Original Article

Omission of staging PET/CT linked to reduced survival in stage III non-small cell lung cancer: insights from the LUCAS project real-world data

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Background: Stage III non-small cell lung cancer (NSCLC) is a highly heterogeneous stage due to its subgroups (IIIA–IIIC) comprising both resectable and unresectable tumors. Accurate determination of the extent of the disease is essential for excluding stage IV and choosing the optimal treatment regimen. Whole body positron emission tomography and computed tomography scan (PET/CT) is recommended as an initial staging imaging in locally advanced NSCLC. Despite international guidelines for NSCLC diagnosis and treatment, they are not always adhered to due to various reasons. Even in such a groundbreaking study, the phase 3 trial PACIFIC investigating the efficacy of durvalumab as consolidation therapy in patients with stage III NSCLC PET/CT was not mandatory. With the premise that whole body PET/CT of the trunk is essential for diagnosing stage III NSCLC, we performed a retrospective study evaluating the relationship of the use of PET/CT versus conventional staging with CT of the chest and abdomen, in terms of survival.

Methods: This retrospective study of stage III NSCLC patients used the Czech lung cancer registry LUCAS, which was established in June 2018. As of the data export (up to February 9, 2022), a total of 703 patients were eligible for the analysis. Overall survival (OS) was compared using Kaplan-Meier analysis and a Cox regression model. Continuous variables were tested using the Mann-Whitney test, and categorical variables using the Pearson's Chi-square or Fisher's exact test.

Results: A total of 703 patients were included in the cohort with an average age of 69 years. PET/CT was

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performed on 354 patients, and conventional staging using chest and abdominal CT on 349 patients. The median OS among patients with PET/CT was 20.9 months [95% confidence interval (CI): 18.1–23.7], and it was statistically significantly higher (P<0.001) than among patients without PET/CT, where the median OS was 9.0 months (95% CI: 7.3–10.6). The observed effect of PET/CT was also statistically significant when comparing individual stages (IIIA, IIIB, IIIC). The multivariate Cox model confirmed the use of PET/CT as an independent prognostic factor. The most common reason for omission of PET/CT was the local or time unavailability of the examination.

Conclusions: Omission of PET/CT can mean a significant decrement in survival for the patients in stage III NSCLC, likely due to poor staging and suboptimal treatment. Routine use of PET/CT is strictly recommended for the optimal management of stage III NSCLC patients even outside the high-income countries.

Keywords: Lung cancer; staging; positron emission tomography and computed tomography (PET/CT); survival; stage III

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Introduction

Background

Lung cancer is the world's leading cancer in incidence and mortality in both men and women. Around 6,500 new lung cancer cases are diagnosed annually in the Czech Republic. Three-quarters of these cases are non-small cell lung cancer (NSCLC), and the rest are small cell lung cancer (SCLC) (1). Stage III NSCLC is an advanced stage of lung cancer, with different subgroups according to the extent of the primary tumor (T) and affliction of regional lymph nodes (N). Stage III (8th edition) comprises both resectable and unresectable tumors. For instance, we can meet resectable large tumors with invasion to the chest wall (T4) but without lymph node involvement (N0), and on the other hand relatively small tumors (3–4 cm, T2a) with unresectable lymph nodes involvement (namely invasive N2). Stage III NSCLC often requires a multimodal approach with the combination of treatments—local treatment (surgery or radiotherapy) plus systemic treatment (perioperative, neoadjuvant, adjuvant, or concurrent). Tumors unsuitable for local treatment (usually IIIC) are treated like stage IV. Positron emission tomography (PET), ideally combined with computed tomography (PET/CT) of the whole body in extent of torso, is an essential diagnostic method for stage III NSCLC. It is crucial for excluding metastatic stages and determining the optimal treatment plan for patients with potentially curative intent, such as surgery, radical radiotherapy, chemoradiotherapy. Accurate staging with PET/CT is more effective than CT of the chest and abdomen in detecting distant metastases, particularly in unexpected locations (5–29% more) (2-5). PET/CT changes the choice of therapeutic approach in up to 30–40% of NSCLC cases (6). PET/CT is also of prognostic importance (7,8).

Highlight box

Key findings

- Positron emission tomography and computed tomography (PET/CT) has been validated as an independent prognostic factor in stage III non-small cell lung cancer (NSCLC).
- The prognostic significance of PET/CT was confirmed for stage IIIA, IIIB and IIIC.

What is known and what is new?

- Accurate staging using whole-body PET/CT is essential for locally advanced lung cancers to exclude stage IV and settle an appropriate treatment. It has not yet been determined, if the omission of PET/CT is accompanied with survival decrement in stage III NSCLC.
- Findings strongly endorse the integration of PET/CT as an indispensable diagnostic modality in managing patients with stage III NSCLC.

What is the implication, and what should change now?

- Routine use of PET/CT is strictly recommended for the optimal management of stage III NSCLC patients even outside the high-income countries.

Rationale and knowledge gap

Initial PET/CT of the trunk is recommended for diagnosing both early and advanced lung cancer in European and American guidelines (5,9). European Society for Medical Oncology (ESMO) guidelines recommend PET/CT for all patients considered for curative treatment. However, National Comprehensive Cancer Network (NCCN) guidelines do not recommend PET/CT for tumors smaller than 3 cm, without hilar node involvement, where the risk of unexpected mediastinal metastases and distant metastases is minimal. A systematic review that included 18 studies from ten countries on PET/CT in lung tumors and solitary lung lesions, despite the heterogeneity of the studies, documented the cost-effectiveness of PET/CT over conventional CT staging (10,11). Yet, there are still significant differences in using PET/CT for staging in real-world practice. Even in such groundbreaking study, phase 3 trial PACIFIC (NCT02125461) investigating the efficacy of durvalumab as consolidation therapy in patients with stage III NSCLC PET/CT was not mandatory (12,13).

Numerous studies have documented the sensitivity, specificity, and accuracy of PET/CT in lung cancer staging (14,15). It must be emphasized repeatedly that both more accurate M and N staging by PET/CT increases the chances of selecting the correct treatment for patients and for high-quality treatment. It has been reported that up to 35% of NSCLC cases staged with CT experience a change in staging when evaluated with PET. In the majority of cases, this results in upstaging leading to a change in treatment approach. The impact of PET on staging has shown an up-stage in 33–41%, and down-stage in 9.5–10% of cases (16-18). A meta-analysis showed that PET/CT has a sensitivity and specificity of 84% and 89%, respectively, compared to conventional staging with CT, which has 57% and 84%, respectively. Some studies have demonstrated that 17–24% of patients with stage III disease were upstaged to stage IV due to unexpected metastases detected by PET/CT (19).

However, publications demonstrating the benefit of PET/CT in terms of prolonged overall survival (OS) compared to conventional chest and abdominal CT staging are limited. Most research focuses on early-stage patients, consistently showing about a 20% reduction in unnecessary thoracotomy. Some studies showed no differences in stages I, II, but significant differences were noted in resectable stage III (20,21). In radiotherapy, PET/CT is invaluable for radiotherapy planning. It allows for better delineation of the extent of the disease gross tumor volume (GTV) and functional tumor volume (FTV), especially in areas of atelectasis or inflammation behind tumor stenosis. This accuracy is crucial for the quality of radiation treatment and its effects, including OS (22). A pivotal paper evaluating the benefit of PET/CT *vs.* CT staging in the context of survival among a broad population of lung cancer patients was published. It was found that PET/CT use was correlated with higher levels of care and resulted in lower mortality in patients with NSCLC. The study has several limitations. The primary concern is that therapeutic options improved over those 13 years (23).

Objective

The aim of our study was to evaluate the use of whole-body PET/CT as an initial staging modality for patients enrolled in the LUCAS project, diagnosed with clinical stage III NSCLC. Additionally, we aimed to assess whether the performance of PET/CT correlates with OS. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-108/rc).

Methods

LUCAS registry

The data source for the presented study is the national registry—LUCAS. The LUCAS registry is a joint project of the Czech Pneumological and Phthisiological Society, Czech Medical Association of J. E. Purkyně. LUCAS registry focuses on monitoring and continuously evaluating the extent, structure, and quality of care for lung cancer patients in the Czech Republic [code C34 according to the International Classification of Diseases, version 10 (ICD-10)] from establishing the diagnosis through their entire lifespan. Established on June 1, 2018, the LUCAS registry prospectively follows lung cancer patients across 11 pneumo-oncology centers in the Czech Republic, of which seven are included in the current analysis. The project is registered at ClinicalTrials.gov under registration number NCT04228237. All participants were required to sign an informed consent form as a prerequisite to their participation in the registry. The study had been approved by the Ethics Committee of University Hospital Olomouc, Faculty of Medicine and Dentistry, Palacky University (No. 63/18 MEK 13). The study was conducted in accordance

with the Declaration of Helsinki (as revised in 2013).

In the LUCAS registry, basic demographic and clinical characteristics, performance status (PS) assessment according to the Eastern Cooperative Oncology Group (ECOG), morphological, immunohistochemical, immunochemical, and molecular genetic characteristics, data about pharmacotherapy (including types, combinations and sequences), data about other interventions (including surgery, radiotherapy and endobronchial therapy), are recorded.

All the data and results published in this article were processed in cooperation with OAKS Consulting s.r.o., responsible for project management and output processing.

Study population

Eligible patients had histologically or cytologically confirmed locally advanced NSCLC, stage III, and met the study conditions based on the inclusion and exclusion criteria.

Inclusion criteria were: age ≥18 years, histologically or cytologically confirmed diagnosis of locally advanced NSCLC stage III, complete data of monitored parameters: ECOG score for PS (ECOG PS), smoking status, morphological diagnosis, tissue collection method, date of diagnosis, and Tumor Nodes Metastasis (TNM) Classification of Malignant Tumors.

Exclusion criteria were: SCLC, neuroendocrine type of tumor, unknown tumor type, staging CT done in the center prior to PET/CT, and incomplete data of monitored parameters: ECOG PS, smoking status, morphological diagnosis, tissue collection method, date of diagnosis establishment, and TNM. A patient with NSCLC was defined as having the following tumor types: adenocarcinoma; adenosquamous carcinoma; carcinoma NOS (not otherwise specified); squamous cell carcinoma; large cell carcinoma, and large cell carcinoma referred to as "other non-squamous". A non-smoker is defined as a patient who has never smoked in their life. A former smoker is defined as a patient who has not smoked for at least 1 year. Tumor location was determined according to the ICD-10 diagnosis code: C34.0—main bronchus; C34.1—upper lobe bronchus or lung; C34.2—middle lobe bronchus or lung; C34.3—lower lobe bronchus or lung; C34.8—overlapping lesion of bronchus and lung; C34.9—bronchus or lung, unspecified.

Methods of staging

Methods of staging were as follows: in the PET/CT group—whole-body PET/CT (in extent of torso), bronchoscopy, endobronchial ultrasound (EBUS)/endoscopic ultrasonography (EUS) if indicated (for surgery candidates with positive mediastinal lymph nodes on PET/CT), and optional brain magnetic resonance imaging (MRI). In the CT group: chest and abdomen CT, bronchoscopy, EBUS/EUS if indicated (for surgery candidates with positive mediastinal lymph nodes on CT) and optional brain CT or MRI.

PET/CT and CT imaging

PET/CT examinations were performed on devices of different manufacturers and using local examination protocols. Despite variations, all centers followed standard procedures generally recommended for lung cancer staging. All examinations utilized ^{18}F-fluorodeoxyglucose [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) after a fasting period of at least 6 hours and with glycemic control maintained. The blood glucose cut-off for PET/CT was set at 180 mg/dL. The radiopharmaceutical activity was adjusted based on the patient's weight as per recommendations, and examinations were performed approximately 60 minutes post-application. PET/CT was conducted in the extent of the whole-body, respectively "torso", typically including the brain. Most centers employed full-dose CT during PET/CT imaging. PET/CT and CT protocol parameters (kV, mA, time for one bed position, slice thickness, etc.) were used according to the local standard of each center.

Statistical analysis

Kaplan-Meier method was used to estimate the OS. The date of death was obtained from the Czech Statistical Office on 31 March 2022. These data were supplemented with death information from the "Reimbursement payment (K-batch)" and the CLADE information system for manual data entry into the LUCAS registry. Subsequently, duplicates were removed. Living patients were censored at the last date they were known to be alive. Moreover, a few patients were censored at the date of loss to follow-up. Basic statistics such as the proportion of patients with a recorded event and median OS with a 95% confidence interval (CI) were presented. The log-rank test (Mantel-Cox) and Cox regression model were used to compare survival between the study groups. The influence of a given variable on OS is then quantified using hazard ratios (HRs). For a categorical variable, for instance, patients have a 2-fold higher risk of

Table 1 Basic demographics and clinical characteristics

Characteristics	Total (N=703)
Patients with PET/CT, n (%)	354 (50.4)
Sex, n (%)	
Male	468 (66.6)
Female	235 (33.4)
Age at diagnosis† (years)	
Mean (SD)	68.97 (8.301)
Median	70.00
5th; 95th percentile	54.00; 81.00
<65, n (%)	183 (26.0)
≥65, n (%)	520 (74.0)
Year of diagnosis, n (%)	
2018	117 (16.6)
2019	255 (36.3)
2020	185 (26.3)
2021	143 (20.3)
2022	3 (0.4)
Smoking status, n (%)	
Smoker	368 (52.3)
Former smoker	252 (35.8)
Non-smoker	60 (8.5)
Unknown	23 (3.3)
Performance status, n (%)	
0	149 (21.2)
1	395 (56.2)
2	106 (15.1)
3	19 (2.7)
Not evaluated	34 (4.8)
Stage, n (%)	
IIIA	284 (40.4)
IIIB	287 (40.8)
IIIC	132 (18.8)
Type of tumor, n (%)	
Adenocarcinoma	242 (34.4)
NOS	40 (5.7)
Adenosquamous carcinoma	15 (2.1)
Squamous cell carcinoma	390 (55.5)
Other non-squamous	16 (2.3)
Treatment regimens, n (%)	
Without intervention	153 (21.8)
Chemoradiotherapy (platinum-based)	65 (9.2)
Surgery	132 (18.8)
Chemotherapy	303 (43.1)
Radiotherapy	50 (7.1)

†, age at diagnosis C34 morphologically. N, total number of patients; PET/CT, positron emission tomography and computed tomography; SD, standard deviation; NOS, not otherwise specified.

an event at an HR =2 for a given category than patients in the reference category if the values of the other variables remain unchanged. Continuous variables were tested using the Mann-Whitney test; either Pearson's χ^2 test or Fisher's exact test was used for categorical variables. Hypothesis testing was performed at a 5% significance level. P values lower than this level correspond to statistically significant differences. The analysis was performed using IBM SPSS Statistics 29, and R software was utilized to plot the survival curves.

Results

The primary parameter for evaluation was the presence or absence of PET/CT.

The LUCAS registry was established in June 2018. At the date of data export up to February 9, 2022, 703 patients were eligible for the assessment based on inclusion and exclusion criteria (first patient included in the register on June 1, 2018). Baseline characteristics can be seen in *Table 1*. The median age of all patients was 69 years, the majority were men (66.6%) and current or former smokers (88.1%). The percentage of IIIA, IIIB, IIIC were 40.4%, 40.8% and 18.8% respectively. Most of the patients had ECOG PS score 1 (56.2%). Fifty-five point five percent of patients had squamous cell carcinoma.

A total of 354 (50.4%) patients underwent whole-body PET/CT as an initial staging method and 349 (49.6%) patients underwent conventional staging using CT of the thorax and abdomen. Differences are present between the two arms (Table S1), resulting from retrospective patient evaluation. There were significant differences in the PET/

Table 2 Overall survival of patients according to PET/CT status

Parameters of overall survival	Non-PET/CT (N=349)			PET/CT (N=354)			Comparison (P value)
	N	Number of events, n (%)	Median survival (months) (95% CI)	N	Number of events, n (%)	Median survival (months) (95% CI)	
Total population	349	262 (75.1)	9.0 (7.3–10.6)	354	185 (52.3)	20.9 (18.1–23.7)	<0.001
Stage IIIA	116	81 (69.8)	11.0 (5.9–16.0)	168	71 (42.3)	34.2 (24.0–44.4)	<0.001
Stage IIIB	153	110 (71.9)	9.3 (6.9–11.6)	134	77 (57.5)	20.4 (16.7–24.0)	<0.001
Stage IIIC	80	71 (88.8)	6.1 (3.0–9.2)	52	37 (71.2)	13.4 (8.9–17.8)	0.01

PET/CT, positron emission tomography and computed tomography; N, total number of patients; CI, confidence interval.

CT use across the centers. The use of PET/CT as an initial imaging ranged between 2.8–96.6% (Table S2). The most common reason for omitting PET/CT was limited local and time availability of the examination. No statistically significant changes of the PET/CT use were found in the centers over the course of time (Table S3).

Since there was a difference in some parameters (age, smoking status, PS, type of tumor, stage, T classification of tumor, and treatment regimens), a Cox regression model was performed to account for the influence of these variables on PET/CT performance and its effect on OS.

The median OS was statistically significantly higher in patients with PET/CT than with only CT—20.9 (95% CI: 18.1–23.7) *vs.* 9.0 (95% CI: 7.3–10.6) months, P<0.001. The statistically significant difference was observed for various stages (IIIA, IIIB, IIIC) as presented in *Table 2*. The median OS in PET/CT group *vs.* CT group in stage IIIA, IIIB and IIIC was 34.2 *vs.* 11.0, 20.4 *vs.* 9.3 and 13.4, *vs.* 6.1 months, respectively. Differences in OS between groups are illustrated using Kaplan-Meier curves in *Figure 1*.

Multivariate analysis using Cox regression model

Cox regression model showed that a statistically significant difference in OS according to the PET/CT status was independent prognostic factor when adjusted for basic clinical and demographic characteristics. The results of Cox regression model are presented in *Table 3*.

Discussion

Our aims were to evaluate the use of staging whole-body PET/CT in the LUCAS registry project and determine whether performing PET/CT correlates with the survival. In our study, there are significant differences between the centers in the use of PET/CT as an initial staging method. We found that survival of patients who underwent staging using PET/CT of the trunk was more than twice that of those with conventional staging using CT of the thorax and abdomen (20.9 *vs.* 9.0 months). The most pronounced difference was seen in stage IIIA disease. The use of staging whole-body PET/CT was identified as an independent prognostic factor for survival in stage III NSCLC patients when adjusted for basic clinical and demographic characteristics (age, sex, stage, histology, PS, smoking, type of treatment). Our 4-year retrospective study showed no significant differences in the indication for PET/CT within individual years, suggesting that time does not play a crucial role in our findings.

In the literature, there is limited data evaluating the benefit of staging with PET/CT *vs.* CT in terms of OS. Most research focuses on early-stage patients, with consistent evidence of approximately a 20% reduction in unnecessary thoracotomy and survival benefits only in stage III patients (20,24). In our study, the greatest difference in survival was found in stage IIIA patients, who are potentially resectable, with survival being more than three times higher compared to the CT group (34.2 *vs.* 11.0 months). The reason for better survival in the PET/CT group is more accurate staging and the establishment of appropriate treatment. Some data indicate that around 20% of stage III patients are upstaged to stage IV by PET/CT (19). Despite the fact that PET/CT is routinely recommended in the guidelines for NSCLC patients, it was not mandated in the landmark and practice-changing PACIFIC study. This study in stage III patients demonstrated the benefit of adjuvant durvalumab following successful chemoradiotherapy (12,25). EBUS/EUS is another basic diagnostic procedure in stage III. According to the current recommendations, PET/CT-positive lymph nodules should be verified by invasive mediastinal staging, with EBUS/EUS being the first available option, followed by mediastinoscopy. Mediastinal

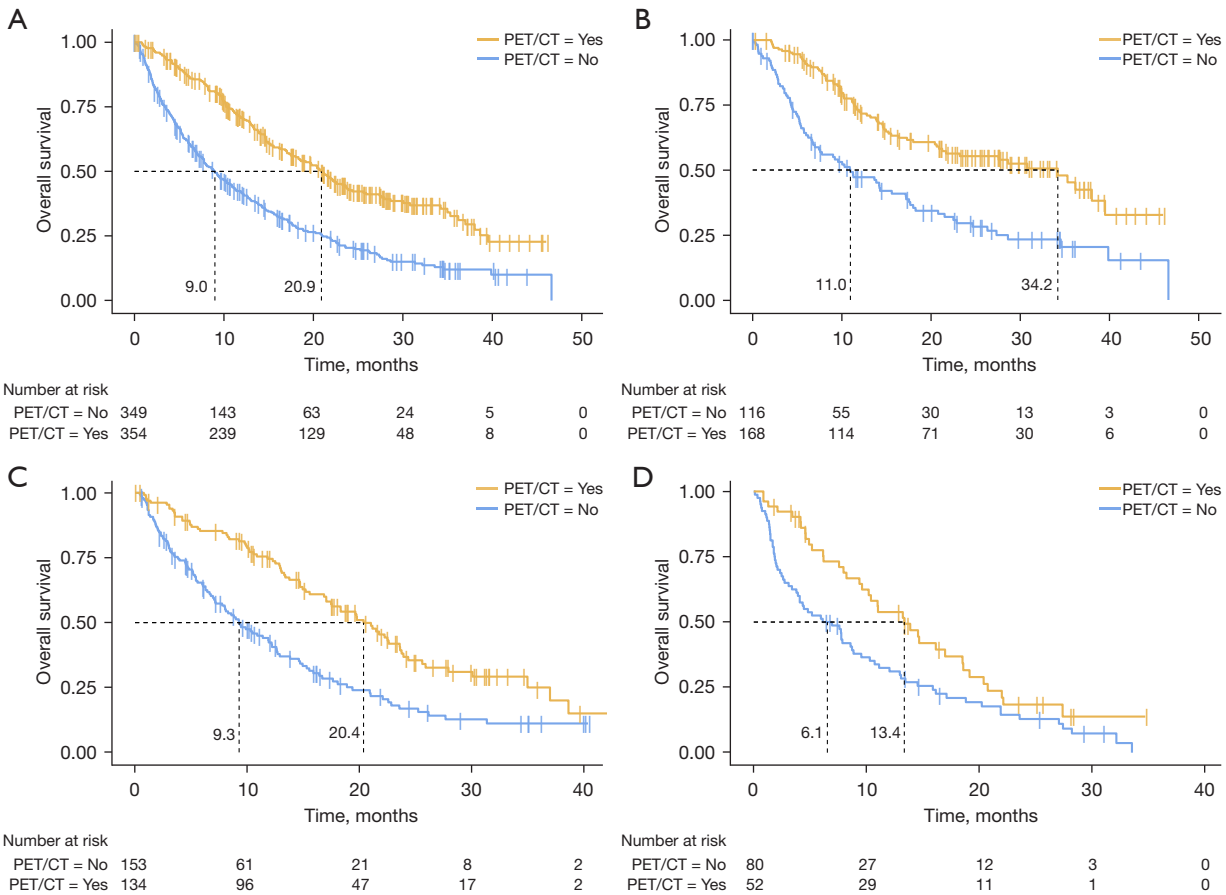

Figure 1 Survival analysis using the Kaplan-Meier curve—comparison of a group of patients according to PET/CT status. (A) Overall survival in patients with stage III; (B) overall survival in patients with stage IIIA; (C) overall survival in patients with stage IIIB; (D) overall survival in patients with stage IIIC. PET/CT, positron emission tomography and computed tomography.

staging with EBUS/EUS was standard for potential surgery candidates across all centers. However, the majority of patients in our study were not candidates for surgery and precise data on biopsy confirmation are not available in our analysis. All centers involved in our study required to meet the quality standards of a Complex Oncology Center in the Czech Republic. It can be assumed that they all adhere to modern diagnostic practices, have access to novel treatments, and employ qualified and experienced pulmonologists, oncologists, surgeons and radiotherapists. However, it should be further investigated in future studies why, despite the availability of modern methods and qualified doctors, there is limited access to PET/CT in some centers. In NSCLC, adherence to guidelines varies and has a negative impact on patient survival (26,27). We must identify and overcome barriers to adherence.

Our study has several limitations. It relied exclusively on the LUCAS registry. Therefore, the main limitation was the retrospective study design. Potential biases include differences in smoking status, age, PS, type of tumor, stage (IIIA–IIIC) between CT and PET/CT subgroups. We have yet to determine the exact impact of treatment regimens across centers. However, given that the study was conducted within one country, we can rule out differences in the availability of treatment regimens between centers. We believe that the sufficient number of patients in this study largely mitigates this potential bias.

Conclusions

Omission of PET/CT can mean a significant decrement in survival for the patient in stage III NSCLC, likely

Table 3 Cox regression model for overall survival

Covariates	Adjusted HR	95% CI	P value
Performance status			
0	Ref.	–	–
1	1.025	0.786–1.337	0.86
2	2.143	1.535–2.991	<0.001
3	2.879	1.616–5.127	<0.001
Not evaluated	0.866	0.514–1.461	0.59
Smoking status			
Smoker	Ref.	–	–
Non-smoker	0.737	0.492–1.105	0.14
Former-smoker	1.149	0.934–1.412	0.19
Unknown	1.165	0.690–1.968	0.57
Sex			
Male	Ref.	–	–
Female	0.903	0.730–1.117	0.35
Age at diagnosis[†]			
<65 years	Ref.	–	–
≥65 years	1.181	0.934–1.495	0.17
Type of tumor			
Adenocarcinoma	Ref.	–	–
NOS	1.101	0.885–1.388	0.65
Adenosquamous carcinoma	1.860	1.033–3.350	0.04
Squamous cell carcinoma	1.108	0.885–1.388	0.37
Other non-squamous	1.789	0.929–3.443	0.08
Stage			
IIIA	Ref.	–	–
IIIB	1.376	1.094–1.730	0.006
IIIC	2.029	1.555–2.649	<0.001
Treatment regimens			
Without intervention	Ref.	–	–
Chemoradiotherapy (platinum-based)	0.417	0.288–0.604	<0.001
Surgery	0.287	0.202–0.409	<0.001
Chemotherapy	0.461	0.288–0.356	<0.001
Radiotherapy	0.616	0.597–0.909	0.02
PET/CT			
No	Ref.	–	–
Yes	0.596	0.485–0.731	<0.001

[†], age at diagnosis C34 morphologically. HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; Ref., reference; PET/CT, positron emission tomography and computed tomography.

due to poor staging and suboptimal treatment. Routine use of PET/CT is strictly recommended for the optimal management of stage III NSCLC patients even outside the high-income countries.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-108/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All participants were required to sign an informed consent form. The study had been approved by the Ethics Committee of University Hospital Olomouc, Faculty of Medicine and Dentistry, Palacky University (No. 63/18 MEK 13). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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