The prognostic value of positron emission tomography/computed tomography in pulmonary metastasectomy

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Background: Although positron emission tomography/computed tomography (PET/CT) findings are prognostic in lung cancer patients, the prognostic value of PET/CT findings in patients with pulmonary metastases has neither been comprehensively investigated nor clarified. The aims of this retrospective study were to evaluate the value of PET/CT and identify novel prognostic indicators for pulmonary metastasectomy.

Methods: Between May 2004 and February 2017, 178 patients underwent PET/CT and resection of pulmonary metastases. After exclusion of patients who underwent biopsy only or duplicate cases, 142 patients were analyzed. Prognostic indicators, including PET/CT findings and outcomes were investigated.

Results: The median follow-up time was 42 months. The primary tumor site was colorectal in 76, kidney in 14, head and neck in 13, breast in 12, stomach in 8, urinary tract in 7, and other organs in 12 patients. The median maximal standardized uptake value (SUV_{max}) was 4.6. The optimal cut-off value, determined by receiver operating characteristic (ROC) analysis, identified the following cut-off values: disease-free interval (DFI) (12 months; SUV_{max} =4.5). Univariable analysis revealed that DFI ≤12 months, incomplete resection, and SUV_{max} ≥4.5 were significant for poor outcome. Multivariable analysis revealed incomplete resection and SUV_{max} ≥4.5 were significant for poor outcome. The 5-year survival rates of patients with SUV_{max} ≥4.5 and SUV_{max} <4.5 were 51.6% and 74.0%, respectively.

Conclusions: Analysis of patients undergoing pulmonary metastasectomy demonstrated that incomplete resection and an SUV_{max} ≥4.5 are significant prognostic indicators. PET/CT findings should be included in estimations of these patients' prognosis.

Keywords: Metastasectomy; prognosis; positron emission tomography/computed tomography (PET/CT)

Introduction

Despite rapid progress in the field of oncology, metastatic disease remains challenging to treat. The lung is the major target organ of metastases, and pulmonary metastasectomy is a common surgical procedure in thoracic surgery. The data on pulmonary metastasectomy are limited because of the lack of prospective randomized studies and selection bias (1-5). The 5-year overall survival rates have been reported to range from 30% to 50% (3,6,7), and the occurrence of oligometastasis (8,9) suggests the possibility of cure for selected patients with a pulmonary metastasis. Therefore, pulmonary metastasectomy is a common surgical procedure for selected patients with pulmonary metastases.

The main issue of concern for pulmonary metastasectomy

is the method of identifying those patients who might obtain survival benefit from pulmonary metastasectomy. Various prognostic factors have been proposed with regard to indications for pulmonary metastasectomy, including the following: disease-free interval (DFI) (6,7), histological features (6), number of metastases (6,7), R0 resection (7), tumor size (9), and metastatic lymph nodes (10-12).

Positron emission tomography/computed tomography (PET/CT) is an imaging technology that uses a radioactive isotope to identify cancer metastases. It is used to estimate the prognosis of patients with various types of malignancies (13). As a method for the preoperative management of patients with primary lung cancer, PET can prevent needless surgery, and PET/CT data from lung cancer patients are used to estimate the prognosis (14,15). Studies on the use of PET/CT for patients with pulmonary metastases are scarce (16-20). We thought that PET/CT could be not only a diagnostic tool (18,19) but also a prognostic tool. Since a high standardized uptake value (SUV) on a PET/CT reflects a higher glucose uptake, it should indicate tumor aggressiveness. To assess PET/CT results for patients with pulmonary metastasis, we conducted a retrospective study of patients with pulmonary metastasis who underwent PET/CT followed by metastasectomy. The aims of this study were to evaluate the value of PET/CT and identify novel prognostic indicators for pulmonary metastasectomy.

Methods

Data collection

Since the patient data remained anonymous, the ethics committee of our institution approved this study (institutional review board no. 29) and waived the need for informed consent. The patient's personal data have been secured. We consider the study outcomes will not affect the future management of the patients.

This was a retrospective study based on a single-center prospectively collected database of patients undergoing pulmonary metastasectomy from May 2004 to February 2017. Inclusion criteria were as follows: first pulmonary metastasectomy, metastasectomy for curative resection, the patient underwent PET/CT. Our database collected the following: patient characteristics [gender, age, past history, smoking habit, serum carcinoembryonic antigen (CEA) level, preoperative respiratory function], tumor status (size, DFI, tumor laterality and number, SUV_{max} value), surgical data (date of metastasectomy, surgical procedure,

completeness of pulmonary resection), and information on patient outcome (date of death or last confirmed survival). The DFI was calculated from the date of initial treatment for the primary tumor to the date of first detection of pulmonary metastasis.

PET/CT

PET/CT was carried out before surgery within 90 days after the patient had undergone contrast-enhanced chest CT. Since our institution does not have PET/CT on site, starting in 2004, patients were referred to another hospital (Yamagata Saiseikai Hospital or Yamagata University Hospital) to undergo PET/CT. The PET/CT protocol was described previously (21). Patients were instructed to fast for 4 hours before scanning, and a blood glucose level was measured to confirm that it was in the normal range. A standard dose of ^{18}F-fluorodeoxyglucose [FDG (3.75 MBq/kg)] was administered intravenously, and PET and CT images were obtained 60 min later by a Discovery LS instrument (General Electric, Milwaukee, Wisconsin, USA) in Yamagata Saiseikai Hospital. In Yamagata University Hospital, the dose of ^{18}FDG was 3.70 MBq/kg; otherwise the images obtained by the Biograph mCT PET/CT scanner (Simens, München, Germany) at that institution used the same settings and conditions that were used at Yamagata Saiseikai Hospital. Scanning was performed from the base of the skull to the level of the midthigh. To determine the SUV_{max} after images were obtained, the region of interest, which was established by the radiologists who evaluated the PET scan, was manually placed over the tumor site on each transaxial slice. The SUV_{max} of each slice was then automatically calculated by software. For patients who had multiple pulmonary metastases, a single lesion with the highest SUV_{max} was used for analysis.

Patients

Between May 2004 and February 2017, 246 patients underwent metastasectomy for pulmonary metastases. Sixty-eight cases not undergoing PET/CT, 32 undergoing repeated metastasectomy, and 4 undergoing exploratory thoracotomy were excluded. We included 13 patients with incomplete resection who had extrapulmonary metastases or contralateral pulmonary metastasis at the time of PET/CT and pulmonary metastasectomy. A total of 142 patients were eligible for this study. The surgical indication, procedure,
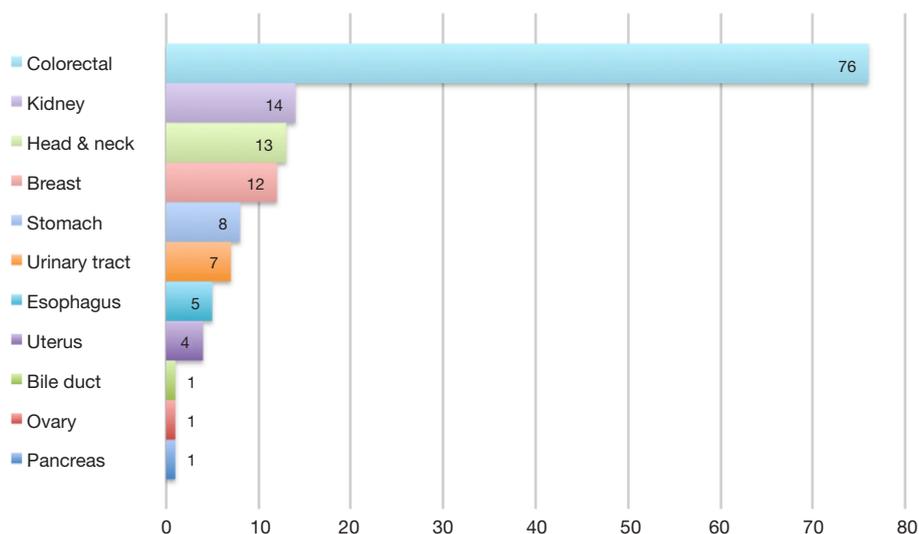
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Figure 1 Primary sites of the pulmonary metastases of the study patient.

and approach for each patient were determined by the consensus of a group of thoracic surgeons. In general, we performed wedge resection for metastatic nodules, and choose segmentectomy for tumors located in the hilum. Lobectomy was selected for multiple nodules located in the same lobe or for tumors >3.0 cm. Lymph node dissection was performed for tumors >3.0 cm. Staged pulmonary metastasectomies were usually performed at 1-month intervals for multiple bilateral nodules. Survival data were updated every 6 months.

Statistical analysis

Receiver operating characteristic (ROC) curve analysis was used to identify the appropriate DFI and SUV_{max} cut-off values. After each case was classified based on the SUV_{max} cut-off value, the Chi-square test was used to evaluate the association between each categorical variable and category of SUV_{max}. The Student t-test was used to compare continuous variables and SUV_{max}. The median follow-up time was estimated by the reverse Kaplan-Meier method. Overall survival was estimated using the Kaplan-Meier method. Overall survival was measured from the date of pulmonary metastasectomy to the date of death from any cause or censored at the date of the patient's last hospital visit. Univariable and multivariable Cox proportional hazards regression analysis was used to identify prognostic indicators of overall survival. Data were analyzed using JMP software, version 11.0 (SAS Institute Inc., Cary,

NC, USA). A P value <0.05 was considered statistically significant.

Results

There were no perioperative deaths. Major complications were seen in 8 patients (5.6%): prolonged air leakage in 3 (2.1%), bleeding and hemothorax in 2 (1.4%), atrial fibrillation in 1 (0.7%), pulmonary edema in 1 (0.7%), and paralysis of the brachial plexus in 1 (0.7%) patient. Regarding the administration of adjuvant therapy after pulmonary metastasectomy, 35 patients received adjuvant therapy, and 38 patients did not receive it. However, data on adjuvant therapy for 69 patients was not available. The Kaplan-Meier estimate of the median length of follow-up was 42 months. Among these followed patients, 32 patients (22.5%) died (cancer: 26; other causes: 2; unknown cause: 4).

Patient characteristics and association with SUV

The primary sites were as follows: colorectal in 76 (53.5%), kidney in 14 (9.9%), head and neck in 13 (9.2%), breast in 12 (8.5%), stomach in 8 (5.6%), urinary tract in 7 (4.9%), esophagus in 5 (3.5%), uterus in 4 (2.8%), bile tract in 1 (0.7%), ovary in 1 (0.7%) and pancreas in 1 (0.7%) (*Figure 1*). *Table 1* shows the patients' demographic data. Almost all cases were unilateral or solitary pulmonary metastases. Wedge resection was the most common procedure. Sublobar resections were performed in 78.1%.

Table 1 Characteristics of patients undergoing pulmonary metastasectomy

Factors	Number (%)
Median age, years [range]	69 [31–86]
Gender	
Male	77 (54.2)
Female	65 (45.8)
Smoking	
Yes	81 (57.0)
No	59 (41.5)
Unknown	2 (1.4)
Serum CEA, ng/mL [range]	2.4 [0.5–67.6]
Median size tumor, cm [range]	1.4 [0.6–6.5]
Median DFI, months [range]	16 [0–288]
Surgical laterality	
Bilateral	14 (9.9)
Unilateral	128 (90.1)
Median number tumors, [range]	1 [1–8]
Multiple	38 (26.8)
Solitary	104 (73.2)
Procedure	
Wedge resection	92 (64.8)
Segmentectomy	19 (13.3)
Lobectomy	31 (21.8)
Curability	
Complete	129 (90.8)
Incomplete	13 (9.2)
Median value SUVmax, [range]	4.6 [0–22.8]

CEA, carcinoembryonic antigen; DFI, disease-free interval; SUV, standardized uptake value.

Figure 2 ROC curve analysis was used to determine the appropriate cut-off values for SUV_{max} (A) and DFI (B) for survival. SUV, standardized uptake value; DFI, disease-free interval; AUC, area under the curve; ROC, receiver operating characteristic.

The SUV_{max} cut-off value for survival was 4.5 [area under the curve (AUC) =0.59] by ROC analysis, and the DFI cut-off value was 12 months (AUC =0.66) (*Figure 2*). *Table 2* shows the associations between the patients' characteristics and SUV_{max}. The tumor size was larger in cases with SUV_{max} ≥4.5. The proportion of non-wedge resection cases was higher with SUV_{max} ≥4.5. Since a large proportion of patients had colorectal primary cancers, the differences between the $SUV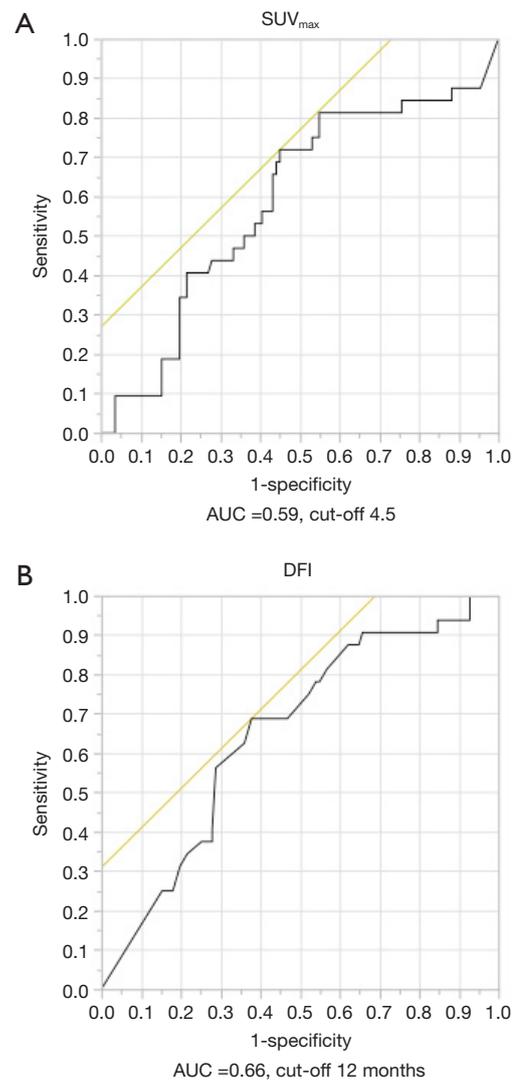_{max}$ values of patients with colorectal primary cancers and of the values of each group with a non-colorectal primary cancer were evaluated, but there was no difference.

Survival and recurrence

Figure 3 shows the Kaplan-Meier curve of the overall survival of all cases. The overall 5-year survival rate after pulmonary metastasectomy was 62.6%. For univariable and multivariable analysis, patients were classified according to

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Table 2 Relationship between the SUV max and patient characteristics*

Factors	SUV$_{max}$ <4.5 [n (%)]	SUV$_{max}$ ≥4.5 [n (%)]	P
Number	70	72	
Age, years (mean ± SD)	65±12	67±13	0.467
Gender			0.726
Male	39 (55.7)	38 (52.8)	
Female	31 (44.3)	34 (47.2)	
Smoking			0.392
Yes	43 (61.4)	38 (54.3)	
No	27 (38.6)	32 (45.7)	
Serum CEA, ng/mL (mean ± SD)	4.1±7.4	4.0±8.3	0.928
Tumor size, cm (mean ± SD)	1.3±0.8	2.2±1.1	<0.001
DFI, months (mean ± SD)	29±50	34±45	0.507
Laterality			0.097
Bilateral	10 (14.3)	4 (5.6)	
Unilateral	60 (85.7)	68 (94.4)	
Number of tumors			0.215
Multiple	22 (31.4)	16 (22.2)	
Single	48 (68.6)	56 (77.8)	
Surgery			<0.001
Wedge	57 (81.4)	35 (48.6)	
Non-wedge	13 (18.6)	37 (51.4)	
Curability			0.812
Complete	64 (91.4)	65 (90.3)	
Incomplete	6 (8.6)	7 (9.7)	
Primary site			0.089
Colorectal	43 (61.4)	34 (52.8)	
Non-colorectal	27 (38.6)	38 (47.2)	

*, chi-square test used for categorical data and unpaired *t*-test used for continuous data. SUV, standardized uptake value; SD, standard deviation; CEA, carcinoembryonic antigen; DFI, disease-free interval.

the following categories based on ROC curve analysis: DFI ≤ or >12 months, and SUV$_{max}$ ≥4.5 or <4.5. At the time of last follow-up, 60 of 142 patients (42.3%) had developed recurrence and 32 (22.5%) had died. Univariable analysis revealed DFI ≤12, incomplete resection, and SUV$_{max}$ ≥4.5 were significant prognostic indicators for overall survival.
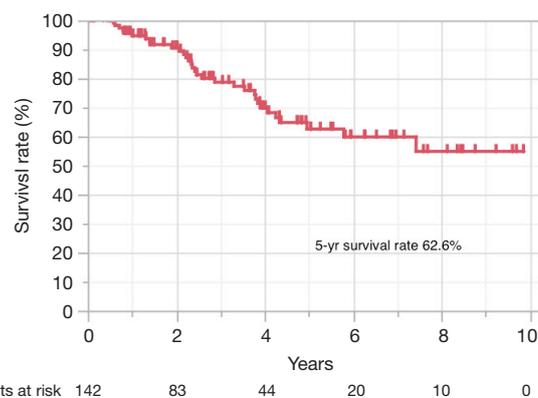
Figure 3 Overall survival of all cases after pulmonary metastasectomy.

By multivariable analysis, the prognostic effects of incomplete resection (P=0.026) and SUV$_{max}$ ≥4.5 (P=0.035) were maintained after correcting for the other candidate prognostic variables.

Based on SUV$_{max}$ values, the 5-year survival rates of patients with values SUV$_{max}$ ≥4.5 and <4.5 were 51.6% and 74.0%, respectively (P=0.022) (*Figure 4A*). Based on DFIs, the 5-year survival rates of patients with DFI ≤12 and >12 months were 50.6% and 73.9%, respectively (P=0.030) (*Figure 4B*). Regarding curability, the 5-year survival rates of patients who received complete resection was 66.2%, whereas none of the patients with incomplete resection survived 5 years (*Figure 4C*).

Because of the small study cohort, survival was calculated for the patients with colorectal primaries versus the patients with non-colorectal primaries. Overall survival was similar for the two groups, colorectal *vs.* non-colorectal patients (P=0.645) (*Table 3*).

Discussion

Although the evidence on performing pulmonary metastasectomy for patients with pulmonary metastases is not sufficient, and the selection of patients for pulmonary metastasectomy includes biases (1-5), metastasectomy is a treatment option, and carefully selected patients can obtain a promising outcome compared to primary lung cancer, because the heterogeneity of the outcomes after pulmonary metastasectomy is associated with the types of primaries. The optimization of patient selection is mandatory for achieving the best outcome.

Various types of prognostic indicators have been reported. The International Registry of Lung Metastases
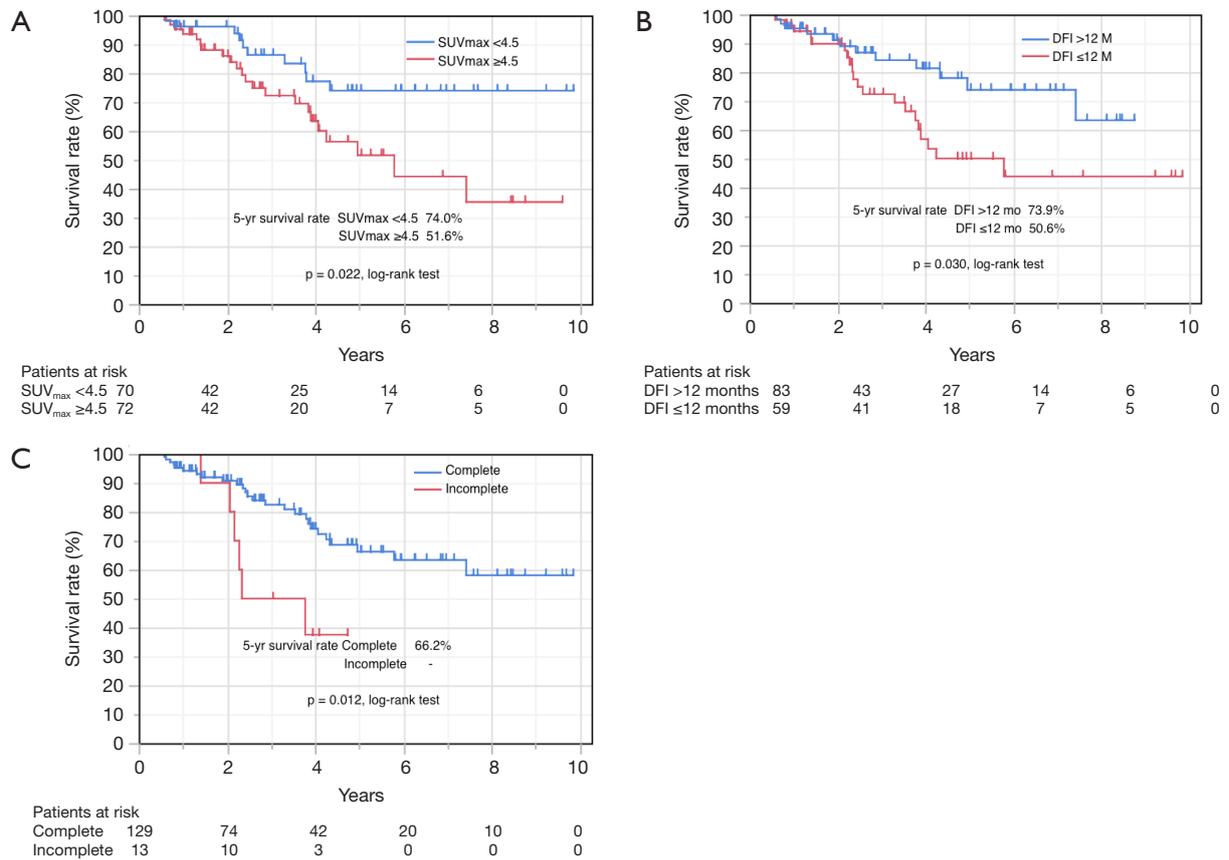
Figure 4 Survival curves. (A) Overall survival based on SUV$_{max}$; (B) overall survival based on DFI; (C) overall survival based on curability. SUV, standardized uptake value; DFI, disease-free interval.

Table 3 Overall survival by prognostic factor*

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age	0.99	0.97–1.02	0.653	0.99	0.97–1.03	0.878
Gender	1.98	0.97–4.28	0.059	2.00	0.68–6.63	0.215
Smoking	1.11	0.55–2.36	0.771	0.70	0.22–2.12	0.530
Serum CEA	1.02	0.99–1.04	0.063	1.03	0.99–1.07	0.072
Max tumor size	1.21	0.87–1.58	0.245	0.78	0.40–1.36	0.403
DFI	2.17	1.07–4.58	0.031	1.77	0.76–4.22	0.188
Surgical side	1.43	0.42–3.68	0.520	0.33	0.05–1.75	0.194
Number of tumors	1.81	0.79–3.81	0.520	1.44	0.38–4.67	0.571
Procedure	0.80	0.40–1.63	0.542	1.00	0.40–2.60	0.989
Curability	3.02	1.11–7.02	0.032	4.57	1.22–15.0	0.026
SUV$_{max}$	2.34	1.13–5.20	0.021	2.87	1.08–7.97	0.035

*, Cox proportional hazards model. CI, confidence interval; DFI, disease-free interval; CEA, carcinoembryonic antigen; SUV, standardized uptake value.

previously studied 5,206 patients and found that DFI >3 years and a solitary pulmonary metastasis were favorable prognostic indicators (6). In this study, we identified curability, DFI, and SUV$_{max}$. Curability is recognized as an essential prognostic factor. While DFI is also widely accepted, Robert *et al.* reported that DFI was not prognostic (9). In fact, patients with a slowly growing tumor tend to achieve a long DFI, but DFI depends on the duration of follow-up period and the modalities used for postoperative monitoring. In addition, both CT and PET/CT can identify very small metastatic deposits. However, how do we diagnose small lung nodules as a pulmonary metastasis? Based on this reasoning, we thought that DFI might be controversial in regard to its prognostic value.

Prognostic indicators should be associated with the biological characteristics of the tumor. Tumor doubling time is a prognostic factor related to tumor biology. Chojniak *et al.* explored the doubling time of pulmonary metastases. They reported that 30% of cases had metastases that did not change in size, and the tumor doubling time varied remarkably among the patients (22). Tumor doubling time requires radiological follow-up after a metastasis is identified, and the tumor doubling time of cases with multiple pulmonary metastases might be difficult to determine.

The SUV is a semiquantitative PET/CT parameter that is calculated based on the accumulation of FDG adjusted by body weight and dose of injected FDG. The SUV is affected by many factors and lacks both reproducibility and standardization. However, it is a useful value for evaluating tumor biology. Promising PET/CT information has been obtained on extra-thoracic malignancies. A systematic review and meta-analysis found that PET/CT is an accurate diagnostic modality for patients with potentially resectable hepatic metastases from colorectal cancer (23). For breast cancer, PET/CT provides benefits for the initial management, and assessments of treatment response and recurrence (24). The SUV$_{max}$ is correlated with histological characteristics and prognosis (25). A high SUV$_{max}$ is significant for recurrence in gastric cancer (26), disease-free survival in endometrial cancer (27), and survival in esophageal cancer (28). The SUV$_{mean}$ was associated with disease-free survival in cancers of the head and neck (29).

Studies have been published on the relationship between pulmonary metastasis and PET/CT (16-20). PET/CT of patients with metastatic pulmonary tumor can provide preoperative information that is important for the decision to perform lung surgery. Pastorino *et al.* revealed

that preoperative PET/CT could reduce the number of unnecessary pulmonary metastasectomies (17). PET/CT has been used as a diagnostic tool for differentiating between malignant and benign pulmonary nodules (18,19). Veronesi *et al.* reported that the SUV$_{mean}$ was 3.9±2.5 (median 3.6) in 43 pulmonary metastases, and higher in colon cancer than in sarcoma metastases, but the difference was not significant (16). Fortes *et al.* reported that metastasis size was correlated with PET positivity (19), and Pastorino *et al.* likewise showed that size is related to PET sensitivity (17). PET/CT had not been sufficiently explored with regard to outcomes after pulmonary metastasectomies. Kaira *et al.* suggested that the T/M ratio, which is the ratio of the peak SUV of the tumor to the mean SUV of the mediastinum, was related to the outcome of patients with a pulmonary metastasis, but only in univariable analysis (20). The present study could show that SUV$_{max}$ ≥4.5 is significant prognostic indicator. A pulmonary metastasis with an elevated SUV is thought to manifest aggressive biological characteristics. However, PET positivity has not been found to be associated with the intratumoral density of microvessels (16). Further basic research is needed to clarify these relationships.

In this study, the 5-year survival rates of patients with SUV$_{max}$ ≥4.5 and <4.5 were 51.6% and 74.0%, respectively, which are higher than reported by previous studies (6,7) of patients undergoing pulmonary metastasectomy. We postulate that because PET/CT can detect other distant metastatic lesions and lead to the study exclusion of more advanced cases, our good results might be reflective of stage migration (5).

This study has several limitations. Firstly, the study patients had various types of cancers, which have different biological behaviors and for which PET/CT has shown different sensitivities (16-19). We did not find significant differences in SUV$_{max}$ values for the survival of patients with colorectal primaries versus non-colorectal primaries. Since half the cases in our study were pulmonary metastases from colorectal cancer, it is possible that we showed the outcome of patients with pulmonary metastases from colorectal cancer. PET studies show that the modality is not sensitive for sarcoma (16), but our study did not include cases of sarcoma and we could not provide data on sarcoma. In addition, renal cell carcinoma generally shows low FDG uptake. However, in our study, the number of cases with renal cell carcinoma was only 14 (10%); therefore, we could not clarify the prognosis of a low FDG uptake in renal cell carcinoma metastases.

The SUV_{max} might be a unique prognostic factor regardless of the type of primary malignancy; however, we need to collect more data since the numbers of our cases with different types of primary tumor were too small. Moreover, Morris *et al.* revealed that SUVs of distant metastases might vary based on their location (30). Notably, although the SUV_{max} of bone metastases was prognostic for patients with newly diagnosed breast cancer, the SUV_{max} of pulmonary metastases in these patients was not prognostic (30). Secondly, we performed a single-center study, and we could not confirm the reproducibility of our data. To confirm our results, we are planning a prospective study on the effectiveness of SUV_{max} for patients undergoing pulmonary metastasectomy. Thirdly, the median follow-up time was 42 months, which is not adequate. More than 5 years of follow-up are needed to confirm the benefits of SUV_{max} for patients undergoing pulmonary metastasectomy (1,7). Fourthly, we used two types of PET/CT scanners because the study patients were seen at two different institutions. Differences between scanners might have affected SUV_{max} values. To resolve the problem, SUV_{max} values would have to be corrected. Finally, pulmonary metastasectomy is performed for carefully selected patients. Chemotherapy and other treatments for metastatic cancer enable patients to obtain improved survival. We also did not include patients without surgery, so we do not know if the same results would be obtained for these patients. Given these limitations, our results should be interpreted cautiously; we need more cases to confirm our results.

Conclusions

In conclusion, we found significant correlation between survival and SUV_{max} values of patients with pulmonary metastasis who underwent resection. However, this is a single-center study of patients with various types of primary malignancies. A prospective observational multicenter study is needed to confirm our results.

Acknowledgements

Footnote

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