The role of FDG-PET and PET/CT in the diagnosis and staging of head and neck cancer

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An estimated 644,000 cases of head and neck cancer are diagnosed worldwide each year, with head and neck squamous cell carcinoma (HNSCC) accounting for over 90% of these. Common presenting sites include the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx.1 While chronic tobacco use and alcohol consumption are well-established risk factors,2 human papillomavirus (HPV) infection of the upper aerodigestive tract has been causally linked to tumorigenesis.3 In particular, the increasing rates of oropharyngeal cancers, especially young non-smokers, have been directly attributed to HPV infection.

The diagnostic workup of HNSCC typically includes history and physical examination, endoscopic-guided biopsy and high-resolution contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). While CT and MRI have traditionally been the cornerstones of the imaging workup, 2-fluoro-[18F]-deoxy-2-D-glucose positron emission tomography (FDG-PET) plays an increasing role in the diagnosis, staging and follow-up of HNSCC patients.1,4,5

**FDG-PET AND PET/CT IMAGING**

FDG, a glucose analogue labelled with the radionuclide 18F, preferentially accumulates in cells that have an increased glycolytic rate – a characteristic feature of cancer cells.6 FDG-PET is thus a functional imaging modality that detects cellular metabolic changes, unlike CT and MRI, which rely on structural abnormalities. The positrons emitted by the radionuclide annihilate nearby electrons and create photons that are captured by an array of detectors and reconstructed into a 3D image. Although PET alone is limited by its lack of anatomic localization, the advent of the hybrid PET/CT scanner has overcome this by fusing PET and CT images acquired in a single session, permitting detailed visualization of both structural and functional aspects of disease.1,4-6

**STAGING OF HEAD AND NECK CANCER**

**TNM STAGING**

HNSCC is staged according to the size and extent of the primary tumour (T), regional lymph node involvement (N) and the presence of distant metastases (M).4 Accurate staging at the time of diagnosis is the most important factor for planning management and determining prognosis.4,7 Since the preservation or restoration of function is a top priority in the management of patients with HNSCC, function-sparing strategies such as minimally invasive surgery or (chemo)radiotherapy are often considered as first-line treatments.8 Thorough clinical assessment, including imaging, is vital to optimal staging of HNSCC. Furthermore, re-evaluation of patients following treatment may be especially challenging in HNSCC, due to difficulty in obtaining pathology. The following subsections review the clinical indications for FDG-PET and PET/CT in staging HNSCC.

**PRIMARY TUMOUR**

While PET and PET/CT have been shown to be at least as effective as CT or MRI at detecting primary tumours, these modalities are not used in standard practice to T-stage newly diagnosed HNSCC because their anatomic resolution is not as high as that of MRI or contrast-enhanced multislice CT.9-13 An early tumour may have poor FDG uptake and its detection on the scan may be obscured by cross contamination of physiologic activity from surrounding tissues – the so-called ‘spillover effect’.14 CT and MRI are useful for initial T-staging, since their high spatial resolution and soft-tissue contrast can demonstrate subtle abnormalities and accurately delineate tumour volume.

**CARCINOMA OF UNKNOWN PRIMARY**

In 2-9% of patients with newly diagnosed HNSCC, cervical node metastases are clinically evident at biopsy but the primary tumour cannot be identified by conventional workup, which includes physical examination, CT, MRI and endoscopic-guided biopsy.15 PET/CT has proven to be significantly more sensitive than CT (94.0 versus 71.6%, respectively, P < 0.001) at detecting carcinomas of unknown primary.16 Rusthoven et al. reviewed 16 studies published between 1994 and 2003 and found that among 302 patients with a negative conventional workup, FDG-PET detected the primary tumour in 74 patients (24.5%).17 In a more recent review, Al-Ibraheem et al. performed a meta-analysis of 8 studies published between 2000 and 2009.5 FDG-PET or PET/CT were able to detect the unknown primary in 51 of 180 patients with an otherwise inconclusive workup. Delineation of a primary tumour is essential for delivering targeted therapy, minimizing therapeutic morbidity caused by wide-field irradiation and improving prognosis.18 A recent report noted that findings made by FDG-PET changed therapeutic management in 25% of patients.19 In light of this evidence, PET/CT may have an important role in the diagnostic assessment of carcinoma of unknown primary.5

**CERVICAL NODE METASTASES**

Cervical node status is the most important prognostic factor in HNSCC.7 Cure rate declines by nearly 50% when cervical metastases are present.20 Metastatic lymph nodes are found in approximately half of patients at the time of diagnosis.21 PET/CT has been shown to have better sensitivity and specificity for pathologic cervical nodes than MRI and CT, likely because the latter rely on nodal size and contrast-enhancement criteria which are not specific and can miss metastases in normally sized nodes.22,23 Nevertheless, CT is generally used for local staging of clinically manifest cervical nodes at initial diagnosis, due to its clinical availability and accurate T-staging of the primary tumour.
CLINICALLY NEGATIVE (N0) NECKS
If clinical examination fails to identify metastatic cervical lymph nodes in patients with primary HNSCC, these patients are said to have a clinically negative (N0) neck. Since the probability that these patients actually have a pathological neck varies between 10-45%, elective neck dissection is recommended in cases where the risk of occult cervical mets is greater than 20%.4 While PET/CT is the most accurate imaging modality for detecting occult metastases, the role of PET/CT in the assessment of N0 necks is still controversial.7 Microscopic disease or nodal metastases located adjacent to the primary tumour may evade radiographic detection and contribute to false-negatives. Two studies reported sensitivity and specificity ranging from 67-79% and 82-95%, respectively, leading the authors to conclude that PET/CT is not yet accurate enough to inform the need for surgical dissection in cases of occult nodal disease.24,25

SECOND PRIMARY (SYNCHRONOUS) MALIGNANCY AND DISTANT METASTASES
Patients with advanced HNSCC are at higher risk for developing distant metastases and for presenting with a second primary (synchronous) tumour.26 The latter being defined as a histologically distinct malignancy, separated from the primary tumour by at least 2cm of normal mucosa.27 The cost of missing distant metastases or synchronous tumours at the time of initial diagnosis is high. Curative therapies are often associated with significant morbidity, necessitating the careful selection of patients with nonmetastatic disease who may benefit from the treatment and not eventually succumb to previously undetected distant disease.28 Aggressive subtypes, such as nasopharyngeal carcinoma, have a tendency to metastasize to the lungs, liver and bone; hence, the conventional imaging workup for distant metastases is comprised of chest radiography, abdominal ultrasound, and skeletal scintigraphy (bone scan). Several reports have assessed the efficacy of PET/CT in staging distant metastases and synchronous tumours and found that it is the most sensitive, specific and accurate modality and may replace conventional techniques.14,28,29 A multicentre prospective study of 92 patients found that PET/CT had a higher sensitivity (63%) than chest CT (37%), due to its ability to image the whole body with a single scan and detect distant hypermetabolic foci.30 PET/CT can therefore be considered as the modality of choice for the diagnostic workup of distant metastases and synchronous tumours.7

RESIDUAL AND RECURRENT DISEASE
The reliance of CT and MRI on morphologic criteria often makes the detection of post-treatment residual tumour activity or recurrent disease difficult, since the regional head and neck anatomy may be distorted after therapeutic (chemo)radiotherapy and/or surgery.4 Al-ibraheem et al. reviewed the utility of PET and PET/CT for identifying disease recurrence in head and neck cancers.5 Among 7 studies published between 2004 and 2009, PET or PET/CT demonstrated high sensitivity (83-100%) and relatively high specificity (78-98%) and accuracy (81-90%), often significantly outperforming CT and MRI. Inflammation and infection are common treatment sequelae that may increase FDG uptake in certain tissues; hence, the addition of CT to PET is especially important in these situations in order to distinguish truly pathologic areas from post-irradiated tissue.12,22 The anatomical landmarks provided by CT have been shown to decrease the number of equivocal hypermetabolic foci and therefore reduce the amount non-invasive imaging and invasive biopsies required for diagnosis of recurrence.12

LIMITATIONS
False-positives
In addition to the post-irradiation changes discussed above, increased FDG uptake may occur in benign hyperplastic conditions such as thyroid or pleomorphic adenomas. Regional physiologic FDG uptake in lymphoid tissue, salivary glands, strained or excessively used skeletal muscles and activated brown fat tissue may also confound interpretation and be erroneously attributed to malignancy.4,6 It is recommended that positive results be confirmed by biopsy.6

False-negatives
Since the spatial resolution of FDG-PET is limited to 4-10mm, its ability to precisely localize small tumours or microscopic tissue involvement is often diminished in the head and neck region. Tumours with low metabolic rate and poor avidity for FDG uptake may also be difficult to characterize on PET scans.6

SUMMARY AND RECOMMENDATIONS
In 2009, Yoo and Walker-Dilks reviewed the data and made recommendations for the use of FDG-PET in head and neck cancer.31 The guidelines, part of an initiative of the Program in Evidence-Based Care for Cancer Care Ontario, are consistent with the findings reviewed here and are summarized in Table 1. It is worthwhile to note that studies examining PET and PET/CT were not distinguished in the report; however, the hybrid system clearly confers a diagnostic advantage over either modality alone.4,7 Despite its limitations, increasing use of PET/CT for the diagnosis, staging and follow-up of HNSCC patients has provided physicians with a powerful tool that will continue to improve patient outcomes as the technology advances and clinical guidelines are refined.

REFERENCES

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**Table 1. Recommendations for FDG-PET in head and neck cancer. Adapted from Yoo and Walker-Dilks.31**

<table>
<thead>
<tr>
<th>FDG-PET and PET/CT are recommended for:</th>
<th>Diagnosis/Staging</th>
<th>Recurrence/Restaging</th>
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<td>M and bilateral nodal staging of advanced HNSCC displaying equivocal conventional imaging</td>
<td>identification of unknown primary site, in addition to conventional imaging and diagnostic panendoscopy</td>
<td>restaging patients who are being considered for major salvage treatment (surgery or other)</td>
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