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Original article

Predictors of malignancy in pure branch duct type intraductal papillary mucinous neoplasm of the pancreas: A nationwide multicenter study

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ABSTRACT

Background/Objectives: Prediction of malignancy in patients with BD-IPMNs is critical for the management. The aim of this study was to elucidate predictors of malignancy in patients with 'pure' BD-IPMNs who had a main pancreatic duct (MPD) diameter of ≤5 mm according to the most recent international consensus criteria and in whom MPD involvement was excluded on postoperative histology.
Methods: We identified 177 patients with 'pure' BD-IPMNs based on preoperative imaging and postoperative histology from 15 tertiary referral centers in Korea. BD-IPMNs with low-grade ($n = 72$) and moderate-grade ($n = 66$) dysplasia were grouped as benign and BD-IPMNs with high-grade dysplasia ($n = 10$) and invasive carcinoma ($n = 29$) were grouped as malignancy.
Results: On univariate analysis, particular symptoms (jaundice and clinical pancreatitis), CT findings (cyst size > 3 cm, the presence of enhancing mural nodules) and EUS features (the presence of mural nodules, the mural nodule size > 5 mm) were significant risk factors predicting malignant BD-IPMNs. Multivariate analysis revealed that the cyst size > 3 cm (odds ratio = 9.9), the presence of enhancing mural nodules on CT (odds ratio = 19.3) and the mural nodule size > 5 mm on EUS (odds ratio = 14.9) were the independent risk factors for the presence of malignancy in BD-IPMNs ($p < 0.001$).

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Conclusions: The cyst size > 3 cm, the presence of enhancing mural nodules on CT, the mural nodule size > 5 mm on EUS are three independent predictors of malignancy in patients with 'pure' BD-IPMNs.
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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas can be classified as main duct (MD) type, branch duct (BD) type and mixed or combined type based on the tumor location in the pancreatic ducts [1]. BD-IPMNs have less frequency of malignancy and lower risk for the progression toward malignancy, compared with MD—or mixed type IPMNs [2]. Incidentally found BD-IPMNs continue to increase and not infrequently encountered in a routine practice, probably because of wider use of high-resolution abdominal imaging and increased awareness of the disease. Furthermore, IPMNs typically occur in the elderly and frequently are located in the head of the pancreas [2]. In select patients with BD-IPMNs, therefore, the operative risk may overweigh the risk of malignancy. Thus, it is clinically important to elucidate predictors of malignancy in patients with BD-IPMNs.

The first international consensus guidelines (ICG) for the management of IPMNs were reported in 2006 [3]. Retrospective validation of this old guidelines showed that the 2006 ICG had good sensitivity but poor specificity in differentiating benign from malignant IPMNs [4,5]. Accordingly, more specific guidelines to assess the presence of malignant transformation were needed and ICG were revised in 2012 [1]. The 2012 ICG adopted the low threshold for main pancreatic duct (MPD) dilation in the type definition to increase the sensitivity for radiologic diagnosis of main duct type [6]. The cutoff value of MPD diameter for differentiating between MD- and BD type was lowered to 5 mm, from 10 mm of the 2006 ICG. Many previous studies on patients with 'presumed' BD-IPMNs based on radiologic imaging, which used the old definition of BD-IPMNs, inevitably include patients with mixed type IPMNs [7—11]. Risk factors for predicting malignant transformation in 'pure' BD-IPMNs without MPD involvement may be different from MD—or mixed type IPMNs [12].

The purpose of this nationwide multicenter study was to elucidate the risk factors for the presence of malignancy in patients with 'pure' BD-IPMNs that had an MPD diameter (≤5 mm) meeting a diagnostic criterion of BD type in 2012 ICG and in whom MPD involvement was excluded on postoperative histology.

Methods

Patient population

Between 2004 and 2012 from 15 tertiary referral centers in Korea, researchers identified 249 patients with presumed BD-IPMNs on radiology reports, who underwent pancreatic resection for suspicious malignant transformation or having high-risk for the progression toward malignancy (Fig. 1). Of these patients, 62 patients who had dilated MPD (>5 mm) were excluded. In addition, 10 patients were excluded due to MPD involvement on surgical pathology reports. Finally, 177 patients were regarded as having 'pure' BD-IPMNs and included in the final analysis. The study protocol was approved by the institutional review boards of each center.

Routine preoperative examinations included the clinical evaluation, routine blood tests and contrast-enhanced abdominal CT. The enhancing mural nodules on CT image were defined as an enhancing protrusion along the cyst wall on any phase of a dynamic study. MPD diameter and cyst size were recorded as the maximum dimension measured on cross-sectional imaging of preoperative abdominal CT. Mural nodule size in cysts was determined by EUS. Age, sex, symptoms, biochemical laboratory data and all available preoperative imaging results were analyzed to enable the identification of risk factors predicting malignancy. Symptoms included pancreatitis attributed to BD-IPMNs and obstructive jaundice in the presence of a cyst at the head of the pancreas.

Histopathological grades of resected specimens were assessed according to the WHO classification system of 2010 and classified into low-grade, moderate-grade, and high-grade dysplasia and IPMNs associated with invasive carcinoma [13]. For the analysis, BD-IPMNs with low-grade or moderate-grade dysplasia were grouped as benign and BD-IPMNs with high-grade dysplasia and invasive carcinoma were grouped as malignant. This classification was based on the assumption that BD-IPMNs with high-grade dysplasia or invasive carcinoma should be surgically resected, as recommended by ICG and other investigators [1,3].

Statistical analyses

Statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are expressed as medians and ranges and were compared using the Mann-Whiney *U* test. Categorical variables were compared using the chi-square and the Fisher's exact probability tests. Multivariate logistic regression models were used to estimate the effects of possible predictive factors on BD-IPMNs malignancy. The inclusion of variables in the models was based on existing knowledge of risk factors for malignant BD-IPMNs and mural nodule characteristics that were readily discernible on abdominal CT and EUS. The optimal cutoff points for the predictive factors for discriminating between malignant and benign BD-IPMNs were sought using receiver operating characteristic (ROC) curves that were generated by calculating the sensitivities and specificities at several predetermined cutoff points. The area under the ROC curve (AUC) expressed how well the factor is able to discriminate between patients with malignant IPMNs and those with benign IPMNs. Higher values indicate better discrimination: a value of 0.5 indicates no predictive discrimination, whereas a value of 1.0 indicates perfect separation of patients [14]. The level of significance was set at $p < 0.05$.

Results

Patient characteristics and histopathological findings

A total of 177 patients meeting the BD-IPMNs criterion were enrolled at the participating centers. Demographics and clinical features of these subjects are detailed in Table 1. Of the 177 patients in the current study, 108 were males and 69 were females with a median age of 63 years (range 30—87 years). As an initial presentation, 113 patients (63.8%) were asymptomatic. Acute pancreatitis and jaundice were more common in malignant group.

For histologic classifications, 72 (40.7%) patients had low-grade dysplasia, 66 (37.3%) had moderate-grade dysplasia, 10 (5.6%) had

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