Flow-metabolic phenotype of pancreatic ductal adenocarcinoma: a new prognostic biomarker?

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Aims and objectives

International guidelines advise contrast enhanced computed tomography (CECT) for diagnosis and staging of pancreatic ductal adenocarcinoma (PDAC) (1), which is currently the fourth leading cause of cancer-related death in the US with a 5 year survival of approximately 6% (1).

In addition to evaluation of tumor invasion and metastatic spread, evaluation of attenuation patterns could be appropriate. PDAC usually shows hypoattenuation patterns during the arterial to portal venous phase (PVP) (2-5). The reported incidence of isoattenuating PDAC, which is associated with lower tumor cellularity, more prominent loose desmoplastic stroma, less tumor necrosis and more frequent intratumoral acinar tissue and islet cells, varies from 5.4% to 45% (2-11) and has a better overall survival (4-5).

\(^{18}\)FDG-PET is widely used to assess tumor metabolism and can be correlated with tumor aggressiveness. Integration of information on attenuation value on CECT and uptake pattern on \(^{18}\)FDG-PET can be used to define a qualitative flow-metabolic phenotype of a tumor. The attenuation value reflects the vascularity of the tumor and the amount of \(^{18}\)FDG uptake its metabolic activity. Glycolysis is typically constitutively upregulated in carcinomas and persists even under normoxic conditions, a phenomenon termed the "Warburg effect" (12). The balance between tumor vascularity and glucose metabolism offers substantial information concerning tumor adaption to the microenvironment. Matched high glucose metabolism with increased vascularity represents a different biologic status compared with mismatched high metabolism with lower vascularity, the latter indicating adaptation to hypoxia. Poor vascularity with low glucose metabolism suggests a failure of the adaptive response to hypoxia and/or reduced intrinsic oncogenic effects. Low vascularity with high glucose uptake represents appropriate metabolic tumor adaptation to hypoxic stress, whereas low vascularity with low glucose uptake represents a failure of adaptation. The flow-metabolic phenotype in breast carcinoma, colorectal cancer and head and neck tumors is correlated to survival (13-16). PDAC with a low flow and high uptake tend to have an aggressive behavior (17).

The purpose of this study was to investigate the relationship between the qualitative flow-metabolic phenotype and overall survival of pancreatic ductal adenocarcinoma (PDAC) using tumor attenuation on CECT and uptake pattern on \(^{18}\)FDG-PET.
Methods and materials

A retrospective analysis was performed of all patients with pancreatic malignancy who received both a CECT and a $^{18}$FDG-PET scan between 2006 and 2014. The imaging protocols were conform prevailing guidelines. The outcome measures were to determine overall survival of different CT attenuation and $^{18}$FDG uptake patterns and the qualitative flow metabolic phenotype.

CT scans were reviewed by a radiologist (JH) with 14 years of experience in abdominal radiology. The CT images were evaluated both qualitatively as well as quantitatively by measuring the Hounsfield unit (HU) value of tumor and pancreas parenchyma. A circular region of interest (ROI) was placed in the tumor and in the parenchyma of the pancreatic head, body and tail in the PVP, which was defined as enhancement of both portal vein and the hepatic veins. Isoattenuating PDAC was qualitatively defined as a tumor visually not discernible from surrounding pancreas parenchyma or quantitatively as a difference in attenuation value of less than 10 HU between surrounding pancreas parenchyma (HUP) and pancreas tumor (HUT): -10 # HUP - HUT # 10. Hypoattenuating PDAC was qualitatively defined as a tumor visually darker than surrounding pancreas parenchyma or quantitatively as a difference in attenuation value of more than 10 HU between surrounding pancreas parenchyma and tumor: HUP - HUT # 10. Hyperattenuating PDAC was qualitatively defined as tumor visually brighter than surrounding parenchyma or quantitatively as a difference in attenuation value of more than 10 HU in the tumor compared to surrounding pancreas parenchyma: HUP - HUT # -10.

The $^{18}$FDG uptake of the tumor was compared to the uptake of the liver and defined as: low/no uptake (pattern 4 and 7), homogeneous high (pattern 1 and 5) or heterogeneous high uptake (pattern 2, 3 and 6). Homogeneous uptake was defined as uniform uptake in the part of or in the entire tumor. Heterogeneous uptake was defined as multifocal or ring-shaped uptake or an undefined uptake pattern (Figure 1). Two observers (MG and LG) individually scored each $^{18}$FDG-PET scan and reached consensus.

Overall survival was measured from the day of PET until death. Censoring was performed for deaths not caused by cancer, loss to follow up (n = 6) or survival at the end of December 2014.

Statistics
Kaplan-Meier curves and log-rank test were used to correlate flow-metabolic phenotypes to overall survival (OS). A Chi-square test was used to analyze the differences in
frequencies between PET uptake patterns and CT attenuation. A statistical significant result was defined as $P < 0.05$. 
Fig. 1: 18FDG-PET uptake patterns: 1: unifocal hotspot, 2: multifocal hotspots, 3: ring, 4: homogeneous low uptake, 5: homogeneous high uptake, 6: undefined pattern and 7: no uptake.

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Results

A total of 128 patients with suspected pancreatic malignancy received both a CECT scan and a $^{18}$FDG-PET scan. Exclusion criteria were lack of histopathological proof of PDAC (N = 17) and pathological diagnosis other than PDAC, such as ampulla of Vater carcinoma (N = 1), cholangiocarcinoma (N = 9) and duodenum tumor (N = 1). Finally, 100 patients (52 male, 48 female, median age 65.5 ± 8.9 yrs) were included. All tumors were histopathologically proven and curative resection was performed in 41 patients.

Three hyperattenuating PDACs were excluded from analysis. There was a significant difference in OS between hypo- and isoattenuating tumors with a median OS of 35 ± 4.6 weeks and 63 ± 18.1 weeks respectively) ($P = 0.003$) (Figure 2).

Heterogeneous $^{18}$FDG-uptake (median OS 33±5.3 wks) has a worse OS compared to both homogenous $^{18}$FDG-uptake (median OS 46 ± 4.8 wks) and no/low $^{18}$FDG-uptake (median OS 63 ± 18.8 wks) ($P = 0.033$) (Figure 3).

A cross correlation of CECT attenuation and $^{18}$FDG-PET uptake pattern showed hypoattenuating PDAC with high $^{18}$FDG-PET uptake has the poorest prognosis (median OS 32 ± 2.9 wks), whereas isoattenuating PDAC with low $^{18}$FDG-PET uptake has the best prognosis (median OS 63 ± 24.7 wks) ($P = 0.009$) (Figure 4) (Table 1).
**Fig. 2:** OS in iso- and hypoattenuating tumors on CECT.

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Fig. 3: OS in different uptake patterns on 18FDG-PET.

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Fig. 4: OS in cross correlated attenuation on CECT and uptake pattern on 18FDG-PET.

Table 1: Median overall survival for different groups of 18FDG-uptake and CECT attenuation.

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Conclusion

Isoattenuating PDAC was a prognostic factor and correlated with a better overall survival compared to hypoattenuating tumors. In our study, low/no $^{18}$FDG-PET uptake is correlated with better overall survival compared to high homo- and heterogeneous $^{18}$FDG-PET uptake. Heterogeneous uptake had the worst overall survival. Despite differences in set-up, this is comparable to other studies (23,34). This study confirmed low perfusion and high metabolism was associated with poorer overall survival rates in PDAC. These findings support the hypothesis that hypoxic tumors with high glucose metabolism represent a particularly aggressive tumor type(13), which was found in breast(15), lung(14) and colorectal cancer(16,18) as well. Additionally, these tumors are associated with greater treatment resistance (16).

Hypoattenuation could be associated with pathological features, such as abundant stroma or necrosis. Also, necrosis is a result of reduced vascularization, which complicates the perfusion of chemotherapeutic agent in the tumor. A hypoattenuating tumor therefore may reflect a hypovascular and hypoxic tumor with a poor response to chemo- and or radiation therapy. Supporting this hypothesis, Park et al observed that high perfusion in pancreatic cancer was associated with increased response to chemoradiotherapy(19). Thus, the flow-metabolic phenotype might not only predict prognosis, but using these features, it could also be a biomarker for the prediction of (neo)adjuvant chemotherapy resistance.

There are several limitations to this study. First, as this was a retrospective study the CT scans were not uniform regarding scan protocol, amount and injection flow rate of contrast agent, which all effect the attenuation difference between tumor and surrounding pancreas parenchyma. However the percentage of isoattenuating tumors in our study, 35%, was comparable to the literature(2-7, 8-11). Second, selection bias was introduced in this study, as only patients who were eligible for resection on CECT received a $^{18}$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(20). Third, the total number of patients included in the analysis may be too limited to demonstrate difference in overall survival in all 4 different CT-PET groups appropriately, as total number of patients included in group with low are small (N = 8 isoattenuating, N = 8 hypoattenuating). Additionally, we had to exclude hyperattenuating tumors from analysis due to insufficient number of patients in this group. Therefore, a prospective study with adequate sample size calculation is recommended. Finally, in this study only one phase (PVP) of a dynamic contrast-enhanced CT (i.e. CT-perfusion) was used. Therefore the blood flow in the tumor cannot be quantified. The blood flow could
be quantitatively analysed using CT-perfusion in a prospective study with CT perfusion and $^{18}$FDG-PET.

This is the first study in which CT attenuation obtained in the portovenous phase of a routine contrast-enhanced CT is combined with $^{18}$FDG-PET uptake and correlated to the overall survival. CT attenuation and $^{18}$FDG uptake reflect qualitative flow and metabolism of the tumor and define its imaging phenotype. We conclude that there is a different overall survival in different qualitative "flow-metabolic phenotypes" of pancreatic ductal adenocarcinoma. Thus, the flow-metabolic phenotype can be used as a prognostic factor for overall survival.
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