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Imaging bile duct tumors: staging

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Abstract

Cholangiocarcinoma (CC) is the most frequent neoplasm of the biliary system. According to its anatomic origin in the biliary tree it is usually classified as intrahepatic, perihilar, or extrahepatic distal CC. Tumors originated in these areas differ in biological behavior and management. The stratification of the patients aligned to therapeutic options and prognosis is a key point in the management of CC. Thus, specific staging systems have been designed for each anatomical location. They are precise for surgical planning, to establish prognosis after surgery, or to compare the benefits of different therapeutic approaches, but they are less accurate to stratify patients into a therapeutic decision algorithm. Imaging tools, mainly multidetector computed tomography and magnetic resonance imaging (MRI), allow full assessment of the diagnosis and extension of the tumor. They are especially useful in establishing the correct diagnosis and determining resectability, which reaches a high negative predictive value, identifying those patients in whom surgery will not be effective. We will discuss the different staging systems for CC, the radiologic characteristics with classical and recently described signs that allow a confident diagnosis of the disease and the criteria for resectability of biliary tract malignancies.

Key words: Cholangiocarcinoma—Staging—MDCT—MRI—Review

Cholangiocarcinoma (CC) is usually classified, attending to its origin in the biliary tree, as intrahepatic (iCC), perihilar (pCC), also called Klatskin tumor, and distal (dCC). This distinction is associated with a different biology and management of these tumors. The landmark to distinguish iCC from pCC is the second-order biliary ducts [1]. Those tumors originated in the right, left, or common ducts are considered pCC [2]. The junction of the cystic duct in the common duct, even though variable in its insertion, is the landmark to distinguish between pCC and dCC [3]. Although an anatomic overlap may exist between iCC involving the major hepatic ducts and the exophytic type of pCC, further division of pCC into isolated sclerosing pCC and mass-forming tumor pCC has not demonstrated benefit in terms of survival [4]. The iCC type accounts for less than 10% of the total cases, the pCC type represents about 50% of them, and dCC represents more than 40% of the cases [5].

The silent clinical character of this disease leads to limited early clinical diagnosis, reducing the options for a potentially curative surgical treatment. Thus, prognosis is poor with median survival less than 24 months [4]. Curative surgery is achieved in only 25–30% of patients, with the majority having unresectable disease. The incidence of distant metastases at presentation is up to 20–30% [6].

Several staging systems have been proposed for different locations of CC, but none of them clearly stratify patients for therapeutic options and they lack enough prognostic accuracy and external validation [4]. The different staging systems and radiologic characteristics of CC that may determine the treatment options and prognosis for the patients will be reviewed for each location.

Intrahepatic cholangiocarcinoma

iCC is the second most frequent intrahepatic malignant primary liver tumor, after hepatocellular carcinoma (HCC) and the most common one in the absence of liver cirrhosis. Current evidence is that surgery is the only effective treatment, but resectability remains very low, at 10–20% of patients. Recently reported 5-year survival rates range between 30% and 35% [7–9]. The Liver Cancer Study Group of Japan (LCSGJ) distinguished three macroscopic growth types for iCC: mass-forming, periductal-infiltrating, and intraductal growth types [1]. The mass-forming type forms a definite mass, located in the liver parenchyma and is the most common form of

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iCC [10], representing up to 86% of all of them [6]. The periductal-infiltrating type is defined as iCC which extends mainly longitudinally along the bile duct wall, often resulting in dilatation of the peripheral bile duct. The intraductal growth type proliferates toward the lumen of the bile duct forming papillary projections or like a tumor thrombus.

The presence of multiple lesions, both satellite nodules or intrahepatic metastases, and vascular invasion have predicted a worse prognosis in a cohort of 598 patients, better than other factors as tumor size [10]. Tumor size larger >5 cm was not an independent predictor of survival in that series. So, the 7th edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system has shifted to consider the presence of at least one of these factors to assign a T2 category (Table 1) [2, 11]. Median survival was 53 months for stage II and 16 months for stage III, and it better predicted survival than other classification systems in a series of 522 patients [12]. Other factor associated to bad prognosis was the presence of lymph node metastases, also with a poor median survival of 16 months. Another study demonstrated that females, AJCC stage, and R0 resection were independent favorable predictors of survival on multivariate analysis [13].

Table 1. TNM staging system for intrahepatic cholangiocarcinoma [11]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
T4	Tumor with periductal invasion
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Distant metastasis (M)	
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

Different imaging modalities may be used in the evaluation of iCC to characterize the lesions and to identify those items that determine prognosis. Computed tomography (CT) and magnetic resonance imaging (MRI) are both helpful in the detection and characterization of the primary tumor. On CT iCC typically presents as a low attenuation mass with an incomplete peripheral enhancement in the arterial phase, that may become isodense or hypodense during the portal venous phase. Active tumor is present in this peripheral area. Meanwhile, the central zone of the tumors is enhanced on delayed images typically obtained 5–10 min after the contrast injection (Fig. 1). When necrosis or mucin develops in the center of the lesions, they remain hypodense. Capsular retraction of the liver parenchyma due to the dense fibrotic nature of the tumor may be seen in up to 21% of cases [14]. Dilatation and mural thickening of the peripheral intrahepatic ducts may also be observed [15]. iCC is usually hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. Their central area may be either hypo- or hyperintense on T2-weighted images, due to the presence of dense fibrosis, edema, or mucin. The enhancement pattern is similar to that observed on CT. Some iCC may show an atypical appearance with marked arterial

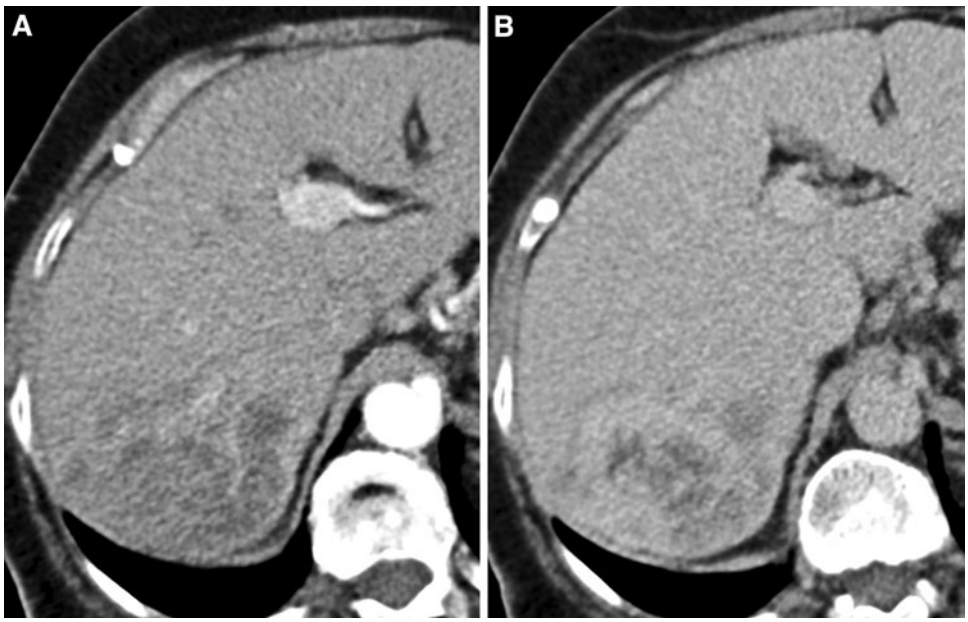

Fig. 1. Intrahepatic cholangiocarcinoma. The tumor is heterogeneous with minimal enhancement in the arterial phase (**A**), and shows a more evident enhancement on images obtained 5 min later (**B**).

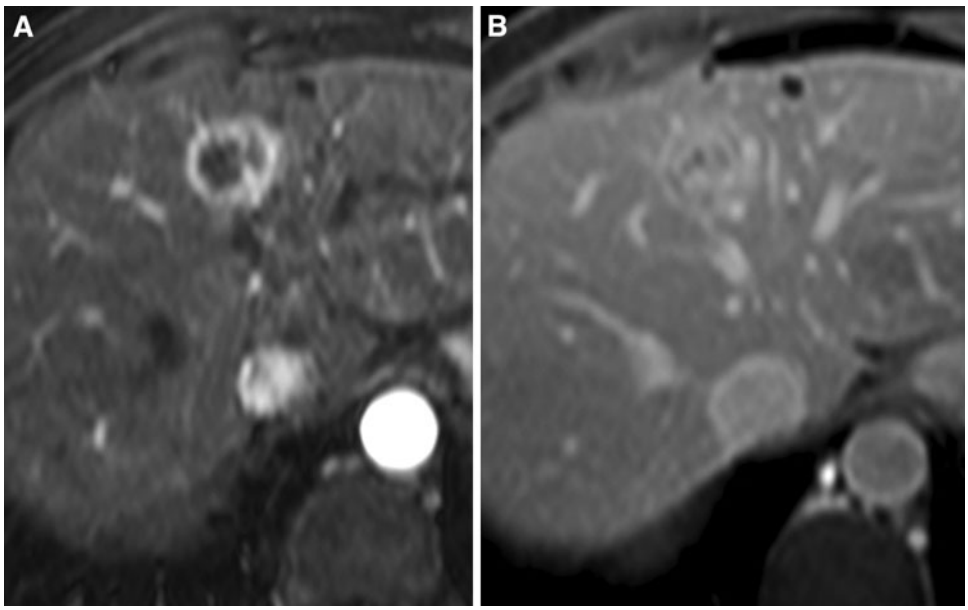

Fig. 2. Intrahepatic cholangiocarcinoma in a cirrhotic patient. The tumor shows intense peripheral enhancement in the arterial phase (**A**), and is heterogeneous and slightly hyperintense in a delayed phase (**B**).

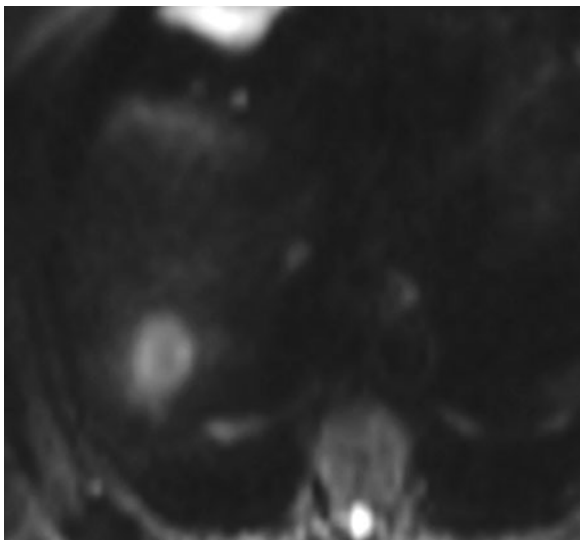

Fig. 3. Intrahepatic cholangiocarcinoma in a cirrhotic patient. DWI obtained with a *b* value of 800 s/mm^2. The target appearance of this tumor has been described as highly specific [18].

enhancement involving larger areas of the tumor. This finding, more frequently observed in patients with liver cirrhosis, has been associated to a better prognosis [16]. Dynamic CT or MRI can help to distinguish iCC from HCC in cirrhotic patients. In a series of 31 confirmed nodules in cirrhotics, all of them showed progressive (81%) or stable (19%) contrast uptake along dynamic series (Fig. 2). No iCC showed a washout pattern, a profile specific for HCC [17]. More recently, Park et al. [18] reported a target appearance on diffusion weighted imaging (DWI) as a reliable sign for distinguishing small mass-forming iCC from small HCC, although a 100% specificity for a correct diagnosis of HCC was not achieved for this sign (Fig. 3). If a liver tumor in a cirrhotic patient does not show washout in delayed phases a biopsy is mandatory for diagnosis, because a confident differentiation between iCC and HCC is not possible by imaging alone. Treatment options are different for both tumors; for instance, liver transplantation is not recommended for cirrhotic patients with iCC.

Contrary to pCC, the literature on staging in iCC by imaging is poor. Satellite nodules may be detected on CT or MRI, usually if they are larger than 1–2 cm [19]. However, preoperative imaging failed in the detection of multiple satellite lesions in 37% of patients operated from a solitary iCC [20]. MRI after injection of liver-specific contrast medium may be helpful in the detection of satellite nodules. In a series, 28% of these nodules were only visible in the hepatospecific phase [21]. Vascular involvement, depicted in approximately 50% of cases, is more often present in the portal tree than in the hepatic veins [19]. When segmental or lobar atrophy is present, it is frequently associated with ipsilateral portal vein encasement. The accuracy of both CT and MRI for portal vein involvement is high, and the false-negative cases are due to smaller involvement of segmental portal branches [22]. On the contrary, both techniques have a lower accuracy (77%) to detect lymph node involvement, and underestimation is frequent [22]. 2-Fluoro-2-deoxy-D-glucose-integrated positron emission and computed tomography (FDG PET/CT) has a little role in the diagnosis of the primary biliary tumors because CT and MRI are at least as sensitive as PET/CT for tumor detection and characterization. Although, sensitivity for detection of nodular type of iCC is high (85–100%), it is lower for the infiltrating type (67–81%). PET/CT is valuable in detecting distant spread of tumor (Fig. 4). It is more accurate than CT to detect both lymph node metastases (76–89% vs. 61–79%) and distant metastases (88–94% vs. 63–78%)

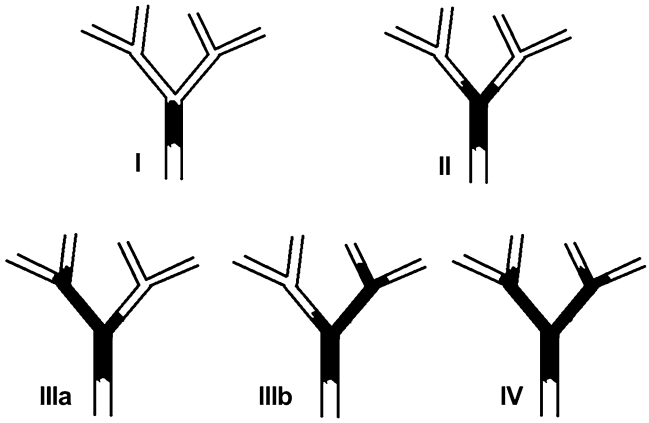

Fig. 4. Scheme illustrating the different options in the modified Bismuth–Corlette classification.

[23, 24]. Moreover, it can modify the treatment in as much as 24% of patients with iCC [25].

Surgical resection is the only therapy associated with long-term survival in these patients, but no consensus exists about defining resectability. As a R0 resection seems to be associated with longer survival, patients who are not good candidates for curative resection are those with metastatic disease or those with multiple intrahepatic lesions, with extensive vascular invasion or those with comorbidities. Lymph node metastases are not a formal contraindication for surgery, although these patients have a worse prognosis [2, 26, 27].

Perihilar cholangiocarcinoma

The primary biliary tumors arising between the right and left and the common hepatic duct up to the cystic duct insertion are classified as pCC, and are also called Klatskin's tumors [4]. Different staging systems have been used to classify pCC, and up to now there is no optimal staging system. The modified Bismuth–Corlette system has been one of the more widely used (Fig. 5) [28]. It focuses only in the level of the ductal infiltration of the tumor. Thus, tumors are classified as type I when they involve the common hepatic duct below the confluence of the left and right hepatic ducts; type II when they involve the hepatic bile duct confluence, without invasion above this level; type III when they extend up to one of the right (type IIIa) or left (type IIIb) hepatic duct bifurcations; and type IV when they reach to both the right and left hepatic ducts, the secondary intrahepatic biliary ducts or involves multiple and discontinuous sites in the right and left ducts. This system was proposed as a guide for surgery, and it does not take into account the lateral extension of the tumor, so it does not provide prognostic information. Moreover, variations in the anatomy of the biliary ducts may change the applicability of the Bismuth–Corlette system (Fig. 6) [3].

The Blumgart group, at The Memorial Sloan-Kettering Cancer Center (MSKCC) developed a system to determine resectability (Table 2). It not only classified tumors in three T groups according to their location and extent of bile duct involvement, as the Bismuth–Corlette system, but also considered portal venous invasion and hepatic lobar atrophy [29]. It was developed after reviewing a series of 225 cases, and reported an accuracy of 86% in the preoperative staging of the local extent of the disease for the three T groups proposed, with significant correlation to R0, N2, and M1 status and survival. It was also validated later in a larger group of patients by the same group [30]. However, the system does not evaluate the presence of nodal or distant metastases. Moreover, in the validation series, 295 patients underwent surgery but only 53% could be resected with curative intent. Other authors have not found correlation between these T stages, resectability, and survival [31].

In the 7th edition of the AJCC/UICC staging system, pCC has been separated from extrahepatic dCC and staged as a different disease (Table 3) [11]. Besides the TNM grouping it has additional descriptors for the residual tumor (R) and histological differentiation (G). It is used to stage tumors after surgical resection but fails to preoperatively indicate local resectability of the tumor.

In order to provide information regarding resectability, indications for liver transplantation, and prognosis, a new surgical staging system for pCC has been introduced by an international CC leaders working group [3]. This new system takes into account eight characteristics for staging: the size of the tumor, (<1, 1–3, or ≥ 3 cm), the extent of the disease in the biliary ducts following the Bismuth–Corlette classification, the morphology of the tumor (sclerosing, mass-forming, mixed, or polypoid), the presence of hepatic artery or portal vein encasement (tumor–vessel contact $\geq 180°$), the volume of the potential liver remnant, the status of lymph node metastases (hilar and along the hepatic artery vs. celiac and periaortic), the presence of distant metastases, and the presence of underlying liver disease. This system has shown some weak points: the tumor size has not shown prognostic implications in several studies; the presence of lobar atrophy has not shown prognostic value in multivariate analysis; so, it gives more information for surgical planning than for prognosis, and criteria for vascular involvement are not firmly established [32]. The validity of this system will require a large prospective series. The authors have created a registry to enable every center to prospectively enter data on their patients with pCC (www.cholangioca.org).

Widely recognized independent prognostic factors for pCC include lymph node metastatic status, tumor differentiation, and R0 resection [4]. In summary, there is currently no optimal staging system for pCC. Those commented before are more useful to help in the surgical

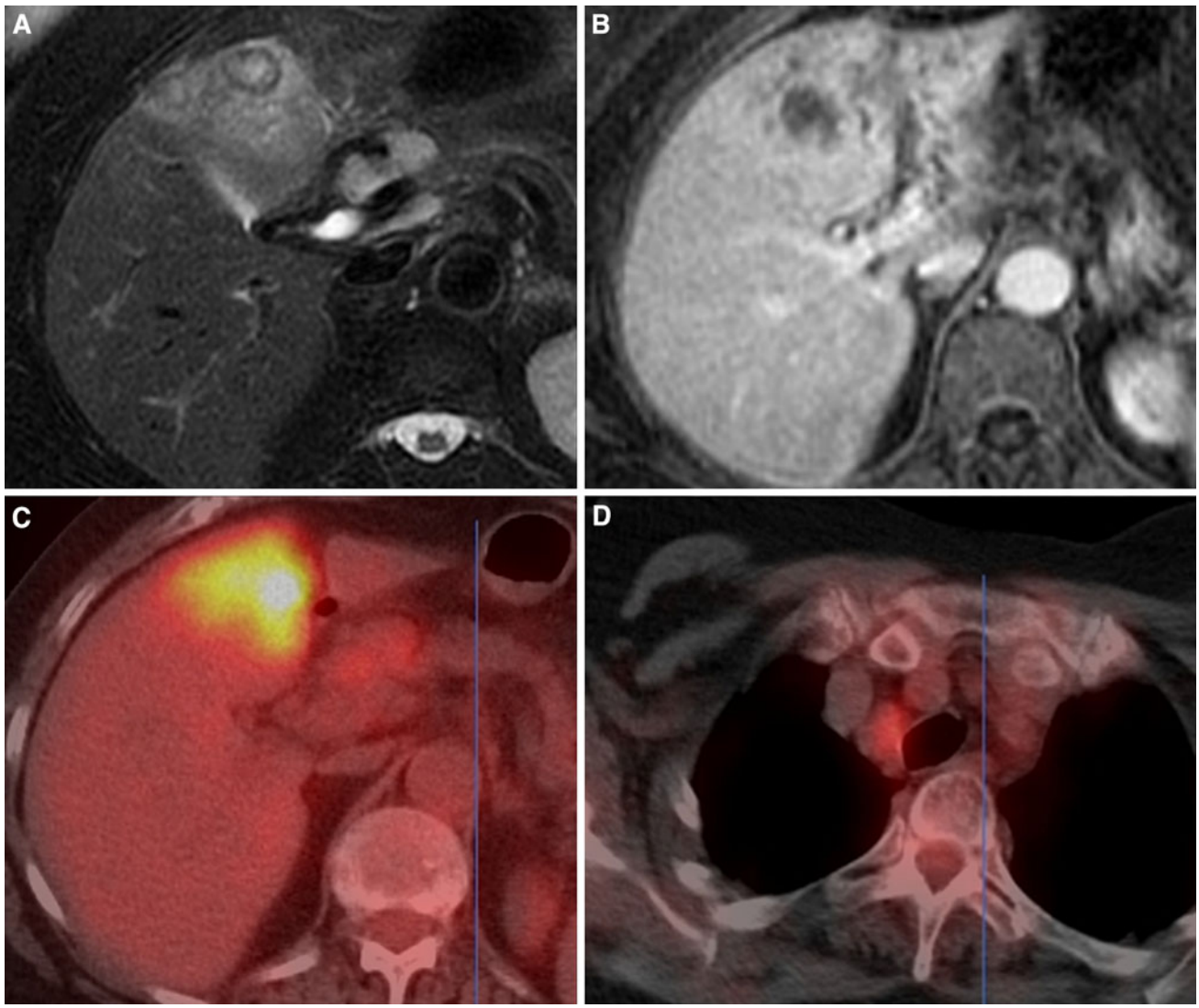

Fig. 5. Intrahepatic cholangiocarcinoma. A left liver mass is hyperintense on T2-weighted images (**A**) and is heterogeneous and predominantly isointense on delayed enhanced images (**B**). PET/CT (**C**, **D**) demonstrate metabolic activity in the lesion, a more frequent finding in intrahepatic cholangiocarcinoma than in perihilar cholangiocarcinoma. The added value of PET/CT is the demonstration of distant disease, as in this case, in the mediastinal lymph node, excluding the patient for radical surgery.

planning, but are limited in prognostic information or in the selection for good surgical candidates. Clearly, investigation on new classification systems is necessary.

Three main growing patterns may be observed in pCC: an exophytic (mass-forming) type, a periductal-infiltrating type, also referred to as a sclerosing type, and an intraductal type. Periductal-infiltrating tumors can form an associated mass, showing a mixed growing pattern and they are the most common subtype of pCC. Intraductal tumors vary from preneoplastic lesions to invasive carcinomas, and the later are frequently well-differentiated neoplasms. They can be subclassified further into papilloma type, intraductal growing type, mucin-producing type, and cystic type [2]. Tumors that originate in the common bile duct present with painless, obstructive jaundice and are often smaller lesions with a somewhat better prognosis. Those arising from the right or left hepatic ducts do not cause jaundice until later stages and so, tend to be larger and infiltrate the surrounding hepatic parenchyma.

Cross-sectional imaging techniques may show a focal mural thickening with luminal obliteration and proximal bile duct dilatation. Periductal thickening may be associated with a mass, focal liver atrophy, vascular encasement, involved lymph nodes, and distant metastases. Tumor signal may be mildly to markedly increased on T2-weighted images. About 80% show enhancement on arterial and/or portal phases on CT or MRI and most of them show late enhancement due to their sclerotic nature (Fig. 7) [33]. When small tumors are isodense or

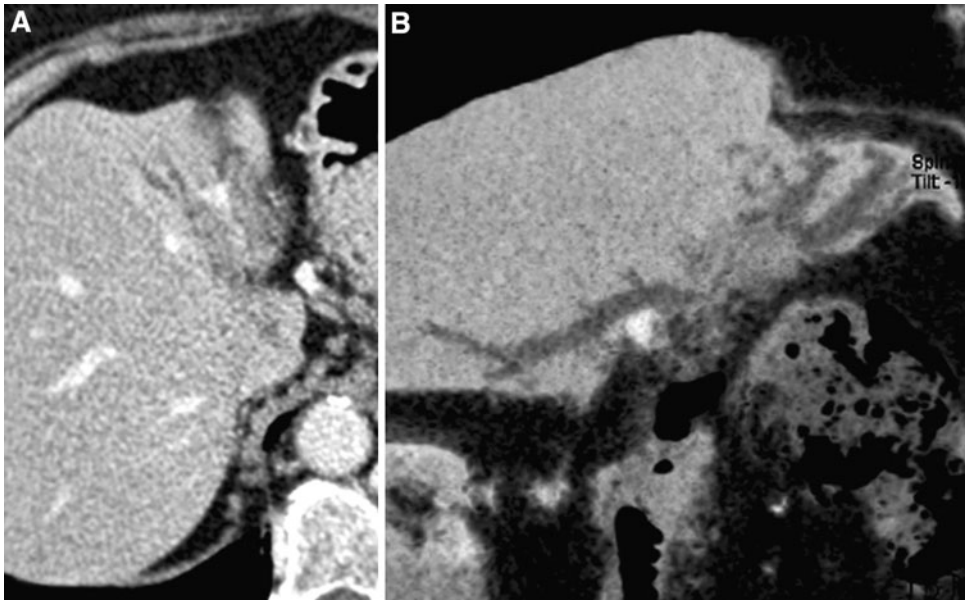

Fig. 6. A left-sided perihilar cholangiocarcinoma, with a mass-forming component invades the left portal vein and dilates the bile ducts and causes parenchymal atrophy in the left lateral segment (**A**). Right hepatic ducts are not dilated, but an infero-posterior duct, indicating its independent origin from the left duct (**B**). Variants in the biliary tree are not considered in the Bismuth–Corlette classification.

Table 2. Proposed T-stage criteria for hilar cholangiocarcinoma at the Memorial Sloan-Kettering Cancer Center [29]

Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicals
T2	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicals and ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicals; or unilateral extension to second-order biliary radicals with contralateral portal vein involvement; or unilateral extension to second-order biliary radicals with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement

Table 3. TNM staging system for perihilar cholangiocarcinoma [11]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes
Distant metastasis (M)	
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

isointense with regards to normal neighbor structures, they may be difficult to identify. Intrahepatic bile duct dilation and segmental hepatic atrophy, if present, mark the site of origin of the neoplasm. Magnetic resonance cholangiopancreatography (MRCP) allows for a detailed evaluation of the normal and obstructed bile ducts.

Unfortunately these findings are not pathognomonic of Klatskin tumor. Neuroendocrine tumors, metastases, primary or secondary sclerosing cholangitis associated to autoimmune pancreatitis, and recurrent cholangitis may also show similar findings [34, 35]. Also, segmental biliary dilatation may occur after cholecystectomy or distal

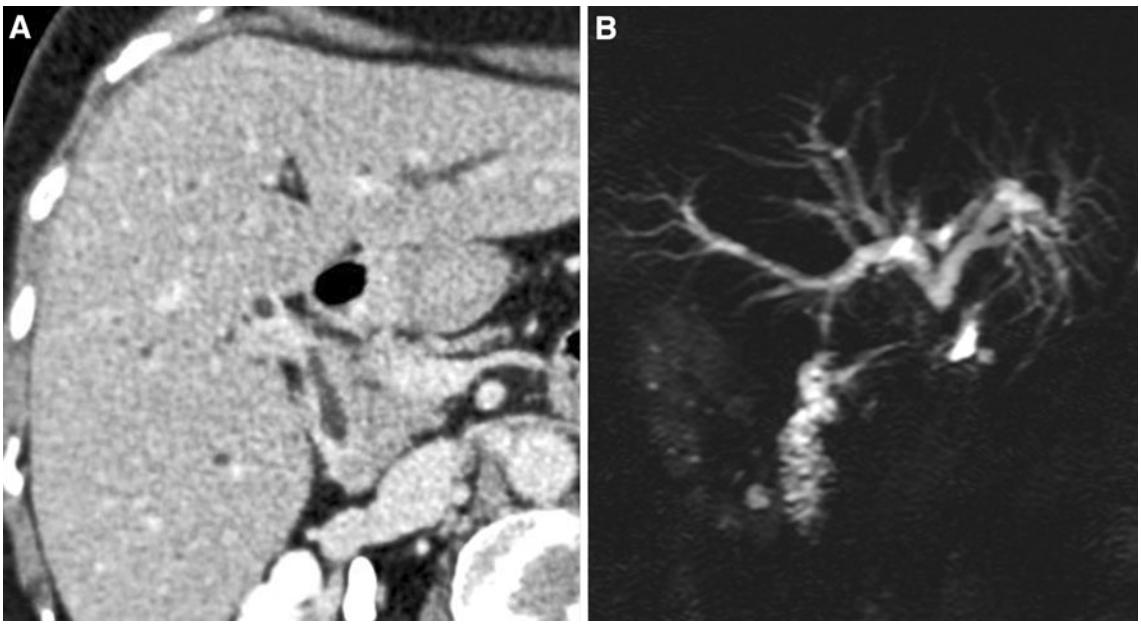

Fig. 7. Sclerosing type of perihilar cholangiocarcinoma. Mural thickening with contrast enhancement in the portal venous phase is present in the common duct (**A**). It causes dilatation of the upward biliary tree, visible at magnetic resonance cholangiopancreatography (**B**). Right and left ducts remain in continuity, a finding that fits the definition of a Bismuth–Corlette type I tumor.

gastric surgery. Benign strictures are more regular, symmetrical, and smooth shaped, while malignant ones are abrupt and irregular or may be associated with local or distant extension. MRI with MRCP was very useful to identify pCC in a series of 230 patients with primary sclerosing cholangitis, 10% of whom developed a pCC in the follow-up, with a reported sensitivity of 89% and accuracy of 76% [36]. Moreover, the use of DWI has shown a significantly higher detection rate than MRCP alone (94.3% vs. 74.3%) in a series of 56 patients with suspected pCC [37]. A *b* value of 800 s/mm^2 was the more suitable for tumor detection, with a contrast-to-noise ratio between tumor and normal liver higher than those for T2-weighted images. Also, ADC value correlated with the cellular differentiation degree, showing lower ADC values those poorly differentiated tumors [38].

Nodular type of pCC may be confined to the ductal tree. In these cases, distinguishing this condition from the less aggressive intraductal growing type tumor may be difficult. Some findings as papillary or irregular polypoid shape of the intraductal growing tumor, lack of constriction of the tumor-bearing segment, hypoenhancement of the tumor during the equilibrium phase, tumor multiplicity, upstream and downstream bile duct dilatation, and no bile duct wall thickening adjacent to the tumor favor the diagnosis of intraductal growing type. If at least two of these six features are present, sensitivity and specificity in the correct diagnosis reaches 95% and 70%, respectively [39]. Mucin-producing intraductal papillary neoplasm of the bile ducts (IPMN-B) is becoming a specific type of neoplasm. It shares histopathologic features with intraductal papillary mucinous neoplasms of the pancreas and is often associated with mucin over-production. Unlike biliary mucinous cystic neoplasm, IPMN-B communicates with the bile ducts, a finding that can be recognized on MRCP. When malignant transformation occurs, IPMN-B is classified as intraductal growing type CC. These tumors often can be completely resected and have a more favorable prognosis [40].

Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiopancreatography have been considered the standard of reference for evaluating the ductal extent of pCC. They allow tissue sampling by washing, brushing, or biopsying the intraductal tumor. Also, therapeutic drainage can be undertaken when necessary. Nevertheless both are invasive, operator-dependent, and associated with procedural risks including duodenal perforation, biliary leakage, cholangitis, bleeding, and pancreatitis [41]. So they are used when cytological diagnosis or decompression of the biliary tree is required.

Biopsy may be required in some cases to confirm the diagnosis, but a cytological diagnosis of pCC is difficult. Endoscopic brushing of the biliary ducts shows a limited sensitivity of 20% due to the scanty cells usually obtained [42]. Percutaneous biopsy in periductal-infiltrating cancers is often not possible if they are not associated with a mass. Also, endoscopic US-guided biopsy is not warranted due to the risk of seeding. Recently, chromosomal

analysis using fluorescent in situ hybridization has been established as an additional test for biliary tissue samples, with a sensitivity of 47% and a specificity of 97% for detection of pCC in patients with primary sclerosing cholangitis [43]. Although not disposable in many centers, this method seems promising in equivocal cases.

The extent of ductal involvement can be accurately predicted in 84% of patients combining CT and transhepatic cholangiography [44]. Direct multidetector computed tomography (MDCT) cholangiography, introducing contrast medium through a previously biliary drainage, has also shown excellent results in the determination of the extension of bile duct invasion at primary and secondary confluences in a series of 11 patients with pCC [45]. MRI with MRCP shows a superb anatomical demonstration of the biliary tree without invasive procedures (Fig. 8). The reported accuracy of MRCP in determining the extent of bile duct tumors ranges from 71% to 96% [41]. pCC has a tendency to spread between the hepatocyte plates, along the duct walls and adjacent to nerves, with perineural invasion found in as many as 81% of cases. This is a cause of underestimation of the tumoral extension. Delayed periductal enhancement on MRI has shown a strong correlation (0.93) with this periductal spread and improves the diagnostic accuracy of MRCP in assessing biliary infiltration and resectability [46].

Diagnostic criteria for vascular involvement have been proposed, imported form that used in pancreatic cancer: vessel contour deformity, vascular stenosis or occlusion related to the tumor, or vessel–tumor contact ≥ 180°. Portal venous involvement in pCC narrows and encases the vessels, in contrast to HCC that commonly invades the vascular lumen (Fig. 9). These signs have shown accuracies of 93% and 85% for depiction arterial and portal vein invasion, respectively [44]. When segmental or lobar atrophy is present, ipsilateral encasement of the portal vein is often detected.

Signs for regional nodal involvement include short-axis diameter >10 mm, the presence of central necrosis irrespectively of node size, or lymph node hyperattenuation compared with liver parenchyma in the portal phase. However, sensitivity of CT in the detection of regional lymph node metastases is only of 54% [44].

Radiologic criteria for unresectability defined by the group of the MSKCC are widely accepted (Table 4) [29]. Nevertheless, only in 50% of those patients who did not meet these criteria and who underwent exploration with curative intent, a resection of all gross tumor was performed, and only 39% achieved a R0 resection. Modified criteria for unresectable disease have also been proposed: contralateral hepatic artery invasion, segmental main or contralateral portal vein invasion longer than 2 cm, biliary extension to the contralateral secondary confluence farther than 2 cm from the hepatic hilum, enlarged lymph nodes at the right side of the celiac axis and portocaval area, and ancillary findings such as peritoneal seeding and liver parenchymal changes of lobar atrophy. Attending these criteria the positive predictive value for assessing resectable disease was 71–85%, the negative predictive value for assessing unresectable disease was 85–92%, and accuracy for overall resectability was

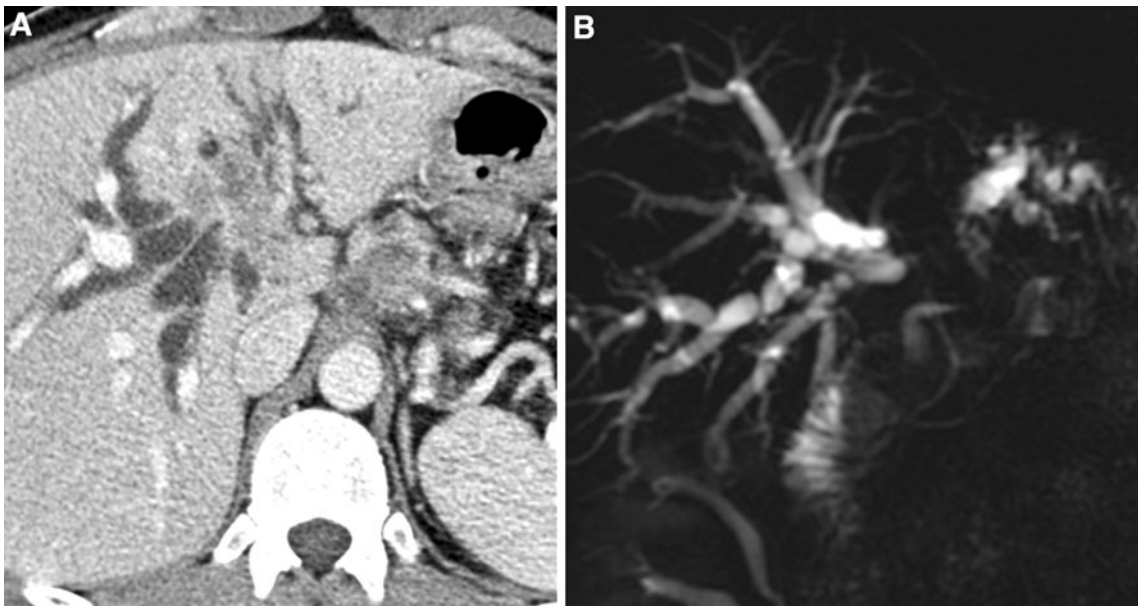

Fig. 8. Perihilar cholangiocarcinoma centrally located in the liver. CT (**A**) shows a typical hypodense tumor involving the biliary tree. Magnetic resonance cholangiopancreatography (**B**) depicts the biliary extension, with infiltration of the second-order right ducts and the main left duct. This is a type IIIa configuration in the Bismuth–Corlette classification. Enlarged and necrotic lymph nodes are visible in the celiac area (N2), precluding a radical resection with a R0 margin.

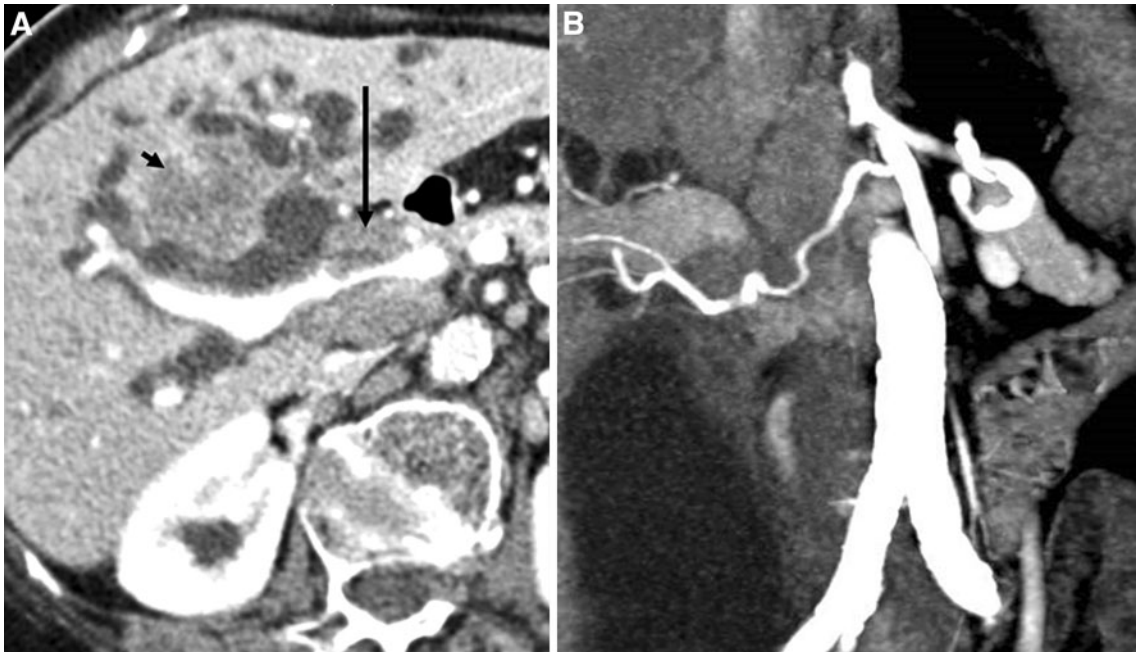

Fig. 9. Perihilar cholangiocarcinoma. CT in the portal phase (**A**) shows a mass-forming tumor (*long arrow*) and a huge extension into the liver parenchyma (*short arrow*). The hilar tumor locally infiltrates and stenoses the portal trunk. The arterial phase (**B**) also shows infiltration of the common hepatic artery.

Table 4. Criteria for unresectability of perihilar cholangiocarcinoma [29]

Patient factors
Medically unfit or otherwise unable to tolerate a major operation
Hepatic cirrhosis
Local tumor-related factors
Tumor extension to secondary biliary radicals bilaterally
Encasement or occlusion of the main portal vein proximal to its bifurcation
Atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion
Atrophy of one hepatic lobe with contralateral tumor extension to secondary biliary radicals
Unilateral tumor extension to secondary biliary radicals with contralateral portal vein branch encasement or occlusion
Metastatic disease
Lung, liver, or peritoneal metastases
Histologically proven metastases to N2 lymph nodes

74–87% in two series of 55 and 32 patients, respectively [44, 47]. Local tumor extent such as portal vein invasion and hepatic lobar atrophy does not preclude resection. Volume calculation of liver remnant after planned surgery may be required to optimize surgery. Long-term survival has been seen only in patients who underwent extensive liver resections, suggesting that bile duct excision alone is less effective [29, 30, 48]. In contrast to iCC, pCC shows less uptake of FDG, so the sensitivity for tumor detection is low for PET/CT, but it has shown a higher sensitivity and specificity for distant metastases, in particular for lymph node detection. So, it may impact on the selection of the therapeutic approach [25, 49].

A recent meta-analysis published in 2012 concerning different radiologic techniques in the evaluation of staging pCC included a review of 16 articles, the majority of them related to CT performance [50]. An estimated overall accuracy of 86% was observed for CT in the evaluation of ductal extent of the tumor. The sensitivity and specificity for evaluation of portal vein, hepatic artery, and lymph node involvement were 89% and 92%, 83% and 93%, and 61% and 88%, respectively. So, CT showed acceptable accuracy for assessment of ductal extent and vascular involvement, but low sensitivity for nodal status. Authors also reported that the reviewed CT, MRI, ultrasound, or PET/CT papers studying diagnostic accuracy for pCC staging were sparse and with moderate methodological quality.

Distal cholangiocarcinoma

dCC originates between the insertion of the cystic duct in the extrahepatic channel and the ampulla of Vater. The 7th edition of AJCC/UICC TNM staging classification is the only one that considers them as independent tumors regarding pCC (Table 5) [2, 11]. They have different

Table 5. TNM Staging system for distal cholangiocarcinoma [11]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
T4	Tumor involves the celiac axis, or the superior mesenteric artery
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

treatments and prognostic characteristics. Complete removal of tumor is possible in up to 90% of cases, usually requiring a pancreaticoduodenectomy but 5-year survival rate after curative resections reaches only 25–50% of the patients [6]. This classification shares some of the features of the pCC one. For example, both consider T1 category when tumors are confined to the bile duct wall and T2 when they invade beyond the bile duct without invasion of adjacent organs. However, one study found that the degree of tumor depth infiltration with thresholds in 5 and 12 mm was the strongest predictor for outcome on multivariate analysis [51], much better than the distinction between intra and extramural extension proposed by the AJCC/UICC classification. T3 and T4 categories share features with pancreatic cancer. T3 indicates neighbor visceral involvement and T4 celiac or superior mesenteric artery infiltration. Nodal staging of bile ducts tumors is also different for dCC. It has been published that the presence of two or more involved nodes after surgery impacts negatively on prognosis, with
3- and 5-year survival rates of 10% and 0%, respectively [52]. Besides tumor depth and lymph node invasion other factors that worsen prognosis are pancreatic infiltration, perineural and vascular invasion, and R0 resection [4].

Radiologic morphology of dCC does not differ from more proximal pCC. Both MRI with MRCP and CT are important tools for diagnosis and staging. Tumors show soft tissue attenuation, enhancement on delayed images, and usually show an abrupt termination of the common channel, with an infiltrative thickening of the bile duct wall or an intraductal papillary or nodular mass, mimicking a bile duct stone. As for pCC, differential diagnosis includes benign diseases such as inflammatory conditions, choledocal lithiasis, and periampullary and pancreatic tumors or rarely metastases.

In conclusion, different classification systems have been developed to stage CC. Although they delineate the prognosis of the patients, most of them are fully applicable only after surgery. Ongoing research is being directed toward presurgical systems that anticipate the benefits for the patients in terms of survival. Imaging tools are of pivotal importance to enable a specific diagnosis and to discard those patients with extended tumors for radical extirpation.

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