



# Role of Imaging in the Management of Patients with Potentially Resectable CRLM

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## Introduction

Assessment of CRLM resection has rapidly changed over the years, as more lesions are deemed operable due to the expanding criteria for resectability [1]. Liver resection with curative intent necessitates addressing or removing all detectable disease sites. Preoperative imaging is essential to determine the location and extent of CRLM, proximity of lesions to vascular structures, predicting future liver remnant and identifying extrahepatic disease [2]. Moreover, full imaging assessment such as with MRI is important prior to chemotherapy, as treatment can change the appearance of metastatic lesions and affect hepatic parenchyma reducing sensitivity of CT and/or PET for CRLM evaluation [3]. In this chapter, we discuss the integral role of current imaging techniques in the management of patients with potentially resectable CRLM.

## Role of Imaging in Detection of CRLM

### Ultrasound

Conventional ultrasound (US) is widely used for the assessment of CRLM due to its low cost, absence of radiation exposure, and wide availability. US provides a pooled sensitivity of 63% and specificity of 97.6% for CRLM detection [4]. However, it is the addition of contrast-enhanced US (CEUS) with agents that has dramatically

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increased the sensitivity for CRLM detection up to 80–90%, which is comparable to that by computed tomography [5, 6]. US contrast agents consist of tiny microbubbles that carry a strong safety profile and can be used in patients with impaired renal function [7]. In patients who have contraindications to iodinated contrast material, CEUS is a viable alternative and superior to non-contrast-enhanced CT in the characterization of focal liver pathology [8].

On US, CRLM often appear as hypoechoic lesions and less commonly may have similar or higher echogenicity relative to normal hepatic parenchyma [9]. CRLM, which are not visualized during preoperative imaging assessment, may be detected with the use of real-time ultrasound intraoperatively [10]. Intraoperative US (IOUS) also facilitates localization of deep-seated, nonpalpable lesions while mapping major hepatic veins, providing real-time guidance during surgery [10]. Patients with multiple CRLM benefit greatly from IOUS due to its high specificity (94–98%) and detection rate of tumors missed on prior imaging [11]. Additionally, contrast-enhanced IOUS may identify small tumor residuals, which is important to ensure microscopically margin-negative resection [12].

While some limitations regarding lesion characterization can be overcome with CEUS, accurate diagnosis is highly examiner dependent and requires experienced operator training [13]. Evaluation of multiple lesions simultaneously is also challenging with CEUS [14]. Neoadjuvant chemotherapy (NAC) can significantly alter liver echotexture (lesion and parenchyma) interfering with sensitivity and specificity of US [14]. Other challenges include limited spatial resolution of transcutaneous probes, assessing patients with obese habitus, high-lying diaphragm, and uncooperative patients [13].

## Computed Tomography (CT)

Multidetector CT (MDCT) is the preferred modality for CRLM assessment in the USA due to its ability to image the liver and potential sites of extrahepatic metastases (e.g., chest, nodes, and peritoneum) in one examination [15]. MDCT is also widely available, reliable, and able to accommodate patients with body habitus limitations (e.g., obesity). Improved resolution and faster scanning speed with MDCT has enabled imaging of the entire abdomen and pelvis during a single breath hold, effectively eliminating respiratory motion artifacts [16]. Acquisition of thin slices allows for reconstruction of high-quality images in different planes and rendering reformatted images are now integral to any CT protocol [17]. The use of iodinated contrast media (ICM) to adequately detect and characterize CRLM has been advocated and is recommended by the current national comprehensive cancer network (NCCN) guidelines [18]. A recent meta-analysis reported 82% sensitivity and 73.5% specificity for CRLM detection using contrast-enhanced CT (CECT) [19] (Table 5.1). Oral contrast media is desirable but not mandatory, as it helps with better evaluation of extrahepatic pathologies, such as eliminating false-positive peritoneal metastases.

**Table 5.1** Diagnostic performance of CECT, EOB-MRI, and PET-CT for CRLM detection

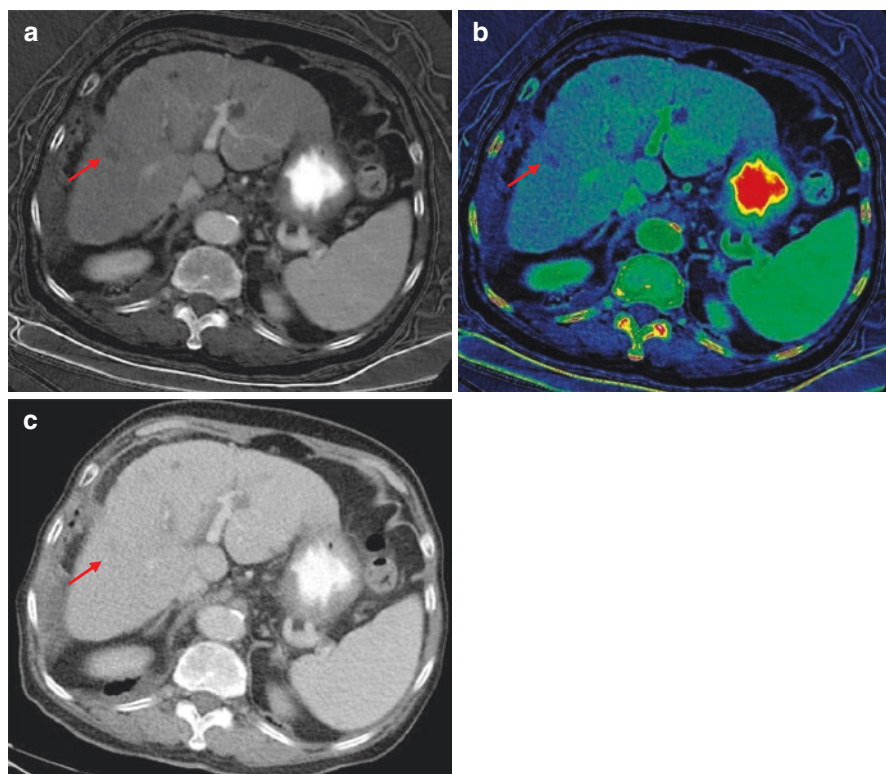
Modality	Diagnostic performance	
CT	Sensitivity	82% (74.0–88.1)
	Specificity	73.5% (53.7–86.9)
EOB-MRI	Sensitivity	93.1% (88.4–96.0)
	Specificity	87.3% (77.5–93.2)
PET-CT	Sensitivity	74.1% (62.1–83.3)
	Specificity	93.9% (83.9–97.8)

Reported 95% confidence interval for mean sensitivity and specificity in a meta-analysis between 2004 and 2016 [19].

This table compares the diagnostic performance of MDCT, gadoxetate disodium-enhanced MRI, and FDG PET-CT for diagnosing CRLM. The meta-analysis found that MRI was significantly more sensitive than CT ( $p < 0.001$ ) and PET-CT ( $p < 0.001$ ). PET-CT had the highest specificity, but not statistically significant compared to MRI ( $p = 0.59$ ). MRI and PET-CT had significantly higher specificity than CT ( $P = 0.01$  and  $P < 0.001$ ). EOB = Gadoxetate disodium (Gd-EOB-DTPA, Eovist in the USA)

Dynamic contrast-enhanced CT (CECT) involves multi-phase acquisition including true non-contrast, arterial, portal-venous and delayed phase. CRLM are typically hypovascular lesions and appear hypoattenuating compared to normal liver tissue with heterogeneous enhancement on portal venous phase [17]. Since CRLM are hypovascular, arterial phase is typically used for presurgical planning [20]. On delayed images, CRLM can show wash-out contrary to benign pathologies (e.g., hemangiomas) [17]. Newer generation dual-energy CT scanners (DECT), which are becoming mainstream, have further bolstered the role of CT with novel post-processing techniques that improve lesion conspicuity by enhancing the liver-to-lesion contrast [21, 22] (Fig. 5.1).

Limitations of CT include low sensitivity for detecting small lesions (<10 mm) and identifying CRLM in patients receiving NAC (Tables 5.1 and 5.2) [19, 23]. NAC significantly decreases the sensitivity of CRLM detection as treated lesions shrink in size [3]. Furthermore, NAC may also cause liver steatosis which reduces hepatic parenchymal attenuation leading to diminished lesion to liver contrast [24]. Patients with a history of iodinated contrast media allergies or impaired renal function are not ideal candidates for CECT [25]. In addition, ionizing radiation exposure for oncologic patients who often require repeated imaging can be of concern. These limitations can be addressed to some extent with DECT scanners, which can minimize radiation exposure by eliminating the need for true non-contrast images and allow for reduced contrast media dose while maintaining high image quality [26–28]. Moreover, DECT applications are empowering CT with better diagnostic capabilities for small lesion detection and characterization [29, 30].



**Fig. 5.1** Dual-Energy CT to improve lesion conspicuity. An 85-year-old male with multiple CRLM. Post-contrast axial reconstructions of material density-iodine in gray scale (a) and color-overlay (b) show better conspicuity of a hepatic lesion (arrows), which is hard to visualize on conventional single-energy CT image (c)

**Table 5.2** Diagnostic performance of CECT and CEMRI for CRLM detection according to size

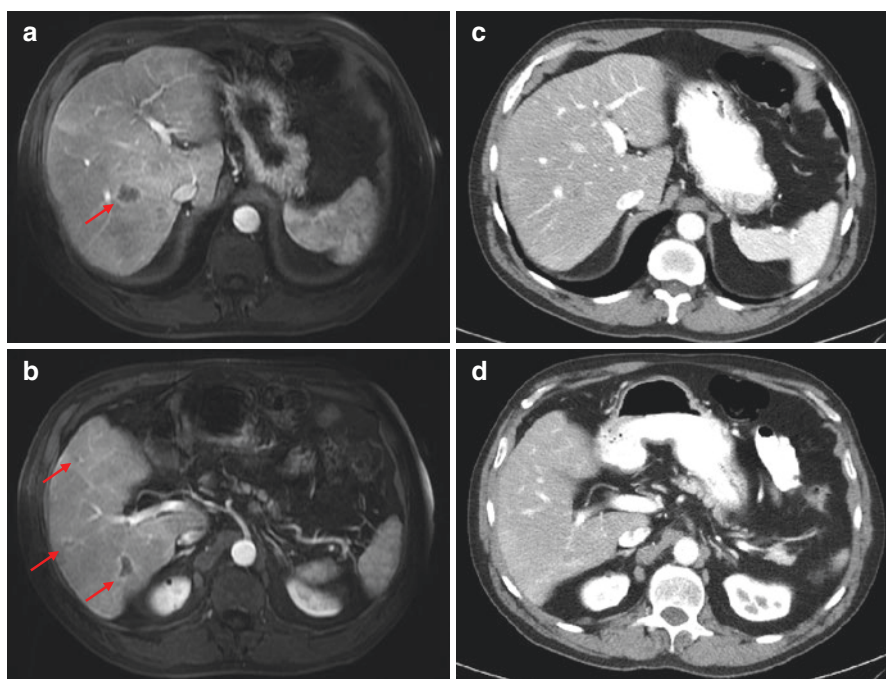
Modality	Diagnostic performance	Lesion size	
		<10 mm	≥10 mm
CECT	Sensitivity PL	47.3%	86.7%
		(40–55)	(78–93)
CE-MRI	Sensitivity PL	60.2%, $p < 0.006$	89%
		(54–66)	(82–94)

Reported 95% confidence interval for mean sensitivity on a per lesion basis in a meta-analysis between 1990 and 2010 [23]. PL per-lesion

This table compares the diagnostic performance of contrast enhanced CT (CECT) and contrast-enhanced MRI (CE-MRI) for diagnosing CRLM based on lesion size. For lesions less than 10 mm, MRI had significantly higher sensitivity than CT ( $p = 0.006$ ). There was no statistical significance between CT and MRI for lesions of size 10 mm or more ( $p = 0.617$ )

## Magnetic Resonance Imaging (MRI)

MRI is the modality of choice for evaluating CRLM and has proven to be highly effective for hepatic parenchymal assessment. Compared to CT, MR images offer superb soft tissue contrast, which improves diagnoses of intrahepatic lesions due to greater liver-to-lesion contrast difference (Fig. 5.2) [17]. MRI also excels in detecting small lesions (<10 mm) and identifying CRLM in patients undergoing NAC or have hepatic steatosis (Tables 5.2 and 5.3) [19, 23, 31]. Dynamic contrast-enhanced MRI (CE-MRI) with hepatobiliary agents and diffusion-weighted imaging (DWI) has further improved CRLM detection and characterization of indeterminate lesions, especially for small lesions [32–35]. Gadoxetate disodium (Gd-EOB-DTPA, Eovist in the USA) is the most commonly used hepatobiliary agent with MRI for CRLM detection with a pooled sensitivity of 93.1% (Table 5.3) [19].



**Fig. 5.2** Value of MRI for detection of metastasis in background of fatty liver. A 58-year-old male with CRLM and diffuse hepatic steatosis. Post-contrast T1-weighted axial MR images (a, b) reveal peripherally enhancing hypointense lesions (arrows) that are not discernible on post-contrast axial CT (c, d) images due to uniformly low attenuation of background liver parenchyma suggesting diffuse hepatic steatosis

**Table 5.3** Diagnostic performance of CECT, EOB-MRI, and PET-CT for CRLM detection according to chemotherapy status

Modality	Diagnostic performance	Chemotherapy status	
		Without NAC	With NAC or mixed
CECT	Sensitivity	88% (80–96)	78%, $p < 0.001$ (69–87)
	Specificity	76% (50–100)	72% (49–94)
EOB-MRI	Sensitivity	96% (93–99)	89%, $p < 0.001$ (82–95)
	Specificity	88% (78–98)	86% (74–97)
PET-CT	Sensitivity	79% (63–95)	72% (58–85)
	Specificity	92% (79–100)	95% (88–100)

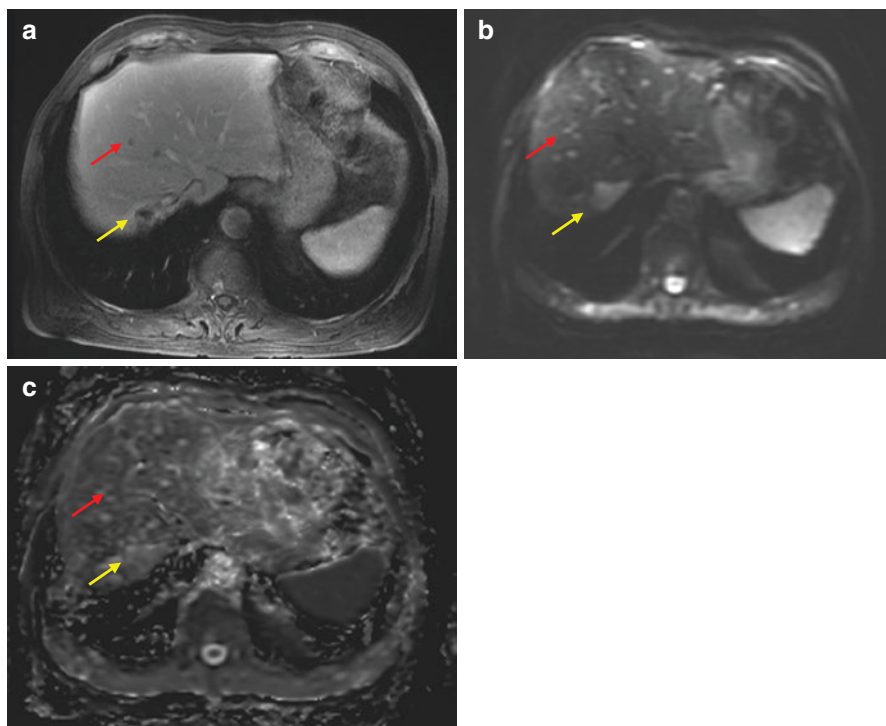
Reported 95% confidence interval for mean sensitivity and specificity in a meta-analysis between 2004 and 2016 [19].

This table compares the diagnostic performance of MDCT, gadoxetate disodium-enhanced MRI, and FDG PET-CT for diagnosing CRLM based on neoadjuvant chemotherapy (NAC) status. The meta-analysis found that neoadjuvant chemotherapy significantly decreased the sensitivity for CT (78% vs. 88%) and MRI (89% vs. 96%), although it did not significantly decrease the sensitivity for PET-CT ( $P = 0.19$ )

MRI sequences for CRLM assessment usually include a combination of T1-weighted (T1W), T2-weighted (T2W), and diffusion-weighted images (DWI) [36]. CRLM typically appear hypointense in precontrast T1W images and hyperintense in T2W images [36]. On dynamic CE-MRI, CRLM appear mostly hypointense, similar to CECT [36]. Eovist allows for further assessment of intrahepatic lesions with hepatobiliary (HB) phase (20 minutes after contrast injection) [37]. On HB phase, normal hepatocytes appear hyperintense due to eovist uptake, whereas CRLM do not retain contrast remaining hypointense and appear more conspicuous [37]. On DWI, CRLM become hyperintense compared to the normal liver due to diffusion restriction [38]. However, some benign lesions may also appear hyperintense (T2 shine-through effect) on DWI and can be differentiated from CRLM by the use of apparent diffusion coefficients (the “ADC” map) [35] (Fig. 5.3).

Limitations of MRI include contraindications such as imaging patients with metal implants and claustrophobia. Increased patient compliance such as longer breath holds and lying still for a lengthy period is required to avoid motion-related imaging artifacts, which can adversely affect diagnostic image quality [36]. Additionally, DWI have inherent limitations due to low spatial resolution and poor signal-to-noise ratio [39]. However, technological advancements in MRI scanners with more dedicated software can address some of these limitations to improve image quality [39].





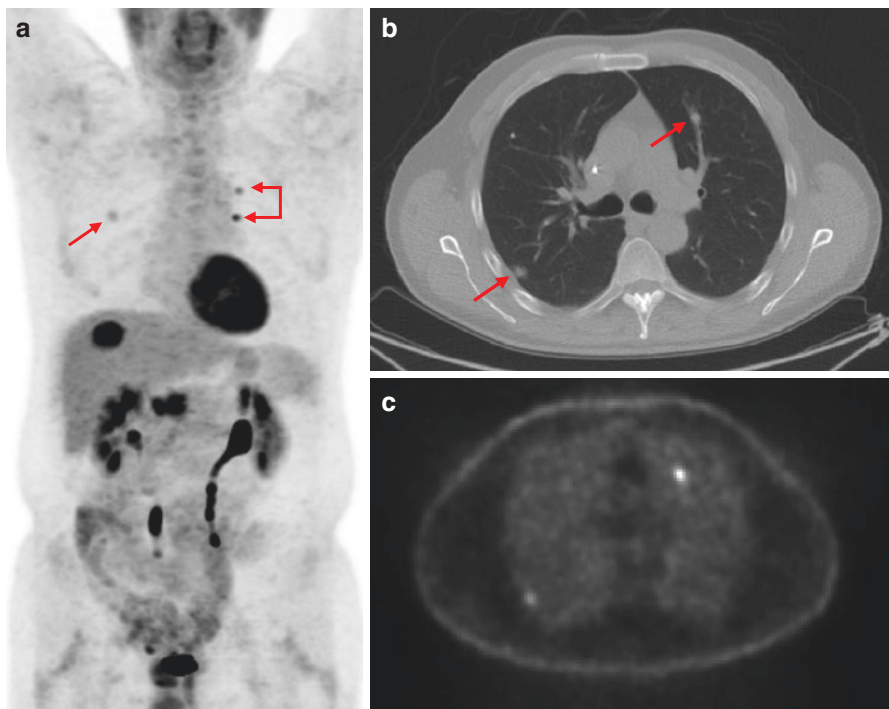
**Fig. 5.3** Advantage of DWI for distinguishing benign vs. malignant lesions. A 45-year-old female with CRLM. Post-contrast axial T1 weighted (a) reveal tiny hypoenhancing lesions (red arrow) in segment VIII and a larger nodular peripherally enhancing lesion in segment VII (yellow arrow). All lesions appear hyperintense on DWI (b). Corresponding ADC map (c) shows segment VIII lesions as hypointense suggestive of restricted diffusion that indicates metastasis, whereas the segment VII lesion remains hyperintense suggestive of T2 shine through indicating benign etiology

## Positron Emission Tomography (PET)

PET with 18-fluoride deoxyglucose (FDG) analogue is a whole-body imaging technique providing molecular and metabolic information for CRC evaluation [40]. The main advantage of PET imaging is the superior detection of extrahepatic metastases, which can eliminate unnecessary surgical intervention (Table 5.4) [40–43]. FDG-PET has also demonstrated great value in clarifying equivocal findings for the presence of metastases on CT or MRI [40–43]. On FDG-PET, diagnosis of metastases is based on focal FDG uptake exceeding the uptake of the surrounding tissue (Fig. 5.4) [44]. Currently, FDG-PET is routinely

**Table 5.4** Advantages and disadvantages of CT, MRI and PET imaging for CRLM assessment

Modality	Advantages	Disadvantages
CT	Quick, reliable method for initial screening and detection of CRLM High-quality images can be generated for vascular assessment when planning for resection	Small lesion detectability and characterization (<10 mm) Poor lesion conspicuity in hepatic steatosis Low sensitivity for detecting CRLM in patients receiving NAC Radiation exposure concern
MRI	Detecting small lesions (<10 mm) Superior lesion conspicuity higher tissue contrast and availability of hepatocyte contrast agents	DWI and ADC maps have inherent image quality limitations Patient-related factors (claustrophobia, uncooperative, metallic prosthesis)
PET	Detecting extrahepatic metastases and disease recurrence Determining management if conventional imaging is equivocal for the presence of metastatic disease	Small lesion detectability and characterization (<10 mm) Hypermetabolic processes may lead to false-positive FDG uptake. Patients receiving NAC within 4 weeks of their PET scan may have high false-negative results



**Fig. 5.4** Role of PET-CT. A 46-year-old male with CRLM. PET (a) shows moderate FDG uptake by lung nodules in the left upper lobe and one in the right lower lobe, which is suggestive of extrahepatic metastases (arrows). Axial CT scan (b) and its corresponding FDG-PET (c) showing the pulmonary nodules



performed with CT (PET-CT) to improve localization of lesions and detection of CRLM [44, 45]. Through the detection of additional liver CRLM and/or extrahepatic disease, PET-CT was shown to change planned surgical management in 24% of patients [46]. FDG-PET with MRI (PET-MRI) is a relatively newer technique that has shown great potential in CRLM detection [47, 48]. In a recent comparative study, PET-MRI had significantly higher sensitivity and diagnostic accuracy (92.2% and 96.1%, respectively) than PET-CT (67.8% and 82.4%, respectively) [49]. This is likely due to the inherent advantages of MRI in differentiating tissue contrast and lesion detection. However, literature data regarding diagnostic performance are limited, as PET-MRI is available only in a few highly specialized centers.

Limitations with PET imaging include reduced sensitivity for small lesion detection and assessing lesions in patients receiving NAC [50, 51]. The physiologic hepatic parenchymal uptake of FDG along with the inherent low resolution of PET can limit the sensitivity for small lesion detection [51]. Additionally, patients receiving NAC within 4 weeks of their PET scan may have high false-negative results due to reduction in lesion size and tumor metabolic activity [50]. Hypermetabolic processes such as chronic infection or inflammation may also lead to false-positive FDG uptake [52]. Studies have reported that 5–8% of CRC patients are falsely upstaged by PET-CT preoperatively [53]. Patient compliance factor such as respiratory motion is an additional challenge when performing PET-CT [54].

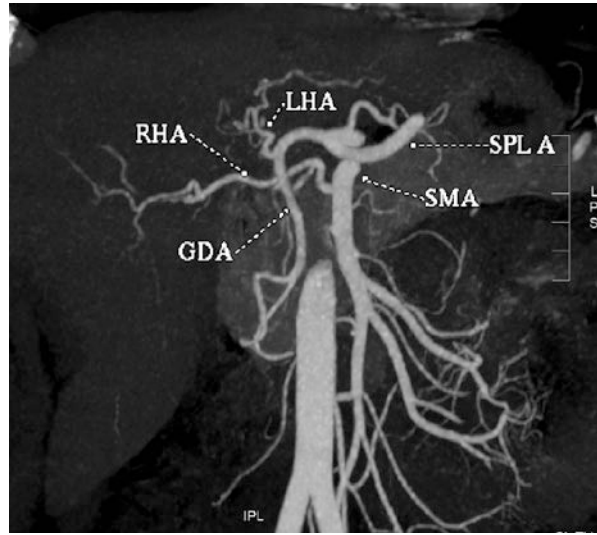
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## Role of Imaging in Surgical Planning for CRLM

### Vascular Assessment

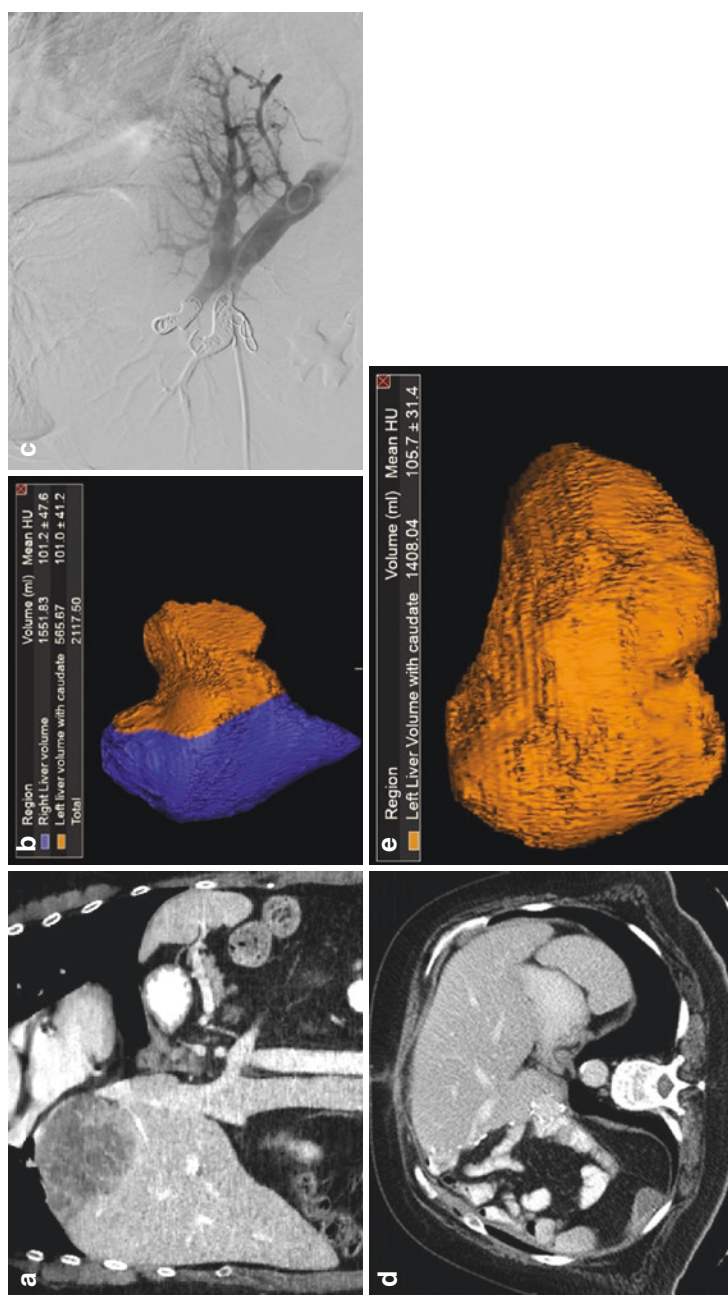
The localization of CRLM relative to vascular structures is important to determine feasibility and planning of hepatic resection. A preoperative vascular “road map” can identify anomalous or aberrant hepatic vascular supply to avoid inadvertent injury to the liver (Fig. 5.5). In addition, knowledge of the vascular map aids in determining the best hepatectomy plane. CT angiography (CTA) is preferred over MR angiography, especially for complex hepatic resection due to rapid acquisition, less susceptibility to motion artifacts, and thin collimation [55]. High-quality multiplanar reconstruction (MPR) and three-dimensional images can be obtained with CT to display the liver vascular anatomy in any desired plane [55]. The proximity of liver lesions to the hepatic vasculature can then be illustrated to decide the best surgical approach [56].

**Fig. 5.5** Image post processing for Vascular Mapping. A 36-year-old male with CRLM. Coronal reformatted CT angiography in maximum intensity projection (MIP) reconstruction shows replaced right hepatic artery (RHA) arising from the superior mesenteric artery (SMA). *LHA* left hepatic artery, *SPL A* splenic artery, *GDA* gastroduodenal artery

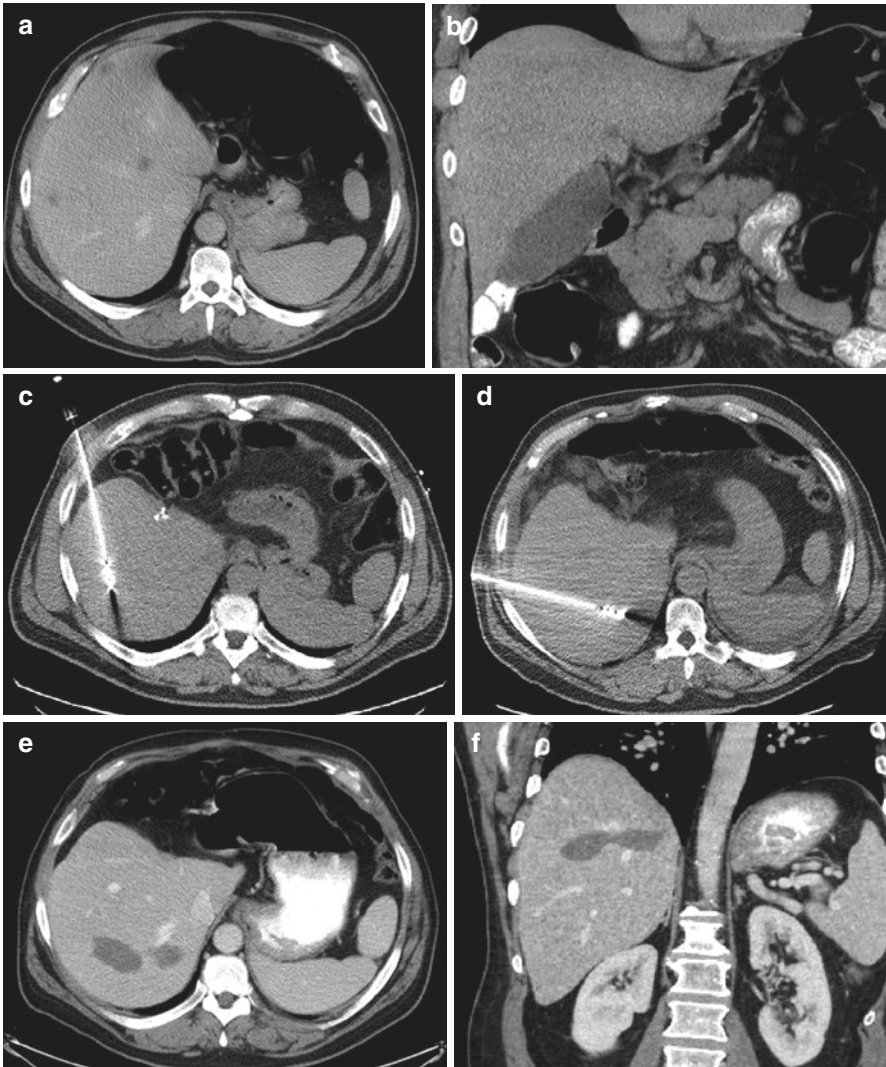


## Liver Volumetry

A crucial factor for planning surgical resection is predicting the future liver remnant (FLR) volume to avoid risk of hepatic insufficiency and subsequent mortality [57]. Preoperative estimation of the FLR is used to determine whether the functional reserve is enough to meet metabolic demands of the liver after surgery [57]. Three-dimensional reconstruction images can be used to generate precise volume measurements of the liver lobes [57, 58]. Approximately 25–30% and 40% of the preoperative liver volume should be preserved for those with normal and abnormal parenchyma (e.g., steatosis, fibrosis), respectively [59]. When FLR is deemed inadequate and CRLM is unresectable, portal vein embolization (PVE) can be performed. PVE induces hypertrophy in the remaining liver to maximize the remnant liver volume and increase resectability rate with high clinical success (Fig. 5.6) [60]. A recent meta-analysis showed that 96.1% of patients who undergo PVE develop sufficient liver lobe hypertrophy [60]. CT performed 1 month following embolization can then estimate any increase in FLR [61]. Any remaining CRLM lesions in the non-resected lobe can be treated with other methods such as radiofrequency ablation (Fig. 5.7) [62]. An area of high density or signal intensity on non-contrast CT and thin regular peripheral rim enhancement are expected after ablative therapy. Complete non-enhancement of the ablated lesions is considered evidence of full tumor necrosis at subsequent follow-up.



**Fig. 5.6** CT volumetric analysis of the liver. A 56-year-old female with liver metastases who underwent portal vein embolization prior to right hepatectomy. CECT axial (a) image and corresponding 3D volumetric analysis (b) shows the pre-embolization volume of the right lobe (volume = 1552 cm) and left lobe with caudate (volume = 566 cm). Digital subtraction angiography image (c) demonstrates successful embolization of the anterior and posterior branches of right portal vein with particles and coils. (d) Axial CT (d) and three-dimensional volume-rendered CT image (e) obtained 3 months after embolization and resection reveal left hepatic lobe hypertrophy (volume = 1408 cm<sup>3</sup>). Note: Blue = right hepatic lobe; Gold = left hepatic lobe with caudate



**Fig. 5.7** Imaging of ablation zone. A 56-year-old male status pre and post left hepatectomy for CRLM. Post-contrast CT in axial (a) and coronal (b) planes show multiple liver metastases in both lobes of the liver. Left hepatectomy was performed and right lobe lesions in segment VII were treated with radio-frequency ablation (c, d). Follow-up CT, after 3 months, (e, f) shows two non-enhancing hypodense regions suggestive of normal post ablation zone changes with no evidence of residual tumor

## Conclusion

Imaging studies play a crucial role in the detection and characterization of CRLM to identify potential surgical candidates. The role of ultrasound has improved with the addition of microbubble contrast agents and remains a valuable tool for intraoperative decision-making. MDCT is most commonly used for initial CRLM detection and staging. MRI is the modality of choice for CRLM assessment, particularly for characterizing and detecting small lesions. MRI is also superior to CT and PET for hepatic evaluation in patients receiving NAC or have underlying hepatic steatosis. High-quality 3D images can be reconstructed from CT or MRI for vascular assessment and FLR estimation to guide the surgical approach. PET has proven essential prior to surgery for its superior extrahepatic disease detection. While each modality has its advantages for patient assessment, a multi-modal imaging approach is required to maximize safety and efficacy of CRLM resection.

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