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EDITORIAL – HEPATOBILIARY TUMORS

# Early Recurrence Following Resection of Distal Cholangiocarcinoma: A New Tool for the Toolbox

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Clinical research in biliary tract cancer presents significant challenges. The relatively low and highly variable incidence of biliary tract adenocarcinoma, compared with other primary adenocarcinomas, requires that three anatomic subtypes of cholangiocarcinoma (intrahepatic, perihilar, and distal) and gallbladder carcinoma be pooled to achieve sufficient power to test hypotheses. The landmark ABC-02 trial, which established cisplatin and gemcitabine as the preferred systemic therapy for advanced disease, included 149 (36.3%) gallbladder tumors, 241 (58.8%) undifferentiated bile duct tumors, and 20 (4.9%) ampullary tumors.[1] More recently, the BILCAP study, which established capecitabine as the standard adjuvant regimen, included 84 (18.8%) intrahepatic, 128 (28.6%) perihilar, and 156 (34.9%) distal cholangiocarcinomas (DCCs), and 79 (17.7%) gallbladder carcinomas.[2] Attempts to overcome these issues with administrative data are fraught with error, as frequent changes to the International Classification of Diseases and Related Health Problems (ICD) codes for cholangiocarcinoma over time have led to miscoding of anatomic subtypes, and inconsistent code utilization globally.[3]

Although histologically similar, mounting evidence of heterogeneity from molecular profiling studies confirms our long-held beliefs that biliary tract cancers are distinct malignancies. For example, isocitrate dehydrogenase-1 (IDH-1) mutations and fibroblast growth factor receptor (FGFR) 2 gene translocations occur almost exclusively in intrahepatic cholangiocarcinoma, while KRAS proto-oncogene mutations (KRAS) and receptor tyrosine-protein kinase erbB-2 amplifications (ERBB2) are more common in extrahepatic cholangiocarcinoma and gallbladder carcinoma.[3] Clinically, although all biliary tract cancers may cause biliary obstruction, presenting symptoms are highly variable, and the anatomic location of the primary has important implications for the diagnostic evaluation, therapy sequence recommended, type of resection pursued (if feasible), and patterns of recurrence. As a result, we now understand that the pooling of heterogeneous biliary tract malignancies for clinical research may not be appropriate in all circumstances. Studies of targeted therapy and the multimodal management of localized disease, for example, are instances where a homogeneous cohort of anatomic subtypes may be preferred when feasible.

Understanding the management, prognosis, and treatment sequencing of DCC is an unmet need. Although frequently studied with other biliary tract cancers, DCC often resembles adenocarcinoma of the pancreatic head in presentation and recurrence and requires a similar approach to curative resection. However, the historic pooling of DCC with other biliary tract cancers has partially obfuscated our understanding of unique characteristics pertinent to management and prognosis and has limited our efforts to identify the preferred multimodality sequence for curative intent.

In this issue of *Annals of Surgical Oncology*, Sahara et al. attempt to address these issues. Using data from the US extrahepatic biliary malignancy consortium, they examine the risk of early recurrence (ER) following curative resection of DCC, and develop a novel score that may identify patients at greater risk for ER at initial diagnosis.[4] The authors identified 245 patients treated with upfront



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resection at 10 high-volume US institutions between 2000 and 2015, of which 67 (27.3%) recurred within 12 months of surgery (defined as ER). No differences in the rates of ER were identified between patients who did or did not receive adjuvant therapy (28.7% vs. 25.0%, $p = 0.55$). Not surprisingly, the median and 5-year OS of patients with ER was dramatically worse (11.3 months and 0%, respectively) than those not experiencing ER (44.5 months and 41.1%, $p < 0.001$). In addition, patients with ER had a worse 1-year OS following recurrence than those with late recurrence (14.9% vs. 32.7%, $p = 0.001$), and 1-year OS following recurrence was not influenced by receipt of adjuvant therapy (24.3% with adjuvant therapy vs. 22.4% without, $p = 0.36$). On multivariable Cox regression, factors associated with ER included neutrophil-to-lymphocyte ratio (NLR) >9.0, peak total bilirubin >1.5 mg/dL, need for major vascular resection, and presence of lymphovascular invasion on surgical pathology.

The authors subsequently used the β-coefficients from the Cox regression to develop the DIstal Cholangiocarcinoma Early Recurrence (DICER) scoring model to predict risk of ER preoperatively. To do this, peak total bilirubin >1.5 mg/dL was assigned 1 point, while NLR >9.0 and the need for major vascular resection were each assigned 2 points. Study patients were then classified into three ER risk categories (low, intermediate, and high) according to the DICER score (0, 1–2, and 3–5 points, respectively), and discriminative performance to predict ER was tested and compared with American Joint Committee on Cancer (AJCC) stage classifications. While AJCC stages I, II, and III failed to discriminate ER rates (25.6% vs. 29.4% vs. 44.4%, $p = 0.15$), the rates of ER significantly increased among each DICER category (10.6% vs. 26.8% vs. 57.6%, $p < 0.001$). To validate these findings, the authors then tested the DICER score in an external cohort of 97 Japanese patients and found similar results, as rates of ER substantially increased in each risk category (3.4% vs. 32.7% vs. 55.6%, $p < 0.001$).

As noted above, previous literature examining biliary tract cancer is often limited by a low incidence, inaccuracies in coding, and heterogeneous cohorts. Through the collaborative efforts of this consortium[5–7] and other multi-institutional studies,[8,9] Dr. Pawlik and colleagues have dramatically advanced our understanding of this disease by conducting rigorous and thoughtful analyses of large homogenous cohorts. This study is no different, and Sahara and colleagues should be commended for enhancing our understanding of recurrence and prognosis for patients with DCC undergoing resection.

As the authors allude in their discussion, the logical next step is to wonder 'how might these results impact our treatment recommendations for DCC patients?' Although the standard of care for both localized DCC and resectable pancreatic ductal adenocarcinoma (PDAC) has historically been an upfront surgical approach followed by adjuvant systemic therapy, the preferred sequence for PDAC has recently and rapidly shifted toward a neoadjuvant approach. [10] Proponents of neoadjuvant therapy in resectable PDAC cite numerous benefits, including early treatment of micrometastatic disease, assessment of in vivo therapeutic response, increased receipt of systemic therapy, possibly increased chances of margin negative resection, and a biologic 'test of time' to potentially decrease the rates of nontherapeutic pancreatectomy in patients with occult disease.[11] Moreover, growing evidence suggests neoadjuvant therapy prior to pancreaticoduodenectomy for PDAC is associated with similar or improved postsurgical outcomes and reduced pancreatic fistula rates.[12,13]

Nonetheless, many differences still remain between resectable PDAC and localized DCC. First, although evidence to support neoadjuvant therapy in PDAC is growing, literature supporting a similar approach in DCC is sparse[14] and is limited by the many problems above. Second, unlike PDAC, where the presence of a mass allows for biopsy and reliable pathologic confirmation of malignancy, the diagnosis of adenocarcinoma can be more difficult to achieve in DCC,[3,15] complicating consideration of a neoadjuvant approach. Third, although systemic therapy is recommended for all patients with PDAC, less is known about which patients with localized DCC benefit from systemic therapy. Thankfully, the study by Sahara et al.[4] offers new insight into this clinical challenge. In addition to a comprehensive multidisciplinary evaluation and imaging review, the DICER score may help identify patients at increased risk for poor outcomes at initial presentation and could further inform clinical decisions regarding recommended multimodal management.

However, there is still much work to be done. Additional prospective and ideally randomized studies will be necessary to examine the impact of changes to multimodal treatment sequencing on patients with localized DCC, particularly those at high-risk for poor outcomes. Going forward, to better inform clinical practice and improve patient outcomes, future randomized and observational studies of biliary tract cancer should thoughtfully determine whether pooling or splitting of anatomic subgroups is appropriate. Ultimately, as the science of targeted therapy and personalized cancer care improves, we may someday find that our preferred multimodal management approach for a patient with biliary tract cancer will be determined by the tumor's molecular profile as opposed to its anatomic location.[3,16]

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