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Original paper

PET-CT in mediastinal staging of non-small cell lung cancer: analysis of false results

Adam Kużdżał[1,A,B,C,D,E#], Błażej Kużdżał[1,A,B,C,D,E#], Konrad Moszczyński[2,B,D], Sofiia Popovchenko[3,B,D], Monika Bryndza[3,B,D], Katarzyna Żanowska[4,B,D], Łukasz Trybalski[4,B,D], Janusz Warmus[4,B,D], Piotr Kocoń[4,5,A,B,C,D,E]

[#]These authors contributed equally to this work.

[1]Maria Skłodowska-Curie National Institute of Oncology, National Research Institute, Cracow, Poland
[2]Department of Coronary Artery Disease and Structural Heart Disease, Institute of Cardiology, Warsaw, Poland
[3]Students Scientific Society, Jagiellonian University College of Medicine, Cracow, Poland
[4]Department of Thoracic Surgery, John Paul II Hospital, Cracow, Poland
[5]Department of Thoracic Surgery, Jagiellonian University College of Medicine, Cracow, Poland

Abstract

Purpose: To analyse the risk and factors associated with false-negative (FN) and false-positive (FP) positron emission tomography-computed tomography (PET-CT) results in the mediastinal staging of non-small cell lung cancer.

Material and methods: This retrospective cohort study analysed data from a prospective database. It included patients with lung cancer who underwent preoperative staging with PET-CT, endobronchial ultrasound, and endoscopic ultrasound, followed by curative-intent anatomical lung resection with systematic lymph node dissection. Statistical analyses were performed to identify factors associated with FN and FP PET-CT results.

Results: Data from 781 patients were analysed. FN results were significantly associated with more advanced PET-CT-based stages and CT-based stage IIB. FP results were significantly associated with male sex, adenocarcinoma histology, CT-based disease stage, and SUV_{max} values of the primary tumour and lymph nodes.

Conclusions: False-negative PET-CT results in the diagnosis of mediastinal lymph node involvement were more likely to occur in PET-CT-based stages IB and IIB and less likely to occur in stage IIIA. FP results were more likely to be expected in men, with higher SUV_{max} values of the primary tumour and a more advanced CT-based stage of the disease.

Key words: PET-CT, non-small cell lung cancer, mediastinal staging, false-negative results, false-positive results, lymph node metastasis.

Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide [1,2]. Management strategies are highly stage-dependent, making accurate pretreatment staging essential. Positron emission tomography (PET) using 18-fluorodeoxyglucose (18-FDG) combined with computed tomography (CT), referred to as positron emission tomography-computed tomography (PET-CT), is the key imaging modality for the mediastinal staging of lung cancer [3,4]. Despite its superior diagnostic performance, PET-CT is susceptible to false-negative (FN) and false-positive (FP) results, which may negatively affect therapeutic decision-making. FN results compromise the negative predictive value by failing to detect mediastinal (N2) lymph node disease, potentially leading to inappropriate primary

Correspondence address:
Adam Kużdżał, Department of Radiology, Maria Skłodowska-Curie National Institute of Oncology, National Research Institute, 11 Garncarska St., 31-115 Cracow, Poland, e-mail: adam.kuzdzal@krakow.nio.gov.pl

Authors' contribution:
A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

surgical treatment. Conversely, FP results diminish the positive predictive value, risking overstaging and the unnecessary exclusion of curative surgery-based treatments. Prior studies using small cohorts have reported conflicting results. This study aimed to identify factors associated with FN and FP PET-CT results in a large patient cohort using standardised imaging and pathological protocols for consistent results.

Material and methods

The study complies with the Declaration of Helsinki (2013) [5] and was approved by the relevant Ethics Committee. Patient consent was not required because the analysis included de-identified data obtained from medical records.

Clinical questions: What are the risks of FN and FP PET-CT results in the mediastinal staging of lung cancer? Which factors are associated with the FN and FP results?

This retrospective cohort study analysed data sourced from a prospective database.

Location: Department of Thoracic Surgery, John Paul II Hospital, Cracow, Poland.

Characteristic of patients

Consecutive patients with lung cancer who underwent complete resection were included. Inclusion criteria were as follows: age > 18 years; clinical stage I-IVA (including only oligometastatic stage IV cases); preoperative staging with PET-CT, endobronchial ultrasound (EBUS), and endoscopic ultrasound (EUS); and curative anatomical lung resection. Patient data used for analysis included sex, age, body mass index (BMI), tumour histological type and grade, lobar location of the primary tumour, disease stage assessed separately by CT, PET-CT, and combined EBUS and EUS (referred to as combined ultrasound or compression ultrasound [CUS]), and SUV_{max} values of the primary tumour and lymph nodes, both intrapulmonary (N1) and mediastinal (N2).

Intervention

The preoperative diagnostic workup included PET-CT, bronchoscopy, EBUS, and EUS for all patients. PET-CT imaging was performed using a Discovery 690 scanner (General Electric HealthCare, Chicago, Illinois, USA) with a weight-based 18-FDG dose calculation of 3-4 MBq/kg and an upper blood glucose limit of 11 mmol/l. The protocol included CT attenuation correction imaging and lung window reconstruction (80-210 mA, 3.75-mm section thickness, and 0.8-second gantry rotation speed). Whole-body PET-CT (2.5-mm section thickness) was performed using non-attenuation-corrected (NAC) and measured attenuation-corrected (MAC) images and the Q.Clear algorithm. The reconstructions used were Q.Clear, SharpIR, Q.AC, and VUE Point HD. The SUV_{max} was calculated using PET Odyssey software. Each study was independently assessed by a radiologist and nuclear medicine specialist.

CUS procedures were conducted by endoscopists experienced in tracheobronchial and esophagogastric endoscopy. Samples from each lymph node station were prepared separately, and cytological smears were fixed in 96% ethanol. CUS procedures have been detailed elsewhere [6].

Lung resections were performed by certified thoracic surgeons with standard lymph node dissection according to the European Society of Thoracic Surgeons guidelines. Dissected nodal stations included the following: right side (2R, 4R, 3A, 7, 8, and 9); left side (5, 6, 7, 8, and 9) [7].

Lymph nodes from each station were dissected separately, fixed in 10% buffered formalin, and labelled. Cytological and histological specimens were examined by an experienced lung pathologist using standard light microscopy images with haematoxylin and eosin staining.

Endpoints

The primary endpoints were FN and FP results of CUS. Additional analyses examined associations between these results and clinical characteristics, including patient age, sex, BMI, tumour histological type and grade, lobar location of the primary tumour, disease stage assessed separately using CT, PET-CT, and CUS, SUV_{max} of the primary tumour, SUV_{max} of N1 lymph nodes, and SUV_{max} of N2 lymph nodes.

Statistical analysis

Statistical software (StatSoft version 13.5 PL; StatSoft, Tulsa, Oklahoma, USA) was used for the analyses. Uni- and multivariate logistic regression models identified the factors associated with false-negative and false-positive PET-CT results in mediastinal lymph nodes. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated for factors such as sex, age, BMI, grade, SUV_{max}, tumour location, tumour histological type, and CT- and PET-CT-based stage. Statistical significance was set at $p < 0.05$.

Results

Data from 781 patients were analysed, and the characteristics of the study population are presented in Table 1. Regarding mediastinal lymph node involvement, PET-CT results included 43 false-negative (8%, 43/540), 173 false-positive (71.8%, 173/241), 497 true-negative (92%, 497/540), and 68 true-positive results (28.2%, 68/241).

Logistic regression analysis showed a significantly higher risk of FN PET-CT results in patients with a PET-CT-based stage IB and IIB and CT-based stage IIB. The risk of FN results was significantly smaller with PET-CT-based stage IIIA. Compared with PET-CT-based stage IA, the OR for stage IB, IIB, and IIIA were 3.36, 3.42, and 0.17, respectively (p = 0.002-0.015). For CT-based stage IIB,

Table 1. Characteristics of the study group

Characteristic	Value
Sex, *n* (%)	
Male	535 (68.5)
Female	246 (31.5)
Age [years], mean (range)	65 (30-97)
BMI, mean (range)	26.5 (15.2-53.5)
Histological type, *n* (%)	
SCC	389 (49.8)
ADC	235 (30.1)
ASC	65 (8.3)
LCC	25 (3.2)
OTH	67 (8.6)
Grade, *n* (%)	
0	35 (4.5)
1	50 (6.4)
2	431 (55.2)
3	228 (29.2)
4	37 (4.7)
Primary tumour location, *n* (%)	
RUL	213 (27.3)
RML	30 (3.8)
RLL	125 (16.0)
RCE	60 (7.7)
LUL	198 (25.3)
LLL	116 (14.9)
LCE	39 (5.0)
CT stage, *n* (%)	
I	444 (56.8)
II	238 (30.5)
III	88 (11.3)
IVA	11 (1.4)
PET stage, *n* (%)	
I	325 (41.6)
II	178 (22.8)
III	259 (33.1)
IVA	19 (2.5)
T SUV, mean (range)	13.0 (0-66.8)

ADN – adenocarcinoma, ASC – adeno-squamous carcinoma, BMI – body mass index, CT – computed tomography, LCC – large-cell carcinoma, LCE – left central, LLL – left lower lobe, LUL – left upper lobe, OTH – other histological types, PET – positron-emission tomography, RCE – right central, RLL – right lower lobe, RML – right middle lobe, RUL – right upper lobe, SCC – squamous-cell carcinoma, T SUV – standarised uptake value of primary tumour

the OR was 3.56 (p = 0.008). No significant association was found between the risk of FN results of PET-CT and other CT-based stages and the following factors: sex (p = 0.245), age (p = 0.684), BMI (p = 0.575), tumour histological type (p: 0.119-0.932) and grade (p = 0.339), lobar location of the primary tumour (p: 0.178-0.667), SUV_{max} values of the primary tumour (p = 0.956), N2 lymph nodes (p = 0.249), and N1 lymph nodes (p = 0.795) (Table 2).

Table 2. Association between clinical characteristics and false-negative results of positron emission tomography in detecting N2 disease

Characteristic	OR (95% CI)	*p*-value
Sex	0.688 (0.366-1.293)	0.245
Age	1.007 (0.970-1.046)	0.684
BMI	0.980 (0.915-1.050)	0.575
Grade	1.206 (0.820-1.774)	0.339
SUV_T	0.998 (0.956-1.042)	0.956
SUV_{N2}	0.105 (0.002-4.852)	0.249
SUV_{N1}	1.015 (0.906-1.137)	0.795
Primary tumour location*		
RML	1.266 (0.523-3.061)	0.559
RLL	0.973 (0.255-1.771)	0.422
RC	0.633 (0.078-5.087)	0.667
LUL	2.040 (0.721-5.767)	0.178
LLL	1.255 (0.491-3.210)	0.634
Primary tumour location, right lung vs. left lung	1.278 (0.682-2.395)	0.443
Primary tumour location, lower lobes vs. upper lobes	0.806 (0.388-1.675)	0.564
Histological type#		
ADN	1.709 (0.870-3.356)	0.119
OTH	0.961 (0.393-2.350)	0.932
CT stage$		
IB	2.331 (0.848-7.274)	0.077
IIA	2.484 (0.848-7.274)	0.097
IIB	3.563 (1.385-9.161)	0.008
IIIA	1.021 (0.207-5.035)	0.979
PET stage$		
IB	3.360 (1.257-8.981)	0.002
IIA	5.581 (1.840-16.928)	0.107
IIB	3.421 (1.264-9.256)	0.015
IIIA	0.174 (0.020-1.463)	0.015

#SCC was used as reference. *Right upper lobe was used as reference. $Stage IA was used as reference.
ADN – adenocarcinoma, BMI – body mass index, CI – confidence interval, CT – computed tomography, LLL – left lower lobe, LUL – left upper lobe, OR – odds ratio, OTH – other histological types, PET – positron-emission tomography, RCE – right central, RLL – right lower lobe, RML – right middle lobe, SUV_{N1} – standardised uptake value of hilar and intrapulmonary lymph nodes, SUV_{N2} – standardised uptake value of mediastinal lymph nodes, SUV_T – standardised uptake value of primary tumour

Analysis of the risk of FP PET-CT results showed a significant association with male sex (OR = 1.925, p = 0.001), SUV_{max} of the primary tumour (OR = 1.055, p < 0.001), SUV_{max} of N2 nodes (OR = 0.859, p < 0.001),

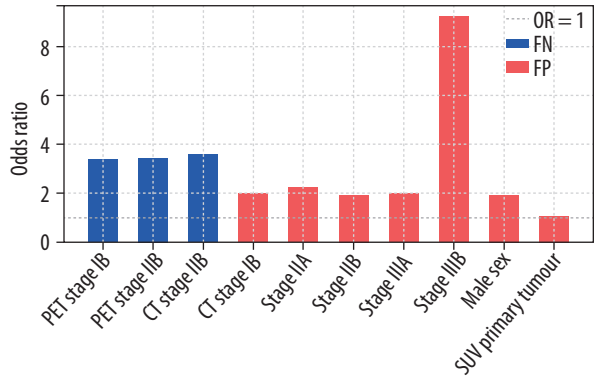

Figure 1. Odds ratios (OR) for false-negative (FN) and false-positive (FP) results

SUV_{max} of N1 nodes (OR = 0.937, p = 0.043), adenocarcinoma histology (OR = 0.489, p = 0.013), and CT-based stage of the disease (OR for stage IB, IIA, IIB, IIIA, and IIIB: 1.995, 2.212, 1.928, 1.969, and 9.220, respectively; p: 0.001-0.019). No significant association was found between the risk of FP PET-CT results and age (p = 0.526), BMI (p = 0.217), tumour grade (p = 0.360), or lobar location of the primary tumour (p: 0.280-0.939) (Figure 1, Table 3).

Discussion

This study, analysed the largest cohort to date, evaluating factors influencing FN and FP PET-CT results in the diagnosis of mediastinal lymph node metastasis of lung cancer.

The FN and FP result rates in our study were consistent with those reported in prior studies [8-12].

Logistic regression analysis showed that FN PET-CT results concerning the mediastinal lymph nodes were strongly associated with advanced PET-CT-based stages. In stages IB and IIB, the odds ratio of the FN result was more than 3 times larger than that of stage IA. In addition, the OR for the CT-based IIB stage was more than 3 times larger. However, the PET-CT-based stage IIIA OR was not clinically significant (OR = 0.17, 95% CI: 0.02-1.46). Other factors, such as sex, age, BMI, histological tumour type and grade, lobar location of the primary tumour, SUV_{max} of the primary tumour, N2 lymph nodes, and N1 lymph nodes, showed no significant impact on FN PET-CT results. These results clarify conflicting results reported from previous studies. Some studies identified an association between higher primary tumour SUV_{max} values and FN rates [8,10-12], whereas others found a correlation with lower SUV_{max} values [13,14]. Similarly, adenocarcinoma histology has been linked to both high and low FN rates [8,10,11]. Other statistically significant factors included tumour differentiation, tumour location, and tumour size. The smaller sample sizes of these studies (n: 112-388) may have been insufficient for reliable subgroup analyses.

Regarding FP PET-CT results, significant associations were identified with male sex (OR = 1.93), adenocarcinoma histology, and CT-based stage of the disease. There was also a correlation between the SUV_{max} of the primary tumour and those of the N2 and N1 nodes; however, the difference was not significant (OR: 1.06, 0.86, and 0.94, respectively). The analysis showed no correlation between age, BMI, tumour grade, and lobar location of the primary tumour.

Notably, male sex as a risk factor for FP PET-CT results has not been previously reported. Other factors, such as adenocarcinoma type and SUV_{max} of the primary tumour, have been mentioned by some authors in the context of FP results [13]. Furthermore, some authors found a correlation between a lower SUV_{max} of the primary tumour and a higher FP rate, which was not observed in our study [11,12].

These conflicting outcomes, both in terms of FP and FN results, may be due to the much smaller numbers of patients included in the published studies [8-14].

Table 3. Association between clinical characteristics and false-positive results of positron emission tomography in detecting N2 disease

Characteristic	OR (95% CI)	p-value
Male sex	1.925 (1.290-2.872)	0.001
Age	1.006 (0.986-1.027)	0.526
BMI	0.976 (0.940-1.014)	0.217
Grade	1.102 (0.894-1.357)	0.360
SUVT	1.055 (1.030-1.080)	< 0.001
SUVN2	0.859 (0.792-0.932)	< 0.001
SUVN1	0.937 (0.880-0.998)	0.043
Primary tumour location*		
RML	1.116 (0.685-1.817)	0.657
RLL	0.982 (0.617-1.562)	0.939
RC	0.687 (0.249-1.892)	0.468
LUL	1.250 (0.648-2.409)	0.505
LLL	0.734 (0.418-1.287)	0.280
Primary tumour location, right lung vs. left lung	1.120 (0.798-1.572)	0.509
Primary tumour location, lower lobes vs. upper lobes	1.181 (0.781-1.784)	0.428
Histological type#		
ADN	0.489 (0.321-0.744)	0.013
OTH	0.629 (0.442-1.083)	0.963
CT stage$		
IB	1.995 (1.118-3.560)	0.019
IIA	2.212 (1.156-4.236)	0.016
IIB	1.928 (1.185-3.136)	0.008
IIIA	1.969 (1.154-3.359)	0.012
IIIB	9.220 (3.512-24.207)	< 0.001

#SCC was used as reference. *Right upper lobe was used as reference. $Stage IA was used as reference.

ADN – adenocarcinoma, BMI – body mass index, CI – confidence interval, CT – computed tomography, LLL – left lower lobe, LUL – left upper lobe, OR – odds ratio, OTH – other histological types, PET – positron-emission tomography, RCE – right central, RLL – right lower lobe, RML – right middle lobe, SUV_{N1} – standardised uptake value of hilar and intrapulmonary lymph nodes, SUV_{N2} – standardised uptake value of mediastinal lymph nodes, SUV_{T} – standardised uptake value of primary tumour

The strength of our study is the analysis of 781 patients, which, to the best of our knowledge, is the largest cohort published to date. This large sample size enhanced the statistical power and reliability of the findings, particularly regarding the subgroup analysis. Standardised imaging and pathological protocols across all patients reduced variability and increased the consistency and reliability of the results. Comprehensive preoperative diagnostic workups, including PET-CT, bronchoscopy, EBUS, and EUS, ensured accurate initial staging and robust evaluations of PET-CT performance.

Logistic regression models were employed to identify the factors associated with FN and FP PET-CT results. Both uni- and multivariate models were constructed to provide a thorough analysis of the potential influencing factors. These findings have clinical implications and potentially improve the interpretation of PET-CT results in the mediastinal staging of non-small cell lung cancer. This could lead to more accurate staging and, consequently, more appropriate treatment decisions.

The main limitations of this study were its retrospective design and single-institution cohort, which may not fully represent the diversity in patient demographics, disease characteristics, and treatment practices across different healthcare settings and populations. Further prospective studies with larger and more diverse patient cohorts are needed to validate these findings and identify additional factors affecting PET-CT performance.

Conclusions

False-negative PET-CT results for mediastinal lymph node involvement are more likely in patients with PET-CT-based stages IB and IIB and CT-based stage IIB. An increased risk of false-positive PET-CT results can be expected in men, with higher SUV_{max} values of the primary tumour, and a more advanced CT-based stage of the disease.

Disclosures

1. Institutional review board statement: The study complies with the Declaration of Helsinki and was approved by the relevant Ethics Committee. Approval number: 118.0043.1.287.2024.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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