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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

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ABSTRACT

Introduction: Accurate assessment of cervical lymph node status is essential in patients with head and neck squamous cell carcinoma (HNSCC) as it influences prognosis and treatment decisions. During patient workup, lymph node status is often examined by ultrasound guided fine needle aspiration cytology (USgFNAC). ^{18}F-Fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG PET-CT) is frequently used to assess primary tumor and distant metastases but provides information on lymph node status as well. It is possible that FDG PET-CT (if already made for abovementioned indications) can predict the results of USgFNAC in subgroups of lymph nodes based on FDG-uptake and size. The objective of this study is to identify maximum standardized uptake (SUVmax) and short axis diameter cutoff values of lymph nodes at which FDG PET-CT can reliably predict USgFNAC results.

Methods: One hundred and seventeen patients with HNSCC were retrospectively analyzed. Patients were included when FDG PET-CT and USgFNAC were available. SUVmax measurements were performed and compared to the USgFNAC results.

Results: Using USgFNAC as a reference standard, the area under the curve of the receiver operating curve was 0.91. At an SUVmax cutoff value of 4.9, the accuracy of FDG PET-CT was the highest (85%). Lymph nodes with short axis diameter $\geq$1.0 cm and SUVmax $\geq$4.9 were in 91% positive on USgFNAC. If SUVmax was below 2.2, no nodes were positive on USgFNAC. Of all lymph nodes 52% either had a short axis diameter $\geq$1.0 cm and SUVmax $\geq$4.9 or an SUVmax <2.2. FDG PET-CT and USgFNAC results were very similar in these nodes.

Conclusions: By measuring SUVmax values and minimal axial diameters of lymph nodes and using appropriate cutoff values, FDG PET-CT can predict the results of USgFNAC examinations in half of the examined lymph nodes. This information may lead to a reduction of USgFNAC examinations in HNSCC patients if FDG PET-CT is already performed for other indications.

Introduction

The presence of cervical lymph node metastases is an important prognostic factor in patients with head and neck squamous cell carcinoma (HNSCC). It is associated with reduced survival and affects treatment decision-making [1–4]. Accurate determination of the lymph node status is therefore of great importance in order to reduce over- and under-treatment.

Ultrasound guided fine needle aspiration cytology (USgFNAC) is frequently used to identify or confirm tumor positive lymph nodes. Other objectives during diagnostic workup of HNSCC patients are identification of occult distant metastases and preparation for radiation treatment planning if indicated, for this ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG PET-CT) is often used [5–7]. However, FDG PET-CT provides information on lymph node status as well

and might be able to differentiate benign from malignant nodes based on quantitative measurements [8,9].

We hypothesize that FDG PET-CT criteria can be developed to accurately identify lymph nodes which are positive or negative on USgFNAC. These criteria may reduce the need to perform USgFNAC for the detection of lymph node metastases in subgroups of patients who already underwent FDG PET-CT for (whole body) staging or in preparation for primary (chemo)radiotherapy. Reducing the number of USgFNAC examinations could result in shortened diagnostic workup time, reduced costs and decreased patient discomfort.

Methods

The database of the radiology department of a tertiary care center was retrospectively screened for HNSCC patients who

had received USgFNAC within 1 month before or after an FDG PET-CT from January 2013 until August 2015. Only patients with a diagnosis of HNSCC confirmed by biopsy and histopathological examination were included in the final analysis. PET-CT and USgFNAC were performed as part of routine diagnostic workup. The institution review board approved this study with a waiver of informed consent.

FDG PET-CT

PET of the head and neck area was acquired using a TruePoint Biograph mCT40 scanner (Siemens, Erlangen, Germany). After a fasting period of at least six hours, patients received intravenous injection of 2 MBq/kg ^{18}F-FDG. Approximately, 60 min after the administration of the tracer head and neck, PET images were acquired according to the European Association of Nuclear Medicine (EANM) recommendations [10]. The following parameters were used during imaging: a low dose CT scan was performed using care dose 4D and care kV, reference parameters: 40 mAs, 120 kV; subsequently, two 4-minute bed positions PET with time-of-flight and point spread function (TrueX) reconstruction, four iterations, 21 subsets, with a filter of 5 mm full width at half maximum, slice thickness 3 mm. SUV calculations were performed using lean body mass corrected formula.

USgFNAC

The examination was conducted by sonography radiologists using a IU 22 ultrasound machine (Philips Healthcare, Best, The Netherlands) with a 12–5 MHz linear-array transducer. Lymph nodes with a rounded shape, absence of a visible fatty hilum or suggested necrosis were considered abnormal and were targeted for aspiration cytology. Furthermore, cytology was obtained from all lymph nodes with a short axis diameter greater than 5 mm with the exception of level II lymph nodes where a 7 mm short axis diameter cutoff was used. Lastly, nodes considered positive on FDG PET-CT were targeted for aspiration irrespective of short axis diameter. A 21 gauge needle was used to obtain the cytology samples. For each targeted node, two needle passes were performed with application of suction. The obtained aspirates were directly smeared onto separate glass microscope slides. If by visual inspection the amount of material was deemed insufficient or too bloody, a third pass was performed.

Image analysis

All lymph nodes from which cytology was obtained were retrospectively analyzed on FDG PET-CT. Localization of individual lymph nodes was based on the anatomical location described in the original ultrasound report. In some cases, ultrasound images were compared to FDG PET-CT in order to select the correct node. If the node could not be localized, for example, due to multiple pathological lymph nodes in the same level or incomplete reporting, a second observer compared the ultrasound and FDG PET-CT images. If this did not obtain a clear consensus, the node was excluded from analysis. SUVmax was measured by drawing a region of interest around the lymph node in the imaging software Syngo.via (Siemens Healthcare GmbH, Erlangen, Germany). The short axis diameter measurements were performed on the CT images. Both the first and second observer had access to the ultrasound report but were blinded to the outcome as described by the cytology report.

Statistical analyses

Histograms and receiver operating characteristic (ROC) curves were used to determine the correlation between SUV and cytological examination. USgFNAC was used as the reference test in order to calculate the positive predictive value, negative predictive values and other test characteristics of FDG PET-CT. An independent samples t-test was used to determine the difference in SUVmax between USgFNAC positive and negative lymph nodes. All statistical analyses were performed with SPSS (IBM Corp., Released 2015, IBM SPSS Statistics for Windows, Version 23.0, IBM Corp, Armonk, NY).

Sensitivity analysis

Robustness of the results was tested after the final analysis. First, all cytopathology reports were retrospectively reviewed by a cytopathologist (M.B.) and for all lymph nodes with an SUVmax $\geq$4.0 and a negative USgFNAC, cytology slides were revised. During this process, lymph nodes with an unreliable conclusion due to low cell counts of the cytology sample were recorded. Second, the study's results were recalculated with the omission of these lymph nodes. The results were also recalculated by considering all of these lymph nodes as positive and finally as all negative regardless of their original outcome.

Results

Patients

A total of 142 patients matched the inclusion criteria. Thirty-five patients had received their USgFNAC before the FDG PET-CT with four patients having both examinations less than seven days apart. Twenty-five patients were excluded for analysis: in 22 patients, it was not possible to match any nodes examined by USgFNAC to the FDG PET-CT images. One patient could not be analyzed because the FDG PET-CT was not performed according to EANM guidelines. In two patients, it was not possible to reliably determine the lymph node status of the specific lymph nodes from the cytology report due to incomplete reporting.

For the final analysis, 170 lymph nodes in 117 patients were included. On USgFNAC, 96 nodes were diagnosed positive and 71 nodes negative for squamous cell carcinoma (SCC). For three lymph nodes, the diagnosis of the initial cytological examination was inconclusive due to low cell counts. Patients characteristics are shown in Table 1 and an example of the imaging and cytology is shown in Figure 1.

For the nodes that could not be matched ($n = 29$) to the FDG PET-CT images, the USgFNAC was positive for SCC in nine cases, nonmalignant in 19 and inconclusive in 1.

**Table 1.** Baseline patient characteristics.

|	Patients ($n = 117$)	Percentage (%)
Gender		
Male	87	74
Female	30	26
Tumor location		
Oral cavity	12	10
Oropharynx	53	45
Nasopharynx	13	11
Hypopharynx	29	25
Larynx	10	9
T-stage		
T1–T2	40	34
T3–T4	77	66
N-stage		
N0	20	17
N1	17	15
N2	5	4
N2a	4	3
N2b	40	34
N2c	29	25
N3	2	2
M-stage		
M0	108	92
M1	9	8
HPV		
Positive	14	12
Negative	45	38
Unknown	58	50

TNM: AJCC 7th edition.

SUVmax

The average SUVmax of the examined lymph nodes was 7.1, ranging from 1.5 to 25.7. The distribution of SUVmax values is shown in Figure 2.

The SUVmax of USgFNAC proven lymph nodes metastases was higher than in USgFNAC negative lymph nodes. Positive lymph nodes had an average SUVmax of 9.5 (SD 5.1). Nonmalignant lymph nodes had a significantly different average SUVmax of 3.9 (SD 2.5; $p < .001$) (Figure 3).
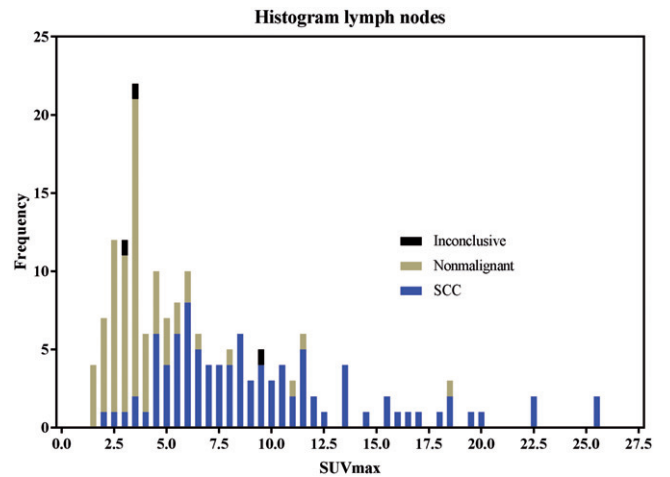

Figure 2. Histogram of all lymph node SUVmax values in bins of 0.5 with their corresponding USgFNAC results.
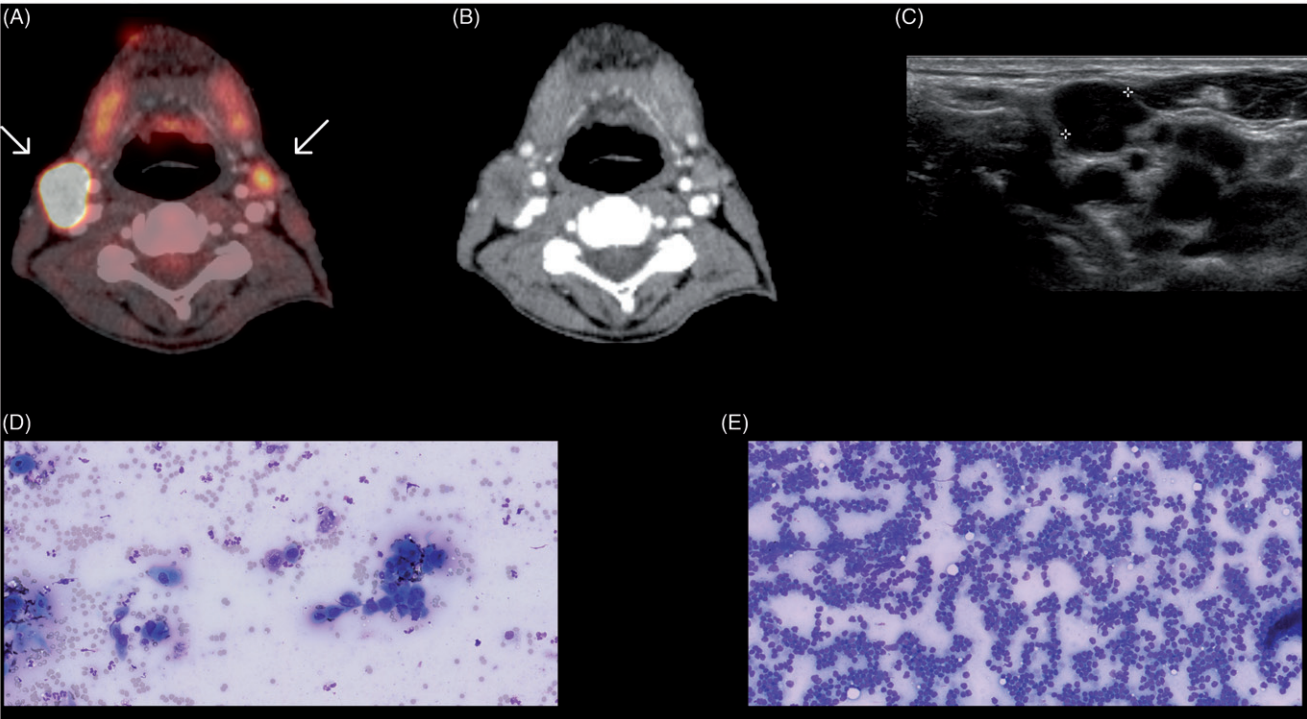
Figure 1. Examples of imaging and cytology: (A) FDG PET-CT image, the white arrows point to lymph nodes. The large lymph node on the right side of the patient (left on the image) had an SUVmax of 12.13, the smaller node on the left had an SUVmax of 3.25. (B) The corresponding CT image. (C) The ultrasound image of the smaller node in the left neck, the distance between both crosses on the image is 0.8 cm. (D) Aspiration cytology of the right lymph node showing metastases (40× magnification). (E) Aspiration cytology of the left lymph node without metastases (40× magnification).
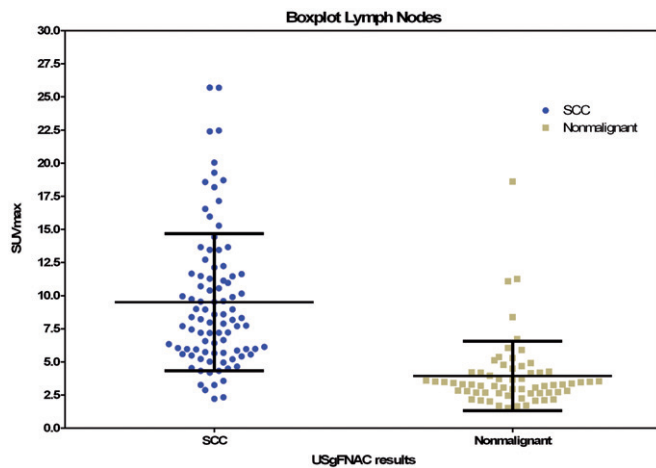
Figure 3. Boxplot of lymph node SUVmax values grouped by USgFNAC results. The black bars represent mean and standard deviation.
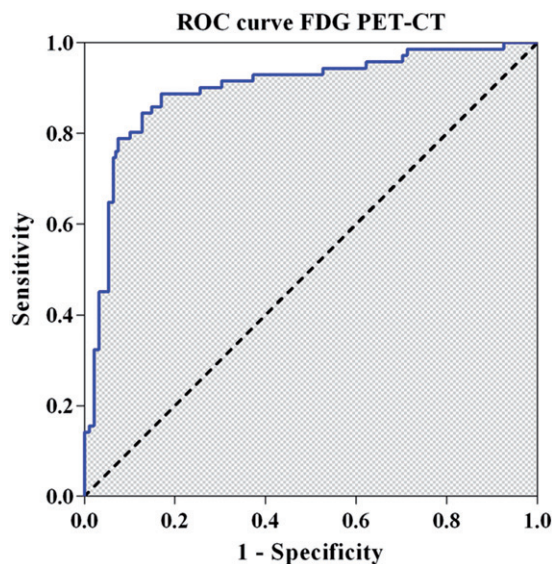
Figure 4. ROC curve FDG PET-CT vs. USgFNAC.

Table 2. 2 × 2 contingency table at the cutoff of SUVmax 4.9.

		USgFNAC		
		SCC	Other	Total
SUVmax	≥4.9	84	11	95
	<4.9	12	60	72
	Total	96	71	167

When comparing SUVmax to the USgFNAC results (reference standard), an area under the ROC curve of 0.91 was found (Figure 4). The cutoff value with the highest accuracy (86%) was at SUVmax 4.9. Corresponding test characteristics at this point are: sensitivity 88%, specificity 85%, PPV 88%, NPV 83%. Table 2 shows the 2 × 2 contingency table of FDG PET-CT using this cutoff value. The three lymph nodes with an initial inconclusive cytology report were excluded for this analysis.

All nodes (n = 10) with SUVmax values lower than 2.2 had a corresponding negative USgFNAC. Table 3 shows the test characteristics of FDG PET-CT using different cutoff values.

Table 3. Test characteristics at several SUVmax cutoff values.

	Test characteristics				
SUVmax cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
2.0	100%	6%	59%	100%	60%
4.0	95%	72%	82%	91%	85%
5.0	86%	86%	89%	82%	86%
6.0	71%	92%	92%	70%	80%
8.0	53%	94%	93%	60%	71%
10.0	35%	96%	92%	53%	61%

The underlined values are the highest in that category among this group.

Lymph node size

The average size of all examined lymph nodes, as measured on PET-CT, was 1.2 cm (range 0.3–3.8). Lymph nodes with positive cytology results had on average a short axis diameter of 1.4 cm (SD 0.6) compared to 0.9 cm (SD 0.3) for nodes with a negative cytology. This difference was statistically significant $p<.001$.

Figure 5 shows the short axis diameter and SUVmax value of all individual lymph nodes sorted by the outcome of the USgFNAC. The cytology result for the nodes in the upper right quadrant (SUVmax ≥4.9 and short axis diameter ≥1.0 cm) was positive in 71, negative in six of the cases and inconclusive in one case resulting in a positive predictive value for USgFNAC results of 91% (71/78) if lymph nodes with SUVmax ≥4.9 and short axis diameter ≥1.0 cm were considered test positive.

The group with a high (≥4.9) SUVmax but a short axis diameter of <1.0 cm consisted of 17 lymph nodes out of which 12 were positive for SCC and five nonmalignant according to USgFNAC examination (PPV = 71%).

Sensitivity analysis

Retrospective revision of the cytology report and slides yielded five lymph nodes with an uncertain negative conclusion and four lymph nodes with an uncertain positive conclusion due to low cell counts. Additionally, in one lymph node revision revealed suspicion of a B-cell lymphoma (SUVmax 4.2). These lymph nodes represented 6% (10/170) of all lymph nodes. Omission of these nodes or considering all these nodes positive or negative did not significantly influence the study result: the sensitivity of FDG PET-CT using an SUVmax 4.9 cutoff changed from 88% to 83% and the PPV changed from 88% to 92% by considering all these nodes positive. When omitting the nodes from analyses PPV changed to 91%. In all other cases, PPV and sensitivity remained the same when rounded to the nearest whole number. In conclusion, revision of the original cytology report changed the outcome of the USgFNAC in 10 cases, this had a very limited effect on the study results.

Discussion

This study shows that quantitative analysis of PET-CT images can be used to identify groups of lymph nodes in which FDG-PET can accurately predict the USgFNAC results. Of all lymph nodes in this study, 52% were selected by using an
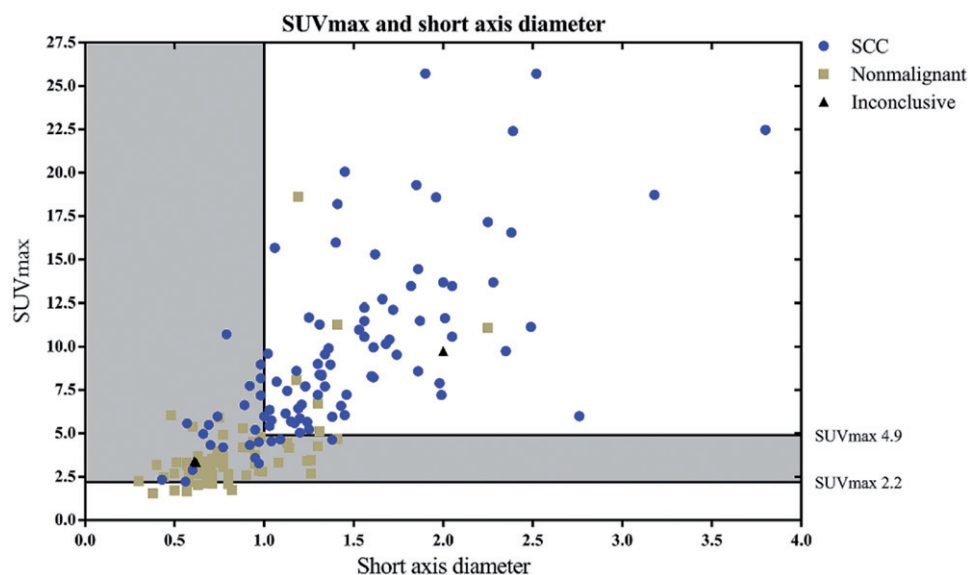
Figure 5. The horizontal line represents the SUVmax cutoff point with the highest accuracy (4.9). The vertical line separates nodes with a short axis diameter of >1.0 cm from those with a diameter of <1.0 cm. Lymph nodes with short axis diameter ≥1.0 cm and SUVmax ≥4.9 were in 69/76 positive on USgFNAC. Lymph nodes with SUVmax <2.2 were in 10/10 negative on USgFNAC. In all other lymph nodes (short axis diameter <1.0 cm with SUVmax ≥2.2 and short axis diameter ≥1.0 cm and SUVmax ≥2.2 but <4.9), no pattern in USgFNAC results was observed.

SUVmax <2.2 or ≥4.9 combined with a short axis diameter of ≥1.0 cm. This indicates that in around half of all nodes USgFNAC performed after FDG PET-CT only confirms but does not provide additional information concerning the presence of lymph node metastases. Different sensitivity analyses showed the robustness of these findings.

It is important to note that six (4%) lymph nodes which were designated positive by the above criteria had a nonmalignant or inconclusive USgFNAC. This result could be either be considered as false positive FDG PET-CT, or as false negative USgFNAC either due to sampling error or insufficient material [11]. Unfortunately, no neck dissection was performed and no comparison with the gold standard, i.e., histopathological examination of the resected lymph nodes, was possible.

This comparison between quantitative FDG PET-CT using SUVmax and histopathology has been done by others. Kitajima et al. [12] report an optimal SUVmax cutoff value of 3.5 for differentiating between malignant and benign lymph node metastases in 36 oral SCC patients, while Matsubara et al. [13] examined 498 lymph nodes and found all nodes with an SUVmax of 4.5 or greater to contain lymph node metastases. These values are in line with the optimal cutoff found in our study 4.9. Although the methodologies of these studies are not directly comparable to ours, they do provide some evidence that the FDG PET-CT criteria reported in our study not only determine when USgFNAC is unnecessary but also discriminate positive from negative nodes. The results might not be completely similar due to differences in imaging protocols. Our study tried to find a cutoff value using standardized EANM directives in order to improve comparability between centers. Furthermore, these studies solve the difficulty of adequately matching a lymph node on FDG PET-CT with the corresponding lymph node in the neck dissection specimen by correlating lymph node levels or neck sides, scoring a true positive if a lymph node is positive on

FDG PET-CT and any metastatic node is found by histopathological examination in the corresponding neck level or side. This method is reasonably effective when determining the presence of positive lymph nodes, but it lacks the accurate correlation needed for quantitative analysis. This might be possible by describing lymph node location based on surrounding anatomical structures during the neck dissection procedure. In contrast, one of the strengths of this study is that it correlates individual lymph nodes identified on FDG PET-CT with the pathology results obtained with USgFNAC of the same lymph node. This allows analysis of SUVmax of individual positive and negative lymph nodes.

FDG PET-CT is often performed during HNSCC workup in order to detect or delineate the primary tumor or to detect distant metastases. Additionally, in clinical practice, FDG PET-CT examination will generally occur before USgFNAC as the aspiration of a lymph node might induce an inflammatory reaction. Inflammation causes accumulation of the FDG tracer resulting in a 'hot' lymph node on FDG PET-CT images [14]. This hot node might be erroneously considered metastatic. Therefore, FDG PET-CT images will be available in many HNSCC patients prior to USgFNAC results even though it is generally more expensive. As this study shows, these images can then be used to select lymph nodes of HNSCC patients which would not benefit from additional USgFNAC examinations.

It should be taken into consideration that cytological analysis of lymph nodes has an extremely high specificity and can confirm the presence of a lymph node metastasis in patients with HNSCC [15]. Also cytomorphological evaluation can confirm the squamous nature of the metastasis and exclude or diagnose metastasis of other tumors. This is particularly important in patients with a known history of other malignancies. Finally, due to the cellular material obtained through USgFNAC, molecular examinations like HPV analysis and tumor DNA sequencing can be performed [16,17].

Limitations of this study are the retrospective design of the study which might have hindered accurate correlation between ultrasound images and FDG PET-CT images. Even though great care was taken to match lymph nodes from which cytology was obtained and SUVmax measurements, it is possible that in some cases the measured node was a different node than the node from which cytology was obtained. Second, the conclusions are based on a single center analysis. External validation of the reported cutoff values may be necessary to determine generalizability of results to other centers.

In conclusion, this study describes a pragmatic approach to predict the results of USgFNAC examinations of cervical lymph nodes in HNSCC patients by quantitative FDG PET-CT parameters and reduce the need for USgFNAC after FDG PET-CT already performed for other indications.

Disclosure statement

No potential conflict of interest was reported by the authors.

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