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HEPATOBILIARY-PANCREAS

Glypican-1 circulating exosomes: a promising clue to individualize surveillance of pancreatic cysts?

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The Editor

We read with great interest the article published by Imbe et al. [1] in *European Radiology* (Jan 2018) titled 'Validation of the American Gastroenterological Association (AGA) guidelines on management of intraductal papillary mucinous neoplasms: more than 5 years of follow-up'. In this paper, the authors discuss a 'hot' topic in pancreatic diseases related to the best approach for managing cystic lesions, which are being diagnosed more frequently since the increasing use of sectional imaging modalities. In this validation study, data were analysed for 392 patients with intraductal papillary mucinous neoplasms (IPMNs) and at most one high-risk feature who were periodically followed up for more than 1 year with imaging tests (group 1) and for 159 IPMN patients without worsening high-risk features after 5 years (group 2: stop surveillance group). In the first group, pancreatic cancer (PC) was identified in 12 patients (27.3 %) when endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was indicated and none in the non-EUS-FNA indication group ($p < 0.01$). On the other hand, in the 'stop surveillance group', PC was identified in three patients (1.9 %) at 84, 103 and 145 months, respectively. These observations led the authors to conclude that PC risk and mortality for IPMNs not showing significant change for 5 years is likely to be low, and the non-EUS-FNA indication can provide reasonable decisions; however, three patients without worsening high-risk features for 5 years developed PC, so the 'stop surveillance strategy' supported by AGA guidelines [2] should be reconsidered.

In fact, controversy exists about the best algorithm to manage these apparently low-risk lesions. Older guidelines such as the ones proposed by the International Consensus [3] and the European Consensus [4] suggest a life-long closer follow-up. On the other hand, the more recent guidelines by the American Gastroenterology Association [2] recommend discontinuation of surveillance at 5 years in the absence of significant changes.

In the same line of investigation, in a recent study published by Crippa et al. [5] in the *American Journal of Gastroenterology*, the authors support the idea that active surveillance beyond 5 years is required for presumed branch-duct intraductal papillary mucinous neoplasms (BD-IPMN) with no high-risk stigmata (HRS) or worrisome features (WF) undergoing non-operative management. In the Crippa et al. study [5], 144 patients with BD-IPMN were followed for a median of 84 months, with at least annual magnetic resonance imaging and/or magnetic resonance cholangiopancreatography, and changes during follow-up were observed in 48 % of the patients. Remarkably, new-onset WF/HRS was observed in 26 patients (18 %) after a median follow-up period of 71 and 77.5 months from diagnosis, respectively, and without previous changes in 19 (73 %) of them. Although considering the study limitations, these observations led the authors to conclude that discontinuation of surveillance of these apparently 'inoffensive' lesions cannot be recommended and, instead, an algorithm with intensification of follow-up is proposed after 5 years of follow-up. Nevertheless, the authors recognize that discontinuation of surveillance should be considered in patients who are unfit for surgery because of age and/or relevant comorbidities.

In the same issue of the *American Journal of Gastroenterology*, the Editorial by James Farrell [6] titled 'Stopping pancreatic cyst surveillance', critically discusses the pros and cons of different approaches to BD-IPMN management. In James Farrell's opinion, sufficient data (especially

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cost-effectiveness studies) are still lacking for a proper decision for continuing or stopping surveillance of presumed low risk BD-IPMNs. This controversy needs to balance the real risk of malignancy or developing malignancy and IPMN-related mortality, with the patient's life expectancy, quality-of-life expectations and mortality from non-pancreatic-related causes. Although highlighting the occurrence of the late events during surveillance described by Crippa et al. [5], James Farrell [6] advocates that more prospectively collected information about risks of malignancy after cyst stability for 5–10 years is need. Moreover, the strategy proposed by Crippa et al. [5] raises some critical issues related to the significant costs associated with repeat imaging. In fact, the improved life expectancy and survival from non-pancreatic malignancies, in association with growing diagnosis of ever smaller BD-IPMNs, makes this issue more critical.

What seems consensual is that, in the future, the development of biomarkers dedicated to identify IPMNs with different risks of being or becoming malignant will certainly help to minimize this controversy. Several promising molecular biomarkers have been described [7]. Nevertheless, to date, besides the recognized value of carcinoembryonic antigen levels in the cyst's fluid, none of them have proved to show definitive superiority in risk stratification of pancreatic cysts.

In this field, our group is conducting a prospective study combining endoscopic ultrasound findings and characterization of a group of serum and tissue molecular biomarkers in patients diagnosed with pancreatic adenocarcinoma (PDAC) or harbouring a risk condition for it, including chronic pancreatitis, family history of PDAC or an associated hereditary syndrome, as well as a diagnosis of IPMN or other cystic mucinous neoplasms (CMNs).

The molecular markers we have been studying include a panel of microRNAs and, most importantly, the recently described glypican-1 (GPC1), a cell surface proteoglycan, overexpressed in PDAC and specifically enriched on cancer-cell-derived circulating exosomes (crExos) [8]. Melo et al. [8] demonstrated that levels of GPC1+ crExos correlated with tumour burden and the survival of patients with PDAC. Interestingly, in our ongoing study, preliminary data indicate that levels of GPC1+ crExos are significantly higher in patients with PDAC as well as in some patients with CMNs, when compared to other associated group risks. In fact, in our cohort of CMNs (diagnosed with clinical, biochemical and echoendoscopic criteria), data on serological biomarkers seem to be categorized into two possible distinct groups of patients: those with GPC1+ crExos levels as high as PDAC patients and those with levels similar to control groups. In the near future we will know if this is truly a clue for stratifying pancreatic mucinous cysts according to their malignant potential and enable us to perform an individualized management approach.

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• performed at one institution

References

1. Imbe K, Nagata N, Hisada Y et al (2018) Validation of the American Gastroenterological Association guidelines on management of intraductal papillary mucinous neoplasms: more than 5 years of follow-up. Eur Radiol 28:170–178. https://doi.org/10.1007/s00330-017-4966-x
2. Vege SS, Ziring B, Jain R et al (2015) American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 148: 819–822
3. Tanaka M, Fernandez-del Castillo C, Adsay V et al (2012) International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 12:183–197
4. Del Chiaro M, Verbeke C, Salvia R et al (2014) European experts consensus statement on cystic tumours of the pancreas. Dig Liver Dis 45:703–711
5. Crippa S, Pezzilli R, Bissolati M et al (2017) Active surveillance beyond 5 years is required for presumed branch-duct intraductal papillary mucinous neoplasms undergoing non-operative management. Am J Gastroenterol 112:1153–1161
6. Farrell JJ (2017) Stopping pancreatic cyst surveillance? Am J Gastroenterol 112:1162–1164
7. Singh H, McGrath K, Singhi AD (2017) Novel biomarkers for pancreatic cysts. Dig Dis Sci 62:1796–1807
8. Melo SA, Luecke LB, Kahlert C et al (2015) Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature 523: 177–182