.6-2.7 cm) and 101 (short axis median size 0.7 cm, range 0.3-1.2 cm) negative by ERS. As expected, positive nodes were significantly larger than negative nodes ($p=0.03$). The median sFF was significantly lower for positive (0.63) compared withnegative nodes (0.79) ($p<0.0001$)(figure 5a).Nodal sFF ROC-AUC was 0.86 for classification of metastatic nodal disease. 28 nodes were included from 13patients for treatment response analysis(fig4).10/13 patients responded to treatment and 3/13 were non-responders by PCWG-2PSA criteria; providing 21nodes in the responder and 7nodes in the non-responder groups respectively. sFF nodal characteristics for the responder and non-responder nodes are given in fig5c. Baseline median sFF was lower for nodes in the responder(0.58a.u.) compared with non-responder(0.75a.u.) group($p<0.0001$). Median (delta)sFF (following ADT) was 31% (range 6.1to 230.9) in the responder and -6.5% (range -24.2 to 20.6) in the non-responder group($p<0.01$), see fig 5d. The ROC-AUC of (delta)sFF was 0.85.

Discussion

Our results highlight the potential of sFF as a marker of nodal disease status and treatment response in patients with rPCa. Prior work demonstrated that sFF measurements is highly repeatable and can be used to assess bone lesions (10). Here we show that sFF can provide a quantitative imaging biomarker able to(ROC-AUC of 0.85) to classify pre-treatment nodal disease status. Furthermore, we show that (delta)sFF may help identify non-

responding lymph nodes (ROC-AUC 0.86). We derived an ERS, employing follow-up WB-MRI and PSA and accounting for limitations in performance of routine imaging tests. Our initial results appear promising, prompting on-going analysis of the remaining 80 patients with follow-up WB-MRI. Future work will focus on assessing the value of sFF in bone lesions and finally in clinical decision making for patients with rPCa.

Conclusion

sFF has value as a quantitative imaging biomarker with potential to classify lymph nodes disease status and monitor treatment response in patients with rPCa

Acknowledgements

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Figures

Table 1. Showing MRI sequence parameters.

WB-MRI sequence parameters on Phillips Ingenia MR scanner (3 Tesla)

	T2-TSE	mDixon (pre- and post-contrast)	DWI (b0, 1000)
	Transverse	Coronal	Transverse
TE (ms)	80	2.303	71
TR (ms)	1214.69	3.5	6304.5
Space between slices	5.5	2.5	5.5
Number of slices	40	120	40
Slice thickness (mm)	5	5	5
Acquisition matrix	500*497	240*238	124*118
ETL	89	2	39
Number of averages	1	1	2
Pixel bandwidth (Hz)	538	1847	3354
Pixel spacing	0.78/0.78	1.04/1.04	2.08
Flip angle	90	15	90

Figure 1. Showing MRI sequence parameters.

Figure 2

Outcome	PET status	Treatmemt	Size change	PSA change
Positive	Any	Yes	↑↓concordant with PSA	↑↓concordant with size
Positive	Any	No	↑	↑
Negative	Negative	No	↓or ←→	Any
Negative	Positive	No	↓	Any
Negative	Negative	Yes	←→	Any
Unknown	Positive	Yes	←→	Any
Unknown	Any	Yes	↑↓discordant with PSA	↑↓discordant with size
Unknown	Negative	No	↑↓discordant with PSA	↑↓discordant with size
Unknown	Positive	No	←→	Any
Unknown	Positive	No	↑	↓or←→

Figure 2 Showing enhanced-reference-standard (ERS) for nodal selection. This was based on the combination of PET status, pre & post treatment size and PSA changes

Figure 3 Bland Altman plot for intra-observer reliability of contrast-enhanced water-only mDixon sequence.

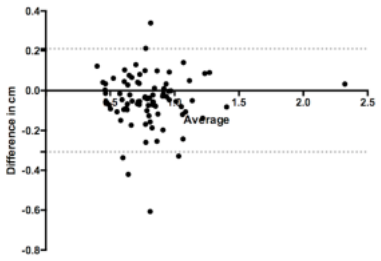

Figure-3-Intra-observer-reliability-of-contrast-enhanced-water-only-mDixon-sequence.

To define size measurement error,10 patients underwent repeated (2 occasions separated by 2 weeks) measurement of short axis diameter of selected nodes by an expert radiologist. Bland-Altman 95% limits of agreement (LoA) were calculated from 85 nodes (median size 0.75cm, (range 0.43-2.3 cm), median number per patient 4) as 0.2 to -0.3 cm. 95% LoA were used within the ERS as a threshold to define significant size change between baseline and follow-up WB-MRI studies. Prostate-cancer-working-group-2 PCWG2 (9) criteria (increase of ≥25% for PSA progression or a reduction ≥50% for PSA response) were used to determine significant PSA change.

Patient number	Node number	Location	PET status	Baseline SAD (cm)	Follow-up SAD (cm)	Baseline PSA (µg/L)	Follow-up PSA (µg/L)	PCWG-2 PSA Response?	% sFF change
1	1	External iliac	Pos	2.8	1.3	5.5	2	Yes	53.9
	2	Retroperitoneal	Neg	1.1	0.7				16.14
	3	External iliac	Neg	1.1	0.7				230.9
2	4	Para-aortic	Neg	1.14	0.8	3.8	0.8	Yes	11.14
	5	Axillary	Neg	0.8	0.38				10.22
3	6	External iliac (medial)	Pos	1	0.6	4	2	Yes	50.26
	7	External iliac (lateral)	Pos	0.82	0.5				31.25
	8	Para-aortic	Neg	1	0.67				9.51
	9	Axillary	Neg	1	0.6				27.58
4	10	Cervical	Neg	0.8	0.47	4	1.9	Yes	38.2
5	11	External iliac	Pos	0.72	0.4	28.3	4.7	Yes	28.99
	12	Para-aortic	Neg	0.74	0.4				49.78
	13	Internal iliac	Pos	1.2	0.5				63.46
	14	Retro-crural	Neg	0.91	0.5				11.52
	15	Peritoneal	Neg	1.3	0.9				37.17
6	16	Para-aortic	Neg	1.24	0.9	4.7	1.9		7.34
	17	Left cervical	Neg	0.9	0.48				6.09
7	18	External iliac	Pos	0.8	0.45	4.2	2		40.12
8	19	External iliac	Pos	1.54	0.7	1.9	0.4		17.36
9	20	External iliac	Pos	1.1	0.5	6.3	0.1		38.4
10	21	External iliac	Pos	1.32	0.8	2.5	1.2		76.5
11	22	Common iliac (upper)	Neg	0.5	0.9	14	18	No	-13.27
	23	Common iliac (lower)	Neg	0.4	0.7				-24.25
	24	Para-aortic	Neg	0.5	0.9				-6.56
12	25	Para-aortic (upper)	Neg	0.6	1	5.6	9	No	-4.38
	26	Para-aortic (lower)	Neg	0.7	1				20.65
13	27	Left para-aortic	Neg	0.5	0.86	3.7	6.5	No	0.55
	28	Right para-aortic	Neg	0.7	1.05				-15.8

Figure 4 showing PET status, size & PSA changes, fat fraction changes and outcome status of the 28 positive nodes (13 patients). 1 patient (2 positive nodes) was excluded, as the patient didn't have systemic therapy. All patients assessed had ADT. The nodes in green are responders while those in red are non-responders .

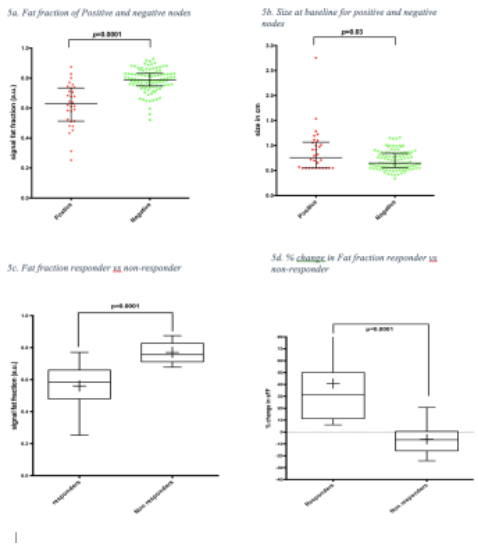

Figure 5 showing fat fraction and size characteristics of positive vs negative nodes(5a &5b). Then the fat fraction characteristics of responder vs non-responder nodes at baseline(5c) and following treatment.