Original Study

Semiquantitative assessment of FDG uptake in primary tumours on dynamic PET/CT for lymph node metastasis evaluation in patients with lung cancer: a prospective study

Running head: Semiquantitative assessment of FDG uptake in primary tumours

Authors: Moriaki Yamanaka[1], Takayoshi Shinya[1], Yoichi Otomi[1], Michiko Kubo[1], Yuta Arai[1], Hiroaki Toba[2], Yoshimi Bando[3], Hideki Otsuka[4], Masafumi Harada[1]

Affiliations:

[1]Department of Radiology, Tokushima University Hospital. 2-50-1, Kuramoto-cho, Tokushima City, Tokushima, 770-8503, Japan

[2]Department of Thoracic and Endocrine Surgery and Oncology, Institute of Health Biosciences, Tokushima University Graduate School. 2□50□1, Kuramoto□cho, Tokushima City, Tokushima, 770-8503, Japan

[3]Division of Pathology, Tokushima University Hospital. 2-50-1, Kuramoto-cho, Tokushima City, Tokushima, 770-8503, Japan

[4]Department of Medical Imaging/Nuclear Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, 2□50□1, Kuramoto□cho, Tokushima City, Tokushima 770□8503, Japan

Corresponding author:

Moriaki Yamanaka, Department of Radiology, Tokushima University Hospital, 2-50-1 Kuramoto-Cho, Tokushima 770-8503, Japan

E-mail: yamanaka_tokudai@yahoo.co.jp, Tel: +81-88-633-7173, Fax: +81-88-633-7174

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Abstract

Objective: To semiquantitatively estimate fluorine-18-fluorodeoxyglucose (FDG) uptake in primary lung cancer cells using dynamic and dual-time-point (DTP) positron emission tomography/computed tomography (PET/CT) to obtain a diagnostic index for lymph node (LN) metastasis.

Methods: Forty-five patients with lung cancer underwent dynamic and DTP PET/CT examinations. All primary lesions and LN metastases were evaluated pathologically. At each time phase, we assessed the maximum standardised uptake value (SUVmax), metabolic tumour volume (MTV), and total lesion glycolysis (TLG) of the primary tumours. We investigated the relationship between semiquantitative index and the presence of LN metastasis for each case and for all cases satisfying indications for segmentectomy. In cases with LN metastasis, we assessed the SUVmax of pathologically proven metastatic LNs and non-metastatic LNs in each dynamic phase for evaluating temporal change.

Results: Among 45 patients, 15 had 17 LN metastasis. SUVmax, MTV, and TLG of primary tumours at each time phase were significantly associated with

LN metastasis ($p < 0.05$). In receiver operating characteristic analysis, dynamic second and third phases showed high diagnostic ability for LN metastasis. The temporal change in SUVmax in the dynamic phase between primary tumours and metastatic LNs were significantly different ($p = 0.065$). The temporal change in SUVmax was significantly lower in non-metastatic LNs than in primary tumours and metastatic LNs ($p < 0.0001$).

Conclusions: Semiquantitative assessment of FDG uptake in dynamic second and third phases and the assessment of temporal changes in SUVmax on dynamic PET/CT scans were important predictors in diagnosing LN metastasis.

Keywords: Fluorodeoxyglucose F18, positron emission tomography computed tomography, lung cancer, lymphatic metastasis

Introduction

In lung cancer, the status of hilar and mediastinal lymph nodes (LNs) is one of the most significant factors that determine tumour staging and the most appropriate therapy [1,2]. ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is one of the most widely used molecular imaging techniques for detecting and staging tumours, as elevated glucose metabolism is indicative of malignancies [3]. Generally, FDG uptake in metastatic LNs is significantly higher than that in non-metastatic LNs in patients with lung cancer [4,5]. Recently, dual-time-point (DTP) PET/computed tomography (CT) scans are useful for evaluating LN metastasis in patients with lung cancer [6,7]. However, benign LNs could also show high FDG uptake due to hypermetabolism especially in LNs associated with pulmonary infectious or granulomatous disease and could cause false-positive results in patients with lung cancer even in DTP PET/CT study [4-8]. Moreover, previous reports suggested some limitations of single-time-point (STP) and DTP PET/CT in LN metastasis detection in lung cancer [4,6]. Al-Sarraf et al. reported that in lung cancer patients who are clinically staged as N2/N3 negative in the mediastinum

by integrated PET/CT, 16% would have occult N2 disease following resection [9].

From a different perspective, several studies identified that quantitative evaluation by maximum standardised uptake value (SUVmax) of a primary tumour is useful in detecting the presence or absence of LN metastasis [10,11]. In contrast, Akthar et al. reported that a high SUVmax of a primary tumour on STP PET/CT is not associated with occult nodal metastasis in lung cancer [12].

Dynamic PET/CT is expected to be more helpful in understanding the early pathophysiological mechanisms after FDG administration. Previous studies reported the usefulness of dynamic PET/CT in tumour diagnosis, grading, and prognosis estimation [13,14,15]. Moreover, a recent study demonstrated that negative FDG uptake in LNs in dynamic PET/CT scans could be an important predictor of non-metastatic LNs [16]. However, the diagnostic abilities of dynamic and DTP PET/CT for LN metastasis, which involves calculation of SUVmax of the primary tumour, in patients with lung cancer have not been clarified.

In lung cancer surgery, lobectomy is the gold standard [17]. However, the indication of segmentectomy is expanding, and several studies have

reported non-inferiority of segmentectomy to lobectomy in early stage lung cancer. Nevertheless, the absence of LN metastasis is important in indicating segmentectomy [18,19,20]. However, some reports demonstrated that LN staging is often upstaged after surgery in early stage lung cancer [21,22] and showed that obtaining an accurate assessment of the presence or absence of LN metastasis before segmentectomy is difficult. Khullar et al. analysed data from the National Cancer Database; they found that no LN sampling was performed in 21% of segmentectomies and reported that insufficient and inadequate lymphadenectomy resulted in worse long-term outcomes [23]. A more accurate assessment of the presence or absence of LN metastasis may lead to a more accurate decision on the need for segmentectomy, thereby improving patient outcomes. We hypothesised that semiquantitative assessment of FDG uptake in primary lung tumour by dynamic PET/CT scans may help investigate tumour activity and obtain a useful index that determines the presence or absence of LN metastasis.

In this prospective study, we aim to evaluate the FDG uptake in the primary lung tumour semiquantitatively using dynamic and DTP PET/CT scans. We investigated the diagnostic value of semiquantitative parameters for the

presence or absence of LN metastasis as well as the diagnostic significance of dynamic and DTP PET/CT scans in the indication of segmentectomy. Moreover, we assessed the temporal change in FDG uptake in the primary tumour and LNs during the dynamic phase and analysed the differences among primary tumour, metastatic LN, and non-metastatic LN.

Methods

Patients

We prospectively studied patients with suspected primary lung cancer. The inclusion criteria were as follows: patients who had been diagnosed with lung cancer by pathological analyses; those who were evaluated for the presence or absence of LN metastasis by pathological analyses; those without malignancy, except lung cancer; those who received no therapy for lung cancer before PET/CT examination; and those without history of heart and renal disease. Between February 2016 and February 2017, 45 patients who underwent dynamic PET/CT and consecutively DTP PET/CT were enrolled in this prospective study. We used the TNM 8th edition staging system for pathologic

staging, which was defined by the International Association for the Study of Lung Cancer (IASLC) [24]. Among the 45 lesions analysed in the present study, overall, 30 of our cases overlapped with 34 of those mentioned in a previous paper, i.e. 34 patients were assessed for FDG uptake in their LNs, and optimal scan timing for nodal staging was determined [16].

Moreover, we evaluated the FDG uptake in the primary tumours and investigated the diagnostic ability of the evaluation for LN metastasis. This prospective study was approved by our institutional review board and ethics committee. All patients signed a written informed consent form prior to participating. All procedures involving human participants were conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Indication for segmentectomy

We considered the following items as indications for segmentectomy: single tumour; suspected non-small cell lung cancer (NSCLC); surgical margin of approximately >2 cm; maximum tumour diameter of ≤2 cm; 2 cm < tumour diameter ≤3 cm; and a consolidation/tumour ratio (CTR) ≤0.5 (CTR

measurement is according to the JCOG0201 definition [25]). These items were determined according to the protocols of two on-going clinical trials (i.e. JCOG0802/WJOG4607L, JCOG1211) [26,27]. We also investigated the diagnostic value of the parameters for the presence or absence of LN metastasis in 19 patients who satisfied the aforementioned criteria.

FDG PET/CT procedures

Before the intravenous administration of FDG (3.0 MBq/kg), all patients fasted for >6 h and had a blood glucose level of <160 mg/dL. PET/CT imaging was performed using a single PET/CT system (Discovery PET/CT 710; GE Healthcare, Chicago, IL, USA), which has list-mode data acquisition and enables four-dimensional data acquisition (i.e. dynamic studies). Moreover, all patients underwent dynamic and DTP FDG PET/CT examinations. In the first acquisition, a low-dose CT scan was acquired for PET attenuation correction, anatomical information, and image fusion. In the second acquisition, dynamic PET/CT imaging was conducted as list-mode continuous scanning, with every measured value stored as raw data with the exact time stamp beginning five min after the FDG bolus and continuing for 30 min.

Dynamic series was acquired with the field of view over the lung tumour of interest and the hilar and mediastinal LNs (limited to the single bed position with coverage in the patient's longitudinal direction of 15.042 cm). Patients were asked to lie motionless for the duration of the dynamic study. We subsequently reconstructed the data as three frames at 600-s intervals. The list-mode files were reconstructed on the PET/CT scanner. The frames were reconstructed using three-dimensional attenuation-weighted ordered-subset expectation maximisation with two iterations and 16 subsets (VUE Point FX; GE Healthcare) with a 4-mm post-reconstruction Gaussian filter, attenuation image segmentation, and a 192×192-pixel matrix. Subsequently, the patients were transferred to a waiting room and remained there until the next scanning procedure, which was conducted 60 min after tracer administration.

The DTP PET/CT scanning region encompassed the body from the vertex of the skull to the proximal thigh on the 1-h early scan and the whole thorax on the 2-h delayed scan. Before performing the DTP PET/CT scan, a second low-dose CT scan was immediately obtained for attenuation correction over the shooting range. Early and delayed PET scans were acquired in eight-bed positions for 120 s and four-bed positions for 180 s, respectively. Each

scan used the identical image reconstruction method of the dynamic FDG PET scan. Dynamic and DTP PET/CT procedures used at our institution were similar to the procedures described in the literature [16].

PET/CT image analysis

All PET/CT images were reviewed by two board-certified nuclear medicine physicians with 20 and 18 years of experience. Both were blinded to all clinical, pathological, and other imaging findings relevant in the evaluation of FDG uptake by the primary tumour. If their results differed, they discussed them until a consensus was reached. We carefully placed the volume of interest (VOI) on the lung mass and LNs on the viewer (AW server 2.0, GE Healthcare). For the semiquantitative analysis of FDG uptake, we adopted the SUV. The SUVs were calculated as follows: SUV = radioactivity concentration (Bq/kg) × [body mass (kg)/injected radioactivity (Bq)]. To minimise partial-volume effects, the SUVmax within VOIs was used. SUVmax was defined as the voxel with the highest count within the VOI. Volumetric parameters, such as metabolic tumour volume (MTV) and total lesion glycolysis (TLG), were also assessed. For MTV and TLG calculation, a fixed SUV value of 2.5 was used to define the VOI boundaries

[28,29]. MTV was calculated automatically by summing the total volumes of voxels in the VOI. TLG was calculated by multiplying MTV by the average SUV value, i.e. 2.5. The SUVmax, MTV, and TLG of the lung mass were measured for each dynamic phase (i.e. first dynamic phase, 5–15 min; second dynamic phase, 15–25 min; and third dynamic phase, 25–35 min), the 1-h early phase, and the 2-h delayed phase.

Secondarily, we referred to pathology reports when a pathologically proven LN metastasis was identified, we carefully placed the VOI on the LN to exclude FDG accumulation in the normal tissue and large vessels on PET/CT images. We assessed the SUVmax of pathologically proven metastatic LNs and non-metastatic LNs in each dynamic phase. For the analyses of LNs, pathology reports and previously published LN maps were used as references [30,31]. The maximum diameters of each tumour lesion and LN were measured on axial low-dose CT images.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. For non-normally distributed data, Mann–Whitney U test was performed to analyse the differences in semiquantitative parameters in each time phase and tumour size according to the presence of metastatic LN in all participants and in patients who satisfied the indications for segmentectomy based on CT scans. If the Mann–Whitney U test revealed a significant difference in each index, an additional receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performances. Discrimination was assessed using the area under the ROC curve (AUC). Significant differences between two AUCs, as determined from the ROC curve, were assessed with DeLong's test. In the case with LN metastasis, repeated-measures analysis of variance (ANOVA) was performed to examine the temporal change in SUVmax in the dynamic phase.

All statistical analyses were conducted using EZR version 1.40 (Saitama Medical Centre, Jichi Medical University, Omiya, Saitama, Japan; available at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which is a graphical user interface for R [32]. Statistical significance was set at p

< 0.05.

Results

Patient characteristics

Pathological diagnoses of primary lung cancers were made based on surgery (n = 36), bronchofibrescopy (n = 7), and CT-guided biopsy (n = 2). Pathological diagnoses of the presence or absence of LN metastasis was confirmed by surgery (n = 36: 28 lobectomy, eight segmentectomy) and LN biopsy (n = 9). Fifteen patients had 17 LN metastases (Table 1).

Semiquantitative analysis of PET/CT

. The SUVmax, MTV, and TLG of the primary tumour are significantly different between the group with and that without LN metastasis in each time phase. Tumour size was significantly different between the two groups (Table 2).

ROC curve analysis for lymph node metastasis prediction

. The cut-off values yielded moderate sensitivity and moderate specificity.

Compared with the AUCs of the ROC analysis in other time phases, the AUCs of SUV, MTV, and TLG in the second dynamic phase had the highest value (AUC for SUVmax = 0.703, MTV = 0.767, and TLG = 0.763). However, DeLong's test did not reveal any significant differences between the AUCs for all parameters ($p > 0.05$ for all) (Table 3).

Semiquantitative analysis of PET/CT for the patients satisfying indications for segmentectomy

Concerning the SUVmax, MTV, and TLG of the primary tumour for patients who satisfied the indications for segmentectomy based on CT scans; five had LN metastasis out of the 19 patients. Histopathological examinations also revealed 14 adenocarcinomas (three cases with LN metastasis), three squamous cell carcinomas (two cases with LN metastasis), one adenosquamous cell carcinoma (without LN metastasis), and one small cell carcinoma (without LN metastasis). The SUVmax, MTV, and TLG of the primary tumour were significantly different between the group with LN metastasis and that without LN metastasis in each time phase. Tumour size showed no significant difference between the two groups. (Table 4)

ROC curve analysis for the patients satisfying the indications for segmentectomy

ROC curves were obtained to determine the appropriate cut-off values for each parameter for differentiating lung cancers with LN metastasis and without LN metastasis for the patients satisfying the indications for segmentectomy on CT scans (Figure 1). The cut-off values yielded high sensitivity and high specificity. Compared with the AUCs of the ROC analysis in other time phases, the AUCs of SUV, MTV, and TLG in the third dynamic phase had the highest value (AUC for SUVmax = 0.943, MTV = 0.929, and TLG = 0.957). However, DeLong's test did not reveal any significant differences between the AUCs for all parameters ($p > 0.05$ for all) (Table 5).

Temporal changes in SUVmax of the primary tumour, metastatic LN, and non-metastatic LN in the dynamic phases

Of the 15 cases with LN metastasis, five were excluded because the metastatic LNs were clustered with the primary lesion (n = 2), the LN number

corresponding to LN map could not be specified (n = 2), and biopsy was performed in the cervical LN and dynamic PET/CT is out of range (n = 1).

The enrolled 10 cases had 12 metastatic LNs and 15 non-metastatic LNs. The size of metastatic LN was 18.3±12.8 mm (mean±SD, range; 5-51 mm) and the size of non-metastatic LN was 7.3±2.6 mm (mean±SD, range; 4-12 mm). We identified all 27 LNs using PET/CT and assessed the SUVmax in each dynamic phase by referring to LN maps [30,31].

The temporal changes in SUVmax of the primary tumour, metastatic LN, and non-metastatic LN. No significant difference in SUVmax between the primary tumour and metastatic LN was noted ($p = 0.101$). In the dynamic phase, the SUVmax of non-metastatic LN is significantly lower than that of the primary tumour and metastatic LN ($p < 0.0001$).

In the repeated-measures ANOVA, no significant difference in the temporal change in SUVmax in the dynamic phase between the primary tumour and metastatic LN was found ($p = 0.065$). The temporal change in SUVmax of non-metastatic LN is significantly lower than that of the primary tumour and metastatic LN ($p < 0.0001$) (Figure 2).

Discussion

In this study, we investigated the diagnostic value of semiquantitative analyses for FDG uptake in primary lung cancer with dynamic PET/CT scans and DTP PET/CT scans for detecting LN metastasis. SUVmax, MTV, and TLG of the primary tumour in the dynamic scans and DTP PET/CT scans were statistically associated with the presence or absence of LN metastasis. In the ROC analysis, SUVmax, MTV, and TLG in the second dynamic phase show a high diagnostic ability for LN metastasis. In third dynamic phase, the same parameters had a high diagnostic ability for the presence or absence of LN metastasis specifically in patients satisfying the indications for segmentectomy based on CT scans. Moreover, the temporal change in SUVmax of the primary tumour is parallel to the SUVmax of metastatic LN and increases more rapidly than the SUVmax of non-metastatic LN.

In this study, FDG uptake is continuously higher in patients with LN metastasis than in those without LN metastasis at all time phases in both dynamic and DTP scans. In addition, the parameters of dynamic scans tended to be better predictors than the parameters of DTP PET/CT scans based on the

AUC of the ROC analysis for the accurate diagnosis of the presence or absence of LN metastasis; however, DeLong's test did not reveal any significant difference between all parameters. Previous reports demonstrated that the primary lung cancer lesions with LN metastasis have a higher activity compared with those without metastasis and that the SUVmax of the primary tumour in STP PET/CT scans is useful for the diagnosis of the presence or absence of LN metastasis in lung cancer [33,34,35]. FDG is transported into cells via glucose transporters, with glucose transporter 1 (GLUT1) as the most common mediator for glucose uptake [36]. Zhang et al. reported that the primary tumour with LN metastasis presents higher levels of GLUT1 expression than that without LN metastasis. Moreover, another report also revealed that high expression of GLUT1 is also correlated with advanced tumour stages in patients with lung cancer [37]. High GLUT1 overexpression and increased FDG uptake in primary tumours indicated higher tumour activity and aggressiveness of the tumour. These results indicated that FDG uptake in a primary lesion could be a potential parameter for LN metastasis and dynamic PET/CT scans may help improve the diagnostic capacity of STP and DTP PET/CT scans.

In addition, we also investigated the diagnostic value of SUVmax, MTV,

and TLG for the presence or absence of LN metastasis in patients satisfying the indications for segmentectomy based on CT scans, as described previously. SUVmax, MTV, and TLG of the primary tumour in the dynamic phases and DTP scans were statistically associated with the presence or absence of LN metastasis. In the ROC analysis, the SUVmax, MTV, and TLG in the third dynamic phase showed the highest diagnostic ability. An accurate evaluation of the presence or absence of LN metastasis is crucial in the decision to perform segmentectomy. Nevertheless, Detterbeck et al. reported that the false-negative rate is 10% for the presence of LN metastasis with preoperative CT imaging in patients with peripheral tumours up to 3 cm [38]. FDG PET/CT scans could estimate intratumoural lymphatic vessel invasion (ILVI) in clinical stage 1A NSCLC nodules [39]. ILVI is significantly associated with LN metastasis in patients with clinical stage 1 NSCLC [40]. Moreover, Higashi et al. reported that tumours with a low FDG uptake have a low incidence of ILVI and that small lesions (<3 cm) with a low FDG uptake have a low incidence of LN metastasis [41]. PET/CT is a useful tool for diagnosing LN metastasis in early stage lung cancer. However, Ghaly et al. revealed that pathological upstaging due to nodal metastasis occurs in 9.6% in the those with clinical stage N0 based on STP

PET/CT scans [42]. The results of our study revealed that dynamic scans, especially the third dynamic phase, could be an important predictor of the indication for segmentectomy in addition to CT imaging.

Furthermore, we investigated the temporal change in SUVmax of the primary tumour, metastatic LN, and non-metastatic LN. The SUVmax of the primary tumour and that of metastatic LN showed no significant difference and changed in parallel over time. The SUVmax of the primary tumour and metastatic LN were significantly higher and increased more rapidly over time than the SUVmax of non-metastatic LN. Our study is the first to compare the temporal changes in SUVmax of the primary tumour, metastatic LN, and non-metastatic LN in the dynamic phase and to analyse statistically their relationship. The results also suggested that the primary tumour and metastatic LN have a similar change in accumulation in the dynamic phase and a different change in accumulation from that in non-metastatic LN. The evaluation of the temporal change in SUVmax of primary tumours and LNs in the dynamic phase could be a potentially new tool for diagnosing LN metastasis.

This study has some limitations. Our prospective study included a relatively small number of patients without detailed pathological information,

such as the presence or absence of invasive lymphatic vessels and immunohistochemistry findings including the expression of glucose transporters in the tumour. We also did not analyse the kinetic modelling of FDG PET. Thus, future larger multicentre prospective studies with kinetic analysis and more detailed pathological and immunohistochemistry findings are necessary to identify the most valuable parameter and determine the timing for LN metastasis evaluation with semiquantitative analysis of the primary tumour. Despite these limitations, to our knowledge, our study is the first to reveal that assessment of FDG uptake in primary lung cancer on dynamic PET/CT scans is useful to accurately determine the presence or absence of LN metastasis. Moreover, this study showed that dynamic scanning could be a potential predictor for segmentectomy indications, specifically in patients who satisfied the indications for segmentectomy based on CT scans. In addition, we also revealed that assessment of the temporal change in SUVmax of primary tumours in the dynamic phase could help estimate the activity of metastatic LNs and may in turn lead to a more accurate diagnosis of LN metastasis.

Conclusion

Semiquantitative assessment of FDG uptake on dynamic PET/CT, especially in the dynamic second phase as well as in the 1-h early and 2-h delayed phases, might be a useful method to assess the presence or absence of LN metastasis in patients with lung cancer. In addition, SUVmax, MTV, and TLG in the third dynamic phase as well as the 1-h early and 2-h delayed phases show excellent diagnostic ability for LN metastasis in patients satisfying the indications for segmentectomy. Dynamic and DTP PET/CT procedures might be useful diagnostic tools for the indication of segmentectomy. Moreover, the temporal change in SUVmax of the primary tumour in the dynamic phase could be parallel to the change in SUVmax of metastatic LNs. The assessment of temporal change in SUVmax of primary tumour in the dynamic phase might be an essential predictor of metastatic LNs.

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References

1. Scott WJ, Gobar LS, Terry JD, Dewan NS, Sunderland JJ. Mediastinal lymph node staging of non-small-cell lung cancer: a prospective comparison of computed tomography and positron emission tomography. J Thorac Cardiovasc Surg. 1996;111:642–8.

2. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. Radiology. 2004;231:305–32.

3. Strauss LG. Fluorine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. Eur J Nucl Med. 1996; 23:1409-15.

4. Zhao L, He ZY, Zhong XN, Cui ML. (18)FDG-PET/CT for detection of mediastinal nodal metastasis in non-small cell lung cancer: a meta-analysis. Surg Oncol. 2012;21:230–6.

5. Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu

H, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med. 2003;139:879–92.

6. Suga K, Kawakami Y, Hiyama A, Sugi K, Okabe K, Matsumoto T, et al. Differential diagnosis between (18)F-FDG-avid metastatic lymph nodes in non-small cell lung cancer and benign nodes on dual-time point PET/CT scan. Ann Nucl Med. 2009; 23:523-31

7. Shinya T, Rai K, Okumura Y, Fujiwara K, Matsuo K, Yonei T, et al. Dual-time-point F-18 FDG PET/CT for evaluation of intrathoracic lymph nodes in patients with non-small cell lung cancer. Clin Nucl Med. 2009; 34:216-21.

8. Al-Sarraf N, Gately K, Lucey J, Wilson L, McGovern E, Young V. Lymph node staging by means of positron emission tomography is less accurate in non-small cell lung cancer patients with enlarged lymph nodes: analysis of 1145 lymph nodes. Lung Cancer. 2008; 60:62–8.

9. Miyasaka Y, Suzuki K, Takamochi K, Matsunaga T, Oh S. The maximum standardized uptake value of fluorodeoxyglucose positron emission tomography of the primary tumour is a good predictor of pathological nodal involvement in clinical N0 non-small-cell lung cancer. Eur J Cardiothorac Surg 2013; 44:83-7.

10. Nakamura H, Saji H, Marushima H, Kimura H, Tagaya R, Kurimoto N, et al. Standardized uptake values in the primary lesions of non-small-cell lung cancer in FDG-PET/CT can predict regional lymph node metastases. Ann Surg Oncol 2015; 22:1388-93.

11. Al-Sarraf N, Aziz R, Gately K, Lucey J, Wilson L, McGovern E, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. Eur J Cardiothorac Surg 2008; 33:104-9.

12. Akthar AS, Ferguson MK, Koshy M, Vigneswaran WT, Malik R. Limitations of PET/CT in the detection of occult N1 metastasis in clinical stage I(T1-2aN0)

non-small cell lung cancer for staging prior to stereotactic body radiotherapy. Technol Cancer Res Treat 2017; 16:15-21.

13. Okazumi S, Dimitrakopoulou-Strauss A, Schwarzbach MH, Strauss LG. Quantitative, dynamic F-FDG-PET for the evaluation of soft tissue sarcomas: relation to differential diagnosis, tumor grading and prediction of prognosis. Hell J Nucl Med. 2009;12:223–8.

14. Belakhlef S, Church C, Jani C, Lakhanpl S. Early dynamic PET/CT and 18F-FDG blood flow imaging in bladder cancer detection: novel approach. Clin Nucl Med. 2012;37:366–8.

15. Nakajima R, Abe K, Kondo T, Tanabe K, Sakai S. Clinical role of early dynamic FDG-PET/CT for the evaluation of renal cell carcinoma. Eur Radiol. 2016;26:1852–62.

16. Shinya T, Otomi Y, Kubo M, Kinoshita M, Takechi K, Uyama N, et al. Preliminary clinical assessment of dynamic 18F-fluorodeoxyglucose

positron emission tomography/computed tomography for evaluating lymph node metastasis in patients with lung cancer: a prospective study. Ann Nucl Med. 2019; 33:414–23.

17. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg.1995;60:615-23.

18. Altorki NK, Yip R, Hanaoka T, Bauer T, Aye R, Kohman L, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg. 2014; 147:754-64.

19. Dziedzic R, Zurek W, Marjanski T, Rudzinski P, Orlowski TM, Sawicka W, et al. Stage I non-small-cell lung cancer: long-term results of lobectomy versus sublobar resection from the Polish National Lung Cancer Registry. Eur J Cardiothorac Surg. 2017 ;52:363-9.

20. Gu C, Huang Z, Dai C, Wang Y, Ren Y, She Y, et al. Prognostic analysis of

limited resection versus lobectomy in stage IA small cell lung cancer patients based on the surveillance, epidemiology, and end results registry database. Front Genet. 2018; 9:568.

21. Licht PB, Jørgensen OD, Ladegaard L, Jakobsen E. A national study of nodal upstaging after thoracoscopic versus open lobectomy for clinical stage I lung cancer. Ann Thorac Surg. 2013; 96:943-9.

22. Cerfolio RJ, Bryant AS. Survival of patients with true pathologic stage I non–small-cell lung cancer. Ann Thorac Surg. 2009; 88:917-22.

23. Khullar OV, Liu Y, Gillespie T, Higgins KA, Ramalingam S, Lipscomb J, et al. Survival after sublobar resection versus lobectomy for clinical stage ia lung cancer: An analysis from the national cancer data base. J Thorac Oncol 2015; 10:1625-33.

24. Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, et

al. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2014; 9:1618-24.

25. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol. 2011 ;6:751-6.

26. Nakamura K, Saji H, Nakajima R, Okada M, Asamura H, Shibata T, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol. 2010 ;40:271-4.

27. Aokage K, Saji H, Suzuki K, Mizutani T, Katayama H, Shibata T, et al. A non-randomized confirmatory trial of segmentectomy for clinical T1N0 lung cancer with dominant ground glass opacity based on thin-section computed tomography (JCOG1211). Gen Thorac Cardiovasc Surg. 2017 ;65:267-72.

28. Park SY, Cho A, Yu WS, Lee CY, Lee JG, Kim DJ, et al. Prognostic value of total lesion glycolysis by 18F-FDG PET/CT in surgically resected stage IA non-small cell lung cancer. J Nucl Med. 2015; 56:45-9.

29. Hyun SH, Ahn HK, Kim H, Ahn MJ, Park K, Ahn YC, et al. Volume-based assessment by (18)F-FDG PET/CT predicts survival in patients with stage III non-small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2014; 41:50-8.

30. El-Sherief AH, Lau CT, Wu CC, Drake RL, Abbott GF, Rice TW. International association for the study of lung cancer (IASLC) lymph node map: radiologic review with CT illustration. Radiographics. 2014; 34:1680–91.

31. Kim JH, van Beek EJ, Murchison JT, Marin A, Mirasadraee S. The International Association for the study of lung cancer lymph node map: a radiologic atlas and review. Tuberc Respir Dis (Seoul). 2015; 78:180–9.

32. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’for

medical statistics. Bone Marrow Transplant. 2013; 48:452–8.

33.Downey RJ, Akhurst T, Gonen M, Vincent A, Bains MS, Larson S, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. J Clin Oncol. 2004; 22:3255-60.

34. Kanzaki R, Higashiyama M, Fujiwara A, Tokunaga T, Maeda J, Okami J, et al. Occult mediastinal lymph node metastasis in NSCLC patients diagnosed as clinical N0-1 by preoperative integrated FDG-PET/CT and CT: Risk factors, pattern, and histopathological study. Lung Cancer 2011; 71:333-7.

35. Zhang S, Li S, Pei Y, Huang M, Lu F, Zheng Q, et al. Impact of maximum standardized uptake value of non-small cell lung cancer on detecting lymph node involvement in potential stereotactic body radiotherapy candidates. J Thorac Dis 2017; 9:1023-31.

36. Baschnagel AM, Wobb JL, Dilworth JT, Williams L, Eskandari M, Wu D, et

al. The association of (18)F-FDG PET and glucose metabolism biomarkers GLUT1 and HK2 in p16 positive and negative head and neck squamous cell carcinomas. Radiother Oncol. 2015; 117:118-24.

37. Zhang B, Xie Z, Li B. The clinicopathologic impacts and prognostic significance of GLUT1 expression in patients with lung cancer: A meta-analysis. Gene. 2019; 689:76-83.

38. Detterbeck FC. Diagnosis and treatment of lung cancer: An evidence-based guide for the practicing clinician. WB Saunders Company; 2001.

39. Okada M, Nakayama H, Okumura S, Daisaki H, Adachi S, Yoshimura M, et al. Multicenter analysis of high-resolution computed tomography and positron emission tomography/computed tomography findings to choose therapeutic strategies for clinical stage IA lung adenocarcinoma. J Thorac Cardiovasc Surg. 2011; 141:1384-91

40. Kang DY, Lee S. Lymphatic vessel invasion and lymph node metastasis in

patients with clinical stage I non-small cell lung cancer. Thorac Cardiovasc Surg. 2014; 62:521-4

41. Higashi K, Ito K, Hiramatsu Y, Ishikawa T, Sakuma T, Matsunari I, et al. 18F-FDG uptake by primary tumor as a predictor of intratumoral lymphatic vessel invasion and lymph node involvement in non-small cell lung cancer: analysis of a multicenter study. J Nucl Med. 2005; 46:267-73.

42. Ghaly G, Rahouma M, Kamel MK, Nasar A, Harrison S, Nguyen AB, et al. Clinical predictors of nodal metastases in peripherally clinical T1a N0 non-small cell lung cancer. Ann Thorac Surg. 2017; 104:1153-8.

Table 1 Patient and tumour characteristics

Characteristics	Distribution
Sex (n)	
Male/Female	30/15
Age (years)	
Mean±SD (range)	69±7 (51–84)
Histopathological type (n)	
Adeno/Squamous/Adenosquamous/Large/Small	21/13/6/1/4
T stage (n)	
T1a/T1b/T1c/T2a/T2b/T3/T4	13/6/1/13/4/3/5
N stage (n)	
N0/N1/N2/N3	30/7/4/4
Tumour size (mm)	
Mean±SD (range)	31.9±16.7 (8–99)

SD standard deviation, *Adeno* adenocarcinoma, *Squamous* cell carcinoma, *Adenosquamous* cell carcinoma, *Large* large-cell carcinoma, *Small* small-cell carcinoma

Table 2 SUVmax, MTV, and TLG of the primary tumour between LN groups

Item		LN metastasis	Non-LN metastasis	p value
Tumour number		15	30	
First dynamic phase	SUVmax	5.23±2.02	3.97±2.74	0.034
	MTV(cm^3)	47.71±87.16	14.40±35.98	0.005
	TLG(g)	177.77±326.31	61.73±166.43	0.006
Second dynamic phase	SUVmax	7.11±3.27	5.07±4.13	0.028
	MTV(cm^3)	51.02±86.94	15.07±36.54	0.004
	TLG(g)	199.28±328.23	74.61±199.05	0.004
Third dynamic phase	SUVmax	8.61±4.12	6.15±5.31	0.036
	MTV(cm^3)	55.07±94.05	16.10±37.90	0.004
	TLG(g)	262.18±472.83	96.79±274.02	0.005
Early phase	SUVmax	13.69±6.50	9.65±8.28	0.046
	MTV(cm^3)	56.75±98.34	17.59±40.47	0.008

	TLG(g)	380.12±731.04	137.97±383.64	0.011
Delayed phase	SUVmax	17.54±7.87	12.13±10.73	0.037
	MTV(cm^3)	61.49±107.64	19.21±42.11	0.004
	TLG(g)	472.50±931.99	178.87±485.50	0.008
Size (mm)		39.73±19.02	27.93±14.23	0.014

The data are presented as mean ± the standard deviation. The p value is based on the comparison of the semiquantitative values between metastatic and non-metastatic lymph nodes (Mann–Whitney *U* test).

LN lymph node, *SUVmax* maximum standardised uptake value, *MTV* metabolic tumour volume, *TLG* total lesion glycolysis

Table 3 Performance parameters of semiquantitative analyses for diagnosing the presence or absence of LN metastasis in all patients.

SUVmax	1st phase	2nd phase	3rd phase	Early	Delayed
Cut-off value	3.81	5.63	6.94	11.69	14.93
Sensitivity (%)	80.0	73.3	73.3	73.3	73.3
Specificity (%)	63.3	70	70	66.7	63.3
AUC	0.696	0.702	0.693	0.684	0.692
MTV(cm^3)	1st phase	2nd phase	3rd phase	Early	delayed
Cut-off value	4.32	4.82	5.69	10.69	14.23
Sensitivity (%)	80	80	80	73.3	73.3
Specificity (%)	70	70	66.7	76.7	76.7
AUC	0.754	0.767	0.766	0.743	0.766
TLG(g)	1st phase	2nd phase	3rd phase	Early	delayed
Cut-off value	18.85	22.35	22.70	42.75	41.55
Sensitivity (%)	73.3	73.3	80	73.3	73.3
Specificity (%)	73.3	73.3	66.7	73.3	63.3
AUC	0.751	0.763	0.757	0.733	0.746

SUV standardised uptake value, *MTV* metabolic tumour volume, *TLG* total

lesion glycolysis, *AUC* area under the curve

Table 4 SUVmax, MTV, and TLG of the primary tumour between the LN groups in patients satisfying the indications of segmentectomy based on CT scans

Item		LN metastasis (+)	Non-LN metastasis	p value
Tumour number		5	14	
First dynamic phase	SUVmax	4.38±1.95	2.22±1.04	0.034
	MTV(cm^3)	2.16±1.98	0.28±1.98	0.044
	TLG(g)	7.20±6.88	0.74±1.33	0.034
Second dynamic phase	SUVmax	6.39±3.11	2.41±1.41	0.003
	MTV(cm^3)	2.80±2.06	0.36±0.62	0.014
	TLG(g)	10.63±8.96	1.08±1.94	0.014
Third dynamic phase	SUVmax	8.05±3.78	2.71±1.89	0.002
	MTV(cm^3)	3.51±2.16	0.48±0.87	0.003
	TLG(g)	14.62±10.35	1.70±3.20	0.001
Early phase	SUVmax	13.74±4.86	4.08±4.08	0.003

	MTV(cm^3)	3.68±1.12	0.96±1.33	0.005
	TLG(g)	16.78±7.21	3.27±5.06	0.002
Delayed phase	SUVmax	18.03±7.26	5.03±5.41	0.003
	MTV(cm^3)	4.21±1.42	1.13±1.51	0.003
	TLG(g)	23.82±15.30	4.33±6.92	0.002
Size (mm)		23.40±5.68	18.43±6.43	0.298

The data are presented as mean ± the standard deviation. The p value is based on the comparison of the semiquantitative values between metastatic and non-metastatic lymph nodes (Mann–Whitney *U* test).

LN lymph node, *SUVmax* maximum standardised uptake value, *MTV* metabolic tumour volume, *TLG* total lesion glycolysis

Table 5 Performance parameters of the semiquantitative analyses for diagnosing the presence or absence of LN metastasis in patients satisfying the indications of segmentectomy based on CT scans.

SUVmax	1st phase	2nd phase	3rd phase	Early	Delayed
Cut-off value	2.78	2.39	3.28	7.10	9.35
Sensitivity (%)	80	92.9	100	100	100
Specificity (%)	71.4	80	78.6	78.6	78.6
AUC	0.829	0.929	0.943	0.929	0.929
MTV(cm^3)	1st phase	2nd phase	3rd phase	Early	Delayed
Cut-off value	1.83	2.13	2.35	2.65	2.65
Sensitivity (%)	60	80	80	100	100
Specificity (%)	100	100	92.9	85.7	85.7
AUC	0.814	0.871	0.929	0.914	0.929
TLG(g)	1st phase	2nd phase	3rd phase	Early	Delayed
Cut-off value	5.80	5.96	9.00	12.4	14.1
Sensitivity (%)	60	80	80	100	100
Specificity (%)	100	100	100	92.9	92.9
AUC	0.829	0.871	0.957	0.943	0.943

SUV standardised uptake value, *MTV* metabolic tumour volume, *TLG* total lesion glycolysis, *AUC* area under the curve

Figure legends

Figure 1

A receiver operating characteristic curve shows the performance of the maximum standardised uptake value, metabolic tumour volume, and total lesion glycolysis of the primary lung tumour in the third dynamic phase for differentiating lung cancers with lymph node (LN) metastasis and those without LN metastasis in patients satisfying the indications for segmentectomy based on computed tomography scans.

Figure 2

Repeated-measures ANOVA reveal the relationship of temporal changes in maximum standardised uptake value (SUVmax) of the primary tumour, metastatic lymph node (LN), and non-metastatic LN. Mean attenuation value of SUVmax in each phase of each targets. Error bars show the standard deviation. SUV1, SUVmax in the first dynamic phase; SUV2, SUVmax in the second dynamic phase; and SUV3, SUVmax in the third dynamic phase.

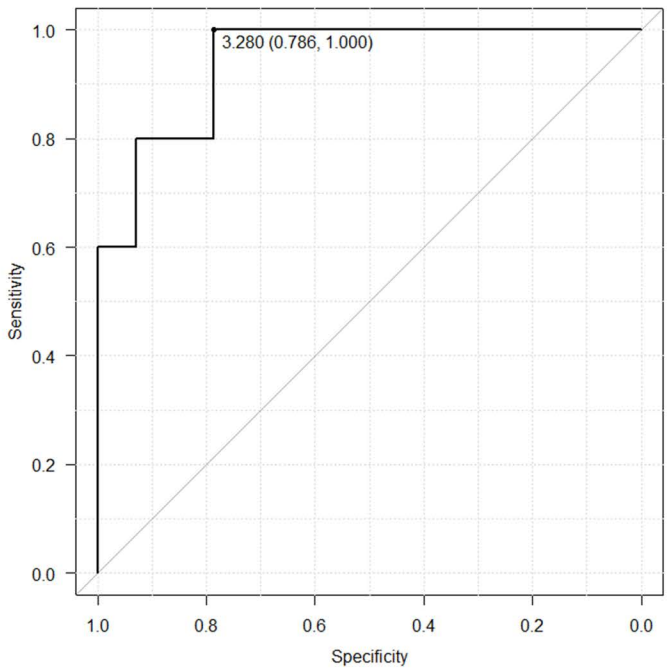
Figure 3

A 69-year-old woman with adenocarcinoma without lymph node (LN) metastasis. Primary tumour (arrow) size is 22 mm and segmentectomy is performed. Dynamic and dual-time-point positron emission tomography/computed tomography images show low fluorodeoxyglucose accumulation in the primary tumour and LN (not shown) in all time phases. (a. first dynamic phase, maximum standardised uptake value (SUVmax) = 2.19; b. second dynamic phase, SUVmax = 2.18; c. third dynamic phase, SUVmax = 1.98; d. early phase, SUVmax = 2.76; e. delayed phase, SUVmax = 3.07).

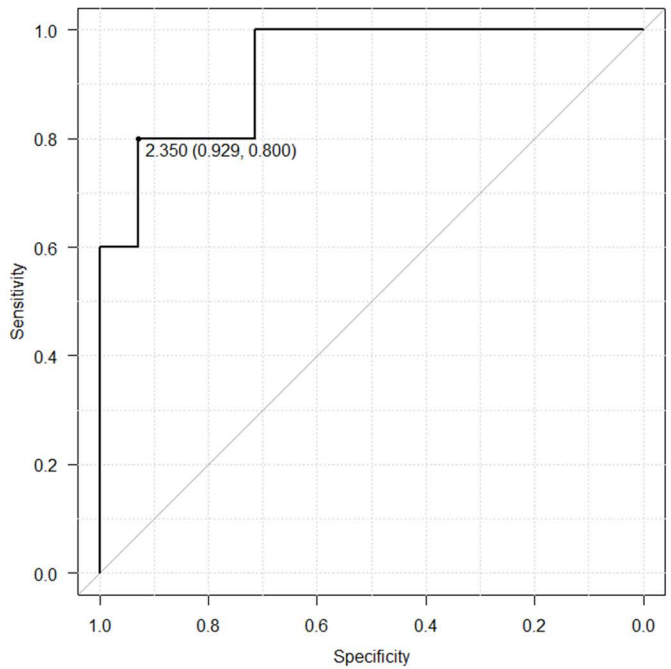
Figure 4

A 65-year-old man with squamous cell carcinoma with lymph node (LN) metastasis. Primary tumour size is 45 mm and lobectomy is performed. Dynamic and DTP PET/CT images (a,f. first dynamic phase; b,g second dynamic phase; c,h. third dynamic phase; d,i. early phase; e,j. delayed phase) reveal intense fluorodeoxyglucose (FDG) accumulations in the primary tumour (arrow) and pathologically proven metastatic LN (#7, circle) in all time phases. The FDG accumulations increases over time. In contrast, FDG accumulation in

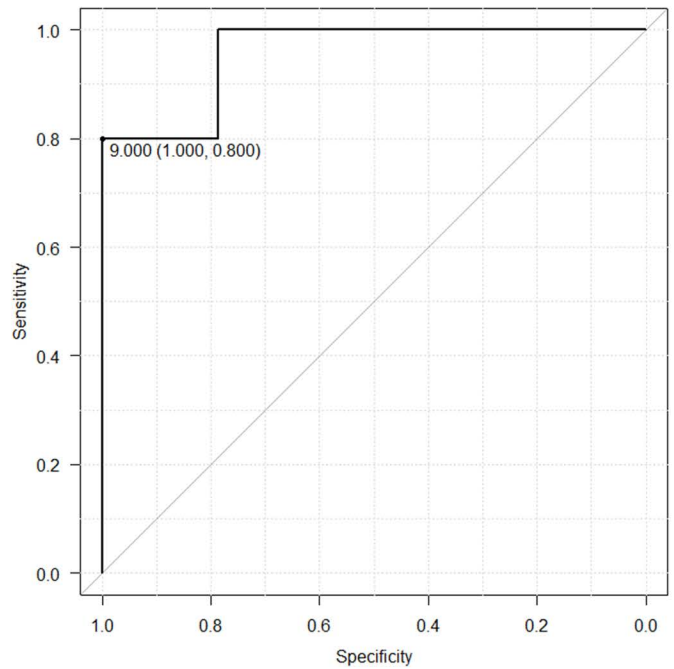
non-metastatic LN (#11, arrow head) is not increased over time. Maximum standardised uptake value (SUVmax) in each phase: primary tumour 4.19→5.76→7.37→12.16→15.65; metastatic LN (#7) 5.33→6.79→8.34→13.81→15.66; and non-metastatic LN (#11) 1.82→1.68→1.91→1.29→1.39.



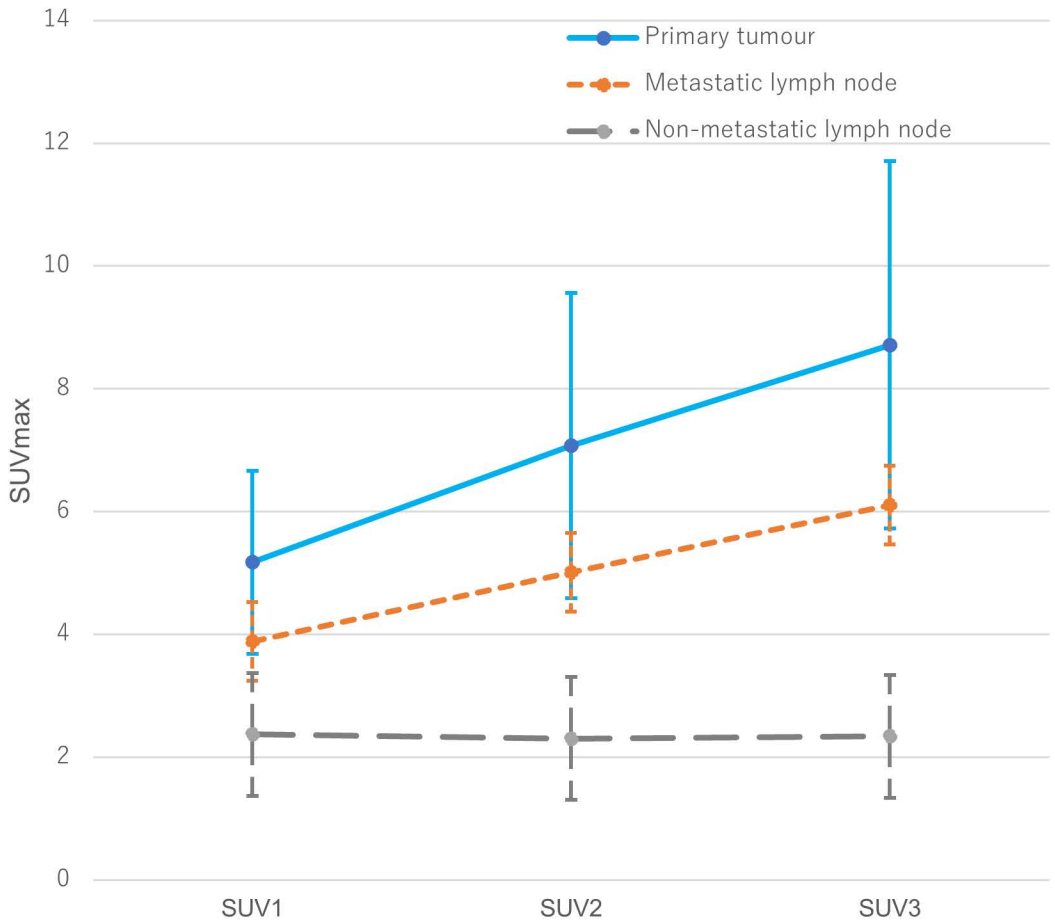
SUVmax in the third phase
(AUC=0.943)



MTV in the third phase
(AUC=0.929)



TLG in the third phase
(AUC=0.957)

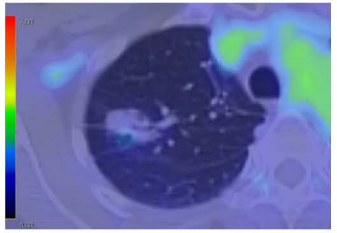

14
12
10
8
6
4
2
0
SUVmax
Primary tumour
Metastatic lymph node
Non-metastatic lymph node
SUV1
SUV2
SUV3

CASE. 69-year-old female

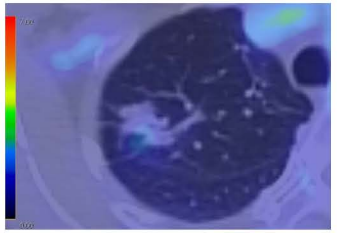
Primary tumour without LN metastasis

a First dynamic phase

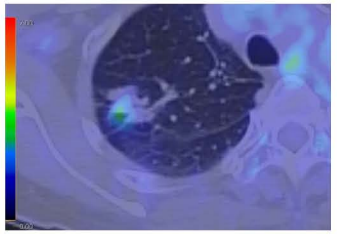
b Second dynamic phase



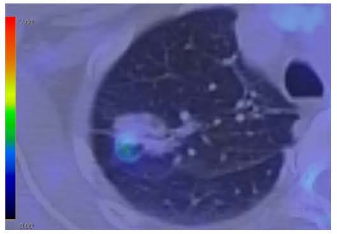
c Third dynamic phase



d Early phase



e Delayed phase



CASE: 65-year-old male