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Review article

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Comparison between anatomical cross-sectional imaging and ^{18}F-FDG PET/CT in the staging, restaging, treatment response, and long-term surveillance of squamous cell head and neck cancer: a systematic literature overview

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The outcome of head and neck squamous cell cancer depends primarily on its prompt diagnosis and treatment. Unfortunately, in many cases ominous prognostic factors such as lymph node metastases or osteomandibular extension are present at the time of diagnosis. We review the relative efficacy of contrast-enhanced computed tomography (ceCT), MRI, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/computed tomography (CT) in the early detection of head and neck squamous cell cancer, as well as its impact on treatment management and outcomes. Medline and Web of Knowledge databases, from 2000 to January 2013, were evaluated. Ninety-seven reports were selected, but only 11 studies comparing PET or PET/CT with CT and 11 comparing PET or PET/CT with MRI were found appropriate for analysis. ceCT and MRI continue to be the reference imaging modalities for the study of primary tumors, especially in the evaluation of the extension of disease and its relationship with nearby anatomical structures. There is increasing evidence that ^{18}F-FDG PET/ceCT can provide accurate anatomical details similar to ceCT alone, as well as accurate information on osteomandibular tumor invasion similar to MRI. The major advantage of PET/CT over other imaging methods is its ability to detect relatively small lymph node metastases located in difficult-to-interpret positions. PET/CT is also highly sensitive for the detection of distant metastases and in assessing the response to chemotherapy or chemoradiation treatment and in predicting outcome. ceCT and MRI are the gold standards for evaluating primary and osteomandibular tumoral infiltration. ^{18}F-FDG PET/CT plays a major role in the detection of lymph node and distant metastases, in assessing the response to neoadjuvant/adjuvant chemotherapy or chemoradiation therapy, and in predicting outcome. *Nucl Med Commun* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Squamous cell cancer (SCC) is the most common malignant tumor of the head and neck (HN) and the 11th most frequent cause of cancer-related death, particularly among heavy smokers and drinkers in the 50–60-year-old male population. Because of frequent late diagnosis, the prognosis of head and neck squamous cell cancer (HNSCC) is generally poor with an estimated recurrence rate of 30%. SCC can be treated surgically. Radiation and chemotherapy may be stand-alone or adjuvant treatments. The therapies of choice for small HNSCC (T1–T2, N0, M0) include surgery, external beam radiation therapy, and a combination of radiation and chemotherapy. Larger tumors (T3–T4, N +) are treated with a combination of surgery and radiochemotherapy [1]. Surgical treatment requires excision and complex reconstruction involving distant soft tissue and, if necessary, bony tissue transfer. Reconstructive surgery significantly distorts the anatomy and renders postoperative imaging challenging [1]. Chemotherapeutic treatments should reduce the risk for metastatic or recurrent disease. New therapeutic approaches include the use of immunotherapy and gene therapy.

Besides the size and location of the primary tumor, it is also crucial to evaluate the extension to locoregional lymph nodes. The presence of lymph node metastasis to the neck is a major indicator of reduced survival in HNSCC. Neck dissection in its various forms is the standard surgical treatment for clinical and subclinical metastatic lymph nodes. A clinically negative (cN0) neck

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is defined as the absence of palpable or radiographically enlarged lymph nodes [2]. Despite a cN0 neck, a patient could have subclinical or occult lymph node metastasis. Given the potential for occult malignant deposits, what is the best form of management in HNSCC patients? Patients with a cN0 neck could simply be observed or they could receive an elective neck dissection or be treated with elective neck radiation. Supporters of elective neck dissection suggest that the pathological presence of metastatic disease requires adjuvant therapy. In contrast, opponents of elective neck dissection cite the costs associated with performing a neck dissection in all N0 patients. HN surgeons believe that management decisions to electively treat a cN0 neck should be based on a risk–benefit analysis of the morbidity associated with treatment and on the incidence of occult metastases. The majority of surgeons use an occult metastatic potential of 20% or higher to determine the need for elective treatment of the cN0 neck [3]. Multiple studies have shown improved locoregional control of disease when surgery and radiation therapy are combined [4]. Jackel *et al.* [4] retrospectively recruited 118 patients with N1 HNSCC. They examined the recurrence rates in patients treated with surgery alone and in those treated with surgery and postoperative radiation. The 3-year recurrence rates were 11.2 and 2.9%, respectively. In another study, Kao *et al.* [5] evaluated 297 patients with positive nodal disease (N1–N3) treated with definitive surgery with or without radiation. They showed improved 5-year survival for all nodal groups when combined surgery and radiation therapy was compared with surgery alone. Therefore, for patients with resectable N2 or N3 disease, neck dissection followed by postoperative irradiation is indicated.

Approximately one-third of HNSCC patients have early-stage disease, whereas two-thirds of them present with advanced disease. HNSCC often metastasizes to regional lymph nodes rather than hematogenously. Local adjuvant treatments do not address distant metastases [6]. Few studies have reported the incidence of distant metastases at presentation in HNSCC patients. Dennington *et al.* [7] and Black *et al.* [8] found distant metastases at presentation in 7 and 12% of patients with advanced-stage disease, respectively. The most frequent sites of distant metastases are the lungs, bone, and liver. Obviously, their detection at the time of initial evaluation influences treatment choices.

Imaging and head and neck cancer

The effectiveness of surgical treatment depends on the complete excision of all tumor tissue, and therefore accurate preoperative tumor-node metastasis staging is essential. The initial diagnosis and staging of HNSCC is based on physical and endoscopic examination [9]. Contrast-enhanced computed tomography (ceCT), MRI, and sonography have been used for the localization of primary HN tumors and regional lymph node metastases, and for determining their relationship with adjoining anatomical structures [10]. Discrimination between reactive and enlargement lymph nodes and tumor-infiltrated nodes on the basis of morphological criteria may be problematic [11]. Conversely, for the evaluation of response to treatment, the presence of fibrosis or other therapeutic effects cannot be distinguished from residual or recurrent cancer tissue. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET imaging has become a well-established modality for both staging and therapeutic assessment of HN tumors [12–18].

International guidelines

European guidelines [19] for HNSCC recommend different imaging approaches for each phase of disease: (i) diagnosis should be assessed by physical examination, chest radiograph, HN endoscopy, and HN ceCT or MRI. MRI is the preferred staging procedure for most HN tumors with the exception of laryngeal and hypopharyngeal cancers. Chest computed tomography (CT) may be performed to determine the presence of pulmonary metastatic disease or second lung primaries. The role of ^{18}F-FDG PET in staging is not clearly defined. In general, PET has a lower specificity than sensitivity and may be more useful for metastatic staging than for neck node evaluation. (ii) Treatment planning depends on primary tumor location and extension; therefore, a correct initial staging is necessary. (iii) Local, regional, and metastatic recurrence should be accurately evaluated by imaging. (iv) Treatment response should be evaluated by clinical examination and HN ceCT or MRI. ^{18}F-FDG PET/CT may be used to evaluate the response to radiotherapy or concomitant chemoradiation therapy at the neck level. This may help to decide upon the usefulness of a neck node dissection. Follow-up should include physical examination and imaging. ^{18}F-FDG PET/CT may be useful in the presence of doubtful findings, particularly after combined chemoradiation treatment. The negative predictive value of ^{18}F-FDG PET/CT is superior to its positive predictive value.

According to National Comprehensive Cancer Network (NCCN) guidelines (version 1.2012), PET or PET/CT is recommended for stage III (T3, N0, M0, or T1–3N1M0) and stage IV (T1–T4, N0–N3, M0–M1) cancer because it may alter management by upstaging patients [20]. Moreover, after either radiation or chemoradiation therapy, post-treatment evaluation with imaging (i.e. ceCT and/or MRI with contrast, PET/CT) guides the use of neck dissection [21–24]. If PET/CT is used for follow-up, the first scan should be performed at $\sim$12 weeks after treatment to reduce the false-positive rate [22,25].

The goal of this systematic literature review is to compare the advantages and limitations of imaging techniques currently used in clinical practice, such as ceCT, MRI,

and ^{18}F-FDG PET or PET/CT, from diagnosis to follow-up in HNSCC patients.

Search strategy

A computer literature research for studies on human patients was performed to identify articles that compared the diagnostic performance of ^{18}F-FDG PET or PET/CT with other imaging modalities for head and neck cancer. The Medline and Web of Knowledge databases from 2000 to January 2013 were used with the following key words: 'head and neck' AND 'cancer' AND 'PET' OR 'PET/CT' AND 'MRI' OR 'CT' 'head and neck' AND 'cancer' OR 'head and neck cancer' AND 'FDG' OR 'FDG' AND 'PET' OR 'PET/CT' AND 'CT' OR 'MRI'. Without any limits, we found 158 and 133 articles, respectively, for Medline and Web of Knowledge. On using some limits, such as species (human), article type (original articles, comparative studies, multicenter study), and language (English), 65 and 71, respectively, reports were included. Therefore, 136 articles met the inclusion criteria, but 39 were duplicates. References of articles found in the literature search were also examined to find additional reports that met the inclusion criteria. Ninety-seven reports were selected, but only 11 studies comparing PET or PET/CT with CT and 11 studies comparing PET or PET/CT with MRI were found appropriate for analysis. Articles on nasopharyngeal cancer and PET were excluded, as these HN cancers are significantly different from other HN cancers on the basis of occurrence, causes, diagnostics, clinical behavior, and treatment. The following items were searched for in each of these series: number of patients, design of the study, reference standard, sensitivity, specificity, and other diagnostic data of ^{18}F-FDG PET or PET/CT and CT or MRI. Table 1 lists the identified studies comparing PET or PET/CT with ceCT and MRI in HNSCC.

PET and PET/CT versus CT

Table 2 summarizes the results from selected studies comparing ceCT with PET or PET/CT with ^{18}F-FDG in different settings of HNSCC.

Initial staging

Primary tumor assessment

Two studies [30,33] were identified comparing PET and CT in the evaluation of primary HNSCC. Kitigawa *et al.* [30] prospectively recruited 23 consecutive HNSCC patients who were evaluated before and after treatment with PET, MRI, and CT; 20 of them also underwent ^{67}Ga scintigraphy. All PET images showed a high ^{18}F-FDG uptake in the primary tumor. PET detected a small superficial tumor of the tongue, lower lip, or mandibular gingiva in five patients that were not detected by CT or MRI or ^{67}Ga scintigraphy. ^{18}F-FDG PET was more sensitive than CT in detecting primary HNSCC, with comparative sensitivities of 100 and 68.2%, respectively, primarily because the tumors expressed high metabolic activity [44,45]. On the basis that PET/CT has value in characterizing the primary lesion, Rodrigues *et al.* [33] tried to optimize the protocol for PET/CT for staging of primary HN cancer. They compared the performance of a dedicated HN PET/CT with that of ceCT, an optimized whole-body (WB) PET/CT scan, and ceCT in HNSCC patients without clinical evidence of metastasis. The authors retrospectively recruited 44 patients who had undergone primary tumor resection and unilateral or bilateral neck dissection. The gold standard for ascertaining the presence or absence of tumor was histopathology. The primary tumor was correctly identified by ceCT, WB PET/CT, and HN PET/ceCT in 71, 92, and 95% of cases, respectively. WB PET/CT did not identify three (8%) small primary tumors. The HN PET/ceCT protocol failed to identify the primary tumor in two patients (5%). HN PET/ceCT also misidentified a site of periodontal disease, whereas ceCT suggested a primary tumor site in two patients (5%) not confirmed by histopathology. Rodrigues *et al.* [33] showed no statistical difference between WB and HN PET/CT protocols, but both of them demonstrated significantly better performance compared with ceCT in identifying the primary site of the tumor. Histological analysis of the surgical specimen demonstrated peritumoral infiltration in 31 of 38 primary tumors (82%), which was correctly identified in 21 of 31 cases (68%) by both ceCT and WB PET/CT protocols and in 22 of 31 cases (71%) by the HN PET/ceCT protocol.

In SCC of the oral cavity close to the mandible, the exclusion of osteomandibular involvement is a major determinant both for a therapeutic approach and for prognosis [46]. Two groups of researchers studied this subset of patients. Gu *et al.* [38] retrospectively recruited 46 patients suspected of having a mandibular invasion who underwent ceCT and MRI before surgery. Imaging showed concordant findings in 37 patients (80.4%). The number of false-negative results was higher for ceCT than for PET/CT (seven vs. five, respectively), whereas only PET/CT showed a single false-positive result. The specificity for ceCT and PET/CT was 100 and 97.1%, respectively. From the combination of both imaging modalities, the diagnostic accuracy of PET/ceCT was found to be greater (91.3 vs. 84.8 and 87%, respectively, for ceCT and PET/CT alone). Moreover, Goerres *et al.* [31] evaluated and compared the performance of PET and CT. The authors suggested that the identification of bone involvement in HNSCC is reliably performed with thin-section helical ceCT, with accuracy similar to that of PET/CT (97 vs. 94%, respectively).

Cervical lymph node assessment

Five cervical lymph node assessment studies were included in our analysis. Yoon *et al.* [36] retrospectively studied 67 HNSCC patients to compare the diagnostic performance of four imaging tools [ceCT, PET/CT, MRI,

Table 1 Studies comparing PET or PET/CT with ceCT and MRI for HNSCC

N	References	Study design	Total patients	Aims of study	Timing PET
1	Braams *et al.* [26]	Prospective	12	To investigate the usefulness of ^{18}F-FDG PET in the identification of lymph node metastases of SCC of the oral cavity, compared with analysis of clinical, MRI and histopathological findings	Staging
2	Lauberbecher *et al.* [27]	Prospective	22	To evaluate the accurate preoperative assessment of tumour extent and lymph node involvement by PET and MRI	Staging
3	Adams *et al.* [28]	Prospective	60	To compare ^{18}F-FDG PET detection of regional lymph nodes metastasis vs. CT, MRI and histology	Staging
4	Stuckensen *et al.* [29]	Prospective	106	To assess the role of ^{18}F-FDG PET at initial staging in comparison with US, CT and MRI	Staging
5	Kitagawa *et al.* [30]	Prospective	23	To compare the diagnostic accuracy of ^{18}F-FDG PET and imaging modalities (MRI, CT and ^{67}G scintigraphy)	Staging
	Kitagawa *et al.* [30]	Prospective	23	To compare the diagnostic accuracy of ^{18}F-FDG PET and imaging modalities (MRI, CT and ^{67}G scintigraphy)	Response to treatment
6	Goerres *et al.* [31]	Prospective	31	To compare the accuracy of ceCT with PET/CT	Staging
7	Andrade *et al.* [32]	Retrospective	28	To assess the response to treatment of PET/CT vs. ceCT for detection of persistent disease	Response to treatment
8	Rodrigues *et al.* [33]	Retrospective	44	To compare WB PET/CT protocol with ceCT in preoperative staging of HNSCC	Staging
	Rodrigues *et al.* [33]	Retrospective	44	To compare HN PET/CT protocol with ceCT in preoperative staging of HNSCC	Staging
9	Ng *et al.* [34]	Prospective	160	To compare the diagnostic accuracies of PET/CT than ceCT for the detection of distant metastases	Staging
10	Seitz *et al.* [35]	Retrospective	66	The assess the impact of adding ^{18}F-FDG PET/CT to MRI for oral and nodal staging	Staging
11	Yoon *et al.* [36]	Retrospective	67	To compare the diagnostic performance of four imaging techniques (CT, MRI, US, and PET/CT) and their combined use for the detection of neck lymph node metastases in pts with SCC of HN	Staging
12	Ghanooni *et al.* [37]	Prospective	32	To compare diagnostic value of MRI and ^{18}F-FDG PET during the surveillance period (after 4 months)	After treatment
	Ghanooni *et al.* [37]	Prospective	32	To compare diagnostic value of MRI and ^{18}F-FDG PET during the surveillance period (after 12 months)	After treatment
13	Gu *et al.* [38]	Retrospective	46	To compare the diagnostic accuracy of CT/MRI/PET-CT vs. their combination	Staging
14	Chan *et al.* [39]	Prospective	116	To compare diagnostic value of 3T WB MRI and ^{18}F-FDG PET for the assessment of distant metastases in patients with OHSCC	Staging
15	Ng *et al.* [40]	Prospective	79	To evaluate the clinical difference between ^{18}F-FDG PET and MRI in detecting malignancy in treated OHSCC	Restaging
16	Haerle *et al.* [41]	Prospective	34	(1) To compare the accuracy of ceCT and PET/CT vs. ^{18}F-FDG PET vs. non-enhanced ^{18}F-FDG PET/CT vs. ^{18}F-FDG/ceCT (2) To assess the potential correlation between SUV_{max} and the grade of lymph node necrosis	Staging
17	Stoeckli *et al.* [42]	Prospective	76	To assess the best modality among CT, US, US-guided FNAC and PET/CT for cervical assessment in HNSCC	Staging
18	Fakhry *et al.* [43]	Retrospective	37	To evaluate the role of ^{18}F-FDG PET for detecting distant metastases in comparison with CT and US	Restaging

CeCT, contrast-enhanced computed tomography; CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; FNAC, fine-needle aspiration cytology; HN, head and neck; HNSCC, head and neck squamous cell cancer; OHSCC, oral head squamous cell carcinoma; PET, positron emission tomography; SCC, squamous cell cancer; US, ultrasonography; WB, whole-body.

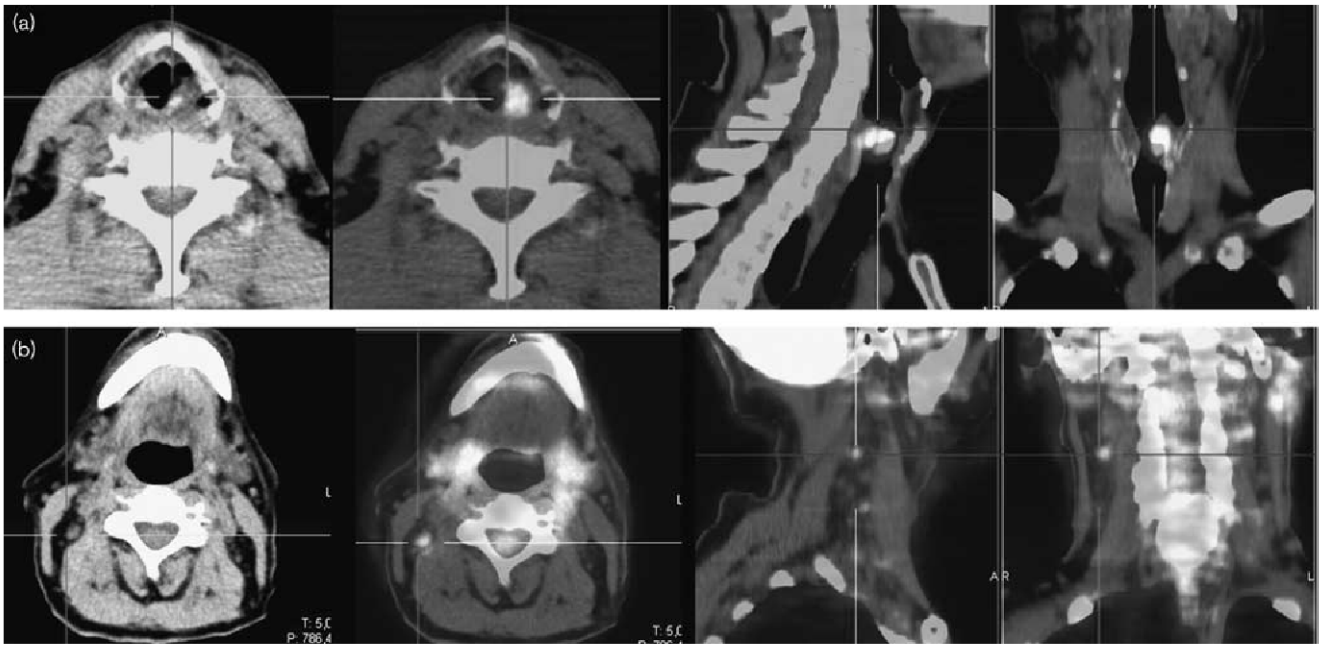
and ultrasonography (US)] for the detection of neck lymph node metastases. Lesion-based analysis demonstrated that the performances of ceCT and PET/CT were similar, with diagnostic accuracies of 95.3 and 95%, respectively. Second, Adams *et al.* [28] compared the performance of MRI, CT, and ^{18}F-FDG PET in lymph node staging; their results demonstrated specificities of 79, 85, and 94%, respectively. In particular, CT was not able to distinguish between malignant and inflamed tissues, and, predictably, the smallest lymph node metastasis detected by CT was 1 cm in diameter, whereas ^{18}F-FDG PET was able to localize smaller lymph node metastases (0.6 cm in diameter) (Fig. 1). Moreover, both CT and MRI correctly staged about 50% of patients when compared with histopathological findings, whereas ^{18}F-FDG PET revealed no malignant lymph node involvement in 23 of 29 patients (79%). To identify the diagnostic tool that could better assess necrotic lymph nodes, considering that human papillomavirus infection has been proposed to be an additional factor for the development of cystic–necrotic lymph nodes transformation in tonsillar SCC, Haerle *et al.* [41] compared the accuracy of ceCT, ^{18}F-FDG PET, ^{18}F-FDG PET/CT, and ^{18}F-FDG PET/ceCT. They recruited 34 patients with untreated tonsillar SCC and showed that, for the correct nodal classification and differentiation between N0 and N+, ceCT and ^{18}F-FDG PET/ceCT perform equally well and better than ^{18}F-FDG PET/CT or ^{18}F-FDG PET alone. Using ceCT as the diagnostic tool, Rodrigues *et al.* [33] studied the diagnostic accuracy of ceCT, WB PET/CT, and HN PET/ceCT in the detection of nodal metastases both on a per-level and per-patient basis. The HN PET/ceCT protocol showed a higher diagnostic accuracy (96%) compared with the others (81% for ceCT and 89% for WB PET/CT) for the detection of lymph node metastases. In particular, the main advantage of HN PET/ceCT when compared with WB PET/CT was in the detection of lymph nodes less than 15 mm in diameter. Stoeckli *et al.* [42] prospectively recruited 76 untreated HNSCC patients to compare the accuracy of CT, US, US-guided fine-needle aspiration cytology, and PET/CT with their histological neck dissection specimen. Among all the diagnostic tools listed above, only US-guided fine-needle aspiration cytology

Table 2 Comparison of diagnostic accuracies between PET or PET/CT and ceCT for staging, restaging, or for the evaluation of treatment response

		ceCT									PET or PET/CT								
Timing of imaging (reference)	Analysis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	TP	FN	FP	TN
Staging[a] [28]	Lesion based	90[b]	94[b]	58[b]	99[b]	93[b]	105	12	75	1092	82	85	35	98	85	96	21	175	992
Response to treatment [32]	Patient based	77	93.3	90.9	82.4	85.7	10	3	1	14	92.3	46.7	60	87.5	67.9	8	8	7	12
Staging[a] [31]	Patient based	100	91	86	100	94	12	0	2	20	92	100	100	96	97	11	1	0	22
Staging[a] [41]	Patient based	70.7	50	85.3	29.4	66.7	–	–	–	–	85.3	45.5	82.9	50	75.6	–	–	–	–
Staging[a] [42]	Patient based	86.4	76.9	95	52.6	84.8	–	–	–	–	86.9	53.8	89.8	46.7	81.1	–	–	–	–
Staging[a] [36]	Lesion based	81.1	98.2	90.9	95.8	95	60	14	6	322	77	99	97	95	95	57	17	2	326
Staging[c] [38]	Patient based	58	97	88	87	87	7	1	1	33	42	100	100	83	85	5	7	0	34
Staging[d] [30]	Patient based	100*	100*	100*	100*	100*	23	0	0	0	68	0	94	0	65	15	7	1	0
Response to treatment [30]	Patient based	100[b]	89[b]	67[b]	100[b]	91[b]	4	0	2	17	75	59	30	91	62	3	1	7	10
Staging[d] [33]	Patient based	92	100	10	67	93	–	–	–	–	71	67	93	27	70	–	–	–	–
Staging[d] [33]	Patient based	95	83	97	71	93	–	–	–	–	71	67	93	27	70	–	–	–	–
Restaging [43]	Patient based	92[b]	87[b]	74[b]	97[b]	71[b]	11	1	4	1	100	94	86	100	88	12	0	2	3
Staging[e] [34]	Patient-based	76.9[b]	94[b]	71.4[b]	95.5[b]	91.3[b]	20	6	8	126	50	97.8	81.3	91	90	13	13	3	131

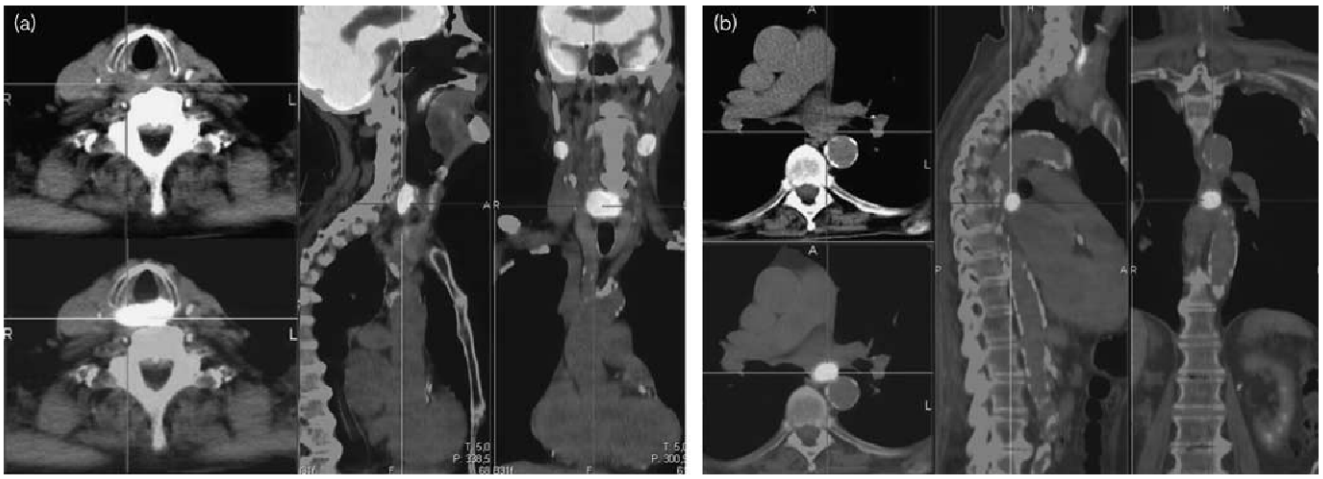
ceCT, contrast-enhanced computed tomography; CT, computed tomography; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.
[a]Lymph node metastasis.
[b]PET.
[c]Osteomandibular invasion.
[d]Primary tumor.
[e]Distant metastasis and secondary cancer.

Fig. 1



A 61-year-old woman presenting for initial staging for laryngeal cancer. PET/CT was able to identify the primary cancer ($SUV_{max}=5.6$) (a) and a normal-sized metastatic level 5 lymph node ($SUV_{max}=4.8$) (b) that was inconspicuous on CT.

Fig. 2



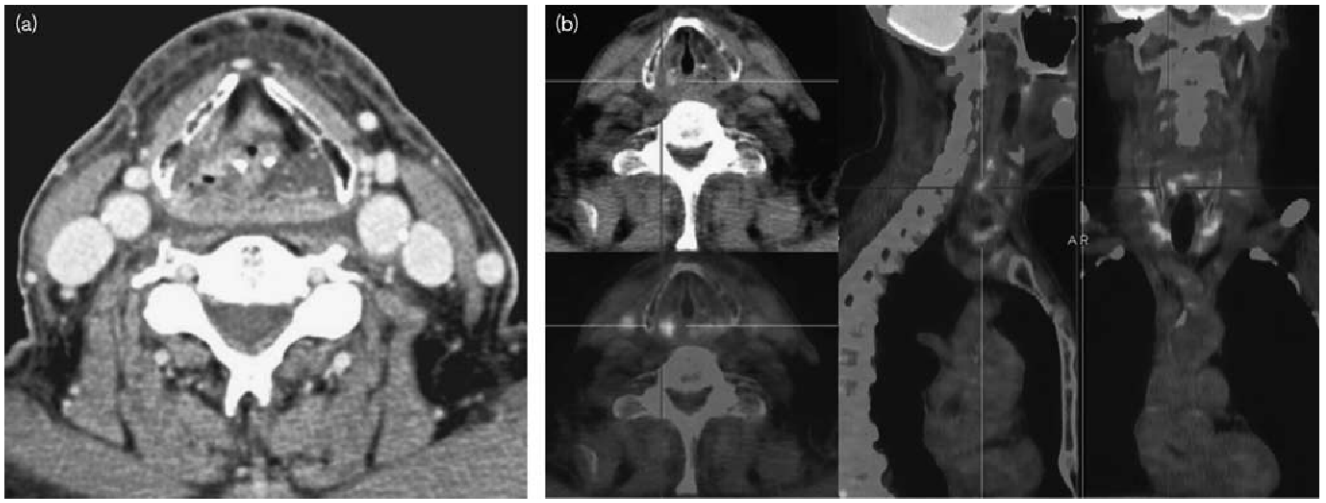
A 56-year-old man presenting for initial staging for laryngeal cancer. Prominent FDG uptake is noted in the posterior laryngeal tumor (a). An ^{18}F-FDG-avid subcarinal metastasis (b) is less apparent on CT. The patient has stage IV laryngeal cancer.

correlated minimally better with the histological staging in the differentiation of N0 from N+ (86.3%), showing a performance level similar to that of PET/CT (84.8%) and CT (81.1%), these latter imaging modalities being considered more expensive.

Involvement of distant organs

Only two of the retrieved papers analyzed distant metastasis. Ng *et al.* [34] compared the diagnostic yields of ^{18}F-FDG PET and extended-field ceCT for evaluating their ability to detect distant metastasis or synchronous second tumor in HNSCC patients. They prospectively recruited 160 untreated HNSCC patients (oropharynx or hypopharynx) with negative chest radiography, liver sonography, and bone scintigraphy for distant metastasis or synchronous second tumor. The accuracy of ^{18}F-FDG PET was found to be similar to that of ceCT (91.3 and 90.0%, respectively), and visual correlation between metabolic and anatomic images

Fig. 3



A 75-year-old male with recurrent laryngeal cancer after chemotherapy and radiotherapy. Postradiotherapy assessment ceCT (a) was interpreted as negative. The ^{18}F-FDG PET/CT scan (b) was positive for recurrent right posterior laryngeal disease.

increased the accuracy to 95.6%. Moreover, Rodrigues *et al.* [33] showed that out of 44 patients, all clinically staged as M0 before PET/CT, only WB PET/CT was able to identify the involvement of mediastinal lymph nodes in one patient (Fig. 2), which was not apparent on ceCT.

Assessment of response to treatment

Two studies reported a comparison between ^{18}F-FDG PET and ceCT in the assessment of response to treatment in HNSCC patients. In particular, Kitagawa *et al.* [30] evaluated 23 patients who underwent ^{18}F-FDG PET/CT, ceCT, and MRI before and after chemoradiotherapy. Patients underwent ^{18}F-FDG PET/CT later than 4 weeks after combined treatment, whereas ceCT was performed within 2 weeks. Post-treatment images for primary lesions were correlated with histological results. ^{18}F-FDG PET/CT identified all patients with residual disease, demonstrating sensitivity and specificity higher than those of ceCT (100 and 89% vs. 75 and 59%, respectively) (Fig. 3). Similarly, Andrade *et al.* [32] compared the performance of ^{18}F-FDG PET/CT with that of ceCT for the detection of persistent disease after chemoradiotherapy. ^{18}F-FDG PET/CT was performed at 4–8 weeks and again later than 8 weeks after treatment, thus testing two different time intervals and identifying the best timing. The authors found that at 4–8 weeks the accuracy of PET/CT and CT was similar; conversely, after 8 weeks, the accuracy of PET/CT was higher (100%) than that of ceCT (54.5%).

Follow-up and restaging

The performance of CT and ^{18}F-FDG PET relative to follow-up and/or restaging was evaluated by Fakhry *et al.* [43]. The authors enrolled 37 candidates for salvage surgery for locoregional recurrences of HNSCC who underwent ^{18}F-FDG PET/CT for metastasis research. ceCT revealed no false-negative results, whereas PET/CT missed a subcentimeter lung metastasis. ceCT had only one false-positive result in the lung and mediastinum each, compared with PET/CT (false-positive rate 11%). The authors concluded that PET/CT can sometimes be useful for evaluating primary HN tumor and lymph node involvement before salvage surgery. PET/CT can be helpful as second-line examination in addition to standard workup.

MRI versus PET or PET/CT

Table 3 summarizes the results of comparison of MRI and PET or PET/CT with ^{18}F-FDG in different settings of HNSCC.

Staging

Nine studies focused on staging assessment (two on primary tumor, five on lymph node metastases, one on osteomandibular invasion, and one on distant metastases), reporting a sensitivity ranging from 58.3 to 96.7% for MRI and from 70 to 100% for PET/CT and PET. Most of the studies were performed on the basis of a patient-based analysis. Kitagawa *et al.* [30] compared the accuracies of ^{18}F-FDG PET with those of MRI and ^{67}Ga scintigraphy for primary lesion detection, reporting higher sensitivity (100%) for PET than for the other imaging modalities (78.3, 68.2, and 40%, for MRI, CT, and ^{67}Ga scintigraphy, respectively). In the study by Seitz *et al.* [35], MRI had a higher sensitivity and specificity compared with PET/CT in detecting the primary tumor (100 vs. 80% and 96.72 vs. 60%, respectively), in particular for T1 tumors.

Laubenbacher *et al.* [27] compared MRI and PET for the detection of primary tumor and metastatic lymph nodes.

The authors reported that both MRI and PET clearly demonstrated the tumors, although they correctly staged only seven patients and overstaged about half of the patients. On the basis of individual lymph nodes, PET correctly identified 75 of 83 histologically proven malignant lymph nodes, whereas 19 of 438 were falsely positive as a result of inflammatory reactions. Conversely, MRI had a sensitivity of 78.3%, but 28.8% of enlarged lymph nodes identified were falsely positive, therefore demonstrating a low specificity. Similarly, Stuckensen *et al.* [29] compared the lesion-based diagnostic accuracies of MRI, ^{18}F-FDG PET, CT, and US for the detection of lymph node metastasis, reporting a sensitivity of 70 and 64%, respectively, for PET and MRI and a lower specificity for MRI than for PET (69 vs. 82%, respectively). On a lesion-based analysis, Braams *et al.* [26] reported a very high sensitivity for PET for lymph node detection (91%) as compared with a low MRI sensitivity (36%), but MRI had the highest specificity (94%). This latter finding was correlated with a smaller number of reactive lymph nodes falsely identified by MRI compared with PET (2 vs. 16, respectively). In contrast, Yoon *et al.* [36] reported a similar sensitivity, specificity, and accuracy for PET/CT and MRI in the detection of lymph node metastases (81.1 vs. 77%, 98.2 vs. 99.4%, and 95 vs. 95.3%, respectively; $P > 0.05$). Finally, Adams *et al.* [28] reported the highest accuracy for lymph node metastases for PET (93%).

Gu *et al.* [38] compared the diagnostic accuracies of CT, MRI, and PET/CT for the evaluation of mandibular invasion in patients with SCC of the oral cavity. PET/CT and MRI demonstrated the same performance in this setting, and in particular their combination was characterized by the highest accuracy (93.5%). In general, MRI is superior to CT for detecting tumor invasion into the medullary cavity of the mandible [47,48]. On T1-weighted images, medullary invasion is readily detected by the presence of a hypointense zone instead of the usual fatty T1 hyperintensity. MRI has an advantage over CT related to dental artifacts, but motion artifacts produced by tongue movements and swallowing can cause poor image quality. It has been reported that false-positive results can be caused by periodontal inflammatory conditions, osteoradionecrosis, partial volume effects, dental extraction defects, and chemical shift artifacts induced by bone marrow fat [47–49]. On analyzing the singular accuracy for PET/CT, MRI, and CT, we found that low sensitivities may be related to minimal invasion into the cortical bone. Therefore, the results from this study concluded that the combined use of the supplementary modalities had higher sensitivity compared with each imaging modality alone (83.3 vs. 41.7–58.3%) without reduction in specificity (100 vs. 97.1–100%). In accordance with the results of Chan *et al.* [39], PET/CT was more accurate than WB MRI for the detection of bone, liver, aerodigestive tract, and distant lymph node metastases. In contrast, contrast-enhanced MRI has a higher sensitivity than ^{18}F-FDG PET/CT for detecting brain metastasis.

Restaging

Compared with ^{18}F-FDG PET, anatomical imaging modalities such as CT and MRI are inadequate for the consistent discrimination between residual/recurrent tumor and post-treatment changes. Ng *et al.* [40] compared the ability of PET/CT with that of WB MRI for the detection of residual/persistent tumor or second tumor in patients with already-treated HNSCC. The authors retrospectively studied 79 patients with HNSCC treated with definitive concurrent chemotherapy and at high risk for residual disease or with suspected recurrence. Twenty-nine patients were found to have malignancies: 19 had residual/recurrent tumors, six had secondary primary tumor, and four had both. The diagnostic yields of PET/CT and WB MRI for detecting malignancies were 26.6 and 20.3%, respectively. For detecting local recurrence of disease, PET/CT was slightly superior to MRI, with a higher sensitivity (75 vs. 56.3%, $P = 0.25$) and a higher specificity (98.4 vs. 96.8%, $P = 0.5$), although not significantly so. Moreover, for the detection of regional lymph node recurrences, PET/CT had a similar sensitivity but a slightly lower specificity compared with MRI (69.2 vs. 61.5, $P = 0.99$; 95.5 vs. 98.5%, $P = 0.50$; respectively). Finally, the patient-based sensitivities of PET/CT and WB MRI for the detection of distant malignant disease were similar (69.2 vs. 76.9%, respectively). In the study by Seitz *et al.* [35] MRI and PET/CT proved to have high sensitivity (100% sensitivity) and specificity (98 and 95%, respectively) in patients with suspected recurrent tumor.

Response to treatment and follow-up

Ghanooni *et al.* [37] evaluated the performance of PET/CT against that of MRI at 4 and 12 months after radiotherapy by means of visual analysis and from a semiquantitative point of view. For the visual analysis, the authors used a five-point scoring system (0 = no lesion; 1 = benign; 2 = lesion in regression; 3 = lesion stable or in progression; and 4 = not interpretable). Moreover, on the basis of an receiver opetating curve analysis, a cutoff value of SUV_{max} set at 5.8 was used for separating malignant from benign lesions with sensitivity and specificity of 85 and 100%, respectively. Comparison of the diagnostic performances of PET/CT and MRI after 4 and 12 months by means of visual analysis revealed a higher performance for PET/CT (sensitivity, 92 vs. 70% and 100 vs. 75%, respectively). Furthermore, authors found that the use of the SUV_{max} cutoff of 5.8 led to a smaller number of false-positive results compared with the visual assessment, particularly after 4 months from treatment (increase in specificity from 81 to 87%). According to Kitagawa *et al.* [30], the sensitivity of PET/CT was almost identical to that of MRI or CT for

Table 3 Comparison of diagnostic accuracies between PET or PET/CT and MRI in staging, restaging, or for the evaluation of treatment response

		PET or PET/CT									MRI								
Timing (reference)	Analysis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	TP	FN	FP	TN
Staging[a] [39]	Patient based	83.3	95.3	78.9	96.4	93.2	15	3	5	81	66.7	96.5	80	93.2	91.3	12	6	3	82
4 months from therapy [37]	Lesion based	92	81	55	98	83	11	1	9	38	70	74	43	90	88	11	1	6	41
12 months from therapy [37]	Lesion based	100	86	27	100	86.7	3	0	8	49	75	85	25	98		3	1	9	50
Staging[b] [38]	Patient based	58.3	97.1	87.5	86.8	87	7	33	1	5	58.3	97.1	87.5	86.8	87	7	33	1	5
Restaging [40]	Patient based	72.4	94	86.1	87.5	85.5	21	8	3	47	55.2	90	77.2	76.2	77.6	16	13	5	45
Staging[c] [35]	Patient based	96.7	60	96.7	60	–	–	–	–	–	100	80	98.4	100	–	–	–	–	–
Staging[d] [36]	Lesion based	81.1	98.2	90.9	95.8	95	60	14	6	322	77	99.4	96.7	95	95.3	57	17	2	326
Staging[d] [28]	Lesion based	90[e]	94[e]	58[e]	99[e]	93[e]	105	12	75	1092	80	79	27	98	79	94	23	250	917
Staging[d] [26]	Patient based	91[e]	88[e]	48[e]	99[e]	52[e]	–	–	–	–	36	94	44	92	55	–	–	–	–
Staging[d] [29]		70[e]	82[e]	81[e]	71[e]	75[e]	–	–	–	–	64	69	71	62	66	–	–	–	–
Staging[d] [27]	Patient based	90[e]	96[e]	80[e]	98[e]	95[e]	75	8	19	419	78	71	34	94	72	65	18	126	312
Staging[c] [30]		100[e]	100[e]	100[e]	100[e]	100[e]	23	0	0	0	78	–	100	0	78	18	5	0	0
Response to treatment [30]	Lesion based	100[e]	89[e]	67[e]	100[e]	91[e]	4	0	2	17	100	41	23	100	50	3	0	10	7

CT, computed tomography; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.
[a]Distant metastasis and second cancer.
[b]Osteomandibular invasion.
[c]Primary tumor.
[d]Lymph node metastasis.
[e]PET.

residual tumor (100 vs. 75 vs. 100%, respectively), but it was more accurate in identifying nonviable tumor cells (specificity of post-treatment ^{18}F-FDG PET vs. CT and MRI: 89.5 vs. 58.8% and 41.2%, respectively).

Discussion

The most important times for defining the tumor/nodal/metastasis staging of HNSCC are at initial diagnosis, during evaluation of response to neoadjuvant or adjuvant treatment, while restaging after radical surgery, and finally during long-term surveillance. At each of these critical time points, it is important to choose the diagnostic tool that provides the best evaluation for patients with HNSCC.

CT and MRI remain the methods of choice for the evaluation of primary tumor in patients with HN cancer because of their better anatomic resolution, although Rodrigues *et al.* [33] demonstrated that optimizing all imaging protocols – namely, performing HN PET/ceCT after 150 min from tracer injection and using 12-min bed positions – can increase the detection of primary cancer, reaching an accuracy of 93%. Moreover, Kitagawa *et al.* [30] and Seitz *et al.* [35] found a sensitivity of 96.7 and 100%, respectively, for the primary tumor for PET/CT and PET alone, demonstrating the potential of testing tumor aggressiveness by functional imaging. Similarly, on a per-level basis, the diagnostic accuracy for the detection of lymph node metastases was 96% by a combined protocol (PET and ceCT) [33]. However, it is often difficult to differentiate metastatic from nonmetastatic reactive nodes with CT and MRI, because the diagnosis of metastatic nodes is based on measurement of nodal size. PET has limitation in spatial resolution, and the presence of nodal necrosis can be associated with low glycolytic activity, but the association of anatomical and functional imaging is helpful. Both CT and PET or PET/CT demonstrated some limitations in the detection of osteomedullary invasion of the mandible and jawbone, whereas MRI had well-defined advantages; however, as Goerres *et al.* [31] demonstrated, cortical invasion is better determined by ceCT. Acquisition of thinner slices may enhance the sensitivity for detecting mandibular invasion for PET/CT. PET/ceCT is currently the best answer for the question: what is the most accurate tool for the staging of HNSCC?

The limitations of cross-sectional imaging are more evident after surgery and chemoradiotherapy. Therapy is less likely to alter the performance of PET/CT for the differentiation of residual disease from fibrotic tissue, thus allowing the early introduction of salvage treatment. The diagnostic performance of functional imaging depends on the time interval between last therapy and imaging scan, with higher accuracies after 4–8 weeks [32] and 4 months [37].

In some cases PET/CT is better than other cross-sectional imaging modalities, whereas in other cases it seems inferior to US. These findings can be due to (i) small numbers of patients studied, (ii) different sites of HN tumors, (iii) different acquisition protocols, (iv) equipment differences, and (v) inconsistent interpretation criteria. Although much debate has been generated about the nonuniformity of ^{18}F-FDG PET/CT protocols, it should be noted that the same issue is inherent in MRI and CT as well. On the basis of the present literature search, the majority of studies were performed using MRI at 1.5 T, and in many cases the criteria

Table 4 Pros and cons of imaging modalities for head and neck squamous cell cancer

	PET or PET/CT		MRI		CT	
	Pros	Cons	Pros	Cons	Pros	Cons
Staging	(1) Can locate primary tumor, particularly with enhanced HN protocol [33] (2) Can evaluate HPV correlated-necrotic lymph nodes particularly with ceCT [41] (3) Localizes smaller lymph node metastases [28] (4) Detects distant metastases and synchronous cancers [39,42]	(1) Low osteomandibular lesion specificity (2) Limited utility in T1 tumors [35]	(1) Can detect T1 tumors [35] (2) Can evaluate tumor invasion into medullary cavity of the mandible [38] (3) Sensitive for brain metastasis [39]	(1) Metastases in normal-sized lymph node can be missed [27]	(1) High accuracy for the identification of osteomandibular invasion [31]	(1) Low accuracy for detection of primary tumor if performing with a nonspecific protocol (2) Reactive nodes and not enlarged lymph node metastases can be missed [33,41]
Restaging	Sensitive for residual disease [40]	–	High accuracy similar to PET/CT	–	–	–
Response to treatment	Useful for the identification of residual tumor [30,32,35]	–	–	Difficult to different between necrosis and residual cancer	–	No clear differentiation between necrosis and residual cancer
Follow-up	High accuracy to assess for recurrence after 12 months [37]	–	–	–	May identify lymph node recurrence before salvage surgical treatment [43]	–

ceCT, contrast-enhanced computed tomography; CT, computed tomography; HN, head and neck; HPV, human papillomavirus.

for lymph node malignancy ranged between 5 and 15 mm in diameter. Similarly, variable PET or PET/CT criteria of abnormality were applied. Moreover, CT images were acquired in a few cases with a dedicated protocol and with different pixel sizes/slice thicknesses (1.82–5 mm). Differences between manufacturers and acquisition protocols may contribute to variable accuracies and difficulties in comparing different studies. The main advantage, according to some authors [50–52], is that MRI avoids radiation exposure and may be less expensive than PET/CT in some countries. Of note, although ^{18}F-FDG PET/CT involves radiation, its total effective dose using a low-dose CT protocol is about 8–11 mSv, which is lower than that of a WB diagnostic ceCT scan, which can be as high as 14–18 mSv. Table 4 compares the pros and cons of imaging modalities for HNSCC.

New tracers and nuclear imaging prospective

Several fluorinated tracers for PET imaging can be used in HNSCC. The PET tracer 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) is proposed for treatment evaluation after radiotherapy and chemotherapy, but it does not seem to solve the problem of specificity raised with ^{18}F-FDG, in particular for the differentiation of metastatic and inflammatory lymph nodes in HNSCC patients [53,54]. ^{18}F-Fluoromisonidazole (^{18}F-MISO), 1-α-D-(5-deoxy-5-[^{18}F]fluoroarabinofurabinosyl)-2-nitroimidazole (^{18}F-FAZA), and ^{18}F-FDG have been used for testing the hypoxia status [55,56] in the post-treatment phase, such as after neoadjuvant chemoradiation [57]. In contrast, because of its low sensitivity, ^{18}F-fluoroethylthyrosine (^{18}F-FET) PET/CT cannot be a substitute for ^{18}F-FDG [58].

Finally, in a recent report by Platzek *et al.* [59], PET/MRI showed potential for improving the diagnostic imaging in patients in whom the soft-tissue contrast provided by ceCT was deemed insufficient – for example, in HN tumors – thus combining reduction in radiation exposure and improvement in diagnostic performance.

Conclusion

Currently available technologies and algorithms should be optimized to achieve improved diagnostic performance. Moreover, for the best evaluation of HNSCC patients from diagnosis to long-term follow-up, physicians should have knowledge about the benefits of diagnostic imaging in clinical practice, both in terms of cost-saving and cost-effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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