Acta Oncologica, 2010; 49: 252–255

informa
healthcare

LETTER TO THE EDITOR

Diffusion-weighted MRI of the liver for early tumor response assessment: Promising technique but evidence is still lacking

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To the Editor,

With great interest we read the article by Eccles et al. [1], who showed the promise of diffusion-weighted magnetic resonance imaging for the early assessment and prediction of liver cancer response to (radio) therapy. Since more minimally invasive treatment options for hepatic malignancies emerge, much attention is aimed at the possibility to evaluate tumor response with imaging techniques early after initiation of therapy because this will allow adjusting individual treatment regimes more rapidly. The currently accepted criteria for determining tumor response are the Response Evaluation Criteria in Solid Tumors (RECIST) in which decrease in tumor size is measured by anatomic imaging. However, the RECIST criteria are limited in that they only allow assessment of therapeutic efficacy months after onset of therapy [2]. Functional tissue changes may occur well before structural changes become visible, and in this respect DWI has recently frequently been suggested as a potentially powerful alternative to the RECIST criteria. DWI allows quantification of the diffusivity of water molecules in biological tissue by means of apparent diffusion coefficient (ADC) measurements. Since the ADC has been reported to inversely correlate with cellularity, an early increase in tumor ADC may well correspond to tumor necrosis and successful therapy [2]. Although promoted as a very promising technique by many investigators, including Eccles et al. [1], DWI has not been implemented yet in routine clinical practice, perhaps due to the lack of strong evidence regarding its effectiveness. Our aim was therefore to identify all relevant studies that investigated the use of DWI for the evaluation of tumor response in liver malignancies, and to provide an overview of the current evidence for its clinical use.

We performed a thorough search in MEDLINE (1966–2009) and EMBASE (1980–2009) using synonyms for any 'liver malignancies' (e.g. metastases from any primary tumor and/or primary liver cancer), any 'therapy' (e.g. local, regional or systemic therapy), and 'DWI'. We only included articles that evaluated tumor response to therapy. The exclusion criteria were animal studies and languages other than English, German or Dutch. Subsequently, we identified and collected relevant articles and critically appraised these articles. After critical appraisal we compared the outcome of the different studies. The search yielded a total of 485 articles. Ten articles eventually met our inclusion and exclusion criteria and were analyzed. An overview of the characteristics and results of the studies is presented in Tables I and II. All studies showed an overall increase in ADC with a decrease in tumor size after onset of (minimally invasive) therapy. Interestingly, no study investigated both the changes in ADCs in responders and non-responders, and compared these ADCs with RECIST or outcome. Moreover, the available studies on this subject may have suffered from several methodological flaws. First, six of ten studies [3–8] were performed by the same study group. Furthermore, applied acquisition protocols and durations of follow-up varied widely among the different research groups which make it difficult to compare their results (Table I). In addition, all studies included a relatively low number of patients, ranging from only six to 38. Seven studies [3–5,7,8,11,12] may have suffered from selection bias by only including patients that underwent DWI before and after treatment or by selecting lesions with a minimal size [7,12] or a maximum number of lesions per patient [11]. Furthermore, in seven studies [3–9] the results were

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(Received 21 September 2009; 3 November 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841860903464007

Table I. Methodology DWI.

					Methodology DWI						Follow-up MRI			
Article	Tumor	Therapy	No. patients	TR (ms)	TE (ms)	B-value (s/mm^2)	Acquisition	Slice thickness (mm)	Slice gap (mm)	Excitations	Interval[b]	Before therapy (days[c])	Interval Pre- and post therapy (days[c])	Last treatment – follow-up MRI (days[c])
Buijs [3]	Breast-metastasis	TACE	14	5000–6500	110	500	Breathhold	8	2	NA	I	4 ± 5	60 ± 32	54 ± 33
Liapi [7]	Neuro-endocrine metastasis	TACE	26	5000–6500	110	500	Breathhold	8	2	NA	NA	NA	206 ± 201	NA
Rhee [10]	HCC	^{90}Y	20	2500	82	0, 500	One or more breathholds	8	4	NA	II	NA	NA	NA
Buijs [4]	Ocular melanoma metastasis	TACE	6	5000–6500	110	500	Breathhold	8	2	NA	I	16 (1–45)[d]	79 (32–161)[d]	33 (21–45)[d]
Marugami [12]	Colorectal metastasis	HAIC	11	1400	67	0, 500, 1000	Free breathing	7	NA	2	III	NA	NA	NA
Vossen [8]	Leiomyo-sarcoma metastasis	TACE	10	5000–6500	110	500	Breathhold	8	2	NA	I	9 ± 18	57 ± 22	48 ± 24
Deng [9]	HCC	^{90}Y	6	2500	82	0, 500	One or more breathholds	8	4	NA	28–70 days	NA	NA	NA
Kamel [5]	HCC	TACE	38	5000–6500	110	500	Breathhold	8	2	NA	I	26 ± 10	111 ± 56	45 ± 15
Kamel [6]	HCC	^{90}Y	13	5000–6500	110	500	Breathhold	8	2	NA	I	24 (5–47)[d]	55 (39–77)[d]	34 (28–47)[d]
Cui [11]	Colorectal/ gastric metastasis	Chemo	29	NA	2750/ min	0, 800	Breathhold	6	1	4	IV	NA	NA	NA

[b]I: 4–6 weeks after TACE and every 6–8 weeks, II: 0–3 weeks before and 1 and 3 months after therapy, III: Before and 9 days and 3 months after therapy, IV: Before, 3, 7 and 42 days after therapy

[c]Mean ± SD, [d]Mean with range, TR: repetition time, TE: echo time, HCC: hepatocellular carcinoma, TACE: transarterial chemoembolization, ^{90}Y: Yttrium-90 radioembolization, HAIC: Hepatic arterial infusion chemotherapy, NA: not available

Table II. Results.

Article	ADC (mean ± SD)			Therapeutic response (RECIST)	Tumorsiz (mean ± SD)			Survival (months)
	All patients	Responders	Non-responders		All patients	Responders	Non-responders	
Buijs [3]	26.5% ± 33.7%	NA	NA	Complete: 0 Partial[a]: 26%	−18.2% ± 60.0%	NA	NA	25
Liapi [7]	18.5% ± 35.8%	NA	NA	Complete: 0 Partial: 23%	−17.9% ± 55.4%	NA	NA	78
Rhee [10]	1 month: 10.5% ± 23.1% 3 months: 11.0% ± 14.0%	21.7% ± 14.9%[x]	−22.6 ± 8.13%	NA	−18,5% ± 31.5%	−33.3% ± 19.7%[x]	27.6% ± 16.4%	NA
Buijs [4]	47.8% ± 54.8%	NA	NA	0	−16.3% ± 67.3%	NA	NA	NA
Marugami [12]	NA	Min-ADC: 17.9% ± 17.6%[0] Mean-ADC: 7.5% ± 16.5%[0]	Min-ADC: −10.5% ± 10.4% Mean-ADC: −6.7% ± 14.5%	NA	−11.7% (range −45.5–54.5%)	NA	NA	NA
Vossen [8]	20.3% ± 24.9%	NA	NA	0	−2.1% ± 68.8%	NA	NA	21
Deng [9]	56.1% ± 38.5%	NA	NA	NA	NA	NA	NA	NA
Kamel [5]	17.2% ± 38.4%	NA	NA	0	−10.0% ± 51.3%	NA	NA	19
Kamel [6]	18.2% ± 15.2%	NA	NA	0	−2.1% ± 50.0%	NA	NA	12
Cui [11]	NA	day 3: 25.4% ± NA day 7: 26.2% ± NA	day 3: 7.2% ± NA day 7: 9.7% ± NA	NA	NA	−38.6% ± 22.1%	−11.0% ± 50.0%	NA

ADC: Apparent diffusion coefficient, RECIST: Response Evaluation Criteria in Solid Tumors, NA: not available

[a]On a lesion-by-lesion basis. On a patient-by-patient basis all patients were non-responders

[x]Responders are patients who exhibited tumor shrinkage at 3 months after ^{90}Y therapy

[0]lesions with a reduction ratio > 0%

reported as overall change in ADC without specifying a responder and a non-responder group; consequently, no conclusion can be drawn on the capability of ADC measurements in discriminating reponders from non-responders based on these results. The studies that did make this distinction did not compare ADC analyses with RECIST or outcome. Instead, patients were classified as responders when their lesions showed a decrease in size [10,12] rather than using the RECIST criteria that define (partial) respons as decrease of 30% or more in the sum of the longest diameter of target lesions. Furthermore, the gold standard for tumor response evaluation to which ADC should be compared, is an issue of continuous scientific debate in itself. Although RECIST criteria are currently the gold standard, it has been proven that they have limitations too, since they rely completely on structural (not functional) changes of the tumor after therapy.

Concluding, in patients with hepatic malignancies that are treated with minimally invasive techniques, studies showed an overall increase in ADC with a decrease in tumor size. However, there is currently no convincing evidence that ADC is able to predict early tumor response to therapy or outcome. Well-designed prospective studies and standardization of imaging and follow-up protocols across different research groups are needed to bring this promising application of DWI closer to clinical practice and, eventually, improve the management and outcome of patients with hepatic malignancies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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