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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

# Does FDG PET/CT have a role in determining adjuvant chemotherapy in surgical margin-negative stage IA non-small cell lung cancer patients?

**Hye Lim Park[1] · Ie Ryung Yoo[1] · Sun Ha Boo[1] · Sonya Youngju Park[1] · Jae Kil Park[2] · Sook Whan Sung[2] · Seok Whan Moon[2]**

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## Abstract

**Purpose** To evaluate the prognostic value of FDG PET/CT metabolic parameter compared to clinico–pathological risk factors in surgical margin-negative stage IA non-small cell lung cancer (NSCLC) patients.

**Methods** 167 patients with consecutive FDG PET/CT scans from 2009 to 2015 performed for staging of NSCLC stage IA with plans for curative surgery were retrospectively reviewed. Maximum standardized uptake value (SUVmax) of primary tumor and mean SUV of liver were acquired from PET/CT. Tumor-to-liver SUV ratio (TLR) was calculated. Charts were reviewed to obtain basic patient characteristics (age, sex, smoking history, LDH, histologic subtype) and high-risk factors for adjuvant chemotherapy (tumor size, poorly differentiation, vascular invasion, and sub-lobar resection). Patients were dichotomized into two groups using optimal cut-off from receiver operating characteristic curve analysis of TLR to predict recurrence. Statistical analysis was done using Cox regression analysis and Kaplan–Meier method. Factors with $P < 0.2$ in univariate analysis were included in multivariate analysis.

**Results** Recurrence rate was 12.6% (21/167). Median disease-free survival (DFS) was 47.2 months while 2-year and 5-year DFS rates were 93% and 86%, respectively. The optimal cut-off for TLR was 2.3. In univariate analysis, *P* value of sex, vascular invasion, and TLR were less than 0.2. In multivariable analysis, high TLR was the only factor that showed significant association with tumor recurrence (hazard ratio 3.795, $P = 0.0048$).

**Conclusions** TLR was an independent prognostic factor for recurrence and TLR could be an important risk factor to be considered in decision-making for adjuvant chemotherapy, even for those with stage IA NSCLC.

**Keywords** Carcinoma · Non-small cell lung · Positron emission tomography–computed tomography · Stage IA · Prognosis

## Introduction

5-year survival rate of non-small cell lung cancer (NSCLC) stage IA has been reported to be 80–93% (Maeda et al. 2010; Monirul Islam et al. 2013). However, the recurrence rate is too high to ignore, with reported rate of 15–30% (Ko et al. 2015). The need for selecting patients for adjuvant chemotherapy in early stage of NSCLC remains an unresolved issue. Adjuvant chemotherapy is not recommended for stage IA NSCLC. For cases with surgical margin-positive stage IA NSCLC, re-resection or radiation therapy is recommended. Recent NCCN guidelines suggest the following high-risk factors for adjuvant chemotherapy in patients with margin-negative stage IB and IIA NSCLC: poorly differentiated tumors, vascular invasion, sub-lobar resection, tumor larger than 4 cm, visceral pleural involvement, and incomplete lymph node sampling.

Fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) is mandatory in initial workup for NSCLC. PET parameters such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total glycolysis

✉ Ie Ryung Yoo
iryoo@catholic.ac.kr

[1] Division of Nuclear Medicine, Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea

[2] Department of Thoracic and Cardiovascular Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

(TLG) are known as prognostic factors for recurrence and survival in patients with NSCLC (Kurtipek et al. 2015; Liu et al. 2016; Shin et al. 2017; Vu et al. 2013; Zhang et al. 2013). SUVmax is the highest SUV in region of interest. MTV and TLG are representative volumetric parameters from FDG PET. MTV is the volume of voxel with higher SUV over threshold. TLG is the product of multiplying MTV by mean SUV. MTV and TLG are difficult to use in daily practice because they are time consuming. In addition, special software is needed to measure and calculate these parameters. Thus, tumor to liver ratio (TLR) was chosen as the PET parameter for this study to overcome the variation of different scanners and inconvenience of measuring volume parameters, and to help physicians intuitively perceive the effect of uptake on prognosis. Whether high-risk factors considered for adjuvant chemotherapy in stage IB and IIA or PET parameters are applicable to surgical margin-negative stage IA as well is currently unclear. Therefore, the objective of this study was to evaluate the prognostic value of the metabolic parameter TLR obtained from F-18 FDG PET/CT compared to clinicopathological risk factors in surgical margin-negative stage IA NSCLC patients for whom adjuvant chemotherapy is recommended.

## Materials and methods

### Patient population

This retrospective study was approved by our Institutional Review Board. Informed consent was waived. Clinical records of all consecutive NSCLC patients who underwent FDG PET/CT for initial staging and curative resection from January 2009 to December 2015 were reviewed. Patients with surgical stage IA NSCLC according to the lung cancer staging system from the American Joint Committee on Cancer 7th edition were included. Exclusion criteria were patients with adenocarcinoma in situ, minimally invasive adenocarcinoma, comorbidity other cancer, surgical margin positive on pathology, history of neo-adjuvant or adjuvant therapy, or multiple lung cancer. Chest radiography and chest CT with physical examination were performed every 6 months for 2 years after operation and then every year thereafter. We followed up the patients' data until April 2018. Diagnosis of tumor recurrence was made based on pathologic result or imaging studies such as FDG PET/CT, CT, MRI, or bone scan. Recurrence was categorized into loco-regional recurrence (mediastinum, supraclavicular lymph node, or surgical bed including bronchial stump), distant metastasis (pleura, contralateral lung or extrathorax), and loco-regional recurrence with distant metastasis.

### F-18 FDG PET/CT protocol and imaging analysis

All patients fasted for at least 6 h before FDG PET/CT scan. 3.7–5.5 MBq/kg F-18 FDG was injected intravenously and scanning was started 60 min later. No intravenous contrast agent was administered. Images were acquired using a combined PET/CT in-line system (Biograph Duo, Biograph TruePoint, Siemens Medical Solutions, Knoxville, TN, USA; and Discovery 710D, GE Healthcare, Milwaukee, WI, USA). The acquisition time was 2–3 min per bed position. All patients were in supine position during PET/CT scanning. Non-contrast-enhanced CT began at the orbitomeatal line and progressed to the proximal thigh using a standard protocol: 130 kVp, 80 mAs, 5 mm slice thickness (Biograph Duo); 120 kVp, 50 mAs, 5 mm slice thickness (Biograph TruePoint); and 120 kVp, variable mAs adjusted by topographic image, 2.5 mm slice thickness (Discovery 710D). PET scans of the same body region were followed immediately. CT data were used for attenuation correction. Images were reconstructed using a standard ordered-subset expectation maximization algorithm.

FDG PET/CT data were interpreted by two board-certified nuclear medicine specialists. All FDG PET/CT scans were assessed using software XD3 (Mirada Medical, Oxford, UK). For semi-quantitative analysis, SUVmax of FDG PET was measured by visually placing the region of interest around the site of increased FDG uptake of primary cancer. To compensate for the difference arising from three different scanners, correction by mean SUV of liver was used to compute the ratio of the tumor to liver SUV (TLR). For mean SUV of liver, we drew three non-overlapping spherical volume of interest (VOI) with a diameter of 3 cm in the liver (two in the right lobe and one in left lobe) and calculated the mean value (supplement).

### Statistical analysis

All statistical analyses were carried out using SAS system for Windows V9.4. All continuous values are described as mean ± standard deviation (SD) (range). *T* test, Chi-square test, and exact test with Scheffe correction were performed to compare variables according to TLR. Disease-free survival (DFS) was defined as the time from the date of curative surgery until the first evidence of disease recurrence. In addition to metabolic parameters, high-risk factors for considering adjuvant chemotherapy (tumor size, poor differentiation, vascular invasion, and sub-lobar resection) and clinical factors [age, sex, smoking history, lactate dehydrogenase (LDH), and histology subtype] were included in uni- and multivariate analyses for DFS. All

patients were dichotomized into two groups using optimal cut-off from receiver operating characteristic (ROC) curve analysis of TLR for recurrence prediction. Tumor size was categorized by T stage as T1a and T1b. Operation method was divided as lobectomy/pneumonectomy and sub-lobar resection (wedge resection and segmentectomy). The cut-off value of LDH was 450. Cox proportional-hazards model was used for univariate and multivariate analyses. Variables were included in multivariate analysis if $P < 0.2$ in univariate analysis. Kaplan–Meier plot by log-rank test was used for survival curves. $P$ values $< 0.05$ were considered to indicate statistical significance.

## Results

A total of 167 patients were included (mean age 62.9 ± 10.2 years, range 36–92 years), including 83 males and 84 females. Performance statuses of all patients were 0 or 1. Mean SUVmax and TLR of 167 primary tumors were 4.0 ± 3.5 and 1.8 ± 1.7, respectively. TLR showed a very strong association with SUVmax ($P < 0.001$, $r = 0.975$ by Pearson correlation). Cut-off value of TLR was determined to be 2.3 using ROC curve analysis (area under curve 0.6649, $P = 0.0035$). There was no difference of mean SUV of liver between the high- and low-TLR groups (2.20 ± 0.32 vs. 2.25 ± 0.35, $P = 0.366$ by $t$ test). Associations between characteristics of patients and TLR using a cut-off value of 2.3 are summarized in Table 1. High-TLR group included bigger portions of male, T1b, non-adenocarcinoma, presence of vascular invasion, and poorly differentiated tumor compared to low-TLR group.

At the time of analysis, median DFS was 47.2 months (range 1.3–103.3 months). Twenty-one (12.6%) patients had recurrence. The time interval to recurrence ranged from 6.7 to 62.0 months. Recurrence had 12 cases within 2 years and 9 cases for more than 2 years. Two of nine patients developed recurrence over 5 years (60.1 months and 62 months). 2-year and 5-year DFS rates were 93% and 86%, respectively. Regarding recurrence sites, there were 7 loco-regional recurrences, 11 distant metastases, and 3 loco-regional with distant metastases. Loco-regional recurrence sites included operation bed ($n = 1$), operation bed and mediastinal LN ($n = 1$), and mediastinal LNs ($n = 5$). Distant metastasis sites were lung, 4; pleura, 2; brain, 1; bone, 1; abdominal LN, 1; lung and pleura, 1; and lung and muscle, 1. Loco-regional recurrence with distant metastasis sites was operation bed and liver, 1; lung and mediastinal LN, 1; and mediastinal LNs and pleura, 1.

In univariate analysis, high TLR showed significant association with recurrence ($P = 0.007$). $P$ values of sex and vascular invasion were less than 0.2. We included sex, vascular invasion and TLR in multivariate analysis. In multivariate analysis, only TLR was an independent prognostic factor for recurrence ($P = 0.0048$, hazard ratio 3.795, 95% confidence interval 1.503–9.583) (Table 2; Fig. 1).

When comparing the DFS according to TLR, median DFS for high TLR and low TLR were 42.1 and 48.6 months, respectively. For the high TLR group, 2-year and 5-year DFS rates were 83% and 71%, respectively. For the low-TLR group, 2-year and 5-year DFS rates were 96% and 91%, respectively (Fig. 2).

## Discussion

Stage IA NSCLC is the stage that could be cured by surgical resection. If surgical pathology is proven to be margin negative, there is no recommendation for adjuvant therapy. However, the recurrence rate of stage IA has been reported to be about 15–30% (Anwar et al. 2018; Ko et al. 2015). In our study, 12.6% (21/167) of patients had recurrence, although the surgical margin was negative. Within 2 years after curative surgery, recurrence is the most frequent in NSCLC (Maeda et al. 2010; Song et al. 2014). Twelve patients in this study had recurrent tumor during the first 2 years after surgery. More than half (57.1%, 12/21) of the recurrence occurred in 2 years. Maeda et al. (2010) have suggested that recurrence rate at 5 years after surgery is 4.8% and vascular invasion influences late recurrence. In our study, two patients had recurrence at 5 years after surgical resection. The recurrence sites of both patients were mediastinal LNs which were confirmed by bronchoscopy biopsy. However, these two patients in our cohort did not have vascular invasion. This discrepancy in results might arise from a small number of patients with late recurrence in the present study compared to the study of Maeda et al. Tumor recurrence is associated with poor survival. Therefore, we should consider adjuvant therapy to patients with high-risk factor for recurrence.

In this study, the only independent poor prognostic factor for recurrence was high TLR. Well-known prognostic factors such as tumor size, vascular invasion, sub-lobar resection, or poor differentiation did not show statistical significance for recurrence. These clinico-pathologic factors are used as high-risk factors when considering adjuvant therapy in stage IB and IIA. Reported prognostic factors for recurrence in NSCLC stage I in previous articles were tumor size, visceral pleural invasion, vascular invasion, and PET parameters such as SUVmax, MTV, and SUVmax corrected with lean body mass (Horn et al. 2007; Jeong et al. 2017; Kang et al. 2018; Ko et al. 2015; Maeda et al. 2010). A few FDG PET/CT studies have determined factors predicting recurrence or survival of stage IA (Ko et al. 2015; Park et al. 2015). Park et al. (2015) have reported that total lesion glycolysis is a

**Table 1** Patient characteristics according to TLR

| Parameters | TLR < 2.3 ($n = 125$) | TLR ≥ 2.3 ($n = 42$) | $P$ |
|---|---|---|---|
| Age | 62.5 ± 9.6 | 64.0 ± 11.9 | 0.4186 |
| Sex | | | 0.0037 |
| Male | 54 (43.2%) | 29 (69.1%) | |
| Female | 71 (56.8%) | 13 (31.0%) | |
| Smoking history | | | 0.0102 |
| Non-smoker | 38 (30.4%) | 22 (52.4%) | |
| Smoker | 87 (69.6%) | 20 (47.6%) | |
| ECOG PS | | | NA |
| 0 or 1 | 74 (59.2%) | 24 (57.1%) | |
| ≥ 2 | 0 (0.0%) | 0 (0.0%) | |
| NA | 51 (40.8%) | 18 (42.9%) | |
| LDH | | | 0.6522 |
| ≤ 450 | 87 (69.6%) | 31 (73.8%) | |
| > 450 | 37 (29.6%) | 11 (26.2%) | |
| NA | 1 (0.8%) | | |
| Operation method | | | 1 |
| Lobectomy or pneumonectomy | 113 (90.4%) | 38 (90.5%) | |
| Sub-lobar resection | 12 (9.6%) | 4 (9.5%) | |
| Tumor size (T stage) | | | 0.042 |
| ≤ 2 cm (T1a) | 78 (62.4%) | 18 (42.9%) | |
| > 2 cm (T1b) | 47 (37.6%) | 24 (57.1%) | |
| Pathology | | | < 0.0001 |
| Adenocarcinoma | 123 (98.4%) | 30 (71.4%) | |
| Squamous cell carcinoma | 1 (0.8%) | 11 (26.2%) | |
| Others | 1 (0.8%) | 1 (2.4%) | |
| Vascular invasion | | | 0.0027 |
| Positive | 3 (2.4%) | 7 (16.7%) | |
| Negative | 122 (97.6%) | 35 (83.3%) | |
| Differentiation | | | < 0.0001 |
| WD or MD | 123 (98.4%) | 32 (76.2%) | |
| PD | 1 (0.8%) | 9 (21.4%) | |
| NA | 1 (0.8%) | 1 (0.8%) | |
| Disease-free survival | 50.8 ± 23.6 | 43.4 ± 23.7 | 0.0792 |

*TLR* tumor-to-liver SUV ratio, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *NA* not available, *LDH* lactate dehydrogenase, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated

significant prognostic factor for overall survival in stage IA NSCLC, but not for recurrence.

Poor differentiation is correlated with high FDG uptake (Vesselle et al. 2008). In this study, more patients with poorly differentiated tumor were included in the high-TLR group. Differentiation is a well-known prognostic factor in not only NSCLC, but also other malignant tumors. Therefore, the NCCN guidelines suggest adjuvant chemotherapy in patients with poorly differentiated cancer, even in margin-negative NSCLC stage IB and IIA. However, according to our study results, TLR was the only independent prognostic factor and differentiation was not associated with tumor recurrence. Metabolic parameter from FDG PET/CT could be a stronger prognostic factor than differentiation in stage IA.

TLR was chosen as a possible prognostic factor among various metabolic and volumetric parameters from FDG PET/CT although there were studies showing that metabolic parameters other than TLR were good prognostic factors in NSCLC (Ko et al. 2015; Park et al. 2015). There are two advantages of choosing TLR which uses liver activity as reference. The first advantage is that it is practical for routine clinical use. Common sites for reference values of FDG PET were liver and mediastinal blood pool. Deauville five-point scale for response evaluation of lymphoma also uses blood pool and liver activity as reference for dividing

**Table 2** Univariable and multivariable analyses for DFS

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | *P* | HR (95% CI) | *P* | HR (95% CI) |
| Age (1 year increase) | 0.7615 | 0.993 (0.952–1.036) | | |
| Sex (male/female) | 0.1265 | 0.493 (0.199–1.222) | 0.4334 | 0.687 (0.269–1.757) |
| Smoking history (no/yes) | 0.2653 | 1.627 (0.691–3.832) | | |
| LDH (≤ 450/> 450) | 0.4264 | 1.43 (0.592–3.453) | | |
| Operation method (pneumonectomy or lobectomy/sub-lobar resection) | 0.9453 | 1.052 (0.245–4.524) | | |
| Tumor size (≤ 2 cm/> 2 cm) | 0.232 | 1.689 (0.715–3.990) | | |
| Pathology | | | | |
| Squamous cell carcinoma | 0.742 | 1.277 (0.297–5.49) | | |
| Others | 0.9913 | 0 (0) | | |
| Vascular invasion (negative/positive) | 0.0791 | 2.993 (0.88–10.177) | 0.4983 | 1.551 (0.435–5.529) |
| Differentiation (WD or MD/PD) | 0.9891 | 0 (0) | | |
| TLR (< 2.3/≥ 2.3) | 0.0007 | 4.477 (1.884–10.641) | 0.0048 | 3.795 (1.503–9.583) |

*DFS* disease-free survival, *HR* hazard ratio, *LDH* lactate dehydrogenase, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *TLR* tumor-to-liver SUV ratio

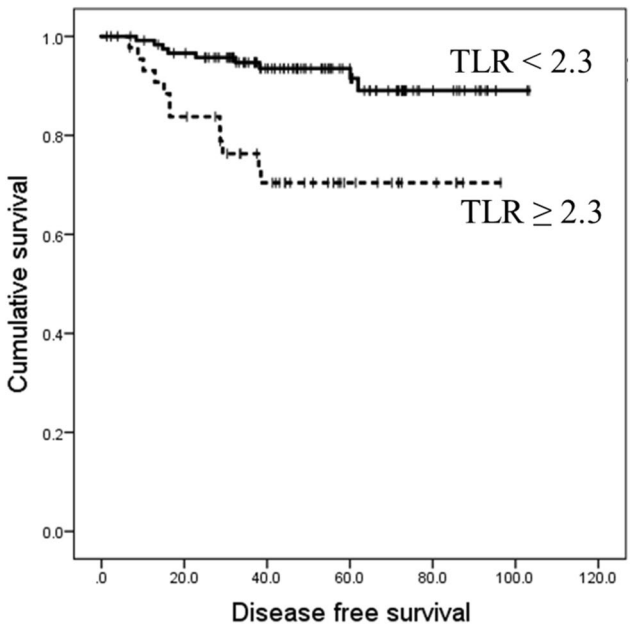


**Fig. 1** Cumulative disease-free survival curve according to TLR

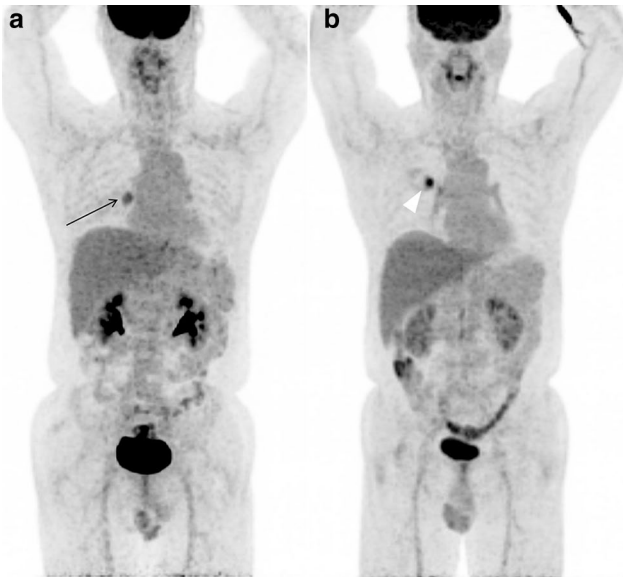


**Fig. 2** Case comparison of recurrence status according to TLR. Two patients with stage IA non-small cell lung cancer underwent right upper lobectomy. Final pathology for both was adenocarcinoma without vascular invasion and T stage of 1b. The patient on the left (**a**) had well-differentiated cancer with TLR of 1.8 (black arrow) while the one on the right (**b**) had moderately differentiated cancer with TLR of 2.8 (white arrowhead). Disease-free survival for the former was 53.9 months while the latter recurred in the lobectomy bed at 6.7 months

the score. We chose the liver for reference organ because (1) liver activity is stable over time (Paquet et al. 2004), and (2) our study cohort was limited to stage IA, ruling out any lesions in the abdomen that could affect liver activity in contrast to the blood pool, which may be closely related to the mediastinum. To reduce intra-patient variability, we measured FDG uptake using three non-overlapping VOIs two in the right hepatic lobe and one in the left hepatic lobe, and calculated the mean value. On maximum intensity projection images, visual comparison intensity between primary tumor and liver is intuitive, easy, and time saving compared to quantitative analysis for MTV or TLG. Clinicians can easily recognize primary tumor uptake compared to liver uptake using picture archiving and communication system (PACS) without using a separate work station. Another issue using

volumetric parameter is determination of the cut-off. Volumetric parameter is not practical for daily clinical setting. The second advantage is that TLR can overcome heterogeneity from differences among PET/CT scanners.

In this study, we found that FDG PET parameter was the most useful prognostic factor to decide whether adjuvant chemotherapy should be given among known high-risk clinico-pathologic factors. However, prospective study with large number of patients is needed to validate this result and determine whether adjuvant chemotherapy in selected patients can improve their survival.

Limitations of this study include its retrospective design, relatively small number of patients, and single-center experience. We included TLR as the only PET metabolic parameter. Comparison among PET parameters such as MTV, TLG, and tumor heterogeneity factors should be conducted to verify the role of TLR as a prognostic factor.

In conclusion, the recurrence rate of our cohort of stage IA NSCLC was 12.6%. Metabolic parameter TLR from FDG PET/CT in patients with stage IA NSCLC was an independent prognostic factor for recurrence in comparison with clinico-pathologic high-risk factors. TLR could be a biomarker for selecting patients for adjuvant chemotherapy, even for patients with stage IA NSCLC. We should consider adjuvant chemotherapy if tumor uptake is approximately more than twice higher than liver uptake, even for stage IA patients without other high-risk factors.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval and informed consent** For this retrospective study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

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