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Value of [18F]FDG PET-CT in the follow-up of surgically treated oral tongue squamous cell carcinoma: single centre cohort analysis on 87 patients

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ABSTRACT

Background: To evaluate the diagnostic performance of [18F]fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) scan in detecting local recurrences in patients with surgically treated oral tongue squamous cell cancer (OTSCC).

Material and methods: Eighty-seven patients who had undergone surgery for OTSCC were monitored clinically and [18F]FDG-PET/CT and magnetic resonance (MR). PET uptakes were classified as functional (Type A), suspicious (Type B), or highly suggestive of local recurrence (Type C). A multidisciplinary team (MDT) evaluated case-by-case the surveillance strategy based on PET uptake.

Results: Fifty-nine patients presented FDG-PET uptake during follow-up: this report was significantly more frequent in patients who received flap reconstruction than in those without (73% vs 50%; p = 0.05). In 13 patients with Type A (n = 1), Type B (n = 9), and Type C (n = 3) uptakes an additional MR was considered preferable and discovered recurrence in 12.PET-CT had 9 true positives, 17 false positives, 71 true negatives, and no false-negative, resulting in sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of 100%, 80.7%, 34.6%, and 100%.

Conclusions: The present results demonstrated a change in diagnostic strategy, as decided by the MDT, in about one-fifth of patients. The results should prompt in designing a rational surveillance schedule in surgically treated OTSCC.

KEY words: tongue carcinoma; PET/CT; [18F]FDG PET/CT; magnetic resonance imaging

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Introduction

The incidence of oral tongue squamous cell carcinoma (OTSCC) is increasing worldwide and, although the peak is seen around the 6th decade, there is evidence of its increasing occurrence among the youngest, presumably due to early initiation of smoking habits and alcohol consumption [1–3]. The therapeutic management of this type of tumour has not changed substantially in the last few decades and mainly relies on surgery alone for early T categories, while multimodal approaches (surgery followed by radiotherapy [RT] or chemoradiotherapy [CRT]) are applied to more advanced lesions. Surgical management of T1-T2 OTSCC consists of surgical excision with wide free margins (ranging between 1 and 2 cm) [4], while in case of larger tumours with a depth of invasion (DOI) superior to 10 mm (staged as T3 or higher according to the 8th Edition of the AJCC-UICC TNM Staging System) [5] some authors systematically perform a compartmental

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hemiglossopelvectomy to improve loco-regional control [6–8]. This surgical technique aims to the "en bloc" removal of the entire hemitongue and floor of mouth compartment along with its connective, neuromuscular, vascular, and lymphatic structures (also known as the T-N tract) connecting it to the adjacent neck levels. As a mandatory step after compartmental resection, a free or pedicled flap reconstruction is required, which frequently produces a certain degree of distortion of the anatomical configuration of the residual hemitongue and floor of the mouth [9, 10].

Computed tomography (CT) and magnetic resonance (MR) are the imaging modalities of choice in the pretreatment setting [11–14], the latter being more sensitive and specific, especially in terms of DOI evaluation [15]. According to the National Comprehensive Cancer Network (NCCN) guidelines [16] [^{18}F]fluorodeoxyglucose positron emission tomography/CT ([^{18}F]FDG-PET/CT) should also be considered in the preoperative evaluation of advanced (III–IV) stages due to a higher probability of unfavourable scenarios such as contralateral and/or lower neck lymph node metastases, and distant disease. During OTSCC follow-up, imaging plays also an essential role, especially in the detection of submucosal relapses, which may be missed at clinical evaluation. However, the algorithm for post-treatment follow-up is still a matter of debate. NCCN guidelines assert that annual repetition of the pretreatment imaging modality may be indicated in areas difficult to be appropriately visualized on clinical examination. As a general rule, the higher contrast resolution of MR is expected to improve the differentiation between muscle, scar, flap and recurrent tumour, as compared to CT [17]. On the other hand, in a large multicentric study, Mehanna et al. [18] demonstrated that [^{18}F]FDG-PET/CT performed 3 months after CRT can replace planned neck dissection in a significant number of patients thanks to its very high negative predictive value (NPV) in assessing nodal metastases. Furthermore, [^{18}F]FDG-PET/CT is unsurpassed to rule out distant metastases.

The role of PET/CT in assessing local control after surgery, however, has not been widely investigated. Müller et al. [19] compared contrast-enhanced CT, unenhanced PET/CT, and the combination of PET and contrast-enhanced CT in the follow-up of a small cohort of oral cancer patients after surgical treatment and flap reconstruction, finding that a combination of techniques gave the best performance in assessing loco-regional control. However, the issue of false-positive uptake in the floor of the mouth caused by different physiological factors should be considered, as recently suggested by Haerle et al. [20].

The aim of this study is therefore to investigate the role of [^{18}F]FDG-PET/CT in monitoring local control in a cohort of patients surgically treated for OTSCC.

Material and methods

The local Institutional Review Board approved this retrospective observational study.

Patients

The clinical and follow-up records of 87 patients (56 men, 31 women; age range, 45–87 years; mean, 67 years) surgically treated for OTSCC in the Department of Otorhinolaryngology-Head and Neck Surgery of a tertiary referral academic Institution between December 2012 and February 2017, were retrospectively reviewed. Patient baseline characteristics, type of treatment delivered, T, N and surgical margins features of the primary tumour are detailed in Table 1.

Follow-up policy

According to the NCCN guidelines [16], the institutional follow-up protocol consisted of clinical examination (every 2 months for the first 2 years, every 4 months for the third year, and then every 6 months until the 5th year) and imaging (PET-CT 3 months after surgery, MR at 9 months, then, alternatively, PET-CT and MR, every 6 months for 2 years and every year until the 5th year).

Patients with suspicious or positive findings at imaging were discussed in the multidisciplinary team (MDT) and submitted to:

— biopsy and PET-CT when a suspect was raised on the routine follow-up MR;
— MR when a suspect was raised on the routine follow-up PET-CT;
— watchful-waiting when the level of a suspect on either MR or PET-CT was considered low after the MDT review.

Only patients for whom PET-CT and MR studies were available and with at least 1 year of follow-up were included in the present study. The Median follow-up time was 36 months (range 12–90 months)

Table 1. Patient baseline characteristics and type of surgery

Age, mean (range)	67 (45–87)
Sex M:F	56:31
Type of surgery	
hemiglossopelvectomy	57 (67%)
transoral partial glossectomy	22 (25%)
anterior pelvectomy	3 (3%)
mandibulectomy	3 (3%)
total glossectomy	2 (2%)
Reconstruction flaps n = 68	
Radial Forearm free flap	29 (42.5%)
Antero Lateral thigh free flap	26 (38%)
Fibula free flap	3 (4.5%)
Lateral Dorsi free flap	3 (4.5%)
Facial artery myo-mucosal flap	1 (1.5%)
Scapular composite osteocutaneous fla	2 (3%)
Tranverse Rectus Myocutaneous free flap	2 (3%)
Iliac crest	2 (3%)
T stage*	
T1	13 (15%)
T2	20 (23%)
T3	39 (45%)
T4a	15 (17%)
N stage*	
N0	48 (55%)
N1	10 (11%)
N2a	2 (2%)
N2b	9 (10%)
N2c	3 (3%)
N3b	15 (17%)

*AJCC cancer staging. 8th ed.

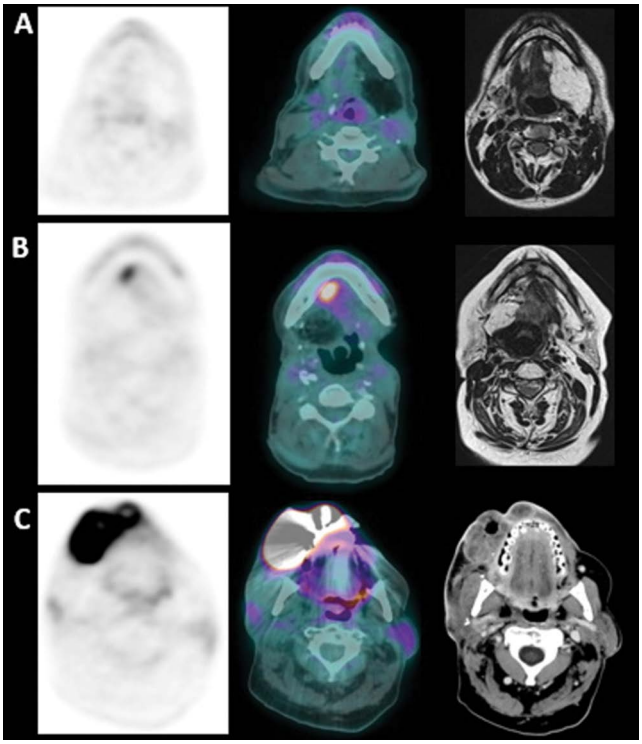

Figure 1. A. A representative case of type-A functional FDG uptake in the oral cavity (axial PET, PET/CT fused and contrast-enhanced images; B. in a 48-year old male treated for left-side tongue cancer. An example of type-B suspicious uptake on the left side in a 66-year old male treated for tongue carcinoma (axial PET, PET/CT fused and T-2 MRI images; C. A case of type-C FDG uptake on the right lip and cheek consistent with relapse (axial PET, PET/CT fused and T-2 MRI images

PET-CT imaging and interpretation

PET-CT was performed after at least 6 hours fasting and with a glucose level lower than 150 mg/dL. The activity of 3.5–4.5 MBq/kg of [^{18}F]FDG was administered intravenously and images were acquired 60 ± 10 minutes after injection of the radiotracer. Imaging was from the vertex to the mid-thigh using a Discovery 690 or a Discovery ST PET-CT system (General Electric Company, Milwaukee, WI, USA) with standard parameters (CT: 80 mA, 120 kV without contrast; 2.5–4 minutes per bed with a PET-step of 15 cm). The reconstruction was performed in a 128 × 128 matrix and with a 60 cm field of view. Patients were instructed to void before imaging acquisition, while no oral or intravenous contrast agents were administered or bowel preparation used for any patient. PET images were analysed visually by two nuclear medicine physicians with more than 15 years of experience in head and neck imaging. Every focal radiotracer uptake different from the physiological distribution and higher than background was regarded as suspicious or highly suggestive of recurrent disease. In case of discordant opinions, a third nuclear medicine physician was consulted. When present, PET uptakes in the oral cavity were classified as functional (Type A), suspicious (Type B), or highly suggestive of neoplastic recurrence (Type C) (Figure 1). In the case of highly suggestive uptakes, MR was used to confirm the diagnosis and possibly stage the relapse.

An MDT composed of radiologists, nuclear medicine physicians, head and neck surgeons, and medical and radiation oncologists evaluated each case with PET radiotracer uptake to decide whether further diagnostic assessment by MR was necessary. The decision was made in consensus and was based on site of uptake, clinical and endoscopic findings, and re-assessment of the fusion CT scans.

MR imaging and interpretation

All the examinations were performed on a 1.5 T scanner (MagnetomAera, Siemens Healthcare, Erlangen, Germany). The MR protocol included: T2-weighted sequences on the axial and coronal planes (and/or sagittal plane, when necessary), T1-weighted, diffusion-weighted imaging (DWI), and post-contrast 3D fat-saturated gradient echo (VIBE) on the axial plane; the latter was also reconstructed on coronal and sagittal planes.

MR studies were reported by a team of five radiologists with extensive experience in head and neck imaging. A recurrence was suspected in the presence of nodular lesion with contrast enhancement and restriction at DWI. T2 hypointense tissue with faint contrast enhancement and no DWI restriction was a scar. T2 hyperintense tissue with variable contrast enhancement and increased water diffusivity at DWI was inflammatory oedema or granulation tissue.

The standard of reference was histology for resected or biopsied lesions and long-term follow-up in the case of negative PET-CT and MR studies.

Statistical analysis

Descriptive statistics were used for patients' characteristics, type of surgery, and type of PET uptake. The diagnostic performance of PET-CT was assessed in terms of sensitivity, specificity, PPV, and NPV. A Chi-square test was used to compare the frequency of PET uptake in patients with and without reconstruction by pedicled or free flaps. The threshold of statistical significance was set at 0.05. Statistical analyses were performed using Medcalc statistic software (Mariakerke, Belgium)

Results

A pathological diagnosis of local recurrence was diagnosed in 9 (10%) patients: in 2 of these (22%), PET-CT identified a subclinical local recurrence during routine follow-up while, in the remaining 7, the recurrence was clinically evident and PET-CT and MR were performed just to confirm and appropriately stage the disease.

A total of 208 PET-CT reports were screened in such a cohort of 87 patients. In 59 (68%) patients FDG uptake in the oral cavity was seen at PET-CT during follow-up; in detail, uptake was present in 49 (73%) patients who received flap reconstruction and in 10 (50%) without ($p = 0.05$). The characteristics of PET uptake are summarized in Table 2.

In 13 (22%) patients with PET uptake in the oral cavity, the MDT agreed to change the routine follow-up schedule by prescribing an additional MR scan. In 12 (92%) cases, MR was triggered by a Type B (9 patients) or Type C (3 patients) uptake. In one patient, MR was performed despite the PET uptake having been classified as Type A, because of clinical suspicion. In one case of Type C uptake, the MDT opted for a surveillance policy due to the patient's poor general condition.

Table 2. Summary of types of PET radiotracer uptake, additional MRI needed and final diagnoses

PET uptake in the oral cavity	59/87 33/59 type A 15/59 type B 11/59 type C
Need for additional MRI	13/87 9/13 type B uptake 3/13 type C uptake 1/13 type A uptake (clinically suspicious recurrence)
Additional MRI results	11/13 negative 7/11 type B 3/11 type C 1/11 type A 1/13 positive: type B 1/13 suspicious: type B
The final diagnosis in patients with additional MRI	**12/13 negative** (negative MRI or suspicious in 1 case) **1/13 recurrence** (positive MRI)

In 12 (92%) cases with PET uptake in the oral cavity, the final diagnosis was no recurrence, while in one a recurrence was confirmed. In 12 cases, MR agreed with the final diagnosis. In one, MR findings were considered suspicious and a short-term follow-up was suggested. Long-term follow up confirmed no recurrence (one false positive) (Table 2). The single case of Type C uptake in which the MDT opted for watchful waiting showed no recurrence on long-term follow-up

Diagnostic performance of PET-CT

When considering no uptake and Type-A uptake as negative findings, and Type B and C uptake as positive findings, PET-CT had 9 true positives, 17 false positives, 71 true negatives, and no false-negative, resulting in a sensitivity, specificity, PPV, and NPV of 100%, 80.7%, 34.6%, and 100%, respectively. If the 7 cases in which PET-CT was used to stage clinically evident recurrences are excluded, PPV drops down to 10.5%, while the other statistical descriptors remain unchanged. In 13 cases, an inconclusive PET triggered an additional MR scan: in 12 of them, the final diagnosis turned out to be negative.

Discussion

In the absence of strict indications, even on international guidelines, the schedule and results of imaging follow-up of OTSCC are variable and largely influenced by factors like the type and number of patients treated, local facilities, geographic, and economic constraints. Clinical surveillance is universally considered the mainstay: in some centres, imaging is performed only in clinically suspicious cases, whereas in others it is fully integrated into the follow-up strategy also of clinically negative patients. In the authors' centre, a scheduled follow-up consisting of clinical examination and alternating [18F]FDG-PET/CT and MR scans has been adopted. The first imaging examination in the follow-up timeline, namely [18F]FDG-PET/CT, is performed 3 months after surgery, as suggested by the international guidelines, to limit false-positive results related to inflammatory changes [16].

While confirming the very high NPV of [18F]FDG-PET/CT in assessing local recurrences, the results of this study raise concerns about the very low PPV caused by the high number of false-positive results. Several PET radioisotope uptakes were reported as physiological (Type A) by nuclear medicine physicians experienced in head and neck imaging and were considered negative for this analysis. The presence of such physiological uptake has been described by Haerle et al. [20], who reported a strong prevalence of FDG uptake at the level of the mylohyoid muscle.

This is probably due to its activation during deglutition which, unlike chewing and talking, is an involuntary movement and thus cannot be completely avoided during the FDG uptake phase.

The largest portion of Type B PET uptakes (15 out of 59) did not determine changes of the standard follow-up protocol after discussion within the MDT: based on free pathological margins on the specimen, absence of symptoms, and unequivocally negative clinical evaluation, no additional study was prescribed. Only one (11%) patient with Type B uptake, further investigated with an additional MR scan, had a pathologically proven diagnosis of recurrence. Moreover, in 4 cases with Type C uptake (3 submitted to an additional MR, and once submitted to watchful waiting policy) recurrences were negative. These results question the possibility to make an accurate distinction between pathological and non-pathological uptakes, even in a tertiary care hospital with well-equipped nuclear medicine and experienced physicians.

In patients with flap reconstruction, among which the incidence of suspicious PET uptakes was significantly higher, the most common site for FDG uptake was seen deep in the floor of the mouth, near the interface between native tissue and flap. Such finding was retrospectively explained as a compensatory hyperactivation of the contralateral extrinsic oral muscles which, in such a distorted and asymmetric anatomy, may retract the flap. In line with these observations, Müller et al. [19] analysed a small cohort of 17 oral cancer patients who underwent surgery followed by reconstruction to demonstrate the added value of contrast-enhanced CT compared with standard FDG-PET with unenhanced CT. They found that by using contrast-enhanced CT, the specificity increased from 58% to 89%. This suggests that contrast-enhanced CT performed simultaneously with PET or as a second step, can improve the interpretation of PET findings and help to reduce the number of false-positive findings. In the authors' protocol, only plain CT was performed simultaneously with PET. CT images were used to assess the presence of solid tissue with mass effect at the uptake site but did not provide information about tissue vascularization. Although the absence of information provided by contrast enhancement may be a limitation of this study, it must be emphasized that simultaneous acquisition of PET and contrast-enhanced CT is not a routine procedure in most centres (for example, it is not feasible with old scanners), and the separate acquisition of contrast-enhanced CT or MR as a second step would impact on logistics and costs.

In this study, state-of-the-art MR proved to be a very accurate technique in clarifying suspicious PET findings and, in most cases, ruled out local relapse. This result does not imply an overall superiority of MR compared to [18F]FDG-PET/CT as the latter is very effective in assessing nodal and distant spread.

The main strength of this study is the relatively large number of homogeneously treated OTSCC patients, all followed by the same MDT with a PET/CT scan, while its main limitation is represented by its retrospective design. Moreover, semiquantitative analysis of PET uptake based on standardized uptake value was not performed given that, so far, no studies are establishing its usefulness in this setting. Despite the above-mentioned limitations, however, the results of this study suggest a more rational use of PET/CT, which might be reserved to patients with a high risk of distant metastases or to those in whom, for neck treatment, a watchful waiting policy is preferred over prophylactic dissection [18].

In times of economic constraints, a compelling evaluation of the real efficacy of a given follow-up policy in cancer patients is mandatory. For what concerns advanced OTSCC, which is currently often treated with all the available therapeutic modalities and reconstructive techniques, an expensive follow-up based on the liberal use of PET-CT (plus clinical examination and MR when needed) seems unjustified in terms of clinical benefits.

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