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Prognostic value of quantitative PET/CT in patients with a non-small cell lung cancer and another primary cancer

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Abstract

Objective—The staging and management of patients with newly diagnosed non-small cell lung cancer (NSCLC) in the setting of recently diagnosed other (metachronous or synchronous) primary cancer are challenging. This retrospective cohort study was conducted to test our hypothesis that baseline FDG PET/CT parameters, including whole-body metabolic tumor volume (MTV_{WB}), total lesion glycolysis (TLG_{WB}) and maximum standardised uptake value (SUV_{maxWB}) are associated with overall survival (OS) of such patients.

Materials and Methods—A total of 110 NSCLC patients (52 men and 58 women, aged 68.6 ± 7.8 years) with other primary malignant cancers who had baseline FDG PET/CT scans were retrospectively reviewed. MTV_{WB}, TLG_{WB} and SUV_{maxWB} were measured. Kaplan-Meier analysis with the log-rank test and Cox regression models were used to assess the association of OS with FDG PET/CT parameters and clinical risk factors.

Results—Kaplan-Meier analysis and univariate Cox regression models demonstrated significant associations of OS with ln(MTV_{WB}), ln(TLG_{WB}), ln(SUV_{maxWB}), TNM stage, and treatment type

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(surgery versus no treatment). Multivariable Cox regression models showed a significant relationship of OS with $\ln(\text{MTV}_{\text{WB}})$ ($HR = 1.368$, $P = 0.001$), $\ln(\text{TLG}_{\text{WB}})$ ($HR = 1.313$, $P < 0.001$) and $\ln(\text{SUV}_{\text{maxWB}})$ ($HR = 1.739$, $P = 0.006$), adjusted for age, treatment type, tumor histology, and TNM stage. TNM stage was not significantly associated with OS when MTV_{WB} , TLG_{WB} or $\text{SUV}_{\text{maxWB}}$ were included in the multivariable models.

Conclusion— MTV_{WB} , TLG_{WB} , and $\text{SUV}_{\text{maxWB}}$ from baseline FDG PET/CT are individually associated with OS of patients with both NSCLC and other primary malignant tumors; independent on age, treatment type, tumor histology and TNM stage.

Keywords

FDG; non-small cell lung cancer; survival analysis; metabolic tumor burden; synchronous cancer; metachronous cancer

Introduction

The presence of an additional primary tumor in a lung cancer patient is not uncommon. Duchateau *et al* [1] showed that 17.2% of patients with NSCLC had a history of another primary malignancy and 4% of NSCLC patients had two or more other primary malignant tumors in addition to non-small cell lung cancer (NSCLC). The TNM staging and management of such NSCLC patients are usually not complicated if the metachronous primary cancer has been in remission for years. One study demonstrated that recurrence-free probabilities of NSCLC at 3 years and 5 years from the point of 5 years after NSCLC tumor resection were 92% and 87%, respectively [2]. The 5-year recurrence-free probabilities from the point of 5 years after complete NSCLC tumor resection were 65 to 89%, dependent on lymph node involvement and presence of intratumoral vascular invasion [2]. Another study found that the 5-year recurrence-free probability from the point 5 years after primary tumor resection was 93% in stage IA NSCLC (3). However, the staging and treatment of recently diagnosed NSCLC patients who have another recent metachronous primary cancer or another synchronous primary cancer are challenging, due to the difficulty in distinguishing NSCLC metastases from recurrence or metastases of the other metachronous primary cancer or synchronous primary cancer. Therefore, treatment decision making is difficult and standardised treatment for such patients has not been established.

One method of facilitating decision making in this situation is to establish tumor aggressiveness by using maximum standardised uptake value ($\text{SUV}_{\text{maxWB}}$), and to assess metabolic tumor burden by using whole-body metabolic tumor volume (MTV_{WB}) and total lesion glycolysis (TLG_{WB}) on FDG PET/CT. To our knowledge, the relationship between these quantitative PET measurements and OS in NSCLC patients with other primary tumors has not been reported. The $\text{SUV}_{\text{maxWB}}$, MTV_{WB} , and TLG_{WB} have been found to be strongly associated with overall survival (OS) in patients with NSCLC [3–7]. An important association has also been demonstrated between patient survival and metabolic tumor burden in other types of cancer such as small cell lung cancer, head and neck cancer, thyroid cancer, pancreatic cancer, breast cancer, oesophageal carcinoma and gynaecological malignancies [8–14]. We hypothesise that MTV_{WB} , TLG_{WB} and $\text{SUV}_{\text{maxWB}}$ are associated with OS in

patients who have a NSCLC and another metachronous or synchronous primary cancers. This study was performed to test this hypothesis.

Materials and Methods

This study was approved by our institutional review board, and the requirement to obtain informed consent was waived.

Inclusion and Exclusion Criteria

Identification of patients with pre-treatment PET/CT was done in two steps: 1) merging the list of all patients with histopathologically confirmed NSCLC who were diagnosed and/or treated in our hospital (identified by our Cancer Registry personnel based on ICD 9 diagnosis codes) with the list of all FDG PET/CT patients between February of 2004 and December of 2014, which gave us the list of all NSCLC patients who had an FDG PET/CT study and were treated in our medical centre; and 2) all those NSCLC patients who met the following inclusion criteria were initially selected from the merged list: (a) had a baseline whole-body FDG PET/CT scan before initial treatment of NSCLC in our medical centre, (b) no known brain metastasis (our standard FDG PET/CT scan does not cover the entire brain), and (c) with a diagnosis of another type of metachronous or synchronous primary cancer besides NSCLC. Based on the SEER definition [15], we defined the other primary cancer as “synchronous” if it was diagnosed within 2 months either before or after the FDG PET/CT scan was conducted for the evaluation of current NSCLC; otherwise the other cancers were classified as “metachronous”. NSCLC patients presenting with metachronous primary cancer(s) more than two months after the FDG PET scan for the diagnosis or staging of NSCLC were excluded from this study since the other primary cancer(s) was unknown at the time of managing the NSCLC. NSCLC patients with a history of metachronous primary cancer(s) diagnosed more than five years before the FDG PET scan for the diagnosis or staging of NSCLC were also excluded as their current NSCLC staging and their management was not expected to be complicated by their history of metachronous primary cancer(s) because most cancer recurrence occurs within the first 5 years after treatment [2]. Patients with prior history of basal cell carcinoma of the skin were also excluded from the study, as such tumors rarely metastasize [16].

Clinical and Survival Data

Clinical data relevant to OS were collected by our Cancer Registry and confirmed by the authors (XZ, FL, TW, YP), including patient's age, gender, date of the baseline FDG PET/CT, NSCLC and histopathology, cancer therapy, and date of diagnosis of the other metachronous or synchronous primary cancer(s). The clinical TNM stage was assigned to each patient according the 7th edition of AJCC TNM staging system for lung cancer based on FDG PET/CT and diagnostic CT [17]. The NSCLC treatment plans for all subjects were determined by the patient's care oncologist(s) at the time of initial management. The NSCLC treatment types used for the analyses in this study included “surgery” with curative intent (surgery alone or in combination with chemotherapy, radiation therapy or chemotherapy plus radiation therapy), “other treatments” (chemotherapy, radiation therapy and chemotherapy plus radiation therapy), and no cancer treatment.

OS was the primary end point of the study and was defined as the interval from the date of the baseline FDG PET/CT to the date the patient died of any cause or the date of last contact. Patients who were last known to be alive were censored at the date of last contact.

FDG PET/CT Data Acquisition and Analysis

All the patients underwent a whole-body FDG PET/CT scan from mid-thigh to mid-head, in accordance with the National Cancer Institute guidelines [18]. In our medical centre, all patients fasted for at least 4 h before intravenous administration of 370–555 MBq of ^{18}F -FDG. A whole-body static PET scan was acquired starting at the thighs and proceeding to the skull base 90 ± 30 min following injection of the ^{18}F -FDG. The plasma glucose levels of all patients were less than 200 mg/dl before FDG administration. An early group of 70 (63.6%) patients from February 2004 to February 2012 had FDG PET/CT scans performed with a scanner equipped with high-resolution bismuth germanate detectors and a dual-slice CT (Reveal HD, CTI, Knoxville, TN, USA). These PET images were acquired and reconstructed as described in a prior study [6]. In brief, PET scans were obtained with an acquisition time of 3–5 min per cradle position, with a 26.6% axial overlap at the borders of the field of view to avoid artefacts. PET images were reconstructed using ordered-subsets expectation maximisation (OSEM) iterative algorithms with 8 subsets, 2 iterations, and 128×128 pixels. The slice thickness was 2.4 mm, the pixel size within transverse slices was 5.2 mm, with 5 mm full-width at half-maximum (FWHM) three-dimensional (3D) Gaussian smoothing after reconstruction. We used the 3D imaging mode with Fourier rebinning and analytic scatter correction. In a later group of 24 (21.8%) patients from April, 2012 to November 2014, PET studies were acquired on a Siemens mCT scanner equipped with lutetium oxyorthosilicate (LSO) scintillator crystals, time-of-flight, and a 64 slice CT (Siemens Healthcare, Knoxville, Tennessee, USA). These PET images were reconstructed by using time of-flight ordered-subsets expectation maximisation iterative reconstruction with 24 subsets, 2 iterations. The image matrix was 256×256 , corresponding to a 3-mm in-plane pixel size with a plane thickness of 3 mm. Both PETs were calibrated to be accurate against our dose calibrator. In an additional 16 patients (14.5%) from Feb 2009 to December 2014, technically adequate whole-body FDG PET/CT scans were obtained from external imaging centres.

All PET image analysis was conducted with the PET Edge tool of the MIM software (MIM Software Inc, Cleveland, OH, USA) which uses a gradient method, as described in prior studies (Fig. 1) [4,6]. The MTV, TLG, and SUV_{max} of all the FDG-avid tumors throughout the whole body were measured by a radiologist who has 10 years of experience in general radiology and was trained in FDG PET/CT (XZ). A nuclear radiologist with more than 10 years of experience in FDG PET checked every case the general radiologist measured. The procedure was the same as described previously [6]. Both of the readers were blinded to patient survival status and survival time but not blinded to the clinical information. They also made use of the PET/CT report and the diagnostic CT report.

Statistical Analysis

Survival curves for OS were constructed using the Kaplan-Meier method and log-rank tests were carried out to evaluate OS differences among different patient groups.

The natural logarithmic transformation of the continuous variables (MTV_{WB} , TLG_{WB} , and SUV_{maxWB}) was used to achieve more normally distributed data. Univariate and multivariable Cox proportional hazards models [19] were used to evaluate the association between OS and potential prognostic variables, including $\ln(MTV_{WB})$, $\ln(TLG_{WB})$, $\ln(SUV_{maxWB})$, age, gender, lung cancer histological subtype, TNM stage, and lung cancer treatment type. All the variables in the Cox models satisfied the proportional-hazards assumption, as tested using Schoenfeld residuals. In order to perform multivariable Cox proportional hazards analyses, a correlation coefficient matrix and the variance inflation factor (VIF) were calculated to check for the problem of multicollinearity. The potential risk variables with either a P value less than 0.15 in the univariate Cox proportional hazards models, or established clinical importance for OS, were included in a series of multivariable models. The Gonen and Heller's Concordance indices (GHCI), with a range from 0 to 1, provided a global assessment of the fitted Cox proportional hazard models and bootstrap methods were used to estimate the accuracies of GHCI after model selection. All statistical tests were performed using STATA/SE software version 14 (StataCorp LP, Texas) and a two-tailed P value <0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

There were 203 consecutive NSCLC patients with a diagnosis of another type of primary cancer diagnosed/treated in our hospital. Eighteen patients were excluded because the metachronous primary cancer(s) were confirmed more than 2 months following the FDG PET/CT scan for the evaluation of NSCLC, and another 75 patients were excluded because their metachronous primary cancer(s) were diagnosed more than 5 years before their NSCLC diagnosis. Therefore, 110 patients (52 men, 58 women; mean age of 68.6 years) were finally included in this study. One hundred and three patients presented with only one metachronous or synchronous primary cancer besides NSCLC, and seven patients had two metachronous or synchronous primary cancers.

Among the 103 patients with one other primary cancer, 47 patients had one other synchronous cancer and 56 patients had one other metachronous cancer. Among the seven patients with two other primary cancers, one patient had two other synchronous cancers, four patients had two other metachronous cancers, and two patients had one other metachronous and one other synchronous cancer. In total, among the 110 patients in the current study, there were 117 other primary cancers, including 51 synchronous cancers and 66 metachronous cancers.

The characteristics of the patients are summarised in Table 1. The origins of the other metachronous or synchronous primary cancers are shown in Table 2. The median of the time interval between PET/CT scans and the diagnosis date of other synchronous cancer was one day before the PET/CT (range: 57 days before PET/CT to 60 days after PET/CT), while the median of the corresponding time interval for metachronous primary cancer was 1045 days (range: 69 to 1825 days before PET/CT). Seventy-three patients died during follow-up. The median survival time was 2.4 years (95% confidence interval 0.9 to 4.3 years).

Kaplan-Meier analysis and the log-rank test

There were statistically significant differences in OS between the groups separately dichotomised by the median values of MTV_{WB} ($P < 0.001$), TLG_{WB} ($P < 0.001$), and SUV_{maxWB} ($P < 0.001$). Increased survival was observed in the patients with low values of these measures (Fig. 2). There was also a statistically significant association of OS with TNM stage ($P = 0.003$) and treatment type ($P < 0.001$). No statistically significant association was observed between OS and quartiles of age ($P = 0.175$), gender ($P = 0.371$), or NSCLC histological subtype ($P = 0.385$).

Univariate Cox regression analysis

The univariate Cox regression analysis results are shown in Table 3. There was a significant association of OS with ln(MTV_{WB}) ($P < 0.001$), ln(TLG_{WB}) ($P < 0.001$), ln(SUV_{maxWB}) ($P < 0.001$), TNM stage (stage III versus stage I, $P < 0.001$; and stage IV versus stage I, $P < 0.01$), and one of the lung cancer treatment type ("surgery" compared with no treatment, $P < 0.001$). The HR was 1.477 for ln(MTV_{WB}), 1.372 for ln(TLG_{WB}), and 1.983 for ln(SUV_{maxWB}), respectively. The HRs of TNM stage III and IV were 2.70 and 2.806 compared with stage I, respectively. The HR for "surgery" compared with no cancer treatment was 0.228. Patient's age, gender, and tumor histology were not significantly associated with OS (all $P > 0.05$). Based on 500 bootstrap replicates, the GHCI with 95% confidence intervals for models containing ln(MTV_{WB}), ln(TLG_{WB}), and ln(SUV_{maxWB}) are shown in Table 3. The GHCI values and their 95% confidence limits for ln(MTV_{WB}) and ln(TLG_{WB}), were similar, and significantly greater than that of TNM stage (both $P < 0.05$). The GHCI of ln(SUV_{maxWB}) was not significantly different from that of TNM stage ($P = 0.183$).

Multivariable Cox regression models

A correlation coefficient matrix showed that ln(TLG_{WB}) was strongly correlated with ln(MTV_{WB}) ($r_s = 0.97$) and ln(SUV_{maxWB}) ($r_s = 0.84$), and ln(SUV_{maxWB}) was moderately correlated with ln(MTV_{WB}) ($r_s = 0.72$) [20]. The VIF of ln(MTV_{WB}) was 35.4 and that of ln(TLG_{WB}) was 51.3, suggesting that problems could be caused by multicollinearity between these variables, while that of ln(SUV_{maxWB}) was 5.1. Therefore three final multivariable Cox regression models were established using ln(MTV_{WB}), ln(TLG_{WB}), or ln(SUV_{maxWB}) separately, and they showed that ln(MTV_{WB}), ln(SUV_{maxWB}), and ln(SUV_{maxWB}) were significantly associated with patient OS (all $P < 0.01$), even after adjusting for patient age, NSCLC clinical TNM stage, tumor histology and treatment type. Patients who had "surgery" were associated with better OS compared with no cancer treatment (all $P < 0.001$ in the models containing ln(MTV_{WB}), ln(TLG_{WB}), and ln(SUV_{maxWB}), respectively. TNM stages (stage II, III and IV relative to stage I) were not significantly associated with OS in the multivariable Cox regression models (all $P > 0.05$). Based on 500 bootstrap replicates, the GHCI values and their 95% confidence limits for ln(MTV_{WB}), ln(TLG_{WB}), and ln(SUV_{maxWB}) were similar in the multivariable models (Table 4).

Discussion

Quantitative PET measures such as TLG_{WB} , MTV_{WB} , and SUV_{maxWB} have been shown to be significantly associated with patient OS in different types of malignant tumors including NSCLC (4–15). This study demonstrates that baseline TLG_{WB} , MTV_{WB} , and SUV_{maxWB} are independently associated with the OS of patients with a NSCLC and another metachronous or synchronous primary cancer, even after adjusting for patient age, TNM stage, tumor histology and cancer therapy type. Patients with lower MTV_{WB} , TLG_{WB} , and SUV_{maxWB} had better OS. The potential clinical implication is to use MTV_{WB} , TLG_{WB} , and/or SUV_{maxWB} to further stratify patients into different risk groups, as shown in Fig. 2.

MTV_{WB} and TLG_{WB} measurements have not been widely used in clinical practice because manual segmentation of the tumor contour is time consuming. However, with advances in computer-software, it has become less time consuming and practical for clinical use. Recently we have demonstrated that semi-automatic tumor segmentation and quantification can be used on primary tumors of NSCLC for this purpose and is much less time consuming than manual tumor segmentation and quantification [21]. In the current study, the tumor was segmented semi-automatically. The radiologists identified the centre and long and short axes of each tumor in the body, then the computer program automatically segmented the tumor. In rare cases, manual adjustment may be needed to segment the tumor. We also have demonstrated that MTV measurement of the primary tumor in NSCLC varies less than SUV measurement between 1 hour and 2 hours after FDG injection [22]. In addition, our group and others have also demonstrated that MTV_{WB} and TLG_{WB} have low inter-observer variability [3,6,7].

The SUV_{max} of the primary lung tumor has been the most commonly measured PET parameter when analysing the prognostic capability of PET [23]. Although it remains a subject of debate whether SUV_{max} provides additional prognostic information compared to TNM stage [24,25], in this study the whole-body tumor SUV_{max} did show a statistically significant association with the patient OS in both univariate and multivariable Cox regression analyses; even after adjusting for other prognostic factors, including TNM stage.

As expected, the current study demonstrated strong correlations of TLG_{WB} with MTV_{WB} , and SUV_{maxWB} ; since TLG by its definition is the product of MTV and SUV_{mean} . Therefore we think that MTV_{WB} and TLG_{WB} are interchangeable in potential clinical applications of this study. But the correlation between MTV_{WB} and SUV_{maxWB} was moderate and they represent different PET tumor characteristics, whole-body metabolic tumor burden and intensity of glucose metabolic activity, respectively.

The TNM stage is sometimes difficult to determine in NSCLC patients with a recent history of metachronous primary cancer or synchronous primary cancer; the tumors could be due to NSCLC or recurrence/metastasis of other metachronous primary cancer or a synchronous other primary tumor. Our study failed to demonstrate a significant association of TNM stage with patients' OS in the multivariable Cox regression models that contained $\ln(MTV_{WB})$, $\ln(TLG_{WB})$, or $\ln(SUV_{WB})$. This suggests that quantitative PET/CT measurement can provide additional prognostic information not available from TNM stage.

Although it is difficult to eliminate possible patient selection bias since the patients were managed based on their health conditions and tumor stage in this retrospective study, it is worth mentioning that the Kaplan-Meier analysis, univariate, and multivariable Cox regression models consistently demonstrated better OS in “surgically” treated patients than in those who were not treated with cancer therapies, even after adjustment for age and TNM stage as well as metabolic tumor burden [$\ln(\text{MTV}_{\text{WB}})$ or $\ln(\text{TLG}_{\text{WB}})$] or FDG uptake [$\ln(\text{SUV}_{\text{maxWB}})$] (here “surgically” treated means any therapy that included surgery).

There are some potential limitations to our study. First, this is a retrospective study and the results need to be further verified by other retrospective studies with large sample size or by prospective observational studies. Second, we didn't divide the patients into subgroups according to their other primary cancer type because of the relatively small sample size. The other primary cancers in this study cohort were heterogeneous in location, most commonly taking place in the lung or breast, followed by the head and neck, and, finally, the urinary system. Thirdly, the performance status was not included in our survival analyses because not all patients included in this study had their performance status recorded in their medical records. However, the association of the performance status and OS has not been consistently demonstrated in the literature [26–28]. Poor performance status can, in some cases, be due to high tumor burden [26].

Conclusion

MTV_{WB} , TLG_{WB} , and $\text{SUV}_{\text{maxWB}}$ from the baseline FDG PET/CT are individually associated with OS of patients with both NSCLC and metachronous or synchronous primary malignant tumors; independent on age, treatment type, tumor histology and TNM stage.

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References

1. Duchateau CS, Stokkel MP. Second primary tumors involving non-small cell lung cancer: prevalence and its influence on survival. *Chest*. 2005; 127(4):1152–1158. [PubMed: 15821189]
2. Maeda R, Yoshida J, Hishida T, Aokage K, Nishimura M, Nishiwaki Y, et al. Late recurrence of non-small cell lung cancer more than 5 years after complete resection: incidence and clinical implications in patient follow-up. *Chest*. 2010; 138(1):145–150. [PubMed: 20382716]
3. Zhang H, Wroblewski K, Liao S, Kampalath R, Penney BC, Zhang Y, et al. Prognostic value of metabolic tumor burden from (18)F-FDG PET in surgical patients with non-small-cell lung cancer. *Acad Radiol*. 2013; 20(1):32–40. [PubMed: 22999369]
4. Zhang H, Wroblewski K, Appelbaum D, Pu Y. Independent prognostic value of whole-body metabolic tumor burden from FDG-PET in non-small cell lung cancer. *International journal of computer assisted radiology and surgery*. 2013; 8(2):181–191. [PubMed: 22644386]

5. Liao S, Penney BC, Zhang H, Suzuki K, Pu Y. Prognostic value of the quantitative metabolic volumetric measurement on 18F-FDG PET/CT in Stage IV nonsurgical small-cell lung cancer. *Academic radiology*. 2012; 19(1):69–77. [PubMed: 22142679]
6. Liao S, Penney BC, Wroblewski K, Zhang H, Simon CA, Kampalath R, et al. Prognostic value of metabolic tumor burden on 18F-FDG PET in nonsurgical patients with non-small cell lung cancer. *European journal of nuclear medicine and molecular imaging*. 2012; 39(1):27–38. [PubMed: 21946983]
7. Chen HH, Chiu NT, Su WC, Guo HR, Lee BF. Prognostic value of whole-body total lesion glycolysis at pretreatment FDG PET/CT in non-small cell lung cancer. *Radiology*. 2012; 264(2): 559–566. [PubMed: 22692034]
8. Oh JR, Seo JH, Chong A, Min JJ, Song HC, Kim YC, et al. Whole-body metabolic tumour volume of 18F-FDG PET/CT improves the prediction of prognosis in small cell lung cancer. *European journal of nuclear medicine and molecular imaging*. 2012; 39(6):925–935. [PubMed: 22270509]
9. Pak K, Cheon GJ, Nam HY, Kim SJ, Kang KW, Chung JK, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2014; 55(6):884–890.
10. Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, et al. Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. *The Journal of clinical endocrinology and metabolism*. 2000; 85(3):1107–1113. [PubMed: 10720047]
11. Lee JW, Kang CM, Choi HJ, Lee WJ, Song SY, Lee JH, et al. Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis on Preoperative (1)(8)F-FDG PET/CT in Patients with Pancreatic Cancer. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2014; 55(6):898–904.
12. Son SH, Lee SW, Jeong SY, Song BI, Chae YS, Ahn BC, et al. Whole-Body Metabolic Tumor Volume, as Determined by F-FDG PET/CT, as a Prognostic Factor of Outcome for Patients With Breast Cancer Who Have Distant Metastasis. *AJR Am J Roentgenol*. 2015:1–8. [PubMed: 25539228]
13. Lemarignier C, Di Fiore F, Marre C, Hapdey S, Modzelewski R, Gouel P, et al. Pretreatment metabolic tumour volume is predictive of disease-free survival and overall survival in patients with oesophageal squamous cell carcinoma. *European journal of nuclear medicine and molecular imaging*. 2014; 41(11):2008–2016. [PubMed: 25037871]
14. Miller TR, Grigsby PW. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. *International journal of radiation oncology, biology, physics*. 2002; 53(2):353–359.
15. Lynch, C. The Biology of Multiple Primary Cancers. In: Howes, H., editor. *A Review of the Definition for Multiple Primary Cancers in the United States Workshop Proceedings From December 4–6, 2002*. Princeton, New Jersey: Springfield (IL): North American Association of Central Cancer Registries; 2003 May.
16. Vu A, Laub D Jr. Metastatic Basal cell carcinoma: a case report and review of the literature. *Eplasty*. 2011; 11:ic8. [PubMed: 21559224]
17. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007; 2(8):706–714. [PubMed: 17762336]
18. Shankar LK, Hoffman JM, Bacharach S, Graham MM, Karp J, Lammertsma AA, et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2006; 47(6):1059–1066.
19. Hair RA, JF.; Tatham, RL.; Black, WC. *Multivariate Data Analysis*. 7th. Prentice Hall; 2009.
20. Lee HS, Kim HO, Hong YS, Kim TW, Kim JC, Yu CS, et al. Prognostic value of metabolic parameters in patients with synchronous colorectal cancer liver metastasis following curative-intent colorectal and hepatic surgery. *J Nucl Med*. 2014; 55(4):582–589. [PubMed: 24549284]

21. Obara PLH, Wroblewski K, Zhang CP, Hou P, Jiang Y, Chen P, Pu Y. Quantification of metabolic tumor activity and burden in patients with NSCLC: Is manual adjustment of semi-automatic gradient based measurements necessary? *Nucl Med Commun*. 2015; 36(9):782–789. [PubMed: 25888358]
22. Liu H, Chen P, Wroblewski K, Hou P, Zhang CP, Jiang Y, Pu Y. Consistency of Metabolic Tumor Volume of Non-Small Cell Lung Cancer Primary Tumor Measured from 18F-FDG PET/CT at Two Different Tracer Uptake Times. *Nucl Med Commun* 2016. 2016 Jan; 37(1):50–56.
23. Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, et al. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2010; 5(5):612–619.
24. Sasaki R, Komaki R, Macapinlac H, Erasmus J, Allen P, Forster K, et al. [18F]fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005; 23(6): 1136–1143. [PubMed: 15718309]
25. Vesselle H, Freeman JD, Wiens L, Stern J, Nguyen HQ, Hawes SE, et al. Fluorodeoxyglucose uptake of primary non-small cell lung cancer at positron emission tomography: new contrary data on prognostic role. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2007; 13(11):3255–3263. [PubMed: 17545531]
26. Lee P, Weerasuriya DK, Lavori PW, Quon A, Hara W, Maxim PG, et al. {A figure is presented}Metabolic Tumor Burden Predicts for Disease Progression and Death in Lung Cancer. *International Journal of Radiation Oncology Biology Physics*. 2007; 69(2):328–333.
27. Lee P, Bazan JG, Lavori PW, Weerasuriya DK, Quon A, Le QT, et al. Metabolic tumor volume is an independent prognostic factor in patients treated definitively for non-small-cell lung cancer. *Clin Lung Cancer*. 2012; 13(1):52–58. [PubMed: 21703935]
28. Grivaux M, Zureik M, Marsal L, Asselain B, Peureux M, Chavaillon JM, et al. Five-year survival for lung cancer patients managed in general hospitals. *Rev Mal Respir*. 2011; 28(7):e31–e38. [PubMed: 21943545]

Figure 1.

Axial, sagittal, coronal PET/CT fusion images and maximum intensity projection PET image (A, B, C, and D, respectively), from a baseline positron emission tomography scan at initial staging of non-small cell lung cancer of a 68-year-old male with a new diagnosis of non-small cell lung cancer (adenocarcinoma) and a synchronous diagnosis of head and neck cancer (oral squamous carcinoma), showing the measurements of metabolic tumor volume, total lesion glycolysis, and standardised uptake value of whole-body tumor. Coloured regions of- interest (ROIs) show the tumor contours segmented with the commercially

available PET Edge tool of the MIM software. A to D show a tumor and its contour in the right lower lobe and D shows all the tumors and their contours.

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Number at risk

MTV < 16.6	55	48	39	29	21	14	7	4	3	2	2
MTV >= 16.6	55	29	21	13	9	7	4	2	2	2	0

Number at risk

TLG <63.7	55	48	38	27	19	12	6	4	3	2	2
TLG >= 63.7	55	29	22	15	11	9	5	2	2	2	0

Number at risk											
SUVmax ≤ 8.6	56	48	38	28	21	16	8	4	3	3	2
SUVmax > 8.6	54	29	22	14	9	5	3	2	2	1	0

Fig. 2.

Kaplan–Meier survival curves demonstrate significant differences in OS between groups dichotomised by the median value of MTV_{WB} (A), TLG_{WB} (B), and SUV_{maxWB} (C). The log-rank tests yield $P < 0.001$ for all.

Table 1

Summary of Patients Characteristics

Variable	All patients (N = 110)
Primary cancers per patient	
2 primaries	103 (93.6%)
3 primaries	7 (6.4%)
Age (years)	
Mean±SD	68.6 ± 7.8
Gender	
Female	58 (52.7)
Male	52 (47.3)
Vital Status	
Alive or censored	37 (33.6)
Death	73 (66.4)
Histology (Lung cancer)	
Adenocarcinoma	53 (48.2)
Squamous cell carcinoma	42 (38.2)
Other	15 (13.6)
PET parameters	
MTV _{WB} (ml) *	16.62 (2.89 – 58.21)
TLG _{WB} (ml) *	63.71 (7.06 – 327.13)
SUV _{maxWB} *	8.56 (4.21 – 13.23)
TNM stage (Lung cancer)	
I	35 (31.8)
II	12 (10.9)
III	19 (17.3)
IV	44 (40.0)
Treatment category	
No treatment	11 (10.0)
“Surgery”	61 (55.5)
Other treatment	38 (34.5)

Note. – Except where indicated, data are numbers of patients, with percentages in parentheses.

* Data are medians with interquartile ranges in parentheses.

TLG_{WB} = whole-body total lesion glycolysis, MTV_{WB} = whole-body metabolic tumor volume, SUV_{maxWB} = whole-body maximum standardized uptake value.

Sixty-one patients had surgery (15 with wedge resection, two with segmental resection, three with resection of more than one lobe but less than the whole lung, 34 with lobectomy with mediastinal lymph node dissection, and 7 resections greater than one lobe but less than a full pneumonectomy).

Other treatments included chemotherapy and radiation therapy. Forty-eight patients had chemotherapy. Among them, 45 patients were treated with multiple chemotherapy agents including cis-platin or carboplatin and one or more other drugs (5-Fluorouracil, ipilumimab, Bevacizumab, Etoposide, Tarceva, Cetuximab, Gemcitabine, Vinorelbine, Navelbine, Crizotinib, Paclitaxel, toxotere, Pemetrexed, or hydroxyurea). Two patients had chemotherapy with Tarceva only, and one with Taxol only. In three patients chemotherapy was recommended but unknown if it was performed.

Thirty-seven patients had radiation therapy to the chest. For curative purposes, twenty-one patients were treated with 3D conformal techniques with conventional dose fractionation scheme and three were treated with Stereotactic Body Radiation Therapy techniques. One was with IMRT, Eleven patients had either palliative or incomplete therapy; treatment details for one patients were unknown.

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Table 2

Pathological diagnosis of other primary cancers

Other primaries	Total, N (%)	Metachronous, N (%)	Synchronous, N (%)
Lung cancer	23 (19.7)	8 (12.1)	15 (29.4)
Breast cancer	21 (17.9)	17 (25.8)	4 (7.8)
Head/neck cancer	21 (17.9)	8 (12.1)	13 (25.5)
Uroepithelium cancer	15 (12.8)	12 (18.2)	3 (5.9)
Lymphoma/leukemia/myeloma	11 (9.4)	6 (9.1)	5 (9.8)
Colorectal cancer	10 (8.5)	6 (9.1)	4 (7.8)
Prostate cancer	5 (4.3)	3 (4.5)	2 (3.9)
Skin cancer	4 (3.4)	3 (4.5)	1 (2.0)
Esophagus/stomach cancer	3 (2.6)	0 (0.0)	3 (5.9)
Cervix/uterus cancer	2 (1.7)	2 (3.0)	0 (0.0)
Liver cancer	1 (0.9)	0 (0.0)	1 (2.0)
Pancreas cancer	1 (0.9)	1 (1.5)	0 (0.0)
Total	117 (100.0)	66 (100.0)	51 (100.0)

Note: "Synchronous" defined as other primary cancer diagnosed within 2 months of FDG PET CT for the evaluation of NSCLC, otherwise "metachronous" (< five years before the FDG PET for the evaluation of NSCLC).

Table 3

Univariate Cox Regression Analysis for predicting Overall Survival

Variable	HR	95% CI	P Value
Age	0.976	0.944, 1.009	0.160
Gender			
Female *	1.000	...	...
Male	1.235	0.776, 1.965	0.373
Tumor histology			
Adenocarcinoma *	1.000	...	...
Squamous cell carcinoma	1.318	0.791, 2.197	0.289
Other	1.513	0.762, 3.001	0.237
TNM stage (NSCLC)			
I *	1.000	...	...
II	1.603	0.651, 3.943	0.305
III	2.806	1.360, 5.791	0.005
IV	2.740	1.510, 4.971	0.001
Therapy (Lung cancer)			
No treatment *	1.000	...	...
“Surgery”	0.228	0.113, 0.462	<0.001
Other treatment	0.775	0.388, 1.546	0.469
PET parameters			
ln(MTV _{WB})	1.477	1.272, 1.714	<0.001
ln(TLG _{WB})	1.372	1.216, 1.549	<0.001
ln(SUV _{maxWB})	1.983	1.455, 2.703	<0.001

Notes:

* The group that served as the reference group.

95% CI = 95% confidence interval, ln = natural logarithmic transformation, NSCLC= non-small cell lung cancer. Other abbreviations are the same as in Table 1. “Surgery” means any treatment that included surgery. The GHCI values (and their 95% CI) for ln(MTV_{WB}) = 0.685 (0.623, 0.747) and for ln(TLG_{WB}) = 0.685 (0.626, 0.744) were significantly greater than that for TNM stage = 0.612 (0.560, 0.664) ($P=0.013$ and 0.012 respectively). The GHCI of ln(SUV_{maxWB}) = 0.655 (0.600, 0.709) was not significantly different from that of TNM stage ($p=0.183$).

Table 4

Multivariable Cox Regression Models for Overall Survival Analysis

Model and Variable	HR	95%CI	P Value	GHCI
Model 1				0.740
ln(MTV _{WB})	1.368	1.141, 1.641	0.001	
TNM stage (NSCLC)				
I *	1.000	...	...	
II	0.936	0.360, 2.434	0.892	
III	1.091	0.454, 2.617	0.846	
IV	1.280	0.630, 2.600	0.495	
Model 2				0.741
ln(TLG _{WB})	1.313	1.127, 1.530	<0.001	
TNM stage (NSCLC)				
I *	1.000	...	...	
II	0.960	0.374, 2.468	0.933	
III	1.039	0.432, 2.498	0.932	
IV	1.243	0.613, 2.519	0.546	
Model 3				0.729
ln(SUV _{maxWB})	1.739	1.172, 2.581	0.006	
TNM stage (NSCLC)				
I *	1.000	...	...	
II	1.330	0.525, 3.368	0.548	
III	1.269	0.544, 2.965	0.581	
IV	1.604	0.821, 3.132	0.167	

Note: Models 1–3 were adjusted for patient's age, tumor histology and treatment received. GHCI = Gonen and Heller's Concordance indices.

* The group that served as the reference group. Other abbreviations are as in Table 1.