

Review Article

Preoperative imaging for hepatic resection of colorectal cancer metastasis

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ABSTRACT

Despite recent advances in chemotherapeutic agents, the prognosis for metastatic colon cancer remains poor. Over the past two decades, hepatic metastasectomy has emerged as a promising technique for improving survival in patients with metastatic colon cancer and in some cases providing long-term cure. To maximize safety and efficacy of metastasectomy, appropriate pre-operative imaging is needed. Advancements in computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have led to improved detection of occult lesions and better definition of surgical anatomy. While CT, PET and MRI have a comparable sensitivity for detection of large liver metastases, MRI excels at detection of subcentimeter liver metastases compared to CT and FDG-PET, especially with the combination of diffusion weighted imaging (DWI) and hepatocyte-specific contrast agents. CT may be useful as a screening modality or in preoperative planning such as volumetric estimation of the remnant liver size or in defining preoperative arterial anatomy for hepatic artery infusion pump placement. While technologic advancements have led to unprecedented image quality and clarity, this does not replace the need for a dedicated, competent radiologist with experience in hepatic imaging.

KEY WORDS

Colorectal metastases; preoperative imaging; hepatic artery infusion pump; volumetrics; hepatic resection

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Introduction

Colorectal cancer represents the third most common malignancy in the United States afflicting 140,000 patients annually. In a majority of cases, diagnosis is made when cancer is confined to the wall of the colon or rectum and draining lymph nodes. In approximately 20% of patients, however, evidence of cancer spread to distant organs is found concurrent with discovery of the primary lesion. In addition, up to 70% of patients with stage I-III disease initially will develop metastases (stage IV) at some point following diagnosis. The most common site of hematogenous spread is the liver, with 40% of stage

IV patients having liver only disease (1). Despite recent advances in chemotherapeutic agents, the prognosis for metastatic colon cancer remains poor, with few patients surviving beyond 5 years. In the past two decades, hepatic metastasectomy has emerged as a promising technique for improving survival in patients with metastatic colon cancer and in some cases providing long-term cure. In a large multi-institutional review of 1568 patients, Nordlinger *et al.* (2) demonstrated the safety of hepatic metastasectomy with 2.3% operative mortality and actuarial 5-year survival of 28%. The authors identified plurality and size of tumors as predictors of recurrent disease and eventual death. In a retrospective review of 1001 patients undergoing liver resection for colorectal metastases at Memorial Sloan-Kettering Cancer Center, Fong *et al.* (3) reported similar low operative mortality (2.8%) and 5-year survival of 37% with 22% of patients alive at 10 years. Multivariate analysis revealed node positive primary, presence of extrahepatic disease, CEA >200 ng/ml, >1 tumor, size >5 cm and short disease free interval as predictors for early recurrence and poor overall survival. Using this data, a clinical risk score was created that can help predict who will benefit most from surgical intervention.

No potential conflict of interest.

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Because results from hepatic metastasectomy have been so favorable, a randomized trial assessing its efficacy and safety is impossible at the present time. Therefore, review of retrospective data has been the only means by which to predict those who will recur early and have limited survival. The common poor predictors amongst the various studies have included the size of the primary tumor, presence of multiple hepatic lesions and evidence of extrahepatic disease (2-5). These factors can be best determined preoperatively using cross-sectional imaging. Historically, ultrasonography (US) was the method of choice for identifying hepatic metastases, but advancements in computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have led to improved detection of occult lesions and better definition of surgical anatomy.

Planning resection

There are many anatomic factors to consider when planning hepatic resection for metastatic disease. When assessing feasibility of resection, it is important to identify the number of segments involved, proximity of lesions to arteries, veins and bile ducts, as well as predict the amount of remnant liver following resection. In most (but not all) patients, involvement of the main portal vein, hepatic artery or common bile duct reflects advanced disease that is not amenable to surgical correction, and alternative options such as palliative chemotherapy are usually recommended. The same is true for multifocal bilobar disease in which resection would leave a diminutive liver remnant insufficient for regeneration and normal hepatic function. Optimal preoperative imaging should readily identify small lesions and provide clear views of the hepatic artery, portal vein and hepatic veins avoiding an unnecessary laparotomy and aborted resection.

While high quality preoperative imaging can help determine resectability, it is equally important in resection planning. With the exception of planned two-stage hepatic resections, the goal of metastasectomy is usually removal of all metastatic lesions while preserving as much unaffected tissue as possible; maintaining segmental arterial blood supply as well as venous and biliary drainage is necessary to achieve this goal. This is rarely an issue for peripherally located lesions, which can typically be removed by wedge resection with little risk to major vessels or bile ducts. However, lesions located deep in the liver parenchyma close to the hilum or hepatic veins require careful attention and planning. For example, a small lesion located close to the origin of the middle hepatic vein may require sacrificing that vessel. Failure to subsequently remove the segments of liver that drain through this vessel may result

in significant hepatic congestion and necrosis. This often means performing an extended hepatectomy removing up to 80% of the hepatic parenchyma. If this lesion is not identified preoperatively on appropriate contrast-enhanced imaging and a larger resection is not anticipated, the patient may be left with inadequate liver reserve. When recognized preoperatively, the portal vein supplying the planned resected lobe can be embolized prior to operation, allowing hypertrophy of the contralateral liver, thereby increasing remnant liver volume and reducing the risk of postoperative liver failure.

Identifying lesions within the liver parenchyma can be difficult when extensive hepatic fibrosis or steatosis is present. This is often the case in patients who have received preoperative chemotherapy, particularly oxaliplatin- and irinotecan-based regimens (6). Sinusoidal congestion and fatty replacement can lead to unpredictable alterations in the appearance of the liver resulting in false positive and negative studies. Radiologists reviewing images should be familiar with the extent of pre-imaging chemotherapy to better guide their study evaluation.

Often more than one modality is required to garner the necessary preoperative information. For example, while CT is most commonly used for routine cross-sectional imaging, MRI may be better for identifying occult liver lesions and their proximity to major vessels, and a PET scan better for ruling out extra-hepatic disease. MRI may also be very useful for distinguishing benign tumors from metastases (see below).

Hepatic artery infusion (HAI)

It is well established that neoplasms within the liver receive a majority of their blood supply via the hepatic artery (7). This anatomic fact has been exploited to deliver chemotherapy directly to the hepatic artery by surgically implanted catheters and pumps. Multiple trials of arterial infusion of floxuridine (FUDR) in patients with unresectable hepatic colorectal metastases have been performed with objective response rates of 50-80% (8-11). Indications for HAI therapy have expanded to include adjuvant treatment following hepatic resection (12) and neoadjuvant therapy to allow resectability (13). Although not widely practiced, primarily due to the expertise required for pump placement, maintenance and chemotherapy management, HAI therapy is associated with promising results and is used frequently in some centers.

In planning for hepatic artery pump placement, a complete survey of the hepatic arterial anatomy is needed. This is best accomplished with CT angiography with multiplanar and 3D reconstructions. In the normal hepatic

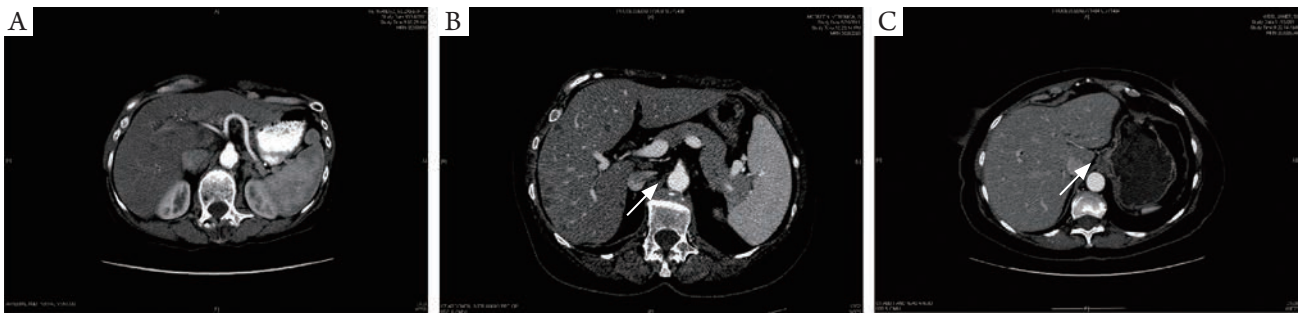


Figure 1. Aberrant hepatic arterial anatomy. Cross-sectional imaging can help identify anomalous arterial anatomy prior to placement of hepatic artery infusion pumps. (A) depicts a normal hepatic artery originating from the celiac trunk, white arrows in (B) and (C) show replaced right and left hepatic arteries, respectively.

arterial anatomy, the common hepatic artery branches from the celiac trunk (Figure 1 A) and gives rise to the gastroduodenal artery (GDA). It is through this branch that the hepatic arterial catheter is placed with the tip at the GDA orifice. This allows for infusion into the proper and subsequently the right and left hepatic arteries. Variations in arterial anatomy occur in approximately 25% of patients (14) and can have a dramatic impact on pump placement and subsequent function. The most common variation is a replaced right or accessory left hepatic artery (Figure 1 B, C) that originates from the superior mesenteric or left gastric artery, respectively. Other anatomic anomalies such as a late takeoff of the right gastric artery are important to recognize as this can lead to inappropriate delivery of toxic chemotherapy to the stomach.

Modalities of hepatic imaging

As previously stated, there are a variety of imaging techniques that can be used to identify lesions within the liver parenchyma, each with their own sensitivity, specificity and resolution. Multiple modalities are often used in the same patient, taking advantage of strengths that one may have over the other. The following is specific information for each imaging technology including strengths and weaknesses:

Computed tomography (CT)

Multidetector computed tomography (MDCT) is routinely used for follow-up of oncology patients, providing robust and rapid imaging of the chest, abdomen and pelvis for detection of liver and extrahepatic metastases. Intravenous iodinated contrast agents are routinely used to improve the detection of liver metastases, which are relatively inconspicuous on non-contrast CT. On routine contrast-enhanced CT (CECT) performed during the portal

venous phase, liver metastases are typically hypovascular with variable heterogeneity depending on their size and prior chemotherapy (Figure 2 A). Since colorectal liver metastases are hypovascular, the addition of arterial phase imaging generally does not improve their detection (15,16). However, arterial imaging is helpful for pre-surgical or pre-embolization planning.

An important limitation to CECT is in the detection and characterization of subcentimeter liver lesions, which are interpreted as too small to characterize (17). In addition, the development of fatty liver, which is not uncommon following chemotherapy, can further limit the detection of liver metastases. Nevertheless, the spatial resolution of MDCT is superior to MRI and PET, and is especially useful for presurgical planning and identification of aberrant anatomy (18).

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) examinations generate multiple sequences that highlight different physical properties of water and fat protons in normal and pathologic tissue. Compared to CT, MRI generates lower resolution images that can be prone to artifacts, but benefits from increased soft tissue contrast. In a typical liver MRI, a combination of T1 weighted (T1w), T2 weighted (T2w) and diffusion weighted imaging (DWI) sequences are obtained prior to and following the administration of intravenous gadolinium binding contrast agent (GBCA). Colorectal liver metastases typically demonstrate low signal (hypointensity) compared to liver parenchyma on pre-contrast T1w images, hyperintensity on T2w, and hyperintensity on DWI sequences (Figure 2 C, E, F). Following the administration of intravenous contrast, liver metastases are typically hypovascular with an irregular rim of enhancement (Figure 2 D).

In the last decade, major advances in liver MRI include the development of high resolution volumetric imaging

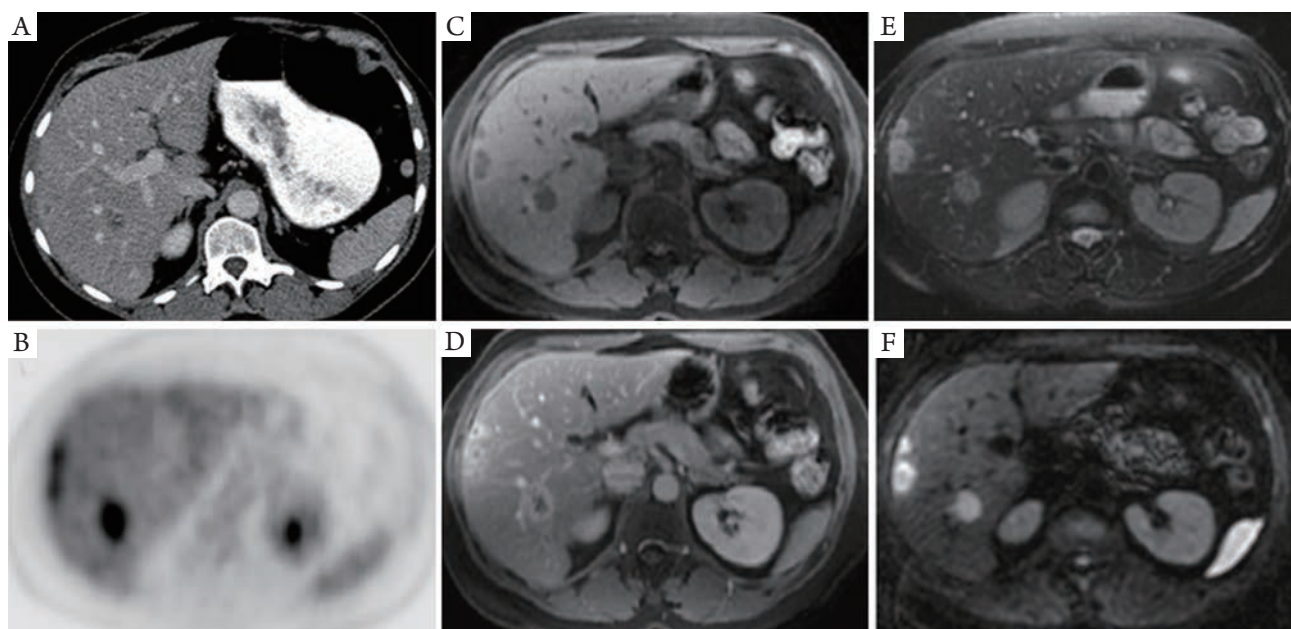


Figure 2. Colorectal liver metastases on CT, PET, and MRI. A 48-year-old woman with multiple liver metastases in the right hepatic lobe imaged on contrast-enhanced CT (A), ^{18}F FDG-PET (B), and MRI (C-F), within a five-week period. On MRI, T1 weighted pre-contrast (C), T1 weighted post-contrast (D), T2 weighted (E) and diffusion weighted imaging (F) sequences are obtained routinely.

approaching the resolution of MDCT, parallel imaging to reduce scan time, higher static magnetic field strengths (3.0 T versus 1.5T), advances in DWI, and hepatocyte-specific contrast agents (19-22). Gd-EOB-DTPA (Eovist or Primovist, Bayer Healthcare Pharmaceuticals, Wayne, NJ) and Gd-BOPTA (MultiHance, Bracco Diagnostics, Princeton, NJ) are two hepatocyte-specific contrast agents that undergo both biliary and renal excretion, as opposed to more traditional GBCAs that only undergo renal excretion, such as Gd-DTPA (Magnevist, Bayer Healthcare Pharmaceutical). With Gd-EOB-DTPA and Gd-BOPTA, delayed hepatobiliary phase T1w images are obtained where normal hepatocytes are markedly hyperintense compared to liver metastases, which do not retain the contrast agent (Figure 3). From our experience, the combination of DWI with Gd-EOB-DTPA MRI yields the highest sensitivity for small liver metastases.

MRI may not be the examination of choice for every patient. Patients with contraindications to MRI (e.g. implantable pacemakers), or unable to tolerate MRI (e.g. due to claustrophobia) would preferably undergo preoperative imaging with CT. Motion related imaging artifacts that can severely dampen the diagnostic quality of MRI will occur in patients who are unable to breath hold for longer than 20 seconds.

Positron emission tomography (PET)

Positron Emission Tomography (PET) is performed to

detect the uptake of a glucose analog, ^{18}F -fluorodeoxyglucose (FDG) in hypermetabolic tumors. FDG-PET is now routinely performed in combination with CT, either with or without intravenous contrast, and excels at the detection of colorectal liver and extrahepatic metastases (23). On PET, hypermetabolic liver tumors demonstrate high uptake (Figure 2 B). However, physiologic background liver uptake of FDG in combination with the inherent low resolution of PET can limit the sensitivity for detection of small liver metastases (24). The use of intravenous contrast during the CT portion of the examination is preferred, improving the detection of liver metastases (25).

Comparison between modalities

A recent meta-analysis was performed on prospective studies using CT, MRI, FDG PET (Table 1) between 1990 and January 2010 on metastatic colorectal patients who had not undergone any prior therapy (26). This analysis found large heterogeneity in the methodologies between studies, which is expected when reviewing studies spanning 20 years. The authors concluded that CT generally had the lowest sensitivity, especially for lesions smaller than 10 mm. They also found that MRI had significantly increased sensitivity over the years, especially comparing studies before and after 2004 (from 70 to 85% sensitivity), and recommended MRI as the first line modality, with FDG-PET playing a role for extrahepatic disease detection.

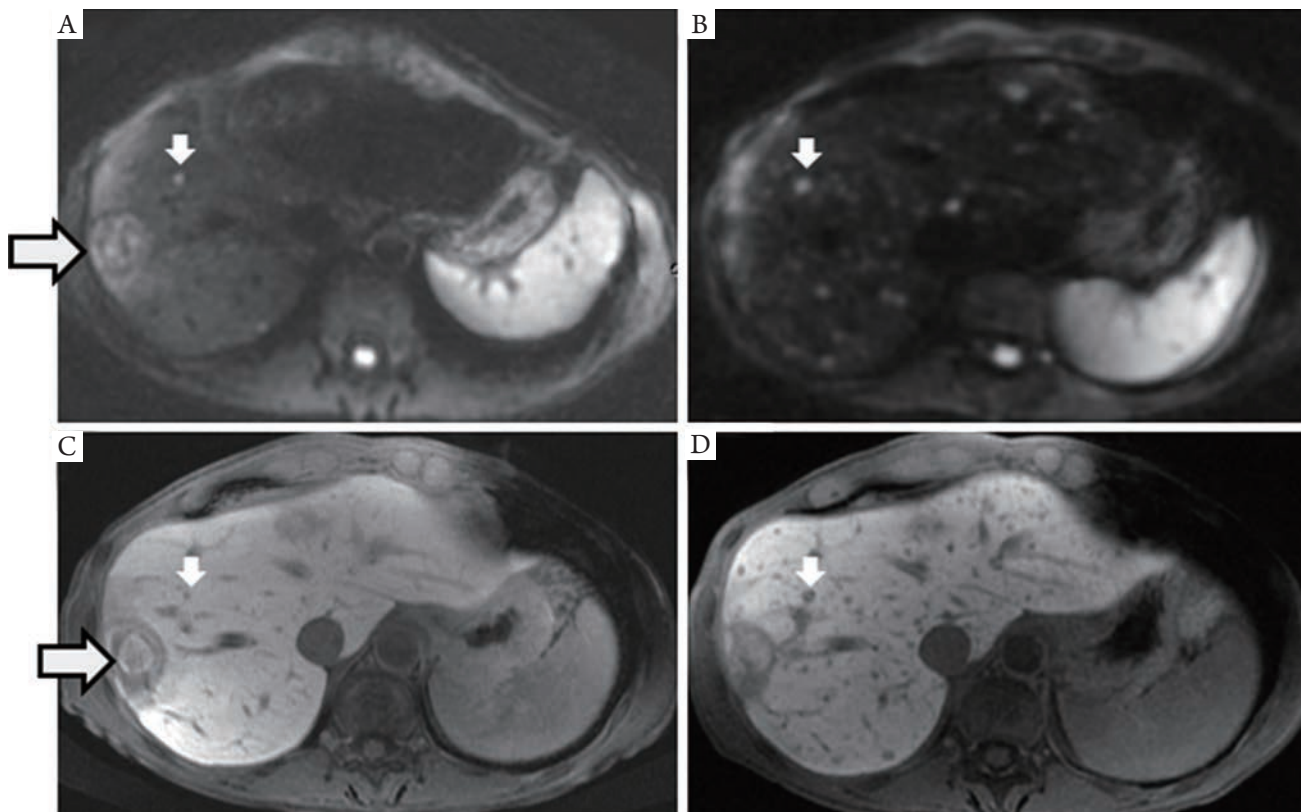


Figure 3. Small colorectal liver metastases on MRI using delayed hepatobiliary phase imaging and diffusion weighted imaging. A 52-year-old woman who underwent percutaneous radiofrequency ablation in the right hepatic lobe (large arrow), developed a 3-mm recurrence within two months (small arrow), visible on (A) diffusion weighted imaging (DWI) and (B) delayed hepatobiliary phase imaging with Gd-EOB-DTPA. Two months later, this recurrence grew to 7 mm and innumerable additional metastases appeared, as seen on (C) DWI and (D) delayed hepatobiliary phase imaging.

Table 1. Sensitivity and specificity of CT, MRI, FDG-PET.

| | CECT | MRI | PET | PET-CT* |
|-------------------------|--------|--------|--------|---------|
| Sensitivity per lesion | 69-79% | 75-85% | 67-91% | 55-75% |
| Specificity per patient | 93-96% | 90-95% | 93-98% | 93-99% |

Reported 95% confidence interval for sensitivity on a per lesion basis, and specificity on a per patient basis in a meta-analysis of CECT, MRI, PET, and PET-CT between 1990 and 2010 (26). *Only one prospective PET-CT study was included in this meta-analysis.

A recent study comparing multi detector CT, contrast-enhanced US and MRI from Japan found the highest sensitivity for MRI (95%) compared to CT and US (63% and 73% respectively) (27). In this study, MRI was performed with both DWI and delayed hepatobiliary phase imaging using Gd-EOB-DTPA. A limitation in studies comparing imaging modalities for detection of liver metastases is the lack of an absolute reference standard. Histopathologic proof, imaging follow-up and intraoperative ultrasound are often combined as a reference standard, which limits the sensitivity for small metastases and leads to verification bias. In addition, imaging modalities are rarely compared on a

lesion-by-lesion basis in the same cohort of patient, leading to selection bias, particularly in favor of MRI and FDG-PET.

In a study comparing MRI with Gd-EOB-DTPA versus PET with CECT in 68 patients undergoing both modalities, MRI demonstrated a higher sensitivity and specificity compared to PET-CECT, especially for lesions smaller than 1 cm (28). A similar study comparing MRI with Gd-EOB-DTPA versus PET-CT (without contrast) also showed a higher sensitivity for MRI (29). These studies reflect our own institutional experience: CT, FDG-PET and MRI have a comparable sensitivity for detection of large liver

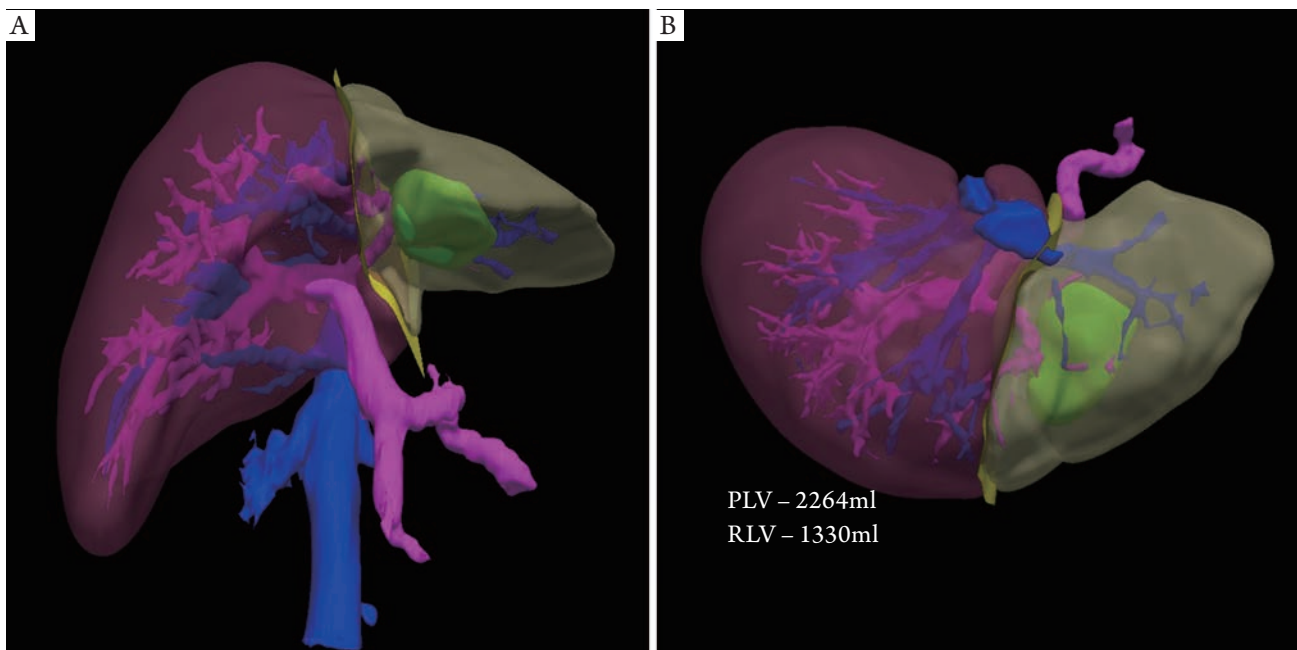


Figure 4. Volumetric analysis of the liver to estimate remnant liver volume. Three-dimensional reconstructions can be created from cross-sectional imaging using specialized computer software. Here, a program from Pathfinder Therapeutics, Nashville, TN, is used to plan a left hepatectomy. The lesion is depicted in green and a resection plane can be drawn to avoid major vessels while maintaining an adequate margin. Preoperative liver volume (PLV) and remnant liver volume (RLV) can be calculated and displayed.

metastases (Figure 1). However, MRI excels at detection of subcentimeter liver metastases compared to CT and FDG-PET, especially with the combination of DWI and hepatocyte-specific contrast agents (Figure 2).

Volumetrics

One of the most important factors to consider when planning liver resection is the amount of functional parenchyma that will remain after surgery. This is a product of the preserved parenchymal volume and the overall hepatic function. A cursory estimation of liver function can be assessed preoperatively by measurement of hepatic synthetic capability such as production of albumin or clotting factors or its ability to clear bilirubin from the blood. If a more quantitative determination of liver function is needed, a MEGX test can be performed, which evaluates the liver's ability to convert lidocaine to its metabolite, monoethylglycinexylidide (30). Alternatively, an indocyanine green (ICG) clearance test may be used, which measures the rate of removal of a hepatically excreted dye from the bloodstream (31). This may be particularly important in patients who have been treated with hepatotoxic chemotherapy preoperatively. To estimate the volume of remnant liver following resection, volumetrics is used. First described by Heymsfield (32) in the late 1970s,

CT volumetrics uses multiple axial cross-sectional images to recreate the three-dimensional structure of the liver. Using a two-dimensional image from the CT, the outline of the liver is manually traced using appropriate software. This is repeated every 5-10 mm until the entire volume of the liver is calculated. Tumors, cysts and prior ablation cavities should be excluded as these do not significantly contribute to hepatic function. Next, this process is repeated, but this time the outline of the proposed liver remnant is drawn. Typically the venous phase of the CT scan is used for volumetric analysis so that the segmental liver anatomy can be readily identified. The quotient of the calculated remnant and total liver volumes provides the future liver remnant volume, which represents the percentage of hepatic parenchyma remaining. There are currently multiple computer based programs that have automated this process allowing for 3D views of the liver, resection plane and remnant segment (Figure 4).

Multiple studies have demonstrated that CT-based volumetric measurement results in a reliable estimation of remnant liver volume with very little interobserver variability (33-35). While no data exist regarding the minimum amount of remnant liver following resection, most agree that 25-30% and 40% of the preoperative volume should be preserved for those with normal and abnormal parenchyma (ie, fibrosis, cirrhosis, steatosis due to

preoperative chemotherapy, etc), respectively.

Conclusion

With the increased use of hepatic metastasectomy comes a need for improved imaging techniques to better identify and characterize extent of disease within the liver and elsewhere. While technologic advancements have led to unprecedented image quality and clarity, this does not replace the need for a dedicated, competent radiologist with experience in hepatic imaging. The goals of preoperative imaging should be identification of intra- and extrahepatic disease, relevant liver anatomy and remnant liver volume. Because no one radiologic modality is sufficient to achieve all of these goals, some combination of imaging techniques is needed. At our institution, surveillance and staging imaging is performed with contrast-enhanced CT scans for ease of acquisition and relative low cost. If indeterminate lesions are identified in the liver, MRI may be used to better characterize these lesions and relevant anatomy, as well as rule out the presence of occult disease. MRI is particularly useful for assessing lesions in the presence of steatosis, a common finding after extensive chemotherapy treatment. PET scan is often performed to identify extrahepatic disease and occasionally to better characterize marginal liver lesions. If hepatic artery infusion pump placement is considered, CT angiography with 3D reconstruction is obtained to identify appropriate arterial anatomy. High quality preoperative imaging also allows calculation of the future liver remnant volumes, which is important when extended resections are planned, particularly in the setting of underlying hepatic parenchymal disease. The authors find it particularly helpful to present cases and images at a multidisciplinary tumor board where radiologists, surgeons, oncologists and other physicians can openly discuss findings and prepare the appropriate treatment plan.

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