[^{18}F]FDG-PET/CT improves the detection of synchronous malignancies at primary staging of oral squamous cell carcinoma – A retrospective study

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1. Introduction

Oral and oropharyngeal cancer is the sixth most common malignancy in the world, and originates in more than 90% of cases in squamous cells (Lingen et al., 2008). The main risk factors for OSCC are alcohol consumption and tobacco smoking (Marron et al., 2010). Both exogenous carcinogens may act synergistically (Mello et al., 2019), affecting both the oral cavity and the oropharynx, as well as the mucosal surfaces of the entire respiratory system and digestive tract (Gandini et al., 2008). The hypothesized 'field cancerization' (Slaughter et al., 1953) explains why patients with OSCC have an increased risk for developing a second primary cancer, particularly in head-and-neck sites, the esophagus, and the lung and bronchus (Chuang et al., 2008). Although second primary

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malignancies occur most often metachronously, 6–8% of the patients with head-and-neck squamous cell carcinoma (HNSCC) show synchronous malignancies at the time of primary tumor diagnosis (Erkal et al., 2001; Schwartz et al., 1994; Shapshay et al., 1980). Current guidelines for clinical practice account for this risk by recommending the evaluation of the upper aerodigestive tract (UADT) for synchronous primary malignancies (SPM) at initial tumor staging (Leitlinienprogramm Onkologie, 2021). These guidelines explicitly highlight 'a great need for research in clarifying the importance of panendoscopy for the detection of secondary tumors' (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft), 2021). The question of whether PET/CT imaging can prevent more invasive diagnostics requiring general anesthesia is part of an ongoing debate (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft), 2021) (see Fig. 1).

Panendoscopy combines the examination of the oral cavity, pharyngolaryngoscopy, tracheobronchoscopy, and esophagoscopy, and thus allows for the evaluation of a large proportion of epithelial structures at risk. Furthermore, it enables immediate biopsy and histopathological analysis of suspicious lesions. In the case of a finding, therapeutic strategies (surgery vs non-surgical approaches) can be evaluated, since panendoscopy includes an assessment of extent, accessibility, and resectability of a lesion. However, the requirement for general anesthesia, the delay of primary tumor treatment, and complications such as dental damage or esophageal perforation are some reasons why routine panendoscopy at primary staging is increasingly being questioned, particularly for non-drinking and non-smoking patients (Valentin et al., 2021).

Recent (prospective) studies have augmented the evidence for the benefit of using positron emission tomography (PET) and [^{18}F] fluorodeoxyglucose ([^{18}F]FDG) in primary tumor delineation, preoperative staging, and posttherapeutic management of OSCC (Breik et al., 2020; Lopez et al., 2017, 2018; Ng et al., 2005, 2006; Zrnc et al., 2018). Aside from the improved staging of cervical lymph node involvement, this approach enables accurate whole-body screening for SPM, including the assessment of the entire aerodigestive tract. Therefore, the aim this study was to show the non-inferiority of [^{18}F]FDG-PET/CT as compared with panendoscopy for the detection of SPM within the UADT in patients with newly diagnosed, treatment-naïve OSCC.

2. Materials and methods

2.1. Patients

This retrospective study evaluates patients with newly diagnosed OSCC who were admitted for surgery between January 2013 and July 2016. The clinical work-up for the primary staging of OSCC comprised clinical examination, panendoscopy of the UADT, and, if practicable, imaging with cervical magnetic resonance imaging (MRI). The current analysis was performed as secondary analysis of a prospective cohort on the diagnostic performance of [^{18}F]FDG-PET/CT for the detection of cervical lymph node metastases (Linz et al., 2021). Inclusion criteria were defined as follows: (i) histopathological confirmation of OSCC in (ii) patients without prior treatment, as well as primary staging with (iii) [^{18}F]FDG-PET/CT and (iv) panendoscopy prior to treatment initiation. The institutional review board of the University Hospital of Würzburg (286/12) approved the study, and written informed consent was obtained from all subjects.

2.2. Imaging

All patients underwent [^{18}F]FDG-PET imaging on an integrated PET/CT scanner (Siemens Biograph mCT 64, Siemens Healthineers, Knoxville, USA). Patients were instructed to fast for at least 4–6 h prior to imaging and blood glucose levels were confirmed to be below 160 mg/dl before the intravenous injection of 298 ± 24 MBq [^{18}F]FDG. PET emission data were acquired 60 min after the

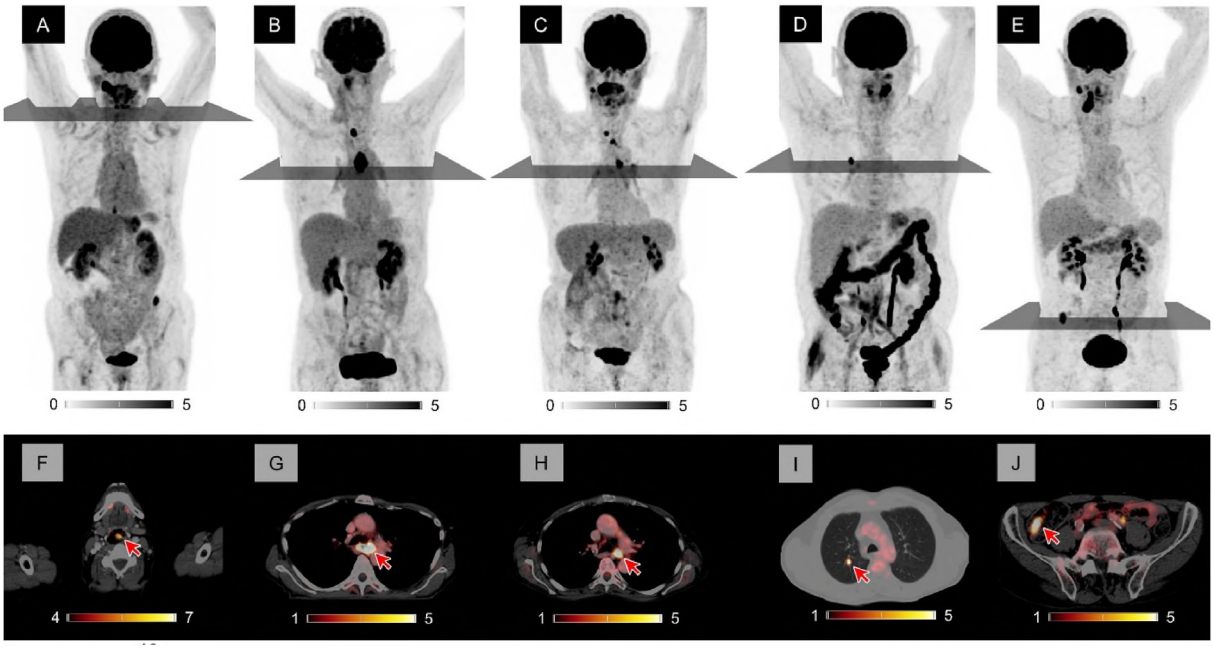

Fig. 1. [^{18}F]FDG-PET/CT imaging in five patients with oral squamous cell carcinoma. The upper panels show maximum intensity projections of [^{18}F]FDG-PET with suspicious findings within (A–C) and beyond (D, E) the coverage of panendoscopy. The lower panels show one corresponding transaxial PET/CT slice of each lesion (F–J). Histopathological analysis of obtained tissue samples revealed synchronous secondary malignancies of the epiglottis (A/F), the esophagus (B/G and C/H), the lung (D/I), and the colon (E/J). Whilst the secondary malignancis of examples A/F and B/G were also detected by pandendoscopy, this was not the case for example C/H. Color bars indicate standardized uptake values.

radiotracer's injection in 3D-mode from the vertex of the skull to the proximal thighs (matrix = 200 × 200, 2-min emission time per bed position). Subsequently, diagnostic CT scans were performed with contrast enhancement (dose modulation with 180 mAs quality reference, 120 kV, matrix = 512 × 512, slice thickness = 5 mm, increment = 30 mm/s, rotation time = 0.5 s, pitch index = 1.4). Furthermore, a dedicated head and neck acquisition with one bed position, 3-min emission time, and a second contrast-enhanced CT was acquired (180 mAs, 120 kV, matrix = 512 × 512, slice thickness = 3 mm, increment = 30 mm/s, rotation time = 1.0 s, pitch index = 0.9). PET data were reconstructed iteratively (3 iterations, 24 subsets, a Gaussian filtering of 2.0 mm full width at half maximum) with CT-based attenuation correction using standard software (HD. PET, Siemens Esoft, Siemens Healthineers, Erlangen, Germany). Whole-body- and cervical PET/CT were evaluated by two experienced, board-certified nuclear medicine physicians (J.B. and C.L.) on a syngo.via workstation (Siemens Healthineers, Erlangen, Germany) reaching a consensus diagnosis. Increased tracer uptake foci with reference to normal tissue and blood pool and/or to the presence of morphological alterations on CT images were considered positive for secondary malignancies as well as for distant nodal and organ metastasis. Subsequent consensus reading served to resolve differences between the two readers. Of relevance, the raters were blinded to panendoscopy findings and results of histopathological analysis.

2.3. Panendoscopy

Prior to the definitive tumor treatment, all patients underwent diagnostic panendoscopy. This procedure is not exactly defined in the literature. -Panendoscopy was performed according to the consensus guidelines of the German Association of the Scientific Medical Societies (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, 2019) by one experienced and examined ENT specialist and one training fellow, respectively. Rigid endoscopes were inserted approximately 28 cm (27.4 ± 2.2 cm) in order to examine the upper two thirds of the esophagus, where the majority of squamous cell carcinomas is located. The procedure includes the examination of the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx as well as tracheoscopy and esophagoscopy (the covered area was defined as UADT for this study). Biopsies were taken in order to exclude or confirm malignancies. The histopathological findings of obtained biopsy samples were defined as diagnostic parameter for the comparison with [^{18}F]FDG-PET/CT.

2.4. Reference standard

A combination of histopathological findings and clinical follow-up was defined as composite reference standard. Histopathological samples of lesions that were suspicious for a second malignancy were obtained during endoscopy or after [^{18}F]FDG-PET/CT, if appropriate. For patients without immediate extraction of tissue samples for histopathological analysis due to designated treatment priorities, clinical follow-up until December 2020 including imaging (CT, MRI, and/or [^{18}F]FDG-PET/CT) and tumor-specific diagnostic procedures were defined as reference standard. Clinical follow-up was also set as reference standard in patients without suspicion for a SPM after [^{18}F]FDG-PET/CT and UADT panendoscopy.

2.5. Statistical analysis

The software R (R v3.6.1, http://www.R-project.org/) and the R package 'DTComPair' were used for statistical analysis. Sensitivity (SN), specificity (SP), positive (PPV) and negative predictive values (NPV) of both, [^{18}F]FDG-PET/CT and panendoscopy for the detection of SPMs within the UADT were assessed. Their performance was compared by using the McNemar test (Mc, 1947) and relative predictive values (Moskowitz and Pepe, 2006). Additionally, the diagnostic accuracy of [^{18}F]FDG-PET/CT in detecting SPMs within the whole body was estimated. For patients who presented with more than one suspicious finding, the findings were assumed to be independent cases.

3. Results

3.1. Patients

The inclusion criteria were met by 182 patients (age: 63.3 ± 12.0 years, 77 females). In 149 patients, [^{18}F]FDG-PET/CT was performed 5.0 ± 16.7 days prior to panendoscopy. In the remainder, panendoscopy preceded [^{18}F]FDG-PET/CT imaging with a mean interval of 9.7 ± 7.7 days. After primary staging, 167 patients underwent surgical treatment consisting of primary tumor resection and selective or complete neck dissection. The remaining patients received primary radiotherapy (n = 2), combined radiochemotherapy (n = 8), or combined radiochemotherapy and neck dissection (n = 1). Four enrolled patients were not treated due to relevant comorbidities without treatment priority of the OSCC (n = 1) or because patients declined any therapy (n = 3). Detailed information on primary tumor localizations and tumor stages and gradings according to the TNM classification of OSCC (Edge and Compton, 2010) is given in Table 1.

3.2. Histopathological analysis

3.2.1. Upper aerodigestive tract

Twelve tissue samples from suspicious lesions were collected during UADT panendoscopy and one specimen derived from biopsy at follow-up. Histopathological analysis confirmed eight SPMs of the UADT, whereas this was ruled out in five cases. Two subjects showed low-to medium-grade intraepithelial dysplasia, and one patient each had oral leukoplakia, oral candidiasis, and mechanical alterations of the epithelium. Note that a histopathological confirmation of malignancy in obtained biopsy samples was defined as the diagnostic parameter for panendoscopy. Therefore, only one case with epithelial dysplasia, which was also scored suspicious in [^{18}F]FDG-PET/CT, was considered for statistical analysis, while the number of cases with histopathological diagnosis as a reference standard was n = 9. The localizations of suspicious findings and SPMs are given in Table 2.

3.2.2. Whole body

An additional 12 specimens were obtained by biopsy and/or surgical treatment to clarify suspicious whole-body [^{18}F]FDG-PET/CT findings. SPMs were confirmed in ten cases. In one patient, histopathological analysis revealed a lymph node metastasis of the primary tumor, while one subject had low-to medium-grade intraepithelial dysplasia of the colon. Of note, these two cases were considered negative for SPM in statistical analysis (Table 3).

3.3. Clinical follow-up

Median clinical follow-up time was 18 months (range: 1–85 months). In four patients, clinical follow-up confirmed SPMs, whereas this was ruled out in one case (all outside the UADT, Table 3). Out of 160 patients with negative findings at primary staging, one patient was diagnosed with pulmonary cancer 19 months later. A diligent review of the regular follow-up visits, including radiological imaging, revealed that the cancer was not visible at primary staging, so the pulmonary cancer was considered

Table 1
Patient characteristics.

Age, years		
	Mean	63.3
	Range	23–88
Sex, *n* (%)		
	Male	105 (55.9)
	Female	77 (42.3)
	Total	182
Localization of primary, *n* (%)		
	Buccal mucosa	12 (6.6)
	Palate	8 (4.4)
	Mandibular mucosa	31 (17.0)
	Maxillary mucosa	24 (13.2)
	Oropharyngeal mucosa	22 (12.1)
	Floor of the mouth	36 (19.8)
	Tongue	49 (26.9)
	Total	182
Treatment, *n* (%)		
	Surgery	167 (91.8)
	Radiotherapy	2 (1.1)
	Radiochemotherapy	8 (4.4)
	Radiochemotherapy and neck dissection	1 (0.5)
	No treatment	4 (2.2)
	Total	182
Primary tumor stage, *n* (%)		
	pT1	55 (32.9)
	pT2	58 (34.7)
	pT3	11 (6.6)
	pT4	43 (25.7)
	Total	167
Local lymph node metastases, *n* (%)		
	pN0	97 (58.1)
	pN1	28 (16.8)
	pN2a	1 (0.6)
	pN2b	33 (19.8)
	pN2c	8 (4.8)
	Total	167
Grading, *n* (%)		
	G1	17 (10.2)
	G2	100 (59.9)
	G3	38 (22.8)
	G4	1 (0.6)
	n/a	11 (6.6)
	Total	167

Table 2
Localization and histopathological results of [^{18}F]FDG-PET/CT and panendoscopy findings within the upper aerodigestive tract.

Localization	Detected by		Histopathological result	
	PET/CT *n*	Panendoscopy *n*	Confirmed *n* (%)	Excluded *n* (%)
Palate	1	1	1 (100)	–
Oropharynx	1	–	–	1 (100)
Epiglottis	3	3	3 (100)	–
Larynx	1	1	1 (100)	–
Upper esophagus	3	2	3 (100)	–
Total	9	7	8 (88.9)	1 (11.1)

as metachronous. Of the included patients, 159 did not show any evidence of SPM during the observation period. However, in 25 patients, the follow-up time was less than 6 months after primary treatment.

3.4. Reference diagnosis

According to the composite reference standard, 18 of the 182 patients had an SPM at primary staging (disease prevalence: 9.9%, 95% confidence interval: 6.0–15.2%). In six cases, tumors were localized in the UADT (3.30% [1.22–7.04%]). Since two patients had two and one patient had three synchronous malignancies, the total number of detected malignancies was 22 (UADT: 8) and the number of cases was accordingly adjusted for statistical analysis to $n = 186$ (UADT: $n = 184$).

3.5. Imaging

[^{18}F]FDG-PET/CT detected 22 out of 22 synchronous malignancies (SN: 100% [100–100%]) and yielded false-positive results in four cases (SP: 97.6% [95.2–99.9%]). PPV and NPV were 84.6% (70.7–98.5%) and 100% (100–100%), respectively. For SPMs of the UADT, the diagnostic measures were 100% SN (100–100%), 99.4% SP (98.3–100%), 88.9% PPV (68.4–100%), and 100% NPV (100–100%).

Table 3
Localization and histopathological results of [^{18}F]FDG-PET/CT findings outside of the upper aerodigestive tract.

Localization	*n*	Confirmed by		Excluded by	
		Histopathological analysis *n* (%)	Clinical follow-up *n* (%)	Histopathological analysis *n* (%)	Clinical follow-up *n* (%)
Parotid gland	1	–	–	1 (100)	–
Thyroid	1	1 (100)	–	–	–
Lower esophagus	1	1 (100)	–	–	–
Lung	2	2 (100)	–	–	–
Mammary	2	2 (100)	–	–	–
Liver/pancreas	2	–	2 (100)	–	–
Colon	4	3 (75)	–	1 (25)	–
Uterus	1	1 (100)	–	–	–
Prostate	2	–	1 (50)	–	1 (50)
Lymphatic system	1	–	1 (100)	–	–
Total	17	10 (58.8)	4 (23.5)	2 (11.8)	1 (5.9)

3.6. Panendoscopy

Biopsies were taken from 12 suspicious lesions (proven SPM, $n = 7$; low-to medium-grade dysplasia, $n = 2$; oral leukoplakia, $n = 1$; oral candidiasis, $n = 1$; mechanical alterations, $n = 1$). Panendoscopy detected SPMs of the UADT with 87.5% SN (64.6–100%), and 100% SP (100–100%; PPV: 100% [100–100%]; NPV: 99.4% [98.3–100%]).

3.7. PET/CT vs panendoscopy

The comparison of [^{18}F]FDG-PET/CT and panendoscopy revealed no significant differences for SN (100% vs 87.5%; $p = 0.32$), SP (99.4% vs 100%; $p = 0.32$), NPV (100% vs 99.4%; $p = 0.32$), and PPV (88.9% vs 100%; $p = 0.32$) (see also Table 2 for false-positive and false-negative results).

4. Discussion

In this study, [^{18}F]FDG-PET/CT showed an equivalent diagnostic performance when compared with panendoscopy for the detection of secondary malignancies of the UADT, and detected whole-body SPM with high accuracy. The findings suggest that [^{18}F]FDG-PET/CT is a reliable diagnostic alternative for secondary cancer screening in the preoperative staging of OSCC. The role of pandendoscopy relates to the increased risk for SPM of the UADT, and the convenient combination of mucous membrane inspection and immediate biopsy in cases of visible abnormalities (Chow et al., 2009; Metzger et al., 2019; Prabhu et al., 2014; Wang et al., 2011). However, an ongoing epidemiological shift from smoking-related to HPV-associated OSCC reduces the risk for SPM of the UADT in Western populations (Pytynia et al., 2014; Marur et al., 2010) and thus the benefit of routine panendoscopy, while the detrimental aspects of this invasive procedure, with general anesthesia, remain (Noor et al., 2018; Valentin et al., 2021). In contrast, [^{18}F]FDG-PET/CT is a non-invasive, widely available modern imaging modality (Gao et al., 2020). In our study cohort, it detected all the proven SPMs and, additionally, one case of esophageal cancer that was missed by UADT pandendoscopy. Moreover, the number of false-positive results was limited to a single patient. This case turned out to have oropharyngeal low-to medium-grade epithelial dysplasia, which represents a precancerous lesion of OSCC. These findings confirmed the high sensitivity of [^{18}F]FDG-PET/CT for detecting squamous cell carcinoma (Lopez et al., 2018; Linz et al., 2021; Szyszko and Cook, 2018), although the well-known difficulty in differentiating tumor metabolism and inflammatory processes must be mentioned (Wong, 2008). In contrast, pandendoscopy has the advantage of allowing immediate biopsy of suspicious lesions for histopathological analysis, and thus elimination of false-positive results. Furthermore, the assessment of lesion accessibility and resectability can inform therapeutic considerations.

As mentioned earlier, false-negative findings of panendoscopy can occur; one patient in our study had an SPM in the lower esophagus, while two subjects had synchronous lung cancer. Although the latter were not considered for the comparison of both modalities, the mucosal area at risk due to drinking and smoking is larger than that accessible to panendoscopy, and might be further restricted by the individual's anatomy. Another reason to extend the screening for SPMs beyond the coverage of panendoscopy is that alcohol and smoking may also be involved in the carcinogenesis of other malignancies, such as breast, liver, or large intestine cancer (Gandini et al., 2008; Boffetta and Hashibe, 2006). This was also reflected by the results of our study, with 14 out of 22 SPMs (63.6%) being located outside the UADT, of which nine had localizations suggestive of a causal association with the same risk factors (lung, breast, gastrointestinal).

The overall prevalence of SPMs in our cohort was in close agreement with previous studies on head-and-neck oral squamous cell carcinoma patients (Dhooge et al., 1998; Strobel et al., 2009). The increased glucose metabolism of various tumor entities makes [^{18}F]FDG-PET/CT a highly sensitive screening modality for SPM, as shown by the excellent sensitivity within this study cohort. Again, the risk of false-positive findings is present (Wong, 2008), although in our cohort they were caused by premalignant lesions in two cases (i.e. low-to medium-grade intraepithelial dysplasia of the colon and a lymph node metastasis in the parotid gland), and were related to unspecific/reactive [^{18}F]FDG uptake in only one patient.

Some limitations of this study need to be mentioned. The clinical follow-up was shorter than 6 months in 25 patients rated negative for SPM. In order to avoid a prevalence bias, these subjects were not excluded, assuming the same high NPV of [^{18}F]FDG-PET/CT as in patients who were followed-up for more than 6 months. Furthermore, [^{18}F]FDG-PET/CT was performed before endoscopy in 81.9% of enrolled patients, so results of endoscopy cannot be considered independent from PET/CT findings, whereas, conversely, PET/CT ratings were blinded to pandendoscopy. However, a possible effect on the study outcome would be in favor of UADT endoscopy and, therefore, the finding of non-inferiority was not affected.

5. Conclusion

[^{18}F]FDG-PET/CT imaging has the potential to replace routine pandendoscopy in the clinical work-up of patients with newly diagnosed OSCC, and promises to improve patient care by providing highly sensitive whole-body malignancy screening. When malignancy is suspected in [^{18}F]FDG-PET/CT, subsequent

tissue sampling is required Future prospective studies assessing the true reduction in invasive procedures, as well as cost/benefit efficacy, are warranted.

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Declaration of competing interests

The authors certify that there are no conflicts of interest with any financial organization regarding the material discussed in this manuscript.

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