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HEAD AND NECK

Role of 18F-FDG PET/CT in evaluating lymph node status in patients with head and neck squamous cell carcinoma

Ruolo della PET/CT con 18F-FDG nella stadiazione linfonodale dei pazienti con carcinoma squamocellulare del distretto testa collo

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SUMMARY

Objective. The presence of cervical lymph node metastases (CLNM) at diagnosis is one of the most relevant negative prognostic factors in patients with head and neck squamous cell carcinoma (HNSCC). The aim of this study was to analyse 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) PET/CT findings for the identification of primary tumours and CLNM in a sample of patients affected by HNSCC. Moreover, a maximum standardised uptake value (SUVmax) threshold for the detection of CLNM was estimated. Clinical variables (i.e. smoking and alcohol habits), and tumour features (i.e. EBV and HPV positivity) were also evaluated in relation to FDG PET/CT findings.

Methods. We retrospectively analysed patients who underwent FDG PET/CT for HNSCC staging between 2015-2020 at the University Hospital of Ferrara. All patients had cytological or histological confirmation of suspected cervical lymph nodes.

Results. In total, 65 patients were enrolled (53 males, 12 females, median age 65.7 years). CLNM of patients with smoking habit had significantly higher SUVmax values than those of patients with previous smoking habit and non-smokers (p = 0.04). p16 positive HNSCC demonstrated a trend for higher SUVmax values on CLNM, in comparison to p16 negative tumours (p = 0.089). ROC curve analysis identified 5.8 as the best cut-off value of SUVmax for the detection of CLNM (AUC = 0.62, sensitivity 71.4% and specificity 72.7%).

Conclusions. FDG PET/CT is a useful tool to evaluate CLNM in patients with HNSCC, particularly in those with smoking habit and p16 positive disease. A SUVmax cut-off of 5.8, combined with the use of conventional radiological investigations, may represent a useful tool in the identification of CLNM.

KEY WORDS: squamous cell carcinoma, ^{18}F-FDG, PET/CT, lymph node metastasis, standardized uptake value

RIASSUNTO

***Obiettivo**. La presenza di metastasi linfonodali laterocervicali (CLNM) al momento della diagnosi è uno dei fattori prognostici negativi più rilevanti nei pazienti affetti da carcinoma squamocellulare del distretto testa-collo (HNSCC). Lo scopo di questo studio è quello di analizzare i risultati della PET/CT con 2-deossi-2[^{18}F]fluoro-D-glucosio (FDG) nell'identificazione dei tumori primitivi e delle CLNM in un campione di pazienti affetti da HNSCC. È stata stimata una soglia del massimo valore di captazione standardizzato (SUVmax) per l'individuazione di CLNM. I dati ottenuti dalla metodica FDG PET/CT sono stati correlati alle variabili cliniche dei pazienti (come l'abitudine tabagica, l'assunzione di alcool) e alle caratteristiche del tumore (ad esempio, la positività a EBV e HPV).*

***Metodi**. Abbiamo analizzato retrospettivamente i dati dei pazienti sottoposti presso l'Azien-*

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da Ospedaliera Universitaria di Ferrara, tra il 2015-2020, a FDG PET/CT per la stadiazione di HNSCC. Tutti i pazienti avevano una conferma citologica o istologica dei linfonodi cervicali sospetti.
Risultati. *Sono stati arruolati 65 pazienti (53 maschi, 12 femmine, età mediana 65,7 anni). I pazienti con abitudine tabagica presentavano valori di SUVmax a livello di CLNM significativamente più elevati rispetto a quelli dei pazienti con pregressa abitudine tabagica e dei non fumatori (p = 0,04). Gli HNSCC p16 positivi hanno dimostrato una tendenza a un valore di SUVmax più elevato a livello di CLNM, rispetto a quelli p16 negativi (p = 0,089). L'analisi della curva ROC ha identificato 5,8 come il valore ottimale di cut-off di SUVmax per il rilevamento delle CLNM (AUC = 0,62, sensibilità 71,4% e specificità 72,7%).*
Conclusioni. *La FDG PET/CT è uno strumento utile per valutare le CLNM nei pazienti affetti da HNSCC, in particolare se presente abitudine al fumo e malattia p16 positiva. La metodica PET, abbinata all'utilizzo delle indagini radiologiche convenzionali, ha permesso di ottimizzare l'iter diagnostico in ambito oncologico del distretto testa-collo, rappresentando anche un utile strumento per l'identificazione delle CLNM.*

PAROLE CHIAVE: *carcinoma squamocellulare, ^{18}F-FDG, PET/C, metastasi linfonodali latero-cervicali, SUVmax*

Introduction

Head and neck cancers are the sixth most frequent neoplasm globally and squamous cell carcinoma (SCC) accounts for 90% of histological diagnoses [1]. In 2021 in the USA, 66,010 new diagnoses of cancer of the oral cavity, oropharynx and larynx were estimated, with 14,620 deaths from the disease. The 5-year survival was estimated to be 66% for oral cavity and pharynx and 61% for laryngeal cancers [2]. Worldwide, the incidence of SCC in the head and neck regions varies according to the geographic area and strongly correlates with the distribution of risk factors such as alcohol abuse, exposure to tobacco smoke, and viral infections. Smoking is clearly established as a causal factor in the development of SCC at many sites, including the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx [3]. Moreover, the presence of cervical lymph node metastases at the time of diagnosis is one of the most important prognostic factors and highly influences the patient's management [4,5]. In this scenario, FDG Positron Emission Tomography/Computed Tomography (PET/CT) is increasingly being used as staging tool, for evaluation of treatment response and detection of residual disease [6,7]. In particular, in a meta-analysis carried out by Sun et al., FGD PET showed a sensitivity and specificity of 84% and 96%, respectively, in identifying regional nodal metastases [8]. FDG PET can provide an in-vivo representation of lesional glucose metabolism, which is correlated with cell proliferation index and aggressive tumour behaviour [9]. Maximum standardised uptake value (SUVmax) is commonly used as a semi-quantitative parameter in PET/CT as it expresses the hottest point within a lesion. The aim of this study was to analyse FDG PET findings in assessment of nodal metastases of patients affected by HNSCC, to correlate it with histopathological features and to estimate a maximum SUVmax threshold for detection of cervical lymph node metastases by an ROC curve.

Materials and methods

This retrospective study was conducted at the University Hospital of Ferrara. All patients with primary HNSCC receiving FDG PET for staging at the Nuclear Medicine Unit between January 2015 and December 2020 were identified. Patients studied before 2015 were imaged with a different tomograph and were therefore excluded in order to analyse uniform records. Only patients with at least one cytological or histological confirmation of suspected cervical lymph node were enrolled in the study. Patients with previous history of head and neck malignancies or previous cervical lymph nodes treatment (surgical or conservative) were excluded.
An analysis of patients' records was performed: data on gender, age, BMI, smoking and drinking habits, clinical and pathological stage, surgical or conservative treatment, tumour grading, p16 status, immunohistochemistry for EBV and HPV, histopathological confirmation of lymphovascular invasion, perineural infiltration, and extranodal extension (ENE), SUVmax of primary tumour, suspected lymph node metastases and suspected distant metastases at staging FDG PET, and identification of suspicious cervical lymph node levels according to FDG PET parameters and cytological and histological results were collected.
SUVmax of the primary tumour (T) and the two most suspicious lymph node levels (N) were recorded for each patient. Any SUVmax values of both T and N in relation to the variables listed above were explored. In order to evaluate the SUVmax predictivity in identifying cervical nodal metastases, all cases with at least one lymph node suggestive for metastasis at FDG PET corresponding to a metastasis confirmed by cytology or histology in the same neck level were considered positively matching. Therefore, all laterocervical bilateral levels were evaluated by experienced nuclear physicians, also analysing the contextual low-dose CT images and considering SUVmax value of 2.5 as a cut-off.
Smoking was defined as a current daily consumption of cigar or cigarettes. Alcohol consumption was defined as a daily intake of more than 3 units of alcohol (1 unit = 8 g). Non-smokers were defined as patients who had stopped smoking for at least six months.

FDG PET acquisition protocol and interpretation

All patients were required to fast for 6-8 h and maintain adequate hydration before the scan. Diabetic patients had blood glucose measured before ^{18}F-FDG delivery. Those with a fasting glucose above 190 mg/dl were postponed until adequate therapy was established. Images were acquired with an acceptable range of 50-70 min after FDG injection (1 mCi/10 kg) using a standard technique on a dedicated 3D PET/CT system (Biograph mCT Flow; Siemens Medical Solutions, Malvern, PA, USA), as suggested by the European Association of Nuclear Medicine (EANM) procedure guidelines for tumour imaging [10].

A low-dose CT scan (120 kV and 80 mA/s) was performed for attenuation correction of the PET emission data acquired from the mid-thigh to the skull vertex. PET/CT images were processed and analysed on a Syngo.Via Workstation (Siemens Healthineers). Final PET/CT images were reconstructed along axial, coronal and sagittal planes with a dedicated workstation by an expert nuclear medicine physician. A MIP (Maximum Intensity Projection) image was stored for each patient. Every focal deviation from physiological distribution, background, or blood-pool and liver uptakes was reported, be it hyper- or hypo-metabolic. Pathological findings were considered a focal area of increased radiotracer uptake or diffusely increased uptake, excluding sites of physiological distribution, in comparison with surrounding tissues. Circular regions of interest (ROIs) were drawn around the lesion and the system automatically adapted the ROI into 3-dimensional volume of interest (VOI) and SUVmax was then calculated.

Statistical analysis

A descriptive analysis of all variables with their frequencies was performed. Numerical data were expressed as absolute values, or percentages, or mean ± standard deviation, or median (range). For discrete variables, the chi-square (χ^2) test was used to investigate a possible correlation between the intra-variable distribution, pathological lymph node status and FDG PET positivity. The correspondence between pathological lymph node status and FDG PET positivity was also evaluated with a χ^2 test. The mean values of SUVmax on T and N were compared to dichotomous variables (t-test) and multimodal variables (ANOVA). A ROC curve was obtained to estimate the threshold value of SUVmax indicative for lymph node metastasis. All analyses were considered statistically significant for p values < 0.05. Statistical analysis was performed using the SPSS 20.0 program for Windows.

Results

Patient and tumour characteristics

A total of 65 patients with HNSCC were included (53 males and 12 females) with a mean age of 65.7 ± 10.6 years (range 41-91). The baseline characteristics are shown in Table I.

Regarding smoking habit, 33.9% of patients were active smokers, 30.8% were ex-smokers and only 15.4% had never smoked. The highest prevalence of primary tumours was found in the oral cavity and oropharyngeal (64.6%). In particular, 33.9% of patients were affected by oropharynx SCC (the most affected subsite being the palatine tonsil, 17%), and 30.7% by oral SCC (the most involved subsite being the oral tongue, 20%). Unknown primaries were present in 13.8% of cases; other tumour sites in order of frequency were: larynx (10.8%), hypopharynx (6.3%), nasopharynx (3.1%) and lip (1.5%).

Based on histopathological information about the specimen (biopsy or surgical), tumour grading could be established in 44 cases. Two patients (3.1%) were classified as G1, 23 patients (35.4%) as G2, and 19 (29.2%) as G3. In the remaining 21 cases, patients lacked anatomopathological analysis to establish grading since they did not undergo surgery. Most patients (72.3%) had advanced clinical stage (IV).

Twenty-nine patients underwent first-line surgical treatment. In 25 cases, surgical resection margins were free of disease (R0), whereas in 4 cases, resection margins showed microscopic residual disease (R1). Considering also the 9

Table I. Description of the cohort studied.

Population features	N (%)
	Cohort n = 65 (100%)
Gender	
Male	53 (81.5)
Female	12 (18.5)
Mean age at diagnosis (years ± SD)	65.7 ± 10.6
BMI	
Underweight (≤ 18.4)	6 (9.2)
Normal weight (18.5-24.9)	31 (47.7)
Overweight (≥ 25)	21 (32.3)
N.A.	7 (10.8)
Smoking habit	
Yes	22 (33.8)
No	10 (15.4)
Ex	20 (30.8)
N.A.	13 (20)
Alcohol consumption	
Yes	31 (47.7)
No	16 (24.6)
Ex	1 (1.5)
N.A.	17 (26.2)

continues ▶

Table I. Description of the cohort studied *(follows)*.

Population features	N (%)
Tumour site	
Oropharynx	**22 (33.9)**
Palatine tonsils	11 (17)
Base of tongue	6 (9.2)
Epiglottic vallecula	1 (1.5)
Uvula	2 (3.1)
Soft palate	2 (3.1)
Oral cavity	**20 (30.7)**
Tongue	13 (20)
Floor of mouth	2 (3.1)
Alveolus and gingiva	3 (4.6)
Buccal mucosa	1 (1.5)
Lip mucosa	1 (1.5)
Unknown primary	**9 (13.8)**
Larynx	**7 (10.7)**
Supraglottis	4 (6.1)
Glottis	3 (4.6)
Hypopharynx	**4 (6.3)**
Pyriform sinus	4 (6.3)
Nasopharynx	**2 (3.1)**
Lip	**1 (1.5)**
Grading	
G1	2 (3.1)
G2	23 (35.4)
G3	19 (29.2)
N.A.	21 (32.3)
Clinical stage	
I	5 (7.7)
II	8 (12.3)
III	5 (7.7)
IV	47 (72.3)

SD: standard deviation; BMI: Body Mass Index; N.A.: not available.

Table II. Histopathological features in surgically-treated patients.

	Cohort (n = 38, 100%)
Surgical margins	
R0	25 (65.8)
R1	4 (10.5)
N.A.	9 (23.7)
Lympho-vascular invasion	
No	31 (81.6)
Yes	7 (18.4)
Perineural infiltration	
No	33 (86.8)
Yes	5 (13.2)
Extranodal extension	
No	29 (76.3)
Yes	9 (23.7)

N.A.: not available.

patients diagnosed with cervical SCC metastases from unknown primary, a total of 38 patients underwent surgery as first-line treatment on T or N (Tab. II), while the others were treated with chemo-radiotherapy. Anatomopathological analysis of the surgical specimen of T or N showed perineural infiltration in 5 cases (13.2%) and lympho-vascular invasion in 7 cases (18.4%). ENE was detected in 9 of 38 surgical specimens (23.7%).

Immunohistochemistry correlations

In 33 of 65 patients, immunohistochemical investigation of p16 (p16INK4a cyclin-dependent kinase) was carried out on cytological or histological samples. Fifteen samples were positive, while 18 were negative. In 48 of 65 patients, HPV-DNA research was carried out. Among those, 12 were positive and 36 resulted negative. Of the 22 patients with SCC localised in the oropharynx, 18 underwent both p16 and HPV-DNA testing: in 16 of 18 cases, concordance was found between the two tests; 9 patients (50%) were positive for both and 7 patients (38.8%) were negative. Two of 18 patients resulted positive for p16 and negative for HPV-DNA, respectively. Of the remaining four patients, two underwent only the HPV DNA test resulting in a negative case and a positive case, while two patients underwent only the test for p16 that resulted negative.

Analysis of SUVmax of primary tumour

The analysis of SUVmax values of the primary tumour according to patients' variables and tumour characteristics (Tab. III) revealed a statistically significant correlation with tumour site and perineural infiltration status (Fig. 1). Nasopharyngeal SCC showed a significantly higher mean SUVmax value of T compared to other tumour sites ($p = 0.01$); furthermore, mean SUVmax values of T were found to be significantly higher in tumours without perineural invasion compared to those with documented perineural invasion ($p = 0.048$). Nonetheless, these results could be influenced by the small number of patients affected by nasopharyngeal carcinoma with perineural infiltration.

Analysis of lymph node SUVmax values

The difference in terms of SUVmax values of N between the group of positively *vs* negatively matching FDG PET findings and nodal metastases was statistically significant (median SUVmax 16.7 ± 11 *vs* 6.5 ± 4.8 respectively; $p < 0.0001$).

Table III. Analysis of SUVmax of primary tumours.

Variables	N	Mean SUVmax T	SD	T-test	P value	Diff. mean SUVmax	95% CI	
							Lower	Upper
Gender				1.289	0.203	4.35	-2.429	11.139
Male	43	19.74	9.82					
Female	10	15.38	8.67					
Age								
< 65 years	24	17.42	12.67	-1.024	0.32	-2.73	-8.099	2.629
≥ 65 years	29	20.15	6.23					
BMI								
Underweight	6	17.70	10.25					
Normal weight	24	20.24	10.97	0.344	0.710			
Overweight	17	17.90	8.02					
Alcohol consumption								
Yes	16	17.64	7.13	-0.475	0.638	-1.485	-7.817	4.846
No	24	1.13	11.04					
Smoking habit								
No	8	16.63	8.51					
Yes	19	18.50	12.43	1.169	0.845			
Ex	17	19.08	6.62					
p16 status								
Negative	18	18.12	8.75	-0.617	0.543	-1.90	-8.234	4.434
Positive	10	20.05	5.61					
HPV status								
Negative	30	17.94	8.81	-0.373	0.711	-1.20	-7.768	5.354
Positive	8	19.15	4.21					
Lympho-vascular invasion								
No	29	18.90	11.26	0.866	0.393	4.543	-6.148	15-235
Yes	5	14.36	7.14					
Perineural infiltration								
No	31	19.36	10.53	2.053	0.048	12.79	0.102	25.493
Yes	3	6.56	6.04					
Grading								
G1	2	20.55	9.40					
G2	21	18.49	12.14	0.040	0.961			
G3	13	19.51	8.50					
Tumour site								
Oral cavity-Lip	19	17.96	8.64					
Hypopharynx	5	19.44	8.72					
Oropharynx	19	18.06	7.70	3.750	**0.010***			
Nasopharynx	2	42.60	23.19					
Larynx	7	18.04	7.93					

SD: standard deviation; Diff.: difference.

Patients with higher SUVmax values in cervical lymph nodes showed a significantly higher risk of nodal metastasis confirmed by cytology or histology (Tab. IV, Fig. 2).

The analysis of cervical lymph nodes SUVmax values according to patients' variables and tumour characteristics (Tab. V) revealed a significant correlation with smoking habit: smokers had significantly higher SUVmax values of N than patients with previous smoking habit and non-

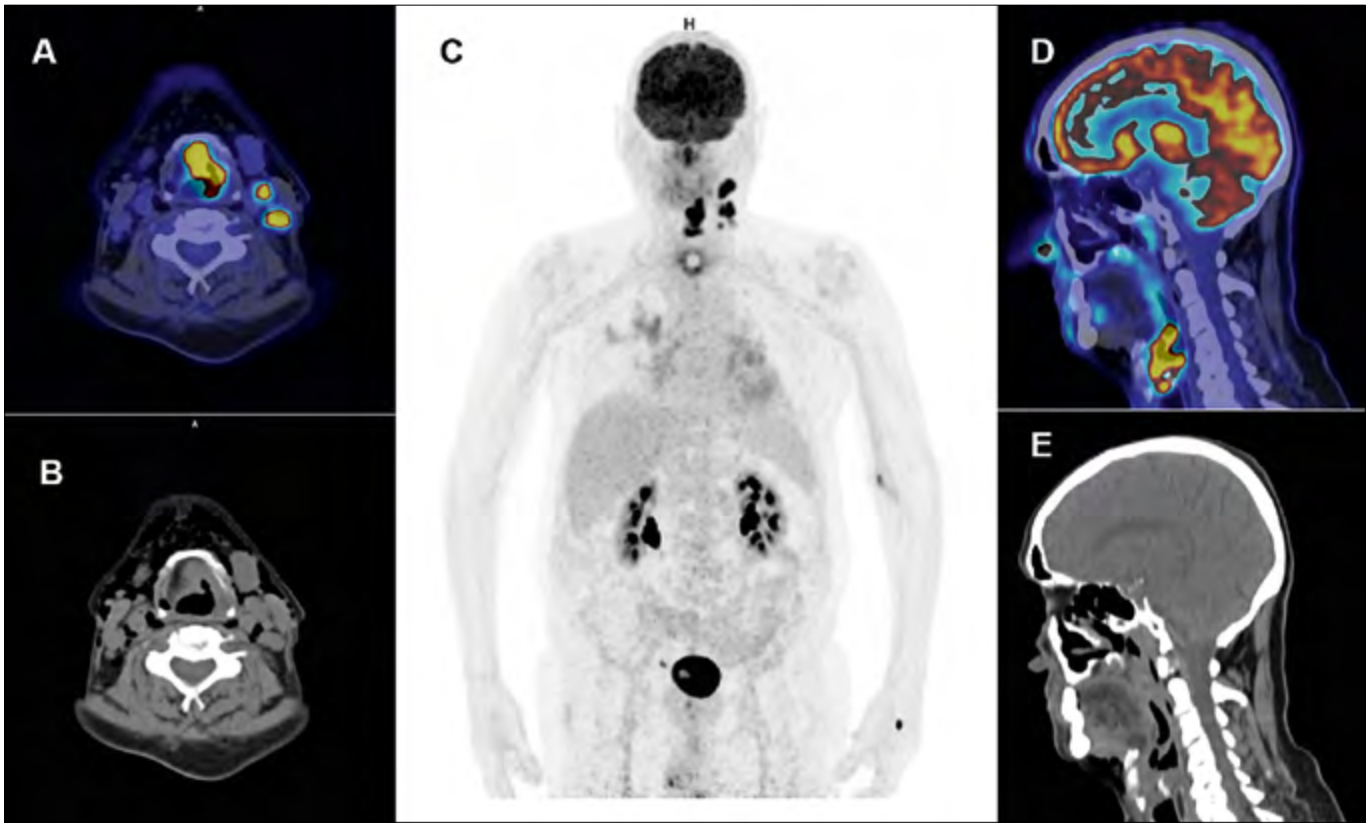

Figure 1. Pre-surgical FDG. PET/CT scan (**A-B**): transaxial images of PET/CT and CT (**C**): maximum intensity projection; (**D-E**): sagittal images of PET/CT and CT) of a 71-year-old man with diagnosis of infiltrating squamous cell carcinoma of the larynx metastasised to several left laterocervical lymph nodes. FDG PET/CT showed intense uptake both at the primary laryngeal lesion and left laterocervical lymph nodes. Afterwards, the patient was treated with surgery followed by adjuvant chemoradiotherapy.

smokers (median SUVmax values 15.5 ± 10.2, 11.1 ± 8.1 and 7.4 ± 4.1, respectively; p = 0.04).

As for SUVmax of T, p16 status did not significantly influence SUVmax values of N, not even in the group with oropharyngeal SCC. Nonetheless, all p16 positive patients showed a trend for higher SUVmax values of N in comparison to p16 negative ones (median SUVmax 17.1 ± 14.9 *vs* 10 ± 7.4, respectively; p = 0.089).

The ROC curve to estimate the threshold value of SUVmax indicative for lymph node metastasis revealed an area under the curve of 0.62. This analysis identified a cut-off value of SUVmax of 5.8, with a sensitivity of 71.4% and a specificity of 72.7% (Fig. 3).

Discussion

FDG PET is an effective and accurate tool in oncology, which is complementary to conventional radiological methods and is useful for both staging disease and post-treatment evaluation. For the head and neck regions, FDG PET is also widely used for an accurate assessment of cervical lymph node status [11]. Actually, the presence of cervical lymph node metastases at

Table IV. Matching of FDG PET and cyto/histologic results.

Variable	FDG PET and cyto/ histologic matching	N	Mean SUVmax N	SD	T-test	P	Diff. mean SUVmax	95% CI	
								Lower	Upper
SUVmax N									
	No	23	6.51	4.82	-4.218	< 0.0001	-10.18	-14.991	-5.355
	Yes	42	16.69	10.98					

SD: standard deviation; Diff.: difference.

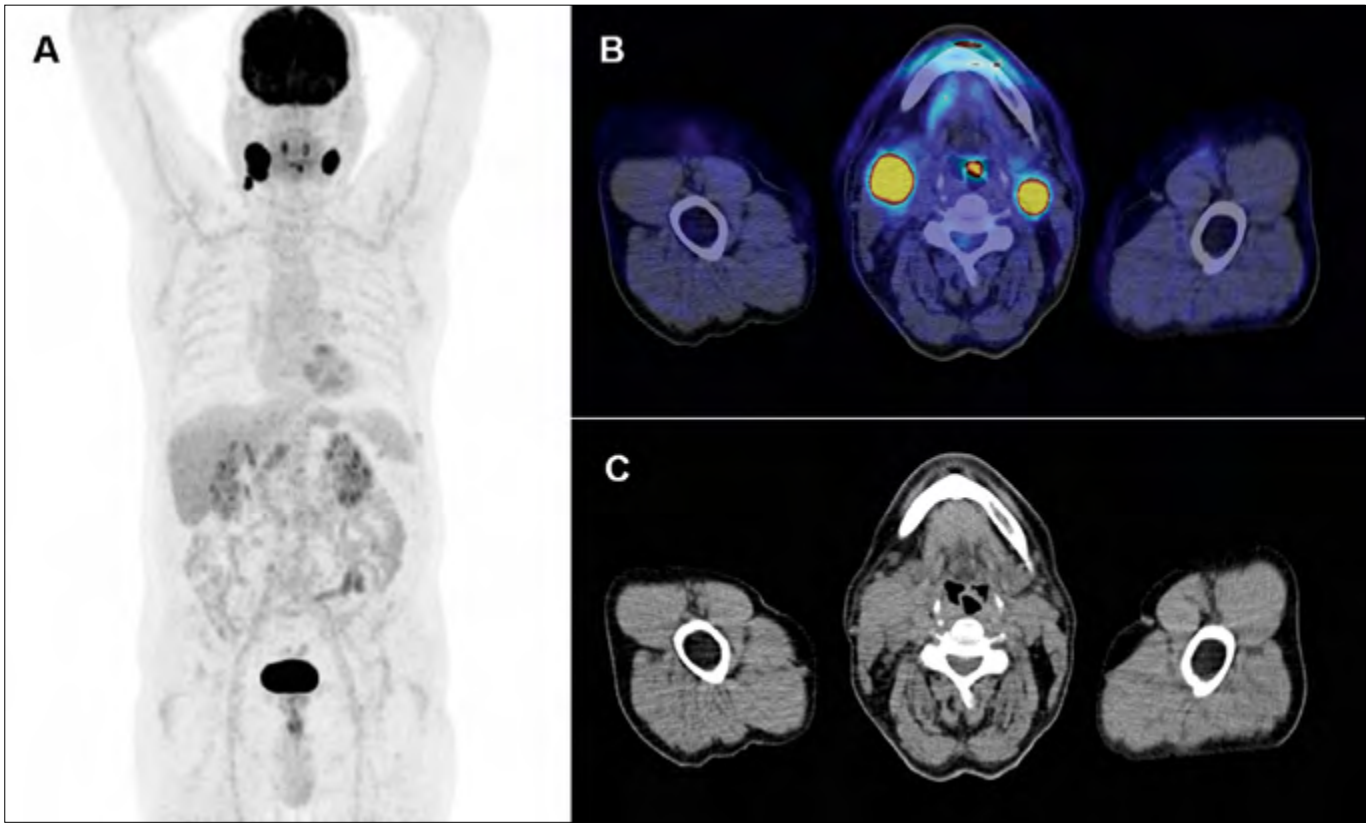

Figure 2. Staging FDG PET/CT scan. (**A**): maximum intensity projection; (**B-C**): transaxial images of PET/CT and CT) of a 61-year-old man affected by a voluminous squamous cell carcinoma involving left base of tongue and epiglottis. Images show intense uptake in correspondence of the primary tumour and particularly of lymph node metastases. The patient was subsequently treated with surgery followed by adjuvant chemoradiotherapy.

diagnosis is one of the most important negative prognostic factors in patients with HNSCC, and therefore correct lymph node staging is necessary for adequate planning of treatment protocols [12,13]. FDG PET is used to predict tumour aggressiveness and surgical outcome, and metabolic parameters such as SUVmax are commonly used for this purpose [14].

In the present study, we aimed to evaluate possible correlations between SUVmax values of both the primary tumour site and neck lymph nodes and clinical-pathological features of a cohort of HNSCC patients. Statistical analyses revealed that nasopharyngeal SCC showed significantly higher mean SUVmax of T than other primary tumour sites. Lee et al. performed a retrospective study on 225 patients, comparing FDG uptake values in benign nasopharyngeal disease versus malignant nasopharyngeal pathology. The group with nasopharyngeal carcinoma showed more intense uptake values than the group with benign pathology (SUVmax 10.4 ± 4.6 *vs* 3.9 ± 1.4 respectively, $p < 0.001$). The cut-off of SUVmax indicating nasopharyngeal malignancies was 6.00 [15]. Nonetheless, the study conducted by Ma et al. concluded that FDG uptake in the nasopharynx could be considered physiological if SUV-

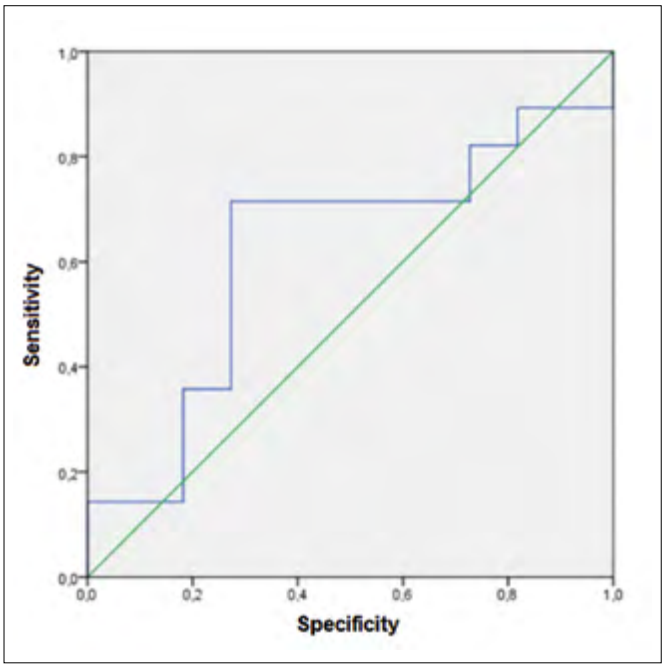

Figure 3. ROC curve of SUVmax of cervical lymph nodes.

Table V. Analysis of cervical lymph node SUVmax values according to patient variables and tumour characteristics.

Variables	N	Mean SUVmax N	SD	T-test	P value	Diff. mean SUVmax	95% CI	
							Lower	Upper
Gender								
Male	53	12.92	8.94	-0.270	0.788	-0.91	-7.634	5.818
Female	12	13.83	16.03					
Age								
< 65 years	31	13.93	13.37	0.600	0.55	1.61	-3.79	7.01
≥ 65 years	34	12.32	6.93					
BMI								
Underweight	6	11.75	10.33					
Normal weight	31	13.71	11.56	1.147	0.325			
Overweight	21	9.47	6.55					
Alcohol consumption								
Yes	16	9.73	7.09	-1.012	0.317	-2.47	-7.391	2.448
No	31	12.20	8.32					
Smoking habit								
No	10	7.42	4.14					
Yes	22	15.51	10.17	3.390	**0.042***			
Ex	20	11.11	8.06					
EBV status								
Negative	5	15.70	9.55	4.96	0.061	11.3	-0.75	23.35
Positive	2	4.40	2.68					
p16 status								
Negative	18	10.03	7.43	-1757	0.089	-7.03	-15.19	1.13
Positive	15	17.06	14.93					
HPV status								
Negative	36	14.01	9.72	-0.822	0.415	-3.11	-10.72	4.50
Positive	12	17.11	15.41					
Lymphovascular invasion								
No	37	11.57	8.49	0.736	0.470	1.50	-2.73	5.73
Yes	8	10.07	4.21					
Perineural infiltration								
No	40	11.11	7.38	-0.317	0.766	-1.76	-16.75	2.21
Yes	5	12.88	12.20					

SD: standard deviation; Diff.: difference.

max was lower than 7.6, whereas further investigation should be required when SUVmax was higher than 11.0 [16]. A meta-analysis by Li et al. indicated a SUVmax between 7.8 and 18.0 as a cut-off threshold in nasopharyngeal carcinoma [17]. In the present study, the mean SUVmax of nasopharyngeal SCC was 42.6 ± 23.2, and significantly higher than the values currently available in the literature. However, the sample of patients diagnosed with nasopharyngeal SCC is extremely small compared to other primary tumour sites, and this inhomogeneity could be responsible for the SUVmax discrepancies.

In the present study, no statistically significant relationship was found between SUVmax of both T and N and p16 or HPV DNA status. Nevertheless, a trend of lymph node SUVmax was highlighted, as it tended to be higher in p16-positive than in p16-negative SCC. Tahari et al. conducted a retrospective study of 123 patients with oropharyngeal SCC who were screened for high-risk HPV by in situ hybridisation. The mean SUVmax of T in HPV-negative SCC was significantly higher than in HPV-positive ones (10.4 *vs* 12.4, p = 0.007). On the other hand, comparison of medium SUVmax values of cer-

vical lymph nodes showed that values tended to be higher in HPV-positive nodal metastases compared to HPV-negative ones, even if not statistically significant [18]. Kendi et al. investigated the association between SUVmax values and p16 positivity in a cohort of patients with oral cavity and oropharyngeal SCC. Higher medium SUVmax values were shown for p16-positive cervical nodal metastases than those obtained for p16-negative lesions [19]. Often HPV-positive oropharyngeal cancers are diagnosed at more advanced stages and in the presence of nodal metastases, which could justify the trend identified. Clark et al. defined a cut-off for SUVmax > 10.8 that could predict p16 status with an odds ratio of 4.9 [20].

Another significant finding of the present study (and – to the best of our knowledge – the first reported in the literature) focused on smoking habit because smokers showed a significant higher cervical lymph node SUVmax compared to non-smokers or ex-smokers, even if no difference was found considering SUVmax of the primary tumour. Similarly, in a retrospective study by Pleitz et al. no significant difference was found when comparing the mean SUVmax of T in active smokers versus non-smokers in either the group of patients with oropharyngeal cancer or in the group with laryngeal cancer. However, to the best of our knowledge, no data were provided that compared the SUVmax of N in smokers to non-smokers [21].

In the present study, the efficacy of PET in detecting cervical lymph node metastases was evaluated: the higher the SUVmax, the more likely there was correspondence with a nodal metastasis confirmed by cytology or histology. ROC analysis of SUVmax values for the detection of cervical node metastasis from SCC revealed an area under the curve of 0.62. The analysis identified the cut-off value of SUVmax at 5.8, with a sensitivity of 71.4% and a specificity of 72.7%. On a sample of 23 patients with HNSCC, Murakami et al. defined a cut-off value of SUVmax that varied according to lymph node size: 1.9 for lymph nodes smaller than 10 mm, 2.5 for those between 10-15 mm, and 3.0 for nodes larger than 15 mm. Based on these data, a sensitivity of 79% and a specificity of 99% were calculated [22]. Furthermore, Lim et al. on a sample of 74 patients with HNSCC defined a cut-off of SUVmax ≥ 3.16 for the diagnosis of lymph node metastases, with a sensitivity of 74.4% and a specificity of 84.9%. In addition, the authors suggested the use of a ratio between lymph node SUVmax and background SUVmax of the healthy tissue, in order to standardise evaluation criteria across different centres as much as possible [23].

In 2015, Kitajima et al. found that PET/CT correctly indicated the primary tumours in all enrolled patients (36 patients with HNSCC), with a mean SUVmax of 15.5 ± 6.6. The SUVmax of pathological lymph nodes was significantly higher than the SUVmax of benign lymph nodes (6.03 ± 4.22 *vs* 1.98 ± 0.84). Lymph nodes with a SUVmax > 5.25 were all found to be involved by metastasis, with a mean SUVmax of 11.41 ± 3.93 for metastatic lymph nodes with extracapsular extension (ECE) and 5.13 ± 3.60 for metastatic lymph nodes without ECE [24]. The cut-off value identified in our study is slightly higher than the values reported in the literature; the heterogeneity of primary tumour sites could be co-responsible for this result. To date, in the literature, there is still no universally accepted SUVmax threshold for detection of cervical lymph node metastases. However, in order to standardise SUVmax threshold values as much as possible, it may be useful to supplement cervical lymph node SUVmax with other parameters. These include lymph node size and background SUVmax.

Moreover, we would like to highlight that in our study the difference, in terms of SUVmax values of cervical nodes among positively *versus* negatively matching FDG PET findings and lymph node metastases, was significant. Considering this point, Lowe et al., in their prospective and multicentre trial, highlighted the high negative predictive value (≥ 87%) of FDG PET for clinically N0 on the basis of the neck dissection results in a large cohort of 287 patients [25]. These findings suggest that, nowadays, FDG PET may assist the clinician in deciding on the best therapy in HNSCC, integrating conventional radiological investigations.

Although the role of FDG PET in the diagnostic approach of HNSCC is well known, the available data on its reliability in distinguishing cervical lymph node SCC metastases from granulomatous diseases or benign reactive lymph nodes is not completely clear to date. For this aim, PET/CT should always be compared with other conventional imaging methods.

Conclusions

Over the last 20 years, FGD PET has become a very popular and important diagnostic tool in the diagnostic algorithm of HNSCC, although it is still complementary to conventional radiological investigations.

We found a positive correlation between higher SUVmax values and confirmation of lymph node metastases on cytology or histopathology, especially in patients with a smoking habit. The best cut-off of SUVmax value to detect cervical lymph node metastases was 5.8.

In the future, the identification of a standardised and reliable SUVmax threshold for head and neck regions, combined with PET derived volumetric parameters and better morphological definition of images, will allow further improvement of the reliability of FDG PET.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MC, CB, LU, AC, SP: work conceptualization and writing; NO, LU, MC, VC, AB, AM: data curation; IC: statistical analysis; CC, LU, MB, AC, CB, SP: revision and editing. All authors have read and agree with the final version of the manuscript.

Ethical consideration

No Ethical Committee approval was required for this study. This study was conducted in compliance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration (2008); the research did not affect patient care in any way, since only patient data were retrieved and reviewed.

Written informed consent was obtained from each participant/patient for study participation and data publication.

References

1 Machiels JP, Leemans RC, Golusinski W, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1462-1475. https://doi.org/10.1016/j.annonc.2020.07.011

2 American Cancer Society. American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021, pp. 1-72.

3 IARC Working Group on the evaluation of carcinogenic risks to Humans. Personal habits and indoor combustions. A review of human carcinogens, Volume 100. Lyon: IARC; 2012. pp. 319-331.

4 Kumar T, Patel MD. Pattern of lymphatic metastasis in relation to the depth of tumor in oral tongue cancers: a clinico pathological correlation. Indian J Otolaryngol Head Neck Surg 2013;65:59-63. https://doi.org/10.1007/s12070-012-0504-y

5 Sparano A, Weinstein G, Chalian A, et al. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 2004;131:472-476. https://doi.org/10.1016/j.otohns.2004.04.008

6 Chen YJ, Rath T, Mohan S. PET – computed tomography in head and neck cancer: current evidence and future directions. Magn Reson Imaging Clin N Am 2018;26:37-49. https://doi.org/10.1016/j.mric.2017.08.003

7 Manca G, Vanzi E, Rubello D, et al. 18F-FDG PET/CT quantification in head and neck squamous cell cancer: principles, technical issues and clinical applications. Eur J Nucl Med Mol Imaging 2016;43:1360-1375. https://doi.org/10.1007/s00259-015-3294-0

8 Sun R, Tang X, Yang Y, et al. 18FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: a meta-analysis. Oral Oncol 2015;51:314-320. https://doi.org/10.1016/j.oraloncology.2015.01.004

9 Annunziata S, Cuccaro A, Tisi MC, et al. FDG-PET/CT at the end of immuno-chemotherapy in follicular lymphoma: the prognostic role of the ratio between target lesion and liver SUVmax (rPET). Ann Nucl Med 2018;32:372-377. https://doi.org/10.1007/s12149-018-1243-2

10 Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42:328-354. https://doi.org/10.1007/s00259-014-2961-x

11 Linz C, Brands RC, Herterich T, et al. Accuracy of 18-F fluorodeoxyglucose positron emission tomographic/computed tomographic imaging in primary staging of squamous cell carcinoma of the oral cavity. JAMA Netw Open 2021;4:e217083. https://doi.org/10.1001/jamanetworkopen.2021.7083

12 Peltenburg B, de Keizer B, Dankbaar JW, et al. Prediction of ultrasound guided fine needle aspiration cytology results by FDG PET-CT for lymph node metastases in head and neck squamous cell carcinoma patients. Acta Oncol 2018;57:1687-1692. https://doi.org/10.1080/0284186X.2018.1529426.

13 Yamaga E, Toriihara A, Nakamura S, et al. Clinical usefulness of 2-deoxy-2-[18F] fluoro-D-glucose-positron emission tomography/computed tomography for assessing early oral squamous cell carcinoma (cT1-2N0M0). Jpn J Clin Oncol 2018;48:633-639. https://doi.org/10.1093/jjco/hyy065

14 Werner J, Hüllner MW, Rupp NJ, et al. Predictive value of pretherapeutic maximum standardized uptake value (Suvmax) in laryngeal and hypopharyngeal cancer. Sci Rep 2019;9:8972. https://doi.org/10.1038/s41598-019-45462-y

15 Lee N, Yoo IR, Park SY, et al. Significance of incidental nasopharyngeal uptake on 18F-FDG PET/CT: patterns of benign/physiologic uptake and differentiation from malignancy. Nucl Med Mol Imaging 2015;49:11-18. https://doi.org/10.1007/s13139-014-0299-8

16 Ma C, Zou R, Huo Y, et al. 18F-FDG uptake characteristics in differentiating benign from malignant nasopharyngeal lesions in children. Biomed Res Int 2015;2015:354970. https://doi.org/10.1155/2015/354970.

17 Li Q, Zhang J, Cheng W, et al. Prognostic value of maximum standard uptake value, metabolic tumor volume, and total lesion glycolysis of positron emission tomography/computed tomography in patients with nasopharyngeal carcinoma. Medicine (Baltimore) 2017;96:e8084. https://doi.org/10.1097/MD.0000000000008084

18 Tahari AK, Alluri KC, Quon H, et al. FDG PET/CT imaging of oropharyngeal squamous cell carcinoma: characteristics of human papillomavirus-positive and -negative tumors. Clin Nucl Med 2014;39:225-231. https://doi.org/10.1097/RLU.0000000000000255

19 Kendi ATK, Magliocca K, Corey A, et al. Do 18F-FDG PET/CT parameters in oropharyngeal and oral cavity squamous cell carcinomas indicate HPV status? Clin Nucl Med 2015;40:E196-E200. https://doi.org/10.1097/RLU.0000000000000691

20 Clark J, Jeffery CC, Zhang H, et al. Correlation of PET-CT nodal SUVmax with p16 positivity in oropharyngeal squamous cell carcinoma. J Otolaryngol Head Neck Surg 2015;44:1-5. https://doi.org/10.1186/s40463-015-0091-5

21 Pleitz J, Sinha P, Dressler E, et al. Correlation of positron emission tomography/computed tomography scan with smoking, tumor size, stage and differentiation in head and neck cancer patientspositron emission tomography/computed tomography. World J Nucl Med 2017;16:51-55. https://doi.org/10.4103/1450-1147.181156

22 Murakami R, Uozumi H, Hirai T, et al. Impact of FDG-PET/CT imaging on nodal staging for head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2007;68:377-382. https://doi.org/10.1016/j.ijrobp.2006.12.032

23 Lim RSM, Ramdave S, Beech P, et al. Utility of SUVmax on 18 F-FDG PET in detecting cervical nodal metastases. Cancer Imaging 2016;16:1-8. https://doi.org/10.1186/s40644-016-0095-z

24 Kitajima K, Suenaga Y, Minamikawa T, et al. Clinical significance of SUVmax in 18F-FDG PET/CT scan for detecting nodal metastases in patients with oral squamous cell carcinoma. Springerplus 2015;4:718. https://doi.org/10.1186/s40064-015-1521-6

25 Lowe VJ, Duan F, Subramaniam RM, et al. Multicenter trial of [18F]fluorodeoxyglucose positron emission tomography/computed tomography staging of head and neck cancer and negative predictive value and surgical impact in the N0 neck: results from ACRIN 6685. J Clin Oncol 2019;37:1704-1712. https://doi.org/10.1200/JCO.18.01182