Staging of Head and Neck Squamous Cell Cancer With Extended-Field FDG-PET

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Background: Accurate baseline staging is necessary to appropriately treat head and neck squamous cell carcinoma. [F-18]-fluorodeoxyglucose positron emission tomography (FDG-PET) is valuable for locoregional staging of primary head and neck disease. The effectiveness of FDG-PET for the detection of distant metastatic or synchronous disease remains unproven.

Objective: To investigate the utility of FDG-PET extended into the abdomen (extended-field FDG-PET) for wide-field staging of head and neck tumors.

Methods: This is a prospective institutional study of 35 consecutive patients diagnosed with American Joint Committee on Cancer (AJCC)-defined stage II-IV squamous cell carcinoma of the oral cavity, oropharynx, or larynx between September 2000 and June 2002. Thirty-three patients (94%) were eligible for analysis. All patients were routinely staged with chest radiography, liver function tests, and extended-field FDG-PET. Chest or abdominal computed tomographic scans were used as corroborative studies and were obtained only when one of the above tests indicated distant disease.

Results: Of 33 patients, 7 (21%) had evidence of distant disease by extended-field FDG-PET—4 with metastases and 3 with synchronous primary cancers of the aerodigestive tract. [F-18]-fluorodeoxyglucose PET detected hepatic, bone, gastrointestinal, and mediastinal disease not identified by chest radiography or liver function tests. Two of the 7 patients with FDG-avid distant disease had false-negative staging by all other tests, including computed tomography.

Conclusions: Extended-field FDG-PET is feasible and may improve staging of primary head and neck squamous cell carcinoma. Use of staging FDG-PET must be explicitly described in reports from centers engaged in prospective research to facilitate comparison with historical results.


Two thirds of patients diagnosed with squamous cell carcinoma of the head and neck are staged with locoregionally advanced (American Joint Committee on Cancer [AJCC] stage III/IV) disease.1 Depending on the site of tumor origin, approximately 10% of patients with locally advanced disease present with distant metastases.2,3 Moreover, head and neck cancer is frequently associated with synchronous or metachronous secondary malignancies of the aerodigestive tract.4,6 Patients with locally advanced disease may have up to a 50% risk for some form of synchronous or metachronous malignancy beyond the head and neck.7 Detection of distant metastases or secondary cancers is of key importance. Although modern treatment approaches offer improved local disease control, they are morbid, costly, and generally would be withheld in the presence of widespread disease. Current staging protocols generally include chest radiographs and/or liver function tests, both of which are of questionable value.8,9 Chest computed tomographic (CT) scanning is a more sensitive (nearly 90%) alternative.10 However, chest CT scanning may miss early mediastinal metastases and does not address other potential sites of distant disease. Hepatic or bone-based metastases are not common at the time of disease presentation11 but have been documented in up 4% of cases.12 Previous reports have emphasized that extrapolmonary metastases rarely develop in the absence of lung involvement.11 This has led some to recommend chest CT alone as the most effective means of pretreatment screening.12

A recent alternative approach to staging is [F-18]-fluorodeoxyglucose (fluorodeoxyglucose F 18) positron emission tomography (FDG-PET). This modality...
permits large field-of-view imaging, and has been shown to be effective in the locoregional staging of primary and neck disease.\textsuperscript{14,15} It may also outperform chest CT scanning for staging the mediastinum.\textsuperscript{16} This study summarizes our prospective experience gauging the feasibility of FDG-PET imaging inclusive of the abdomen (extended-field FDG-PET) as the primary imaging technique for upfront staging outside the neck of patients diagnosed with stage II-IV oral cavity, pharyngeal, and laryngeal cancer.

**METHODS**

Thirty-five consecutive patients who were potentially eligible for organ preservation therapy were enrolled into a prospective trial studying pretreatment FDG-PET scanning of AJCC stage II-IV squamous cell carcinoma of the oral cavity, oropharynx, or larynx. The institutional review boards of both the University of Washington and the VA Puget Sound Health Care System (VAPSHCS), Seattle, approved the trial, and all enrolled patients provided informed consent. The Departments of Otolaryngology and Radiation Oncology at VAPSHCS evaluated all 35 patients between September 2000 and June 2002. Two patients did not undergo scanning, one because of refractory diabetes mellitus and the other because of acute airway obstruction precipitating immediate surgical intervention. Therefore, a total of 33 patients underwent FDG-PET and are included for analysis. All evaluated patients were systematically staged following direct laryngoscopy and tissue biopsy diagnosis with plain chest radiographs, serum liver function panels (alanine aminotransferase, aspartate aminotransferase, and total bilirubin), and contrast-enhanced CT scans of the head and neck. We performed CT scans of the chest or abdomen only to characterize abnormalities found by FDG-PET or other tests. Abnormal radiographic or FDG-PET findings were pathologically confirmed with biopsy procedures. In the case of patients with multiple distant FDG-avid sites, only the most accessible abnormality in each patient was targeted for biopsy. Plain film radiographs and/or spine magnetic resonance imaging were obtained to confirm bone-based metastases visualized by FDG-PET.

We performed FDG-PET imaging with a General Electric ADVANCE scanner (General Electric, Milwaukee, Wis) operating in 2-dimensional high-sensitivity mode. Patients underwent overnight fasting, and plasma glucose was measured prior to each study to ensure a plasma concentration of 150 mg/mL or less. Approximately 7 to 10 mCi (259-370 MBq) of FDG was administered intravenously to each patient. A postinjection delay of 45 minutes was strictly observed prior to imaging. Four 15-cm axial fields of view extending inferiorly from the midcricoid were used. This permitted imaging of the entire liver and upper abdomen, while excluding excreted FDG signal in the bladder. Pelvis and lower extremities were also excluded from the images. Three-minute transmission (using a germanium 68 rotating source) and 7-minute emission image captures were performed. Images were reconstructed using a filtering algorithm that yielded an image resolution of at least 10 mm. An experienced nuclear medicine specialist (J.R.) evaluated all FDG-PET images, blinded to the results of standard staging procedures. Positron emission tomography–defined abnormalities were defined as any site displaying increased uptake over normal surrounding soft tissue.

Short of autopsy, there is no “gold standard” to determine the presence or absence of metastatic disease. Although patients with test results suggestive of metastases can undergo biopsy (which provides insight into “false-positive” rates), patients with normal test results are typically not examined further, so it is impossible to determine rates of false-negative test results. Without this knowledge about actual disease prevalence, standard measures of test accuracy such as sensitivity, specificity, positive predictive values, and negative predictive values cannot be used. Therefore, in this study we compared the rates at which each test detected histologically confirmed distant disease. In the subset of patients who underwent neck dissections immediately after PET scanning, we report FDG-PET sensitivity and specificity for detecting disease in cervical nodes.

The analyzed cohort included 15 laryngeal, 11 oropharyngeal, and 7 oral cavity primary cancers. Consistent with the VA patient population as a whole, all patients were men and had a mean age of 60 years (range, 47-79 years). Most patients (22 [66%] of 33) had AJCC stage IV disease. Disease site and stage breakdown are summarized in Table 1.

The primary tumor was identified by FDG-PET in all 33 cases (100% primary disease sensitivity). In the 13 patients who underwent immediate neck dissection surgery following PET scanning, 6 of 6 pathologically positive neck sides were correctly staged as node positive by FDG-PET (100% sensitivity), while 9 of 10 pathologically negative neck sides were correctly staged as negative by FDG-PET (90% regional disease specificity).

Over 21% of patients (7 of 33) had distant foci of disease discovered by PET scanning. Of these 7 patients, 4 had metastatic disease and 3 had synchronous malignant tumors beyond the head and neck. All 4 of the patients with metastatic disease had N2 or N3 neck disease. Three patients had lung (parenchymal and/or mediastinal) involvement, and 2 patients had bone-based disease (1 patient had both sites involved). Surprisingly, and of particular relevance to extended-field PET imaging, 3 of these 4 patients had liver metastases as well (a representative case is shown in Figure 1). Physiologic uptake of FDG by the colon in the area of the hepatic flexure can be misinterpreted as intrahepatic metastases. This was ruled out for each of these 3 patients through corroborative CT scanning and biopsies that confirmed metastatic disease.

As stated above, 3 patients (9%) had evidence for a synchronous malignancy demonstrated by FDG-PET. One patient with stage IV N2 oral cavity disease was shown to have a cancer of the distal esophagus, while another patient with T3 N0 glottic laryngeal disease had a synchronous non–small cell lung cancer (this was believed to represent a second primary, since it was a solitary lower lobe mass originating from a bronchus). A third patient with stage IV oral cavity disease had a focus of intense FDG uptake in the hepatic flexure of the colon, subsequently diagnosed as a stage II adenocarcinoma via colectomy.

Table 2 summarizes the number and location of metastases and synchronous cancers in patients with distant disease. The test results for chest radiography, liver function tests, CT scanning, and PET are provided for each cell of Table 2. A total of 13 distant disease sites in these 7 patients were detected by extended-field FDG-PET. Computed tomographic scans frequently failed to
detect disease found by PET scanning, and appeared to perform worse in the mediastinum, where it detected disease in only 1 of 3 patients found to have mediastinal involvement by PET (Figure 2). Computed tomography fared better with parenchymal lung disease, whereby all 4 patients with FDG-avid parenchymal lung lesions were found to have disease by chest CT scanning as well. However, an abdominal CT failed to identify the stage II colon tumor found by PET scan.

Screening chest radiography detected only 2 of 4 patients with metastatic or secondary lung disease, and elicited false-positive results in 3 patients, consisting of nodular or interstitial infiltrates that were negative on both CT scanning and FDG-PET. Liver function test results were only marginally abnormal (mildly elevated aspartate aminotransferase at 44-46 U/L [institutional normal range, 0-37 U/L], with normal alanine aminotransferase and bilirubin values) in 2 of the 3 patients with liver metastases. Two patients had false-positive findings (markedly elevated alanine aminotransferase and aspartate aminotransferase values) due to underlying alcoholic cirrhosis.

Overall, 2 of the 7 patients with distant disease demonstrated by extended-field FDG-PET (one with mediastinal adenopathy and the other with stage II colon carcinoma) were understaged by all other screening evaluations, including CT scans, which were false-negative.

One false-positive result was elicited by FDG-PET in a patient with stage III oropharyngeal disease. This patient had an FDG-avid right axillary node, which was subsequently attributed to FDG radiotracer extravasation and/or inflammation caused by multiple previous intravenous line placements in the right upper extremity. A biopsy was not performed on the area owing to a low index of suspicion, and no disease progression developed in this region during 14 months of follow-up.

**COMMENT**

Functional imaging with FDG-PET complements anatomic imaging technologies and has been shown to improve the clinical staging of head and neck cancer. Examples of this include upfront locoregional disease staging, delineating recurrent disease from posttherapeutic changes, and longitudinal monitoring of disease response to therapy.17-20 Reports in the literature also provide evidence that FDG-PET can effectively screen for lung metastases or second primary tumors.10,16

We prospectively incorporated FDG-PET into our clinical staging pathway for patients with head and neck squamous cell carcinoma. Our primary intent was to study the feasibility of using FDG-PET to regionally stage head and neck disease for the purposes of treatment design. The study cohort was homogeneous and was reflective of the patient population eligible for organ preservation therapy (eg, locally advanced disease of the larynx, oropharynx, and oral cavity). We complemented FDG-PET with traditional methods of total body staging (chest radiographs and serum liver function panels). Chest and abdominal CT studies were used as corroborative studies only as indicated by FDG-PET or other screening test results.

Table 1. Study Cohort Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
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<tbody>
<tr>
<td>Subsite</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>15 (46)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11 (33)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>7 (21)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>2 (6)</td>
</tr>
<tr>
<td>T2</td>
<td>13 (40)</td>
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<tr>
<td>T3</td>
<td>9 (27)</td>
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<tr>
<td>T4</td>
<td>9 (27)</td>
</tr>
<tr>
<td>N stage</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>12 (37)</td>
</tr>
<tr>
<td>N1</td>
<td>4 (12)</td>
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<tr>
<td>N2</td>
<td>13 (39)</td>
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<tr>
<td>N3</td>
<td>4 (12)</td>
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<tr>
<td>AJCC stage</td>
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</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>5 (15)</td>
</tr>
<tr>
<td>III</td>
<td>6 (18)</td>
</tr>
<tr>
<td>IV</td>
<td>22 (67)</td>
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Abbreviation: AJCC, American Joint Committee on Cancer.

[F-18]-fluorodeoxyglucose PET has been demonstrated to improve staging accuracy and detection of occult distant disease for other cancer sites, including lung, esophagus, and lymphoma.21 We wanted to document this ability for head and neck cancer in our institutional cohort. We obtained fields of view extending into the abdomen (without the use of a Foley catheter, the lower pelvis must be excluded to eliminate signal from excreted FDG into the bladder). Previous FDG-PET series investigating head and neck cancer staging focused only on pulmonary metastases and did not review abdomen or lower spine with FDG-PET.10,16

Our experience with upfront FDG-PET staging provides 2 interesting findings. First, FDG-PET appeared to be feasible and detected disease that was not identified with CT scans, particularly in the mediastinum. Also, 3 of 4 patients presenting with distant metastases in this series had hepatic metastases, including 1 patient without lung involvement. Such a high proportion of liver involvement has not been reported for staging protocols absent FDG-PET.12 Another patient had an intra-abdominal secondary malignancy (colon adenocarcinoma) that was detected at an early, curable stage by FDG-PET. This would have been missed by routine techniques or by chest CT scanning. Taken together, these findings suggest that extended-field FDG-PET alone has the potential to outperform any combination of traditional staging techniques.

This interpretation must be tempered by the limitations of this series. Although prospective in design, the primary intent of this trial was to detail the impact of FDG-PET on regional disease localization. For this reason, we did not incorporate a direct head-to-head comparison between FDG-PET and CT scanning. A viable, less expensive alternative to FDG-PET would be extended-field CT scanning with inclusion of the chest and liver. This is itself not a standard test for staging, but a direct comparison with FDG-PET may be a focus of future study. [F-18]-Fluorodeoxyglucose PET is potentially prone to false-
negative results for parenchymal lung lesions smaller than 1 cm that can be visualized by CT scanning. Although our experience and that of others\(^1^4-1^7\) shows that FDG-PET is highly sensitive, we do not presume that it can detect all locations of distant cancers, especially small subclinical lesions. Finally, PET is susceptible to false-positive results in lymph nodes affected by inflammation, as demonstrated in one of our patients with a false-positive result in a benign axillary node. We should note that false-positive FDG-PET findings in the axilla could also be caused by extravasation of FDG radiotracer into the antecubital region during intravenous injection, resulting in ipsilateral axillary lymph node uptake.\(^2^2\)

Our study cohort contained predominantly advanced-stage cases. Such patients are currently targeted by modern organ preservation trials. Our results closely agree with earlier reports that suggest the risk for distant metastases in such patients is high and that such risk is closely related to nodal stage.\(^7,1^1\) All patients in our cohort found to have metastases also had node-positive stage IV primary disease. Therefore, it is reasonable to reserve the use of FDG-PET screening for patients with node-positive stage III/IV disease. However, the risk for secondary cancers in earlier-stage patients, especially those with laryngeal primary tumors, remains elevated and may benefit from longitudinal surveillance with FDG-PET.

Given traditional limitations of therapy to control locoregional disease recurrence, staging of distant sites has remained a somewhat lower priority until recently. As local disease control improves with newer strategies, distant disease staging and control will become a more pressing issue. Already, several groups using aggressive taxane-based induction chemotherapy or definitive chemoradiotherapy have demonstrated a reversal of the expected pattern of treatment failure, with more study subjects experiencing distant disease relapses than locoregional failures.\(^2^3-2^5\)

The potential impact of FDG-PET, as with all new diagnostic technologies, on staging and treatment selection cannot be overstated. Routine use of FDG-PET to screen patients for entry into organ preservation trials may provide crucial advantages in locoregional staging accuracy, but may also introduce stage migration.\(^2^6-2^7\) Stage migration occurs when more sensitive technologies (such as PET) “migrate” patients with previously undetectable metastatic disease out of an early stage (improving the survival of that group) and place them into a stage with advanced disease (improving this group’s survival as well). The net benefits of these changes are not yet clear, and the clinical impact of stage migration requires further study.

Figure 1. A, Representative extended-field \([F-18]\)-fluorodeoxyglucose positron emission tomographic (FDG-PET) scan of a patient with a T2 N2 squamous cell carcinoma of the left tonsil (primary tumor indicated by the arrow). B, Extended-field FDG-PET scan of a patient with metastatic squamous cell carcinoma originating from the oropharynx. A solitary hepatic nodule is demonstrated on coronal projection (arrow). This was subsequently confirmed by biopsy. Normal accumulation of FDG radiotracer is seen in both kidneys.
effect is that there is improvement in stage-specific survival, but no change in overall survival. This produces biased comparisons with historical cohorts and limits the applicability of clinical outcome improvements. There remains little mention of the use of PET scanning for the staging of patients enrolled into early-phase institutional trials. We would therefore recommend detailed disclosure of PET implementation (and diagnostic standards for staging) in future published trial reports.

CONCLUSIONS

In our study, extended-field FDG-PET (which images the abdomen and much of the axial skeleton) improved de-
tection of distant disease. The current staging pathway for our institution’s research protocols has evolved from standard techniques (chest radiography, serum chemistry panels, and chest CT scanning) to extended-field FDG-PET alone. The use of PET may simultaneously improve not only locoregional therapy planning, but also patient selection for aggressive curative therapy. Given the increasing acceptance and reimbursement for PET studies in general oncology practice, the use of PET for screening for head and neck cancer clinical trials should be carefully documented to optimize applicability to historical results and current clinical practice.

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