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EDITORIAL

Extrahepatic biliary cancer: New staging classification

Dhakshinamoorthy Ganeshan, Fanny E Moron, Janio Szklaruk

Dhakshinamoorthy Ganeshan, Janio Szklaruk, Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States

Fanny E Moron, Department of Diagnostic Radiology, Baylor College of Medicine, Houston, TX 77030, United States

Author contributions: Szklaruk J, Ganeshan D and Moron FE contributes to drafting the article, critical revision of the article and final approval of the version to be published; Szklaruk J participates in conception and design, acquisition of data, analysis and interpretation of data.

Correspondence to: Dr. Janio Szklaruk, Professor of Radiology, Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Unit 1473, Houston, TX 77030,

United States. jszklaru@mdanderson.org

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Abstract

Tumor staging defines the point in the natural history of the malignancy when the diagnosis is made. The most common staging system for cancer is the tumor, node, metastases classification. Staging of cancers provides useful parameters in the determination of the extent of disease and prognosis. Cholangiocarcinoma are rare and refers to cancers that arise from the biliary epithelium. These tumors can occur anywhere along the biliary tree. These tumors have been previously divided into extrahepatic and intrahepatic lesions. Until recently the extrahepatic bile duct tumors have been considered as a single entity per American Joint Commission on Cancer (AJCC) staging classification. The most recent changes to the AJCC classification of bile duct cancers divide the tumors into two major categories: proximal and distal tumors. This practical classification is based on anatomy and surgical management. High quality cross-sectional computed tomography (CT) and/or magnetic resonance (MR) imaging of the abdomen are essential information to accurately stage this tumors. Imaging plays an important role in diag-

nosis, localization, staging and optimal management of cholangiocarcinoma. For example, it helps to localize the tumor to either perihilar or distal bile duct, both of which have different management. Further, it helps to accurately stage the disease and identify the presence of significant nodal and distant metastasis, which may preclude surgery. Also, it helps to identify the extent of local invasion, which has a major impact on the management. For example, extensive involvement of hepatic duct reaching up to second-order biliary radicals or major vascular encasement of portal vein or hepatic arteries precludes curative surgery and patient may be managed by palliative therapy. Further, imaging helps to identify any anatomical variations in the hepatic arterial or venous circulation and biliary ductal system, which is vital information for surgical planning. This review presents relevant clinical presentation and imaging acquisition and presentation for the accurate staging classification of bile duct tumors based on the new AJCC criteria. This will be performed with the assistance of anatomical diagrams and representative CT and MR images. The image interpretation must include all relevant imaging information for optimum staging. Detailed recommendations on the items required on the radiology report will be presented.

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Key words: American Joint Commission on Cancer; Staging; Bile duct tumors; Computed tomography; Magnetic resonance

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INTRODUCTION

Staging of cancers provides useful parameters in the determination of the extent of disease and prognosis. The most recent changes to the American Joint Commission on Cancer (AJCC) classification of bile duct cancers divide the tumors into two major categories: proximal and distal tumors and this has major implications in the management of these tumors. In this review, the anatomy, epidemiology, clinical presentations, imaging presentation, staging, and managements of bile duct tumors will be presented with the assistance of anatomical diagrams and radiological imaging.

EPIDEMIOLOGY

The tumors of the bile duct are rare, estimated at 2% of all cancers with an incidence of 0.01%-0.046 % in autopsy series. This percentage includes intrahepatic and extrahepatic tumors. There are countries with a higher incidence of malignancy such as Israel and Japan^[1]. And in certain populations such as the United States Native American there is a higher incidence of bile duct tumors^[2]. The patients present mostly in the 6th to 7th decade of life. The risk factors for extrahepatic bile duct tumors are (1) congenital cystic changes as seen secondary to Caroli's disease or polycystic liver disease; (2) primary sclerosing cholangitis; (3) ulcerative colitis; (4) exposure to chemicals (i.e. thorotrast); and (5) medication such as oral contraceptives and methyldopa^[3,4]. These are shared with other cholangiocarcinoma (bile duct, intrahepatic cholangiocarcinoma, and gallbladder cancers, Figure 1). The method for tumor development is unknown and various possible pathways has been proposed. For example, it is has been proposed that these tumors may developed as a result of (1) chronic inflammatory process in the bile ducts^[4]; (2) mutations; and (3) parasite induced DNA damage^[5].

CLINICAL PRESENTATION

The clinical presentation of bile ducts tumors may mimic the signs and symptoms of pancreatic head cancer (i.e., painless jaundice). The degree of jaundice is dependent on the extent of biliary involvement. The sparing of disease in segments of the biliary tree can compensate in the excretion of bile ducts and result in a delay in the clinical presentation. Other symptoms associated with biliary cancer include diarrhea, weight loss and fever. In the setting of distal bile duct tumors, the tumor may present with symptoms of cholecystitis secondary to Mirizzi's -like presentation, obstruction of the cystic duct. In contrast, the proximal bile duct tumor will not present with obstruction of the gallbladder. The blood work for suspected bile duct tumors may demonstrate elevated levels of CA 19-9 serum markers and abnormal liver function tests^[6,7].

PATHOLOGICAL CLASSIFICATION OF CHOLANGIOCARCINOMA

The anatomy of the biliary tree can be divided into intra-

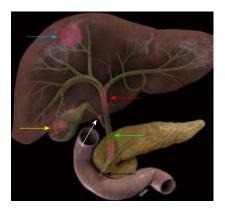


Figure 1 Anatomical distribution of cholangiocarcinoma. The intrahepatic cholangiocarcinoma present most as solid masses in the liver (blue arrow), gall-bladder (GB) cancer present as solid mass in the GB (yellow arrow), proximal bile duct tumors present mostly as infiltrating masses (red arrow), middle bile duct tumors (green arrow), and distal bile duct tumors (black arrow). The cystic duct is labeled with a white arrow.

hepatic and extrahepatic bile ducts. The extrahepatic bile ducts can be further divided into proximal, middle, and distal bile ducts (Figure 1). The proximal extrahepatic bile duct extends from the confluence of the right and left hepatic bile ducts to the level of the cystic duct. The middle portion of the extrahepatic bile ducts extends from the cystic duct to the level of the duodenum. The distal ducts are composed of the bile duct that extends to the level of the ampulla (Figure 1). A more detail classification of hilar tumors is provided by the Bismouth-Corlette classification (Figure 2). This classification is based on tumors that are within 1 cm of the common hepatic duct (Klatskin tumors)[8,9]. These are divided into five types of tumors: the tumors that do not extend to the bifurcation of the right and left extrahepatic bile ducts (Type I), tumors that extend to the bifurcation (Type II), tumors that extend to either the right (Type IIIa) or the left (Type IIIb) intrahepatic bile ducts, and tumors that extend to both the right and left (Type IV) intrahepatic bile duct tumors.

IMAGING

Various invasive and noninvasive imaging techniques are used in the diagnosis and staging of cholangiocarcinoma. The invasive tests include endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, optical coherence tomography and spy glass endoscopy. The noninvasive imaging tests include ultrasound, multidetector computed tomography (MDCT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT). However, MDCT and magnetic resonance imaging (MRI) are the most common imaging modalities used in the primary staging of these malignancies. Standard techniques of MDCT and MRI used for imaging extrahepatic cholangiocarcinoma have been described before and we have tabulated the technique used in our institute^[10](Tables 1-3).

The pre-surgical evaluation of the bile tumor requires high quality cross sectional imaging (CT and MR). An



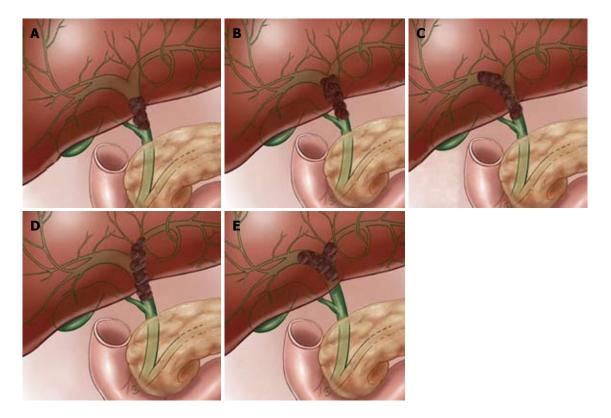


Figure 2 Hilar tumor classification. A: Type I hilar tumors are proximal bile duct tumors that do not extend to the bifurcation; B: Type II tumors extend to the bifurcation without extension into the intrahepatic bile ducts; C:Type III a proximal bile duct tumors correspond to tumors that extend to the right intrahepatic bile ducts; D: Type III b proximal bile duct tumors correspond to tumors extend to the right and left intrahepatic bile ducts.

Table 1 Pluitidetector computed tomography parameters		
Parameter	Value	
Detector collimation	0.5 to 0.75	
Pitch	0.984	
kVp	120	
Contrast	125 cc of intravenous optiray 350	

able 1 Multidetector co

optimal protocol will provide the required information to properly staged the tumor, selection of surgical candidates and for surgical planning [11]. The imaging protocol is a multiphasic post-contrast examination with very thin slices and multiplanar reconstructions. The CT exam is obtained at 2.5 mm slice thickness with 0.625 mm reconstructions following the intravenous administration of iodinated contrast^[12,13]. On CT, the tumor has soft tissue attenuation and enhances on delayed imaging. The MR exams are obtained with a combination of pre- and postcontrast imaging. The pre-contrast exam combines T1 and T2 weighted images. These include very fluid sensitive sequence - T2 weighted images^[11]. This series provide a magnetic resonance cholangiopancreatography (MRCP; Figure 3). The MRCP provides a map of the biliary tree similar to that seen on endoscopic retrograde cholangiopancreatography (ERCP) (Figure 3). The CT images can generate similar CT cholangiopancreatography (CTCP) utilizing minimum intensity projection to visualize the bile ducts (Figure 4). The post-Gd MR exams are obtained at 4mm slice thickness with a 2 mm overlap. A

post-contrast multiphasic exam is performed. On MR, the tumor has low signal on T1 weighted images, slightly intense on T2 weighted images (less than fluid), and show delayed enhancement (Figure 5). Hepatocyte specific contrast agent have been used to generate post-contrast images of the biliary tree^[14].

The image presentation of malignant tumors on CT and MR include: (1) abrupt termination of the ducts; (2) thickened and enhancing bile duct wall; (3) atrophy of the liver segments; (4) crowding of the vessels; and (5) intrahepatic bile duct dilatation^[11]. The tumors may present as an infiltrative process with thickening of the bile duct wall, mostly seen in the proximal tumors. The tumors may also present as papillary or nodular masses. The latter are more common in the distal bile duct tumors^[15]. The papillary bile duct tumor may mimic bile duct stones^[16].

The CT and MR examination not only provides anatomical information of location of the primary bile duct tumor but essential anatomic information such as any evidence of hepatic artery, portal vein, and biliary variant anatomy. The presence of these variants has major implications of selection of surgical candidates and surgical planning.

STAGING

The AJCC has recently published new staging criteria for extrahepatic bile duct tumors^[17]. These tumors were previously grouped into proximal, middle and distal tumors



Table 2 Multidetector computed tomography multiphasic acquisition

Phase of image acquisition	Time of acquisition	Section thickness (mm)	Milliamperage (mA)
Unenhanced liver images		5	250
Arterial phase liver images	Bolus tracking technique or manually at 30-35 s after the onset of contrast material injection	1-2.5	500
Portal venous phase abdomen and pelvis	Acquired 60-65 s after the start of injection	2.5-5	500
Delayed phase	Acquired 3-5 min after the start of injection	5	250

^{2.5-}mm thick coronal and sagittal reformats are reconstructed with images of the portal venous phase.

Table 3 Magnetic resonance imaging protocol

Entry	Feet first			Position	Supine		
Coil type	8 cardiac or	8 cardiac or	8 cardiac or	8 cardiac or	8 cardiac or	8 cardiac or	8 cardiac or
	8 body upper	8 body upper	8 body upper	8 body upper	8 body upper	8 body upper	8 body upper
Series desc	(1) Axial T2	(2) ASSET calib	(3) Axial T1 asset	(4) 3D LAVA XV	(5) Diffusion	(6) 3D 5 min	(7) Fiesta
				Dyn		LAVA XV	
Scan plane	Axial	Axial	Axial pre	Axial	Axial	Axial	Coronal
Image mode	2D	2D	2D in/out phase	3D	2D	3D	2D
Pulse seq	FSE-XL	Fast SPGR	Fast SPGR	Fast SPGR	DW EPI	Fast SPGR	Fiesta
TE1/TE2 (ms)	85		FWIP/FWOP	Min Full	Min (~ 50-60)		Min
TR/#R-R (ms)	4000-6000		150-220		1200-1800		
Flip angle			85	15	NA	15	50-75
ETL (echo train length)	16						
RCV BW1 (kHz)	41.67		62.50	83.33	(125)	83.33	83-125
FOV (cm)	34-44	48	34-44	34-42	38-44	34-44	34-44
SCAN THK (mm)	6	10	5	4	5	4	5
Spacing/#Loc	0	0	0	-2.0	0/36 slices	-2.0	0 or -1
Freq × phase	256 × 192		256 × 192	320 × (160-192)	100×160	320 × (160-192)	192 × 356
NEX	3-4	1	1		6		2
Phase FOV	0.75-1.0	1.0	0.9-1.0	0.75-1.0	1.0	0.70-0.90	0.75 -1.0
Freq dir	R/L	A/P	R/L	R/L	R/L	R/L	S/I

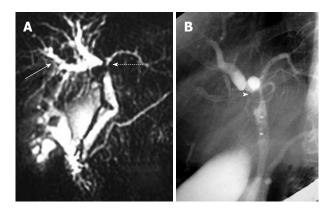


Figure 3 Bile duct tumor. A: Magnetic resonance cholangiopancreatography (MRCP) of a 57-year-old female with a proximal bile duct tumor (dash arrow). There is dilatation of the right intrahepatic bile ducts (solid arrow); B: Corresponding endoscopic cholangiopancreatography of 57-year-old female with proximal bile duct tumor (arrowhead). This is a type III a tumor as per Bismouth-Corlette classification.

but were considered as a single entity and had single TNM classification. Now, the middle group of extrahepatic bile duct tumors have been removed as the treatment of this group is similar to either proximal or distal group. Currently, extrahepatic bile duct tumors are simply classified as perihilar and distal bile duct tumors (Figure 1). Further, these two subgroups have different TNM stag-

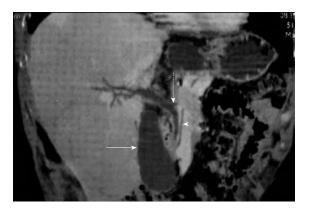


Figure 4 Computed tomography cholangiopancreatography utilizing minimum intensity projection. The common bile duct (dash arrow), the pancreatic duct (arrowhead), and the gallbladder (solid arrow) are visualized and are normal in appearance.

ing as their pathology, treatment and prognosis is variable (Tables 4-6).

Perihilar tumors refer to those located in the extrahepatic biliary tree proximal to the origin of the cystic duct. The early stage (T1) tumor for the extrahepatic bile duct cancers is described as tumor confined to the bile duct wall (Figure 5). On imaging this tumor presents as wall thickening of the bile duct. The low (fat) attenuation of the periductal fat is preserved. The T2 tumors are can-

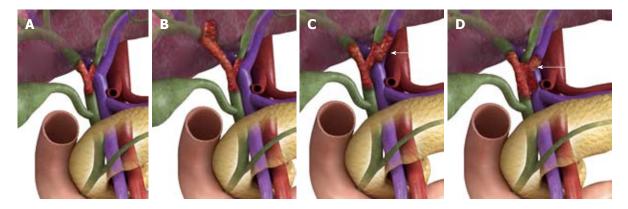


Figure 5 T-staging for proximal bile duct tumors. A: T1 tumors are confined to the bile duct wall without extension to the periductal fat; B: The T2 tumors extend to the periductal fat or the liver; C: T3 tumors have unilateral extension to the portal vein (arrow) or hepatic artery; D: T4 tumors extend to the main portal vein (arrow), common hepatic artery, secondary biliary radicles, or contralateral vascular extension.

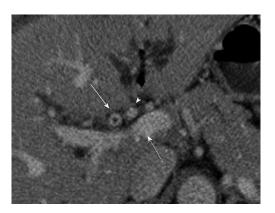


Figure 6 Proximal bile tumor T2 stage. Post-contrast computed tomography exam at the level of the common hepatic duct in a 62-year-old male with biliary cancer. There is enhancement and thickening of the bile duct wall (solid arrow). The fat around the duct is not preserved but the portal vein (dash arrow) and hepatic artery (arrowhead) are spared. Radiologically, this is a T2 tumor due to involvement of periductal fat.

cers that invade the periductal fat (T2a) or the liver (T2b) (Figures 5 and 6). The proximal extrahepatic bile duct tumors may extend to the portal vein or hepatic artery. The unilateral vascular extension is considered T3 (Figure 7), whereas more advanced extension is considered T4. The latter (T4) includes extension into the main portal vein, common hepatic artery, contralateral vascular extension, and involvement of secondary biliary radical (Figure 7). Hepatic parenchymal involvement is now classified as T2 instead of T3 as patients with hepatic parenchymal involvement alone have a better prognosis compared to those with unilateral vascular involvement. [18]

Distal bile duct tumors refer to those located between the junction of the cystic duct-bile duct and the ampulla of Vater. Previously these had the same AJCC classification as the proximal tumors but it has been recognized that these tumors have significant differences in the anatomy compared to the proximal lesions, which affect their resectability. Hence, these lesions have a separate TNM classification.

The TNM staging of the distal bile duct tumors shares some of the features of the proximal bile duct

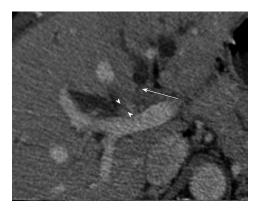


Figure 7 T4 - proximal bile tumor. Post-contrast computed tomography exam at the level of the intrahepatic bile duct in a 58-year-old female with biliary cancer. There is enhancement and thickening of the right intrahepatic bile duct wall (arrowheads). There is abrupt termination of the left intrahepatic bile ducts (arrow) in keeping with tumor extension). Radiologically, this is a T4 tumor due to bilateral involvement of secondary biliary radicles

tumors. For example, in both tumors, the T1 and T2 are confined to the bile duct wall (T1) or invade the bile duct without invasion of adjacent organs (T2) (Figures 8 and 9). The invasion of adjacent organs (pancreas, stomach, and duodenum) is considered T3 for distal bile duct tumors (Figure 10). The invasion of celiac artery and superior mesenteric artery are considered T4 (Figure 10). The T-classification of the distal bile duct cancers shares features with pancreatic cancer.

The nodal staging of bile ducts tumors is also different for the proximal and distal bile duct tumors. The proximal bile duct tumors have three classifications (N0, N1 and N2). N1 nodes refer to regional nodes such as hilar, cystic, pericholedochal, hepatic artery, portal, and posterior pancreaticoduodenal. The N2 nodes refer to distant nodes such as celiac, superior mesenteric artery, and para-aortic nodes. The presence of N2 nodes may disqualify the patient from potential curative surgery. The nodal staging of distal bile duct tumors has two classifications (N0, N1). In contrast to proximal bile duct tumors, the nodal staging is performed at the time of surgery with sampling of at least 12 nodes. This is analog to the

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Table 4 Extrahepatic bile duct tumors (American Joint Commission on Cancer staging 6th edition)

Tumor	TNM classification
T1	Tumor confined to bile duct histologically
T2	Tumor beyond the wall of bile duct
T3	Tumor invades liver, GB, pancreas, and/or ipsilateral
	PV (R or L) or hepatic artery (R or L)
T4	Tumor invades main portal vein or its branches
	bilaterally, common hepatic artery, or adjacent structures
	(colon, stomach, duodenum, abdominal wall)
Node	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including hilar, celiac,
	superior mesenteric, periduodenal and peripancreatic)
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Tumor stage	AJCC staging 6th edition
Stage I A	T1, N0, M0
Stage I B	T2, N0, M0
Stage ∏ A	T3, N0, M0
Stage Ⅱ B	T1 or T2 or T3, N1, M0
Stage III	T4, any N, M0
Stage IV	Any T, any N, M1

T: Tumor; N: Node; M: Metastases; GB: Gallbladder; PV: Pulmonary vein; AJCC: American Joint Commission on Cancer.

Table 6 Distal bile duct tumors (American Joint Commission on Cancer staging 7th edition)

Tumor	TNM classification
T1	Tumor confined to bile duct histologically
T2	Tumor beyond the wall of bile duct
Т3	Tumor invades liver, GB, pancreas, but no involvement
	of celiac axis, or the superior mesenteric artery
T4	Tumor involves the celiac axis, or the superior mesenteric
	artery
Node	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including hilar, celiac,
	superior mesenteric, periduodenal and peripancreatic)
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Tumor stage	AJCC staging 6th edition
Stage I A	T1, N0, M0
Stage I B	T2, N0, M0
Stage II A	T3, N0, M0
Stage ∏B	T1 or T2 or T3, N1, M0
Stage Ⅲ	T4, any N, M0
Stage IV	Any T, any N, M1

T: Tumor; N: Node; M: Metastases; GB: Gallbladder; PV: Pulmonary vein; AJCC: American Joint Commission on Cancer.

management of pancreatic cancer.

On imaging, there are no definite criteria for the diagnosis of malignant nodes^[19]. A node that is larger than 1cm in minimum diameter, round in morphology and heterogeneous in attenuation is likely to be malignant. Proximity to the primary mass also increases the likelihood of malignancy. The MR diffusion weighted images provide optimum contrast between lymph nodes and

Table 5 Perihilar bile duct tumors (American Joint Commission on Cancer staging 7th edition)

Tumor	TNM classification
T1	Tumor confined to bile duct histologically
T2a	Tumor beyond the wall of bile duct into adjacent fat
T2b	Tumor beyond the wall of bile duct into liver parenchyma
T3	Tumor invades ipsilateral portal vein (R or L) or hepatic
	artery (R or L)
T4	Tumor invades
	(1) Main portal vein or its branches bilaterally (or)
	(2) Common hepatic artery (or)
	(3) The second-order biliary radicals bilaterally
	(4) Unilateral second-order biliary radicals with
	contralateral portal vein or hepatic artery involvement
Node	
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 mesenteric
	artery, and/or celiac artery lymph nodes
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Tumor stage	AJCC staging 6th edition
Stage I	T1, N0, M0
Stage II	T2a-b, N0, M0
Stage ∭A	T3, N0, M0
Stage III B	T1 or T2 or T3, N1, M0
Stage IVa	T4, N0 or N1, M0
Stage IVb	Any T, N2, M0 or any T, any N, M1

T: Tumor; N: Node; M: Metastases; GB: Gallbladder; PV: Pulmonary vein; AJCC: American Joint Commission on Cancer.

background anatomy.

The M-staging for the extrahepatic biliary tumors is the similar for proximal and distal bile duct tumors. Metastases may be seen of CT and MR as soft tissue masses in the peritoneum, lungs, adrenals, liver and other sites.

MANAGEMENT

Curative surgery is the best hope for the treatment of bile duct cancers. Depending on the local extent of the tumors, the proximal and distal bile duct tumors resections can involve major *en-bloc* removal of multiple organs with the goal to achieve an R0 resection. The surgical approach differs for proximal and distal bile duct tumors^[20-22].

The resection for proximal bile cancers may include cholecystectomy, resection of extrahepatic bile ducts, regional lymphadenectomy, hepatic lobar resection, caudate lobe resection, Roux-en-Y hepaticojejunostomy, and vascular reconstruction or resection^[21-23]. Liver transplantation is also a consideration in the management of proximal bile duct tumors^[24].

The resection of distal bile duct tumors includes pancreaticoduodenectomy and may include resection of the duodenum, stomach, and colon. In the distal bile duct cancer, the resection includes sampling of at least 12 regional nodes is performed.



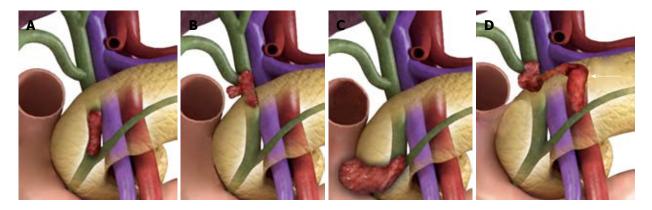


Figure 8 T-Staging for distal bile duct tumors. A: T1 tumors are confined to the bile duct wall without extension to the periductal fat; B: T2 tumors extend to the periductal fat or the liver; C: T3 tumors have adjacent organs without celiac axis or superior mesenteric artery invasion; D:T4 tumors extend to the superior mesenteric artery (arrow) or celiac artery.

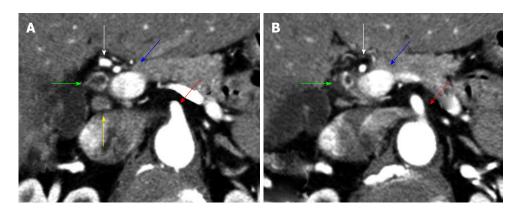


Figure 9 Distal bile duct tumors. Post-contrast computed tomography (CT) examination of the abdomen in a 58-year-old female with cholangiocarcinoma of the bile duct; A: CT image at a cranial location shows dilatation of the bile duct and bile duct enhancement (green arrow); B: CT image at a caudal location shows enhancement of the distal bile duct. There is a small regional lymph node (yellow arrow). The hepatic artery (white arrow), portal vein (blue arrow), and superior mesenteric artery (red arrow) are spared. Radiologically, appearances are consistent with a T1 tumor (periductal fat not involved) and this was confirmed by pathology.

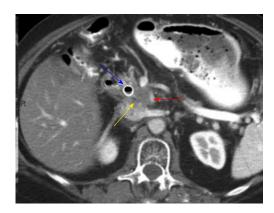


Figure 10 Distal bile duct tumors. Post-contrast computed tomography (CT) examination of the abdomen in a 65-year-old female with cholangiocarcinoma of the bile duct. CT image of the distal bile at the level of the pancreas shows a soft tissue tumor (yellow arrow) in keeping with the tumor. The tumor extends to the superior mesenteric artery (red arrow). There is a biliary stent in place (blue arrow). Radiologically, appearances are consistent with a T4 tumor due to involvement of superior mesenteric artery.

An important role of imaging is to identify features that may preclude surgery - such as marked nodal or distant metastases, involvement of hepatic duct reaching up to second-order biliary radicals, or major vascular encasement of portal vein, common or proper hepatic artery or both the right and left hepatic arteries (16951395).

CONCLUSION

The radiological report may be the only tangible contribution provided to the patient and clinician by the radiologists. A complete report is required to properly managed and stage oncologic patients. In the setting of biliary cancers, the report should include anatomical information such as location of tumors (proximal w distal; segmental involvement), local extent of tumor (fat/organ/vascular invasion), nodal disease location (proximal w distal nodes), and comments on any evidence of metastatic disease. Ancillary but important information such as vascular (arterial, venous, portal) variants to the liver and biliary variants should be carefully evaluated and included in the radiology report.

MRCP and CTCP images are also complementary to the report in providing a visual representation of the primary tumor. The knowledge of tumor staging and management should be the guide to image interpretation by the radiologists. Imaging should help to accurately localize and stage the tumor, highlight presence of features



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which may preclude surgery and warn the surgeons about any surgically relevant anatomical variations. Imaging should help to identify if the tumor is an early stage lesion involving the duct alone (T1) or has advanced such that the periductal fat (T2), major vessels and extensive biliary ductal (T3 and T4) are involved. Current classification has down staged hepatic parenchymal involvement from T3 to T2, which has major implications for prognosis and treatment. The new AJCC classification provides a distinct clinical picture of patients with distal and proximal bile ducts that was absent in the prior classifications with major management implications.

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