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18F-FDG-PET assessment of malignant pleural mesothelioma: Total lesion volume and Total lesion glycolysis; the central role of volume.

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Statement of Translational Significance.

Tumor volume is an important biomarker of survival. In Malignant Pleural Mesothelioma, FDG PET Measurements expressed as Total Lesion Volume or Total Lesion Glycolysis, a measure of metabolic activity, are highly correlated with each other and are both measures of tumor volume.

Short Title

Total Lesion Volume and Total Lesion Glycolysis are both volumes.

ABSTRACT

Cancer Survival is related to tumor volume. 18F-FDG PET measurement of tumor volume holds promise but is not yet a clinical tool. Measurements come in two forms: the total lesion volume (TLV) based on the number of voxels in the tumor and secondly the total lesion glycolysis (TLG) which is the TLV multiplied by the average SUL per voxel of the tumor (SUL is the standardized uptake value normalized for lean mass). In this study we measured tumor volume in patients with malignant pleural mesothelioma (MPM).

METHODS: A threshold-based program in Interactive Data Language (IDL) was developed to measure tumor volume in 18F-FDG PET images. 19 patients with malignant pleural mesothelioma (MPM) were studied before and after two cycles (6 weeks) of chemo-immunotherapy. Measurements included the total lesion volume (TLV), Total Lesion Glycolysis (TLG), the sum of the SULs in the tumor (SUL- total), a measure of total 18F-FDG uptake, and the average SUL per voxel.

RESULTS: Baseline MPM volumes (TLV) ranged from 11 to 2610 cm^3. TLG values ranged from 32 to 8552 cm^3-SUL and were strongly correlated with TLV. While tumor volumes ranged over 3 orders of magnitude, the average SUL per voxel, SUL-average, stayed within a narrow range of 2.4 to 5.3 units. Thus, TLV was the major component of TLG while SUL-average was a minor component and was essentially constant. Further evaluation of SUL-average showed that in this cohort it's two components SUL-total and tumor volume changed in parallel and were strongly correlated, $r= 0.99$, $p<.01$. Thus, whether the tumors were large or small, the 18F-FDG uptake as measured by SUL-total was proportional to the total tumor volume.

Conclusion: TLG equals TLV multiplied by the average SUL per voxel, essentially TLV multiplied by a constant. Thus TLG, commonly considered a measure of "metabolic activity" in tumors, is also in this cohort a measure of tumor volume. The constancy of SUL per voxel is due to 18F-FDG uptake being proportional to tumor volume. Thus, in this study, the 18F-FDG uptake was also a measure of volume.

KEY WORDS: 18F-FDG-PET, PLEURAL MESOTHELIOMA, TLV, TLG

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive tumor which often presents as pleural thickening or rind with involvement of pleural fissures, the chest wall, or mediastinum (1). A strong indicator of cancer prognosis is the size of tumor but determining the size of MPM is a major challenge. Linear measurements are unreliable so a modified RECIST method was developed which measured the thickness of the pleural rind at several levels (2). Another approach is to measure tumor volume directly by CT. New automated CT analysis programs further this effort but as shown in a pilot study scan interpreters can have different perceptions of the extent of disease as well as the separation of tumor from adjacent normal tissue (3).

Against this background is the use of 18F-FDG-PET imaging not only for tumor localization, response to therapy and recurrence but also as a measure of tumor volume and metabolic activity. Applied to MPM, 18F-FDG-PET imaging provides a simple approach for measuring both tumor volume and metabolic activity. One approach is to define a SUL threshold above which voxels are counted as the total lesion volume (TLV) (4-7). A second measurement that can be obtained from 18F-FDG PET images is the total lesion metabolic activity commonly designated Total Lesion Glycolysis (TLG) (8). TLG equals the TLV multiplied by the average SUL in the tumor (8). Previous reports of MPM have shown that TLV, TLG or both are correlated with overall patient prognosis (5-7, 9-11).

For this report we used a background threshold based program to analyze 18F-FDG PET images for tumor volume (TLV) (4) and metabolic activity (TLG). Subjects were patients with MPM who received an anti-mesothelin immunotoxin with chemotherapy. We explored the relationship of total volume (TLV), the total 18F-FDG uptake by MPM (SUL-total), the average

SUL per voxel in the tumor (SUL-average) and the total lesion glycolysis (TLG). We found that in this cohort in addition to TLV, TLG was also a measurement of tumor volume.

MATERIALS AND METHODS

Patients

Nineteen patients (84% male), median age 67 (52 to 76) years, with histologically confirmed malignant pleural mesothelioma, measurable stage III and IV disease, were enrolled in a phase 1 study of the antimesothelin immunotoxin SS1P in combination with pemetrexed and cisplatin (12). Pemetrexed and cisplatin were administered every 3 weeks for up to 6 cycles while SS1P was administered intravenously on days 1, 3, and 5 every 3 weeks for 2 cycles i.e. for only the first 6 weeks. For the study CT and 18F-FDG PET/CT scans were obtained at baseline and every 6 weeks. Thoracic CT scans were analyzed by measuring tumor thickness at the chest wall and mediastinum at three levels, according to the modified RECIST procedure (2). Only the baseline and 6 week results were used for this report. The study protocol was approved by the National Cancer Institute (NCI), National Institutes of Health, Institutional Review Board and all patients gave written informed consent in accordance with the NCI Institutional Review Board regulations.

18F-FDG PET/CT Studies

Patients fasted 4-6 hours before 18F-FDG PET/CT imaging, had fasting blood glucose values of less than 200 mg/dl and were studied about 1 hour after administration of about 370, 555 or 740 MBq of 18F-FDG. Images were acquired with either the Siemens Biograph 128 or GE Discovery ST and were processed using iterative reconstruction (3 iterations 21 or 22 subsets) with point spread function (PSF) correction or both PSF and time of flight corrections.

[18F]-FDG PET/CT volume measurements were considered exploratory and not used for treatment decisions.

18F-FDG PET/CT image analysis

18F-FDG PET measurements were expressed as the standardized uptake value normalized to lean body mass (SUL). A background threshold-based program written in Interactive Data Language (IDL v.8.0) quantified the tumor volume and overall 18F-FDG activity. The threshold was determined by measuring the average SUL activity within a 3 cm diameter sphere in the liver and then multiplying this value by 1.5 and adding two times the SEM of the voxels within the sphere (13). (Mean liver SUL at baseline and 6 weeks was 1.81+/- 0.04, and 1.80+/- 0.04, p=0.15.) This created a mask of positive voxels which was further edited to exclude non-tumor tissue (eg. brain, heart, kidney etc.) and compared to 18F-FDG- PET images to ensure all tumor was included. Thirty-eight 18F-FDG PET studies were analyzed in duplicate; their mean values are reported here. The percent coefficient of variation (%CV) of duplicate analyses of TLV was 2.5%; 95% CI 7.0% (14, 15).

To validate the accuracy of the IDL program we assessed thirty five malignant nodules (thyroid cancer, neuroendocrine tumors and lymphoma; approved NIH clinical protocol 18F-FDG studies; patients were deceased at the time of the current analysis so that under 45 CFR 46, IRB approval or an exemption for this research was unneeded) comparing the 18F-FDG PET volumes to those in contemporary CT studies using a PACs CT volume measurement program (16). Nodules were selected because visually they had uniform 18F-FDG activity without evidence of necrosis. The CT volumes ranged from 0.5 to 428 cc. 18F-FDG PET and CT measurements were nearly identical, a regression line relating the two had a slope of 0.982

and a y intercept of 0.4 (Fig. 1). The percent coefficient of variation (%CV) of duplicate analyses of nodule volumes was 1.2%; 95% CI 3.3% (14, 15).

Measurements and Calculations

The IDL program made two measurements. It first determined the number of voxel's with SULs equal to or greater than the threshold. Multiplying this value by the volume of a single voxel gave the total lesion volume, TLV (Fig. 2A). The SULs in these voxels were then summed to give the total SUL in the tumor (SUL-total). (Fig. 2B). Because the SUL-total is affected by voxel size, all SUL-total values were corrected to represent 16.9 voxels/ml, the largest voxel size encountered in this study.

Two further calculations were made: the average SUL per voxel (SUL-average) was calculated by dividing the SUL-total by the number of voxels in the tumor (Fig. 2C) and the total lesion glycolysis, (TLG), which equaled the total lesion volume, TLV, multiplied by the SUL-average. (Fig. 2D).

Statistical Methods

The relationship between pairs of measurements, TLV, TLG, SUL-average and SUL-total was determined using Spearman correlation analysis (Table 1). The results were interpreted as strong correlation, $|r| > 0.70$; moderately strong correlation, $0.50 < |r| < 0.70$; or weak correlation, $|r| < 0.30$. Since p-values test r=0; the most important information is the magnitude of the correlation.

RESULTS

TLV, TLG, and SUL-average

Baseline volumes of TLV ranged from 11 to 2610 cm^3 and the corresponding values of TLG ranged from 32 to 8552 cm^3-SUL. With 6 weeks of therapy there was a dramatic reduction of both TLV and TLG with median response of 75% in each (Supplemental Figs 1 and 2). After 6 weeks of therapy, TLV values ranged from 0 to 1460 cc and the corresponding TLG values were 0 to 4470 cm^3-SUL. Both at baseline and 6 weeks, TLG and TLV were strongly correlated as were the percent changes of the two with therapy (Table 1).

As is evident in Fig. 2C, there was minimal variation of SUL-average despite the wide range of tumor volumes. When compared to TLV, SUL-average values were relatively minor contributors of TLG, ranging from 2.4 to 5.3 and averaging the same before and after therapy (3.64+/- 0.16 baseline vs 3.61+/- 0.16 at 6 weeks, p=0.87) (Fig. 3). Thus, as in Fig. 4A, side by side comparison of TLG and TLV and Fig. 4B showing the changes of the two measurements with therapy, TLG was essentially determined by TLV. The dominance of TLV in TLG is also evident in plots of survival versus TLV and TLG, Figs. 5A and 5B. Except for the shift to the right in the TLG figure, the two curves appear very similar.

SUL-total and TLV

The average SUL per voxel, SUL-average, equals the sum of the SULs in the tumor, SUL-total, divided by the total number of voxels. Another expression is SUL-total / tumor volume multiplied by the volume of a single voxel. The reason that SUL-average was relatively constant was that the ratio of SUL-total to tumor volume was relatively constant. As shown in Fig. 6, SUL-

total is linearly related to tumor volume. SUL-total is also strongly correlated with TLV (Table 1). Since SUL-total is an expression of total 18F-FDG uptake, the relationship of SUL-total to tumor volume also means that the 18F-FDG uptake by these tumors is essentially proportional to the volume. Side by side comparison of SUL-total and TLV (Fig. 7A) as well as the changes of the two measurements with therapy (Fig. 7B) show that as these tumors enlarged or responded to therapy, 18F-FDG uptake per tumor volume remained constant.

DISCUSSION

Important for this study was to show that the 18F-FDG volume program was both accurate and reproducible and that the measurements were consistent with visual interpretation of MPM 18F-FDG PET scans before and after therapy (Supplemental Fig. 1). 18F-FDG PET measurement of total lesion volume (TLV) was also correlated with modified RECIST measurements at baseline, $r = 0.67$, $p<.01$ and at 6 weeks, $r = 0.63$, $p<.01$. Similar to other reports (5, 6, 10, 11), Kaplan Meier analysis of baseline 18F-FDG tumor volumes was also an indicator of patient survival (Supplemental Fig. 3). Perhaps more important was that the relationship of baseline 18F-FDG PET volume to survival (Fig. 5A) was similar to results in earlier reports where CT was used to measure volume. Pass et al. in a ground breaking report showed that MPM volumes of less than 100cc were associated with a median survival of 22 months compared to 9 months for larger tumors (17). A more recent multicenter study also showed favorable survival for tumors less than 100 cc and short survival for tumors larger than 500cc (18).

The similarity of the plots of survival versus TLV and TLG (Figs. 5A and 5B) led to the analysis of SUL-average the second component of TLG. A surprising finding was that although tumor volumes varied greatly, SUL-average was not dependent on tumor size; its values always resided within a narrow range; and its two components, SUL-total and TLV were highly correlated and linearly related. It's unknown whether the constancy of SUL-average is a peculiarity of mesothelioma or a more universal characteristic of tumors. However, it appears that as MPM tumors enlarge the uptake of 18F-FDG increases but in proportion to the change in size. Additionally, the consistent relationship of 18F-FDG uptake to tumor volume was still evident after two cycles of therapy that led to dramatic reductions of tumor volume. An

assumption about cancers is that as they grow, there is an increase in “metabolic activity” and 18F-FDG uptake per cell related to increases in Glut-1 transport and Hexokinase (19, 20). But that does not seem to be the case with MPM where the volume and 18F-FDG uptake maintain a constant ratio.

Total Lesion Glycolysis (TLG) was first defined by Larson et al. as a measure that could be used to assess tumor response to therapy (8). The idea was that the change of metabolic activity (TLG) was a measure of cell killing. TLG equals TLV multiplied by the SUL-average. TLG is clearly a surrogate for total metabolic activity but because of the constancy of SUL-average, TLG in the context of MPM also reflects a volume. And, it may explain that patient survival is related to TLG because cancer survival is related to tumor volume. Therapy led to concordant responses of TLG and TLV (Fig. 4B). Again, because of the constancy of SUL-average the relationship between TLG and TLV is one of cause and effect: a change of TLV leads to a change in TLG. Thus, as described by Larson et al. a reduction TLG an indicator of tumor metabolism is a measure of cell killing, but in this instance the measured change in TLG is due to the loss of tumor volume.

In the original article describing TLG, the SUVaverage (Standardized Uptake Value body weight average) “was computed by placing a region of interest within the perimeter of the tumor region containing... the SUVmaximum” (8). Thus, like SUVmaximum, SUVaverage was a local value and like SUVmaximum its value could change with therapy so that it was included as a response variable in the 1999 European Organization for Research and Treatment of Cancer (EORTC) 18F-FDG PET recommendations (21). The SUL-average described in this current report, however, is a global measurement representative of the entire tumor and calculated as the SUL-total divided by the total number of voxels in the tumor. Although the original definition

of TLG has been carried forward (22), it is now recognized that there is a second form of the measurement based on total volume of tumor for which the SUVaverage value is calculated from the entire volume (23). In our studies we found that the SUL-average has two characteristics. The first is that it is relatively constant for a wide range of tumor sizes. Second we found that values of SUL-average were not related to overall survival (Supplemental Fig. 4). This is consistent with an earlier report of Veit-Haibach who found that the change of SUVaverage ("SUVmean") values after therapy were not predictive of patient outcome (6). In reports where the entire volume of MPM tumor was measured using FDG PET images, the SUVaverage values were in the same range as our SUL-average results. Using an FDG PET global volume of interest program Veit-Haibach, et al, studied total tumor volume, TLG and SUVaverage ("SUVmean") in 41 MPM patients (6). The SUVaverage ("SUVmean") values varied from 2.5-6.4 with PET measured volumes ranging from 2.5 to 1799 cm^3 (6). In another study of 13 patients with MPM, Lee found SUVaverage ("SUVavg") values ranging from 2.9-6.1 for PET volumes of 14.1 to 3056 ml (5). In 8 MPM patients, Genestreti found that SUVaverage ("SUVmean") ranged from 1.91 to 3.36 and values were not significantly different before and after therapy (24).

The use of regional SUVaverage values to calculate TLG or the emphasis on finding clinically relevant measurements, could have led investigators away from noticing the relative constancy of SUVaverage and the finding that in MPM, total 18F-FDG uptake (SUL-total) was proportional to tumor volume (TLV) specifically metabolic tumor volume. In the current study, the constant proportionality of SUL-total to TLV over a wide range of tumor sizes suggests that the average FDG uptake per cell is constant despite differences in volume. The relationship of FDG uptake to cell number was previously shown by histopathologic analyses. In tumors taken

from patients who had FDG PET scans, the FDG uptake correlated with the number of tumor cells, their density in tissue and their mitotic activity (20, 25, 26). FDG uptake as a measure of cell number may also apply to studies where the total metabolic activity in tumor or tumors is measured. In 1993, Alavi, et al, originated the concept of total metabolic activity, a value obtained by multiplying total volume by FDG uptake per 100 cc's of tissue. (27). Recently, the concept of global tumor glycolysis, the sum of TLGs to describe entire disease burden in patients with multiple tumors has received more interest as a robust response indicator that could be used clinically in an ongoing fashion (28, 29).

There are potential limitations to this study. First, the data were obtained from a single study involving a small number of patients. However, other reports of MPM where SUVmean values were similar to ours, help to validate our findings. Second, malignant pleural mesothelioma is spread over surfaces rather than being a localized tumor mass. Whether this contributes to the specific results is unknown, but certainly, the findings should be tested with other cancers. Third, tumor types with higher metabolic activity may behave quite differently. Last, our method for determining TLV from 18F- FDG PET scans is a background threshold approach in which liver was used as the background tissue (4). Our method for determining the threshold was patterned after Percist01 except that instead of setting the threshold as the average liver activity multiplied by 1.5 plus two standard deviations, we replaced standard deviations with two standard errors (13). This lowered our threshold so that small lesions visible in the 18F-FDG PET scans were included in the measured volume. With this threshold, the segmented MPM volume was, image-wise, consistent with the visible extent of disease.

Conclusion:

In conclusion, tumor volume is an important biomarker of survival. 18F-FDG PET measurements expressed as Total Lesion Volume or Total Lesion Glycolysis often considered a measure of metabolic activity are highly correlated with each other and are both measures of volume. In this study of MPM, there was a cause and effect relationship between tumor volume and total lesion glycolysis (TLG). This study also showed that total 18F-FDG uptake, measured as SUL-total was always proportional to the total metabolic volume of the tumor (TLV) even when tumors varied greatly in size or after response to therapy. This finding was totally unexpected since standard teaching suggests that change in metabolism as measured by FDG uptake precedes the change in volume. MPM may be a special case where FDG uptake per cell, and cell proliferation change together. To an extent, our results are a reflection of measuring the entire visible tumor. The relationship of FDG uptake to total metabolic tumor volume is a global characteristic that may not reflect regional variation such as in areas that include SUVmax and SUVpeak.

To conclude, this study showed that TLG and SUV-total uptake in malignant pleural mesothelioma were measurements that reflected the tumors' total metabolic volume. Whether these results are found in other tumors needs further study.

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KEY POINTS

QUESTION: Is 18F-FDG tumor uptake a measure of metabolism or of tumor volume?

PERTINENT FINDINGS: In a cohort of patients with malignant pleural mesothelioma (MPM) studied with 18F-FDG PET scans, the average SUV/SUL concentration per voxel was essentially constant, range 2.4-5.3, despite tumor size varying from 1 to 2610 cc, meaning that the Total Lesion Glycolysis, tumor volume multiplied SUV/SUL average per voxel, was a volume measurement. The reason that SUV/SUL average per voxel was relatively constant was due to 18F-FDG uptake by these tumors being proportional to their volume indicating the 18F-FDG uptake itself was a measure of tumor volume.

IMPLICATION FOR PATIENT CARE: 18F-FDG tumor uptake commonly considered a measure of tumor metabolism is also a measure of tumor volume, a finding which applies to MPM and probably other tumors as well.

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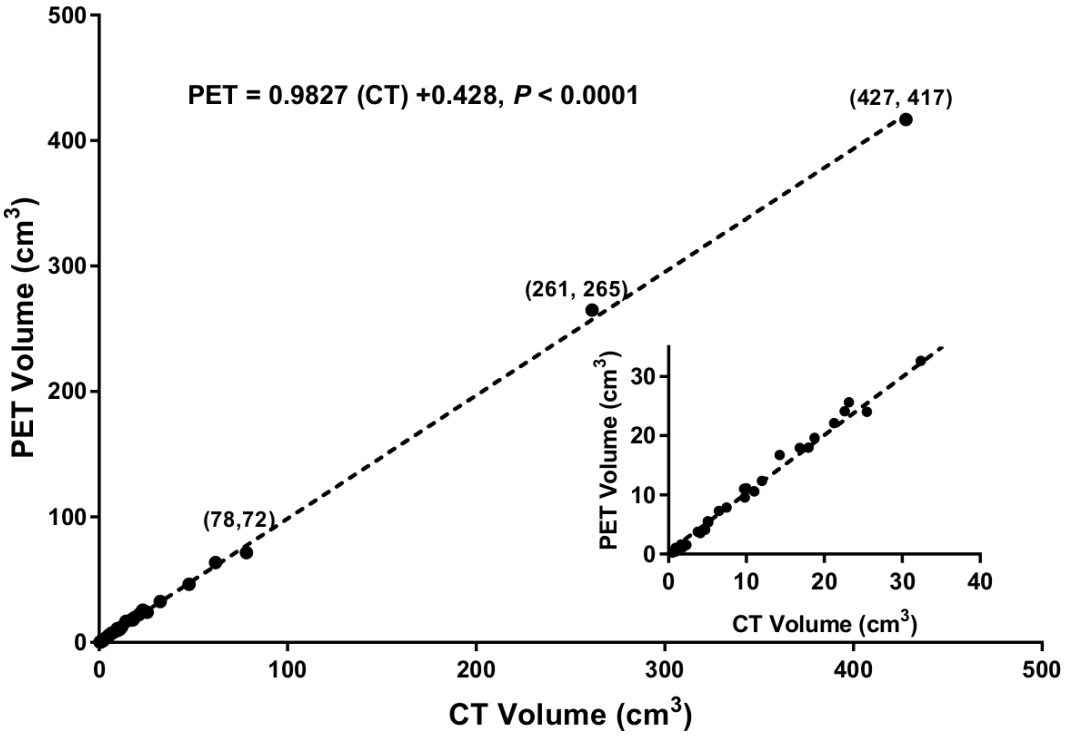


Figure 1: Tumor Nodule, Volumes: 18F-FDG PET vs CT. Measurements in duplicate. Inset: Nodules less than 40 cm^3.

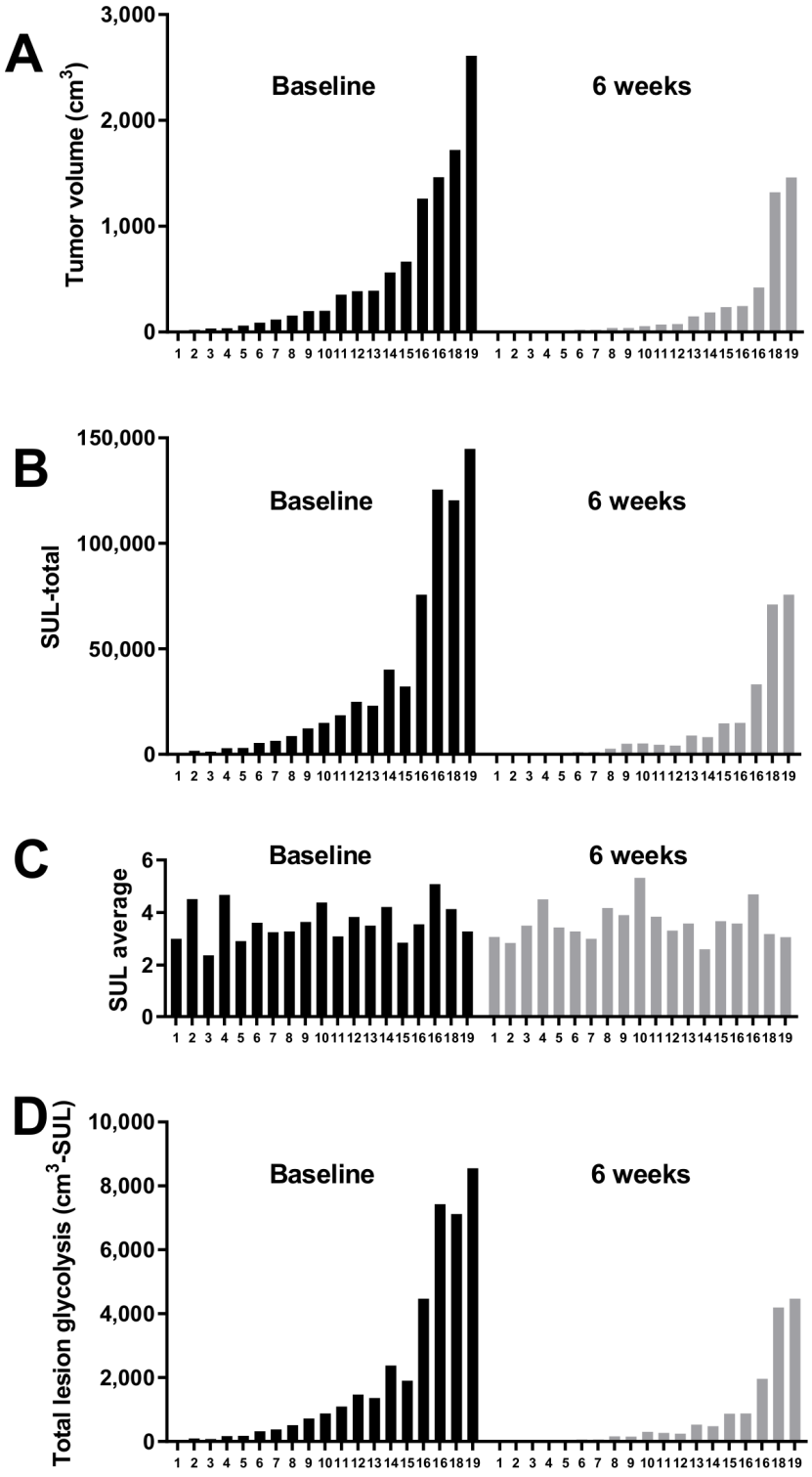


Figure 2: 19 Patients -Baseline and 6 week A: Total Lesion Volume; B: SUL-total; C: SUL-average; D: Total Lesion Glycolysis. Order based on volume at baseline and 6 weeks.

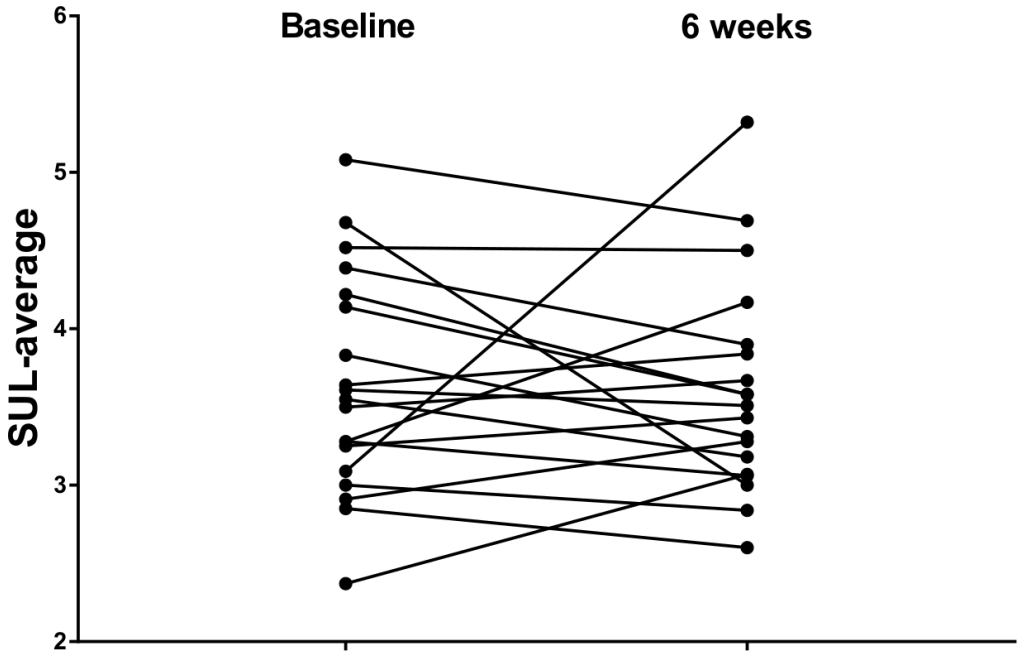


Figure 3: SUL-average; baseline and 6 weeks.

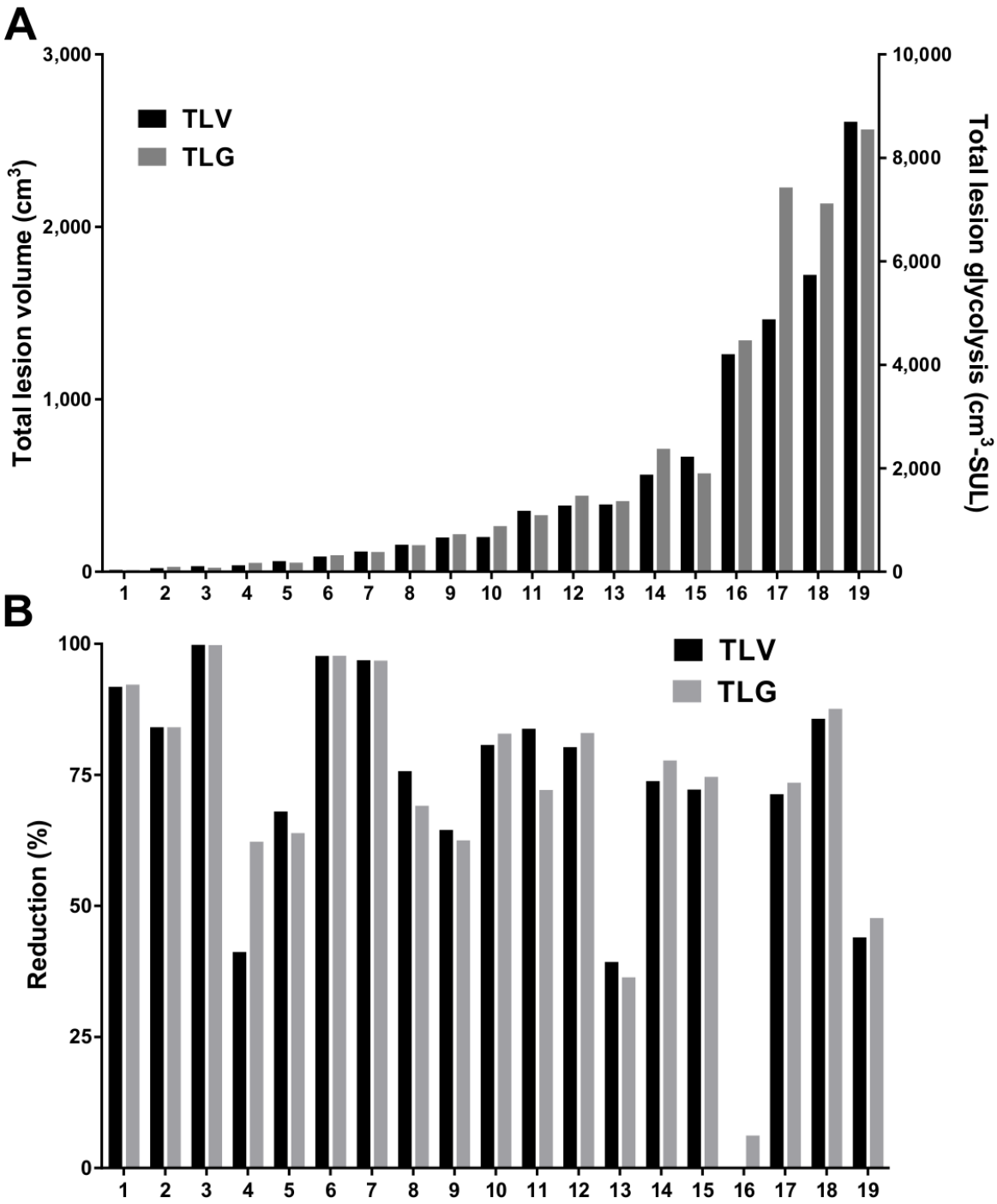


Figure 4: 19 patients sorted by volume; Total Lesion volume (TLV), Total Lesion Glycolysis (TLG); A: Baseline values; B: Response to Therapy.

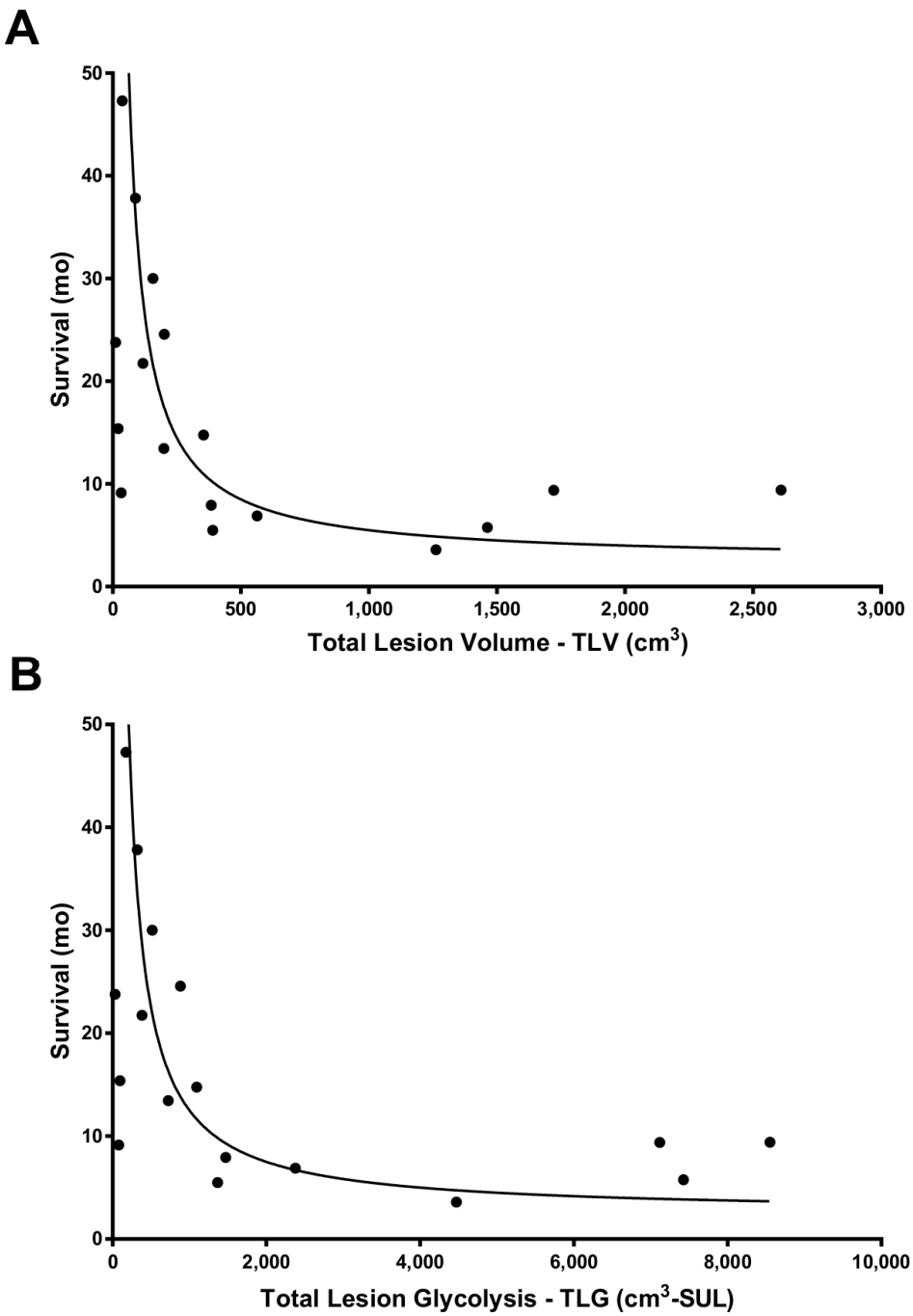


Figure 5: Survival Association Curves A: Survival vs Total Lesion Volume; Solid line:Inverse function: Survival = 3000/TLV +2.5; B: Survival vs Total Lesion Glycolysis; Solid line:Inverse function: Survival = 10000/TLV +2.5.

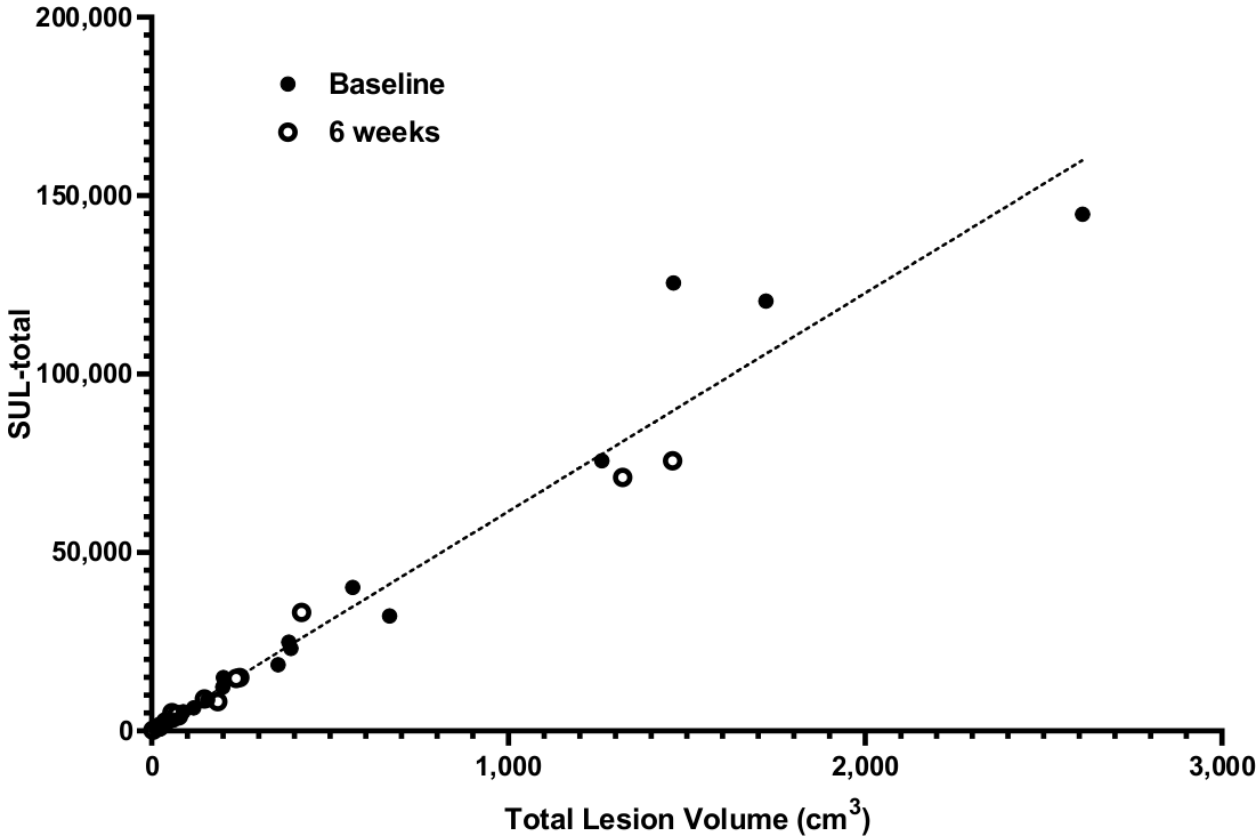


Figure 6:. Linear plot of SUL-total vs Total Lesion Volume (TLV). Baseline and 6 weeks values. Linear Regression includes all data: SUL-total = 61.18 * (TLV) + 326. r2 = 0.9575, p < .0001.

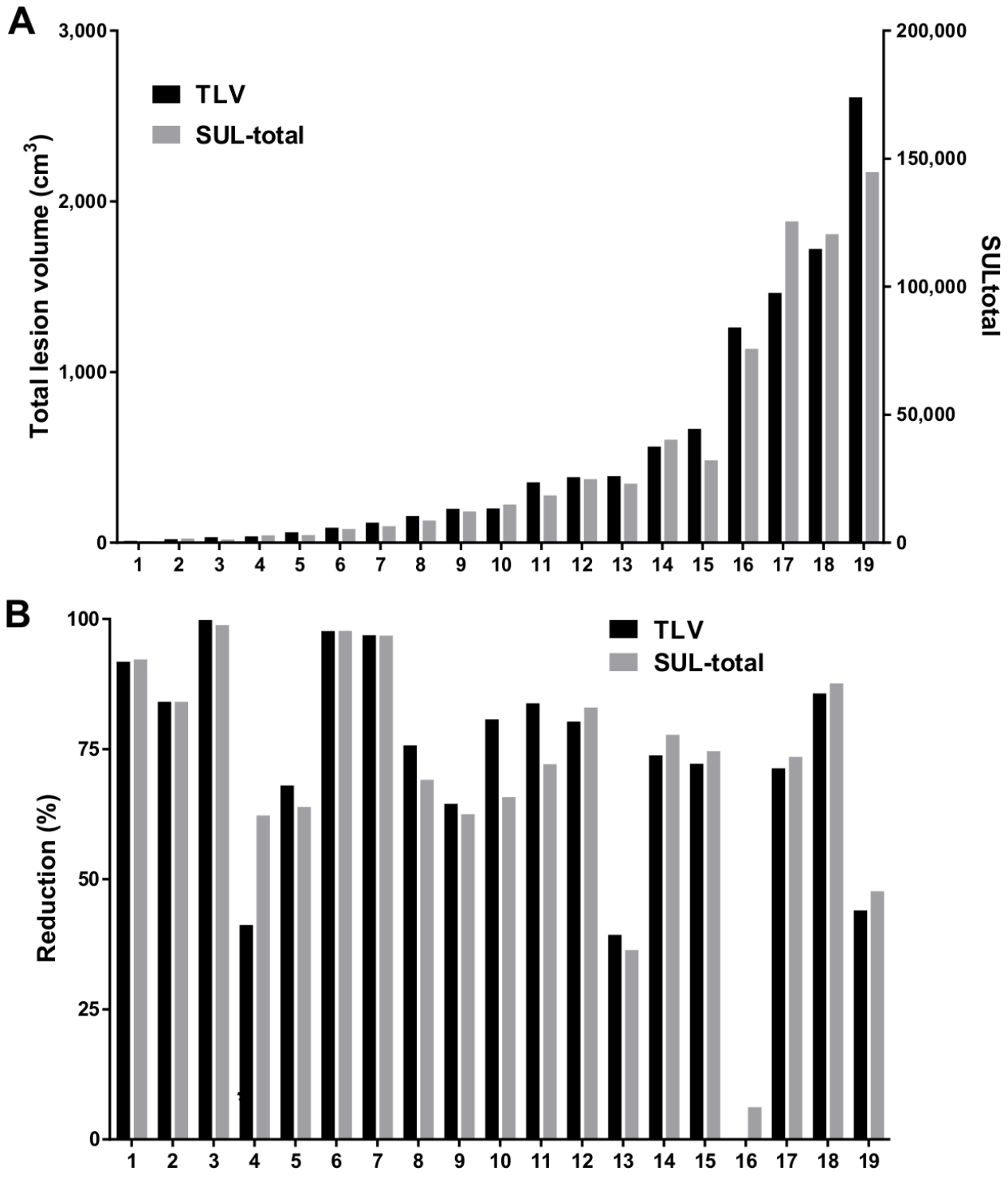


Figure 7: 19 patients - Sorted by Volume; Total Lesion volume (TLV) & SUL-total A: Baseline values B: Response to Therapy

		Baseline		
	TLV	**TLG**	**SUL-average**	**SUL-total**
TLV	**--**	**0.99**	**0.20**	**0.99**
		< .01	**0.41**	**< .01**
		6 weeks		
TLV	**--**	**0.99**	**0.10**	**0.98**
		< .01	**0.67**	**< .01**
		Therapy Response		
TLV	**--**	**0.95**	**-0.29**	**0.93**
		< .01	**0.23**	**< .01**

Table 1: Spearman Correlations (r): TLV: Total Lesion Volume; TLG: Total Lesion Glycolysis; SUL-average: average SUL per voxel; SUL-total: sum of SULs in tumor. Therapy Response: Correlations of Responses calculated as (Baseline value–6 weeks value) / Baseline value.

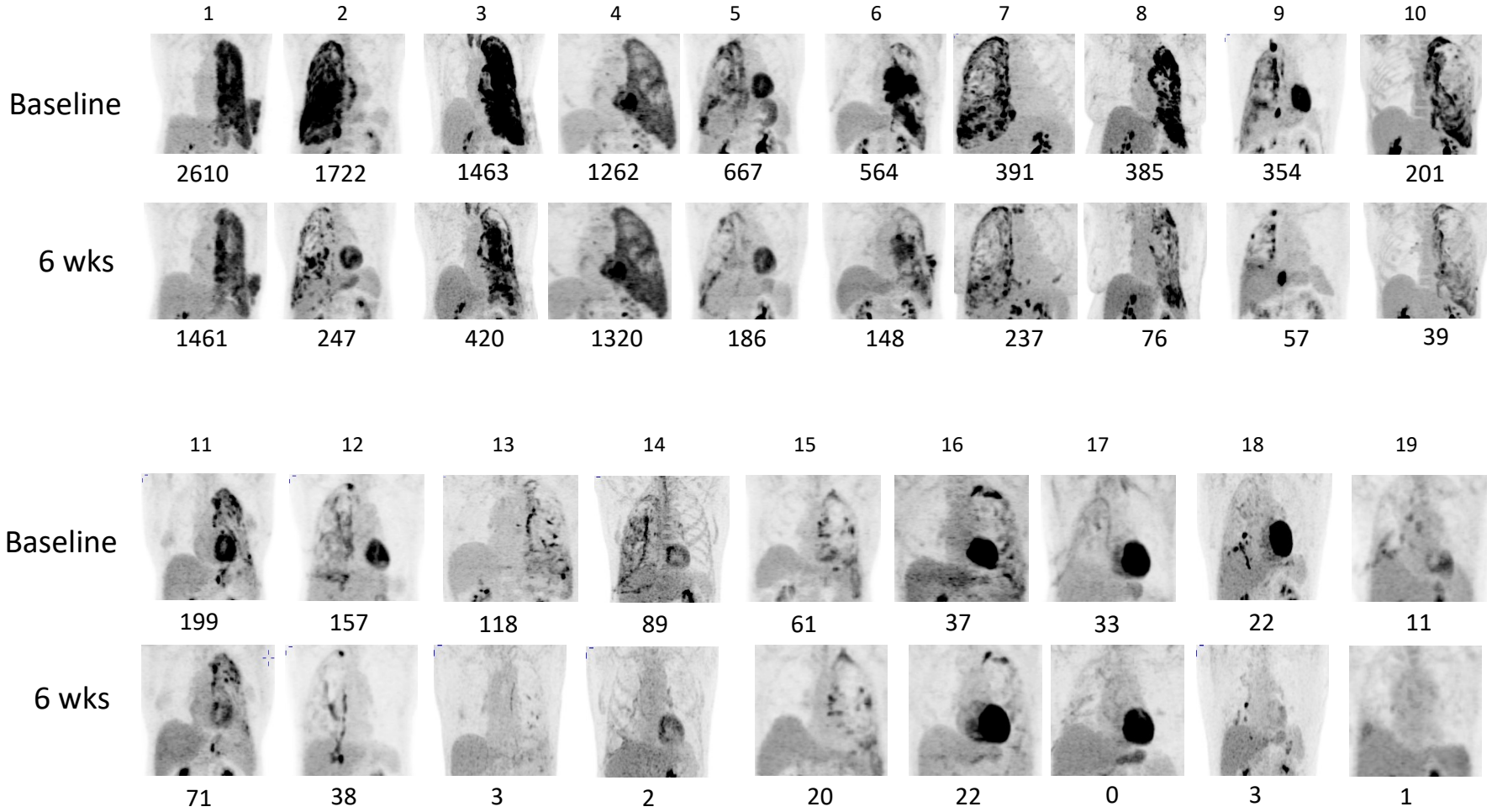


Figure 1. FDG PET (MIP) images of the thorax of the nineteen pleural mesothelioma patients. The order of the images in both the baseline and 6 weeks set is based on the Total Lesion Volume at baseline. The measured total lesion volumes are listed below each image. Baseline: before therapy; 6 wks: after two Cycles of SS1P immunotoxin + premetrexed + cisplatinin therapy.

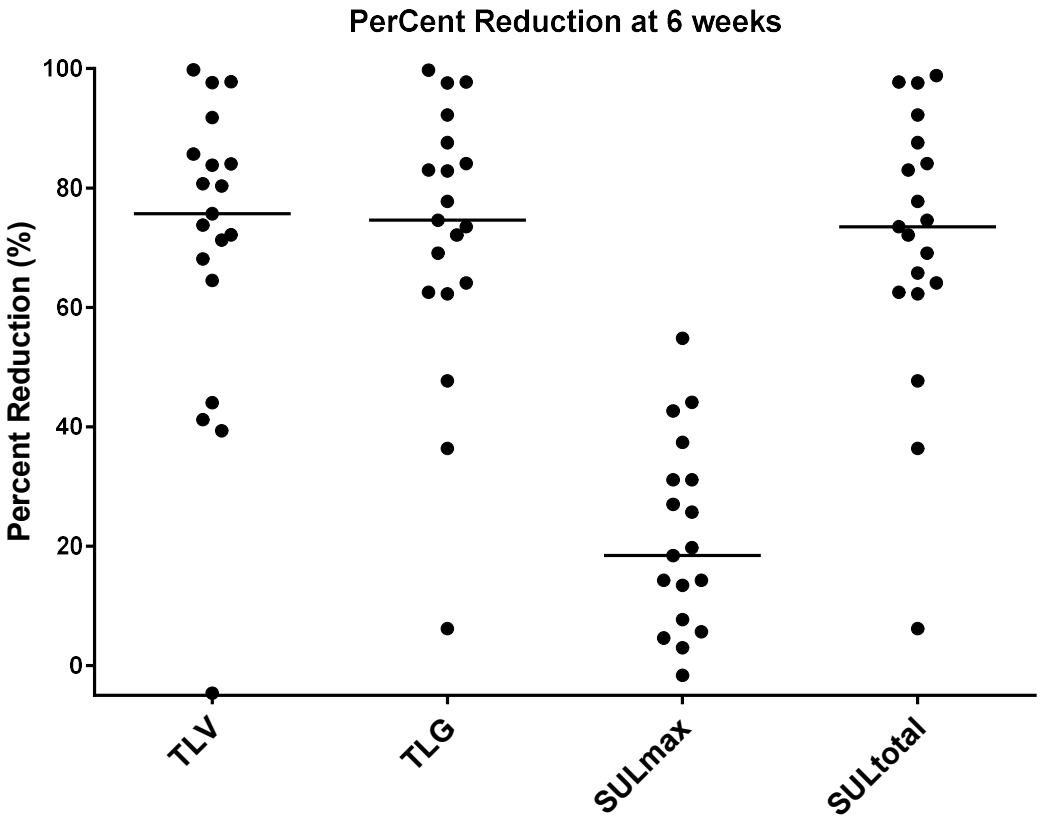
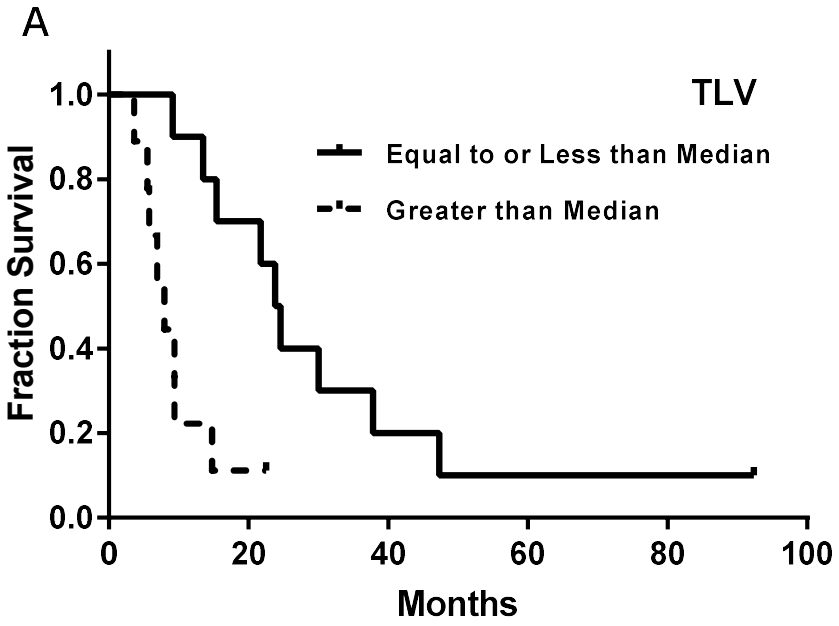


Figure 2: Percent Reduction (Response) of Total Lesion Volume (TLV), Total Lesion Glycolysis (TLG), SULmax, SULtotal. Lines show median values. 19 patients with pleural mesothelioma following two Cycles of SS1P immunotoxin + premetrexed + cisplatinin therapy.



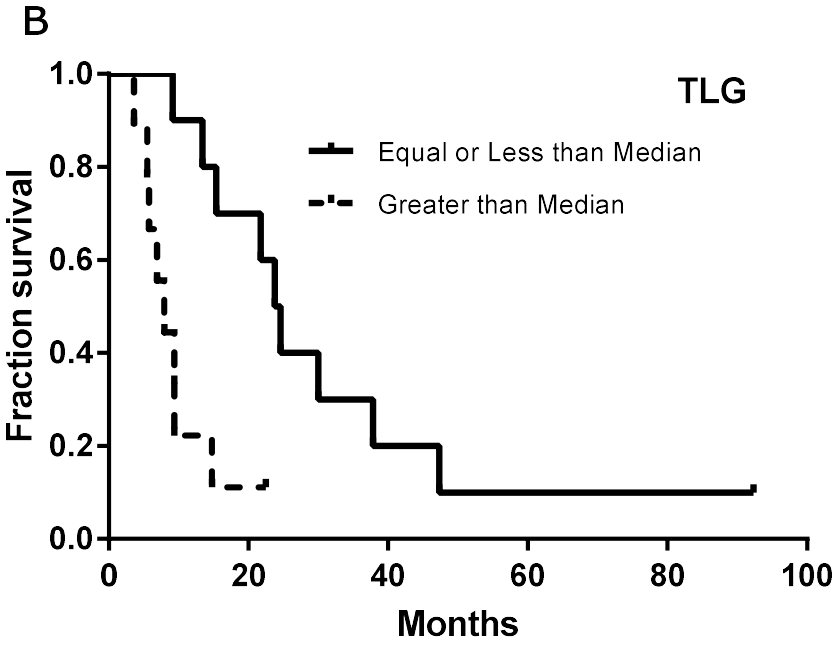


Figure 3. Kaplan-Meier plot of overall survival (OS). Measurements from FDG PET images of A) total lesion volume (TLV), and B) total lesion glycolysis (TLG) in 19 patients with pleural mesothelioma gave identical plots. For analysis patient groups were developed based on their median values of TLV and TLG.

	Median Value	Median OS (months) if value less than equal to median	Median OS (months) if value greater than median	P
TLV baseline (cc)	201	24.1	7.9	0.0031
TLG baseline (SUL-cc)	882	24.1	7.9	0.0031

Kaplan-Meier Analysis:

For Kaplan-Meier Analysis, FDG PET images of 19 patients with malignant pleural mesothelioma obtained before therapy were analyzed for Total Lesion Volume (TLV) and Total Lesion Glycolysis (TLG). Data were divided into two groups of 10 and 9 patients apiece (10 less than or equal to the median verses 9 greater than the median). Overall survival (OS) was calculated at the same time in months for treatment initiation (on- study date), until death resulting from any cause. A two-tailed log rank test was used to determine the significance of difference between each pair of curves based on the group parameters.

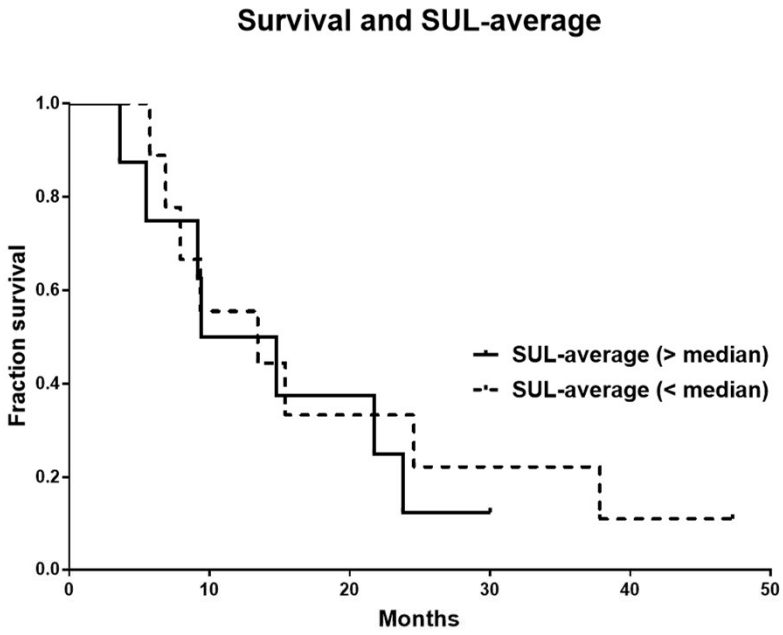


Figure 4. Kaplan-Meier Analysis, FDG PET images of 19 patients with malignant pleural mesothelioma obtained before therapy were analyzed for SUL-average calculated a SUL-total divided by the total number of voxels in the tumor. For analysis patient groups were developed based on their median values of SUL-average¶

¤	Median Value¤	Median OS (months) if value less than equal¶ to median¤	Median OS (months) if value greater than median¤	P¤
SUL-average baseline¤	3.64¤	12.09¤	13.4¤	0.65¤

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