Comparing 3 guidelines on the management of surgically removed pancreatic cysts with regard to pathological outcome CME

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Background and Aims: Currently, 3 guidelines are available for the management of pancreatic cysts. These guidelines vary in their indication for resection of high-risk cysts. We retrospectively compared the final pathologic outcome of surgically removed pancreatic cysts with the indications for resection according to 3 different guidelines.

Methods: Patients who underwent pancreatic resection were extracted from our prospective pancreatic cyst database (2006-present). The final histopathologic diagnosis was compared with the initial indication for surgery stated by the guidelines of the International Association of Pancreatology (IAP), European Study Group on Cystic tumors of the Pancreas and American Gastroenterological Association (AGA). We considered surgery in retrospect justified for malignancy, high-grade dysplasia, solid pseudopapillary neoplasms, neuroendocrine tumors or symptom improvement. Furthermore, we evaluated the patients with suspected intraductal papillary mucinous neoplasm (IPMN) separately.

Results: Overall, 115 patients underwent pancreatic resection. The preoperative diagnosis was correct in 83 of 115 patients (72%) and differentiation between benign and premalignant in 99 of 115 patients (86%). In retrospect, surgery was justified according to the aforementioned criteria in 52 of 115 patients (45%). For patients with suspected IPMN (n = 75) resection was justified in 36 of 67 (54%), 36 of 68 (53%), and 32 of 54 (59%) of patients who would have had surgery based on the IAP, European, or AGA guidelines, respectively. The AGA guideline would have avoided resection in 21 of 75 (28%) patients, versus 8 of 75 (11%) and 7 of 75 (9%) when the IAP or European guideline would have been applied strictly. Nevertheless, 4 of 33 patients (12%) with high-grade dysplasia or malignancy would have been missed with the AGA guidelines, compared with none with the IAP or European guidelines.

Conclusion: Although fewer patients undergo unnecessary surgery based on the AGA guidelines, the risk of missing malignancy or high-grade dysplasia with this guideline seems considerably high. (Gastrointest Endosc 2017;85:1025-31.)

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Pancreatic cysts are common, as they are found in 2.4% to 19.6% of the general population.[1-4] Although most patients with suspected premalignant cysts undergo surveillance, 3 current guidelines provide indications for surgical resection based on symptoms or the (perceived) risk of malignancy.[5-7]

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According to the guidelines of the International Association of Pancreatology (IAP),[6] the European Study Group on Cystic tumors of the Pancreas[5] and the American Gastroenterological Association (AGA)[7] resection is indicated in patients with a mucinous cystic neoplasm (MCN) or solid pseudopapillary neoplasms (SPN). In patients with intraductal papillary mucinous neoplasm (IPMN) the guidelines vary in their advice (Table 1). Most guidelines advise resection in case of involvement of the main pancreatic duct (ie, main duct [MD]- or mixed type [MT]-IPMN).[5-8] However, the AGA guideline does not recommend resection for main duct dilatation alone, but requires presence of a nodule or malignant cytology as well. Resection of side branch (SB)-IPMNs is only indicated

when a patient is symptomatic or when there are (combinations of) signs of malignant progression, such as jaundice, an enhancing nodule, or suggestive cytology.

The primary goal of the management of patients with premalignant pancreatic cysts is alleviation of symptoms and preventing malignancy, while avoiding unnecessary surgery. The natural history of pancreatic cysts is, however, not completely clear, but it is known from other types of tissues that dysplasia does not always progress to malignancy.[9,10] Nevertheless, surgical resection of pancreatic cysts with high-grade dysplasia is generally accepted.[11] Currently, it is unclear whether the accuracy of the guidelines of the IAP, the European Study Group, and the AGA is comparable for predicting high-grade dysplasia or malignancy. Therefore, the aim of this study was to compare the final pathologic outcome of surgically removed pancreatic cysts with an indication for resection according to the 3 different guidelines.

METHODS

Patients

Since November 2006, all patients presenting at our tertiary care center with a potential neoplastic pancreatic cyst were registered in a prospective database. We retrospectively analyzed all patients who underwent surgery because of their cysts up to September 2015. The decision for surgical treatment was made in our multidisciplinary hepato-pancreato-biliary team meetings, in the vast majority according to the IAP guidelines of 2006 and 2012.[6,12] The diagnosis was made based on the combination of findings on magnetic resonance imaging (MRI), CT, or EUS with or without cyst fluid analysis, depending on the investigations that were performed. Resection was considered for suspected pancreatic malignancy (pancreatic ductal adenocarcinoma or malignant pancreatic cyst), MCN, SPN, cystic neuroendocrine tumors (NET), and pancreatic cysts causing symptoms (eg, SB-IPMN with recurrent pancreatitis or serous cystic neoplasm [SCN] causing abdominal pain or gastric outlet obstruction). When IPMN was suggested, patients were referred for surgery if a patient had at least one high-risk stigmata: an (enhancing) nodule, pancreatic duct (PD) dilatation of 10 mm or more, jaundice or cytology suspicious of malignancy. Relative indications for surgery in patients with an IPMN were presence of one or more worrisome features: PD dilation between 5 and 9 mm, cyst size $\geq$ 3 cm, cyst growing in size, thickened or enhancing cyst walls or abrupt caliber change of the PD with distal pancreatic atrophy. Before 2006, cyst size $\geq$ 3 cm and PD dilatation $>$ 6 mm were absolute indications for surgery; after 2006, these were relative indications.[12] Our medical ethical committee agreed on this retrospective analysis of prospectively collected observational data.

Outcomes

Data on patient demographics, symptoms, imaging, operation characteristics, and histopathology were extracted from the database. Cyst size was recorded as the maximal diameter on imaging (MRI, CT, or EUS) as stated in the report. If multiple cysts were present, the size of the largest cyst was used for the analyses. Cyst growth was defined as increase in size $\geq$ 10 mm between the first and latest imaging.[13] The PD was considered dilated when the diameter was 5 mm or greater.[6] Level of dysplasia was recorded as the highest grade of dysplasia, subdivided into nondysplastic, low-grade, borderline or high-grade dysplasia, or malignancy.[14] Follow-up duration was recorded as time in months between the initial cyst diagnosis (the first cross-sectional imaging on which the cyst was detected) and last available imaging data. Survival data were collected using the municipal personal records database that contains the personal details of all Dutch inhabitants (August 29, 2016).

Accuracy of the preoperative diagnosis was calculated as the number of patients in whom the correct preoperative diagnosis was made. For this analysis, MD- and MT-IPMN were considered as the same entity. We also calculated the number of patients in whom the preoperative differentiation between benign (SCN, non-neoplastic pancreatic cyst) and premalignant (MCN, IPMN, SPN, NET, malignancy) was correct.

We subdivided pancreatic cysts into 3 groups based on the pathologic outcome; malignant cysts (invasive malignancy and high-grade dysplasia, SPN, NET), premalignant cysts (MCN or IPMN with no, low-grade, or borderline dysplasia) and benign cysts (eg, SCN, pancreatic fluid collection). In light of the histopathologic outcomes, we considered surgery justified in retrospect for the malignant subgroup or in patients with symptom improvement after resection of a symptomatic cysts (ie, recurrent pancreatitis, gastric outlet obstruction, or abdominal pain). Surgery was considered overtreatment in retrospect in patients with premalignant cysts or benign cysts or in patients without symptom improvement after resection of a cyst suspected to cause symptoms.

Furthermore, we evaluated the number of patients with suspected IPMN in whom resection was indicated according to the IAP, European, and AGA guidelines (Table 1). We considered resection if there was at least 1 absolute indication present or at least 2 relative indications. Regarding the IAP guideline, the presence of any nodule was considered a high-risk stigma because enhancement could not be specified in all patients, as it was often discovered during EUS without the use of intravenous contrast.

Statistical analysis

Descriptive statistics were computed for all study variables. Data were analyzed with IBM SPSS version 22.0 (IBM, Armonk, NY). Categorical data were reported as frequency or percentage. Continuous data were reported as mean $\pm$ SD or as median and interquartile range (IQR), depending on the distribution. Survival was assessed using