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LETTER TO THE EDITOR

Mind the gap: extent of use of diffusion-weighted MRI in children with rhabdomyosarcoma

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Sir,

We undertook a systematic review of the use of advanced functional imaging in the management of rhabdomyosarcoma in children and young people (age ≤24 years) [1]. Studies of PET, PET-CT or diffusion-weighted MRI were eligible for inclusion if they included ≥10 patients with histologically proven rhabdomyosarcoma. We identified two studies of PET and six of PET-CT with a total of 272 patients with a diagnosis of rhabdomyosarcoma. The results of the review are reported in full elsewhere [2]. No study of diffusion-weighted MRI that we identified met inclusion criteria, but these seven papers (see Table 1) represent the extent of published data regarding the use of this imaging modality in rhabdomyosarcoma.

These seven studies evaluated a total of 263 patients, of whom 122 had malignant tumours (the others had benign lesions or other conditions). Twenty-nine patients received a diagnosis of rhabdomyosarcoma. The number of patients with rhabdomyosarcoma ranged from 1 to 11. Only one study enrolled ≥10 patients with rhabdomyosarcoma and this (like the studies with fewer rhabdomyosarcoma patients) used diffusion-weighted MRI for the differential diagnosis of malignancy rather than the management of patients with an existing diagnosis.

The location of the rhabdomyosarcoma tumours was frequently not specified, but six papers reported the location of lesions for the whole enrolled population. We can therefore determine that 10 patients with rhabdomyosarcoma had orbital primary tumours, 11 had head and neck primaries, 2 had bladder wall tumours and 1 each had pelvic and prostate primaries. The location of the remainder is unclear.

The six full-text studies were assessed for quality using a tool adapted from previous health technology assessment reviews [2, 3]. Five studies had clear inclusion criteria, four used consecutive recruitment of patients and three were prospective with adequate participation. Three used multiple assessors of the imaging who were blinded to the reference standard. Statistical analyses were generally appropriate.

The methods used to acquire apparent diffusion coefficient (ADC) values and the ADC maps varied significantly in the referenced papers, with differing diffusion-weighted b factors (b values) utilised, different approaches to drawing the relevant regions of interest, few or only one observer, and in one study both 1.5-T and 3-T MRI scanners were used. This reflects the known issues with apparent diffusion coefficient measurements. The element of subjectivity in the determination of the region of interest, the difficulties with reproducibility and the variety of possible b values that can be used can all contribute to a lack of precision.

The reported results provided little information specific to rhabdomyosarcoma. They primarily reported hypointensity and ADCs of rhabdomyosarcoma tumours. The largest case series reported that malignant tumours had statistically significantly lower mean ADC compared to benign lesions and that rhabdomyosarcoma patients had the lowest mean ADC, statistically significantly lower than that in mucoepidermoid carcinoma. One study reported that fibrous orbital tumours including rhabdomyosarcoma showed homogeneous diffusion restriction, which contrasted to nonfibrous lesions such as hemangiomas. One study reported hypointensity and ADC range for three rhabdomyosarcoma cases. Finally two studies reported the exact ADC for the four included

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Table 1 Summary of identified case series using diffusion-weighted MRI in the care of children with rhabdomyosarcoma

Study	*n*	*n* (malignancies)	*n* (RMS)	b factors/values	Radiologist	Tumoural region of interest	Tumour location	RMS-specific ADC results	Further comments	Summary of quality
Abdel Razek (2009) [4]	78	28	11	0.500, 1,000 s mm^{-2}	*n*=1	ROI, avoid cystic. Largest lymph node measured.	Head & neck	RMS had lowest mean ADC ($0.78\pm0.07 \times 10^{-3}$ mm^2 s^{-1}), significantly lower than mucoepidermoid carcinoma ($P<0.001$)	Inflammatory nodes disappeared after antibacterial therapy	Prospective series but unclear selection criteria and unclear/poor imaging assessment
Humphries (2007) [5]	19	11	2	0, 500 and 1,000 s mm^{-2}	*n*=1	ROI along circumference but within boundary, solid areas after T2-W and post-contrast T1-W evaluation of the tumours	All except 3 abdominal; RMS pelvic/ prostate	Histopathology count: 134.5 & 179 cells/high power field ADC: 1.42 & 1.00 $\times 10^{-3}$ mm^2 s^{-1} Mean=1.21×10^{-3} mm^2 s^{-1}	Repeated ROIs and median ADC values 3–12 months later, compared	Generally good prospective series but unclear if consecutive recruitment
Study	*n*	*n* (malignancies)	*n* (RMS)	b factors/ values	Radiologist	Tumoural region of interest	Tumour location	RMS-specific ADC results	Further comments	Summary of quality
Kocaoglu (2010) [6]	26 (31 lesions)		15	2 Retrospective series with consecutive recruitment	0 and 800 s mm^{-2}	*n*=2, 2 readers in results	ROI by consensus, avoid non-enhancing necrotic areas	Abdominal; both RMS urinary bladder wall	ADC 1.09 & 0.94 $\times 10^{-3}$ mm^2 s^{-1} Mean=1.02×10^{-3} mm^2 s^{-1}	ROC curve analysis for optimum cut-off values for ADC. Visual assessments too. ADC values measured 5 times
Lope (2009) [7]	27	11	7	*	*	*	Orbital	Fibrous orbital tumours including RMS showed homogeneous diffusion restriction in contrast to nonfibrous lesions (e.g., hemangiomas)	*	Retrospective*

Table 1 (continued)

Study	*n*	*n* (malignancies)	*n* (RMS)	b factors/values	Radiologist	Tumoural region of interest	Tumour location	RMS-specific ADC results	Further comments	Summary of quality
Neubauer (2012) [8]	44	10	1 relapse	50, 800 s mm^{-2}	*n*=1 for quantitative analysis	Circular ROI, "representative portion"	Head & neck, trunk, extremity	No results specific to RMS	Minimum, maximum, mean ADC values recorded	Retrospective series with unclear/poor imaging assessment
Study	*n*	*n* (malignancies)	*n* (RMS)	b factors/values	Radiologist	Tumoural region of interest	Tumour location	RMS-specific ADC results	Further comments	Summary of quality
Oka (2008) [9]	37	31	3	0, 500, 1,000 s mm^{-2}	*n*=2	3 × 120-140 mm^2 ROIs, Avoid cystic and/or necrotic areas	Not reported	No results specific to RMS	Minimum, mean ADC values	Generally good-quality retrospective series
Roshdy (2010) [10]	32	16	3	0, 500, 1,000 s mm-2	NR	ROI not clearly defined	Orbital	B 0 hypo B 1,000 hyper ADC 1.01 to 1.42 ADC 1.01 to 1.42 × 10^{-3} mm^2 s^{-1}	Mean ADC values reported	Prospective series with clear selection but unclear/poor on other criteria including imaging assessment

* Abstract only: could not be fully assessed. *ADC* apparent diffusion coefficient, *RMS* rhabdomyosarcoma, *ROI* region of interest

rhabdomyosarcoma cases, accompanied by cell counts in one series. Two studies did not report any rhabdomyosarcoma-specific results. The range of mean ADCs reported for rhabdomyosarcoma was 0.78 to 1.21 × 10^{-3} mm^2 s^{-1}. The mean from the largest series appears lower than the lowest range from any of the other three studies reporting data, suggesting heterogeneity.

These reasonable-quality case series represent the only data relevant to the use of diffusion-weighted MRI in paediatric rhabdomyosarcoma. They were identified following comprehensive searching and rigorous screening using specified inclusion criteria. This indicates that diffusion-weighted MRI has been used only for diagnostic purposes, and primarily in patients with head and neck (including orbital) lesions, who accounted for 21 of the 29 included rhabdomyosarcoma patients. The impact of this technology on the staging and management of paediatric rhabdomyosarcoma remains unknown; this clear and complete assessment of the information published should provide the basis for future studies assessing this modality. Staging of rhabdomyosarcoma primaries requires both imaging and biopsy to determine extent and histological type. Lymphadenopathy is poorly characterised, resulting in a reliance on nodal size and a low threshold for biopsy. Normal lymph nodes have demonstrated restricted diffusion, similar to nodes infiltrated by malignant cells. Diffusion-weighted imaging has some potential to improve discrimination of nodal involvement and it can guide biopsy of tumours by avoidance of biopsy of the cystic or necrotic components of a mass. However there is a potential for ADC maps to show artefactual results as a consequence of restricted diffusion resulting from calcified or sclerosed lesions.

Our results highlight the dearth of studies of diffusion-weighted imaging in children with rhabdomyosarcoma. Prospectively collected cohorts of patients with blinded assessments and full ascertainment of outcomes are required, potentially comparing their predictive value to PET-CT as well as conventional imaging, to produce an effective evaluation of this advanced functional imaging technology in this indication. In order to maximise the reliability of the ADC, studies should incorporate measures such as multiple blinded assessors and evaluation of both initial and follow-up assessments by the same assessors.

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