Evaluation and Management of the Unknown Primary Carcinoma of the Head and Neck

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Key Words
Squamous cell carcinoma, head and neck, unknown primary, extracapsular spread, metastasis

Abstract
Squamous cell carcinoma of unknown primary origin in the head and neck is encountered as a recurring clinical problem in head and neck cancer clinics, affecting 3% to 25% of patients. This article describes the clinical presentation, appropriate evaluation, and treatment strategies for this important subgroup. Treatment—best carried out with multidisciplinary teams of specialists experienced in the care of head and neck cancer patients—is curative for most of these patients. (JNCCN 2008;6:1068–1075)

Metastatic carcinoma in the cervical lymph nodes without obvious evidence of a primary source is a common clinical entity and occurs in approximately 3% to 5% of head and neck malignancies. Most of these carcinomas arise from primaries in the upper aerodigestive tract but may also arise from other sites, including the thyroid, esophagus, and lung. Histologically, squamous cell carcinoma (SCC) represents up to 90% of metastatic disease in the cervical lymph nodes with unknown primary tumor and has diverse histologies, including head and neck melanoma, lymphoma, and adenocarcinoma, with rare tumors constituting the remainder.

A study of the national cancer registry of Denmark found the incidence of unknown primary squamous cell carcinoma of the head and neck (HNSCC) to be 0.34 per 100,000 population. This rate has remained steady over the past 20 years, despite a rising overall incidence of HNSCC, suggesting that some progress is being made in detecting the primary site of these malignancies. However, the unknown primary remains a challenging diagnostic and therapeutic entity, with fewer than 60% of primary tumors being discovered. This article focuses on the diagnosis, management, and outcomes of metastatic HNSCC of unknown primary site.

Evaluation
Physical Examination
The initial step in evaluation involves careful physical examination of the patient by a trained head and neck specialist. Most unknown primaries originate (where they are eventually identified) in the palatine tonsil, base of tongue, or nasopharynx. Evaluation of these sites requires particular attention, including palpation of the tonsil and base of tongue. Thorough examination should include the head and neck skin to exclude cutaneous malignancy, and fiberoptic endoscopy of the nasopharynx, oropharynx, larynx, and hypopharynx (Figure 1).

If the tumor from which the cervical metastasis arises is not identified after history and head and neck physical examination, it is initially defined as an unknown primary. A landmark 1944 study by Martin and Morfit showed that of 218 patients with unknown primaries, 52% were identified through physical examination by the referring physician or on presentation to their department, with an additional 16% identified through serial examination within the following 2 weeks. Jones et al. reported similar findings in a study of 268 patients, of whom 147 (55%) had a primary site identified through history and physical examination alone.
The location of the lymph node metastasis may also be informative. Up to 85% of neck masses present in levels II and III and are most often derived from upper aerodigestive tract primaries. Metastases to the low neck (level IV and supraclavicular nodes) are often from sites below the clavicle, including lung and gastrointestinal tract. These masses are typically excluded from studies of unknown head and neck primaries and are not discussed further in this article. Level V lymph nodes commonly result from cutaneous or nasopharyngeal primaries.

**Biopsy**

Tissue diagnosis is critical in determining appropriate therapy for metastatic disease to the neck. In the absence of a defined primary site on physical examination, the next step in evaluation is a fine needle aspiration (FNA) biopsy. With experienced cytopathologic examination, 82% to 96% of FNA biopsies are estimated to be diagnostic.

Accuracy of diagnosis can occasionally be increased through judicious use of immunohistochemical staining, typically in the context of an undifferentiated malignancy. A nondiagnostic biopsy should be repeated. Depending on the location of the mass, the yield of FNA may be improved with CT or ultrasound guidance.

Open biopsy should be considered only after multiple nondiagnostic FNA biopsies or if strong clinical suspicion of lymphoma exists. Historically, open node biopsy was condemned by Martin and Morfit as “an ill-advised and needless surgery.” Some authors have suggested an increased rate of local complications, recurrence, and distant metastasis with open biopsy, but recent studies have shown no difference in regional control or survival after open neck biopsy if the definitive treatment is appropriate (i.e., neck dissection or radiation therapy).

**Conventional Radiologic Evaluation**

Radiologic studies are a cornerstone of the evaluation of patients with head and neck cancer. Contrast-enhanced CT (CECT) or MRI with gadolinium contrast from the skull base to the diaphragm is preferred. CECT is generally the preferred initial examination because of its excellent spatial resolution, speed, and cost-efficiency. MRI has superior soft-tissue resolution and is particularly useful for evaluating the base of the tongue, skull base, and nasopharynx.

Inclusion criteria in published studies allow either MRI or CECT; therefore, few data show one examination to be superior. One early study before widespread use of MRI for head and neck neoplasms showed that 20% of unknown primaries could be detected with CT. Recent studies suggest detection of previously occult primary sites in 17% to 22% of patients using CT or MRI.

**PET**

PET and PET/CT are increasingly used to evaluate the unknown primary, but the exact indications for these studies are unclear (Table 1). PET has been reported to detect primary tumors in 8% to 50% of HNSCCs for which the primary was not identified by physical examination and routine imaging. In a meta-analysis of 16 studies, Rusthoven et al. found a discovery rate of 24.5% for PET scan, with 90% sensitivity, 75% specificity.
The potential for false-negative PET findings, particularly for primaries of the palatine tonsil, has been noted by multiple authors.27,28 Current NCCN Clinical Practice Guidelines in Oncology: Occult Primary (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org) recommend PET in the context of a complete evaluation, including panendoscopy and after conventional radiologic studies have failed to identify the primary site.29 Several studies have also investigated the role of PET/CT fusion-imaging in detecting the unknown primary. Wartski et al.30 studied 38 patients with no diagnosis after evaluation, including conventional radiography and endoscopy with biopsy. Of this group, 68% had positive PET/CT, and of these 17 of 26 underwent a second endoscopy with biopsy, resulting in diagnosis of the primary site in 13 of 38 (34.2%).

Direct comparison of PET, PET/CT, and CT showed no significant difference in the rate of identification of a potential primary site for PET, PET/CT fusion, or PET and CT read side-by-side; however, no histologic verification of tumor at the identified site was provided.31

**Surgical Evaluation**

**Diagnostic Endoscopy:** Surgical endoscopy plays an important role in evaluating patients with head and neck cancer. Despite the emphasis on radiologic detection of primary tumors, endoscopy with biopsy is the gold standard for diagnosis. Many imaging studies exclude patients with a diagnosis made at first endoscopy. Panendoscopy can identify previously occult primary tumors in 16% to 26% of cases.9,11,22

A point of controversy in diagnostic endoscopy is the taking of random or directed biopsies. Most unknown primaries discovered are found in only a few anatomic sites: the nasopharynx, tonsil, base of tongue, and pyriform sinus, which has caused most head and neck surgeons to advocate biopsies of these sites even in the absence of visible abnormalities.32,33 Lee et al.34 reported that 3 of 33 (9%) unknown primaries were detected on directed biopsies with no obvious mucosal abnormalities. Other data on this practice are sparse.

The tonsil is a common source of unknown primary tumors of HNSCC. Righi and Sofferman35 first showed the usefulness of tonsillectomy in discovering the primary site of SCC metastatic to the cervical lymph nodes. Multiple studies have confirmed that the rate of occult primary disease in the ipsilateral tonsil is between 18% and 30%.36-38 Koch et al.39 also advocated bilateral tonsillectomy because of a 10% incidence of contralateral disease and the rare discovery of bilateral disease in their study population. Current NCCN guidelines recommend at least performing an ipsilateral tonsillectomy when evaluating the unknown head and neck primary.29

**Molecular Studies**

Molecular examination of cervical metastasis is a promising new methodology for diagnosing the primary tumor site. The concept of field cancerization, as

### Table 1 Diagnostic Usefulness of PET imaging for Head and Neck Squamous Cell Cancer of Unknown Primary

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Modality</th>
<th>Discovery</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rusthoven</td>
<td>2004</td>
<td>302*</td>
<td>PET</td>
<td>24.5%</td>
<td>89.3%</td>
<td>74.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al.</td>
<td>2005</td>
<td>26</td>
<td>PET</td>
<td>30.8%</td>
<td>66%</td>
<td>92.9%</td>
<td>88.8%</td>
<td>78.8%</td>
</tr>
<tr>
<td>Regelink et al.</td>
<td>2002</td>
<td>50</td>
<td>PET</td>
<td>32%</td>
<td>100%</td>
<td>94%</td>
<td>89%</td>
<td>100%</td>
</tr>
<tr>
<td>Johansen</td>
<td>2008</td>
<td>60</td>
<td>PET</td>
<td>29%</td>
<td>86%</td>
<td>69%</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>Stoeckli</td>
<td>2003</td>
<td>18</td>
<td>PET</td>
<td>29%</td>
<td>63%</td>
<td>90%</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>Wartski</td>
<td>2007</td>
<td>38</td>
<td>PET/CT</td>
<td>68%</td>
<td>92.8%</td>
<td>73.3%</td>
<td>76.4%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Fleming</td>
<td>2007</td>
<td>22</td>
<td>PET/CT</td>
<td>72.7%</td>
<td>94.1%</td>
<td>100%</td>
<td>100%</td>
<td>77.8%</td>
</tr>
<tr>
<td>Zanation</td>
<td>2005</td>
<td>10</td>
<td>PET/CT</td>
<td>60%</td>
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</tr>
<tr>
<td>Freudenberg</td>
<td>2005</td>
<td>21</td>
<td>PET/CT</td>
<td>57%</td>
<td>85.7%</td>
<td>100%</td>
<td>100%</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
*Meta-analysis of 16 PET-only studies.
†Values could not be calculated from data given.
described by Slaughter et al.,40 others,41–43 and recently verified with molecular studies, suggests that the pattern of genetic alterations in a tumor is distinct and has led researchers to attempt to identify similarities between tumors and lymph node metastases.

Califano et al.44 used microsatellite analysis to characterize tumors from cervical metastases. Genetic alterations present in the tumor were matched to those in the putative primary site in 55% of cases, despite the primary site being visually and histologically normal. The microsatellite profile was also able to distinguish between different subsites, including base of tongue, tonsil, false vocal cord, floor of mouth, and pyriform sinus.

Viral DNA has also been evaluated as a potential method to identify the unknown primary. Epstein-Barr virus (EBV) is associated with the development of nasopharyngeal carcinomas. Presence of EBV DNA in a cervical lymph node, as detected by polymerase chain reaction from FNA, correlates closely with a nasopharyngeal primary.45 Detection of human papillomavirus (HPV) increasingly implicated as a causative factor in the development of a subset of SCCs of the oropharynx, can also aid in the identification of a possible primary site. In a study of 253 patients with HNSCC, Gillison et al.46 reported the presence of HPV in 55% of oropharyngeal tumors but only 14% of nonopharyngeal sites. HPV can be particularly associated with tonsillar/oropharyngeal carcinomas, of which 50% to 75% contain HPV DNA compared with 6% to 10% of other head and neck sites.47 More recent investigations have demonstrated concordance between the HPV status of cervical metastases and primary tumor sites, particularly oropharyngeal tumors.48,49 Although not definitive, the presence of HPV in lymph node metastasis strongly indicates a primary in the oropharynx, and specifically the tonsil.

Management

Despite an extensive search, most unknown primary tumors associated with cervical lymph node metastases are never identified. The prognosis for such patients is not dependent on T stage, but is closely related to nodal staging, with overall survival (OS) at 5 years decreasing with N stage from 70% to 80% for N1 disease to 20% to 35% for N3 disease (staging table available at: http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf).13,51,54 The optimal treatment for this challenging patient group is controversial, but there is increasing consensus that multimodality therapy tailored to the extent of neck disease offers the best outcome.

Surgery

No randomized prospective clinical trials exist on surgery alone for treatment of neck metastases of unknown primary, but some data can be derived from larger retrospective studies. Although limited by selection bias, multiple studies have reported the efficacy of neck dissection alone for early-stage neck disease (N1 and selected N2A).

In a study of 277 patients with an unknown primary, Grau et al.17 reported on a group of 23 patients who were treated with neck dissection alone. Although the risk for emergence of the primary was higher in patients treated with surgery alone compared with those treated with surgery and adjuvant radiation therapy (54% vs. 15%; P < .0001), OS and disease-specific survival were not statistically different; this is likely because of selection for higher-stage disease in the latter group. In a series of 24 patients who refused radiation after neck dissection, Coster et al.15 found no recurrences in 19 patients with N1 or small N2 disease without extracapsular spread (ECS). More advanced nodal disease or ECS was associated with a 63% risk for regional recurrence within 5 years. An informal review of the published data from 4 studies by Nieder and Ang16 calculated a 25% rate of appearance of the primary tumor, 34% recurrence rate, and 66% OS at 5 years for patients treated with surgery alone. Several studies have examined the extent of surgery required for N1 disease. Excisional biopsy alone is associated with increased regional recurrence and decreased survival.1 However, no difference in cause-specific survival or recurrence is noted when the neck is definitively treated with radiation after neck biopsy compared with formal neck dissection.13,19,20

Radiation Therapy

Radiation therapy has been used alone and in combination with surgery to treat patients with cervical metastasis of unknown primary. The most common treatment studied for the unknown primary involved unilateral comprehensive neck dissection followed by irradiation of the neck bilaterally and mucosal irradiation of the upper aerodigestive tract (comprehensive irradiation), targeting the most likely primary
sites (nasopharynx, base of tongue, tonsil, hypopharynx). Various modifications of doses and regimens have been studied and are discussed in more detail later.

**Radiation Alone**: A multicenter retrospective trial of 213 patients found a regional failure rate of 50%, distant metastasis of 14%, and 5-year OS of 37% for patients treated with radiation alone. A similar retrospective study by Harper et al. found a 20% recurrence rate and 5-year OS of 48% for a group of 69 patients, of whom 57% received radiation alone. However, the study population in both cases is likely biased towards patients with more extensive disease (unreadable by neck dissection). Studies of patients treated with ipsilateral neck irradiation alone generally showed poorer outcomes, with 41% to 54% regional recurrence rates, 38% rate of distant metastasis, and 33% to 36% 5-year survival rates. In a group of 87 patients treated for neck disease from unknown primary, Beldi et al. reported significantly improved OS (57.6% vs. 24%; P < .01) in patients treated with comprehensive irradiation compared with those treated with ipsilateral neck irradiation alone. Contrary results have been reported by others, including Weir et al., who found no significant difference in outcome for patients treated with neck irradiation alone versus comprehensive neck irradiation.

**Surgical Excision and Radiation**: The most common treatment algorithm for the unknown primary consists of ipsilateral neck dissection followed by comprehensive radiation of the neck and upper aerodigestive tract mucosa. This combined approach has generally yielded the best outcome for patients in several retrospective studies. Nieder and Ang compiled the results of 6 earlier studies involving 387 patients, and found that the combined approach had an 18% nodal recurrence rate, 20% rate of development of distant metastasis, and 35% to 63% rate of 5-year OS. More recent reports from multiple institutions have shown comparable rates of nodal recurrence (9%–21%), distant metastasis (11%–15%), OS (47%–79%), and disease-specific survival (67%–74%) for SCC of unknown primary treated with a similar approach.

Subgroup analysis from some studies has elucidated factors that may influence treatment and outcomes. ECS is well-known to be an independent risk factor for decreased survival, recurrence, and distant metastasis in HNSCC. Colletier et al. reported the M. D. Anderson experience of 136 patients with unknown primary, of whom 22 had ECS. The recurrence rate in these patients was 16% versus 0% for patients without ECS (P < .004). In a study of 87 patients with HNSCC, Beldi et al. reported a 31.2% OS for patients with ECS versus 57.5% for patients without. Other institutional series from the Mayo Clinic and Memorial Sloan-Kettering suggest the negative prognostic significance of ECS in treatment of the unknown primary.

Emergence of the primary tumor is often discussed in the literature, but the true significance of this finding is unclear. Studies before the use of radiation therapy found high rates of emergence of the primary tumor with surgery alone, which portended a poor outcome. More recent studies, including groups treated with surgery alone, have found a 32% to 66% incidence of emergent primary tumor, although none were able to show a significant difference in survival at 5 years. Radiation decreases the rate of emergence of the primary tumor to 7% to 12% with ipsilateral treatment, and 2% to 10% for comprehensive radiation. Unfortunately, patients who experience recurrence after radiation have a low salvage (6%) compared to those recurring after surgery alone (59%).

Comprehensive irradiation of bilateral necks and the entire mucosa results in a high degree of toxicity, including xerostomia, mucositis, skin damage, dysphagia, and stricture. Strategies to reduce the collateral damage from the extensive radiation delivered to patients with unknown primaries have been studied. Bhide et al. showed that intensity-modulated radiation therapy (IMRT) could be delivered in a manner allowing sparing of the parotid while still providing adequate mucosal coverage. A recent study from Memorial Sloan-Kettering used IMRT to treat 21 patients with unknown primaries. The preliminary analysis at 2 years shows disease-free survival of 90% and OS of 85%, with significant reduction in grade 1 to 2 xerostomia (57% vs. 43%) and in patients requiring gastrostomy (72% vs. 43%) with IMRT versus conventional radiation. Use of IMRT in this patient group seems promising for the reduction of morbidity, but caution must be applied until more studies validate the efficacy of this approach.

**Chemotherapy**

Chemotherapy, as single modality treatment for HNSCC, is not curative. By extension, patients with unknown primary tumors have not historically been
treated with chemotherapy alone, unless the treatment was believed to be palliative. The concept of intensifying therapy with the addition of chemotherapy to standard surgery and radiation regimens has been attempted since the late 1980s. de Braud et al. added chemotherapy to neck dissection and radiation in either an adjuvant or a neoadjuvant role and found that the addition of chemotherapy improved median survival from 24 to 37 months in patients with advanced disease (56% N3, 44% N2). In study by Kirschner et al., 11 of 48 patients underwent concurrent chemotherapy and radiation after neck dissection and showed no benefit for adding chemotherapy to standard treatment. Argiris et al. retrospectively reviewed patients treated with 5 different chemotherapy regimens (including 2 neoadjuvant) and reported a 5-year progression-free survival of 87% and OS of 75%, but could not identify an optimal treatment regimen.

A more uniform regimen of neck dissection followed by concurrent treatment with conventional fractionation and 3 cycles of cisplatin showed a 5% rate of neck recurrence, 11% rate of distant metastasis, and 90% OS rate at 2 years. Both patients with recurrence had N3 disease with ECS and died of their disease in less than 1 year. No further recurrences or disease-related deaths occurred after 20 months, precluding actuarial OS or relapse-free survival calculation. These studies suggest that adding chemotherapy to treatment benefits patients with advanced nodal disease or ECS. Current NCCN guidelines advocate consideration of concurrent chemoradiation after neck dissection for patients with N2/N3 disease or ECS. Although not explicitly discussed in this article, combined therapy confers increased toxicity to patients undergoing these regimens, which must be considered in therapeutic decisions. Currently, no data are available on use of targeted therapy for patients with unknown primaries, but this may be a promising area for future investigation.

Summary
SCC of unknown head and neck primary origin is encountered as a recurring clinical problem in head and neck cancer clinics, affecting 3% to 25% of patients. Prospective study of this group is difficult because frequency is low and diagnostic/imaging techniques are increasingly sophisticated. After a comprehensive head and neck evaluation, many centers proceed to neck dissection and then postoperative radiotherapy, with or without concomitant chemotherapy, based on the surgical pathology. The finding of ECS argues for concomitant chemoradiotherapy. Patients with extensive cervical nodal disease at presentation or level IV involvement are candidates for induction or adjuvant chemotherapy. However, these therapeutic strategies are based on extrapolations from studies of patients with known primary sites, and this must be considered in formulating treatment plans. Short of prospective multicenter trials designed to compare the efficacy of surgical resection and postoperative treatment based on surgical pathology versus definitive chemoradiotherapy, further review of outcomes from the NCCN collective patient data bank is warranted.

References
Unknown Primary Carcinoma of the Head and Neck


