Diagnosis, Staging, Radiation Treatment Response Assessment, and Outcome Prognostication of Head and Neck Cancers Using PET Imaging: A Systematic Review

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KEYWORDS

- PET/CT • Diagnosis • Staging • Radiation treatment response • Outcome prognostication
- Head and neck cancer • Hypoxia • Systematic review

KEY POINTS

- **Diagnosis:** ¹⁸F-FDG PET/CT is recommended before pan-endoscopy or other invasive procedures in the workup for head and neck squamous cell carcinoma (HNSCC) of unknown primary.
- **Staging:** ¹⁸F-FDG PET/CT is recommended in patients with locoregionally advanced HNSCC given its high level of accuracy in detecting nodal disease and sensitivity for distant metastases.
- **Radiation treatment response:** ¹⁸F-FDG PET/CT at 12 weeks after completion of definitive chemoradiation negates the need for planned neck dissection in up to 80% of cases without compromising overall survival.
- **Outcome prognostication:** PET tracers of hypoxia are promising prognostic biomarkers in HNSCC that merit further validation.

INTRODUCTION

[¹⁸F]Fluorodeoxyglucose (¹⁸F-FDG) PET/computed tomography (CT) imaging has become an indispensable tool in all phases of oncologic management and is particularly useful for head and neck malignancies. In cases of head and neck cancer of unknown primary origin, ¹⁸F-FDG PET/CT increases the likelihood of identifying the primary tumor and establishing the diagnosis. Furthermore, ¹⁸F-FDG PET/CT is important in the

accurate staging of locally advanced cases of head and neck squamous cell carcinoma (HNSCC), which can greatly affect recommendations for treatment. Following definitive chemoradiation, ¹⁸F-FDG PET/CT is validated as a means of treatment response assessment and negates the need for planned neck dissection in most cases. Several hypoxia PET tracers have been studied in the context of radiotherapy dose escalation and prognostication.

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METHODS

A comprehensive literature search was conducted to inform this summary of evidence-based practices related to PET/CT in head and neck cancer. The search included articles published from first occurrence of the search syntax through the end date of March 31, 2019 on EMBASE, Web of Science, and PubMed. Search terms were: head and/or neck cancer and PET/CT, with either staging, nodal sensitivity, postradiation assessment, or hypoxia tracer. Case reports or poster/presentation abstracts were automatically excluded. Titles and abstracts of the searched articles were initially screened for topical relevance and originality of scientific contribution, eliminating a large number of unrelated or noncontributory abstracts. To this remaining group of abstracts, 24 additional abstracts were added from other sources including expert opinion and citations from additional high-impact publications found through the literature search. The abstracts were then classified into 4 major groups, namely diagnosis, staging, radiation treatment response, and prognostication, and at least 2 postgraduate physicians were assigned to each group to review the data in more detail. After additional removal of unrelated, nonoriginal, or noncontributory material, the final set of selected abstracts was used to form the evidence basis of this review. See **Fig. 1** for more details.

DIAGNOSIS

Head and Neck Squamous Cell Carcinomas of Unknown Primary

Head and neck squamous cell carcinomas of unknown primary (HNSCCUP) make up 3% to 5% of all head and neck cancers. ^{18}F -FDG PET/CT is part of the standard workup for HNSCCUP and generally should be performed before pan-endoscopy and/or biopsies that may lead to false-positive findings on ^{18}F -FDG PET/CT. Primary tumor detection rates attributable to inclusion of ^{18}F -FDG PET/CT in the workup of HNSCCUP are summarized in **Table 1**.

Postreconstruction Tumor Persistence or Recurrence

Following regional or free-flap reconstruction, tumor persistence and/or recurrence is difficult to detect by physical examination alone. Post-treatment changes along the perimeter of the flap are difficult to distinguish from the tumor using cross-sectional imaging alone. The

addition of ^{18}F -FDG PET to cross-sectional imaging improves the specificity of identifying tumor persistence or recurrence over contrast-enhanced cross-sectional imaging alone (**Table 2**).

Thyroid Incidentalomas

^{18}F -FDG-avid thyroid lesions incidentally discovered on whole-body ^{18}F -FDG PET/CT scans, or “incidentalomas,” may lead to a diagnosis of thyroid cancer. The prevalence of incidentalomas is 1% to 3% and roughly one-third of these lesions are expected to be malignant; thus, all thyroid nodules with ^{18}F -FDG uptake should undergo biopsy (**Table 3**). Furthermore, the level of ^{18}F -FDG uptake provides insight into the histology of the thyroid carcinoma (**Table 4**). Well-differentiated thyroid carcinomas have high ^{131}I uptake and poor ^{18}F -FDG uptake. Conversely, poorly differentiated thyroid carcinomas—such as Hurthle cell carcinomas and anaplastic thyroid carcinomas—have poor ^{131}I uptake and more ^{18}F -FDG-avidity. ^{18}F -FDG PET is more sensitive in detecting lesions of medullary thyroid carcinoma when calcitonin exceeds 1000 ng/mL or carcinoembryonic antigen (CEA) exceeds 5 ng/mL.

STAGING

T Staging

^{18}F -FDG PET/CT is part of the standard workup of locoregionally advanced HNSCC because it improves the accuracy of nodal staging and detects more distant lesions than cross-sectional imaging alone. However, for the purpose of T-stage designation, ^{18}F -FDG PET/CT generally offers no improvement over conventional CT and/or MRI alone (**Table 5**) with the exception of oral cavity cancer in patients with dental artifact.¹⁷ Roh and colleagues¹³ compared the diagnostic utility of ^{18}F -FDG PET/CT with ^{18}F -FDG PET alone or CT/MRI in 167 patients with newly diagnosed HNSCC. In the detection of primary tumors, the researchers found that ^{18}F -FDG PET alone had a sensitivity of 98%, ^{18}F -FDG PET/CT had a sensitivity of 97%, and CT/MRI had a sensitivity of 86% to 88%. Although ^{18}F -FDG PET/CT offers higher sensitivity compared with CT/MRI, the investigators note that ^{18}F -FDG PET/CT does not provide enough anatomic depth and surrounding structure detail necessary for surgical planning for primary tumor resection, so that CT/MRI is still required. Seitz and colleagues¹⁴ evaluated the impact of combined ^{18}F -FDG PET/CT versus MRI alone for T and N staging of 66 patients with oral and

Fig. 1. PRISMA diagram: PET/CT utility in head and neck cancer systematic review.

oropharyngeal cancer. For primary tumors, ^{18}F -FDG PET/CT had a sensitivity of 96.7% and a specificity of 60%, whereas MRI had a sensitivity of 100% and a specificity of 80%. Seitz and colleagues¹⁴ found no statistical difference between ^{18}F -FDG PET/CT and MRI in detecting primary disease ($P \geq .72$). Both imaging modalities had 100% sensitivity for detecting recurrent lesions. These investigators concluded that ^{18}F -FDG PET/CT and MRI have similar detection for primary tumors, and ^{18}F -FDG PET/CT is not

a superior imaging modality for staging primary tumors.

N Staging

By contrast, most studies show that the sensitivity of CT and/or MRI alone in detecting nodal involvement is relatively poor and ^{18}F -FDG PET significantly outperforms cross-sectional imaging in identifying malignant nodes (**Table 6**). Nguyen and colleagues¹⁸ conducted a retrospective

Table 1
Diagnostic utility of ¹⁸F-FDG PET/CT for head and neck squamous cell carcinoma of unknown primary

Study, Year	Design	Primary Detection Rate (%)	Sensitivity (%)	Specificity (%)
Rusthoven et al, ¹ 2004	Systematic review of 16 studies (1994–2003)	74 of 302 (25)	88	75
Johansen et al, ² 2008	Prospective	18 of 60 (30)	87	68
Rudmik et al, ³ 2011	Prospective	11 of 20 (55)	95	62
Lee et al, ⁴ 2015	Prospective	31 of 56 (55)	69	88

review of 71 patients with HNSCC who underwent MRI or CT and ¹⁸F-FDG PET/CT before neck dissection. They found that both CT or MRI alone and ¹⁸F-FDG PET/CT statistically correlated with pathologic findings ($P = .0001$; $P = .0001$), but ¹⁸F-FDG PET/CT had a statistically higher prediction of true pathologic disease compared with CT or MRI alone for primary disease and nodal disease ($P = .005$ and $P = .013$, respectively). In detecting cervical lymph nodes as confirmed by pathologic staging, ¹⁸F-FDG PET/CT had sensitivity of 94.5%, specificity of 89.9%, PPV (positive predictive value) of 90.8%, and NPV (negative predictive value) of 93.9%, whereas CT or MRI alone had sensitivity of 79.4%, specificity of 89.9%, PPV of 89.2%, and NPV of 80.5%. ¹⁸F-FDG PET/CT was more reliable at identifying positive disease compared with CT or MRI alone ($P = .005$). Therefore, the authors recommend the use of ¹⁸F-FDG PET/CT over CT or MRI alone when assessing cervical lymph node metastases.

Park and colleagues²⁰ conducted a prospective study of 160 patients with HNSCC using histopathology from neck dissections as the reference standard, finding that 58.8% (94/160) of patients had neck metastasis in 973 levels and 20 patients (21.3%) had contralateral neck metastasis. The researchers found that in per-patient, per-side, and per-level analyses, ¹⁸F-FDG PET/CT was more

sensitive than CT/MRI (91.5% vs 73.4%, $P < .001$; 91.1% vs 69.6%, $P < .001$; 91.1% vs 53%, $P < .001$, respectively). Additionally, for contralateral neck metastasis, ¹⁸F-FDG PET/CT was more sensitive and accurate than CT/MRI (85.0% vs 45%, $P = .008$; 91.6% vs 80.3%, $P = .008$, respectively). Fleming and colleagues²² found that in 67 patients who underwent ¹⁸F-FDG PET/CT before neck dissection for nodal metastasis, ¹⁸F-FDG PET/CT had a PPV of 92.7% and in 20 patients undergoing bilateral neck dissection, the accuracy of ¹⁸F-FDG PET/CT was 89.7%. Owing to the high PPV, the investigators recommend imaging patients newly diagnosed with head and neck cancer with ¹⁸F-FDG PET/CT to detect lymph node metastases.

M Staging

Furthermore, ¹⁸F-FDG PET increases the sensitivity and specificity when added to CT or MRI in detecting distant metastases (Table 7). For distant metastases, Chan and colleagues²¹ found that ¹⁸F-FDG PET/MRI had a sensitivity of 90% and a PPV of 93.1%, whole-body MRI had a sensitivity of 86.7% with a PPV of 78.88%, and ¹⁸F-FDG PET/CT had a sensitivity of 83.3% and a PPV of 83.3%. For bone metastases ¹⁸F-FDG PET/MRI had a higher PPV (100%) compared with ¹⁸F-FDG PET/CT (81.8%). Furthermore, Chan

Table 2
Diagnostic utility of ¹⁸F-FDG PET/CT following reconstructive surgery

Study, Year	Design	n	Surveillance Technique	Sensitivity (%)	Specificity (%)
Oliver et al, ⁵ 2008	Retrospective	11	PET/CT	88	86
Müller et al, ⁶ 2015	Retrospective	27	PET/CT CT	88 75–88	79–89 68–79

Table 3
Systematic reviews of ^{18}F -FDG PET-detected thyroid incidentalomas

Study, Year	No. of Studies; No. of Patients	Prevalence of Incidentalomas (%)	Proportion of Incidentalomas that Are Malignant (%)	Mean SUV_{max} for Malignant Lesions
Shie et al, ⁷ 2009	18; 55160 (1998–2007)	1.0	33	6.8 ± 4.6
Bertagna et al, ⁸ 2012	27; 147505 (no start date until 2012)	2.5	33–38	No reliable SUV cutoff

and colleagues²⁴ conducted a prospective study of 103 patients with untreated oropharyngeal or hypopharyngeal SCC. Eighteen (17.5%) of the patients had either a distant metastasis or a second primary cancer. On a per-lesion basis, ^{18}F -FDG PET/CT had a higher sensitivity (81.0%) than whole-body MRI (61.9%) ($P = .125$). Kao and colleagues²³ conducted a retrospective cohort study looking at the role of ^{18}F -FDG PET/CT within 6 months after radiation therapy in patients with head and/or neck cancer. The researchers found that for secondary tumor sites or distant metastases, ^{18}F -FDG PET/CT offered a sensitivity of 93%, a specificity of 96%, a PPV of 81%, and an NPV of 98%.

RADIATION TREATMENT RESPONSE ASSESSMENT

^{18}F -FDG PET/CT has become an important aspect of the postradiation response assessment.²⁵ ^{18}F -FDG PET/CT at 12 to 16 weeks after definitive chemoradiation in locally advanced HNSCC has been shown to have an NPV of greater than 90%, and planned neck dissection can be deferred in cases of radiographic complete treatment response.²⁶ Mehanna and colleagues²⁷ reported a randomized controlled trial (“PET-NECK”) that tested the non-inferiority of a surveillance ^{18}F -FDG PET/CT

performed 12 weeks after definitive chemoradiation versus planned neck dissection in mostly N2 and a few N3 (3%) HNSCCs. Patients who had a complete response at the primary site but an incomplete or equivocal response in the neck underwent neck dissection 4 weeks after ^{18}F -FDG PET/CT. The 2-year overall survival was similar in the 2 arms (85% and 82%) but 80% fewer neck dissections were performed with ^{18}F -FDG PET/CT surveillance, resulting in overall cost savings. This can also allow for less patient morbidity. However, it should be noted that ^{18}F -FDG PET/CT has a low PPV because there are high rates of false positives that often lead to additional imaging and unnecessary biopsies^{28,29} and neck dissections in individual cases.

PROGNOSTICATION

[^{18}F]Fluoromisonidazole PET/Computed Tomography

Tumor hypoxia has been shown to correlate with worse treatment outcomes and is thought to be a major driver in treatment resistance as well as carrying a poor prognosis for patients.^{30,31} Hypoxia has been shown to trigger angiogenesis, increase radioresistance, and reduce the effectiveness of surgery.³² Polarographic electrodes were the first method used to measure

Table 4
Sensitivity of ^{18}F -FDG PET in detecting thyroid carcinomas

Study, Year	Population	Sensitivity (%)	Specificity (%)
Leboulleux et al, ⁹ 2007	^{18}F -FDG PET/CT	83	84
Riemann et al, ¹⁰ 2013	^{18}F -FDG PET/CT	92	95
	^{131}I -WBS	65	94
Treglia et al, ¹¹ 2012	Medullary thyroid carcinoma (MTC): calcitonin <150; ≥ 1000 ng/mL	40; 75	—
	MTC: CEA <5; ≥ 5 ng/mL	45; 69	—
Poisson et al, ¹² 2010	Anaplastic thyroid carcinoma	62	—

Table 5
T-staging utility of ¹⁸F-FDG PET/CT for head and neck squamous cell carcinomas

Study, Year	Design	n	Comparison	T-Stage Accuracy (%)* or Sensitivity (%)	
				PET	Comparison
Roh et al, ¹³ 2007	Retrospective	167	CT/MRI	97–98*	86–88*
Seitz et al, ¹⁴ 2009	Retrospective	66	MRI	97	100
Kanda et al, ¹⁵ 2013	Retrospective	30	MRI	67–87*	90*
Chaput et al, ¹⁶ 2018	Retrospective	35	MRI	83	63

tumor hypoxia, but this invasive technique was limited logistically and technically and was not recommended for widespread clinical use.³³ [¹⁸F]Fluoromisonidazole (¹⁸F-FMISO) PET/CT was the first hypoxia tracer introduced and has therefore been studied the most (Table 8).^{32,35,39,40,44,45} ¹⁸F-FMISO PET/CT has limitations including slow cellular washout in nonhypoxic tissue, which could lead to false positives, but also has a relatively short half-life that limits the amount of time available to wait for cellular washout.³⁵ Previous pattern-of-failure studies using ¹⁸F-FMISO PET/CT have suggested that up to 50% of locoregional failures in HNSCCs occur because of hypoxia.³⁹ Löck and colleagues³⁰ showed that residual tumor hypoxia demonstrated by ¹⁸F-FMISO PET/CT is associated with treatment resistance in HNSCC. The investigators recommended that hypoxia measured by ¹⁸F-FMISO PET/CT after week 2 of radiation treatment should identify patients who are at high risk of locoregional failure from chemoradiation. Lee and colleagues³⁴ assessed ¹⁸F-FMISO uptake based on ¹⁸F-FDG PET/CT gross tumor volume (GTV), and high areas of ¹⁸F-FMISO uptake were targeted for a boost using intensity-

modulated radiation therapy (IMRT). Pigorsch and colleagues⁴⁶ studied whether dose escalation to the GTV would improve 2-year locoregional control and overall survival. This ESCALOC trial, a prospective randomized phase III trial, used cisplatin chemotherapy and an IMRT-based simultaneous integrated boost for patients with locoregionally advanced HNSCC. The total dose escalation to GTV was up to 80.5 Gy to the primary tumor and lymph nodes >2 cm. These investigators expect a 15% locoregional control benefit at 2 years.

¹⁸F-HX4 PET/Computed Tomography

¹⁸F-HX4 is a hydrophilic variant of the 2-nitroimidazole class of radiotracers that includes ¹⁸F-FMISO and may offer a faster clearance time, and can theoretically distinguish between necrotic-hypoxic false-negative regions and viable hypoxic tumor cells.³¹ Betts and colleagues³¹ evaluated tumor hypoxia of the primary tumor in 3 patients with newly diagnosed HNSCC using ¹⁸F-HX4 PET/CT scanning before definitive chemoradiation. The level of ¹⁸F-HX4 tumor uptake varied between patients, suggesting a difference

Table 6
N-staging utility of ¹⁸F-FDG PET/CT for head and neck squamous cell carcinomas

Study, Year	Design	n	Comparison	N-Stage Accuracy (%)* or Sensitivity (%)		N-Stage Specificity (%)	
				PET	Comparison	PET	Comparison
Roh et al, ¹³ 2007	Retrospective	167	CT/MRI	89	79	—	—
Seitz et al, ¹⁴ 2009	Retrospective	66	MRI	84	74	—	—
Kanda et al, ¹⁵ 2013	Retrospective	30	MRI	77*	63*	—	—
Nguyen et al, ¹⁸ 2013	Retrospective	71	CT/MRI	95	79	90	90
Roh et al, ¹⁹ 2014	Prospective	91	CT/MRI	71	50	81	87
Park et al, ²⁰ 2016	Prospective	160	CT/MRI	92	73	—	—
Chan et al, ²¹ 2018	Retrospective	113	WB MRI	100	94	—	—

Table 7
M-staging utility of ^{18}F -FDG PET/CT for head and neck squamous cell carcinomas

Study, Year	Design	n	Comparison	M-Stage Sensitivity (%)		M-Stage Specificity (%)	
				PET	Comparison	PET	Comparison
Kao et al, ²³ 2009	Retrospective	240	None	93	—	96	—
Chan et al, ²⁴ 2011	Prospective	103	WB MRI	81	62	—	—
Kanda et al, ¹⁵ 2013	Retrospective	30	MRI	77	46	96	99
Chan et al, ²¹ 2018	Retrospective	113	WB MRI	90	87	—	—

in oxygenation profiles between histologically similar tumors.

^{18}F -FX4 PET/Computed Tomography

Thirty-two patients with HNSCC underwent ^{18}F -FX4 PET/CT at baseline and after approximately 20 Gy, in addition to blood hypoxia marker monitoring with carbonic anhydrase IX (CAIX), plasma osteopontin, and vascular endothelial growth factor (VEGF).³⁸ At baseline, tumor hypoxia was detected in 69% (22 of 32 patients) of the GTVs. The hypoxic fraction (HF) decreased from $21.7\% \pm 19.8\%$ (baseline) to $3.6\% \pm 10.0\%$ (during treatment) ($P < .001$). Although the researchers observed marked changes in hypoxia from the ^{18}F -FX4 PET/CT, there were no significant changes in CAIX and VEGF during treatment.³⁸ Concentrations of osteopontin did weakly correlate with the mean standardized uptake value (SUV_{mean}) of ^{18}F -FX4 PET/CT ($R = 0.52$, $P = .03$). Hypoxia PET/CT tracers may offer more sensitivity in monitoring changes in tissue hypoxia throughout treatment compared with blood markers.

^{18}F -EF5 PET/Computed Tomography

Komar and colleagues³³ used ^{18}F -EF5 PET imaging to assess tumor hypoxia in HNSCC patients. The researchers also evaluated tumor blood flow with the perfusion tracer ^{15}O -H₂O. Fifteen patients with 13 primary tumors and 5 lymph node metastases were included in the study. A voxel-to-voxel analysis found that all regions with high blood flow as measured by the ^{15}O -H₂O tracer had an ^{18}F -EF5 tumor-to-muscle ratio (T/M) of less than 1.5, and there was a positive correlation between blood flow and T/M ($r = 0.621$, $P < .0001$). By contrast, areas with minimal blood flow (<30 mL/100 g/min) showed a negative correlation between blood flow and T/M ($r = -0.042$, $P = .259$). Importantly, blood flow and hypoxia decreased and increased, respectively, at approximately the

same rate ($r = 0.295$, $P < .0001$). In the first human study of ^{18}F -EF5 PET hypoxia marker, Komar and colleagues³³ observed that ^{18}F -EF5 accurately indicated hypoxia on PET imaging, had uniform access to all tissues, and was excreted primarily via the kidneys with no detectable metabolism. The researchers proposed a 3-h time point as the optimal time for detecting hypoxia-specific binding for head and neck cancer and a T/M threshold of 1.5 to determine the presence of hypoxia using ^{18}F -EF5.

Komar and colleagues⁴⁷ determined the predictive value for overall survival of pretreatment PET/CT imaging using ^{18}F -FDG, ^{18}F -EF5, and ^{15}O -H₂O in 22 patients with HNSCC treated with chemoradiation. Parametric blood flow was calculated using dynamic ^{15}O -H₂O PET images using a 1-tissue compartment while the metabolic activity of tumors and SUV was calculated based on ^{18}F -FDG images. T/M uptake ratios were calculated based on ^{18}F -EF5 images, and a T/M ratio of 1.5 was considered a significant threshold in determining tumor hypoxia subvolumes. Komar and colleagues⁴⁷ found a shorter overall survival with metabolically active tumor volume ($P = .008$, hazard ratio [HR] 1.108), maximum ^{18}F -EF5 T/M ratio ($P = .0145$, HR 4.084), and tumor hypoxia subvolumes ($P = .0047$ HR 1.112). There were no statistically significant correlations among ^{18}F -FDG SUV_{max} , ^{18}F -EF5 T/M ratio, and blood flow. Compared with ^{18}F -FDG uptake, high uptake of the hypoxia tracer ^{18}F -EF5 was strongly correlated with poor clinical outcomes.

$[^{18}\text{F}]$ -Fluoroazomycin Arabinoside PET/Computed Tomography

Servagi-Vernat and colleagues³⁷ imaged 12 patients with locally advanced HNSCC with $[^{18}\text{F}]$ -fluoroazomycin arabinoside (^{18}F -FAZA) PET/CT before treatment, after 7 fractions, and after 17 fractions of definitive chemoradiation. Ten of the 12 patients had hypoxic volumes identified

Table 8
Select hypoxia tracer studies in head and neck squamous cell carcinomas

Study, Year	n	Tracer	Significance
Lee et al, ³⁴ 2008	10	¹⁸ F-FMISO	Assessed ¹⁸ F-FMISO uptake based on ¹⁸ F-FDG PET/CT GTV and high areas of ¹⁸ F-FMISO uptake were target for an IMRT boost. The areas of hypoxia received 84 Gy and GTV received 70 Gy
Komar et al, ³³ 2008	15	¹⁸ F-EF5	¹⁸ F-EF5 accurately indicated hypoxia on PET imaging
Choi et al, ³⁵ 2010	8	¹⁸ F-FMISO	Defined hypoxic tumor volume using a tumor-to-cerebellum ratio (T/C) of 1.3 as the threshold for ¹⁸ F-FMISO PET/CT
Lanning et al, ³⁶ 2014	21	¹⁸ F-FMISO	Of the 13 patients with nodal hypoxia on original scan, 6 underwent dose de-escalation at the indexed lymph node. IMRT dose de-escalation demonstrated no clinical evidence of disease or unremarkable treatment toxicity at 3-mo follow-up
Servagi-Vernat et al, ³⁷ 2015	12	¹⁸ F-FAZA	Successfully dose-escalated areas found to be hypoxic with ¹⁸ F-FAZA PET/CT to 86 Gy
Zegers et al, ³⁸ 2016	32	¹⁸ F-HX4	Detected tumor hypoxia in 69% (22 of 32 patients) of the GTVs. HF decrease from 21.7% ± 19.8% (baseline) to 3.6% ± 10.0% (during treatment) (<i>P</i> <.001)
Boeke et al, ³⁹ 2017	54	¹⁸ F-FMISO	Compared the pretherapeutic hypoxic subvolumes detected by ¹⁸ F-FMISO PET/CT with the spatial location of failures using CT or ¹⁸ F-FDG PET/CT
Crispin-Ortuzar et al, ³² 2017	75	¹⁸ F-FMISO	Propose that ¹⁸ F-FDG PET/CT could be a viable alternative to detect hypoxia if ¹⁸ F-FMISO PET/CT is unavailable
Grkovski et al, ⁴⁰ 2017	75	¹⁸ F-FMISO	Found that ¹⁸ F-FMISO PET dynamic imaging revealed more detail on tumor microenvironment and assessment of chemoradiation response compared with a single static image based on pharmacokinetic modeling
Welz et al, ⁴¹ 2017	25	¹⁸ F-FMISO	10 patients randomized to dose-escalated 77 Gy/35 fractions to hypoxic regions. 2-y locoregional control was significantly worse in the patients with hypoxia who received standard chemoradiation compared with the nonhypoxia tumor patients who received standard chemoradiation (44.4% vs 100%, <i>P</i> = .048)
Suh et al, ⁴² 2017	15	⁶⁴ Cu-ATSM	Identified 16 genes that were positively associated and 5 genes that were negatively associated with hypoxia volume (adjusted <i>P</i> <.1; 8 genes had adjusted <i>P</i> <.05; hypoxic volume-associated gene signature)
Betts et al, ³¹ 2019	3	¹⁸ F-HX4	Evaluated tumor hypoxia of the primary tumor in a small series of patients (3) with newly diagnosed HNSCC using ¹⁸ F-HX4 PET/CT scan before chemoradiation
Bandurska-Luque et al, ⁴³ 2019	45	¹⁸ F-FMISO	Found that bigger lymph node metastases had similar hypoxia levels compared with primary tumors while smaller lymph node metastases were less hypoxic
Löck et al, ³⁰ 2019	50	¹⁸ F-FMISO	58 hypoxia-associated genes were correlated with tumor-to-background ratio and hypoxic volume

by ¹⁸F-FAZA PET/CT. After the second scan, 7 patients had a previously nonhypoxic, newborn hypoxic voxel that appeared in the primary tumor and/or a lymph node. After the third scan, only 3 patients still had newborn voxels. Treatment planning occurred in three phases after each

¹⁸F-FAZA PET/CT scan, with the goal of delivering a fixed dose of 86 Gy to any voxels defined as hypoxic. ¹⁸F-FAZA PET/CT-detected hypoxic regions were dose-escalated without substantial dose increase to surrounding tissues. The researchers found that implementing hypoxia-

tracing scans before and during treatment allowed them to plan in multiple phases and adapt to changes in hypoxia status over time.

[⁶⁴Cu]Diacetyl-bis(N-Methylthiosemicarbazone) PET/Computed Tomography

Suh and colleagues⁴² compared hypoxia biomarkers and gene expression in oropharyngeal SCC diagnostic biopsies using [⁶⁴Cu]diacetyl-bis(N-methylthiosemicarbazone) (⁶⁴Cu-ATSM) PET/CT hypoxia tracer imaging. Using a cohort of 15 patients, the authors identified 16 genes that were positively associated and 5 genes that were negatively associated with hypoxia volume (adjusted $P < .1$; 8 genes had adjusted $P < .05$; hypoxic volume-associated gene signature). In addition, a 21-gene signature was associated with inferior 3-year progression-free survival (HR 1.5 (1.0–2.2), $P = .047$).

SUMMARY

In summary, ¹⁸F-FDG PET is a tool in the diagnosis, staging, and radiation treatment response assessment of head and neck cancers that is supported by substantial evidence. In cases of HNSCCUP, the addition of ¹⁸F-FDG PET to cross-sectional imaging increases the likelihood of identifying the primary site. In thyroid incidentalomas, ¹⁸F-FDG avidity raises the suspicion of malignancy and can lead to the diagnosis of thyroid cancers. Furthermore, ¹⁸F-FDG PET is a useful staging tool, particularly in the nodal and distant metastatic assessment of HNSCC. Post-treatment response assessment with ¹⁸F-FDG PET is recommended at roughly 12 weeks for HNSCCs. Finally, many non-¹⁸F-FDG tracers that reflect hypoxia, proliferation, and metabolism are actively being studied and have promise in the prognostication of different cancer types and the targeting of resistant disease.

SUPPLEMENTARY DATA

Supplementary content related to this article can be found at <https://doi.org/10.1016/j.cpet.2019.08.010>.

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