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Research Article

The Prognostic Value of ^{18}F-Flurodeoxyglucose Positron Emission Tomography/Computed Tomography Parameters in Patients with Adenocarcinoma of the Pancreas Treated with Pancreaticoduodenectomy in Western Australia: A Retrospective Study

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Abstract

Background: The use of ^{18}F-Flurodeoxyglucose (^{18}F-FDG)- Positron Emission Tomography/Computed Tomography (PET/CT) to determine the prognosis of pancreatic cancer remains unclear. Identifying prognostic factors in the pre-operative setting is important to ensure surgery is appropriate for the individual. The maximum standardised uptake value (SUVmax) obtained from ^{18}F-FDG-PET/CT scans is the commonest parameter for pre-operative lesion assessment. Two alternative parameters: Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG) are recent measurements for pancreatic cancer. This retrospective cohort study was performed to measure the association between preoperative ^{18}F-FDG uptake and prognosis after pancreaticoduodenectomy. **Methods:** Analysed data (2009 to 2018) obtained from medical database of all patients with pancreatic cancer at two Perth hospitals were analysed. Inclusion criteria were histologically or cytologically proven malignant adenocarcinoma that was treated with surgery. Excluded were other histological pancreatic cancer variants and patients without pre-operative ^{18}F-FDG PET/CT scans. For statistical analysis, SUVmax, MTV and TLG values of the cancers were obtained with tumour size, stage and grade. Overall Survival (OS) and Disease-Free Survival (DFS) were calculated using the Kaplan-Meier method with log rank analysis. Cut-off values for continuous ^{18}F-FDG parameters were determined by Receiver Operating Characteristics (ROC). **Results:** 48 patients' records were analysed. An SUVmax value > 3.5, MTV(2.5) > 2 or TLG(40%) > 6 correlated significantly with poorer OS and DFS ($P < 0.05$). **Conclusion:** The study suggests that SUVmax, TLG(40%) and MTV(2.5) may be utilised as pre-operative tool for determining if surgery is appropriate. These results need to be validated with a larger cohort.

Keywords: MTV; Pancreatic carcinoma; PET/CT; SUVmax; TLG

Introduction

Pancreatic cancer is the 5th leading cause of cancer death in Australia with an overall five-year survival of approximately 7.7% [1]. Many patients are asymptomatic in the early stages and are often diagnosed late in the disease process [2]. Surgical resection is typically the treatment of choice with a significant improvement in prognosis but only 15-20% of people are appropriate for resection, and of these, 15% live to five years [1]. Resectability depends on the extent of local and systemic disease, with the presence of the latter deemed an absolute contraindication to curative surgery [3]. A Queensland study of 121 patients undergoing curative surgery highlighted the importance of preoperative assessment of resectability [4]. Patients with clear margins had a one-year survival of 85% compared to 50% in those with positive margins [4]. Surgical resection is recommended for tumours which are localised with no metastases, no significant comorbidities, good status (based on Eastern Co-operative Oncology Group (ECOG) score), no evidence of superior mesenteric vein or portal vein distortion and clear fat planes around these vessels including the celiac axis [5]. Definitions become less clear when tumours have "borderline" margins making the decision for surgery difficult. Patients with borderline resectable disease represent an imprecise spectrum encompassing radiologically and technically resectable and unresectable disease [6]. The issue of margin status is compounded by significant potential morbidity and poor patient outcomes associated with curative surgery. Tumours at surgical margins (R2 resection) are not appropriate for surgery as outcomes are comparable if the patient did not undergo surgery. Therefore subsequent poor quality of life due to a failed oncological clearance has no palliative benefit to the individual [3].

Currently CA 19-9 is the only biological predictor of prognosis but is not specific. Other investigations like MRI, CT and laparoscopy are limited to only providing the anatomical assessment of tumours meaning there is a risk of unnecessary operations on biologically aggressive cancers. Recently though, many clinicians utilise the glucose analogue, ^{18}F-Flurodeoxyglucose (^{18}F-FDG) as a tracer of Positron Emission Tomography (PET)/ Computed Tomography (CT) scans.

^{18}F-FDG PET/CT assessment of pancreatic cancer is relatively new but widely used for other cancers such as breast, lung and colorectal. The maximum Standardised Uptake Value (SUVmax) obtained from ^{18}F-FDG PET/CT scans is the commonest way of measuring tumour activity [7]. SUVmax is a method to quantify this uptake but does not reflect volumetric or the heterogeneity [8]. Clinicians therefore alternatively use the same ^{18}F-FDG PET/ CT scans to generate volumetric parameters such as Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG). These measures indicate the metabolic volume and activity of the tumour. There is limited knowledge of SUV, MTV and TLG in prognosticating pancreatic cancer and evaluating biology [9]. This study is aimed at analysing how these parameter values correlate to the prognosis of pancreatic adenocarcinoma (the commonest form of malignancy) and if so, we want to know what cut-off values are best at assessing disease burden in the preoperative setting.

Methods

This study was performed in accordance with the ethical standards established in the appropriate version of the Declaration of Helsinki (as revised at the 64th World Medical Association Assembly, 2013) and conducted under the ethics approval by the South Metropolitan Health Service Human Research Ethics Committee (HREC ref:15-040-1) and the University of Notre Dame Human Research Ethics Committee (HREC ref:018068F).

Patients

This retrospective study evaluated all patients who underwent pancreaticoduodenectomy for pancreatic cancer through the Hepatobiliary Unit of the Western Australian South Metropolitan Health Service (2009-2017). The following inclusion criteria were applied: a) patients diagnosed with malignant adenocarcinoma by histology/cytology and b) underwent surgical resection. Patients were excluded from the study if they were a) diagnosed with other histological variants such as pancreatic neuroendocrine, intraductal papillary mucinous neoplasm and cholangiocarcinoma, and b) had no pre-operative ^{18}F-FDG PET/CT scan. In total, 48 patients were found to meet the selection criteria. All patients underwent pancreaticoduodenectomy under the same team of hepato-biliary surgeons, comprised of three fellowship-trained hepato-biliary clinicians at Fremantle Hospital and Fiona Stanley Hospital. The same surgical technique was performed in all patients.

Data Collection

All health records were obtained manually, extracted and computed into REDCap (Research Electronic Data Capture) electronic database under the management of The University of Western Australia. REDCap is a secure web-based application that provides an interface for validated data entry, tracking data input and manipulation, and for exporting to external statistical packages. Progress notes, histopathology and biochemical results were obtained from a database widely used by the Western Australian Health Department.

Clinical Data

Information regarding patients' age, gender, surgical date, date of death if deceased, any post-operative cancer recurrence and any presence of metastasis were assessed. The tumour pathology and type were evaluated.

^{18}F-FDG PET/SCAN

These parameters were retrievable from a radiological database (Syngo.Via, Version VB20). With the aid of a nuclear physician, all PET/CT scans were reviewed. Circular Regions Of Interest (ROI) were manually placed over areas of abnormal uptake in the pancreas. The software calculated the ROIs to give an SUVmax value. MTV(2.5) measured tumour regions greater or equal to an SUVmax of 2.5 while MTV(40%) were tumour regions equal or over 40% SUVmax. The product of SUVmean and MTV(x) gives TLG(x). In cases where a primary tumour was difficult to interpret, the original scan report was referred to clarify if there was a true increase or an artificial stent related uptake.

Tumour grade(G)

The following grading was recorded: G1-well differentiated (low grade), G2: moderately differentiated, G3-poorly differentiated (high grade) and G4-undifferentiated (high grade). For this study, G1 was labelled as Group 1 and G2 as Group 2. G3 and G4 were combined and labelled as Group 3.

Tumour Staging

The American Joint Cancer Committee (AJCC) was used for tumour staging.(5) For this study, "Early" group encompassed tumours classified 1a and 1b. Tumours staged at 2a and beyond were grouped as "Advance". Tumour sizes were collected and categorised as follows: S1: ≤ 20mm, S2: 20mm < X ≤40mm and S3: > 40mm.

Primary/Secondary Outcomes

Primary: Overall Survival (OS) is defined as length of time (days) patient is alive after surgery. Secondary: Disease Free Survival (DFS) is defined as time (days) patient is metastasis-free after surgery. Recurrence is defined as radiological evidence of intra-abdominal soft tissue around the surgical site or of distant metastasis.

Statistical Analysis

Patient characteristics (age, gender) and clinical presentations (grade, size, AJCC, presence of invasion) were described as percentages. The ^{18}F-FDG parameter results were initially described by mean and SD. These Continuous variables were compared between groups with one-way ANOVA. If any significance were obtained, then post hoc analysis (Tukey's Test) would follow. Kaplan-Meier survival method with log rank analysis was utilised to study OS for age, sex, size, grade, AJCC, PNI and LVI. DFS was obtained for all variables except age and sex. Cut-off values for continuous ^{18}F-FDG parameters were determined by Receiver Operating Characteristics (ROC). The cut-off points established for SUVmax, MTV(2.5), TLG(2.5), MTV(40%) and TLG(40%) were 3.5, 2,10.82, 3.9 and 6 respectively. These corresponded to a sensitivity of at least 70% for the detection of Advance stage according to the AJCC.

OS and DFS statistics were analysed at these cut-off values with the Kaplan-Meier survival method and log rank calculation. ANOVA analysis was also performed to evaluate the relationship of the mean ^{18}F-FDG values with tumour sizes and grades. All statistical tests were two-tailed with P≤ 0.05 indicating statistical significance. Analysis was performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, N.Y., USA).

Results

A total of 48 patients with malignant adenocarcinoma were analysed. The average OS was 5.02 years (95% Confidence Interval (CI) 4.00-6.04). The one-year and three-year survival rates were 83% and 59% respectively. No further deaths occurred between the third- and fifth-year mark. The average age of the participant sample was 64.92 years (95% CI 62.45-67.38) and 58.3% were male. Table 1 describes the patients' clinical characteristics. Gender and age were not correlated to OS according to the Kaplan-Meier survival curve ($p > 0.05$). This was also observed for DFS. Mean OS for under 65 years and over 65 were 1751.47 days (95% CI 1202-2299.96) and 1584.03 days (95% CI 1191.07-1977.00) respectively. One-way ANOVA analysis was performed to compare the tumour properties with each ^{18}F-FDG PET/CT parameter (Table 2). The only tumour presentation that was statistically significant with the levels of the SUVmax, TLG and MTV was the size ($p < 0.05$). Post hoc test was subsequently applied to analyse if there were any differences between the three categories. For SUVmax, Tuckey's Test showed no significant difference between S1 and S2 but significant differences between S1 with S3 and S2 with S3 ($p = 0.00$). This was also observed in TLG(2.5) and TLG(40%). For pre-op MTV(2.5) and MTV(40%), The Kaplan-Meier survival analysis indicated no strong association in tumour size with differences in OS or DFS. The presence of LVI and PNI (Table 3) had a negative impact on OS but was statistically insignificant for DFS ($p > 0.05$). The mean OS was less in the Early group (1079.75 days) compared to the Advance group (1737.77 days) with one-year survival at 75% in the Early compared to 85% in Advance. The Early group did not experience further deaths beyond the first year. The Advance group continued to show deterioration and by the three-year interval only 54% remained alive. The initial sharp drop in OS for the Early group was secondary to a surgical complication death.

OS and DFS were statistically significant ($P < 0.05$) when patients were categorised either above or below the cut-off points (Figure 1A-J) for all of the ^{18}F-FDG parameters except TLG(2.5) and MTV(40%). When OS and DFS was observed at the one-year, three-year and five-year interval, patients who were below the established cut-off had better prognosis. In evaluating the pattern

and nature of ^{18}F-FDG uptake with respect to tumour size and histological picture, each size category was stratified to the appropriate grade. The mean ^{18}F-FDG parameter values for the combined tumour size and grade were analysed and plotted (Figure 2A-2E).

Characteristic	Number of patients (%)
Number of patients	48
Sex	
Male	28 (58.3%)
Female	20 (41.7%)
Age (years)	
<65	22 (46%)
≥65	26 (54%)
Lympho-vascular Invasion	
Yes	24 (50%)
No	24 (50%)
Peri-neural Invasion	
Yes	30
No	18
AJCC* Stage	
Early: 1a/1b	8 (16.7%)
Advance: ≥2a	40 (83.3%)
Size	
S1: ≤20mm	14 (29.2%)
S2:20mm<X≤40mm	24 (50%)
S3: >40mm	10 (20.8%)
Tumour Grade	
Group 1: G1	10 (20.8%)
Group 2: G2	31 (64.5%)
Group 3: G3/G4	7 (14.7%)
SUVmax†	
≤3.5	15 (31.3%)
>3.5	33 (68.7%)
TLG‡ (2.5)	
≤10.8	16 (33.33%)
>10.8	32 (66.66%)
TLG (40%)	

≤ 6	15 (31.3%)
>6	33 (68.7%)
MTV§ (2.5)	
≤ 2	15 (31.3%)
>2	33 (68.7%)
MTV (40%)	
≤3.9	18 (37.5%)
>3.9	30 (62.5%)
*AJCC: American Joint Cancer Committee; † SUVmax: Standardised Uptake Value; ‡ TLG: Total Lesion Glycolysis; § MTV: Metabolic Tumour Volume	

Table 1: Baseline characteristics of evaluable patients.

Tumour Characteristic		Pre-Op SUVMAX*	Pre-Op TLG† (2.5)	Pre-Op MTV‡ (2.5)	Pre-Op TLG(40%)	Pre-Op MTV(40%)
Tumour Grade						
Group 1: G1	Mean	7.18	130.19	21.22	83.25	10.45
	SD	8.34	206.78	27.42	120.08	11.07
Group 2: G2	Mean	7.46	85.85	15.26	52.14	7.47
	SD	8.37	158.16	20.4	94.28	7.88
Group 3: G2/G3	Mean	6.77	85.04	22.04	56.92	12.74
	SD	3.38	86.45	21.02	46.31	9.11
P Value= (Combined Groups)		0.98	0.743	0.641	0.67	0.3
Tumour Stage (AJCC§)						
Advance: ≥2a	Mean	8.09	106.44	19.63	65.8	9.86
	SD	7.94	168.82	22.58	99.02	8.91
Early: 1a/1b	Mean	3.36	37.61	6.78	26.92	3.89
	SD	5.28	86.86	13.95	58.75	6.74
P Value= (Combined Groups)		0.12	0.27	0.129	0.29	0.08
Tumour Size						
S1: ≤20mm	Mean	3.67	12.32	2.97	8.38	1.74
	SD	4.72	18.01	4.2	11.63	2.37
S2: >20mm,≤40mm	Mean	7.08	82.01	19.03	51.94	10.43
	SD	5.18	83.22	17.77	46.08	8.35
S3: >40mm	Mean	12.91	241.78	34.13	148.33	15.08

	SD	12.46	282.27	31.75	166.4	9.55
P Value= (Combined Groups)		0.012	0.001	0.001	0.001	0
LVI**						
Absent	Mean	7.06	87.61	14.28	53.81	6.9
	SD	9.32	167.22	20.15	104.21	9.3
Present	Mean	7.54	102.33	20.7	64.83	10.82
	SD	5.91	154.64	23.33	84.8	8.024
P Value= (Combined Groups)		0.83	0.75	0.31	0.69	0.13
PNI††						
Absent	Mean	9.06	135.37	20.7	82.18	9.27
	SD	10.36	223.7	25.89	135.74	9.76
Present	Mean	6.24	70.73	15.56	45.6	8.62
	SD	5.53	101.39	19.16	55.19	8.36
P Value= (Combined Groups)		0.22	0.18	0.44	0.2	0.81
Total	Mean	7.3	94.97	17.49	59.32	8.86
	SD	7.72	159.51	21.8	94.15	8.82

*SUVMax: Standardised Uptake Value (Maximum); † TLG: Total Lesion Glycolysis; ‡ MTV: Metabolic Tumour Volume; § AJCC: American Joint Cancer Committee; **LVI: Lympho-vascular Invasion; ††PNI: Peri-neural Invasion

Table 2: Tumour Characteristics with Respect to PET/CT Scan Parameters.

Characteristic	Kaplan-Meier Analysed with Log Rank OS*		Kaplan-Meier Analysed with Log Rank DFS†	
	Average Days (95% CI) SEM‡	P	Average Days (95% CI) SEM	P
Lympho-vascular Invasion				
Yes	758.06 (577.17-938.95) SEM: 92.29	0.005	761.93 (912.65-1314.73) SEM: 98.04	0.235
No	2204.32 (1763.79-2644.85) SEM: 224.76		1227.26 (964.73-1489.79) SEM:133.94	
Peri-neural Invasion				
Yes	1363.82 (890.28-1837.37) SEM: 241.61	0.003	963.61(708.69-1218.53) SEM:130.06	
No	2150.72 (1912-2389) SEM: 121.75		1189.95 (955.65-1424.252) SEM: 119.54	0.051
AJCC§ Stage				
Early: 1a/1b	1079.75 (671.15-1488.35) SEM: 208.47	0.54	692.14 (236.72-1147.56) SEM: 161.01	0.046
Advance: ≥2a	737.77 (1312.80-2162.76) SEM: 216.83		579.6 (464.31-694.89) SEM: 58.83	
Size				
S1: ≤20mm	1932.38(1259.08-2605.68) SEM: 343.52	0.85	1299.12 (963.54-1634.69) SEM: 171.21	0.4
S2: >20mm, <40mm	1509.97 (1071.97-1947.97) SEM: 223.47		757.93 (562.34-953.53) SEM: 99.79	

S3: >40mm	1254.84 (839.25-1670.43) SEM: 212.04		937.40 (570.25-1304.55) SEM: 187.32	
Tumour Grade				
Group 1: G1	908.00 (608.18-1207.82) SEM: 152.97	0.93	1007.88 (754.91-1260.84) SEM: 129.06	0.005
Group 2: G2	1730.31(1256.38-2204.23) SEM: 241.80		1066.83 (813.37-1320.29) SEM: 129.32	
Group 3: G3/G4	1572.93 (409.71-769.91) SEM: 409.71		533.86 (289.95- 777.76) SEM: 124.44	
SUVmax**				
≤3.5	2448.49 (2024.50-2872.50) SEM: 216.33	0.018	1411.37 (1169.44-1653.30) SEM: 123.43	0.04
>3.5	281.48 (903.16-1659.81) SEM:193.02		874.09 (664.44-1083.73) SEM: 106.96	
TLG†† (2.5)				
≤10.8	2312.77 (1839.13-2786.43) SEM:241.66	0.058	1340.47 (1076.76-1604.19) SEM 134.55	0.1
>10.8	1312.87 (927.76-1697.98) SEM: 196.49		894.10 (681.16-1107.03) SEM: 108.64	
TLG (40%)				
≤ 6	2448.49 (2024.50-2872.50) SEM: 216.33	0.018	1411.37 (1169.44-1653.30) SEM: 123.43	0.04
>6	1281.48 (903.16-1659.81) SEM:193.02		1281.48 (903.16-1659.81) SEM:193.02	
MTV‡‡ (2.5)				
≤2	2448.49 (2024.50-2872.50) SEM: 216.33	0.018	1411.37 (1169.44-1653.30) SEM: 123.43	0.04
>2	1281.48 (903.16-1659.81) SEM:193.02		874.09 (664.44-1083.73) SEM: 106.96	
MTV (40%)				
≤3.9	2177.75 (1663.90-2691.62) SEM: 262.17	0.12	1346.08 (1089.67-1602.49) SEM: 130.82	0.06
>3.9	1348.99 (957.21-1740.78) SEM:199.89		883.64 (668.07-1099.20) SEM: 109.98	

*OS: Overall Survival; †DFS: Disease Free Survival; SEM: Standard Error of Mean; §AJCC: American Joint Cancer Committee **SUVmax: Standardised Uptake Value; ††TLG: Total Lesion Glycolysis; ‡‡MTV: Metabolic Tumour Volume

Table 3: Correlation Between Variables and Overall Survival.

Figures 1A-1J: Overall Survival and Disease-free Survival for All ^{18}F-FDG Parameters

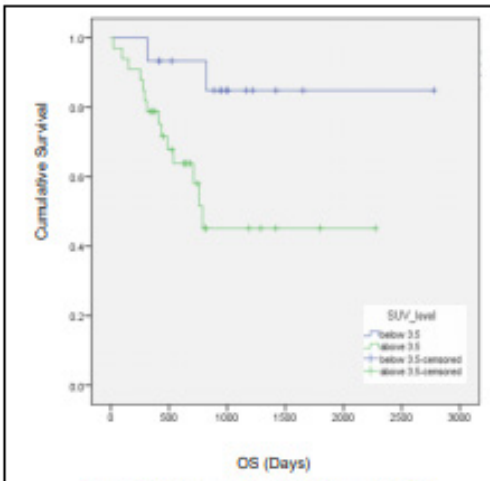

Figure 1A: Preoperative SUVMax with OS

	Below 3.5	Above 3.5
One-Year OS	93.30%	78.80%
Three-Year OS	84.80%	45.20%
Five- Year OS	84.80%	45.20%

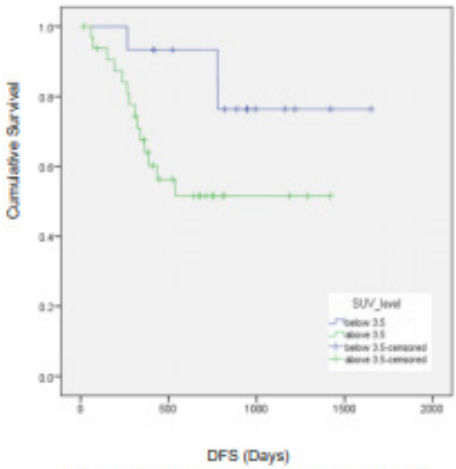

Figure 1F: Preoperative SUVMax with DFS

	Below 3.5	Above 3.5
One-Year DFS	93.30%	64.00%
Three-Year DFS	76.40%	51.60%
Five- Year DFS	-	-

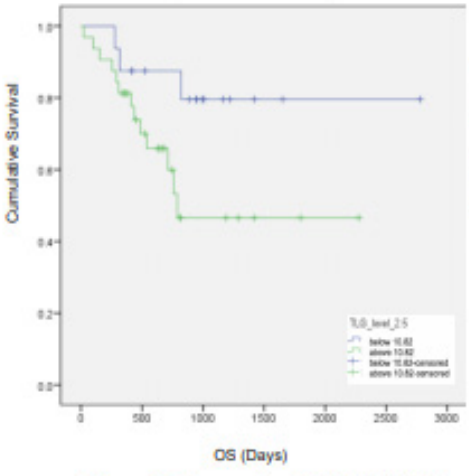

Figure 1B: Preoperative TLG (2.5) with OS

	Below 10.82	Above 10.82
One-Year OS	87.50%	81.30%
Three-Year OS	79.50%	46.60%
Five- Year OS	79.50%	46.60%

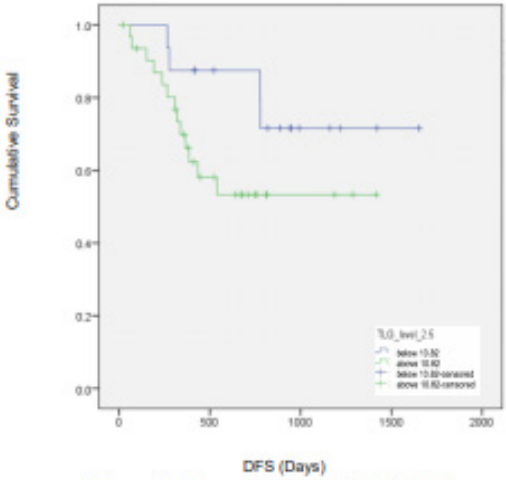

Figure 1G: Preoperative TLG(2.5) with DFS

	Below 10.82	Above 10.82
One-Year DFS	87.50%	66.20%
Three-Year DFS	71.60%	53.3%
Five- Year DFS	-	-

Figures 1A-1J: Overall Survival and Disease free Survival for All ^{18}F-FDG Parameters

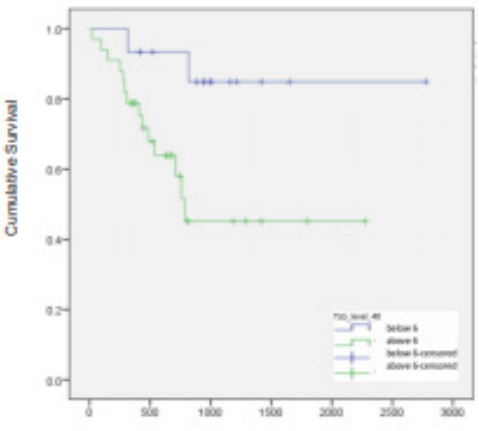

Figure 1C: Pre-Operative TLG(40%) with OS

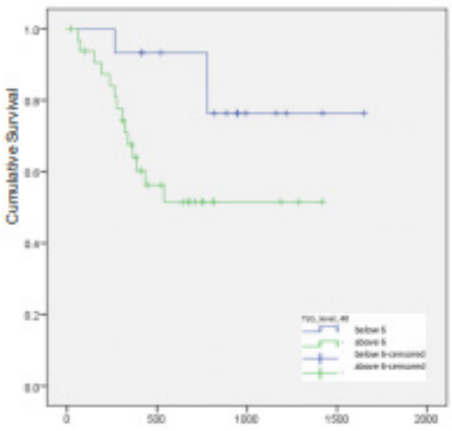

Figure 1H: Pre-Operative TLG(40%) with DFS

	Below 6	Above 6
One-Year OS	93.30%	78.80%
Three-Year OS	84.80%	45.20%
Five- Year OS	84.80%	45.20%

	Below 6	Above 6
One-Year DFS	93.30%	64.00%
Three-Year DFS	76.40%	51.60%
Five- Year DFS	-	-

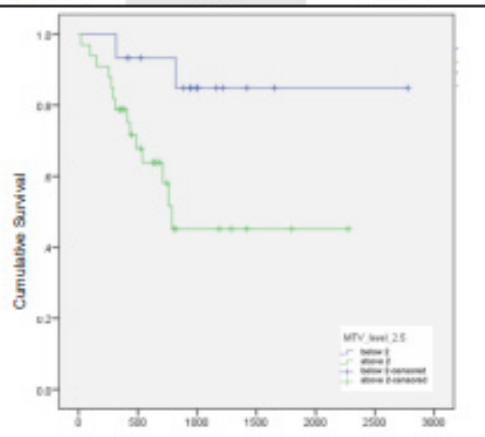

Figure 1D: Pre-Operative MTV(2.5) with OS

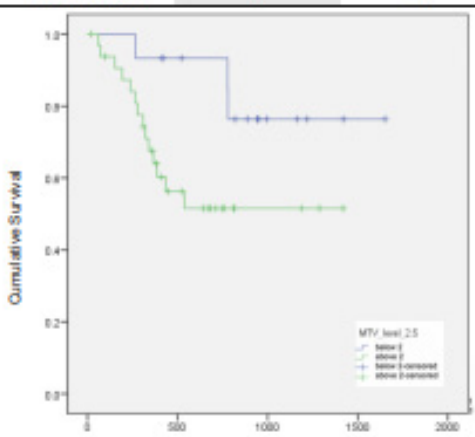

Figure 1I: Pre-Operative MTV(2.5) with DFS

	Below 2	Above 2
One-Year OS	93.30%	78.80%
Three-Year OS	84.80%	45.20%
Five- Year OS	84.80%	45.20%

	Below 2	Above 2
One-Year DFS	93.30%	64.00%
Three-Year DFS	76.40%	51.60%
Five- Year DFS	-	-

Figures 1A-1J: Overall Survival and Disease-free Survival for All ^{18}F-FDG Parameters

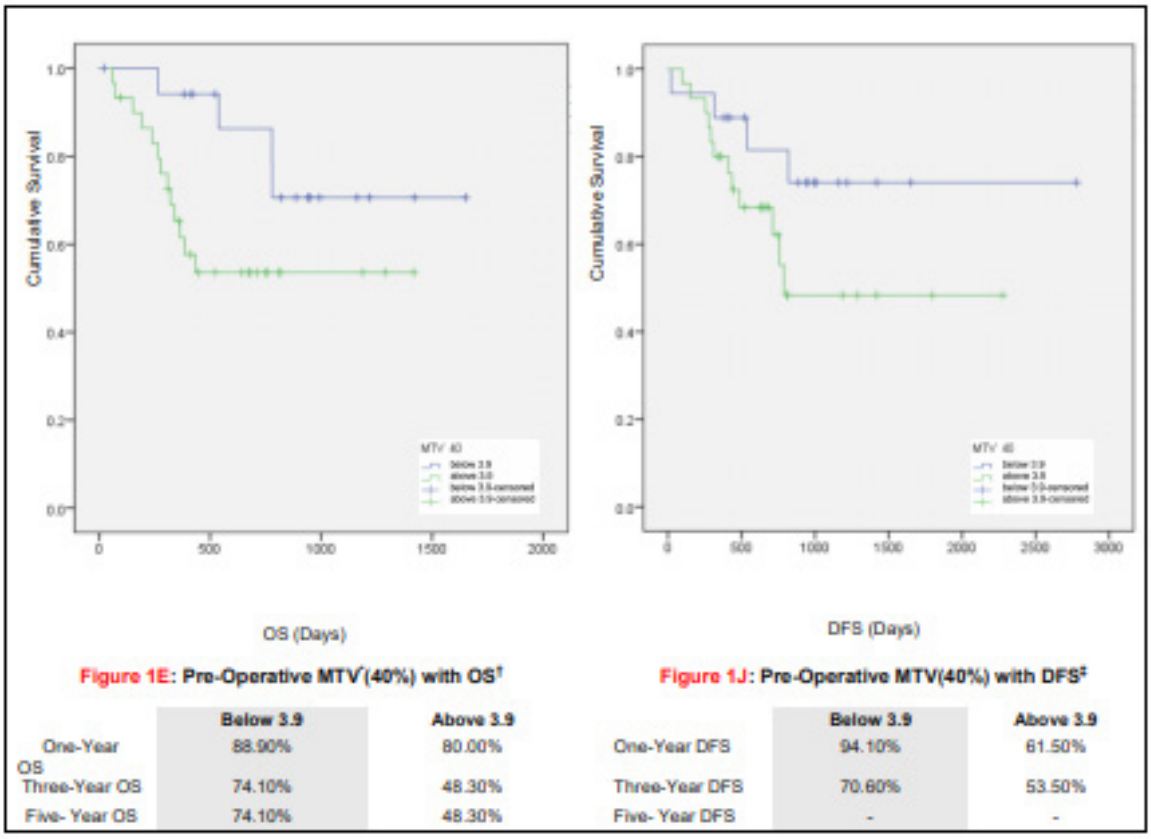

Figure 1E: Pre-Operative MTV (40%) with OS†

	Below 3.9	Above 3.9
One-Year OS	88.90%	80.00%
Three-Year OS	74.10%	48.30%
Five- Year OS	74.10%	48.30%

Figure 1J: Pre-Operative MTV(40%) with DFS‡

	Below 3.9	Above 3.9
One-Year DFS	94.10%	61.50%
Three-Year DFS	70.60%	53.50%
Five- Year DFS	-	-

*TLG: Total lesion Glycolysis; *MTV: Metabolic Tissue Volume; † OS: Overall Survival

‡ DFS: Disease Free Survival

Figure 1: Kaplan-Meier Survival Curve for Overall Survival (OS) and Disease-Free Survival (DFS) for all 18F-flurodeoxyglucose (18F-FDG) parameters. Comparison of OS between preoperative A: maximum standardised uptake (SUVmax) below 3.5 with above 3.5, B: total lesion glycolysis (2.5) (TLG(2.5)) below 10.82 with above 10.82, C: TLG(40%) below 6 with above 6, D: metabolic tissue volume(2.5) (MTV(2.5)) below 2 with above 2, E: MTV(40%) below 3.9 with above 3.9. Comparison of DFS between preoperative F: SUV(max) below 3.5 with above 3.5, G: TLG(2.5) above 10.82 with below 10.82, H: TLG(40%) below 6 to above 6, I: MTV(2.5) below 2 and above 2, J: MTV(40%) below 3.9 to above 3.9.

Figures 2: Tumour Size (≤ 20mm, 20 < X ≤ 40mm and > 40mm) and Grade and Respective Mean ^{18}F-FDG Parameter Value

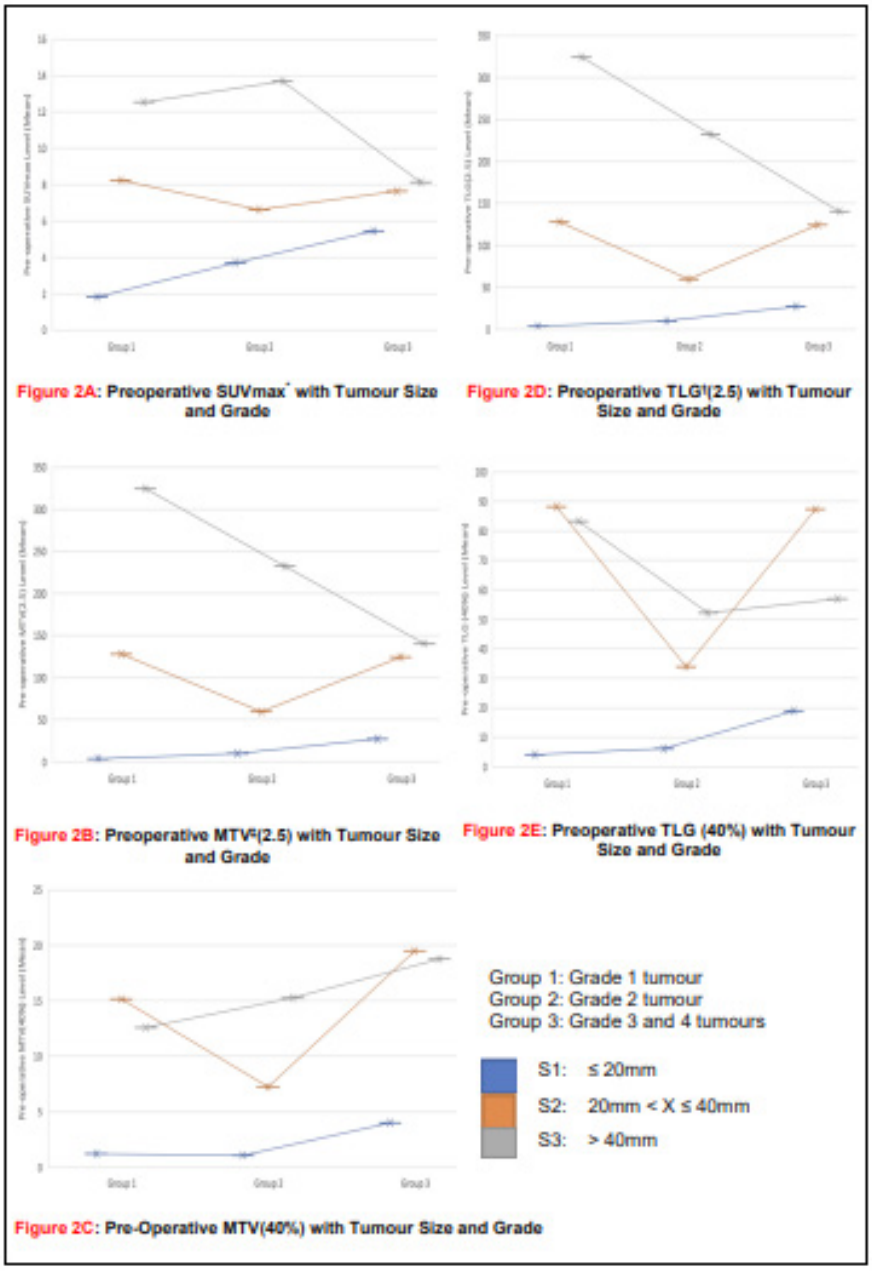

Figure 2A: Preoperative SUVmax* with Tumour Size and Grade

Figure 2D: Preoperative TLG†(2.5) with Tumour Size and Grade

Figure 2B: Preoperative MTV‡(2.5) with Tumour Size and Grade

Figure 2E: Preoperative TLG (40%) with Tumour Size and Grade

Figure 2C: Pre-Operative MTV(40%) with Tumour Size and Grade

*SUVmax: Standardised Uptake Value (Maximum); † TLG: Total Lesion Glycolysis; ‡ MTV: Metabolic Tumour Volume.

Figure 2: Relationship between tumour size (S1:< 20mm, S2:20mm ≤ X <40mm, S3: >40mm) and tumour grade (group 1- grade1 tumour, group 2- grade 2 tumour and group - :grade 3 and 4) versus mean preoperative A: maximum standardised uptake (SUVmax), B: metabolic tissue volume (2.5) (MTV(2.5)), C:MTV(40%), D: total lesion glycolysis (2.5) (TLG(2.5)), E: TLG(40%). Number of patients in each category: S1/Group 1: three, S1/Group 2: eight, S1/Group 3: three, S2/Group 1: 5, S2/Group 2: 16, S2/Group 3: three, S3/Group 1: two, S3/Group 2: seven, S3/Group 4: one.

Discussion

The use of ^{18}F-FDG PET/CT is relatively new in Western Australia. Its use for diagnosis, staging, evaluating response to treatment and detecting recurrence in pancreatic cancer is becoming more accepted around the world and studies have reported its clinical role in predicting prognosis and guiding clinicians to tailor effective treatment [9]. The literature suggests that a high SUV value at diagnosis is more strongly correlated with poor survival than a low SUV value [9]. This finding has been reported in other forms of cancers such head and neck cancers, skin, bone and hepatocellular carcinoma [10]. MTV and TLG have been considered as superior alternative methods since these capture the volumetric metabolic activity and thus reflect the tumour burden. Nevertheless, their use in pancreatic cancer have been a novelty with many studies consisting of small sample sizes resulting in limited statistical power. A meta-analysis published in 2017 [9] found that high SUVmax values were associated with poor OS and DFS. The authors indicated that the cut-off values for SUVmax ranged from 3.4-6.8 and acknowledged further research was needed to establish appropriate thresholds in delineating poor OS and DFS. The cut-off values set in this retrospective study were able to reflect differences in OS and DFS with TLG(40%), MTV(2.5) and SUVmax to be most statistically significant. Not many studies have explored the calibration setting for MTV and TLG with respect to pancreatic cancer thus choice between 2.5 or 50% requires further exploration.

In contrast to our findings, a study by Wang, et al. [11] reported that tumour size was a predictor of poor prognosis. Despite tumour size being statistically significant with the level of all ^{18}F-FDG parameters, this variable was not strongly associated with OS or DFS. An interesting relationship between mean ^{18}F-FDG uptake with tumour size and grade can be seen in Figures 2A-2E. One may hypothesise that tumours in Group 2, having a larger volume of neoplastic cells, were more in a transitional phase where mixtures of high metabolic and low metabolic regions conglomerate. This may have led to an overall drop in ^{18}F-FDG uptake. The literature suggests malignant cells have increased glucose uptake due to the increased expression of GLUT-1 [12] and glycotic enzymes. However, other emergent studies on ^{18}F-FDG uptake paint a different story. Macroscopic solid cancers have a complex microenvironment comprising of well-defined regions of non-cancerous stroma, cancer cells and necrosis [13]. Cancer cells may divide and differentiate depending on the environment that they are in. Cancer cells close to blood vessels are well oxygenated and proliferate at a high rate [13]. Cancer cells that are far away from blood vessels or close to areas of necrosis are more exposed to hypoxic conditions and have a low proliferation rate [14]. Cellular proliferation and hypoxia are independent entities but the process of tumour hypoxia is secondary to cancer cells proliferating faster than angiogenesis. Studies have shown that proliferating malignant cells located in well oxygenated regions have a lower ^{18}F-FDG uptake compared to hypoxic zones [15]. In a malignant lesion, areas of low

^{18}F-FDG uptake may either indicate a well proliferating state or necrosis. This may explain the unusual curves found for TLG. A high ^{18}F-FDG uptake may mean the cancer cells are in a low proliferating rate but a lack of uptake does not equate to the absence of cancer cells [13]. Further research is necessary regarding TLG and clinicians may need to interpret TLG with caution. Areas of well oxygenated zones may be due to an early phase perfusion and a balanced metabolism process [13]. Thus as cancer cells become more proliferative, aggressive and encroach on rich blood supplied regions, the ^{18}F-FDG value may be low. This will have significant implications since clinicians need to recognise that ^{18}F-FDG is not a specific cancer-avid PET tracer and may impact on treatment monitoring. This retrospective study has a number of limitations with its retrospective nature and small sample size. This is an ongoing trial and sample size will continue to increase with the expansion into a third centre. This study did not explore or investigate if adjuvant and neoadjuvant therapy were completed which are known to influence OS and DFS.

We recommend that if a patient's tumour burden encompasses one of the following on imaging:

- SUVmax value > 3.5
- MTV(2.5) > 2 or
- TLG(40%) > 6

this correlated significantly with poorer OS and DFS ($P < 0.05$) and therefore palliative care may be more appropriate. Surgical intervention should be approached with caution with open discussion with the patient.

In conclusion, patients with higher cut-off values in SUVmax, MTV(2.5) and TLG(40%) as set in the study had poorer OS and DFS. Therefore, these parameters may facilitate in prognostication and guide decision for surgery. This may ensure resection is only reserved for patients who are most likely to benefit from treatment. Additional multicentre studies are required to further understand the prognostic value of ^{18}F-FDG and ascertain the optimal calibration for pancreatic cancer.

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