Editorial Commentary

International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas: what is the breaking news?

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Comment on: Ohtsuka T, Fernandez-Del Castillo C, *et al.* International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 2024;24:255-70.

Keywords: Guidelines; intraductal papillary mucinous neoplasms (IPMNs); hepato-pancreato-biliary surgery (HPB surgery); surveillance

Submitted Nov 21, 2024. Accepted for publication Dec 11, 2024. Published online Jan 09, 2025.
doi: 10.21037/hbsn-2024-662
View this article at: https://dx.doi.org/10.21037/hbsn-2024-662

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are increasingly recognized in clinical practice and still represent a challenge for involved clinicians. The most common dilemma remains "to operate or surveillance" and three primary guidelines (the last in 2017) (1) have been introduced to reduce the number of unnecessary pancreatic operations and their associated morbidity and mortality rates.

In July 2022, a new meeting was held in Kyoto by the International Association of Pancreatology (IAP) aiming at revising the 2017 guidelines for the management of IPMN of the pancreas. The main purpose was to revise and perform a systematic review of the actual collected evidence regarding five main topics: revision of high-risk stigmata (HRS) and worrisome features (WF), surveillance for non-resected IPMN, surveillance after surgical resection of IPMN, revision of pathological aspects, and investigation of molecular markers in cyst fluid (1).

Regarding the first topic (i.e., the revision of HRS and WF), the newly published evidence-based guidelines underscore the pivotal role of endoscopic ultrasonography (EUS) as a diagnostic tool since it provides a higher spatial resolution, allowing both a more detailed imaging compared to other modalities and a discrimination between malignant and benign IPMN (2). Nevertheless, EUS-guided fine needle aspiration (EUS-FNA) has been widely reported in literature as an effective instrument for both tissue sampling for pathological diagnosis and comprehensive genomic profile tests (3-5).

However, in the previous revised Fukuoka guidelines published in 2017, the diagnostic role of EUS was limited because EUS procedure could not be performed with same availability and quality at all institutions (6).

To note, several studies reported that EUS [including contrast-enhanced EUS (CE-EUS)] can be comparable or even superior to multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) in the detection of high-grade dysplasia (HGD) and invasive carcinoma (IC) in IPMN since in some cases main pancreatic duct (MPD) dilatation and the presence of tiny papillary projections on the cyst wall can be underestimated by MDCT or MRI (7-10).

In addition to the above-mentioned revision, the novel guidelines kept unchanged most of the WF published in the previous version, except for new onset or recent exacerbation of diabetes mellitus (DM) and cyst growth rate. According to recent works, newly diagnosed DM is quite common in IPMN patients and frequently associated with a higher risk of HGD and IC (11,12).

According to a recent meta-analysis, the overall prevalence of preoperative DM among included studies was

25%, whereas new-onset DM was described in 68 out of 1,202 patients (6%) (12). DM could be a direct consequence of ductal system obstruction following mucin production and associated chronic inflammatory processes (i.e., chronic pancreatitis). However, a clear definition of "new onset" and "deterioration" of DM are still lacking and additional evidence is needed in order to consider DM in the risk stratification of patients with IPMN (13).

Regarding cystic growth rate, recent literature reported that IPMN cystic growth rate can be regarded as a predictor for progression to HGD/IC ranging from ≥0.96 to ≥3.5 mm/year, with a rate of ≥2.5 mm/year described most frequently (14). The newly endorsed cystic growth rate (i.e., ≥2.5 mm/year) highlights the dynamic state of IPMN progression to HGD/IC, suggesting its possible role in the development of nomograms to be discussed with patients based on their comorbidity status, surgical candidacy, diagnostic tool availability and feasibility and, above all, patients' expectations and preferences.

Another key aspect introduced in the new guidelines is the clear definition of duration of surveillance for non-resected small IPMNs, giving the possibility of interrupting surveillance in case of clinical stability lasting for a period of 5 years, with the forewarning that concomitant pancreatic ductal adenocarcinoma (PDAC) (i.e., carcinoma not originating from IPMN) will always represent an option a possibility. This revision has important clinical and economic implications. First of all, it highlights the importance of a patient-centered vision, in terms of awareness of the disease burden and life expectancy. Nevertheless, when discussing surveillance timing, the potential benefits and risks are to be considered in terms of economic expenditure, psychological and economic burden on patient and health care. For this reason, long-time surveillance was reported to be highly unlikely to be cost-effective and the potential benefit in terms of life expectancy is still underreported (15). However, the survival benefit of surveillance among low-risk, stable-sized BD-IPMNs after 5 years warrants further exploration through high-quality studies before recommending surveillance cessation with certainty (16).

Another important aspect of IPMN is that clinically significant lesions after margin negative pancreatectomy might appear in remnant pancreas in a median cumulative 5-year incidence of 10% (17) and this risk continues to increase even after 5 years. HGD in the pathological specimen and the presence of the family history of pancreatic adenocarcinoma are the risk factors for developing clinically significant lesions (18). So, extended surveillance has been advocated for these patients at least until they are fit for surgery (19).

Revision of pathological aspects emphasizes the opportunity to avoid the term malignancy in favor to HGD or IC reported separately. Three re-known subtypes of IPMN are associated with different prognoses: the gastric type with a more favorable prognosis (mostly low-grade BD-IPMN), followed by intestinal type and pancreatobiliary type with the highest risk of neoplastic progression. Most BD-IPMNs are indolent gastric subtypes, but molecular studies reported that the gastric subtype may be the ancestor of the other subtypes with HGD or IC components and it should not to be considered as no-risk.

Detection of molecular markers in cyst fluid, although still evolving, has created an intriguing appeal for the diagnosis and treatment of IPMNs. The main utility of molecular analysis remains the discrimination between mucinous from non-mucinous tumors and the obvious impact on the management of such lesions. Assessment of mutations for TP53, SMAD4 and others, may be a useful tool for detection of HGD or invasive cancer but the sensitivity of the test is low. Moreover, molecular analysis is not easily available and the high cost represents a financial barrier to universal adaptation. Today, these advanced techniques are limited to centers with high expertise in the management of cystic pancreatic neoplasms.

In conclusion, the main goal achieved by these guidelines was to highlight the need for a management algorithm tailored to the patient's clinical status and disease burden. Despite the fact that most of the described studies do not manage to provide the highest and strongest level of recommendations (i.e., level 1, grade A–B), they still can be considered evidence-based for the impact and valuable benefit in terms of tailored management and patient's risk awareness from both clinical and pathological point of view. At the moment, the optimal treatment strategy between surgery and surveillance of IPMNs should be driven by patients' health and psychological status, risk of malignancy, and centers' expertise and diagnostic tool availability.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *HepatoBiliary Surgery and Nutrition*. The article did not undergo external peer review.

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2024-662/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Sperti C, Belluzzi A. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas: what is the breaking news? HepatoBiliary Surg Nutr 2025;14(1):155-158. doi: 10.21037/hbsn-2024-662