Evidence-Based PET for Head and Neck Tumours

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Gaetano Paone

4.1 Introduction

Head and neck cancer (HNC) accounts for approximately 5% of all malignant tumours with a continuous growing incidence. Head and neck squamous cell carcinoma (HNSCC) represents the majority of HNC [1, 2]. Nodal involvement is frequent in HNC patients, whereas distant metastases are rather uncommon at the time of initial diagnosis and are found approximately in 10% of patients. There is a clear association with life-style and factors as alcoholism, smoking, alimentary factors and viruses for the etiological role, while increasing T and N stages remain the most important adverse prognostic factor [3, 4]. Diagnosis of HNC is usually achieved clinically with endoscopy to obtain direct tissue biopsies. Conventional Imaging (CI), including ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) is important for the evaluation of local extension and to provide information about infiltration, involvement of surrounding structures and regional nodal involvement. There is growing evidence, however, that these modalities have limitations for the diagnostic accuracy of nodal involvement and distant metastases. ^{18}F -FDG PET/CT, allowing

the analysis of both metabolic and anatomic features, is a very useful imaging tool in HNC, in particular for disease staging, detection of carcinoma of unknown primary (CUP), treatment monitoring, evaluation of residual or recurrent disease and for prognostic information [5–7].

4.2 Staging

Accurate staging of disease extension at the time of diagnosis is the most important factor for treatment planning and patients prognosis. Furthermore, providing information in early stage of disease is extremely useful for selecting high-risk patients with impact on specific-treatment selection.

4.2.1 T Staging

^{18}F -FDG PET/CT has high accuracy in detecting the primary tumour but a moderate diagnostic performance than CI to identify the real tumour extension and infiltration of surrounding tissue and structures. These data are necessary for adequate therapeutic strategy and patient prognosis. False-negative results occur on ^{18}F -FDG PET/CT when the primary tumour is superficial or small, but also in areas of high physiologic activity such as in pharyngeal lymphoid tissue. False-positive results of ^{18}F -FDG PET/CT may be due to

G. Paone (✉)
Clinic of Nuclear Medicine and Molecular Imaging,
Imaging Institute of Southern Switzerland, Ente
Ospedaliero Cantonale, Bellinzona, Switzerland
e-mail: gaetano.paone@eoc.ch

inflammatory processes. In literature, we found conflicting data; preliminary studies have shown divergent results of ^{18}F -FDG PET/CT in diagnosis and staging of HNSCC. Rohde et al. compared the diagnostic accuracy of ^{18}F -FDG PET/CT for diagnosing HNSCC in comparison with standard CI showing a pooled sensitivity of 89.3% and specificity of 89.5% for ^{18}F -FDG PET/CT and a pooled sensitivity and specificity of 71.6% and 78.0%, respectively, for CI. The authors concluded that ^{18}F -FDG PET/CT is highly accurate in diagnosing patients suffering from HNSCC [8]. Chen et al. compared MRI, CT and ^{18}F -FDG PET/CT in the diagnosis of local and metastatic nasopharyngeal carcinomas. Their analysis suggested that MRI has good accuracy in diagnosis of T stage, whereas CT has a good performance in diagnosis of N stage and ^{18}F -FDG PET/CT shows a good accuracy in diagnosis of M stage [9]. Similarly for evaluation of extracapsular spread (ECS), CT and MRI may be similarly effective, whereas evidence was lacking for ^{18}F -FDG PET/CT and US [10]. ^{18}F -FDG PET/CT can provide, instead, more useful clinical information and higher sensitivity and specificity (pooled sensitivities and specificity 90% and 89%, respectively) to delineate the presence and extent of mandibular involvement in patients with oral cavity cancer, especially in cases of contextual dental artefacts [11, 12]. For evaluation of precancerous and tumour lesions of larynx, Mannelli et al. expressed the need to integrate different imaging methods, proposing a flow chart that allows to stratify patients and select the most appropriate procedure [13].

Overall, the current practice is not in favour of ^{18}F -FDG PET/CT as gold standard for T staging in HNC in exception of cases with suspect mandibular involvement in oral cavity cancer. The preliminary data about ^{18}F -FDG PET/MRI demonstrated high sensitivity and moderate specificity of this technique in the diagnosis of HNC lesions, showing also a better tumour delineation. Further investigations are needed to define the real impact of ^{18}F -FDG PET/MRI in HNC and whether the technique can improve the detection rate of occult primary HNC [14].

4.2.2 Nodal and Distant Metastases Detection

Lymph nodal involvement is the most important prognostic factor in patients with HNSCC with a significant impact on outcome in terms of disease free survival and overall survival. Lymph nodal (N) metastases occur in approximately 50% of HNC patients at the time of diagnosis with a consequent survival decrease. An accurate N staging is therefore a fundamental step. Similarly, the detection of distant metastases at initial staging influences the prognosis avoiding unnecessary radical treatments. Metastases (M) are frequently found in the lungs, followed by the liver and bone.

Several data in the literature confirm an excellent diagnostic accuracy of ^{18}F -FDG PET/CT in N and M staging. A meta-analysis of Vellayappan et al. assessed the diagnostic accuracy of ^{18}F -FDG PET/CT for staging nasopharyngeal carcinoma (NPC), showing good accuracy of ^{18}F -FDG PET/CT for N staging (pooled sensitivity and specificity were 84% and 90%, respectively) and for M staging (pooled sensitivity and specificity were 87% and 98%, respectively), but not for T classification [15]. Similarly, Shen et al. confirmed in their meta-analysis an excellent diagnostic performance of ^{18}F -FDG PET/CT for detecting lymph node and distant metastases in patients with NPC with a pooled sensitivity and specificity of 89% and 96%, respectively [16]. Considering only the detection accuracy for regional nodal metastases in HNC before treatment, ^{18}F -FDG PET/CT showed good diagnostic performance [17, 18]. Moreover, compared with CI, ^{18}F -FDG PET/CT may have higher per-neck-level sensitivity [19]. These values are even more significant excluding clinically N0 patients with greater accuracy values for ^{18}F -FDG PET/CT. Several data showed moderate sensitivity of ^{18}F -FDG PET/CT for detection of cervical lymph nodal metastases in clinical N0 HNSCC patients with absence of significant better diagnostic accuracy compared to CI; conversely, ^{18}F -FDG PET/CT has a higher specificity and negative predictive value for the detection of cervical metastatic lymph nodes compared to the other imaging

modalities in clinical N0 HNSCC [20–22]. Avoiding elective neck dissection is a fundamental step in the diagnostic-therapeutic flow chart of these patients in order to minimize morbidity and health costs. At present elective neck dissection in patients with clinical N0 should not be based upon cross-sectional imaging. A combination of CI and sentinel node biopsy seems to be the preferred staging strategy to reduce the risk of occult metastases in clinical N0 HNSCC [23].

On the other hand, the excellent diagnostic performance of ^{18}F -FDG PET/CT for detecting distant metastases is clearly underlined in the literature [24–29]. Xu et al. showed a pooled sensitivity and specificity of 85.7% and 98.1%, respectively, for ^{18}F -FDG PET/CT, resulting in a significantly better M staging than CI [26]. This was mainly due to the superior diagnostic performance of ^{18}F -FDG PET/CT compared to CI in detecting bone metastases [27]. In this setting, ^{18}F -FDG PET/CT has higher sensitivity compared to bone scintigraphy [28]. On the other hand, for detection of liver metastases ^{18}F -FDG PET/CT requires further optimization and integration with CI, especially contrast-enhanced CT and MRI [25]. About lung metastases, a meta-analysis demonstrated that ^{18}F -FDG PET/CT is a valuable diagnostic tool for diagnosing lung malignancies in patients with HNSCC [29].

4.3 Prognostic Value

The prognostic value of ^{18}F -FDG PET/CT has been widely discussed with controversial results. Relevant limiting factors are the variability and reproducibility of each individual parameter. Overall, maximum standardized uptake value (SUV_{max}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were significant prognostic predictors in patients with HNC [30–36].

No significant correlation was found between metabolic parameters of ^{18}F -FDG PET/CT in HNC and human papillomavirus (HPV) status [37]. Furthermore, the semi-quantitative PET/CT parameters were not related to histopathological parameters in HNSCC, as Ki67 and p53 [38].

4.4 Post-treatment Evaluation

Relevant applications of ^{18}F -FDG PET/CT in HNC are delineation of the tumour volume for radiation treatment planning, discrimination of post-treatment changes, evaluation of response to multimodality therapy and detection of recurrence.

About radiation therapy planning, Jeong et al. found that ^{18}F -FDG-avid HNC apparently require 10–30% more radiation dose than FDG-non-avid tumours, supporting radiotherapy boosts for ^{18}F -FDG-avid tumours; prospective studies are still required in this field [39].

The role of intra-therapy and post-therapy ^{18}F -FDG PET/CT in predicting long-term survival outcomes in patients treated for HNC has been widely studied. Sheikhabaei et al. reported that positive results of intra-therapy or post-therapy ^{18}F -FDG PET/CT could significantly predict the 2- and 5-year risk of death or disease progression [40]. The same group confirmed the high diagnostic performance of ^{18}F -FDG PET/CT in detecting local, regional and distant recurrences in curatively treated patients with HNC. The pooled sensitivity and specificity of follow-up ^{18}F -FDG PET/CT for detection of recurrence were 92% and 87%, respectively [41]. These data support its use in clinical practice as confirmed also by other studies that highlight the high accuracy of ^{18}F -FDG PET/CT performed after the completion of therapy both in NPC and HNSCC before salvage treatment [42–44]. ^{18}F -FDG PET/CT is also superior to MRI in distinguishing recurrent NPC from fibrosis or scar tissue after radiotherapy in irradiated fields with distortion of normal architecture [45]. Treatment-to-time scan remains a debated aspect. Several works have indicated that early ^{18}F -FDG PET/CT was less accurate than more delayed imaging after therapy, particularly Cheung and coauthors supported the use of ^{18}F -FDG PET/CT more than 12 weeks after radiotherapy with or without chemotherapy for the assessment of residual or recurrent HNC [46]. Recently, Helsen et al. confirmed that ^{18}F -FDG PET/CT performed within 6 months after chemo-radiotherapy in HNSCC patients is the method of choice for ruling out residual/recurrent

nodal disease reducing the need for therapeutic intervention [47]. Finally, sensitivity and specificity of ^{18}F -FDG PET/CT in identifying local failure following curative radiotherapy or surgery for HNSCC were significantly improved when imaging was performed 3 months after end of treatment [48].

4.5 Carcinoma of Unknown Origin and Incidental Findings

Several studies have investigated the accuracy of ^{18}F -FDG PET/CT to identify carcinoma of unknown origin (CUP) in patients with cervical lymph nodal metastases. Generally, the most common sites of detection include the palatine tonsils and the base of the tongue, with increase of false-negative results when the primary tumour is small or adjacent to physiological uptake sites. Zhu et al. showed a high sensitivity (97%) and a moderate specificity (68%) for the detection of CUP in patients with cervical nodal metastases [49].

Finally, Treglia et al. calculated the pooled prevalence and risk of malignancy of incidental focal ^{18}F -FDG uptake in the parotid glands. The pooled prevalence of this finding is about 1% of all ^{18}F -FDG PET/CT. Although these incidental findings are benign in most of the cases, complementary evaluation is needed to exclude malignant lesions or with possible malignant degeneration [50].

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