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Evaluation of MR Biomarkers for Assessment of Response with RECIST Criteria: Comparison of the Measurements of Neuroendocrine Tumor Liver Metastases (NETLM) with Various MR sequences and at Multiple Phases of Contrast Administration

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Abstract

PURPOSE—Our aim was to compare the inter-observer and intra-observer variability for the measurement of the size of liver metastases in patients with carcinoid tumors with various MR series.

METHOD AND MATERIALS—In this, retrospective IRB approved study, 30 patients with liver metastases from a carcinoid primary had a complete MR examination of the abdomen at 1.5T with Gd-EOB-DTPA. The complete MR examination included: T1 (in/out-of-phase, T2, DWI, Pre- and Post-Gd-EOB-DTPA 3D gradient echo (4 phases plus 20min (HBP-Gd). Four readers review each series independently. The measurement for each lesion was compared to HBP-Gd images. The sensitivity for detection of each lesion was compared to HBP-Gd. Variance component analysis

was used to estimate variance due to patient, lesion within patient, and reader by sequence. Linear mixed model was used to compare lesion size between sequences.

RESULTS—The HBP-Gd had the smallest inter-reader variability. There was no significant difference between series with respect to inter-reader variability. Lesion sizes measured in DWI was significantly higher. T2W was the closest to HBP-Gd. Lesion sizes measured with the other sequences were significantly smaller. There was significant difference in sensitivity of lesion detection of some series when compared to HBP-Gd.

CONCLUSION—HBP-Gd series had the smallest inter-reader variability and is the recommended series to measure lesion size for evaluation of response to treatment.

Keywords

Neuroendocrine Tumors; Gd-EOB-DTPA; RECIST

Introduction

Magnetic resonance imaging of the liver is performed with a combination of non-contrast and post-contrast imaging. This results in an examination with multiple series. For example, the post-Gd images include multiple phases following IV contrast administration.

Neuroendocrine tumor liver metastases (NETLM) are commonly hypo intense on the T1 weighted images (TWI), hyper intense on the T2 weighted images (T2WI) and on diffusion weighted images, (DWI) show restricted diffusion. On the post-Gd series, the NETLM are commonly hypervascular on the post-Gd series and demonstrate washout relative to the liver [1–4]

Gd-EOB-DTPA is a hepatobiliary MR contrast agent. Approximately 50% of this agent is excreted through the liver. The liver uptake is dependent on the expression of Organic Anion Transporting Polypeptide 1B3 (OATP1B3) and other polypeptides. [4–6]. Metastatic disease, i.e. NETLM, does not express these proteins and do not demonstrate uptake of the agent in the hepatobiliary phase of contrast administration.

The MR examination of the liver with Gd-EOB-DTPA usually includes a late arterial phase (fluoro triggered at approx. 20s), a portal venous phase (approx. 60s), delayed phased (approx. 2min), 5min post- Gd and 20min post-Gd images. The combination of these post-Gd images and pre-Gd images (T1 (in/out-of-phase), T2W, and DWI) results in at least 9 set of images of the same anatomy. The appearance and size of NETLM may vary depending on the MR series or phase of contrast administration.

The response to treatment of liver metastases can be assessed with the RECIST criteria. This criteria depends on the measurement of lesion diameter and a specific threshold diameter change. This threshold change in diameter will define a lesion that is stable disease (SD), shows partial response (PR) or shows progression of disease (PD) [7]. For example, for a lesion that measures 1cm prior to treatment, an increase in size to 1.2 cm or larger will be considered as PD. (Table 1).

We hypothesized that the NETLM measurements would change depending on the MR sequences and phases of contrast enhancement. This may result in sufficient variation that may exceed the size threshold for partial response or progression of disease as defined by the RECIST criteria. We also hypothesized that a specific MR series will result in a superior inter-observer variability of lesion size measurement.

Our goal is to measure the size of the NETLM on the various MR series (T1, T2, DWI, pre- and post-Gd) and to compare the measurements of the size of NETLM between observers and between MR series. We proposed that the series with the highest inter-observer agreement should be selected as the best series for the evaluation of treatment response based on the RECIST criteria. Our secondary goal is to compare the detection of NETLM between the various MR series.

Methods

Patient Population

This is a retrospective institutional IRB approved study. Informed consent was waived. During a 23 month period 759 examinations of the abdomen were obtained with Gd-EOB-DTPA in patients with NETLM. Inclusion criteria that included patients with a diagnosis of NETLM, patients who had no prior liver directed therapy and patients that had a complete MR examination performed at 1.5T with the same platform (GEMS Milwaukee Wisconsin) were applied. This resulted in 30 patients that met all the inclusion criteria.

MR examination

The complete MR examination consisted of T1 weighted sequence. This included in-phase (IP) and out-of-phase (OOP) images. The T2W were obtained with a fast spin echo sequence. DWI (at B values of 0 and 800s/mm² or at B values of 50, 400, and 800 s/mm²), pre-contrast and post-Gd-EOB-DTPA injected at 1cc/sec. 3D spoiled gradient echo Liver Acquisition Volume Acquisition (LAVA, GEMS, Milwaukee Wisconsin) series were obtained. The post-Gd MRI was acquired in the late arterial phase (fluoro-triggered at approximately 20s), 60s, 120s, 600s, 20min (hepatobiliary phase; HBP) (Table 2). The patients were not excluded if pre- or post-systemic therapy has been initiated. Only a single time period in the patient's treatment timeline was used for the measurement of NETLM lesion size.

Target Lesion Identification and Lesion Measurement

One experienced radiologist selected a maximum of 4 target lesions per patient on the PACS (Picture Archive and Communication System; IntelliSpace, Koninklijke, Philips, Andover MA). An electronic arrow was placed near each target lesion on the hepatobiliary phase (HBP), 20min post-Gd, of contrast administration.

The lesions were characterized as liver metastases based on the clinical history of a pathological confirmed primary neuroendocrine tumor, the official radiology report, and the independent evaluation of the MR examination by the experienced reader. This diagnosis was also confirmed later by the individual assessment of the other readers based on the

pattern of enhancement. NETM typically enhance in the early arterial phase, and wash out on the delayed phase of contrast. They have a high signal on the T2 and the DWI and a low signal on the T1 weighted images (need ref).

Four experienced abdominal radiologists reviewed the entire MR examination. This included the radiologists that placed the arrow on each lesion. In each series, each of the four readers individually, reviewed the HBP images and identified the maximum of 4 lesions per patient. Then each reader placed an electronic ruler on the diameter of each of the target liver metastases on each series. A total of 9 electronic rulers were placed on the images and were saved in the PACS. One ruler placed for each of the following series: (i) in-phase, (ii) out-of-phase, (iii) T2W, (iii) DWI, (iv) pre-Gd, (v) late arterial, (vi) 60s, (vii) 120s, (viii) 600 and (ix) 20min series, respectively. For the DWI, one B-value was selected to measure the lesion (B-0, 50, 400, or 800sec/mm²).

To minimize bias, the measurements were not recorded at the time the rulers were placed. Also to minimize reader bias the review of the images was performed by series and not by lesion. The readers reviewed each series separately. If a lesion that was detected on the HPB and was not seen on another series, it was considered “not detected”. In this situation, the reader placed a region of interest-circle (rather than a ruler) in the expected location of the lesion. This was to alert that at the time of the actual measurements recording, that the reader had looked at the anatomic location and did not detect a lesion to measure. A lesion was considered detected by a series if at least 3 out of the 4 readers detected that lesion in that series.

Once all the rulers were saved in the PACS system, at a later time, two radiologists that were also readers, in consensus *recorded* a single measurement for each of the liver lesion on each series. This was performed for each of the 30 patients for the 4 radiologists. This session also confirmed that all radiologists measured the same corresponding lesions. The consensus recording of the lesion size was used to diminish transcription errors. The measurements were read back and forth between the two recording radiologists to minimize any “dyslexic” errors. During this recording of measuring data no actual lesion measurement was performed. The 2 radiologists only recorded the measurement on the electronic ruler placed by each radiologists.

Statistical Analysis

The comparison of mean lesion size for each patient by sequence was evaluated based on linear mixed model. Patient lesion within patient, and reader were considered as random effect in the linear mixed model. Lesion size was transformed to the logarithmic scale before modeling due to skewness in the data. The HPB was used as reference sequence for pairwise comparisons. This was decided as this was the original series used to identify the lesions. Dunnett’s adjustment was used to control overall type I error rate at 5% for all pairwise comparisons.

The sensitivity for detection of each lesion was compared to HBP-Gd images. Variance was estimated using variance component analysis. Sources of variation include: between patients, between lesions within patient, between readers, and random error (noise). Percent

variation was calculated as estimated variance divided by the sum of all variance. P-value is for test against the null hypothesis that variance is equal to zero. All tests were two-sided and p-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS version 9 (SAS Institute, Cary, NC).

Results

Patient demographics

17 male and 13 female (average age 63 y.o; 35–84 year old) patients were included in the study. 103 NETLM were evaluated in our study. 37 NELM were smaller than 2cm, 63 measured between 2–5cm, and 3 NETLM were larger than 5cm.

Lesion size and detection

There was no significant difference in the mean size of the lesion when compared to the HBP, T2WI, arterial and the 5 min-post Gd sequence (Tables 3 and 4). When comparing the size measurement on the HBP with the size of the lesion measured in DWI, the measurement of lesion size on DWI series were on average 6% higher than those on T1W 20min $P < .0001$ (Table 3). T2W was the closest to HBP-Gd ($p > 0.99$). Lesion sizes measured with the other sequences were significantly smaller than those measured in HBP-Gd (Table 3). All of the other sequences produced lesion size not significantly different from T1W 20min. (Table 4). When comparing the smallest measurement to the largest measurement of the same lesion between series, a size difference of more than 20% was observed in more than 67% of the lesions (67, 75, 82, and 85% for each reader; Figure 1). A 20% increase is the threshold for PR on the RECIST criteria.

Some lesions were not detected in all series (Figure 1). The gold standard for lesion detection was the HBP as this was the series selected to identify the lesions. The sensitivity of detection for all series was less than for HBP-Gd (Table 5). However, of the entire set, T1 out-of-phase and the post-Gd at the late arterial phase, 60s and 300s were significantly different. If we set 95% lesion detection as target rate, sequences that detected 93% or less lesions will be considered inadequate: This includes T1 (out-of-phase), T1 post-Gd (arterial, 60s, and 300s).

Inter-reader variance

Inter-reader variance was less than 1% of total variance for all sequences (Table 5). The 20 minute HBP post-Gd series had the smallest inter-reader variability and post-Gd at 60s had the largest (Table 6).

Discussion

To our knowledge, the comparison of lesion size measurement for NETLM for each of the MR sequences and phases of contrast administration utilizing Gd-EOB-DTPA has not been published.

In our results we found that lesion detection depended on the series use for measurement. Using 95% lesion detection as target rate, sequences that detected 93% or less lesions were

significantly lower than target. This includes T1 (out-of-phase), T1 post-Gd (arterial, 60s, and 300s). The decreased sensitivity of the out-of-phase series was mainly due to the obscuration of liver lesions in a fatty liver. In this setting, there is a loss of contrast between lesion and liver on the T1 (out-of-phase) series [8]. The NETLM are hypervascular tumors that usually show arterial enhancement and washout [9, 10]. However, when the arterial phase was suboptimal (due to timing of injection or motion artifacts) lesion detection is compromised [11–14]. For the 60s and 300s, the lack of detection was probably due to the lack of washout relative to liver at these times. At the 300s post-Gd images there are competing factors of washout of the NETLM and the enhancement of the liver due to Gd-EOB-DTPA uptake [13, 14]. This results in decreased contrast.

Our results also indicate that Gd-EOB-DTPA provided a relative higher sensitivity for lesion detection. This should be cautiously interpreted in the context that the HPB was considered the gold standard. In our results, we also found for 67% of the lesions (for one reader), the difference in lesion size measurements of the same lesion in different series by the same reader was larger than 20%. This is of potential major clinically significant difference as difference may characterize a lesion as progressive disease by RECIST criteria just comparing the MR series in the same study.

Our results also indicate that the 20min HPB series provided the lowest inter-reader variability. This may have been due to the clear definition of the margin of the lesion. In addition, there is lack of blurring of the margin due to edema. The relative improve definition allow the detection of the similar angle for the measurement of lesion diameter. On irregular lesion margins, the angle to of the ruler to the back of the patient between readers 1 and 2, were different. We did not quantify the difference in the angle of the electronic ruler between readers. This inter-observer variability may be of important clinical significance as the assessment of response to treatment by RECIST criteria may be measured by different radiologists. Thus, we recommend the HPB series to evaluate changes in liver size following treatment.

For non-Gd enhanced images, the T2WI is the recommended series for the evaluation of lesion size on sequential imaging. This concurs with prior reports of the value of T2WI in the assessment of liver lesions with MR in patients with NETLM [2]. The T2W provides high contrast between lesion and liver. Although DWI is also T2-weighted series, the artifacts due to motion degrades the evaluation.[15]

Our study has some limitations. The NETLM were not all pathological proven. However, the combination of clinical history of pathologically proven NET primary tumor and the evaluation of the MR imaging features (by each of the four readers) provides high certainty to the diagnosis. One of the limitations is that we used the HBP to assess the index lesions. Another limitation is the retrospective nature of the examination. This resulted in slightly inconsistent MR techniques. To minimize this limitation we only selected a single MR platform at 1.5T and only complete MR examinations. Another limitation was that the DWI images were not all obtained at the same B-values. To minimize this limitation, the readers were free to select the images with the B-value that provided the most confident measurement. Another limitation is that the electronic ruler placement for each lesion was

performed at the same seating for all series. However, to wait the minimum of 1–2 weeks gap between measurements would have resulted in a minimum of 10 to 18 weeks of data recording. This 1–2 week will minimize any bias in the placement of the ruler. To minimize this limitation, the reader did not record the measurement at the time the electronic ruler was placed. The measurements were recorded at a later time. By placing the ruler and not recording the measurement the radiologist was not able to adjust the ruler to fit previous measurement. To also minimize this limitation, the reader did not look at the actual measurement generated during the placement of the ruler. This limitation was further reduced by including four readers. Evaluation of these results to other malignancies with metastatic disease to the liver may yield similar results. This evaluation may be an important direction of MR research in the near future.

In conclusion, although the study had some limitations, we suggest that in the assessment of liver metastases from neuroendocrine tumor with RECIST criteria a single series is to be selected to measure the lesions. Based on our data the 20min hepatobiliary phase is the best series to measure NETLM. This should be the considered the best series for imaging evaluation of tumor response by RECIST criteria in NETLM.

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Figure 1.

65 year old female with neuroendocrine tumor liver metastases. (a –f) Liver lesion measurements by the same reader on the same lesion. (a) Axial T1 in-phase image of the liver. The metastatic mass in segment IV measured 2.15cm on this series. The arrows are for demonstration purpose only. (b) Axial T1 out-of-phase image of the liver. On this series, the same lesion in segment IV measured 2.46cm. (c) Axial T2WI image of the liver. The metastatic mass in segment IV measured 2.94cm. (d) Axial DWI ($B = 800 \text{ mm}^2/\text{sec}$) image of the liver. The same lesion measured 2.67cm. (e–j) pre-Gd, late arterial phase, portal venous, 120s, 300s, and 20min 3D gradient echo images, respectively. The lesion in segment IV measured: 2.75cm, *not seen on the late arterial phase*, 2.08cm, 2.6cm, 2.45cm, and 2.74cm, respectively. The difference between the smallest measurement and largest measurement was 0.79cm. For the 2.15cm measurement, this corresponds to an increase of 36% in size. Figures (k–m) compares the measurements of the same lesion in segment IV at

the hepatobiliary phase for the other 3 readers: (k) 2.62cm, (l) 2.81cm, and (m) 2.67cm, respectively. The maximum difference between the readers for this lesion was 0.19cm.

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Table 1

Definition of objective response according to the RECIST criteria.

	RECIST
Response	Modification of the sum of the longest diameter of each target lesion
Complete Response	Disappearance of all the target lesions confirmed at 4 weeks
Partial Response	At least 30% decreased in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter, confirmed at 4 weeks
Stable Disease	Absence of criteria of partial response or progressive disease
Progressive Disease	At least 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesions

Table 2

MRI pulse sequence protocol.

	T1 (OOP)	T1 (IP)	T2 (FS)	Pre- and Post-Gd	DWIEPI
	2D FSPGR	2D FSPGR		3D FSPGR	(B-0, 400, 800)
# ECHOES/SHOTS	2	2	1	1	1
TE1/TE2 (ms)	2.2–2.4	4.2–4.8	85	min	Min (~ 50–60)
TR/#R-R (ms)	120	120			
FLIP ANGLE	85	85		15	
ETL			16		
FOV (cm)	48	48	48	48	48
SCAN THK (mm)	6	6	6	5–6 (–2.5)	6
FREQ × PHASE	256 × 160	256 × 160	256 × 160	256 × 128	100 × 160
NEX	1	1	4	1	1, 4, 6
PHASE FOV	0.9–1.0	0.9–1.0	0.75–1.0	0.75–1.0	0.75–1.0

TR: Repetition time, TE: echo time, ETL: echo train length, FS: Fat Saturated, FOV: field of view, THK: Thickness, NEX: number of acquisition. Post-Gd images were obtained at late arterial phase (fluoro-triggered), 60s, 180s, 300s, and 20min post-Gd injection. Gd-EOB-DTPA was injected at 0.25mmol/kg at 1cc/sec.

Table 3

Summary of estimated mean lesion size by sequence based on linear mixed model.

Sequence	Estimated Mean Size (cm)	95% LCL	95% UCL	Significantly Different from T1W 20min
DWI	1.90	1.61	2.24	Yes
T1W 20min	1.80	1.53	2.12	N/A
T1W 5min	1.74	1.48	2.06	No
T1W arterial	1.84	1.55	2.17	No
T1W 120s	1.69	1.44	2.00	Yes
T1W in	1.72	1.46	2.03	Yes
T1W out	1.74	1.47	2.05	Yes
T1W 60s	1.67	1.41	1.97	Yes
T1W pre	1.72	1.46	2.03	Yes
T2W	1.80	1.52	2.12	No

Table 4
Summary of pairwise comparison between all sequences with T1W 20min as reference.

Sequence	Reference Sequence	Estimated Mean Ratio in Size	Adjusted 95% LCL	Adjusted 95% UCL	Adjusted P-value
DWI	T1W 20min	1.06	1.02	1.09	<.0001
T1W 5min	T1W 20min	0.97	0.94	1.00	0.05
T1W art	T1W 20min	1.02	0.99	1.06	0.54
T1W eq	T1W 20min	0.94	0.91	0.97	<.0001
T1W in	T1W 20min	0.96	0.93	0.99	0.0014
T1W out	T1W 20min	0.96	0.93	1.00	0.02
T1W port	T1W 20min	0.93	0.90	0.96	<.0001
T1W pre	T1W 20min	0.96	0.93	0.99	0.001
T2W	T1W 20min	1.00	0.97	1.03	>0.99

Table 5

Summary of lesion detection by sequence. A lesion is considered detected by a sequence if at least 3 out of the 4 readers detected that lesion using the sequence. T1W 20min was set as gold standard for assessing lesion detection rate.

Sequence	Number of Lesions Detected by At Least 3 out of 4 Readers	%Detection (T1W 20min as Gold Standard)
T1W 20min	103	100.00
T1W 5min	93	90.29
T1W arterial	69	66.99
T1W 120s	95	92.23
T1W in	94	91.26
T1W out	90	87.38
T1W 60s	91	88.35
T1W pre	95	92.23
T2W	100	97.09
DWI	96	93.20

Table 6
Summary of inter-reader variability by sequence. Variance was estimated using variance component analysis.

Sequence	Source of Variation	Estimated Variance	95% LCL	95% UCL	P-value	Percent of Total Variation
T1W 20min	Inter-Reader	0.0011	0	0.0033	0.29	0.035%
T1W out	Inter-Reader	0.0018	0	0.0062	0.41	0.051%
DWI	Inter-Reader	0.0020	0	0.0069	0.41	0.062%
T2W	Inter-Reader	0.0022	0	0.0063	0.28	0.068%
T1W 5min	Inter-Reader	0.0024	0	0.0071	0.30	0.070%
T1W 120s	Inter-Reader	0.0026	0	0.0073	0.29	0.074%
T1W pre	Inter-Reader	0.0031	0	0.0088	0.30	0.088%
T1W arterial	Inter-Reader	0.0042	0	0.0130	0.36	0.093%
T1W in	Inter-Reader	0.0036	0	0.0100	0.28	0.106%
T1W 60s	Inter-Reader	0.0141	0	0.0463	0.39	0.456%