METASTASIS TO THE SUBMANDIBULAR GLAND IN HEAD AND NECK CARCINOMAS

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Abstract: Background. The purpose of this retrospective chart review was to determine whether and how the submandibular gland is involved in metastases of squamous cell carcinoma of the head and neck.

Methods. We reviewed the records of all patients for whom pathology specimens were available after neck dissection for primary head and neck cancers at two institutions.

Results. One hundred sixty-nine patients were included in the study, 27 underwent bilateral neck dissections, and 196 submandibular glands were resected and sent for pathology. One hundred forty-four glands had normal histologic findings. Normal or benign histologic changes were present in 187 glands. Three submandibular glands showed invasion from a locally involved lymph node, and six had direct extension from a primary lesion. The primary lesions were all ipsilateral to the involved gland and originated from cancers of the floor of the mouth, alveolar ridge, and tongue. No submandibular glands showed pathologic evidence of metastases.

Conclusions. Because the submandibular gland has no intraparenchymal lymph nodes, its involvement in upper aerodigestive tract carcinomas must be through extension from a locally involved lymph node or the primary tumor. Previous work has demonstrated that the submandibular gland can undergo transplantation out of the neck with subsequent reimplantation, as a possible means of protection from the effects of radiation.

We demonstrated the submandibular gland to be involved only in cases of ipsilateral oral cavity tumors or metastasis to ipsilateral level I lymph nodes. We conclude that it is oncologically sound to consider transplantation and reimplantation of the contralateral submandibular gland for patients with head and neck squamous cell carcinoma when level I lymph nodes are unlikely to be involved. © 2004 Wiley Periodicals, Inc. Head Neck 26: 1064–1068, 2004

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Carcinomas of the head and neck affect 70,000 people every year in the United States. Treatment often involves surgical excision of the affected area followed by radiation therapy. Eighty percent of patients with head and neck cancer in the United States receive at least one course of radiation as a component of their therapy.1 Radiation therapy of the head and neck has significant associated morbidity, including injury to the major and minor salivary glands resulting in xerostomia. Xerostomia as a radiation-induced injury to the salivary glands was first described by the French radiobiologist Jean Bergonie in 1911.2 Radiation treatment with as little as 35 Gy causes permanent salivary dysfunction, and, despite the availability of some newer pharmacoe-
Saliva is important for everyday functions, and its absence causes significant discomfort to those affected. Saliva enhances taste, speech and swallowing, facilitates irrigation and lubrication, and protects the mucous membranes of the upper digestive tract. It also has antimicrobial and buffering properties that protect the teeth from dental caries and chronic fungal infections and enhances remineralization of tooth enamel. The dental complications of radiation-induced xerostomia often lead patients to undergo complete dental extractions. However, comfortable use of prosthetic dentures or other dental appliances after total extractions is hindered by the persistent xerostomia.

Current therapy for xerostomia includes synthetic saliva, gustatory stimulants, autologous saliva storage, acupuncture, electrostimulation, and various medications, although most patients make do with frequent sips of water. None of these treatments can adequately improve the patient's quality of life, and some are associated with significant side effects. For example, pilocarpine hydrochloride, a widely used cholinergic antagonist, stimulates residual salivary gland tissue not destroyed by radiation therapy, but its side effects, including sweating, headache, rhinitis, dizziness, and urinary frequency, make it an intolerable treatment for many patients.

Attention has turned to prevention of xerostomia in patients undergoing radiation therapy. Although shielding of the salivary glands is a desirable method to preserve salivary function, local shielding can compromise oncologic treatment and is usually not effective. Surgical options to preserve salivary gland function by preventing damage to the submandibular gland during radiation are being considered. Preservation of one submandibular gland is adequate to prevent xerostomia.

In 1982, Bourdin et al proposed that the transposition of the contralateral submandibular gland to the submental region can prevent xerostomia after salivary gland irradiation during radiotherapy for oropharyngeal cancer. The researchers obtained good results in most cases treated, with conserved salivary secretion as confirmed by scintigraphy, but they warn that this method should be reserved for patients with oropharyngeal cancer without lymph node metastases to the contralateral side. More recently, Jha and Seikaly have shown that submandibular gland transfer to the anterior submental region allows for shielding of the gland during radiation therapy and preventing xerostomia. In other words, Jha and Seikaly demonstrated that a single submandibular gland prevented symptomatic xerostomia and that their patients had a more mild radiotherapy course with less mucositis and weight loss. This provides support that a single gland may be adequate to prevent xerostomia. Of course, by remaining pedicled, the authors needed to be very careful in modifying the radiation field to avoid the gland, and they therefore limit the situations in which this technique can be applied. Spiegel et al demonstrated that it is possible to transplant the submandibular gland to the groin area in rabbits and to transfer it back to the neck area with the gland maintaining its integrity and function. They propose that this is a promising preventive treatment for xerostomia in patients with head and neck cancers about to undergo radiation therapy. Although this work by Spiegel et al is likely the first study to demonstrate that microvascular transplantation and subsequent replantation of the same organ is possible, certainly many questions remain before this can be proven as a successful technique in preventing postirradiation xerostomia. In this work, the rabbits did not receive radiation to the neck before replantation of the organ. Radiation treatments affect blood vessels and nerves. Although there is large clinical experience with successful microvascular tissue reconstruction, including sensate flaps, into radiated head and neck tissue, the particular effect this may have on salivary gland replantation can be reasonably expected to be minimal but is in reality unknown.

Another important question is whether this procedure is oncologically sound in a patient with a head and neck squamous cell carcinoma. That is, does squamous cell carcinoma metastasize to the submandibular gland? Clearly, it would be unwise to transplant a potentially cancerous organ. Metastatic spread of a neoplasm to the salivary glands is unusual, and if it occurs, the parotid gland is more likely to be affected. It has been postulated that unlike the parotid gland, the submandibular gland is unlikely to be the host tissue for metastases because of its lack of lymph nodes or vessels. When the submandibular gland is involved in metastatic cancer, it is through hematogenous spread of cancers originating outside the head and neck.
This study aims to determine whether and how the submandibular gland is involved in metastases of squamous cell carcinoma of the head and neck.

METHODS
This retrospective study reviewed the records of patients who underwent neck dissections for cancer at the Boston University and the University of California San Francisco medical centers from 1996 to 2001. All patients who underwent dissection for primary head and neck lesions and for whom pathology specimens were available were included in the study.

We reviewed the pathology reports of 169 patients, including 103 men and 66 women, with mean age of 63 years (range, 21–91 years). Of the 169 patients, 27 had bilateral neck dissections, thus 196 submandibular glands were available to examine. Primary tumors included the tongue ($n = 54$), floor of the mouth ($n = 25$), tonsillar fossa ($n = 15$), base of tongue ($n = 15$), retromandibular trigone ($n = 11$), alveolar ridge ($n = 11$), palate ($n = 6$), buccal mucosa ($n = 6$), lip ($n = 5$), and the posterior pharynx ($n = 2$). Twelve patients had primary tumors involving multiple structures.

RESULTS
Of the 196 submandibular glands examined, 144 had no tumor involvement with completely normal histologic findings. Three submandibular glands showed local invasion from an involved lymph node, and six had direct extension from the primary lesion. All of these were from ipsilateral cancers of the floor of the mouth, alveolar ridge, and tongue (Table 1). Histologic examination of the remaining glands revealed inflammation and changes consistent with radiation therapy, chronic sialadenitis, atrophy, sialometaplasia, and oncocytosis. No submandibular glands showed pathologic evidence of metastases.

DISCUSSION
Metastasis to the submandibular gland occurs more commonly through hematogenous spread of cancers residing outside the head and neck. Vessecchia et al.\textsuperscript{16} performed a review of the literature that revealed more than 100 cases of metastases to the submandibular gland. Most metastases arose from primary tumors at distant sites, such as the breast, lungs, or the genitourinary system. There have been case reports of metastases to the submandibular gland from uterus leiomyosarcoma.\textsuperscript{17} Case reports of submandibular gland metastases from the breast have been described by several authors.\textsuperscript{18–21} Bilateral submandibular gland involvement in a patient with advanced breast cancer has also been reported.\textsuperscript{22}

In the 1970s, Evans and Cruickshank\textsuperscript{23} observed that even with advanced carcinoma present in the adjacent submandibular lymph areas, it is unusual for the submandibular gland to be involved. More recently, Junquera et al.\textsuperscript{24} evaluated the involvement of the submandibular gland in 31 patients with squamous cell carcinoma of the floor of the mouth. Histopathologic examination identified cervical node metastasis in 34.1% of the ipsilateral neck dissections. Cervical periglandular metastases were found in 31.7% of neck dissections, but in no case was microscopic affection of the submandibular gland found. Although periglandular metastases in carcinoma of the floor of mouth are frequent, submandibular gland involvement is unusual. Contralateral submandibular gland involvement from head and neck carcinoma has not been reported.

Our own review of patients with head and neck cancer who underwent neck dissection demonstrated that in no case did a squamous cell carcinoma metastasize to the submandibular gland. The submandibular gland was only involved in cases in which the primary tumor was in close proximity to the gland, or when meta-

<table>
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<th>Table 1. Pathology of submandibular glands (SMG).</th>
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<td>Histology</td>
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<td>Normal</td>
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<td>Malignant Changes:</td>
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<td>Direct extension from primary tumor</td>
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<tr>
<td>Floor of Mouth</td>
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<td>Floor of Mouth and Alveolar Ridge</td>
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<td>Floor of Mouth and Tongue</td>
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<td>Local invasion from involved lymph node</td>
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<td>Floor of Mouth</td>
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<td>Tongue</td>
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<tr>
<td>Alveolar Ridge</td>
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<tr>
<td>Benign Changes:</td>
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<td>Inflammation and changes consistent with radiation therapy</td>
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<td>Chronic Sialadenitis</td>
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Metastasis to level I of the neck had occurred with extension from a locally involved lymph node into the submandibular gland. Clearly, it would be unwise to dissect out for transplantation a submandibular gland that is ipsilateral to a tumor of the floor of mouth or mandible, or one in which metastasis to the submental region is likely. However, in cancers in which contralateral neck disease is not suspected, the submandibular gland is very unlikely to be involved with carcinoma and would seem to be available to use for a xerostomia prevention procedure.

Spiegel et al have been successful in transplanting the submandibular gland in rats and in transplanting and replanting the submandibular gland in rabbits. These methods can theoretically be applied to patients with head and neck cancers who are going to undergo radiation therapy. Removal of the submandibular gland from the radiation field during treatment would protect the gland from harm, and subsequent reimplantation into the neck region could resolve the patient’s xerostomia. Spiegel et al found that the reimplanted rabbit gland both survived and was functional; however, the volume of saliva from the denervated gland was not calculated because of limitations in the rabbit model. The size of the submandibular ganglion should allow for reinnervation of the submandibular gland on reimplantation in a human, although as with all neural repairs, the degree to which this will be successful or functional is not predictable. Before now, the transplantation and replantation method of xerostomia prevention has not been attempted in humans because of the fear of transplanting cancerous tissue to the distant site that would be temporarily hosting the gland. This study demonstrates that squamous cell carcinoma of the head and neck is unlikely to metastasize to the submandibular gland. Thus, we extrapolate that submandibular gland transfer is a promising and oncologically sound treatment alternative for xerostomia prevention.

CONCLUSION

Because the submandibular gland has no intraparenchymal lymph nodes, its involvement in upper aerodigestive tract carcinomas must be through extension from a locally involved lymph node or from distant metastases of a primary tumor. Previous work has demonstrated that the submandibular gland can undergo transplantation out of the neck with subsequent reimplanta-

tion, a technique protecting the salivary tissue from the effects of radiation.

We demonstrated the submandibular gland to be involved only in cases of ipsilateral oral cavity tumors or metastasis to ipsilateral level I lymph nodes. We conclude that it is oncologically sound to consider transplantation and replantation of the contralateral submandibular gland in patients with head and neck squamous cell carcinoma when level I lymph nodes are unlikely to be involved.

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