Positron Emission Tomography in the Management of Unknown Primary Head and Neck Carcinoma

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Objective: To assess the role of positron emission tomography (PET) in the management of unknown primary carcinoma of the head and neck region.

Design and Setting: Prospective case series at an academic medical center.

Patients: Twenty-six patients with an open excisional biopsy or a fine-needle aspiration biopsy finding that confirmed squamous cell carcinoma of the cervical lymph nodes and no visible primary tumor (as determined by results of a comprehensive physical examination and computed tomography and/or magnetic resonance imaging) underwent PET. The standard evaluation consisted of a comprehensive head and neck examination that included fiberoptic laryngoscopy/nasopharyngoscopy, computed tomography and/or magnetic resonance imaging, and PET followed by panendoscopy with selected biopsies and tonsillectomy.

Main Outcome Measures: Sensitivity, specificity, and positive and negative predictive values of PET to detect an occult primary tumor.

Results: The PET detected 8 occult primary tumors in 26 patients (detection rate, 30.8%). Four occult primary tumors (2 at the base of the tongue and 2 in the tonsil) were detected during routine panendoscopy with negative PET findings. The sensitivity of PET was 66.0%, with a specificity of 92.9%. The positive predictive value was 88.8%, and the negative predictive value was 76.5%.

Conclusions: Positron emission tomography can be a valuable tool to identify a subset of patients with an occult primary tumor in the head and neck region. In addition, it can be used to screen for primary tumors below the clavicle. Early identification of the primary tumor may allow for more accurate tumor staging and targeted radiotherapy to minimize adverse effects and complications. A normal PET finding, however, does not eliminate the need for a careful panendoscopy with directed biopsies and tonsillectomy.
neck examination, including fiberoptic laryngoscopy and nasopharyngoscopy. Routine imaging included CT and/or MRI with sections from the skull base to the mediastinum. All patients underwent a standard chest x-ray (posteroanterior and lateral). If no primary tumor was identified, our traditional approach included panendoscopy with directed biopsies of the tongue base and nasopharynx and bilateral tonsillectomy. In addition, any suspicious areas (eg, nodular lesions, erythema, or induration) underwent biopsy. In this protocol, all patients underwent total-body PET before panendoscopy. The patients were instructed to fast for 8 hours before PET. Positron emission tomography was performed after injection of 14.7 mCi (543.9 MBq) of fludeoxyglucose F 18. Whole-body PET was obtained in multiple bed positions (axial, coronal, and sagittal) after a 45- to 60-minute uptake delay. The PET results were read as positive or negative for an occult primary tumor site.

All patients then underwent panendoscopy with directed biopsies of the base of the tongue and nasopharynx and a bilateral tonsillectomy (if tonsils were present). The PET findings were used to guide the surgeon (F.R.M.) to perform multiple deep biopsies. A true-positive result included a positive PET finding with a positive corresponding biopsy finding for squamous cell carcinoma. A true-negative result included a negative PET finding and negative biopsy findings from the base of the tongue and nasopharynx and normal tonsils on histopathologic examination. A false-positive result included a positive PET finding with negative biopsy findings, and a false-negative result included a negative PET finding with positive biopsy findings on panendoscopy. The sensitivity, specificity, positive predictive value, and negative predictive value of PET to detect an occult primary tumor were calculated.

Overall, 27 consecutive patients with an unknown primary carcinoma of the head and neck region were entered into this protocol. One patient did not complete the PET secondary to diabetic hyperglycemia, leaving 26 patients available for analysis. Of the 26 patients, 24 (92%) were men and 2 (8%) were women. The mean age was 59.2 years (range, 39-78 years). Results of the neck staging for the study group included N1 in 7 patients, N2a in 6 patients, N2b in 6 patients, N2c in 2 patients, and N3 in 5 patients. In 8 patients, the primary occult tumor was detected by PET (Figure 1) (3 in the palatine tonsils, 2 at the base of the tongue, 2 in the lung, and 1 in the hypopharynx). One patient had a false-positive PET finding, with a positive PET finding in the left tonsillar fossa but a negative finding on pathologic analysis of the tonsil specimen. The overall primary tumor detection rate was 30.8%. Of these 8 primary tumors detected by PET, 2 of the primary tumors (1 in the palatine tonsil with an obvious submucosal nodule and 1 small 2-cm superficial mucosal ulcer in the apex of

![Figure 1. Case example of a true-positive positron emission tomography (PET) finding. A, Axial computed tomography (CT) demonstrates a left enlarged lymph node with central necrosis. Results of the fine-needle aspiration biopsy were positive for squamous cell carcinoma. B, Axial CT demonstrates a normal, symmetrical nasopharynx. C, Axial CT demonstrates a normal, symmetrical oropharynx. D, PET demonstrates a positive node finding in the left side of the neck (corresponding to the CT finding) along with a positive finding in the left oropharynx/tonsillar fossa. Panendoscopy with tonsillectomy confirmed a small submucosal tonsillar squamous cell carcinoma measuring 1.2 cm.](image-url)
the pyriform sinus) would have been detected with careful panendoscopy. In these cases the PET finding simply guided the surgeon to the physical examination finding. The remaining 6 primary tumors were detected only because the PET finding was positive and corresponding deep biopsy specimens were taken. In addition, 4 patients had false-negative PET findings with positive biopsy findings on endoscopic examination (2 in the palatine tonsil and 2 at the base of the tongue). All 4 false-negative PET findings demonstrated small foci of tumor measuring 0.8, 1, 2, and 5 mm (Figure 2).

The overall sensitivity of PET was 66.0% and the specificity was 92.9%. The positive predictive value of PET was 88.8% and the negative predictive value was 76.5%. There were no complications during the obtainment of the PET studies.

**COMMENT**

The diagnosis and management of an unknown primary carcinoma of the cervical region remain controversial. The goal of the diagnostic evaluation is to identify a small occult primary tumor that is not detectable on results of a careful office examination (including fiberoptic examination). Despite more sophisticated imaging studies, including CT and MRI, as many as 5% of all head and neck cancers will fall into the unknown primary category. Mendenhall et al. have shown that greater than 80% of the primary tumors, when found, will reside in the tonsils and base of the tongue. More recently, several authors have shown that the palatine tonsils can harbor the occult primary tumor in up to 30% to 40% of cases, and in 10% of the cases the primary carcinoma can be located in the tonsil contralateral to the neck mass. This has led to the recommendation to perform bilateral tonsillectomy in conjunction with the panendoscopy and biopsy of the base of the tongue and nasopharynx.

Positron emission tomography, in contrast to CT and MRI, is a nuclear medicine study that capitalizes on the fact that the neoplastic cells demonstrate preferential uptake of the glucose analogue. This uptake can guide the surgeon to regions for biopsy during the panendoscopy. Our prospective data demonstrate a tumor detection rate of 30.8% (8/26 patients), with 6 of the 8 sites in the head and neck region (including 5 primary tumors in Waldeyer’s ring and 1 in the hypopharynx). The remaining 2 primary tumors were found in the lungs. We have labeled these as primary lung tumors with synchronous cervical metastases from an unknown primary tumor in the head and neck region. Less likely would be the presence of cervical metastases from a primary lung cancer. Previous retrospec-

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**Figure 2.** Case example of a false-negative positron emission tomography (PET) finding. A, Axial computed tomography (CT) demonstrates a right enlarged lymph node. Results of the fine-needle aspiration biopsy were positive for squamous cell carcinoma. B, Axial CT demonstrates a symmetrical oropharynx. C, Axial CT demonstrates a symmetrical nasopharynx. D, PET demonstrates a positive lymph node finding in the right side of the neck with no suspicious uptake in the upper aerodigestive tract. Results of panendoscopy with tonsillectomy demonstrated a 2-mm occult right tonsillar carcinoma.
tive reports in the literature suggest PET detection rates of 24% to 27% for an occult head and neck primary carcinoma. In addition to the ability to detect an occult primary tumor in the head and neck region, PET can serve as an excellent screening tool for distant metastatic disease or a synchronous/primary tumor in the lungs. Wax et al have demonstrated a high sensitivity of 100% and a positive predictive value of 85% for PET imaging to differentiate a malignant from a benign pulmonary lesion. In our case series, 2 patients were diagnosed as having an occult primary lung carcinoma, including one patient who presented with a large left neck mass (level III-IV) with a paralyzed left true vocal fold and another who presented with bilateral cervical neck masses. In both cases, the screening chest x-ray findings (posterioranterior and lateral) were read as normal. Obviously these findings can alter the tumor staging, treatment plan, and long-term prognosis.

Overall, the use of PET helped detect 8 primary occult tumors in this series of 26 patients (30.8% detection rate) with metastatic squamous cell carcinoma of the cervical region. As noted in the “Results” section, 6 of the 8 tumors detected by PET would not have been detected with routine panendoscopy and biopsy/tonsillectomy. The remaining 2 tumors (1 in the pala-
tine tonsil and 1 in the hypopharynx lesion) were detected on routine panendoscopy. The value of the PET was in guiding the surgeon to the location of the primary tumor and ruling out any synchronous tumors. Despite the addition of the PET to the routine workup, 4 patients had a negative PET finding but the primary tumor was detected on panendoscopy and directed biopsy findings (Figure 2). These data suggest that, although a positive PET finding can guide the surgeon to a potential primary tumor site, a negative PET finding does not preclude the need for a careful panendoscopy with directed biopsies. In all 4 cases of a false-negative PET finding in our series, the primary tumor was small (typically <5 mm) and only detected on histopathologic analysis. It has been suggested that a critical tumor volume of greater than 5 to 10 mm is required for a positive PET finding. Newer imaging techniques, including PET-CT fusion and next-generation PET, may improve our ability to detect the smaller occult primary tumors. The PET-CT fusion allows the physiological detail of the nuclear medicine study to be fused onto the anatomic detail of the CT image. A recent study comparing PET with PET-CT fusion in 68 patients with head and neck cancer demonstrated a significant advantage of PET-CT fusion. With PET-CT fusion, the percentage of equivocal lesions was decreased by 53%, and the diagnostic accuracy for cancer was increased from 90% to 96%. In addition, although 6 malignancies were missed with PET, only 1 was missed with PET-CT fusion. Overall, the PET-CT fusion findings altered the clinical diagnosis/staging in 18% of the 68 patients in that study.

To conclude, PET can be a valuable tool to identify the occult primary tumor in patients who present with a metastatic carcinoma in the cervical region. In addition, it can serve as a valuable screening tool for occult metastatic disease and synchronous primary tumors (particularly in the lungs). A negative PET finding, however, does not eliminate the need for a careful panendoscopy with directed biopsies and tonsillectomy.

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REFERENCES