e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2024, Volume 29, Number 1, pages: 97–102
DOI: 10.5603/rpor.99360
Submitted: 13.09.2023
Accepted: 23.01.2024

Value of [^{18}F]FDG PET/CT parameters of the primary tumor in assessing overall survival in NSCLC patients with cN1–cN3 lymph nodes involvement

Paulina Cegla[1], Frank Hofheinz[2], Rafał Czepczyński[3, 4], Kamila Witkowska[3], Jörg van den Hoff[2], Maciej Trojanowski[5], Agnieszka Bos-Liedke[6], Witold Cholewinski[7, 1]

[1]Department of Nuclear Medicine, Greater Poland Cancer Centre, Poznan, Poland
[2]Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research, Dresden, Germany
[3]Department of Nuclear Medicine, Affidea, Poznan, Poland
[4]Department of Endocrinology, Metabolism and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland
[5]Greater Poland Cancer Registry, Greater Poland Cancer Centre, Poznan, Poland
[6]Department of Biomedical Physics, Adam Mickiewicz University, Poznan, Poland
[7]Department of Electroradiology, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Background: The aim of this retrospective study was to assess the value of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT parameters in cN1-cN3 non-small cell lung cancer (NSCLC) patients.

Materials and methods: 59 consecutive patients (35 M, 24 F) with NSCLC who underwent pretreatment [^{18}F]FDG PET/CT were enrolled to this study. Several primary tumor PET parameters, including the maximum and mean standardized uptake value (SUV_{max} and SUV_{mean}), the metabolic active tumor volume (MTV) and the total lesion glycolysis (TLG = MTVxSUV_{mean}), were extracted and analysed. Overall survival was defined as time from primary diagnosis to death or the last info.

Results: In the whole analysed group 44 patients underwent curative treatment, while 15, because of the severity of the disease, were classified for palliative treatment. Univariate Cox analysis of clinical and metric PET parameters revealed that MTV was a significant prognostic factor for OS ($p = 0.024$), while TLG and curative treatment showed a trend for significance ($p < 0.1$). In multivariate Cox regression (MTV and curative treatment) MTV remained a significant factor ($p = 0.047$).

Conclusions: Metabolic tumor volume of the primary tumor was the only independent prognostic factor for cN1–cN3 NSCLC patients.

Key words: positron emission tomography/computed tomography; NSCLC; overall survival

Rep Pract Oncol Radiother 2024;29(1):97–102

Introduction

Lung cancer is one of the most common cause of cancer incidence and mortality worldwide [1]. The treatment and prognosis for the non-small cell lung cancer (NSCLC) are poor and identifying the prognostic factors for these patients is challenging and in clinical interest [2]. Common-

Address for correspondence: Paulina Cegla PhD, Department of Nuclear Medicine, Greater Poland Cancer Centre, Garbary 15, 61–866 Poznan, Poland; e-mail: paulina.cegla@wco.pl

ly used tumor-nodes-distant metastasis (TNM) classification still remains the primary and mostly independent prognostic factor for overall survival (OS) in NSCLC patients [3]. Standard imaging techniques in staging and assessing therapy response in NSCLC includes computed tomography (CT), rentgenography (RTG), endoscopic examination, endobronchial ultrasonography (EBUS) or esophageal ultrasonography (EUS) and, more recently, positron emission tomography/computed tomography with the most commonly used radiopharmaceutical — ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) which has been a helpful imaging modality over the past decade in diagnosis and assessing therapy response in NSCLC [2, 3]. Overall survival is highly dependent on the stage of the disease and, according to some authors, preoperative [^{18}F]FDG uptake in primary tumor is associated with OS and time to recurrence (TTR) [2, 4]. Moreover, an [^{18}F]FDG PET-derived parameters provide additional information to the TNM stage, especially metabolic parameters of the tumor expressed with metabolic tumor volume (MTV) and total lesion glycolysis (TLG) vary with TNM stage and thus can be used as a biological description system for lung cancer [5].

The aim of the study was to assess [^{18}F]FDG PET-derived parameters of the primary tumor on overall survival in patients with cN1-cN3 NSCLC.

Table 1. Patient and tumor characteristics

Characteristics	Value
Age (years)	
Mean ± SD Median	68 ± 11 68
Sex	
Male	35 (59.3)
Female	24 (40.7)
Curative treatment	
Yes	44 (75)
No	15 (25.4)
Surgery	
Yes	9 (15)
No	50 (84.7)
T stage	
T1	8 (13.6)
T2	13 (22)
T3	17 (28.8)
T4	21 (35.6)
N stage	
N1	20 (33.9)
N2	18 (30.5)
N3	21 (35.6)
M stage	
M0	59 (100)
UICC stage	
II	8 (13.6)
III	51 (86.4)

SD — standard deviation; T — tumor stage; N — lymph node stage; M — metastasis; UICC — Union for International Cancer Control

Materials and methods

Patients characteristics

In the present study 59 consecutive patients (35 male, 24 female) with untreated NSCLC were included retrospectively. All patients gave their informed consent for the examination. Most of the patients (n = 44) received an curative treatment, while in 12 patients with N3 stage and 3 with T4 stage, because of the tumor involvement, palliative treatment was performed. A summary of patient and tumor characteristics is given in Table 1. Patients with the presence of distant metastases were excluded from the analysis. All patients had been fasting for at least 6 hours before the examination (average glucose level was 102.91 ± 23.41 mg/dL). OS was defined as time from primary diagnosis (taken from Greater Poland Cancer Registry) to death or the last info. Patients' clinical stage was defined using the TNM 8th edition. Ethical approval as well as Bioethics Committee approval was waived, because of the retrospective nature of the study.

[^{18}F]FDG PET acquisition

All patients underwent a hybrid [^{18}F]FDG PET/CT scan prior to therapy. [^{18}F]FDG PET/CT scans (3D PET acquisition, 90 s per bed position) were performed on a Gemini TF PET/CT (Philips Healthcare, Best, The Netherlands). Data acquisition started 45 ± 25 min (50–70) after intravenous (*i.v.*) injection of [^{18}F]FDG with mean activity of 364 ± 75 MBq. Scans were performed from the skull vertex to mid-thigh with scan time 1.30 min per table. CT scans (100–150 mAs, 120 kV,

slice thickness of 5 mm) were performed before PET imaging without changing the patient's position. Tomographic images were reconstructed using the BLOB-OS-TF reconstruction (3 iterations, 33 subsets) and CT based attenuation correction.

Image analysis

The metabolically active part of the primary tumor was delineated in the PET data by an automatic algorithm based on adaptive thresholding considering the local background [6, 7]. For the resulting regions of interest (ROI) the maximum and mean standardized uptake value (SUV_{max} and SUV_{mean}), the metabolic active tumor volume (MTV) and the total lesion glycolysis (TLG = MTVxSUV_{mean}) were computed. ROI definition and analysis was performed using the ROVER software, version 3.0.62 (ABX, Radeberg, Germany).

Statistical analysis

Survival analysis was performed with respect OS. The association of OS with clinical as well as quantitative PET parameters was analyzed using univariate Cox proportional hazard regression in which the PET parameters were included as metric parameters. PET parameters showing a significant effect in this analysis were further analyzed in univariate Cox regression using binarized PET parameters. The cutoff values were calculated by minimizing the p-value in univariate Cox regression as described in [8]. The probability of survival was computed and rendered as Kaplan-Meier curves. Independence of parameters was analyzed by multivariate Cox regression.

Statistical significance was assumed at a P-value of less than 0.05. Statistical analysis was performed with the *R language and environment for statistical computing* version 4.1.1 [9].

Results

Patient and tumor characteristics is presented in Table 1.

Univariate Cox analysis of clinical parameters and metric PET parameters revealed MTV as a significant prognostic factor for OS ($p = 0.024$). TLG and curative treatment showed a trend for significance ($p < 0.1$) (Tab. 2). Other investigated parameters did not reach significance and were, therefore, not further analysed.

After binarization also TLG was a significant factor for OS (HR = 2.06, 95% CI: 1.05–4.05, $p = 0.035$) in univariate analysis. However, this analysis revealed a notably larger HR for MTV (HR = 3.08, 95% CI: 1.46–4.05, $p = 0.003$) compared to TLG. Corresponding Kaplan-Meier curves are shown in Figure 1. In multivariate Cox regression (MTV and curative treatment) MTV remained a significant factor (HR = 1.01, 95% CI: 1.0–1.02, $p = 0.047$) indicating its independent prognostic value.

Table 2. Cox regression with respect to overall survival (OS). Univariate Cox regression. Positron emission tomography (PET) parameters were included as metric parameters

Parameter	HR	95% CI	p-value
Sex male	1.44	0.79–2.63	0.23
Age >68y	0.87	0.48–1.57	0.64
Curative treatment	0.57	0.3–1.1	0.096
Surgery	0.67	0.3–1.5	0.33
T-stage >3	1.62	0.88–2.97	0.12
N-stage >1	1.41	0.75–2.65	0.29
UICC-stage >II	1.38	0.58–3.28	0.46
MTV	1.01	1–1.02	0.024
TLG	1.001	1–1.002	0.068
SUV_{max}	0.97	0.91–1.03	0.37
SUV_{mean}	0.96	0.87–1.07	0.44

HR — hazard ratio; CI — *confidence interval*; UICC — Union for International Cancer Control; MTV — metabolic tumor volume; TLG — total lesion glycolysis; SUV_{max} — maximum standardized uptake value; SUV_{mean} — mean standardized uptake value

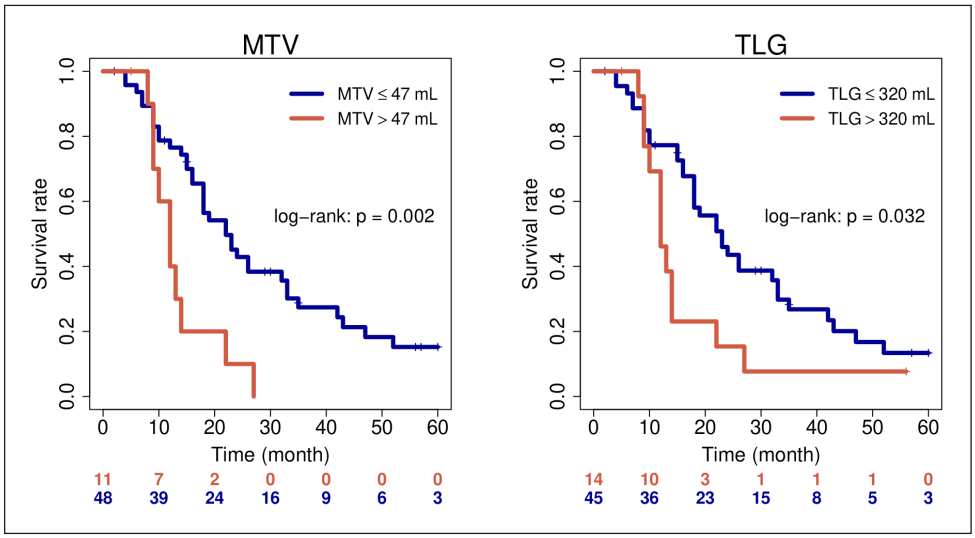

Figure 1. Kaplan-Meier curves with respect to overall survival (OS). MTV — metabolic active tumor volume; TLG — total lesion glycolysis

Discussion

Multiple authors in their works showed that MTV and TLG are independent prognostic factors for OS. Nappi et al. in their study conducted on a group of 103 NSCLC patients staged IIIB and IV showed that primary tumor SUV_{max}, up to 6.3, MTV up to 8.4 cm^3 and TLG up to 259 is associated with worse progression free survival in NSCLC patients [2]. Moreover, they also noted that in patients with lymph node involvement primary tumor MTV showed significantly ($p < 0.05$) better outcome in those with lower values compared to those with higher primary MTV values. The cut-off value for discrimination of these two groups was 10.9 cm^3 (94% sensitivity, 54% specificity) [2]. Our study in multivariate COX analysis discriminate 1 potential PET-derived parameters for OS in NSCLC patients with N1-N3 lymph node involvement. The MTV value obtained in our study varies from those presented by Nappi et al., which might be caused by the notably smaller group of patients in this study.

Wang et al. on a group of 92 nonsurgical NSCLC patients showed in univariate analysis that OS was associated with MTV (cut-off 10 ml) and TLG (100 g) [10]; however, in multivariate analysis OS was not essential to any of [^{18}F]FDG PET-derived parameters, neither for primary tumor nor lymph nodes [16]. In our study we observed that only MTV remained a significant independent prognostic value in respect to OS in NSCLC patients.

Chardin et al. indicate that poor OS is associated with primary tumor MTV above 36.5 cm^3 ($p < 0.001$) and TLG above 267 ($p < 0.001$) [11], while Kwon et al. noted that patients in stage I NSCLC and tumor size > 3 cm and $SUV_{max} > 9$ of primary tumor showed a poor 3-year survival rate [4]. 41% of patients with SUV_{max} value between 7.2 and 14.2 were still alive, while in SUV_{max} with less than 3.4 — 77% of patients showed 5-year survival rate [4]. This study indicate that only primary tumor MTV is a significant prognostic factor in stage cN1-cN3 NSCLC patients, while other clinical and PET-derived parameters did not show any association with OS in the analysed group.

In a recent published meta-analysis by Pellegrino et al. it was noted that volumetric PET-based parameters like MTV and TLG were relevant prognostic factors in NSCLC patients either in staging, after induction therapy or in the assessing response to applied therapy and are better in determination of OS and PFS than SUV_{max} [12]. They also noted that the higher SUV_{max}, MTV and TLG of the primary tumor caused the risk of recurrence or death increase in NSCLC patients. Im et al. in their study showed that TLG as well as MTV were strong predictors in early and advanced stages [13]. In another study Hyun et al. performed an analysis on a group of 161 patients with stage IIIA-N2 NSCLC and noticed that T stage is associated with OS and SUV_{max} value of the primary tumor with DFS [14]. Our analysis showed that no clinical param-

eters were significant for OS, while from PET-derived parameters only MTV of the primary tumor was significant in stage cN1–cN3 non-small-cell lung cancer.

Ma et al. on a group of 203 NSCLC patients showed that MTV is associated with OS in an early stage of disease, while no significant differences were noted in a late stage in Cox multivariate analysis [15]. Machtay et al. proceeded a large prospective and multi-centre study on a group of 250 stage III NSCLC patients and showed that pre-treatment SUV_{max} is not associated with survival rates in these patients [16]. Similarly, in a recent study, even on a notably lower group of patients, we concluded the same results as presented above: SUV_{max} did not show any association with respect to OS, while MTV was significant.

A limitation of this study is that it was conducted on a small group of patients and it was a retrospective study. Furthermore, all patients were diagnosed with NSCLC; however, we don't have data about histology of NSCLC: squamous cell carcinoma or adenocarcinoma, which might also have an influence on the results obtained. Nevertheless, our study showed comparable results in terms of MTV of the primary tumor, which might be used to stratify patients in cN1–cN3 NSCLC.

Conclusion

The metabolic volume of the primary tumor is an independent prognostic factor in NSCLC patients with cN1-cN3 lymph node involvement and should be taken into account in assessing OS in these patients. Commonly used SUV_{max} of the primary tumor was not a predictor in the assessed group. Further studies on a larger and homogenous group of patients are needed to confirm obtained results.

Conflicts of interest

Authors declare no conflict of interest.

Funding

None declared.

Ethical approval

Ethical approval was not necessary for the preparation of this article because of the retrospective nature of the study.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
2. Nappi A, Gallicchio R, Simeon V, et al. [F-18] FDG-PET/CT parameters as predictors of outcome in inoperable NSCLC patients. Radiol Oncol. 2015; 49(4): 320–326, doi: 10.1515/raon-2015-0043, indexed in Pubmed: 26834517.
3. Finkle JH, Penney BC, Pu Y. An updated and validated PET/CT volumetric prognostic index for non-small cell lung cancer. Lung Cancer. 2018; 123: 136–141, doi: 10.1016/j.lungcan.2018.07.019, indexed in Pubmed: 30089584.
4. Kwon W, Howard BA, Herndon JE, et al. FDG Uptake on Positron Emission Tomography Correlates with Survival and Time to Recurrence in Patients with Stage I Non-Small-Cell Lung Cancer. J Thorac Oncol. 2015; 10(6): 897–902, doi: 10.1097/JTO.0000000000000534, indexed in Pubmed: 25811445.
5. Cegla P, Bryl M, Witkowska K, et al. Differences between TNM classification and 2-[F]FDG PET parameters of primary tumor in NSCLC patients. Rep Pract Oncol Radiother. 2021; 26(3): 445–450, doi: 10.5603/RPOR.a2021.0072, indexed in Pubmed: 34277098.
6. Hofheinz F, Langner J, Petr J, et al. An automatic method for accurate volume delineation of heterogeneous tumors in PET. Med Phys. 2013; 40(8): 082503, doi: 10.1118/1.4812892, indexed in Pubmed: 23927348.
7. Hofheinz F, Pötzsch C, Oehme L, et al. Automatic volume delineation in oncological PET. Evaluation of a dedicated software tool and comparison with manual delineation in clinical data sets. Nuklearmedizin. 2012; 51(1): 9–16, doi: 10.3413/Nukmed-0419-11-07, indexed in Pubmed: 22027997.
8. Bütof R, Hofheinz F, Zöphel K, et al. Prognostic Value of Pretherapeutic Tumor-to-Blood Standardized Uptake Ratio in Patients with Esophageal Carcinoma. J Nucl Med. 2015; 56(8): 1150–1156, doi: 10.2967/jnumed.115.155309, indexed in Pubmed: 26089549.
9. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna 2021.
10. Wang D, Koh ES, Descallar J, et al. Application of novel quantitative techniques for fluorodeoxyglucose positron emission tomography/computed tomography in patients with non-small-cell lung cancer. Asia Pac J Clin Oncol. 2016; 12(4): 349–358, doi: 10.1111/ajco.12587, indexed in Pubmed: 27550522.
11. Chardin D, Paquet M, Schiappa R, et al. Baseline metabolic tumor volume as a strong predictive and prognostic biomarker in patients with non-small cell lung cancer treated with PD1 inhibitors: a prospective study. J Immunother Cancer. 2020; 8(2), doi: 10.1136/jitc-2020-000645, indexed in Pubmed: 32709713.
12. Pellegrino S, Fonti R, Pulcrano A, et al. PET-Based Volumetric Biomarkers for Risk Stratification of Non-Small Cell Lung Cancer Patients. Diagnostics (Basel). 2021; 11(2), doi: 10.3390/diagnostics11020210, indexed in Pubmed: 33573333.

13. Im HJ, Pak K, Cheon GiJ, et al. Prognostic value of volumetric parameters of (18)F-FDG PET in non-small-cell lung cancer: a meta-analysis. Eur J Nucl Med Mol Imaging. 2015; 42(2): 241–251, doi: 10.1007/s00259-014-2903-7, indexed in Pubmed: 25193652.
14. Hyun SH, Ahn HK, Ahn MJ, et al. Volume-Based Assessment With 18F-FDG PET/CT Improves Outcome Prediction for Patients With Stage IIIA-N2 Non-Small Cell Lung Cancer. AJR Am J Roentgenol. 2015; 205(3): 623–628, doi: 10.2214/AJR.14.13847, indexed in Pubmed: 26295651.
15. Ma W, Wang M, Li X, et al. Quantitative F-FDG PET analysis in survival rate prediction of patients with non-small cell lung cancer. Oncol Lett. 2018; 16(4): 4129–4136, doi: 10.3892/ol.2018.9166, indexed in Pubmed: 30214552.
16. Machtay M, Duan F, Siegel BA, et al. Prediction of survival by [18F]fluorodeoxyglucose positron emission tomography in patients with locally advanced non-small-cell lung cancer undergoing definitive chemoradiation therapy: results of the ACRIN 6668/RTOG 0235 trial. J Clin Oncol. 2013; 31(30): 3823–3830, doi: 10.1200/JCO.2012.47.5947, indexed in Pubmed: 24043740.