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18F-FDG-PET/CT for the Assessment of the Contralateral Neck in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC)

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18F-FDG-PET/CT for the Assessment of the Contralateral Neck in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC)

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Objectives/Hypothesis: The aim was to compare the value of 18-Fluoro-Deoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) regarding contralateral lymph node (LN) metastasis in the neck.

Study Design: Retrospective analysis of 61 patients staged by 18F-FDG-PET/CT.

Methods: Cytology/histology served as a reference standard. Further, metabolic midline invasion (MI) of the primary tumor and the presence of bilateral LN metastases were assessed.

Results: A true positive rate in the ipsilateral neck of 80% versus 65% in the contralateral neck was found ($P = 0.067$). Median-standardized uptake value (SUV)-max for suspicious LN ipsilaterally was 7.6 versus 5.8 contralaterally ($P = 0.038$). There was no positive correlation between metabolic MI and bilateral metastasis ($P = 0.82$).

Conclusions: The rate of true positive detected LN by 18F-FDG-PET/CT is less on the contralateral neck side; therefore, all suspicious LNs should be verified by cytology. A high SUV in the contralateral neck suggests metastatic disease regardless of nodal size. Metabolic MI needs to be addressed carefully as it was not predictive for bilateral LN involvement.

Key Words: 18F-FDG-PET/CT, staging, contralateral neck, head and neck squamous cell carcinoma.

Level of Evidence: 4.

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INTRODUCTION

Patients who present with advanced head and neck squamous cell carcinoma (HNSCC) often have associated cervical lymph node metastases, which are a significantly negative prognostic factor. Accurate pretreatment staging of the cervical lymph node basins is essential for proper treatment planning, especially in patients with advanced T stage tumors where the probability of bilateral cervical lymph nodes metastases is high.[1,2] Regional lymph node involvement is one of the utmost prognostic factors with regard to the patient's outcome.[3] In patients with multiple lymph node metastases, the prognosis drops by approximately 50%.[4] These patients present mostly in a later stage of tumor development by suffering from a tumor showing a midline invasion and expansion of the primary through multiple levels.[5] To date, most studies on initial nodal staging have focused on computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound-guided fine needle aspiration cytology (USgFNAC).[6–10] Since the introduction of 18-Fluoro-Deoxyglucose (18F-FDG) positron emission tomography (PET) and the fusion of 18F-FDG-PET with CT, some authors have advocated metabolic imaging for neck staging.[11–13] Recent studies have clearly shown improved accuracy for fused 18F-FDG-PET/CT over 18F-FDG-PET alone.[14–16] However, there is still no consensus on the best imaging modality. The reported sensitivity and specificity using USgFNAC for neck staging varies from 63% to 100%, respectively.[7] Stoeckli et al.[17] recently found USgFNAC to be the most accurate initial neck staging method, whereas Veit-Haibach et al.[18] proposed 18F-FDG-PET/CT as the first line imaging method for neck staging.

A well-known drawback of 18F-FDG-PET/ CT is the high rate of false positive findings due to inflammation or movement of the patient during the examination,[19,20] resulting in a lower positive predictive value. Further investigations create additional costs and burden the patient. Moreover, reports have recently suggested that there could be a difference in the accuracy of 18F-FDG-PET/ CT in staging the ipsilateral versus the contralateral neck. The primary aim of this article is to critically examine this institution's experience to determine if 18F-FDG-PET/ CT scan can be reliably used to initially stage the contralateral neck with advanced T stage HNSCC.[21] Our clinical impression over the years is in line with these suggestions, and it leads to the presumption that 18F-FDG-PET/ CT findings may be false positive more often for the contralateral side, compared to the findings on the ipsilateral neck side (Fig. 1). A well-known risk factor for bilateral cervical lymph node metastasis is the midline-invasion of the primary.[22] Due to the anatomic distribution of the lymphatic drainage in the head and neck, the localization of the primary is one

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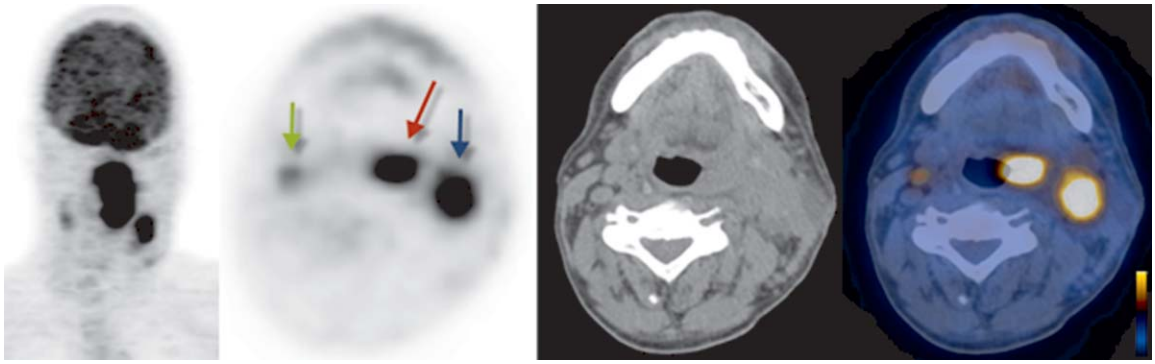

Fig. 1. Squamous cell cancer of the left mesopharynx, midline crossing, only ipsilateral lymph node metastasis. From left to right: "Maximum intensity projection" PET image (MIP), axial PET, CT, and fused PET/ CT. SUV primary tumor 16 (red arrow), ipsilateral lymph node 7.2 (blue arrow), contralateral lymph node 4.0 (green arrow).

of the main factors influencing lymphatic metastases.[23,24] Well-lateralized primaries tend to metastasize to the ipsilateral side only, whereas tumors involving structures of the midline tend to metastasize to both sides[5] (Fig. 2).

The aims of this study were threefold: 1) to compare the rate of occurrence of true positive lymph nodes in 18F-FDG-PET/ CT by assessing the ipsi- and contralateral side of the neck (the standard of reference was the FNAC or histopathology result); 2) to determine a cutoff standardized uptake value (SUV) max, which could be used as a reliable tool to differentiate from true regional metastases and false positive lymph node involvement; 3) to investigate an association of midline invasion of the primary in 18F-FDG-PET/ CT, with true positive findings on the contralateral side.

MATERIALS AND METHODS

Patients

A total of 515 patients suffering from HNSCC were primarily assessed by 18F-FDG-PET/ CT between 2001 and 2008 at the Department of Otolaryngology, Head and Neck Surgery, University Hospital Zurich, Switzerland. This patient cohort does not represent a consecutive group of all patients diagnosed with HNSCC within the given time frame. The cohort consisted mainly of patients with advanced disease (T3/ T4 and/ or N2/ N3, respectively), who were referred for 18F-FDG-PET/ CT to exclude distant metastases at the time of initial staging. The 18F-FDG-PET/ CT was not used for assessing occult disease. For this study, patients with a history of previous neck dissection or radiotherapy, or with local or regional recurrence were excluded. All 515 radiological reports were initially reviewed by a head and neck surgeon (N.K.). According to these reports, 18F-FDG-PET/ CT demonstrated increased 18F-FDG uptake bilaterally in 91 cases. Nodes were judged as metastatic if the uptake was clearly higher than that in the background tissue, and if the uptake matched with a lymph node on the corresponding CT image. Thirty patients were excluded due to missing data; therefore, a total of 61 patients were included for complete analysis. This work was conducted in accordance with the local guidelines established by the ethics committee for a retrospective evaluation. All 61 18F-FDG-FDG-PET/ CT scans were reviewed by two nuclear medicine specialists, with specific emphasis on regional neck metastasis (H.T.F.; K.F.P.). The metabolic activity and the size of all suspicious lymph nodes were retrospectively analysed.

Standard of Reference

As a routine initial staging procedure, all patients at our institution underwent ultrasound guided fine needle aspiration (USgFNAC) for neck staging, meaning that all sonografically suspicious lymph nodes were fine needle aspirated under ultrasonogaphic (US) guidance. The ultrasound examinations were performed by head and neck surgeons certified for US imaging according to the Swiss Ultrasound Society (SGUM). During the above-mentioned time period, a Siemens Sonoline Antares

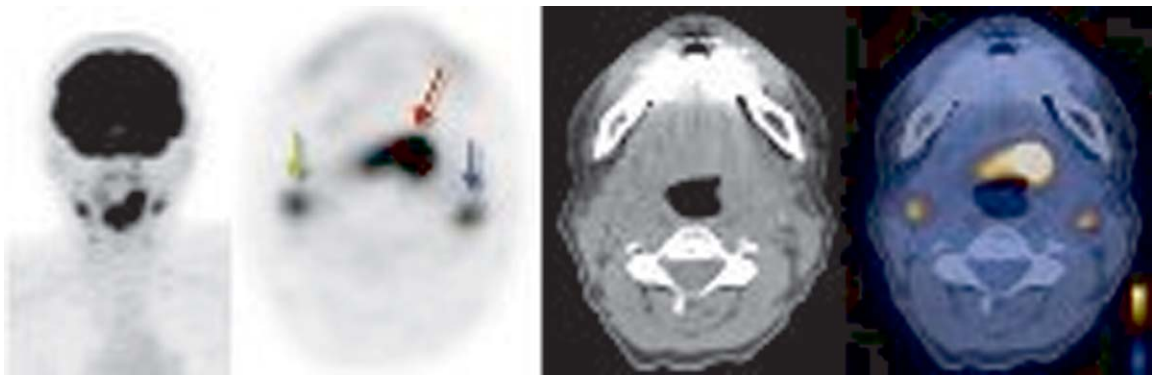

Fig. 2. Squamous cell cancer of the left vallecula, midline crossing, bilateral lymph node metastasis. From left to right: "Maximum intensity projection" PET image (MIP), axial PET, CT, and fused PET/ CT. SUV primary tumor 9.7 (red arrow), ipsilateral lymph node 4.1 (blue arrow), contralateral lymph node 4.3 (green arrow).

ultrasonograph with a 10.5-MHz linear transducer (Siemens Medical Solutions, Erlangen, Germany) was used. For biopsies, a 24-gauge needle attached to a 10-ml syringe and syringe holder (Cameco Ltd., London, UK) was chosen. Under ultrasound guidance, the needle was gently pushed forward in a longitudinal direction to the transducer, through the skin into the middle of the mass. The following ultrasound characteristics of the examined lymph nodes were evaluated: a minimal axial diameter of 7 mm for level II and 5 mm for the remainder of the neck lymph nodes; a diameter of <2, comparing long- to short axis or spherical shape (supportive criterion in borderline sizes); and hypoechoic sonomorphology.

A total of 54 patients underwent cytological verification for every suspicious lymph node detected by 18F-FDG-PET/ CT; whereas in seven patients, the histopathology of the neck dissection served as the standard of reference. The cytological and histological specimens, respectively, were examined according to an institutionally standardized pathology protocol.

Imaging Protocol

The inline PET/ CT system (Discovery LS or Discovery ST with a multi-slice helical CT, GE Healthcare) enabled the acquisition of coregistered CT and PET images in the same session. Prior to injection of a standard dose of approximately 350 MBq of FDG, patients fasted for at least 4 hours. The scan started approximately 60 minutes after the injection. All patients were examined in the supine position with arms down. The CT data were acquired during free shallow breathing with 140 kV, 80 mA, 0.5 second tube rotation, 4.25-mm section thickness, and a scan length of 867 mm with 22.5 second scan time. The PET data were acquired immediately after the CT with a scan time of 3 minutes per table position, resulting in a total scan time of 18 minutes for six table positions from head to pelvic floor. The CT was used for the reconstruction of the PET images with regard to attenuation correction. The PET reconstruction process used a standard 2-dimensional iterative algorithm [ordered subset expectation maximization (OSEM)].

The measurement of the lymph nodes and the outline of volumes of interest (VOI) for the calculation of SUV max were done by a nuclear medicine physician with vast experience in neuroradiology. The SUV corresponds to the measured tissue concentration (Bq/ ml) divided by the injected dose normalized to the patient's weight (g). The SUV max corresponds to the voxel within a VOI with the highest activity and is calculated by commercially available software (Advantage workstation, software version 4.4, GE Healthcare).

Statistical Analysis

Both means of SUV max and of lymph node size of the contralateral and ipsilateral neck side were compared by using the unpaired or paired student *t* test when appropriate. Variations of proportion were examined through Chi square or the Fisher exact tests. A *P* value of <0.05 was considered statistically significant. Choosing a confidence interval of 0.95, *P* values <0.01 were considered to be significant. True positive rate, false positive rate, and SUV cutoff values of the optimal test performance to detect ipsi- and contralateral lymph node metastases were calculated by the area under the curve, generated according to the receiver operating characteristic method (ROC). All statistical analyses were performed with SPSS 17.0 software.

RESULTS

Patient's and Tumor Characteristics

Between 2001 and 2008, 91/ 515 (17.6%) radiological reports mentioned 18F-FDG-PET/ CT, showing bilateral suspicious cervical metabolic 18F-FDG-uptake. Due to missing data, 30 patients needed to be excluded, resulting in 61 patients eligible for further evaluation. Patient and tumor characteristics are shown in Table I. Forty-seven out of 61 patients (77%) presented with advanced stage disease (Stage III/ IV [International Union against Cancer (UICC), 1997]).

TABLE I.
Patient's and Tumor Characteristics (n = 61).

Women		20 (32.8%)
Men		41 (67.2%)
Mean (years)		60
Range		33–84
Location of primary HNSCC		
Nasopharynx		5 (8.2%)
Oral cavity		30 (49.2%)
Oropharynx		10 (16.4%)
Hypopharynx		8 (13.1%)
Larynx		8 (13.1%)
T classification	T1	3 (4.9%)
	T2	11 (18%)
	T3	15 (24.6%)
	T4	32 (52.5%)

The Analysis of the Ipsi- And Contralateral Suspicious Lymph Nodes Detected By 18F-FDG-PET/ CT

Suspicious ipsilateral 18F-FDG-uptake could be confirmed by cytology/ histology in 49/ 61 cases. This translates to a true positive rate for the ipsilateral neck of 80%. On the contralateral side, 18F-FDG-PET/ CT was able to detect 40/ 61 true positive lymph node metastases confirmed by cytology/ histology. This translates to a true positive rate for the contralateral side of 65%. There was no significant difference found between both sides ($P = 0.067$). In comparison, suspicious ipsilateral findings on the ultrasound were confirmed by cytology/ histology in 51/ 61 cases. This translates to a true positive rate for the ipsilateral neck of 83%. On the contralateral side, ultrasound was able to detect 48/ 61 true positive lymph node metastases, confirmed by cytology/ histology. This translates to a true positive rate for the contralateral side of 79%.

SUV Max of Suspicious Bilateral Lymph Node Involvement

Statistical analysis revealed a mean SUV max for the ipsilateral lymph nodes of 7.6 (range, 1.9–22.7), compared to 5.8 (range, 2.1–39.6) for the contralateral side ($P = 0.038$). Further analysis revealed significant differences between true positive and false positive findings for both neck sides: The ipsilateral mean SUV max for the true positives was 8.4 (range, 1.9–22.7), compared to 4.4 (range, 2–9.7) found for the false positives ($P = 0.01$). Looking at the contralateral side, the mean SUV

TABLE II.
Correlation Between SUV-Max of Both Neck Sides and Lymph Node Size (n = 56).

		P Value
SUV-Max Lymph Node		
Ipsilateral	7.6 (SD ± 4.8; range 1.9–22.7)	*P* value 0.038
Contralateral	5.8 (SD ± 6.0; range 2.1–39.6)	
SUV-Max True Versus False Positive Lymph Nodes		
Ipsilateral true positive	8.4 (SD ± 4.9; range 1.9–22.7)	*P* value 0.01
Ipsilateral false positive	4.4 (SD ± 2.4; range 2–9.7)	
Contralateral true positive	7.3 (SD ± 7.2; range 2.1–39.6)	*P* value 0.016
Contralateral false positive	3.3 (SD ± 1.5; range 1.5–8)	
Lymph Node Size		
Ipsilateral	1.7 cm (SD ± 0.94; range 0.5–4.7)	*P* value 0.001
Contralateral	1.3 cm (SD ± 0.62; range 0.7–4.1)	

max of the true positives was 7.3 (range, 2.1–39.6), compared to 3.3 (range, 1.5–8) found for the false positives ($P = 0.016$). There was no significant difference ($P = 0.43$) for comparison between the mean SUV max of true positives on the ipsilateral and the contralateral side (Table II). A cutoff SUV max of 3.7 or higher on the ipsilateral side (translating to a sensitivity of 87% and a specificity of 64%) and 3.5 or higher on the contralateral side (translating to a sensitivity of 74% and a specificity of 71%) was found to be most accurate in differentiating between physiological or pathological 18F-FDG-uptake using ROC-analysis (Figs. 3 and 4).

Analysis of the Lymph Node Size Using 18F-FDG-PET/CT

The most current reliable criterion for evaluation of the integrity of lymph nodes and the selection of which lymph node should be aspirated is the size measured as the minimal axial diameter (MAD) during ultrasound.[25–27] In our series, the mean MAD of the suspicious lymph nodes on the ipsilateral side was 1.7 cm (range 0.5–4.7), compared to the lymph nodes on the contralateral side with a mean MAD of 1.3 cm (range 0.7–4.1; *P* value 0.001; Table II).

Midline Invasion of the Primary and Contralateral Lymph Node Involvement Detected by 18F-FDG-PET/ CT

Out of 41/ 61 patients showing a midline invasion of the primary in the 18F-FDG-PET/ CT scan, 26 (63%) patients were found to have a true positive contralateral cervical lymph node metastasis. In the remaining 20 primaries without midline invasion, a true positive contralateral lymph node metastasis was found in 14 cases (70%; $P = 0.82$).

DISCUSSION

In this study, we demonstrated a difference in the detection of regional metastases between the ipsi- and contralateral side of the neck by using 18F-FDG-PET/ CT in patients suffering from HNSCC.

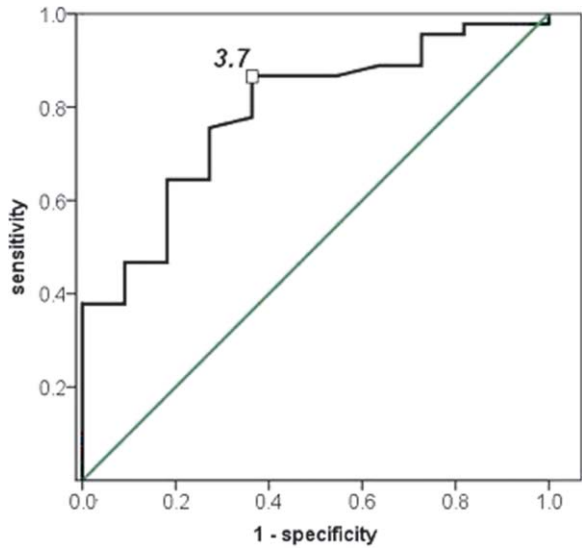

Fig. 3. Cutoff SUV max ipsilateral of 3.7 (sensitivity = 87%; specificity = 64%).

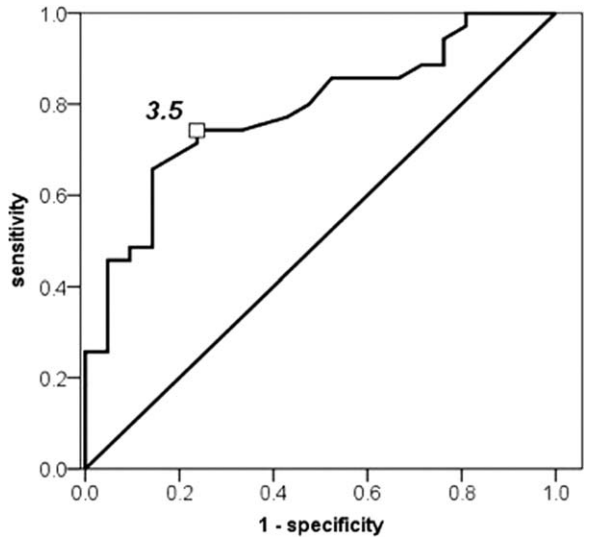

Fig. 4. Cutoff SUV max contralateral 3.5 (sensitivity = 74%; specificity = 71%).

In recent years, the application of 18F-FDG-PET/ CT in diagnosis, staging, and posttherapeutic surveillance has become a well-accepted method for head and neck oncologists/ surgeons.[6–9,28,29] Most authors agree that 18F-FDG-PET/ CT is a reliable staging method to exclude distant metastases[30,31] and to detect second primaries in high risk patients.[1] However, there is still no consensus on its value for neck staging. A number of studies have compared metabolic imaging to conventional imaging methods, such as CT or MRI for initial neck staging.[6–10] Stoeckli et al. prospectively compared 18F-FDG-PET/ CT to CT, US, and USgFNAC, respectively.[17] They found a rate of 16% in overstaging the N2c- neck by using 18F-FDG-PET/ CT, compared to 13% for CT and 7% for USgFNAC. Based on these results, we used cytology workup of every suspicious lymph node as a standard of reference next to the histological workup after neck dissection.

A recent study by Kim et al. comparing the metabolic findings with the histological workup of the neck dissection found 18F-FDG-PET/ CT to be less sensitive in detecting contralateral than ipsilateral neck metastases.[21] These results are in line with our clinical impression over the years, leading to this retrospective analysis of the value of 18F-FDG-PET/ CT, with special emphasis on staging the contralateral neck. Using a retrospective study design, we were able to show a difference in detecting true positive findings for the ipsi- (80%) versus the contralateral side (65%) using 18F-FDG-PET/ CT. Although our findings are not statistically significant, they show an important trend. Further, when comparing these findings with the results of US (83% true positive rate for ipsilateral side, and 79% for the contralateral side, respectively), the limitation of 18F-FDG-PET/ CT as being less specific on the contralateral side becomes obvious.

While using the FNA cytology or the histopathology of the neck dissection as a standard of reference, other possible parameters that could be taken for an analogical evaluation have to be mentioned. For example, it is reasonable to inquire about follow-up data on regional control for initial FNA negative untreated patients. However, our cohort consisted entirely of patients with advanced disease (T3/ T4 and/ or N2/ N3, respectively). Out of them, we only evaluated those with bilateral FDG-accumulation in the 18F-FDG-PET/ CT. Although having, as reported, false positive accumulation in the 18F-FDG-PET/ CT, compared to the findings of the FNA cytology or the histopathology of the neck dissection, the concept of therapy included almost entirely a bilateral radiation of the neck. Therefore, a detailed follow-up regarding this specific question in our population is not available and reflects a limitation of our study.

The mean SUV max is significantly increased on the ipsilateral side, compared to the contralateral side ($P = 0.038$). One might argue that this is due to the different lymph node sizes we found for the two sides of the neck ($P = 0.001$). However, no significant difference was found comparing the mean SUV max for the true positives on both sides, but SUV max values between the true and false positive lymph nodes on each side were significantly different. Therefore, we were able to strengthen our subjective impression that low SUV max of the contralateral, compared to the ipsilateral 18F-FDG-uptake in lymph nodes, are likely false positive. Additionally, analyzing the smallest true positive lymph nodes in our series, the smallest ipsilateral node was 0.5 cm in axial diameter, compared to 0.7 cm contralaterally. These results tend to emphasize how relatively unimportant lymph node size is regarding bilateral metabolic activity, whereas SUV max seems to be reliable when interpreting 18F-FDG-accumulations regarding this specific issue. In summary, a high SUV max in the contralateral neck suggests metastatic disease, regardless of nodal size.

Other authors have reported a cut-off SUV max to differentiate between true positive and false positive 18F-FDG-PET/ CT findings when staging the neck. Pansare et al.[32] found an SUV max > 2.5 most likely to be malignant, whereas an SUV max < 2.5 was malignant in only 13% of cases. In a 2011 retrospective study, Nguyen et al.[33] found an SUV max threshold for cervical lymph nodes of 2.2 to be the most accurate (sensitivity of 98% and specificity of 83%) in differentiating between malignant and benign tissue. Other studies have reported SUV max thresholds of 1.9 to 3.0 for cervical lymph node staging.[8,34–37] In our study, we found an SUV max of 3.7 or higher on the ipsilateral side, translating to a sensitivity of 87% and a specificity of 64% with regard to malignancy. For the contralateral side, an SUV max of 3.5 or higher translates to a sensitivity of 74% and a specificity of 76% with regard to malignancy. After all, the published values are over a wide range and also differ from what we have found in this study. Therefore, we do not believe that one single SUV value will emerge that can differentiate tumor from inflamed nodes. Further, there is a difference to be found between the ipsi- and the contralateral side, showing a potential danger for misinterpreting 18F-FDG-PET/ CT findings, especially on the contralateral side. In a previous study, we have looked at different histopathological parameters and correlated them with SUV max and its predictive value. We found a correlation with advanced T-classification only.[38] The controversy in using SUV max to diagnose malignancy is ongoing. In our opinion, the interpretation of 18F-FDG-PET/ CT findings regarding regional disease should be based primarily on visual findings looking at the morphology and shape of the lymph nodes and not essentially on SUV measurements. Furthermore, a contrast-enhanced (ce) CT instead of a native CT fused with an 18F-FDG-PET might be of more importance to help with the problem of regional disease, as shown in an earlier publication.[39]

Finally, we have looked at a potential correlation of midline invasion of the primary in 18F-FDG-PET/ CT, with true positive findings in the contralateral neck. From a clinical aspect, the higher false positive 18F-FDG-PET/ CT findings in the contralateral neck (65% vs. 80%; $P = 0.067$) in patients with lateralized tumors is expected, given the spread pattern of HNSCC with a lower pretest probability of metastasis in the contralateral neck. However, and interestingly, midline invasion

of the primary tumor was not found to be associated with a higher true positive rate for the contralateral neck ($P = 0.82$). This may be due to peritumoral inflammation overstaging the primary tumor with increased 18F-FDG-uptake. In summary, the complex anatomical structures and the presence of benign tissue showing physiological 18F-FDG-uptake make the head and neck region a complex part of the body for interpreting metabolic imaging.[40]

The authors acknowledge the potential limitation on the reported findings as a consequence of having had to eliminate one-third of the selected patient cohort due to missing data.

CONCLUSION

18F-FDG uptake differs between the ipsi- and contralateral side of the neck in patients suffering from HNSCC. A high SUV max in the contralateral neck suggests metastatic disease regardless of nodal size. The implications of the study are to prevent unnecessary neck dissections and radiation to uninvolved necks. Due to our results we recommend proper analyses of each suspicious FDG accumulation. This work might be a small step towards a more patient-centered medicine with more individualized therapy. Midline invasion detected by 18F-FDG-PET/ CT needs to be addressed carefully as it was not predictive for bilateral lymph node involvement.

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