MANAGEMENT OF THE UNKNOWN PRIMARY CARCINOMA: LONG-TERM FOLLOW-UP ON A NEGATIVE PET SCAN AND NEGATIVE PANENDOSCOPY

Frank R. Miller, MD,1 Anand B. Karnad, MD,2 Tony Eng, MD,3 David H. Hussey, MD,3 H. Stan McGuff, DDS,4 Randal A. Otto, MD1

1 Department of Otolaryngology-HNS, University of Texas Health Science Center San Antonio, 7703 Floyd Curl Dr., San Antonio, Texas 78229. E-mail: millerfr@uthscsa.edu
2 Department of Medical Oncology, University of Texas Health Science Center San Antonio, San Antonio, Texas
3 Department of Radiation Oncology, University of Texas Health Science Center San Antonio, San Antonio, Texas
4 Department of Pathology, University of Texas Health Science Center San Antonio, San Antonio, Texas

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Abstract: Background. The unknown primary carcinoma in the head and neck has been estimated to represent up to 7% of all head and neck carcinomas. In an attempt to identify the occult primary tumor the evaluation of this patient population has included a complete head and neck examination, flexible fiberoptic endoscopy, and imaging with CT/MRI. More recently, positron emission tomography (PET) has been advocated as a tool to detect primary tumors.

Methods. A cohort of 31 patients with fine-needle aspiration biopsy–confirmed squamous cell carcinoma were prospectively entered into a diagnostic protocol to identify the occult primary tumor. The diagnostic protocol included a comprehensive head and neck examination, flexible fiberoptic endoscopy, and imaging with CT/MRI. More recently, positron emission tomography (PET) has been advocated as a tool to detect primary tumors.

Results. The PET detected 9 occult primary tumors in the 31 patients (detection rate, 29%). Five occult primary tumors (2 base of tongue and 3 palatine tonsil) were detected during panendoscopy despite a negative PET. The combination of PET and panendoscopy detected 45.2% of the unknown primary tumors.

Conclusions. A negative PET study in patients with an occult primary head and neck carcinoma does not preclude the need for panendoscopy with biopsy to detect the occult primary tumor. The risk of subsequent primary tumor appears to be low in patients with a negative PET and a negative panendoscopy (<6%).

The diagnosis, evaluation, and treatment of the unknown primary squamous cell carcinoma (SCC) in the head and neck continues to generate controversy. The incidence of the unknown primary in the head region has been estimated to be from 3% to 7% of all head and neck cancers. The classic evaluation for the unknown primary tumor site consisted of a careful office examination including fiberoptic laryngoscopy/nasopharyngoscopy supplemented by imaging studies (including CT and/or MRI) followed by panendoscopy. More recently fluorodeoxyglucose F 18–labeled positron emission tomography (PET) has been advocated in the work-up of patients with an unknown primary carcinoma in the head and neck region. In a prospective study from our institution, Miller et al have demonstrated that PET can be a valuable tool to identify the primary occult tumor. In this study, the PET scan was able to detect the occult tumor in approximately 30% of the patients. Overall the PET had a positive predictive value of 88.8% and a specificity of 92.9%. Other reports in the literature would support the use of PET imaging or PET/CT imaging in the evaluation of this patient population.

The purpose of this study was to analyze the clinical utility and predictive value of the negative PET to predict the subsequent presentation of the primary tumor and metastatic disease with an emphasis on the clinical treatment plan. In addition, the impact of N-classification and extracapsular spread (ECS) were analyzed in relation to locoregional control and survival.

**MATERIALS AND METHODS**

All patients with a diagnosis of an unknown primary squamous cell carcinoma (SCC) of the head and neck region were eligible for this study. Institutional review board approval was obtained from The University of Texas Health Science Center at San Antonio and the South Texas Audie Murphy Veterans Affairs Hospital, San Antonio. Eligible subjects had results of an open excisional biopsy or fine-needle aspiration biopsy that confirmed SCC of the cervical lymph nodes. All patients then underwent a standard protocol to identify an occult primary carcinoma. The protocol consisted of a comprehensive head and neck examination including flexible fiberoptic endoscopy of the upper aerodigestive tract, CT and/or MRI imaging with cuts from the skull base to the mediastinum along with a chest X-ray (posteroanterior and lateral). The CT and/or MRI were reviewed by a neuroradiologist and attending surgeon (FRM, RAO) with attention focused on identifying a potential occult primary tumor. If no primary tumor was identified (based on the examination and imaging) the patient underwent a total body PET study as described in a previous study. The PET imaging was performed prior to panendoscopy and utilized to guide the surgeon to risk sites. The PET scan was performed prior to panendoscopy to avoid the issue of doing a post-panendoscopy PET that may create a false-positive study secondary to the recent biopsy/tonsillectomy. The PET study was read as positive or negative for an occult primary tumor site. After the PET scan was completed, each patient underwent a panendoscopy with appropriate directed biopsies of the base of the tongue and nasopharynx and a bilateral tonsillectomy. The findings of the PET scan were utilized to guide the surgeon (FRM) to perform multiple deep biopsies. A true positive was a positive PET scan with a positive corresponding biopsy for SCC. A true negative was a negative PET scan and negative biopsies from the base of tongue and nasopharynx as well as normal tonsils on histopathologic examination. A false positive was a positive PET scan with negative biopsies, and a false negative was a negative PET scan with positive biopsies on panendoscopy. The sensitivity, specificity, positive predictive value, and negative predictive value of PET imaging to detect an occult primary tumor were calculated.

In the event that the primary tumor was detected by PET and panendoscopy, the disease was staged appropriately according to American Joint Committee on Cancer standards and a treatment plan was formulated based on the recommendation of our multidisciplinary head and neck tumor board. In the set of patients with no identified primary tumor (negative examination and CT/MRI imaging followed by a negative PET and negative panendoscopy), treatment options consisted of primary surgery (including neck dissection) and postoperative radiation therapy or primary radiotherapy +/- chemotherapy. Long-term follow-up was then assessed for the subsequent development of a primary tumor, regional neck recurrence, and distant metastases.

**RESULTS**

Thirty-two consecutive patients with an unknown primary carcinoma in the head and neck region were entered into the protocol. One patient did not complete the PET due to hyperglycemia and
was eliminated from the analysis. Of the 31 patients available for analysis, 27 (87.1%) were men and 4 (12.9%) were women. The mean age was 60.5 years (range, 39–81). The N-classification for the 31 patients included N1 in 10 patients, N2a in 7 patients, N2b in 3 patients, N2C (both bilateral N1) in 2 patients, and N3 in 9 patients.

The PET scan was able to detect a biopsy-confirmed primary SCC in 9 patients (4 palatine tonsils, 2 base of tongue, 2 lung, 1 hypopharynx). The 7 primary head and neck tumors that were detected were all ipsilateral to the cervical neck mass. The 2 lung cancers were considered primary lung cancers with synchronous cervical metastases from an unknown primary in the head and neck region. This yielded a primary tumor detection rate of 29.0% (9 of 31). Five additional patients with a negative PET scan had the primary tumor detected on panendoscopy and directed biopsy/tonsillectomy (3 palatine tonsil, 2 base of tongue). These 5 primary tumors were all ipsilateral to the cervical neck mass. There was 1 false positive PET study (enhancement in the ipsilateral tonsil but negative pathology). The overall primary tumor detection rate (PET plus panendoscopy) was 45.2% (14 of 31 cases). These 14 cases underwent standard tumor staging and were treated based on tumor board recommendations. The overall sensitivity of PET to detect a primary tumor was 64.3%, and the specificity was 94.1%. The positive predictive value of PET was 90%, and the negative predictive value was 76.2% (Figures 1 and 2).

Overall the analysis resulted in 17 cases being classified as true unknown primary carcinoma (negative PET and negative panendoscopy with biopsy/tonsillectomy). These 17 patients were presented at our multidisciplinary head and neck tumor board. The N-classification for this group was N1 in 7 patients, N2a in 4 patients, N2b in 2 patients, and N3 in 4 patients (Table 1). In cases where the neck metastases were considered surgically resectable the patients were offered a neck dissection followed by postoperative radiation therapy as determined by the final pathology report. In general, patients with N2 or greater N-classification or N1 with extracapsular extension on histology were recommended to undergo postoperative radiation therapy. Standard radiation therapy included definitive external beam radiation (XRT) including an anterior supraclavicular field of 4500 cGy, right and left lateral neck fields of 5000 cGy to 6000 cGy, and 6100 cGy to 7200 cGy to the potential primary sites in the oropharynx and nasopharynx. The daily fraction sizes were 180 to 200 cGy. In the 1 case in which the neck was considered unresectable (invasion prevertebral muscle and carotid artery), the patient was treated with chemotherapy and radiation therapy followed by a salvage radical neck dissection (Table 1, subject 17).

When analyzed according to N-classification, there were 7 patients with T0N1 neck status. All 7...
underwent selective neck dissections (SND) (including levels 1 to 5), and 6 of the 7 had a single node with no ECS. None of these patients received postoperative radiation therapy, and all remain no evidence of disease (NED) at a mean follow-up of 41.2 months (range, 30 to 60 months). The 1 patient who was staged N1 but had ECS on final pathology did not receive postoperative XRT and developed a neck recurrence at 11 months. He was salvaged with a radical neck dissection followed by XRT and remains NED at 28 months. There were 6 patients with T0N2 N-classification (including N2a in 4 patients and N2b in 2 patients). In the N2a patients, 2 were treated with SND and 2 were treated with modified radical neck dissection (MRND) with sacrifice of the internal jugular vein and sternocleidomastoid muscle. In a similar fashion to the N1 neck, the only neck recurrence in the N2a group occurred in the patient who demonstrated ECS but refused postoperative XRT. This patient was salvaged with a RND followed by XRT and remains NED at 25 months. There were 2 patients with disease staged as N2b and both underwent SND. The 1 N2b patient that refused postoperative XRT subsequently developed a primary tumor in the base of tongue at 16 months (ipsilateral to the original neck disease) that was staged as T2N0. He was subsequently treated with chemotherapy and XRT and remains NED at 6 months.

Overall there were 4 patients with disease staged as T0N3 at presentation. Three of these patients were treated with a radical neck dissection followed by postoperative XRT. Disease in the fourth patient was considered unresectable (extensive invasion prevertebral muscle and carotid artery). He was treated with primary chemotherapy and XRT and subsequently underwent a salvage RND. As noted in Table 1, the final outcome for the N3 patients was poor, with 1 patient developing a regional neck recurrence at 9 months, 1 patient developing lung metastases at 7 months, and a third patient developing a second primary cancer (small cell lung). Of these 4 patients, only 1 was alive without evidence of disease (Table 1).

Overall 3 of the 17 patients with an unknown primary carcinoma developed a neck recurrence.

Table 1. Patient treatment and outcome (n = 17).

<table>
<thead>
<tr>
<th>ID</th>
<th>N classification</th>
<th>ECS</th>
<th>Primary treatment</th>
<th>Adjuvant treatment</th>
<th>Status</th>
<th>Follow-up</th>
</tr>
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<tr>
<td>1</td>
<td>N1</td>
<td>no</td>
<td>SND</td>
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<td>NED</td>
<td>30 mo</td>
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<td>2</td>
<td>N1</td>
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<td>SND</td>
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<td>NED</td>
<td>33 mo</td>
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<td>3</td>
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<td>no</td>
<td>SND</td>
<td>None</td>
<td>NED</td>
<td>36 mo</td>
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<td>SND</td>
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<td>NED</td>
<td>40 mo</td>
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<tr>
<td>5</td>
<td>N1</td>
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<td>SND</td>
<td>None</td>
<td>NED</td>
<td>48 mo</td>
</tr>
<tr>
<td>6</td>
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<td>no</td>
<td>SND</td>
<td>None</td>
<td>NED</td>
<td>60 mo</td>
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<td>7</td>
<td>N1</td>
<td>yes</td>
<td>SND</td>
<td>None</td>
<td>Neck recurrence</td>
<td>11 mo</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salvage RND/XRT</td>
<td>28 mo</td>
</tr>
<tr>
<td>8</td>
<td>N2a</td>
<td>no</td>
<td>SND</td>
<td>XRT</td>
<td>NED</td>
<td>28 mo</td>
</tr>
<tr>
<td>9</td>
<td>N2a</td>
<td>no</td>
<td>SND</td>
<td>XRT</td>
<td>NED</td>
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<td>10</td>
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<td>XRT</td>
<td>NED</td>
<td>22 mo</td>
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<td>11</td>
<td>N2a</td>
<td>yes</td>
<td>MRND</td>
<td>Refused</td>
<td>Neck recurrence</td>
<td>9 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salvage RND/XRT</td>
<td>9 mo</td>
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<tr>
<td>12</td>
<td>N2b</td>
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<td>SND</td>
<td>XRT</td>
<td>Refused Primary tumor BOT 16 mo</td>
<td>21 mo</td>
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<tr>
<td>13</td>
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<td>yes</td>
<td>SND</td>
<td>Refused</td>
<td>Rx XRT/Chemotherapy</td>
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<td>14</td>
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<td>XRT</td>
<td>NED</td>
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<td>15</td>
<td>N3</td>
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<td>RND</td>
<td>XRT</td>
<td>Small cell lung cancer</td>
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<td>16</td>
<td>N3</td>
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<td>RND</td>
<td>XRT</td>
<td>Dead second primary</td>
<td>27 mo</td>
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<td>17</td>
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<td>RND</td>
<td>Unresectable Palliative chemotherapy</td>
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<td></td>
<td>Lung metastases</td>
<td>18 mo</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DOD</td>
<td>21 mo</td>
</tr>
</tbody>
</table>

Abbreviations: ECS, extracapsular spread; SND, selective neck dissection; MRND, modified radical neck dissection; RND, radical neck dissection; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; BOT, base of tongue; XRT, external beam radiation.
(1 N1 with ECS, 1 N2a with ECS, and 1 N3 with gross ECS). The subsequent risk for the development of a primary carcinoma in the upper aerodigestive tract was low (1 of 17, 5.8%) in the patients who had a negative PET and negative panendoscopy with biopsy/tonsillectomy.

**DISCUSSION**

The diagnosis, work-up, and treatment of the unknown primary carcinoma of the head and neck continues to generate controversy. The majority of the studies in the literature are single-institution retrospective reviews done over an extended time period. As such the work-up and diagnostic techniques have varied considerably. The quality of the work-up over the years has simply reflected the emerging technologies available to the clinician including CT scan, MRI, fiberoptic imaging, and, more recently, PET imaging and PET-CT fusion techniques. In addition, it was not uncommon to have reports that included diverse histologies including adenocarcinoma, melanoma, small cell carcinoma, and poorly differentiated carcinoma. The purpose of this project was to prospectively assess a standardized diagnostic protocol with an emphasis on the role of PET imaging to detect the primary tumor at the time of initial presentation and assess the subsequent manifestation of a primary SCC in the upper aerodigestive tract. In other words, does PET imaging help us to detect the primary tumor and, if the PET imaging followed by panendoscopy is negative for a primary tumor, what is the risk of subsequent primary tumor presentation? These questions can have significant implications for the application of radiation therapy to the upper aerodigestive tract to “prevent” a primary tumor from occurring. Our definition of an unknown primary carcinoma of the head and neck necessitates a complete and careful head and neck examination including fiberoptic laryngoscopy. The patient then underwent imaging including CT scan and/or MRI in an attempt to identify the primary occult tumor. We would emphasize that the head and neck examination is the single most important first step, as many patients who present with metastatic SCC in a cervical lymph node will have the primary tumor detected by an experienced head and neck surgeon. If the physical examination and imaging were nondiagnostic, the PET scan was utilized to help guide the surgeon at the time of panendoscopy with biopsy. Overall the PET scan detected 9 biopsy-confirmed occult primary tumors (7 in the head and neck region and 2 lung primary tumors) in the 31 patients (detection rate 29%). This is in agreement with previous reports in the literature that have suggested that PET scanning can detect approximately one third of occult primary tumors. The PET scan is not without limitations in that 5 occult primary tumors were detected on panendoscopy despite a negative PET. As we have previously reported, these 5 occult tumors were all small in size measuring <5 mm. These 5 occult primary tumors were detected during routine guided biopsy of the at-risk primary tumor sites. This would suggest that the PET study is helpful but a negative PET scan does not eliminate the need for careful endoscopy with biopsy of the at-risk sites (tonsil, base of tongue, and nasopharynx).

Of particular interest is our subset of 17 patients with a true unknown primary carcinoma of the head and neck (negative PET and negative panendoscopy with biopsy/tonsillectomy). Only 1 of these 17 patients (5.8%) developed a subsequent primary tumor of the upper aerodigestive tract. The staging in this patient was TON2b. He underwent a neck dissection and refused postoperative XRT. He subsequently developed a small base of tongue primary tumor 16 months after the neck dissection. He went on to receive chemotherapy and radiation therapy and remains without disease at 6 months. Our experience would suggest that in patients with a complete negative work-up (negative PET and negative panendoscopy), the risk of a primary tumor is extremely low. As such the potential primary tumor does not significantly impact the long-term survival of this patient population.

The treatment and the control of the neck disease is the single most important component in the management of this patient population. As depicted in Table 1, our approach has been to offer the patient a primary neck dissection as this provides complete removal of the cervical disease and provides a detailed pathologic report that can guide recommendations for adjuvant therapy. Our preference is to perform SND with preservation of the key structures (spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein). In our patient population with an N1 pathologic neck (n = 7), we performed SND. In 6 of the 7 cases, no ECS was noted and there have been no neck recurrences in this population with a mean follow-up of 41.2 months (range, 30–60 months). None of these 6 patients received postoperative radiation therapy. The 1 patient with N1 N-classi-
fication who developed a neck recurrence was noted to have ECS. These findings are in agreement with previous data from Coster et al, who found that patients with a pathologically N1 neck and no ECS can be managed by neck dissection alone. In a similar fashion to our data, ECS was noted to be the single most important predictor of neck recurrence and regional disease control. In the patient population with N1 N-classification, we prefer to perform a staging neck dissection in hopes of avoiding radiation therapy and preserving it for any subsequent primary tumor of the upper aerodigestive tract. Other options advocated for the management of the N1 neck include primary radiation therapy, particularly in patients who have undergone an open neck biopsy. Mack et al have demonstrated a 95% regional neck control rate in patients who have undergone an open excisional biopsy followed by definitive radiation therapy.

In the patient population with more advanced (N2/N3)-classification, we have performed SND or modified radical neck dissection, depending on intraoperative findings. As depicted in Table 1, 1 neck recurrence was noted in the series of 6 patients with N2 staging (subject 11). In this case, ECS was noted in the pathology report but the patient refused subsequent radiation therapy. Radiation therapy was recommended based on the N-classification and the presence of ECS. Radiation therapy dosing includes treatment of both sides of the neck and potential primary tumor sites including Waldeyer's ring. The value of adjuvant radiation therapy in patients with N2-N3 or ECS has been demonstrated in a number of studies.

Coster et al demonstrated that patients with advanced pathologic N-classification (N2-N3) or ECS have a better regional neck control and improved survival if radiation therapy is given postoperatively.

In our series, 4 patients with N3 neck disease met the criteria for an unknown primary carcinoma. As shown in Table 1, the N3 neck patients form a difficult group. Three of the 4 underwent radical neck dissection followed by postoperative radiation therapy. Of these 3 patients, 1 remains with disease, 1 developed a second primary small cell lung cancer, and 1 developed a local neck recurrence. The fourth N3 neck was inoperable and the patient underwent palliative chemoradiotherapy with distant metastases developing at 7 months. As shown in Table 1, 2 of the 4 patients with N3 necks are dead and a third is alive with disease. This experience with the N3 neck shows that these patients are at a significant risk for regional neck recurrence as well as metastatic disease. This patient population typically will need combined-modality therapy in the form of surgery and postoperative radiation therapy plus consideration for chemotherapy. The overall poor prognosis for the N3 neck has been demonstrated in multiple studies.

CONCLUSION

PET imaging can be a valuable adjunct in the work-up and management of the patient with an unknown primary carcinoma of the head and neck. In our experience, the PET was able to identify approximately 30% of the occult primary tumors. A negative PET scan does not preclude the need for panendoscopy with biopsy to detect the occult primary tumor. The true value of the PET is in the small subset of patients that have had a careful head and neck examination by an experienced head and neck surgeon and negative imaging studies (including CT/MRI). In this select situation, the PET may help guide the surgeon at panendoscopy/biopsy. We would advocate a whole body PET study in the evaluation of patients with an unknown primary only after the complete head and neck examination (including fiberoptic endoscopy) and neuroradiologic review of the CT/MRI.

We do not believe that routine utilization of PET imaging has a role in the initial staging of most head and neck carcinomas. The emerging experience with PET-CT fusion may have a role in staging as well as assessing the response to therapy. The overall risk of the subsequent manifestation of a primary tumor of the upper aerodigestive tract was very low (5.8%) in patients that have had a negative PET and a negative panendoscopy with biopsy. The overall risk of regional neck recurrence was elevated in patients with advanced neck disease (N2-N3) and in patients with ECS. Postoperative radiation therapy can reduce the risk of subsequent neck nodal recurrence in patients with advanced neck disease or ECS.

REFERENCES


