5
Digestive Organs

Standard Imaging Methods for Digestive Organs (liver)

A Imaging of the liver

CT

Dynamic studies, in which contrast medium is rapidly injected and multiphase imaging that includes the arterial phase is performed, are essential to differentiate liver tumors, detect hypervascular tumors such as hepatocellular carcinoma, and stage malignancies.[1-3] Portal venous phase contrast-enhanced CT is typically performed for purposes such as watchful waiting of patients with malignant tumors. It is recommended that, with CT image reconstruction, diagnostic interpretation be performed with a slice thickness of ≤ 5 mm using a computer viewer.

1. Non-contrast CT (Fig. 1)

Although the diagnostic performance of non-contrast CT in liver tumors is limited, it is performed to examine fat and calcification in tumors and changes in the CT numbers for the liver parenchyma as a result of conditions such as fatty liver and hemosiderosis and to evaluate contrast enhancement in tumors by comparison with contrast-enhanced CT. Moreover, metastatic liver tumors that become obscure after contrast-enhanced CT are therefore identifiable only by CT performed before contrast-enhanced CT. Contrast tends to persist in liver lesions with non-contrast CT if observations during interpretation are performed using a narrow window width (WW) of 200 to 250 HU and a window level (WL) of 30 to 40 HU.

2. Contrast-enhanced CT

① Imaging method

(1) Contrast medium dose

The contrast medium dose administered is 520 to 600 mgI per kg body weight (1.73 to 2 mL per kg with a contrast concentration of 300 mgI/mL).

(2) Contrast medium injection

Multiphase contrast-enhanced CT: An injection rate that provides for a contrast medium injection time of approximately 30 seconds is used.

Normal contrast-enhanced CT: The contrast medium is generally injected at a rate of ≥ 2 mL/s (Maximum contrast enhancement of the liver depends on the iodine dose, not on the injection rate.).

② Multiphase contrast-enhanced CT (Figs. 1 and 2)

(1) Imaging phases

Late arterial phase imaging is essential to differentiate liver tumors and diagnose hypervascular tumors such as hepatocellular carcinoma, and multiphase imaging of 2 or 3 phases is performed for these purposes using combinations of the late arterial phase, portal venous phase, and equilibrium phase.

(2) Timing of imaging for each time phase

Late arterial phase: Start imaging at the time of contrast media injection + 5 to 10 seconds. To adjust for individual differences in the time needed for the contrast medium to reach the abdomen, the use of bolus tracking is recommended, with imaging started 20 to 25 seconds after the CT number of the aorta increases to 100 HU.

Portal venous phase: Approximately 70 seconds after the start of contrast medium injection.

Equilibrium phase: Approximately 180 seconds after the start of contrast medium injection.

③ Normal contrast-enhanced CT

Imaging is performed in the above-mentioned portal venous phase (timing of imaging is 70 to 90 seconds after the start of injection).

With regard to the contrast medium dose, the optimal dose for portal venous phase images was investigated. It is often considered that an increase of 50 HU in liver contrast enhancement is needed to detect liver lesions in the portal venous phase, and the iodine dose per kg body weight needed to obtain this 50-HU increase has been reported to be 521 mgI if chronic liver disease is not present.[4, 5] Moreover, an iodine dose of ≥ 600 mgI per kg body weight is considered necessary to produce adequate contrast enhancement in areas such as the liver, portal vein, pancreas, and aorta.[6] In obese patients, who have a high body fat percentage, it has been noted that determining the contrast medium dose based on body weight tends to result in an excessive iodine dose. Determining the dose based on lean body mass has been reported to be useful in such patients.[7, 8]

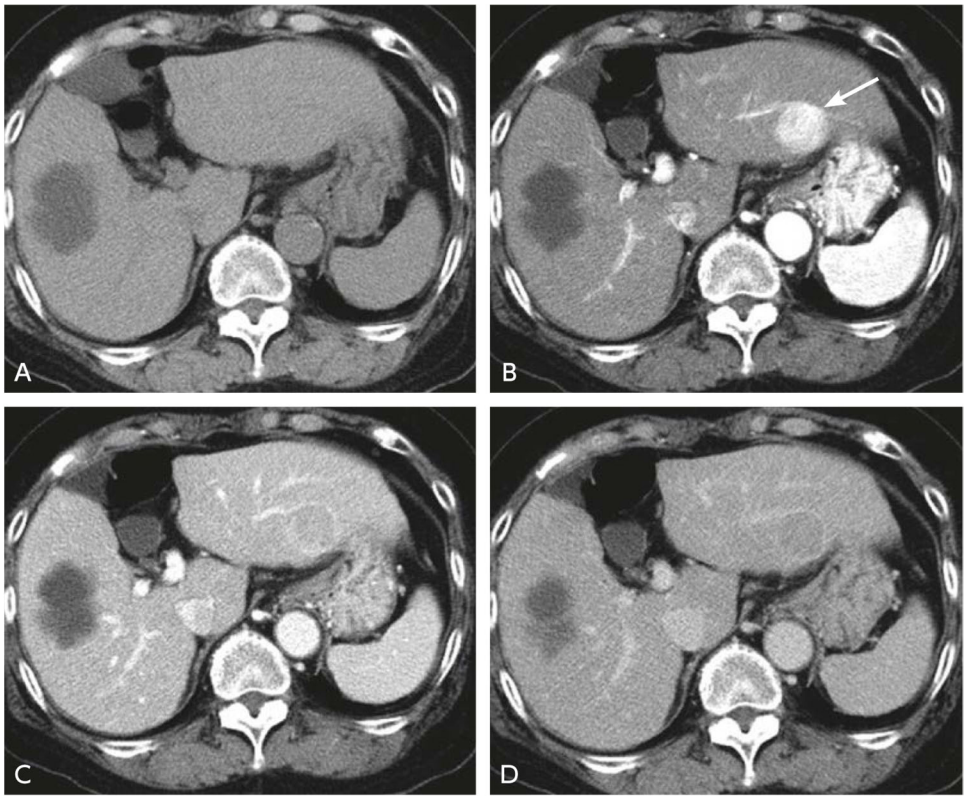

Figure 1. Multiphase contrast-enhanced CT (moderately differentiated hepatocellular carcinoma)

A: Before contrast imaging, B: Late arterial phase, C: Portal venous phase, D: Equilibrium phase
Hepatocellular carcinoma (→) of a liver with S2 steatosis is well visualized in the arterial phase, and the capsule is visualized in the equilibrium phase.

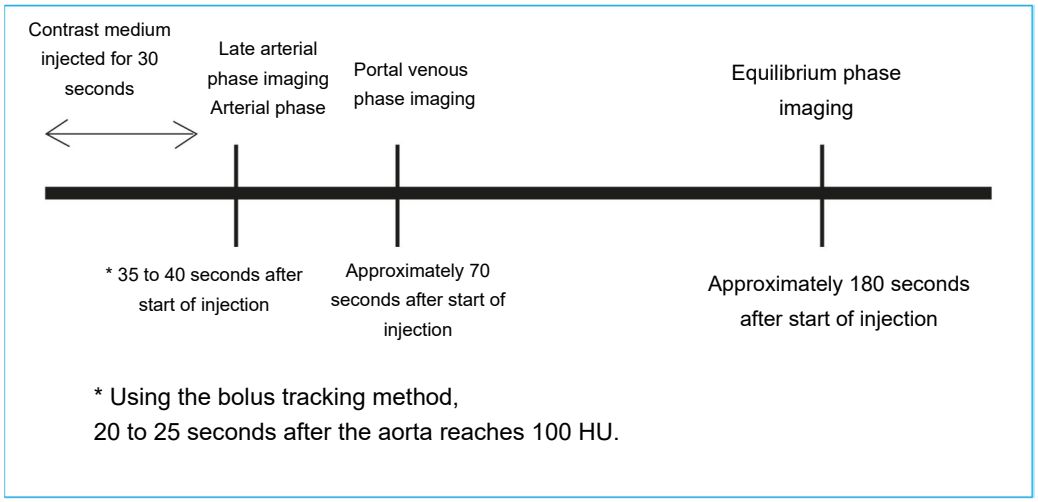

Figure 2. Standard multiphase contrast-enhanced CT imaging method

The contrast medium dose is 520 to 600 mgI per kg body weight (1.73 to 2 mL/kg with a 300 mgI/mL preparation). The late arterial phase is essential, and it is combined with the portal venous and equilibrium phases to perform 2- or 3-phase multiphase imaging.

In determining the contrast medium injection rate, an injection dose per unit time (mL/s) is used. Using a fast injection rate to administer a higher dose of iodine per unit time, arterial contrast enhancement increases, which is advantageous for visualizing hypervascular tumors.[9] Similar arterial contrast enhancement can be expected with the use of a high-concentration contrast medium (350 to 370 mgI/mL). However, if the contrast medium injection time varies with the patient's weight, the optimal timing of CT imaging will also vary. Consequently, rather than using a fixed injection rate, it is more reasonable to use a fixed injection time to enable the timing of the imaging to remain constant.[10]

In classifying the timing of multiphase CT imaging of the liver, the early and late arterial phases are classified as early phases, and the portal venous and equilibrium phases (delayed phase) are classified as transitional phases. Hepatocellular carcinoma is often hypervascular, and visualizing its enhancement during the late arterial phase and washout and capsular enhancement during the transitional phases is therefore important for its detection and qualitative diagnosis.[11] As a transitional phase, the portal venous phase is useful for evaluating tumor invasion of the portal and hepatic veins, and adding the equilibrium phase improves diagnostic performance in hepatocellular carcinoma.[12]

With regard to the timing of late arterial phase imaging, imaging of the liver begins at the contrast medium injection time + 5 to 10 seconds.[13] Thus, if contrast medium is injected for 30 seconds, imaging of the liver begins 35 to 40 seconds after the start of intravenous injection. However, a method that establishes fixed timing for imaging in this way may result in inappropriate timing due to individual differences in the time required for the contrast medium to reach the abdominal arteries. Particularly for patients in whom contrast medium reaches the abdomen slowly due to heart disease, imaging may begin too early, and sufficient contrast medium may not have reached the tumor from the hepatic artery in time for imaging. To adjust for such individual differences in imaging timing, the bolus tracking method is recommended. With this method, monitoring imaging of the abdomen is performed after the start of contrast medium injection, and imaging of the liver is started after the contrast medium is confirmed to have reached the abdominal aorta. With the use of the bolus tracking method, imaging of the liver is generally started 20 to 25 seconds after the CT number of the abdominal aorta reaches 100 HU. Similarly, the time needed for the contrast medium to reach the abdominal aorta can also be measured by the test injection method. With this method, a small amount of contrast medium is injected as a test, and the abdomen is continuously imaged. Portal venous phase imaging is performed approximately 70 seconds after the start of contrast medium injection, and equilibrium phase imaging is performed approximately 3 minutes after the start of injection.

In hypovascular liver tumors such as liver metastases, contrast peaks in the portal venous phase, when contrast enhancement of the liver is at its maximum. The maximum contrast enhancement of the liver in the portal venous phase depends on the iodine dose administered, not on the contrast medium injection rate. Consequently, for imaging in the portal venous phase only, rapid injection of the contrast medium is not necessary, and an injection rate of $\geq$ 2 mL/s is generally used. For interpretation and diagnosis, CT images reconstructed with a slice thickness of $\leq$ 5 mm and interpretation using a computer viewer is preferable.[14]

Ultrasound (Table 1, Figs. 3 and 4)

In January 2007, health insurance coverage began for a perflubutane preparation, Sonazoid®, a second-generation contrast medium for ultrasound. From the perspectives of cost and minimal invasiveness, normal ultrasonography is very useful for screening, and contrast-enhanced ultrasonography is also very useful for visualization, differentiation, and treatment efficacy evaluation. However, contrast-enhanced ultrasonography is burdensome with respect to examination time and labor intensiveness, and it is therefore considered a test not for screening, but for detailed examinations.

The imaging protocol involves imaging in the arterial-dominant phase, which is equivalent to the arterial phase of CT, after intravenous injection of 0.010 mL/kg of contrast medium, then subsequently imaging in the portal venous-dominant phase, which is equivalent to the portal venous phase of CT, in order to evaluate tumor arterial blood flow. After 10 minutes of imaging, the contrast medium is taken up by the liver parenchyma (Kupffer cells), and imaging is performed in the Kupffer phase, during which the liver parenchyma is hyperechoic. Hepatocellular carcinoma is visualized as hypoechoic in this phase because it contains no Kupffer cells, making it highly visualizable. Administration of additional contrast medium at this point enables arterial blood flow and hemodynamics to be evaluated for lesions first visualized in the Kupffer phase and facilitates differentiation and treatment efficacy evaluation.[15)]

Table 1. Ultrasound example

Contrast medium: bolus injection of 0.010 mL/kg of Sonazoid® (Daiichi-Sankyo)
Frequencies used: 4 MHz, 6.5 MHz
MI value: 0.2
Focal point: 1 point (depth: approximately 10 cm)
Frame rate: 10 to 14 Hz

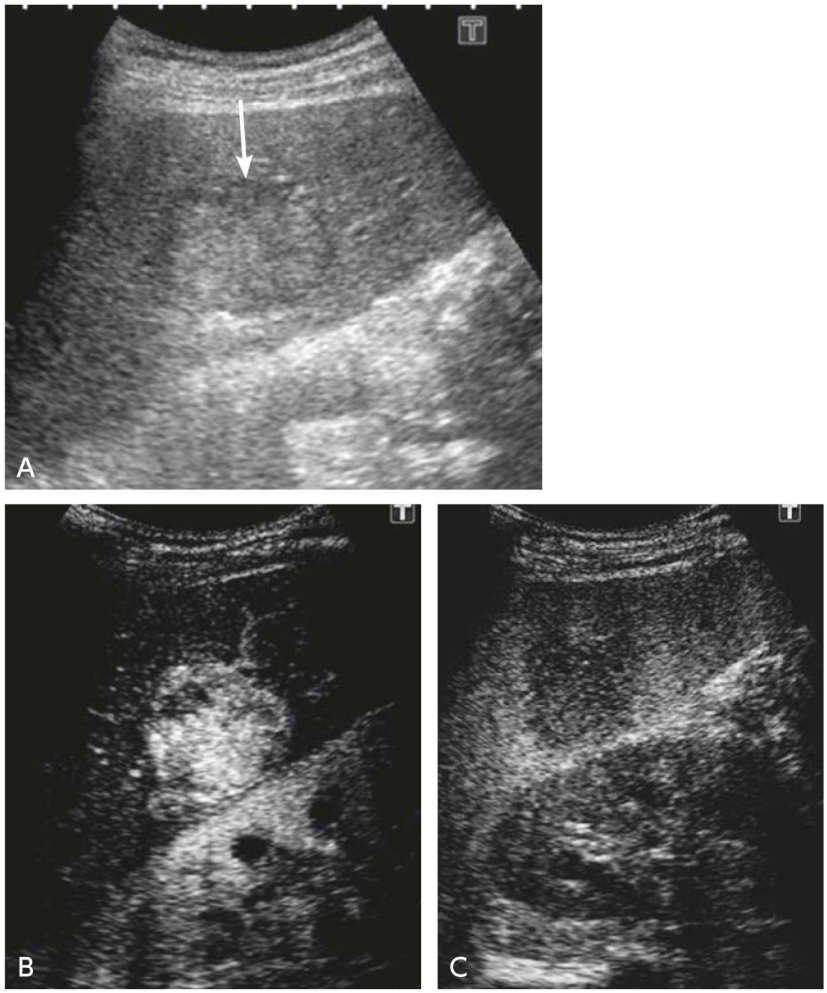

Figure 3. Ultrasound images (moderately differentiated hepatocellular carcinoma)

A: B-mode ultrasound image; B: perflubutane contrast-enhanced ultrasound image, arterial-dominant phase;
C: perflubutane contrast-enhanced ultrasound image, Kupffer phase
With perflubutane contrast-enhanced ultrasonography, enhancement of hepatocellular carcinoma (→) is seen in the arterial-dominant phase, and the hepatocellular carcinoma is hypoechoic in the Kupffer phase.

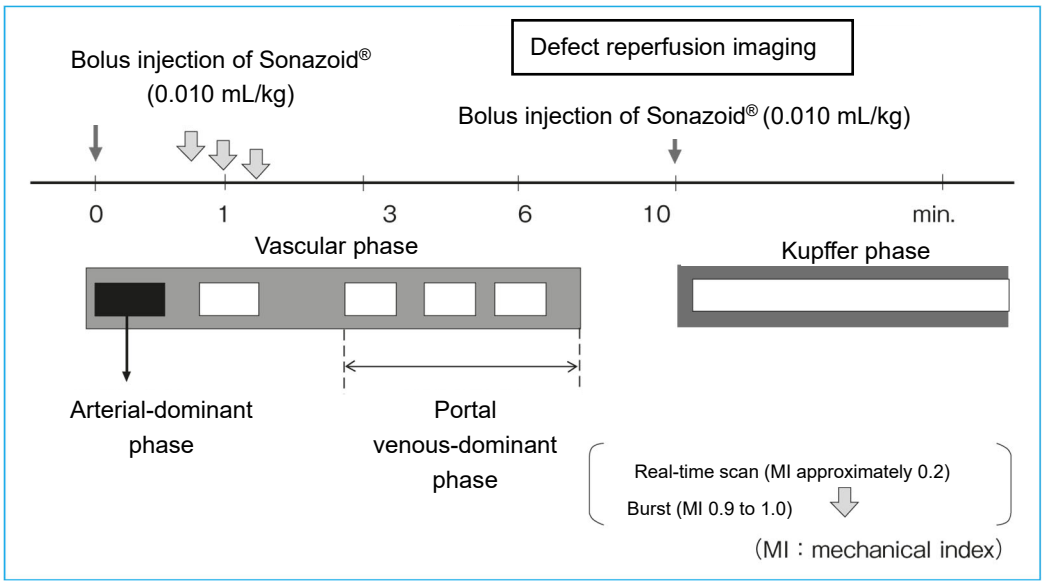

Figure 4. Basic imaging method using Sonazoid® (longitudinal section image)

MRI

Phased array coils are used for liver MRI diagnosis. Although non-contrast MRI and Gd-EOB-DTPA (EOB/Primovist®) contrast-enhanced MRI are often performed to diagnose liver tumors, imaging using an extracellular fluid gadolinium contrast medium or, when a gadolinium contrast medium is contraindicated, imaging using a superparamagnetic iron oxide (SPIO, Resovist®) contrast medium is performed when only blood flow information is needed. Diagnostic interpretation using a slice thickness of ≤ 5 mm and a computer viewer is recommended.

1. Non-contrast MRI (Fig. 5)

Imaging according to the following sequences is recommended, generally by transverse plane imaging.

① T1-weighted images: Breath-hold in-phase and out-of-phase (opposed phase) GRE images are essential.

② T2-weighted images (essential): Acquisition of respiratory-gated, fat-suppressed, FSE-T2-weighted and breath-hold SSFSE (HASTE), T2-weighted images is recommended. The addition of heavy T2-weighted imaging with a TE of ≥ 150 ms is useful for differentiating cysts and hemangiomas with long T2 values and malignancies.

③ Diffusion-weighted images (recommended): Imaging is performed using the echo-planar imaging (EPI) technique. The b-value is typically ≥ 400 s/mm^2.

④ Steady-state coherent image (sequence names: True FISP, balanced FFE, FIESTA, True SSFP; recommended): Concurrent fat suppression is also recommended.

2. Gd-EOB-DTPA contrast-enhanced MRI (EOB-MRI, Figs. 6 and 7)

Dynamic studies and hepatobiliary phase imaging are performed by Gd-EOB-DTPA contrast-enhanced imaging. To shorten the length of MRI tests, a Gd-EOB-DTPA dynamic study is performed after non-contrast MRI (T1-weighted imaging) and before hepatobiliary phase imaging are performed; T2-weighted imaging, diffusion-weighted imaging, and steady-state coherent imaging may also be performed.[16)]

① Imaging method

Contrast medium dose: 0.1 mL/kg of Gd-EOB-DTPA.

Contrast medium injection method: The Gd-EOB-DTPA dose is small, and rapid injection is unnecessary.[17)] As in CT, with varying injection times, the optimal timing of imaging differs between individuals. Consequently, as with CT, a constant injection time can be used by adjusting the injection time or diluting the contrast medium.[18)] Because the contrast medium dose is small, a saline chaser is essential.

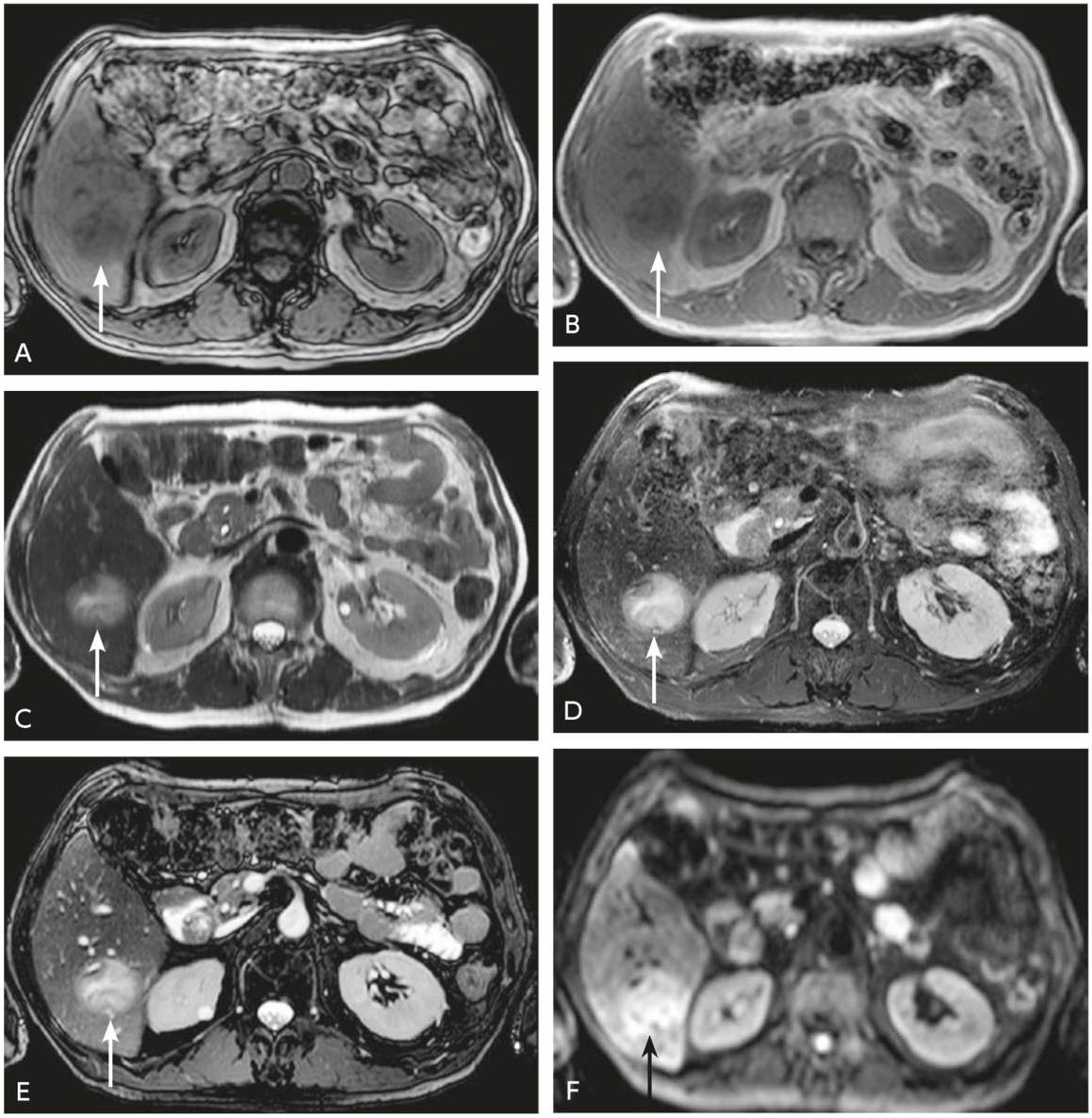

Figure 5. Non-contrast MRI (moderately differentiated hepatocellular carcinoma)

A: T1-weighted (opposed phase, GE imaging); B: T1-weighted (in phase, GRE imaging);
C: T2-weighted (breath-hold, HASTE imaging); D: Fat-suppressed, T2-weighted (respiratory-gated, FSE imaging);
E: Fat-suppressed, 3D balanced (FFE imaging); F: Diffusion-weighted imaging
Hepatocellular carcinoma (→) is visualized as a low-signal area with T1-weighted imaging and as a high-signal area with T2-weighted and diffusion-weighted imaging.

② Imaging method

(1) Imaging sequence

Fat-suppressed, T1-weighted, 3D GRE imaging is recommended.

(2) Slice thickness

A thickness of ≤ 5 mm is recommended.

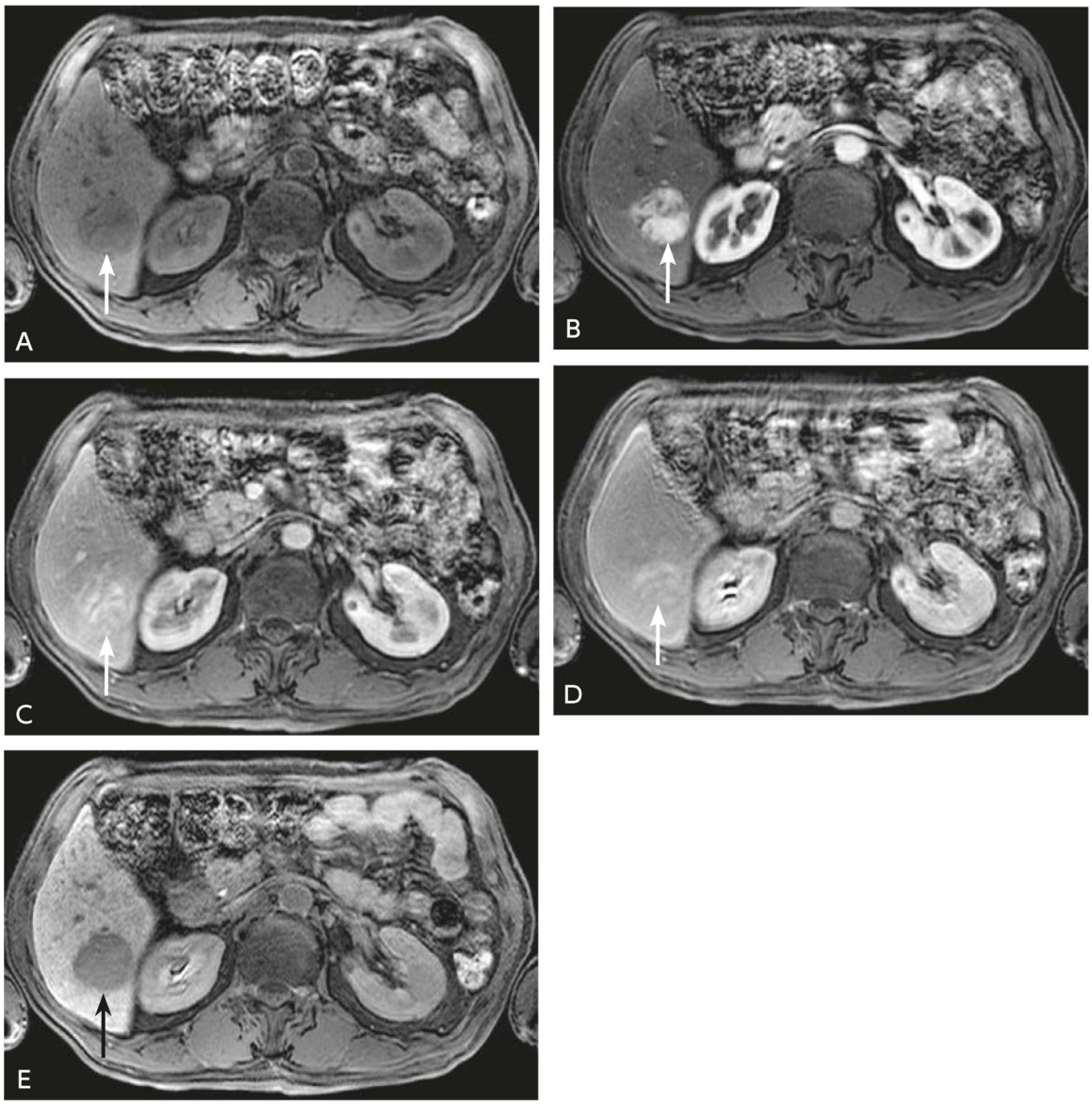

Figure 6. EOB-MRI (moderately differentiated hepatocellular carcinoma)

Fat-suppressed, T1-weighted (3D GRE imaging)

(A: Before contrast-enhanced imaging, B: arterial phase, C: portal venous phase, D: transitional phase, E: hepatobiliary phase
Hepatocellular carcinoma (→) is enhanced during the arterial phase and visualized as a low-signal area during the hepatobiliary phase due to decreased contrast medium uptake.

(3) Imaging plane

Transverse plane imaging. In the hepatobiliary phase, the addition of coronal and sagittal imaging is recommended.

(4) Imaging timing

Arterial phase: The bolus tracking method is recommended for determining the timing of imaging. Using the arrival of the contrast medium in the abdomen or descending aorta as the trigger, arterial phase imaging is performed so that the center of k-space occurs approximately 15 to 20 seconds after the trigger.[19] When fixed imaging timing is used, imaging is performed so that the center of k-space occurs approximately 30 seconds after the start of injection. For the portal venous phase, it is approximately 70 seconds after the start of contrast medium injection.

Transitional phase: 2 to 3 minutes after contrast medium injection.

Hepatobiliary phase: Beginning from 20 minutes after contrast medium injection. In patients with good liver function and imaging of the liver parenchyma, imaging can be performed at approximately 15 minutes after injection.

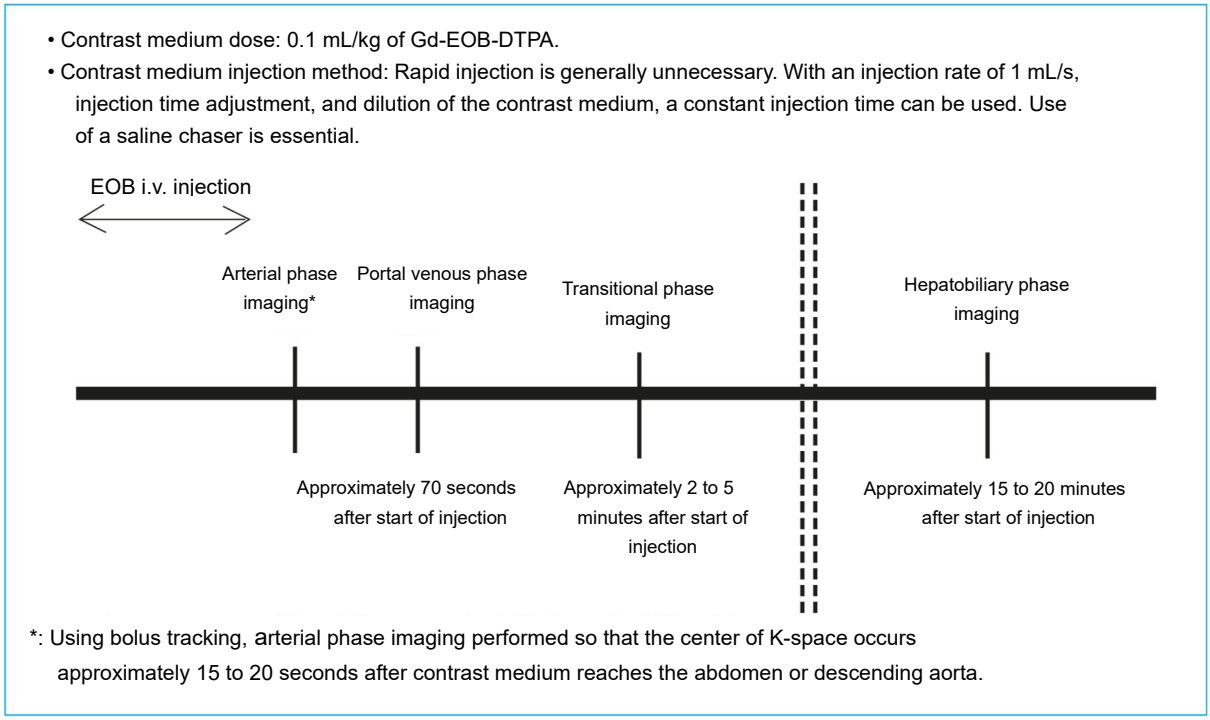

Figure 7. Standard EOB-MRI imaging method

3. Dynamic MRI using an extracellular gadolinium contrast medium

After non-contrast MRI imaging is performed, pre-contrast, arterial-phase, portal venous phase, and equilibrium-phase imaging is performed by the same method as used for the above-mentioned EOB-MRI imaging. A contrast medium dose of 0.2 mL/kg is used.

4. Superparamagnetic iron oxide (SPIO) MRI imaging (SPIO-MRI)

Imaging is performed beginning 10 minutes after intravenous administration of a 0.45 mg/kg (8 μmol/kg) iron dose. The following imaging sequences are recommended.

① Long TE-GRE imaging (TE ≥ 8 ms; transverse, sagittal, and coronal plane imaging recommended)

② Fat-suppressed, respiratory-gated, T2-weighted, FSE, transverse plane imaging

In addition, diffusion-weighted imaging and steady-state coherent imaging can be added.

Hepatocellular carcinoma generally appears as a low-signal area on T1-weighted images. However, some highly differentiated hepatocellular carcinomas appear as a high-signal area on T1-weighted images. Breath-hold in-phase and out-of-phase (opposed phase) GRE imaging is performed as T1-weighted imaging. Fat deposits in tissue appear as high-signal areas on in-phase imaging and areas of decreased signal intensity on out-of-phase imaging, enabling fatty degeneration of hepatocellular carcinoma to be observed. This is also useful for differentiating tumors and focal fat deposits.

Liver malignancies generally appear as high-signal areas on T2-weighted images. Although approximately 95% of hepatocellular carcinomas have been found to appear as high-signal areas on T2-weighted images, highly differentiated carcinomas may appear as areas of isointensity.[20] Respiratory-gated, fat-suppressed FSE T2-weighted imaging is useful for detecting hepatocellular carcinoma.[21, 22] Although the breath-hold SSFSE (HASTE) method is an inferior method for hepatocellular carcinoma detection because the T2 value of hepatocellular carcinoma is not very long, it enables visualization as a high signal of cysts and hemangiomas, which have long T2 values, and is useful for their differentiation.[22] Heavily T2-weighted imaging with a long TE of ≥ 150 ms is particularly useful for differentiating hemangiomas, cysts, and malignancies.[23]

Diffusion-weighted imaging is considered useful for detecting metastatic liver tumors.[24] Although it is inferior to contrast-enhanced MRI for detecting hepatocellular carcinoma, and its ability to detect hepatocellular carcinoma is limited,[25] it is useful in cases where a contrast study cannot be performed.

Steady-state coherent imaging enables blood flow and quiescent fluids to be visualized as a high signal in images that reflect T2/T1 contrast. Because it enables non-contrast-enhanced visualization of the portal vein, hepatic vein, and bile duct, it is useful for diagnosing vascular and bile duct invasion of hepatocellular carcinoma. Concurrent use of fat suppression is recommended.

As contrast-enhanced MRI tests to diagnose hepatocellular carcinoma, dynamic studies using extracellular gadolinium contrast media which, as in the case of CT, permit blood flow evaluation and contrast studies using SPIO contrast media, which are liver-specific and taken up by Kupffer cells, have been performed in the past. Currently, however, except in cases where a gadolinium contrast medium cannot be used, blood flow evaluations based on dynamic studies using Gd-EOB-DTPA contrast media and evaluations based on hepatocyte function determined by hepatobiliary phase imaging are recommended.

Standardization of diagnostic imaging terminology

Standardization of diagnostic imaging terminology for liver-related fields has been proposed for the American College of Radiology's reporting and data system (RAD) project. For the liver imaging reporting and data system (LI-RADS), the time phases for contrast-enhanced ultrasound (Lumason, Sonovue, Definity), dynamic CT, and dynamic MRI are defined as follows (for more information, see the American College of Radiology website).

Arterial phase (contrast-enhanced ultrasound, contrast-enhanced CT, and MRI): The time phase of post-contrast imaging in which the hepatic artery is completely enhanced and the hepatic veins (antegrade flow) are not enhanced more than the liver parenchyma.

Portal venous phase (contrast-enhanced ultrasound, contrast-enhanced CT, and MRI): The time phase of post-contrast imaging in which the portal and hepatic veins are enhanced more than the liver parenchyma and the images are acquired no more than 2 minutes after injection of a contrast agent.

Equilibrium phase (same as delayed phase; contrast-enhanced CT, and MRI using an extracellular gadolinium contrast medium): The time phase of post-contrast imaging in which the portal and hepatic veins are enhanced more than the liver parenchyma and the images are acquired at least 2 minutes after injection of a contrast agent.

Transitional phase (EOB-MRI): A time phase in which the signal intensities of the liver vessels and liver parenchyma are comparable in imaging performed after the arterial phase of contrast-enhanced MRI using a liver-specific contrast medium (a time phase between the portal venous and hepatobiliary phases).

Hepatobiliary phase (EOB-MRI): A time phase in which a liver-specific contrast medium is fully taken up by hepatocytes and excreted by the biliary system.

Standard imaging methods (gallbladder and bile duct)

B Imaging of the gallbladder and bile duct

Introduction

Although ultrasound is generally first used as a screening evaluation of the biliary system, there are regions that are difficult to visualize, such as the lower bile duct. Consequently, the use of CT or MRI is often necessary for close examination. The biliary system occupies an anatomically small region, and high spatial resolution is therefore needed to evaluate lesions that develop in this region. CT, which provides excellent spatial resolution and enables imaging to be performed over a broad area in a short time, is normally the first-line modality. However, MRI, with its excellent contrast resolution, is useful in cases such as when visualization of the biliary system as a whole is important.

CT

A slice thickness thinner than that used for the liver is recommended (at least approximately 2 mm). Imaging is performed using a thinner slice thickness (≤ 1 mm) if the objective is vascular reconstruction similar to that used for the liver. The imaging method and timing are the same as for the liver protocol. An example imaging protocol is shown in Table 2.

1. Imaging method used when the presence of calculus is suspected

The plain phase plays the central role in determining whether a calculus is present (Fig. 8A).[26] This is because it is sometimes difficult to distinguish faint calcified calculi from enhanced surrounding tissue on contrast-enhanced imaging (Fig. 8B). The portal venous-dominant phase is useful for evaluating the extent and severity of associated inflammation or complications such as abscesses. There has also been a report indicating that portal venous phase imaging alone is sufficient to diagnose calculi.[27]

Table 2. CT protocol [for 64-row multidetector computed tomography (MDCT)]

Tube voltage: 120 kVp, current: auto mAs
Image SD: 10/5 mm reconstruction
Detector: 0.5 mm × 64 or 1 mm × 32
Table speed: 26.5 mm/rot
Imaging timing: Trigger of 150 HU enhancement for arteries (early arterial phase); imaging performed for arterial-dominant phase 20 seconds later, for portal venous-dominant phase 60 seconds later; and for equilibrium phase 240 seconds later.
Collimation: 0.5 mm or 1 mm, Slice thickness: 1 or 2 mm
Contrast medium concentration: 300 to 370 mgI/mL (equivalent to 600 mgI/kg)
Injection time: 30 seconds, Needle: 20-G indwelling needle

2. Imaging method used if a tumor is suspected

In addition to qualitative diagnosis, imaging is often performed in 3 phases: plain, arterial-dominant, and portal venous-dominant phases. The arterial-dominant phase is useful for evaluating lesion vascularity and determining vascular anatomy. The portal venous phase, because it allows sufficient enhancement of the surrounding blood vessels and their related tissues, is useful for evaluating the extent of tumors. In addition, the equilibrium phase is useful for tumor characterization (persistent and delayed enhancement of adenocarcinoma, the most common type).[28, 29] Images reconstructed by multiplanar reconstruction (MPR) or coronal planar reconstruction (CPR) are useful for evaluating longitudinal progression of bile duct cancer, and their proactive use is recommended.[29]

○ Drip-infusion-cholangiography CT (DIC-CT)

Non-contrast CT of the entire liver is performed approximately 1 hour after intravenous injection of meglumine iotroxate. To determine the anatomy of the biliary system, it is assumed that reconstruction is performed by maximum intensity projection (MIP) or volume rendering (VR), and imaging and

reconstruction are therefore performed with a slice thickness of ≥ 1 mm.[30] Meglumine iotroxate is an iodine contrast medium for DIC, and its use was temporarily halted due to its numerous adverse reactions. However, its use was partially revived with the emergence of DIC-CT. When using it, greater attention should be paid to adverse reactions than when using regular iodine contrast media. In patients with normal liver function and no biliary dilatation, meglumine iotroxate can enable the biliary system anatomy to be determined at high spatial resolution. In the presence of impaired liver function, excretion of contrast medium into the biliary tract becomes impaired, resulting in poor visualization. Caution is therefore required in such cases.

MRI

MRI is indicated in cases such as the following: when there are doubts about a diagnosis based on dynamic CT by MDCT (a calculus that is completely isodense on CT may occur in rare cases); to evaluate the biliary tract as a whole; to evaluate cystic lesions; or if the patient has an iodine allergy.

1. Imaging method used when the presence of calculus is suspected

Magnetic resonance cholangiopancreatography (MRCP) has an important role as a sequence. The two imaging methods used for MRCP are a single-slice 2D method using thick slices 4 to 8 cm in thickness (Fig. 8C) and a 2D or 3D multislice method. The 3D multislice method has a long imaging time, and it is performed over several minutes, using respiratory gating or diaphragm navigation.[31] If the 3D multislice method is successful, high-resolution images of the biliary tract as a whole can be obtained by MIP (Fig. 8B), and examination of the original images can yield detailed information (Fig. 8E). Consequently, this method alone is sufficient. However, depending on the respiratory status of the patient, it may not always be successful, and imaging using a 2D method (single slice or multislice) under breath-hold is also recommended as a backup measure. A point to be noted during evaluations is that a small calculus that is completely surrounded by bile will, in principle, not be displayed in an MIP image (regardless of whether 2D or 3D) when observed from any angle. Consequently, the original image is always checked. A related point is that, with the 2D method using thick slices, areas with calculi are readily observed as areas of signal attenuation. In addition, normal T1-weighted and T2-weighted imaging is added, and diffusion-weighted imaging is also added if possible to detect any incidentalomas. Moreover, because some calculi (particularly intrahepatic bile duct stones) may appear as high-signal areas on T1-weighted images,[32] the addition of high-resolution, fat-suppressed, 3D T1-weighted imaging is also desirable (Fig. 8F). Balanced sequences enable imaging with a high signal-to-noise ratio to be performed in a short time and can therefore also be added as an option in cases where breath-holding is difficult (Fig. 8G). A contrast study is unnecessary as long as there are no comorbidities such as tumors. Examples of imaging protocols are shown in Table 3.

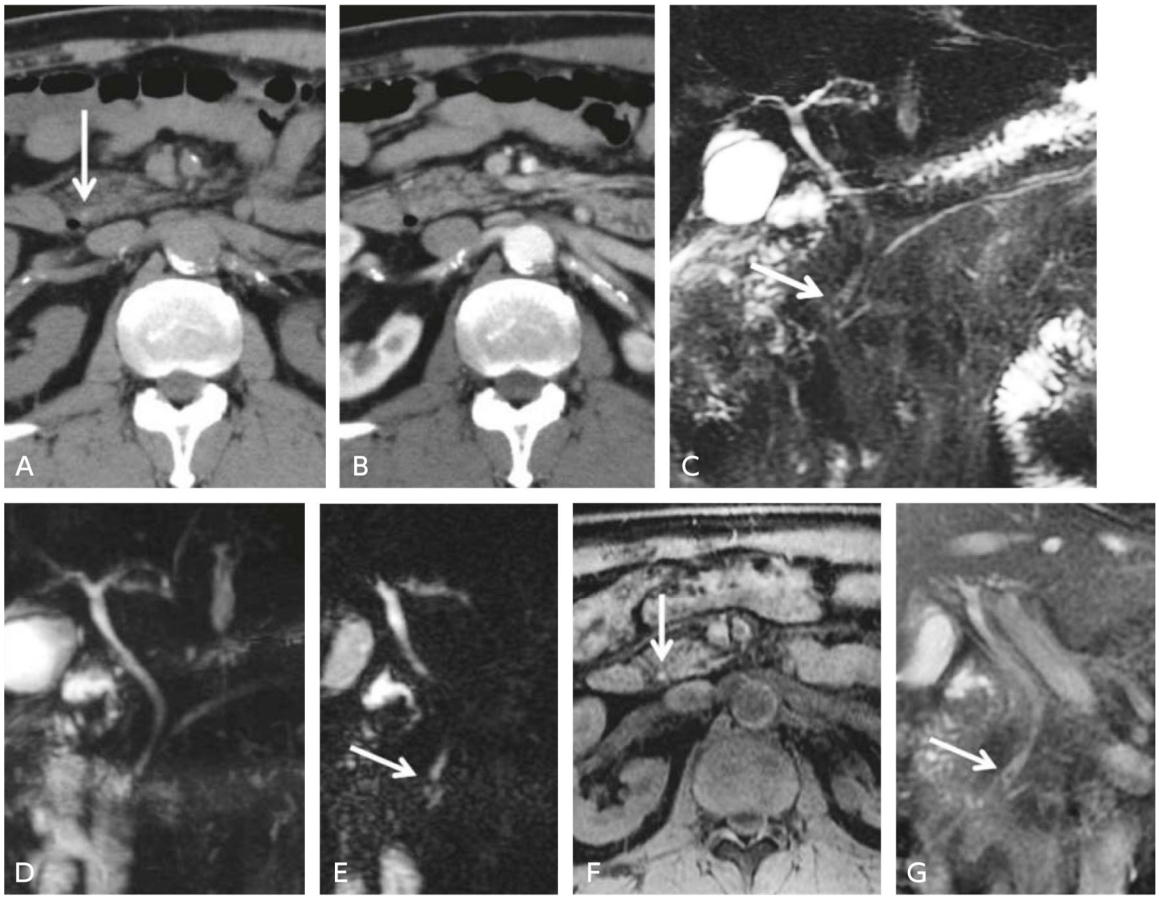

Figure 8. Calculus at the lower end of the common bile duct

A: Non-contrast CT: Small calculus barely visible (→).
B: Contrast-enhanced CT: Pancreatic parenchyma is enhanced, making it difficult to identify the calculus.
C: 2D single-shot, thick-slice MRCP: The calculus is visible (→).
D: 3D MRCP (MIP image): Intestinal fluid may obscure the calculus, making it difficult to identify with this image alone.
E: 3D MRCP (original image): The calculus is visible (→).
F: 3D MRI (T1-weighted, transverse image): The calculus is clearly visualized as a high-signal area (→).
G: Balanced sequence: The calculus is visible (→).

○ Oral contrast media

Oral contrast media that use manganese or iron preparations contribute to improved MRCP image quality by inhibiting the signal from excess fluid accumulated in the gastrointestinal tract. However, when evaluation of the papillary region is required due to conditions such as pancreaticobiliary maljunction, the presence of a sufficient amount of fluid in the duodenum can facilitate interpretation. Moreover, although rare, in the case of sphincter of Oddi dysfunction following papillotomy or a similar procedure, the contrast medium may reflux into the bile duct, preventing evaluation of this area. Care is thus required in this regard.[33] Therefore, rather than administering an oral contrast medium to all patients from the beginning, the recommended protocol is to first perform thick-slice 2D MRCP imaging in 3 to 5 directions and administer an oral contrast medium after determining whether one is needed (Table 3).

Table 3. Examples of MRCP protocols (1.5-T system, phased array coil)

Imaging Method	Sequence	TR/TE	Slice Thickness/ Interval, etc.	Other
(1) 2D MRCP/coronal plane, oblique coronal plane	Breath-hold, fat-suppressed, FSE	∞/800 (ETL approximately 256)	4 to 8 cm	3 to 5 directions, liver and pancreas included
(2) T1/T2-weighted/coronal plane	Breath-hold balanced sequence	3.5/1.8	6 to 4/0 mm	Optional
Oral contrast medium administered as needed				
(3) T2-weighted/transverse plane	FSE	∞/320 (ETL approximately 93)	5 to 6/0 mm	Extent: liver to papilla
(4) T1-weighted/transverse plane	Breath-hold 2D GRE (dual echo)	250/2.3 & 4.2	5 to 6/0 mm	Optional Extent: liver to papilla
(5) T1-weighted/transverse plane	Breath-hold, fat-suppressed 3D GRE or respiratory-gated, fat-suppressed 2D SE	4.3/2.1 (flip angle, 15°) 250/5.5 (flip angle, 70° to 90°)	4/-2 mm	Extent: liver to papilla
(6) 3D MRCP/coronal plane or 2D MRCP	Fat-suppressed FSE	1,300/650 (ETL approximately 124) ∞/87 (ETL 128)	2/-1 mm 5 to 6/0 mm	Evaluated using MIP and original image, with liver and pancreas included

Table 4. Examples of biliary system contrast-enhanced MRI protocols (including MRCP)

Imaging Method	Sequence	TR/TE	Slice Thickness/ Interval, etc.	Other
(7) 2D MRCP/coronal plane, oblique coronal plane	Breath-hold, fat-suppressed FSE	∞/800 (ETL approximately 256)	4 to 8 cm	3 to 5 directions, liver and pancreas included
(1) T1/T2-weighted imaging/coronal plane	Breath-hold balanced sequence	3.5/1.8	6 to 4/0 mm	Optional
(2) T2-weighted/transverse plane	2D FSE	∞/120 (ETL approximately 80)	5 to 6/0 mm	Extent: liver to papilla
(3) T1-weighted/transverse plane	Breath-hold 2D GRE (dual echo)	150/2.3 & 4.2 (flip angle, 70° to 90°)	6/0 mm	Extent: liver to papilla
(4) T1-weighted/transverse plane	Respiratory-gated, fat-suppressed 2D EPI	250/5.5 (flip angle, 70° to 90°)	6/0 mm	Optional Extent: liver to papilla
(5) Diffusion weighted/transverse plane	Free-breathing, fat-suppressed 2D EPI	5,000/65 (b-value = 0, 800 to 1,000 s/mm^2)	5 to 6/0 mm	
(6) Dynamic MRI/transverse plane or oblique	Breath-hold fat-suppressed 3D GRE or breath-hold, fat-suppressed 2D GE	4.3/2.1 flip angle, 15°) 150/4 flip angle, 70° to 90°)	4/-2 mm 5 to 6/0 mm	Extent: liver to papilla Plane determined to suit tumor
Oral contrast medium administered as needed				
(7) 3D MRCP/coronal plane or 2D MRCP	Fat-suppressed 3D FSE	1,300/650 (ETL approximately 124) ∞/87 (ETL 128)	2/-1 mm 5 to 6/0 mm	Evaluated using MIP and original image, liver and pancreas included

2. Imaging method used when a tumor is suspected

Dynamic MRI is performed in the arterial-dominant and portal venous phases and through the equilibrium phase,[34] with the use of high spatial resolution (≤ 3 to 4 mm thickness) 3D T1-weighted imaging recommended. If 3D imaging cannot be performed, the general orientation of the lesion is first determined by means such as single-shot 2D MRCP. Multislice dynamic 2D T1-weighted imaging is then performed in the optimal direction for visualizing the lesion. Examples of imaging protocols are shown in Table 4.

○ Oral contrast medium administration during dynamic MRI and MRCP and its timing

Because an oral contrast medium shortens T1, the presence of such a medium during dynamic MRI imaging can not only make it difficult to evaluate the intestinal tract itself, but artifacts from peristalsis can also produce noise in the periphery and make it difficult to evaluate enhancement of biliary tract lesions. On the other hand, the gadolinium preparations used in dynamic imaging shorten T2 of the background after intravenous injection and are useful for improving MRCP image quality. Consequently, it has also been suggested that MRCP should be performed as needed after oral contrast medium administration following the completion of dynamic imaging (Table 4).

Standard imaging methods (pancreas)

C Imaging of the pancreas

Introduction

If pancreatic disease is suspected, ultrasonography is first performed for screening. Although ultrasonography is useful for evaluating dilatation of the main pancreatic duct and detecting lesions at the junction of the head and body of the pancreas, the scope of observation can be limited by gas in the gastrointestinal tract. Multidetector CT (MDCT) provides excellent spatial resolution and enables imaging to be performed with thin sections. It is therefore considered the most useful test for pancreatic disease. If a pancreatic tumor is suspected, dynamic contrast-enhanced CT is recommended, except in patients for whom contrast media are contraindicated. MRI provides excellent contrast resolution, and new information can be obtained by combining it with ultrasound and CT. For example, MRI is superior even to CT for detecting cystic lesions. Moreover, MRCP enables the overall appearance and dilatation and stenosis of the main pancreatic duct, gallbladder, and biliary tract to be evaluated more easily than with CT. MRI is therefore recommended when an abnormality is suspected based on ultrasonography or CT.

CT (Fig. 9)

As with the biliary system, it is recommended that CT of the pancreas be performed with thinner section thickness (1 to 3 mm) than used for the liver. When the aim is to create 3D-reconstruction images, imaging is performed with even thinner section thickness (0.5 to 1.25 mm), and the data are stored on the image server. An MDCT imaging protocol (example) for pancreatic tumors is shown in Table 5.

1. Imaging method used when a pancreatic tumor such as pancreatic cancer is suspected

After unenhanced CT (which is optional), a high-concentration contrast medium is injected over a standardized period of 30 seconds, and dynamic contrast-enhanced CT is performed for 4 phases: the early arterial phase, late arterial phase (pancreatic parenchyma phase), portal venous phase, and equilibrium phase (≥ 180 seconds). The extent of the imaging in the arterial phase is from the liver to the pancreas or kidney. In the portal venous and equilibrium phases, imaging is performed from the liver to the pelvis so that changes such as peritoneal metastasis are not overlooked.

Imaging in the early arterial phase is performed to evaluate the arterial anatomy and create CT angiography. The late arterial phase, also called the pancreatic parenchymal phase, is the optimal phase to demonstrate pancreatic cancer because the normal pancreatic parenchyma shows peak contrast enhancement. Pancreatic cancer, which is hypovascular, appears as a hypodense lesion and contrasts highly with the normal pancreatic parenchyma. Liver metastasis and portal venous tumor invasion are evaluated in the portal venous phase. In the equilibrium phase, pancreatic cancer, which has an abundant fibrous stroma, undergoes delayed enhancement. Evaluating the contrast enhancement pattern from the arterial phase to the equilibrium phase is useful for the differential diagnosis of pancreatic mass lesions. Because liver metastases of pancreatic cancer occasionally show AP shunt-like enhancement, attention should be paid to the presence or absence of early enhancement of the liver parenchyma in the late arterial phase. In addition, MPR is useful for preoperatively evaluating peripancreatic arterial and venous anatomy and vascular invasion.

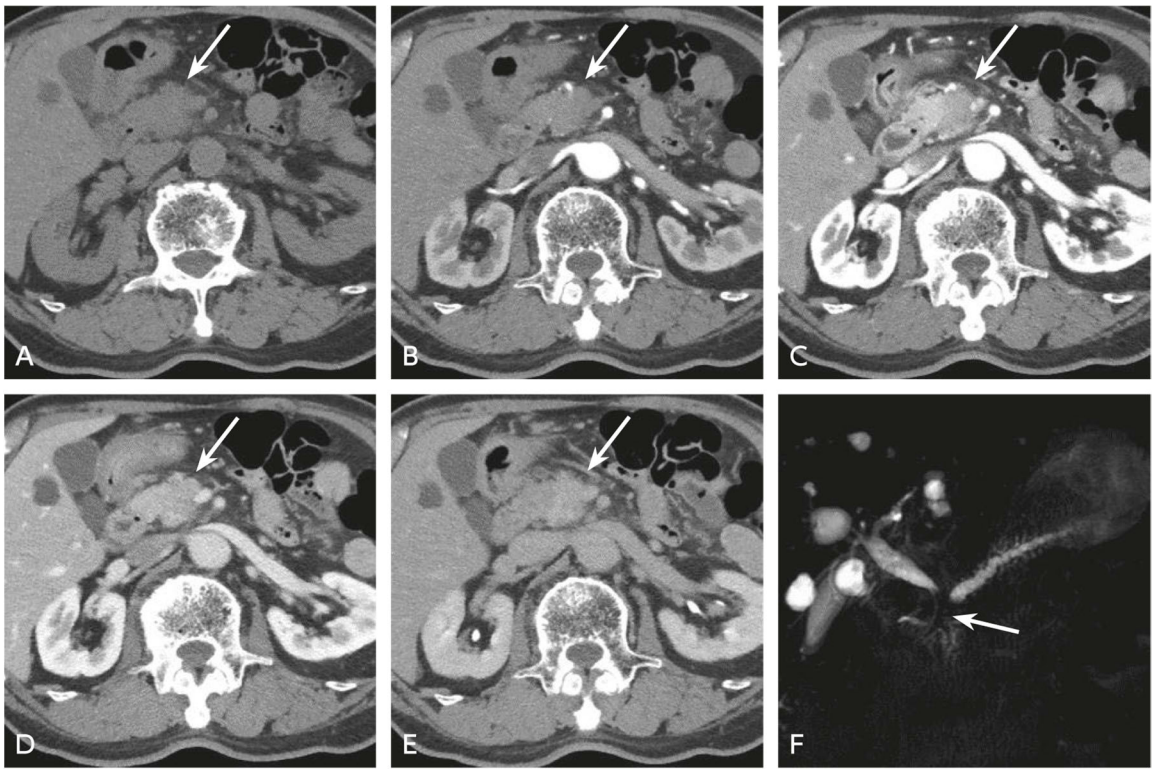

Figure 9. Dynamic CT and MRCP of pancreatic head cancer

A: unenhanced CT, B to E: dynamic CT, B: early arterial phase, C: late arterial phase (pancreatic parenchymal phase), D: portal venous phase, E: equilibrium phase, F: 2D thick-slab MRCP (breath-hold)
Pancreatic head cancer (→) is hypovascular and shows hypodensity, and it is most distinct in the late arterial phase I of dynamic CT. Pancreatic cancer undergoes delayed enhancement, and, in this example, it shows isodensity with the surrounding pancreatic parenchyma in the portal venous phase (D) and faint hyperdensity in the equilibrium phase (E). With MRCP, occlusion and upstream dilatation of the main pancreatic duct and common bile duct are seen as a result of pancreatic head cancer.

Table 5. MDCT imaging protocol (example) for pancreatic tumors

	Sites of Imaging	Imaging Start Time	Section Thickness
Unenhanced (pre-contrast)	Liver to kidney		3 mm 1 mm
Early arterial phase*	Liver to kidney	CT number increase of +100 HU for descending aorta	3 mm 1 mm
Late arterial phase (pancreatic parenchyma phase)	Liver to kidney	45 seconds after start of administration	3 mm 1 mm
Portal venous phase	Liver to kidney	60 seconds after start of administration	3 mm 1 mm
Equilibrium phase imaging	Liver to pelvis	240 seconds after start of administration	3 mm 1 mm

Contrast medium: 600 MgI/kg (100 mL high concentration syringe maximum)
Contrast media injection time: 30 seconds
* Using the bolus tracking method

For follow-up CT, attention should be paid to reducing radiation exposure, and phases considered unnecessary should be omitted as appropriate.

2. Imaging method used when pancreatitis is suspected

Imaging is performed in 4 phases: non-contrast CT and dynamic contrast-enhanced CT in the late arterial phase (pancreatic parenchymal phase), portal venous phase, and equilibrium phase (≥ 180 seconds after injection). Non-contrast CT is useful for diagnosing conditions such as hemorrhagic changes associated with calcification and fat necrosis of the pancreas and the choledocholithiasis that cause pancreatitis. The CT grade of acute pancreatitis is determined by contrast-enhanced CT. The arterial phase is useful for diagnosing a pseudoaneurysm, which is occasionally seen in pancreatitis associated with a pancreatic pseudocyst. Moreover, because acute pancreatitis may occur due to a pancreatic neoplasm such as pancreatic cancer, the presence or absence of tumors can also be evaluated in the arterial phase. The portal venous phase is useful for diagnosing venous thrombosis and venous stenosis associated with pancreatitis.

With regard to watchful waiting in pancreatitis, repeating dynamic contrast-enhanced CT is of little significance for a brief period of watchful waiting, and consideration is given to imaging mainly in the portal venous phase and adding other phases to suit the objectives.

MRI (Figs. 9 and 10)

An example of an MRI imaging protocol for pancreatic tumors is shown in Table 6.

The MRI imaging protocol for pancreatic disease involves a basic sequence of T2-weighted, T1-weighted plus diffusion-weighted images and MRCP (3D and 2D). Dynamic contrast-enhanced MRI is also performed as needed. T2-weighted images are combined with fat suppression as appropriate, obtaining both in-phase and out-of-phase (opposed-phase) T1-weighted images. In-phase and out-of-phase

T1-weighted images and their subtraction images are useful for diagnosing focal fatty replacement. With diffusion-weighted images, imaging is performed using b-values of 0 s/mm^2 and approximately 800 s/mm^2 or 1,000 s/mm^2, and an apparent diffusion coefficient (ADC) map is generated.

MRCP consists of 2D and 3D images, and the MIP images and original MRCP images are used for diagnosis. Erratic breathing during respiratory-gated 3D MRCP can result in poor-quality images that are unevaluable. It is therefore preferable to also perform breath-hold MRCP to ensure that good image quality is obtained. Single-shot fast-spin echo (SSFE) T2-weighted imaging provides the advantages of not only clear visualization of the pancreatic duct and biliary tract, but also visualization of solid organs such as the liver and pancreas and changes such as tumors at the same time, adding coronal and oblique coronal plane imaging as appropriate.

In fat-suppressed T1-weighted images acquired before contrast-enhanced imaging, the signal for normal pancreatic parenchyma is a high signal intensity. Therefore, the signal decreases if a tumor, fibrosis, or inflammation is present. If a contrast medium is not used, close attention is paid to the pancreas signal in fat-suppressed T1-weighted images. In addition, bleeding often results from the fat necrosis associated with severe acute pancreatitis. Hemorrhagic fat necrosis in or near the pancreas appears as a high signal intensity on fat-suppressed T1-weighted images, which facilitates diagnosis. However, a point that should be noted with fat-suppressed T1-weighted imaging is that the use of an oral contrast medium (high signal intensity on T1-weighted images) on MRCP narrows the dynamic range, reducing the contrast between lesions and the pancreas.

For dynamic MRI, which involves the rapid injection of an extracellular gadolinium contrast medium, 3D GRE (field echo), which provides high spatial resolution, is recommended. It also enables reconstructed images in the coronal and sagittal planes to be generated from the transverse plane images. Dynamic MRI that uses fat suppression provides better lesion contrast. Because MRI provides excellent contrast resolution, MRI and dynamic contrast-enhanced MRI may be useful in detecting even poorly defined lesions on dynamic CT.

Screening for liver metastases is important for patients in whom pancreatic cancer is suspected. Gd-EOB-DTPA (EOB/Primovist®) may be used to exclude liver metastases. An advantage of EOB-MRI is that it enables the presence or absence of pancreatic lesions and liver metastases to be evaluated at the same time. A disadvantage, however, is that if MRCP imaging is also performed, it must be performed before contrast-enhanced imaging, which lengthens the duration of testing.

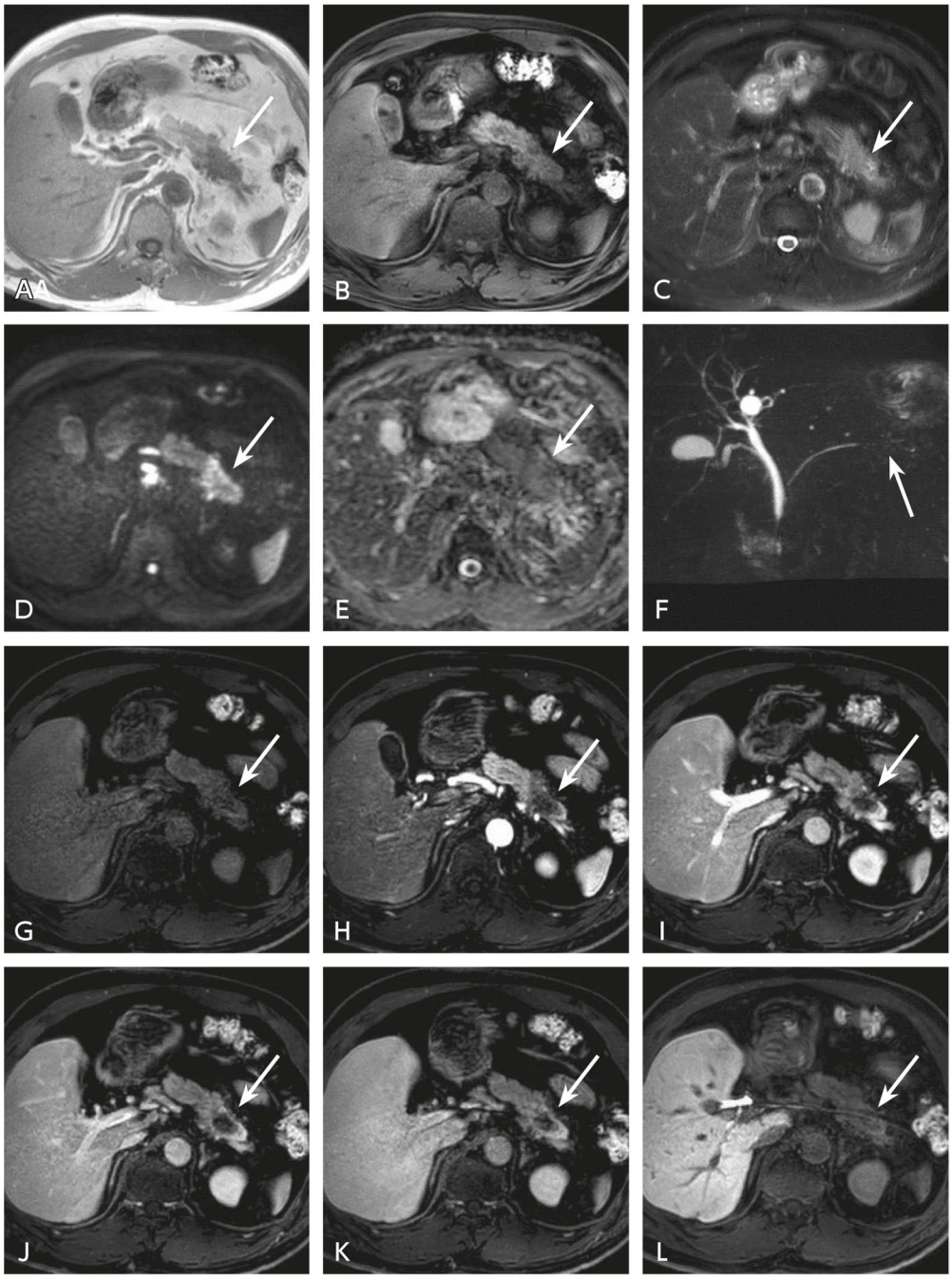

Figure 10. MRI of pancreatic tail cancer

A: T1-weighted image (in phase); B: fat-suppressed T1-weighted image; C: fat-suppressed T2-weighted image; D: diffusion-weighted image (b-value = 1,000 s/mm^2); E: ADC map; F: MRCP (3D, respiratory gated); G to K: EOB-MRI (G: before contrast-enhanced imaging, H: arterial phase, I: arterial phase + 30 seconds, J: arterial phase + 90 seconds, K: arterial phase + 180 seconds); L: hepatobiliary phase (20 minutes after injection)

Pancreatic tail cancer (→) shows a low signal intensity on T1-weighted images (A and B) and a high signal intensity on the T2-weighted image (C). On the diffusion-weighted image (D), it shows a high signal intensity mainly at the lesion margins. With MRCP (F), an obstruction of the main pancreatic duct is seen at the site of the tumor. In the arterial phase of dynamic MRI (H), the tumor is seen to be hypovascular, with enhancement seen mainly in the margins in the 2nd and 3rd phases (I and J) of the arterial phase. Persistent faint contrast enhancement is also seen in the tumor margins on the hepatobiliary phase (K).

Table 6. Pancreatic tumor MRI protocols (example)

Sequence	Plane	2D or 3D	FOV (mm)	Slice Thickness (mm)	Gap (mm)	Number of slices	Breathing
Balanced sequence	Coronal	2D	380	6	1	16	Breath-hold
Fat-suppressed T2-weighted images *	Transverse	2D	380	5	1	25	Breath-hold
T1-weighted images, in/out		2D	380	5	1	25	Breath-hold
Fat-suppressed T1-weighted images **		3D	380	6	–	25	Breath-hold
Diffusion-weighted images (EPI)		2D	380	5	1	25	Diaphragmatic gating
MRCP	Coronal (radial)	2D	300	10	–	10	Breath-hold
MRCP	Coronal	2D	300	4	0	22	Breath-hold
MRCP	Transverse	2D	300	4	0	20	Breath-hold
MRCP	Coronal	3D	300	2 (reconstruction, 1 mm)	–	80	Respiratory-gated
Fat-suppressed T1-weighted images	Transverse (dynamic)	3D	380	3 (reconstruction, 1.5 mm)	–	133	Breath-hold
Fat-suppressed T1-weighted images	Transverse (delay)	3D	380	6	–	25	Breath-hold

* Breath-hold T2-weighted images and MRCP are single-shot T2-weighted images.

**T1-weighted images acquired using GRE.

Standard imaging methods (gastrointestinal tract)

D Imaging of the gastrointestinal tract

Introduction

Gastrointestinal tract imaging using barium sulfate has traditionally been used in Japan as a major diagnostic imaging examination of the gastrointestinal tract, with the indications covering from screening to preoperative work-up. In recent years, however, remarkable advances in endoscopy have allowed endoscopy to be the main modality for both diagnostic and therapeutic endoscopies from the esophagus to the rectum. Currently, the main roles of gastrointestinal tract imaging have become defining the location and extent of lesions and evaluating critical features such as luminal stenosis, deformity, or fistula formation before and after treatment (chemo/chemoradiotherapy). The indications and techniques vary depending on the organ (Table 7). Specifically for the large bowel, CT colonography (CTC) has been developed thanks to advances in the technologies of CT equipment and applications, and it is widely accepted in clinical practice. There are several kinds of three-dimensional (3D) viewing options, including virtual enema, virtual endoscopy, and computed tomography angiography (CTA), which can be produced

by a single CT examination and provide useful anatomical information about colorectal cancer before surgery. In 2012, the revised medical service fees included an additional amount for CT colonography as a test for patients with suspected colorectal malignancies.

Gastrointestinal imaging (Fig. 11)

Basically, barium sulfate is used as a contrast agent under fluoroscopy to screen the gastrointestinal tract from the pharynx and esophagus to the rectum and anus. The use of low-viscosity barium sulfate at a high concentration of approximately 200% W/V is the basic procedure for the upper gastrointestinal tract, whereas agglutination-resistant barium at a concentration of less than half is used in the lower gastrointestinal tract. An aqueous iodine contrast medium can be an alternative for cases with suspected gastrointestinal perforation or obstruction (note that the aqueous iodine contrast medium is contraindicated for patients with suspected aspiration because of pulmonary toxicity). The test requires an empty gastrointestinal tract, and an anticholinergic agent or glucagon is injected intramuscularly to inhibit secretion and peristalsis, unless motility is being evaluated. A simple test can evaluate lesion location, luminal deformity and stenosis, fistula formation, and motility of the gastrointestinal tract. In addition, distending the gastrointestinal tract with a gas, called double-contrast technique, enables extremely detailed examination of radiological features. Carbon dioxide gas is administered using effervescent granules taken orally or air via a nasal catheter to distend the esophagus, stomach, duodenum, and small bowel. Air is administered via a transanal balloon catheter to distend the large bowel.

Table 7. Main indications for gastrointestinal tract contrast-enhanced imaging

	Indication
Esophagus	Esophageal cancer, achalasia (including similar conditions)
Stomach	Gastric cancer, screening/gastric cancer examinations
Duodenum	Duodenal tumor (adenoma, carcinoma, duodenal papillary neoplasm)
Small bowel	Inflammatory bowel disease (e.g., Crohn’s disease)
Large bowel	Colorectal cancer, inflammatory bowel disease (e.g., ulcerative colitis)
Other	After surgery

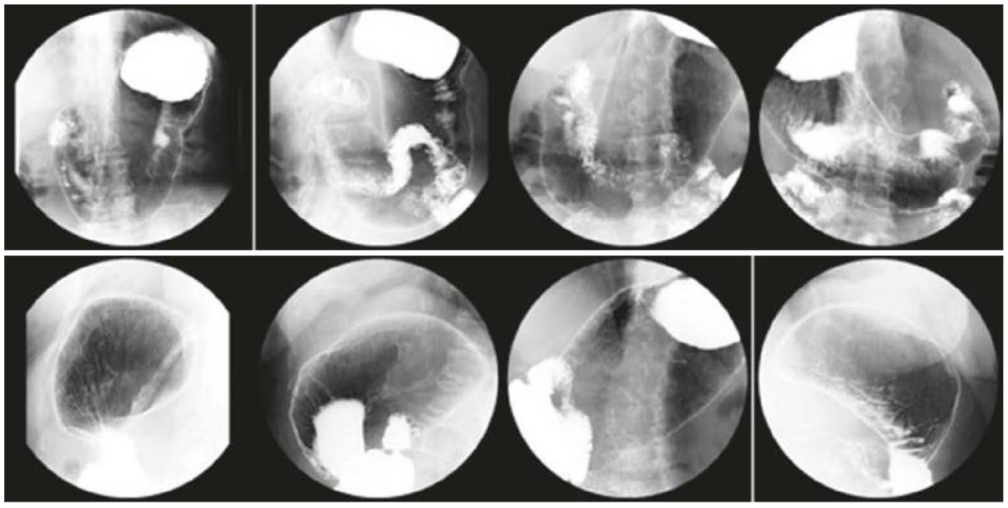

Figure 11. Examples of gastrointestinal series

Basic imaging method for population-based screening of the Japanese Society of Gastrointestinal Cancer Screening, 8 patient positions, using 150 mL of 200% W/V low-viscosity barium sulfate

1. Upper gastrointestinal tract imaging (Upper GI series)

Preparation: Fasting for at least 12 hours. Injection of an anticholinergic agent or glucagon immediately before the test.

Oropharynx and hypopharynx: Not mandatory but helpful in some situations. A small amount of contrast medium administered orally is enough to observe the first part of an upper gastrointestinal series. The dilution and amount of contrast medium and the patient's posture in drinking it (no jaw lift) should be considered depending on the patient's condition, such as risk of aspiration.[35)]

Esophagus: Mainly to evaluate neoplastic lesions. Use of a nasogastric tube is desirable to visualize a lesion better. Esophageal distension can be obtained by injection of contrast medium via the tube, followed by addition of air, which is the best imaging condition for close evaluation. Basically, the location and extent of a lesion are estimated on the frontal view, and the invasion depth of the lesion is estimated indirectly by lateral deformity or extensibility on the lateral view. Serial radiography covering the entire process (contrast medium passing through the esophagus) offers desirable images rather than one shot.

Stomach and duodenum: For the stomach, the Japanese Society of Gastrointestinal Cancer Screening recommends a standard imaging method covering the entire stomach using the double-contrast technique (references 2 to 6 and Fig. 12) as a screening test.[36-40)] Preoperative evaluation of a neoplastic lesion is also possible with this technique. Use of a nasogastric tube is desirable to visualize a lesion better. Gastric distension can be obtained by an adequate amount of contrast medium followed by air via the tube, which offers good image quality for close evaluation. Basically, the location and extent of a lesion are estimated

on the frontal view, and the invasion depth of the lesion is estimated indirectly by lateral deformity and extensibility on the lateral view (Fig. 12). For the duodenum, a special technique is applied (distal to the duodenal bulb), called hypotonic duodenography. It involves fixing a balloon in place at the duodenal bulb and injecting the contrast medium under an intravenous antispasmodic agent and delivering air. However, it involves a high degree of technical difficulty and requires skill.

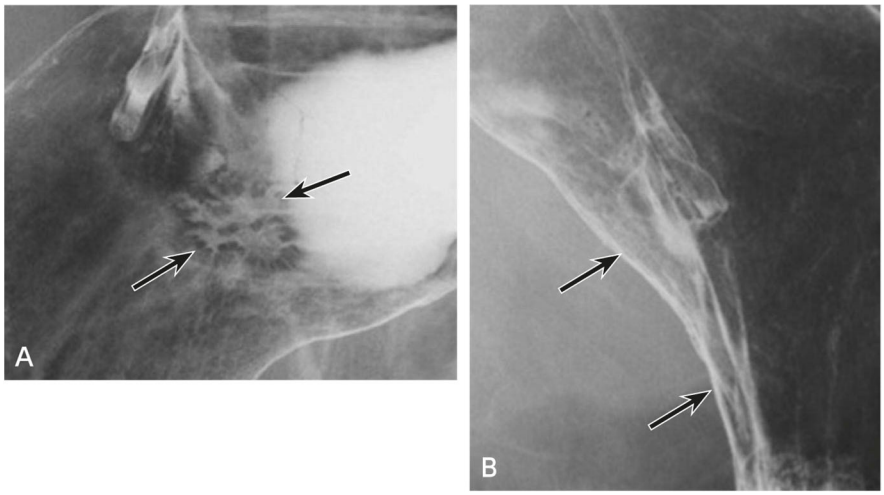

Figure 12. Early gastric cancer (T1a, tubular adenocarcinoma)

A: Upper gastrointestinal series (frontal view): The lesion shows slight depression on the posterior wall of the upper gastric body, indicating type 0-IIc gastric cancer (→).
B: Upper gastrointestinal series (lateral view): The lesion shows no lateral deformity, indicating mucosal cancer with no submucosal invasion (→).

2. Lower gastrointestinal tract imaging

Small bowel: A simple examination as a latter part of an upper gastrointestinal series called small bowel follow-through is used as a screening test. A special examination called small bowel enteroclysis is used to evaluate inflammatory bowel disease such as Crohn's disease or, occasionally, malignancies. An oral laxative is administered the day before the examination. Balloon probe insertion (the tip is placed distal to the ligament of Treitz under fluoroscopic guidance) is desirable to administer the appropriate amount of contrast medium and air. Sufficient distension of the small bowel is required for the double-contrast technique to accurately evaluate the lesions. To avoid overlap within the pelvis during imaging, compression, positional changes, and longitudinal observation are implemented.

Large bowel (Barium enema): Preparation includes a low-residue diet and laxative (modified Brown's method) on the day before the test or a combination of a low-residue diet the day before the test and an intestinal lavage agent on the day of the test. An anticholinergic agent or glucagon is injected intramuscularly immediately before the test. Following a contrast medium enema, air is delivered, and

double-contrast visualization of the entire colon is attempted in at least 2 directions. Basically, the location and extent of a lesion are estimated on the frontal view, and invasion depth of the lesion is estimated indirectly by lateral deformity and extensibility on the lateral view. Use of an aqueous iodine contrast medium should be considered for a case with possible intestinal perforation or obstruction.

CT

CT is used as a preoperative test for gastrointestinal tract malignancies mainly to evaluate lymph node involvement and distant metastases. Evaluation of the primary lesion is also possible depending on its size and spread. A thoracoabdominal scan using single-phase contrast-enhanced CT is common to scan from the lung to the pelvis. Multiphase contrast-enhanced CT including the arterial phase is helpful to visualize vessels for preoperative mapping. Gastrointestinal tract distention is required to evaluate the primary lesion at the same examination as well. The stomach is distended by administration of carbon dioxide gas (effervescent granules) taken orally. The large bowel is distended by carbon dioxide gas via a transanal catheter after preparation using a laxative agent, which technique is called CT colonography (CTC).

Example of CTC in colorectal cancer before surgery (Fig. 13)

Procedure: Administration of 2 to 3 L of carbon dioxide gas under monitoring of the amount and pressure via a transanal catheter. An antispasmodic agent may be intramuscularly injected as needed.

Scan: Three-phase (arterial, portal venous, and equilibrium phases) scanned data are loaded to the workstation for 3D reconstruction.

Protocol (CTC＋CT arterial portography): Tube voltage, 120 K; tube current, AEC; rotation time, 0.5 seconds; slice thickness, 0.5 mm; high-speed pitch used, 1.0,100 rows. CTC + CTA 370 mg/mL of contrast medium, injection pressure 4 mL/s (saline chaser), with bolus tracking technique, 30 seconds after CTA imaging.

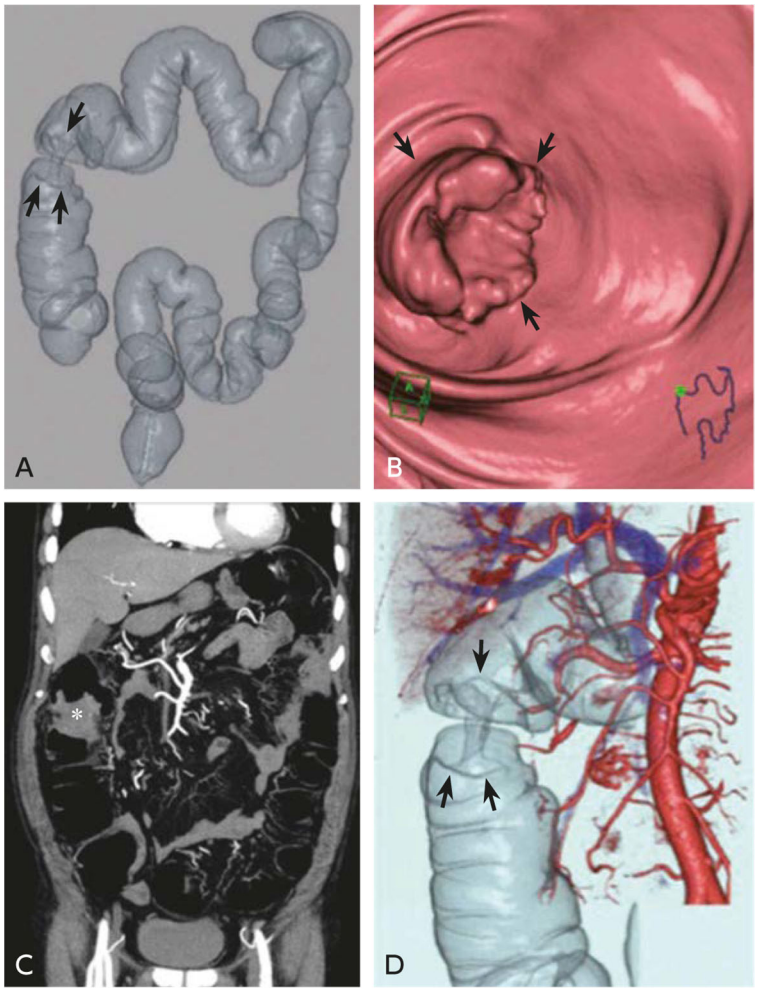

Figure 13. CTC of ascending colon cancer

A: Virtual enema, B: virtual endoscopy, C: 2D MIP (coronal plane), D: CTC + CTA (arterial phase + portal venous phase)
The photographs show type 2 colon cancer locating in the ascending colon (→).

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BQ 36 Which imaging examinations are recommended for hepatocellular carcinoma screening in patients with chronic liver disease?

Statement

Abdominal ultrasonography at intervals of 3 to 6 months is the main recommendation.

For patients in an ultra-high-risk group, the additional use of EOB-MRI or abdominal dynamic contrast-enhanced CT every 6 months to 1 year is considered.

Background

Although hepatitis B virus (HBV), hepatitis C virus (HCV), and lifestyle play major roles as causes of hepatocellular carcinoma, hepatitis B incidence has leveled off, hepatitis C incidence is declining, and non-B and non-C hepatitis, including steatohepatitis, is increasing (secondary source 1). A reduction in cancer incidence has been seen with a sustained virologic response (SVR) in patients with chronic hepatitis B who were taking nucleoside analogs and with antiviral agents in patients with chronic hepatitis C. However, these patients are acknowledged to be at considerable risk of cancer. Consequently, patients with chronic type C or B liver disease and patients with nonviral liver cirrhosis are considered candidates for periodic screening for hepatocellular carcinoma. Particularly in patients with liver cirrhosis, which is a group at ultra-high risk for cancer, screening based on tumor markers and diagnostic imaging increases the opportunity for curative treatment due to early detection of hepatocellular carcinoma and may contribute to improved prognosis.[1)]

Explanation

1. Abdominal ultrasonography at 3- to 6-month intervals

Ultrasonography is easy to perform, minimally invasive, and inexpensive, and it is therefore widely used in hepatocellular carcinoma screening of groups at high and ultra-high risk of hepatocellular carcinoma. A randomized, controlled trial (RCT) found that periodic surveillance for hepatocellular carcinoma may improve prognosis.[1)] In addition, surveillance intervals were compared in 2 RCTs. A trial that compared 3- and 6-month intervals for ultrasonographic surveillance of patients with liver cirrhosis found no significant difference with respect to the primary endpoint, the incidence of hepatocellular carcinoma ≤ 30 mm in size, and no difference in overall survival.[2)] A trial that compared 4- and 12-month intervals found that, although more patients with tumors ≤ 2 cm in size were detected with 4-month intervals, no significant difference in 4-year survival was seen.[3)] Although the likelihood of detecting tumors shows small increases as the screening intervals shorten, the cost increases. These guidelines adhere to the established recommendations for Japan: screening by ultrasonography is recommended every 6 months for the high-risk group (chronic

hepatitis) and every 3 to 4 months for the ultra-high-risk group (patients with liver cirrhosis). At present, however, no literature that provides strong evidence regarding screening intervals has been identified.

2. Concurrent use of dynamic contrast-enhanced MRI using Gd-EOB-DTPA or dynamic CT

If ultrasound detects nodules or the patient is in an ultra-high-risk group, differential diagnosis of the nodules and further investigation of hepatocellular carcinoma are carried out by dynamic CT or MRI using an extracellular gadolinium contrast medium or by dynamic MRI using a hepatocyte-specific contrast medium (Gd-EOB-DTPA, EOB/Primovist®; EOB-MRI). In patients for whom CT and MRI contrast media are contraindicated, perflubutane (Sonazoid®) contrast-enhanced ultrasound is recommended. If ultrasound visualization is poor, dynamic CT/MRI imaging may be performed for surveillance and nodule detection. CQ2 of the 2017 guidelines for the diagnosis and treatment of liver cancer asked, "Who are the candidates for surveillance and how is it conducted?" The response was the following strong recommendation: "Patients with chronic type C or B liver disease and patients with nonviral liver cirrhosis are candidates for periodic hepatocellular carcinoma screening. The screening mainly involves abdominal ultrasonography and tumor marker measurement at 3- to 6-month intervals. Concurrent dynamic CT or dynamic MRI is also considered for patients in an ultra-high-risk group, such as patients with liver cirrhosis (secondary source 2)." In an RCT that compared the usefulness of abdominal ultrasonography performed every 6 months with that of annual contrast-enhanced CT in 163 patients with compensated liver cirrhosis, detection sensitivity and specificity for hepatocellular carcinoma in the study population, which had an annual cancer incidence of 6.6%, were 71.4% and 97.5%, respectively, in the abdominal ultrasonography group and 66.7% and 94.4%, respectively, in the CT group. Thus, superior sensitivity was seen in the group that underwent abdominal ultrasonography every 6 months. Moreover, testing costs were lower in this group. No reports on the usefulness of combining dynamic contrast-enhanced CT with ultrasonography for imaging screening have been identified. However, the concurrent use of CT or MRI approximately once a year for hepatocellular carcinoma (HCC) screening is common in ultra-high-risk groups, which have a high pre-test probability of the presence of HCC.

Many studies that have compared dynamic CT and EOB-MRI with respect to HCC detection sensitivity have reported EOB-MRI to be superior in this regard. In a multicenter study of diagnostic performance in HCC ≤ 2 cm in diameter, detection sensitivity for HCC showed a trend toward greater sensitivity with EOB-MRI (≤ 10 mm: 38.0% to 55.4%, 10 to 20 mm: 71.1% to 87.3%) than with dynamic CT (≤ 10 mm: 26.1% to 47.3%, 10 to 20 mm: 65.7% to 78.4%).[4] The report attributed this to the usefulness of the hepatobiliary phase. One study found that the diagnostic performance of EOB-MRI did not differ from that of ultrasound or dynamic CT without the hepatobiliary phase, but it was greater when the hepatobiliary phase was added.[5] The superiority of EOB-MRI in HCC diagnosis is particularly pronounced in the detection of mainly small lesions ≤ 2 cm in size and early (hypovascular) HCC.[6] A meta-analysis of HCC detection with dynamic CT and EOB-MRI found higher sensitivity and diagnostic accuracy with EOB-MRI

than with dynamic CT, and that the differences were particularly marked for HCC lesions smaller than 2 cm.[7)]

With regard to the use of EOB-MRI in HCC screening, EOB-MRI was found to be more cost-effective than MRI using extracellular gadolinium contrast medium and CT in HCC-related diagnosis and treatment of patients with hepatitis and liver cirrhosis in Japan.[8)] Moreover, in the surveillance of patients with liver cirrhosis, EOB-MRI was found to provide a higher detection rate and result in fewer false-positives than other modalities.[9)] However, there has been limited reporting on the usefulness of EOB-MRI in screening, and no literature on the usefulness of its combined use with ultrasonography has been identified. In addition, dynamic MRI using extracellular gadolinium contrast media and EOB-MRI have been reported to be comparable with respect to HCC diagnostic accuracy. Consequently, EOB-MRI cannot be regarded as absolutely superior. One factor in this is poor contrast with HCC due to poor Gd-EOB-DTPA uptake in non-cancerous areas resulting from hepatic dysfunction.[10, 11)] Caution is therefore required when using EOB-MRI in patients with liver cirrhosis.

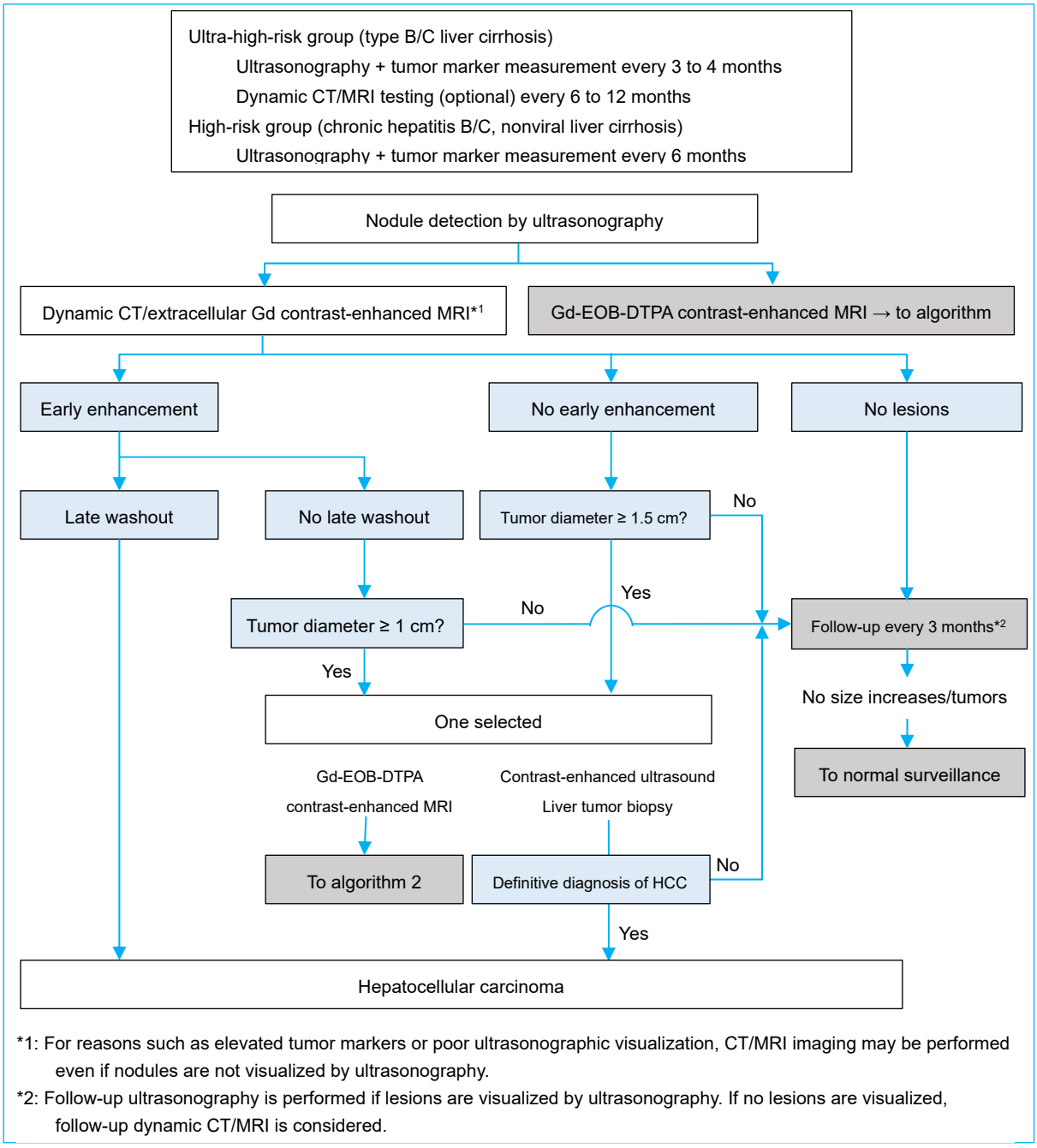

Figure 1. Hepatocellular carcinoma diagnostic algorithm 1

Jointly prepared by the Japan Radiological Society and the Japan Society of Hepatology. Copyright held by the Japan Society of Hepatology. The same algorithm was presented in the 2021 Guidelines for the Diagnosis and Treatment of Liver Cancer.

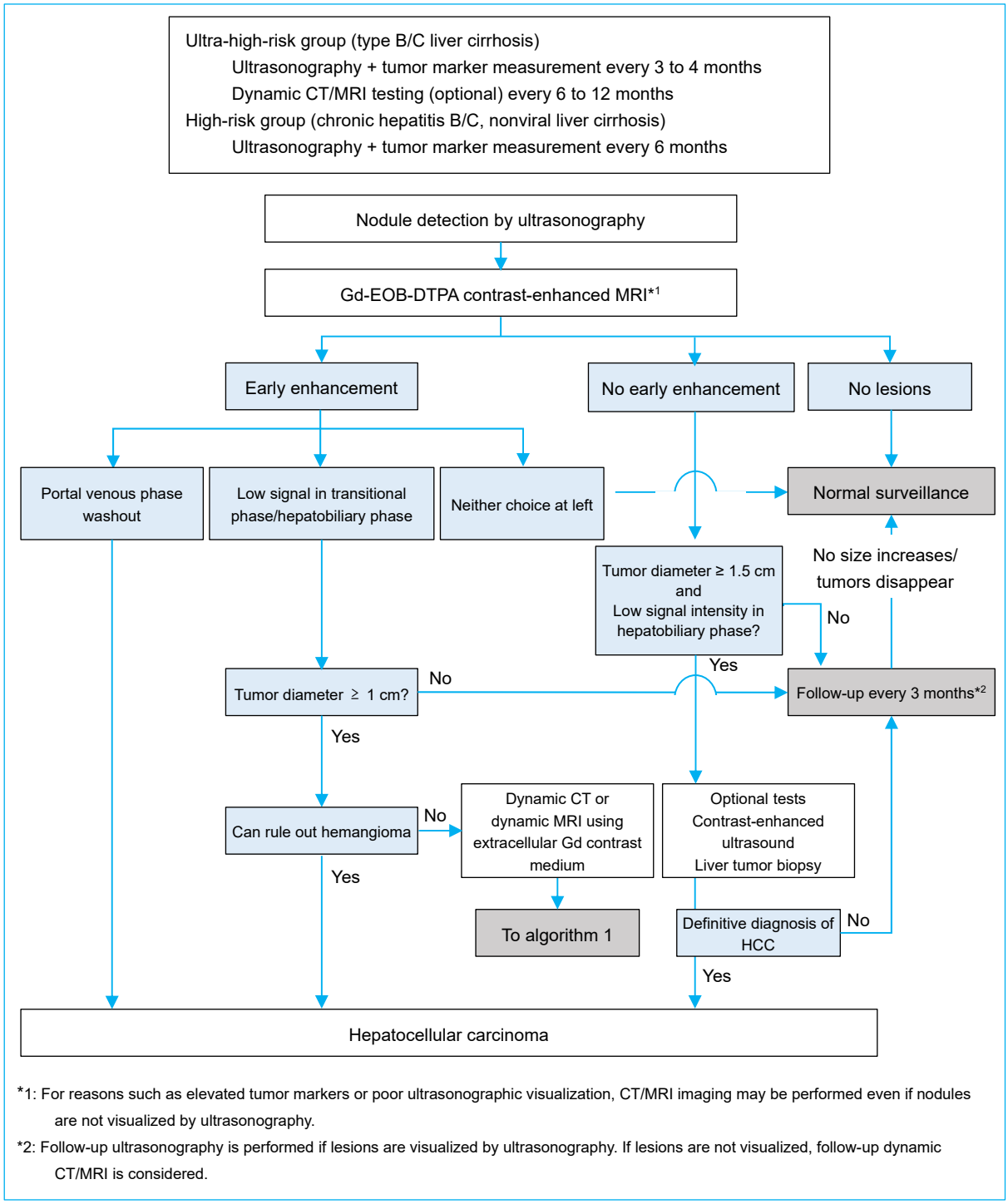

Figure 2. Hepatocellular carcinoma diagnostic algorithm 2

Jointly prepared by the Japan Radiological Society and the Japan Society of Hepatology. Copyright held by the Japan Society of Hepatology. The same algorithm was presented in the 2021 guidelines for the diagnosis and treatment of liver cancer.

3. Perflubutane (Sonazoid®) contrast-enhanced ultrasonography

An examination of the diagnostic performance of perflubutane contrast-enhanced ultrasonography found a trend toward greater detection sensitivity for HCC lesions ≤ 2 cm in size with perflubutane contrast-enhanced ultrasound (67.6%) and EOB-MRI (76.5%) than with dynamic CT (52.9%), though the differences were not significant.[10] In addition, detection performance with respect to hypovascular well-differentiated HCC was found to be greater with EOB-MRI than with perflubutane contrast-enhanced ultrasonography. This was reported to be related to the fact that perflubutane uptake decreases later than Gd-EOB-DTPA uptake in early HCC during the process of multistep carcinogenesis.[8] On the other hand, perflubutane contrast-enhanced ultrasonography enables blood flow to be evaluated in real time and is excellent for evaluating nodule blood flow. It is therefore considered useful as a diagnostic imaging modality that complements EOB-MRI. Perflubutane contrast-enhanced ultrasonography is not widely used clinically. This is due to the lack of skilled operators and the complexity of the procedure, in addition to the fact that it has disadvantages specific to ultrasonography (extensive dead space makes whole-liver evaluation difficult, limited objectivity of findings). It is therefore not well suited as a test to be performed next in patients with suspected intrahepatic lesions based on ultrasonography. However, in view of the fact that it offers the advantage of the greatest sensitivity to slight nodule hypervascularization, it is recommended for diagnosis in patients for whom hypervascularization detection is difficult and important, as in the case of well-differentiated HCC (including early HCC).

4. Summary

The main modality for HCC screening based on imaging is ultrasonography performed every 3 to 6 months, with consideration given to the concurrent use of EOB-MRI and dynamic contrast-enhanced CT, which provide high diagnostic performance. However, in view of the fact that the cost of EOB-MRI testing is 8 to 9 times the cost of abdominal ultrasound, it may be unlikely that the increased cost is offset by the increase in survival time. Moreover, the MRI systems used in the studies cited in this document were high-performance MRI systems, and the diagnostic performance of lower-performance MRI systems may be poorer. It should also be noted that the diagnostic performance of EOB-MRI is lower in patients with poor liver function or obstructive jaundice. Careful judgement is therefore required regarding the concurrent use of EOB-MRI. In view of the fact that high-performance MRI systems are not widely available, the current reality is that ultrasound and dynamic CT must be relied on for imaging screening.

Search keywords and secondary sources

PubMed was searched for the period through October 2019 using the keywords HCC, US, CT, MRI, screening, Sonazoid, and EOB. Thirteen articles were selected from the search results. The selected articles concerned HCC imaging screening, with a focus on comparisons of diagnostic performance. In addition, 2 articles identified in a hand search were included, for a final total of 15 articles used.

In addition, the following were referenced as secondary sources

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CQ 9 Is EOB-MRI recommended to differentiate HCC from hemangioma for lesions that show hypervascularity but no washout in patients with chronic liver disease?

Recommendation

Not performing EOB-MRI is weakly recommended.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 80% (8/10)

CQ 10 Is EOB-MRI recommended to differentiate from hypervascular pseudolesions for lesions that show hypervascularity but no washout in patients with chronic liver disease?

Recommendation

Performing EOB-MRI is weakly recommended.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 100% (10/10)

Background

In patients with chronic liver disease, a typical HCC imaging finding with a test that uses an extracellular contrast medium, such as contrast-enhanced CT, is a lesion that shows arterial phase enhancement and washout from the portal venous phase to the equilibrium phase. Even with HCC, however, there are cases in which washout is not clearly seen, making differentiation from hemangioma and hypervascular pseudolesions problematic. Although HCC is malignant, hemangiomas and hypervascular pseudolesions are benign. It is therefore clinically important to accurately differentiate between them with imaging.

Explanation

1. Is EOB-MRI recommended to differentiate HCC from hemangioma?

With EOB-MRI, lesions other than HCC also show strong enhancement in the arterial-dominant phase and show low signal intensity compared with the surrounding liver tissue from the transitional phase to the hepatobiliary phase. Referred to as a pseudo-washout appearance, it often poses problems for distinguishing high-flow hemangiomas, where the nodules as a whole show strong enhancement during early contrast imaging, from small HCC. However, no randomized studies have yet been conducted to prospectively examine the ability of EOB-MRI to differentiate hemangioma from HCC. Consequently, the retrospective, observational studies that have examined differentiation of these 2 conditions are summarized below.

In a study that used EOB-MRI to examine 50 nodules in 43 patients with high-flow hemangiomas that exhibited a pseudo-washout appearance and 113 nodules in 62 patients with hypervascular small HCC (all lesions less than 20 mm in diameter), Nam et al. found that the ADC determined from diffusion-weighted images and the contrast-to-noise ratio (CNR) determined from T2-weighted images were significantly higher for the high-flow hemangiomas than for the hypervascular small HCCs. The area under the receiver-operating characteristic curve (AUROC) for the ability to distinguish hemangioma from HCC was 0.995 (95% CI, 0.969 to 1.000; sensitivity, 98%; specificity, 97.3%) using the ADC, which was significantly better than the AUROC of 0.915 (95% CI, 0.861 to 0.953) obtained using the CNR from T2-weighted images. On the other hand, the ability to distinguish hemangioma from HCC was also high with qualitative visual assessment (AUROC, 0.988 to 0.999; sensitivity, 90% to 94%; specificity, 98.2% to 100%), with high interrater agreement (κ-value, 0.80).[1)]

Similarly, Choi et al. used EOB-MRI with concurrent intravoxel incoherent motion (IVIM) diffusion-weighted imaging to examine 20 hemangioma nodules, 91 HCC nodules, 27 intrahepatic cholangiocarcinoma nodules, 9 mixed liver cancer nodules, 9 metastatic liver cancer nodules, and 5 nodules of other types, for a total of 161 nodules in 161 patients (all lesions at least 20 mm in diameter). They reported that hemangiomas and liver malignancies differed significantly with respect to the molecular diffusion coefficient (Dslow) for ADC and IVIM, and that the AUROC for the ability to discriminate between hemangioma and liver malignancies was 0.907 (95% CI, 0.850 to 0.948; sensitivity, 90.0%; specificity, 80.9%) for ADC and 0.933 (95% CI, 0.882 to 0.967; sensitivity, 95.0%; specificity, 83.8%) for Dslow. On the other hand, no significant differences in ADC and Dslow were seen between liver malignancies, indicating that combining diffusion-weighted imaging with EOB-MRI is likely to improve the ability to distinguish HCC from hepatic hemangioma, but also the ability to distinguish it from other liver malignancies.[2)]

Although there has not yet been sufficient investigation of the use of EOB-MRI to distinguish HCC from hemangioma, the above findings indicate that combining it with diffusion-weighted imaging may provide clinically adequate diagnostic performance. However, when used to distinguish between such lesions, there have been no investigations that have compared the diagnostic performance of EOB-MRI combined with diffusion-weighted imaging with the diagnostic performance of other modalities (e.g., ultrasound, extracellular contrast-enhanced MRI).

2. Is EOB-MRI recommended for differentiating from hypervascular pseudolesions?

In patients with chronic liver disease, hypervascular pseudolesions are often observed in extracellular contrast-enhanced imaging examination such as contrast-enhanced CT due to changes such as the hyperplastic nodules seen with AP shunt development and in heavy users of alcohol. These are rarely definitively diagnosed pathologically, but rather it is considered appropriate to lump them together as hypervascular pseudolesions clinically. No RCTs have been identified that have used EOB-MRI for direct comparisons with respect to HCC and hypervascular pseudolesion imaging findings and differentiation.

Consequently, the retrospective, observational studies that have examined differentiation between HCC and hypervascular pseudolesions are summarized below.

In a study that examined 28 hypervascular hyperplastic nodules and 29 hypervascular HCC lesions ≤ 3 cm in size in patients with alcoholic liver cirrhosis, low-intensity to isointense signal intensity was seen in diffusion-weighted images in nodules ≤ 16 mm in size, with no washout seen in either the portal venous phase or the transitional phase or both. These 3 variables were independent predictors of hypervascular hyperplastic nodules. When 2 of these 3 variables were seen, the diagnostic performance for hypervascular hyperplastic nodules was as follows: sensitivity, 92.9% (26/28); specificity, 75.9% (22/29); and diagnostic accuracy, 84.2% (48/57). When all 3 variables were seen, diagnostic performance was as follows: sensitivity, 60.7% (17/28); specificity, 100% (29/29); and diagnostic accuracy, 80.7% (46/57).[3)]

In an investigation that examined 28 benign nodules comprising hemangiomas (11 lesions), AP shunts (15 lesions), and nonspecific benign lesions (2 lesions), and 111 HCC lesions, the indices of the diagnostic performance of EOB-MRI for HCC were sensitivity of 95% (107/111) and specificity of 96% (27/28) for reader 1 and sensitivity of 95% (106/111) and specificity of 96% (27/28) for reader 2. The indices of the diagnostic performance of dynamic CT for HCC were sensitivity of 84% (95/111) and specificity of 100% (28/28) for reader 1 and sensitivity of 89% (99/111) and specificity of 100% (28/28) for reader 2. Thus, for reader 1, sensitivity was higher with EOB-MRI than with dynamic CT ($p = 0.005$). No significant difference in sensitivity ($p = 0.052$) was seen between the modalities for reader 2 or in specificity for readers 1 and 2 ($p = 0.317$ for both).[4)]

In an investigation that examined 32 hypervascular pseudolesions with nodular morphology (mean size, 11.5 mm) and 123 hypervascular HCC lesions (mean size, 16.4 mm), the HCC lesions, as compared with the pseudolesions, were significantly larger, a significantly higher proportion showed high signal intensity on T2-weighted and diffusion-weighted images, and a significantly higher proportion showed low signal intensity during the hepatobiliary phase ($p < 0.0001$). The signal intensity ratio for the lesions and parenchyma in the hepatobiliary phase was significantly lower for the HCC lesions. Using a cutoff of 0.84, sensitivity was 91% (112/123), and specificity was 91% (29/32). In addition, when a high-intensity signal in a diffusion-weighted image was used as the diagnostic criterion for HCC lesions and hypervascular pseudolesions, sensitivity was 67% (83/123), and specificity was 100% (32/32).[5)]

An investigation that examined 53 hypervascular pseudolesions and 44 HCC lesions ≤ 2 cm in size compared the diagnostic performance of EOB-MRI (diagnostic criteria were arterial phase enhancement and low signal intensity in the hepatobiliary phase) and dynamic CT (diagnostic criteria were arterial phase enhancement and low signal intensity in the equilibrium phase) based on independent 5-point scale assessments by 2 raters. The results showed that EOB-MRI provided higher sensitivity than dynamic CT, with no significant difference in specificity [Reader 1 (EOB-MRI vs. CT): sensitivity, 93.9% (31/33) vs. 54.5% (18/33), $p = 0.001$; specificity, 92.6% (25/27) vs. 96.3% (26/27), $p = 1$. Reader 2: sensitivity, 90.9% (30/33) vs. 54.5% (18/33) $p = 0.0018$; specificity, 92.6% (25/27) vs. 96.3% (26/27), $p = 1$]. No significant

differences in the Az value were seen [Reader 1: 0.975 vs. 0.892 (p = 0.069), Reader 2: 0.966 vs. 0.888 (p = 0.106)].[6)]

In an investigation that examined 52 nodular lesions ≤ 1 cm in size that showed arterial phase enhancement and low signal intensity in the hepatobiliary phase (30 malignant lesions and 22 benign lesions), no washout was seen in 16.7% of the HCC lesions (5/30) and 50% of the benign lesions (11/22). That is, 16 nodules were lesions without washout, which indicates hypervascularity. Of these, 11 nodules [68.8% (11/16)] were benign, and 5 [31.3% (5/16)] were HCC lesions. Thus, the absence of washout was more frequent in benign lesions.[7)]

Although there has been insufficient examination of the use of EOB-MRI to distinguish between HCC and hypervascular pseudolesions, the above findings indicate that lesions that are hypervascular but do not show washout are more often benign lesions than HCC, and that EOB-MRI exhibits high diagnostic performance in distinguishing between such lesions. However, no definitive evidence has been shown that EOB-MRI is non-inferior or superior to other modalities (e.g., contrast-enhanced ultrasound, contrast-enhanced MRI using extracellular gadolinium contrast media) when used to distinguish between such lesions, and this remains a topic for future investigation.

Search keywords and secondary sources

PubMed was searched for articles on distinguishing HCC from hemangioma using the following keywords: hemangioma, gadoxetic acid, EOB, liver cancer, hepatic cancer, malignancy, and hepatocellular carcinoma. Of the 19 articles extracted, 2 were cited.

PubMed was searched for articles on distinguishing HCC from hypervascular pseudolesions using the following keywords: hepatic, liver, hypervascular, pseudo lesion, pseudo-lesion, benign, gadoxetic acid, EOB, and hepatocyte-specific. Of the 49 articles extracted, 3 were cited. In addition, 2 second-hand citations from these 3 articles were cited, for a total of 5 articles cited.

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CQ 11 Is EOB-MRI recommended for diagnosing non-hypervascular lesions in patients with chronic liver disease?

Recommendation

Performing EOB-MRI is strongly recommended.

Recommendation strength: 1, strength of evidence: moderate (B), agreement rate: 100% (11/11)

CQ 12 Is periodic follow-up recommended for diagnosing non-hypervascular lesions in patients with chronic liver disease?

Recommendation

Follow-up using EOB-MRI (or dynamic CT) is strongly recommended.

Recommendation strength: 1, strength of evidence: moderate (B), agreement rate: 100% (11/11)

Background

With contrast-enhanced imaging in patients with chronic liver disease, the detection of nodules that do not exhibit hypervascularity and lack normal hepatocellular function on perflubutane contrast-enhanced ultrasound or EOB-MRI increases in the arterial phase, and these nodules are known to include HCC precursor lesions.

There have been many reports of the hypervascularization (malignant transformation) of non-hypervascular lesions since the retrospective investigation by Kumada et al. in 2011.[1)] However, the names used for these lesions are not established and vary depending on the article. Those that show low signal intensity in the hepatobiliary phase of EOB-MRI are readily detected, and the hepatobiliary phase imaging mechanism suggests a risk of malignant transformation. Consequently, the term “hepatobiliary phase hypointense nodule without arterial phase hyperenhancement” was proposed by the Liver Imaging Reporting and Data System (LI-RADS) HBA Working Group.[2)] In Japan, lesions that do not show early enhancement are also called “hypovascular lesions.” They include a considerable number of lesions that are in the process of multistage cancer development and are on the borderline between hypervascularity and hypovascularity. In view of the fact that early enhancement detection performance varies depending on the modality, the term “non-hypervascular lesions” is considered appropriate.

Explanation

1. Is EOB-MRI recommended for diagnosing non-hypervascular lesions in patients with chronic liver disease?

Among non-hypervascular nodules that show low signal intensity in the hepatobiliary phase of EOB-MRI, 44% are advanced HCC, 20% early HCC, 27.5% high-grade dysplastic nodules, and 8% low-grade dysplastic nodules and regenerative nodules.[3] Although there is selection bias, it should be noted that this includes advanced HCC, which obviously should be considered a target for treatment.

Many studies of diagnostic performance in non-hypervascular nodules, which show low signal intensity in the hepatobiliary phase of EOB-MRI, examined nodules that were detectable in the hepatobiliary phase, and there is insufficient evidence concerning diagnostic performance in nodules that could not be detected in the hepatobiliary phase. Of the non-hypervascular nodules detected in the hepatobiliary phase of EOB-MRI, 35% are also detectable by contrast-enhanced CT.[4] Because the rate of detection of non-hypervascular nodules with contrast-enhanced CT is relatively low, EOB-MRI is useful for detecting such nodules.

The diagnostic performance of each modality in HCC (≤ 2 cm in size) was found to be 53% for contrast-enhanced CT, 68% for contrast-enhanced ultrasound, 77% for EOB-MRI, and 88% for CT angiography.[5] In some cases, nodules are diagnosed as non-hypervascular using 1 modality, but visualized as hypervascular when re-examined using another modality. For example, 33% of HCC nodules determined to be non-hypervascular based on CT and MRI were diagnosed as hypervascular by contrast-enhanced ultrasound.[6] Consequently, it is preferable for non-hypervascularity to be diagnosed using multiple modalities.

The significance of detecting non-hypervascular nodules using EOB-MRI and its contribution to prognosis remain unclear based on the above findings. However, EOB-MRI tends to be an excellent modality for detecting non-hypervascular nodules, and its use in mapping hepatocellular lesions in the liver in patients with chronic liver disease is therefore recommended. It should be noted that non-hypervascular nodules that show low signal intensity in the hepatobiliary phase of EOB-MRI include not only early HCC and dysplastic nodules that subsequently undergo hypervascularization, but also advanced HCC. Differentiation needs to proceed carefully by also considering the findings obtained with other modalities.

2. Is periodic follow-up recommended for diagnosing non-hypervascular lesions in patients with chronic liver disease?

Periodic imaging procedures to screen for HCC are recommended for patients with chronic liver disease. It is therefore difficult to imagine that a non-hypervascular lesion found in the liver of a patient with chronic liver disease would be neglected and follow-up not performed. In addition, no RCTs have been identified that examined whether biopsy and/or treatment should be performed after a non-hypervascular lesion is discovered and of the effectiveness of biopsy and treatment in such cases. Consequently, the consensus views of experts on the guidelines and related matters and the observational studies that have

examined the frequency with which non-hypervascular lesions are hypervascularized (malignant transformation) and the factors involved in this process are summarized below.

First, the results of a meta-analysis by Suh et al. that summarized prospective and retrospective, observational studies of the frequency with which non-hypervascular lesions are hypervascularized (malignant transformation) showed that the rate of hypervascularization of non-hypervascular lesions detected in the hepatobiliary phase of EOB-MRI was 18% at 1 year, 25% at 2 years, and 30% at 3 years.[7)]

With regard to the strategy for addressing non-hypervascular lesions, a review of the literature on liver biopsy[8)] noted that, although guidelines such as the 2011 guidelines of the American Association for the Study of Liver Diseases (AASLD) recommended biopsy for hepatic lesions that do not show typical contrast enhancement in procedures such as CT and MRI (secondary source 2),[9)] the indications for biopsy are being reduced in recent guidelines in view of its invasiveness and the possibility of sampling error. The 2017 AASLD guidelines (secondary source 3) state that, although 1 to 2-cm nodules in patients with liver cirrhosis that do not show typical contrast enhancement are unlikely to be HCC, either a second imaging examination or follow-up needs to be performed for such nodules.

Nearly all of the reports concerned with the factors related to hypervascularization have been reports of retrospective, observational studies. Two of the articles in the relevant literature have described prospective assessments. The primary objective of these studies was to examine the added diagnostic value of diffusion-weighted imaging[10)] and contrast-enhanced ultrasound,[6)] as indicated in the previous section.

The previously mentioned meta-analysis by Suh et al.[7)] found that the factor most strongly related to hypervascularization was size (≥ 9 to 10 mm) when detected.

Examination of each report showed that they included a mix of investigations of non-hypervascular lesions as a whole and investigations in which lesions were further limited according to the underlying liver disease and MRI signal pattern. In broad terms, factors that have been found to increase risk are lesion size,[11-13)] high signal intensity on T1-weighted and diffusion-weighted images,[10, 13)] past history of HCC,[11, 14)] and high signal intensity on T1-weighted images.[14)] High signal intensity in the hepatobiliary phase of EOB-MRI was reported to be a risk-reducing factor.[12)] Three of these articles are summarized below.

An examination of 633 non-hypervascular lesions that showed high signal intensity in the hepatobiliary phase found that the frequency of hypervascularization was lower than indicated in previous reports.[14)] Hypervascularization was seen in 4% of patients (95% CI, 1.74% to 9.55%) and 0.4% of lesions (95% CI, 0.20% to 0.95%) in 1 year. Multivariate analysis showed the only hypervascularization-related factor to be initial lesion size (continuous value). With the lesions categorized as < 10 mm or ≥ 10 mm in size, a significant difference was seen in non-hypervascularization time ($p = 0.0022$). The 1-year cumulative hypervascularization rate was 0.10% (95% CI, 0.02% to 0.57%) for lesions < 10 mm and 1.31% (95% CI, 0.56% to 3.07%) for lesions ≥ 10 mm.

In a retrospective study of 114 non-hypervascular lesions in 60 patients that did not show high signal intensity on T2-weighted images,[11)] 27 lesions in 21 patients transformed to HCC during the observation period (median duration of observation, 503 days; range, 203 to 1,521 days), and 87 lesions in 47 patients

did not transform to HCC (median duration of observation, 949 days; range, 103 to 254 days). High signal intensity on T1-weighted images [hazard ratio (HR), 2.693; 95% CI, 1.157 to 6.264; p = 0.021] and a past history of HCC (HR = 2.64, p = 0.021) were associated with hypervascularization.

A retrospective investigation by Yang et al. examined 222 non-hypervascular lesions in 97 patients that showed low signal intensity in the hepatobiliary phase of EOB-MRI and did not show high signal intensity on T2-weighted images.[14] A multivariate analysis showed significant relationships for past history of HCC at new onset (HR, 3.493; 95% CI, 1.335 to 9.138; p = 0.011), high signal intensity on T1-weighted images (HR, 2.778; 95% CI, 1.172 to 6.589; p = 0.020), and high signal intensity on diffusion-weighted images (HR, 19.917; 95% CI, 7.050 to 56.271; p = 0.001). In an ROC analysis, the cutoff value for the growth rate (reciprocal of volume-doubling time) was 0.72×10^{-3}/day.

To examine how long a follow-up is necessary and how long the intervals between tests should be, the observation durations in the articles cited here were summarized. The median durations for the 16 articles included in the meta-analysis by Suh et al.[7] ranged from 186 to 886 days, and the measures of central tendency (median for 7 articles, mean for 3 articles) for the duration of observation of non-hypervascular lesions in the other original articles ranged from 167 to 997 days. In the above-mentioned investigation of non-hypervascular lesions that did not show high signal intensity on T2-weighted images,[14] the lesions were observed for a mean of 997 days (range, 137 to 1,804 days). The authors, Yang et al., stated that only 3 lesions were hypervascularized over 3 years, and that all 3 had hypervascularization-related factors. They therefore surmised that, if lesions that lack these factors were observed for 3 years, their risk of malignant transformation would be low.

There is little evidence concerning the optimal intervals for imaging procedures in the follow-up of non-hypervascular lesions, and this subject is not mentioned in the AASLD guidelines (secondary source 2). Japan's guidelines for the diagnosis and treatment of liver cancer recommend that follow-up using ultrasound or contrast-enhanced CT/MRI be performed every 3 months (secondary source 1).

Supplementary information appears occasionally in the form of reports on the prognosis of patients with non-hypervascular lesions and the risk of HCC occurring at other locations in the liver. The relevant literature is as follows.

In a retrospective investigation by Gyoda et al. of patients who underwent liver resection, 52.2% of non-hypervascular HCC had progressed to classical HCC in year 3 after initial liver resection. In addition, no significant differences were seen after 1 and 3 years between the 36 patients in the group with non-hypervascular nodules and the 75 patients in the group without such nodules with respect to the cumulative incidence rates for classical HCC at different locations from non-hypervascular nodules and non-hypervascular nodules (Group with non-hypervascular nodules: classical HCC, 32.8% at 1 year and 67.1% at 3 years; non-hypervascular nodules, 14.3% at 1 year and 27.5% at 3 years. Group without non-hypervascular nodules: classical HCC, 19.9% at 1 year and 43.4% at 3 years; non-hypervascular nodules, 4.8% at 1 year and 18.1% at 3 years. Classical HCC, p = 0.097; non-hypervascular nodules, p = 0.280). It was concluded that whether non-hypervascular lesions should be resected at the same time as the

primary tumor was unclear based on these findings. Next, no significant differences were seen between HCV-positive patients treated with direct-acting antivirals (DAAs) and those not treated with DAAs with respect to the cumulative hypervascularization rate of non-hypervascular lesions at 12, 18, or 24 months after initial resection. The cumulative hypervascularization rates were 11.8%, 24.2%, and 25.2%, respectively, for the DAA-treated patients and 9.1%, 15.2%, and 24.9% for the DAA-untreated patients ($p = 0.617$).[15] Because the study subjects were patients with relatively advanced disease, selection bias is a concern.

To summarize the above findings, because the 3-year cumulative hypervascularization rate of non-hypervascular lesions was 30%, such lesions should not be neglected. However, clear evidence is lacking with regard to whether non-hypervascular lesions ought to be biopsied and treated. The view of specialists in recent years has been that performing a biopsy when a lesion is first detected is not desirable when its invasiveness is weighed against the prospective benefits, and that either an additional second imaging procedure or follow-up imaging procedure should be performed.

Search keywords and secondary sources

PubMed was searched using the following keywords: hypovascular, hypervascular, hyperenhanced, without early enhancement, without arterial enhancement, lack hypervascular, ultrasonography, ultrasound, hepatitis, liver, liver disease, chronic, and cirrhosis. Of the 28 articles extracted, 12 were cited. In addition, 1 article published after the search and 4 second-hand citations were cited, for a total of 17 articles cited.

In addition, the following were referenced as secondary sources.

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BQ 37 Which imaging findings are used to diagnose classical (hypervascular) HCC?

Statement

Typical imaging findings for classical (hypervascular) HCC are the following.

Dynamic contrast-enhanced CT: early enhancement in the arterial-dominant phase and washout from the portal venous phase to the equilibrium phase. EOB-MRI: early enhancement in the arterial-dominant phase and washout in the portal venous-dominant phase, low signal intensity from the transitional phase to the hepatobiliary phase.

Perflubutane contrast-enhanced ultrasound: hyperechoic in the arterial-dominant phase, washout in the portal venous-dominant phase, hypoechoic in the Kupffer phase.

Other findings specific to HCC include a capsular structure, mosaic structure, and tumor thrombus. Corona enhancement in the late phase of CT hepatic arteriography (CTHA) is also useful for diagnosis.

Background

In the past, HCC detected in the clinical setting was often advanced HCC (mainly moderately differentiated) that exhibited the properties of hypervascularity on imaging. With advances in diagnostic imaging, small HCCs that did not exhibit hypervascularity (mainly highly differentiated) also came to be detected. To distinguish between these types, the conventional and typical hypervascular HCC is called classical HCC. In the diagnostic imaging of classical (hypervascular) HCC, it is important to evaluate tumor blood flow status by contrast-enhanced CT, MRI, or ultrasonography, and combining this with other findings can provide extremely high diagnostic performance.

Explanation

This BQ was created by consolidating CQ75 (Which tests are useful for diagnosing classical (hypervascular) HCC?) and CQ76 [Are CT during hepatic arteriography (CTHA), CT during arterial portography (CTAP), and angiography recommended as tests to be performed before HCC resection?] from the 2016 edition of these guidelines. Perflubutane (Sonazoid®) contrast-enhanced ultrasound, dynamic contrast-enhanced CT, and Gd-EOB-DTPA (EOB, Primovist®) contrast-enhanced MRI (EOB-MRI) are all useful for diagnosing classical (hypervascular) HCC, and their use is strongly recommended. Of these modalities, EOB-MRI is considered to provide high detection performance in detecting small lesions.[1-6] Because these imaging procedures are already standard approaches, the question was changed from a CQ to a BQ, and the matter of which kinds of imaging findings are important is discussed here.

There are 2 forms of carcinogenic processes for HCC, *de novo* carcinogenesis and multistage carcinogenesis. In the latter case, changes in the status of blood flow in the lesion continually occur during the malignant transformation process.[7-9] As dysplastic nodules become early HCC, portal vein blood flow,

which provides the cells with nutrients, decreases, and it nearly disappears in highly differentiated to moderately differentiated HCC. On the other hand, arterial blood flow increases in highly differentiated to moderately differentiated HCC. Classical (hypervascular) HCC refers to moderately differentiated HCC in which portal vein blood flow has disappeared, and arterial blood flow has increased. Early enhancement on CT or MRI reflects this increase in arterial blood flow. In multistage carcinogenesis, changes also occur in outflow veins. If a peritumoral pseudocapsule forms, the portal vein branches in the pseudocapsule become outflow vessels. Due to flow of contrast medium from the portal vein branches to the surrounding liver parenchyma, strong enhancement (corona enhancement) of the liver parenchyma surrounding the nodule is seen in the late phase of CTHA,[7] as is washout on CT or MRI. Early enhancement in the arterial-dominant phase and washout after the portal venous-dominant phase on dynamic contrast-enhanced CT, EOB-MRI, or perflubutane contrast-enhanced ultrasound are therefore typical imaging findings in classical (hypervascular) HCC. In addition, corona enhancement on dynamic contrast-enhanced CT/MRI or CTHA is useful for diagnosis.[7, 10]

The early enhancement on dynamic contrast-enhanced CT/MRI mentioned above refers to the phenomenon whereby the increase in attenuation (or signal intensity) of the tumor is greater than that of the background liver parenchyma. Findings in which the tumors show lower density or signal intensity than the surrounding liver parenchyma before contrast enhancement and iso-density or iso-intensity in the arterial dominant phase are also treated as early enhancement. Imaging must therefore be performed before contrast-enhanced imaging to evaluate early enhancement. Although this is the general view of early enhancement in Japan, it should be noted that, under the LI-RADS system of the American College of Radiology, higher attenuation (higher signal intensity) compared with the liver parenchyma in the arterial phase is defined as arterial phase hyperenhancement (APHE), regardless of the attenuation (signal intensity) before contrast-enhanced imaging. On the other hand, washout refers to relative hypodensity in a nodule compared with the surrounding liver parenchyma in phases such as the portal venous-dominant phase.

In addition, to evaluate early tumor enhancement on dynamic contrast-enhanced CT/MRI, arterial-dominant-phase imaging must be performed with appropriate timing. If it is performed too early, early enhancement cannot be observed because sufficient contrast medium will not have reached the tumor. If early enhancement is not seen even though HCC is suspected, the timing of the imaging should be examined to determine whether it was appropriate.

EOB-MRI cannot evaluate tumor blood flow during the equilibrium phase because the timing of the equilibrium phase of CT or MRI using an extracellular contrast medium corresponds to the transitional phase in EOB-MRI. If washout cannot be verified in the portal venous-dominant phase, a modality such as dynamic contrast-enhanced MRI using an extracellular gadolinium contrast medium or CT is added as necessary.

If rigorous evaluation of the presence or absence of early enhancement is required clinically, CTHA, which can provide the most accurate blood flow information, can be considered. CTHA makes it possible

to evaluate not only early enhancement, but also corona enhancement. Corona enhancement is enhancement seen around a tumor in the late phase of CTHA. With CTHA, it is visualized in nearly all patients with HCC and is very useful for diagnosing microscopic HCC. However, CTHA requires selective catheter insertion into the hepatic artery, making it more invasive than other tests. Consequently, opportunities to perform CTHA for diagnosis alone are limited.

Characteristic gross pathological findings in HCC include capsule formation, an internal mosaic structure, and tumor thrombus of portal and hepatic veins. These gross pathological findings can also be observed by imaging, making such imaging findings useful in the qualitative diagnosis of HCC.

Search keywords and secondary sources

PubMed was searched using the following keywords: hepatocellular carcinoma, sensitivity, specificity, contrast-enhanced, Sonazoid, US, multiphasic, MDCT, CT, gadoxetate, gadoxetic, Gd-EOB-DTPA, Primovist, MR, magnetic resonance, CTHA, CT, and hepatic arteriography.

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BQ 38 Which imaging examinations are recommended for diagnosing liver tumors in patients with decreased kidney and liver function?

Statement

Non-contrast-enhanced MRI tests, including diffusion-weighted imaging, and ultrasonography, including perflubutane contrast-enhanced imaging, are useful and can be performed safely and are recommended in patients with decreased kidney and liver function. In patients with decreased kidney function, the types of contrast-enhanced CT or MRI that can be considered are EOB-MRI in patients with an estimated glomerular filtration rate (eGFR) of 30 to 60 mL/min/1.73 m^2 and SPIO-contrast-enhanced MRI in those with an eGFR of < 30 mL/min/1.73 m^2. In dialysis patients, SPIO-contrast-enhanced MRI and contrast-enhanced CT can be considered.

There has been insufficient examination of the appropriate selection of tests and contrast media for contrast-enhanced CT/MRI in patients with decreased liver function corresponding to Child-Pugh class C.

Background

The use of iodine and gadolinium contrast media is restricted in patients with decreased kidney function, and enhancement with Gd-EOB-DTPA (EOB, Primovist®) and SPIO (Resovist®) decreases in patients with decreased liver function. Consequently, restrictions on testing and decreased diagnostic performance are concerns in patients with decreased kidney or liver function.

Explanation

The ultrasound contrast medium perflubutane (Sonazoid®)[1] and the liver-specific MRI contrast medium SPIO[2, 3] do not affect kidney function and are not known to have increased adverse reactions caused by decreased kidney function. The tests that use these media can therefore be performed normally in patients with decreased kidney function.

Iodine contrast medium administration increases the risk of contrast-induced nephropathy (CIN) in patients with decreased kidney function and an eGFR < 30 mL/min/1.73 m^2, making it difficult to perform contrast-enhanced CT in such patients. With the addition of risk factors such as advanced age and diabetes mellitus associated with chronic kidney disease (CKD), the risk increases even with an eGFR ≥ 30 mL/min/1.73 m^2.

The risk of nephrogenic systemic fibrosis (NSF) increases with the use of gadolinium contrast media in patients with decreased kidney function. Consequently, extracellular gadolinium contrast media and Gd-EOB-DTPA are generally not administered to dialysis patients, patients with CKD and an eGFR < 30 mL/min/1.73 m^2, and patients with acute renal failure. If, after the benefits and risks have been examined, it is concluded that a gadolinium contrast medium must be used, the use of gadodiamide (Omniscan®) or gadopentetate dimeglumine (Magnevist®), for which there have been many reports of NSF, is avoided.

Because Gd-EOB-DTPA is excreted from the liver, as well as the kidneys, it is sometimes thought that it may be superior to an extracellular gadolinium contrast medium. However, Gd-EOB-DTPA clearance actually decreases significantly in dialysis patients, which is known to reduce enhancement of the liver parenchyma.[4] Its use in dialysis patients is therefore not recommended.

There has been insufficient investigation into the selection of the appropriate contrast medium and test for a given eGFR when considering contrast-enhanced CT or MRI in patients with decreased kidney function. Consequently, the recommendations in these guidelines are limited to provisional recommendations. With an eGFR of 30 to 60 mL/min/1.73 m^2, the risk of NSF is not particularly high, and EOB-MRI, which provides high diagnostic performance, is therefore recommended. Because the risk of NSF increases with an eGFR < 30 mL/min/1.73 m^2, there is some doubt about whether to recommend EOB/Primovist® contrast-enhanced MRI or Resovist® contrast-enhanced MRI. However, the package insert for EOB/Primovist® states that administration of the product is to be avoided in such patients, and it is likely to be administered frequently. In light of these considerations, Resovist® contrast-enhanced MRI is recommended in these patients. For dialysis patients, it is recommended that gadolinium contrast media be avoided and that Resovist® contrast-enhanced MRI or contrast-enhanced CT be selected, depending on the circumstances of the facility.

In patients with decreased liver function, enhancement in the hepatobiliary phase of Gd-EOB-DTPA decreases,[5-7] and enhancement in what is referred to as the Kupffer phase of SPIO imaging also decreases.[8] As a result, the worse liver function is based on Child-Pugh class, the greater the decrease in the HCC diagnostic performance of GD-EOB-DTPA.[9] With Child-Pugh class B or C, the contrast between liver parenchyma and HCC has been found to be better with an extracellular gadolinium contrast medium in the equilibrium phase than with Gd-EOB-DTPA in the hepatobiliary phase.[10] There has been insufficient examination of the appropriate selection of contrast-enhanced CT or contrast-enhanced MRI in patients with decreased liver function corresponding to Child-Pugh class C.

Although it cannot outperform contrast-enhanced MRI, diffusion-weighted imaging has been shown to be consistently useful.[11] It may be more important than usual in patients with decreased kidney and liver function. However, its diagnostic performance in HCC decreases in patients with decreased liver function.[9]

Search keywords and secondary sources

PubMed was searched using the following keywords: Pugh, Child score, liver function, ICG, liver failure, contrast media, EOB, gadolinium, SPIO, superparamagnetic iron, iodinated contrast, iodine contrast, Sonazoid, diagnostic imaging, MRI, magnetic resonance, tomography, X-ray computed, computed tomography, computed tomographic, ultrasonography, liver, chronic kidney disease, renal impairment, renal function, diffusion-weighted, DWI, carcinoma, hepatocellular, hepatocellular carcinoma, and hepatocellular carcinomas.

The period searched was through June 2019.

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BQ 39 When is the use of extracellular gadolinium contrast media and Gd-EOB-DTPA recommended for contrast-enhanced MRI of liver tumors?

Statement

The use of extracellular gadolinium contrast media and Gd-EOB-DTPA is recommended for contrast-enhanced MRI of liver tumors in the cases indicated in the Explanation section.

Background

The preparations currently used in Japan for contrast-enhanced MRI of liver tumors are extracellular gadolinium contrast media, liver-specific contrast media (Gd-EOB-DTPA), and superparamagnetic iron oxide (SPIO) contrast media. Although there has been debate regarding the roles of each of these media in planning and implementing testing in the clinical setting, this has not been examined in RCTs, except in certain conditions, and it has not been addressed in the various previous guidelines. This BQ discusses the matters that ought to be considered in selecting an extracellular gadolinium contrast medium or Gd-EOB-DTPA from among the preparations that can be used in Japan, based on the currently available information and the opinions of specialists.

Explanation

1. Conditions and circumstances for which an extracellular gadolinium contrast medium is recommended more strongly than Gd-EOB-DTPA

An extracellular gadolinium contrast medium is recommended instead of Gd-EOB-DTPA for the following conditions and circumstances.

① The patient has markedly impaired liver function or severe liver cirrhosis

EOB-MRI is unlikely to produce adequate contrast enhancement of the liver parenchyma in the hepatobiliary phase if a condition such as hyperbilirubinemia or severe siderosis in the liver parenchyma is seen. In such cases, use of an extracellular gadolinium contrast medium is considered while taking kidney function into account.[1)]

② The main purpose is diagnosing a hepatic hemangioma

In hepatic hemangioma, pooling is obscure in the transitional and hepatobiliary phases of EOB-MRI, resulting in a tendency for pseudo-washout findings. When hepatic hemangioma needs to be rigorously distinguished from other liver tumors, an extracellular gadolinium contrast medium is recommended. Another concern is that with EOB-MRI, findings of persistent enhancement are obscured due to fibrosis in

conditions such as intrahepatic cholangiocarcinoma. Consequently, an extracellular gadolinium contrast medium is considered when such findings may be useful in diagnosis.[2)]

③ The main purpose is confirming arterial phase enhancement

The gadolinium concentration in Gd-EOB-DTPA is approximately 1/4 that in general extracellular gadolinium contrast media. Therefore, in theory, there may be cases in which tumor enhancement in the arterial phase is indistinct with Gd-EOB-DTPA. In patients for whom evaluation of tumor enhancement in the arterial phase is clinically important, use of an extracellular gadolinium contrast medium is considered.

④ Specificity is considered more important than sensitivity in HCC diagnosis

With dynamic EOB-MRI, the enhancing capsule appearance of HCC in the portal venous and transitional phases may be indistinct due to contrast medium uptake by the liver. In addition, washout may also be seen with conditions such as hemangioma (pseudo-washout). When these findings are important clinically or for diagnostic imaging purposes, use of an extracellular gadolinium contrast medium in repeat or follow-up MRI should also be considered.[3)]

⑤ Transient dyspnea (or transient severe body movement) occurred in the arterial phase with previous EOB-MRI

Breath-holding in the arterial phase may be inadequate. In consideration of the test objectives, the use of an extracellular gadolinium contrast medium is therefore considered.

⑥ Close examination of a blood vessel or abdominal organ other than the liver is necessary

Use of an extracellular gadolinium contrast medium, which has a high gadolinium concentration, is useful in cases, such as for 3D reconstruction of the hepatic artery or portal vein. Use of an extracellular gadolinium contrast medium is also considered when taking into account differences in diagnostic accuracy for liver tumor lesions.

2. Conditions and circumstances for which Gd-EOB-DTPA is recommended more strongly than an extracellular gadolinium contrast medium

Gd-EOB-DTPA is recommended more strongly than an extracellular gadolinium contrast medium for the following conditions and circumstances.

① Diagnosing hypovascular HCC

There are many reports indicating that the use of Gd-EOB-DTPA rather than an extracellular gadolinium contrast medium ought to be considered when the objective is to detect early HCC in patients with chronic hepatitis or liver cirrhosis. However, different study results have also been reported in recent years.[4)]

② Preoperative testing for HCC

To detect microscopic HCC and intrahepatic metastases with high sensitivity, the use of Gd-EOB-DTPA for preoperative MRI in patients with HCC should be considered first.

③ To detect metachronous multiple HCC and recurrence after HCC therapy

The use of Gd-EOB-DTPA, which facilitates detection of microscopic lesions, ought to be considered to detect intrahepatic recurrence in patients who have undergone HCC resection. However, arterial phase enhancement of the site of recurrence may be useful for diagnosing recurrence after localized treatment such as radiofrequency ablation (RFA), and there is no definitive evidence regarding the comparative usefulness of the contrast media.

④ Definitive diagnosis of a pseudolesion was difficult in a previous contrast-enhanced CT or extracellular contrast-enhanced MRI test due to abnormal blood flow

Because a pseudolesion can be verified as such based on Gd-EOB-DTPA uptake, the use of Gd-EOB-DTPA in repeat testing or follow-up MRI ought to be considered.

⑤ Preoperative testing in patients with liver metastasis

Gd-EOB-DTPA enables better visibility of microscopic lesions than extracellular gadolinium contrast media and, therefore, ought to be used in preoperative MRI.

⑥ Differentiating between HCC or hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH)

In FNH, Gd-EOB-DTPA uptake is often seen in the hepatobiliary phase,[5, 6] which makes Gd-EOB-DTPA more useful than an extracellular gadolinium contrast medium for differential diagnosis.

⑦ Functional information on the biliary system needs to be obtained at the same time as information on a liver tumor

It is possible that a condition such as a biliary fistula can be definitively diagnosed based on the kinetics of Gd-EOB-DTPA, which is excreted in the bile.[7, 8] However, consideration is given to the fact that static and morphological information can also be obtained by MRCP when an extracellular gadolinium contrast medium is used.

Although the advantages of both contrast media are indicated above, there are also reports that describe using both in the same test to optimize these advantages. However, no improvement in diagnostic performance in liver malignancies was seen when Gd-EOB-DTPA was additionally administered after administration of an extracellular contrast medium,[7] and this procedure is not covered by insurance. It is therefore not recommended.

Search keywords and secondary sources

PubMed was searched using the keywords extracellular, hepatobiliary, and magnetic resonance, with the conditions ‘adult’ and ‘human’ specified. The Ichushi and Cochrane Library databases were searched using equivalent keywords. The period searched was through June 2019; hits were obtained for 99 articles. Of these, 15 articles that discussed the different roles of these contrast media in liver tumor diagnosis were referenced.

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CQ 13 What are the circumstances in which screening for extrahepatic metastasis of HCC is recommended, and when it is implemented, what are the recommended target organs and imaging examinations?

Recommendation

In patients positive for risk factors for extrahepatic metastasis of HCC (tumor occlusion of portal vein; AFP, > 200 ng/mL; PIVKA-II, ≥ 300 mAU/mL; platelet count, ≤ 1.3×10^5/μL; high level of primary tumor FDG accumulation; < 65 years old), CT, bone scintigraphy, and FDG-PET targeting the lungs, lymph nodes, bone, and adrenals are weakly recommended.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 91% (10/11)

CT or MRI to screen for brain metastasis is weakly recommended for patients with an abnormal neurological examination and patients positive for pulmonary metastasis.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 91% (10/11)

Background

The circumstances in which screening for extrahepatic metastasis is recommended when treating HCC were examined, along with the target organs and testing methods recommended.

Explanation

The treatment strategy for HCC depends on whether extrahepatic metastasis of HCC is present. If the patient is positive for extrahepatic metastasis, systemic chemotherapy is recommended; if the patient is negative, localized treatment is recommended.[1)] Whether screening for extrahepatic metastasis is necessary is determined based on whether risk factors are present.[2-6)] The lungs, lymph nodes, bone, adrenals, and brain are prioritized as target organs. The risk factors are: age < 65 years; worsening of intrahepatic lesions; tumor occlusion of the portal vein; alpha-fetoprotein (AFP), > 200 ng/mL; protein induced by vitamin K absence of antagonist-II (PIVKA-II), ≥ 300 mAU/mL; platelet count, ≤ 1.3×10^5/μL; and a high level of FDG accumulation in the primary tumor.[2-6)] The frequency of metastasis by metastasis destination is 6% to 29% for the lungs, 5% to 20% for the lymph nodes, 2% to 10% for bone, 1% to 10% for the adrenals, and 0.2% to 0.6% for the brain.[2-5)] The frequency of extrahepatic metastasis at new onset is 1.0% to 2.3%[4, 7)] and it increases to 2% to 24% during subsequent follow-up.[2, 3)]

The standard method used to screen for lung, lymph node, and adrenal metastases is CT. An imaging extent of chest to pelvis can detect most extrahepatic metastasis.

The standard methods used to screen for bone metastases are FDG-PET and bone scintigraphy. Although there is currently insufficient evidence of the superiority of either method, the detection sensitivity of bone scintigraphy has been reported to be somewhat lower.[8)] In addition, the detection sensitivity of FDG-PET

has been reported to be high,[9, 10] and FDG-PET has been found to outperform bone scintigraphy.[11, 12] These findings indicate that, when both tests can be performed, it is appropriate to prioritize FDG-PET. Moreover, the excellent performance of FDG-PET in diagnosing extrahepatic metastasis of HCC, including bone metastasis, provides support for prioritizing FDG-PET in identifying metastasis when unexplained tumor marker elevation is seen.[13] Most HCC bone metastases are osteolytic, and the vertebral bodies account for approximately half of the metastasis destinations.[7] In addition, PET/CT can be used to evaluate the risk of compression fracture and spinal canal stenosis. Consequently, its use further increases the accuracy of metastasis screening. Although there have been case reports describing HCC bone metastasis diagnosis using PET with ^{68}Ga prostate-specific membrane antigen (^{68}Ga-PSMA, not approved in Japan), which is used to diagnose bone metastasis of prostate cancer, whether it is superior to previous tests is unknown.[14]

The standard methods of screening for brain metastasis are contrast-enhanced CT and contrast-enhanced MRI. However, the frequency of HCC brain metastasis is low,[2-5] and a high proportion of patients who are positive have concomitant pulmonary metastasis.[7] It is therefore appropriate to screen patients with symptoms, neurological signs, and pulmonary metastasis.

Search keywords and secondary sources

PubMed was searched using the following keywords: neoplasm staging, risk, neoplasm metastasis, metastases, extrahepatic, brain, cerebral, cerebrum, bone, skeletal, carcinoma, hepatocellular, hepatocellular carcinoma, hepatocellular carcinomas, extrahepatic, positron-emission tomography, bone scan, scintigraphy, and scintigram.

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FQ 4 How should the efficacy of molecularly-targeted drugs and radiation therapy for HCC be evaluated?

Statement

Although the criteria for evaluating the response to a molecularly-targeted drug for HCC include the modified Response Evaluation Criteria in Solid Tumors (mRECIST), Response Evaluation Criteria in Cancer of the Liver (RECICL), European Association for Study of the Liver (EASL), and Choi criteria, no conclusion has yet been reached regarding which criteria are the most useful for prognosis prediction. Given the current situation, the criteria considered appropriate for each facility should be selected. Moreover, the existing criteria may not be suitable for evaluating the response to radiation therapy.

Background

Liver cancer chemotherapy underwent major changes with the emergence of molecularly-targeted drugs such as sorafenib and lenvatinib. However, it has been noted that, because these drugs occasionally produce tumor necrosis without shrinking the tumor, existing criteria such as the RECIST criteria, which use only lesion size to evaluate the treatment response, would evaluate the local treatment response as poor despite the fact that tumor necrosis was seen, resulting in a discrepancy between the local treatment effect and prognosis. To improve on this point, criteria have been proposed that take into account the fact that the area of poor contrast in the tumor interior is the area of tumor necrosis, such as the mRECIST, EASL, RECICL, and Choi criteria.[1-4)]

Explanation

1. Evaluating the efficacy of molecularly-targeted drugs

Liver cancer-related guidelines recommend evaluating efficacy using criteria that take tumor necrosis into account. In the AASLD consensus statement and the EASL guidelines, combining mRECIST and RECIST version 1.1 is recommended to evaluate local treatment efficacy when systemic treatment is administered (secondary sources 1 and 2). The 2017 guidelines for the diagnosis and treatment of liver cancer recommend using criteria that take tumor necrosis into account, such as the mRECIST, RECICL, and EASL criteria (secondary source 3).

However, evidence that validates the effectiveness of these criteria in evaluating local effects is limited. In examining the relationship between the evaluation of local effects using mRECIST and overall survival, a study comparing nintedanib and sorafenib and a study comparing brivanib and placebo after sorafenib therapy found that the evaluation could be used as a surrogate parameter for overall survival.[5, 6)] Three reports of retrospective investigations that have compared the different criteria have been published.[7-9)] Although clear differences between the criteria were shown, no conclusion has yet been drawn regarding which criteria are the most useful for prognosis prediction. Given the current situation, the criteria

considered appropriate for each facility should be selected from among the mRECIST, RECICL, and EASL criteria, which are recommended in various guidelines, and the newly proposed Choi criteria.

2. Evaluating efficacy following radiation therapy

With regard to radiation therapy for HCC, CQ48 of the 2017 guidelines for the diagnosis and treatment of liver cancer indicates that stereotactic body radiation therapy can be administered (weakly recommended) for a variety of patients with recurrence after local treatment, including patients who do not respond to transarterial chemoembolization (TACE), and for HCC for which other local treatment is difficult. Under current circumstances, radiation therapy is considered a treatment that is selected according to the patient. Studies of radiation therapy for HCC have often used the no-enlargement rate seen with long-term follow-up for local evaluation. This is attributed to the fact that two imaging findings not seen with other treatment methods complicate post-radiation therapy evaluation.

The first such finding is arterial phase enhancement of background liver parenchyma in the irradiation field.[10-14] This complicates the evaluation of viable areas and measurement of lesion size for evaluation criteria that take tumor enhancement into account, such as mRECIST. Such background liver parenchyma enhancement persists for several months, and if the enhancement is nodule-like, it is observed as pseudo-progression, which appears as if it were an enlargement of the tumor enhancement region.[15]

The second finding is that it takes a long time for the tumor enhancement to disappear after treatment. Consequently, there is a risk that treatment efficacy may be underestimated over a short-term clinical course.[14] An investigation by Oldrini et al. that used the mRECIST criteria found that, among lesions that showed a long-term treatment effect, residual tumor enhancement was seen on MRI in 62% of the lesions at 3 months posttreatment and in 19% at 6 months.[16] An investigation using contrast-enhanced ultrasound also found that it took several months for tumor enhancement to disappear.[17] The most recent RECICL criteria (2019 edition) added language indicating that efficacy is evaluated based on the maximum effect seen within 6 months posttreatment. However, in an investigation by Okubo et al., 82% of lesions were evaluated as treatment effect 4 (TE4) by contrast-enhanced CT, but 91% of lesions evaluated as TE3 were locally controlled at 1 year posttreatment. The authors therefore noted that treatment efficacy may be underestimated using the RECICL criteria.[18]

The above considerations indicate that the use of existing criteria, such as the mRECIST, EASL, and RECICL criteria, may not be appropriate for evaluating treatment efficacy after radiation therapy.

3. Overview of plans for possible future studies?

With regard to the evaluation of treatment efficacy following chemotherapy, a study is needed that uses overall survival or localized long-term follow-up observation as the reference standard and examines its relationship to the results of treatment efficacy evaluations based on the various criteria. This can be implemented as a retrospective analysis using existing clinical study data or as a sub-analysis of a study being considered.

For the evaluation of treatment efficacy following radiation therapy, it will be necessary to develop specialized criteria for such therapy. This is needed because of the contrast enhancement of the background liver parenchyma that occurs with treatment, and because it has been noted that a long time is needed for tumor enhancement to disappear after treatment. Information should be comprehensively collected, including information related to posttreatment imaging findings and the formulation and assessment of criteria for evaluating these findings.

Search keywords and secondary sources

PubMed was searched using the following keywords: HCC, chemotherapy, radiation, post-treatment, objective response, response, evaluation, and imaging. Relevant articles were selected from the search results.

With regard to radiation therapy, articles on external radiation beam therapy using X-rays or proton beams were selected. Articles on other treatment methods not commonly used in Japan (e.g., Y-90 transarterial radioembolization) were excluded.

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BQ 40 Which imaging examinations are recommended to evaluate the efficacy of TACE in HCC?

Statement

Dynamic CT or dynamic MRI is recommended to evaluate the efficacy of TACE in HCC.

Background

Transcatheter arterial chemoembolization (TACE) for HCC is a treatment that involves injecting an embolizing agent into the arteries that feed a tumor to induce tumor ischemia and necrosis to destroy the tumor. Unlike treatments such as the anticancer chemotherapies generally used for malignancies, no reduction in tumor size is often seen early after treatment, and the use of the RECIST criteria, which are widely used to evaluate treatment efficacy in solid cancers, is therefore often inappropriate. Consequently, treatment efficacy is assessed based on an evaluation of the degree to which the embolizing agent accumulates in the tumor and an evaluation of whether blood flow has disappeared from the tumor site.

Explanation

Features of hypervascular HCC are early enhancement with dynamic CT and dynamic MRI and imaging findings indicating washout. Although early enhancement findings disappear at the site of tumor necrosis following TACE, this is often not accompanied by a reduction in tumor size, particularly immediately after TACE.

Because treatment efficacy evaluation using the RECIST criteria, which are widely used to evaluate treatment efficacy in solid cancers, is based on the amount of change in the tumor diameter following treatment, it is difficult to use the RECIST criteria when evaluating the response to TACE.

With Lipiodol®-TACE, which is performed using an iodized poppy seed oil fatty acid ester (Lipiodol®), an oil-based contrast medium, the area in the tumor where Lipiodol® accumulates is concluded to be in an ischemic state and necrotic. Consequently, if non-contrast CT performed immediately after or 1 month after TACE shows complete Lipiodol® accumulation, a treatment effect can be anticipated. A treatment effect is also likely when the diameters of HCC lesions in which Lipiodol® has accumulated show consistent reduction during TACE follow-up.

However, if Lipiodol® accumulation in the HCC lesions is not uniform in the lesions as a whole, and deficits are seen, tumor necrosis in that region may be inadequate. Moreover, residual or recurrent tumors may be present in the periphery of the site of Lipiodol® accumulation. Consequently, an evaluation is needed of the presence or absence of tumor enhancement using a contrast-enhanced imaging procedure.

Tumor blood flow can be evaluated by dynamic CT or dynamic MRI using a contrast medium or by contrast-enhanced ultrasound.

Dynamic CT permits a more objective evaluation than ultrasound, can be performed with a shorter testing time than MRI, and can be performed at many facilities. It therefore plays a central role in evaluating HCC treatment efficacy. However, strong absorption of Lipiodol® can hinder the detection of tumor enhancement in recurrent lesions, and dynamic MRI becomes necessary when it is difficult to assess whether enhancement is present.

MRI is superior to CT in that it can detect trace amounts of contrast medium with greater sensitivity and is little affected by image modification resulting from Lipiodol® accumulation.[1-3] Moreover, MRI enables blood flow to be evaluated in patients who have an iodine allergy. However, shortcomings of MRI are poor throughput and the fact that the examination takes longer than a CT examination.

The hepatocellular MRI contrast medium Gd-EOB-DTPA (EOB, Primovist®) offers the advantage of enabling lesions to be evaluated from the perspectives of both blood flow and liver function. Consequently, contrast-enhanced MRI performed to evaluate liver tumors has often been switched from contrast-enhanced MRI using a conventional extracellular gadolinium contrast medium to EOB-MRI using Gd-EOB-DTPA.

It should be noted that arterial phase images can be poor with EOB-MRI due to artifacts resulting from transient severe motion (TSM), making it difficult to evaluate tumor enhancement. In addition, Shinagawa et al. reported seeing early enhancement of the peritumoral liver parenchyma and pseudotumors showing low signal intensity in the hepatobiliary phase with EOB-MRI within 1 month after TACE. Caution must therefore be exercised when using EOB-MRI to evaluate the response to HCC therapy with TACE.[4]

Contrast-enhanced ultrasound also enables blood flow at sites of recurrence to be evaluated without the evaluation being affected by Lipiodol® accumulation.[5] Currently, the second-generation ultrasound contrast medium perflubutane (Sonazoid®) is the main contrast medium used. Perflubutane contrast-enhanced ultrasound is superior to CT and MRI with respect to spatial and temporal resolution and is therefore very useful for evaluating the hemodynamics of a single HCC lesion or a small number of such lesions. However, it should be understood that ultrasonography has disadvantages, such as: the presence of dead space; the fact that ultrasound attenuates in deep tissue, making evaluation difficult; and the fact that observing a large number of lesions with a single test is difficult due to problems related to the contrast medium dose and test duration.

Performing TACE using spherical embolization agents has been permitted in Japan since 2014. Because Lipiodol® is not used concurrently in TACE that is performed using a spherical embolization agent, residual tumor blood flow can be evaluated without concern about image modification by Lipiodol®. A method of evaluating the treatment efficacy of TACE using spherical embolization agents will likely be established in the future as cases accumulate.

Search keywords and secondary sources

PubMed was searched using the following keywords, and relevant articles were selected from the search results: HCC, TACE, therapeutic effect, and imaging.

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BQ 41 Which imaging examinations are recommended to evaluate the efficacy of RFA in HCC?

Statement

Dynamic CT or dynamic MRI is recommended to evaluate the efficacy of RFA in HCC.

Background

Radiofrequency ablation (RFA), a local treatment for HCC, can destroy tumors by ablating them to induce coagulation necrosis. No reduction in tumor size is seen immediately after RFA therapy, making it difficult to use the RECIST criteria, which are based on size, to evaluate the efficacy of the treatment. To achieve cure, the scope of ablation must include a certain amount of the margin of the periphery rather than just approach the tumor border. Efficacy is therefore evaluated using a contrast medium to determine the scope of ablation, including the tumor.

Explanation

Dynamic CT using iodine contrast media and dynamic MRI using extracellular gadolinium contrast media or hepatocellular contrast media Gd-EOB-DTPA (EOB, Primovist®) do not have dead space and enable more objective blood flow evaluation than ultrasound, making them suitable for evaluating RFA treatment efficacy.

CT systems are installed even in relatively small hospitals, and CT has a short test duration and good throughput, whereas MRI systems are not installed in all hospitals, and MRI has a long test duration and poor throughput. However, treatment efficacy must be evaluated by MRI when the patient is allergic to the iodine contrast media used in CT or when the lesion can be visualized only in the hepatobiliary phase of MRI, particularly EOB-MRI, such as in hypovascular HCC. However, it should be noted that post-RFA HCC shows high signal intensity on T1-weighted images due to the ablation effect, and it may therefore be difficult to assess whether contrast enhancement is present with dynamic contrast-enhanced MRI.[1)]

Perflubutane (Sonazoid®) contrast-enhanced ultrasound is superior to CT and MRI with respect to spatial and temporal resolution and is therefore very useful for evaluating the hemodynamics of a single HCC lesion or a small number of such lesions. However, ultrasonography also has disadvantageous features that make evaluation difficult, such as the presence of dead space and the fact that ultrasound attenuates in deep tissue.

The treatment efficacy of RFA in HCC is ensured by obtaining an adequate safety margin. Although studies by Nakazawa et al. and Kim et al. indicated that a safety margin of approximately ≥ 5 mm should be obtained,[2, 3)] depending on the site where HCC is present (e.g., near a large blood vessel, in the hepatic margin, or other sites where puncture is difficult), obtaining an adequate safety margin may not be technically feasible. Three-dimensional CT (3D CT)[4)] and pre- and post-RFA CT fusion imaging[5)] have

been reported to be useful for evaluating the safety margin. Moreover, CT has been found to enable HCC treatment efficacy to be evaluated immediately after RFA (1 week after).[6)]

Corona enhancement of HCC indicates the outflow tract of tumor blood flow.[7)] This holds important significance for HCC progression, and it is therefore important to consider this the extent of the safety margin.

In a separate case-control study, contrast-enhanced 3D ultrasound using perflubutane was used to evaluate the ablation zone and residual tumors after RFA for HCC, and the results were found to agree well with those obtained with 3D CT.[8)] However, compared with ultrasound, CT and MRI are less operator-dependent, making it easier to objectively assess the change in tumor diameter and whether a safety margin has been obtained.

No reports of large investigations of RFA efficacy evaluation using Gd-EOB-DTPA have been identified. Investigation of this topic is therefore needed.

Search keywords and secondary sources

PubMed was searched using the following keywords, and relevant articles were selected from the search results: HCC, RFA, therapeutic effect, and imaging.

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BQ 42 Is EOB-MRI recommended for the definitive diagnosis of focal nodular hyperplasia?

Statement

Findings for the hepatobiliary phase of EOB-MRI are useful for the definitive diagnosis of focal nodular hyperplasia (FNH), and EOB-MRI should the first choice when selecting a modality.

Background

FNH manifests as a hypervascular, hyperplastic hepatocellular nodule that typically occurs in normal liver and is considered a reactive lesion that develops in response to abnormal regional blood flow. Although there have been many articles published on methods of diagnostic imaging for FNH, many of these reports use pathology findings or dynamic CT/MRI findings as the gold standard. This suggests that typical dynamic CT/MRI findings are sufficient basis for diagnosis at the clinical level. However, the diagnosis can actually be uncertain in some patients and is often confirmed by a finding of an isointense to high-intensity signal compared with the surrounding liver parenchyma or of a distinctive doughnut-shaped or ring-shaped high-signal area in the hepatobiliary phase of EOB-MRI.

Explanation

The typical imaging findings for FNH are summarized below.

1. Abdominal ultrasound

Although its echogenicity is varied, it is often hypoechoic. Typical findings with Doppler ultrasound and contrast-enhanced ultrasound include visualization of spoke-wheel-shaped vascularization or central vascularization, central scar that is hypoechoic and not contrast-enhanced, enhancement of the nodule as a whole or centrifugal arterial enhancement in the early phase of contrast-enhanced ultrasound, and hyperechoic to isoechoic enhancement in the late phase.[1-3)]

2. Dynamic CT and MRI

On non-contrast CT, FNH shows uniform isodensity or hypodensity internally[4)] and lobularity in the margins.[4, 6)] On MRI, although low signal intensity on T1-weighted images and high signal intensity on T2-weighted images are common, the signal can vary.[6, 7)] On diffusion-weighted imaging, isointense to high-intensity signals are common.[6, 7)] Common findings in dynamic studies are enhancement in the arterial phase[4, 5, 8)] and isodensity compared with the surrounding liver parenchyma from the portal venous phase to the delayed phase.[4, 5, 8)] The main drainage route in FNH is the hepatic veins,[9)] and thus a finding of early venous return is an aid in diagnosis. Central scarring shows hypodensity/low signal intensity in the early phase, contrast enhancement from the late phase onward, and high signal intensity on T2-weighted images.[4, 6)]

3. EOB-MRI

In the hepatobiliary phase of EOB-MRI, FNH shows an isointense to high-intensity signal compared with the surrounding liver parenchyma in most patients (≥ 90%).[10, 11] Central scar shows low signal intensity in the hepatobiliary phase of EOB-MRI.[11] FNH appears as a donut-shaped or ring-shaped high-intensity signal including a central low-intensity that is slightly larger than the pathological central scar.[12, 13]

Although FNH can often be diagnosed by dynamic contrast-enhanced CT/MRI or contrast-enhanced ultrasound, there have been few reports of studies that have performed straightforward comparisons of the diagnostic accuracy of the various diagnostic imaging modalities based on high-level evidence. Bartolotta et al. compared non-contrast-enhanced ultrasound with contrast-enhanced ultrasound and reported that the characteristics findings of FNH (spoke wheel vascularization, central scarring) were more easily seen with contrast-enhanced ultrasound.[2] No studies have compared ultrasound with EOB-MRI, and the superiority of these two modalities therefore cannot be compared. In 2008, Zech et al. reported that the rate at which FNH was diagnosed with certainty was significantly higher with EOB-MRI than with non-contrast-enhanced MRI or dynamic CT (2 of 3 readers).[11] A systematic review published in 2015 confirmed the usefulness of EOB-MRI.[8]

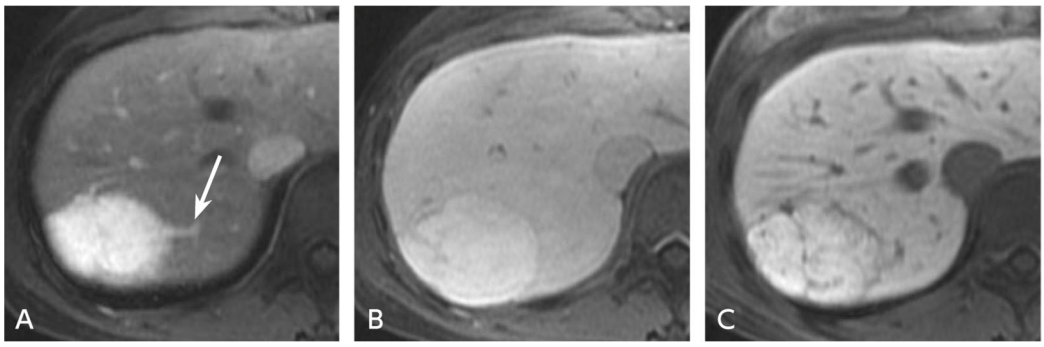

Figure　Focal nodular hyperplasia (woman in her 20s)

A: EOB-MRI, arterial-dominant phase: A 5-cm mass, enhanced in its entirety, is seen in S7/8. Early visualization of a vein (early venous return) is seen near the mass (→)

B: EOB-MRI, transitional phase: The mass shows slightly high signal intensity compared with the surrounding liver.

C: EOB-MRI, hepatobiliary phase: The mass shows higher signal intensity than background liver. Restiform low-intensity signals thought to be scarring are distinct in the interior.

Conditions for consideration in the differential diagnosis of FNH based on imaging include hepatocellular adenoma (HCA), HCC, metastasis, and hepatic angiomyolipoma. Of these, distinguishing FNH from HCA, which, like FNH, is a benign hepatocellular tumor that often occurs in normal liver, is difficult, but important because of differences in its treatment. Treatment of FNH basically involves watchful waiting, whereas surgery is recommended for HCA, particularly when ≥ 5 cm in size or when it increases in size, and in cases such as when it occurs in male patients in view of developments such as complicating intra-abdominal hemorrhage and malignant transformation. Grazioli et al. compared the

frequency of various EOB-MRI findings in 68 FNH lesions and 43 HCA lesions and found that 93% of the HCA lesions (40/43) showed low-intensity signals, whereas 91% of the FNH lesions (62/68) showed isointense to high-intensity signals, which were considered useful findings for distinguishing between the 2 types.[10] In addition, several reports of evidence level 2 have been published,[14, 15] and a systematic review published in 2015 found a high diagnostic rate for the hepatobiliary phase of EOB-MRI in distinguishing between FNH and HCA. However, the number of articles remains small, and it has been suggested that the estimated diagnostic accuracy may be higher than its actual value.[16]

With contrast-enhanced ultrasound, on the other hand, contrast enhancement is known to begin with central vessels in FNH and spread in a centrifugal pattern, which has been shown to be useful for diagnosing FNH and distinguishing it from HCA.[3, 17, 20] Subclassifications of HCA have been proposed and their genetic, pathological, and clinical features elucidated in recent years. In the 2010 WHO classification, 4 subtypes were proposed: hepatocyte nuclear factor 1α-inactivated HCA (H-HCA), inflammatory HCA (I-HCA), β-catenin activated HCA (B-HCA), and unclassified HCA (U-HCA). In the 2019 WHO classification, further refined subclassifications were proposed. Imaging features have also been established for HCA subclassifications,[19-21] with the existence of subtypes that show high signal intensity in the hepatobiliary phase of EOB-MRI reported (some B-HCA and I-HCA).[21] In these cases, greater care needs to be exercised in differentiating from FNH. Points that can be used to differentiate include the fact that arterial phase enhancement is stronger in FNH than in HCA,[10, 13, 22] and that changes such as fatty changes, hemorrhage, and necrosis are rarer in FNH than in adenomas.

Although conventional dynamic CT/MRI and contrast-enhanced ultrasound can also be used to diagnose FNH adequately, the findings from the hepatobiliary phase of EOB-MRI are useful for the definitive diagnosis of FNH. EOB-MRI should therefore be the first choice when selecting a modality in cases where FNH is suspected.

Search keywords and secondary sources

PubMed was searched for the period through June 2019 using the following keywords: focal nodular hyperplasia, Gd-EOB-DTPA, and gadoxetic acid. Hits were obtained for 81 articles. For reference, an additional search was performed using the keywords magnetic resonance imaging, CT, and ultrasound.

In addition, the following were referenced as secondary sources.

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BQ 43 Is dynamic CT recommended for diagnosing mass-forming intrahepatic cholangiocarcinoma?

Statement

Dynamic CT is a useful test for the qualitative diagnosis of lesions and for determining a treatment method, and its use is therefore recommended when mass-forming intrahepatic cholangiocarcinoma is suspected.

Background

Intrahepatic cholangiocarcinoma is broadly classified, based on macroscopic appearance, as the mass-forming type, periductal infiltrating type, and intraductal growth type.[1,2] However, because peripheral intrahepatic cholangiocarcinoma often shows a mass-forming-type morphology, an explanation limited to this type is included.

Explanation

Intrahepatic cholangiocarcinoma shows hypodensity on non-contrast CT, and ring-shaped enhancement is a feature of it in the arterial phase of dynamic CT. The sensitivity of dynamic CT is 60%, with specificity of 65.5%.[3,4] If the tumor diameter is < 3 cm, the early enhancement pattern varies from ring-shaped to uniform.[4, 5] Persistent enhancement, a characteristic finding, is seen in 67% of tumors.[3] It is attributed to an abundant stromal component at the center of the tumor.[5] An accessory finding in approximately 60% of tumors is dilatation of the distal bile duct.[6] Moreover, dynamic CT is useful and widely used for staging intrahepatic cholangiocarcinoma.[5, 7] Its sensitivity and specificity are 89% and 92%, respectively, for portal vein invasion and 84% and 93%, respectively, for hepatic artery invasion,[8] and its diagnostic rate for bile duct invasion is 79.7%.[9]

With regard to the diagnostic performance of contrast-enhanced ultrasound in intrahepatic cholangiocarcinoma, its sensitivity ranges from 60% to 90%, and specificity ranges from 65% to 98%.[10, 11] With regard to the discrimination ability of MRI in HCC, its sensitivity has been found to range from 68.8% to 93.5% and specificity from 86.2% to 97.7%.[12-15] With FDG-PET, sensitivity of 100% and specificity of 85% to 90% have been found for the mass-forming type ≥ 1 cm in size.[16-19] Although FDG-PET is highly useful in diagnosing malignancy, there have been no reports indicating that it is useful for the differential diagnosis of hepatic masses.

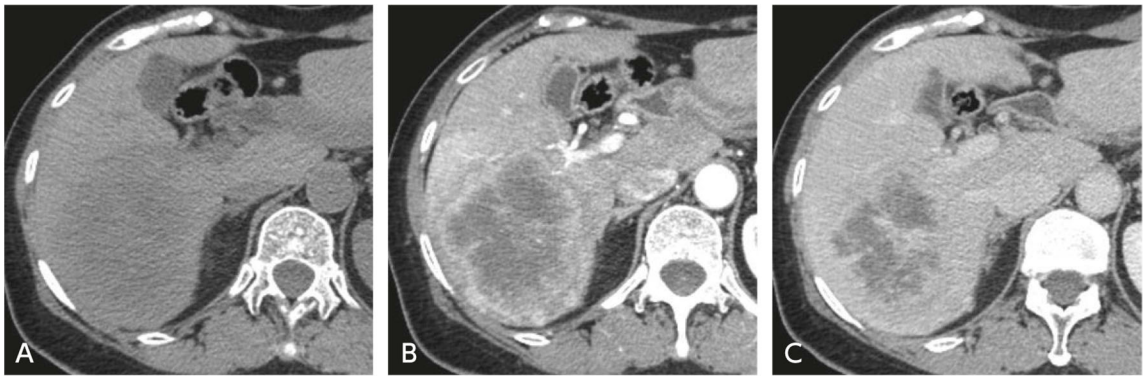

Figure　Intrahepatic cholangiocarcinoma (mass-forming type)

A: Non-contrast CT: A tumor lesion with hypodensity is seen in the right hepatic lobe.

B: Dynamic CT, arterial-dominant phase: Ring-shaped enhancement is seen in the tumor margins.

C: Dynamic CT, equilibrium phase: Delayed enhancement is seen in the tumor interior.

Search keywords and secondary sources

PubMed was searched using the following keywords: bile duct cancer, intrahepatic cholangiocarcinoma CT, MRI, and FDG-PET.

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BQ 44 Is EOB-MRI recommended for diagnosing liver metastasis (metastatic liver tumors)?

Statement

EOB-MRI is strongly recommended for diagnosing liver metastasis.

The addition of diffusion-weighted imaging to EOB-MRI has been shown to improve diagnostic performance for lesions < 1 cm in size, and their combined use is therefore recommended.

Hemangioma diagnosis may be difficult with EOB-MRI and therefore requires a comprehensive assessment.

Background

Metastatic liver cancer ("liver metastasis" below) is a disease more frequently encountered than primary liver cancer in routine clinical care. The objectives of diagnostic imaging in this case vary greatly, ranging from the exploratory examination of whether lesions are present used in follow-up to a qualitative diagnosis performed when hepatic lesions are identified and to a diagnostic workup that encompasses the extent and locations of the lesions and is performed in order to select treatment. In recent years, the usefulness of MRI (EOB-MRI) using the liver-specific contrast agent (Gd-EOB-DTPA) in diagnosing liver metastasis has come to be widely recognized.

Explanation

The primary imaging examinations used to diagnose liver metastasis are ultrasound, contrast-enhanced CT, MRI, and FDG-PET. Angiographic CT is not recommended due to its invasiveness. A meta-analysis published in 2002 that examined detection sensitivity in liver metastasis of gastrointestinal cancer, including esophageal cancer, gastric cancer, and colorectal cancer, found sensitivity of 55% for ultrasound, 72% for contrast-enhanced CT, 76% for MRI, and 90% for FDG-PET, with FDG-PET sensitivity being significantly higher than that of the other modalities. At this point, EOB-MRI was not being used clinically and was therefore excluded from the analysis.[1)] As evidence of the high diagnostic performance of EOB-MRI in liver metastasis, a meta-analysis published in 2012 found sensitivity and specificity of 93% and 95%, respectively, and an AUROC of 0.98,[2)] whereas a subsequent meta-analysis in 2018 in colorectal cancer found sensitivity and specificity of 82% and 74% for contrast-enhanced CT, 93% and 87% for EOB-MRI, and 74% and 94% for FDG-PET, respectively, showing superior diagnostic performance with EOB-MRI than with the other imaging examinations.[3)] The use of diffusion-weighted imaging in combination with EOB-MRI will likely increase diagnostic performance. Sensitivity was found to increase to 96% with combined use of diffusion-weighted images as compared with 91% without combined use and to improve from 83% to 91% when only sub-centimeter metastases are indicated to be evaluated.[4)]

Studies of the usefulness of EOB-MRI have often examined liver metastasis in colorectal cancer patients, because patient prognosis can be expected to improve with surgical resection. With the addition of EOB-MRI to contrast-enhanced CT, the treatment plan was found to change for between 19% and 37% of patients,[5-7] and this is the most highly recommended test method for preoperative evaluation, according to the American College of Radiology (ACR) Appropriateness Criteria®. In recent years, preoperative therapy and conversion therapy administered before liver resection following chemotherapy have been widely used for colorectal liver metastasis. EOB-MRI was also found to be effective for the diagnosis of colorectal liver metastasis after chemotherapy, and no difference in diagnostic performance was observed depending on whether chemotherapy was administered.[8] However, performing EOB-MRI for diagnosis of all liver metastases is unreasonable considering the various testing circumstances and cost. It is therefore appropriate to use contrast-enhanced CT, which covers a whole-body check-up, for screening and follow-up imaging examination. An example of tumors other than colorectal cancer for which surgical resection is known to be useful is liver metastasis of neuroendocrine neoplasms. Compared with other sequences or MRI using an extracellular gadolinium contrast agent, the hepatobiliary phase images in EOB-MRI have been found to provide better lesion contrast and identification and a higher rate of interobserver agreement for liver metastases of neuroendocrine neoplasms. However, no studies have compared EOB-MRI with contrast-enhanced CT or FDG-PET.[9, 10] Liver metastasis from pancreatic ductal adenocarcinoma is a disease that is inoperable when it is identified. The detection sensitivity of EOB-MRI for liver metastases from pancreatic ductal adenocarcinoma has been found to be superior to that of contrast-enhanced CT, with patient-based sensitivity of 82% for EOB-MRI and 60% for contrast-enhanced CT and lesion-based sensitivity of 93% for EOB-MRI and 75% for contrast-enhanced CT.[11] EOB-MRI also prevailed in a comparison with MRI using an extracellular gadolinium contrast agent: sensitivity was 95% for EOB-MRI and 84% for extracellular gadolinium contrast-enhanced MRI.[12]

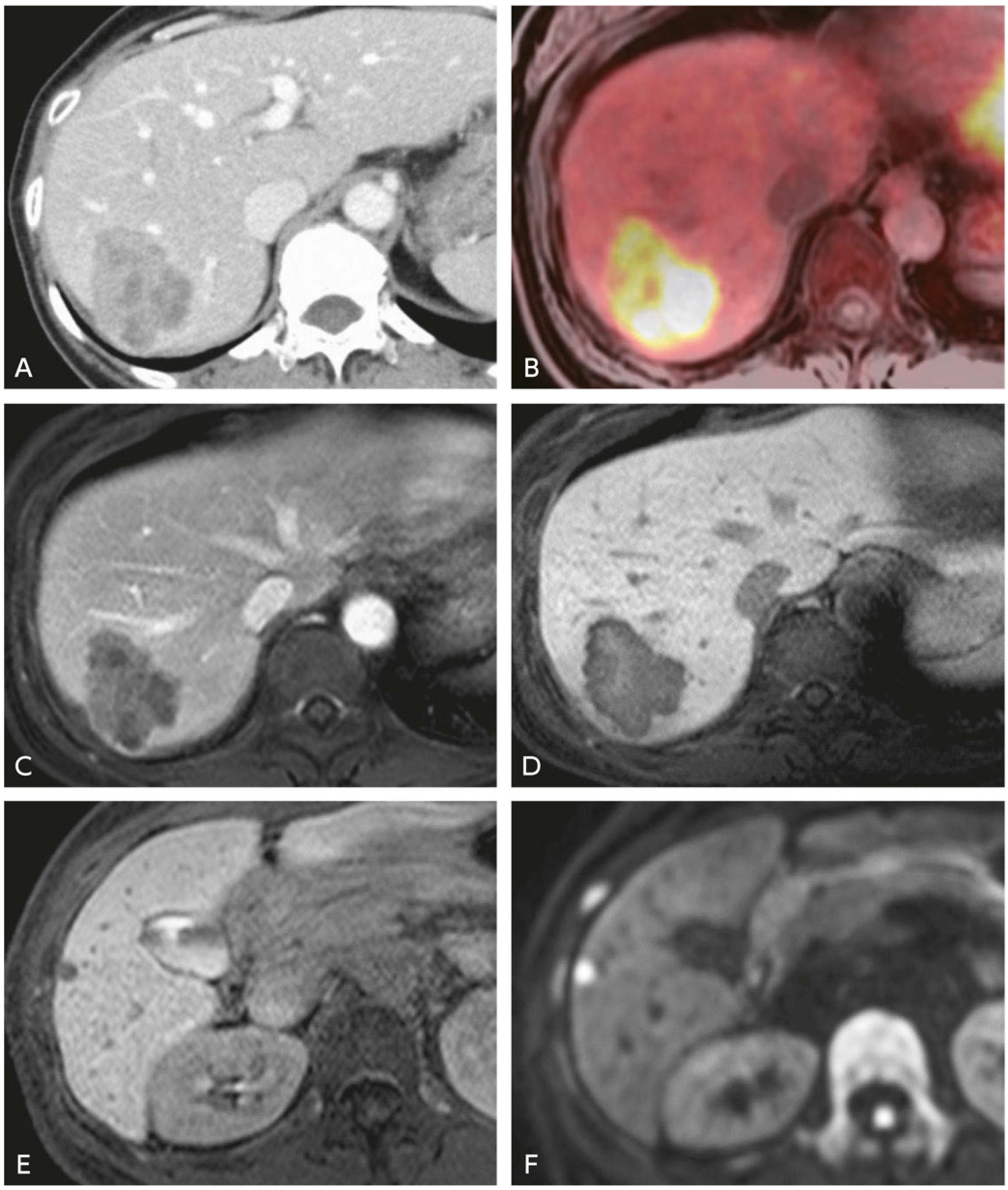

Figure　Liver metastasis of colorectal cancer (woman in her 50s)

A: Contrast-enhanced CT: A lobular, unevenly imaged liver metastasis is seen in liver segment S7.

B: FDG-PET: Increased FDG accumulation seen.

C: EOB-MRI, portal venous phase: As with contrast-enhanced CT, a lobular, unevenly imaged liver metastasis is seen.

D, E: EOB-MRI, hepatobiliary phase: Contrast is good (D), and a 1-cm nodule showing low signal intensity is seen in liver segment S6 (E).

F: MRI, diffusion-weighted imaging: High signal intensity shown, possible microscopic liver metastasis.

As noted previously, although EOB-MRI provides excellent diagnostic performance for liver metastasis, caution is required in diagnosing hemangioma. Because Gd-EOB-DTPA is taken up by hepatocytes beginning approximately 90 seconds after injection of the contrast agent, the concept of an equilibrium phase does not exist for dynamic studies in EOB-MRI. Consequently, the pooling and persistent enhancement in the equilibrium phase images that are useful findings for diagnosing hemangioma may not

be obtainable with EOB-MRI. The lack of pooling and persistent enhancement is highly observed for high-flow hemangiomas and small hemangiomas.[13, 14] To diagnose hemangioma, careful observation for imaging findings such as an area of marginal punctate enhancement in the arterial phase or markedly high signal intensity in T2-weighted images is desirable, along with the combined use of an extracellular gadolinium contrast medium.[5, 15]

Search keywords and secondary sources

PubMed was searched using the following keywords, and further selections were made from the results: liver metastasis, gadoxetic acid, gadoxetate disodium, EOB, and MRI.

In addition, the following was referenced as a secondary source.

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FQ 5 Is contrast-enhanced MRI recommended for distinguishing benign from malignant cystic lesions of the liver?

Statement

Although the discrimination ability of contrast-enhanced MRI with respect to cystic lesions of the liver is limited, and there is a lack of scientific evidence in this regard, it is useful to a certain extent, and its implementation for this purpose can therefore be considered.

Background

Various modalities are considered useful for distinguishing benign from malignant cystic lesions of the liver, such as ultrasound, contrast-enhanced CT, contrast-enhanced MRI, and FDG-PET. Although there have been many previous reports regarding the use of ultrasound, contrast-enhanced CT, and contrast-enhanced MRI, the sample sizes in nearly all of these reports have been small. Consequently, the evidence level is not high. Moreover, there have been very few reports of the usefulness of FDG-PET. This FQ focuses on the ability of contrast-enhanced MRI to distinguish between benign and malignant cystic lesions of the liver.

Explanation

There are a variety of cystic lesions of the liver, including: cysts of the liver parenchyma, such as simple hepatic cysts; congenital hepatic cysts, including Caroli's disease and bile duct-derived cysts; and inflammatory and neoplastic cystic tumors. Malignant cystic tumors of the liver also vary widely and encompass tumors such as: those that arise from cystic lesions; HCC; metastatic liver cancer; and cystic degeneration of solid tumors, such as undifferentiated cancer. Therefore, it is considered inappropriate to lump them together as malignant cystic tumors. Of these types of cystic lesions, this discussion focuses on distinguishing benign from malignant mucinous cystic neoplasms (MCNs) and non-invasive from invasive intraductal papillary neoplasms of the bile duct (IPNB). Although they have often been reported as hepatic biliary cystadenomas/cystadenocarcinomas, these lesions will be consolidated under MCNs in these guidelines.

All contrast-enhanced MRI is useful for detecting the septum and solid portion of an MCN in distinguishing benign from malignant neoplasms. Ultrasound and contrast-enhanced CT are also useful. Although both benign and malignant features are seen with septal enhancement and mural nodules, mural nodules are frequently associated with malignancy, and a papillary solid tumor and nodular thickening of the septum are findings that suggest malignancy (sensitivity, 67% to 100%).[1-6] With any of the modalities, there are limits to the extent to which these findings can detect tumors in accordance with a small solid portion or wall.[7]

In distinguishing non-invasive from invasive IPNB, a tumor diameter of ≥ 2.5 cm on contrast-enhanced MRI, multiplicity, thickening of the bile duct wall, and invasion of surrounding organs are frequent findings in invasive IPNB (Fig.). When these findings are present, the recurrence-free survival rate is low, and multiplicity is a negative prognostic factor for recurrence-free survival.[8] A histographic analysis of ADC values in diffusion-weighted images found that skewness was useful for distinguishing between non-invasive and invasive IPNB.[9]

The strengths of MRI are that it is useful for evaluating size and vascular and hepatic invasion and for elucidating internal features such as blood vessels.[5] There have been almost no reports of EOB-MRI.

Similar to contrast-enhanced MRI, contrast-enhanced CT is useful for evaluating size and vascular and hepatic invasion. However, a strength of contrast-enhanced CT is its excellent spatial resolution, which makes it useful for evaluating size, elucidating anatomical location relationships, and evaluating aspects such as bile duct and blood vessel invasion.[1, 3, 10] On the other hand, it cannot distinguish between benign and malignant in the presence or absence of calcification, and although the likelihood of malignancy is high with hemorrhage, this is not considered a finding specific to malignancy.[4, 5]

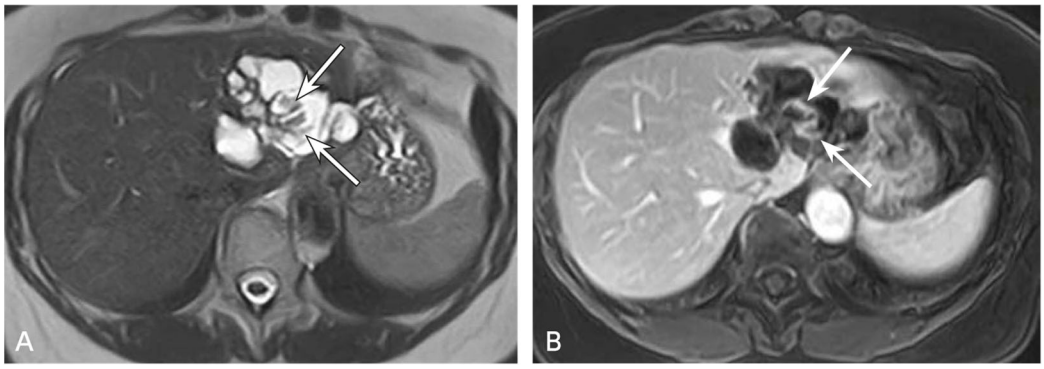

Figure　Patient (woman in her 50s)

A: MRI (single-shot T2-weighted image)

B: Gadolinium contrast-enhanced MRI (fat-suppressed T1-weighted image)

A cystic mass with a maximum size of approximately 6 cm that connects with the dilated bile duct is seen in the lateral segment of the left hepatic lobe. Internally, a papillary solid portion (→) is seen in association with an area of contrast enhancement with a maximum size of 2.3 cm. No tendency for multiplicity or a clear finding of extramural invasion is seen. The findings suggest non-invasive IPNB.

With regard to ultrasonography, a strength of this modality is that it is the optimal test for elucidating the internal aspects of a cyst, such as mucus and the septum.[1, 3] Ultrasound has also been found to be useful for determining whether mural nodules are present in cystic disease.[11] In addition, it is useful for diagnosing solid tumors that appear to be cystic lesions on CT or MRI, such as undifferentiated sarcomas.[12] It has been reported that distinguishing biliary sludge, mucus plugs, and calcification from solid portions can be difficult with ultrasound, and that visualization of solid portions is better with CT.[13-15] In recent years, contrast-enhanced ultrasonography has also been found to be useful.[16] In distinguishing benign from malignant MCNs, honeycomb contrast in the arterial phase was found to be common in benign MCNs,

whereas hypoechoicity in the late phase resulting from poor contrast enhancement was reported to be common in malignant cases.[17)]

With FDG-PET, the standard uptake value (SUV) has been reported to be useful in distinguishing non-invasive from invasive IPNB.[18)]

For each modality, the sample sizes in nearly all of the studies have been small, and the evidence is therefore lacking. It would be helpful in the future to conduct investigations that have large sample sizes and that compare the diagnostic performance of the different modalities.

Although all of the modalities are currently limited in their discrimination ability, they each have a different characteristic capacity for discrimination, and combining them for diagnosis is therefore desirable.

Search keywords and secondary sources

Five types of searches of PubMed were performed using the keywords shown below. In the primary search, 2,256 articles were extracted, and 18 were eventually used.

1. liver, cystic tumor, diagnosis, malignant, imaging
2. biliary cystadenocarcinoma, imaging
3. intraductal papillary neoplasm of bile duct, imaging
4. mucinous cystic neoplasm, liver
5. mucin producing, liver

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BQ 45 Which imaging examinations are recommended for determining whether cholecystocholedocholithiasis is present?

Statement

Ultrasound is strongly recommended as an initial test.

If a bile duct stone is suspected, MRI or MRCP is also strongly recommended.

Although CT has lower sensitivity for bile duct stones than MRI/MRCP, its use can also be considered.

Although endoscopic retrograde cholangiopancreatography (ERCP) is not recommended purely for diagnosis, it should be given priority when its use as a treatment is necessary.

Plain radiography is not recommended due to the radiation exposure involved and its low detection performance.

Background

Various diagnostic imaging methods have long been used to detect cholecystolithiasis and bile duct stones. Moreover, many studies have been conducted that have examined and compared the diagnostic performance of the tests. This discussion summarizes these methods and determines a recommendation level for the use of each test in clinical care. Because there have been relatively few reports of intrahepatic bile duct stones, these guidelines focused on choledocholithiasis.

1. Plain radiography

Pigment stones with a high calcium content (calcium bilirubinate stones, black stones) are X-ray-positive calculi, and 15% to 20% of all such stones have sufficient calcification to be recognized by plain radiography.[1)] Although inexpensive, plain radiography is inadequate for diagnosing cholecystocholedocholithiasis and is not recommended due to the radiation exposure involved and its low detection sensitivity.[2, 3)]

2. Ultrasound (US)

This is a safe and inexpensive test with reported accuracy of 93% for cholecystolithiasis.[4)] However, possibly because its diagnostic usefulness is assumed, there have been no recent reports on its use in diagnosis. A meta-analysis of the diagnostic performance of emergency department bedside US in cholecystolithiasis (8 articles, 710 patients) found that its sensitivity was 89.8% (95% CI, 86.4% to 92.5%), and specificity was 88% (95% CI, 83.7% to 91.4%).[5)] Its sensitivity and specificity in choledocholithiasis have been reported to be 25% and 89%, respectively,[6)] and 63% and 95%, respectively.[7)] The Japanese Society of Gastroenterology's guidelines for the diagnosis and treatment of gallstones indicate that US is useful as a primary test for gallstones and recommended it as the initial diagnostic imaging method for determining whether a bile duct stone or cholecystolithiasis is present, although problems remain regarding its detection performance in bile duct stones.

3. CT

A 1987 investigation concerning CT cholecystolithiasis detection rates found sensitivity of 79.1%, specificity of 100%, and accuracy of 89.8%.[8] The diagnostic performance of CT has improved with advances in CT systems. The guidelines for the diagnosis and treatment of gallstones strongly recommend CT as a next test to be performed after US when cholecystolithiasis is suspected. Relatively recent studies of the use of CT reported sensitivity of 65% and specificity of 84% with non-contrast-enhanced CT in bile duct stones[9] and sensitivity of 88.9%, specificity of 92.6%, and accuracy of 90.7% when CT was used with multiplanar reconstruction (MPR) in choledocholithiasis.[10] Non-contrast-enhanced CT is considered the CT standard for determining whether calculi are present. Six articles reported sensitivity of 65% to 100% and specificity of 84% to 100% with CT using drip infusion cholangiography (DIC).[11] However, this is not considered a standard test for cholecystocholedocholithiasis in view of considerations such as adverse reactions to iodine contrast media, radiation exposure, and reduced visualization with hyperbilirubinemia.

4. MRI/MRCP

A meta-analysis of 67 reports (4,711 patients) with appropriate diagnostic criteria found that the sensitivity of MRCP for biliary tract disease was 95%, and specificity was 97%. Sensitivity was 92% for calculi and 88% for malignancies.[12] It was concluded that MRCP is a noninvasive and appropriate test for biliary tract disease. However, although there have been few articles on the diagnosis of cholecystolithiasis with MRCP, as with US, there appears to be no divergence of opinion regarding its usefulness. On the other hand, a comparison of 10 articles on the diagnosis of choledocholithiasis with MRCP found that sensitivity ranged from 80% to 100%, specificity from 83% to 100%, and diagnostic accuracy from 81.3% to ≥ 95%.[13] However, it was reported that the diagnostic performance of MRCP was not high in microliths ≤ 5 mm in size.[14] Two meta-analyses (301 patients and 405 patients) of studies comparing MRCP and endoscopic ultrasound (EUS) both found no significant difference in diagnostic performance between MRCP and EUS.[15, 16] Although it has been reported that there are few cases in which ERCP is avoidable based on information from MRCP,[17] MRI and MRCP are recommended as non-invasive test methods for cholecystocholedocholithiasis in symptomatic patients.

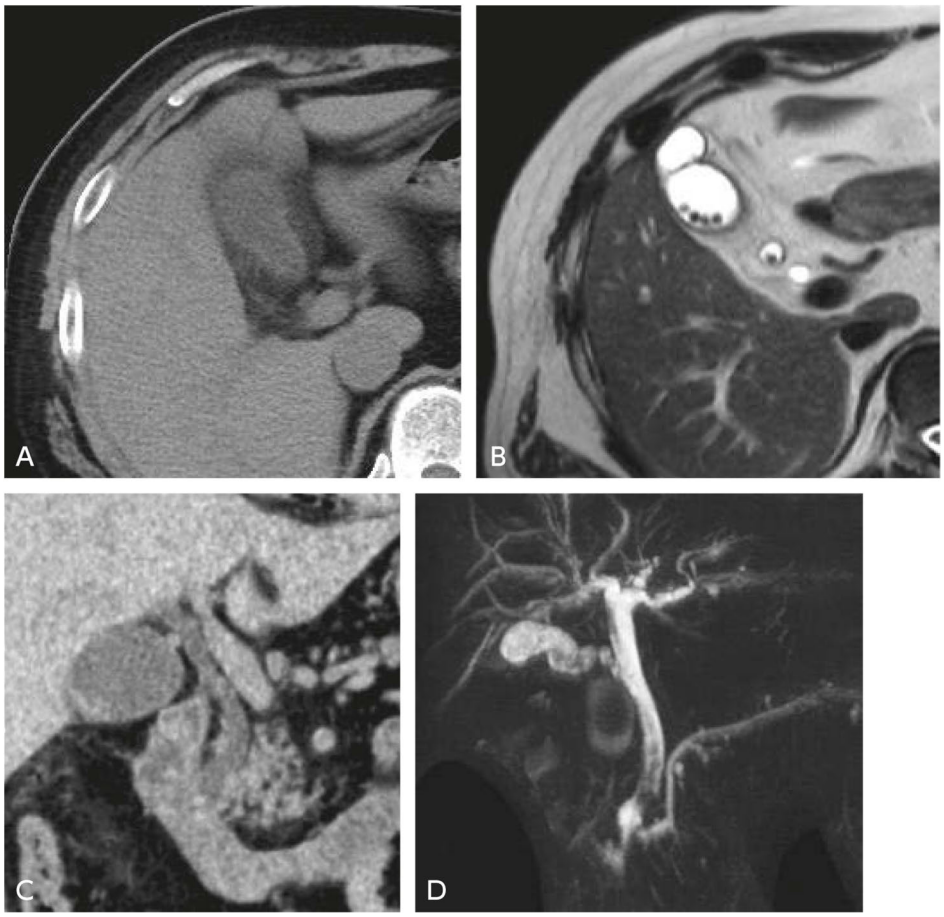

Figure Cholecystolithiasis

A: Non-contrast CT, transverse image, B: MRI, T2-weighted, transverse image, C: Non-contrast CT, coronal image, D: MRCP

In many cases, calculi cannot be visualized even with the improved image quality of the latest CT technology. Calculi in the gallbladder or common bile duct are either indistinct with non-contrast CT (A, C), they are visualized as areas of signal void on T2-weighted imaging (B) and MRCP (D).

5. ERCP

The bile duct stone detection rate of ERCP is high, and as mentioned above, it has been reported that there are few cases in which ERCP can be avoided based on information from MRCP.[17] On the other hand, ERCP carries risks that can by no means be ignored, such as a risk of pancreatitis and cholangitis.[15] Even when it is used only for diagnosis, pancreatitis occurs in 3% to 5% of patients. The mortality rate ranges from 0.2% to 0.5%. Consequently, although ERCP is not recommended purely for diagnosis, it should be given priority when its use as a treatment is necessary. Similarly, high spatial resolution and calculus detection rates have been reported with both EUS and intraductal US. However, because they are invasive tests, they are considered when a diagnosis is not obtained with MDCT or MRI/MRCP.

Search keywords and secondary sources

PubMed was searched using the following keywords: gallstones, cholecystolithiasis, choledocholithiasis detection radiography, abdominal ultrasonography tomography, X-ray computed cholangiopancreatography, magnetic resonance cholangiography, cholangiopancreatography, and endoscopic retrograde.

In addition, the following secondary sources were used as references.

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BQ 46 Which imaging examinations are recommended if acute cholecystitis is suspected?

Statement

It is strongly recommended that ultrasound be performed initially in patients with suspected acute cholecystitis.

CT and MRI/MRCP are recommended when a definitive diagnosis is difficult based on clinical findings and ultrasonography or when local complications are suspected.

Background

Acute cholecystitis is an inflammatory disease that occurs in the gallbladder. In 85% to 95% of cases, the cause is cholecystolithiasis. Other causes include: aftereffects of surgery, trauma, or burns; long-term intravenous feeding; malignancies; hepatic arterial infusion therapy; diabetes mellitus; collagen disease; medications; infection; and torsion abnormality. A diagnosis of acute cholecystitis is established through a comprehensive assessment based on considerations such as: (1) local signs of inflammation, such as Murphy's sign or mass palpation, spontaneous pain, or tenderness in the right upper quadrant; (2) systemic inflammation findings, such as fever, or white blood cell (WBC) count or C-reactive protein (CRP) elevation; and (3) imaging findings. Diagnostic imaging plays a particularly important role in the diagnosis and severity assessment of acute cholecystitis. Ultrasonography is recommended as the imaging examination to perform initially for reasons such as its low invasiveness, widespread availability, ease of use, and cost-effectiveness. Other imaging examinations used include CT, MRI/MRCP, plain radiography, cholescintigraphy, and drip infusion cholecystocholangiography. The usefulness of ultrasonography in diagnosing acute cholecystitis and comparisons with other imaging examinations are summarized below.

Explanation

1. Usefulness of ultrasonography

Ultrasonography is the best modality for the morphological diagnosis of acute cholecystitis due to its low invasiveness, widespread availability, ease of use, and cost-effectiveness. All of the following guidelines recommend that ultrasonography be performed as the initial imaging examination in patients with suspected acute cholecystitis: the Tokyo Guidelines 2018, European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, National Institute for Health and Care Excellence (NICE) Internal Clinical Guidelines, 2016 World Society of Emergency Surgery (WSES) Guidelines on acute calculous cholecystitis, and the American College of Radiology (ACR) Appropriateness Criteria® (secondary sources 1 to 6). The sensitivity of ultrasonography in diagnosing acute cholecystitis was reported to be 81% (95% CI, 75% to 87%), and specificity was reported to be 83% (95% CI, 73% to 87%).[1)] Ultrasound findings

include maximal abdominal tenderness from pressure of the ultrasound probe over the visualized gallbladder (sonographic Murphy's sign), gallbladder distention (long axis diameter ≥ 8 cm, short axis diameter ≥ 4 cm), gallbladder wall thickening (≥ 4 mm), cholecystolithiasis, debris echo, pericholecystic fluid, a sonolucent layer (hypoechoic layer) in the gallbladder wall, a striated intramural lucency, and an increased Doppler signal (Fig.).[2-7] Combining several findings can increase diagnostic accuracy.[4, 8, 9] Among them, the sonographic Murphy's sign, although of inferior sensitivity, has excellent specificity and is useful by itself for diagnosis. It is considered a more accurate finding when combined with the presence of cholecystolithiasis.[7-9] Although gallbladder wall thickening is also an important finding suggestive of acute cholecystitis, it also has many other causes, such as infection, inflammation, and tumors. It should therefore be combined with other findings, such as the presence of cholecystolithiasis and the sonographic Murphy's sign, for evaluations.[9, 10] In evaluating the severity of acute cholecystitis, attention is paid to pericholecystic abscesses, hepatic abscesses, hypoechoic areas around the gallbladder, intraluminal membranes, irregular thickening of the gallbladder wall, rupture of the gallbladder wall, and intramural/intraluminal gas, which indicates emphysematous cholecystitis.

2. CT

The diagnostic performance of CT is inferior to that of ultrasonography. It is therefore not necessary to perform CT for all patients.[11] It should be performed when definitive diagnosis is difficult based on clinical findings and ultrasonography or when local complications are suspected. Findings include gallbladder distention, gallbladder wall thickening, high-attenuation gallbladder bile, pericholecystic fluid collection, pericholecystic fat stranding, subserosal edema, transient focal enhancement of the liver adjacent to the gallbladder, focal irregularity or defect in an enhanced part of the gallbladder wall, pericholecystic abscesses, and gas in the gallbladder.[12, 13] Enhancement of the liver parenchyma around the gallbladder in the arterial phase can be an important finding in the diagnostic imaging of mild acute cholecystitis that is difficult to definitively diagnose by ultrasonography.[14, 15] CT is superior to ultrasonography and useful for diagnosing local complications such as perforation and abscess.[16, 17] Findings indicating possible gangrenous cholecystitis include intramural/intraluminal gas, intraluminal membranes, pericholecystic abscesses, and focal irregularity or a defect in an enhanced part of the gallbladder wall.[13] Findings useful for distinguishing acute cholecystitis from chronic cholecystitis are gallbladder distention, gallbladder wall thickening, pericholecystic fluid collection, and transient focal enhancement of the liver adjacent to the gallbladder. Combining multiple findings has been reported to increase diagnostic performance.[18]

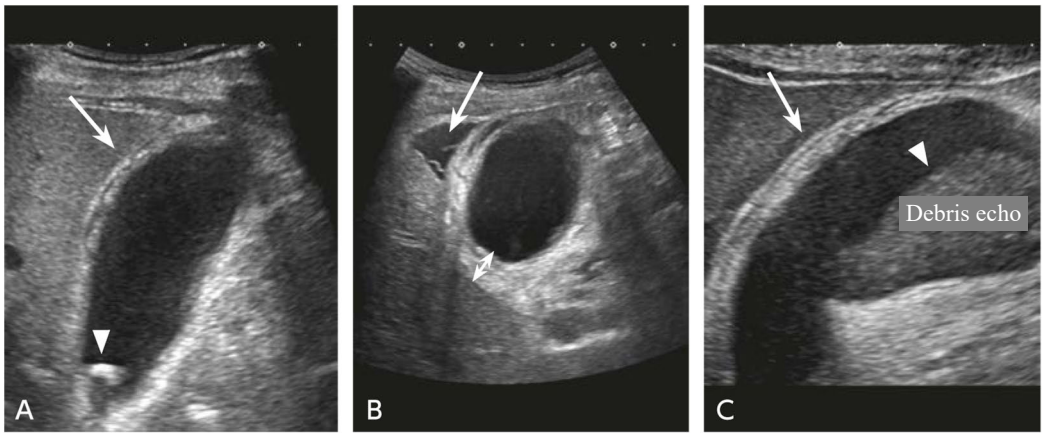

Figure　Acute cholecystitis (ultrasound appearance)

Gallbladder distention, an impacted gallstone (▷), and a sonolucent (hypoechoic) layer in the gallbladder wall (→) are seen (A).
Wall thickening (↔) and pericholecystic fluid collection (→) are seen (B).
Debris echo (▷) and a striated intramural lucency are seen (C).

3. MRI and MRCP

MRI tests provide high-density resolution and are therefore useful for diagnosing acute cholecystitis. Sensitivity of 85% (95% CI, 66% to 95%) and specificity of 81% (95% CI, 69% to 90%) have been reported for MRI, and its diagnostic accuracy is comparable to or better than that of ultrasonography.[1, 19, 20] However, the test requires the patient to remain still, and it cannot be performed in patients who have metal in their body. From the perspectives of test duration and economic considerations, its use is recommended when a definitive diagnosis cannot be obtained based on clinical findings and ultrasonography. Findings include gallbladder distention, wall thickening, mural or mucosal hyperenhancement, pericholecystic fluid collection, a high-signal area in adipose tissue around the gallbladder on T2-weighted images, transient focal enhancement of the liver adjacent to the gallbladder, and gallstones.[20, 21] The finding of a high-signal area in adipose tissue around the gallbladder on T2-weighted images is particularly useful for diagnosis.[20] Detection of stones in the gallbladder neck, cystic duct, and common bile duct with MRI/MRCP is superior to detection by ultrasonography.[19, 22] Increased enhancement of the gallbladder wall and transient focal enhancement of the liver adjacent to the gallbladder are useful for distinguishing acute from chronic cholecystitis.[21, 23]

4. Plain radiography

There are no plain radiography findings specific to acute cholecystitis. However, it can be used to diagnose conditions that need to be distinguished from acute cholecystitis, such as gastrointestinal perforation and intestinal obstruction, which makes it useful for differential diagnosis.

5. Cholescintigraphy

Although ^{99m}Tc-labeled hepatobiliary iminodiacetic acid (HIDA) uptake by the liver and excretion through the common bile duct are visualized with cholescintigraphy, acute cholecystitis can be diagnosed if the gallbladder is not visualized. Morphine-augmented cholescintigraphy, which involves administration of morphine hydrochloride, has a high diagnostic rate.[24] In severe acute cholecystitis, inflammation that extends to the surrounding liver parenchyma is visualized as the rim sign, which is considered a finding of high specificity.[25] Diagnostic sensitivity and specificity for acute cholecystitis were 94% (95% CI, 92% to 96%) and 90% (95% CI, 85% to 93%), respectively, giving cholescintigraphy the highest diagnostic accuracy of all modalities, including ultrasonography.[1] However, its use in acute cholecystitis is limited due to the test duration, level of radiation exposure, and economic considerations.

6. Drip infusion cholangiography, drip infusion cholangiography-CT

Performing plain radiography or CT imaging after intravenous drip infusion of an iodine contrast medium is a technique that can be used for morphological and functional evaluation of the gallbladder. It was previously the only cholangiographic method other than intraoperative cholangiography to be used to diagnose acute cholecystitis and cholecystolithiasis. However, it is now rarely performed because its diagnostic performance in acute cholecystitis is low,[26] superior modalities have emerged, and allergic reactions to the contrast media occur frequently.

Search keywords and secondary sources

PubMed was searched using the following keywords: cholecystitis ultrasonography tomography, X-ray computed magnetic resonance imaging radionuclide imaging cholangiography. The period searched was through June 2019.

In addition, the following secondary sources were used as references.

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BQ 47 Which imaging examinations are recommended if acute cholangitis is suspected?

Statement

It is recommended that ultrasonography and CT be used in a complementary fashion when acute cholangitis is suspected.

Background

Acute cholangitis is a pathophysiology in which the biliary tract becomes obstructed for any reason, resulting in cholestasis and abnormal bacterial growth. Elevated intraductal pressure causes reflux of infected bile from the bile duct to the veins, resulting in systemic infection. Because the patient's condition may worsen rapidly due to sepsis, acute cholangitis requires a rapid and appropriate response. The diagnostic criteria for acute cholangitis are that the diagnosis is definitive if one item in A, one item in B, and one item in C of the following is seen and that acute cholangitis is suspected if one item in A and one item in either B or C are seen: A, a finding indicating systemic inflammation (fever, inflammatory response on blood tests); B, a finding indicating cholestasis (jaundice, abnormal liver function test); and C, an imaging finding indicating the presence of a bile duct lesion [bile duct dilatation, a cause of cholangitis (e.g., bile duct stenosis, bile duct stone, or a stent)]. That is, diagnostic imaging has major significance in acute cholangitis that can be summarized under 2 categories: determining whether there is a biliary tract occlusion or dilatation; and diagnosing the cause of occlusion. Diagnostic imaging is also useful for evaluating complications such as abscess formation and portal vein thrombosis and distinguishing acute cholangitis from other disorders. Severity is evaluated based on the usual clinical information. Consequently, no diagnostic imaging criteria are used for this purpose.

Explanation

1. Ultrasonography

In patients with suspected acute cholangitis, ultrasonography is the test that should be performed initially, being the best modality in terms of simplicity, low invasiveness, widespread availability, and economy.[1, 2)] Although the test findings include biliary tract dilatation, thickening of the bile duct wall, and biliary tract emphysema, all are nonspecific.[3)] If a bile duct stone is visualized in addition to these findings, it provides stronger evidence for a diagnosis. However, the sensitivity of a diagnosis of choledocholithiasis based on ultrasonography ranges from 25% to 68%, which cannot be considered adequate.[4)] It also has shortcomings such as the fact that the accuracy of an ultrasound test can depend on the skill of the operator and the condition of the patient (e.g., unable to hold breath or remain still, marked intestinal gas, comorbid pneumobilia).[5)]

2. CT

Compared with ultrasonography, CT makes a broader range of diagnoses possible and provides better objectivity. The CT findings in cholangitis are nonspecific findings, such as biliary tract dilatation, biliary tract emphysema, and thickening of the bile duct wall. In addition, inhomogeneous enhancement of the liver as a whole in the arterial phase of dynamic CT has been reported to be indicative of active inflammation (Figs. 1 and 2).[6] Dynamic CT is also useful for determining the cause of a bile duct obstruction, such as a calculus or pancreaticobiliary tumor, and for evaluating whether a complication such as a hepatic abscess or portal vein thrombosis is present (Figs. 1 and 2). Although tests such as non-contrast CT are useful for identifying a stone as the cause of an obstruction,[7] the absorption value of the calculus depends on calcium concentration (calcium phosphate, calcium carbonate) in the calculus. Consequently, the detection sensitivity of CT for bile duct stones is only 25% to 90%.[8, 9]

3. MRI and MRCP

Both MRI and MRCP are also useful for visualizing bile duct stones that cause obstruction[10, 11] and for visualizing malignant disease.[10, 12] Because they can elucidate the biliary system as a whole, they are also useful for guidance during drainage. Although their diagnostic performance in choledocholithiasis is excellent, with sensitivity and specificity both ≥ 90%,[10, 11, 13] decreased sensitivity has been reported for small calculi (≤ 6 mm).[11, 14] They are not first-line tests from the perspectives of widespread availability and simplicity. However, they are suitable for evaluation when the cause of bile duct stenosis cannot be determined by ultrasound or CT. Although it is excellent for evaluating bile duct stenosis caused by obstructions such as bile duct stones or tumors,[15] ERCP is an invasive test performed for treatment (drainage) purposes and is not used solely for diagnosis.

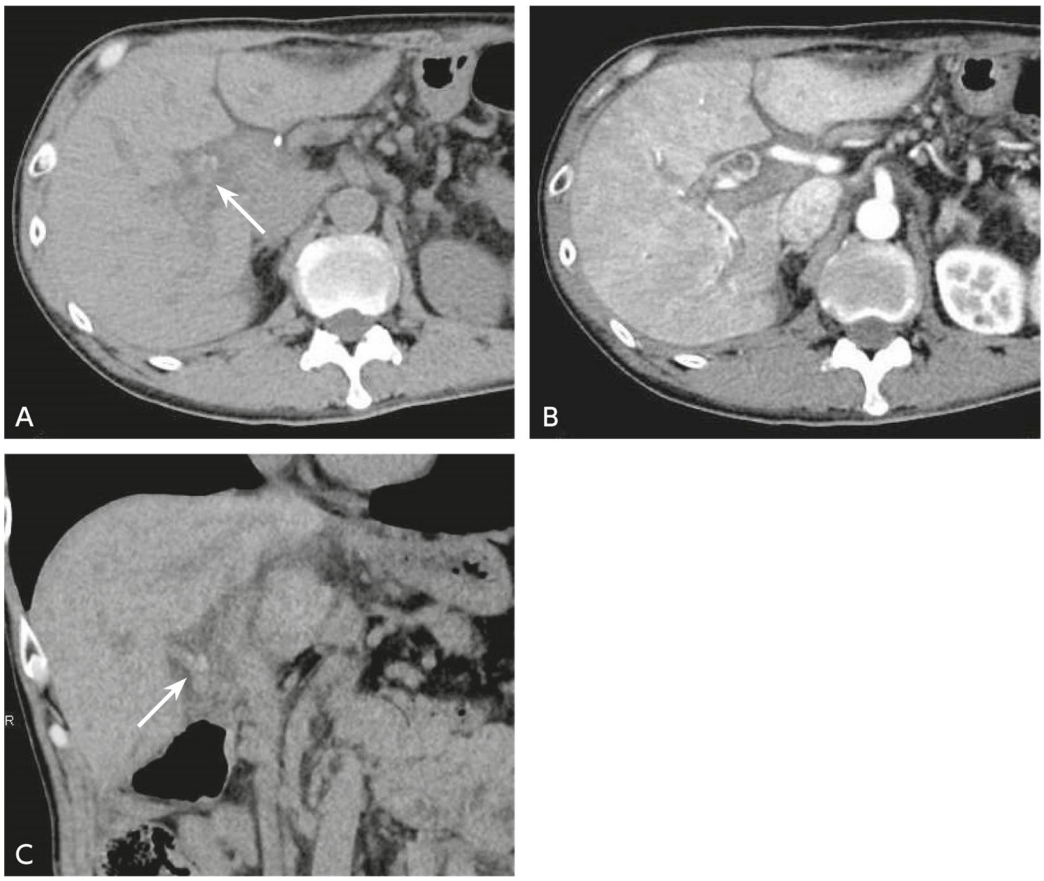

Figure 1. Concomitant bile duct stone impaction and acute cholangitis (man in his 60s)

A: Non-contrast CT, transverse image; B: Contrast-enhanced CT, arterial phase transverse image; C: Non-contrast CT, coronal image

Hyperdense calculi (→) are seen in the bile duct on non-contrast CT. On contrast-enhanced CT, wall thickening and enhancement of the bile duct are seen, with diffuse inhomogeneous enhancement of the liver parenchyma. The findings are suggestive of acute cholangitis.

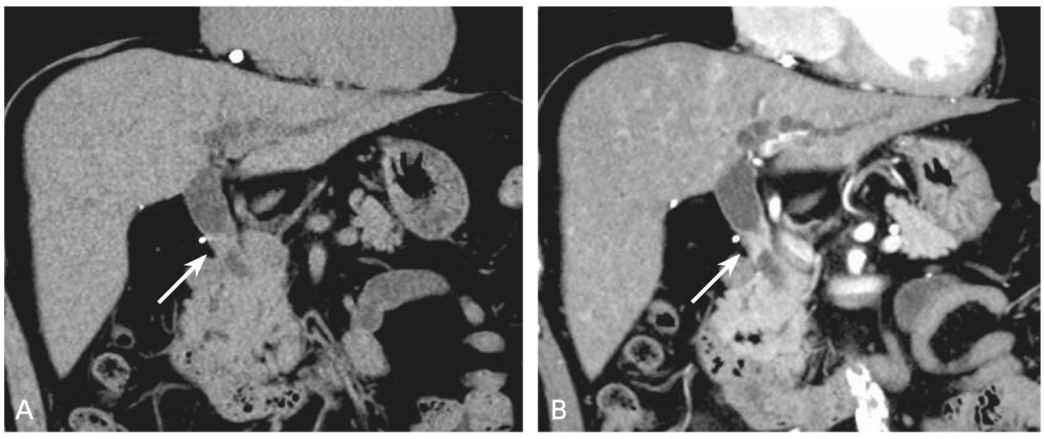

Figure 2. Concomitant bile duct cancer and acute cholangitis (man in his 60s)

A: Non-contrast CT, coronal image; B: Contrast-enhanced CT, arterial phase, coronal image

On non-contrast CT, wall thickening is seen in the distal bile duct, along with distinct contrast enhancement (→). The upstream portion of the bile duct is dilated, and inhomogeneous contrast enhancement is seen in the liver parenchyma, indicating concomitant cholangitis.

Search keywords and secondary sources

PubMed was searched using the following keywords: cholangitis and radiography, ultrasonography computed tomography, magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography.

In addition, the following secondary sources were used as references.

1) Committee for the Revision and Publication of Guidelines for the Diagnosis and Treatment of Acute Cholangitis and Cholecystitis, Ed: 2018 Guidelines for the Diagnosis and Treatment of Acute Cholangitisand Cholecystitis, Igakutosho Shuppan, 2018.
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FQ 6 Is contrast-enhanced CT recommended when gallbladder cancer is suspected?

Statement

Although the supporting evidence for its use in distinguishing gallbladder cancer from cholecystitis and in evaluating metastasis cannot be considered sufficient, contrast-enhanced CT is recommended for qualitative diagnosis and determining a treatment strategy when gallbladder cancer is suspected.

Background

When gallbladder wall thickening or a protruding lesion is seen, in addition to benign diseases such as cholecystitis and gallbladder adenomyomatosis, gallbladder cancer should be considered. Transabdominal ultrasonography is generally used as the primary screening test for gallbladder lesions, and contrast-enhanced CT is the most frequently used as the detailed diagnostic imaging method, because it provides high spatial resolution and can be used to evaluate not only the features of gallbladder lesions, but also progression into surrounding tissue. These guidelines show that contrast-enhanced CT is useful for differentiating from benign conditions and determining a treatment strategy when gallbladder cancer is suspected. In addition, it is considered a recommendation grade when comparing contrast-enhanced CT with other imaging modalities such as MRI.

Explanation

With multiphase dynamic contrast-enhanced CT, vascular anatomy and local blood flow can be evaluated, and one can evaluate gallbladder lesions from multiple directions using multiplanar reconstruction. Consequently, good diagnostic accuracy of 84% to 85% has been shown in staging gallbladder cancer with contrast-enhanced CT.[1, 2)] In addition, preoperative vascular mapping has been used by creating 3D CT angiograms. On the other hand, although there has been a somewhat small number of reports on the evaluation of gallbladder cancer using MRI, MRCP is superior for evaluating bile duct invasion and obtaining anatomical information on the bile duct (e.g., pancreaticobiliary maljunction).[3)] Moreover, EOB-MRI has been reported to be useful for evaluating liver invasion[4)] and screening for hepatic metastases.[5)]

The morphology of gallbladder cancer can be mainly classified into the following 3 types: (1) protruding lesions (polypoid lesions); (2) lesions with thickened walls; and (3) massive masses with direct liver invasion. In protruding lesions, a size ≥ 1 cm and morphological features such as having a broad base are important findings suggestive of malignancy, and the additional blood flow evaluation based on multiphase imaging is helpful in the diagnosis. In the case of gallbladder cancer, the difference in the CT numbers in the portal venous and equilibrium phases is small (≤ 10 HU, as a rule) on 3-phase dynamic contrast-enhanced CT (arterial, portal venous, and equilibrium phases) because there is a tendency for

delayed enhancement due to fibrosis in gallbladder cancer, and this is useful as an index for differentiating from benign lesions.[6] Investigations of the differential diagnosis of benign and malignant lesions using diffusion-weighted MRI images reported sensitivity of 78% to 97% and specificity of 78% to 92%.[7, 8] In lesions with thickened walls, early enhancement of the smooth inner layer of the luminal surface is a finding suggestive of chronic cholecystitis, and, on the other hand, the findings of luminal surface irregularity, laminar tearing, and thick inner layer enhancement suggest gallbladder cancer. However, neither CT nor MRI can provide adequate diagnostic performance in distinguishing benign from malignant lesions.[9, 10] In advanced cancers appearing as massive masses, assessing whether there is arterial or portal venous–invasion and evaluating distant metastasis, particularly lymph node and liver metastases, are important for determining a treatment strategy, and for this purpose, CT and MRI are superior to other modalities.[11, 12, 13-15] In particular, contrast-enhanced CT is superior to MRI, because it can rapidly scan extensive areas at one time and elucidate anatomical locations in detail (including blood vessel variations).

Visualization of Rokitansky-Aschoff sinuses (RASs) in the lesion wall by MRCP is useful for differentiating from gallbladder adenomyomatosis.[16] In addition, it has been reported that a similar finding (cotton ball sign) can be identified with high sensitivity by contrast-enhanced CT imaging, and that it is also useful for the differential diagnosis.[17] Diagnosing local invasion depth is important for deciding on an operative procedure and for prognosis prediction. The diagnostic accuracy of invasion depth diagnosis (T-stage classification) using CT has been reported to be between 71% and 93%, indicating relatively high diagnostic performance.[18-21] On contrast-enhanced MRI, delayed enhancement of the base of a protruding gallbladder cancer lesion (subserosal enhancement) has been reported to be an indicator of subserosal invasion (T2).[22] However, for intramural lesions of stage T2 or lower, EUS, which can visualize the layered structure of the gallbladder wall, is the best modality.[9, 12, 23] For lesions of stage T3 or higher that invade beyond the serosa, as in the case of direct liver invasion, CT is superior even to EUS, which has a limited scope of observation. Sensitivity of 80% to 100% and specificity of 81% to 95% have been reported with CT.[9-12, 18, 24] In addition, the diagnostic performance of MRI is nearly equal to that of CT, the sensitivity and specificity of MRI being 67% to 100% and 86% to 100%, respectively.[9, 13-15]

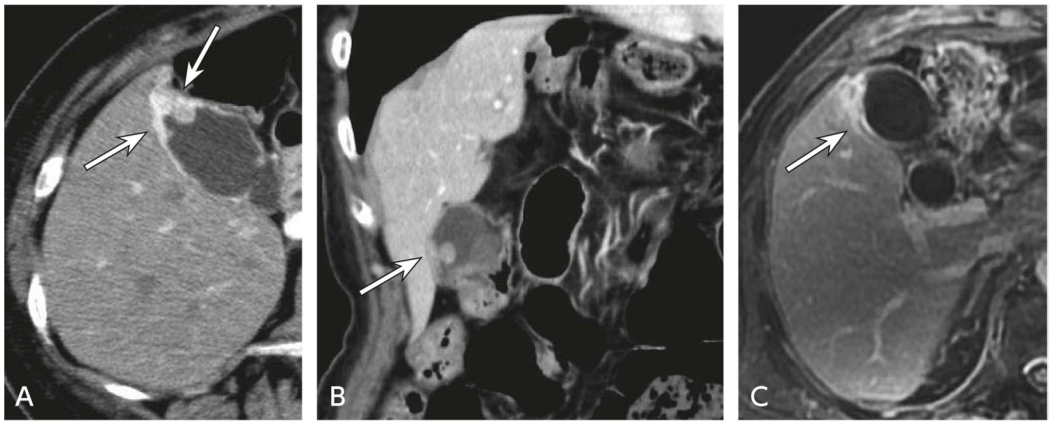

Figure 1. Gallbladder cancer, T2

A: CT, arterial phase; B: CT, portal venous phase, MPR, coronal image; C: EOB-MRI, portal venous phase
An irregularly shaped protruding lesion with a broad base that is showing inhomogeneous enhancement is seen in at the base of the gallbladder. Enhancement of the wall around the base of the protruding lesion (subserosal enhancement, →) is seen on both CT and MRI, suggesting subserosal invasion (T2). In the MPR coronal image, the border with the liver is distinct, and liver invasion can be concluded to be absent.

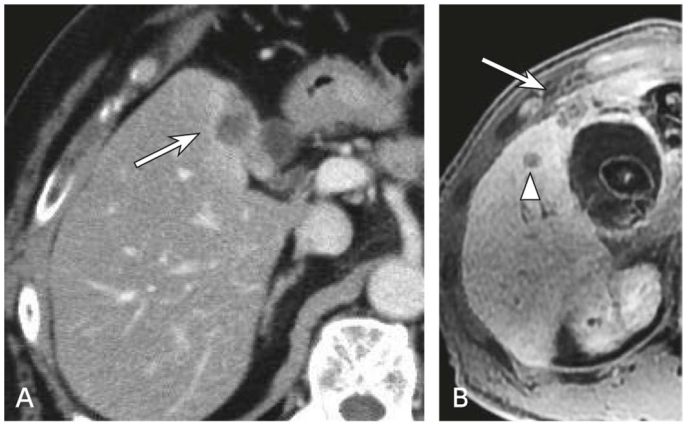

Figure 2. Gallbladder cancer, T3aM1 liver invasion

A: CT, portal venous phase; G: EOB-MRI, hepatobiliary phase, 20 min
An enhanced mass (→) is seen at the base of the gallbladder, mainly at the border, and is invading the liver. Similarly, a mass that is invading the liver is seen in the hepatobiliary phase of EOB-MRI, and hepatic metastasis (▷) showing low signal intensity is also seen nearby.

The sensitivity of MRI for lymph node metastasis has been reported to be 75%, slightly better than that of CT.[25] However, it is currently diagnosed based only on size (≥ 1 cm) and morphology (round), and diagnostic accuracy is therefore limited to < 80%.[26, 27]

To summarize, contrast-enhanced CT enables multiplanar reconstruction images to be evaluated, is excellent for gallbladder cancer staging, and is also used for vascular mapping. It is therefore the core test for determining a treatment strategy, including aspects such as an operative procedure, and its use is recommended. Additional information that differs from that obtained with CT can be obtained with MRI. MRI is useful for evaluating the biliary tract using MRI/MRCP and liver metastasis using EOB-MRI, and diffusion-weighted imaging aids in distinguishing benign from malignant lesions. On the other hand, for

intramural lesions (≤ T2) in early-stage gallbladder cancer, contrast-enhanced CT and MRI, whose ability to visualize the layered structure of the wall is limited, are lacking in usefulness. A test that provides high local resolution, such as EUS, is better for diagnosing such lesions. The diagnostic performance of contrast-enhanced CT in evaluating gallbladder cancer is also expected to improve in the future, and continued verification is needed.

Search keywords and secondary sources

PubMed was searched using the following keywords: gallbladder cancer, gallbladder carcinoma, gallbladder malignant, CT, and MRI. The appropriate articles from among the 304 relevant articles identified were included in a hand search.

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FQ 7 Is contrast-enhanced CT recommended when extrahepatic bile duct cancer is suspected?

Statement

When extrahepatic bile duct cancer is suspected, contrast-enhanced CT is recommended for diagnosis and to evaluate local progression, although the evidence supporting its use to differentiate from cholangitis and evaluate metastasis is inadequate.

Background

When bile duct stenosis is suspected, consideration is given to malignancies, typified by bile duct cancer, and to benign stenosis such as cholangitis and traumatic and postoperative stenosis. However, distinguishing between them is not necessarily easy and currently often relies on cytology. When bile duct cancer is diagnosed, it is clinically important to evaluate whether surgery is indicated. CT is the most frequently used diagnostic imaging modality, and these guidelines show the diagnostic performance of contrast-enhanced CT in diagnosing extrahepatic bile duct cancer and determining operability. In addition, they consider a recommendation grade when comparing contrast-enhanced CT with other imaging modalities such as MRI.

Explanation

Distinguishing benign from malignant bile duct stenosis is not necessarily easy. It is often a struggle to differentiate bile duct cancer from benign stenosis such as traumatic and postoperative stenoses, particularly forms of cholangitis such as primary sclerosing cholangitis and IgG4-related sclerosing cholangitis.[1-3] For bile duct stenosis localized to the hilar or distal bile duct, distinguishing IgG4-related sclerosing cholangitis from bile duct cancer is often clinically problematic.[4] However, there have been few reports on the use of contrast-enhanced CT/MRI in differentiating these conditions. In diagnosing bile duct cancer based on imaging, the detection of tumors, lymph node metastasis, vascular invasion, and remote metastasis is instructive.[5-7] However, it has been reported that when these findings are lacking, tapered, funnel-shaped stenosis of the bile duct is suggestive of IgG4-related sclerosing cholangitis, and abrupt stenosis of the bile duct is suggestive of bile duct cancer (Figs. 1 and 2).[8, 9] However, there is no established view on differentiation between these conditions for imaging findings related to the thickness and contrast enhancement of the bile duct wall.[8-11] The examination above indicates that there is currently little evidence regarding differentiation between bile duct cancer and benign bile duct stenosis based on contrast-enhanced CT, and that further investigation is needed in this area.

On the other hand, MRCP is useful for visualizing the dilated bile duct upstream from a stenosis and is particularly good for visualizing the extent of stenosis and multiple bile duct stenoses.[12, 13] Diagnostic accuracy of ≥ 90% has been reported with MRCP alone in diagnosing primary sclerosing cholangitis,

which is characterized by multifocal bile duct stenoses.[13, 14] However, the diagnostic performance of MRCP alone for the differential diagnosis of bile duct obstruction is not currently considered adequate. Moreover, diffusion-weighted imaging or dynamic study with three-dimensional fat-suppressed T1-weighted imaging has been reported to contribute to the detection and staging of bile duct cancer.[15] However, further investigation is needed regarding the use of MRI to distinguish malignant from benign lesions.

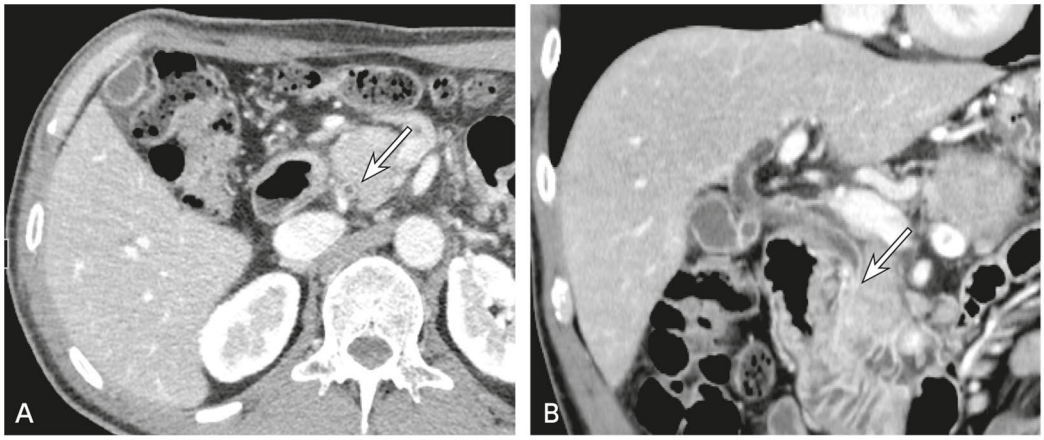

Figure 1. IgG4-related sclerosing cholangitis

A: Contrast-enhanced CT, transverse image: Thickening of the full circumference of the bile duct wall is seen with contrast enhancement (→).

B: Contrast-enhanced CT, coronal image: Funnel-shaped, tapered stenosis is seen from the upper to the lower part of the bile duct (→).

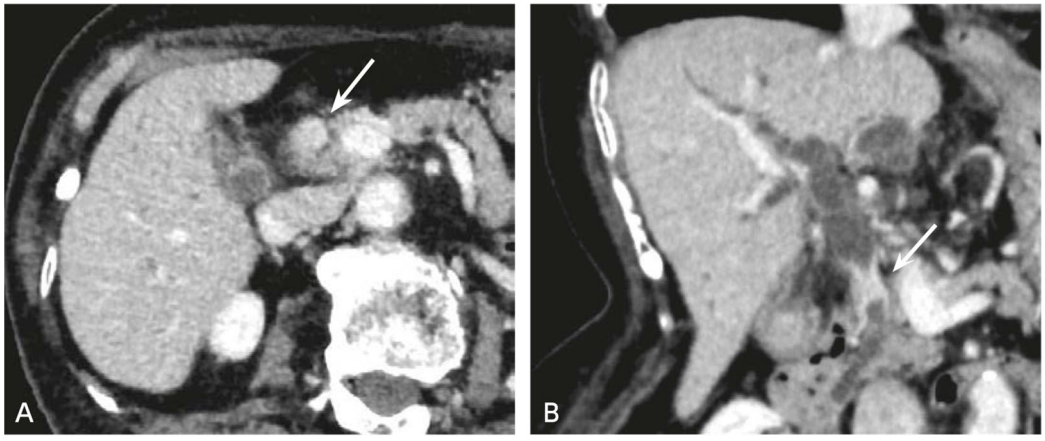

Figure 2. Distal bile duct cancer

A: Contrast-enhanced CT, transverse image: Obstruction and thickening of the full circumference of the bile duct wall are seen with contrast enhancement (→).

B: Contrast-enhanced CT, MPR, coronal image: Abrupt stenosis of the middle and lower bile duct and dilatation of the upstream bile duct are seen (→).

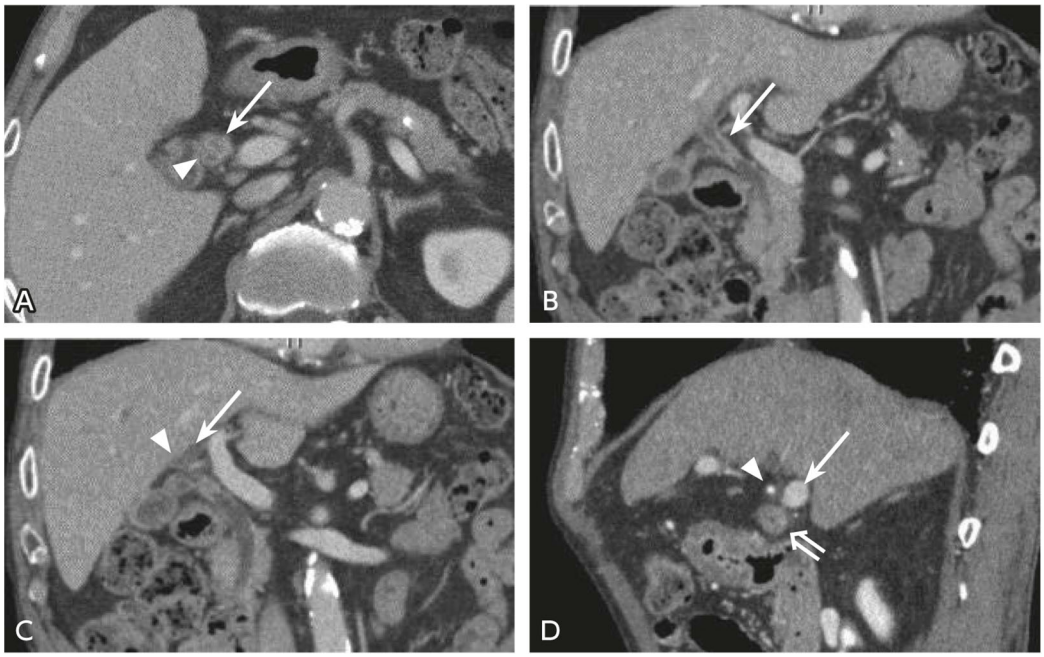

Figure 3. Hilar cholangiocarcinoma

A: Contrast-enhanced CT, transverse image: Wall thickening and enhancement are seen in the common hepatic duct (→) and cystic duct (▷).

B: Contrast-enhanced CT, MPR, coronal image: Wall thickening and enhancement of the common hepatic duct (→) extend caudally, but there are no findings in the downstream portion of the bile duct.

C: Contrast-enhanced CT, MPR, coronal image, 7 ventral slices of B: Neither wall thickening nor enhancement is seen in the left hepatic duct (→) or right hepatic duct (▷).

D: Contrast-enhanced CT, MPR, sagittal image: The wall thickening and enhancement of the common hepatic duct (⇒) are seen to be separated from the right hepatic artery (▷) and portal vein (→).

Contrast-enhanced CT is suitable for obtaining general anatomical information, and it enables the sites of bile duct cancer and the extent of progression into the surrounding areas to be evaluated.[16, 17] Factors considered in judging operability based on imaging include progression along the bile duct, invasion of the hepatic artery and portal vein, the presence or absence of lymph node metastasis, and the presence or absence of distant metastasis. A meta-analysis of these factors found diagnostic accuracy of 86% for progression along the bile duct as determined by contrast-enhanced CT (Fig. 3).[18] Sensitivity and specificity of 83% and 93%, respectively, have been reported for the presence or absence of hepatic artery invasion and 89% and 92%, respectively, for the presence or absence of portal vein invasion. Thus, high diagnostic performance has been found for both. For lymph node invasion, however, specificity was maintained at 88%, but sensitivity decreased to 61%. A meta-analysis by Zhang et al. found that evaluations of operability that took into account the presence or absence of distant metastasis provided sensitivity of 95%, whereas specificity decreased to 69%.[19] The findings suggest that problems remain with the evaluation of microscopic distant metastases, including lymph node invasion and liver metastases. Although MRI/MRCP is considered an alternative to contrast-enhanced CT as a diagnostic imaging method, the meta-analysis by Zhang et al. found that, in evaluations of operability, the sensitivity and specificity of

MRI/MRCP were 94% and 71%, respectively, indicating diagnostic performance equal to that of contrast-enhanced CT.[19] However, there have been few reports on this subject, and investigations that have made comparisons in the same subjects are limited in number.[20, 21] A candidate diagnostic imaging method for supplementing evaluations of lymph node invasion and distant metastasis performed using contrast-enhanced CT is FDG-PET. The sensitivity of FDG-PET for lymph node invasion and distant metastasis (75.9% and 88.3%, respectively) has been reported to be significantly higher than that of contrast-enhanced CT (60.9% and 78.7%, respectively).[20] Consequently, although contrast-enhanced CT shows good diagnostic performance for local progression, its diagnostic performance in evaluating metastasis is limited. The diagnostic performance of contrast-enhanced CT in extrahepatic bile duct cancer is expected to improve with further technological innovation, and continual verification will be required in the future.

Search keywords and secondary sources

PubMed was searched using the following keywords: contrast-enhanced, CT, MRI, MRCP, extrahepatic cholangiocarcinoma, sensitivity, specificity, accuracy, ROC, cholangitis, and human. The period searched was from January 1989 to August 2020, and 519 articles were extracted in the primary screening. After an additional hand search was performed, the 21 articles extracted were examined in the secondary screening.

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BQ 48 Is MRI recommended for diagnosing acute pancreatitis and evaluating its severity?

Statement

MRI is recommended for diagnosing bile duct stones that cause pancreatitis and pancreatic necrosis associated with hemorrhage. It is recommended as an alternative to CT in patients with iodine allergy or renal dysfunction.

Background

In response to the 2012 revision of the Atlanta classification, which reflected the international consensus on acute pancreatitis, the 2015 Guidelines for the Diagnosis and Treatment of Acute Pancreatitis, 4th Edition were published in Japan in 2015 (secondary source 1). The guidelines essentially establish 4 categories of local complications of pancreatitis encompassing the presence or absence of necrosis and a time axis divided at 4 weeks after onset. Detailed references to treatments (particularly endoscopic therapy, interventional radiology, and minimally invasive surgical therapy) are then provided for the categories. In addition to diagnosing acute pancreatitis early, it is important to diagnose its severity early, diagnose the changes in severity over time, and provide interventional treatment early in patients with severe disease. Diagnostic imaging plays a major role in local evaluation of the pancreas and in evaluating systemic complications that arise.

Explanation

MRI is useful for screening for causes of pancreatitis,[1)] diagnosing the nature of fluid accumulations, and selecting treatment.[2, 3)] Serosanguineous fluid accumulations show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The necrotic component of fluid accumulations containing mixed necrotic material shows high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. However, because the necrotic component undergoes liquefaction over time, a mixture of low and high signal intensities may become pronounced on T2-weighted images. Moreover, in interstitial edematous pancreatitis, the pancreatic parenchyma shows high signal intensity on T2-weighted images, which is particularly useful for diagnosing pancreatitis in patients with mild pancreatic enlargement. Another advantage of MRI over CT is that MRI does not involve radiation exposure. MRI is contraindicated in patients fitted with devices such as non-compatible pacemakers.

The normal pancreas shows higher signal intensity than the liver on T1-weighted images and near isointensity with the liver on fat-suppressed T2-weighted images, reflecting the high protein content of the acinar cells. In acute edematous pancreatitis, for example, only pancreatic enlargement can be diagnosed by CT; the presence or absence of inflammation (edema) cannot be evaluated. Acute edematous pancreatitis shows low signal intensity on T1-weighted images and high signal intensity on fat-suppressed T2-weighted

images in proportion to the severity of edema, which can shed light on the fact that inflammatory edema has actually occurred in an enlarged pancreas.[4-6] Diagnostic performance is also comparable to that of CT in the diagnosis of peripancreatic fluid collection and thickening of the prerenal fascia.[4, 6]

Although differentiating peripancreatic fat necrosis and fluid collection can pose difficulties with CT, fat necrosis and fluid are clearly distinguishable based on signal intensity with MRI (higher signal intensity for fat necrosis than fluid on T1-weighted images and slightly lower signal intensity for fat necrosis than fluid on T2-weighted images).[4, 6-9] Although hemorrhagic fat necrosis is frequently seen in severe acute pancreatitis, differentiating fat necrosis from simple effusion accumulation is often difficult based solely on CT density. Because fat necrosis of the retroperitoneal space or transverse mesocolon is often associated with hemorrhage, it shows high signal intensity (low signal intensity for effusion) on fat-suppressed T1-weighted images and can therefore be easily diagnosed. Areas of pancreatic necrosis can be visualized as regions of poor contrast enhancement by contrast-enhanced MRI.[8-11] and are often associated with hemorrhage in pancreatic pseudocysts. In the acute phase of hemorrhage, they show hyperdensity on non-contrast CT, enabling diagnosis. However, intracystic hemorrhage changes to hypodensity over time, making the diagnosis of hemorrhage difficult with CT. With MRI, subacute phase hemorrhage, which occurs after at least 1 week, shows high signal intensity on both T1-weighted and T2-weighted images, making diagnosis easy.[12]

MRCP provides high visualizability of gallstones and choledocholithiasis, regardless of the presence or absence of calcification. It should therefore be used aggressively when bile duct stones are not clearly visualized with ultrasound or CT.[13-15] Small gallstones and common bile duct stones can be overlooked when MRCP with MIP alone is used. Consequently, the presence or absence of stones always needs to be determined by consulting the original MRCP images or thin-section T2-weighted images acquired from multiple directions.

Although bile duct stones generally show low signal intensity on T2-weighted images and a variety of signal intensities on T1-weighted images, high signal intensity on T1-weighted images is particularly common in the case of bilirubin stones, which are frequently intrahepatic stones and common bile duct stones. An advantage of MRCP is that, in addition to enabling the diagnosis of stones, it can easily show the overall appearance of the bile and pancreatic ducts.[14, 15] MRCP can also diagnose congenital anomalies that can cause pancreatitis, such as choledochal cysts, pancreaticobiliary maljunction, and pancreas divisum, even without performing ERCP.[16, 17]

Search keywords and secondary sources

PubMed was searched using the following keywords: acute pancreatitis, MRI, and magnetic resonance imaging. The period searched was through June 2019; hits were obtained for 135 articles. An additional hand search was also performed.

In addition, the following were referenced as secondary sources.

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BQ 49 Is CT recommended for diagnosing chronic pancreatitis?

Statement

CT is useful for diagnosing chronic pancreatitis. To diagnose early chronic pancreatitis, however, careful examination using a modality such as EUS is considered necessary.

Background

In Japan, the Clinical Diagnostic Criteria for chronic pancreatitis have been used in diagnosing chronic pancreatitis. The 2009 revision of the diagnostic criteria, the 2009 chronic pancreatitis Clinical Diagnostic Criteria, incorporated the concept of early chronic pancreatitis (secondary source 1). The revised diagnostic criteria are also referenced in examining the usefulness of CT in diagnosing chronic pancreatitis.

Explanation

Chronic pancreatitis is defined as a pathophysiology in which chronic changes such as irregular fibrosis, cellular infiltration, loss of parenchyma, and tissue granulation occur within the pancreas and, if they progress, are associated with decreased pancreatic exocrine and endocrine secretion. Often irreversible, it is classified as alcoholic or nonalcoholic, depending on the cause. Because they are reversible, autoimmune pancreatitis (AIP) and obstructive pancreatitis are currently handled as separate types of chronic inflammation of the pancreas.

Reports from other countries on the diagnosis of chronic pancreatitis that examined chronic pancreatitis diagnostic rates with CT reported sensitivity ranging from 74% to 91% and specificity ranging from 78% to 98%.[1-3] Examination by parameter showed sensitivity and specificity of 53% and 94%, respectively, for diffuse calcification of the pancreas and 43% and 88%, respectively, for pancreatolithiasis. Thus, the findings for specificity were high.[4] CT is therefore considered useful for diagnosis (Fig.), and its usefulness in chronic pancreatitis is reflected in the 2015 Guidelines for the Diagnosis and Treatment of Chronic Pancreatitis, Revised 2nd Edition, the 2014 Guidelines for Endoscopic Treatment of Pancreatolithiasis, and the consensus on the diagnosis and treatment of local complications of pancreatitis (e.g. pancreatic pseudocysts and infected walled-off necrosis; secondary sources 2 to 4).

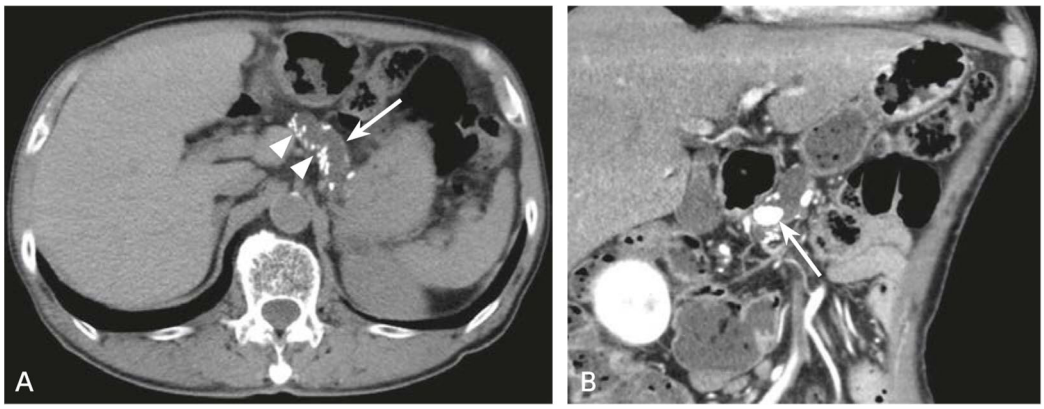

Figure　Chronic pancreatitis

A: Non-contrast CT, transverse image: Atrophy of the pancreatic parenchyma and dilatation of the main pancreatic duct are seen (→). Scattered calcification is present in the pancreatic parenchyma (▷).

B: Contrast-enhanced CT, arterial phase, oblique coronal image: Pancreatolithiasis is seen in the main pancreatic duct (→).

Table　Imaging findings for early chronic pancreatitis (quoted from secondary source 1)

a. Either a or b is seen.

a. At least 2 of the 7 EUS findings below are seen, including at least 1 of findings (1) to (4).

(1) Lobularity, honeycombing type

(2) Non-honeycombing lobularity

(3) Hyperechoic foci, non-shadowing

(4) Stranding

(5) Cysts

(6) Dilated side branches

(7) Hyperechoic MPD margin

b. Irregular dilatation is seen in 3 or more branch pancreatic ducts in ERCP images.

In addition, the concept of early chronic pancreatitis disease was incorporated into the 2009 chronic pancreatitis Clinical Diagnostic Criteria. In diagnosing early chronic pancreatitis, patients for whom a definitive or near-definitive diagnosis of chronic pancreatitis cannot be obtained and who have least 2 of the following 4 clinical findings are suspected of having chronic pancreatitis: repeated episodes of upper abdominal pain; abnormal blood or urine pancreatic enzyme levels; impaired pancreatic exocrine secretion; and sustained alcohol consumption of 80 g (pure ethanol equivalent) or more per day. For patients with suspected chronic pancreatitis, early (within 3 months) careful examination by EUS or ERCP is recommended, and those with the imaging findings shown in the table are diagnosed with early chronic pancreatitis. The Rosemont classification uses criteria based on EUS, and the CT finding of early chronic pancreatitis is not included in the diagnostic criteria of the current revision (secondary source 1). Reports from other countries have also indicated that CT, compared with EUS and ERCP, in early chronic pancreatitis is not sensitive[5, 6], and its diagnostic performance is not high[7, 8]. The 2009 chronic pancreatitis Clinical Diagnostic Criteria state that, because of the problem of procedural accidents, EUS is first performed for the diagnostic imaging of early chronic pancreatitis, and ERCP is then performed as needed

in symptomatic patients strongly suspected of having pancreatic lesions. Thus, careful examination with a procedure such as EUS is considered necessary for diagnostic imaging of early chronic pancreatitis.

Search keywords and secondary sources

PubMed was searched using the following keywords: chronic pancreatitis, diagnosis, computed tomography, sensitivity, and specificity. The Ichushi and Cochrane Library databases were searched using equivalent keywords. The period searched was from January 1990 to June 2019; hits were obtained for 209 articles. In addition, 2 articles were added with a hand search.

Furthermore, the following were referenced as secondary sources.

1) Research Committee for Intractable Pancreatic Diseases, Ministry of Health, Labour and Welfare, Ed.: 2009 Chronic Pancreatitis Clinical Diagnostic Criteria. Pancreas 24: 645-646, 2009.
2) Japanese Society of Gastroenterology, Ed.: 2015 Guidelines for the Diagnosis and Treatment of Chronic Pancreatitis, Revised 2nd Edition, Nankodo, 2015.
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BQ 50 Are CT and MRI recommended for diagnosing autoimmune pancreatitis (AIP)?

Statement

CT and MRI are recommended for detecting AIP lesions and screening for extra-pancreatic lesions. Keeping in mind that differentiating from other diseases, particularly pancreatic cancer, is difficult with CT or MRI alone in some patients, it is recommended that histological differentiation by a method such as biopsy under EUS guidance be performed to the extent possible.

Background

AIP is clinically and histologically classified into two subtypes, types 1 and 2; type 1 is overwhelmingly the most frequent type in Japan. Consequently, AIP refers to type 1 AIP below. AIP is known as a pancreatic manifestation of IgG4-related disease that involves systemic organs. Its characteristics include preferential occurrence in middle-aged and elderly men, high serum IgG4 levels, a variety of associated extra-pancreatic lesions, and responsiveness to steroid therapy. Particularly because AIP is responsive to steroid therapy, it is important that it be suspected and diagnosed appropriately.

Explanation

AIP is a systemic, IgG4-related disease that manifests as pancreatic lesions. Its diagnosis requires a comprehensive assessment of clinical, imaging, and pathology findings. Imaging studies in particular are important as the start of diagnosis of the disease, and they play a major role in detecting extra-pancreatic lesions (IgG4-related lesions). Because changes such as cell infiltration, fibrosis, and obliterative phlebitis occur in the affected area in AIP, imaging findings also reflect these changes. Well-known AIP imaging findings that have been reported are sausage-shaped pancreatic enlargement, a capsule-like rim, and diffuse narrowing of the pancreatic duct. The capsule-like rim in particular is a highly specific and important finding, even though it is seen infrequently. With dynamic CT, the affected area is visualized as hypodense compared with normal pancreatic parenchyma in the pancreatic parenchymal phase and shows gradually increasing enhancement through the venous phase.[1-3)] A capsule-like rim similarly consists mainly of fibrillary elements and, therefore, shows a similar gradually increasing enhancement pattern. With MRI, the parenchyma in the affected area shows low signal intensity on T1-weighted images, faint high signal intensity on T2-weighted images, and is associated with slightly decreased diffusion. In addition to changes in the pancreatic parenchyma, the appearance of the pancreatic duct is important for AIP diagnosis. Although the evaluation of pancreatic duct appearance has been limited to evaluation by endoscopic retrograde pancreatography (ERP) in diagnostic criteria in Japan, with advances in MRI systems, particularly the increased availability of 3T systems, the most recent diagnostic criteria (secondary source 1) have added MRCP findings (extensive pancreatic duct non-visualization/narrowing, narrowing “skip”

lesions) for the evaluation of pancreatic duct appearance. Consequently, the importance of MRI in AIP diagnosis is expected to increase further.

AIP is classified as the diffuse, segmental, and focal types according the extent of the affected pancreatic parenchyma. With the diffuse type, which shows lesions in nearly the entire pancreas, AIP can be strongly suspected based on previously reported CT and MRI imaging findings, and it can be diagnosed relatively easily by combining these findings with serum IgG4 levels. In patients with the segmental or focal type, however, it is important to distinguish it from other diseases, particularly pancreatic cancer. Because the treatment and prognosis of the two conditions are entirely different, careful attention must be paid to their differentiation. Their contrast enhancement patterns and MRI signals are similar, particularly with focal-type lesions, making it difficult to distinguish between them based on images. Imaging findings known to be useful for differentiation are the duct-penetrating sign, which indicates penetration through a mass by the pancreatic duct, and homogeneous contrast enhancement in the venous phase, which reflects the limited intralesional necrosis and degeneration in AIP. In addition to these findings, Sugiyama et al. found that intralesional speckled enhancement seen in a mass with dynamic MRI is useful for differentiation.[4-6] Enhancement along a pancreatic duct running through a mass lesion is also seen. In addition to these imaging findings, there are also reports regarding the usefulness of diffusion-weighted imaging.[7-9] All of the imaging findings reported have indicated its usefulness for distinguishing focal AIP from pancreatic cancer. However, the findings are not absolutely conclusive. Given the current situation, in addition to imaging findings, it is important to comprehensively evaluate serum IgG4 levels and the presence or absence of extra-pancreatic lesions. In patients for whom differentiation is difficult, histological differentiation should be performed by biopsy under EUS guidance. To repeat, keeping in mind the fact that AIP is a pancreatic manifestation of IgG4-related disease, it is necessary to be thoroughly familiar with at least the typical features of typical extra-pancreatic lesions (e.g., of the salivary glands, lacrimal glands, bile duct, pancreas, and aorta).[10-13] Contrast-enhanced CT, which permits an extensive area to be screened at one time, is useful for screening for systemic extra-pancreatic lesions, and screening for other organ involvement is required when AIP is suspected.

Search keywords and secondary sources

PubMed was searched using the following keywords: autoimmune pancreatitis, CT, and MRI. The period searched was through June 2019; hits were obtained for 313 articles. An additional hand search was also performed.

In addition, the following were referenced as secondary sources.

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CQ 14 Is contrast-enhanced MRI recommended for the differential diagnosis of pancreatic masses?

Recommendation

Contrast-enhanced MRI is weakly recommended for the differential diagnosis of pancreatic masses.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 100% (8/8)

Background

Pancreatic mass lesions encompass a wide variety of diseases, ranging from malignant tumorous lesions that require treatments such as surgery and chemotherapy, such as pancreatic cancer, neuroendocrine tumors, malignant lymphoma, and solid pseudopapillary neoplasms (SPNs), to diseases for which conservative treatment is selected, such as AIP and mass-forming pancreatitis. In view of the level of invasiveness of surgery for pancreatic disease, qualitative diagnosis by means of non-invasive imaging is important. Although evaluations using contrast-enhanced CT, MRI and EUS play a central role in the differential diagnosis of pancreatic mass lesions, articles showing the usefulness of MRI for evaluating pancreatic mass lesions have been sporadic as MRI imaging systems have improved in recent years. Contrast-enhanced MRI in particular, with its high contrast resolution, is excellent for evaluating the interior characteristics of masses and therefore shows good efficacy for the differential diagnosis of pancreatic masses. For these guidelines, a systematic review was conducted regarding the usefulness of contrast-enhanced MRI in the differential diagnosis of pancreatic mass lesions.

Explanation

This review specified as outcomes the qualitative diagnosis of pancreatic mass lesions, allergic reactions that occur with contrast medium administration, nephropathy associated with contrast medium administration, and test duration, and it identified reference articles using the search criteria indicated below.

In addition to T1-weighted and T2-weighted non-contrast-enhanced MRI, evaluation by diffusion-weighted imaging and MRCP has become feasible in recent years. However, the searches performed for the current review did not yield any articles on a direct comparison of diagnostic performance with non-contrast-enhanced and contrast-enhanced MRI. Moreover, there were no relevant articles on allergic reactions that occur with contrast medium administration, nephropathy associated with contrast medium administration, or test duration within the scope of the search.

An investigation comparing the diagnostic performance of CT and MRI in AIP and pancreatic cancer found that AUC and sensitivity with MRI were both equal to or greater than with CT.[1)] MRI was superior with respect to the visualization of masses and main pancreatic duct stenosis and the detection of homogeneous delayed enhancement in AIP and the visualization of masses and main pancreatic duct

stenosis in pancreatic cancer. Although CT and MRI findings have both been reported to be useful in differentiating from pancreatic cancer, neither modality has been clearly shown to be superior, and findings such as serum IgG4 levels and extra-pancreatic lesions currently need to be comprehensively evaluated.

The 2017 international diagnostic guidelines for intraductal papillary mucinous neoplasms (IPMNs, secondary source 1) recommend resection when CT or MRI findings show high-risk stigmata and thorough examination by EUS and consideration of surgery or follow-up when worrisome features are present. Investigations that compared CT and MRI in evaluating the malignancy grade of IPMNs found CT and MRI to be comparable in detecting findings indicative of malignancy risk, such a high-risk stigmata and worrisome features.[2, 3] However, they found MRI to be useful in detecting enhancement of a thickened cyst wall, which is considered a worrisome feature.[3]

An investigation that compared CT and MRI in the differential diagnosis of solid pancreatic masses ≤ 3 cm in size (127 patients with pancreatic ductal carcinoma, 43 with neuroendocrine tumors, 10 with SPNs, 7 with localized AIP, and 6 with metastatic pancreatic tumors) found that MRI was superior in sensitivity, but that CT and MRI performed comparably in qualitative diagnosis.[4]

An investigation that compared CT and MRI in diagnostic performance for the differential diagnosis of cystic pancreatic masses ≤ 3 cm in size (14 patients with branch-type IPMNs, 12 with mixed-type IPMNs, 6 with MCNs, and 6 with retention cysts or pseudocysts) found that MRI was superior in morphological evaluation, but CT and MRI performed comparably in qualitative diagnosis and in evaluating benign or malignant lesions.[5]

Caution is required regarding the fact that, although infrequent, problems such as anaphylactic shock can occur with the use of contrast media in contrast-enhanced MRI and nephrogenic systemic fibrosis (NSF) with the use of gadolinium contrast media in patients with severe nephropathy.

The findings described above indicate that contrast-enhanced MRI has a discrimination ability that is equal to or slightly better than that of CT for the differential diagnosis of pancreatic masses, and that its diagnostic performance in evaluating the malignancy grade of IPMNs is equal to that of CT and EUS.

Taking these considerations into account, when differentially diagnosing pancreatic masses in routine clinical practice, judgments should be made based on factors such as the radiation exposure and presence or absence of contrast medium allergy and nephropathy of the individual patient. In particular, caution should always be exercised regarding complications resulting from the use of contrast media. It is known that MRI, even with non-contrast-enhanced sequences, can provide useful information for evaluating the internal characteristics of pancreatic mass lesions and an overview of the pancreatic and bile ducts. Consequently, investigations comparing the diagnostic performance of contrast-enhanced and non-contrast-enhanced MRI are anticipated in the future.

Search keywords and secondary references

PubMed was searched using the following keywords: pancreas, pancreatic mass, magnetic resonance imaging, contrast-enhanced, and diagnosis. The period searched was through June 2019; hits were obtained for 234 articles. The primary screening yielded 21 candidate articles, and the full text of 14 of these articles was searched. As a result, 5 articles were used in the review.

In addition, the following was referenced as a secondary source.

1) Tanaka M et al: Revision of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 17: 738-753, 2017

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CQ 15 Is diffusion-weighted MRI recommended for diagnosing the benign or malignant nature of pancreatic tumors?

Recommendation

Diffusion-weighted MRI is weakly recommended because ADC values can assist in estimating the malignancy grade of P-NETs.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 100% (8/8)

Diffusion-weighted MRI is weakly recommended for IPMNs because examining ADC values and diffusion restriction can assist in diagnosing malignant IPMNs.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 100% (8/8)

Background

MRI plays an important role in diagnostic imaging of the abdomen. Because treatment strategies for pancreatic tumors differ greatly depending on whether they are benign or malignant, and the 5-year survival rate for pancreatic cancer is < 10%, accurately distinguishing between malignant pancreatic tumors, typified by pancreatic cancer, and benign tumors is extremely important. Consequently, this discussion focuses on diffusion-weighted MRI and examines whether diffusion-weighted images are useful in the differential diagnosis of benign and malignant pancreatic tumors.

Explanation

For this CQ, examination time (importance, 1 point) and test cost (importance, 3 points) were specified as harmful outcomes, and sensitivity and specificity in diagnosing benign or malignant pancreatic tumors (importance, 9 points) were established as beneficial outcomes. The literature search for this CQ yielded 8 articles that examined pancreatic neuroendocrine tumor (P-NET) grades and 7 articles that examined distinction between benign and malignant IPMNs.

Of the articles that examined P-NET grades, 2 were examined with 3T MRI,[1, 2] 5 were examined with 1.5T MRI,[3-7] and 1 was examined with 1.5T and 3T MRI scanners.[8] Of these 8 articles, 7 reported that ADC values are useful. These included reports showing higher ADC values for grade 1 (G1) tumors than for G2 or G3 tumors (Pereira et al.[5], De Robertis et al.[7], Toshima et al.[8]), a report showing lower ADC values for G3 tumors than for G1 or G2 tumors (Kulali et al.[3]), a report showing significant differences between the ADC values for G1, G2, and G3 tumors (Lotfalizadeh et al.[4]), a report showing a correlation between the ADC value and WHO tumor grade (Kim et al.[1]), and a report showing a significant difference between the ADC values for G1 and G2 tumors (Kim et al.[6]). One of the 8 articles reported finding no significant differences between ADC values, and an article by Hwang et al. reported seeing no significant differences between the ADC values for G1 tumors and those for G2 and G3 tumors.[2] Based on these

findings, the use of ADC values appears to assist in estimating the malignancy grade of P-NETs, and diffusion-weighted MRI is therefore weakly recommended.

Of the articles that examined differentiation between benign and malignant IPMNs, 3 were examined with 3T MRI,[9-11] 3 were examined with 1.5T MRI,[12-14] and 1 was examined with 1.5T and 3T MRI scanners.[15] Six of these 7 articles mentioned ADC values, 4 of which reported significant differences between the ADC values for benign and malignant tumors,[11-14], 2 of the 6 reported finding no significant differences.[9, 15] Four of the 7 articles mentioned diffusion restriction. An article by Kim et al. reported that multivariate analysis showed diffusion restriction to be the only independent imaging parameter that predicted the malignancy of IPMNs.[9] An article by Jang et al. reported that diffusion restriction was seen at a high frequency in the malignant group on visual assessments.[10] Articles by Kang and Ogawa et al. reported finding significantly higher rates of diffusion restriction in malignant IPMNs than in benign IPMNs.[11, 13] Based on these findings, diffusion-weighted MRI is weakly recommended for IPMNs, because examining ADC values and diffusion restriction in areas where tumors are present can assist in diagnosing malignant IPMNs.

Based on the foregoing, diffusion-weighted MRI is weakly recommended for P-NET grading because the use of ADC values can assist in estimating the malignancy grade of P-NETs. In addition, diffusion-weighted MRI is weakly recommended for IPMNs, because examining ADC values and diffusion restriction in areas where tumors are present can assist in diagnosing malignant IPMNs.

Variability in ADC values is seen depending on the type of equipment and facility. Consequently, the use of ADC values in qualitative diagnosis requires an understanding of the reliability and limitations of diffusion coefficients,[16] and this should be considered when the ADC value is used to diagnose benign and malignant tumors.

Although this is only a point for reference, there are discrepancies in the literature regarding differences in ADC values between pancreatic cancer and P-NETs. Whereas Li and Shindo et al. reported significantly lower ADC values in pancreatic cancer than in P-NETs,[17, 18] Guo and De Robertis et al. reported significantly lower ADC values in P-NETs.[19, 20] Wagner et al. reported that ADC values change with the proportions of fibrosis, necrosis, and cell density within the tumors,[21] indicating that the structural components of the cells of pancreatic tumors may affect the changes in ADC values. Consequently, room for debate remains regarding the use of ADC values to distinguish pancreatic cancer from P-NETs.

Search keywords and secondary references

PubMed was searched using the following keywords: pancreatic tumor, diffusion-weighted imaging, magnetic resonance imaging, pancreas, and diagnosis. The Ichushi and Cochrane Library databases were searched using equivalent keywords. The period searched was from January 1990 to June 2019; hits were obtained for 240 articles. In addition, 2 articles were added with a hand search. In the primary screening, 37 articles were extracted, and those whose content was judged unsuitable in the secondary screening were excluded. Ultimately, a qualitative systematic review was conducted using 15 articles.

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BQ 51 Is abdominal MRI recommended to detect pancreatic cancer?

Statement

Abdominal MRI and CT are equally useful for detecting pancreatic cancer.

Background

The usefulness of contrast-enhanced MDCT using dynamic imaging to detect pancreatic cancer has been established.[1, 2)] MRI also provides high detection performance of pancreatic cancer, and it is described in detail here.

Explanation

In many patients, pancreatic cancer is already unresectable when it is diagnosed, and this is the main reason for its poor prognosis. When pancreatic cancer is suspected and in high-risk groups, accurate detection or exclusion by diagnostic imaging is desirable.

Among reports from other countries on diagnostic performance in pancreatic cancer,[1-7)] a meta-analysis by Toft et al., considered to be the most reliable (literature search for period from January 2004 to June 2015) that carefully selected 52 original articles (total of 3,567 pancreatic cancer patients), examined the diagnostic performance of MRI and found sensitivity of 93% (95% CI, 88% to 96%), specificity of 89% (95% CI, 82% to 94%), and diagnostic accuracy of 90% (95% CI, 86% to 94%).[1)] With CT, sensitivity was 90% (95% CI, 87% to 93%), specificity was 87% (95% CI, 79% to 93%), and diagnostic accuracy was 89% (95% CI, 85% to 93%), comparable to the values seen for MRI. The report indicated that the diagnostic performance of endoscopic ultrasonography and extracorporeal ultrasonography was also comparable to that of MRI. However, the specificity of PET/CT was a low 70% (95% CI, 54% to 84%), and its diagnostic accuracy was 84% (95% CI, 79% to 89%). It was therefore concluded that PET/CT is inferior to the other imaging modalities.

The most prominent feature of MRI is that it allows for more special imaging techniques than CT. One such technique is diffusion-weighted imaging, which many reports indicated was useful for detecting pancreatic cancer. Takakura et al. reported that an imaging technique that added diffusion-weighted imaging to MRCP resulted in a diagnostic accuracy rate that was comparable to that of 2-phase contrast-enhanced MDCT (MRI, 84%; contrast-enhanced MDCT, 86%), even when not used in combination with contrast-enhanced MRI.[8)] In addition, Park et al. reported that, with the addition of diffusion-weighted imaging to conventional MRI (including gadolinium contrast-enhanced imaging) for small pancreatic cancers ≤ 3 cm in size, the detection sensitivity of two readers (reader 1: 75% to 98%, reader 2: 76% to 96%) improved significantly compared with the normal imaging method.[6)] Moreover, MRCP alone was found to provide high sensitivity and specificity of 84% and 97%, respectively, in

detecting pancreatic cancer, with no significant difference seen compared with the detection performance of ERCP (sensitivity, 70%; specificity, 94%).[7)]

Based on these findings, abdominal MRI is recommended for detecting pancreatic cancer. However, its detection performance is comparable to that of contrast-enhanced MDCT, and the selection of MRI should therefore be considered by taking into account the patient's background and the facility's diagnostic imaging equipment.

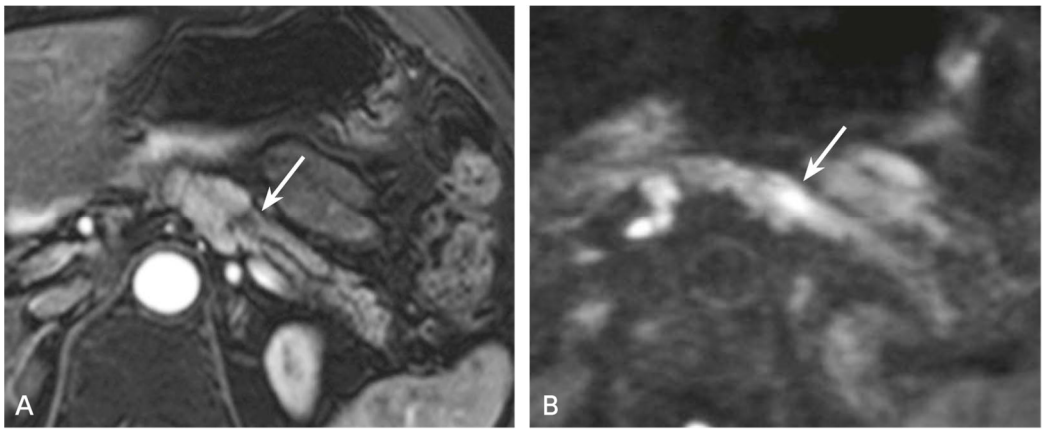

Figure　Pancreatic body cancer

A: Contrast-enhanced MRI, arterial-dominant phase: An area of poor contrast enhancement approximately 1 cm in size (→) is seen in the pancreatic body, along with dilatation of the upstream main pancreatic duct and atrophy of the pancreatic parenchyma. The same lesion showed gradually increasing contrast enhancement with dynamic imaging (not shown).
B: MRI, diffusion-weighted image, b-value = 1,000 s/mm^2: A nodular lesion that appears as a region of high signal intensity (→) is seen in the pancreatic body, consistent with the lesion site indicated by dynamic contrast-enhanced imaging. The finding supports a diagnosis of pancreatic body cancer.

Search keywords and secondary references

PubMed was searched using the following keywords: pancreatic carcinoma, diagnosis, MRI, sensitivity, and specificity. The period searched was from January 1990 to June 2019; hits were obtained for 84 articles. In addition, 5 articles were added with a hand search.

The following were also referenced as secondary sources.

1) Clinical Practice Guidelines for Pancreatic Cancer 2019

References

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BQ 52 Is abdominal MRI recommended to determine pancreatic cancer progression?

Statement

Abdominal MRI is comparably useful to CT for comprehensively determining the progression of pancreatic cancer. However, EOB-MRI is superior for diagnosing hepatic metastasis.

Background

The 2016 diagnostic imaging guidelines strongly recommended MDCT using dynamic imaging to evaluate pancreatic cancer progression. Many reports have indicated that MRI is also useful for determining pancreatic cancer progression, and that is described in detail here.

Explanation

A meta-analysis by Li et al. regarding the detection of vascular invasion to determine pancreatic cancer progression found that the sensitivity and specificity of abdominal MRI were 63% (95% CI, 48% to 77%) and 93% (95% CI, 86% to 98%), respectively.[1)] By comparison, sensitivity and specificity were 73% (95% CI, 67% to 79%) and 95% (95% CI, 93% to 97%), respectively, for CT and 66% (95% CI, 85% to 97%) and 95% (95% CI, 93% to 97%), respectively, for EUS. Thus, CT was found to be superior in terms of sensitivity for vascular invasion. Evaluation by adding multiplanar reconstruction to dynamic MDCT imaging has reported it to be superior to MRI, including contrast-enhanced MRI and MRCP, for determining local progression.[2)] On the other hand, a meta-analysis of vascular invasion assessment by Zhang et al. found no significant differences between MRI and CT. Sensitivity and specificity were 67% (95% CI, 59% to 74%) and 94% (95% CI, 91% to 96%), respectively, for MRI and 71% (95% CI, 64% to 78%) and 92% (95% CI, 89% to 96%), respectively, for CT.[3)] Based on an assessment within the analysis, the report included an additional statement indicating that evaluation by MRA did not contribute to additional information on vascular invasion.

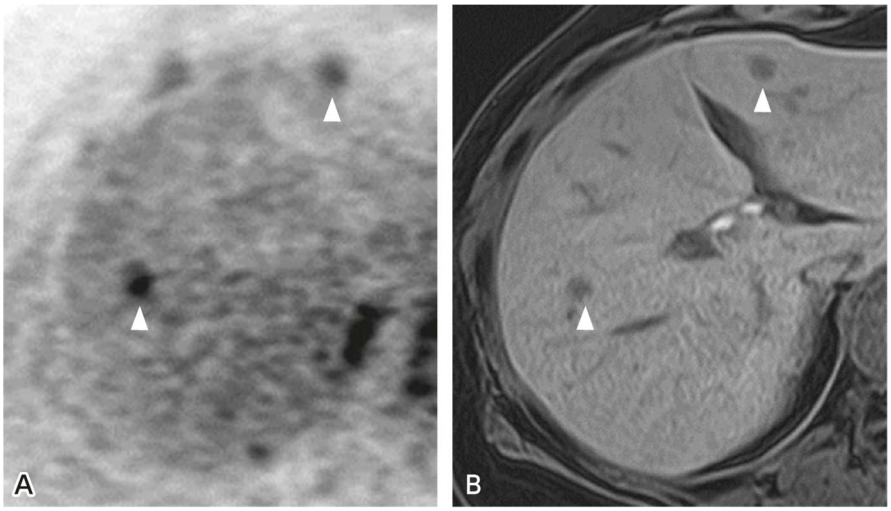

Figure　Multiple hepatic metastases of pancreatic cancer

A: MRI, diffusion-weighted imaging, b-value = 1,000 s/mm^2, reverse contrast image: The presence of high-signal-intense nodules ≤ 1 cm in size (▷) is seen in both liver lobes, suggesting multiple hepatic metastases.
B: EOB-MRI, hepatobiliary phase: Low-signal-intense areas (▷) are seen in the hepatobiliary phase of contrast enhancement, consistent with the high-signal-intense nodules seen with diffusion-weighted imaging. The finding supports a diagnosis of multiple hepatic metastases.

There have been many studies that have evaluated the usefulness of MRI in determining not only local progression, but also the resectability of pancreatic cancer.[4-6)] Park et al. compared dynamic contrast-enhanced MRI and MRCP with contrast-enhanced MDCT by specifying the following as criteria for unresectability and found that the two modalities were comparable with respect to diagnostic performance in determining resectability: (1) distant metastasis (liver, peritoneum, abdominal paraaortic lymph nodes); (2) peripancreatic vascular invasion (celiac artery, hepatic artery, superior mesenteric artery); (3) advanced portal vein/superior mesenteric artery invasion; and (4) invasion of surrounding organs (stomach, spleen, colon).[4)] Koelblinger et al. obtained similar results for evaluation by 3T MRI and 64-row MDCT (both dynamic imaging).[5)]

In recent years, the liver-specific MRI contrast medium Gd-EOB-DTPA has received attention for its use in evaluating hepatic metastasis (Fig.).[7, 8)] In addition to having the features of conventional extracellular gadolinium contrast media, it can be used to evaluate the liver parenchyma in the hepatobiliary phase (usually approximately 20 minutes after contrast medium injection) because it is taken up by normal hepatocytes. Motsugi et al. found no difference between EOB-MRI and dynamic contrast-enhanced MDCT with respect to the detection performance of pancreatic cancer, but they reported better sensitivity for hepatic metastases with contrast-enhanced MRI than with contrast-enhanced MDCT.[7)] In addition, a meta-analysis by Vreugdenburg et al. found that the sensitivity of EOB-MRI for small metastatic lesions (< 1 cm in diameter) was 2.21-fold greater than that of CT, a significant difference.[8)] However, specificity was roughly comparable, that of EOB-MRI being 0.92-fold that of CT. There have also been occasional reports that diffusion-weighted MRI is useful in evaluating pancreatic cancer hepatic metastasis.[9)]

These findings indicate that the usefulness of MRI in determining pancreatic cancer progression is comparable to that of MDCT. Abdominal MRI is therefore recommended to determine pancreatic cancer progression. However, its use in combination with MDCT and decisions on when to use one or the other depend on the circumstances of the facility.

Search keywords and secondary references

PubMed was searched using the following keywords: pancreatic cancer, staging, MRI, sensitivity, and specificity. The period searched was from January 1990 to June 2019; hits were obtained for 148 articles. Another 4 articles were added with a hand search.

In addition, the following was referenced as a secondary source.

1) Clinical Practice Guidelines for Pancreatic Cancer 2019

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BQ 53 Are CT and MRI recommended to determine the malignancy grade of P-NETs?

Statement

Contrast-enhanced CT and MRI are useful for evaluating the malignancy grade of P-NETs.

Contrast-enhanced CT and MRI are tests that are widely used to locally diagnose P-NET and screen for hepatic metastasis, and it is recommended that malignancy grade be determined at the same time.

Background

In recent years, the frequency of P-NET detection, particularly the detection of small nonfunctional tumors, has increased with improvements in diagnostic imaging, such as CT and MRI, and the increased availability of histological diagnosis by means such as endoscopic ultrasound-guided aspiration.[1)] The sensitivity of dynamic contrast-enhanced CT and MRI in detecting P-NETs is high, at 82% (95% CI, 67% to 96%) and 79% (95% CI, 54% to 100%), respectively,[2)] and the Guidelines for the Diagnosis and Treatment of Pancreatic and Gastroenteropancreatic Neuroendocrine Neoplasms (NENs), 2nd Edition treat them as tests of recommendation grade A that are useful for locally diagnosing functional and nonfunctional lesions and screening for their metastasis (secondary source 1).

Although neuroendocrine neoplasms are treated as malignancies, their malignancy grades vary widely, from those with a clinical course and prognosis that resemble those of benign neoplasms to highly malignant neoplasms that progress weekly or monthly. In the 4th edition of the 2010 WHO classification of tumors of the digestive system, neuroendocrine neoplasms are classified as grade 1 (G1) and grade 2 neuroendocrine tumors (NETs), which are well differentiated and have a low proliferative capacity, and neuroendocrine carcinomas (NECs), which are poorly differentiated and have a high proliferative capacity (secondary source 2). This classification is very highly correlated with prognosis.[3)] Many studies have examined the relationship between the WHO classification and imaging findings, and CT and MRI have been reported to be useful in evaluating the malignancy grade of P-NETs. This section will provide an overview of the P-NET imaging findings that have been reported to suggest malignancy.

Explanation

Many retrospective, cohort studies and case-control studies have been conducted, and multiple articles have reported that the results of the studies with large sample sizes indicate that the CT and MRI findings suggestive of lesions with high proliferative capacity include the following: (1) large in size; (2) irregular nature of tumor borders; (3) weak contrast enhancement in the arterial phase of dynamic CT (or MRI); (4) weak contrast enhancement in the portal venous phase of dynamic CT (or MRI); (5) inhomogeneous contrast enhancement; (6) vascular invasion present; (7) local invasion present; (8) pancreatic duct (upstream pancreatic duct dilatation) present; (9) mix of cystic or necrotic components present; (10) strong

diffusion restriction; (11) edema of surrounding lymph nodes present; and (12) hepatic metastasis present.[4-11] In addition, studies have also directly analyzed the relationship between imaging findings and prognosis (recurrence-free survival and progression-free survival rates and overall survival rates) and, similar to the findings described above, found that factors such as the following were associated with a poor clinical prognosis: large in size; irregular borders; contrast enhancement (hypovascular, inhomogeneous, gradually increasing); vascular invasion; bile and pancreatic duct dilatation; isointensity to hypointensity on T2-weighted images; lymph node edema; and hepatic metastasis.[5-7, 11-14] In other words, typical P-NETs are often small in size, round or cylindrical with a distinct border, and show marked and homogeneous enhancement in the arterial phase of dynamic CT (early arterial phase to pancreatic parenchymal phase).[15] Those that exhibit these typical findings are likely to be lesions that have a low proliferative capacity and a good prognosis. Conversely, lesions that show atypical imaging findings often pose problems for qualitative diagnosis, particularly differentiation from invasive pancreatic ductal carcinoma, and if they are NENs, they may be lesions with a high proliferative capacity with a poor prognosis.

When the WHO classification of digestive system tumors was revised in 2019, the malignancy grade classification of P-NENs was changed (secondary source 3). Specifically, the 5th edition of the WHO classification further divided NENs with a high proliferative capacity into 2 groups: G3 NETs, which are well-differentiated tumors in the NET category; and neuroendocrine carcinomas (NECs), which are poorly differentiated tumors not in the NET category. NECs and NETs are considered genetically and biologically different tumors, and their treatment strategies and prognoses are completely different. Distinguishing between them is therefore important. Somatostatin receptor scintigraphy is useful for distinguishing between NECs and NETs based on functional imaging. Although G3 NETs have a high proliferative capacity, it has been found that their function is often maintained and that they accumulate frequently, whereas NECs have been reported to accumulate relatively infrequently.[16]

Search keywords and secondary references

PubMed was searched using the following keywords: pancreatic, neuroendocrine, CT, and MRI. The period searched was through June 2019; hits were obtained for 1,222 articles. A hand search was also performed.

In addition, the following were referenced as secondary sources.

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BQ 54 Which imaging examinations are recommended when intestinal obstruction is suspected?

Statement

Plain radiography, ultrasound, and CT are recommended when intestinal obstruction is suspected. However, contrast-enhanced CT is useful for detailed evaluation.

Background

Intestinal obstruction is a condition of impaired intestinal transit caused by mechanical obstructions; ileus is a different condition caused by functional disorders. It is clinically important to diagnose the location, cause, and signs of intestinal ischemia of the intestinal obstruction at an early stage. The diagnosis of intestinal obstruction has been conventionally made based on plain radiography. Currently, ultrasound and CT are widely accepted as standard diagnostic tools. The following is an overview of the efficacy of these diagnostic modalities based on previous diagnostic imaging guidelines and additionally the 2015 clinical practice guidelines for acute abdomen (secondary source 1), supplemented by data from the latest literature, mainly reviews.

Explanation

Plain radiography, which is simple, low cost, and minimally invasive, but allows observation of the entire abdomen as a single test, has been used as a routine test in patients with acute abdomen. Its advantage includes evaluation of intestinal gas patterns associated with intestinal obstruction.[1)] However, pooled data from 4 articles including prospective studies showed that the sensitivity and specificity of plain radiography for intestinal obstruction were 65% and 75%, respectively.[2-5)] The diagnostic performance of ultrasound based on the pooled data from 4 articles showed that the sensitivity and specificity were 92% and 95%, respectively.[2, 3, 6, 7)] The diagnostic performance of CT based on the pooled data from 7 articles showed sensitivity and specificity of 94% (95% CI, 71% to 100%) and 78% (95% CI, 57% to 100%), respectively.[3, 4, 8-12)] According to a small prospective study by Suri et al. testing the diagnostic performance of plain radiography, ultrasound, and CT, CT showed the highest sensitivity (93%) and specificity (100%) in diagnosing intestinal obstruction. CT also showed the best result for identifying the cause of intestinal obstruction (87%), better than both ultrasound (23%) and plain radiography (7%).[3)]

It is important to promptly and accurately diagnose strangulated intestinal obstruction, which generally requires emergent surgery. Contrast-enhanced CT is useful for assessing changes in intestinal wall thickness, intestinal wall contrast enhancement, mesenteric congestion, and ascites. According to the systematic review by Millet et al., contrast enhancement of the intestinal wall and mesenteric fluid accumulation are significantly associated with intestinal ischemia.[13)] A meta-analysis of diagnosis of intestinal ischemia using contrast-enhanced (2-phase) CT showed sensitivity of 93.3% and specificity of

95.9%.[14] Non-contrast CT is desirable when considering a possible diagnosis of intestinal intramural hematomas showing hyperdensity, which may be misdiagnosed as normal intestinal wall enhancement on contrast-enhanced CT alone.[15] In the case of incomplete small bowel obstruction that may not show definite behavior on CT, administration of a water-soluble contrast medium to the small intestine is helpful.[16] It is also useful for evaluating emergent status requiring surgery for an adhesive small bowel obstruction.[17] In evaluating large bowel obstruction, CT is the first choice. However, in the case of large bowel obstruction caused by neoplastic obstruction, volvulus, and intussusception, a barium enema may be indicated. A water-soluble contrast medium should be used for the patient with possible perforation.

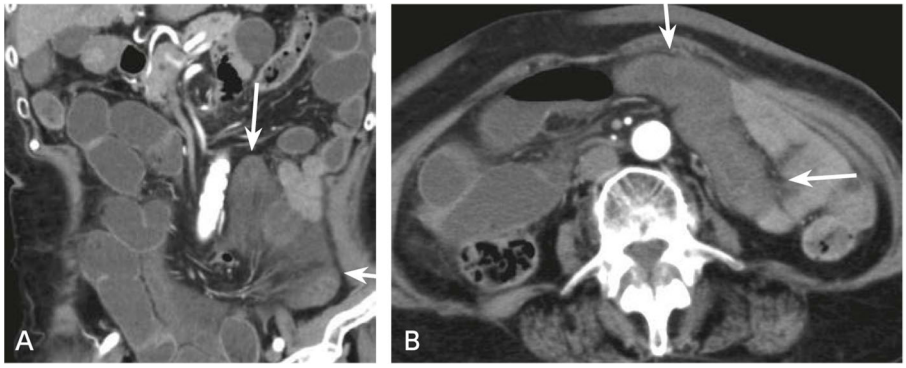

Figure　Strangulated intestinal obstruction

A: Contrast-enhanced CT (coronal image): The small intestine lesion shows closed-loop obstruction (→).
B: Contrast-enhanced CT (transverse image): The closed-loop obstruction shows poor contrast enhancement, which indicates bowel ischemia (→).

Search keywords and secondary references

The following keywords were searched on PubMed: bowel obstruction, CT, ultrasonography, and abdominal radiographs.

In addition, the following was referenced as a secondary source.

1) Committee for the Publication of Clinical Practice Guidelines for Acute Abdomen, Ed.: 2015 Clinical Practice Guidelines for Acute Abdomen. Igaku-Shoin, 2015.

References

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BQ 55 Which imaging examinations are recommended when acute appendicitis is suspected?

Statement

Either ultrasound or CT is recommended as an imaging examination when acute appendicitis is suspected. However, CT provides superior accuracy. Use of a contrast medium in CT is unnecessary.

Background

Acute appendicitis is a type of acute abdomen typically requiring emergent surgery. Its differential diagnosis includes colonic diverticulitis, which should be differentiated to provide appropriate treatment. Ultrasound and CT are commonly used as imaging examinations for acute appendicitis.

Ultrasound is a common examination used for suspected acute abdomen that is easy to access and mobile (can be performed at the bedside), with no radiation exposure. However, the diagnostic performance varies depending on the operator's skill and the patient's condition, such as intestinal gas. CT can cover a broad range of conditions and test objectively with a rapid scan, which is widely used for diagnosing acute abdomen.[1, 2)] The following is an overview of the efficacy of these diagnostic modalities based on previous diagnostic imaging guidelines and, in addition, the 2015 clinical practice guidelines for acute abdomen (secondary source 1), supplemented by data from the latest literature, mainly reviews.

Explanation

Regarding the diagnostic performance of ultrasound in acute appendicitis, a meta-analysis by Terasawa et al. reported sensitivity of 86% (95% CI, 83% to 88%) and specificity of 81% (95% CI, 78% to 84%)[3)]. The meta-analysis by Doria et al. reported sensitivity of 83% (95% CI, 78% to 87%) and specificity of 93% (95% CI, 90% to 96%).[4)] Regarding the diagnostic performance of CT, the meta-analysis by Terasawa et al. reported sensitivity of 94% (95% CI, 91% to 95%) and specificity of 95% (95% CI, 93% to 96%), and the meta-analysis by Doria et al. reported sensitivity of 94% (95% CI, 92% to 95%) and specificity of 94% (95% CI, 94% to 96%). CT showed significantly better sensitivity than ultrasound. However, the diagnostic performance of ultrasound may be higher in Japan than in the reports from Europe and the United States, where the body habitus of the subjects is quite different. CT also has an advantage over ultrasound in diagnosing cases with perforation. Accordingly, CT is recommended as a primary test for adult patients with acute abdomen.

The addition of contrast media increases the sensitivity of CT in diagnosing acute appendicitis.[5)] Another report showed that contrast media improves the detectability of the appendix on CT, though it does not increase the diagnostic accuracy for acute appendicitis.[6)] Contrast-enhanced CT is therefore recommended when the diagnosis is uncertain. In particular, contrast-enhanced CT has an advantage in diagnosing perforated appendicitis.[4)]

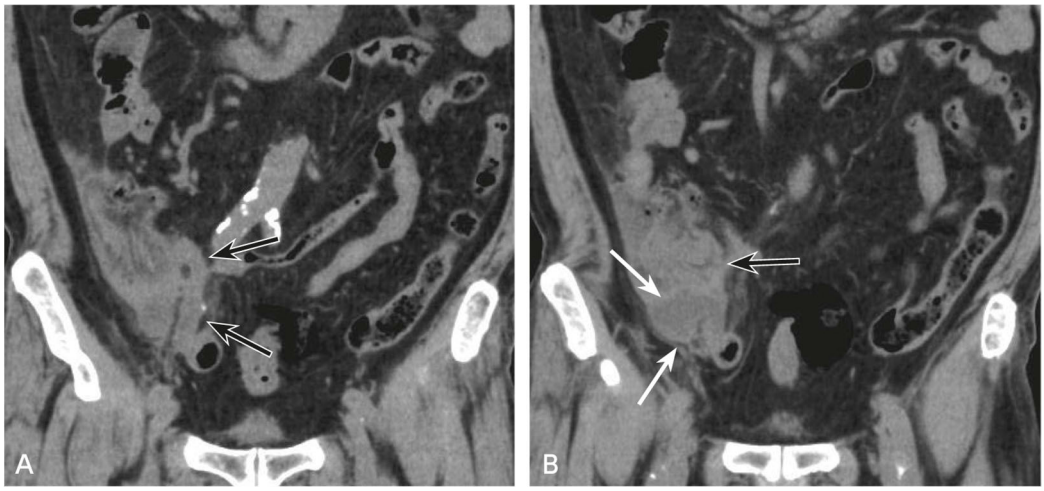

Figure 1. Acute appendicitis

A: Non-contrast CT (coronal image): The CT shows an enlarged appendix (→).

B: Non-contrast CT (coronal image): The right side of the enlarged appendix shows a ruptured appendiceal wall (→) and abscess formation (⇨).

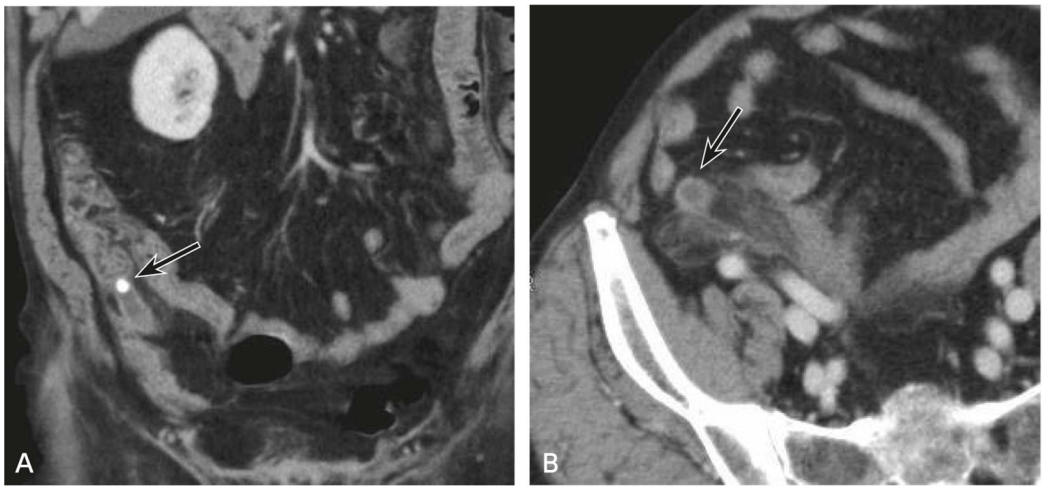

Figure 2. Acute appendicitis

A: Contrast-enhanced CT (coronal image): The CT shows a fecalith in the appendiceal base (→).

B: Contrast-enhanced CT (transverse image): The CT shows an enlarged appendix with increased density of the surrounding adipose tissue (→).

Search keywords and secondary references

The following keywords were searched on PubMed: acute appendicitis, CT, and ultrasonography.

In addition, the following was referenced as a secondary source.

1) Committee for the Publication of Clinical Practice Guidelines for Acute Abdomen, Ed.: 2015 Clinical Practice Guidelines for Acute Abdomen. Igaku-Shoin, 2015.

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BQ 56 Which imaging examinations are recommended when colonic diverticulitis is suspected?

Statement

CT is recommended when colonic diverticulitis is suspected.

Background

Colonic diverticulitis is a common cause of acute abdomen often treated conservatively. It sometimes affects the right-side colon, which mimics acute appendicitis that requires emergent surgery. Ultrasound or CT is commonly used as an imaging examination for colonic diverticulitis.

Ultrasound is a common examination used for suspected acute abdomen that is easy to access and mobile (can be performed at the bedside), with no radiation exposure. However, the diagnostic performance varies depending on the operator's skill and the patient's condition, such as intestinal gas. CT can cover a broad range of conditions and test objectively with a rapid scan, which is widely used for diagnosing acute abdomen.[1, 2)] The following is an overview of the efficacy of these diagnostic modalities based on previous diagnostic imaging guidelines and the guidelines for colonic diverticulosis (diverticular bleeding and diverticulitis), supplemented by data from the latest literature, mainly reviews.

Explanation

According to the pooled data from 4 articles, the diagnostic performance of CT for colonic diverticulitis showed sensitivity of 89%, specificity of 99%, a positive predictive value of 99%, and a negative predictive value of 90%.[3-6)] Pooled data from 4 articles regarding the diagnostic performance of ultrasound showed sensitivity of 91%, specificity of 92%, a positive predictive value of 92%, and a negative predictive value of 91%.[7-10)] A systematic review by Andeweg et al. reported that the sensitivities of ultrasound and CT were 90% and 90%, respectively, and their specificities were 95% and 96%, respectively.[11)]

CT should be used as a standard imaging examination for diagnosing colonic diverticulitis because the severity classification is based on the CT features. However, ultrasound may be used as a first choice for diagnosing colonic diverticulitis because of the reported evidence that ultrasound is useful in diagnosing and evaluating treatment response,[12)] and it shows diagnostic performance similar to CT.[13)] Ultrasound may also be the first choice when there is no CT equipment available, although ultrasound has limitations, including inconsistent results depending on operators, lack of reproducibility, and low sensitivity in diagnosing peritonitis that can be detected on CT.[11, 14)]

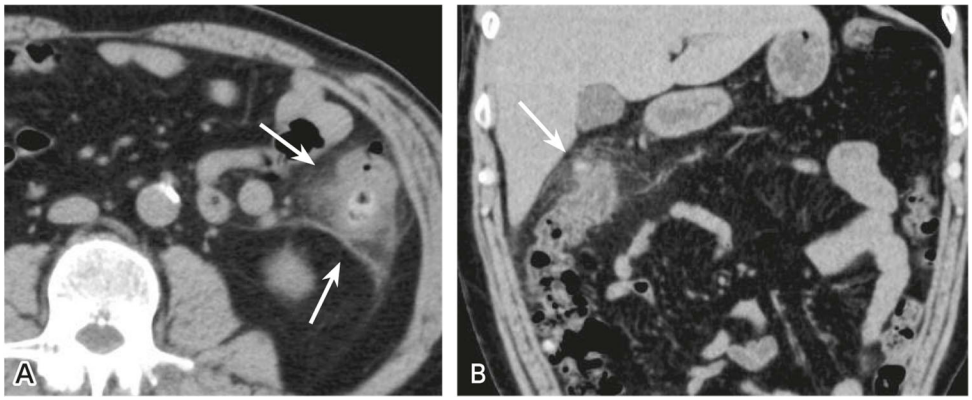

Figure　Colonic diverticulitis

A: Non-contrast CT (transverse image): The CT shows a hyperdense diverticulum in the transverse colon and increased density of surrounding adipose tissue (→).

B: Non-contrast CT (coronal image): A hyperdense diverticulum located in the hepatic flexure seen in figure A (→).

Search keywords and secondary references

The following keywords were searched on PubMed: diverticulitis, CT, and ultrasonography.

The following was referenced as a secondary source.

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BQ 57 Which imaging examinations are recommended for staging of esophageal cancer?

Statement

Contrast-enhanced CT and PET are recommended for staging of esophageal cancer.

Background

Staging of esophageal cancer is generally undertaken after a definitive diagnosis by endoscopy, including subsequent endoscopic ultrasound (EUS) to estimate invasion depth. (EUS diagnosis for staging is beyond the scope of this article.) Contrast-enhanced CT is widely accepted for assessing TNM elements. MRI is not commonly used. PET may detect lesions that are absent or ill-defined on contrast-enhanced CT. An upper gastrointestinal series using barium sulfate has been conventionally performed in Japan to locate and estimate the invasion depth of esophageal cancer. The following is an overview of the efficacy of these diagnostic modalities based on previous diagnostic imaging guidelines and supplemented by data from the latest literature, mainly reviews.

Explanation

EUS, which provides high resolution, is superior to contrast-enhanced CT for evaluating the invasion depth of superficial cancer. Differentiating among T1, T2, and T3 is difficult for advanced cancer, which is visualized as wall thickening on contrast-enhanced CT. It is clinically important to distinguish between T3 and T4, which invades to extra-esophageal organs, which is a contraindication to surgery. The diagnostic performance of CT for T4 lesions focusing on the fat layer between the tumor and the neighboring organs showed sensitivity ranging from 88% to 100% and specificity from 85% to 100%.[1, 2)] Contrast enhancement of the tumor border in the early phase of dynamic contrast-enhanced CT may correspond to adventitial invasion.[3)] Recent advances in MDCT which enables production of various 3D images has not yielded additional value for the diagnosis of esophageal cancer. The upper gastrointestinal series using barium sulfate has been conventionally accepted as a method to evaluate invasion depth focusing on lateral deformity in Japan. However, there is no scientific evidence supporting its use for esophageal cancer staging. The advantage of barium sulfate includes diagnosis of location and monitoring esophageal passage, which may be better than endoscopy. (Fig. A, B)

The diagnostic performance of contrast-enhanced CT for lymph node metastasis is not fully reliable. Commonly, the criteria for metastatic nodes are size ≥ 10 mm for intrathoracic and intraperitoneal regions and short-axis diameter ≥ 5 mm for the supraclavicular region,[4, 5)] although metastatic nodes may show no enlargement. Using a criterion of ≥ 10 mm yields sensitivity ranging from 30% to 60% and specificity ranging from 60% to 80%.[6, 7)]

PET has advantages of providing an overview and examining TNM elements within a single test covering the whole body. PET/CT is an advanced PET fused with CT, which overcomes the low resolution of PET. In the evaluation of primary tumors, early-stage cancer is not detectable with PET, and FDG accumulation has no correlation with invasion depth.[8, 9] PET/CT has a significant advantage over CT in diagnosing lymph node metastasis by detecting FDG accumulation (Fig. C). The sensitivity and specificity of PET for lymph node metastasis have been reported to range from 51% to 65.5% and 84% to 100%, respectively.[10, 11] With regard to distant metastasis, PET can detect unexpected metastasis with an incidence of 5% to 28%.[12]

MRI has not been commonly used for cancer staging because of lower temporal resolution and narrower scanning range than CT and artifacts caused by breathing or heartbeats. Currently, high-resolution T2-weighted imaging has improved lesion detection and diagnosis of invasion depth of esophageal cancer with an accuracy of 81%. The sensitivity and specificity in diagnosing lymph node metastasis have been reported to range from 25% to 62% and from 65% to 78%, respectively.[12]

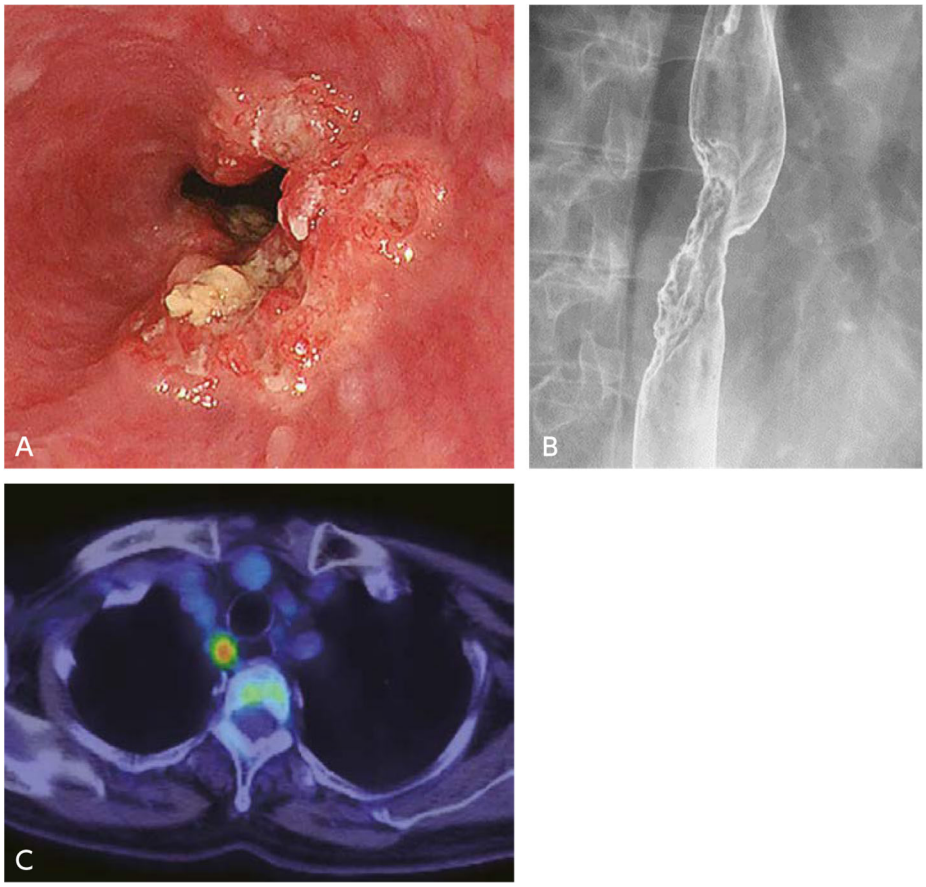

Figure Esophageal cancer

A: Endoscopy: A rough, irregular type 2 lesion forms luminal stenosis.

B: Upper gastrointestinal series: Irregular type 2 tumor located in the middle thoracic esophagus forming luminal stenosis.

C: PET/CT fusion image: A mediastinal lymph node (right recurrent nerve) shows definite FDG accumulation, indicating positive nodal metastasis.

Search keywords and secondary references

In view of the information provided in the diagnostic imaging guidelines 2016, the following keywords were searched on PubMed, limited to articles published since 2016: esophageal cancer, CT, MRI, PET, diagnosis, and staging.

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BQ 58 Which imaging examinations are recommended for staging of gastric cancer?

Statement

Contrast-enhanced CT is recommended for staging of gastric cancer.

Background

Staging of gastric cancer is generally undertaken after a definitive diagnosis by endoscopy including subsequent endoscopic ultrasound (EUS) to estimate invasion depth. (EUS diagnosis for staging is beyond the scope of this article.) Contrast-enhanced CT is widely accepted for assessing TNM elements. MRI is not commonly used. PET is also rarely used. An upper gastrointestinal series using barium sulfate has been conventionally performed in Japan to locate and estimate the invasion depth of gastric cancer. The following is an overview of the efficacy of these diagnostic modalities based on previous diagnostic imaging guidelines and supplemented by data from the latest literature, mainly reviews.

Explanation

EUS, which provides high resolution, is superior to contrast-enhanced CT for evaluating the invasion depth of early cancer. Advanced cancer is visualized as wall thickening on contrast-enhanced CT, and the addition of gastric wall distension (created using a foaming agent or water) provides detailed diagnosis. Furthermore, multiplanar reconstruction or 3D images based on MDCT improve diagnostic accuracy for the primary tumor (Fig. A, B).[1-3] Since gastric cancer shows histological diversity, the CT enhancement pattern varies depending on the histological structure of tumors (Fig. C).[4] The CT staging criteria by Chen et al., with diagnostic accuracy of 89%, have been widely accepted.[1] Recently, dual-energy CT has also been used for diagnosing gastric cancer.[5] MRI is specifically useful in differentiating T3 from T4 tumors.[6] An upper gastrointestinal series using barium sulfate, which provides an overview of the entire stomach and locates the tumor, has been conventionally accepted in Japan (Fig. D). It shows a specific advantage over endoscopy in estimating extension and infiltration of diffusely infiltrative gastric cancer. However, there is no scientific evidence supporting the use of upper gastrointestinal series for gastric cancer staging.

CT diagnosis of lymph node metastasis based on size is not fully reliable, although there have been numerous reports showing lymph node metastasis based on size. Chen et al. reported diagnostic accuracy of 78% with node size ≥ 8 mm defined as positive for metastasis.[1] MRI has not been established as clinically useful for diagnosing lymph node metastasis, although diffusion-weighted imaging has added value to increase sensitivity.[7] PET and PET/CT have had limited use for staging of lymph node metastasis because of their low sensitivity, despite the high specificity of greater than 95%. [8]

Gastric cancer metastasizes hematogenously to the liver. It is critically important to diagnose peritoneal dissemination, which is a contraindication to radical resection. Contrast-enhanced CT has been used as a

reliable test for diagnosing distant spread.[9] Ascites is a sign of peritoneal dissemination detected on CT, with sensitivity and specificity of 51% and 97%, respectively.[10] MRI and PET do not show added value in diagnosing distant metastasis.[11, 12]

Search keywords and secondary references

In view of the information provided in the diagnostic imaging guidelines 2016, the following keywords were searched on PubMed limited to articles published since 2016: gastric cancer, CT, MRI, PET, diagnosis, and staging.

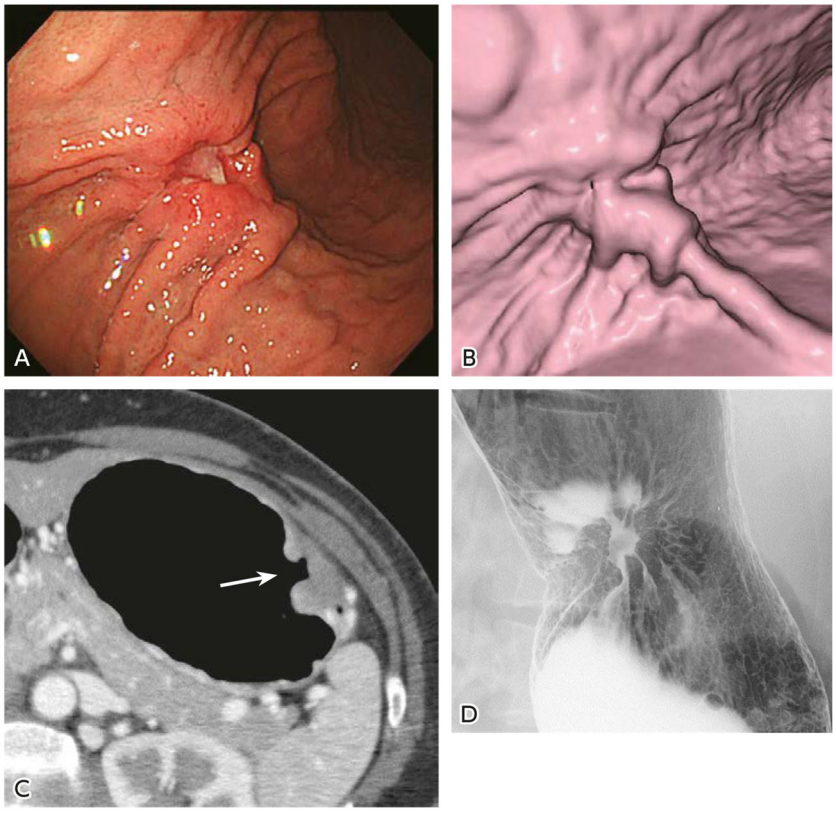

Figure　Advanced gastric cancer

A: Endoscopy: A type 3 lesion shows mucosal fold convergence in the greater curvature of the gastric body.
B: 3D CT, gastrography: Virtual endoscopy shows similar findings as optical endoscopy.
C: Contrast-enhanced CT (early phase, transverse image): The lesion shows thickening of the left wall of the stomach (→). Hypodensity in the early phase suggests poorly differentiated adenocarcinoma.
D: Upper gastrointestinal series: The image clearly visualizes a type 3 lesion in the middle gastric body.

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BQ 59 Which imaging examinations are recommended for staging of colorectal cancer?

Statement

Contrast-enhanced CT is recommended for staging of colorectal cancer. MRI is recommended for diagnosing local invasion of rectal cancer. PET is recommended as limited use for diagnosing lymph node and hepatic metastases.

Background

Staging of colorectal cancer is generally undertaken after a definitive diagnosis by endoscopy, including subsequent endoscopic ultrasound (EUS) to estimate invasion depth. (EUS diagnosis for staging is beyond the scope of this article.) Most colorectal cancers are at an advanced stage at the time of diagnosis, whereas early-stage colorectal cancer is very rare. Contrast-enhanced CT is widely accepted for assessing TNM elements. CT colonography (CTC), a CT technique specific to the colorectum, has been generally used as a preoperative test (see BQ 60). Since treatment options for rectal cancer vary depending on local status, MRI, which provides excellent spatial resolution, is suitable for pretreatment evaluation. MRI is also used to examine hepatic metastasis. PET has limited use. A barium enema has been conventionally performed in Japan to locate and estimate invasion depth of colorectal cancer. The following is an overview of the efficacy of these diagnostic modalities based on previous diagnostic imaging guidelines and supplemented by data from the latest literature, mainly reviews.

Explanation

Advanced cancer is visualized as wall thickening on contrast-enhanced CT, and the addition of colorectal wall distension (CTC) provides detailed diagnosis. Diagnosis of invasion depth can be estimated according to lateral deformity based on 3D images, with diagnostic accuracy ranging from 77.6% to 79% (Fig. A, B, C).[1, 2] MRI has a greater diagnostic accuracy than CT in the local diagnosis of rectal cancer, although it depends on the equipment protocol.[3] High-resolution T2-weighted MRI improves lesion detection and local staging (Fig. D).[4] A phased-array coil is commonly used in Japan, whereas a transrectal coil is not common. The sensitivity and specificity of MRI in diagnosing invasion depth of rectal cancer have been reported to be 87% and 75%, respectively.[4] Diffusion-weighted imaging, recently standardized as an MRI sequence, also improves the diagnosis of invasion depth.[5] A barium enema has been conventionally accepted as a method to evaluate invasion depth focusing on lateral deformity in Japan. However, there is no scientific evidence supporting its use for colorectal cancer staging. Recently, the barium enema has been replaced by the air enema image of CTC (see BQ 60).

CT diagnosis of lymph node metastasis based on size is not fully reliable. MRI diagnosis based on size shows sensitivity ranging from 56% to 94% and specificity ranging from 67% to 83%. PET and PET/CT

show superior specificity, ranging from 85% to 95%.[6] PET is also suitable for evaluating hepatic metastasis, with sensitivity and specificity of 93%. Maffione et al. reported that PET results influenced the treatment strategy in 24% of patients with colorectal cancer.[7] More recently, whole-body PET/MRI has enabled highly accurate staging of colorectal cancer.[8, 9]

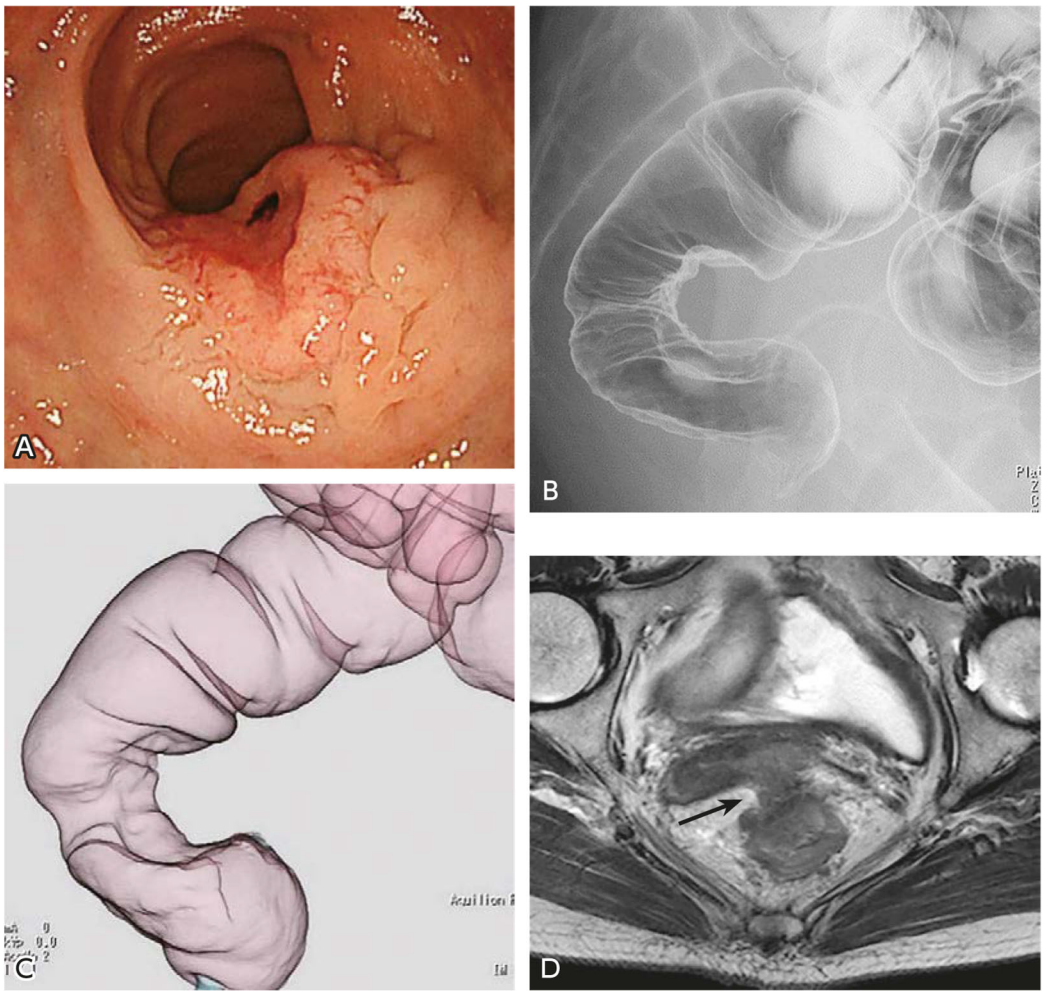

Figure Advanced rectal cancer

A: Endoscopy: A type 2 ulcerating lesion with a submucosal tumor-like protrusion.

B: Barium enema: The lesion shows deficit-like deformation in the anterior rectal wall, indicating a large tumor with deeper invasion.

C: CTC: The lesion shows similar findings to those seen on barium enema examination.

D: MRI, T2-weighted image: The tumor shows thickening in the anterior rectal wall and invades extensively to the uterus (→).

Search keywords and secondary references

In view of the information provided in the diagnostic imaging guidelines 2016, the following keywords were searched on PubMed limited to articles published since 2016: colorectal cancer, CT, MRI, PET, diagnosis, and staging.

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BQ 60 Is CT colonography recommended for the local diagnosis of advanced colorectal cancer?

Statement

CT colonography is recommended for the local diagnosis of advanced colorectal cancer.

Background

CT colonography (CTC) is a 3D CT technique specific to the colorectum. A barium enema has been conventionally used in Japan as a preoperative test for colorectal cancer, and in recent years, it has been replaced by CTC. Performing CT immediately after colonoscopy is reasonable for CTC (within one day), and it allows examination of the primary tumor and lymph node and distant metastases with a single test (see BQ 59). In 2012, the revised medical service fees included an additional amount for CTC as a test for patients with suspected colorectal malignancies.

There are no CTC guidelines available in Japan. The present guidelines provide an overview based on the guidelines jointly published by two academic societies, the European Society of Gastrointestinal and Abdominal Radiology and the European Society of Gastrointestinal Endoscopy (secondary source 1), supplemented by data from the latest literature.

Explanation

According to the published data from randomized, controlled studies, multicenter studies, single-center studies, and meta-analyses, CTC showed similar diagnostic accuracy to colonoscopy and superior accuracy to barium enema in detecting colorectal cancer and polyps in symptomatic and asymptomatic patients. According to the SIGGAR studies, the lesion detection rate of CTC was significantly higher than that of barium enema (7.3% vs. 5.6%, $p < 0.039$) and comparable to that of colonoscopy (secondary source 1). Offermans et al. compared CTC and colonoscopy in locating colorectal cancer and found that the error rate was significantly lower with CTC than with endoscopy (13.2% vs. 21.6%, $p < 0.001$).[1)] Kanazawa et al. reported that diagnostic accuracy in the local diagnosis of colorectal cancer was significantly higher with CTC than with endoscopy (98% vs. 90%, $p < 0.05$; Fig. A, B, C).[2)]

Search keywords and secondary references

The following keywords were searched on PubMed for the period since 2016: CT colonography, colorectal cancer, and barium enema.

In addition, the following secondary source was used as a reference.

1) Spada C et al: Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline. Endoscopy 46: 897-915, 2014

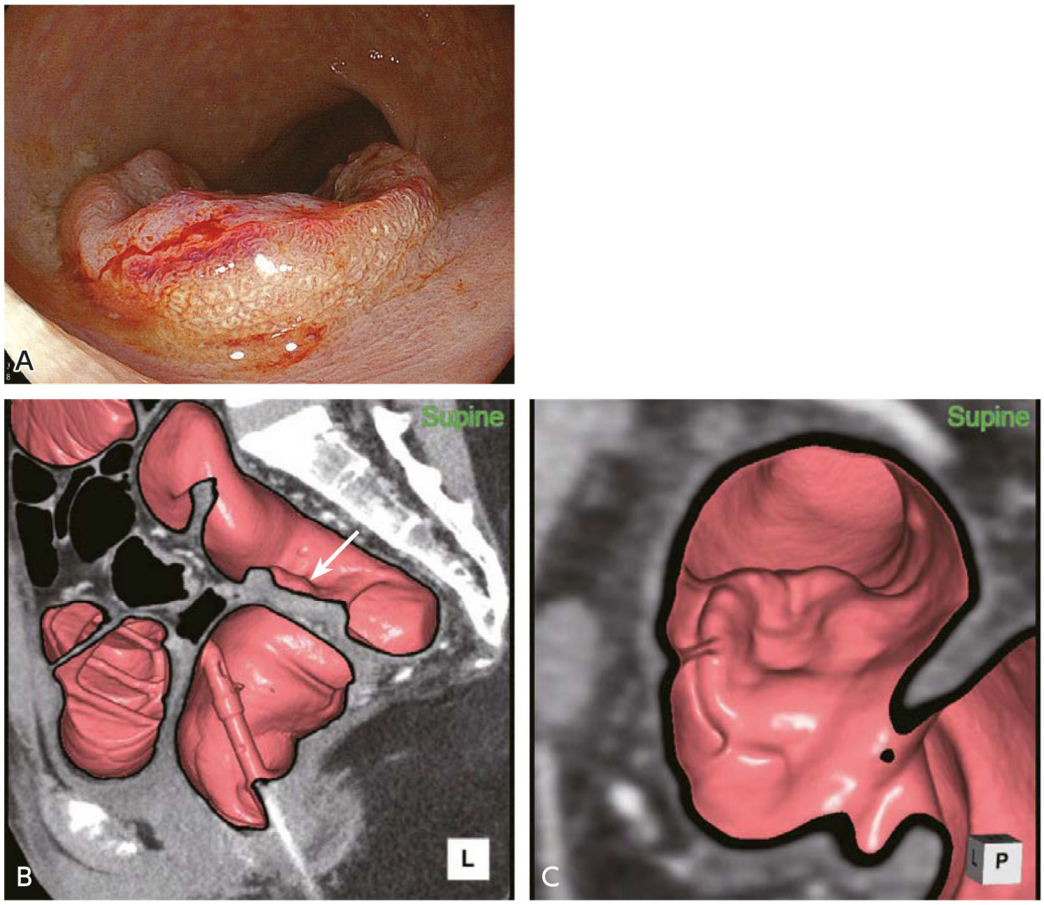

Figure　Advanced rectal cancer

A: Endoscopy: Type 2 advanced rectal cancer.

B: CTC (fusion of virtual colonoscopy and MPR): Type 2 cancer located in the anterior wall of the rectosigmoid segment (RS) of the rectum (→). Anatomical information is clearly visualized on CTC.

C: CTC (fusion of virtual colonoscopy and MPR): The lesion shows findings similar to those seen on colonoscopy.

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