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Non-FDG Radiopharmaceuticals in Head and Neck PET Imaging: Current Techniques and Future Directions

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Positron emission tomography has become a standard in the staging of head and neck cancer as well as can be used in locating unknown primary malignancies, monitoring disease response, and identifying disease recurrence. Although 18F-fluoro-2-deoxy-D-glucose is by far the most frequently used radiopharmaceutical in head and neck imaging, glycolysis is not the only metabolic process or biochemical pathway that can be visualized. In addition, 18F-fluoro-2-deoxy-D-glucose positron emission tomography can be limited due to the nonspecific nature of alterations in glucose metabolism. In this review, we will cover multiple of the emerging radiotracers that have been applied clinically or are in development as promising tools to better image certain malignancies and delineate disease from treatment effects. The potential advantages and disadvantages of these radiopharmaceuticals will also be discussed.
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Introduction

Nuclear medicine has played a major role in the diagnosis and treatment of malignancies for several decades. With the development of positron emission tomography (PET) tracers in combination with computed tomography (CT) imaging, functional imaging now plays an even more pivotal role in lesion localization, characterization, and disease staging. This is especially true in head and neck cancer imaging where PET has become standard in cancer staging as well as can be used in locating unknown primary malignancies, monitoring disease response, and identifying disease recurrence. Although 18F-fluoro-2-deoxy-D-glucose (FDG) is by far the most frequently used radiopharmaceutical in head and neck imaging, glycolysis is not the only metabolic process or biochemical pathway that can be visualized. In addition, FDG PET can be limited due to the nonspecific nature of altered glucose metabolism. In this review, we will cover multiple of the emerging radiotracers that have been applied clinically or are currently being developed for head and neck imaging. These targeted radiotracers hold the promise for better imaging of certain malignancies and may be useful in more accurate delineation of disease from treatment effects. The potential advantages and disadvantages of these radiopharmaceuticals will also be discussed.

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Alternatives to FDG

Amino Acids

Amino acids are building blocks of proteins, precursors for many other biomolecules, and crucial in many metabolic cycles upregulated in cancer cells. Because of the increased need for amino acids in the setting of malignancy, amino acid-based radiopharmaceuticals have become a large area of study and development. In vitro and in vivo studies have shown an enhanced uptake of amino acid-based radiopharmaceuticals in malignancies compared to the surrounding tissues; however, in contrast to FDG, the uptake of amino acid-based radiopharmaceuticals is low in hypoxic, inflammatory tissues. Because hypoxia and inflammation often occur in the early phase after therapy, in theory, amino acid-based radiopharmaceuticals may be better suited to differentiate between postradiation inflammation and residual cancer. Also, some amino acid radiopharmaceuticals can more

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specifically target biomolecules and metabolic pathways of interest, potentially making these radiopharmaceuticals better able to diagnose certain types of cancers involving the head and neck.[1]

Gallium-68-Labeled Somatostatin Analogs

68Ga-labeled somatostatin analogs (68Ga-SSA) include several tracers sharing a similar structure (Gallium-68 DOTA-DPhe1-Tyr3-Octreotide, Gallium-68 DOTA, 1-Nal3-Octreotide, 68Ga-DOTA-Tyr3-Octreotate), formed by a chelator compound (DOTA) used for labeling with Gallium-68 (18Ga, a positron-emitting radio-isotope). This chelate is attached to a somatostatin analog oligopeptide with specific affinity for somatostatin receptors.[2] Similar to scintigraphy with Indium-111-radiolabeled somatostatin analogs, 68Ga-SSA PET/CT is utilized in neuroendocrine tumors with somatostatin receptor overexpression, particularly somatostatin receptor 2 subtype; however, 68Ga-SSAs have several advantages compared to Indium-111 tracers including a higher affinity for the somatostatin receptor 2 subtype, a broader affinity profile for different somatostatin receptor subtypes (high affinity for somatostatin receptor 2, 3, and 5 subtypes for 68Ga-DOTA- NOC), and improved spatial resolution thanks to PET/CT technology.[3] In addition, 68Ga-SSAs are radioactive labeled without the need for an onsite cyclotron for production such as is required for 18F-labeled tracers.[3]

In the head and neck, pheochromocytomas and paragangliomas (PPGLs) are the most common primary neuroendocrine tumors (Figs. 1 and 2); however, neuroendocrine tumors may also originate in the sinonasal region, aerodigestive tract (eg, larynx), or thyroid (eg, medullary thyroid carcinoma [MTC]) and may also occur in the head and neck as nodal metastases from a primary malignancy outside of the head and neck (Fig. 3). In addition to origination from parasympathetic nervous system in the head and neck, PPGLs can occur in many areas of the body, arising from sympathetic lineage-derived cells in adrenal medulla and

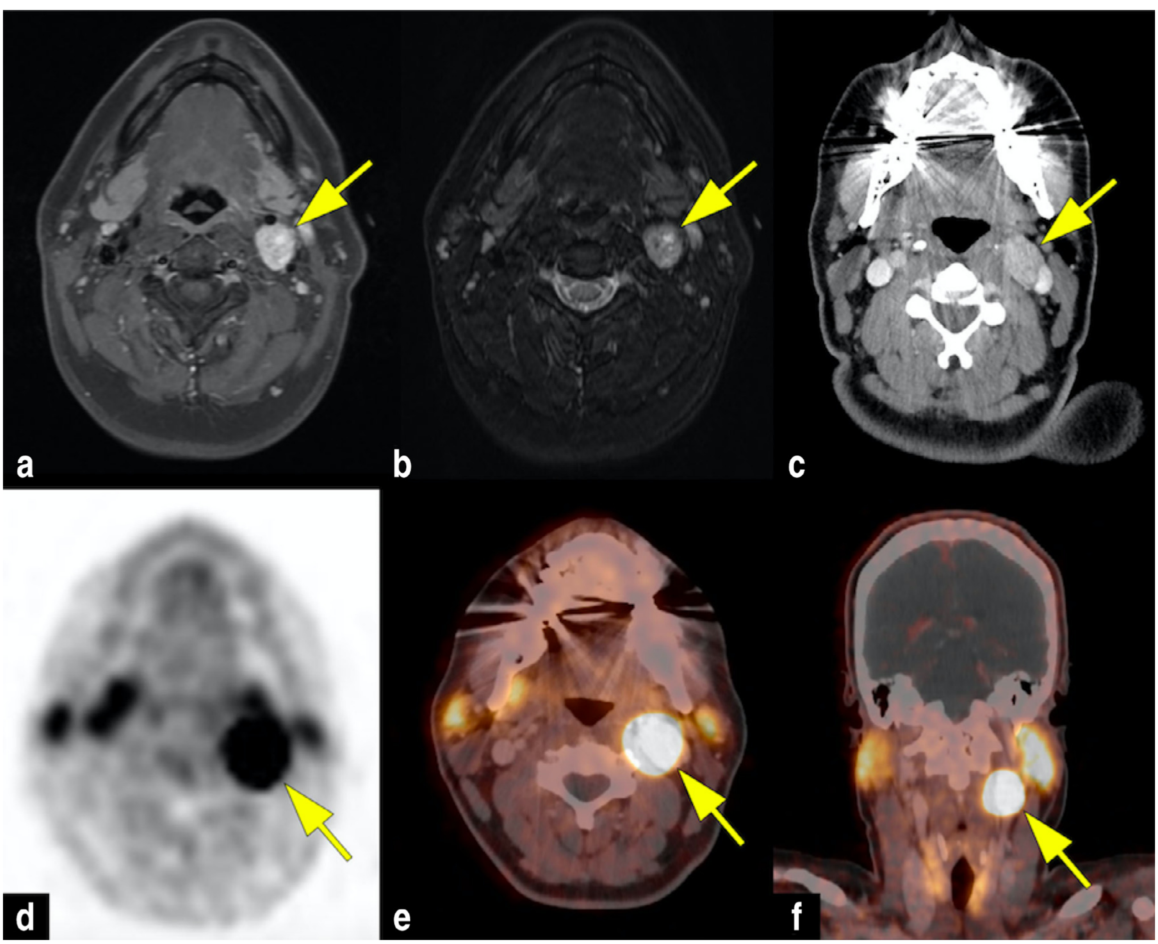

Figure 1 Carotid body tumor (glomus caroticum paraganglioma) in a 53-year-old woman. MRI of the neck with axial T1 postcontrast fat saturation (a) and axial T2 fat saturation (b) images shows an enhancing, T2 hyperintense mass splaying the internal and external carotid arteries. Axial contrast-enhanced CT (c) show the mass to be avidly enhancing. Axial 68Ga-DOTATATE PET (d) shows avid radiotracer uptake corresponding to the mass. Fused axial (e) and coronal (f) images of the 68Ga-DOTATATE PET/CT demonstrate excellent localization of the lesion to the area of 68Ga-DOTATATE uptake. The mass's location at the carotid bifurcation with internal and external carotid separation, as well as uptake of 68Ga-DOTATATE definitively diagnoses this lesion as a carotid body tumor, a common location where paragangliomas can occur in the head and neck.

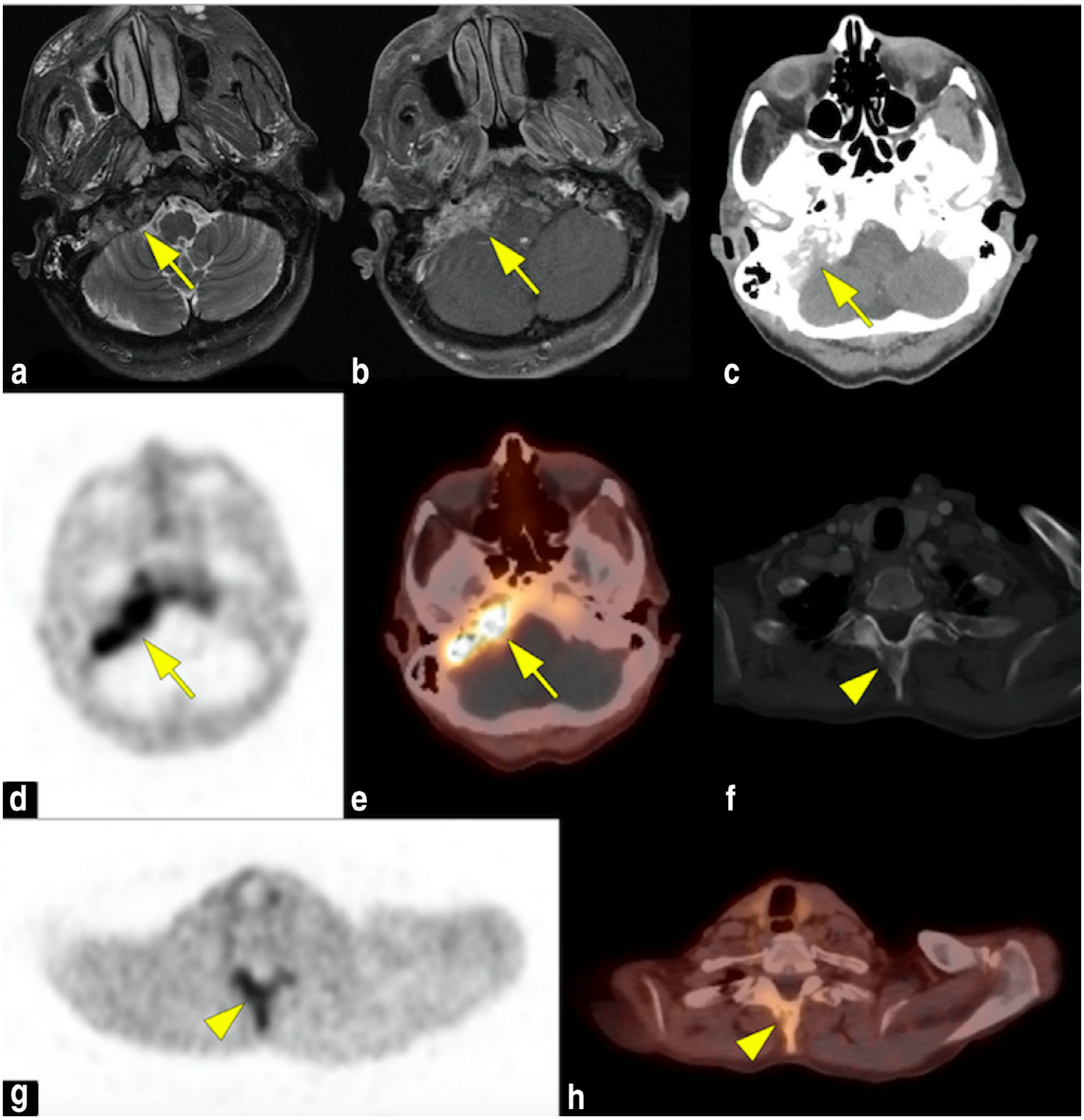

Figure 2 A 72-year-old woman with a right skull base malignant paraganglioma (arrows) near the jugular foramen. MRI shows a heterogeneously hyperintense skull base lesion on axial T2-weighted MRI with fat saturation (a), which enhances on axial T1-weighted postcontrast MRI with fat saturation (b). There is corresponding bone destruction on axial CT (c). Axial 68Ga-DOTATATE PET (d) and fused axial 68Ga-DOTATATE PET/CT (e) show avid radiotracer uptake within the skull base lesion. Note a mildly expansile and lytic lesion involving the T2 posterior elements (arrowheads) on axial bone CT (f), which shows radiotracer uptake on axial 68Ga-DOTATATE PET (g) and fused axial 68Ga-DOTATATE PET/CT (h) images. These findings are consistent with a malignant paraganglioma with osseous metastases later confirmed by biopsy.

extraadrenal thoracic and abdominal paraganglia.[4] Functional imaging with 68Ga-SSAs can play an important role in the confirmation of diagnosis, staging or restaging, selection of targeted radionuclide therapy, and disease response in these lesions.[5]

Recently, Han et al performed a systematic review and meta-analysis of the performance of 68Ga-SSA PET in the detection of PPGLs.[6] Thirteen studies were included for qualitative synthesis. Per-lesion detection rates of 68Ga-SSA PET were consistently higher (ranging from 92% to 100%) than other imaging modalities, including 18F-fluorohydroxyphenylalanine (18F-FDOPA) PET, 18F-FDG PET, and 123/131I-metaiodobenzylguanidine scintigraphy. Nine studies (215 patients) with no specific inclusion criteria for subtype were quantitatively synthesized, and the pooled detection rate was 93% (95% confidence interval [CI], 91%-95%), which was significantly higher than that of 18F-FDOPA PET (80% [95% CI, 69%-88%]), 18F-FDG PET (74% [95% CI, 46%-91%]), and 123/131I-metaiodobenzylguanidine scan (38% [95% CI, 20%-59%], $P < 0.001$ for all).[6] Therefore, this group concluded 68Ga-SSA PET exhibited superior performance for lesion detection over other functional imaging modalities suggesting 68Ga-SSA PET

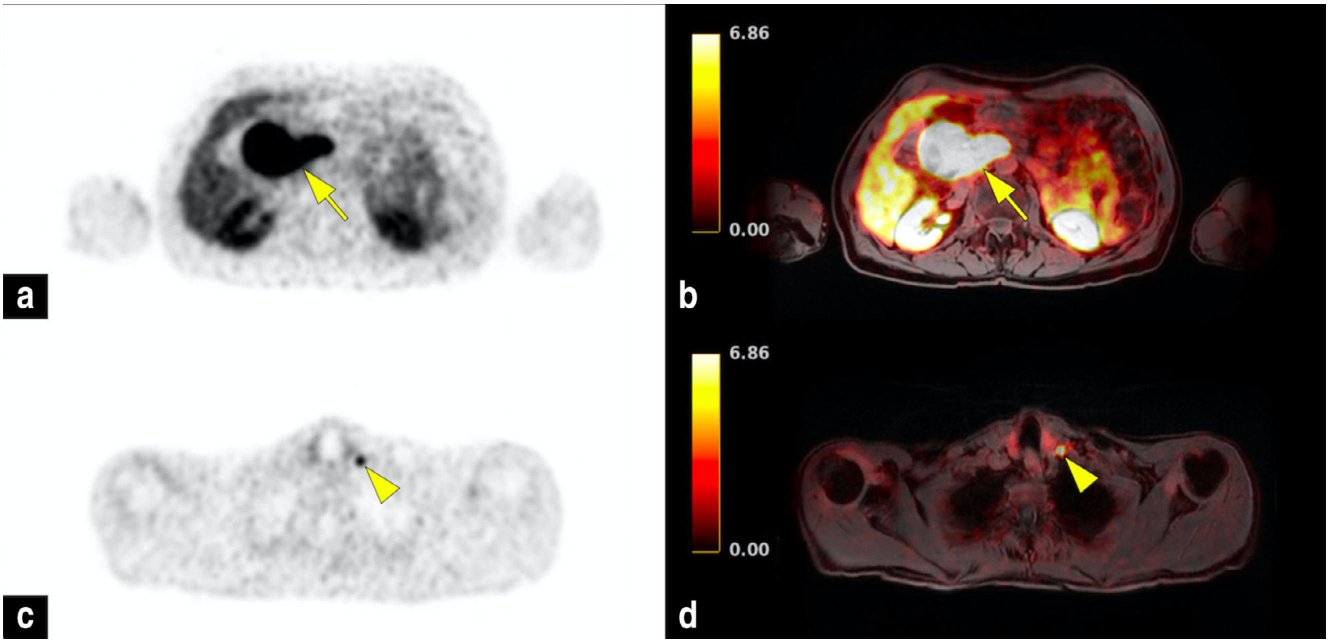

Figure 3 A 62-year-old woman with metastatic neuroendocrine carcinoma. Note a large mass (yellow arrows), which demonstrates avid radiotracer uptake on axial 68Ga-DOTATATE PET (a) and localizes to the pancreatic head and uncinate process with involvement of the duodenum on fused axial 68Ga-DOTATATE PET/CT (b) image, concerning for primary neuroendocrine carcinoma. In the lower neck there is focal radiotracer uptake (yellow arrowhead) on axial 68Ga-DOTATATE PET (c) which localizes to a normal sized lymph node (yellow arrowhead) just lateral to the left thyroid lobe on fused axial 68Ga-DOTATATE PET/CT (d) images, consistent was neuroendocrine carcinoma cervical metastasis. (Color version of figure is available online.)

as a first-line imaging modality for the primary staging or restaging of PPGLs.[6]

L-3-[18F]-Fluoro-Alpha-Methyltyrosine (FMT)

Other tyrosine-based tracers have been less studied and have yielded fewer promising results compared to the tyrosine octreotate tracers. In experimental tumors, FMT shows a higher contrast of tumor to normal tissue, as well as a higher uptake compared to both FDG and C11-MET in preclinical studies.[7-10] One animal study[11] showed a much steeper decline of FMT compared to FDG shortly after irradiation of an induced tumor. This is of interest because results obtained with FDG in humans in the early postradiation phase are poor. Unfortunately, the results obtained in vivo utilizing FMT are less impressive and comparable to those obtained with C11-labeled amino acids. Also, studies evaluating head and neck cancer and FMT are limited. One study evaluated FMT and FDG in 36 patients with an untreated maxillofacial malignancy. Both FMT and FDG visualized all malignancies, but FMT showed a better contrast between tumor and surrounding tissues.[12] Due to the limited studies available, one cannot come to any conclusion as to FMT's utility in imaging head and neck cancer at this time.

O-(2-[18F] Fluorethyl)-L-Tyrosine (FET)

There are slightly more studies dealing with head and neck cancer and FET compared to FMT. Pauleit et al performed a feasibility study that showed FET identified all 8 head and neck cancers.[13] Larger trials are limited in number but have shown FET to be more specific but less sensitive for head and neck cancer diagnosis. The first study included 21 patients with suspicion of squamous cell carcinoma (SSC) of the head and neck, all of which received FDG and FET PET before treatment. The sensitivity of FET was 75% and the specificity 95%, compared to a sensitivity of 93% and the specificity 79% for FDG.[14] A second study included 27 patients, 15 for initial staging, and 12 for therapy evaluation after radiation. The sensitivity of FDG and FET was 95% and 64%, and the specificity 63% and 100%, respectively.[15] The authors of those papers as well as others that followed have come to the same conclusions: although a better specificity compared to FDG was confirmed, FET did not appear to be suited as a first-line PET tracer in head and neck SSC imaging due to insufficient sensitivity. Based upon these results, FET does not appear to be an adequate replacement FDG in the staging head and neck tumors; however, it may show potential in selected cases in order to favor a "wait and see" approach after radiation when an FDG positive and FET negative lesion is found.

L-[Methyl-11C]-Methionine (MET)

MET is also a frequently used radiolabeled amino acid which can be used more broadly in head and neck cancer than radioligands targeting somatostatin receptors. In addition, MET is convenient to produce with rapid synthesis and high radiochemical yields without the need for complex purification steps. MET has high uptake almost immediately after injection in the liver, kidney, pancreas, and salivary glands.[16] While there is some MET uptake in inflamed tissue, uptake of MET in tumor cells is significantly higher with autoradiography demonstrating MET uptake predominantly in viable tumor cells with low uptake in macrophages and nonviable tumor cells.[17]

Although MET has been used in the visualization of intracranial tumors, lymphoma, melanoma, breast, pelvic, parathyroid, and lung cancer, up to now there have been only a limited number of studies dealing with methionine in head and neck cancer. The number of patients included has been small and the results inconsistent, which make the findings hard to interpret[7,18-23]; however, preclinical studies validating MET in the evaluation of therapy showed a faster decline of MET in the postradiation phase compared to FDG.[11,24] Minn et al[25] also reported that MET use in vitro was better correlated with tumor proliferative activity in squamous head and neck carcinoma than FDG, a finding that might be due to the relation of methionine to DNA metabolism.

The excellent in vitro results with MET have not yet been confirmed in vivo with the current in vivo results obtaining similar sensitivities and specificities for head and neck cancer detection compared to FDG; however, especially with regards to therapy evaluation, there is not much data. Because the specificity of FDG is low in the early postradiation phase and MET might be able to detect early changes in DNA metabolism, MET could be a viable alternative to FDG and obtain valuable prognostic information early in treatment.[1] Additional studies are needed to evaluate the in vivo use of MET in head and neck cancer prior to any wide spread clinical application.

L-3,4-Dihydroxy-6-[18F] Fluorophenylalanine (18F-FDOPA)

18F-FDOPA is a radiolabeled analog of L-DOPA used to evaluate the central dopaminergic function of presynaptic neurons. 18F-FDOPA is most commonly used in Parkinson disease to image the degree of dopamine-containing neuron loss in striatum of the brain; however, 18F-FDOPA can be used to evaluate other lesions of neuroendocrine origin. Although 68Ga-SSAs appear to outperform 18F-FDOPA PET in PGGLs,[6] the use of 18F-FDOPA PET in MTC has been promising. Several studies have demonstrated 18F-FDOPA as the most sensitive and specific imaging modality for detecting residual disease in MTC patients with high plasmatic calcitonin levels.[26-36] A recent meta-analysis including 139 patients showing a 66% detection rate on a per patient basis and 71% on a per lesion basis. 18F-FDOPA PET/CT is also superior to 18F-FDOPA or 68Ga-SSA PET/CT for restaging in patients with known residual or recurrent disease.[26,37,38] Overall, 18F-FDOPA PET/CT appears to be of interest at least for postoperative staging when disease recurrence is suspected and could guide the choice and interpretation of conventional imaging.[3]

Nucleosides

Nucleosides are the building stones of DNA, and therefore, are directly linked to cell proliferation. The only nucleoside that has been clinically used to date is thymidine.

3′-Deoxy-3′-[18F] Fluorothymidine (FLT)

The nucleoside thymidine is exclusively linked to DNA. Thymidine is phosphorylated by the enzyme thymidine kinase one with the phosphorylated thymidine then trapped intracellularly. During DNA synthesis, the degree of increased thymidine kinase one activity is an accurate reflection of cellular proliferation.[39] Both 11C and 18F-labeled thymidine (FLT) are available as tracers, but FLT is much more extensively studied in the literature.

Most FLT studies focus on malignancies outside of the head and neck with comparable results to FDG. Of the more limited FLT head and neck studies, a couple of the studies focused on primary laryngeal cancers showing sensitivity rates of 85% for both FLT and FDG.[40,41] Been et al also included postradiation patients as well with 3 of the 14 patients developing recurrent disease after primary radiotherapy, 2 of which were visualized by FDG and 1 by FLT.[40] Troost et al demonstrated in 10 stage II or higher head and neck carcinomas an elevated uptake in metastatic as well in nonmetastatic lymph nodes with a sensitivity of 100% and specificity of 16.7%.[42] In Figure 4, there is similar radiotracer uptake on both the FDG and FLT PET in a subject with right lateral tongue SSC. These early studies were not promising for the use of FLT in staging head and neck cancer relative to FDG.

Studies evaluating FLT in therapy evaluation have been more interesting. This is because a decrease in the cellular proliferation rate is one of the earliest events in the response to successful tumor treatment. Murayama et al irradiated mice with inoculated SSC and found that tumor uptake of FLT decreased in the first day after radiation, while the uptake of FDG decreased after 7 days and MET after 3 days.[11] Menda et al demonstrated a steep decline FLT uptake in 8 human patients after 10 Gy.[43] In Troost et al's study, 10 patients with oropharyngeal cancer underwent FLT PET/CT before and twice during treatment. They found that standardized uptake values in FLT declined after 1 week of radiotherapy, while the gross tumor volume declined after 4 weeks.[44]

While these findings seem promising for the use of FLT more immediately after radiotherapy, FLT declines rapidly during radiation most likely because the surviving cancer cells will not be in a proliferating phase. Because of this, a sharp decline in FLT uptake does not necessarily mean an excellent response to radiotherapy. In addition, the sensitivity for FDG to detect residual tumor has been shown to be higher when compared with FLT.[1] One study compared FLT and FDG PET shortly before and 10 weeks after radiotherapy in 10 patients with laryngeal cancer. FDG missed one out of 3 residual tumors, whereas FLT missed 2 of the 3 residual tumors.[40] Larger studies are needed to further discern the use of FLT in head and neck cancer.

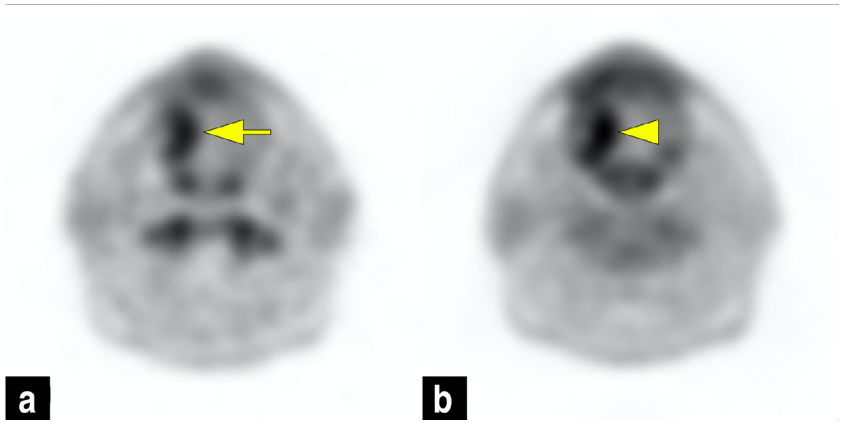

Figure 4 A 72-year-old man with squamous cell carcinoma of the right lateral tongue. Axial FDG PET (a, arrow) and axial FLT PET (b, arrowhead) images show similar focal radiotracer uptake in the right lateral tongue extending adjacent to the right retromolar trigone and right floor of mouth corresponding to the biopsy-proven malignancy.

Choline

Choline is a precursor for the biosynthesis of phospholipids. Because phospholipids are essential components of all cell membranes and the biosynthesis of the cell membranes are increased in proliferating malignancies, choline could be an excellent radiopharmaceutical to visualize tumor proliferation. Choline has been successfully linked to 11C and methyl 18F (Fig. 5).

Due to its reduced renal excretion and upregulation of choline kinase in prostate cancer, 11C-choline is become largely the first choice in molecular imaging of prostate cancer; however, use in head and neck SCC has been limited with these studies showing sensitivity and specificity rates of 11C-choline are similar or slightly worse compared to those obtained with FDG.[45,46] As with FLT, 11C-choline should differentiate well between radiation-induced tissue changes and local tumor recurrence; however, clinical data on head and neck SCC have been lacking thus far.

Choline has been used in another area of head and neck imaging—the detection of hyperfunctioning parathyroid glands. Hyperparathyroidism is a common endocrine disorder caused by hyperfunctioning parathyroid glands. The correct detection and localization of hyperfunctioning parathyroid glands is challenging, but crucial to guiding surgical treatment, particularly in patients with primary hyperparathyroidism.[47] There is a growing body of data regarding the role of radiolabeled choline PET in this setting, both linked to 11C and methyl 18F. Treglia et al performed a systematic review and meta-analysis, which included 18 studies in the systematic review and 14 articles (517 patients) selected for the meta-analysis. The meta-analysis provided the following results on a per-patient analysis of choline PET in hyperparathyroidism: sensitivity 95% (95% CI: 92%-97%), PPV 97% (95% CI: 95%-98%) and DR 91% (95% CI: 87%-94%). On a per lesion analysis, pooled sensitivity and PPV were 92% (95% CI: 88%-96%) and 92% (95% CI: 89%-95%), respectively with no significant heterogeneity was found among the selected studies.[47] The meta-analysis concluded that radiolabeled choline PET demonstrated excellent diagnostic performance in detecting hyperfunctioning parathyroid glands in patients with hyperparathyroidism; however, the authors also point out large multicenter studies and cost-effectiveness analyses are needed to better define the role of this imaging method.[47]

Hypoxia-Specific Tracers

Hypoxic head and neck tumors have higher risk of local recurrence, higher rates of distant metastases, and are more resistant to radiation and chemotherapy.[35,36] Visualizing hypoxic areas within tumors may therefore enable more targeted therapy, such as increased radiation doses to these regions in the hope of improving patient outcomes. Preclinical studies showed that PET can visualize hypoxia in vivo with testing of several tracers including 18F-fluoromisonidazole (18F-FMISO), 18F-fluoroazomycin arabinoside (18F-FAZA), 60Cu-labeled methylthiosemicarbazone, and 18F-2-(2-nitro-1H-imidazol-1-yl)-N- (2,2,3,3,3-pentafluoropropyl)-acetamide.[1] We will discuss the 2 most studied of these in head and neck cancer.

[18F] Fluoromisonidazole

18F-FMISO has been used most frequently to visualize tumor hypoxia in head and neck cancer patients. Imidazole derivates are trapped in hypoxic cells, and 18F-FMISO is a 2-nitroimidazole molecule. A relatively large study of 73 head and neck cancer patients found that 18F-FMISO PET was effective in quantifying regional hypoxia.[48] Another research group also concluded that 18F-FMISO has the potential to predict response to radiotherapy[49] and showed the value of correlated FDG and FMISO scanning in predicting treatment response in patients.[50] However, the clinical application of 18F-FMISO is hampered due to high lipophilicity and slow clearance from normal tissues. This leads to a low target-to-background ratio making identification of hypoxia somewhat difficult.

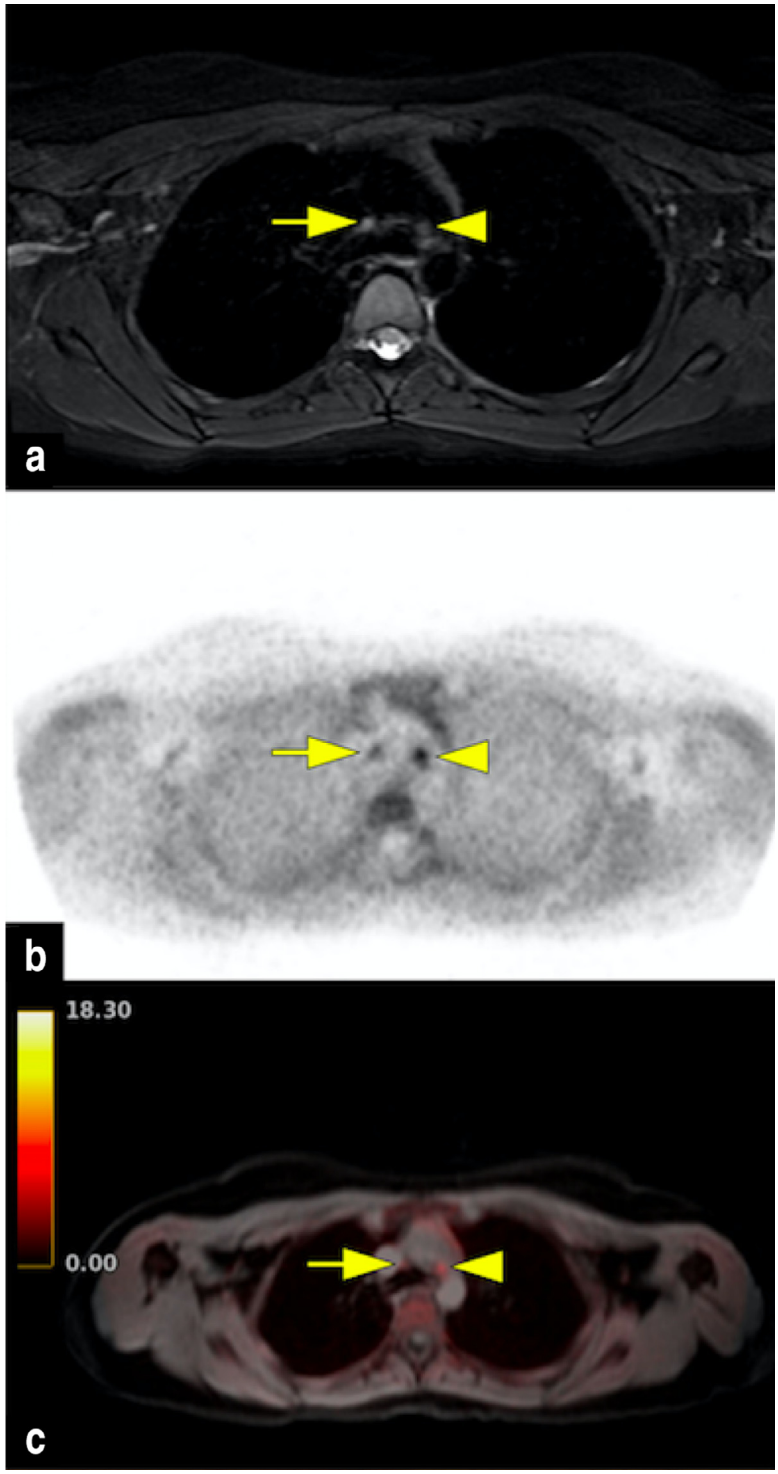

Figure 5 A 58-year-old man with a history of prior right parathyroid adenoma removal and persistent hypercalcemia. Axial T2-weighted fat saturated MRI of the upper mediastinum and chest (a) shows 2 subcentimeter hyperintense lesions with one in the aortopulmonary window (arrowheads) and the second directly anterior to the right mainstem bronchus near the carina (arrows). On axial 18F-fluorocholine PET (b), both of the subcentimeter lesions demonstrate radiotracer uptake, which is better localized on the fused 18F-fluorocholine PET/CT (c) image. The patient had resolution of his prior hyperparathyroidism following removal of both lesions.

[18F] Fluoroazomycin Arabinoside (FAZA)

18F-FAZA, a relatively new imidazole radiopharmaceutical, shows faster clearance from blood and nontarget tissues. Although 18F-FAZA PET clinical studies have been done, only a few were in head and neck cancer. One pilot study sought to evaluate the proper timing of 18F-FAZA PET imaging and test the feasibility of 18F-FAZA PET in 11 untreated head and neck cancer patients. This study acquired good quality 18F-FAZA PET images; however, the authors suggested further studies to evaluate intratumoral differences in 18F-FAZA kinetics.[51] In a phase I/II study, Postema et al showed clear 18F-FAZA uptake in the primary tumor in 5 of the 9 head and neck cancer patients. Two of those subjects had additional uptake in cervical metastases, and 1 subject had uptake in a neck metastasis but not at the primary site. Based on the initial good imaging properties, the authors concluded that 18F-FAZA is a very promising tracer for assessing tumor hypoxia.[52] By applying hypoxia sensitizers or by using specific intensity modulated radiotherapy, theoretically hypoxia markers have great potential for targeted therapy of hypoxic tumors.

Monoclonal Antibodies

Advances in molecular and cellular biology lead to the discovery of novel molecular targets on tumor cells. This includes key molecules involved in cell proliferation, cell differentiation, and cell death in addition to angiogenesis, invasion, and metawstasis. Monoclonal antibodies (MAbs) can be bound to these molecules and then linked to a positron emitting radionuclide, making molecular targets visible on PET. Despite the advances, the development of radiolabeled MAbs has been limited. This is due to several requirements of a radiolabeled Mab including that the emitter should allow facile, efficient, and stable coupling to the MAb. Also, the physical half-life ($t^{1/2}$) should be compatible with pharmacokinetics of the MAb, and to obtain sufficient binding, the $t^{1/2}$ should be several days. Although the binding time of MAb fragments are shorter, the $t^{1/2}$ of C11 is too short to allow labeling of either MAbs or MAb fragments. The half-life of 18F could be sufficient in case of MAb fragments, but unfortunately, the weakness of the bond between the 18F-labeled MAb fragment and the target limits their development.[1]

More suitable are long-lived positron emitters like 124I, 64Cu, and 89Z with only a few head and neck studies in the current literature.[1] Niu et al labeled panitumumab, a MAb against EGFR protein, with 64Cu. The 64Cu-DOTA-panitumumab tracer was then evaluated on nude mice with human head and neck carcinoma cell lines. The tumors with the lowest EGFR protein expression showed the highest 64Cu-DOTA-panitumumab accumulation, whereas SQB20 tumors with the highest EGFR expression showed the lowest 64Cu-DOTA-panitumumab accumulation.[53] Eiblmaier et al labeled cetuximab and showed a positive correlation between 64Cu-DOTA-cetuximab and EGFR expression in 5 head and neck cell lines.[54] L19-SIP, an antibody fragment directed against the ED-B domain of fibronectin and an excellent marker for tumor angiogenesis, has been successfully labeled to 124I. Verel et al showed that 124I-L19-SIP in an injected head and neck tumor cell line could be visualized in 8 nude mice.[55] The same group published a study in which the volume of the tumors was less than 50 mm^3, and all tumors could be visualized by 124I-L19-SIP.[56] A feasibility study with 89Zr-labeled c-mAb U36, a MAb against CD44, showed that all primary tumors and 18 of 25 positive neck levels could be visualized by immunoPET.[57] In another study with 89Zr-labeled c-mAb U36, CD44 was found to be homogeneous in 96% of all primary HNSCC and lymph node metastases.[58]

The ability to study specific tumor characteristics not only in samples but also in vivo by dynamic imaging of the whole tumor would be groundbreaking; however, the large-scale application of MAb tracers is limited by the difficult and labor-intensive production. As a result, the number of publications is still small at this time, and it is difficult to forecast what the actual value of PET imaging of MAbs will be in the future.

Conclusion

While FDG remains by far the most frequently used radiopharmaceutical in head and neck imaging, multiple novel PET radiotracers show promise. In particular, 68Ga-SSA are highly sensitive and specific from the detection of PPGLs, 18F-FDOPA for MTC, and choline PET for hyperfunctioning parathyroid adenomas; however, in the detection of primary and recurrent head and neck squamous cell carcinoma, the novel non-FDG functional agents do not have sufficient evidence for routine clinical use at this time. Further studies are needed to better evaluate the targeted amino acid, nucleoside, hypoxia, and MAbs radiopharmaceuticals.

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