REVIEW ARTICLE

Role of ^{18}F-FDG PET-CT in head and neck squamous cell carcinoma

Ruolo della PET-CT con ^{18}F-FDG nel carcinoma squamoso del distretto testa-collo

P. CASTALDI[1*], L. LECCISOTTI[1*], F. BUSSU, F. MICCICHÈ[3], V. RUFINI[1]

[1]Institute of Nuclear Medicine, [2]Institute of Otolaryngology, [3] Institute of Radiotherapy, Università Cattolica del Sacro Cuore, Rome, Italy

SUMMARY

The role of PET-CT imaging in head and neck squamous cell carcinoma during pre-treatment staging, radiotherapy planning, treatment response assessment and post-therapy follow-up is reviewed with focus on current evidence, controversial issues and future clinical applications. In staging, the role of ^{18}F-FDG PET-CT is well recognized for detecting cervical nodal involvement as well as for exclusion of distant metastases and synchronous primary tumours. In the evaluation of treatment response, the high negative predictive value of ^{18}F-FDG PET-CT performed at least 8 weeks from the end of radio-chemotherapy allows prevention of unnecessary diagnostic invasive procedures and neck dissection in many patients, with a significant impact on clinical outcome. On the other hand, in this setting, the low positive predictive value due to possible post-radiation inflammation findings requires special care before making a clinical decision. Controversial data are currently available on the role of PET imaging during the course of radio-chemotherapy. The prognostic role of ^{18}F-FDG PET-CT imaging in head and neck squamous cell carcinoma is recently emerging, in addition to the utility of this technique in evaluation of the tumour volume for planning radiation therapy. Additionally, new PET radiopharmaceuticals could provide considerable information on specific tumour characteristics, thus overcoming the limitations of ^{18}F-FDG.

KEY WORDS: ^{18}F-FDG • PET-CT • Carcinoma • Squamous cell • Head and neck tumours

RIASSUNTO

In questa review è analizzato il ruolo della PET-CT nei carcinomi squamosi del distretto testa-collo in fase di stadiazione, nella pianificazione del trattamento radiante, nella valutazione della risposta al trattamento radio-chemioterapico e nel follow-up, tenendo conto dei dati attualmente disponibili, delle questioni controverse e delle future applicazioni cliniche. In fase di stadiazione, è ampiamente riconosciuto il ruolo della PET-CT con ^{18}F-FDG nella valutazione del coinvolgimento linfonodale, nonché nella esclusione della presenza di metastasi a distanza e di tumori primitivi sincroni. Nella valutazione della risposta al trattamento, l'elevato valore predittivo negativo della ^{18}F-FDG PET-CT, effettuata almeno 8 settimane dopo la fine del trattamento radio-chemioterapico, consente di evitare in molti pazienti inutili procedure diagnostiche invasive nonché la dissezione del collo, con conseguente significativo impatto clinico. D'altra parte, in questa fase il basso valore predittivo positivo della metodica, causato dai possibili falsi positivi secondari alla concomitante flogosi post-attinica, deve essere tenuto in particolare considerazione prima di prendere una decisione clinica. Dati controversi sono attualmente disponibili sul ruolo dell'imaging PET durante il trattamento radio-chemioterapico. Negli ultimi anni, è emerso il ruolo prognostico della ^{18}F-FDG PET-CT nei carcinomi a cellule squamose del distretto testa-collo, così come l'utilità di questa tecnica nella valutazione del volume del tumore per la pianificazione del trattamento radiante. Inoltre, nuove prospettive provengono dall'impiego dei nuovi radiofarmaci PET che potrebbero fornire notevoli informazioni su caratteristiche biologiche specifiche del tumore, superando di conseguenza i noti limiti del ^{18}F-FDG.

PAROLE CHIAVE: *^{18}F-FDG • PET-CT • Carcinoma squamoso • Tumori di testa e collo*

Introduction

^{18}F-fluorodeoxy-D-glucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) has become an important diagnostic tool for evaluation of head and neck squamous cell carcinomas (HNSCCs), and is applied in various clinical settings, ranging from pre-treatment staging to radiotherapy planning, treatment response assessment and post-therapy follow-up [1] [2]. Although ^{18}F-FDG is the most commonly used PET tracer for oncologic purposes, its use in HNSCCs suffers from some limitations due to the complex anatomy of this region and the small size of the anatomical structures, as well as the physiological uptake of ^{18}F-FDG in normal

* Paola Castaldi and Lucia Leccisotti equally contributed to this paper sharing the first authorship.

organs that may influence image interpretation. ^{18}F-FDG uptake reflects glucose metabolism and can be observed in several normal tissues with wide variability of the normal pattern, including brain, vocal cords, salivary glands, cervical muscles, lymphoid tissue and brown fat, as well as in various benign tumours, such as common Warthin's tumour [3]. Moreover, the inflammatory processes that occur in patients submitted to surgery or radiotherapy are a frequent cause of false positive PET results, since the activated inflammatory cells show increased ^{18}F-FDG uptake [4][5]. Finally, artefacts related to patient movement or metal dental prostheses may further limit interpretation of PET images, thus requiring non-attenuation corrected PET data evaluation [6][7]. PET-CT scanners currently allow quick and high resolution imaging, and can correlate anatomical location with functional information. The recent introduction of whole-body PET-magnetic resonance imaging (MRI) in clinical practice offers new opportunities for integrated functional-anatomic imaging [8][9]. This review will focus on the use of ^{18}F-FDG PET-CT in various clinical scenarios of HNSCCs with attention to PET radiopharmaceuticals other than ^{18}F-FDG, and the new perspectives offered by PET-MRI.

Pre-treatment staging

Accurate assessment of disease extension is essential to plan the most appropriate treatment, with important implications for patient outcomes. In clinical practice, the conventional diagnostic strategy of HNSCC patients includes detailed physical examination and endoscopy followed by imaging modalities such as neck ultrasound, neck MRI and neck-chest CT for the assessment of disease extent and diagnosis of synchronous second primary tumours (SPTs). Recent studies have shown that ^{18}F-FDG PET-CT is more accurate than conventional staging in HNSCCs, thus resulting in a change of therapeutic management in about one-third of patients [10-12].

Primary tumour assessment
Even though ^{18}F-FDG PET-CT detects primary HNSCC with high sensitivity (> 95%), primary tumour assessment is generally performed with clinical examination, endoscopy and MRI [13][14]. The main limitation of standard PET-CT, if performed with low-dose unenhanced CT, is its inability to accurately assess the site, extent of tumour spread and relationship between the tumour and adjacent structures. This limitation can only partially be overcome by with contrast-enhanced PET-CT [12]. Initial reports on the use of integrated PET-MRI in HNSCCs showed better tumour delineation and good correlation between the metabolic parameters obtained using PET-MRI and PET-CT [9][15]. In patients with cervical lymph node metastasis from a carcinoma of unknown origin, ^{18}F-FDG PET-CT represents a useful diagnostic tool to detect the primary

tumour, with a detection rate of 25-38.5% [16-18]. Future studies with PET-MRI will determine whether the technique can improve the detection rate of occult primary head and neck tumours [9].

Cervical lymph node assessment
The main indication of ^{18}F-FDG PET-CT in newly diagnosed HNSCCs is detection of cervical lymph node involvement, which is one of the most important prognostic factors. With regards to node involvement, the main limitation of all imaging techniques is the high rate of false negative results, staged as cN0, which turn out to be pN+ after neck dissection. Sentinel lymph node biopsy has several limitations that limit its routine clinical employment in the head and neck [19].
This awareness is the basis of the indications for prophylactic neck treatment by international guidelines [20]; however, this approach may lead clinicians to unnecessarily treat a number of necks with relevant morbidity. Data from the literature support the superiority of PET-CT over morphologic imaging in detecting lymph node involvement [12]. A clear advantage of functional imaging is that an alteration in the size or structure of lymph nodes is not required to detect lesions (Fig. 1). However, it must be stressed that small lymph node lesions may be missed (possible false negative results), and that inflamed lymph nodes may take up the tracer (possible false positive results). In particular, the finite spatial resolution of a PET-CT scanner (4-6 mm) limits its sensitivity for microscopic disease that is detectable only by histopathology after neck dissection. For this reason, a negative ^{18}F-FDG PET-CT scan for lymph node involvement does not justify a "wait and see" approach in all cases; the decision to perform neck dissection in patients with negative morphological and functional imaging still relies essentially on the evaluation of risk factors and tumour characteristics such as T-stage and histopathological features [12][21][22]. Preliminary data with PET-MRI report good sensitivity (85%) and specificity (92%) for nodal staging, higher than PET-CT, but with the same limitation of under-staging a certain number of patients with micrometastases [9].

Distant metastasis assessment
The screening for distant metastases is important in patients with advanced disease, especially with nodal involvement, and in naso- and hypopharyngeal carcinomas. The most common sites are lungs, bone and liver (Fig. 2). In this context, a higher accuracy of ^{18}F-FDG PET-CT than CT for detection of distant metastasis has been clearly demonstrated, except for small lung lesions. Moreover, in approximately 13% of cases the improvement in detection of distant lesions leads to a change of management with important consequences for patient survival [23-25].
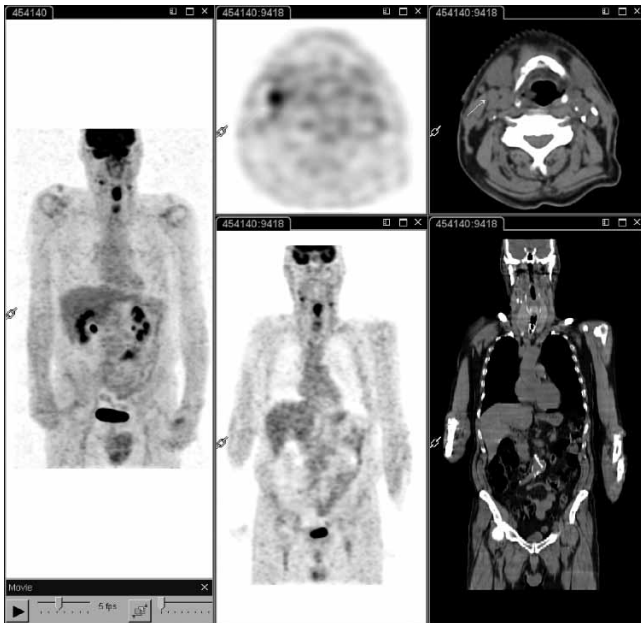
Second primary tumour assessment

Second primary tumours (SPTs) can occur in 5-10% of HNSCC patients and are more frequent in the head and neck region, oesophagus and lungs (Fig. 3). SPTs are no-
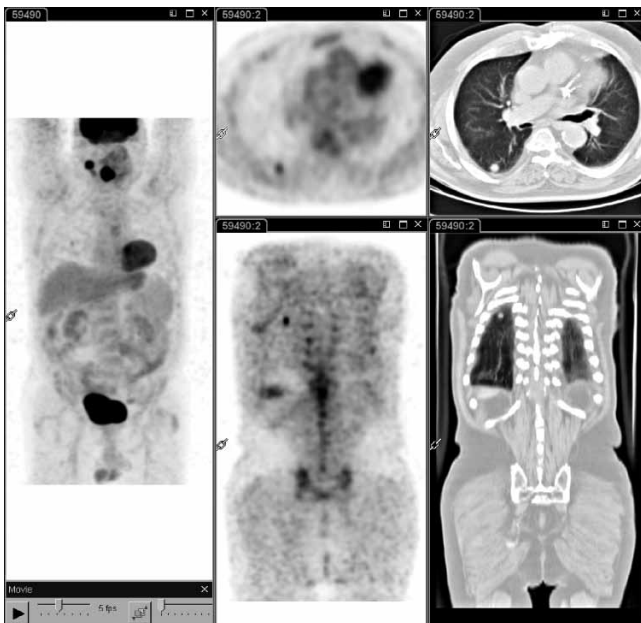

Fig. 1 . 18F-FDG PET-CT performed at staging in a patient with laryngeal carcinoma. Whole body PET-CT (left panel) shows intense 18F-FDG uptake of the primary tumour as well as two lateral cervical nodes, one of which on the right side demonstrates a short axis less than 10 mm in the transaxial plane of CT (middle and right panels; white arrow). These findings have both prognostic and therapeutic implications: the patient is candidate for radio-chemotherapy with bilateral cervical nodal irradiation.

tably the first cause of death with a decisive impact on overall survival rates of early stage HNSCC patients [26]. 18F-FDG PET-CT is an accurate method to detect second primaries, with a high negative predictive value and a relatively lower positive predictive value as inflammation and benign hyperplasia in the head and neck region, and benign or precancerous intestinal polyps can result in false positive PET findings [12 27]. Nonetheless, PET-CT, by detecting second primary lesions, can impact both the treatment choice and, most of all, the overall survival of early stage HNSCCs that already have a very good disease specific survival [28].

## Prognostic significance of pre-treatment PET-CT

Despite the substantial changes in treatment strategies over the past two decades, disease control in HNSCCs is still heterogeneous, since patients with similar clinico-pathological features undergoing the same treatment may differ widely in response to treatment and prognosis [29]. Thus, the identification of further prognostic factors along with TNM staging could help to identify high-risk patients who respond poorly to conventional therapy, and could benefit from intensification or switch of treatment modality. In this context, the prognostic value of various 18F-FDG pre-treatment parameters including maximal and mean standardized uptake value (SUV_{max} and SUV_{mean}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) is under investigation [30]. The utility of these parameters has been evaluated with conflicting results [30-32]. The main criticism is the variable behaviour of

Fig. 2. 18F-FDG PET-CT performed at staging in a patient with laryngeal carcinoma. Whole body PET-CT (left panel) shows intense 18F-FDG uptake of the primary tumour and a right lateral cervical lymphadenopathy. In addition, a round solid pulmonary nodule with high 18F-FDG uptake is evident in the apical segment of the lower lobe of the right lung, suggesting a metastatic lesion (middle and right panels).
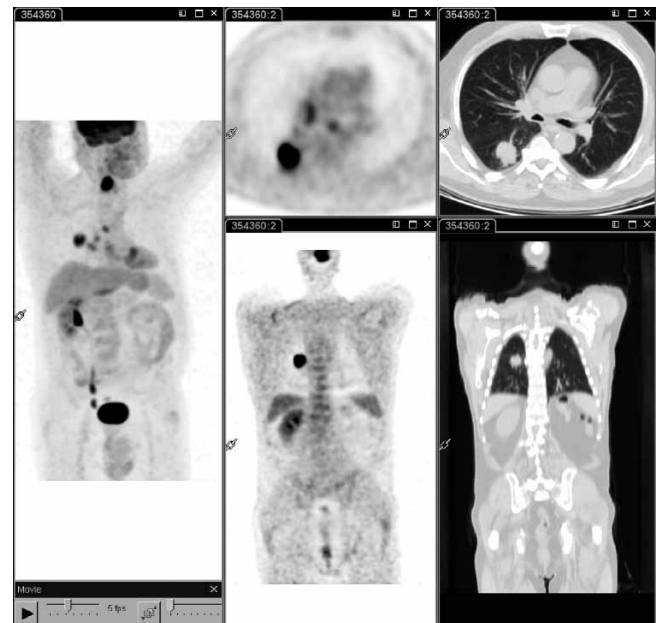
Fig. 3. 18F-FDG PET-CT performed at staging in a patient with laryngeal carcinoma. Whole body PET-CT (left panel) shows intense 18F-FDG uptake in the primary tumour as well as in a lung mass located in the apical segment of the right lower lobe; mediastinal lymph nodes with increased activity are also associated (left and middle panels). These findings suggest a second primary tumour.

the different metabolic parameters, each showing potential pitfalls in terms of calculation and reproducibility.

Radiotherapy planning

Molecular imaging with ^{18}F-FDG provides a unique opportunity for radiation treatment planning in HNSCCs in terms of selection and delineation of target volumes as well as dose planning [33]. Looking at *target volume selection*, the added value of ^{18}F-FDG PET-CT is identification of the occult primary tumour in patients with cervical lymph node metastasis with the possibility of decreasing the radiotherapy target volume, and consequently the acute and late side effects of radiotherapy, as well as detection of distant metastases with high sensitivity [16-18]. For accurate *delineation of target volumes and organs at risk*, the goal of using molecular imaging is to optimize the treatment plan thanks to its superior sensitivity and contrast resolution over anatomical imaging techniques [34]. In the initial experience of Daisne et al., gross tumour volume (GTV) delineated from ^{18}F-FDG PET was closest to the pathologic GTV from surgical specimens, and significantly smaller than GTV delineated by CT and MRI [35]. However, subsequent data were less consistent [34]. The main drawback is the lack of a standardized method for functional volume segmentation, which heavily influences the volume and shape of the resulting GTV [34-36]. Further applications of ^{18}F-FDG PET-CT for radiotherapy planning are under clinical investigation, and include the possibility of directing dose escalation to ^{18}F-FDG-avid sub-volumes of the tumour as well as adapting the radiotherapy plan during treatment thanks to the information on the biological and molecular tumour changes induced by therapy [34-37]. Moreover, the possibility of targeting radiation-resistant regions within the tumour on the basis of biologic information of molecular imaging is under investigation, for example the identification of the hypoxic volume within the GTV by using hypoxia-related PET tracers to deliver higher doses to hypoxic cells [38].

Treatment response assessment

An accurate evaluation of response is essential in the management of patients with HNSCC treated with radio-chemotherapy. ^{18}F-FDG PET-CT is commonly used to assess treatment response, since it identifies viable tumour within residual masses, thus overcoming the known limitations of morphological imaging modalities [39-42]. In particular, ^{18}F-FDG PET-CT has a high negative predictive value (> 95%) that can spare the patient of unnecessary diagnostic invasive procedures and neck dissection in many cases (about 75%), with a significant impact on patient outcome and morbidity, and a low risk of under-treatment (about 2%) [12 41]. Several studies have demonstrated that in patients with a complete metabolic response neck dissection can be avoided, even in the presence of residual node abnormalities by conventional imaging [43 44] (Fig. 4); considering the additional morbidity of neck dissections in irradiated necks, this approach can be considered a relevant achievement in head and neck oncology. Unfortunately, the positive predictive value is low, due to the high number of false positive results related to post-radiation inflammation [45]. To reduce the number of false positive findings, it is crucial to accurately select high risk patients (i.e. HPV negative), to know radiation treatment volume and choose the timing for PET-CT post-treatment assessment. There is general consensus to set the optimum time for ^{18}F-FDG PET-CT at 8-12 weeks, thereby reducing both false positive and false negative findings, while the the latter is related to the presence of undetectable microscopic residual disease. ^{18}F-FDG PET-CT was considered to be useful in selective cases to assess response to induction treatment in patients enrolled in larynx preservation trials to assess the risks and benefits of treatment [46]. Correlating the post-treatment metabolic response with clinical outcomes, the data indicate that ^{18}F-FDG PET-CT performed at the end of radio-chemotherapy provides prognostic information, as it strongly correlates with local and regional control and survival. However, controversial results are reported regarding the role of PET-CT performed early during treatment [5 29 47 48]. In a series of 26 patients treated with radio-chemotherapy for HNSCC, our group did not find a significant correlation between the "early" changes of FDG uptake in
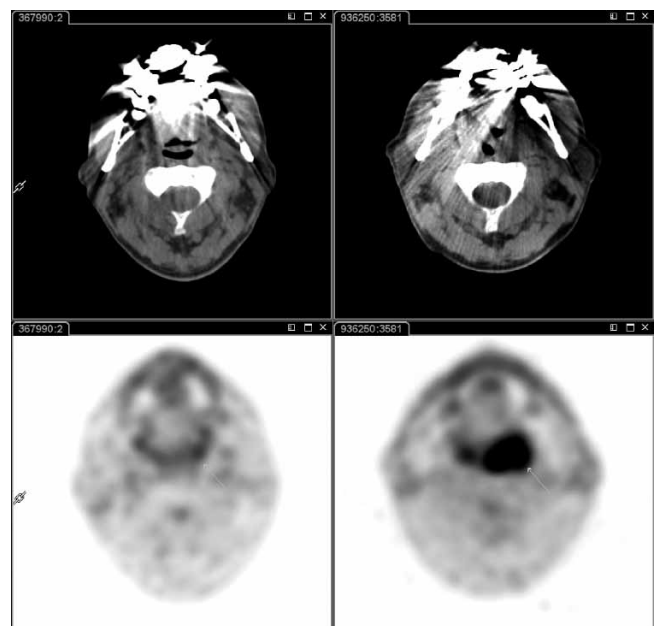
Fig. 4. ^{18}F-FDG PET-CT at baseline (right panel) and 8 weeks after the end of radio-chemotherapy (left panel). At baseline, intense ^{18}F-FDG uptake is evident in the left oropharyngeal region (white arrow); after radio-chemotherapy, ^{18}F-FDG uptake was no longer visible, suggesting complete metabolic response to treatment.

the primary tumour and lymph node involvement and local and regional control, respectively, or between the overall metabolic response at PET-CT and clinical outcome [29]. Our results on the unreliability of 18F-FDG PET-CT for the early assessment of response to radio-chemotherapy in HNSCC are in contrast with the recent study by Hentschel et al. who showed that a decrease of 50% or more of SUVmax from the beginning (0 Gy) to week 1 or 2 of treatment (10 or 20 Gy) is a potential prognostic marker for patients with HNSCC [48].

Post-therapy follow-up

Despite initial aggressive treatment, loco-regional or distant recurrence can occur in HNSCC patients, especially within the first year; early detection of loco-regional disease may improve survival by increasing the effectiveness of salvage therapy, which is the most effective modality in this setting; in contrast, the real advantage of early detection of distant metastases in asymptomatic patients is still unclear [12]. At morphologic imaging and physical examination, detection of loco-regional recurrence or residual disease may be difficult due to the presence of treatment-induced changes that could not be differentiated from residual/recurrent disease. Several studies involving both patients with suspected recurrence and those without clinical symptoms have demonstrated that PET-CT imaging is superior to physical examination and conventional imaging to detect recurrent loco-regional disease, as well as distant lesions and metachronous primary tumours [42 49-53]. For patients with a PET positive result, biopsy is recommended due to a relatively high false positive rate related to post-treatment inflammation [12]. A recent systematic review and meta-analysis of studies assessing the diagnostic performance of 18F-FDG PET and PET-CT in response assessment and surveillance imaging of HNSCC patients reported a high NPV (> 94%) and a suboptimal PPV (< 60%) both for the primary site and cervical nodes [54].

PET radiopharmaceuticals other than 18F-FDG

It is well known that 18F-FDG is not a specific marker of malignancy, since 18F-FDG uptake in normal or active inflammatory tissues may occur, thus limiting image interpretation. To overcome these drawbacks, more specific PET tracers reflecting specific biologic tumour characteristics may be useful to differentiate tumours by inflammation; these tracers, which are under clinical investigation, include 18F-fluorothymidine for DNA synthesis (18F-FLT), 18F-fluoroethyl-L-thyrosine (18F-FET) and L-methyl-11C-methionine (11C-MET) for amino acid uptake and protein synthesis [55-57]. Among these tracers, 18F-FLT seems to be the most promising because of its specificity [33]. Moreover, tracers that allow *in vivo* detection and quantification of tumour hypoxia such as 18F-fluoromisonidazole (18F-FMISO) or 18F-fluoroazomycin-arabinofluranoside (18F-FAZA) and 18F-3-[F]fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3,-triazol-1-yl)-propan-1-ol (18F-HX4) are of growing interest; in fact, hypoxia is not a rare event in HNSCCs with important consequences on treatment response since hypoxic cells are more resistant to the cytotoxic effects of ionizing radiation [55 57-59] (Table I).

Our attitude in clinical practice

In our Centre, we usually perform pre-treatment 18F-FDG PET-CT evaluation in all patients with HNSCC who are candidates for primary irradiation (± chemotherapy), with the exception of early glottic lesions, and in all cases with high risk of distant metastases (hypopharyngeal and rhinopharyngeal primary tumours, cN3 cases). The most relevant clinical information coming from this pre-treatment scan is refinement of neck staging and evaluation of distant metastases or second primaries; both inquiries have a substantial impact on treatment planning. We also

Table I. PET radiopharmaceuticals other than 18F-FDG.

PET Radiopharmaceutical	Molecular Target	Indications	Clinical application	References
18F-FLT	Proliferation	Staging-restaging Response evaluation Adaptive radiotherapy	Experimental	56, 60-62
18F-FET 11C-MET	Protein synthesis	Staging-restaging Adaptive radiotherapy	Experimental Early clinical	63, 64
18F-FMISO 18F-FAZA 18F-HX4	Hypoxia	Staging Response Evaluation Adaptive radiotherapy	Experimental	59, 65-70
68Zr/124I-anti EGFR	Targeting of EGFR	Targeted therapies	Experimental	71
18F-Annexin	Apoptosis	Response evaluation	Experimental	72
18F-Galacto-RGD	Neoangiogenesis	Response evaluation Targeted therapies	Experimental	73

FLT = fluorothymidine; FET = fluoroethyl-L-thyrosine; MET = L-methyl-methionine; MISO = fluoromisonidazole; FAZA = fluoroazomycin-arabinofluranoside; HX4 = 3-[F]fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3,-triazol-1-yl)-propan-1-ol; EGFR = epidermal growth factor receptor; RGD = arginine-glycine-aspartate.

prescribe ^{18}F-FDG PET-CT in patients with cervical metastases and no primary site at conventional assessment. For treatment response evaluation, we usually perform a PET-CT scan 8-12 weeks after the end of radio-chemotherapy. Patients with a complete metabolic response are referred to periodic follow-up, whereas patients showing a positive scan after treatment undergo subsequent evaluation including, when indicated, biopsy.

During follow-up, especially in the first year when most recurrences occur, we perform ^{18}F-FDG PET-CT when a recurrence is suspected and a confirmatory biopsy would be associated with significant morbidity, as in case of neck node enlargement, tissue deep under a reconstructive flap, significant persistent post-irradiation toxicity and, in general, difficult exposure requiring general anaesthesia for an adequate biopsy sampling.

Conclusions

^{18}F-FDG PET-CT is particularly useful for staging, restaging and radiotherapy planning as well as for assessment of treatment response in HNSCC patients, due to its superior accuracy over clinical examination and conventional anatomic imaging. The main limitations, especially in the post-treatment setting, are possible false positive results due to inflammation and the inability to detect microscopic disease. In the future, new tracers other than ^{18}F-FDG, as well as PET-MRI imaging, will provide clear advantages in several clinical scenarios.

References

1   Oyen WJ, Marres HA, Kaanders JH. *Progress in nuclear medicine procedures in head and neck oncology.* Q J Nucl Med Mol Imaging 2011; 55:485-6.

2   Corvò R. *Evidence-based radiation oncology in head and neck squamous cell carcinoma.* Radiother Oncol 2007;85:156-70.

3   Schwarz E, Hurlimann S, Soyka JD, et al. *FDG-positive Warthin's tumors in cervical lymph nodes mimicking metastases in tongue cancer staging with PET/CT.* Otolaryngol Head Neck Surg 2009;140:134-5.

4   Kubota R, Yamada S, Kubota K, et al. *Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography.* J Nucl Med 1992;33:1972-80.

5   Hentschel M, Appold S, Schreiber A, et al. *Serial FDG-PET on patients with head and neck cancer: implications for radiation therapy.* Int J Radiat Biol 2009;85:796-804.

6   Wong RJ. *Current status of FDG-PET for head and neck cancer.* J Surg Oncol 2008;97:649-52.

7   Burrell SC, Van den Abbeele AD. *2-Deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography of the head and neck: an atlas of normal uptake and variants.* Mol Imaging Biol 2005;7:244-56.

8   Loeffelbein DJ, Souvatzoglou M, Wankerl V, et al. *PET-MRI fusion in head-and-neck oncology: current status and implications for hybrid PET/MRI.* J Oral Maxillofac Surg 2012;70:473-83.

9   Buchbender C, Heusner TA, Lauenstein TC, et al. *Oncologic PET/MRI, part 1: tumors of the brain, head and neck, chest, abdomen, and pelvis.* J Nucl Med 2012;53:928-38.

10 Czernin J, Allen-Auerbach M, Schelbert HR. *Improvements in cancer staging with PET/CT: literature-based evidence as of September 2006.* J Nucl Med 2007;48(Suppl 1):78S-88S.

11 Connell CA, Corry J, Milner AD, et al. *Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma.* Head Neck 2007;29:986-95.

12 Mak D, Corry J, Lau E, et al. *Role of FDG-PET/CT in staging and follow-up of head and neck squamous cell carcinoma.* Q J Nucl Med Mol Imaging 2011;55:487-99.

13 Roh JL, Yeo NK, Kim JS, et al. *Utility of 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography and positron emission tomography/computed tomography imaging in the preoperative staging of head and neck squamous cell carcinoma.* Oral Oncol 2007;43:887-93.

14 Baek CH, Chung MK, Son YI, et al. *Tumor volume assessment by 18F-FDG PET/CT in patients with oral cavity cancer with dental artifacts on CT or MR images.* J Nucl Med 2008;49:1422-8.

15 Boss A, Stegger L, Bisdas S, et al. *Feasibility of simultaneous PET/MR imaging in the head and upper neck area.* Eur Radiol 2011;21:1439-46.

16 Rusthoven KE, Koshy M, Paulino AC. *The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor.* Cancer 2004;101:2641-9.

17 Johansen J, Petersen H, Godballe C, et al. *FDG-PET/CT for detection of the unknown primary head and neck tumor.* Q J Nucl Med Mol Imaging 2011;55:500-8.

18 Wong WL, Sonoda LI, Gharpurhy A, et al. *18F-fluorodeoxyglucose positron emission tomography/computed tomography in the assessment of occult primary head and neck cancers--an audit and review of published studies.* Clin Oncol (R Coll Radiol) 2012;24:190-5.

19 Antonio JK, Santini S, Politi D, et al. *Sentinel lymph node biopsy in squamous cell carcinoma of the head and neck: 10 years of experience.* Acta Otorhinolaryngol Ital 2012;32:18-25.

20 Pfister DG, Ang KK, Brizel DM, et al. *Head and neck cancers.* J Natl Compr Canc Netw 2011;9:596-650.

21 Schoder H, Carlson DL, Kraus DH, et al. *18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI.* J Nucl Med 2006;47:755-62.

22 Stoeckli SJ, Steinert H, Pfaltz M, et al. *Is there a role for positron emission tomography with 18F-fluorodeoxyglucose in the initial staging of nodal negative oral and oropharyngeal squamous cell carcinoma.* Head Neck 2002;24:345-9.

23 Brouwer J, Senft A, de Bree R, et al. *Screening for distant metastases in patients with head and neck cancer: is there a role for (18)FDG-PET?* Oral Oncol 2006;42:275-80.

24. Ng SH, Chan SC, Liao CT, et al. *Distant metastases and synchronous second primary tumors in patients with newly diagnosed oropharyngeal and hypopharyngeal carcinomas: evaluation of (18)F-FDG PET and extended-field multi-detector row CT.* Neuroradiology 2008;50:969-79.

25. Lonneux M, Hamoir M, Reychler H, et al. *Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study.* J Clin Oncol 2010;28:1190-5.

26. Narayana A, Vaughan AT, Fisher SG, et al. *Second primary tumors in laryngeal cancer: results of long-term follow-up.* Int J Radiat Oncol Biol Phys 1998;42:557-62.

27. Strobel K, Haerle SK, Stoeckli SJ, et al. *Head and neck squamous cell carcinoma (HNSCC)--detection of synchronous primaries with (18)F-FDG-PET/CT.* Eur J Nucl Med Mol Imaging 2009;36:919-27.

28. Dinapoli N, Parrilla C, Galli J, et al. *Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population.* Strahlenther Onkol 2010;186:607-13.

29. Castaldi P, Rufini V, Bussu F, et al. *Can "early" and "late" 18F-FDG PET-CT be used as prognostic factors for the clinical outcome of patients with locally advanced head and neck cancer treated with radio-chemotherapy?* Radiother Oncol 2012;103:63-8.

30. Higgins KA, Hoang JK, Roach MC, et al. *Analysis of pretreatment FDG-PET SUV parameters in head-and-neck cancer: tumor SUVmean has superior prognostic value.* Int J Radiat Oncol Biol Phys 2012;82:548-53.

31. Xie P, Li M, Zhao H, et al. *18F-FDG PET or PET-CT to evaluate prognosis for head and neck cancer: a meta-analysis.* J Cancer Res Clin Oncol 2011;137:1085-93.

32. Schinagl DA, Span PN, Oyen WJ, et al. *Can FDG PET predict radiation treatment outcome in head and neck cancer? Results of a prospective study.* Eur J Nucl Med Mol Imaging 2011;38:1449-58.

33. Gregoire V, Chiti A. *Molecular imaging in radiotherapy planning for head and neck tumors.* J Nucl Med 2011; 52:331-334

34. Arens AI, Troost EG, Schinagl D, et al. *FDG-PET/CT in radiation treatment planning of head and neck squamous cell carcinoma.* Q J Nucl Med Mol Imaging 2011;55:521-8.

35. Daisne JF, Duprez T, Weynand B, et al. *Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen.* Radiology 2004;233:93-100.

36. Schinagl DA, Vogel WV, Hoffmann AL, et al. *Comparison of five segmentation tools for 18F-fluoro-deoxy-glucose-positron emission tomography-based target volume definition in head and neck cancer.* Int J Radiat Oncol Biol Phys 2007;69:1282-9.

37. Troost EG, Schinagl DA, Bussink J, et al. *Clinical evidence on PET-CT for radiation therapy planning in head and neck tumours.* Radiother Oncol 2010;96:328-34.

38. Lee NY, Mechalakos JG, Nehmeh S, et al. *Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study.* Int J Radiat Oncol Biol Phys 2008;70:2-13.

39. Kao J, Vu HL, Genden EM, et al. *The diagnostic and prognostic utility of positron emission tomography/computed tomography-based follow-up after radiotherapy for head and neck cancer.* Cancer 2009;115:4586-94.

40. Passero VA, Branstetter BF, Shuai Y, et al. *Response assessment by combined PET-CT scan versus CT scan alone using RECIST in patients with locally advanced head and neck cancer treated with chemoradiotherapy.* Ann Oncol 2010; 21:2278-83.

41. Weber WA. *Assessing tumor response to therapy.* J Nucl Med 2009;50(Suppl 1):1S-10S.

42. Isles MG, McConkey C, Mehanna HM. *A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy.* Clin Otolaryngol 2008;33:210-22.

43. Ware RE, Matthews JP, Hicks RJ, et al. *Usefulness of fluorine-18 fluorodeoxyglucose positron emission tomography in patients with a residual structural abnormality after definitive treatment for squamous cell carcinoma of the head and neck.* Head Neck 2004;26:1008-17.

44. Porceddu SV, Pryor DI, Burmeister E, et al. *Results of a prospective study of positron emission tomography-directed management of residual nodal abnormalities in node-positive head and neck cancer after definitive radiotherapy with or without systemic therapy.* Head Neck 2011;33:1675-82.

45. Yao M, Smith RB, Hoffman HT, et al. *Clinical significance of postradiotherapy [18F]-fluorodeoxyglucose positron emission tomography imaging in management of head-and-neck cancer-a long-term outcome report.* Int J Radiat Oncol Biol Phys 2009;74:9-14.

46. Lefebvre JL, Ang KK. *Larynx preservation clinical trial design: key issues and recommendations-a consensus panel summary.* Int J Radiat Oncol Biol Phys 2009;73:1293-303.

47. Farrag A, Ceulemans G, Voordeckers M, et al. *Can 18F-FDG-PET response during radiotherapy be used as a predictive factor for the outcome of head and neck cancer patients?* Nucl Med Commun 2010;31:495-501.

48. Hentschel M, Appold S, Schreiber A, et al. *Early FDG PET at 10 or 20 Gy under chemoradiotherapy is prognostic for locoregional control and overall survival in patients with head and neck cancer.* Eur J Nucl Med Mol Imaging 2011;38:1203-11.

49. Abgral R, Querellou S, Potard G, et al. *Does 18F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up?* J Nucl Med 2009;50:24-9.

50. Liu T, Xu W, Yan WL, et al. *FDG-PET, CT, MRI for diagnosis of local residual or recurrent nasopharyngeal carcinoma, which one is the best? A systematic review.* Radiother Oncol 2007;85:327-35.

51. Lowe VJ, Boyd JH, Dunphy FR, et al. *Surveillance for recurrent head and neck cancer using positron emission tomography.* J Clin Oncol 2000;18:651-8.

52. Krabbe CA, Pruim J, Dijkstra PU, et al. *18F-FDG PET as a routine posttreatment surveillance tool in oral and oropharyngeal squamous cell carcinoma: a prospective study.* J Nucl Med 2009;50:1940-7.

53. Terhaard CH, Bongers V, van Rijk PP, et al. *F-18-fluoro-deoxy-glucose positron-emission tomography scanning in de-*

tection of local recurrence after radiotherapy for laryngeal/pharyngeal cancer. Head Neck 2001;23:933-41.

54 Gupta T, Master Z, Kannan S, et al. *Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis.* Eur J Nucl Med Mol Imaging 2011;38:2083-95.

55 Bussink J, van Herpen CM, Kaanders JH, et al. *PET-CT for response assessment and treatment adaptation in head and neck cancer.* Lancet Oncol 2010;11:661-9.

56 Troost EG, Bussink J, Hoffmann AL, et al. *18F-FLT PET/CT for early response monitoring and dose escalation in oropharyngeal tumors.* J Nucl Med 2010;51:866-74.

57 Gornik G, Weber W. *New tracers beyond FDG in head and neck oncology.* Q J Nucl Med Mol Imaging 2011;55:529-40.

58 van Loon J, Janssen MH, Ollers M, et al. *PET imaging of hypoxia using [18F]HX4: a phase I trial.* Eur J Nucl Med Mol Imaging 2010;37:1663-8.

59 Chen L, Zhang Z, Kolb HC, et al. *18F-HX4 hypoxia imaging with PET/CT in head and neck cancer: a comparison with 18F-FMISO.* Nucl Med Commun 2012;33:1096-102.

60 Hoshikawa H, Nishiyama Y, Kishino T, et al. *Comparison of FLT-PET and FDG-PET for visualization of head and neck squamous cell cancers.* Mol Imaging Biol 2011;13:172-7.

61 Hoshikawa H, Kishino T, Mori T, et al. *Comparison of (18) F-FLT PET and (18) F-FDG PET for detection of cervical lymph node metastases in head and neck cancers.* Acta Otolaryngol 2012;132:1347-54.

62 Kishino T, Hoshikawa H, Nishiyama Y, et al. *Usefulness of 3'-deoxy-3'-18F-fluorothymidine PET for predicting early response to chemoradiotherapy in head and neck cancer.* J Nucl Med 2012;53:1521-7.

63 Haerle SK, Fischer DR, Schmid DT, et al. *18F-FET PET/CT in advanced head and neck squamous cell carcinoma: an intra-individual comparison with 18F-FDG PET/CT.* Mol Imaging Biol 2011;13:1036-42.

64 Hasebe M, Yoshikawa K, Ohashi S, et al. *A study on the prognostic evaluation of carbon ion radiotherapy for head and neck adenocarcinoma with C-11 methionine PET.* Mol Imaging Biol 2010;12:554-62.

65 Zygogianni A, Kyrgias G, Kouvaris J, et al. *A new role of PET/CT for target delineation for radiotherapy treatment planning for head and neck carcinomas.* Hell J Nucl Med 2012;15:139-43.

66 Hendrickson K, Phillips M, Smith W, et al. *Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: potential for guiding intensity modulated radiation therapy in overcoming hypoxia-induced treatment resistance.* Radiother Oncol 2011;101:369-75.

67 Bowen SR, van der Kogel AJ, Nordsmark M, et al. *Characterization of positron emission tomography hypoxia tracer uptake and tissue oxygenation via electrochemical modeling.* Nucl Med Biol 2011;38:771-80.

68 Kikuchi M, Yamane T, Shinohara S, et al. *18F-fluoromisonidazole positron emission tomography before treatment is a predictor of radioth*erapy *outcome and survival prognosis in patients with head and neck squamous cell carcinoma.* Ann Nucl Med 2011;25:625-33.

69 Yamane T, Kikuchi M, Shinohara S, et al. *Reduction of [(18) F]fluoromisonidazole uptake after neoadjuvant chemotherapy for head and neck squamous cell carcinoma.* Mol Imaging Biol 2011;13:227-31.

70 Wang W, Lee NY, Georgi JC, et al. *Pharmacokinetic analysis of hypoxia (18)F-fluoromisonidazole dynamic PET in head and neck cancer.* J Nucl Med 2010;51:37-45.

71 Niu G, Li Z, Xie J, et al. *PET of EGFR antibody distribution in head and neck squamous cell carcinoma models.* J Nucl Med 2009;50:1116-23.

72 Hu S, Kiesewetter DO, Zhu L, et al. *Longitudinal PET imaging of doxorubicin-induced cell death with (18)F-Annexin V.* Mol Imaging Biol 2012;14:762-70.

73 Beer AJ, Grosu AL, Carlsen J, et al. *18Fgalacto-RGD positron emission tomography for imaging of alphavbeta3 expression on the neovasculature in patients with squamous cell carcinoma of the head and neck.* Clin Cancer Res 2007;13:6610-6.

Address for correspondence: Vittoria Rufini, Istituto di Medicina Nucleare, Università Cattolica del Sacro Cuore, l.go A. Gemelli 8, 00168 Roma, Italy. Tel. +39 06 30154978. Fax +39 06 3058185. E-mail: v.rufini@rm.unicatt.it