Detection of Occult Bone Metastases From Head and Neck Squamous Cell Carcinoma

Impact of Positron Emission Tomography–Computed Tomography With Fluorodeoxyglucose F 18

Devraj Basu, MD, PhD; Barry A. Siegel, MD; Douglas J. McDonald, MD, MS; Brian Nussenbaum, MD

Objectives: To assess the ability of positron emission tomography–computed tomography with fluorodeoxyglucose F 18 (FDG-PET/CT) to provide early, accurate detection of bone metastases from head and neck squamous cell carcinoma (HNSCC) and to determine the impact of detecting occult bone metastases on patient care.

Design: Retrospective medical chart review.

Setting: Single academic medical center.

Patients: The study population comprised 13 patients with FDG-PET/CT scans detecting bone lesions suggestive of HNSCC metastases. These patients were identified from a retrospective review of 683 consecutive FDG-PET/CT scans performed for initial staging (n=198) or restaging (n=485) of HNSCC between October 2002 and December 2005.

Main Outcome Measures: Rate of biopsy confirmation of bone lesions detected by FDG-PET/CT as suggestive of metastases, presence of concurrent symptoms or laboratory serologic evidence for bone metastasis, timing of bone metastasis detection relative to initial diagnosis of HNSCC, and change in therapeutic decision making based on bone metastasis detection.

Results: Eleven FDG-PET/CT studies that detected bone metastasis were performed to restage a suspected or known recurrence, and 2 studies were performed for radiographic restaging of disease after completion of therapy. Bone biopsy confirmation was performed in 5 patients, and 4 of the biopsy results were positive for metastatic HNSCC. All patients lacked clinical symptoms of bone involvement, and 82% (n=9) had serum alkaline phosphate levels in the normal (n=7) or minimally elevated (n=2) range. At the time of bone metastasis detection, 6 of the 12 patients (50%) had no other identifiable distant metastatic disease. Furthermore, 2 patients (17%) lacked disease at any other local, regional, or distant site. The identification of bone metastases influenced therapeutic decisions in 5 of 13 cases (38%).

Conclusion: Use of FDG-PET/CT in restaging HNSCC allows for detection of occult bone metastases, and this early detection frequently influences therapeutic decision making.

locoregional control, bone was the only detected site in 12% of cases.17

Detecting occult bone metastases is critical for staging several malignancies. Fludeoxyglucose F 18-PET has been shown to be useful for detecting bone metastases from both lung and breast carcinomas and bone involvement by lymphoma and myeloma.18 For detecting malignant involvement of the vertebral column, FDG-PET/CT has been shown to have better specificity than FDPG-PET or CT alone.19 Whole body magnetic resonance imaging has been shown to have a high sensitivity for detection of bone metastases from solid tumors that may slightly exceed that of FDG-PET/CT, although little direct comparative data exist.20

For HNSCC, bone metastases traditionally have only come to attention through pain symptoms, pathologic fractures, or abnormal laboratory test results, all of which are insensitive for early lesions.19,21 Because of the low frequency of bone metastases and the high percentage of equivocal findings, bone scintigraphy is not routinely performed for staging HNSCC.11,22 Screening for distant metastases at sites other than the lungs is usually not recommended for HNSCC.11,23

Positron emission tomography–computed tomography is essentially a full-body study, imaging from the vertex of the head to the mid thighs. Because this imaging modality is able to detect disease volume as low as 1 cm\(^3\) in an anatomically precise manner, unsuspected findings throughout the body are sometimes described by the radiologist. As the clinicians at our institution have gained further experience with FDG-PET/CT for HNSCC, we began to increasingly recognize FDG-avid bone lesions suggestive of metastases that were otherwise asymptomatic. The aims of this study were to determine the ability of FDG-PET/CT to detect occult bone metastases from HNSCC, to define the clinical context of occurrence, and to determine the impact that early detection has on the management of these patients.

**METHODS**

This study was approved by the Human Studies Committee at Washington University School of Medicine, St Louis, Missouri. The study population was derived from a billing database search of all FDG-PET/CT imaging studies performed for HNSCC at our institution from October 1, 2002, until December 31, 2005. The radiologist’s report for each FDG-PET/CT study was reviewed for the description of findings suggestive of bone metastasis. A retrospective medical chart review was then performed on the patients with suspected bone metastasis. The data collected included the patient’s age, primary tumor site, initial presenting stage, indication for the FDG-PET/CT scan, locations of bone lesions, status of locoregional control, presence of other distant disease, prior therapies, time from completion of prior therapies to lesion detection, whether the lesion was biopsied, results of prior FDG-PET/CT scans, and subsequent therapy given to the patient. The medical charts were also reviewed for the presence of other more conventional indicators of bone metastasis including presence of associated clinical symptoms, serum alkaline phosphatase levels, and serum total calcium levels. Similarly, radiology reports were reviewed for the presence of a visible lesion on plain film in cases where one had been obtained.

When available, results were recorded from bone biopsy specimens obtained to confirm the diagnosis of radiographic lesions seen on FDG-PET/CT. Biopsies of suspicious bone lesions were generally performed when there were no other distant metastatic sites and the patient had resectable locoregional disease. Biopsy specimens were obtained using an open technique with general anesthesia or using CT guidance to obtain a core biopsy specimen.

All FDG-PET/CT scans were performed at Washington University School of Medicine using a Siemens biograph Duo PET/CT scanner (Siemens Medical Solutions USA, Inc, Malvern, Pennsylvania). After intravenous administration of FDG, noncontrast CT scans were obtained for attenuation correction and for fusion with emission FDG-PET scans. A series of overlapping emission FDG-PET scans was then obtained. The imaging area spanned the region from the vertex of the head to the upper thighs. Imaging characteristics of a bone lesion suggestive of metastases included a focal area of FDG-avid uptake that corresponded to changes seen on the CT correlative scans (Figure). A total of 683 patients were identified who underwent FDG-PET/CT imaging for staging (n=198) or restaging (n=485) of HNSCC. Previously undetected bone lesions suggestive of metastases were identified in 13 patients. Eleven of these patients underwent imaging for restaging of suspected or known recurrence, and 2 patients underwent restaging to assess disease response after completion of chemoradiotherapy. These 13 patients accounted for 2.7% of all restaging FDG-PET/CT scans.

The FDG-avid bone lesions were associated with lytic (n=11) or sclerotic (n=2) findings on the correlative CT scans. Of the 13 patients, 5 underwent a bone biopsy, and all yielded diagnostic specimens. Of these 5 patients, 4 (80%) had the radiographic diagnosis histologically confirmed. A single patient was found to have isolated Rosai-Dorfman disease of bone, which is a rare nonmalignant hypermetabolic bone lesion.24 This patient was excluded from further analysis. No patients experienced complications from the bone biopsy.

Among the remaining 12 patients, FDG-PET/CT detected solitary bone metastases (n=6) and multiple bone metastases (n=6) with equal frequency. Twenty-seven bone lesions were detected in these 12 patients. The sites of involvement were the pelvis (n=9), femur (n=5), humerus (n=3), vertebra (n=3), rib (n=3), scapula (n=2), sternum (n=1), and clavicle (n=1). Six patients were found to also have disease at other visceral sites. While all 6 of these patients had lung metastases, 4 also had evidence of liver metastases. Single cases of additional metastasis to the adrenal gland, retroperitoneum, and spleen were also identified in these patients.

The Table summarizes the patient data. All patients had advanced-stage disease at initial presentation, and most developed bone metastases early in the posttherapeutic course. The mean time from initial diagnosis to FDG-PET/CT detection of bone metastasis was 13 months, with a median of 8 months and a range from 2 to 47 months. In fact, bone metastasis was detected in 2 patients (patients 1 and 2) on imaging performed 2 months before completion of prior therapies.
after initial diagnosis. Patient 1 had a pretreatment FDG-PET/CT scan showing no bone lesions, but patient 2 did not have an initial staging FDG-PET/CT prior to starting treatment. Therefore this patient may have had FDG-PET/CT–detectable bone metastases at initial presentation.

Commonly used indicators of bone metastasis were reviewed to evaluate whether FDG-PET/CT allowed for earlier diagnosis. No patients were documented to have bone pain at the time the FDG-PET/CT was performed. Furthermore, conventional laboratory indicators of bone metastasis were also normal in most patients. Among the 11 individuals in whom such tests were available, 9 (82%) had serum alkaline phosphatase levels in the normal (n=7) or minimally elevated (n=2) range. The other 2 patients had alkaline phosphatase levels of 391 and 1361 IU/L. Both of these patients had normal serum total calcium levels. Serum total calcium levels were normal in 9 patients (82%). Among 14 bone lesions from 8 patients further evaluated by plain films, only 36% (n=5) were apparent. Only 1 patient with positive findings on plain films had an elevated calcium level, with the rest having normal laboratory serologic findings. Other than plain films, no additional imaging, including magnetic resonance imaging, was used to evaluate bone metastases suspected on FDG-PET/CT.

The detection of occult bone metastasis with FDG-PET/CT was evaluated for its impact on patient care based on the other restaging findings. Six patients were found to have multiple sites of distant disease in addition to the bone metastases, including the lungs. For these patients, a chest CT scan would have likely detected the lung metastases. For the other 6 patients, bone metastasis was detected without evidence of other sites of distant disease. Among these 6 patients, 2 (patients 7 and 9) had no other detectable local or regional disease. Thus, early detection had an impact on the initiation of palliative measures and provided prognostic information. The other 4 patients (patients 3, 5, 8, and 12) had bone metastases detected in the presence of advanced local and/or regional recurrent disease, with 3 of these patients having resectable disease. The additional finding of bone metastases made any curative-intent salvage surgery unfeasible. Thus, detection of occult bone metastasis on FDG-PET/CT influenced therapeutic decision making in 5 of 13 patients (38%).

The rapidly growing use of FDG-PET/CT for staging HNSCC has created new insight into understanding the timing and distribution of distant metastases. In particular, the whole-body coverage of FDG-PET/CT may facilitate early identification of less common distant lesions not detectable through traditional radiographic restaging using chest CT. This study suggests that routine use of FDG-PET/CT in restaging HNSCC can facilitate early detection of occult bone metastases and that this detection often influences therapeutic decision making.

The addition of FDG-PET/CT to initial staging and restaging HNSCC has a measurable impact on treatment selection, as shown in prior retrospective and prospective studies. The ability of FDG-PET/CT to detect occult bone metastasis by FDG-PET/CT was shown to influence therapeutic decision making in 5 of 13 cases (38%). In 2 cases, restaging FDG-PET/CT identified bone metastases that were the only known foci of malignancy, thus having a dramatic impact on their prognosis and allowing prompt consideration for palliative therapy. Three patients had locally and/or regionally resectable recurrences in the absence of other distant lesions. Diagnosis of bone metastasis in these 3 patients was pivotal in selecting a palliative treatment approach.
lignancies. No patients in this study were clinically symptomatic from the bone metastasis at the time of diagnosis by FDG-PET/CT. This contrasts with prior studies that described pain and/or neurologic dysfunction in all patients presenting with vertebral metastases from HNSCC. In the absence of symptoms, use of alkaline phosphatase has previously been advocated as a screening test for bone metastasis despite having a reported sensitivity of 20%. In our series, only 2 (18%) of the individuals with presumed or histologically confirmed bone metastases had suspiciously elevated alkaline phosphatase levels and only 2 (18%) had elevated serum calcium levels, confirming the poor utility of these serologic tests to detect bone metastases. Also, FDG-PET/CT appeared far more effective than plain films for visualizing metastatic bone lesions. Previous studies support FDG-PET/CT as a superior imaging modality for detecting bone metastases from a variety of different cancers compared with FDG-PET or CT alone. Fluorodeoxyglucose F 18–PET/CT has previously been shown to overcome the limitations of CT, which yielded normal or nonspecific results in 54% of patients with FDG-PET/CT–detected bone metastases. In contrast, our study showed that all of the occult detected bone metastases were associated with morphologic changes on the correlative CT scans from the FDG-PET/CT studies. The higher frequency of positive CT findings in our study may reflect the biological behavior of bone metastases from HNSCC, which was not included in the study by Nakamoto et al. Bone biopsy was performed rather than bone scintigraphy when diagnosis confirmation was needed. Since we did not perform bone scans on our patients, we cannot directly compare bone scintigraphy to FDG-PET/CT for detecting occult bone metastases from HNSCC. In the present study, FDG-PET/CT was performed for obtaining radiographic evaluation at local, regional, and distant sites rather than specifically looking for bone metastases, which would be the major utility of bone scintigraphy.

A single false-positive finding on FDG-PET/CT scan in this series occurred in a patient with no other evidence of malignancy, illustrating the importance of biopsy confirmation in some cases. However, 8 of the remaining 12 patients in this series did not undergo biopsy confirmation. In contrast to the 4 patients with positive biopsy results, biopsy confirmation in these 8 individuals would have had no therapeutic implications. In 6 of the 8 cases, histologic confirmation was not pursued because distant disease to other viscera was present. Biopsy was not sought in another patient who was noted concurrently to have locally unresectable recurrent nasopharyngeal carcinoma. Finally, a single patient with locoregional disease control and no other distant metastases may have benefited from histologic confirmation, which was not pursued because of the convincing appearance of diffuse skeletal metastases on FDG-PET/CT.

These results also provide new insight into the anatomic distribution of bone metastasis as related to HNSCC. There was a predilection for pelvic and femoral metastases, accounting for more than 50% of the lesions detected. Of the 12 patients, 6 (50%) had multiple sites of skeletal metastases, 6 (50%) had distant disease at other visceral sites, and 2 (17%) had bone metastases in the absence of other locoregional or distant disease.

It continues to be an area of controversy when FDG-PET/CT should be applied for the initial staging of HNSCC, and a retrospective study has suggested a notable impact on clinical decision making in this setting. In our series, bone metastases were only detected by FDG-PET/CT in the context of restaging evaluations. However, contrary to the belief that bone metastases occur as a late phenomenon, skeletal involvement within 1 year of initial diagnosis was more frequently identified in this series. Notably, many practitioners are not routinely using imaging modalities for initial staging that would identify bone metastases, and thus rare instances of bone metastases potentially de-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial Tumor Site(s)</th>
<th>Initial T/N Stage</th>
<th>Primary Therapy</th>
<th>Time Until Bone Lesion Detection, mo</th>
<th>Specific Indication for Restaging FDG-PET/CT</th>
<th>Bone Metastasis Site(s)</th>
<th>Lesion Biopsied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Supraglottis</td>
<td>T3N2c</td>
<td>Surgery/RT</td>
<td>2</td>
<td>Suspected recurrence</td>
<td>Pelvis, femur, humerus</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Floor of mouth</td>
<td>T3N2c</td>
<td>Surgery</td>
<td>2</td>
<td>Suspected recurrence</td>
<td>Pelvis, femur, spine, sternum, scapula</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Base of tongue</td>
<td>T3N2c</td>
<td>Chemo/RT</td>
<td>4</td>
<td>Suspected recurrence</td>
<td>Femur</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Base of tongue</td>
<td>T2N3</td>
<td>Chemo/RT</td>
<td>6</td>
<td>Known persistence</td>
<td>Humerus</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Oral tongue</td>
<td>T2N2b</td>
<td>Surgery/RT</td>
<td>7</td>
<td>Suspected recurrence</td>
<td>Pelvis</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Posterior wall of oropharynx</td>
<td>T3N2b</td>
<td>Surgery/RT</td>
<td>7</td>
<td>Known recurrence</td>
<td>Pelvis</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Base of tongue</td>
<td>T4aN2c</td>
<td>Surgery</td>
<td>9</td>
<td>Suspected recurrence</td>
<td>Pelvis, femur, spine, rib</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Nasopharynx</td>
<td>T4N2c</td>
<td>Surgery</td>
<td>11</td>
<td>Suspected recurrence</td>
<td>Rib</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Base of tongue</td>
<td>T3N2b</td>
<td>Surgery</td>
<td>13</td>
<td>Routine surveillance</td>
<td>Pelvis</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Pyriform sinus</td>
<td>T3N2b</td>
<td>Chemo/RT</td>
<td>14</td>
<td>Known recurrence</td>
<td>Pelvis</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Tonsil</td>
<td>T2N2c</td>
<td>Surgery/chemo/RT</td>
<td>37</td>
<td>Known recurrence</td>
<td>Pelvis, femur, spine, rib, scapula, clavicle</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>(1) Unknown</td>
<td>T1N2b</td>
<td>Surgery</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>(2) Pyriform</td>
<td>T2N0</td>
<td>Surgery</td>
<td>47</td>
<td>Known recurrence</td>
<td>Pelvis, humerus</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: Chemo, chemotherapy; FDG-PET/CT, positron emission tomography–computed tomography with fluorodeoxyglucose F 18; RT, radiation therapy.

* Measured as time from initial diagnostic biopsy to detection of bone metastasis on restaging FDG-PET/CT to the nearest month.
tectable by FDG-PET/CT at initial presentation may go unidentified. In support of this notion, occult bone metastasis from an advanced-stage oral cavity squamous carcinoma was recently identified on an initial staging FDG-PET/CT at our institution. This patient had an asymptomatic, biopsy-proven sternal metastasis identified as the only site of distant disease. This detection occurred prior to initiating therapy, thus changing the treatment goals from curative to palliative.

This institutional experience with early detection of occult bone metastases from HNSCC using FDG-PET/CT further emphasizes its unique capabilities as a restaging tool. When a FDG-PET/CT suggests bone metastases, strong consideration should be given to bone biopsy as the next step when a therapeutic decision would change based on histologic confirmation of this diagnosis. Our findings further demonstrate a notable impact on HNSCC therapy from the use of FDG-PET/CT for restaging disease. Better understanding of the full capacity of FDG-PET/CT in this regard will need to be shown with future well-designed prospective studies.

Submitted for Publication: August 13, 2006; final revision received January 16, 2007; accepted April 3, 2007.

Correspondence: Brian Nussenbaum, MD, Department of Otolaryngology—Head & Neck Surgery, Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8115, St Louis, MO 63110 (nussenbaumb@ent.wustl.edu).

Author Contributions: Drs Basu, Siegel, McDonald, and Nussenbaum had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Basu, Siegel, McDonald, and Nussenbaum. Acquisition of data: Basu, Siegel, McDonald, and Nussenbaum. Analysis and interpretation of data: Basu, Siegel, McDonald, and Nussenbaum. Drafting of the manuscript: Basu and Nussenbaum. Critical revision of the manuscript for important intellectual content: Basu, Siegel, and McDonald. Administrative, technical, and material support: McDonald and Nussenbaum. Study supervision: McDonald and Nussenbaum.

Previous Presentation: This study was presented at the American Head & Neck Society 2006 Annual Meeting & Research Workshop on the Biology, Prevention and Treatment of Head & Neck Cancer; August 19, 2006; Chicago, Illinois.

Additional Contributions: James S. Lewis Jr, MD, in the Department of Pathology and Immunology at the Washington University School of Medicine, provided the photomicrograph and accompanying pathologic description in the Figure.

REFERENCES