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The Role of PET/CT with ^{18}F-FDG in the Assessment of Therapeutic Response of Head and Neck Cancer

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Abstract
Purpose of Review To make a brief review on the pre-treatment evaluation of head and neck squamous cell carcinoma (HNSCC) with positron emission tomography/computed tomography with 18F-Fluoro-deoxy-glucose (^{18}F-FDG PET/CT) and to discuss the use of this method after treatment, with emphasis on the evaluation of therapeutic response.
Recent Findings The ^{18}F-FDG PET/CT pre-treatment evaluation is recommended at III–IV staging to determine metastasis foci. At post-evaluation, the use of ^{18}F-FDG PET/CT is very important to confirm the therapeutic response based on its high negative predictive value (NPV), mostly when it is made after 12 weeks the last radiotherapy dose. Specific imaging criteria aid in the detection of active tumor lesions. Moreover, the ^{18}F-FDG PET/CT can determine early failure treatment and overall survival and progression-free survival. Recently, the ^{18}F-FDG PET/CT surveillance was showed an important tool to follow up HNSCC patients with stage N2 or N3 disease.
Summary The ^{18}F-FDG PET/CT is essential in the management of HNSCC, mainly at post-treatment evaluation. Its findings can determine a complementary therapy or even avoid an aggressive and unnecessary approach. So, careful analysis using imaging interpretation criteria has been central to an accurate assessment of HNSCC patients.

Keywords Head · Neck · Cancer · Therapy · PET · ^{18}F-fluoro-deoxy-glucose

Abbreviations

CT	Computed tomography
FDG	^{18}F-Fluoro-deoxy-glucose
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
PET	Positron emission tomography
SUV	Standard uptake value

Introduction

Head and neck cancer (HNC) ranks as the 7th most common cancer, with a significant increase in the global incidence over the past decade [1]. Head and neck squamous cell carcinoma (HNSCC) is the most common form of HNC [2, 3], accounting for about 3.2% of all malignancies [4•]. More than 600,000 cases of HNC cancers occur

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worldwide, with 300,000 patients dying of the disease each year [5]. The incidence varies concerning primary site onset, as well as geographic and ethnic populations [6]. More than 90% are squamous cell carcinomas, and the disease typically appears in the oropharynx, oral cavity, hypopharynx, or larynx [3]. HNSCC represents the third common cause of cancer death [3]. Mortality and morbidity associated with these malignancies remain high, which causes an impact on the quality of life, with a 5-year survival rate about 50% when there are lymph nodes metastases [3].

The development of HNSCC is multifactorial, resulting from the interaction of both environmental factors and genetic inheritance [3]. Alcohol abuse and tobacco smoking are major risk factors for HNSCC. The risk was correlated with the intensity and duration of the smoking habit. Human papillomavirus (HPV) is also considered risk factor, particularly in oropharyngeal carcinogenesis. The incidence of HPV-associated head and neck squamous cell carcinoma is increasing, but it is associated with improved survivorship and increased long-term survival [3, 5].

The likelihood of cervical metastatic lymph nodes in HNSCC depends on location, histology, and staging of the primary tumor. The presence of metastatic nodes (Fig. 1) carries poor prognosis. In turn, approximately 7–25% of patients with advanced stage HNSCC have distant metastases at initial presentation. The most common sites of metastasis are lung, bone, and abdomen [2].

HNSCC treatment choice depends on the primary site, surgical resectability [7], performance status of the patient, co-morbidity, prior treatment, recurrence-free interval, symptoms, and patient preference [1]. Over the past decades, independently of the primary tumor, conservative treatments with curative intent have increased significantly in the management of HNSCC, both in early and advanced stage disease [5, 6]. While in the early-stage disease it is routinely treated with surgery or radiation alone, the locally advanced disease typically requires site-specific multimodal therapy [1, 5]. The advent of functional organ preservation has shifted the treatment paradigm [7]. Treatment options for these patients include supportive care in addition to surgery, radiotherapy, concurrent chemoradiation therapy, single-agent or combination chemotherapy [1, 5]. However, the overall risk of locoregional recurrence and distant metastasis remains high, varying from less than 10% to more than 50%, based on histological classification, primary site, and stage [6].

Precise diagnostic assessment of tumor extension is of critical importance for ensuring that patients receive proper and cost-effective treatment [8•]. Several challenges in the management of HNSCC can be found in these patients. In diagnosis, for example, clinics may be non-specific and depends on the tumor site. Some cancers escape detection by detailed physical examination, endoscopy, and conventional cross-sectional imaging [8•].

Computed tomography (CT) and magnetic resonance imaging (MRI) are the standard conventional imaging modalities for evaluating patients with HNSCC [4•, 8•]. These widely used non-invasive imaging methods are based on morphologic criteria, such as nodal size and contrast enhancement patterns. On the other hand, ^{18}F-fluoro-deoxy-glucose (FDG) positron emission tomography (PET) is a molecular imaging modality that assesses the metabolic status of tumors [4•, 8•].

Positron emission tomography (PET) combined with computed tomography (CT) using ^{18}F-FDG (^{18}F-FDG PET/CT) is useful in the evaluation of HNSCC. ^{18}F-FDG PET/CT can be used for delineation of extent of primary tumor, detection of an unknown primary tumor origin or synchronous second primary tumor, detection of regional lymph node metastasis (Fig. 1), detection of distant metastasis, directed biopsies to ensure histological verification, planning radiotherapy, and prediction of disease recurrence and survival [2, 4•, 7, 8•, 9•]. After therapeutic, this functional modality can be valuable in the assessment of therapy response, detection of residual primary tumor, long-term surveillance [2, 4•, 7, 8•, 9•].

In this article, we will make a brief review about pre-treatment evaluation of HNSCC with ^{18}F-FDG PET/CT and will discuss the use of this method after treatment, with emphasis on the evaluation of therapeutic response.

Pre-treatment Evaluation

Before initiation of treatment, HNSCC staging it is made by using clinical examination, imaging, and endoscopy with tissue biopsy or fine needle aspiration [2]. Appropriate imaging enables directed biopsies to ensure histological verification and assessment of tumor extension [8•]. Although there are some limitations in the PET/CT technique, including artifacts, lower soft tissue contrast, and resolution as compared to MRI, several studies have shown that PET/CT is superior to conventional imaging in initial staging [2]. Especially by detection of unexpected cervical lymph node disease and distant metastasis (Fig. 2), ^{18}F-FDG PET/CT can alter management and treatment [2]. National Comprehensive Center Network practice guideline in HNSCC, update in 2015, suggested that ^{18}F-FDG PET/CT should be considered for initial staging of the oral cavity, oropharyngeal, hypopharyngeal, nasopharyngeal, glottic, supraglottic cancers, ethmoid sinus tumors, and maxillary sinus tumors for stage III-IV disease, as well as mucosal melanoma and primary occult tumor [5].

There is no definitive recommendation for routine use of ^{18}F-FDG PET/CT in initial T staging, in spite of some authors found that such a PET/CT could upstage T staging

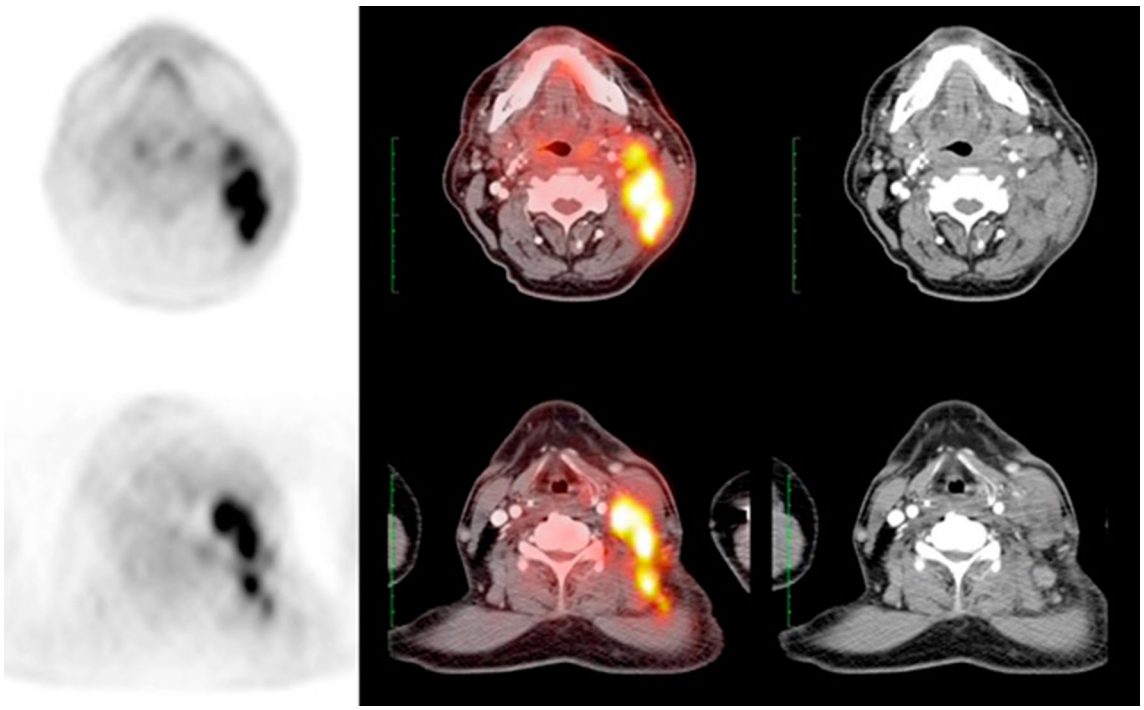

Fig. 1 ^{18}F-FDG PET/CT shows hypermetabolic lymph nodes in a patient presenting with metastatic cervical lymphadenopathy

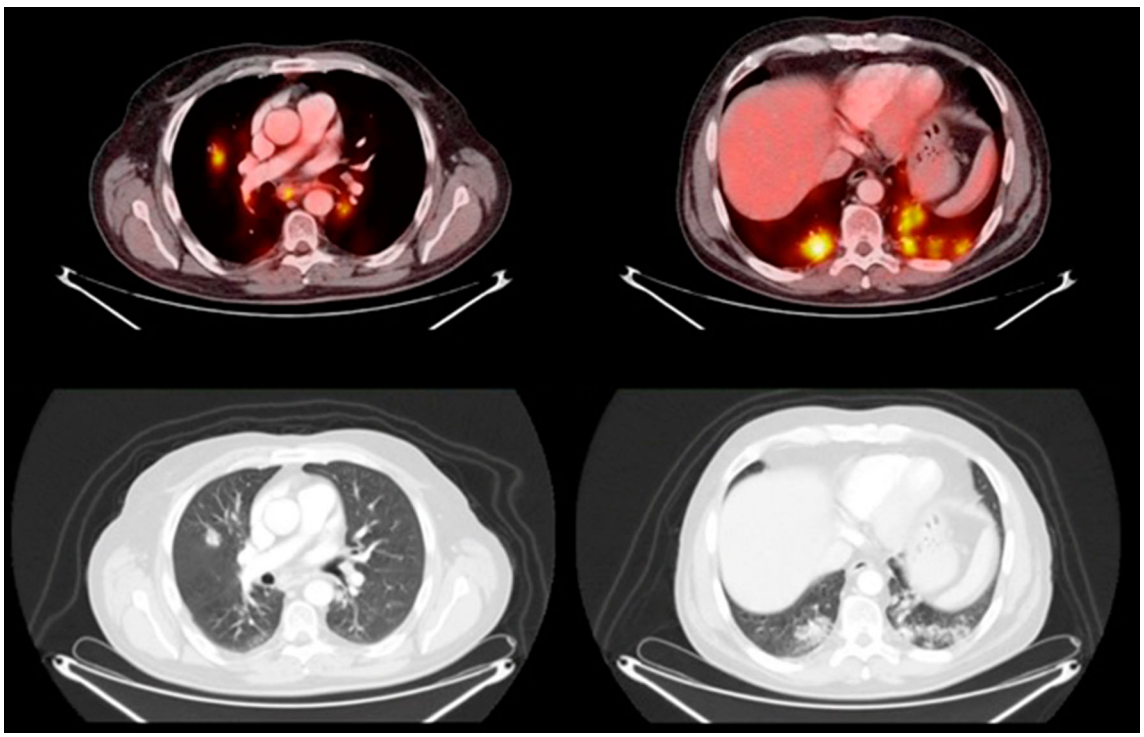

Fig. 2 Lung metastasis at a nasopharyngeal squamous cell carcinoma FDG avid on PET/CT

with subsequent changes in treatment planning [2]. Its impact on the initial staging is mostly related to the ability to detect metastatic or additional disease. A multicenter prospective study found an upstage of TNM classification with a change of management of 13.7% of the patients [10]. The higher sensitivity and specificity (80 and 86%, respectively) of ^{18}F-FDG PET/CT as compared to other conventional diagnostic modalities (75 and 79%,

respectively) is because PET can show FDG hypermetabolism in normal-sized metastatic lymph nodes. However, false-positive results occur because inflammatory nodes and adjacent granulation tissue can increase uptake. Overall, ^{18}F-FDG PET/CT is also more accurate than conventional imaging in detecting metastatic foci (Fig. 3), with a sensitivity and specificity of around 87.5 and 95%, respectively [2].

Regarding detection of occult primary tumor (Fig. 4), which is present in about 2–7% of HNSCC patients with metastatic cervical lymphadenopathy without primary site established, various studies show that ^{18}F-FDG PET/CT can identify primary cancer with 62–93% sensitivity, 33–93% specificity, 56–89% positive predictive value (PPV), and 25–96% negative predictive value (NPV) [2]. The majority of the primary cancers are found in the palatine tonsils or base of tongue [2].

Post-treatment Evaluation

Appropriate Timing

One challenge related to ^{18}F-FDG PET/CT indication is the best time to do it because the treatment of HNSCC can determine a local inflammatory process and confuse the interpretation [11].

Its performance during treatment is still not well established, differently as in other tumors, such as lymphoma. Some studies have found no significant metabolic response at 2 weeks after initiation of radiochemotherapy and have concluded that there is no predictive value of ^{18}F-FDG PET/CT for early response to treatment [12••]. On the other hand, there is evidence that reductions in metabolically active tumor volume (MTV) and total lesion glycolysis (TLG) after the first cycle of chemotherapy can identify non-responders and change the proposed conduct [13]. We have not yet adopted interim ^{18}F-FDG PET/CT in our routine, and we believe that new studies evaluating induction chemotherapy or chemoradiotherapy may clarify the role of PET at this time of treatment with greater safety.

At the end of the treatment, the role of ^{18}F-FDG PET/CT is well established. It is not recommended to undergo the

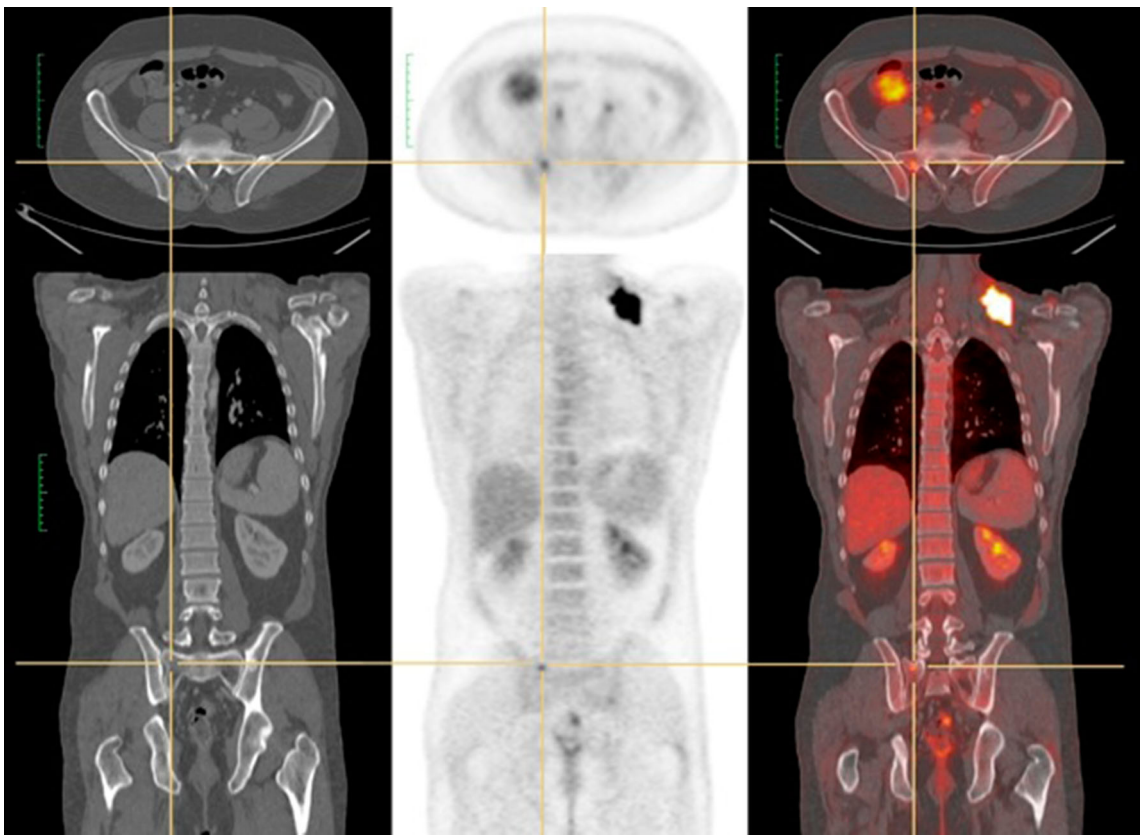

Fig. 3 Bone metastasis at initial staging of a nasopharyngeal squamous cell carcinoma detected by ^{18}F-FDG PET/CT. The bone lesion was not detected by conventional imaging. In this case, the PET/CT changed the management

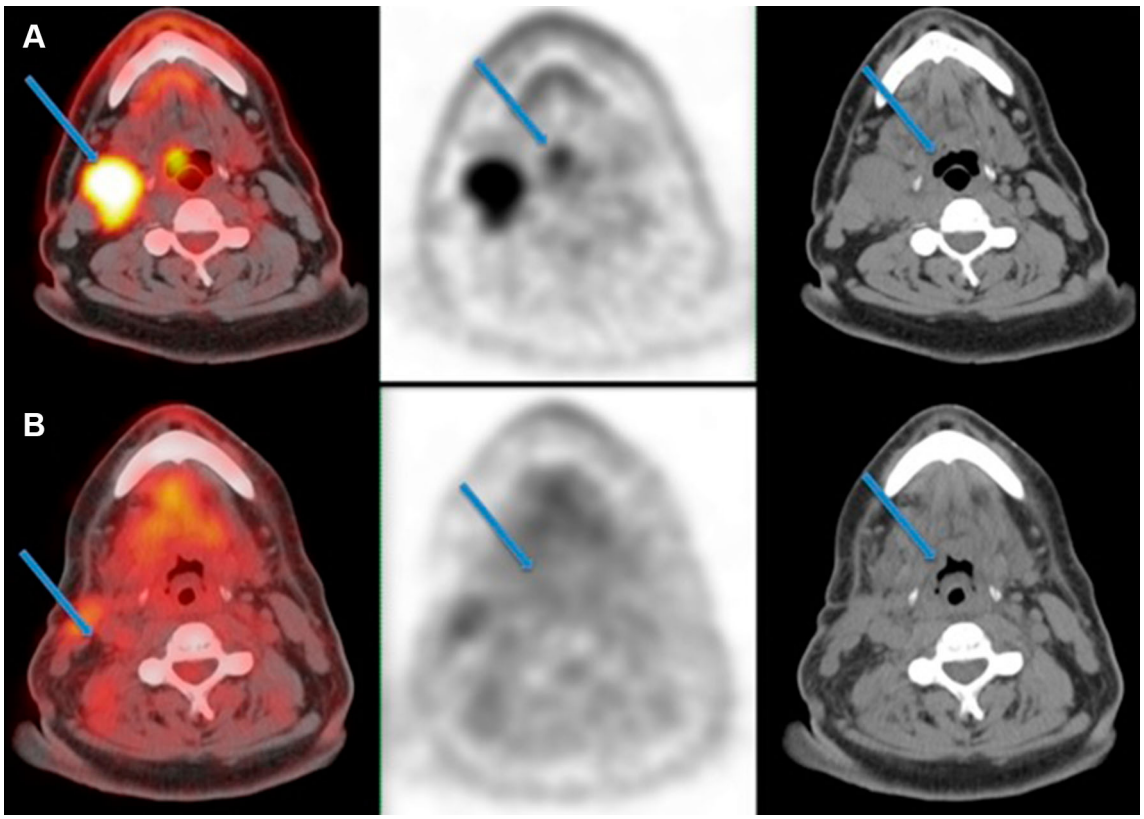

Fig. 4 A 50-year-old male patient with squamous cell carcinoma in the right cervical lymph nodes with a hidden primary tumor. **a** PET-CT shows hypermetabolic lymph nodes and hypermetabolic focal area in the ipsilateral nasopharynx, without definition of CT lesion, confirmed by biopsy as neoplasia. **b** PET-CT post-treatment shows regression nasopharynx lesion and cervical lymph node disease

test less than 8 weeks after treatment, especially when radiotherapy has been performed, due to the low PET/CT accuracy [11, 12••]. Several studies agreed that the main cause of false-positive is the post-therapeutic inflammatory process, especially after radiotherapy, but the occurrence of inflammation is lower as we perform PET/CT later [11, 12••, 14••, 15•, 16]. A meta-analysis found that exams performed 12 weeks after complete therapy had a significant impact on the diagnostic accuracy [14••]. Other studies have shown that ^{18}F-FDG PET/CT after 4 months of the end of treatment has a high negative predictive value for both primary and lymph node diseases and therefore should be considered especially before the indication of salvage surgery [15•, 16]. In cases where treatment is limited to the surgical procedure, PET/CT after 3 months is also highly accurate, and with a positive predictive value higher that found in situations where radiotherapy is part of the therapeutic, probably due to post-actinic inflammatory process [17]. Therefore, ^{18}F-FDG PET/CT is suggested to be performed 16 weeks after the end of treatment, and it does not recommend for less than 8–10 weeks [11, 12••, 16].

It is necessary attention to the risk of false-positive when there are ^{18}F-FDG uptake findings in organs or lymph node networks infrequently related to the spread of head and neck tumors (Fig. 5). In these situations where doubts arise due to their low positive predictive value [14••], ^{18}F-FDG PET/CT should not be seen as an exclusive diagnostic method, but as a tool to guide a biopsy [15•], which will allow a more precise analysis and will reduce unnecessary aggressive actions.

Small tumor size and reduction of target/non-target ratio are considered false-negative events in the post-therapeutic evaluation of HNSCC [11]. In these situations, even with the observer's experience, the follow-up will be fundamental for the accurate identification of the residual disease.

Criteria for Interpretation

Even adopting the best time to perform the ^{18}F-FDG PET/CT, the interpretation and standardization of the findings are not simple. The qualitative analysis of the images, identified by the intensity of ^{18}F-FDG uptake, is the most basic tool of interpretation and is dependent on the observer's experience. In general, the possibility of residual disease must be considered when there is a focal and asymmetric uptake of ^{18}F-FDG, with an intensity higher than the concentration of adjacent structures (muscles and

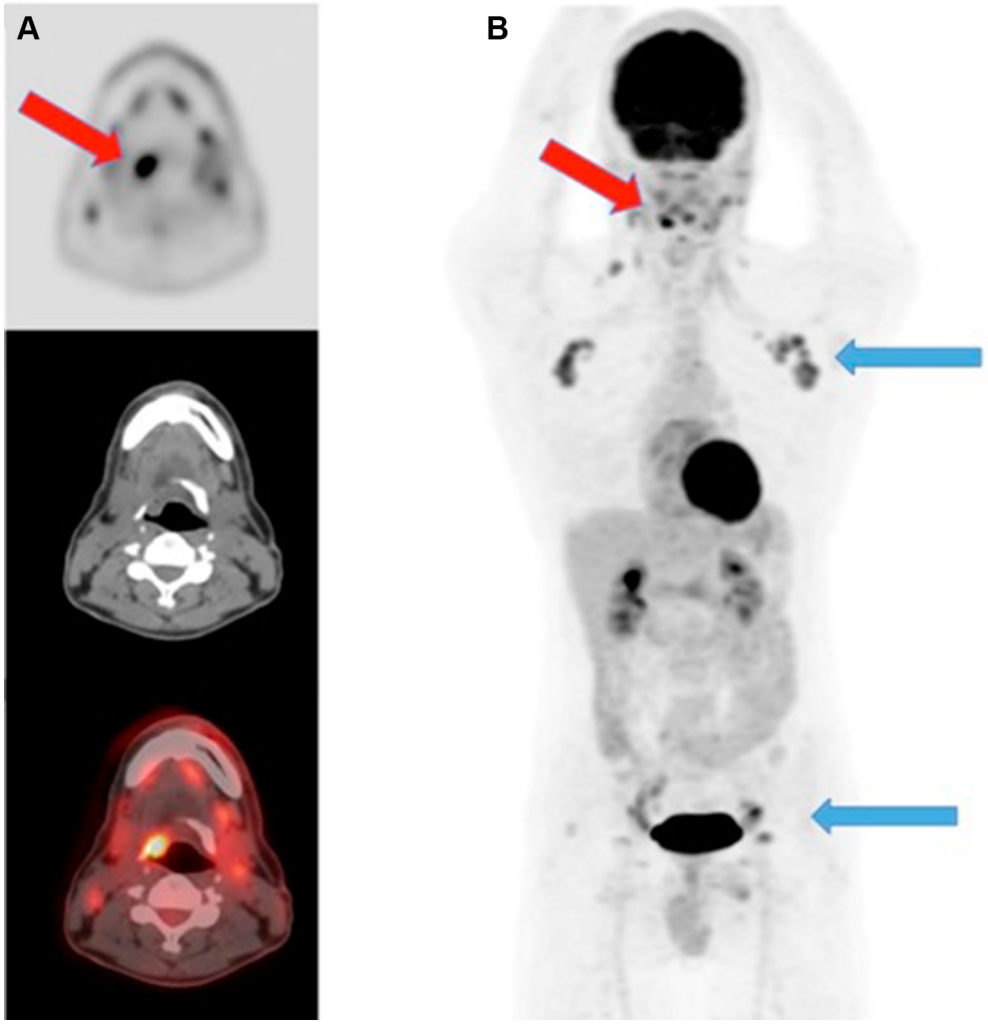

Fig. 5 A 55-year-old patient at staging of right vallecular's squamous cells tumor. **a** 18F-FDG uptake in the primary lesion (red arrows) and bilateral cervical lymph nodes. **b** Numerous axillary and inguinal lymph nodes showing 18F-FDG uptake (blue arrows). The axillary lymph node biopsy shows inflammatory reaction. Patient follow-up identified HIV infection (Color figure online)

blood vessels) [18•, 19]. Thus, diffuse ^{18}F-FDG uptake, especially in sites submitted to radiation, should represent inflammatory processes [19].

Another form of evaluation is the quantitative analysis of parameters related to tumor uptake and metabolism, which tries to establish a standardization in the interpretation of the findings. The most used parameter is the measurement of the maximum SUV (SUVmax). However, the interpretation based only on the SUVmax should not be adopted for the differentiation between residual neoplasia and inflammation, since there is no widely accepted cut-off value [19]. Also, several factors may influence the variability of SUVmax quantification among patients and institutions [19].

The comparative analysis of the SUVmax over the period of follow-up of patients has proved useful in the post-therapeutic evaluation of HNSCC. An early study has demonstrated that SUVmax values after radiotherapy were significantly lower in responder patients, as well as higher relative reduction of SUVmax after treatment [20•]. Using sequence images, another study showed that a fall rate higher than 55% could differentiate responders from non-responders with sensitivity and specificity of 86 and 95%, respectively [18•].

Another form of interpretation and standardization of response assessment is the Hopkins criteria, which is based on a qualitative scoring scale (see Table 1), where ^{18}F-FDG activities in the internal jugular vein (IJV) and liver are used as references, and compared with the uptake of the lesion (primary or lymph node) [21••]. In Hopkins criteria, the overall score is determined by the highest score between primary lesion and lymph node lesion, regardless of the side of the neck. Definition of a ^{18}F-FDG PET/CT negative for residual tumor disease includes scores 1, 2,

Table 1 Hopkins criteria [21••]: FDG uptake in primary lesion and lymph node disease compared to internal jugular vein (IJV) and liver uptake

Score	FDG uptake	Response therapy level
1	Focal and less than IJV	Complete metabolic response
2	Focal, higher than IJV but less than liver	Likely complete metabolic response
3	Diffuse, higher than IJV or liver	Likely post radiation inflammation
4	Focal and higher than liver	Likely residual tumor
5	Focal and intensely greater than liver	Residual tumor

and 3, and positive scores 4 and 5. A new lesion, not seen in the baseline study, should be considered a disease progression. The Hopkins criteria show excellent interobserver agreement, have the high negative predictive value, and are a predictor of survival in patients with HNSCC submitted to chemoradiotherapy treatment (Fig. 6) [21••, 22].

Clinical Usefulness and Prognostic Value

Currently, the main clinical role of ^{18}F-FDG PET/CT post-therapeutic assessment has been related to salvage surgery indication in patients undergoing chemoradiotherapy [23•, 24••]. Even considering the low rate of tumor recurrence in patients with no evidence of disease at the conventional methods (CT and MRI) and the risk of complications associated with the procedure, the salvage surgery is still quite indicated [24••]. Thus, the use of metabolic images would be able to predict the early recurrence risk, implying in the decision to indicate surgery [24••]. In a retrospective study, Kim et al. had demonstrated that, in addition to the high negative predictive value (98.3%), ^{18}F-FDG PET/CT could predict early failure of locoregional and systemic therapy and indicate a reduction in overall and progression-free survival, when SUVmax had been above of 4.4 [23•]. Moreover, there was no significant difference in overall survival between patients undergoing or not salvage surgery, despite the small number of selected cases [23•].

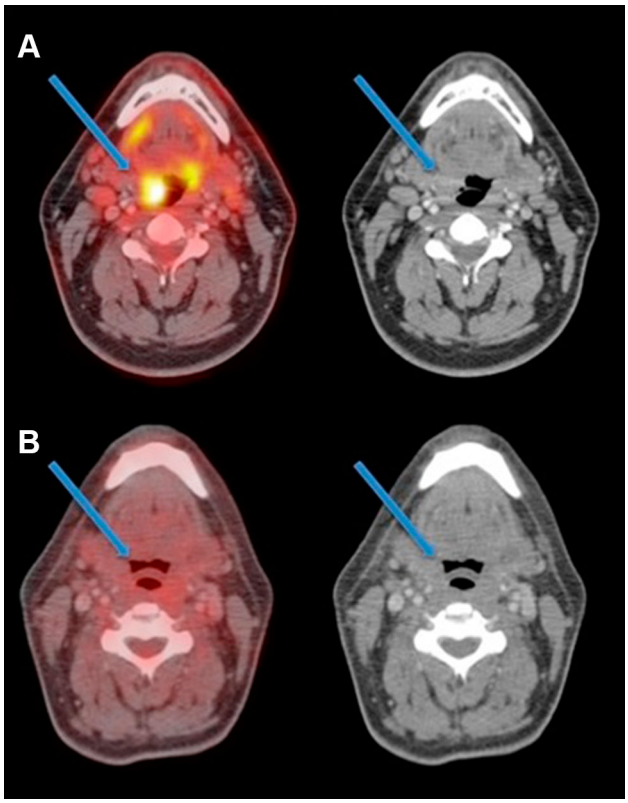

Fig. 6 A 49-year-old female patient with a diagnosis of squamous cell carcinoma undergoing chemotherapy and concomitant radiotherapy. **a** PET-CT shows a nodular image, poorly delimited, occupying the right vallecula (SUVmax = 10.7), determining asymmetry of the oropharynx. **b** PET-CT post-treatment shows complete response, with epiglottis thickening

The PET-NECK Trial Management Group, in a prospective, randomized, controlled study had demonstrated that surveillance guided by ^{18}F-FDG PET/CT in patients with advanced HNSCC undergoing chemoradiotherapy was not inferior to surgical resection when overall survival was analyzed, even in the HPV-positive patients [24••].

Other studies have also shown the prognostic value of ^{18}F-FDG PET/CT in the post-therapy evaluation of HNSCC. Kao et al. have shown that PET-CT negative within 6 months after the end of radiotherapy was associated with better locoregional control, distance control, progression-free survival, and overall survival in 2 years [25]. In a retrospective study, Taghipour et al. have used ^{18}F-FDG PET/CT to evaluate patients submitted to primary surgical resection. The authors demonstrated that PET/CT positive results in lower survival rate in several situations (patients treated with surgery alone, treated with chemotherapy, radiotherapy or both after surgery, patients in early stages or advanced stages of the disease) [17]. In the same study, the impact of positive findings on post-operative PET/CT was also significant to identify suspicious lesions without previous signs, to exclude disease in patients with clinical suspicion and to indicate new treatment in cases of residual disease [17].

Comparison of Imaging Methods

The anatomic changes resulting from the treatment used, such as scars and inflammatory reactions induced by radiation make it difficult to evaluate tumor recurrence [26]. Thus, imaging methods play a crucial role in tumor evaluation. As previously discussed, ^{18}F-FDG PET/CT accumulated evidence suggesting its use as a valuable imaging modality for the management of HNSCC [24••]. On the other hand, MRI is a well-established method for evaluating HNSCC, whose advantages include the absence of ionizing radiation, high contrast for soft tissue signal versatility, physiological performance, and reduction of dental artifacts compared to PET/CT [26]. Studies have compared PET/CT, MRI, and combined PET/magnetic resonance imaging (PET/MRI) to reinforce the best aspects of each method and their potentialities [27].

In this direction, Ghanooni et al. have evaluated the diagnostic performance of ^{18}F-FDG PET/CT and MRI in the follow-up of patients with HNSCC to detect recurrence. It was a prospective study in which the authors have included 32 patients undergoing PET/CT and MRI before and after treatment (2 weeks, 4 and 12 months after completion). Pre-treatment PET/CT and MRI evaluations have detected almost all lesions, with a sensitivity of 94%. It should be added that MRI has been more sensitive than PET/CT to determine the local extension. On the other hand, in the evaluation of the 4-month recurrence, ^{18}F-FDG PET/CT have shown a sensitivity of 92%, while MRI sensitivity was 70%. At 12 months, diagnostic performance has been equivalent. Interestingly, the PET/CT initial images, 2 weeks after radiotherapy, have shown sensitivity and specificity of 86 and 85%, respectively, placing the ^{18}F-FDG PET/CT as able of differentiating residual tumor from radiation-induced alterations [27].

In another study, the authors have correlated ^{18}F-FDG PET/CT, CT, and MRI with histopathology in salvage surgery for residual disease after primary non-surgical treatment. Thirty-nine patients who received chemotherapy, radiotherapy or a combination of both were recruited. Fifty-six hemi-necks were dissected, and 37 were found with metastatic lymph node disease and 22 with residual disease. In a neck analysis, the accuracy found was 89 and 78% for ^{18}F-FDG PET/CT and CT/MRI, respectively. These data point ^{18}F-FDG PET/CT as superior to morphological methods in the evaluation of residual and lymph node disease [28].

Finally, Queiroz et al. have confronted PET/CT and PET/MRI with ^{18}F-FDG in the detection of recurrence using venous contrast in morphological CT and MRI images [29]. They have studied 87 patients submitted sequentially to PET/CT and PET/MRI with ^{18}F-FDG to evaluate recurrence of HNSCC. There was no significant difference in the findings between the methods, with a sensitivity of 91.5 and 90.6% for PET/MRI and PET/CT, respectively. However, the authors have pointed out a higher degree of artifacts in PET/CT evaluations [29].

Conclusion

At pre-treatment evaluation, ^{18}F-FDG PET/CT in HNSCC it is recommended to detect metastasis foci in III-IV staging HNSCC. The post-therapeutic PET/CT it is the main indication, especially after chemoradiotherapy. Many studies have demonstrated that the ^{18}F-FDG PET/CT has prognostic and predictive values after therapy. It can determine management changes defining new therapy or avoiding an unnecessary surgery. Thus, precise evaluation of images based on specific criteria plays a crucial role in the correct follow-up of HNSCC patients.

Author Contribution WEFMA, FAP, and ETR designed the research. LWA had primary responsibility for final content. All authors contributed towards, read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest Wilson Eduardo Furlan Matos Alves, Felipe Arriva Pitella, Euclides Timoteo da Rocha, and Lauro Wichert-Ana each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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