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EDITORIAL

Sentinel Lymph Node - Work Hypothesis in Sinonasal Carcinoma Treatment

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ABSTRACT

Although rare, sinonasal malignancies (SNM) can be lesions of immense importance. Approximately 60-70% of sinonasal malignancies (SNM) occur in the maxillary sinus and 20-30% occurs in the nasal cavity itself. The lymphatic drainage of the sinuses and nasal cavity include levels I-III as well as the parapharyngian nodes. Elective regional lymph node dissections became controversial because of overtreatment of the many patients without lymph node metastases. Lymphatic metastasis is the most important mechanism of spread in sinonasal squamous cell carcinoma considering the vast network of vessels in this area. The indications and type of neck dissection to be performed in the positive node neck and management of the N0 neck remain controversial. The sentinel lymph node concept is based on the Halsted theory that stressed the importance of locoregional cancer treatment because of the far site spread. Each patient with head and neck malignancies, including sinonasal carcinoma have about 2-3 sentinel lymph nodes of which up to 40% of them contain metastases.

Keywords: sinonasal malignancies, regional lymph node, N0 neck, sentinel lymph node

INTRODUCTION

Although rare, sinonasal malignancies (SNM) can be lesions of immense importance. They produce few if any signs while the tumor is in its early stages. This problem is exacerbated by the fact that the initial manifestations (eg, unilateral epistaxis, nasal obstruction) mimic signs and symptoms of many common but less serious conditions. Approximately 60-70% of sinonasal malignancies (SNM) occur in the maxillary sinus and 20-30% occurs in the nasal cavity itself. Squamous cell carcinoma (SCCA) constitutes over 80% of all malignancies that arise in the nasal cavity and paranasal sinuses. Approximately 70% occurs in the maxillary sinus, 12% in the nasal cavity, and the remainder in the nasal vestibule and remaining sinuses (1).

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Several variants of carcinoma are often considered variants of squamous cell carcinoma of the nasal cavity and paranasal sinuses. These include verrucous carcinoma, basaloid squamous cell carcinoma, spindle cell carcinoma, and transitional or cylindrical cell carcinoma (2).

The idea that squamous cell carcinoma (SCCA) and adenocarcinoma in this area are associated with exposure to nickel dust, mustard gas, thorotrast, isopropyl oil, chromium, or dichlorodiethyl sulfide is well established. Wood dust exposure, in particular, is found to increase the risk of SCCA 21 times and the risk of adenocarcinoma 874 times (3).

Approximately 300 lymph nodes are located in the head and neck, and they comprise 30% of the total 800 lymph nodes in the human body. The lymphatic drainage of the sinuses and nasal cavity include levels I-III. In addition, the retropharyngeal lymph nodes can be site of drainage for the posterior ethmoidal cells, posterior nasal cavity, and sphenoid sinuses (4,5). Treatment of the N0 neck in sinonasal malignancy (SNM) is typically not recommended.

Lymphatic tumor spread and its implications for treatment and survival have been studied for centuries. Different theories regarding the dissemination of solid tumors have been introduced, based on experimental data and observations during follow-up of cancer patients. These resulted in discussion about the place of regional lymph node dissection in the treatment of diseases that were thought either to be systemic from the beginning or to spread initially to lymph nodes. Elective regional lymph node dissections became controversial because of overtreatment of the many patients without lymph node metastases. These patients suffer from associated morbidity without survival benefit. With the introduction of the sentinel node concept, a minimally invasive procedure became available for detection of occult lymph node metastases. This report describes the history and the validation of the technique, with particular reference to breast cancer (6). ❑

PATHOPHYSIOLOGY

Once they occur solid tumors tend to spread via different mechanisms. Lymphatic metastasis is the most important mechanism of spread in sinonasal squamous cell carcinoma considering the vast network of vessels in this area. The risk of lymph node involvement by metastasis varies depending on the site of origin, size of primary tumor, histological grade of the primary tumor, perineural invasion, perivascular invasion, and extracapsular spread. Having to deal with such patients the physician has to take into consideration a multimodal approach and an individualized treatment for each patient (7). There have been developed guidelines for good medical practice in this field of expertise but they are yet to resolve the N0 neck management.

The indications and type of neck dissection to be performed in the positive node neck and management of the N0 neck remain controversial. Management is based on personal experience, data gathered from retrospective studies and new and improved methods of imaging. Radical neck dissection was the first attempt at adequately treating metastatic cervical lymphatic spread. The tumor growth at the primary site is due to several mechanisms that lead to the alteration of the normal proliferation and destruction processes of the cells including dysfunction in cellular proliferation, differentiation, and death (8). Mutations due to chemical carcinogens, radiation, or viruses may cause activation of oncogenes in normal cells, multiple genetic mutations, and/or modification of tumor suppressor genes, which may cause alterations in growth control.

Tumor cells move through the basement lamina of the epithelium and the stroma into the lymphatic and vascular channels (ie, the tumor progresses from carcinoma *in situ* to microinvasive tumor) causing a far site inoculation of the clonal population. This process is related to the production of cytokines, enzymes, and growth factors that destroy the basement membrane and create abnormal angiogenesis, which, in turn, triggers neovascularization and growth.

Evolution of the technique of lymphatic mapping

The research for sentinel node biopsy applied from halfway through the twentieth century did not produce any enthusiasm for the concept. The reason for this might be that these techniques, only based on the typical anatomical patterns, were not reproducible and did not take into account the interindividual variability

of lymphatic drainage. Morton and coworkers introduced blue dye mapping as a key point in the general acceptance of sentinel node biopsy. After a feasibility study in a feline model, they injected patent blue or isosulfan blue intradermally at the primary tumor site in melanoma patients. An incision was subsequently made over the site of expected lymphatic drainage, not more after 20 minutes after injection and the lymphatic channel was visually identified. This channel was followed to the first draining lymph node by meticulous dissection (9,10). Visualization of lymphatic drainage is a technique that has been used priory by Haagensen et al who describe the old anatomical studies using injections of various tracer fluids in the lymphatic vessels. Sappey tried to clarify the intricate lymphatic system of the breast using mercury injections at the end of the eighteenth century. Surgeons and nuclear medicine physicians later visualized the lymphatic system with vital dyes and radioactive isotopes. In recent times head and neck cancers benefit from these studies in order to assess the need for lymphatic tissue preservation versus radical neck dissection accordingly to the staging of the disease.

The concept of lymphatic mapping with sentinel node biopsy

Lymphatic mapping was only recently introduced in current medical practice in the 20th century. Morton et al have used cutaneous lymphoscintigraphy with colloidal gold since 1977 to identify the lymphatic drainage pattern of melanomas located at ambiguous sites. In addition to this preoperative procedure, they also developed a technique for intraoperative mapping to selectively remove lymph nodes on the direct drainage pathway from the primary melanoma (11). According to their hypothesis this sentinel node was considered to be the first site of metastatic disease.

The concept of sentinel node biopsy is based on two basic principles: the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin in direct relation to the site of the primary tumor, and the functioning of a first lymph node as an effective filter for tumor cells. With the widespread use of sentinel node biopsy, sufficient data was provided to prove that sequential lymphatic dissemination and entrapment of tumor cells in first draining lymph nodes occur (12). The sentinel lymph node concept is based on the Halsted theory that stressed the importance of locoregional cancer treatment because of the far site spread.

First descriptions of a sentinel node

A normal-appearing node at the junction of the anterior and posterior facial vein was sent for frozen section investigation during a total parotidectomy in 1951. In the description of Gould, the pathology report was 'lymph node with metastatic tumor'. Intraoperative examination of this lymph node in its typical anatomical location guided the decision to perform a radical neck dissection during the following parotidectomies.

Two decades later, Cabañas observed the existence of a sentinel node in the lymphatic drainage of the penis. Lymphangiographic studies elucidated the precise location of such sentinel nodes. Sentinel node biopsy was introduced in 1977 by Cabanas and has been improved on since 1990, primarily in breast cancers and melanoma (13). In recent years, however, a few multicenter trials and meta-analyses have reported positive results. These have encouraged us to further research this aspect.

Sinonasal squamos cell carcinoma metastasis

The most important prognostic factor as well a survival rate array is represented by the metastatic spread in the lymph nodes. Thus the need for a correct staging of the cervical mass tumor:

NX: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis is observed.

N1: Metastasis is observed in a single ipsilateral lymph node, measuring 3 cm or less in greatest dimension.

N2a: Metastasis in a single ipsilateral lymph node is observed and measures more than 3 cm but less than 6 cm in greatest dimension.

N2b: Metastasis is found in multiple ipsilateral lymph nodes; none of the nodes measure greater than 6 cm in their greatest dimension.

N2c: Metastasis in bilateral or contralateral nodes is observed; no nodes are larger than 6 cm in their greatest dimension.

N3: Metastasis is observed in a lymph node that measures greater than 6 cm in its greatest dimension.

Nasopharyngeal Carcinoma

- N1 – Unilateral <6 cm
- N2 – Bilateral <6 cm
- N3a >6 cm
- N3b – Extension to the supraclavicular fossa

Neck dissection

Having been introduced by Crile in 1906 the radical neck dissection hasn't become the golden rule in the treatment of cervical node metastasis until 1950s. Martin proclaimed the concept according to which a cervical lymph node excision for cancer is inadequate unless the entire fatty tissue and lymphatic tissue are removed. This is only possible if the excision includes the sinal nerve, the internal jugular vein and the sternocleidomastoid muscle. In fact he postulated that any technique that preserves the spinal nerve should be banned irrevocably (14-16). Unfortunately the excision of these three important anatomical structures derived into significant increase in morbidity, both functional and esthetic. In recent years several studies pointed out the lack of necessity for radical neck dissection for all node metastasis which lead to a series of modifications for this technique.

The "Academy's Committee for Head and Neck Surgery and Oncology" published in 1991 an official report on neck dissection after analyzing several techniques. Thus, it was concluded that there are four major types of neck dissection and several other subtypes:

1. Radical neck dissection
2. Modified radical neck dissection:
   - subtype I (preserving of the spinal nerve);
   - subtype II (preserving of the spinal nerve and the internal jugular vein);
   - subtype III (preserving of the spinal nerve, the internal jugular vein and the sternocleidomastoid muscle).
3. Selective neck dissection:
   - supraomohyoid neck dissection;
   - posterolateral neck dissection;
   - lateral neck dissection;
   - anterior neck dissection.
4. Wide radical neck dissection.

Neck dissection in case of carcinomas of head and neck were classified according to the extension of tissue removal and received firm indications (17,18):

- Radical - gold standard operation
- Modified radical - preservation of non lymphatic structures
- Selective - preservation of lymph node groups
- Extended - removal of additional lymph node groups or non lymphatic structures

Sentinel lymph node associated with sinonasal carcinoma

Although rare sinonasal squamos cell carcinoma is a malignancy that should benefit from the study of drainage node basins in order to establish the staging of the disease and therefore the proper management (19,20). Its late clinical onset results into lymph node metastasis with high impact on prognostic and survival rate. Surgical treatment resides in oncological removal of the primary tumor and the cure of lymph node metastasis. Sentinel lymph node concept is yet to be determined if positive or negative in the perspective of neck dissection and other adjuvant therapies.

The concept of sentinel lymph node needs to assess the lymphatic nodes and vessels via different techniques such as: stains, lymphography, radioactive elements and radiolabeled isotopes (21).

According to O'Brien's research on mapping lymphatic vessels in head and neck there are several difficulties in this process. He concluded that it is difficult for the physician to visualize the lymphatic channels using lymphoscintigraphy because of the proximity to the injection site when using injected dyes or radiotracers. Moreover the radiotracer travels fast in the lymphatic vessels thus making the investigation time dependant (22,23). After such maneuvers are performed there is the possibility of not distinguishing the first echelon nodes from second-echelon nodes, making the concept of sentinel node disputable. The size of the nodes is very important because small nodes are sometimes very hard to be spotted such as those in the parotid gland. ❑

CONCLUSIONS

Sinonasal squamos cell carcinoma is a rare malignancy that has a late clinical onset. The tumor growth is in direct relation to the far site metastasis rate, including lymph nodes. Several

techniques have been developed in order to establish the relationship between tumor type, staging, grading and site of origin and lymphatic spread and colonization. Limited incision guided by lymphoscintigraphy and gamma probe followed by frozen section analysis lead to the conclusion that sentinel nodes are found in more than 90% of cases. This is a relative measure of the step made towards lymph node detection because experience of the physician matters. Surgeons with less than 10 cases have a success rate of a little over 50% in detecting sentinel lymph nodes. Lymphoscintigraphy revealed unexpected bilateral or contralateral disease in about 14% of patients, thus making us consider the possibility of personal and individual lymph pathways drainage. Each patient with head and neck malignancies, including sinonasal carcinoma have about 2-3 sentinel lymph nodes of which up to 40% of them contain metastases. By using fine section frozen analysis we can increase the sensitivity to about 95%. It is better to use immunohistochemical staining, although false negative rates can reach to as high as 10%. There is a better sensitivity for T1/T2 lesions. Most false negative results are associated with larger T3 lesions.

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