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Roles of metabolic tumor volume and total lesion glycolysis on ^{18}F-FDG PET/CT, CA19-9 levels, and complete blood count parameters in predicting survival in patients with unresectable or metastatic pancreatic cancer

AIM: *In this study, we aimed to investigate the roles of volume based ^{18}F-FDG PET/CT parameters, CA19-9 levels, and complete blood count parameters in predicting survival in patients with unresectable and/or metastatic pancreatic ductal adenocarcinoma.*
MATERIALS AND METHOD: *Fifty-seven pancreatic cancer patients who were followed in University of Health Sciences Gazi Yasargil Training and Research Hospital between January 2017 and June 2020, declined surgical treatment and/or radiation therapy or had medically inoperable, unresectable, or metastatic disease, and received chemotherapy were included in the study. ^{18}F-FDG PET/CT images of patients were evaluated and calculated metabolic tumor volume (MTV) and total lesion glycolysis (TLG) parameters were compared with CA19-9 levels and complete blood count parameters. Patients were assessed in two groups as survivors and non-survivors.*
RESULTS: *Total MTV and total TLG on ^{18}F-FDG PET/CT were significantly higher among non-survivors than survivors (p: 0.023 and 0.034, respectively). Multivariate Cox regression analysis revealed that TLG higher than 46 g/ml.cm^3, MTV higher than 11.02 cm^3 (OR 0.987, 95%CI 0.976-0.999, p:0.029 and OR 0.246, 95%CI 0.089-0.685, p: 0.007, respectively) and elevated MPV (OR:0.785, 95% CI 0,574-0.976, p:0.042) were independent prognostic factors for predicting mortality.*
CONCLUSION: *TLG >46 g/ml.cm^3 and MTV >11.02 cm^3 in ^{18}F-FDG PET/CT and elevated MPV in complete blood count are independent prognostic factors for predicting mortality in patients with unresectable or metastatic pancreatic cancer who are treated with chemotherapy.*

KEY WORDS: Pancreatic cancer, Metabolic tumor volume, Total lesion glycolysis, Mean platelet volume

Introduction

Pancreatic cancer is one of the most lethal malignancies among gastrointestinal system cancers. According to GLOBOCAN 2018 data, it is the 11th most common type of cancer with 458,918 new cases and 432,242 deaths. Pancreatic cancer is responsible for 4.5% of akk deaths caused by cancer and it is the 7th leading cause of cancer-related deaths [1]. Approximately 20% of patients are suitable for surgical resection at the time of diagnosis, while 40-50% present with metastatic disease. Expected survival in patients with metastatic disease is as low as 3 to 6 months [2-3]. Numbers from the US National Cancer Institute show that only 10% of patients with pancreatic cancer were diagnosed at local,

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resectable stage. Five-year survival rate at that stage is 32%, yet it declines to 12% in locally advanced tumors. Fifty-two percent of patients have metastatic disease at the time of diagnosis and their 5-year survival rate is 3%. When all patients with pancreatic cancer are considered, 5-year survival rate is only 9% [4]. Despite the recent advancements in diagnostic and therapeutic methods, the majority of pancreatic cancer patients unfortunately die. This indicates that novel diagnostic, risk scoring, and therapeutic tools are required.

Positron emission tomography/computerized tomography (PET/CT) performed using ^{18}F-labeled glucose analogue 2-deoxy-D-glucose (FDG) is among the most common imaging modalities used for staging, evaluating treatment response, and follow-up of cancer patients. Energy demands for the proliferation of cancer cells are met with high glucose uptake and Warburg effect [5]. Increased glucose uptake cells can be visualized with PET/CT using FDG, providing evidence about the location and spread of the tumor. Maximum standardized uptake value (SUVmax) has been used to quantify the metabolic activity of tumors. However, recent studies have shown that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) parameters calculated on ^{18}F-FDG PET/CT are more useful than SUVmax in demonstrating the tumor burden and predicting prognosis in several malignancies [6,7].

Since its discovery in 1979, carbohydrate antigen 19-9 (CA19-9) is used in tumor staging, evaluation of resectability, overall survival and treatment response in patients with pancreatic cancer, as reported in numerous studies [8].

In this study, we aimed to investigate the roles of MTV, TLG, CA19-9 levels, and complete blood count parameters in predicting survival in pancreatic cancer patients treated with chemotherapy.

Materials and Method

Study Design

One hundred and two patients who were followed in University of Health Sciences Gazi Yasargil Training and Research Hospital between January 2017 and June 2020, had a pathologically confirmed diagnosis of pancreatic ductal adenocarcinoma, and underwent PET/CT imaging for staging were evaluated for our study. Fifty-seven patients who declined surgical treatment and/or radiation therapy or had medically inoperable, unresectable, or metastatic disease, and received solely chemotherapy based on their age and performance scores were included. Patients who underwent surgical excision, received radiation therapy and/or chemoradiotherapy, were lost to follow-up, or whose digital records could not be reached were excluded. Subjects were stratified as survivors and non-survivors. All patients were radiologically staged at the time of diagnosis. Metabolic and volume-based parameters obtained from ^{18}F-FDG PET/CT imaging and simultaneous CA19-9 levels and complete blood count parameters were evaluated, and their roles in predicting survivals were assessed. This study was conducted in concordance with the current law, Good Clinical Practice guidelines, and the ethical principles of Declaration of Helsinki. Approval of the institutional review board was also obtained (Approval no: 2019/280).

^{18}F-FDG PET/CT Protocol

All patients were asked to fast and cease intravenous (IV) glucose intake at least 6 hours before the imaging. Patients with blood glucose ≤140 mg/dl were injected with 3.5-5.5MBq/kg of ^{18}F-FDG. One hour after the F-FDG injection, CT images [120kV, 80mAs/slice, 700mm transaxial eld of view (FOV), no gap, 64×0.625 mm collimation, pitch of 1.4, 0.5 s rotation time, 3.3mm slice thickness, and 512×512 matrix] from the vertex to the middle of the thigh were obtained in the supine position, using the 4-ring, 20cm axial FOV Discovery IQ PET/CT device (GE Healthcare, Milwaukee, WI, USA). Bedside PET [20 cm 3D FOV,

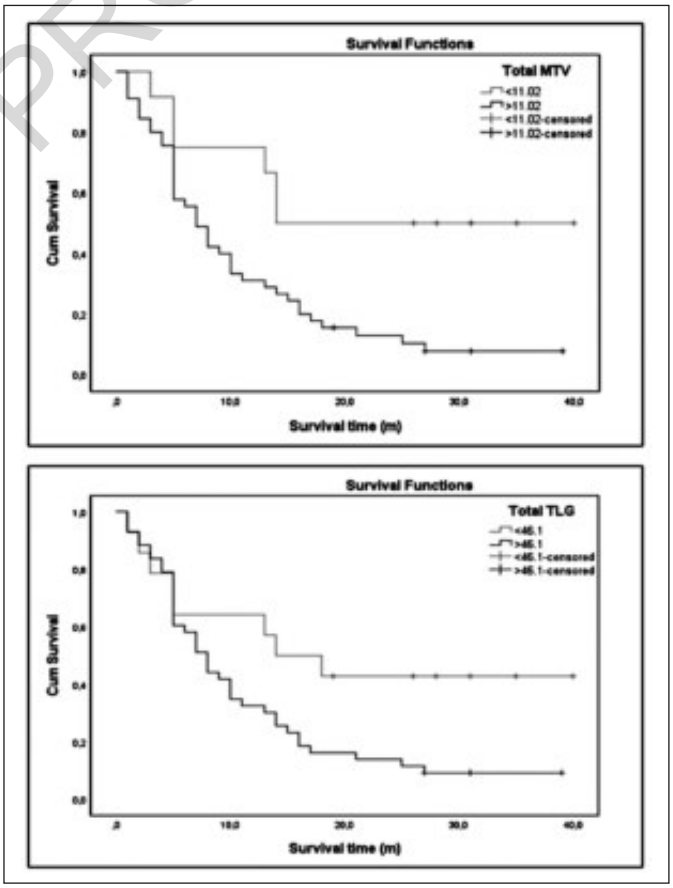

Fig. 1: Total MTV and total TLG survival graphics.

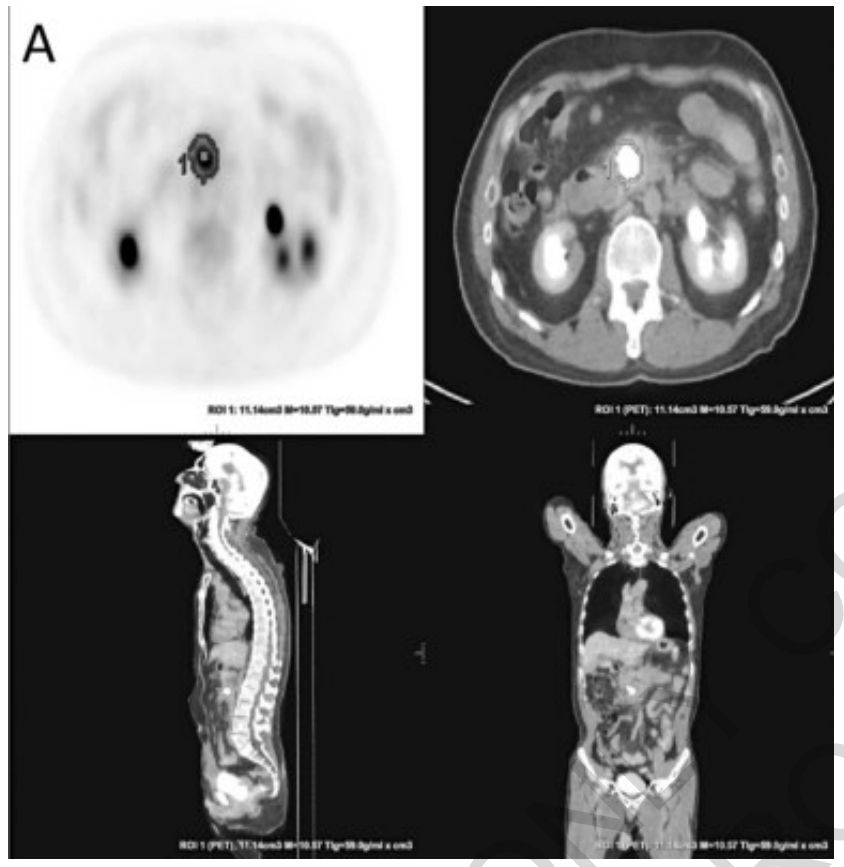

Fig. 1: A) A 71-year-old female patient with pancreas adenocarcinoma; primary tumor MTV: 21,62 cm^3, primary tumor TLG: 63,6 $g/ml.cm^3$, primary tumor SUVmax: 4,64;
B) liver metastasis MTV: 93,77 cm^3, liver metastasis TLG: 308,3 $g/ml.cm^3$, liver metastasis SUVmax: 5,6.

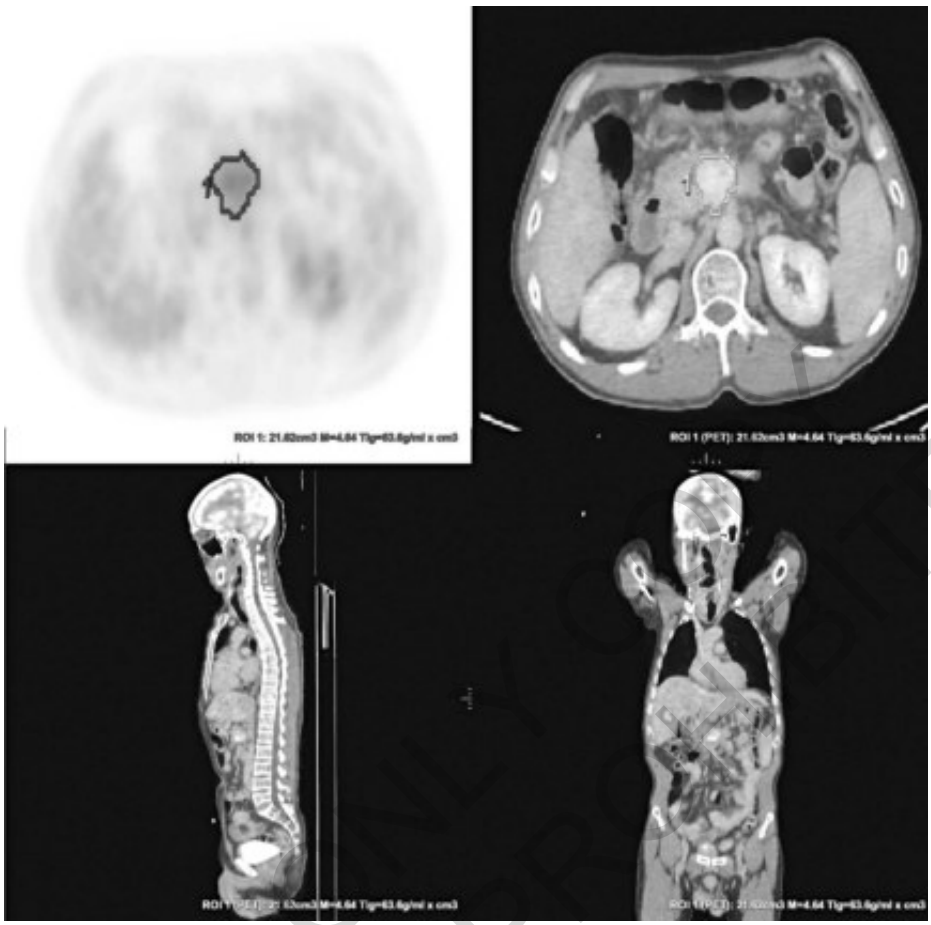

Fig. 3: A) 63-year-old female patient with pancreas adenocarcinoma; primary tumors MTV: 11,14 cm^3, primary tumors TLG: 59,0 $g/ml.cm^3$, primary tumors SUVmax: 10,57.

ordered subset expectation-maximization algorithm (OSEM), 5 iterations/12 subsets, full width at half maximum (FWHM) 3mm] images were obtained from 2.5 minutes onwards.

Image Evaluation

FDG PET/CT images were evaluated by a nuclear medicine specialist with 10 years of experience using PET Volume Computerized Assisted Reporting (PET-VCAR; GE Healthcare) and Advantage Workstation (version 4.7; GE Healthcare) programs. Volumes of interest (VOI) were drawn manually in three planes to include the primary pancreatic lesion, regional lymph nodes, and distant metastases (liver, lung, bone, etc.). The MTV, SUVmax and TLG (MTV×SUVmean) values were obtained for each lesion using a SUV threshold of 40%. Whole body MTV (MTV_{wb}) and whole body TLG (TLG_{wb}) values were calculated by summing MTV and TLG values from all lesions.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Normality of single-variable parameters were assessed using Shapiro test, while homogeneity of variance was assessed with Levene's test. When comparing two independent groups in terms of quantitative parameters, independent samples t test was used together with Bootstrapping results, while Mann-Whitney U test was used with Monte Carlo results. When comparing categorical variables, findings of Fisher's exact test and Fisher-Freeman-Holton test were analyzed with Monte Carlo simulation. The impact of parameters on survival were assessed using Kaplan-Meier (product limit method) or Log Rank (Mantel-Cox) analyses. Effects of prognostic variables on mortality and survival were tested using Cox regression analysis Backward Stepwise (Wald) and Enter methods.
Quantitative variables were described as mean ± SD (standard deviation) or median (25^{th} – 75^{th} percentile),

Table I - *Patients characteristics.*

	n	%
Gender		
Female	27	47,4%
Male	30	52,6%
Localization		
Corpus	15	26,3%
Head	32	56,1%
Tail	6	10,5%
Unicanat	4	7,0%
Mortality		
Alive	10	17,5%
Exitus	47	82,5%
T		
T1	7	12,3%
T2	19	33,3%
T3	15	26,3%
T4	16	28,1%
N		
N0	28	49,1%
N1	15	26.3%
N2	14	24.6%
M		
M0	34	59,6%
M1	23	40.4%
TNM		
I-II	17	29,8%
III	17	29,8%
IV	23	40,4%

	Mean±SD.	Min.	Q1	Q2	Q3	Max.
Age	62.07±13.24	22,0	53,0	63,0	73,0	85,0
Survival time (m)	12.42±10.57	1,0	5,0	8,0	17,0	40,0
Pancreas MTV	22.56±24.98	0,4	10,2	16,3	27,3	175,0
Pancreas TLG	90.00±84.66	1,1	38,5	67,8	106,2	458,3
Pancreas SUVmax	7.25±3.30	2,7	5,3	6,6	8,2	18,6
Pancreas tumor size	34.61±14.19	9,0	26,0	32,0	45,0	70,0
Total MTV	79.84±166.82	0,4	13,6	22,9	41,7	1034,2
Total TLG	312.75±637.46	1,1	49,5	92,7	172,0	3.833,3
Ca19-9	2450.61±3953.7	1,5	40,1	516,3	2511	18966
Neutrophil	5.05±1.83	1,9	3,7	4,9	6,1	11,4
Lymphocyte	1.72±0.65	0,5	1,3	1,7	2,1	3,5
NLR	3.29±1.64	1,1	2,1	3,1	3,8	9,5
Platelet	238.80±99.16	109,0	176,0	218,0	302,0	663,0
MPV	9.79±1.16	5,8	9,1	9,8	10,6	12,5
PLR	153.87±73.99	50,3	112,2	131,9	167,8	335,9

SD.: Standard Deviation, Min.: Minimum, Q1: Percentile 25, Q2:Percentile 50 (Median), Q3: Percentile 75, Max.: Maximum, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio

while categorical variables were described as n (%). All variables were evaluated within 95% confidence interval and $p<0.05$ was considered significant.

Results

Among 57 patients, 30 (52.6%) were male and 27 (4714%) were female. Median age of all patients was 63 years (range: 22-85) and there was no statistically significant difference between survivors and non-survivors (p: 0.963). Head of the pancreas was the most common tumor location with 32 (56.1%) patients, followed by body with 15 (26.3%) patients, tail with 6 (10.5%) patients, and the uncinate process with 4 (7%) patients. Twenty-three (40.4%) patients had metastatic disease, while 17 (29.8%) patients had stage 3 disease and 17 (29.8%) patients had stage 1-2 disease. Forty-seven (82.5%) patients died during the study period while 10 (17.5%) patients survived.

TABLE II - *Comparison of groups.*

		Alive (n=10) Mean±SD.	Exitus (n=47) Mean±SD.	P
Age		61.90±12.85	62.11±13.46	0.963 t
Pancreas tumor size		31.70±11.25	35.23±14.77	0.383 t
Lymphocyte		1.55±0.40	1.76±0.69	0.208 t
MPV		11.33±0.90	9.68±1.18	0.044 t
		Median (Q1 / Q3)	**Median (Q1 / Q3)**	
Survival time (m)		31 (27 / 35)	7 (4 / 13)	<0.001[u]
Pancreas MTV		8.975 (2.99 / 15.64)	17.58 (12.3 / 29.12)	0.054[u]
Pancreas TLG		35.15 (14.6 / 73.4)	72 (43.6 / 123)	0.068[u]
Pancreas SUVmax		5.21 (4.16 / 7.69)	6.67 (5.45 / 8.22)	0.259[u]
Ca19-9		318.2 (26.93 / 1839)	516.3 (409 / 2693)	0.527[u]
Neutrophil		5.23 (4.66 / 5.79)	4.87 (3.64 / 6.19)	0.848[u]
NLR		3.11 (2.62 / 4.51)	3.11 (1.97 / 3.84)	0.523[u]
Platelet		244.5 (183 / 282)	209 (163 / 302)	0.273[u]
PLR		158.92 (123.57 / 247.27)	131.13 (107.77 / 163.59)	0.125[u]
Total MTV		10.585 (2.99 / 299)	23.6 (15.76 / 56.6)	0.023[u]
Total TLG		44.55 (14.6 / 107.4)	95.12 (63.6 / 210.3)	0.034[u]
		n (%)	**n** (%)	
Total MTV				
	<11.02	6 (60.0) sp	6 (12.8)	0.022[rc]
	>11.02	4 (40.0)	41 (87.2) ss	AUC (SE):0.732 (0.093)
Total TLG				
	<46.1	6 (60.0) sp	8 (17.0)	0.034[rc]
	>46.1	4 (40.0)	39 (83.0)ss	AUC (SE):0.715 (0.093)
Gender				
	Female	6 (60)	21 (44.7)	0.492[fe]
	Male	4 (40)	26 (55.3)	
Localization				
	Corpus	3 (30)	12 (25.5)	0.738[ff]
	Head	6 (60)	26 (55.3)	
	Tail	0 (0)	6 (12.8)	
	Unicanat	1 (10)	3 (6.4)	
T				
	T1	1 (10)	6 (12.8)	0.779[ff]
	T2	5 (50)	14 (29.8)	
	T3	2 (20)	13 (27.7)	
	T4	2 (20)	14 (29.8)	
N				
	N0	7 (70)	21 (44.7)	0.156[ff]
	N1	3 (30)	12 (25.5)	
	N2	0 (0)	14 (29.8)	
M				
	M0	8 (80)	25 (53.2)	0.166[fe]
	M1	2 (20)	22 (46.8)	
TNM				
	I-II	4 (40)	13 (27.6)	0.277[ff]
	III	4 (40)	13 (27.7)	
	IV	2 (20)	21 (44.7)	

t Independent Samples T test(Bootstrap), u Mann Whitney U test (Monte Carlo), fe Fisher Exact Test(Exact), ff Fisher Freeman Halton test(Monte Carlo), rc Roc Curve Analysis (Youden index J - Honley&Mc Nell), AUC: Area under the ROC curve, SD. Standard Deviation, Q1: Percentile %25, Q3: Percentile %75, SE.:Standard Error, ss Sensitivity, sp Specificity, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.

All patients received single-agent or combination chemotherapy. Median survival of all patients was 8 months (range: 1-40). Median pancreas MTV and median total MTV were 16.3 cm^3 (range: 0.4-175) and 22.9 cm^3 (range: 0.4-1034), respectively. Median pancreas TLG and median total TLG were 67.8 g/ml.cm^3 (range: 1.1-458.3) and 92.7 g/ml.cm^3 (range: 1.1-3.833,3), respectively. Median CA19-9 level was 516.3 U/ml (range: 1.5-18966) (Table I).

No significant differences were observed between survivors and non-survivors in terms of pancreatic tumor size, tumor stage, tumor location, pancreas SUVmax,

TABLE III - *One and 3 year survival.*

		Dead n(%)	Alive n(%)	Estimate Survival Mean ± Se.	Estimate Proportion Surviving at the 1/3 Year	P Value
Gender						
Female		21(77.8)	6(22.2)	15.2±2.70	48.1 / 21.6	0,496
Male		26(86.7)	4(13.3)	12.7±2.19	33.3 / 12.5	
Localization						
Corpus	I	12(80.0)	3(20.0)	11.8±2.58	33.3 / 20	P(I-II)= 0.832 P(II-III)= 0.260
Head	II	26(81.3)	6(18.8)	14.6±2.30	43.8 / 18.2	P(I-III)=0.394 P(II-IV)=0.910
Tail	III	6(100.0)	0(0.0)	9.2±4.10	33.3 / 0	P(I-IV)=0.887 P(III-IV)=0.490
Unicanat	IV	3(75.0)	1(25.0)	13.3±5.53	50 / 25	
T						
T1	I	6(85.7)	1(14.3)	12.1±3.68	42.9 / 14.3	P(I-II)= 0.495 P(II-III)= 0.120
T2	II	14(73.7)	5(26.3)	17.3±3.25	52.6 / 26.3	P(I-III)=0.671 P(II-IV)=0.348
T3	III	13(86.7)	2(13.3)	10.7±3.04	26.7 / 13.3	P(I-IV)=0.970 P(III-IV)=0.679
T4	IV	14(87.5)	2(12.5)	11.9±2.43	37.5 / 8.3	
N						
N0	I	21(75.0)	7(25.0)	17.4±2.71	57.1 / 23.1	P(I-II)= 0.011
N1	II	12(80)	3(20)	12.0±1.09	34.3 / 15.1	P(I-III)=0.002
N2	III	14(100)	0(0)	9.6±3.04	25.3 / 12.6	P(II-III)= 0.026
M						
M0		25(75.8)	8(24.2)	17.3±2.39	54.5 / 23.6	0,012
M1		22(91.7)	2(8.3)	8.4±1.69	20.8 / 6.3	
TNM						
I-II		13(69.2)	4(30.8)	26.8±4.61	76.9 / 30.8	P(1-II/III)= 0.019
III		13(76.5)	4(23.5)	16.8±3.20	47.1 / 22.1	P(I-II/IV)=0.008
IV		21(91.3)	2(8.7)	8.3±1.76	47.1 / 22.2	P(III-IV)=0.043
Total MTV						
<11.02		6(50.0)	6(50.0)	24.5±4.58	66.7 / 50	0,006
≥ 11.02		41(91.1)	4(8.9)	11.0±1.55	31.1 / 7.8	
Total TLG						
<46.1		8(57.1)	6(42.9)	21.5±4.45	64.3 / 42.9	0,033
46.1		39(90.7)	4(9.3)	11.5±1.63	32.6 / 9.3	
Overall		47(82.5)	10(17.5)	14.0±1.74	40.4 / 16.9	

Kaplan Meier Test [Log Rank (Mantel-Cox)] , SE: Standard Error, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

pancreas MTV, and pancreas TLG values measured in PET/CT, CA19-9 levels, and complete blood count parameters (lymphocyte, neutrophil, platelet, neutrophil/lymphocyte ratio [NLR] and lymphocyte ratio [PLR]) at the time of diagnosis (p>0.05 for all). Statistical analyses revealed that total MTV and total TLG on ^{18}F-FDG PET/CT and mean platelet volume (MPV) in complete blood count were significantly higher among non-survivors than survivors (p: 0.023, p: 0.034, and P:0.044 respectively) (Table II). Cutoff values for predicting mortality were determined to be 11.02 cm^3 for total MTV and 46.1 g/ml.cm^3 for total TLG by ROC analyses (AUC (SE):0.732 (0.093) p:0.022 and AUC (SE):0.715 (0.093) p:0.034, respectively). Patients with total MTV>11.02 cm^3 and total TLG > 46.1 g/ml.cm^3 had higher overall mortality (Fig. 1). Kaplan-Meier analyses evaluating the 1- and 3-year overall survival revealed that higher N and TNM stage, metastatic disease, total MTV>11.02 cm^3 and total TLG>46.1 g/ml.cm^3 were associated with shorter 1- and 3-year overall survival (p<0.05 for all). On the other hand, patients' sex, tumor location, T stage, and CA19-9 levels had no statistically significant association with survival (p>0.05 for all) (Table III).

According to univariate Cox regression analyses, MTV>11.02 cm^3, total TLG>46.1 g/ml.cm^3, lymph node and distant organ metastases, and elevated MPV were prognostic parameters predicting mortality (p<0.05 for all) (Table IV).

Multivariate Cox regression analysis revealed that the presence of lymph node and distant organ metastases, total TLG>46 g/ml.cm^3, total MTV> 11.02 cm^3, and elevated MPV were independent prognostic factors for predicting mortality. No significant association was observed between other parameters and mortality (Table V).

Discussion

In this study, we aimed to investigate the roles of volume based ^{18}F-FDG PET/CT parameters, CA19-9 levels, and complete blood count parameters in predicting survival in patients with unresectable and/or metastatic pancreatic ductal adenocarcinoma. Our findings indicate that the presence of lymph node and distant organ metastases, total TLG>46 g/ml.cm^3, total MTV> 11.02 cm^3. and elevated MPV are independent prognostic fac-

TABLE IV - *Cox Regression univariate analysis.*

	B (SE.)	P	Odds Ratio	95% CI for Odds Ratio Lower	Upper
Age	-0.001 (0.012)	0,952	0,999	0,976	1,023
Pancreas MTV	0.001 (0.004)	0,860	1,001	0,992	1,009
Pancreas TLG	0.001 (0.001)	0,543	1,001	0,998	1,004
Pancreas SUVmax	0.011 (0.037)	0,772	1,011	0,940	1,087
Pancreas size	0.015 (0.011)	0,178	1,015	0,993	1,038
Lymphocyte	-0.077 (0.244)	0,751	0,925	0,574	1,493
Ca19-9	0.000 (0.000)	0,437	1,000	1,000	1,000
Neutrophil	-0.017 (0.081)	0,831	0,983	0,839	1,152
MPV	0.697 (0.355)	0,049	2,008	1,001	4,03
NLR	0.018 (0.090)	0,842	1,018	0,853	1,215
Platelet	-0.003 (0.002)	0,071	0,997	0,994	1,000
PLR	-0.002 (0.002)	0,259	0,998	0,994	1,002

Cox Regression-Enter Method, C.I. :Confidence interval B: regression coefficients SE: Standard error, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, MPV: Mean platelet volüme, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.

TABLE V - *Cox Regression multivariant analysis.*

	P	Odds Ratio	95% CI for Odds Ratio Lower	Upper
MPV	0,042	0.785	0,574	0,976
Total TLG (Categorical)	0,029	0,987	0,976	0,999
N	0,012	0,668	0,488	0,913
M	0,017	0,405	0,193	0,851
Total MTV (Categorical)	0,007	0,246	0,089	0,685

Cox Regression-Backward Stepwise (Wald) Method, C.I. :Confidence interval, B: regression coefficients SE: Standard error, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, MPV: Mean platelet volume.

tors for predicting mortality.

Because of its aggressive nature and potential for early metastasis, pancreatic cancer is associated with high mortality rates. Even though surgery is still the treatment of choice in patients diagnosed with local disease, Bilimoria et al. showed that 38.2% of patients diagnosed at the resectable stage cannot undergo surgical treatment because of age, comorbidities, performance score or patient refusal [9]. Considering that the risk of pancreatic cancer increases with age with the highest peak between 60 to 80 years, the number of surgical candidates is expected to be low [10].

Biological behavior of pancreatic cancer is evaluated with pathological examination of the surgical specimen. Aggressive tumor characteristics include increased tumor burden, number of metastatic lymph nodes, high tumor grade, presence of neural and lymphovascular invasion, and positive surgical margins [11-17]. However, prognostic markers that should be considered in the management of unresectable or metastatic disease are yet to be determined. Jeong et al. evaluated 87 patients and Hyung-Jun et al. evaluated 51 patients, and they both concluded that TLG and MTV on preoperative ^{18}F-FDG PET/CT predicted disease-free survival and overall survival in patients with pancreatic cancer [18,19]. Similar to operated cancer patients, Avani et al. showed that MTV and TLG values were independent prognostic factors affecting survival in patients with locally advanced disease receiving chemoradiotherapy [20]. Eyas et al. conducted a study with operable and metastatic patients and found that TLG was significantly associated with overall survival [21]. In the current study, even though pancreas SUVmax, CA19-9 levels, and T-N-M stages were not statistically different between survivors and non-survivors among a population of pancreatic cancer patients with unresectable or metastatic disease ($p>0.05$ for all), MTV and TLG values at the time of diagnosis were significantly higher in non-survivors than survivors.

ROC analyses performed determined cutoff values for predicting mortality to be 11.02 cm^3 for total MTV and 46.1 $g/ml.cm^3$ for total TLG. Patients with MTV and TLG higher than these cutoffs had lower 1- and 3-year survival rates than patients with lower volumetric parameters. Multivariate analyses revealed that total TLG>46 $g/ml.cm^3$ and total MTV> 11.02 cm^3 were independent prognostic factors for predicting mortality. Our cutoffs are close to 55 $g/ml.cm^3$ TLG and 11 cm^3 MTV cutoffs determined by Eyas et al. in their study with a sample population similar to the current study [21].

Various studies have shown that platelets function in several stages of cancer growth and development of metastases [22,23]. MPV is a widely used parameter for indicating the volume of circulating platelets and acts a marker of platelet activation [24]. Platelet activation promotes invasion of cancer cells and development of metastases by damaging the vascular endothelium. Also, thrombotic state caused by platelet activation can reduce blood

flow, disrupting immune cell response. Growth factors secreted from platelets during coagulation including platelet-derived growth factor and vascular endothelial growth factor also promote cancer growth [25]. However, data about the association of pancreatic cancer with MPV are contradictory. In their study with pancreatic cancer patients, Xue et al. found that preoperative MPV was significantly higher than postoperative MPV (p<0.001). Yet, multivariate analyses failed to demonstrate MPV as an independent variable in predicting prognosis [26]. On the other hand, Jibin et al. assessed pancreatic cancer patients with hepatic metastases and demonstrated that MPV above 8.7 fL predicts mortality.

In the current study, elevated MPV was determined to be an independent parameter predicting mortality in univariate and multivariate analyses among survivors and non-survivors. This finding indicates that MPV is another prognostic marker that should be considered to predict mortality along with total TLG and total MTV in the management of unresectable or metastatic disease.

The first limitation of our study is its retrospective nature.

However, most of the studies in the literature on the subject are also designed retrospectively. Second limitation of our study is evaluating a heterogenous population. Third, only radiological imaging was used in staging without histopathological confirmation. However, because none of the patients underwent surgery, pathological staging was not possible. Forth is the limited sample size because we only included patients from a single center.

Conclusion

In this heterogenous patient population with pancreatic cancer, MTV and TLG values obtained from ^{18}F-FDG PET/CT and MPV in the CBC were independent prognostic factors for predicting mortality. Our findings can help guide clinicians in tailoring individualized therapies.

Riassunto

In questo studio, abbiamo indagato il ruolo dei parametri PET/CT 18F-FDG basati sul volume, i livelli di CA19-9 e i parametri emocromocitometrici completi nella previsione di sopravvivenza in pazienti con adenocarcinoma duttale pancreatico non operabile e/o metastatico.

La casistica si riferisce a 57 pazienti affetti da cancro del pancreas che sono stati seguiti presso l'Università di Scienze della Salute Gazi Yasargil Training and Research Hospital tra gennaio 2017 e giugno 2020. Si tratta di pazienti o inoperabili perché non resecabili o con metastasi oppure che hanno rifiutato il trattamento chirurgico e/o la radioterapia, e sono stati trattati con chemioterapia. Le immagini PET/TC 18F-FDG dei pazienti sono state valutate e sono stati confrontati i parametri del volume metabolico tumorale (MTV) e della glicolisi totale delle lesioni (TLG) calcolati con i livelli di CA19-9 e con i parametri emocromocitometrici completi. I pazienti sono stati valutati in due gruppi come sopravvissuti e non sopravvissuti.

Risultati: MTV totale e TLG totale su PET/TC 18F-FDG erano significativamente più alti tra i non sopravvissuti rispetto ai sopravvissuti (p: 0,023 e 0,034, rispettivamente). L'analisi di regressione multivariata di Cox ha rivelato che TLG superiore a 46 g / ml.cm3, MTV superiore a 11,02 cm3 (OR 0.987, IC 95% 0.976-0.999, p: 0.029 e OR 0.246, IC 95% 0.089-0.685, p: 0.007, rispettivamente) e MPV elevato (OR: 0,785, IC 95% 0,574-0,976, p: 0,042) erano fattori prognostici indipendenti per la previsione della mortalità.

Conclusione: TLG> 46 g / ml.cm3 e MTV> 11,02 cm^3 nella PET/TC 18F-FDG e MPV elevato nell'emocromo completo sono fattori prognostici indipendenti per la previsione della mortalità nei pazienti con carcinoma pancreatico non resecabile o metastatico trattati con chemioterapia.

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Commento e Commentary

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Il cancro del pancreas è una delle neoplasie più letali tra i tumori del sistema gastrointestinale ed è responsabile del 4,5% dei decessi per cancro e settima causa di decessi correlati al cancro. Circa il 20% dei pazienti al momento della diagnosi è destinabile a resezione chirurgica, mentre il 40-50% presenta già malattia metastatica. Una stratificazione accurata per la previsione dei risultati basata solo sulla fase anatomica è difficile. Un sistema prognostico più accurato e affidabile che incorpori caratteristiche aggiuntive dei tumori, come informazioni biologiche e molecolari, può essere necessario per ottenere una migliore previsione della prognosi e per scegliere la modalità di trattamento e il piano di follow-up più appropriati per i casi da malattia localmente avanzata e metastatica. La tomografia a emissione di positroni / tomografia computerizzata con fluorodeossiglucosio 8F (PET / TC 18F-FDG) è un test non invasivo sempre più disponibile per la neoplasia basata sul metabolismo del glucosio. Recentemente è stato dimostrato che è utile per la stadiazione iniziale e per l'individuazione di malattie ricorrenti in molti tipi di tumori, compreso il cancro del pancreas. F-FDG PET è utile non solo per la diagnosi e la stadiazione, ma anche per valutare l'attività proliferativa e i gradi di malignità dei tumori che riflettono la prognosi. Il valore di assorbimento standardizzato (SUV) del tumore primario, un parametro semiquantitativo derivato dalla PET 18F-FDG, è un fattore prognostico significativo per vari tipi di cancro. Nonostante sia un punto di riferimento clinicamente popolare, SUV ha un unico valore voxel e non può essere utilizzato per indicare il metabolismo dell'intero tumore e delle lesioni metastatiche. In effetti, molti studi che hanno indicato il SUV come un fattore prognostico significativo non hanno analizzato i parametri che riflettono il volume del tumore. Studi recenti hanno riportato che i parametri PET volumetrici, come il volume metabolico del tumore (MTV) e la glicolisi totale delle lesioni (TLG), utilizzando un volume di interesse automatico basato sulla soglia (VOI) erano predittori prognostici migliori per la sopravvivenza nei pazienti con mesotelioma pleurico maligno, cancro esofageo e carcinomi a cellule squamose della testa e del collo avanzati.

In questo numero di Ann Ital Chir, Erkan Erdur et al. Hanno studiato il ruolo dei parametri PET / CT 18 F-FDG basati sul volume, i livelli di CA19-9 e i parametri emocromocitometrici completi nel predire la sopravvivenza in pazienti con adenocarcinoma duttale pancreatico non resecabile e / o metastatico.
I loro risultati hanno indicato che MTV totale e TLG totale su 18 F-FDG PET / CT erano significativamente più alti tra i non sopravvissuti rispetto ai sopravvissuti ed erano fattori prognostici indipendenti per prevedere la mortalità.
Questo è in effetti il MTV™ primo passo in un nuovo parametro funzionale PET / TC che potrebbe aiutare nella stratificazione della terapia aggressiva in pazienti con MTVtotale alto a causa della loro prognosi infausta.
Sono necessari ulteriori studi per quantificare la robustezza delle caratteristiche [18 F] FDG-PET / CT e per supportare le analisi radiomiche PET in pazienti con adenocarcinoma duttale pancreatico avanzato.

* * *

Pancreatic cancer is one of the most lethal malignancies among gastrointestinal system cancers and is responsible for 4.5% of deaths caused by cancer and it is the 7 th leading cause of cancer-related deaths. Approximately 20% of patients are suitable for surgical resection at the time of diagnosis, while 40-50% present with metastatic disease.
Accurate stratification for outcome prediction based only on anatomic stage is difficult.
A more accurate and reliable prognostic system incorporating additional features of tumors, such as biological and molecular information, may be necessary to obtain a better prediction of prognosis and to choose the most appropriate treatment modality and follow-up plan for locally advanced and metastatic pancreatic cancer ^{8}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an increasingly available noninvasive test for malignancy based on glucose metabolism. It was recently demonstrated to be valuable for initial staging and for the detection of recurrent diseases in many kinds of tumors, including pancreatic cancer. F-FDG PET is useful not only for diagnosing and staging, but also for evaluating the proliferative activity and malignancy grades of tumors reflecting prognosis. The standardized uptake value (SUV) of the primary tumor, a semi-quantitative parameter derived from ^{18}F-FDG PET, is a significant prognostic factor for various types of cancers.
Despite being a popular landmark clinically, SUV has a single voxel value and cannot be used to indicate the metabolism of the whole tumor and metastatic lesions.
In fact, many studies that have indicated SUV as a significant prognostic factor did not analyze parameters reflective of tumor volume. Recent studies have reported that volumetric PET parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), using a threshold-based automatic volume of interest (VOI) were better prognostic predictors for survival in patients with malignant pleural mesothelioma, esophageal cancer, and advanced head and neck squamous cell carcinomas.
In this issue of Ann Ital Chir Erkan Erdur et al investigated the roles of volume based 18 F-FDG PET/CT parameters, CA19-9 levels, and complete blood count parameters in predicting survival in
patients with unresectable and/or metastatic pancreatic ductal adenocarcinoma.
Their results indicated that Total MTV and total TLG on 18 F-FDG PET/CT were significantly higher among non-survivors than survivors and they were independent prognostic factors for predicting mortality.
This is indeed the first step in a new functional PET/TC parameters that might help in the stratification of aggressive therapy in high MTV total patients due to their poor prognosis.
More studies are needed to quantify the robustness of [18 F] FDG-PET/CT features and to support PET radiomic analyses in patients with advanced pancreatic ductal adenocarcinoma.