PET/CT in Head and Neck Tumours

6

Wai Lup Wong

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FDG PET/CT has an established role in the assessment of head and neck squamous cell cancer (H&N SqCC). As such, the focus of the chapter will be on FDG PET/CT and H&N SqCC. Separate short commentaries are provided on the role of FDG PET/CT for other tumours and on the evolving role of radio-tracers beyond FDG. Specific comments relevant to H&N haematolymphoid disorders is included in the appendix.[1]

[1] Please see Appendix 9.

W.L. Wong
Paul Strickland Scanner Centre, Department of Nuclear Medicine,
Mount Vernon Hospital, Northwood, UK
e-mail: wailup.wong@nhs.net

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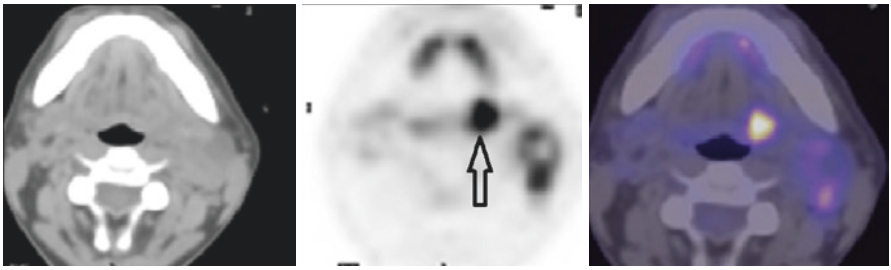

Fig. 6.1 60 year old man presented with an enlarged node in the LT neck. USS with FNAC showed SqCC. Usual assessment including CT and MR shows no primary site. FDG PET/CT shows the neck node and intense focal FDG uptake in the left tongue base (*hollow arrow*). EUA and biopsies confirm a primary malignancy in left tongue base

6.1 Primary Diagnosis

There is universal agreement for using FDG PET/CT in people with malignant neck nodes and no primary site identified on usual assessment [1]. FDG PET/CT influences management plan primarily, by increasing detection of the primary site [2, 3]. The diagnostic rate to an extent depends on the investigations prior to FDG PET/CT, and the more the investigations the lower the detection rate. In addition, FDG PET/CT improves diagnosis of nodal disease, detects unexpected distant metastases, albeit infrequently.[2] Finally, occasionally but importantly, FDG PET/CT detects occult synchronous cancers, most often silent colon and lung cancers [2, 3]. Currently, many centres offer people FDG PET/CT after clinical assessment and CT/MR shows no primary site, and prior to EUA and biopsy. Increase in confidence in the use of FDG PET/CT and availability of scanners is leading to the view that FDG PET/CT should be considered the initial investigation reserving CT/MR only if necessary for treatment planning [5] (Fig. 6.1).

6.2 Staging

FDG PET/CT plays two important roles here: firstly, for staging people with high risk of disseminated disease [1]. In a significant number in this group, FDG PET/CT detects metastases not diagnosed on usual assessment [6–8]. There is however divergence in guidance as to whom should be offered FDG PET/CT. Perhaps for three reasons. Firstly, there is no consensus with regard to definition of "high risk" amongst clinicians. Second, there is the further variation influenced by cost-benefit considerations. The decision as to who should have FDG PET/CT, is made on balancing the probability of detecting metastases against the cost of detection. In other words, the number of FDG PET/CTs required to detect one person with metastases

[2] A retrospective cohort study of 78 people, one of the largest studies in this area, FDG PET/CT detected primary tumours in 30 people not identified on usual assessment including flexible fibre-optic nasoendoscopy and CT/MR/both, unexpected contralateral neck nodal disease in 2, and mediastinal nodal disease 1, and liver metastases 1 [4].

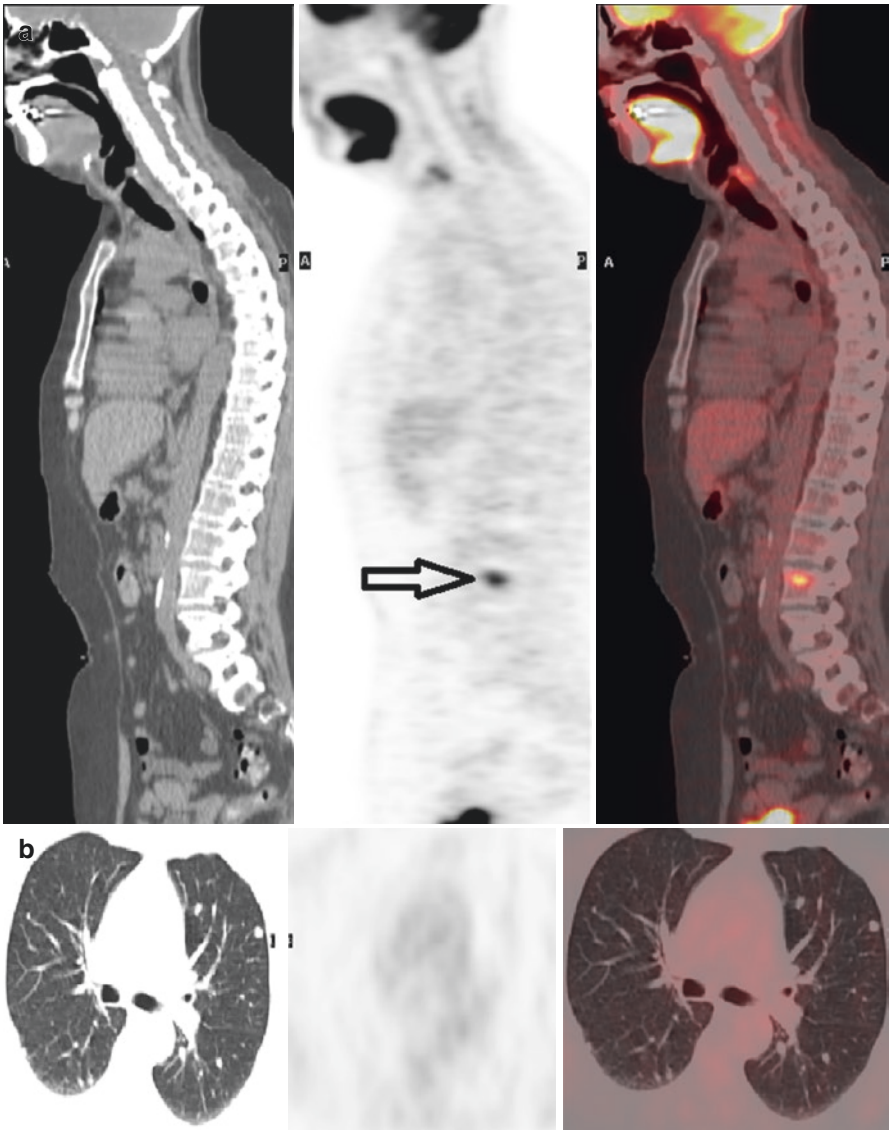

Fig. 6.2 (**a**) FDG PET/CT confirms the primary site in the tongue and neck nodal disease. It also shows a bone metastasis (*hollow arrow*). (**b**) FDG PET/CT also shows small non FDG avid lung metastases

balanced against the cost of false positive results. The tipping point applied varying between guideline making groups. And thirdly, the increasing view was that guidelines should be flexibly implemented.[3] Recent NICE guidelines recommend offering FDG PET/CT only to people with T4 nasopharyngeal and hypopharyngeal cancer and for people with advanced neck disease (N3) [5]. Other guidelines recommend FDG PET/CT more extensively [1] (Figs. 6.2a and 6.2b).

[3] Please see Appendix 8.

Secondly, in common with other cancers, FDG PET/CT has a key role in the investigations of lesions indeterminate on usual assessment including in lung, liver, and adrenal glands, when improved characterisation can change the treatment plan [1].

6.3 Response Assessment

The role of FDG PET/CT in this area is evolving. With revived enthusiasm in chemotherapy for H&N SqCC, there is interest in non-invasive imaging which can distinguish responders from non-responders early during treatment.[4] FDG PET/CT has been shown to predict early-on response to neo-adjuvant chemotherapy in a variety of solid tumours including oesophageal carcinoma.[5] There is currently one published study for H&N SqCC. In 15 patients, an FDG response after two cycles of chemotherapy predicted event-free survival [9].

6.4 Post-treatment Assessment

FDG PET/CT is misleading before 8 weeks post-chemo-radiotherapy. On the other hand, FDG PET/CT has a high negative predictive value, greater than 90%, 8 weeks or more after [10–17]. A recent study perhaps provides convincing evidence of the value of FDG PET/CT in this area.[6]

FDG PET/CT has two main roles in people suspected of recurrence: first, to confirm the diagnosis. FDG PET/CT is superior to CT/MR for distinguishing recurrence from treatment sequlae [19, 20] (Figs. 6.3 and 6.4). However, state-of-the-art MR techniques have not been included in this comparison. That said, in a significant number of people the recurrence is obvious on clinical assessment or standard CT/MR and does not require PET/CT. Secondly, the role is to accurately delineate the extent of disease dissemination. Here, for a significant number of people, FDG PET/CT is of limited relevance as the decision to take a palliative approach has already been made, prior to FDG PET/CT.[7]

[4] Please see Chap. 3.3 for further details on the role of chemotherapy in the treatment of H&N SqCC.

[5] Please see monogram on oesophageal cancer.

[6] In 564 H&N SqCC people with advanced neck nodal disease following chemoRT, 282 were recruited into the ND arm, 282 had FDG PET/CT 8–12 weeks following chemoRT and ND only if FDG PET/CT showed residual disease. 54 NDs were performed in the surveillance arm with 22 surgical complications; 221 NDs in the ND arm with 85 complications. FDG PET/CT surveillance was cost effective compared to planned ND with a £1, 415 per person saving and an additional gain of 0.07 QALY [18].

[7] Please see Chap. 3.4 and 3.6.

Fig. 6.3 FDG PET/CT shows appearance consistent with recurrent disease in the tongue base (*arrowhead*). Initial biopsies showed inflammation only. Deeper re-biopsies focussing on the FDG avid area confirmed active disease. Results of the initial biopsy are not surprising, as the recurrence is under the surface of the tongue base

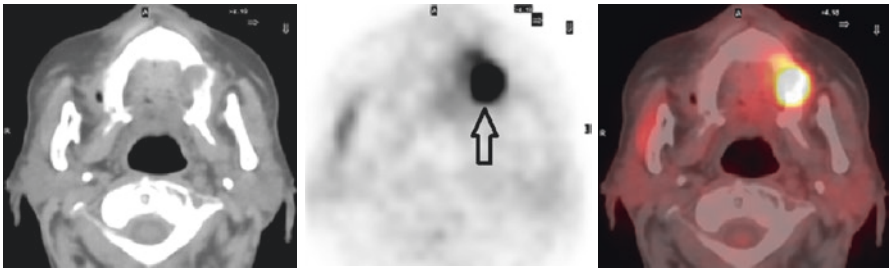

Fig. 6.4 A 76-year-old man with previously treated H&N cancer represents with trismus. FDG PET/CT shows recurrence in the left floor of mouth extending into the maxilla (*hollow arrow*), a difficult site to biopsy. It also shows FDG uptake in the normal right masseter muscle abutting the mandible due to trismus

6.5 Radiotherapy (RT) Planning

FDG PET/CT is increasingly used for radiotherapy target volume delineation [21]. Benefits include inter-observer variability in gross tumour volume (GTV) delineation reduction, GTV size reduction and identification of tumour that would not otherwise have been treated but for PET/CT, reducing geographical misses. However, two major challenges prevail. Firstly, inflammation leads to tumour margin overestimation. Secondly, there is presently no reliable, universally accepted, standardised method of identifying tumour margins. Notwithstanding, two small retrospective studies show significantly better overall survival and event-free survival applying FDG PET/CT-based IMRT, compared with the control group. More studies are needed to clarify the benefits of FDG PET/CT in this area.

6.6 Normal Variants and Artefacts

Brown adipose tissue FDG uptake can be difficult to distinguish from adjacent small FDG avid nodes, especially when there is slight mis-registration of PET to CT.

Skeletal muscle FDG uptake is usually linear and symmetrical and does not pose a diagnostic quandary. Occasionally, pre-vertebral muscle FDG uptake and especially when asymmetrical, needs separating from pre-vertebral nodal FDG uptake, and this may not be possible without resorting to correlation with MR or post-intravenous contrast CT.

Dental amalgam causes FDG uptake in the anterior two thirds of the mouth. In practice this rarely poses a clinical dilemma. If there is doubt as to the cause direct inspection will often provide reassurance.

Detecting an occult primary site can be challenging as it requires distinguishing normal Waldeyer's ring lymphoid tissue FDG uptake in nasopharynx, tongue base (lingual tonsil) and palatine tonsils from FDG uptake from an occult primary tumour arising at these sites, these being common sites for an occult primary tumour. That said, the role of FDG PET/CT is not to make the diagnosis but to increase the number of malignancies diagnosed at EUA and biopsy. In this setting a low threshold for diagnosing abnormality should be adopted and any asymmetrical FDG uptake at these sites reported. SUV is of limited use because of the overlap of values between tumour and normal lymphoid tissue [22] (Fig. 6.5).

Thyroid FDG uptake is considered in another monogram in the series. But beware of a node adjacent to thyroid mimicking a thyroid nodule. Rarely parathyroid adenomas can cause confusion.

6.7 Limitations/Pitfalls

As on CT/MR, branchial cysts can be challenging to distinguish from necrotic nodes. No FDG uptake in the wall of the lesion favours the diagnosis of a branchial cyst. On the other hand, presence of FDG uptake in the lesion wall does not assist, as both pathologies can show this appearance, necrotic node due to tumour and inflammation and branchial cyst due to inflammation.

Benign and malignant parotid gland lesions cannot be distinguished. Both pathologies show intense FDG uptake.

Interpretation of FDG uptake in H&N nodes deserves comment. Firstly, nodes with mild and moderate FDG uptake in the H&N. In this group, PET/CT analysis on grounds of FDG avidity to distinguish between malignant and benign is of limited value. That said, FDG PET/CT can be useful by highlighting possible unexpected nodal disease. In some people highlighting possible additional nodal disease will justify further neck assessment, most often initially with ultrasound and fine needle aspiration cytology. In others, treatment may be modified to include the suspicious node/nodes. Determining which nodes are potentially significant is largely influenced by the probability of nodal disease at the location. In other words, if the node lies in the nodal drainage area for the primary site and there is a moderate to high probability for nodal disease at this site then the node notwithstanding its relatively small size and mild FDG uptake requires reporting. On the other hand, if a node lies outside the drainage area and there is low probability for disease at this site then it

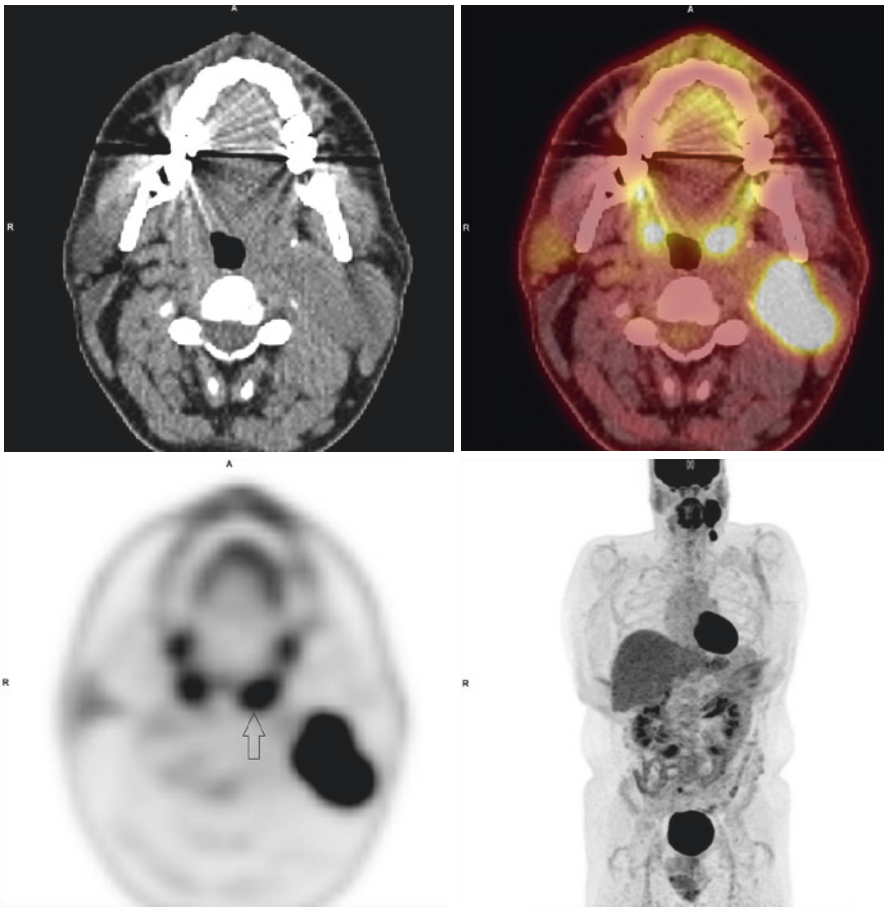

Fig. 6.5 A person with squamous cell cancer in the left neck. Indirect laryngoscopy, CT and MR shows no primary site. FDG PET/CT identified slightly more prominent FDG uptake in the left palatine tonsil compared with the right palatine tonsil and with left glosso-tonsillar sulcus narrowing. Endoscopic biopsies confirm a left palatine tonsil primary site

is unlikely that the node contains tumour. For example, a right level II node, 8 mm, mildly FDG avid, SUVmax 3.0, in a person with nasopharyngeal cancer must be viewed with much more suspicion that such as node in a person with a left maxillary antral cancer. Secondly, with regard to FDG uptake in chest nodes careful distinction needs to be made between those due to sarcoid-like reaction and cancerous nodes. The pattern of FDG uptake assists. FDG uptake in normal sized nodes which include those in paratrachea, both hila and subcarina, would favour sarcoidosis. Especially if there are no FDG avid neck nodes, but even when there is neck nodal disease (Fig. 6.6).

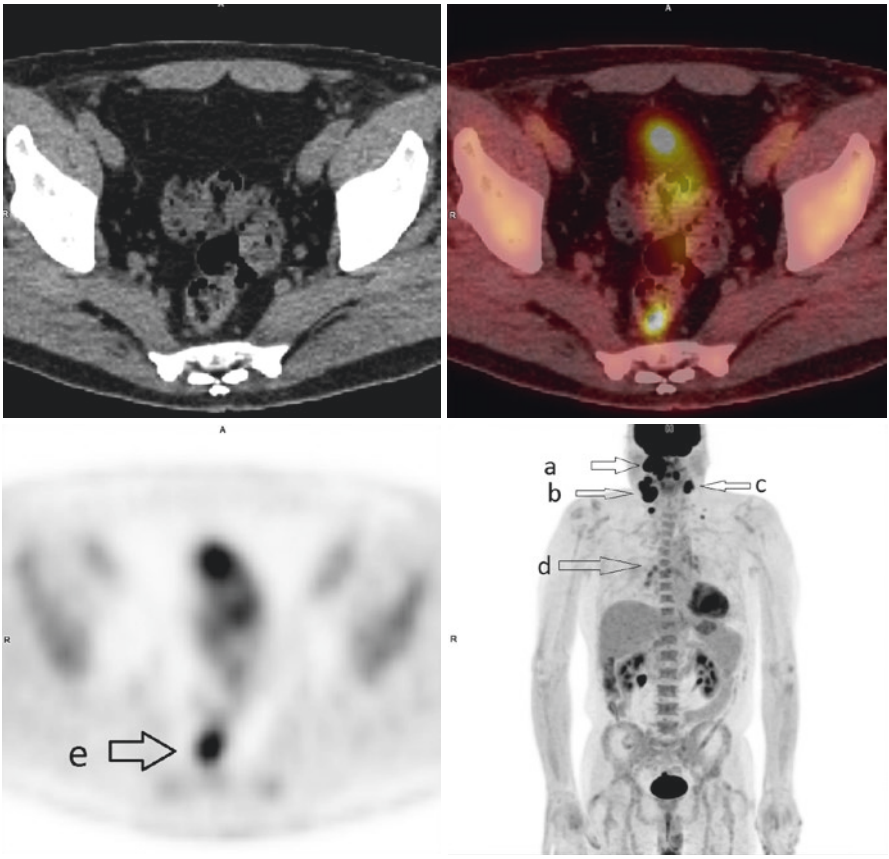

Fig. 6.6 A person with a tongue base cancer (*a*), right neck nodal disease (*b*), left neck nodal disease (*c*), intense FDG uptake in normal size nodes in the chest in the right paratrachea, both hila and subcarina due to sarcoid-like reaction (*d*), unexpected synchronous rectal cancer (*e*)

Post treatment, before making the diagnosis of residual or recurrent disease FDG uptake due to treatment sequelae needs careful consideration. Please see chapter on "18F FDG PET-CT: Normal Variants, Artefacts and Pitfalls in Head and Neck Malignancy".

There is a commonly held view that recent biopsies cause focal FDG uptake in the H&N. This concern is probably overestimated as biopsies usually are tiny and limited to the mucosa.

6.8 FDG PET/CT for H&N Non-SqCC

There is limited evidenced guidance for the use of FDG PET/CT here, beyond anecdotal reports, as these tumours are extremely rare. Notwithstanding, FDG PET/CT is often done prior to treatment and for several reasons: firstly to demonstrate

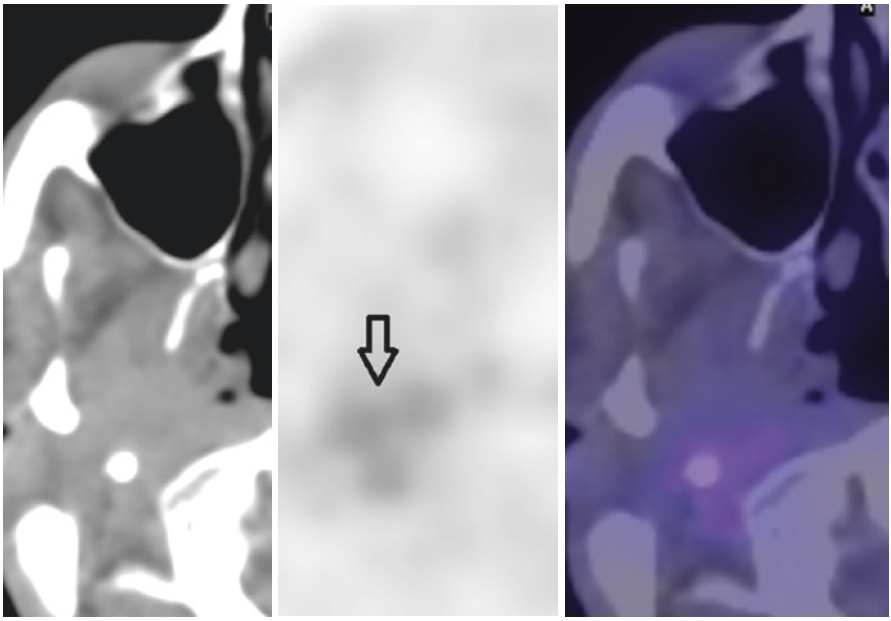

Fig. 6.7 A person with recurrent mucoepidermoid cancer in the skull base with bone destruction locally. FDG PET/CT shows only mild FDG uptake, SUVmax 3.2 (*hollow arrow*)

that the tumour is FDG avid. And if so, FDG PET/CT is considered for pre-treatment staging, and subsequently to detect residual/recurrent disease.[8]

6.9 PET Radiotracers Beyond FDG

6.9.1 Thymidine 3-Deoxy-3-^{18}F-Fluorothymidine (FLT)

Currently, its only potential role is in more accurately distinguishing lung metastases and from benign lesions, compared with FDG [23–25]. However, if it is confirmed that FLT is only taken up by malignant cells, then this may of value on the rare occasion when more information on extent of disease at the primary site is required after usual assessment for treatment planning. Also, FLT may be effective for detecting residual disease following RT and chemotherapy and for predicting outcome to RT and chemo-RT [26–28].

[8] Specific caution: salivary gland cancers and especially muco-epidermoid and adenoid cystic cancers can show paucity of FDG avidity, and especially when they recur (Figs. 6.7 and 6.8).

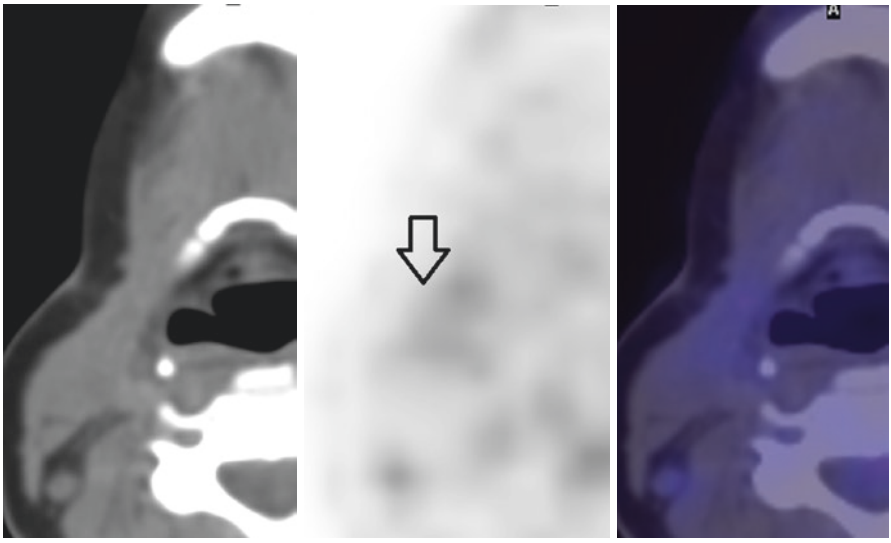

Fig. 6.8 A person with recurrent adenoid cystic cancer. FDG PET/CT shows only very mild FDG uptake, SUVmax 2.9 (*hollow arrow*)

6.9.2 Radiotracers for Detecting Hypoxia

There has been considerable interest in PET tracers which can detect hypoxia in H&N SqCC, because inadequate treatment of hypoxic cells is one of the main causes of failure to effectively treat the primary site. Hypoxic cells require three times more radiation to kill compared with non-hypoxic cells; often it is not possible to deliver the required dose because of the damage it will cause to surrounding to normal tissue. Imaging of hypoxia would provide the opportunity to apply RT to the sub-volume of hypoxic cells only [29, 30].

Fluorinated nitromidazole compounds, including 1-[2-nitro-1-imidazolyl-3[^{18}-F] fluoro-2-propanol ([^{18}F]FMISO), have been used of imaging hypoxia in H&NSqCC.[9] Copper isotopes of varying half-life, including ^{60}Cu, ^{61}Cu, ^{62}Cu and ^{62}Cu labelled to copper-diacetyl-bis(N^4-methylthiosemicabazone) [Cu-ATSM] and copper-pyruvaldehyde-bis(N^4-methylthiosemicarbazone [Cu-PTSM], have also been studied. There is as yet no one clear front runner. [^{18}F]FMISO is the most commonly used and best validated tracer and most studies have shown correlation between hypoxia and [^{18}F]FMISO uptake [31]. But it is only slowly cleared from the blood compartment and the radiotracer passively diffuses into the cell which takes a relatively long time. This means that for imaging to be effective it has to be done between 2 and 3 h post-injection [32] There are as yet inadequate data to recommend the other tracers as superior.

[9] Other florinated nitromidazole compounds that have been studied include 1-(5-[^{18}F]fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitro-imidazole ([^{18}F] FAZA), ^{18}F-2-(2-Nitro-imidazol-1-yl)-*N*-(3,3,3-trifluropropyl)-Acetamide [^{18}F–EF3] and ^{18}F–Fluoroerythronitromidazole [^{18}F–FETNIM].

6.9.3 11C–Choline PET/CT

In a pilot study ^{11}C–choline improved the delineation of orbital and skull involvement compared with FDG PET/CT in people with nasopharyngeal cancer [33]. This is because physiological ^{11}C–choline uptake in brain and extra-ocular eye muscles is minimal compared with FDG. The advantage of 11C–choline beyond this specific scenario has been questioned [34].

Key Points

- FDG PET/CT has an established role in the assessment of head and neck squamous cell cancer.
- There is universal agreement for using FDG PET/CT in people with malignant neck nodes and no primary site identified on usual assessment.
- In people with malignant neck nodes and no primary site identified on usual assessment, FDG PET/CT influences management plan primarily by increasing detection of the primary site.
- Increase in confidence in the use of FDG PET/CT and availability of scanners, is leading to the view that FDG PET/CT should be considered the initial investigation people with malignant neck nodes and no primary site identified on usual assesment, reserving CT/MR only if necessary for treatment planning.
- In people with primary head and neck squamous cell cancer, FDG PET/CT detects metastases not diagnosed on usual assessment
- FDG PET/CT is misleading before 8 week's post-chemo-radiotherapy. On the other hand, FDG PET/CT has a high negative predictive value, greater than 90%, 8 weeks or more after.
- Post treatment, before making the diagnosis of residual or recurrent disease FDG uptake due to treatment sequelae needs careful consideration.
- There is a commonly held view that recent biopsies cause focal FDG uptake in the head and neck. This concern is probably overestimated as biopsies usually are tiny and limited to the mucosa.
- There is limited evidenced guidance for the use of FDG PET/CT for head and neck non squamous cell cancer.
- There is divergence in guidance as to whom should be offered FDG PET/CT.

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