Positron Emission Imaging of Head and Neck Cancer, Including Thyroid Carcinoma

Heiko Schöder and Henry W.D. Yeung

Most positron emission tomography (PET) imaging studies in head and neck cancer are performed using the radiotracer 18-fluorodeoxyglucose (^{18}FDG). PET with FDG has become a standard clinical imaging modality in patients with head and neck cancer. It contributes valuable information in localizing a primary tumor in patients with neck nodal metastases from an unknown primary, in the staging of primary head and neck cancer, and in the detection of recurrent disease. In addition, FDG-PET provides independent prognostic information in patients with newly diagnosed and recurrent head and neck cancer. PET/CT improves lesion localization and accuracy of FDG-PET and is strongly recommended in patients with head and neck cancer. After thyroidectomy, FDG-PET has proven useful in patients with clinical or serological evidence of recurrent or metastatic thyroid carcinoma but negative whole body iodine scan. PET shows metastatic disease in up to 90% of these patients, thereby providing a rational basis for further studies and therapy. In patients with medullary thyroid cancer with elevated calcitonin levels following thyroidectomy, FDG-PET has a sensitivity of 70-75% for localizing metastatic disease. Occasionally incidental intense FDG uptake is observed in the thyroid gland on whole body PET studies performed for other indications. Although diffuse FDG uptake usually indicates thyroiditis, focal uptake has been related to thyroid cancer in 25-50% of cases and should therefore be evaluated further if a proven malignancy would cause a change in patient management.
© *2004 Elsevier Inc. All rights reserved.*

HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC) is the sixth most common cancer worldwide. In the United States, it accounts for approximately 2% of all cancers and 2% of cancer death. Nevertheless, HNSCC is an important topic in oncologic imaging, because imaging findings can aid significantly in the detection, staging and treatment evaluation of these tumor. Patients presenting with primary tumors that are confined at the time of initial diagnosis (T1/2N0M0) have an excellent cure rate. Unfortunately, at the time of initial diagnosis many patients already have regional nodal metastases (45%) or even distant metastases (10%). Also noteworthy is the approximately 5% annual rate of second primaries in HNSCC patients, mostly occurring in the upper aerodigestive tract.

Probably 98% of PET studies in patients with head and neck cancer are performed using FDG as the radiotracer. Consequently, and similar to most other malignancies, our knowledge and experience is largely based on these FDG studies. For the purpose of this practical review we will therefore only discuss FDG-PET, although brief reference will be made to alternate tracers at the end of the text.

Neck Metastases from an Unknown Primary Tumor

This condition, also known as carcinoma of unknown primary, accounts for 3-15% of all cancer diagnoses and for approximately 1-2% of head and neck cancers. For practical purposes, this entity should be defined as the combination of: no history of previous malignancy, no clinical or laboratory evidence for primary neoplasm, neck mass that is histologically or cytologically proven to be carcinoma. Occurrence of nodal metastases in neck levels I-III increases the likelihood for a primary HNSCC. However, in 5-40% of cases a primary malignancy is never identified during diagnostic evaluation and long-term follow-up.

Role of Imaging

Cross-sectional imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]) are routinely used in these patients, but oftentimes without providing additional information. PET has been used for the evaluation of patients with unknown primary for a number of years. The number of patients studied exceeds 300 and the percentage of primary tumors detected is quoted from 10 to 60%.[1-11] This wide range of results is largely related to two factors: varying inclusion criteria and methods of verification. In particular the definition of "unknown primary" varies considerably between studies. Categorically speaking, the term unknown primary should only be used after clinical examination, CT/MRI and endoscopy have failed to reveal a primary tumor. Unfortunately, only few studies use such a strict definition. In addition, the sensitivity of PET is oftentimes stated incorrectly: if only lesions that were missed by PET but detected by other means are called as false negative, the resulting sensitivity will be much better than when all negative studies are classified as false negative (by definition, all patients with neck metastasis have a primary tumor somewhere in the body). A summary of larger PET studies in patients with unknown

Table 1. PET Performance in Detecting Unknown Primary Tumors with Cervical Lymphadenopathy (at Least 10 Patients, Full Article)

	Patients	PET Abnormality	PET Only Detected	TP	Unconf.	FP	FN	% Tumor Detected	More dz. on PET
Bohuslavizki et al[1]	44	15	All	15	1	5	0	34%	Y
Braams et al[11]	13	4	NR	4	0	0	1	31%	NR
Hanasono et al[10]	20	7	NR	7	4	NR	3	35%	Y
Jungehulsing et al[2]	27	7	All	6	1	0	NR	22%	Y
Fogarty et al[3]	21	8	All	1	2	5	0	5%	Y
Greven et al[4]	13	7	All	1	1	6	2	8%	NR
Mendenhall et al[5]	24	20	1	7	NR	NR	2	29%	Y
Stokkel et al[6]*	10	9	All	6	0	1	0	60%	Y
Regelink et al[7]	50	16	4	16	NR	2	0	32%	Y
Aassar et al[8]	15	10	5	8	0	2	0	53%	Y
Kole et al[9]	16	4	All	4	0	NR	3	25%	Y
Total	253	107		75			30		

NR, not reported.
*FDG-SPECT.

primary is shown in Table 1, and a patient example in Fig 1.

Potential reasons for a false-negative PET studies include a small primary tumor (although lesions as small as 4 mm can be detected as long as there is intense FDG uptake); low metabolic activity (cystic, necrotic tumor or lymph nodes); or the primary tumor was accidentally removed at time of neck dissection.

Practical Approach and Take-Home Message

Because of inconsistencies in patient selection and the reporting of results, the question of whether PET should be used at all in this clinical scenario has stirred some controversy.[12] However, we think that PET can be a valuable tool in patients with neck metastases from an unknown primary, provided that patients are appropriately selected. Indeed, we propose that these patients should undergo a thorough head and neck examination by an otorhinolaryngologist or head and neck surgeon, followed by FDG-PET. Other imaging studies rarely contribute valuable information, and it is extremely unlikely that these will identify a primary tumor that cannot be detected by PET. If the PET study is positive, biopsies can be obtained from the suggested location. If the PET is negative, panendoscopy with biopsy sampling from suspected locations (based on the location of the lymph node and statistical considerations) can be performed. Depending on the results of these biopsies, the patient may proceed to surgery or radiation therapy.

Primary Tumor Staging

PET for T-Staging

At the time the patient is referred for staging (imaging) studies, the primary tumor has already been diagnosed, and a clinical head and neck examination has assessed the status of lymph nodes in the neck. The first goal of imaging studies is therefore to determine the

extent of the primary tumor, in particular with regard to structures whose involvement may alter the surgical approach (eg, bone invasion, orbital invasion, skull base invasion, tumor "tracking" along nerves and blood vessels). This can be done by either CT or MRI, and PET has little to contribute in this regard. In the few studies that have addressed the ability of PET and CT/MRI to actually visualize a clinically proven primary tumor, PET generally had a higher sensitivity than other imaging studies. This is related to the fact that smaller or submucosal malignancies may be difficult to distinguish from adjacent tissues with anatomic imaging studies alone. For instance, in a recent study from Australia involving 40 patients with HNSCC (mostly tumors of the oral cavity), FDG-PET detected 35/40 primaries (88%), compared with CT, which only detected 18 of the 35 primaries imaged (51%). Of the 17 primaries not detected by CT, 11 were clearly visualized by FDG-PET.[13]

Nodal Staging

The second goal of PET imaging in primary staging is the assessment of the nodal status in the neck. The presence of nodal metastases is an independent prognostic factor for survival in patients with head and neck cancer, it decreases the overall survival by approximately one half.[14] The prognosis worsens additionally with the number of lymph nodes involved,[15] with extracapsular spread of nodal disease[16-18] and with metastases located in the lower neck.[19,20]

The presence and extent of nodal metastases may affect patient management. Early removal of neck nodal metastases also has prognostic implications.[21] Accurate nodal staging of the neck is therefore important.

The clinical neck examination and anatomic imaging studies suffer from a lack of sensitivity and specificity in
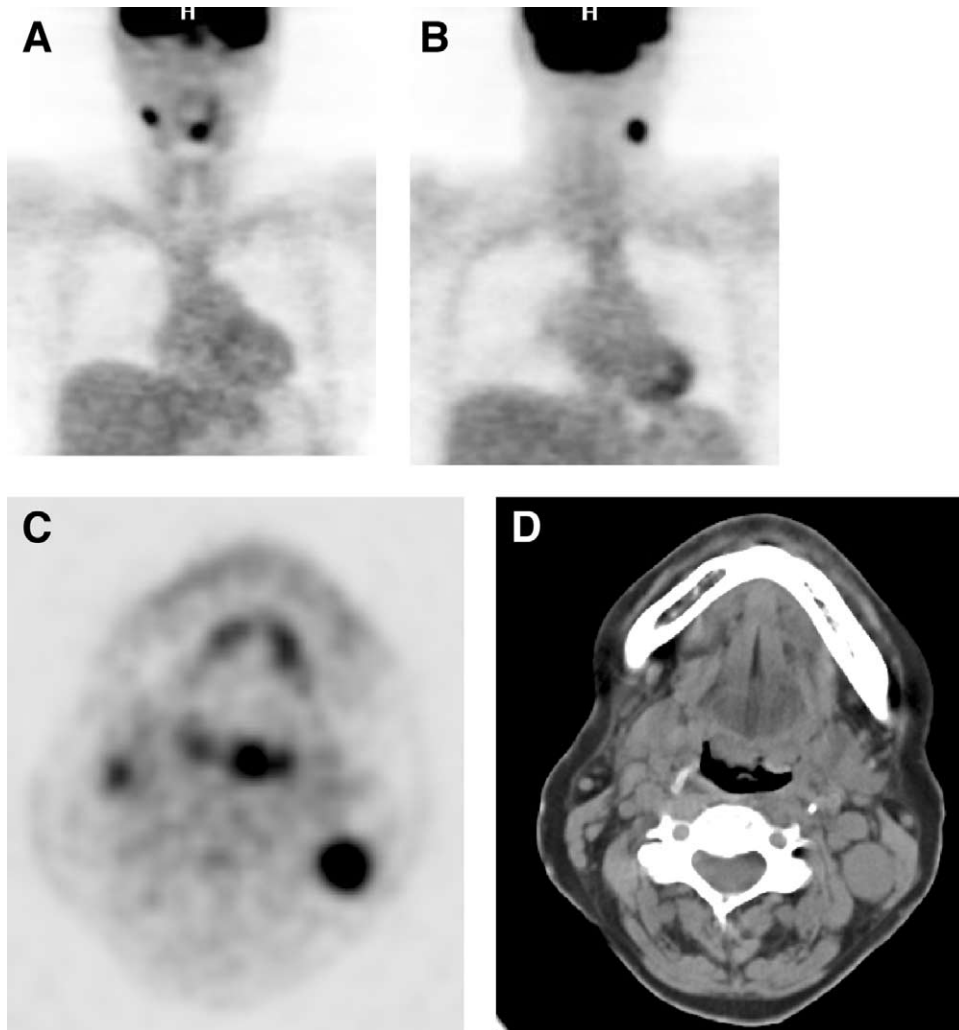
Fig 1. Carcinoma of unknown primary in a 56-year-old female with bilateral enlarged lymph nodes, proven to be carcinoma. Positron emission tomography was performed for detection of an unknown primary. An outside magnetic resonance imaging study (not shown here) only revealed cervical lymphadenopathy. Coronal (A, B) and transaxial (C) positron emission tomography images show abnormal fluorodeoxyglucose uptake in bilateral level II/II neck nodes and in the mid neck. The corresponding (noncontrast) computed tomography (D) does not demonstrate a clear abnormality, but on positron emission tomography/computed tomography fusion images the primary was clearly localized to the left vallecula and left base of tongue. Biopsy confirmed moderately differentiated squamous cell carcinoma.

assessing the extent of nodal disease (Table 2).[22-27] With CT and MRI lymph nodes are primarily characterized based on size criteria. Although other parameters, such as grouped location, central necrosis and contrast enhancement, can be used, CT and MRI frequently have false negative rates between 10% and 30%.

Numerous studies have compared the accuracy of anatomic imaging modalities and FDG-PET for the detection of nodal metastases in the neck.[13,24,27-32] A summary of findings is shown in Table 3. In most studies PET had a higher sensitivity and specificity than CT, MRI, or ultrasound. However, because of the lack of anatomic information PET alone may not be accurate in

determining the exact nodal station involved by metastases (eg, level II versus level III). It should also be noted that recently introduced superparamagnetic contrast agents, such as ferrum oxide particles, appear to increase the accuracy of MRI for nodal staging in the neck.[33,34]

Reasons for false-negative PET studies may include a small tumor burden in metastatic nodes, cystic degeneration of metastatic nodes only surrounded by a small rim of viable tumor tissue, low tracer uptake in the metastatic node, and imaging artifacts. Nodal metastases in close proximity to the primary tumor may not be detectable as separate hypermetabolic focus when the primary show very intense tracer uptake.

Table 2. Diagnostic Performance of Various Methods for Staging of Neck Lymph Nodes

Method	Sensitivity (Range)	Specificity (Range)
Palpation	60-75%	75-85%
CT/MR	61-97%	21-100%
PET	87-90%	80-93%
US	64-84%	66-100%

Averaged data from references 22-27.

Assessment of Distant Metastases and Synchronous Second Primary Malignancies

Distant metastases are rare in patients with head and neck cancers, but the frequency increases with higher T-stage and size and number of tumor-involved lymph nodes. Patients with nodal metastases in the lower neck or supraclavicular region have a higher chance for distant metastases, too. In general, patients with HNSCC have a higher propensity for synchronous second primaries as compared with many other malignancies. For instance, in a smaller series evaluating the role of FDG imaging in head and neck cancer, Stokkel and coworkers[35] found a synchronous second primary in 12 of 68 patients in their series, although a technically inferior dual-head gamma camera was used. Five of these second primaries were also detected by clinical examination, chest radiograph or CT, so that the PET detection rate was really 7/68, or 10%.

In a recent prospective study of 33 patients with stage II-IV carcinoma of the oral cavity, oropharynx and larynx, FDG-PET detected distant metastases or synchronous second primary tumors in the aerodigestive tract in almost 30% of cases (7 distant metastases and 3 synchronous second primary tumors).[36] Based on our own experience a second primary or distant metastases outside the neck will be detected in 3-8% of cases, depending on the stage and location of the primary tumor. Indeed, this was also reported in a large retrospective analysis, unrelated to PET imaging, where the risk for synchronous second primary tumors also approached 8%.[37]

Although the routine use of other staging modalities, such as bone scan, chest CT or abdominal ultrasound is not indicated because of the low yield of positive findings,[38,39] we recommend and routinely perform PET imaging from the skull base to the floor of the pelvis for appropriate N and M staging in patients with head and neck cancer. Both distant metastases and potential synchronous primaries in the aerodigestive tract are very likely to be hypermetabolic and therefore easily detectable by FDG-PET.

Practical approach and take-home message. FDG-PET has good sensitivity and specificity for the detection of primary tumors in the upper aerodigestive tract and a higher accuracy for nodal staging of the neck than any other imaging modality. Distant metastases or synchronous second primary tumors are occasionally detected; therefore, the imaged field of view should extend from the skull base to the floor of the pelvis.

Treatment Evaluation

Depending on the stage and location of the disease, treatment options in head and neck cancer include surgery, radiation therapy alone, or radiation therapy in

Table 3. Studies Comparing CT, MR, US, and PET with Histopathology for Nodal Staging of the Neck

	N	CT/MR/US	CT/MR/US		PET		Remarks
			Sen	Spec	Sen	Spec	
Kresnik et al[28]	24		58	58	100	91	Conventional imaging (CT, MR, US) ± 6 weeks of PET; PET upstaging in 20% of pts.
Stuckensen et al[29]	106	CT	66	74	70	82	Prospective study, 1196 lymph nodes, PET detected second primary or distant mets in 10 pts, maximum accuracy for any modality only 76%
		MR	64	69			
		US	84	68			
Di Martino et al[30]	50	CT	84	96	84	90	Prospective study
		US	84	88			Color duplex US
Stokkel et al[31]	54	CT	85	86	96	90	Prospective study, data per neck side
		US	64	100			US with fine needle
		US	82	66			US without fine needle
Adams et al[24]	60	CT	82	85	90	94	Prospective study, 117/1284 LN w/mets
		MR	80	79			
		US	79	–			
Kau et al[27]	70	CT	65	47	87	94	Prospective study, based on neck sites, LN > 1.5 cm or indirect signs
		MR	88	41			
McGuirt et al[32]	45	CT	82	–	82	82	Prospective study
Hannah et al[13]	40	CT	81	81	82	94	Prospective study

combination with (concurrent) chemotherapy, possibly followed by surgery. If surgery is the primary treatment modality, this may be followed by radiation therapy, depending on the stage and aggressiveness of the primary tumor, status of surgical margins etc. With the latter approach, imaging studies during or immediately at the end of therapy are usually not necessary. In contrast, patients with locally advanced disease (stage III-IV) may undergo combined chemo- and radiation therapy with curative intent, which may be followed by salvage surgery in case of residual or recurrent disease. In addition, protocols consisting of chemo- and radiation therapy now are also used in some patients with the intent of organ preservation (larynx, tongue). It is in these groups of patients that early assessment of treatment response (or detection of residual disease) is of critical importance because prompt salvage surgery improves local control of the disease. CT and MRI rely on structural changes and are notoriously unreliable in this setting. Because of treatment related edema and inflammation, which may cause alteration of normal tissue planes and nonspecific enhancement after administration of intravenous contrast, these studies frequently can not assess the presence of residual disease with sufficient accuracy. Metabolic PET imaging contributes valuable information in this setting. It allows for the early detection of local and regional disease whose treatment will improve local disease control with the extrapolation that this will also improve survival or at least quality of life.

Chemotherapy Alone or Combined Chemo- and Radiation Therapy

A number of studies have shown that PET can monitor the response to chemo- or radiation therapy in patients with head and neck cancer and may differentiate responders from nonresponders;[40-45] metabolic changes during therapy appear to correlate with tumor growth rate.[46]

Brun and coworkers[47] studied 47 patients with head and neck cancer undergoing radical radiation- or combined chemoradiation therapy. Almost two thirds of these patients had stage IV disease. FDG-PET was performed before and 1 to 3 weeks after the initiation of therapy (ie, during the course of treatment). PET data were analyzed using SUV and quantitative measurements (metabolic rate of glucose, MRGl). Patients with complete response had, on average, lower posttreatment SUV and MRGl than those without complete response, but there was considerable overlap. Interestingly, the pretreatment SUV was lower in patients who showed a complete response to therapy (median 8.0 versus 12.0). Posttreatment SUV was not different between responders and nonresponders (median 4.4 versus 7.7, $P = 0.07$), but quantitative measurements showed lower glucose metabolism in responders as compared with nonresponders (MRGl median 14 versus 27 μmol/min/100 g).

Goerres and coworkers[48] studied 26 patients with stage III-IV HNSCC, and PET was performed at 6 weeks after the end of combined chemo- and radiation therapy (median dose 70 Gy). PET correctly detected residual disease in 10 patients (38%) and correctly excluded residual disease in 14 patients; one patient each had a false-positive and false-negative study. Hence, the sensitivity and specificity were 91% and 93%, with an accuracy of 92% for the detection of residual disease, metastases or second primaries. Interestingly, in 2 patients the 6-week PET also revealed a second primary tumor or distant metastasis, which had not been detected at the time of initial staging.

In patients with locally advanced disease, chemotherapy or combined chemo- and radiation therapy are also used in the neoadjuvant setting. Neoadjuvant treatment is given to render locally advanced disease surgically resectable, to allow for organ preservation (for instance in patients with larynx cancer), to improve survival and reduce metastasis.

PET contributes valuable information in this setting. For instance, FDG-PET appeared to distinguish accurately between responders and nonresponders to neoadjuvant chemotherapy in an organ-conservation protocol.[45] All 27 patients enrolled had tissue biopsies taken before and after therapy. At the end of treatment 21 patients were found to be responders and 6 to be nonresponders. Using visual analysis and SUV, the study had a sensitivity of 90% and specificity of 83%. In another study in 15 patients undergoing neoadjuvant chemoradiation therapy, lesions with higher pretreatment SUV (>7) showed residual viable tumor cells after treatment in 3 of 8 cases, whereas all lesions with SUV <7 were treated successfully.[42] All 7 tumors with posttreatment SUV of <4 showed no viable cells on resection, whereas 3/7 tumors with posttreatment SUV >4 did show residual viable tumor cells. In another study in 23 patients the same authors separately analyzed the accuracy of various imaging modalities for the assessment of residual disease after neoadjuvant chemoradiation therapy:[44] FDG-PET was more accurate than MRI or CT in detecting residual disease (specificity 89% versus 41%, 59%) in the primary tumor following treatment, although no such difference was noted for nodal metastases.

Radiation Therapy Alone

Greven and coworkers have repeatedly investigated the role of FDG-PET in the assessment of response to radiation therapy.[49-51] One of their recent studies[51] evaluated 45 patients before and at 1, 4, 12 and 24 months after high-dose radiation therapy. Thirty-six patients were studied 1 month after radiation therapy. Of these, all six scans interpreted as positive for residual

disease were true positive, whereas 7 of the 28 scans interpreted as negative were false negative, and residual tumor was found in 4/5 equivocal studies. Twenty-eight patients had PET performed at 4 months after radiation therapy. All 18 negative scans were true negative, 6/7 positive scans were true positive and residual cancer was found in 2/3 equivocal scans. The authors concluded that imaging at 4 mos after radiation therapy was more accurate than at 1 month. However, it needs to be emphasized that no imaging studies were acquired between 1 and 4 months. In our own experience a time interval of 6 to 8 weeks after treatment is usually sufficient to avoid most false positive and false negative findings.

FDG-PET has the ability to detect patients with more aggressive disease before therapy and to differentiate between responders and nonresponders to (chemo-) radiation therapy. However, most studies suffer from limitations related to small sample size and the methods of data analysis (data dichotomized based on median SUV in study population, use of arbitrary cut-off values etc.). In addition, quantitative measurements of FDG utilization, as used in some of these studies, are not practical in a clinical routine setting. Larger, prospective studies in a well-defined setting are needed to determine the clinical value of PET in these patients conclusively.

Practical Approach and Take-Home Message

The treatment response to chemo- and radiation therapy can be monitored with FDG-PET. A negative PET scan obtained at least 6 weeks after the end of therapy excludes residual disease with high certainty. A positive scan obtained at least 6 weeks after end of therapy suggests residual disease, unless there are clinical signs of inflammation/infection to explain PET abnormalities. The clinical significance of PET changes during and immediately after the end of therapy is the subject of ongoing studies; these results should not be used in isolation to guide patient management decisions.

Recurrent Disease

The early detection of recurrent head and neck cancer is important in determining the ability to perform salvage surgery, which can improve the clinical outcome of these patients. For instance, patients with recurrent early stage HNSCC who undergo salvage surgery have a 70% 2-year relapse-free survival, whereas those with recurrent advanced stage disease HNSCC undergoing salvage surgery have a 22% 2-year RFS.[52] It is therefore critically important to detect potential recurrences early in the course of events. An imaging modality used for this purpose should have a high sensitivity for the detection of disease, but at the same time not yield too many false-positive findings.

CT and MRI, which rely on structural changes, are notoriously unreliable in this setting because of treatment related alterations of tissue planes, nonspecific contrast enhancement etc.[53,54] However, the PET interpretation may also be complicated because postsurgical changes can involve distortions of the normal anatomy related to resection and surgical reconstruction, involving various soft tissue flaps, bone grafts, bone plates, surgical obturators etc.[55,56]

The role of FDG-PET for the detection of local recurrent head and neck cancer was initially investigated in a number of smaller, retrospective studies.[25,50,57-59] It is now clearly established that FDG-PET has a high sensitivity and specificity for the detection of recurrent disease in patients with head and neck cancer, regardless of the primary treatment modality used (surgery versus radiation therapy).[10,25,28,57,60-69] Results of larger, more recent PET studies are shown in Table 4, and a patient example is shown in Fig 2. As a rule, clinically detectable recurrent disease is extremely unlikely in the setting of an entirely negative PET scan. FDG uptake, not related to tumor, can sometimes cause false positive (nontumor-related FDG uptake considered to represent tumor; see Fig 3) or false negative (tumor-related FDG uptake misinterpreted as normal variant, inflammation) interpretations. With adequate patient preparation, certain sources of nontumor-related FDG uptake can be eliminated or at least correctly identified (eg, laryngeal muscle uptake, radioactive saliva in the throat or vallecula epiglottica, nonspecific FDG uptake in brown fat tissue of the neck) but others cannot (treatment-related inflammation). Nevertheless, some false positive findings may be unavoidable. Accordingly, the sensitivity for the detection of recurrent head and neck cancer is consistently high, but specificity in the treated postsurgical area is lower than elsewhere in the neck or at remote sites, such as lung or bone,[68,69] (see Table 4). Across all studies the negative predictive value is consistently high. Therefore, one can conclude that patients with suspected recurrence but negative PET scan do not require any further evaluation. In contrast, positive predictive value and specificity are somewhat lower for local recurrence at or near the site of the primary tumor, related to a number of false-positive findings. Nevertheless, if used in a clinical algorithm, a positive PET scan requires a biopsy; if this biopsy is negative for recurrent cancer and does not provide reasons for a false-positive PET scan (inflammation, infection, radiation necrosis etc.), close clinical follow-up and potential repeat biopsy may be required.

Recurrence Versus Treatment-Related Changes

Some studies specifically confirmed the ability of FDG-PET to distinguish between tumor recurrence and radiation therapy-induced changes.[50,62,63,70] Teerhard and coworkers[63] studied 75 patients with laryngeal or oro-/hypopharyngeal cancer, using FDG and a dual-head gamma camera

Table 4. Imaging of Recurrent Head and Neck Cancer

	N	RD	CT/MR			PET			Remarks
			Sen	Spec	Acc	Sen	Spec	Acc	
Li et al[60]	43	22	53	79	66	91	86	88	
Hanasono et al[10]	34	7	75	65	75	100	85	90	
Kresnik et al[28]	15	7	62	57	60	88	57	73	
Stokkel et al[61]	48	24				100	71		Dual-head γ-camera
Fischbein et al[25]	35	–				100	94		For primary site
						93	77		For nodal disease
Lapela et al[65]	15	–				88	86		
McGuirt et al[62]	38	–			61			79	
Terhaard et al[63]	75	37				92	63		First PET only (4 mos. post RT) including follow-up scan if equivocal, dual-head gamma camera
						97	82		
Lonneux et al[64]	44	26	73	50	64	96	61	81	All pts; early + late PET
			25	38	33	100	25	50	<12 weeks after all therapy
			90	60	75	96	90	94	>12 weeks after all therapy
Lapela et al[65]	56	37	59/91	100/78	81/84	84/95	93/84	88/90	Sensitive vs. specific reading
Yen et al[66]	67	21	62	44	49	100	93	95	Nasopharyngeal only
Lowe et al[67]	44	16	38	85		100	93		Prospective, PET at 2 and 10 months for all findings
Wong et al[68]	143	72				96	72		
						97	79		Local recurrence at site of primary
						92	95		Regional disease elsewhere in neck
						94	96		Distant disease
Kunkel et al[69]	97	33				83	81		For all findings
						87	67		Local recurrence
						87	99		Nodal metastases
						71	93		Distant metastases, second primary

and visual image analysis. Local recurrence was eventually diagnosed in 37 patients. A negative FDG study correctly excluded recurrent disease in 24 patients, but missed it in 3 patients. A positive PET scan was less reliable, correctly identifying 34 cases of recurrence, but at the expense of 14 false-positive findings. Of note, the number of false-positive findings decreased on subsequent PET scans. The smallest tumor detected was 4 mm. The authors therefore suggested an approach whereby a positive PET scan, because it indicates high risk for recurrence, should trigger biopsy. If the biopsy is negative, a follow-up PET scan should be obtained; if the intensity of FDG uptake declines with time no further study is needed. Otherwise, repeat biopsy is suggested. Conversely, a negative PET scan almost certainly excludes recurrent disease (NPV-89%). In this context it also interesting that in this study, 160 laryngoscopies under anesthesia with biopsy were necessary to detect local recurrence in 37 of the 75 patients, translating into a sensitivity of 51%—a truly poor performance for any diagnostic test. Unless there is strong clinical suspicion for recurrence, repeated biopsies should therefore be avoided as these are associated with a higher rate of complication in the irradiated tissue, in particular in the larynx.

Role of SUV Measurements

Although initial studies created much hope that quantitative or SUV analysis might be a suitable means for the detection of recurrent disease,[50,57] subsequent work proved that this is clearly not the case. For instance, Lapela and coworkers[65] reported a wide overlap in SUVs for disease recurrence (range, 2.1-36.9) versus nontumor-related FDG accumulation (range, 1.5-9.3). Several authors have used ROC analysis to determine the best cut-off for an SUV that distinguishes between recurrent disease and benign conditions;[64,65,68] for instance, Wong and coworkers[68] found that an SUV of 3.2 provided the best trade-of between sensitivity (92%) and specificity (70%), yielding an area under the curve of 0.88 ± 0.02. These numbers may provide some guidance but may vary, for instance depending on the specific patient population and imaging protocol. Of note, there seems to be agreement, that interpretation of the PET study by an experienced PET reader provides the highest
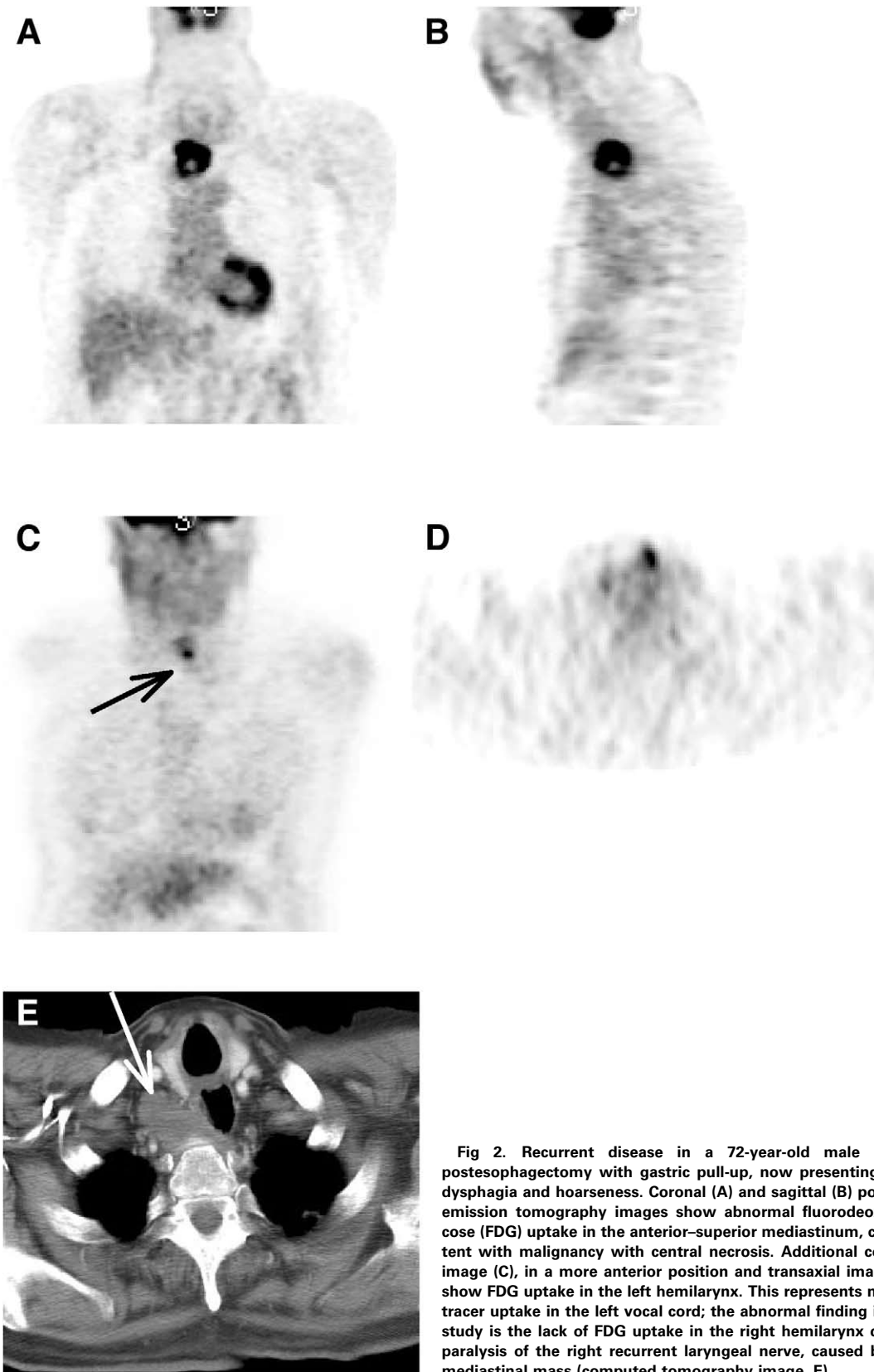
Fig 2. Recurrent disease in a 72-year-old male status postesophagectomy with gastric pull-up, now presenting with dysphagia and hoarseness. Coronal (A) and sagittal (B) positron emission tomography images show abnormal fluorodeoxyglucose (FDG) uptake in the anterior–superior mediastinum, consistent with malignancy with central necrosis. Additional coronal image (C), in a more anterior position and transaxial image (D) show FDG uptake in the left hemilarynx. This represents normal tracer uptake in the left vocal cord; the abnormal finding in this study is the lack of FDG uptake in the right hemilarynx due to paralysis of the right recurrent laryngeal nerve, caused by the mediastinal mass (computed tomography image, E).
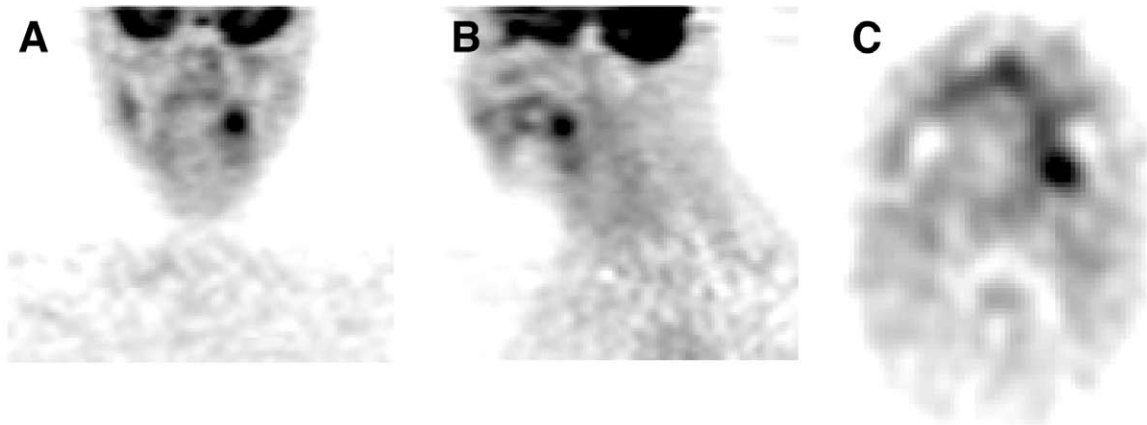
Fig 3. False-positive study of a 65-year-old male, status post chemo- and radiation therapy, for carcinoma at the base of tongue, now presenting with pain and trismus. Positron emission tomography images show abnormal fluorodeoxyglucose uptake in the left mandible (A, coronal; B, sagittal; C, transaxial). Physical examination revealed exposed, necrotic appearing bone of the mandible. Debridement and curettage were performed; the specimen showed acute and chronic osteomyelitis.

accuracy.[64,65,68] Hence, SUV measurements should be used judiciously; they may aid in the interpretation but are not a surrogate for readers experience and should not be the sole criterion on which study interpretation rests.

PET for Surveillance of High-Risk Patients

All of the above studies were conducted in patients who were clinically suspected of having recurrent carcinoma. In contrast, Lowe and coworkers[67] performed routine PET imaging in 44 patients with stage II or IV head and neck cancer who were at higher risk for recurrence. During the first year of follow-up, PET was performed at 2 and 10 months, thereafter as considered necessary by the treating physician. All patients participated in an organ-preservation protocol that involved neoadjuvant chemotherapy, radiation therapy and surgical salvage (if needed). Thirty patients completed their treatment and were considered NED at the end of the protocol. Of these, 16 developed recurrent disease and 14 remained NED during the first year of f/u. PET had a sensitivity of 100% and specificity of 93% for identifying recurrences during that time period. Notably, 5/16 recurrences were detected by PET only, while the other recurrences were also identified by CT/MR or clinical examination. Early detection of recurrent disease is likely to improve the success rate for any secondary therapy, but it is nevertheless difficult to justify such a surveillance strategy without further supporting data. Moreover, PET studies for the sole purpose of surveillance are currently not reimbursed.

Practical Approach and Take-Home Message

FDG-PET is highly accurate in the detection of recurrent HNSCC. The interpreting nuclear medicine physician should be familiar with treatment-related changes that can cause false-positive studies. A negative PET scan excludes recurrence with high certainty; positive PET findings should be assessed further by biopsy, unless there is clear clinical recurrence. If the biopsy is negative, a follow-up PET scan is suggested 2 to 3 months later. If the SUV decreases, malignancy is unlikely and no further intervention is needed. If the SUV is unchanged or increases, repeat biopsy is suggested, unless there is another obvious explanation, such as infection, fistula or radionecrosis.

Prognostic Value of FDG-PET Imaging in Patients with Head and Neck Cancer

Several studies have shown that FDG-PET by itself can assess the aggressiveness and proliferation rate of HNSCC[71-73] and therefore correlates with patient prognosis, regardless of the treatment modality used.[43,74,75] In both untreated patients as well as patients with recurrent disease, the intensity of FDG uptake in the tumor appears to predict the ultimate outcome after therapy.[68,69,74,75] In patients with recurrent disease, clinical PET interpretation and SUV are independent prognostic markers for relapse-free and overall survival[68,69] However, there is currently no proof that the information derived from such studies should alter the patient management; whether a clinically established treatment approach should be changed or modified in individuals with poor prognosis based on PET findings should be investigated further as part of research protocols.

PET/CT in Head and Neck Cancer

PET/CT is a new imaging modality providing an almost simultaneous acquisition of anatomic and metabolic imaging data. This modality has been used increasingly for clinical oncologic imaging since 2001. Emerging data
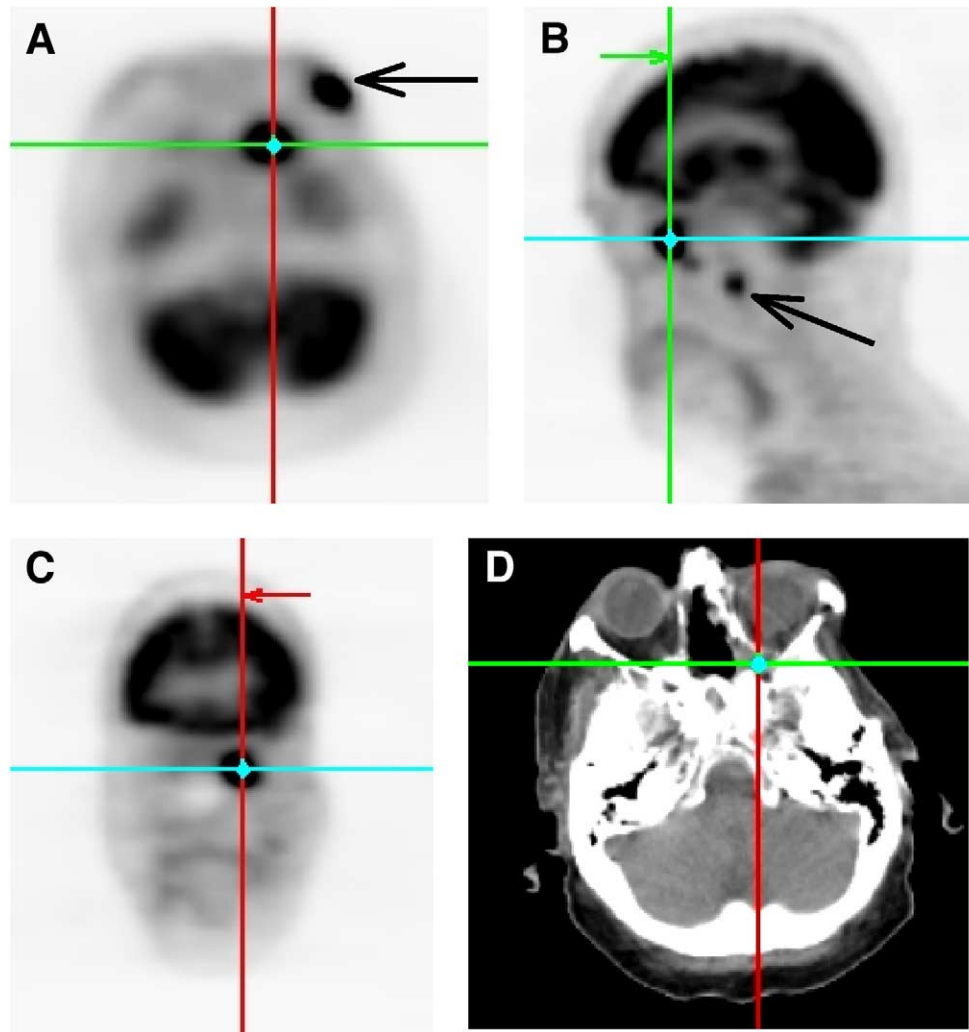
Fig 4.   Value of positron emission tomography/computed tomography (PET/CT) in a 66-year-old male status post craniofacial resection for olfactory neuroblastoma. Abnormal fluorodeoxyglucose uptake noted on transaxial (A), sagittal (B), and coronal (C) PET images localizes to the left orbit on corresponding CT (D) of a combined PET/CT study. In addition, the PET also shows recurrence in the left temporal bone (black arrow on transaxial PET) and in a retropharyngeal node (black arrow on sagittal PET). (Color version of figure is available online.)

demonstrate that the combination of PET and CT in one image set improves the anatomic localization of PET abnormalities, decreases the number of equivocal PET interpretations,[76] and improves the diagnostic accuracy for staging of lung and colorectal cancer as compared with PET or CT alone.[77-79] With regard to head and neck cancer we have outlined above that PET alone is a highly valuable imaging technique in the primary staging and detection of recurrent disease. Unfortunately, many PET interpretations oftentimes suffer from the lack of anatomic information in PET images. This is particularly critical in the head and neck region because of close proximity of various anatomic structures and the high frequency of normal variants in FDG uptake in the head and neck. Accordingly, we have

recently shown that in patients with head and neck cancer, PET/CT is a more accurate imaging modality than PET alone because PET/CT fusion imaging allows to establish a clear diagnosis (benign versus malignant) and localize abnormalities with high certainty (Fig 4). In addition, the routine clinical application of this new modality also translates into improvements in patient management.[80] Therefore, we now use PET/CT as the standard imaging modality in patients with head and neck cancer.

THYROID CARCINOMA

Nuclear medicine has been one of the mainstays of management of thyroid disease. Since the early 1950s, the whole body scan (WBS) using tracer dose of iodine-
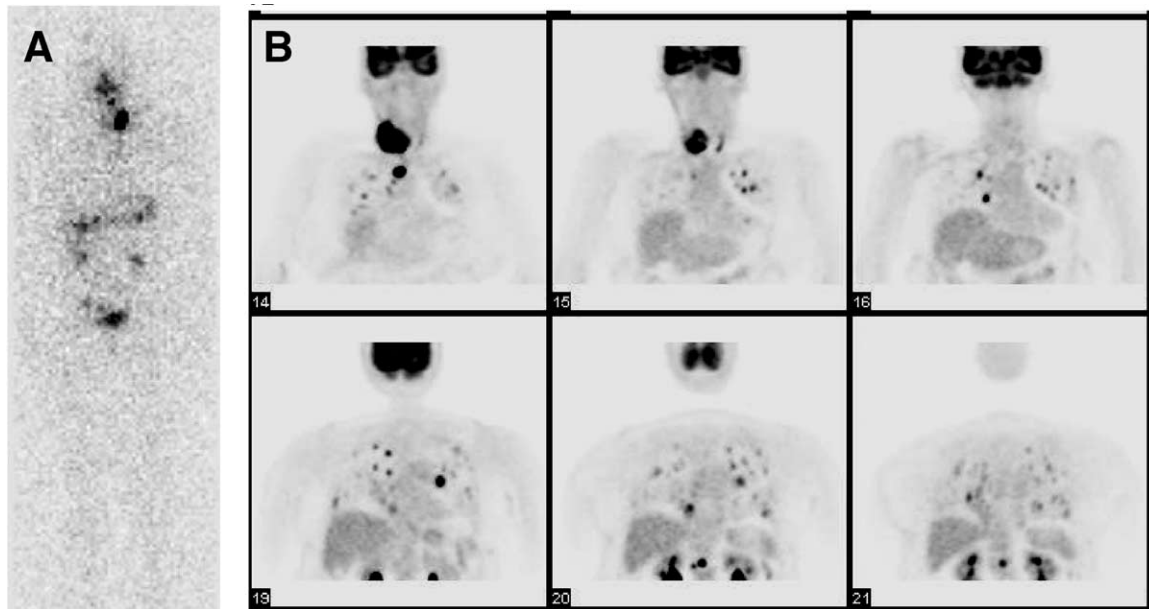
Fig 5.   FDG-PET in differentiated thyroid cancer in a 73-year-old female, status postsubtotal thyroidectomy 4 years ago for locally invasive well differentiated papillary thyroid cancer, followed by radioactive iodine ablation and external beam radiation to the neck. Recent computed tomography scan showed an enlarging mass in the right thyroid bed. [131]I WBS (A) showed a focus of intense uptake in the left thyroid bed, but no abnormality on the right side. Coronal slices of the positron emission tomography with fluorodeoxyglucose (B) show intense activity in the mass in the right thyroid bed, as well as multiple lung metastases. Fine-needle aspiration of the right thyroid bed mass confirmed thyroid cancer metastasis.

131 (^{131}I) has been widely used for detection of metastases of differentiated thyroid cancer (DTC). High dose ^{131}I has also been widely used for the ablation of thyroid remnant in the neck as well as therapy of metastatic diseases detected on the diagnostic WBS. The efficacy of this approach has been confirmed repeatedly in multiple large studies.[81-83] The management of thyroid cancer patients changed in the early 1970s with the clinical introduction of serial thyroglobulin measurements; this is now considered one of the most sensitive tests in the detection of metastatic DTC.[84] Indeed, a recent consensus report[85] proposed a surveillance guideline using only thyrotropin (TSH) stimulated thyroglobulin levels for low risk patients who have undergone total or near total thyroidectomy and ^{131}I ablation. Routine use of WBS in this group of patients is deemed not necessary. In contrast, WBS is still indicated for high-risk patients or patients with elevated serum thyroglobulin. Controversy exists regarding the management of patients with high serum thyroglobulin and negative WBS. Empirical treatment with a therapeutic dose of ^{131}I will result in a positive post therapy scan and a decline in the serum thyroglobulin level in the majority of these patients,[86,87] although it remains to be seen if this strategy results in longer survival.[88] FDG-PET can localize metastatic disease in a number of these patients and thereby guide further management.

PET-FDG in Differentiated Thyroid Cancer

Early studies found a low sensitivity of FDG-PET in the detection of metastases.[89] However, others reported a sensitivity of 50% in 58 unselected patients with DTC, thyroidectomy and prior radioactive iodine (RAI) ablation,[90] and in a large multicenter study with un-selected patients, the sensitivity of FDG-PET for localizing metastatic disease in patients with DTC was 75%.[91]

As early as 1987, Joensuu and coworkers[89] noticed metabolic heterogeneity between metastases of DTC in a study showing tumors that accumulated only FDG, only ^{131}I, or both. This was confirmed in more recent studies.[92,93] It became apparent that there were patients with positive WBS but negative FDG-PET and vice versa. Even in the same patient the accumulation of FDG and iodine may differ between different metastatic sites (Fig 5). Feine and coworkers[94] coined the term "flip flop" in describing the alternating pattern of either ^{131}I or FDG uptake in thyroid cancer metastases.

The utility of FDG-PET scan in patients with elevated serum thyroglobulin and negative WBS was confirmed in several studies,[95-99] and the sensitivity of FDG-PET in detecting metastases in these cases ranges from 71% to 94%. For instance, Wang and coworkers reported FDG-PET detected metastatic disease in 12/17 patients (71%) with elevated thyroglobulin and negative WBS.[97] In this series PET was also positive in 5/16 patients with low

thyroglobulin but high clinical suspicion, although only 2 findings were true positive. Helal and coworkers prospectively looked at 37 patients with DTC who had undergone resection, RAI ablation and presented with elevated thyroglobulin levels but negative WBS. FDG-PET scan was positive in 28 patients (76%), including 19 of 27 patients with no previously detected metastases by conventional imaging.[98] In a prospective study of 24 patients with DTC, negative WBS and elevated thyroglobulin levels, Frillings and coworkers reported a sensitivity of 94.6% in the detection of metastases, with specificity of 25%. PET results changed surgical tactics in 9/24 patients.[99] Schluter studied 118 PET scans in 64 thyroid cancer patients with elevated serum thyroglobulin (n = 48) or clinical suspicion of metastases (n = 16) and negative WBS.[100] The positive predictive value of FDG-PET scan was 83% (34/41) whereas the negative predictive value was 25% (5/20). Treatment was directly changed in 19/24 patients with true positive PET studies (30% of the entire cohort). They also pointed out that true positive FDG-PET findings were correlated positively with increasing serum thyroglobulin levels.

In addition to lesion detectability, there is also evidence that FDG-PET is an independent prognostic indicator in thyroid cancer.[93,94,101,102] In a study by Wang and coworkers., which included 125 patients with negative WBS, positive FDG-PET, elevated thyroglobulin with a clinical follow-up of up to 41 months, multivariate analysis demonstrated that the single strongest predictor of survival was the volume of FDG-avid disease.[101] More recently the same group showed strong inverse correlation between the SUV for FDG uptake in metastatic lesions and survival in thyroid cancer patients.[102]

The WBS with ^{131}I is more sensitive for localizing recurrent or metastatic disease when TSH levels are elevated, either due to withdrawal of thyroid hormone replacement therapy or due to administration of exogenous TSH. However, there is no consensus regarding whether an FDG-PET should also be performed under TSH stimulation, although it has been shown that the expression of glucose transporters and glucose uptake in (cultured) thyroid cells is increased with TSH stimulation.[103,104] Earlier studies employed different patient preparations.[90,92,97] One study suggested that the state of TSH stimulation did not affect results[97] and one multicenter study even showed lower sensitivity of FDG-PET when imaging was performed during TSH stimulation (67% as compared with 91% during thyroid hormone therapy). However, more recent studies seem to suggest that sensitivity or at least the clarity of findings improves with TSH stimulation. For instance, Moog and coworkers studied 10 patients prospectively with FDG-PET both under TSH suppression as well as in the hypothyroid, TSH stimulated state.[105] They found an average increase of 63% in the tumor to background ratio after

TSH stimulation for 15 of the 17 lesions that showed FDG uptake (decreased background activity and increased tumor uptake). In one patient, a lesion was seen in the thyroid bed only under TSH stimulation. Petrich and coworkers studied 30 patients with negative WBS and elevated thyroglobulin levels and compared FDG-PET images obtained under TSH suppression with those obtained under stimulation with recombinant human TSH (rhTSH).[106] They found more "tumor-like lesions" (78 versus 22) in more patients (19 versus 9) when patients had received rhTSH. Tumor to background ratios (2.54 versus 5.51) and SUV (2.77 versus 2.05) were also higher with TSH stimulation.

In conclusion, FDG-PET is useful in patients with clinical evidence of metastatic DTC but negative WBS. It serves to identify sites of disease, providing valuable information in directing further investigation and management. If a solitary metastasis is confirmed with CT or MRI, surgical resection with curative intent is indicated. Nonresectable regional disease can be treated with external beam irradiation, while widespread disease may be amenable to experimental chemotherapy. Identification of distant metastases may also spare the patient the morbidity of aggressive local curative maneuvers.

Hürthle Cell Carcinoma

Hürthle cell cancer is a histologic subtype of DTC that is clinically more aggressive. The tumor frequently shows little or no iodine uptake, but can be identified with FDG-PET: a meta-analysis of two studies and 35 patients showed a sensitivity of 92% and specificity of 82%.[107] A sensitivity of 92% (12/13 patients) was also reported in another recent study.[108] More importantly, in 7 of these 13 patients PET showed disease not identified by other imaging methods.

Anaplastic Thyroid Cancer

This is an extremely aggressive tumor and imaging is not required for staging, since all patients are classified as stage IV at diagnosis. As a result FDG-PET scan in anaplastic thyroid cancer has not been studied systemically. However, in our own experience and in some case reports[89] this malignancy usually shows intense FDG uptake, and in selected cases FDG-PET may be helpful in directing treatment and evaluating the efficacy of therapy (Fig 6).

Medullary Thyroid Cancer

Medullary thyroid cancer is a rare calcitonin secreting tumor originating from the parafollicular C cells. The primary treatment modality is surgical resection. A PET study may be requested in patients with high serum calcitonin level after surgery. The number of patients studied for this purpose is limited, but it appears that FDG-PET can identify metastatic disease more fre-
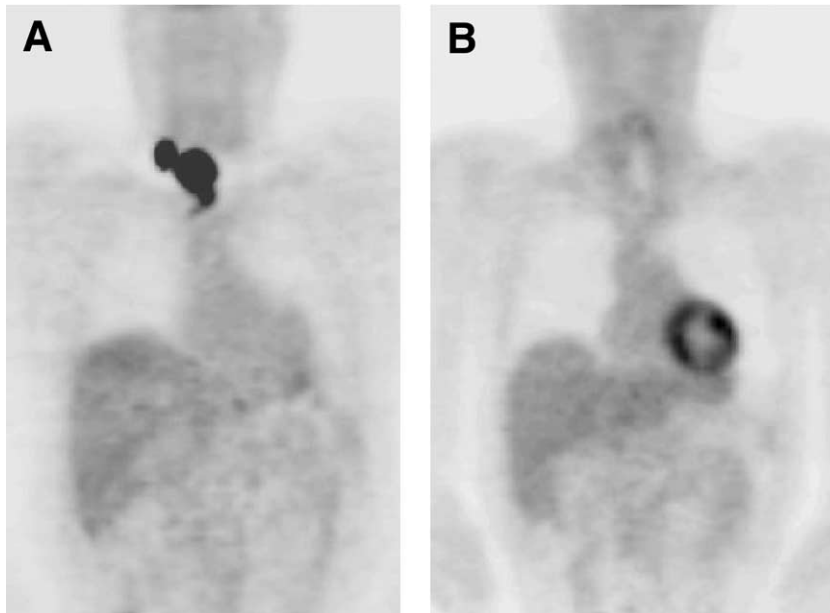
Fig 6. Anaplastic thyroid carcinoma. This 52-year-old male patient had local tumor recurrence after a complete thyroidectomy for anaplastic thyroid cancer. Positron emission tomography for staging of recurrent disease (A) showed intense fluorodeoxyglucose uptake in the right thyroid bed and a right supraclavicular lymph node. He was treated with external beam radiation and chemotherapy with good response, both clinically and on follow-up positron emission tomography (B). Three years later he was still alive and disease free.

quently than other imaging studies. A study of 20 patients reported a sensitivity of 76%,[109] and in a large multicenter study the sensitivity of 78% among 55 patients in whom histologic confirmation was obtained.[110] Interestingly, there was no correlation between the calcitonin level and the probability of lesion detection. Indeed it has been suggested that more undifferentiated cancer, which secretes less calcitonin, may show higher FDG uptake, analogous to the situation in DTC. Novel, more specific PET tracers, such as 6-^{18}F-fluorodopamine[111] or ^{18}F-DOPA[112] may be more appropriate for the detection of recurrent or metastatic medullary thyroid cancer.

Thyroid Incidentaloma

The normal thyroid gland shows low grade FDG uptake or is usually not visualized on the whole-body FDG-PET scan. Occasionally, diffusely or focally increased FDG uptake is seen as an incidental finding in the thyroid gland. In a large series of patients it was proven that diffuse thyroid FDG uptake is usually an indicator of chronic thyroiditis.[113] In contrast, focal FDG activity in the thyroid gland has been associated with malignancy.[114,115] In a retrospective review of over four thousand patients, Cohen and coworkers found incidental diffuse thyroid FDG uptake in 31 patients (0.69%) and focal uptake in 71 patients (1.57%).[116] Fourteen of the patients with focal uptake had thyroid biopsy: 7 had thyroid cancer, and the other 7 had benign pathology (nodular or lymphoid hyperplasia and atypical cell of indeterminate origin). Patients with malignant lesions had a significantly higher SUV (6.92 ± 1.54), compared with those with benign lesions (3.37 ± 0.21, $P = 0.04$).

The one patient with diffuse uptake and biopsy had Hashimoto's thyroiditis. Among 1330 subjects (999 cancer patients, 331 healthy subjects undergoing cancer screening) Kang and coworkers[117] noted incidental diffuse thyroid FDG uptake in 8 (0.6%) and focal uptake in 21 individuals (1.58%). Four of the 15 focal incidentalomas (27%) whose histological diagnoses were available showed papillary carcinoma. Hence the risk of cancer was lower than in previous studies, but still large enough to warrant further evaluation of such findings. Again, the SUV in malignant lesions was higher than in benign lesions (16.5 ± 4.7 versus 6.5 ± 3.8). Of note, the prevalence of thyroid incidentaloma was similar for cancer patients and healthy individuals. All eight patients with diffuse FDG uptake in the thyroid glands had clinical signs and symptoms of thyroiditis.

In summary, diffusely increased thyroid FDG uptake is most likely benign, usually due to chronic thyroiditis, whereas focal FDG uptake in the thyroid gland has a significant risk of being malignant (27-50%); histologic diagnosis should therefore be obtained for focal lesions if the nature of the thyroid disease changes management.

PET Imaging with [124]Iodine

[124]Iodine has a half-life of 4.2 days and a relatively complex decay scheme, with 22% of the disintegrations producing positrons of relatively high energies (1532 keV and 2135 keV), as well as a number of high energy gamma and X-rays, with energy as high as 1691 keV. Despite the high abundance of high energy gamma photons images of satisfactory quality can be acquired and quantitation of tracer uptake can be performed with only minor degradation in image resolution and quanti-

tation.[118] Indeed, PET with [124]I provides images of higher spatial resolution and lesion contrast compared with either planar scintigraphy or SPECT using ^{131}I, resulting in better lesion detection. The recent introduction of PET/CT has improved the localization of focal [124]I accumulation.[119] This is invaluable in [124]I imaging where most normal structures show little uptake, making localization of lesions difficult, if not impossible. The main purpose of [124]I PET imaging is lesion dosimetry, which would provide a more scientific basis for determining the necessary activity for treatment with [131]Iodine.[120,121] However, because of problems with radiopharmaceutical availability and cost, it is unlikely that iodine-124 PET dosimetry would be routinely used clinically.

CONCLUSION

PET imaging with FDG has become standard clinical practice in patients with head and neck cancer. It contributes valuable information in the primary staging of the disease, in particular in nodal staging of the neck and in the assessment for distant metastases or synchronous second primary malignancies. FDG-PET is very accurate in the detection of recurrent disease and should be used as the imaging modality of choice in patients at high risk for or with clinically suspected recurrence. PET can be used for the treatment evaluation in patients undergoing chemotherapy or combined chemo- and radiation therapy. Imaging at least 6 weeks after the end of therapy appears more accurate. Because the intensity of tracer uptake in tumor tissue correlates with tumor proliferation and aggressiveness, FDG-PET provides independent prognostic information in both patients with primary and recurrent HNSCC with regard to relapse-free and overall survival. PET imaging with various radiolabeled amino acids does not appear to be superior to FDG imaging in head and neck cancer. The recent introduction of PET/CT fusion imaging into clinical practice has improved the accuracy of PET interpretation in patients with head and neck cancer. Due to shorter imaging time, greater certainty and higher accuracy in image interpretation and a positive effect on patient management, all patients with head and neck cancer in our institution are now imaged exclusively by PET/CT.

In patients with evidence of recurrent or metastatic thyroid carcinoma but negative WBS, FDG-PET shows metastatic disease in up to 90% of cases. In patients with medullary thyroid cancer with elevated calcitonin levels following thyroidectomy, FDG-PET has a sensitivity of 70-75% for localizing metastatic disease. Incidentally noted intense focal FDG uptake in the thyroid gland can be related to thyroid cancer in 25 to 50% of cases and should therefore be evaluated further if a proven malignancy would cause a change in patient management.

REFERENCES

1. Bohuslavizki KH, Klutmann S, Kroger S, et al: FDG-PET detection of unknown primary tumors. J Nucl Med 41:816-822, 2000

2. Jungehulsing M, Scheidhauer K, Damm M2[F]-fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. Otolaryngol Head Neck Surg 123:294-301, 2000

3. Fogarty GB, Peters LJ, Stewart J, et al: The usefulness of fluorine 18-labelled deoxyglucose positron emission tomography in the investigation of patients with cervical lymphadenopathy from an unknown primary tumor. Head Neck 25:138-145, 2003

4. Greven KM, Keyes JW Jr, Williams DW 3rd, et al: Occult primary tumors of the head and neck: Lack of benefit from positron emission tomography imaging with 2-[F-18]fluoro-2-deoxy-D-glucose. Cancer 86:114-118, 1999

5. Mendenhall WM, Mancuso AA, Parsons JT, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Head Neck 20:739-744, 1998

6. Stokkel MP, Terhaard CH, Hordijk GJ, et al: The detection of unknown primary tumors in patients with cervical metastases by dual-head positron emission tomography. Oral Oncol 35:390-394, 1999

7. Regelink G, Brouwer J, de Bree R, et al: Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. Eur J Nucl Med Mol Imaging 29:1024-1030, 2002

8. AAssar O, Fischbein NJ, Caputo GR, et al: Metastatic head and neck cancer: role and usefulness of FDG-PET in locating occult primary tumors. Radiology 210:177-181, 1999

9. Kole AC, Nieweg OE, Pruim J, et al: Detection of unknown occult primary tumors using positron emission tomography. Cancer 82:1160-1166, 1998

10. Hanasono MM, Kunda LD, Segall GM, et al: Uses and limitations of FDG positron emission tomography in patients with head and neck cancer. Laryngoscope 109:880-885, 1999

11. Braams JW, Pruim J, Kole AC, et al: Detection of unknown primary head and neck tumors by positron emission tomography. Int J Oral Maxillofac Surg 26:112-115, 1997

12. Nieder C, Gregoire V, Ang KK: Cervical lymph node metastases from occult squamous cell carcinoma: cut down a tree to get an apple? Int J Radiat Oncol Biol Phys 50:727-733, 2001

13. Hannah A, Scott AM, Tochon-Danguy H, et al: Evaluation of 18 F-fluorodeoxyglucose positron emission tomography and computed tomography with histopathologic correlation in the initial staging of head and neck cancer. Ann Surg 236:208-217, 2002

14. O'Brien C, Smith J, Soong S, et al: Neck dissection with and without radiotherapy—prognostic factors, patterns of recurrence and survival. Am J Surg 152:456-463, 1986

15. Leemans CR, Tiwari R, Nauta JJ, et al: Recurrence at the primary site in head and neck cancer and the significance of

neck lymph node metastases as a prognostic factor. Cancer 73:187-190, 1994

16. Johnson J, Barnes E, Myers E: The extracapsular spread of tumors in cervical node metastasis. Arch Otolaryngol Head Neck Surg 107:725-728, 1981

17. Johnson JT, Myers EN, Bedetti CD, et al: Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. Arch Otolaryngol 111:534-537, 1985

18. Snyderman NL, Johnson JT, Schramm VL Jr, et al: Extracapsular spread of carcinoma in cervical lymph nodes. Impact upon survival in patients with carcinoma of the supraglottic larynx. Cancer 56:1597-1599, 1985

19. Grandi C, Boracchi P, Mezzanotte G, et al: Analysis of prognostic factors and proposal of a new classification for nasopharyngeal cancer. Head Neck 12:31-40, 1990

20. Jones AS, Roland NJ, Field JK, et al: The level of cervical lymph node metastases: their prognostic relevance and relationship with head and neck squamous carcinoma primary sites. Clin Otolaryngol 19:63-69, 1994

21. Haddadin KJ, Soutar DS, Oliver RJ, et al: Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head Neck 21:517-525, 1999

22. van den Brekel MW, Stel HV, Castelijns JA, et al: Cervical lymph node metastasis: Assessment of radiologic criteria. Radiology 177:379-384, 1990

23. Curtin H, Ishwararn H, Mancuso H, et al: Comparison of CT and MRI imaging in staging of neck metastases. Radiology 207:123-130, 1998

24. Adams S, Baum RP, Stuckensen T, et al: Prospective comparison of 18F-FDG-PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med 25:1255-1260, 1998

25. Fischbein NJ, Os AA, Caputo GR, et al: Clinical utility of positron emission tomography with 18F-fluorodeoxyglucose in detecting residual/recurrent squamous cell carcinoma of the head and neck. AJNR Am J Neuroradiol 19:1189-1196, 1998

26. Kao CH, Hsieh JF, Tsai SC, et al: Comparison of 18-fluoro-2-deoxyglucose positron emission tomography and computed tomography in detection of cervical lymph node metastases of nasopharyngeal carcinoma. Ann Otol Rhinol Laryngol 109:1130-1134, 2000

27. Kau R, Alexiou C, Laubenbacher C, et al: Lymph node detection of head and neck squamous cell carcinomas by positron emission tomography with fluorodeoxyglucose F 18 in a routine clinical setting. Arch Otolaryngol Head Neck Surg 125:1322-1328, 1999

28. Kresnik E, Mikosch P, Gallowitsch HJ, et al: Evaluation of head and neck cancer with 18F-FDG-PET: a comparison with conventional methods. Eur J Nucl Med 28:816-821, 2001

29. Stuckensen T, Kovacs AF, Adams S, et al: Staging of the neck in patients with oral cavity squamous cell carcinomas: A prospective comparison of PET, ultrasound, CT and MRI. J Craniomaxillofac Surg 28:319-24, 2000

30. Di Martino E, Nowak B, Hassan HA, et al: Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. Arch Otolaryngol Head Neck Surg 126:1457-61, 2000

31. Stokkel MP, ten Broek FW, Hordijk GJ, et al: Preoperative evaluation of patients with primary head and neck cancer using dual-head 18fluorodeoxyglucose positron emission tomography. Ann Surg 231:229-34, 2000

32. McGuirt WF, Williams DW 3rd, Keyes JW Jr, et al: A comparative diagnostic study of head and neck nodal metastases using positron emission tomography. Laryngoscope 105:373-375, 1995

33. Anzai Y, Piccoli CW, Outwater EK, et al: Evaluation of neck and body metastases to nodes with ferumoxtran 10-enhanced MR imaging: phase III safety and efficacy study. Radiology 228:777-788, 2003

34. Mack MG, Balzer JO, Straub R, et al: Superparamagnetic iron oxide-enhanced MR imaging of head and neck lymph nodes. Radiology 222:239-244, 2002

35. Stokkel MP, Moons KG, ten Broek FW, et al: 18F-fluorodeoxyglucose dual-head positron emission tomography as a procedure for detecting simultaneous primary tumors in cases of head and neck cancer. Cancer 86:2370-2377, 1999

36. Schwartz DL, Rajendran J, Yueh B, et al: Staging of head and neck squamous cell cancer with extended-field FDG-PET. Arch Otolaryngol Head Neck Surg 129:1173-1178, 2003

37. Schwartz LH, Ozsahin M, Zhang GN, et al: Synchronous and metachronous head and neck carcinomas. Cancer 74:1933-1938, 1994

38. Onizawa K, Yoshida H: Evaluation of 67 Ga citrate and 99m Tc bone scintigraphy at initial examination for primary oral squamous cell carcinoma. J Oral Maxillofac Surg 61:913-917, 2003

39. Nilssen EL, Murthy P, McClymont L, et al: Radiological staging of the chest and abdomen in head and neck squamous cell carcinoma–are computed tomography and ultrasound necessary? J Laryngol Otol 113:152-154, 1999

40. Minn H, Paul R, Ahonen A: Evaluation of treatment response to radiotherapy in head and neck cancer with fluorine-18 fluorodeoxyglucose. J Nucl Med 29:1521-1525, 1988

41. Rege SD, Chaiken L, Hoh CK, et al: Change induced by radiation therapy in FDG uptake in normal and malignant structures of the head and neck: quantitation with PET. Radiology 189:807-812, 1993

42. Kitagawa Y, Sadato N, Azuma H, et al: FDG-PET to evaluate combined intra-arterial chemotherapy and radiotherapy of head and neck neoplasms. J Nucl Med 40:1132-1137, 1999

43. Kitagawa Y, Sano K, Nishizawa S, et al: FDG-PET for prediction of tumour aggressiveness and response to intra-arterial chemotherapy and radiotherapy in head and neck cancer. Eur J Nucl Med Mol Imaging 30:63-71, 2003

44. Kitagawa Y, Nishizawa S, Sano K, et al: Prospective comparison of 18F-FDG-PET with conventional imaging modalities (MRI, CT, and 67Ga scintigraphy) in assessment of combined intraarterial chemotherapy and radiotherapy for head and neck carcinoma. J Nucl Med 44:198-206, 2003

45. Lowe VJ, Dunphy FR, Varvares M, et al: Evaluation of chemotherapy response in patients with advanced head and neck cancer using [F-18]fluorodeoxyglucose positron emission tomography. Head Neck 19:666-674, 1997

46. Reisser C, Haberkorn U, Dimitrakopoulou-Strauss A, et al: Chemotherapeutic management of head and neck malignancies with positron emission tomography. Arch Otolaryngol Head Neck Surg 121:272-276, 1995

47. Brun E, Kjellen E, Tennvall J, et al: FDG-PET studies during treatment: Prediction of therapy outcome in head and neck squamous cell carcinoma. Head Neck 24:127-135, 2002

48. Goerres GW, Schmid DT, Bandhauer F, et al: Positron emission tomography in the early follow-up of advanced head and neck cancer. Arch Otolaryngol Head Neck Surg 130:105-109; discussion 120-121, 2004

49. Greven KM, Williams DW 3rd, Keyes JW Jr, et al: Positron emission tomography of patients with head and neck carcinoma before and after high dose irradiation. Cancer 74:1355-1359, 1994

50. Greven KM, Williams DW 3rd, Keyes JW Jr, et al: Distinguishing tumor recurrence from irradiation sequelae with positron emission tomography in patients treated for larynx cancer. Int J Radiat Oncol Biol Phys 29:841-845, 1994

51. Greven KM, Williams DW 3rd, McGuirt WF Sr, et al: Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. Head Neck 23:942-946, 2001

52. Goodwin WJ Jr: Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: When do the ends justify the means? Laryngoscope 110:1-18, 2000

53. van den Brekel MW: Lymph node metastases: CT and MRI. Eur J Radiol 33:230-238, 2000

54. Anzai Y, Carroll WR, Quint DJ, et al: Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18]fluoro-D-glucose PET and MR imaging diagnoses. Radiology 2000:135-141, 1996

55. Cordeiro P: General principles of reconstructive surgery for head and neck cancer, in Harrison L, Sessions R, Hong W (eds): Head and Neck Cancer. A Multidisciplinary Approach. Philadelphia, Lippincott-Raven, 1999, pp 197-216

56. Zlotolow I: Dental oncology and maxillofacial prosthetics, in Harrison L, Sessions R, Wong W (eds): Head and Neck Cancer. A Multidisciplinary Approach. Philadelphia, Lippincott-Raven, 1999, pp 151-168

57. Lapela M, Grenman R, Kurki T, et al: Head and neck cancer: detection of recurrence with PET and 2-[F-18]fluoro-2-deoxy-D-glucose. Radiology 197:205-211, 1995

58. McGuirt WF, Greven KM, Keyes JW Jr, et al: Positron emission tomography in the evaluation of laryngeal carcinoma. Ann Otol Rhinol Laryngol 104:274-278, 1995

59. Rege S, Maass A, Chaiken L, et al: Use of positron emission tomography with fluorodeoxyglucose in patients with extracranial head and neck cancers. Cancer 73:3047-3058, 1994

60. Li P, Zhuang H, Mozley PD, et al: Evaluation of recurrent squamous cell carcinoma of the head and neck with FDG positron emission tomography. Clin Nucl Med 26:131-135, 2001

61. Stokkel MP, Terhaard CH, Hordijk GJ, et al: The detection of local recurrent head and neck cancer with fluorine-18 fluorodeoxyglucose dual-head positron emission tomography. Eur J Nucl Med 26:767-773, 1999

62. McGuirt WF, Greven KM, Keyes JW Jr, et al: Laryngeal radionecrosis versus recurrent cancer: a clinical approach. Ann Otol Rhinol Laryngol 107:293-296, 1998

63. Terhaard CH, Bongers V, van Rijk PP, et al: F-18-fluoro-deoxy-glucose positron-emission tomography scanning in detection of local recurrence after radiotherapy for laryngeal/pharyngeal cancer. Head Neck 23:933-941, 2001

64. Lonneux M, Lawson G, Ide C, et al: Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope 110:1493-1497, 2000

65. Lapela M, Eigtved A, Jyrkkio S, et al: Experience in qualitative and quantitative FDG-PET in follow-up of patients with suspected recurrence from head and neck cancer. Eur J Cancer 36:858-867, 2000

66. Yen RF, Hung RL, Pan MH, et al: 18-fluoro-2-deoxy-glucose positron emission tomography in detecting residual/recurrent nasopharyngeal carcinomas and comparison with magnetic resonance imaging. Cancer 98:283-287, 2003

67. Lowe VJ, Boyd JH, Dunphy FR, et al: Surveillance for recurrent head and neck cancer using positron emission tomography. J Clin Oncol 18:651-658, 2000

68. Wong RJ, Lin DT, Schoder H, et al: Diagnostic and prognostic value of [(18)F]fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol 20:4199-4208, 2002

69. Kunkel M, Forster GJ, Reichert TE, et al: Detection of recurrent oral squamous cell carcinoma by [18F]-2-fluorodeoxyglucose-positron emission tomography: implications for prognosis and patient management radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. Cancer 98:2257-2265, 2003

70. Farber LA, Benard F, Machtay M, et al: Detection of recurrent head and neck squamous cell carcinomas after radiation therapy with 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography. Laryngoscope 109:970-975, 1999

71. Minn H, Clavo AC, Grenman R, et al: In vitro comparison of cell proliferation kinetics and uptake of tritiated fluorodeoxyglucose and L-methionine in squamous-cell carcinoma of the head and neck. J Nucl Med 36:252-258, 1995

72. Haberkorn U, Strauss LG, Reisser C, et al: Glucose uptake, perfusion, and cell proliferation in head and neck tumors: relation of positron emission tomography to flow cytometry. J Nucl Med 32:1548-1555, 1991

73. Jacob R, Welkoborsky HJ, Mann WJ, et al: [Fluorine-18]fluorodeoxyglucose positron emission tomography, DNA ploidy and growth fraction in squamous-cell carcinomas of the head and neck. ORL J Otorhinolaryngol Relat Spec 63:307-313, 2001

74. Halfpenny W, Hain SF, Biassoni L, et al: FDG-PET. A possible prognostic factor in head and neck cancer. Br J Cancer 86:512-516, 2002

75. Allal AS, Dulguerov P, Allaoua M, et al: Standardized uptake value of 2-[(18)F] fluoro-2-deoxy-D-glucose in predicting outcome in head and neck carcinomas treated by radiotherapy with or without chemotherapy. J Clin Oncol 20:1398-1404, 2002

76. Bar-Shalom R, Yefremov N, Guralnik L, et al: Clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management. J Nucl Med 44:1200-1209, 2003

77. Lardinois D, Weder W, Hany TF, et al: Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 348:2500-2507, 2003

78. Antoch G, Stattaus J, Nemat AT, et al: Non-small cell lung cancer: Dual-modality PET/CT in preoperative staging. Radiology 229:526-533, 2003

79. Cohade C, Osman M, Leal J, et al: Direct comparison of (18)F-FDG-PET and PET/CT in patients with colorectal carcinoma. J Nucl Med 44:1797-1803, 2003

80. Schöder H, Yeung H, Gonen M, et al: Head and neck cancer: Clinical usefulness and accuracy of PET/CT image fusion. Radiology 231:65-72, 2004

81. Blahd WH, Nordyke RA, Bauer FK: Radioactive iodine (I 131) in the postoperative treatment of thyroid cancer. Cancer 13:745-756, 1960

82. Maxon HR, Thomas SR, Chen IW: The role of nuclear medicine in the treatment of hyperthyroidism and well-differentiated thyroid adenocarcinoma. Clin Nucl Med 6:P87-P98, 1981

83. Mazzaferri EL, Young RL: Papillary thyroid carcinoma: A 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 70:511-8, 1981

84. Robbins R, Drucker W, Hann L, et al: Advances in the detection of residual thyroid carcinoma. Adv Intern Med 46:277-294, 2001

85. Mazzaferri EL, Robbins RJ, Spencer CA, et al: A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 88:1433-1441, 2003

86. Pacini F, Lippi F, Formica N, et al: Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. J Nucl Med 28:1888-1891, 1987

87. Pineda JD, Lee T, Ain K, et al: Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. J Clin Endocrinol Metab 80:1488-1492, 1995

88. McDougall IR: ^{131}I treatment of ^{131}I negative whole body scan, and positive thyroglobulin in differentiated thyroid carcinoma: what is being treated? Thyroid 7:669-672, 1997

89. Joensuu H, Ahonen A, Klemi PJ: 18F-fluorodeoxyglucose imaging in preoperative diagnosis of thyroid malignancy. Eur J Nucl Med 13:502-506, 1988

90. Dietlein M, Scheidhauer K, Voth E, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography and iodine-131 whole-body scintigraphy in the follow-up of differentiated thyroid cancer. Eur J Nucl Med 24:1342-1348, 1997

91. Grunwald F, Kalicke T, Feine U, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography in thyroid cancer: Results of a multicentre study. Eur J Nucl Med 26:1547-1552, 1999

92. Grunwald F, Schomburg A, Bender H, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography in the follow-up of differentiated thyroid cancer. Eur J Nucl Med 23:312-319, 1996

93. Feine U, Lietzenmayer R, Hanke JP, et al: Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med 37:1468-1472, 1996

94. Feine U, Lietzenmayer R, Hanke JP, et al: [18FDG whole-body PET in differentiated thyroid carcinoma. Flipflop in uptake patterns of 18FDG and 131I]. Nuklearmedizin 34: 127-134, 1995

95. Altenvoerde G, Lerch H, Kuwert T, et al: Positron emission tomography with F-18-deoxyglucose in patients with differentiated thyroid carcinoma, elevated thyroglobulin levels, and negative iodine scans. Langenbecks Arch Surg 383:160-163, 1998

96. Chung JK, So Y, Lee JS, et al: Value of FDG-PET in papillary thyroid carcinoma with negative 131I whole-body scan. J Nucl Med 40:986-992, 1999

97. Wang W, Macapinlac H, Larson SM, et al: [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (131)I whole body scans and elevated serum thyroglobulin levels. J Clin Endocrinol Metab 84:2291-2302, 1999

98. Helal BO, Merlet P, Toubert ME, et al: Clinical impact of (18)F-FDG-PET in thyroid carcinoma patients with elevated thyroglobulin levels and negative (131)I scanning results after therapy. J Nucl Med 42:1464-1469, 2001

99. Frilling A, Tecklenborg K, Gorges R, et al: Preoperative diagnostic value of [(18)F] fluorodeoxyglucose positron emission tomography in patients with radioiodine-negative recurrent well-differentiated thyroid carcinoma. Ann Surg 234:804-811, 2001

100. Schluter B, Bohuslavizki KH, Beyer W, et al: Impact of FDG-PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin and negative 131I scan. J Nucl Med 42:71-76, 2001

101. Wang W, Larson SM, Fazzari M, et al: Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab 85:1107-1113, 2000

102. Robbins R, Reibke R, Drucker W, et al: Real-time prognosis in metastatic thyroid cancer based on FDG-PET scanning. Thyroid 13:701, 2003 (abstr)

103. Haraguchi K, Rani CS, Field JB: Effects of thyrotropin, carbachol, and protein kinase-C stimulators on glucose transport and glucose oxidation by primary cultures of dog thyroid cells. Endocrinology 123:1288-1295, 1988

104. Filetti S, Damante G, Foti D: Thyrotropin stimulates glucose transport in cultured rat thyroid cells. Endocrinology 120:2576-2581, 1987

105. Moog F, Linke R, Manthey N, et al: Influence of thyroid-stimulating hormone levels on uptake of FDG in recurrent and metastatic differentiated thyroid carcinoma. J Nucl Med 41:1989-1995, 2000

106. Petrich T, Borner AR, Otto D, et al: Influence of rhTSH on [(18)F]fluorodeoxyglucose uptake by differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 29:641-647, 2002

107. Plotkin M, Hautzel H, Krause BJ, et al: Implication of 2-18fluor-2-deoxyglucose positron emission tomography in the follow-up of Hürthle cell thyroid cancer. Thyroid 12:155-161, 2002

108. Lowe VJ, Mullan BP, Hay ID, et al: 18F-FDG-PET of patients with Hürthle cell carcinoma. J Nucl Med 44:1402-406, 2003

109. Brandt-Mainz K, Muller SP, Gorges R, et al: The value of fluorine-18 fluorodeoxyglucose PET in patients with medullary thyroid cancer. Eur J Nucl Med 27:490-496, 2000

110. Diehl M, Risse JH, Brandt-Mainz K, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography in medullary thyroid cancer: results of a multicentre study. Eur J Nucl Med 28:1671-1676, 2001

111. Gourgiotis L, Sarlis NJ, Reynolds JC, et al: Localization of medullary thyroid carcinoma metastasis in a multiple endocrine neoplasia type 2A patient by 6-[18F]-fluorodopamine positron emission tomography. J Clin Endocrinol Metab 88: 637-641, 2003

112. Hoegerle S, Altehoefer C, Ghanem N, et al: 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. Eur J Nucl Med 28:64-71, 2001

113. Yasuda S, Shohtsu A, Ide M, et al: Chronic thyroiditis: Diffuse uptake of FDG at PET. Radiology 207:775-778, 1998

114. Ramos CD, Chisin R, Yeung HW, et al: Incidental focal thyroid uptake on FDG positron emission tomographic scans may represent a second primary tumor. Clin Nucl Med 26:193-197, 2001

115. Wiesner W, Engel H, von Schulthess GK, et al: FDG-PET-negative liver metastases of a malignant melanoma and FDG-PET-positive Hürthle cell tumor of the thyroid. Eur Radiol 9:975-978, 1999

116. Cohen MS, Arslan N, Dehdashti F, et al: Risk of malignancy in thyroid incidentalomas identified by fluorodeoxyglucose-positron emission tomography. Surgery 130:941-946, 2001

117. Kang KW, Kim SK, Kang HS, et al: Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. J Clin Endocrinol Metab 88:4100-4104, 2003

118. Pentlow KS, Graham MC, Lambrecht RM, et al: Quantitative imaging of iodine-124 with PET. J Nucl Med 37:1557-1562, 1996

119. Freudenberg LS, Antoch G, Gorges R, et al: Combined PET/CT with iodine-124 in diagnosis of spread metastatic thyroid carcinoma: A case report. Eur Radiol 13:L19-L23, 2003 (suppl)

120. Larson SM, Robbins R: Positron emission tomography in thyroid cancer management. Semin Roentgenol 37:169-174, 2002

121. Eschmann SM, Reischl G, Bilger K, et al: Evaluation of dosimetry of radioiodine therapy in benign and malignant thyroid disorders by means of iodine-124 and PET. Eur J Nucl Med Mol Imaging 29:760-767, 2002