Role of FDG PET / CT Imaging in Brain, Head and Neck Cancers

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Introduction

PET/CT with 18F-FDG is now established as an important imaging modality in many clinical conditions, particularly in oncology.

Many tumours demonstrate high glucose metabolism as one of the hallmarks of cancer.

PET/CT provides combined anatomic and physiologic (glucose metabolism) information that may be used for initial diagnosis, staging, restaging, treatment response assessment, and prognosis in patients with cancer.

Common malignant brain tumours

Benign and malignant primary brain tumours, metastases, nontumoral conditions such as demyelination, infection/ abscesses, and infarction present as space-occupying lesions (SOL). Clinical presentation and laboratory findings in conjunction with MRI features are used to achieve a specific diagnosis.

Occasionally, MRI features can overlap and an accurate diagnosis becomes difficult. PET using fluorine-18-fluorodeoxyglucose (18F-FDG) measures metabolic activity of tumours and has been used to image brain tumours for indications such as establishing a diagnosis, assessing response to therapy, and as a prognostic marker.[1]

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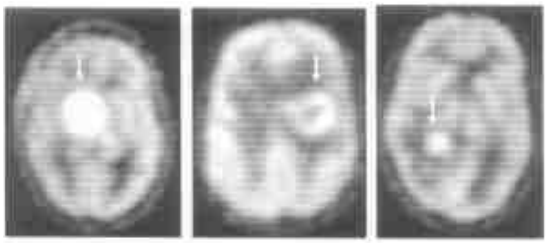

CNS lymphomas, Glioblastomamultiforme (GBM), and metastases account for the majority of malignant brain SOL.

CNS lymphomas show a higher glucose concentration compared with GBM and metastases. SUVmax cutoff of 15.5 could differentiate lymphoma from GBM and metastases with a sensitivity of 84% and a specificity of 80%.[2]

18 F-FDG PET to be useful in differentiating lymphoma from other nonmalignant CNS lesions in patients with AIDS.

18F-FDG uptake in GBM and metastases can be similar and can cause problems in interpretation; however, this issue can be overcome as the whole-body nature of PET examination can detect the primary tumour in most patients.

In addition to its ability to characterise brain lesions as lymphomas, 18F-FDG PET can detect systemic or extracranial sites of lymphomatous involvement.

Head and neck cancers

PET can be used to measure blood flow and to evaluate metabolic processing and receptor mediated function. -

FDG PET is an effective means of detecting head and neck cancer. PET has both greater sensitivity (86%-100%) and greater specificity (69%-87%) than CT (67%-82% and 25%-56%, respectively) for the detection of both primary tumours and lymph node metastases. In addition, inflammation of head and neck tissues due to mucosal ulceration, associated infection, and treatment-related effects may result in nonspecific FDG uptake.

The most powerful application of PET-CT has been the detection of residual or recurrent head and neck neoplasm after treatment.

Post-treatment effects make it difficult to distinguish normal post therapy tissue changes from tumour recurrence clinically, radiologically, and histologically. Neck dissection and flap reconstruction distort the normal neck anatomy and make detection of recurrent neoplasm challenging on the basis of structural changes alone.

Radiation therapy can further complicate imaging by making tissue planes indistinct and by causing oedema that may produce an increase in tissue volume.

Serial imaging with CT and MR imaging is the mainstay for monitoring patients with head and neck tumours. Stability of a lesion over several months suggests scar, whereas interval growth indicates residual or recurrent neoplasm; however, potential treatment time may have been lost, and the stage of cancer may progress.

PET has proved to be a useful adjunct in detecting tumour and differentiating recurrent tumour from post-therapy tissue necrosis.

Detection of Recurrent Cranial Base Neoplasm

Recurrent skull base neoplasm is notoriously difficult to detect with anatomic imaging techniques.

Successful treatment of skull base neoplasm is predicated on precisely localising tumour and differentiating it from scar.

The high negative predictive value of FDG PET/CT may allow those with negative findings at post-treatment FDG PET to avoid neck dissection, although continued short-interval clinical and imaging follow-up is essential.

The US-guided procedure maybe performed for further work-up when FDGPET/ CT images show either a lymph node larger than 1 cm without FDG uptake or a lymph node smaller than 1 cm with FDG uptake.

Even after the absence of residual disease is established, continued surveillance is necessary with clinical examinations at regular intervals.

Regular surveillance is especially important in the first 2 years after treatment, since two-thirds of disease recurrences are found during that initial period.

FDG PET/CT may be performed when there is a suspicion of recurrence or at regular 6 to 12 month intervals in asymptomatic patients. Patients who have had one primary head and neck cancer are at an increased risk for a second (metachronous) primary malignancy.

Nasopharynx carcinoma (NPC)

The World Health Organisation classification of NPC recognises three histologic types.

Keratinising squamous cell carcinoma (type1), Nonkeratinising carcinoma (type 2a) and Undifferentiated carcinoma (Type 2b).

The mucosal spread of this tumour shows a preference for superior spread to the skull base, rather than inferior spread to the oropharynx.[3] Tumour often spreads submucosally and through areas of lesser resistance of the pharyngobasilar fascia and into the deep spaces of the neck.

Deep infiltrating tumours may be found even when the nasopharyngeal component is small. The nasal cavity is commonly involved by NPC. Minimal invasion of tumour to the margin of the choanal orifice is common. Inferior superficial extension down to the mucosa of the oropharynx. Parapharyngeal spread occurs when tumour spreads posterolaterally and usually involves lateral penetration through the levator palatini muscle and pharyngobasilar fascia to involve the tensor palatini muscle and parapharyngeal fat space.

Invasion of the parapharyngeal space is associated with an increased risk of distant metastases and tumour recurrence. Further posterolateral spread may also involve the carotid space and encase the carotid artery.

Retropharyngeal spread occurs when tumour spreads posteriorly to involve longus capitis muscles and prevertebral space. This region contains lymphatics and a venous plexus, and so invasion of the prevertebral space is associated with an increased risk of distant metastases. Bulky disease continuing down to the foramen magnum and upper cervical spine. NPC has a propensity to invade the skull base at diagnosis.

The clivus, pterygoid bones, body of the sphenoid, and apices of the petrous temporal bones are most commonly invaded. CT reveals permeative or erosive bone changes of the skull base or spread along foraminal pathways. Also, sclerosis of the pterygoid process with increased attenuation of medullary cavity or thickening of cortical bone may be detected. Tumour frequently invades the skull base foramina (foramen rotundum, oval, and lacerum and vidian canal) and fissure (pterygomaxillary and petroclival). Tumour extended into the pterygopalatine fossa provides a route of spread to the orbit, infratemporal fossa, nasal cavity, and middle cranial fossa. Paranasal sinus involvement occurs as a result of direct extension. Maxillary sinus involvement occurs after nasal or infratemporal maxillary wall erosion.

Meningeal involvement appears as nodular enhancement, often along the floor of middle cranial fossa or posterior to the clivus. Invasion of cavernous sinus can lead to multiple cranial palsies. Orbital invasion is a marker of extensive disease. Infiltration of the medial and lateral pterygoid muscles, infratemporal fat, and temporalis muscle is found when tumours extend laterally from the parapharyngeal space, pterygoid base, or the pterygomaxillary fissure. Hypopharynx is the most inferior site of tumour invasion.

MRI is an accurate test for the diagnosis of NPC. MRI aids in the accurate staging of NPC by detecting primary tumour spread; parapharyngeal, orbital, and paranasal involvement; and spread to lymph nodes (LNs), especially the retropharyngeal LNs.[4] CT has long been used for staging NPC, especially for the detection of skull base tumour involvement with lytic or sclerotic lesions. FDG PET/CT has a sensitivity of 97-100% and specificity of 73-97% in assessing-cervical nodes in patients with NPC, and MRI has a sensitivity of 84-92% and specificity of 73-97%. FDG PET/ CT being particularly useful in assessing lower cervical node metastases. Whole-body FDG PET/ CT has the ability to assess both the primary tumour and the distant metastases in a single examination.

FDG PET/CT is increasingly used in radiotherapy planning of NPC. FDG PET can provide the Gross tumour volume (GTV) that needs to be irradiated. FDG PET has the potential to assess the response of the tumour early during treatment. FDG PET has a significantly higher specificity for recurrence than MRI (96% vs 63%, respectively; $p = 0.04$).[5] PET/CT often provides an easier method for differentiating tumour recurrence from fibrosis.

MRI and FDG PET have complementary roles, with MRI contributing to T staging and FDG PET having greater efficacy for N and M staging.[6]

Oropharynx carcinoma

The oropharynx is the part of the pharynx that is posterior to the oral cavity, between the nasopharynx and the hypopharynx. The oropharynx contains the base (posterior one-third) of the tongue, palatine tonsils, soft palate, and oropharyngeal mucosa. The anatomic subdivisions of the oropharynx are (a) the base of the tongue and (b) the tonsils.

Squamous cell carcinomas (SCC) of the oral cavity and oropharynx may spread in three general ways: (a) by direct extension over mucosal surfaces, muscle, and bone, (b) by dissemination via lymphatic drainage pathways, and (c) by extension along neurovascular bundles.

A large percentage of oral and oropharyngeal SCCs initially manifest with a neck mass that represents the involvement of cervical nodes.

SCCs in the oral tongue manifest with regional disease in 40% of patients, whereas SCCs in the lip, buccal mucosa, and hard palate are less likely to manifest with lymphadenopathy.

CT findings of osseous involvement include cortical erosion adjacent to the primary lesion, aggressive periosteal reaction, abnormal attenuation in bone marrow, and pathologic fractures. Imaging features of perineural spread include foraminal enlargement and replacement of normal fat within the neural foramen.

Lip

The lip is the most common site of SCC of the oral cavity (approximately 40% of cases). Lip lesions are easily assessed with direct visualisation, and only infiltrative tumours with uncertain margins require imaging.

Buccal Mucosa and Gingiva

Evaluation of a buccal or gingival

mucosal lesion should address the extent of submucosal spread, osseous involvement, involvement of the retromolar trigone and pterygomandibular raphe, and cervical lymphatic spread. Involvement of the mandible, as opposed to the maxilla, introduces the possibility of perineural or intramedullary extension. Tumour involvement of the maxilla may also allow spread in to the paranasal sinuses. Tumour extension into the retromolar trigone and pterygomandibular raphe is of particular concern because these structures provide numerous routes of spread, making surgical treatment more difficult.

Floor of the Mouth

Superficial lesions at this site are often difficult to assess at imaging. However, imaging is necessary to define the extent of disease because it is difficult to ascertain the depth of invasion at physical examination. Evaluations of SCC of the floor of the mouth should include a determination of the extent of submucosal invasion (whether the midline is crossed, whether the tumour extends into the submandibular space), involvement of the neurovascular pedicle, mandibular osseous involvement, and cervical lymphatic involvement.

Oral Tongue

Evaluation of an oral tongue lesion requires assessments for involvement of the submucosa, the intrinsic musculature of the tongue, the neurovascular bundle, bone, and cervical lymph nodes, as well as invasion across the midline of the tongue.

SCCs of the oral tongue occur predominantly along its lateral and ventral surfaces. Oral tongue lesions tend to spread along the submucosa and may involve the floor of the mouth and the mandibular gingiva.

Hard Palate

Primary SCC of the hard palate is rare and often represents extension from an adjacent gingival lesion. SCC of the hard palate may extend laterally to invade the maxillary alveolar ridge or superiorly to involve the nasal cavity and maxillary sinuses.

Perineural spread of palatine lesions is best evaluated with MR imaging.[7]

Base of the Tongue

The base of the tongue extends from the circumvallate papillae anteriorly to the valleculae inferiorly. Evaluation of SCCs of the base of the tongue should include a determination of the extent of (a) submucosal involvement, (b) involvement of the intrinsic muscles of the tongue, (c) crossing of the midline of the tongue, (d) invasion of the pre-epiglottic fat, (e) osseous involvement, and (f) cervical lymphatic spread.

The primary lymphatic drainage is to level II, III and IV lymph nodes. SCCs of the tongue base often originate on one side and spread laterally to the tonsillar pillars, anteriorly to the sublingual space, or posteriorly under the valleculae.

Tonsils

Tonsillar subsites include the anterior and posterior tonsillar pillars, which overlie the palatoglossus and palatopharyngeus muscles, respectively, and the palatine tonsils.

Evaluation of tonsillar SCC primarily involves the assessment of submucosal

invasion because there are multiple unobstructed routes by which the tumour may spread into the nasopharynx, parapharyngeal space, masticator space, skull base, and tongue base.

CT is usually the modality of choice for the initial imaging study; however, with tonsillar SCCs, as with SCCs of the retromolar trigone, MR imaging is more useful for a complete evaluation of soft-tissue extension.

Evaluation of a tonsillar SCC should include a determination of the extent of (a) submucosal extension, (b) involvement of the pterygoid muscles, (c) extension along the pterygomandibular raphe to the skull base, (d) osseous involvement, and (e) involvement of the cervical lymph nodes.

Most SCCs of the tonsil originate in the anterior tonsillar pillar. These tumours tend to spread superiorly along the palatoglossus muscle to the hard and soft palates. From there, they may continue to spread along the tensor and levator palatine muscles as well as the pterygoid muscles. Tonsillar SCCs also may spread upward to the nasopharynx. Anterior and medial spread tend to occur along the superior constrictor muscles to the pterygomandibular raphe, by means of which the tumour may gain access to the skull base and cranial nerves. Tumour also may extend posteriorly to the retropharyngeal or carotid space or inferiorly to the tongue base.

Osseous involvement in tonsillar SCCs occurs primarily along the pterygoid plates and the maxilla. Lymphatic involvement is common.

Roles and Limitations of PET /CT

Combining assessment of FDG activity with the use of size criteria and morphologic findings can further decrease the error rate. FDG PET/ CT does have an advantage in staging nodal disease, offering a sensitivity of 90% and a specificity of 94%, compared with CT (sensitivity, 82%; specificity, 85%), MRI (sensitivity, 80%; specificity, 79%), and ultrasound(sensitivity, 72%). PET/ CT is the modality of choice for the detection of metastases and has a sensitivity, specificity, and accuracy of 92%, 99%, and 98%, respectively.

FDG PET/CT detects distant metastases or a second primary tumour in up to 15% patients with squamous cell carcinoma of the head and neck, with true-positive findings noted for 82%; such finding in scan significantly alter treatment planning.

FDG PET/ CT has been shown to alter the management of 13.7-5 5% of patients with squamous cell carcinoma of the head and neck.

FDG PET/ CT performed after initial chemoradiotherapy has a high specificity (90-95%) and a high negative predictive value (92-97%), adding confidence to exclusion of disease recurrence, and that it can be used to defer lymphnode dissections. Another use for PET/CT imaging of head and neck cancer is to locate an unknown primary tumour site after lymph node biopsy reveals squamous cell carcinoma.

However, the main limitation of FDG PET/CT is low sensitivity (35-71%) and a positive predictive value (38-50%)

necessitating the concurrent use of traditional imaging modalities for disease surveillance.

Fasciculations in the remaining denervated tongue, which are a postsurgical finding after hemiglossectomy, have intense FDG activity. The abnormal FDG activity resulting from fasciculations should not be mistaken for recurrent tumour.

Laryngeal carcinoma

Patients with laryngeal carcinoma have been found to have a higher risk for second primary carcinomas, usually involving the lung and upper aerodigestive tracts.[8]

The negative prognostic factors include invasion of the laryngeal cartilage, extranodal spread of disease, invasion of the pre-epiglottic and paraglottic fat, and carotid artery fixation.

However, even in patients with T codes of early stage SCC, baseline FDG PET/ CT images with intravenous administration of contrast material should be obtained to use for comparison at subsequent post-treatment follow-up. The metabolic activity of the primary tumour measured as the standardised uptake value (SUV) can have prognostic implications. Schwartz et al looked at 63 patients with SCC of the head and neck and found that a pretreatment SUV of less than 9 in the primary tumour was predictive of a lower rate of local recurrence and improved disease-free survival compared with a primary tumour SUV of 9 or more.[9]

Similarly, Minn et al found that an SUV of more than 9.0 in a primary tumour was predictive of advanced clinical stage, low-to-moderate histologic grade of differentiation, and poor overall disease survival.[10]

Supraglottic SCC.: Approximately 30% of all laryngeal SCCs arise in the supraglottis. Early nodal metastases are common because of the rich lymphatic network draining to the upper deep cervical nodes. Assessment of the inferior margin of supraglottic SCC is of prime importance because involvement of the laryngeal ventricles, arytenoids cartilages, or the anterior commissure of the larynx precludes treatment with supraglottic laryngectomy.

SCC arising from the aryepiglottic fold can grow either anteriorly into the epiglottis or laterally into the paraglottic space. SCC arising from the epiglottis can spread anteriorly into the pre-epiglottic space or laterally into the pharyngeal wall or can spread along the glossoepiglottic fold to reach the base of the tongue.

Glottic SCC.:Approximately 60% of laryngeal SCCs arise in the glottis. Because these lesions involve the true vocal cord, patients tend to present early with hoarseness.

Nodal metastases are relatively uncommon. Tumours can spread through the anterior commissure to invade the opposite cord. Soft-tissue thickening of the anterior commissure of more than 1 mm indicates malignant invasion. In addition, any FDG uptake in the opposite cord at PET imaging should raise suspicion for malignant involvement. Once tumour has invaded the anterior commissure, it can spread further anteriorly into the thyroid cartilage, superiorly into the paraglottic

space, or inferiorly into the subglottis. Glottic tumours can also spread posteriorly into the posterior commissure, arytenoid cartilage, cricoid cartilage, or cricoarytenoid joint. Defining the inferior extent of the tumour is critical because subglottic involvement necessitates total laryngectomy.

Subglottic SCC.: SCC of the subglottis is rare, accounting for only 5% of laryngeal SCCs. Because the mucosa] surface of the subglottis is closely applied to the cricoid cartilage, any tissue seen on the airway side of this region should be considered tumour. SCC has a poor prognosis because patients only present when the tumour is large and has invaded the surrounding soft tissues, which can result in stridor. Subglottic SCC can spread superiorly into the true cords and supraglottis, inferiorly into the trachea, anteriorly through the cricothyroid membrane into the thyroid gland, or posteriorly into the cricoid cartilage and oesophagus.

Hypopharyngeal SCC: The most common malignant tumour of the hypopharynx is SCC (95%). Hypopharyngeal SCC tends to be more aggressive than laryngeal SCC and also has a rich lymphatic drainage, which results in a high incidence (50%-75%) of nodal metastases at the time of diagnosis. Carcinomas of the hypopharynx are most common in the piriform sinus (60%), followed by the postcricoid area (25%), and lastly, the posterior pharyngeal wall (15%). Tumours on the anterior wall of the piriform sinus can spread anteriorly into the paraglottic space and those tumours arising laterally in the piriform sinus spread posterolaterally into the soft tissues of the neck, eroding the thyroid cartilage.

The CT criteria for malignant adenopathy are based on the size and morphologic structure, 1.5 cm or more in greatest dimension for level I or II nodes, 0.8 cm or more in greatest dimension for nodes in the retropharynx, and more than 1 cm in greatest dimension for others.

If the node appears amorphous with a speculated or indistinct border, extranodal (extracapsular) spread should be suspected. Specifically, if the carotid artery is completely surrounded by tumour ("carotid fixation") most surgeons will not operate.

The overall accuracy of FDG PET/ CT is significantly higher ($P < .05$) than that of CT alone in identifying nodal disease in the neck on a level-by-level basis. FDG PET has been shown to be most useful in detecting nodal metastases in patients with more-advanced T nodes, when nodal disease is more likely. The combination of FDG PET with CT is most useful in detecting occult metastases in patients with advanced-stage SCC of the head and neck. The most common site of metastatic disease is the lung, followed by bone and the abdomen. FDG PET may be used to detect occult metastases.

It is well established that patients with head and neck SCC have an increased likelihood of a second primary cancer. Synchronous tumours usually occur in the lung or the upper aerodigestive tract, likely caused by risk factors similar to those for SCC.[11]

Combined FDGPET/ CT imaging have superior diagnostic accuracy in detecting recurrent head and neck cancer compared with MR imaging and CT. In a large meta-analysis, Isles et al found that the pooled sensitivity and specificity of FDG PET in the detection of residual or recurrent head and neck SCC were 94% and 82%, respectively.[12] Brun et al demonstrated that decreased FDG activity in the early phase of combined chemotherapy and radiation therapy for head and neck SCC is associated with greater tumour response, survival, and local control. Conversely, persistent FDG uptake indicates incomplete or poor response to therapy, which can alert the clinician to modify treatment.[13]

Protocol to be useful in the follow-up of patients with head and neck SCC: (a) contrast-enhanced CT 1 month after definitive therapy, (b) FDG PET/contrast-enhanced CT every 3 months for the 1st year, (c) FDG PET/contrast-enhanced CT every 6 months for the 2nd year, and (d) FDGPET/contrast-enhanced CT annually thereafter for 5 years or until recurrence.

Pitfalls

Tumours with inherently low FDG uptake such as salivary gland neoplasms and necrotic neoplasms may yield false-negative results.

Salivary gland neoplasms and spindle cell neoplasms may not be FDG avid.

Low-grade adenoid cystic and mucoepidermoid carcinomas might show only faint uptake or none at all.[14]

Mandibular osteonecrosis, a rare complication in this patient population, also may be depicted as a focal area of increased uptake at FDG PET/CT. This appearance may cause it to be mistaken for skeletal metastasis.

Scanner resolution also limits the evaluation of small malignancies or subcentimeter nodal metastases, which may not be detected because the current resolution of FDG PET is about 5-7 mm.

Specific pitfalls in post-treatment imaging of the larynx with FDG PET include slight homogeneous FDG uptake caused by tissue healing at (a) the tracheostomy site, (b) the tracheo-oesophageal puncture site for a placement of a voice valve (a prosthetic valve placed to allow for speech in laryngectomy patients), (c) anastamoses from free-flap reconstruction of a neopharynx[70].

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Intracerebral haemorrhage: no good treatment but treatment helps

When intracerebral haemorrhage is complicated by intraventricular haemorehage the prognosis is even worse; more than half of patients are estimated to die during the acute phase and most survivors are disabled by the brain injury.

Daniel Hanley and colleagues tested whether scheduled intraventricular boluses of the thrombolytic drug alteplase (given through clinically indicated ventriculostomy catheters) could improve functinal outcomes in patients with intraventricular haemorrhage from intrcerebral haemorrhage by accelerating resolution of the intraventricular clot.

No differences were noted in the self-reported measure of quality of life between the two groups.

Yet, there is a lot of learn from this trial.

The power analysis, based on previous data, estimated that 22% of the control group would achieve a good functional outcome, but the rate in CLEAR III was 45%.

Some data suggest that the deleterious effects of intraventricular haemorrhage might be caused primarily by the hydrocephalus it produces.

My experience in practice has been that residual hydrocephalus after intraventricular haemorrhage is often underdiagnosed and consequently undertreated.

Well-designed neutral trials can teach us a lot. Based on the results of CLEAR III, intraventricular alteplase cannot be recommended at present for the treatment of intraventricular haemorrhage in clinical practice. However, its administration is safe and aggressive clearance of the intraventricular clot, when truly achieved, might improve morbidity and mortality. There is some support for dual simultaneous ventricular drainage catheters for patients with severe intraventricular haemorrhage.

We might not have great specific treatments for intracerebral haemorrhage or intraventricular haemorrhage, but doing what we can is still very useful.

Alejandro A Rabinstein, The Lancet, 2017, Vol 389