Limitations of FDG-PET and FDG-PET With Computed Tomography for Detecting Synchronous Cancer in Pharyngeal Cancer

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Objective: To analyze the ability of fluorine-18 fluoro-deoxyglucose positron emission tomography (FDG-PET) and the fusion of FDG-PET with computed tomography (FDG-PET/CT) to detect synchronous upper gastrointestinal tract (UGI) cancer in newly diagnosed pharyngeal squamous cell carcinoma (SCC). Synchronous UGI cancer is a significant problem in treating pharyngeal SCC, particularly for Japanese populations reported to be at high risk. Good results have been reported from the use of FDG-PET and FDG-PET/CT in staging head and neck SCC (HNSCC). An additional advantage is that both techniques are expected to prove useful in detecting synchronous cancer.

Design: Retrospective analysis of medical records.

Setting: Aichi Cancer Center, Nagoya, Japan.

Patients: Forty-three Japanese patients with pharyngeal SCC were assessed for the ability of FDG-PET and FDG-PET/CT to detect synchronous UGI cancer via a comparison with UGI Lugol chromoendoscopy. The patients had undergone 17 FDG-PET and 26 FDG-PET/CT scans before treatment.

Main Outcome Measure: Sensitivity of FDG-PET and FDG-PET/CT to detect synchronous UGI cancer.

Results: Pathologically, 6 patients with esophageal SCC (14%) and 4 with stomach adenocarcinoma (9%) were diagnosed on the basis of suspect lesions detected by UGI Lugol chromoendoscopy. One patient was found to have stage T2 esophageal cancer by FDG-PET/CT, but no patients had UGI cancer. The sensitivity of detecting T1 UGI cancer by FDG-PET and FDG-PET/CT was 0%.

Conclusions: The choice of diagnostic technique must be based on the site and histologic characteristics of the synchronous tumor. Although FDG-PET and FDG-PET/CT are still the preferred techniques for staging HNSCC, neither replaces Lugol chromoendoscopy for detecting synchronous UGI cancer in high-risk populations.

The objective of this study is to warn the otolaryngology–head and neck surgery community that FDG-PET and FDG-PET/CT cannot be relied on to detect a second mucosal UGI tumor.

METHODS

This study was conducted from May 2003 to November 2006 and received retrospective approval from the institutional review board at the Aichi Cancer Center. Initial clinical interpretations of imaging were used, and FDG-PET and FDG-PET/CT studies were not reinterpreted to resolve discrepancies. Examinations using FDG-PET, FDG-PET/CT, and Lugol chromoendoscopy were conducted only after receiving informed consent from all patients.

The criteria in this study were as follows: (1) for an index tumor, pharyngeal SCC was diagnosed by histopathologic analysis in patients with no history of malignant neoplasms; (2) FDG-PET or FDG-PET/CT was conducted before treatment; (3) UGI chromoendoscopy was performed before treatment; (4) serum glucose levels at no time exceeded 200 mg/dL, and no insulin was used. (To convert glucose to millimoles per liter, multiply by 0.0555.) One patient was excluded for a serum glucose level exceeding 200 mg/dL. A total of 43 Japanese patients were evaluated: 17 by FDG-PET and 26 by FDG-PET/CT scans. Each patient first underwent an FDG-PET or FDG-PET/CT scan. The tumor stage was staged according to the American Joint Committee on Cancer TNM classification system. Table 1 lists the clinical characteristics of all patients. Before treatment, a routine clinical examination was performed, including nasopharyngoscopy, chest radiography, and enhanced CT scanning from skull base to neck.

All patients were scanned using either FDG-PET (Advance NXi; General Electric Co, Fairfield, Connecticut) or FDG-PET/CT (Discovery LS; General Electric Co) at the Nagoya PET Imaging Center. The preferred technique was FDG-PET/CT, and FDG-PET alone was performed only if the schedule did not allow FDG-PET/CT. Patients fasted for 6 hours before receiving an intravenous injection of 5 to 10 mCi of FDG; they then sat quietly for 60 minutes before undergoing imaging.

Patients were scanned from the mid thigh to the skull vertex. The helical CT (LightSpeed plus; General Electric Co) scan data were collected at 20 to 100 mA, 140 kV, with a 4.25-mm section width. The CT portion was acquired in less than 35 seconds. Immediately after the CT scan, a PET scan was performed starting at the mid thigh using an acquisition time of 3 minutes per bed position with a 3-slice overlap. Images were reconstructed using a 2-dimensional, ordered subset expectation maximization algorithm with 28 subsets and 4 iterations. A Gaussian-based, 6-mm, full-width half-maximum (FWHM) postfilter and 4.3-mm FWHM loop filter were used during reconstruction.

All images were interpreted by 2 radiologists (T.T. and M.N.) who compiled each report after they achieved consensus on each case. Each radiologist was a university instructor who had undergone radiology fellowship training. Each had radiology experience that included the practice of nuclear medicine for more than 12 years, the reading of about 15 000 FDG-PET and/or FDG-PET/CT scans in the past 6 years, and authorship experience of articles on FDG-PET. About 15% of their FDG-PET and FDG-PET/CT scanning experience was devoted to head and neck imaging.

Both radiologists had access to primary cancer information, including the diagnosis of oropharyngeal cancer, but neither was given any information on UGI Lugol chromoendoscopy. The FDG-PET and FDG-PET/CT images were evaluated by visual inspection. A focus was considered positive if activity was significantly above the expected background and could not be explained by a normal structure.

All patients underwent UGI Lugol chromoendoscopy at the Aichi Cancer Center. After a conventional examination of the esophagus, stomach, and duodenum, about 10 mL of 3.4% Lugol iodine solution was sprayed over the entire esophageal mucosa. In this examination, any suspect lesions were photographed and biopsied by 2 gastroenterologists who had no access to the FDG-PET or FDG-PET/CT scan reports. Biopsy specimens were diagnosed by a pathologist according to the guidelines of the Japanese Society for Esophageal Diseases or the general rules for clinical and pathologic recording of gastric carcinoma by the Japanese Gastric Cancer Association. The mean interval between each examination was 7 days (range, 0–28 days). Patients diagnosed with UGI cancer underwent further appropriate staging procedures. In cases of abnormal FDG uptake, an additional diagnostic workup was performed for pathologic confirmation. For statistical analysis, the sensitivity and specificity of FDG-PET and FDG-PET/CT were calculated.

RESULTS

After UGI Lugol chromoendoscopy, 20 patients underwent biopsy of suspect lesions (47%); 10 of these were diagnosed as synchronous UGI cancer (23%). Six patients with esophageal SCC (14%) and 4 with stomach adenocarcinoma (9%) were diagnosed. No synchronous UGI lesions were located at the gastroesophageal junction, an area that normally has increased uptake making detection of small lesions nearly impossible on both FDG-PET and FDG-PET/CT. Synchronous UGI cancer was diagnosed in 10 patients: 7 T1, 2 T2, and 1 T3. Pathologic analysis revealed 10 patients entirely free of malignant neoplasms. Table 2 summarizes the FDG-PET findings and the stages of synchronous UGI cancer in the 10 patients where this was found. No patient was diagnosed with UGI cancer by FDG-PET, the sensitivity of which was 0%. Findings of FDG-PET revealed no false positives at the UGI site, for a specificity of 100%. Table 3 lists the FDG-PET/CT findings and the stages of synchronous UGI cancer found in 6 patients. By FDG-PET/CT, 1 patient was found to have esophageal SCC detected at a clinical stage of T2N0M0, for a sensitivity of 17% (Figure 1). The FDG-PET/CT studies returned no

Table 1. Patient Characteristics by Type of Imaginga

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FDG-PET</th>
<th>FDG-PET/CT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>17</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>Men</td>
<td>17</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Women</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age (age range), y</td>
<td>66 (49-86)</td>
<td>64 (40-81)</td>
<td>65 (40-86)</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>13</td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>13</td>
<td>18</td>
<td>31</td>
</tr>
</tbody>
</table>

Abbreviations: FDG-PET, fluorine-18 fluorodeoxyglucose positron emission tomography; FDG-PET/CT, the fusion of FDG-PET with computed tomography.

a Unless otherwise indicated, data are reported as number of patients.
false-positive results at the UGI site, for a specificity of 100%. None of the 7 patients with synchronous T1 UGI cancer were diagnosed by either FDG-PET or FDG-PET/CT, giving it a sensitivity of 0% (Figure 2).

The sensitivity of FDG-PET for detection of pharyngeal SCC was 94% (16 of 17); for FDG-PET/CT, it was 100% (26 of 26). A negative FDG-PET result in 1 patient with pharyngeal SCC was actually found to be T1 hypopharyngeal SCC. Other than in pharyngeal and UGI sites, 3 lesions were indicated to be synchronous cancer by FDG-PET or FDG-PET/CT. One of the 3 lesions was detected as prostate cancer by FDG-PET, with the final diagnosis being T3N1M0 prostate adenocarcinoma. The remaining 2 lesions indicated by FDG-PET/CT were diagnosed as maxillary fungus sinusitis and colon adenoma. No lesion was indicated by other examinations.

**COMMENT**

An emerging imaging technique based on differences in glucose uptake between a cancerous lesion and the surrounding normal tissue, FDG-PET has been reported to produce good results in staging and evaluating HNSCC.

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**Table 2. Ability of FDG-PET to Detect Upper Gastrointestinal Cancer**

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Pharyngeal Site</th>
<th>Detection</th>
<th>Site (Subsite)</th>
<th>Diagnosis</th>
<th>Stage^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/66</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Esophagus (lower thoracic)</td>
<td>SCC</td>
<td>pT1N0M0</td>
</tr>
<tr>
<td>M/77</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Stomach (antrum)</td>
<td>Tub2</td>
<td>cT2N0M0</td>
</tr>
<tr>
<td>M/73</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Stomach (corpus)</td>
<td>Tub1</td>
<td>pT1N0M0</td>
</tr>
<tr>
<td>M/73</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Stomach (corpus)</td>
<td>Por1</td>
<td>cT3N1M0</td>
</tr>
</tbody>
</table>

Abbreviations: FDG-PET, fluorine-18 fluorodeoxyglucose positron emission tomography; Por1, solid, poorly differentiated adenocarcinoma; SCC, squamous cell carcinoma; Tub1, well-differentiated tubular adenocarcinoma; Tub2, moderately differentiated tubular adenocarcinoma.

^aClinical or pathologic stage, according to the American Joint Committee on Cancer.

**Table 3. Ability of FDG-PET/CT to Detect Upper Gastrointestinal Cancer**

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Pharyngeal Site</th>
<th>Detection</th>
<th>Site (Subsites)</th>
<th>Diagnosis</th>
<th>Stage^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/62</td>
<td>Hypopharynx</td>
<td>True positive</td>
<td>Esophagus (lower thoracic)</td>
<td>SCC</td>
<td>cT2N0M0</td>
</tr>
<tr>
<td>M/77</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Esophagus (upper thoracic)</td>
<td>SCC</td>
<td>cT1N0M0</td>
</tr>
<tr>
<td>M/66</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Esophagus (mid thoracic)</td>
<td>SCC</td>
<td>cT1N0M0</td>
</tr>
<tr>
<td>M/46</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Esophagus (mid thoracic)</td>
<td>SCC</td>
<td>cT1N0M0</td>
</tr>
<tr>
<td>F/63</td>
<td>Hypopharynx</td>
<td>False negative</td>
<td>Stomach (antrum)</td>
<td>Tub1</td>
<td>cT1N0M0</td>
</tr>
<tr>
<td>M/40</td>
<td>Oropharynx</td>
<td>False negative</td>
<td>Esophagus (mid-thoracic)</td>
<td>SCC</td>
<td>cT1N0M0</td>
</tr>
</tbody>
</table>

Abbreviations: FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography with computed tomography; SCC, squamous cell carcinoma; Tub1, well-differentiated tubular adenocarcinoma.

^aClinical or pathologic stage, according to the American Joint Committee on Cancer.

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**Figure 1.** Maximum-intensity projection positron emission tomography (PET) (A) and transaxial PET with computed tomography (B) of a 62-year-old man with primary hypopharyngeal cancer (panel A, top arrow) as well as synchronous lower thoracic esophageal cancer (panel A, bottom arrow; panel B, arrow).
In the present study, the sensitivity of 94% for detecting a pharyngeal SCC site may reflect the high capability. Stokkel et al\textsuperscript{12} and Nishiyama et al\textsuperscript{13} evaluated the usefulness of FDG-PET in detecting synchronous cancer in HNSCC. Its capacity to scan the entire body at once significantly increased the rate of detection compared with a conventional workup. However, it should be noted that a conventional workup does not include UGI endoscopy.

As to the ability of FDG-PET to detect primary esophageal cancer, Kato et al\textsuperscript{17} reported that the mean sensitivity at all stages was 78%, but at a depth of T1b or more (involving the submucosa), it was 85%. However, the ability to detect a superficial lesion at, for example, stage T1a was 25%. Himeno et al\textsuperscript{18} reported 0% ability to detect such a lesion by FDG-PET and clearly indicated the limitations of FDG-PET for diagnosis of esophageal cancer confined to mucosa (Tis and T1a). This is thought to be because detection by FDG-PET requires a certain minimum tumor volume. As for the use of FDG-PET to detect primary stomach cancer, Mochiki et al\textsuperscript{19} reported that the mean sensitivity of primary cancer visualizations at all stages was 75%, while that of T1 was 40%; T2, 86%; T3, 90%; and T4, 100%.

The important factors influencing detectability vary; sometimes intense background activity in the normal wall may limit FDG-PET ability. Yamada et al\textsuperscript{20} reported that the detectability of stomach cancer depends on the depth of invasion and histologic subtype, such as signet-cell carcinoma and nonsolid, poorly differentiated adenocarcinoma, which may show low FDG uptake. Based on several reports,\textsuperscript{17,20} although FDG-PET shows high sensitivity in advanced UGI cancer, it has extremely low sensitivity in superficial UGI cancer.

From the standpoint of the stage of synchronous UGI cancer, Makuuchi et al\textsuperscript{5} detected esophageal cancer in 11.8% of the patients in their study of 788 subjects with head and neck cancer. Around three-quarters of those patients had an early superficial lesion. Previous studies\textsuperscript{5-8} have reported that most synchronous esophagus cancers in pharyngeal SCC were early superficial lesions.

In the present study, 2 of 9 synchronous UGI lesions not detected by FDG-PET or FDG-PET/CT were early superficial lesions. Therefore, we surmise that the depth of the tumor invasion affects detection. However, the final pathologic subtype of the remaining 7 lesions could not be decided because radiotherapy or palliative chemotherapy had been performed for the uncured pharyngeal lesions. We therefore consider that factors such as histologic subtype, depth, and gastritis cause difficulties in detection from the biopsy specimen and endoscopic findings. Based on a re-review of our false-negative cases, we believe that the lesions’ small size and superficial depth were the main causes for the false-negative findings.

Although the ability of FDG-PET/CT to detect UGI cancer is not clearly known, the principle of fusion suggests that its detection capacity might be higher than that of FDG-PET alone.\textsuperscript{14,16,21} However, the sensitivity of the detection of synchronous UGI cancer by FDG-PET/CT was only 17% in the present study, a finding most likely based on the low sensitivity for detection by each FDG-PET and CT independently. Neither FDG-PET nor FDG-PET/CT has been a primary way to detect mucosal disease.

The major clinical significance of screening UGI cancer in pharyngeal SCC by FDG-PET lies in its ability to detect advanced lesions, which would have a major impact on survival. In past studies,\textsuperscript{17,19} FDG-PET has shown a high sensitivity to the detection of advanced UGI cancer in particular, and there have been several reports that lesions showing FDG uptake are associated with a poorer survival rate than lesions that show no FDG uptake. Stokkel et al\textsuperscript{12} reported that UGI endoscopy may be omitted in patients without signs of synchronous cancer on FDG-PET, and FDG-PET may prove useful as a guidance tool for endoscopy and biopsy. Screening by FDG-PET/CT may be similar to screening by FDG-PET.

In the present study, 1 patient had T2 esophageal cancer detected by FDG-PET/CT, whereas no patients had T1 esophageal or stomach cancer detected by either FDG-PET or FDG-PET/CT. Of 43 patients, 1 was found to have prostate cancer by FDG-PET (2%). However, no patients with advanced stomach cancer were diagnosed. Synchronous advanced UGI cancer may be partially overlooked by FDG-PET or FDG-PET/CT.

Our study analyzed synchronous UGI cancer, which plays an important role in pharyngeal SCC.\textsuperscript{1,3} In particular, the aggressive nature of esophageal cancer means that lymphatic metastases often occur when the tumor reaches the submucosal layer, even though in the initial stages patients may be asymptomatic. Léon et al\textsuperscript{3} reported that 27 of 1845 patients with HNSCC developed a second esophageal cancer (1.4%) and that the actuarial data indicated a 3-year survival rate of 0% from the diagnosis. Tanabe et al\textsuperscript{9} reported the rate of synchronous UGI cancer in pharyngeal cancer to be 28% in Japanese populations reported to be at high risk. Although Lugol chromoendoscopy showed poor specificity in the present study (50%), detecting only abnormal mucosa and not specifically neoplastic mucosa, it has nonetheless been recommended for identifying second esophageal cancers by many au-
From a US clinical viewpoint, Lugol chromoendoscopy is not part of the conventional workup for detecting synchronous cancer in pharyngeal cancer because synchronous UGI cancer in pharyngeal cancer is rare.

A number of studies in the literature have reported the detection of synchronous cancer in HNSCC by FDG-PET or FDG-PET/CT, and FDG-PET or FDG-PET/CT findings have been confirmed by conventional workups. In particular, FDG-PET/CT may be more useful for synchronous lung cancer in high-risk American populations with oral or pharyngeal cancer. However, no studies have included UGI endoscopy in their conventional workups. In a high-risk Japanese population, our study found that both FDG-PET and FDG-PET/CT exhibit extremely low ability to detect synchronous UGI cancer in pharyngeal SCC. In particular, the sensitivity to the detection of stage T1 UGI cancer by FDG-PET and FDG-PET/CT was 0%.

The types of synchronous cancers encountered in HNSCC depend heavily on which types of cancers are endemic. As an additional advantage, FDG-PET and FDG-PET/CT may be more useful for synchronous cancer depending on which second cancer is endemic. When both FDG-PET and FDG-PET/CT are used for pharyngeal SCC in high-risk populations, it is necessary to keep in mind the limitations of these 2 techniques for detecting early UGI cancer; neither FDG-PET nor FDG-PET/CT should be the method of choice for detecting synchronous UGI cancer. In conclusion, the sensitivity of FDG-PET and FDG-PET/CT in the detection of stage T1 UGI cancer was 0% in Japanese patients with pharyngeal SCC. Although FDG-PET and FDG-PET/CT are still the preferred technique for staging HNSCC, neither replaces Lugol chromoendoscopy for detecting synchronous UGI cancer in high-risk populations.

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REFERENCES


