ORIGINAL ARTICLE

A REVIEW OF MRI APPEARANCES OF LIPIODOL IN CONVENTIONAL TACE (cTACE) TREATED HEPATOCELLULAR CARCINOMAS

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Background: The global burden of patients affected by chronic liver disease (CLD) has shown a steady rise over the last few decades and is now considered the 11th most frequent cause of death globally. In addition, as the world population is facing increased obesity rates coupled with alcohol consumption, these rates are predicted to continue to rise. The Objective was to assess the appearance of Lipiodol retention upon different MRI sequences with a special focus on non-contrast sequences. Lipiodol Trans-arterial chemoembolization (TACE) has become the standard treatment for unresectable hepatocellular carcinoma (HCC) without vascular invasion. However, data regarding Lipiodol TACE imaging via MRI is limited and results are not familiar to radiologists for regular assessment of treatment response. **Methods:** After IRB and EC approval, we included all those patients who underwent TACE treatment with Lipiodol and chemotherapeutic agent; having both 4-6-week post-treatment CT and MRI imaging. This criterion was fulfilled by a total of 25 patients. Only lipiodol-containing areas within the lesion were noted for signal intensities on all MRI sequences and labelled as hyperintense, isointense, hypointense and mixed intensity. Data was entered and analyzed by SPSS v27. Frequencies and percentages were calculated for qualitative data. **Results:** The most sensitive sequence in detecting Lipiodol retention was Fat suppressed T1 imaging sequence, with low signal intensity seen on T1 weighted fat-suppressed sequences in up to 76% of lesions. While on non-fat suppressed T1 weighted images, 60% of Lipiodol retention areas appeared hyperintense. 52% of lesions showed a hypointense appearance on the T2 weighted sequence. A much more variable appearance was seen in Diffusion-weighted imaging sequences demanding cautious interpretation. MR patterns were clearer in patients having more than 50% lipiodol retention on CT and lesion size more than 2 cm. **Conclusion:** While MRI is deemed as a reliable and most useful imaging modality for assessing HCC's following lipiodol TACE it requires cautious interpretation with knowledge of variable signal appearance seen on different imaging sequences.

Keywords: Lipiodol; Magnetic resonance imaging; Computed tomography; Hepatocellular carcinoma; Retention pattern

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INTRODUCTION

The global burden of patients affected by chronic liver disease (CLD) has shown a steady rise over the last few decades and is now considered the 11th most frequent cause of death globally.[1] In addition, as the world population is facing increased obesity rates coupled with alcohol consumption, these rates are predicted to continue to rise.[1] Worldwide CLDs account for more than 2 million deaths annually.[1] CLD over time leads to the development of cirrhosis which is present in 70–90% of patients who have primary liver cancer regardless of the aetiology.[1] Worldwide liver cancer/hepatocellular carcinoma (HCC) is ranked as the sixth most common cancer. While it is the fourth most common cause of cancer-related mortality[2] by the end of 2030 it is projected to become the third leading cause of cancer-related mortality if the current trends continue[3]. CLD is the commonest underlying aetiology for the development of HCC as it is found in more than 90% of HCC patients. The strongest risk factors are cirrhosis, chronic infection with HBV or HCV and NAFLD/NASH-associated CLD.[2,3]

The treatment choice for HCC is tailored to the patient's health status and disease stage following a tumour board discussion as per Barcelona Clinic Liver Cancer Scheme (BCLC) guidelines. BCLC guidelines take into account liver function, tumour stage, cancer-related symptoms and performance status of the patient and categorize patients into five stages: stage 0/very early, stage A/early, stage B/ intermediate, stage C/advanced and stage D/terminal stage.[4] Among these strata; the majority of the patients present with BCLC stage B or intermediate disease. For BCLC stage 0 and stage A the treatment of choice is liver transplantation and where not possible surgical resection or ablative

techniques can be used. Unfortunately the majority of patients present with BCLC stage B / intermediate disease and if they are not suitable for liver transplantation then the main treatment modality remains trans-arterial chemoembolization (TACE).[4] As there is often a time lag in procuring a suitable liver for transplant purposes TACE can be used in these patients as a bridge to transplantation or if no deceased donor or living related donor can be found then; TACE can be offered as the sole palliative treatment option alongside systemic chemotherapy if appropriate.

TACE can be performed using chemotherapeutic agent emulsified in an ethiodized oil (Lipiodol) called conventional TACE (cTACE) or DEB-TACE using drug eluting beads/microspheres. Several randomized controlled trials (RCTs), systemic reviews and meta-analysis have confirmed the supremacy of cTACE over the best supportive care for intermediate/BCLC stage B HCCs and cTACE has been considered a standard treatment option for BCLC stage B/ intermediate stage HCCs.[5]

Regarding cTACE; the drug-carrying capacity of the ethiodized oil combined with the synergistic effect of arterial embolic material increases the anti-cancer effect of the chemotherapeutic agent. Lipiodol is the most widely adopted ethiodized oil for TACE due to its multifunctional properties. It is accumulated in HCC and when injected with a chemotherapeutic drug provides better benefit than the drug alone. It gives an embolic effect to the tumour microcirculation.[6] Further; Lipiodol can be used as an imaging marker for Computed Tomography (CT) apart from its drug carrying ability. It can also use as a tumour response marker based upon the fact that the proportion of Lipiodol tumour retention can be used to determine tumour necrosis.[7] Lipiodol can stay opaque to various forms of radiation and thus, it can be used in CT imaging.[8]

Imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) play a key role in assessing treatment response after TACE.[6] The CT imaging findings after TACE have been widely reported in the literature but due to the radiopaque properties of Lipiodol, subtle areas of arterial enhancement cannot be readily appreciated and residual disease is not reliably quantified.[7,8] The volume of data characterizing the imaging appearances of Lipiodol on MRI following cTACE is limited and variable. In addition, the imaging findings on MRI are not familiar to many diagnostic radiologists who are not too infrequently asked to report these studies, especially when the patient is unable to attend the tertiary referral centre for follow-up.[8] Therefore, there is a need to quantify and characterize the typical and atypical imaging appearances following cTACE on MRI and in addition, we have been able to correlate these findings to those seen on CT in the same cohort of patients. In this study, we assessed areas of Lipiodol retention based on their signal intensities on dynamic MRI performed post cTACE in those patients who had also undergone CT evaluation immediately before MRI with only a short time lag between the two studies.

MATERIAL AND METHODS

This retrospective cross-sectional study was conducted after IRB and EC approval and informed consent was waived. The study was conducted from January 2018 to December 2021. Only those patients who underwent Lipiodol TACE (cTACE) treatment and had both CT and MRI examination in the ensuing 4-6 weeks were enrolled in the study. A total of 25 patients fulfilled the criterion.

MRI was performed on a 1.5T Toshiba Titan MRI scanner. T1 weighted non-fat suppressed images, T2 weighted images, Diffusion-weighted images (DWI), apparent diffusion coefficient (ADC) maps and T1 weighted fat-suppressed sequences along with dynamic MRI, i.e., post contrast images were obtained. Liver CT scans were performed via Somatom Definition Edge Siemens (128-slice CT scanner) and 320-slice Toshiba Aquillon one. Dynamic post contrast images along with non-contrast images were obtained.

All images were reviewed for desired data on the Picture Archiving and Communication System (PACS) at the workstation. The patients were divided into two study groups based on Lipiodol retention on CT. Group 1 consisted of post-treatment lesions with more than 50% uptake while group 2 consisted of post-treatment lesions with less than 50% uptake. The pattern of signal intensity in the lipiodol retention areas within the lesions was noted on all MRI sequences and labelled as hyperintense, isointense, hypointense and mixed depending upon MR intensity. Post-treatment lesion size was also noted and compared. Data was entered and analyzed by SPSS v27. Frequencies and percentages were calculated for qualitative data.

RESULTS

The mean age of the patients was 60±8.5 with male preponderance (n=18, 72%). On T1 weighted non-fat suppressed images, 15 (60%) of the Lipiodol retention areas appeared hyperintense, 7 (28%) appeared hypointense and 3 (12%) remained isointense. On T2 weighted images, 13 (52%) appeared hypointense, 8 (34%) hyperintense, 1 (4%) isointense and 3 (12%) showed mixed intensity signals. Diffusion-weighted images showed 11 (44%) to be hypointense, 6 (24%) hyperintense, 7 (28%) isointense and 1 (4%) showed mixed intensity. ADC maps showed 11 (44%) Lipiodol retention areas as hypointense similar to DW imaging, while 3 (12%) hyperintense, 10 (40%) isointense and 1 (4%) showed mixed

intensity. Fat-suppressed T1 weighted images showed the best demarcation with 19 (76%) being hypointense, 3 (12%) hyperintense and 3 (12%) remaining isointense (Figure-1).

Size-wise distribution showed post treatment lesion size to be the major determiner, i.e., less than <5cm lesion having a higher ratio of more than 50 % lipiodol retention on CT (Figure-2). However, no significant statistical difference was found ($\chi 2$=1.54, *p*=0.23). Among group 1 (n=16) having more than 50% lipiodol retention on CT, 14 out of 16 i.e. 75% of the lipiodol retention areas in cTACE treated HCCs appeared hyperintense on T1 weighted images, 10 out of 16, i.e., 62.5% appeared hypointense on T2 and 13 out of 16, i.e., 81.25% appeared hypointense on fat suppressed images. On DW and ADC maps 8 out of 16, i.e., 50% appeared hypointense. Figure-3 shows a detailed pattern of MR intensities in post treatment lesions with more than 50% uptake.

Among group 2 (n=10) having less than 50% Lipiodol retention on CT, 4 out of 10, i.e., 40% of the lipiodol treated HCCs appeared hyperintense on T1 weighted images, 4 out of 10, i.e., 40 % appeared hyperintense on T2 and 6 out of 10, i.e., 60 % appeared hypointense on fat suppressed images. On DW and ADC maps 40 % and 60% appeared isointense. Figure-4 shows a detailed pattern of MR intensities in the post treatment lesions with less than 50% uptake. Since fat sat images showed the best differentiation pattern, we looked for the size wise distribution on fat suppressed images. Table 1 shows the cross tabulation of fat suppressed image signal intensity and size.
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Less than 2 cm sized post-treatment lesions showed a less clear pattern on Fat-Sat MRI compared to larger ones. A significant relation was observed for post-treatment lesions being hypointense with a size more than 2 cm ($\chi 2$=6.57, *p*-value-0.009). However, no such pattern was observed for other imaging sequences.

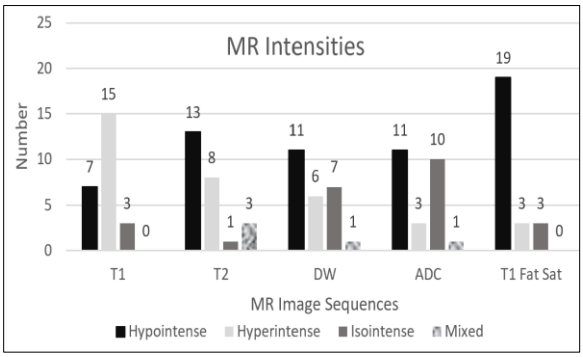


Figure-1: Lipiodol retention upon MRI after TACE treatment.

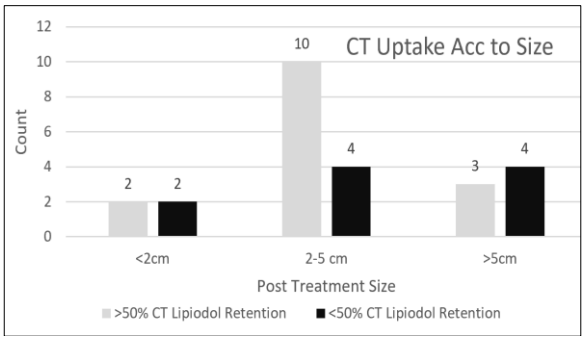


Figure-2: Size wise distribution of pattern of CT uptake

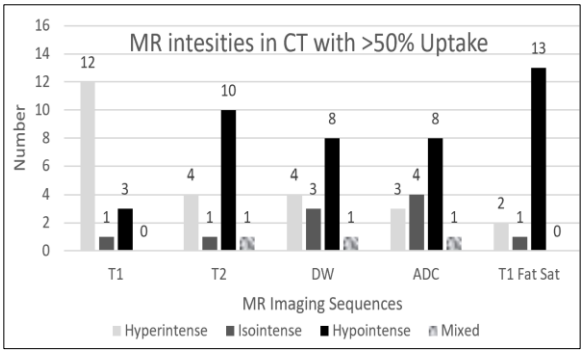


Figure-3: Pattern of MR intensities in post treatment lesions with more than 50% uptake.

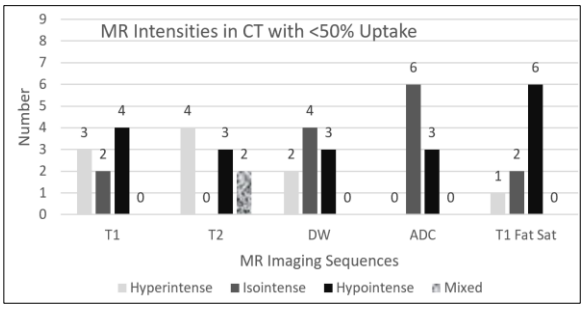


Figure-4: Pattern of MR intensities in post treatment lesions with more than 50% uptake.

Table-1: Fat Sat T1 signal intensity* Post Treatment size Cross tabulation

Count					
		Post Treatment Size			Total
		<2cm	2-5cm	>5cm	
Fat Sat T1	Hyperintense	2	0	1	3
	Isointense	1	2	0	3
	Hypointense	1	12	6	19
Total		4	14	7	25

DISCUSSION

For the majority of stage B BCLC / intermediate stage patients; TACE remains the most suitable treatment. This procedure results in tumour necrosis as a combination of chemotherapeutic agents along with arterial embolic

material is delivered within the tumour bed using an endovascular technique. Lipiodol retention in Lipiodol mediated TACE therapy is an indicator of the extent of tumour necrosis and can be readily assessed with MRI and CT.[9]

Various studies in the literature have reported the superiority of MRI over CT scan for assessment of post cTACE response as inherent hyperdense properties of lipiodol on CT scan can mask residual disease. Among MRI sequences; the highest demarcation was observed with fat suppressed T1-weighted images as shown in Figure 5. The reason for this behaviour is the fatty acid nature of Lipiodol. The results are concordant with a previous study, in which a similar pattern was obtained with the highest demarcation observed by a lipid suppression technique in T1-weighted images with more than half of lipiodol-treated HCCs (63%) showing low signal intensity.[8] The reason for the lesions appearing hypointense is easily understood and related to the inherent lipid content in Lipiodol which is suppressed on the T1 fat saturation sequences giving a low signal.[8] What is less well understood is why a few lesions appear bright on fat suppression and are hypothesized to be related to haemorrhage, coagulative necrosis or liquefying necrosis which are common in cTACE treated tumours as shown in Figure 6. Hyperintense regions with liquefying necrosis will correspond with diffusion restriction on ADC maps.[10,11]

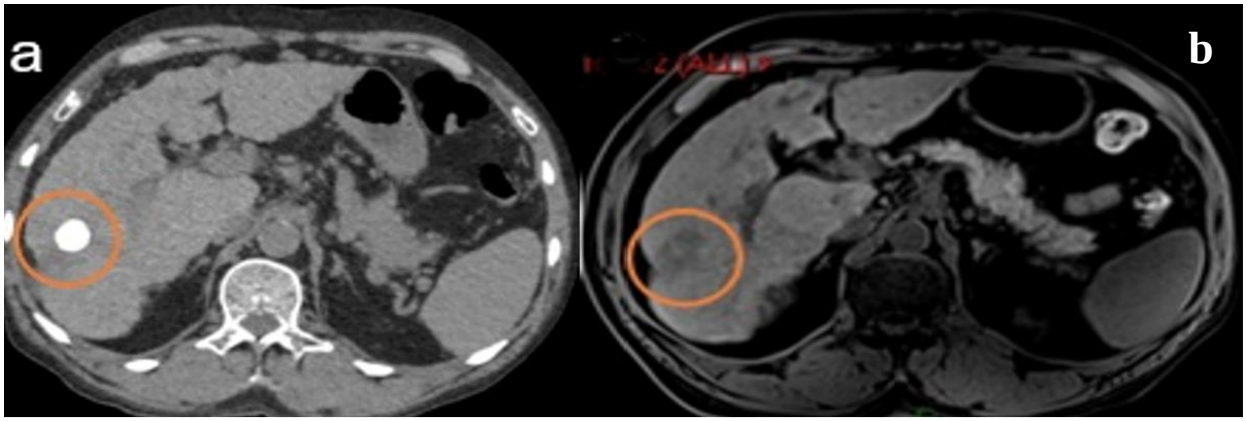
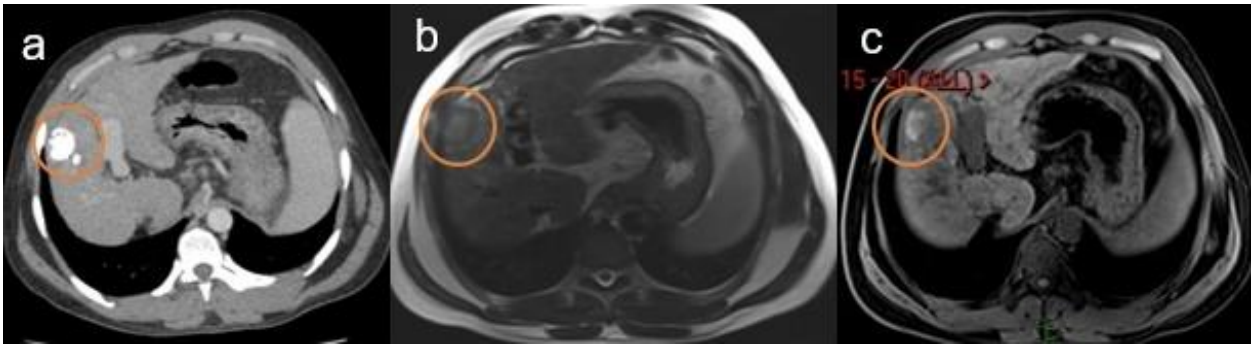


Figure-5: a and b. Figure 5a shows concentrated lipiodol in a lesion on CT scan. Figure 5b axial non contrast T1 fat-suppressed image showing lipiodol within the lesion appears as low signal intensity on T1 fat suppressed sequence.



Figures-6 a, b and c. Figure 6a shows concentrated lipiodol in a lesion on CT scan. Figure 6b and 6c show axial T2WI and axial non contrast T1 fat-suppressed image showing lipiodol within the lesion appears with high signal intensity on both T2WI and T1 fat suppressed sequence.

T1 non-fat suppressed weighted images showed the majority of the Lipiodol treated HCCs to be hyperintense, the reason is that the lipid natured substances appear bright on T1 weighted non-fat suppressed sequences.[12] While on T2 weighted sequences, the majority of the lesions appeared hypo-intense, which is in-line with previous observations about fat intensive dark images in T2-weighted images[8] but no conclusive demarcation can be drawn from the results. In the case of ADC and diffusion, facilitated diffusion usually shows a good therapeutic response but due to the necrosed nature of the tumour, however, diffusion restriction may also be observed.[13] In our case only 8% showed diffusion restriction, 16% showed facilitated diffusion, and 28% of lesions were hypointense on both DWI and ADC maps. 48% of

lesions showed no specific pattern on DWI and ADC sequences.

The specificity and sensitivity of MRI can be further enhanced by utilizing subtraction imaging, especially in those cases where cTACE treated lesions exhibit hyperintense signals even on T1 fat suppressed images as seen in 3 of our cases. El Said et al took the dynamic fat suppressed images and performed the subtraction technique on pre contrast and post contrast images and showed the sensitivity and specificity of subtraction dynamic MRI to be 97% and 100% respectively.[14] Results of Metwally *et al* also showed dynamic subtraction imaging to have a sensitivity of 96% and specificity of 100%[15]. Since dynamic subtraction technique was not part of our imaging protocol hence could not be looked at in this retrospective study.

In this study, we have demonstrated the most commonly seen patterns and imaging characteristics on MRI sequences in lesions having >50% Lipiodol retention as confirmed on CT. The final analysis shows 81.25% of the lesions on T1 weighted fat suppressed images appeared hypointense whereas, on T1 weighted non-fat suppressed images, 75% of the cases were hyperintense (bright). Thus, these results show a clear demarcation for patients with greater than 50% CT lipiodol retention. In a previous study, tumour volumes were studied with both MRI and CT using volumetric lipiodol deposition as a reference, and it was concluded that MRI has a better sensitivity compared to CT scan.[9] In another study, for detection of post cTACE viable / residual tumour, MRI was deemed superior to multidetector CT (MDCT), considering inherently hyperdense properties of lipiodol on CT scan.[14,16]

However, in lesions with less than 50% CT Lipiodol retention, MRI results have not provided clear demarcations. Only 60% hypointense signal patterns were observed in T1 fat suppressed images whereas, 40% were hyperintense in both T1 and T2 weighted images thus exhibiting poor demarcation. In summary, MRI uses non-ionizing radiation as compared to CT, especially so when frequent follow-up imaging is performed and is good at suppressing inherent hyperdense CT appearances of lipiodol; it can be argued with these results that MRI is a reliable alternative and superior to CT scans for response evaluation in post cTACE treated lesions.

The limitations of our study include; a unicentric study with a relatively small sample size as the absence of post cTACE CT imaging led to the exclusion of the majority of the cases. Subtraction imaging was also not available in our study to confirm its significance. Further studies with larger sample sizes and with the use of subtraction imaging on MRI can be performed in the future to increase the credibility of MRI follow-up further.

CONCLUSION

Areas of post treatment lipiodol retention can be best detected on T1 weighted Fat suppressed images, where lipiodol appears as hypointense. On T1, Lipiodol retention appears as hyperintense and T2 as hypointense. Further utilizing subtraction imaging techniques on fat suppressed T1 weighted MRI results indicate MRI can be used as a reliable and effective means for observing Lipiodol retention and detecting residual disease in cTACE treated HCCs.

We found diverse and more variable appearance of lipiodol on Diffusion weighted imaging sequences therefore it should be interpreted with caution as no clear restriction or facilitated diffusion pattern was observed. MR patterns were clearer in patient having more than 50% lipiodol retention upon CT and lesion size more than 2 cm. While MRI is deemed as a reliable and most useful imaging modality for assessing HCC's following lipiodol TACE it requires cautious interpretation with knowledge of variable signal appearance seen on different imaging sequences.

AUTHORS' CONTRIBUTION

ZAK: Conceptualization and proofreading. AIR: Literature search, proofreading, editing. MR: Data collection, data analysis, write-up. JA: Literature search, write-up. HA: Data collection and interpretation. AAF: Data collection, proofreading.

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