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Comparison of Thallium-201 and F-18 FDG SPECT Uptake in Squamous Cell Carcinoma of the Head and Neck

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PURPOSE: To compare the uptake of 2-[F-18] fluoro-2-deoxy-D-glucose (fludeoxyglucose F-18; F-18 FDG) and thallous chloride Tl 201, using single-photon emission CT (SPECT), for the detection and location of squamous cell carcinoma of the head and neck. **METHODS:** Five patients with biopsy-proved squamous cell carcinoma of the upper aerodigestive tract underwent both F-18 FDG and thallium-201 SPECT on the same day. F-18 FDG SPECT was performed using a dual-head gamma camera equipped with commercially available, extremely high-energy collimators (full width half-maximal height, 17 mm for 511 keV photons). Tumor size was estimated at 1.0 to 5.0 cm^3 in these cases. **RESULTS:** F-18 FDG SPECT showed five of five primary tumors. In two of the five cases, normal salivary gland activity severely limited thallium SPECT, and the tumors could not be definitively identified. Two of four lymph node groups that were positive for metastatic disease by CT criteria were shown by F-18 FDG SPECT. None were seen with thallium imaging. In one case, F-18 FDG SPECT was able to show a tumor that was not visible on CT. **CONCLUSIONS:** F-18 FDG has advantages over Tl-201 as a squamous cell carcinoma imaging agent (primarily because of its reduced salivary activity). F-18 FDG SPECT has potential as a viable, less expensive alternative to F-18 FDG positron emission tomography. The ultimate value of F-18 FDG SPECT imaging for detecting occult malignancy, monitoring therapeutic effectiveness, or evaluating tumor recurrence remains to be determined in patients with squamous cell carcinoma of the head and neck.

Index terms: Carcinoma; Neck, neoplasms; Neck, radionuclide studies; Single-photon emission computed tomography (SPECT); Radionuclide imaging, comparative studies

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Over the past 10 to 15 years, the evaluation of squamous cell carcinoma of the head and neck has dramatically improved with the advent of computed tomography (CT) and magnetic resonance (MR) imaging. These modalities have enhanced the ability both to detect and to determine the full extent of tumors in the head and neck region. CT and MR have also improved staging of squamous cell carcinoma by allowing detection of clinically occult nodal metastases (1). Despite these advances, conventional CT and MR imaging fall short in several important areas. These areas include differentiating recurrent tumor from posttherapeutic necrosis, monitoring therapeutic response, and detecting early tumors or lymph node metastases before anatomic distortion.

Imaging via radiochemistry versus anatomy is one of the strengths of nuclear imaging. Because imaging is dependent on the metabolic activity of the constituent cellular tissue and not just on size or anatomic distortion, radionuclide imaging can enable detection of occult carcinoma and monitoring of therapeutic response. Two of the most commonly used radiopharmaceuticals in this regard are thallium-201 and 2-[F-18] fluoro-2-deoxy-D-glucose (fludeoxyglucose F-18; F-18 FDG). Both radiopharmaceuticals have been shown effective for imaging of a variety of primary tumors (2, 3). Both radiopharmaceuticals have also proved beneficial in the differentiation of recurrent in-

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tracranial neoplasm from posttherapeutic necrosis (4–9). Because of their similar applications, there has been debate as to which agent is the preferred radiopharmaceutical for tumor imaging. Both imaging agents have been shown to have potential for the detection of squamous cell carcinoma of the head and neck and associated metastatic lymphadenopathy (10–13). The purpose of this study was to compare prospectively Tl-201 and F-18 FDG uptake for the detection of primary squamous cell carcinoma of the head and neck. In particular, we studied F-18 FDG single-photon emission CT (SPECT) imaging as a potential alternative to positron emission tomography (14).

Materials and Methods

Five patients (four men, one woman) with squamous cell carcinoma of the head and neck were evaluated. All patients were reviewed initially at a multidisciplinary tumor board and had previously undergone full clinical examination in the otolaryngology department. All patients had a pathologic diagnosis of squamous cell carcinoma by biopsy. Two patients had evidence of metastatic adenopathy by CT criteria in four separate nodal groups, two of which were shown to be metastatic squamous cell carcinoma by biopsy. All patients were treated initially with radiation therapy for their underlying tumors, and all imaging was performed before treatment. Estimated tumor volumes by CT or endoscopy ranged from 1.0 to 5.0 cm^3. We studied the detection of the primary tumor site in patients with squamous cell carcinoma of the head and neck as a preliminary basis for future studies involving the detection of unknown primary tumors and differentiation of recurrent tumors from radiation necrosis in the extracranial head and neck. This study is approved by the institutional review board at our institution.

Contrast-enhanced CT studies were performed with a GE 9800 scanner (General Electric, Milwaukee, Wis). Imaging protocol consisted of 3-mm contiguous axial images from the base of the skull through the hyoid bone. Three-millimeter-thick sections with 2-mm intersection spacing were then obtained to the thoracic inlet. On CT, any node with an area of low attenuation not related to artifact or fat was considered positive for nodal metastasis, regardless of size. Otherwise, upper internal jugular nodes (group II) greater than 1.5 cm in diameter and submandibular, middle, and low internal jugular nodes greater than 1 cm were considered positive.

After a 12-hour fast, all patients were given 4 mCi of thallous chloride Tl 201 (half-life, 73 hours) intravenously. Imaging was performed 5 minutes after injection, using a multihead SPECT scanner (TRIAD, Trionix Research Laboratory, Twinsburg, Ohio) equipped with ultra-high-resolution low-energy collimators (full width half-maximal height; 8 mm for 140 keV). SPECT imaging involved rotating each of the three detector heads for 120° consisting of 40 stops (3° per stop) at 35 seconds per stop. Imaging matrix was 128 × 128 × 64 (3.28 mm per pixel). SPECT images were reconstructed using a Hamming filter (0.7 frequency cutoff). Images were oriented into 1-cm-thick sections in transverse, coronal, and sagittal planes. Weighted planar reprojections (1 per exponential) of the SPECT data were created in multiple views (36 images at 6° intervals).

After completion of the thallium study, patients underwent a F-18 FDG (half-life, 2 hours) SPECT examination (14). Ten millicuries (370 mBq) of F-18 FDG was administered intravenously in the still-fasting patient. Imaging was performed 30 to 45 minutes after administration of radiotracer. Imaging was performed on a dual-head camera (BIAD, Trionix), equipped with extremely high-energy collimators. SPECT imaging involved rotating each detector 180°, which consisted of 30 stops (6° per stop) at 20 s per stop. Imaging matrix was 128 × 128 × 64 (5.28 mm per pixel). Each study consisted of three sequential 10-minute SPECT acquisitions, which were subsequently summed into one composite study. These sequential studies were used to eliminate reconstruction artifacts from concurrent radioactive decay or changes in radiotracer distribution. SPECT images were reconstructed using a Hamming filter (0.5 cycles per centimeter frequency cutoff). Images were oriented into 1-cm-thick sections in transverse, coronal, and sagittal planes. Weighted planar reprojections (1 per exponential) of the SPECT data were created in multiple views (36 images at 6° intervals).

Tl-201 and F-18 FDG image interpretations were performed by two blinded readers. Each reader was requested to analyze the studies in the following manner. The amount of uptake for both thallium and FDG was graded on a 0+ to 3+ scale with 0+ indicating no uptake; 1+, uptake less than salivary glands; 2+, uptake equal to salivary glands; and 3+, uptake greater than salivary glands. The degree of confidence of interpretation was graded on a subjective 1 to 5 scale with 1 indicating no tumor; 2, probably no tumor; 3, uncertain; 4, probable tumor; and 5, definite tumor. Areas of abnormal uptake were correlated later with clinical and CT examinations. Any disagreements were resolved by joint review.

Results

The results are summarized in the Table. The location of the tumors varied and included the anterior tonsillar pillar, piriform sinus, nasopharynx, and base of tongue. Estimated tumor volumes on CT and endoscopy ranged from 1 to 5 cm^3. Histologically, three tumors were poorly differentiated, two tumors moderately differentiated forms of squamous cell carcinoma.

Four tumors were present on contrast-enhanced CT studies. One tumor was not demonstrated on CT, but was detected by endo-

scopic biopsy. This patient initially presented with bilateral neck masses which were biopsy proved to represent metastatic cervical lymphadenopathy. CT demonstrated enlarged bilateral group II nodes; however, no infiltrating masses were demonstrated in the upper aerodigestive tract. Diagnosis was based on results from an endoscopic biopsy of a superficial lesion arising from the base of tongue on the right side. The total volume of this tumor was estimated at endoscopic examination to be approximately 1 cm^3.

In all patients, thallium imaging demonstrated prominent focal uptake within the normal salivary glands and the thyroid gland. F-18 FDG demonstrated intense uptake within the brain, but did not demonstrate significant selective uptake within the normal extracranial head and neck tissues.

All primary tumors demonstrated 3+ FDG uptake with an interpretation of "definitely abnormal." Although thallium uptake was demonstrated in all tumors, the diagnostic confidence was hindered by adjacent salivary gland uptake in those tumors involving the oropharynx (Fig 1). The occult tumor of the tongue base described above was readily detected with FDG with a high degree of confidence. On thallium imaging, this lesion did demonstrate uptake less than the normal salivary glands and was thought to be probably abnormal, but the location and extent of disease could not be evaluated because of adjacent salivary gland activity (Figs 2A–C).

Clinical and radiographic findings in five patients with squamous cell carcinoma

Patient	Tumor Location	Tumor Volume, cm^3	Histologic Grade	CT Positive Node Location	Amount of Tumor Uptake‡		Degree of Confidence in Tumor Identification§	
					FDG	Thallium	FDG	Thallium
1	Postnasal cavity	5	Poorly differentiated	None	3+	3+	5	4
2	R anterior tonsillar pillar and retromolar trigone	5	Moderately differentiated	None	3+	3+	5	5
3	R tonsillar fossa	5	Moderately differentiated	R group II*	3+	1+	5	5
4	R piriform sinus	1.5	Poorly differentiated	R group II*	3+	2+	5	5
5	R base of tongue	1	Poorly differentiated	Bilateral group II†	3+	1+	5	4

* Nodal group that demonstrated FDG uptake.

† Nodal group that did not demonstrate FDG uptake.

‡ Uptake scaled relative to salivary glands: 0+ = no uptake; 1+ = less than; 2+ = equal to; 3+ = greater than.

§ Scale: 1 = no tumor; 2 = probably no tumor; 3 = uncertain; 4 = probable tumor; 5 = definite tumor.

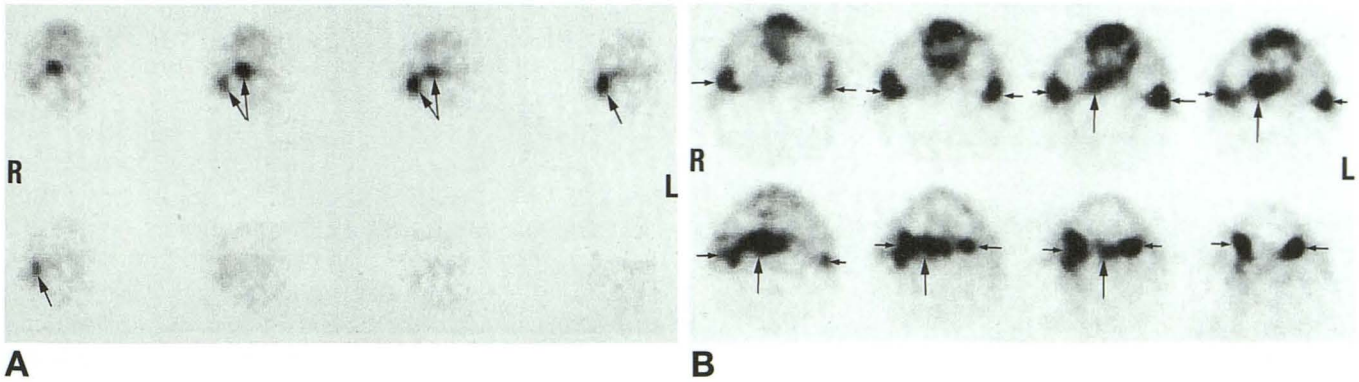
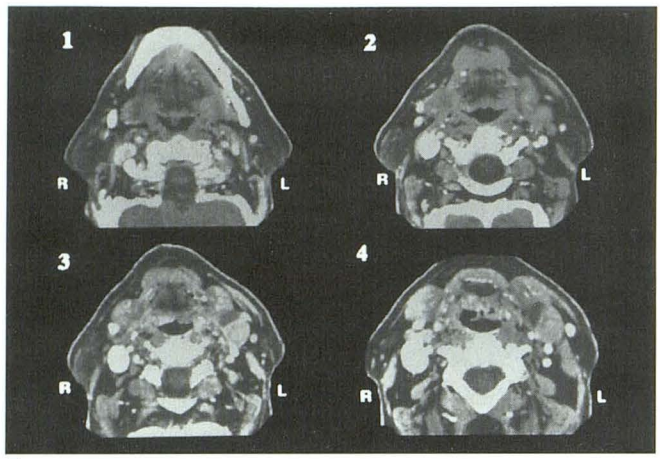


Fig 1. *A*, Axial SPECT FDG images obtained through the oral cavity demonstrate intense uptake within a "dumbell-shaped" squamous cell carcinoma of the right tonsil and soft palate (*arrows*). No other significant uptake is noted within the oral cavity or adjacent salivary glands.

B, Axial SPECT thallium images obtained through the same area as in *A* demonstrate very prominent uptake in the parotid glands (*small arrows*). The full extent of the tumor (*large arrows*) cannot be completely discerned because of the adjacent activity of the parotid glands.



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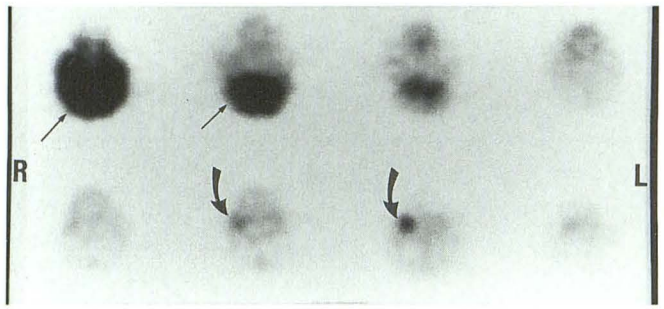

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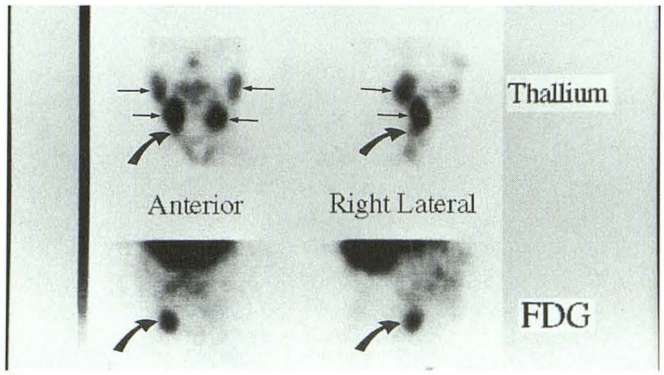

C

Fig 2. *A*, CT images through the base of the tongue show no definite evidence of tumor.

B, Axial images from F-18 FDG SPECT study show marked brain uptake (*straight arrows*), and asymmetric abnormal uptake in the right base of the tongue (*curved arrows*), which is suspicious for tumor.

C, Anterior and right lateral planar reprojection images from the SPECT acquisitions. The F-18 FDG study clearly shows the tumor (*curved arrows*) in the right tongue base, with minimal activity or interference from normal structures. On the thallium images, the tumor (*curved arrows*) cannot be seen easily or differentiated from the adjacent normal salivary gland activity (*straight arrows*).

Four nodal groups were *obviously* positive for metastatic involvement by CT criteria. Two of the four nodal groups that were positive for metastatic disease by CT criteria demonstrated 3+ FDG uptake. These were the two lymph node groups that had positive biopsies. The two lymph node groups that were positive for metastasis by CT criteria but did not demonstrate FDG uptake were not biopsied because confirmation of neoplastic involvement would not have altered the patients' treatment. None of these four nodal groups demonstrated thallium uptake separate from adjacent salivary gland uptake.

Discussion

Preliminary studies of imaging of squamous cell carcinoma of the head and neck have been performed with both Tl-201 (planar and SPECT) and F-18 FDG (single-photon planar images and positron emission tomography) (10–13). Early results have demonstrated uptake in both the primary tumor and in associated nodal metastases. These same radiotracers have been used in the brain as well, for detection of primary brain tumors and for the differentiation of recurrent tumor from radionecrosis (4–9). We have used thallium SPECT extensively in this regard (9), whereas many investigators have used F-18 FDG (4–7). We prefer to use Tl-201 in the brain because its tumor-to-normal brain uptake ratio is higher than that of F-18 FDG. Thallium does not show significant uptake in the normal brain with an intact blood-brain barrier, but F-18 FDG shows marked uptake in normal brain, frequently masking tumor uptake. The purpose of the current study was to determine the potential of Tl-201 versus F-18 FDG in head and neck tumor imaging.

We directly compared the two radiopharmaceuticals by imaging the same neoplasm to determine which agent should be used for further investigation in head and neck cancer. Thallium is a preferred agent for this use because of its relatively low cost and availability. Also, it has been used for years as either a myocardial perfusion agent or a tumor detection agent with its biokinetics extensively studied. Preliminary reports regarding F-18 FDG positron emission tomography imaging have reported a high sensitivity for the detection of primary tumors of the head and neck with a high tumor-to-nontumor

ratio (10, 11). In these same studies, F-18 FDG positron emission tomography has been reported to have about a 70% sensitivity for the detection of associated nodal metastases. Imaging head and neck tumors with F-18 FDG single-photon techniques has also demonstrated a high preliminary sensitivity for the detection of the primary tumor site (13).

In our limited patient population, we demonstrated that there is no significant interference from adjacent salivary or thyroid gland activity on F-18 FDG SPECT of squamous cell carcinoma of the head and neck. All tumors imaged with F-18 FDG were readily seen by a blinded reader with a high degree of confidence. The extent of two tumors could not be determined on Tl-201 imaging, and one tumor could not be definitively diagnosed. Tumor detection by thallium imaging was hindered by normal background uptake within the salivary glands and thyroid gland. It is readily known that there are disadvantages to using Tl-201 for imaging the oral cavity and oropharyngeal tumors, compared with F-18 FDG. Based on these preliminary findings, we are going to use F-18 FDG for further investigations of the extracranial head and neck. However, image fusion techniques that superimpose nuclear medicine studies using Tl-201 with CT or MR may diminish problems with tumor detection in the oral cavity caused by salivary gland uptake.

In our series, neither thallium nor FDG reliably detected nodal groups that were positive for metastatic disease based on CT criteria. There was, however, a preference for FDG uptake over thallium in those nodal groups that were positive by CT criteria. Metastatic squamous cell carcinoma in these two nodal groups was confirmed by biopsy, but the other two nodal groups without F-18 FDG uptake showed obvious CT abnormalities (however, these two nodal groups were not biopsied). As such, FDG detected all the limited number of biopsied lymph nodes in our study. Because of our small population size, no meaningful measurement of sensitivity can be made.

A newer agent, technetium Tc 99m sestamibi (Cardiolite, Dupont Nemours, Billerica, Mass), is a thallium analog and has been used recently as a thallium replacement for either heart or tumor imaging. We chose not to evaluate sestamibi because of its greater cost, although it does have better imaging characteristics than thallium. Our current study, despite its small numbers, shows that normal salivary gland activity limits thallium imaging of head and neck cancers. Sestamibi will likely suffer from a similar problem. Recently, differential washout of sestamibi has been used to separate parathyroid adenomas from overlying normal thyroid tissue (15). The normal salivary glands did not show the washout phenomenon that occurred in the thyroid, and salivary uptake was prominent, so differential washout will likely not occur between squamous cell carcinoma and the salivary glands. Also, both Tl-201 and sestamibi can show asymmetrical salivary uptake and washout in obstructed salivary glands. Although sestamibi remains unstudied for squamous cell carcinoma location in the head and neck, we would predict less than ideal results.

One unique facet of our work is the use of SPECT equipment instead of standard positron emission tomography instrumentation (14). This difference is based on our desire to find a relatively inexpensive imaging method. By using SPECT equipment and commercially supplied F-18 FDG, we avoided the tremendous fixed cost of a cyclotron/positron emission tomography center. Minn et al (13) used planar single-photon imaging of F-18 FDG with similar results.

Because of the high tumor-to-background ratio, the spatial resolution (full width half-maximal height, 1.7 cm) of our system was not a detriment in imaging small tumors. Both tumors that had volumes estimated at less than 1.5 cm were readily detected with a high degree of confidence with F-18 FDG SPECT, including one tumor that was 1 cm^3 in total volume by clinical examination and not seen on a contrast-enhanced CT study. At our institution, imaging of F-18 FDG using SPECT equipment has been validated (14), and we are currently using F-18 FDG SPECT on a routine clinical basis for evaluation of myocardial viability and tumor detection, as well as in ongoing research projects.

The use of F-18 FDG for detection and evaluation of the extent of clinically palpable tumors is not a needed application of this modality. CT provides anatomic detail far superior to FDG imaging. Initial studies suggest that the degree of FDG uptake does not correlate with the histologic grade of squamous cell carcinoma of the head and neck (13).

However, because tumor detection is based on metabolic activity and not solely on tumor size, F-18 FDG imaging has several important potential advantages over anatomical imaging. F-18 FDG imaging does show promise for the

detection of clinically occult tumors not seen on CT or MR. This potential application was demonstrated in both our preliminary experience using F-18 FDG SPECT and a study by Jabour et al (11) in which an occult tumor was detected with standard F-18 FDG positron emission tomography imaging. As in the brain, F-18 FDG has potential in the differentiation of recurrent tumor from postradiation necrosis in the extracranial head and neck. Finally, F-18 FDG may have a future role in the monitoring of therapeutic effects of chemotherapy or radiotherapy.

In conclusion, our preliminary study found F-18 FDG SPECT to be superior to Tl-201 SPECT for imaging primary squamous cell carcinoma and any associated nodal metastases of the extracranial head and neck, although the differences are not statistically significant in such a population. Detection of thallium uptake within the tumors was hindered by a high background uptake within the salivary glands. Our findings also suggest that F-18 FDG SPECT has potential as a reliable imaging technique that has widespread availability and avoids the high fixed costs of a positron emission tomography/cyclotron center.

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