Metastatic Carcinoma of the Neck of Unknown Primary Origin

Evolution and Efficacy of the Modern Workup

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Objective: To assess the efficacy of various diagnostic modalities in detecting occult primary tumor location.

Design: Retrospective medical record study.

Setting: Academic head and neck oncology practice.

Patients: A total of 183 consecutive patients with metastatic carcinoma of the neck from an unknown primary tumor during a 10-year period, after exclusion of those with previous history of head and neck cancer, a primary tumor site evident on physical examination, or primary tumors of the neck.

Main Outcome Measures: Identification of primary tumor location by various imaging modalities and panendoscopy with directed biopsies.

Results: Primary tumor location was identified in 84 patients (45.9%). Preoperative imaging (computed tomography [CT], magnetic resonance imaging, positron emission tomography [PET], and/or PET-CT fusion scan) identified sites suggestive of primary tumor location in 69 patients. Subsequent directed biopsy of these sites yielded positive results in 42 cases (60.9%). The rate of successful identification of a primary tumor for each of the imaging modalities was as follows: CT scan of the neck, 14 of 146 patients (9.6%); magnetic resonance imaging of the neck, 0 of 13 patients (0%); whole-body PET scan, 6 of 41 patients (14.6%); and PET-CT fusion study, 23 of 52 patients (44.2%) (P = .001). The highest yield in identifying primary tumor sites was obtained in patients who had undergone PET-CT plus panendoscopy with directed biopsies with or without tonsillectomy: 31 of 52 patients (59.6%).

Conclusion: Diagnostic workup including PET-CT, alongside panendoscopy with directed biopsies including bilateral tonsillectomy, offers the greatest likelihood of successfully identifying occult primary tumor location.


Cervical metastasis of squamous cell carcinoma from an unknown primary site occurs in approximately 2% to 4% of head and neck tumors. When a primary tumor is not identified, most centers advocate treatment including wide-field radiotherapy, which results in significant morbidity. Therefore, a good deal of effort is spent in attempting to identify occult primary tumor sites in this patient group. Since early descriptions of this problem in the literature, the workup and management of these cases has remained controversial.1-3

Customarily, the evaluation of this group of patients has involved complete head and neck examination, office endoscopy, and imaging studies such as computed tomography (CT) and/or magnetic resonance (MR) imaging of the head and neck. Patients are traditionally then examined under anesthesia with triple endoscopy (direct laryngoscopy, esophagoscopy, and bronchoscopy).2-4 Controversies associated with these evaluations include the best imaging modality to detect the primary tumor site, the role of directed (or “random”) biopsies of mucosal sites likely to harbor occult primary tumors, and the appropriateness of unilateral or bilateral tonsillectomy.5,6

In recent years, technologies in imaging have emerged that have proved useful in head and neck cancer. Specifically, positron emission tomography (PET)7 and the fusion of PET with CT imaging (PET-CT)8 have been applied to this patient group. The PET imaging relies on fludeoxyglucose F 18, a glucose analogue that is taken up by cells by means of normal transport mechanisms and phosphorylated by hexokinase II, but is then trapped within the cells and undergoes no further metabolism. Groups of cells with high metabolic...
This study expands the previously reported experience by our group, in which we evaluated the relative effectiveness of direct tonsillectomy vs deep tonsil biopsies in detecting occult primary tonsillar tumors. In that study, patients with primary tumors detected by imaging or by visual panendoscopy were excluded from our analysis. In the present study, we included those patients to study the usefulness of such examinations.

From January 1997 through June 2007, the clinic and operative records of the Head and Neck Oncology clinic at the James Cancer Hospital of The Ohio State University were examined for patients presenting with metastatic carcinoma of the neck. Patients were excluded if there was a history of head and neck cancer, if a primary tumor site was evident on physical examination, or if primary tumors of the neck (such as lymphoma or sarcoma) were diagnosed.

Once patients were identified, a complete medical record review was performed. Records from our clinic as well as from referring physicians’ offices were included in the analysis. Data collected included demographic information, physical examination findings, radiologic imaging results, and pathology results. When patients had undergone imaging or pathological testing before referral, the reports of these studies were obtained and reviewed.

Patients diagnosed as having unknown primary cancer in our practice undergo, with few exceptions, imaging studies and examination under anesthesia with panendoscopy. If no primary tumor is evident during endoscopy, directed biopsies are obtained from the nasopharynx, tonsils (deep biopsies or unilateral or bilateral tonsillectomy), base of the tongue, and hypopharynx. When imaging studies detect suspicious primary tumor sites, we will carefully examine and obtain biopsy specimens from these areas during endoscopy. If no obvious primary tumor is evident, directed biopsy specimens are also obtained from the remainder of the foregoing locations.

A neck dissection is usually performed with the patient under the same general anesthetic. When open biopsy has been performed, the previous incision is excised in continuity with the neck contents. The results from these procedures were reviewed and recorded.

Data were analyzed by means of Fisher exact test. Institutional review board approval for this study was obtained from the Office of Responsible Research Practices at The Ohio State University.

RESULTS

PRESENTATION

During the period from January 1997 through June 2007, 2245 patients with noncutaneous squamous cell carcinoma of the head and neck were examined and treated at our institution. From this population, we identified 183 patients (8.2%) diagnosed as having metastatic carcinoma (squamous cell, poorly differentiated, lymphoepithelial, or sarcomatoid) of the neck from an unknown primary tumor. Of the 183 patients, 141 were male (77.0%) and 42 female (23.0%). The age ranged from 17 to 86 years, with a median age of 55 years.

Nine patients (4.9%) presented with bilateral neck masses, and 174 (95.1%) presented with unilateral neck disease. The involved levels of the neck were as follows: level I, 10 patients (5.7%); level II, 136 (78.2%); level III, 62 (35.6%); level IV, 15 (8.6%); and level V, 22 (12.6%). (56 patients [32.2%] had nodes involving multiple levels. No individuals in this group of patients had findings on physical examination or office endoscopy suggestive of the primary tumor location. In patients who had undergone previous excisional biopsy, the referring surgeon’s original physical examination report was reviewed when available in our records. Thirty-three patients were referred to us after a panendoscopy had been performed; none of these revealed the primary tumor site. Repeat endoscopy in all patients was performed by us; primary tumor sites were identified in 7 cases.

IMAGING

Patients were examined by 1 or more of 4 different radiologic studies: CT scan of the neck (146 patients [79.8%]), MR imaging of the neck (13 [7.1%]), whole body fludeoxyglucose PET scan (41 [22.4%]), or whole body fludeoxyglucose PET-CT fusion scan (52 [28.4%]). Before referral, 130 patients had undergone CT scanning; 13, MR imaging; 12, PET scanning; and 4, PET-CT studies. These were not repeated by our group, but 2 of the patients with PET scans subsequently had PET-CT studies at our facility. Outside radiology reports were available for all examinations for review.

Use of PET scanning at our institution began in 2001 (mobile PET service with ECAT ACCEL PET scanner [Siemens, Malvern, Pennsylvania] or Discovery PET scanner [GE Healthcare, Buckinghamshire, England]). The PET-CT fusion scans became available at our institution in 2005 (Siemens Biograph 16 LSO PET-CT scanner). We were unable to obtain data about the brand and generation of scanners used at other institutions. During the 10-year period studied, the trends reflecting our practice’s use of various imaging modalities for patients with unknown primary cancer is shown in Figure 1.

IDENTIFICATION OF PRIMARY TUMOR SITE

CT Scan of the Neck

One hundred forty-six patients underwent CT scan of the neck. Thirty possible primary tumor sites were detected on imaging. Subsequent pathological examination confirmed the primary tumor site in 14 of these radiographically suspicious sites. Thus, CT scan detected the primary tumor site in 14 of 146 patients (9.6%).

Management was changed in 2 patients (1.4%) because of findings of a neck CT. In both cases, bilateral neck dissections were performed after the CT scan detected nonpalpable suspicious lymphadenopathy in the neck. Thirty possible primary tumor sites were detected by imaging or by visual panendoscopy were excluded from our analysis.

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METHODS

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contralateral neck. In both patients, the contralateral neck specimens showed additional metastatic disease.

MR Imaging of the Neck

Thirteen patients underwent MR imaging of the neck. Three possible primary tumor sites were identified on imaging, and none of these sites had a primary tumor on biopsy. No changes in management occurred because of MR imaging findings.

PET Scan

Fludeoxyglucose PET scanning was performed in 41 patients. Fourteen possible primary tumor sites were detected in 13 patients. Subsequent biopsies confirmed 6 of these 14 possibilities. Overall, PET scans detected the primary tumor sites in 6 of 41 patients (14.6%). In 4 of the 41 patients (9.8%), management was altered on the basis of the PET findings. Two patients had biopsies of sites (anterior floor of mouth and maxillary sinus) in addition to the standard directed biopsies; in both cases, the pathological findings were benign. In 1 patient a lung lesion prompted a thoracic surgery consultation and further imaging studies; no other studies demonstrated the lesion, and this was considered a false-positive result. Finally, 1 patient (2.4%) underwent bilateral neck dissection because of contralateral neck findings on PET; the specimen was positive for metastatic disease.

PET-CT Fusion Scan

Fifty-two patients underwent PET-CT fusion scans. Thirty possible primary tumor sites were identified in 27 patients. The location of the primary tumor site was confirmed in 23 of these 30 lesions during subsequent endoscopy. In total, the primary tumor site was identified in 23 of 52 patients (44.2%) by PET-CT. Seventeen of these 23 patients had also undergone previous CT scan of the neck, and the primary tumor was undetected in all 17 of the CT scans.

Twelve of 52 patients (23.0%) had additional PET-CT findings that prompted management changes; these changes are summarized in Table 1.

Location of Identified Primary Tumors

Overall, 85 occult primary tumor sites in 84 patients (45.9%) were identified; 1 patient had occult tumors in both tonsils. The locations of the primary tumor sites were the tonsil in 34 patients (40.5%), base of the tongue in 28 (33.3%), oropharynx in 6 (7.1%), hypopharynx in 11 (13.1%), nasopharynx in 4 (4.8%), and lung in 1 (1.2%). The neck levels involved in the patients with identified primary tumors is given in Table 2. Notably, 62 (73.8%) of occult tumors that were identified were located in the base of the tongue or tonsils.

Of the 99 patients in whom complete initial workup (examination, imaging, and panendoscopy with biopsies) did not disclose a primary tumor site, 67 underwent radiotherapy, 21 received chemoradiotherapy, and 11 were lost to follow-up. In this group, 3 primary tu-

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**Table 1. Management Changes Owing to PET-CT Findings**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Finding</th>
<th>Change in Management</th>
<th>Result a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung parenchyma activity</td>
<td>Thoracic surgery consultation, further imaging</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Thoracic vertebra activity</td>
<td>Further imaging</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Colon activity</td>
<td>GI consultation, colonoscopy</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Contralateral neck activity</td>
<td>Bilateral neck dissection</td>
<td>Positive</td>
</tr>
<tr>
<td>5</td>
<td>Tip of tongue activity</td>
<td>Biopsy</td>
<td>Negative (histoplasmosis)</td>
</tr>
<tr>
<td>6</td>
<td>Subpectoral lymph node activity</td>
<td>Thoracic surgery consultation, biopsy</td>
<td>Positive (lung cancer detected)</td>
</tr>
<tr>
<td>7</td>
<td>Contralateral neck activity</td>
<td>Bilateral neck dissection</td>
<td>Negative (noncaseating granulomas)</td>
</tr>
<tr>
<td>8</td>
<td>Mediastinal and abdominal lymph node activity</td>
<td>Thoracic surgery consultation, biopsy</td>
<td>Negative (noncaseating granulomas)</td>
</tr>
<tr>
<td>9</td>
<td>Liver and bone lesions suggestive of metastases</td>
<td>Neck dissection canceled, general surgery consultation, biopsy</td>
<td>Positive</td>
</tr>
<tr>
<td>10</td>
<td>Contralateral neck activity</td>
<td>Bilateral neck dissection</td>
<td>Positive</td>
</tr>
<tr>
<td>11</td>
<td>Small-bowel activity</td>
<td>Bilateral neck dissection</td>
<td>Positive</td>
</tr>
<tr>
<td>12</td>
<td>Contraindicated neck activity</td>
<td>Bilateral neck dissection</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastroenterology; PET-CT, positron emission tomography–computed tomography.

a Positive or negative indicates whether a histologically confirmed malignant neoplasm was identified in the location of the suggestive finding.
mor locations were later discovered after subsequent treatment had been completed: 1 each in the lung, nasal cavity, and tonsil.

Accuracy of Imaging Studies

The number of true- and false-positive and negative results were totaled for each of the imaging modalities. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were calculated for each modality by means of these values. Results are summarized in Table 3.

We then compared the results for the patients who underwent PET-CT scanning with those of patients who did not. In the 131 patients who did not undergo PET-CT studies, 53 primary tumors were identified (40.5%). Fifty-two patients underwent PET-CT studies, and primary tumors were found in 31 (59.6%, \( P = .02 \)).

Therapy for patients with cervical lymph node metastases centers on treatment of both the involved cervical lymph nodes and the primary tumor site. When the primary tumor site remains occult, putative mucosal sites are usually irradiated along with both sides of the neck in our institution. In contrast, identification of the primary tumor site allows for more precise and/or conformal therapy, thereby theoretically reducing morbidity associated with wide-field irradiation.

Since the first descriptions of patients with unknown primary tumors of the head and neck in the literature, much has changed in the workup and treatment of these patients. Improvements in understanding of lymphatic drainage pathways allow clinicians to focus physical examination on likely mucosal sites, based on the location of metastatic cervical nodes.\(^{11}\) Physical examination and office endoscopy are able to disclose primary tumors in at least 55% of patients who present with metastatic cervical lymphadenopathy.\(^{1,12}\) Several diagnostic imaging modalities, such as CT or MR imaging, as well as metabolic imaging, such as PET or PET-CT fusion, have all been suggested as useful diagnostic adjuncts in the treatment of these patients.\(^{3,13}\) It remains unclear which of these modalities offers the best yield in detecting occult tumors.\(^{14,15}\) Of the 183 patients in this study, 41

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**Table 2. Location of Lymphadenopathy in Patients With Identified Primary Tumor Sites**

<table>
<thead>
<tr>
<th>Neck Level Involved</th>
<th>Tonsil (n = 34)</th>
<th>Base of Tongue (n = 28)</th>
<th>Oropharynx (n = 6)</th>
<th>Hypopharynx (n = 11)</th>
<th>Nasopharynx (n = 4)</th>
<th>Lung (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>32</td>
<td>24</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>11</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>V</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Multiple levels</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Table 3. Utility of Imaging Modalities in Detecting Occult Primary Tumors**

<table>
<thead>
<tr>
<th>Modality</th>
<th>CT of Neck (n = 146)</th>
<th>MR Image of Neck (n = 13)</th>
<th>PET Scan (n = 41)</th>
<th>PET-CT Fusion Scan (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of primary tumor by imaging, No. (%)</td>
<td>14 (9.6)</td>
<td>0</td>
<td>6 (14.6)</td>
<td>23 (44.2)(^b)</td>
</tr>
<tr>
<td>Changes in management, No. (%)</td>
<td>2 (1.4)</td>
<td>0</td>
<td>4 (9.8)</td>
<td>12 (23.0)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>21.5</td>
<td>0</td>
<td>42.9</td>
<td>74.2</td>
</tr>
<tr>
<td>Specificity</td>
<td>80.7</td>
<td>62.5</td>
<td>72.4</td>
<td>72.0</td>
</tr>
<tr>
<td>PPV</td>
<td>46.7</td>
<td>0</td>
<td>42.9</td>
<td>76.7</td>
</tr>
<tr>
<td>NPV</td>
<td>56.8</td>
<td>50.0</td>
<td>72.4</td>
<td>69.2</td>
</tr>
<tr>
<td>Accuracy</td>
<td>50.0</td>
<td>31.3</td>
<td>55.1</td>
<td>68.3</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; MR, magnetic resonance; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

\(^a\)To calculate sensitivity, specificity, PPV, NPV, and accuracy, the following definitions and formulas were used. In all cases, the criterion standard was considered to be the results of the endoscopy and biopsies. A true-positive (TP) result was defined as an abnormality described on a study's report that was later shown by biopsy results to be malignant. A true-negative (TN) result was defined as a scan without abnormalities, followed by endoscopy and biopsy results in which no malignant neoplasm was identified. A false-positive (FP) result refers to a study with an abnormality that was subjected to biopsy, with negative results. A false-negative (FN) result refers to a study without abnormalities, but the subsequent biopsy's results demonstrated a malignant neoplasm. With the use of these definitions, sensitivity = TP/(TP + FN), specificity = TN/(TN + FP), PPV = TP/(TP + FP), NPV = TN/(FN + TN), and accuracy = (TP + TN)/all studies.

\(^b\)\( P = .001 \) when comparing other modalities with PET-CT.
(22.4%) had PET scans and 52 (28.4%) had PET-CT fusion studies. These modalities proved useful, not only for identifying occult primary tumors, but also for detecting contralateral neck activity and distant metastases.

Rusthoven et al. reviewed 16 studies, involving a total of 302 patients, regarding the effectiveness of PET alone in detecting unknown primary tumors. The sensitivity, specificity, and accuracy of PET in this role were 88.3%, 74.9%, and 78.8%, respectively (vs 42.9%, 72.4%, and 55.1% in our study). Rusthoven et al calculated that PET detected the primary tumor in a total of 74 of 302 patients (24.5%), compared with 6 of 41 (14.6%) in our study. In addition, Rusthoven and coworkers’ review described detection of new regional metastases in 15.9%, and distant metastases in 11.2%, vs 2.4% and 0%, respectively, in our study.

In contrast to PET, there exists relatively little published literature regarding the effectiveness of PET-CT fusion studies in unknown primary cancer of the neck. Studies by Nassenstein et al. and Wartski et al. detailed the detection of occult primary tumors by PET-CT in 11 of 39 patients (28.2%) and 13 of 38 patients (34.2%), respectively. In both of these studies, however, PET-CT was performed after a panendoscopy (with negative results of biopsies) had already been performed. In contrast, Roh et al. and Pelosi et al. used PET-CT before panendoscopy, similar to our study. In those reports, PET-CT detected occult primary tumors in 14 of 44 patients (31.8%) and 8 of 18 patients (44.4%), respectively.

In our series, 52 patients underwent PET-CT. Twenty-seven patients (51.9%) had PET-CT findings suggestive of a primary tumor. Subsequent biopsies of these areas demonstrated carcinoma in 23 patients (44.2%). This proportion was significantly higher than for any of the other imaging modalities ($P = .001$).

False-negative studies were identified in each of the 4 modalities. Random biopsies or a tonsillectomy subsequently demonstrated the location of occult primary tumors in each of these cases. For CT scans, 51 of 146 patients had positive results of biopsies but negative findings on scans (24 tonsil, 19 base of the tongue, 3 nasopharynx, 3 hypopharynx, and 2 oropharynx). For MR images, 5 of 13 were false-negative (3 base of the tongue, 1 tonsil, and 1 oropharynx). Eight of 41 PET scans were false-negative (3 base of the tongue, 2 tonsil, 1 each in hypopharynx, nasopharynx, and oropharynx). Finally, 8 of 52 PET-CT studies were false-negative (4 base of the tongue and 4 tonsil). Presumably, the occult primary tumors in these cases were too small to be visualized on CT or MR images or to generate sufficient uptake of fluordeoxylucose for detection on PET.

The presence of false-positive and false-negative scan results is a convincing argument to continue the tradition of panendoscopy with directed biopsies with or without tonsillectomy. Given that most identified tumors (73.8%) were located in either the tonsils or the base of the tongue, special attention should be directed to these areas during clinical examination, evaluation of imaging studies, and panendoscopy.

We also examined whether PET-CT identified any primary tumors that would otherwise have gone undetected. In 9 patients, the site of a PET-CT finding was examined during endoscopy and found to be normal in appearance and by palpation. Subsequent biopsies of these sites were positive for malignant neoplasms. In these 9 patients, tumors were identified in the tonsil (4 patients), base of the tongue (3 patients), lateral pharynx (1 patient), and nasopharynx (1 patient). It is unclear whether random biopsy of those sites alone (without prior knowledge of the PET-CT finding) would have detected the primary tumors, although the endoscopist undoubtedly paid special attention to these sites on the basis of the PET-CT findings. Figure 2 displays the results from patients who underwent initial PET-CT, followed by endoscopy and biopsy.

We compared the various combinations of diagnostic modalities performed in these patients. It does not appear that addition of PET alone offered a significant advantage in the detection of primary tumor location because we observed no significant difference between the group of patients who underwent PET scanning and those who had not undergone metabolic imaging. In contrast, after the introduction of PET-CT at our institution, primary tumors were detected in a significantly higher proportion of patients (31 of 52 [59.6%]) compared with those who did not undergo PET-CT (53 of 131 [40.5%]) ($P = .02$). These results would seem to indicate that fusion of PET with CT appears to allow more precise localization of small and often otherwise clinically undetectable tumors. As such, the combination of PET-CT with panendoscopy and directed biopsies (with or without tonsillectomy) appears to offer the most sensitive method of detecting occult primary tumor location. We believe it is advantageous to have the results of such imaging before panendoscopy, so that special attention can be directed toward identified suspicious sites. As the technology of metabolic imaging improves, we would expect that smaller and smaller lesions will be detectable by PET.

In conclusion, scanning with PET-CT is highly useful in the workup of patients with unknown primary car-
cinoma metastatic to the neck, yielding significantly higher rate of detection of occult primary tumor location than other imaging modalities. However, given the significant number of both false-positive and false-negative results associated with existing metabolic imaging, PET-CT remains an adjunct to other traditional methods, including panendoscopy with directed biopsies (particularly tonsillectomy and base of the tongue biopsies). As such, we recommend the combination of PET-CT, panendoscopy, and directed biopsies (including bilateral tonsillectomy) as part of the routine diagnostic workup of these patients.

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Author Contributions: Dr Agrawal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Waltonen, Ozer, Schuller, and Agrawal. Acquisition of data: Waltonen and Hall. Analysis and interpretation of data: Waltonen and Agrawal. Drafting of the manuscript: Waltonen and Agrawal. Critical revision of the manuscript for important intellectual content: Ozer, Hall, Schuller, and Agrawal. Statistical analysis: Waltonen. Obtained funding: Agrawal. Administrative, technical, and material support: Agrawal. Study supervision: Schuller and Agrawal.

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REFERENCES