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Original Article

Volumetric PET Parameters Predict Prognosis after Definitive Chemoradiotherapy with Cisplatin/Docetaxel for Stage III Non-Small Cell Lung Cancer

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The aim of this study was to investigate whether volumetric positron emission tomography (PET) parameters are prognostic predictors in stage III non-small cell lung cancer patients receiving definitive concurrent chemoradiotherapy (CCRT) with cisplatin/docetaxel. Cases involving definitive CCRT were reviewed retrospectively, and the maximum standardized uptake value, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were calculated. The relationships between these PET parameters and prognosis were analyzed. MTV and TLG were significant predictors of distant metastasis-free survival (DMFS) ($p = 0.0003$ and 0.0005, respectively) and progression-free survival (PFS) ($p = 0.001$ and 0.0007, respectively). The three-year DMFS rates in patients with low and high MTV were 13.3% and 64.6%, respectively, and the corresponding values in those with low and high TLG were 13.3% and 65.2%, respectively. The three-year PFS rates in patients with low and high MTV were 13.3% and 57.8%, respectively, and the corresponding values in patients with low and high TLG were 13.3% and 57.8%, respectively. However, MTV and TLG were not predictors of local control or overall survival. We demonstrated that volumetric PET parameters were predictors of patients receiving definitive CCRT. Our findings contradict the findings of previous reports and warrant further research to validate them.

Key words: volumetric positron emission tomography parameters, distant metastasis-free survival, chemoradiotherapy, cisplatin/docetaxel, non-small cell lung cancer

Definitive concurrent chemoradiotherapy (CCRT) is one of the standard treatments for unresectable stage III lung cancer. When administered concurrently with a cisplatin/docetaxel regimen, it shows a trend toward improved median progression-free time and 2-year overall survival (OS) compared with second-generation chemotherapy [1]. Patients receiving cisplatin/docetaxel also tend to show a lower rate of distant metastases at the first recurrence site in comparison with those who receive second-generation chemotherapy. Recent studies have shown that the administration

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of durvalumab after CCRT improves progression-free survival (PFS) and OS. The incidence of new metastatic lesions was 33.8% in the CCRT-alone group and 22.5% in the durvalumab group, which was probably attributable to the improvement in PFS as a result of the suppression of distant metastases. Since the appearance of distant metastases suggests that curing the disease has generally become more difficult, biomarkers for predicting distant metastases are desired.

^{18}F-Fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) is useful for the staging and prognosis of malignant tumors. Although the maximum standard uptake value (SUVmax) has been adopted as a PET parameter [2], volumetric evaluations can facilitate assessments of overall tumor activity in addition to single-voxel assessments such as SUVmax [3,4]. Volumetric PET parameters for lung cancer have been reported to be useful in assessing responses to CCRT [5,6] and chemotherapy [7]. Although some studies have examined the correlation between volumetric PET parameters and OS or PFS in patients receiving chemoradiotherapy, only a few studies have examined the distant metastasis-free survival rate (DMFS). Moreover, even fewer reports have included cases in which a cisplatin/docetaxel regimen was concurrently used [8].

Thus, the purpose of this study is to investigate whether volumetric PET parameters can serve as predictors of DMFS for non-small cell lung cancer (NSCLC) patients who received CCRT with cisplatin/docetaxel.

Materials and Methods

Patients. The study was approved by the institutional ethics committee (No. 1809-018). Patients who received CCRT between April 2006 and December 2017 at the authors' hospital were reviewed retrospectively. Staging was performed according to the 7th edition of the TNM Classification of Malignant Tumors. Lymph nodes with a short diameter of 1 cm or more were defined as metastases. Lymph nodes of less than 1 cm were defined as metastases if accumulations were observed on PET/CT as judged by a board-certified radiologist. If a biopsy or resection was required in addition to imaging, at the discretion of the respiratory physicians, lymph node metastasis was diagnosed pathologically. The eligibility criteria were as follows: staging with a specified PET/CT device, stage III NSCLC, definitive radiotherapy, concurrent use of chemotherapy with cisplatin/docetaxel [1], and no administration of neoadjuvant therapy before the start of CCRT. After treatment, follow-up CT and magnetic resonance imaging were performed periodically, with intervals determined by the individual respiratory physician. All procedures were in compliance with the ethical standards of the 1964 Declaration of Helsinki and subsequent modifications. Written informed consent was obtained before CCRT. In accordance with the rules of the ethics committee, opportunities to opt out of the study were provided before this research was started.

Treatment. Indications for definitive CCRT for all cases were discussed at the respiratory conference and finally determined by a board-certified chest medical oncologist and a radiation oncologist. All patients received three-dimensional conformal radiotherapy with an isocenter prescription. CT scans for the radiation treatment plan and irradiation were performed at 2-10 mm intervals. The gross tumor volume included the primary tumor and a clinically diagnosed metastatic lymph node. The clinical target volume margin and planning target volume margin were both 5-10 mm. Non-metastatic subcarinal and ipsilateral hilar nodal stations were included in cases of elective nodal irradiation [9,10]. The definitive radiation dose was delivered by a linear accelerator (Mevatron, ONCOR, or Primus; Canon Medical Systems, Tochigi, Japan). The chemotherapy regimens consisted of cisplatin/docetaxel based on a prospective study of Okayama Lung Cancer Study Group Trial 0007 [1]. Durvalumab was not used because this drug was not launched in Japan within the survey period.

PET/CT protocol. All patients fasted for at least 6 hours before the imaging assessments. The PET/CT scans were acquired using a Biograph 16 PET/CT scanner (Siemens Healthcare, Erlangen, Germany) at 90 min after the intravenous administration of FDG (3.7 MBq/kg). For photon attenuation correction and anatomical localization, a low-dose CT scan was initially obtained from the level of the head to the mid-thigh with a tube voltage of 120 kV, an automatic tube current modulation using a reference tube current of 50 mAs, and a section thickness of 3 mm. Subsequently, PET imaging was performed in three-dimensional mode for 3 min per bed position. PET data were recon-

structed using an ordered subsets expectation maximization algorithm and the following parameters: 5 iterations, 4 subsets, 168×168 matrix, and a section thickness of 3 mm.

PET/CT image analysis. Measurements of SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were performed using specialized software (Syngo. via Siemens Healthcare, Erlangen, Germany). The volume of interest (VOI) was manually drawn at the primary tumor and lymph node metastasis on PET/CT images, and the software automatically delineated the contour of the target lesion (primary tumor and lymph node metastases) inside the VOI using an isocontour threshold method. We set the absolute threshold for SUVmax at 2.5 to define the MTV based on a meta-analysis showing that fixed absolute thresholds were suitable for evaluating the prognostic value of MTV [4], and the cutoff for the fixed value was an SUV of 2.5 [3]. The delineation of the target lesion was visually checked by a board-certified radiologist who did not have access to the patients' prognoses. The SUVmax, MTV, and TLG values of the delineated target lesion were automatically calculated. The MTV was defined as the metabolic volume of the target lesion with an SUV exceeding the defined threshold of 2.5. TLG values were calculated by multiplying the mean SUV of the target lesion by the MTV.

Statistical analysis. Survival curves were estimated using the Kaplan-Meier method. The medians of the volumetric PET parameters were used as the cutoff values. Variables were grouped into 2 categories for statistical analyses, and the medians were adopted as cutoff values for continuous variables. The relationships between the PET/CT parameters and the local control rate (LC), DMFS rate, PFS rate, and OS rate were analyzed using the log-rank test for univariate analysis and the Cox proportional hazard model for multivariate analysis. The comparison between the two groups was performed using Student's *t*-test. We calculated the mean follow-up interval of the CT, magnetic resonance imaging, and PET/CT examinations until the last day of follow-up for patients without recurrence and until the day of recurrence for patients with recurrence. A p value < 0.05 (two-sided) was considered to be statistically significant. R software, version 3.5.1 (R Foundation for Statistical Computing) was used for all statistical analyses.

Results

The median follow-up period from the start of treatment was 25.1 (range: 5.9-118.1) months. Thirty patients met the eligibility criteria, and Table 1 shows their characteristics. The total dose of definitive radiotherapy was 60 Gy/30 fractions in all patients. Cisplatin/docetaxel chemotherapy was used for all patients, and cisplatin/vinorelbine was used as the second course in one patient because of a drug allergy. For mediastinal tumors, 11 patients underwent endobronchial ultrasound-guided transbronchial needle aspiration biopsy, 1 underwent endoscopic ultrasound-guided fine-needle aspiration biopsy, 1 underwent endobronchial ultrasound-guided transbronchial needle aspiration biopsy and open chest biopsy, and 1 underwent a biopsy by mediastinoscopy. For supraclavicular lymph nodes, 3 patients underwent a biopsy. Among recurrent patients, the longest time to recurrence was 40 months; therefore, the examination intervals were measured up to 40 months for patients without recurrence. The average examination intervals in the high and low TLG groups were 10.98 weeks and 8.00 weeks (95% confidence interval of difference: −0.51 to +6.47), respectively, and the difference was not significant ($p = 0.09052$). The median SUVmax, MTV, and TLG were 16.04 (range: 5.90-35.83), 78.82 cm^3 (range: 15.09-547.00 cm^3), and 588.07 (range: 47.09-4160.73), respectively. There were no significant differences in the average values of SUVmax, MTV2.5, or TLG2.5 between the adenocarcinoma and squamous cell carcinoma groups ($p = 0.0656$, 0.196 and 0.103, respectively).

Table 2 shows the results of the univariate analysis of factors related to DMFS and PFS. In the univariate analysis, MTV and TLG were significant predictors of DMFS ($p = 0.0003$ and 0.0005, respectively), and SUVmax was not ($p = 0.2$). MTV and TLG were significant predictors of PFS ($p = 0.001$ and 0.0007, respectively), and SUVmax was not ($p = 0.08$). There were no significant factors in the multivariate analysis.

Figures 1 and 2 show the Kaplan-Meier curves of DMFS and PFS divided into 2 groups by the median values of the SUVmax, MTV, and TLG. The three-year DMFS rate was 28.6% in patients with a low SUVmax and 47.6% in those with a high SUVmax, 13.3% in patients with a low MTV and 64.6% in those with a high MTV, and 13.3% in patients with a low TLG and 65.2% in those with a high TLG (Fig. 1). The three-year PFS

Table 1 Patient characteristics

			%
Age (years)	Median (range)	64 (36–84)	–
Sex	Male	26	87
	Female	4	13
T stage	1	6	20
	2	6	20
	3	1	3
	4	14	47
	x	3	10
N stage	0	1	3
	1	5	17
	2	10	33
	3	14	47
Clinical stage	IIIA	7	23
	IIIB	23	77
Histology	Adenocarcinoma	11	37
	Squamous cell carcinoma	17	57
	Non-small cell carcinoma	2	7
Lobe[a]	Upper	21	70
	Lower	6	20
Laterality[a]	Right	17	57
	Left	11	33
Smoking History	Never	1	3
	Former	15	50
	Current	14	47
FEV1 (l)[a]	Median (range)	2.17 (1.12–4.11)	–
ECOG-PS	0	12	40
	1	18	60
Cycles of concurrent chemotherapy	1	1	3
	2	29	97
Cycles of adjuvant chemotherapy	0	28	93
	1	2	7
SUVmax	Median (range)	16.04 (5.90–35.83)	–
MTV (cm^3)	Median (range)	78.82 (15.09–547.00)	–
TLG	Median (range)	588.07 (47.09–4160.73)	–

ECOG-PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 sec; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume of SUVmax more than 2.5; TLG, total lesion glycolysis of SUVmax more than 2.5.
[a]These factors have missing values.

rate was 28.6% in patients with a low SUVmax and 41.2% in those with a high SUVmax, 13.3% in patients with a low MTV and 57.8% in those with a high MTV, and 13.3% in patients with a low TLG and 57.8% in those with a high TLG (Fig. 2).

SUVmax, MTV, and TLG were not predictors for LC ($p = 0.5$, 0.5, and 0.5, respectively) (Fig. 3). Lower age, histology of adenocarcinoma, and two cycles of concurrent chemotherapy were associated with a higher LC in the univariate analysis ($p = 0.03$, 0.03, and 0.005, respectively). There were no significant factors in the multivariate analysis. SUVmax, MTV, and TLG were not predictors for OS ($p = 0.7$, 0. 5 and 0. 6, respectively) (Fig. 4). The histology of the adenocarcinoma was associated with a higher OS on univariate analysis ($p = 0.0008$). Elective nodal irradiation was performed in 7 patients and was not found to be correlated with LC ($p = 0.5$), DMFS ($p = 0.8$), PFS ($p = 0.3$), or OS ($p = 0.8$).

Discussion

In this study, we demonstrated that volumetric PET parameters were predictors of which patients had received definitive CCRT.

The outcome of chemoradiotherapy for stage III lung cancer has been shown to be significantly improved by

Table 2 Univariate analyses of factors associated with distant metastasis-free survival and progression-free survival

Factor		DMFS		PFS	
		event/total	*p*-value	event/total	*p*-value
Age (years)	<64	10/15	0.5	10/15	0.6
	≥64	11/15		11/15	
Sex	Male	19/26	0.8	19/26	0.6
	Female	2/4		2/4	
T stage[a]	1–2	10/12	0.7	10/12	0.8
	3–4	10/15		10/15	
N stage	0–1	4/6	0.8	4/6	0.9
	2–3	17/24		17/24	
Clinical stage	IIIA	4/7	0.5	4/7	0.9
	IIIB	17/23		17/23	
Histology	Adenocarcinoma	8/11	0.05	8/11	0.2
	others	13/19		13/19	
Lobe[a]	Lower lobe	5/6	0.8	5/6	0.6
	Upper lobe	15/21		15/21	
Laterality[a]	Right	12/17	0.3	12/17	0.6
	Left	8/10		8/10	
Smoking history	Never/Former	10/16	0.2	10/16	0.3
	Current	11/14		11/14	
FEV1 (l)[a]	<2.2	11/15	0.8	11/15	0.9
	≥2.2	10/13		10/13	
ECOG-PS	0	8/12	0.7	8/12	0.9
	1	14/18		13/18	
Cycles of concurrent chemotherapy	1	1/1	0.7	1/1	0.4
	2	20/29		20/29	
Cycles of adjuvant chemotherapy	0	19/28	0.2	19/28	0.2
	1	2/2		2/2	
SUVmax	<16	12/14	0.2	12/14	0.09
	≥16	9/16		9/16	
MTV (cm^3)	<79	14/15	0.0003	14/15	0.0005
	≥79	7/15		7/15	
TLG	<590	14/15	0.001	14/15	0.0007
	≥590	7/15		7/15	

DMFS, distant metastases free survival; ECOG-PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 sec; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume of SUVmax more than 2.5; PFS, progression-free survival; TLG, total lesion glycolysis of SUVmax more than 2.5.
[a]These factors have missing values.

the use of durvalumab [11,12]. The improvement in PFS and OS could be attributed to the reduction of distant metastases. However, radiation pneumonitis is one of the serious adverse events of radiotherapy, and the rate of grade 5 adverse events has been reported to be 2.5% [13] and 4.4% [10]. In addition, one of the major adverse events associated with immune checkpoint inhibitors is pneumonitis [14]. Thus, these drugs can be used only after considering the balance between their benefits and the risk of pneumonitis; therefore, predictive biomarkers of distant metastases prior to CCRT are desirable, as they can assist the attending physician in determining whether to administer durvalumab.

PET is a useful imaging technique for prediction in addition to diagnosis, staging, and radiotherapy planning in the case of malignancy [15,16]. Although SUVmax was initially adopted as a predictor for patients who received radiotherapy [2], volumetric PET parameters have recently been adopted as prognostic factors. In our study, SUVmax was not a predictor of LC, DMFS, PFS, or OS, but the volumetric PET parameters MTV and TLG were predictors of DMFS and PFS. Because SUVmax is a single-voxel value representing the most intense FDG uptake in the mass [4], it does

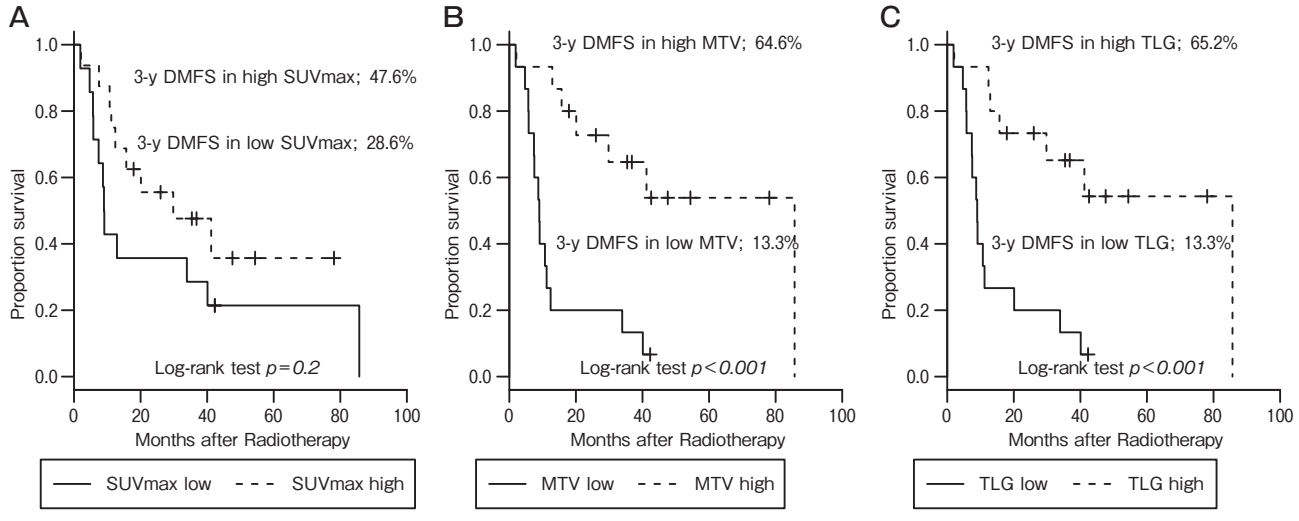

Fig. 1 Subgroup analysis of distant metastasis-free survival; (A) SUVmax; (B) MTV; (C) TLG.

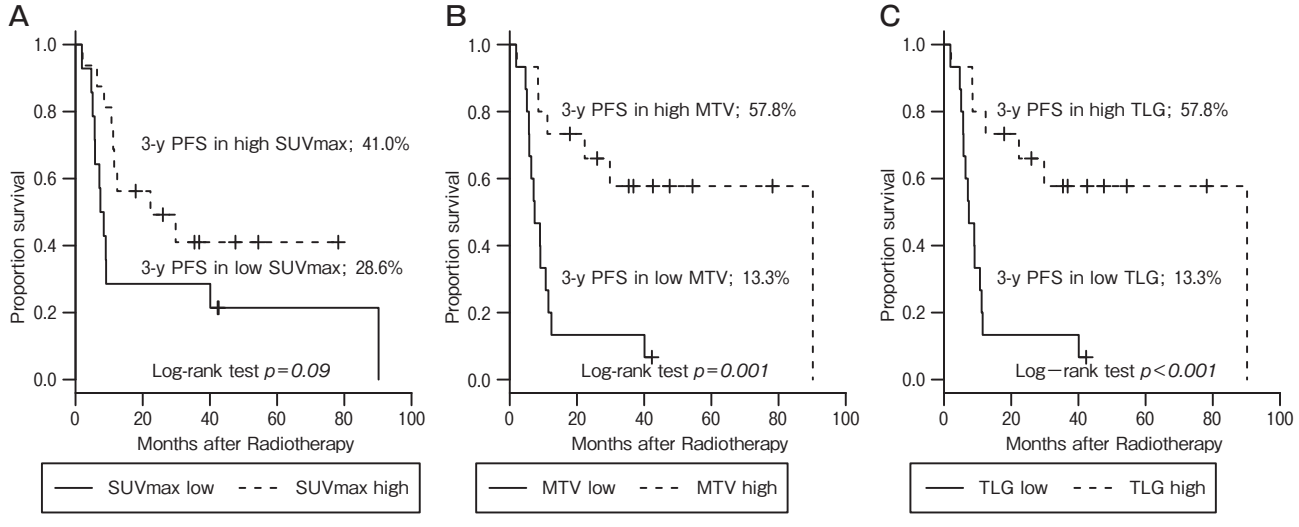

Fig. 2 Subgroup analysis of progression-free survival; (A) SUVmax; (B) MTV; (C) TLG.

not always represent the volume or burden of the highly active lesions in malignant tumors. In addition, the tumor composition is heterogeneous, and tumors are composed of non-active components such as necrotic tissue [17] or fibrotic scars, which may cause inaccuracies in assessments based on SUVmax values. SUVmax is also highly sensitive to image noise [18]. In contrast to SUVmax, the MTV and TLG of volumetric PET represent both the three-dimensional tumor volume and metabolic activity. In studies involving surgical resection for early stage disease [19], CCRT for stage II-III disease [5, 20], preoperative CCRT followed by surgery for stage IIIA-N2 disease [21], and chemotherapy for stage III-IV disease [7], researchers concluded that volumetric PET parameters are more useful as predictors than SUVmax. Consistent with these reports, volumetric PET parameters were more useful than SUVmax as prognostic factors in our study.

In our study, higher MTV and TLG resulted in higher DMFS and PFS rates, which contradicted the results of a previous report [8]. To the best of our knowledge, no papers have obtained the same results as our study. The treatment options for stage III lung cancer are wide-ranging and include surgery, preoperative

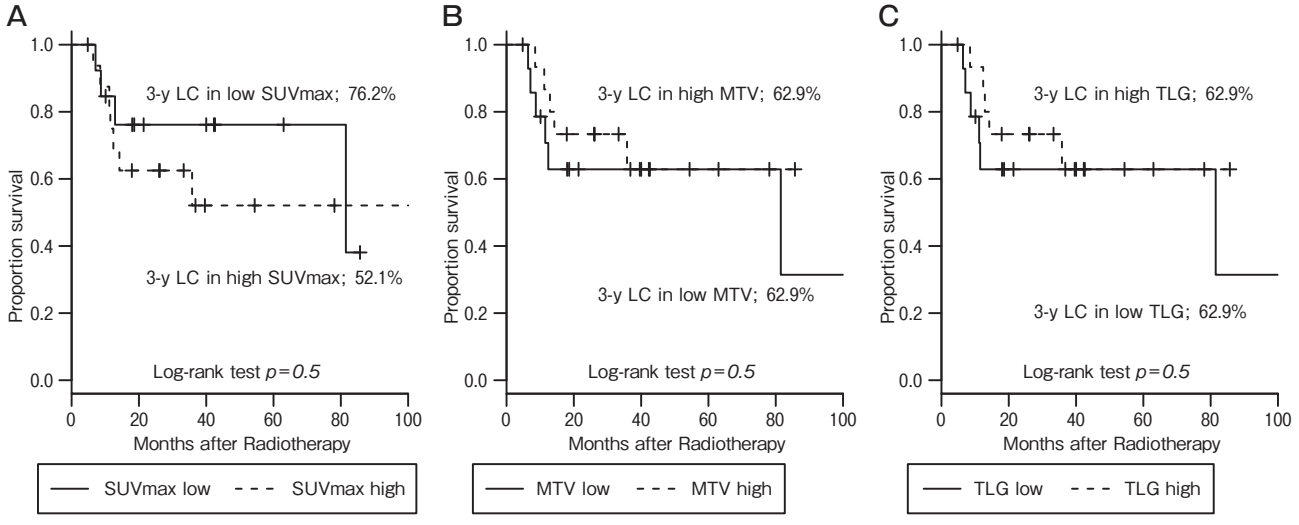

Fig. 3 Subgroup analysis of local control rate; (A) SUVmax; (B) MTV; (C) TLG.

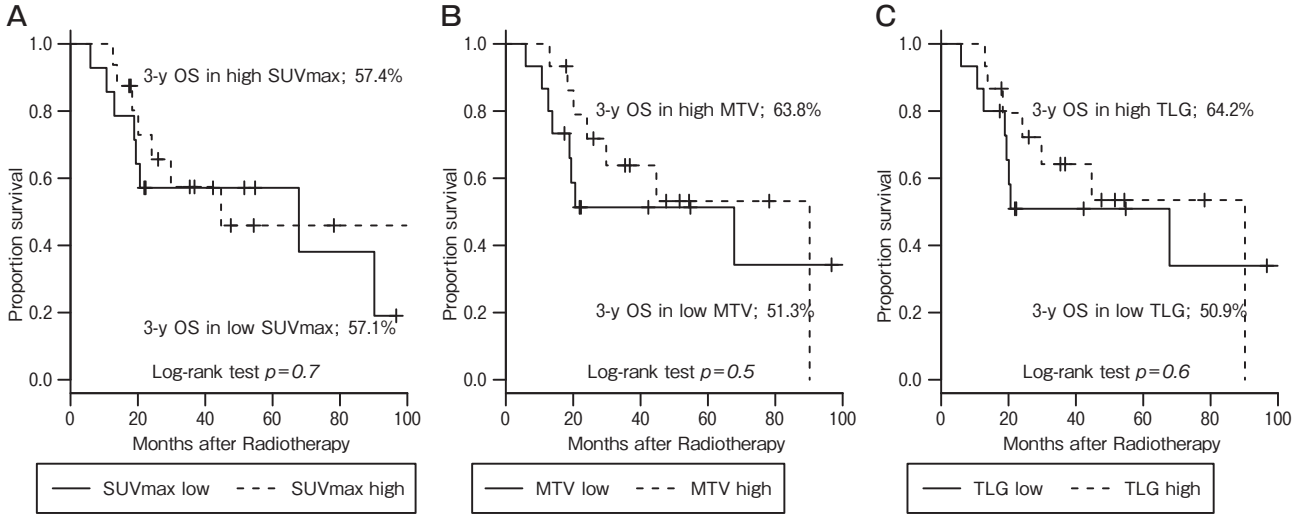

Fig. 4 Subgroup analysis of overall survival; (A) SUVmax; (B) MTV; (C) TLG.

radiotherapy followed by surgery, chemoradiotherapy, and chemotherapy; therefore, indications for definitive radiotherapy may vary greatly among institutions. While our study used standardized regimens of chemotherapy and radiation doses, many previous reports have mixed different regimens and radiation doses [8], and this may have been responsible for the variation in results. Other possible explanations for the discrepant results are described below. PET accumulation is higher in poorly differentiated tumors [22]. Radiation therapy is highly effective for poorly differentiated tumors, which may explain the successful results in the high MTV and TLG groups. Docetaxel leads to a G2-M-phase cell cycle arrest of tumor cells and has a synergistic effect with radiotherapy [23]. There may have been more tumor cells with higher activity and shorter doubling times in the group with higher PET parameters, which may have resulted in a greater effect of CCRT in these patients. Ganeshan *et al.* found that the computed tomographic texture in NSCLC is associated with tumor hypoxia and angiogenesis [24]. Cook *et al.* reported that prognosis can be predicted by texture analysis of intra-tumoral image heterogeneity with PET images of NCSLC patients who received chemoradiotherapy [25].

Thus, the volumetric PET value is not a simple expression of glucose metabolism and tumor burden and may indicate the influence of these more complicated factors. Data from additional studies and more research are warranted to validate these points.

Volumetric PET parameters were not prognostic factors for OS despite being prognostic factors for PFS. This difference in the predictive utility of PET for OS can be attributed to post-recurrence treatments such as molecular target drugs and immune checkpoint inhibitors [26]. The pathology of adenocarcinoma was associated with a high OS rate. Pemetrexed is not recommended because of its lower benefit in patients with squamous cell carcinoma compared to patients with adenocarcinoma [27], while bevacizumab is not recommended because squamous cell carcinoma is a risk factor for serious adverse events [28]. It has been speculated that adenocarcinomatous pathology was a favorable prognostic factor in OS because of differences in drug indications and efficacy after recurrence.

We believe that the results of our study can help determine treatment strategies and the frequency of follow-up examinations after definitive CCRT. The addition of durvalumab after definitive CCRT improves the prognosis and should be prescribed by physicians as much as possible. Due to concerns regarding radiation pneumonitis, cases with a V20 of 35% or more were excluded from the PACIFIC study [11, 12], and clinical use in such cases requires great caution. Since the proton beam can produce a better dose distribution than the X-ray, the V20 value can be reduced [29]. Thus, the option of proton beam therapy may also be considered for patients with high V20 values who are likely to develop distant metastases as a result of volumetric PET parameters. The prognosis is poor for those patients having both spinal metastases and rapidly progressing symptoms. The 6-month survival rate for the good prognosis group with slower symptom progression is 92.0%, whereas that for the poor prognosis group with rapid symptom progression is 11.3% [30]. Therefore, early identification of distant metastases is as important as the treatment protocol. It may be possible to improve a patient's prognosis by assessing metastases at a short interval after CCRT in a group in which distant metastasis is likely to occur based on volumetric PET parameters.

There are some limitations to our study. First, this study was a retrospective analysis with a small sample size, which may be subject to unmeasurable bias. Second, there may be selection bias because the attending physicians in the authors' institutions tended to prioritize surgery after preoperative CCRT over definitive CCRT in stage III NCSLC. Third, Cook *et al.* reported that PET texture analysis of intra-tumoral image heterogeneity can predict prognosis [25], but we did not perform texture analysis. Fourth, since there were only 6 patients with a known pathological differentiation grade, we could not perform a statistical analysis of the effect of the degree of differentiation on the PET value. Fifth, the interval at which the examinations were performed was not standardized, which could have affected DMFS and PFS. Despite these limitations, we showed that the group with high volumetric PET parameters had a high DMFS rate.

In conclusion, we demonstrated that volumetric PET parameters could serve as predictors in stage III NSCLC patients who received definitive CCRT with cisplatin/docetaxel. Volumetric PET parameters may help physicians determine the best treatment modality and the most effective timing of follow-up examinations. Our findings are contrary to those of previous reports, and further research is warranted to validate these results.

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