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Using Total Lesion Glycolysis as Prognostic Factor for Locally Advanced Pancreatic Cancer Diagnosed by ^{18}F-FDG PET/CT

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METABOLIC parameters of maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) are recognized as prognostic indicators for survival for various cancers types. Their role in predicting outcomes for pancreatic cancer remains underexplored. This study conducted to examining the predictive value of SUVmax, TLG and MTV on overall survival (OS) in 60 pancreatic cancer patients diagnosed with pathological TNM stages I and II, utilizing ^{18}F-FDG PET images obtained pre-treatment. In this study, the analysis revealed that TLG exhibited superior sensitivity in predicting OS compared to MTV, like to SUVmax. Univariate and multivariate analyses, TLG emerged as an exclusive independent prognostic marker for OS (hazard ratio [HR] 2.04, 95% confidence interval [CI] 175- 2.61, *P*=0.002; HR 4.04, 95% CI 1.05-6.61, *P*=0.04, respectively). These findings suggested that TLG's role as an independent prognostic indicator for OS and highlight its superior predictive capability compared to MTV in patients with locally advanced pancreatic cancer (LAPC) pre-treatment.

Keyword: ^{18}F-FDG PET, Pancreatic Cancer, Survival Analysis, Total Lesion Glycolysis, Prognosis.

Introduction

Pancreatic cancer (PCa) is a formidable malignancy characterized by its aggressive nature and often late-stage diagnosis. Emerging from the tissues of the pancreas, an essential organ involved in digestion and blood sugar regulation, this cancer type presents significant challenges in terms of detection, treatment, and prognosis [1].

Despite being relatively rare compared to other cancers, PCa carries a disproportionately high mortality rate. Symptoms are often nonspecific and vague, leading to delayed diagnosis until the disease has advanced to an incurable stage. This underscores the critical importance of early detection methods and heightened awareness of potential risk factors [2,3].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) scan is vital tool in diagnosis and management of PCa [4]. By combining functional and anatomical data, PET-CT provides detailed insights into tumor metabolism and localization. It aids in early detection, accurate staging, and treatment planning, monitoring treatment response, and detecting recurrence. PET-CT has revolutionized the care of PCa patients, enabling more precise diagnosis and personalized treatment strategies [5].

Prognosis, the forecast of the likely outcome or course of a disease, is a critical aspect of medical care. It guides treatment decisions, helps patients and families understand the expected course of their condition, and informs healthcare providers about potential risks and outcomes [6].

Prognostic factors are characteristics or variables associated with progression and outcome of a disease. These factors can include demographic information, clinical features, laboratory results, imaging findings, and molecular markers. By analyzing prognostic factors, healthcare professionals can estimate the likelihood of disease recurrence, progression, or survival [6].

Total Lesion Glycolysis (TLG) can consider as a prognostic factor holds significant promise in the realm of medical diagnostics, particularly

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in oncology [6]. TLG used to assesses metabolic activity of tumors measured through the total metabolic tumor volume multiplied by the mean standardized uptake value of all lesions. This metric, calculated from imaging ^{18}F-FDG-PET/CT, and the derivative value of TLG considered important prognostic value which had ability to provide insights into tumor aggressiveness, treatment response, and patient outcomes. By capturing the metabolic activity of the entire tumor burden, rather than individual lesions, TLG offers a more holistic perspective on disease progression and patient prognosis [7,8].

The context of locally advanced pancreatic cancer (LAPC), related to TLG analysis holds particular significance. This aggressive malignancy poses significant challenges in terms of diagnosis, treatment, and prognosis. By incorporating TLG as a prognostic factor, clinicians can potentially enhance risk stratification, treatment planning, and patient management [8, 6].

Moreover, TLG assessment may facilitate personalized medicine approaches by characterization patients who are likely to benefit from specific therapies or intensification of treatment regimens. Additionally, TLG could serve as a important tool for monitoring outcome and detecting disease recurrence in pancreatic cancer patients undergoing therapy [9].

However, while TLG is important prognostic factor, further research is needed to validate its utility across different cancer types, refine its measurement techniques, and standardize its clinical implementation.

The aim of this work to assess the prognostic significance of TLG in (LAPC) detected by ^{18}F-FDG-PET/CT using texture analysis.

Material and Method

This retrospective analysis received approval from Dar-Alfouad Hospital (approval number: 2021-0031). All procedures adhered strictly to the pertinent guidelines and regulations, with informed consent acquired from all participating patients.

Patients

Sixty patients were enrolled in this preliminary investigation. In this retrospective analysis utilizing a prospectively curate database, participants were eligible if they possessed a histological confirmation of untreated LAPC, lacked additional suspected distant metastases on imaging, including staging ^{18}F-FDG PET/CT, pre treatment and were classified as having pathological stage I or II disease based on the TNM (Tumor-Nodal-Metastasis) staging criteria outlined in the 2002 edition (6th edition) of the American Joint Committee on Cancer (AJCC).

PET-CT imaging and image analysis

Patients underwent a 6-hour fast and ensured serum glucose concentrations were below 200 mg/dl before receiving intravenous injections of 185–370 MBq of ^{18}F-FDG (4 MBq/kg or “0.1 mCi/kg” of body weight). PET/CT scans for all patients were conducted using a GE Discovery LS16 PET/CT scanner. During imaging, patients were a supine-position and both arms extended cranially, also breathed quietly. PET images were acquired at 2.0 minutes per-bed frame for patients weighing between (50-60) kg, 2.5 minutes per-bed frame for patients weighing between (60-90) kg, and 3.0 minutes per-bed frame for patients weighing 90.0 kg or more.

PET scanning was conducted according to standard clinical protocols. This institution adhered to identical procedures for patient preparation, ^{18}F-FDG preparation, and imaging protocols. Central interpretation and quantification of all PET/CT images were carried out using a unified workstation running General Electric AW 4.6 (Advanced Workstation) OS (v20111012).

Features extraction and analysis

All patients images were stored and reported to a personal computer (PC) equipped with Chang-Gung-Image-Texture-Analysis (CGITA) toolbox version 1.4, which contained the analysis code (CGITA is an open-source software code with a graphical user interface for Texture Analysis (TA) running on MATLAB (Math Works Inc., version 2015a) [10]). Subsequently, PET images were loaded into the CGITA toolbox and then extract the interested features.

A semiautomatic contouring was performed by 2 nuclear medicine physicians, each with 12 years of experience. The select isocontour threshold set to an absolute SUV value equal to 3.0, as suspicious for malignancy in pancreatic cancer [11]. Regions of interest (ROIs) were selected on axial slices of the fused PET images for each patient, within the tumor’s edge (example shown in Figure 1).

In the second step, non-cubic voxel grids were resample or interpolated into cubic voxels of 2mm, and the process involved quantifying the original intensities into a discrete range of values within the Volume of Interest (VOI), set between the minimum and maximum values. Dimensions of the matrices used to calculate various texture features. Bin number64 were employed for this purpose.

Thirdly, texture features of conventional PET metrics such as mean standardized uptake value (SUVmean), maximum standardized uptake value

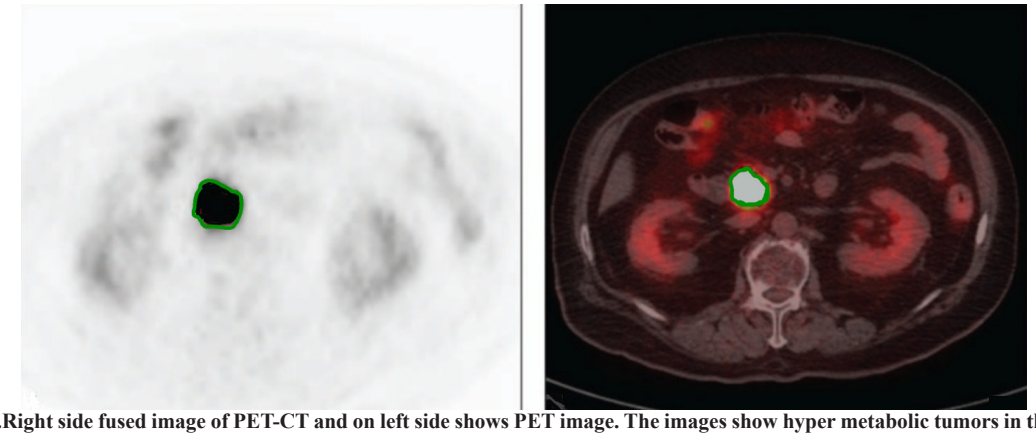

Fig. 1.Right side fused image of PET-CT and on left side shows PET image. The images show hyper metabolic tumors in the head of the pancreas and selected ROI site in tumor.

(SUVmax), metabolic tumor volume (MTV), SUVpeak and TLG, were extracted for each VOI. SUVmax is calculated as SUVmax= tracer uptake in ROI / (injected activity/patient weight) and peak of SUV refer to mean SUV within a 1-cm³ spherical volume centered on the maximum pixel [12,13].

Outcome Pointe

The prognostic significance of SUVs, MTV, and TLG, overall survival (OS) assessed and served as the clinical endpoint.

OS refer to duration from date of first diagnosis for cancer, until patients either the most recent follow-up or death (up to May 01, 2023).

Statistical analysis

Statistical analyses were derivative using the SPSS program (IBM Corp, Armonk, New York, version 23). A *p*-value of less than 0.05 defined as statistically significant value. Univariate and multivariate comparisons were conducted using a Cox proportional hazard model, and hazard-ratio (HR) along with the 95% confidence interval (CI) was calculated. All tests were two-sided.

Results

Patient characteristics

Table 1.summarizes the characteristics of the patients included in the study. Sixty pancreatic cancer patients (male: female = 57:3). The median follow up duration was 5.5 months (range, 3-8).

TABLE 1. Clinico-pathological characteristicsof the studied patients with Pancriatic Ca.

Characteristic		n
Age at diagnosis	≥ 70Y	16
	< 70Y	44
Sex	Male	57
	Female	3
Alcohol drinking	Yes	58
	No	2
Tumor location	Head/neck	41
	Body/tail	19
Lymphatic invasion	Yes	8
	No	52
Pathological T-status	T1	23
	T2	28
	T3	9
Pathologic N-status	N0	10
	N1	8
	N2a	17
	N2b	25
Pathological TNM stage	Stage I	7
	Stage II	53

TABLE 2. Analyzed univarite data of the 2-year control and survival rates of DSS, DFS and OS in pancreatic cancer patients (Total n = 60).

Risk factors	disease-specific survival		p-value	disease-free survival		p-value	overall survival		p-value
(n)	HR	(95% CI)		HR	(95% CI)		HR	(95% CI)	
Pathological T-status									
pT1 (23)	1.71	(1.25- 2.35)	0.008	1.66	(1.27-2.34)	0.001	1.54	(1.17-2.03)	0.004
pT2 (28)									
pT3 (9)									
Pathological N-status									
pN0(10)	1.39	(1.05-1.84)	0.014	1.36	(1.06-1.76)	0.011	1.18	(0.93-1.49)	0.065
pN1(8)									
pN2a(17)									
pN2b(25)									
TNM stage									
pStage I(7)	3.99	(1.57-10.14)	0.002	2.39	(2.53-8.49)	0.002	2.31	(1.16-4.59)	0.007
pStage II(53)									
Tumor thickness									
≥ 21.49 (25)	1.38	(1.04- 3.40)	0.037	2.91	(2.11-2.27)	0.019	2.04	(1.19-3.47)	0.009
< 21.49 (35)									
Tumor depth									
≥ 20mm (18)	3.35	(1.16-4.76)	0.017	2.37	(1.36-3.75)	0.006	2.48	(1.31-4.7)	0.006
< 20mm (42)									
SUVmax									
≥15.93 (30)	3.29	(2.72-2.31)	0.059	2.21	(1.65-1.79)	0.092	1.28	(0.75-2.16)	0.001
<15.93 (30)									
MTV									
≥16.38 (30)	1.05	(0.58-1.88)	0.092	1.34	(0.73-2.12)	0.325	1.09	(0.64-1.84)	0.751
<16.38 (30)									
TLG									
≥98.92 (30)	1.24	(1.57-2.87)	0.092	1.70	(1.76-2.21)	0.541	3.04	(2.61-1.75)	0.002
<98.92 (30)									

Note. HR = hazard ratio, CI = confidence interval, TNM = Tumor Node Metastasis, SUVmax = maximum standardized uptake value, MTV = metabolic tumor volume, TLG = total lesion glycolysis, SUVmax = maximum standardized uptake value .

TABLE 3. Multivariate analysis for DSS, DFS and OS among patients with Pancreatic cancer (Total n = 60).

Risk factors[a]	disease-specific survival		*p-value*	disease-free survival		*p-value*	overall survival		*p-value*
(n)	HR	(95% CI)		HR	(95% CI)		HR	(95% CI)	
TNM stage									
pStage I(7)	2.78	(1.29-3.67)	0.031	1.08	(3.26-6.5)	0.013	2.85	(1.16-6.95)	0.021
pStage II(53)									
Tumor depth									
≥ 20mm (18)	2.90	(1.91-3.77)	0.086	2.88	(1.97-2.61)	0.059	2.42	(1.27-4.58)	0.004
<20mm (42)									
TLG									
≥ 9.33 (30)	2.20	(1.18-4.11)	0.013	1.34	(1.15-3.41)	0.014	4.04	(1.05-6.61)	0.04
< 9.33 (30)									
SUVmax									
≥ 21.49 (30)	1.70	(2.95-5.42)	0.060	1.71	(1.87-3.02)	0.075	1.04	(0.35-1.45)	0.25
< 21.49 (30)									

Extracted metabolic parameter as prognostic factors for outcome

Comparative examination of OS considering clinic-pathologic variables alongside metabolic-parameters. The median OS exhibited minimal variation concerning the progression of disease stages. Notably, among all patients, those in the low TLG group demonstrated significantly prolonged OS compared to those in the high TLG group, in contrast to MTV. Univariate analyses result shows high TLG and SUVmax with OS (HR=2.04, 95% Confidence Interval [CI] 1.75-2.61, *P*=0.002; HR=1.28, 95% CI 0.75-2.16, *P*=0.001) (Table 2).

In multivariate analysis, the utilization of combined diagnostic factors underscored the sustained significance of TLG in association with OS among patients with LAPC (HR 4.04, 95% CI 1.05-6.6) (Table 3).

Discussion

The explored data explained the prognostic significance of various metabolic parameters obtained from pre-treatment ^{18}F-FDG PET/CT scans in individuals with LAPC. While MTV did not show a correlation with OS, both SUVmax and TLG were identified as significant independent prognostic marker for OS, especially in cases of LAPC.

Regarding the imaging parameters for FDG-PET/CT, these study findings represent a notable advancement compared to previous research [12, 14, and 15]. SUVmax has been identified as a significant predictor of early recurrence in respectable PCa [14, 15], while in old study; MTV and TLG have shown prognostic significance in non-respectable locally advanced pancreatic cancer [12].

TA, a novel computational technique and have important for assessing tumor heterogeneity [16], has gained attention due to its ability to capture the diversity of the tumor microenvironment. Although the clinical utility of tumor heterogeneity remains under scrutiny, both histopathology and imaging data have been employed for its analysis, with recent focus on nuclear imaging data [17].

Nonetheless, conflicting findings regarding the efficacy of TA for ^{18}F-FDG PET/CT have been reported [17, 18].

In this study, TA was conducted using 3D-volume data, and various textural parameters from PET/CT were comprehensively compared with established clinic-pathologic and metabolic parameters. The results underscored the significance of extracted textural metabolic parameters as predictors of prognosis, particularly highlighting TLG as a crucial parameter for predicting (OS), alongside SUVmax.

Recent studies have indicated the accuracy of both MTV and TLG as predictive volumetric parameters for OS [7], with others affirming their utility in non-surgical pancreatic cancer [19]. However, MTV has not consistently demonstrated superiority over TLG as a prognostic parameter, particularly concerning OS.

There are disparities in SUV, MTV, and TLG among different tumor prognosis and here in pancreatic cancer have been investigated through texture analysis. While similarities exist between SUVmax and TLG as prognostic parameters affecting OS, such similarities do not necessarily extend to MTV and SUVmax. Variations in tumor histology observed in various studies might influence the distinct prognostic roles attributed to TLG and MTV. Therefore, additional large-scale population-based analyses are necessary to clarify the influence of tumor histology on metabolic parameters in pancreatic cancer.

This study concludes that the results confirmed that TLG stands as an independent prognostic factor for OS in LAPC, outperforms MTV and similar SUVmax in particularly with pre-treatment patients with LAPC. Introducing a novel prognostic stratification integrating conventional clinic-pathological parameters with TLG could offer enhanced prognostic insights.

Although demonstrating the benefits and promise of texture analysis in PET/CT imaging especially with survival terms, thorough clinical assessment with extended follow-up periods is imperative to ascertain the true impact of these methods on patient outcomes.

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استخدام تحلل السكر الكلي للخلايا السرطانية "TLG" كعامل نذير لسرطان البنكرياس المتقدم والذي تم تشخيصه بواسطة المسح الذري بالإصدار البوزيتروني والمقطعي

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تعتبر قيمة الامتصاص المعيارية القصوى (SUVmax)، وحجم الورم الأيضي (MTV)، وتحلل السكر الكلي للخلايا السرطانية (TLG) المقاسة من صور المسح الذري بالإصدار البوزيترونيمؤشرات نذيرية للأورام السرطانية. لا يزال دور هذه المؤشرات النذيرية في التنبؤ بنتائج سرطان البنكرياس غير مستكشف بعد.

أجريت هذه الدراسة لفحص القيمة التنبؤية لـ (SUVmax وTLG وMTV) على البقاء على قيد الحياة بشكل عام (OS) في ستين مريضًا مصابين بسرطان البنكرياس وتم تشخيصهمبالمراحل المرضية الأولى والثانية (اعتمادا على نظام التدريج للسرطانات"TNM""مدى الورم (T)، ومدى الانتشار إلى العُقَد الليمفاوية (N)، ووجود ثانويات ورم خبيث (M)")؛ ذلك باستخدام صور المسح الذري بالإصدار البوزيتروني والمقطعي التي تم الحصول عليها بفحص المرضي قبل العلاج.

كشفت النتائج أن (TLG) أظهرت حساسية فائقة في التنبؤ بالبقاء على قيد الحياة مقارنة بـ (،(MTV SUVmax)). كما أظهرت التحليلات الإحصائية أحادية المتغير ومتعددة المتغيرات، وبروز(TLG) كعلامة تشخيصية مستقلة وحصرية لمعدل البقاء على قيد الحياة. أشارت هذه النتائج إلى دور (TLG) كمؤشر تشخيصي مستقل للبقاء على قيد الحياة والذي يُسَلِّط الضوء على قدرته التنبؤية الفائقة مقارنة بـ (MTV) في المرضى الذين يعانون من البنكرياس المتقدم قبل خضوعهم للعلاج.