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Added value of digital FDG-PET/CT in disease staging and restaging in patients with resectable or borderline resectable pancreatic cancer☆,☆☆,☆☆☆

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ABSTRACT

Background: We studied the added value of *digital* FDG-PET/CT in disease staging and restaging compared to the standard work-up with contrast enhanced CT (ceCT) and CA19-9 in patients with resectable or borderline resectable pancreatic cancer who received neo-adjuvant therapy. Primary endpoints were tumor response compared to ceCT and CA19.9 as well as the ability to detect distant metastatic disease.

Methods: 35 patients were included in this dual-center prospective study. FDG-PET using *digital* photon counting technology combined with CT scans were acquired before (T_1) and after neo-adjuvant therapy (T_2). Patients were staged and restaged based on standard protocol with ceCT and CA 19.9, while all PET/CT scans were stored securely and not included in clinical decision making. After the pancreatic resection, an expert team retrospectively assessed the CT tumor diameter, CA19-9, tumor FDG-uptake, and appearance of metastatic disease of all patients for both time points.

Results: CA19-9 levels, CT tumor diameter, and tumor FDG-uptake on PET significantly decreased from T_1 to T_2 ($p = 0.017$, $p = 0.001$, and $p < 0.0001$). The change in FDG-uptake values showed a strong positive correlation with the change in CT tumor diameter and change in CA19-9 ($R = 0.75$ and $R = 0.73$, respectively). In addition, small-volume liver lesions were detected on *digital* PET/CT in 5/35 patients (14%), 4 of which were pathology confirmed at laparotomy. Only one of these five cases was detected on baseline staging ceCT (3%).

Conclusion: We found that adding *digital* PET/CT strengthens restaging after neo-adjuvant therapy based on the observed strong correlation with ceCT tumor diameter and Ca19.9. Also, *digital* PET/CT was found to detect occult metastatic disease not visualized on ceCT, that would have resulted in altered disease staging and therapeutic strategy in a substantial proportion of patients.

☆ This article is the continuation of a previous abstract communicating the interim results, presented at the Society of Nuclear Medicine & Molecular Imaging conference, 2021.☆☆ → *de Jong, Tonke* et al. *"The added value of digital FDG-PET/CT in disease staging and restaging in patients with resectable pancreatic cancer: an interim analysis." (2021): 1374-1374.*☆☆☆ The study was supported by a research collaboration between Isala and Philips Healthcare. The content of the article was solely the responsibility of the authors.

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Abbreviations

BR	borderline resectable
CA19-9	cancer antigen 19–9
CBD	common bile duct
ceCT	contrast-enhanced computed tomography
FOLFIRINOX	folinic acid fluorouracil irinotecan oxaliplatin
FDG-PET/CT	fluorodeoxyglucose-positron emission tomography/computed tomography
FNA	fine needle aspiration cytology
HPB	hepato-pancreato-biliary
LAPC	locally advanced pancreatic cancer
NAT	neoadjuvant therapy
PDAC	pancreatic ductal adenocarcinoma
PERCIST	positron emission tomography response criteria in solid tumors
RECIST	response evaluation criteria in solid tumors

1. Introduction

The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) is extremely poor. Upon diagnosis, only 20% of patients can undergo resection with curative intent, whereas 40% present with locally advanced pancreatic cancer (LAPC), and 40% with metastatic disease. Neoadjuvant therapy (NAT) is playing an increasing role. Emerging evidence is showing clear benefits of NAT for borderline resectable (BR) and locally advanced pancreatic cancer (LAPC), which is driving a shift from up-front surgery to treatment with NAT, even in resectable pancreatic cancer [1,2]. The purpose of NAT is not only to decrease tumor size to facilitate margin-negative resection and to optimally select surgical candidates, but also to increase the relative proportion of patients who are able to receive chemotherapy (as compared to the adjuvant setting).

To carefully select surgical candidates after neo-adjuvant treatment, accurate assessment of response is crucial in re-staging and determining resectability [3–7]. However, traditional cross-sectional imaging modalities for this purpose such as contrast enhanced CT (ceCT) and/or MRI, poorly predict response, rendering NAT radiologic evaluations relatively ineffective [7–10]. The main response parameter in these modalities is based on tumor size [11], which is unreliable due to the inability to differentiate treatment-related necrosis, therapy-induced fibrosis and tumor-associated pancreatitis from residual vital tumor tissue [3,5,12]. The same holds true for a CT-based observed change in tumor attenuation. Cassinotto et al. [13] showed that the diagnostic performance of ceCT to predict resectability decreased after neo-adjuvant treatment (58% vs. 83%). Similarly, Ferrone et al. [14] showed that ceCT after FOLFIRINOX treatment no longer adequately predicted resectability of the tumor. This underlines the critical need for improved methods to objectively determine the adequacy of response to NAT.

Besides cross-sectional imaging, the serum CA19-9 level is commonly used as a biochemical marker for (re)staging for PDAC. It has added value for monitoring response to systemic therapy and correlates with overall survival [15]. Adding a 30% decrease in CA19-9 levels to RECIST-assessment of LAPC following neo-adjuvant chemotherapy was shown to improve the diagnostic accuracy for predicting resectability, especially in patients with RECIST-stable disease [16]. However, the utility of CA 19.9 also has limitations, since 10% of patients are upfront non-secretors and up to one-third have normal levels at presentation (normo-secretors). Also, variability exists regarding what constitutes an appropriate NAT response (ie, stability, partial stability, or normalization) [17,18]. In addition, patients with cholangitis or pancreatitis may show increased CA19-9 causing false positives [19].

FDG-PET/CT has been evaluated for monitoring the (neo)adjuvant treatment response in various malignancies, including pancreatic cancer [20–22]. It provides insight into tumor viability during NAT, and reveal metabolic changes earlier than changes in radiologic tumor size [23]. Studies using analog PET-CT have demonstrated improved visualization of local tumor response to neo-adjuvant therapy when compared to ceCT as well as improved sensitivity for detecting distant metastatic disease, especially in the liver [19–21,24–33]. The PET-PANC study showed that in patients with primary suspected pancreatic malignancies non-therapeutic laparotomy was avoided in 21% of patients [25]. Based on this study, PET-CT was added to the staging recommendations in the UK NICE guidelines [34].

A recent meta-analysis revealed that metabolic parameters derived from PET/CT can be useful as prognostic markers in pancreatic ductal adenocarcinoma [17]. Two recent studies showed that FDG-PET/CT response correlates with survival in borderline resectable and locally advanced pancreatic cancer [19,32]. Importantly, the study of Abdelrahman et al. [19] showed that PET/CT could also predict the surgical specimen histological response, which is the most direct evidence of NAT effect, and this was superior to CA 19–9 response alone. Given these results, FDG-PET/CT may be the optimal modality for preoperative assessment of NAT response, allowing improved stratification of patients into specific downstream options (i.e., proceed to surgery, continue with current NAT, or switch chemotherapy).

Despite these encouraging results, PET/CT still remains controversial in standard practice for pancreatic cancer in many institutions. International consensus guidelines outside the UK recommend that FDG-PET/CT may be used in suspected pancreatic cancer patients per institutional preference in high risk patients, but is not a substitute for high-quality contrast-enhanced CT (ce-CT) [2,35]. This is most likely due to the inherently variable FDG-uptake of pancreatic adenocarcinoma and the well-known low specificity for differentiation between malignant and inflammatory tissue, combined with the relatively low spatial resolution of conventional analog PET/CT [29].

Recently, a new generation of *digital* PET/CT scanners was introduced by several vendors, that provide improved image quality, diagnostic confidence, and accuracy as compared to analog PET/CT as shown in a number of studies [36–39]), but this has not yet been shown in pancreatic cancer. The aim of this study was to evaluate the added value of *digital* PET/CT compared to the standard work-up with ceCT and CA19-9 alone, as a staging and restaging imaging modality in patients with resectable or borderline resectable pancreatic cancer, who were treated with neo-adjuvant therapy. Primary endpoints were the evaluation of primary tumor response compared to standard ceCT and CA19.9, as well as the ability to detect distant metastatic disease.

2. Methods

2.1. Study design and patient selection

This prospective dual-center study (PandigiPET) was initiated and performed at Isala, a large teaching hospital and regional hepatopancreatobiliary (HPB) center, and also performed at the Leiden University Medical Center, a large academic HPB center, both in the Netherlands. All patients had resectable or borderline resectable PDAC confirmed with fine needle aspiration (FNA) cytology without evidence of distant metastases in initial and preoperative ceCT-scans. All patients participated in the large national multicenter randomized control trial (PREOPANC-2) [40], comparing neo-adjuvant FOLFIRINOX to gemcitabine-based neo-adjuvant chemoradiotherapy. Participants were included between September 2018 and February 2021. All participants signed written informed consent. The Medical Ethical Committee of Isala Hospital (METC Isala, Zwolle, the Netherlands) approved the study protocol (171,220). The study was registered at the Dutch Trial Register with identifier NTR7442 [41].

The clinical workflow is shown in Fig. 1. All patients with PDAC in

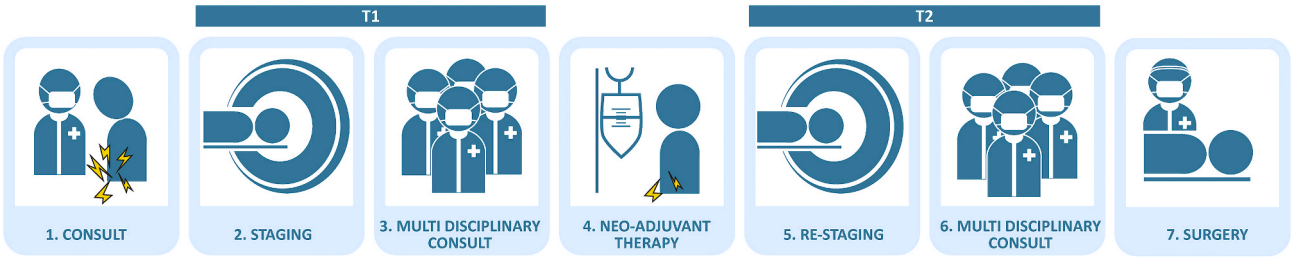

Fig. 1. Workflow of patients with resectable and borderline resectable pancreatic cancer. 1) Patient gets first consult, 2) T1: Initial staging, consisting of a diagnostic ceCT scan, CA19-9 serum levels, EUS & histology, and an additional digital PET scan, 3) Multi-disciplinary consult to agree on treatment method, 4) Neo-adjuvant therapy, being Folfirinox-, or radiochemotherapy, 5) T2: Re-staging, consisting of a diagnostic ceCT scan, CA19-9 serum levels, and an additional digital PET scan, 6) Multidisciplinary consult: Preoperative assessment, 7) Surgical exploration: The surgeon decides to perform the PPPD or not, depending on resectability and metastases.

the pancreatic head region received a common bile duct (CBD) metal stent prior to the start of neo-adjuvant therapy. FDG-PET/CT acquisition was added to the standard clinical workflow of these patients. FDG-PET using digital photon counting technology combined with low-dose CT scans and conventional CT scans of the abdomen were acquired before (T_1) and after (T_2) finishing neo-adjuvant therapy, referred to as PET_1 and PET_2, and CT_1 and CT_2, respectively. CA19-9 serum levels were also measured at T_1 and T_2 ($CA19\text{-}9_1$ and $CA19\text{-}9_2$, respectively). The time intervals between T_1 and the start of neo-adjuvant therapy, and T_2 and the end of neo-adjuvant therapy was typically less than two weeks.

Importantly, all *digital* FDG-PET/CT images were stored outside regular electronic medical records and PACS systems and could not be viewed and analyzed until after patients' surgery. Therefore, the PET-images have not influenced the care pathway in any way, which allowed us to retrospectively assess their added value in staging and restaging and determine the potential impact on clinical outcomes.

Patients with RECIST non-progressive disease on ceCT underwent exploratory laparotomy and pancreatic resection after completion of neo-adjuvant therapy. Diagnostic laparoscopy was not part of the routine workup. In case any previously undetected distant metastases were observed at exploratory laparotomy, these were confirmed by biopsy and frozen section histology, and the surgery was subsequently terminated without performing resection.

After the surgery all patients' images and data were reviewed and analyzed by an expert multidisciplinary HPB team, consisting of two nuclear medicine specialists, an HPB-radiologist and an HPB-surgeon.

Primary endpoint of this exploratory study was the added (clinical) value of *digital* PET/CT, evaluated by assessing primary tumor response compared to ceCT and CA19.9 as well as the ability to detect of distant metastatic disease.

2.2. Digital PET/CT data acquisition and reconstruction

Patients fasted for at least 6 h before scanning. Blood glucose levels were measured to ensure a value below 10 mmol/L before intravenous injection of the tracer (^{18}F-FDG). We used a dedicated tracer dose depending quadratically on patients' body weight ranging from 185 to 500 megabecquerel of FDG [42]. All PET/CT scans were acquired with a time-of-flight PET/CT scanner with *digital* silicon photomultipliers readout (Vereos, Philips Healthcare), EARL certified. The PET acquisition time was 6 min per bed position for all patients. We used high-resolution PET reconstructions because they are better suited for small lesion detection [43]. We applied an ordered subset expectation maximization time-of-flight-PET reconstruction with 2 × 2x2 mm3 voxels, 3 iterations, and 17 subsets, without post-smoothing, as described in greater detail in Ref. [44]. Three to four bed positions were applied with a relatively long acquisition time of 6 min per bed position. All PET scans were acquired on the same PET/CT scanner.

2.3. Staging and restaging: primary response evaluation and emerging metastatic disease

The expert HPB-team evaluated four staging and restaging parameters blinded to patient names and numbers at T_1 and T_2: 1) CT tumor diameter as measured by the radiologist, 2) plasma CA19-9, 3) semi-quantitative tumor FDG-uptake on PET as measured by the nuclear medicine specialists, and 4) the detection of previously unrecognized or emerging metastatic disease (by both the radiologist and the nuclear medicine specialists).

The team systematically evaluated all sets of PET-, CT- and fused PET-CT images for differences in the local- and distant staging of the pancreatic cancer at T_1 and T_2 according to pre-set (re)staging parameters as outlined in the Preopanc-2 study protocol [29]. After the scoring was completed, we compared the findings with surgical outcomes.

Baseline ceCT-staging was done by assessing standard parameters of pancreatic tumors, including primary tumor location and size, vascular involvement, as well as nodal involvement and distant metastases. The radiologist performed ceCT-restaging of patients according to the RECIST1.1 criteria [11], comparing the last CT_1 prior to chemotherapy with CT_2 three months after the start of neo-adjuvant therapy.

PET-restaging was performed by semi-quantitative measurements of tumor uptake, by placing a 1 cm^3 spherical volume of interest (VOI) inside the tumor at the location with the highest visual uptake, for PET_1 and PET_2. The standardized uptake values within the VOIs were determined and corrected for lean body mass (SUL_{peak}), following the PERCIST guidelines [45,46]. We did not place the VOI inside the region of the CBD-stent, whose location was verified on CT, because of the frequent high FDG-uptake in the CBD, most likely due to low-grade inflammation. In addition, we measured background activity in a 3-cm diameter spherical VOI in the right side of the liver, thereby excluding vessels and ducts. We considered a tumor quantitatively measurable at the initial staging when SUL_{peak} at T_1 was greater than or equal to 1.5 times the background activity at T_1.

2.4. Statistics

We used combined box- and scatter plots to depict changes between T_1 and T_2 for the three primary tumor response parameters; CT tumor diameter, CA19-9, and PET uptake. A paired-sample *t*-test tested for significant differences between the means for all three parameters at T_1 and T_2. A p-value of 0.05 was considered to indicate statistical significance. We calculated the percentage change at T_1 and T_2 for the three primary tumor response parameters and used linear regression models to describe the relations between these variables. We used the correlation coefficient (R) as a measure of goodness of fit for these models, where: $R \leq 0.19$, $0.20 \leq R \leq 0.39$, $0.40 \leq R \leq 0.59$, $0.60 \leq R \leq 0.79$, and $R \geq 0.8$ were considered very weak, weak, moderate, strong, and very strong, respectively. Patients with non-elevated CA19-9 levels at the time of diagnosis (i.e. <34 U/mL) were censored from the analyses. All

data- and statistical analyses were performed using Matlab (version 2020a, The MathWorks, Inc., Natick, Massachusetts, United States). Continuous variables are described as mean ± standard deviation.

3. Results

3.1. Patient characteristics and data

In total, 39 patients were included, 35 of which were eligible for final analysis. Four patients were withdrawn from the study protocol for urgent medical reasons or death during the study period. Patient characteristics are shown in Table 1. A total of 35 patients (68 ± 9 years, 174 ± 8 cm, 77 ± 13 kg) participated in the trial. Fifty-one percent of the patients completed gemcitabine-based neo-adjuvant chemoradiotherapy, 43% received FOLFIRINOX neo-adjuvant chemotherapy, and 6% did not complete the intended neo-adjuvant therapy due to poor health status or disease progression. Two patients did not undergo exploratory laparotomy, one due to urgent medical reasons, and the other due to disease progression during neo-adjuvant therapy. Five patients did not undergo pancreatic resection at exploratory laparotomy due to previously undetected liver metastases (n = 4) or due to technical irresectability due to arterial involvement of the tumor (n = 1). The time interval between CT_1 and CT_2 was 96 ± 28 days and 113 ± 30 days between PET_1 and PET_2. Typically, the time interval between CT_1 and PET_1 was 1–2 weeks and CT_2 and PET_2 were done on the same day.

The tumor diameter on CT was not measurable for one patient on CT_1 and for three patients on CT_2. CA19-9 levels could not be used for five patients at T_1 and eight patients at T_2, because the values were either below the clinically relevant cut-off value of 34 U/mL at T_1, or the measurements were lacking. According to PERCIST, 10 patients did not have measurable tumors at T_1.

Table 1
Patient and scan characteristics (n = 35).

Gender (n)		
	Male	20
	Female	15
Age (in years)[a]	68 ± 9.3	
Body weight (in kg)[a]	77 ± 13	
Administered FDG-activity (in MBq)[a]		
	PET_1 (n = 35)	235 ± 95
	PET_2 (n = 33)	224 ± 83
Location primary tumor (n)		
	Head	1
	Body	31
	Tail	3
Tumor diameter on CT (in mm)		
	At T_1 (n = 34)	31 ± 10
	At T_2 (n = 32)	25 ± 12
Neo-adjuvant therapy (n)		
	FOLFIRINOX	18
	Gemcitabine chemoradiotherapy	15
	No full treatment	2
ΔT (in days)[a]		
	Between CT_1 and CT_2	96 ± 28
	Between PET_1 and PET_2	113 ± 30
Stent placement (n)		
	Before neo-adjuvant therapy	23
	After neo-adjuvant therapy	2
	No stent	10
Exploratory laparotomy (n)		
	Yes	33
	No	2
Surgery (n)		
	Yes	28
	No	7

[a] Continuous variables are described as mean ± standard deviation.

3.2. Primary tumor response evaluation

The mean tumor response parameters (CA19-9, CT diameter, and tumor FDG-uptake on PET) significantly decreased from T_1 to T_2 ($p = 0.017$ for CA19-9 serum levels, $p = 0.001$ for tumor diameter on CT, and $p < 0.0001$ for uptake values on PET), as shown by the combined box- and scatter plots in Fig. 2. From T_1 to T_2, CA19-9 serum levels increased in 15% (4/27) of the patients (mean increase [min-max]: 95.5 U/mL [20–176]), tumor diameters increased on CT in 19% (6/31) of the patients (mean increase [min-max]: 5 mm [1–15]), and uptake values on PET increased in 16% (4/25) of the patients (mean increase [min-max]: 1.6 [0.7–3.4]). All four patients with increased uptake values on PET, also had increased tumor diameters on CT from T_1 to T_2. Only two of these patients had increased CA19-9 serum levels.

We found a strong positive correlation between the change in uptake values on PET and change in CA19-9 serum levels ($R = 0.73$), as well as for the change in uptake values on PET and the change in tumor diameter on CT ($R = 0.75$), as shown in Fig. 3. We found a moderate correlation between the change in CA19-9 and the change in tumor diameter on CT ($R = 0.45$). Please note the relatively large 95% confidence interval for this last correlation as compared to the other two.

3.3. Emerging metastatic disease

On *digital* PET/CT scans, small-volume liver lesions were detected in 5 out of 35 patients (14%) before and/or after neo-adjuvant therapy (T_1 and/or T_2), which were all histologically confirmed as metastases during laparotomy (4/5) or diagnosed as progressive disease on postoperative follow-up imaging shortly after surgery (1/5). Only one of these five cases could be retrospectively detected on the baseline staging ceCT (3%). In 4 other patients (11%) baseline ceCT was described as normal, but retrospectively the expert team considered the liver metastases status to be unclear (Table 2).

Fig. 4 shows FDG-PET images of one of the patients where liver metastases were observed on PET_1. In the lower right figure, we see the pancreatic lesion, the retro pancreatic node, and two liver metastases which were not detected on staging ceCT.

These results indicate that if *digital* PET/CT had been a routine part of staging and restaging, exploratory laparotomy could have been prevented in 4/35 patients (11%). Also, neo-adjuvant treatment regimens could have been prevented in 3/35 patients (9%), who would then have been offered palliative treatment at baseline.

4. Discussion

In this study *digital* PET/CT demonstrated a clear added value to standard ceCT and CA 19–9 in the staging of pancreatic cancer and response evaluation after neo-adjuvant therapy. We found strong positive correlations between the change in uptake values on PET and the change in CA 19-9 serum levels, as well as the change in tumor diameter on ceCT, respectively. Furthermore, *digital* PET/CT imaging allowed detection of small-volume liver metastases (<1 cm in diameter) in 14% of patients, whereas in retrospect only 3% could have been detected by ceCT. It would therefore have significantly altered disease stage and thereby prevented non-therapeutic laparotomy in 11% of patients. This is in line with the meta-analysis of Versteijne et al. showing that on average 10–20% of patients who are planned for surgical exploration do not undergo resection, because metastatic or locally unresectable disease is found at surgery that was not anticipated on imaging [47]. More accurate detection of smallvolume distant metastatic disease at the initial staging will also prevent some patients from receiving unnecessary neo-adjuvant therapy and allow the design of an optimal personalized palliative treatment strategy at an earlier stage, which is likely to improve the patient's overall quality of life. Taken together, we conclude *digital* PET/CT to be a valuable addition to the routine work-up and response evaluation of pancreatic cancer patients.

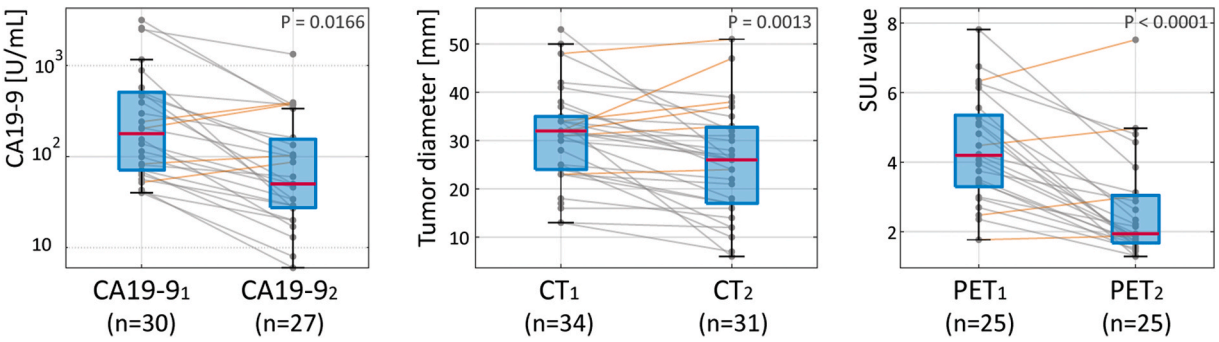

Fig. 2. Combined box- and scatter plots of the primary tumor response evaluation before neo-adjuvant therapy (T1) and after (T2). All response parameters show a decrease in means from T1 to T2 ($P < 0.05$).

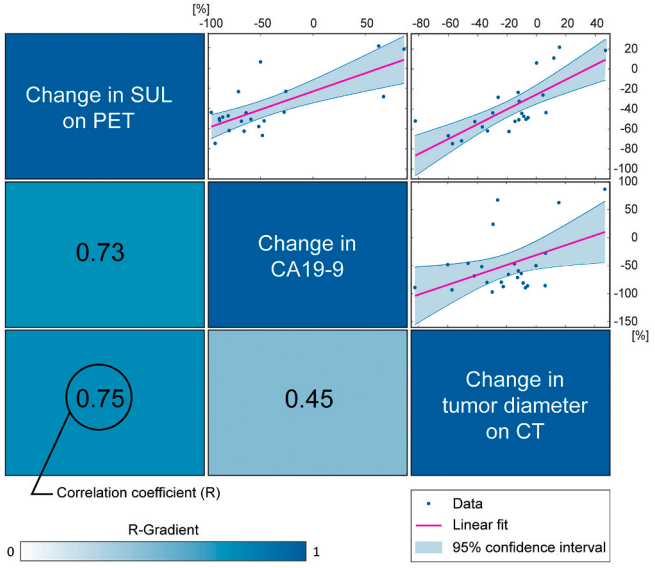

Fig. 3. Linear correlation matrix of change in tumor response parameters before neo-adjuvant therapy and after neo-adjuvant therapy. The change in uptake values on PET correlated strongly and positively with the change in CA19-9 and change in tumor diameter on CT. Regression lines (pink) and 95% confidence intervals of mean standard deviation are visualized.

Another preoperative staging modality is laparoscopy, which is routinely performed in some centers to exclude peritoneal metastases prior to pancreatic resection, but was not included in this study protocol. In patients with resectable disease after standard imaging, non-resectable (metastatic) cancer is detected by staging laparoscopy in 12–20% of cases on average [48–50]. Since we have now shown that *digital* PET/CT can detect small-volume metastatic disease, it may offer significant added value in the diagnostic work-up. Notably, whereas laparoscopy can only demonstrate metastases located on the peritoneal surface, *digital* PET/CT can also detect small intraparenchymal lesions. In cases whereby metastatic disease is decisively demonstrated on *digital* PET/CT, a staging laparoscopy (and exploratory surgery) will not be needed, avoiding an unnecessary invasive procedure for the patient with its associated cost, inconvenience and risk. Also, when staging laparoscopy is routinely performed in the same session prior to the planned laparotomy and metastatic disease is found, the laparotomy will then be abandoned causing substantial loss of valuable planned operating time (usually 5–6 h for pancreatic resection). Taken together, our findings suggest that *digital* PET/CT offers additional value (complementary to staging laparoscopy) in detecting small-volume metastatic disease in pancreatic cancer.

With regard to assessing the local tumor response after neo-adjuvant therapy, the change in FDG-uptake showed a strong positive correlation with both tumor diameter and CA 19-9 decrease. This suggests that the combination of *digital* PET/CT, diagnostic ceCT and CA 19–9 may help to further improve staging and restaging and support the appropriate selection of surgical candidates. The observed correlation with CA 19–9 response was expected, but the correlation with ceCT tumor diameter was somewhat surprising, given the known ineffectivity of traditional cross-sectional imaging for this purpose. Although *digital* PET/CT cannot directly demonstrate vascular involvement, it may also have added value after careful fusion with diagnostic CT, whereby a decrease in FDG-uptake around major vessels after neo-adjuvant therapy in locally advanced cases (especially when accompanied by a significant drop in serum CA19-9) may suggest downstaging and potential improved resectability, even when the lesion mass appears unchanged on ceCT [51].

Table 2
Five patients (14%, n = 5/35) were suspected of liver metastases on PET at T_1 or T_2, only one of which was detected on standard CeCT. In four of these patients, liver metastases were confirmed by histology at exploratory laparotomy (11%).

	Suspected of liver metastases on				Confirmed with/by		
	CT_1	CT_2	PET_1	PET_2	Surgeon at laparotomy	Pathology	Follow-up
1	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	N/A
2	No	No	**YES**	**YES**	**YES**	**YES**	N/A
3	No	No	No	**YES**	**YES**	**YES**	N/A
4	No	No	**YES**	No	**YES**	**YES**	N/A
5	No	No	**YES**	**Unclear**[b]	No	N/A[a]	Highly suspected of liver metastases on MRI and CT (After 5 months post-operative)
6	No	No	No	**Unclear**	No	N/A	Medical issues, no metastases on CT (After 8 months post-operative), rise of CA19-9
7	No	No	No	**Unclear**	No	N/A	Pulmonal metastases (After 5 months post-operative)
8	No	No	**Unclear**	No	No	N/A	No liver metastases at autopsy (After 6 months post-operative)
9	**Unclear**	**Unclear**	No	No	No	N/A	Highly suspected of liver metastases (After 3 months post-operative)

[a] N/A = not applicable, because liver metastases were not observed at exploratory laparotomy (pathology column), or liver metastases was already confirmed by pathology after exploratory laparotomy (Follow-up column).
[b] Unclear = the expert team was unsure whether liver metastases were visible or not.

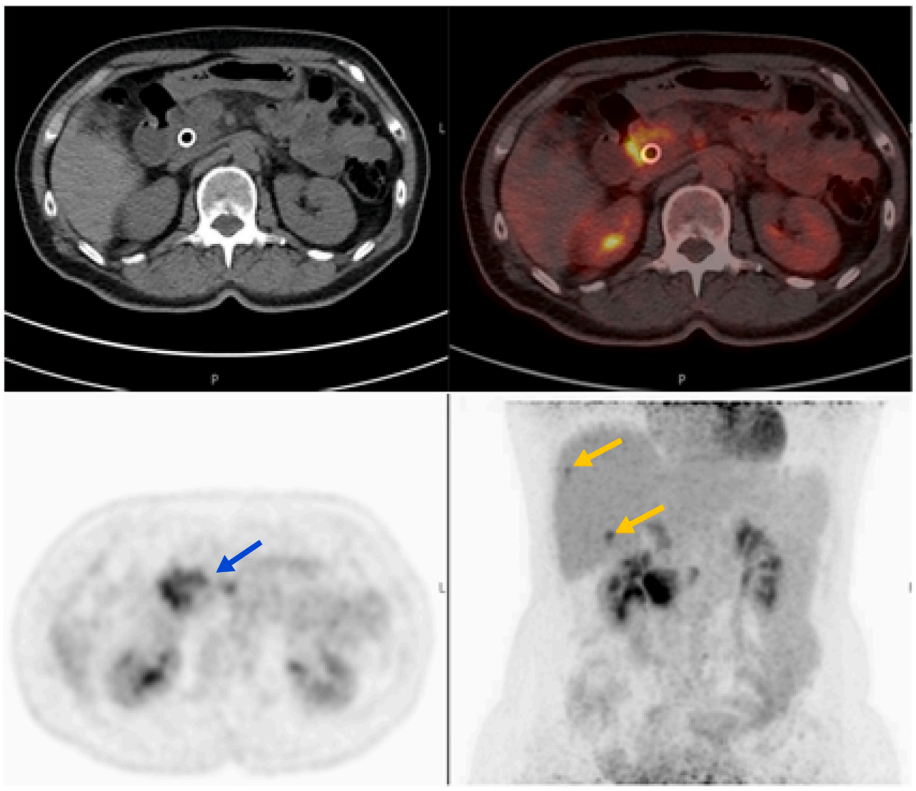

Fig. 4. Four panel FDG-PET$_1$ image with low dose CT. Upper left: stent in the common bile duct. Lower left: intense uptake in the pancreatic head (blue arrow) and a positive lymph node retro pancreatic. Upper right: fusion image. Lower right: MIP projection showing the pancreatic lesion, the retro pancreatic node as well as two liver metastases (yellow arrows) which were not detected on ceCT.

A drawback of FDG PET-imaging is that FDG-uptake could be observed around the common bile duct and intrahepatic biliary ducts when a plastic or metal wall-stent was in situ, which is most likely due to local inflammation [52]. Frequently at least large parts of a pancreatic head tumor can still be easily recognized in conjunction to the common bile duct. Future innovations may result in the development of new PET/CT-tracers with lower inflammatory uptake [53].

In the original clinical evaluation studies of FDG-PET/CT pancreatic cancer did not emerge as an appropriate indication, although in many hospitals it remained in use for selected cases [54–56]. For many years FDG-PET/CT remained controversial in standard practice for pancreatic cancer mostly due to the inherent drawbacks of FDG combined with the relatively low spatial resolution of conventional analog PET-scanners [29]. Only recently, some more promising results in pancreatic cancer were reported, all using analog PET-scanners [20,21,24–30]. The observed superior image quality and accuracy in our study are likely the result of *digital* scanning technology in combination with high resolution reconstructions and a relatively long acquisition time [36–39]. Together, these developments allow FDG- PET/CT imaging to rise to the level where it now may start to have more clinical relevance. It is likely that the current trend towards very-large field-of-view PET-scanners will even further improve sensitivity and potential clinical value [57].

Tumor viability within the resected specimen is the only objective direct NAT response test and is considered the most independent predictor of survival. Therefore, histological disease response would ideally be used as gold standard in studies evaluating diagnostic accuracy of neo-adjuvant therapy response, which we did not include in our protocol. The reason is that pathologists consider the histology in pancreatic cancer of limited use for response evaluation because of the crude design, interobserver variability, and limited accuracy of currently available histological grading systems. Comparative studies for these grading systems are lacking and a standardized and widely accepted score has not been established [58,59]. In our cohort almost all histological results were graded in the category "partial response" (i.e. between 5% and 95% remaining tumor cells). Also, a baseline tissue sample is not available for comparison as the primary diagnosis of pancreatic cancer is routinely established by FNA rather than needle core biopsy. To date, there is only one recent study showing that PET-CT correlated with NAT pathology response and predicted survival [19].

Another limitation of this study is the relatively small cohort. Larger prospective confirmative studies are needed, which are currently planned at our center. These studies will need to further address the exact role and value of *digital* PET/CT relative to staging laparoscopy, and show the cost effectiveness of *digital* PET/CT as part of routine diagnostic work-up protocols. Also, a larger follow up study may allow analysis of the potential correlation between the change in FDG-uptake and survival.

Our study has important strengths: This was a prospective study being a side-study of the national multicenter randomized control trial (PREOPANC-2). Furthermore, PET$_1$ and PET$_2$ were blinded for the care team until after surgery, and were purposely not included in the routine workup and clinical decision making. This allowed unbiased assessment of clinical staging in hindsight without having the PET/CT result interfere with standard workup and actual clinical workflow of patients.

5. Conclusion

This study demonstrates an added value of *digital* PET/CT compared to standard ceCT and CA19-9 in the staging of pancreatic cancer and response evaluation after neo-adjuvant therapy. We found a strong positive correlation between the change in uptake values on PET and the change in CA 19-9 serum levels as well as the change in tumor diameter on ceCT, respectively. Furthermore, *digital* PET/CT imaging allowed detection of small-volume liver metastases in 14% of patients, whereas in retrospect only 3% could have been detected by ceCT. It would therefore have significantly altered disease stage and thereby prevented

non-therapeutic laparotomy in 11% of patients. Taken together, the results would justify the addition of *digital* PET/CT to routine work up in a larger follow up study as a next step to validate the results and to show cost-efficiency.

Author statement

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