Ann Surg Oncol (2022) 29:4683–4685
https://doi.org/10.1245/s10434-022-11713-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – PANCREATIC TUMORS

Invited Editorial: Comprehensive Analysis of Molecular Biological Characteristics of Pancreatic Ductal Adenocarcinoma Concomitant with Intraductal Papillary Mucinous Neoplasm

Ippei Matsumoto, MD, PhD

Department of Surgery, Kindai University Faculty of Medicine, Osakasayama, Osaka, Japan

Despite significant efforts in management over the past decades, pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignant diseases, with a 5-year survival rate of <10% in all stages of the disease. The incidence of PDAC is increasing globally and is projected to become the second leading cause of cancer-related deaths by 2030.[1] Intraductal papillary mucinous neoplasm (IPMN) is regarded as a precursor lesion of PDAC because IPMN has the potential to progress to invasive carcinoma (PDAC derived from IPMN). By contrast, PDAC develops independently of IPMN in the pancreatic duct (PDAC concomitant with IPMN). Traditionally, these entities are defined by radiological images, macroscopic findings, and the relationship and presence of a histological transition between the two lesions.[2]

PDAC concomitant with IPMN was first reported by Tanaka et al.[3] in 1997. They reported a case of in situ pancreatic carcinoma concomitant with IPMN diagnosed using segmental balloon cytology for preoperative localization. Since then, several investigators have reported the incidence and timing of metachronous development of concomitant PDAC during surveillance for IPMN with and without surgical resection.[4–7] The cumulative 5-year incidence of the development of concomitant PDAC ranges from 2.2 to 8.8% during surveillance for IPMN without resection.[8] Oyama et al.[9] reported 38 patients with PDAC derived from IPMN and 30 patients with PDAC concomitant with IPMN from a total of 9231 patients with branch-duct type (BR)-IPMN during surveillance. The overall incidence rates of PDAC were 3.3%, 6.6%, and 15.0% at 5, 10, and 15 years after the initial diagnosis, respectively. Long-term surveillance for detection of concomitant PDAC during surveillance for IPMN is thus necessary.[8]

The prognosis of PDAC derived from IPMN is believed to be more favorable than that of conventional PDAC (PDAC without IPMN in the pancreas). A recent meta-analysis comparing the pathological features of intraductal papillary mucinous carcinoma (IPMC) and conventional PDAC found that IPMC was associated with better prognosis;[10] however, the results were not reliably assessed because conventional PDAC showed a more advanced disease state than IPMC. Conventional PDAC presented lower rates of T1 tumors and higher rates of node involvement, perineural invasion, vascular invasion, R1 resection, and poor differentiation.[10,11] Several studies comparing matching parameters have been reported; however, the results were inconsistent and included selection biases.[11] Therefore, whether IPMC has a favorable prognosis remains unclear.

To understand the mechanisms and pathways of progression to IPMN-related PDAC, recent research has been conducted using genetic analysis. Omori et al.[12] classified lesions into three subtypes according to their analyses of mutations in pancreatic cancer-associated genes and the expression of tumor suppressors. PDAC contains driver mutations shared by all concurrent IPMN (sequential subtype). This subset is characterized by less diversity in incipient foci with frequent GNAS mutations. PDAC and IPMN had identical KRAS mutations but different GNAS mutations, although the lesions were adjacent (branch-off subtype). PDAC patients had driver mutations that were

First Received: 18 March 2022
Accepted: 23 March 2022
Published Online: 13 April 2022

I. Matsumoto, MD, PhD
e-mail: ippeimm@gmail.com

not found in concurrent IPMNs (de novo subtype). Patients with PDAC of the branch-off subtype showed better disease-free survival (DFS) than those with de novo or sequential subtypes. These results were consistent with the results reported by Felsenstein et al.[13]

Based on the current evidence, PDAC concomitant with IPMN develops independently from the related IPMN; however, it is unclear whether PDAC concomitant with IPMN is a disease entity independent of conventional PDAC. Previous reports have shown that PDAC concomitant with IPMN has a better prognosis than conventional PDAC.[2,14] These findings suggest that PDAC concomitant with IPMN may have more favorable biological behaviors or may be diagnosed earlier than conventional PDAC. In this issue of *Annals of Surgical Oncology*, Tsujimae et al.[15] reported the results of a comprehensive analysis of the molecular biological characteristics of PDAC concomitant with IPMN compared with those of conventional PDAC. This single-center retrospective study included 158 patients with surgically resected PDAC (21 patients with PDAC concomitant with IPMN and 137 patients with conventional PDAC). They evaluated four major gene alterations (KEAS, TP53, SMAD4, and CDKN2A) in the tumor, immune and fibrotic environments of the tumor, and prognosis using propensity score matching. They found that there was no difference between the two groups in terms of the types of genes altered and the total number of gene alterations before and after matching. There was no difference in the immune (CD4, CD8, and FOXP3 T-cell infiltration) and fibrotic status (collagen fiber area) of the tumor after matching between the two groups, and there were no significant differences in DFS and overall survival (OS) before and after matching between the two groups. The multivariable-adjusted Cox proportional hazards model showed that concurrent IPMN did not affect the prognosis. They concluded that PDAC concomitant with IPMN may be better treated as the same disease entity as conventional PDAC.

The results of this study may be expected according to the genetic de novo developmental pathway, which indicates independent development from concurrent IPMN.[12] However, this is the first report of a comprehensive analysis comparing PDAC concomitant with IPMN with conventional PDAC. Although this was a single-center retrospective study with a relatively small number of subjects, the study was well-designed and conducted and the patients were carefully selected. First, all patients underwent upfront surgery. Patients who received neoadjuvant therapy, which may affect the results, were excluded from the study. However, information regarding adjuvant therapy is lacking. Second, they excluded four patients with GNAS alteration because the mutation is a characteristic of PDAC derived from IPMN. Third, patients with mucinous carcinoma as well as anaplastic carcinoma, adenosquamous carcinoma, and acinar cell carcinoma were excluded from the study. None of the patients who had PDAC concomitant IPMN had a main ductal (MD)-IPMN. There were 19 patients with BR-IPMN and two patients with mixed-type IPMNs. Mucinous carcinoma is believed to have originated almost exclusively from MD-IPMN of the intestinal phenotype.[11] Before propensity matching, the proportion of patients with advanced cancer among those with conventional PDAC was significantly higher. This is in accordance with previous reports.[2,10,11] Conversely, there was no difference in DFS and OS between the two groups, likely because of the small number of subjects. After matching, there was no difference in prognosis between the two groups, therefore a large-scale validated study is required to clarify the prognosis of IPMN-related PDAC. Finally, characterization of the molecular pathways involved in PDAC and IPMN is needed for further improvement of clinical outcomes in patients with IPMN and PDAC.

DISCLOSURES Ippei Matsumoto declares no conflicts of interest.

REFERENCES

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74:2913–21.
2. Yamaguchi K, Kanemitsu S, Hatori T, et al. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. *Pancreas*. 2011;40:571–80.
3. Tanaka M, Yokohata K, Konomi H, Yamaguchi K, Chijiiwa K, Ohta M. Segmental balloon cytology for preoperative localization of in situ pancreatic cancer. *Gastrointest Endosc*. 1997;46:447–9.
4. Ingkakul T, Sadakari Y, Ienaga J, Satoh N, Takahata S, Tanaka M. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. *Ann Surg*. 2010;251:70–5.
5. Tanno S, Nakano Y, Koizumi K, et al. Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. *Pancreas*. 2010;39:36–40.
6. Maguchi H, Tanno S, Mizuno N, et al. Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. *Pancreas*. 2011;40:364–70.
7. Kamata K, Kitano M, Kudo M, et al. Value of EUS in early detection of pancreatic ductal adenocarcinomas in patients with intraductal papillary mucinous neoplasms. *Endoscopy*. 2014;46:22–9.
8. Tanaka M, Fernandez-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17:738–53.
9. Oyama H, Tada M, Takagi K, et al. Long-term risk of malignancy in branch-duct intraductal papillary mucinous neoplasms. *Gastroenterology*. 2020;158:226–37 e225.
10. Aronsson L, Bengtsson A, Toren W, Andersson R, Ansari D. Intraductal papillary mucinous carcinoma versus pancreatic

ductal adenocarcinoma: a systematic review and meta-analysis. *Int J Surg*. 2019;71:91–9.
11. Mas L, Lupinacci RM, Cros J, Bachet JB, Coulet F, Svrcek M. Intraductal papillary mucinous carcinoma versus conventional pancreatic ductal adenocarcinoma: a comprehensive review of clinical-pathological features, outcomes, and molecular insights. *Int J Mol Sci*. 2021;22(13):6756.
12. Omori Y, Ono Y, Tanino M, et al. Pathways of progression from intraductal papillary mucinous neoplasm to pancreatic ductal adenocarcinoma based on molecular features. *Gastroenterology*. 2019;156:647–61.e2.
13. Felsenstein M, Noe M, Masica DL, et al. IPMNs with co-occurring invasive cancers: neighbours but not always relatives. *Gut*. 2018;67:1652–62.
14. Kang MJ, Lee KB, Jang JY, et al. Disease spectrum of intraductal papillary mucinous neoplasm with an associated invasive carcinoma invasive IPMN versus pancreatic ductal adenocarcinoma-associated IPMN. *Pancreas*. 2013;42:1267–74.
15. Tsujimae M, Masuda A, Ikegawa T, et al. Comprehensive analysis of molecular biological characteristics of pancreatic ductal adenocarcinoma concomitant with intraductal papillary mucinous neoplasm. *Ann Surg Oncol* 2022. https://doi.org/10.1245/s10434-022-11704-z