Newly detected liver nodules with a history of colorectal cancer: are they metastatic? Review of 2,632 cases in a single center

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Background: The diagnosis of newly detected liver nodules in patients with colorectal cancer (CRC) is crucial for determining prognosis and treatment. Accurate identification of benign nodules can help avoid unnecessary therapy. The aim of our study was to retrospectively review patients with CRC who underwent liver resection for benign liver nodules misdiagnosed as CRC metastasis (CRLM) in our institution.

Methods: We reviewed all patients with a history of CRC who underwent liver resection from January 2012 to December 2019 in our institution. We specifically focused on nodules pathologically confirmed as benign. The pathology was rechecked by an independent pathologist. The clinicopathological characteristics of these patients were collected. Preoperative imaging examinations, including ultrasound (US), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT) were reviewed.

Results: From 2012 to 2019, a total of 2,632 patients with CRC who were preoperatively diagnosed CRLM received liver resection, among which 2,584 (98.2%) cases were proven to be malignant, and 48 (1.8%) cases were benign. Among these 48 cases, 24 were pathologically confirmed as focal nodular hyperplasia (FNH), 9 were peliosis, 10 were inflammatory lesions, and 5 were hemangioma. At least one preoperative imaging examination indicated CRLM, with a median size of 2.0 cm (range, 0.4–8.0 cm). Before liver resection, ten patients received chemotherapy after the discovery of liver nodules.

Conclusions: It should be noted that newly detected liver nodules in patients with a history of CRC could be benign. Accurate diagnosis of liver nodules in CRC is necessary to avoid overtreatment and to identify cost-effective medication.

Keywords: Colorectal cancer liver metastasis (CRLM); focal nodular hyperplasia (FNH); peliosis hepatis; hemangioma

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Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide. According to GLOBOCAN 2018, over 1.8 million new CRC cases and 881,000 deaths occurred in 2018, ranking third in terms of incidence but second in terms of mortality (1). The liver is the most common site for CRC metastasis (CRLM), which is the most common cause of death. Over 50% of patients with CRC will eventually develop liver metastasis (2), which needs immediate interference (3).

Surgical resection remains the most effective treatment for CRLM (4-6). Studies have shown that selected patients undergoing surgery to remove CRLM can have a median 5-year survival of 38% (7); for patients with solitary liver metastases, the 5-year overall survival rate can reach as high as 71% following resection (8,9). Therefore, frequent surveillance and early diagnosis of liver metastasis are crucial for patients with CRC (3). The National Comprehensive Cancer Network (NCCN) suggests that patients with CRC at high risk of recurrence or metastasis should undergo abdominal CT every 3 to 6 months for 2 years, and then every 6 to 12 months for up to 5 years (10).

The incidence of benign liver lesions is very high in patients with CRC (11-14). Schwartz et al. (14) reviewed CT images obtained from 435 patients with CRC during a 24-month period, and found small hepatic lesions (lesions 1 cm or less in diameter) in 13% (n=57) of the patients, among which only 14% (8/57) were metastases. Jang et al. (11) found that small liver nodules (15 mm or smaller) existed in 25.5% of patients with CRC, among which only 11.2% were metastases. CRLM could share similar imaging features with benign liver nodules on imaging examinations, including ultrasound (US), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT), especially for small ones (20 mm or smaller) (15,16). The actual number of small hepatic lesions in patients with CRC was certainly underreported, which highlights the importance of accurate diagnosis of indeterminate liver nodules.

In our practice, we also noted that some newly detected liver nodules were radiologically misdiagnosed as CRLM and pathologically confirmed as benign. To analyze the reason for misdiagnosis, and to avoid further unnecessary surgeries and other invasive treatments, we retrospectively reviewed all patients with a history of CRC who underwent liver resection for liver nodules in our institution.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-8153),

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our Institutional Review Board approved the retrospective study (B2021-229). Due to the nature of retrospective study, no written informed consent was obtained from patients.

Study population

We retrospectively reviewed all patients with CRC who underwent liver resection for liver nodules from January 2012 to December 2019 at Zhongshan Hospital of Fudan University. All the nodules were indicated to be CRLM by at least one imaging examination, and the indications for surgery were as follows (2): (I) based on liver anatomy and the extent of liver metastases, the metastatic lesions can be completely removed (R0) while preserving adequate liver function; (II) patients should be fit to undergo such surgical treatment, without extrahepatic metastases that are not suitable for surgery, or with only pulmonary nodules that do not restrict the resectability of the liver metastases. The diagnosis was confirmed by pathology, and those confirmed to be benign nodules were rechecked by an independent pathologist.

Data collection

Clinical information such as age, sex, preoperative carcinoembryonic antigen (CEA), tumor characteristics (diameter, number, location, etc.), and therapeutic approaches were collected. The detailed clinicopathological features are listed in *Table 1*. Preoperative imaging examinations, including US, MRI, and PET-CT were reviewed.

Statistical analysis

All data were collected retrospectively from the hospital's electronic database. Statistical analyses were performed with SPSS 17.0 software (SPSS, Chicago, IL).

Results

From 2012 to 2019, a total of 2,632 patients with CRC

Table 1 Clinicopathological characteristics of the 48 patients

Variables	FNH (N=24)	Peliosis (N=9)	Inflammatory lesion (N=10)	Hemangioma (N=5)	Total (N=48)
Age (years), median (range)	51 (30 to 68)	48 (33 to 65)	64 (56 to 74)	64 (55 to 71)	59 (30 to 74)
Sex, n (%)					
Male	15 (62.5.0)	4 (44.4)	5 (50.0)	3 (75.0)	27 (56.3)
Female	9 (37.5.0)	5 (55.6)	5 (50.0)	2 (25.0)	21 (43.7)
No. of lesions, n (%)					
Single	18 (75.0)	7 (77.8)	9 (90.0)	4 (80.0)	38 (79.2)
Multiple	6 (25.0)	2 (22.2)	1 (10.0)	1 (20.0)	10 (20.8)
Tumor diameter (cm), median (range)	1.6 (1.0 to 4.8)	1.5 (1.0 to 7.0)	1.7 (0.4 to 5.0)	2.0 (1.0 to 8.0)	2.0 (0.4 to 8.0)
Tumor diameter (cm), n (%)					
≤2	17 (70.8)	8 (88.9)	8 (80.0)	3 (60.0)	36 (75.0)
>2	7 (29.2)	1 (11.1)	2 (20.0)	2 (40.0)	12 (25.0)
Localization, n (%)					
Unilobar	20 (83.3)	9 (100.0)	10 (100.0)	4 (80.0)	43 (89.6)
Bilobar	4 (16.7)	0 (0.0)	0 (0.0)	1 (20.0)	5 (10.4)
Primary tumor, n (%)					
Colon	14 (58.3)	3 (33.3)	7 (70.0)	4 (80.0)	28 (58.3)
Rectum	10 (41.7)	6 (66.7)	3 (30.0)	1 (20.0)	20 (41.7)
History of hepatic metastases, n (%)					
No	22 (91.7)	8 (88.9)	8 (80.0)	5 (100.0)	43 (89.6)
Yes	2 (8.3)	1 (11.1)	2 (20.0)	0 (0.0)	5 (10.4)
History of chemotherapy, n (%)					
No	0 (0.0)	0 (0.0)	7 (70.0)	2 (40.0)	9 (18.8)
Yes	24 (100.0)	9 (100.0)	3 (30.0)	3 (60.0)	39 (81.2)
Chemotherapy for liver nodule, n (%)					
No	18 (75.0)	8 (88.9)	9 (90.0)	3 (60.0)	38 (79.2)
Yes	6 (25.0)	1 (11.1)	1 (10.0)	2 (40.0)	10 (20.8)
Misdiagnosed by US, n (%)	21/24 (87.5)	7/9 (77.8)	9/10 (90.0)	3/5 (60.0)	40/48 (83.3)
Misdiagnosed by MRI, n (%)	17/24 (70.8)	7/9 (77.8)	8/10 (80.0)	4/5 (80.0)	36/48 (75.0)
Misdiagnosed by PET-CT, n (%)	7/13 (53.8)	1/3 (33.3)	3/4 (75.0)	2/3 (66.7)	13/23 (56.5)
Number of false diagnosis (US, MRI, or PET-CT), n (%)					
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	7 (29.2)	4 (44.4)	2 (20.0)	2 (40.0)	15 (31.3)
2	14 (58.3)	4 (44.4)	5 (50.0)	2 (40.0)	25 (52.1)
3	3 (12.5)	1 (11.1)	3 (30.0)	1 (20.0)	8 (16.7)

MRI, magnetic resonance imaging; US, ultrasonography; PET-CT, positron emission tomography-computed tomography.
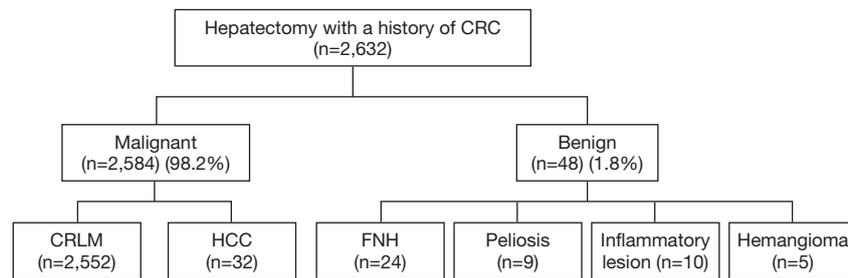
Figure 1 Study design and the number in each category.

who were preoperatively diagnosed CRLM received liver resection, and 2,584 cases were malignant (98.2%), consisting of 2,552 CRLM and 32 HCC. The remaining 48 cases (1.8%) were proven to be benign, among which 24 cases were diagnosed as FNH, 9 cases were hepatic peliosis, 10 cases were inflammatory lesions, and 5 cases were confirmed to be hemangioma (*Figure 1*).

The median age of the 48 patients was 59 years (range, 30–74 years), with 27 male and 21 female patients. Five of the 48 cases (10.4%) had a prior history of liver surgery for hepatic metastasis; 39 of the 48 patients (81.2%) had received chemotherapy (oxaliplatin, fluorouracil, or irinotecan) before the discovery of the liver nodules, and 10 patients (20.8%) received chemotherapy after. The median size of the tumor was 2.0 cm (range, 0.4–8.0 cm), with 36 (75%) lesions less than 2 cm. In 38 of the 48 cases (79.2%), the lesion was single, and multiple lesions (two or more nodules) were observed in 10 cases (20.8%) (*Table 1*). In these 48 patients, CEA levels were all normal. For all 48 patients, recovery was uneventful.

All 48 patients received US and MRI tests, and 23 patients received PET-CT tests. At least one preoperative imaging examination (US, MRI, or PET-CT) indicated CRLM, 15 cases had 1 false misdiagnosis, 25 had 2 false results, and 8 had 3 false results. Among these 3 imaging examinations, US had the highest rate of misdiagnosis [40/48 (83.3%)], the misdiagnosis rate of MRI was 75% (36/48), and PET-CT had the lowest rate of misdiagnosis [13/23 (56.5%)]. All 48 patients received preoperative color Doppler US, but none of them underwent contrast enhanced US for preoperative diagnosis. Likewise, all 48 patients received preoperative dynamic contrast-enhanced MRI with gadolinium, but none of them underwent gadoxetic acid-enhanced MRI.

Most patients could not provide former liver imaging examinations, which we could compare with; therefore, we could not determine if the nodules had existed before

CRC or emerged after CRC. However, we also listed specific features of the nodules (CRLM, FNH, peliosis, inflammatory lesion, hemangioma) in the research.
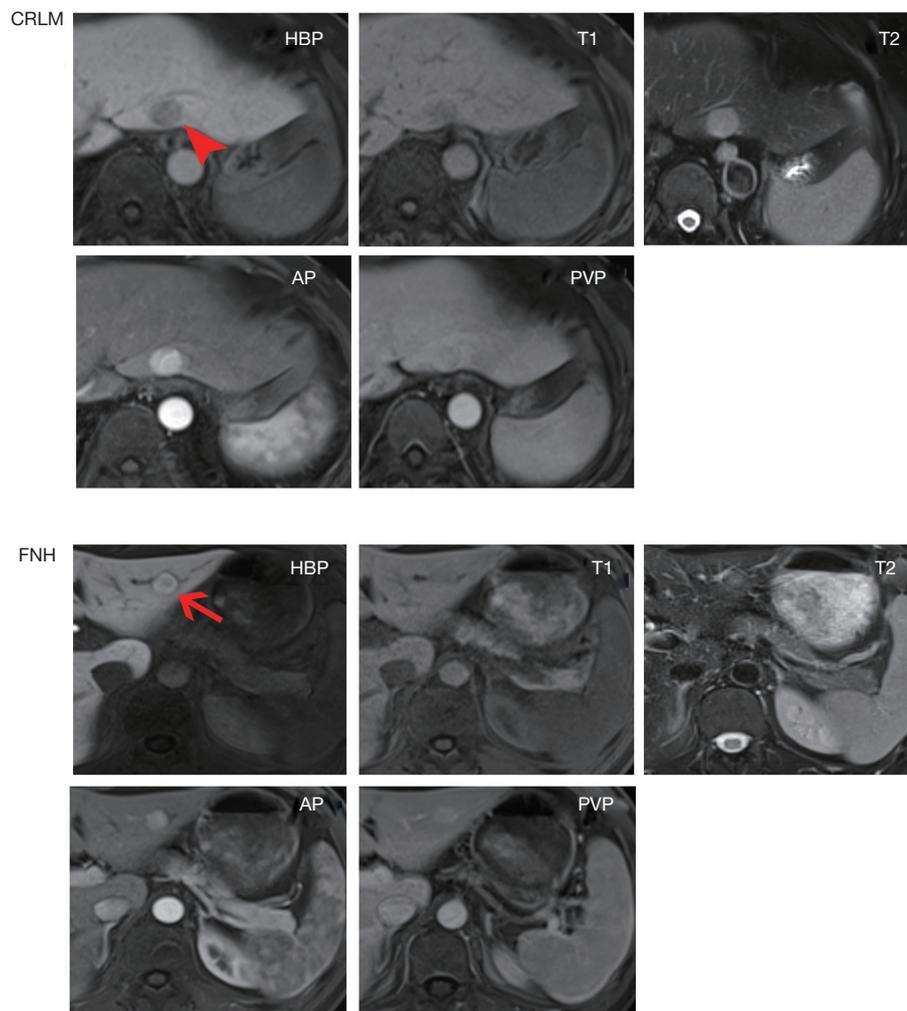
CRLM

The appearance of CRLM on US is usually inhomogeneous. Virtually any sonographic appearance may occur in CRLM, and hypoechoic halos are common. The MR imaging features of most CRLMs were hypointense on T1-weighted imaging, mild-moderate hyperintense on T2-weighted imaging, hyperenhancement on arterial phase (AP), and iso- or hyperintense on portal venous phase (PVP) (*Figures 2,3*).

FNH

FNHs generally have a capsule-free, well-circumscribed isoechoic appearance on US and may exhibit a "central scar". Doppler US usually shows the central arteries having a spoke-wheel pattern. The MR imaging features of most FNHs were hypointense on T1-weighted imaging, mild-moderate hyperintense on T2-weighted imaging, hyperenhancement on arterial phase (AP), and iso- or hyperintense on portal venous phase (PVP) (*Figure 2*). The median size of the FNH was 1.6 cm (range, 1.0–4.8 cm). Tumor growth was observed in 2 of the 24 patients (8.3%), where one nodule had grown from 0.5 to 2.3 cm, and another from 0.5 to 1.5 cm. All patients had received chemotherapy before the discovery of the liver nodules, and 6 (25%) received chemotherapy after.

Peliosis

On US, peliosis may appear as pseudocystic areas in the hepatic parenchyma. These lesions can be hypoechoic in an otherwise normal liver, or they may appear hyperechoic in the setting of hepatic steatosis. Doppler studies can demonstrate the vascular nature of the lesion. The MR

Figure 2 CRLM (red arrowhead) and FNH (red arrow) can be differentiated according to the signal intensity of HBP on gadoxetic acid-enhanced MRI. CRLM: hypointensity on HBP, hypointensity on T1-weighted imaging, mild-moderate hyperintensity on T2-weighted imaging, hyperenhancement on AP, iso-or hyperintensity on PVP. FNH: hyperintensity on HBP, hypointensity on T1-weighted imaging, mild-moderate hyperintensity on T2-weighted imaging, hyperenhancement on AP, iso-or hyperintensity on PVP. HBP, hepatobiliary phase; AP, arterial phase; PVP, portal venous phase.

imaging features of peliosis are hypointense on T1-weighted imaging, mild-moderate hyperintense on T2-weighted imaging, mild enhancement on AP, and gradual enhancement on PVP (*Figure 3*). The median size was 1.5 cm (range, 1.0–7.0 cm). All patients had received chemotherapy before the discovery of the liver nodules, and 1 (11.1%) received chemotherapy after.
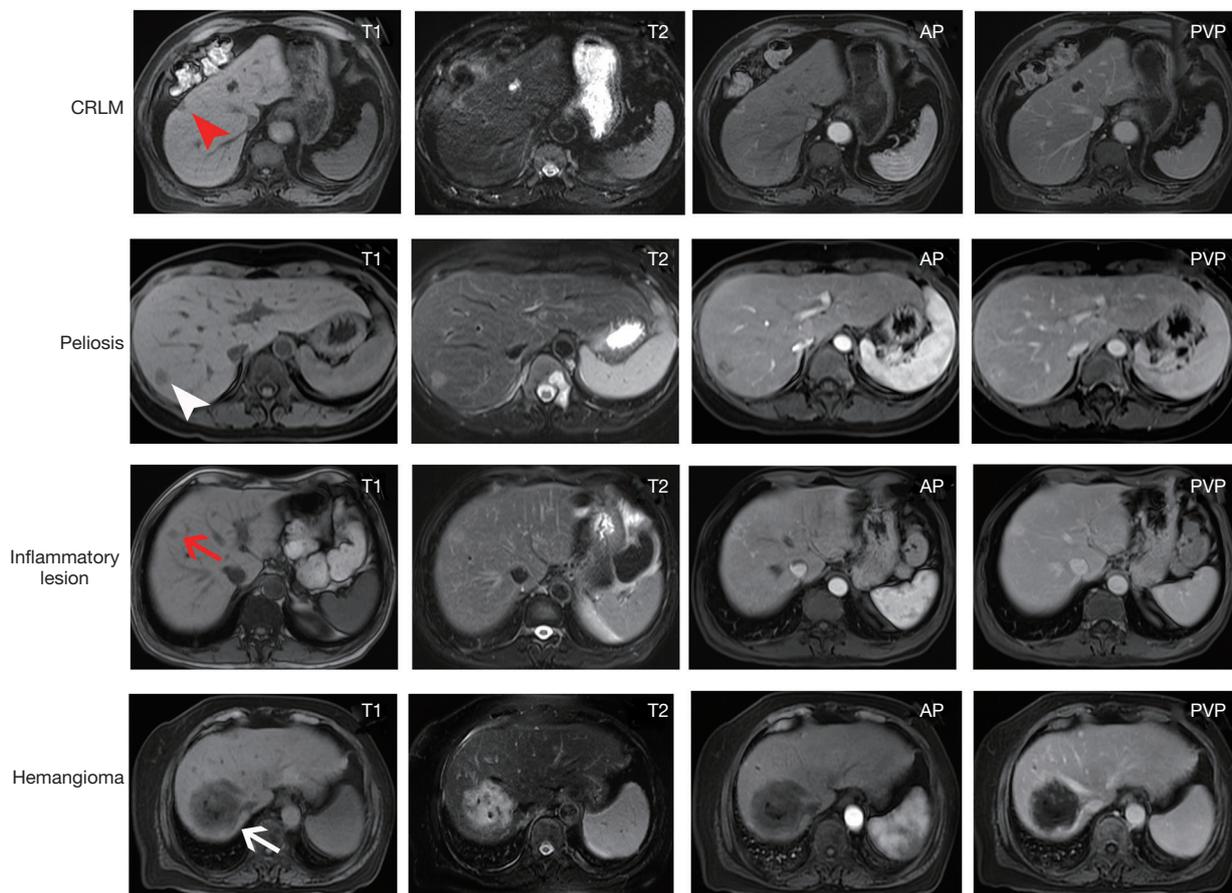
Inflammatory lesion

The appearance of inflammatory lesion on US varies depending on the cause of the disease. The MR imaging

features of most inflammatory lesions were hypointense on T1-weighted imaging, mild-moderate mild hyperintense on T2-weighted imaging, mild or peripheral enhancement on AP, and gradual enhancement on PVP (*Figure 3*). The median size was 1.7 cm (range, 0.4–5.0 cm). Two cases were confirmed to be parasitosis, 1 case was an immunoglobulin G4 (IgG4)-related inflammatory lesion, and 1 patient had abdominal infection during previous surgery for colon cancer.

Hemangioma

Hemangioma is a well-circumscribed, round shaped hyper-

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Figure 3 CRLM (red arrowhead), peliosis (white arrowhead), inflammatory lesion (red arrow), and hemangioma (white arrow) could share similar imaging features on dynamic contrast-enhanced MRI with gadolinium. CRLM: hypointensity on T1-weighted imaging, mild-moderate hyperintensity on T2-weighted imaging, peripheral enhancement on AP, mild or peripheral enhancement on PVP. Peliosis: hypointensity on T1-weighted imaging, mild-moderate hyperintensity on T2-weighted imaging, mild enhancement on AP, gradual enhancement on PVP. Inflammatory lesion: hypointensity on T1-weighted imaging, mild-moderate mild hyperintensity on T2-weighted imaging, mild or peripheral enhancement on AP, gradual enhancement on PVP. Atypical hemangioma: hypointensity on T1-weighted imaging, most moderate hyperintensity with intralesional low intensity on T2-weighted imaging, peripheral enhancement on AP, mild gradual enhancement on PVP. HBP, hepatobiliary phase; AP, arterial phase; PVP, portal venous phase.

echoic and homogeneous lesion on US. The MR imaging features of most hemangiomas can be hypointense on T1-weighted imaging, hyperintense on T2-weighted imaging, peripheral enhancement on AP, and mild gradual enhancement on PVP. The median size was 2.0 cm (range, 1.0–8.0 cm), with 3 (60%) lesions being less than 2 cm. The 8 cm hemangioma cannot be easily diagnosed on MRI because the mass showed moderate hyperintensity rather than significant hyperintensity on T2-weighted imaging, due to the presence of fibrosis within the hemangioma (*Figure 3*).

Discussion

The diagnosis of newly discovered liver nodules in the background of CRC is important; however, the nodules are usually small, and differentiation between malignant and benign liver nodules may be challenging (14,17). In this study, we reported 48 patients with CRC who underwent liver resection for benign liver nodules misdiagnosed as CRLM preoperatively in our institution from 2012 to 2019. These nodules were pathologically confirmed as benignities, including FNH, peliosis, inflammatory lesions,

and hemangioma.

Although newly detected liver nodules in patients with CRC should be highly suggestive of metastasis, some benign nodules, such as focal nodular hyperplasia (FNH), hepatic peliosis, and steatosis, may occur in patients with CRC, especially after chemotherapy and molecularly targeted therapy (18). Accurate identification of liver nodules with a history of CRC can help avoid unnecessary therapy. Therefore, the diagnosis of small hepatic nodules in the background of CRC is important, but sometimes difficult.

In all 48 patients we reviewed, at least one preoperative imaging examination indicated CRLM. It is often difficult to characterize small indeterminate liver nodules with a history of CRC. For nodules inclined to be benign, fine needle aspiration is often useful to confirm the diagnosis. Nevertheless, pathological confirmation is not always essential if reasonable results can be achieved with imaging studies; in addition, it may cause potential dissemination for nodules to be malignant. PET-CT provides high accuracy in detecting local recurrence and distant metastasis, such as CRLM (19). However, false negative results are often seen in patients with CRLM, which might be due to negative uptake of fludeoxyglucose after receiving chemotherapy or targeted therapy.

In this study, we found that conventional Doppler US had the highest rate of misdiagnosis (83.3%), partly because the result relies more on the subjective judgment of the examiner. In addition, it is challenging for grey-scale US to distinguish benign from malignant lesion 2 cm or less in diameter. Contrast-enhanced ultrasound (CEUS), on the contrary, can be used to observe the contrast agent in the lesions in real time, and is invaluable in providing characterization of indeterminate liver lesions on CT, MRI, and PET-CT (20). CEUS markedly improves the diagnostic accuracy of CRLM (21), FNH (22), hemangioma (23), etc. In addition, contrast agents, which are gas-filled particles (microbubbles), can be safely administered more than once during the same examination, and can be administered to pregnant women (24), patients with renal insufficiency (25), and without iodine/gadolinium-related anaphylactoid-type reaction (26). For these reasons, CEUS plays a complementary problem-solving role for indeterminate liver lesions

CRLM could share similar imaging features with FNH, peliosis, inflammatory lesion, and hemangioma on dynamic contrast-enhanced MRI (*Figures 2,3*). FNH is the most common type to be misinterpreted as CRLM in this study.

It can be well characterized by a central stellate scar on contrast dynamic CT/MRI. However, the prevalence of the central scars is less than 50%, and it is even lower when the lesion is smaller than 2 cm (15,16). Peliosis is also benign and characterized by a proliferation of the sinusoidal hepatic capillaries and cystic blood-filled cavities distributed in the liver (27). Studies have shown that chemotherapy-induced peliosis will regress after drug withdrawal, and no surgery is needed (28,29). Studies also showed that peliosis could be misdiagnosed (30,31).

In this study, we found that all patients with FNH and peliosis had received chemotherapy before the discovery of liver nodules. Chemotherapy has been shown to be associated with benign hepatic lesions, such as sinusoidal obstruction syndrome (SOS), FNH, and peliosis (18). SOS has been widely observed in patients receiving oxaliplatin-based chemotherapy (18,32,33), which is characterized by occlusion of the terminal hepatic venules and hepatic sinusoids, as well as sinusoidal endothelial injury. Wicherts *et al.* (18) showed that SOS was observed in 15% of patients treated with oxaliplatin compared to 4% of patients treated with an oxaliplatin-naïve regimen. Several studies have demonstrated that FNH can be induced by sinusoidal obstruction syndrome (SOS) (34-36), and peliosis is also associated with SOS (37,38). In addition, these lesions due to chemo injury could be misinterpreted as metastasis (36,37,39), especially when the nodules are smaller than 1 cm in diameter (14,17). In this study, the nodules were relatively small (1.6 cm for FNH and 1.5 cm for peliosis), which increased the difficulty of accurate diagnosis.

In the inflammatory group, we observed various causes such as parasitosis, IgG4-related inflammatory lesions, and abdominal infection. The nodules showed various enhancement patterns on contrast-enhanced MRI, depending on the histopathologic findings, which makes the diagnosis much more complicated. Hemangioma is relatively easier to identify due to the typical appearance on MRI, which is a smooth, well-demarcated, homogeneous mass that has low signal intensity on T1-weighted images, hyperintense on T2-weighted images, and peripheral and gradual enhancement on contrast-enhanced imaging (40). However, in clinical practice, small liver nodules after chemotherapy may not demonstrate characteristic radiological features and cannot be diagnosed easily. In addition, giant hemangiomas may develop a collagenous scar or fibrous nodule, which makes the diagnosis more confusing (*Figure 3*) (41).

Gadoxetic acid-enhanced MRI is highly sensitive for

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differentiation between benign and malignant lesions, according to the signal intensity on the hepatobiliary phase (HBP) (42-44). On HBP, FNHs, peliosis, and some inflammatory lesions can be isointense or hyperintense (45-47), while CRLMs are usually hypointense (*Figure 2*) (48). The European Society for Medical Oncology (ESMO) suggests that for lesions <10 mm in diameter, MRI is a more sensitive modality than CT, and gadoxetic acid-enhanced MRI is associated with higher accuracy of lesion detection (49-51). The China CRLM Guideline Group also recommends gadoxetic acid-enhanced MRI rather than conventional MRI or CT when necessary (2). In China, however, even hepatobiliary doctors have not fully realized the importance of gadoxetic acid-enhanced MRI, and due to the longer scan time and higher cost compared to dynamic contrast-enhanced MRI with gadolinium, gadoxetic acid-enhanced MRI has not been applied as a routine examination of liver imaging. In all 48 patients reviewed in our study, no one had performed gadoxetic acid-enhanced MRI. We also surveilled another 5 patients with CRC with suspected FNH who did not receive surgery or chemotherapy. All 5 patients underwent gadoxetic acid-enhanced MRI, FNH was considered without pathological confirmation, and the liver nodules were stable to the latest follow-up. Therefore, for patients with CRC with small indeterminate liver nodules, we strongly recommend gadoxetic acid-enhanced MRI.

Our study has several limitations. Because of the retrospective, single-centered nature of the study, selection bias exists, and the true incidence of benign and malignant liver nodules in patients with CRC is surely underestimated. Large, multicenter, prospective studies are needed to increase the accuracy in identifying indeterminate liver nodules in patients with CRC.

Conclusions

Most patients with CRC would refer to surgeons when liver nodules first appear. With improvements in safety in hepatic surgery, overtreatment of liver nodules in patients with CRC is becoming increasingly intense. However, surgeries are always accompanied by potential morbidity and mortality, especially for patients with CRLM who receive preoperative chemotherapy. Since CEUS and gadoxetic acid-enhanced MRI can easily differentiate FNHs, peliosis, and some inflammatory lesions from CRLM, it should be offered to patients with CRC with indeterminate liver nodules, which could further minimize unnecessary surgeries and other invasive treatments.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-8153

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-8153

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-8153). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our Institutional Review Board approved the retrospective study (B2021-229). Due to the nature of retrospective study, no written informed consent was obtained from patients.

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