Editorial

Guidelines for the management of pancreatic cystic lesions: many options, too few solutions?

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In a recent issue of *HepatoBiliary Surgery and Nutrition*, Cheung *et al.* presented the Hong Kong consensus recommendations for the management of pancreatic cystic lesions (PCLs) (1). These consensus recommendations were generated by a multidisciplinary panel comprised of local experts using an iterative Delphi process. The authors cataloged a comprehensive series of best-practice recommendations adapted to the healthcare infrastructure in Hong Kong, highlighting clinical approaches and modern challenges in PCL management.

The increased use of cross-sectional imaging has led to a rise in the number of incidentally detected PCLs, the most common of which are intraductal papillary mucinous neoplasms (IPMNs) (2). IPMNs are premalignant lesions that exhibit variable propensity for malignant transformation to pancreatic ductal adenocarcinoma (PDAC). Surgical resection is commonly recommended for advanced main-duct IPMNs, which are more likely to harbor high-grade dysplasia and invasive cancer. In contrast, branch-duct IPMNs uncommonly progress to PDAC, and their risk of progression correlates, in part, with cyst size. As communicated by the experts in Hong Kong, the overarching goal of PCL management is to resect high-risk lesions prior to malignant transformation. However, given the limitations of radiographic and endoscopic techniques to reliably detect advanced neoplasia, the potential benefits of surgical resection must be carefully weighed against the attendant morbidity and mortality of pancreatic surgery (3,4). Accordingly, the variable and unpredictable natural history of PCLs mandates longitudinal surveillance and clinical judgment to distinguish between low- versus high-risk PCLs.

The Hong Kong consensus recommendations aim to address modern PCL clinical conundrums by providing a pragmatic, resource-conscientious framework for PCL risk stratification. This work adds to a growing body of society guidelines from the International Association of Pancreatology (IAP) (5), American Gastroenterological Association (AGA) (6), American College of Gastroenterology (ACG) (7), and European Study Group on Cystic Tumours of the Pancreas (ESGCTP) (8). There are several nuances unique to the Hong Kong group's recommendations. First, similar to the latest update of the IAP (Kyoto) guidelines, this group has recognized new onset diabetes mellitus (NODM) as a worrisome feature, reflecting the growing body of evidence that NODM is associated with, and often precedes, PDAC diagnosis (9). Thus, serial screens for NODM with glycosylated hemoglobin (HbA1c) and partnerships with primary care physicians to track serum glucose levels over time may be performed as elements of PCL surveillance. Second, for PCLs without worrisome features, the Hong Kong group recommends a standardized surveillance

protocol—every 6 months for the first year and yearly thereafter—irrespective of cyst size. This recommendation is consistent with the ESGCTP guidelines, but contrasts with the IAP (Kyoto) guidelines, which prescribe surveillance intervals based on the size of the largest PCL. Third, the Hong Kong group recommends that surveillance be continued lifelong provided the patient remains fit for surgery. The AGA guidelines recommend discontinuation of surveillance after 5 years if no changes or concerning features are observed in PCLs. Based on recently published analyses, the updated IAP (Kyoto) guidelines give the option of either continuing surveillance lifelong or stopping surveillance for <2 cm cysts that do not demonstrate morphologic changes or worrisome features for at least 5 years (10). Taken together, and compared with the other consensus guidelines, the Hong Kong recommendations fall within the more conservative end of the spectrum with respect to surveillance intervals and duration.

The variability among different consensus guidelines, along with the apparent lack of specificity in translating various worrisome features into surgical action, reflects the challenges of risk stratifying IPMNs using imaging and clinical features alone (11). A better understanding of the molecular pathogenesis of IPMNs progression and the identification of diagnostic and predictive biomarkers of high-grade dysplasia or invasive cancer may help to refine guidelines. To this end, integration of next-generation sequencing (NGS) of pancreatic cyst fluid has been championed as an approach to diagnose and risk stratify PCLs (12,13). Alterations in genes such as *TP53*, *SMAD4*, *PIK3CA*, and *PTEN* have been associated with advanced neoplasia. The recently updated PancreaSeq Genomic Classifier is a 74-gene DNA/RNA-targeted panel that has a reported 82% sensitivity and 100% specificity for advanced neoplasia and outperformed existing PCL guidelines based on radiographic and clinical factors (12). Such a genomic classifier assay can be particularly useful to quantify the preoperative risk of advanced neoplasia in cases where indeterminate cyst characteristics or significant patient comorbidities may dampen perceived benefits of surgical resection. While cyst fluid NGS assays provide near time readouts for underlying advanced neoplasia, they are not predictive of the long-term risk of IPMNs malignant transformation. Moreover, as indicated by the Hong Kong panel, the technology and clinical laboratory infrastructure to perform and interpret cyst fluid NGS are not widely available in Hong Kong or at many other centers. These factors underscore the importance of developing regional partnerships to establish sample processing standards and facilitate timely access to pancreas cyst fluid NGS testing in appropriate patient populations. Notably, to date, cyst fluid NGS has not been integrated in consensus recommendations, and represents an evolving aspect of PCL management that has yet to be fully contextualized in the field.

Similar to other consensus guidelines, the Hong Kong consensus recommendations do not distinguish between PCLs arising in high-risk individuals (HRIs; those with a pathogenic germline alteration in a PDAC predisposition gene and/or with a familial pancreatic cancer kindred) versus average-risk individuals. Indeed, evidence from multiple studies indicate that IPMNs are more prevalent in HRIs (14). Moreover, the risk of malignant transformation may be higher in IPMNs arising in HRIs compared to presumed "sporadic" IPMNs (15). Among HRIs, there is evidence to suggest a higher risk of IPMNs neoplastic progression in patients with a germline susceptibility compared to those with a familial pancreatic cancer kindred (15). Thus, IPMNs risk stratification strategies may further benefit from consideration of an individual's hereditary risk for developing PDAC.

Collectively, the Hong Kong consensus guidelines build on existing guidelines and highlight certain regional practice variations. Importantly, the sheer magnitude of patients with PCLs underscores the pressing need to operationalize programs that balance an individual's PDAC risk with the constraints of healthcare funding, technological resources, and patient/provider-based logistics. Directing patients with PCLs to multidisciplinary pancreatic cyst clinics, where surgeons, gastroenterologists, radiologists, pathologists, and advanced practice providers with enriched expertise may collaborate, is one strategy to maximize resource efficiency and streamline patient management. Furthermore, shared infrastructure consolidates research efforts and enables patient participation in prospective research registries, large-scale consortia, and clinical trials. Such efforts will be critical to inform future iterations of PCL consensus guidelines that may integrate clinical, radiographic and molecular biomarkers to refine risk stratification and surveillance strategies. The Hong Kong authors should be commended on their efforts to efficiently utilize healthcare resources and shared expertise through uniform guidelines for the benefit of PCL patients.

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