Jpn J Radiol (2015) 33:776–789
DOI 10.1007/s11604-015-0495-1

REVIEW

Present and future role of FDG-PET/CT imaging in the management of head and neck carcinoma

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Received: 11 October 2015 / Accepted: 16 October 2015 / Published online: 27 October 2015

Abstract Integrated positron emission tomography/computed tomography (PET/CT) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) is a useful technique for acquisition of both glucose metabolic and anatomic imaging data using a single device in a single diagnostic session, and has opened a new field in clinical oncologic imaging. FDG-PET/CT has been used successfully for the initial staging, restaging, monitoring of the response to therapy, and prognostication of head and neck carcinoma. The present review discusses the current role of FDG-PET/CT in the management of head and neck carcinoma, focusing on its usefulness and limitations for imaging in these patients.

Keywords Fluorodeoxyglucose (FDG) · Positron emission tomography/computed tomography (PET/CT) · Head and neck carcinoma · Staging · Restaging

Introduction

In the late 1990s, positron emission tomography (PET) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), which exploits the increased utilization and high uptake of glucose by malignant cells, opened a new field in clinical oncologic imaging. Intrinsically, PET images lack anatomic information, and precise localization of any suspicious lesions may be difficult. Recently, however, integrated positron emission tomography/computed tomography (PET/CT), in which a full-ring-detector clinical PET scanner and multidetector-row helical CT scanner are combined, has made it possible to acquire both metabolic and anatomic imaging data using a single device in a single diagnostic session, providing precise anatomic localization of suspicious areas of increased FDG uptake. In a clinical setting, FDG-PET/CT has achieved a significant improvement in diagnostic accuracy and exerted a considerable impact on patient management, including initial staging, optimization of treatment, restaging, monitoring of the response to therapy, and prognostication of various malignant tumors including head and neck carcinoma. Here we review the current and future roles of FDG-PET/CT in the management of head and neck carcinoma, discussing its usefulness and limitations for imaging in these patients.

Initial staging

Head and neck cancer (HNC) ranks as the sixth most common cancer worldwide, the vast majority of cases being head and neck squamous cell carcinoma (HNSCC) [1]. Most patients present with complicated locally advanced disease requiring multidisciplinary treatment plans employing combinations of surgery, radiation therapy and chemotherapy. Tumor staging is critical for therapeutic planning, and there are multiple challenges including accurate tumor localization with precise delineation of the tumor volume

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(T stage), neck lymph node (LN) staging (N stage), and detection of distant metastasis (M stage).

FDG-PET/CT is being used increasingly for staging of HNSCC, and has a considerable impact on treatment decision-making [2–8]. In comparison to morphological imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI), PET/CT is particularly advantageous in allowing assessment of neck nodes, potential distant metastases and synchronous second primaries in a single examination. Lonneux et al. [9] performed a multicenter prospective study to evaluate the impact of PET/CT on the initial staging and management of 233 patients with HNSCC. The group found that PET/CT improved the TNM classification of the disease and altered the management of 13.7 % of the patients, mainly due to the ability of PET/CT to detect metastatic or additional disease. In 2014, the National Comprehensive Center Network updated the clinical practice guidelines for PET/CT imaging of head and neck cancer and suggested the use of PET/CT for initial staging of oral cavity, oropharyngeal, hypopharyngeal, glottic, and supraglottic cancers for stage III–IV disease, as well as mucosal melanoma and nasopharyngeal carcinoma (World Health Organization class 2–3 and N2–3 diseases) [1].

T staging

The T stage at each site is determined by the size of the primary tumor and invasion into deep structures. Contrast-enhanced CT (ceCT) and MRI have been the primary imaging modalities for evaluation of HNSCC T stage because of their superior anatomic resolution and tissue contrast in comparison to PET/CT (Fig. 1). There is no clear recommendation for routine use of PET/CT in initial T staging. MRI remains the preferred imaging method for assessment of invasion in the nasopharynx, oral cavity, perineural areas and bone marrow, whereas CT is the modality of choice for assessment of larynx and bony cortex invasion [10–12]. Although MRI is the modality of choice for detection of perineural spread due to its high tissue contrast, on PET/CT, perineural spread can present as abnormal linear or curvilinear hypermetabolic activity along the trigeminal or facial nerves [12].

N staging

Pretreatment assessment of neck metastasis is important for therapeutic planning and prognostication in patients

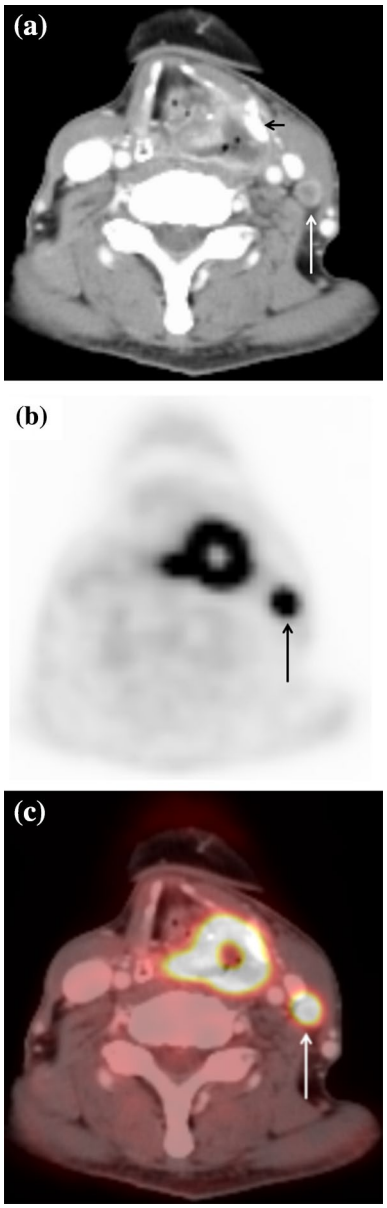

Fig. 1 A 60-year-old man with neck node metastasis arising from hypopharyngeal cancer (pT4N2b). **a** Contrast-enhanced CT shows a 4-cm mass with rim enhancement and central necrosis in the left hypopharyngeal piriform fossa, suggesting hypopharyngeal cancer. Sclerotic change is observed at the proximate left thyroid cartilage (*short arrow*), suggesting invasion of the thyroid cartilage (cT4a). One 10 × 13-mm swollen lymph node is also seen at left level III (*long arrow*), suggesting the presence of nodal cancer spread. **b** FDG-PET and **c** fused PET/CT show doughnut-shaped intense FDG uptake (SUV_{max}: 12.8) corresponding to the hypopharyngeal mass and intense FDG uptake (SUV_{max}: 11.9) corresponding to the ipsilateral neck node (*long arrow*), confirming the hypopharyngeal cancer and neck nodal metastasis. The patient underwent resection of the primary tumor with bilateral neck dissection, and examination of the histopathological specimen revealed extensive lymph node involvement by cancer in this node (hypopharyngeal cancer, pT4N2bM0)

with HNSCC [13]. The likelihood of neck LN metastasis in HNSCC patients depends on the location, histology and staging of the primary tumor. Predominance of certain levels was seen for each primary site. Levels I, II, and III were at highest risk for metastasis from cancer of the oral cavity, and levels II, III, and IV were at highest risk for metastasis from carcinomas of the oropharynx, hypopharynx, and larynx [14]. Especially, the most common site of neck regional LN is level I for cancer of the oral cavity, level II for cancer of the oropharynx, and levels II and III for cancers of the hypopharynx, and larynx. At present, neck dissection with histologic examination of LNs is still the most reliable staging procedure. Preoperative nodal status is usually evaluated by clinical examinations such as palpation, ultrasonography (US), CT, and MRI. Unfortunately, CT and MRI, which evaluate morphologic parameters such as nodal size, internal architecture and contrast enhancement pattern, have been shown to have only limited value for this purpose [15]. Doppler US with fine-needle aspiration can overcome some of these limitations, but the results are dependent on the skill level of the sonographer, and this may be impractical in some cases because the number of questionable nodes may be high.

Several studies have evaluated the diagnostic utility of FDG-PET or PET/CT for detection of neck LN metastases of HNSCC (Fig. 1). Data from those studies demonstrated variations in sensitivity, specificity and accuracy, with respective values of 67–95, 76–99 and 77–97 % [16–32] (Table 1). In a meta-analysis, Kyzas et al. [33] reviewed 32 studies of 1236 patients with HNSCC and reported that the overall sensitivity and specificity of FDG-PET for assessment of nodal disease was 80 and 86 %, respectively, but dropped to 50 and 87 %, respectively, for cN0 patients. Sun et al. [34] reviewed 24 studies of 1270 patients with HNSCC to assess nodal metastasis, and reported that the mean [95 % confidence interval (CI)] pooled per-patient, per-neck-side, and per-neck-level sensitivities/specificities of FDG-PET/CT were 91 % (82–95 %)/87 % (80–92 %), 84 % (75–90 %)/83 % (77–88 %), and 80 % (71–87 %)/96 % (94–97 %), respectively. Across 13 studies (3460 neck levels) with per-neck-level data, the sensitivity and specificity of FDG-PET/CT were 84 % (72–91 %) and 96 % (95–97 %), and those of conventional imaging (CT, MRI, and CT/MRI) were 63 % (53–72 %) and 96 % (95–97 %), respectively. Some groups have used visual assessment [16, 17, 21–23, 26, 31] and other groups have used quantitative assessment using maximum standardized uptake value (SUV_{max}) [18–20, 24, 25, 27–30]. To our knowledge, there have been no reports which directly compared the difference in diagnostic performance between visual and quantitative assessment, and therefore the superiority of the two methods has not been clarified. Murakami et al. [18] reported the size-based SUV_{max} cutoff and Jeong et al. [19] reported the level-based SUV_{max} cutoff.

Recently, Roh et al. [31] demonstrated that PET/CT is superior to CT/MR imaging for detection of occult cervical metastatic nodes in 91 patients who were neck palpation-negative (69 vs 39 % on a per-level basis, $p < 0.001$). On the other hand, several reports have indicated that FDG-PET or PET/CT offers no advantage, especially for evaluation of the N0 neck in patients with early oral cancer [17, 23], and therefore its diagnostic value remains controversial.

Although FDG-PET is a functional method based on the increased glucose metabolism of cancer cells, regardless of node size, and PET/CT can often detect metastatic LNs measuring 6–9 mm, FDG-PET has several limitations. FDG uptake by small deposits of tumor cells is often poorly depicted owing to partial volume effects. Moreover, its registration is limited to a certain LN size, because the spatial resolution of recent PET scanners is technically limited to 4–6 mm. On the other hand, FDG-PET is not 100 % specific because inflammatory reactive nodes and adjacent granulation tissue can increase uptake, yielding a false positive result. Although FDG-PET/CT does not yet have the ability to replace neck dissection as the diagnostic standard of care, in the future, the development of dual time point PET, new tumor-specific tracers and PET scanners with a higher resolution may increase the potential to detect occult LN metastases.

In summary, the spatial resolution of PET (approximately 4–6 mm) is not sufficient to allow the detection of early neck node involvement and micrometastases, and PET/CT cannot replace neck dissection as the diagnostic standard.

M staging

Approximately 4–15.4 % of patients with HNSCC have distant metastases at initial presentation [2, 6]. The most common sites of metastasis include the lung, bone and abdomen. Whole-body FDG-PET/CT is more accurate than conventional imaging for detection of metastatic foci [8]. A meta-analysis involving 15 studies with 1445 patients by Xu et al. [35] revealed that the sensitivity and specificity of FDG-PET/CT was around 87.5 % (95 % CI, 78.7–93.6 %) and 95 % (95 % CI, 93.1–96.4 %), respectively. It is very important to detect distant metastases early in the workup, as it can impact prognosis and management. Extensive surgery with curative intent may result in significant morbidity and mortality, and may be avoided in the event of documented distant metastases. FDG-PET/CT is recommended when distant spread is suspected in patients with locoregionally advanced HNSCC. However, negative findings of FDG-PET/CT do not completely rule out the presence of metastasis [35].

In the pulmonary parenchyma, FDG-PET efficiently depicts supracentimetric pulmonary nodules.

Table 1 Studies evaluating FDG-PET/CT or PET for neck lymph node staging in patients with HNSCC

Authors	Refs.	Year	No. of patients	Modality	Analysis unit	FDG-PET/CT or PET result					Comparison imaging
						Sen (%)	Spe (%)	PPV (%)	NPV (%)	Acc (%)	
Ng et al.	[16]	2005	124	PET	Per-neck-level (493)	75	93	72	94	89	CT/MRI
Schoder et al.	[17]	2006	31	PET/CT	Per-neck-side (36)	67	85	50	88	81	
					Per-neck-level (142)	67	96	50	98	94	
Murakami et al.	[18]	2007	23	PET/CT	Per-neck-level (112)	79	99	94	96	96	CT/MRI
Jeong et al.	[19]	2007	47	PET/CT	Per-neck-level (242)	92	99	97	97	97	CT
Nabmias et al.	[20]	2007	70	PET/CT	Per-neck-side (83)	88	76	78	86	82	
Roh, et al.	[21]	2007	167	PET (104)	Per-patient (167)	90–91	87–88	88–92	86–90	89	CT/MRI
				PET/CT (63)	Per-neck-level (864)	87–90	93–94	77	96–98	92–93	
Yamazaki et al.	[22]	2008	26	PET	Per-neck-side (35)	74	92	94	65	80	CT
Krabbe et al.	[23]	2008	73	PET/CT	Per-neck-side (146)	90	81	62	96	83	
Piao et al.	[24]	2009	89	PET/CT	Per-neck-level (345)	84	91	75	94	89	
Yoon et al.	[25]	2009	67	PET/CT	Per-neck-level (402)	81	98	91	96	95	CT, MRI and US
Richard et al.	[26]	2010	50	PET/CT	Per-neck-level (504)	83	94	78	95	92	
Iyer et al.	[27]	2010	111	PET/CT	Per-patient (111)	95	88	95	88	93	
Kim et al.	[28]	2011	114	PET/CT	Per-neck-side (228)	83	91	85	89	88	
					Per-neck-level (899)	79	95	78	95	92	
Matsubara et al.	[29]	2012	38	PET/CT	Per-neck (498)	77	97	76	98	95	CT and US
Nguyen et al.	[30]	2014	71	PET/CT	Per-neck-side (142)	95	90	91	94	93	CT and MRI
Roh et al.	[31]	2014	91	PET/CT	Per-patient (91)	71	81	73	80	77	CT/MRI
					Per-neck-side (121)	72	85	72	85	80	
					Per-neck-level (466)	69	92	62	94	89	
Joo et al.	[32]	2014	157	PET/CT	Per-neck-level (1252)	90	96	88	94	93	

HNSCC head and neck squamous cell carcinoma, *Ref* reference, *Sen* sensitivity, *Spe* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *Acc* accuracy, *CT* computed tomography, *MRI* magnetic resonance imaging, *US* ultrasound

However, because of the partial volume effect and respiratory movements, PET lacks sensitivity for smaller nodules. Careful scrutiny of the CT data obtained during the hybrid PET/CT examination can reveal small nodules without FDG uptake. It should be noted that free-breathing CT is less efficient than standard diagnostic thoracic CT.

In summary, FDG-PET/CT is a useful modality for detection of distant metastases, showing high sensitivity and specificity.

Carcinoma of unknown primary origin

Two to 7 % of HNSCC patients present with metastatic cervical lymphadenopathy from undefined primary sites [36], despite a complete history (nonspecific symptoms or no symptoms), thorough physical examination/office flexible fiberoptic endoscopy (small submucosal lesion), or conventional contrast-enhanced CT/MRI (small lesion obscured by normal lymphoid tissue). The majority of such primary cancers arise in the palatine tonsils or base of the tongue. Various studies have shown that PET/CT is able to identify the primary cancer in 29–54 % of cases with 62–93 % sensitivity, 33–93 % specificity, 56–89 % positive predictive value (PPV) and 25–96 % negative predictive value (NPV) [37, 38]. In recent years, Lee et al. [39] have demonstrated that FDG-PET/CT showed higher sensitivity (69 %) for detection of occult primary tumors than did ceCT (16 %) ($p < 0.001$) or combined ceCT and MRI (41 %, $p = 0.039$) in 56 patients with cervical metastasis from an unknown primary tumor.

Synchronous second primary cancer

The association between synchronous primary tumors in the aerodigestive tract is a well-known phenomenon that has been explained by the concept of "field cancerization" [40]. The mucous epithelium of the head and neck, esophagus and lung is exposed to common carcinogenic agents, leading to multiple carcinomas in these regions. Strong epidemiologic evidence implicates tobacco as the main carcinogen and alcohol as a promoter of carcinogenesis. Approximately 7.4–18 % of patients with HNSCC have a synchronous second primary malignancy [2, 6, 7]. Panendoscopy studies have shown that the prevalence of synchronous esophageal SCC ranges from 5.1 to 47.1 % [41, 42]. A meta-analysis has revealed that FDG-PET/CT had 87.5 % sensitivity and 95 % specificity for detection of synchronous primary cancer or distant metastasis [43] (Fig. 2). Negative findings of FDG-PET/CT do not completely exclude the presence of synchronous primary cancer. Strobel et al. [7] performed FDG-PET/CT for 589 patients with HNSCC, 9.5 % of whom had synchronous primary cancers, of which 84 % were detected using FDG-PET/CT. In 80 % of the patients, FDG-PET/CT led to a change of therapy because of detection of synchronous primary cancer.

However, due to the limited spatial resolution of PET/CT, small and superficially growing tumors can sometimes be invisible. Nakaminato et al. [42] demonstrated that in routine esophagogastroduodenoscopy screenings with iodine staining and FDG-PET/CT scans before initial treatment of hypopharyngeal cancer, the prevalence of esophageal cancers was 51.5 %, of which FDG-PET/CT detected only 20.7 %. FDG-PET/CT cannot replace esophagogastroduodenoscopy because of its limited ability to detect superficial esophageal cancer.

In summary, FDG-PET/CT and esophagogastroduodenoscopy are complementary, and their use in combination may be the most sensitive approach for detection of synchronous second primary tumors at an early treatable stage in patients with HNSCC.

Restaging

Despite continuing advances in surgical and non-surgical therapeutic strategies, up to 40 % of HNSCC patients suffer recurrence even after therapy [44]. However, postsurgical and radiation-induced changes in normal tissues may interfere with the early detection of recurrence by regular standard examinations of the head and neck, including physical examination, endoscopic examination, CT and MRI [45].

FDG-PET, which exploits the increased utilization of glucose by malignant cells, has made it possible to diagnose cancer recurrence and distant metastasis at the preclinical stage before it becomes evident by conventional imaging modalities [46]. Many studies have confirmed the usefulness of FDG-PET/CT as a post-treatment tool for patients with HNSCC (Figs. 3, 4). Data from those studies have demonstrated 60–100 % sensitivity, 65–98 % specificity and 66–99 % accuracy [47–73] (Table 2). Isles et al. [74] conducted a meta-analysis of 27 studies involving 1871 patients with HNSCC for whom FDG-PET or PET/CT had been conducted after radiotherapy/chemotherapy, and reported that the mean pooled sensitivity/specificity of FDG-PET or PET/CT for detection of recurrent tumors in the area affected by the primary HNSCC was 94/82 %, whereas the corresponding values for CT (67/78 %) and MRI (81/46 %) were lower; for detection of LN metastasis, the corresponding value was 74/88 %. Gupta et al. [75] conducted a meta-analysis of 51 trials involving 2335 patients to assess the diagnostic performance of post-treatment FDG-PET or PET/CT imaging for HNSCC, and reported that the mean (95 % CI) pooled sensitivity, specificity, PPV, and NPV of FDG-PET or PET/CT for detection of recurrent tumors in the primary HNSCC-affected area were 80 % (74–85 %), 88 % (85–90 %), 59 % (53–65 %), and 95 % (94–97 %), respectively. The corresponding values for neck nodes were 73 % (67–78 %), 88 % (86–89 %), 52 % (47–58 %), and 95 % (93–96 %), respectively. FDG-PET/CT shows a very high NPV and moderate PPV for evaluation of local and regional recurrence in patients with HNSCC. If the NPV remains exceptionally high, and a surveillance scan shows a negative response following definitive treatment, then remaining viable disease seems unlikely, thus offering a guide to therapeutic

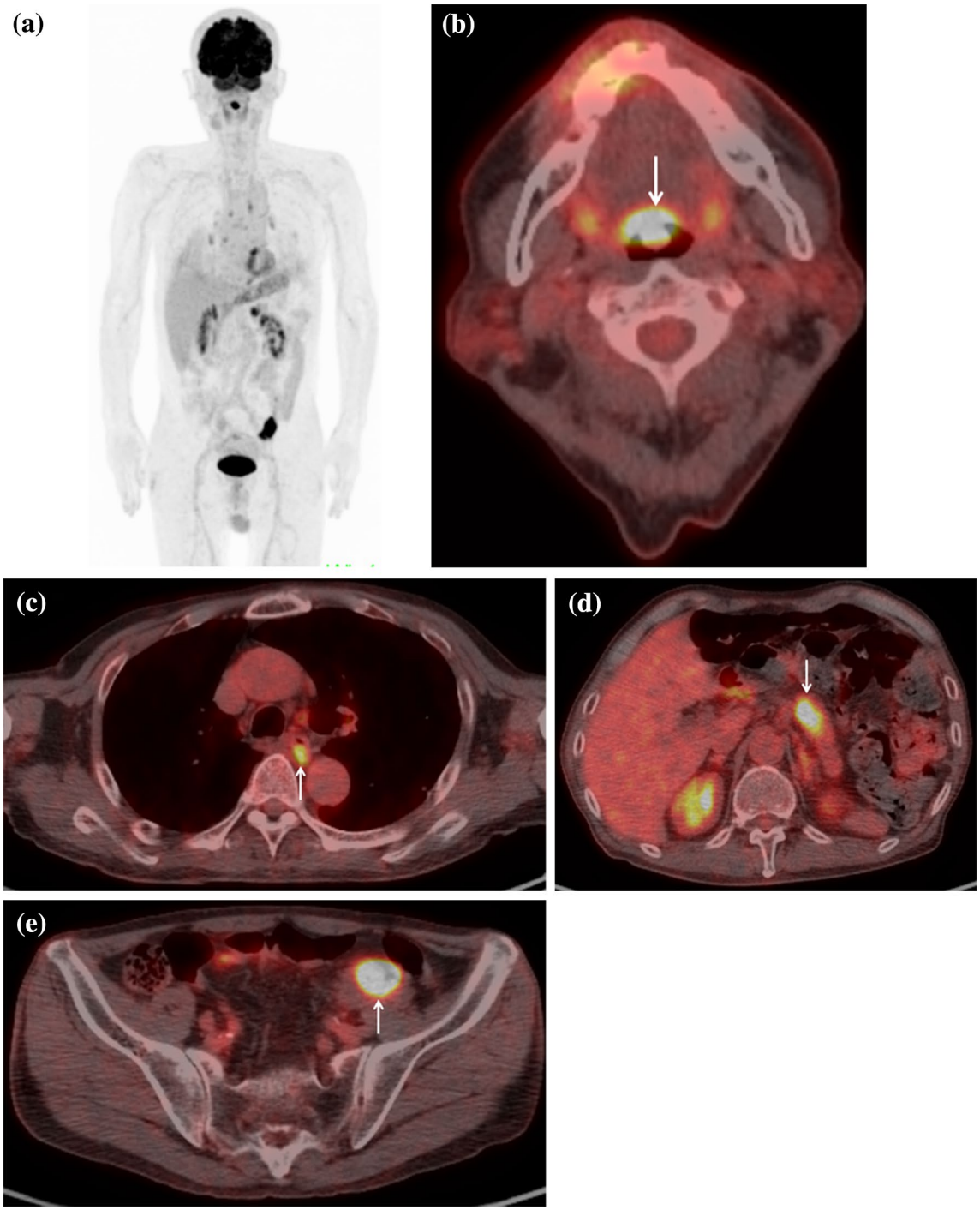

Fig. 2 A 71-year-old man with four cancers of the oropharynx, esophagus, pancreas, and sigmoid colon. **a** Maximum intensity projection (MIP) of FDG-PET shows abnormal FDG uptake in the oropharynx, mediastinum, upper abdomen and pelvis. **b** FDG-PET/CT shows intense FDG uptake (SUV_{max}: 8.9) corresponding to the uvula (*arrow*), suggesting orophayngeal cancer. **c** FDG-PET/CT shows moderate FDG uptake (SUV_{max}: 4.5) corresponding to the esophagus (*arrow*), suggesting esophageal cancer. **d** FDG-PET/CT shows intense FDG uptake (SUV_{max}: 9.7) corresponding to the pancreatic body (*arrow*), suggesting pancreatic cancer. **e** FDG-PET/CT shows intense FDG uptake (SUV_{max}: 13.1) corresponding to the sigmoid colon (*arrow*), suggesting colon cancer. Examination of the histopathological specimen confirmed four cancers arising from the oropharynx, esophagus, pancreas, and sigmoid colon

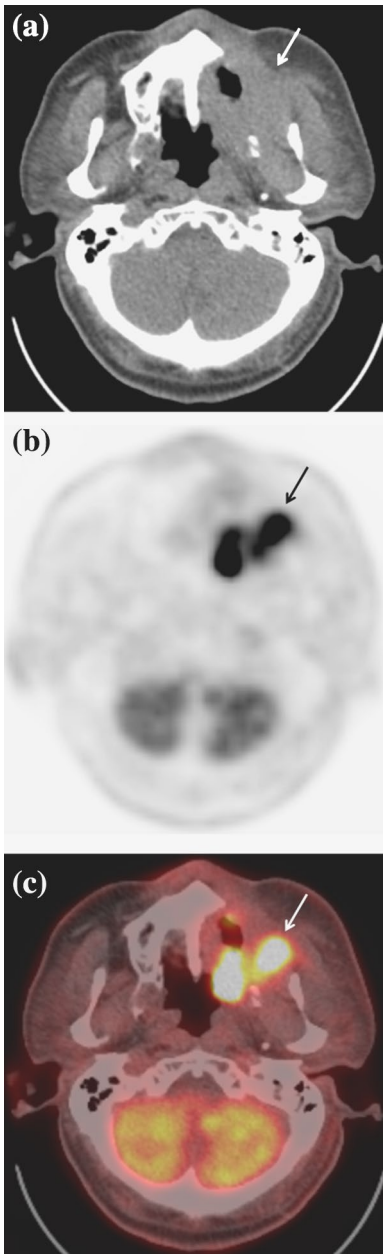

Fig. 3 A 65-year-old man with local recurrence of maxillary sinus cancer 5 months after surgery. **a** CT of FDG-PET/CT shows a soft-tissue density area at the surgical site (*arrow*), suggesting local recurrence. **b** FDG-PET and **c** fused PET/CT show intense FDG uptake (SUV_{max}: 20.5) corresponding to the soft-tissue density area (*arrow*), confirming local recurrence. Examination of the histopathological specimen revealed cancer tissue

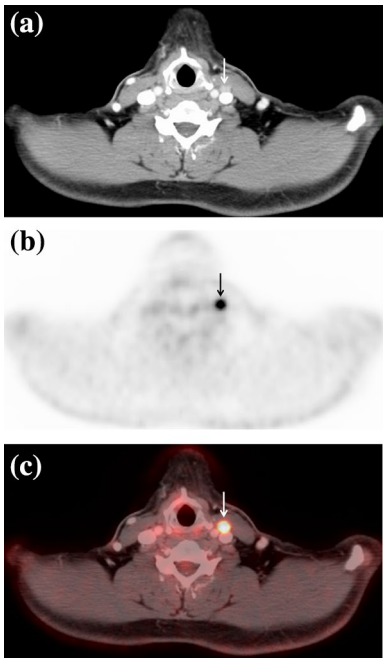

Fig. 4 A 70-year-old man with neck lymph node recurrence of oral tongue cancer 6 months after surgery. **a** Contrast-enhanced CT shows a 7 × 7-mm left neck lymph node with enhancement in the left neck area (*arrow*), with an equivocal interpretation of nodal recurrence. **b** FDG-PET and **c** fused PET/CT show intense FDG uptake (SUV_{max}: 11.4) corresponding to the left neck node (*arrow*), confirming recurrence in the neck node. The histopathological specimen revealed extensive involvement of cancer in this lymph node

decision-making. A moderate PPV is due to treatment-related FDG-avid inflammation or infection in LNs, salivary gland, muscles, and soft tissue [76].

Although early and accurate detection of residual/recurrent disease by FDG-PET/CT can facilitate appropriate therapeutic management, the optimal timing of the first response assessment by PET/CT after definitive treatment is controversial. It is suggested that PET/CT should be performed no sooner than 2 months after completion of treatment to avoid any false-positive results; persistent local inflammation, infection, non-infectious inflammation or granulation are known to give rise to false-positive results when FDG-PET is employed. However, it may be performed sooner if recurrent disease is clinically suspected. Although Kim et al. [51] have prospectively evaluated the response to radiotherapy using FDG-PET 4 weeks after the completion of radiotherapy in patients with HNSCC, Isles et al. demonstrated that the sensitivity of FDG-PET was decreased if the interval between treatment and scan was less than 10 weeks [74]. At many institutions, an interval of 12 weeks has generally been recommended to balance the drawbacks of imaging too early versus too late [76]. Kostakoglu et al. [66] have recommended that a post-treatment scan be conducted 3–4 months after completion of treatment, followed by another scan within the first year. Paidpally et al. [77] have reported that the proportion of FDG-PET/CT studies yielding indeterminate results because of possible treatment-related inflammation stabilizes between 4 and 24 months after treatment, and that the most appropriate timing for post-therapy PET/CT is between 3 and 4 months.

Table 2 Studies evaluating FDG-PET/CT or PET for restaging in patients with HNSCC

Authors	Refs.	Year	No. of patients	Modality	Site	FDG-PET/CT or PET result					Median time to post PET (range) (months)	Comparison imaging
						Sen (%)	Spe (%)	PPV (%)	NPV (%)	Acc (%)		
Branstetter et al.	[47]	2005	46	PET/CT	L&R	98	92	88	99	94	NA	Enhanced CT
Ryan et al.	[48]	2005	103	PET	L&R&D	85	93	70	97	92	2 (0–55)	
Nayak et al.	[49]	2007	43	PET/CT	R	88	91	70	97	90	(1–6)	
Halpern et al.	[50]	2007	49	PET/CT	L&R	88	78	95	50	86	NA	PET
Kim et al.	[51]	2007	97	PET	L&R	88	96	65	99	95	1	
Lee et al.	[52]	2007	159	PET	L&M	93	87	81	95	89	2–6, 6–12, 12–24 and >24	
Comoretto et al.	[53]	2008	63	PET/CT	L&R	82–95	89–98	85–95	86–98	86–97	(2–14)	Enhanced MRI
Ong et al.	[54]	2008	65	PET/CT	L&R	71	89	38	97	88	12 (8–27)	
Krabbe et al.	[55]	2009	48	PET	L&R&D	97	72	46	99	77	3, 6, 9 and 12	
Rabalais	[56]	2009	52	PET/CT	R	100	88	40	100	88	3.0 (1.0–7.4)	
Gourin et al.	[57]	2009	64	PET/CT	D	86	84	60	95	85	5.3 (3–42)	
Kao et al.	[58]	2009	80	PET/CT	L&R&D	94	90	64	99	NA	(2–40)	
Abgral et al.	[59]	2009	91	PET/CT	L&R&D	100	85	77	100	90	11.6 (7–16)	
Yao et al.	[60]	2009	188	PET	L&R	86	86–97	32–71	99	86–96	3.8 (1.3–10.9)	
Kim et al.	[61]	2011	39	PET/CT	L&R	79–91	65–93	77–81	85–92	79–89	(2–7)	Enhanced CT/ MRI
Zundel et al.	[62]	2011	52	PET/CT	L&R	100	65	19	100	67	(4–6)	Physical examination
Zhang et al.	[63]	2011	62	PET/CT	L&R&D	60	69	48	79	66	2.3 (1–4)	
Yi et al.	[64]	2012	82	PET/CT	D	86	84	52	97	84	6 (1–15)	
Beswick et al.	[65]	2012	388	PET/CT	L&R&D	100	NA	NA	NA	NA	6 (2–43)	
Kostakoglu et al.	[66]	2013	99	PET/CT	L&R&D	100	87	57	100	89	3.5 (2.3–8)	CT, physical examination/ endoscopy
Ho et al.	[67]	2013	100	PET/CT	L&R&D	80–100	92–99	35–75	99–100	96–99	3, 12 and 24	
Rangswamy et al.	[68]	2013	103	PET/CT	L	100	75–83	68–74	100	82–89	19 (3–60)	Enhanced CT
Dunsky et al.	[69]	2013	123	PET/CT	L&R&D	NA	NA	NA	NA	NA	8.9 (0.8–26)	
Kim et al.	[70]	2013	143	PET/CT	L&R&D	93–96	91–95	72–83	98–99	92–94	5 (2–9) and 13 (9–20)	
Koshkareva et al.	[71]	2014	61	PET/CT	L&R&D	61	95	84	85	85	2.3 (1.5–3.8)	
Robin et al.	[72]	2015	116	PET/CT	L&R&D	96	87	65	99	89	5.6	
Suenaga et al.	[73]	2015	170	PET/CT	L&R&D	83	92	73	95	90	11 (2–78)	Enhanced CT

HNSCC head and neck squamous cell carcinoma, *Sen* sensitivity, *Spe* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *Acc* accuracy, *NA* not available, *L* local persistent or recurrent, *R* regional nodal recurrence, *D* distant metastasis, *CT* computed tomography, *MRI* magnetic resonance imaging

It is important to detect distant metastases early in the workup, as this can change prognosis and management. Extensive surgery with curative intent may cause significant morbidity and mortality, and may be better avoided if distant metastases can be demonstrated, thus switching the focus to palliative chemoradiation options. PET/CT is recommended when distant spread is suspected in patients with locoregionally advanced HNSCC. A meta-analysis involving 10 studies with 756 patients by Gao et al. [78] revealed that the sensitivity and specificity of FDG-PET/CT was around 92 % (95 % CI, 83–96 %) and 95 % (95 % CI, 91–97 %), respectively.

In summary, FDG PET/CT is very useful for cancer restaging in patients with documented or suspected HNSCC recurrence, and is more efficient than PET alone and conventional imaging methods. An interval of 12 weeks has generally been recommended as most common, optimal timing for FDG-PET examination after finishing treatment.

Monitoring of response to therapy

PET/CT is superior to CT for distinguishing metabolically active tumors from residual anatomic deformity after completion of chemoradiation therapy. Four studies have compared the performance of FDG-PET or PET/CT with that of ceCT for detection of persistent disease after radiotherapy with or without chemotherapy. Porceddu et al. [79] evaluated a PET-directed policy for neck management in node-positive HNSCC patients after definitive radiotherapy with or without concurrent systemic therapy. In that study, 112 patients achieving a complete response at the primary site underwent post-therapy nodal response assessment for 12 weeks using PET and diagnostic CT, and 50 CT abnormalities were observed following completion of therapy. Forty-one of these abnormalities were highlighted only on the basis of PET characteristics. None of the patients ultimately developed recurrent disease, and the false positivity rate for CT alone was 38 %. Moeller et al. [80] evaluated the extent to which FDG-PET/CT might improve assessment of the response to radiation therapy in 98 HNC patients who underwent FDG-PET/CT and ceCT imaging 8 weeks after completion of treatment. When the optimal threshold SUV_{max} for prediction of failure in primary tumors and nodes was taken as 6.5 and 2.8, respectively, the sensitivity, specificity, PPV, and NPV were 70, 94, 58 and 96 %, respectively, for primary tumors and 75, 76, 27, and 96 %, respectively, for neck nodes, when post-radiation FDG-PET/CT was used to discriminate responders from non-responders. They concluded that FDG-PET/CT has little merit over CT alone for assessment of the response to radiation therapy in unselected patients with locally advanced HNSCC, whereas it may improve assessment of the response to treatment in high-risk patients, such as those with human papillomavirus (HPV)-negative disease. Kitagawa et al. [81] reported 23 patients who underwent FDG-PET later than 4 weeks after treatment, whereas ceCT was performed within 2 weeks. FDG-PET identified all patients with residual disease, demonstrating sensitivity and specificity higher than those of ceCT (100 and 89 vs 75 and 59 %, respectively). Andrade et al. [82] reported performing FDG-PET/CT at 4–8 weeks, and again later than 8 weeks after treatment, thus testing two different time intervals and identifying the best timing in 28 patients with HNC. The authors found that the accuracies of PET/CT and CT were similar within 4–8 weeks, whereas beyond 8 weeks the accuracy of PET/CT was higher (100 %) than that of ceCT (55 %).

Although clinical parameters and structural imaging cannot reliably predict the presence of residual metastatic neck disease, post-treatment FDG-PET with high NPV may be justified [76]. In one of the previously cited studies [54], planned neck dissection would have been considered in 51 patients because of the presence of residual enlarged LNs, but disease was in fact present in only 7 of them. PET/CT findings in the study by Ong et al. [54] could have reduced the number of planned neck dissections by 75 % (from 51 to 13) while missing disease in 2 % (2/84 heminecks). Other investigators have suggested that negative FDG-PET/CT results after chemoradiotherapy could reduce the number of planned neck dissections by more than 80 % [49].

The potential clinical utility of PET for early response assessment during chemoradiotherapy has not been studied systematically. Data for other malignancies suggest that a significant decline in FDG uptake between baseline and interim PET after a few cycles of chemo- or chemoradiotherapy might indicate a better prognosis and a high likelihood of achieving a complete response. Only a single small study has attempted to address this issue in HNSCC [83]. Using coincidence camera imaging, that study noted an early and significant decline in FDG uptake in 47 patients with locally advanced disease after one cycle of chemotherapy or 24 Gy of radiotherapy. When dichotomized by the median SUV, individuals with lower FDG uptake showed a better rate of locoregional control. However, a closer analysis of the study results revealed that similar prognostic information could also be derived from the baseline scan alone. Therefore, although interesting, the study remained largely inconclusive. In particular, it remains unclear at what interim time point during the course of therapy a PET scan should be performed and how interim PET findings might alter patient management (good local control rates with concurrent chemoradiotherapy, lack of an established alternative therapy). In general, focal and asymmetric FDG uptake with an intensity greater than that in surrounding

normal tissues (in particular, muscle) and blood vessels should be considered suggestive of residual disease. In contrast, diffuse (nonfocal) FDG uptake within the radiation field is usually an indicator of post-radiation inflammation. One of the initial trials that established concurrent chemoradiotherapy for locoregionally advanced HNSCC reported high-grade toxic effects in 82 % of patients, including grade 3 or 4 mucositis in 41 % and laryngeal toxicity in 14 % [84]. This report has obvious implications for imaging studies: laryngeal edema and treatment-induced infiltrative changes in perilaryngeal soft tissues are commonly observed on post-treatment CT, along with nonspecific contrast enhancement patterns. Likewise, increased laryngeal or oropharyngeal FDG uptake may be observed for prolonged periods after chemoradiotherapy. In most cases, this uptake will be of mild to moderate intensity and will be diffuse throughout the larynx or along the oropharyngeal walls.

There are also limited data on the role of PET in assessing the response to induction chemotherapy before subsequent concurrent chemoradiotherapy. This is a topic of growing interest to medical oncologists. It is conceivable that PET with either FDG or ^{18}F-3′-deoxy-3′ fluorothymidine (FLT) [85] after induction chemotherapy might help in this decision. For instance, if a patient shows little or no metabolic response after induction chemotherapy, this might indicate a low likelihood of cure with subsequent chemoradiotherapy; perhaps such patients would benefit from immediate salvage surgery after induction therapy or should be enrolled for more aggressive chemoradiotherapy protocols.

In summary, further analysis is needed to assess the potential clinical utility of interim PET for early response assessment during chemoradiotherapy or the response to induction chemotherapy before subsequent concurrent chemoradiotherapy.

Prognostic value

Tumor FDG uptake has been associated with various cellular characteristics such as cell viability and proliferative activity [86]. Thus, it is expected that analyses of metabolic parameters, which are independent of morphologic changes, would offer an important opportunity to predict individual tumor behavior. High FDG uptake by a tumor may be correlated with poor outcome, and thus such patients should receive more aggressive treatment combinations.

The prognostic value of FDG-PET for prediction of clinical outcomes in patients with HNSCC has not been assessed fully and is still controversial. Several authors have demonstrated that SUV_{max} in the primary HNSCC tumor [87–93] or neck LN metastasis [94–97] could be predictive of outcome. However, SUV_{max} shows the highest intensity of FDG uptake within the region of interest or volume of interest, and cannot represent total tumor uptake for the entire tumor mass. Recently, there has been increasing interest in the use of volumetric parameters of metabolism such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV and mean SUV can be measured by contouring margins defined by thresholds. Then, TLG can be calculated by multiplying MTV by mean SUV, which weights the volumetric burden and metabolic activity of tumors. Several authors have demonstrated that MTV [93, 98–102] and TLG [98–100, 102, 103] in a primary HNSCC could be predictive of outcome. Park et al. [104] reviewed 13 studies comprising 1180 HNSCC patients and confirmed the superiority of MTV and TLG relative to SUV_{max}: first, patients with a high MTV showed a 3.06-fold higher risk of adverse events or a 3.51-fold higher risk of death than patients with a low MTV; second, patients with a high TLG had a 3.10-fold higher risk of events or a 3.14-fold higher risk of death than patients with a low TLG; third, patients with a high SUV_{max} showed a 1.83-fold higher risk of adverse events or a 2.35-fold higher risk of death than patients with a low SUV_{max}.

In summary, FDG-PET/CT including SUV_{max}, MTV, and TLG may have prognostic value in HNSCC patients; however, more studies are needed to clarify this.

Human papilloma virus-positive oropharyngeal squamous cell carcinoma

HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) represents an emerging disease that differs from HPV-negative OPSCC in natural history and prognosis. HPV-positive OPSCCs are often associated with cystic LN metastases and have a higher rate of nodal involvement than do HPV-negative OPSCCs [105]. The better prognosis and outcome of HPV-positive patients would likely warrant less intense imaging follow-up during the 5-year follow-up period after treatment. However, manifestation of distant metastases later in the disease course and at unusual sites with a disseminating phenotype would require a longer follow-up with FDG-PET/CT [106].

Conclusion

FDG-PET/CT can allow combined metabolic and morphological assessment of tumors with significant improvements in diagnostic accuracy and considerable impact on patient management, initial staging, restaging, monitoring the response to therapy, and prognostication of HNSCC.

Further analysis is needed to evaluate the potential clinical utility of interim PET for early response assessment during chemoradiotherapy or the response to induction chemotherapy before subsequent concurrent chemoradiotherapy.

Compliance with ethical standards

Conflict of interest We have no financial support or relationship to declare that may pose a conflict of interest.

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