Magnetic resonance evaluations of biliary malignancy and condition at high-risk for biliary malignancy: Current status

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Abstract
Tumors of the biliary tree are relatively rare; but their incidence is rising worldwide. There are several known risk factors for bile duct cancers, and these seem to be associated with chronic inflammation of the biliary epithelium. Herein, 2 risk factors have been discussed, primary sclerosing cholangitis and reflux of pancreatic juice into the bile duct, as seen in such an abnormal union of the pancreatic-biliary junction because magnetic resonance imaging (MRI) is used widely and effectively in the diagnosis of these diseases. When biliary disease is suspected, MRI can often help differentiate between benignity and malignancy, stage tumors, select surgical candidates and guide surgical planning. Nowadays remarkable technical advances in magnetic resonance technology have expanded the clinical applications of MRI in case of biliary diseases. In this article, it is also discussed how recent developments in MRI contribute to the diagnosis of the bile duct cancer and the evaluation of patients with risk factors affecting bile duct cancer.

Core tip: Tumors of the biliary tree are relatively rare; but their incidence is rising worldwide. When biliary disease is suspected, magnetic resonance imaging (MRI) can often help differentiate between benignity and malignancy, stage tumors, select surgical candidates and guide surgical planning. Nowadays remarkable technical advances in magnetic resonance technology have expanded the clinical applications of MRI in case of biliary diseases. In this article, it is also discussed how recent developments in MRI contribute to the diagnosis of the bile duct cancer and the evaluation of patients with risk factors affecting bile duct cancer.

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INTRODUCTION
Bile duct malignancies are relatively rare, estimated at 2% of all cancers with an incidence of 0.01%-0.04% in autopsy series[1]; however their incidence is rising worldwide[2,3]. The several known risk factors account for bile duct cancers, and these seem to be associated with chronic inflammation of the biliary epithelium[4-7]. The exact mechanism of tumor development is not completely understood and various possible pathways have been proposed, including chronic inflammatory process in the bile duct, mutation, and parasite-induced DNA damage[8-11]. When biliary disease is suspected, optimal imaging studies provide the required information for differentiating between benign and malignant tumors, tumor staging, selection of surgical candidate, and surgical
planning of bile duct cancer. Various imaging modalities, invasive and noninvasive, are employed in diagnosis and staging of bile duct tumors\cite{1,12}. The invasive methods include endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), intraductal ultrasonography (IDUS), percutaneous transhepatic cholangiography (PTC), and optical coherence tomography. Noninvasive imaging methods include ultrasonography (US), multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). ERCP and PTC are not used as diagnostic tools alone owing to invasive nature. Nowadays ERCP is used for interventions such as biopsy, drainage and EUS/IDUS. US, EUS and IDUS are useful technique for screening biliary diseases particularly gallbladder disease; however their efficacy depends on operator skill and experience. MDCT are accurate and useful imaging techniques for the evaluation of biliary diseases. MDCT offers detailed information about the biliary tree and surrounding structures; however, it has some demerits such as ionized radiation and adverse reaction of intravenous contrast materials. MRI is a reliable noninvasive common imaging tool for the diagnosis and pre-surgical evaluation of bile duct tumors. MRI has many advantages over other modalities: (1) it is completely noninvasive, does not require exposure to ionizing radiation, and does not cause patient discomfort; (2) it does not require expert technicians with sophisticated technical skills. Therefore MRI has become an important diagnostic tool for bile duct diseases.

Moreover nowadays remarkable technical advances in magnetic resonance (MR) technology have increased the clinical applications of MRI for diagnosing biliary diseases\cite{12-15}. In this article, it is discussed how developments in MRI have improved the evaluation of patients with risk factor affecting bile duct cancers and the diagnosis of bile duct cancers.

**MRI TECHNIQUE**

A pre-procedural fasting is recommended for gallbladder distension and gastric emptying. When fluid is present in the stomach and duodenum, visualization of the bile duct may be obscured by interposition of bile loop. Therefore administration of oral contrast agent (iron oxide particles, blueberry juice or pineapple juice) is recommended.

Most institutes may perform MR examinations at 1.5 T with a torso coil. Although imaging at 3 T can improve the signal-to-noise ratio and spatial resolution, it may be hampered by dielectric effects, banding, and other pulse sequence-related effects\cite{16-19}. The pulse sequences used for MRI of the bile duct are usually axial T1- and T2-weighted imaging, MR cholangiopancreatography (MRCP), and axial diffusion-weighted imaging (DWI). T1-weighted image may be used under an intravenous contrast material. Most gadolinium contrast agents produce an enhancement pattern similar to that observed with iodine-based CT contrast. The advent of the hepatocyte-specific contrast agents (Gd-EOB-DTPA, Gd-BOPTA, etc.) allows the usual early-phase imaging of the arterial, portal, and venous phases, plus delayed-phase hepatic parenchymal and biliary imaging, taking advantage of the fact that about 50% of injected dose of these contrast agents are excreted via the biliary system\cite{19,20}.

MRCP use 2 varieties of T2-weighted sequences. One is obtained with a single-shot turbo spin-echo T2-weighted sequence by using a long echo time to selectively display the fluid filled bile ducts. The other is obtained by using a navigator-based respiratory-triggered three-dimensional acquisition sequence with a longer acquisition time\cite{21}. The differences of both are small, and thus either or both are used for MRCP accordingly.

DWI can obtain additional information derived from the microscopic motion of proton in water, which is not possible by using conventional MRI. DWI is a sensitive sequence for the detection of tumors and inflammation of the bile ducts. It has the advantage of quantitative data analysis through the generation of apparent diffusion coefficient (ADC) maps, which can contribute to objective disease assessment and monitoring of response to therapy\cite{22-25}.

MRI can allow us to evaluate the analysis of bile and pancreatic juice flow, which may have relate to carcinogenesis of the bile duct tumors. Although by now the flow analysis of the bile duct based on MRI was held by a continuous MRCP examination after secretin injection, a new method [time-spatial labeling inversion pulse (SliP) imaging] become to evaluate the flow analysis easier and faster than before\cite{26}.

**CLINICAL INDICATION**

**Benign biliary diseases and condition at a high-risk for malignancy**

Risk factors for bile duct carcinoma include (1) primary sclerosing cholangitis (PSC), (2) reflux of pancreatic juice into the common bile duct, such as in an abnormal arrangement of the pancreato-biliary ductal system (AAPB), (3) exposure to chemicals, and (4) medication such as oral contraceptives and methyldopa\cite{4-7}. In this chapter, MRI applications for benign biliary diseases and condition at a high-risk for malignancy are discussed about PSC and reflux of pancreatic juice into the bile duct because MRI is used widely and effectively for these entities (Table 1).

**PSC:** PSC is a chronic cholestatic liver disease of possible autoimmune origin, characterized by intra- and extrahepatic bile duct inflammation and fibrosis\cite{6,27-31}. PSC is the most common risk factor for cholangiocarcinoma in Western countries, with a prevalence of cholangiocarcinoma ranging from 8% to 25%\cite{27}. Diagnostic criteria for PSC include (1) typical cholangiographic abnormalities; (2) clinical, biochemical, and hepatic histologic finding; and (3) the exclusion of secondary cause of sclerosing cholangitis.

The diagnosis of PSC was based on characteristic...
choledochographic finding in combination with clinical, biochemical, and histologic features. Therefore ERCP was considered the standard method for diagnosis of PSC. However, owing to developments in MR technology, MRCP has become another important modality. The result of a meta-analysis showed that MRCP had high sensitivity and very high specificity for the diagnosis of PSC.\cite{43,45} The radiological characteristics of PSC mimic those of cholangiocarcinoma.\cite{43} Both make differential diagnosis quite difficult even with current diagnostic modalities including MRI.

**AAPB:** AAPB is a congenital anomaly defined as the junction of the pancreatic and bile ducts being located outside the duodenal wall. As the contraction of the sphincter of Oddi within the duodenal wall does not functionally affect the junction in patients with this congenital abnormality, continuous pancreaticobiliary reflux occurs, resulting in a high incidence of biliary cancer. AAPB can be divided into (1) AAPB with biliary dilatation (choledochal cyst) and (2) AAPB without biliary dilatation.

**AAPB with choledochal cyst:** Choledochal cysts are rare congenital biliary tract anomalies characterized by biliary tree dilatation. Although the incidence in the Western population is 1 in 100000 to 150000 live births, it is much higher in Asian countries, particularly Japan, where they can be found in up to 1 in 1000 live births. Choledochal cysts are usually classified into several types, based on anatomical findings. According to Todani’s classification system, choledochal cysts include five main types. In Todani’s classification system, almost all patients with choledochal cyst are classified into 3 types (type Ia, Ic and IV-A), and that associated with AAPB. Biliary tract malignancies were seen in 10%-30% of patients with choledochal cyst and it increases with age.\cite{46,47} A prompt and accurate diagnosis of choledochal cyst, follow by surgical is therefore essential.

In diagnostic imaging, researchers have shown that MRCP can offer diagnostic information equivalent to that of ERCP for assessment of choledochal cysts in adults.\cite{46,47} Figure 2). Although MRCP should not replace ERCP totally in pediatric patients, MRCP should be considered the first-choice imaging technique for evaluation of choledochal cysts. MRCP can provide pre-operative information about minute structure of AAPB.
AAPB without choledochal cyst: AAPB patients without choledochal cyst, similar to those with choledochal cyst, experience continuous reciprocal reflux between pancreatic juice and bile. Because the hydro pressure within the pancreatic duct is usually greater than that within the bile duct, pancreatic juice frequently refluxes into the bile duct in these patients, which results in a high incidence of cancer of the biliary tract.

Although AAPB patients with and without choledochal cyst have a risk of biliary malignancy, the usual sites of malignancy differ. To the contrast bile duct and gallbladder cancers were seen in 34% and 65% of AAPB with choledochal cysts, only gallbladder cancer was found in almost all of 38% of AAPB without biliary dilatation. Once AAPB is diagnosed, prophylactic flow-diversion surgery (bile duct resection and biloenteric anastomosis) is performed for patients with choledochal cyst.

Treatment of patients with AAPB without biliary dilatation is controversial. Prophylactic cholecystectomy is performed in many institutions. However, some surgeons propose excision of the extrahepatic bile duct, together with gallbladder.

The diagnostic criteria for AAPB have been established on the basis of ERCP. Although Kamisawa et al have reported that MRCP can be used to detect AAPB (Figure 3), they have also reported that some atypical cases with relative short common channel cannot be diagnosed by MRCP, and should be confirmed by ERCP.

AAPB cases with choledochal cysts have clinical symptoms due to cholangitis or pancreatitis in childhood, and thus they tend to be diagnosed in childhood. Patients without choledochal cysts are usually not diagnosed until adulthood, when they have already progressed to advanced stage gallbladder carcinoma, which has a poor prognosis. An appropriate strategy is necessary to detect and manage these cases. Takuma et al have suggested that MRCP should be performed in patients who are found to have gallbladder wall thickening by US.

**Pancreatic juice reflux without AAPB**

Recently, several case series have been published on the reflux of pancreatic juice into the bile duct without a morphologically AAPB, and the correlation of such cases with biliary diseases, especially biliary malignancies, is drawing attention. These cases could not be detected by existing imaging modalities based on morphological change.

Several reports have shown that high amylase levels in bile samples on ERCP, which indicate reflux of pancreatic juice, or reflux of contrast medium into the pancreatic duct during intraoperative cholangiography, were found in 26%-87% of patients with normal pancreatico-biliary duct anatomy. Researchers have shown that MRCP can be used to detect pancreatic juice reflux in those patients. In patients without AAPB, reflux of pancreatic juice into the common bile duct can be indirectly observed by using secretin-stimulating MRCP. The cause of such reflux may be dysfunction of the sphincter of Oddi.

The new method of time-SLIP technique, used in vascular studies, has the potential to visualize pancreatic juice flow directly. Researchers have shown that this method can be used to detect pancreatic juice flow reflux in the normal patients (Figure 5). The new
Figure 4 Flow of pancreatic juice by time-spatial labeling inversion pulse imaging. A: Magnetic resonance cholangiopancreatography image; B: Time-spatial labeling inversion pulse image obtained by applying labeling pulse box surrounded by lines to the body and tail portions of the main pancreatic duct, not showing movement; C: Flow of pancreatic juice in duct from body into the head of pancreas is identified by high signal intensity (arrow).

Figure 5 Pancreatic juice reflux into the biliary tree by time-spatial labeling inversion pulse imaging. A 56-year-old female patient underwent magnetic resonance imaging after abnormal laboratory findings. Magnetic resonance cholangiopancreatography revealed normal morphology, but time-spatial labeling inversion pulse imaging showed pancreatic juice reflux into the biliary tree. A: Magnetic resonance cholangiopancreatography image; B: Flow of pancreatic juice from body of the pancreas into the head of the pancreas is identified by high signal intensity (arrows).

**BILIARY MALIGNANCIES**

In general, the diagnosis of biliary tumors, particularly early detection and differential diagnosis, is still challenging, although many sensitive direct and indirect techniques have been adopted.

**Cholangiocarcinoma**

Cholangiocarcinoma arise from the epithelial cells lining the biliary tree. Intrahepatic cholangiocarcinoma arise within the intrahepatic ducts and extrahepatic cholangiocarcinoma originate in the bile duct along the hepatoduodenal ligament. Extrahepatic biliary carcinomas are further divided into hilar, also called Klatskin tumors, and distal tumors. Hilar tumors represent approximately 60%-70% of cholangiocarcinoma, distal tumors represent 20%-30%, and intrahepatic cholangiocarcinomas represent 5%-10%.

The tumors are rare, estimated at 3% of all gastrointestinal cancers. They are the second most common type of primary hepatic tumors. This ratio includes intrahepatic and extrahepatic tumors. The patients present mostly in the 6th and 7th decades of life.

The pathologic classification of cholangiocarcinoma categorizes into 3 types: mass-forming, periportal infiltrating, and intraductal growing. The intraductal growing type is currently thought to be the counterpart of intraductal papillary mucinous neoplasm of the pancreas.

MRI with MRCP is usually considered the modality of choice for the diagnosis of cholangiocarcinomas. Several studies have shown that MRI has sensitivity and specificity > 90%. However, its ability to differentiate between benign and malignant obstruction is low and variable, according to the authors.

**Intrahepatic cholangiocarcinoma:** Intrahepatic cholangiocarcinoma is the second most common primary hepatic malignant tumors after hepatocellular carcinoma. The important prognostic factors of intrahepatic cholangiocarcinoma are tumor size, lymph node metastasis, and vascular invasion.

The mass-forming type makes up a large percentage of intrahepatic cholangiocarcinoma, and shows an irregular shaped solid mass with peripheral rim enhancement.
and incomplete concentric pooling of contrast material on dynamic studies\[13,70-72\]. The MRI appearances depend on the degree of fibrosis, coagulative necrosis, cell debris, and mucin production. Capsular retraction, bile duct dilatation distal to the tumor, vascular encasement, and central scar have been also reported.

Several researchers have reported that the use of hepatocyte-specific contrast agent (Gd-EOB-DTPA) may aid in the diagnosis of intrahepatic cholangiocarcinoma\[73-76\]. They have shown that Gd-EOB-DTPA enhanced images displayed increased lesion conspicuity and better delineation of daughter nodules and intrahepatic metastases. Other researchers have reported that DWI may be also useful for detection of bile duct cancers\[77,78\] (Figure 6).

**Extrahepatic biliary cancer:** Extrahepatic biliary carcinomas are divided into hilar, also called Klatskin tumors, and distal tumors. Hilar tumors represent approximately 60%-70% and distal tumors 20%-30%\[15,16\]. The most common pattern of tumor growth is focal infiltration of the ductal wall or the periductal-infiltrating type, resulting in focal strictures. The mass-forming and intraductal-growing types are less common\[14\].

The role of MRI is to detect and characterize the tumor, and determine respectability. On cross-sectional MRI, the lesion appears ill-defined, and moderately hypo- to isointense on T1-weighted images and mildly iso- to hyperintense on T2-weighted images as compared to adjacent liver parenchyma.

Hilar bile duct cancers are most commonly of the infiltrative type and less frequently exophytic or polypoid lesions\[14\]. Many studies have reported that MRI, including MRCP, is useful in the staging of perihilar bile duct cancers\[79-84\] (Figure 7). MRI cannot assess tumor in stented ducts\[81,82\]. Minimal invasion along the mucosa and in the perineural space may escape detection if it is below the limit of resolution\[82,83\].

Distal extrahepatic cholangiocarcinomas are most commonly of the infiltrative type and grow intramurally, beneath the bile duct epithelium. The accuracy of MRCP is reported to be comparable to that of ERCP for differentiating extrahepatic bile duct carcinoma from benign stricture\[96,97,99\]. Although some overlap exists, in general the presence of a long segment of extrahepatic bile duct stricture with irregular margins and asymmetric narrowing is suggestive of cholangiocarcinoma, whereas a short segment with regular margins and symmetric narrowing indicates a benign cause\[97\]. The addition of a contrast-enhanced dynamic study to evaluate the longitudinal tumor extent of bile duct cancers is controversial. One report has shown favorable results, but another report showed no improvement in diagnostic accuracy\[100,101\].

Several researchers have reported on the utility of

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**Figure 6** Intrahepatic cholangiocarcinoma in a 70-year-old man. A: Axial T2-weighted image shows high signal intensity liver mass (arrow); B: Diffusion-weighted imaging shows high signal intensity in the lesion (arrow).

**Figure 7** Hilar bile duct cancer in an 84-year-old woman. A: Axial T2-weighted image shows wall thickening and high signal intensity of hilar bile duct (arrow); B: Diffusion-weighted imaging shows high signal intensity in the lesion (arrow); C: Magnetic resonance cholangiopancreatography shows occlusion of the hilar bile duct (arrow).
DWI in these lesions, and it may play an important role in the diagnosis of extrahepatic tumors\cite{95,96} (Figure 8).

**Gallbladder cancer**

Primary carcinoma of the gallbladder is the most common malignancy of the biliary tract. Spread of gallbladder carcinoma to the liver is common due to the thinness of the gallbladder's smooth muscular layer and the proximity to the liver, allowing spread to lymphatic channels\cite{97-101}. Gallbladder carcinomas exhibit 3 typical patterns: polypoid, mural thickening, and diffusely infiltrative\cite{102}. Nearly 70% of gallbladder carcinoma present as diffusely infiltrative lesions\cite{103}.

Usually, US is used as an initial diagnostic modality. As a second step, CT, MRI with MRCP, and/or traditional cholangiography is often used for obtaining additional information. Comparative studies of CT and MRI with MRCP are desirable.

The role of MRI is to characterize the tumor, and determine respectability\cite{103,104}. Gallbladder carcinoma usually exhibits low to intermediate signal intensity on T1-weighted sequences and heterogenous hyperintensity on T2-weighted sequences with a characteristically ill-defined contour\cite{105}. In the polypoid and mural thickening types, lesion more than 10 mm in diameter or which enhance after intravenous contrast material, are usually malignant. The diffusely infiltrative type, the tumor appears as a large solid mass in the gallbladder fossa, obscuring the gallbladder. The presence of gallstones within the mass may be helpful in making the diagnosis. In tumor staging, differentiation between stage T1 (lesions confined to the muscular layer) and stage T2 (lesions confined to subserosal or perimuscular connective tissue) is important, because vastly different operative procedures used depending on the stage. Yoshimitsu et al\cite{101} have reported that submucosal enhancement on a delayed phase dynamic MRI study is a useful sign for differentiating between the stages.

Several researchers have showed that DWI may be useful in the diagnosis of gallbladder carcinoma\cite{106-109} (Figure 9). The sensitivity and specificity of conventional MRI alone was 74% and 68%-83%, respectively; these values increased when DWI was used along with conventional MRI\cite{24}.

**Ampullary cancer**

Ampullary carcinoma tends to appear as small mass that causes biliary obstruction. Although CT and MRI are used to evaluate ampullary carcinoma, it is difficult to diagnose because of the small tumors and difficulty of differentiating between the tumors and surrounding normal structure. MRI, including MRCP, has been reported to be more accurate than CT\cite{106,107}. MRI in ampullary carcinoma has a high sensitivity and low specificity\cite{110}. EUS and ERCP are usually used to identify ampullary carcinoma.

Histologically, most ampullary carcinoma develop

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**Figure 8** Distal extrahepatic cholangiocarcinoma in an 83-year-old woman. A: Axial T2-weighted image shows wall thickening and slight high mass of the distal common bile duct (arrow); B: Diffusion-weighted imaging shows high signal intensity in the lesion (arrow); C: Magnetic resonance cholangiopancreatography shows occlusion of the distal common bile duct (arrow).

**Figure 9** Gallbladder carcinoma in a 56-year-old woman. A: Axial T2-weighted image shows focal wall thickening (arrow); B: Diffusion-weighted imaging shows high signal intensity in the lesion (arrow); C: Magnetic resonance cholangiopancreatography shows a filling defect in the gallbladder (arrow). Abnormal arrangement of the pancreato-biliary ductal system is identified.
from 1 of 2 types of epithelium, resulting in an intestinal-type adenocarcinoma arising from the intestinal epithelium lining the duodenal papilla and pancreaticobiliary-type adenocarcinoma developing from the biliary epithelium of the ampullary portion. The subtypes of ampullary tumors have different prognoses. Chung et al.[11] have shown MRI may be helpful in determining the subtypes of ampullary tumors.

Several studies have reported that DWI has the potential for differentiating malignant ampullary tumors from benign ampullary tumors[114,115]. Researchers have reported that malignant tumors have a low ADC value compared to that of benign tumors (Figure 10).

CONCLUSION

MRI is a promising non-invasive imaging technique for evaluating biliary lesions. MRI can be used for diagnosis, tumor characterization, preoperative planning, and follow-up of malignant biliary lesions.

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