

New Staging System and a Registry for Perihilar Cholangiocarcinoma

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Perihilar cholangiocarcinoma is one of the most challenging diseases with poor overall survival. The major problem for anyone trying to convincingly compare studies among centers or over time is the lack of a reliable staging system. The most commonly used system is the Bismuth-Corlette classification of bile duct involvement, which, however, does not include crucial information such as vascular encasement and distant metastases. Other systems are rarely used because they do not provide several key pieces of information guiding therapy. Therefore, we have designed a new system reporting the size of the tumor, the extent of the disease in the biliary system, the involvement of the hepatic artery and portal vein, the involvement of lymph nodes, distant metastases, and the volume of the putative remnant liver after resection. The aim of this system is the standardization of the reporting of perihilar cholangiocarcinoma so that relevant information regarding resectability, indications for liver transplantation, and prognosis can be provided. With this tool, we have created a new registry enabling every center to prospectively enter data on their patients with hilar cholangiocarcinoma (www.cholangioca.org). The availability of such standardized and multicenter data will enable us to identify the critical criteria guiding therapy. (HEPATOLOGY 2011;53:1363-1371)

Cholangiocarcinoma (CCA) arises from the malignant transformation of the bile duct epithelium; it represents approximately 10% of

all primary hepatobiliary cancers and accounts for approximately 2% of all malignancies.^{1,2} Several lines of evidence indicate that the incidence of CCA has increased over the past 3 decades.^{3,4} These tumors can develop anywhere along the biliary tree and represent a quite heterogeneous group with distinct patterns, epidemiologies, clinical presentations, and prognoses. The most commonly used classification of CCA has three groups based on the location along the biliary tree: intrahepatic cholangiocarcinoma (IHC); perihilar cholangiocarcinoma (PHC), which is also called a Klatskin tumor⁵; and distal CCA. The IHC type accounts for less than 10% of the total cases, whereas the PHC type represents about two-thirds of the cases, and distal CCA represents about a quarter of the cases.⁶ PHC can be defined as tumors that involve or are in close vicinity to the bile duct confluence. We suggest a definition of PHC, which includes tumors above the junction of the cystic duct up to and including the second biliary branches of the right and left bile ducts.

The only chance of a cure for this type of cancer is complete surgical resection of the tumor and perhaps liver transplantation in highly select cases. Most of these cancers have a dismal prognosis, and the current 5-year

Abbreviations: AJCC, American Joint Committee on Cancer; CCA, cholangiocarcinoma; IHC, intrahepatic cholangiocarcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; PHC, perihilar cholangiocarcinoma; TNM, tumor-node-metastasis; UICC, Union for International Cancer Control.

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After the expert opinion conference organized by the European Hepato-Biliary Association (Brussels, Belgium, November 2007), the authors created an international cholangiocarcinoma working group to design a new staging system and a registry.

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survival rate after surgery, even in select cases, rarely exceeds 30%.⁶⁻⁹ Currently, no effective neoadjuvant or adjuvant therapy is available for enhancing the results of complete resection.¹⁰ One major issue in identifying the best surgical approach for PHC (e.g., local bile duct resection, major hepatectomy, or liver transplantation) has been the lack of a convincing staging system,^{11,12} which would enable the comparison of results over time and among centers.¹³ A recent consensus conference that was organized by the European Hepato-Pancreato-Biliary Association (Brussels, Belgium, November 2007) and was reported in *HPB*^{4,14,15} identified the need for a new staging system as the highest priority for further development. The coauthors of this article were all involved with this conference and consequently created an international group to overcome this shortcoming by working on a new staging system.

Recently, a group of experts¹⁶ proposed a new staging system for IHC; the various grades were validated with a large database available in the United States. In this article, we focus on PHC, the most common and challenging form of CCA. Our aim is to propose a simple, reproducible, easily applicable, and informative staging system. To achieve this goal and enable international acceptance, the staging will be established by the consensus of a group of international experts in the field. First, we discuss the need for a staging system. Next, we review the currently available staging systems. Then, we present the information needed to establish a valuable staging system. Finally, we submit our proposal for a new staging system. In contrast to IHC, it is currently not possible to test the ability of the new staging system to predict the natural history of the disease or the outcome after surgery because this information is not available in any large database. Our goal, therefore, is to offer a descriptive system that will enable us to test correlations of various tumor characteristics with survival or other outcomes once a prospective database is available. Upon the publication of this article, we will open a professionally designed, online-based registry for PHC that is based on the new proposal www.cholangioca.org.

Rationale for a Valuable Staging System for PHC

A staging system for patients with cancer must ideally (1) provide information about the prognosis and natural history of the disease, (2) serve as a guide for therapy, and (3) enable convincing comparisons of therapies among various institutions and over time.¹⁷ In so-called surgical diseases, a staging system is crucial for

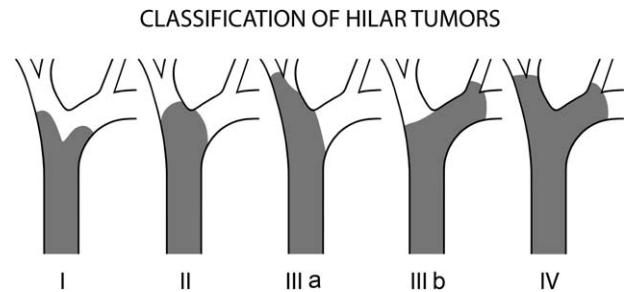


Fig. 1. Original drawing from the Bismuth-Corlette classification (by courtesy of Professor Henri Bismuth, Paris, France).

deciding between an aggressive approach (i.e., chance for cure) and only palliative alternatives. Another criteria for a good staging system is its ability to identify patients for the best type of surgery (e.g., local resection versus extensive resection or even liver transplantation).

Staging systems for cancer usually describe the extent of the disease according to the primary tumor and its spread. The tumor-node-metastasis (TNM) classification is the gold standard for many cancers because it is simple to understand, applies to many types of cancers, and provides information on the primary tumor (T), the lymph node status (N), and distant metastases (M).^{17,18} Unfortunately, this system is of little help when local factors, such as the precise localization of the tumor along the bile duct, are crucial to predicting the natural history of the disease and choosing the therapy. In the case of PHC, critical factors influencing outcomes and therapy include the location and extension of the tumor along the biliary tree, the involvement of the liver, and the presence of encasement of the portal or hepatic artery system. Before we move to a proposal for a new system, the next logical step is to critically analyze the available classifications.

Current Available Staging Systems

The three systems most commonly used to evaluate PHC in most parts of the world are the modified Bismuth-Corlette system,^{19,20} the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM classification,²¹ and the Memorial Sloan-Kettering Cancer Center (MSKCC) classification.²²

Bismuth-Corlette System. This classification, proposed by Bismuth and Corlette in the 70s,²⁰ focuses exclusively on the level and extension of the tumor invasion along the biliary tree (Fig. 1). Lesions are classified as type I (the tumor involves only the

Table 1. TNM Classification of Extrahepatic Bile Duct Tumors According to the AJCC/UICC 7th Edition

Primary Tumor (T)			
TX	The primary tumor cannot be assessed.		
T0	No evidence of a primary tumor		
Tis	Carcinoma <i>in situ</i>		
T1	The tumor is confined to the bile duct histologically.		
T2a	The tumor invades the surrounding adipose tissue beyond the wall of the bile duct.		
T2b	The tumor invades the adjacent hepatic parenchyma.		
T3	The tumor invades unilateral branches of the portal vein or hepatic artery.		
T4	The tumor invades the main portal vein or its branches bilaterally, the common hepatic artery, the second-order biliary radicals bilaterally, or the unilateral second-order biliary radicals with contralateral portal vein or hepatic vein involvement.		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed.		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis (cystic duct, common bile duct, hepatic artery, and portal vein)		
N2	Metastasis to periaortic, pericaaval, superior mesentery artery, and/or celiac artery nodes		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

This table was adapted from *AJCC Cancer Staging Handbook*.²¹

common hepatic duct below the confluence of the left and right hepatic ducts), type II (the tumor involves the hepatic bile duct confluence, but there is no invasion above the confluence), type III (the tumor affects the right or left hepatic duct in addition to the biliary confluence; type IIIa refers to the right hepatic duct, and type IIIb refers to the left one), or type IV (the tumor involves both the right and left hepatic ducts and the confluence and reaches the secondary intrahepatic biliary system or involves multiple discontinuous sites in the right and left ducts).

The Bismuth-Corlette classification system^{19,20} is possibly the system most commonly used worldwide to stage PHC, although it fails to provide other key information such as vascular encasement, lymph node involvement, distant metastases, and atrophy of a part of the liver. Thus, it logically does not correlate with

patient survival. Although this system was primarily conceived to serve as a guide for surgical strategy (e.g., types I and II indicate local resection, type III indicates associated liver resection, and type IV indicates unresectability), recent practice in many specialized centers no longer follows the original concept. In addition, variations in the anatomy of the branches often change the applicability of the Bismuth-Corlette system.^{19,20}

TNM Classification for Extrahepatic Bile Duct Tumors. This classification is based on the pathological findings known as pathological staging (pathological TNM), as shown in Table 1. It is usually associated with the histological classification based on World Health Organization data (Table 2) and is, therefore, mostly used to stage tumors after surgical resection. For example, the TNM staging system²³ is incorporated into the seventh edition of *AJCC Cancer Staging*,²¹ mostly for grouping patients with a specific histological type of the extrahepatic biliary tract such as adenocarcinoma^{17,23}; however, sarcoma and carcinoid tumors are excluded.

Besides the stage grouping shown in Table 1, the TNM classification has additional descriptors for the residual tumor (which is labeled “R”): Rx means that the presence of the residual tumor cannot be assessed, R0 represents no residual tumor, R1 reveals a microscopic residual tumor, and R2 denotes a macroscopic residual tumor. In addition, the histological grade (“G”) is expressed as Gx (no assessment), G1 (well differentiated), G2 (moderately differentiated), G3 (poorly differentiated), or G4 (undifferentiated).

In the current AJCC/UICC edition,²¹ vessel invasion does affect the tumor category (T3 or T4), but it fails to indicate local resectability of the tumor. Although this classification fits within the standard TNM system for all cancers and appears simple, it is mostly used postoperatively and therefore fails to

Table 2. World Health Organization Classification of Carcinomas of the Extrahepatic Bile Ducts

Adenocarcinoma
Papillary adenocarcinoma
Adenocarcinoma, intestinal type
Adenocarcinoma, gastric foveolar type
Mucinous adenocarcinoma
Clear cell adenocarcinoma
Signet-ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Small cell (oat cell) carcinoma
Large cell neuroendocrine carcinoma
Undifferentiated carcinoma
Biliary cystadenoma

This table was adapted from *AJCC Cancer Staging Handbook*.²¹

Table 3. Tumor Staging According to the MSKCC Classification

Tumor Stage (T)	Description
T1	The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. There is no portal vein involvement or liver atrophy.
T2	The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. There is ipsilateral portal vein involvement or ipsilateral hepatic lobar atrophy.
T3	The tumor involves the biliary confluence with bilateral involvement up to secondary biliary radicles, unilateral extension to secondary biliary radicles with contralateral portal vein involvement, unilateral involvement up to secondary biliary radicles with contralateral hepatic lobar atrophy, or main/bilateral portal vein involvement.

This table was adapted from Jamagin et al.²²

distinguish between the various surgical options. Its usefulness in the preoperative setting is thus limited.

MSKCC Classification. In an attempt to fill the gap of predicting resectability and, therefore, outcomes, Blumgart's group at MSKCC²² proposed a staging system that classifies PHC according to three factors related to the local extension of the tumor, the location of bile duct involvement, and the presence of portal vein invasion and hepatic lobar atrophy, although the size of the remnant liver is not specified (Table 3). This classification was tested in a series of 225 patients from that institution and showed an accuracy of 86% in the preoperative staging of the local extent of the disease.²²

This staging system is different than the two others discussed because of the specific attempt to predict resectability. There are some limitations, however. First, the system is complicated, and some clinicians may have difficulty in using it. Second, this system does not evaluate the presence of nodal or distant metastases or the involvement of the artery. Finally, this staging system was designed exclusively on the basis of the criteria of resectability from a single institution, which may not correspond to the current concept of PHC resectability in many other centers. Thus, because of the recent developments in liver surgery, the evolving concept of unresectability, and the new advances in liver transplantation, this system appears somewhat obsolete. More detailed information on vessel invasion is currently crucial for adequate preoperative and surgical staging.¹²

In summary, although each system does provide valuable information, none offers a reproducible classification system for the natural history of the disease or indicates surgical resectability. Thus, there is an urgent need to identify a common language for describing PHC. This step is

crucial for allowing comparisons of results from different centers and clinical trials. Such an attempt is quite timely because accumulating data over the past decade have failed to identify factors predicting R0 status although extended liver resection, associated vascular resection or liver transplantation have offered the best results.

New Proposal by the International Cholangiocarcinoma Group for the Staging of PHC

On the basis of the evaluation of the aforementioned grading systems and the need for a simple and reproducible staging system for PHC, we propose a classification using some parameters from previous staging systems that focuses on the presentation of the data in a systematic manner to ease understanding and reproducibility (Table 4). The Bismuth-Corlette classification is kept for the assessment of the bile duct (which is labeled "B" for bile duct or Bismuth); the letters "a" and "b" are omitted and are replaced by "R" (for right hepatic duct) and "L" (for left hepatic duct; Fig. 2A). Thus, the label indicating one of the four types (depending on the localization of the tumor) will follow "B"; for example, B2 indicates invasion of the bile duct confluence by the tumor. Additionally, the tumor size should be labeled as T1 (1 cm), T2 (1-3 cm), or T3 (≥ 3 cm). The choice of a 3-cm cutoff for T3 is based on accumulating data indicating a better prognosis for smaller tumors^{6,22,24}; this includes excellent outcomes after liver transplantation in the absence of any extrahepatic spread.²⁵ The macroscopic form (which is labeled "F") will also be recorded as the periductal or sclerosing type (sclerosing), the nodular or mass-forming type (mass), or the polypoid or intraductal type (polypoid).²⁶ Often, a distinction between the sclerosing type and the mass-forming type is difficult.²⁶⁻²⁹ Therefore, we propose to add a mixed type of tumor (mixed).

The next factors providing information about the natural history and the choice of therapy include involvement of the vessels. This information has become paramount in light of several studies reporting excellent long-term outcomes after portal resection³⁰⁻³⁴ and even arterial resection.³⁵⁻³⁸ In this regard, the portal vein is labeled "PV" (Fig. 2B), and the hepatic artery is labeled "HA" (Fig. 2C); it is also important to highlight when both the vein and the artery are free (HA0 and PV0, respectively). We reached a consensus to label arterial and venous involvement when there is evidence that the tumor encompass more than 180° of the circumference of the vessel. This was mostly based

Table 4. Proposed Classification System

Label	Side/Location*	Description
Bile duct (B)†		
B1		Common bile duct
B2		Hepatic duct confluence
B3	R	Right hepatic duct
B3	L	Left hepatic duct
B4		Right and left hepatic duct
Tumor size (T)		
T1		<1 cm
T2		1-3 cm
T3		≥3 cm
Tumor form (F)		
Sclerosing		Sclerosing (or periductal)
Mass		Mass-forming (or nodular)
Mixed		Sclerosing and mass-forming
Polypoid		Polypoid (or intraductal)
Involvement (>180°) of the portal vein (PV)		
PV0		No portal involvement
PV1		Main portal vein
PV2		Portal vein bifurcation
PV3	R	Right portal vein
PV3	L	Left portal vein
PV4		Right and left portal veins
Involvement (>180°) of the hepatic artery (HA)		
HA0		No arterial involvement
HA1		Proper hepatic artery
HA2		Hepatic artery bifurcation
HA3	R	Right hepatic artery
HA3	L	Left hepatic artery
HA4		Right and left hepatic artery
Liver remnant volume (V)		
V0		No information on the volume needed (liver resection not foreseen)
V%	Indicate segments	Percentage of the total volume of a putative remnant liver after resection
Underlying liver disease (D)		
		Fibrosis
		Nonalcoholic steatohepatitis
		Primary sclerosing cholangitis
Lymph nodes (N)‡		
N0		No lymph node involvement
N1		Hilar and/or hepatic artery lymph node involvement
N2		Periaortic lymph node involvement
Metastases (M)§		
M0		No distant metastases
M1		Distant metastases (including liver and peritoneal metastases)

*"R" indicates right, and "L" indicates left.

†Based on the Bismuth classification.^{19,20}

‡Based on the Japanese Society of Biliary Surgery classification.⁴⁸

§Based on the TNM classification.²¹

on available data showing an 80% to 100% probability of vessel invasion in the presence of tumor involvement exceeding 180° of the circumference of the portal vein in a series of patients with pancreatic cancer.³⁹

Similar data were reported for the portal vein and hepatic artery in a small series of PHC patients.⁴⁰

For simplicity and consistency, we propose the same labeling used for the bile duct with a range of 1 to 4 (depending on the level of the tumor involvement) as well as the addition of "R" or "L" to describe the right or left side, respectively. For example, tumor infiltration localized to the right portal vein and right hepatic artery branches above the bifurcation should be represented as PV3-R, HA3-R (Fig. 3A,B).

Another key factor found to be crucial for improved long-term survival in most recent series is the en bloc R0 resection combining the bile duct with major hepatectomy (most commonly modified extended right hemihepatectomy).^{24,26-30,35,36,41} The presence of hemiliver atrophy and the size of the putative remnant liver after surgery are, therefore, central factors predicting resectability. Such information must be included in the staging system. However, the definitions of hemiliver atrophy and the minimal residual volume accepted after resection vary among centers.⁴²⁻⁴⁴ The presence of underlying disease also affects the minimal residual volume associated with good outcomes.⁴⁵⁻⁴⁷ Therefore, instead of using an arbitrary term such as liver atrophy, we propose to provide information regarding the actual volume, which is labeled "V". Our consensus is to have the label "V" used with the percentage of the total volume or body weight ratio. For example, a remnant segment 2-4 volume corresponding to 50% of the total liver volume should be indicated as V50%-seg 2-4 (Fig. 3B). Thus, the minimal volume considered for safe resection can be set by each center, and the recorded data can be conclusively compared with data from other centers. Volume information should be provided only for lesions for which a liver resection is foreseen.

The presence of underlying liver disease is an important risk factor for surgery, and a larger residual volume is necessary for safe resection.^{32,38,45} Therefore, we propose to add the letter "D" to indicate the presence of an underlying disease such as fibrosis, nonalcoholic steatohepatitis, or primary sclerosing cholangitis.

The staging system must also provide information about the lymph node status and distant metastases. Lymph nodes are labeled "N". On the basis of the Japanese Society of Biliary Surgery classification,⁴⁸ we propose N1 for positive periportal or hepatic artery lymph nodes and N2 for positive para-aortic lymph nodes.³⁵ Metastases, including liver and peritoneal metastases, are marked as "M" and are graded according to the TNM classification.²¹

The preoperative assessments and tests chosen to preoperatively stage patients with PHC are not

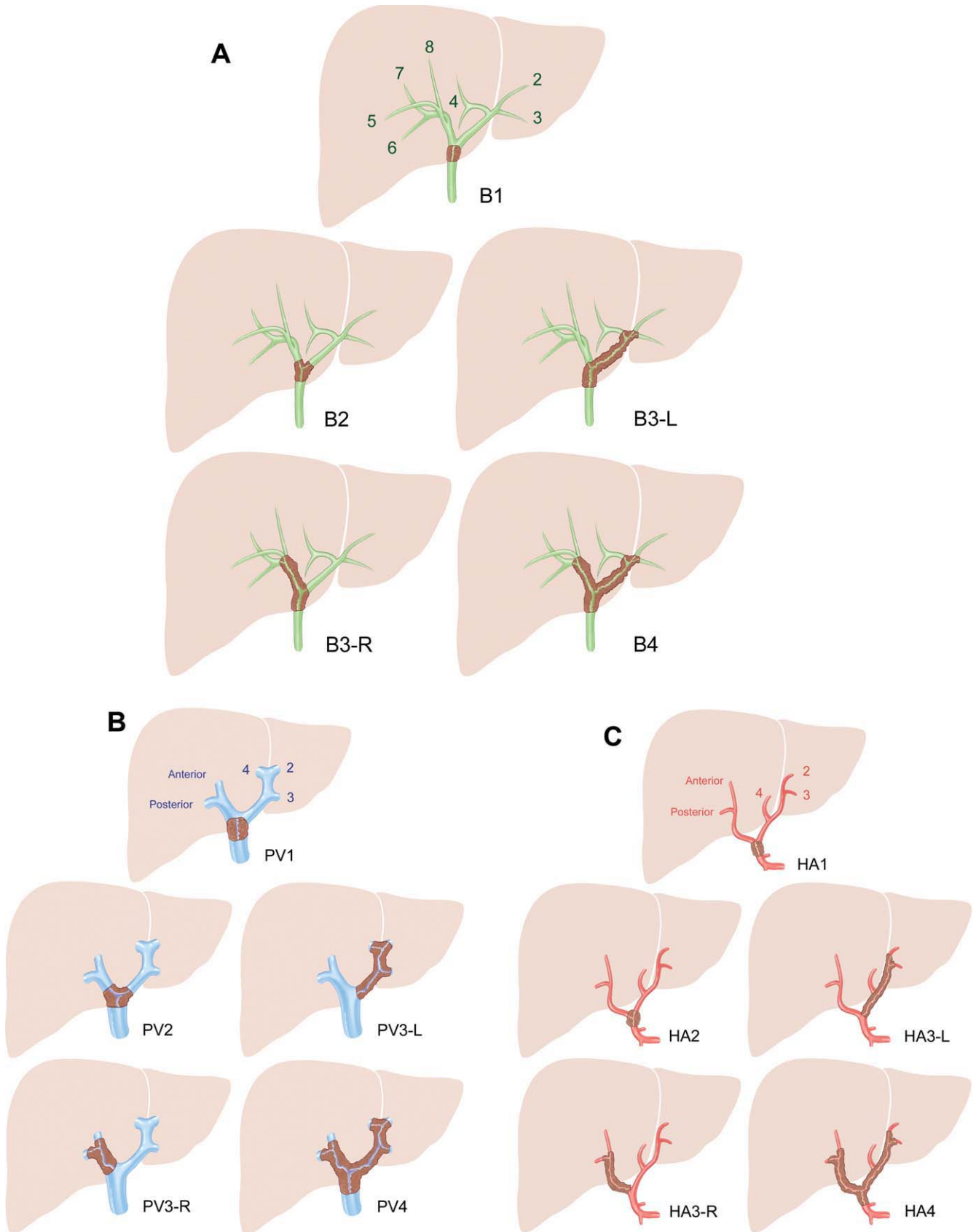


Fig. 2. New classification for (A) the biliary system (which is labeled “B”), (B) portal vein involvement (“PV”), and (C) hepatic artery involvement (“HA”). The bile duct staging is based on the Bismuth-Corlette classification.¹⁹ Involvement of the portal vein or hepatic artery is considered when the tumor encompasses more than 180° of the circumference.

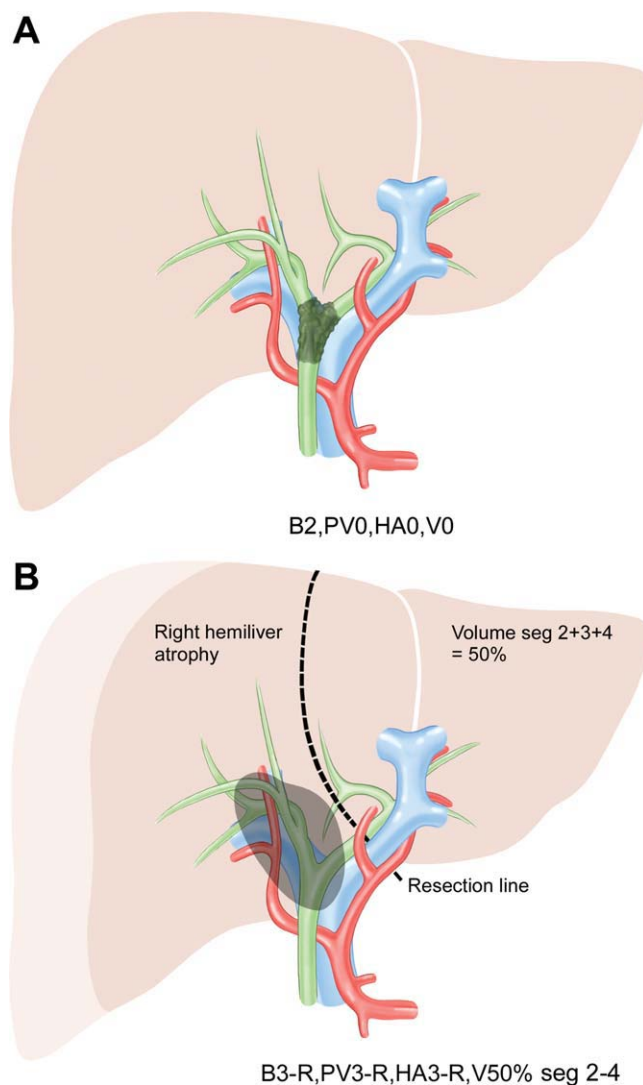


Fig. 3. Examples of the application of the new classification to (A) a 2.5-cm tumor involving the bile duct confluence and (B) a larger tumor involving the right biliary system, hepatic artery, and portal vein that is associated with right hemiliver atrophy.

uniform.^{28,49-52} Currently, the best imaging modalities for assessing CCA are contrast-enhanced magnetic resonance imaging and magnetic resonance angiography technology^{49,53} (including magnetic resonance cholangiography^{54,55}). Invasive testing such as arteriography is no longer used in most centers. However, percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography with stent placement as well as a cytology assessment is routinely performed in most centers to relieve cholestasis and to make a diagnosis.^{41,56} Endoscopic ultrasound is also increasingly used for further assessment of the extent of the tumor (including vascular invasion) and often offers valuable access for tumor and lymph node biopsy.^{57,58} This is particularly relevant in patients considered for liver

transplantation because the Mayo Clinic protocol^{25,59} and other modified Mayo protocols⁶⁰⁻⁶¹ exclude all patients with lymph node metastases. Finally, many centers routinely add a positron emission tomography/computed tomography scan with intravenous contrast to exclude pulmonary and other distant metastases.⁶²⁻⁶³ For the purpose of the registry, we will allow every center to select its own workup strategy, but the test used to establish the various staging criteria will be recorded.

In summary, the proposed staging system provides transparent information about the anatomical location of the tumor along the bile duct (which is labeled “B”), the involvement of the portal vein (“PV”), the involvement of the hepatic artery (“HA”), the volume of the future remnant liver (“V”), the lymph node (“N”), and metastases status (“M”). Additionally, the tumor size (“T”), the tumor form (“F”), and the underlying disease (“D”) are important pieces of information that are now included and may help us to better stage PHC. The staging should ideally be performed before surgery (e.g., after portal vein embolization) and after surgery, and it should include all intraoperative information and results from macroscopic and microscopic examinations. With the publication of this new classification system, we will implement a new registry that will be available at www.cholangioca.org.

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References

1. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996;224:463-473.
2. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. *N Engl J Med* 1999;341:1368-1378.
3. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *Lancet* 2005;366:1303-1314.
4. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)* 2008;10:77-82.
5. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. *Am J Med* 1965;38:241-256.
6. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245:755-762.
7. Aljiffry M, Abdulelah A, Walsh M, Peltekian K, Alwayn I, Molinari M. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. *J Am Coll Surg* 2009;208:134-147.
8. Rosen CB, Heimbach JK, Gores GJ. Surgery for cholangiocarcinoma: the role of liver transplantation. *HPB (Oxford)* 2008;10:186-189.
9. Nathan H, Pawlik TM, Wolfgang CL, Choti MA, Cameron JL, Schulick RD. Trends in survival after surgery for cholangiocarcinoma: a 30-year population-based SEER database analysis. *J Gastrointest Surg* 2007;11:1488-1496.

10. Lazaridis KN, Gores GJ. Cholangiocarcinoma. *Gastroenterology* 2005;128:1655-1667.
11. Nishio H, Nagino M, Oda K, Ebata T, Arai T, Nimura Y. TNM classification for perihilar cholangiocarcinoma: comparison between 5th and 6th editions of the AJCC/UICC staging system. *Langenbecks Arch Surg* 2005;390:319-327.
12. Kondo S, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. *J Hepatobiliary Pancreat Surg* 2008;15:41-54.
13. Blechacz BR, Sanchez W, Gores GJ. A conceptual proposal for staging ductal cholangiocarcinoma. *Curr Opin Gastroenterol* 2009;25:238-239.
14. Toouli J, Gigot JF, Gouma D, Belghiti J, Clavien PA. Editorial. *HPB (Oxford)* 2008;10:71.
15. Esposito I, Schirmacher P. Pathological aspects of cholangiocarcinoma. *HPB (Oxford)* 2008;10:83-86.
16. Nathan H, Aloia TA, Vauthey JN, Abdalla EK, Zhu AX, Schulick RD, et al. A proposed staging system for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2009;16:14-22.
17. Sobin LH. TNM: principles, history, and relation to other prognostic factors. *Cancer* 2001;91:1589-1592.
18. Greene FL, Sobin LH. The staging of cancer: a retrospective and prospective appraisal. *CA Cancer J Clin* 2008;58:180-190.
19. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg* 1992;215:31-38.
20. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 1975;140:170-178.
21. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti III A. Perihilar Bile Ducts. In: *AJCC Cancer Staging Handbook*. 7th ed. Chicago, IL: Springer; 2010:718.
22. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001;234:507-517.
23. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumors*. 7th ed. New York, NY: John Wiley & Sons; 2009.
24. Ito F, Agni R, Rettammel RJ, Been MJ, Cho CS, Mahvi DM, et al. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence. *Ann Surg* 2008;248:273-279.
25. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Kremers W, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation* 2006;82:1703-1707.
26. Sakamoto E, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, et al. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. *Ann Surg* 1998;227:405-411.
27. Igami T, Nagino M, Oda K, Nishio H, Ebata T, Yokoyama Y, et al. Clinicopathologic study of cholangiocarcinoma with superficial spread. *Ann Surg* 2009;249:296-302.
28. Nimura Y. Staging cholangiocarcinoma by cholangioscopy. *HPB (Oxford)* 2008;10:113-115.
29. Kato M, Nimura Y, Kamiya J, Kondo S, Nagino M, Miyachi M, et al. Carcinoma of the common bile duct with superficial spread to the intrahepatic segmental bile ducts: a case report. *Am Surg* 1997;63:943-947.
30. Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999;230:808-818.
31. Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. *Ann Surg* 2003;238:720-727.
32. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg* 2006;243:364-372.
33. Nagino M, Kamiya J, Arai T, Nishio H, Ebata T, Nimura Y. "Anatomic" right hepatic trisectionectomy (extended right hepatectomy) with caudate lobectomy for hilar cholangiocarcinoma. *Ann Surg* 2006;243:28-32.
34. Kondo S, Katoh H, Hirano S, Ambo Y, Tanaka E, Okushiba S. Portal vein resection and reconstruction prior to hepatic dissection during right hepatectomy and caudate lobectomy for hepatobiliary cancer. *Br J Surg* 2003;90:694-697.
35. Sakamoto Y, Sano T, Shimada K, Kosuge T, Kimata Y, Sakuraba M, et al. Clinical significance of reconstruction of the right hepatic artery for biliary malignancy. *Langenbecks Arch Surg* 2006;391:203-208.
36. Yamanaka N, Yasui C, Yamanaka J, Ando T, Kuroda N, Maeda S, et al. Left hemihepatectomy with microsurgical reconstruction of the right-sided hepatic vasculature. A strategy for preserving hepatic function in patients with proximal bile duct cancer. *Langenbecks Arch Surg* 2001;386:364-368.
37. Shimada H, Endo I, Sugita M, Masunari H, Fujii Y, Tanaka K, et al. Hepatic resection combined with portal vein or hepatic artery reconstruction for advanced carcinoma of the hilar bile duct and gallbladder. *World J Surg* 2003;27:1137-1142.
38. Nagino M, Nimura Y, Nishio H, Ebata T, Igami T, Matsushita M, et al. Hepatectomy with simultaneous resection of the portal vein and hepatic artery for advanced perihilar cholangiocarcinoma: an audit of 50 consecutive cases. *Ann Surg* 2010;252:115-123.
39. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR Am J Roentgenol* 1997;168:1439-1443.
40. Okumoto T, Sato A, Yamada T, Takase K, Matsushita T, Tsuda M, et al. Correct diagnosis of vascular encasement and longitudinal extension of hilar cholangiocarcinoma by four-channel multidetector-row computed tomography. *Tohoku J Exp Med* 2009;217:1-8.
41. van Gulik TM, Kloek JJ, Ruys AT, Busch OR, van Tienhoven GJ, Lameris JS, et al. Multidisciplinary management of hilar cholangiocarcinoma (Klatskin tumor): extended resection is associated with improved survival. *Eur J Surg Oncol* 2011;37:65-71.
42. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 2007;356:1545-1559.
43. Nagino M, Ando M, Kamiya J, Uesaka K, Sano T, Nimura Y. Liver regeneration after major hepatectomy for biliary cancer. *Br J Surg* 2001;88:1084-1091.
44. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 1990;107:521-527.
45. Clavien PA, Oberkofler CE, Raptis DA, Lehmann K, Rickenbacher A, El-Badry AM. What is critical for liver surgery and partial liver transplantation: size or quality? *HEPATOLOGY* 2010;52:715-729.
46. Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *HEPATOLOGY* 1997;26:1176-1181.
47. Uesaka K, Nimura Y, Nagino M. Changes in hepatic lobar function after right portal vein embolization. An appraisal by biliary indocyanine green excretion. *Ann Surg* 1996;223:77-83.
48. Japanese Society of Biliary Surgery. *General Rules for Surgical and Pathological Studies on Cancer of Biliary Tract*. 5th ed. Tokyo, Japan: Kanehara; 2003.
49. Vogl TJ, Schwarz WO, Heller M, Herzog C, Zangos S, Hintze RE, et al. Staging of Klatskin tumours (hilar cholangiocarcinomas): comparison of MR cholangiography, MR imaging, and endoscopic retrograde cholangiography. *Eur Radiol* 2006;16:2317-2325.
50. Choi JY, Kim MJ, Lee JM, Kim KW, Lee JY, Han JK, et al. Hilar cholangiocarcinoma: role of preoperative imaging with sonography, MDCT, MRI, and direct cholangiography. *AJR Am J Roentgenol* 2008;191:1448-1457.
51. Chung YE, Kim MJ, Park YN, Lee YH, Choi JY. Staging of extrahepatic cholangiocarcinoma. *Eur Radiol* 2008;18:2182-2195.
52. Choi JY, Lee JM, Lee JY, Kim SH, Lee MW, Han JK, et al. Assessment of hilar and extrahepatic bile duct cancer using multidetector CT: value of adding multiplanar reformations to standard axial images. *Eur Radiol* 2007;17:3130-3138.

53. Park HS, Lee JM, Choi JY, Lee MW, Kim HJ, Han JK, et al. Preoperative evaluation of bile duct cancer: MRI combined with MR cholangiopancreatography versus MDCT with direct cholangiography. *AJR Am J Roentgenol* 2008;190:396-405.
54. Choi JY, Kim MJ, Lee JM, Lee JY, Kim SH, Kim KW, et al. Magnetic resonance cholangiography: comparison of two- and three-dimensional sequences for assessment of malignant biliary obstruction. *Eur Radiol* 2008;18:78-86.
55. Zidi SH, Prat F, Le Guen O, Rondeau Y, Pelletier G. Performance characteristics of magnetic resonance cholangiography in the staging of malignant hilar strictures. *Gut* 2000;46:103-106.
56. Kloek JJ, van der Gaag NA, Aziz Y, Rauws EA, van Delden OM, Lameris JS, et al. Endoscopic and percutaneous preoperative biliary drainage in patients with suspected hilar cholangiocarcinoma. *J Gastrointest Surg* 2010;14:119-125.
57. DeWitt J, Misra VL, Leblanc JK, McHenry L, Sherman S. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. *Gastrointest Endosc* 2006;64:325-333.
58. Harewood GC. Endoscopic tissue diagnosis of cholangiocarcinoma. *Curr Opin Gastroenterol* 2008;24:627-630.
59. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005;242:451-458.
60. Robles R, Figueras J, Turrion VS, Margarit C, Moya A, Varo E, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004;239:265-271.
61. Kadry Z, Mullhaupt B, Renner EL, Bauerfeind P, Schanz U, Pestalozzi BC, et al. Living donor liver transplantation and tolerance: a potential strategy in cholangiocarcinoma. *Transplantation* 2003;76:1003-1006.
62. Kim JY, Kim MH, Lee TY, Hwang CY, Kim JS, Yun SC, et al. Clinical role of 18F-FDG PET-CT in suspected and potentially operable cholangiocarcinoma: a prospective study compared with conventional imaging. *Am J Gastroenterol* 2008;103:1145-1151.
63. Petrowsky H, Wildbrett P, Husarik DB, Hany TF, Tam S, Jochum W, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. *J Hepatol* 2006;45:43-50.