Pancreatology xxx (2015) 1–7

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

# Imaging morphological changes of intraductal papillary mucinous neoplasm of the pancreas was associated with its malignant transformation but not with development of pancreatic ductal adenocarcinoma

Natsuko Kawada [a, c, *], Hiroyuki Uehara [b], Shigenori Nagata [a], Mutsumi Tsuchishima [c], Mikihiro Tsutsumi [c], Yasuhiko Tomita [a]

[a] Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan
[b] Department of Gastroenterology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan
[c] Department of Hepatopancreatobiliary Medicine, Kanazawa Medical University Japan

ARTICLE INFO

*Article history:*
Available online xxx

*Keywords:*
Morphological changes
IPMN
Concomitant PDAC
Methods of follow-up
Fukuoka guidelines

ABSTRACT

*Background/objective:* A considerable number of branch duct intraductal papillary mucinous neoplasm (BD-IPMN) developed not infrequently pancreatic malignancy, either as part of IPMN (malignant IPMN) or as concomitant pancreatic ductal adenocarcinoma (PDAC). To date, imaging morphological changes predicting occurrence of malignancy in BD-IPMN are not well-investigated. This study aimed to evaluate the relationships between occurrence of malignancy in BD-IPMN and imaging morphological changes of the tumors observed during follow-up.

*Methods:* 515 BD-IPMN patients with mural nodule <10 mm and negative cytology were included. 19 patients developed malignant IPMN and 8 patients developed concomitant PDAC during mean follow-up of 4.7 years. The following imaging morphological features were assessed: cyst/main pancreatic duct (MPD) diameter, occurrence of additional cyst/mural nodule.

*Results:* Growth rate of cyst/MPD diameter were significantly larger in patients who developed malignant IPMN compared to those in patients whose IPMN remained benign ($p = 0.013$, $p = 0.01$). Occurrence of additional cyst/mural nodule were more frequently observed in patients who developed malignant IPMN ($p = 0.009$, $p = 0.04$). In contrast, none of the factors associated with imaging morphological changes of IPMN were shown to be significantly different between patients who developed concomitant PDAC and patients whose IPMN remained benign. Growth rate of MPD diameter and occurrence of additional cyst were independent factors associated with development of malignant IPMN (odds ratio 21.5, and 5.62, respectively).

*Conclusions:* Imaging morphological changes of IPMN, such as growth rate of MPD diameter and occurrence of additional cyst, could be indicators for development of malignant IPMN, but not for development of concomitant PDAC.



## Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a unique clinical entity of pancreatic neoplasms characterized by intraductal proliferation of mucin-producing epithelial cells resulting in cystic dilation of pancreatic duct [1]. Since 1982 when first reported by Ohashi et al. to our knowledge [2], characteristics of IPMN have been gradually elucidated. IPMN are classified into three types, main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), or

* Corresponding author. Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari, Osaka 537-8511, Japan. Tel.: +81 6 6972 1181; fax: +81 6 6981 4059.
*E-mail address:* natz.kawada@gmail.com (N. Kawada).

http://dx.doi.org/10.1016/j.pan.2015.08.004

mixed type according to the location of the tumor [3,4]. Microscopically, IPMN are classified into four categories based on increasing nuclear and architectural atypia and invasive features: low-grade dysplasia, intermediate-grade dysplasia, high-grade dysplasia, or invasive carcinoma [5]. The latter two, considered to be malignant, are treated by surgical resection, whereas the former two are managed conservatively as long as they remain benign.

International consensus guidelines for the management of IPMN and mucinous cystic neoplasm of the pancreas were established in 2006 (the Sendai guidelines) [3]. According to the Sendai guidelines, surgery was recommended for all MD-IPMN and for selected cases of BD-IPMN (i) symptomatic, ii) cyst diameter ≥30 mm, iii) dilated main pancreatic duct (MPD) ≥6 mm, iv) presence of mural nodule, v) positive cytology). However, a considerable number of benign IPMN were resected, therefore, the Sendai guidelines were revised in 2012 to the Fukuoka guidelines. Accordingly, surgical resections were restricted for BD-IPMN and observation was allowed for the selected cases of MD-IPMN [4]. As a consequence, more IPMN are followed up without immediate resection.

Follow-up methods recommended by the Fukuoka guidelines in patients without “high risk stigmata” are short interval imaging examinations at baseline to establish the stability of IPMN, followed by annual history/physical as well as imaging examinations and serologic marker surveillance. Shorter interval surveillance (3–9 months) should be considered in patients whose IPMN progresses toward “high risk stigmata”. Thus, the surveillance strategies proposed by the Fukuoka guidelines seem to be focusing on imaging morphological changes of IPMN including changes of cyst diameter and occurrence of mural nodule. However, there are few studies assessing imaging morphological changes of IPMN as indicator for development of pancreatic malignancy during the follow-up of IPMN [6,7].

The aim of this study was to evaluate if imaging morphological changes of IPMN could be indicators for development of pancreatic malignancy in BD-IPMN. For this purpose, the relationships between occurrence of malignancy in BD-IPMN and imaging morphological changes of the tumors were investigated.

## Methods

### *Patients*

Consecutive patients who were diagnosed with BD-IPMN by endoscopic retrograde pancreatography (ERP) and pancreatic juice cytology at Osaka Medical Center for Cancer and Cardiovascular Diseases were selected. IPMN were diagnosed when the following typical features were observed: dilated orifice of duodenal papilla, secretion of mucus during duodenoscopy, or filling defect in the MPD during ERP indicating the presence of mucus. Classification of IPMNs as BD-IPMN or MD-IPMN was determined according to the location of main tumor as evaluated by imaging examinations. Patients who were diagnosed as MD-IPMN were excluded from this study.

This study protocol was approved by the institutional review board of Osaka Medical Center for Cancer and Cardiovascular Diseases.

### *Evaluation of imaging morphological features*

The following imaging morphological features were evaluated: number of cysts, cyst and MPD diameter, and presence of mural nodule at the initial and the last examinations. The cyst and MDP diameters were recorded from medical reports. All imaging data were reviewed, and cyst and/or MPD diameter were re-measured whenever required.

A cyst was defined as a dilated branch duct of >5 mm in size with communication to the MPD. Cyst and MPD diameters were measured in contrast enhanced multidetector CT. A mural nodule was defined as solid component within cyst or in the MPD identified by trans-abdominal ultrasound (US) or endoscopic ultrasound (EUS). When required, contrast enhanced US was performed to discriminate the mural nodule from mucus. A mural nodule was considered to be present when the nodule size was >3 mm by EUS or US. Patients whose IPMN harbored mural nodule at the initial examinations were excluded.

### *Methods of follow-up*

The patients having BD-IPMN with mural nodule of <10 mm and negative cytology were managed conservatively with close follow-up by imaging examinations (US, EUS, CT, or magnetic resonance imaging/cholangiopancreatography (MRI/MRCP)) and by serological examinations (carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen) at 3–6 months interval. If any suggestive signs of development of pancreatic malignancy (increasing cyst and/or MPD diameter, occurrence of mural nodule or elevated serum tumor marker) were detected during follow-up, patients subsequently underwent further examinations (ERP and pancreatic juice cytology). When the nodule size ≥10 mm and/or positive cytology were confirmed, the IPMN was considered as malignant and surgery was recommended. Non-resected IPMN was considered as benign only when IPMN did not show obvious malignant signs consisting of occurrence of a solid tumor in the pancreas and/or elevated serum tumor marker during entire follow-up period, after negative cytology. Patients whose follow-up period was less than 1 year were excluded.

Patients who developed pancreatic malignancy (malignant IPMN or concomitant PDAC) during follow-up were defined as cases, and age-sex-matched patients whose IPMN remained benign during follow-up were defined as controls.

### *Evaluation of imaging morphological changes of IPMN during follow-up*

The frequency of occurrence of newly developed cyst after the initial examinations, which was defined as additional cyst in this study, and the frequency of occurrence of mural nodule were evaluated. The increase in cyst and MPD diameter observed during follow-up was calculated by the following formula: (diameter at the last examinations, mm) − (diameter at the initial examinations, mm). The growth rate of cyst and MPD diameter was calculated by following formula: (increase in diameter, mm)/(follow-up period, years).

Imaging morphological changes (occurrence of additional cyst/mural nodule and/or increase in cyst/MPD diameter) were considered as present in patients who developed pancreatic malignancy when several factors associated with morphological changes were shown to be greater compared to those in the control group.

From the factors which were shown to be significantly different between patients who developed pancreatic malignancy and patients whose IPMN remained benign, the independent factors associated with the development of pancreatic malignancy were further analyzed by logistic regression analysis.

### *Differentiation between malignant IPMN and concomitant pancreatic ductal adenocarcinoma (PDAC)*

Differentiation between malignant IPMN and concomitant PDAC was made by determining the topological relationship, and the



Please cite this article in press as: Kawada N, et al., Imaging morphological changes of intraductal papillary mucinous neoplasm of the pancreas was associated with its malignant transformation but not with development of pancreatic ductal adenocarcinoma, Pancreatology (2015), http://dx.doi.org/10.1016/j.pan.2015.08.004