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SURGICAL MANAGEMENT OF PANCREATIC MUCINOUS CYSTIC NEOPLASMS (MCNS)

S.D.D. ……..

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CHAPTER 1

NATURAL HISTORY AND MANAGEMENT OF MCNS

INTRODUCTION

Pancreatic mucinous cystic neoplasms (MCN) are rare mucin-producing cystic tumors. They are predominantly found, incidentally, in middle-aged women and usually located in the pancreatic body or tail. They are differentiated from other mucin producing neoplasms by the presence of ovarian-type stroma.[1] They have been classified separately from intraductal papillary mucinous neoplasms (IPMNs) by the World Health Organization (WHO) since 1996[2] and the Armed Forces Institute of Pathology (AFIP) from 1997.[3] The current management of MCN is defined by the consensus European,[4] International Association of Pancreatology (IAP)[5] and the American Association of Gastroenterology guidelines.[6] However, the malignant potential of these lesions remains uncertain, with differing rates of malignant potential being described. Since the criteria for surgical resection differs between the current guidelines, we have performed a systematic review of the literature to better define the natural history and prognosis of these lesions and to inform recommendations for future management.

METHODS

We performed a systematic review of the literature using the PubMed, EMBASE and the Cochrane Library. The search was limited to studies published in the English language between 1970 and 2015. MeSH terms were decided by a consensus of the authors [Figure 1]. The search was restricted to title, abstract and keywords. Articles that described only outcomes for other cystic lesions of the pancreas or that included fewer than five patients with an MCN were excluded. Case reports, abstracts as well as reviews were also excluded. All references were screened for potentially relevant studies not identified in the initial literature search. The following variables were extracted for each report when available: age, gender, presence of ovarian-type stroma, associated symptoms, location, communication with main pancreatic duct, histology, survival, surgical complications and length of follow-up. Tumors with invasive carcinoma but not carcinoma in situ were

classified as malignant. 52 papers were included in the final analysis [Figure 1, Table 1].

RESULTS

MCNs mainly occur in women (female: male ratio 20:1) with a peak incidence in the 5th decade. They are usually located in the pancreatic body or tail (93 - 95%) and rarely communicate with the main pancreatic duct (0-33%).[7-11] Studies suggest 10-49% of surgically resected neoplastic cysts are MCNs.[12,13]

1. Pathophysiology

Pancreatic MCNs are defined pathologically as mucin-producing cysts that are surrounded by ovarian-type stroma (not found in other pancreatic neoplasms).[14,15] The origin of ovarian stroma is unknown, but it contains oestrogen and progesterone hormone receptors which appears to drive the tumour growth and may explain the predominance for these lesions to occur in women.[16]

Resected MCNs are typically large solitary masses[17] (average diameter: 7-10 cm, range: 2-36 cm, [Table 3]). Septations are common, leading to formation of multilocular cysts. Invasive carcinoma should be suspected if mural nodules or a solid component is present.[17]

MCNs are lined by tall columnar mucin producing epithelial cells.[14,15] The epithelium can be associated with low to high-grade dysplasia or invasive cancer (present in 0-34%) [Table 1]. Invasive cancer in MCN pathologically resembles pancreatic ductal adenocarcinoma (PDAC).[18] Rates of associated malignancy in MCN are much lower than in other mucinous cystic lesions; main duct-IPMNs (35.7-100%) and branch duct-IPMNs (8.2-51%)[19] suggesting MCNs may take longer to undergo malignant transformation or have lower malignant potential.

Like PDAC, malignant transformation of MCNs is associated with mutations in KRAS and PIK3CA oncogenes, tumour suppressor genes TP53, DPC4/SMAD4, RNF43 and P16INK4A/CDKN2A and the disruption of the hedgehog and Wnt signalling pathway.[20] Somatic mutations in PIK3CA occur frequently in MCN,[21] less commonly in IPMN[22] and not at all in PDAC.[23] In MCN and IPMN[22] the mutation was only found in areas of high-grade dysplasia and coexisted with the KRASG12D mutation, suggesting that together they may trigger the final steps of

carcinogenesis. In advanced MCN, inactivation of TP53 may also contribute to malignant transformation.[24]

2. Clinical presentation

Many MCNs are discovered incidentally[12,25,26] but some patients report mild or vague abdominal pain, abdominal heaviness or fullness, an abdominal mass, nausea or vomiting, back pain, recurrent pancreatitis or rarely jaundice [Figure 2, Table 2].[12,18,26-28]

Symptoms can be present for years, but being non-specific can lead to delays in diagnosis. Whether symptoms predict malignant transformation in MCN remains unclear,[25] but it should be suspected in any MCN patient if weight loss or back pain is present.[18,26] Invasive disease is more common in older patients.[19]

3. Assessment and Diagnosis

Serum tumor markers

Serum tumor markers alone cannot be used to diagnose MCN or differentiate them from other cystic lesions, but they are potentially useful in differentiating malignant and benign cystic lesions as high levels of CEA and CA-19.9 are suggestive of malignant transformation.[25,29-31]

Radiology

The European cystic tumor guidelines recommend that a CT or MRCP is performed to diagnose and characterize all cystic lesions of the pancreas.[4] International guidelines suggest cross-sectional imaging is only necessary once lesions reach 10mm, if detected by another method.[19] MRI is preferable for diagnosing and characterizing small lesions.[4] Most MCNs are currently diagnosed at around 10mm in size, but this has fallen over time [Figure 2].[4]

Imaging features predictive of malignant transformation[32] include: cyst size ≥3cm (OR = 62), mural nodule (OR = 9.3), dilated main pancreatic duct ≥ 6 mm (OR = 7.3) or peripheral eggshell calcification.[32] Imaging features and final pathology often correlate poorly, so where uncertainty remains surgical resection is still recommended.[33]

Endoscopic ultrasound (EUS)

Being a safe and well-tolerated procedure (adverse events: pancreatitis, bleeding, infection in <2%), EUS with fine needle aspiration (FNA) is often employed in the assessment and surveillance of cystic lesions of the pancreas,[34,35] although its absolute utility in surgical decision-making continues to be debated.[4,19,33,36]

Cyst fluid obtained at EUS-FNA can be immediately assessed for the "string-sign" which suggests a mucinous lesion.[37] It is then typically sent for biochemical and cytological assessment. A raised carcinoembryonic antigen (CEA) (>192 ng/mL) and a low amylase are typical of an MCN.

Obtaining sufficient fluid for cytological and biochemical assessment can be challenging in small cysts, especially when mucinous (as contents are viscous and difficult to aspirate).[38] Current research strategies are therefore evaluating through the needle optical biopsy (Mauna Kea Technologies, Paris)[39] protein and genetic markers [40,41] which can be performed on smaller samples. Research is ongoing to validate these novel techniques.

4. Treatment

Surveillance

Current guidelines advocate surgery for the majority of patients with an MCN. However, in lesions <4cm, that are asymptomatic and without worrisome features, the rate of associated malignancy is just 0.03%.[42] Therefore surveillance of small MCNs (<4cm) appears to be a safe strategy, but currently this is only advocated by the European guidelines. Mostly these lesions are diagnosed in young women, who will require long-term surveillance by MRI or EUS,[4,19] 6-monthly during the first year, then annually if stable, as long as they are fit for surgical resection. Surveillance is inconvenient, anxiety provoking and costly and in this group the risks of surgical resection and postoperative complications (chronic diabetes and pancreatic endocrine insufficiency) need to be balanced against continued surveillance.[42]

Surgical management

In MCNs <4cm and without worrisome features, organ-preserving pancreatic resection is recommended, including parenchyma sparing resections (middle pancreatectomy) and non-anatomic resections (excision, enucleation, uncinatectomy). In lesions >4cm or that have features suggestive of invasive

malignancy (mural nodules, peripheral egg-shell calcification), an oncological resection with lymphadenectomy is recommended.[4,19]

MCNs are usually located in the body/tail of the pancreas and require a distal pancreatectomy[26] which can be done without splecentomy if the suspicion of malignancy is low. Lesions in the body require an extended left resection. Postoperative mortality following these operations is almost zero, but morbidity remains significant (pancreatic fistula in 10-30%).[43]

A middle pancreatectomy can be considered for small lesions in the body/neck but this is more challenging than a distal resection and postoperative complications are higher (fistula in 34%).[33,44,45] Alternatively small tumors (<2cm) without malignant features can be managed by enuculation,[18,46] but again rates of pancreatic fistula are increased (30-50%).[46,47] Intraoperatively a pathologist uses a frozen section from the proximal margin, to assess the completeness of resection and if an oncological resection is required.[4]

For MCNs occurring in the head, a pancreatico-duodenectomy (pylorus-preserving or Whipple) is performed.[26] Postoperative mortality is 0-6% in high volume centres, but postoperative complications remain common (40-60%).[48]

Laparoscopic resections have been performed in selected patients with benign MCNs[49] but lower rates of postoperative complications were not seen.[26] The utility of laparoscopic resections is malignant MCNs remains unclear.

Oncology

No conclusive data exists for neo-adjuvant or adjuvant therapy for malignant MCNs. Current treatment options have been extrapolated from the management of PDAC and invasive IPMN and typically include gemcitabine or fluorouracil.[4] Reports from small series of patients receiving adjuvant chemotherapy in invasive MCN have demonstrated a survival advantage.[26]

Follow-up after resection

Complete resection of a non-invasive MCN is curative, recurrence has not been reported,[4] and further postoperative surveillance is therefore not required.[17,18] Invasive MCN should be followed-up like PDAC (regular CA19-9 and annual cross-sectional imaging).[4] Whether this management of malignant MCN improves prognosis over a symptom based assessment alone remains unknown.[19]

5. Prognosis

MCNs of <4cm have a low prevalence of malignant transformation.[25] Non-invasive MCNs have an excellent prognosis,[13] making resection prior to malignant transformation vital.[4] Complete resection of a non-invasive MCN is curative[19] regardless of the degree of cellular atypia and five-year survival is 100% [Table 4].[13] Surgical series have reported that 0-34% of resected MCNs are associated with invasive cancer, however these series have included larger lesions with more features of concern.[4] In lesions <4cm and without worrisome features, malignant transformation occurred in only 0.03%.[50] Five-year survival in patients with invasive MCNs ranges from 0-75%.[19,25]

DISCUSSION

To date this is the largest systematic review of the natural history and prognosis of MCNs. These tumors represent about 20% of all resected pancreatic cystic tumours and occur almost exclusively in middle-aged women. Growth of these lesions and rates of malignant progression are thought to be driven by the hormones oestrogen and progesterone, their receptors are present in the ovarian-type stoma of MCNs and these lesions grow rapidly when concentrations of these hormones rise e.g. in pregnancy. MCNs are often asymptomatic at the time of diagnosis, typically being discovered during abdominal investigations performed for another reason. In symptomatic patients, the most common symptoms are abdominal or back pain.

The accuracy of pre-operative investigations for diagnosing an MCN ranges from 47-83% depending on the modality used and if it has been employed in combination with other tests.[33,36,51,52] No substantial differences exist between CT, MRI or EUS for detecting features of concern associated with MCN and test selection is best decided based on trying to limit a patients exposure to ionising radiation and local expertise. For surveillance radiation-free investigations such as MRI or EUS should be used.[4]

Historically surgical resection was advocated for all surgically fit patients with an MCN.[19] However, these lesions are increasingly detected at an earlier stage [Figure 2] and appear to be associated with much lower rates of malignancy than previously thought. The recent European consensus guidelines have advocated a less

aggressive management approach for these lesions in certain situations e.g. when <4cm in size and in the absence of features of concern.[4] In indeterminate lesions or when the radiological features are inconclusive or contradictory the management is more challenging and surgical resection remains the safest approach, if there is sufficient clinical concern.

Given that the majority of surgically resected MCNs are benign, especially if small in size, a "non-oncological resection" or parenchyma sparing resection is the preferred approach. Where any suspicion of malignant transformation remains, a radical resection is mandatory. For benign MCN no follow-up is needed after radical resection, as the risk for recurrence is absent. For lesions with invasive cancer, the 5-year survival rate is approximately 60% and regular surveillance is recommended.

Although our review has included all recent published series of surgically resected MCN, a potential limitation is that many of the series report the findings of a single centre and contain relatively few patients. In addition, many old series did not define MCNs by the presence of ovarian-type stroma, so may have inadvertently included non-MCN lesions, which may explain the higher rates of malignancy and differences in associated features seen in these early series.[8,53,54] Larger multicentre studies, with thorough radiological and pathological characterization of MCNs are needed to fully validate the findings of this review.

CONCLUSION

Our comprehensive systematic review supports emerging trends in the literature that MCNs are probably more indolent lesions than was previously thought. They have a low aggressive behavior, with exceptionally low rates of malignant transformation when less than 4cm in size, are asymptomatic and lack worrisome features on pre-operative imaging. Conservative management, particularly of small MCNs appears to be a reasonable strategy. This differs significantly from the natural history of small BD-IPMNs, supporting the need to differentiate mucinous cyst subtypes pre-operatively, where possible. These findings support the management of MCN advocated by the recent European Guidelines.

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TABLES AND FIGURES

Figure 1. Search flowchart of systematic literature review. MeSH terms were decided by a consensus of the authors and were restricted to the title, abstract and keywords.

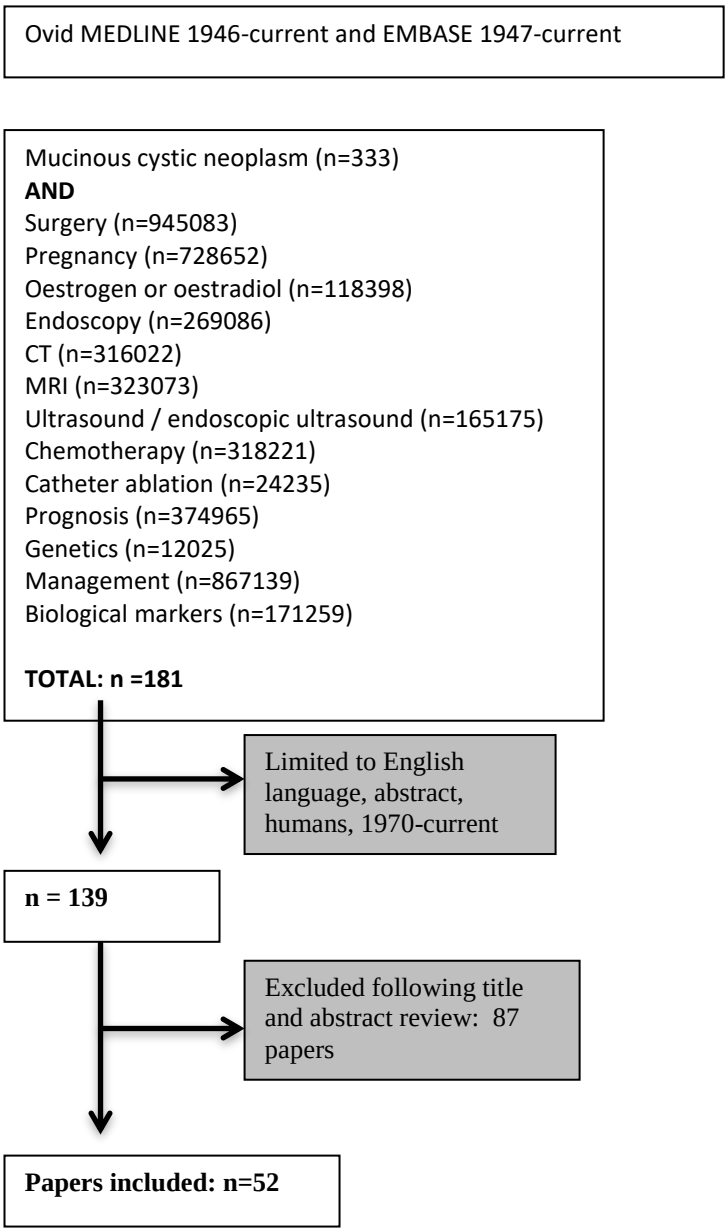
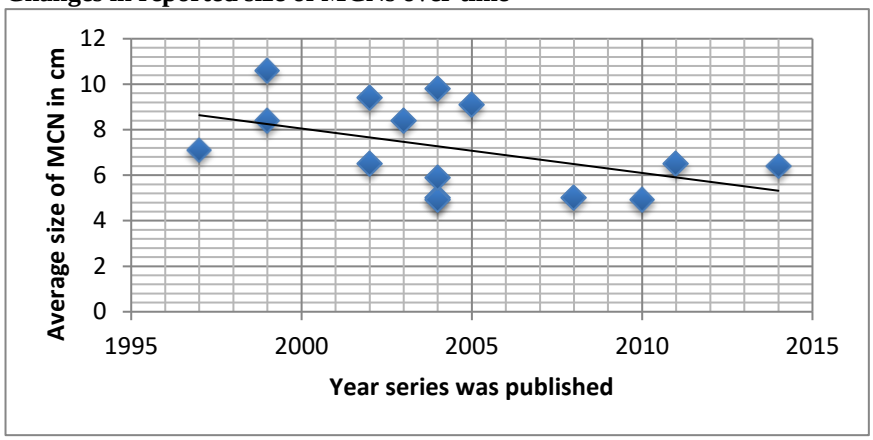
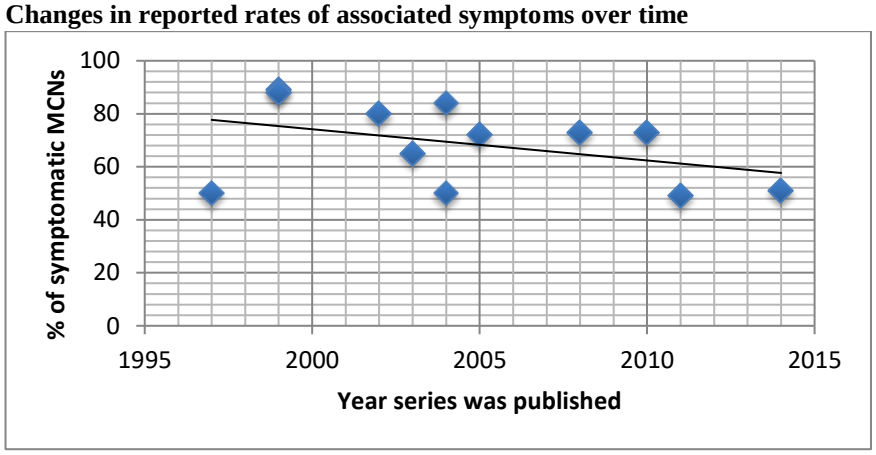


Figure 2. Changes in features of surgically resected MCNs where all (or a proportion) of the lesions have been defined by the presence of ovarian type stroma

A. Changes in reported size of MCNs over time



B. Changes in reported rates of associated symptoms over time



C. Changes in reported rates of associated invasive malignancy over time

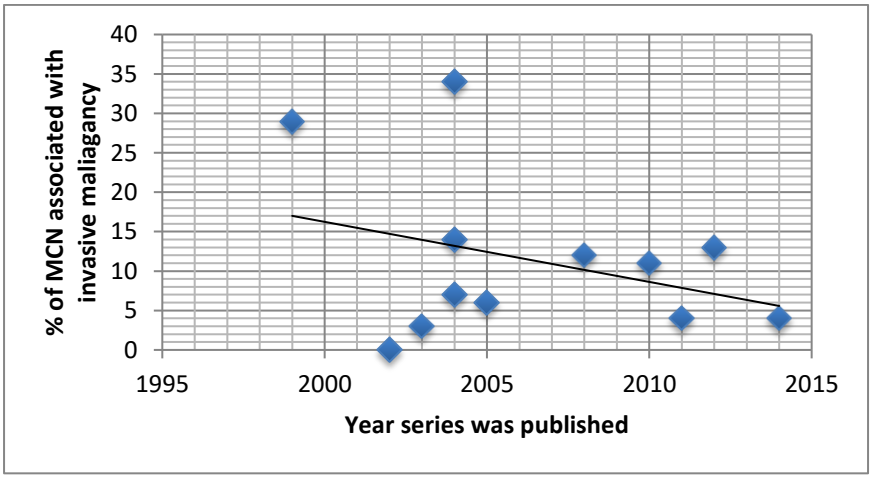


Table 1. Patient demographics and rates of associated carcinoma in situ and invasive cancer in surgically resected case series of patients with MCNs.

Author and year	Ovarian stroma present % (n)	N	Average age in years (range)	M:F	CIS or invasive cancer % (n)	Invasive cancer % (n)
Studies where MCNs were defined by the presence of ovarian stroma						
Fukushima, 1997 [7]	90% (9)	10	49 (29-61)	0:10	40% (4)	NR
*Zamboni, 1999 [8]	86% (48)	56	48 (18-78)	0:56	39% (22)	29% (16)
*Thompson, 1999 [27]	100% (130)	130	45 (20-95)	0:130	54% (70)	NR
Shimizu, 2002 [9]	100% (6)	6	53 (40–68)	0:6	33% (2)	0% (0)
Hara, 2002 [55]	100 % (5)	5	54 (36–69)	0:5	40% (2)	NR
Izumo, 2003 [10]	100% (34)	34	44 (24–81)	0:34	12% (4)	3% (1)
Kosmahl, 2004 [11]	100% (32)	32	47 (23-78)	0:32	44% (14)	34% (11)
*Reddy, 2004 [28]	100% (56)	56	48 (17–78)	1:55	11% (6)	7% (4)
Sawai, 2004 [56]	100% (8)	8	57 (33–80)	0:8	25% (2)	NR
Yeh, 2004[57]	100% (7)	7	55 (NR)	0:7	14% (1)	14% (1)
*Crippa, 2008 [18]	100% (163)	163	45 (16-82)	8:155	17% (28)	12% (19)
*Crippa 2010 [42]	100% (168)	168	45 (16-82)	8:160	17% (29)	11% (19)
*Yamao, 2011 [17]	100% (156)	156	48 (19-84)	3:153	17% (27)	4% (6)
*Baker, 2012 [58]	100% (291)	291	NR	9:282	NR	13 (38)
Park, 2014 [25]	100% (90)	90	48 (NR)	1:89	10% (9)	4% (4)
Studies which used criteria other than presence of ovarian stroma when defining MCN						
^Compagno, 1978 [1]	NR	41	49 (20–82)	6:35	46% (29)	NR
^Warshaw, 1990 [59]	NR	42	MCN: 59 (NR), MCA: 63 (NR)	10:32	64% (27)	NR
Shyr, 1996 [60]	NR	10	48 (26–72)	2:8	80% (8)	NR
Sugiyama, 1997 [61]	NR	18	52 (22–65)	7:11	67% (12)	NR
Wilentz, 1999 [62]	NR	61	56 (NR)	18:43	48% (29)	33% (20)
*^Le Borgne, 1999 [63]	NR	228	MCN: 52 (20-80) MCA: 64 (29-89)	80:148	34% (78)	NR
Scott, 2000 [64]	NR	13	53 (22–82)	3:10	77% (10)	NR
^Sarr, 2000 [54]	NR	84	MCN: 48 (19–82) MCA: 64 (NR)	14:70	NR	8.3% (7)
Shima, 2000 [65]	NR	6	51 (37–74)	0:6	33% (2)	NR
Yamaguchi, 2000 [66]	NR	21	53 (NR)	3:18	52% (11)	NR
Fujino, 2001 [67]	NR	14	51 (36–71)	5:9	57% (8)	NR
Yeh, 2002 [68]	NR	12	45 (19–70)	5:7	67% (8)	NR
*Kim, 2003 [69]	NR	15	51 (NR)	2:13	0% (0)	0% (0)
Spinelli, 2004 [70]	NR	19	NR	NR	16% (3)	NR
Goh, 2005 [71]	44% (8)	18	43 (25–73)	1:17	17% (3)	6% (1)
*Suzuki, 2004 [72]	Present in 42% (73) and indefinite in a further 37%	179 (6 cases not surgically resected)	56 (19–74)	0:179	31% (53)	NR
Allen, 2006 [73]	NR	25	NR	NR	24% (6)	12% (3)
Theruvath, 2010 [74]	NR	32	49 (NR)	2:30	16% (5)	NR

** Includes patients from more than one centre. ^: Possibly includes some cases of IPMN as well as MCN. MCN: Mucinous Cystic Neoplasm, MCA: Mucinous Cyst adenocarcinoma, CIS: Carcinoma in Situ, NR: Not recorded.*

Table 2. Clinical symptoms associated with resected MCNs where all (or a reported proportion) of lesions have been defined by the presence of ovarian-type stroma

Author and year	All MCNs: symptoms % (n)	Benign MCN: symptoms % (n)	MCA with invasion: symptoms % (n)	Symptom duration	Abdominal Pain / discomfort % (n)	Back Pain % (n)	Dyspepsia / Reflux / PUD % (n)	Abdo Mass % (n)	AP % (n)	DM % (n)	N+V % (n)	Diarrhoea % (n)	Constipation % (n)	Weight loss % (n)	Lethargy % (n)	Bleeding/ anaemia % (n)	Jaundice % (n)	Other % (n)
Fukushima 1997 [7]	50% (3/6)	60% (3/5)	0% (0/1)	NR	17% (1)	17% (1)	0% (0)	17% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	NR	0% (0)	0% (0)
Zamboni 1999 [8]	89% (50/56)	85% (29/34) (exc CIS)	95% (21/22) (inc CIS)	NR	70% (39)	0% (0)	16% (9)	7% (4)	0% (0)	0% (0)	2% (1)	0% (0)	2% (1)	10% (6)	0% (0)	NR	0% (0)	0% (0)
Thompson 1999 [27]	88% (114)	NR	NR	Few days - 34 years	72% (94)	0% (0)	2% (3)	43% (56)	13% (17)	4% (5)	18% (23)	5% (6)	0% (0)	7% (9)	0% (0)	5% (7)	2% (3) (all MCA)	Cholecystitis/ cholelithiasis 12% (16)
Hara 2002 [55]	80% (4)	67% (2) (exc CIS)	100% (2) (inc CIS)	NR	60% (3)	20% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Izumo 2003 [10]	65% (22)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reddy 2004 [28]	84% (47)	NR	NR	NR	52% (29)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	4% (24)	0% (0)	0% (0)	21% (12)	0% (0)	0% (0)	2% (1)	0% (0)
Sawai 2004 [56]	50% (4)	NR	NR	NR	13% (1)	13% (1)	0% (0)	0% (0)	0% (0)	0% (0)	13% (1)	0% (0)	0% (0)	0% (0)	13% (1)	0% (0)	0% (0)	0% (0)
Suzuki, 2004 [72]	44% (78)	36% (43)	57% (30)	NR	25% (45)	0% (0)	0% (0)	0% (0)	4% (7)	13% (23)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	Hyperamylasemia 2% (3), CLP 1% (2), CP 1% (1)
Goh, 2005 [71]	72% (13)	NR	NR	Mean: 9 months	72% (13)*	72% (13)*	0% (0)	44% (8)	6% (1)	18% (3)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Crippa 2008 [18]	73% (118)	72% (97)	75% (21)	Pain: Median 12 weeks (range: 1-102)	60% (98)	0% (0)	0% (0)	12% (20)	9% (15)	0% (0)	0% (0)	0% (0)	0% (0)	12% (19)	10% (17)	0% (0)	0% (0)	0% (0)
Crippa 2010 [42]	73% (122)	NR	NR	NR	62% (104)	0% (0)	0% (0)	0% (0)	6% (9)	6%(9)	0% (0)	0% (0)	0% (0)	16% (27)	0% (0)	0% (0)	1% (1)	0% (0)
Yamao 2011 [17]	49% (67)	46% (51)	48% (11)	NR	0% (0)	0% (0)	0% (0)	0% (0)	6% (10)	5% (7)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	Hyperamylasemia 1% (1)
Park 2014 [25]	51% (46)	52% (42)	44% (4)	NR	23% (21)	0% (0)	11% (10)	12% (11)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	4% (4)

**Abdominal and back pain symptoms recorded together, AP: Acute pancreatitis, CP: chronic pancreatitis, CLP: cystic lesion of the pancreas, MCN: Mucinous Cystic Neoplasm, MCA, Mucinous cyst adenocarcinoma, CIS: Carcinoma in Situ, DM: Diabetes Mellitus, N+V: Nausea and vomiting, PUD: Peptic ulcer disease, pts: patients, exc: excludes, inc: includes*

Table 3. Radiological features associated with benign and malignant MCNs where all (or a reported proportion) of lesions have been defined by the presence of ovarian type stroma

NR: Not recorded, LGD: MCN with low grade dysplasia, IGD: MCN with intermediate grade dysplasia, HGD/CIS: MCN with high grade dysplasia / carcinoma in situ, NR: Nor reported, N/A: Not applicable, ^: Determined by pancreatography at ERCP preoperatively, 3 cases (60%) did have a pancreatic duct connection in the resected specimen

Author and year	All MCN						Benign MCN (including CIS)					MCA with invasive cancer				
	Average size in cm (range)	Head % (n)	Body / tail % (n)	Solid component % (n)	Septations / multilocular cysts % (n)	PD communication % (n)	Average size in cm (range)	Head % (n)	Body / tail % (n)	Solid component % (n)	Septations / multilocular cysts % (n)	Average size in cm (range)	Head % (n)	Body / tail % (n)	Solid component % (n)	Septations / multilocular cysts % (n)
Fukushima 1997 [7]	7.1 (2-20)	0% (0)	100% (10)	20% (2)	20% (7)	33% (2/6)	7.1 (2-20)	0% (0)	100% (10)	20% (2)	20% (7)	7.1 (2-20)	0% (0)	100% (10)	20% (2)	20% (7)
Zamboni 1999[8]	8.4 (2-23)	7% (4)	93% (52)	20% (11)	64% (35)	0% (0)	LGD: 7 (2-23) IGD: 9.6 (3.5-18) HGD/CIS: 7.8 (5-12)	5% (2)	95% (38)	3% (1)	55% (22)	9.8 (3-18)	13% (2)	87% (13)	67% (10)	87% (13)
Thompson 1999[27]	10.6 (1.5-30)	6% (5)	94% (125)	NR	99% (128)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shimizu 2002[9]	6.5 (2–11)	0% (0)	100% (6)	NR	83% (5)	0% (0)	6.5 (2–11)	0% (0)	100% (6)	NR	83% (5)	N/A	N/A	N/A	N/A	N/A
Izumo 2003 [10]	8.4 (2.5-25)	0% (0)	100% (34)	NR	NR	17% (4/23)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reddy 2004[28]	5 (0.6-35)	7% (4)	93% (52)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kosmahl, 2004 [11]	9.8 (2.7-23)	6% (2)	94% (30)	NR	NR	0% (0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crippa 2010[42]	4.9 (0.8-15)	3% (5)	97% (163)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hara 2002[55]	9.4 (8–13)	0% (0)	100% (5)	60% (3)	100% (5)	0% (0)^	8.7 (4.5-13)	0% (0)	100% (2)	33% (1)	100% (3)	11 (8-13)	0% (0)	100% (2)	100% (2)	100% (2)
Sawai 2004[56]	4.9 (4.0–7.5)	0% (0)	100% (8)	25% (2)	88% (7)	NR	NR	0% (6)	100% (6)	17% (1)	NR	NR	0% (0)	100% (2)	50% (1)	NR
Suzuki, 2004 [72]	5.9 (0.18-23)	19% (32)	81% (125)	28% (48)	NR	12% (22)	5.4	NR	NR	NR	NR	7.2	NR	NR	NR	NR
Goh, 2005 [71]	9.1 (3-18)	0% (0)	100% (18)	NR	NR	0% (0)	8.5 (NR)	0% (0)	100% (NR)	27% (4)	NR	14.0 (NR)	0% (0)	100% (3)	100% (3)	NR
Crippa 2008[18]	5.0 (0.8-15.0)	3% (5)	97% (158)	15% (24)	38% (62)	0% (0)	4.5 (0.8-15)	4% (5)	96% (130)	4% (6)	37% (50)	8 (2-13)	0% (0)	100% (28)	64% (18)	43% (12)
Yamao 2011[17]	6.5 (1-26)	1% (1)	99% (155)	27% (42)	NR	18% (25)	6 (NR)	1% (1)	99% (128)	22% (28)	NR	9 (NR)	0% (0)	100% (27)	52% (14)	NR
Park 2014[25]	6.4 (NR)	12% (11)	88% (79)	10% (6)	56% (35)	5% (3)	6.6 (NR)	6% (5)	94% (76)	5% (3)	57% (33)	5.5 (NR)	11% (1)	89% (8)	60% (3)	40% (2)

Table 4. Survival and recurrence in benign and malignant MCNs where all (or a reported proportion) of lesions have been defined by the presence of ovarian type stroma

Author and year	Benign mucinous cystic neoplasm (MCN)					MCA with CIS or invasive cancer				
	N	Average age in years (range)	5 year survival	Recurrence	Average follow-up in months (range)	N	Average age in years (range)	5 year survival	Recurrence	Average follow up in months (range)
Fukushima 1997 [7]	6	53 (48-61)	NR	0	80 (36-187)	4	44 (29-51)	NR	1 – DOD	161 (20-257)
Zamboni 1999 [8]	40	45 (18-73)	NR	0	**LGD:** 43 (4-114) **IGD:** 70 (9-180)	22 (6 with CIS)	**MCN + CIS:** 50 (27-78) **Invasive MCA:** 56 (27-78)	NR	**MCN + CIS:** 0/6 **Invasive MCA:** 8 /16– All DOD at 2, 3, 4, 10, 12, 25, 27, 45 months (Median: 11 months).	23 (2-134)
Hara 2002 [55]	3	50 (36-65)	NR	0	57 (34-77)	2	61 (52-69)	NR	**MCN+CIS:** 0/1 **Invasive MCA:** 1 /1– DOD at 12 months	54 (12-96)
Shimizu 2002 [9]	4	NR	NR	0	57 (6-124)	2 (both with CIS)	N/A	NR	**MCN+CIS:** 0/2	13 (15-80)
Izumo, 2003 [10]	30	NR	NR	0	62 (2-238)	4	NR	NR	2 – both DOD	73 (4-245)
Reddy, 2004 [28]	50	NR	NR	0	(All MCNs: 15(1-203))	6 (2 with CIS)	**Invasive MCA:** 51 (37-67)	NR	**MCN+CIS:** 0/2 **Invasive MCA**: 3/4– all DOD	(All MCNs: 15(1-203))
Sawai, 2004 [56]	6	NR	NR	0	(All MCNs: 42 (4-95))	2	NR	NR	1 - DOD	(All MCNs: 42 (4-95))
Suzuki, 2004 [72]	118	52 (19-8)	100%	0	NR	53	61 (61-85)	**MCN+CIS:** 100% **Invasive MCA:** 38%	11 – all DOD	NR
Goh, 2005 [71]	17	NR	NR	0	(All MCNs: 15 (0-63))	3 (2 with CIS)	NR	NR	**MCN+CIS:** 0/2 **Invasive MCA:** 0/1	(All MCNs: 15 (0-63))
Crippa, 2008 [18]	135	44 (16-79)	**Non-invasive MCN:** 100%	0	(All MCNs: 57 (4-204))	28 (9 with CIS)	50 (27-82)	**Invasive MCA:** 57%	**MCN + CIS:** 0/9 **Invasive MCA:** 7/19 (37%) - all DOD 6.5 months (range 2-17) after diagnosis. Mean recurrence occurred at 32.5 months (range, 4 – 99)	(All MCNs: 57 (4-204))
Crippa, 2010 [42]	149	NR	**Non-invasive MCN:** 100%	0	(All MCNs: 50 (2-233))	29 (10 with CIS)	NR	**Invasive MCA:** 58%	**MCN + CIS:** 0/10 **Invasive MCA:** 7/19 (37%) - all DOD 6.5 months (range 2-17) after diagnosis. Mean recurrence occurred at 32.5 months (range, 4 – 99)	(All MCNs: 50 (2-233))
Yamao, 2011 [17]	129	48 (NR)	99%	0	NR	27 (21 with CIS)	51 (NR)	**MCN + CIS or invasive cancer:** 87% **Invasive MCA:** 0%	**MCN+ CIS:** 1/21 – DOD (possibly due to leakage of cyst contents) **Invasive MCA:** 2/6 – DOD	NR
Park, 2014 [25]	86	48 (NR)	NR	NR	40.5 (NR)	9 (5 with CIS)	47 (NR)	**MCN+ CIS:** 75% **Invasive MCA:** 75%	**MCN+CIS:** 0/5 **Invasive MCA:** 1/4	37.9 (NR)

MCN: Mucinous Cystic Neoplasm, MCA: Mucinous Cystadenocarcinoma, DOD: Died of disease, CIS: Carcinoma in Situ, NR: Not recorded

CHAPTER 2

MULTICENTRE STUDY OF 211 RESECTED MCNS

INTRODUCTION

Pancreatic mucinous cystic neoplasms (MCN) have been defined by the World Health Organisation from 2000 as well-demarcated cystic lesions, lined by a mucin-producing columnar epithelium overlying an ovarian-type stroma[1-3]. Although MCNs are relatively rare tumours, the overall incidence of Pancreatic Cystic Neoplasms (PCN) is increasing[4-6]. MCNs are estimated to account for between 10-45% of all resected PCN[7,8].

Although MCNs are classified as neoplastic lesions[9] their actual malignant potential remains uncertain, with rates of associated invasive cancer ranging anywhere between 0 and 34% in the current literature[10]. Associated malignancy was substantially higher in older studies, but these series included many larger lesions and lesions classified prior to the latest WHO pathological criteria for MCN, so may have inadvertently incorporated a proportion of intraductal papillary mucinous neoplasms (IPMNs), potentially explaining the higher rates of malignancy seen[11]. More recent series, although often describing a single centers experience, suggest that malignant transformation in MCN may be a much rarer finding, especially when the tumours are small in size (<4cm)[12-16].

The current management of a PCN is defined by a number of consensus guidelines from the International Association of Pancreatology (IAP)[17], Europe[18], and the American Gastroenterology Association[19]. The IAP and European guidelines specifically mention the management of MCN and both stipulate that where the diagnosis is certain and the patient is an operative candidate then surgical resection should be performed. Within the European consensus statement on cystic lesions of the pancreas, there is a proviso that where the diagnosis is uncertain and there are no associated worrisome features and the lesion is less than 4cm, then management of a MCN as a branch duct IPMN, with surveillance may be appropriate. However, to date very few studies have described the natural history of small MCNs to support this management strategy.

As the guidelines for MCN to date, have primarily advocated surgical resection, very few studies have described which worrisome features would predict malignant transformation if these lesions were to be surveyed. With the exception of a single multi-institution US study, worrisome features in MCN have been drawn from small singe centre experiences or extrapolated from findings in IPMN. Further large patient cohorts that have undergone careful classification and long-term follow up are therefore needed to better inform the natural history and optimal criteria for surgical resection in these lesions.

The aims of this large multi-institution study are to determine the rate of associated malignancy in resected MCNs and to determine predictor features, clinical and radiological, for malignant transformation in MCN.

PATIENTS AND METHODS

Setting and study design: A multicentre retrospective study from nine pancreatic centres from across Europe.

Inclusion criteria: In each centre all patients who had a MCN resected between January 1st 2003 and December 31st 2015 were included in the study. Cases were identified though individual unit's pancreatic cyst databases, multidisciplinary team meeting records and pathology records.

Exclusion Criteria: After a local review of the pathology report any patients with an MCN without ovarian-type stroma were excluded from the study.

Data Recorded: For each patient, the medical records were reviewed in each centre and the following information, where available, was recorded in the study spreadsheet: name of hospital, gender, age at diagnosis and medical history (score of the American Society of Anaesthesiology (ASA score), diabetes, smoking, previous pancreatic disease, previous cancer, family history of cancer). Any associated symptoms were also recorded and an MCN was defined as symptomatic when identified on imaging performed for the evaluation of abdominal or back pain, obstructive jaundice, acute/recurrent pancreatitis or any documented history of recent weight loss. The following preoperative blood tests, when available, were recorded; amylase, serum carcinoembryonic antigen (CEA; normal range <4.0 ng/mL), serum carbohydrate antigen 19-9 (CA 19-9; normal range <37 U/mL).

Radiological data recorded included type of scan; ultrasound, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), fine needle aspiration (FNA). From the cross-sectional imaging (CT or MRI/MRCP), the following features were recorded including lesion size (maximal dimension), location and number of cystic lesions, presence of a solid component (mural nodules, solid component, calcification of the cyst or the wall, wall thickening), presence of septations, features of acute or chronic pancreatitis, and dilatation of the pancreatic duct to >6mm or biliary tree. For patients undergoing EUS-FNA, cytology and biochemistry (CEA and Amylase) results were also recorded. Operative details recorded included date of surgery and type of resection, post-operative adverse events (according to Clavien-Dindo grading), 30-day mortality, final histology, length of follow-up (time from surgery to the last MCN-related or other relevant outpatient appointment), follow-up imaging data and evidence of recurrence.

Histopathological analysis. The diagnosis of an MCN was confirmed locally in each centre. Presence of ovarian type stroma was considered mandatory for the diagnosis and inclusion in the study. In cases where the original report was inconclusive and in all male patients a second review by an experienced local pancreatic pathologist was undertaken to confirm the diagnosis. Dysplasia was classified in accordance with the most aggressive histological epithelial changes as defined by the World Health Organisation (WHO) classification system[9]. Tumours were graded as having low or intermediate grade dysplasia, high-grade dysplasia including carcinoma in situ, and malignant when invasive carcinoma was present[9].

Statistics. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc.,Chicago, IL, USA). In the tables, "n" indicates the number of patients with available data. Chi-square or Fisher's exact test was applied for analysis of categorical variables. Median values and inter-quartile ranges were considered for continuous variables. The non-parametric Manne-Whitney test was used to compare continuous variables. Multiple logistic regression models were used to identify independent factors for malignant transformation. Long-term survival was analysed using Kaplan Meier. Two-tailed p value of less than 0.05 was considered to be significant.

RESULTS

Two hundred and eleven (211) patients with a histologically confirmed surgically resected MCN were included in the study. Median age at the time of surgery was 53 (range 18–82) years and 95.7% (202/211) were women. 63% were considered symptomatic and in 37% the MCN was an incidental finding. 89.6% patients had a CT scan, with the remainder having an MRI/MRCP. 28.4% patients had both a CT and MRI. Pre-operatively, the median tumor size was 55 (range 12-230) mm and an MCN was suspected in 49.7%, an IPMN in 11.6% and the lesion remained indeterminate in 38.8%. Mural nodules were present in 23.4%, cyst wall calcification in 18.8% and septations in 52.9% of the cases. In 8.8% the diameter of the main pancreatic duct was ≥6 mm [Table1]. 39% patients had an EUS and a fine needle aspiration was performed in 28%. Cytology had a sensitivity, specificity, PPV and NPV of 66.67%, 98.11%, 66.67%, 98.11% respectively for malignant transformation.

A distal pancreatectomy was performed in 82.9%, pancreatico-duodenectomy in 8.5% and an enucleation in 4.3%. 30-day morbidity was 0.9% with a 30-day morbidity of 37.9%; Clavien-Dindo Grade 1 in10.4%, Grade 2 in15.2%, Grade 3 in 9.5%, Grade 4 in 1.9% and Grade 5 in 0.9% of patients.

The median resected tumor size was 55.5 (range 20-300) mm. Invasive cancer was present in 16.1% (34/211), with high-grade dysplasia (HGD) seen in a further 6.2% (13/211) of patients. For patients with invasive MCN cancer, the tumour was classified as stage Ia in 9 (26.5%) patients, stage Ib in 8 (23.5%), stage IIa in 6 (17.6%), stage IIb in 6 (17.6%) and stage III in 5 (14.7%) patients. An R0 resection was achieved in 58.8% (20/34) of the cases.

Malignant transformation was associated with presence of symptoms (88.2 vs 58.2%; p=0.001), especially those presenting with pancreatitis (26.5 vs 9.6%; p=0.018), jaundice (20.6 vs. 1.7%; p<0.0001), or who had significant weight loss (32.3 vs. 6.2%; p<0.0001), and had elevated serum CA19-9 (68.8 vs 16.0%; p<0.001) [Table 2].

The rate of invasive cancer correlated with increasing tumour size [Figure 1a]. In lesions greater than 12 cm the rate invasive cancer was 45.8% compared to just

10% in lesions less than 4 cm and 5% in lesions less than 3 cm. Five cases of invasive cancer occurred in patients less than 4cm in size and like all cases of invasive malignancy in this study, they were all associated with at least one pre-operative feature of concern [Table 4]. When stratified by sex the rate of malignancy in lesions less than 4cm in female patients decreased to 2.9% (HGD 5.9%) compared to 25% in men (HGD 25%) [Figure 1b and c].

On univariate analysis, we found that, presence of symptoms, previous pancreatitis, jaundice, raised Ca19-9, recent weight loss, tumour size, and mural nodules were associated with invasive cancer. On multivariable analysis, weight loss (OR 2.703; 95% CI 1.501–14.569, p=0.004), raised CA19-9 (OR 10.874; 95% CI 1.888–24.533, p<0.001), tumour size (OR 1.019; 95% CI 1.003–1.035, p=0.020) and mural nodules (OR 6.856; 95% CI 1.302–36.111, p=0.023) were found to be independent factors of malignant transformation. The model was a good predictor of malignant transformation with Nagelklerke R Square value of 0.711 [Table 3].

Median survival for patients with a malignant MCN was 44 months (range 0-167 months), 12 patients died during the follow up; 10 from disease recurrence. Although not significant, the survival trend was also worse in male patients than female patients (Figure 2).

DISCUSSION

MCNs are neoplastic cystic tumours of the pancreas, which have the potential to evolve into an invasive cancer. They have been classified separately from IPMNs by the World Health Organization (WHO) since 1996[2], and the Armed Forces Institute of Pathology (AFIP) from 1997[3]. In this large cohort of patients, resected after the introduction of the new pathological classification of MCN, the overall rate of associated invasive cancer was low; 16.1% compared to up to 34% in some earlier publications[10]. Rates of HGD were lower than in other singles centre series[12,16,20] at 6.2% but similar to the rate found in a recent multicentre study from North America[21].

In real life, differentiating small MCN from other uni- and oligocystic tumors (i.e. branch duct-IPMN and serous cystadenoma) remains a significant clinical challenge, as to date features which predict invasive malignancy in MCN have been

poorly characterised and often overlap with other cystic lesions of the pancreas[14]. The pre-operative uncertainty in defining these lesions was clearly reflected in this study with less then 50% of MCNs being correctly classified prior to resection. Current guidelines are clear and consistent when the diagnosis of MCN is certain, recommending surgical resection. However when the pre-operative diagnosis is less clear, as in a large proportion of cases in this study the European guidelines, have suggested that if the lesion is small in size (<4cm) and is without worrisome feature, then a period of surveillance may be appropriate to better define the diagnosis prior to surgery, however few studies have explored the natural history of MCN to support the safely of this proposed management strategy[18]. Over time the size at which MCNs are detected has decreased. In these small lesions features of concern are often absent, so cyst diameter has remained the most important radiologic predictor of malignant transformation. At what size patients should be referred for surgical resection in MCN remains uncertain. As part of this large cohort study we therefore compared the rate of invasive malignancy and HGD of different size lesions. Invasive cancer occurred in 9.8% in lesions less than 4cm and 5.3% less than 3cm. In the five cases of invasive cancer in lesions less than 4cm, like with all cases of cancer or HGD in this study, at least one pre-operative worrisome feature was present to prompt surgical management. When stratified by sex the rate of associated invasive cancer in women with lesions less than 4cm was 5.5% and in lesions less than 3cm was just 2.9%. Although this is retrospective data drawn from surgically resected cases and will need to be confirmed by prospective surveillance studies, these finding do support the conservative management of MCN advocated by the European guidelines, particularly in women with suspected MCNs without worrisome features that are small in size (<4cm). Low rates of malignant transformation in small MCN without worrisome features has been observed in other case series[12,16,20,22-25]. Which features other than size, that predicts malignant transformation in MCN, has often been poorly defined and extrapolated from mixed PCN cohorts. Therefore, in the second part of this study we aimed to better define worrisome feature for this lesion. On multivariate analysis, apart from lesion size, we found that raised Ca 19-9 and solid component were predictive of invasive cancer. MCN differ from other PCN, predominantly occurring in female patients.

Whether MCNs, defined by the presence of ovarian-type stroma, can even occur in male patients has been debated[26], but a number of case reports in male patients have been reported[12,16,20]. In this study with careful pathological characterization, just 4.3% occurred in men, one of the lowest rates reported to date. Rates of invasive caner and high-grade dysplasia were also more common in men than women and appeared to occur at an earlier stage when the lesions were still small in size, [Table 2]. Surgical resection should therefore always be considered in male patients with a suspected MCN. In addition to tumour size this study also found that a raised CA 19-9 and solid component were also independent predictors of invasive cancer. Other case series and multicentre studies have also suggested CA19-9 as risk factor for malignancy in MCN.(16, 21) A solid component or the presence of a mural nodule has also been consistently identified by a number of studies and suggested as the most reliable factor to predict malignancy in MCN[12,14,16,22,25,28,29]. This data in addition to defining which cases of MCN can be safely surveyed when the pre-operative diagnosis is unclear, also allows us to define a cohort of patients who may be suitable for non-radical resection or emerging ablative techniques. It also allows us to better quantify actual risk of malignancy in patients who are unfit for surgery or who refuse surgery for any reason. The median survival of patients with a malignant MCN in this study was 44 months (range 0-167 months) which is similar to other types of malignant PCN and superior to pancreatic ductal adenocarcinoma[8]. However, a trend towards worse survival was also observed in male patients, which was somewhat unexpected and perhaps further supports the apparent aggressive nature of MCN in male patients. In other female predominant PCN such as solid pseudopapillary tumours, male patients have also been observed to have a poorer prognosis[27].

Strengths and Limitations. This study has several strengths, it analyses a large cohort of carefully characterized patients with a pathologically confirmed MCN, where ovarian-type stoma was present in all cases. The dataset includes comprehensive demographic, clinical, radiological, surgical, pathological and follow-up data, which has allowed us to better define features, which predict malignant transformation. Potential limitations include that most cases have been recruited from tertiary referral centres, so the proportion of high-risk lesions and

malignant cases may be higher. Large community based cohorts and surveillance cohorts of PCN have reported much lower incidences of associated malignancy[29]. However, without being able to pathologically define MCN lesions it would be impossible to carry out this study in this group. Some patients included in the study, may have been included in previously reported case series.

CONCLUSION

In conclusion, in female patients in this large multicentre study, malignancy or HGD was solely seen in MCNs with symptoms or worrisome features on preoperative imaging, regardless of the size of the tumour. In males, the risk of malignancy was significantly higher than in females, suggesting that operative treatment should be considered in all male patients with a suspected MCN of any size. In female patients conservative management seems to be a safe approach for suspected MCNs of any size without symptoms or worrisome features.

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TABLES AND FIGURES

Table 1. Characteristics and radiological features of study cohort.

	%	N
Demographics and clinical symptoms		
Sex		
• Male	4.3	9/211
• Female	95.7	202/211
Age, *years* median (interquartile range)		53 (43-63)
BMI, median (interquartile range)		25 (23-29)
Presence of symptoms	63.0	133/211
• Abdominal pain	46.0	97/211
• Acute or recurrent pancreatitis	12.3	26/211
• Weight loss	10.4	22/211
• Jaundice	4.7	10/211
Pre-operative radiological features		
Location		
• Head/uncinate	10.9	23/211
• Body	27.5	58/211
• Tail	55.9	118/211
• Missing data	5.7	12/211
Tumour size, mm median (interquartile range)		55 (30-91)
Mural nodules	23.4	37/158
Cyst wall calcifications	18.8	32/170
Dilated main pancreatic duct	8.8	14/159
Septations	52.9	83/157
Suspected pre-operative diagnosis		
• MCN	49.7	73/147
• IPMN	11.6	17/147
• Uncertain	38.8	57/147
Surgery performed and outcomes		
Type of surgery		
• Distal pancreatectomy	82.9	175/211
• Pancreatico-duodenectomy	8.5	18/211
• Enucleation	4.3	9/211
• Other*	4.3	9/211
30-day adverse events	37.9	80/211
Peri-operative 30-day mortality	0.9	2/211
Presence of invasive cancer	16.1	34/211

* Includes total pancreatectomies and multi-visceral resections. BMI Body Mass Index.

Table 2. Features of benign and malignant MCN stratified by sex.

	All patients (n=211)			Female (n=202)			Male (n=9)		
	Patients with invasive cancer (n = 34)	**Patients with benign disease including HGD (n=177)**	**p value**	**Patients with invasive cancer (n = 31)**	**Patients with benign disease including HGD (n=171)**	***p value***	**Patients with invasive cancer (n=3)**	**Patients with benign disease including HGD (n=6)**	***p value***
Risk factors, clinical symptoms and serum tumour markers									
Male	3 (8.8)	6 (3.4)	0.161						
Age, *years* median (interquartile range)	55 (44-66)	52 (43-62)	0.349	53 (43-64)	51 (43-61)	0.565	68 (64-68)	70 (60-79)	0.905
Smoking	5 (35.7)	29 (29.3)	0.765	3 (25.0)	27 (28.7)	1.000	2 (100)	2 (40)	0.429
BMI, median (interquartile range)	25 (23-28)	26 (23-29)	0.732	25 (23-29)	25 (23-30)	0.943	24 (22-24)	27 (24-28)	0.250
Diabetes mellitus	1 (3.3)	14 (8.5)	0.475	1 (3.7)	12 (7.5)	0.696	0 (0.0)	2 (33.3)	0.50
Presence of symptoms	30 (88.2)	103 (58.2)	**0.001**	27 (87.1)	98 (57.3)	**0.001**	3 (100.0)	5 (83.3)	1.000
Jaundice	7 (20.6)	3 (1.7)	**<0.001**	5 (16.1)	2 (1.2)	**0.001**	2 (66.7)	1 (16.7)	0.226
History of pancreatitis	9 (26.5)	17 (9.6)	**0.018**	8 (25.8)	15 (8.8)	**0.012**	1 (33.3)	2 (33.3)	1.000
Recent weight loss	11 (32.4)	11 (6.2)	**<0.001**	8 (25.8)	10 (5.8)	**0.002**	3 (100.0)	1 (16.7)	**0.048**

Raised serum Ca19-9	11 (68.8)	13 (16.0)	**<0.0001**	9 (69.2)	13 (16.9)	**<0.001**	2 (66.7)	0 (0.0)	0.143
Cross-sectional imaging features									
Size of tumour, mm median (interquartile range)	100 (45-131)	52 (30-85)	**0.001**	111 (54-133)	52 (30-86)	**<0.001**	30 (28-30)	33 (17-49)	0.714
Mural nodules	12 (60.0)	25 (18.1)	**<0.001**	10 (58.8)	22 (16.5)	**<0.001**	2 (66.7)	3 (60.0)	0.741
Dilation of the main pancreatic duct	4 (21.1)	10 (7.1)	0.067	3 (18.8)	7 (5.2)	0.074	1 (33.3)	3 (60.0)	1.00
Septations	12 (57.1)	71 (52.2)	0.815	10 (55.6)	70 (53.4)	1.000	2 (66.7)	1 (20.0)	0.464
Cyst wall calcification	7 (35.0)	25 (19.4	0.142	6 (35.3)	24 (19.4)	0.201	1 (33.3)	1 (20.0)	1.000
Head location	7 (20.6)	16 (9.0)	0.067	4 (12.9)	13 (7.6)	0.304	3 (100)	3 (50)	0.464
CBD dilatation	4 (18.2)	4 (3.0)	**0.014**	2 (10.5)	3 (2.3)	0.122	2 (66.7)	1 (20.0)	0.464

Data are presented as absolute number (percentage) unless otherwise indicated. BMI Body Mass Index CBD Commune Bile Duct.

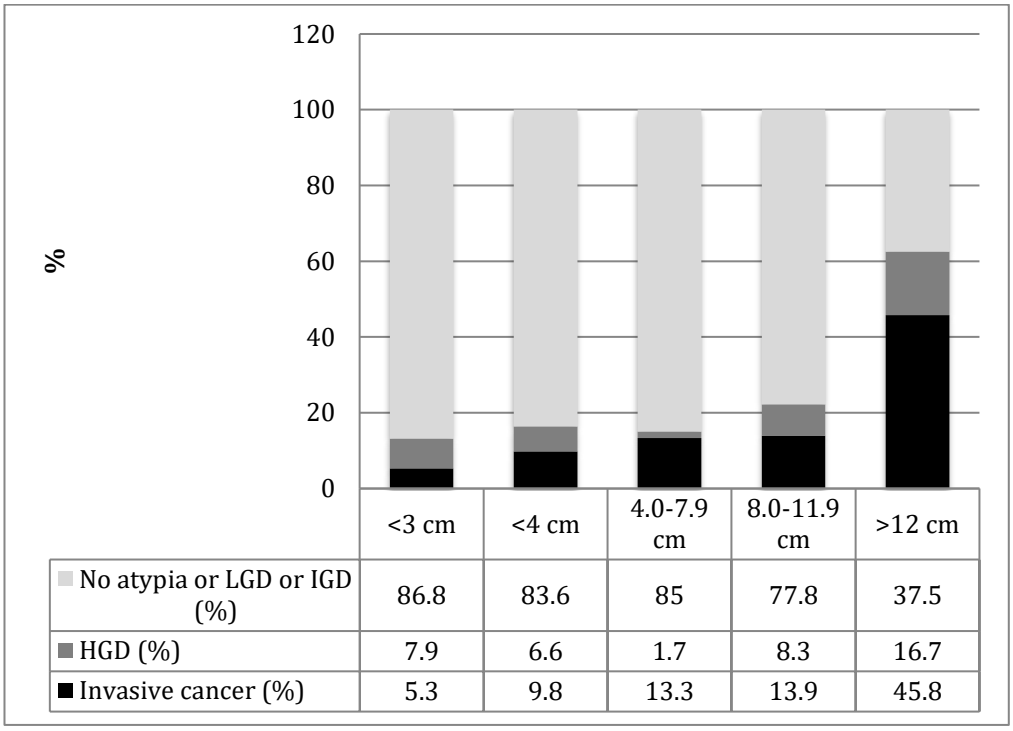
Table 3. Binary Logistic Regression of Preoperative Risk Factors for invasive adenocarcinoma in mucinous cystic neoplasms

Variable	**Univariate analysis**		**Multivariate analysis**	
Clinical features	**OR (95% CI)**	***p value***	**OR (95% CI)**	***p value***
Male gender	2.758 (0.655-11.615)	0.167		NS
Symptomatic	5.388 (1.820-15.949)	**0.002**		NS
History of pancreatitis	3.388 (1.362-8.428)	**0.009**		NS
Jaundice	15.037 (3.664-61.712)	**<0.001**		NS
Weight loss	7.217 (2.812-18.526)	**<0.001**	2.703 (1.501-14.569)	**0.004**
Serum Ca19-9	11.508 (3.424-38.677)	**<0.001**	10.874 (1.888-24.533)	**<0.001**
Median size (mm)	1.017 (1.008-1.026)	**<0.001**	1.019 (1.003-1.035)	**0.02**
Tumour location: Head of pancreas	2.609 (0.982-6.932)	0.054		NS
Solid component	6.780 (2.509-18.319)	**<0.001**	6.856 (1.302-36.111)	**0.023**
Dilation of main pancreatic duct	3.467 (0.967-12.428)	0.056		NS

Table 4. Age, sex, worrisome features associated with invasive MCNs of less than 4cm

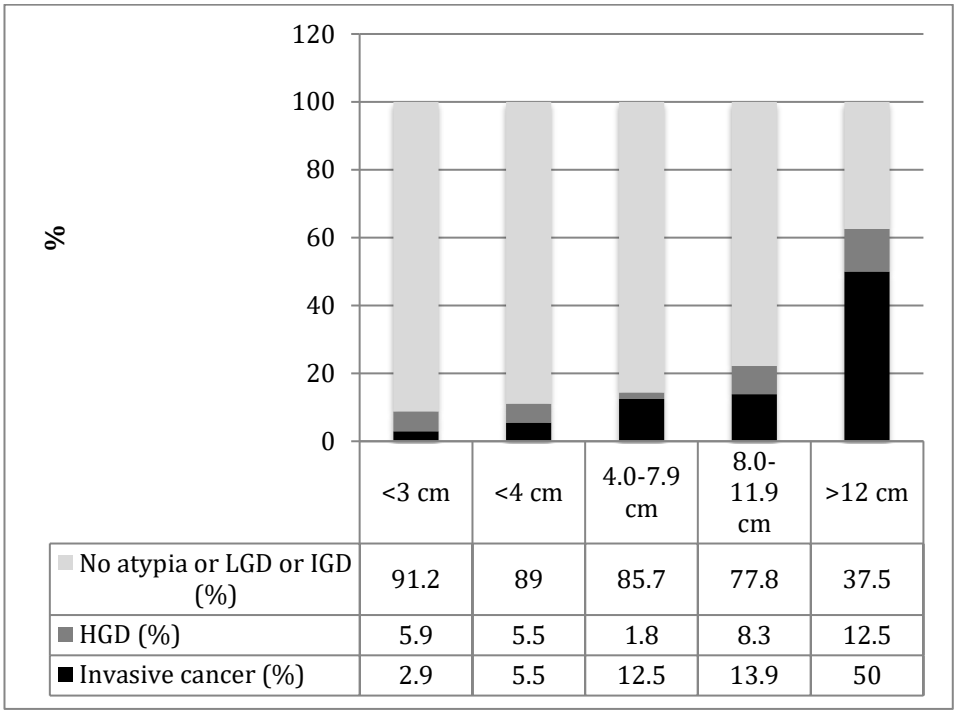
	Age	Sex	Tumour size	Worrisome features
Case 1	74	F	33	Symptoms, raised Ca 19-9, dilated main PD
Case 2	70	M	28	Symptoms, raised Ca 19-9, mural nodules, cyst wall calcification, septations
Case 3	37	F	35	Symptoms, mural nodules
Case 4	64	M	30	Symptoms, raised Ca 19-9, septations, dilated CBD
Case 5	65	F	16	Symptoms

Figure 1a. Prevalence of invasive cancer at different tumour sizes



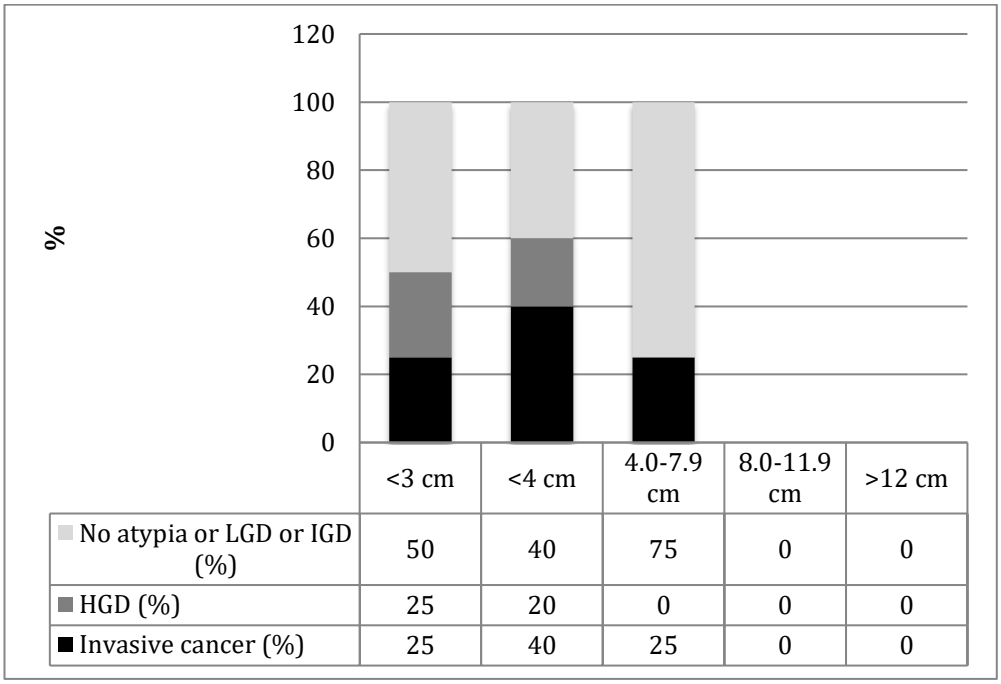
	<3 cm	<4 cm	4.0-7.9 cm	8.0-11.9 cm	>12 cm
No atypia or LGD or IGD (%)	86.8	83.6	85	77.8	37.5
HGD (%)	7.9	6.6	1.7	8.3	16.7
Invasive cancer (%)	5.3	9.8	13.3	13.9	45.8

Figure 1b. Prevalence of invasive cancer at different tumour sizes in women



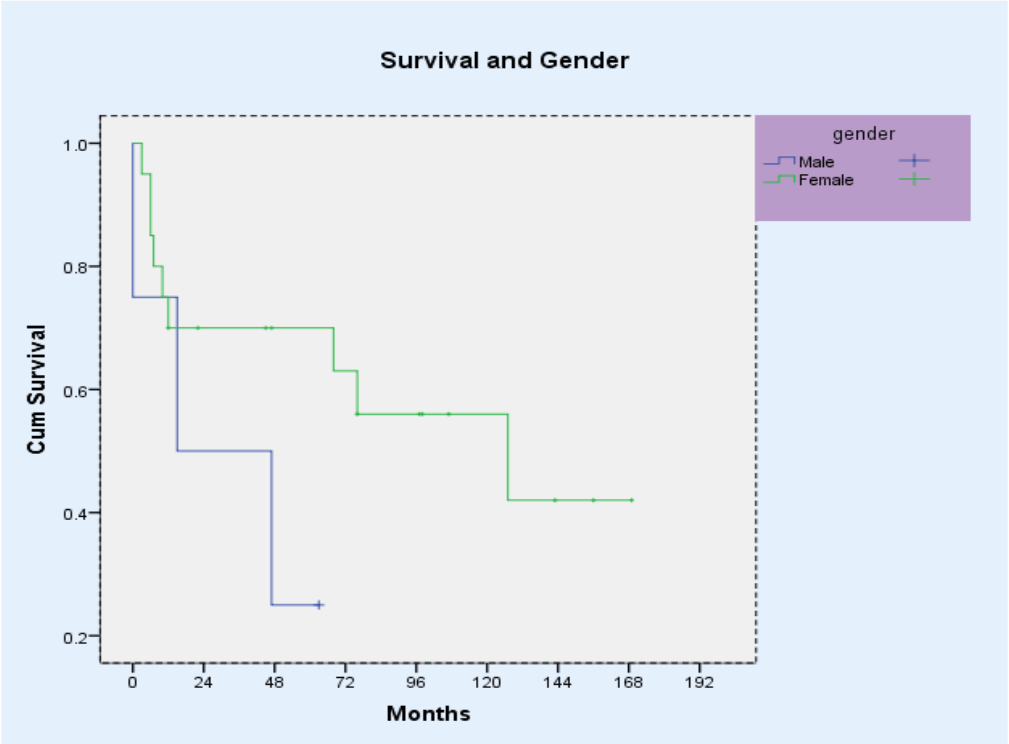
	<3 cm	<4 cm	4.0-7.9 cm	8.0-11.9 cm	>12 cm
No atypia or LGD or IGD (%)	91.2	89	85.7	77.8	37.5
HGD (%)	5.9	5.5	1.8	8.3	12.5
Invasive cancer (%)	2.9	5.5	12.5	13.9	50

Figure 1c. Prevalence of invasive cancer at different tumour sizes in men



	<3 cm	<4 cm	4.0-7.9 cm	8.0-11.9 cm	>12 cm
No atypia or LGD or IGD (%)	50	40	75	0	0
HGD (%)	25	20	0	0	0
Invasive cancer (%)	25	40	25	0	0

Figure 2. Kaplan-Meier curve for patients undergoing surgical resection for invasive MCNs in men and women (n=34).



CHAPTER 3

MCNS AND PREGNANCY

INTRODUCTION

Mucinous Cystic Neoplasms (MCN) of the pancreas are neoplastic cysts lined by mucin-producing columnar epithelium and a distinctive ovarian-type stroma (OS) underlying it, as a characteristic histological feature [1,2]. Nowadays, they are being diagnosed with increasing frequency due to the aging population and the widespread of cross-sectional imaging[3,4], but few studies have been performed investigating their true incidence or prevalence. Some papers show that they account between 10-45% of all resected pancreatic cystic neoplasms (PCN), and together with IPMN (Intraductal Papillary Mucinous Neoplasms), they represent the majority of neoplastic cysts of the pancreas.[5-7] MCN occur almost exclusively in women (98-99.7%; female: male ratio 20:1), usually in peri-menopausal period (women aged 40-60 years), with the incidence peak in the 5th decade.[8,9] They are almost always located in the pancreatic body or tail (93%), without communication to pancreatic ducts. They use to be asymptomatic lesions, often found incidentally. The female predominance, presence of ovarian stroma, and estrogen (ER) and/or progesterone hormone receptors (PR), are findings that strongly suggest an hormonal dependence, but this relationship still remains unclear.[10,11] In fact, similar mucinous cystic tumors have been found in other organs, like the Hepatobiliary Cystadenoma or Cystadenocarcinoma and Mixed Epithelial and Stromal Tumor of the kidney (MEST) described almost exclusively in women and with a characteristic OS[10,12]. It is widely known that pancreatic MCNs always carry malignant potential, but real data are unknown, with reported rates of malignancy between 4-34%.[13] Nevertheless, latest single centre case-series[14-17] and clinical practice suggest that the majority of them are benign cysts with slow growth (less than 1cm per year), and with an excellent prognosis, even when High Grade Dysplasia (HGD) is present, in the absence of invasive disease.[6,18,19] This

uncertainty surrounding their natural history makes surgical criteria differ among different consensus guidelines.[20-22]

A special and extremely rare circumstance is the diagnosis of MCN during pregnancy, and nowadays it represents a huge clinical challenge. A growing number of papers reporting such cases are appearing during last years, and they seem to show a certainly different behaviour when these tumors develop in pregnant women, with a possible role for female sex hormones in a faster tumorigenesis and malignant transformation that remains unclear. Besides, pre-surgical diagnostic process is limited to non-ionizing imaging techniques such as abdominal ultrasound or MRI and invasive techniques like EUS are not always recommended (EUS), so the evidence of invasive malignancy can be frequently inconclusive in the moment of diagnose. The risk of severe associated complications, Foetal Intrauterine Growth Restriction or rupture of the cyst related to Valsalva during vaginal delivery are other uncertainties that remains unknown. In this context, best time for surgery is also unclear, being the most important goal minimal maternal and foetal risk.

In conclusion, to date there is no evidence enough to suggest the correct rules for the management of MNCs associated with pregnancy. The aim of this chapter is to establish a management protocol by analysing 3 cases from our clinical experience and all cases reported in the literature, drawing on demographic, diagnostic, therapeutic and prognostic data.

Case 1. Zaragoza, Spain. February 2008

A 37-year-old woman gravida1-para1 was referred to our department after being operated by laparoscopy in relation to ectopic pregnancy (10th week of pregnancy). During surgery, a cystic tumor of 8cm was discovered in the pancreatic tail. Abdominal Ultrasound performed 2 months before didn´t show any abnormal finding. Abdominal Ultrasound and Abdominal C after surgery, showed a large (80 x 60 cm), well circumscribed hypoechoic cystic tumor at the upper left abdominal quadrant, with no mural nodules inside de cyst. The final diagnose of pancreatic mucinous cystadenoma was established. Despite its size, patient didn´t mention any complaint or clinical sign and abdominal palpation was normal. Serum analysis

including levels of tumor markers (CEA, Ca 19-9), Amylase, and all other blood laboratory determinations were within normal limits.45 days after laparotomy, resection of the tumor with distal pancreatectomy was performed. Because no sign of invasion was observed, the spleen was preserved. Histology showed a columnar mucinous epithelium lining the inner walls of the cystic tumor, without atypia or abnormal mitotic activity and with an OS under it. The diagnosis was benign MCN, with tumor-free margins and nonaffected lymph nodes (R0 Resection). Immunohistochemistry for ER) and/or PR was not developed. The annually follow up didn`t show any recurrence and the patient has been asymptomatic during the follow up period.

Case 2. Tampere, Finland

A 28 years old women, had abdominal pain secondary to acute pancreatitis during the first trimester of her pregnancy. An Us scan showed a big pancreatic mass to the tail of the pancreas. MRI scan confirmed the presence of 8 cm mass associated with mural nodules. The diagnosis of symptomatic MCN associated with radiological features of malignancy was made. Following MDT, the plan for distal pancreatectomy during the second trimester was concorded. The patient had a distal pancreatectomy as planned. he had normal post-operative course without any complication. The histology showed MCN with high grade dysplasia. She had a vaginal delivery at 42 weeks without any complications. The annually follow up didn`t show any recurrence and the patient has been asymptomatic during the follow up period.

Case 3. Southampton, Great Britain

A 23-year-old woman had back and epigastric pain during her pregnancy. Abdominal Us scan showed pancreatic cyst in the tail (no size was mentioned). Never had pain before. The patient didn`t attend her clinical appointments for further investigations. 1 years later, the patient came back to the clinic for abdominal pain. She was extensively investigated by; abdominal Us scan, Ct scan, MRCP and EUS which showed 6x7 cm cystic mass at the pancreatic tail. The

diagnosis of Mucinous cystadenoma was established. In presence of symptoms and the size of the lesion, the decision for distal Pancreatectomy was made. She had normal post-operative course without any complication. The histology showed a columnar mucinous epithelium lining the internal wall of the cyst, with an ovarian type Struma, absence of cancer. The diagnosis of benign MCN was made. Immunohistochemistry for estrogen and/or progesterone receptors was not done. The annually follow up didn`t show any recurrence and the patient has been asymptomatic during the follow up period.

MATERIAL AND METHODS

In addition to our 3 cases identified in our multicentre database, covering operated MCNs between 2003-2015, a literature search (PubMed database, Embase, Cochrane Library) for articles published between January 1970-January 2016 was performed, using the following search terms, decided by a consensus of the authors: pancreas AND mucinous cystic neoplasm OR mucinous cyst AND pregnancy OR delivery. Only English and Japanese-language reports were identified, and we didn´t apply any language limitation. The search was restricted to title, abstract and keywords. Only lesions detected during pregnancy or during postpartum in a clear temporary relationship with pregnancy period were included.

A total of 30 cases were selected. In 22 of them there was no diagnostic doubt because the presence of ovarian-type Struma (OS) was specified in pathologic description (Table 1).

Those cases in which the presence of OS was not mentioned (a total of 8), were selected using the following criteria: We only consider those lesions with morphological characteristics described that made confusion with other pancreatic cysts virtually impossible. Must meet two or more of the following requirements: final pathologic diagnose of MCN (even without mentioning OS), typical location in body/tail, big size, lack of communication with the pancreatic duct (Table 2).

The following variables were extracted when available: age and gestational age at diagnose, number of previous pregnancies, medical history (at least 6 months before), gestational diabetes, symptoms, complications and physical examination,

size, location and evidenced growth, serum levels of CEA, Ca19.9, Amylase and Hemoglobin, diagnose imaging techniques and presence of high risk features, pathological diagnose, presence of ovarian stroma, grade of dysplasia/invasive carcinoma, hormonal receptors, analysis of cystic fluid, surgery time, surgical complications, length of follow-up, type of delivery, maternal and fetal prognosis.

RESULTS

30 operated MCN cases diagnosed during pregnancy were included in the study. All lesions had a pathological diagnosis of MCN, and in 22/30 (73.3%) ovarian type stroma was reported.

Epidemiology

The median age at diagnose was 30.5 years (range 21-38). 8/25 cases (32%) were diagnosed during first pregnancy, 15/25 cases (60%) during second pregnancy, and only 2 women had had 3 or more pregnancies before. 12/30 cases, (40%) were diagnosed during the first trimester, 8/30 (26.7%) during the second trimester, 4/30 during the third trimester and 6/30 after delivery (range 1-8 months after delivery).

Morphological Characteristics

27/30 lesions (93.4%) were located in the body and/or tail of the pancreas (2 in the body (6.7%), 14 in the tail (46.7%), and 12 (40%) in both body and tail). Only in 2 cases (6.7%) it was reported in the head. Median tumor size at diagnose was 11.73 cm (range 4.5-19 cm). The rate of cyst growth during pregnancy was monitored in 12 patients, and was faster than reported in MCNs in general (< 1cm per year). Calculated median growth was 3.67 (range 1-6.8 cm) from within the median 3.5 months (range 1-8 months) approximately, from diagnosis to operation.

Clinical presentation

At least 6 months prior to diagnosis, 13/30 (43.3%) patients were asymptomatic. At the time of diagnosis, 21/30 cases (70%) were associated with abdominal discomfort/pain, 16/30 (53.3%) showed a palpable abdominal mass, and only 6/30 (20%) were incidental findings. Complications secondary to the MCNs were found in 7/30 patients (23.3%): 2/7 had acute Pancreatitis, 2/7 had upper Gastrointestinal Bleeding and 3/7 cases were complicated by acute Abdomen secondary to tumor

rupture requiring urgent operation during the first or third trimesters.

Diagnosis and pre-operative investigations

In 23/28 cases (82.1%), first diagnostic imaging technique was Abdominal Ultrasound, and a Magnetic Resonance completed the study in 14/28 (50%) of these cases. Only 5 women (17,9%) were studied by EUS, with only 2 FNA that were not informative. In 2 cases the diagnosis of the cyst was made intraoperatively by emergency surgery (caesarean delivery due to acute abdominal pain in an advanced pregnancy of 36 weeks, urgent laparotomy due to acute abdomen and suspected ectopic pregnancy). High Risk features were identified in 6/27 cases (22,2%), all of them with MR and/or EUS. All cases were described like "mural nodules" or "mass forming lesions inside the cyst" with no cases of egg peripheral calcifications described. Only 3/6 (50%) of these pre-surgery high risk lesions were confirmed as high grade dysplasia (2) or invasive carcinoma (1) in the later pathological analysis. On the other side, 2 cases of HGD and 4 cases of Invasive Carcinoma didn´t show any High-Risk features during the imaging pre-operative investigations, however, 3 of them were studied only by Abdominal Ultrasound.

Cystic fluid analysis: Cyst fluid analysis had a mucinous appearance in 17/21 cases (80.9%). In most cases (16/21) it was obtained during surgery. Cyst fluid CEA was elevated in all the 8 cases where it was measured (range 837-66.898 ng/ml). 50% of these cases showed HRD/IC (range 837-66898ng/ml), but the other 50% didn´t show any malignancy in the pathological analysis (range 2219-32800ng/ml), confirming its low predictive value for malignancy. Cyst fluid Ca 19.9 was measured in 6 cases (range 22->50000 UI/ml), only in 2 cases levels were <1000 UI/ml. 2/4 cases with Ca 19.9 level > 1000UI/ml showed HGD / IC, and curiously the case with the lowest level (22 IU /ml) showed HGD too. Cyst fluid Amylase was reported in 5 cases, always < 500 UI/l (range 7-463UI/l), endorsing the lack of communication with the main pancreatic duct.

Surgery

Most the cases were operated on in the second trimester (11/30 (37.5%)) or postpartum (14/30 (44.8%)). 5/30 cases (17.7%) needed to be urgently operated on in the first (3/30) or third trimesters (2/30) due to severe complications associated.

According to the location of lesions, in 25/30 cases a Distal Pancreatectomy was performed, in 1/30 a Pancreatico-duodenectomy and 4/30 Enucleations.

Pathology

High Grade Dysplasia or Invasive Cancer was present in 5/30 (16,7%) and 7/30 (23,3%) respectively. The immune- histochemical analysis was reported in 19 cases, with a positive result for hormonal receptors (progesterone (PgR) and/or estrogen (EsR)) in 14/19 (73,7%) of cases, with the following distribution: 10/19 PgR&EsR (+), 3 PgR(+), 1EsR(+) and 5 PgR&EsR (-).

Delivery and follow up

Natural (vaginal) delivery was possible in 20/30 cases (66,7%), 7 of them operated during the postpartum with cyst sizes ranging 4,5-16cm, demonstrating a low risk of rupture of the cyst with the Valsalva maneuver. Cesarean was necessary in 23.3% of cases (7/30), 1 case of ectopic pregnancy and 2 abortions were reported: 1 spontaneous abortion in 10th week of gestation not thought to be associated with the MCN, and 1 voluntary interruption of pregnancy at 8th week.

Despite the high rate of malignant transformation, during the follow-up no cases of systemic recurrence were observed and local recurrence occurred only in 3/27 cases: one following an R1 resection, one with a synchronous anaplastic pancreatic carcinoma, and one ruptured MCN with an associated invasive carcinoma. With a median follow up of 32 (range 6-132) months, fetal and maternal prognosis after delivery was excellent.

DISCUSSION

Pancreatic MCN are lesions with female predominance, characterized by the existence of an underlying ovarian stroma with estrogen and progesterone receptors, not found in other pancreatic neoplasms. These data strongly suggest that their appearance and subsequent development may have a clear hormonal dependence. In fact, similar mucinous cystic tumors have been found in other organs, like the Hepatobiliary Cystadenoma or Cystadenocarcinoma and Mixed Epithelial and Stromal Tumor of the kidney (MEST) described almost exclusively in women and with a characteristic ovarian stroma.[10,12]

Under normal conditions, they occur during perimenopause period, being usually small, asymptomatic, and with a slow growth rate (<1 cm per year). Its appearance during pregnancy is an extremely rare condition but its behavior is clearly different, probably in relation to their responsiveness to high levels female sex hormones, as the results described in our series shown.

Pancreatic MCN diagnosed during pregnancy appear at a much younger age and they are more frequent in women with 1 or more previous pregnancies, with no differences regarding the trimester in which the diagnosis occurs.

Regarding to the location within the gland, the MCN in pregnancy have the same distribution of the rest of MCN, being more frequent in pancreatic body and/or tail (93,7%).

Mean size at diagnosis tends to be larger than usual (11.3cm vs 8,7cm[9,23] and often develop more rapidly. In our series, they show a mean growth rate 3.67cm in a median of 3.5 months approximately, from diagnosis to operation, getting even, in some cases, to double its size in a few months.[11]

In our opinion, a possible explanation to its larger size and growth rate is the strong hormonal activity during pregnancy and its influence on the ovarian stroma. The origin of ovarian stroma in MCN of the pancreas is unknown. Zamboni et al[18] have proposed that the primitive mesenchyme and endoderm-derived epithelium in organs such as the pancreas and liver could proliferate because of hypersensitivity to female sex hormone stimulation exacerbated during pregnancy. An alternative hypothesis is that primary yolk cells were implanted into the pancreas erroneously due to the proximity of the genital tract to the dorsal pancreas during 7th week of embryogenesis. The dorsal pancreatic enlarge gives rise mainly to the pancreatic body and tail, and this could explain the predilection of MCN for the distal pancreas. Whatever the origin was, this tissue has hormonal receptors to progesterone and or estrogen. In our series, 73,7% cases showed positivity to hormonal receptors in the immune-histochemical analysis.

Another observation suggesting the possible hormonal influence in MCN development is the case reported by Tanaka et al[24] in a 53-years-old woman with a 10-year history of a stable pancreatic cyst, that after starting hormone replacement

therapy experimented a gradual increase of the size of the cyst, which after pancreatectomy was diagnosed as an MCN carcinoma.

If high levels of estrogen and/or progesterone during pregnancy can increase the cyst malignancy potential and favor malignant transformation remains still unclear. In fact, there is some evidence about the correlation between a worse prognosis in cyst with histological atypicality and a decrease in progesterone receptor immunoreactivity. But as the size is considered a risk factor for malignancy on its own, and the rapid proliferation may be an additional risk factor, MCN diagnosed during pregnancy should be considered high-risk lesions. Our results support this theory, and malignancy (HGD or Invasive Cancer) was present in 40% cases, clearly superior to that described for the MCN outside the time of pregnancy (12-20%).[14,23]

At diagnosis, most lesions are symptomatic, and severe associated complications are frequent (24,7%). These facts can have a double explanation. First, the larger size of the cysts and especially the higher growth rate can promote early onset of symptoms. Second, the high rate of malignancy can also be the cause of symptoms. Thus, the guidelines and expert consensus for management of MCN consider the appearance of symptoms as a risk criteria for malignancy, recommending surgical removal.

In our series, most cases didn´t show any warning symptoms during at least 6 months before diagnosis, which supports that the cyst did not exist before pregnancy, or at least that it began its growth at the same time. Another fact supporting this theory is that most patients with a growing palpable mass, a small pancreatic cyst had been diagnosed in a previous pregnancy.

Most common symptom observed in our series was epigastric abdominal pain or discomfort or the presence of a palpable abdominal mass. Jaundice was not a frequent symptom in these patients, probably related to its unusual location in pancreatic head.

Diagnostic process of MCN during pregnancy is limited to non-ionizing imaging techniques. In our series, Abdominal Ultrasound, Magnetic Resonance and

Endoscopic Ultrasound were useful techniques for diagnosis but they were worthless to detect high risk features for malignancy (MR positive predictive value 50%). However, our series has the limitation of being a historical series with many cases reported before 2000, in which availability and quality of MR and EUS would be probably much lower than today. According to the known reported data, the diagnostic value of cytology observed in our series was very low, so that the probably advisable diagnostic test for MCN associated with pregnancy remains the MRI, despite its insufficient accuracy, especially considering the invasiveness and low superiority of EUS-FNA.

Most patients were operated during the second trimester of pregnancy (traditionally considered the safest) or during postpartum. In our series, only a single case of MCN related complications was reported in a woman who was operated in the second trimester. A very important step is to decide the most appropriate modality of delivery. Theoretically, a large pancreatic cystic mass can induce Intrauterine Growth Restrictions with specific fetal morbidity[11,19] and cystic rupture

In our series, uneventful vaginal delivery was possible in 67% of cases. No cases of cyst rupture related to Valsalva or Intrauterine Growth Restriction was reported.

With a median follow up of 32 (range 6-132) months, fetal and maternal prognosis after delivery was excellent, with only 3 cases reported of local recurrence in relation with poor prognosis factors: one case following an R1 resection, one with a synchronous anaplastic pancreatic carcinoma, and one ruptured MCN with an associated invasive carcinoma.

CONCLUSION

Pancreatic MCNs diagnosed during pregnancy are often large and grow rapidly. They appear predominantly in younger women, with one or more previous pregnancies. Most lesions are symptomatic at diagnose. The Immuno-histochemical analysis showed a positive result for hormonal receptors (Progesterone and/or Estrogen) in almost 74% of cases, endorsing their obvious hormonal dependence. The malignancy observed was higher than usual, with 40% of operated lesions showing HGD or Invasive Carcinoma in Pathological analysis,

so surgical resection should be recommended when an MCN is diagnosed during pregnancy. The second trimester seems to be a safe time for intervention with low rates of adverse events, but postpartum could be an option too in individualized cases (small size, without high risk features and asymptomatic).

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TABLES

Table 1. Patient demographics and MCNs characteristics

Author	Age	Size	Location	Hormonal Receptors	Ovarian-type Stroma	Pathological diagnose
Millastre, 2015	37	8 cm	Tail	NR	✓	Benign MCN
Shamali, 2015	23	7 cm	Tail	NR	✓	Benign MCN
Antila, 2015	28	8 cm	Tail	NR	✓	MCN with HGD
Kosumi, 2015	33	6 cm	Body-Tail	PG(+) ES(+)	✓	Benign MCN
Takashima, 2014	28	7 cm	Head	PG(+) ES(+)	✓	MCN with HGD
Tica, 2013	27	11,6 cm	Body-Tail	(-)	✓	Benign MCN
Iusco, 2012	28	16 cm	Tail	PG(+) ES(+)	✓	MCN with IC
Tsuda, 2012	28	14 cm	Body-Tail	PG(+) ES(+)	✓	MCN with HGD
Naganuma, 2011	32	11 cm	Head	PG (+)	✓	MCN with IC
Shirakawa, 2010	34	19 cm	Tail	PG(+) ES(+)	✓	MCN
Brown, 2009	38	10 cm	Body-Tail	NR	✓	MCN with HGD (R1)
Hakamada, 2008	38	10 cm	Tail	PG (+)	✓	MCN + Anaplastic Carcinoma
Ikuta, 2008	30	18 cm	Tail	PG(+) ES(+)	✓	MCN with LGD
Berindoague, 2007	31	15 cm	Body-Tail	(-)	✓	MCN with IC
Wiseman, 2007	32	15 cm	Tail	PG(+) ES(+)	✓	MCN with LGD
Komatsu, 2007	31	15 cm	Body-Tail	PG(+) ES(+)	✓	MCN with LGD
Ishikawa, 2007	33	12 cm	Body-Tail	(-)	✓	Benign MCN
Herring, 2007	34	19 cm	Body-Tail	PG(+) ES(+)	✓	MCN with HGD
Kitagawa, 2006	25	15 cm	Body	PG(+)	✓	Benign MCN
Kato, 2005	33	17 cm	Body-Tail	PG(+) ES(+)	✓	Benign MCN
Lopez, 2005	26	15 cm	Body-Tail	NR	✓	Benign MCN

Table 2. Demographics and MCNs characteristics in patients with Ovarian-type Stoma not reported

Author	Age	Size	Location	Hormonal Receptors	Ovarian Stroma	Pathological diagnose
Boyd, 2012	21	17,2cm	Body	NR	NR	MCN with LGD
Asciutti, 2010	31	8,3 cm	Tail	NR	NR	Benign MCN No communication with pancretic ducts
Ozden, 2007	32	15 cm	Tail	(-)	NR	Cystadenocarcinoma growing inside a Mucinous cystadenoma
Yuzefovich, 2007	22	15 cm	Tail	NR	NR	Benign Mucinous Cystadenoma
Matsumago, 2004	28	20 cm	Tail	PG (+)	NR	Mucinous Cystadenocarcinoma
Olsen, 1993	25	5 cm	Tail	NR	NR	Benign MCN
Baiochi, 1990	29	10 cm	Tail	NR	NR	Cystadenocarcinoma growing inside a Mucinous cystoadenoma
Smithers, 1986	33	10 cm	Body-Tail	NR	NR	Cystadenocarcinoma of the pancreas
Ganepola, 1999	37	12 cm	Body-Tail	PG(+) ES(+)	NR	Benign MCN

CHAPTER 4

SUMMARY

Pancreatic mucinous cystic neoplasms (MCNs) have been defined by the World Health Organisation from 2000 as well-demarcated cystic lesions, lined by a mucin-producing columnar epithelium overlying an ovarian-type stroma. Although MCNs are classified as neoplastic lesions their actual malignant potential remains uncertain, with rates of associated invasive cancer ranging anywhere between 0 and 34% in the current literature.

The current management of MCNs is defined by a number of consensus guidelines from the International Association of Pancreatology (IAP), Europe, and the American Gastroenterology Association. The IAP and European guidelines specifically mention the management of MCN and both stipulate that where the diagnosis is certain and the patient is an operative candidate then surgical resection should be performed. Within the European consensus statement on cystic lesions of the pancreas, there is a proviso that where the diagnosis is uncertain and there are no associated worrisome features and the lesion is less than 4cm, then management of a MCN as a branch duct IPMN, with surveillance may be appropriate.

Our comprehensive systematic review supports emerging trends in the literature that MCNs are probably more indolent lesions than was previously thought. They have a low aggressive behavior, with exceptionally low rates of malignant transformation when less than 4cm in size, are asymptomatic and lack worrisome features on pre-operative imaging. Conservative management, particularly of small MCNs appears to be a reasonable strategy. This differs significantly from the natural history of small BD-IPMNs, supporting the need to differentiate mucinous cyst subtypes pre-operatively, where possible.

Our large multicentre cohort concluded that, in female patients, malignancy or HGD was solely seen in MCNs with symptoms or worrisome features on preoperative imaging, regardless of the size of the tumour. In males, the risk of

malignancy was significantly higher than in females, suggesting that operative treatment should be considered in all male patients with a suspected MCN of any size. In female patients conservative management seems to be a safe approach for suspected MCNs of any size without symptoms or worrisome features.
Pancreatic MCNs diagnosed during pregnancy are often large and grow rapidly; this suggests a strong correlation between this type of lesions and hormones.

These findings support the management of MCN advocated by the recent European Guidelines. The conclusion of this thesis should change the management of patients with MCNs in many centres worldwide.