USE OF INTEGRATED $^{18}$F-FDG PET/CT TO IMPROVE THE ACCURACY OF INITIAL CERVICAL NODAL EVALUATION IN PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Abstract: Background. We investigated the accuracy of performing cervical nodal evaluation with using integrated $^{18}$F-fluorodeoxyglucose positron emission tomography (PET)/CT for squamous cell carcinoma (SCC) of the head and neck as compared with using PET and contrast-enhanced CT (CECT) alone.

Methods. The presence of metastatic lymphadenopathy in each cervical nodal group (level I–VI) and the nodal (N) classification of 47 patients with SCC of the head and neck were determined by using PET, CECT, and PET/CT, respectively, and the results were verified according to the histopathologic findings.

Results. Among the 91 foci that had abnormal uptake on PET, the combined PET/CT images provided additional information over PET for the anatomical localization and lesion characterization of 18 sites (19.8%) in 17 patients (36.2%). PET/CT also showed the best results among the three imaging modalities for the sensitivity, specificity, and accuracy (91.8, 98.9, and 97.1%, respectively) for predicting metastatic nodes on a level-by-level analysis, and PET/CT had a higher accuracy (85.1%) for the pathologic nodal classification over the clinical examinations (68.1%) or PET (70.2%).

Conclusions. Combined PET/CT images are more accurate than the PET or CECT images alone for conducting cervical node evaluation in the patients suffering with head and neck SCC.

Keywords: head and neck neoplasms; squamous-cell carcinoma; tumor staging; positron-emission tomography; computed tomography

Contrast-enhanced CT (CECT) has generally been the mainstay modality for evaluating lymph node metastasis for a long time. In the late 1990s,
a new functional imaging method, ie, positron emission tomography (PET) using F-18 fluoro-deoxyglucose (FDG), was suggested as another good modality for diagnosing nodal metastasis in many malignant diseases. Many studies have already reported that FDG PET has a higher sensitivity and specificity for detecting lymph node metastasis in head and neck cancer than do the other conventional imaging modalities. However, conventional PET has some limitations for the exact identification and accurate anatomical localization of disease.

Recent advances in technology have made it possible to fuse the anatomical images with the functional images through the use of computer hardware. There are several reports showing improved diagnostic accuracy with using a PET/CT fusion image. However, the usefulness of PET/CT for head and neck cancer has been described only recently. Furthermore, only a few reports have mentioned the diagnostic usefulness of PET/CT imaging over conventional PET or CT imaging for classifying cervical lymph node disease in head and neck cancer.

In this study, we investigated the accuracy of evaluating cervical nodes using PET/CT fusion images for squamous cell carcinoma (SCC) of the head and neck in comparison with using PET or CECT.

MATERIALS AND METHODS

Subjects. From June 2003 to October 2004, 136 consecutive patients who were initially diagnosed with SCCs of the head and neck underwent prospective FDG PET/CT for the initial tumor staging. Among them, 56 patients who underwent cervical lymph node dissection or primary tumor removal were initially included in this study. Nine of these 56 patients were excluded from further analysis due to the long time interval between their PET/CT and CECT scans and the neck dissection (>30 days). Finally, 47 patients (41 men and 6 women; mean age, 56.3 ± 10.4 years) were eligible for inclusion in this study. Nine of these 56 patients were excluded from further analysis due to the long time interval between their PET/CT and CECT scans and the neck dissection (>30 days). Finally, 47 patients (41 men and 6 women; mean age, 56.3 ± 10.4 years) were eligible for inclusion in this study. The primary tumor sites were as follows: the oral cavity in 21 patients, the larynx in 11 patients, unknown primary cancer in 5 patients, the oropharynx in 5 patients, the hypopharynx in 4 patients, and the parotid gland in 1 patient. The institutional review board of Samsung Medical Center approved the protocol for this study.

All the study subjects underwent PET/CT and CECT preoperatively with a time interval of less than 1 month between the 2 studies. The N classification for the 47 patients in this study was determined according to the American Joint Committee on Cancer (AJCC) staging manual (6th edition, 2002) and by using the clinical and radiographic information.

The final diagnoses were histopathologically proven after surgery for all the patients.

Integrated ^18^F-FDG PET/CT. All the patients fasted for at least 6 hours prior to the PET study. The PET/CT scans were performed using a GE Discovery LS PET/CT scanner (General Electric, Milwaukee, WI). Whole-body CT scanning was performed by a continuous spiral technique using an 8-slice helical CT with a gantry rotation speed of 0.8 second. The CT scan data were collected with the following parameters: 40 to 80 mAs, 120 KeV, a section width of 5 mm, and a table feed of 5 mm per rotation. No intravenous or oral contrast agent was used. After the CT scan, an emission scan was performed from the thigh to the head for 5 minutes per frame for a total of 45 minutes after the intravenous injection of 370 MBq FDG. The attenuation-corrected PET images using the CT data were reconstructed by using an ordered subset expectation maximization algorithm (28 subsets, 2 iterations), and they were displayed in a 128 × 128 matrix (pixel size = 4.29 × 4.29 mm² with a slice thickness of 4.25 mm). Accurate coregistration of the separate CT and PET scan data was performed with commercially available software (eNTEGRA, Elgems, Haifa, Israel). The standardized uptake values (SUVs) were acquired with use of the attenuation-corrected images, the amount of injected FDG, the body weight of each patient, and the cross-calibration factors between the PET and the dose calibrator.

Contrast-Enhanced CT. Apart from the PET/CT scan, an enhanced CT scan (LightSpeed Ultra or Ultra 16, GE, Milwaukee, WI) of the head and neck was performed with the following parameters: 160 mAs, 120 KeV, a section width of 3.75 mm, and a table feed of 8.75 mm per rotation. For contrast enhancement, 90 mL of an iodinated contrast agent (Ultravist 300, Schering, Berlin) was injected intravenously at 3 mL/second. The scan delay time was 30 seconds and an automated injector was used for the administration of the contrast media.

Image Analysis. Two experienced nuclear medicine physicians working together reviewed the
PET image and the fused PET/CT images, but they were not informed about the primary tumor site and the clinical information. Two experienced radiologists who specialized in interpreting head and neck sections read the CECT images. These reviewers were blinded to the results of the other imaging examinations or to the final pathologic results, and they performed all the image interpretation. Image interpretation concentrated on detecting the presence of cervical metastatic lymphadenopathy in each of the cervical nodal groups (level I–VI) on both sides of the neck, and they determined the nodal stage for each patient.11

First, the nuclear medicine physicians reviewed just the attenuation-corrected PET images without the CT images for correcting the attenuation, and the physicians found those lesions that had a focally increased uptake of contrast agent, which suggested lymph nodes. The anatomical location (level I–VI) and the significance of each lesion (benign or malignant) were determined using the maximal SUV of each lesion with a cut-off of 3.5. A cut-off SUV of 4.0 was used in this study for the jugulodigastric nodes, which is where reactive hyperplasia is frequently found.12 To directly compare the results of PET and PET/CT, we adopted the values (pSUV = 3.5 and 4.0) of our previous study for non-small cell lung cancer because there has been no strict cut off point for the SUV in the literature to differentiate benign from malignant tissues in both the primary site and the cervical lymph nodes in head and neck cancer.12

The nuclear medicine physicians then reviewed the PET images, the CT images, and the fused PET/CT images; they reevaluated the lesions for determining their anatomical location and if there was any significant possibility for malignancy. For example, a non-nodal focal uptake in a blood vessel, muscle, or salivary gland that mimicked a lymph node was considered benign. A lymph node with peripheral low attenuation suggesting a fatty hilum on the CT image was considered benign even if it had a high FDG uptake.13 On the other hand, a lymph node containing a lucent portion on the CT image that was suggestive of necrosis and a low FDG uptake on the PET image was considered malignant even if it had a low FDG uptake.13

For the CECT scan, the 2 radiologists independently determined the location (level I–VI) and the significance (benign or malignant) of the visualized cervical lymph nodes. If a discrepancy of interpretation occurred, they discussed the results of interpretation and made a final joint decision on the node status. Regional lymph nodes of the head and neck region that were greater than 10 mm on the long-axis diameter were considered to be malignant.13 The size criterion of 15 mm on the long-axis diameter was applied for the submandibular and jugulodigastric nodes. In addition, a lymph node with a central lucency that suggested necrosis was considered malignant, regardless of its size.13 The lymph nodes with a borderline size of 8 to 10 mm (10–15 mm for the submandibular and jugulodigastric nodes) were staged as having tumor involvement if there were other signs of malignancy such as a spherical lymph node shape or pathologic contrast enhancement.13

The diagnostic accuracies of the PET, PET/CT, and CECT scans for evaluating the cervical nodes were compared with the histopathologic results, respectively, in terms of the individual nodal groups (level I–VI) and the nodal classification.

**Surgical Procedures.** All subjects underwent ipsilateral or bilateral neck dissection performed by head and neck surgeons, with the interval being less than 1 month from the surgery to the time of the PET/CT or CECT scans.

Bilateral neck dissection was performed in 17 of the total 47 patients, and unilateral neck dissection was performed in the remaining 30 patients. The extent of neck dissection was determined according to the preoperative CECT or PET/CT information. A total of 64 (17 + 47) sides of the neck lymph node basin were dissected by way of radical neck dissection (n = 3), modified radical neck dissection (n = 18), extended supramedial neck dissection (n = 9), suprathyroid neck dissection (n = 10), lateral neck dissection (n = 21), or highly selective neck dissection that targeted just 1 or 2 neck levels (n = 3).

The surgeon dissected all the visible or palpable lymph nodes on a level-by-level basis, giving consideration to the results of the preoperative staging work-up, including the PET/CT and CECT scans. Those dissected nodes were then analyzed histopathologically, and the laboratory results were compared with the results of the PET/CT and CECT scans.

**Statistical Analysis.** The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for identifying the cervical nodal metastasis of each dissected neck level were
determined for the CECT, PET, and PET/CT fusion images. The accuracy for determining the nodal staging on the CECT, PET, and PET/CT fusion images was also done in comparison with the pathologic nodal stage. Statistical differences between the imaging modalities were analyzed by employing the McNemar test for the paired variables and Fisher's exact test for the nonpaired variables. \( p \) values less than .05 were considered to indicate statistical significance.

**RESULTS**

**Improved Anatomic Localization and Lesion Characterization.** A total of 91 foci that showed focally increased FDG uptake were considered to be lymph nodes after the interpretation of the PET images alone (Figure 1).

In 9 patients, the PET/CT fusion imaging improved the anatomic localization of 9 foci (9.9\%) with regard to the lymph node level (ie, a change of the lymph node level), over using the PET images alone. The fused PET/CT images had adequate image quality to determine the level of each lymph node that showed an increased FDG uptake. In our series, there were no differences between the CECT and integrated PET/CT images for determining the level of each node that showed an increased uptake.

Another 4 foci (4.4\%) that showed high FDG uptake in 4 patients on the PET images were suggestive of malignant lymph nodes, and they were reclassified as non-nodal benign lesions (blood vessel, neck muscle, submandibular gland, or parotid gland) after reviewing the fused PET/CT images (Figure 2). Three lymph nodes (3.3\%) that showed high FDG uptake in 3 patients on the PET images were suggestive of malignant lymph nodes, and they were reclassified as benign nodal lesions after reviewing the fused PET/CT images because they had peripheral low attenuation that suggested the presence of a reactive fatty hilum. All 3 of those nodes were confirmed histopathologically to be benign lymph nodes (Figure 3). In 1

![Figure 1](image1.png)

**FIGURE 1.** Improved anatomic localization and lesion characterization according to the positron emission tomography (PET)/CT image analysis. PET/CT provided additional information for the anatomic localization or the lesion characterization over using the PET images alone in 18 sites (19.8\%) of 17 patients (36.2\%), and it correctly changed the nodal classification in 7 of the 47 study patients (14.9\%) over using just the PET images.

![Figure 2](image2.png)

**FIGURE 2.** (A) The positron emission tomography (PET) image of a 69-year-old man with supraglottic cancer showed an abnormally high focal FDG uptake at the left neck level II area that mimicked a metastatic lymph node (maximum standardized uptake value, 6.5). (B, C) However, the CT and fused PET/CT images demonstrated that it was not a lymph node, but rather it was an intraparotid lesion that was not related to any metastatic lymph node. It was confirmed histopathologically to be a benign Warthin's tumor in the left parotid gland. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
patient, 2 foci that showed mild FDG uptake at the right neck level I area on the PET image were suggestive of benign nodes, and they were classified with the single malignant nodes with necrosis after reviewing the fused PET/CT images; these 2 nodes were confirmed histopathologically to be malignant.

Therefore, for a total of 91 foci that had abnormal FDG uptake on the PET/CT images, the PET/CT images provided additional information for the anatomic localization or lesion characterization over the PET images at 18 sites (19.8% in 17 patients (36.2%). Using the PET/CT images allowed the reviewers to correctly change the nodal stage for 7 of those 47 patients over using the PET images alone.

**Improved Cervical Node Evaluation.** Cervical lymph nodes were dissected at 242 neck levels (I:II:III:IV:V:VI = 42:68:59:49:21:3), and this included all the lymph nodes that were suspicious for malignancy on the preoperative work-up: malignant cells were found at 61 neck levels (I:II:III:IV:V:VI = 6:22:21:9:3:0). There were 4 neck levels in 2 patients with malignant lymph nodes that had no significant focal FDG uptake. The maximal SUV of the malignant lymph nodes with significant FDG uptake (mean SUV, 11.9 ± 6.5; range, 2.8–27.7) was significantly higher than the maximal SUV of the benign lymph nodes with significant FDG uptake (mean SUV, 3.7 ± 0.9; range, 2.1–5.7; \(p < .001\)).

Figure 4 shows the diagnostic results of each imaging modality for evaluating cervical nodes on a level-by-level analysis in comparison with the histopathologic findings. There were no significant differences for the diagnostic results between the PET and the CECT images. On the contrary, the combined PET/CT images showed significantly better results than did the PET images alone, except for the negative predictive value. PET/CT also showed significantly better results than those results of the CECT, except for the sensitivity and the negative predictive value. There was no case where PET was correct and PET/CT was incorrect for evaluating the cervical nodes. For 14 cervical lymph node groups, the CECT and PET/CT showed different results for the presence of malignant lymph nodes. The results of the PET/CT images were correct for 12 of those 14 neck levels (85.7%), based on confirmation via the histopathologic results.

Table 1 shows the results of the clinical examinations and each imaging modality for determining the nodal classification in comparison with the pathologic nodal classification. Twenty-seven patients (57.4%) had pathologically malignant lymph nodes. The PET/CT images showed a high accuracy of 85.1% for determining the pathologic nodal classification of each patient; this was significantly better than the accuracy of the clinical examination (68.1%) or with using the PET images (70.2%) alone. Discrepancies for determining the nodal classification of each patient between the PET/CT images and the PET images alone were found in 7 cases (14.9%). The nodal classification using the PET/CT images was correct in all of those 7 cases in comparison with the pathologic nodal classification.
DISCUSSION

Our results demonstrated that the integrated FDG PET/CT images significantly improved the anatomical localization and lesion characterization when performing cervical nodal evaluation over the PET images alone for the patients with head and neck SCC. More importantly, this improvement in anatomical localization and lesion characterization resulted in the correct differentiation between the malignant nodes and the benign lesions in 20% of the focal lesions that had an increased FDG uptake and in 36% of the subjects. Furthermore, the sensitivity, specificity, and diagnostic accuracy for detecting the neck levels with malignant nodal involvement were significantly improved by using the fused PET/CT images; the PET/CT images showed a 15% increase for the accuracy of nodal staging over using the PET images alone. The authors used the maximal focal FDG uptake values when evaluating anatomic localiza-
tion and lesion characterization of the lymph nodes, which helped to more accurately estimate the character and status of the individual lymph nodes. To directly compare the diagnostic accuracy of PET and PET/CT for the lymph node status, we adopted threshold values of the FDG uptake (pSUV = 3.5 and 4.0). 

The sensitivity and specificity of PET in our study were 80.3 and 92.8%, respectively, which was similar to those values of the previous reports, ie, a sensitivity of 82% to 91% and a specificity of 83% to 100%. However, the sensitivity (90.2%) and specificity (93.9%) of CECT in our study were higher than those of the previously reported data (81%–84% for sensitivity, 81%–85% for specificity). These differences may be partly explained by the analysis of the thin-sectioned (3–4 mm) CT images and according to the ability to interpret images by a specialized head and neck radiologist.

There have not been many studies concerning the utility of FDG PET/CT for head and neck cancer. A recent study showed the superiority of using PET/CT fusion images for the diagnostic accuracy of depicting head and neck cancer compared with PET. However, they did not analyze the lymph node metastasis by the nodal classification, as based on the level system, which is important for surgical planning. In addition, they included different cell types of head and neck cancers, and this may have potentially affected the interpretation of the PET images. In the present study, we focused on SCCs in the head and neck, and all the subjects underwent neck node dissection. Therefore, we were able to directly compare the diagnostic accuracy for cervical nodal evaluation between the PET, CECT, and PET/CT images on a neck level basis with the pathologic findings.

Many previous studies have stated that FDG PET was superior to the conventional imaging modalities for the evaluation of neck lymph node metastases in head and neck cancer. However, these studies did not provide anatomical information, and most of them did not perform a level-by-level analysis for evaluating the cervical nodes. In this study, the diagnostic results of using PET alone without reviewing the CT images were not better than those of using CECT for the cervical nodal evaluation in terms of both the individual neck levels and the nodal classification. This supports the mandatory clinical practice of performing correlative interpretation of the conventional PET images with the additional anatomical imaging, including CECT or MRI. On the basis of our results, there were no cases or neck levels for which the PET images provided additional or correct diagnostic information for cervical node evaluation over the combined PET/CT images. Therefore, because of its definite advantages, PET/CT should be performed rather than just conventional PET for the patients with head and neck cancer.

Among the 3 imaging modalities, PET/CT showed the best results for the initial cervical nodal classification and also for detecting the individual neck levels with metastatic nodes. This was partly the result of the anatomical and morphological information provided by the CT images. Especially, the alleged CT criteria for differentiating benign from malignant cervical lymph nodes, such as the presence of necrotic nodes and nodes with a peripheral fatty hilum, contributed to the improved accuracy of using PET/CT for the cervical nodal evaluation together with the SUV measurement. This suggests that CT findings also help to interpret the PET/CT images for the patients with head and neck cancer. For the nodal classification, PET/CT was correct in all 7 cases that showed different results from interpreting the PET images. Of the 14 neck levels where CECT and PET/CT showed different results for the presence of malignant lymph nodes, the results of the PET/CT were correct for 12 neck levels (85.7%) in comparison with the histopathologic results.

PET/CT also has an additional advantage for conducting whole-body imaging; this may be useful for detecting distant metastases or a second primary cancer. If PET/CT can fully replace the conventional work-up for distant metastasis or double primary cancer, then the cost of PET/CT may be acceptable. Further study is needed to prove PET/CT’s cost-effectiveness.

Eighteen of 47 patients (38.3%) were initially classified as the clinical N0 classification based on the physical examination and the CECT images. Among them, 4 patients (4 of 18, 22.2%) showed a positive result for malignancy in lymph nodes by using PET/CT; however, the final histopathology in 3 patients revealed no malignant cells in their lymph node basins and only 1 had malignant cells in the lymph node group, as the PET/CT images predicted. On the contrary, 3 patients supposedly had malignant-negative lymph nodes according to PET/CT, but they had positive lymph nodes according to the CECT images received a final pathologic classification of N0. Although there was a limitation due to the small number patients for drawing any conclusions, we think that
PET/CT has no advantage over CECT in detecting occult metastasis for the head and neck cancer patients who have the clinical N0 classification. One of the reasons for this may be that PET or PET/CT can only detect the lymph nodes that have a certain volume of malignant cells sufficient to change the glucose metabolism, and neither of these modalities can detect micrometastasis.

In 5 of 47 patients (10.6%), we changed the extent of neck dissection after using the PET/CT images. Three patients with malignancy-negative lymph nodes, as reported by PET/CT, but who had positive lymph nodes according to CECT, were able to avoid comprehensive neck dissection. In 1 patient, the results of PET/CT changed the contralateral selective neck dissection to a contralateral comprehensive neck dissection. In another patient, PET/CT changed the nodal classification of N2b to N1, so therapeutic supraomohyoid neck dissection was applied to this patient instead of a modified radical neck dissection. PET/CT correctly predicted the nodal status for these 5 patients according to the final histopathologic report.

In conclusion, integrated PET/CT is more accurate than conventional PET and CECT alone for evaluating the cervical nodes in the patients with head and neck SCC.

REFERENCES