COMMENTARY

Diagnostic Advancement of Early Pancreatic Cancer

Masataka Kikuyama*

Department of Gastroenterology, Tokyo Women's Medical University Hospital, 8-1, Kawada-cho, Shinjuku-ku, Tokyo, Japan

ABBREVIATIONS

FFPA: Focal Pancreatic Parenchymal Atrophy, MPD: Main Pancreatic Duct, PCIS: Pancreatic Carcinoma *in Situ* , PDAC: Pancreatic Ductal Adenocarcinoma, POPS: Peroral Pancreatic Duct Scope, SPACE: Serial Pancreatic-juice Aspiration Cytologic Examination

DESCRIPTION

Pancreatic Ductal Adenocarcinoma (PDAC) is associated with a poor prognosis; the five-year survival is <10% [1,2]. Various factors are associated with patient prognosis, including anatomical and biological features of the pancreas. Anatomical features of the pancreas include how close it is to the main vessels, allowing for their invasion and rendering the PDAC unresectable [3]. Biological features include pancreatic stellate cells that induce epithelial mesenchymal transition and invasion [4]; chemoresistance (<20% efficacy) [5]; and difficulty in early diagnosis, when the PDAC lesion is small [6]. The anatomical and biological features of the pancreas and its chemoresistance cannot be managed, though the difficulty of diagnosing early PDAC can be overcome *via* advances in technology and diagnostic methods.

Traditional diagnostic methods for PDAC include Ultrasonography (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI), which are adapted for patients at risk of PDAC or those with suspicious lesions. However, these methods are not enough to diagnose early PDAC, leading to a poor prognosis.

US is used to observe the abdominal organs, though observation of the whole pancreas is challenging [7], limiting the diagnosis of PDAC [8] especially at an early stage [9]. The pancreas is located in the retroperitoneal space and is far from the abdominal surface, especially in obese patients. Moreover, the pancreatic tail is located behind the stomach, and the air contained in the stomach obstructs ultrasound transmission [7]. CT provides clear images of abdominal organs and is the most common method to observe the pancreas, though PDAC <2 cm are difficult to diagnose *via* CT [10]. MRI is the preferred diagnostic method as it is noninvasive and able to depict cystic lesions; however, small, solid tumors are difficult to diagnose *via* MRI [11]. Diffusion-weighted MRI is expected to be an accurate diagnostic tool for PDAC; however, no studies regarding the detection of small PDAC using MRI have been reported [12].

Endoscopic Ultrasonography (EUS) is a novel examination method for PDAC [11-14]. US has a superior ability to reveal minute abnormalities in organs if the organ can be observed clearly. While abdominal US cannot effectively evaluate the pancreas, placing the US probe on an endoscopic tip overcomes this problem; the pancreas can be visualized through the gastrointestinal tract. EUS has a higher sensitivity for diagnosing PDAC than conventional diagnostic methods [11-15] and a superior negative predictive value [13]. Moreover, EUS can provide a histopathological examination of pancreatic lesions [16] *via* EUS-guided fine-needle aspiration. Therefore, EUS is useful for the evaluation of patients at risk for PDAC [15,17].

However, although EUS can be used to detect small PDAC, tumors <4 mm cannot be detected [9]. Moreover, PDAC of any size is invasive, originates from pancreatic ductal epithelium, and has the potential to metastasize. Lymph node metastasis have been reported in a patient with a PDAC lesion with a diameter of 4 mm [18]. Therefore, methods to diagnose PDAC at stage 0 (Pancreatic Carcinoma *in Situ* (PCIS)) must be developed to improve patient prognosis as PCIS does not metastasize.

However, PCIS cannot be directly observed using imaging. In contrast to intraepithelial pancreatic mucinous neoplasia, the intraductal epithelium of a normal Main Pancreatic Duct (MPD) has a diameter of 1-2 mm, rendering observation of the pancreatic duct epithelium using a peroral pancreatic duct scope (POPS) challenging [19]. In addition, the mucosal features of PCIS remain unknown. Therefore, the diagnosis of PCIS

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Correspondence Masataka Kikuyama

Department of Gastroenterology, Tokyo Women's Medical University Hospital, 8-1, Kawada-cho, Shinjuku-ku, Tokyo, Japan

E-mail kikuyama.masataka@twmu.ac.jp

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via the observation of the pancreatic mucosa is nearly impossible. The identification of indirect findings associated with PCIS is necessary. MPD stricture has been used as an indirect finding [9,20], though its sensitivity is low [20].

Focal Pancreatic Parenchymal Atrophy (FPPA) is a novel and specific finding of PCIS [21]. FPPA is a more sensitive marker of PDAC than MPD stricture [21]. FPPA presents as an irregularly shaped focal defect in the pancreatic parenchyma on CT or MRI. The shape is categorized as one of three types [21]: Cave-in type, a focal indentation of the pancreatic surface; slimness type, longitudinal but focal atrophy of the pancreatic parenchyma with a shaggy appearance; or slit type, a cuneiform defect of the pancreatic parenchyma. Histopathologically, FPPA is defined as the atrophy of the pancreatic parenchyma replaced by adipose tissue with fibrosis and chronic inflammatory cell infiltration [21] surrounded by pancreatic parenchyma without significant change. FPPA is observed around or adjacent to the pancreatic duct with an intraepithelial neoplastic change.

Single cytology of aspirated pancreatic juice during ERCP has a low sensitivity for PDAC (50%) [22]. Serial Pancreatic-juice Aspiration Cytologic Examination (SPACE) is a novel cytology method with a 100% sensitivity for PDAC [23,24]. SPACE allows for six times-cytology of pancreatic juice aspirated through a nasopancreatic tube [23]. Repeated pancreatic juice cytology contributes to the improved sensitivity [25]. In a previous study, SPACE was positive for PDAC in 46% of patients with FPPA [26]. In patients with FPPA accompanied with pancreatic cystic lesions, SPACE was positive for 51% of patients [27]. Large FPPA areas (>269.79 mm^2) are significantly related with positive results on SPACE [27]. Patients with positive cytology results often undergo surgical resection of the FPPA area, revealing PCIS in the resected specimen in 65%-84% of patients [26,27]. Moreover, Focal pancreatic parenchyma atrophy could be a harbinger of pancreatic cancer [28].

However, FPPA can occur in patients with any degree of pancreatic intraepithelial neoplasia [21]. Patients with FPPA who undergo surgery due to positive SPACE results do not always have histopathological HGP/CIS [26,27]. The mechanisms underlying FPPA remain unclear. Although Focal Pancreatic Parenchymal Atrophy (FPPA) is a novel finding of PCIS, there are many problems that should be resolved.

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CONFLICTS OF INTEREST

The author declares that there is no conflict of interest.

REFERENCES

1. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016; 22(44): 9694–9705. [PMID: 29631305]

2. Bengtsson A, Andersson R, Ansari D. The actual 5-Year survivors of pancreatic ductal adenocarcinoma based on real-world data. Sci Rep. 2020; 10(1): 16425. [PMID: 33009477]

3. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014; 155: 977-988. [PMID: 24856119]

4. Pothula SP, Pirola RC, Wilson JS, Jeremy SW, Minoti VA. Pancreatic stellate cells: aiding and abetting pancreatic cancer progression. Pancreatology. 2020; 20(3): 409e418. [PMID: 31928917]

5. Lee HS, Park SW. Systemic Chemotherapy in advanced pancreatic cancer. Gut Liver. 2016; 10(3): 340-347. [PMID: 27114434]

6. Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, et al. Japan pancreatic cancer registry; 30 Year Anniversary: Japan pancreas society. Pancreas. 2012; 41(7): 985-992. [PMID: 22750974]

7. Saunders HM. Ultrasonography of the pancreas. Probl Vet Med. 1991; 3(4): 583-603. [PMID: 1802271]

8. Liu L, Huang X, Li X, Ma L, Zhao X, Yang X. Ultrasound combined with computed tomography in pancreatic cancer. J BUON. 2019; 24(4): 1562-1567. [PMID: 31646809]

9. Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, et al. Multicenter study of early pancreatic cancer in Japan. Pancreatology. 2018; 18(1): 61-67. [PMID: 29170051]

10. Yoon SH, Lee JM, Cho JY, Lee KB, Kim JE, Moon SK, et al. Small (≤ 20 Mm) pancreatic adenocarcinoma: Analysis of enhancement patterns and secondary signs with multiphasic multidetector CT. Radiology. 2011; 259(2): 442-452. [PMID: 21406627]

11. Harinck F, Konings ICAW, Kluijt I, Poley JW, van Hooft JE, van Dullemen HM, et al. A multicenter comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. Gut. 2016; 65(9): 1505-1513. [PMID: 25986944]

12. Robertis RD, Martini PT, Demozzi E, Corso FD, Bassi C, Pederzoli P, et al. Diffusion weighted imaging of pancreatic cancer. World J Radiol. 2015;7(10): 319-328. [PMID: 26516428]

13. Helmstaedter L, Riemann JF. Pancreatic cancer EUS and early diagnosis. Langenbecks Arch. Surg. 2008; 393(6): 923-927. [PMID: 18247044]

14. Yasuda I, Iwashita T, Doi S, Nakashima M, Moriwaki H. Role of EUS in the early detection of small pancreatic cancer.

Dig Endosc. 2011; 23 (Suppl. 1): 22-25. [PMID: 21535195]

15. Kitano M, Yoshida T, Itonaga M, Tamura T, Hatamaru K, Yamashita Y. Impact of endoscopic ultrasonography on diagnosis of pancreatic cancer. J Gastroenterol. 2019; 54(1): 19-32. [PMID: 30406288]

16. Bhutani MS, Konduru P, Joshi V, Saxena P, Suzuki R, Irisawa A, Yamao K. The role of endoscopic ultrasound in pancreatic cancer screening. Endosc Ultrasound. 2016; 5(1): 8-16. [PMID: 26879161]

17. Kikuyama M, Kamisawa T, Kuruma S, Chiba K, Kawaguchi S, Terada S, et al. Early diagnosis to improve the poor prognosis of pancreatic cancer. Cancers. 2018; 10(2): 48. [PMID: 29439461]

18. Kawaguchi S, Kikuyama M, Satoh T, Terada S, Kanemoto H, Arai K. Minimally invasive ductal pancreatic carcinoma without low echoic area on endoscopic ultrasound examination: a case report. J Jan Pancreas Soc. 2017; 32(5): 852-858.

19. Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, et al. Initial experience of peroral pancreatoscopy combined with narrow-band imaging in the diagnosis of intraductal papillary mucinous neoplasms of the pancreas (with videos). Gastrointest Endosc. 2007; 66(4): 793-797. [PMID: 17905024]

20. Kalady MF, Peterson B, Baillie J, Onaitis MW, Abdul-Wahab OI, Howden JK, et al. Pancreatic duct strictures: identifying risk of malignancy. Ann Surg Oncol. 2004; 11(6): 581-588. [PMID: 15150064]

21. Nakahodo J, Kikuyama M, Nojiri S, Chiba K, Yoshimoto K, Kamisawa T, et al. Focal parenchymal atrophy of pancreas: an important sign of underlying high-grade pancreatic intraepithelial neoplasia without invasive carcinoma, i.e., carcinoma *in situ* . Pancreatology. 2020, 20, 1689-1697. [PMID: 33039293]

22. Kameya S, Kuno N, Kasugai. The diagnosis of pancreatic cancer by pancreatic juice cytology. Acta Cytol. 1981; 25(4): 354-360. [PMID: 6945001]

23. Iiboshi T, Hanada K, Fukuda T, Yonehara S, Sasaki T, Chayama K. Value of cytodiagnosis using endoscopic nasopancreatic drainage for early diagnosis of pancreatic cancer: establishing a new method for the early detection of pancreatic carcinoma *in situ*. Pancreas. 2012; 41(4): 523-529. [PMID: 22504379]

24. Satoh T, Kikuyama M, Kawaguchi S, Kanemoto H, Muro H, Hanada K. Acute pancreatitis-onset carcinoma in situ of the pancreas with focal fat replacement diagnosed using Serial Pancreatic-juice Aspiration Cytologic Examination (SPACE). Clin J Gastroenterol. 2017; 10(6): 541-545. [PMID: 28986726]

25. Kimura H, Furukawa Y, Yamasaki S, Kagawa K, Sakano A, Hananoki M, et al. A study of the usefulness of pancreatic juice cytology obtained *via* an Endoscopic Nasal Pancreatic Drainage (ENPD) tube.Nihon Shokakibyo Gakkai Zassi. 2011; 108(6): 928-36. [PMID: 2164670]

26. Kikuyama M, Nakahodo J, Honda G, Horiguchi S, Suzuki M, Chiba K, et al. Effectiveness of focal pancreatic parenchymal atrophy in diagnosing high-grade pancreatic intraepithelial neoplasia/carcinoma in situ. MRAJ. 2021;9(8): 1-16.

27. Kikuyama M, Nakahodo J, Honda G, Suzuki M, Horiguchi S, Chiba K, et al. Pancreatic duct epithelial malignancy suggested by large focal pancreatic parenchymal atrophy in cystic diseases of the pancreas. Pancreatology. 2023;23(4):420-428. [PMID: 37003856]

28. Nakahodo J, Kikuyama M, Fukumura Y, Horiguchi S, Chiba K, Tabata H, et al. Focal pancreatic parenchyma atrophy is a harbinger of pancreatic cancer and a clue to the intraductal spreading subtype. Pancreatology. 2022:22(8);1148-1158. [PMID: 36273992]

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