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CLINICAL INVESTIGATION **Head and Neck**

IMPACT OF FDG-PET/CT IMAGING ON NODAL STAGING FOR HEAD-AND-NECK SQUAMOUS CELL CARCINOMA

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Purpose: To evaluate the impact of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging on nodal staging for head-and-neck squamous cell carcinoma (SCC).

Methods and Materials: The study population consisted of 23 patients with head-and-neck SCC who were evaluated with FDG-PET/CT and went on to neck dissection. Two observers consensually determined the lesion size and maximum standardized uptake value (SUV_{max}) and compared the results with pathologic findings on nodal-level involvement. Two different observers (A and B) independently performed three protocols for clinical nodal staging. Methods 1, 2, and 3 were based on conventional modalities, additional visual information from FDG-PET/CT images, and FDG-PET/CT imaging alone with SUV data, respectively.

Results: All primary tumors were visualized with FDG-PET/CT. Pathologically, 19 positive and 93 negative nodal levels were identified. The SUV_{max} overlapped in negative and positive nodes <15 mm in diameter. According to receiver operating characteristics analysis, the size-based SUV_{max} cutoff values were 1.9, 2.5, and 3.0 for lymph nodes <10 mm, 10–15 mm, and >15 mm, respectively. These cutoff values yielded 79% sensitivity and 99% specificity for nodal-level staging. For Observer A, the sensitivity and specificity in Methods 1, 2, and 3 were 68% and 94%, 68% and 99%, and 84% and 99%, respectively, and Method 3 yielded significantly higher accuracy than Method 1 ($p = 0.0269$). For Observer B, Method 3 yielded the highest sensitivity (84%) and specificity (99%); however, the difference among the three protocols was not statistically significant.

Conclusion: Imaging with FDG-PET/CT with size-based SUV_{max} cutoff values is an important modality for radiation therapy planning. © 2007 Elsevier Inc.

PET/CT imaging, Head-and-neck cancer, Nodal staging, GTV.

INTRODUCTION

Advances in sophisticated radiotherapy (RT) techniques, notably three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT), render the precise delineation of the gross tumor volume (GTV) essential for RT planning. This is particularly important in head-and-neck squamous cell carcinoma (SCC) where normal and abnormal structures are in close proximity. In the interpretation of morphologic imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), the GTV boundary is often vague in the presence of inflammatory changes around the tumor or interference by metal artifacts, and their normal appearance on these images renders the detection of metastatic lymph nodes difficult. These factors contribute to a marked variability in GTV assessments even among experienced radiation oncologists, resulting in a possible geographic miss of the tumor or unnecessary irradiation of normal tissues (1).

Functional imaging with 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), which provides information about glucose metabolism, may improve the consistency of GTV delineation (2–4). 18F-fluorodeoxyglucose PET and its quantitative parameter, the standardized uptake

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value (SUV), have been used to evaluate the staging, treatment response, and recurrence detection of a wide range of solid cancers, including head-and-neck SCC. The sensitivity and specificity of FDG-PET for the detection of nodal involvement reportedly were 61–96% and 80–99%, respectively; with CT/MRI they were 53–82% and 71–97% (4–7). On the other hand, because of the limited anatomic resolution of FDG-PET, precise tumor localization requires careful correlation with structural images. Imaging with PET/CT provides the morphologic information of CT and the functional information of PET (8–12).

Although FDG-PET/CT imaging has been used in the evaluation of head-and-neck SCC, its role in initial staging has not been fully addressed (13–15). Some studies reported that RT planning was changed on the basis of information yielded on FDG-PET/CT fused images; however, they did not provide pathologic confirmation of the imaging findings (16–18). The purpose of this study was to evaluate the impact of FDG-PET/CT imaging on nodal staging for head-and-neck SCC.

METHODS AND MATERIALS

Written prior informed consent to undergo FDG-PET/CT imaging and receive treatments was obtained from all patients. The institutional review board of our hospital approved this retrospective study; patient informed consent for inclusion in this study was waived. To protect patient privacy, we removed all identifiers from our records at the completion of our analyses.

Patients, diagnosis, and treatment

Between December 2004 and January 2006, 54 patients who had undergone pretreatment evaluation at our hospital for head-and-neck SCC were introduced to an extramural PET center for routine FDG-PET/CT imaging. Of these, 23 (20 men, 3 women; mean age, 66.9 years; age range, 26–82 years) went on to resection of the primary tumor (1 laryngeal, 3 mesopharyngeal, 7 hypopharyngeal, 12 oral cavity tumors) with neck dissection and were studied further. All patients had undergone preoperative conventional workup, including ultrasound, contrast-enhanced CT, and MRI of the head and neck. On routine radiology reports, the nodal level (I–V), defined by the American Joint Committee on Cancer classification of cervical lymph nodes and based on their level and location, and the diagnosis of cervical lymph node malignancy based on CT or MRI findings, conformed with accepted morphologic criteria. That is, (*1*) all level II nodes were $>$1.5 cm and all level I, III, IV, and V and retropharyngeal nodes were $>$1.0 cm in maximum axial diameter, (*2*) all nodes manifested internal central or peripheral attenuation suggestive of necrosis, (*3*) there was extracapsular extension, and/or (*4*) obliteration of fat or perivascular soft tissue planes (8, 19).

The decision to perform selective or radical neck dissection was made by experienced head-and-neck surgeons and based on clinical TNM stage and patient performance status. Thus, patients with N0 disease underwent selective unilateral dissection, those with unilateral adenopathy received modified radical unilateral dissection, and patients with bulky unilateral disease or bilateral adenopathy were treated by bilateral selective or radical neck dissection. Neck dissection specimens were removed en bloc and divided into the nodal levels. Pathologic findings on the lymph nodes were recorded at each anatomic level. Retropharyngeal lymph nodes were excluded from this study because they were not sampled by neck dissection.

FDG-PET/CT imaging

18F-fluorodeoxyglucose PET and CT scans were obtained on the same day with the patient supine and the head immobilized with a neutral-position head cradle and tape. 18F-fluorodeoxyglucose PET imaging was with a whole-body 3D PET scanner (Allegro; Philips Medical Systems, Cleveland, OH) (20). The patients fasted for 4–6 h before receiving the FDG injection, and their blood glucose levels were recorded. Images from the skull base to the pelvis were acquired approximately 60 min after the intravenous administration of 5–10 mCi (185–370 MBq) of FDG. To minimize normal muscle uptake, patients lay in a quiet, dark room. Transmission images for attenuation correction were acquired with a single ^{137}Cs source that creates CT-like images. The transmission and emission images were reconstructed using the 3D-RAMLA (row-action maximum likelihood algorithm) iteration reconstruction algorithm; the reconstructed images had a slice thickness of 4 mm and a matrix of 128 $\times$ 128.

Noncontrast-enhanced CT images were obtained on a four-channel multidetector row CT scanner (Robusto; Hitachi Medico Technology, Chiba, Japan); the slice thickness was 3.75 mm, the matrix 512 $\times$ 512. Computed tomography data were transferred to the PET system, and image registration was performed using Syntegra software (Philips Medical Systems). The CT and ^{137}Cs transmission images were registered, and then FDG-PET/CT fused images were obtained by exchanging the ^{137}Cs transmission images with FDG-PET images. Registration was with a combination of automatic and manual methods.

The SUV, an index of glucose metabolism on FDG-PET images, is the ratio between the measured and expected uptake if FDG were distributed evenly throughout the body; thus, SUV = FDG uptake in each voxel/(injected dose/body weight). The maximum value of SUV (SUV_{max}) in the region of interest (ROI) was used for evaluation. On routine clinical radiology reports, the criteria for FDG-PET identification of malignancy were (*1*) tracer uptake judged visually to be greater than in surrounding normal soft tissue, and (*2*) SUV_{max} $>$2.5 (4).

FDG-PET/CT data reviews

Two observers, a radiation oncologist (R.M.) and a nuclear medicine/radiation oncology specialist (H.U.) with 15 and 23 years of experience in diagnosing and treating head-and-neck malignancies, respectively, consensually reviewed lymph node findings on FDG-PET/CT images. The maximum axial diameter and SUV_{max} of a represented lymph node and the area of the largest SUV were recorded at each nodal level (I–V) and compared with pathologic findings on nodal-level involvement. For nodal levels without detected lymph nodes, the SUV_{max} was scaled in the anatomic area and the diameter was considered $<$10 mm. The maximum axial diameter and the SUV_{max} of primary lesions were also recorded.

Clinical nodal staging

Two different observers independently performed three protocols for clinical nodal staging. Observer A (T.H.) was a radiologist and Observer B (R.N.) a radiation oncologist with 16 and 20 years of experience, respectively, in diagnosing and treating head-and-neck malignancies.

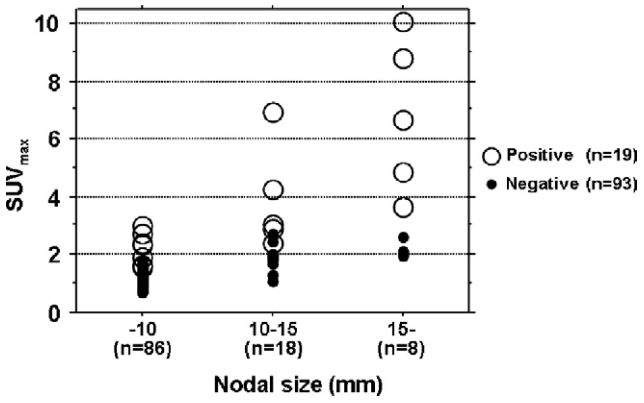

Fig. 1. Scatter plot of maximum standardized uptake values (SUV_{max}) with respect to nodal size at 112 nodal levels.

Method 1 (conventional modalities) consisted of clinical nodal staging based on conventional modalities (routine physical and endoscopic examinations, CT and MRI studies with routine clinical radiology reports) without information from FDG-PET/CT imaging.

Method 2 (additional FDG-PET/CT) consisted of clinical nodal staging based on conventional modalities and additional visual information from FDG-PET/CT images with routine clinical radiology reports.

Method 3 (FDG-PET/CT alone) consisted of clinical nodal staging based on FDG-PET/CT imaging alone with SUV data. The observers could reference not only the size and SUV_{max} of lymph nodes but also their level and laterality and the site and size of the primary tumor. Each observer performed Method 3 at least 6 months after performing Methods 1 and 2.

With each method, each nodal level on either side of the neck was classified as involved or not involved. Clinical nodal staging was compared with pathologic findings by one of the authors (R.M.).

Statistical analysis

In FDG-PET/CT data reviews, receiver operating characteristics analysis was used to determine the SUV_{max} cutoff value for lymph node involvement. To evaluate the statistical significance of differences in the pathologic accuracy of clinical nodal level staging, Methods 2 and 3 were compared with Method 1, applying McNemar's test to each observer. Statistical analyses were carried out with StatFlex Version 5.0 (Artec; Osaka, Japan). Values of $p < 0.05$ were considered to denote significant differences.

RESULTS

Dissection was performed at 35 neck sites; of the 23 patients, 11 underwent unilateral and 12 bilateral dissections; 28 positive and 529 negative lymph nodes were pathologically isolated from 112 nodal levels, of which 19 were positive and 93 negative. Pathologically, 1 patient had T1, 6 had T2, 9 had T3, and 7 had T4 tumors; nodal involvement was N0 in 8, N1 in 8, N2b in 6, and N2c in 1 patient.

In all 23 primary tumors, FDG-PET/CT fused images demonstrated FDG accumulation. Based on FDG-PET/CT data reviews, the median SUV_{max} of the primary tumors was 8.91 (range, 2.39–21.00), and the median axial diameter was 29.8 mm (range, 8.1–56.8 mm). The SUV_{max} was 2.39 in the smallest primary tumor (diameter 8.1 mm) and >3.0 in the other 22 tumors, all of which were >15 mm in diameter.

The median SUV_{max} of pathologically positive node levels was 2.90 (range, 1.57–10.07). The SUV_{max} overlapped in negative and positive nodes <15 mm in diameter (Fig. 1). Receiver operating characteristics analysis of the SUV_{max} of nodal sizes suggested that the size-based cutoff value was 1.9 for nodes <10 mm in diameter, 2.5 for those 10–15 mm, and 3.0 for >15 mm. These cutoff values yielded 79% sensitivity (15 of 19) and 99% specificity (92 of 93) for nodal-level staging (Table 1, Figs. 2 and 3). In Method 3 for nodal staging, two independent observers (T.H. and R.N.) consulted on the size-based SUV_{max} cutoff values.

Compared with conventional modalities (Method 1), the addition of FDG-PET/CT fused images (Method 2) increased pathologically correct lymph node staging from 14 (61%) to 17 (74%) and from 17 (74%) to 19 (83%) for each observer. Among the three protocols, FDG-PET/CT imaging with SUV data (Method 3) yielded the most correct lymph node staging: 19 (83%) and 20 (87%) of the patients were correctly staged by each observer (Table 2). For nodal-level staging, the sensitivity and specificity of Methods 1, 2, and 3 were 68% and 94%, 68% and 99%, and 84% and 99%, respectively, for Observer A; Method 3 yielded significantly higher accuracy than Method 1 ($p = 0.0269$). For Observer B, sensitivity and specificity were greatest with Method 3 (84% and 99%, respectively); however, the dif-

Table 1. Diagnostic accuracy of SUV_{max} cutoff values for nodal levels

Nodal size (mm)	Cutoff value	Sensitivity (%)	Specificity (%)	Accuracy (%)
<10	1.9	67 (6/9)	100 (77/77)	97 (83/86)
	2.5	22 (2/9)	100 (77/77)	92 (79/86)
	3.0	11 (1/9)	100 (77/77)	91 (78/86)
10–15	1.9	100 (5/5)	38 (5/13)	56 (10/18)
	2.5	80 (4/5)	92 (12/13)	89 (16/18)
	3.0	60 (3/5)	100 (13/13)	89 (16/18)
>15	1.9	100 (5/5)	0 (0/3)	63 (5/8)
	2.5	100 (5/5)	67 (2/3)	88 (7/8)
	3.0	100 (5/5)	100 (3/3)	100 (8/8)
Total	1.9	84 (16/19)	88 (82/93)	88 (98/112)
	2.5	58 (11/19)	98 (91/93)	91 (102/112)
	3.0	47 (9/19)	100 (93/93)	91 (102/112)
	Grading values	79 (15/19)	99 (92/93)	96 (107/112)

Abbreviation: SUV_{max} = maximum standardized uptake value.
Note: Data in parentheses are the numbers used to calculate the percentage. Based on receiver operating characteristics analysis, the size-based SUV_{max} cutoff values were 1.9, 2.5, and 3.0 for lymph nodes <10 mm, 10–15 mm, and >15 mm in diameter, respectively. These cutoff values yielded 79% sensitivity and 99% specificity.

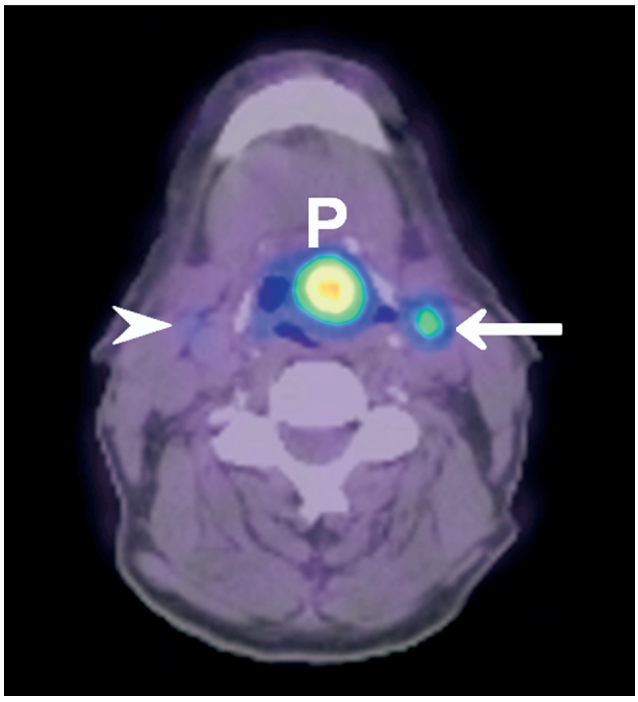

Fig. 2. A 79-year-old man with supraglottic squamous cell carcinoma (pT3N2c). The 18F-fluorodeoxyglucose positron emission tomography/computed tomography image shows the 35-mm diameter primary tumor (P) with a maximum standardized uptake value (SUV_{max}) of 11.7. Pathologically confirmed positive lymph nodes are also demonstrated at the right level II (diameter = 6 mm; SUV_{max} = 2.4) (arrowhead) and left level II (diameter = 13 mm; SUV_{max} = 6.9) (arrow).

ference among the three protocols was not statistically significant (Table 3).

DISCUSSION

18F-fluorodeoxyglucose PET, a functional imaging methodology that provides information about tissue glucose metabolism, has been used for the evaluation of head-and-neck SCC. In our study, FDG-PET/CT fused images demonstrated FDG accumulation in all of the 23 primary tumors we examined. Among three protocols for nodal staging, FDG-PET/CT imaging with SUV data (Method 3) yielded the most correct lymph node staging for each observer. Previous studies of nodal staging with FDG-PET alone reported 61–96% sensitivity and 80–99% specificity (4–7). However, they used different methods to calculate these parameters and based their results on the number of patients, the neck side, neck level, or lymph nodes. Evaluation based on the number of lymph nodes tends to favor specificity, owing to the presence of a large number of negative nodes (5). The limited resolution of FDG-PET may render it difficult to estimate the number of positive nodes. If FDG-PET yields different results at different sites on the same side of the neck or for the same patient, its sensitivity and specificity cannot be defined accurately. Hannah *et al.* (7) demonstrated that the sensitivity of FDG-PET/CT imaging based on neck levels and patients was 61% and 82%, respectively, suggesting that sensitivity and specificity calculations that are based on the neck level represent a better method for nodal staging (6, 8, 14). We consider nodal-level staging an appropriate method for RT planning in patients with head-and-neck SCC because we must select nodal levels that are included in the irradiated volume.

Ng *et al.* (6), who evaluated nodal-level staging with FDG-PET in 124 patients with oral cavity carcinoma, reported that sensitivity and specificity were 75% and 93%, respectively. They also showed that sensitivity and specificity increased somewhat upon visual fusion of FDG-PET and CT/MRI compared with FDG-PET alone, although the improvement was not statistically significant. Dammann *et al.* (14) reported that FDG-PET facilitated the correction of overdiagnosis by CT or MRI, although without statistical significance. Although FDG-PET/CT imaging may provide additional information for nodal staging, its role in the evaluation of normally sized lymph nodes is controversial, and its major advantage may lie in the easier differentiation of normal from abnormal FDG accumulations (13–15, 21).

Because it measures metabolic activity, FDG-PET is valuable for characterizing the nature of a lesion. Malignant cells actively metabolize glucose; consequently, they manifest high FDG accumulation on PET images. Maximum standardized uptake cutoff values ranging between 2.0 and 3.0 are used to differentiate between malignant and benign lesions (3, 4, 9, 22). However, FDG is not a tumor-specific tracer. Various inflammatory processes can lead to increased FDG uptake and potentially return false-positive results. Conversely, three factors (the presence of small lesions, low tumor metabolic activity, and hyperglycemia) may yield false-negative

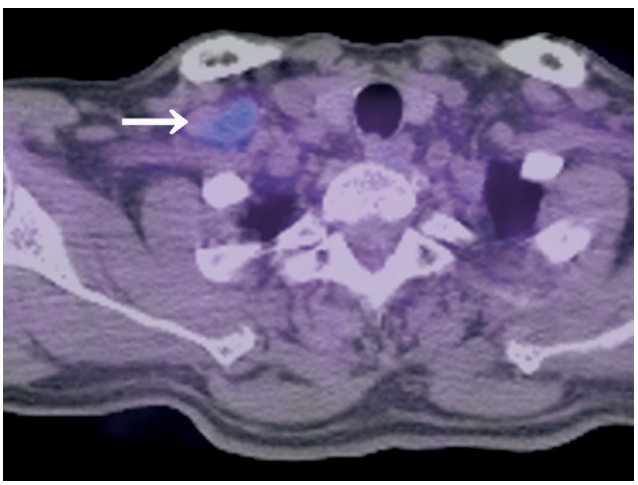

Fig. 3. A 70-year-old man with right maxillary squamous cell carcinoma (pT3N0). The 18F-fluorodeoxyglucose positron emission tomography/computed tomography image shows a pathologically confirmed negative lymph node at the right level IV (diameter = 23 mm; maximum standardized uptake value = 2.6) (arrow).

Table 2. Clinical nodal staging with three protocols in 23 patients

	Method 1				Method 2				Method 3			
Pathology	N0	N1	N2b	N2c	N0	N1	N2b	N2c	N0	N1	N2b	N2c
Observer A												
N0 (n = 8)	6	2			7	1			8			
N1 (n = 8)	1	4	2	1	1	6	1			6	2	
N2b (n = 6)	1	1	4		1	1	4			2	4	
N2c (n = 1)			1				1					1
Observer B												
N0 (n = 8)	6	2			8				8			
N1 (n = 8)	1	6		1	1	6	1			7	1	
N2b (n = 6)		1	5			1	5			2	4	
N2c (n = 1)			1			1						1

Note: Data are number of patients. Observer A was a radiologist, Observer B a radiation oncologist. Methods 1, 2, and 3 for clinical nodal staging were based on conventional modalities, additional visual information from 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) images, and FDG-PET/CT imaging alone with standardized uptake value data, respectively.

FDG-PET results (4, 22). In the evaluation of small lesions, the sensitivity of FDG-PET decreases with their decreasing size (9, 13). Because several factors affect the SUV, a diagnosis based purely on the SUV is inappropriate (5, 9). Our study demonstrated that although the SUV_{max} accurately characterized lymph nodes >15 mm in diameter, it was not reliable with respect to nodes <15 mm, probably because of the partial volume effect attributable to the limited resolution of PET images. Underestimation of the true concentration activity is suspected in lesions whose diameter is less than twice the resolution of the PET scanner at full-width at half-maximum (FWHM). Using phantoms, the resolution of our scanner was 5.5 mm at FWHM; however, actual spatial resolution is lower because of patient movement, scatter, and noise (20).

As a potentially more accurate method to correct the SUV for the partial volume effect, Hickeson *et al.* (22) proposed determining the lesion volume on CT and the number of counts throughout the entire volume of the area showing increased FDG uptake, and correcting for background. We considered the size-based grading SUV_{max} cutoff values for lymph nodes; they were 1.9 for nodes <10 mm in diameter, 2.5 for those 10–15 mm, and 3.0 for nodes >15 mm. These values yielded 79% sensitivity and 99% specificity and were comparable to rates obtained by experienced observers using visual evaluation, including ultrasound, contrast-enhanced CT, MRI, and FDG-PET/CT images (Method 2). Practically, FDG-PET/CT imaging including SUV data and the size-based grading SUV_{max} cutoff values (Method 3) may yield higher accuracy because observers can reference the level and laterality of the lymph nodes and the site and size of the primary tumor. Additional investigations are currently underway to obtain prospective results regarding the SUV_{max} cutoff values.

Table 3. Clinical nodal level staging with three protocols at 112 levels

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Observer A			
Method 1	13/19 (68)	87/93 (94)	100/112 (89)
Method 2	13/19 (68)	92/93 (99)	105/112 (94)
Method 3	16/19 (84)	92/93 (99)	108/112 (96)*
Observer B			
Method 1	15/19 (79)	89/93 (96)	104/112 (93)
Method 2	15/19 (79)	92/93 (99)	107/112 (96)
Method 3	16/19 (84)	92/93 (99)	108/112 (96)

Note: Data in parentheses are the numbers used to calculate the percentage. Observer A was a radiologist, Observer B a radiation oncologist. Methods 1, 2, and 3 for clinical nodal level staging were based on conventional modalities, additional visual information from 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) images, and FDG-PET/CT imaging alone with SUV data, respectively.

* According to McNemar's test, Method 3 was significantly superior to method 1 (p = 0.0269).

The size-based grading SUV_{max} cutoff values for lymph nodes may apply to primary tumors. However, the cutoff value is one method to distinguish malignant from benign lesions, and other methods for quantitative GTV delineation using FDG-PET/CT imaging await development. Furthermore, the appropriate cutoff values must be determined for each PET scanner and for each institution.

Although we used software fusion, FDG-PET/CT fused images can be obtained by three means—visual (6), software (8, 16), and hardware fusion (10, 11). In hardware fusion, the PET and CT images are acquired during one imaging procedure on a combined PET/CT scanner (10). Such hybrid instruments reportedly yield significantly better diagnostic accuracy in lung cancer than does visual fusion of FDG-PET and CT (11). Radiotherapy planning based on a combined PET/CT simulator has been introduced, and it is worthwhile to evaluate whether this cutting-edge equipment provides advantages for

nodal staging and RT planning in patients with head-and-neck SCC (17, 23). It is also worth considering whether all of the currently used radiologic examinations, such as ultrasound, contrast-enhanced CT, MRI, and FDG-PET/CT imaging, are necessary to diagnose head-and-neck SCC.

In conclusion, FDG-PET/CT imaging with size-based grading SUV_{max} cutoff values provides high-accuracy nodal staging in patients with head-and-neck SCC. It is an important modality for RT planning, although lesions <15 mm in diameter may be missed.

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