World Journal of Surgery

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Published Online: 7 November 2006

World J Surg (2006) 30: 2236–2245
DOI: 10.1007/s00268-006-0126-1

A Review of Mucinous Cystic Neoplasms of the Pancreas Defined by Ovarian-type Stroma: Clinicopathological Features of 344 Patients

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Abstract

Introduction: Despite formal definitions of mucinous cystic neoplasms (MCNs) and intraductal papillary neoplasms (IPMNs) by the World Health Organization (WHO) and Armed Forces Institute of Pathology (AFIP), several controversies with regard to MCNs remain. The aim of this review was to determine the clinicopathological features of MCNs defined by ovarian-type stroma (OS) as proposed by the WHO and AFIP and to compare them with MCNs defined by less stringent criteria.

Methods: A MEDLINE search was conducted to identify English-language articles on pancreatic MCNs from 1996 to 2005. Twenty-five studies were identified. The studies were divided into 2 groups: group A included 10 studies with 344 patients whereby the presence of OS was a criteria for the diagnosis of MCNs, and group B, included 15 studies comprising 761 patients whereby the presence of OS was not mandatory for the diagnosis of MCNs.

Results: Patients in group A (MCNs as defined by OS) were almost always female (99.7%), with a mean age of 47 (range, 18–95) years. MCNs were located predominantly in the body or tail of the pancreas (94.6%) and had a mean size of 8.7 cm (range, 0.6–35 cm); 76% were symptomatic, 6.8% demonstrated ductal communication, and 27% were malignant. At a mean follow-up of 57.5 (range, 1–264) months and 43 (range, 2–257) months after surgery, 97.9% of benign and 61.9% of malignant neoplasms were disease free, respectively. Patients in group B were older and had a higher proportion of males. Neoplasms were more evenly distributed in the pancreas, were smaller, communicated more frequently with the pancreatic duct, and were composed of a higher proportion of malignant tumors compared with group A. Their clinicopathological features were intermediate between those of group A and patients with IPMN.

Conclusion: Pancreatic MCNs with OS have unique and distinct clinicopathological features. MCNs should be defined by the presence of OS, as it is the most reliable way of distinguishing MCNs from IPMN. Adoption of ''looser'' criteria will result in misclassification of some IPMNs as MCNs.

Presented in part at the 7th World Congress of the International Hepato-Pancreato-Biliary Association, Edinburgh, 3-7 Sept 2006 (oral presentation).

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Cystic neoplasms of the pancreas are rare primary neoplasms. These tumors were first classified and divided into serous cystic neoplasms and mucinous

cystic neoplasms by Compagno and Oertel in 1978.[1,2] Mucin-producing neoplasms are generally regarded as malignant or premalignant whereas their serous counterparts are almost universally benign. Mucin-producing neoplasms were formally defined and classified as two separate entities, i.e. mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) by the World Health Organization (WHO) in 1996[3] and the Armed Forces Institute of Pathology (AFIP) in 1997.[4] MCNs were defined as large, thick-walled, septated cysts with no communication with the ductal system occurring in females. Histologically, these cysts are characterized by the presence of ovarian-type stroma (OS). On the other hand, IPMNs are intraductal neoplasms with papillary proliferation of the ductal epithelium frequently with mucin hypersecretion resulting in cystic dilatation of the main pancreatic duct or it branches.

Despite the formal definitions of MCNs and IPMNs by the WHO and AFIP, several controversies with regard to these entities remain. Three key controversial areas include: (1) whether the presence of OS is mandatory for the diagnosis of MCNs, (2) whether it occurs almost exclusively in females, and (3) whether the absence of communication with the pancreatic duct may distinguish MCNs from IPMNs.[3,4,5] These three issues remain unresolved. Hence, with these issues in mind, we reviewed the literature over the past 10 years (since the formal definitions of MCNs by the WHO and AFIP) for studies of MCNs. The aim of this review was to determine the clinicopathological features of MCNs defined by OS as proposed by the WHO and AFIP and to compare them with MCNs defined by less stringent criteria.

METHODS

A MEDLINE search was conducted from January 1996 to December 2005 to identify key English-language articles on pancreatic MCNs by using the key words ''pancreatic mucinous cystic neoplasm,'' ''pancreatic mucinous cystic tumor,'' ''pancreatic cyst,'' and ''pancreatic cystic neoplasm.'' Additional studies were identified by a manual search of the references of key articles and reviews. Only studies involving 5 or more patients with the relevant clinicopathological data were included. Case reports, abstracts, and reviews were excluded. Twenty-three studies published during the 10-year period were identified.[5–27] In addition, we included two ''key'' studies published prior to the search period.[2,28]

ANALYSIS

Two aggregated data sets were then constructed. The first, group A, included studies whereby the presence of OS was a criteria for the diagnosis of MCNs, which are the main focus of the present study. Ten studies were included comprised of 344 patients.[6–15] It is important to note that in two studies,[6,7] not all, but the vast majority (86% and 90%, respectively), of MCNs had OS. The second data set, group B, included studies whereby the presence of OS was not mandatory for the diagnosis of MCNs. There were 15 studies comprising 761 patients.[2,16–28] The relevant clinicopathological data including age, gender, percentage of MCNs with OS, presence of symptoms, location of neoplasm, communication with pancreatic duct, histology, and survival were collected, and a pooled analysis was conducted for each group. The median value of a parameter was used when the mean was not available. Tumors with invasive carcinoma and carcinoma in situ were classified as malignant. Results of the pooled analysis for groups A and B were compared with each other and a third group consisting of patients with IPMNs. The clinicopathological features of patients with IPMNs were obtained from a pooled analysis of 1,671 patients from six recent studies published in the last 2 years.[27,29–33] These six studies were identified via a MEDLINE search of English-language articles between 2004 and 2005 using the key words ''intraductal papillary mucinous neoplasm'' and ''intraductal papillary mucinous tumor.'' Only studies with more than 50 patients were included.

RESULTS

The clinicopathological features of the 344 patients in group A and 761 patients in group B are summarized in Tables 1, 2, and 3. The 344 patients in group A (MCNs as defined by OS) were almost always female (99.7%), who had a mean age of 47 (range, 18–95) years. Neoplasms were located predominantly in the body or tail of the pancreas (94.6%) and had a mean size of 8.7 cm (range, 0.6–35 cm). Seven-six percent of patients were symptomatic; 6.8% neoplasms demonstrated ductal communication, and 27% were malignant. Mean tumor size of malignant neoplasms was 10.2 cm (range, 3–30 cm). Only one of the 40 malignant MCNs was less than 4.5 cm. At a mean follow-up of 57.5 (range, 1–264) months and 43 (range, 2–257) months after surgery, 97.9% of benign and 61.9% of malignant neoplasms were disease free, respectively.

Table 1.
Clinicopathological features of mucinous cystic neoplasms (MCNs)

Study	Number (year range)	Ovarian stroma (%)	Age (year range)	Female	Distal lesion	Mean size (cm)	Symptomatic	Communication
Group A: MCNs defined by OS								
Fukushima (Kashiwa and Tokyo, 1997)	10	9 (90%)	49 (29–61)	10 (100%)	10 (100%)	7.1 (2–20)	3/6 (50%)	2 (20%)
Zamboni (Verona, 1999)	56	48 (86%)	48 (18–78)	56 (100%)	52 (93%)	8.4 (2.0–23)	50 (89%)	0
Thompson (AFIP, 1999)	130 (1979–1993)	130 (100%)	45 (20–95)	130 (100%)	125 (94%)	10.6 (1.5–30)	94 (88%)	NA
Shimizu (Aichi, 2002)	6 (1985–2000)	6 (100%)	53 (40–68)	6 (100%)	6 (100%)	6.5 (2–11)	NA	0
Hara (Japan, 2002)	5 (1975–2000)	5 (100%)	54 (36–69)	5 (100%)	5 (100%)	9.4 (8–13)	4 (80%)	3 (60%)
Izumo (Kyushu, 2003)	34 (1982–2001)	34 (100%)	44 (24–81)	34 (100%)	34 (100%)	8.4 (2.5–25)	22 (65%)	4/23
Kosmahl (Kiel, 2004)	32 (1971–2003)	32 (100%)	47 (23–78)	32 (100%)	27 (84%)	9.8 (2.7–23)	NA	0
Reddy (Mayo, 2004)	56 (1986–2003)	56 (100 %)	48 (17–78)	55 (98%)	52 (94%)	5.0 (0.6–35)	47 (94%)	NA
Sawai (Nagoya, 2004)	8 (1994–2003)	8 (100%)	57 (33–80)	8 (100%)	8 (100%)	4.9 (4.0–7.5)	4 (50%)	NA
Yeh (Yale, 2004)	7 (1994–2001)	7 (100%)	55	7 (100%)	NA	NA	NA	NA
Total	344	335 (97.4%)	47 (18–95)	343 (99.7%)	319/337 (94.6%)	8.7 (0.6–35)	224/295 (75.9%)	9/132 (6.8%)
Group B: Studies of MCNs whereby the presence of OS was not mandatory								
Campagno (AFIP, 1978)	41	NA	49 (20–82)	35 (85%)	39 (95%)	10.5 (2.0–19)	34 (83%)	NA
Warshaw (MGH, 1990)	42 (1978–1990)	NA	62	32 (76%)	22 (52%)	5.6	32 (76%)	0/26
Shyr (Taipei, 1996)	10 (1985–1994)	NA	48 (26–72)	8 (80%)	10 (100%)	10 m (4–30)	NA	0
Sugiyama (Kyorin, 1997)	18 (1980–1996)	NA	52 (22–65)	11 (61%)	15 (83%)	9.9 (3.0–18)	17 (94%)	4 (22%)
Wilentz (Hopkins, 1999)	61 (1984–1998)	NA	56	43 (70%)	35 (57%)	5.4	NA	NA
Le Borgne (France, 1999)	228 (1984–1996)	NA	56 (20–89)	148 (65%)	121 (53%)	6.4 (1.0–22)	188 (82%)	17 (7.5%)
Scott (Edinburgh, 1999)	13 (1990–1997)	NA	53 (22–82)	10 (7.7%)	9 (6.9%)	7.9 (3–15)	NA	2/4 (50%)
Sarr (Mayo, 2000)	84 (1940–1997)	NA	51 (19–82)	70 (83%)	64 (78%)	NA	84 (100%)	NA
Shima (Okayama, 2000)	6 (1984–1998)	NA	51 (37–74)	6 (100%)	6 (100%)	7.7 (4–13)	4 (67%)	3/5 (60%)
Yamaguchi (Kyushu, 2000)	21 (1982–1997)	NA	53	18 (86%)	17 (81%)	5.5	NA	NA
Fujino (Kobe, 2001)	14 (1982–1999)	NA	51 (36–71)	9 (64%)	12 (86%)	8.3 (3–17)	NA	NA
Yeh (Chang Gung, 2002)	12 (1993–1998)	NA	45 (19–70)	7 (58%)	7 (58%)	NA	NA	NA
Kim (MDACC and Korea, 2003)	15 (1991–2001)	NA	51	13 (87%)	15 (100%)	4.7	NA	NA
Suzuki (Japan, 2004)	179 (1992–2001)	73 (42.2%)	56 (19–74)	179 (100%)	125/173 (72%)	5.9 (0.2–23)	78 (44%)	21/173 (12.1%)
Goh (SGH, 2005)	18 (1990–2004)	8 (44%)	43 (25–73)	17 (94%)	18 (100%)	9.1 (3.0–18)	13 (72%)	0
Total	762	81/197 (41%)	53 (19–89)	606 (79.5%)	515/756 (68.1%)	6.6 (0.2–23)	450/616 (73%)	47/454 (10%)

OS: ovarian-type stroma; NA: not applicable; MCNs: mucinous cystic neoplasms; AFIP: Armed Forces Institute of Pathology; MGH: Massachusetts General Hospital; MDACC: MD Anderson Cancer Center; SGH: Singapore General Hospital.

Table 2.
Malignant potential and outcome of mucinous cystic neoplasms (MCNs)

Study	N (year)	Adenoma	Borderline	Carcinoma *in situ*	Invasive	Outcome of benign tumors		Outcome of malignant tumors	
Group A: MCNs defined by OS						Adenoma	Borderline	Carcinoma *in situ*	Invasive
Fukushima (Kashiwa and Tokyo, 1997)	10	6 (60%)		4 (40%)		Mean 80 m (36–187); 0 recurrence		Mean 160.5 m (20–257);1 recurrence (1 dod)	
Zamboni (Verona, 1999)	56	22 (39.3%)	12 (21.4%)	6 (10.7%)	16 (28.6%)	Median 52 m (4–180 m);0 recurrence		Med 76 m (21–134);0 recurrence	
Thompson (AFIP, 1999)	130 (1979–1993)	60 (46%)	70 (53.8%)			Mean 96 m (24–264 m);4 recurrence (1 dod)	Mean 112 m (24–408);9 recurrences (7 dod)		
Shimizu (Aichi, 2002)	6	4 (66%)		2 (33%)	0	Mean 57 m (6–124 m);0 recurrence		Mean 12.5 m (15–80 m);0 recurrence	NA
Hara (Fushiko, 2002)	5 (1975–2000)	3 (60%)		2 (40%)		Mean 57 m; 0 recurrence		54; m; recurrence (1 dod)	
Izumo (Kyushu, 2003)	34 (1982–2001)	28 (82.4%)	2 (5.9%)	3 (8.8%)	1 (2.9%)	Mean 61.7 m (2–238 m);0 recurrence		Mean 73 m (4–245);2 recurrences (2 dod)	
Kosmahl (Kiel, 2004)	32 (1971–2003)	10 (31%)	8 (25%)	14 (44%)		NA		NA	
Reddy (Mayo, 2004)	56 (1986–2003)	50 (89%)	0	2 (4%)	4 (7%)	Median 15 m (1–203 m);0 recurrence		0 recurrence	3 recurrence (3 dod)
Sawai (Nagoya, 2004)	8 (1994–2003)	6 (75%)		2 (25%)		Median 41.9 m (3.8–95.4);0 recurrence		1 recurrence (1 dod)	
Yeh (Yale, 2004)	7 (1994–2001)	4	2	0	1	NA		NA	
Total	344	157/214 (73.4%)		57/214 (26.6%)		Mean f/u: 57.5 m (1–264 m); Disease-free: 185/189 (97.9%)		Mean f/u: 43 m (2–257 m); Disease-free: 26/42 (61.9%)	
Group B: Studies of MCN whereby OS was not a definite criteria									
Campagno (AFIP, 1978)	41	8 (19.5%)	14 (34.1%)	19 (46.3%)		Mean 80.4 m (6–204 m); 3/15 recurrences (3 dod)		Mean 80.4 m (6–204 m); 9/14 recurrences (9 dod)	
Warshaw (MGH, 1990)	42 (1978–1990)	15 (36%)		27 (64%)		NA		4/17 recurrences (4 dod)	

Table 2.
Continued

Study	N (year)	Adenoma	Borderline	Carcinoma *in situ*	Invasive	Outcome of benign tumors		Outcome of malignant tumors	
						Adenoma	Borderline	Carcinoma *in situ*	Invasive
Shyr (Taipei, 1996)	10 (1985–1994)	NA	NA	NA	NA	3 unresectable, mean 2.5 m; 2 resectable, died mean 12.5 m; 5 resectable, alive mean 56 m			
Sugiyama (Kyorin, 1997)	18 (1980–1996)	6 (33%)		12 (67%)		5 year survival; No recurrences		5 year survival; 8 recurrences (8 dod)	
Wilentz (Hopkins, 1999)	61 (1984–1998)	27 (44%)	5 (8.2%)	9 (15%)	20 (33%)	Mean f/u: 58.8 m 0/24 recurrence	58.8 m 0/2 recurrence	58.8 m; 0/9 recurrence	50.4 m 8/15 recurrences (8 dod)
Le Borgne (France, 1999)	228 (1984–1996)	137 (60.1%)	13 (5.7%)	78 (34.2%)		Mean f/u 47 m 1/147 recurrence (1 dod)		Resected group: 63% 5-year survival rate	
Scott (Edinburgh, 1999)	13 (1990–1997)	3 (23%)		10 (7.7%)		Median f/u 45 m (6–92 m); 4 recurrences (2 dod)			
Sarr (Mayo, 2000)	84 (1940–1997)	54 (64%)	23 (27%)		7 (8.3%)	Mean 132 m (24–372 m) 0/53 recur	Mean f/u 96 m (24–300 m) 0/22 recurrence	5/6 recurrences (5 dod)	
Shima (Okayama, 2000)	6 (1984–1998)	4 (67%)		2 (33%)		F/u 24–120 m 0 recurrence		F/u 24–120 m 0 recurrence	
Yamaguchi (Kyushu, 2000)	21 (1982–1997)	10 (48%)		11 (52%)		0 recurrence		5 recurrences (5 dod)	
Fujino (Kobe, 2001)	14 (1982–1999)	6 (43%)		8 (57%)		Mean f/u :153 m (7–209 m); 0 recurrence		Mean f/u: 69 m (2–197 m); 2 recurrences (2 dod)	
Yeh (Chang Gung, 2002)	12 (1993–1998)	4 (33%)		8 (67%)		NA		NA	
Kim (MDACC, 2003)	15 (1991–2001)	10 (67%)	5 (33%)	0		NA		NA	
Suzuki (Japan, 2004)	179 (1992–01)	116/171 (67.8%)	2/171 (1.2%)	53/171 (31.0%)		0/103; recurrence	0/1; recurrence	0/15; recurrence	11/24; recurrence (11 dod)
Goh (SGH, 2005)	18 (1990–2004)	11 (61%)	4 (22%)	2 (11%)	1 (5.6%)	Median f/u: 15 m (0–63 m) 0 recurrence		Median f/u: 15 m (0–63 m); 0 recurrence	
Total	762	400/660 (60.6%)		260/660 (39.3%)		Mean f/u: 70.6 m (0–209 m); Disease-free: 382/386 (99.0%)		Mean f/u: 61.4 m (0–204 m); Disease-free: 84/136 (61.8%)	

MCN: mucinous cystic neoplasms; OS: ovarian-type Stroma; NA: not applicable; m: months; f/u: follow-up; dod: dead of disease

Table 3.
Pathological features of mucinous cystic neoplasms (MCNs) with ovarian-type stroma (OS)

Study	Inhibin	ER	PR	Luteinized cell	Malignant neoplasm size (cm) (range)
Fukushima (Kashiwa and Tokyo, 1997)	NA	NA	NA	NA	10 (4.5–20.0)
Zamboni (Verona, 1999)	37 (66%)	12 (22%)	26 (48%)	Most	9.2 (3–18); 1 < 5 cm
Thompson (AFIP, 1999)	NA	15/65 (23%)	46/65 (71%)	NA	Atypia 10.6 (2–30)
Shimizu (Aichi, 2002)	NA	NA	NA	NA	11 (11)
Hara (Fushiko, 2002)	NA	0	5 (100%)	3 (60%)	10.5 (8–13)
Izumo (Japan, 2003)	29 (85.3%)	21 (61.8%)	28 (82.4%)	11 (32.4%)	15.6 (10–25)
Kosmahl (Kiel, 200 4)	NA	NA	NA	NA	NA
Reddy (Mayo, 2004)	NA	NA	NA	NA	> 5 cm
Sawai (Nagoya, 2004)	NA	8 (100%)	8 (100%)	NA	NA
Yeh (Yale, 2004)	7 (100%)	2 (28.5%)	7 (100%)	7 (100%)	NA
Total	73/97 (75%)	58/170 (34%)	120/175 (69%)	21/46 (46%)	10.2 (3–30)

ER: estrogen receptor; PR: progesterone receptor; NA: not applicable; AFIP: Armed Forces Institute of Pathology.

A comparison between the clinicopathological features of patients in groups A and B and IPMNs are summarized in Table 4. Patients in group B were older, had a higher proportion of males, had neoplasms more evenly distributed in the pancreas, which were smaller, communicated more frequently with the pancreatic duct, and were composed of a higher proportion of malignant tumors compared with those in group A. Clinicopathological features were intermediate between those of group A and patients with IPMNs. However, disease-free survival of patients in group A were similar to those in group B (Table 4.)

DISCUSSION

Since the landmark papers by Compagno and Oertel in 1978,[1,2] there have been many studies of MCNs in the literature. However, the diagnostic criteria adopted by these different studies were inconsistent even though many of these reports had been written after the formal definitions of IPMNs and MCNs had been clearly defined and differentiated by the WHO[3] in 1996 and AFIP[4] in 1997. Whether the presence of OS is essential for the diagnosis of MCNs remains controversial and has yet to be resolved. Opponents of the criteria argue that the absence of OS cannot and should not be the sole criteria for ruling out a MCN. They argue that OS may sometimes be observed in only a small part of the cyst wall and thus it may be missed if the pathological examination is less than exhaustive.[34] Furthermore, some have suggested that MCN may lose its OS with malignant transformation.[9,34]

Recently, an international work group led by Tanaka and Chari published guidelines for the management of IPMNs and MCNs.[35] The group concluded that the presence of OS should be a prerequisite for the diagnosis of MCNs, as in the absence of another definitive marker, it is currently impossible to determine if a mucin-producing neoplasm is indeed an MCN based on other criteria. Furthermore, making exceptions to this rule would lead to misclassification of IPMNs as MCNs. They further proposed the term ''indeterminate mucin-producing cystic neoplasm of the pancreas'' for a subset of cystic lesions that did not have the typical features of IPMNs and did not demonstrate OS.[35]

Our present review confirms the findings of Tanaka *et al.*[35]. It demonstrates that when the definition of MCNs as proposed by the WHO and AFIP is adopted and the presence of OS is essential for its diagnosis, MCNs have unique clinicopathological features. In this review of 344

Table 4.
Comparison between the clinicopathological features of group A, group B, and intraductal papillary neoplasms (IPMNs)

	Group A MCNs with OS	Group B MCNs without OS	IPMNs[a]
No. patients	344	762	1671
OS	335 (97.4%)	81/197 (41.1%)	0
Age (years)	47 (18–95)	53 (19–89)	66 (27–95)
Female	343 (99.7%)	606 (79.5%)	732 (44%)
Distal lesion	319/337 (94.6%)	515/756 (68.1%)	452 (27%)
Mean size (cm)	8.7 (0.6–35)	6.6 (0.2–23)	3.2
Symptomatic	224/295 (75.9%)	450/616 (73.1%)	755/1327 (57%)
Ductal communication	9/132 (6.8%)	47/454 (10.3%)	All communicate by definition
Benign	157/214 (73.4%)	400/660 (60.6%)	863/1656 (52%)
Malignant	57/214 (26.6%)	260/660 (39.3%)	793/1656 (48%)
Disease free, benign tumors	185/189 (97.9%)	382/386 (99.0%)	NA
Disease free, malignant tumors	26/42 (61.9%)	84/136 (61.8%)	NA

MCNs: mucinous cystic neoplasms; OS: ovarian-type Stroma; NA: not applicable; IPMNs: intraductal papillary mucinous neoplasms.

[a]Clinicopathological data of patients with IPMNs were obtained from a pooled analysis of six recent large studies in the last 2 years.[27,29–33]

cases of MCNs with OS, MCNs occurred almost exclusively in females (99.7%), were almost always located in the body or tail of the pancreas (94.6%), and rarely communicated with the pancreatic duct (6.8%). In studies whereby this stringent criteria was not adopted, the patients were found to be older, there were a higher proportion of males, and cysts were more frequently located in the proximal pancreas and were smaller in size. Importantly, the clinicopathological features of MCNs when not defined by OS were intermediate between that of IPMNs and MCNs with OS. These observations support the hypothesis that many cases in series that did not adopt a stringent criteria were contaminated by IPMNs. Hence, the higher proportion of malignant tumors observed with MCNs without OS is probably a result of this ''contamination'' rather than the hypothesis that MCNs may lose their OS with malignant change.

OS is a characteristic tissue of MCNs and is composed of densely packed, spindle-shaped cells with round or elongated nuclei and sparse cytoplasm.[27] The stroma is also known to contain small nests of epithelioid-like cells representing luteinized stromal cells with positive staining for inhibin. The occurrence of ovarian-like mesenchymal stroma is not limited to pancreatic MCNs but is often observed in cystadenomas of the hepatobiliary system[36] and has even been observed in a case of pancreatic lymphangioma.[37] Cystadenomas of the hepatobiliary system occur almost exclusively in women. Devaney *et al.*[38] found ovarian-type stroma in 60 of 70 patients with hepatobiliary cystadenomas, all of whom were female.

The origin of OS in MCNs of the pancreas is still unknown.[39] Zamboni *et al.*[7] proposed that its histiogenesis could be due to the stimulation of endodermal immature stroma by female hormones or that primary yolk cells are implanted in the pancreas, as buds of the genital tract and dorsal pancreas are adjacent to each other during embryogenesis. The dorsal pancreatic enlage gives rise mainly to the pancreatic body and tail, and this could explain the predilection of MCNs for the distal pancreas.[7] The marked female predominance and the expression of estrogen receptors in some tumors support the role for hormonal factors in its pathogenesis.[40] However, the presence of estrogen and progesterone receptors do not necessarily mean that OS are ectopic ovarian tissue, as these receptors are commonly identified in normal tissue of other organs, such as muscle fiber of the uterus and islet cells of the pancreas.[41]

The occurrence of MCNs with OS in males is extremely unusual, and to the best of our knowledge, only 4 definitive cases have been reported in the English literature.[13,41–43] Three of these cases demonstrated positive staining for estrogen and progesterone receptors.[41–43] Another case report[39] in the literature of a male patient with MCNs containing sarcomatous stroma provided indirect evidence of a male patient with MCNs demonstrating OS, as it is thought that the sarcomatous stroma originated from OS.[39] The pathophysiology of OS in male patients remains an enigma, as there is no chance for female hormones or lutein cells to affect its development.[41] It is possible that OS represents a secondary change in the growth of the tumor.[41]

The absence of communication of the cyst with the pancreatic duct has been used by some [7,18] as a criteria for diagnosing MCNs and differentiating these neoplasms from IPMNs. However, this criteria is unreliable as demonstration of communication depends on several factors,

including the imaging modality and the thoroughness of the pathologist.[5] Hence, it is frequently difficult to demonstrate ductal communication, especially for some cases of branch-duct IPMNs. To further complicate matters, MCNs may also show communication with the pancreatic ducts.[44] The present review confirms that a small proportion of MCNs may demonstrate communication with the pancreatic duct.

Results of the present analysis suggest that size is a reliable predictor of the malignant potential of an MCN. None of the 40 malignant (carcinoma in situ or invasive) MCNs were less than 3 cm, and only 1 was less than 4.5 cm (3 cm). Careful analysis of the data revealed that the 3-cm neoplasm was from the series of Zamboni *et al.*[7] whereby 8 patients had neoplasms that did not demonstrate OS, and five of these eight neoplasms were malignant. The 3-cm malignant MCN was located in the head of the pancreas. Hence, it is likely that the malignant neoplasm was not a ''true'' MCN but a branch-duct IPMN instead. This finding is important, as it suggests that smaller MCNs, especially those in patients with a limited life expectancy, may be managed conservatively. Conservative management of small (< 3 cm) MCNs has been adopted in some institutions, such as the Mayo clinic.[13]

The ability of noninvasive MCNs to progress into invasive carcinoma has led to a debate regarding its prognosis.[45] This progression model implies that noninvasive MCNs that are completely resected should not recur.[45] However, some investigators have reported recurrence after complete resection of noninvasive MCNs.[2,8,45] This recurrence may partly be attributed to contamination of some of these series' with IPMNs. However, even in the present analysis of MCNs with OS, there were four recurrences among the 189 patients with benign or borderline MCNs. All four recurrences occurred in the study by Thompson *et al.*,[8] and some investigators have attributed this paradox to incomplete sampling.[45] This potential error secondary to inadequate sampling has also been acknowledged by the authors. Hence, we agree with other investigators that ''true'' noninvasive MCN does not recur after complete resection.

Currently, both MCNs and IPMNs are considered at the very least premalignant and should be resected. Hence, some may consider the differentiation between the two entities purely academic. However, key differences between MCNs and IPMNs, including multifocality, recurrence after resection, prevalence of frank malignancy, and occurrence of other synchronous and metachronous malignancies, have a major impact on the surgical treatment and subsequent follow-up of the two entities.[5,13,35]

The results of the present study suggest that the disease-free survival of patients with MCNs defined by OS (benign, 98% and malignant, 62%) compared with MCNs defined by less stringent criteria (benign, 99% and malignant, 62%) are similar. This may suggest that there is little clinical value in distinguishing these two groups. However, one must be cautious when interpreting these results, as the average patient follow-up was only 5 years or less. Furthermore, there was a higher proportion of malignant tumors associated with MCNs defined by less stringent criteria.

In summary, this review demonstrates that pancreatic MCNs with OS have unique and distinct clinicopathological features. Presently, MCNs should be defined by the presence of OS, as it is the most reliable way for distinguishing MCNs from IPMNs. Adoption of ''looser'' criteria will result in misclassification of some IPMNs as MCNs.

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