Use of ^{18}F-FDG PET/CT to predict short-term outcomes early in the course of chemoradiotherapy in stage III adenocarcinoma of the lung

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Abstract. The purpose of the present prospective study was to evaluate the use of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in the assessment of therapy response and the prediction of short-term outcomes by maximum and mean standardized uptake values (SUVmax and SUVmean, respectively), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) following chemoradiotherapy (CRT) in patients with stage III adenocarcinoma of the lung. The study included a total of 15 patients, all of whom underwent two serial ^{18}F-FDG PET/CT scans prior to and following 60-Gy radiotherapy with a concurrent cisplatin/pemetrexed combined chemotherapy regimen. SUVmax, SUVmean, MTV and TLG were determined. Short-term outcomes were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) and the PET Response Criteria in Solid Tumors (PERCIST). Post-CRT SUVmax, ΔSUVmax, ΔMTV and ΔTLG varied significantly between responders and non-responders (P=0.009, P=0.015, P=0.006 and P=0.004, respectively). The differences in SUVmax, SUVmean, carcinoembryonic antigen, MTV and TLG between the responders and the non-responders at the initial ^{18}F-FDG PET/CT scans were not statistically significant (P>0.05). The overall response rate was significantly higher (P=0.01) when evaluated using PERCIST compared with evaluation using RECIST. It was concluded that post-CRT SUVmax, ΔSUVmax, ΔMTV and ΔTLG may be used to differentiate the responders from the non-responders following CRT for stage III adenocarcinoma of the lung. This would aid in deciding whether or not to increase dosages or to incorporate a boost treatment without the requirement to suspend therapy.

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Abbreviations: NSCLC, non-small cell lung cancer; RT, radiotherapy; CRT, chemoradiotherapy; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PERCIST, PET Response Criteria In Solid Tumors; RECIST, Response Evaluation Criteria In Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival

Key words: fluorodeoxyglucose, positron emission tomography, treatment monitoring, adenocarcinoma of the lung

Introduction

Lung cancer is the primary cause of cancer-associated mortality worldwide. Approximately 85% of these fatalities are accounted for by non-small cell lung cancer (NSCLC) (1), of which the most common histopathological type in recent decades has been adenocarcinoma (2). The majority of patients with NSCLC are not amenable to curative resection with locally advanced or advanced disease (3). The standard treatment for these patients is platinum-based combination chemotherapy with concurrent radiotherapy (RT), which can improve survival for certain patients (4). However, the 5-year overall survival (OS) rate for lung cancer remains at 15% (5), as not all patients respond to the chemoradiotherapy (CRT) due to high levels of toxicity. Therefore, early predictions of therapy response and patient outcome are particularly important, such that patients who are be likely to benefit from treatment may be identified.

In light of this, it has been suggested that the non-invasive molecular imaging tool, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), may aid in alleviating these problems. Over time, ^{18}F-FDG PET has become an accepted method for staging and evaluating therapeutic response in NSCLC patients (6,7). In a prospective study, Mac Manus *et al* (8) demonstrated that the post-treatment ^{18}F-FDG PET response was more significantly associated with survival compared with the post-treatment computed tomography (CT) in patients treated with determinate radiation or CRT. The major advantage of ^{18}F-FDG PET when compared with

structural imaging techniques is the detection of a change in cellular metabolism earlier than any change in the tumor size. Therefore, ^{18}F-FDG PET could be used as a sensitive tool to predict treatment response (9). The purpose of the present study was to evaluate different ^{18}F-FDG PET/CT parameters, including maximum standardized uptake values (SUVmax), mean standardized uptake values (SUVmean), metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as survival prognostic factors in patients with stage III NSCLC. The prognoses were determined by ^{18}F-FDG PET/CT prior to and following 60-Gy radiotherapy with a concurrent cisplatin/pemetrexed chemotherapy regimen.

Patients and methods

Patients. The present study is a prospective study of 14 consecutive patients with locally advanced NSCLC (stage IIIA/IIIB) who were treated with concurrent CRT in Shandong Cancer Hospital Affiliated to Shandong University (Jinan, Shandong, China) between May 2015 and May 2016. The following inclusion criteria were used: Stage III NSCLC [using American Joint Committee on Cancer (7th edition)] (10); histopathologically confirmed primary adenocarcinoma; an Eastern Cooperative Oncology Group (ECOG) Performance Status (11) of 0 or 1; and complete physical examination, serum tumor marker determination, blood count and serum biochemistry. The exclusion criteria were as follows: RT or surgery of the chest within 3 months prior to entering the study; and a previous history of cancer or diabetes mellitus. This study was approved by the Institutional Review Boards and Ethics Committees of Shandong Cancer Hospital Affiliated to Shandong University. All procedures involving human participants were in accordance with the ethical standards of the institution and/or national research committee, and with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants included in the study.

CRT. All patients were treated with conventionally fractioned RT at 5 doses of 2 Gy per week up to a total dose of 60-66 Gy, based on a ^{18}F-FDG PET/CT scans. RT was delivered by three-dimensional conformal RT or intensity modulated RT techniques with 6-MV photons (based on lesion size and fitness of target volume). The primary tumor and any clinically involved lymph nodes were included in the gross tumor volume, and planning target volume included the gross tumor volume with a margin of 0.8 cm. All patients were treated with 2-cycles of concurrent chemotherapy with cisplatin (25 mg/m^2 on days 1-3 iv. drip) and pemetrexed (500 mg/m^2 on day 1 iv. drip). This was repeated every 21 days for a total of four to six cycles. Standard premedication of dexamethasone and antihistaminergic drugs was provided for the pemetrexed treatment.

^{18}F-FDG PET/CT image acquisition. ^{18}F-FDG PET/CT scans were performed with a Discovery LS PET-CT system (GE Healthcare Life Sciences, Little Chelfont, UK). All patients had been resting and fasting for at least 6 h prior to the scan and their serum glucose levels were measured to ensure a value of <6.6 mmol/l. Following intravenous injection with 5.0 MBq/kg ^{18}F-FDG, patients rested for 45-60 min. Emission scans were obtained from the skull to the thighs for 5 min per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm per slice. CT data were also collected. During ^{18}F-FDG PET/CT scanning, quiet respiration was required to ensure the quality of images. The total time varied between 25 and 30 min per patient. PET images were reconstructed with CT-derived attenuation correction using an ordered subset expectation maximization algorithm. Pre-treatment ^{18}F-FDG PET/CT scans were conducted 1-3 days prior to the start of RT as part of the initial staging. Repeat whole-body ^{18}F-FDG PET/CT scans were performed once the total RT dose had reached 60 Gy in order to evaluate the therapeutic effect.

Interpretation of ^{18}F-FDG PET/CT images. Interpretation of ^{18}F-FDG PET/CT imaging was performed by nuclear medicine physicians, who were affiliated to our hospital and were blinded to patient histories, using consensus criteria. SUVmean and SUVmax were acquired using attenuation-corrected images. SUVmax of the primary tumor was obtained in the transaxial view. An SUV cutoff of 2.5 was used to measure MTV and thus, MTV was defined as the sum of voxels exhibiting an SUV of 2.5 or more. When all the hypermetabolic tumor foci were segmented, the EBW workstation (Philips Healthcare, Andover, MA, USA) calculated MTV automatically, defined as the total volume of all tumors in the body. The SUVmean was obtained by the same method as the SUVmax. TLG was calculated as the product of the MTV and the SUVmean. The percentage change (Δ) in each of the parameters (P) between pre- and post-treatment was calculated using the following formula: $\Delta P=[(Ppre-Ppost)/Ppre] \times 100$

Response evaluation. PERCIST was used to evaluate the effect of CRT treatment, while RECIST (12) was used to evaluate the short-term outcome at 4 weeks after termination of CRT. Evaluations were made blinded to the ^{18}F-FDG PET/CT scans. The responders were defined as exhibiting a complete response (CR) or a partial response (PR) according to RECIST. Patients with an outcome of stable disease (SD) or progressive disease (PD) were subsequently classified as non-responders.

Statistical analysis. The Statistical Package for SSPS v.17.0 (SPSS, Inc., Chicago, IL, USA) was used. Quantitative data, including SUVmean, SUVmax, MTV and TLG, are expressed as mean ± standard deviation. Statistically significant differences between unpaired quantitative parameters were analyzed using Student's t-test. The difference in response evaluated by RECIST and PERCIST was analyzed using the χ^2 test. All P-values were two-sided, and statistical significance was indicated by $P<0.05$.

Results

Patient characteristics. Table I presents the clinical characteristics of all patients involved in the present study. ^{18}F-FDG PET/CT images were available for 14 patients. The median age of the study population was 64 years (range, 55-82 years), 71.4% of the participants were male and the proportion of never-smokers was 21.4%. All patients had histologically confirmed adenocarcinoma. According to the RECIST criterion (12), a total of 6 patients (1 with CR and 5 with PR) were assessable for response, and the overall response rate

Table I. Clinicopathological features of 14 patients with non-small cell lung cancer.

Characteristics	Value
Age, years[a]	64±8.91
Sex, n (%)	
Male	10 (71.4)
Female	4 (28.6)
Smoking status, n (%)	
Non-smoker	3 (21.4)
Smoker	11 (78.6)
Stage, n (%)	
IIIA	9 (64.3)
IIIB	5 (35.7)
RECIST, n (%)	
Complete response	1 (7.1)
Partial response	5 (35.7)
Stable disease	7 (50.0)
Progressive disease	1 (7.1)
PERCIST, n (%)	
Complete metabolic response	1 (7.15)
Partial metabolic response	7 (50.0)
Stable metabolic response	5 (35.7)
Progressive metabolic response	1 (7.1)

[a]Mean ± standard deviation. RECIST, Response Evaluation Criteria in Solid Tumors; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors.

was 42.9%. By contrast, 7 patients exhibited SD while only 1 patient exhibited PD.

^{18}F-FDG metabolic changes. The pre- and post-treatment ^{18}F-FDG uptake parameters, listed in Table II, were determined by two nuclear medicine physicians. SUVmax, SUVmean, MTV and TLG at baseline ^{18}F-FDG PET/CT scans exhibited no statistically significant differences between the responders and the non-responders (P>0.05). In the responders (42.9%), SUVmax fell from 11.7±4.3 to 5.0±3.9 following initial CRT. In the non-responders (57.1%), the SUVmax increased from 12.8±4.9 to 12.9±3.8. There was a mean reduction in SUVmax of 51.9% and an increase of 0.5% in responders and non-responders, respectively. The ΔSUVmax, ΔMTV and ΔTLG differed significantly between responders and non-responders (P=0.015, P=0.006 and P=0.004, respectively). Similarly, post-CRT SUVmax and CEA levels were significantly higher in responders compared with those in non-responders (P=0.009 and P=0.019, respectively). Fig. 1 depicts typical examples of ^{18}F-FDG PET/CT scans in patients with responding and non-responding tumors.

When applying the PERCIST at post-CRT ^{18}F-FDG PET/CT, 8/14 patients (57.1%) exhibited a CR or a PR, while 6/14 patients (42.9%) exhibited SD. The differences in outcome between the PERCIST and the RECIST evaluations were statistically significant (P=0.01) and the overall response rate was higher when evaluated by the former. This is consistent with the previous observation that cellular metabolism changes more rapidly than tumor size.

Discussion

Unresectable, locally advanced, stage III NSCLC remains a therapeutic challenge for oncologists. Despite the development of numerous treatment modalities the 5-year survival rate of patients with NSCLC remain unsatisfactory. Patients at the same stage of cancer and receiving the same treatment, may experience different outcomes (13). Therefore, prognostic tools are required in order to determine optimum treatment strategies. The present study investigated the role of ^{18}F-FDG PET/CT parameters in the prognosis prediction of NSCLC, such that any required dose-escalation or treatment addition could be put into effect without a break from therapy.

Observations of increased ^{18}F-FDG uptake in the majority of lung cancer types and subsequently reduced uptake following successful treatment have led to increased enthusiasm for the use of ^{18}F-FDG PET/CT in assessing therapeutic response (14,15). ^{18}F-FDG PET/CT is known to provide more time-efficient and more accurate results than those provided by standard morphological imaging (16). In addition, ^{18}F-FDG uptake can be used to predict the pathological response of residual metabolic activity in tumors following RT (17), and is a reliable prognostic factor for survival rate in patients with NSCLC (17-19). A number of researchers recommend a delay of 6-8 weeks or longer following RT prior to performing the post-treatment ^{18}F-FDG PET/CT scan (20). However, this would result in a break in therapy if the treatment regime were to be changed based on the findings of the scan. In the present study, ^{18}F-FDG PET/CT scans were repeated using 60-Gy RT, which reflects the final dose most frequently used clinically. Undertaking this analysis toward the end of treatment may be useful for determining whether or not additional dose escalation is required, and would allow adequate time to incorporate a boost treatment without requiring a break in therapy.

The SUV is currently the most widely used semi-quantitative parameter of ^{18}F-FDG uptake to evaluate therapeutic response in tumors. The RTOG 0235 trial (21) demonstrated that higher survival was significantly associated with a lower post-CRT peak SUV (P=0.02). Furthermore, Xu *et al* (22) and Bollineni *et al* (23) concluded that a lower post-CRT SUVmax was associated with higher regional and distant control rates (P=0.003 and P=0.002, respectively) in patients with NSCLC. It was also reported by the M.D. Anderson Cancer Center that the disease-free survival and OS time were associated with the post-RT SUVmax in patients with NSCLC (24). A meta-analysis of 18 trials revealed that a lower post-RT SUVmax was significantly associated with an improved local control rate and overall survival time (25). In line with this, the present study identified that the post-CRT SUVmax and ΔSUVmax differed significantly between responders and non-responders (P=0.009 and P=0.015, respectively).

However, SUVmax is a single-pixel value reflecting the maximum intensity of ^{18}F-FDG activity in tumors, and we therefore suggest that it does not account for changes in the distribution of a tracer within a lesion and in the extent of metabolic abnormality. Therefore, the alternative use of SUVmean,

Table II. Changes in the parameters of pre-treatment and post-treatment FDG PET/CT scans.

Parameters	All patients	Non-responders	Responders	P-value
SUVmax				
PET-1	12.16±4.34	12.81±4.94	11.72±4.32	0.721
PET-2	8.19±5.31	12.96±3.85	5.01±3.39	0.009
ΔP	28.92±40.10	-5.53±21.03	51.89±32.34	0.015
SUVmean				
PET-1	4.82±1.22	4.99±0.89	4.69±1.47	0.729
PET-2	3.81±1.42	4.74±1.35	3.19±1.17	0.088
ΔP	19.91±22.03	5.71±14.51	29.38±21.87	0.096
MTV				
PET-1	79.85±90.83	111.46±132.55	58.78±54.54	0.401
PET-2	50.53±93.29	114.54±129.91	7.86±8.77	0.072
ΔP	36.45±57.25	-16.69±35.69	71.88±37.01	0.006
TLG				
PET-1	405.76±503.81	612.96±765.01	267.62±220.20	0.316
PET-2	240.08±450.52	551.04±624.27	32.76±50.69	0.070
ΔP	42.48±52.71	-7.33±24.39	75.69±36.57	0.004

SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PET-1, pre-treatment PET scan; PET-2, post-treatment PET scan; ΔP, the difference between PET-2 and PET-1.

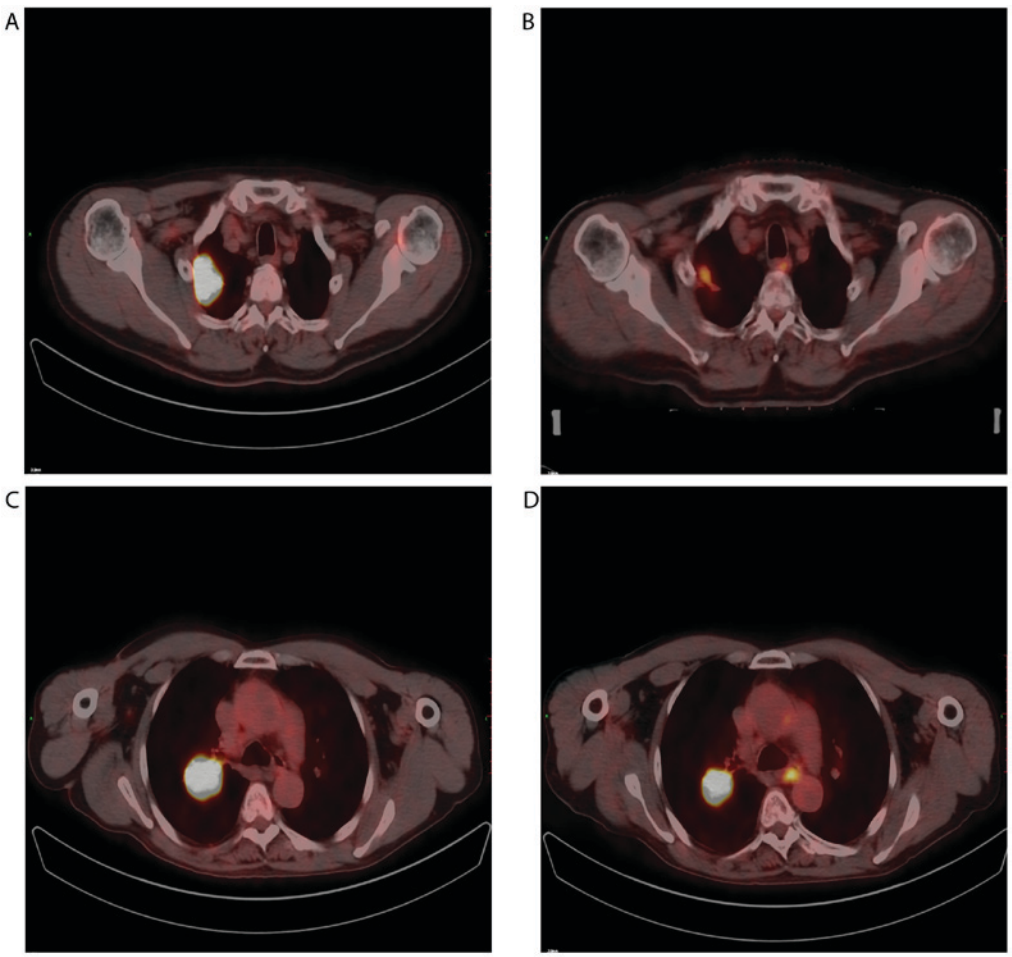

Figure 1. Typical examples of ^{18}F-FDG PET/CT scans in patients with non-responding and responding tumors. (A) Pre-treatment non-responding ^{18}F-FDG PET/CT; (B) post-treatment non-responding ^{18}F-FDG PET/CT; (C) pre-treatment responding ^{18}F-FDG PET/CT; (D) post-treatment responding ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography.

MTV and TLG, which incorporate the tumor size and its metabolism, is proposed. The MTV is assessed using semi-automatic analysis, which configures the volume of the metabolically active areas of the tumor with an SUV value of 2.5. TLG is then calculated as the product of SUVmean and MTV. A study undertaken by Satoh *et al* (26) revealed that MTV and TLG were reliable predictive parameters of disease-free survival, while SUVmax was not, suggesting that MTV and TLG may be more reliable variables than SUVmax for predicting outcomes in NSCLC. The same study also speculated that as tumors become larger, the single-voxel-based SUVmax is less likely to reflect the overall aggressiveness of the tumor, as it does not consider the volume of the metabolically active areas. A study undertaken by Lee *et al* (27) reported that, when used in isolation, high MTV values reflecting tumor burden are poor prognostic variables for disease progression and survival in patients with stage I-IV NSCLC. An increase of 25 cm^3 in the MTV value resulted in a 5.4-fold increase in the risk of disease progression and a 7.6-fold increase in the risk of mortality. Therefore, the present study also incorporated these parameters. Furthermore, it was concluded that ΔSUVmax, ΔMTV and ΔTLG all differed significantly between responders and non-responders (P=0.015, P=0.006 and P=0.004, respectively), while no significant difference was observed in either the pre- or post-treatment parameters between responders and non-responders. Due to the fact that TLG represents a combination of SUV and MTV, and MTV represents the degree of ^{18}F-FDG uptake and the volume of metabolically active tumors, these parameters may offer an improved metabolic index of tumor burden.

The present study only included cases of histopathologically confirmed primary adenocarcinoma, as previous literature had reported that the type of pathology may affect the uptake of ^{18}F-FDG. For example, Casali *et al* (28) reported that the SUVmax was significantly associated with histological subtypes; the median SUVmax was 5.1 in patients with adenocarcinoma and 8.3 in those with other types of NSCLC. Adenocarcinomas also exhibited a significantly lower SUVmax than that observed in the other tumor types (P<0.001). Additionally, Vesselle *et al* (29) reported that adenocarcinomas exhibited reduced ^{18}F-FDG uptake and lower Ki-67 scores than those of squamous cell carcinomas or large cell undifferentiated carcinomas. Therefore, only patients with adenocarcinoma were included in the present study in order to minimize the effects of different histological subtypes.

As it has been reported that the assessment of the predictive value of SUVmax for NSCLC requires consideration of primary tumor size, the evidence acquired here is not sufficient to suggest that ^{18}F-FDG uptake could provide prognostic information in a primary NSCLC (30). Furthermore, tumor size has been revealed to be a significant factor in prognosis, and thus survival in NSCLC. Notably, a number of studies have demonstrated that SUVmax increases with increasing tumor size (31). Clinical studies undertaken by Takeda *et al* (32) demonstrated that a tumor size >5 cm was markedly associated with a poor prognosis at 5-year survival rate in patients with NSCLC. For the aforementioned reasons, tumor size was also considered in the present study, but was identified to not significantly impact SUVmax and SUVmean (P=0.216 and P=0.349, respectively; data not shown).

In conclusion, the present study demonstrated that ^{18}F-FDG PET/CT scans could differentiate responders from non-responders in advanced NSCLC patients following CRT, as post-CRT SUVmax, ΔSUVmax, ΔMTV and ΔTLG were all significantly associated with the response of the lesion. This finding may aid in deciding upon future treatment options, including changes in dosages and the incorporation of boost treatments. Furthermore, the relative speed with which the results can be obtained would remove the requirement for a break in therapy. However, further clinical studies including larger patient populations are required to fully establish the potential of this approach.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

XZ performed the research and drafted the manuscript. YZ participated in the design of the study and performed the statistical analysis. YY conceived the study, participated in its design and coordination, and assisted in drafting the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards and Ethics Committees of Shandong Cancer Hospital Affiliated to Shandong University. Informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ramalingam SS, Owonikoko TK and Khuri FR: Lung cancer: New biological insights and recent therapeutic advances. CA Cancer J Clin 61: 91-112, 2011.
2. Ladanyi M and Pao W: Lung adenocarcinoma: Guiding EGFR-targeted therapy and beyond. Mod Pathol 21 (Suppl 2): S16-S22, 2008.
3. Martin J, Ginsberg RJ, Venkatraman ES, Bains MS, Downey RJ, Korst RJ, Kris MG and Rusch VW: Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. J Clin Oncol 20: 1989-1995, 2002.

4. Strauss LT, Herndon J, Chang J, Parker WY, Levy DA, Bowens SB, Zane SB and Berg CJ,CDC: Abortion surveillance-United States, 2001. MMWR Surveill Summ 53: 1-32, 2004.
5. Spiro SG and Silvestri GA: One hundred years of lung cancer. Am J Respir Crit Care Med 172: 523-529, 2005.
6. Dwamena BA, Sonnad SS, Angobaldo JO and Wahl RL: Metastases from non-small cell lung cancer: Mediastinal staging in the 1990s-meta-analytic comparison of PET and CT. Radiology 213: 530-536, 1999.
7. Cerfolio RJ, Ojha B, Bryant AS, Raghuveer V, Mountz JM and Bartolucci AA: The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with nonsmall cell lung cancer. Ann Thorac Surg 78: 1017-1023, 2004.
8. Mac MMP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK and Ball DL: Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. J Clin Oncol 21: 1285-1292, 2003.
9. Novello S, Vavala T, Levra MG, Solitro F, Pelosi E, Veltri A and Scagliotti GV: Early response to chemotherapy in patients with non-small-cell lung cancer assessed by [18F]-fluoro-deoxy-D-glucose positron emission tomography and computed tomography. Clin Lung Cancer 14: 230-237, 2013.
10. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds): American Joint Committee on Cancer (AJCC) From the AJCC Cancer Staging Manual. 7th edition. Springer-Verlag, New York, NY, 2010.
11. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5: 649-655, 1982.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
13. Birim O, Kappetein AP, van Klaveren RJ and Bogers AJ: Prognostic factors in non-small cell lung cancer surgery. Eur J Surg Oncol 32: 12-23, 2006.
14. Weber WA, Petersen V, Schmidt B, Tyndale-Hines L, Link T, Peschel C and Schwaiger M: Positron emission tomography in non-small-cell lung cancer: Prediction of response to chemotherapy by quantitative assessment of glucose use. J Clin Oncol 21: 2651-2657, 2003.
15. Hoekstra CJ, Stroobants SG, Smit EF, Vansteenkiste J, van Tinteren H, Postmus PE, Golding RP, Biesma B, Schramel FJ, van Zandwijk N, *et al*: Prognostic relevance of response evaluation using [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. J Clin Oncol 23: 8362-8370, 2005.
16. Shiraishi K, Nomori H, Ohba Y, Kaji M, Mori T, Shibata H, Oya N and Sasaki J: Repeat FDG-PET for predicting pathological tumor response and prognosis after neoadjuvant treatment in nonsmall cell lung cancer: Comparison with computed tomography. Ann Thorac Cardiovasc Surg 16: 394-400, 2010.
17. Yamamoto Y, Nishiyama Y, Monden T, Sasakawa Y, Ohkawa M, Gotoh M, Kameyama K and Haba R: Correlation of FDG-PET findings with histopathology in the assessment of response to induction chemoradiotherapy in non-small cell lung cancer. Eur J Nucl Med Mol Imaging 33: 140-147, 2006.
18. Eschmann SM, Friedel G, Paulsen F, Reimold M, Hehr T, Budach W, Dittmann H, Langen HJ and Bares R: Repeat 18F-FDG PET for monitoring neoadjuvant chemotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 55: 165-171, 2007.
19. Mac MMP, Hicks RJ, Matthews JP, Wirth A, Rischin D and Ball DL: Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. Lung Cancer 49: 95-108, 2005.
20. Avril NE and Weber WA: Monitoring response to treatment in patients utilizing PET. Radiol Clin North Am 43: 189-204, 2005.
21. Machtay M, Duan F, Siegel BA, Snyder BS, Gorelick JJ, Reddin JS, Munden R, Johnson DW, Wilf LH, DeNittis A, *et al*: Prediction of survival by [18F]fluorodeoxyglucose positron emission tomography in patients with locally advanced non-small-cell lung cancer undergoing definitive chemoradiation therapy: Results of the ACRIN 6668/RTOG 0235 trial. J Clin Oncol 31: 3823-3830, 2013.
22. Xu X, Yu J, Sun X, Yang G, Li K, Fu Z, Han A and Zheng J: The prognostic value of 18F-fluorodeoxyglucose uptake by using serial positron emission tomography and computed tomography in patients with stage III nonsmall cell lung cancer. Am J Clin Oncol 31: 470-475, 2008.
23. Bollineni VR, Widder J, Pruim J, Langendijk JA and Wiegman EM: Residual ^{18}F-FDG-PET uptake 12 weeks after stereotactic ablative radiotherapy for stage I non-small-cell lung cancer predicts local control. Int J Radiat Oncol Biol Phys 83: e551-e555, 2012.
24. Lopez Guerra JL, Gladish G, Komaki R, Gomez D, Zhuang Y and Liao Z: Large decreases in standardized uptake values after definitive radiation are associated with better survival of patients with locally advanced non-small cell lung cancer. J Nucl Med 53: 225-233, 2012.
25. Na F, Wang J, Li C, Deng L, Xue J and Lu Y: Primary tumor standardized uptake value measured on F18-Fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: Meta-analysis. J Thorac Oncol 9: 834-842, 2014.
26. Satoh Y, Onishi H, Nambu A and Araki T: Volume-based parameters measured by using FDG PET/CT in patients with stage I NSCLC treated with stereotactic body radiation therapy: Prognostic value. Radiology 270: 275-281, 2014.
27. Lee P, Weerasuriya DK, Lavori PW, Quon A, Hara W, Maxim PG, Le QT, Wakelee HA, Donington JS, Graves EE and Loo BW Jr: Metabolic tumor burden predicts for disease progression and death in lung cancer. Int J Radiat Oncol Biol Phys 69: 328-333, 2007.
28. Casali C, Cucca M, Rossi G, Barbieri F, Iacuzio L, Bagni B and Uliano M: The variation of prognostic significance of Maximum Standardized Uptake Value of [18F]-fluoro-2-deoxy-glucose positron emission tomography in different histological subtypes and pathological stages of surgically resected non-small cell lung carcinoma. Lung Cancer 69: 187-193, 2010.
29. Vesselle H, Salskov A, Turcotte E, Wiens L, Schmidt R, Jordan CD, Vallières E and Wood DE: Relationship between non-small cell lung cancer FDG uptake at PET, tumor histology, and Ki-67 proliferation index. J Thorac Oncol 3: 971-978, 2008.
30. Ikushima H, Dong L, Erasmus J, Allen P, McAleer MF, Zhuang Y, Sasaki R and Komaki R: Predictive value of 18F-fluorodeoxyglucose uptake by positron emission tomography for non-small cell lung cancer patients treated with radical radiotherapy. J Radiat Res 51: 465-471, 2010.
31. Mery CM, Pappas AN, Burt BM, Bueno R, Linden PA, Sugarbaker DJ and Jaklitsch MT: Diameter of non-small cell lung cancer correlates with long-term survival: Implications for T stage. Chest 128: 3255-3260, 2005.
32. Takeda S, Fukai S, Komatsu H, Nemoto E, Nakamura K and Murakami M; Japanese National Chest Hospital Study Group: Impact of large tumor size on survival after resection of pathologically node negative (pN0) non-small cell lung cancer. Ann Thorac Surg 79: 1142-1146, 2005.