A multinational cohort study of the risk of malignancy in pancreatic mucinous cystic neoplasms without worrisome features or symptoms

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Abstract

Background: Pancreatic mucinous cystic neoplasms MCNs are rare mucin-producing cystic tumours defined by the presence of ovarian-type stroma. MCNs have a malignant potential and thus surgery is frequently performed. In this cohort study we aim to better define the criteria for surgical resection in MCN.

Methods: This multicentre retrospective study included all resected MCNs between 2003-2015 in participating centres. Lesions without ovarian-type stroma were excluded. Patient characteristics, preoperative findings, histopathology and follow-up data were recorded.

Results: The study included 211 patients. Median age was 53 (range 18–82) years and 95.7 per cent (202 of 211) occurred in women. Median pre-operative tumour size was 55 (range 12-230) mm. Thirty-two of the 211 (16.1 per cent) were malignant and high-grade dysplasia (HGD) was found in a further 6.2 per cent (n=13). A third of MCNs in men were associated with invasive cancer compared to 15.3 per cent in women. Five cases of malignant transformation occurred in MCNs <4cm. All cases of malignancy or HGD were associated with symptoms or features of concern on pre-operative cross-sectional imaging. On multivariate analysis, raised CA19-9 (OR 10.9; 95 per cent confidence interval (c.i.):1.9–24.5 p<0.001), mural nodules (OR 6.9; 95 per cent c.i..:1.3–36.1, p=0.023), weight loss (OR 2.7; 95 per cent c.i.:1.5–14.6, p=0.004) and tumour size (OR 1.019; 95 per cent c.i.: 1.0–1.0, p=0.020) were independent factors, predictive of malignant transformation.

Conclusions: Small indeterminate MCNs without symptoms or features of concern may safely be observed and have a low risk of malignant transformation.

Introduction

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,[1] and the Armed Forces Institute of Pathology (AFIP) from 1997.[23] Pancreatic mucinous cystic neoplasms are defined as well-demarcated cystic lesions, lined by a mucin-producing columnar epithelium overlying an ovarian-type stroma.[1] Although MCNs are relatively rare tumours, the overall incidence of Pancreatic Cystic Neoplasms is increasing.[2-4] MCN are estimated to account for between 10-45% of all resected pancreatic cysts.[5, 6]

Although MCN are classified as neoplastic lesions[7] their actual malignant potential remains uncertain, with rates of associated invasive cancer ranging anywhere between 0 and 34% in the current literature.[8] 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 (IPMN), potentially explaining the higher rates of malignancy observed.[9] Recent publications from single centres have suggested that malignant transformation in MCN may actually be rare, especially when the tumours are small in size (<4cm).[10-16]

The current management of a pancreatic cystic neoplasms is defined by a number of consensus guidelines from the International Association of Pancreatology (IAP),[17] European expert consensus statement on cystic tumours of the pancreas,[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 surveillance may be appropriate. However, to date very few studies have described the natural history of small MCN to support this management strategy and no one has validated the current recommendation within the European guidelines.

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 recent systematic review[20] and a single multi-institution US study,[21] 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 of these lesions. The aim of this large multi-institution European study was to determine the rate of associated malignancy in resected MCN, define which clinical and radiological features predicted malignant transformation and validate the management guidelines for MCN proposed by the European consensus statement on pancreatic cystic neoplasms.

Patients and methods

Setting and study design

A multicentre retrospective, observational study from nine pancreatic centres from across Europe [Supplementary Table 1]. The study was conducted in accordance with STROBE guidelines for case-control studies.

Ethics

The study protocol was reviewed and ethical approval obtained from the local review board in each centre. In the UK the Health Research Authority deemed the study to be primarily an audit of current practice and therefore formal ethical review was not required. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Inclusion criteria

All consecutive patients with a histologically confirmed MCN of the pancreas resected between January 1st 2003 and December 31st 2015 in each participating centre. 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, American Society of Anaesthesiology (ASA) score, diabetes, smoking, previous pancreatic disease, previous cancer, family history of cancer.

Any associated symptoms were also recorded; 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 undertaken, 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: 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 main pancreatic duct to >6mm (upstream of the cyst) or biliary tree dilatation. For patients undergoing EUS-FNA, cytology and cyst fluid 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),[22] 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 performed to confirm the diagnosis. Dysplasia was classified in accordance with the most aggressive histological epithelial changes as defined by the World Health Organization (WHO) classification system.[7] Tumours were graded as having low or intermediate grade dysplasia, high-grade dysplasia including carcinoma in situ, and malignant when invasive carcinoma was present.[7]

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 Mann-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 log rank analysis. All tests were two-tailed and a P-value < 0.050 was considered to be significant.

Results

Two hundred and eleven 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 per cent (202/211) were women. Sixty three percent of the patients were symptomatic and in 37 per cent the diagnosis was made incidentally during abdominal cross-sectional imaging performed for other reasons. Ninety percent of patients were investigated with CT with the remainder having an MRI/MRCP. Twenty eight percent of patients had both a CT and MRI. On pre-operative imaging, the median tumour size was 55 (range 12-230) mm and an MCN was suspected clinically in 49.7 per cent (73/147), an IPMN in 11.6 per cent (17/147) and the diagnosis remained uncertain in 38.8 per cent (57/147) of the cases. Mural nodules were present in 23.4 per cent, cyst wall calcification in 18.8 per cent and septations in 52.9 per cent of the cases. In 8.8 per cent the diameter of the main pancreatic duct was ≥6 mm (upstream of the cyst) [Table1]. In addition to cross-sectional imaging by CT or MRI 39 per cent of patients had an EUS and an FNA was performed in 28% of patients. Cytology had a sensitivity, specificity, positive predictive value and negative predictive value of 66.7 per cent, 98.1 per cent, 66.7 per cent, 98.1 per cent respectively for malignant transformation.

A distal pancreatectomy was performed in 82.9 per cent, pancreatoduodenectomy in 8.5 per cent and an enucleation in 4.3 per cent. Mortality at 30-days was 0.9 per cent. 30-day morbidity was 37.9 per cent; classified as Clavien-Dindo Grade 1 in 10.4 per cent, Grade 2 in 15.2 per cent, Grade 3 in 9.5 per cent and Grade 4 in 1.9 per cent.

The median resected tumour size was 55.5 (range 20-300) mm. Invasive cancer was present in 16.1 per cent (34/211), with high-grade dysplasia (HGD) seen in a further 6.2 per cent (13/211) of patients. For patients with invasive MCN cancer, the tumour was classified as stage Ia in 9 (26.5 per cent) patients, stage Ib in 8 (23.5 per cent), stage IIa in 6 (17.6 per cent), stage IIb in 6 (17.6 per cent) and stage III in 5 (14.7 per cent) patients. Malignant transformation was associated with presence of symptoms (88.2 vs. 58.2 per cent; p=0.001), especially in those presenting with pancreatitis (26.5 vs. 9.6 per cent; p=0.018), jaundice (20.6 vs. 1.7 per cent; p<0.0001), or who had significant weight loss (32.3 vs. 6.2 per cent; p<0.0001) [Table 2].

The rate of invasive cancer correlated with increasing tumour size [Figure 1a]. In lesions greater than 12 cm the rate of invasive cancer was 30 per cent, compared to just 5 per cent in lesions 3.0-3.9 cm and 6 per cent in lesions 0-2.9 cm. When stratified by sex the rate of malignancy in lesions less than 3cm in female patients decreased to 3 per cent (HGD 3 per cent) compared to 25 per cent in men (HGD 25 per cent) [Figure 1b and c]. All patients with malignant lesions or HGD, regardless of tumour size had symptoms or one or more feature of concern on cross-sectional imaging [Table 4].

On univariate analysis, we found that presence of symptoms, previous pancreatitis, jaundice, raised Ca19-9, recent weight loss, tumour size and mural nodules were significant risk factors predictive of invasive cancer. On multivariate analysis, raised CA19-9 (OR 10.5; 95 per cent c.i.: 2.9-18.2, $p<0.001$), mural nodules (OR 3.6; 95 per cent c.i.: 1.3-20.6, $p=0.002$), weight loss (OR 3.4; 95 per cent c.i.:2.3–12.3, $p=0.034$) and tumour size (OR 4.2; 95 per cent c.i.: 3.0–11.0, $p=0.001$) remained independent factors of malignant transformation. The model was a good predictor of malignant transformation with Nagelklerke R Square value of 0.7 [Table 3].

Median survival for patients with a malignant MCN was 44 months (range 0-167 months), 12 patients died during follow up of which 10 was due to disease recurrence. A non-significant but notable difference in survival was also observed between men and women ($p=0.134$) [Figure 2].

Discussion

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.[8] Rates of HGD were lower than in other single centre series [12, 13, 16] at 6.2% but similar to the rate found in a recent multicentre study from North America.[21]

In clinical practice, differentiating MCN from other uni- and oligocystic tumors (i.e. branch duct-IPMN and serous cystadenoma) remains a significant 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.[24] When pancreatic cysts are small the diagnosis can be especially difficult as many of the typical radiological features (i.e. communication with the main pancreatic duct in case of BD-IPMNs) are not present. The pre-operative uncertainty in defining these lesions was clearly reflected in this study, with less than half of MCN being correctly classified prior to resection. Current guidelines are clear and consistent when the diagnosis of MCN is certain, recommending surgical resection in all patients. 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 features, 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 the last three decades the size at which MCN are detected has decreased.[20] Given that features of concern are often absent in small lesions, cyst diameter has remained the most important radiologic predictor of malignant transformation. At what size of MCN patients should be referred for surgical resection remains uncertain. In this large cohort study, invasive cancer occurred in 9.8% of lesions less than 4cm and 5.3% less than 3cm. In the five cases of invasive cancer in lesions less than 4cm [Table 4], as well as all cases of cancer or HGD in this study, at least one pre-operative worrisome feature was present to prompt surgical resection. 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 retrospective data was drawn from surgically resected cases and will need to be confirmed by prospective surveillance studies, these findings do suggest that the

conservative management of indeterminate cystic lesions which are probably an MCN, is feasible, as advocated by the European guidelines. Particularly in small lesions (<4cm), occurring in women without worrisome features.

MCN differ from other pancreatic cystic neoplasms, by predominantly occurring in female patients. Whether MCN, defined by the presence of ovarian-type stroma, can even occur in male patients has been debated,[25] but a number of cases in male patients have been described.[12, 13, 16] In this study with careful pathological characterization, just 4.3% of MCN occurred in men, one of the lowest rates reported to date. Rates of invasive cancer and high-grade dysplasia were also much more common in men than women and appeared to occur at an earlier stage when the lesions were still small in size [Table 2].

In the multivariate analysis, in addition to tumour size, this study also found that a raised CA 19-9 and a solid component were also independent predictors of invasive cancer. This supports the findings of other studies which have also found that CA19-9,[13, 21] and the presence of a solid component or a mural nodule to be reliable predictors of invasive malignancy in MCN.[10, 13, 15, 16, 24, 26]

The survival of patients with a malignant MCN is superior to pancreatic ductal adenocarcinoma.[6] A non-significant difference in survival was also observed between male and female patients, which although unexpected, perhaps further supports the more aggressive behavior MCN observed in male patients in this cohort and others.[21] In other female predominant pancreatic cystic neoplasms, such as solid pseudopapillary tumours, male patients have also been observed to have a poorer prognosis.[28] All cases of malignancy were solely seen in MCN with symptoms or worrisome features, regardless of tumour size. A raised CA19-9, a solid component, weight loss or large tumour size (≥4cm) predicted malignant transformation in these lesions. Therefore in small indeterminate lesions without symptoms or features of concern, a more conservative approach is potentially feasible, as advocated in the European consensus statement on cystic tumours of the pancreas.

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 pancreatic cystic neoplasms 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.

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Table 1. Characteristics and radiological features of study cohort

	%	n
Demographics and clinical symptoms		
Sex		
• Female	95.7	202/211
• Male	4.3	9/211
Age, *years* median (interquartile range)		53 (43-63)
BMI*, *kg/m²* 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 process	10.9	23/211
• Body	27.5	58/211
• Tail	55.9	118/211
• Missing data	5.7	12/211
Median tumour size, *mm* (interquartile range)		55 (30-91)
Mural nodules	23.4	37/158
Cyst wall calcification	18.8	32/170
Dilated main pancreatic duct	8.8	14/159
Septations	52.9	83/157
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

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

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
Personal history of cancer	2 (5.9)	13 (7.3)	1.000	2 (6.5)	12 (7.0)	1.000	0 (0)	1 (16.6)	1.000
Family history of pancreatic cancer	0 (0)	8 (4.5)	0.360	0 (0)	8 (4.7)	0.611	0 (0)	0 (0)	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)	**<0.001**	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)	1.000
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: Common Bile Duct

Table 3. Binary logistic regression of preoperative risk factors for invasive adenocarcinoma arising from a MCN

Variable	**Univariate analysis**			**Multivariate analysis**	
Clinical features	**OR (95% CI)**	***p* value**		**OR (95% CI)**	***p* value**
Male gender	2.76 (0.66-11.62)	0.167			NS
Symptomatic	5.39 (1.82-15.95)	**0.002**			NS
History of pancreatitis	3.39 (1.36-8.43)	**0.009**			NS
Jaundice	15.04 (3.66-61.71)	**<0.001**			NS
Weight loss	7.22 (2.81-18.53)	**<0.001**		3.40 (2.34-12.34)	**0.034**
Serum Ca19-9	11.51 (3.42-38.68)	**<0.001**		10.54 (2.85-18.23)	**<0.001**
Tumour size *	5.09(1.47-17.61)	**0.010**		4.23 (3.02-11.03)	**0.001**
Tumour location: Head of pancreas	2.61 (0.98-6.93)	0.054			NS
Solid component	6.78 (2.51-18.32)	**<0.001**		3.55 (1.31-20.55)	**0.002**
Dilation of main pancreatic duct	3.47 (0.97-12.43)	0.056			NS

***** Tumour size was used as a categorical variable ≥ 4cm

Supplementary Table 1. Age, sex, worrisome features associated with invasive MCNs of less than 4cm

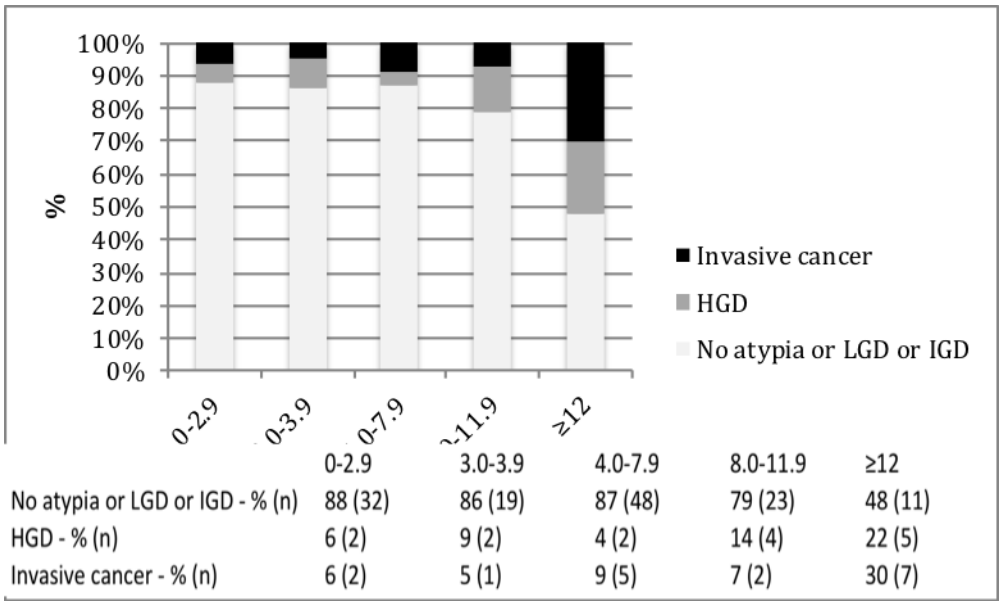
	Age	Sex	Tumour size	Worrisome features
Case 1	74	F	33	Symptoms, raised Ca 19-9, dilated main PD
Case 2	70	M	28	Symptoms, raised Ca 19-9, mural nodules, cyst wall calcification, septations
Case 3	37	F	35	Symptoms, mural nodules
Case 4	64	M	30	Symptoms, raised Ca 19-9, septations, dilated CBD
Case 5	65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

Supplemental table 2. Cases provided by each participating centres in the cohort:

Centre	Country	N. of cases	Percentage
Tampere University Hospital	Finland	47	22.3
University College London	United Kingdom	33	15.6
Southampton University Hospital	United Kingdom	31	14.7
Department of Surgery, Karolinska University Hospital	Sweden	30	14.2

Freeman Hospital, Newcastle	United Kingdom	27	12.8
Miguel Servet University Hospital, Zaragoza	Spain	15	7.1
Chirurgische Klinik, Klinikum rechts der Isar, Technische Universität München	Germany	13	6.2
Ciudad Real University Hospital	Spain	8	3.8
Nijmegen University Hospital	Netherlands	7	3.3

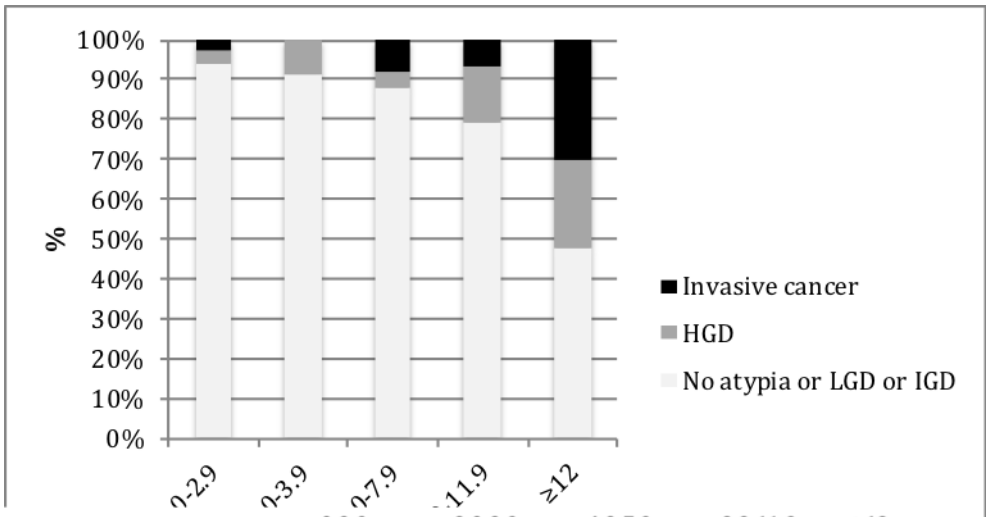
Figure 1a. Percentage of associated invasive cancer at different tumour sizes



	0-2.9	3.0-3.9	4.0-7.9	8.0-11.9	≥12
No atypia or LGD or IGD - % (n)	88 (32)	86 (19)	87 (48)	79 (23)	48 (11)
HGD - % (n)	6 (2)	9 (2)	4 (2)	14 (4)	22 (5)
Invasive cancer - % (n)	6 (2)	5 (1)	9 (5)	7 (2)	30 (7)

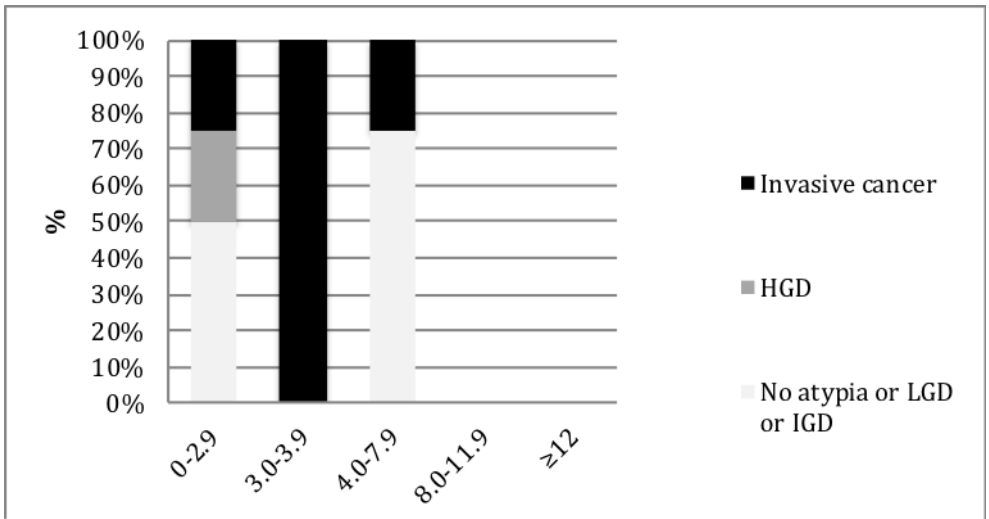
Figure 1b. Percentage of associated invasive cancer at different tumour sizes

in women



	0-2.9	3.0-3.9	4.0-7.9	8.0-11.9	≥12
No atypia or LGD or IGD - % (n)	94 (30)	91 (19)	88 (45)	79 (23)	48 (11)
HGD - % (n)	3 (1)	9 (2)	4 (2)	14 (4)	22(5)
Invasive cancer - % (n)	3 (1)	0 (0)	8 (4)	7 (2)	30 (7)

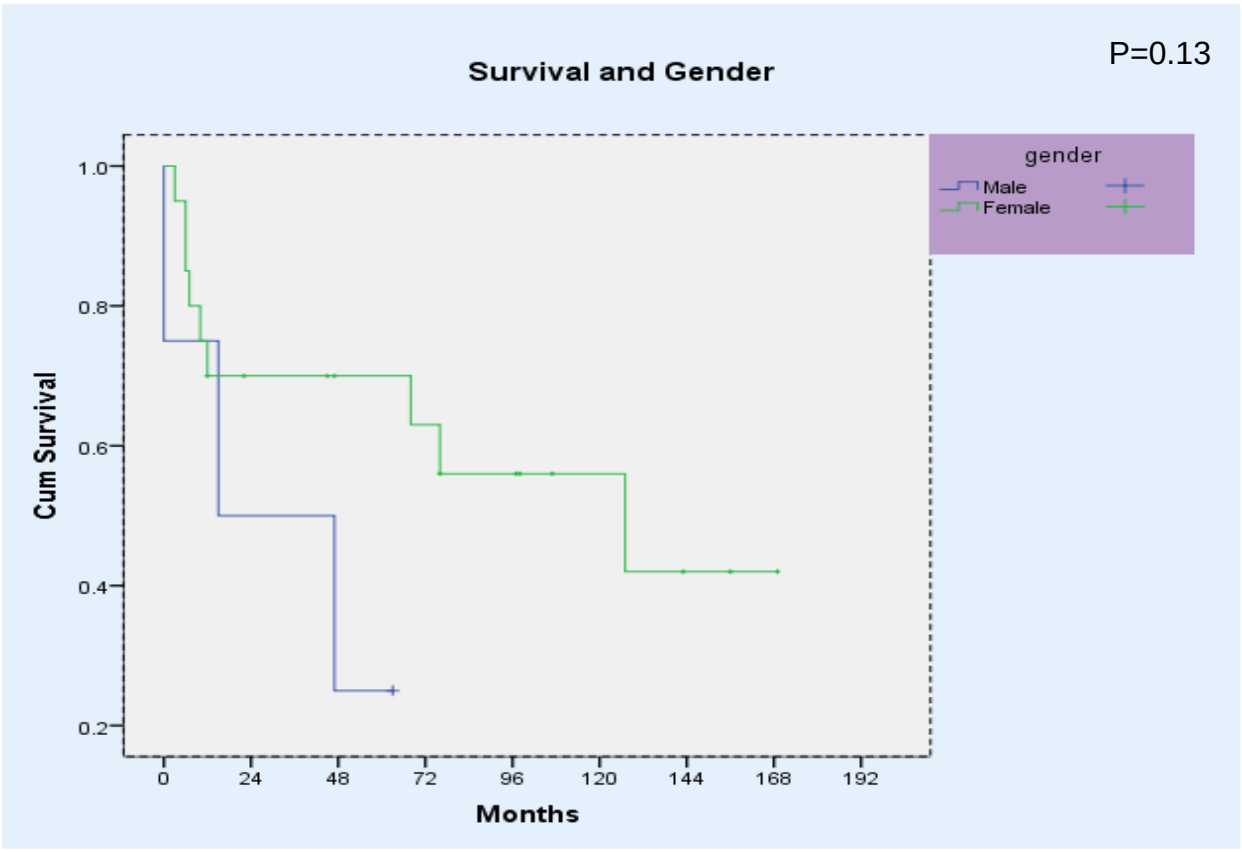
Figure 1c. Percentage of associated invasive cancer at different tumour sizes in men



	0-2.9	3.0-3.9	4.0-7.9	8.0-11.9	≥12
No atypia or LGD or IGD - % (n)	50 (2)	0 (0)	75 (3)	0 (0)	0 (0)
HGD - % (n)	25 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Invasive cancer - % (n)	25 (1)	100 (1)	25 (1)	0 (0)	0 (0)

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

P=0.13


Survival and Gender
gender
Male
Female
Cum Survival
1.0
0.8
0.6
0.4
0.2
0
24
48
72
96
120
144
168
192
Months