Commentary

19

Masao Tanaka

19.1 Commentary

Among the various types of cystic neoplasms of the pancreas, the management of solid pseudopapillary neoplasm (SPN) does not have any controversy. Mucinous cystic neoplasm (MCN) described in this chapter also poses little controversy to the clinician who happens to diagnose them by some imaging modalities. Most of the MCNs found incidentally are still benign and represent currently a very good indication for laparoscopic distal pancreatectomy or local resection (enucleation) when feasible. Serous cystic neoplasms (SCNs) also presented in this chapter do not need resection unless they are indistinguishable from other types of cystic neoplasm detailed in the chapter, such as intraductal papillary mucinous neoplasm (IPMN) or MCN, when SCN takes on a macrocystic or oligocystic appearance as opposed to its typical microcystic appearance.

In contrast to SPN, MCN, and SCN, IPMN of the pancreas, especially the branch duct type (BD-IPMN), excites a lot of controversies in regard to differentiation from other pancreatic cysts, diagnosis of malignancy, and need for and type of operative/non-operative management. BD-IPMNs must be differentiated from MCNs, macrocystic or oligocystic SCNs, epidermoid cysts, lymphoepithelial cysts, and cystic variants of other neoplasms. Even with complete understanding of the imaging characteristics of each entity (Tanaka et al. 2006), it is sometimes difficult to differentiate BD-IPMNs confidently from MCNs, macrocystic or oligocystic SCNs, and lymphoepithelial cysts preoperatively.

Because it is especially important to differentiate non-mucinous cysts from IPMNs and MCNs with malignant potential, endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) is receiving enthusiastic interest lately. A high level of carcinoembryonic antigen (CEA) in the cystic fluid is characteristic of mucinous cysts. Although the cut-off concentration that provides a confident diagnosis of mucinous epithelium varies from report to report (>367 (Lewandrowski et al. 1993), >800 (van der Waaij et al. 2005), ≥480 (Linder et al. 2006), >800 (Attasaranya et al. 2007), and >192 ng/ml (Brugge et al. 2004)), an increased value of even >5 ng/ml is highly suggestive of a mucinous neoplasm. Although the CEA levels are not necessarily consistent with levels of other molecular markers, including a glycan variant of MUC-5AC (Haab et al. 2010), mucin-like carcinoma-associated antigen (Khalid et al. 2009), *KRAS* mutations (Bernard et al. 2002) and CA72-4 (Jang et al. 2005), the diagnostic sensitivity was reported to improve when combined (Haab et al. 2010; Sawhney et al. 2009).

The diagnosis of malignant transformation of BD-IPMN remains controversial at present.

M. Tanaka
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
e-mail: masaotan@med.kyushu-u.ac.jp

R. Mantke et al. (eds.), *International Practices in Pancreatic Surgery*,
DOI 10.1007/978-3-540-74506-8_19,

The original Sendai guidelines recommend resection of BD-IPMN with one or more of five criteria for suspected malignancy, i.e., positive pancreatic juice cytology, the presence of mural nodules, cyst size >3 cm, dilation of the main pancreatic duct, and abdominal pain (Tanaka et al. 2006). Nevertheless, 80–85 % of all BD-IPMNs resected according to these guidelines are benign. Therefore, we need to identify other diagnostic aids that would avoid or at least minimize a "false positive" resection. Based on the understanding of histologic subtypes, i.e., gastric, intestinal, pancreatobiliary, and oncocytic, and the recent observation that the intestinal subtype is more likely to de-differentiate into malignancy, selection of the intestinal subtype may be helpful to distinguish BD-IPMNs with a greater tendency for malignant transformation. A few such attempts have been reported by immunohistochemical or molecular analysis of cells contained in the pancreatic juice (Hibi et al. 2007; Nakata et al. 2009).

On the contrary, the authors of this chapter have suggested that even small BD-IPMNs ≤3 cm without malignant stigmata ("Sendai-negative") have a relatively high risk of malignancy. Among their 69 patients with "Sendai-negative" BD-IPMNs, 25 % had in situ or invasive carcinoma. Lee et al. (2008) claimed that one of 30 BD-IPMNs resected with no Sendai criteria had carcinoma in situ; however, the absence of mural nodules was judged by CT, MR, or EUS in both of these studies. It is well accepted that EUS is the most sensitive modality to evaluate the presence or absence of a mural nodule and not CT or MR. In a collective series of 349 patients who underwent EUS initially to prove the absence of mural nodule, there were 7 patients who underwent resection without any of the Sendai criteria during a median follow-up of 3.5 years, and none of them had carcinoma (Maguchi et al. 2011). There have been four series describing clearly the relationship of malignancy to the size and the presence/absence of mural nodules. In 124 BD-IPMNs <3 cm without mural nodules, there was no single case of malignancy (Tanaka 2011).

If expertise in EUS-FNA and cytologic interpretation of "high grade atypia" in the cyst fluid are available, the cytologic analysis of the cyst fluid obtained by EUS-FNA might add diagnostic value, although the sensitivity is often limited by scant cellularity of the aspirate and contamination by gastrointestinal mucosal cells (van der Waaij et al. 2005; Pitman and Deshpande 2007; Pitman et al. 2010; Frossard et al. 2003; Belsley et al. 2008; Recine et al. 2004; Michaels et al. 2006; Layfield and Cramer 2005; Emerson et al. 2006; Maire et al. 2003, 2008). Cells with "high-grade atypia" in mucinous cyst fluid obtained by EUS-FNA indicated the presence of malignancy with a sensitivity of 72 % and an accuracy of 80 % (Pitman et al. 2010). The same group claimed that "high-grade atypia" was the most sensitive predictor of malignancy even in small (≤30 mm) BD-IPMNs (67 %), compared to mural nodules and a dilated main pancreatic duct which were highly specific (>90 %) but insensitive (39–44 %) (Genevay et al. 2011).

Follow-up surveillance of BD-IPMNs without malignant signs is an especially challenging problem in the management of IPMNs. EUS seems to be the best modality but has the drawbacks of increased cost, invasiveness, and intraobserver and interobserver variability. In reality, we cannot subject all patients to routine surveillance by EUS. How and how often to detect malignant changes of BD-IPMNs and to survey the development of distinct ductal adenocarcinoma remain very important controversies. Since we reported the occurrence of in situ or invasive ductal carcinoma concomitant with a benign BD-IPMN (Tanaka et al. 1997; Yamaguchi et al. 1997, 2002), this phenomenon has attracted increasing attention. Several reports have suggested that 3–9 % of patients with BD-IPMNs had or developed pancreatic ductal carcinoma distinct from IPMN-related invasive cancer (Tanaka 2011). During a median follow-up of 87 months, in 60 patients with BD-IPMNs, even when <1 cm in size, developed 5 ductal carcinomas (8 %) (Uehara et al. 2008). Worsening diabetes and high or increasing levels of serum CA19-9 predicted the presence of ductal carcinoma (Ingkakul et al. 2010; Kanno et al. 2010). Also, older age, smaller size of BD-IPMN, and smaller caliber of the main pancreatic duct were reported to be associated with the development of ductal

carcinoma compared with the patients who did not develop ductal carcinoma (Tanno et al. 2010). The appropriate method and interval of surveillance of BD-IPMNs remain to be further investigated.

References

Attasaranya S, Pais S, LeBlanc J, McHenry L, Sherman S, DeWitt JM (2007) Endoscopic ultrasound-guided fine needle aspiration and cyst fluid analysis for pancreatic cysts. JOP 8:553–563

Belsley NA, Pitman MB, Lauwers GY, Brugge WR, Deshpande V (2008) Serous cystadenoma of the pancreas: limitations and pitfalls of endoscopic ultrasound-guided fine-needle aspiratio biopsy. Cancer 114:102–110

Bernard P, Scoazec JY, Joubert M, Kahn X, Le Borgne J, Berger F, Partensky C (2002) Intraductal papillary-mucinous tumors of the pancreas: predictive criteria of malignancy according to pathological examination of 53 cases. Arch Surg 137:1274–1278

Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL (2004) Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology 126:1330–1336

Emerson RE, Randolph ML, Cramer HM (2006) Endoscopic ultrasound-guided fine-needle aspiration cytology diagnosis of intraductal papillary mucinous neoplasm of the pancreas is highly predictive of pancreatic neoplasia. Diagn Cytopathol 34:457–462

Frossard JL, Amouyal P, Amouyal G, Palazzo L, Amaris J, Soldan M, Giostra E, Spahr L, Hadengue A, Fabre M (2003) Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. Am J Gastroenterol 98:1516–1524

Genevay M, Mino-Kenudson M, Yaeger K, Konstantinidis IT, Ferrone CR, Thayer S, Fernandez-del Castillo C, Sahani D, Bounds B, Forcione D, Brugge WR, Pitman MB (2011) Cytology adds value to imaging studies for risk assessment of malignancy in pancreatic mucinous cysts. Ann Surg 254(6):977–983

Haab BB, Porter A, Yue T, Li L, Scheiman J, Anderson MA, Barnes D, Schmidt CM, Feng Z, Simeone DM (2010) Glycosylation variants of mucins and CEACAMs as candidate biomarkers for the diagnosis of pancreatic cystic neoplasms. Ann Surg 251:937–945

Hibi Y, Fukushima N, Tsuchida A, Sofuni A, Itoi T, Moriyasu F, Mukai K, Aoki T (2007) Pancreatic juice cytology and subclassification of intraductal papillary mucinous neoplasms of the pancreas. Pancreas 34:197–204

Ingkakul T, Sadakari Y, Ienaga J, Satoh N, Takahata S, Tanaka M (2010) Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. Ann Surg 251:70–75

Jang JY, Kim SW, Ahn YJ, Yoon YS, Choi MG, Lee KU, Han JK, Kim WH, Lee YJ, Kim SC, Han DJ, Kim YI, Choi SH, Cho BH, Yu HC, Yoon DS, Lee WJ, Lee KB, Kim YC, Lee KS, Kim MW, Kim HJ, Kim HJ, Park YH (2005) Multicenter analysis of clinicopathologic features of intraductal papillary mucinous tumor of the pancreas: is it possible to predict the malignancy before surgery? Ann Surg Oncol 12:124–132

Kanno A, Satoh K, Hirota M, Hamada S, Umino J, Itoh H, Masamune A, Asakura T, Shimosegawa T (2010) Prediction of invasive carcinoma in branch type intraductal papillary mucinous neoplasms of the pancreas. J Gastroenterol 45:952–959

Khalid A, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM (2009) Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc 69:1095–1102

Layfield LJ, Cramer H (2005) Fine-needle aspiration cytology of intraductal papillary-mucinous tumors: a retrospective analysis. Diagn Cytopathol 32:16–20

Lee CJ, Scheiman J, Anderson MA, Hines OJ, Reber HA, Farrell J, Kochman ML, Foley PJ, Drebin J, Oh YS, Ginsberg G, Ahmad N, Merchant NB, Isbell J, Parikh AA, Stokes JB, Bauer T, Adams RB, Simeone DM (2008) Risk of malignancy in resected cystic tumors of the pancreas < or =3 cm in size: is it safe to observe asymptomatic patients? A multi-institutional report. J Gastrointest Surg 12:234–242

Lewandrowski KB, Southern JF, Pins MR, Compton CC, Warshaw AL (1993) Cyst fluid analysis in the differential diagnosis of pancreatic cysts. A comparison of pseudocysts, serous cystadenomas, mucinous cystic neoplasms, and mucinous cystadenocarcinoma. Ann Surg 217:41–47

Linder JD, Geenen JE, Catalano MF (2006) Cyst fluid analysis obtained by EUS-guided FNA in the evaluation of discrete cystic neoplasms of the pancreas: a prospective single-center experience. Gastrointest Endosc 64:697–702

Maguchi H, Tanno S, Mizuno N, Hanada K, Kobayashi G, Hatori T, Sadakari Y, Yamaguchi T, Tobita K, Doi R, Yanagisawa A, Tanaka M (2011) Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. Pancreas 40:364–370

Maire F, Couvelard A, Hammel P, Ponsot P, Palazzo L, Aubert A, Degott C, Dancour A, Felce-Dachez M, O'toole D, Lévy P, Ruszniewski P (2003) Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. Gastrointest Endosc 58:701–706

Maire F, Voitot H, Aubert A, Palazzo L, O'Toole D, Couvelard A, Levy P, Vidaud M, Sauvanet A, Ruszniewski P, Hammel P (2008) Intraductal papillary mucinous neoplasms of the pancreas: performance of pancreatic fluid analysis for positive diagnosis and the prediction of malignancy. Am J Gastroenterol 103:2871–2877

Michaels PJ, Brachtel EF, Bounds BC, Brugge WR, Pitman MB (2006) Intraductal papillary mucinous neoplasm of the pancreas: cytologic features predict histologic grade. Cancer 108:163–173

Nakata K, Nagai E, Ohuchida K, Aishima S, Hayashi A, Miyasaka Y, Yu J, Mizumoto K, Tanaka M, Tsuneyoshi M (2009) REG4 is associated with carcinogenesis in the 'intestinal' pathway of intraductal papillary mucinous neoplasms. Mod Pathol 22:460–468

Pitman MB, Deshpande V (2007) Endoscopic ultrasound-guided fine needle aspiration cytology of the pancreas: a morphological and multimodal approach to the diagnosis of solid and cystic mass lesions. Cytopathology 18:331–347

Pitman MB, Genevay M, Yaeger K, Chebib I, Turner BG, Mino-Kenudson M, Brugge WR (2010) High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol 118:434–440

Recine M, Kaw M, Evans DB, Krishnamurthy S (2004) Fine-needle aspiration cytology of mucinous tumors of the pancreas. Cancer 102:92–99

Sawhney MS, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, Brown A, Chuttani R, Pleskow DK (2009) Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. Gastrointest Endosc 69:1106–1110

Tanaka M (2011) Controversies in the management of pancreatic IPMN. Nat Rev Gastroenterol Hepatol 8:56–60

Tanaka M, Yokohata K, Konomi H, Yamaguchi K, Chijiiwa K, Ohta M (1997) Segmental balloon cytology for preoperative localization of in situ pancreatic cancer. Gastrointest Endosc 46:447–449

Tanaka M, Chari S, Adsay V, Castillo CF, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S (2006) International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 6:17–32

Tanno S, Nakano Y, Sugiyama Y, Nakamura K, Sasajima J, Koizumi K, Yamazaki M, Nishikawa T, Mizukami Y, Yanagawa N, Fujii T, Obara T, Okumura T, Kohgo Y (2010) Incidence of synchronous and metachronous pancreatic carcinoma in 168 patients with branch duct intraductal papillary mucinous neoplasm. Pancreatology 10:173–178

Uehara H, Nakaizumi A, Ishikawa O, Iishi H, Tatsumi K, Takakura R, Ishida T, Takano Y, Tanaka S, Takenaka A (2008) Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. Gut 57:1561–1565

van der Waaij LA, van Dullemen HM, Porte RJ (2005) Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc 62:383–394

Yamaguchi K, Nakamura K, Yokohata K, Shimizu S, Chijiiwa K, Tanaka M (1997) Pancreatic cyst as a sentinel of in situ carcinoma of the pancreas. Report of two cases. Int J Pancreatol 22:227–231

Yamaguchi K, Ohuchida J, Ohtsuka T, Nakao K, Tanaka M (2002) Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. Pancreatology 2:484–490