WHAT IS THE CURRENT STATE-OF-THE-ART IMAGING FOR DETECTION AND STAGING OF CHOLANGIOCARCINOMA?

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ABSTRACT
Cholangiocarcinoma is an adenocarcinoma that arises from the bile duct epithelium and is the second most common primary hepatobiliary cancer, after hepatocellular cancer, with approximately 2,500 cases annually in the U.S. However, cholangiocarcinoma remains a relatively rare disease, accounting for <2% of all human malignancies. Although the entire biliary tree is potentially at risk, tumors involving the biliary confluence or the right or left hepatic ducts (hilar cholangiocarcinoma) are most common and account for 40%–60% of all cases. Most patients present with advanced disease that is not amenable to surgical treatment. The median survival time for patients with intrahepatic cholangiocarcinoma without involvement of the hilum varies among centers from 18–30 months. The median survival time for patients with perihilar cholangiocarcinoma is slightly less, varying from 12–24 months. Despite the overall poor prognosis, survival after surgical treatment of hilar cholangiocarcinoma has improved during the past 10–15 years. This review highlights the imaging features of cholangiocarcinoma, with particular emphasis on the imaging techniques that can best assess tumor resectability and guide the surgeon regarding the potential extent of resection required in operable candidates. The Oncologist 2006;11:913–922

INTRODUCTION
Cholangiocarcinoma is an adenocarcinoma that arises from the bile duct epithelium and is the second most common primary hepatobiliary cancer, after hepatocellular cancer, with approximately 2,500 cases annually in the U.S. [1]. However, cholangiocarcinoma remains a relatively rare disease, accounting for <2% of all human malignancies [2]. Although the entire biliary tree is potentially at risk, tumors involving the biliary confluence or the right or left hepatic ducts (hilar cholangiocarcinoma) are most common and account for 40%–60% of all cases. The latter includes the proximally located hilar tumor of the bifurcation with a subtype of the so-called “Klatskin” tumor following Klatskin’s original description in 1965 [3]. About one fourth are distal extrahepatic tumors, and the remainder are intrahepatic (beyond the second order bile ducts) [4]. While the vast majority of cases of cholangiocarcinoma are sporadic, predisposing factors include clonorchiasis, intrahepatic stone disease, choledochal cyst, Caroli disease, primary sclerosing cholangitis, and a history of chemical and thorium dioxide exposure (Thorotrast) [1].

Most patients present with advanced disease that is not amenable to surgical treatment. The median survival time for patients with intrahepatic cholangiocarcinoma without involvement of the hilum varies among centers from 18–30 months. The median survival time for patients with perihilar cholangiocarcinoma is slightly less, varying from 12–24 months. Despite the overall poor prognosis, survival after surgical treatment of hilar cholangiocarcinoma has improved during the past 10–15 years. This review highlights the imaging features of cholangiocarcinoma, with particular emphasis on the imaging techniques that can best assess tumor resectability and guide the surgeon regarding the potential extent of resection required in operable candidates. The Oncologist 2006;11:913–922
lar cholangiocarcinoma is slightly less, varying from 12–24 months [5, 6]. Despite the overall poor prognosis, survival after surgical treatment of hilar cholangiocarcinoma has improved during the past 10–15 years. This is principally a result of the adoption of a more aggressive surgical technique, with combined partial hepatectomy, leading to an increase in the proportion of margin-negative (R0) resections [7]. Patients with R0 resections have a reported 5-year survival rate of up to 37%, versus 0% for margin-positive (R1) resections [8]. This review highlights the imaging features of cholangiocarcinoma, with particular emphasis on the imaging techniques that can best assess tumor resectability and guide the surgeon regarding the potential extent of resection required in operable candidates.

**Staging**

Currently, there are three main staging systems for patients with cholangiocarcinoma: the American Joint Committee on Cancer (AJCC) staging system (Table 1) [9], the Bismuth–Corlette classification system (Fig. 1) [10], and the Blumgart modifications [11].

Both the AJCC and Bismuth–Corlette staging systems are based entirely on the extent of ductal involvement by the tumor and do not account for other factors that would play a role in evaluating successful resection, such as potential hepatic artery or portal venous involvement with tumor and the functional status of the underlying liver. While some studies have demonstrated a correlation between tumor stage and survival [12], others have failed to do so [13]. Burke et al. [11] addressed this by modifying the AJCC staging system to account for biologic factors that would improve the clinical and prognostic usefulness of the current system.

**Surgical Techniques**

Because of advanced stage at presentation, <20% of patients are estimated to be amenable to a formally curative surgical resection. Several factors influence resectability, including the location and extent of the tumor and presence of comorbid conditions such as cirrhosis, cardiopulmonary disease, sepsis, or cholestasis. Advanced disease stage (bilateral involvement of hepatic ducts to the level of the secondary biliary radicals, atrophy of one liver lobe with encasement of the contralateral portal vein branch, atrophy of one liver lobe with contralateral secondary biliary radical involvement), distant metastases, extensive regional lymphadenopathy and vascular encasement (proper hepatic artery invasion, encasement or occlusion of the main portal vein proximal to the bifurcation, or bilateral involvement of hepatic arteries), or invasion all preclude resection. The goals of surgery are complete tumor excision with negative histological margins, relief of symptoms relating to biliary obstruction, and restoration of biliary continuity. Operation for hilar cholangiocarcinoma requires a supraduodenal bile duct excision, portal lymphadenectomy, cholecystectomy, biliary-enteric reconstruction, and, in most cases, a partial hepatectomy. Operation for distal bile duct cancers consists of either a pancreaticoduodenectomy or, less commonly, a local bile duct excision. Although resection has long been recognized as the most effective therapy for hilar cholangiocarcinoma [14], the importance of partial hepatectomy is a relatively recent development [12, 15, 16]. Hilar resections combined with partial hepatectomy have resulted in more R0 resections and improved long-term survival in recent years [7].

![Figure 1. Bismuth–Corlette classification according to the extent of ductal involvement](http://theoncologist.alphamedpress.org/)

| Table 1. Current American Joint Commission on Cancer staging system for cholangiocarcinoma |
|----------------------------------------|----------------|--------------|----------------|
| Stage 0 | T\textsubscript{n} | N\textsubscript{0} | M\textsubscript{0} |
| Stage I | T\textsubscript{1} | N\textsubscript{0} | M\textsubscript{0} |
| Stage II | T\textsubscript{2} | N\textsubscript{0} | M\textsubscript{0} |
| Stage III | T\textsubscript{1} or T\textsubscript{2} | N\textsubscript{1} or N\textsubscript{2} | M\textsubscript{0} |
| Stage IVA | T\textsubscript{3} | Any N | M\textsubscript{0} |
| Stage IVB | Any T | Any N | M\textsubscript{1} |

Abbreviations: M\textsubscript{0}, no distant metastasis; M\textsubscript{1}, distant metastasis; N\textsubscript{0}, no regional lymph node metastasis; N\textsubscript{1}, metastasis to hepato-duodenal ligament lymph nodes; N\textsubscript{2}, metastasis to peripancreatic, periportal, celiac, and/or superior mesenteric artery lymph nodes; T\textsubscript{1}, tumor invades the subepithelial; T\textsubscript{2}, tumor invades the perifibromuscular connective tissue; T\textsubscript{3}, tumor invades adjacent organs; T\textsubscript{4}, carcinoma in situ.
The accumulated results from many centers show convincingly that only R0 resection can be considered potentially curative and that hepatic resection is often required to achieve this objective [8, 11, 12, 16–20]. Preoperative hypertrophy of the future remnant liver, induced by unilateral portal vein embolization, has been shown to minimize the associated risk for postoperative liver failure [21]. Intrahepatic cholangiocarcinoma is generally treated by hepatic resection alone [22, 23]. Patients with distal extrahepatic tumors and cancers of the ampulla of Vater generally undergo pancreatoduodenectomy. Commonly, a pylorus-preserving Whipple procedure is performed.

**IMAGING**

The role of imaging is to aid differentiation of benign from malignant causes of biliary stricture, determine resectability in patients with malignant disease, and preoperatively stage those patients with potentially resectable tumors. Accurate delineation of the tumor extent poses a great challenge to modern imaging methods. This is not least because of the fact that sclerosis and fibrosis of surrounding tissue may be difficult to differentiate from tumor, and microscopic tumor extension along the perineural spaces is impossible to resolve [24]. Even surgical exploration cannot always reveal the true extent of the tumor with special regard to bile ducts and liver parenchyma.

**Differentiating Benign from Malignant Hilar Strictures**

Benign bile duct strictures, which have several possible causes (e.g., cholangitis, traumatic and postsurgical sequelae, chronic pancreatitis, and papillary stenosis) may mimic infiltrative cholangiocarcinoma [25]. Several imaging modalities are useful in determining the etiology of biliary obstruction. Endoscopic ultrasound in combination with fine-needle aspiration cytology (EUS-FNA) is a useful diagnostic tool for obtaining a preoperative tissue diagnosis, particularly when attempting to differentiate benign from malignant etiologies of hilar obstruction [26].

Contrast enhancement of the bile ducts during the portal venous phase is an important sign that may aid differentiation of malignant from benign strictures on computed tomography [27]. A recent meta-analysis revealed that magnetic resonance cholangiopancreatography had a >80% sensitivity in differentiating benign from malignant biliary obstruction [28]. Although preliminary evidence, a study by Berr et al. [29] showed a significant difference between fluorodeoxyglucose (FDG) activity in benign strictures associated with primary sclerosing cholangitis and cholangiocarcinoma on positron emission tomography (PET) imaging.

**Ultrasound**

**Intrahepatic Cholangiocarcinoma**

The mass-forming type of cholangiocarcinoma is typically a large mass as a result of late presentation. There are no specific ultrasound (US) imaging features to distinguish it from other solid intrahepatic mass lesions (Fig. 2). The infiltrative intrahepatic type may present as focal segmental intrahepatic biliary duct dilatation.

**Hilar and Distal Extrahepatic Cholangiocarcinoma**

US is usually the initial diagnostic imaging procedure in most cases of suspected extrahepatic cholangiocarcinoma that present with jaundice to assess for biliary dilatation. Unfortunately, US may fail to detect infiltrative biliary duct cancer, especially when tumors are small, but an abrupt change in the caliber of bile ducts may indicate the location of a tumor (Fig. 3).

The sensitivity and specificity of US differ with tumor type, quality of the equipment, and experience of the operator [30]. Therefore, the determination of the extent of a cancer and staging workup generally rely on other imaging modalities.

**Computed Tomography**

Computed tomography (CT) is often the initial diagnostic test for most indications in the abdomen because of its versa-
ility and availability and because it helps to survey the entire abdomen for potential metastatic disease (Figs. 4 and 5).

The speed and thin-section acquisition capability of multidetector row CT (MDCT) enable rapid multiphasic scanning through the region of interest. With modern scanners, the entire upper abdomen can be covered with a collimation of <1 mm in one breathhold. With these data, high-quality multiplanar reconstructions can be acquired, which are helpful for assessing the anatomy of the biliary system [31]. Using postprocessing techniques, the biliary tree and liver vasculature can be mapped to determine local staging (Fig. 6). The CT appearance of cholangiocarcinoma is largely dependent on its anatomic location within the biliary tree.

**Intrahepatic Cholangiocarcinoma**

Peripheral, intrahepatic cholangiocarcinomas typically present as mass-like lesions with irregular margins, which do not show significant enhancement in the central parts of the lesion during the arterial and portovenous phases. The tumors show typically delayed enhancement because of interstitial contrast media uptake (Fig. 7). Frequently noted adjunct signs in peripheral cholangiocarcinoma include capsular retraction and dilatation and thickening of the peripheral intrahepatic ducts [32].

**Hilar and Distal Extrahepatic Cholangiocarcinoma**

Hilar cholangiocarcinoma may be infiltrative (>70% of cases), a polypoidal intraductal mass, or an exophytic mass similar to intrahepatic mass-forming cholangiocarcinoma. Infiltrative hilar cholangiocarcinoma may manifest as a thickening of the ductal wall on contrast-enhanced CT, which is often hypoattenuating relative to the liver parenchyma in the portovenous phase and hyperattenuating in the delayed phase [33]. Nonunion of the right and left hepatic ducts with or without a visibly thickened wall is a typical finding of infiltrating hilar cholangiocarcinoma. Dilatation of the intrahepatic bile ducts in a single, small hepatic lobe with hypertrophy of the contralateral lobe suggests the atrophy–hypertrophy complex, as seen with tumors chronically obstructing a single lobe and invading the ipsilateral portal vein [34] (Figs. 8 and 9).

**Figure 3.** Ultrasound (US) image of the right lobe of the liver from a curved transducer. This figure demonstrates markedly dilated intrahepatic ducts without evidence of a focal mass lesion. This is a typical US finding in small Klatskin tumors.

**Figure 4.** Oral and i.v. contrast-enhanced axial computed tomography image through the liver in the portal-venous/delayed phase. This figure demonstrates an irregular infiltrating left lobe mass with associated capsular retraction and focal biliary dilatation. Note also, however, the enhancing gastrohepatic ligament nodes (arrows), suggesting nodal involvement.

**Figure 5.** Oral and i.v. contrast-enhanced axial computed tomography (CT) image through the lower abdomen in the portal-venous/delayed phase. This image illustrates the power of CT as a survey examination. Note the multiple soft tissue nodules in the mesentery consistent with metastatic disease (arrow).
The extent of intraductal tumor spread tends to be underestimated with CT, and the reported sensitivity of CT for the detection of tumor extension along the biliary radicals is variable. In a study with thin-section spiral CT, microscopic carcinoma invasion of the intrahepatic bile ducts was found to be more extensive at pathology than was suggested by helical CT in all patients [35, 36]. A recent study has reported a CT sensitivity for detection of the extent of bile duct involvement of 84%. However, this was in combination with cholangiography [37].

In dynamic contrast-enhanced CT, the arterial and portal-venous enhancement phases are separated, and the vascular structures can be displayed such that CT angiography using MDCT provides vascular details equivalent to those with catheter angiography in detecting clinically relevant anatomy of the hepatic arteries and portal vein in the context of preoperative planning for tumor resection [33, 37–39]. Regarding detection of small lymph node and peritoneal metastases, CT has limited sensitivity of approximately 50% for N2 metastases [37]. The overall accuracy of CT for assessing resectability is in the range of 60%–75% [37, 38, 40].

**Figure 6.** A representative contrast-enhanced axial computed tomography image of the liver from a young patient who presented with jaundice shows a heterogeneously enhancing mass in dome of the liver with possible invasion into the IVC (arrow). These features are typical of a peripheral, intrahepatic cholangiocarcinoma.

**Figure 7.** Reconstructed computed tomography image in the coronal plane of the same patient as in Figure 6. This figure highlights the multiplanar capability of multidetector row computed tomography in order to demonstrate the liver vasculature. Note the tumor relationship with the inferior vena cava (arrow) is better appreciated on this view.

**Figure 8.** Axial computed tomography image with oral and i.v. contrast medium from a patient with hilar cholangiocarcinoma demonstrating intrahepatic biliary dilatation in both the left and right lobes of the liver. In addition, there is a subtle soft tissue thickening in the region of the confluence of the left and right hepatic ducts consistent with a cholangiocarcinoma (arrow).

**Figure 9.** The corresponding minimum intensity projection coronally reformatted computed tomography image from the same patient as in Figure 8 demonstrating intrahepatic biliary dilatation in both the left and right lobes of the liver with a soft tissue mass in the proximal common hepatic duct (arrow) consistent with a Klatskin tumor.
Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) along with magnetic resonance cholangiopancreatography (MRCP) is ideally suited to evaluate the bile ducts above and below a stricture and also identifies intrahepatic mass lesions. Because of their intrinsic high tissue contrast and multiplanar capability, MRI and MRCP are able to detect and preoperatively assess patients with cholangiocarcinoma, investigating all involved structures, such as the bile ducts, vessels, and hepatic parenchyma. MRCP is largely operator independent, but special care should be taken to improve biliary tree depiction. In addition, when patients are referred for MRI, the biliary tree has often collapsed because of a preceding biliary drainage. In such cases, the evaluation of biliary pathologies is virtually impossible by MRCP. Ideally, therefore, MRCP should be performed before biliary drainage whenever possible.

Intrahepatic Cholangiocarcinoma

On MR images, cholangiocarcinomas appear hypointense on T1-weighted images and hyperintense on T2-weighted images [41]. Central hypointensity can be seen on T2-weighted images and corresponds to fibrosis. On dynamic MR images, cholangiocarcinomas show moderate peripheral enhancement followed by progressive and concentric filling in the tumor with contrast material. Pooling of contrast within the tumor on delayed MR images may be seen in peripheral cholangiocarcinoma, similar to CT (Fig. 10).

Hilar and Distal Extrahepatic Cholangiocarcinoma

Hilar cholangiocarcinoma has similar signal intensity to that of peripheral tumors both on T1- and T2-weighted images. Most are typically hypovascular tumors compared with adjacent liver parenchyma, showing a heterogeneous enhancement that gradually increases to a peak on delayed images [42]. MRCP, with half Fourier techniques, can produce excellent noninvasive cholangiographic images that depict hilar obstruction and subsequent dilatation of upstream bile ducts [43]. The accuracy of MRCP in assessing the level and the morphology of bile duct obstruction is comparable with that of direct cholangiography by endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography [41, 44–46].

In a small series, MRCP accurately assessed the level of bile duct involvement, according to the Bismuth–Corlette classification in 84% (10/12) of patients [47] (Figs. 11 and 12).

Dynamic contrast-enhanced MRI is comparable with angiography in the assessment of portal vasculature invasion in patients with cholangiocarcinoma [46]. In one series, portal invasion was accurately detected with dynamic MRI studies in eight (67%) patients, overestimated in 8% of patients, and underestimated in 25% of patients [47]. Tumor invasion into arterial or venous vessels can also be depicted. A recent MR study showed sensitivities, specificities, and accuracies comparable with those of digital subtraction angiography [48] (Fig. 13).

For detection and assessment of invasion into the liver parenchyma of peripheral intrahepatic and hilar cholangiocarcinoma, not only gadolinium chelates but also ferumoxide contrast agents are helpful because of their high tumor–liver contrast [49]. Novel tissue-specific MR contrast agents with hepatobiliary and reticuloendothelial cell affinity have shown the potential to enhance the detection as well as staging of liver tumors. Because of the longer imaging window available with these contrast agents, high spatial resolution imaging of the liver can be performed in multiple short breathholds. A new MR contrast agent, gadobenate, has recently received U.S. Food and Drug Administration approval. It has a dual mode of action with initial extracellular circulation and a delayed liver-specific uptake. Therefore a single-contrast agent may serve both for liver lesion characterization and lesion detection. Ultra-small iron-oxide (USPIO) particles contrast agents with lymph node specificity allow selective negative enhancement of normal lymphoid tissue and thus may help characterize lymph nodes as benign or malignant. USPIO particles are taken up by the lymph nodes 24–36 hours following i.v. infusion. The normal lymph node demonstrates signal loss as a result of the susceptibility effect on T2*-weighted images, whereas the pathologic nodes maintain their native signal intensity [50].
PET
PET and PET/CT using the glucose analog FDGue is a rapidly evolving functional imaging modality that has proved useful for preoperative staging of a number of tumor types. It is well established that a variety of malignant tumors avidly accumulate FDG. Both CT and MRI are limited in the detection and characterization of metastasis to the lymph nodes and peritoneum. In general, metastatic disease to the N2 level or additional lymph nodes at the celiac, periporal, or superior mesenteric levels suggests advanced disease and should be considered a contraindication to resection. However, these findings are often made only after surgical exploration, despite extensive presurgical staging, and may preclude curative resection. FDG-PET is of value for discovering unsuspected distant metastases particularly in patients with peripheral cholangiocarcinoma because of the likelihood of distant metastases at the time of diagnosis [51] and the high FDG uptake in the peripheral type. This may have a significant impact on clinical decision making and on the management of peripheral cholangiocarcinoma (Figs. 14 and 15).

Figure 11. Coronally reconstructed magnetic resonance angiography image demonstrating tumor invasion of the right portal vein (arrow).

Figure 12. Coronal T2-weighted magnetic resonance cholangiopancreatography image from a patient with a Klatskin’s tumor has been shown. Note bile duct strictures at the hilar confluence with resultant proximal biliary dilatation.

Figure 13. Endoscopic retrograde cholangiopancreatography image from the same patient as in Figure 12 demonstrating multiple strictures at the hila with intrahepatic biliary ductal dilatation but lacking the anatomic detail of the corresponding magnetic resonance cholangiopancreatography image in Figure 12.

Figure 14. Fused positron emission tomography/computed tomography (PET-CT) axial image in a patient with a pathologically proven cholangiocarcinoma demonstrating increased fluorodeoxyglucose uptake in a small-size gastrohepatic ligament lymph node suggestive of metastatic disease.
In a series by Kim et al. [52] unsuspected distant metastases were found in four of the 21 patients, all of whom had peripheral cholangiocarcinoma. In the assessment of hilar cholangiocarcinoma, FDG-PET did not perform better than conventional imaging. However, the authors concluded that it might play a role in cases of suspected hilar cholangiocarcinoma with ambiguous radiological findings and nonconfirmatory biopsy results. In a similar study, FDG-PET led to a change in surgical management in 30% (11 of 36) of patients evaluated for cholangiocarcinoma because of detection of unsuspected metastases [53]. Kluge and colleagues [54] found that PET is highly sensitive and specific for the detection and localization of cholangiocarcinoma. However they concluded that it is not suitable for detection of regional lymph node metastases.

Figure 15. Fused positron emission tomography/computed tomography (PET-CT) axial image in the same patient as in Figure 14 demonstrating increased fluorodeoxyglucose uptake in a more distal para-aortic node (arrow) consistent with metastatic disease.

In their study, regional or hepatoduodenal lymph node metastases were detected with PET in only 2 of 15 cases, whereas distant metastases (peritoneal carcinomatosis, pulmonary metastases) were diagnosed in 7 of 10 cases. In a more recent study, Kato and coworkers [55] found that FDG-PET accurately evaluated the N component of the disease in 86% of patients, compared with 50% with CT. PET performs poorly in patients with mucinous cholangiocarcinoma, which is not FDG avid [56].

Screening in High-Risk Individuals

Currently, sufficient evidence is not available to support a benefit for screening in the early detection of cancerous or precancerous lesions. Also, there are no recommendations for screening patients with risk factors such as primary sclerosing cholangitis and chronic hepatitis for detecting bile duct cancers. However, in high-risk patients with elevated CA-19-9 levels, FDG-PET or PET/CT may play a role in the detection of early tumors. By virtue of increased metabolic activity in neoplasms, areas of greater FDG uptake may suggest cholangiocarcinoma.

Conclusion

Imaging plays a crucial role in aiding the differentiation of benign and malignant disease, defining the location and extent of cholangiocarcinoma, as well as directing biopsy with EUS, US, or CT. PET and PET/CT have the potential to identify sites of extrahepatic metastases.

Disclosure of Potential Conflicts of Interest

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