Abstract:  
Background. Head and neck squamous cell carcinoma (HNSCC) commonly spreads to regional deep cervical nodes. In most cases, these metastases present as firm, solid masses in the designated lymph node chains. A distinct subset of metastatic nodes present as cystic masses, with most of the volume made up of a liquid center surrounded by a thin solid rim. It has been observed that certain squamous cell carcinoma (SCC) subsites are more likely to produce metastases that are cystic. These sites predominantly include primary tumors of tonsil tissue from Waldeyer’s ring. In the past, these cystic cancers often have been erroneously diagnosed as branchiogenic carcinomas, that is, a branchial cleft cyst that has undergone malignant degeneration. Today, most authors have concluded that so-called branchiogenic carcinomas are actually cystic metastases in the neck probably arising from an oropharyngeal primary SCC. The purpose of this work is to consider the phenomenon of cystic lymph node metastasis in head and neck cancer in depth.  

Methods. A review of the relevant English-language literature linking cystic metastasis and head and neck cancer was performed.  

Results. These studies indicate that lateral cystic masses in adults often represent an occult primary cancer originating in the epithelium within Waldeyer’s ring.  

Conclusions. Adult patients who are initially seen with a lateral cystic neck mass must be presumed to have a cancer until proven otherwise. The mass should be biopsied by fine needle aspiration (FNA). However, negative FNA findings may be misleading; therefore, an excisional biopsy and examination under anesthesia with directed biopsies of Waldeyer’s ring and bilateral tonsillectomy should be considered a part of the diagnostic workup.

Keywords: tonsil carcinoma; branchiogenic carcinoma; cystic metastasis; neck carcinoma; oropharyngeal carcinoma; solid metastasis; head and neck cancer; Waldeyer’s ring

Branchial cleft cysts are the most common congenital cause of a neck mass. The proportion of metastatic squamous cell carcinoma (SCC) in cysts initially presumed to be of branchial cleft origin has been reported to range from 11% to 21%.1–3 In 1881, Von Volkman4 first theorized that malignant lesions of the lateral aspect of the neck arise from remnants of the branchial clefts. This premise received wide acceptance during the first half of the 20th century. At that time, these lesions were labeled “branchiogenic carcinomas,” and no attempt was made to search for the primary tumor site. In 1935, Crile5 reported 28 cases of neck masses called branchiogenic carcinomas. As a result of this article, many patients with cystic malignant nodes in the neck were thought to have a branchiogenic carcinoma, and again no
primary tumor was sought. In 1944, Hayes Martin\textsuperscript{6,7} challenged this position. Martin urged that a biopsy be the initial, and not the final, part of the clinical investigation and that a thorough search for a primary tumor be made. He contended that these tumors were nearly always secondary to a primary tumor in the head and neck, which could and should be identified and treated. He proposed that the diagnosis of branchiogenic carcinoma, a distinct entity from a cystic nodal metastasis, be made only if certain criteria were satisfied. Gourin and Johnson\textsuperscript{8} found no examples that met these criteria in their series of 121 patients with an initial diagnosis of lateral cervical cyst, and Neel and Pemberton\textsuperscript{9} found no such cases in 319 patients with lateral neck cysts. Thus, it is now accepted that branchial cleft carcinomas are either nonexistent or exceedingly rare. This work is intended to better explain the entity of the cystic lymph node metastasis as a component of a subset of head and neck squamous cell carcinoma (HNSCC).

**MATERIALS AND METHODS**

We performed a thorough review of the relevant English-language literature linking cystic metastasis and HNSCC. The literature search was performed by means of MEDLINE using the MeSH words: cystic metastasis and head and neck cancer, Waldeyer’s ring, tonsil cancer, tongue base cancer, oropharyngeal cancer, malignant branchial cleft cyst, branchioma, and branchiogenic carcinoma. Other databases searched were library catalogs, online computer library center (OCLC) first search, and Institute for Scientific Information (ISI) web of science databases.

**RESULTS**

This review indicates that lateral cystic masses in the adult most often represent an SCC originating in the epithelium of Waldeyer’s ring—tonsil, tongue base, and nasopharynx (see Table 1; refs. 3, 10–21).

**DISCUSSION**

A subset of HNSCC arises from the epithelial layer covering the lymphoid tissue of Waldeyer’s ring. Waldeyer’s ring is a collection of lymphoid tissue that includes the adenoid bed in the nasopharynx, the pharyngeal or faucial tonsils, and the lingual tonsils situated on the tongue base.

**Table 1.** Clinicopathologic characteristics of cystic lymph node metastasis from head and neck squamous cell cancer and recommended clinical investigation for lateral cervical cyst.

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<th>Characteristics</th>
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<td>May not be associated with the usual risk factors of smoking and alcohol abuse</td>
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<td>Patient population frequently younger than those with solid metastatic SCC</td>
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<td>Primary tumors are often occult</td>
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<td>Prognosis better than with noncystic lymph node metastasis</td>
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<td>Site of origin</td>
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<td>Waldeyer’s ring: 33%–62%</td>
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<td>Faucial tonsil: 43%–64%</td>
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<td>Tongue base: 37%–60%</td>
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<td>Nasopharynx: 1.3%–8.0%</td>
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Recommended Clinical Investigation for Lateral Cervical Cyst in Adults

- Imaging
  - Ultrasound, CT, MRI, Integrated PET/CT
  - FNA\textsuperscript{3,10,13,15,19–21}
  - Whether FNA is positive or negative for SCC, if clinical suspicion exists, then the patient should undergo examination under anesthesia, panendoscopy-directed biopsies of Waldeyers ring, and possible tonsillectomy
  - If FNA of CLNM is positive for SCC: Neck dissection
  - If FNA of CLNM is negative for SCC: Excisional neck biopsy with frozen section and preparation to continue to neck dissection based on malignant findings

The tonsils and faucial arches are covered by a nonkeratinizing stratified squamous epithelium with crypts that embryologically derive from the second pharyngeal pouch. Depending on the location, the epithelium that lines the mucosa or the crypts varies from squamous, respiratory, or metaplastic squamous (transitional) in character. The interface with the underlying lymphoid tissue is sometimes poorly defined and irregular.\textsuperscript{22}

A marked predilection exists for cystic morphology in cervical metastases arising from SCC of Waldeyer’s ring.\textsuperscript{1,8,15,16} The incidence of cystic lymph node metastasis arising from SCC of Waldeyer’s ring has been reported to be as high as 37% to 62% of those with nodal metastasis.\textsuperscript{16,17} In 10% of malignant cystic metastasis ultimately found to originate in Waldeyer’s ring, no primary tumor is initially apparent.\textsuperscript{5}

Among HNSCC arising in Waldeyer’s ring, faucial and lingual tonsil tumors are the most common primary sites to give rise to cystic metastasis. In a series of 136 cases with cystic metastasis, Thompson and Heffner\textsuperscript{15} found the primary tumor site to be the tonsil in 64%. They stressed that this group of tumors represents a subtype of
tonsil cancer. The unique features of this subtype of tonsil cancer are its propensity for moderately large cystic metastasis in lymph nodes of the jugulodigastric region coupled with relatively small or occult primary tumors.

They also maintained that cystic cervical metastasis together with a primary tumor diagnosed in the base of the tongue is in actuality a cancer originating in the lingual tonsil, in other words histologically transitional type, tonsillar crypt epithelium, rather than the usual SCC, which occurs at the base of the tongue. In addition, a small percentage (4.7%) of the primary cancers in their study originated from the nasopharyngeal lymphoid tissue (adenoid). In a series of 101 patients with SCC arising in Waldeyer's ring, Regauer et al found 62% to harbor cystic metastasis. Of these, 35 were primary palatine tonsil SCC, 23 base of tongue primary tumors, and two cases were from nasopharyngeal tumors. They reported cystic change to be present at a microscopic level in as many as 50% of metastases from a primary SCC in Waldeyer's ring, with 35% of patients having cystic metastases greater than 5 mm in diameter.

The phenomenon of cystic metastasis is not unique to oropharyngeal primary malignancies and has been reported to occur in association with primary cancer of the thyroid (papillary type), esophagus, and uterine cervix.3,15,17

**Mechanism of Cystic Development.** The mechanism of cyst formation in cystic metastases has not been fully explained.3,16,23,24 Gross pathologic features of cystic lymph node metastasis include a well-circumscribed node usually surrounded by a thick fibrous capsule (Figure 1). The cut surface is often filled with granular, thick, tenacious, and purulent or thin yellow, brown, or hemorrhagic fluid. If a patient has a known head and neck primary tumor, the presence of central lymph node necrosis is a strong indicator of malignancy.25 However, cystic metastasis should be distinguished from necrosis and liquefaction in an otherwise solid node.

Cystic degeneration with a central collection of cellular debris has been observed in most cystic metastases.16 This phenomenon is thought to occur because of pseudocystic change resulting from spontaneous degradation of keratin within the carcinomatous lymph node deposit.17 In other cases, a true cyst cavity is formed. This cyst is lined by neoplastic epithelium in the central portion of the lymph node, with lymphoid elements occupying the periphery of the node.2

In an attempt to explain the genesis of fluid-filled cystic metastases, Regauer et al searched for specific morphologic and immunohistochemical criteria associated with fluid-filled cystic metastases in 90 cases. They analyzed the cytokeratin (CK) profile of primary and metastatic carcinoma with special focus on the expression of CK7, a putative marker for ductal differentiation. CK7 was expressed in submucosal minor salivary gland acini and ducts but not in the squamous surface epithelium of the Waldeyer's ring. They found that cytokeratin (CK7)-positive carcinomas produced CK7-positive cystic nodal metastases, whereas no solid CK7-positive nodal metastases were identified. They concluded that a subset of carcinomas occurring in Waldeyer's ring area seem to arise from large excretory ducts of submucosal minor salivary glands with only limited surface or crypt involvement, express CK7, and produce CK7-positive cystic nodal metastases and thus should be termed basaloid SCC.

**Clinical Behavior.** Waldeyer's ring primary tumors with cystic metastases often display unique clinical features. Cystic SCC metastasis are generally not associated with the usual risk factors of smoking and alcohol abuse,10 and they often present in a younger patient population than those with solid metastatic SCC.11

Primary SCC tumors that produce these malignant cysts often do so very early, at times discovered before presentation of a primary tumor itself. In cases in which the primary tumor is located in the tonsil, it is often not obvious clini-
If not suspected and the tonsil is not excised and analyzed for malignancy, the tumor may take months to manifest. Primary tumors located in the tonsil that present with a cystic neck metastasis are said to be associated with a slower growth rate than would be expected from tumors that produce solid SCC metastases.15

The indolent growth of the primary tumor can be partially explained by the nature of the tonsillar crypt lymphoepithelium from which they arise. The intimate functional relationship of lymphocytes with crypt lymphoepithelium might explain the apparently slow-growing, indolent nature of many of the crypt epithelial carcinomas.15 A tumor capable of evading immunologic reaction might preferentially occur because the epithelium from which these primary tumors arise is normally a site of immunocytologic reaction involving immunocompetent cells and epithelium.27,28

Investigations. Detecting malignancy within a cyst can be difficult for a variety of reasons. Imaging such as CT, MRI, and ultrasonography and more recently positron emission tomography (PET)/CT25 can detail the size and morphology of cervical lymph nodes (Figure 2). Although these imaging techniques can show suggestive features of malignancy (Figure 3), they are often inconclusive, and the absence of a clinically detectable primary tumor makes the diagnosis more difficult.

Fine-needle aspiration (FNA) cytology is a useful technique when applied to solid cervical nodes, because the false-positive and false-negative rates are low (1%–3%).29 Sheahan et al30 found FNA to be a helpful tool in the assessment of cystic metastatic lesions, citing a sensitivity of 73% in the diagnosis of malignancy.

Most other authors, however, have found that cytologic assessment of the aspirate from cystic metastasis is less precise, and the false-negative rate of FNA in the diagnosis of SCC in cystic metastases ranges from 50% to 67%.3,8 Aspirates of solid lymph nodes usually yield semisolid material that is highly cellular. In a histologic analysis of resected SC cystic metastases, Regauer et al reported that the cyst contents consisted of cellular debris and necrotic keratinocytes in most cases; some cysts contained only homogenous eosinophilic fluid, and some cyst cavities were completely empty.

Thus, the aspirate of a cystic lesion can be difficult to interpret because of its hypocellularity from dilutional effect of the cyst fluid. Large quantities of inflammatory cells and cellular debris may be present as well, because there is commonly an associated inflammatory reaction suggesting an inflamed or infected benign cyst.8,31

Sack et al19 demonstrated an expanding role of image-guided FNA in the evaluation of head and
neck lesions. Specifically, this study showed that ultrasound-guided FNA could aid in the specific sampling of solid areas within predominantly cystic masses. In this study, this was demonstrated on thyroid nodules and has not been shown specifically in metastatic cystic lymph nodes.

In an effort to improve on the diagnosis if these lesions, Nordemar et al. performed image cytometry DNA analysis on cytologic specimens of 51 patients with solitary cysts in the lateral region of the neck. The authors found that in 53% of the cases with cystic metastasis, image cytometry DNA analysis revealed aneuploidy, indicating malignancy, whereas DNA analysis showed diploidy in all benign cases. They concluded that image cytometry DNA analysis increases the diagnostic sensitivity in cases of suspected malignant cystic metastasis and is a valuable supplement to conventional FNA for these lesions.

A false-negative finding on FNA biopsy leads to delay in searching for the primary tumor site, as well as delay in the onset of adequate oncologic treatment.

Furthermore, if the surgeon goes on to perform a simple cyst excision, the neck tissues are violated, resulting in scar and making subsequent surgery more difficult. If cancer is not suspected, the opportunity to perform an adequate comprehensive or selective neck dissection and take biopsy specimens from the likely primary tumor sites (tonsil, base of the tongue) while the patient is under general anesthesia is forfeited. Common surgical dogma maintains that violating a neck by performing an open biopsy of the cyst could not only delay the definitive treatment but also jeopardize cure by seeding malignant cells into the surrounding soft tissue.

It is, therefore, recommended that all adult patients presenting with lateral cervical cystic masses be investigated by radiologic imaging, CT/MRI and FNA cytology, followed by an excisional biopsy of the cystic mass with intraoperative frozen section evaluation. If the mass is found to harbor SCC, the surgeon should be prepared to do a panendoscopy of the head and neck, a bilateral tonsillectomy, and a comprehensive neck dissection. Tissue from biopsies and tonsillectomy should be very thoroughly examined, because the primary tumor may be quite small and could be missed on serial representative sections. Because the tumor is often well differentiated and obscured by lymphocytes, a tiny primary tumor can easily be overlooked.

**Human Papillomavirus.** We find it interesting to note that a similar subset of HNSCC has been linked to both tumorigenic human papillomavirus (HPV) and cystic lymph node metastasis morphology. One question that arises is whether there is an association between the distinct morphology of the metastatic lymph nodes of cancer that originate in Waldeyer’s ring and the presence of HPV infection.

Several recent studies have consistently pointed to the oropharynx as the predominant site for HPV-associated tumors. Among these, HPV DNA is most closely associated with SCC of the palatine and lingual tonsil, with a frequency between 40% and 70%.

The prevalence rate of HPV may even be higher in lymph node metastases from tonsillar primary tumors, because HPV-related tumors may have an enhanced propensity for metastatic spread. With the recognition that HPV is an important causative factor in the development of a subset of HNSCCs, viral probes have been used as a tool to suggest the primary tumor origin of FNA samples from regional metastasis. In this study, HPV-16 was detected in 71% of metastases from the oropharynx but in none of the metastases from other sites.

**CONCLUSION**

Malignant cystic lymph node(s) arising in the neck of an adult should raise a suspicion of a malignant process in the lymphoepithelial tissue of Waldeyer’s ring. Investigation should include imaging studies and an FNA; however, if these are not conclusive, an excisional biopsy should be performed. A panendoscopy with guided biopsies, tonsillectomy, and possible neck dissection should be considered, depending on findings at biopsy. In the future, molecular assays that clearly differentiate between malignant and benign may be effective for this purpose. Cystic metastasis in HNSCC may represent a disease variant distinct from the cause of solid metastasis.

**REFERENCES**