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HEAD AND NECK

SUV_{max} for predicting regional control in oropharyngeal cancer

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Abstract

Purpose To investigate the predictive value of pretherapeutic metabolic tumor imaging using 18-fluorodeoxyglucose positron emission tomography (FDG-PET) for regional response in oropharyngeal cancer patients undergoing primary (chemo) radiation.

Methods Retrospective analysis of oropharyngeal cancer patients treated with primary (chemo)radiation at the University Hospital Zurich from 2010 to 2019 with available FDG-PET. The SUV_{max} of the largest lymph node metastases was recorded. Regional response was assessed using posttherapeutic FDG-PET at 12 weeks and regional recurrence-free survival.

Results 95 patients with a mean age of 68.5 years (SD 10.3) were included. The median pretherapeutic nodal SUV_{max} was 8.3 (interquartile range 4.4–13.3). A pretherapeutic nodal SUV_{max} above 6 significantly predicted poorer regional recurrence-free survival (log-rank test, $P=0.009$) in univariate analysis. However, in multivariate analysis SUV_{max} above 6 was not significant in predicting regional recurrence-free survival (Cox regression $P=0.189$). Clinical N category showed a trend in which a more severe stage had a poorer regional survival (Cox regression $P=0.073$).

Conclusion The SUV_{max} of the largest lymph node metastasis seems to play a role in predicting regional response in oropharyngeal cancer patients, after stratifying for N category. More research is needed to investigate whether highly metabolically active disease is less likely to respond to chemoradiation.

Keywords Fluorodeoxyglucose F18 · Papillomavirus infections · Squamous cell carcinoma of head and neck · Positron emission tomography computed tomography · Lymphatic metastasis

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is an aggressive malignancy of the head and neck, classically caused by exposure to extrinsic carcinogens such as tobacco smoke and alcohol [1]. In the past decades, human papillomavirus (HPV)-associated OPSCC has gained importance leading to a lower incidence of smoking and alcohol-associated OPSCC despite an increasing overall incidence of OPSCC, especially in individuals younger than 60 years [2]. HPV-positive OPSCC classically presents with a small primary tumor and advanced nodal disease with cystic degeneration. This tumor type usually has a more favourable prognosis compared to their HPV-negative counterparts [3, 4] when treated with intensified treatment [5].

OPSCC can be treated by surgery, radiotherapy with or without concomitant chemotherapy, or with a combination of modalities. There is considerable controversy about the optimal primary treatment as both methods (surgery followed by (chemo)radiation vs. chemoradiation followed by surgery) have specific advantages and drawbacks [6]. Surgical resection prior to radiotherapy has the advantage of potentially reducing the radiation volume and obviating the need for concomitant chemotherapy [7, 8]. However, in case of multiple lymph node metastases and/or extranodal extension, adjuvant radiotherapy with or without concomitant chemotherapy is indicated [7, 8].

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For very aggressive disease, an upfront tri-modality approach might be necessary.

Primary chemoradiation on the other hand has the advantage to potentially prevent tri-modality treatment and shorten the overall treatment time [7, 9]. However, in case of persistence, salvage treatment is necessary, which is associated with poorer oncological and functional outcome for both the primary tumor region and the neck [10]. Hence, a pretherapeutic prediction of response to chemoradiation in OPSCC would be desirable.

18-fluorodeoxyglucose positron emission tomography (FDG-PET) has been evaluated as a prognostic tool in the pretherapeutic setting. FDG-PET can not only be used for staging in head and neck cancers [11–14], it may also be used to predict tumor aggressiveness and radio-oncological and surgical outcomes [15–17]. Metabolic tumor parameters derived from FDG-PET, such as the maximum standardized uptake value (SUV_{max}), are commonly used for this purpose. Increased metabolic activity and glucose uptake are known to inversely correlate with tumor hypoxia and hence tumor aggressiveness through the Warburg effect [18–20].

The role of FDG-PET in the posttherapeutic setting for both local and regional response is established [21]. In the pretherapeutic setting, its value is also well established in predicting local response. However, the literature for regional response shows conflicting results [22, 23]. One possible explanation might be a so far unassessed bias due to cystic degeneration of lymph nodes seen commonly in HPV-positive disease [4]. Studies on the effect of cystic degeneration on metabolic tumor imaging are scarce. A study by Haerle et al. shows that cystic degeneration of lymph nodes may lead to low SUV_{max} values and can be hard to detect on non-enhanced FDG-PET/CT or non-enhanced CT alone [24]. The rate of HPV-positivity in that patient cohort had not been outlined.

Owing to better soft tissue contrast, if readily available, MR is commonly preferred over CT when evaluating soft tissue in the head and neck area [25]. Therefore, FDG-PET/MR may provide better diagnostic results than FDG-PET/CT in detecting cystic degeneration, particularly with small lymph nodes, thus solving the aforementioned bias.

Therefore, we reviewed OPSCC patients treated with primary chemoradiation in order to assess the role of metabolic tumor imaging in the prediction of tumor response, taking into consideration cystic degeneration of nodal metastases in relation to tumoral p16 positivity. We also evaluated and compared the diagnostic performance of PET/CT and PET/MR.

Materials and methods

Study population

The experimental protocol of the study was approved by the local ethics review board (*Kantonale Ethikkomission Zürich*, protocol number 2016-01,799, including amendment of December 14th, 2018). All research was conducted according to the relevant regulations and guidelines. Informed consent of all participating patients has been obtained for the examination. We included patients treated at the Department of Otorhinolaryngology-Head and Neck Surgery of the University Hospital Zurich, Zurich, Switzerland, between 2010 and 2019. Inclusion criteria were available pre- and posttherapeutic FDG-PET, either PET/CT or PET/MR; pretherapeutic FDG-PET performed within 6 weeks of treatment start; posttherapeutic FDG-PET performed at 12 ± 1 weeks after completion of chemoradiation. Included were patients with lymph nodes that were considered malignant according to the FDG-PET/CT or FDG-PET/MR report, owing to nodal characteristics such as enlargement, irregular margins and signs of extracapsular spread, pathologic uptake of FDG and other signs of malignancy [26]. Patients presenting with multiple synchronous head and neck squamous cell carcinomas, patients with distant metastatic disease at initial presentation, patients not treated with curative intent, patients with primary surgical treatment, patients treated with neo-adjuvant chemotherapy and patients who have not completed radiotherapy treatment of at least 60 Gray (Gy) were excluded.

We set up a database with the required data from patients included in the study with detailed data on age, gender, smoking, drinking habits, clinical and pathological stage, p16 status, presence of extranodal extension as proven by histopathology, number of lymph nodes with increased FDG uptake on pretherapeutic PET, follow-up time, recurrence, disease-specific survival and overall survival. We determined the clinical N classification using ultrasound-guided fine-needle aspiration biopsy (US-FNAB) of suspicious lymph nodes. Smoking was defined as a current daily consumption of cigars or cigarettes. Alcohol consumption was defined as a daily intake of more than 3 units of alcohol. 1 unit of alcohol was defined as 8 g of pure alcohol. Recurrence was divided into local and regional recurrence, according to tumor recurrence at the primary site or in regional lymph nodes, respectively. Distant failure was defined as disease occurring in non-regional lymph nodes and/or distant sites. Follow-up time was calculated from the day of chemoradiation completion to the last follow-up visit. In case of recurrence, the time to recurrence was calculated from the day of chemoradiation

completion to the day of cytological or histological proof of recurrence. A diffuse, "block-type" p16INK4A overexpression in tumor tissue by immunohistochemistry served as a surrogate marker for HPV-driven carcinogenesis of oropharyngeal squamous cell carcinoma [27]. Patients were staged using the TNM staging system, 7th edition.

The primary outcome of the study was the prediction of therapy response of nodal disease according to pretherapeutic metabolic tumor imaging data. Secondary outcomes were the effect of cystic degeneration in metastatic lymph nodes on pretherapeutic metabolic tumor imaging data and the detection of cystic degeneration in metastatic lymph nodes by FDG-PET/MR compared to FDG-PET/CT.

PET/CT and PET/MR imaging

PET scans were obtained according to standard procedures. All patients fasted for at least 4 h prior to the scan. Patients were injected with a standardized dose of 3.5 MBq of FDG per kg body weight (PET/CT) or 3.0 MBq FDG per kg body weight (PET/MR) or with a BMI-adapted body-weight-dependent dosage protocol (used on digital PET scanners from 2018 on) [28]. All patients had a blood glucose level below 10 mmol/l before imaging. During the uptake time of 1 h, patients rested in a silent, warm and dimmed environment. Scans were acquired using integrated PET/CT scanners (Discovery VCT, Discovery 690, Discovery MI, GE Healthcare, Waukesha, WI) or an integrated PET/MR scanner (Signa PET/MR, GE Healthcare). Scans included either a diagnostic CT scan of the neck after administration of iodinated contrast medium, or a diagnostic regionalized PET/MR scan of the neck using gadolinium-based contrast medium [29]. Detailed technical acquisition protocols have been published previously [29, 30].

Tumoral FDG uptake

Tumoral FDG uptake was obtained under supervision of a board-certified nuclear physician and radiologist (MWH). The SUV_{max} of the largest lymph node was recorded. SUV_{max} was calculated automatically using a standard formula [maximum activity in region of interest ÷ (injected dose × body weight)]. Further, the most active lymph node was compared with the activity of the liver and the blood within the internal jugular vein and scored from 1 to 5 according to the Hopkins criteria [31]. Correct analysis of FDG uptake was ensured through side-by-side reading of the corresponding CT or MR images of the tumor in the axial, coronal, and sagittal plane. Borders of regions of interest (ROI) were set by manual adjustment to exclude adjacent physiologic FDG-avid structures. A written report by a doubly board-certified nuclear medicine physician/radiologist was available for all FDG-PET/CT and FDG-PET/MR exams. Complete metabolic response was defined as a score of 2 or less according to the Hopkins criteria [31].

Cystic degeneration of lymph nodes

A board-certified neuroradiologist (SP) reviewed the largest metastatic lymph node for cystic degeneration on CT and MR imaging alone. Cystic lymph nodes typically have a comparably thin wall and are characterized by components being replaced by fluid density or intensity. On contrast-enhanced CT, this was assessed by measuring the hypodense areas and recording their Hounsfield units (HU). Lymph nodes with < 25 HU were defined as cystic. Cystic appearance was assessed on MR imaging using T1-weighted and T2-weighted images. Cystic degeneration and necrotic change were grouped together as cystic. Figure 1 demonstrates 2 patients with and 2 patients without cystic degeneration imaged on a FDG-PET/CT and on a FDG-PET/MR scan, respectively.

Statistical analysis

For continuous variables, distribution was evaluated for normality according to Gauss' theorem. For normally distributed variables (age, node size), mean and standard deviations are given, and comparison among study groups was done using the t-test. For non-normally distributed variables (smoking, SUV_{max} of lymph node, follow-up time), median and interquartile range (IQR) are given. To compare distribution among samples, the nonparametric Mann–Whitney *U* test was used for two samples. Categorical variables were presented as counts (proportions [%]). Binary variables were associated in contingency tables using the two-tailed Pearson chi-squared test. The Mantel–Haenszel statistics was used to calculate the hazard ratio and the 95% confidence interval (95% CI). We used a receiver operating characteristic (ROC) curve to select the best cut-off value for pretherapeutic SUV_{max} to predict regional recurrence. Survival curves were built according to Kaplan–Meier, and the log-rank test was used to compare factors. Cox's Regression Model was used to predict survival in a multivariate analysis. A *P* value lower than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS® 26.0.0.1 software (IBM®, Armonk, NY, USA).

Results

Patient and tumor characteristics

We included a total of 95 patients with OPSCC and metastatic lymph nodes on FDG-PET/CT or -/MR imaging treated with chemoradiation. The baseline characteristics

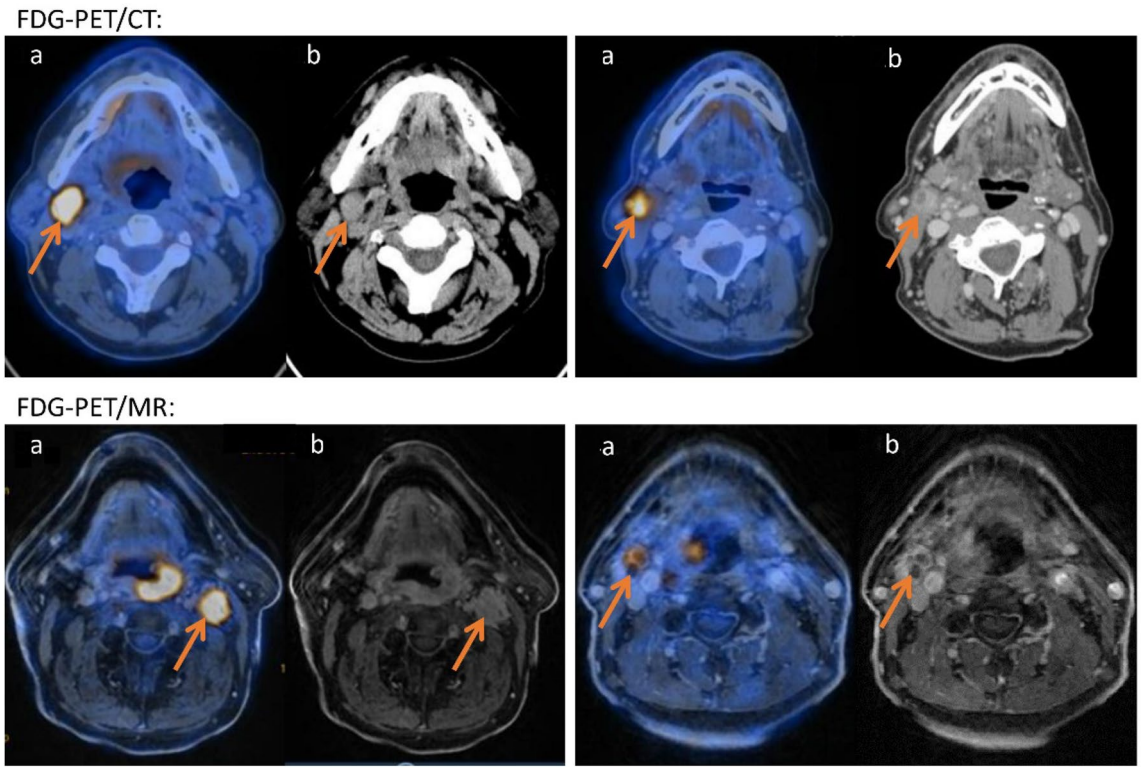

Fig. 1 **1a**, **b** Axial FDG-PET/CT and CT image, respectively, demonstrating a level II lymph node without cystic degeneration. **2a**, **b** Axial FDG-PET/CT and CT image, respectively, demonstrating a level II lymph node with cystic degeneration. **3a**, **b** Axial FDG-PET/MR and MR image, respectively, demonstrating a level II lymph node without cystic degeneration. **4a**, **b** Axial FDG-PET/MR and MR image, respectively, demonstrating a level II lymph node with cystic degeneration

according to the study group are shown in Table 1. All 95 patients received local radiotherapy treatment with a median of 70 Gy (IQR 70–70). Furthermore, 67 patients (70.5%) received concomitant chemotherapy, and 19 patients (20.0%) cetuximab. Thirty-one patients (32.3%) presented with recurrence during follow-up. Five of these patients suffered from local recurrence (16.1%), fifteen from regional recurrence (48.4%), four from local and regional recurrence (12.9%) and seven from distant recurrence (22.6%). The median follow-up time for the cohort was 16 months (IQR 7.8–27 months).

In 56 patients (58.9%), the largest lymph node was cystic and in 39 patients it was non-cystic (41.1%). The median pretherapeutic nodal SUV_{max} was 8.3 (IQR 4.4–13.3). The median posttherapeutic nodal SUV_{max} was < 1 (IQR < 1–2.5).

Imaging characteristics of lymph node metastases

Cystic lymph nodes were significantly larger than non-cystic lymph nodes (independent-samples Mann–Whitney *U* Test $P = 0.013$, Fig. 2).

Cystic lymph nodes had significantly higher pretherapeutic SUV_{max} in comparison to non-cystic lymph nodes (independent-samples Mann–Whitney *U* Test, $P < 0.001$, Fig. 3). The posttherapeutic nodal SUV_{max} did not differ between both groups (independent-samples Mann–Whitney *U* Test $P = 0.226$).

We found no statistically significant correlation between tumoral p16 status and the presence of cystic degeneration of lymph nodes (Mantel–Haenszel HR 1.6 (95% CI 0.65–3.71, $P = 0.319$).

Detection of cystic degeneration with FDG-PET/CT and FDG-PET/MR

There were 72 (75.8%) pretherapeutic FDG-PET/CT scans available and 23 (24.2%) pretherapeutic FDG-PET/MR scans. Cystic degeneration was detected on FDG-PET/CT images in 43 cases, while cystic degeneration was present on FDG-PET/MR images in 13 cases.

The detection of cystic degeneration of metastatic lymph nodes by FDG-PET/CT was equal to FDG-PET/MR (Pearson Chi-Square test, $x^2 = 0.074$ $P = 0.786$, Fig. 4).

Table 1 Baseline characteristics of study cohort

Variable	No. of patients = 95
Age (years)	
Mean (SD)	68.5 (10.4)
Gender	
Male	70 (73.7%)
Female	25 (26.3%)
Smoker	
Yes	39 (43.3%)
No	51 (56.7%)
Pack years in lifetime	
< 10 py	30 (32.3%)
≥ 10 py	63 (67.7%)
Alcohol consumption per day	
< 3 units	61 (65.6%)
> 3 units	22 (23.7%)
Former abuse	5 (5.4%)
None	5 (5.4%)
p16 status	
Positive	55 (57.9%)
Negative	34 (35.7%)
N/A	6 (6.4%)
Tumor subsite	
Tonsil, tonsillar pillars and glossotonsillar sulcus	46 (48.4%)
Base of tongue	34 (35.8%)
Vallecula	7 (7.4%)
Soft palate/Uvula	5 (5.3%)
Not specified oropharynx	2 (2.1%)
Posterior wall	1 (1.1%)
Clinical T category	
T1 + T2	23 (24.2%)
T3 + T4	72 (75.8%)
Clinical N category by US/FNAB	
N0	18 (19.4%)
N1	44 (47.3%)
N2	27 (29.0%)
N3	4 (4.3%)
Positive nodes that show uptake on PET scan	
0	5 (5.3%)
1	18 (18.9%)
2	24 (25.3%)
≥ 3	48 (50.5%)
Size of largest node (mm)	
Median (IQR)	21.5 (12–30)
Regional response	
Regional failure	19 (19.8%)
Regional control	76 (80.2%)

IQR interquartile range, *SD* standard deviation. Percentage consideration cases with complete information

Pretherapeutic nodal $SUV_{max} > 6$, clinical N category and nodal size predict poorer regional response

There was a total of 19 (19.8%) patients showing nodal tumor persistence of regional lymph nodes metastasis at a median time of 2 months after the end of treatment (IQR 2–4).

Using a receiver operating characteristic (ROC) curve, the best potential cut-off value for pretherapeutic SUV_{max} was 6 (Fig. 5, sensitivity 84.2%, specificity 43.4%, $P = 0.089$).

In a univariable analysis, pretherapeutic nodal SUV_{max} above 6 significantly predicted poorer regional recurrence-free survival (log-rank test, $P = 0.009$) (Table 2; Fig. 6).

Furthermore, more severe clinical N category by US/FNAB was a significant predictor of poorer regional recurrence-free survival (log-rank test $P = 0.010$) (Table 2).

Using a receiver operating characteristic (ROC) curve, the best potential cut-off value for node size was 19.5 mm (sensitivity 89.5%, specificity 49.3%, $P = 0.001$). The biggest lymph node being larger than 19.5 mm significantly predicted a poorer regional recurrence-free survival (log-rank test $P < 0.001$) (Table 2).

In univariable analysis, p16 status and cystic degeneration alone did not predict a poorer regional survival (log-rank test, $P = 0.968$ and $P = 0.647$, respectively). Furthermore, smoking, alcohol, clinical T category, Hopkins criteria and extranodal extension found on imaging did not predict a poorer regional survival (log-rank test $P = 0.769$, $P = 0.934$, $P = 0.877$, $P = 0.613$ and $P = 0.899$, respectively) (Table 2).

In multivariate analysis, there were no significant predictors of poor regional recurrence-free survival

Pretherapeutic SUV_{max} above 6 was not significant in predicting poorer regional survival in multivariate analysis (Cox regression $P = 0.189$, 95% CI = 0.581–15.735). Clinical N category showed a trend in which a more severe stage had a poorer regional survival (Cox regression $P = 0.073$, 95% CI = 0.937–4.242) (Table 3).

Discussion

In this study, we evaluated the predictability of regional response after chemoradiation by metabolic tumor imaging in OPSCC. We showed that a high pretherapeutic nodal SUV_{max} was associated with poor regional response. Also, more severe clinical N category and larger nodal size were predictors of poor regional response. However, in a multivariate analysis these variables were not significant. Clinical N category showed a trend in which a more severe category was associated with poorer regional survival. Cystic lymph nodes had a higher pretherapeutic SUV_{max} and were larger

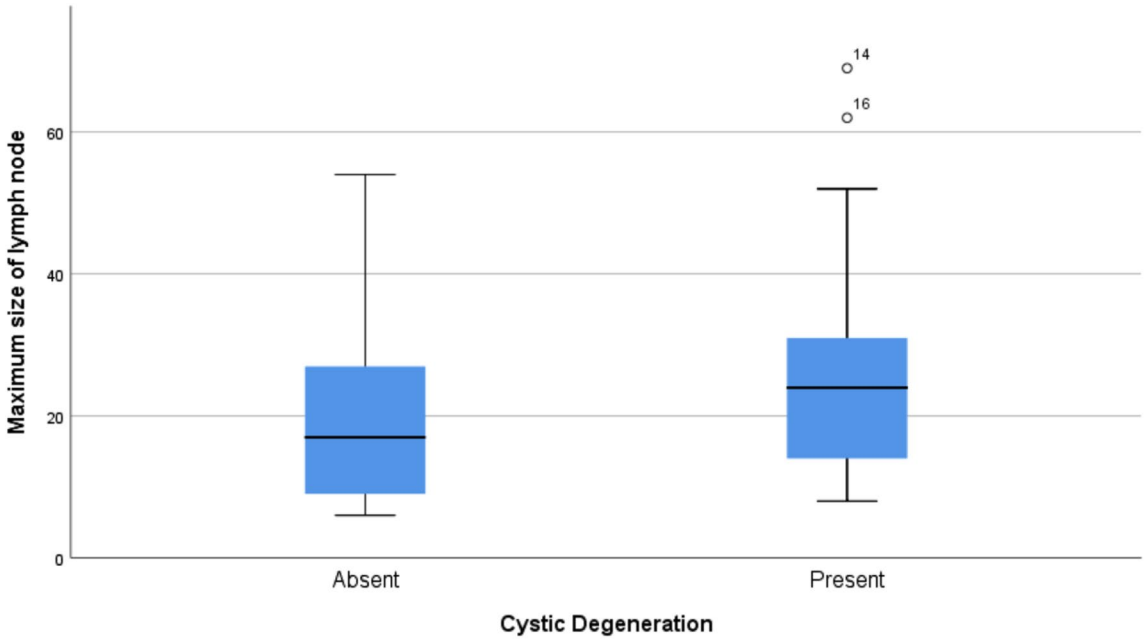

Fig. 2 A box-plot showing the difference of the maximum size of the lymph node between cystic and non-cystic lymph nodes and its spread. Nodes were significantly larger when cystic degeneration was present (independent-samples Mann–Whitney *U* Test $P = 0.013$)

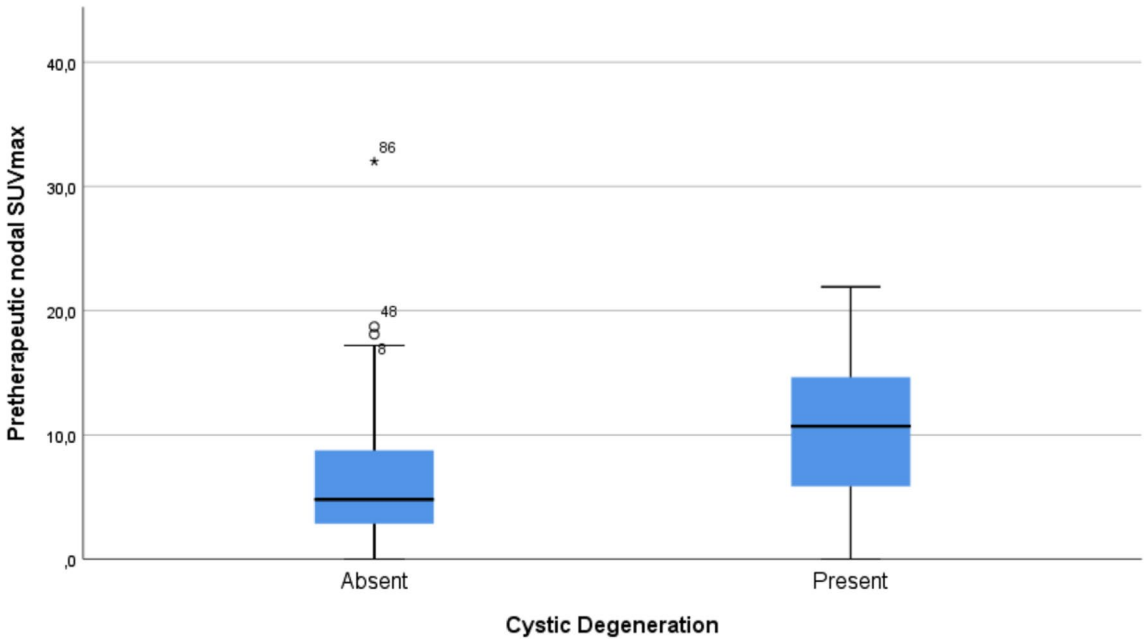

Fig. 3 A box-plot showing the correlation between pretherapeutic SUV_{max} across cystic degeneration. Cystic lymph nodes exhibited significantly higher SUV_{max} (independent-samples Mann–Whitney *U* Test, $P = 0.000$)

compared to their non-cystic counterparts. The rate of detection of cystic metastases was similar for FDG-PET/MR and FDG-PET/CT.

While the evidence is quite definite with regard to the predictability of local response using the pretherapeutic SUV_{max} of the primary tumor [32, 33], study results on pretherapeutic nodal SUV_{max} and therapy outcome are somewhat controversial [22, 23, 34]. Several studies examined prediction of survival and recurrence using metabolic tumor imaging prior to therapy. However, they did not investigate regional

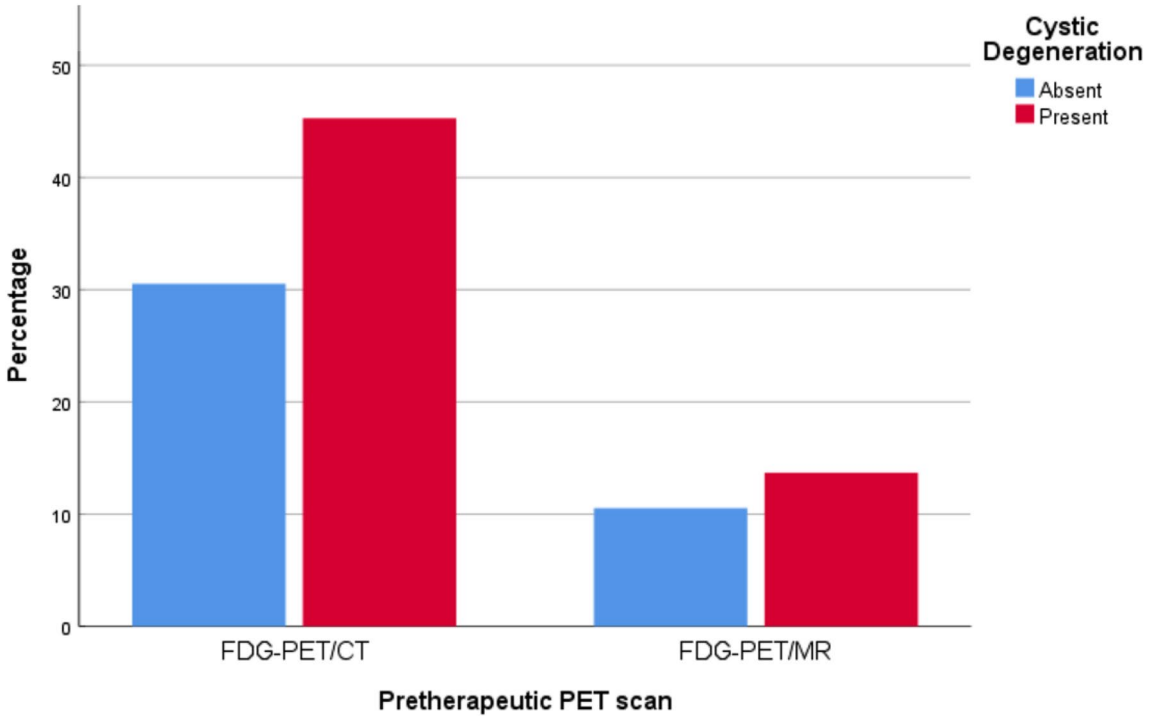

Fig. 4 A bar chart showing the detection of cystic degeneration of lymph nodes with FDG-PET/CT and FDG-PET/MR. No association was found between cystic lymph nodes and the type of scan (Pearson Chi-Square test, $x^2 = 0.074$ $P = 0.786$)

recurrence specifically. Schwartz et al. found that the pretherapeutic nodal SUV_{max} does not predict local recurrence and disease-free survival [22]. However, their study cohort of 36 patients was rather heterogeneous, with several types of HNSCC, partly treated with primary chemoradiation and partly with primary surgery. Liao et al. evaluated the prognostic value of pretherapeutic nodal SUV_{max} in 108 relapsed oral cavity squamous cell carcinoma patients and found that a pretherapeutic nodal SUV_{max} of ≥ 4.2 was predictive of poor prognosis [35]. In a retrospective analysis of 212 head and neck cancer patients, the pretherapeutic SUV_{max} of a lymph node was predictive for distant recurrence, but not for overall failure or local failure [34].

Studies regarding regional response using the pretherapeutic nodal SUV_{max} are scarce. Differently from results in our study, Schwartz et al. found in an analysis of N2–3 stage head and neck cancer patients that a pretherapeutic nodal SUV_{max} above the median value of their study cohort was not associated with regional relapse [36]. However, they included not only oropharyngeal cancer but also laryngeal cancer and hypopharyngeal cancer, with more advanced N stages compared to our study. The median nodal SUV_{max} in their cohort was 10.6, which is considerably higher compared to our cohort. In contrast, Liao et al. showed that in 120 patients with oral cavity squamous cell carcinoma the pretherapeutic nodal SUV_{max} was a predictor for the 5-year regional control and survival [23]. However, in their study, patients were treated with primary surgery and not with chemoradiation. Similar to our study, Inokuchi et al. found that the pretherapeutic nodal SUV_{max} above 6 predicted worse outcome, including nodal progression-free survival. [37]. Their cohort included a variety of HNSCC subtypes and also patients with incomplete radiation treatment (< 60 Gy). Unlike the aforementioned studies, our study consists of a comparably homogeneous cohort of OPSCC patients.

Radiologically found extranodal extension was not a predictor of regional recurrence. Shaw et al. showed in a cohort of 400 patients with oral squamous cell carcinoma that the incidence of regional recurrence was higher in metastatic nodes with extranodal extension [38]. However, their patients were treated with surgery instead of chemoradiation and extranodal extension was histologically proven. Furthermore, they did not perform a survival analysis to examine if extranodal extension is a predictor of regional recurrence. Benchetritt et al. found in a meta-analysis with 3603 patients that neither radiologically, nor pathologically diagnosed extranodal extension was associated with locoregional recurrence in HPV-positive oropharyngeal cancer [39].

The preferred assessment for extranodal extension would be pathologic evaluation after neck dissection. Maxime et al. concluded that diagnostic performance of imaging modalities shows variations between studies [40]. According to the authors, this may be due to significant

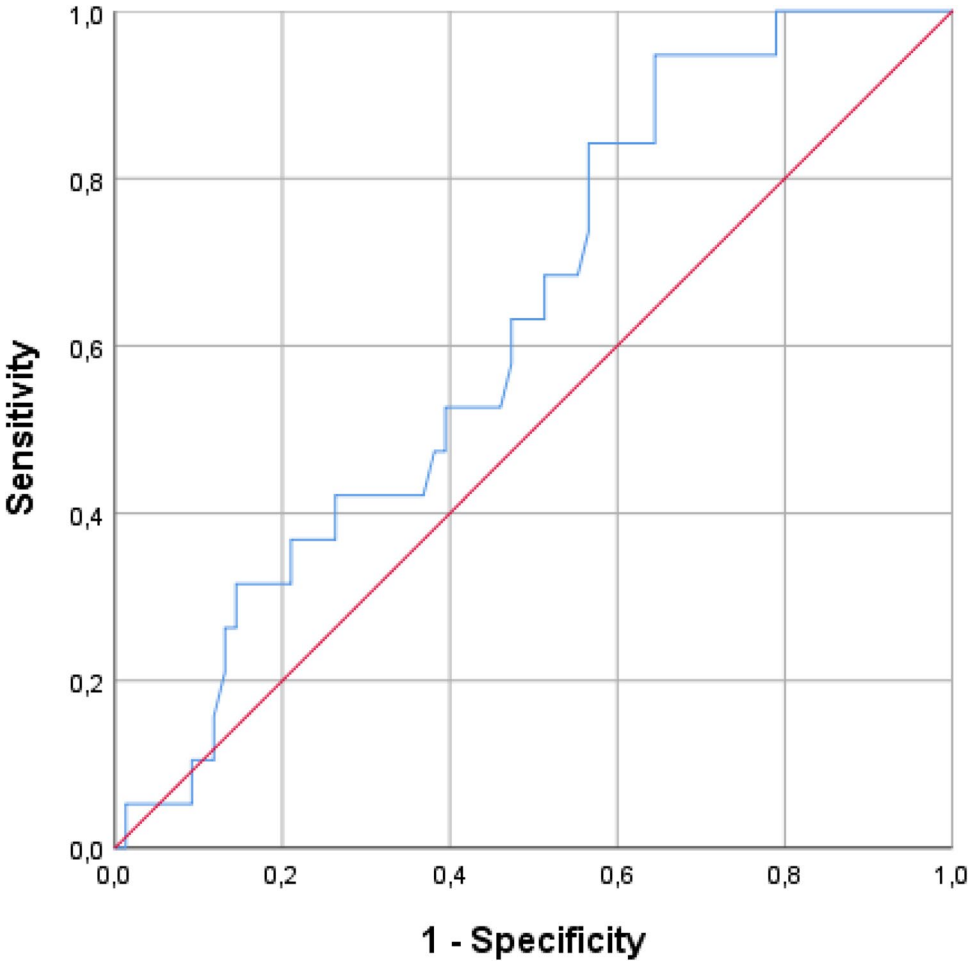

Fig. 5 ROC curve analysis for pretherapeutic SUV_{max} on predicting regional recurrence. The area under the ROC curve was 0.627 (95% CI 0.501–0.752, $P = 0.089$) and 6 was determined as best potential cut-off value in predicting regional recurrence sensitivity 84.2%, specificity 43.4%

Table 2 Univariable survival analysis

Variable	Number of cases	Number of events	Mean survival time + SE	*P* value (Log-rank)
Pretherapeutic SUV_{max}	95	19	58.4 ± 4.0	0.009
Clinical N category	93	17	58.7 ± 4.0	0.010
Size of biggest lymph node	88	19	57.3 ± 4.1	< 0.001
P16 status	89	18	57.8 ± 4.3	0.968
Cystic degeneration	95	19	58.4 ± 4.0	0.647
Smoking	90	18	58.2 ± 4.0	0.769
Alcohol	93	18	58.7 ± 4.0	0.934
Clinical T category	95	19	58.4 ± 4.0	0.877
Hopkins criteria	88	19	57.3 ± 4.1	0.613
Extranodal extension	22	10	12.9 ± 2.6	0.899

SE standard error. Extranodal extension as found on PET scan

variations in the histological and radiological diagnostic criteria of extranodal extension. Other variables that were not predictive of regional recurrence-free survival were p16 status, cystic degeneration, smoking, alcohol, clinical T category and Hopkins criteria. While it is known that P16 status and clinical T category are predictors for overall survival in HNSCC [3, 4], they might not be predictive of regional survival.

In our study, cystic degeneration was equally well detected by FDG-PET/MR and FDG-PET/CT. The median size of cystic lymph nodes was 21.5 mm (IQR 12–30) in our study, which might render their detection easier. One

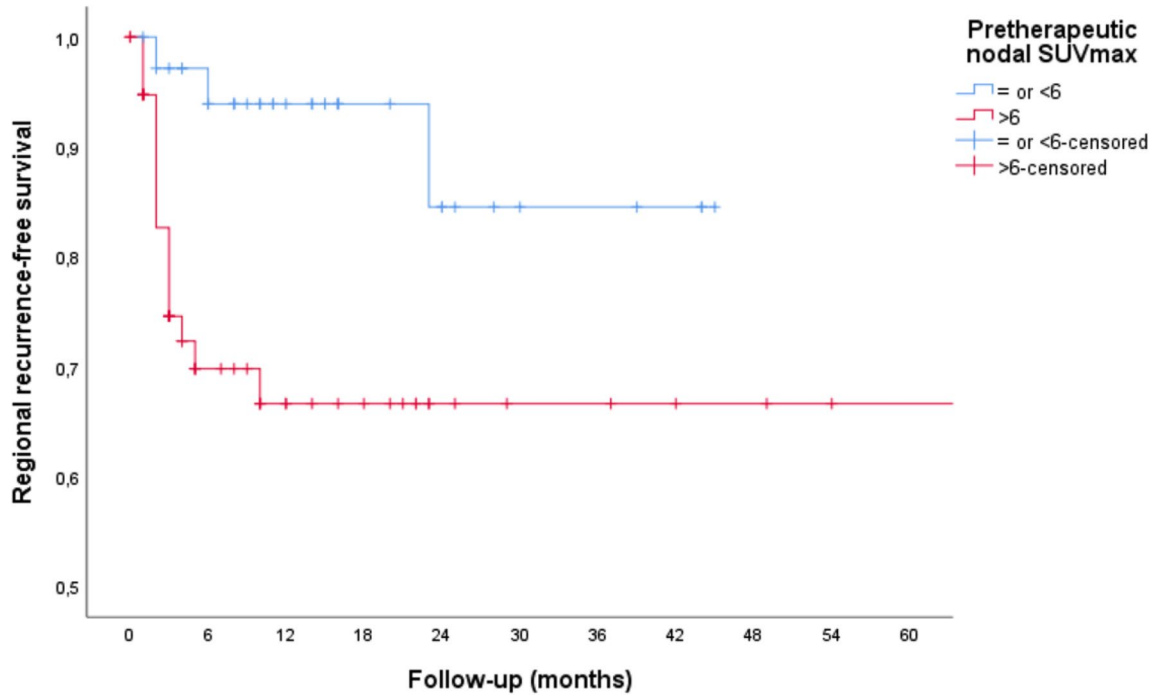

Fig. 6 Kaplan–Meier plot showing regional recurrence-free survival for pretherapeutic nodal $SUV_{max} \leq 6$ and $SUV_{max} > 6$. Pretherapeutic nodal SUV_{max} above 6 significantly predicted poorer regional recurrence-free survival (log-rank test, $P = 0.009$)

Table 3 Multivariable survival analysis

Variable	Hazard ratio	95% CI	*P* value
Pretherapeutic SUV_{max}	3.0	0.581–15.735	0.189
Clinical N category	2.0	0.937–4.242	0.073

CI confidence interval

caveat is the fact that, since we examined a cohort of OPSCC with primary chemoradiation, there was no histopathologic standard of reference available to define cystic degeneration. Hence, both imaging modalities could only be compared with each other. Of note, all PET/CT scan were acquired with iodinated contrast medium, which increases the soft tissue discrimination compared to non-enhanced PET/CT, potentially making it more "comparable" to PET/MR.

Our study shows that cystic lymph nodes are linked to a higher pretherapeutic SUV_{max}. Very few studies have investigated the relationship between SUV_{max} and cystic lymph nodes, and contradicting results have been published. Haerle et al. found a significant inverse correlation between SUV_{max} and the grade of necrosis in 29 patients [24]. On the other hand, cystic degeneration of lymph nodes has been associated with HPV-positive disease [13, 26, 30], which in turn was shown to yield higher nodal SUV_{max} by Clark et al.[41]. It is open to question whether HPV-negative disease with cystic lymph nodes also shows increased nodal SUV_{max} compared to non-cystic lymph nodes.

An explanation for these conflicting results may be that cystic lymph nodes are virtually not differentiable from necrotic lymph nodes using CT imaging. Central necrosis is caused by neoplastic infiltration in the medulla obstructing lymphatic flow, which results in poor blood supply [42, 43] and poor oxygenation. Through the Warburg effect, this induces upregulation of glycolysis and glucose transporters. Deron et al. showed that SUV_{max} is correlated with an upregulation of glucose transporters and the number of apoptotic cells in a tumor [44]. An aggressive tumor, requiring a lot of glucose, will grow fast, causing hypoxia and consequently central necrosis, the former being associated with chemoradiation resistance [18–20]. Such a tumor will show high SUV_{max} owing to high glucose uptake in tumor cells, at least in the non-necrotic part of the tumor. This might explain why cystic degeneration might in fact be associated with a higher SUV_{max}, as observed in our study.

Overall, the results of our study may have several implications, since we show that highly metabolically active disease is less likely to respond to chemoradiation in a univariate analysis. In a multivariate analysis SUV_{max} was not a predictor of regional survival. Therefore, the clinical relevance of SUV_{max} in predicting response to chemoradiation is limited. We found that clinical N category is a more important predictor for regional recurrence-free survival. In case of recurrence, salvage surgery is necessary which is associated with poor oncological and functional outcome for both the primary tumor and the neck [10]. Whether surgeons might

consider upfront surgery in highly metabolically active disease should be further investigated, preferably in a prospective setting and on a larger scale.

Some studies showed benefits when using upfront surgical treatment in more advanced oropharyngeal cancer. A retrospective analysis of the National Cancer Database (NCD) on base of tongue SCC reported that survival in stage III–IV disease is improved in patients treated with upfront surgery combined with radiation treatment compared to (chemo)radiation and surgical treatment alone [45]. Similarly, Kamran et al. in an analysis of the NCD database for oropharyngeal cancer showed that survival is improved when using primary surgery with adjuvant (chemo)radiation in locally advanced oropharyngeal cancer compared to primary radiation-based treatment [46]. In a cohort of 360 patients with oropharyngeal cancer, Wuerdemann et al. also indicated that upfront surgery in advanced stages had survival benefits compared to (chemo)radiation [47].

Our study has some limitations: first, the design was retrospective. Second, patients were staged using the TNM staging system 7th edition, as the 8th edition was not adopted during the initial diagnosis of the majority of the patients. Third, we had a relatively low number of patients, particularly in the FDG-PET/MR group, which makes the statistical analysis harder and gives rise to significance fallacy as well as beta error. Fourth, follow-up time of our patients was rather short. Also, for most patients, only p16 IHC testing was performed, which was considered a surrogate for the HPV status in our study. However, also the 8th edition TNM staging system considers only the p16 status as indicator of HPV-mediated carcinogenesis. For an improved determination of the HPV status of the tumor, p16 IHC should be combined with HPV DNA qPCR or even HPV RNA qPCR alone should be used [48].

Conclusion

In conclusion, metabolic tumor imaging and clinical N stage showed a trend in predicting regional response in oropharyngeal cancer patients. A pretherapeutic nodal SUV_{max} above 6 predicted a poorer regional recurrence-free survival in univariable analysis. Hence, highly metabolically active disease may be less likely to respond to chemoradiation. However, a more severe clinical N category seems to play a bigger role in predicting regional response. More research is needed, preferably in a prospective setting and on a larger scale, to find out whether metabolically active disease will benefit from upfront surgery. In addition, cystic lymph nodes were indicative of a higher pretherapeutic nodal SUV_{max} irrespective of tumoral p16 positivity. This could be explained by the association of necrosis with poor oxygenation which in turn is correlated with high SUV_{max} through the Warburg effect.

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