Prognostic significance of integrating total metabolic tumor volume and EGFR mutation status in patients with lung adenocarcinoma (#90178)

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Prognostic significance of integrating total metabolic tumor volume and EGFR mutation status in patients with lung adenocarcinoma

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Background The objective of this study was to investigate the prognostic significance of total metabolic tumor volume (TMTV) derived from baseline ^{18}F-2-fluoro-2-deoxyglucose (^{18}F- FDG) positron emission tomography/computed tomography (PET/CT), in conjunction with epidermal growth factor receptor (EGFR) mutation status, among patients with lung adenocarcinoma (LUAD).

Methods We performed a retrospective analysis on 141 patients with LUAD [74 males, 67 females, median age 67 (range 34-86)] who underwent ^{18}F-FDG PET/CT and had their EGFR mutation status determined. Optimal cutoff points for TMTV were determined using time-dependent receiver operating characteristic curve analysis. The survival difference was compared using Cox regression analysis and Kaplan–Meier curves.

Results The EGFR mutant patients (n = 79, 56.0%) exhibited significantly higher 2-year progression-free survival (PFS) and overall survival (OS) rates compared to those with EGFR wild-type (n = 62, 44.0%), with rates of 74.2% vs. 69.2% (P = 0.029) and 86.1% vs. 67.7% (P = 0.009), respectively. The optimal cutoff values of TMTV were 36.42 cm^3 for PFS and 37.51 cm^3 for OS. Patients with high TMTV exhibited significantly inferior 2-year PFS and OS, with rates of 22.4% and 38.1%, respectively, compared to those with low TMTV, who had rates of 85.8% and 95.0% (both P < 0.001). In both the EGFR mutant and wild-type groups, patients exhibiting high TMTV demonstrated significantly inferior 2-year PFS and OS compared to those with low TMTV. In multivariate analysis, EGFR mutation status (hazard ratio, HR, 0.41, 95% confidence interval, CI 0.18–0.94, P = 0.034) and TMTV (HR 8.08, 95% CI 2.34–28.0, P < 0.001) were independent prognostic factors of OS, whereas TMTV was also an independent prognosticator of PFS (HR 2.59, 95% CI 1.30–5.13, P = 0.007).

Conclusion Our study demonstrates that the integration of TMTV on baseline ^{18}F-FDG PET/CT with EGFR mutation status improves the accuracy of prognostic evaluation for patients with LUAD.

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Abstract

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Introduction

Lung cancer continues to be a prominent contributor to global cancer-related deaths, showing minimal progress in prognosis despite advancements made in the field of diagnosis and treatment approaches (Siegel et al., *2023;* Xia et al., *2022*). Lung adenocarcinoma (LUAD) represents a predominant subtype of non-small cell lung cancer (NSCLC), accounting for approximately 40% of all cases among pulmonary malignancies (Kleczko et al., *2019;* Zhang et al., *2022*). Advances in molecular research have resulted in the emergence of promising treatments for advanced NSCLC, such as gefitinib, a targeted agent that effectively inhibits epidermal growth factor receptor (EGFR) tyrosine kinase (Yi et al., *2023*). Patients with NSCLC harboring EGFR mutations and treated with tyrosine kinase inhibitors (TKIs) achieved significantly prolonged progression-free survival (PFS) and/or overall survival (OS) compared to those receiving conventional chemotherapy (Zhong et al., *2021;* Liu et al., *2021;* Greenhalgh et al., *2021;* Sperduto et al., *2017;* Cadranel et al., *2012*). The presence of EGFR mutations has been proposed as a crucial determinant of prognosis in individuals with NSCLC (Wu et al., *2010;* Choi et al., *2012;* Deng et al., *2021*), but the predictive significance of EGFR mutations in NSCLC patients remains controversial (Zhang et al., *2014;* Lin et al., *2017*). Due to a paucity of studies specifically investigating the prognostic impact stratified by clinical TNM stages, histologic subtypes, or metabolic phenotypes on ^{18}F-2-fluoro-2-deoxyglucose (^{18}F-FDG)

positron emission tomography/computed tomography (PET/CT), it becomes challenging to adequately control for confounding variables.

At present, the utilization of ^{18}F-FDG PET/CT is extensive in the management of lung cancer and has been recognized for providing prognostic insights through metabolic parameters (e.g., maximum standardized uptake value of primary tumors [$pSUV_{max}$], total metabolic tumor volume [TMTV], and whole-body total lesion glycolysis [TLG_{WB}]) derived from PET images (Pellegrino et al., *2019;* Mahmoud et al., *2022;* Monaco et al., *2021;* Chen et al., *2012*). Essentially, patients diagnosed with lung cancer who exhibit elevated $pSUV_{max}$, TMTV and TLG_{WB} values are indicative of a poor prognosis. The occurrence of EGFR mutations in individuals diagnosed with lung cancer generally results in a positive reaction to targeted treatment, which contributes to prolonged survival. However, several studies have reported inconsistent findings regarding the correlation between EGFR mutation and decreased ^{18}F-FDG uptake in lung cancer, with some indicating a negative association and others suggesting otherwise (Shi et al., *2022;* Hong et al., *2020;* Ko et al., *2014*). Additionally, certain studies have failed to identify any significant correlations between these factors (Chung et al., *2014;* Lee et al., *2015*). The inconsistent findings could be attributed to the limited sample size and potential confounding variables, such as the TNM stage and histological subtype of the tumor.

NSCLC can be categorized into two primary subtypes, LUAD and squamous cell carcinoma (SCC), each exhibiting distinct features. Wang et al. demonstrated that it is crucial to analyze LUAD and lung SCC separately to obtain precise prognostic information due to significant outcome differences between these two distinct cancer types (Wang et al., *2020*). In this study, we specifically chose LUAD as the subject and hypothesized that the presence of EGFR mutations could serve as a prognostic indicator for patients with LUAD; however, further stratification by metabolic parameters on ^{18}F-FDG PET/CT is necessary to refine these results.

Therefore, we conducted a retrospective analysis to investigate the prognostic significance of the TMTV derived from baseline ^{18}F-FDG PET/CT scans in conjunction with EGFR mutation status among patients diagnosed with LUAD.

Materials & Methods

Patient selection

We retrospectively analyzed a cohort of 1,104 patients diagnosed with lung cancer who underwent ^{18}F-FDG PET/CT at Ningbo No.2 Hospital in China between October 2019 and March 2022. To be eligible for the study, patients were required to meet specific criteria, which included: (i) no prior pretreatment before undergoing ^{18}F-FDG PET/CT, (ii) a confirmed diagnosis of LUAD through histopathological examination, (iii) determination of EGFR mutation status, and (iv) at least one month of follow-up. The study included a cohort of 141 individuals who were diagnosed with LUAD, selected according to the established criteria (Figure 1). Table 1 presents a comprehensive summary and comparison of clinical characteristics and metabolic parameters for study participants with wild-type and mutant EGFR, encompassing age, sex, smoking status, clinical TNM stages, $pSUV_{max}$, MTV and TLG of the primary tumors (pMTV and pTLG), as well as TMTV and TLG_{WB}. Individuals who had smoked less than 100 cigarettes in their lifetime were categorized as never smokers, while the rest of the participants were considered smokers (Kawaguchi et al., *2010*). The research plan obtained approval from the Institutional Review Board of Ningbo No.2 Hospital, and informed consent was not required (protocol No. YJ-NBEY-KY202108401).

Technique for PET/CT Scanning

The PET/CT scan procedure employed a GE Discovery 710 PET scanner (GE Healthcare, Chicago, IL, USA). Prior to the examination, patients were instructed to observe a fasting period of at least six hours, and their glucose levels were verified to be below 7.0 mmol/L. A dosage of 5.2-7.4 MBq/kg of ^{18}F-FDG was administered, followed by a PET/CT scan conducted after a time interval of 45-60 minutes. The low-dose CT scan parameters were set as follows: an X-ray tube voltage of 140 kV, current of 10 mA, rotation duration of 0.5 s, and collimation width of 40 mm. Following this, a three-dimensional PET scan was conducted from the base of the skull to the upper thigh, with each bed position scanned for 2.5 minutes. An iterative algorithm reconstruction utilizing CT data was employed to acquire PET, CT, and fused PET/CT images. The Xeleris Workstation (GE Healthcare) was utilized for image analysis in transverse, sagittal, and coronal planes.

Analysis of PET/CT Imaging

The PET and CT images were independently evaluated by two experienced nuclear medicine

physicians (MQJ and QLG) with a minimum of 10 years of clinical practice. The SUV_{max} value was utilized to quantify the intensity of ^{18}F-FDG uptake in the lesion, considering abnormal uptake as metabolic activity surpassing that observed in the surrounding background. A region of interest (ROI) was manually delineated around the tumor lesions, focusing on the area exhibiting the most significant uptake of ^{18}F-FDG. The SUV_{max} represents the highest standardized uptake value within this ROI. To derive TLG values, a range of margin thresholds were applied to each individual lesion. This involved calculating the product of SUV_{mean} and MTV, which provides an assessment of both tumor burden and metabolic activity. The margin threshold used for determining MTV was equivalent to 41% of the SUV_{max} for each lesion (Lang et al., *2021*). If the lesions were large and clustered to an extent where individual lesions could not be distinguished, they were classified as a cluster. Specialized software was employed for automated measurements to ensure complete reproducibility. Last, at the patient level, the TLG_{WB} was calculated by summing all lesion values.

Analysis of EGFR mutations

The presence of EGFR mutations was determined through histological analysis of primary tumors, metastatic lymph nodes or organs obtained via surgical resection, fiberoptic bronchoscopy biopsy, or fine-needle aspiration. In all instances, the specimens were fixed in a 10% buffered neutral formalin solution and subsequently embedded in paraffin wax. According to the manufacturer's instructions, DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue sections using the QIAamp DNA FFPE Tissue Kit manufactured by Qiagen NV in Venlo, Netherlands. Polymerase chain reaction was carried out on an Mx3000PTM real-time PCR system developed by Stratagene located in La Jolla, USA. The amplification-refractory mutation system, in conjunction with an EGFR 29 Mutation Detection Kit from Amoy Diagnostics in Xiamen, was employed to determine the presence of EGFR mutations. Tumors were categorized as harboring EGFR mutations if exon mutations were detected; otherwise, they were considered wild-type tumors.

Statistical Analysis

The demographic data of the patients are presented using descriptive statistics. Median values with interquartile ranges (IQRs) were reported for metabolic parameters, including $pSUV_{max}$,

pMTV, pTLG, TMTV and TLG_{WB}. To evaluate variations in continuous variables among different groups, Mann–Whitney tests were conducted. PFS was determined as the time period from the first PET/CT scan until either confirmed disease progression or death, whereas OS was computed from the initial PET/CT scan to either all-cause mortality or last follow-up, whichever occurred earlier. Time-dependent receiver operating characteristic (ROC) curve analysis was employed to determine the optimal cutoff values of $pSUV_{max}$, TMTV and TLG_{WB} for PFS and OS. The predictive performance was assessed by calculating the area under the ROC curve (AUC). The 2-year PFS and OS rates were estimated using Kaplan–Meier curves. Differences in survival between groups were evaluated by the log-rank test. Both univariate and multivariate analyses were conducted using the Cox regression model. R software (version 3.60, http://www.r-project.org) was utilized for statistical analyses, and GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA) was used to generate graphs. Statistical significance was determined by a two-tailed p value < 0.05.

Results

Patient characteristics

Table 1 presents a comprehensive overview of the clinical and metabolic profiles of patients with wild-type and mutant EGFR, encompassing factors such as age, sex, smoking status, clinical TNM stage, $pSUV_{max}$, TMTV and TLG_{WB} data. In the cohort of 141 participants, comprising 74 males and 67 females, the average age was 66.6 ± 9.8 years (with a median age of 67), ranging from 34 to 86 years. PFS was followed up for a median duration of 16 months (ranging from 1 to 36 months), with IQRs of 9-26 months. Regarding OS, the follow-up period lasted for a median of 21 months (ranging from 3 to 38 months), with IQRs of 11-27 months. During the entire follow-up period, a total of 26 deaths were recorded. The study population as a whole demonstrated a 2-year PFS rate of 66.3% and an OS rate of 78.2%, as shown in Figure 2.

Outcomes according to EGFR mutation status

The presence of EGFR mutations was observed in 79 (56.0%) patients, as indicated in Table 1, while the remaining patients (n = 62, 44.0%) were classified as EGFR wild-type. Based on our findings, patients with EGFR mutations demonstrated significantly higher rates of 2-year PFS (Fig. 3A) and OS (Fig. 4A) than those with wild-type EGFR, with rates of 74.2% vs. 69.2% (P = 0.029) and 86.1% vs. 67.7% (P = 0.009), respectively.

Outcomes according to metabolic parameters

In our study, we analyzed various metabolic parameters, including $pSUV_{max}$, pMTV, pTLG, TMTV and TLG_{WB}. The AUCs for predicting 2-year PFS were 0.791, 0.804, 0.842, 0.898 and 0.888, respectively, while those for predicting 2-year OS were 0.809, 0.822, 0.855, 0.911 and 0.894, respectively. The parameter with the highest predictive value in both PFS and OS was TMTV; therefore, it was chosen to evaluate prognostic significance in our studies. The optimal cutoff values for TMTV were determined to be 36.42 cm^3 and 37.51 cm^3 for predicting 2-year PFS and OS, respectively. Patients with high TMTV exhibited significantly inferior 2-year PFS (Fig. 3B, $P < 0.001$) and OS (Fig. 4B, $P < 0.001$), with rates of 22.4% and 38.1%, respectively, compared to those with low TMTV, who had rates of 85.8% and 95.0%.

Outcomes according to the integration of EGFR mutation status and TMTV

In the EGFR mutant group, patients with a high TMTV ($\geq$ 36.42 cm^3) exhibited significantly inferior 2-year PFS compared to those with a low TMTV ($<$ 36.42 cm^3), while similar observations were made in the EGFR wild-type group, where the respective 2-year PFS rates were 27.6% vs. 90.0% (Fig. 3C, $P < 0.001$) and 17.6% vs. 80.0% (Fig. 3D, $P < 0.001$). Patients with EGFR mutations and a high TMTV of $\geq$ 37.51cm^3 exhibited significantly lower 2-year OS than those with a low TMTV of $<$ 37.51cm^3. The same trend was seen in the EGFR wild-type group, where the respective 2-year OS rates were 48.1% vs. 97.8%. (Fig. 4C, $P < 0.001$) and 26.5% vs. 90.7% (Fig. 4D, $P < 0.001$).

Clinical distribution based on TMTV in predicting PFS and OS

Furthermore, we conducted an assessment of the clinical characteristics and EGFR mutation status in relation to both PFS and OS, stratifying patients based on the optimal cutoff values with low and high TMTV (Table 2). Patients with high TMTV often presented in advanced stage and

were predominantly male, while there was no significant difference in age or smoking status. The presence of EGFR mutations, typically observed in patients with low TMTV, demonstrated a significant difference in OS but not in PFS (Table 2).

Univariate and multivariate Cox regression analysis of survival

In the univariate analysis, smoking status, TNM stage, TMTV and EGFR mutation status were identified as significant predictors of PFS in patients with LUAD. Additionally, TNM stage, TMTV and EGFR mutation status were found to be predictive of OS (Table 3). The significant factors were subjected to multivariate analysis, revealing that TNM stage and TMTV independently predicted PFS, while EGFR mutation status and TMTV independently predicted OS (Table 3).

Discussion

In the present study, we have demonstrated that both the EGFR mutation status and the TMTV, determined on baseline ^{18}F-FDG PET/CT, are independent prognostic factors for OS in patients with LUAD. Furthermore, we found that TMTV is also an independent prognostic factor for PFS in LUAD patients. When evaluating the prognostic significance of EGFR mutation status, it is crucial to consider the level of TMTV. The combination of pretreatment TMTV and EGFR mutation status has the potential to enhance accuracy in predicting prognosis and aid in decision-making regarding intensive therapy.

The prognostic role of EGFR mutation status in patients with lung cancer was investigated as early as 2004 to 2005 (Taron et al., *2005;* Lynch et al., *2004*). Patients with EGFR mutations tend to have a high response to TKIs, leading to prolonged survival (Han et al., *2005*). Nonetheless, there has been considerable fluctuation in the outcomes over the past twenty years. Mitsudomi et al. demonstrated that the presence of genetic alterations in the EGFR gene is associated with improved survival outcomes following gefitinib therapy among NSCLC patients who experience recurrence after surgery (Mitsudomi et al., *2005*). However, Deng et al. discovered a contradictory result indicating that EGFR was a significant negative prognostic indicator in patients with radiologic solid and different forms of LUAD (Deng, Zhang, Ma, Fu, Deng, Li & Chen, *2021*). In comparison to the wild-type group, patients with EGFR mutations

exhibited notably higher occurrences of brain and bone metastases (Deng, Zhang, Ma, Fu, Deng, Li & Chen, *2021*). Interestingly, Liu and Li et al found that primary resected LUAD does not exhibit substantial prognostic significance in relation to EGFR mutations (Liu et al., *2014;* Li et al., *2019*).

Overall, several factors may have contributed to these disparate findings. First, the patient cohorts exhibited heterogeneity in terms of TNM staging, with some only at stage I and having undergone radical surgery while others were at stages I-IV with varying treatment modalities (Deng, Zhang, Ma, Fu, Deng, Li & Chen, *2021;* Liu, Zhao, Pang, Yuan, Li & Wang, *2014;* Li, Li, Lin, Li, Yu, Wang, Dong, Yu, Li, Liu, et al., *2019*). Second, the sample size enrolled in these studies varied greatly from 59 to 1512 patients (Deng, Zhang, Ma, Fu, Deng, Li & Chen, *2021;* Mitsudomi, Kosaka, Endoh, Horio, Hida, Mori, Hatooka, Shinoda, Takahashi & Yatabe, *2005*). Third, there was also histological diversity among the cohorts, with some being enrolled as NSCLC and others solely as LUAD (Zhang, Wang, Zhang, Cai, Pan, Long, Chen, Zhou & Yin, *2014;* Li, Li, Lin, Li, Yu, Wang, Dong, Yu, Li, Liu, et al., *2019*). To a certain extent, the prognostic significance of EGFR mutation status in lung cancer has captured the attention of researchers. Our study demonstrates that EGFR mutation is an independent and favorable prognostic factor for patients with LUAD.

The incidence of EGFR mutations is reportedly higher in patients diagnosed with LUAD, particularly among female individuals, never-smokers, and East Asian populations (Shi et al., *2015;* Shi et al., *2014*). Our study consistently observed these findings. ^{18}F-FDG PET/CT has become a widely utilized tool in the management of lung cancer, encompassing diagnosis, treatment response assessment and prognostication (Lim et al., *2022;* Peng et al., *2022*). In terms of prognosis, high metabolic activity as measured by ^{18}F-FDG PET/CT is typically indicative of poor survival outcomes in patients with LUAD. Relevant investigations have been conducted to explore the associations between EGFR mutation status and metabolic parameters on FDG PET/CT (Jiang et al., *2022;* Jiang et al., *2023;* Guo et al., *2021*). We previously observed that male patients with NSCLC harboring EGFR mutations frequently exhibit low $pSUV_{max}$ (Jiang, Chen, Guo, Zhang, Gao, Zhang, Zhao & Zheng, *2023*). Similar findings were also reported by Wang et al (Wang et al., *2022*). In this study, a lower level of metabolic parameters, including $pSUV_{max}$, pTLG, TMTV and TLG_{WB}, was associated with a higher incidence of EGFR mutations. However, a number of factors may influence the correlations between EGFR mutation status and

SUV_{max} in LUAD, particularly with regard to smoking status (Gao et al., *2023*). Furthermore, a greater intratumor heterogeneity factor was observed in EGFR-mutant LUAD patients than in those with wild-type EGFR (Ni et al., *2023*). Therefore, the integration of EGFR mutation status and ^{18}F-FDG metabolic activity is imperative and holds paramount significance for a comprehensive evaluation of prognostic outcomes in patients with LUAD.

Accordingly, we investigated the prognostic value of various metabolic parameters, including $pSUV_{max}$, pMTV, pTLG, TMTV and TLG_{WB}. Upon comparison of these parameters, TMTV exhibited the highest prognostic efficacy for patients diagnosed with LUAD. A meta-analysis comprising thirty-six studies and 5807 patients demonstrated that elevated $pSUV_{max}$, MTV, and TLG_{WB} were associated with a poor prognosis in surgical NSCLC patients (Liu et al., *2016*). Salavati et al found that volumetric parameters derived from both primary tumors and whole-body lesions exhibit comparable prognostic value for survival in stage IIB/III NSCLC patients (Salavati et al., *2017*). As stated, both the EGFR mutation status and metabolic parameters can serve as crucial factors for assessing treatment response sensitivity and prognosis, exhibiting a significant correlation between them. However, there have been limited studies integrating EGFR mutation status and metabolic parameters to evaluate the prognosis of patients with LUAD. In our findings, not only in EGFR wild-type patients but also in those with EGFR mutations, the parameter of TMTV could effectively stratify them into distinct prognostic groups. It is crucial to take into account the volumetric parameter of TMTV when prognosticating based on EGFR mutation status.

However, it is important to acknowledge its limitations. First, the delineation of lesions relied on a single threshold technique, and although CT images were incorporated for improved accuracy, the choice of threshold value can still impact the quantification of tumor volume, average SUV, and TMTV. Future research should explore alternative thresholds to optimize these measurements since there is currently no standardized approach for determining the optimal cutoff value for SUV_{max}. Second, the duration of follow-up was relatively short, and the sample size was limited. Third, this study was conducted retrospectively at a single center. Therefore, it is necessary to validate these findings through larger-scale prospective randomized studies involving multiple institutions.

Conclusions

In conclusion, both the EGFR mutation status and the TMTV measured on baseline ^{18}F-FDG PET/CT can independently serve as prognostic factors for OS in patients with LUAD. Furthermore, the TMTV is also an independent predictor for PFS in LUAD patients. Integrating them may enhance the predictive accuracy for patient outcomes, which could be valuable for clinicians when making decisions regarding treatment modalities and follow-up.

Acknowledgements

Funding

This work was supported by the Exploration Project of Natural Science Foundation of Zhejiang Province (grant No. LTGY23H180004), the Ningbo Public Service Technology Foundation, China (grant No. 2021S176), the Ningbo Clinical Research Center for Medicine Imaging (grant No. 2021L003), and the Provincial and Municipal Co-construction Key Discipline for Medical Imaging (grant No. 2022-S02).

References

Siegel RL, Miller KD, Wagle NS, Jemal A. 2023. Cancer statistics, 2023. *CA Cancer J Clin* 73 (1):17-48 doi 10.3322/caac.21763

Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N, Chen W. 2022. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl)* 135 (5):584-590 doi 10.1097/CM9.0000000000002108

Kleczko EK, Kwak JW, Schenk EL, Nemenoff RA. 2019. Targeting the Complement Pathway as a Therapeutic Strategy in Lung Cancer. *Front Immunol* 10:954 doi 10.3389/fimmu.2019.00954

Zhang H, Liu Y, Xu Z, Chen Q. 2022. miR-873 and miR-105-2 May Affect the Tumour Microenvironment and are Potential Biomarkers for Lung Adenocarcinoma. *Int J Gen Med* 15:3433-3445 doi 10.2147/IJGM.S352120

Yi M, He T, Wang K, Wei Y. 2023. Comparison of gefitinib plus chemotherapy versus gefitinib alone for advanced non-small-cell lung cancer: A meta analysis. *Clinics (Sao Paulo)* 78:100152 doi 10.1016/j.clinsp.2022.100152

Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Wei YC, Liu YY, Chen C, Cheng Y, Yin R, Yang F, Ren SX, Li XF, Li J, Huang C, Liu ZD, Xu S, Chen KN, Xu SD, Liu LX, Yu P, Wang BH, Ma HT, Yang JJ, Yan HH, Yang XN, Liu SY, Zhou Q, Wu YL. 2021. Gefitinib Versus Vinorelbine Plus Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFR-Mutant NSCLC: Final Overall Survival Analysis of CTONG1104 Phase III Trial. *J Clin Oncol* 39 (7):713-722 doi 10.1200/JCO.20.01820

Liu SY, Bao H, Wang Q, Mao WM, Chen Y, Tong X, Xu ST, Wu L, Wei YC, Liu YY, Chen C, Cheng Y, Yin R, Yang F, Ren SX, Li XF, Li J, Huang C, Liu ZD, Xu S, Chen KN, Xu SD, Liu LX, Yu P, Wang BH, Ma HT, Yan HH, Dong S, Zhang XC, Su J, Yang JJ, Yang XN, Zhou Q, Wu X, Shao Y, Zhong WZ, Wu YL. 2021. Genomic signatures define three subtypes of EGFR-mutant stage II-III non-small-cell lung cancer with distinct adjuvant therapy outcomes. *Nat Commun* 12 (1):6450 doi 10.1038/s41467-021-26806-7

Greenhalgh J, Boland A, Bates V, Vecchio F, Dundar Y, Chaplin M, Green JA. 2021. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. *Cochrane Database Syst Rev* 3 (3):CD010383 doi 10.1002/14651858.CD010383.pub3

Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, Sneed P, Boyle J, Kirkpatrick JP, Mak KS, Shih HA, Engelman A, Roberge D, Arvold ND, Alexander B, Awad MM, Contessa J, Chiang V, Hardie J, Ma D, Lou E, Sperduto W, Mehta MP. 2017. Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). *JAMA Oncol* 3 (6):827-831 doi 10.1001/jamaoncol.2016.3834

Cadranel J, Mauguen A, Faller M, Zalcman G, Buisine MP, Westeel V, Longchampt E, Wislez M, Coudert B, Daniel C, Chetaille B, Michiels S, Blons H, Solassol J, De Fraipont F, Foucher P, Urban T, Lacroix L, Poulot V, Quoix E, Antoine M, Danton G, Morin F, Chouaid C, Pignon JP. 2012. Impact of systematic EGFR and KRAS mutation evaluation on progression-free survival and overall survival in patients with advanced non-small-cell lung cancer treated by erlotinib in a French prospective cohort

(ERMETIC project--part 2). *J Thorac Oncol* 7 (10):1490-1502 doi 10.1097/JTO.0b013e318265b2b5

Wu M, Zhao J, Song SW, Zhuo M, Wang X, Bai H, Wang S, Yang L, An T, Zhang Y, Duan J, Wang Y, Guo Q, Liu X, Liu N, Wang J. 2010. EGFR mutations are associated with prognosis but not with the response to front-line chemotherapy in the Chinese patients with advanced non-small cell lung cancer. *Lung Cancer* 67 (3):343-347 doi 10.1016/j.lungcan.2009.04.011

Choi YJ, Cho BC, Jeong YH, Seo HJ, Kim HJ, Cho A, Lee JH, Yun M, Jeon TJ, Lee JD, Kang WJ. 2012. Correlation between (18)f-fluorodeoxyglucose uptake and epidermal growth factor receptor mutations in advanced lung cancer. *Nucl Med Mol Imaging* 46 (3):169-175 doi 10.1007/s13139-012-0142-z

Deng C, Zhang Y, Ma Z, Fu F, Deng L, Li Y, Chen H. 2021. Prognostic value of epidermal growth factor receptor gene mutation in resected lung adenocarcinoma. *J Thorac Cardiovasc Surg* 162 (3):664-674 e667 doi 10.1016/j.jtcvs.2020.05.099

Zhang Z, Wang T, Zhang J, Cai X, Pan C, Long Y, Chen J, Zhou C, Yin X. 2014. Prognostic value of epidermal growth factor receptor mutations in resected non-small cell lung cancer: a systematic review with meta-analysis. *PLoS One* 9 (8):e106053 doi 10.1371/journal.pone.0106053

Lin CY, Wu YM, Hsieh MH, Wang CW, Wu CY, Chen YJ, Fang YF. 2017. Prognostic implication of EGFR gene mutations and histological classification in patients with resected stage I lung adenocarcinoma. *PLoS One* 12 (10):e0186567 doi 10.1371/journal.pone.0186567

Pellegrino S, Fonti R, Mazziotti E, Piccin L, Mozzillo E, Damiano V, Matano E, De Placido S, Del Vecchio S. 2019. Total metabolic tumor volume by 18F-FDG PET/CT for the prediction of outcome in patients with non-small cell lung cancer. *Ann Nucl Med* 33 (12):937-944 doi 10.1007/s12149-019-01407-z

Mahmoud HA, Oteify W, Elkhayat H, Zaher AM, Mohran TZ, Mekkawy N. 2022. Volumetric parameters of the primary tumor and whole-body tumor burden derived from baseline (18)F-FDG PET/CT can predict overall survival in non-small cell lung cancer patients: initial results from a single institution. *Eur J Hybrid Imaging* 6 (1):37 doi 10.1186/s41824-022-00158-x

Monaco L, Gemelli M, Gotuzzo I, Bauckneht M, Crivellaro C, Genova C, Cortinovis D, Zullo L, Ammoni LC, Bernasconi DP, Rossi G, Morbelli S, Guerra L. 2021. Metabolic Parameters as Biomarkers of Response to Immunotherapy and Prognosis in Non-Small Cell Lung Cancer (NSCLC): A Real World Experience. *Cancers (Basel)* 13 (7) doi 10.3390/cancers13071634

Chen HH, Chiu NT, Su WC, Guo HR, Lee BF. 2012. Prognostic value of whole-body total lesion glycolysis at pretreatment FDG PET/CT in non-small cell lung cancer. *Radiology* 264 (2):559-566 doi 10.1148/radiol.12111148

Shi A, Wang J, Wang Y, Guo G, Fan C, Liu J. 2022. Predictive value of multiple metabolic and heterogeneity parameters of (18)F-FDG PET/CT for EGFR mutations in non-small cell lung cancer. *Ann Nucl Med* 36 (4):393-400 doi 10.1007/s12149-022-01718-8

Hong IK, Lee JM, Hwang IK, Paik SS, Kim C, Lee SH. 2020. Diagnostic and Predictive Values of (18)F-FDG PET/CT Metabolic Parameters in EGFR-Mutated Advanced Lung Adenocarcinoma. *Cancer Manag Res* 12:6453-6465 doi 10.2147/CMAR.S259055

Ko KH, Hsu HH, Huang TW, Gao HW, Shen DH, Chang WC, Hsu YC, Chang TH, Chu CM, Ho CL, Chang H. 2014. Value of (1)(8)F-FDG uptake on PET/CT and CEA level to predict epidermal growth factor receptor mutations in pulmonary adenocarcinoma. *Eur J Nucl Med Mol Imaging* 41 (10):1889-1897 doi 10.1007/s00259-014-2802-y

Chung HW, Lee KY, Kim HJ, Kim WS, So Y. 2014. FDG PET/CT metabolic tumor volume and total lesion glycolysis predict prognosis in patients with advanced lung adenocarcinoma. *J Cancer Res Clin Oncol* 140 (1):89-98 doi 10.1007/s00432-013-1545-7

Lee SM, Bae SK, Jung SJ, Kim CK. 2015. FDG uptake in non-small cell lung cancer is not an independent predictor of EGFR or KRAS mutation status: a retrospective analysis of 206 patients. *Clin Nucl Med* 40 (12):950-958 doi 10.1097/RLU.0000000000000975

Wang BY, Huang JY, Chen HC, Lin CH, Lin SH, Hung WH, Cheng YF. 2020. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. *J Cancer Res Clin Oncol* 146 (1):43-52 doi 10.1007/s00432-019-03079-8

Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, Saito R, Kawahara M, Maruyama Y. 2010. Gender, histology, and time of diagnosis are important factors

for prognosis: analysis of 1499 never-smokers with advanced non-small cell lung cancer in Japan. *J Thorac Oncol* 5 (7):1011-1017 doi 10.1097/JTO.0b013e3181dc213e

Lang D, Ritzberger L, Rambousek V, Horner A, Wass R, Akbari K, Kaiser B, Kronbichler J, Lamprecht B, Gabriel M. 2021. First-Line Pembrolizumab Mono- or Combination Therapy of Non-Small Cell Lung Cancer: Baseline Metabolic Biomarkers Predict Outcomes. *Cancers (Basel)* 13 (23) doi 10.3390/cancers13236096

Taron M, Ichinose Y, Rosell R, Mok T, Massuti B, Zamora L, Mate JL, Manegold C, Ono M, Queralt C, Jahan T, Sanchez JJ, Sanchez-Ronco M, Hsue V, Jablons D, Sanchez JM, Moran T. 2005. Activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor are associated with improved survival in gefitinib-treated chemorefractory lung adenocarcinomas. *Clin Cancer Res* 11 (16):5878-5885 doi 10.1158/1078-0432.CCR-04-2618

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. 2004. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 350 (21):2129-2139 doi 10.1056/NEJMoa040938

Han SW, Kim TY, Hwang PG, Jeong S, Kim J, Choi IS, Oh DY, Kim JH, Kim DW, Chung DH, Im SA, Kim YT, Lee JS, Heo DS, Bang YJ, Kim NK. 2005. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 23 (11):2493-2501 doi 10.1200/JCO.2005.01.388

Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, Hatooka S, Shinoda M, Takahashi T, Yatabe Y. 2005. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 23 (11):2513-2520 doi 10.1200/JCO.2005.00.992

Liu WS, Zhao LJ, Pang QS, Yuan ZY, Li B, Wang P. 2014. Prognostic value of epidermal growth factor receptor mutations in resected lung adenocarcinomas. *Med Oncol* 31 (1):771 doi 10.1007/s12032-013-0771-9

Li R, Li Q, Lin S, Li W, Yu L, Wang L, Dong X, Yu L, Li S, Liu W, Li B. 2019. Prognostic implication of EGFR mutation status and subtype in resected lung adenocarcinoma patients irrespective of therapy. *Clin Transl Oncol* 21 (3):298-303 doi 10.1007/s12094-018-1922-4

Shi Y, Li J, Zhang S, Wang M, Yang S, Li N, Wu G, Liu W, Liao G, Cai K, Chen L, Zheng M, Yu P, Wang X, Liu Y, Guo Q, Nie L, Liu J, Han X. 2015. Molecular Epidemiology of EGFR Mutations in Asian Patients with Advanced Non-Small-Cell Lung Cancer of Adenocarcinoma Histology - Mainland China Subset Analysis of the PIONEER study. *PLoS One* 10 (11):e0143515 doi 10.1371/journal.pone.0143515

Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G, Yang PC. 2014. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 9 (2):154-162 doi 10.1097/JTO.0000000000000033

Lim CH, Park SB, Kim HK, Choi YS, Kim J, Ahn YC, Ahn MJ, Choi JY. 2022. Clinical Value of Surveillance (18)F-fluorodeoxyglucose PET/CT for Detecting Unsuspected Recurrence or Second Primary Cancer in Non-Small Cell Lung Cancer after Curative Therapy. *Cancers (Basel)* 14 (3) doi 10.3390/cancers14030632

Peng L, Du B, Cui Y, Luan Q, Li Y, Li X. 2022. (18)F-FDG PET/CT for assessing heterogeneous metabolic response between primary tumor and metastases and prognosis in non-small cell lung cancer. *Clin Lung Cancer* 23 (7):608-619 doi 10.1016/j.cllc.2022.08.001

Jiang M, Zhang X, Chen Y, Chen P, Guo X, Ma L, Gao Q, Mei W, Zhang J, Zheng J. 2022. A Review of the Correlation Between Epidermal Growth Factor Receptor Mutation Status and (18)F-FDG Metabolic Activity in Non-Small Cell Lung Cancer. *Front Oncol* 12:780186 doi 10.3389/fonc.2022.780186

Jiang M, Chen P, Guo X, Zhang X, Gao Q, Zhang J, Zhao G, Zheng J. 2023. Identification of EGFR mutation status in male patients with non-small-cell lung cancer: role of (18)F-FDG PET/CT and serum tumor markers CYFRA21-1 and SCC-Ag. *EJNMMI Res* 13 (1):27 doi 10.1186/s13550-023-00976-5

Guo Y, Zhu H, Yao Z, Liu F, Yang D. 2021. The diagnostic and predictive efficacy of (18)F-FDG PET/CT metabolic parameters for EGFR mutation status in non-small-cell lung cancer: A meta-analysis. *Eur J Radiol* 141:109792 doi 10.1016/j.ejrad.2021.109792

Wang J, Wen X, Yang G, Cui Y, Hao M, Qiao X, Jin B, Li B, Wu J, Li X, Ren X. 2022. The predictive value of (18)F-FDG PET/CT in an EGFR-mutated lung adenocarcinoma population. *Transl Cancer Res* 11 (7):2338-2347 doi 10.21037/tcr-22-1726

Gao J, Shi Y, Niu R, Shao X, Shao X. 2023. Association Analysis of Maximum Standardized Uptake Values Based on (18)F-FDG PET/CT and EGFR Mutation Status in Lung Adenocarcinoma. *J Pers Med* 13 (3) doi 10.3390/jpm13030396

Ni M, Wang S, Liu X, Shi Q, Zhu X, Zhang Y, Xie Q, Lv W. 2023. Predictive value of intratumor metabolic and heterogeneity parameters on [(18)F]FDG PET/CT for EGFR mutations in patients with lung adenocarcinoma. *Jpn J Radiol* 41 (2):209-218 doi 10.1007/s11604-022-01347-1

Liu J, Dong M, Sun X, Li W, Xing L, Yu J. 2016. Prognostic Value of 18F-FDG PET/CT in Surgical Non-Small Cell Lung Cancer: A Meta-Analysis. *PLoS One* 11 (1):e0146195 doi 10.1371/journal.pone.0146195

Salavati A, Duan F, Snyder BS, Wei B, Houshmand S, Khiewvan B, Opanowski A, Simone CB, 2nd, Siegel BA, Machtay M, Alavi A. 2017. Optimal FDG PET/CT volumetric parameters for risk stratification in patients with locally advanced non-small cell lung cancer: results from the ACRIN 6668/RTOG 0235 trial. *Eur J Nucl Med Mol Imaging* 44 (12):1969-1983 doi 10.1007/s00259-017-3753-x

Figure 1

Figure 1 Flowchart of patient selection

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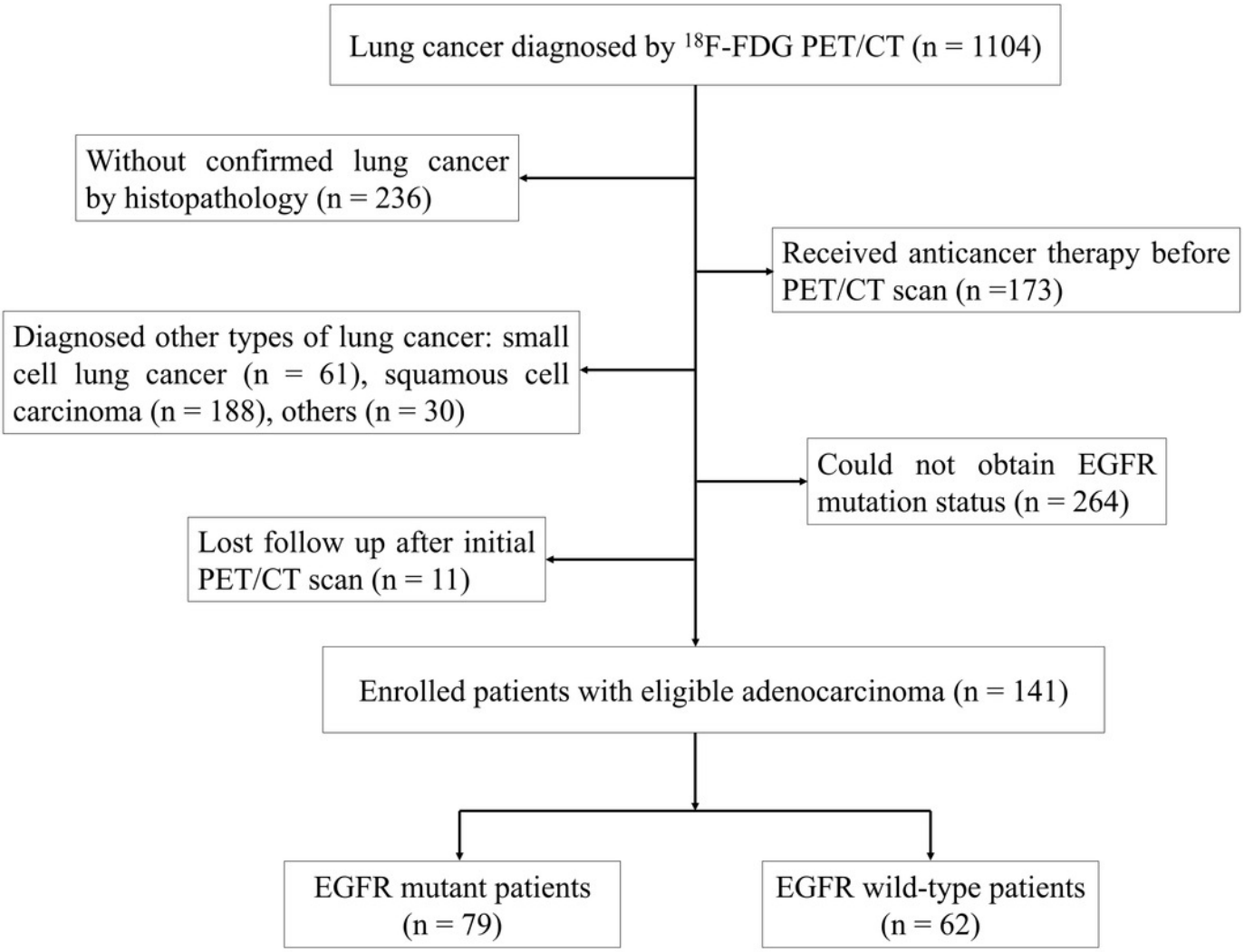


Figure 2

Figure 2 Survival analysis.

Kaplan–Meier plots depicting the progression-free survival (A) and overall survival (B) of all patients.

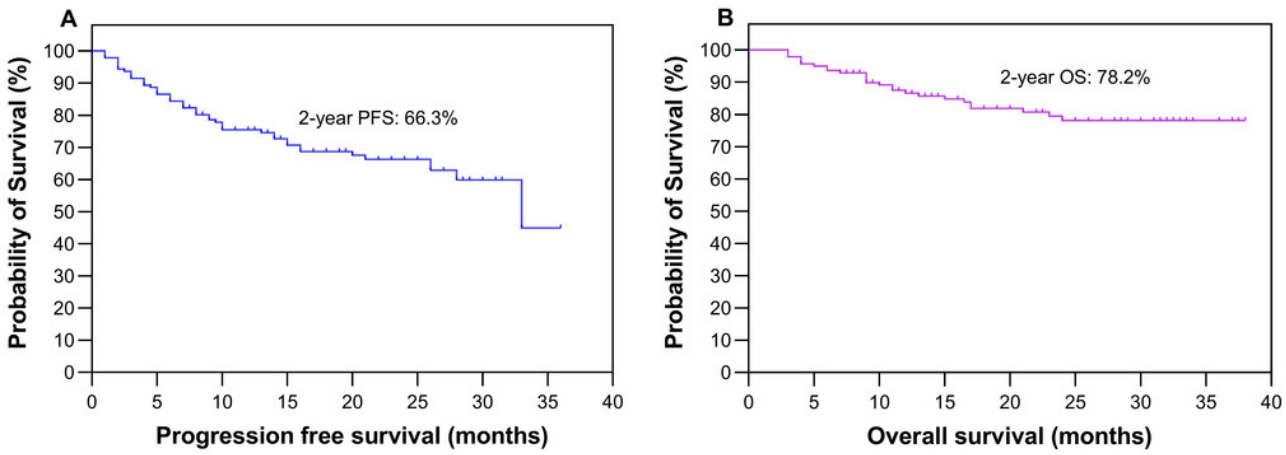
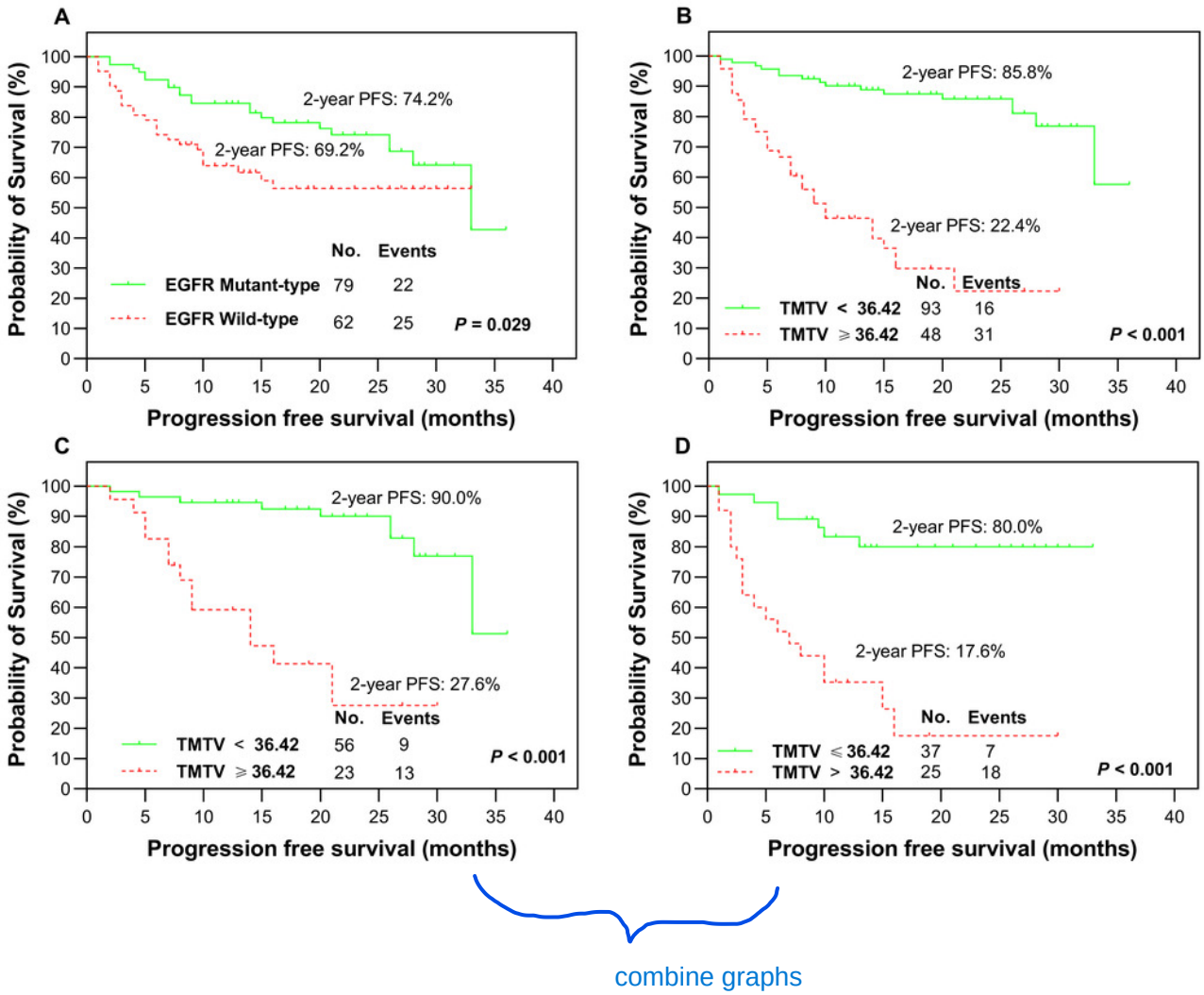


Figure 3

Figure 3 Survival comparision.

Kaplan–Meier plots were generated to analyze progression-free survival (PFS) in patients based on their EGFR mutation status (mutant-type vs. wild-type, A) and TMTV (≥ 36.42 cm^3 vs. < 36.42 cm^3, B). The optimal cutoff value of TMTV was used to restratify PFS in patients with LUAD, specifically in the EGFR mutant group (C) and wild-type group (D).

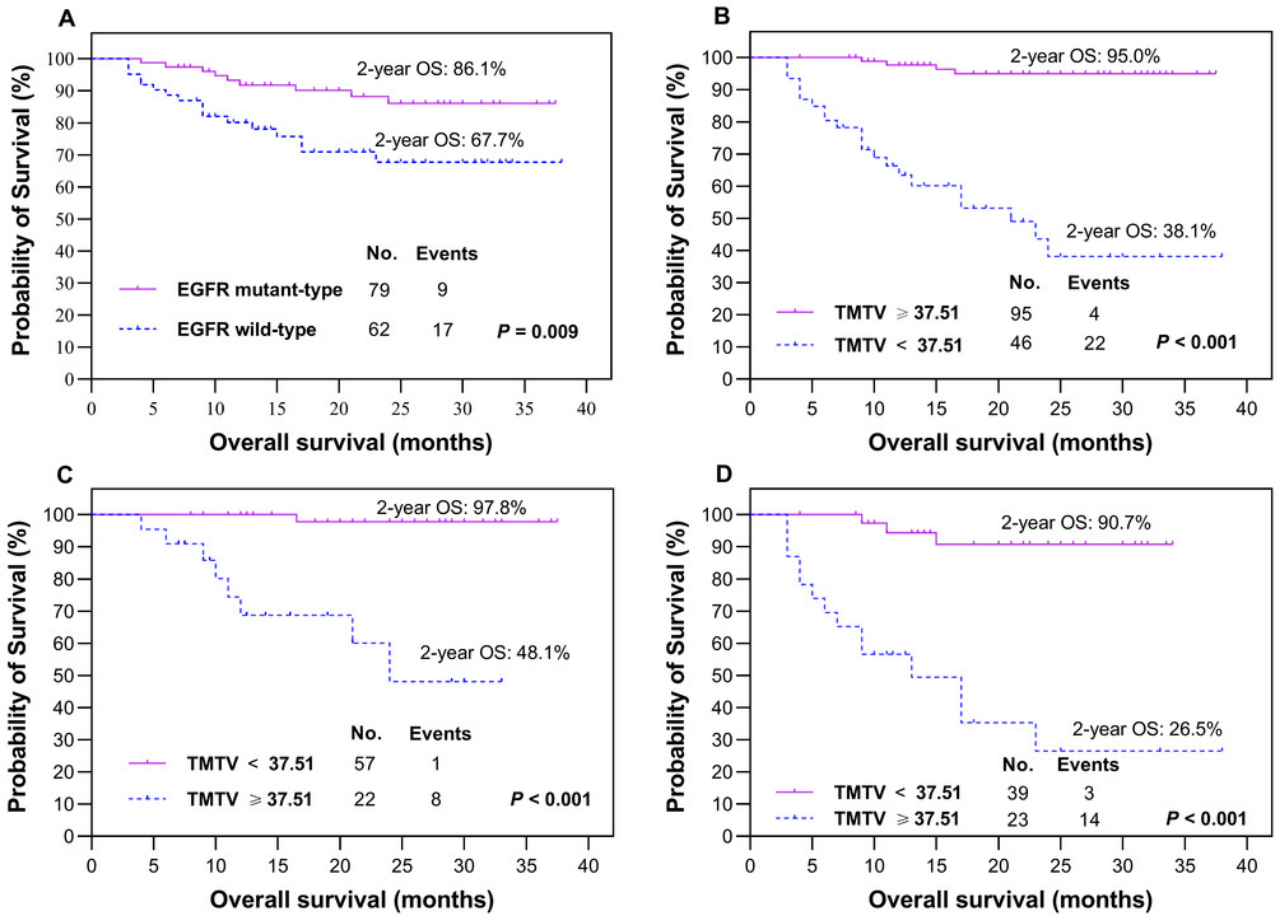


combine graphs

Figure 4

Figure 4 Survival comparision.

Kaplan–Meier plots were generated to analyze overall survival (OS) in patients based on their EGFR mutation status (mutant-type vs. wild-type, A) and TMTV (≥ 37.51 cm^3 vs. < 37.51 cm^3, B). The optimal cutoff value of TMTV was used to restratify OS in patients with LUAD, specifically in the EGFR mutant group (C) and wild-type group (D).



combine graphs.

Table 1(on next page)

Table 1 Comparison of clinical features and metabolic parameters between EGFR wild-type and mutant-type patients with adenocarcinoma

Comparison of clinical features and metabolic parameters between EGFR wild-type and mutant-type patients with adenocarcinoma

Table 1. Comparison of clinical features and metabolic parameters between EGFR wild-type and mutant-type patients with adenocarcinoma

Characteristics	Total	EGFR		*P* value
		Wild-type	Mutant-type	
Age, years				0.439
Median	67	68	67	
Range	34-86	34-86	36-85	
Gender (n, %)				0.006
Male	74 (52.5)	41 (29.1)	33 (23.4)	
Female	67 (47.5)	21 (14.9)	46 (32.6)	
Smoking history (n, %)				0.001
Never-smoker	96 (68.1)	33 (23.4)	63 (44.7)	
Ever-smoker	45 (31.9)	29 (20.6)	16 (11.3)	
Clinical TNM stage (n, %)				0.570
I	52 (36.9)	20 (14.2)	32 (22.7)	
II	21 (14.9)	8 (5.7)	13 (9.2)	
III	19 (13.5)	10 (7.1)	9 (6.4)	
IV	49 (34.7)	24 (17.0)	25 (17.7)	
$pSUV_{max}$				0.044
Median	8.96	10.53	8.56	
IQR	6.31-12.91	7.23-14.64	5.91-12.00	
pMTV				0.057
Median	6.87	9.95	4.39	
IQR	2.59-229.39	3.25-38.0	2.52-19.95	
pTLG				0.032
Median	36.93	62.98	20.65	
IQR	9.77-188.5	12.08-249.3	9.05-116.1	
TMTV				0.048
Median	14.83	28.43	9.47	
IQR	3.72-54.86	4.87-74.39	3.52-45.42	
TLG				0.025
Median	88.17	147.4	30.73	
IQR	12.67-322.9	25.52-508.1	10.43-249.9	

Table 2(on next page)

Table 2. Distribution of patient characteristics between TMTV groups in assessing progression free survival and overall survival

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Characteristics	PFS			OS		
	TMTV ≥ 36.42 cm^3	TMTV < 36.42 cm^3	*P* value	TMTV ≥ 37.51 cm^3	TLG < 37.51 cm^3	*P* value
Age (y, Median, IQR)	68 (61-74)	67 (62-72)	0.769	67 (61-74)	67 (62-72)	0.889
Gender			0.028			0.018
Male	42 (62.7)	32 (43.2)		45 (62.5)	29 (42.0)	
Female	25 (37.3)	42 (56.8)		27 (37.5)	40 (58.0)	
Smoking status			0.106			0.074
Never	41 (61.2)	55 (74.3)		44 (61.1)	52 (75.4)	
Ever or current	26 (38.8)	19 (25.7)		28 (38.9)	17 (24.6)	
TNM stage			< 0.001			< 0.001
I-II	9 (13.4)	64 (86.5)		11 (15.3)	62 (89.9)	
III-IV	58 (86.6)	10 (13.5)		61 (84.7)	7 (10.1)	
EGFR mutation status			0.065			0.007
Mutant-type	32 (47.8)	47 (63.5)		32 (44.4)	47 (68.1)	
Wild-type	35 (52.2)	27 (36.5)		40 (55.6)	22 (31.9)	

Table 3(on next page)

Table 3. Univariate and multivariate Cox regression analysis of clinical factors, metabolic parameters and EGFR mutation status in relation to patient's outcome

Table 3. Univariate and multivariate Cox regression analysis of clinical factors, metabolic parameters and EGFR mutation status in relation to patient's outcome

Table 3. Univariate and multivariate Cox regression analysis of clinical factors, metabolic parameters and EGFR mutation status in relation to patient's outcome

Characteristic	Univariate analysis for PFS			Multivariate analysis for PFS			Univariate analysis for OS			Multivariate analysis for OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.03	1.00-1.06	0.080				1.05	1.01-1.10	0.023	1.04	1.00-1.08	0.041
Gender			0.150						0.141			
Male	Reference						Reference					
Female	0.65	0.36-1.17	0.150				0.55	0.24-1.22	0.141			
Smoking history			0.049			0.085			0.179			
Never-smokers	Reference						Reference					
Smokers	1.79	1.00-3.19	0.049	1.72	0.93-3.18	0.085	1.70	0.78-3.71	0.179			
TNM stage			< 0.001			< 0.001			0.008			
I	Reference			Reference			Reference			Reference		
II	1.76	0.29-10.6	0.535	1.64	0.27-10.1	0.594	5.12	0.46-56.4	0.183	1.95	0.15-24.6	0.606
III	14.5	4.02-52.0	< 0.001	8.53	2.18-33.4	0.002	21.3	2.56-177	0.005	5.55	0.51-59.9	0.158
IV	18.3	5.57-60.2	< 0.001	11.7	3.23-42.6	<0.001	25.2	3.34-189	0.002	4.43	0.43-45.1	0.209
TMTV			< 0.001			0.007			<0.001			<0.001
< 36.42	Reference			Reference						/		
≥ 36.42	7.34	3.88-13.9	< 0.001	2.59	1.30-5.13	0.007						
< 37.51				/			Reference			Reference		
≥ 37.51							17.5	5.99-51.3	<0.001	8.08	2.34-28.0	<0.001
EGFR mutation			0.032			0.078			0.012			0.034
Wild-type	Reference			Reference			Reference			Reference		
Mutant-type	0.53	0.30-0.95	0.032	0.59	0.32-1.06	0.078	0.35	0.16-0.79	0.012	0.41	0.18-0.94	0.034

HR = Hazard Ratio, CI = Confidence Interval, OS = Overall Survival