Editorial

Cholangiocarcinoma: three different entities based on location

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Cholangiocarcinoma is a relatively rare malignancy that arises from the biliary tract epithelium and accounts for 3% of all gastrointestinal cancers (1). Despite improvement in survival over the past few decades, long-term survival following potentially curative resection remains poor with a 5-year survival rate of 20–40% (2-4). For this reason, gaining a better understanding of the different types of cholangiocarcinoma, prognostic factors, and gene signatures is vital to guide efficacious treatment and subsequently improving outcomes. As such, we read with great interest the manuscript by Hang *et al.* entitled, "*Cholangiocarcinoma: anatomical location-dependent clinical, prognostic, and genetic disparities*". In their study, the authors identified 11,710 patients from Surveillance, Epidemiology, and End Results Cancer Registries (SEER) and 45 patients from The Cancer Genome Atlas with intrahepatic, perihilar, or distal cholangiocarcinoma to compare tumor location with incidence, postoperative survival, prognostic factors, and genetic heterogeneities (5).

Historically, intrahepatic bile duct cancer was included in the staging schema for liver cancer, which was largely based on data derived from hepatocellular carcinoma, and perihilar and distal cholangiocarcinoma were grouped together as extrahepatic bile duct cancer (6). It was not until the release of the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual in 2010 that the heterogeneity between intrahepatic, perihilar, and distal cholangiocarcinoma was fully recognized (7). In the 7th edition, separate staging classifications were defined for intrahepatic, perihilar, and distal cholangiocarcinoma. With respect to intrahepatic cholangiocarcinoma (tumor arising proximal to the second-order bile ducts), the decision to separate it from hepatocellular carcinoma and create a unique staging system was based upon prior studies demonstrating that tumor size was not a significant prognostic factor and that distinct growth patterns including mass forming, periductal infiltrative, and mixed types had prognostic impact (7). For perihilar cholangiocarcinoma (tumor arising between the second-order bile ducts and the cystic duct-bile duct junction), Ebata *et al.* demonstrated that patients with involvement of adjacent liver parenchyma have a better prognosis than individuals with vascular invasion following resection (8). This finding was incorporated in the 7th edition of the AJCC Cancer Staging Manual (7). With respect to distal cholangiocarcinoma (tumor arising between the cystic duct-bile duct junction and the ampulla of Vater), Hong *et al.* reported that tumor depth was most strongly associated with survival (9). This finding was incorporated in the 8th edition of the AJCC Cancer Staging Manual which was released in 2018 (10).

In the study by Hang *et al.*, the authors further highlight the differences among intrahepatic, perihilar, and distal cholangiocarcinoma (5). In accordance with other studies, the incidence among the three types was highest for perihilar (48%) followed by intrahepatic (46.6%) and distal (5.3%) (11,12). In contrast, the proportion of patients who underwent surgery was highest for distal (37.8%) followed by perihilar (36.3%) and intrahepatic (18.5%).

Patients with intrahepatic disease were more likely to have distant metastasis (43.5%) compared with perihilar (30.3%) and distal (30.1%) cholangiocarcinoma. Prognosis also differed substantially between the types with respect to 5-year overall survival (intrahepatic =3.7%, perihilar =7%, distal =1.9%) and 5-year overall survival following surgery (intrahepatic =16.7%, perihilar =16.4%, distal =5.7%). This finding differed somewhat from that of a retrospective cohort study that included 564 patients who underwent surgical exploration at Johns Hopkins Hospital over a 31-year time period (intrahepatic =40%, perihilar =10%, distal =23%) (3). However, these differences may be secondary to selection bias.

The authors also performed stratified analyses for each of the anatomical locations to identify disparities in prognostic factors following surgery. Not surprisingly, stage was associated with overall survival for all three types. For intrahepatic and perihilar, age, tumor differentiation, and lymph node metastasis were also significant factors. Lymph node dissection was a significant prognostic factor only for hilar cholangiocarcinoma. This may in part be due to the fact that lymphadenectomy for intrahepatic cholangiocarcinoma is underutilized and has not consistently demonstrated a survival benefit (13). However, lymph node evaluation does provide accurate staging and guides adjuvant treatment decisions. For perihilar cholangiocarcinoma, it appears that retrieval of at least 4 lymph nodes following resection is required for accurate staging and may be associated with a survival benefit (14,15). However, one of the most important prognostic factors that was not analyzed in the study is margin status. Multiple studies have demonstrated worse survival for patients with a positive margin following resection of intrahepatic, perihilar, and distal cholangiocarcinoma compared to those with a negative margin (3,16-18). Furthermore, studies suggest that a negative margin width ≥10 mm has a significant survival advantage and thus should be obtained for intrahepatic cholangiocarcinoma (16,19).

While most of the differences between intrahepatic, perihilar, and distal cholangiocarcinoma identified in this study by Hang *et al*. confirmed data from previous studies, the most potentially impactful difference noted was the disparities in prognosis-predictive genes, protein domains, and potential processes and pathways for recurrence between intrahepatic and perihilar cholangiocarcinoma (5). The authors identified the top genes for effectiveness in prognostic estimation for intrahepatic and perihilar cholangiocarcinoma, which has not been previously described. These findings highlight the importance of studying each of the cholangiocarcinoma types separately with respect to genomic profiling to identify potential target points for new therapeutic modalities, which is especially important given that clinical trials have demonstrated that adjuvant chemotherapy and radiation provide only a modest survival benefit for a malignancy already associated with poor long-term survival (20,21). In addition to R0 resection, future clinical trials involving targeted therapy will likely be the key to further improvement in survival for these aggressive malignancies.

In conclusion, the recent manuscript by Hang *et al*. provides further evidence into the diagnostic, molecular, and prognostic disparities between intrahepatic, perihilar, and distal cholangiocarcinoma. Further studies should aim to utilize these data to evaluate precision personalized therapies for these aggressive malignancies.

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Footnote

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