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Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 123800

Manuscript Type: CORRESPONDENCE

De-escalating surveillance in branch duct intraductal papillary mucinous neoplasms: Balancing surveillance burden with long-term oncologic risk

Risk-adapted BD-IPMN surveillance

Abstract

A recent observational study by Hopley *et al*. provided significant insights into the potential for de-escalating surveillance in patients with branch duct-intraductal papillary mucinous neoplasms (BD-IPMN). Their findings regarding early front-loaded surgery and the low risk of malignancy in stable cysts measuring < 30 mm with low CA19-9 Levels (< 43 KU/L) after 2 years represent a valuable contribution to pancreatology. However, the study's reliance on the timing of discovery rather than the biological history of the disease may introduce discovery-phase enrichment bias. Furthermore, the decision to discharge patients at 5 years must be balanced against the lifelong cumulative risk of concomitant pancreatic cancer and variations in surgical fitness among the elderly. Although de-escalation is clinically promising, individualized risk-adapted surveillance approaches remain essential.

Key Words: Intraductal papillary mucinous neoplasm; Surveillance; Pancreatic cancer; De-escalation; CA19-9; Concomitant pancreatic ductal adenocarcinoma

Core Tip: This letter critically appraises the study by Hopley *et al*. on the de-escalation of BD-IPMN surveillance. While the proposed criteria for de-escalation are timely, we emphasize that the front-loaded nature of surgery may partly reflect discovery bias and therefore may not fully represent the intrinsic biological timing of

disease progression. We highlight the need for tailored surveillance based on individual surgical fitness and the persistent long-term risk of dual carcinogenesis involving both IPMN progression and concomitant pancreatic ductal adenocarcinoma, which continues beyond the 5 years.

TO THE EDITOR

We read with great interest the article by Hopley *et al.*, "Branch duct intraductal papillary mucinous neoplasms: How ready are we to de-escalate surveillance?" (*World Journal of Gastroenterology*) [1]. The authors provide valuable insights into optimizing surveillance, suggesting that for patients with stable cysts measuring < 30 mm and CA19-9 Levels < 43 KU/L for 2 years, surveillance intensity can be de-escalated, with discharge considered at 5 years. We commend the authors for their analysis of a large cohort (n = 1191); nonetheless, we would like to offer several critical perspectives and constructive suggestions.

A central concern lies in the interpretation of the "front-loaded" surgery phenomenon. While the authors noted that most resections occurred within the first 2 years, it is difficult to determine whether this reflects the disease's early biological stage or merely the "discovery phase." This early clustering of surgeries may partly reflect discovery-phase enrichment bias rather than the intrinsic biological timing of malignant progression. Specifically, if early resections result from the immediate evaluation of incidentally detected lesions rather than true rapid biological progression, excluding these patients from long-term follow-up analyses may lead to an overestimation of the safety of early surveillance discontinuation. In contrast, multicenter studies have intentionally excluded resections within the first 12 months to avoid this "discovery bias" [2]. We acknowledge that Hopley *et al.* may have adopted a pragmatic, "real-world" approach that includes discovery-phase events, reflecting actual clinical presentations encountered in routine practice. While this perspective is highly valuable for informing clinical policy, interpreting these pragmatic findings as definitive evidence of the underlying biological course of the disease still warrants caution,

particularly because such observations may not fully capture the long-term natural history of low-risk cysts that progress slowly over decades [3, 4].

Hopley *et al*. adopted a single 30-mm threshold for stepwise surveillance de-escalation. However, more granular size-based stratification may provide a more nuanced framework. Recent evidence, including the 2024 International Kyoto Guidelines, suggests that biological behavior differs significantly across size strata [5]. For example, BD-IPMNs < 20 mm generally exhibit indolent behavior, whereas cysts measuring 20–29 mm demonstrate a higher cumulative incidence of progression within a shorter timeframe [6, 7]. Consequently, a single < 30-mm category may obscure risk heterogeneity and lead to premature discontinuation of surveillance in selected patients. Incorporating these established size strata may enhance the precision of surveillance de-escalation strategies.

The suggestion to discharge patients after 5 years of stability also warrants careful consideration, given the risk of "dual carcinogenesis." Importantly, surveillance of BD-IPMN serves two distinct oncological purposes: Monitoring the progression of the index cyst itself and detecting concomitant pancreatic ductal adenocarcinoma (PDAC) arising elsewhere in the gland. Longitudinal studies have demonstrated that the cumulative incidence of malignancy in BD-IPMN continues to increase even after 5 years of stability, reaching approximately 15% at the 15-year mark [8]. Critically, patients with BD-IPMN face a persistent risk of concomitant pancreatic ductal adenocarcinoma (PDAC) elsewhere in the gland, with an annual rate of 0.4%–1.1% [9]. As this risk is often independent of the original cyst's stability, discharging patients at 5 years may result in missed opportunities for early detection of these separate, aggressive malignancies. While surveillance de-escalation (*i.e.*, lengthening the intervals between imaging) represents a reasonable strategy for carefully selected low-risk patients, complete discontinuation is a distinct decision that warrants substantially greater caution in individuals with preserved life expectancy and acceptable surgical candidacy.

Another important consideration relates to surgical fitness and aging. The authors suggest that the benefit of surveillance decreases after 2 years, primarily due to a decline in patient fitness. However, in an increasingly aging society, chronological age does not always correlate with surgical suitability. Frailty, rather than chronological age, may determine the clinical utility of continued surveillance. The 2024 International Kyoto Guidelines emphasize a tailored approach, recommending that surveillance continue for as long as a patient remains a candidate for surgery [5].

Many elderly patients retain excellent performance status and a life expectancy exceeding 10 years, warranting individualized follow-up rather than standardized discharge based on age-related assumptions [8, 10, 11]. Consequently, rather than relying on chronological age alone, the decision to discontinue surveillance should be based on a comprehensive assessment integrating cyst biology, competing cancer risks, and patient-level surgical fitness. Future strategies should integrate longitudinal monitoring of biochemical markers with comprehensive fitness assessments and emerging blood-based biomarkers to identify patients at increased risk of PDAC.

CONCLUSION

Hopley *et al*. proposed a clinically relevant framework for de-escalating BD-IPMN surveillance. However, the subjective nature of determining surgical fitness and the persistent long-term risk of dual carcinogenesis limit the generalizability of a universal 5-year discharge rule. While surveillance de-escalation is both reasonable and clinically necessary in selected low-risk patients, routine discharge after 5 years may be premature for individuals with preserved life expectancy and an ongoing risk of concomitant PDAC. We advocate for a stratified approach in which surveillance de-escalation may be appropriate for many patients, whereas complete discharge remains a highly individualized decision that may be justified in selected patients with severe frailty, limited life expectancy (*e.g.*, less than 10 years), or a strong preference against future surgical intervention.