Metastatic Squamous Neck Cancer With Occult Primary Treatment (PDQ®): Treatment - Health Professional Information [NCI]

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General Information About Metastatic Squamous Neck Cancer With Occult Primary

Diagnosis
The diagnosis of an occult primary tumor is made only if no primary tumor is detected after careful search and does not appear during therapy. Patients with cervical lymph node metastases histologically related to a previously treated primary tumor and patients with lymphomas and adenocarcinoma are excluded. If the biopsy is an undifferentiated carcinoma (in particular, a lymphoepithelioma), the most probable primary site is in Waldeyer ring; for example, the nasopharynx, base of tongue, or tonsil. Most epidermoid carcinomas metastatic to lymph nodes of the upper half of the neck will originate from a head and neck primary site. Squamous carcinomas metastatic to the lower neck may represent a primary site in the head and neck, esophagus, lung, or genitourinary tract. A search for primaries in these areas must be undertaken before assuming that the primary is occult. Primary tumors arising in the nasopharynx may be secondary to Epstein-Barr Virus (EBV) infection, and EBV genomic material may be detectable in cervical nodal tissue after DNA amplification using the polymerase chain reaction. Such a finding should lead to an in-depth search for a primary in the nasopharynx.[1]

The extent of investigation and type of treatment must be individualized depending on the patient's age and wishes, and on the site, histology, and extent of metastatic lymph node involvement of the tumor. When a patient qualifies as having squamous carcinoma of the neck with occult primary, he or she should be checked for other obvious metastatic disease, such as lung, liver, or bone, since this would affect the locoregional approach to therapy.[2]

Survival
Three-year, disease-free survival rates following surgery and/or radiation therapy for unknown squamous primaries range from 40% to 50% in patients with N1 disease to
38% and 26% for patients with N2 and N3 disease, respectively. Patients who later develop primary lesions have poor survival rates compared to those patients whose primaries remain occult, for example 30% versus 60%.

**Follow-up**

Patients with neck metastases from an undetectable primary should be given the benefit of definitive treatment. Despite the ominous situation of an undiscovered primary, a significant number of patients do achieve cure by both surgical and radiotherapeutic approaches. In some patients, long-term repeat examinations will eventually disclose the primary tumor, and at a treatable stage.

**References:**


**Cellular Classification of Metastatic Squamous Neck Cancer With Occult Primary**

This section helps lead the clinician and pathologist through a differential diagnosis for an unknown primary presenting with cervical node metastases. The therapeutic section, however, relates only to squamous carcinoma and assumes that the primary physician has worked with the pathologist as described below to eliminate other possibilities that would require alternative therapies.

The pathologist plays a central role in evaluating an occult primary tumor. A thorough evaluation of an adequate specimen through histologic or immunohistochemical techniques, and, when appropriate, electron microscopy (EM) provides guidance for the clinical evaluation that ensues. A critical interaction should exist between the pathologist, oncologist, and primary physician.

The complexity of the pathologic evaluation tends to be inversely related to the degree of differentiation of the tumor. For instance, for well or moderately differentiated tumors, the pathologic diagnosis of an epithelial cancer is often readily apparent, in contrast to lymphoma, sarcoma, melanoma, or a germ cell tumor. Commonly used stains such as mucicarmine or diastase-sensitive Periodic Acid Schiff (PAS) can be important in confirming the diagnosis of certain tumors of gastrointestinal or renal origin.

If the clinician is faced with a male patient younger than 50 years with a poorly differentiated tumor, serum levels of bHCG and AFP should be obtained and specimens
should be evaluated with immunohistochemical stains for bHCG and AFP. Certain of these tumors respond to platinum-based combination chemotherapy in a manner similar to extragonadal germ cell malignancies, and this group of patients should be so treated unless other alternative diagnoses are made.[1]

Special studies can help in differentiating more poorly differentiated tumors. Often, a generic distinction is important between a poorly differentiated tumor of epithelial, hematopoietic, neuroendocrine, or neuroectodermal origin (i.e., melanoma).

- **Immunohistochemical:**
  Immunohistochemical studies can be important in making these broad distinctions, in particular, studies that evaluate staining for keratins, leukocyte common antigen (LCA), and S-100, a neuroectodermal antigen expressed in melanomas.[2]

- **Polymerase chain reaction:**
  In patients with suspected nasopharyngeal carcinoma, DNA amplification of Epstein-Barr virus (EBV) genomes can be used for diagnosis with tissue provided by fine-needle aspiration biopsy. The presence of EBV in metastases from an occult primary tumor suggests the development of overt nasopharyngeal carcinoma.[3]

Acinar spaces and microacini are seen with adenocarcinomas. Electron dense secretory granules are seen in tumors of neuroectodermal origin. Premelanosomes can be found in most amelanotic melanomas. But these features are generally associated with differentiation along a particular line. Often poorly differentiated tumors do not display such characteristics, and EM evaluation would be of little value. The use of EM may aid in distinguishing a primary diagnosis not obtained by light microscopy approximately 10% of the time.[4,5,6]

**References:**

Stage Information for Metastatic Squamous Neck Cancer With Occult Primary

Definitions of TNM

The American Joint Committee on Cancer has designated staging by TNM classification to define metastatic squamous neck cancer with occult primary.[1]

### Table 1. Regional Lymph Nodes (N)\(^a\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis.</td>
</tr>
<tr>
<td>N1(^b)</td>
<td>Metastasis in a single ipsilateral lymph node, (\leq 3) cm in greatest dimension.</td>
</tr>
<tr>
<td>N2(^b)</td>
<td>Metastasis in a single ipsilateral lymph node, (&gt;3) but not (&gt;6) cm in greatest dimension; or in multiple ipsilateral lymph nodes, none (&gt;6) cm in greatest dimension; or in bilateral or contralateral lymph nodes, none (&gt;6) cm in greatest dimension.</td>
</tr>
<tr>
<td>N2a(^b)</td>
<td>Metastasis in single ipsilateral lymph node (&gt;3) but not (&gt;6) cm in greatest dimension.</td>
</tr>
<tr>
<td>N2b(^b)</td>
<td>Metastases in multiple ipsilateral lymph nodes, none (&gt;6) cm in greatest dimension.</td>
</tr>
<tr>
<td>N2c(^b)</td>
<td>Metastases in bilateral or contralateral lymph nodes, none (&gt;6) cm in greatest dimension.</td>
</tr>
<tr>
<td>N3(^b)</td>
<td>Metastasis in a lymph node (&gt;6) cm in greatest dimension.</td>
</tr>
</tbody>
</table>


\(^b\) A designation of “U” or “L” may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical/radiological ECS should be recorded as E-- or E+, and histopathologic ECS should be designated En, Em, or Eg.

### Table 2. Distant Metastasis (M)\(^a\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis.</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis.</td>
</tr>
</tbody>
</table>


Untreated
Untreated metastatic squamous neck cancer with occult primary means that a patient is newly diagnosed and has had no prior treatment except supportive care.

References:


Untreated Metastatic Squamous Neck Cancer With Occult Primary

Patients with neck nodes from a presumed unknown primary tumor should be evaluated as follows:

1. Surgical biopsy or excision to establish a histologic diagnosis, but only after an aerodigestive tract primary has been carefully ruled out as in the following procedures:
   - Direct nasopharyngoscopy, laryngoscopy, bronchoscopy, and esophagoscopy, with biopsy of any suspicious area.
     - If no suspicious lesions are found, random biopsies of the nasopharynx, base of tongue, tonsil, and pyriform sinus on the side of the lesion should be performed.
     - If the tonsil is not present, biopsy of the tonsillar fossa should be performed.
     - Sinus x-rays are probably indicated; if an abnormality is found, it should be biopsied as well.

2. Selected other studies if indicated. In the detection of head and neck tumors and in the distinction of lymph nodes from blood vessels, magnetic resonance imaging offers an advantage over computed tomography scans and should be considered in the initial evaluation of the patient with metastatic squamous cell cancer in cervical lymph nodes.[1] Positron emission tomography may be helpful in determining the primary site.[2] Patients should be managed with either a full course of radiation therapy or adequate neck dissection, when possible. In cases of massive homolateral adenopathy that is fixed or bilateral nodes, radiation therapy should be administered first. The radiation fields should also include the nasopharynx, base of tongue, and pyriform sinuses. If radiation therapy is the primary mode of treatment and the neck mass persists upon completion of radiation therapy, cervical lymph node dissection should be performed. Patients with metastatic carcinoma in the supraclavicular region are best managed with a full course of radiation therapy followed by surgical dissection if palpable tumor persists. Careful continued follow-up of these patients is of utmost importance. Depending on the likely site of origin and histology, chemotherapy appropriate to the most treatable site may be indicated.
Accumulating evidence has demonstrated a high incidence (>30%-40%) of hypothyroidism in patients who received external-beam radiation therapy to the entire thyroid gland or the pituitary gland. Thyroid function testing of patients should be considered prior to therapy and as part of post-treatment follow-up.[3,4]

**Standard treatment options:**

1. Radical neck dissection.
2. Radiation therapy.[5,6] Intensity-modulated radiation therapy may have less short- and long-term toxicity than conventional radiation therapy in terms of xerostomia, acute dysphagia, and skin fibrosis.[7,8]
3. Combined surgery and radiation therapy.[9]

**Treatment options under clinical evaluation:**

1. Chemotherapy followed by radiation therapy.[10]
2. Simultaneous chemotherapy and hyperfractionated radiation therapy.[11]
3. Clinical trials for advanced tumors should be considered.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with untreated metastatic squamous neck cancer with occult primary. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References:**


Recurrent Metastatic Squamous Neck Cancer With Occult Primary

The prognosis for most treated cancer patients with progressing, recurring, or relapsing disease is poor, regardless of cell type or stage. Deciding on further treatment depends on many factors, including the specific cancer, prior treatment, site of recurrence, as well as individual patient considerations. Treatments that are under clinical evaluation are appropriate and should be considered when possible.

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials that are now accepting patients with recurrent metastatic squamous neck cancer with occult primary. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

Changes to This Summary (09 / 25 / 2015)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

An editorial change was made to this summary.

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About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of metastatic squamous neck cancer with occult primary. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

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The lead reviewers for Metastatic Squamous Neck Cancer With Occult Primary Treatment are:

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