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Potential role of hybrid positron emission tomography in pre-operative assessment of primary salivary gland carcinomas

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Abstract

Objective. The added value of hybrid positron emission tomography is increasingly recognised in head and neck cancer. However, its potential role in salivary gland carcinomas has been scarcely investigated.

Methods. A consecutive cohort of 45 salivary gland carcinoma patients who underwent pre-therapeutic hybrid positron emission tomography and surgical resection was reviewed. This study investigated whether maximum standardised uptake value correlated with tumour phenotype.

Results. Tumours of high-grade disease on histology (salivary duct carcinoma, carcinoma ex pleomorphic adenoma) had higher maximum standardised uptake value (Kruskal–Wallis test, $p = 0.011$) than low-grade tumours (adenoid cystic carcinoma and acinic cell carcinoma). Patients with pathologically confirmed node-positive disease had significantly higher maximum standardised uptake value of the primary tumour than patients with pathologically confirmed node-negative disease (Kruskal–Wallis test, $p = 0.012$).

Conclusion. Maximum standardised uptake value of the primary tumour may guide clinical decision-making in patients with salivary gland carcinomas, as a high maximum standardised uptake value is associated with high-grade tumour histology and the presence of lymph node metastases. Clinicians may consider more aggressive surgery for these patients.

Main Article

Dr G Morand takes responsibility for the integrity of the content of the paper

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Introduction

Hybrid positron emission tomography (PET) relies on the combination of cross-sectional imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) with PET. It allows for functional imaging of disease, as most malignancies rely energetically on anaerobic glycolysis (Warburg effect) and thus consume high quantities of glucose. Hybrid PET has been used for staging the primary tumour, and nodal and distant metastasis in head and neck cancer, but its use has been mainly reported for squamous cell carcinoma (SCC) of the head and neck.[1] Quantification of ^{18}F-fluorodeoxyglucose (FDG) uptake of a particular tumour is also possible, and has been shown to be of prognostic importance in several subsites of head and neck SCC.[2–4]

For salivary gland cancer, there are very few reports on the potential diagnostic value of hybrid PET-based metabolic tumour imaging.[5,6] A drawback is that certain subtypes of salivary gland carcinomas show an intrinsically very low glucose uptake, thereby limiting the potential of hybrid PET.[6] On the other hand, several benign salivary gland tumours may exhibit high FDG uptake, particularly those with oncocytic or oxyphilic differentiation.

It remains unclear whether hybrid PET may serve as a prognostic tool also in salivary gland carcinomas. This study aimed to examine whether maximum standardised uptake value ('SUVmax') is of prognostic value and can serve as a surrogate marker of tumour aggressiveness, and thus assist in treatment decisions. We therefore analysed tumour site and size, and regional lymph node involvement, pre-PET and post-PET, as well as the maximum standardised uptake value of the primary tumour.

Materials and Methods

This study was reported according to the Enhancing the Quality and Transparency of Health Research 'Equator' Network reporting guidelines, specifically following the Strengthening the Reporting of Observational Studies in Epidemiology ('STROBE') criteria.

This retrospective study was approved by the local ethics committee, Kantonale Ethikkommision Zürich. It was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery of the University Hospital Zurich, Switzerland, and included patients treated between 2010 and 2019.

All patients with primary malignant carcinoma of the salivary glands who underwent pre-operative hybrid PET with known histology data were included. Patients without documented willingness to provide their medical data for retrospective research were not included. Patients with benign salivary gland disease or with a history of skin cancer of the head and neck and possible metastasis to the parotid gland were excluded.

Patients were staged in accordance with Union for International Cancer Control tumour–node–metastasis staging for head and neck cancer, eighth edition (2017).[7]

Histology

The histological characteristics of the surgical specimens (grading, tumour stage and extent of nodal disease) were assessed. All surgical pathology diagnoses were reviewed by an experienced board-certified pathologist (NJR). Tumour entities were (re-)classified according to the 2017 *WHO Classification of Head and Neck Tumors*.[7] Tumours were graded with regard to the respective entity: grade 1 (low grade), grade 2 (intermediate grade) or grade 3 (high grade). For corroboration of specific entity diagnosis in several cases, molecular pathology was performed by an experienced molecular biologist (SNF) using our custom-made salivary gland neoplasm specific next-generation sequencing panel.[8] For diagnosis of primary SCC of the salivary glands, no clinical evidence or history of another SCC was mandatory.

Hybrid positron emission tomography

Fasted patients (at least 4 hours) were injected with a standardised dose of ^{18}F-FDG per kilogram of body weight. The FDG dosage protocols depended on the type of scanner used (details have been published previously).[9]

The standardised uptake value was calculated automatically (activity in volume of interest / (injected dose × body weight)). The maximum standardised uptake value was defined as the hottest voxel within the volume of interest. For analysis of FDG uptake, correct placement of volumes of interest on PET images was ensured by side-by-side reading of the corresponding CT or MRI scans. A written radiological report by a doubly board-certified nuclear medicine physician or radiologist was available for all FDG-PET/CT and FDG-PET/MRI scans.

Statistical analysis

For continuous variables, distribution was evaluated for normality pursuant to Gauss's theorem. For normally distributed variables (age), mean and standard deviations are given. For non-normally distributed variables (follow-up time, maximum standardised uptake value), median and interquartile range are given. In order to compare distribution among non-normally distributed samples, the non-parametric Kruskal–Wallis test was used. Correlations were assessed with the Spearman rho test. A p-value lower than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 25.0.0.1 software (IBM, Armonk, New York, USA).

Results

There were a total of 45 patients, with a median age at diagnosis of 67 years (standard deviation = 15.6 years). Most patients had advanced tumours at initial presentation, with 18 out of 45 patients (40.0 per cent) having positive nodal disease. Further details are presented in Table 1.

Table 1. Patient demographics and clinical characteristics

Variable	All patients
Age (mean ± SD; years)	65 ± 15.6
Gender (*n* (%))	
– Male	35 (77.8)
– Female	10 (22.2)
Grading (*n* (%))	
– Low grade	9 (22.0)
– Intermediate grade	8 (19.5)
– High grade	24 (58.5)
– N/A	4 (8.8)
Pathologically confirmed nodal (N) classification (*n* (%))	
– N_0	22 (48.9)
– N_1	5 (11.1)
– N_{2a}–N_{2b}	13 (28.9)
– N_{2c}–N_3	5 (11.1)
Histological subtype (*n* (%))	
– Salivary duct carcinoma	13 (28.9)
– Adenoid cystic carcinoma	2 (5.0)
– Mucoepidermoid carcinoma	4 (9.0)
– Carcinoma ex pleomorphic adenoma (different entities)	8 (17.8)
– Primary squamous cell carcinoma	5 (11.1)
– Acinic cell carcinoma	5 (11.1)
– Lymphoepithelial carcinoma	1 (2.2)
– Adenocarcinoma NOS	2 (5.0)
– Epithelial-myoepithelial carcinoma	2 (5.0)
– Poorly differentiated carcinoma, small cell neuroendocrine carcinoma	1 (2.2)
– Combined salivary duct carcinoma + poorly differentiated neuroendocrine carcinoma	1 (2.2)

*Total $n = 45$. SD = standard deviation; N/A = not available; NOS = not otherwise specified

Surgical resection was the primary treatment modality for most patients (41 out of 45, 91.1 per cent), with 14 patients (34.1 per cent) undergoing radical parotidectomy, 14 (34.1 per cent) undergoing (sub)total parotidectomy and 11 (26.9 per cent) undergoing superficial parotidectomy. Two patients (4.9 per cent) had a primary tumour of the submandibular gland.

All patients with high-grade or advanced-stage tumours (29 out of 44) underwent post-operative radiotherapy, three of whom underwent post-operative chemoradiation.

One patient suffered from a primary Epstein–Barr virus associated lymphoepithelial carcinoma of the parotid gland and underwent primary curative chemoradiation. Two further patients showed distant metastases (in the lung and liver) and underwent palliative treatment with chemotherapy or immunotherapy.

Metabolic tumour imaging

The median maximum standardised uptake value of the primary tumour was 7.7 (interquartile range = 4.25–12.25). Statistical analysis revealed a significant difference (Kruskal–Wallis test, $p = 0.044$) between maximum standardised uptake

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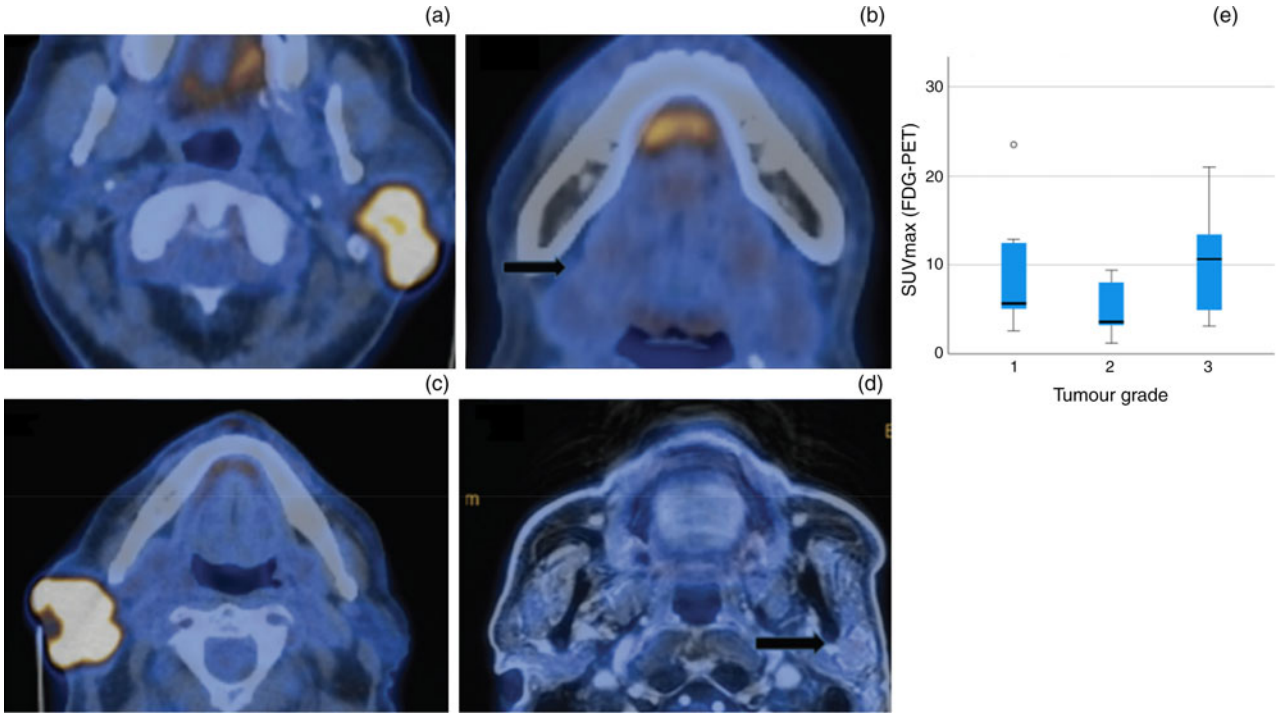

Fig. 1. Representative axial fused hybrid positive emission tomography images showing patients with: (a) salivary duct carcinoma of the left-sided parotid gland with a high maximum standardised uptake value (14.7), (b) an adenoid cystic carcinoma with a low maximum standardised uptake value (3.1; arrow), (c) squamous cell carcinoma of the right-sided parotid gland with a high maximum standardised uptake value (21.0) and (d) an acinic cell carcinoma of the left-sided parotid gland with a low maximum standardised uptake value (2.6; arrow). (e) Box plot showing pre-therapeutic maximum standardised uptake value (SUVmax) of the primary tumour by primary tumour grade (independent-samples Kruskal–Wallis test, $p = 0.044$). FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography

value and tumour grade, with high-grade histology tumours showing higher maximum standardised uptake values (Figure 1).

When comparing the maximum standardised uptake values of primary tumour and salivary gland tumour type, statistical analysis revealed a significant difference: the maximum standardised uptake value was higher for salivary duct carcinoma and SCC (Kruskal–Wallis test, $p = 0.011$) than for adenoid cystic carcinoma and acinic cell carcinoma (Table 2).

Maximum standardised uptake value and nodal disease

Patients with pathologically confirmed node-positive disease had a significantly higher maximum standardised uptake value of their primary tumour than those with pathologically confirmed node-negative disease (Kruskal–Wallis test, $p = 0.012$) (Figure 2a). Further, statistical analysis showed a positive correlation between the number of positive nodes and the maximum standardised uptake value of the primary tumour (Spearman, $r = 0.478$, $p = 0.005$) (Figure 2b).

Discussion

This single-institution retrospective study analysed the maximum standardised uptake value of hybrid FDG-PET and assessed its correlation with histological parameters of salivary gland carcinomas. The primary objective of our study was to determine whether pre-therapeutic hybrid PET could provide added diagnostic value in pre-therapeutic decision-making, given that cytology and standard cross-sectional imaging have limitations. We therefore sought to explore whether hybrid PET imaging could assist in providing further diagnostic insight.

Previous clinical research on this subject is limited. The few existing studies report a prognostic value of FDG-PET, especially maximum standardised uptake value, with regard to salivary gland carcinomas and nodal disease.[5,6,10] This is particularly relevant as the presence of nodal disease itself has prognostic value.[5,6] However, differences among tumour entities have not been addressed in detail until now.

We believe that our results potentially have a two-fold clinical impact. First, high maximum standardised uptake value is

Table 2. SUVmax of different salivary gland tumour types

		SUVmax			
Tumour type	Cases (*n*)	Median	25th percentile	50th percentile	75th percentile
Salivary duct carcinoma	14	10.7	5.77	10.70	11.95
Adenoid cystic carcinoma	3	3.5	3.10	3.50	–
Primary SCC or miscellaneous	13	9.4	4.75	9.40	20.00
Mucoepidermoid carcinoma	4	5.7	4.02	5.75	19.22
Acinic cell carcinoma	5	3.4	1.90	3.40	5.45

SUVmax = maximum standardised uptake values; SCC = squamous cell carcinoma

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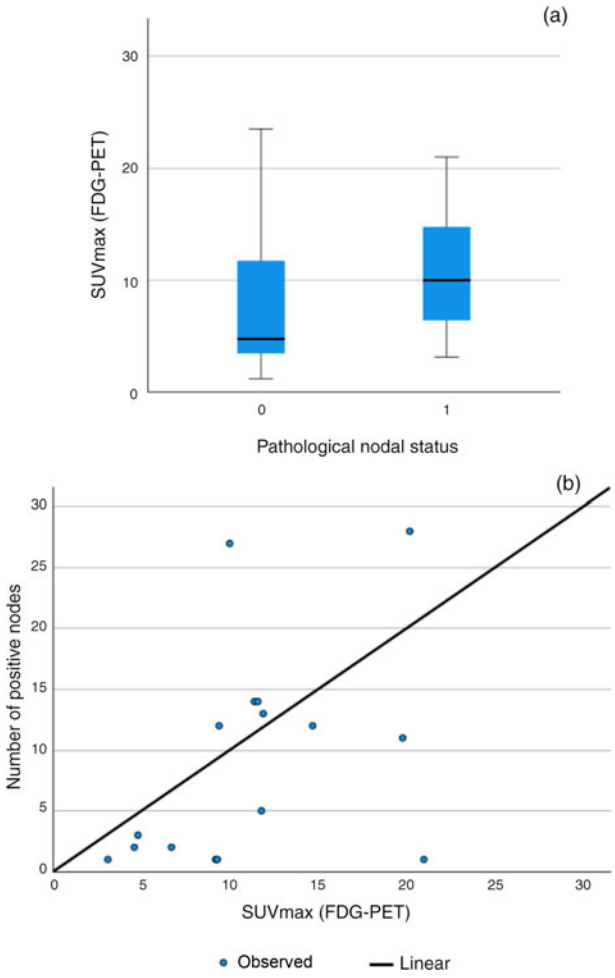

Fig. 2. (a) Maximum standardised uptake value of the primary tumour by nodal status (0 = pathologically confirmed node-negative disease, 1 = pathologically confirmed node-positive disease) (Kruskal–Wallis test, $p = 0.012$). (b) Correlation of maximum standardised uptake value of the primary tumour with number of positive nodes (Spearman, $r = 0.478$, $p = 0.005$). SUVmax = maximum standardised uptake value; FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography

associated with a higher grade of primary tumour. For tumours of the parotid gland, surgical margins are often limited because of proximity to the facial nerve. While most authors agree that, even for high-grade disease, every attempt should be made to preserve a functional nerve when not grossly infiltrated, the additional pre-operative information that a tumour is of high grade would certainly suggest obtaining patient consent for facial nerve sacrifice, especially if its function is already compromised or is limited pre-operatively. Nevertheless, pre-operative decision-making should also consider the results of fine needle aspiration biopsy, as benign neoplasms may also show high FDG avidity (particularly oncocytic or oxyphilic tumours), owing to their high number of mitochondria. On the other hand, oncocytic variants of several carcinoma entities may also exhibit a high maximum standardised uptake value.

Second, a high maximum standardised uptake value was associated with positive nodal disease. Therefore, a high maximum standardised uptake value of the primary tumour may prompt surgeons to opt more frequently for elective treatment of the neck, as it is more likely that occult nodal disease will be detected upon final pathological examination.

Our study has several limitations. First the sample size was limited. Hence, we could not perform multivariable analysis to assess whether the maximum standardised uptake value of the primary tumour was related more to the tumour grade or to the presence of nodal metastasis. This issue could be solved in a future meta-analysis, which this study could be part of. Another limitation of our study is the relative heterogeneity of the cohort. However, the latter is almost unavoidable when primary tumours of the salivary glands are analysed. Previous studies were of similar heterogeneity and size, hence our study remains well within the standards established for this type of analysis.[5,6,10] Finally, while hybrid PET revealed some important features of the tumour phenotype, one should bear in mind that benign entities, such as Warthin's tumour, may also demonstrate high FDG uptake. The cytological investigation and diagnosis of Warthin's tumour is however straightforward, such that one can easily rule out this differential.

Future studies shall investigate the role of hybrid PET as a pre-operative adjunct in the diagnostic process, especially in cases of uncertain malignant neoplasm (Milan System for Reporting Salivary Gland Cytopathology category 4b) or atypia of undetermined significance (Milan category 3). This gives the opportunity for a further study as indications for hybrid PET continue to expand.

- This study reports on hybrid positive emission tomography (PET) in a primary salivary gland cancer cohort ($n = 45$)
- High-grade tumours (e.g. salivary duct, carcinoma ex) show a high maximum standardised uptake value on pre-therapeutic hybrid PET
- Low-grade tumours (e.g. acinic cell) show a low maximum standardised uptake value on pre-therapeutic hybrid PET
- High maximum standardised uptake value of primary tumour predicts presence and extent of nodal disease
- Hybrid PET can be used as an adjunct diagnostic tool in salivary gland cancer

Data availability statement. The datasets generated for this study can be obtained upon reasonable request by e-mail to the corresponding author.

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