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Guidelines

Evidence-based Guideline Recommendations on the Use of Positron Emission Tomography Imaging in Head and Neck Cancer

J. Yoo *, S. Henderson †, C. Walker-Dilks †

* *Department of Otolaryngology-Head and Neck Surgery, Schulich School of Medicine & Dentistry, Western University, Victoria Hospital, London Health Sciences Centre, Ontario, Canada*

† *Program in Evidence-based Care, Cancer Care Ontario, McMaster University, Hamilton, Ontario, Canada*

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Abstract

Aims: To provide evidence-based practice guideline recommendations on the use of fluoro-2-deoxy-D-glucose positron emission tomography (PET) for diagnosis, staging and assessing treatment response, restaging or recurrence of head and neck cancer.

Materials and methods: A systematic review by Facey *et al.* (*Health Technology Assessment* 2007;11(44):iii–iv, xi–267) was used as the evidence base for recommendation development. As the review was limited to August 2005, the evidence base was updated to July 2011 using the same search strategies for MEDLINE and EMBASE used in the original review. The authors of the current systematic review drafted recommendations, which were reviewed, adapted and accepted by consensus by the Ontario provincial Head and Neck Disease Site Group and a special meeting of clinical experts.

Results: The results of the Facey *et al.* review for head and neck cancer included five other systematic reviews and 31 primary studies. The 2005 to 2011 update search included four additional systematic reviews and 53 primary studies. Recommendations were developed based on this evidence and accepted by consensus.

Conclusions: PET is recommended in the M and bilateral nodal staging of all patients with head and neck squamous cell carcinoma where conventional imaging is equivocal, or where treatment may be significantly modified. PET is recommended in all patients after conventional imaging and in addition to, or prior to, diagnostic panendoscopy where the primary site is unknown. PET is recommended for the staging and assessment of recurrence of patients with nasopharyngeal carcinoma if conventional imaging is equivocal. PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

Key words: Diagnosis; FDG-PET; head and neck cancer; neoadjuvant therapy; recurrence/restaging; staging

Introduction

Cancers of the larynx, pharynx, nasal cavity, oral cavity, paranasal sinuses, salivary glands and tongue are collectively known as head and neck cancers. These tumours affect physiological functions that are essential for communication and nutrition and specifically affect swallowing, speech and aesthetics. According to the Canadian Cancer Statistics, the estimated number of new cases in 2012 for cancers of the oral cavity and larynx were 4000 and 1050, respectively [1]. Most of these cancers affect males. Patients presenting with head and neck tumours often have significant medical co-morbidities. Specifically, tobacco use and alcohol consumption put individuals at risk for developing a head and neck malignancy.

Due to the promising results of the use of positron emission tomography (PET) for diagnosis, staging and detecting recurrence of head and neck cancers and other cancers, the Ontario PET Steering Committee made a special request to the Clinical Council of Cancer Care Ontario to co-lead the development of guidance regarding the clinical

Author for correspondence: S. Henderson, Cancer Care Ontario, Program in Evidence-based Care, McMaster University, Juravinski Hospital Site, G Wing, 2nd Floor, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada. Tel: +1-905-527-4322x42854; Fax: +1-905-526-6775.

E-mail address: ccopgi@mcmaster.ca (S. Henderson).

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use of PET imaging. The Program in Evidence-Based Care (PEBC), worked with the PEBC Disease Site Groups (DSGs) to synthesise the clinical research and draft recommendations for 10 disease sites (brain, cervical, colorectal, oesophageal, head and neck, melanoma, ovarian, pancreatic, small cell lung cancer and testicular).

Target Population

The target population for this review and clinical practice guideline is patients with head and neck cancer. Its purpose is to find answers to the following research questions:

- What benefit to clinical management does PET or positron emission tomography/computed tomography (PET/CT) contribute to:
  - The diagnosis or staging of head and neck cancer?
  - The assessment of treatment response for head and neck cancer?
  - The assessment of recurrence of head and neck cancer when recurrence is suspected but not proven?
  - The restaging at the time of the documented recurrence for head and neck cancer?

As these questions were identified to guide the development of guidelines across all cancers, they may not be equally relevant in the consideration of head and neck cancer. The objective of these questions is to provide evidence-based recommendations on the use of fluoro-2-deoxy-D-glucose (FDG) PET for diagnosis, staging, assessing treatment response and restaging or recurrence of head and neck cancer. These recommendations will be useful in informing clinical decision-making regarding the appropriate role of PET imaging and in guiding priorities for future PET imaging research.

Materials and Methods

This practice guideline was developed by the Head and Neck Cancer DSG of Cancer Care Ontario's PEBC using the methods of the Practice Guidelines Development Cycle [2]. The practice guideline is intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

In order to develop the recommendations, a systematic review was undertaken. This paper concentrates on the identification of evidence and the development of recommendations with respect to head and neck cancer.

Systematic Review

Literature Search

A scoping review undertaken by a PEBC methodologist to identify any existing systematic reviews on PET imaging in the cancers of interest yielded such a review. A systematic review by Facey *et al.* [3] evaluated the effectiveness of FDG-PET imaging in several selected cancers, including head and neck cancer. It included both systematic reviews and primary studies dating from 2000 to August 2005.

Because the Facey *et al.* review [3] sufficiently covered the evidence of interest to address the questions identified above, its results were used for the evidence base from 2000 to August 2005, and its search strategies were carried out in MEDLINE and EMBASE to update the literature to July 2011. The search strategies used are available upon request from the corresponding author of this review.

Study Selection Criteria

All systematic reviews and primary studies in the Facey *et al.* review [3] that addressed the questions of interest in this current review (diagnosis, staging, treatment response, recurrence and restaging) with respect to head and neck cancer were included. The inclusion criteria of the Facey *et al.* [3] review were used to select systematic reviews and primary studies identified in the update search. These criteria were as follows.

Other systematic reviews were included in the update if:

- They were dedicated to FDG-PET in head and neck cancers in humans;
- They contained evidence related to diagnostic accuracy, change in patient management, clinical outcomes or treatment response.

Primary studies were included in the update if:

- They were prospective clinical studies of FDG-PET in head and neck cancers;
- They were published after the end date of the search in the Facey *et al.* [3] review;
- They were published as a full article in a peer-reviewed journal;
- They reported evidence related to diagnostic accuracy, change in patient management or clinical outcomes;
- They included $\geq$12 patients with head and neck cancer;
- They used a suitable reference standard (pathological confirmation and clinical follow-up) when appropriate.

The citations and abstracts from the update searches were reviewed by two PEBC methodologists (CWD and SH) and marked as relevant or not according to the inclusion criteria. The methodologist and the clinical lead author reviewed the relevant citations and the full text of the articles to make the final decision on inclusion.

Synthesising the Evidence

The Facey *et al.* review [3] did not pool individual studies, and no meta-analysis of studies from the update search was

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planned due to an a priori expectation of heterogeneity among the studies. Facey *et al.* [3] extracted data into separate tables for systematic reviews and primary studies for each type of management decision. The same approach was used for data extraction for the evidence from the update search. Full text and data extractions of the studies were provided to the clinical lead author to aid in the formulation of the recommendations.

Consensus

Disease Site Group Consensus Process

The clinical lead author wrote summaries of the key evidence, draft recommendations and qualifying statements for the questions pertaining to diagnosis/staging, assessment of treatment response and recurrence/restaging. The ensuing documents were circulated to all members of the head and neck DSG and discussed during a teleconference. The recommendations that were generated during this process are referred to below as the draft DSG recommendations. The intent of these recommendations was to guide discussion at the consensus meeting.

Provincial Consensus Process

The provincial consensus meeting took place on 19 September 2008. It was conducted as follows:

- Consensus meeting participants sat at tables set up to discuss a particular disease site. Participating at the head and neck cancer table were the clinical lead author, other DSG members attending, and other invited health professionals. DSG members had reviewed the draft recommendations during the DSG consensus process; other invited health professionals had not.
- The recommendations and summary of key evidence drafted by the clinical lead author and refined and confirmed by the head and neck DSG were presented to the group at the head and neck cancer table.
- During small-group discussion at the head and neck table in the morning and discussion among all consensus meeting participants in the afternoon, the recommendations underwent further refinement and modification. The attendees then voted on the revised recommendations to indicate their extent of agreement on a scale from 1 to 9 (1 indicating strong agreement, 5 indicating no agreement or disagreement, and 9 indicating strong disagreement). The attendees' ratings were used to assess the level of consensus achieved by the meeting participants on each recommendation.

After the consensus meeting, the exact wording of the recommendations was edited for consistency with the recommendations resulting from the other disease site discussions. These modifications included using emphatic, unambiguous language (i.e. *PET is recommended…*) and removing the need to distinguish between PET and PET/CT. It was made clear at the consensus meeting that PET imaging alone is being phased out and PET/CT imaging is the current standard. Thus, the term PET is used to cover PET and PET/CT imaging. The recommendations that result from this consensus process are referred to below as the final recommendations. It should be noted that the recommendation report underwent a literature update in July 2011. The DSG consensus was not considered necessary for the 2011 literature update because the evidence was consistent with the existing evidence base and no significant changes were made to the existing final recommendations.

Results

Literature Search Results

The results from the health technology assessment (HTA) review by Facey *et al.* [3] for head and neck cancer included five systematic reviews and 31 primary studies. The 2005 to 2011 update included four systematic reviews and 53 primary studies. One study, [4], was identified by the lead author *post hoc* and was not identified via the systematic search. At the time of this recommendation report, this paper was an electronic publication only and was not indexed in the MEDLINE or EMBASE databases. As it met the inclusion criteria of the systematic literature review, it was included in the literature review. Data extracted from the primary studies from the updated search can be found in the Appendix. The key evidence identified from the Facey *et al.* [3] review and the primary studies and newly published systematic reviews from the update search are described below.

Key Evidence

Diagnosis/Staging

The HTA review by Facey *et al.* [3] included one systematic review of four primary studies and one additional primary study and showed that PET was sensitive and specific and useful where doubt exists with conventional imaging (i.e. where CT/magnetic resonance imaging give different results). One prospective study showed that PET/CT detected one more unknown primary tumour (12 of 21) than PET and both methods were more sensitive than CT.

Nineteen primary studies in the 2005–2008 update evaluated the utility of FDG-PET or PET/CT in the diagnosis and staging of head and neck cancers. Several studies [5–19] all indicated that PET was superior to conventional imaging for the diagnosis and staging of head and neck squamous cell carcinoma and provided additional information that heightened staging accuracy. Four studies

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[20–23] indicated that the addition of PET improved primary tumour delineation and nodal staging and subsequently changed the clinical management of several patients in each study.

With respect to the diagnosis of an occult primary tumour, the HTA review by Facey *et al.* [3] included two systematic reviews (each with eight primary studies) and two additional primary studies. The studies showed that PET can detect primary unknown tumours in patients with cervical lymph node metastases. PET detects 30% of primary tumours, including those missed by conventional imaging. The 2005 to 2011 update included two primary studies [24,25]. One study showed that PET is better than conventional imaging in detecting the site of the primary tumour [24]. The other primary study indicated that patients with cervical metastasis and an unknown primary site benefitted from PET/CT before panendoscopy [25].

Fifteen studies evaluated the utility of FDG-PET or PET/CT in the detection of metastatic disease. In each study, PET scanning was more accurate than conventional imaging in identifying metastatic disease.

Recurrence and Restaging

Two systematic reviews with 15 and 10 primary studies, and seven additional primary studies were included in the UK HTA [3]. The studies showed that PET sensitivity was about 80%, with specificity at least 90%, which was somewhat more accurate than CT/magnetic resonance imaging for restaging or recurrence. In the 2005 to 2011 update, 10 additional primary studies were included. Patients being evaluated for locoregional recurrence and considered for salvage should have PET in order to help tailor further therapy. Examples include larynx, skull base and nasopharynx, salivary gland and neck disease [24,26–30]. Abgral *et al.* [31] and Isles *et al.* [32] confirmed the effectiveness of PET in assessing for recurrence of head and neck squamous cell carcinomas in patients. Contrary to this, Inohara *et al.* [33] found PET to be of no additional value to determine the persistence of nodal disease after chemoradiotherapy. With respect to the role of PET in assessing the status of neck lymphadenopathy after radiation or chemoradiation, the evidence suggests that PET-directed management of the neck after therapy appropriately spares neck dissections in patients with PET-negative residual CT abnormalities [4].

Recommendations

Diagnosis/Staging

The draft DSG recommendations were:

- PET should be used in the diagnosis and staging of patients with advanced stage head and neck squamous cell carcinoma (stage III, IV).

There was general agreement among the large group with this recommendation, and some changes were suggested with respect to specific components. It was recommended that ‘diagnosis’ be omitted and ‘M’ and ‘bilateral nodal staging’ be added. It was also requested that doubt about conventional imaging be made clearer by using the term ‘equivocal’.

- PET should be used in all patients where the primary site is unknown.

Some additions were suggested to this recommendation in both the morning and afternoon discussions. ‘Unknown’ was clarified as meaning ‘after conventional imaging’, and it was agreed that this be included in the recommendation. It was also suggested that the recommendation not exclude what is usually carried out (i.e. panendoscopy). During the large group discussion, issues were raised about when PET would be done, for instance, after panendoscopy? The response was to do PET first because then a targeted panendoscopy can be carried out. Furthermore, the PET may result in a false-positive finding if conducted shortly after the biopsy.

- PET should be used for staging patients at moderate or high risk of distant metastatic disease (e.g. nasopharyngeal carcinoma, unexplained symptoms in early stage patients, stage III–IV).

There was debate during the small group discussion about the coverage of this recommendation. The suggestion was made that the most important aspect was nasopharyngeal carcinoma, and the decision was made to change the recommendation to emphasise nasopharyngeal carcinoma. There was general agreement among the large group with this recommendation, with the additional indication of the lack of clinical evidence of distant disease.

Recurrence/Restaging

- PET should be used for restaging patients being considered for major salvage treatment (surgery or other).

No major issues were raised during the discussion of this recommendation.

Final Recommendations

After recommendations were put to vote during the meeting, these final recommendations were suggested:

- PET is recommended in the M and bilateral nodal staging of all patients with head and neck squamous cell carcinoma where conventional imaging is

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equivocal, or where treatment may be significantly modified.
- PET is recommended in all patients after conventional imaging and before, or in addition to, diagnostic panendoscopy where the primary site is unknown.
- PET is recommended for the staging and assessment of recurrence in patients with nasopharyngeal carcinoma if conventional imaging is equivocal.
- PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

Discussion

There is a significant role for PET in the diagnosis and staging of head and neck cancers because of its value in detecting distant and regional disease in addition to conventional imaging practices. PET provides incremental information when determining the site of an occult primary tumour. There is strong evidence that PET imaging is valuable in detecting distant metastatic disease and is better than conventional imaging. The advantage of PET is overwhelming for patients at high risk for distant disease, which include locally advanced disease and nasopharyngeal carcinoma.

With respect to recurrence and tumour surveillance after treatment, the evidence suggests that sites of disease that are clinically accessible for assessment did not benefit from PET imaging. For disease sites that were either not clinically accessible or difficult to examine, PET imaging showed significant advantages over conventional evaluation. However, the data supporting the recommendation are compelling but sparse. Prospective data through the Ontario provincial registry and through additional clinical trials should be collected in order to provide additional information on this issue.

Review and Update

Practice guidelines developed by the PEBC are reviewed and updated as needed. Please visit the Cancer Care Ontario website (www.cancercare.on.ca) for the full report and subsequent updates.

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Appendix

Positron emission tomography (PET) for head and neck cancers: summary of the primary study evidence from 2005 to 2011

Reference	Objective	No. patients	PET	Reference test	Comparison test	Blinding	Results	Conclusions
Diagnosis/staging								
[5]	Evaluate the role of dual-phase FDG-PET in the staging of NPC.	95	Imaged from head to upper thigh	Biopsy if feasible. Follow-up if biopsy not feasible	None	Nuclear medicine physicians blinded to other imaging results and clinical data	Overall distant metastasis: FDG-PET: sensitivity = 100%, specificity = 90.1%, PPV = 63.6%, NPV = 100%, accuracy = 91.6% By metastatic site: Lung: sensitivity = 100%, specificity = 97.8%, accuracy = 97.9%, PPV = 60%, NPV = 100% Mediastinum: sensitivity = 100%, specificity = 96.6%, accuracy = 96.8%, PPV = 66.7%,	FDG-PET stages N and M disease of NPC more accurately and sensitively than does the conventional work-up. Patients with advanced node disease, particularly N3 disease, would benefit the most from FDG-PET.

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Appendix (*Continued*)

Reference	Objective	No. patients	PET	Reference test	Comparison test	Blinding	Results	Conclusions
							NPV = 100% Liver: sensitivity = 100%, specificity = 98.9%, accuracy = 98.9%, PPV = 75%, NPV = 100% Bone: sensitivity = 100%, specificity = 96.7%, accuracy = 96.8%, PPV = 57.1%, NPV = 100% Infraclavicular LN: sensitivity = 100%, specificity = 97.8%, accuracy = 97.9%, PPV = 50%, NPV = 100%	
[34]	Assess the impact of better image quality from OHR images on diagnostic yield in the staging of malignancies in the head and neck area.	28	FDG-PET	Histology	SWR versus OHR based images	Nuclear medicine physicians blinded to the final pathological diagnosis	Primary tumour: FDG-PET SWR images: sensitivity = 92% FDG-PET OHR images: sensitivity = 100% LN metastases: FDG-PET SWR images: sensitivity = 11%, specificity = 89%, PPV = 33%, NPV = 68% FDG-PET OHR images: sensitivity = 44%, specificity = 74%, PPV = 44%, NPV = 74%	Routine whole-body PET reconstruction parameters may prove inadequate for the head and neck area. Image reconstruction adapted to low photon attenuation in the head and neck area may improve image quality and the diagnostic value of FDG-PET, despite higher false positive rate attributable to the fact that visualisation of FDG accumulation in benign reactive LN is also enhanced.
[35]	Determine the usefulness of dual-phase FDG-PET in assessing primary NPC and its regional nodal metastases.	84	Images from the head and neck to upper thigh and then 3 h later from the head and neck to upper chest	Histology, clinical and imaging follow-up	MRI	Nuclear medicine physicians blinded to relevant clinical information, except for primary diagnosis	PET at 40 min and at 40 min + 3 h and MRI all had 100% sensitivity and 100% accuracy to detect the main tumour. Total lesions: PET at 40 min: sensitivity = 97.7%, specificity = 94.9%, accuracy = 96.7% PET at 40 min + 3 h: sensitivity = 98.9%, specificity = 95.5%, accuracy = 97.6% MRI: sensitivity = 93.5%, specificity = 91.1%,	FDG-PET is superior to MRI in identifying lower neck nodal metastasis of NPC. Additional 3 h FDG-PET contributes no further information in the detection of primary tumours or locoregional metastatic nodes in untreated patients with NPC. MRI and FDG-PET have an equal ability to identify primary tumours and retropharyngeal, upper

							accuracy = 92.6% Metastatic LN PET at 40 min: sensitivity = 96.6%, specificity = 94.9%, accuracy = 95.8% PET at 40 min + 3 h: sensitivity = 98.3%, specificity = 95.5%, accuracy = 97% MRI: sensitivity = 90.5%, specificity = 91.1%, accuracy = 90.8%	neck, and supraclavicular LN.
[26]	Assess the role of PET/CT compared with PET and CT in laryngeal carcinoma; also evaluate the impact of PET/CT results on patient care	42	Whole body PET with non-contrast enhanced CT	Histology	Contrast-enhanced CT and PET	Nuclear medicine physicians not blinded to patient data	Diagnosis by PET/CT examination: PET/CT: sensitivity = 92%, specificity = 96%, PPV = 96%, NPV = 92%, accuracy = 94% PET: sensitivity = 92%, specificity = 73%, PPV = 76%, NPV = 90%, accuracy = 86% CT: sensitivity = 88%, specificity = 8%, PPV = 52%, NPV = 40%, accuracy = 51% Diagnosis by lesion: PET/CT: sensitivity = 96%, specificity = 96%, PPV = 96%, NPV = 96%, accuracy = 96% PET: sensitivity = 96%, specificity = 61%, PPV = 71%, NPV = 95%, accuracy = 79% CT: sensitivity = 83%, specificity = 38%, PPV = 56%, NPV = 70%, accuracy = 61% Impact on patient care: PET/CT altered care for 25/42 patients Previously planned diagnostic procedures eliminated in 13 patients Planned therapy changed in 9 patients (8 patients down-staged, 1 patient up-staged).	The performance of PET/CT is better than standalone PET or CT in patients with cancer of the larynx. PET/CT had a major impact on management of 59% of patients. When a PET/CT study is negative, additional clinical and radiological follow-up can be postponed, at least temporarily. A positive PET/CT scan should encourage the head and neck surgeon to obtain a biopsy from the larynx and guide it to a metabolically active area.
[36]		48		Histology	CT and MRI	NR		

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Appendix (*Continued*)

Reference	Objective	No. patients	PET	Reference test	Comparison test	Blinding	Results	Conclusions
	Assess the impact of the addition of whole body PET scanning to their institution's standard investigation protocol for new patients with head and neck SCC (CT and MRI)		Multi-ring PET, scan from mid-thigh to crown of skull				Identify primary tumour: PET: 41/45 correctly identified CT: 40/45 correctly identified MRI: 41/45 correctly identified Cervical node dissection: PET: sensitivity = 70%, specificity = 75%, PPV = 82.3%, NPV = 60%, accuracy = 71.9% CT: sensitivity = 40%, specificity = 83.3%, PPV = 80%, NPV = 45.5%, accuracy = 56.2% MRI: sensitivity = 55%, specificity = 83.3%, PPV = 84.6%, NPV = 52.6%, accuracy = 65.6% Note: The sensitivity, PPV and accuracy for each test reported in the publication are not correct. The numbers above are based on calculated 2 × 2 tables, for which the numbers contained within were obtained from the text and tables of the publication.	PET is comparable with current conventional imaging modalities in detecting primary tumours. The high rate of false-positive results of PET in nodal metastasis highlights the higher sensitivity of PET in detecting nodal disease. PET only slightly improved the classification of N+ necks PET has no considerable role to play in N0 neck imaging protocols PET is less sensitive than both CT and MRI in detecting occult nodal disease. PET proved to be disappointingly similar to CT and MRI in an attempted identification of a small number of unknown primaries. PET was not reliable in detecting distant metastasis, as the rate of false-positive findings was high. However, interpretation of results is limited by the small number of study patients with distant metastases. These findings cast doubt on the merit of the routine addition of PET to the current investigative radiology protocols for presenting head and neck SCC patients. Maximum SUV is a reasonable index of malignancy in head and neck SCC primary

								and metastatic tumour. This study established a maximum SUV of 3.2 for nodal tumour.
[6]	Evaluate FDG-PET and skeletal scintigraphy for detecting bone metastasis in endemic NPC patients at initial staging	30 of 202 eligible patients were found to have bone metastasis	PET scans from vertex to upper thighs	Clinical and/or radiological follow-up (histology, skeletal scintigraphy, PET, MRI)	Whole-body skeletal scintigraphy	Nuclear physicians blinded to individual patient data	Detection of bone metastasis (patient based): PET: sensitivity = 70%, specificity = 98.8%, accuracy = 94.6% Skeletal scintigraphy: sensitivity = 36.7%, specificity = 97.7%, accuracy = 88.6%	FDG-PET is more sensitive and accurate than skeletal scintigraphy to detect bone metastasis, especially for lesions in the vertebral spine.
[37]	To develop and test a new gamma-sensitive probe with electronic collimation capable to detect 511 keV positron annihilation quanta	36	FDG-PET	Histology	Ultrasound, positron emission probe	NR	Detection of LN involvement: PET: sensitivity = 86%, specificity = 80%, PPV = 85%, NPV = 80%, accuracy = 83% Positron emission probe: sensitivity = 95%, specificity = 60%, PPV = 77%, NPV = 90%, accuracy = 81% Ultrasound: sensitivity = 95%, specificity = 40%, PPV = 69%, NPV = 86%, accuracy = 72%	PET has the highest specificity as compared with positron emission probe and ultrasound, but lower sensitivity. PET and positron emission probe had similar accuracies
[38]	Assess the clinical usefulness of FDG-PET, CT/MRI and their visual correlation in oral SCC patients with palpably negative neck	134	Images from the vertex to the upper thighs	Histology	CT/MRI	Nuclear medicine physicians blinded to CT/MRI findings	Patient basis: FDG-PET: sensitivity = 51.4%, specificity = 91.9%, accuracy = 81.3%, PPV = 69.2%, NPV = 84.3% CT/MRI: sensitivity = 31.4%, specificity = 91.9%, accuracy = 76.1%, PPV = 57.9%, NPV = 79.1% FDG-PET + CT/MRI: sensitivity = 57.1%, specificity = 96%, accuracy = 85.8%, PPV = 83.3%, NPV = 86.4% For results from different levels see study summary	FDG-PET is superior to CT/MRI for detecting palpably occult neck metastasis of oral SCC. Because FDG-PET could reduce the probability of occult neck metastasis to less than 15% in T1 to T3 tumours, it should be indicated for evaluation of these subpopulations.
[39]	Investigate the diagnostic potential of FET-PET in patients	21	FET-PET and FDG-PET	Histology	CT	Nuclear medicine physicians blinded to clinical information	FDG-PET: sensitivity = 93%, specificity = 79%,	FET may not replace FDG in the PET diagnostics of head and

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Appendix (*Continued*)

Reference	Objective	No. patients	PET	Reference test	Comparison test	Blinding	Results	Conclusions
	with head and neck SCC by comparing FET with FDG and conventional imaging using CT						accuracy = 83% FET-PET: sensitivity = 75%, specificity = 95%, accuracy = 86% CT: sensitivity = 64%, specificity = 86%, accuracy = 80%	neck cancer but may be a helpful additional tool in selected patients by allowing better differentiation of tumour tissue from inflammatory tissue. The sensitivity of FET PET in SCC is inferior to that of FDG-PET because of lower SUVs.
[40]	Determine the diagnostic accuracy of FDG-PET/CT in patients with head and neck SCC and N0 neck who were scheduled to undergo elective neck dissection as part of their routine surgical treatment.	31	Scans of the head and neck from the midskull to the thoracic inlet	Histology	None	Nuclear medicine physicians not blinded to clinical or CT/MRI data	Primary tumour: PET/CT: sensitivity = 87.1 Nodal levels: PET/CT: sensitivity = 67%, specificity = 95%, PPV = 50%, NPV = 98%, accuracy = 94% Neck sides: PET/CT: sensitivity = 67%, specificity = 85%, PPV = 60%, NPV = 88%, accuracy = 80%	FDG-PET can identify LN metastases in a segment of patients with oral cancer and N0 neck. A negative test can exclude metastatic deposits with high specificity. Despite reasonably high overall accuracy, the clinical application of PET/CT in the N0 neck may be limited by the combination of limited sensitivity for small metastatic deposits and a relatively high number of false-positive findings. The surgical management of the N0 neck should therefore not be based on PET/CT findings alone.
[41]	Evaluate whether further reduction of occult metastatic disease in oral carcinoma can be achieved by adding FDG-PET scanning to the preoperative work-up	30 (2 patients excluded), left with 28 patients	Scans of head and neck area	Surgery, histology	Ultrasound-guided fine needle aspiration	NR	LN metastases: FDG-PET: sensitivity = 33%, specificity = 76%, accuracy = 63%	In patients with cN0 SCC of the oral cavity, FDG-PET does not contribute to the preoperative work-up. FDG-PET does not replace SOHND as a staging procedure.
[12]	Determine the incremental value of PET/CT over conventional assessment for staging, post-treatment assessment of response	76	Images of neck, thorax, abdomen, and pelvis	Cytology, histology and/or clinical and radiological follow-up	Conventional assessment	Not blinded	Staging: 35 patients had staging PET/CT scan. PET/CT change TNM classification in 12 (34%) patients: 2 patients were down-staged and 10 were up-	PET/CT has a major incremental impact in the staging of patients with head and neck SCC.

	and ongoing follow-up in head and neck SCC						staged. Clinical impact: high 4/35, medium 10/35 Accuracy assessment not possible because most patients did not receive histopathological confirmation.	
[42]	Assess the role of PET/CT compared with PET and CT separately in head and neck cancer. The impact of PET/CT results on patient treatment also investigated.	90	Whole body PET and non-contrast enhanced CT	Histology ($n = 56$) and clinical and radiological follow-up ($n = 28$)	Contrast enhanced CT and/or MRI (CI) of head and neck	Images analysed independently of each other	Diagnosis for malignancy: PET/CT: sensitivity = 88.5%, specificity = 94.5%, PPV = 93.9%, NPV = 89.7%, accuracy = 91.6% PET: sensitivity = 88.5%, specificity = 70.9%, PPV = 74.2%, NPV = 86.7%, accuracy = 79.4% CI: sensitivity = 92.3%, specificity 18.2%, PPV = 51.6%, NPV = 71.4%, accuracy = 54.2% PET/CT altered further clinical management in 51 (56%) of patients. PET/CT eliminated the need for previously planned diagnostic procedures in 24 patients. PET/CT results led to changes in planned therapy in 21 patients. Staging: PET/CT: sensitivity = 100%, specificity = 100%, PPV = 100%, NPV = 100%, accuracy = 100% PET: sensitivity = 100%, specificity = 67%, PPV = 92%, NPV = 100%, accuracy = 93% CI: sensitivity = 100%, specificity = 33%, PPV = 85%, NPV = 100%, accuracy = 86%	PET/CT has high diagnostic performance in the assessment of head and neck cancer and induced a change in further clinical management in more than half of the study population. When a PET/CT study is negative, additional clinical and radiological follow-up can be postponed, at least temporarily. A positive study should encourage and guide the surgeon to obtain tissue diagnosis.

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Appendix (*Continued*)

Reference	Objective	No. patients	PET	Reference test	Comparison test	Blinding	Results	Conclusions
[43]	Evaluate the accuracy of evaluating cervical LN using PET/CT fusion images for SCC of the head and neck compared with using PET or contrast-enhanced CT.	47	Scans from the thigh to the head	Histology	Contrast-enhanced CT	Nuclear medicine physicians blinded to information about primary tumour site and clinical information	Detection of cervical LN disease PET/CT: sensitivity = 91.8%, specificity = 98.9%, PPV = 96.6%, NPV = 97.3%, accuracy = 97.1% PET: sensitivity = 80.3%, Specificity = 92.8%, PPV = 79%, NPV = 93.3%, accuracy = 89.7% Contrast-enhanced CT: sensitivity = 90.2%, specificity = 93.9%, PPV = 83.3%, NPV = 96.6%, accuracy = 93%	Combined PET/CT images are more accurate than the PET or contrast-enhanced CT images alone for conducting cervical node evaluation in patients with head and neck SCC.
[44]	Compared FDG-PET with CT/MRI for preoperative staging of patients with SCC of the oropharynx	32	Scans from head to mid-thigh	Histology	CT/MRI	Nuclear medicine physicians blinded to CT/MRI and pathology results	CT/MRI correctly identified tumours in 25/32 patients FDG-PET correctly identified tumours in 30/32 patients By presence of positive neck side: FDG-PET: sensitivity = 96.5%, specificity = 90%, PPV = 96.5%, NPV = 90%, accuracy = 94.9% CT/MRI: sensitivity = 75.9%, specificity = 90%, PPV = 95.6%, NPV = 56.2%, accuracy = 79.5% By presence of positive cervical levels FDG-PET: sensitivity = 95.7%, specificity = 86.2%, PPV = 73.8%, NPV = 98%, accuracy = 89% CT/MRI: sensitivity = 78.7%, specificity = 87.1%, PPV = 71.2%, NPV = 91%, accuracy = 84.7%	FDG-PET is superior to CT/MRI in detection of primary tumours and metastatic neck disease of oropharyngeal SCC. The improved preoperative staging of FDG-PET may help in planning treatment, but its accuracy is insufficient to replace pathological staging based on neck dissection.

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[7]	Evaluate the ability of combined FDG-PET/CT to detect second primary cancers and distant metastases in head and neck cancer	349 eligible patients (of 425 recruited)	PET and CT scans from skull base to upper thighs	Histology	Further conventional imaging work-ups	Nuclear medicine physicians not blinded to patient information	Detection of second primary of distant metastases Sensitivity = 97.5%, specificity = 92.6%, PPV = 62.9%, NPV = 99.7%, accuracy = 93.1%	Combined FDG-PET/CT is useful as a primary screening method for detecting second primary cancers and distant metastases in patients with primary HNC. FDG-PET/CT had high sensitivity, specificity and NPV but low PPV, suggesting that additional diagnostic methods are essential to rule out false positives and to avoid false upstaging to M1 for appropriate therapeutic planning.
[8]	To compare the diagnostic efficacies of FDG-PET, clinical work-up and their combination for primary staging in patients with NPC.	300	Images form vertex to upper thigh	Histology and clinical follow-up	Clinical work-up (including MRI, radiography, ultrasound, whole-body scintigraphy)	Nuclear medicine physician blinded to patient clinical findings	Patient based: PET: sensitivity = 82%, specificity = 97.1%, accuracy = 94% Clinical work-up: sensitivity = 32.8%, specificity = 96.7%, accuracy = 83.7% PET + clinical work-up: sensitivity = 83.6%, specificity = 93.7%, accuracy = 91.7%	FDG-PET is superior to clinical work-up in primary M staging of non-keratinising NPC. The diagnostic efficacy did not improve by combining PET with clinical work-up. Therefore, PET can replace clinical work-up in primary M staging of non-keratinising NPC.
[9]	Compare the effectiveness of FDG-PET with MRI in determining the pretherapeutic tumour staging of patients with head and neck SCC	34	Whole body PET scans	Histology	MRI	NR	Primary tumour detection: sensitivity = 97% LN metastases PET: sensitivity = 100%, specificity = 87.5%, PPV = 77.8%, NPV = 100% MRI: sensitivity = 85.7%, specificity = 87.5%, PPV = 75%, NPV = 93.3%	PET is not superior to MRI in the pretherapeutic evaluation of head and neck cancers. PET seems to be useful to detect distant metastases.
[45]	Compare the diagnostic ability of FMT-PET and FDG-PET for the diagnosis of maxillofacial tumours	43 total- 36 with malignant tumour, 10 with benign tumour	Both FMT and FDG-PET Scans from head to thigh	Histology	FMT versus FDG	NR	FMT-PET had better contrast than FDG-PET in 27/36 patients with malignant lesions. ROC analysis primary lesion: FMT-PET: sensitivity = 83%, specificity = 80%, PPratio = 93%, NPratio = 57%, accuracy = 83%	FMT and FDG uptakes in malignant tumours were significantly higher than those in benign tumours. Both FMT- and FDG-PET could differentiate between malignant and benign lesions, and they were almost equally effective in detecting maxillofacial

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							FDG-PET: sensitivity = 81%, specificity = 80%, PPratio = 94%, NPratio = 53%, accuracy = 80% Diagnosis of LN metastasis FMT-PET: sensitivity = 70%, specificity = 96%, PPratio = 88%, NPratio = 89%, accuracy = 89% FDG-PET: sensitivity = 90%, specificity = 81%, PPratio = 64%, NPratio = 96%, accuracy = 83%	tumours. FMT-PET had better contrast between malignant lesions and normal structures than FDG-PET, because FMT uptake in the normal organs was significantly lower than FDG uptake.
[46]	Investigate the role of FDG-PET/CT in the preoperative prediction of the presence and extent of neck disease in patients with N0 and N+ neck designations in oral/ head and neck cancer.	70	Whole body CT and PET scans from base of the brain to upper thigh followed by scans from the orbits to the top of the aorta	Histology	None	Radiologist blinded to pathology findings	Identification of neck disease: Overall: sensitivity = 48%, specificity = 99% N0 neck: sensitivity = 79%, specificity = 82% N+ neck: sensitivity = 95%, specificity = 25% Identification of nodal disease: Overall: sensitivity = 88%, specificity = 76% N0 neck: sensitivity = 26%, specificity = 99% Note: a single patient contributed 32 of 53 false-negative nodes N+ neck: sensitivity = 62%, specificity = 99% Note: a single patient contributed 15 of 46 false-negative nodes	The oral/head and neck oncology surgeon should not base the need for neck surgery in clinically negative or positive necks based on the result of the PET/CT scan. Time-honoured principles of surgical management of the cervical LN should continue to form the basis for decision making in this discipline.
[47]	Determine the use of FDG-PET in preoperative staging of salivary gland cancer	34	Whole-body FDG-PET	Histology of primary tumours and LN	CT	PET image interpretation was done blinded to CT and pathology results	FDG-PET more sensitive than CT in detecting primary tumours and metastatic neck disease Primary tumours: PET	In patients with salivary gland malignancies, FDG-PET is clinically useful in initial staging, histological grading,

							sensitivity = 91%, CT sensitivity = 79% Positive neck findings: PET: sensitivity = 93%, specificity = 85%, PPV = 88%, NPV = 92%, accuracy = 89% CT: sensitivity = 80%, specificity = 77%, PPV = 80%, NPV = 77%, accuracy = 79% Cervical levels with metastases PET: sensitivity = 81%, specificity = 90%, PPV = 81%, NPV = 90%, accuracy = 86% CT: sensitivity = 56%, specificity = 92%, PPV = 79%, NPV = 80%, accuracy = 80%	and monitoring after treatment but not in predicting patient survival.
[48]	Assess the value of combined PET/CT over PET for initial staging in patients with newly diagnosed head and neck SCC	167	Scans from skull base to upper thighs	Histology	PET + CT/MRI versus PET/CT + CT/MRI	NR	Primary tumour: PET: sensitivity = 98%, CT/MRI: sensitivity = 86% PET/CT: sensitivity 97%, CT/MRI: sensitivity = 88% Cervical metastases: PET: sensitivity = 90%, specificity = 88%, PPV = 92%, NPV = 86%, accuracy = 89%; CT/MRI: sensitivity = 77%, specificity = 81%, PPV = 86%, NPV = 71%, accuracy = 79% PET/CT: sensitivity = 91%, specificity = 87%, PPV = 88%, NPV = 90%, accuracy = 89%; CT/MRI: sensitivity = 76%, specificity = 83%, PPV = 83%, NPV = 76%, accuracy = 79%	Compared with PET alone, preoperative FDG-PET/CT may not yield significantly improved diagnostic accuracy in patients with head and neck SCC. Despite their high accuracy, PET and PET/CT may not abrogate the need for conventional imaging and pathologic staging based on primary resection and neck dissection.
[49]	Evaluate PET/CT in detecting mandibular tumour involvement in cancer of the oral cavity and oropharynx	17	FDG-PET	Histology	CT	Nuclear medicine physician blinded to radiologist's findings	PET/CT: sensitivity = 100%, specificity = 85%, PPV = 60%, NPV = 100% CT: sensitivity = 33%, specificity = 100%, PPV = 100%, NPV = 87%	These results encourage the use of PET/CT when assessing mandibular invasion.
[29]	To determine the utility of pre-and postoperative PET/CT scans in staging and	47	PET/CT	Histopathology	None	No blinding.	PET/CT: sensitivity = 77%, specificity = 81%, PPV = 83%, NPV = 76%	PET/CT imaging offers accurate anatomical data and tumour

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	follow-up of skull base tumours.						Clinical management was changed in 11 patients: upstaging occurred in 1 patient preoperatively and 10 patients postoperatively.	staging in the skull base.
[20]	Investigate the potential impact of using PET/CT image fusion for the management of patients with head and neck carcinoma. Specifically, we analysed how PET/CT may change the clinical stage and the delineation of gross tumour volume for radiation treatment planning.	22	Whole-body PET	Histopathology. The clinical stage was defined according to the 2002 American Joint Committee on Cancer-International Union Against Cancer classification	CT	Not specified	PET/CT imaging led to a change in the TNM categories and in the clinical stage in 5/22 (22%) cases compared to CT alone	The study showed that FDG-PET/CT images for primary head and neck carcinoma had a potential impact on both tumour staging and treatment planning. A clinical stage variation was observed in 22% of cases. Based on the data as well as the other literature results, the future scenario of imaging for radiotherapy of head and neck tumours may include the use of functional imaging such as FDG-PET/CT with the aim to characterise the biological features of the tumour and to optimise the use of highly conformal and biologically effective radiation treatment.
[21]	What was impact of FDG-PET/CT on general therapy management and radiotherapy planning in patients with stage IV head and neck tumours.	35	Whole-body PET	Histopathology	Pan-endoscopy and local tumour spread has been mapped by CT in 26 patients and by MRI in 9 patients.	3 specialist physicians from the fields of radiotherapy, nuclear medicine and radiology jointly carried out a visual and semi-quantitative interpretation of the whole-body PET/CT scans.	FDG-PET/CT detected distant metastases for the first time in 6 patients (17.1%). A second primary tumour was visualised in 5 patients (14.3%), in 2 patients as a solitary pulmonary focus. Compared with the morphometric definition, nodal status based on metabolic activity was up-staged in 12 patients (34.3%) – with 4 patients (11.4%) showing pathological glucose utilisation in the retropharyngeal	FDG-PET/CT in American Joint Committee on Cancer stage IV head and neck cancer yielded additional diagnostic information in 65.7% of patients, with subsequent modification of treatment strategy in 17.1% and implementation of further curative therapy in 5.7%. Based on the findings of FDG-PET/CT, the modification of radiotherapy was

							LNs – and down-staged in 8 patients (22.9%). Overall, FDG-PET/CT yielded additional diagnostic information in 23 patients (65.7%). On the basis of the information yielded by FDG-PET/CT, treatment strategies were modified from curative to palliative in 6 patients (17.1%). Because of the diagnosis of a second primary tumour, 2 patients (5.7%) received additional curative therapy as part of an interdisciplinary treatment strategy. In the light of FDG-PET/CT, the changes in nodal status based on metabolic activity (i.e. up-staging or down-staging) resulted in modification of radiotherapy volume and dose in 20 patients (57.1%). Overall, FDG-PET/CT resulted in a treatment change or radiotherapy modification in 23 patients (65.7%)	carried out in 57.1% of patents in the study. From the radiotherapist's perspective, therefore, the implementation of FDG-PET/CT to refine and optimise the baseline staging of stage IV head and neck cancer is indubitably useful and justifiable.
[22]	Compared parotid glands, chiasma, and gross tumour volume as determined on CT and MRI by 2 different operators, and evaluated whether the use of 18F-FDG-PET/CT has changed the treatment planning volumes	35	Whole-body PET	Histopathology	CT and MRI	Volumes were delineated by a head and neck specialised radiotherapist and reviewed by a head and neck specialised radiologist	The use of 18F-FDG-PET/CT changed the treatment design in 6 of 21 patients. In 2 patients, 18F-FDG-PET/CT indicated intrathoracic metastasis, subsequently proved histologically, and they were switched to palliative treatment. In another patient, 18F-FDG-PET/CT showed extension to the skull base that was not initially detected by other image modalities but was confirmed by	The 18F-FDG-PET/CT proved to be helpful for metastasis detection and detection of LN extension, and is therefore useful for more accurate treatment design

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							bone CT. In further 3 patients, bilateral rather than unilateral LN extension was detected by 18F-FDG-PET/CT and confirmed by fine-needle biopsy.	
[23]	To evaluate the effect of the use of 18F-FDG-PET/CT in radiotherapy target delineation for head and neck cancer compared with CT alone.	38	Skull to the upper abdomen	Histopathology	CT	A nuclear medicine physician (PC), with expertise in PET imaging, visually interpreted the 18F-FDG-PET studies and defined the 18F-FDG-PET-positive regions interpreted as malignant on the emission images.	Combined 18F-FDG-PET/CT determined a change in the tumour stage in 6 of 38 cases. All changes were related to additional nodal information.	The implementation of combined PET/CT imaging has the potential to improve primary tumour delineation and nodal staging for imaging experts and non-experts, such as trainees in radiation oncology or radiation oncologists without experience in head-and neck cancer, thus reducing equivocal image interpretations and improving evaluator confidence.
[13]	Evaluate the clinical utility of FDG-PET/CT as well as CT and MRI in the identification of nodal metastasis in the contralateral neck in patients with head and neck SCC.	114	Not stated	Histopathology	CT, MRI	PET/CT images were interpreted by an experienced nuclear medicine physician. CT and MRI results were interpreted by an experienced radiologist. No specific information on blinding was reported.	PET/CT detected the presence or absence of cervical metastasis in the ipsilateral and contralateral neck in 105 (92%) and 95 (83%) patients, respectively. CT/MRI accurately detected the presence of cervical nodal metastases in the ipsilateral and contralateral neck in 99 (87%) and 95 (83%) patients, respectively. The sensitivity and accuracy of PET/CT was significantly superior to that of CT/MRI on contralateral neck ($P < 0.05$ each). It was not on the ipsilateral neck ($P = 0.063$). The sensitivity and accuracy of PET/CT were significantly higher than that of CT/MRI on both sides of	Combined PET/CT is superior to CT/MRI in detecting metastatic cervical nodes in patients with head and neck SCC who underwent bilateral neck dissection. PET/CT and CT/MRI had low sensitivity in identifying contralateral cervical metastases, due to the limitations of these imaging modalities in assessing small LN. Findings indicate that preoperative imaging modalities may not nullify the need for contralateral neck surgery or radiation therapy indicated in patients with head and neck SCC.

							the neck ($P < 0.01$ each). The sensitivity of PET/CT for detecting contralateral metastatic nodes was significantly higher than that of CT/MRI, both on a per-patient (58% versus 25%, $P = 0.031$) and a per-level (52% versus 36%, $P = 0.008$) basis, but the sensitivities of both methods were low.	
[14]	Evaluate the impact of FDG-PET/CT as an adjunct to conventional imaging in the management of nasopharyngeal cancer for both the initial staging and assessment of post-treatment response.	48	PET/CT scan incorporating the neck thorax, abdomen and pelvis	Histopathology	Conventional imaging (CT or MRI)	PET/CT images were interpreted by and experienced nuclear medicine physician. CT and MRI results were interpreted by an experienced radiologist. No specific information on blinding was reported.	The clinical impact of PET/CT was high (i.e. changed treatment modality or intent) in 4 (8%) patients; medium (treatment modality was unchanged but radiotherapy planning technique or dose was altered) in 12 (25%) patients, and low (no change in treatment modality or intent) in 32 (66%) patents. 21 patients were scanned for post-treatment response. PET/CT was less frequently equivocal than MRI (3 versus 8/21). A complete metabolic response on PET/CT was associated with a 93% NPV for subsequent recurrence.	PET/CT is a valuable staging tool for the detection of occult metastatic disease and defining the extent of neck nodal disease. Post-treatment, a complete metabolic response on PET/CT has a very high NPV with fewer equivocal results than MRI.
[50]	Prospectively assess the sensitivity and specificity of FDG-PET/CT for detecting neck LN metastases in patients with oral cavity SCC, with pathological results as the reference standard. Investigate whether pretreatment visual scores in the neck LN may improve risk stratification	473	Head to mid-thigh	Histopathology	CT or ultrasound biopsy	Two experienced nuclear medicine physicians and 1 radiologist interpreted FDG-PET (PET/CT) images. Interpretation was based on visual evaluation, and decisions were reached by consensus	FDG-PET correctly diagnosed 164 of 211 patients with neck metastases and 152 of 262 subjects without pathological neck metastases, resulting in a patient-based sensitivity and specificity of 77.7% and 58.0%, respectively.	PET findings at the neck LN have limited sensitivity and specificity for primary staging of oral cavity SCC.
[15]	The study was designed to address the impact of whole-body 18F-FDG-PET imaging	233	Whole-body PET imaging (from head to mid-thighs)	Histology	Conventional staging (physical examination, neck palpation, fibroscopic and direct	After conventional staging was carried out a multidisciplinary meeting was held, and	Staging: PET stage and conventional stage were discordant in 100 patients (43%), for	The study showed that adding 18F-FDG-PET imaging significantly improved the pre-

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	used in conjunction with the usual staging work-up on the initial staging and therapeutic management with head and neck SCC				endoscopic examination with biopsy, CT or MRI)	the TNM stage and therapeutic decision were set in envelope 1. PET images were read by experienced nuclear medicine physicians who were blinded to the results of the conventional staging process. Results of the PET scan were sent to the referring clinician who reported to the multidisciplinary team which then integrated PET results with the conventional staging into envelope 2.	whom a gold standard was available in 60 patients. PET was accurate in 47 patients and inaccurate in 13 patients. For these 100 patients with discordant results, the sensitivity of PET staging was 91% (95th CI), specificity was 63% (95th CI), PPV was 75% (95th CI), NPV 85% (95th CI), accuracy was 22% and positive likelihood ratio was 0.14. PET staging was found to be statistically significantly more accurate than conventional staging ($P < 0.0001$). Impact on patient management: A significant change in patient management was observed in 32 patients (13.7% of the patient population; in 5.2% of patients because of a change in N stage and in 8.6% because of a change in the M stage).	therapeutic TNM classification of head and neck SCC. This higher staging accuracy resulted in altering patient management in 13.7% of patients, with the greater impact being a result of the detection of metastatic or additional disease. The results support the implementation of 18F-FDG-PET imaging in the routine imaging work-up of head and neck SCC.
[17]	Prospective comparison of the diagnostic capability of FDG-PET/CT and whole body MRI and their combination in detecting malignancy in treated oropharyngeal or hypopharyngeal SCC	79	Whole body FDG-PET/CT	Pathology or follow-up imaging	Whole body MRI	Two radiologists and two nuclear medicine physicians independently analysed the whole body MRI and PET/CT findings, respectively. The readers were blinded to the other imaging findings but were aware of the study protocol.	The patient-based sensitivity of PET/CT was higher than that of MRI (72.4 versus 55.2%, $P = 0.13$). Combined interpretation of PET/CT and MRI raised the sensitivity up to 75.9%. The false-positive rate of PET/CT (12.5%) was lower than that of MRI (23.8%), but there were no significant differences in terms of specificity (94.4 versus 90.0%, $P = 0.5$). Combined interpretation of PET/CT and MRI did not improve specificity.	PET/CT showed a trend towards higher diagnostic capability than MRI in detecting residual/recurrent tumours or second primary tumours in oropharyngeal or hypopharyngeal SCC, although the results were not statistically significant. The combined use of PET/CT and MRI provided more added value to MRI alone than to PET/CT alone. Additional PET/CT can be useful in patients with questionable MRI findings for the

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								presence of malignancy. Therefore, PET/CT should be the procedure of choice in the evaluation of oropharyngeal or hypopharyngeal SCC patients treated by definitive concurrent chemoradiotherapy considered at high risk for residual disease or in the presence of suspected recurrence.
[18]	Define the added value of whole-body FDG-PET in screening for distant metastases in patients with head and neck squamous cell carcinoma and risk factors.	92	Whole-body PET	Histopathology	Chest CT	The interpreters were blinded to the alternative modality and clinical outcome.	Accuracy of PET and PET/CT in the detection of distant metastases PET: sensitivity = 53%; specificity = 93%; PPV = 80%; NPV = 80%; accuracy = 80% PET/CT: sensitivity = 63%; specificity = 95%; PPV = 86%; NPV = 84%; accuracy = 84% Accuracy of PET and PET/CT in the detection of distant metastases and synchronous primary tumours PET: sensitivity = 58%; specificity = 93%; PPV = 85%; NPV = 76%; accuracy = 78% PET/CT: sensitivity = 66%; specificity = 94%; PPV = 89%; NPV = 80%; accuracy = 83% Accuracy of PET and PET/CT in the detection of distant metastases patients with locoregional control PET: sensitivity = 68%; specificity = 93%; PPV = 79%; NPV = 89%; accuracy = 86% PET/CT: sensitivity = 82%, specificity = 95%; PPV = 86%; NPV = 93%; accuracy = 91%	FDG-PET is a valuable tool in screening for distant metastases in head and neck SCC patients with high risk factors. Screening with a combination of CT of the thorax and whole-body FGD-PET decreases over-treatment. It results in a reduction of futile mostly extensive treatments in these patients.
[19]	Establish the diagnostic accuracy of FDG-PET for LN metastases in	26	Whole-body PET	Histopathology	CT	All PET images were visually interpreted by at least 2 experienced	The sensitivity, specificity, accuracy, PPV and NPV per neck	FDG-PET is a useful tool for preoperative evaluation of the neck

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	head and neck SCC, and to ascertain the factors that affect this accuracy, determining the smallest detectable size of disease by means of analysing tumour involvement of each metastatic node histological sections.					nuclear medicine physicians by consensus. The lesions were considered to be positive if a definite, localised area with higher uptake than the surrounding normal tissue was present, excluding physiological uptake.	side for FDG-PET were 74% (17/23), 92% (11/12), 80% (28/35), 94% (17/18) and 65% (11/17), respectively.	because it accurately detects metastatic LN ≥10 mm in diameter and had fewer false-positive results than CT. The high specificity of FDG-PET for LN metastases may play an important role in avoiding unnecessary neck dissection.
Treatment response								
[51]	Identify the value of PET scanning in determining which patients with N+ necks who have undergone curative chemotherapy for SCC of the upper aerodigestive tract have viable residual cervical metastases and therefore would benefit from post-treatment neck dissection.	19 patients, 2 with bilateral neck dissection, therefore, 21 neck specimens	Whole body PET	Histology or clinical follow-up	None	NR	To detect residual metastases: sensitivity = 75%, specificity = 64.7%, PPV = 33%, NPV = 91.7% 7 patients met all inclusion criteria but did not complete salvage neck dissection. Post-treatment PET scans were carried out at 14.6 weeks and all were negative for residual disease. Clinical follow-up of this cohort has shown only one neck recurrence in the 8 necks with a mean follow-up of 11.5 months, which is in agreement with the study group that completed post-treatment neck dissection.	PET imaging may be a useful tool to guide the surgeon. PPV low (33%), but a negative PET scan may allow the surgeon to avoid unnecessary neck dissection (NPV = 91.7%).
[52]	Determine the role of PET in detecting locally residual/recurrent NPC in comparison with MRI	112	PET scans from head to upper thigh	Histology if possible, if not possible, clinical and imaging follow-up	MRI	Nuclear imaging physicians blinded to MRI results	Treatment response (residual tumour) PET: sensitivity = 75%, specificity = 94.4%, PPV = 33.3%, NPV = 99%, accuracy = 93.8% MRI: sensitivity = 75%, specificity = 89.8%, PPV = 21.4%, NPV = 99%, accuracy = 89.3% SUV: tumour = 6.5 ± 1.8; non-tumour 2.8 ± 0.8,	FDG-PET shows superior specificity in assessing treatment response for NPC patients with initial T4 disease, as compared with MRI. FDG-PET results should be interpreted with caution in patients with initial T1-2 disease because ICBT may induce false-positive findings. Gold standard to

							$P = 0.001$ Retrospective ROC analysis led to decision to use SUV cut-off value of 4.2	determine residual NPC should consist of both nasopharyngeal biopsy and clinical/ imaging follow-up
[28]	Compare the efficacies of whole-body PET and conventional work-up in evaluating the treatment response for patients with locoregional advanced NPC after primary curative treatment and investigates the impact of PET on patient management	131	Scanned from head to upper thigh	Image-guided biopsy on suspected malignant lesions, if possible. If not possible, close clinical or imaging follow-up for at least 6 months	Clinical work-up	Nuclear medicine physicians blinded to clinical work-up results	Treatment response: Overall: In stage II disease FDG-PET: sensitivity = 100%, specificity = 95.7%, accuracy = 95.8% Clinical work-up: sensitivity = 25%, specificity = 96.7%, accuracy = 95.3% In stage IVa-b disease FDG-PET: sensitivity = 91.7%, specificity = 97.6%, accuracy = 97.2% Clinical work-up: sensitivity = 58.3%, specificity = 91.7%, accuracy = 89.4% For local, regional LN and distant results see study summary page Clinical impact of FDG-PET on management of 131 patients with NPC after curative treatment Stage III disease: negative = 11%, no change = 85%, positive = 4% Stage IVa-b disease: negative = 5%, no change = 57%, positive = 38%	The sensitivity and specificity of PET in revaluating the treatment response for patients with stage IVa-b NPC were higher than those of clinical work-up. The sensitivity of PET was higher but the specificity of PET and clinical work-up were similar in patients with stage III NPC. PET resulted in positive impacts on the management of one third of patients with stage IVa-b NPC. The main positive impacts were reducing unnecessary imaging follow-up in patients with T4 disease and disclosing unexpected residual second primary tumours. The impact on patients with stage III NPC was less prominent.
[53]	Understand if SUV is a significant predictor for local response, either before or 3 months after concurrent chemoradiotherapy and to determine if the changes in SUV, between the two measurements, were a reliable predictor for local response versus non-response to	39 (42 recruited but 3 excluded)	PET from head to upper thigh	Clinical follow-up with biopsies carried out when there were positive, concordant, equivocal or discordant lesions on MRI and PET scans	MRI	Nuclear medicine physicians blinded to knowledge of MRI findings when analysing PET scans	3 of 4 non-responders were detected by the 3 month post-therapy PET scan and the other from the 6 month post-therapy PET scan which was carried out because of equivocal PET and MRI findings at 3 months. Non-responders: Before concurrent chemoradiotherapy SUV = 15.6; after SUV = 5.5	The SUV for stage T4 NPC, 3 months after the completion of concurrent chemoradiotherapy was a significant predictor for local tumour response. The cut-off SUV of 4.0 at 3 months after concurrent chemoradiotherapy was useful to predict the outcomes of local treatment that can be

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	concurrent chemoradiotherapy						Responders: Before concurrent chemoradiotherapy SUV = 10.9; after SUV = 2.1 3 months after concurrent chemoradiotherapy SUV was lower in responders versus non-responders All responders had SUV < 4.0 and all non-responders had SUV > 4.0	offered as a diagnostic reference for recurrent or residual tumour for NPC treatment. Both the baseline SUV and change in SUV between baseline and 3 months after concurrent chemoradiotherapy were only marginally significant predictors for local tumour response.
[12]	Determine the incremental value of PET/CT over conventional assessment for staging, post-treatment assessment of response and ongoing follow-up in head and neck SCC	76	Images of neck, thorax, abdomen, and pelvis	Cytology, histology and/or clinical and radiological follow-up	Conventional assessment	Not blinded	Treatment response: 30 patients had PET/CT to assess treatment response. PET/CT altered the assessment of locoregional response in 13 (43%) patients. Primary site: 8/30 had altered response assessment on PET/CT vs. conventional assessment: 6 showing partial response on conventional assessment and complete metabolic response on PET/CT were true negative. 2 were false positive Nodal site: 10/30 had altered response assessment on PET/CT versus conventional assessment: 8 showing partial response on conventional assessment and complete metabolic response on PET/CT were true negative, 1 was true positive, and 1 patient died without knowledge of true neck node status. Clinical impact: high 11/30 (37%) Accuracy: primary site = 4 false positives,	PET/CT has a major incremental impact in the post-treatment management of patients with head and neck SCC. PET/CT has a very high NPV for residual/recurrent locoregional disease in post-treatment evaluation, determining those patients in whom ongoing observation rather than surgical intervention is appropriate and safe management. The addition of post-treatment PET/CT scan into the patient's post-treatment management paradigm now constitutes optimal post-treatment care.

							nodal sites = 3 false positives, distant sites = 1 false positive Follow-up 30 patients had 35 follow-up PET/CT scans, 28 for suspected recurrence and 7 for routine surveillance. Clinical impact: high = 12/35 (34%) Accuracy: primary site = 3 false positive, nodal site = 1 false positive, distant site = 7 false negative.	
[42]	Assess the role of PET/CT compared with PET and CT separately in head and neck cancer. The impact of PET/CT results on patient treatment also investigated.	90	Whole body PET and non-contrast enhanced CT	Histology ($n = 56$) and clinical and radiological follow-up (n = 28)	Contrast-enhanced CT and/or MRI (CI) of head and neck	Images analysed independently of each other	Performance for treatment response PET/CT: sensitivity = 87%, specificity = 100%, PPV = 100%, NPV = 75%, accuracy = 91% PET: sensitivity = 87%, specificity = 100%, PPV = 100%, NPV = 75%, accuracy = 91% CI: sensitivity = 87%, specificity = 33%, PPV = 77%, NPV = 50%, accuracy = 72%	When a PET/CT study is negative, additional clinical and radiological follow-up can be postponed, at least temporarily. A positive study should encourage and guide the surgeon to obtain tissue diagnosis.
[54]	Evaluate the clinical efficacy of FDG-PET performed 1 month after the completion of radiotherapy for determining the response to radiotherapy in patients with head and neck SCC	97	PET/CT from skull base to pelvis	Histology and clinical follow-up	None	NR	Sensitivity = 88.2%, specificity = 95.5%, PPV = 65.2%, NPV = 98.8% and accuracy = 94.9% to detect residual disease (total) Sensitivity = 83.3%, specificity = 91.8%, PPV = 58.8%, NPV = 97.5%, accuracy = 90.7% to detect primary tumour Sensitivity = 100%, specificity = 98.9%, PPV = 83.3%, NPV = 100%, accuracy = 99% to detect nodal disease SUV response to treatment: Primary tumour: before	FDG-PET carried out 1 month after the end of radiotherapy is a valuable diagnostic method for evaluating the response to radiotherapy in patients with head and neck SCC. If patients have negative FDG-PET findings, we recommend only 1 month of follow-up; however, when positive FDG-PET findings are observed, further evaluation is needed. FDG-PET results should be interpreted with caution in patients with initial T1-2 disease because ICBT

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Appendix (*Continued*)

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							treatment = median 6.5 [range 2.3-23.0]; after treatment = median 1.8 [range: basal status value = 9.7]. LN: before treatment = median 5.6 [range: 1.2-16.8]; after treatment = median 1.8 [range: basal status value = 8.6]	may induce false-positive findings. Gold standard to determine recurrent NPC should consist of both nasopharyngeal biopsy and clinical/imaging follow-up
[16]	The primary aim of the study was to analyse the accuracy and benefit of PET in staging and assessing treatment response in patients treated with primary chemoradiotherapy for mucosal carcinomas of the head and neck. The secondary aim was to compare PET results with clinical examination and conventional imaging.	78	PET scans extended from the mid-cerebrum to the anterior superior iliac spine	Histopathology	Standard clinical evaluation (endoscopic evaluation with biopsy), CT and MRI	No information on blinding outlined in the study.	The sensitivity and specificity of PET were 82% and 95%, respectively. PPV and NV were also 82% and 95% with an overall accuracy of 92%. The likelihood ratio of a positive test was 0.19. When the researchers compared the accuracy of PET, conventional imaging and clinical outcomes they found that PET had a better accuracy in predicting a complete response (PET versus clinical $P < 0.002$; PET versus conventional imaging $P < 0.001$)	The researchers showed that a complete response on post-treatment PET is accurate (NPV = 95%) in predicting clinical outcome in mucosal head and neck cancer treated with chemoradiotherapy. PET resulted in important management changes when patients were identified as having distant metastatic disease. Patients who have a complete response on repeat PET have a significant survival advantage over those who do not. The researchers believe that PET should be considered the standard of care in the evaluation of mucosal head and neck cancer treated with chemoradiotherapy.
[55]	Compare the accuracy of radiation response assessment by FDG-PET/CT and contrast-enhanced CT and define patient subsets that would probably derive maximal benefits from the addition of FDG-PET/CT imaging to	98	Not stated	Histopathology	Contrast-enhanced CT	Interpreter blinded to results of other modality	Accuracy of FDG-PET for the prediction of treatment response for primary tumours: sensitivity = 70%; specificity = 93.7%; NPV = 96.1%; PPV = 58.3% Accuracy of FDG-PET for the prediction of treatment response for	The results of this study do not support the broad application of FDG-PET/CT for radiation response assessment in unselected head and neck cancer patients. However, FDG-PET/CT may be in imaging modality of choice for

	conventional response assessment.						nodal tumours sensitivity = 75%; specificity = 76.1%; NPV = 96.2%; PPV = 27.3%	patients with highest risk disease, particularly those with human papillomavirus-negative tumours.
Recurrence/restaging								
[10]	Evaluate the value of FDG-PET for distant metastases in at-risk head and neck SCC patients	34	Images from mid-femur to cranial vault	Chest CT, biopsy or clinical follow-up	None	Nuclear medicine physicians blinded to results of the other examinations and final clinical diagnosis	FDG-PET correctly identified 1 patient with distant metastases and 3 patients with second primary tumours. Increased FDG uptake in 5 patients were not confirmed during follow-up During revised reading of 9 suspicious PET scans, 1 was true positive for distant metastases and 2 were true positive for second primary tumours. PET was equivocal in 4, of which 1 was positive for second primary tumour.	Whole body FDG-PET may have additional value in screening for distant metastases and second primary tumours, if applied to the subset of patients who are at substantial risk. Whether this application of FDG-PET will indeed be (cost)-effective, is now studied in a larger cohort of patients in a multicentre study. Finally, these initial data suggest that in this patient population, the use of PET/CT scanners might be productive as apparent discrepancies can be solved readily while preserving the yield of whole body FDG-PET.
[11]	Assess the efficacy of PET in detecting distant metastases in NPC patients with M0 staging based on conventional imaging	140 total (118 newly diagnosed, 22 disease recurrent)	FDG-PET	CT-guided or sonography-guided biopsy, if possible. If not possible, clinical follow-up (MRI/CT/PET) carried out at 3-6 months	None	Nuclear imaging physicians blinded to other imaging results	To detect distant metastases: sensitivity = 100%, specificity = 86.9%	PET has made a major impact on the detection of distant metastases in NPC patients with primary lesions and stage M0 disease, especially those who also have stage N2-3 disease. Because of the higher incidence of distant metastases in patients with recurrent NPC than in those with primary tumours, FDG-PET is also recommended for assessing recurrent NPC before embarking on salvage therapy. Cost of FDG-PET and occurrence and rate of false-positive uptake

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Appendix (*Continued*)

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								are still problematic. The most important contribution of FDG-PET for patients with NPC is the ability to reveal occult distant metastases on chest radiography, liver sonography, and conventional bone scanning.
[52]	Determine the role of PET in detecting locally residual/recurrent NPC in comparison with MRI	34	PET scans from head to upper thigh	Histology if possible, if not possible, clinical and imaging follow-up	MRI	Nuclear imaging physicians blinded to MRI results	Local recurrence PET: sensitivity = 95.5%, specificity = 83.3%, PPV = 91.3%, NPV = 90.9%, accuracy = 91.2% MRI: sensitivity = 95.5%, specificity = 75%, PPV = 87.5%, NPV = 90%, accuracy = 88.2% SUV tumour: 8.5 ± 3.8, non-tumour 2.6 ± 1.0, $P < 0.001$ Retrospective ROC analysis led to decision to use SUV cut-off value of 4.2	FDG-PET has equal sensitivity but higher specificity to detect recurrent NPC as compared with MRI
[27]	Evaluate the value of FDG-PET in detecting recurrent laryngeal carcinoma after radiotherapy	30	Scans from base of skull to clavicle	Biopsy	None	Nuclear medicine physicians not blinded to clinical information	To detect recurrence: FDG-PET: sensitivity = 88%, specificity = 82%, PPV = 64%, NPV = 95%, accuracy = 83%	FDG-PET promising to detect recurrent laryngeal carcinoma after radiotherapy, and selecting patients for direct laryngoscopy. FDG-PET may help avoid futile invasive procedures. Disparities among observers remain, thus training is necessary to improve consistency of reporting in clinical practice and trials.
[56]	Compare the accuracy of helical contrast material-enhance CT alone with that of coregistered PET/CT and coregistered SPECT/CT for detecting bone invasion in	34	PET-CT	Bone resection and soft tissue adjacent to bone was also obtained to rule out bone involvement	SPECT/CT, contrast-enhanced CT	Nuclear medicine physicians were blinded to the results of SPECT/CT and contrast-enhanced CT, but knew the clinical information	Detection of bone invasion PET/CT: sensitivity = 100%, specificity = 91%, accuracy = 94%, PPV = 86%, NPV = 100% SPECT/CT:	The identification of bone involvement in patients with oral cavity carcinomas is reliably carried out with helical CT and thin sections. In patients who

	patients scheduled to undergo surgery because oral cavity carcinoma with possible bone invasion was suspected on the basis of clinical evaluation.						sensitivity = 92%, specificity = 86%, accuracy = 88%, PPV = 79%, NPV = 95% Contrast-enhanced CT: sensitivity = 92%, specificity = 100%, accuracy = 97%, PPV = 100%, NPV = 96% Whole body examination for distant bone metastasis: Skeletal scintigraphy did not depict distant bone metastases in 34 patients PET/CT depicted distant metastases in 1 patient (lung, thoracic wall and mediastinum) and verified by ultrasound-guided biopsy of the thoracic wall at autopsy	undergo PET/CT for whole-body staging or repeat staging, the CT information from PET/CT is reliable, whereas FDG uptake does not help better identify bone invasion.
[57]	Determine if FDG-PET provides clinically relevant diagnostic and prognostic information for the management of oral SCC patients after salvage surgery	41	PET scans of viscerocranium, neck, thorax and epigastric region	Clinical and/or radiological follow-up (pathology, CT, obvious clinical evidence of tumour progression identified in follow-up)	None	Nuclear imaging physicians who were not blinded	Identification of tumour sites (overall): sensitivity = 85% FDG-PET for re-staging after recurrent oral cavity SCC: 1) Local recurrence: sensitivity = 92%, specificity = 75%, PPV = 63%, NPV = 95% 2) LN metastases: sensitivity = 88%, Specificity = 98%, PPV = 93%, NPV = 97% 3) Distant metastases: sensitivity = 73%, specificity = 97%, PPV = 89%, NPV = 91%	FDG-PET can facilitate re-staging and clinical management in "high-risk" patients with oral cavity SCC SUV $\leq$ 4 suggests promising outcome, which SUV > 4 indicated a fatal disease course.
[42]	Assess the role of PET/CT compared with PET and CT separately in head and neck cancer. The impact of PET/CT results on patient treatment also investigated.	90	Whole body PET and non-contrast enhanced CT	Histology ($n = 56$) and clinical and radiological follow-up ($n = 28$)	Contrast enhanced CT and/or MRI (CI) of head and neck	Images analysed independently of each other	Performance for distant metastases: PET/CT: sensitivity = 93%, specificity = 100%, PPV = 100%, NPV = 88%, accuracy = 95% PET: sensitivity = 92%, specificity = 71%, PPV = 87%, NPV = 83%, accuracy = 86% CI: sensitivity = 100%, specificity = 29%,	In assessment of locoregional disease, PET/CT provides better anatomic localisation of foci with abnormal FDG uptake and significantly reduces the number of FP or equivocal PET and CI results. When a PET/CT study is negative, additional clinical and radiological follow-up

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							PPV = 74%, NPV = 100%, accuracy = 71% Performance for locoregional disease: PET/CT: sensitivity = 78%, specificity = 93%, PPV = 82%, NPV = 91%, accuracy = 88% PET: sensitivity = 78%, specificity = 69%, PPV = 52%, NPV = 88%, accuracy = 72% CI: sensitivity = 83%, specificity = 14%, PPV = 29%, NPV = 67%, accuracy = 35%	can be postponed, at least temporarily. A positive study should encourage and guide the surgeon to obtain tissue diagnosis.
[31]	Determine the benefits of hybrid 18F-FDG-PET/CT in detecting subclinical locoregional recurrence of head and neck SCC and distant metastases	91	Whole-body 18F-FDG-PET/CT	Histology	Histopathology for locoregional findings and radiotherapy, CT or MRI for distant metastasis	All images were interpreted qualitatively by 2 nuclear medicine physicians without prior knowledge of the follow-up status of the patients.	The sensitivity and specificity or 18F-FDG-PET/CT in the study for the diagnosis of head and neck SCC recurrence were 100% (30/30) and 85% (52/61), respectively. The PPV was 77% (30/39). The overall NPV was 100% (52/52). The overall accuracy was 90% (82/91).	The results of the study confirmed the high-effectiveness of 18F-FDG-PET/CT in assessing for recurrence of head and neck SCC in patients who have been considered cured of the disease. The findings suggest that 18F-FDG-PET/CT is more accurate than conventional follow-up physical examinations alone in such patients. The systematic use of PET/CT at 12 months of the usual follow-up could be proposed, but cost-effectiveness and survival impact remain to be evaluated.
[33]	The study was designed to address whether CT or 18F-FDG-PET is superior in its ability to detect persistent nodal disease after definitive chemoradiotherapy in patients with node-positive head and neck SCC	48	Whole-body PET scanning	Histology	CT scans	Each image was reviewed by 2 experienced nuclear radiologists and interpretation was made by consensus.	The sensitivity, specificity, accuracy, PPV, and NPV of CT or 18F-FDG-PET in detecting the pathology of persistent or recurrent nodal disease. Statistical analysis revealed no significant difference between the two imaging modalities in terms of specificity,	Post-treatment 18F-FDG-PET is of no additional value to determine the indication of a planned neck dissection in this setting. It seems that patients with a complete regional response on CT at 7 weeks after chemoradiotherapy can be spared from

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							accuracy, PPV and NPV whereas CT was superior to F-FDG-PET in sensitivity ($P = 0.046$)	planned neck dissection, regardless of initial node stage.
[4]	Determine the proportion of patients that were appropriately spared a neck dissection as defined by the absence of subsequent nodal failure.	112	Skull vertex to mid-thigh	Pathology and follow-up	CT	2 nuclear medicine physicians independently reviewed all the datasets on dedicated display systems.	The NPVs for PET and CT nodal response assessment were 98.1% and 96.8%, respectively. False-positive findings occurred in 1.8% of cases for PET and 38% for CT with corresponding PPVs of 77.8, and 14% respectively. Outcomes based on N classification and p16 status:. For the p16-positive group, the NPVs and PPVs were 98.2% and 66.7 respectively, for PET compared with 96.7% and 6.9%, respectively, for CT.	PET provided additional valuable information over contrast enhanced CT alone in an appropriately selected population allowing the avoidance of unnecessary neck dissections. The study shows that PET directed management of the neck after definitive chemoradiotherapy in N+ head and neck squamous cell carcinoma appropriately spares neck dissections in patients with PET-negative residual nodal abnormalities without compromising isolated nodal control.
[58]	Evaluate the roll of FDG-PET in post-CRT surveillance of head and neck SCC. Compare the diagnostic utility of PET and CT.	54	Whole-body PET	Histopathology	Chest CT	2 nuclear medicine physicians visually interpreted PET images and an experienced specialist reviewed all reports with the knowledge of clinical information.	PET showed better performance than CT in post-CRT surveillance. Considering all 54 post-CRT PET scans, sensitivity for detecting primary tumours was 100%, specificity was 93%, PPV was 80% and NPV was 100%. For cervical diseases, sensitivity was 100%, specificity 98%, PPV 92% and NPV 100%. For distant metastases, sensitivity was 100%, specificity was 98%, PPV was 86% and NPV was 100%. PET had a high impact on the clinical management on 16/44 patients (36%)	FDG-PET in an effective non-invasive tool in the post-CRT surveillance of head and neck SCC with both excellent sensitivity and PPV. Results showed that it provided early information concerning distant metastases, smaller tumours and second primary cancers in the upper aerodigestive tract for some selected patients.
Unknown primary								
[24]		30			Contrast enhanced CT			

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	Assess the utility of PET-CT compared with contrast-enhanced CT in predicting persistent cancer either at the primary site or cervical lymphatics in patients with advanced oropharyngeal cancer treated with concurrent chemoradiotherapy		PET-CT scans from skull vertex to midabdomen	Biopsy (primary tumour) or neck dissection (neck)		Nuclear radiologist blinded to contrast enhanced CT results	Primary site: PET-CT: sensitivity = 50%, specificity = 84.6%, PPV = 20%, NPV = 95.7%, accuracy = 82.1% CECT: sensitivity = 50%, specificity = 88.5%, PPV = 25%, NPV = 95.8%, accuracy = 85.7% LN (neck): PET-CT: sensitivity = 100%, specificity = 69.5%, PPV = 36.3%, NPV = 100%, accuracy = 74.1% CECT: sensitivity = 100%, specificity = 52.2%, PPV = 26.7%, NPV = 100%, accuracy = 59.3%	PET-CT seems to be superior to contrast enhanced in predicting persistent disease in the neck after chemoradiotherapy for oropharyngeal or unknown primary cancer, but not at the primary site. The possibility of a false-positive result in the neck remains high, and thus overtreatment may result. Even more concerning are the false-negative results.
[25]	Clinical utility of PET/CT in the work-up of head and neck SCC with an unknown primary in a cohort of patients subjected to a standardised diagnostic protocol. Primary objective was to determine whether the addition of a preoperative PET/CT improves the detection rate of the primary site compared with the traditional approach of expert clinical examination with endoscopy, preoperative CT/MRI and panendoscopy with biopsies of high-risk regions.	20	PET/CT of the thoracic inlet to the upper thighs and a dedicated FDG-PET/CT of the neck	Histopathology	High resolution CT or chest X-ray	Images were interpreted by a radiologist with subspecialty training in nuclear medicine.	PET/CT was positive in 14 of 20 patients (70%) with the base of tongue the most common site (8, 40%) followed by the tonsil (4, 20%). Traditional imaging identified the primary site in 5 patients (25%) whereas PET/CT directed biopsy identified the primary site in 11 patients (55%). The approaches were found to be statistically significant ($P = 0.03$) in favour of PET/CT directed approach. The sensitivity and specificity of PET/CT were 92 and 63%, respectively. The PPV and NPV were 79 and 83%, respectively	Patients with cervical metastasis and an unknown primary site after undergoing clinical examination benefit from PET/CT prior to panendoscopy. Until more evidence is available the authors believe that bilateral tonsillectomy should remain part of the standard panendoscopy in this patient population.

CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; LN, lymph node; MRI, magnetic resonance imaging; OHR, optimised head and neck reconstruction; ROC, receiver operating characteristic; NPC, nasopharyngeal carcinoma; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; SPECT, single photon emission computed tomography; SUV, standardised uptake value; SWR, standard whole body reconstructions. FET, [(18)F]fluoroethyl-L-tyrosine; SOHND, Supra-omohyoid neck dissection; FMT, [(18)F]alpha-methyltyrosine; CI, Conventional Imaging; CRT, Chemoradiotherapy; ICBT, intracavitary brachytherapy.

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