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Original article

Mucinous cystic neoplasm of the pancreas: Is surgical resection recommended for all surgically fit patients?

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ABSTRACT

Background: Surgical removal of mucinous cystic neoplasms (MCNs) is usually recommended because of the risk of malignancy. However, increased experience of MCNs suggests that the incidence of invasion is lower than had been thought. This study was designed to establish more reasonable surgical indications for MCN through re-assessment using strict pathologic diagnostic criteria.
Methods: Ninety-four patients who underwent surgical removal of MCNs at Seoul National University Hospital from 1991 to 2012 were retrospectively analyzed. Pathologic results were re-evaluated by an experienced pathologist. Medical records and radiologic images were reviewed to determine factors predicting malignancy.
Results: Of the 94 patients, 4 were found to have intraductal papillary mucinous neoplasms (IPMNs). Of the 90 MCNs, 60 (66.7%) were low-grade, 21 (23.3%) were intermediate-grade, and 5 (5.5%) were high-grade dysplasias; and 4 (4.4%) were invasive carcinoma. Mural nodules on CT scan ($p = 0.005$) and abnormal serum CA19-9 concentration ($p = 0.029$) were significant predictors of malignancy. All MCNs less than 3 cm in size with normal serum tumor markers were benign and all malignant MCNs had cyst fluid CA19-9 over 10,000 units/ml. The five year disease specific survival rates were 98.8% for all patients and 75.0% for those with invasive MCNs.
Conclusion: MCNs had a low prevalence of malignancy. Regardless of the histological grade, long-term outcome was excellent. Therefore, in the absence of specific symptoms, surgery may not be indicated for MCNs <3 cm without mural nodules or elevated serum tumor markers. Validation by a prospective study with very careful design is needed.

1. Introduction

Mucinous cystic neoplasms (MCNs) were originally defined as tumors with mucin-producing columnar epithelium supported by "ovarian stroma," with all MCNs of the pancreas classified as pre-cancerous lesions, regardless of their epithelial differentiation [1]. Moreover, this classification system replaced the terms "cystadenoma" and "cystadenocarcinoma" with "mucinous cystic neoplasm with overt or latent malignancy."

MCNs of the pancreas are currently diagnosed more frequently owing to improvements in high resolution imaging and the increased number of asymptomatic individuals undergoing imaging procedures. However, the clinical characteristics and malignancy rates of MCNs vary widely [2]. Observational strategies are contraindicated by the malignant potential of these tumors, whereas surgery carries various risks, including the possibility of pancreatic fistula following pancreatectomy in patients with an otherwise normal pancreas.

The wide range of clinical characteristics of MCNs may result from the misclassification of intraductal papillary mucinous neoplasms (IPMNs) as MCNs, since IPMNs have greater malignant potential than MCNs [2,3]. This misclassification not only resulted in a greater variety of clinicopathological characteristics, but also in increased malignancy rates and the prediction of a poorer prognosis than in patients with MCN alone. To establish more secure surgical indications for MCN, we retrospectively re-assessed clinical and pathological findings in patients with MCN, using uniform pathologic criteria, and analyzed factors predictive of malignancy in these patients.

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2. Patients and methods

We retrospectively evaluated 94 patients diagnosed with MCN who underwent pancreatectomy at Seoul National University Hospital from 1991 to 2012. All surgical specimens and slides were reviewed by an experienced gastrointestinal pathologist to confirm the presence of mucin-producing columnar epithelium supported by ovarian stroma. Tumors were categorized according to WHO classification [4] as MCNs with low-grade (adenoma), intermediate-grade (borderline neoplasm), or high-grade (carcinoma in situ) dysplasia or as invasive carcinoma. High-grade dysplasia (HGD) and invasive carcinoma were considered malignant. However, we discriminate high-grade dysplasia MCNs and invasive carcinoma in the analysis of the survival. Because the prognosis of invasive MCN is still poor, but not that of carcinoma in situ or HGD [5].

Radiologic images were reviewed with regard to factors predictive of malignancy, including wall calcification, multilobularity, mural nodules, wall thickness, dilatation of the main pancreatic duct, communication with the main pancreatic duct and evidence of pancreatitis on preoperative computed tomography (CT) scan. Wall calcification was defined as a high attenuation lesion in the cyst wall on non-contrast CT; multilobularity by the contour of the cyst (Fig. 2); and mural nodules as solid nodules $\geq$5 mm on CT, magnetic resonance imaging or endoscopic ultrasound (Fig. 3). Wall thickness was determined by the thickest wall measured on CT, pancreatic duct dilatation as a diameter over 3 mm on CT; pancreatic duct communication as continuity between the cyst and the pancreatic duct on endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography or CT, and pancreatitis as peripancreatic infiltration or fluid collection on CT.

Electronic medical records were reviewed to assess patients' clinical characteristics and long-term follow-up outcomes.

For statistical analysis, continuous data were expressed as means $\pm$ standard deviations. Normally and non-normally distributed continuous variables were compared using Student's t tests and Mann–Whitney U tests, respectively. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. p values < 0.05 were considered significant. All statistical analyses were performed using SPSS® ver. 18.0 for Windows (SPSS, Chicago, IL).

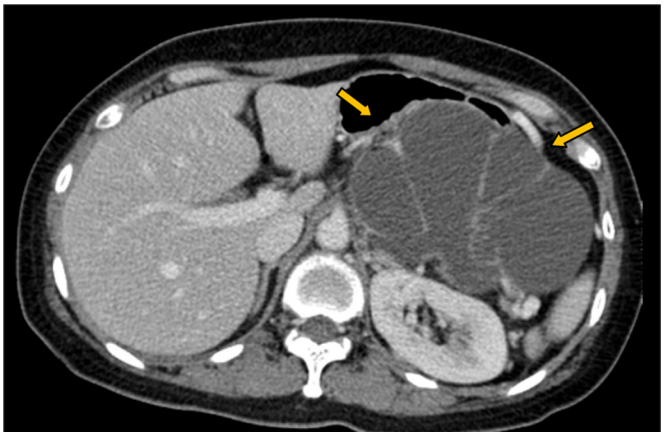

Fig. 2. Preoperative CT images of a patient with multilobular MCN.

3. Results

3.1. Pathologic re-assessment

Of the 94 patients with resected MCN, four were found on pathologic review to be IPMNs and were excluded from analysis. Of the 90 MCNs, 60 (66.7%) were low-grade, 21 (23.3%) were intermediate-grade, and 5 (5.5%) were high-grade dysplasias; and 4 (4.4%) were invasive carcinomas. Detailed pathologic result of 4 invasive carcinoma were; 1 T1N0, 2 T2N0 and 1 T4N1 with paraaortic node metastasis. Only T4N1 specimen showed angiolymphatic and nerve invasion. For comparison, patients were divided into two groups: those with benign (low- and intermediate-grade dysplasia; $n = 81$) and malignant (high-grade dysplasia and invasive carcinoma; $n = 9$) MCNs.

3.2. Patient demographics and clinical presentations

Demographic and clinical characteristics are summarized in Table 1. Mean patient age was 47.9 years. Only one of the 90 patients was male, a 55-year-old man who presented with indigestion. Abdominal CT showed a 3 cm sized cystic mass in the pancreatic body, for which he later underwent a central pancreatectomy. He was confirmed as having a low-grade MCN with ovarian stroma. The chief complaints of the 90 patients included asymptomatic pancreatic cysts (48.9%), abdominal pain (23.3%), palpable mass (12.2%), indigestion (11.1%) and others (4.4%). Nineteen patients had history of follow-up after detection of pancreatic cystic mass. And they had been followed up for a median 3.7 years (range 0.3–12.0 years), recommended surgery in 16 due to the increase in tumor size during observation. Mean growth of cyst size was 1.8 cm (range 0.5–5.5 cm) during follow-up period and their final pathologic results were 18 benign and 1 HGD MCN. Mean preoperative serum CEA and CA19-9 concentrations were higher in the 9 patients in the malignant group than in the 81 in the benign group, but the differences were not statistically significant. The only patient with elevated serum CEA had a malignant MCN, and elevated serum CA19-9 was significantly more frequent in patients with malignant than benign MCNs (sensitivity 55.6%, specificity 80.2%, predictability 77.8%). Cystic fluid analysis results were available for 40 patients. None of the patients with malignant MCNs had cystic fluid CA19-9 concentrations below 10,000 IU/mL, whereas 5 with benign

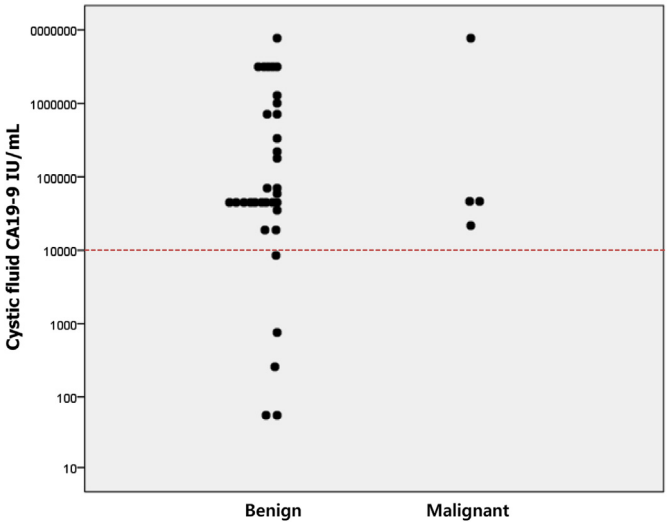

Fig. 1. Distribution of cystic fluid CA19-9 concentration in patients with benign and malignant mucinous cystic neoplasms.