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PET in face and neck tumours

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Abstract

FDG-PET is a useful tool in the imaging of head and neck tumours. It can be used to stage the primary tumour, to assess response to therapy and most importantly for the detection of recurrent tumour. The advantages and limitations of this technique are discussed in this article.

Keywords: *FDG-PET; PET-CT; head and neck cancer; staging; recurrent disease; response to therapy.*

Introduction

Positron emission tomography (PET) is an imaging technique that can map functional and metabolic activity before structural changes have taken place. PET scanning using $[2-^{18}F]$fluoro-2-deoxy-D-glucose (^{18}FDG) can differentiate malignant from normal tissue based on enhanced glycolysis by tumour cells and can thus identify tumour in normal sized lymph nodes, differentiate sinus malignancy from secretions and fibrosis from tumour. PET appears to be the best imaging method for assessing recurrent tumour although there are problems with false positives due to inflammation[1]. It is also possible to quantify uptake in absolute units, a factor that may increase sensitivity when monitoring metabolic changes after treatment, with a reduction in uptake correlating with tumour regression and a high initial uptake predicting a poorer outcome[2]. There is increased uptake of ^{18}FDG in infection and low grade tumour may have similar uptake ratios to infection.

A further advantage of PET is the ability to perform whole body scanning to identify synchronous primary tumours, distant metastases and identify the site of the primary in patients who present with cervical node metastases[1,3]. Positron emission tomography has limited spatial resolution that is not as good as computed tomography (CT) or magnetic resonance imaging (MRI) but the development of combined PET-CT has overcome this problem.

Patients are fasted for 6 h prior to the PET examination. Transmission scans are acquired in addition to emission scans so an attenuation corrected image can be generated. In combined PET-CT scanners the CT scan is used to generate the transmission map, with a consequent decrease in overall acquisition time, as well as provide anatomic co-registration. 18-FDG (350 MBq) is injected and after a wait of approximately 1 h for the tracer to be taken up by the tissues the images are acquired from the vertex to the pelvis. Standardised uptake values (SUVs) can be calculated (SUV = activity in region of interest (ROI)/volume of ROI/injected activity/weight of patient) and can be corrected for partial volume effect. Patients are instructed to remain silent to limit physiologic uptake in the vocal cords.

Normal uptake in the head and neck

There is a spectrum of normal and physiologic uptake in the head and neck and these patterns must be recognised[4].

Thyroid gland

This has a variable appearance with minimal, diffuse or focal uptake. Focal uptake is non-specific and may be seen in thyroid adenomas or in thyroid malignancy. Irrespective of the primary tumour being investigated focal thyroid uptake, which is seen in 4% of all studies may represent a second primary in 38% of patients and intense uptake should be further investigated[5]. Diffuse

symmetrical uptake may be seen in a normal thyroid as well as in autoimmune thyroiditis.

Salivary glands

FDG is taken up by the salivary glands and excreted into the saliva. The parotid and submandibular salivary glands usually show mild uptake (Fig. 1). Focal uptake may be seen in both benign and malignant lesions including Worthin tumours, pleomorphic adenomas and lymphoma. Benign granulomatous conditions such as sarcoidosis will also demonstrate increased uptake. FDG-PET cannot be used to differentiate benign from malignant parotid disease[6].

Muscles

Uptake in muscles is not uncommon and usually appears as linear symmetric uptake. Focal uptake is often in myotendinous junctions and this is well shown on PET-CT. Uptake is frequently seen in the sternocleidomastoid muscles, myelohyoid and the pterygoid muscles and the inferior oblique capitis. This uptake may be symmetrical or asymmetrical. If the patients are hyperglycaemic and are give insulin prior to the scan there may be increased FDG uptake into muscles and fat.

Oropharynx and nasopharynx

Uptake is commonly seen in the adenoids, lingual tonsils and palatine tonsils (Fig. 2). Mucosal uptake will also occur.

Larynx

Uptake is frequently seen in the muscles of phonation including the cricopharyngeus and in the vocal cords especially if the patient talks during FDG uptake. Vocal cord palsy can be identified by asymmetric uptake of FDG and correlated with the CT to distinguish it from laryngeal tumour (Fig. 3). Uptake is also seen in the constrictor muscles if the patient coughs.

Fat

Intense uptake may be seen in brown fat, this can easily be distinguished from lymphadenopathy or muscle with PET-CT.

Artefacts

Prosthetic devices may produce relatively photopaenic areas on both PET and PET-CT, but there are some artefacts generated by the use of CT for attenuation correction. These may occur if intravenous contrast is used as the dense contrast material in venous structures may cause areas of intense accumulation on the attenuated corrected PET but not on the non-attenuated PET. Small malignant lymph nodes immediately adjacent to a contrast artefact may be obscured.

Indications for FDG-PET

The indications for FDG-PET include staging the primary tumour including nodal disease and distant metastases, treatment planning, response to treatment, identifying an unknown primary and probably, most importantly, identifying recurrent disease.

Staging the primary tumour

Extent of primary disease

FDG-PET has limited value in assessing the primary tumour providing no information on the pattern of local spread, the presence of deep infiltration, bone and cartilage destruction or perineural spread[7]. The development of integrated PET-CT has overcome some of these problems, providing additional information in 18–20% of patients compared to PET alone[8,9] however bone invasion is better identified with contrast enhanced CT[10] nevertheless PET-CT may be helpful in defining the extent of tumour better than CT alone especially in post surgical cases. Lesions are considered suspicious for malignancy if the SUV is greater than 2.5–3, although inflammatory lesions may have similar values and variable physiologic uptake may cause some problems. The spatial resolution of PET-CT is approximately 5–7 mm and lesions smaller than 1 cm may be missed or have a SUV less than 3 because of partial averaging.

The initial SUV does appear to provide some prognostic information about response to therapy[11] but not the risk of relapse after treatment[12].

Cervical lymph node assessment

Nodal staging is very important for the appropriate management of head and neck tumours. Clinically negative, but tumour positive nodes are detected in 7.5–19% of cases.

On CT normal lymph nodes are well-defined round or oval structures of similar attenuation to muscle. Nodes greater than 1 cm, except the jugulo-diagastric nodes, which may be up to 1.5 cm in length, are considered abnormal. Groups of smaller nodes are also suspicious with numerous nodes 8–15 mm in length or 8–9 mm in axial diameter suggestive of malignancy.

The results of a meta-analysis of CT vs. physical examination have shown that CT is more sensitive,
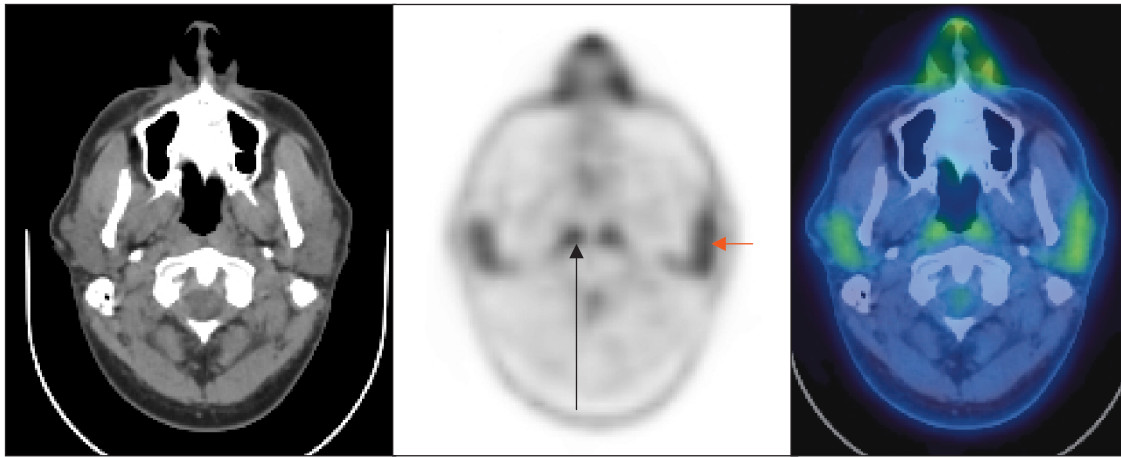
Figure 1 **Normal FDG-PET-CT. Axial scan with low grade uptake in the adenoids (long arrow) and parotid (short arrow).**
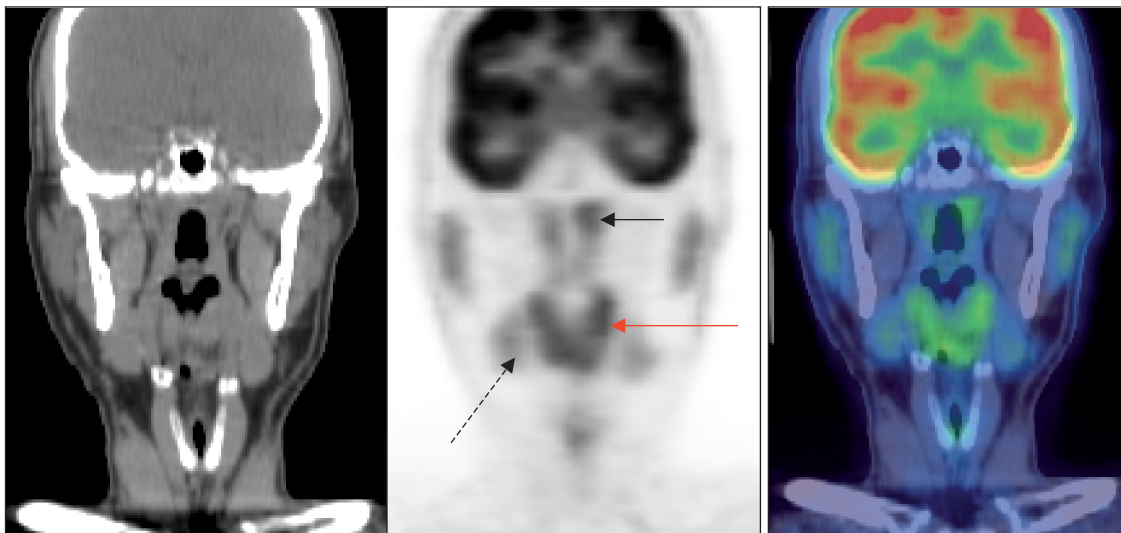

Figure 2 **Normal FDG-PET-CT. Axial scan with uptake in a normal palatine (short arrow) and lingual (long arrow) tonsils. Low grade uptake also in the submandibular salivary gland (broken arrow).**

specific and accurate than physical examination (PE) alone but not significantly so. The sensitivity of CT was 83% (PE 74%), specificity 83% (PE 81%) and accuracy 83% (PE 77%). Overall physical examination identified 75% of pathological nodes, however if the modalities were added the detection rate rose to 91%[13]. The addition of MRI has not added anything and one study comparing MRI and physical examination found the sensitivity and specificity were 75% and 97% for physical examination and 73% and 95% for MRI[14]. Curtin *et al.*[15] found CT has a negative predictive value of 84% (MRI 79%), and a positive predictive value of 50% (MRI 52%). The use of ultra small superparamagnetic iron oxide particles (SPIO) as lymphangiographic agents in MRI does offer potential for improvement with a recent study by Mack *et al.*[16] using this technique reported sensitivity of 86% and specificity of 100%

for metastatic nodes, although micrometastases may be missed.

PET utilises activity rather than size and has a reported sensitivity for nodal detection of 80–96% with specificity of 90–94% (Fig. 4). In a recent study FDG-PET was superior to both MRI and CT for the detection of cervical nodal metastases with a sensitivity for FDG-PET of 90% (CT 82%, MRI 80%) and specificity 94% (CT 85%, MRI 79%)[17].

Metastases

FDG-PET is a whole body imaging system and so can identify distant metastases and second primary malignancy. FDG-PET will identify more metastases than CT or MRI. Sigg *et al.*[18] reported FDG-PET sensitivity and specificity for nodal disease of 94% and
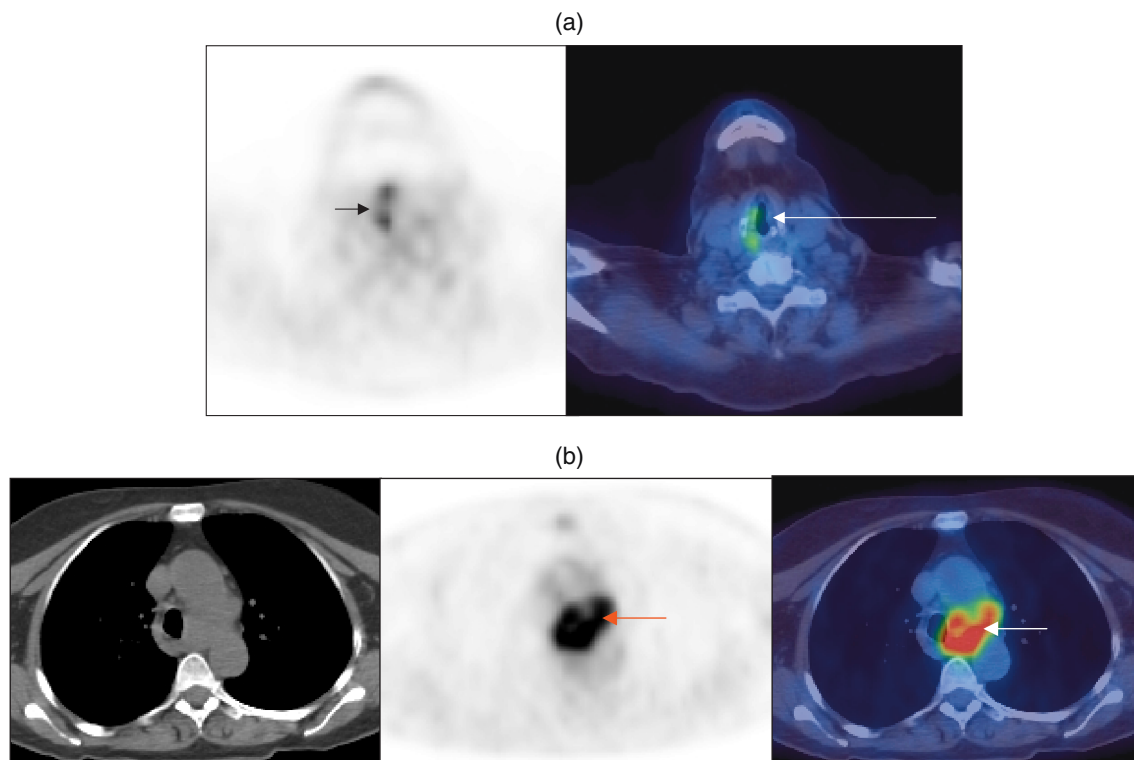
(a)

(b)

Figure 3   **PET-CT in a patient with a left vocal cord palsy. (a) PET-CT of the neck. Uptake is seen in the normal right vocal cord (short arrow). The CT confirms the left cord palsy (long arrow). (b) PET-CT of the chest. The cause of the cord palsy is the malignant lesion in the aorto-pulmonary window (arrow).**
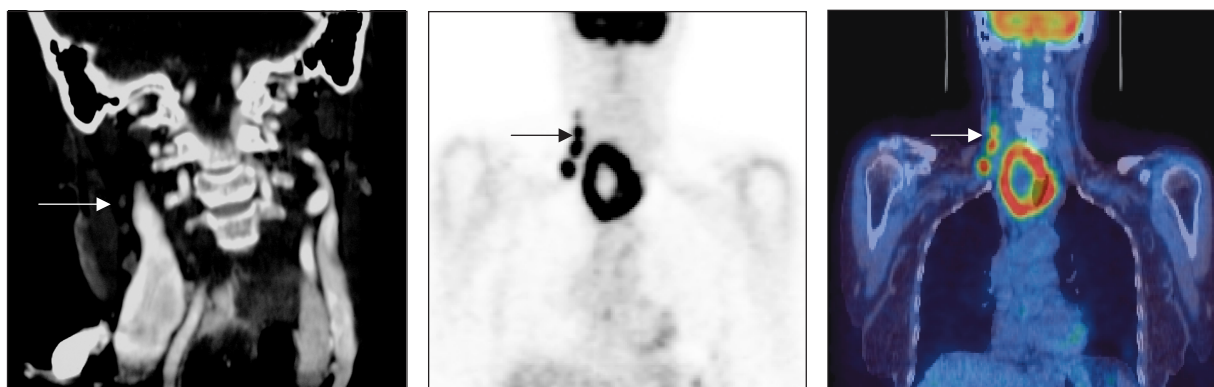

Figure 4   **Patient with carcinoma of the thyroid. PET-CT shows intense metabolic activity in lymph nodes indicating malignancy. Some of the nodes (arrow) would be called normal based on CT size criteria.**

97% and for distant metastases of 83% and 100%, it also provided additional information compared to CT and altering management in 11% of patients.

Recurrent disease

The distortion following neck dissection and the inflammatory reaction and loss of fat planes following radiotherapy makes identification of tumour very difficult using either CT or MRI. This is a particular problem with base of skull tumours where post therapy bone or cartilage necrosis and soft tissue desmoplastic changes may mimic malignancy. Serial imaging is undertaken with stability or a decrease in size of a lesion indicating scarring whereas growth indicates tumour. However this may lead to a delay in diagnosis or unnecessary biopsy as radiotherapy effects may lead to an initial increase in the size of a mass. In addition it may be difficult to know which part of the lesion to biopsy making sampling errors common (Fig. 5).

Using FDG-PET, which depends on cellular activity and is not influenced by anatomical distortion is very
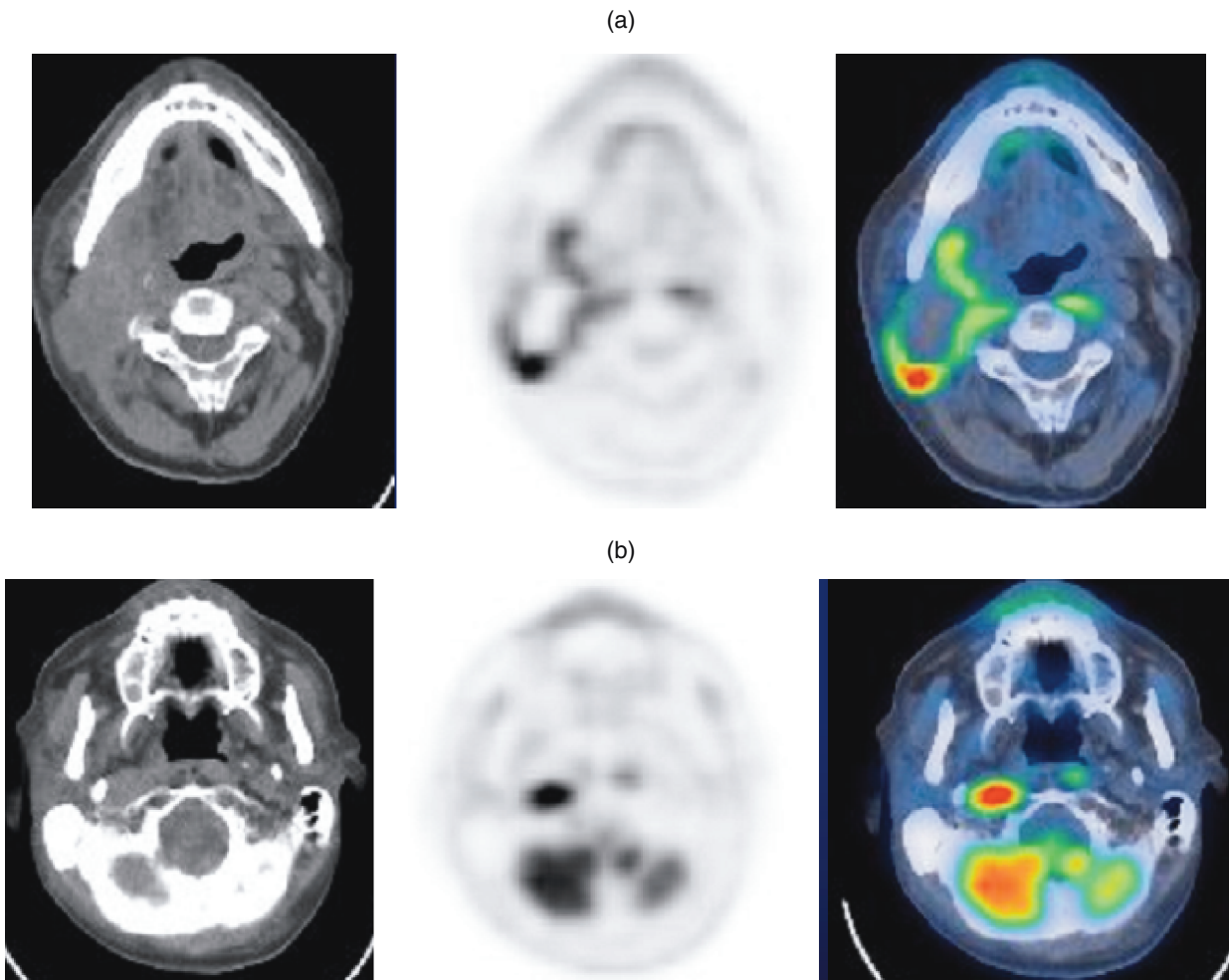
(a)

(b)

Figure 5 **Patient with recurrent squamous cell carcinoma of the tongue. (a) There is uptake in an involved lymph node with a necrotic photo-paenic centre. Initial biopsy of this node revealed no malignancy (sampling error). (b) Intense metabolic activity in an involved retropharyngeal node.**

helpful in these cases and at present this is one of the main indication for FDG-PET in head and neck cancer[19,20]. Following chemo-radiotherapy FDG-PET is more sensitive and specific (88% and 81%) than CT/MRI (75% and 30%) and more importantly FDG-PET has a high negative predictive value of 91% so a negative PET may preclude further invasive procedures[21]. The development of PET-CT may improve specificity compared to PET alone.

Directing biopsy

FDG-PET is superior to either CT or MR alone in direction biopsies and decreasing sampling errors; Lowe *et al.*[22] found the sensitivity and specificity for FDG-PET to be 90% and 83%, respectively, for residual disease and in two cases sampling errors produced false negative biopsy results. In addition repeat PET-CT will allow assessment of the change in uptake of FDG in tumour (SUV) and this may be useful in indicating response to therapy.

Radiotherapy planning

FDG-PET will provide more accurate information on the extent of tumour than MR or CT and will allow a decrease in the gross tumour volume (GTV). It is however unable to depict superficial tumour extension[23]. PET-CT is also useful to delineate the GTV in intensity-modulated radiotherapy (IMRT) leading to a change in volume in 57% of patients compared to CT alone[24].

Response to therapy

PET-CT may become a powerful tool for following response to therapy. Reduction in uptake appears to correlate with a decline in the number of viable cells and a metabolic response may precede changes in tumour volume. There are some limitations to using FDG-PET in this manner. The timing of the scan is very important. Surgery causes an inflammatory reaction and

may give false positive results and immediately following chemotherapy there may be false negative results and at least 3 weeks should elapse after chemotherapy. However FDG-PET does not appear to be sufficiently sensitive (40–75%) or specific (25–64%) in identifying the presence of residual disease (micrometastases) in cervical nodes after completion of chemotherapy[25,26] and so cannot predict the need for post treatment neck dissection.

The timing after radiotherapy (RT) is also important, scans which are positive after 4 weeks indicate residual disease, but a negative scan is unreliable with a NPV of 14%[27], however a scan at 4 months may more accurately reflect disease with a negative predictive value of 100%, suggesting that no biopsy will be needed for at least one year if the PET is negative[28]. Greven *et al.*[29] found FDG-PET useful for the initial imaging of head and neck cancer but the initial SUV did not predict response to RT, and the 1 month post-RT scan was inaccurate (35% false negative) with the 4-month post-RT scan a better predictor for the presence of residual tumour.

Goerres *et al.*[30] found FDG-PET performed at 6 weeks after completion of chemo-radiotherapy will provide both sensitive (91%) and specific (93%) information about residual disease and will also provide information about distant metastases or second primary tumours.

Unknown primary

Cervical metastases are common manifestations of occult head and neck malignancy. Pan-endoscopy is undertaken and a routine tonsillectomy may be performed as this may reveal an occult primary. If no tumour is identified CT and MRI are often requested. Blind biopsy will be positive in 10% of patients with CT/MR guided biopsy increasing the positive rate to 20%[7].

The use of PET in patients with nodal metastases in the neck but no obvious primary is contentious. Greven *et al.*[31] suggested there was no benefit because of the high false positive rate (46%) as there is physiologic uptake in lymphoid tissue which will decrease the sensitivity of FDG-PET; other authors found FDG-PET increases the detection rate in up to 40%[32,33] and is helpful in patient management in 53%[34]. A normal FDG-PET does not, however, eliminate the need for panendoscopy and tonsillectomy[35].

Thyroid cancer

Thyroid cancer demonstrates variable uptake with well-differentiated carcinomas being less avid than undifferentiated tumours. FDG-PET may be positive in the presence of a raised thyroglobulin level but negative iodine scan[38] with a positive scan indicating disease but a negative scan may not exclude recurrent papillary cancer (NPV 27%)[37]. Iagaru *et al.*[36] reported that FDG-PET was 88% sensitive and 75% specific for recurrent papillary carcinoma.

Conclusion

FDG-PET has established itself as a useful tool for the staging of head and neck cancer, for identifying residual and recurrent disease and assessing the response to therapy. The combination of PET-CT will optimise the technique and improve accuracy. The development of tumour–specific ligands will increase the usefulness of PET-CT in the detection of the initial tumour and in evaluation of tumours with low FDG avidity.

References

[1] Kresnik E, Mikosch P, Gallowitsch HJ *et al.* Evaluation of head and neck cancer with 18F-FDG PET: a comparison with conventional methods. Eur J Nucl Med 2001; 28: 816–21.

[2] Halfpenny W, Hain SF, Biassoni L, Maisey MN, Sherman JA, McGurk M. FDG-PET. A possible prognostic factor in head and neck cancer. Br J Cancer 2002; 86: 512–16.

[3] Cook GJR, Maisey MN. The current status of clinical PET imaging. Clin Radiol 1996; 51: 603–13.

[4] Blodgett TM, Fukui MB, Snyderman CH *et al.* Combined PET-CT in the head and neck. Radiographics 2005; 25: 897–912.

[5] Choi JY, Lee KS, Kim HJ *et al.* Focal thyroid lesions incidentally identified by integrated 18F-FDG PET/CT: clinical significance and improved characterization. J Nucl Med 2006; 47: 609–15.

[6] Rubello D, Nanni C, Castellucci P *et al.* Does 18F-FDG PET/CT play a role in the differential diagnosis of parotid masses. Panminerva Med 2005; 47: 187.

[7] Keyes JW, Watson NE, Williams DW, Greven KM, McGuirt WF. FDG PET in head and neck cancer. AJR 1997; 169: 1663–9.

[8] Goshan E, Davidson T, Yahalom R, Talmi YP, Zwas ST. PET/CT in the evaluation of patients with squamous cell cancer in head and neck. Int J Oral Maxillofac Surg 2006; 35: 332–6.

[9] Schoder H, Yeung HW, Gonen M, Kraus D, Larson SM. Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion. Radiology 2004; 231: 65–72.

[10] Goerres GW, Schmid DT, Schuknect B, Eyrich GK. Bone invasion in patients with oral cancer: comparison of conventional CT with PET/CT and SPECT/CT. Radiology 2005; 237: 281–7.

[11] Allal AS, Slosman DO, Kebdani T, Allaouna M, Lehmann W, Dulguer P. Prediction of outcome in head-and-neck cancer patients using the standardized uptake value of 2-[18]fluoro-2-deoxy-D-glucose. Int J Radiat Oncol Biol Phys 2004; 59: 1295–300.

[12] Dobert N, Kovacs AF, Menzel C *et al.* The prognostic value of FDG PET in head and neck cancer. Q J Nucl Med Mol Imaging 2005; 49: 253–7.

[13] Merritt RM, Williams MF, James TH, Porubsky ES. Detection of cervical metastasis. A meta-analysis comparing computed tomography with physical examination. Arch Otolaryngol Head Neck Surg 1997; 123: 149–52.

[14] Di Martino E, Nowak B, Hassan HA *et al*. Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. Arch Otolaryngol Head Neck Surg 2000; 126: 1457–61.

[15] Curtin HD, Ishwaran H, Mancuso AA, Dalley RW, Caudry DJ, McNeil BJ. Comparison of CT and MR imaging in staging of neck metastases. Radiology 1998; 207: 123–30.

[16] Mack MG, Balzer JO, Straub R, Eichler K, Vogl TJ. Superparamagnetic iron oxide-enhanced MR imaging of head and neck lymph nodes. Radiology 2002; 222: 239–44.

[17] Adams S, Baum RP, Stuckensen T, Bitter K, Hor G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med 1998; 25: 1255–60.

[18] Sigg MB, Steinert H, Gratz K, Hugenin P, Stoeckli S, Eyrich GK. Staging of head and neck tumours: [18F] fluorodeoxyglucose positron emission tomography compared with physical examination and imaging modalities. J Oral Maxillofac Surg 2003; 61: 1022–9.

[19] Fukui MB, Blodgett TM, Snyderman CH *et al*. Combined PET-CT in the head and neck. Diagnostic uses and pitfalls of oncologic imaging. Radiographics 2005; 25: 913–30.

[20] Wong RJ, Lin DT, Schroder H *et al*. Diagnostic and prognostic value of [(18)F] fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol 2002; 20: 4199–420.

[21] Kubota K, Yokoyama J, Yamaguchi K *et al*. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. Eur J Nucl Med Mol Imaging 2004; 31: 590–5.

[22] Lowe V, Dunphy F, Varvares M *et al*. Evaluation of chemotherapy response in patients with advanced head and neck cancer using [F-18] fluorodeoxyglucose positron emission tomography. Head Neck 1997; 19: 666–74.

[23] Daisne JF, Duprez T, Weynand B *et al*. Tumor volume in pharyngeal squamous cell carcinoma. Comparison at CT, MR imaging and FDG PET and validation with surgical specimen. Radiology 2004; 233: 93–100.

[24] Wang D, Schultz CJ, Jursinic PA *et al*. Initial experience of FDG-PET/CT guided IMRT of head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2006; 65: 143–51.

[25] Brkovich VS, Miller FR, Karnad AB, Hussey DH, McGuff HS, Otto RA. The role of positron emission tomography scans in the management of the N-positive neck in head and neck squamous cell carcinoma after chemotherapy. Laryngoscope 2006; 116: 855–8.

[26] Gourin CG, Williams HT, Seabolt WN, Herdman AV, Howington JW, Terris DJ. Utility of positron emission tomography-computed tomography in identification of residual nodal disease after chemoradiation for advanced head and neck cancer. Laryngoscope 2006; 116: 705–10.

[27] Rogers J, Greven KM, McGuirt WE *et al*. Can post-RT neck dissection be omitted for patients with head-and-neck cancer who have a negative PET scan after definitive radiation therapy? Int J Radiat Oncol Biol Phys 2004; 58: 694–69.

[28] Conessa C, Herve S, Foehrenbach H, Poncet JL. FDG-PET scan in local follow-up of irradiated head and neck squamous cell carcinomas. Ann Otol Rhinol Laryngol 2004; 113: 628–35.

[29] Grevan KM, Williams DW, McGuirt WF *et al*. Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. Head Neck 2001; 23: 942–6.

[30] Goerres GW, Schmid DT, Bandhauer F *et al*. Positron emission tomography in the early follow-up of advanced head and neck cancer. Arch Otolaryngol Head Neck Surg 2004; 130: 105–9.

[31] Greven KM, Keyes JW Jr, Williams DW 3rd, McGuirt WF, Joyce WT 3rd. Occult primary tumors of the head and neck: lack of benefit from positron emission tomography imaging with 2-[F-18] fluoro-2-deoxy-D-glucose. Cancer 1999; 86: 114–8.

[32] Aassar OS, Fischbein NJ, Caputo GR *et al*. Metastatic head and neck cancer: role and usefulness of FDG PET in locating occult primary tumors. Radiology 1999; 210: 177–81.

[33] Braams J, Pruim J, Kole A *et al*. Detection of unknown primary head and neck tumors by positron emission tomography. Int J Radiat Oncol Biol Phys 2004; 58: 694–7.

[34] Wong WL, Saunders M. The impact of FDG PET on the management of occult primary head and neck tumours. Clin Oncol 2003; 15: 461–6.

[35] Miller FR, Hussey D, Beeram M, Eng T, McGuff HS, Otto RA. Positron emission tomography in the management of unknown primary head and neck carcinoma. Arch Otolaryngol Head Neck Surg 2005; 131: 626–9.

[36] Nahas Z, Goldenberg D, Fakhry C *et al*. The role of positron emission tomography/computed tomography in the management of recurrent papillary thyroid carcinoma. Laryngoscopy 2005; 115: 237–43.

[37] Lind P, Kohlfurst S. Respective roles of thyroglobulin, radioiodine imaging, and positron emission tomography in the assessment of thyroid cancer. Semin Nucl Med 2006; 36: 194–205.

[38] Iagaru A, Masamed R, Singer PA, Conti PS. 2-Deoxy-2-[(18)F]fluoro-D-glucose-positron emission tomography and positron emission tomography/computed tomography diagnosis of patients with recurrent papillary thyroid cancer. Mol Imaging Biol 2006 Jun 7; [Epub ahead of print].