Positron emission tomography/computer tomography in the evaluation of head and neck cancer treatment

Severina Šedienė¹, Ilona Kulakienė¹, Viktoras Rudžianskas²

¹Lithuanian University of Health Sciences, Medical Academy
²Lithuanian University of Health Sciences, Oncology Institute

ABSTRACT
The role of 18F-fluorodeoxy-D-glucose positron emission tomography-computed tomography (18F-FDG PET/CT) imaging in head and neck carcinoma (HNC) during pre-treatment staging, treatment response assessment after induction chemotherapy, radiotherapy planning and after entire therapy, follow-up is analyzed with attention on contemporary evidence. The 18F-FDG PET/CT is properly established in staging for distinction of cervical nodal involvement or rejection of distant metastases. Recently, many papers on the assessment of treatment response of 18F-FDG PET/CT have been published. 18F-FDG PET/CT performed in 2 weeks after the completion of induction chemotherapy (ICT) prevents from irrelevant invasive procedures, such as full neck dissection, with a significant impact on clinical outcome. 18F-FDG PET/CT completed in 8 weeks after the radio-chemotherapy treatment also has a high negative predictive value. From another point of view, the low positive predictive value due to feasible post-ICT and radiation therapy inflammation findings needs adequate attention to make a clinical decision. Recently, 18F-FDG PET/CT imaging in head and neck carcinoma has emerged, especially in radiotherapy planning for tumour volume delineation. In the near future, there are some expectations that new PET radiopharmaceuticals would present significant information on specific tumour characteristics, and all possible limitations of 18F-FDG may be avoided.

Keywords: 18F-FDG, PET/CT, Head and neck cancer

1. INTRODUCTION
Head and neck cancer comprises malignancies of the upper aerodigestive tract. Even though the different sites are anatomically very close, their prognosis and response to treatment are surprisingly different. More than 85% of head and neck cancer arise from squamous cells [1]. The five year overall survival (OS) for head and neck cancer patients is quite poor, commonly reported as less than 60%, but with heterogeneity between the head and neck cancer sites [2]. The assessment of the therapy response varies widely between institutions. It usually consists of a combination of clinical evaluation and imaging. In recent years, functional imaging with PET/CT has gradually been incorporated in clinical practice. 18F-FDG PET/CT is applied in various clinical settings, ranging from pre-treatment staging to treatment planning and response assessment after induction chemotherapy or chemo-radiotherapy, as well as post-therapy follow-up [3, 4]. 18F-FDG uptake represents glucose metabolism. Most of the cases of glucose metabolism can be visible in the tissue of several organs, for example, brain, liver, kidneys, salivary glands, etc. Although 18F-FDG is the most commonly used PET tracer for oncological purposes, its use in HNC suffers from some limitations due to the complex anatomy of this region and the small size of the anatomical structures. After surgery, chemotherapy or radiotherapy treatment, inflammatory cells could be activated; therefore, they would show increased 18F-FDG uptake, and those PET/CT scans could be interpreted as false positive PET results [5]. With all the mentioned limitations, PET/CT imaging is still fast with high resolution images; at the same time, there is a very comprehensive correlation between an anatomical location and function-
al images. This review will focus on the use of 18F-FDG PET/CT in various clinical situations of head and neck cancer.

2. PET/CT FOR PRE-TREATMENT STAGING AND METASTATIC DISEASE EVALUATION

In routine clinical practice, HNC patients’ diagnostic strategy involves accurate physical examination and endoscopy. Clinical examination usually is followed by several imaging modalities, for instance, neck ultrasound, magnetic resonance imaging (MRI) or contrast-enhanced computer tomography (ceCT) for the evaluation of disease extent or possible second primary tumour. Precise evaluation of disease extension is significant in planning the most specific treatment, with important findings for patient outcomes. There are few current studies which have shown that 18F-FDG PET/CT is more accurate than conventional imaging in head and neck, and the results make it possible to individualize and change therapeutic management for more than 30% of patients [6-8]. Connell et al. showed that in 34% of patients TNM classification was changed after a PET scan, which had a direct clinical impact on almost half of them [7]. Primary HNC tumour is generally discovered with clinical examination, endoscopy, CT and MRI, despite high sensitivity (> 95%) 18F-FDG PET/CT imaging [9]. Standard PET/CT with low-dose non-enhanced CT has its own limitations, especially when there is a need to distinguish the precise location, extent of tumour spread and tumour invasion to adjacent structures. Contrast-enhanced PET/CT just partially can overcome those limitations [8]. PET plays an important role in the detection of primary tumour in case of cancer of unknown origin (CUP). 18F-FDG PET/CT performed for patients with cervical lymph node metastasis without the primary tumour detects primary tumour in about 25–38.5% cases [10, 11].

Patients with advanced disease, particularly with hypopharyngeal carcinomas and nodal involvement, should be checked for distant metastases. The most frequent sites for metastases are lungs, bone and liver (Fig. 1).

Figure 1. 18F-FDG PET/CT performed at staging in a patient with laryngeal carcinoma. Whole body PET/CT (a) shows intense 18F-FDG uptake of the primary tumour and a right lateral cervical lymphadenopathy (b). In addition, a high 18F-FDG uptake is evident in the first lumbar vertebral body, suggesting a metastatic lesion (c and d)
18F-FDG PET/CT has higher accuracy for detection of distant metastasis than CT. Therefore, in around 13% of clinical cases with detected distant lesions, a change in the treatment strategy has resulted in improvement of major outcomes for patient survival [12, 13].

18F-FDG PET/CT is a precise method to determine second primaries, with a high negative predictive value. Also, a relatively lower positive predictive value of PET/CT following inflammation and benign hyperplasia diagnosis was noticed in the head and neck region, which may result in false positive PET findings [14]. Second primary tumors may occur in 5–10% of HNC patients and are more often detected in the head and neck region, esophagus and lungs (Fig. 2).

Figure 2. 18F-FDG PET/CT performed at staging in a patient with oropharyngeal carcinoma. Whole body PET/CT (a and b) shows intense 18F-FDG uptake in the primary tumour as well as in a gastric mass located in the body segment of the dorso-medial part (c and d). These findings suggest a second primary tumour.
Secondary primary tumours are notably the first cause of death with a decisive impact on overall survival rates of early stage HNC patients [15]. PET/CT by detecting second primary tumour may change the treatment strategy and overall survival of HNC [16].

3. CERVICAL LYMPH NODE EVALUATION

In a meta-analysis by Kyzas et al., pretreatment lymph node staging capability was estimated and showed a sensitivity of 79% and a specificity of 86% in patients with different types of HNC [17]. In a one study analysis, it was demonstrated that PET before panendoscopy was cost-effective in N1-N2 tumours [18]. The results of the study suggest that PET should be performed before treatment in advanced stage (III and IV) tumours, tumours with an increased risk of distant metastases and in the diagnosis of CUP [19]. In our institution and mostly in all European centers, the main indication of 18F-FDG PET/CT in newly diagnosed HNC is identification of cervical lymph node involvement. The main disadvantages of these studies are false negative results. However, more and more data from the literature maintain superiority of PET/CT over morphological imaging in lymph node involvement identification [8]. The biggest advantage of functional imaging is that even small or normal size lymph nodes with a typical structure could be detected as metastatic lesions (Fig. 3).

Nevertheless, it should be considered that small lymph nodes may be missed (as a false negative result), and sometimes reactive or inflammatory lymph nodes may accumulate the tracer (possible false positive results). However, PET/CT scanner has its limitation, for example, spatial resolution is limited to 5 mm, and accordingly microscopic disease or metastases could be missed. Thus, an 18F-FDG PET/CT scan without lymph node involvement does not validate a surveillance approach in all cases. The ultimate decision to perform neck dissection in patients with negative morphological and functional imaging still depends mainly on the assessment of risk factors and tumour characteristics [20, 21]. Sentinel lymph node scintigraphy in this case may be a solution.

According to literature, positron emission tomography-magnetic resonance (PET/MR) has higher sensitivity and specificity for nodal involvement (85% and 92%, respectively) than 18F-FDG PET/CT, but spatial resolution has the same limitation for patients with micrometastases [22].

3. RADIOTHERAPY PLANNING

Radiation therapy is routinely planned on pre-treatment CT images. Low soft tissue resolution and dental artefacts may especially make the primary tumour delineation difficult. Delineation studies incorporating functional imaging
of the primary site have been performed and PET has been shown to be more accurate in defining gross tumour volume (GTV) than CT or MRI alone. However, all modalities have failed to detect superficial tumour extension [23]. 18F-FDG PET/CT is a perfect tool for tumour target volume selection with the possibility of reducing the radiotherapy target volume and, therefore, reducing acute or late side effects after the radiotherapy treatment [10, 11]. For precise delineation of target volumes, molecular imaging has better sensitivity and contrast resolution; thus, it is possible to optimize the treatment plan [24]. In one study, GTV delineated by 18F-FDG PET/CT...
PET/CT was significantly smaller than GTV delineated by CT and MRI. It was noticed that GTV delineated by PET/CT was approximately close to the pathologic GTV from a surgical sample [23].

The main limitation of PET/CT is the deficiency of a standardized method for functional volume segmentation [25]. Currently, there are few clinical investigations of 18F-FDG PET/CT for radiotherapy planning experimenting with dose escalation for metabolically active tumours, and in some cases adjusting the radiotherapy plan during treatment [24-26].

Recently, molecular imaging, especially its application in finding out the fundamental biological information, has been under investigation. In various trials, new hypoxia-related PET tracers, because of their possibility to recognize the tumour hypoxic region and radiation-resistant tumour within the GTV, are most often involved in the radiation planning process. Those hypoxic cells will be provided with higher doses of radiation [27].

4. TREATMENT RESPONSE EVALUATION

A precise assessment of response is substantial in the management of patients with head and neck tumour treated with induction chemotherapy and later on with chemo-radiotherapy. The evaluation of treatment response varies widely between institutions. It usually comprises a combination of clinical evaluation and imaging. Usually, morphological imaging such as MRI, CT or ultrasound can be used. In recent years more centers have started treatment response evaluation after ICT treatment. Later on, functional imaging with PET has gradually been incorporated in the evaluation of therapy response. 18F-FDG PET/CT can identify viable tumour and overcome the most commonly occurring limitations of morphological imaging modalities [28, 29]. However, after radiation therapy, the inflammation process can be very active, which may lead to a high number of false positive findings and a low positive predictive value of PET/CT [30]. By choosing proper timing for PET/CT post-treatment evaluation, it is possible to decrease the number of false positive findings.

There is a suggestion that an optimum time to perform 18F-FDG PET/T for patients treated with induction chemotherapy is 10–14 days after treatment and 8–12 weeks after radiotherapy. In latest treatment planning, patients with a complete metabolic response may avoid neck dissection, despite the presence of remaining node irregularity detected by conventional imaging [31] (Fig. 4).

Although a completely negative PET scan at the end of therapy typically suggests a good prognosis, it does not necessarily correspond to a complete absence of cancer cells, as 18F-FDG PET/CT is unable to discriminate between minimal tumour burden and no tumour burden. Hence, the recognition of different prognostic factors could help to establish high-risk patients who respond poorly to therapy and could benefit from amplification or treatment changing modality. Accordingly, the prognostic value of different 18F-FDG parameters, such as maximum and mean standardized uptake value (SUVmax and SUVmean), total lesion glycolysis (TLG) and metabolic tumour volume (MTV), are analyzed in some clinical trials [32]. Several studies have shown that a reduction of at least 45% of primary tumour MTV or TLG after induction chemotherapy may predict progression free survival in patients with advanced HNC [33, 34]. This enables identification of patients at risk of treatment failure at an early time-point, permitting treatment individualization and consideration of alternative strategies such as radiotherapy dose-escalation or surgery. In some studies, the efficacy of these parameters has been assessed with controversial results [32, 35]. The main deficiency is that different metabolic parameters could change in a few different ways, depending on the calculation and reproducibility model.

The prognostic benefit of 18F-FDG PET/CT, performed at the end of radio-chemotherapy, for regional control and survival has been observed after comparison between post-treatment metabolic response and clinical outcomes. However, some studies have shown controversial results about the role of PET/CT performed early during treatment [5, 36]. Castaldi et al. in his study
Figure 4. 18F-FDG PET/CT performed at staging (a and b) and after induction chemotherapy (lower panels) in a patient with tongue carcinoma. PET/CT (upper panels) shows intense 18F-FDG uptake of the primary tumour and very faint uptake of the primary tumour in 10 days after induction chemotherapy (c and d). These findings have both prognostic and therapeutic implications.
did not find a significant correlation among the "early" changes of FDG uptake in the head and neck tumour and lymph node involvement [36]. In contrast with this study, Hentschel et al. showed that a decrease of 50% or more of SUVmax from the treatment beginning to the first or second week of treatment (10 or 20Gy) was a likely prognostic tool for patients with head and neck cancer [5].

5. PET IN THE FOLLOW-UP SITUATION

Even after initial very aggressive treatment, regional or distant recurrence can arise in head and neck cancer patients, particularly during the first year. Salvage therapy and PET/CT might be proper diagnostic tools for early detection of regional disease, herewith changing the survival rate. Detection of recurrence or residual disease with routine imaging, such as CT or MRI, may be complicated because of treatment-induced tissue changes that could be easily misinterpreted with scar tissue, recurrent or residual disease. Several retrospective studies have implied the value of PET/CT in the follow-up, at 3 to 6 and at 12 months post-therapy far exceeding the ability of a physical examination for detection of recurrences with high sensitivity, specificity and predictive values [37]. Mostly asymptomatic recurrences are diagnosed within the first year and almost all within two years, and approximately half of them are distant metastases [38]. It should be considered that when PET/CT is positive, biopsy is suggested due to a moderately high false positive rate according to post-treatment inflammation [8]. In one systematic review, assessing the diagnostic performance of 18F-FDG PET/CT in response evaluation and surveillance, imaging of HNC patients showed a high negative predictive value for the primary site and cervical nodes [39].

6. OUR EXPERIENCE

In our hospital, usually pre-treatment 18F-FDG PET/CT evaluation in patients with head and neck cancer who are candidates for surgery is performed. The most significant clinical information coming from this pre-treatment scan is improvement of neck staging and assessment of distant metastases or the second primary tumour. In our opinion, this examination provides a substantial impact on treatment planning. 18F-FDG PET/CT is also performed in patients with cervical squamous cell cancer metastases and unknown primary tumour on a regular basis at our institution. For treatment response evaluation, an interim PET/CT scan 10–14 days after the end of induction chemotherapy is usually performed. Patients with a complete or partial metabolic response are referred to chemo-radiotherapy. In other cases, the treatment plan is changed by a multidisciplinary team consensus. During follow-up, particularly in the first year, 18F-FDG PET/CT is performed when morphological imaging results are uncertain or possible recurrence is not detected but diagnosed recurrence will radically change further treatment and prognosis of a patient.

7. CONCLUSIONS

18F-FDG PET/CT is very useful for head and neck cancer staging, restaging, induction chemotherapy response assessment and radiotherapy planning, because it is more precise over morphological imaging. Currently, the biggest limitation, particularly in the post-treatment situation, is feasible false positive results because of inflammation and the inability to discover microscopic disease. It is possible that in the future, new tracers other than 18F-FDG, as well as PET/MRI imaging, will provide superior results in various clinical situations.
APPENDIX B

Figure A1

Figure A2

Figure A3

Figure A4
REFERENCES