Non-Invasive Differentiation of Liver Hemangiomas and Colorectal Metastases: The Role of Apparent Diffusion Coefficient in Reducing Unnecessary Liver Biopsies

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Abstract- Diffusion-weighted imaging (DWI) and the calculation of the Apparent Diffusion Coefficient (ADC) provide valuable functional information at the molecular level, which can aid in distinguishing hepatic lesions. This study aims to assess the role of MRI DWI and ADC values in differentiating between hepatic hemangiomas and colorectal liver metastases (CRLMs), focusing on lesion size and potential to reduce reliance on liver biopsy. In this prospective observational study conducted from January 2019 to February 2020 at Hiwa Cancer Hospital, 61 patients with newly diagnosed colorectal cancer (CRC) and suspicious liver lesions underwent abdominal MRI. Lesions were characterized using DWI with two b-values (b=50 and b=800 sec/mm²), and ADC values were calculated for both hemangiomas and metastases. The histopathological diagnosis of CRLM was confirmed for all cases. The study excluded larger or necrotic lesions and focused on lesion size influencing ADC values and ratios. Statistical analysis was performed using SPSS version 25. Hemangiomas demonstrated significantly higher ADC values and ADC ratios than metastases, particularly in smaller lesions (≤21.5 mm), with a $P<0.001$. In lesions >21.5 mm, while ADC values were less pronounced, ADC ratios remained significantly higher for hemangiomas ($P=0.02$). ADC values in left lobe lesions were slightly higher than those in the right lobe, although this difference did not reach statistical significance . MRI DWI with ADC measurement is valuable for differentiating hepatic hemangiomas from colorectal liver metastases, especially in smaller lesions. The significantly higher ADC values and ratios in hemangiomas can help avoid unnecessary biopsies and reduce the risk of metastasis seeding, which is particularly crucial in patients with resectable liver metastases.

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Introduction

Liver metastases are the most common type of liver lesion, occurring about 40 times more frequently than primary liver tumors. The liver is the most common site for metastasis in colorectal cancer (CRC) patients, both synchronously and metachronously. Isolated hepatic metastasis is reported in approximately 35% of CRC cases, and ultimately, 50-70% of CRC patients will develop liver metastasis throughout their disease (1,2). Early detection of liver metastasis is crucial, as it significantly influences treatment decisions and offers a potential opportunity for metastasectomy, which has been shown to improve survival outcomes (3).

In contrast, hemangioma is the most common benign liver lesion, with a prevalence of up to 20% in the general population (4). Due to its high frequency, atypical presentations of hemangioma are not uncommon, which can pose a diagnostic challenge. Approximately 42% of hemangiomas are

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subcentimetric, and while hemangiomas typically remain stable over time, about 17% may exhibit enlargement, with 40% of hemangiomas showing some degree of growth annually. While most hemangiomas are solitary lesions, up to 50% of cases may involve multiple lesions, often presenting with atypical imaging characteristics (5,6).

Magnetic Resonance Imaging (MRI) is the preferred imaging modality for detecting and evaluating focal liver lesions. However, even with dynamic liver MRI, differentiating between hemangioma and vascular metastasis can be challenging, leading to increased costs and diagnostic uncertainty (7). The introduction of Diffusion-Weighted Imaging (DWI) has expanded MRI's role by providing functional information at the molecular level, allowing it to act as a biomarker for tissue characteristics. Highly cellular liver metastases typically exhibit low Apparent Diffusion Coefficient (ADC) values, while benign lesions such as hemangiomas tend to show higher ADC values (8).

Several imaging features can lead to misinterpretation of liver lesions. For instance, capsular retraction is commonly associated with liver metastasis, but it is not exclusive to metastasis and may also be observed in hemangiomas (9). Furthermore, hemangiomas can sometimes appear non-enhancing on contrast imaging or demonstrate contrast retention, which can mimic metastatic lesions (10). Additionally, hemangiomas may not always exhibit the typical high signal on T2-weighted images (T2WI), which is often seen in benign lesions, making it more difficult to distinguish them from metastases (11). Conversely, necrotic metastases may show hyperintensity on T2WI, similar to the appearance of hemangiomas. These overlapping imaging characteristics can result in significant diagnostic confusion, underscoring the importance of quantitative ADC measurements to aid in the differentiation of hemangiomas and metastases, particularly in oncology patients (12).

Although liver biopsy is considered a relatively safe procedure, it carries inherent risks, including mechanical complications such as hemorrhage, as well as oncological risks like tumor seeding. These risks are especially concerning in patients with colorectal cancer liver metastasis (CRLM), as biopsy-induced seeding can lead to poor outcomes and reduced survival rates in those with resectable liver metastasis (13,14). Interestingly, imaging techniques alone provide approximately 98% accuracy in the preoperative characterization of solid liver lesions, with imaging and tumor markers offering superior diagnostic capabilities over liver biopsy in many cases (15).

Given the risks associated with liver biopsy and the potential for misdiagnosis based on imaging alone, the role of MRI DWI and ADC values in differentiating between hepatic hemangiomas and metastases from colorectal cancer becomes increasingly essential. This approach may help avoid unnecessary biopsies, reduce the risk of metastatic seeding, and provide more accurate preoperative assessments, particularly in patients with resectable liver metastases. This study aims to assess the role of DWI MRI and the numerical differentiation of ADC values in distinguishing between hepatic hemangiomas and liver metastases of colorectal cancer origin.

Materials and Methods

This observational study was conducted prospectively from January 2019 to February 2020 at Hiwa Cancer Hospital in Sulaimani, Kurdistan Region, Iraq. The study included 61 patients who had recently been diagnosed with CRC and were found to have suspicious liver lesions on abdominal CT scans as part of their metastatic workup. Based on recommendations from a multidisciplinary team, all patients underwent abdominal MRI for further lesion characterization. Only patients with confirmed histopathological diagnoses were included to ensure histopathological validation, regardless of lesion size. In cases where multiple liver lesions (either metastases or hemangiomas) were present, only one lesion per patient was selected to reduce variability, and this single lesion was examined histopathologically. All CRLMs were confirmed to be adenocarcinomas. Ethical approval for the study was obtained from the University of Sulaimani College of Medicine, and informed consent was obtained from all patients.

Histopathologic diagnosis

The histopathological diagnosis of colorectal liver metastases (CRLMs) was confirmed by liver biopsy. All CRLM lesions were confirmed as adenocarcinomas. The histologic diagnosis was based on standard criteria, including identifying glandular structures, nuclear atypia, mitotic activity, and mucin production.

Diagnostic approach for liver lesions

Hepatic hemangiomas are defined as benign vascular lesions composed of clusters of blood vessels. These lesions are most commonly asymptomatic and are often discovered incidentally on imaging. On MRI,

hemangiomas typically demonstrate a peripheral nodular enhancement pattern on contrast-enhanced imaging, with high signal intensity on T2-weighted sequences due to their blood vessel content. The diagnosis of hepatic hemangiomas in this study was based on characteristic imaging features observed on dynamic contrast-enhanced MRI, and histopathological confirmation was not performed, as the imaging characteristics are generally sufficient to establish the diagnosis.

MRI imaging protocol

All patients were scanned using a Siemens 1.5T MR system (MAGNETOM Aera). The MRI protocol included the following sequences:

- Axial Diffusion-Weighted Imaging (DWI): TR/TE=7100/64 ms, acquired with two b-values: b=50 and b = 800 sec/mm².
- Coronal and Axial T2 Haste: TR/TE = 1000/89 ms.
- Axial T2 Haste Fat Suppression: TR/TE=1000/93 ms.
- Axial Opposed-Phase In/Out-Phase T1WI VIBE Dixon: In-phase TR/TE=6.8/4.8 ms, out-of-phase TR/TE=6.8/2.4 ms.
- Axial and Coronal Pre-Contrast T1WI VIBE Dixon: TR/TE=6.8/4.8 ms.
- Axial Pre- and Post-Contrast T1 Fat Suppression VIBE: TR/TE=4.8/2.3 ms.

Bowel preparation

To minimize motion artifacts and partial volume effects from gastrointestinal contents, patients underwent bowel preparation the day before the MRI scan using castor oil (Ricinus communis). This preparation method was chosen due to its effectiveness and lack of recognized side effects.

Contrast administration

All patients received an intravenous injection of gadolinium contrast (0.1 mL/kg body weight) before imaging.

Diffusion-weighted imaging and ADC calculation

Axial diffusion-weighted sequences were acquired with two different b-values (b=50 and b=800 sec/mm²), using a breath-holding technique to improve lesion detection. The MR scanner generated ADC maps using these b-values, allowing for precise ADC measurements of the lesions.

For each lesion, a circular region of interest (ROI) was placed (0.5-2 cm²) on the lesion itself, excluding areas of necrosis. In cases of necrotic lesions, the ROI was placed on the enhancing component of the lesion after gadolinium contrast administration. An ROI was placed on enhancing liver tissue outside of the hepatic vessels following contrast administration to assess the ADC value of normal liver parenchyma.

Image analysis

ADC measurements were obtained using a dedicated workstation (HP server-based, syngo. via Version: VB10B, EZIO MX 241W). MR images were reviewed and analyzed by two expert radiologists with over ten years of experience in abdominal imaging. Both radiologists were blinded to the histopathological findings and conducted the review in consensus.

This imaging protocol, combined with quantitative ADC analysis, allowed for detailed characterization of the liver lesions and facilitated the differentiation between hepatic hemangiomas and metastases from colorectal cancer.

Statistical analysis

The statistical analysis for this study was performed using IBM SPSS Statistics software (Version 25.0, IBM Corp., Armonk, NY, USA). Data were expressed as means±standard deviations (SD) for continuous variables and frequencies (percentages) for categorical variables. Data distribution was assessed using the Shapiro-Wilk test to determine whether the variables followed a normal distribution.

To compare the ADC values between hepatic hemangiomas and liver metastases from colorectal cancer (CRLMs), the independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. The mean ADC values and ADC ratios (ADC of hemangiomas vs. ADC of metastases) were compared for statistical significance.

Results

Table 1 presents the distribution of hepatic lesions, including hemangiomas and metastases, in terms of gender, location, size, and age range. Most hepatic lesions in this cohort were metastatic, located predominantly in the right liver lobe, and more common in females. Lesions were most frequently found in the 41-70-year age range, with a predominant size of 20-30 mm. Hemangiomas were more commonly found in younger patients and were smaller in size compared to metastases.

Table 2 provides the ADC values and ADC ratios (ADC of lesion/ADC of parenchyma) for hepatic hemangiomas and metastases, with further stratification based on lesion size. The analysis reveals that hemangiomas exhibit significantly higher ADC values and ADC ratios compared to metastases, particularly in lesions ≤21.5 mm. In smaller lesions, the difference in ADC values and ratios between hemangiomas and metastases was statistically significant (P<0.001). Additionally, although the ADC values for both hemangiomas and metastases were similar in larger lesions (>21.5 mm), the difference remained significant (P=0.02) for ADC ratios.

Although the difference between right and left lobe lesions was not statistically significant, we observed that lesions in the left lobe tended to have higher ADC values and ADC ratios, as illustrated in Figure 1.

The MRI findings of a hemangioma in a patient with left-sided colonic carcinoma and the MRI features of CRLM in a postoperative patient are presented in Figures 2 and 3, respectively.

Table 1. Distribution of hepatic lesions by gender, size, location, and age range

No. and % of lesions		Gender distribution		Location	
		Male	Female	Rt. lobe	Lt. lobe
Hemangioma(n)	28	10	18	21	7
Metastasis(n)	33	19	14	23	10
Total(n)	61	29(47.54%)	32 (52.46%)	44 (72.13%)	17 (27.87%)

Size and no. of lesions		Age range distribution of hepatic lesions			
Size(mm)	**no.**	**Age range group (year)**	**No. of Hemangioma**	**No. of Metastasis**	**Total No. of lesions & %**
<20	16	31-40	7	3	10 (16.3%)
20-30	20	41-50	10	7	17 (27.8%)
30-40	9	51-60	5	7	12 (19.6%)
40-50	6	61-70	5	13	18 (29.5%)
>50	10	71-80	1	3	4 (6.5%)
Total	61	-	28 (45.9%)	33 (54.1%)	61 (100%)

Table 2. Comparison of ADC values and ADC ratios in hepatic hemangiomas and metastases based on lesion size

Variable	Hemangioma (×10^{-3}mm^2/s)		Metastasis (×10^{-3}mm^2/s)	
	Lesions ≤21.5mm	**Lesions >21.5mm**	**Lesions <35mm**	**Lesions ≥ 35mm**
ADC Range	1.395-3.115		0.566-1.188	
Mean ADC value	2.302 ± 0.379	2.117 ± 0.454	0.886±0.12	0.911±0.178
	2.209±0.428		0.899 ± 0.153	
Mean ADC value of parenchyma	1.059 ± 0.055		1.043±0.1	
Range and Mean ADC ratio	1.312 – 2.903		0.482 – 1.223	
	2.087 ± 0.401		0.867±0.157	

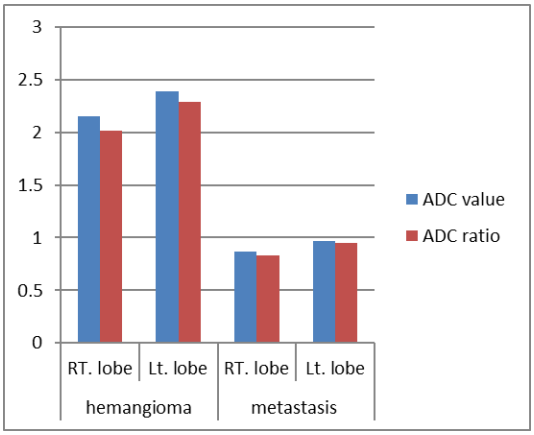

Figure 1. Comparison of ADC value and ratio (×10−3mm2/s) of right and left lobe lesions

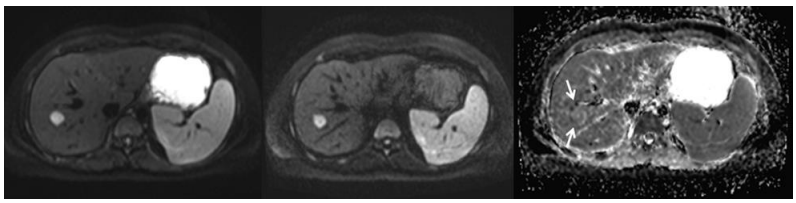

Figure 2. A 31-year-old female with left-side colonic carcinoma, iso-intense lesion on the ADC map seen in the right lobe (ADC value was 1.395 × 10−3mm2/s), which proved to be a hemangioma. (A and B) hyper-intense lesion on DWI at b value 50 and 800 respectively, (C) iso-intense lesion (arrow) on ADC map compared with liver background

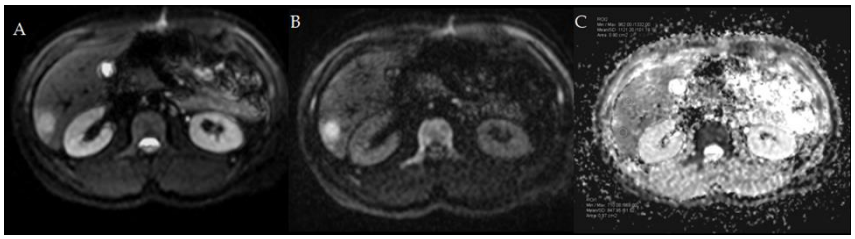

Figure 3. A 38-year-old man with colonic carcinoma; on a post-operative follow-up examination, he developed a liver lesion (ADC value was 0.847 ×10−3mm2/s), which is confirmed to be CRLM. (A and B) hyper-intense lesion on DWI at b value 50 and 800 respectively, (C) hypo-intense lesion on ADC map in comparison with liver background

Discussion

The preset study aimed to evaluate the role of DWI and ADC measurements in differentiating between hepatic hemangiomas and metastases, particularly in patients with CRC. While liver biopsy is considered the gold standard for the histopathological confirmation of focal liver lesions (FLLs), it is an invasive procedure that carries significant risks, including the potential for malignant seeding and hematogenous metastasis (16,17). Previous studies have documented seeding rates of 6%, 10%, and 19%, respectively (18-20). Additionally, liver biopsy has been associated with an increased risk of hematogenous metastasis, a concern emphasized by Kim *et al*. (21).

The effective treatment for isolated CRLM often involves metastatic resection, which has been shown to provide long-term survival benefits (22). This underscores the importance of accurately distinguishing between liver hemangiomas and metastatic lesions (22). Non-invasive imaging modalities, such as DWI, provide an invaluable tool for numerical differentiation, as they are less costly, non-invasive, and can significantly influence clinical decision-making and patient outcomes (23). Furthermore, definitive diagnostic imaging can guide neoadjuvant chemotherapy for downstaging liver metastases, reducing the need for biopsy, as demonstrated by Sheth *et al.*, (24).

Hemangiomas generally appear hyperintense on ADC maps, whereas metastases are typically hypointense. Our study's findings demonstrate that hemangiomas show significantly higher mean ADC values (2.209±0.428×10^{-3} mm^2/s) and ADC ratios (2.087±0.401) compared to CRLMs, which exhibited lower ADC values (0.899±0.153×10^{-3} mm^2/s) and ratios (0.867±0.157). These results are consistent with the findings of Bruegel *et al*., (25), Cieszanowski *et al*., (26), and Ergelen *et al*., (27), That demonstrated the ADC value and ADC ratio of hemangiomas were significantly higher than those of CRLMs. Based on these findings, lesions with an ADC value greater than 1.4 or an ADC ratio exceeding 1.3 are likely hemangiomas. In contrast, lesions with ADC values and ratios around 1.2 or lower strongly indicate metastasis.

A common source of variability in ADC values across different studies stems from various technical factors, including differences in MRI hardware, DWI parameters, b-values, and the regions of interest (ROI) used for ADC measurement. Other contributing factors include field strength, image quality, signal-to-noise ratios, and vendor-specific differences (28,29). Furthermore, factors such as motion artifacts, hepatic parenchymal diseases (e.g., hepatitis, cirrhosis), metabolic liver diseases, hepatic steatosis, and lesion size and location can influence ADC values (30). For example, larger lesions may have higher ADC values due to necrosis or complications like hemorrhage, inflammation, or thrombosis, particularly in larger

hemangiomas (31).

Previous studies have suggested that liver lesions in the left lobe may be more prone to misclassification or exhibit falsely elevated ADC values due to cardiac pulsation, bowel peristalsis, gas, and partial volume effects from adjacent structures (32,33). However, our study found no statistically significant difference between right and left lobe lesions. Interestingly, we observed that lesions in the left lobe exhibited slightly higher ADC values. Despite this, there were no misdiagnoses in our cohort, which is consistent with the findings of Parikh *et al*., (34).

We hypothesize that the rigorous bowel preparation in our study, including castor oil and fasting before MRI, helped significantly reduce motion artifacts and partial volume effects, particularly in the left lobe and peripheral lesions. This is especially relevant for hemangiomas, often located peripherally or subcapsularly (35).

Our study also highlighted the variation in ADC values concerning lesion size. Parikh *et al*., (34) observed a median size of 35 mm for metastases and 21.5 mm for hemangiomas, caution should be exercised when interpreting ADC values for larger lesions, as they may exhibit heterogeneous internal structures that affect diffusivity.

Several studies have investigated ADC values of hepatic hemangiomas and metastases from various primary cancers (25,26,34). However, our study focused on two potentially confounding liver lesions in CRC patients. This approach eliminated the diagnostic overlap that can arise when comparing metastatic lesions from different primary tumors. Since metastases are a heterogeneous group of lesions, their ADC values can vary based on histological type, vascularity, and other factors, as supported by Yalmiz *et al*., (6), Bruegel et al. (25), Ergelen *et al*., (27), Darbar *et al*., (36), and Javadrashid *et al*., (37).

To the best of our knowledge, this is the first study to specifically compare ADC values and ADC ratios for liver hemangiomas and metastases in CRC patients. While Heijmen *et al*., (38) and Koh *et al*., (39) investigated CRLM, they focused on different aspects. Koh *et al*., concluded that CRLM ADC values may be higher than liver parenchyma, likely due to central necrosis in chemotherapy-treated metastases (39). In contrast, our findings suggest that newly diagnosed liver metastases in CRC patients exhibit lower ADC values than normal liver parenchyma, reflecting the higher cellularity and restricted diffusivity of metastatic lesions, particularly in early-stage metastases.

Previous studies have proposed that the ADC ratio may be a more reliable diagnostic tool than ADC values when distinguishing between benign and malignant liver lesions or between hemangiomas and metastases from various primary tumors (6,40). According to Caraiani *et al*., (40) and Colagrande *et al*., (41), the ADC ratio can improve diagnostic accuracy. However, Yilmaz *et al*., (6) reported that ADC ratios did not provide additional diagnostic information beyond that obtainable from ADC values alone.

In our study, ADC values alone were sufficient to distinguish between hemangiomas and metastases. We found no additional diagnostic benefit from the ADC ratio. This may be because our cohort lacked underlying liver parenchymal disease. In cases with liver parenchymal disease, the ADC ratio is particularly valuable for differentiating lesions against a background of abnormal liver tissue, a concept supported by previous studies (42,43,6).

Our findings indicate that ADC values provide a reliable and non-invasive method for distinguishing between liver hemangiomas and metastases in newly diagnosed CRC patients with otherwise healthy liver parenchyma. Accurate ADC estimation offers a valuable alternative to liver biopsy, minimizing the risk of biopsy-induced metastasis, which can trigger neoangiogenesis and hematogenous spread, particularly in patients considered for hepatectomy. Also, the results showed that while ADC values are effective for differentiation, the ADC ratio does not offer significant additional diagnostic value over the individual ADC values in healthy liver tissue. Furthermore, errors from artifacts and partial volume effects in ADC mapping can be minimized with proper bowel preparation and fasting before MRI scanning. This approach ensures more accurate lesion characterization, particularly in challenging cases involving CRC metastases and benign hemangiomas.

Limitations

A key strength of our study lies in its focused approach, addressing potentially confusing lesions in a healthy liver background. By considering only one lesion per patient for analysis, we reduced variability and ensured our results were more precise. Additionally, we observed that the partial volume effect on the ADC map, caused by adjacent structures such as gastrointestinal tract contents, can be effectively minimized through fasting before MRI scanning. This careful methodology enhances the accuracy of ADC

measurements and reduces artifacts that could otherwise skew results. However, a notable limitation of our study is the relatively small sample size, which may affect the generalizability of our findings.

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