Pancreatic steatosis on computed tomography is an early imaging feature of pre-diagnostic pancreatic cancer: a preliminary study in overweight patients

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Pancreatology 21 (2021) 428–433

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Pancreatic steatosis on computed tomography is an early imaging feature of pre-diagnostic pancreatic cancer: A preliminary study in overweight patients

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ARTICLE INFO

Article history:
Received 16 September 2020
Received in revised form
7 December 2020
Accepted 7 January 2021
Available online 16 January 2021

Keywords:
Fatty pancreas
Imaging biomarker
Obesity

ABSTRACT

Background: The prevalence of pancreatic ductal adenocarcinoma (PDAC) is on the rise, driven by factors such as aging and an increasing prevalence of obesity and diabetes mellitus. To improve the poor survival rate of PDAC, early detection is vital. Recently, pancreatic steatosis has gained novel interest as a risk factor for PDAC. This study aimed to investigate if pancreatic steatosis on computed tomography (CT) is an early imaging feature in patients with pre-diagnostic PDAC.

Methods: A retrospective case-control study was performed. Patients diagnosed with PDAC (2010–2016) were reviewed for abdominal non-contrast CT-imaging 1 month-3 years prior to their diagnosis. Cases were matched 1:4 with controls based on age, gender and imaging date. Unenhanced CT-images were evaluated for pancreatic steatosis (pancreas-to-spleen ratio in Hounsfield Units <0.70) by a blinded radiologist and results were compared between cases and controls.

Results: In total, 32 cases and 117 controls were included in the study with a comparable BMI (29.6 and 29.2 respectively, $p = 0.723$). Pancreatic steatosis was present in 71.9% of cases compared to 45.3% of controls (Odds ratio (OR) 3.09(1.32–7.24), $p = 0.009$). Adjusted for BMI and diabetes mellitus, pancreatic steatosis on CT remained a significant independent risk factor for PDAC (Adjusted OR 2.70(1.14–6.58), $p = 0.037$).

Conclusion: Pancreatic steatosis measured on CT is independently associated with PDAC up to three years before the clinical diagnosis in overweight patients. If these data are confirmed, this novel imaging feature may be used to identify high-risk individuals and to stratify the risk of PDAC in individuals that already undergo PDAC screening.

Background

Pancreatic ductal adenocarcinoma (PDAC) is a largely incurable disease with a 5-year survival rate of only 9% [1]. The poor survival rate is predominantly caused by its late diagnosis in advanced stages. To improve the survival of PDAC, detection strategies should focus on early diagnosis that enables curative treatment. Since the overall prevalence of PDAC is low and population screening is not recommended, identification of high-risk individuals is imperative to enhance early detection and improve survival in PDAC.[2]Several studies established modifiable risk factors for the development of PDAC, including smoking, diabetes and obesity [3–6]. In recent years, pancreatic steatosis has gained significant novel interest in the pathophysiology of PDAC as it has been demonstrated to be strongly correlated with obesity and precancerous pancreatic intraepithelial neoplasia (PanIN) lesions in resection specimens

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https://doi.org/10.1016/j.pan.2021.01.003

[7–10]. Pancreatic steatosis is used as an umbrella term for fat accumulation in the pancreas with various etiologies; and identical to PDAC, it is positively associated with obesity, age and diabetes mellitus (DM) [11–14]. Since the prevalence of obesity is rising, with an estimated current global prevalence of 39%, research on the natural history and long-term effects of pancreatic steatosis and its relation with the metabolic syndrome have emerged [15]. Studies have demonstrated that pathological changes of steatosis are an important and independent determinant of PDAC and that these pathological changes are correlated with the attenuation of the pancreas on computed tomography (CT) [7–9,16,17]. One of these studies found that a low pancreas-to-spleen ratio on CT was a strong predictor for the presence of PDAC and that it can be used as an imaging feature for the detection of PDAC. However, these studies were all performed when the diagnosis of PDAC was already established. Since pancreatic steatosis can be caused by fatty infiltration due to obesity and metabolic syndrome as well as by tumor ductal obstruction leading to acinar cell death with fatty replacement, the predominant pattern and timeline of changes in the CT-attenuation of the pancreas during the development of PDAC remain unclear [18,19]. The purpose of this case-control study was to investigate if pancreatic steatosis on CT is an early imaging feature in patients with pre-diagnostic pancreatic cancer. We aimed to elucidate the utility of pancreatic steatosis as an accurate early imaging feature of PDAC, whether it can be used for identification of high-risk individuals or as a high-risk feature in individuals that are already enrolled in PDAC-screening.

Methods

Study design A single-center, retrospective, observational case-control study was conducted to evaluate pancreatic steatosis on pre-diagnostic CT studies in patients that eventually were diagnosed with PDAC compared to controls without an eventual diagnosis of PDAC.

Case selection

Electronic medical records of all patients with confirmed PDAC, diagnosed between 2010 and 2016 at Mayo Clinic Florida, were retrospectively reviewed. Patients who underwent unenhanced CT imaging 1 month–3 years prior to the diagnosis of PDAC were included in the study. We hypothesized that early imaging features of PDAC would be visible up to 3 years before PDAC diagnosis. If a subject had more than one CT in that time frame, the CT study closest in time to the PDAC diagnosis was selected. Patients were excluded when (1) pre-diagnostic CT reported an obvious pancreatic mass (2) CT was conducted within 4 weeks after abdominal surgery (3) PDAC was a recurrence or arose from a mucinous cystic neoplasm (4) patients had a previous history of pancreatic surgery or splenectomy (Supplement 2). Control selection Controls were, if applicable, selected in a 4:1 ratio to cases. Controls were defined as patients with unenhanced CT-imaging who did not develop PDAC within 3 years after imaging. Controls were matched to cases by gender, age and date of imaging (±3 months) and were randomly selected by searching the internal radiologic database Illuminate Insight™ [20]. Electronic medical records were reviewed to ascertain control subjects had at least three years follow-up after imaging in which they did not develop PDAC. Controls were excluded if (1) patients were lost to follow up within 3 years after imaging (2) the CT was conducted within 4 weeks after abdominal surgery (3) patients had a history of pancreatic or extrahepatic biliary malignancy (4) patients had previous history of pancreatic surgery or splenectomy.

Data collection

Clinical variables of age, gender, body mass index (BMI), serum lipid profile, history of diabetes mellitus (DM), alcohol abuse, smoking, pancreatic diseases and a family history of PDAC were retrospectively collected from electronical medical records. CT-images were collected for both cases and controls. The stage of pancreatic cancer at diagnosis was reported for cases, according to the American Joint Committee on Cancer (AJCC, 8 th edition) [21].

CT protocols and assessment of pancreatic steatosis

Adipose tissue on unenhanced CT is characterized by a negative attenuation, measured in Hounsfield Units (HU) (i.e. −150 and −30 HU). One abdominal radiologist with 7 years of experience (C.W.B) evaluated all CT studies and was blinded for case-control status. CT-attenuation was measured in the non-contrast phase on a dedicated workstation using Visage 7.1 Picture Archiving and Communication System (PACS) (Fig. 1). Attenuation of the spleen was measured to normalize pancreatic attenuation, since the pancreas-to-spleen attenuation ratio (P/S) and the pancreas minus spleen attenuation difference (P-S) are both significantly correlated with pathology confirmed pancreatic steatosis [16,17,22]. In the pancreas, attenuation was measured in nine circular 1 cm [2] regions of interest (ROIs) in the head (n = 3), body (n = 3) and tail (n = 3). Splenic attenuation was also measured with circular 1 cm^2 ROIs and averaged over three measurements. Vasculature, visible lesions, pancreatic duct and peripheral margins were avoided in the measurements. The mean attenuation of both spleen and pancreas were calculated and used for further analysis. Pancreas-to-spleen (P/S) attenuation ratio and the difference between pancreatic and splenic attenuation (P − S) were calculated and compared between cases and controls. The presence and extent of pancreatic steatosis was compared between subgroups of cases who underwent CT-imaging ≤ 6 months and >6 months before the diagnosis of PDAC. In cases, the P/S ratio was compared between eventually cancerous and non-cancerous parts of the pancreas. Pancreatic steatosis was defined as a P/S ratio <0.70 [17].

Statistical analysis

Microsoft Excel was used for data management and JMP Pro (v14.1.0 SAS Institute Inc, North Carolina, USA) for the statistical analysis. Continuous variables were reported as mean (standard deviation; SD) or median (range or interquartile range; IQR) and compared based on either Student T-test or Mann-Whitney *U* test. Comparison of continuous variables in related samples was performed using a paired T-test or Wilcoxon signed-rank test. Categorical variables were presented as frequencies with percentages and compared using the Chi-square test or Fisher's exact test. Odds ratio (OR) with 95% confidence interval (95% CI) were estimated for pancreatic steatosis in cases compared to controls. Two-sided P-values less than 0.05 were considered statistically significant. Variables that were significantly associated with PDAC in univariate analyses were considered for multivariable analyses. Logistic regression was utilized for multivariable analysis and results were reported in adjusted OR (95% CI). Subjects with missing data in one of the variables included in the logistic regression were excluded from the analyses.

Ethics

The study protocol was approved by the Institutional Review Board of Mayo Clinic Florida (18–002403). Informed consent was waived considering the retrospective nature of the study.

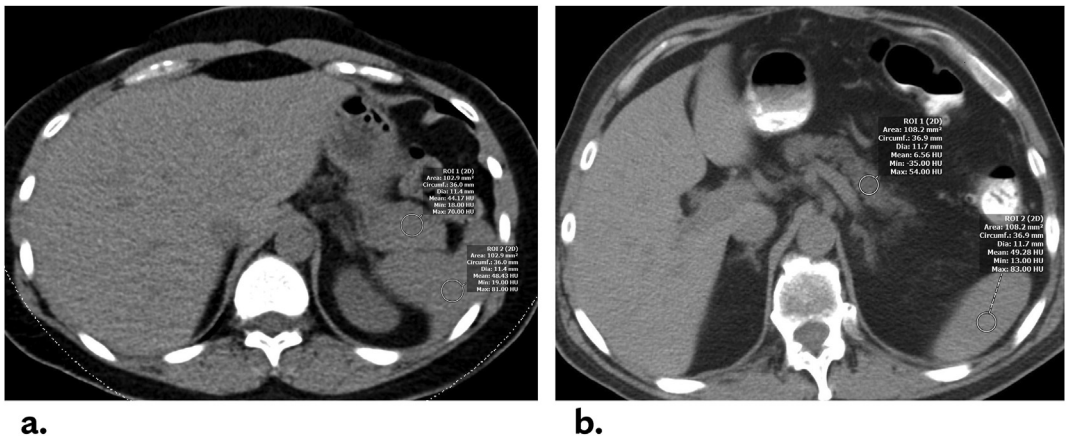

Fig. 1. Measuring attenuation of the pancreas and spleen on unenhanced CT-images. Region-of-interests (ROI) of 1 cm^2 are placed in the pancreatic and splenic parenchyma. Fig. 1a shows slightly less attenuation in Hounsfield Units (HU) in the pancreatic tail as compared to the spleen. Fig. 1b shows lower attenuation in the pancreatic body as compared to the spleen.

Table 1
Baseline characteristics at time of CT-imaging.

	Cases (n = 32)	Controls (n = 117)	p-value
Male (%)	22 (68.8)	83 (70.9)	0.8098[c]
Age, years (SD)	68.1 (11.6)	68.6 (10.3)	0.8387[b]
BMI (kg/m^2) (SD)	29.6 (4.9)	29.2 (5.5)	0.7234[b]
Diabetes mellitus (%)	18 (56.3)	37 (31.9)	0.0116[c]
History of			
- Smoking (%)	20 (62.5)	64 (54.2)	0.4036[c]
- Alcohol abuse (%)	3 (9.4)	9 (7.8)	0.7226[a]
- Chronic pancreatitis (%)	2 (6.7)	1 (0.9)	0.1060[a]
- Pancreatic cystic lesion (%)	4 (13.3)	6 (5.1)	0.3891[a]
- Any type of cancer (%)	11 (34.3)	47 (40.2)	0.5513[c]
- Family history of pancreatic cancer (%)	4 (12.9)	7 (6.0)	0.2430[a]
Serum lipids at time of imaging	Cases (n = 14)	Controls (n = 38)	p-value
- Total cholesterol (mg/dL), median (IQR)	151.5 (126.3–289.5)	162.0 (126.3–189.5)	0.5705[d]
- LDL cholesterol (mg/dL), median (IQR)	97 (63.3–133.3)	75.8 (61.0–107.0)	0.2582[d]
- HDL cholesterol (mg/dL), median (IQR)	39 (36.0–49)	49 (40.8–60.3)	0.0245[d]
- Triglycerides (mg/dL), median (IQR)	144 (115.5–184)	127 (89.3–154.0)	0.15[d]

BMI; Body mass index. Family history of pancreatic cancer was defined as one or more first degree relatives with pancreatic cancer.
[a] Fisher's Exact Test.
[b] Student's T Test.
[c] ChiSquare test.
[d] Mann-Whitney *U* test.

Results

Clinical characteristics at time of imaging

In total, 32 cases were identified and matched with 117 controls. Both cases and controls had a mean BMI in the overweight range (29.6 and 29.2 respectively, p = 0.723). Clinical characteristics of cases and controls are summarized in Table 1. CT images were obtained with a median of 7.6 months (range 1.6–30.8) before the diagnosis of PDAC. At the time of diagnosis, pancreatic masses were

Table 2
Measures of pancreatic steatosis on CT in cases versus controls.

	Cases (n = 32)	Controls (n = 117)	Odds Ratio (95% CI)	P-value
P/S < 0.70	23 (71.9%)	53 (45.3%)	3.09 (1.32–7.24)	0.0094[a]
•≤6 months prior to diagnosis	11 (78.6%)	18 (38.3%)	5.91 (1.45–24.90)	0.0081[a]
•> 6 months prior to diagnosis	12 (66.7%)	35 (50.0%)	2.00 (0.67–5.93)	0.2061[a]
P/S, median (IQR)	0.61 (0.34)	0.73 (0.50)	–	0.0628[b]
•≤6 months prior to diagnosis	0.55 (0.29)	0.76 (0.48)	–	0.0388[b]
•> 6 months prior to diagnosis	0.65 (0.40)	0.69 (0.55)	–	0.4786[b]
P − S, median (IQR)	−19.1 (13.2)	−12.3 (22.4)	–	0.0307[b]
•≤6 months prior to diagnosis	−21.2 (9.4)	−11.0 (19.9)	–	0.0372[b]
•> 6 months prior to diagnosis	−12.9 (25.1)	−15.9 (19.5)	–	0.2530[b]

P/S; pancreas-to-spleen attenuation ratio. P-S; pancreas minus spleen attenuation difference. Pancreatic steatosis on CT is defined as a pancreas-to-spleen ratio of less than 0.70.
[a] ChiSquare test.
[b] Mann-Whitney *U* test.

Table 3
Predictors for PDAC in univariate and multivariable analyses.

	Univariate analysis			Multivariable analysis		
	Odds ratio	95% CI	p-value	Adjusted odds ratio	95% CI	p-value
Diabetes mellitus	3.19	1.36–7.44	0.0060	3.29	1.30–8.33	0.0119
Pancreatic steatosis	2.74	1.14–6.58	0.0210	2.70	1.06–6.85	0.0369
BMI >25 kg/m^2	1.06	0.35–3.14	0.9152	0.48	0.14–1.68	0.2519

Pancreatic steatosis; defined as a pancreas-to-spleen attenuation ratio of less than 0.70.
PDAC; pancreatic ductal adenocarcinoma. BMI; body mass index.

Table 4
P/S ratio in cancerous part compared to non-cancerous part of the pancreas.

Location of pancreatic mass at diagnosis	P/S cancerous part Median (IQR)	P/S non-cancerous part Median (IQR)	Median (IQR) difference P/S cancerous versus healthy	p-value
Head (n = 18)	0.63 (0.37)	0.63 (0.43)	0.04 (0.39)	0.52[a]
Body (n = 7)	0.69 (0.35)	0.68 (0.35)	0.10 (0.13)	0.27[a]
Tail (n = 5)	0.52 (0.70)	0.24 (0.88)	0.08 (0.43)	0.63[a]

P/S; pancreas-to-spleen attenuation ratio.
[a] Wilcoxon signed rank test.

localized in the head in 56.3% of cases (n = 18), body in 21.9% (n = 7), and tail in 15.6% (n = 5). Two patients (6.2%) had pancreatic masses that extended beyond one part of the pancreas. Cases were diagnosed in respectively stage IA (6.2%), stage IIA (21.9%), stage IIB (37.5%), stage III (12.5%) and in stage IV (21.9%) of the disease, according to the AJCC 8th edition. Controls had a median PDAC-free follow-up of 5.8 years (range 3.3–12.2). The indication for CT-imaging in cases and controls are summarized in Supplement 1.

Pancreatic steatosis on CT as an early imaging feature of PDAC

Pancreatic steatosis on CT was found in 71.9% and in 45.3% of pre-diagnostic PDAC cases and controls, respectively (p = 0.0094). Pancreatic steatosis was associated with PDAC in a pre-diagnostic phase (OR 3.09, 95% CI 1.3–7.2). Significant differences between cases and controls were found for all measures of pancreatic steatosis and results are shown in Table 2. The differences were demonstrated most clearly in the subgroup of cases that underwent CT-imaging ≤6 months prior to the PDAC diagnosis. BMI of cases in this subgroup was 30.1 (4.8) and of controls 28.9 (5.0) (p = 0.48). In the subgroup that underwent prior imaging >6 months before the diagnosis, BMI was 29.3 (5.2) in cases and 29.5 (5.9) in controls (p = 0.91). Results of the multivariable analysis are shown in Table 3. Pancreatic steatosis was independently associated with PDAC (adjusted OR 2.7, 95% CI 1.06–6.85). In the univariate analysis, only DM and pancreatic steatosis measures were significantly associated with the eventual diagnosis of PDAC. To avoid the risk of overfitting, no more than three predictor variables were included in the logistic regression [23]. BMI was chosen as third predictor given its strong correlation with pancreatic steatosis. The multivariable analysis included 29 cases and 105 controls, because information on BMI and DM status were lacking in some cases.

Attenuation cancerous versus non-cancerous part of the pancreas

The P/S ratio was slightly higher in the part of the pancreas where later the cancerous lesion was diagnosed compared to the "healthy" parts of the pancreas, but these findings were minimal and non-significant (Table 4).

Discussion

This study demonstrates that pancreatic steatosis on CT is independently associated with PDAC when the disease is still in a pre-diagnostic phase (adjusted OR 2.7, 95% CI 1.06–6.85). Therefore, pancreatic steatosis may be an early imaging biomarker of PDAC prior to the direct appearance of the tumor. The association was most clearly demonstrated in the subgroup of cases that underwent imaging ≤6 months of the diagnosis, and although the same trend was observed in the group that underwent imaging >6 months prior to the diagnosis, the latter was not significant. This non-significance may partially be explained by the small sample size and relatively high prevalence of pancreatic steatosis in the control subjects of this subgroup (50.0%). In other studies that examined steatosis of the pancreas on CT for various benign diseases, pancreatic steatosis was found in 30–51% of the patients, comparable to the results in our controls and considerably lower than found in our pre-diagnostic PDAC population [17,24]. In the present study, BMI in both cases and controls was nearly in the obese range and may have contributed to the high prevalence of pancreatic steatosis. The BMI of both cases and controls in this study was similar to the average BMI across the United States [15].

As stated earlier, both PDAC and pancreatic steatosis are positively associated with aging, obesity and DM [3,4,11–14]. Knowledge about the exact role that steatosis has in the development of PDAC is lacking. Pancreatic steatosis is hypothesized to be a consequence of PDAC – by acinar cell death and fatty replacement due to ductal tumor obstruction – or to play an independent role on itself in the oncogenesis of PDAC. With this in mind, Rebours and colleagues investigated 110 pancreas specimens that were resected for small benign neuroendocrine tumors [9]. PanIN were found in more than half of the specimens (65%) and this was strongly associated with fatty infiltration of the pancreas, especially intralobular, and independent from age or DM (OR 17.9, 95% CI (4.9–88.1)). Obesity, subcutaneous and visceral fat were found to be both significantly correlated with the presence of pancreatic steatosis and PanIN. The pancreatic infiltration of fat was not only found around the PanIN lesion, but throughout the pancreatic specimen, proposing that pancreatic steatosis preceded the origination of PanIN. Additionally, steatosis of the pancreas may not only act as a risk factor for PDAC, it has also been shown to increase lymphatic tumor dissemination and lethality of PDAC [25,26].

In a previously conducted pathology-based case-control study, increased infiltration of adipocytes into pancreatic specimens of PDAC patients has been demonstrated as compared to controls, independent of confounders such as DM and obesity [7]. The study could not elucidate if fatty infiltration was triggered by obstruction of the pancreatic duct or due to fat accumulation induced by

obesity and metabolic syndrome. The results of our study show that pancreatic steatosis on CT is already present multiple months to years before diagnosis, suggesting that the fatty changes in PDAC occur early or before malignancy onset, confirming the earlier discussed results of Rebours et al. [9] The same study also showed that the area and severity of fat infiltration was associated with the localization of the cancerous lesion, an association which we could not confirm in our small sample size (Table 4) [7]. Previous studies indicated that P/S ratio and P − S attenuation difference is closely linked to pathological fat infiltration found in the pancreas [16,17,22]. Fukuda and colleagues calculated a cut-off value for P/S of <0.70 with high predictive reliability for pancreatic steatosis, hence this value was used in the present study [17]. In their study, a sensitivity and specificity of 79% for pathological pancreatic steatosis was found using this cut-off value and additional research is necessary to validate these results. They also demonstrated that P/S was low regardless of the stage that PDAC was in, indicating that steatosis is already present in early diagnostic stages of PDAC. Only one study previously reported the correlation between PDAC and pancreatic steatosis on CT at the time of PDAC diagnosis [17]. A comparable OR for pancreatic steatosis was found in preoperative PDAC patients as compared to controls (OR 3.4, 95% CI (1.8–6.7)). However, our study suggests that pancreatic steatosis on CT is already detectable in the majority of patients up to 3 years before PDAC diagnosis and that the prevalence is significantly higher compared to age- and gender-matched controls.

Our study was limited due to several factors. We performed a single-center, retrospective, case-control study with a restricted case sample size and one radiologist that evaluated all CT-images. Future studies should focus on prospective evaluation and follow-up of patients with pancreatic steatosis to confirm our results and to objectify the course of pancreatic steatosis in the build-up to PDAC. Another potential limitation of this study was the high BMI among cases and controls, which may make the results less generalizable to a population with a normal BMI. In addition, steatosis of the pancreas was quantified using CT-attenuation and pathological correlation of fat infiltration was not possible considering the retrospective design of the study. Furthermore, measuring pancreatic steatosis on CT does not differentiate between intralobular and extralobular fat infiltration and is not a "gold standard" biopsy. Sensitivity and specificity are not 100% using this method, so results may be interpreted with caution. However, measuring pancreatic fat *in vivo* is difficult, since biopsies are accompanied by a risk of complications and a single biopsy is not likely to be representative for the total fat content of the pancreas. Other imaging techniques, like magnetic resonance spectroscopy or Iterative Decomposition with Echo Asymmetry and Least squares estimation (IDEAL)-MRI may be superior to CT for assessing pancreatic fat without the exposure to radiation, although these methods may not be broadly available [27,28].

In conclusion, pancreatic steatosis measured on CT is independently associated with PDAC up to three years before the clinical diagnosis in overweight patients. Identifying imaging features of pre-diagnostic PDAC are of paramount importance to increase early detection and survival. Since screening for PDAC is only recommended in high-risk individuals, this novel imaging feature can potentially be used to stratify the risk of PDAC in individuals that already undergo PDAC screening, after confirmation of these findings in additional studies.

Acknowledgements

Conflicts of interest SAH, CWB, AC, MTR, MR: No conflicts to disclose. JEvH: Consultancy fee: Boston Scientific, Medtronics and Cook Medical. Research grant: Cook medical. MBW: Consulting: Virgo Inc, Cosmo/Aries Pharmaceuticals, Anx Robotica (2019), Covidien, GI Supply. Research grants: Fujifilm, Boston Scientific, Olympus, Medtronic, Ninepoint Medical, Cosmo/Aries Pharmaceuticals. Stock/Stock Options: Virgo Inc. Consulting on behalf of Mayo Clinic: GI Supply (2018), Endokey, Endostart, Boston Scientific, Microtek, General payments/Minor Food and Beverage: Synergy Pharmaceuticals, Boston Scientific, Cook Medical.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.01.003.

Author contributions

SAH: Conception and design, drafted the manuscript, data collection, data analysis and interpretation. CWB: radiological data collection and interpretation, critically reviewed the manuscript. AC and MTR: data collection and interpretation, critically reviewed the manuscript. MBW and JEvH: interpretation of data, critically reviewed the manuscript. MR: Conception and study design, interpretation of data, critically reviewed the manuscript. All authors provided final approval for submission and publication.

Funding

Mayo Clinic's Early Detection of Pancreatic Cancer Program is funded by the Champions for Hope/Funk-Zitiello foundation.

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