Due to the complex anatomy of the head and neck, imaging of tumors in this region can be challenging. As a result, physiologic imaging using positron-emission tomography (PET) has proven to be a valuable complement to conventional anatomic imaging. Recently, the combination of PET with computed tomography (CT) has been shown to be superior to single-modality imaging in lung cancer.[1] In this manuscript, we review all available literature regarding the use of fused PET-CT imaging for tumors of the head and neck.

**PET-CT Fusion**

PET is a physiologic imaging modality that characterizes different tissues in the body according to metabolism.[2,3] In contrast, CT and magnetic resonance imaging (MRI) are anatomic imaging modalities. When sufficiently large, tumors can also distort surrounding structures and, as a result, can be detected with anatomic imaging. Therefore, the integration of PET and CT allows for accurate description of a malignancy based on information from two separate tumor characteristics.

Anatomic and physiologic images can be fused by two methods: hardware and software. Hardware fusion uses a combined PET-CT scanner. The software technique uses anatomic landmarks to coregister images from separate CT or MRI scanners to the images acquired from PET. Currently, the software technique is more common because it is less expensive and more readily available.[4]

Several radioactive tracers can be used to image metabolically active tissues in physiologic imaging. Currently, the most commonly used tracer with PET is 18-fluorodeoxyglucose (FDG). FDG is a radioactively labeled glucose analog that is taken up by tissue in the same fashion as normal glucose, thus becoming concentrated in cells with high glucose utilization. Single-photon emission computed tomography (SPECT), the predecessor of PET, uses FDG or technetium-99m methoxyisobutylisonitrile (Tc-MIBI) as tracers. Tc-MIBI is a cationic and lipophilic molecule that accumulates tissues with high mitochondrial content, including neoplastic cells and myocardium.[5,6] Tc-MIBI SPECT and FDG-PET have been compared in head and neck cancer. Kao et al reported improved detection of recurrent nasopharyngeal carcinoma with FDG-PET over Tc-MIBI SPECT.[5] Similarly, Henze et al described superior detection rates of primary hypopharyngeal and laryngeal carcinomas using FDG-PET over Tc-MIBI SPECT.[7]

**Detection and Staging of Head and Neck Cancer**

**Primary Tumors**

Numerous studies have established the value of FDG-PET in the initial work-up of head and neck cancer. Martino et al reported that FDG-PET had a sensitivity of 95% and specificite.
PET-CT accurately detected tumors, because both FDG-PET and using image fusion for tumor detection as 77%, 82% and 79%, respectively.[13] This compared favorably to sensitivity, specificity, and accuracy of PET alone, described as 74%, 73%, and 74%, respectively. Wolf et al reported that tumors were detected by CT in only 12 of 17 cases, compared to detection in all 17 cases with PET-CT.[4] Wong et al found that PET coregistered with CT or MRI correctly staged head and neck cancer in 17 of 18 patients, compared to correct staging in only 11 of 18 with CT or MRI alone.[11] In addition, Antoch et al reported accurate TNM staging using PET-CT in 7 of 13 patients with head and neck cancer and 10 of 12 patients with cancer of unknown primary. By comparison, MRI correctly staged only 4 of 13 patients with head and neck cancer and 8 of 12 patients with cancer of unknown primary.[12] Table 1 shows that PET-CT correctly staged head and neck cancer in 84% while PET and CT/MRI correctly staged 64% and 56% of patients, respectively.

Fused PET-CT has also been shown to be better than anatomic imaging alone in the detection of tumor invasion at specific anatomic sites. Wong et al reported that PET-CT correctly detected tumor invasion at 121 of 124 anatomic landmarks, compared with correct detection in 86 of 124 locations with CT alone.[12] Table 1 shows that PET-CT correctly staged head and neck cancer in 84% while PET and CT/MRI correctly staged 64% and 56% of patients, respectively.

The change in lesion characterization due to added information from fused PET-CT was correct in six of these seven cases. Moreover, in seven cases, information from PET-CT led to the retrospective discovery of a lesion that was initially missed on PET. Five of these seven were later verified as tumor on biopsy.

Recurrent Disease
Several studies have established the efficacy of FDG-PET in recurrent disease. McGuirt et al reported that PET provided a distinct advantage over clinical examination and conventional imaging in the detection of tumor recurrence after RT.[15] Wong et al compared CT or MRI coregistered with FDG-PET to CT or MRI alone in the staging of recurrent disease.[11] This study reports accurate staging in 9 of 10 cases using combined imaging and 8 of 10 using CT or MRI alone.

In a second study of 68 patients with head and neck cancer, PET-CT was compared to PET alone with respect to accuracy of diagnosis and impact on patient care.[16] Of the patients analyzed, 16 had newly diagnosed head and neck cancer, 34 had recurrent disease, 8 had cancer of unknown primary, and 10 were being evaluated for residual disease after chemotherapy or radiation. PET-CT images were found to have a 74% better anatomic localization in areas previously treated with surgery or irradiation and 58% better anatomic localization in untreated areas. PET-CT significantly reduced the fraction of lesions judged to be equivocal by 53% and also had a higher accuracy of depicting cancer than did PET (96% vs 90%, P = .03). PET-CT altered patient management in 12 (18%) of the 68 patients and was thought to have a significant impact on patient care.

Among the reported limitations of physiologic imaging in recurrent disease is the inaccuracy of FDG-PET in

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>PET-CT</th>
<th>PET</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoch et al, 2003[12]</td>
<td>13</td>
<td>7</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>46/55 (84%)</td>
<td>9/14 (64%)</td>
<td>23/41 (56%)</td>
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CT = computed tomography; MRI = magnetic resonance imaging; NA = not available; PET = positron-emission tomography.
the early follow-up period after treatment. Keyes et al reported a high false-negative rate (17%) for PET in detecting recurrence 1 month after RT, compared to no false-negatives at 4- and 12-month follow-up scans.[17]

**PET-CT and RT Planning**

**Advantages of PET-CT**

The increased sensitivity and specificity of FDG-PET in the nodal staging of head and neck cancer has been well documented, and the anatomic information added by combined PET-CT can lead to even greater accuracy in the staging process. Several studies have evinced a clear role for PET-CT fusion in the management and RT planning of non–small-cell lung cancer.[18-23] Fewer data are available regarding the role of PET-CT fusion in patients with head and neck cancer.

In three recent studies of patients with head and neck cancer, PET-CT fusion was found to have an impact on RT target delineation.[24-26] In a study of 21 patients with nasopharyngeal or oropharyngeal primaries, Nishioka et al found that PET-CT detected 39 positive nodes in contrast to only 28 nodes detected by clinical exam and CT/MRI. In four patients, nodal status was increased, which had an impact on target delineation. Parotid sparing became possible in 71% of patients whose upper neck areas near the parotid glands were tumor free by PET-CT and except for one patient, no recurrences were seen at 18 months when the PET/CT defined volumes were used as the gross tumor volume.[24]

Daisne et al reviewed 10 patients with locally advanced oropharyngeal cancers who had MRI and PET coregistration with CT simulation images. They found that the average gross target volume (GTV) was 37% larger when MRI and PET were coregistered with CT in comparison to CT alone.[25] Ciernik et al performed a study assessing the feasibility of integrated PET-CT in RT planning. These data include a subset of 12 patients with head and neck cancer. Of these patients, six had a significant change (> 25%) in GTV determined using PET-CT compared to the GTV defined by CT alone. The mean change

![Figure 1: CT Axial Slice of a Patient With Left Nodal Metastasis From an Oropharyngeal Tumor—The arrows point to the computed tomography (CT)-defined (red line) and positron-emission tomography (PET)-defined (purple-shaded area) gross tumor volume (GTV). The red-shaded area corresponds to the tonsil tumor bed.](image1)

![Figure 2: Dose-Volume Histogram of Left Cervical Node From Patient in Figure 1—Arrows point to the computed tomography (CT)-defined gross tumor volume and positron-emission tomography (PET)-defined gross tumor volumes (GTVs), illustrating the amount of dose that each receives. The treatment can be tailored using intensity-modulated radiation therapy to deliver the appropriate dose to not only the CT-GTV but also the PET-GTV. In this case, both the PET- and CT-GTVs are receiving the appropriate dose.](image2)
PET-CT fusion has also been shown to decrease the amount of intraobserver variability in target volume delineation. Ciernik et al reported a decreased variance in GTV defined by the two radiation oncologists in their study using fused PET-CT. The mean difference in GTV for all tumors in the study using CT alone was reported as 26.6 cm³, compared with a mean difference of only 9.1 cm³ using combined imaging.[26] This represents a 65.8% decrease in intraobserver variability using PET-CT.

Because of enhanced detection of regional and distant metastasis, PET-CT has the potential for influencing patient staging and clinical management. Detection of regional nodal disease in head and neck cancer patients can significantly alter the radiation fields used in conventional radiation as well as the target volumes and ultimate doses of intensity-modulated radiation therapy (IMRT). The detection of distant metastasis by PET-CT can change the intent of treatment (from curative to palliative) and the type of treatment that a patient ultimately receives (ie, chemotherapy alone and not chemoradiation). In the future, the use of PET-CT in patients with head and neck cancer may lead to more accurate staging and more precise target volume delineation and consequent radiotherapy volumes and doses.

Emory University Experience

At our institution, we have analyzed the influence of FDG-PET–CT fusion on the management of patients with head and neck cancer. Since July 2002, PET-CT fusion has been an integral component of RT planning for our head and neck cancer patients, who are routinely treated with IMRT. Thus far, we have analyzed 36 patients with head and neck cancer who have been treated with IMRT and received PET-CT fusion as part of their treatment planning. This group included 8 women and 28 men with a mean age of 56 years. Primary site location was the oropharynx in 17 cases, nasopharynx in 5, larynx in 4, paranasal sinuses in 3, oral cavity in 2, and
Three of these patients underwent neck dissections before chemoradiation. Platinum-based chemotherapy was given concurrently with RT in 31 (86%). Changes in TNM score, American Joint Committee on Cancer (AJCC) stage, and management were noted in 13 (36%), 5 (14%), and 9 (25%) patients, respectively, based on PET-CT findings. PET-CT data upstaged AJCC stage in four and downstaged AJCC stage in one patient. RT volume and dose were altered in 5 (14%) and 4 (11%) patients, respectively, while a change in chemotherapy management occurred in 3 (8%). Five patients initially presented with cancer of unknown primary, and PET data confirmed oropharyngeal primaries in two of these patients. Two patients were found to have distant disease, and management goals were changed from curative to palliative. PET data also detected the presence of a synchronous primary lung cancer in one patient.

In the majority of patients, the PET-defined GTV was noted to be congruent with and significantly smaller than the CT-defined GTV. Figures 1 and 2 illustrate the PET- and CT-GTV of a left neck node metastasis and corresponding dose-volume histogram in a patient with oropharyngeal cancer, while Figures 3 and 4 display the PET- and CT-GTV of the primary tumor and corresponding dose-volume histogram in a patient with tonsillar cancer. The dose-volume histograms in Figures 2 and 4 are based on inclusion of only the CT-defined GTV in the planning tumor volume. We are currently evaluating whether the differences between PET- and CT-defined GTV have an impact on dose distribution.

Limitations of PET-CT

Limitations to the use of PET-CT fusion in RT planning include the quality of image fusion between the CT and PET-CT scans, consistency of target delineation with PET by visual determination and not by using an isointensity level or standardized uptake value, patient movement during the combined PET-CT procedure, and patient positioning being different between the CT simulation and the PET-CT. In addition, for head and neck patients, the presence of dental metallic implants or nonremovable bridgework can cause artifacts in attenuation-corrected images using the CT scan obtained with a combined PET-CT camera, and therefore, it is recommended that the nonattenuation-corrected PET images also be evaluated.[27]

At our institution, the quality of image fusion between CT and PET-CT images is evaluated subjectively by using three anatomic reference points in the head and neck for the registration process. An error of 5 mm between the fused images is the upper limit for what is considered an acceptable registration, and a discrepancy of 2 to 3 mm is the standard for most of our fused images. This may have a slight impact on the determination of GTV based on PET-CT. In a study of four patients with head and neck cancer, coregistration accuracy between MRI, PET, and CT ranged from 1.2 to 4.6 mm and was found to be highly consistent and reproducible among observers.[28]

Conclusions

Integrated PET-CT combines physiologic and anatomic imaging to better define malignant disease. In the case of head and neck cancer, PET-CT fusion is superior to FDG-PET or CT/MRI alone in the staging of disease and in distinguishing benign from malignant lesions. Furthermore, PET-CT is highly sensitive in the detection of recurrent disease when performed at least 4 months after treatment.

The greatest benefit of integrated PET-CT, in our review, is in radiotherapy treatment planning and in the detection of distant metastasis. Information from PET-CT can lead to changes in the target volume and RT doses employed and, hence, may be helpful in decreasing late effects of radiotherapy. PET-CT fusion has also been seen to decrease intraobserver variability of radiotherapy target delineation. The detection of distant disease may change the goal of patient management from cure to palliation. Potential weaknesses of PET-CT include limited availability, poor sensitivity in tumors with low FDG uptake, and reduced accuracy in early follow-up after radiotherapy.

In conclusion, combined PET-CT may offer significant advantages over single-imaging modalities in the staging of initial disease and radiotherapy treatment planning in patients with head and neck cancer.

This article is reviewed on pages 246 and 250.

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The Rusthoven/Koshy/Paulino Article Reviewed

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Positron-emission tomography (PET) and computed tomography (CT) fusion imaging is a rapidly evolving technique that is useful in the staging of non–small-cell lung cancer (NSCLC), Hodgkin’s disease, ovarian cancer, gastrointestinal stromal tumors, gynecologic malignancies, colorectal malignancies, and breast cancer. In their article, Rusthoven et al[1] describe the role of PET–CT in head and neck malignancies and include a review of all currently available literature. According to the authors, PET–CT is useful for staging head and neck carcinomas and for target volume delineation during radiation treatment planning.

**Staging Standard**

PET–CT is quickly becoming the standard of care for staging malignancies at certain anatomic sites. A study by Antoch et al[2] compared PET–CT with whole-body magnetic resonance imaging (MRI). The overall tumor-node-metastasis (TNM) stage was correctly determined in 77% of patients with PET–CT and in 54% with MRI. Moreover, compared with MRI, PET–CT had a direct effect on disease management in 12 patients.

In a landmark study by Lardinois et al published in the *New England Journal of Medicine,*[3] PET–CT was found to improve the accuracy of NSCLC staging over PET and CT alone; the combined modality provided additional staging information in 41% of patients. In head and neck tumors, PET–CT again appears to be superior to PET alone, and probably also to PET and CT when both are assessed side by side for detection of tumor invasion and staging accuracy.[4] Schoder et al[5] found that PET–CT was more accurate in depicting cancer than was PET alone, and PET–CT findings resulted in a change in treatment.

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in 12 of 68 patients, further establishing the higher efficacy of PET-CT over PET alone in recurrent head and neck cancer. Therefore, PET-CT may become a “one-stop shop” for oncologic staging of head and neck cancers.\[6\]

Advantages of PET-CT

A major advantage of PET-CT over PET alone is the notable reduction in scanning time. A PET scan is composed of an emission scan, depicting the distribution of fluorine-18 fluorodeoxyglucose (FDG) in the body, and a transmission scan that is used for attenuation correction. For PET, the transmission scan can take approximately 20 minutes, increasing the total scanning time to approximately 50 minutes.\[7\] In PET-CT, the CT data are used for attenuation correction, and a whole-body scan can be performed in under 2 minutes.\[8\]

An additional advantage of PET-CT is that the intrinsic hardware provides high-quality images through coregistration of both image datasets in a relatively fast acquisition time.\[6\] The coregistration of datasets obtained by different techniques (ie, PET with CT or MRI) at different time points may lead to inaccurate anatomic and physiologic delineation of the tumor with respect to normal tissues. These inaccuracies may be caused by anatomic changes, neck repositioning, or head and neck swelling.

Feasibility studies have found that the use of PET-CT for planning three-dimensional (3D) conformal radiation therapy improves the standardization of volume delineation compared with CT alone.\[9,10\] Rusthoven et al[1] report that since July 2002, PET-CT fusion imaging has been an integral planning component for intensity-modulated radiation therapy in patients with head and neck cancer. Changes in the TNM stage have ranged from 14% to 36% with PET-CT, and treatment volume and dose have been altered in 14% and 11% of patients, respectively.

Target Volumes

That said, the authors do not define the appropriate threshold by which physiologic disease is correlated with anatomic disease. The resolution for clinical PET is approximately 5.0 to 7.0 mm, and without pathologic correlation to help determine the true extent of gross and microscopic physiologic disease, the radiation treatment volumes could be altered drastically. Furthermore, partial volume and misregistration effects can extend a portion of the PET-defined target volume into air spaces (ie, the larynx or trachea), which may alter the treatment volume. Rusthoven et al[1] also note that PET-CT is not as sensitive in diagnosing tumors < 2 cm in diameter and may result in false-positive findings in inflammatory tissue or lesions.

Institutional variability in defining the threshold of malignant disease with physiologic imaging can have a profound effect on the contoured biologic tumor volume. By raising or lowering the threshold, the resultant sensitivity is altered, and the volume of contoured disease decreases or increases, respectively. This may ultimately result in the underdose or overdose of the actual tumor volume.

Recently, Scarfone et al[11] found that the threshold of PET images was adjusted on a case-by-case basis to adequately visualize FDG-avid lesions relative to the background, with the resultant “average” threshold being approximately 50% of maximum image intensity. They further expressed concern about the use of PET-CT for radiation treatment planning by pointing out that the optimal threshold needed to standardize the settings has yet to be determined. For this reason, we have resisted the urge to modify treatment planning contours by incorporating PET-CT in radiation treatment planning for head and neck cancer at our institution. Future studies confirming gross and microscopic pathologic disease with PET-CT will help define the appropriate threshold settings to better delineate target volumes.

Conclusions

In the multidisciplinary management of patients with cancer, PET-CT is an exciting and rapidly evolving technique that is improving our ability to make better treatment decisions. The use of PET-CT for staging primary and recurrent head and neck lesions is “ready for prime time,” but its application in head and neck cancer treatment planning should be viewed as investigational until we can better correlate our imaging findings with gross and microscopic pathologic findings and resolve the issues of variable FDG uptake by the tumor and nodal metastases as well as institutional threshold variability.

—Steven J. Frank, MD
—Thomas Yang, MD
—K.S. Clifford Chao, MD

References


A second review, by Drs. Meltzer and Branstetter, appears on page 250.
In their article, Rusthoven and colleagues highlight the utility of combined positron-emission tomography/computed tomography (PET-CT) imaging for diagnosing primary and recurrent head and neck carcinoma, and for defining tumor target volumes for radiotherapy treatment planning in the head and neck. PET offers noninvasive measures of tumor biology yet suffers from limited spatial resolution; the physiologic information obtained with PET is complementary to the high-resolution structural information obtained with CT or magnetic resonance imaging (MRI).

The authors provide us with an up-to-date review of the literature on fluorine-18 fluorodeoxyglucose (FDG)-PET used in conjunction with CT in the head and neck cancer patient. FDG-PET has been shown to be effective for staging and restaging head and neck cancer, and monitoring therapeutic response. However, the highly detailed anatomy and variable physiologic uptake of FDG in the head and neck—both of which are altered by surgery and other cancer therapies—emphasize the special advantages of combining structural and functional imaging in head and neck cancer.

**Combined Scan vs Post Hoc Fusion**

Rusthoven et al note that PET and CT data can be coregistered by a post hoc fusion of images acquired on separate scanners, or can be coregistered after acquisition on a single combined PET-CT scanner. The authors do not differentiate between studies based on data from a single combined scanner and studies based on post-hoc fusion. However, we feel it is appropriate to emphasize that retrospective fusion of image data acquired on separate devices is fraught with pitfalls in the head and neck.

Since the relative spatial relationships among head and neck structures vary from scan to scan, and fixing the neck in a hard collar is cumbersome, registration of individually acquired PET and CT images is difficult to achieve without the introduction of complex nonlinear algorithms. Reports on the accuracy of rigid-body approaches do not adequately reflect the real life setting. Patient considerations—including the need for two imaging procedures rather than one, and potential changes in tumor and nontumoral tissue characteristics if the time delay between acquisition of the PET and CT images is weeks or months—further strengthen the favorability of combined scanners over post hoc techniques.

**Shifting Clinical Protocols**

Until recently, serial imaging with CT or MRI was the predominant approach to monitoring the head and neck cancer patient, with PET imaging reserved (when available) for difficult cases. However, the increasing prevalence of combined PET-CT scanners at both academic medical centers and in the community has shifted clinical protocols at some institutions to involve or substitute PET-CT studies at regular intervals.

Recently, Schoder and colleagues evaluated 68 head and neck cancer patients with PET-CT.[4] FDG-PET images were initially evaluated by consensus and lesions graded as benign, equivocal, or malignant. Then the CT data were made available, and the incremental benefit of PET-CT over PET alone was assessed. The accuracy of PET significantly increased from 90% to 96%, and the fraction of equivocal lesions was reduced by 53%. Branstetter et al prospectively demonstrated (in 65 patients) improved detection of malignancy in the head and neck with combined PET-CT images relative to both FDG-PET and contrast-enhanced CT alone when each modality was interpreted separately by expert readers.[5]

Rusthoven et al note that PET is less reliable immediately after cancer treatment, both surgical and nonsurgical. Although false-negative results from microscopic deposits of viable tumor may never be obviated, we believe that false-positive results are diminished with the use of PET-CT instead of PET, and with greater experience of the interpreting radiologists.

**Impact on Radiation Therapy**

Literature on the application of PET-CT as a basis for radiation treatment planning is limited, yet its potential benefit is evident, particularly for intensity-modulated radiotherapy, where accurate delineation of tumor and spared normal structures may limit patient morbidity. Work by Scarfone and colleagues demonstrated the modification of tumor target volume definitions when FDG-PET information was added to CT simulation data.[6]

Ciernik et al specifically evaluated the utility of combined-scanner PET-CT images for target volume delineation.

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tion in 39 patients with solid tumors of the lung, pelvis, and head and neck.[7] The addition of overlay PET data either reduced or increased the target volume more than 25% in 56% of cases, including 6 of the 12 head and neck tumor cases studied. Furthermore, the use of integrated PET-CT information for treatment planning for three-dimensional conformal radiation therapy decreased volume delineation variability between two oncologists who independently conducted treatment planning first with CT alone, then using PET-CT.

Rusthoven et al review their own preliminary work as well as these and other recent studies that suggest PET-CT imaging may affect radiation therapy planning in a substantial and positive way. We agree that PET-CT will have a strong impact on radiation planning in the head and neck. We also appreciate their note of caution that awareness of CT-based attenuation artifacts and reconstruction of non–attenuation-corrected images is warranted.[8]

It is particularly important that referring ENT surgeons become aware of the utility of PET-CT in radiation planning. Patients who are likely to be treated nonsurgically benefit from the application of a customized radiation planning mask during PET-CT scanning. This mask can dramatically improve the reproducibility of patient position between diagnostic and treatment scans. Thus, nonsurgical patients should be seen by a radiation oncologist before the PET-CT is obtained, to ensure that the scan is performed properly.

—Carolyn Cidis Meltzer, MD
—Barton F. Branstetter IV, MD

References