

FDG-PET in Head and Neck, and Thyroid Cancer

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FDG-PET 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. (*Chang Gung Med J* 2005;28:284-95)

Key words: FDG-PET, head and neck cancer, thyroid cancer.

Background

Head and neck cancer is the sixth most common cancer worldwide. It comprises 2% of all cancers in the USA, and 2% of all deaths. Imaging is vital for detection, staging, and treatment. Early stage head and neck cancer (T1/2 N0 M0) is curable; however, those patients who develop local and/or distant metastases have a worse prognosis. Most patients with nodal metastases have a 45% survival rate; those with M1 have a 10% survival rate. Also there is a possibility of a second primary, which has about a 5% annual incidence, depending on the series.

Role of FDG-PET in head and neck cancer

FDG-PET is used in several ways (1) tumor staging; (2) nodal staging; (3) post-treatment setting;

and (4) monitoring response to therapy.

FDG-PET in tumor staging

FDG-PET imaging is not a perfect test, even with PET-CT today, which is the best mode of operation. It is still necessary to evaluate the patient's history, particularly the physical findings from the head and neck surgeon, as well as have the pertinent expertise required to evaluate the scans accurately.

In tumor staging, PET-CT is usually used to find the primary tumor in a patient who has an unknown primary. Cancers of unknown primary comprise about 3-15% of all cancers and 1-2% of head and neck cancers, depending on the series. These patients have no history of cancer. There is no clinical or laboratory evidence of a primary tumor. They present

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with a neck mass, which by biopsy is proven to be cancer. Some data suggest that if there are nodes in Levels I-III, the likelihood of head and neck cancer is greater. In older series, the primary tumor was detected in 5-40% of cases. Improvement of the detection rate is an area where PET-CT can make a contribution.

FDG-PET in detection of unknown primary tumors in head and neck cancer

The detection rate with FDG-PET ranges from 10% to 60%, with the difference apparently due to patient selection and verification of strict clinical criteria. The usual clinical approach for these patients is a complete head and neck exam. Most tumors can be identified if the study is well done. That is followed by an FDG-PET/CT scan and CT with intravenous contrast. If a lesion is found, it is then biopsied based on PET-positive findings. It is more difficult to perform the diagnostic PET study if the biopsy is done before the PET-CT scan.

Inevitably, in our experience, the PET scan will be negative in the majority of patients, and a panendoscopy and multiple biopsies will be needed. In a review of many series, based on a total of 253 patients, FDG-PET identified the presence of a primary tumor in an average of one third of cases. Hence the patient was spared unnecessary or systemic treatment (Table 1).

Case study: Unknown primary

This is a typical case (Figs. 1 and 2). A 68-year-old man presented with a left neck mass. The physi-

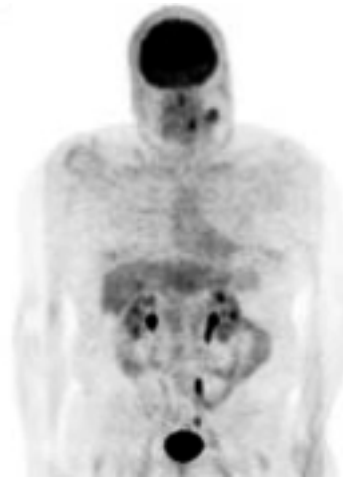


Fig. 1 Case study: unknown primary.

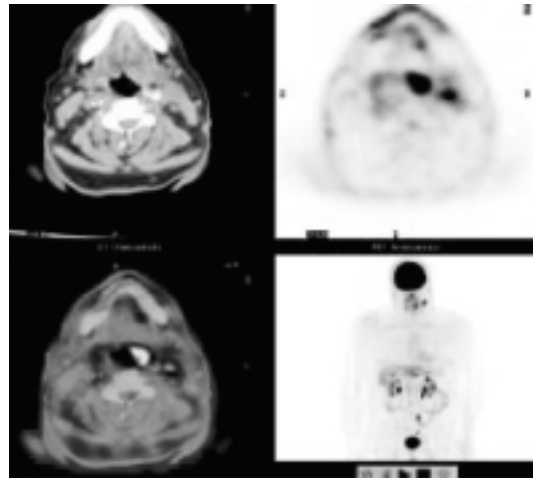


Fig. 2 Case study: unknown primary.

Table 1. Use of FDG-PET to Identify Primary Tumors

Authors	N	TP	FP	TN	% Tumor
Bohuslavizki	44	15	5	0	34
Braams	13	4	0	1	31
Hanasono	20	7	NR	3	35
Jungehulsing	27	6	0	NR	22
Fogarty	21	1	5	0	5
Greven	13	1	6	2	8
Mendenhall	24	7	NR	2	29
Stokkel	9	6	1	0	60
Regelink	50	16	2	0	32
Aassar	15	8	2	0	53
Kole	16	4	NR	3	25
Total	253	75			30

cal exam showed no mucosal lesions; a fiber optic exam of the upper aerodigestive tract was negative. PET-CT and diagnostic CT were performed. However, the CT scan with intravenous contrast did not find the tumor; only in retrospect was it found. On the PET scan the neck lesion was very easy to see, but a submucosal lesion was also seen in the left base of the tongue. The biopsy showed invasive keratinizing squamous cell carcinoma (SCCA) in one of 16 nodes with extracapsular extension.

Case study: Unknown primary

In this case (Figs. 3 and 4) of a 38-year-old chef who presented with a left neck mass for 2 months, a



Fig. 3 Case study: unknown primary.

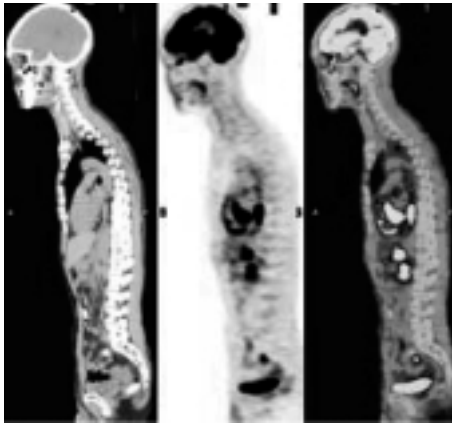


Fig. 4 Case study: unknown primary.

complete head and neck exam was negative, and PET-CT was performed to identify the unknown primary. On the PET-CT scan, the neck nodes and the presence of a linear area of activity were seen. The sagittal view showed intense activity, probably in the region of the esophagus, which on biopsy proved to be poorly differentiated squamous cell esophageal cancer. Thus, a patient may have not only head and neck cancer, but there may be a cancer elsewhere, in the breast, lung or esophagus.

CT and MRI are the best modalities for most cases of tumor staging. However, for cancers of the oral cavity, the staging can be done by a good physical exam. Most of the time surgeons can see the primary tumor. CT-MRI is best for locations in the bone, skull base, or orbital invasion. Even with PET-CT, perineural spread is difficult to see; it is best

seen with MRI. PET is limited, although it has high sensitivity, e.g., submucosal tumors. There are some intriguing data showing that intensity of uptake predicts outcome; however, more studies are needed to verify this finding.

In central nervous system lymphomas, FDG metabolism is high, as in high-grade gliomas. FDG-PET is also used in HIV patients with enhancing lesions, but toxoplasmosis has low FDG metabolism. FDG-PET is also used in lymphomas as a guide to stereotactic biopsy and response assessments.

FDG-PET in nodal staging

Nodal involvement in head and neck cancer is an independent prognostic indicator. Positivity of nodes decreases the overall survival significantly by about 50%. The prognosis depends on the number of nodes involved, the lower the neck level, and whether there is extracapsular invasion. Early resection, however, definitely improves prognosis.

False negatives in nodal staging

There are false negatives, about 10-30%, even with CT and MR studies because of the size criteria. Although we can try to improve the reading of the CT and MR, depending on the enhancement patterns, other factors, such as the presence of necrosis in the nodes and the grouping of the nodes, can determine if they are abnormal. In FDG-PET, there may be a 10-20% false-negative rate depending on the type of tumors. Nodes can be missed based on nodal station localization, necrosis, low volume, and whether it is adjacent to the primary. One of the limitations in our early studies was the inability to localize the nodes very well. PET staging is not as precise as surgical staging.

Oral SCCA with N0 neck

Pre-operative staging of the N0 neck in patients with oral SCCA is hindered by the relatively high false-negative/-positive rates of conventional imaging techniques. In an intriguing paper from the Institute of Nuclear Medicine in London, the authors showed that PET cannot identify nodal disease in patients with N0 necks, i.e., patients on physical exam who do not have palpable nodes or radiologic evidence of neck metastasis. The aim of this study was to evaluate the utility of FDG-PET and sentinel lymph node (SLN) imaging and biopsy to determine

the true disease status of the loco-regional lymphatics.

Methods

Nineteen patients with biopsy proven disease without palpable or radiological evidence of neck metastases underwent preoperative whole-body FDG-PET in the head and neck and SLN imaging. SLN technique was performed using 4 peri-tumoral injections of ^{99m}Tc labeled albumin colloid each of 10 MBq. Surgery included a neck dissection. Histology of the resultant specimen was correlated with that of the SLN and reoperative imaging.

Results

Tumors were found, but PET failed to identify small volume disease. In all patients SLN harvesting was feasible. In 15 of 19 patients the SLN and the residual neck dissection were negative for tumor. In three of 19 patients the SLN were positive for tumor as were other neck nodes. In one patient the SLN was negative, but another single tumor positive node was identified in the neck. FDG-PET failed to identify nodal disease in all four patients with histologically proven lymph node metastase (1.2-2.5 cm).

Conclusion

In this study, the patients with oral SCCA could best be evaluated with SLN imaging and biopsy with probe and Patent Blue Dye guided harvest. SLN can predict cervical nodal status. This is one of the earlier prospective studies to demonstrate that while PET is still better than CT and MRI because of its high sensitivity and specificity, it may still not be good enough to identify small volume or microscopic disease. Adequate staging by surgical neck resection is still necessary.

Staging neck cancer of head and FDG-PET

The aim of this study was to compare FDG-PET and CT, MRI, sonographic and histopathological findings to detect cervical lymph node metastases of head and neck cancer in 60 patients with histologically proven SCCA before surgery. Preoperative endoscopy (including biopsy), CT, MRI, and sonography of the cervical region were performed in all patients within 2 weeks before whole-body FDG-PET.

Results

There were a total of 1,284 lymph nodes, 117 of which showed metastatic involvement. FDG-PET had the highest sensitivity (90%) and specificity (94%) for detecting lymph node metastases than CT (sensitivity of 82% and specificity of 85%) and MRI (sensitivity of 80% and specificity of 79%). When FDG-PET was compared with conventional imaging modalities, the correlations were statistically significant for PET versus CT ($p = 0.017$), PET versus MRI ($p = 0.012$), and PET versus sonography ($p = 0.0001$), respectively. Quantitative analysis of FDG uptake in lymph node metastases using body weight-based standardized uptake values (SUVBW) showed no significant correlation between FDG uptake (3.7 ± 2.0) and histological grading of tumor-involved lymph nodes ($p = 0.9$). Interestingly, benign lymph nodes had increased FDG uptake as a result of inflammatory reactions (SUVBW-range: 2-15.8).

Conclusions

This prospective, histopathologically controlled study confirms FDG-PET as the procedure with the highest sensitivity and specificity for detecting lymph node metastases of head and neck cancer. The optimal diagnostic modality may be a fusion image showing the increased metabolism of the tumor and the anatomical localization.

Nodal cancer staging

Nodal metastases can be seen very well with FDG-PET imaging. Tables 2 and 3 summarize data from Schoder and Yeung showing the improved sensitivity and specificity of FDG-PET imaging over physical exam, CT, MRI, as well as ultrasound.

Case study

This patient presented with an oral cavity lesion (Fig. 5), which proved to be SCCA. Although the tumor could be seen very well when the patient's mouth was open, PET-CT also identified the involvement of enlarged nodes. Thus, PET-CT can actually identify small volume disease or nodes of less than 1 cm that do not meet precise criteria for CT imaging. This patient also had a secondary tumor in the esophageal region, which was proven by biopsy. The possibility of finding secondary cancers underscores the importance of performing whole body imaging. This patient had palliative radiotherapy including

Table 2. Comparison of Imaging Modalities for Staging Head and Neck Cancer 3

Imaging	Sensitivity	Specificity
PE	60-75%	85-85%
CT-MR	61-97%	21-100%
PET	87-90%	80-93%
US	64-84%	66-100%

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Table 3. Comparison of Imaging Modalities for Nodal Staging of Head and Neck Cancer 3

Nodal staging	N	Imaging modality	Sen*	Spec*	Sen†	Spec†
Kresnik et al.	24		58	58	100	91
Stuckensen et al.	106	CT	66	74	70	82
		MR	64	69		
		US	84	68		
Di Martino et al.	50	CT	84	96	84	90
		US	84	88		
Stokkel et al.	54	CT	85	86	96	90
		US	64	100		
		US	82	66		
Adams et al.	60	CT	82	85	90	94
		MR	80	79		
		US	79	-		
Kau et al.	70	CT	65	47	87	94
		MR	88	41		
McGuirt et al.	45	CT	82	-	82	82
Hannah et al.	40	CT	81	81	82	94

* CT/MRI/US

† PET

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treatment for the esophageal primary.

Staging for distant metastases and second primary in head and neck cancer

Although distant metastases are rare (3-8%, depending on the series), their likelihood increases with increasing T/N stage, particularly if the patient presents, as in this case, with supraclavicular nodal involvement (see Fig. 5). There is a greater incidence of synchronous second primary in the aerodigestive tract. For this reason we still do a survey from the skull base to the pelvis, which can easily be done with PET-CT.

FDG-PET after therapy

Most of our patients are seen after therapy. Surgery or radiotherapy (RT) is curative. Surgery followed by RT can sometimes be done; at surgery the

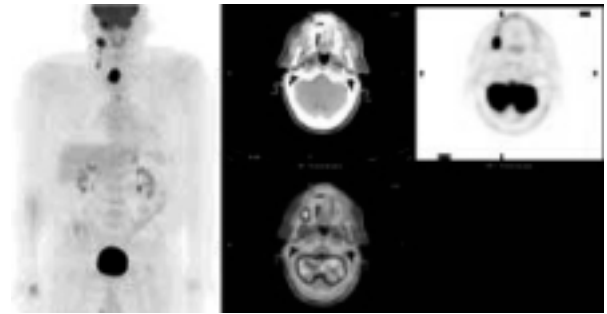


Fig. 5 Case study: 79-year-old man with right tongue cancer.

pathology report allows us to evaluate for prognosis. However, in patients with locally advanced head and neck cancer, chemotherapy/RT or multiple modality treatment could be potentially curative. The question always concerns the early response assessment for surgery for possible residual disease. This is one area where FDG-PET imaging may be difficult to use because of the question of possible post-treatment inflammation. It is extremely difficult to determine whether FDG activity seen on the PET scan represents post-treatment inflammation or early recurrence. A biopsy has to be performed, but it is very difficult to biopsy areas that have had local radiation or RT. We recognize the possibility of post-treatment inflammation. Development of a certain level of expertise and communication with the surgeon are essential to avoid making the wrong decision in these cases.

Case study

Here is an example of one such patient from our Center, a 76-year-old Caucasian man who noted a painless mass in his right neck approximately a month and a half earlier. He was given an antibiotic, but there was no change in the right neck mass. He finally had an FNA of the mass in Austin on September 2, 2003, which revealed SCCA. Extensive nodal involvement was treated with chemotherapy and RT, and 6 weeks after treatment the post-treatment scan showed improvement anatomically. Apparently the patient had a CT scan of the head and neck in August, which revealed the large right level II lymph node measuring approximately 5 cm. However, the report and the films were unavailable for review. He also had a negative CT of the chest at an outside institution. An examination

under anesthesia with directed biopsies on September 2, 2003 revealed no definitive diagnosis of a primary. On September, 16, 2003, at our Center, a repeat biopsy of the right neck mass confirmed poorly differentiated SCCA. On the same day, he had a chest X-ray that revealed no evidence of primary. There was a prominent right hilar region on the lateral view. Review of the CT chest scan of the chest revealed no primary in the chest (Fig. 6).

Under the impression of unknown primary metastatic to right neck level II lymph node, he had a definitive radiation to a total dose of 66 Gy in 30 fractions to the right level II lymph node. The ipsilateral neck will receive 60 Gy and the contralateral neck will receive a dose of 54 Gy. All mucosal sites will be treated as well as the larynx. The lower neck will be treated using a single AP field of 6 MV photons to 50 Gy with a midline block after 44 Gy. The right mid-neck will be boosted by an additional 10 Gy to a total dose of 60 Gy using a single AP field (Fig. 7).

Timing of FDG-PET after chemotherapy/radiotherapy

What is the optimal time to image? Some data indicate that 6 weeks after the end of chemotherapy/RT may provide up to 92% accuracy in identifying residual disease. Considerable work has been done to evaluate the response at end of the entire cycle of chemotherapy, indicating that even with chemotherapy or chemotherapy/RT sensitivity may be as high as 90% and specificity 83%. With RT

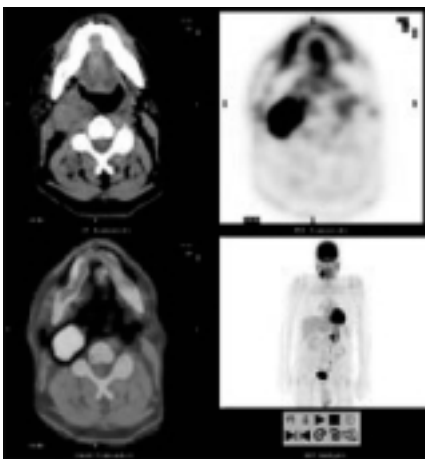


Fig. 6 Unknown primary metastatic to the right neck before IMRT.

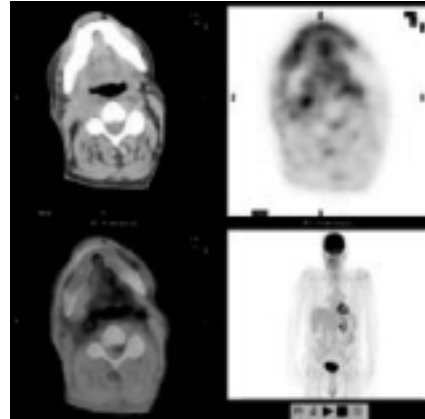


Fig. 7 Unknown primary metastatic to the right neck after IMRT.

alone Greven et al more recently found that evaluation at 4 months was more accurate than at 1 month.

Timing is the most crucial factor, although it also depends on the type of radiation delivered and other factors. Nevertheless, the rule is that the longer the delay in obtaining an FDG-PET scan, the better are the chances of obtaining more specific information to be able to accurately discriminate between post-treatment effect and recurrent disease.

Recurrent disease

FDG-PET has high sensitivity and specificity irrespective of prior surgery, chemotherapy/RT or both, whereas CT and MRI are limited by post-therapy changes. The extensive data on recurrence indicate very good accuracy for sensitivity and specificity for identifying recurrence in these patients (Table 4).

A negative PET scan provides very reliable data; the NPV in the neck is very good with a negative study. But a positive PET scan is very worrisome and should be read with caution because there could be many variants post-therapy and because the background activity could be affected by the type, delivery, and direction of RT. Biopsy may be an option or follow-up. If the follow-up PET scan is positive or the patient has a low likelihood of recurrence, then they may be followed up at 3 months, i.e., a short-interval follow-up. If it is inflammation, it tends to decrease or remain stable; if it is disease recurrence, it manifests itself very intensely at the end of the follow-up period.

Table 4. Accuracy of PET versus CT-MR for Identifying Recurrence of Disease in Head and Neck Cancer

Recurrence:	n	CT-MR (%)			PET (%)		
		Sens	Spec	Acc	Sens	Spec	Acc
Li et al.	43	53	79	66	91	86	88
Hanasono et al.	34	75	65	75	100	85	90
Kresnik et al.	15	62	57	60	88	57	73
McGuirt et al.	38			61			79
Lonneux et al.	44	73	50	64	96	61	81
		90*	60*	75*	96*	90*	94*
Lapela et al.	56	91	78	84	95	84	90
Yen et al.	67	62	44	49	100	93	95
Lowe et al.	44	38	85		100	93	
Wong et al.	143				96-94	72-96	
Kunkel et al.	97				1-83	67-96	

*> 12 weeks after therapy

This case is an example of the importance of the patient's history. A 79-year-old man presented with a right neck mass and hoarseness. A right thyroid lobectomy was performed in June, 2003, followed by a complete neck dissection a month later that demonstrated medullary thyroid cancer. He was treated with postoperative IMRT.

Then he presented with pulmonary lesions. A PET scan (Fig. 8) showed two spots in the neck with some faint but discrete activity in the lung nodules, enough for us to determine that there was disease in the lungs. There was very intense activity in the right

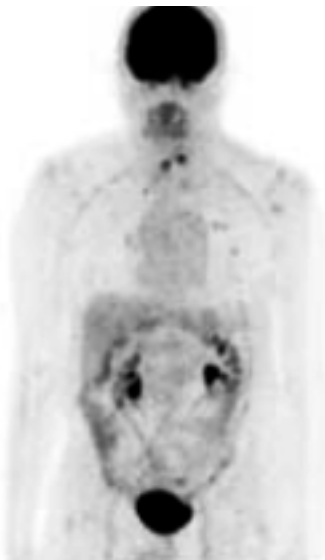


Fig. 8 Case study. A79-year-old man presented with a right neck mass and

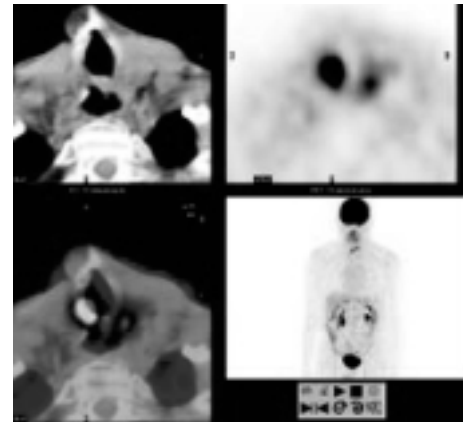


Fig. 9 Case study. A79-year-old man presented with a right neck mass and

region. However, because the hoarseness and all disease manifestations were on the right side, we would have expected a variant to be active on the left side. The activity actually proved to be a Teflon injection in the vocal cord. Patients with recurring pharyngeal nerve paralysis can have injections of material into the vocal cord that can cause a false positive. So it was not recurrent disease in this case.

By contrast, here is a straightforward case of post-treatment effects (Figs. 10 and 11). This was a 53-year-old African-American woman with T4 SCCA of the larynx, post-laryngectomy, and bilateral neck dissection. She had a recent history of one episode of dysphagia. The PET-CT scan showed inflamed tissue in the right retromolar trigone with some white plaques, which were seen on the CT scan. There was an adrenal lesion, which was negative, and the primary recurrence area was very intensely hot, which was verified by biopsy. These cases can be called with confidence because there is very little doubt about the results.

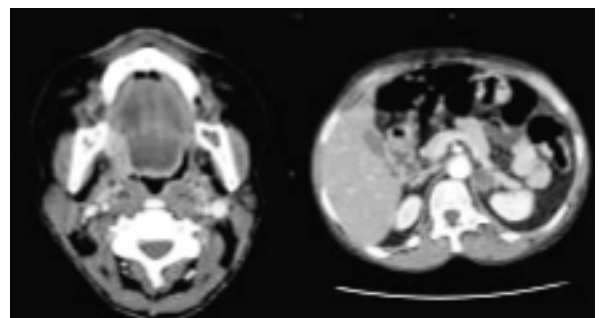


Fig. 10 Post-treatment effects.

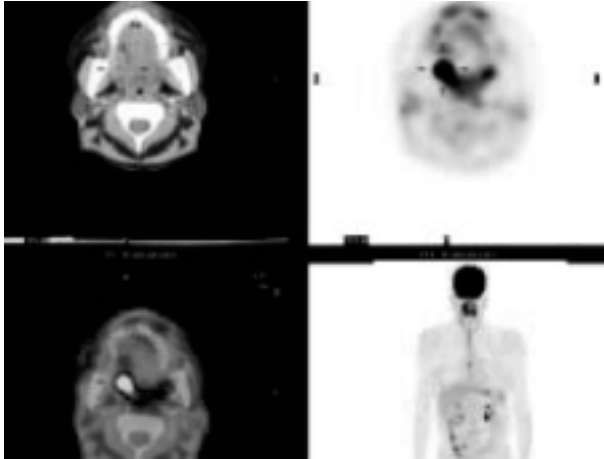


Fig. 11 Post-treatment effects.

Role of FDG-PET-CT in head and neck cancer

PET-CT is the clinical standard at MD Anderson Cancer Center. It improves localization of tumors and discriminates between the variants and recurrent disease. The limitations are the inability to tilt the gantry. When diagnostic CT scans of the head and neck are performed, the gantry has to be tilted to avoid the dental fillings and all the artifacts introduced by the dental fillings. To overcome this limitation of the PET-CT scan, the patient's neck is hyperextended. Intravenous contrast is needed for better delineation of the small structures of the head and neck.

There are some intriguing data, also from our group, that IV contrast, if not required immediately after injection, does not interfere significantly with quantification. For a diagnostic scan, our protocol is the two-step scan, first of the head and neck, and then a whole-body survey to exclude secondary or metastatic disease. Our specific protocol for head and neck scans involves the following:

Patient preparation

Followings are essential procedures for a whole body PET-CT scan in our center in head and neck cancer patients. There are (1) fasting for at least 6 hours; (2) encourage water intake; (3) high protein and low carbohydrate diet at last meal; and (4) well controlled diabetic patients; (5) Xanax 0.5 mg p.o., at 5-10 minutes before injection of FDG (6) medications are not contraindication. Besides, the patient

should be fasted to minimize carbohydrate intake and to minimize heart activity because we also survey for secondary cancer, although it is rare. A low-dose sedative ensures that the patient will not have any skeletal muscle contractions that can interfere with interpretation of the studies.

PET-CT scanning technique

In MD Anderson, we give an i.v. bolus injection of 15-20 mCi of FDG to the patient. We give the patient a higher dose than is usual and then wait up to about 90 minutes. We delay our imaging substantially. The CT scan is done in a diagnostic mode. The dose (120 K vp, 320 mAs) is identical to that used for a diagnostic CT alone because it allows us to compare the CT scan of the PET-CT together with the diagnostic CT to provide comparability with old studies. A head and neck scan is done first, followed by a whole-body survey; however, a single survey can be done if initial diagnosis or staging are not needed.

Radiotherapy planning (RTP) with PET-CT

Thirty years ago the fields of radiology and radiotherapy diverged, but now they are coming back together. Nuclear medicine physicians are working closely with radiologists because the expertise of imaging specialists meets some of the needs of physicians in radiation oncology to use PET imaging to help with treatment planning. Interpretation of the PET scan is not that simple, however. It cannot be used for contouring, so the CT component is still used here. There also has to be a component of tumor thresholding, as well as edge detection because the scans can be made very dark or very light. There are specific needs for image registration: flat tabletop, immobilization, external lasers, and the ability to transfer different RT platforms (e.g., DICOM). Different manufacturers make different platforms for RT planning. With lung cancer staging, lesion motion studies are needed for gating as well as breathhold studies.

PET-CT versus CT alone for treatment planning

There are changes in terms of dose targeting to the gross tumor volume depending on the findings of PET versus CT alone. There are no outcome data yet comparing patient outcomes for those treated with

PET-CT versus CT alone. However, a good pilot study of six patients with head and neck cancer demonstrated that, as has been seen with lung cancer imaging, there appear to be differences in the treatment plan using FDG-PET versus CT alone. The aim of this investigation was to evaluate the influence and accuracy of FDG-PET in target volume definition as a complementary modality to CT for patients with head and neck cancer.

Methods

Gross target volume (GTV) and pathologic nodal volumes were first defined in the conventional manner based on CT. A segmentation and surface-rendering registration technique was then used to coregister the FDG-PET and CT planning image data. CT-GTV was then modified based on the PET data to form final PET-CT treatment volumes. IMRT was then used to demonstrate dose targeting to the CT-GTV or the PET-CT-GTV.

Results

One patient was PET-negative after induction chemotherapy. The CT-GTV was modified in all remaining patients based on FDG-PET data. The resulting PET-CT-GTV was larger than the original CT volume by an average of 15%. In five cases, FDG-PET identified active lymph nodes that corresponded to lymph nodes contoured on CT. The pathologically enlarged CT lymph nodes were modified to create final lymph node volumes in three of five cases. In one of six patients, FDG-avid lymph nodes were not identified as pathologic on CT. In two of six patients, registration of the independently acquired PET and CT data using segmentation and surface rendering resulted in a suboptimal alignment and, therefore, had to be repeated. RTP using IMRT demonstrated the capability of this technique to target anatomic or anatomic/physiologic target volumes. In this manner, metabolically active sites can be intensified to greater daily doses.

Conclusion

Inclusion of FDG-PET data resulted in modified target volumes in RTP for head and neck cancer. PET and CT data acquired on separate, dedicated scanners may be coregistered for therapy planning; however, dual-acquisition PET-CT systems may be

considered to reduce the need for reregistrations. It is possible to use IMRT to target dose to metabolically active sites based on coregistered PET-CT data.

FDG-PET in thyroid cancer

There is usually very little activity in the thyroid. Diffuse activity seen in the thyroid is usually subclinical thyroiditis. If focal activity is seen, it is usually a malignant process. Focal lesions are very worrisome. Several series have been done, one from our group and a more recent one just published, demonstrating that a high probability of malignancy can be identified in very focal lesions. These lesions are usually confirmed by ultrasoundguided biopsies, and most prove to be thyroid carcinoma.

Our group reported a retrospective review of the whole-body PET scans of four patients with cancer (2 women; age, 49 to 78 years) in whom focal thyroid uptake was visualized and subsequently correlated with thyroid cancer based on cytologic or histopathologic data.

Results

Of the four patients referred for FDG-PET scans, two had lung cancer, one had prostate cancer, and one had an unknown primary tumor. Maximum and average SUV ranged from 3.7 and 2.3, to 53 and 34, respectively. These findings were correlated with cytologic (2 patients) or histopathologic data (2 patients) that confirmed thyroid cancer. In two patients, their treatment was changed, and total thyroidectomy was performed; in one patient, the SUV of the focal thyroid accumulation (maximum, 7.9; average, 4.8) were less than the cutoff values for thyroid cancer noted in the literature. The clinical condition of the other two patients did not permit additional investigation or treatment for thyroid cancer.

Conclusion

Increased focal thyroid uptake on whole-body FDG-PET scans should not be overlooked, even when it is not marked, and should prompt further investigation to rule out cancer.

PET imaging in the region of the neck has limitations, however. Thus, if PET imaging fails to localize disease, we still routinely ask for an ultrasound of the neck region. Otherwise, small volume disease could be missed.

Management of well-differentiated thyroid cancer

The management of well-differentiated thyroid cancer is surgical. ^{131}I Iodine therapy with whole-body scans has improved the prognosis of these high-risk patients. The development of the TSH assay allows us to give adequate suppression of thyroid hormone. Thyroglobulin (TGB) measurements are becoming more readily available and reliable, so we can assess low-risk patients following ^{131}I ablation without scanning. High-risk patients, on the other hand, are still scanned with ^{131}I . Inevitably, there are some patients who have ^{131}I negative scans with rising TGB; these comprise approximately 20% of all differentiated metastatic thyroid cancer lesions. In the past, empiric therapy was the rule for these patients. However, our group tested the hypothesis that lesions that did not concentrate iodine but did produce TGB could be localized by PET.

Methods

We performed FDG-PET on 37 patients with differentiated thyroid cancer after surgery and radioiodine ablation that had negative diagnostic ^{131}I whole body scans during routine follow-up.

Results

In those with elevated TGB levels, FDG-PET localized occult disease in 71%, was false-positive in one, and was false-negative in five patients. The majority of false-negative FDG-PET occurred in patients with minimal cervical adenopathy. Surgical resections, biopsies, ^{131}I therapy, and differentiation therapy were performed based on the PET results. These FDG-PET results changed the clinical management in 19 of 37 patients. In patients with elevated TGB levels, FDG-PET had a positive predictive value of 92%. In patients with low TGB levels, FDG-PET had a negative predictive value of 93%. No FDG-PET scans were positive in stage I patients; however, they were always positive in stage IV patients with elevated TGB levels. An elevated TSH level (i.e., hypothyroidism) did not increase the ability to detect lesions.

Conclusion

FDG-PET is able to localize residual thyroid cancer lesions in patients who have negative diagnostic FDG-PET in Head and Neck, and Thyroid

Cancer ^{131}I whole body scans and elevated TGB levels, although it was not sensitive enough to detect minimal residual disease in cervical nodes.

Therefore, in this study, we demonstrated that PET changes clinical management. If the disease is localized in the neck, it can be resected; if it is a solitary lesion, focused RT can be delivered to the site. If the disease is systemic, a trial of ^{131}I RT can be attempted, or a course of experimental therapy can be tried. None of the recent experimental drugs has had equal efficacy with ^{131}I -avid tumors, unfortunately.

Case study

This is an example of one such patient. This patient had thyroid cancer, post-surgery, radioiodine ablation, and then presented with abnormally high TGB and a negative scan. Traditionally a CT survey is done, which was done for this patient, but it was unable to locate the source of the TGB. However, the PET scan done 3 months later easily demonstrated an abnormality, and with PET-CT integration the localization was precise (Fig. 12). This case demonstrated to us and our referring physicians the power of the PET-CT modality because the lesion had been missed months earlier. This is now an obvious lesion, although in reality it was present on a single slice, so that it was relatively simple to miss.

Regarding the CT as a tool only for attenuation correction is severely limiting the capability to diagnose disease more precisely. Currently, the trend will be to use CT for attenuation correction and diagnosis. The writing is not on the wall; the reality is here. We have worked with surgeons, oncologists, and

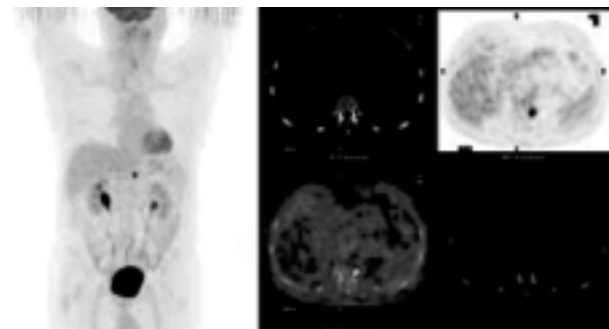


Fig. 12 Case study. Patient with thyroid cancer, post-surgery, radioiodine ablation, and presenting with abnormally high TGB and a.

radiation oncologists. We need to work even harder, particularly with nuclear medicine physicians to strike a mutually acceptable alliance to share PET and learn CT. I see more resistance among nuclear medicine physicians to learn CT than among radiologists to learn PET.

Prognostic value of FDG-PET in thyroid cancer

Poorly differentiated thyroid cancer lesions often lose the ability to concentrate radioactive ^{131}I and exhibit increased metabolic activity, as evidenced by enhanced glucose uptake. Patients who have FDG-avid disease do very poorly. That was the conclusion of a study our group undertook to evaluate 125 high-risk thyroid cancer patients who had previous thyroidectomies. FDG-PET scanning was incorporated into the routine follow-up of their annual evaluations. The patients had diagnostic ^{131}I whole-body scans, serum TG measurements, and additional imaging studies as clinically indicated.

Results

During 41 months of follow-up, 14 patients died. Survival was reduced in those over 45 years of age who had distant metastases, PET-positive scans, high rates of FDG uptake, and high volume of the FDG-avid disease ($>125\text{ mL}$). Survival did not correlate with gender, ^{131}I uptake, initial histology, or grade. The single strongest predictor of survival was the volume of FDG-avid disease. The 3-year survival probability of patients with FDG volumes of less than 125 mL was 0.96 (95% confidence interval, 0.91-1.0) compared with 0.18 (95% CI, 0.04-0.85) in patients with FDG volume more than 125 mL . Only one death (of leukemia) occurred in the PET-negative group ($n = 66$). Of the 10 patients with distant metastases and negative PET scans, all were alive and well.

Conclusions

Patients over 45 years of age with distant metastases that concentrate FDG are at the highest risk. Once distant metastases are discovered in patients with differentiated thyroid carcinoma, FDG-PET can identify high and low risk subsets. Subjects with a FDG volume greater than 125 mL have significantly reduced short term survival.

Other cancers can be imaged with PET-CT, such as anaplastic thyroid cancer but they are very intense.

Medullary thyroid cancer can be imaged with PET better than most studies, although F18 dopa appears to be quite promising in the identification of medullary thyroid cancer.

^{124}I -sodium-iodide PET

^{124}I -sodium-iodide PET is a good alternative. It has a half-life of 4.2 days, 22% positron decay, and high gamma rays, but images with high resolution and contrast can be done. PET-CT is crucial in the use of this tracer because there is very little background for localization. Its limitations are its availability and high cost. A very high energy cyclotron is needed to produce this material.

Summary

FDG-PET 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.

REFERENCES

1. Roelcke U, Leenders KL. Positron emission tomography

- in patients with primary CNS lymphomas. *J Neurooncol* 1999;43:231-6.
- 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* 1998;25:1255-60.
 - Schoder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. *Semin Nucl Med* 2004;34:180-97.
 - 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* 2004;130:105-9.
 - 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* 1999 40:1132-7.
 - Scarfone C, Lavelly WC, Cmelak AJ, et al. Prospective feasibility trial of radiotherapy target definition for head and neck cancer using 3-dimensional PET and CT imaging. *J Nucl Med* 2004;45:543-52.
 - 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* 2001;26:193-7.
 - 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 ¹³¹I whole body scans and elevated serum thyroglobulin levels. *J Clin Endocrinol Metab* 1999;84:2291-302.
 - 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* 2000;85:1107-13.
 - Erdi YE, Macapinlac H, Larson SM, et al. Radiation dose assessment for ¹³¹I therapy of thyroid cancer using ¹²⁴I PET imaging. *Clin Positron Imaging* 1999;2:41-6.