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Original Article

Diagnostic Concordance and Preoperative Risk Factors for Malignancy in Pancreatic Mucinous Cystic Neoplasms

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Background/Aims: As pancreatic mucinous cystic neoplasms (MCNs) are considered premalignant lesions, the current guidelines recommend their surgical resection. We aimed to investigate the concordance between preoperative and postoperative diagnoses and evaluate preoperative clinical parameters that could predict the malignant potential of MCNs.

Methods: Patients who underwent surgical resection at Samsung Medical Center for pancreatic cystic lesions and whose pathology was confirmed to be MCN, between July 2000 and December 2017, were retrospectively analyzed.

Results: Among a total of 132 patients 99 (75%) were diagnosed with MCN preoperatively. The most discordant preoperative diagnosis was an indeterminate pancreatic cyst. The proportion of male patients was higher (24.2% vs 7.1%, p=0.05) in the diagnosis-discordance group and the presence of worrisome features in radiologic imaging studies, such as wall thickening/enhancement (12.1% vs 37.4%, p=0.02) or solid component/mural nodule (3.0% vs 27.3%, p=0.02), was lower in the diagnosis-discordance group. The presence of symptoms (57.7% vs 34.9%, p=0.02), tumor size greater than 4 cm (80.8% vs 55.7%, p=0.04), and radiologic presence of a solid component/mural nodule (42.3% vs 16.0%, p=0.01) or duct dilatation (19.2% vs 6.6%, p=0.01) were significantly associated with malignant MCNs.

Conclusions: In our study, the overall diagnostic concordance rate was confirmed to be 75%, and our findings suggest that MCNs have a low malignancy potential when they are less than 4 cm in size, are asymptomatic and lack worrisome features on preoperative images. **(Gut Liver 2022;16:637-644)**

Key Words: Mucinous cystadenoma; Mucinous cystadenocarcinoma; Pancreatic neoplasm; Diagnostic accuracy

INTRODUCTION

With the increased use of advanced cross-sectional imaging modalities and the generalization of health screening examinations, pancreatic cystic neoplasms (PCNs) have been recognized more frequently in clinical practice compared to before.[1,2] In Korea, the prevalence of incidentally detected PCNs was 2.1% and the annual incidence of PCNs has increased gradually.[1,3] The World Health Organization outlines four general categories for the histological classification of PCNs: serous cystic neoplasms, mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and solid pseudopapillary neoplasms.[4,5] The biological behavior of these lesions covers a wide spectrum, ranging from benign to borderline and malignant.[6]

Among these lesions, MCNs and IPMNs are known as premalignant lesions. Surgical resection is considered for the management of MCNs and IPMNs with the possibility of malignant transformation.[7] Recently, some reports indicating MCNs to be less aggressive than previously thought have been emerging.[8,9] Therefore, making a precise preoperative diagnosis is crucial from the viewpoint of two aspects: risk of over-treatment with unnecessary surgery and risk of under-treatment that would retain a potentially

malignant tumor. However, there are few studies on the accuracy of preoperative diagnostic assessment.[6,10-12] Moreover, these past studies focused on overall PCNs.

Although both MCNs and IPMNs are premalignant lesions, MCNs have not been studied in much detail, as opposed to IPMNs. Current international consensus guidelines have also mostly focused on IPMNs.[13,14] Therefore, in this study, we aimed to investigate the concordance between preoperative and postoperative diagnoses and evaluate preoperative clinical parameters that would predict the malignant potential of MCNs.

MATERIALS AND METHODS

1. Patients

We retrospectively analyzed patients who underwent surgical resection for pancreatic cystic lesions and whose pathology was confirmed to be MCN at Samsung Medical Center between July 2000 and December 2017. All available clinical information including demographic, serum tumor marker, radiologic, surgical, and pathologic data was collected from the medical records.

Preoperative diagnoses were made by clinicians mostly based on imaging studies. All patients had preoperatively undergone at least one cross-sectional imaging study, including computed tomography (CT) or magnetic resonance imaging (MRI). Imaging performed outside the hospital was formally reviewed by the radiologists at our institution. Some of the patients additionally underwent endoscopic ultrasound (EUS), with or without cystic fluid aspiration and/or fine needle aspiration, when cross-sectional imaging was ambiguous. When a patient underwent more than one imaging study and had several diagnostic impressions, the clinician made a high-probability diagnosis considering various factors comprehensively.

Considering the malignant potential and consensus guidelines,[13,15,16] all patients diagnosed with MCNs preoperatively, underwent surgical resection. In addition, some patients who were not diagnosed with MCNs preoperatively were operated for the following reasons: presence of highly suspected malignant features, increment in the tumor size, diagnostic purpose, presence of symptoms or concomitant complications.

The postoperative pathologic diagnosis was made on the basis of the World Health Organization histological classification. Epithelial dysplasia was graded on the basis of the most severe focus identified.[5,17] We classified MCNs as benign and malignant in accordance with the histologic grade. Low-grade dysplasia or intermediate-grade dysplasia was considered as a benign lesion and high-grade dysplasia/carcinoma *in situ* (HGD/CIS) or an invasive mucinous cystadenocarcinoma was considered as a malignant lesion.

The study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (IRB number: 2018-08-006-011). Because of the retrospective design, the informed consent was waived.

2. Statistical analysis

Continuous variables were compared using the Mann-Whitney test. Categorical variables were compared using the chi-square or Fisher exact test. To identify factors associated with diagnostic concordance and malignant MCNs, a univariate binary logistic regression analysis was performed. A multivariable binary logistic regression model was created for variables that were statistically relevant in the univariate analyses. p-values <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline Characteristics of Patients with Mucinous Cystic Neoplasms

Characteristics	Value (n=132)
Sex	
Female	117 (88.6)
Male	15 (11.4)
Age, yr	50 (39-60)
Chief symptom	
Asymptomatic	80 (60.6)
Abdominal pain/discomfort	40 (30.3)
Palpable mass	8 (6.1)
Indigestion	4 (3.0)
Tumor marker	
CA19-9, U/mL	12.8 (6.4–32.3)
Location	
Head & neck	14 (10.6)
Body	31 (23.5)
Tail	87 (65.9)
Size, cm	4.5 (3–8)
Histologic grade	
Low-grade dysplasia	88 (66.7)
Intermediate-grade dysplasia	18 (13.6)
High-grade dysplasia/carcinoma *in situ*	10 (7.6)
Invasive mucinous cystadenocarcinoma	16 (12.1)
Surgical procedure	
Distal pancreatectomy	108 (81.8)
Pancreatoduodenectomy	11 (8.3)
Enucleation	8 (6.1)
Central pancreatectomy	3 (2.3)
Subtotal pancreatectomy	2 (1.5)

Data are presented as the number (%) or median (interquartile range).
CA19-9, carbohydrate antigen 19-9.

RESULTS

1. Patients characteristics

A total of 132 patients with confirmed histology of MCN after surgical resection were analyzed. Their baseline characteristics are shown in Table 1. The patients were mostly middle-aged (median 50 years) women (88.6%). More than half of the patients were asymptomatic, but visited our clinic for the evaluation of pancreatic cystic lesions found incidentally. The patients who initially had symptoms complained of abdominal pain/discomfort (30.3%), palpable masses (6.1%), and indigestion (3%).

Most of the tumors were located at the pancreatic body and tail (89.4%). The median tumor size of the resected specimens was 4.5 cm. In terms of the histologic grade, 88 (66.7%) patients revealed low-grade dysplasia; 18, intermediate-grade dysplasia (13.6%); 10, HGD/CIS (7.6%); and 16, invasive mucinous cystadenocarcinoma (12.1%). Most of the patients underwent distal pancreatectomy; other procedures including pancreatoduodenectomy, enucleation, central pancreatectomy, and subtotal pancreatectomy were performed considering the location of the tumor.

For evaluating pancreatic cystic lesions, the patients underwent several imaging studies including CT, MRI, and EUS. The numbers of diagnostic imaging modalities performed preoperatively are shown in Table 2. Among all the patients, 63 (47.7%) underwent a single imaging study (CT or MRI alone) and 69 (52.3%) underwent more than two imaging studies before surgical resection.

Table 2. Numbers of Diagnostic Imaging Modalities Performed Preoperatively

Variable	No. (%) (n=132)
One modality	63 (47.7)
CT alone	56 (42.4)
MRI alone	7 (5.3)
Two modalities	55 (41.7)
CT+MRI	25 (18.9)
CT+EUS	29 (22.0)
MRI+EUS	1 (0.8)
Three modalities	
CT+MRI+EUS	14 (10.6)

CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound.

2. Diagnostic concordance

A total of 99 patients were diagnosed with MCNs preoperatively and the overall diagnostic concordance rate was 75%. When the total study period was divided into three parts, the diagnostic concordance rate increased over time as shown in Fig. 1. The detailed information of diagnostic discrepancies is shown in Table 3. The most discordant preoperative diagnosis in patients with MCNs was an indeterminate pancreatic cyst (9.8%). Other preoperative misdiagnoses were IPMN (3.8%), solid pseudopapillary neoplasm (4.5%), serous cystic neoplasm (0.8%), pseudocyst (2.3%), pancreatic simple cyst (0.8%), pancreatic hemorrhagic cyst (0.8%), omental cyst (0.8%), left adrenal gland cyst (0.8%), and peritoneal origin tumor (0.8%). The reasons that the patients with diagnosis dis-

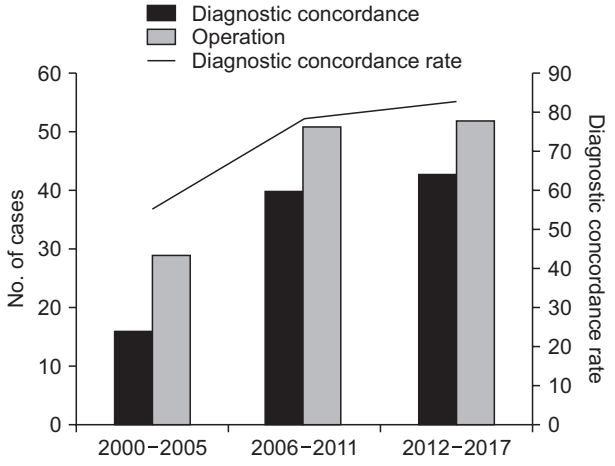

Fig. 1. Diagnostic concordance rate.

Table 3. Comparison between Preoperative and Postoperative Diagnoses

Preoperative diagnosis	No. (%) (n=132)	Postoperative histology			
		Benign group		Malignant group	
		LGD	IGD	HGD/CIS	Invasive
Mucinous cystic neoplasm	99 (75.0)	68	10	10	11
Intraductal papillary mucinous neoplasm	5 (3.8)	3	1	-	1
Solid pseudopapillary neoplasm	6 (4.5)	2	2	-	2
Serous cystic neoplasm	1 (0.8)	1	-	-	-
Pseudocyst	3 (2.3)	1	1	-	1
Others	5 (3.8)	3	2	-	-
Indeterminate	13 (9.8)	10	2	-	1

LGD, low-grade dysplasia; IGD, intermediate-grade dysplasia; HGD, high-grade dysplasia; CIS, carcinoma *in situ*.

cordance underwent operation were as follows: exclusion of malignancy, increment in the tumor size, diagnosis and treatment for symptomatic patients, and presence of concomitant complications such as hemoperitoneum or peritonitis. In terms of the histology, the proportion of patients with invasive mucinous cystadenocarcinoma was 11.1% in the diagnosis-concordance group. Invasive mucinous cystadenocarcinoma was also diagnosed in the diagnosis-discordance group and the proportion was 15.2%. Since we defined HGD/CIS as a malignant lesion, 10 patients (10.1%) considered to have malignancy in the diagnosis-concordance group. However, there was no patient with HGD/CIS in the diagnosis-discordance group.

In the univariate analyses to evaluate factors influencing diagnostic concordance, the following factors were not significant: age, presence of symptoms, serum carbohydrate antigen 19-9 (CA19-9) level, location, size, histologic grade, and number of imaging modalities (Table 4). On the other hand, in the diagnosis-discordance group, the proportion of male patients was higher (24.2% vs 7.1%, p=0.05) than in the diagnosis-concordance group. In addition, the presence of worrisome features in imaging studies such as wall thickening/enhancement (12.1% vs 37.4%, p=0.04) or a solid component/mural nodule (3.0% vs 27.3%, p=0.03) was lower in the diagnosis-discordance group. In the multivariable analyses, all of these variables remained as factors independently associated with diagnostic concordance.

3. Risk factors for HGD/CIS or invasive carcinoma in MCNs

Of all the 132 patients, 26 (19.7%) were diagnosed with malignant MCNs, including HGD/CIS and invasive mucinous cystadenocarcinoma (Table 5). In the univariate analyses, presence of symptoms (57.7% vs 34.9%, p=0.006), serum CA19-9 level (median 51.7 U/mL vs median 11.6 U/mL, p=0.000), tumor size (median 6 cm vs median 4 cm, p=0.05), tumor size greater than 4 cm (80.8% vs 55.7%, p=0.03), and radiologic presence of a solid component/mural nodule (42.3% vs 16.0%, p=0.03) or duct dilatation (19.2% vs 6.6%, p=0.01) were significantly associated with malignant MCNs. Among these variables, all except serum CA19-9 level and median tumor size were remained independently associated with malignant MCNs in the multivariable analyses. There was no association of gender, age, location, radiologic presence

Table 4. Factors Influencing Diagnostic Concordance in Mucinous Cystic Neoplasm

Variable	Diagnosis-concordance group (n=99)	Diagnosis-discordance group (n=33)	p-value	
			Univariate analysis	Multivariable analysis
Sex			0.05*	0.05*
Female	92 (92.9)	25 (75.8)		
Male	7 (7.1)	8 (24.2)		
Age, yr	51 (40–60)	46 (33–61)	0.36	NA
Presence of symptoms			0.42	NA
Yes	36 (36.4)	16 (48.5)		
No	63 (63.6)	17 (51.5)		
Tumor marker			0.31	NA
CA19-9, U/mL	12.6 (6.2–27.1)	14.1 (7.1–38.3)		
Location				
Head & neck	11 (11.1)	3 (9.1)	0.61	NA
Body	21 (21.2)	10 (30.3)	0.32	NA
Tail	67 (67.7)	20 (60.6)	0.49	NA
Size, cm	4.5 (3.0–8.0)	5.0 (2.7–7.6)	0.68	NA
Histologic grade			0.53	NA
LGD/IGD	78 (78.8)	28 (84.8)		
HGD/CIS/invasive	21 (21.2)	5 (15.2)		
Worrisome features at images				
Wall thickening/enhancement	37 (37.4)	4 (12.1)	0.04*	0.02*
Solid component/mural nodule	27 (27.3)	1 (3.0)	0.03*	0.02*
Duct dilatation	11 (11.1)	1 (3.0)	0.27	NA
No. of imaging modalities			0.98	NA
One	43 (43.4)	20 (60.6)		
Two or three	56 (56.6)	13 (39.4)		

Data are presented as the number (%) or median (interquartile range).
CA19-9, carbohydrate antigen 19-9; LGD, low-grade dysplasia; IGD, intermediate-grade dysplasia; HGD, high-grade dysplasia; CIS, carcinoma *in situ*; NA, not available.
*Statistically significant, p<0.05.

Table 5. Risk Factors for High-Grade Dysplasia/Carcinoma *In Situ* or Invasive Carcinoma in Mucinous Cystic Neoplasms

Variable	Benign group (n=106)	Malignant group (n=26)	Univariate analysis	Multivariable analysis	
			p-value	OR (95% CI)	p-value
Sex			0.21	NA	NA
Female	95 (89.6)	22 (84.6)			
Male	11 (10.4)	4 (15.4)			
Age, yr	49 (38–58)	53 (40–61)	0.15	NA	NA
Presence of symptoms			0.01*	3.93 (1.29–12.03)	0.02*
Yes	37 (34.9)	15 (57.7)			
No	69 (65.1)	11 (42.3)			
Tumor marker			0.00*	1.00 (1.00–1.00)	0.40
CA19-9, U/mL	11.6 (6.0–21.6)	51.7 (11.3–2,026.3)			
Location					
Head & neck	10 (9.4)	4 (15.4)	0.98	NA	NA
Body	25 (23.6)	6 (23.1)	0.98	NA	NA
Tail	71 (67.0)	16 (61.5)	0.92	NA	NA
Median size, cm	4 (3–8)	6 (4–8)	0.05*	0.90 (0.75–1.07)	0.23
Size			0.03*	3.97 (1.04–15.21)	0.04*
<4 cm	47 (44.3)	5 (19.2)			
≥4 cm	59 (55.7)	21 (80.8)			
Worrisome features at images					
Wall thickening/enhancement	30 (28.3)	11 (42.3)	0.52	NA	NA
Solid component/mural nodule	17 (16.0)	11 (42.3)	0.03*	4.59 (1.42–14.85)	0.01*
Duct dilatation	7 (6.6)	5 (19.2)	0.01*	8.54 (1.75–14.58)	0.01*
No. of imaging modalities			0.31	NA	NA
One	53 (50.0)	10 (38.5)			
Two or three	53 (50.0)	16 (61.5)			

Data are presented as number (%) or median (interquartile range).
OR, odds ratio; CI, confidence interval; CA19-9, carbohydrate antigen 19-9; NA, not available.
*Statistically significant, p<0.05.

of wall thickening/enhancement, or number of imaging modalities with malignant MCNs.

DISCUSSION

The number of pancreatic cystic lesions has recently increased. The increased use of cross-sectional imaging modalities and the improved resolution of these modalities have enabled the detection of many incidental lesions. Previous studies in Korea reported the prevalence of PCNs to range from 0.47% to 2.1%.[1,18] Among pathology-confirmed PCNs, either surgically or non-surgically (proven by either biopsy or cytological examination), the mucinous type neoplasms such as IPMNs (41.0%) and MCNs (25.2%) were more common than the non-mucinous type including solid pseudopapillary neoplasms (18.3%) and serous cystic neoplasms (15.2%).[3] Since both IPMNs and MCNs have the possibility of malignant transformation, the international consensus guidelines have proposed surgical resection for mucinous type neoplasms. Notably, the management of IPMNs continues to evolve and the indications for the resection of branch duct IPMNs have recently been revised in detail.[14] For the management of MCNs however, these same guidelines have constantly recommended surgical resection for all patients with MCNs without any risk stratifications. Only lately has the European Study Group proposed that presumed MCNs without concerning features (≥40 mm, presence of symptoms, or presence of mural nodules) could be followed up carefully by MRI, EUS, or a combination of both.[9] Despite the aggressive treatment strategy, the diagnostic accuracy and risk factors for malignancy of MCNs have not been studied as well as those for IPMNs. Indeed, the accurate preoperative diagnosis of each type of PCN is very important because this would determine the treatment strategy. However, accurately diagnosing MCNs preoperatively remains challenging. Only few reports currently exist on the preoperative diagnostic assessment of MCNs. Even if data on this specific topic are limited, the accuracy of cross-sectional imaging modalities for MCNs ranges from 60% to 79.7%.[6,10,11] To overcome the imperfection of preoperative diagnosis, various additional techniques including EUS-guided cystic fluid analysis, fine needle aspiration, and even molecular work have been performed.[19] In addition, little is known about the factors associated with malignant MCNs. To the best of our knowledge, a few studies have evaluated the preoperative risk factors for MCN malignancy, to date.[7,9]

Thus, we first investigated the concordance between preoperative and postoperative diagnoses for identifying the diagnostic accuracy of MCNs, in this study. Since the final diagnosis depends on histology after surgical resection, we had to analyze only patients who were confirmed to have MCNs in the postoperative pathology and use the term "concordance" instead of "accuracy." We found that the overall diagnostic concordance rate was 75%, which was in the range previously reported by other studies. Considering that most discordant cases were indeterminate cysts (9.8%), the concordance of diagnosis was quite high in this study. In our data, male sex or the absence of worrisome radiologic features such as wall thickening/enhancement or a solid component/mural nodule was associated with diagnostic discordance. The reason for this could be that these factors did not match the traditional features of MCNs. Notably, in this study, the proportion of male patients was relatively higher than in past reports regarding the occurrence of MCNs in men as controversial.[20-22] Because we ascertained the presence of ovarian-type stroma in all male patients with MCNs in our study, we believe that MCNs can occur in male patients. Therefore, we think that clinicians should not rule out MCNs in male patients although their probability is low.

Secondly, we evaluated the risk factors that would predict malignant potential preoperatively in patients with MCNs. Malignant MCNs including HGD/CIS and invasive mucinous cystadenocarcinoma were present in 19.7%. Previous studies which included HGD/CIS as malignancy, as in our study, reported this ratio to range from 14.9% to 17.3%.[7,22] We found that the presence of symptoms or worrisome radiologic features such as duct dilatation or a solid component/mural nodule was associated with malignancy. Postlewait *et al.*[7] recently reported male sex, a pancreatic head and neck location, larger MCNs, a solid component or mural nodule, and duct dilatation as preoperative risk factors. Unlike the studies that included postoperative pathological parameters, their study was noteworthy in they dealt with only preoperative clinical parameters. Compared to their study, the proportion of malignant MCNs was higher in our study. In terms of risk factors, the radiologic presence of duct dilatation or a solid component/mural nodule was also associated with malignancy, as in their study. Instead of sex, location, or size, however, the presence of symptoms was significantly associated with malignant MCNs.

Recently, the European Study Group published the European evidence-based guidelines.[9] The differences in the management of MCNs from the international consensus guidelines were that instead of recommending surgical resection for all patients diagnosed with MCNs, those with a size of MCN less than 4 cm and without any symptoms or presence of worrisome features such as a mural nodule could be observed for progress. A meta-analysis reported by Nilsson *et al.*[8] provided background evidence, and according to their report, MCNs are probably more indolent lesions than were previously thought and among those less than 4 cm in size, only 0.03% were associated with invasive cystadenocarcinoma. Likewise, the presence of symptoms or worrisome radiologic features, but not size, was associated with malignant MCNs, in our study. To validate the suitability of this size criterion, we additionally analyzed the association between malignancy and size based on the criterion of 4 cm, and found that a size of 4 cm or more was significantly associated with malignancy. Five patients (19.2%) were diagnosed with malignant MCNs with sizes less than 4 cm. Among them, two were diagnosed with an invasive cystadenocarcinoma and three with HGD/CIS. All patients with invasive cancer had both, a size more than 3 cm and the radiologic presence of a solid portion or mural nodule. These findings in our study support the recent European guidelines for the more conservative management of MCNs.

This single-center retrospective observational study has some limitations. The study subjects were limited to patients who underwent surgery. Although this was inevitable to find a definite MCN, there might have been bias in selection because it excluded patients with MCNs who did not undergo surgical resection. In addition, not all subjects received the same imaging tests and this might potentially affect the diagnostic accuracy. Because the target study period was long, the images were read by a large number of radiologists and endoscopists but we did not review the imaging studies again for objectification. Finally, patients evaluated only by CT imaging before surgery accounted for the largest proportion (42.4%). Magnetic resonance cholangiopancreatography is more sensitive than CT for identifying communication between the PCN and the pancreatic duct system and the presence of mural nodule or internal septations, and EUS is also used to identify additional features when considering surgical resection of PCN.[9] CT alone might be insufficient for preoperative evaluation, and as mentioned above, it might affect diagnostic accuracy.

In conclusion, the overall diagnostic concordance rate of 75% in patients with MCNs was quite high in our study. Male sex or the absence of worrisome radiologic features such as wall thickening/enhancement or a solid component/mural nodule was associated with diagnostic discordance. Moreover, our study supports the emerging trends in the literature that MCNs have low malignant potential when they are smaller than 4 cm, asymptomatic and when

there is a lack of worrisome features on preoperative imaging.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: J.K.P. Acquisition, analysis, or interpretation of data: G.H.K., K.C., N.P. Writing and drafting of the manuscript: G.H.K., K.C., N.P. Critical revision of the manuscript for important intellectual content: K.T.L., J.K.L., K.H.L., J.S.H., I.W.H., S.H.K. All authors approved the final submission.

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