学位論文

Total Lesion Glycolysis Ratio in Positron Emission Tomography/Computed Tomography Images During Neoadjuvant Chemotherapy Can Predict Pathological Tumor Regression Grade and Prognosis in Patients with Locally Advanced Squamous Cell Carcinoma of the Esophagus

（食道癌術前補助化学療法患者における PET-CT の TLG 値減少率を用いた組織学的治療効果及び予後予測に関する検討）

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Total lesion glycolysis ratio in positron emission tomography/computed tomography images during neoadjuvant chemotherapy can predict pathological tumor regression grade and prognosis in patients with locally advanced squamous cell carcinoma of the esophagus

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Synopsis

This retrospective study elucidated that changes in tumor lesion glycolysis on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography during neoadjuvant chemotherapy can predict both histological response of neoadjuvant chemotherapy and survival after subsequent esophagectomy in patients with esophageal squamous cell carcinoma.

Abstract

Background: The usefulness of quantitating tumor lesion glycolysis (TLG) from ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) findings as a tool for determining the effect of neoadjuvant chemotherapy (NAC) in esophageal squamous cell carcinoma (ESCC) has not yet been established.

Methods: The cohort of this retrospective study comprised 46 patients who had undergone NAC and subsequent esophagectomy for locally advanced ESCC between January 2008 and December 2017. PET/CT was conducted before and after NAC to assess its therapeutic effect. Associations between changes in TLG values during NAC and clinicopathological findings, pathological tumor regression grade (TRG), and prognosis were assessed.

Results: Most patients received two courses of DCF (Docetaxel, Cisplatin, and Fluorouracil) as NAC. The mean TLG value of the primary tumor decreased significantly after NAC. The median follow-up period was 41 months. Kaplan–Meier method analyzed by the log-rank test showed that low TLG ratio (≤0.4) and low SUV_{max} ratio (≤0.6) were associated with favorable survival outcomes (*P*=0.0073 and *P*=0.032, respectively). Univariate and multivariate analysis revealed that TLG ratio and achievement of pathological cure were independent prognostic factors for overall survival. TLG ratio was also associated with pathological TRG (TRG 0–1a vs. 1b–3) (*P*=0.0016).

Conclusions: TLG ratio before and after NAC is clinically useful in predicting both histological response and survival outcome after NAC and subsequent esophagectomy in patients with ESCC.

Introduction

Despite recent advances in multimodal treatment, esophageal cancer remains refractory to treatment. The outcomes of surgery alone in patients with locally advanced esophageal cancer are unsatisfactory and perioperative treatments in addition to surgery are gradually being developed. Neoadjuvant chemotherapy (NAC) for locally advanced esophageal cancer reportedly prolongs survival compared with surgery alone[1, 2] and has become the standard treatment for cStage II/III esophageal squamous cell carcinoma (ESCC) in Japan.

Pathological tumor regression grade (TRG) after neoadjuvant treatments is associated with survival outcome in patients with gastroesophageal cancer.[3] In general, the efficacy of NAC in solid tumors is assessed using computed tomography (CT) in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST).[4] However, accurate evaluation of gastrointestinal tumors is difficult because of the lack of a modality that can precisely measure tumor volume. Thus, more satisfactory evaluation methods are being sought.

^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT is a potent candidate for evaluating residual tumor activity in gastrointestinal tumors. The maximum standardized uptake value (SUV_{max}) is useful for assessing the presence of residual cancer after NAC[5]; however, SUV_{max} can be affected by inflammation and serum blood glucose concentration. Additionally, it does not reflect the residual tumor volume, which may result in incorrect assessment of the effect of NAC.

Total lesion glycolysis (TLG) is calculated by multiplying metabolic tumor volume (MTV) by mean SUV (SUV_{mean}). TLG reflects both tumor activity and tumor volume and may be a better tool for evaluating the effect of NAC and prognostic outcome than SUV_{max}. In esophageal cancer, the effect of treatment as assessed by TLG may be associated with prognostic outcome in patients who have undergone definitive chemoradiotherapy (CRT).[6] However, to the best of our knowledge, no studies have elucidated the usefulness of TLG in predicting treatment and prognostic outcomes after NAC and surgery for ESCC. Thus, in the current study, we examined TLG ratio before and after NAC in patients with locally advanced ESCC and assessed the usefulness of TLG in

estimating the pathological TRG after NAC and survival outcomes after subsequent surgery.

Materials and Methods

Patients

Between August 2008 and December 2017, 194 patients with resectable locally advanced esophageal cancer received NAC followed by surgery at the Department of Gastroenterological Surgery, Kumamoto University Hospital. Sixty-six of these patients underwent FDG-PET/CT examination both before and after NAC. Twenty of these 66 patients were excluded, 13 because they had tumor SUV_{max} ≤4.0 on the initial FDG-PET/CT, two because TLG could not be measured accurately, and five because they had histological types other than SCC. Consequently, 46 patients were eligible for this study. Clinical, surgical, and pathological data were collected from among the data that had been prospectively entered into our institution's clinical database. The pretreatment tumor stage was classified according to the Union for International Cancer Control (UICC) TNM staging, version 7. Our institutional ethics committee approved this study (Registry No. 1808). Written informed consent was obtained from all patients and this study was conducted according to the Declaration of Helsinki.

PET/CT imaging

All FDG-PET/CT examinations were performed using a 3D PET/CT scanner (Gemini GXL 16; Philips Medical Systems, Cleveland, OH, USA). All patients fasted for at least 5 hours before the imaging procedure and underwent two routine whole-body PET/CT scans in a single session: at 60–90 min (early scan) and 120–150 min (delayed scan) after intravenous administration of FDG (185–370 MBq). The early scan data were analyzed in this study. The early scan comprised firstly performing CT (4-mm slice thickness) and then performed emission measurements in 3D mode with a 144 × 144 matrix.

Image analysis

PET and CT images were transferred to the 3D-radiotherapy planning system (RTPS, Pinnacle^3 9.10; Philips Medical Systems, Fitchburg, MA, USA). SUV_{max}, SUV_{mean}, and MTV of the primary tumor were measured. Each tumor was examined with an ellipsoid-shaped volume of interest that included the entire lesion in the axial, sagittal, and coronal planes. A fixed-threshold-based analysis, using SUV 4.0, was chosen for measuring PET volumetric variables.[7]

TLG was calculated by multiplying MTV by SUV_{mean}. The relative changes in SUV_{max} and TLG before and after NAC were calculated as: SUV_{max} ratio = postNAC SUV_{max}/preNAC SUV_{max} and TLG ratio = postNAC TLG/preNAC TLG. If postNAC SUV_{max} could not be detected because of a good treatment effect, SUV_{max} ratio was calculated as postNAC SUV_{max}/2.0.

Neoadjuvant chemotherapy

NAC was commonly administered to patients with non-T4, clinical stage II and III ESCC. The major NAC regimen administered was DCF: docetaxel (60 mg/m^2) g administered intravenously (i.v.) on day 1, followed by cisplatin (6 mg/m^2) administered i.v. on days 1–5, and fluorouracil (5-FU; 350 mg/m^2) administered i.v. on days 1–5, repeated every 3 weeks. The remaining patients received the FP regimen: cisplatin (80 mg/m^2), administered i.v. on day 1, followed by 5-FU (800 mg/m^2), administered continuously i.v. on days 1–5, repeated every 4 weeks. We basically conducted two cycles of NAC. Only three patients underwent 3 to 4 cycles of NAC due to the uncertainty of curative resection. Most patients underwent subtotal esophagectomy 3–4 weeks after the last round of NAC.

Surgical procedure

Esophagectomy was defined as subtotal esophagectomy with three-field regional lymph node dissection that required three incisional manipulations (neck, chest, and abdomen). Minimally invasive esophagectomy was performed from May 2011.

Definitions of pathological curative intent

In accordance with the 11th edition of the Japanese classification of esophageal cancer of the Japan Esophageal Society,[8] Cur A was defined as the cases with complete removal of the tumor (i.e. Stage 0–III, R0 resection, and number of dissected nodes > number of positive nodes). Cur C was defined as presence of residual tumor (i.e. R2 resection, evidence of residual tumor in distant organs [M1], lymph nodes, or surgical margin [PM1, DM1, RM1]). Cur B was defined as failure to meet the criteria for Cur A or C.

Follow-up evaluation

The patients were followed up at 3-month intervals. Recurrence was identified by clinical examinations, including CT and endoscopy. CT scanning from the neck to the upper abdomen was performed at least twice a year for 5 years after surgery. Tumor marker concentrations were measured every 3 months until 5 years after surgery. When recurrence was strongly suggested as observed on CT, FDG-PET/CT was considered.

Statistical methods

Statistical significance of differences between categorical variables was evaluated using the χ^2 test, Pearson's correlation coefficient, or Student's *t*-test. Survival curves were generated using the Kaplan–Meier method and were analyzed by the log-rank test. A multivariate Cox proportional hazards model was constructed for analysis of independent prognostic factors. Univariate analysis was used to investigate effects of sex (male vs. female), tumor length (<5 cm vs. ≥5 cm), cT stage (1–2 vs. 3), cN stage (0 vs. 1–3), chemotherapy regimen (DCF vs. FP), pre SUV_{max} (<12.7 vs. ≥12.7), SUV_{max} ratio (<0.6 vs. ≥0.6), pre TLG (<118 cm^3 vs ≥118 cm^3), TLG ratio (<0.4 vs ≥0.4) and pathological curative grouping (AB vs. C). The cutoff values of pre SUV_{max} and pre TLG were set as the median. Because TLG was defined as calculated value of multiplying MTV and SUV_{mean}, TLG ratio is strongly affected by SUV_{max}. Thus, we conducted receiver operating characteristic analysis for OS and confirmed that area under the curve of TLG ratio was superior to that of SUV_{max} ratio (Supplementary Fig 1). Thus, SUV_{max} ratio was excluded from the subsequent multivariate analysis for OS. Results were considered significant

when $p < 0.05$. All statistical analyzes were performed using JMP 12 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The study patients' clinicopathological characteristics are shown in Table 1. The median follow-up period was 41 months. Eight patients (17%) had cT2 lesions and 38 (83%) had cT3 lesion; 85.1% had cN1–3 disease and 84.4% had cStage II or III disease. The seven patients with cStage IV and cM1 were the with only supraclavicular lymph node metastases. Most patients (91%) received the DCF regimen and 85% of all patients received two courses of NAC. Pathological examination showed that two patients (4%) achieved TRG 3 and 16 (34.8%) were considered to be responders (TRG 1b–3) to NAC.

Analysis of response in terms of metabolic variables

PET/CT metabolic variables during NAC are shown in Table 2. SUV_{max}, SUV_{mean} and TLG in the primary tumor were all significantly lower after NAC.

Determination of cutoff values for ratio of metabolic variables (SUV_{max} ratio and TLG ratio) for analysis of OS

The optimal cutoff value for SUV_{max} ratio and TLG ratio for OS that yielded statistically significant separation were determined using a 10% stepwise cutoff analysis (Fig. 1). The cutoff values with the lowest *P*-values were 0.6 for SUV_{max} ratio (*P*=0.0321) and 0.4 for TLG ratio (*P*=0.0073).

Survival outcomes

The Kaplan–Meier curves for OS analysis are shown in Fig. 2. Both high SUV_{max} ratio and high TLG ratio were associated with shorter OS than were low SUV_{max} ratio (*P*=0.0321) and low TLG ratio (*P*=0.0073). Median survivals in the high and low SUV_{max} ratio groups were 24.6 months and 77.8 months, respectively, whereas median survivals in the high and low TLG ratio groups were 17.7 and 76.3 months, respectively.

Prognostic factors for OS

Univariate analysis revealed significant relationships for OS between and TLG ratio and pathological cure. SUV_{max} ratio was excluded from the subsequent multivariate analysis for OS. Multivariate analysis identified that TLG ratio (HR 3.58: 95% CI, 1.46–8.34; *P*=0.006) and pathological curative intent (AB vs. C) (HR 5.16; 95% CI, 1.75–13.7; *P*=0.004) as independent prognostic factors (Table 3).

Clinicopathological predictors

Table 4 shows the relationship between TLG ratio and clinicopathological findings. TLG ratio was significantly associated with ypT stage and TRG, and therefore considered useful for predicting responses (TRG 1b–3) to NAC.

Discussion

In the present study, we found significant correlations between TLG ratio before and after NAC and OS after surgery in patients with locally advanced ESCC. Low TLG ratio was associated with favorable pathological TRG. Low TLG ratio was also an independent prognostic factor for favorable OS along with the better pathological curability (A and B).

The effects of NAC on primary gastrointestinal cancers cannot be determined via RECIST.[4] Thus, other means of precisely assessing therapeutic effects and predicting both pathological TRG and survival outcome have been investigated. Changes in SUV_{max} in ^{18}F-FDG-PET/CT images are currently widely used as an indicator for evaluating the effects of NAC.[5, 9] SUV_{max} is clinically useful because it is routinely calculated and values can easily be compared during NAC. However, it can be affected by inflammation such that associated with gastroesophageal reflux disease. Additionally, it does not reflect the activity of the entire tumor (Fig. 3). We considered that TLG might be more appropriate for assessing therapeutic efficacy because it reflects both residual tumor volume and total activity. Actually, in this study, we found that TLG ratio, and not SUV_{max} ratio, was an independent prognostic factor in patients with locally advanced ESCC who underwent NAC followed by surgery. Similar results with regard to the usefulness of TLG in the evaluation of preoperative

treatment have previously been reported for laryngeal, pharyngeal cancer, lung, and breast cancer.[10-12]

Several studies have examined the usefulness of PET in determining the therapeutic effect of neoadjuvant treatment. Makino et al. reported that MTV is useful for predicting pathological TRG and prognosis after NAC and subsequent surgery in ESCC patients.[13] In addition, Yu et al. reported an association between MTV/minimal apparent diffusion coefficient (MTV/ADC_{min}) in PET/MR imaging and prognosis after neoadjuvant CRT (NACRT).[14] However, to the best of our knowledge, there have not been any studies of the usefulness of TLG in assessing the therapeutic effect of NAC in patients with ESCC. TLG reflects total tumor activity more accurately than MTV because MTV does not include degree of tumor activity as indicated by SUV_{mean}.

Precise assessment of the effect of neoadjuvant treatment is becoming increasingly important because treatment strategies for locally advanced ESCC are gradually changing. NAC and subsequent surgery is the standard treatment in Japan, whereas in Western countries, NACRT is the mainstream treatment for locally advanced ESCC.[15] Formerly, even when a clinical complete response (CR) had been achieved by NAC or NACRT, additional surgery was generally performed. However, a watch and wait strategy is now an acceptable option in patients who achieve CR after neoadjuvant treatment.[16] It is therefore important to specifically predict pathological TRG3 after neoadjuvant treatments. In this study, no patients in the TLG ratio high group had TRG3 (TLG ratio > 4); however, it is difficult to accurately predict TRG3 on the basis of the TLG ratio alone. Several studies have suggested that clinical CR and pathological TRG3 should be confirmed using multiple modalities such as endoscopy (biopsy), CT,[17] MRI,[18, 19] and PET.[20-22] Future investigation is required to establish suitable means of diagnosing clinical CR using multiple modalities.

The present results indicate that improving survival outcomes in patients with high TLG ratios is an important clinical theme. Additional NACRT after NAC may be beneficial for patients in whom the effects of NAC were unsatisfactory.[15] Another option would be to administer adjuvant chemotherapy using a different regimen than was used for NAC. In this study, recurrence-free survival was significantly poorer in the high TLG ratio group than in the low TLG

ratio group (data not shown). Adjuvant chemotherapy with different regimen may reduce micro-metastases and future recurrence.[23, 24] Definitive CRT can also be considered as an alternative to surgery. The current 10% 5-year OS in the high TLG group is considered insufficient. In these patients, surgery could be offered as a salvage treatment for remnant lesions after definitive CRT.

This study has several limitations. First, it was a small retrospective study conducted in a single institution. Second, the NAC regimen, which in current study was mostly DCF, may have affected the usefulness of TLG. Thus, the usefulness of TLG in assessing the therapeutic effect of NAC should be investigated with other potent regimens such as FP or oxaliplatin-based regimens. Third, the SUV threshold used for TLG measurements also affects the results.

In conclusion, we believe that TLG ratio before and after NAC is clinically useful for predicting histological response and long-term survival in patients with ESCC. Future larger multicenter studies are required to more accurately determine the significance of TLG ratio in assessing the therapeutic effect of NAC in patients with ESCC.

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Figure legends

Fig 1. *P*-values (Wilcoxon's test) for the overall survival analysis using different cutoff points for SUV_{max} ratio (A) and TLG ratio (B).

Fig 2. Kaplan–Meier curves of overall survival after surgery. (A) Kaplan–Meier curves for categories of SUV_{max} ratio (Low: < 0.6, High; ≥ 0.6). (B) Kaplan–Meier curves for categories of TLG ratio (Low: < 0.4, High; ≥ 0.4).

Fig 3. Comparison of TLG values of two patients with almost the same SUV_{max}.

Supplementary Fig 1.Receiver operating characteristic curve for overall survival by TLG ratio and SUV_{max} ratio.

Table 1. Patient characteristics

Parameter	n=46
Median age, years (range)	69 (53-80)
Gender	
Male / Female	40 / 6
Tumor location	
Upper third / Middle third / Lower third	8 / 24 / 14
Tumor length	
<5 cm / ≥5 cm	17 / 29
cT stage	
2 / 3	8 / 38
cN stage	
0 / 1 / 2 / 3	2 / 15 / 25 / 4
cM stage	
0 / 1*	39 / 7
cStage	
II / III / IV*	5 / 34 / 7
Median pre SUVmax, (range)	12.5 (4.6-23.8)
Median pre TLG, cm^3 (range)	112 (1.4-594)
Chemotherapy regimen	
DCF / FP	42 / 4
Number of chemotherapy courses	
1 / 2 / 3-4	4 / 39 / 3
ypT stage	
0 / 1 / 2 / 3 / 4	2 / 5 / 9 / 28 / 2
ypN stage	
0 / 1 / 2 / 3	10 / 19 / 10 / 7
Pathological tumor regression grade	
0-1a / 1b / 2 / 3	30 / 6 / 8 / 2

DCF, docetaxel, cisplatin, fluorouracil; FP, fluorouracil, cisplatin; SUV, standardized uptake value; TLG, total lesion glycolysis, * only supraclavicular lymph node metastasis

Table 2. PET metabolic variables

PET metabolic parameter (SUV threshold 4.0)	pre NAC	post NAC	P Value
SUV_{max} (mean, p25-p75)	12.6 (9.6-15.5)	6.6 (2.5-10.1)	<0.0001
SUV_{mean} (mean, p25-p75)	6.9 (5.8-7.7)	6.1 (4.9-7.1)	<0.0001
TLG (cm^3) (mean, p25-p75)	156 (53.3-220)	38.4 (0-40.8)	<0.0001

NAC, neoadjuvant chemotherapy; PET, positron emission tomography; SUV, standardized uptake value; TLG, total lesion glycolysis

Table 3. Results of Cox regression analysis for overall survival

Valuables		Univariate		Multivariate	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender	Male	1 (referent)			
	Female	0.88 (0.21 - 2.58)	0.843		
Tumor length	<5cm	1 (referent)			
	≥5cm	1.74 (0.77-4.27)	0.187		
cT	cT2	1 (referent)			
	cT3	1.42 (0.54 – 5.87)	0.507		
cN	cN0	1 (referent)			
	cN1 - 3	0.75 (0.16 - 13.6)	0.793		
Chemotherapy regimen	DCF	1 (referent)			
	FP	1.24 (0.07 – 6.19)	0.841		
PreNAC SUV_{max}	<12.7	1 (referent)			
	≥12.7	1.23 (0.56 – 2.73)	0.609		
SUV_{max} ratio	<0.6	1 (referent)			

	≥0.6	2.31 (1.04 – 5.14)	0.039		
PreNAC TLG	<118	1 (referent)			
	≥118	1.70 (0.77 – 3.92)	0.188		
TLG ratio	<0.4	1 (referent)			
	≥0.4	2.93 (1.23 – 6.54)	0.017	3.58 (1.46 – 8.34)	0.006
Curability	AB	1 (referent)			
	C	4.01 (1.41 – 9.94)	0.011	5.16 (1.75– 13.7)	0.004

CI, confidence interval; DCF, docetaxel, cisplatin, fluorouracil; FP, fluorouracil, cisplatin; HR hazard ratio; SUV, standardized uptake value; TLG total lesion glycolysis

Table 4. Correlations between TLG ratio and clinicopathological variables

	TLG ratio		*P*-value
	low (n=36)	high (n=10)	
cT stage (2 / 3)	7 / 29	1 / 9	0.463
cN stage (0 / 1-3)	2 / 34	0 / 10	0.316
Chemotherapy regimen (DCF / FP)	32 / 4	10 / 0	0.151
Mean operation time ± standard deviation (min)	538 (89)	521 (82)	0.811
Mean blood loss ± standard deviation (g)	597 (329)	932 (995)	0.088
ypT stage (0-2 / 3-4)	16 /20	0 / 10	0.0016
ypN stage (0 / 1-3)	8 / 28	2 / 8	0.879
Pathological tumor regression grade (0-1a / 1b-3)	20 / 16	10 / 0	0.0016
Postoperative morbidity (CDc 0-I / II-IV)	12 / 24	7 / 3	0.842

CDc, Clavien-Dindo classification; DCF, docetaxel, cisplatin, fluorouracil; FP, fluorouracil, cisplatin

Table 1. Patient characteristics

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0 / 1 / 2 / 3	2 /15 / 25 / 4
cM stage	
0 / 1*	39 / 7
cStage	
II / III / IV*	5 / 34 / 7
Median pre SUVmax, (range)	12.5 (4.6-23.8)
Median pre TLG, cm^3 (range)	112 (1.4-594)
Chemotherapy regimen	
DCF / FP	42 / 4
Number of chemotherapy courses	
1 / 2 / 3-4	4 / 39 / 3
ypT stage	
0 / 1 / 2 / 3 / 4	2 / 5 / 9 / 28 / 2
ypN stage	
0 / 1 / 2 / 3	10 / 19 / 10 / 7
Tumor regression grade	
0-1a / 1b / 2 / 3	30 / 6 / 8 / 2

DCF, docetaxel, cisplatin, fluorouracil; FP, fluorouracil, cisplatin; SUV, standardized uptake value; TLG, total lesion glycolysis, * only supraclavicular lymph node metastasis

Table 2. PET metabolic variables

PET metabolic parameter (SUV threshold 4.0)	pre NAC	post NAC	P Value
SUV_{max} (mean, p25-p75)	12.6 (9.6-15.5)	6.6 (2.5-10.1)	<0.0001
SUV_{mean} (mean, p25-p75)	6.9 (5.8-7.7)	6.1 (4.9-7.1)	<0.0001
TLG (cm^3) (mean, p25-p75)	156 (53.3-220)	38.4 (0-40.8)	<0.0001

NAC, neoadjuvant chemotherapy; PET, positron emission tomography; SUV, standardized uptake value; TLG, total lesion glycolysis

Table 3. Results of Cox regression analysis for overall survival

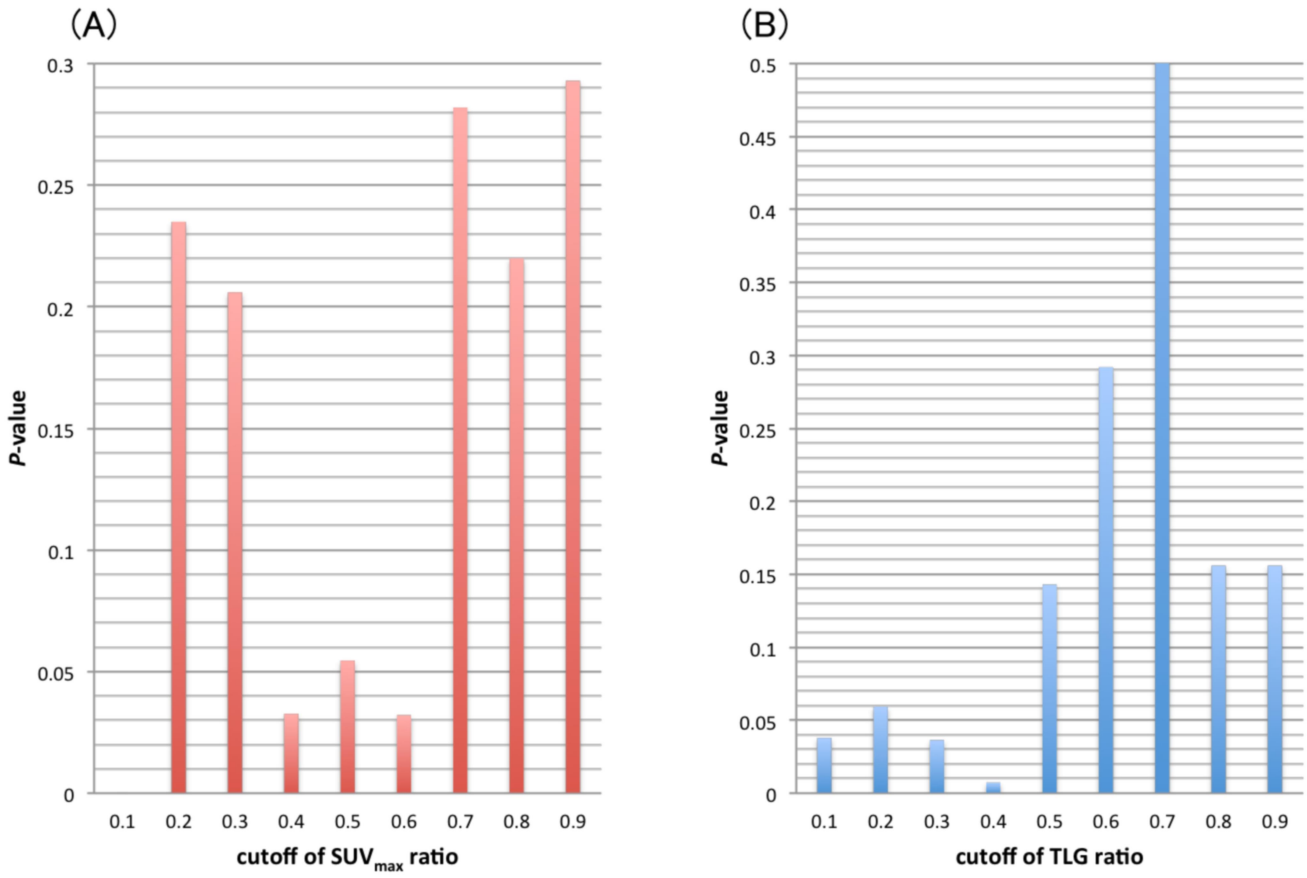
Valuables		Univariate		Multivariate	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender	Male	1 (referent)			
	Female	0.88 (0.21 - 2.58)	0.843		
Tumor length	<5cm	1 (referent)			
	≥5cm	1.74 (0.77- 4.27)	0.187		
cT	cT2	1 (referent)			
	cT3	1.42 (0.54 – 5.87)	0.507		
cN	cN0	1 (referent)			
	cN1 - 3	0.75 (0.16 - 13.6)	0.793		
Chemotherapy regimen	DCF	1 (referent)			
	FP	1.24 (0.07 – 6.19)	0.841		
PreNAC SUV_{max}	<12.7	1 (referent)			
	≥12.7	1.23 (0.56 – 2.73)	0.609		
PreNAC TLG	<118	1 (referent)			
	≥118	1.70 (0.77 – 3.92)	0.188		
TLG ratio	<0.4	1 (referent)			
	≥0.4	2.93 (1.23 – 6.54)	0.017	3.58 (1.46 – 8.34)	0.006
Curability	AB	1 (referent)			
	C	4.01 (1.41 – 9.94)	0.011	5.16 (1.75– 13.7)	0.004

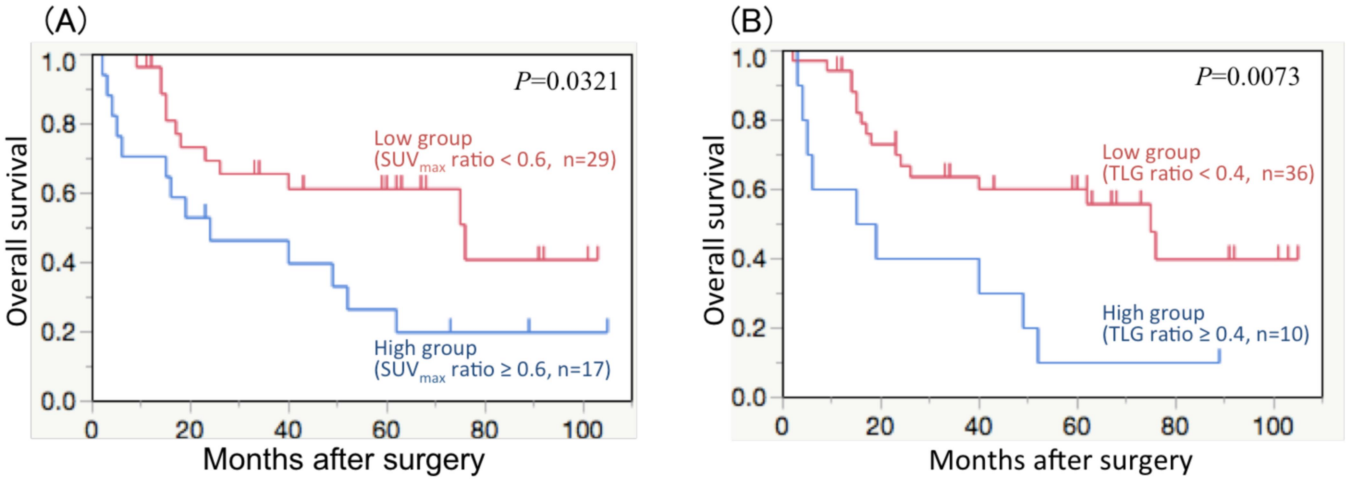
CI, confidence interval; DCF, docetaxel, cisplatin, fluorouracil; FP, fluorouracil, cisplatin; HR hazard ratio; SUV, standardized uptake value; TLG total lesion glycolysis

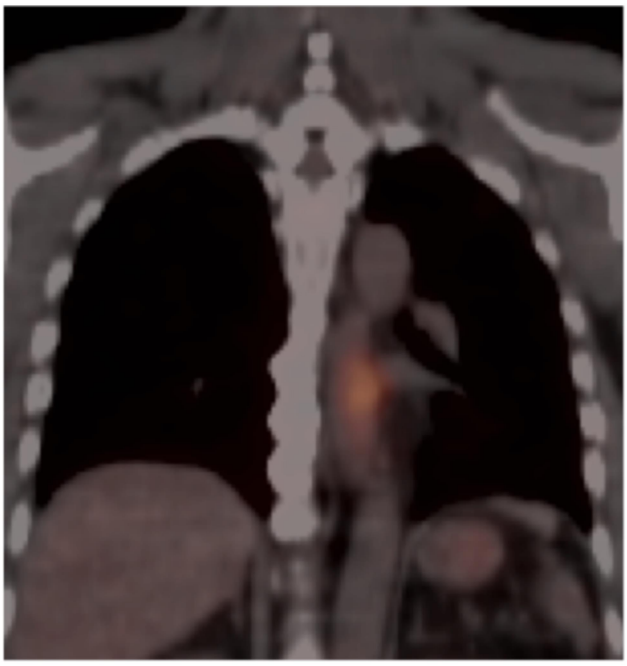
Table 4. Correlations between TLG ratio and clinicopathological variables

	TLG ratio		*P*-value
	low (n=36)	high (n=10)	
cT stage (2 / 3)	7 / 29	1 / 9	0.463
cN stage (0 / 1-3)	2 / 34	0 / 10	0.316
Chemotherapy regimen (DCF / FP)	32 / 4	10 / 0	0.151
Mean operation time ± standard deviation (min)	538 (89)	521 (82)	0.811
Mean blood loss ± standard deviation (g)	597 (329)	932 (995)	0.088
ypT stage (0-2 / 3-4)	16 /20	0 / 10	0.0016
ypN stage (0 / 1-3)	8 / 28	2 / 8	0.879
Pathological tumor regression grade (0-1a / 1b-3)	20 / 16	10 / 0	0.0016
Postoperative morbidity (CDc 0-I / II-IV)	12 / 24	7 / 3	0.842

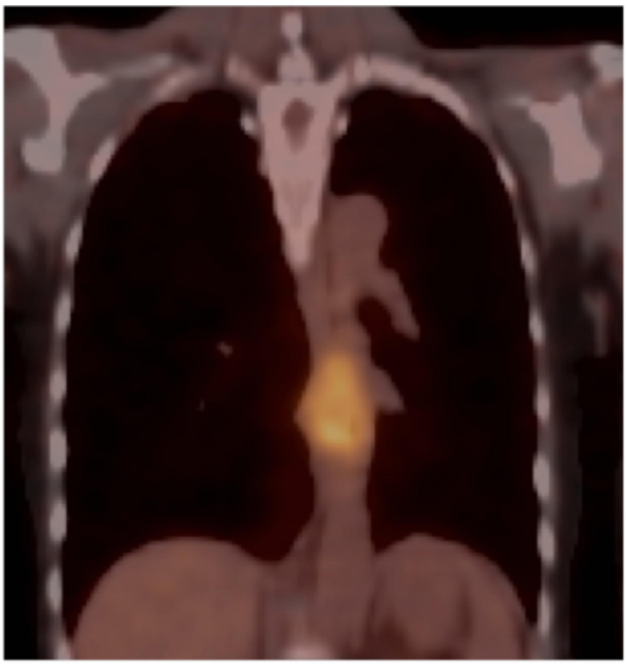
CDc, Clavien-Dindo classification; DCF, docetaxel, cisplatin, fluorouracil; FP, fluorouracil, cisplatin


(A)
0.3
0.25
0.2
0.15
0.1
0.05
0
P-value
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
cutoff of SUVmax ratio
(B)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
P-value
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
cutoff of TLG ratio

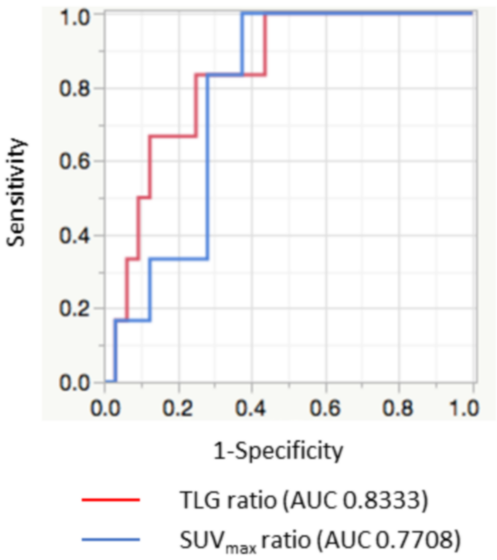

(A)
P=0.0321
Low group
(SUVmax ratio < 0.6, n=29)
High group
(SUVmax ratio ≥ 0.6, n=17)
Overall survival
Months after surgery
(B)
P=0.0073
Low group
(TLG ratio < 0.4, n=36)
High group
(TLG ratio ≥ 0.4, n=10)
Overall survival
Months after surgery



SUV_{max} : 12.2
TLG : 62cm^3



SUV_{max} : 12.3
TLG : 276cm^3


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1-Specificity
TLG ratio (AUC 0.8333)
SUVmax ratio (AUC 0.7708)