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Baseline Metabolic Tumor Volume and Total Lesion Glycolysis Are Associated With Survival Outcomes in Patients With Locally Advanced Pancreatic Cancer Receiving Stereotactic Body Radiation Therapy

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Abstract

Purpose—Although previous studies have demonstrated the prognostic value of positron emission tomography (PET) parameters in other malignancies, the role of PET in pancreatic cancer has yet to be well established. We analyzed the prognostic utility of PET for patients with locally advanced pancreatic cancer (LAPC) undergoing fractionated stereotactic body radiation therapy (SBRT).

Materials and Methods—Thirty-two patients with LAPC in a prospective clinical trial received up to 3 doses of gemcitabine, followed by 33 Gy in 5 fractions of 6.6 Gy, using SBRT. All patients received a baseline PET scan prior to SBRT (pre-SBRT PET). Metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum and peak standardized uptake values (SUV_{max} and SUV_{peak}) on pre-SBRT PET scans were calculated using custom-designed software. Disease was measured at a threshold based on the liver SUV, using the equation $Liver_{mean}$ + [2 × $Liver_{sd}$]. Median values of PET parameters were used as cutoffs when assessing their prognostic potential through Cox regression analyses.

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Conflict of interest: none.

Results—Of the 32 patients, the majority were male (n = 19, 59%), 65 years or older (n = 21, 66%), and had tumors located in the pancreatic head (n = 27, 84%). Twenty-seven patients (84%) received induction gemcitabine prior to SBRT. Median overall survival for the entire cohort was 18.8months (95% confidence interval [CI], 15.7–22.0). An MTV of 26.8 cm^3 or greater (hazard ratio [HR] 4.46, 95% CI 1.64–5.88, *P*<.003) and TLG of 70.9 or greater (HR3.08,95%CI 1.18–8.02,*P*<.021) on pre-SBRT PET scan were associated with inferior overall survival on univariate analysis. Both pre-SBRT MTV (HR 5.13, 95% CI 1.19–22.21, *P* = .029) and TLG (HR 3.34, 95% CI 1.07–10.48, *P* = .038) remained independently associated with overall survival in separate multivariate analyses.

Conclusions—Pre-SBRT MTV and TLG are potential predictive factors for overall survival in patients with LAPC and may assist in tailoring therapy.

Introduction

Pancreatic ductal adenocarcinoma is among the most lethal malignancies, with 45,220 newly diagnosed cases and 38,460 deaths expected in 2013 (1). Survival rates for patients with early stage, resectable disease are poor (2), with only 22% of patients surviving beyond 5 years (3) despite modern, multimodality treatment approaches (4, 5). Most patients will present with unresectable disease at initial presentation (6), for which 5-year survival rates are dismal at less than 2% (7). With poor long-term survival rates and variable responses to therapies, early assessment of an individual's response to treatment can be particularly useful in guiding management of pancreatic cancer patients. Functional imaging has the promising abilities to identify response to treatment and to predict clinical outcomes by assessing the viability of cancer cells following treatment.

Positron emission tomography (PET) is a useful tool in the diagnosis, staging, and surveillance of patients with various malignancies, including pancreatic cancer (8–10). Few studies, however, have evaluated the role of PET parameters in the prognosis of pancreatic cancer. Recently, Schellenberg et al (10) reported an association between low baseline SUV_{max} and improved overall survival (OS) and progression-free survival (PFS) for patients with locally advanced pancreatic cancer (LAPC). PET response correlated with time to progression in patients with LAPC in a study by Bang et al (8). LAPC patients manifesting responses on PET imaging following chemotherapy have been shown to have longer survival (11) and were more likely to undergo successful resection (12) than nonresponders. Others studies have demonstrated an association between standard uptake values (SUV) and tumor size or markers in LAPC patients following chemotherapy and chemoradiation (13), as well as pathologic response following neoadjuvant chemoradiation for resectable pancreatic cancer (14).

These studies focused on SUV measurements as a predictor for clinical outcomes; however, parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are emerging as interesting and perhaps valuable clinical factors in malignancies of the head and neck (15, 16), lung (17, 18), esophagus (19), anus (20), and pancreas (10), as well as lymphoma (21). Some studies further demonstrate that MTV is a stronger predictor than maximum SUV (SUV_{max}) for tumor response (22) and OS(20, 22, 24, 25) and disease-free

survival (20). This study aimed to elucidate the role of pretreatment metabolic volume parameters and SUV (max and peak) as correlates of survival in LAPC patients treated in a prospective trial with chemotherapy and fractionated stereotactic body radiation therapy (SBRT).

Methods and Materials

Patients

This analysis included 32 patients with histologically confirmed LAPC treated at a single institution in a prospective phase 2 clinical trial (NCT01146054), who underwent PET/computed tomography (CT) prior to SBRT. The study was approved by the institutional review board, and all subjects signed a written informed consent form.

Treatment

Participants received up to 3 weeks of gemcitabine chemotherapy administered within 6 weeks prior to SBRT. Gemcitabine was given on a 3-week-on, 1-week-off schedule, administered weekly at a dose of 1000 mg/m^2. Prior to simulation, study participants underwent endoscopic placement of 3 to 5 gold fiducial markers in or adjacent to the primary tumor and subsequently underwent a simulation scan while in the supine position in a custom-made Alpha cradle (Smithers Medical Products, North Canton, OH). Target motion during respiration was characterized by 4-dimensional (4D) CT scan. Motion management was addressed using airway-breathing control when fiducial motion exceeded 5 mm on a simulation scan or kV images.

The gross tumor volume (GTV) was defined by the attending radiation oncologist after reviewing the diagnostic CT, respiration-correlated 4D-CT, pancreatic protocol CT, and PET/CT scans. The final planning treatment volume included a 2- to 3-mm margin expansion of the GTV, unless the margin resulted in expansion into the duodenum or stomach. In those cases, margin expansion was allowed to be nonuniform. SBRT was administered in consecutive 6.6-Gy fractions for 5 days for a total dose of 33 Gy. Approximately 1 to 4 weeks after SBRT, patients continued gemcitabine therapy until disease progression or toxicity occurred. Patients were followed with surveillance CT scans, physical examination, and laboratory tests at 4 to 6 weeks after SBRT and then once every 3 to 4 months.

PET protocol

Of the 32 patients included in this study, 29 had their PET/CT imaging performed at a single center with a Discovery RX model PET/CT scanner (General Electric Medical Systems, Waukesha, WI). The remaining 3 patients were scanned at outside PET/CT imaging centers using identical protocols. All patients were asked to fast for a minimum of 4 hours prior to imaging. Serum glucose levels were measured prior to injection of ^{18}F-labeled fluorodeoxyglucose (FDG). After we ensured that patients' blood glucose levels were <180 mg/dL, patients were injected with 8.1 MBq/kg [^{18}F]FDG 60 minutes prior to image acquisition. In addition, patients were given a diluted oral barium sulfate CT contrast agent

(Readi-Cat2, E-Z-EM Canada Incorporated, Lake Success, NY) prior to imaging. PET/CT scans were acquired from mid-skull to mid-thigh in all patients.

Measurement of MTV and TLG

Image analysis was performed in the Image Response Assessment Team (IRAT) laboratory of the Image Response Assessment Team (IRAT) laboratory of the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins Medical Institution. PET measurements were recorded in units of SUV corrected for lean body mass, and all measurements, including SUV_{peak}, SUV_{max}, MTV, and TLG, were computed using Auto-PERCIST, an in-house–developed software program for automated PERCIST (PET Response Criteria in Solid Tumors [reference 30]) image analysis (Johns Hopkins University, Baltimore, MD). Threshold of disease measurability was calculated using the mean and standard deviation measurements (Liver-mean, Liver-sd) of a 3 cm diameter spherical volume of interest placed within the liver (preferably the right lobe) and applied to the following formula: $Liver_{mean} + [2 \times Liver_{sd}]$. MTV was defined as the volume of tumor tissue that demonstrated metabolic activity at or above the calculated threshold of disease measurability. TLG was defined as the MTV multiplied by the mean SUV within the volume. The MTV for a patient in our study is shown in Figure 1. In cases where multiple, discrete objects of the same disease tissue were detected, the individual MTV and TLG values were summed to create global MTV and TLG values, and the maximum overall SUV_{peak} and SUV_{max} measurements were used for subsequent analysis.

Statistical analysis

All demographic and baseline data were summarized using descriptive statistics. In this preliminary hypothesis-generating dataset, a non—Bonferroni-/non—Dunn-Sidákcorrected dataset, a *P* value of <.05 was used for all significance assessments. Survival outcomes were calculated from date of pathologic diagnosis and analyzed using the Kaplan-Meier method and the log-rank test to assess for differences between subgroups. Local progression was defined by Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 guidelines (23) on follow-up CT scans. Freedom from local progression (FFLP) was calculated using the Kaplan-Meier method, censoring patients without local progression at date of last CT scan. Univariate Cox regression analyses were performed to assess for an association between clinical factors or laboratory values and OS, PFS, and local progression–free survival (LPFS). Age (<65 vs ≥65), baseline carbohydrate antigen 19-9 (Ca 19-9; <90 U/mL vs ≥90 u/mL), Eastern Cooperative Oncology Group (ECOG) performance status (24), tumor location (head vs other location), receipt of induction gemcitabine, and characteristics that demonstrated a univariate association with survival at a significance level of $P \leq .200$ were entered as covariates into a multivariate regression analysis for OS, PFS, and LPFS. Analyses were performed using SPSS software, version 2 (IBM, Chicago, IL).

Results

Patient and tumor characteristics

Baseline clinical characteristics of all patients in this study (n = 32) are summarized in Table 1. The majority of individuals were male (n = 19, 59%) and 65 years or older (n = 21, 66%).

Pancreatic adenocarcinoma was most commonly located in the head of the pancreas (n = 27, 84%). Twenty-seven patients (84%) received at least 1 dose and no more than 3 doses of gemcitabine prior to SBRT.

Pre-SBRT PET scans were conducted after administration of induction gemcitabine in 18 patients (56%). The remaining 14 patients (44%) either did not receive gemcitabine or received the PET scan prior to gemcitabine administration. The median time from pre-SBRT PET scan to the start of SBRT was 0.9 months (range, 0.4–1.5 months). The median pre-SBRT SUV_{max} and SUV_{peak} were 4.6 g/mL (range, 0–9.61 g/mL) and 3.6 g/mL (range, 0–8.16 g/mL), respectively. The median pre-SBRT TLG and MTV were 70.9 (range, 0–462.2 and 26.8 cm^3 (range, 0–123.5 cm^3), respectively. One patient's tumor failed to demonstrate any metabolic activity via PET scan, and thus, values of zero for SUV_{max}, SUV_{peak}, TLG, and MTV were assigned to represent the features of this tumor. There were no differences in the mean pre-SBRT SUV_{max}, SUV_{peak}, MTV, and TLG values for patients who did and did not undergo the pre-SBRT PET scan prior to treatment with induction gemcitabine (all $P>.05$).

Prognostic value of PET parameters

At the time of analysis, 19 patients (59%) had died. Twenty-one patients (66%) experienced disease progression, including 4 patients with local-only progression (13%), 12 patients (38%) with distant-only progression, and 5 patients (16%) with both local and distant components of progression of disease. The median follow-up from the date of diagnosis was 13.4 months (range, 4.0–35.31 months) in all patients and 14.7 months (range, 9.1–35.3 months) among survivors at last follow up. No patients were lost to follow up.

FFLP was 75% at 1 year. The median OS, LPFS, and PFS periods for the entire cohort (n = 32) were 18.8 months (95% confidence interval [CI], 15.7–22.0 months), 13.6 months (95% CI, 8.5–18.7 months), and 6.9 months (95% CI, 2.7–11.1 months), respectively. Specific pre-SBRT PET parameters including SUV_{max}, SUV_{peak}, TLG, and MTV, along with other clinical characteristics, were screened using univariate Cox regression analyses to assess for associations among possible predictive factors and OS, LPFS, and PFS (Table 2). Of the factors assessed, only MTV and TLG were significantly associated with OS and LPFS. Using a median value as a cutoff, tumors displaying a pre-SBRT MTV ≥26.8 cm^3 were associated with inferior patient OS (hazard ratio [HR] 4.46, 95% CI 1.64–5.88, $P = .003$) and LPFS (HR 2.47, 95% CI 1.01–6.04, $P = .048$). Tumors displaying pre- SBRT TLG ≥70.9 were also associated with poor OS (HR 3.08, 95% CI 1.18–8.02, $P = .021$) and LPFS (HR 3.19, 95% CI 1.28–7.92, $P = .013$). Additionally, tumors with pre-SBRT TLG ≥70.9 (HR 2.38, 95% CI 1.04–5.40, $P = .038$), SUV_{max} ≥4.6 g/mL (HR 2.85, 95% CI 1.26–6.46, $P = .012$), and SUV_{peak} ≥3.6 g/mL (HR 1.12, 95% CI 1.12–5.67, $P = .025$) were associated with inferior PFS; however, MTV failed to demonstrate predictive value for PFS in this cohort ($P>.05$). Age, sex, performance status, tumor location, baseline Ca 19-9 (<90 U/mL vs ≥90 U/mL), and receipt of at least 1 dose of induction gemcitabine prior to initiation of SBRT were not significantly associated with OS, LPFS, or PFS (all $P>.05$) on univariate analysis.

Compared to patients with a pre-SBRT MTV of less than 26.8 cm^3, patients with an MTV of 26.8 cm^3 or greater had significantly worse OS at 9.9 months (95% CI 0.5–19.3 months) than at 22.3 months (95% CI 17.5–27.0 months; $P = .002$) (Fig. 2A). Similarly, compared to patients with a pre-SBRT TLG level of less than 70.9, patients with TLG level of 70.9 or greater had significantly worse OS at 12.9 months (95% CI 7.4–18.3 months) than at 22.3 months (95% CI 18.5–26.0 months; $P = .026$) (Fig. 2B). Of note, 1 patient whose tumor did not demonstrate any baseline PET avidity and was thus considered to have an MTV and TLG of zero was alive 33.0 months after diagnosis and was without evidence of progression after treatment with only SBRT and gemcitabine-based chemotherapy.

As MTV and TLG are correlated by their definition, 2 separate multivariate analyses were performed to determine whether univariate results for the associations of pre- SBRT TLG (Table 3) and MTV (Table 4) with OS would persist after accounting for other important clinical variables including age, performance status, tumor location, baseline Ca 19-9, and receipt of induction gemcitabine prior to SBRT. Both pre-SBRT MTV (HR 5.13, 95% CI 1.19–22.21 cm^3, $P = .029$) and TLG (HR 3.34, 95% CI 1.07–10.48, $P = .038$) remained independently associated with OS in their separate multivariate analyses. In the model including TLG, performance status (HR 3.57, 95% CI 1.09–11.65, $P = .035$) and lack of induction gemcitabine prior to SBRT (HR 4.41, 95% 1.01–19.24, $P = .048$) also significantly impacted OS after we accounted for age, tumor location, and baseline Ca 19-9; however, those variables were not significant in the identical model that replaced TLG with MTV. Neither MTV nor TLG remained associated with LPFS or PFS after accounting for the same variables listed above (not shown).

Discussion

We identified the fact that MTV and TLG measured on pre-SBRT PET scans were associated with OS in patients with LAPC. When they were compared using identical multivariate models, MTV emerged as a stronger correlate of OS than TLG ($P = .029$ vs $P = .038$). Given the size of this study, however, we cannot comment on the true significance of this observed difference between MTV and TLG. Notably, we did not find an association between SUV_{max} and SUV_{peak} with OS or LPFS, rather only PFS on univariate analysis alone.

Our study adds to only 1 other report on the potential predictive utility of baseline PET parameters in the setting of LAPC. Schellenberg et al (10) published a retrospective study of 55 patients demonstrating the ability for pre-SBRT SUV_{max} to predict overall and PFS in LAPC patients treated with a single fraction of 25 Gy using SBRT in series with gemcitabine-based chemotherapy. Preradiation SUV_{max} values above and below the median values detected in their cohort was prognostic for OS on univariate analysis. SUV_{max} subgroups of <5, 5 to 10, or >10 were found to be prognostic for both overall and PFS on multivariate analyses. The authors also reported that increased metabolic tumor burden (similar to MTV in our study) was associated with inferior OS on univariate analysis; however, SUV_{max} was a superior independent prognostic factor compared to MTV.

Our study, supported by the data from the abovementioned report, indicates that MTV could be a valuable predictive factor for patients with pancreatic cancer. We report that MTV is a stronger correlate of survival than SUV_{max}. A difference in our definition of the MTV threshold and the use of hypofractionated SBRT instead of a single fraction may have contributed to the difference in our findings regarding the significance of MTV from the study described above. We further demonstrate that TLG was more strongly associated with inferior OS and LPFS than SUV_{max} or SUV_{peak}. These findings may be due to the relatively small sample size of our study, limiting the ability to detect the significance of SUV_{max} or SUV_{peak}. Additionally, measurement of SUV_{max} is based on a single pixel, which is subject to significant noise bias (25).

These data support prior reports of severe hypoxia found within pancreatic cancer (26). Warburg (27) initially proposed that tumors preferentially used glycolysis rather than aerobic respiration. More recently, tumor hypoxia has been demonstrated as the major tumor microenvironmental factor that drives tumors toward a glycolytic phenotype under oxygen-limited conditions. Our report that pancreatic tumors with increased MTV and TLG are associated with worse prognosis is consistent with the observations of prior studies and suggests that hypoxia within pancreatic tumors may contribute to this phenotype (28, 29), although its exact mechanism is an important topic for future research.

While prior studies have investigated the predictive utility of MTV in LAPC (10) and various other cancer sites (10, 15–22), there is no standard definition of MTV, making comparisons between the results of different studies difficult. Volume assessment in prior studies has been based on relative thresholds, various absolute SUV thresholds, and gradient-based thresholds. In this study, MTV was calculated based on the volume of hypermetabolic disease above a threshold defined as the $Liver_{mean} + [2 \times Liver_{sd}]$. This threshold is based on a modification of the threshold criteria used in PET PERCIST, version 1.0 (30). Our rationale for use of this patient-specific threshold was to account for individual variability in radiotracer uptake. As future investigations continue to evaluate MTV (or TLG) as a prognostic marker, the calculation method must be clearly defined.

TLG or MTV as pretreatment-predictive factors, if validated, could be used to adapt therapies for patients at greatest risk for poor survival. All patients in this study received the same treatment protocol; however, patients with high TLG or MTV had inferior OS even when accounting for other potential prognostic factors. These results highlight a particular population with aggressive tumors, distinguished by highly metabolic tumor volumes, that fails to significantly benefit from fractionated SBRT and gemcitabine. We are currently in the process of investigating the association among certain potential biomarkers with increased MTV and TLG. One candidate of interest is SMAD4 expression, which has been previously demonstrated to be highly correlated with the presence of widespread metastasis when unexpressed (31). Additional future studies should focus on the value of MTV and TLG parameters for tailoring treatment.

Although the study is limited by its single-institution nature, all but 3 patients were imaged using the same PET scanner, and all image data were centrally analyzed at our institution. This design limits heterogeneity in imaging technique. Furthermore, patients received

uniform treatment and were closely followed as they were treated on a prospective clinical trial. We are therefore able to more reliably assess the utility of MTV and TLG parameters as potential correlates of survival in pancreatic cancer.

A second limitation in this study is that 56% of patients underwent a pre-SBRT PET scan after receiving induction gemcitabine, whereas the remaining patients had PET scans prior to initiation of chemotherapy. Still, we did not observe significant differences among the pre-SBRT SUV_{max}, SUV_{peak}, MTV, and TLG values for patients who did and did not undergo a PET scan prior to treatment with induction gemcitabine, suggesting a negligible effect of induction chemotherapy on the baseline metabolic parameters of the lesion.

Conclusions

In conclusion, our study indicates that pre-SBRT metabolic volume, quantified as MTV or TLG, is associated with OS in this population of LAPC patients. A standardized definition for disease measurability is necessary to facilitate comparisons among studies. Validation of these results in future clinical trials will be necessary to determine whether patients can be risk-stratified on the basis of MTV or TLG to guide patient counseling and clinical decision making for treatment of pancreatic cancer.

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Summary

Currently, for patients with locally advanced pancreatic cancer, only carbohydrate antigen 19-9 level, performance status, and the ability to undergo surgery after neoadjuvant therapy reliably predict response to treatment and prognosis. This analysis of patients treated in a prospective clinical trial identified baseline metabolic tumor volume and total lesion glycolysis as correlates of survival in locally advanced pancreatic cancer. These parameters could be used in the future to help tailor therapy for this challenging disease.

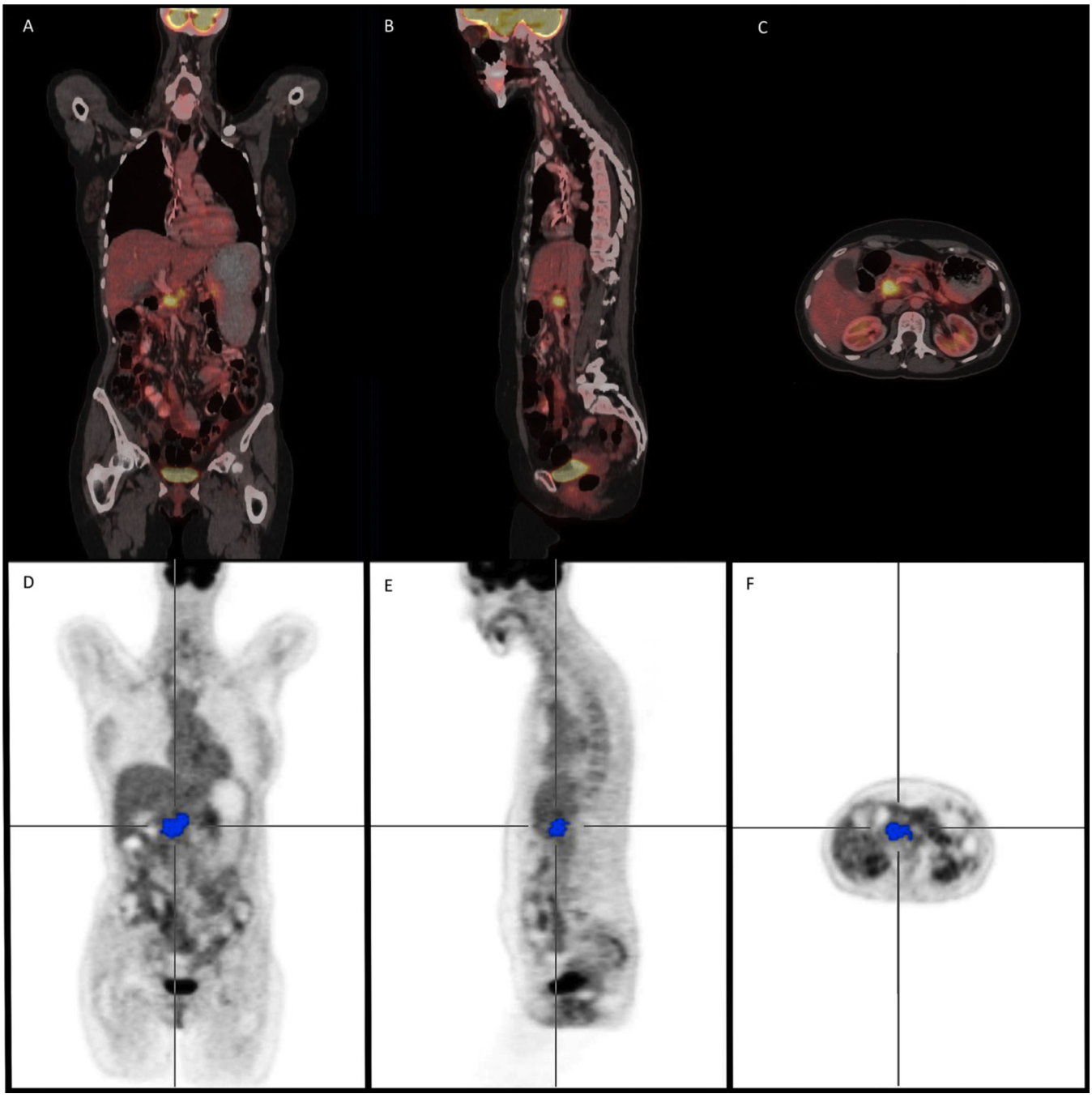

Fig. 1.

Representative PET/CT showing areas of increased metabolic uptake on coronal (A), sagittal (B), and axial (C) images. The MTV of this patient, measuring 23.4 cm^3, is shown in blue on coronal (D), sagittal (E), and axial (F) images. This patient was still alive 26 months after initial pathologic diagnosis. MTV = metabolic tumor volume.

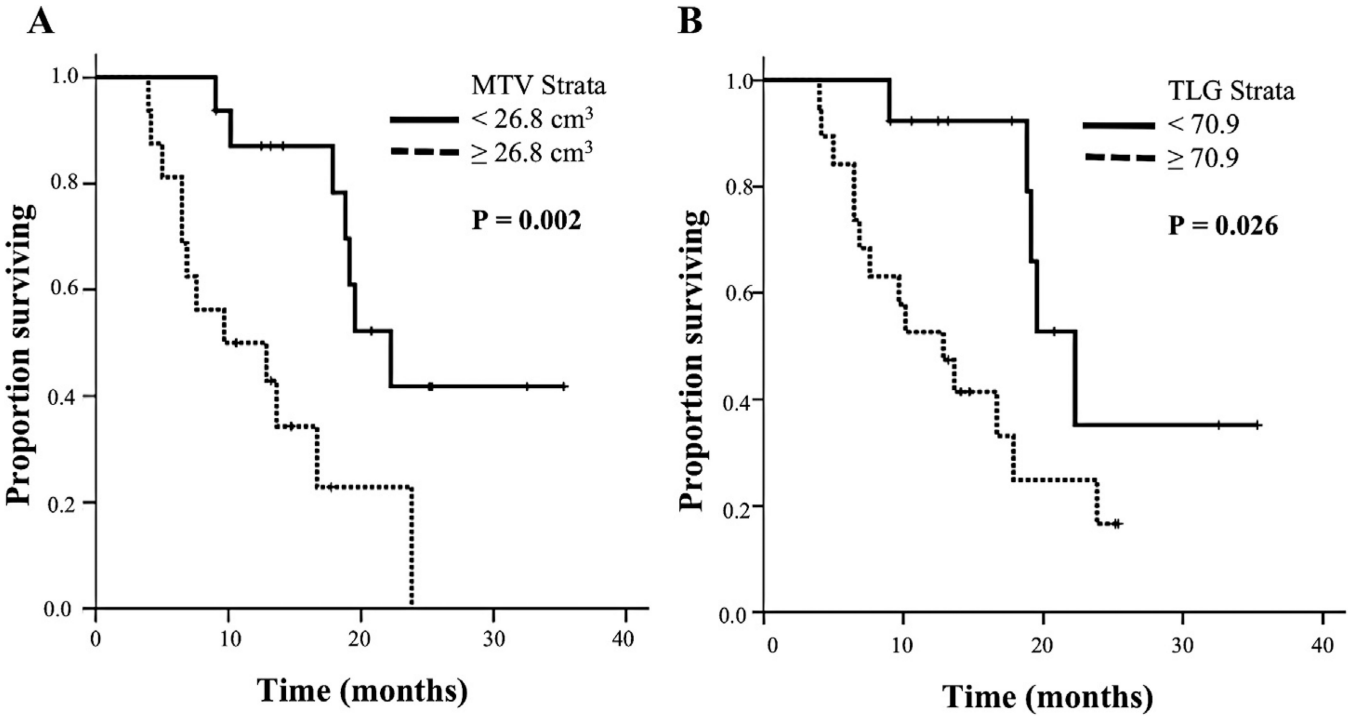

Fig. 2.

Kaplan-Meier univariate analysis of overall survival of patients stratified by pre-SBRT (A) metabolic tumor volume and pre-SBRT (B) total lesion glycolysis above and below the median value. MTV = metabolic tumor volume; SBRT = stereotactic body radiation therapy; TLG = total lesion glycolysis.

Table 1

Demographic and baseline clinical characteristics for the entire cohort (n = 32)

Characteristic	Number of patients
Sex	
Male	19
Female	13
Age	
<65 yrs	11
≥65 yrs	21
Location	
Head	27
Other	5
Baseline Ca 19-9	
<90 U/mL	11
≥90 U/mL	19
Not available	2
Pre-SBRT gemcitabine	
No	5
Up to 1 cycle	27

Abbreviations: Ca 19-9 = carbohydrate antigen 19-9; SBRT = stereotactic body radiation therapy.

Table 2

Cox univariate associations between clinical and pre-SBRT positron emission tomography parameters with overall survival, local progression-free survival, and progression-free survival

	OS			LPFS			PFS		
Parameter	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age									
<65 yrs	1.00	-	-	1.00	-	-	1.00	-	-
≥65 yrs	0.92	0.37–2.30	.857	0.94	0.38–2.31	.896	0.66	0.29–1.51	.321
Sex									
Male	1.00	-	-	1.00	-	-	1.00	-	-
Female	0.86	0.34–2.18	.746	0.74	0.30–1.84	.515	1.69	0.76–3.75	.198
ECOG PFS									
0	1.00	-	-	1.00	-	-	1.00	-	-
1	2.03	0.81–5.01	.132	1.33	0.55–3.17	.528	0.91	0.41–2.01	.818
Location									
Head	1.00	-	-	1.00	-	-	1.00	-	-
Other	2.07	0.57–7.54	.271	1.34	0.38–4.68	.651	1.14	0.38–3.44	.810
Baseline Ca 19-9									
<90 U/mL	1.00	-	-	1.00	-	-	1.00	-	-
≥90 U/mL	1.58	0.58–4.33	.373	1.01	0.40–2.53	.981	1.02	0.44–2.36	.970
Pre-SBRT gemcitabine									
1 cycle	1.00	-	-	1.00	-	-	1.00	-	-
None	1.93	0.64–5.88	.246	1.63	0.54–4.97	.388	1.41	0.47–4.22	.540
Pre-SBRT SUV_{max}									
<4.6 g/mL	1.00	-	-	1.00	-	-	1.00	-	-
≥4.6 g/mL	1.50	0.60–3.74	.386	1.88	0.79–4.48	.155	2.85	1.26–6.46	.012
Pre-SBRT SUV_{peak}									
<3.6 g/mL	1.00	-	-	1.00	-	-	1.00	-	-
≥3.6 g/mL	1.22	0.49–3.05	.666	1.75	0.73–4.2	.209	2.52	1.12–5.67	.025
Pre-SBRT MTV-median									
<26.8 cm^3	1.00	-	-	1.00	-	-	1.00	-	-

	OS			LPFS			PFS		
Parameter	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
≥26.8 cm^3	4.46	1.64–12.1	.003	2.47	1.01–6.04	.048	1.42	0.64–3.16	.395
Pre-SBRT TLG-median									
<70.9	1.00	-	-	1.00	-	-	1.00	-	-
≥70.9	3.08	1.18–8.02	.021	3.19	1.28–7.92	.013	2.38	1.04–5.40	.038

Abbreviations: Ca 19-9 = carbohydrate antigen 19-9; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LPFS = local progression—free survival; MTV = metabolic tumor volume; OS = overall survival; PFS = progression-free survival; SBRT = stereotactic body radiation therapy; SUV_{max} = maximum standardized uptake value; SUV_{peak} = peak standardized uptake value; TLG = total lesion glycolysis.

Table 3

Multivariate associations between patient characteristics and pre-SBRT total lesion glycolysis

Parameter	HR	95% CI	*P*
Age			
<65 yrs	1.00	-	-
≥65 yrs	0.59	0.20–1.74	.339
ECOG PS			
0	1.00	-	-
1	3.57	1.09–11.65	.035
Location			
Head	1.00	-	-
Other	2.42	0.39–15.07	.345
Baseline Ca 19-9			
<90 U/mL	1.00	-	-
≥90 U/mL	0.77	0.22–2.72	.679
Pre-SBRT gemcitabine			
1 cycle	1.00	-	-
None	4.41	1.01–19.24	.048
Pre-SBRT TLG-median			
<70.9	1.00	-	-
≥70.9	3.34	1.07–10.48	.038

Abbreviations: Ca 19-9 = carbohydrate antigen 19-9; CI = confidence interval; ECOG HR = hazard ratio; PS = Eastern Cooperative Oncology Group performance status; SBRT = stereotactic body radiation therapy; TLG = total lesion glycolysis.

Table 4

Multivariate associations between patient characteristics and pre-SBRT metabolic tumor volume

Parameter	HR	95% CI	*P*
Age			
<65 yrs	1.00	-	-
≥65 yrs	0.62	0.21–1.88	.621
ECOG PS			
0	1.00	-	-
1	2.40	0.67–8.55	.177
Location			
Head	1.00	-	-
Other	1.23	0.18–8.47	.836
Baseline Ca 19-9			
<90 U/mL	1.00	-	-
≥90 U/mL	0.49	0.11–2.20	.351
Pre-SBRT gemcitabine			
1 cycle	1.00	-	-
None	4.37	0.96–19.91	.057
Pre-SBRT MTV-median			
<26.8 cm^3	1.00	-	-
≥26.8 cm^3	5.13	1.19–22.21	.029

Abbreviations: Ca 19-9 = carbohydrate antigen 19-9; CI = confidence interval; ECOG HR = hazard ratio; MTV = metabolic tumor volume; PS = Eastern Cooperative Oncology Group performance status; SBRT = stereotactic body radiation therapy.