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Pancreatic Incidentalomas on CT Colonography: Ignore, Follow up or Investigate?#

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Rezumat

Incidentaloamele pancreatice pe colonografia CT: ignorați, urmăriți sau investigați?

Context: Creşterea utilizării metodelor imagistice de evaluare a regiunii abdominale pe secțiuni transversale, aşa cum este colonografia CT (CTC), a condus la creşterea identificării incidentale a leziunilor chistice pancreatice. Aceste descoperiri incidentale sunt o cauză de anxietate în rândul pacienților şi medicilor şi pot duce la creşterea costurilor pentru furnizarea asistenței medicale ca urmare a direcționării pacienților către investigații ulterioare. Acest studiu evaluează prevalența şi gestionarea leziunilor pancreatice chistice descoperite incidental pe CTC într-un centru pancreatic terțiar.

Metode: Studiul are la bază rezultatele CTC şi notele de caz ale pacienților în perioada 2010-2016. În studiu au fost incluşi pacienți din ambele cohorte de screening (National Bowel Cancer Screening) şi non-screening.

Rezultate: Din 4666 de cazuri la care s-a efectuat CTC, în 136 s-a identificat incidental o leziune pancreatică (2,9%) şi în 117 cazuri s-au confirmat leziuni pancreatice chistice (2,5%). Diagnosticul radiologic al neoplasmului mucinos papilar intraductal (IPMN) a fost disponibil în raportul CTC pentru 71 de pacienți. Doisprezece pacienți (0,2%) au fost diagnosticați cu adenocarcinom ductal pancreatic (PDAC) descoperit incidental la CTC, rezecabil în 2 cazuri şi nerezecabil în 10 cazuri, diagnosticul fiind confirmat prin biopsie. Recomandările imagistice de supraveghere ulterioară au

fost făcute pentru 39,3% dintre pacienți în decurs de un an de la diagnosticarea unei leziuni pancreatice chistice pe CTC. Monitorizarea unui pacient cu dilatarea canalului pancreatic de 7 mm a fost întreruptă, însă pacientul a fost diagnosticat ulterior cu PDAC la 21 de luni.
Concluzii: Leziunile pancreatice sunt din ce în ce mai întâlnite incidental pe CTC. Toți pacienții cu formațiuni chistice pancreatice trebuie îndrumați către o echipă multidisciplinară cu experiență în această patologie, pentru discuții în vederea stabilirii managementului oportun.

Cuvinte cheie: colonografie CT, tumoră chistică pancreatică, IMPN, tumoră chistică mucinoasă pancreatică

Abstract
Background: Increasing use of cross-sectional abdominal imaging such as CT colonography (CTC), has resulted in increased identification of incidental pancreatic cystic lesions. Such incidental findings are a cause for anxiety amongst patients and clinicians and can result in increased cost to healthcare delivery resultant from referral to subsequent investigations. Our study explored the prevalence of incidental cystic pancreatic lesions on CTC at a tertiary pancreatic centre, and their management.
Methods: A detailed review of CTC reports and patient case notes between 2010-2016 was undertaken. Patients from both screening (National Bowel Cancer Screening) and non-screening cohorts were included in our study.
Results: 136 of 4666 patients who underwent CTC had an incidental finding of a pancreatic lesion (2.9%) and 117 confirmed cystic pancreatic lesions (2.5%). Radiological diagnosis of intraductal papillary mucinous neoplasm (IPMN) was available in the CTC report for 71 patients. Twelve patients (0.2%) were found to have pancreatic ductal adenocarcinoma (PDAC) incidentally at CTC, 2 resectable and 10 unresectable with the diagnosis confirmed on biopsy. Follow-up surveillance imaging recommendations were made for 39.3% of patients within one year of the diagnosis of a cystic pancreatic lesion on CTC. One patient with pancreatic duct dilatation of 7mm was lost in follow-up and was found to develop PDAC at 21 months.
Conclusions: Pancreatic lesions are increasingly found incidentally on CTC. All patients with pancreatic cystic tumour should be referred to pancreatic multidisciplinary team for discussion to determine management pathway.

Key words: CT colonography, pancreatic cystic tumour, IMPN, pancreatic mucinous cystic tumour

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide and is a major cause of morbidity and mortality (1-3). A range of validated screening modalities are in use which include faecal occult blood test (FOBT), faecal immunohistochemical test (FIT), endoscopy and computed tomographic colonography (CTC) (4).

Computed tomographic colonography is a minimally invasive imaging technique that is highly accurate for detecting colorectal cancer (CRC) and adenomatous polyps (5). CTC is a low radiation computed tomography (CT) of the abdomen and pelvis which involves full bowel purgation and gas insufflation with images obtained in prone and supine position (6-8). CTC is a less invasive alternative to traditional optical colonoscopy, is similarly sensitive with acceptable specificity and preferred by patients (9,10). CTC might be a

particularly suitable test in patients with low-risk symptoms, or in those who are older or have comorbidities.

In contrast to barium enema and colonoscopy used in colorectal examinations, CTC provides supplementary diagnostic information regarding the entire abdomen and pelvis (10). Incidental extracolonic findings are common at screening CTC and were first reported in 2000 (11). The most commonly reported extracolonic findings are renal lesions followed by lung, ovarian, liver and pancreatic lesions (12). Radiologists have a varied threshold for reporting extracolonic findings on CTC, especially those perceived as low risk as per C-RADS guidelines for reporting CTC (13).

Increasing use of cross-sectional abdominal imaging has resulted in increased identification of incidental pancreatic cystic lesions (PCL). The estimated incidence of cystic lesions of pancreas is 2-4.5% in the general population, its prevalence increasing with increasing age (14-18). The differential diagnosis of pancreatic cystic lesions broadly includes neoplastic and non-neoplastic cysts. Neoplastic pancreatic cysts can be further classified into mucin producing cysts (intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN)) and non-mucin producing serous cystadenomas (19). The other less common pancreatic cystic neoplasms include neuroendocrine tumours and pseudopapillary cystic neoplasms (19).

The incidence of pancreatic cystic incidentalomas harbouring invasive malignancy at the time of imaging is extremely low and the development of invasive malignancy in these cysts is low (20). Nevertheless, their diagnosis on cross-sectional imaging triggers significant anxiety for both the patient and their clinicians (20). Overlooking a pancreatic cyst harbouring malignancy has an invariably fatal outcome but surgical resection is associated with significant morbidity and mortality (19-23). It is, however, challenging to achieve an accurate diagnosis and stratify the risk of cancer which makes clinical decision making difficult with this subset of patients (19). Careful consideration is hence called for in opting for the appropriate management for incidental cystic pancreatic lesions. We aimed to determine the prevalence of incidental pancreatic lesions on CTC at our tertiary care high-volume pancreatic centre.

Methods

The radiology database at the Imperial Healthcare Trust (ICHT) was searched for patients who had undergone CTC between 01st January 2010 – 31st July 2016. All categories of referral for CTC were included in the study.

A detailed review of the CTC findings and final report was undertaken in conjunction with reviewing patient notes in whom an incidental pancreatic lesion was identified on CTC.

Patients with a known history of pancreatic cystic lesion (PCL) as indicated by prior imaging outside the above study period were excluded from the study.

Data were obtained on patient demographics and age at time of CTC and on further investigations and follow up. Where available, cytology and histology data were also obtained.

Data analysis were carried out using Microsoft Excel (Microsoft, Washington, USA).

Results

A total of 4666 patients had CTC at ICHT between 2010-2016 of which 136 were noted to have pancreatic incidentalomas on CTC (2.9%) and 117 confirmed cystic pancreatic lesions (2.5%) (*Fig. 1*). The median age at the time of diagnosis of pancreatic incidentaloma was 78 years (range; 42-94 years) and for cystic pancreatic lesions 79 years (range; 42-94 years).

Of the 117 patients with PCL, 71 were IPMN (61%); 25 of these had characteristics of main duct-IPMN, 38 had radiological characteristics of a branch-duct IPMN and 8 others were mixed-type IPMN. Thirty-three patients were diagnosed with PCL with no radiological diagnosis which will be referred to as unspecified PCL in this manuscript (28%). 41% of the IPMNs were confined to head of pancreas,

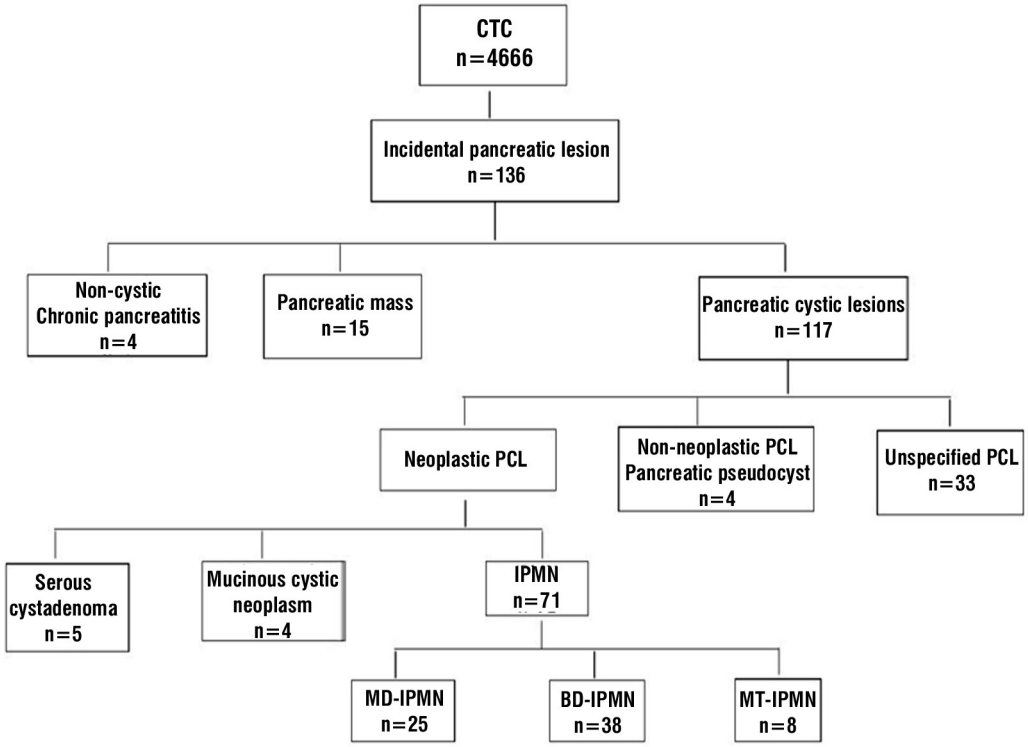

Figure 1. Summary of types of pancreatic incidentalomas identified on CTC
CTC: computerised colonography; PCL: pancreatic cystic lesion; IPMN: intraductal papillary mucinous neoplasm, MD-IPMN: main duct IPMN, BD-IPMN: branch duct IPMN, MT-IPMN: mixed-type IPMN

27% in the body of pancreas and a minority (11%) in the tail of pancreas. The distribution was multifocal in a further 21% of patients. The median cyst size was 1.3 cm (range; 0.4-3cm) at the time of diagnosis and the median size of the main pancreatic duct was 5.5 mm (range; 3-15 mm).

Less than half the patients (n=33) with initial diagnosis of side branch IPMN on CTC had further investigations to characterise the lesion within a year of their CTC (*Table 1*).

Of the 117 patients with incidental PCLs on CTC, 46 (39.3%) patients had further non-invasive imaging within one year; one patient had an invasive, nonsurgical procedure (Endoscopic Ultrasound) and two patients underwent surgical resection.

Where an initial diagnosis of serous cystadenoma was made on CTC (n=5), only one patient had further radiological imaging to characterise the lesion further (MRI pancreas with contrast). Two patients diagnosed with mucinous cystic neoplasm in our study had CT abdomen and pelvis with contrast following CTC.

Eight patients were noted to have features of chronic pancreatitis on CTC; four of whom had pancreatic pseudocyst with no associated main pancreatic duct dilatation. The remaining four patients in this subset had main pancreatic duct dilatation alone on a background of chronic pancreatitis.

Table 1. Summary of further investigations to characterise IPMN

Type of investigation	Number of patients
CT abdomen and pelvis with contrast	10
CT pancreas dual phase	6
MRCP	6
Combination of radiological investigations	8
EUS	1
USS	1
MRI pancreas	1

MRCP: Magnetic resonance cholangiopancreatography; USS: ultrasound scan

Incidental diagnosis of a malignant pancreatic lesion was noted in 12 patients (0.3%) on CTC in our cohort which was inoperable in 10 patients after biopsy to confirm the diagnosis of pancreatic cancer with a radiological diagnosis of IPMN (*Table 2*) and 2 patients resectable who underwent Whipple's operation. The final histology confirmed that 50% of PDAC was arising on a background of IPMN (n=6). One patient who was lost in follow up with a radiological diagnosis of dilated main pancreatic duct which was thought to be due to chronic pancreatitis (PD = 7 mm) on initial CTC but turned malignant 21 months later.

Discussion

Extracolonic findings on CTC were first reported by Hara et al. in 2000 (11). Subsequent prospective randomised controlled trial from Halligan S et al. reported more than half of the patients with symptoms of CRC were found to have extracolonic pathologies (7). Identification of incidental pancreatic lesions is not only a cause for increased anxiety amongst patients and clinicians but it can also result in increased cost to health care delivery resultant from referral to subsequent investigation of these lesions; these patients on an average undergo two or more further investigations. This can also lead to increased morbidity and mortality where patients undergo pancreatic resection.

Intraductal papillary mucinous neoplasms (IPMN) are a distinct entity of cystic pancreatic neoplasms that arise from the epithelium of the main pancreatic duct (MD-IPMN), from its side branches (BD-IPMN), or from both (mixed-type IPMN). They are believed to undergo an adenoma-carcinoma sequence eventually culminating in invasive ductal adenocarcinoma over time. Whilst surgical resection is recommended for MD-IPMNs according to size and other criteria, in contrast, it has been proposed to conservatively observe small SB-IPMNs without immediate resection. The risk of harbouring high grade dysplasia or cancer is between 37-91% for main pancreatic duct dilatation size 5-9.9 mm in surgical series of surgically resected IPMN (24,25). The 5-year risk for developing malignancy is reportedly 45% even for BD-IPMN < 3 cm if the cyst size increases in size by 2 mm per year (26). Current guidelines recommend surgical resection in both MD-IPMN and MT-IPMN with main pancreatic duct dilatation > 5 mm. Major postoperative morbidity is as high as 30% with a mortality of 5% even in high-volume centres for surgical resection (19).

Table 2. Summary of the nature of soft tissue pancreatic lesions identified on CTC

Type of soft tissue pancreatic lesion	Number of patients
Carcinoma of pancreas	12
Neuroendocrine tumour	2
Gastrinoma	1
Autoimmune pancreatitis	1
Lymphoma involving pancreas	1
Mesenteric nodal tumour involving pancreas	1
Unclassified tumour	1

Prevalence of incidental PCLs in our study is consistent with published literature. Though the median cyst size in our cohort was not a high-risk factor, the majority of our patients had a dilated main pancreatic duct (median 5 mm) but surveillance recommendations for further imaging were made in less than half of them. European Consensus guidelines (2018) recommends EUS as an adjunct to other imaging modalities to further characterise PCLs with high-risk features requiring surgical resection (14). MRI has been recommended as the preferred imaging modality for PCL due to its sensitivity for identifying communication between cyst and the pancreatic duct and in detecting the presence of mural nodule or internal septation when present. It is also very sensitive in detection the number of lesions whether single or multiple PCL with an added advantage of lack of ionising radiation.

Recent guidelines suggest lifelong surveillance for patients as long as they are willing and fit and happy to undergo surgical resection as indicated. However, it remains unclear at what interval surveillance imaging should

be performed. The median age at time of CTC in our cohort was high (78 years) and further surveillance imaging were not recommended by radiologists where a diagnosis of a low risk incidental PCL was made. However, we felt that any patient with pancreatic incidentaloma detected on imaging should be referred to pancreatic MDT for discussion to formulate management plan with regards to further investigation ± intervention or follow up as per guidelines (14,20). The incidence of PDAC on a background of IPMN was high in our cohort (50%). Histological confirmation of diagnosis of IPMN was available in all cancer cases who underwent biopsy (n=10) and resection (n=2).

All CTCs in our study were reported by in-house radiologists familiar with interpreting CTC. Though there were no changes made to the CTC protocol during the study period, we did not specifically explore the technical details of the CTC protocol at length. Patients from both screening (National Bowel Cancer Screening) and non-screening cohorts were included in our study. It is difficult to conclude from our study if the incidental pancreatic lesions detected on CTC contributed to the presenting symptoms of patients necessitating the need for CTC.

Radiologists have a varied threshold for reporting extracolonic findings on CTC, especially those perceived as low risk as per C-RADS guidelines for reporting CTC. The prevalence of incidentals PCLs in our study might hence be under reported. Also, CTC which has a low radiation compared to standard contrast-enhanced computed tomo-graphy of abdomen and pelvis has a lower sensitivity in detection of extracolonic lesions. It is uncertain what percentage of patients in our cohort might have had a missed diagnosis of extracolonic findings including incidental PCLs.

There is paucity of data on the natural history and progression of these PCLs into invasive malignancy or high-grade dysplasia. The debate continues regarding the optimal management of PCL. There are conflicting statements regarding the diagnosis and management of these lesions and there is an urgent need for global evidence-based guidelines for the management of PCL to address the numerous clinical dilemmas that remain.

The 'Sendai' guidelines for the management of PCL were developed in 2006 (27). Since its introduction, there have been further guidelines on the management of PCL (14,20, 28-30). The most recent of these are the American Gastroenterological Association (AGA) guidelines 20 and European evidence-based guidelines on pancreatic cystic neoplasms (*Table 3*) (20, 14). Both guidelines are consensus statements based on critical literature review and have conflicting statements on management of PCL. Whilst AGA guidelines are for asymptomatic neoplastic pancreatic cysts, the European guidelines is more comprehensive and includes all PCLs.

Table 3. European evidence-based guidelines for pancreatic cystic neoplasms (14)

	Indication for resection	**Surveillance guidelines**
IPMN	MD-IPMN: all	Lifelong follow up post-surgical resection (if surgically fit and patient is willing to have surgery if indicated): MRI or EUS, clinical evaluation and serum CA 19.9 measurement every 6 months for first 2 years, then yearly surveillance
	MT-IPMN: all	As above for: - IPMN associated invasive carcinoma - High grade dysplasia Follow up as non-resected IPMN where there is low grade dysplasia
	BD-IPMN 1. Absolute indications for resection - positive cytology for malignancy or high-grade dysplasia - presence of a solid mass - tumour related jaundice - enhancing mural nodule (≥ 5 mm) - main pancreatic duct dilatation of ≥ 10 mm	a. Patients with significant co-morbidities, short life expectancy and one relative indication: - 6 monthly clinical evaluation, serum CA 19.9 and MRI and/or EUS

Table 3. European evidence-based guidelines for pancreatic cystic neoplasms (14) (continuation)

	Indication for resection	Surveillance guidelines
	2. Relative indications for resection (patients without significant co-morbidities and one or more relative indications OR patients with significant co-morbidities with two or more relative indications) - cyst growth rate of ≥ 5 mm per year - main pancreatic duct dilatation between 5-9.9 mm, new onset diabetes mellitus - increased levels of CA 19.9 (>37 U/ml; in the absence of jaundice) - cyst diameter ≥ 40 mm - enhancing mural nodules (<5mm) - acute pancreatitis caused by IPMN	b. Asymptomatic patients with no indications of surgery: - 6 monthly clinical evaluation, serum CA 19.9 and MRI and/or EUS - For 1 year followed by yearly clinical evaluation, serum CA 19.9 and MRI and/or EUS
MCN	Surgery if: - lesions ≥ 4 cm - symptomatic - mural nodule irrespective of size of cyst	Cyst diameter < 4 cm: Surveillance similar to non-resected IPMN
SPN	Radical resection in all patients	Not specified
PNET	Cystic PNET > 20 mm	Surveillance is recommended for asymptomatic cystic PNET ≤ 20 mm
SCN	Symptoms related to the compression of adjacent organs	a. Clear diagnosis of SCN in asymptomatic patients: follow up for 1 year; symptom based follow up after 1 year b. SCN diagnosis unclear: surveillance as for non-resected BD-IPMN

Conclusion

Pancreatic cystic lesions are increasingly found when patients undergo cross-sectional imaging for a variety of reasons. Although there is no clear worldwide consensus regarding management, as evidenced by the plethora of clinical guidelines available, there is a definable associated risk of developing invasive disease. We would recommend that all such patients should be referred to pancreatic MDT for discussion to determine management pathway.

Author's Contributions

SM, TP, SP and LRJ contributed to the design of the work; SM, TP, SP contributed to data acquisition and analyses; SM, TP, TG, DC, PT and LRJ contributed to the interpretation of data; SM and TP drafted and revised the manuscript; all authors critically appraised and revised the manuscript; SM, TP and LRJ act as guarantors.

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Conflict of Interest

No competing interests.
All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics Approval

Not required.

Data Sharing

Data are available on reasonable request to the corresponding author.

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