

**TITLE: Malignancies of the Major Salivary Glands**

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## **Epidemiology**

It is estimated that 1 in 100,000 U.S. residents will develop a salivary malignancy at an average age of 56.6 years of age. The most common malignant histology is Tumors of the submandibular and sublingual salivary glands are more likely to be malignant than those in the parotid. Employment in the rubber industry, exposure to nickel alloys, exposure to silica dust, and the use of kerosene as cooking fuel have been associated with an increased risk of a primary salivary malignancy. A history of skin cancer has also been found to be associated with subsequent development of a primary salivary cancer when it originates in the scalp or face, it also presents a risk for metastases to the parotid gland.

## **Diagnosis**

Malignant salivary neoplasms present as a painless mass in approximately 75% of patients. Rarely, patients are initially seen with pain or facial nerve palsy. Though not definitive by any means, a palpable mass arising in a salivary gland, associated with pain, and/or nerve paralysis is more likely to be malignant than benign. It is believed that episodic pain suggests continued obstruction, whereas constant pain is more suggestive of malignancy. Trismus, cervical adenopathy, fixation, numbness, loose dentition, or bleeding also suggest the presence of malignancy.

With a clinical history and physical examination suggestive, physicians should seek to solidify the diagnosis before employing treatment and before counseling a patient on prognosis. Traditionally, FNA has been performed preoperatively for histologic confirmation of malignancy and to aid in operative planning, such as planning for elective neck dissection. In 1997, Tew and others evaluated 195 FNAs and 159 intraoperative frozen sections for parotid tumors. They found that FNA had a 90% sensitivity for malignancy if non-diagnostic biopsies were excluded. They also found that intraoperative frozen section had a 96% sensitivity for malignancy. More recently, in 2005, Zbaren et al reported on 83 patients with primary carcinoma of the parotid and clinically negative necks. This group found that preoperative FNA yielded a 30% false-negative

rate for malignancy. In contrast, intraoperative frozen section diagnosis yielded only 7% false negative. These findings suggest that surgeons should consider the addition of intraoperative frozen section to the diagnostic battery. An incisional biopsy at a site that can be excised during the definitive surgery approximates 100% accuracy and is therefore preferable in those patients in whom the extent of the surgery (e.g., no surgery, nerve sacrifice, total vs superficial parotidectomy) would change with a change in histologic diagnosis.

Imaging can add significantly to the diagnostic workup of salivary malignancies. Ultrasound can provide guidance in obtaining fine-needle biopsy specimens from deep parotid or parapharyngeal space tumors. In patients with cystic or heterogeneous masses, ultrasound ensures sampling of the solid component and may also be helpful in biopsy masses that are difficult to palpate. Computed tomography (CT) with intravenous contrast is routinely used preoperatively and provides excellent detail of the tumor volume, its relation to vascular and bony structures, as well as surveillance of the regional lymphatics. Magnetic resonance imaging (MRI) provides excellent soft tissue detail, which is superior to that of CT and has the advantage of not requiring contrast for vascular detail or ionizing radiation. The usefulness of PET scanning in the setting of salivary gland malignancy is yet to be clearly defined. Keyes and others performed preoperative PET imaging on 26 patients with parotid tumors. A PET scan accurately predicted the nature of the neoplasm in 69%, demonstrated 100% sensitivity for malignancy, and a false-positive rate of 30%. Roh et al, reported this year on thirty-four patients with newly diagnosed salivary gland cancers who underwent CT and 18F-FDG PET before surgical resection with radiotherapy. The diagnostic accuracies of CT and 18F-FDG PET for detecting primary tumors and neck metastases were compared with a histopathologic reference. 18F-FDG PET was more sensitive than CT for the detection of cervical metastases (80.5% vs. 56.1%;  $P < 0.05$ ) at initial staging.

## Treatment

Ablative surgery has long been the mainstay of treatment of the primary tumor in salivary malignancies. Superficial parotidectomy has become the widely accepted form of intervention for most parotid tumors. A higher risk of facial nerve injury and the potential for intraoperative seeding of tumor resulting in recurrence of the tumor has been associated with the use of lesser procedures. Therefore, a superficial parotidectomy has been touted as the minimal surgery of the parotid gland. Overall, the safety of parotidectomy has been well established, and the complication rate remains low. Total parotidectomy may be necessary for tumor extension into the deep parotid lobe or when the tumor primarily arises in the deep lobe. This can be performed with preservation of the facial nerve. Occasionally, patients may require extended parotidectomy, which includes resection of the masseter muscle or the ascending portion of the mandible. Facial nerve sacrifice is not routinely advocated. Nerve preservation in primary salivary malignancy is recommended if the nerve is functioning normally before surgery. Every attempt to dissect the tumor from the individual branches should be undertaken. If tumor is completely encasing the nerve branches, neural sacrifice is limited to the involved branches. In general, tumors of the submandibular gland require complete excision of the gland.

Postoperative radiation to the primary tumor bed should be considered. North et al reported in 1990 on 87 patients with carcinomas of the major salivary glands (70 parotid and 17 submandibular). From 1975 to 1987, they were treated at Johns Hopkins by either surgery or

surgery followed by postoperative radiotherapy (RT). For patients with previously untreated disease, 5 of 19 (26%) treated by surgery alone experienced local recurrence, whereas only 2 of 50 (4%) recurred locally following surgery plus postoperative RT ( $p = 0.01$ ). The determinant 5-year actuarial survival for patients receiving postoperative RT was 75% versus 59% for surgery alone. That same year, Armstrong et al, at Memorial Sloan Kettering reported on 46 patients with previously untreated malignant tumors of major salivary gland origin received combined surgery and postoperative radiotherapy between 1966 and 1982. They were compared with 46 patients treated with surgery only between 1939 and 1965, who were matched according to prognostic criteria. The 5-year determinate survival rates for patients given combined therapy with stage I and II disease versus patients given surgery only was 81.9% versus 95.8%, while for stages III and IV it was 51.2% versus 9.5%, respectively. Local control for stage III and IV disease in patients given combined therapy versus patients given surgery only at 5 years was 51.3% vs 16.8%. For patients with nodal metastases, 5-year determinate survival for the combined-therapy group versus the surgery-only group was 48.9% versus 18.7%, and the corresponding local-regional control was 69.1% versus 40.2%. The results of this analysis suggest that postoperative radiotherapy significantly improves outcome for patients with stage III and IV disease and for patients with lymph node metastases. Chen, in 2007, reported on 207 patients who, over 5 decades, received surgery without XRT as primary modality. He identified patients who were at high risk of locoregional recurrence with surgery alone. Based on these observations, he recommended postoperative XRT for patients with T3-T4 disease, positive surgical margins, high grade tumor histology, or regional nodal metastasis.

There is little dispute that patients with clinical evidence of cervical nodal metastasis require treatment of the neck. Dispute in the literature still exists, though on whether or not to treat clinically negative (N0) necks.

To begin, the risk of occult nodal disease is widely varied in the literature. Armstrong et al studied the incidence of occult nodal metastasis. Of 407 patients with clinically negative necks, neck dissection was done in 90. Occult metastasis was found in 38% of these specimens. To attempt to determine incidence of metastasis related to prognostic factors, the researchers report incidence percentage using all patients with the factor present, even if they did not undergo neck dissection. The cancers with the highest incidence, broken down by histologic subtype, are 41%, 18%, and 14% for epidermoid malignancy, adenocarcinoma, and mucoepidermoid, respectively. It is important to note that mucoepidermoid was not divided into low and high grade histologies. Frankenthaler et al in 1992 reported their estimate of the incidence of occult neck metastasis in parotid cancer only. They retrospectively reviewed 99 charts of patients that had N0 necks and underwent neck dissection. Their overall incidence of occult neck nodes was 12%. By histology, the incidence was 80%, 50%, 25%, 17%, 10% for salivary duct, squamous cell, adenocarcinoma, undifferentiated, and mucoepidermoid cancer, respectively. Stennert, in 2003, reported on 160 consecutive patients over 4 years. At their institution, policy was to perform ipsilateral neck dissection on all major salivary gland cancers, regardless of T stage or histology. This allows evaluation of a true incidence of neck metastasis. This report found the highest incidence in adenocarcinoma (17%) adenoid cystic cancer (16%), and mucoepidermoid cancer (13%).

Estimates can be made on the chance of a patient having subclinical nodal metastasis based on prior studies. Even with these estimates, it is not clear as to which patients should

undergo elective neck dissection or elective neck irradiation. Appropriately treating the neck in salivary malignancy is important for patient outcomes. For instance, overall 5 year survival of patients with and without involvement of the regional nodes is estimated at 10% and 75% respectively for the parotid and 9% and 41% for the submandibular gland. Medina, in 1998, proposed a rationale for neck dissection on N0 necks. He proposed that patients that have factors that are indications for post-operative radiation are also the same ones that are at high risk for nodal metastasis and that these patients should simply undergo neck irradiation simultaneously and forego neck dissection. Medina emphasized that, at the time of his report, the effectiveness of XRT on controlling neck disease had not been studied. In 2005, Zbaren et al reported on 83 patients with primary carcinoma of the parotid and N0 necks. Two treatment groups were studied, one underwent neck dissection, the other was observed. Of note, no strict criteria were used to select patients for one or the other treatment modality and no significant imbalance was found between the 2 groups with respect to demographic, clinical, and pathological variables and treatment modalities of the primary carcinoma. Occult metastases were detected in 8 (20%) of 41 cN0 staged patients who underwent elective neck dissection. Among these patients, 5 had a high-grade carcinoma and 3 had a low-grade carcinoma. The primary carcinoma of these 8 patients was classified as T2 in 4, as T3 in 1, and as T4 in 3 cases. Regional recurrence occurred in none of the patients with an elective neck dissection and in 7 patients in the “observation” group (17%) ( $P = 0.006$ ). Of the 7 patients without neck dissection and neck recurrence, 2 patients were initially given adjuvant radiotherapy to the neck. The actuarial and the disease free survival rates at 5 years for patients with neck dissection were 80% and 86% and 83% and 69% for patients without neck dissection. Based on this study, the authors dispute Medina’s treatment paradigm and recommend elective neck dissection in all primary parotid carcinomas. Chen and others reported in 2006 on 251 patients with clinically N0 necks who received postoperative radiation therapy after gross total tumor resection. Their results showed that none of the 131 patients who received ENI had neck failure compared with 24 of 120 who did not receive ENI. The corresponding 10-year estimates of nodal relapse were 0% and 26%, respectively ( $p = 0.0001$ ). Notably, there were no significant differences in the distribution of clinical and disease characteristics with respect to age, perineural invasion, T-stage, and primary site, among patients treated with and without ENI. The highest crude rates of nodal relapse among those treated without ENI were found in patients with squamous cell carcinoma (67%), undifferentiated carcinoma (50%), adenocarcinoma (34%), and mucoepidermoid carcinoma (29%). There were no neck relapses among patients treated either with or without ENI for patients with adenoid cystic or acinic cell histology. It is clear that, for many patients with clinically N0 necks, based on histology, the risk of harboring occult disease in the regional lymph nodes is low enough that ENI is not warranted. Patients with adenocarcinoma or mucoepidermoid carcinoma appear to be at increased risk for developing nodal relapses without neck treatment, and ENI should strongly be considered for these histologies. These findings also demonstrate that it is reasonable to use ENI as an alternative to neck dissection and should be considered, especially if postoperative radiation will be administered to the primary tumor.

## Conclusions

Malignancies of the major salivary glands represent a rare and diverse group of cancers. Knowledge about tumor staging and histologic grading is necessary for prognostic predictions, patient counseling, and treatment planning. Surgical treatment should be the primary therapy with removal of all gross disease as the surgical goal. Patients should receive postoperative

radiation to the primary site if the tumor is stage III or IV, or if the pathology shows positive margins or perineural invasion. Careful consideration must be given to treatment of the neck, with clinical disease as definite indication for neck dissection and/or neck irradiation. Patients with N0 necks may have a higher incidence of occult metastasis than previously thought. Consideration should be given for elective neck dissection or elective neck irradiation in the N0 neck, especially with high incidence of occult neck metastasis based on histology and stage. Strong evidence suggests that radiation therapy is effective at controlling neck disease and consideration should be given to elective neck irradiation in lieu of neck dissection. Future studies are needed to compare outcomes of elective neck irradiation versus elective neck dissection versus observation in treating the N0 neck.

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