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A conceptual proposal for staging ductal cholangiocarcinoma

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Cholangiocarcinoma (CCA) is a devastating disease with features of bile duct epithelial differentiation. Considerable progress has been made regarding the imaging characteristics of this disease, diagnostic criteria, surgical approaches and palliative management. Conversely, progress regarding medical therapy for advanced CCA has been limited. The design and implementation of Phase II trials has been hampered by the lack of staging systems to stratify patient populations. Until refined stratification schemes are available, results from Phase II trials, even randomized Phase II trials, will be difficult if not impossible to interpret due to marked patient heterogeneity. In this commentary, we will propose schemes to help stratify patients with CCA based on our current understanding of the disease. Biliary tract malignancies include intrahepatic cholangiocarcinoma, ductal cholangiocarcinoma, gallbladder cancers and cancers of the ampulla of Vater. Often, all of these biliary tract cancer subsets are included in medical trials on biliary tract cancers. However, gallbladder cancers, CCA and cancers of the ampulla of Vater are distinct entities with unique molecular signatures, mechanisms of disease dissemination and natural history. Furthermore, CCA exists as two types of cancer, intrahepatic mass forming cancers and cancers involving the large bile ducts. We propose that these two subsets be defined as intrahepatic CCA and ductal CCA (Table 1). Intrahepatic CCA would be classified as intrahepatic mass lesions without causing bile duct obstruction or jaundice. Ductal CCA would involve cancers of the common bile duct, common hepatic duct, right and/or left hepatic ducts including their secondary bifurcation. Terms such as Klatskin tumor, or perihilar CCA, which is a form of ductal CCA should be discouraged. Likewise, the erroneous classification by the Surveillance, Epidemiology, End Result (SEER) database of perihilar CCA as intrahepatic CCA must be corrected [1]. Biliary tract cancers should not be ‘lumped’ together in clinical trials, but rather examined and treated as individual, distinct subsets of biliary tract cancers. Clinical trials should be limited to each specific subset of these cancers including unique trials for intrahepatic and ductal CCA. Staging systems of gallbladder cancer have been well defined [2,3] and therefore, this cancer population can be appropriately stratified and emerging therapies assessed.

Recently, a staging system for intrahepatic CCA has been proposed [4]. This classification is based on number of intrahepatic lesions, presence or absence of vascular invasion and lymph node metastases. In contrast, there is no proposed staging system for ductal CCA. Prior staging systems such as the Bismuth-Collette and the Memorial Sloan Kettering staging system pertain to selection of patients for surgery but were never meant to correlate with survival and do not pertain to patients with advanced disease [5,6]. The optimal staging system for ductal CCA should take into account the following parameters: the stage of the tumor; magnitude of ductal and vascular obstruction and their functional consequences for hepatic function and selection for surgery; the performance status of the patient; and the availability and effectiveness of therapy. Such a staging system has been developed for hepatocellular carcinoma and has been externally validated [7–10]. The tumor stage should take into account the size of the primary

lesion, vascular encasement, the presence or absence of lobar atrophy and extrahepatic spread of the disease. Most primary ductal CCA are difficult to visualize as mass lesions and lack a measurable radial diameter. These neoplasms have a tropism for bile and as such, often encircle and stricture the bile duct causing jaundice. Given this tropism, the cancers also grow longitudinally along the bile duct before growing radially away from the biliary apparatus. Therefore, the identification of mass should be considered as a more advanced cancer than nonvisualized lesions, despite the lack of metastases or a similar clinical presentation (e.g. painless jaundice). We also propose that mass lesions be stratified as 3 cm or less or more than 3 cm based upon our experience. Vascular encasement (a frequent occurrence in this disease) and lobar atrophy (due to longstanding lobar bile duct and/or vascular obstruction) have been identified as adverse prognostic features in surgical studies [5,11]. Such features often suggest a prolonged disease interval between disease development and presentation; a feature favoring sufficient time to develop regional micrometastases. Also, lobar bile duct involvement (e.g. right hepatic duct) with contralateral vascular encasement (e.g. left portal vein encasement) precludes surgical resection, the only established, potentially curative therapy for ductal CCA. Thus, each of these tumor/liver anatomic relationships needs to be incorporated into the staging system. Extrahepatic spread signifies metastases and is always an adverse prognostic finding in any human cancer. CCA has three types of regional metastases: lymphatic spread into regional and more distant lymph nodes; venous invasion with intrahepatic metastases; and peritoneal metastases. Which one of these features portends the more adverse prognosis is not readily apparent and will require further study. Lymph node metastases can be regional with involvement of hilar lymph nodes, periduodenal lymph nodes and/or periaortic lymph nodes. Likely, the more distant the lymph node metastases are from the primary tumor, the worse the prognosis; but again, this is a concept that requires careful validation. Although the presence or absence of lymph node metastases can be difficult to confirm by imaging criteria, the use of endoscopic ultrasound with fine needle aspirates for lymph node cytology has made this distinction more reliable. The ability to relieve cholestasis with placement of biliary stents must also be taken into effect. A recent study suggests that if the bilirubin is less than or equal to 10 mg/dl, jaundice (defined as a serum bilirubin >3 mg/dl) should resolve within 3 weeks [12]. For bilirubin values more than 10mg/dl, it may take 6 weeks to obtain resolution of jaundice. Given these data, the parameters for jaundice resolution would be bilirubin and time-dependent. The inability to relieve jaundice results in impaired liver function secondary to persistent cholestasis and impacts on the overall health and performance status of the patient. This cholestatic liver dysfunction adversely affects survival and, therefore, is a critical component of the staging system. Also, whether surgical exploration is or is not feasible (the only current therapy) will also affect patient outcomes. Based on this analysis and the rationale developed for HCC, we have assimilated these factors into a proposed staging system (Table 2). Any positive parameter within a column would relegate the patient to this stage.

This proposed staging system is virtual at this point in time; however, we are in the process of validating this stratification scheme. Perhaps other objective parameters will also help add precision to this staging system (e.g. serum CA19-9 values >1000 U/ml, CCA complicating primary sclerosing cholangitis, etc.). We encourage others to also validate and refine this proposed schema. We also hope this commentary will galvanize a multidisciplinary effort to develop staging systems for this disease, perhaps lead by a major society (e.g. the American Association for the Study of Liver Diseases, American Society of Clinical Oncology, etc.). Only once such a staging system has been validated can randomized Phase II trials be reliably conducted with more homogenous patient populations for ductal CCA. This is a pressing need as promising targeted therapies are being developed and need to be applied to this subset of biliary tract cancers.

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Table 1
Proposed classification of cholangiocarcinoma

Nomenclature	Location
Ductal cholangiocarcinoma	Common bile duct
	Common hepatic duct
	Right/left hepatic ducts up to and including the secondary bifurcation
Intrahepatic cholangiocarcinoma	Mass within hepatic parenchyma
	Does not involve right or left hepatic ducts
	No jaundice

Table 2
Proposed staging system for ductal cholangiocarcinoma

	Stage I	Stage II	Stage III	Stage IV
Mass lesion	None identified	Unicentric mass ≤ 3 cm	Unicentric mass > 3 cm	Multicentric masses
Metastasis	No	No	Perihilar LN	Distant LN and/or peritoneal
Lobar atrophy and/or vascular encasement	No	Yes	NA	NA
Jaundice resolution with stenting	Yes	Yes	No	NA
ECOG performance status	0–1	0–1	0–1	≥ 2

ECOG, Eastern Cooperative Oncology Group; LN, lymph node; NA, nonapplicable.