**Prognostic value of 18FDG PET-CT volumetric parameters in the survival prediction of patients with pancreatic cancer**

E Mohamed 1, A Needham 2, E Psarelli 2, M Carrol 3 , S Vinjamuri 3,B Sanghera 4, W Wong 4, C Halloran 1,2, P Ghaneh1,2

1 Department of Pancreaticobiliary Surgery, Royal Liverpool University Hospital, Liverpool, UK

2 Liverpool Cancer Research UK Cancer Trials Unit, Liverpool Cancer Research UK Centre, University of Liverpool, Liverpool, UK

3 Department of Nuclear Medicine, Royal Liverpool University Hospital, Liverpool, UK

4 Paul Strickland Scanner Centre, Mount Vernon Hospital, Middlesex, UK

**Correspondence:**

Mr Eyas Mohamed

Department of Molecular and Clinical Cancer Medicine

Sherrington Building

University of Liverpool

Ashton Street

Liverpool

L69 3GE

Email: emohamed@liverpool.ac.uk

Tel no: +44 151 795 8611

Fax no: +44 151 795 5284

**Disclosure of funding received for this work:** None

**Short Running title:** PET-CT prognostic value in pancreatic cancer

**Keywords:** 18 Fluoro-deoxy glucose positron emission tomography-computed tomography, Pancreatic Cancer, Survival, Prognosis

**Conflicts of Interest:** None

**Abstract:** 250 words

**Main text (excluding references):** 3035 words

**This study was presented at the 13th Congress of the European – African Hepato-Pancreato-Biliary Association (E-AHPBA), Amsterdam June 2019**

**Abstract**

**Purpose.** To investigate the value of 18 FDG PET-CT volumetric parameters in the prediction of overall survival (OS) in patients with pancreatic cancer and also, assess their independence relative to well-established clinico-pathological variables.

**Methods.** We conducted a retrospective analysis of patients with a confirmed diagnosis of pancreatic cancer who underwent 18 FDG PET-CT. The tumour maximum standardised uptake value (SUVmax) in addition to SUVmean, metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were calculated. The prognostic value of 18 FDG PET-CT and clinico-pathological parameters for OS were assessed using univariate and multivariable analyses.

**Results.** A sum of 89 patients were analysed in this study. Median survival for patients categorised as having high TLG (≥55)and low TLG (<55) was 18 vs 5 months (p<0.001). Similarly, the respective high vs low SUVmean, MTVcm3 and SUVmax were 18 vs 6 months (p= 0.001), 16 vs 6 months (p=0.002) and 18 vs 6 months (p=0.001). Univariate analysis showed SUVmax, SUVmean, MTV, TLG, tumour size, tumour differentiation and presence of distant metastasis as prognostic factors for OS. On multivariable analysis, TLG (HR 2.0, 95% CI1.26-3.18, p=0.004) and the presence of distant metastasis (HR 3.37, 95% CI 1.97-5.77, p<0.001) were independent prognostic risk factors. Subgroup analysis identified TLG as the only significant PET metric after adjusting for the presence of distant metastasis.

**Conclusions.**18 FDG PET-CT is a useful tool in the preoperative evaluation of patients with pancreatic cancer. Tumour TLG offer an independent prognostic value in both the metastatic and non-metastatic disease settings.

**Introduction**

Invasive ductal adenocarcinoma of the pancreas (PDAC) represent a heath challenge worldwide as it’s hegemonized by a substantially unchanged mortality figures over recent decades. The rising incidence of the disease has made projections for it to become the second commonest cause of cancer-related death in western population by 2030, only a figure to be surpassed by mortality secondary to lung cancer.1 The majority of patients present late in their disease course with evidence of a locally advanced tumour or disseminated metastasis that would preclude a radical therapeutic approach 2–4 while the 5 year survival figures for all stages combined remain low at ~ 10%.5,6

Given the poor survival with current existing therapies, identifying novel prognostic markers is of paramount importance in individualised treatment planning. Multiple prognostic factors are well studied in the literature which include the serum level of carbohydrate antigen 199 (CA 199), tumour size, histological grade, presence of positive lymph nodes, resection margin involvement in addition to lymphovascular, perineural and portovenous invasion.7–13 However, the majority of these factors are only available retrospectively following formal histopathological analysis in resected cases (only 10-15% ) which limit their clinical utility and wide adoption in the majority of patients.

 18 Fluoro-deoxy glucose positron emission tomography-computed tomography (18 FDG PET-CT) is a fast-growing imaging modality of wide spread use in clinical oncology. Its ability to provide functional and anatomical data can help in disease diagnosis, staging and monitoring the response to treatment.14–18 The commonly reported maximum standardised uptake value (SUVmax) represent the metabolic activity in a single voxel within a region of interest (ROI) and therefore, might not be reflective of the true overall local disease burden. Recently, there has been a growing interest in 18 FDG PET-CT volumetric parameters i.e. the metabolic tumour volume (MTV) and total lesion glycolysis (TLG) and their validity as surrogate radiological biomarkers indicative for disease prognosis. However, there is a paucity of studies in the literature that report on their utility in the comprehensive risk assessment of PDAC patients. Therefore, the aim of this study was to assess the prognostic role of 18 FDG PET-CT volumetric parameters and their independence relative to well established clinicopathological variables in informing the overall survival (OS) of patients with PDAC.

**Methods**

**Material and Patients Selection**

We conducted a retrospective review of patients with a confirmed diagnosis of PDAC who underwent 18 FDG PET-CT as part of their diagnostic algorithm at our institution (Royal Liverpool University Hospital) in the period between January 2011 and April 2013. The utility of 18 FDG PET-CT was not part of the standardised diagnostic work up at our institution for patients with suspected PDAC during the study period and was conducted as part of the accrual for the PETPANC trial.19 We screened our local 18 FDG PET-CT registry to identify patients who underwent the nuclear imaging test and who also had a confirmed diagnosis of PDAC based on histological confirmation or clinical data as dictated by our multidisciplinary team. Patients with recurrent pancreatic tumours or rare/cystic tumours of the pancreas were excluded from the study. Patients with iso-metabolic tumours that are difficult to depict from the surrounding normal pancreas with a potential to introduce bias into volumetric tumour measurements were also excluded. None of the included patients received any form of neoadjuvant therapy prior to 18 FDG PET-CT. This study was registered at our local review board, the need for individualised patient consent was waived due to the retrospective nature of the study.

Demographics and clinico-pathological characteristics of patients were extracted from an electronic patient’s record including age, gender, maximal tumour size, tumour location, surgery performed, resection margin status, tumour stage, lymph node status, histological differentiation, presence of distant metastasis, CA19-9 level in addition to tumour’s SUVmax value. Tumour’s SUVmean/MTV/TLG were not calculated in the initial radiological report and were measured retrospectively for the purpose of this study. The OS was retrieved from our hospital database and calculated from the date of conduction of 18 FDG PET-CT until the time of death or censoring.

 **18 FDG PET-CT Procedure & Image analysis**

All of the participants in the study were referred to our supra-regional pancreatic unit with suspected PDAC following the conduction of a preliminary diagnostic work up that usually include radiological assessment with multidetector computed tomography (MDCT). Patients underwent 18 FDG PET-CT scanning within a maximum of two weeks if they consented to participate in the PETPANC trial. Patients fasted for 6 hours prior to the scan. To ensure accurate SUV measurements patient’s weight was obtained using a calibrated class III device that satisfied requirements defined in the Non-Automatic Weighing Instruments Directive 2003 and blood glucose was recorded using a calibrated Boehringer Mannheim glucometer (Boehringer Ingelheim Ltd, Bracknell, UK). For diabetes mellitus patients, only those with a fasting blood glucose <10.0 mmol/l were scanned to reduce false-negative 18 FDG PET-CT results. Patients drank between two and three glasses of water before thenuclear test to ensure good hydration which contributes to the quality of the scan. The dose of radiotracer to be injected was calculated according to the patient’s weight and administered via a peripheral cannula. For two-dimensional scanning 350–530 MBq of FDG was injected. In patients requiring a larger dose because of a larger body weight, the Administration of Radioactive Substances Advisory Committee (ARSAC) certificate holder approval was obtained before giving the larger dose. For three-dimensional scanning 150–350 MBq was injected. Patients remained quiet and inactive during the uptake period in a warm room to avoid artefacts including skeletal muscle FDG uptake and brown adipose tissue uptake. Patients emptied their bladders just prior to positioning on the scanner bed to avoid artefacts from FDG activity in the urinary bladder. The 18 FDG PET-CT emission scan started at 90 minutes after FDG injection. Scanning was carried out on a standard PET-CT table top, beginning at the groin and ending at the base of the orbits and with arms up if a single whole-body scan was performed. Data were reconstructed using ordered subsets expectation maximisation reconstruction parameters on computed tomography for attenuation correction.

The imaging analysis was performed after the radiologist read the report and drew a ROI for calculation of SUVmax within the area of the high FDG uptake that would correspond to the suspected tumour on MDCT images. An area with focal uptake with SUVmax ≥ 2.5 was considered to represent malignancy in-line with previous studies. The SUVmean in addition to MTV and TLG were calculated in retrospect under the supervision of a consultant physicist with a vast experience (>20 years) in nuclear medicine (M.C) by a combination of manual and automated tumour segmentation techniques on a Hermes Hybrid Recon™ desktop.

**Statistical Analysis**

Continuous data in this study were expressed as medians and interquartile ranges (IQR) whereas categorical data were summarised as frequencies and percentages. Kaplan Meier survival curves were constructed by dichotomising 18 FDG PET-CT prognostic variables around their median values and comparisons were made using the log rank test.20 Survival estimates of 18 FDG PET-CT parameters for median, 1 year and 5 year survival were presented alongside their 95% confidence intervals (CI).

Univariate Cox proportional hazard models21 were constructed for each prognostic variable apart from those who were scarcely populated. Hazard ratios were estimated and presented with 95% CI and p-values. Prior to Cox regression, all variables were assessed for proportional hazards through consideration of Schoenfeld residuals. Continuous variables that do not satisfy the proportional hazards assumptions were dichotomised about their median values. Any variable with missing observational data of more than 40% was excluded from multivariate statistical modelling. Variables found to be significant on univariate analysis were entered into the multivariate analysis using stepwise backward selection to identify independent prognostic factors.

Further to this, subgroup analysis was conducted on 18 FDG PET-CT prognostic parameters based on the presence or absence of distant metastases. Estimates of median and 1 year survival were presented according to their hazard ratios and 95% CI’s.

Concordance statistics22 and Akaikes information criterion23 values were calculated and reported in order to measure the predictive accuracy of the univariate models including each 18 FDG PET-CT parameter and also the multivariate models including distant metastases.

**Results**

During the study period, a total of 263 patients with suspected PDAC underwent 18 FDG PET-CT examination at our institution. Out of these, there were 94 patients with a confirmed primary diagnosis of PDAC. After exclusion of patients with incomplete records (n=3) and those with metabolically inactive tumours (n=2), there were 89 patients eligible for the final analysis. The study cohort was comprised of 48 males and 41 females with a median age of 69. The median tumour size was 29mm (range 10-110) while positive lymph nodes were identified in 57% of the cases. The majority of patients did not undergo surgical resection either due to preoperative detection of distant organ metastasis (n=28, 31%), the detection of a locally advanced tumour/unexpected metastasis upon laparotomy (n=7, 8%), poor performance status (n=15, 17%). The clinical characteristics of included patients are summarised in table 1.

The median OS for the entire patient population was 11 months (range 1-82) while 5-year survival for the overall cohort was 8%. In order to perform a comparative analysis for the unadjusted 18 FDG PET-CT derived parameters and their influence on survival we stratified patients into high and low risk groups based on their respective median values. The median (IQR) values for SUVmax, SUVmean, MTV and TLG were 7.8 (5.8-11.2), 5.15 (4.0-6.4), 10mm3 (4.2-20.1) and 55.0 (16.8-108.5) respectively (Table 2).

The median survival for patients with high (≥7.8) and low (<7.8) SUVmax was 18 months (95%CI: 12-26) *vs* 6 months (95%CI: 4-9) respectively (p<0.001). Furthermore, SUVmean (18 vs 6 months, p=0.007), MTV (16 vs 6 months, p= 0.0011) and TLG (18 vs 5 months, p=0.001) showed similar survival trends after stratification based on their respective median values (Figure 1). All median survival estimates pertaining to the FDG PET-CT derived parameters showed a strong statistical difference between high and low risk groups (table 2).

On univariate analysis, variables with a statistically significant predictive value for OS were: SUVmax (p=0.001), SUVmean (p=0.001), MTV (p=0.002), TLG (p<0.001), tumour size (p=0.041), tumour differentiation (p<0.001) and presence of distant metastasis (p<0.001) (Table 3). Of these variables, differentiation was removed from further statistical analysis due to a high percentage of missing data (42%) as well as the anatomical tumour site, resection margin status and operative procedure. Backwards selection including all significant variables from the univariate analysis except for differentiation status identified TLG (HR 2.0, 95% CI1.26-3.18, p=0.004) and the presence of distant metastases (HR 3.37, 95% CI 1.97-5.77, p<0.001) as independent prognostic factors (table 4).

Further to this, we performed a subgroup analysis to assess whether PET derived metrics would hold a prognostic value in patients whether they presented with metastatic disease or not. In patients with metastatic disease, TLG was the only PET metric that attained statistical significance with HR 3.19 (95%CI 1.05-9.68, p=0.041) while MTV showed borderline significance (p=0.077). None of the patients with a high TLG and metastatic disease were alive after 1 year of follow up while the corresponding figure was 43% for patients assigned to the low TLG group. In the group with non-metastatic disease, SUVmax (HR 2.04, 95%CI 1.19-3.51, p= 0.01), SUVmean (HR 2.06, 95%CI 1.20-3.52, p=0.008) and TLG (HR 1.78, 95% CI 1.03-3.08, p =0.04) were independent prognostic factors. TLG was the only PET metric that attained statistical significance in both subgroups (table 5).

The predictive ability of models including distant metastases and each 18 FDG PET-CT prognostic parameter were compared through calculating the C-indices and AIC. The model that included both TLG and metastases showed the best model fit with c-index of 0.68 (SE=0.02) and an AIC= 594.

**Discussion**

In this study, we identified tumour’s TLGin additionto the presence of distant organ metastasis as independent prognostic variables for OS in PDAC. The volumetric parameters of 18 FDG PET-CT were perceived to be better representatives for the overall local tumour burdenas opposed to the SUVmax. In our heterogeneous group of patients, it was the tumour TLG which showed an independent prognostic value (HR 2.0, 95% CI1.26-3.18, p=0.004) while MTV showed borderline significance (p=0.07) in the subgroup of patients with metastatic disease (n= 28).

Pancreatic cancer remain one of the most recalcitrant and formidable malignancies to treat. The majority of patients present with an advanced diseased state that preclude instigation of potentially curative treatments. Furthermore, those who are candidates for curative treatments are berated by high incidences of disease recurrence whilst efficient treatment for those presenting with advanced disease are currently lacking. Therefore, the identification of novel preoperative prognostic markers beyond the conventional histopathological factors is of great importance in stratifying high risk patients into appropriate treatment pathways and could also guide the delivery of upfront or intensified treatment in patients with adverse prognostic features who are anticipated to have a rapidly progressive disease.

The utility of 18 FDG PET-CT has gained wide popularity as it provides an indirect measure of the molecular metabolic activity in vivo which is governed by the hyper-metabolic activity of malignant cells (Warburg effect).24 The injected radiotracer has a high level of uptake in malignant tumours due to the over expression of glucose transporters (in particular GLUT 1) that subsequently becomes trapped following phosphorylation by hexokinases in tumour cells.25–28 The qualitative and quantitative FDG avidity caused by glucose accumulation in malignant cells irrespective of tumour morphology could be depicted on radiological imaging with 18 FDG PET-CT. Hence, the variation in SUV measurements could herald a difference in the inherent biological aggressiveness in different tumours that would translate into varied survival figures. To this effect, the use of the nuclear imaging test extend beyond the traditional role as a diagnostic modality and could be employed in the prediction of the response to treatment with chemotherapy and/or radiotherapy29–31 in addition to disease recurrence and prognosis.32–37

Several studies have examined the role of 18 FDG PET-CT parameters in the survival prediction of patients with PDAC. Yamamato and colleagues 38 identified a high SUVmax of ≥ 6.0 as an independent prognostic factor in a group of 128 patients with resected PDAC (HR 2.05, p = 0.002). They also identified similar to our study a difference in the median OS between high (≥ 6.0) and low (< 6.0) SUVmax groups of 18 vs 37 months respectively (p < 0.001) and also in early disease recurrence (49% vs 5%, p<0.001). In another study, Choi et al 39 identified a similar trend with poor survival among high and low SUVmax groups using a different cut off median value of 3.5 (median OS 23.5 vs 45.4, p=0.01). Maemura et al 32 identified a correlation between a high SUVmax and the presence of distant metastasis while Sperti et al 33 reporting limited survival for patients with SUVmax >4 (178 vs 265 days). It was also reported that a favourable decline in SUV following neoadjuvant chemo-radiotherapy, predicted overall survival as in the study by Chang et al40 of 260 patients with locally advanced tumours supporting its role in biological monitoring of treatment efficacy.

The volumetric parameters of 18 FDG PET-CT has been reported as independent risk predictors for OS and recurrence free survival in patients with resected PDAC.41–43 On comparison of the survival rate of patients with high and low volumetric parameters in our study, a pattern of improved survival on various time points emerged (table 3). However, after incorporation of these into the multivariate analysis, it was the TLG rather than MTV which had an independent prognostic role. This might suggest an intrinsic difference in the metabolic activity within different tumour cells while also accounting for the dense desmoplastic reaction (metabolically inactive) that surrounds tumour cells which is incorporated into the MTV measurement.

Whist the measurement of the SUVmax in malignant tumours is considered quite robust and reproducible as it portray the highest metabolic uptake value within a ROI, there is a lack of consensus about the optimal cut off value that predicts poor survival.29,33,38,44 The volumetric parameters are further compounded by the segmentation method used, image mis-registration, imaging artefact, partial volume effects and time-lapse between injection of radiotracer and subsequent imaging.45,46 Moreover, there is a potential for overestimating the primary volumetric measurements by inclusion of surrounding positive lymph nodes in addition to image glare secondary to biliary prosthesis and/or concomitant obstructive pancreatitis. Conversely, there is the pronounced draw back with iso-metabolic tumours that does not show increased FDG uptake which then lead to false negative results.

There were several limitations within the present study. First, there was an unavoidable selection bias as the analysis was conducted on patients who consented for undergoing 18 FDG PET-CT as part of the accrual for PETPANC trial. Also, the included cohort was composed of a heterogeneous group with a different mix of patients who were assigned to different treatment plans. Due to the retrospective nature of the study, there was a considerable amount of missing data that precluded the inclusion of certain parameters such as the tumour location, type of surgery performed in statistical modelling. In addition, the measurements of the volumetric parameters were conducted in retrospect but nevertheless the readers were blinded to the survival outcomes for patients upon volumetric tumour segmentation and measurement. Finally, our subgroup analysis contained a limited number of patients within each group which limit the adoption of its findings in prospective clinical cohorts.

**Conclusions**

 The role of 18 FDG PET-CT is likely to evolve overtime and could potentially be utilized as a complementary tool along with other well-established clinic-pathological factors in the preoperative risk stratification of PDAC. This study has identified TLG and the presence of distant metastasis asindependent prognostic factors for OS in our heterogenous cohort of PDAC patients. These findings could be incorporated into clinical risk prediction models that can help both patients and clinicians in individualised treatment tailoring.

**References**

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921. doi:10.1158/0008-5472.CAN-14-0155

2. Werner J, Combs SE, Springfeld C, Hartwig W, Hackert T, Büchler MW. Advanced-stage pancreatic cancer: therapy options. *Nat Rev Clin Oncol*. 2013;10(6):323-333. doi:10.1038/nrclinonc.2013.66

3. Ferrone CR, Pieretti-Vanmarcke R, Bloom JP, et al. Pancreatic ductal adenocarcinoma: Long-term survival does not equal cure. *Surgery*. 2012;152(3):S43-S49. doi:10.1016/j.surg.2012.05.020

4. Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. *Nat Rev Dis Prim*. 2016;2:16022. doi:10.1038/nrdp.2016.22

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5-29. doi:10.3322/caac.21254

6. Ryan DP, Hong TS, Bardeesy N. Pancreatic Adenocarcinoma. *N Engl J Med*. 2014;371(11):1039-1049. doi:10.1056/NEJMra1404198

7. Groot VP, Rezaee N, Wu W, et al. Patterns, Timing, and Predictors of Recurrence Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma. *Ann Surg*. 2018;267(5):936-945. doi:10.1097/SLA.0000000000002234

8. Hartwig W, Gluth A, Hinz U, et al. Total Pancreatectomy for Primary Pancreatic Neoplasms. *Ann Surg*. 2015;261(3):537-546. doi:10.1097/SLA.0000000000000791

9. Neoptolemos JP, Stocken DD, Friess H, et al. A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer. *N Engl J Med*. 2004;350(12):1200-1210. doi:10.1056/NEJMoa032295

10. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer Resection. *JAMA*. 2010;304(10):1073. doi:10.1001/jama.2010.1275

11. Strobel O, Hinz U, Gluth A, et al. Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. *Ann Surg*. 2015;261(5):961-969. doi:10.1097/SLA.0000000000000814

12. WINTER J, CAMERON J, CAMPBELL K, et al. 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single-Institution Experience☆. *J Gastrointest Surg*. 2006;10(9):1199-1211. doi:10.1016/j.gassur.2006.08.018

13. Strobel O, Hank T, Hinz U, et al. Pancreatic Cancer Surgery. *Ann Surg*. 2017;265(3):565-573. doi:10.1097/SLA.0000000000001731

14. Schick V, Franzius C, Beyna T, et al. Diagnostic impact of 18F-FDG PET–CT evaluating solid pancreatic lesions versus endosonography, endoscopic retrograde cholangio-pancreatography with intraductal ultrasonography and abdominal ultrasound. *Eur J Nucl Med Mol Imaging*. 2008;35(10):1775-1785. doi:10.1007/s00259-008-0818-x

15. Strobel K, Heinrich S, Bhure U, et al. Contrast-Enhanced 18F-FDG PET/CT: 1-Stop-Shop Imaging for Assessing the Resectability of Pancreatic Cancer. *J Nucl Med*. 2008;49(9):1408-1413. doi:10.2967/jnumed.108.051466

16. Sperti C, Pasquali C, Bissoli S, Chierichetti F, Liessi G, Pedrazzoli S. Tumor Relapse after Pancreatic Cancer Resection is Detected Earlier by 18-FDG PET than by CT. *J Gastrointest Surg*. 2010;14(1):131-140. doi:10.1007/s11605-009-1010-8

17. Schellenberg D, Quon A, Minn AY, et al. 18Fluorodeoxyglucose PET Is Prognostic of Progression-Free and Overall Survival in Locally Advanced Pancreas Cancer Treated With Stereotactic Radiotherapy. *Int J Radiat Oncol*. 2010;77(5):1420-1425. doi:10.1016/j.ijrobp.2009.06.049

18. Moon SY, Joo KR, So YR, et al. Predictive Value of Maximum Standardized Uptake Value (SUVmax) on 18F-FDG PET/CT in Patients With Locally Advanced or Metastatic Pancreatic Cancer. *Clin Nucl Med*. 2013;38(10):778-783. doi:10.1097/RLU.0b013e31829f8c90

19. Ghaneh P, Hanson R, Titman A, et al. 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*. 2018;22(7):1-114. doi:10.3310/hta22070

20. Peto R, Peto J. *Asymptotically Efficient Rank Invariant Test Procedures*. Vol 135.; 1972. https://www.jstor.org/stable/pdf/2344317.pdf?refreqid=excelsior%3Af9052432068fd2eebfb4f31b11ad89e1. Accessed January 29, 2019.

21. Cox DR. *972] 187 Regression Models and Life-Tables*. https://about.jstor.org/terms. Accessed January 29, 2019.

22. Harrell , FE. *Regression Modeling Strategies*. Cham: Springer International Publishing; 2015. doi:10.1007/978-3-319-19425-7

23. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr*. 1974;19(6):716-723. doi:10.1109/TAC.1974.1100705

24. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. *Science (80- )*. 2009;324(5930):1029-1033. doi:10.1126/science.1160809

25. Szablewski L. Expression of glucose transporters in cancers. *Biochim Biophys Acta - Rev Cancer*. 2013;1835(2):164-169. doi:10.1016/j.bbcan.2012.12.004

26. LU K, YANG J, LI D-C, et al. Expression and clinical significance of glucose transporter-1 in pancreatic cancer. *Oncol Lett*. 2016;12(1):243-249. doi:10.3892/ol.2016.4586

27. Kitasato Y, Yasunaga M, Okuda K, et al. 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*. 2014;43(7):1060-1065. doi:10.1097/MPA.0000000000000185

28. Chikamoto A, Inoue R, Komohara Y, et al. Preoperative High Maximum Standardized Uptake Value in Association with Glucose Transporter 1 Predicts Poor Prognosis in Pancreatic Cancer. *Ann Surg Oncol*. 2017;24(7):2040-2046. doi:10.1245/s10434-017-5799-1

29. Choi M, Heilbrun LK, Venkatramanamoorthy R, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using 18F-fluorodeoxyglucose positron emission tomography to monitor clinical outcomes in patients treated with neoadjuvant chemo-radiotherapy for locally advanced pancreatic cancer. *Am J Clin Oncol*. 2010;33(3):257-261. doi:10.1097/COC.0b013e3181a76a0b

30. Kuwatani M, Kawakami H, Eto K, et al. Modalities for evaluating chemotherapeutic efficacy and survival time in patients with advanced pancreatic cancer: comparison between FDG-PET, CT, and serum tumor markers. *Intern Med*. 2009;48(11):867-875. http://www.ncbi.nlm.nih.gov/pubmed/19483354. Accessed November 14, 2018.

31. Bang S, Chung HW, Park SW, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. *J Clin Gastroenterol*. 2006;40(10):923-929. doi:10.1097/01.mcg.0000225672.68852.05

32. Maemura K, Takao S, Shinchi H, et al. Role of positron emission tomography in decisions on treatment strategies for pancreatic cancer. *J Hepatobiliary Pancreat Surg*. 2006;13(5):435-441. doi:10.1007/s00534-006-1102-8

33. Sperti C, Pasquali C, Chierichetti F, Ferronato A, Decet G, Pedrazzoli S. 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. *J Gastrointest Surg*. 2003;7(8):953-9; discussion 959-60. http://www.ncbi.nlm.nih.gov/pubmed/14675704. Accessed November 14, 2018.

34. Akita H, Takahashi H, Ohigashi H, et al. FDG-PET predicts treatment efficacy and surgical outcome of pre-operative chemoradiation therapy for resectable and borderline resectable pancreatic cancer. *Eur J Surg Oncol*. 2017;43(6):1061-1067. doi:10.1016/j.ejso.2017.03.015

35. Lee SM, Kim T-S, Lee JW, Kim S-K, Park S-J, Han S-S. Improved Prognostic Value of Standardized Uptake Value Corrected for Blood Glucose Level in Pancreatic Cancer Using F-18 FDG PET. *Clin Nucl Med*. 2011;36(5):331-336. doi:10.1097/RLU.0b013e31820a9eea

36. Zhu D, Wang L, Zhang H, et al. Prognostic value of 18F-FDG-PET/CT parameters in patients with pancreatic carcinoma. *Medicine (Baltimore)*. 2017;96(33):e7813. doi:10.1097/MD.0000000000007813

37. Wang X-Y. Utility of PET/CT in diagnosis, staging, assessment of resectability and metabolic response of pancreatic cancer. *World J Gastroenterol*. 2014;20(42):15580. doi:10.3748/wjg.v20.i42.15580

38. Yamamoto T, Sugiura T, Mizuno T, et al. Preoperative FDG-PET predicts early recurrence and a poor prognosis after resection of pancreatic adenocarcinoma. *Ann Surg Oncol*. 2015;22(2):677-684. doi:10.1245/s10434-014-4046-2

39. Choi HJ, Kang CM, Lee WJ, et al. Prognostic Value of 18 F-Fluorodeoxyglucose Positron Emission Tomography in Patients with Resectable Pancreatic Cancer. *Yonsei Med J*. 2013;54(6):1377. doi:10.3349/ymj.2013.54.6.1377

40. Chang JS, Choi SH, Lee Y, et al. Clinical Usefulness of 18F-Fluorodeoxyglucose-Positron Emission Tomography in Patients With Locally Advanced Pancreatic Cancer Planned to Undergo Concurrent Chemoradiation Therapy. *Int J Radiat Oncol*. 2014;90(1):126-133. doi:10.1016/j.ijrobp.2014.05.030

41. Im H-J, Oo S, Jung W, et al. Prognostic Value of Metabolic and Volumetric Parameters of Preoperative FDG-PET/CT in Patients With Resectable Pancreatic Cancer. *Medicine (Baltimore)*. 2016;95(19):e3686. doi:10.1097/MD.0000000000003686

42. Xu H-X, Chen T, Wang W-Q, et al. Metabolic tumour burden assessed by 18F-FDG PET/CT associated with serum CA19-9 predicts pancreatic cancer outcome after resection. *Eur J Nucl Med Mol Imaging*. 2014;41(6):1093-1102. doi:10.1007/s00259-014-2688-8

43. Lee JW, Kang CM, Choi HJ, et al. Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis on Preoperative 18F-FDG PET/CT in Patients with Pancreatic Cancer. *J Nucl Med*. 2014;55(6):898-904. doi:10.2967/jnumed.113.131847

44. Chirindel A, Alluri KC, Chaudhry MA, et al. Prognostic Value of FDG PET/CT–Derived Parameters in Pancreatic Adenocarcinoma at Initial PET/CT Staging. *Am J Roentgenol*. 2015;204(5):1093-1099. doi:10.2214/AJR.14.13156

45. Krak NC, Boellaard R, Hoekstra OS, Twisk JWR, Hoekstra CJ, Lammertsma AA. Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. *Eur J Nucl Med Mol Imaging*. 2005;32(3):294-301. doi:10.1007/s00259-004-1566-1

46. Jha P, Bijan B. PET/CT for Pancreatic Malignancy: Potential and Pitfalls. *J Nucl Med Technol*. 2015;43(2):92-97. doi:10.2967/jnmt.114.145458

**Figures and tables legend:**

Table 1. Characteristics of patients included in the study.

Table 2. Univariate analysis for prognostic factors included in the study.

Table 3. Survival information relating to each metric split according to their median values.

Table 4. Multivariate analysis for prognostic factors including the overall study cohort

Table 5. Multivariate sub-group analysis based on the presence or absence of distant metastasis

Table 6. Survival models based on C-statistic and Akaike information criterion

Figure 1. Kaplan Meier survival curves of 18 FDG PET-CT prognostic parameters dichotomised according to their respective median values.

|  |  |  |
| --- | --- | --- |
| **Patient characteristic** |  |  N=89  |
| **Median Age (range)** |  |  | 69(44-85) |
| **Gender** |  |  |  |
|  Male |  |  | 48(54%) |
| Female |  |  | 41(46%)  |
| **Smoking status** |  |  |  |
| Never |  |  | 38(43%) |
| Current |  |  | 18(20%) |
| Ex |  |  | 31(35%) |
| N/A |  |  | 2(2%) |
| **Diabetic** |  |  |  |
| Yes |  |  | 15(17%) |
| No |  |  | 72(81%) |
| N/A |  |  | 2(2%) |
| **Median CA 199 (IQR)** |  |  | 222 (41-685) |
| **Median tumour size (IQR)** |  |  | 29mm(20-35) |
| **Tumour location** |  |  |  |
| Head |  |  | 68(76%) |
| Tail |  |  | 6(7%) |
| body |  |  | 9(10%) |
| Neck |  |  | 6(7%) |
| **Operation** |  |  |  |
| PPPD |  |  | 29(33%) |
| Standard Whipple |  |  | 5(6%) |
| Left pancreatectomy |  |  | 2(2%) |
| Bypass |  |  | 6(7%) |
| Total pancreatectomy |  |  | 2(2%) |
| None |  |  | 43(50%) |
| **Resection margin** |  |  |  |
| R0 |  |  | 12(13%) |
| R1 |  |  | 24(27%) |
| N/A |  |  | 53(60%) |
| **Lymph nodes** |  |  |  |
| Positive |  |  | 51(57%) |
| Negative |  |  | 38(43%) |
| **Differentiation** |  |  |  |
| well |  |  | - |
| Moderate |  |  | 30(34%) |
| Poor |  |  | 21(24%) |
| NA |  |  | 38(42%) |
| **Distant metastasis** |  |  |  |
| Yes |  |  | 28(31%) |
| No |  |  | 61(69%) |
| **UICC stage** |  |  |  |
| 1A |  |  | 5(6%) |
| 1B |  |  | 3(3%) |
| 2A |  |  | 9(10%) |
| 2B |  |  | 35(39%) |
| 3 |  |  | 9(10%) |
| 4 |  |  | 28(32%) |
| **Additional Treatment** |  |  |  |
| Adjuvant chemotherapy |  |  | 29(33%) |
| Palliative chemotherapy |  |  | 27 (30%) |
| Best supportive care |  |  | 19 (21.3%) |
| Unknown |  |  | 14(15.7%) |

Table 1. Characteristics of patients included in the study

|  |  |  |
| --- | --- | --- |
| **Variable** | **Hazard ratio (95% CI)** | **p-value** |
| **PET/CT metrics** |
| SUVmax ≥7.8 <7.8 | 2.11 (1.36-3.29)1.00 | 0.001- |
| SUVmean ≥5.15  <5.15 | 2.07 (1.33-3.21)1.00 | 0.001- |
| MTVcm3 ≥10 <10 | 2.01 (1.30-3.11)1.00 | 0.002- |
| TLG ≥55 <55 | 2.30 (1.47-3.58)1.00 | <0.001- |
| **General** |
| Age ≥ 70  <70 | 1.47 (0.95-2.26)1.00 | 0.082- |
| Sex Female Male | 1.27 (0.82-1.95)1.00 | 0.284- |
| Smoker Never Current Ex | 1.000.99 (0.56-1.75)0.7 (0.42-1.14) | -0.9780.156 |
| Diabetes Yes  No | 0.79 (0.45-1.41)1.00 | 0.431- |
| R status R1 R0 | 1.70 (0.79-3.64)1.00 | 0.175- |
| Lymph nodes Positive Negative | 0.94 (.61-1.44)1.00 | 0.772- |
| Tumour size (mm) ≥30 <30 | 1.58 (1.02-2.44)1.00 | 0.041- |
| Differentiation Poor Moderate | 3.07 (1.65-5.71)1.00 | <0.001- |
| Distant Metastasis Yes No | 3.78 (2.26-6.33)1.0 | <0.001- |
| CA19-9 ≥222 <222 | 1.35 (0.84-2.17)1.00 | 0.217- |

Table2. Univariate analysis for prognostic factors included in the study

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Metric** | **Category** | **Number of deaths** | **Median (95% CI) months** | **1 year survival (95% CI)** | **5 year survival (95% CI)** | **P value** |
| **Overall** | - | 84 | 11 (6-14) | 47% (37-57) | 8% (3-15) | - |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SUVmax** | <7.8 | 41 | 18 (12-26) | 70% (54-81) | 11% (4-23) | 0.001 |
| ≥7.8 | 43 | 6 (4-9) | 24% (13-38) | 4% (0-13) |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SUV mean** | <5.15 | 40 | 18 (11-26) | 66% (50-78) | 11% (4-23) | 0.001 |
| ≥5.15 | 44 | 6 (4-10) | 29% (17-42) | 4% (0-13) |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MTVcm3** | <10 | 41 | 16 (12-25) | 70% (55-82) | 11% (4-23) | 0.002 |
| ≥10 | 43 | 6 (4-9) | 24% (13-38) | 4% (0-13) |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **TLG** | < 55 | 42 | 18 (13-26) | 71% (56-82) | 11% (4-22) | <0.001 |
| ≥55 | 42 | 5 (4-8) | 23% (12-36) | 5% (0-13) |

Table 3. Survival information for overall cohort and each metric split according to their median values.

|  |  |  |
| --- | --- | --- |
| **Variable** | **HR** | **p- value** |
| Metastasis | 3.37 (1.97 – 5.77) | <0.001 |
| TLG\* | 2.00 (1.26 – 3.18) | 0.004 |
|  |  |  |
| SUVmax\* | - | 0.889 |
| MTVmc3\* | - | 0.515 |
| SUVmean\* | - | 0.438 |
| Sex | - | 0.263 |
| Age | - | 0.154 |
| Tumour size | - | 0.791 |

Table 4. Multivariate analysis for prognostic factors including the overall study cohort. \* dichotomised based on their median valuables, HR for non-significant factors was not estimable based on used algorithm.

|  |
| --- |
|  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **PET metric** | **Risk group** | **No pts** | **Median Survival months (95%CI)** | **1 year survival % (95%CI)** | **Hazard ratio (95% CI)** | **P-value** |
| **In the presence of Metastasis:** |
| A1 | TLG | High | 21 | 4 (3-5) | 0%  | 3.19 (1.05-9.68) | 0.041 |
| Low | 7 | 11 (1-14) | 43% (10-73) |
| B1 | SUVmax | High | 19 | 4 (3-6) | 5% (0-20) | 1.19 (0.53-2.68) | 0.677 |
| Low | 9 | 5 (1-13) | 22% (3-51) |
| C1 | SUVmean | High | 19 | 4 (3-6) | 11% (2-28) | 0.95 (0.42-2.13) | 0.900 |
| Low | 9 | 5 (1-11) | 11% (0-39) |
| D1 | MTVcm3 | High | 21 | 4 (3-5) | 0%  | 2.67 (0.90-7.92) | 0.077 |
| Low | 7 | 6 (1-14) | 43% (10-73) |
| **In the absence of Metastasis:** |
| A2 | TLG | High | 23 | 10 (5-14) | 43% (23-62) | 1.78 (1.03-3.08) | 0.040 |
| Low | 38 | 22 (14-30) | 76% (59-87) |
| B2 | SUVmax | High | 26 | 9 (4-12) | 38% (20-56) | 2.04 (1.19-3.51) | 0.010 |
| Low | 35 | 25 (16-34) | 83% (66-92) |
| C2 | SUVmean | High | 26 | 10 (4-13) | 42% (23-60) | 2.06 (1.20-3.52) | 0.008 |
| Low | 35 | 25 (16-30) | 80% (63-90) |
| D2 | MTVcm3 | High | 24 | 10 (5-16) | 46% (26-64) | 1.55 (0.9-2.67) | 0.111 |
| Low | 37 | 20 (14-30\_ | 76% (58-87) |

Table 5. Multivariate sub-group analysis based on the presence or absence of distant metastasis

|  |  |  |
| --- | --- | --- |
| **Model** | **C statistic (se)** | **AIC** |
| **Univariate** |
| SUVmax | 0.59 (0.03) | 612 |
| TLG | 0.60(0.02) | 610 |
| MTVcm3 | 0.59 (0.03) | 614 |
| SUVmean | 0.59 (0.03) | 613 |
| **Multivariate** |
| Metastasis + SUVmax | 0.66 (0.02) | 597 |
| Metastasis + TLG | 0.68 (0.02) | 594 |
| Metastasis + MTVcm3 | 0.67 (0.03) | 597 |
| Metastasis + SUVmean | 0.65 (0.02) | 597 |

Table 6. Survival models based on C-statistic and Akaike information criterion







Figure 1. Kaplan Meier survival curves of 18 FDG PET-CT prognostic parameters dichotomised according to their respective median values