ORIGINAL ARTICLE

Qualitative flow metabolic phenotype of pancreatic cancer. A new prognostic biomarker?

Deniece Riviere[1], Erik Aarntzen[1], Erwin van Geenen[2], David Chang[3,4], Lioe-Fee de Geus-Oei[5], Lodewijk Brosens[6,7], Kees van Laarhoven[8], Martin Gotthardt[1] & John Hermans[1]

[1]Department of Medical Imaging, Radboud University Medical Center, Nijmegen, the Netherlands, [2]Department of Gastroenterology, Radboud University Medical Center, Nijmegen, the Netherlands, [3]Wolfson Wohl Cancer Research Centre, School of Cancer Sciences, University of Glasgow, Bearsden, Glasgow, Scotland, United Kingdom, [4]West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, Scotland, United Kingdom, [5]Department of Radiology, Leiden University Medical Center, Leiden, [6]Department of Pathology, Radboud University Medical Center, Nijmegen, [7]Department of Pathology, University Medical Center Utrecht, Utrecht, and [8]Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands

Abstract

Background: Retrospective analysis to investigate the relationship between the flow-metabolic phenotype and overall survival (OS) of pancreatic ductal adenocarcinoma (PDAC) and its potential clinical utility.

Methods: Patients with histopathologically proven PDAC between 2005 and 2014 using tumor attenuation on routine pre-operative CECT as a surrogate for the vascularity and [^{18}F]FDG-uptake as a surrogate for metabolic activity on [^{18}F]FDG-PET.

Results: In total, 93 patients (50 male, 43 female, median age 63) were included. Hypoattenuating PDAC with high [^{18}F]FDG-uptake has the poorest prognosis (median OS 7 ± 1 months), compared to hypoattenuating PDAC with low [^{18}F]FDG-uptake (median OS 11 ± 3 months; p = 0.176), iso- or hyperattenuating PDAC with high [^{18}F]FDG-uptake (median OS 15 ± 5 months; p = 0.004) and iso- or hyperattenuating PDAC with low [^{18}F]FDG-uptake (median OS 23 ± 4 months; p = 0.035). In multivariate analysis, surgery combined with tumor differentiation, tumor stage, systemic therapy and flow metabolic phenotype remained independent predictors for overall survival.

Discussion: The novel qualitative flow-metabolic phenotype of PDAC using a combination of CECT and [^{18}F]FDG-PET features, predicted significantly worse survival for hypoattenuating-high uptake pancreatic cancers compared to the other phenotypes.

Received 26 July 2023; accepted 17 November 2023

Correspondence

Deniece Riviere, Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, the Netherlands. E-mail: D.Riviere@radboudumc.nl (D. Riviere)

Correspondence

John Hermans, Radboud University Medical Center, Department of Medical Imaging, P.O. Box 9101, 6500 HB, Nijmegen, the Netherlands. E-mail: John.Hermans@radboudumc.nl (J. Hermans)

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis which has gradually improved in the past 20 years.[1] The incidence for PDAC has been estimated to increase by 66% between 2020 and 2040 and it is predicted to be the second cause of cancer related death in 2026.[2] Only 15–20% of the patients diagnosed with PDAC are considered for resection as the remainder of the patients present with locally advanced and/or metastatic disease and curative surgical treatment is no longer possible.[1] The 5-year survival rate is only 9%[3] up to 16.5% for

A conference abstract was published in Pancreatology (https://doi.org/10.1016/j.pan.2018.05.405) following the presentation of preliminary results of this paper.

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

resected patients.[1] Traditional prognostic factors associated with poorer survival include larger tumor size, major blood vessel invasion, the presence of nodal or distant metastasis, the presence of residual disease after resection, high histologic grade, and poor performance status. New therapeutic approaches such as FOLFIRINOX in the neoadjuvant or palliative setting are under investigation.[4–8] Accurate patient stratification prior to treatment is crucial to benefit from these new strategies. Thus, the demand for non-invasive imaging biomarkers that better correlate with tumor biology, as opposed to conventional anatomic-morphologic approaches, is evident.

Previous CT studies have suggested that the physiological vascular information from dynamic contrast-enhanced imaging can have a role in diagnosis, grading and response assessment.[9] The presence of dense desmoplastic stroma, a hallmark of PDAC, leads to a substantial interstitial pressure resulting in vascular collapse and tumor hypoperfusion, which limits oxygen and nutrient availability[10–12] and hinders drug delivery to cancer cells.[13] Tumors that are hypoattenuating on the portal-venous phase on CT scan are more aggressive with poor tumor differentiation, more lymph node metastases, and shorter disease-free survival.[14] Conversely, visually isoattenuating tumors have a better survival after surgery with curative intent.[15] Although [^{18}F]FDG-PET is not able to accurately define tumor extent relative to the surrounding tissues, it has proved useful in modifying the staging of PDAC for 10% of cases, changing the decision making in about 50% of cases and sparing non-useful surgery in 20% of cases, usually due to the detection of previously undetected metastases.[16] Using the tumor glucose metabolism [^{18}F]FDG-PET can be useful to detect local recurrence, assess therapeutic effects, and predict prognosis in PDAC patients.[17–20] [^{18}F]FDG-PET SUVmax was significantly associated with the therapeutic response to chemoradiotherapy in PDAC patients[21] and in a subset of patients with interval metabolic imaging after initial chemotherapy, complete metabolic response highly correlated with major pathologic response.[22,23] Additionally, tumors with higher rates of glycolysis but lower cholesterol synthesis are known to be more aggressive and less sensitive to chemotherapy than tumors with a more cholesterogenic phenotype.[24,25]

Until recently, perfusion and metabolism have mostly been used separately. The balance between tumor vascularity and glucose metabolism offers complementary information concerning tumor adaption to the microenvironment. Matched high glucose metabolism with increased vascularity represents a different biologic status compared to mismatched high metabolism with lower vascularity, with the latter indicating adaptation to hypoxia.[26] Long term adaptation to hypoxic conditions, may facilitate cancer progression and treatment resistance.[27] However, a flow-metabolic phenotype has not been defined for PDAC.

The purpose of this study is to investigate the relationship between the qualitative flow-metabolic phenotype and overall survival of PDAC and its potential clinical utility, using tumor attenuation on routine contrast-enhanced CT (CECT) as a surrogate for the vascularity and [^{18}F]FDG uptake as a surrogate for metabolic activity on [^{18}F]FDG-PET.

Methods

Study design and outcome measures

All adult patients with histopathologically proven PDAC who received both a CECT and a [^{18}F]FDG-PET scan in accordance with prevailing guidelines between 2005 and 2014 were eligible for inclusion. Patients were identified in the electronic medical records of our institution. CT scans and [^{18}F]FDG-PET scans were either performed in our university hospital or in community hospitals. Exclusion criteria were pathological diagnosis other than PDAC and a time interval between CECT and [^{18}F]FDG-PET of more than 60 days.

The primary outcome measure evaluated in this study was overall survival. The institution's electronic medical records and the Statistics Netherlands (CBS), until 31st of December 2021, were used to establish the overall survival. Overall survival was measured from the day of diagnosis until death. Censoring was performed for loss to follow up or survival at 31st of December 2021.

Tumor characteristics such as tumor size and tumor grade were obtained from the pathology report. Tumor size on CECT in portal-venous phase was used in analyses in patients that did not undergo curative resection. Tumor grade was coded well differentiated, moderately differentiated and poorly differentiated. Tumor stage was recorded according to the 8th edition of the AJCC Staging Manual. For patients that did not undergo resection pathological stage was supplemented with clinical stage. Information on treatment (surgery, systemic therapy) was obtained from the electronic medical records.

CT quantitative and qualitative analysis of flow

CT scans were reviewed by a single observer (JH) with 20 years of experience in abdominal radiology. Qualitative and quantitative assessment of attenuation has excellent interobserver agreement,[28] therefore single reader assessment of CT images suffices. Image quality was deemed insufficient in case of severe motion artefacts or low signal to noise ratio (SNR). For image analysis images in the portal-venous phase were used, defined as enhancement of both the portal vein and the hepatic veins, which were extracted from either the CT pancreas protocol or routine abdominal CT images in the absence of a multiphase pancreas CT. The largest tumor diameter was measured in the axial plane, and the images were evaluated in the portal-venous phase. Tumor enhancement was used as a surrogate for the vascularity. Hypoattenuation and isoattenuation qualitatively indicated a state of low and normal blood flow respectively and hyperattenuation a state of increased flow. For quantitative analysis, the Hounsfield unit (HU) value in the tumor was determined, and if possible, the HU value upstream or downstream in the

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

surrounding pancreas parenchyma. A circular region of interest (ROI) with the largest possible diameter was placed in the tumor and in the surrounding pancreas parenchyma of the pancreatic head, body and tail. Isoattenuating PDAC was defined as a difference in attenuation value of less than 10 HU between surrounding pancreas parenchyma (HUP) and pancreas tumor (HUT): $-10 \leq HUP - HUT \leq 10$. Hypoattenuating PDAC was defined as a difference in attenuation value of more than 10 HU between surrounding pancreas parenchyma and tumor: $HUP - HUT > 10$. Hyperattenuating PDAC was defined as a difference in attenuation value of more than 10 HU in the tumor compared to surrounding pancreas parenchyma: $HUP - HUT < -10$. If it was impossible to measure the difference in HU between the tumor and surrounding parenchyma, tumors were visually evaluated. Isoattenuating PDAC was qualitatively defined as a tumor visually not discernible from surrounding pancreas parenchyma. Hypoattenuating PDAC was qualitatively defined as a tumor darker than surrounding pancreas parenchyma, hyperattenuating PDAC was qualitatively defined as a tumor brighter than surrounding parenchyma.

PET qualitative analysis of metabolism

[^{18}F]FDG-PET images were obtained in our university hospital using Siemens EXACT, Siemens Biograph2 and Siemens mCT40 or in community hospitals (n = 3; Philips Gemini GXL, Philips unknown model, unknown vendor and model). The median FDG dose was 236 megabecquerel (range 75–384). [^{18}F]FDG-PET images were reviewed and individually scored using Hermes (Hermes P5 Gold, version 4.6-A) by two observers (MG and LGO) with more than 25 years of experience. Image quality was deemed insufficient in case of severe motion artefacts or low SNR. After visual identification of the primary pancreatic lesion with guidance of CT or MR images, a qualitative evaluation was performed based on [^{18}F]FDG uptake. The [^{18}F]FDG uptake of the tumor was defined low uptake or high uptake compared to uptake of the liver. SUVmax was not measured, because EARL reconstructions were not available for all patients. Discordant results were solved by consensus reading. Different uptake patterns were recorded: focal hotspot, multifocal hotspots, ring-shaped, homogeneous low, homogeneous high, indeterminate, no uptake. High uptake was defined as uptake pattern 1, 2, 3, 5 and low uptake was defined as uptake pattern 4 and 7. Indeterminate pattern contained both high uptake tumors (n = 15) and low uptake tumors (n = 1). Heterogeneous uptake was defined as uptake pattern 1, 2 and 3 (Fig. 1).

Statistics

SPSS (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) was used for all statistical analysis. The summary statistics are presented as the median (± SD and range) for continuous variables, or frequency and percentage for categorical variables. For between-group analyses student t-test was used for comparing means and chi-square test was used for categorical data. Kaplan–Meier curves for overall survival analysis were generated and compared using the Mantel Cox log-rank test. Cox regression survival analysis was performed on various factors to examine possible confounding factors for survival. A statistically significant result was defined as $p < 0.05$.

Results

Population

A total of 137 patients were retrieved from the hospitals' electronic patient database with suspected PDAC who underwent

1		Focal hotspot	High uptake	Heterogeneous	n = 14
2		Multifocal hotspots	High uptake	Heterogeneous	n = 13
3		Ring shaped	High uptake	Heterogeneous	n = 11
4		Low	Low uptake	Homogeneous	n = 8
5		High	High uptake	Homogeneous	n = 22
6		Indeterminate			n = 16
7		No uptake	Low uptake	Homogeneous	n = 9

Figure 1 [^{18}F]FDG-uptake patterns

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

both a CECT scan and a [^{18}F]FDG-PET scan between January 2005 and December 2014 as primary diagnostic workup. After 2014 [^{18}F]FDG-PET was not part of the diagnostic workup anymore. Patients without a histopathological proof of PDAC were excluded (n = 16), as were patients with a pathological diagnosis other than PDAC; cholangiocarcinoma (n = 10), ampulla of Vater carcinoma (n = 3), double tumor of the pancreas (n = 2), duodenum tumor (n = 1), malignant intraductal papillary mucinous neoplasm IPMN (n = 1) and anaplastic carcinoma (n = 1). Three patients were excluded because imaging quality was not sufficient, and seven patients were excluded because the imaging interval was more than 2 months. Finally, 93 patients (50 male, median age 63 years) were included (Table 1). PDAC mostly occurred in the pancreatic head (86%). In 8 patients the tumor diameter could not be reliably measured due to poor demarcation or ill-defined tumor borders. The mean time interval between imaging was 13.2 days (SD 15.2). A curative resection was performed in 39 patients: pancreatoduodenectomy n = 33, distal pancreatectomy n = 5 and subtotal pancreatectomy n = 1. In 30 patients exploratory laparotomy or laparoscopy was performed with or without surgical bypass. The other 24 patients did not undergo surgery. In total, 32 patients received adjuvant and/or palliative systemic therapy. One of these patients also received neoadjuvant chemoradiotherapy, imaging included in this study was performed before treatment. Most patients were too weak to undergo systemic therapy (although performance status was not registered in most patients), some patients choose quality of life over systemic therapy, and in 10 patients data on systemic therapy was missing. At the time of analysis, 89 patients had died, with a median follow up of 9 months (range 1–94 months), with a loss to follow up of n = 4. The median overall survival was 10 months.

Table 1 Demographic characteristics

	All patients (n = 93)	Resectable PDAC (n = 39)
Age years (median)	63 SD 10.3, range 30–80	64 SD 10.3, range 30–78
Gender		
Male	50 (54%)	20 (51%)
Female	43 (46%)	19 (49%)
Tumor location		
Head	80 (86%)	35 (90%)
Body–tail	13 (14%)	4 (10%)
Diameter mm (median)	26 (n = 85) SD 10.0, range 6–60	26 SD 9.9, range 6–60
Tumor grade		
Well	3 (3%)	2(5%)
Moderate	16 (17%)	14 (36%)
Poor	21 (23%)	19 (49%)
Unknown	53 (57%)	4 (10%)
Tumor stage		
I	10 (11%)	9 (23%)
II	17 (18%)	16 (41%)
III	31 (33%)	14 (36%)
IV	35 (38%)	–
Curative surgery	39 (42%)	
Systemic therapy		
Yes	32 (34%)	19 (49%)
No	51 (55%)	17 (44%)
Unknown	10 (11%)	3 (8%)
Overall survival		
Median	10 months	21.2 months
1 year survival	45%	79%
3 year survival	12%	28%
5 year survival	4%	10%

CT patterns

Of the 93 patients, 65 patients had hypoattenuating tumors and 28 patients had iso- or hyperattenuating tumors (Table 2). In 22 patients the difference in HU value between tumor and surrounding pancreatic tissue was not measurable due to upstream atrophy, chronic pancreatitis or diffuse tumor infiltration. In these patients, attenuation was graded visually. Most of these tumors (n = 21) were located in the pancreatic head. There was a statistically significant difference in OS between hypo- and iso- or hyperattenuating tumors with a median OS of 8 ± 0.9 months versus 20 ± 4.2 months (p = <0.001). Iso- or hyperattenuating tumors were all located in the head of pancreas (p = 0.011), had significantly lower tumor stage (p = 0.007) and underwent curative resection more often (p < 0.001). There was no significant difference in overall survival between iso- or hyperattenuating tumors versus hypoattenuating tumors in stage I/II (p = 0.444), stage III (p = 0.089) and stage IV (p = 0.182).

FDG patterns

There were 18 patients with low uptake and 75 patients with high uptake (Table 3). Patients with high [^{18}F]FDG-uptake (median OS 9 ± 0.9 months) had a trend of a worse OS compared to patients with low [^{18}F]FDG-uptake (median OS 19 ± 6.3 months; p = 0.175). There was a significant difference in overall survival between low [^{18}F]FDG-uptake tumors versus high [^{18}F]FDG-uptake tumors in stage IV (p = 0.041).There was no significant difference in stage I/II (p = 0.931) or stage III (p = 0.378). There were several homogenous or heterogeneous (i.e., uni- and multifocal hotspots, ring-shaped) uptake patterns observed (Fig. 1). Patients with heterogeneous tumors (median OS 8 ± 1.2 months) had a significant lower overall survival compared to patients with homogeneous tumors (median OS 13 ± 2.1 months; p = 0.026).

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 2 Demographic characteristics of patients with iso- or hyperattenuating versus hypoattenuating tumors

	Iso- or hyperattenuating (n = 28)	Hypoattenuating (n = 65)	*p*-value
Age years (median)	64 SD 11.5, range 30–80	63 SD 10.1, range 35–79	0.394
Gender			0.182
Male	18 (64%)	32 (49%)	
Female	10 (36%)	33 (51%)	
Tumor location			**0.011**
Head	28 (100%)	52 (80%)	
Body–tail	–	13 (20%)	
Diameter mm (median)	25 (n = 23) SD 10.2, range 6–55	28 (n = 62) SD 9.8, range 14–60	0.055
Tumor grade			0.111
Well	3 (11%)	–	
Moderate	6 (21%)	10 (15%)	
Poor	8 (29%)	13 (20%)	
Unknown	11 (39%)	42 (65%)	
Tumor stage			**0.007**
I	7 (25%)	3 (5%)	
II	6 (21%)	11 (17%)	
III	10 (36%)	21 (32%)	
IV	5 (18%)	30 (46%)	
Curative surgery	19 (68%)	20 (31%)	**<0.001**
Systemic therapy	11 (39%)	21 (32%)	0.503
Overall survival			
Median	20 months	8 months	**<0.001**
1 year survival	75%	32%	
3 year survival	29%	5%	
5 year survival	7%	3%	

Table 3 Demographic characteristics of patients with high versus low [^{18}F]FDG-U=uptake tumors

	High (n = 75)	Low (n = 18)	*p*-value
Age years (median)	63 SD 10.6, range 30–79	63 SD 9.3, range 44–80	0.467
Gender			0.486
Male	39 (52%)	11 (61%)	
Female	36 (48%)	7 (39%)	
Tumor location			0.714
Head	65 (87%)	15 (83%)	
Body–tail	10 (13%)	3 (17%)	
Diameter mm (median)	27 (n = 69) SD 10.4, range 6–60	25 (n = 16) SD 7.8, range 12–39	0.105
Tumor grade			0.104
Well	1 (1%)	2 (11%)	
Moderate	13 (17%)	3 (17%)	
Poor	18 (24%)	3 (17%)	
Unknown	43 (57%)	10 (56%)	
Tumor stage			0.259
I	9 (12%)	1(5%)	
II	13 (17%)	4 (22%)	
III	22 (29%)	9 (50%)	
IV	31 (41%)	4 (22%)	
Curative surgery	30 (40%)	9 (50%)	0.440
Systemic therapy	26 (35%)	6 (33%)	0.607
Overall survival			0.175
Median	9 months	19 months	
1 year survival	40%	67%	
3 year survival	12%	11%	
5 year survival	5%	0%	

Qualitative flow-metabolic phenotype

When taking both CECT and PET features into consideration, there were 55 patients with hypoattenuating tumors and high [^{18}F]FDG-uptake (Fig. 2), 20 patients with iso- or hyperattenuating tumors and high [^{18}F]FDG-uptake (Fig. 3), 10 patients with hypoattenuating tumors and low [^{18}F]FDG-uptake (Fig. 4), and finally 8 patients with iso- or hyperattenuating tumors and low [^{18}F]FDG-uptake (Fig. 5). A cross correlation of CECT attenuation and [^{18}F]FDG-uptake pattern revealed that hypoattenuating PDAC with high [^{18}F]FDG-uptake has the poorest prognosis (median OS 7 ± 0.9 months), compared to hypoattenuating PDAC with low [^{18}F]FDG-uptake (median OS 11 ± 2.6 months; p = 0.176), iso- or hyperattenuating PDAC with high [^{18}F]FDG-uptake (median OS 15 ± 4.5 months; p = 0.004) and iso- or hyperattenuating PDAC with low [^{18}F]FDG-uptake (median OS 23 ± 3.5 months; p = 0.035) (Fig. 6). There was no significant difference in overall survival between the other groups.

Hypoattenuating PDAC with high [^{18}F]FDG-uptake has significantly higher tumor stage (Stage I/II vs II-IV HR 2.846, 95% CI 1.720–4.708, p < 0.001), lower curative resection rates (HR 3.996, 95% CI 2.420–6.597, p < 0.001) and worse overall survival compared to the other flow-metabolic phenotypes (HR 2.042, 95% CI 1.324–3.150, p = 0.001). Surgery, systemic therapy and tumor grade were found to be possible confounders. In multivariate Cox regression analysis surgery combined with tumor differentiation (good-moderate diff HR 0.381, 95% CI 0.176–0.821, p = 0.014; poor diff HR 0.410, 95% CI 0.201–0.839, p = 0.015), tumor stage (HR 2.074, 95% CI 1.019–4.222, p = 0.044), systemic therapy (HR 0.562, 95% CI 0.332–0.952, p = 0.032) and flow metabolic phenotype (HR 1.861, 95% CI

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

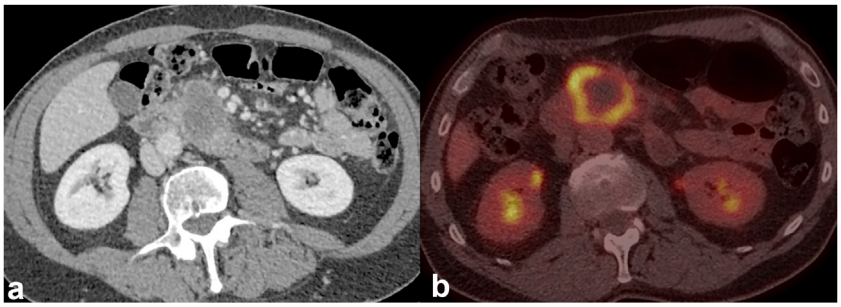


Figure 2 A 64-year-old male with stage 4 PDAC of the pancreatic head (42 mm) and an overall survival of 4 months. The tumor was hypoattenuating on CECT (a) and showed ring-shaped high [^{18}F]FDG-uptake on PETCT (b)

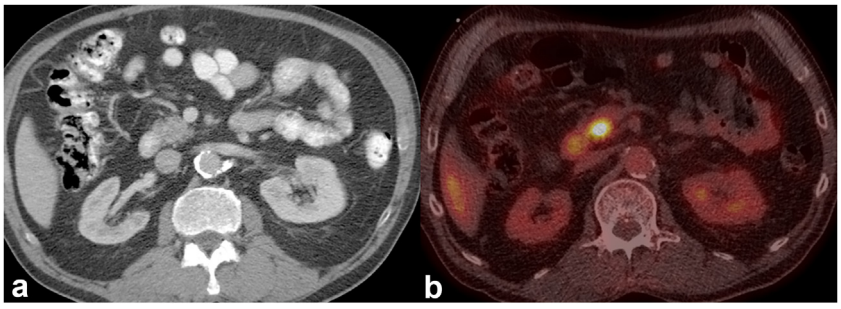


Figure 3 A 77-year-old male with a small (25 mm) poorly differentiated T2N2 PDAC of the pancreatic head who underwent pancreatoduodenectomy with an overall survival of 6 months. The tumor was isoattenuating on CECT (a) and showed homogeneous high [^{18}F]FDG-uptake on PETCT (b)

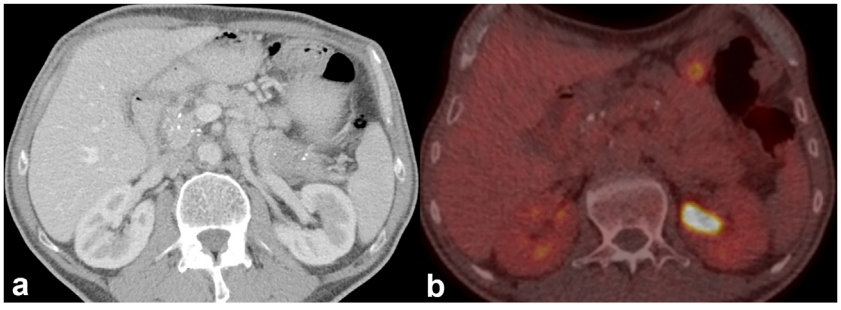


Figure 4 A 56-year-old male with T2N1 PDAC of the pancreatic tail who underwent distal pancreatectomy with an overall survival of 6 months. The tumor (25 mm) was hypoattenuating on CECT (a) and showed low [^{18}F]FDG-uptake on PETCT (b)

1.131–3.060, p = 0.014) remained independent predictors for overall survival. Tumor differentiation was combined with the variable surgery to compensate for missing values in the non-surgically treated patients (no resection was indicator p = 0.017). Missing data occurred in 14 cases in multivariate analysis.

There was no significant difference in overall survival between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage I/II (p = 0.750). There was a significant difference in overall survival between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage III (p = 0.028) and a near significant difference in stage IV (p = 0.056). Additionally, treatment-naïve patients with stage IV tumors had a tendency for a worse prognosis if they had hypoattenuating-high uptake flow-metabolic phenotype with a median overall survival of 4 months versus 6 months in the other phenotypes (p = 0.075). Interestingly, there was no significant difference in overall survival

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

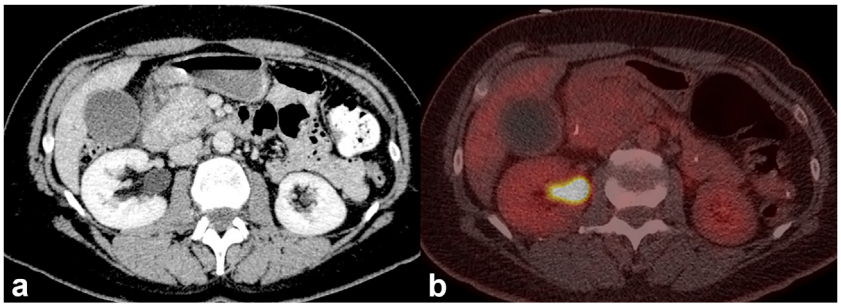
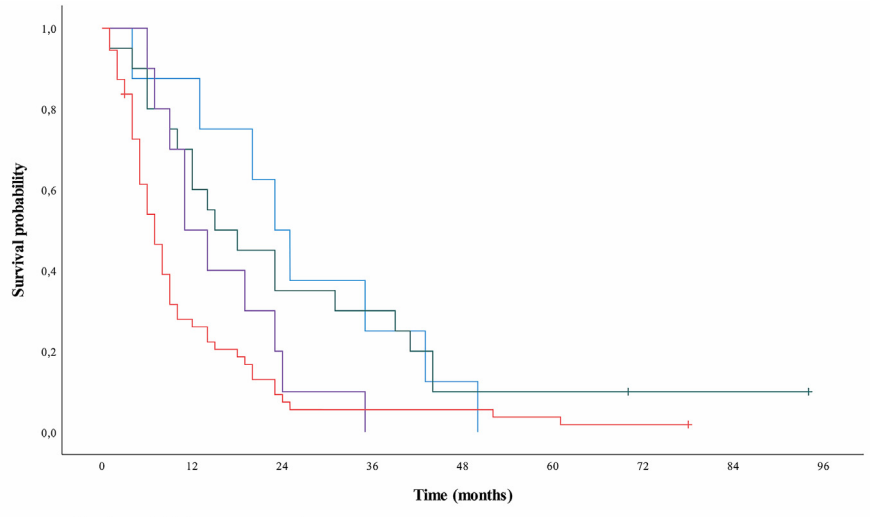


Figure 5 A 44-year-old female with locally advanced PDAC of the pancreatic head who underwent pancreatoduodenectomy after neoadjuvant chemotherapy with an overall survival of 25 months. The tumor was isoattenuating on CECT (a) and showed low [^{18}F]FDG-uptake on PETCT (b)



Numbers at risk (number censored)

iso/hyperattenuating-low uptake (blue)	8	7	4	2	1	0	0	0	0
iso/hyperattenuating-high uptake (green)	20	14	7	6	2	2 (1)	1	1 (1)	0
hypoattenuating-low uptake (purple)	10	5	2	0	0	0	0	0	0
hypoattenuating-high uptake (orange)	55 (1)	15	5	3	3	2	1 (1)	0	0

Figure 6 Kaplan–Meier survival curve, with follow-up duration of 8 years after diagnosis of PDAC (total n = 93). Censored values (+) indicate the last known follow-up time for subjects still alive after diagnosis or lost to follow up. Flow-metabolic phenotype, χ^2 12,694, p = 0.005). Median survival iso-or hyperattenuating-low uptake tumors 23 months, 95% CI 16–30 months (blue), median survival iso-or hyperattenuating-high uptake tumors 15 months, 95% CI 6–24 months (green), median survival hypoattenuating-low uptake tumors 11 months, 95% CI 6–16 months (purple), median survival hypoattenuating-high uptake tumors 7 months, 95% CI 5–9 months (orange)

between patients with stage I/II hypoattenuating-high uptake flow-metabolic phenotype and stage III/IV iso- or hyperattenuating-high uptake flow-metabolic phenotype (p = 0.470) or iso- or hyperattenuating-low uptake (p = 0.603).

Subgroup analysis

Only 15/55 (27%) of hypoattenuating-high uptake tumors underwent curative resection versus 24/38 (63%) of the other phenotypes, and 21/55 (38%) were unexpectedly advanced stage at explorative laparotomy versus 9/38 (24%) of the other phenotypes (p = 0.002). Subgroup analysis of resected patients showed age, gender, tumor location, stage, lymph node ratio, grade and systemic therapy were all possible confounders for overall survival but were not independent predictors in multivariate analysis. After curative resection there was no significant difference in overall survival between hypoattenuating-high uptake tumors versus other phenotypes, whether patients received systemic therapy or not. Subgroup analysis of palliative patients showed age, stage, tumor size and systemic therapy were possible confounders. In multivariate Cox regression analysis

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

tumor stage (HR 3.350, 95% CI 1.439–7.802, p = 0.005), systemic therapy (HR 0.231, 95% CI 0.092–0.580, p = 0.002), tumor size (HR 1.036, 95% CI 1.004–1.069, p = 0.026) and flow metabolic phenotype (HR 4.333, 95% CI 1.525–12.309, p = 0.006) remained independent predictors for overall survival.

Discussion

In this study, we demonstrated that the qualitative flow-metabolic phenotype of PDAC using the combination of CECT and [^{18}F]FDG-PET features, predicted significantly worse survival for hypoattenuating-high uptake PDAC compared to the other phenotypes. Hypoattenuating-high uptake tumors had a median OS of 7 months compared to an OS of 23 months in patients with iso- or hyperattenuating-low uptake tumors. Hypoattenuating PDAC with high [^{18}F]FDG-uptake has significantly higher tumor stage and more advanced stage found at exploratory laparotomy leading to lower curative resection rates. In multivariate analysis surgery combined with tumor grade, tumor stage, systemic therapy and flow metabolic phenotype remained independent predictors for overall survival. Patients with stage I/II hypoattenuating-high uptake flow-metabolic phenotype did not show a significant difference in overall survival compared to those with stage III/IV iso- or hyperattenuating-high uptake flow-metabolic phenotype. In stage III, a significant difference in overall survival was observed between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage III (p = 0.028). A near-significant difference was observed in stage IV. Notably, among patients with stage IV tumors who did not undergo palliative systemic therapy, there was a trend towards a worse prognosis in the hypoattenuating-high uptake flow-metabolic phenotype. These findings support the hypothesis that the combination of high tumor metabolism and low blood flow does represent an aggressive PDAC tumor biology with unfavorable prognostic characteristics. Above all, curative resection remains the best chance of better overall survival. No significant difference in overall survival was observed between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage I/II.

In one previous study with a small number of patients with pancreatic cancer, in which [^{15}O]water was used to measure blood flow, a high SUVmax/blood flow ratio was a strong predictor of poor survival.[29] In this study tumor attenuation on CECT was used as a surrogate for the vascularity, because it is routinely available, in contrast to [^{15}O]water.

[^{18}F]FDG-PET is currently not routinely performed for PDAC. However, it is increasingly being integrated into staging algorithms. For instance, the NICE guidelines in the UK recommend the use of [^{18}F]FDG-PET for individuals with localized disease on CECT who will undergo cancer treatment, whether that involves surgery, radiotherapy or systemic therapy. In combination with the discovery of novel molecular subtypes of PDAC, which use different metabolic pathways as their main source of energy, it is not possible to omit the use of [^{18}F]FDG-PET in PDAC. The subtypes are largely divided into two broad subtypes; the better prognostic classical/progenitor subtype and the worse prognostic squamous/basal-like/quasi-mesenchymal subtype[30–32] characterized by a higher tumor grade, worse overall survival, higher risk of metastasis[33] and liver recurrence.[34] Recent literature showed the worse prognostic squamous subtype is highly catabolic and utilizes glycolysis as their main source of energy and is more sensitive to glycolysis inhibition, which is used as a novel metabolic therapeutic agent.[35] Although it is known that [^{18}F]FDG uptake might be absent in PDAC, it is rarely emphasized in current literature. In this study low [^{18}F]FDG uptake tumors were present in 19% of patients, who demonstrated a trend of better overall survival compared to high [^{18}F]FDG uptake. The squamous subtype is more likely to be associated with body/tail pancreatic cancer,[36] while the prognostically favorable Bailey's immunogenic subtype was almost exclusively found in the pancreatic head tumors.[37,38] Interestingly, in agreement with the previous studies iso- and hyperattenuating tumors (n = 28) all presented in the pancreatic head, had higher curative resection rates and a significant better overall survival.[39,40] This adds to the hypothesis that iso- and hyperattenuating tumors are not early PDAC, but might be different molecular, genomic, metabolic or pathological entities compared to hypoattenuating tumors.[41] Molecular subtyping and information on tumor biology, including tumor aggressiveness and chemosensitivity, may aid in treatment planning and selection.

Stratifying tumors in hypoattenuating versus iso- and hyperattenuating and high versus low uptake does not take into account the heterogeneity of the tumor, which is a well-known hallmark of PDAC[42] and reflected in the macroscopically different uptake patterns that we observed. The [^{18}F]FDG uptake in tumors is heterogeneous due to both neoplastic and non-neoplastic components such as tumor cells, (activated) stromal cells and necrosis and is related to the degree of vascularity, hypoxia, metabolic reprogramming, and proliferative capacity. Equally important, there is the intrinsic metabolic plasticity of pancreatic cancer cells. Tumor cells in hypoxic regions, due to poor perfusion caused by dense stroma, tend to undergo epithelial–mesenchymal transition (EMT) and exhibit elevated glycolysis compared to tumor cells in normoxic areas.[43] EMT is associated with features that negatively effects overall survival, such as tumor invasion, metastases formation and treatment resistance.[44] Our study demonstrated that using both PET and CT have an advantage compared to using either PET or CT alone in predicting overall survival. When comparing the imaging features, demographic and prognostic aspects, the hypoattenuating-high uptake tumors could represent the squamous/basal-like/quasi mesenchymal subtypes enriched with mesenchymal signatures. This is clinically relevant, as chemotherapy responses may differ among the different subtypes. The basal-like population is more sensitive to gemcitabine treatment

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

and less sensitive to modified-FOLFIRINOX (mFFX), while there is a favorable impact of mFFX in classical PDAC.[45–47] Unfortunately, due to the low number of patients who underwent chemotherapy and the missing data on the specific chemotherapeutic regimens, we were unable to assess the potential of using the flow-metabolic phenotype to stratify patients into therapy-resistant groups. Nonetheless, the limited number of patients receiving chemotherapy is consistent with nationwide numbers for the years of inclusion.[1] In future studies, a more comprehensive analysis of this aspect may be particularly relevant in the context of the current era of (neo)adjuvant therapies. The main limitation of this study is the heterogeneous study population, which includes all tumor stages and different treatment strategies, which influences overall survival data and complicates interpretation of the results. Selection bias were introduced in this study, as only patients who were potentially eligible for resection on CECT received an [^{18}F]FDG-PET scan for the exclusion of distant metastasis. This is reflected in the high percentage of resected tumors, 41.0%, whereas normally only 15–20% of the patients undergo surgery. Isoattenuating tumors were found in 28% of patients, which was somewhat higher than the reported prevalence of 5%–23%.[15,48–50] Both may reflect a certain heterogeneity in the study population.

This study demonstrated promising results using routine CECT and [^{18}F]FDG-PET to define a novel qualitative flow-metabolic phenotype that reflects perfusion and metabolism of pancreatic ductal adenocarcinoma. Future integration of [^{18}F]FDG-PET and perfusion CT holds the potential to generate a fully quantitative flow-metabolic phenotype. This approach can be instrumental in facilitating tumor classification and advancing precision medicine. Furthermore, if the flow-metabolic phenotype can effectively distinguish molecular subtypes, it can serve as the foundation for more personalized treatment strategies. Future research may explore the application of machine learning or deep learning to analyze CT and [^{18}F]FDG-PET, as there are different contrast enhancement patterns and [^{18}F]FDG-uptake patterns. Texture analysis could offer a more comprehensive evaluation, considering the typical tissue heterogeneity in PDAC.

Concluding, the qualitative flow-metabolic phenotype of PDAC using the combination of CECT and [^{18}F]FDG-PET features, predicted significantly worse survival for hypoattenuating-high uptake pancreatic cancers compared to the other phenotypes. Hypoattenuating PDAC with high [^{18}F]FDG-uptake has significantly lower resection rates and represents an aggressive tumor biology. This novel flow-metabolic phenotype of PDAC might be useful as a prognostic biomarker.

Acknowledgments

We would like to thank Luuk Swarts for his work on the data collection and Petra Koopmans for statistical support.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and the ethical standards of the institutional research committee.

Conflicts of interest

None.

References

1. Latenstein AEJ, van der Geest LGM, Bonsing BA, Groot Koerkamp B, Haj Mohammad N, de Hingh I *et al*. (2020) Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. *Eur J Cancer* 125:83–93. https://doi.org/10.1016/j.ejca.2019.11.002.
2. Rahib L, Wehner MR, Matrisian LM, Nead KT. (2021) Estimated projection of US cancer incidence and death to 2040. *JAMA Netw Open* 4e214708. https://doi.org/10.1001/jamanetworkopen.2021.4708.
3. Siegel RL, Miller KD, Jemal A. (2020) Cancer statistics, 2020. *CA Cancer J Clin* 70:7–30. https://doi.org/10.3322/caac.21590.
4. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y *et al*. (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817–1825. https://doi.org/10.1056/NEJMoa1011923.
5. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL *et al*. (2018) FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 379:2395–2406. https://doi.org/10.1056/NEJMoa1809775.
6. Janssen QP, Buettner S, Suker M, Beumer BR, Addeo P, Bachellier P *et al*. (2019) Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. *J Natl Cancer Inst*. https://doi.org/10.1093/jnci/djz073.
7. Macedo FI, Ryon E, Maithel SK, Lee RM, Kooby DA, Fields RC *et al*. (2019) Survival outcomes associated with clinical and pathological response following neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapy in resected pancreatic cancer. *Ann Surg* 270:400–413. https://doi.org/10.1097/sla.0000000000003468.
8. Versteijne E, van Dam JL, Suker M, Janssen QP, Groothuis K, Akkermans-Vogelaar JM *et al*. (2022) Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: long-term results of the Dutch Randomized PREOPANC Trial. *J Clin Oncol* 40:1220–1230. https://doi.org/10.1200/jco.21.02233.
9. Perik TH, van Genugten EAJ, Aarntzen E, Smit EJ, Huisman HJ, Hermans JJ. (2021) Quantitative CT perfusion imaging in patients with pancreatic cancer: a systematic review. *Abdom Radiol*. https://doi.org/10.1007/s00261-021-03190-w.
10. Kamphorst JJ, Nofal M, Commisso C, Hackett SR, Lu W, Grabocka E *et al*. (2015) Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein. *Cancer Res* 75:544–553. https://doi.org/10.1158/0008-5472.Can-14-2211.
11. Makohon-Moore A, Iacobuzio-Donahue CA. (2016) Pancreatic cancer biology and genetics from an evolutionary perspective. *Nat Rev Cancer* 16:553–565. https://doi.org/10.1038/nrc.2016.66.

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

12. Orth M, Metzger P, Gerum S, Mayerle J, Schneider G, Belka C *et al*. (2019) Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. *Radiat Oncol* 14:141. https://doi.org/10.1186/s13014-019-1345-6.
13. Schober M, Jesenofsky R, Faissner R, Weidenauer C, Hagmann W, Michl P *et al*. (2014) Desmoplasia and chemoresistance in pancreatic cancer. *Cancers* 6:2137–2154. https://doi.org/10.3390/cancers6042137.
14. Cassinotto C, Chong J, Zogopoulos G, Reinhold C, Chiche L, Lafourcade JP *et al*. (2017) Resectable pancreatic adenocarcinoma: role of CT quantitative imaging biomarkers for predicting pathology and patient outcomes. *Eur J Radiol* 90:152–158. https://doi.org/10.1016/j.ejrad.2017.02.033.
15. Kim JH, Park SH, Yu ES, Kim MH, Kim J, Byun JH *et al*. (2010) Visually isoattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. *Radiology* 257:87–96. https://doi.org/10.1148/radiol.10100015.
16. Ghaneh P, Hanson R, Titman A, Lancaster G, Plumpton C, Lloyd-Williams H *et al*. (2018) PET-PANC: multicentre prospective diagnostic accuracy and health economic analysis study of the impact of combined modality 18fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography with computed tomography scanning in the diagnosis and management of pancreatic cancer. *Health Technol Assess* 22:1–114. https://doi.org/10.3310/hta22070.
17. Kitasato Y, Yasunaga M, Okuda K, Kinoshita H, Tanaka H, Okabe Y *et al*. (2014) Maximum standardized uptake value on 18F-fluoro-2-deoxy-glucose positron emission tomography/computed tomography and glucose transporter-1 expression correlates with survival in invasive ductal carcinoma of the pancreas. *Pancreas* 43:1060–1065. https://doi.org/10.1097/mpa.0000000000000185.
18. Ahn SJ, Park MS, Lee JD, Kang WJ. (2014) Correlation between 18F-fluorodeoxyglucose positron emission tomography and pathologic differentiation in pancreatic cancer. *Ann Nucl Med* 28:430–435. https://doi.org/10.1007/s12149-014-0833-x.
19. Shinoto M, Yamada S, Yoshikawa K, Yasuda S, Shioyama Y, Honda H *et al*. (2013) Usefulness of 18F-fluorodeoxyglucose positron emission tomography as predictor of distant metastasis in preoperative carbon-ion radiotherapy for pancreatic cancer. *Anticancer Res* 33:5579–5584.
20. Yamamoto T, Sugiura T, Mizuno T, Okamura Y, Aramaki T, Endo M *et al*. (2015) Preoperative FDG-PET predicts early recurrence and a poor prognosis after resection of pancreatic adenocarcinoma. *Ann Surg Oncol* 22:677–684. https://doi.org/10.1245/s10434-014-4046-2.
21. Kurahara H, Maemura K, Mataki Y, Sakoda M, Iino S, Kawasaki Y *et al*. (2019) Significance of (18)F-fluorodeoxyglucose (FDG) uptake in response to chemoradiotherapy for pancreatic cancer. *Ann Surg Oncol* 26:644–651. https://doi.org/10.1245/s10434-018-07098-6.
22. Truty MJ, Kendrick ML, Nagorney DM, Smoot RL, Cleary SP, Graham RP *et al*. (2021) Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg* 273:341–349. https://doi.org/10.1097/sla.0000000000003284.
23. Yoo SH, Kang SY, Cheon GJ, Oh DY, Bang YJ. (2020) Predictive role of temporal changes in intratumoral metabolic heterogeneity during palliative chemotherapy in patients with advanced pancreatic cancer: a prospective cohort study. *J Nucl Med* 61:33–39. https://doi.org/10.2967/jnumed.119.226407.
24. Follia L, Ferrero G, Mandili G, Beccuti M, Giordano D, Spadi R *et al*. (2019) Integrative analysis of novel metabolic subtypes in pancreatic cancer fosters new prognostic biomarkers. *Front Oncol* 9:115. https://doi.org/10.3389/fonc.2019.00115.
25. Karasinska JM, Topham JT, Kalloger SE, Jang GH, Denroche RE, Culibrk L *et al*. (2020) Altered gene expression along the glycolysis-cholesterol synthesis axis is associated with outcome in pancreatic cancer. *Clin Cancer Res* 26:135–146. https://doi.org/10.1158/1078-0432.Ccr-19-1543.
26. Miles KA, Williams RE. (2008) Warburg revisited: imaging tumour blood flow and metabolism. *Cancer Imaging* 8:81–86. https://doi.org/10.1102/1470-7330.2008.0011.
27. Kreuzaler P, Panina Y, Segal J, Yuneva M. (2020) Adapt and conquer: metabolic flexibility in cancer growth, invasion and evasion. *Mol Metab* 33:83–101. https://doi.org/10.1016/j.molmet.2019.08.021.
28. Fukukura Y, Kumagae Y, Fujisaki Y, Yamagishi R, Nakamura S, Kamizono J *et al*. (2021) Adding delayed phase images to dual-phase contrast-enhanced CT increases sensitivity for small pancreatic ductal adenocarcinoma. *Am J Roentgenol* 217:888–897. https://doi.org/10.2214/ajr.20.25430.
29. Komar G, Kauhanen S, Liukko K, Seppanen M, Kajander S, Ovaska J *et al*. (2009) Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor aggressiveness. *Clin Cancer Res* 15:5511–5517. https://doi.org/10.1158/1078-0432.Ccr-09-0414.
30. Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S *et al*. (2011) Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat Med* 17:500–503. https://doi.org/10.1038/nm.2344.
31. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC *et al*. (2016) Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 531:47–52. https://doi.org/10.1038/nature16965.
32. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA *et al*. (2015) Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat Genet* 47:1168–1178. https://doi.org/10.1038/ng.3398.
33. Dijk F, Veenstra VL, Soer EC, Dings MPG, Zhao L, Halfwerk JB *et al*. (2020) Unsupervised class discovery in pancreatic ductal adenocarcinoma reveals cell-intrinsic mesenchymal features and high concordance between existing classification systems. *Sci Rep* 10:337. https://doi.org/10.1038/s41598-019-56826-9.
34. Dreyer SB, Upstill-Goddard R, Legrini A, Biankin AV, Jamieson NB, Chang DK *et al*. (2022) Genomic and molecular analyses identify molecular subtypes of pancreatic cancer recurrence. *Gastroenterology* 162:320–324. https://doi.org/10.1053/j.gastro.2021.09.022. e4.
35. Brunton H, Caligiuri G, Cunningham R, Upstill-Goddard R, Bailey UM, Garner IM *et al*. (2020) HNF4A and GATA6 loss reveals therapeutically actionable subtypes in pancreatic cancer. *Cell Rep* 31:107625. https://doi.org/10.1016/j.celrep.2020.107625.
36. Dreyer SB, Jamieson NB, Upstill-Goddard R, Bailey PJ, McKay CJ, Biankin AV *et al*. (2018) Defining the molecular pathology of pancreatic body and tail adenocarcinoma. *Br J Surg* 105:e183–e191. https://doi.org/10.1002/bjs.10772.

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

37. Birnbaum DJ, Finetti P, Birnbaum D, Mamessier E, Bertucci F. (2017) Validation and comparison of the molecular classifications of pancreatic carcinomas. *Mol Cancer* 16:168. https://doi.org/10.1186/s12943-017-0739-z.
38. Birnbaum DJ, Bertucci F, Finetti P, Birnbaum D, Mamessier E. (2019) Head and body/tail pancreatic carcinomas are not the same tumors. *Cancers* 11. https://doi.org/10.3390/cancers11040497.
39. Psar R, Urban O, Cerna M, Rohan T, Hill M. (2021) Improvement of the diagnosis of isoattenuating pancreatic carcinomas by defining their characteristics on contrast enhanced computed tomography and Endosonography with Fine-Needle Aspiration (EUS-FNA). *Diagnostics* 11. https://doi.org/10.3390/diagnostics11050776.
40. Xu H, Hua J, Meng Q, Wang X, Xu J, Wang W *et al*. (2021) Hyperdense pancreatic ductal adenocarcinoma: clinical characteristics and proteomic landscape. *Front Oncol* 11:640820. https://doi.org/10.3389/fonc.2021.640820.
41. Blouhos K, Boulas KA, Tsalis K, Hatzigeorgiadis A. (2015) The isoattenuating pancreatic adenocarcinoma: review of the literature and critical analysis. *Surg Oncol* 24:322–328. https://doi.org/10.1016/j.suronc.2015.09.006.
42. Cros J, Raffenne J, Couvelard A, Poté N. (2018) Tumor heterogeneity in pancreatic adenocarcinoma. *Pathobiology* 85:64–71. https://doi.org/10.1159/000477773.
43. Yan L, Raj P, Yao W, Ying H. (2019) Glucose metabolism in pancreatic cancer. *Cancers* 11:1460. https://doi.org/10.3390/cancers11101460.
44. Wang S, Huang S, Sun YL. (2017) Epithelial-mesenchymal transition in pancreatic cancer: a review. *BioMed Res Int* 2017:2646148. https://doi.org/10.1155/2017/2646148.
45. Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S *et al*. (2018) Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS Trial. *Clin Cancer Res* 24:1344–1354. https://doi.org/10.1158/1078-0432.Ccr-17-2994.
46. O'Kane GM, Grünwald BT, Jang GH, Masoomian M, Picardo S, Grant RC *et al*. (2020) GATA6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer. *Clin Cancer Res* 26:4901–4910. https://doi.org/10.1158/1078-0432.Ccr-19-3724.
47. Collisson EA, Bailey P, Chang DK, Biankin AV. (2019) Molecular subtypes of pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 16:207–220. https://doi.org/10.1038/s41575-019-0109-y.
48. Yoon SH, Lee JM, Cho JY, Lee KB, Kim JE, Moon SK *et al*. (2011) Small (</= 20 mm) pancreatic adenocarcinomas: analysis of enhancement patterns and secondary signs with multiphasic multidetector CT. *Radiology* 259:442–452. https://doi.org/10.1148/radiol.11101133.
49. Ishigami K, Yoshimitsu K, Irie H, Tajima T, Asayama Y, Nishie A *et al*. (2009) Diagnostic value of the delayed phase image for iso-attenuating pancreatic carcinomas in the pancreatic parenchymal phase on multidetector computed tomography. *Eur J Radiol* 69:139–146. https://doi.org/10.1016/j.ejrad.2007.09.012.
50. Prokesch RW, Chow LC, Beaulieu CF, Bammer R, Jeffrey RB, Jr.. (2002) Isoattenuating pancreatic adenocarcinoma at multi-detector row CT: secondary signs. *Radiology* 224:764–768. https://doi.org/10.1148/radiol.2243011284.

© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Hepato-Pancreato-Biliary Association Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).