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ORIGINAL ARTICLE

Observational Study

Branch duct intraductal papillary mucinous neoplasms: How ready are we to de-escalate surveillance?

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Abstract

BACKGROUND

Surveillance of branch duct intraductal papillary mucinous neoplasm (BD-IPMN) is advised to detect pancreatic ductal adenocarcinoma. Unfortunately, current practice means individuals have multiple rounds of investigations as typically surveillance continues until malignant transformation is identified or the patient is considered unsuitable for surgical intervention. This has major financial stress to healthcare providers and psychological burden to the patient. As a supra-regional referral centre, our impression was that many of the BD-IPMN in our surveillance pathway have many relatively unproductive rounds of surveillance and sought to interrogate our 17-year experience of this and determine whether we could improve our pathway.

AIM
To identify phenotypic and biochemical markers which predict IPMN behaviour and identify strategies to minimise investigations and manage surveillance de-escalation.

METHODS
This study was a single centre observational study based around one of the highest volume supra-regional pancreatic referral units in the United Kingdom (Liverpool). Individuals with BD-IPMN who were referred for surveillance were managed under the Liverpool IPMN Surveillance Pathway. Presumed innocent BD-IPMN (without either worrisome or high-risk features) underwent imaging ± endoscopic ultrasound (EUS) examinations for any interval development of high-risk features or worrisome features or symptoms and were either returned to surveillance or underwent definitive care.

RESULTS
Of 1303 patients were included between 1 January 2007 and 31 December 2023, with 1191 (91%) entering surveillance. Median [interquartile range (IQR)] follow up was 9.74 (7.79-11.2) years. Histology was available in all 153 patients who underwent surgery. Serum cancer antigen 19-9 of 43 KU/L (area under the curve = 0.78, 95% confidence interval: 0.70-0.87) and cyst size 30 mm (area under the curve = 0.76, 95% confidence interval: 0.60-0.93) best predicted high-grade dysplasia/malignancy. 134 patients had surgery within 2 years of starting surveillance, median (IQR) time to surgery was 5.0 (2.7-11.3) months, including 32/34 (94%) of the operable pancreatic cancer group. 127 had 2 EUS *vs* 26 who had > 2 EUS, median (IQR) time to surgery of 4.2 (2.2-7.5) and 22.6 (9.0-57.1) months respectively. Surgery was rare after 2 years, due to individuals declining health, as were relevant finding beyond the 2nd EUS.

CONCLUSION
Surveillance could be de-escalated after two years, providing cyst size is < 30 mm and serum cancer antigen 19-9 is < 43 KU/L. As findings are rarer after 5-years, discharge could be considered.

Key Words: Intraductal pancreatic mucinous neoplasm; Branch duct intraductal papillary mucinous neoplasm; Surveillance; Pancreatic ductal adenocarcinoma; De-escalation; Cancer antigen 19-9; Fitness

Core Tip: This study reports outcomes of 1191 participants with branch duct intraductal papillary mucinous neoplasm under surveillance. There are three important findings: Firstly, surgery is front loaded and the opportunity to resect pancreatic ductal adenocarcinoma appears to occur early in surveillance. Secondly, the incremental return of continued investigations, resulting in risk reducing surgery, dramatically diminishes after two years. Lastly, patients who have been in surveillance for more than two years with a serum cancer antigen 19-9 < 43 KU/L and branch duct intraductal papillary mucinous neoplasm stability at < 30 mm have low rates of malignant transformation and surveillance can be de-escalated, with discharge considered at five years.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is both an aggressive and a challenging cancer to manage. Although often diagnosed when patients are already symptomatic and at a later stage, survival is improving, albeit slowly[1-3]. Approaches which employ early detection of pancreatic lesions have the potential to remove tissue before cancer develops and effect a cure. Surveillance of pre-malignant intraductal papillary mucinous neoplasms (IPMN) provide one such opportunity. All International guidelines agree that branch duct IPMN (BD-IPMN) in the absence of multiple worrisome features (WF) or high-risk features (HRF) should enter surveillance for PDAC, with the exception of a sole simple > 3 cm cyst being allowed. Thereafter, surveillance is based on estimated risk of the cysts, which is not described and left to clinician discretion, which can lead to excessive investigations. This comes with an associated cost to healthcare providers and a psychological burden to the patient[4,5]. The evidence to support stopping surveillance at a specific time point is limited, so typically BD-IPMN surveillance continues until malignant transformation is identified or the patient is considered unsuitable for surgical intervention. The American Gastroenterological Association highlighted this in their guidelines when they recommended discontinuing surveillance for individuals with a cyst less than 3 cm with no WF after 5 years[6]. Although controversial at the time, this concept is revisited in the latest Kyoto guidelines[7]. Our cohort of presumed innocent BD-IPMN were analysed to: (1) To identify phenotypic and biochemical markers which predict

IPMN behaviour, notably transformation to malignancy; and (2) Identify strategies to minimise excessive investigations and develop safe rules to manage this de-escalation.

MATERIALS AND METHODS

Study design

This is a translational project from the European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis (EUROPAC), wherein we aim to identify high risk groups for pancreatic cancer surveillance. STROBE[8] was closely adhered to throughout this study. EUROPAC ethics, consents and protocols were approved by the Yorkshire and Humber Research Ethics Committee.

Setting and participants

This study was a single centre observational study based around one of the highest volume supra-regional pancreatic referral units in the United Kingdom (Liverpool), where EUROPAC is based. Any IPMN or cystic lesion felt to be at risk of transformation on referral was assessed and proceeded into standard of care and not surveillance. Presumed innocent BD-IPMN, once determined by the supra-regional pancreatic cancer multi-disciplinary team (MDT), were managed through a bespoke cyst-MDT and surveillance pathway [Liverpool IPMN Surveillance Pathway (LISP), Supplementary Figure 1], with the latest version (v12) encompassing relevant changes from other guidelines. For this study, a presumed innocent BD-IPMN is one that is devoid of either WF or HRF.

Inclusion criteria for LISP: Presumed innocent BD-IPMN as diagnosed on magnetic resonance cholangiopancreatography; definite connection to the main pancreatic duct was not required for diagnosis, provided a consultant radiologist reported the magnetic resonance cholangiopancreatography and the MDT ratified the diagnosis.

Exclusion criteria for LISP: Unclear diagnosis; obvious main duct IPMN or mixed type IPMN; presence of worrisome or high-risk stigmata; overt malignancy or symptoms. Patients already undergoing cyst surveillance prior to the study period were not included.

Eligible participants for this study were identified from the hospital Cancer Registry (Somerset™). Patient demographic and clinicopathological data were extracted from electronic health records. At the point of LISP starting a BD-IPMN > 2 cm and a cancer antigen 19-9 (CA19-9) > 37 KU/L were considered as WF/HRF in addition to: MPD diameter between 5-9 mm (whole MPD or segmental), symptoms (jaundice, pancreatitis or weight loss), any cyst with wall thickness or internal content abnormality, cysts with either wall enhancement or non-enhancing nodules, associated pancreatic tail atrophy or a cyst diameter increase of ≥ 3 mm over one year. The presence of high-grade dysplasia (HGD) or malignancy was confirmed either by histology from surgical specimens, by fine needle aspiration cytology at endoscopic ultrasound (EUS) or by radiological features suggestive of pancreatic malignancy in unfit individuals for whom best supportive care was recommended. Histology definitions of dysplasia for IPMN followed the three-grade system as was the case when LISP was introduced and was kept for consistency and for us to explore the nature of progression of dysplasia in cysts over time[9]. High grade dysplasia as described here maps to high grade dysplasia in the revised system with intermediate and low-grade dysplasia combining into low grade. Our end point of HGD/malignancy maintains robustness despite classification change. Confirmatory histology was not necessary to proceed to surgery[10]. Actionable findings (those requiring surgical or palliative treatment), time to surgery and number of EUS were recorded. EUS was undertaken as per LISP document as outlined in the attached guidance and was undertaken for further investigation of any cyst which developed either WF or HRF or in whom the patient developed new symptoms. Time to any event was recorded from MDT consensus diagnosis of a lesion to the time to event of interest, different pancreatic lesions subsequently characterised during surveillance, were kept in this analysis. Subsequent surgery within this study was only directed to those that entered surveillance and underwent imaging and/or EUS, and in whom a subsequent abnormality was found. Transformed IPMN (t-IPMN) are defined as PDAC originating from an IPMN. Concomitant PDAC (c-PDAC) are defined as adenocarcinoma arising separately and with distinct pathological separation from the unaffected IPMN.

Study objectives

Primarily, this was to identify phenotypic and biochemical markers which predict HGD or IPMN malignancy in a group of presumed innocent BD-IPMN. Secondary outcomes include determining the outcomes of BD-IPMN surveillance, time to develop actionable findings, temporal relationship of dysplasia development and overall survival. These will be used to identify whether de-escalation/stopping rules for surveillance can be modelled.

Statistical analysis

Continuous data are reported as median [interquartile range (IQR)] and categorical data are presented as *n* (%). Analyses are conducted on a complete case basis with no imputation for missing data performed. Time-to-event outcomes of interest are the time from initial scan until surgery and overall survival measured as the time from surgery until death by any cause, with patients censored at the date last known to be alive. Analyses are performed using exploratory and graphical representations with survival data presented using Kaplan-Meier curves. Log rank tests are applied to evaluate differences in time to events of interest between patient groups and hazard ratios are extracted from univariate Cox proportional hazards models. Cumulative incidence curves are used to evaluate the incidence of dysplasia and

malignancy over time. Longitudinal data are dichotomised to determine if patients reached pre-defined thresholds with χ^2/Fisher tests performed to assess the association between these thresholds and HGD or malignancy. The predictive ability of continuous markers is assessed using receiver operating characteristic curves with the area under the curve (AUC) used to measure predictive ability of HGD or malignancy and 95% confidence intervals (CIs) obtained using DeLongs method. To evaluate the possibility of combined effectiveness of multiple markers, multivariable logistic regression models are applied. All analyses are performed using R (version 4). A *P* value of 0.05 is used throughout to determine statistical significance. Surgical complications are recorded as per the International Study Group for Pancreatic Surgery guidelines and by Clavien-Dindo criteria[11-14].

RESULTS

Of 1303 patients with pancreatic cystic lesions were referred to the supra regional MDT between 1 January 2007 and 31 May 2018. Six were excluded who had benign or no abnormality present, leaving 1297. 1191 (92%) patients with presumed innocent BD-IPMN continued into the LISP with 106 IPMN patients being discharged at first MDT; 65 patients ≥ 80 years old, 41 with significant co-morbidity or poor performance status. A further 6 were excluded who had benign or no abnormality present (Figure 1; Table 1). Surveillance follow-up was recorded up to 30 April 2023. Median (IQR) overall follow-up was 9.74 years (7.79-11.2) years.

Prediction of HGD and malignancy

Longitudinal profiles were available for 1075/1297 (82%) of patients who provided information on cyst size, carcinoembryonic antigen (CEA) and CA19-9 (Table 2). Using a cyst size cut-off of 30 mm, patients who have a cyst size ≥ 30 mm were more likely to have a high grade dysplastic/malignant outcome 7/101 (7%) than those with a cyst size < 30 mm 7/884 (1%) ($P < 0.001$). This is maintained for malignancy or HGD only. For patients who had undergone EUS sampling of cyst fluid, 61% (12/17) had a finding of any grade of dysplasia with a CEA value ≥ 450 μg/L, compared to 115/476 (24%) of patients who do not meet this threshold ($P < 0.001$). However, no patients with CEA value ≥ 450 μg/L displayed HGD or malignancy. The cut of 450 μg/L is the standard reference in Liverpool, the same was also true when we analysed the data for a cut off of 192 ng/mL, which is used by most other centres and guidelines. For patients who had undergone EUS sampling of cyst fluid with a CA19-9 value, using a cut-off ≥ 90 KU/L, 15/78 (19%) with a high CA19-9 had a high-grade dysplastic/malignant finding compared to 23/415 (5.5%) of those who did not meet this threshold ($P < 0.001$).

The performance of each marker as a predictor of either HGD or malignancy was evaluated using AUC curve. Figure 2 shows the receiver operating characteristic plot for each predictor AUC (95%CI) and shows that serum CA19-9 of ≥ 43 KU/L [AUC = 0.78 (0.80-0.87)] and cyst size ≥ 30 mm [AUC = 0.76 (0.60-0.93)] are the markers with the best predictive value of HGD/malignancy within a BD-IPMN. Cyst CA19-9 ≥ 42 KU/L [AUC = 0.71 (0.63-0.79)] also shows moderate predictive ability. Adding these models together does not improve predictability in multivariate analysis [AUC = 0.76 (0.49-1)]. CEA either in the serum 4 μg/L [AUC = 0.59 (0.32-0.67)] or cyst 450 μg/L [AUC = 0.56 (0.40-0.71)] showed little ability to predict HGD/malignancy. A further analysis was undertaken to explore the longitudinal profile of serum CA19-9 over time in surveillance, with respect to dysplasia/malignancy (delta value) (Figure 2; Supplementary Table 1). There was little evidence that change in marker outperformed the absolute value (even when an increase in cut off was modelled), AUC = 0.43 (0.02-0.85). When additionally modelled for the relationship between all markers and surgery, over time, size of cysts and serum CA19-9 maintained a weak relationship (Supplementary Figure 2; Supplementary Tables 2 and 3).

Outcome of lesions

Over the course of this study, 483 (41%) patients of the 1191 who were in surveillance underwent cross-sectional imaging plus one or more EUS examinations for interval development of HRF/WF or new symptoms (imaging + EUS group), while 708 (59%) similarly, underwent cross-sectional imaging alone (imaging only group). In the imaging only group, 66/708 (9%) patients had lesions requiring further action compared to 114/483 (24%) in the imaging + EUS group (Figure 1; Table 1). 187 patients in the image alone group were medically discharged for poor performance status. Additionally, a further 117, 23 and 6 following the first, second and third EUS respectively were similarly discharged. 147 patients left surveillance by their own choice. The median (IQR) age of these 480 patients who were discharged or left was 75 (67-79), 194 were female. 156 of this group subsequently died (32.5%), one of whom died from an ampullary carcinoma and received best supportive care, the others from non-pancreas related causes. Another 106 patients died from non-cancer causation during various points of surveillance, 54 were male, median (IQR) age was 73 (67-76) and median (IQR) time in surveillance was 5.41 (2.80-8.05) years. 425 patients continued through LISP without intervention. The overall median (IQR) age of the whole population was 71 (64-77). There was no difference between age of diagnosis and rate of malignant transformation of cystic lesions: 7/213 (3.4%) for those aged 80 or over *vs* 54/1090 (5%) aged under 80, $P = 0.38$.

Time to intervention for lesions requiring action (actionable lesions)

In the surveillance group of 1191, 180 patients were identified with an actionable lesion. 27 did not undergo resection with 153 undergoing surgery, of which 125 had IPMN, including 29 that had transformed to adenocarcinoma (t-IPMN) (Supplementary Table 4). There was an additional five c-PDAC and one pancreatic neuroendocrine tumour (counted in other). A further five serous cystic neoplasms, five mucinous cystic neoplasms [1 intermediate grade dysplasia (IGD) and 4 low grade dysplasia (LGD)] and 12 benign lesions (three retention cysts; two each of pseudocysts, acinar cystadenomas, epithelial cysts, and one each of renal cell carcinoma metastasis and autoimmune pancreatitis both adjacent to an

Table 1 Frequency of endoscopic ultrasounds performed during surveillance relative to the time to surgery and final diagnosis

	IPMN, *n* = 1130	t-IPMN, *n* = 49	c-PDAC, *n* = 12	Other, *n* = 75	SCN, *n* = 37	Total, *n* = 1303
Male/female	450:680	19:30	2:10	31:44	10:27	512:791
Age, median (IQR)	71 (64-78)	74 (67.5-77)	71 (67-73.5)	66 (56-72)	69 (64-75)	71 (64-77)
Discharged	112					112
Total	1018	49	12	75	37	1191
Imaging and EUS during screening						
0 EUS, returned to LISP	645, 450	29	4	27, 4	3, 1	708, 455
1st EUS, returned to LISP	293, 162	11	6	35, 5	26, 6	371, 173
2nd EUS, returned to LISP	63, 33	8	2	8, 1	6, 3	87, 37
3rd EUS, returned to LISP	12, 7	1		5, 1	2, 1	20, 9
4th EUS, returned to LISP	4, 3					4, 3
5th EUS, returned to LISP	1, 1					1, 1
Overall, returned to LISP	1018, 206	49	12	75, 7	37, 10	1191, 678
Treatment < 2 years by imaging and EUS						
0 EUS, surgery < 2 years	28	24	2	3	1	58
1st EUS, surgery < 2 years	47	2	1	9	4	63
2nd EUS, surgery < 2 years	7	2	1	1		11
3rd EUS, surgery < 2 years	2					2
4th EUS, surgery < 2 years						0
5th EUS, surgery < 2 years						
Overall surgery, < 2 years	84	28	4	13	5	134
Overall palliation, < 2 years		6	1			7
Treatment > 2 years by imaging and EUS						
0 EUS, surgery > 2 years	1					1
1st EUS, surgery > 2 years	3		1	1		5
2nd EUS, surgery > 2 years	6	1		3		10
3rd EUS, surgery > 2 years	1			1		2
4th EUS, surgery > 2 years	1					1
5th EUS, surgery > 2 years						
Overall surgery, > 2 years	12	1	1	5	0	19
Overall palliation, > 2 years		14	6			20
Overall surgery	96	29	5	18	5	153
Overall palliation		20	7			27

LISP: Liverpool intraductal papillary mucinous neoplasm screening pathway; EUS: Endoscopic ultrasound; IQR: Interquartile range; IPMN: Intraductal papillary mucinous neoplasm; t-IPMN: Transformed intraductal papillary mucinous neoplasm; c-PDAC: Concomitant pancreatic ductal adenocarcinoma; SCN: Serous cystic neoplasm.

innocent BD-IPMN, where MDT thought there was IPMN-transformation, and finally a duodenal diverticulum). Of the patients with PDAC (n = 61), 39 (34 t-IPMN and 5 c-PDAC) were found < 2 years of surveillance compared to 22 (15 t-IPMN and 7 c-PDAC) found > 2 years in surveillance (not significant). However, significantly more were resected < 2 years (32/39, 82%) than > 2 years (2/22, 9%), P < 0.00001. Apart from one patient in the < 2 years group (c-PDAC) who developed metastatic disease between surveillance intervals, all of the other non-resectable patients were unfit for surgery at the time of diagnosis (Table 1).

Table 2 Longitudinal profiles of physical and biochemical characteristics of cysts for each degree of dysplasia

		LGD	IGD	HGD	Malignant	Not stated	Imaged only	Total
Cyst size (mm)	< 30	33	10	0	7	9	825	884
	> 30	18	11	3	4	5	60	101
	Total	51	21	3	11	14	885	985
Missing		15	5	3	24	6	259	312
Cyst CEA (μg/L)	< 450	56	21	6	32	16	345	476
	> 450	8	4	0	0	0	5	17
	Total	64	25	6	32	16	350	493
Missing		2	1	0	3	4	794	804
Cyst CA19-9 (KU/L)	< 90	54	21	6	17	16	301	415
	> 90	10	4	0	15	0	49	78
	Total	64	25	6	32	16	350	493
Missing		2	1	0	3	4	794	804
Serum CEA (μg/L)	< 5	31	12	3	8	14	635	703
	> 5	2	0	0	0	1	18	21
	Total	33	12	3	8	15	653	724
Missing		33	14	3	27	5	491	573
Serum CA19-9 (KU/L)	< 40	56	22	5	10	15	678	786
	> 40	9	3	1	23	3	55	94
	Total	65	25	6	33	18	733	880
Missing		1	1	0	2	2	411	417

LGD: Low grade dysplasia; IGD: Intermediate grade dysplasia; HGD: High grade dysplasia; CEA: Carcinoembryonic antigen; CA19-9: Cancer antigen 19-9.

All prevalence findings were removed prior to this analysis such that the overall median (IQR) time to surgery from entering surveillance was 5.0 (2.7-11.3) months and 88% of all surgical interventions were within the first two years (134 cases; Figure 3) with eight further cases between two and four years, seven cases between four and six years and only four cases thereafter. Only one of the 29 t-IPMN and one of the five c-PDAC were resected after two years, both between the 6th and 7th year of surveillance (Figure 3). Overall survival following resection of an IPMN subtype is significantly higher than for those who had resections for c-PDAC/t-IPMN (hazard ratio = 5.14, 95%CI: 3.06-8.64, $P < 0.001$; Figure 4).

Fewer patients with 2 or more EUS have an actionable finding or present to surgery. Of the 153 patients who underwent surgery 127 (83%) had 2 EUS *vs* 26 (17%), who had > 2 EUS, with median (IQR) time to surgery of 4.2 (2.2-7.5) and 22.6 (9.0-57.1) months respectively (Figure 3C). Details on surgical procedures and complications is provided as Supplementary Tables 5-7.

Time to observe malignancy

A stacked cumulative incidence plot for each grade of dysplasia or malignancy, from resected individuals was constructed to estimate the median (IQR) time to observe malignancy (t-IPMN and PDAC). Time to observe malignancy was 2.96 (2.11-7.77) years. Time to observe LGD, IGD and HGD (*i.e.,* time to surgery) was 10.41 (9.91-12.01) years, 12.17 (10.14-13.8) years and 10.64 (9.61-17.42) years respectively (Figure 5), with no statistical difference in the time taken to observe each grade of dysplasia: HGD *vs* LGD; $P = 0.754$; HGD *vs* IGD; $P = 0.728$ and IGD *vs* LGD; $P = 0.899$.

DISCUSSION

This study represents the outcomes of surveillance of BD-IPMN over 17 years in a supra-regional pancreas referral unit. The results of this study suggest three important findings: Firstly, that surgery is front loaded and the opportunity to resect PDAC appears to occur early in surveillance. Secondly, the incremental return of continued investigations and the need for optimal true risk reducing surgery dramatically diminishes after two years, mainly due to reduced patient fitness. Lastly, patients who have been in surveillance for more than two years who have a serum CA19-9 < 43 KU/L and BD-IPMN stability at < 30 mm have low rates of malignant transformation and surveillance can be de-escalated and

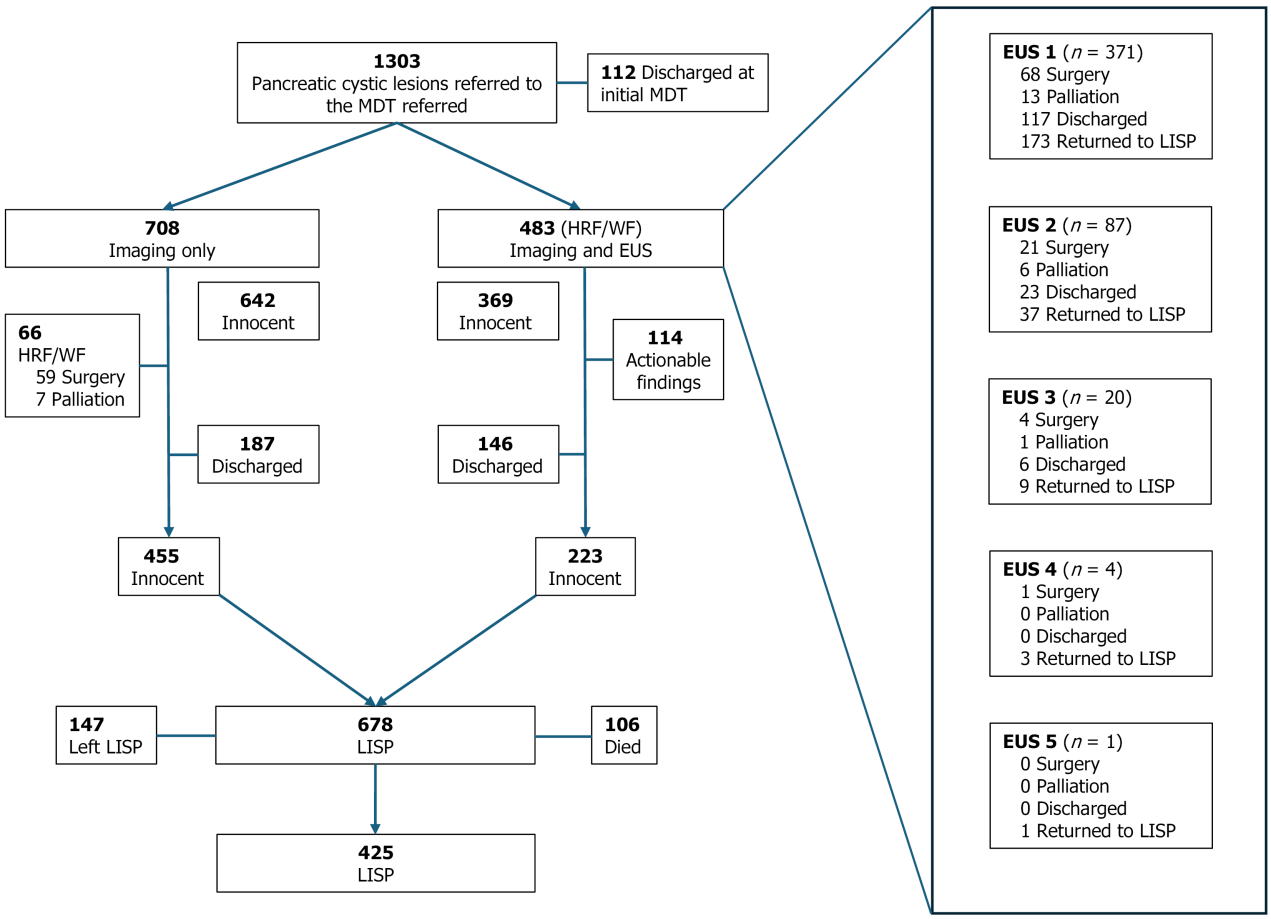


Figure 1 Summary of progression of patients through the cyst surveillance programme. MDT: Multidisciplinary team meeting; HRF: High-risk feature; WF: Worrisome feature; EUS: Endoscopic ultrasound; LISP: Liverpool intraductal papillary mucinous neoplasm surveillance programme.

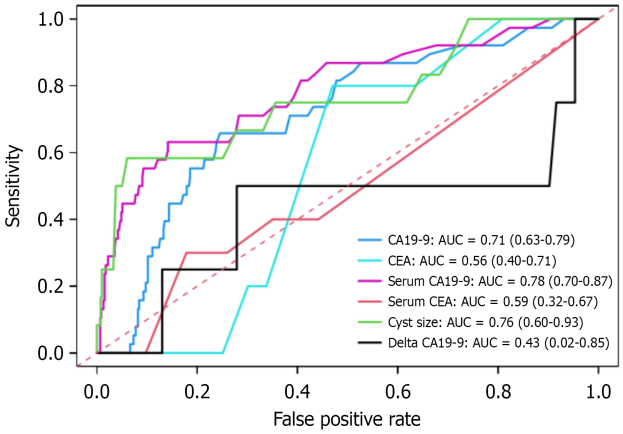
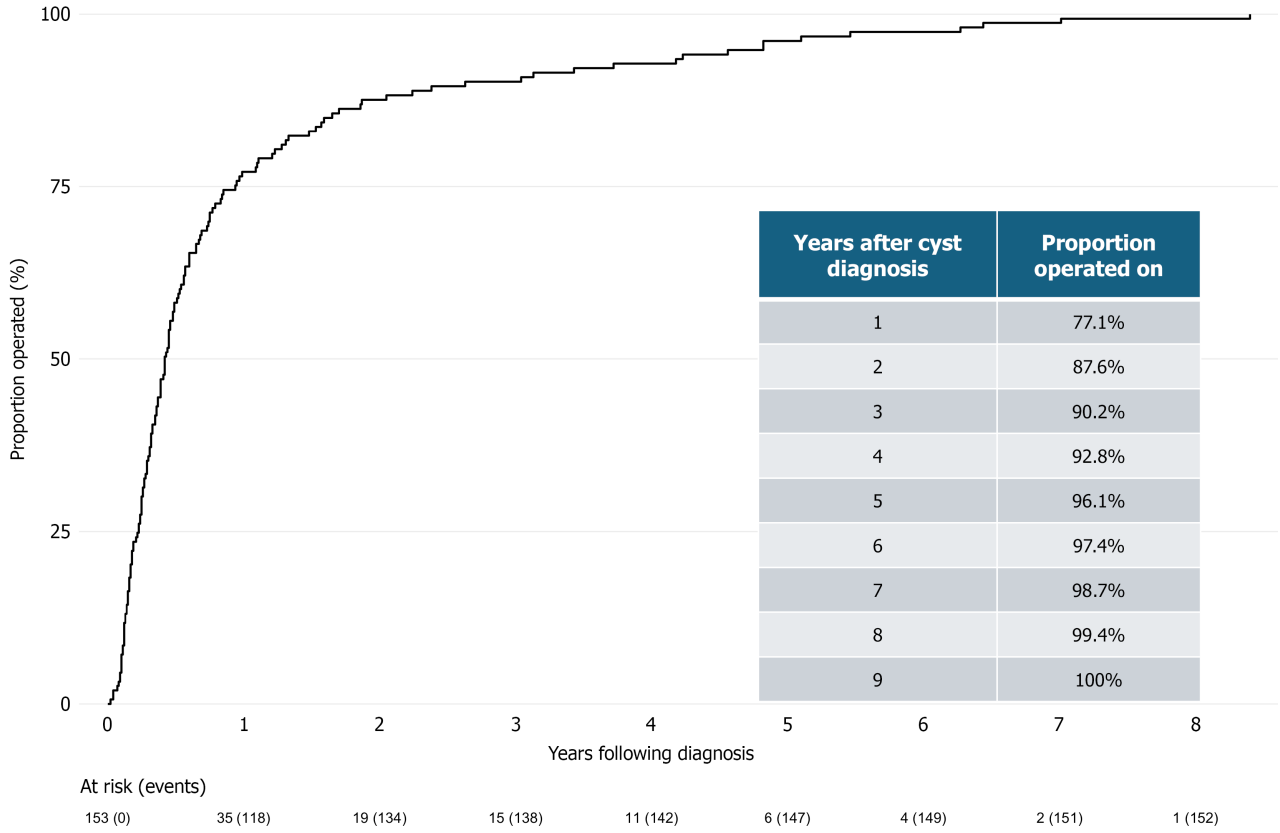


Figure 2 Receiver operator characteristics plot showing the diagnostic ability of maximum cyst size and maximum cyst-fluid and serum cancer antigen 19-9 and carcinoembryonic antigen in predicting high grade dysplasia or malignancy. Cancer antigen 19-9 was additionally modelled for the diagnostic ability of the change in cancer antigen 19-9 (delta value) in predicting high grade dysplasia or malignancy. CA19-9: Cancer antigen 19-9; AUC: Area under the curve; CEA: Carcinoembryonic antigen.

discharge considered at five years.

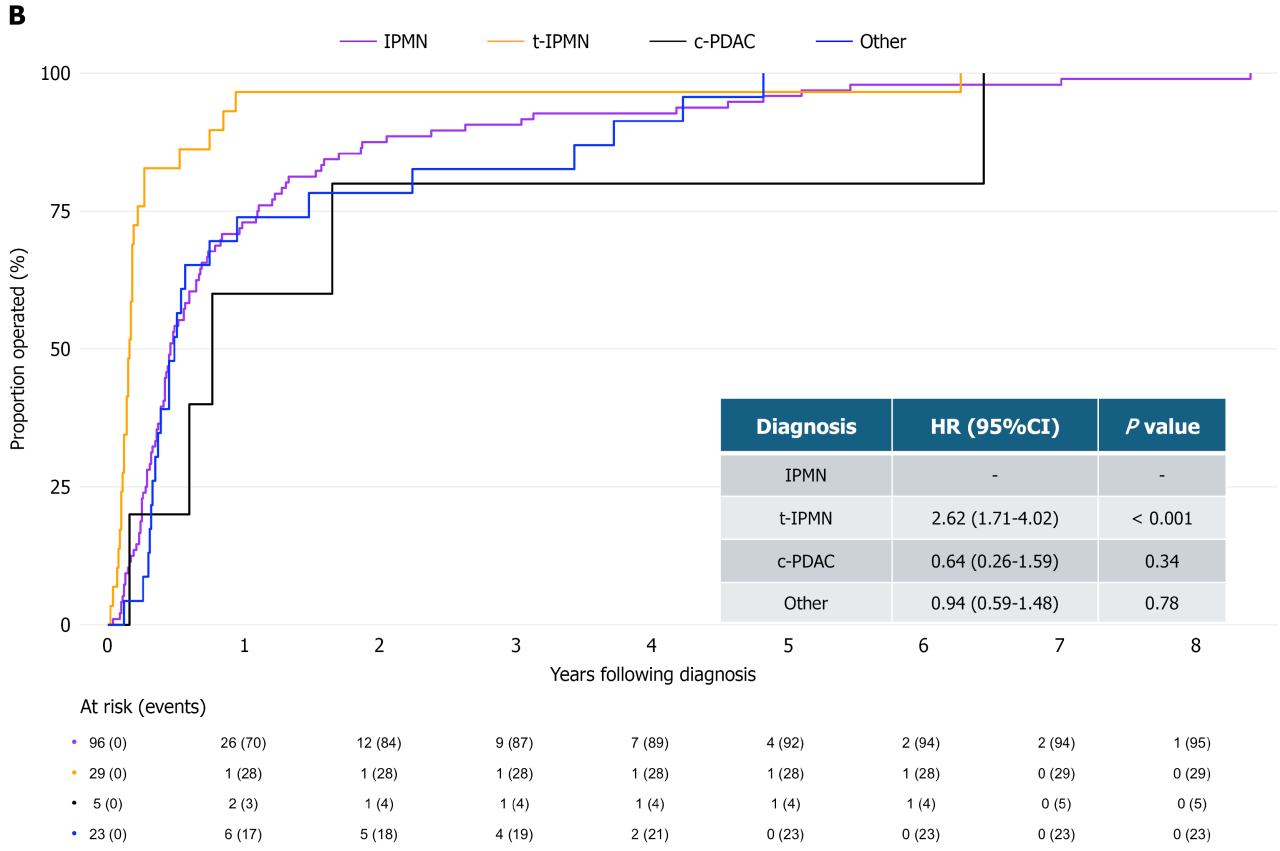
Neither serum nor cyst fluid CEA was able to distinguish malignancy from non-malignancy and serves only as a proxy for mucin content. This is no different if a more standard cut-off of 192 ng/mL for cyst fluid CEA is used as opposed to our unit cut-off of 450 μg/L. Cyst fluid CA19-9 ≥ 42 KU/L [AUC = 0.71 (0.63-0.79)] shows moderate predictive ability but has limited generalisability. However, both serum CA19-9 ≥ 43 KU/L [AUC = 0.78 (0.70-0.87)] and cyst size ≥ 30 mm [AUC = 0.76 (0.6-0.93)] are the markers with the best predictive value of HGD/malignancy within IPMN. When analysed longitudinally, this does not change with time in surveillance (delta value). HGD and malignancy have vastly different

A



Years after cyst diagnosis	Proportion operated on
1	77.1%
2	87.6%
3	90.2%
4	92.8%
5	96.1%
6	97.4%
7	98.7%
8	99.4%
9	100%

B



Diagnosis	HR (95%CI)	*P* value
IPMN	-	-
t-IPMN	2.62 (1.71-4.02)	< 0.001
c-PDAC	0.64 (0.26-1.59)	0.34
Other	0.94 (0.59-1.48)	0.78

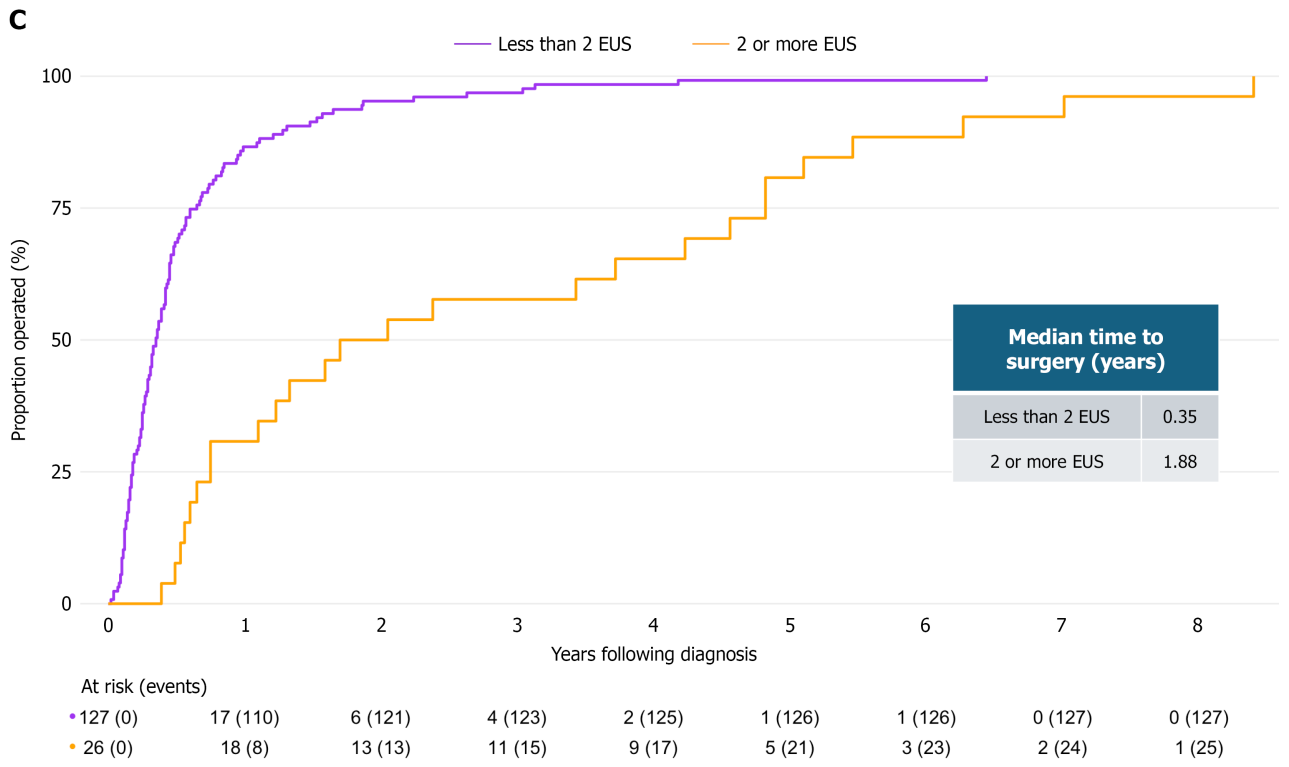


Figure 3 Time to surgery from initial diagnosis. A: Time to surgery (overall) with table showing proportion of surgeries performed per year following cyst diagnosis; B: Time to surgery (subgroups) with table showing difference in time to surgery between subgroups; C: Time to surgery (by number of endoscopic ultrasound) with table showing median time to surgery for each group. IPMN: Intraductal papillary mucinous neoplasm; t-IPMN: Transformed intraductal papillary mucinous neoplasm; c-PDAC: Concomitant pancreatic ductal adenocarcinoma; HR: Hazard ratio; CI: Confidence interval; EUS: Endoscopic ultrasound.

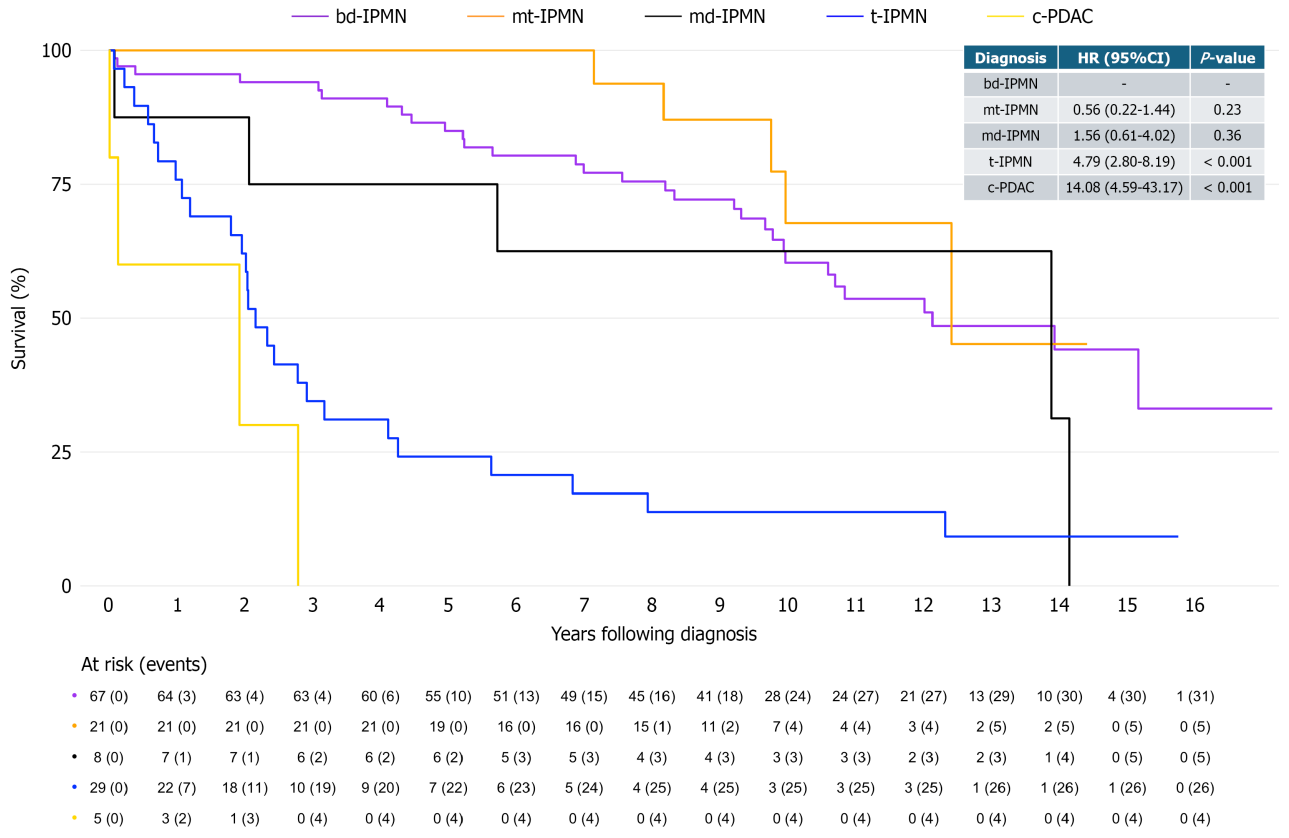


Figure 4 Overall survival following surgery for an intraductal papillary mucinous neoplasm grouped by histological diagnosis. bd-IPMN:

Branch duct intraductal papillary mucinous neoplasm; mt-IPMN: Mixed type intraductal papillary mucinous neoplasm; md-IPMN: Main duct intraductal papillary mucinous neoplasm; t-IPMN: Transformed intraductal papillary mucinous neoplasm; c-PDAC: Concomitant pancreatic ductal adenocarcinoma; HR: Hazard ratio; CI: Confidence interval.

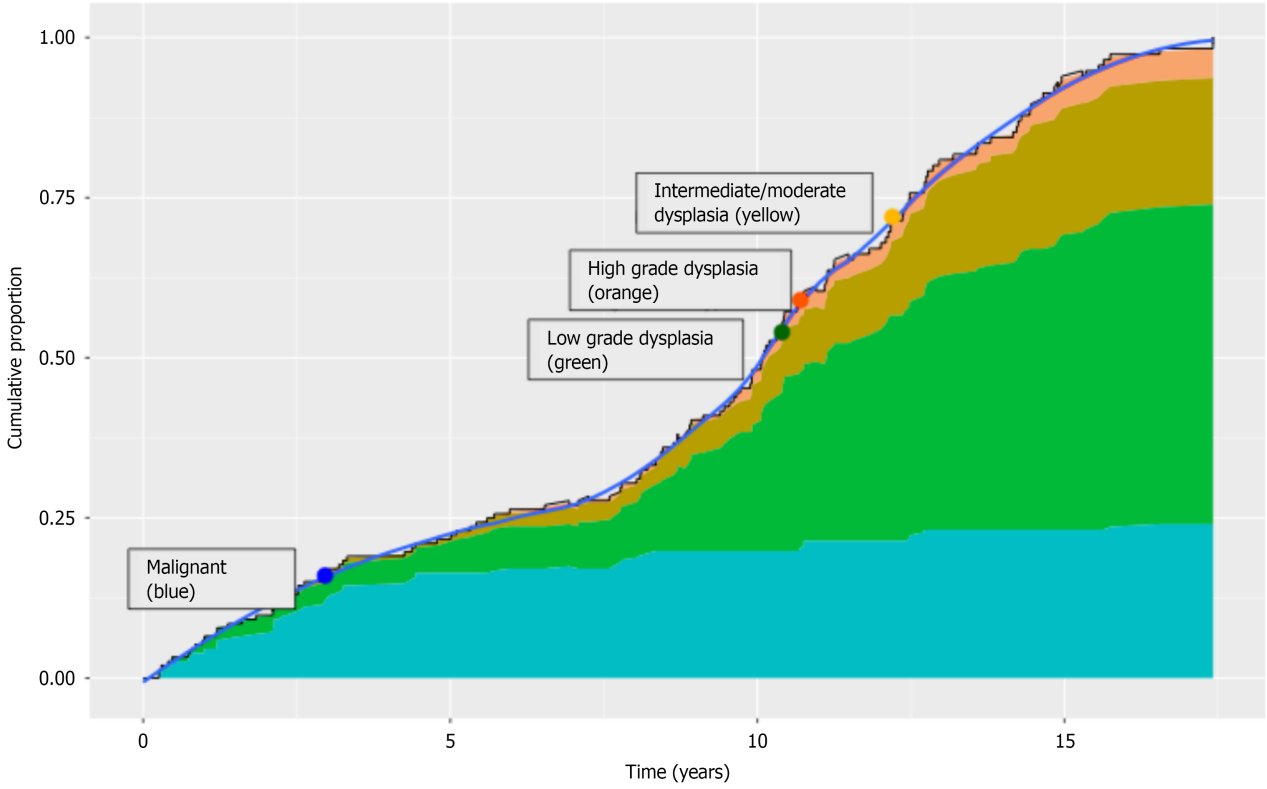


Figure 5 Stacked cumulative incidence plot. Included are the points on the cumulative curve at which each grade of dysplasia reaches 50% of its final proportion. This gives an estimate of the average time required to observe each outcome.

outcomes after surgery; we have grouped these together as they are the more pertinent outcomes, although they are independent of each other in sub-analyses. We have previously published that a CA19-9 > 37 KU/L is a highly specific marker of IPMN malignancy[15]. This study has larger numbers, and we were able to refine a cut off of 43 KU/L. We accept this was optimised for our cohort and that some clinicians will be more comfortable using > 37 KU/L as a standard.

There are limitations to this study. Firstly, it was devised as a retrospective analysis of a prospectively maintained database. Identification of suitable patients for this study relied on the records of the regional pancreatic cyst MDT, which requires patients to be referred by their local clinicians, potentially introducing selection bias. Also, we have maintained the use of the three-grade dysplasia system which was in place at the start of LISP and has been kept for consistency and for use in the stacked cumulative incidence plot, which is no longer standard practice. We have purposely not included other specific factors that affect transformation (WF or HRF) as they are well documented and reviewed elsewhere and wanted to focus on the risk with presumably innocent BD-IPMN without other bias. We do feel that confirmation of innocence is mandatory prior to de-escalation, hence in LISP the cut off for EUS of a cyst remains at 20 mm or greater. Equally, we have not used genetic markers as we have already published that the risk of finding BD-IPMN was independent of genetic predisposition, which is supported in the Kyoto guidelines[7]. Another possible confounder is that those lesions that were found beyond 2 years are by nature slower to establish concerning features or malignancy. That said only one t-IPMN and one c-IPMN that were found after 2 years were amenable to surgery, found at between year 6 and 7 of surveillance, with population fitness being the main limitation to treatment.

The population we have presented can be viewed in different ways. It could be criticised because it ultimately contained several different IPMN lineages and non IPMN lesions. Alternately, because of this it can act as its own denominator population such that comparisons can be made between malignancy, dysplasia and benign lesions. That said, this series represents a real-world population of cystic lesions surveilled in a typical supra-regional centre and reflects that commonality. Likewise, misclassification of lesions is well reported in surgical series[10,16], the data presented here are representative of these contemporaneous accounts. Although the application of next generation sequencing will likely answer some of these problems, it is not yet widely available and is rarely used in the United Kingdom and not available in Liverpool, further reflecting overall generalisability. More detailed health economic modelling is beyond the scope of this paper.

We propose that at 2-years in surveillance, given that the return of important findings is limited in time, operability and to beyond two separate EUS examinations, a more relaxed, less invasive approach could be adopted providing cyst size remains stable < 30 mm with a serum CA19-9 of < 43 KU/L, thereafter. The limitation in operability of such lesions beyond 2 years is related to sequential reduction in patient fitness, in an aging and co-morbid population which is associated with longer length of time in surveillance. It is therefore vital that after each round of surveillance, age, fitness and length of time in follow up should be carefully assessed and discussed with participants. Although these conclusions were independent of age, it is clearly the case that younger individuals will require longer surveillance, albeit only 84/1303 (6.4%) of our cohort were < 50 years old at time of diagnosis. Given that the median age (IQR) at the start of surveillance is 71 (64-78) in this study, after 5 years of surveillance, the majority of patients will be in their late 70s, likely to be in declining health and have greater risk of mortality from non-IPMN/PDAC related causes. These patients, with cyst size and serum CA19-9 stability could, therefore, be considered for discharge from IPMN surveillance. Discontinuing pancreatic cyst surveillance should not be mistaken as there being no risk of PDAC in the future for an individual, as we have clearly shown. Instead, this will ensure that surveillance is targeted towards those who are most likely to benefit from it, which is in line with the requirements of any screening programme as set out by the World Health Organisation and Wilson and Jungner[17].

Crippa *et al*[18] concluded that active surveillance beyond 5 years was necessary due to the development of WF/HRF after 5 years, but even after they applied a strict diagnostic criterion to determine who was included in their study, only 5 individuals had an invasive carcinoma or high grade dysplastic IPMN excised. This degree of selectivity is not consistent with clinical practice and is therefore unlikely to be generalisable. Kwong *et al*[19] conclude that the risk of malignancy in individuals with pancreatic cysts is low beyond 5 years, providing they have less than 2 high risk features after 5 years of surveillance, which is most in keeping with our findings. Unlike Marchegiani *et al*[20], we did not exclude cysts operated on within 12 months as our supposition was that there was a trend to earlier surgery and lack of full characterisation of lesions at initial review. Also, whilst technically a multicentre study with a large cohort, some centres contributed a relatively small number of cases to the Marchegiani cohort, which may inaccurately represent the population served by each contributing centre. More recently, Levink *et al*[21] have reported that individuals with a stable cyst size without WF/HRFs did not have an increased risk of PDAC or HGD compared with the general population. They showed that, for those in their cohort who went on to develop WF/HRFs or develop HGD/PDAC, this happened with a median time of 23 months following the initial detection of a pancreatic cyst, very much in keeping with our observation of 88% surgical intervention taking place within the first two years of surveillance.

CONCLUSION

This observational study represents a real-world analysis of BD-IPMN surveillance that reflects how most surveillance schemes operate, rather than an artificially created cohort. The time has come to think carefully about how intensively and for how long we follow up such patients.

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FOOTNOTES

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