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ORIGINAL ARTICLE

A pilot study of radiologic measures of abdominal adiposity: weighty contributors to early pancreatic carcinogenesis worth evaluating?

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ABSTRACT

Objective: Intra-abdominal fat is a risk factor for pancreatic cancer (PC), but little is known about its contribution to PC precursors known as intraductal papillary mucinous neoplasms (IPMNs). Our goal was to evaluate quantitative radiologic measures of abdominal/visceral obesity as possible diagnostic markers of IPMN severity/pathology.

Methods: In a cohort of 34 surgically-resected, pathologically-confirmed IPMNs (17 benign; 17 malignant) with preoperative abdominal computed tomography (CT) images, we calculated body mass index (BMI) and four radiologic measures of obesity: total abdominal fat (TAF) area, visceral fat area (VFA), subcutaneous fat area (SFA), and visceral to subcutaneous fat ratio (V/S). Measures were compared between groups using Wilcoxon two-sample exact tests and other metrics.

Results: Mean BMI for individuals with malignant IPMNs (28.9 kg/m^2) was higher than mean BMI for those with benign IPMNs (25.8 kg/m^2) (P=0.045). Mean VFA was higher for patients with malignant IPMNs (199.3 cm^2) compared to benign IPMNs (120.4 cm^2), P=0.092. V/S was significantly higher (P=0.013) for patients with malignant versus benign IPMNs (1.25 *vs*. 0.69 cm^2), especially among females. The accuracy, sensitivity, specificity, and positive and negative predictive value of V/S in predicting malignant IPMN pathology were 74%, 71%, 76%, 75%, and 72%, respectively.

Conclusions: Preliminary findings suggest measures of visceral fat from routine medical images may help predict IPMN pathology, acting as potential noninvasive diagnostic adjuncts for management and targets for intervention that may be more biologically-relevant than BMI. Further investigation of gender-specific associations in larger, prospective IPMN cohorts is warranted to validate and expand upon these observations.

KEYWORDS Abdominal obesity; pre-malignant lesions; pancreatic cancer; computed tomography

Introduction

Pancreatic ductal adenocarcinoma (PDAC), commonly known as pancreatic cancer (PC), is the fourth leading cause of cancer deaths world-wide, with high age-standardized incidence rates occurring in North America and Asia[1]. PC is diagnosed in more than 337,000 individuals each year, accounts for 4% of all cancer deaths, and has the lowest five-year relative survival rate of all leading cancers, at 9%[1]. Prognosis is poor because diagnosis typically occurs at a late, incurable stage, and prevention and early detection methods are lacking[1]. Risk factors including age, tobacco, diabetes, pancreatitis, heavy alcohol use, family history, and hereditary conditions explain only a proportion of PCs[1]. Being overweight [body mass index (BMI)≥25 kg/m^2] or obese (BMI≥30 kg/m^2) increases PC risk by 30%[2], has a population attributable fraction up to 16%[3], and influences PC survival[4-6]. Given the rise in the prevalence of obesity in North America and Asia[7,8] and the fact that obesity is a modifiable PC risk factor, an understanding of obesity's role

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in early pancreatic carcinogenesis is crucial for PC prevention and early detection. We contend that commonly-detected PC precursors may be attributed to obesity, and that proper diagnosis and treatment of precursors and underlying obesity offer potential to reduce PC burden.

Intraductal papillary mucinous neoplasms (IPMNs) are macrocystic PC precursors ('precancers') that comprise half of the ~150,000 pancreatic cysts detected incidentally in 3% of computed tomography (CT) scans and 20% of magnetic resonance imaging (MRI) studies each year[9,10], making them more amenable to study than the microscopic PC precursor, pancreatic intraepithelial neoplasia (PanIN). Once detected, the only way to accurately determine IPMN severity/pathology [which spans from low-grade (LG) and moderate-grade (MG) to high-grade (HG) dysplasia & invasive carcinoma] is surgical resection, which is associated with an operative mortality of 2%–4% and morbidity of 40%–50%[11]. Consensus guidelines for IPMN management depend on standard radiologic and clinical features[12]. The guidelines recommend that those with 'high risk stigmata' undergo resection as most harbor HG or invasive disease. High risk stigmata include: main pancreatic duct (MD) involvement/dilatation ≥10 mm, jaundice, or an enhanced solid component/nodule). IPMNs with 'worrisome features' (MD dilation 5–9 mm, size ≥3 cm, thickened cyst walls, non-enhanced mural nodules, or pancreatitis) are recommended for surveillance with an invasive endoscopic ultrasound-guided fine needle aspirate procedure despite poor sensitivity and complications[10,13]. However, consensus guidelines[12] incorrectly predict pathology in 30%–70% of cases[12,14-18], causing under- and over-treatment. Thus, rationale exists for identifying noninvasive markers to improve diagnostic accuracy for IPMNs, especially those without high risk stigmata[19,20].

Increased glucose uptake and energy metabolism is prominent in PDACs[21,22] and correlates with IPMN grade[23]. Therefore, metabolic dysregulation characterized by obesity may also associate with IPMN severity. Only one study of IPMNs[24] has specifically examined if obesity is associated with malignancy. Very high BMI (≥35 kg/m^2) was associated with a high prevalence of malignancy in side branch duct (BD) IPMNs. BD-IPMNs without high risk stigmata are challenging to manage[15-18,25-27], and if obesity is a marker of malignant BD-IPMNs, this could aid in management. One major limitation of prior studies[2-6,24] is that BMI was used to measure obesity. BMI is imprecise and cannot differentiate between subcutaneous fat accumulation (which represents the normal physiological buffer for excess energy intake) and abdominal/visceral adiposity[28], a facilitator of carcinogenesis through metabolic disturbances, inflammation, and fat infiltration in the pancreas[29-36]. Abdominal/visceral fat area (VFA) is a risk factor for pancreatic fat infiltration in patients with PC[37] and PanINs[38], and is associated with poor PC outcomes[31,37,39]. Routine abdominal CT scans are the gold-standard for investigating quantitative radiologic features of abdominal adiposity (such as VFA)[40], yet no published studies of these features exist for IPMN patients. We sought to determine if quantitative radiologic features of obesity extracted from abdominal CT scans can help to distinguish risk of malignant versus benign IPMNs.

Materials and methods

Study population and data

The study population included a fixed cohort of 37 patients with IPMNs whose pre-operative CT images had recently been evaluated as part of a different study[20]. The cases had initially been identified using a prospectively maintained clinical database of individuals who underwent a pancreatic resection for an IPMN between 2006 and 2011 at Moffitt Cancer Center and Research Institute (Moffitt) and provided written consent for medical images and clinical data to be donated for research through protocols approved by the Institutional Review Board (IRB) of the University of South Florida, including Total Cancer Care[41]. For all cases, demographic and clinical data (presenting systems, age at diagnosis, past medical and surgical history, and information on known and suspected cancer risk factors such as smoking, family history, and body mass index calculated from pre-surgical height and weight) was obtained from the electronic medical record and patient questionnaire. Detailed imaging studies, surgical details, pathology results, lab values (serum CA 19-9), and treatment information was collected from the medical record and Moffitt's Cancer Registry.

Histopathologic analysis

Board-certified pathologists with expertise in PDAC and IPMN pathology (KJ, DC, BAC) previously histologically confirmed the diagnosis and degree of dysplasia using World Health Organization guidelines[42]. The final diagnosis represented the most severe grade of dysplasia observed in the neoplastic epithelium. None of the cases received pre-operative chemotherapy or radiation. 'Malignant' cases were classified as having high-grade dysplasia or invasive carcinoma and 'benign' cases were defined by low- or moderate-grade dysplasia.

CT imaging, acquisition, and abdominal obesity assessment

Most of the CT scans from this series of patients were obtained on the Siemens Sensation (16, 40, or 64) using an abdominal or pancreatic CT angio (CTA) protocol according to standard operating procedures described previously[20]. Archived non-enhanced CT images performed within the three months prior to surgery, were acquired from Moffitt's GE Centricity Picture Archiving and Communication System (PACS). The imaging team, led by our board-certified abdominal radiologists (DJ and JC), were blinded to the final pathology. Contrast enhanced axial venous phase images were used and reviewed for high risk stigmata and worrisome features of the pancreatic lesions[12]. Non enhanced axial CT images were utilized and have previously shown to be adequate for visceral and subcutaneous fat measurements[43,44]. Measures of total abdominal fat (TAF) area, VFA, and subcutaneous fat area (SFA) were obtained using the volume segmentation and thresholding tools in AW server version 2.0 software (General Electric, Waukesha, WI, USA). The axial L2-L3 intervertebral disc level was used for analysis because adipose tissue at this level corresponds to whole body quantities[45] and is well distinguished from skeletal muscle and other structures[40,46,47]. CT attenuation thresholds to define adipose tissue were set between –249 and –49 Hounsfield Units[44]. TAF area on an L2–L3 axial slice nearest the superior endplate of L3 was calculated by counting the volume of voxels that meet fat attenuation thresholds divided by slice thickness, which allowed standardization of measurements despite potentially different CT scan protocols. VFA was manually segmented along the fascial plane tracing the abdominal wall[48]. SFA was calculated by subtracting VFA from TAF. The VFA to SFA ratio (V/S) was calculated with V/S>0.4 cm^2 defined as viscerally obese[46,49,50]. Manual tracing of the visceral fascial plane allowed the radiologist to exclude any fat density regions within bowel or fatty lesions within organs.

Statistical analysis

For select variables, descriptive statistics were calculated using frequencies and percents for categorical variables and means and standard deviations (SD) for continuous variables. The distributions of covariates were compared across groups using the Wilcoxon two sample two-sided exact test for continuous variables and Fisher's exact tests for categorical variables. Stratified analyses of BMI and radiologic obesity measures were conducted by gender. Spearman correlations were calculated to evaluate the relationship between BMI and quantitative radiologic obesity measures. Estimates of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for key variables. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Study population characteristics

Radiologic measures of obesity were successfully calculated for 34 of the 37 cases; three cases did not have available scans in our PACS including the axial L2–L3 intervertebral disc level views for adiposity measurement. Clinical, epidemiologic, and imaging characteristics of the 34 cases (17 benign; 17 malignant) investigated in this analysis are in **Table 1** and are in line with published data on other IPMN cohorts[51]. Seventy-six percent with malignant pathology had MD involvement on CT versus 24% with benign pathology (P=0.005). Mean lesion size was higher in the malignant compared to the benign group (3.4 versus 1.9 cm), P=0.003. Malignant IPMNs, particularly those deemed to be invasive, were predominately located in the pancreatic head. The majority of cases (82%) with malignant pathology had one or more high risk stigmata (MD involvement/dilatation> 10 mm, obstructive jaundice with a cystic lesion in the pancreatic head, or an enhanced solid component within the cyst), versus 18% of those with benign pathology (P<0.001). Presence of one or more worrisome features (ie. MD dilation 5–9 mm, cyst size>3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, or acute pancreatitis) was not associated with malignancy (P=0.708) in this cohort. BMI was higher in malignant (28.9 kg/m^2, 95% CI: 26.3–31.4 kg/m^2) versus benign cases (25.8 kg/m^2, 95% CI: 23.3–28.3 kg/m^2), with P=0.045. Mean BMI was similar in males and females, at 27.8 and 27.0 kg/m^2, respectively.

Analysis of quantitative radiologic measures of obesity

Mean VFA was higher in patients with malignant (199 cm^2) versus benign (120 cm^2) IPMNs, but did not reach statistical significance with the Wilcoxon two-sample exact test (P=0.092) (**Table 2**). Mean V/S was substantially higher in malignant versus benign IPMNs, with values of 1.25 cm^2 and 0.69 cm^2, respectively (P=0.013). We found no statistically significant differences between TAF and SFA in the malignant and benign groups.

Table 1 Characteristics of IPMN cases in the study cohort (*n*=34)

Variable	Benign IPMNs (*n*=17)[a]	Malignant IPMNs (*n*=17)[b]	*P*
Age at diagnosis, mean (SD), years	67.5 (10.9)	71.8 (11.3)	0.143
Gender			0.032
Male	3 (18)	10 (59)	
Female	14 (82)	7 (41)	
Race			0.485
White, non-Hispanic	17 (100)	15 (88)	
Black	0 (0)	2 (12)	
Jaundice as presenting symptom			0.103
Yes	0 (0)	4 (24)	
No	17 (100)	13 (76)	
Pre-operative serum CA 19-9 levels, mean (SD) (ng/mL)	18.2 (19.1)	185.5 (350.1)	0.216
Predominant tumor location			0.084
Pancreatic head	6 (35)	12 (71)	
Pancreatic body or tail	11 (65)	5 (29)	
Type of ductal communication			0.005
Main duct or mixed	4 (24)	13 (76)	
Branch duct	13 (76)	4 (24)	
Size of largest cyst, mean (SD) (cm)	1.9 (1.1)	3.4 (1.3)	0.008
Solid component or mural nodule			0.141
Yes	3 (18)	8 (47)	
No	14 (82)	9 (53)	
High risk stigmata			<0.001
Yes	3 (18)	14 (82)	
No	14 (82)	3 (18)	
Worrisome features			0.708
Yes	11 (65)	13 (76)	
No	6 (35)	4 (24)	
BMI, mean (95% CI) (kg/m^2)	25.8 (4.9)	28.9 (4.9)	0.045

Data represent counts (percentages) unless otherwise indicated. Counts may not add up to the total due to missing values, and percentages may not equal 100 due to rounding. *P* value estimated using the Wilcoxon two sample two-sided exact test for continuous variables and Fisher's exact tests for categorical variables.

[a] Benign IPMNs are represented by 2 low-grade and 15 moderate-grade IPMNs.

[b] Malignant IPMNs are represented by 11 high-grade and 6 invasive IPMNs.

Table 2 Quantitative radiologic measures of obesity, by IPMN pathology

Parameter	Benign IPMNs (*n*=17)	Malignant IPMNs (*n*=17)	*P*
TAF area (cm^2)	321.8 (169.5)	391.0 (201.3)	0.259
VFA (cm^2)	120.4 (68.4)	199.3 (125.4)	0.092
SFA (cm^2)	201.3 (132.1)	191.6 (191.6)	0.734
V/S (cm^2)	0.69 (0.5)	1.25 (1.1)	0.013

Data represent mean values and standard deviation. *P* value was estimated using Wilcoxon two sample exact tests.

Males had a higher mean VFA value (202.4 cm^2) than females (133.6 cm^2) and a higher mean V/S value (1.25 cm^2) than females (0.80 cm^2). Stratified analyses revealed that among both males and females, mean BMI, TAF, and VFA values were higher for patients with malignant compared to benign IPMNs, though results were not statistically significant (P>0.05) for either gender (**Table 3**). Among females, V/S was significantly higher for those having malignant IPMNs (P=0.038). While no correlation existed between BMI and V/S (r=0.16, P=0.35), significant positive correlations were found between BMI and VFA (r=0.68, P<0.0001) and between BMI and SFA (r=0.71, P<0.0001).

Of clinical importance, **Figure 1** displays CT scans from two IPMN patients who did not present with high risk

Table 3 Gender-specific differences in BMI and quantitative radiologic measures of obesity, by IPMN pathology

Parameter	Males (3 benign; 10 malignant)	*P*	Females (14 benign; 7 malignant)	*P*
BMI (kg/m^2)	24.0 (2.2); 29.0 (5.2)	0.112	26.2 (5.3); 28.8 (4.8)	0.224
TAF area (cm^2)	209.9 (78.9); 408.9 (227.4)	0.371	328.4 (184.7); 365.3 (171)	0.689
VFA (cm^2)	174.7 (80.7); 210.7 (131.5)	1.000	108.8 (62.7); 183.2 (124.3)	0.197
SFA (cm^2)	116.3 (9.8); 198.3 (113.4)	0.077	219.6 (139.5); 182.2 (95.7)	0.743
V/S (cm^2)	1.5 (0.8); 1.2 (0.5)	0.287	0.5 (0.2); 1.4 (1.7)	0.038

Data represent mean values and standard deviation. *P* values estimated using the Wilcoxon two sample two-sided exact test.

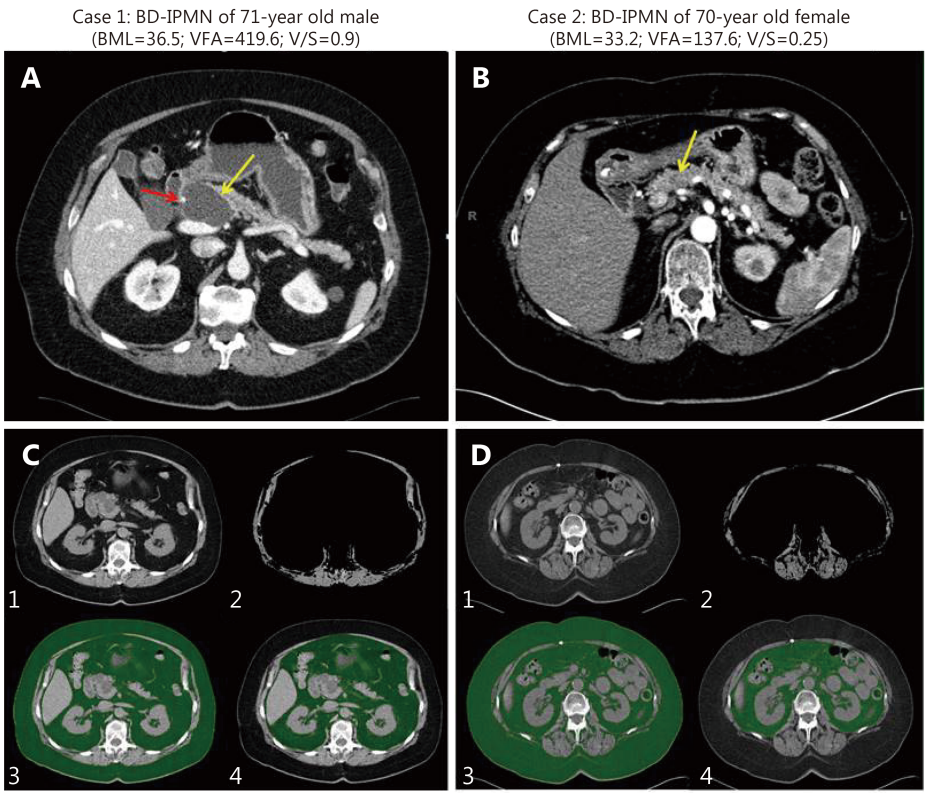

Figure 1 Axial post contrast CTs (A and B) and quantitative segmentation (C and D) for two representative side BD IPMN cases with main pancreatic ducts normal in caliber. Case 1 has a well-demarcated homogenous hypodense 4.8 cm cystic lesion in the pancreatic neck (yellow arrow). The cystic lesion abuts the gastroduodenal artery (red arrow) without definite encasement. Case 2 has a poorly defined 1.3 cm hypoenhancing pancreatic neck lesion (yellow arrow). C and D: (1) Axial CT image through L2–L3 intervertebral disc level. (2) Axial CT subtracted image at superior endplate of L3. Abdominal wall and paraspinal muscle area were segmented and thresholds set to voxels with Hounsfield units (HU) –29 to 150. Visceral fat, intra-abdominal organs, and vasculature were subtracted. Although skeletal muscle indices can be obtained in a complementary manner to visceral fat measurements, these were not directly analyzed in this study. (3) Total abdominal fat with HU thresholds applied to include fat density voxels with HU –249 to –49 (green). (4) Manual segmentation of visceral fat regions (green).

stigmata on imaging. Both have similar BMIs but vastly different VFA and V/S values, with case 1 having higher VFA and V/S and a worrisome feature (cyst size>3 cm) and high-grade pathology and case 2 having lower VFA and V/S and low-grade pathology at resection. These data suggest that visceral fat may be added as another risk factor to potentially aid in directing management towards a necessary surgery to remove what turned out to be a high-grade lesion (case 1) and avoided an unnecessary surgery for a low-grade lesion (case 2). The accuracy, sensitivity, specificity, PPV, and NPV of V/S in predicting malignant IPMN pathology were 74%, 71%, 76%, 75% and 72%, respectively.

Discussion

This pilot project represents the first to study objectively quantitative radiologic measures of obesity as diagnostic markers of IPMN pathology. In addition to observing higher pre-operative BMI values in patients confirmed to have malignant IPMNs, VFA and V/S values were also observed in the malignant IPMN group compared to those with benign IPMNs. We also observed that males with IPMNs had higher VFA and V/S values than female cases, in line with the observation that visceral fat is more common in males[28], and showed that women with benign IPMNs had a significantly lower V/S ratio (0.5 cm^2) than those with malignant IPMNs (1.4 cm^2), Women with benign IPMNs in our cohort appeared to have a higher SFA than other cohort members, consistent with data suggesting that subcutaneous fat may not be a marker of malignancy[28]. Previous authors have suggested that in an asymptomatic adult cohort, men have significantly higher V/S ratios[52]. However, no standardized gender-based V/S values are currently available which suggests further research is needed to define visceral obesity in each gender. Our small cohort, however, had relatively more females in the benign pathology group and more males in the malignant pathology group, so firm conclusions cannot be drawn based on these preliminary findings. Despite this, findings suggest that being overweight or obese, particularly in the intra-abdominal area, may be a prognostic marker for malignant potential of IPMNs. Given that abdominal/visceral adiposity has been shown to influence carcinogenesis and that BMI is an imprecise proxy for abdominal adiposity[29-36], biologically-driven radiologic measures of visceral fat may have greater clinical utility than BMI in predicting IPMN pathology. Further research with a larger sample size is clearly needed to distinguish the relationship between radiologic measures of visceral fat, gender, and malignancy.

Few studies have reported on quantitative radiologic measures of obesity in patients with PDAC. In a study of 9 PDAC cases and matched controls[53], no significant differences in SFA, VFA, TFA, or V/S were observed between the patients and controls. On the other hand, pre-operative visceral fat was shown to be a prognostic indicator in patients with PDAC, with increased visceral fat being associated with worse survival in patients with lymph node metastases[37]. Elevated visceral fat defined by the V/S has also been shown to predict recurrence among locally advanced rectal cancer patients[50]. Collectively, these[37,50] and other studies[31,35] provide plausibility for our observation that VFA and V/S may be associated with more advanced IPMN pathology.

Although limitations of this pilot study include its small size and retrospective design, characteristics of this cohort are representative of other IPMN cohorts, suggesting potential generalizability. External validation in a large, independent data set is warranted. Furthermore, with a larger sample size, multivariable modeling and receiver characteristic curve analyses will be helpful to determine the utility of gender-specific radiologic measures of abdominal obesity in discriminating malignant from benign IPMNs, independent of and in combination with novel molecular and radiologic markers[19,20], standard clinical and radiologic features encompassed by consensus guidelines[12], and BMI.

In summary, use of quantitative radiologic measures of abdominal obesity could provide a noninvasive, rapid, low cost, and repeatable way of investigating features that may potentially aid in personalizing care for patients with pancreatic cancer precursors. Given that a reduction in abdominal adiposity by lifestyle, diet, and/or pharmacologic intervention would be impactful and could translate into a decreased burden of PC, obesity, and other diseases, further studies in this area are warranted.

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Conflicts of interest statement

No potential conflicts of interest are disclosed.

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