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# Update on $^{18}\text{F}$ -Fluorodeoxyglucose/Positron Emission Tomography and Positron Emission Tomography/Computed Tomography Imaging of Squamous Head and Neck Cancers

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This article summarizes the recent literature in  $^{18}\text{F}$ -fluorodeoxyglucose/positron emission tomography (FDG-PET) imaging of head and neck cancers and extends the previous review in this area by Schöder and Yeung in the July 2004 issue of *Seminars in Nuclear Medicine*. Positron emission tomography/computed tomography (PET-CT) imaging is now used widely but has not been adequately evaluated for head and neck cancer. Its accuracy in initial staging is better than CT but may be similar to magnetic resonance imaging. It is not sufficiently accurate in the N0 neck to rule out nodal metastases but may be appropriate if sentinel node mapping is performed in patients with PET studies showing no nodal disease. PET imaging is beginning to be used in radiotherapy treatment planning, where it makes a significant difference by identifying malignant normal size nodes, extent of viable tumor, and distant disease. PET continues to be useful in carcinoma of unknown primary in identification of the primary site. Overall success is around 27% after all other modalities have failed. FDG-PET is being used frequently to assess response to therapy and for surveillance thereafter. The major controversy is when to image after radiotherapy or combined chemo-radiotherapy. One month seems to be too early. The ideal time seems to be 3 to 4 months to avoid both false-positive and false-negative studies. The growing use of PET-CT studies in head and neck cancer will certainly make a significant difference in the treatment and outcome in this disease.

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An excellent detailed review by Schöder and Yeung on positron emission tomography (PET) imaging of head and neck cancers was published in the July 2004 issue of *Seminars in Nuclear Medicine*.<sup>1</sup> As these authors predicted, PET-computed tomography (CT) is becoming the standard imaging modality in head and neck cancer and several recent articles have demonstrated the advantages of PET-CT over PET in evaluating patients with head and neck cancer. PET/CT also is becoming an important tool in radiation treatment planning. Timing of PET after therapy and imaging criteria to assess response to radiotherapy and combination chemoradiation still remains a hotly debated issue. This article summarizes the recent literature in PET in head and neck

cancers to complement the Head and Neck PET Atlas on pages 220-252 in this issue of *Seminars*.

## Initial Staging of Squamous Head and Neck Cancers With FDG-PET

The majority of patients with head and neck cancer present with locally and regionally advanced disease with metastatic spread to cervical lymph nodes. Correct staging of the cervical lymph nodes is critical to determine the necessary extent of surgery (type of neck dissection, unilateral versus bilateral) and for precise delineation of the radiotherapy field. Although the usefulness of  $^{18}\text{F}$ -fluorodeoxyglucose (FDG)-PET imaging is currently well established for recurrent head and neck cancers, its role in the initial staging of these tumors is less certain. FDG-PET appears to be at least as sensitive or slightly more sensitive than conventional imaging for the

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**Table 1** Recent Studies Evaluating the Detection Rate of Distant Disease With FDG-PET in Patients With Head and Neck Cancer

Author	Year	Initial Stage	Detection of Distant Sites Disease	False Positive Cases	Comments
Teknos <sup>9</sup>	2001	12 pts with stage III or IV	3/12	None	2 mediastinal lesions only detected with PET
Schwartz <sup>10</sup>	2003	5 pts with stage II, 28 with stage III or IV	7/33	1/33	2 mediastinal and 1 bone lesion only detected with PET; 4 liver lesions confirmed with CT after positive PET
Goerres <sup>11</sup>	2003	7 pts with stage I or II, 27 pts with stage III or IV	7/34	1/34	Management change in 15% patients based on PET
Sigg <sup>12</sup>	2003	Not reported; 58 pts pretherapy evaluation or suspected recurrence	7/58	1/58	Management change in 5% patients based on PET

detection of nodal metastases in the initial staging of head and neck cancers. Schöder and Yeung<sup>1</sup> reported an average sensitivity and specificity range of 87% to 90% and 80% to 93% for FDG-PET compared with 61% to 97% and 21% to 100% for CT/MRI in detection of nodal metastases, respectively. However, the impact on outcome of improved accuracy of PET in pretherapy staging of cervical nodes is not well established. A recent study performed on 102 patients with buccal mucosa squamous cell cancer (a relatively rare head and neck cancer in the western world) did not demonstrate a significant improvement in locoregional control of disease in patients who were staged with PET despite a higher accuracy of PET in detection of nodal metastasis compared with conventional imaging. It also should be noted that with recent advancements in technology, magnetic resonance imaging (MRI) may equal or potentially surpass the accuracy of PET in initial local staging of head and neck cancers. In a recent article by Dammann and coworkers,<sup>2</sup> which prospectively compared FDG-PET, CT, and MRI in the initial staging of 64 patients, the sensitivity and specificity of MRI in detection of nodal metastasis was reported as 93% and 95%, respectively, compared with 85% and 98% for FDG-PET. In view of its higher sensitivity and optimum anatomic information, the authors of this report recommended MRI as the initial imaging modality for head and neck cancers.

The anatomic information with PET is markedly improved with the use of combined PET-CT systems. PET-CT is almost certainly more accurate than PET alone, although few studies have yet been published comparing PET-CT with other modalities. In a recent pilot study, Syed and coworkers<sup>3</sup> used PET-CT to study 24 patients with head and neck cancer before their treatment. PET-CT downstaged the disease and changed the management in 17% of patients, compared with PET alone, by correctly assigning areas of increased uptake to fat or muscle tissue. PET-CT also significantly improved the confidence in anatomic localization and the interobserver agreement in assigning lesions to specific anatomical territories.<sup>3</sup> PET-CT, MRI, and multi-slice CT are all changing rapidly and improving. It is not clear which is currently the most accurate, although the combination of metabolic imaging

with PET combined with high-resolution CT is likely to be the most powerful technique.

Patients with head and neck cancer and a clinically negative neck (N0 neck) pose another management dilemma to the treating surgeon. Approximately 25% to 30% of these patients are found to have metastatic neck nodes at surgery. This finding means that the majority of patients with N0 necks, who undergo a neck dissection, are unlikely to have a therapeutic effect from this procedure. Several studies have evaluated FDG-PET in this setting, attempting to identify the patients who need radical neck dissection. In 3 studies totaling 48 patients, in which a sentinel node biopsy with immunohistochemistry was used as gold standard, the detection rate of PET was between 0% and 30%, making PET an unreliable modality in this clinical setting.<sup>4-6</sup> This is not unexpected, given that 40% of cervical nodal metastases are less than 1 cm in size and PET detection rate for nodes less than 1 cm is reported at 71%.<sup>7</sup> Kovacs and coworkers,<sup>8</sup> in a recent report, have proposed to use FDG-PET to identify patients who should undergo sentinel node biopsy versus elective node dissection. Given the high specificity of PET in the pretherapy setting, they suggest patients with a positive PET scan undergo a neck dissection whereas a sentinel node biopsy should be performed in patients with a negative PET scan. In their population of 62 patients with head and neck cancer, this algorithm spared unnecessary neck dissections on 12 neck sides with false-positive CT findings and a negative sentinel node biopsy.

Certainly the main advantage of FDG-PET over conventional imaging in pretherapy staging of head and neck cancer is its ability to detect contralateral disease and distant synchronous and/or metastatic disease in the chest and abdomen (Table 1).<sup>9-12</sup> A PET scan, as part of the initial staging, is most helpful in patients with advanced local disease (stage III or IV) who have 10% or greater risk of having distant disease.

## Radiotherapy Planning

PET-CT with FDG is highly accurate in preradiotherapy staging of head and neck cancer, with a reported sensitivity of

**Table 2** FDG-PET in Radiation Therapy Planning

Author	Year	Number of Patients	PET or PET/CT for PET imaging	Change in GTV With PET	Comments
Nishioka <sup>19</sup>	2002	21	PET	increased in 1/21; decreased in 1/21	Sparing of the parotid in 71% of pts with negative PET
Ciernik <sup>15</sup>	2003	12	PET/CT	increased in 2/12; decreased in 4/12	
Heron <sup>20</sup>	2004	21	PET/CT	In primary tumor increased in 3/21, decreased in 14/21. In nodal stations increased in 7/21 and decreased in 3/21	Primary only positive with PET in 3/21; distant metastases detected with PET in 3/21.
Scarfone <sup>18</sup>	2004	6	PET	Increased in 5/6	
Paulino <sup>16</sup>	2005	40	PET/CT	Decreased in 30/40 and increased in 7/40	PET/CT based GTV not included in the high-dose IMRT area in 25% patients with CT-only based GTV.
Schwartz <sup>21</sup>	2005	20	PET	Not reported for individual patients; mean PET/CT based GTV not significantly different from CT only based GTV.	Mean contralateral parotid and laryngeal cartilage dose significantly smaller with PET/CT based GTV.

96% and specificity of 98.5% in nodal level staging.<sup>13</sup> FDG uptake in tumors is also a prognostic indicator, with tumors with high FDG uptake reported to have a high recurrence rate and poor prognosis.<sup>14</sup> These tumors may therefore require multimodality treatment and may benefit from high-dose radiation such as obtained with intensity-modulated radiotherapy (IMRT).

FDG-PET data can be used in radiation treatment planning by importing the PET data into the treatment planning computer and coregistering with the treatment planning CT scan. For precise coregistration, the same immobilization head mask should be used for the planning CT and the PET or PET-CT scan. In a pilot study by Ciernik and coworkers,<sup>15</sup> the coregistration of PET-CT with the planning CT images was highly successful with average deviations of  $1.2 \pm 0.8$  mm in the x axis,  $1.5 \pm 1.2$  mm in the y axis and  $2.1 \pm 1.1$  mm in the z axis. In the clinical setting, Paulino and coworkers<sup>16</sup> have been able to consistently obtain a coregistration error of less than 5 mm. The target volumes (gross tumor volume [GTV]) may be significantly modified when FDG-PET data are incorporated into radiation treatment planning. The target volume may be increased because metabolically active tumor can be detected in normal sized nodes. On the other hand, the PET-based GTV is smaller than CT-based GTV in some patients, because the tumor may be partially necrotic. The radiation dose and volume are modified dramatically, from a curative intent to palliation, if distant metastases are detected on the PET scan. The results of several studies on the use of PET in radiation treatment planning are summarized in Table 2.<sup>19-21</sup>

Although the use of PET is gaining more acceptance in the radiation oncology community, questions remain that need to be addressed before PET-CT is used as a routine tool for radiotherapy planning in head and neck cancer.<sup>17</sup> Contouring the gross tumor volume with PET is not standardized; the GTV on PET can be significantly overestimated with an increased brightness level and can be underestimated by lowering the intensity of the PET images. A total of 50% of the tumor image maximum intensity has been used for contouring by several groups<sup>17,18</sup>; however, this has not been validated in large patient populations. Larger studies are needed to demonstrate the impact of FDG-PET on the outcome of radiotherapy.

## Carcinoma of Unknown Primary of Squamous Cell Origin

Cervical nodal metastases from an unknown primary tumor constitute 2% of newly diagnosed head and neck cancers.<sup>22</sup> Treatment of these patients in most centers includes extensive fields of irradiation to include the entire pharyngeal mucosa, larynx, and bilateral neck. The wide-field irradiation reduces the risk of tumor recurrence; however it causes significant morbidity, particularly in terms of xerostomia.<sup>23</sup> Correct localization of the primary tumor substantially reduces the complication risk of radiotherapy by decreasing the size of the radiation portal. The initial radiological workup of patients with a squamous cell nodal metastasis includes a chest radiograph and computed tomography and/or MRI fol-

**Table 3** Carcinoma of Unknown Primary: Detection of Primary Tumor With FDG-PET After a Negative Panendoscopy and Imaging With CT and/or MRI

Author	Year	N	PET Detection Rate (%)	PET False-Positive Rate (%)	Additional Metastases With PET (%)
Wong <sup>26</sup>	2003	17	29	37	18
Fogarty <sup>27</sup>	2003	21	10	28	44
Johansen <sup>28</sup>	2002	42	24	24	Not reported
Kresnik <sup>29</sup>	2001	15	73	7	Not reported
Jungehulsing <sup>30</sup>	2000	27	26	Not reported	27
Greven <sup>31</sup>	1999	13	8	46	Not reported
Kole <sup>32</sup>	1998	15	27	Not reported	Not reported
<b>Total</b>		<b>150</b>	<b>27</b>		

lowed by endoscopy and directed biopsies. CT and/or MRI can identify up to 50% of the primary tumors in patients, with no findings on the physical examination.<sup>24</sup> The yield of endoscopy is significantly higher if a primary tumor is suggested by radiological exams or physical examination findings. The most common sites of the primary tumor are the tonsil/tonsillar fossa and the base of the tongue.<sup>24</sup>

The available literature on the accuracy and usefulness of FDG-PET in patients with carcinoma of unknown primary consists of many single-center small studies with variable diagnostic workup before the PET scan. Rusthoven and coworkers<sup>25</sup> recently published a detailed review of FDG PET in carcinoma of unknown primary syndrome. The overall detection rate, based on 20 studies between 1992 and 2003, was 24.5% in a total of 302 patients. In a subset of studies in which PET was performed after a negative endoscopy and negative CT and/or MRI, the detection rate was similar, 27% in 150 patients (Table 3).<sup>26-32</sup> Given these findings, PET probably should be performed as the initial test and biopsies under endoscopy should be directed according to PET findings, as proposed by Drs Schöder and Yeung.<sup>1</sup> FDG-PET also finds additional local and distant metastases in an average of 27% of patients, which certainly changes the radiation field or the objective of treatment from cure to palliation when distant disease is identified.<sup>25</sup> One of the limitations of PET in this clinical setting is the relatively high false-positive rate related to variable physiologic uptake of FDG in head and neck structures. Since the previous review in the *Seminars*, Gutzeit and coworkers have reported their initial experience using PET-CT for detection of unknown primary tumors that included 18 patients with cervical nodal metastases. The sensitivity of CT, PET, side-by-side PET and CT evaluation, and coregistered PET-CT were 25%, 25%, 29% and 36%, with no statistically significant difference among the modalities in this small patient population.<sup>33</sup>

## Evaluation of Response to Radiation and/or Chemoradiation Therapy

Klabbers and coworkers<sup>34</sup> compiled a detailed analysis of all FDG-PET studies for detection of residual and recurrent head

and neck tumors after radiation and/or chemoradiation published between 1994 and early 2003. The weighted average for sensitivity and specificity for PET was 86% and 73% respectively, compared with 56% and 59% for CT and/or MRI.<sup>34</sup> The interval between end of treatment and imaging varied considerably among these studies. Although the optimum time for PET imaging after treatment is still debated, in most practices PET imaging is usually deferred for 3 to 4 months after radiation because of the significantly lower false negative rate at 4 months compared with 1 month.<sup>35</sup>

However, earlier evaluation is highly desirable in many patients treated with chemoradiation, who are potential candidates for salvage surgery, if residual disease is present. These are usually patients with initially unresectable, locally advanced disease, or with resectable, locally advanced laryngeal and hypopharyngeal cancers where better functional preservation can be obtained with primary chemoradiation therapy. Most surgeons prefer to perform salvage surgery within 6 to 8 weeks after radiation, before postradiation fibrotic changes develop in the neck.<sup>36</sup> Clinical evaluation and anatomic diagnostic imaging with CT and/or MRI are unreliable immediately after therapy. Several recent articles have evaluated the use of PET in early evaluation of treatment within 4 to 8 weeks of therapy. Goerres et al<sup>37</sup> studied 26 patients with advanced head and neck cancer after concomitant chemoradiation and compared the PET findings with histopathology in PET positive cases and clinical follow-up for 6 months in PET negative cases. Using visual assessment only, the sensitivity and specificity for residual disease and distant metastasis in this study were 90.95% and 93.3%, respectively. In another study by Nam and coworkers,<sup>38</sup> 24 patients were imaged with PET 4 weeks after definitive radiation therapy. In this study a  $SUV_{max}$  of 3.0 was used as a threshold to distinguish benign from malignant tissue. PET was correct in 2 patients with residual disease and only 1/22 patients with a negative PET scan developed recurrent disease over a median follow-up of 12 months. Because as many as 50% of the recurrences occur more than 15 months after the treatment,<sup>39</sup> larger clinical studies with long follow-up data are needed before early PET can be confidently used as a routine clinical tool to identify the candidates for salvage surgery.

The accuracy of PET, in addition to the timing of the scan, may vary with the timing of surgery, if surgical histopathology is used as gold standard, since doomed tumor cells may appear viable for several weeks after therapy. Rogers and coworkers<sup>40</sup> in a recent article have found an unacceptably low sensitivity of 45% for a 1-month posttherapy FDG-PET in comparison to the 6- to 8-week posttreatment surgical histopathology. At our institution, salvage surgery is performed later, 3 to 4 months after radiation therapy, to allow maximal effect of radiation on the tumor. Comparing the 3- to 4-month posttherapy PET data with histology from salvage surgery in 15 patients with clinically residual lymphadenopathy, Yao and coworkers reported a sensitivity of 100% and specificity of 82% for detecting residual tumor before salvage surgery.<sup>41</sup> The high sensitivity and negative predictive value (NPV) of an 8- to 12-week PET scan in this clinical setting was recently confirmed by Porceddu and coworkers<sup>42</sup> in a larger study of 39 patients with residual nodal enlargement after chemoradiation. FDG-PET scan findings were correlated either with surgical histopathology and/or a median clinical follow-up of 34 months. The NPV of PET in this series was 97% and the positive predictive value (PPV) was 71%. It should be noted that in both of these studies patients presented with residual clinical lymphadenopathy. FDG PET has also been shown recently to detect recurrent disease after IMRT with high negative predictive value regardless of the clinical status of the patient, when PET was performed for surveillance.<sup>43</sup> In 85 patients who received IMRT either as primary therapy or after surgery, the 3- to 5-month follow-up PET scan had a PPV and NPV of 55% and 98% for the primary tumor and 78% and 100% for nodal disease, respectively. In summary, a PET scan performed 2 to 5 months after therapy has a high NPV so that patients can be safely followed without intervention. Given the relatively low PPV, a positive PET finding needs to be confirmed before management decisions are made.

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