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Original article

Added value of combined endobronchial and endoscopic ultrasound-guided needle biopsy in mediastinal staging of lung cancer

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Abstract

Introduction. Data on the added value of combined endobronchial and endoscopic ultrasound (CUS) following staging with imaging studies are limited. This study aimed to analyze the rates of upstaging and downstaging on CUS.

Material and methods. This retrospective cohort study evaluated lung cancer patients who underwent computed tomography (CT), positron emission tomography (PET), and CUS.

Results. 858 patients were evaluated. The PET-based N2 status was upstaged and downstaged on CUS in 54 (6.3%) and 347 (40.4%) patients, respectively. The PET-based factors T1c–T2b, T4, and N1 were associated with N2 upstaging. Tumor grades 2, 3, and 4; male sex; right lower lobe location; adenocarcinoma and carcinoid histologies; and the PET-based factors T2a–T3, and N2 were associated with N2 downstaging.

Conclusions. PET-based N1 involvement is strongly associated with the probability of N2 upstaging. High tumor grade, male sex, and the PET-based factors T3–4 and N2 are strongly associated with the probability of N2 downstaging.
Keywords: lung cancer, staging, PET, EBUS, EUS

Introduction

Lung cancer is a major cause of cancer-related mortality worldwide [1]. Selection of the appropriate treatment strategy is highly stage-dependent, making accurate assessment of mediastinal lymph nodes a crucial element of the pretreatment workup. Current guidelines recommend initial staging using computed tomography (CT) and positron emission tomography (PET) imaging [2, 3]. However, although PET with 18F-fluoro-2-deoxyglucose (18-FDG) is recommended for mediastinal lymph node assessment, its negative predictive value (NPV) may be suboptimal [4]. The risk of missing N2 metastases is particularly high in patients with centrally located primary tumors, suspected N1 nodes, or advanced T stage [5–8]. This evidence is reflected in the current European Society of Thoracic Surgeons' guidelines, recommending tissue confirmation in all PET-positive mediastinal nodes, also in cases of centrally located primary tumors measuring > 3 cm in diameter or suspected N1 nodes [9]. The preferred technique for tissue confirmation is combined endobronchial and endoscopic ultrasound-guided needle biopsy, referred to as combined ultrasound (CUS). However, data on the association between the upstaging and downstaging rates on CUS and basic patient factors are limited. Thus, the present study aimed to determine the rates of upstaging and downstaging on CUS following computed tomography (CT) and positron emission tomography (PET) and to analyze the correlation between different patient characteristics and the probability of upstaging and downstaging.

Material and methods

Clinical questions

What are the CUS upstaging and downstaging rates following CT? What are the CUS upstaging and downstaging rates following PET? Which factors are associated with the probability of upstaging and downstaging?

Study design and patients

This retrospective cohort study was conducted in the Department of Thoracic Surgery, Endoscopy, and Pathology, John Paul II Hospital, Cracow, Poland. The data of consecutive patients who underwent complete pulmonary resection for lung cancer were extracted from the hospital database. The inclusion criteria were as follows: age 18–90 years; clinical stage I–IVA disease (for stage IVA, only patients with oligometastatic disease were included); and preoperative workup using PET-CT, endobronchial ultrasound (EBUS), and endoscopic ultrasound (EUS). Patient data including age, sex, body mass index (BMI), tumor histological type and grade, lobar location of the primary tumor, T and N factors assessed separately by CT and PET, and maximum standardized uptake values (SUV_{max}) of the primary tumor were analyzed.

Intervention

All patients underwent preoperative diagnostic workup including PET-CT, bronchoscopy, EBUS, and EUS. PET imaging was performed using a Discovery 690 scanner (General Electric HealthCare, Chicago, Illinois, USA). This protocol has been described in detail elsewhere [10]. All CUS procedures were performed under conscious sedation with midazolam, fentanyl, and topical lidocaine for local anesthesia. A BF–UC160F–OL8 video bronchoscope (Olympus Medical Systems Corporation, Tokyo, Japan) was used for EUS, and a GF–UCT160–OL5 video gastroscope (Olympus Medical Systems Corporation) was used for EUS. Fine–needle aspiration biopsies were performed using NA–201SX–4022 (EBUS) and NA–200H–8022 (EUS) needles (Olympus Medical Systems Corporation). All mediastinal lymph nodes measuring > 5 mm along the short axis and all PET positive nodes, regardless of size, were biopsied. Three needle passes were performed at each node to ensure sufficient sample collection.

All CUS procedures were performed by endoscopists with extensive experience in interventional bronchoscopy and esophagogastric endoscopy. Cytological smears were prepared separately for each nodal station and fixed in 96% ethanol for further analysis. A detailed description of the CUS technique was presented previously [11]. Lung resection was performed by certified thoracic surgeons using standard lymph node dissection according to the European Society of Thoracic Surgeons' guidelines [12]. Each nodal station was dissected separately, fixed in 10% buffered formalin, and labeled by the operating surgeon. Cytological and histological specimens were examined by an experienced lung pathologist. Standard light microscopy images with hematoxylin and eosin staining were used.

Statistical analysis

The study endpoint was the rate of upstaging and downstaging of CT-based and PET-based N2 status on CUS. Data were summarized using descriptive statistics. Continuous variables are presented as means and standard deviations (SDs). As most of these variables were skewed, the medians and first (Q1) and third (Q3) tertiles were also provided. Categorical variables are described as counts and proportions (%). The normality of data distribution was assessed using the Shapiro-Wilk test. As the analyzed variables presented skewed distributions in at least one compared group, between-group differences in continuous variables were analyzed using the nonparametric Mann-Whitney U test. Meanwhile, between-group differences in categorical variables were assessed using the chi-squared test, provided that the assumption for the expected value of at least five was met. Otherwise, the Fisher-Freeman-Hamilton exact test was employed in cases where contingency tables were larger than 2 × 2. In some analyses, exact p-values could not be obtained owing to computational limitations observed when very large contingency tables were considered. Thus, the Monte Carlo estimation of the Fisher-Freeman-Hamilton exact p-value [with 99% confidence interval (CI) for the estimated p-value] was provided. The possible effect of different patient characteristics on the odds of upstaging on CUS was evaluated using univariable logistic regression analysis. The same procedure was used for the odds of downstaging. All statistical analyses were performed using IBM SPSS Statistics v.20.0.20 (20) (Armonk, New York, USA). A p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

The analysis included data from 858 patients (68.4% men) aged 30–87 years (mean, 68 years). The baseline patient characteristics are presented in Table I.

Changes in the CT-based N2 stage

The CT-based N2 stage was changed on CUS in 205 (23.9%) patients: upstaged in 76 (8.9%) patients and downstaged in 129 (15%) patients. The factors affecting the probability of N2 upstaging included lobar location of the tumor ($p = 0.017$), CT-based T factor ($p < 0.001$) and N factor ($p = 0.027$). In the univariable logistic regression analysis, the CT-based factors T1a, T1b, T2b, and N1 were significantly associated with a higher probability of N2 upstaging on CUS. Meanwhile, the factors affecting the probability of N2 downstaging included male sex ($p = 0.015$), CT-based T factor ($p < 0.001$), CT-based N factor ($p < 0.001$),

and SUV_{max} of the primary tumor (p = 0.039). Sex; adenocarcinoma histology; and CT-based factors (T1c, T2b, T3, T4, N1, and N2) were associated with a higher probability of N2 downstaging on CUS.

Changes in PET-based stage

The PET-based N2 stage was changed on CUS in 401 (46.7%) patients: upstaged in 54 (6.3%) patients and downstaged in 347 (40.4%) patients. The factors affecting the probability of N2 upstaging included lobar location of the tumor (p = 0.042), PET-based T factor (p = 0.030) and N factor (p = 0.037) (Table II). In the univariable logistic regression analysis, the PET-based factors T1c, T2b, T4, and N1 were associated with a higher probability of N2 upstaging on CUS (Tab. III). Meanwhile, the factors affecting the probability of N2 downstaging included tumor grade (p = 0.001), male sex (p = 0.004), histology (p = 0.046), PET-based T factor (p < 0.001), PET-based N factor (p = 0.041), and SUV_{max} of the primary tumor (p < 0.001) (Tab. IV). In univariable logistic regression analysis, tumor grades 2, 3, and 4; sex; right lower lobe location; adenocarcinoma and carcinoid histologies; and the PET-based factors T2a, T2b, T3, and N2 were associated with a higher probability of N2 downstaging on CUS (Tab. V).

Discussion

The present study shows that CUS increases the sensitivity of detecting mediastinal lymph node metastases and is a valuable addition to PET- and CT-based evaluations of N2 disease. The PET-based and CT-based N2 status was downstaged on CUS in 40.4% and 15% of the patients, respectively. Such a significant effect on PET-based assessments may result from a high number of false-positive results on PET. Overall, 23.9% of the CT-based N2 status and almost half of the PET-based N2 status (46.7%) were changed on CUS. Various factors such as patient sex, histology, CT- and PET-based T factor, CT- and PET-based N factor, tumor location, and SUV_{max} of the primary tumor were associated with the probability of upstaging and downstaging.

Most studies analyzing the diagnostic yield of CUS have focused on comparisons of CUS with EBUS,EUS or of CUS with surgical staging of the mediastinum [13-18]. Although these studies confirmed the high sensitivity and NPV of CUS, data on the added value of CUS after imaging diagnosis are limited. Hegde et al. [19] retrospectively evaluated 161 consecutive patients with radiologically normal mediastinum. Overall, 13% of the patients were upstaged on CUS, higher than 6.3% found in the present study. It should be noted that in

the current study, patients were included regardless of the radiological stage. In a prospective study involving 130 patients from Greece, the sensitivity of PET-CT and CUS was similar (92.2% *vs*. 93.8%), but the NPV differed (83.3% *vs*. 93.4%) [20]. Ohnishi et al. [21] evaluated 115 patients without distant metastasis who underwent PET-CT followed by CUS and found significantly better sensitivity (47.4 *vs*. 71.8) and NPV (75.9 *vs*. 86.6) of CUS. The findings herein are in line with these results. However, none of these studies have analyzed the correlation between CUS results and patient variables.

The strength of this study is the large cohort of patients, with a total of 858 patients evaluated. According to available research, this is the largest study reported to date, enhancing the reliability of the results. Further, the present study is novel as it also analyzes the association of the relative diagnostic yield of CT, PET, and CUS with key patient characteristics, such as age, sex, BMI, tumor histological type and grade, lobar location of the primary tumor, T and N factors assessed separately by TK imaging and PET, and SUV_{max} values. In particular, the results suggest that in patients with PET-based N1 disease, the risk of occult N2 metastasis is high, indicating the need of invasive mediastinal staging despite normal mediastinum on PET. However, this study also has some limitations, including its retrospective nature and single-institution design, and thus, the results may not accurately reflect the general practice of lung cancer staging. Prospective, multi-institutional studies are warranted to further elucidate important issues of endosonography in lung cancer staging.

Conclusions

Positron emission tomography is a reliable modality for ruling out, but not confirming, mediastinal lymph node metastases, making CUS an important diagnostic modality to assess N2 status. PET-based N1 status is strongly associated with the probability of N2 upstaging on CUS. High tumor grade, male sex, and the PET-based factors T3-4 and N2 are strongly associated with the probability of N2 downstaging on CUS.

Article information and declarations

Data availability statement

The data supporting the findings of the article is available from the corresponding author on reasonable request.

Ethics statement

Ethical committee consent was waived because of the retrospective nature of the study.

Authors contributions

Karolina A. Gambuś — conceptualization, data curation, methodology, project administration, writing — original draft preparation.
Błażej W. Kużdżał — conceptualization, data curation, methodology, project administration, writing — original draft preparation.
Konrad Moszczyński — data curation.
Sofiia Popovchenko — data curation.
Artur Szlubowski — data curation, investigation.
Lucyna Rudnicka — data curation, investigation.
Katarzyna Żanowska — data curation, investigation.
Łukasz Trybalski — data curation, investigation.
Aleksander Galas — formal analysis.
Piotr Kocoń — data curation, investigation.

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Conflicts of interest
The authors declare no conflict of interest.
Supplementary material
None.

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Table I. Baseline patient characteristics

Characteristic	Value
Sex n (%)	
Male	587 (68.4)
Female	271 (31.6)
Age	
Mean (range)	68 (30–87)
BMI	
Mean (range)	26.5 (15.2–53.5)
Histological type n (%)	
SCC	415 (48.4)
ADN	265 (30.9)
LCC	27 (3.1)
ASC	70 (8.2)
OTH	81 (9.4)
Grade n* (%)	
0	38 (4.6)
1	52 (6.2)
2	459 (55.2)
3	245 (29.4)
4	38 (4.6)
Lobar location n (%)	
RUL	231 (26.9)
RML	34 (4.0)
RLL	144 (16.8)
RCE	62 (7.2)
KUL	117 (13.6)
LIN	11 (1.3)
LUC	91 (10.6)
LLL	125 (14.6)
LCE	43 (5.0)
Stage by CT n (%)	
IA	269 (31.3)
IB	215 (25.1)
IIA	110 (12.8)
IIB	150 (17.5)
IIIA	82 (9.6)
IIIB	21 (2.4)
IIIC	0 (0)
IVA	11 (1.3)
Stage by PET n (%)	
IA	207 (24.1)
IB	150 (17.5)
IIA	55 (6.4)
IIB	142 (16.6)
IIIA	195 (22.7)
IIIB	77 (9.0)
IIIC	12 (1.4)

IVA	20 (2.3)

*Grade data were available for 832 patients; ADN — adenocarcinoma; ASC — adeno-squamous carcinoma; BMI — body mass index; CT — computed tomography; CUL — culmen; LCC — large-cell carcinoma; LCE — left central; LIN — lingula; LLL — left lower lobe; LUC — left upper central; 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

Table II. Factors associated with endoscopic ultrasound (CUS) upstaging of positron emission tomography (PET)-based stage

Factor	Upstaging CUS *vs*. PET Yes n = 54		No n = 804		p-value
Grade# [n, %]	n = 51		n = 781		P^{FFH-MC} = 0.651 99% CI: 0.639–0.664
0	1	2.0%	37	4.7%	
1	1	2.0%	51	6.5%	
2	30	58.8%	429	54.9%	
3	16	31.4%	229	29.3%	
4	3	5.9%	35	4.5%	
Age Mean (SD) Median (Q1–Q3) Range	 65.0 (7.7) 66.0 (60.0–70.3) 47-81		 65.2 (8.4)* 65.0 (60.0–71.0) 30-87		P^{MW} = 0.845
Sex [n, %]					P^{chi2} = 0.384
Female	20	37.0%	252	31.3%	
Male	34	63.0%	552	68.7%	
BMI Mean (SD) Median (Q1-Q3) Range	 26.4 (4.3) 26.9 (23.4–29.5) 17.0–36.2		 26.5 (4.7)* 26.1 (23.2–29.4) 15.2–53.5		P^{MW} = 0.697
Location [n, %]					P^{FFH-MC} = 0.042 99% CI: 0.037–0.047
RUL	15	27.8%	216	26.9%	
RML	1	1.9%	33	4.1%	
RLL	13	24.1%	131	16.3%	
RCE	5	9.3%	57	7.1%	
CUL	6	11.1%	111	13.8%	
LIN	2	3.7%	9	1.1%	
LUC	1	1.9%	90	11.2%	
LLL	11	20.4%	114	14.2%	
LCE	0	0.0%	43	5.3%	
Histology [n, %]					P^{FFH-MC} = 0.293 99% CI: 0.282–0.305

SCC	20	37.0%	395	49.1%	
AND	22	40.7%	243	30.2%	
LCC	1	1.9%	26	3.2%	
ASC	6	11.1%	64	8.0%	
SCLC	1	1.9%	5	0.6%	
CAR	1	1.9%	34	4.2%	
OTH	3	5.6%	37	4.6%	
CT-based T factor [n, %]					P^{FFH-MC} = 0.030 99% CI: 0.026–0.035
T1a	1	1.9%	93	11.6%	
T1b	9	16.7%	169	21.0%	
T1c	5	9.3%	21	2.6%	
T2a	16	29.6%	247	30.7%	
T2b	12	22.2%	127	15.8%	
T3	8	14.8%	121	15.0%	
T4	3	5.6%	25	3.1%	
Tx	0	0.0%	1	0.1%	
CT-based N factor [n, %]					P^{FFH-MC} = 0.037 99% CI: 0.032–0.041
N0	38	70.4%	673	83.7%	
N1	10	18.5%	63	7.8%	
N2	6	11.1%	66	8.2%	
N3	0	0.0%	2	0.2%	
Primary tumour SUV Mean (SD) Median (Q1–Q3) Range	[n = 49] 12.7 (6.8) 12.2 (7.0–17.5) 2.1–32.7		[n = 758] 12.9 (7.2)* 12.2 (8.1–16.6) 0.0–66.8		P^{MW} = 0.942

#Grade data were available for 832 patients; *p < 0.05 by the Shapiro-Wilk test for normal distribution; ADN — adenocarcinoma; ASC — adeno-squamous carcinoma; BMI — body mass index; Chi2 — chi-square test; CI — confidence interval; CT — computed tomography; CUL — culmen; FFH-MC — Fisher-Freeman-Hamilton exact test with Monte Carlo CIs; LCC — large-cell carcinoma; LCE — left central; LIN — lingula; LLL — left lower lobe; LUC — left upper central; OTH — other histological types; RCE — right central; RLL — right lower lobe; RML — right middle lobe; RUL — right upper lobe; SCC — squamous-cell carcinoma; SCLC — small-cell lung cancer; SUV — standardised uptake value; UMW — U Mann–Whitney's test

Table III. Univariable logistic regression analysis of patient characteristics associated with the probability of endoscopic ultrasound (CUS) upstaging of positron emission tomography (PET)-based stage

Factor	OR	95% CI Lower limit	95% CI Upper limit	p-value
Grade 0 (ref.)	1			

1	0.73	0.04	11.98	0.823
2	2.59	0.34	19.51	0.356
3	2.59	0.33	20.08	0.364
4	3.17	0.31	31.95	0.327
Age [years]	1.00	0.97	1.03	0.882
Sex				
Female (ref.)	1			
Male	0.78	0.44	1.38	0.385
BMI [kg/m^2]	1.00	0.94	1.06	0.929
Location				
RUL (ref.)	1			
RML	0.44	0.06	3.41	0.429
RLL	1.43	0.66	3.10	0.366
RCE	1.26	0.44	3.62	0.664
CUL	0.78	0.29	2.06	0.614
LIN	3.20	0.63	16.16	0.159
LUC	0.16	0.02	1.23	0.078
LLL	1.39	0.62	3.12	0.426
LCE	–#			
Histology				
SCC (ref.)	1			
ADN	1.79	0.96	3.34	0.069
LCC	0.76	0.10	5.88	0.792
ASC	1.85	0.72	4.79	0.204
SCLC	3.95	0.44	35.42	0.220
CAR	0.58	0.08	4.46	0.602
OTH	1.60	0.45	5.64	0.464
PET-based T factor				
T1a (ref.)	1			
T1b	4.95	0.62	39.70	0.132
T1c	22.14	2.46	199.57	0.006
T2a	6.02	0.79	46.07	0.084
T2b	8.79	1.12	68.77	0.038
T3	6.15	0.76	50.03	0.089
T4	11.16	1.11	111.96	0.040
Tx	–#			
PET-based N factor				
N0 (ref.)	1			
N1	2.81	1.34	5.91	0.006
N2	1.61	0.66	3.95	0.298
N3	–#			
Primary tumour SUV	1.00	0.96	1.04	0.885

#Due to limited number of observations the model did not reach reliable estimates; *$p < 0.05$ by the Shapiro-Wilk test for normal distribution; ADN — adenocarcinoma; ASC — adeno-squamous carcinoma; BMI — body mass index; CAR — carcinoid; Chi2 — chi-square test; CI — confidence interval; CT — computed tomography; CUL — culmen; FFH-MC — Fisher-Freeman-Hamilton exact test with Monte Carlo CIs; LCC — large-cell carcinoma; LCE — left central; LIN — lingula; LLL — left lower lobe; LUC — left upper central; OTH — other histological types; RCE — right central; RLL — right lower lobe; RML — right

middle lobe; RUL — right upper lobe; SCC — squamous-cell carcinoma; SCLC — small-cell lung cancer; SUV — standardised uptake value; UMW — U Mann–Whitney's test

Table IV. Factors associated with endoscopic ultrasound (CUS) downstaging of positron emission tomography (PET)-based stage

Factor	Downstaging CUS *vs*. PET Yes n = 347		 No n = 511		p-value
Grade# [n, %]	n = 338		n = 494		$P^{chi2} = 0.001$
0	8	2.4%	30	6.1%	
1	11	3.3%	41	8.3%	
2	192	56.8%	267	54.0%	
3	107	31.7%	138	27.9%	
4	20	5.9%	18	3.6%	
Age					$P^{MW} = 0.248$
Mean (SD)	65.7 (8.1)*		64.9 (8.5)*		
Median (Q1–Q3)	65.0 (61.0–72.0)		65.0 (60.0–71.0)		
Range	30–87		30–83		
Sex [n, %]					$P^{chi2} = 0.004$
female	91	26.2%	181	35.4%	
male	256	73.8%	330	64.6%	
BMI					$P^{MW} = 0.968$
Mean (SD)	26.5 (4.7)*		26.5 (4.6)*		
Median (Q1–Q3)	26.3 (23.2–29.4)		26.0 (23.3–29.4)		
Range	16.7–53.5		15.2–42.0		
Location [n, %]					$P^{FFH-MC} = 0.058$ 99% CI: 0.052–0.064
RUL	100	28.8%	131	25.6%	
RML	10	2.9%	24	4.7%	
RLL	47	13.5%	97	19.0%	
RCE	25	7.2%	37	7.2%	
CUL	45	13.0%	72	14.1%	
LIN	5	1.4%	6	1.2%	
LUC	44	12.7%	47	9.2%	
LLL	46	13.3%	79	15.5%	
LCE	25	7.2%	18	3.5%	
Histology [n, %]					$P^{FFH-MC} = 0.046$ 99% CI: 0.045–0.046
SCC	186	53.6%	229	44.8%	
AND	93	26.8%	172	33.7%	
LCC	14	4.0%	13	2.5%	
ASC	28	8.1%	42	8.2%	
SCLC	2	0.6%	4	0.8%	
CAR	8	2.3%	27	5.3%	
OTH	16	4.6%	24	4.7%	
CT-based T factor [n,					$P^{FFH-MC} < 0.001$

%]					99% CI: < 0.001 to < 0.001
T1a	22	6.3%	72	14.1%	
T1b	57	16.4%	121	23.7%	
T1c	7	2.0%	19	3.7%	
T2a	116	33.4%	147	28.8%	
T2b	70	20.2%	69	13.5%	
T3	67	19.3%	62	12.1%	
T4	7	2.0%	21	4.1%	
Tx	1	0.3%	0	0.0%	
CT-based N factor [n, %]					P^{FFH} = 0.041 99% CI: 0.036–0.046
N0	274	79.0%	437	85.5%	
N1	33	9.5%	40	7.8%	
N2	39	11.2%	33	6.5%	
N3	1	0.3%	1	0.2%	
Primary tumour SUV	n = 331		n = 476		P^{MW} < 0.001
Mean (SD)	14.7 (7.7)*		11.5 (6.6)*		
Median (Q1–Q3)	13.6 (10.0–18.5)		11.0 (6.0–15.5)		
Range	1.2–66.8		0.0–35.0		

#Grade data were available for 832 patients; *p < 0.05 by the Shapiro-Wilk test for normal distribution; ADN — adenocarcinoma; ASC — adeno-squamous carcinoma; BMI — body mass index; Chi2 — chi-square test; CI — confidence interval; CT — computed tomography; CUL — culmen; FFH-MC — Fisher-Freeman-Hamilton exact test with Monte Carlo CIs; LCC — large-cell carcinoma; LCE — left central; LIN — lingula; LLL — left lower lobe; LUC — left upper central; OTH — other histological types; RCE — right central; RLL — right lower lobe; RML — right middle lobe; RUL — right upper lobe; SCC — squamous-cell carcinoma; SCLC — small-cell lung cancer; SUV — standardised uptake value; UMW — U Mann–Whitney's test

Table V. Univariable logistic regression analysis of patient characteristics associated with the probability of endoscopic ultrasound (CUS) downstaging of positron emission tomography (PET)-based stage

Factor	OR	95% CI Lower limit	95% CI Upper limit	p-value
Grade				
0 (ref.)	1			
1	1.01	0.36	2.80	0.991
2	2.70	1.21	6.01	0.015
3	2.91	1.28	6.60	0.011
4	4.17	1.52	11.40	0.005
Age [years]	1.012	0.996	1.029	0.152
Sex				
Female (ref.)	1			
Male	1.54	1.14	2.08	0.005

BMI [kg/m^2]	1.00	0.97	1.03	0.990
Location				
RUL (ref.)	1			
RML	0.55	0.25	1.19	0.129
RLL	0.63	0.41	0.98	0.040
RCE	0.89	0.50	1.57	0.675
CUL	0.82	0.52	1.29	0.388
LIN	1.09	0.32	3.68	0.887
LUC	1.23	0.75	2.00	0.411
LLL	0.76	0.49	1.19	0.235
LCE	1.82	0.94	3.52	0.075
Histology				
SCC (ref.)	1			
ADN	0.67	0.48	0.91	0.012
LCC	1.33	0.61	2.89	0.478
ASC	0.82	0.49	1.37	0.453
SCLC	0.62	0.11	3.40	0.578
CAR	0.36	0.16	0.82	0.015
OTH	0.82	0.42	1.59	0.558
PET-based T factor				
T1a (ref.)	1			
T1b	1.54	0.87	2.73	0.138
T1c	1.21	0.45	3.24	0.711
T2a	2.58	1.51	4.41	0.001
T2b	3.32	1.86	5.94	0.000
T3	3.54	1.96	6.38	0.000
T4	1.09	0.41	2.91	0.862
Tx	–#			
PET-based N factor				
N0 (ref.)	1			
N1	1.32	0.81	2.14	0.267
N2	1.88	1.16	3.07	0.011
N3	1.59	0.10	25.60	0.742
Primary tumour SUV	1.07	1.05	1.09	< 0.001

#Due to limited number of observations the model did not reach reliable estimates; *$p < 0.05$ by the Shapiro-Wilk test for normal distribution; ADN — adenocarcinoma; ASC — adeno-squamous carcinoma; BMI — body mass index; CAR — carcinoid; Chi2 — chi-square test; CI — confidence interval; CT — computed tomography; CUL — culmen; FFH-MC — Fisher-Freeman-Hamilton exact test with Monte Carlo CIs; LCC — large-cell carcinoma; LCE — left central; LIN — lingula; LLL — left lower lobe; LUC — left upper central; OTH — other histological types; RCE — right central; RLL — right lower lobe; RML — right middle lobe; RUL — right upper lobe; SCC — squamous-cell carcinoma; SCLC — small-cell lung cancer; SUV — standardised uptake value; UMW — U Mann–Whitney's test