Management and Outcome of 64 Patients with Pancreatic Serous Cystic Neoplasms

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ABSTRACT

Background: The optimal management approach to pancreatic serous cystic neoplasms (SCNs) is still evolving.

Methods: Consecutive patients with SCN managed at the Liverpool Pancreas Cancer Centre between 2000 and 2013 were retrospectively reviewed.

Results: There were 64 patients, 39 women (60.9%) and 25 men (39.1%). Forty-seven patients (73.4%) had surgical removal and 17 (26.6%) were observed. The possibility of a non-SCN malignancy was the predominant indication for resection in 27 (57.4%) patients. Post-operative morbidity occurred in 26 (55.3%) patients with two (4.3%) deaths. An increased risk of resection was associated with patient's age ($p=0.011$), diagnosis before 2009 ($p<0.001$), pain ($p=0.043$), possibility of cancer ($p=0.009$) and a solid SCN component on imaging ($p=0.002$). Independent factors associated with resection were a diagnosis before 2009 ($p=0.005$) and a solid SCN component ($p<0.001$). Independent factors associated with shorter time to surgical resection were persistent pain ($p=0.003$) and a solid SCN component ($p=0.007$).

Discussion: There was a reduction in the proportion of resections with the application of an observe-only policy for asymptomatic patients with more definite features of SCN. Improved criteria are still required in the remainder of patients with uncertain features of SCN in deciding for intervention or surveillance.

INTRODUCTION

Pancreatic serous cystic neoplasms (SCNs) comprise 10–15% of pancreatic cystic neoplasms and 1–2% of all pancreatic neoplasms [1]. SCNs along with other pancreatic cystic neoplasms including mucinous cystic tumours, cystic pancreatic endocrine neoplasms, solid pseudopapillary neoplasms and intraductal papillary mucinous neoplasms (IPMNs), are increasingly identified as a consequence of the wider application of cross sectional imaging [2-4]. They are either discovered incidentally [2,5] or are associated with non-specific abdominal symptoms due to local expansion [3,6]. In contrast to mucin producing cystic tumours, SCNs are almost always benign with only a small number of primary serous cystadenocarcinomas reported [7-12].

Improvements in pancreatectomy with lower associated mortality have increased our confidence in performing pancreatic resections for ambiguous pancreatic lesions[13,14], however the associated morbidity remains high even in specialized centres [15]. The decision to operate on or observe patients with SCNs, or with equivocal imaging characteristics resembling SCNs, remains very challenging [3,16].

This study aims to contribute to the improved management of SCNs, by identifying factors that influence decision making for resection versus surveillance.

METHODS

Patients with a final diagnosis of SCN were identified from the databases of the Multi-Disciplinary Team of the Liverpool Supra-Regional Pancreas Cancer Centre and the National

Institutes of Health Research (NIHR) Pancreatic Biomedical Research Unit (PBRU) of the Royal Liverpool University Hospital. The diagnosis of SCN was based on radiology [17] and/or pathology following surgical resection [18]. The data refining and analysis was undertaken retrospectively and covered the period from the 1st January 2000 until 31st December 2013. Because of incomplete data for some fields the denominator is given when less than the total number of expected observations.

The Multi-Disciplinary Team included specialist pancreatic surgeons, gastroenterologists, medical oncologists, radiologists and pathologists. All patients were reviewed at the Multi-Disciplinary Team weekly meeting. The diagnosis or differential diagnosis of SCN and the decision to operate or undertake further imaging was made collectively at the meeting and recorded at the time. From 2009 in addition to cross sectional imaging, endoluminal ultrasound (EUS) with fine needle aspiration was used to assist decision making according to the Liverpool pancreatic cyst protocol (which is being prospectively evaluated). In addition to worrying radiological features, the indications for intervention for any type of pancreatic cyst are suspicious cytology, cyst fluid CA 19.9 > 50,000 KU/L and or cyst fluid CEA>450 μg/L [19-21].

The macroscopic imaging diagnosis of SCN was categorised as microcystic (honeycomb) type (cysts < 1cm), macrocystic/oligocystic type (cysts > 1 cm), mixed microcystic and macrocystic type, and solid type [22]. The diagnosis of SCN was histologically confirmed in all patients who underwent a resection. Patient characteristics including demographics, disease presentation, comorbid conditions, radiological and endoscopic evaluation and relevant surgical treatment with pathology, morbidity, mortality, postoperative recovery and length of hospital stay were obtained. Follow up data were collected from Multi-Disciplinary Team proformas, hospital admissions and clinic visits.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR) and were compared using Mood's median test; categorical variables were compared using Fisher's exact probability test (two-tailed). Median resection free period and corresponding episode free periods were calculated by the Kaplan-Meier method and the asymptotic log rank test was used to evaluate significant differences. Univariate logistic regression was used to identify factors predictive of a pancreatic resection. Subsequent multivariate logistic regression was used to assess independent predictors of pancreatic resection vs. observation for SCN patients. We used a stepwise model selection process based on the Akaike's Information Criterion and the Le Cessie – Van Houwelingen test to assess the goodness of fit of the optimal predictive model. Finally, a Cox proportional hazards model was used to assess the effect of various covariates on the resection free period and Scaled Shoenfeld residuals were used to evaluate the proportional hazards assumption. The significance level for all the tests was set to $\alpha = 0.05$. Statistical analyses were performed using R version 3.0.2 (R Development Core Team, 2013) [23].

RESULTS

Sixty four patients with SCN were identified spanning the 14 year time period consisting of 39 (60.9%) women and 25 (39.1%) men, with a median (IQR) age of 70.5 (59-77) years (Table1). There were smoking and alcohol data on 39 patients, of whom 12 (30.8%) were smokers and 19 (48.7%) had excess alcohol intake. Cystic pancreatic lesions were discovered incidentally during work-up for another condition in 31 (55.4%) of 56 patients. Documented presenting symptoms included pain in 15 (27.8%) of 54 patients, diarrhoea in 5 (10.2%) of 49 patients and jaundice in 3 (5.6%) of 54 patients. Diabetes was present at the time of referral in 5 (10.4%) of 48 patients while a single patient (2%) of 49 patients had exocrine insufficiency. Forty-seven patients (73.4%) underwent a resection and 17 (26.6%) were followed up. The indications are shown in Figure 1 (CONSORT).

Imaging

Computed tomography (CT) was the initial diagnostic modality in 50 (78.1%) patients followed by magnetic resonance imaging (MRI) in seven (10.9%), abdominal ultrasound (US) in five (7.8%) and EUS in two (3.1%) patients (Table 1). CT continued to be applied as a monitoring tool in 32 (64%) of 50 patients. In the remaining 18 patients, additional imaging modalities during the follow up period included EUS in nine (14.1%), MRI in two (3.1%), MRI and EUS in four (6.3%), laparoscopic ultrasound in two (3.1%) and positron emission tomography (PET) CT in another (1.6%). The initial diagnosis of SCN in 14 (21.9%) patients did not involve CT, of whom six had an MRI, four had an EUS, three had a transabdominal US and one had a combination of EUS and MRI.

The use of EUS for surveillance was not statistically significant either before (n=6, 23.1%) or after (n=12, 31.6%) 2009 (p=0.575). EUS was more frequently performed in patients with

lesions measuring ≤ 30mm in diameter (N=14, 45.2% vs. N=2 6.7%, p=0.001) but was not associated with subsequent resection (12/18, 66.7% vs 35/46, 76.1%, p=0.533).

On imaging a solid element was present in 25 (46.3%) of 54 cystic lesions, calcifications in 13 (23.2%) of 56 lesions, eight (14.5%) of 55 cysts were hypervascular, there was a dilated (>6mm) main pancreatic duct in nine (16.4%) of 55 patients and there was vascular compression by the cyst in six (10.9%) of 55 patients.

Twenty-six (40.6%) SCNs were located in the head of pancreas, 16 (25%) in the pancreatic tail, 11 (17.2%) in the pancreatic body, six (9.4%) in the body and tail of pancreas, one (1.6%) in the pancreatic head and neck junction, one (1.6%) each in the pancreatic neck and body junction, the pancreatic neck and the uncinate process and one other replaced the entire pancreas. The median (IQR) cyst diameter was 3 (2.1-5.7) cm. Thirty-two (51.6%) of 62 cysts were microcystic, 26 (41.9%) were macrocystic, three (4.8%) were solid type and one (1.6%) was mixed type on imaging.

Cyst analysis

Two patients (both with negative cytology) had cyst CA19-9 and CEA levels of 32,730 KU/L and 1,372 μg/L and 11 KU/L and 5,247μg/L respectively and went on to have a resection, the first a pylorus preserving partial pancreato-duodenectomy (PPPD) and the other a radical left pancreatectomy. Both had a macrocystic SCN on histology.

Three other patients (all with negative cytology) had cyst CA19-9 and CEA levels of 1,513 KU/L and 42μg/L, 61 KU/L and <1μg/L and 68,525 KU/L and 431 μg/L respectively and one had levels unreported; all four remain under surveillance.

Surgical procedures

The concern for the possibility of a non-SCN malignant cyst, the presence of a solid cyst component, relatively younger age and pain were all significantly different between the resected and non-resected groups (Table 1). In addition all but one (96.1%) of 26 patients seen during 2000-2009 had resection compared to 22 (57.9%) of 38 patients seen during 2009-2013 ($p<0.001$). The differences in patient characteristics seen before and after 2009 are depicted in Table 2.

The operations comprised a PPPD in 20 (42.6%) patients, a radical left pancreatectomy (with splenectomy) in 14 (29.8%) patients, a spleen preserving left pancreatectomy in eight (17%) patients, a total pancreatectomy and splenectomy in three (6.4%) patients, a duodenum preserving total pancreatectomy in a single (2.1%) patient and a local excision in the remaining one (2.1%) patient. Combined procedures for simultaneous cancers were performed in three patients: an oesophagectomy for oesophageal cancer, a right hemicolectomy for colon cancer and a left nephrectomy for renal cell carcinoma. Post-operative morbidity occurred in 26 (55.3%) patients including two (4.3%) deaths, both in men who had had a PPPD for concerns of non-SCN malignancy. One was 53 years old with portal hypertension due to Child's B liver disease with a 55 mm cyst with calcification, a dilated main pancreatic duct and compression of the hepatic portal vein with persistent symptoms who developed post-operative liver failure. The other was 68 years old with a large cyst in the head of pancreas, who had a major postoperative bleed which could not be controlled with embolization. The median (IQR) total hospitalization was 20 (12- 28.5) days.

Pathology of resected cysts

On histology all of the lesions were completely excised. There were 29 (61.7%) microcystic SCNs, eight of these with a stellate scar, a classic feature of a microcystic SCN.

There were 17 (36.2%) patients with macrocystic/oligocystic SCNs and one (2.1%) had a solid type SCN. Low grade pancreatic neuroendocrine tumours (PNETs) all with a Ki67 <1%, were identified incidentally on histology in eight of the 17 macrocystic/oligocystic SCN specimens, including in one patient with von Hippel Lindau disease. Another patient with a macrocystic/oligocystic SCN also had a splenic marginal zone lymphoma in the specimen.

The median number (IQR) of lymph nodes removed was 10.5 (3-15) and none had any micro-metastases. Pancreatic intraepithelial neoplasia (PanIN lesions type 1 were identified in 22 (53.7%) of 41 pancreata and one (2.4%) specimen had a PanIN type 2. Pancreatic fibrosis was present in 24 (58.5%) of 41 specimens, which was localized around the SCN in most of the patients.

Independent predictors of pancreatic resection

The factors associated with a significant decrease in SCN resection after 2009 compared with previously were further analysed (Table 2). The concern for the possibility of cancer in a non-SCN lesion (based on imaging) as a reason for resection includes a substantive subjective element and was therefore removed from the subsequent regression analysis. This showed that the presence of a SCN solid component as well as diagnosis before 2009, independently predicted the decision to perform a pancreatic resection for SCNs (Table 3a).

The median and 95% confidence interval (CI) resection free time was 3.7 (3.1 -9.1) months. The median (IQR) follow up period was 3.1 (1.9-4.8) months for SCN patients undergoing

resection and 8.3 (7.0-19.2) months for patients under surveillance. Factors associated with a significantly decreased resection free period were the presence of a SCN solid component on imaging (p=0.002; Figure 2a), a SCN diameter ≤ 30 mm (p=0.032; Figure 2b), concern for a non-SCN malignancy (p=0.035; Figure 2c) and persistent pain (p=0.024; Figure 2d). After excluding the cancer fear factor, the Cox proportional hazards model identified persistent pain and a solid SCN component on imaging as being independently associated with shorter time to surgical resection (Table 3b).

DISCUSSION

Currently there is no standard management for SCNs, with preferences ranging from routine surveillance of all patientss to resection for all SCNs [4,8,9,11,12,15,17]. The risk for progression of an SCN to a serous cystadenocarcinoma is extremely low and previous estimates of up to 3% [8] are now known to be excessive with fewer than 25 cases reported in the world literature [18]. Because there are close similarities on imaging between macrocystic/oligocystic SCNs and mucinous cystic neoplasms and IPMNs it is difficult to differentiate between these lesions prior to committing to expectant management. This difficulty partly accounts for variances in proposed management options [Table 4].

In the present study patients with persistent pain and a solid cyst component, indicating concerns of a non-SCN malignant lesion, independently predicted an earlier operation. Patients with SCN diagnosed before 2009 were more frequently operated upon as compared to being followed up with repeat imaging. This can be attributed to changing referral patterns as well as conceptual changes seeking to reduce intervention rates. There were more patients presenting with pain before 2009 and greater use of cross sectional imaging after 2009. A solid component in the SCN and diagnosis or referral before 2009, were independently associated with a decision to perform a pancreatic resection.

A recent joint study from the multi-disciplinary pancreas cancer units at the Universities of Harvard and New York and the Mayo Clinic, Rochester, Minnesota proposed annual imaging for asymptomatic SCNs and those <4 cm [17]. For asymptomatic thin-walled unilocular cystic lesions <3cm they proposed CT or MRI imaging at 6 and 12 months. If there were more complex features or growth rates > 1 cm per year they recommended more intense follow up or resection. It was proposed that symptomatic cystic lesions, neoplasms with high malignant

potential and lesions >3 cm should be referred for surgical evaluation [17]. In practice such guidelines are difficult to follow as there is no relationship between the diameter of SCNs and the risk of malignancy [12]. Moreover if there is a suspected high risk of malignancy then the observed pancreas lesion on imaging is not a SCN. Serous cystadenocarcinoma cannot be defined by the histological appearances of the pancreatic SCN but rather by its behaviour in the development of metastases to the lymph nodes, liver, peritoneum and elsewhere [18,25].

The largest single centre SCN series of 217 patients from the Johns Hopkins Medical Institutions in Baltimore, Maryland, reported that preoperative CT was suggestive of SCN diagnosis in less than a quarter of patients. They proposed that small neoplasms in the body and tail of the pancreas with pathognomonic SCN features on cross-sectional abdominal imaging (comprising a central stellate scar and/or with multiple microcysts) could be managed conservatively [25]. Thus the key issue remains an accurate and certain diagnosis of SCN especially in the case of non microcystic SCNs, which in the current series comprised 32 (50%) of the 64 patients.

The Verona group were able to prospectively monitor 145 patients with SCN of whom only 23 (15.9%) underwent a pancreatic resection during surveillance [12]. The study indicated that in their particular series significant growth of the SCN was unlikely <7 years from baseline and that macrocystic SCNs, a history of non-pancreatic malignancies and increased age were all predictors of SCN growth. The Verona study concluded that asymptomatic or minimally symptomatic SCNs >4 cm could undergo surveillance of no less than two yearly intervals [12]. The diagnostic accuracy of CT for SCN is around 20-23% rate [25,27,28] so additional cross sectional imaging with MRI and EUS especially for cystic lesions measuring ≤ 30mm with a suspicious solid component might improve decision making [29]. The morbidity of pancreatic

resection remains substantial, and although in most series of SCN the mortality from pancreatic resection is low[15,30], every effort is required to avoid mortality from benign conditions. Recently improved surgical results have been shown in a series of 53 patients who underwent enucleation for localised pancreatic lesions (including neoplastic cysts) compared to a case controlled resection series [31]. This is an important positive development and adds another layer in what is becoming a complex management algorithm for this group of patients.

More accurate means of discriminating SCN from other potentially malignant pancreatic cystic neoplasms is needed with considerable interest in cyst fluid tumour markers [32,33]. Presently we are evaluating cyst levels of CA-199 and CEA but the full contribution to clinical decision making is not yet established [19-21]. The combination of GNAS and KRAS testing appears accurate for diagnosing IPMNs but not for distinguishing mucinous cysts from SCNs and other pancreatic cysts [34]. Cyst fluid may be used to detect high-risk IPMNs employing the Das-1 monoclonal antibody raised against a reactive premalignant colonic epithelial phenotype [35]. A nine miRNA panel may also be able to distinguish high-grade IPMNs, PNETs and pseudopapillary neoplasms from low-grade IPMNs and SCNs [36]. Most recently cyst fluid VEGF-A levels were found to be significantly upregulated in test series of SCNs compared with other pancreatic cysts and with a cut-off of 8,500pg/mL, VEGF-A had a 100% sensitivity and 97% specificity as an SCN biomarker [37]. Whilst all of these pancreatic cyst fluid biomarkers look promising they are still in the evaluation stage and need to be validated in independent cohort. EUS employing high-resolution optical imaging also offers considerable opportunities for differentiating serous from mucinous and other cystic neoplasms, which includes both confocal endomicroscopy [38] and optical coherence tomography [39] but further prospective studies are required to determine the most appropriate diagnostic clinical context .

The present study supports the relatively conservative approach proposed by the Verona group of surveillance in asymptomatic patients with definite features of SCN [12]. Nevertheless, improved criteria are still required in the remainder of patients with uncertain features of SCN in deciding whether to continue surveillance or proceed to resection.

Table 1. Comparison between Resection Group and Observation Group of patients with SCN.

Characteristic	Resection Group (n=47)	Observation Group (n=17)	Numbermissing[a]	Relative Risk	p-value[b]
Female	27 (57.4%)	12 (70.6%)	0	0.87	0.397
Age (years)[c]	68 (58.5, 74)	77 (69, 82)	0	-	**0.011**[d]
Year of Diagnosis					
2000 – 2009 (N=26)	25 (53.2%) (96.1%in period)	1 (5.9%) (3.9% in period)	0	-	**<0.001**
2009 – 2013 (N=38)	22 (46.8%) (57.9% in period)	16 (94.1%) (42.1%in period)			
Diagnostic Imaging					
CT	35 (74.5%)	15 (88.2%)	0	-	0.550
MRI	5 (10.6%)	2 (11.8%)			
EUS	2 (4.3%)	0 (0%)			
US	5 (10.6%)	0 (0%)			
Pain	14 (35.9%)	1 (6.7%)	8, 2	**1.46**	**0.043**
Jaundice	3 (7.7%)	0 (0%)	8, 2	1.42	0.552
Diabetes	5 (12.8%)	0 (0%)	8, 8	1.27	0.568
Incidental discovery	21 (52.5%)	10 (62.5%)	7, 1	0.89	0.563
Possibility of cancer	27 (57.4%)	3 (17.6%)	0	**1.53**	**0.009**
EUS for follow up	12 (25.5%)	6 (35.3%)	0	0.88	0.533
Head and Neck SCN	23 (48.9%)	6 (35.3%)	0	1.16	0.402
Macroscopic type[e]					
Macrocystic/Oligocystic	18 (38.3%)	8 (47.1%)	0	-	0.786
Microcystic	24 (51.1%)	8 (47.1%)			
Solid	3 (6.4%)	0 (0%)			
Mixed	1 (2.1%)	0 (0%)			
Unclassified	1 (2.1%)	1 (5.9%)			
Maximum diameter					
SCN ≤ 30mm	25 (55.6%)	6 (37.5%)	2, 1	1.21	0.255
Solid Component	23 (60.5%)	2 (12.5%)	9, 1	**1.78**	**0.002**
Calcifications	9 (23.1%)	4 (23.5%)	8, 0	0.99	1.000
Hypervascularity	7 (17.9%)	1 (6.3%)	8, 1	1.29	0.414
Pancreatic Duct > 5mm	6 (15.8%)	3 (17.6%)	9, 0	0.96	1.000
Vascular compromise	4 (10.5%)	2 (11.8%)	9, 0	0.96	1.000

a. Resected group, Observation group
b. Fisher's exact test
c. Median (IQR)

d. Mood's two-sample median test: Z= -2.546
e. Based on imaging.

Table 2. Clinical characteristics according to the year of diagnosis in patients with SCN.

Characteristic	Before 2009 (n=26)	After 2009 (n=38)	Number missing[a]	p-value[b]
Female	17 (65.4%)	22 (57.9%)	0	0.609
Age (years)[c]	67 (54.3, 74)	72.5 (62, 78)	0	0.884[d]
Diagnostic Imaging				
CT	17 (65.5%)	33 (86.8%)	0	**0.022**
MRI	3 (11.5%)	4 (10.5%)		
EUS	1 (3.8%)	1 (2.7%)		
US	5 (19.2%)	0 (0%)		
Pain	10 (58.8%)	5 (13.5%)	9, 1	**0.001**
Jaundice	2 (11.8%)	1 (2.7%)	9, 1	0.230
Diabetes	1 (5.9%)	4 (12.9%)	9, 7	0.643
Incidental discovery	7 (38.9%)	24 (63.2%)	8, 0	0.149
EUS for follow up	6 (23.1%)	12 (31.6%)	0	0.575
Macroscopic type[e]				
Macrocystic/ Oligocystic	9 (35%)	17 (44.7%)	0	0.668
Microcystic	14 (54%)	18 (47.4%)		
Solid	1 (4%)	2 (5.3%)		
Mixed	1 (4%)	0 (0%)		
Unclassified	1 (4%)	1 (2.6%)		
Maximum diameter				
SCN ≤ 30mm	11 (45.8%)	20 (54.1%)	2, 1	0.605
Solid Component	7 (38.9%)	18 (50%)	8, 2	0.565
Calcifications	2 (11.1%)	11 (28.9%)	8, 0	0.186
Hypervascularity	2 (11.1%)	6 (16.2%)	8, 1	1.000
Pancreatic Duct > 5mm	4 (23.5%)	5 (13.2%)	9, 0	0.435
Vascular compromise	3 (16.7%)	3 (8.1%)	8, 1	0.381
		Resection group		
Resection criteria				
Possibility of non-SCN cancer	11 (44%)	16 (72.7%)	0	**0.026**
Symptoms	8 (32%)	6 (27.3%)		
Increasing cyst size	6 (24%)	0 (0%)		
Associated malignancy	4 (16%)	5 (23.8%)	0, 1	0.711

a. Resected group, Observation group
b. Fisher's exact test
c. Median (IQR)
d. Mood's two-sample median test: Z= 0.146
e. Based on imaging.

Table 3. Multivariate analyses in patients with SCN: logistic regression model evaluating predictors of pancreatic resection (Table 3a); Cox proportional hazards model analysing factors independently associated with shorter time to surgical resection (Table 3b).

Table 3a.

Parameter*	log(OR) estimate	95% CI	p-value	Goodness of fit test (p-value)	Predicted Probabilities	
Intercept	-0.964	-2.099, 0.007	0.066		27%	27%
Before 2009	3.302	1.372, 6.336	0.005	0.855*	91%	-
Solid Component	3.062	1.452, 5.138	<0.001		99%	89%
Pain	*Excluded due to non-significant contribution in model's fit as assessed by Akaike's Information Criterion.*					
Age						

Table 3b.

Parameter	Hazard Ratio	95% CI	Wald test statistic	p-value
Solid Component*	3.05	1.46, 6.37	2.966	0.003
Pain	2.57	1.29, 5.12	2.688	0.007
PSC >30 mm	*Excluded as having no significant effect on resection free survival after adjusting for "Solid Component" and "Pain" status.*			

*Proportional Hazards assumptions evaluated using scaled Schoenfeld residuals.

Table 4. Larger published series of patients with SCNs undergoing pancreatic resection and/or observation.

Author	Year	Number of Patients	Patients Resected Number (%)	Patients Observed Number (%)	Surveillance Time	Patients with Symptoms Number (%)	Microcystic SCNs Number (%)	Solid Component Number (%)	Cyst Diameter (cm)	Metastatic SCNs No (%)	PNETs[a] Number (%)
Tseng et al.[24]	2005	106	86 (81.1%)	NA[a]	NA	56 (53%)	7 (7%)	NR[c]	Mean=4.9	0 (0%)	1 (1%)
Galanis et al. [15]	2007	158	158 (100%)	NA	NA	101 (64%)	NR	NR	Mean=5.1	2 (1.3%)	NR
Khashab et al. [25]	2011	257	257 (100%)	NA	NA	152 (59%)	NR	NR	Mean=4.9	2 (0,8%)	NR
Kimura et al. [22]	2012	172	82 (47.7%)	90 (52.3%)	Mean=4.5 yrs	34 (20%)	69 (39%)	NR	Mean=4.1	3 (3.7%)	0 (0%)
Malleo et al. [12]	2012	145	23 (15.9%)	122 (84.1%)	Mean=7 yrs	27 (18.6%)	21 (14.5%)	NR	Mean=2.9	0 (0%)	NR
El-Hayek et al.[26]	2013	219	25 (11.4%)	194 (88.6%)	Median=3.2 years	49 (24%)	NR	NR	Median=2	0 (0%)	NR
Gomatos et al.	2013	64	47 (73.4%)	17 (26.6%)	Median=3.4 months	25 (44.6%)	32 (50.0%)	25 (46.3%)	Median=3	0 (0%)	8 (17.4%)

a. Pancreatic neuroendocrine tumours
b. Not Applicable
c. Not Reported

LEGENDS FOR FIGURES

Figure 1. CONSORT diagram describing outcome of the study.

Figure 2. Factors associated with a significantly decreased resection free period due to: the presence of a SCN solid component on imaging (Figure 2a); SCN diameter ≤ 30 mm (Figure 2b); concern for a non-SCN malignancy (Figure 2c); and persistent pain (Figure 2d).

AUTHOR CONTRIBUTIONS

All authors are members of the Liverpool Pancreas Cancer Multidisciplinary Team (Chairman John P Neoptolemos). The surgeons included Ilias P Gomatos, Christopher Halloran, Paula Ghaneh, Robert Sutton, Michael Raraty and John P Neoptolemos. The lead radiologist for the study was Jonathan Evans, the lead pathologist was Fiona Campbell and the lead statistician was Fotis Polydoros. All authors contributed to this study in accordance to the International Committee of Medical Journal Editors guidelines and conform to substantive contributions by all of the authors towards the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and approval of the final version. The data quality assurance, analysis, interpretation and writing of the manuscript was initially conducted by Ilias P Gomatos, Fotis Polydoros and John P Neoptolemos. Subsequent amendments and contributions with final approval was made by all of the authors.

CONFLICTS OF INTEREST

All of the authors declare that they do not have any conflicts of interest.

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