Volume-based parameters on FDG PET may predict the proliferative potential of soft-tissue sarcomas

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ABSTRACT

Introduction: Soft-tissue sarcomas (STS) are rare types of tumors that have variable levels of tumor differentiation. F-18 fluorodeoxyglucose positron emission tomography (FDG PET) has been established as a useful tool for STS patients, and the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are reported to be useful in various cancers. We compared the diagnostic value of four PET parameters (maximum standardized uptake value [SUVmax], SUVmean, MTV, and TLG) from two acquisition timings for predicting the expression of the pathological marker of cell proliferation Ki-67, based on pathological investigation.

Materials and Methods: In this retrospective study, we investigated 20 patients (59±19 yrs old, 18–87 yrs old) with pathologically confirmed STS who underwent FDG PET before surgical intervention. The patients fasted ≥6 hr before the intravenous injection of FDG. The whole body was scanned twice; at an early phase (61.5±2.6 min) and at a delayed phase (118.0±2.1 min) post-injection. The SUVmax, SUVmean, MTV, and TLG of the primary lesion were measured with a tumor boundary determined by SUV ≥2.0. Ki-67 was measured using MIB-1 immunohistochemistry. We used Pearson's correlation coefficient to analyze the relationships between the PET parameters and Ki-67 expressions. The Kaplan-Meier analysis with the log-rank test was performed to compare overall survival between high-group and low-group each of the four PET parameters and Ki-67 expression.

Results: All four PET parameters at each phase showed significant correlations with Ki-67. Among them, the Pearson's correlation coefficient (r) was largest for TLG (r=0.76 and 0.77 at the early and delayed phases, respectively), followed by MTV (0.70 and 0.72), SUVmax (r=0.65 and 0.66), and SUVmean (r=0.62 and r=0.64). From early to delayed phases, the SUVmax and SUVmean both increased in all 20 patients, whereas the MTV

and TLG increased in 13/20 (65%) and 16/20 (80%) patients, respectively. None of the %increases of the PET parameters were significantly correlated with Ki-67. The overall survival was shorter for high-SUVmax, high-SUVmean, high-TLG, and high-Ki-67 groups than the other groups, although the difference did not reach statistical significance.

Conclusion: The SUVmax, SUVmean, MTV, and TLG acquired at both 1 and 2 hr after injection showed significant correlations with Ki-67. Among them, correlation coefficient with Ki-67 expression was highest for TLG, although the best parameter should be determined in a larger population. The delayed-phase FDG PET was equally useful as that of early-phase to predict tumor aggressiveness in STS.

Keywords

soft tissue sarcoma, MTV, TLG, FDG, Ki-67, PET

Introduction

Soft-tissue sarcomas (STSs) are rare types of tumors that have various degrees of malignancy. F-18 fluorodeoxyglucose positron emission tomography (FDG PET), a functional imaging modality that reflects glucose metabolism in vivo, has been an essential tool for predicting the malignant potential, staging, prognosis, and treatment response in STS patients [1,2]. Although the use of PET tracers other than FDG such as F-18 fluorothymidine (FLT) [3] and C-11 methionine (MET) has been reported [4], FDG is still the most widely used PET tracer for STS. The standardized uptake value (SUV), which is used as a relative measure of FDG uptake (commonly normalized to the injected dosage and body weight), is used to semi-quantitatively evaluate STSs. In particular, the maximum of the SUV (SUVmax) within the tumor is mostly applied to express the intensity of FDG uptake in the tumor clinically because of its simplicity and high inter- and intra-observer reproducibility.

Volume-based parameters such as the metabolic tumor volume (MTV) and the total lesion glycolysis (TLG) have been reported to be useful for evaluating various cancers such as lung, head and neck, gynecological cancer, and osteosarcoma [5–9]. These parameters reflect the activity of the glucose metabolism in the entire tumor, whereas the SUVmax reflects only a single voxel (normally, a voxel size <0.1 ml).

In STSs, pathological assessments are needed for the detailed diagnosis and staging to determine treatments [10–12]. Tissue specimens from a surgical procedure are normally stained with hematoxylin and eosin (H&E) to visualize the architecture and cellular features. Immunohistochemical staining techniques are also used to observe the expression of the specific protein in tissues. Ki-67 is a nuclear protein present in proliferating cells, and it is a de facto standard histopathological parameter used as an indicator of cells' proliferative activity. The usefulness of Ki-67 measurement has been

confirmed, and the grading system using Ki-67 was the strongest prognostic factor [13].

Clinical studies of bone and soft-tissue sarcomas showed that the SUVmax was significantly correlated with the mitotic count [14] and Ki-67 expression [15]. FDG uptake, the SUVmax, and the mean standardized uptake value (SUVmean) were shown to be correlated with Ki-67 in other malignant tumors such as non-small cell lung cancer and breast cancer [16–18]. However, it is not yet established whether the MTV or the TLG is correlated with Ki-67. In addition, the optimal uptake time after FDG injection before image acquisition for the purpose of evaluating proliferative activity has been unclear. To address these questions, we compared four PET parameters (the SUVmax, SUVmean, MTV, and TLG) from two acquisition timings (1 and 2 hr post-injection) in relation to Ki-67 expression assessed by a pathological investigation.

Materials and Methods

Patients

In this retrospective study, we investigated a total of 20 patients (10 males, 10 females, age: 59±19 years old, range 18–87 years) who were pathologically confirmed to have STS and underwent FDG PET before any surgical intervention (total resection or biopsy), adjuvant chemotherapy, or radiation therapy at the National Hospital Organization Hokkaido Cancer Center between December 2010 and March 2016. The study population consisted of 17 patients with newly diagnosed STS and 3 with recurrent STS. Of the 20 patients, the tumors of three patients (two newly diagnosed and one recurrent) were diagnosed as low-grade (grade 1) based on Federation National des Centres de Lutte Contre le Cancer (FNCLCC) grading system, which is based on three pathological parameters (tumor differentiation, mitotic count, and tumor necrosis), and the tumors of another 17 patients were diagnosed as high-grade (grade 2, n=7, five newly

diagnosed and two recurrent; and grade 3, n=7, seven newly diagnosed; unclassifiable between grades 2 and 3, n=3, three newly diagnosed). The mitotic count information was not available for the unclassifiable patients. The patient histological types are summarized in Table 1. Tumors existed in the head and neck (n=2), the thorax (n=2), the abdomen (n=7), an upper extremity (n=2), or a lower extremity (n=7). The cancer stage was IB (n=3), IIA (n=6), IIB (n=3), III (n=5) or IV (n=3) based on the American Joint Committee on Cancer (AJCC) staging system ver. 7 (2011).

Image acquisition and reconstruction

An Eminence SET-3000G standalone PET scanner (Shimadzu, Kyoto, Japan) was used for all of the clinical FDG-PET scanning in this patient population. All of the patients fasted for ≥6 hr before a single intravenous injection of FDG (218±63 MBq, range 143–292 MBq; or 3.6±0.5 MBq/kg, range 2.9–4.6 MBq/kg). The blood glucose level was 96±10 mg/dl. No patient showed a blood glucose level ≥150 mg/dl. Each patient's whole body was scanned twice for each study: early imaging at 61.5±2.6 min (range 58–67 min) and delayed imaging at 118±2.1 min (range 113–122 min) after the FDG injection. The transaxial field of view (FOV) was 512 mm in diameter. Three-dimensional emission data were acquired in a continuous bed-movement manner (0.7–0.9 mm/sec). Transmission scanning was subsequently performed with a ^{137}Cs external source for attenuation correction. The transaxial spatial resolution at 1cm from the center of the FOV was 3.5 mm at full-width at half maximum.

Images were reconstructed with the dynamic row-action maximum likelihood algorithm (DRAMA), modified from the row-action maximum likelihood algorithm (RAMLA) [19]. The iteration and filter cycle values for DRAMA were 1 and 128, respectively. The image matrix was 128 × 128 with the voxel size 4.0 × 4.0 × 2.6 mm. A

post-reconstruction smoothing filter was not applied.

Quantitative image analysis

A total of 40 FDG-PET datasets (early and delayed images from 20 patients) were processed to delineate the tumor. These images were displayed on the monitor in a linear grayscale with a fixed window level of SUV 0–6. The four parameters SUVmax, SUVmean, MTV, and TLG were measured for the primary lesion. The SUV was calculated as [tissue radioactivity concentration (Bq/ml)] × [body weight (g)] / [injected radioactivity (Bq)]. The MTV was calculated as the tumor volume within the tumor boundary.

The tumor boundary was determined using a fixed threshold of SUV ≥2.0 based on a reported optimal threshold for osteosarcoma [9]. This threshold is relatively low, as SUV ≥2.5 is more often used for lung cancer and head-and-neck cancer. Because STSs occur in extremities or torso fat tissues, the low surrounding background signal levels allow a low SUV threshold to delineate the tumor excluding background activities. The SUVmax and SUVmean within the boundary were measured. The TLG was calculated as MTV × SUVmean within the same region. For all of the image analyses including the mathematical delineation, and for the parameter calculation, we used Metavol, an open-source software tool that was developed for the efficient measurement of tumor volume on PET-computed tomography (CT) (http://www.metavol.org/) [20].

Pathological assessment

Pathological data were obtained from CT or ultrasound (US)-guided needle biopsies (n=4), excision biopsies (n=6), and resected specimens of tumors (n=10). These surgical procedures were completed within 3 weeks of the PET scans. The tissues were

fixed in buffered formalin and embedded in paraffin. The fixed tissues were sectioned, followed by H&E staining and Ki-67 immunostaining to evaluate cellular proliferation. All pathological diagnoses were made by an experienced pathologist at our institute.

Statistical analysis

The SUVmax, SUVmean, MTV, and TLG values are expressed as the mean ± standard deviation (SD). We used paired t-tests to compare these four PET parameters between the early and delayed phases. We used Pearson's correlation coefficient to analyze the relationships between the PET parameters and Ki-67 expressions, and the relationship between the %increases of the PET parameters and Ki-67 expressions. Receiver operating characteristics (ROC) analysis was performed to evaluate PET parameters for distinguishing high-Ki-67 group from low-Ki-67 group. High and low Ki-67 groups were defined by the median as the cut-off value. The Kaplan-Meier analysis with the log-rank test was performed to compare overall survival (OS) between two groups. OS was defined as the duration from the date of baseline PET scan to death or the date of last contact for surviving patients. The PET parameters and Ki-67 expression were divided into either high group or low group using each median value as the cut-off. P-values <0.05 were considered statistically significant. Statistical calculations were carried out using R ver. 3.2.5 (R Project, http://cran.r-project.org).

Results

The PET parameters at the early and delayed phases

At the early and delayed phases, the SUVmax was 10.2±6.5 and 11.9±7.8, the SUVmean was 4.2±1.5 and 4.5±1.9, the MTV was 217±223 ml and 218±217 ml, and the TLG was 1088±1471 ml and 1240±1684 ml, respectively. Both the SUVmax and the

SUVmean increased in the delayed phase in 20/20 (100%) patients, whereas the MTV and TLG increased in 13/20 (65%) and 16/20 (80%) patients. The MTV did not significantly change over the phases, whereas the SUVmax, SUVmean, and TLG significantly increased from the early phase to the delayed phase (Fig. 1).

Correlations between the Ki-67 expression and the PET parameters

The relationships between Ki-67 expression and the four PET parameters are shown in Figure 2 (early phase) and Figure 3 (delayed phase). Each PET parameter at both phases showed a significant correlation with Ki-67 expression. The Pearson's correlation coefficient was largest for the TLG ($r=0.76$, $p<0.001$ for the early phase, and 0.77, $p<0.001$ for the delayed phases), followed by the MTV ($r=0.70$, $p<0.001$, and 0.72, $p<0.001$), SUVmax ($r=0.65$, $p<0.01$, and 0.66, $p<0.01$), and SUVmean ($r=0.62$, $p<0.01$, and 0.64, $p<0.01$). The differences in correlation coefficients between the SUVmax, SUVmean, MTV, and TLG did not reach significance (p=NS).

Correlation between the Ki-67 expression and the PET parameters' %increases

The relationships between the Ki-67 expression and the %increases of each PET parameter from the early phase to the delayed phase are shown in Figure 4. None of the %increases of the four parameters was significantly correlated with the Ki-67 expression.

ROC analysis

The ROC curves of the four PET parameters at the early phase and the delayed phase are shown in Figure 5. The area under the curve (AUC) was largest for the TLG (0.83 and 0.82 for the early and delayed phases, respectively), followed by the MTV (0.82

and 0.81), the SUVmean (0.72 and 0.76), and the SUVmax (0.75 and 0.74).

Survival analysis

The overall survival was shorter for high-SUVmax, high-SUVmean, high-TLG, and high-Ki-67 groups than the other groups, although the difference did not reach statistical significance. (Supplemental Figure 1).

Representative ^{18}F-FDG-PET images of three patients are shown in Figure 6. As shown in the cases from the left to the right, the Ki-67 expression, SUVmax, and TLG increased whereas the MTV showed a different tendency.

Discussion

Our analyses revealed significant correlations between PET parameters and a proliferation-associated pathological marker (Ki-67) in STS. Each of the four PET parameters showed a significant correlation with the expression of Ki-67. Among them, the Pearson's correlation coefficient was largest for the TLG, followed by the MTV, SUVmax, and SUVmean, although the differences of correlation coefficients did not reach statistical significance.

We also evaluated the usefulness of dual-phase FDG PET imaging for STS. The delayed-phase values of TLG, MTV, SUVmax, and SUVmean were also significantly correlated with the Ki-67 expression, and the degree of correction was equivalent between the early and delayed phases. Moreover, none of the %increases of the early-to-delayed PET parameters was significantly correlated with the Ki-67 expression. We also performed ROC analysis for discriminating high-Ki-67 group from low-Ki-67 group. AUC of MTV and TLG were larger than those of SUVmax and SUVmean at the both phases. Note that each AUC value was equivalent between the early and delayed phases.

Based on these results, we speculate that delayed PET imaging provides no additional information regarding the aggressiveness of STS. Similarly, there were no significant differences according to the Kaplan-Meier analysis between high-group and low-group by any of the four PET parameters or Ki-67 expression in OS, although we cannot conclude until larger population is studied.

Malignant tumors metabolize glucose dominantly via the glycolytic pathway rather than via the TCA cycle, and these tumors thus consume more glucose than normal cells do to produce the same amount of adenosine triphosphate (ATP), which is known as the Warburg effect [21]. In addition, malignant cells may need more ATP to accelerate cell proliferation, which may also increase glucose consumption. In the present study, both the MTV and the TLG were strongly correlated with the Ki-67 expression. One possible reason is that more-rapidly growing tumors may be relatively larger at onset. The SUVmax was also correlated with Ki-67, which was consistent with the report from Watanabe et al. showing that the Ki-67 expression was higher in high-SUVmax sites in non-Hodgkin lymphoma [22]. Theoretically, SUVmax is not the best indicator for at least 2 reasons. First, Ki-67 was not always evaluated at the same site that shows SUVmax. Ki-67 staining of a great number of slices from an entire tumor is not practical, and, in biopsy cases, the highest-FDG-uptake part is not always sampled. Second, many of the tumors were large (>5cm, stage IB, IIB and above) and had strong heterogeneity with micro-necrosis causing underestimation of the maximum concentration of FDG due to partial volume effect. These factors should have weakened the correlation between the SUVmax and Ki-67 expression.

In this context, we investigated the MTV and the TLG because they may have potential to overcome the above shortcomings of SUVmax. In literature, the relationship between Ki-67 and prognostic factors has been reported from several clinical studies of

other malignant tumors [9,23–28]. Byun et al. showed that the MTV can more accurately predict the clinical outcomes of patients with osteosarcoma compared to the SUVmax and TLG on PET [9]. Park et al. showed that the TLG is a better predictive factor than the SUVmax and MTV for the outcomes of patients with NSCLC [28].

In the current study, we observed that both the MTV and the TLG showed larger correlation coefficients than SUVmax, although the difference was not demonstrated statistically. In particular, TLG showed a stronger correlation with Ki-67 than the MTV. One of the reasons is that MTV may not fully reflect the metabolic activity of the tumor. For instance, MTV does not discriminate a voxel full of active cells (e.g., SUV=10) from a voxel with micro-necrotic foci coexisting with active cells (e.g., SUV=3), because these voxels are considered equivalent in the MTV concept. In contrast, TLG can reflect the above difference. Based on the definitions,

$$MTV = nv_0$$

$$SUV_{mean} = \frac{1}{n}\sum_{i}^{n} SUV_i$$

where n is the number of voxels within the VOI, v_0 is the volume of the single voxel, and SUV_i is the SUV of the ith voxel (i = 1,2,3,…,n) within the tumor boundary. Thus, TLG can be expressed as follows:

$$TLG = MTV \times SUV_{mean} = nv_0 \times \frac{1}{n}\sum_{i}^{n} SUV_i = v_0 \sum_{i}^{n} SUV_i$$

The equation indicates that TLG is proportional to the sum of SUV of each voxel within the tumor boundary. Thus, TLG can overcome the problem regarding MTV mentioned above. In addition, SUVmax is underestimated when the area of the highest uptake is smaller than the spatial resolution of the scanner, while TLG can count the spilled-over activity into the surrounding voxels. Therefore, we suggest that TLG may theoretically

most appropriately indicate the malignant potential of the tumor.

Before using volume-based parameters in clinical settings, we should be aware that the MTV and TLG can be affected by differences in PET scanners, the uptake time, and delineation methods [29,30]. Harmonization is needed to use these parameters in multi-center clinical trials [31].

We sought to clarify the usefulness of dual-phase imaging for predicting cell proliferating activities in this retrospective study. Other groups reported that dual-phase imaging was valuable to differentiate between benign and malignant lesions, and the SUVmax increment of the lung cancer could be a prognostic factor [32,33]. In visual assessment, it is well known that dual-phase imaging is also useful to distinguish malignant lymph nodes' uptake from physiological FDG uptake in normal bowels. However, in the present study, the measurements derived from the dual-phase images did not improve the correlation coefficient between the PET parameters and the Ki-67 index. From the early phase to the delayed phase, the SUVmax, SUVmean, and TLG increased significantly, whereas the MTV did not change significantly. Therefore, the dual-phase imaging in this study did not provide additional value compared to single-phase imaging in terms of grading the malignancies. We observed previously that the MTV calculated with a threshold of SUV 2.0 or 2.5 was not affected by the uptake time, whereas higher thresholds (≥3.0) produced MTV values that depended on the uptake time [29]. In addition, the SUVmax and TLG were influenced by the uptake time.

The clinical importance of our present findings is that they can be used to help surgeons predict the pathological aggressiveness of STSs before the operation, and the surgeons can thus modify the surgical procedure (biopsy or resection) based on the information obtained from PET. As a possible treatment strategy, if a tumor shows a large TLG value, the surgeon may plan a more extensive procedure with a larger margin and

more extensive lymph node dissection, and vice versa.

This study has several limitations. First, as this was a retrospective study and included only a small number of patients who underwent surgical intervention, selection bias could have affected the results. Second, the PET scanner used in this study is not a state-of-art PET-CT scanner. Current scanners with higher spatial resolution may generate better images to provide better predictive factors. Third, we calculated the MTV and TLG, but recent studies often use texture parameters that reflect the heterogeneity of tumor metabolism, based on a hypothesis that the more aggressive tumors may tend to be more heterogeneous in metabolism. Further studies are necessary to investigate whether texture analysis provides value additional to that shown by the MTV and TLG in soft-tissue sarcomas.

Conclusions

The SUVmax, SUVmean, MTV, and TLG acquired at both 1 and 2 hr after FDG injection showed significant correlations with the expression of the proliferation marker of Ki-67 in soft-tissue sarcomas. Among them, correlation coefficient with Ki-67 expression was highest for TLG, although the best parameter should be determined in a larger population. The delayed-phase FDG PET was equally useful as that of early-phase to predict Ki-67 expression.

The list of abbreviations

CT: computed tomography

DRAMA: dynamic row-action maximum likelihood algorithm

FDG: fluorodeoxyglucose

FLT: fluorothymidine

FNCLCC: Federation National des Centres de Lutte Contre le Cancer

FOV: field of view

H&E: hematoxylin and eosin

MET: methionine

MTV: metabolic tumor volume

OS: overall survival

PET: positron emission tomography

RAMLA: row-action maximum likelihood algorithm

STS: Soft-tissue sarcomas

SUV: standardized uptake value

SUVmax: maximum of SUV

SUVmean: mean of SUV

TLG: total lesion glycolysis

US: ultrasound

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Availability of data and materials

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Authors' contributions

Design of the study: TK KH

Investigation: TK TS KH NT

Formal analysis: TK KY.

Software: KH.

Supervision: TS MS TT KY NT.

Writing – original draft: TK KH.

Writing – review & editing: TK TS KH MS TT KY NT.

Competing interests

The authors declare that they have no competing interests.

Consent to publish

Not applicable.

Ethics approval and consent to participate

This retrospective study was approved by the institutional ethics committee of Hokkaido Cancer Center. The informed consent was waived from individual participants in the retrospective study according to the institutional ethics committee of Hokkaido

Cancer Center (#27-43). Patient records/information was anonymized and de-identified prior to analysis.

Statement of human rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figure Legends

Fig. 1. The MTV (**c**) did not significantly change, whereas the SUVmax (**a**), SUVmean (**b**) and TLG (**d**) increased significantly from the early phase to the delayed phase.

Fig. 2. Scatter plots of PET parameters at the early phase versus the Ki-67 expression. The SUVmax (**a**), SUVmean (**b**), MTV (**c**) and TLG (**d**) showed significant correlations with Ki-67 expression, and among them, the Pearson's correlation coefficient was largest for the TLG. The Pearson's correlation coefficients did not change at the delayed phase.

Fig. 3. Scatter plots of the PET parameters at the delayed phase versus the Ki-67 expression. Similarly to the early phase (Fig. 2), the SUVmax (**a**), SUVmean (**b**), MTV (**c**) and TLG (**d**) showed significant correlations with Ki-67 expression. The Pearson's correlation coefficient was largest for the TLG.

Fig. 4. Scatter plots of the %increases of the SUVmax (**a**), SUVmean **b**), MTV (**c**) and TLG (**d**) versus the Ki-67 expression. The %increases of all PET parameters were not significantly correlated with Ki-67.

Fig. 5. ROC curves for distinguishing high-Ki-67 group from low-Ki-67 group by PET parameters at the early phase (a) and the delayed phase (b).

Fig. 6. ^{18}F-FDG-PET images (early phase) of three representative patients with soft-tissue sarcomas. (**a**) Synovial sarcoma image with relatively low Ki-67 expression. (**b**) Pleomorphic undifferentiated sarcoma image with moderate Ki-67 expression. (**c**) Dedifferentiated liposarcoma image with high Ki-67 expression. Among them, the Ki-

67 expression, SUVmax, and TLG values showed the same tendency, whereas the MTV did not.

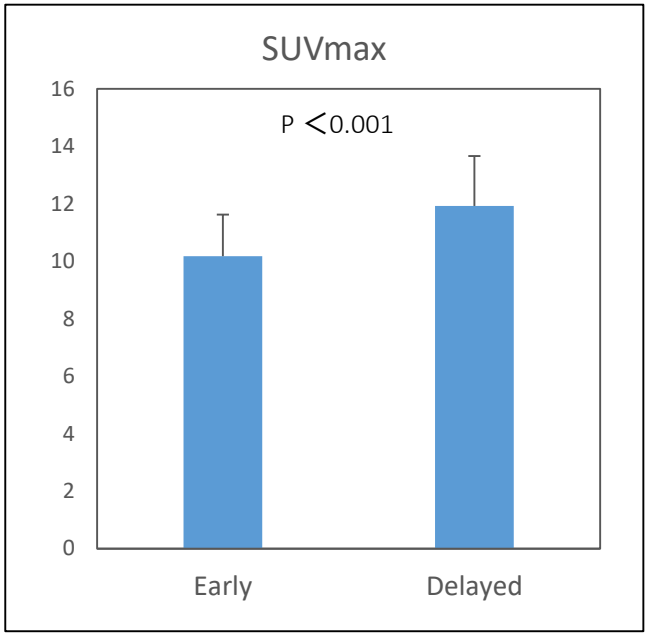
Table 1. Patients and tumor characteristics

Patient age	59±19 (range 18-87)
Patient sex:	
Male	10
Female	10
Tumor location:	
Head and neck	2
Thorax	2
Abdomen	7
Upper extremity	2
Lower extremity	7
Tumor grade:	
FNCLCC grade1	3
FNCLCC grade2	7
FNCLCC grade3	7
Ungradable (between grade 2 and 3)	3
AJCC stage:	
ⅠB	3
ⅡA	6
ⅡB	3
Ⅲ	5
Ⅳ	3
Tumor histology:	
Leiomyosarcoma	3
Liposarcoma	3
Rhabdomyosarcoma	1
Myxofibrosarcoma	1
Synovial sarcoma	1
Extraskeletal Ewing's sarcoma	1
MPNST	3
Undifferentiated	7

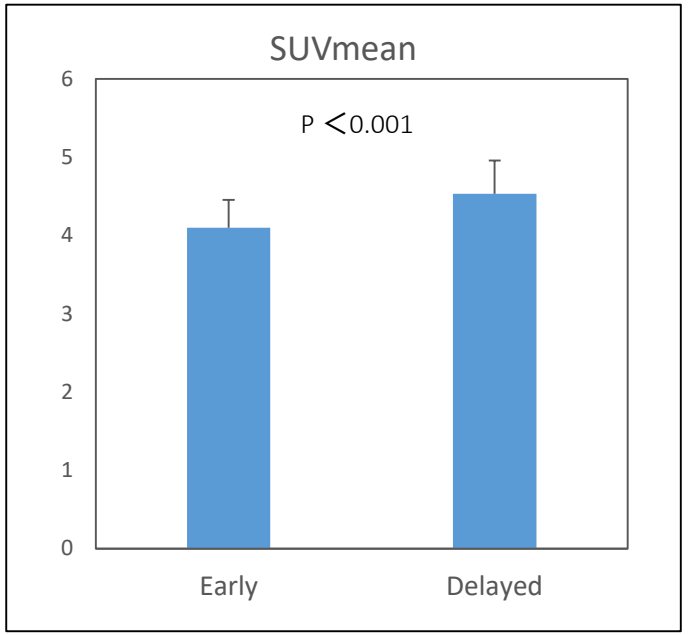
AJCC: American Joint Committee on Cancer, FNCLCC: Federation National des Centres de Lutte Contre le Cancer; MPNST: malignant peripheral nerve sheath tumor.

Fig. 1

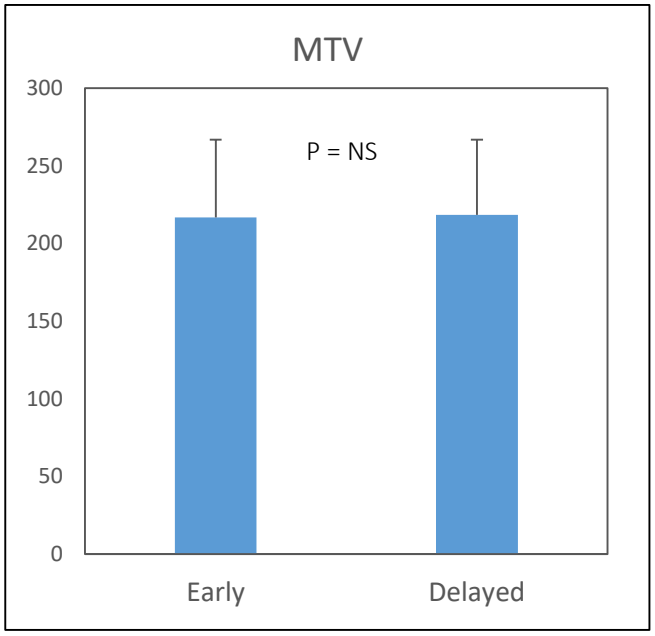
(a)



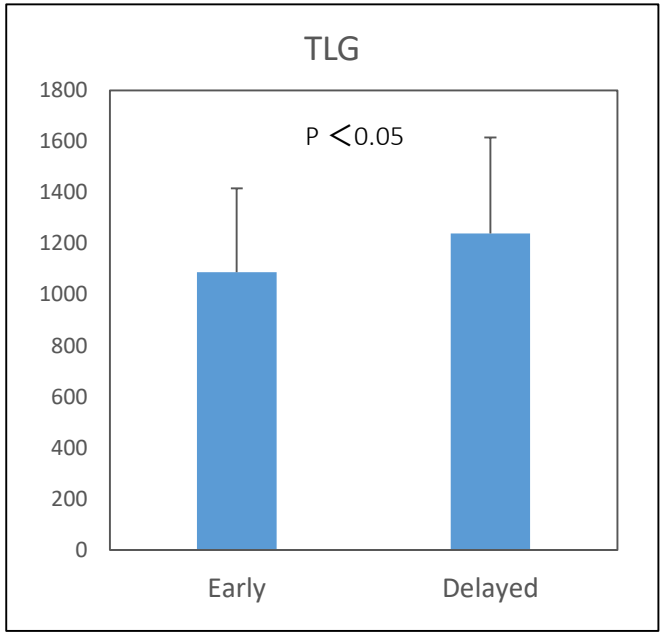
(b)



(c)



(d)



P-value by paired t-test

Fig. 2

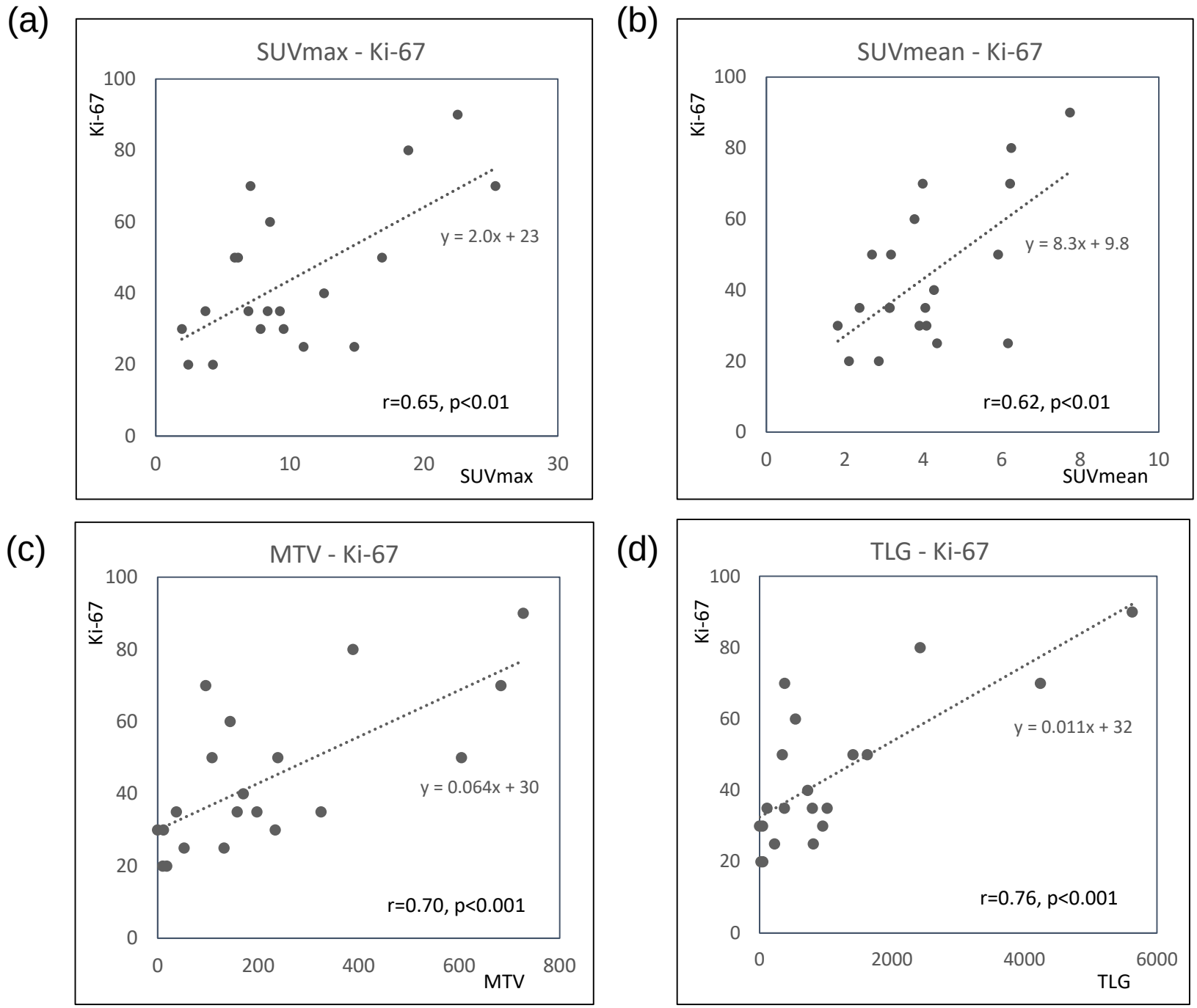

(a)
SUVmax - Ki-67
Ki-67
SUVmax
y = 2.0x + 23
r=0.65, p<0.01
(b)
SUVmean - Ki-67
Ki-67
SUVmean
y = 8.3x + 9.8
r=0.62, p<0.01
(c)
MTV - Ki-67
Ki-67
MTV
y = 0.064x + 30
r=0.70, p<0.001
(d)
TLG - Ki-67
Ki-67
TLG
y = 0.011x + 32
r=0.76, p<0.001

Fig. 3

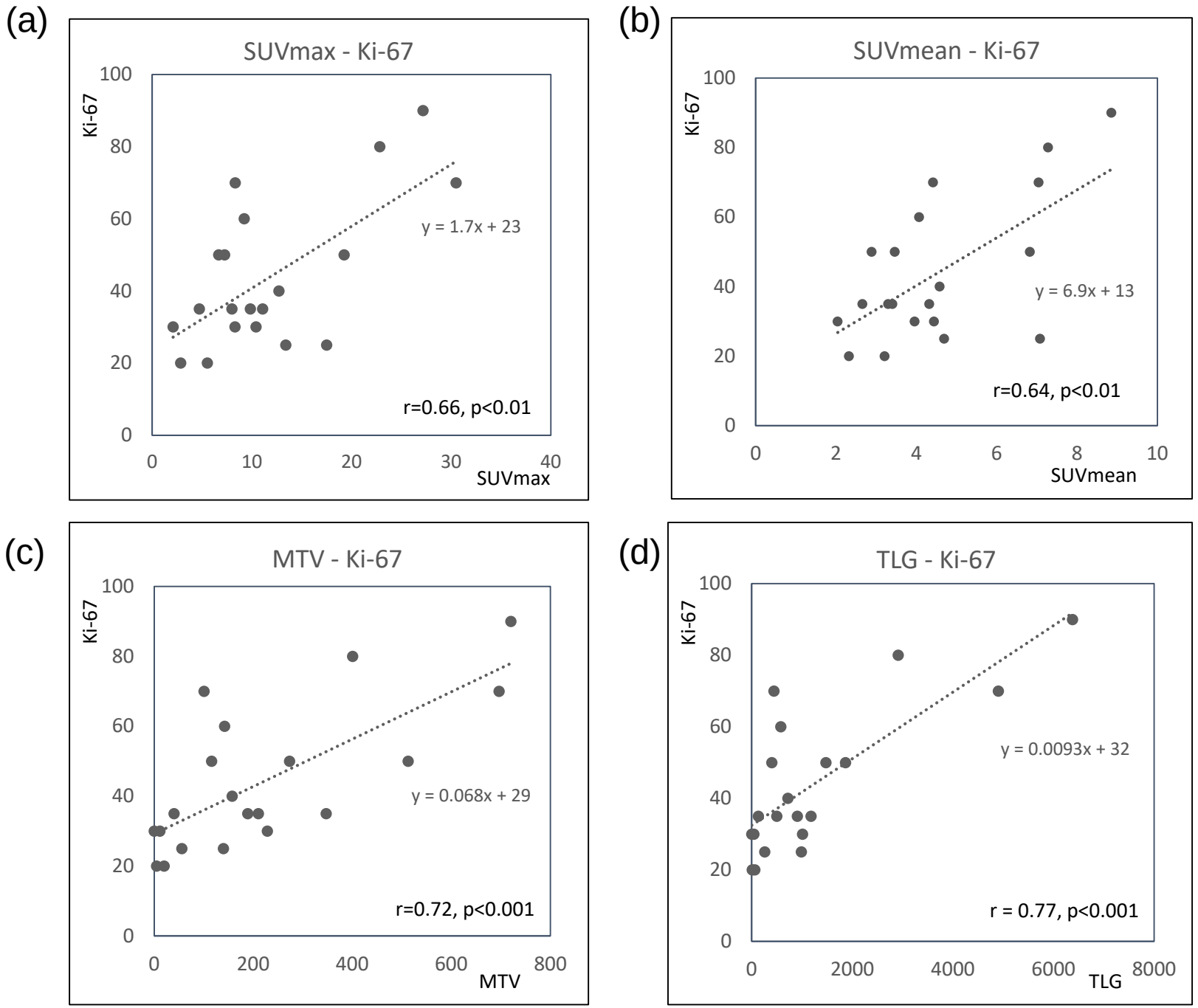

(a)
SUVmax - Ki-67
Ki-67
SUVmax
y = 1.7x + 23
r=0.66, p<0.01
(b)
SUVmean - Ki-67
Ki-67
SUVmean
y = 6.9x + 13
r=0.64, p<0.01
(c)
MTV - Ki-67
Ki-67
MTV
y = 0.068x + 29
r=0.72, p<0.001
(d)
TLG - Ki-67
Ki-67
TLG
y = 0.0093x + 32
r = 0.77, p<0.001

Fig. 4

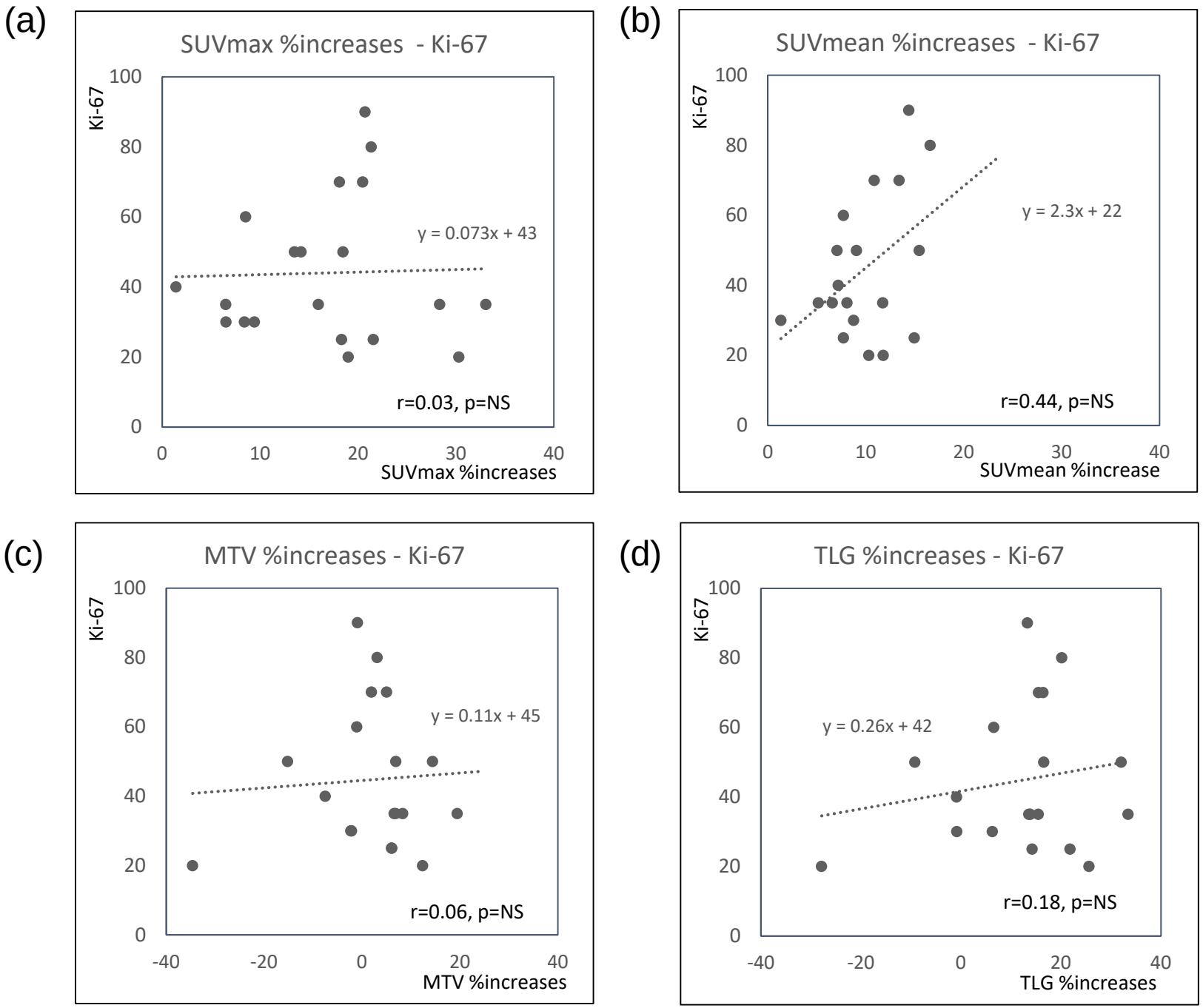
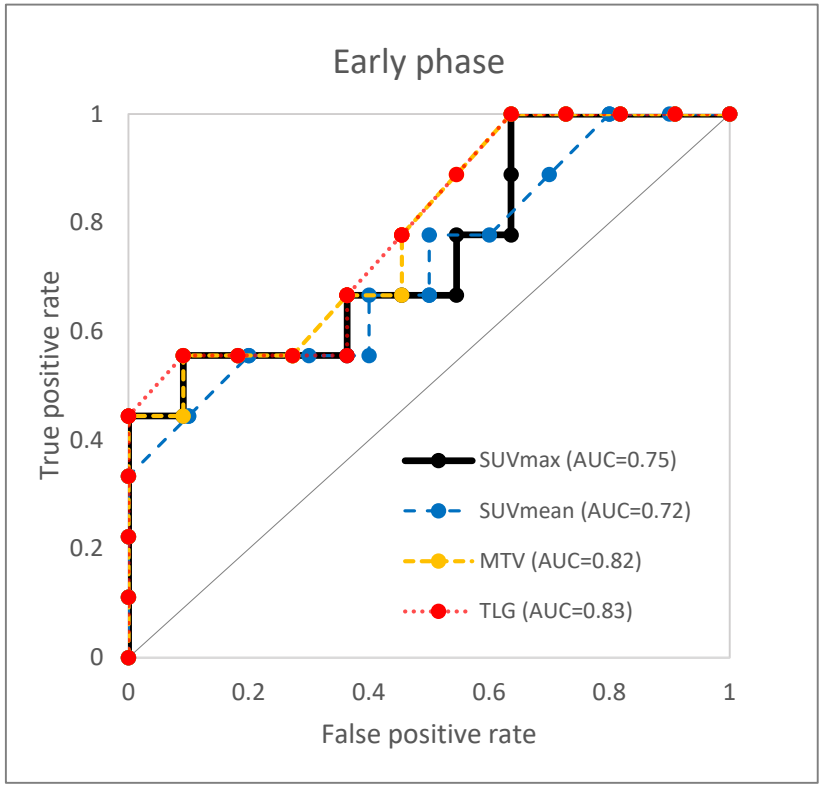

(a)
SUVmax %increases - Ki-67
Ki-67
y = 0.073x + 43
r=0.03, p=NS
SUVmax %increases
(b)
SUVmean %increases - Ki-67
Ki-67
y = 2.3x + 22
r=0.44, p=NS
SUVmean %increase
(c)
MTV %increases - Ki-67
Ki-67
y = 0.11x + 45
r=0.06, p=NS
MTV %increases
(d)
TLG %increases - Ki-67
Ki-67
y = 0.26x + 42
r=0.18, p=NS
TLG %increases

Fig. 5

(a)


Early phase
True positive rate
False positive rate
0
0.2
0.4
0.6
0.8
1
SUVmax (AUC=0.75)
SUVmean (AUC=0.72)
MTV (AUC=0.82)
TLG (AUC=0.83)

(b)

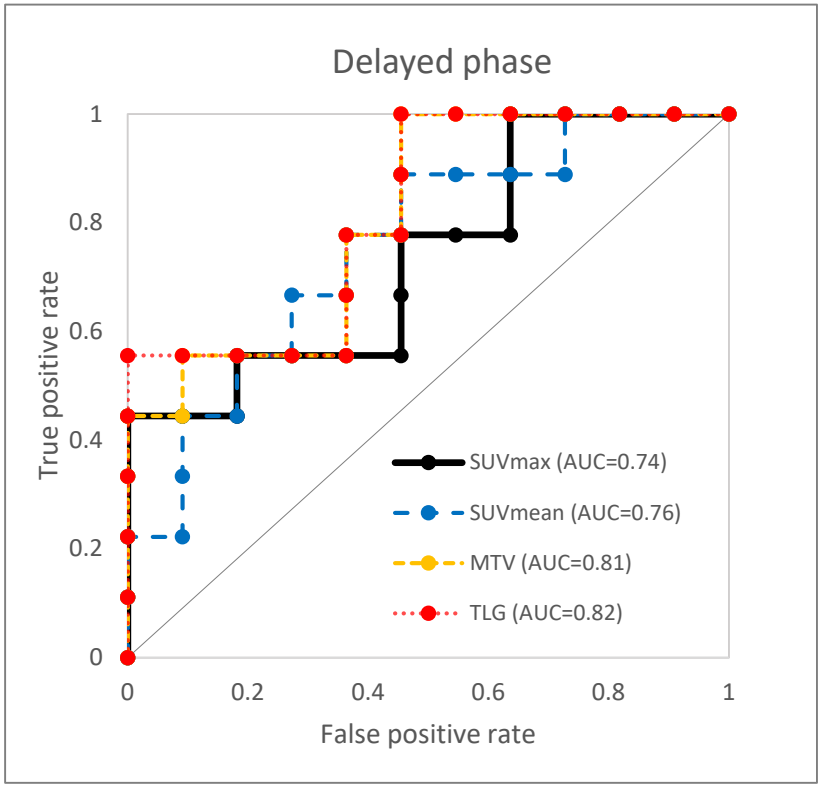
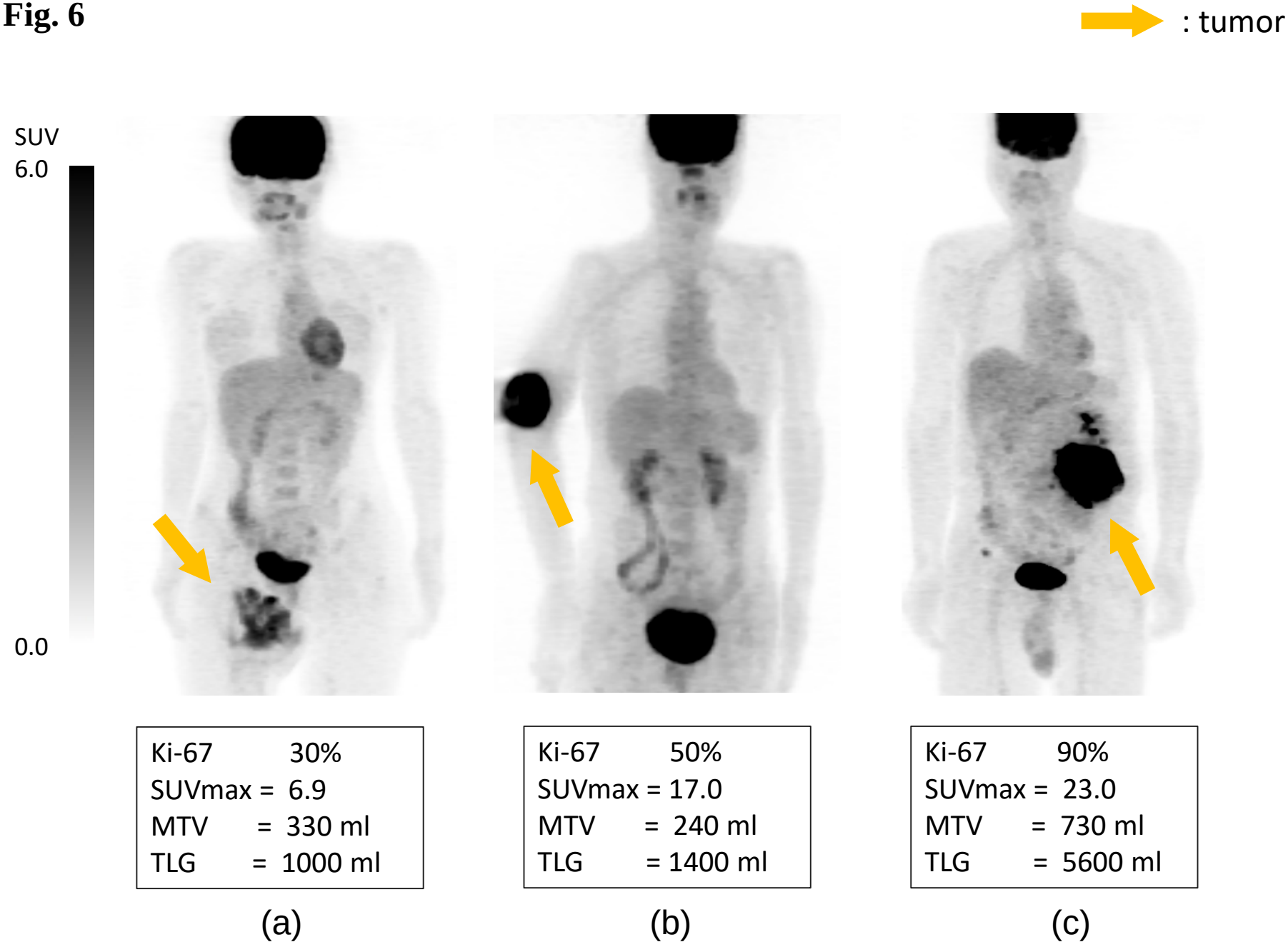

Delayed phase
True positive rate
False positive rate
0
0.2
0.4
0.6
0.8
1
SUVmax (AUC=0.74)
SUVmean (AUC=0.76)
MTV (AUC=0.81)
TLG (AUC=0.82)

Fig. 6


: tumor
SUV
6.0
0.0
Ki-67 30%
SUVmax = 6.9
MTV = 330 ml
TLG = 1000 ml
(a)
Ki-67 50%
SUVmax = 17.0
MTV = 240 ml
TLG = 1400 ml
(b)
Ki-67 90%
SUVmax = 23.0
MTV = 730 ml
TLG = 5600 ml
(c)