

Prognostic Significance of Volume-Based PET Parameters in Cancer Patients

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Accurate prediction of cancer prognosis before the start of treatment is important since these predictions often affect the choice of treatment. Prognosis is usually based on anatomical staging and other clinical factors. However, the conventional system is not sufficient to accurately and reliably determine prognosis. Metabolic parameters measured by ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) have the potential to provide valuable information regarding prognosis and treatment response evaluation in cancer patients. Among these parameters, volume-based PET parameters such as metabolic tumor volume and total lesion glycolysis are especially promising. However, the measurement of these parameters is significantly affected by the imaging methodology and specific image characteristics, and a standard method for these parameters has not been established. This review introduces volume-based PET parameters as potential prognostic indicators, and highlights methodological considerations for measurement, potential implications, and prospects for further studies.

Index terms: Positron emission tomography; ^{18}F -fluorodeoxyglucose; Metabolic tumor volume; Total lesion glycolysis; Prognosis/rinogenesis

INTRODUCTION

Accurate prediction of prognosis is important for the planning of effective treatment regarding cancer patients. However, due to the limitations of the conventional system alone, there is a need for more accurate and reliable

methods of determining prognosis (1-5). In order to accomplish this, all the characteristics of a tumor, including biological, molecular, and clinical features, should be incorporated into the estimation of the patient's prognosis.

^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) has become a standard imaging method for the staging, restaging, and monitoring of treatment response in a variety of tumors. This modality has an advantage over conventional imaging modalities in that it enables quantification of the metabolic activity of a tumor. Quantified metabolic activity can provide valuable information to help prognosticate and assess treatment response in clinical oncology. The standardized uptake value (SUV) is a commonly used parameter for (semi)-quantitative analysis of PET images, and is calculated either pixel-wise or over a region of interest as the ratio of tissue radioactivity concentration and the injected dose adjusted by body weight (6). The maximum SUV (SUV_{max}) is obtained for a 1-pixel region of

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interest (ROI) corresponding to the maximum pixel value in the tumor. This is a frequently used parameter because it provides an observer-independent measurement. Mean SUV (SUV_{mean}), another common parameter, is the mean value of metabolic activity in a chosen region. However, SUV_{max} does not necessarily represent the total tumor activity for the whole tumor mass, because a single pixel may not be representative of nonhomogeneous overall tumor uptake. Peak SUV (SUV_{peak}), which is the average value within a small, fixed-size ROI in the tumor, is a more robust alternative to SUV_{max} . However, this measure shares many limitations with the SUV_{max} , and, more importantly, the ideal size and shape of the ROI has not yet been established (7). Although SUV_{mean} may be more suitable for representing whole tumor activity, it is subjective and prone to observer variability (6).

Volume-based PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been developed (8) to measure metabolic activity in an entire tumor mass. These parameters are intended to measure global changes in tumor glycolysis. MTV is a volumetric measurement of tumor cells with high glycolytic activity, while TLG is defined as the product of the SUV and the lesion volume. Although these parameters are well-described in the literature, using these parameters in routine clinical practice is not easy because their measurement requires a considerable amount of time and effort. However, with the development of software capable of automated volume-of-interest (VOI) assessments, volume-based metabolic parameters have become easily available quantitative PET indices (9). Current clinical oncology guidelines do not yet reflect this advance, and do not include MTV measurements or TLG in characterizing the response to the treatment (8). However, these parameters have the potential to become a useful index for assessing therapeutic response by quantifying the global change in tumor burden during or after treatment. In addition, these parameters can also be used for predicting patient prognosis.

In this review, we focus on methodological considerations of the measurement of MTV and TLG, the potential usefulness of these parameters in assessing therapeutic response and predicting patient prognosis, and compare these parameters to determine performance.

Methodological Considerations

Tumor Delineation Methods

Careful optimization of tumor delineation methods and image characteristics are important for obtaining accurate and reproducible volume-based PET parameters. Various methods for delineating tumor boundaries based on PET images have been reported, including purely manual and automatic methods, as well as several semiautomatic methods (10-14). In the manual method, tumor boundaries are manually drawn by a nuclear medicine physician, radiologist, or radiation oncologist, and the volume of that region is calculated. Manually drawing tumor boundaries can lead to a large variation in tumor volume because the determination of the tumor boundary depends on both the experience of the physician and the contouring protocol used (15). Automatic or semiautomatic methods can be used to delineate tumor boundaries using an isocontour threshold in which all contiguous voxels with values above a chosen threshold are included. An advantage of this method is that inter- and intra- observer variation in tumor volume delineation is reduced. Figure 1 shows a representative example using automatically generated VOIs to measure the MTV of a primary tumor. Automatic and semiautomatic methods with various threshold values have been reported in previous studies. The fixed threshold method is a widely used and simple technique that applies a threshold based on a percentage (typically, 41-70%) of SUV_{max} within the tumor. Results of previous work have shown that the ideal percentage for the threshold SUV to most accurately reflect the pathological tumor size is inversely proportional to the SUV_{max} of the tumor (16, 17). However, the fixed threshold method for measuring tumor volume has several limitations. First, the tumor volume may be significantly affected by noise because the value of SUV_{max} depends on the amount of noise present (6). A second limitation of this method is that if the percentage used for the fixed threshold is too low, the tumor volume may erroneously include a significant proportion of the background (6). To overcome these problems, the isocontour value can be based on the difference between tumor activity and background activity (13). This adaptive threshold method is similar to the fixed threshold method. However, this method adjusts the threshold value relative to the local average background, thereby correcting for the contrast between the tumor and local background (18). The contrast-oriented method applies correction based on the mean of 70% SUV_{max} and

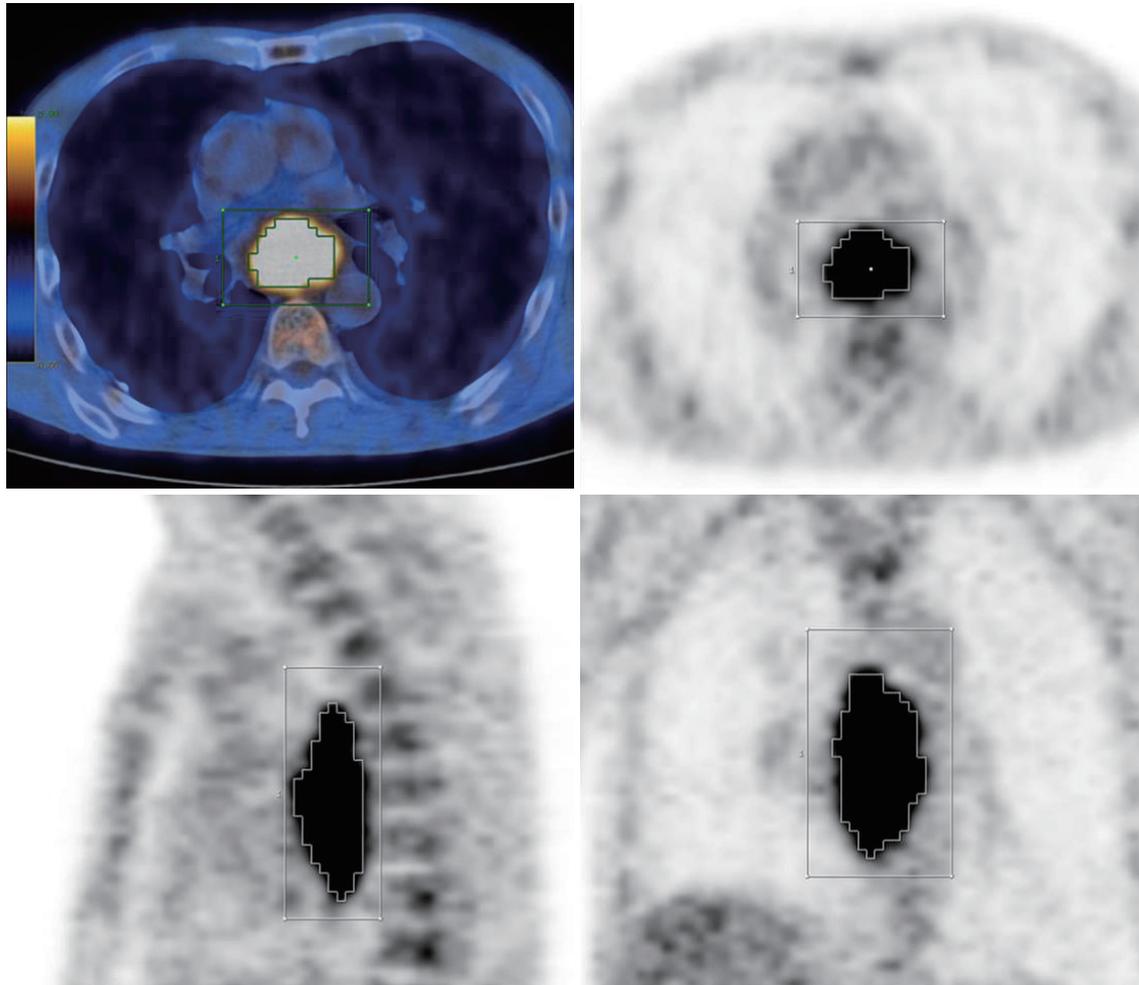


Fig. 1. Measurement of metabolic tumor volume in patients with esophageal cancer. ^{18}F -fluorodeoxyglucose PET/CT images of 53-year-old male patient with esophageal cancer demonstrating measurement of metabolic tumor volume. Boundary of metabolically active tumor was automatically delineated using isocontour, defined as percentage of maximum SUV in tumor (40% in this image). VOI = volume of interest, SUV = standardized uptake values

the background activity for various sphere sizes (18). The absolute SUV method adopts a certain SUV value (e.g., SUV 2.5) that would properly differentiate between benign and malignant lesions as the absolute threshold value for delineating the tumor (14, 19). The problem with this method is that the absolute threshold value may be somewhat arbitrary.

Mediastinal blood pool activity (9, 20, 21) and liver activity (9, 22) can also be used as threshold values. In addition to these methods, there are many other types of automatic and semiautomatic methods, such as the background-subtracted relative threshold level method (18), the gradient-based watershed segmentation method (18), and the fuzzy locally adaptive Bayesian method (23).

It should be noted that there is still no consensus on a standard method for tumor delineation. It is important to use MTV and TLG because the measurement of volume-

based PET parameters is significantly affected by the tumor delineation method (21, 23, 24). A recent study reported that all tumor delineation methods demonstrated a much larger variation in measured metabolic tumor volume (< 29%) compared to SUV (< 11%) when image characteristics and radiotracers were varied (24). In another study, large differences were observed between methods (from -140 to 50% of tumor volume) (23). A recent phantom study showed that a contrast-oriented method provided the most accurate results, on average, over all simulated conditions (18). Another study investigated the impact of tumor delineation methods in patients with esophageal cancer and suggested that the fuzzy locally adaptive Bayesian method may be the most useful method (23). However, while many methods have been proposed for the determination of an optimal threshold in regards to tumor delineation (2, 9, 12, 18-23), a standard method has not yet been established

for clinical use (9). There is some controversy regarding whether the value of volume-based PET parameters in clinical use is affected by the tumor delineation method used. Although the tumor delineation method used had a significant quantitative impact on the absolute value of the PET parameters, the clinical value of the PET parameters may not be affected. In an earlier study evaluating the use of MTV and TLG for predicting recurrence-free survival (RFS) and overall survival (OS) in patients with non-small cell lung cancer, patients with smaller MTV and lower TLG showed longer RFS and OS regardless of the threshold value used (25). A similar result was demonstrated in a recent study of patients with tonsil cancer, in which the value of the metabolic parameters in predicting overall survival was not significantly affected by the selected threshold value (9).

Image Characteristics and Other Factors

The accuracy of PET-based automatic or semiautomatic delineation methods can be affected by many factors, including image resolution and reconstruction settings (10, 11, 26). Previous studies have reported that the performance of various automatic or semiautomatic tumor delineation methods depends on both image resolution and contrast (18, 24). In a recent study that assessed the test-retest variability of tumor delineation methods according to the effects of several image characteristics, the variability of both metabolic tumor volume and SUV varied with radiotracer, image contrast, and image resolution. In that study, there was substantial variability ($\leq 94\%$) in the measured tumor volume when the image resolution or contrast was changed (24). The test-retest variability of the median metabolic volume according to the image characteristics ranged from 8.3% to 23% and from 7.4% to 29% for ^{18}F -FDG and ^{18}F -FLT, respectively. The difference in the test-retest variability of the metabolic tumor volume was larger than that of SUV (24). Another recent study reported that the absolute quantitative value obtained through the tumor delineation method depends on the variation in the tumor-to-background ratio (TBR), image resolution and image noise level, and to a lesser extent, on the number of iterations performed during image reconstruction (18).

The partial-volume effect (PVE) may affect MTV or TLG (27), but PVE correction may not be sufficient to improve the predictive or prognostic value of these parameters. In a study of 50 patients with esophageal cancer, PVE correction

had a significant quantitative impact on the absolute values of the investigated parameters. However, the clinical value of MTV and TLG in predicting the response and OS was not significantly different before and after correction (27).

Breathing motion can also affect the measurement of metabolic tumor volume, and the use of a respiratory gating system allows for a more accurate measurement of tumor volume based on PET images. Measurements of tumor volume in the gated mode have been reported to be reduced up to 34% compared with the non-gated mode. However, TLGs measured in gated and non-gated modes showed consistent results, which can be explained by the reduction in tumor volume being accompanied by an increase in the intensity of the ^{18}F -FDG signal per voxel (28).

Metabolic tumor volume can either be derived from images of the glucose metabolic rate (generated using Patlak analysis) or from SUV images (29). While SUV requires a static scan, images of the glucose metabolic rate can be generated from dynamic scans. Metabolic volumes derived from images of the glucose metabolic rate are generally smaller than those derived from SUV images (29). Metabolic volumes derived from SUV images rather than from the images of glucose metabolic rate tend to produce more extreme values, except when gradient-based methods are used. Median measured metabolic volumes derived from SUV images were larger than those derived from dynamic images (up to a 59% difference) when using a fixed percentage threshold method (29).

Considerations: Application to Studies

Although there has recently been a dramatic increase in the number of studies investigating the value of volume-based metabolic parameters, the extent to which volume-based PET parameters can be significantly influenced by factors such as the tumor delineation method, image resolution, contrast, noise, radiotracer, or reconstruction settings has not been definitively determined. However, it is clear that careful optimization of tumor delineation methods and image characteristics are important for the reproducible measurement of volume-based PET parameters, as this can be affected by the factors mentioned above. In particular, the tumor delineation method has the most significant quantitative impact on the absolute value of these PET parameters, and it is essential to use consistent imaging characteristics and tumor delineation methods in measuring volume-based PET parameters, particularly for longitudinal studies.

Clinical Implications

Prognosis Prediction

Metabolic tumor volume and TLG are potential prognostic indicators for various cancers. The baseline metabolic tumor burdens expressed by these parameters have been

shown to be closely associated with patient prognosis. Table 1 summarizes the literature regarding the prediction of the clinical course before treatment using MTV or TLG. It has been reported that as the volume-based parameters of a tumor become smaller and lower, the prognosis for lung cancer improves (25, 30, 31). Similar results

Table 1. Summary of Literature on Use of Volume-Based PET Parameters in Predicting Prognosis

Authors (Reference)	Modality	Subject No.	Tumor	Study Design	Used PET Parameters	Target Lesion	Significant Prognostic Predictor
Arslan N, et al. (30)	PET	25	Small cell lung cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Tumor sites with visibly increased FDG uptake	TLG
Oh JR, et al. (61)	PET/CT	106	Small cell lung cancer	Retrospective	SUV _{max} , MTV	All malignant lesions	MTV
Zhu D, et al. (62)	PET/CT	98	Small cell lung cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	All malignant lesions	MTV, TLG
Liao S, et al. (31)	PET/CT	169	Non-small cell lung cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Primary tumor, nodal metastases, distant metastases	MTV and TLG
Kim K, et al. (25)	PET/CT	91	Non-small cell lung cancer	Retrospective	SUV _{max} , MTV, TLG	Primary tumor	MTV
Chu KP, et al. (33)	PET/CT	51	Head-and-neck cancer	Retrospective	SUV _{max} , MTV, Velocity (change in MTV or SUV _{max} over time)	Primary tumor and nodal metastasis	MTV velocity
Choi K, et al. (36)	PET/CT	56	Head-and-neck cancer	Retrospective	SUV _{peak} , MTV	Primary tumor and nodal metastasis	MTV
La TH, et al. (34)	PET/CT	85	Head-and-neck cancer	Retrospective	SUV _{max} , MTV	Primary tumor and nodal metastasis	MTV
Chan SC, et al. (32)	PET	196	Nasopharyngeal carcinoma	Prospective	SUV _{max} , MTV, TLG	Primary tumor and nodal metastasis	TLG
Xie P, et al. (35)	PET/CT	41	Nasopharyngeal carcinoma	Retrospective	MTV, TLG	Not available	TLG
Moon SH, et al. (9)	PET/CT	69	Tonsil cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Primary tumor	TLG
Hatt M, et al. (27)	PET/CT	50	Esophageal cancer	Retrospective	SUV _{max} , SUV _{peak} , MTV, SUV _{mean} , TLG	Primary tumor	MTV and TLG
Hyun SH, et al. (17)	PET	151	Esophageal cancer	Retrospective	SUV _{max} , MTV	Primary tumor	MTV
Lee HY, et al. (44)	PET/CT	13	Malignant pleural mesothelioma	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Primary tumor	MTV and TLG
Chung HH, et al. (39)	PET/CT	55	Ovarian cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Tumor sites with visibly increased FDG uptake	MTV and TLG
Kim BS, et al. (40)	PET/CT	45	Cervical cancer	Retrospective	SUV _{max} , MTV	Primary tumor	MTV
Costelloe CM, et al. (42)	PET/CT	31	Osteosarcoma	Retrospective	SUV _{max} , TLG	Primary tumor	SUV _{max} and TLG
Yoo J, et al. (43)	PET/CT	44	Gallbladder cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Primary tumor	TLG
Summary		1376					

Note.— PET = positron emission tomography, SUV_{max} = maximum standardized uptake value, SUV_{mean} = mean SUV, SUV_{peak} = peak SUV, MTV = metabolic tumor volume, TLG = total lesion glycolysis, FDG = fluorodeoxyglucose

have been shown for head and neck cancers (9, 32-36), colorectal cancers (37, 38), esophageal cancers (23, 27), gynecological cancers (39, 40), and others (41-44). Figure 2 illustrates the survival curves according to PET parameters in tonsillar cancer (9). Both MTV and TLG discriminate between the two survival curves better than SUV_{max} indicating that these values may be a useful quantitative index for disease prognosis prior to treatment. Furthermore, the combination of volume-based PET parameters with clinical prognostic factors may significantly improve prognostic stratification in cancer patients. For example, in a study of advanced nasopharyngeal cancer patients, there was a stepwise decrease in local and distant control rates according to a scoring system formulated by combining PET parameters and traditional prognostic factors (32).

Therapeutic Response Evaluation

The parameters we have described can also be useful in assessing therapeutic response. Currently, the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1, which is primarily based on changes in the longest dimension of a tumor, is the standard method for assessing the treatment response in patients with solid tumors (45). However, change in the longest dimension is insufficient to accurately reflect change in tumor burden. In addition, these criteria do not reflect the functional and metabolic changes that may occur with targeted chemotherapy (45). In contrast to conventional chemotherapy, targeted therapies usually do not lead to rapid tumor cell death. Targeted therapies interfere with the tumor signaling pathways, thus inhibiting tumor cell proliferation. Therefore, the previous

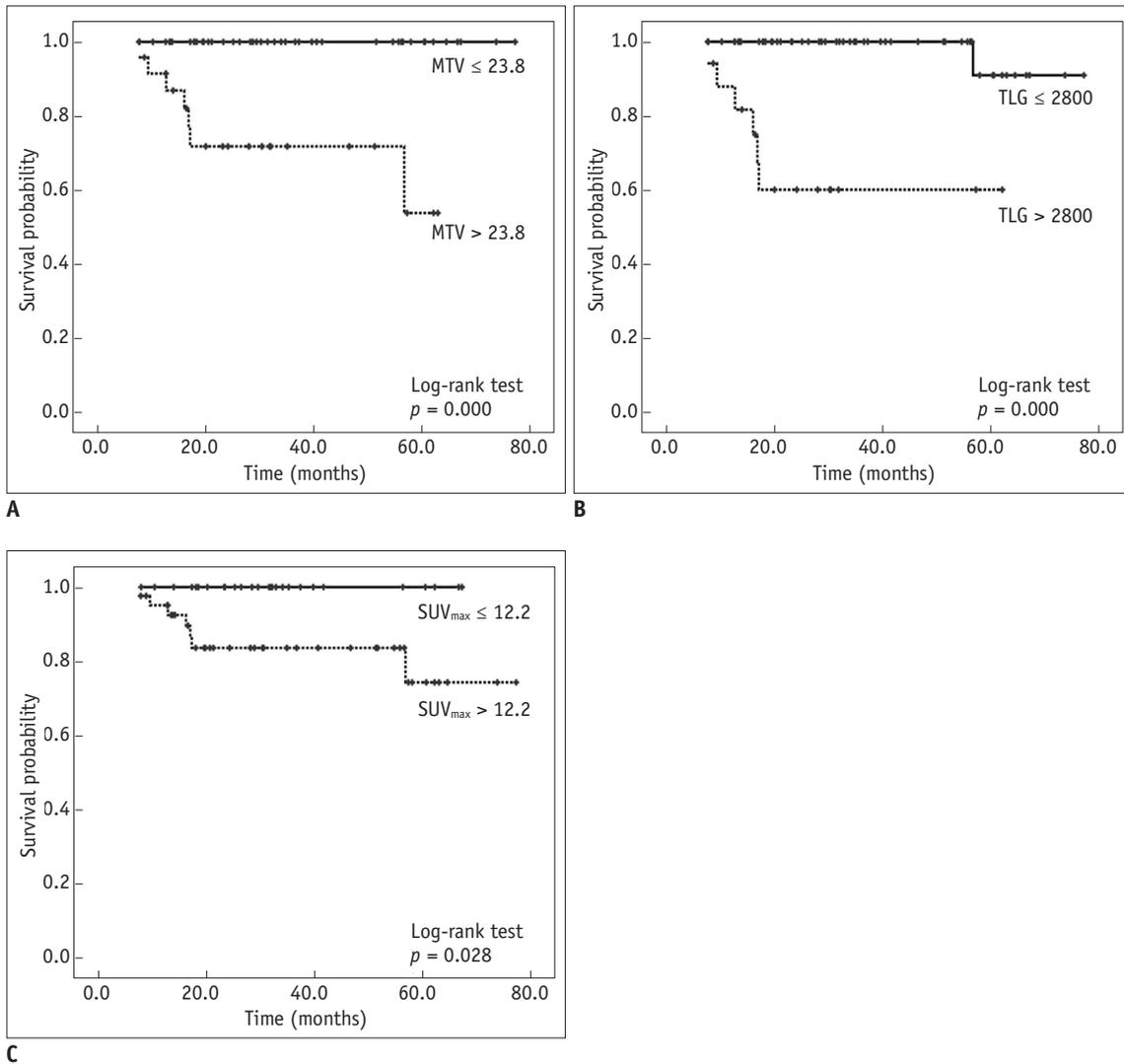


Fig. 2. Kaplan-Meier survival curves for overall survival using MTV (A), TLG (B), and SUV_{max} (C) in 69 patients with squamous cell carcinoma of tonsil. MTV = metabolic tumor volume, TLG = total lesion glycolysis, SUV_{max} = maximum standardized uptake value

morphological approach is not appropriate for assessing the early response to targeted therapies. Metabolic changes as measured by PET may supplement conventional methods in assessing treatment response, thus addressing some of their limitations. Table 2 summarizes the literature on evaluating therapy response using MTV or TLG. Changes in MTV and TLG between pre- and post-treatment scans may be a useful index in the prediction of therapeutic response for various cancers (46). One previous study investigated the relationship between chemotherapy and ¹⁸F-FDG uptake in a mouse model of lymphoma, and found that ¹⁸F-FDG uptake reflected the dose-response relationship of chemotherapy and that TLG was the best parameter for dose-related response assessment (47). These parameters have also been reported to be useful for assessing tumor down-staging and determining the percentage of residual tumor following neoadjuvant treatment, which could potentially assist in treatment planning for patients with rectal cancer (48). In a prospective study of osteosarcoma patients, MTV and TLG were significantly different after therapy between good and poor responders. These parameters had good sensitivity, specificity, positive predictive value, and negative predictive value for predicting histological responses to chemotherapy (49). In another study comparing response evaluation using volume-based PET parameters to a clinical response evaluation based on RECIST and WHO clinical criteria in patients with esophageal cancer, a decrease in MTV and TLG between baseline and post-treatment scans

was the better predictor of histopathologic response and survival than a decrease in clinical response (50). However, while there have been many positive results in previous studies supporting the usefulness of MTV and TLG (48-51), it is difficult to prove that ¹⁸F-FDG PET is superior to conventional imaging techniques in assessing therapy response. For example, a recently published study reported that the correlations of volume-based PET parameters and OS are inferior to those of CT-derived volume parameters in patients with malignant pleural mesothelioma receiving continual pemetrexed- and platin-based treatment (41).

One major shortcoming of using PET parameters in assessing the response to therapy is that ¹⁸F-FDG PET may not differentiate radiation-related inflammation from the residual tumor in patients who received either radiotherapy or chemoradiotherapy (51). A recent prospective study reported that metabolic parameters including TLG were not associated with the prognosis of rectal cancer patients who had received neoadjuvant chemoradiotherapy (52). From this, it can be extrapolated that radiation-related inflammation may be a major obstacle limiting the use of PET parameters in the assessment of radiotherapy response.

Although many previous studies have investigated the usefulness of volume-based PET parameters in predicting prognosis and evaluating treatment response and have shown that MTV and TLG can be useful indicators in a variety of tumors and in various clinical settings, most of these studies are retrospective and use a relatively small

Table 2. Summary of Literature on Use of Volume-Based PET Parameters in Evaluating Treatment Response

Authors (Reference)	Modality	Subject No.	Tumor	Study Design	Used PET Parameters	Target Lesion	Significant Prognostic Predictor
Ruby JA, et al. (52)	PET & PET/CT	127	Rectal cancer	Prospective	SUV _{max} , SUV _{mean} , TLG	Primary tumor	None
Schaefer NG, et al. (41)	PET/CT	41	Malignant pleural mesothelioma	Prospective	Modified RECIST, SUV _{max} , MTV, TLG	According to EORTC criteria	ModRECIST > volume-based PET parameters
Arslan N, et al. (51)	PET	24	Esophageal cancer	Retrospective	SUV _{peak} , SUV _{mean} , TLG, MTV	Primary tumor	MTV
Roedl JB, et al. (50)	PET/CT	51	Esophageal cancer	Retrospective	SUV _{max} , SUV _{mean} , MTV, TLG	Primary tumor	MTV and TLG
Im HJ, et al. (49)	PET/CT	20	Osteosarcoma	Retrospective	SUV _{max} , MTV, TLG	Primary tumor	MTV and TLG
Melton GB, et al. (48)	PET/CT	21	Rectal cancer	Retrospective	SUV _{max} , MTV, TLG, Visual response score	Primary tumor	SUV _{max} and MTV
Summary		284					

Note.— PET = positron emission tomography, SUV_{max} = maximum standardized uptake value, SUV_{peak} = peak SUV, TLG = total lesion glycolysis, MTV = metabolic tumor volume, RECIST = Response Evaluation Criteria in Solid Tumor

number of subjects. Therefore, further well-designed large-scale prospective studies are needed in order to confirm the clinical value of these parameters.

Radiotherapy Planning

Radiotherapy planning is another context in which volume-based PET parameters may be useful (14). When comparing PET-based tumor volume to CT-based tumor volume in intensity-modulated radiotherapy for head-and-neck cancer, one study found that the PET-based tumor volume was smaller, the same size, or larger than the CT-based tumor volume in 75%, 8%, and 18% cases, respectively. In the same study, 75% of study subjects received at least 95% of the prescribed dose obtained using CT on the PET-based tumor volume (14). In another recent study (53) in which ^{18}F -FDG PET/CT scans were performed during radiation therapy after every seventh fraction, the volume of each lesion was measured by an experienced nuclear physician using visual delineation with a 40% SUV_{max} fixed threshold and a semi-automatic adaptive threshold method. An average decrease in SUV_{max} of 50% was observed around 40-45 Gy (i.e., during week 5 of radiation therapy [RT]). The three delineation methods yielded consistent volume measurements before RT and during the first week of radiation therapy; however, as the course of radiation therapy continued, manual delineation appeared to be more reliable (53).

Other Issues

Comparison between MTV and TLG

Standard values for comparing MTV and TLG have not been established. In particular, the question regarding which parameter is superior for predicting outcomes and assessing treatment response still remains (9, 23). There is a great deal of evidence to support the hypothesis that TLG, a combination of SUV and MTV, is the ideal metabolic parameter for tumor burden as it simultaneously represents the degree of ^{18}F -FDG uptake and the size of the metabolically-active tumor mass (9, 30, 32, 35). It has also been reported that the optimal PET-based estimate for the total tumor burden is the sum of TLG over all lesions (54). In addition, in previous studies, TLG was identified as a significant independent predictor of clinical course, associated with OS and RFS, while MTV was not a significant prognostic factor (9, 30, 32, 35). However, a conflicting study reported that only a change in MTV identified

complete responders after neoadjuvant CCRT in patients with esophageal cancer (51). The comparison between TLG and MTV for prognostic prediction and response evaluation remains controversial.

In determining whether MTV and TLG are significant and independent prognostic factors through multiple regression model analysis, we note that multicollinearity, the statistical phenomenon in which variables are strongly correlated with each other, is a substantial barrier to easy interpretation. When two variables are strongly correlated, like MTV and TLG, it is difficult to develop reliable calculations regarding the individual variables (55). One possible alternative to comparing the prognostic value of these parameters is to analyze MTV and TLG in a separate MTV or TLG model, then assess the discriminative performance of each model.

Correlation with Other Imaging and Biological Parameters

Metabolic tumor volume and TLG are generally highly correlated with tumor volume as measured by computed tomography (CT). It has been reported that there is a high correlation between MTV and CT-based volume for lesions greater than 5 cm^3 in size (54). It has also been reported that volume-based PET parameters are positively correlated with T-stage, specifically in the setting of primary nasopharyngeal carcinoma (56). In addition, recently reported data on the relationship between viral load and PET parameters demonstrated that of the tested parameters, total TLG had the highest correlation with Epstein-Barr virus deoxyribonucleic acid, a known prognostic factor in patients with nasopharyngeal carcinoma (57).

Correlations between diffusion-weighted magnetic resonance imaging parameters and volume-based PET parameters have been reported (58). There is a significant positive correlation between the total diffusivity index and TLG (58). This significant correlation between parameters suggests an association between tumor cellularity and metabolic activity (58). Another recent study also reported a significant positive correlation between choline concentration relative to water (Cho/W) as measured by proton magnetic resonance spectroscopy (H-MRS) and TLG (59). Elevated levels of Cho-containing compounds in tumors are related to membrane synthesis (60), and Cho/W is thought to be an index that may reflect cell proliferation (60). The results of that study indicate that volume-based PET parameters most likely indirectly reflect the proliferation of tumor cells.

Further Directions

As discussed above, MTV and TLG are both potential parameters for evaluating patient prognosis and assessing therapeutic response. However, the value of these parameters has not yet been established, and the evidence from previous retrospective studies using different methods for measurement is insufficient for validating these parameters for clinical practice. Therefore, large-scale prospective studies analyzing the effects of methodological factors important in measuring these parameters are needed in order to extend their use. Several important aspects should be considered in planning such studies. First, a tumor delineation method that can provide reliable and reproducible results should be selected, and determination of an optimal threshold may be the most crucial step in the process. Additionally, ease of measurement is also an important factor for methods that will see routine clinical use. Second, the total MTV or TLG of all tumor lesions, including primary tumors and metastasis, most likely reflects tumor burden more precisely than the MTV or TLG of primary tumor lesions. However, in most reported studies, MTV and TLG were only measured in prominent tumor sites with significantly increased FDG uptake. Only a few studies have demonstrated that the MTV of all malignant lesions is an independent predictor for progression and death (61, 62). The target tumor lesions for the measurement of volume-based PET parameters should be extended to the entire tumor burden. Third, the clinical impact of these parameters should be evaluated in further studies. In particular, well-designed studies are needed to establish whether volume-based PET parameters should affect the selection of the treatment plan. We expect that the number of studies of the use of volume-based PET parameters in clinical oncology will continue to increase.

CONCLUSION

The volume-based PET parameters MTV and TLG are useful indices of tumor burden. Although the role of these parameters has not yet been established, they are potentially useful parameters for the prognostication and evaluation of treatment response in cancer patients. In using volume-based PET parameters, careful optimization of tumor delineation methods and image characteristics is crucial, as these parameters can be significantly affected by the tumor delineation method, image resolution, contrast,

noise, the radiotracer used, and the reconstruction settings. In particular, the tumor delineation method used is the most important factor affecting the measurement of these parameters. Many previous studies have demonstrated that these parameters are closely associated with patient prognosis and are related to other established prognostic factors. However, further large-scale prospective studies are needed in order to confirm the value of these parameters.

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