CHAPTER

37 Salivary Gland Malignancies

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INCIDENCE

The overall incidence of salivary gland malignancies in the general population is about 0.9 to 4.0 new cases per 100,000 population per year.

BIOLOGIC CHARACTERISTICS

Prognostic factors relate to histology, grade, primary tumor size and extent, lymph node involvement, gender, and age.

For mucoepidermoid carcinomas, the presence of the hallmark t(11;19)(q21;p13) translocation is a key oncogenic event associated with lower rates of local and distant relapse in fusion positive malignancies.

STAGING EVALUATION

Staging includes a thorough history and physical examination, chest radiography, contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck region, positron emission tomography (PET) scan, and liver function tests.

PRIMARY THERAPY

Compete surgical resection is the primary therapy for major and minor salivary gland cancers. Small cancers, typically arising within minor salivary glands in cosmetically or functionally critical areas, may be treated with primary radiation therapy with moderate success in the patient who refuses surgery. New surgical options including transoral robotic surgery (TORS) now exist, offering improved function preserving surgical options especially for minor salivary gland malignancies.

ADJUVANT THERAPY

Adjuvant radiotherapy has an established role to reduce the risk of locoregional relapse in high-risk indications. These include the presence of a positive or close surgical margin, perineural invasion, high-grade histology, extraglandular extension, bone invasion, and the presence of lymph node metastasis.

EARLY STAGE DISEASE

The 10-year locoregional disease control and overall survival (OS) rates for stages I to III disease treated with surgery and postoperative radiotherapy are ≥80% and ~60%, respectively. When treated with radiotherapy alone, these are ~70% and ~65%, respectively.

LOCALLY ADVANCED DISEASE

The 10-year locoregional disease control and OS rates for stage IV disease treated with surgery and postoperative radiotherapy are ~65% and ~30%, respectively. When treated with radiotherapy alone, these are ~25% and ~20%, respectively.

When treated with neutron beam alone, the 6-year actuarial locoregional and OS rates are ~60% and ~60%, respectively. The use of neutron beam radiation can increase the rate of severe late effects including central nervous system (CNS) injury at the skull base.

PALLIATION

Combination chemotherapy regimens have poor response rates, typically less than 25%. Multiple targeted agents have been investigated, demonstrating less toxicity and the suggestion of disease stabilization but even poorer objective response rates.

The salivary glands are exocrine glands that function to produce saliva. The salivary gland unit is composed of acini of serous or mucinous cells that drain into a branching ductal system composed of cells forming the intercalated duct, striated duct, and excretory duct. Myoepithelial cells surround the acinar cells and the intercalated ducts and function by contracting and forcing saliva through the ductal system. Stem cells are present in the basal layer of the excretory and intercalated ducts that can differentiate into the different elements of the salivary glands.

There are three major paired salivary glands (parotid, submandibular, and sublingual) producing the majority of the saliva. The remaining saliva is produced from more than 600 minor simple unencapsulated tubuloalveolar glands, located throughout the lamina propria of the upper aerodigestive tract mucosa. Approximately 50% of the minor salivary glands are located within the mucosa of the hard palate. These glands are predominately mucous secreting. Minor salivary glands may also be seen in the nasal cavity and paranasal sinuses.

Benign and malignant tumors of diverse histologies may occur in a variety of anatomic sites adding to the complexity in understanding the natural history of salivary gland tumors (SGTs). This heterogeneity and the rare incidence of SGTs add to the challenge in determining the optimal management approach.

ETIOLOGY AND EPIDEMIOLOGY

The causes of SGTs, both benign and malignant, have not been clearly established. Reports consistently suggest etiologic associations with nutritional deficiencies, exposure to ionizing radiation, ultraviolet exposure, genetic predisposition, history

of previous cancer of the skin of the face, occupational exposure, viral (Epstein-Barr virus) infection, alcohol use, hair dye use, and higher educational attainment.[1-5]

Of these associations, exposure to ionizing radiation is associated with a statistically significant, though small risk of for SGTs, both benign and malignant. Radiation-induced malignant SGTs (MSGTs) may occur with higher frequency in the minor salivary glands. Studies have demonstrated not only a strong association[6] but also that the risk has a temporal latency (10 years to 25 years) and a dose-response relationship with the exposure especially for mucoepidermoid carcinomas suggesting a cause-and-effect relationship.[4,7,8] The relative risk is greater for MSGTs than benign SGTs (BSGTs).[4,8] These observations are based on several independent long-term cohort studies of victims of atomic bomb exposure[6,7,9] and patients receiving therapeutic radiation for benign[8] and malignant indications.[4] Although investigators have concluded that higher doses and repeated exposure to radiotherapy increases the develop of radiation-induced SGTs, the nature of the dose-response curve for radiation-induced SGTs is unclear beyond doses ≥4 Gy and may not necessarily always increase the risk of second malignancies.[10,11] However, the atomic bomb data does demonstrate that second malignancies are increased with single exposures up to approximately 3 Gy and that this relationship is at least linear up to 2 Gy. Unlike radiation-induced sarcomas, which appear to be primarily limited to the high doses seen within radiotherapy prescription volumes, SGTs can also be seen to occur in areas receiving low therapeutic doses of radiation with the risk increasing with higher doses.

Salivary gland tumors are regarded as rare with a reported overall incidence in the Western world of approximately 2.5 cases to 3.0 cases per 100,000 per year.[12] MSGTs account for more than 0.5% of all malignancies and approximately 3% to 5% of all head and neck cancers.[12] They comprise approximately 11% of all oropharyngeal cancers.[13] Most patients with MSGTs are in the sixth or seventh decade of life.[14]

The incidence patterns of salivary gland cancers were recently reported in a Surveillance, Epidemiology, and End Results (SEER) population-based study that offers the advantage of eliminating the inherent biases of clinical series.[15] Almost 6400 major salivary gland carcinomas were estimated to have been diagnosed from 1992 to 2006. The most common nonsquamous salivary gland cancers were mucoepidermoid carcinomas followed by adenoid cystic and acinic carcinomas of comparable incidence rates. Males had a 51% higher incidence rate compared to females. The parotid gland accounted for 80% of all major salivary gland malignancies,[15] but tumors of the parotid are in general less likely to be malignant compared to the other major salivary glands and the minor salivary glands of the palate.[12] Except for adenoid cystic carcinomas (ACCs), which were equally seen in the parotid and submandibular glands, other histologies occurred mainly in the parotid gland. Notably, squamous cell carcinomas found in the parotid region usually represent lymph node metastases from cutaneous squamous cell carcinomas rather than primary parotid gland carcinomas.[16]

Among males, the most common nonsquamous salivary gland cancers were mucoepidermoid and adenocarcinoma–not otherwise specified (NOS).[15] Among females, the most common nonsquamous salivary gland cancers were mucoepidermoid, acinic cell, and ACCs. Squamous cell, adenocarcinoma–NOS, and salivary duct carcinomas occurred with more than a twofold higher incidence among males. In contrast, females had a higher incidence of acinic cell carcinoma and ACCs.

Acinic cell carcinomas were more likely to be diagnosed at younger ages compared to other cell types.[15] Incidence ratios of salivary gland cancers were significantly lower among African Americans, Asians, and Pacific Islanders compared to whites. However, incidences of mucoepidermoid carcinoma and ACC were similar among all races.

PREVENTION AND EARLY DETECTION

The recognition that radiation exposure is a risk factor for BSGTs and MSGTs (especially mucoepidermoid carcinomas) argues that long-term surveillance is likely a prudent recommendation for patients with a known history of accidental, diagnostic or therapeutic head and neck radiation exposure. These patients should be counseled about the potential risk of late MSGTs manifesting, especially if their anticipated life span is on the order of 10 years to 25 years given the latency period noted for development of radiation-induced SGTs. It is not clear if younger patients receiving therapeutic radiation are at an increased risk,[4,8] which would necessitate more vigilant observation. Gender does not appear to be a risk factor. Issues of cost-effectiveness of various surveillance investigations and the frequency of follow-up have not been established.

Because a dose-response relationship for developing SGTs from therapeutic radiation has been described (especially for mucoepidermoid carcinomas), this raises the intriguing question of whether this risk may be mitigated with modern radiation treatment planning techniques. Modern radiotherapy techniques have the advantage that the dose and volume of normal tissue irradiated may be reduced. This includes the use of proton radiation with its favorable Bragg peak physical beam characteristic. Details of this are further discussed in considering the role of protons in the management of SGTs. At this time, the possibility that conformal radiotherapy such as protons will reduce the risk of developing SGTs remains speculative and unproven. SGTs have been demonstrated, even with low doses, including doses less than 280 cGy to the parotid glands.[8] Hence, judicious use of diagnostic and therapeutic radiation and avoidance of any unnecessary radiation exposure are currently the most effective preventive strategies that can be recommended.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Significant progress has been made in the understanding of the genetics and molecular biology of salivary gland malignancies. These considerations may be organized based on biologic characteristics of the tumor cell and of the tumor microenvironment. Although many biomarkers have been evaluated and shown to have differential expression compared to normal cells, this review will highlight several that have important potential therapeutic implications especially when shown to have independent prognostic significance.

Salivary Gland Genetic and Molecular Biology

Chromosomal Rearrangements

In recent years, investigations have demonstrated recurrent, nonrandom, and hallmark chromosomal rearrangements, especially translocations that characterize both benign and malignant salivary gland tumors (reviewed in Stenman[17]). These translocations result in fusion oncogenes that affect the apoptotic threshold, cell cycle regulation, tumor angiogenesis, and growth independence. Similar rearrangements have been a common theme among leukemias, lymphomas, sarcomas, and more recently with various epithelial malignancies including thyroid, prostate, and breast carcinomas. Characterizing these recurring translocations and their clinical significance is

an active area of investigation in hopes of identifying future prognostic and therapeutic targets. Several noteworthy observations have been made to date.

In 2003, the recurrent and hallmark t(11;19)(q21;p13) translocation involving CRTC1 at 19p13 and MAML2 at 11q21 was described by several groups demonstrating it to be a key pathogenic event that underlies the development of mucoepidermoid carcinomas (MECs).[18,19] This translocation has been shown to result in the mucoepidermoid carcinoma translocated gene 1–mastermind-like gene family (MECT1–MAML2) (MECT1/TORC1/CRTC1–MAML2) fusion transcript that results in a transcription factor acting on the Notch and the CREB pathways (reviewed in O'Neill[20]).

Okabe et al have demonstrated that this fusion transcript was associated with a longer disease-free survival (DFS) and overall survival (OS) on univariate and multivariate analysis.[21] Others have reported on its favorable independent prognostic impact on survival.[22,23] Lower rates of local and distant relapses have been reported in fusion-positive MECs.[23] It is important to note that these investigations have been retrospective in nature and that prospective evaluation of the prognostic significance of MAML2 translocations remains an area of study.[24] Despite this translocation correlating with low-grade MEC, in multivariate analysis for OS, this translocation was found to be independent of tumor grading raising some to question its ultimate prognostic value.[24,25] Hence, this translocation may be of diagnostic benefit and may potentially identify a favorable cohort of high-grade MECs[26] and help identify a subgroup of high-grade MECs that may be more appropriately categorized as aggressive MEC mimics, such as adenosquamous carcinomas.[23,25] This fusion offers not only the promise of future risk stratified treatment approaches but also insights into the development of novel therapeutic targets. For example, unfavorable fusion-positive MECs are believed to have acquired further somatic mutations conferring increased invasiveness such as deletion in the *CDKN2A (p16)* gene.[27]

Deletions or translocations of the terminal regions of the long arm on chromosome 6 appear to be a consistent and unique event in the development of salivary gland ACCs.[28] Of these, reciprocal translocations involving 6q and the short arm of chromosome 9 have been frequently reported.[29,30] Persson et al have also demonstrated a recurrent and hallmark t(6:9) translocation in ACCs, resulting in the MYB–NFIB fusion oncoprotein.[31] These investigators suggest that this may also be a key oncogenic event in the pathogenesis of ACC[31] leading to the induction of high MYB oncogene expression.[28,31] MYB transcription factors regulate cell proliferation, apoptosis, and differentiation. In turn, high MYB expression can also be seen in MYB–NFIB fusion-negative ACCs as well and may be helpful for future disease stratification because it appears to have potential prognostic significance as part of a molecular prognostic profile.[32]

Mutation Analysis

With advances in massive parallel sequencing, the whole exome and genome sequences of ACCs were recently completed.[33,34] Consistent with the previous report by Persson et al,[31] the whole genome sequencing data confirms frequent t(6, 9) translocation resulting in the MYB–NFIB fusion oncoprotein and frequent chromosomal loss of 1p36, 6q24, 9p, 12q13, and 14q.[33,34] These analyses also demonstrate that ACCs have a lower somatic mutation rate (13 mutations per exome) relative to most adult solid tumors with a wide mutational diversity.[34] Many of the mutated genes encode chromatin remodeling regulators and chromatin-state modifiers (i.e., MGEA5, SMARCA2, SMARCE1, CREBBP, EP300, KDM6A, ATRX, ARID1A, ARID4B, and ARID5B) suggesting epigenetic regulation is important in the development of ACCs. Additionally, genes involved in DNA damage response (i.e., TP53, BRCA1, ATM, ERCC2, and PTPRK), protein kinase A signaling (i.e., PTPRG, PTPRH, RYR2, RYR3, and CALM2), Notch signaling (i.e., NOTCH1, NOTCH2, and SPEN), and FGF-IGF-PI3K signaling (i.e., PIK3CA, PTEN, MAGI1, MAGI2, FGFR2, and FGFR4) are shown to be mutated.[33,34] Presence of activating mutations in the FGF-IGF-PI3K pathway has a particular importance because of the existence of therapeutic agents targeting the pathway in this particularly chemotherapy resistant tumor.

Dysregulation in Growth Factor Receptors

Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (erbB2 or HER2/neu) are members of the EGFR transmembrane receptor family, and when activated, transduce mitogenic signals. Several studies have reported high immunohistochemical expression levels that may be more dominantly expressed in non-ACCs.[35-37] However, the clinical significance of EGFR protein overexpression remains controversial with some multivariate analyses demonstrating both an independent association with poor survival[38] and others demonstrating no independent association with poor survival.[37]

Similarly, erbB2 overexpression has been reported for MSGTs. These include strong overexpression in MECs and in salivary ductal carcinomas (SDCs)[39,40] but rarely for ACCs.[39] Univariate[41,42] and multivariate independent prognostic significance has been reported for erbB2 overexpression.[43,44] Agulnik et al suggest that greater clinical activity with the dual EGFR and erbB2 inhibitor lapatinib may be possible in tumors with both high EGFR and erbB2 expression and that erbB2 may be especially important.[35] Recently, patients with SDCs and erbB2 amplification treated with a trastuzumab-containing regimen containing other targeted agents based on actionable mutations were found to have improved survival compared to patients who did not have actionable mutations.[45] Identifying subgroups of patients more dependent on erbB2 signaling may be important in further defining the therapeutic benefit with erbB2 inhibition because tailoring therapies based on molecular abnormalities may be have therapeutic benefits.

c-KIT/CD117

The KIT protein is a membrane tyrosine kinase receptor, which when activated through binding to the ligands stem cell factor or mast cell growth factor, provide signals for cell survival, proliferation, and differentiation. Its overexpression has been particularly noted in ACCs[46] and has been suggested as one way in which ACCs may be distinguished from polymorphous low-grade adenocarcinomas (PLGAs),[47] though contradictory findings have also been reported.[48]

Although the independent prognostic significance for KIT overexpression has not been evaluated, it has remained an attractive therapeutic target because of the clinical success of imatinib, a small molecule tyrosine kinase inhibitor that competitively inhibits the activation of the KIT receptor and several other structurally similar receptor tyrosine kinases. However, it is clear that it is the nature of any point mutations in the protein that impacts on its response to inhibition with imatinib, a small molecule tyrosine kinase inhibitor, which competitively inhibits the activation of the KIT receptor and several other structurally similar receptor tyrosine kinases. Although several investigators have not demonstrated the presence of mutations, recent studies using more sensitive polymerase chain reaction techniques confirm the presence of multiple mutations in the *c-kit* gene in ACCs.[49] While both gain of function (activating function of the receptor) and loss of function *c-kit* mutations have been described for other malignancies, the therapeutic implications of these recently

described mutations in the therapeutic management of ACCs remains to be determined. Although the independent prognostic significance for KIT overexpression has not been evaluated, it has remained an attractive therapeutic target because of the clinical success of imatinib.

Salivary Gland Tumor Microenvironment

Neoneurogenesis

The study of perineural invasion (PNI) is an important biologic consideration for many cancers especially for MSGTs such as ACCs. The molecular determinants of this mechanism of spread have only begun to receive attention in recent years and have yielded insights to view this spread pattern as an active and reciprocal interaction between malignant cells and peripheral nerves. Observations in other cancer sites currently suggest that PNI is the result of a mutual neurotropic interaction with cancer cells characterized by the release of various paracrine growth factors.[50] As with neoangiogenesis, it is clear that the in-growth of nerve endings into a tumor may be stimulated by the tumor release of various neurotrophins such as brain-derived neurotrophic factor (BDNF),[51] nerve growth factor (NGF), and its receptor tyrosine kinase A (TrkA).[52] Neurotrophin staining has been demonstrated to be present in ACCs. NGF and TrkA have both been correlated with the presence of perineural invasion.[52] Recently, the expression of neurotrophin-3 (NT3) and its receptor TrkC/NTRK3 was demonstrated in ACCs.[53] These tumor-innervating nerve cells may release neurotransmitters that function as proliferative and pro-migratory signals for the tumor cells. Furthermore, nerve fibers are used as routes for tumor cell dissemination. For pancreatic carcinoma, detailed studies of serial sections have demonstrated that tumor cells can progress along branching nerve fascicles in a continuous fashion.[54]

Therapeutically, these insights offer the potential for the development of small molecule inhibitors such as Trk tyrosine kinase inhibitors especially for ACCs in hopes of addressing this pattern of spread.[55] Importantly, radiation has recently been shown to impair PNI not only through direct cancer cytotoxicity but also with prophylactic treatment of the nerve, disruption of paracrine signaling preventing perineural spread in an animal model system.[56] Such observations are important because they have potential radiotherapy treatment planning implications.

Hypoxia

In contrast to other solid malignancies of the head and neck, the role of tumor hypoxia has not been as extensively evaluated in MSGTs. This is an important consideration for MSGTs given their relative resistance to radiotherapy and the improved results seen with neutron radiation, which is less oxygen dependent.

Preliminary investigations using methodologies such as immunohistochemical staining for the oxygen-dependent binding of 2-nitroimidazoles suggest that salivary gland malignancies may be well-oxygenated tumors.[57] This observation would not support the hypothesis that an underlying mechanism for not only the radioresistance but also high rates of distant metastasis characterizing MSGTs is the presence of tumor hypoxia. In a study of 12 patients receiving surgery, the hypoxia-marker pimonidazole was administered preoperatively. Of the 8 patients yielding sufficient tumor specimen for analysis, immunohistochemical staining was not seen for pimonidazole and for the hypoxia inducible factor (HIF)-α or the HIF-1α regulated carbonic anhydrase (CA) IX and glucose transporters (GLUT) 1 and 3. Given that salivary gland malignancies are rare and of diverse histologies, further evaluation is needed before more generalized conclusions can be made.

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

The classification of SGTs is primarily based on morphologic patterns with two classification systems often recognized. This includes the Armed Forces Institute of Pathology (AFIP) and the World Health Organization (WHO). In 2005, the WHO further developed the classification scheme for salivary cancers originally set forth by Foote and Frazell (Box 37-1).[58] The WHO classification includes the following categories: adenomas, carcinomas, nonepithelial tumors, malignant lymphomas, secondary tumors, unclassified tumors, and tumorlike lesions. In contrast, the AFIP classification includes the following categories: benign epithelial neoplasms, malignant epithelial neoplasms, mesenchymal neoplasms, malignant lymphomas, metastatic tumors, and nonneoplastic tumorlike conditions. Speight and Barrett have reported a comprehensive summary of salivary gland histopathology.[12] Given the histologic diversity, this review will highlight histopathologies that impact the pattern of spread and its clinical manifestations.

Important prognostic factors for disease-relapse and survival are summarized in Table 37-1. Practically, histologies may be categorized as high-grade histologies with at a greater risk of nodal and distant metastases or low-grade histologies with a lower risk of nodal metastasis. The former includes high-grade MECs, high-grade adenocarcinoma–NOS, carcinoma ex-pleomorphic adenoma, salivary ductal carcinomas (SDCs), and squamous cell carcinomas. Low-grade histologies include low-grade MECs, ACCs, acinic cell carcinomas (AcCCs), and PLGAs. An intermediate group has also been described consisting of intermediate MECs.

For MECs, the histologic grading has been shown to be of prognostic significance. Several three-tiered grading schemes have been shown to be reproducible and predictive of the patient's outcome by defining low-, intermediate-, and

BOX 37-1 Classification of MSGTs

Carcinoma ex-pleomorphic adenoma
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Adenocarcinoma (NOS)
Acinic cell carcinoma
Squamous cell carcinoma
Myoepithelial carcinoma
Cystadenocarcinoma
Small cell carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial myoepithelial carcinoma
Clear cell carcinoma (NOS)
Basal cell adenocarcinoma
Salivary duct carcinoma
Carcino-sarcoma
Metastasizing pleomorphic adenoma
Large cell undifferentiated carcinoma
Lymphoepithelial carcinomas
Other rare histologic subtypes include malignant sebaceous tumors, mucinous adenocarcinoma, oncocytic carcinoma, and sialoblastoma. In addition, metastatic tumors, hematolymphoid tumors, and sarcomas may involve the salivary glands.

Classification from Barnes L, Eveson J, Reichart PA, et al, editors: World Health Organization classification of tumors. Pathology and genetics of tumors of the head and neck. Lyon, France, 2005, IARC Press.
NOS, *Not otherwise specified.*

high-grade tumors using five histopathologic features yielding a numerical score for differentiation.[59,60] High-grade MEC has a greater proportion of epidermoid cells than mucous-producing cells with a solid tumor appearance often mistaken for squamous cell carcinoma. High-grade disease also increases the risk of nodal metastasis sufficient to warrant elective management (such as a neck dissection). Despite this, the risk of nodal metastasis with low grade (LG) and especially intermediate grade (IG) can still be significant. Ozawa et al reported that, using the Goode grading schema, low- and intermediate-grade MECs had nodal metastases in 24% and 30%, respectively.[61] High grade (HG) MECs demonstrated nodal metastases in 56% of patients. In the modified Healey grading schema, lymph node involvement was 0% (LG), 22% (IG), and 72% (HG). T category also is associated with an increased risk of nodal metastasis for both major and minor salivary gland MECs.[62] T1 HG disease may be at low risk for nodal metastasis in major salivary glands, that is, anatomic sites not involving the mucosa.[62]

TABLE 37-1 Summary of Prognostic Factors

Endpoint	Prognostic Factors
Local relapse	T3 and T4 category, unresectability, and skull-base invasion
Neck metastasis	Male sex, T3 and T4 category, primary site involving the pharynx, high-grade histology especially mucoepidermoid and adenocarcinoma–NOS
Distant metastasis	Clinical perineural invasion, skull-base invasion, nodal metastasis
Survival	Stage IV, nodal metastasis

NOS, *Not otherwise specified.*

Pathways of Spread

When considering all histologies together, the risk of lymph node metastasis is increased with T3 and T4 disease, involvement of a pharyngeal site and high-grade MECs and adenocarcinoma–NOS.[63] Similar observations have been reported with T stage, anatomic site, and histology (Table 37-2).[64] For minor salivary glands, the density of the lymphatics in the anatomic site has a significant influence on the risk of nodal metastases. In general, cancers arising within the

TABLE 37-2 Incidence of Lymph Node Metastases at Initial Diagnosis by Site, Grade, T Category, Size, and Facial Nerve Paralysis

	Clinically Positive (%)	Clinical or Pathologic Positive (%)	Elective Neck Dissection, Occult Metastases (%)	Clinically Negative, Delayed Neck Metastases (%)
SITE				
Parotid	16-25	—	9	8
Submandibular/sublingual	8-44	—	21	8
Minor		—	—	10
Palate	16			
Sinuses or nasal	15			
Tongue	42			
Cheek or lips	15			
Gingiva	21			
Floor of mouth	41			
Larynx	67			
Tonsil	65			
Pharynx	0			
Adenoid cystic	14			
Mucoepidermoid	30			
Adenocarcinoma	24-28			
Malignant mixed	38			
Acinic cell	0			
Small cell	50			
GRADE				
Low	—	2	7	—
Intermediate	—	16	7	—
High	20-40	34	15-49	—
T CATEGORY				
T1-T2	—	—	7	—
T3	—	—	16	—
T4	—	—	24	—
SIZE				
<4 cm	—	—	17	—
≥4 cm	—	—	61	—
FACIAL NERVE PARALYSIS	—	>60	—	—

Data from Armstrong JG, Harrison LB, Thaler HT, et al: Indications for elective treatment of the neck in cancer of the major salivary glands. Cancer 69:615–619, 1992; Byers RM, Jesse RH, Guillamondegui ON, et al: Malignant tumors of the submaxillary gland. Am J Surg 126:458–463, 1973; and Spiro RH, Koss LG, Hajdu SI, et al: Tumors of minor salivary origin: A clinical pathologic study of 492 cases. Cancer 31:117–129, 1973.

oropharynx or nasopharynx have about a 60% incidence of lymph node metastasis compared with 5% to 10% for hard palate and paranasal sinus sites. Minor salivary gland cancers arising within the tongue and floor of mouth have an approximately 40% incidence of lymph node metastasis; those arising within the gingiva have a 20% incidence of lymph node metastasis; nasal cavity, buccal mucosa, and lip have a 15% incidence or less.

ACCs at the primary site have a predilection for PNI as a unique pattern of local disease extension. ACCs occur most commonly in the palate and frequently spread by PNI. PNI may be seen in >50% of cases and spread may occur in both directions along the nerve. Growth along the nerve has been shown to have "skip" areas of involvement and noninvolvement, so that a negative nerve margin does not guarantee a final negative margin. However, a recent study of serial sections for pancreatic carcinoma suggests that PNI may in fact be contiguous along the branching nerve fascicles and that it is the branching nature of the nerve and pathologic sampling of the sections evaluated that contributes to the uncertainty in margin assessment.[65]

The risk of distant metastases is increased with the presence of lymph node metastasis, skull-base involvement, and high-grade histology.[66] Common distant metastatic sites include lung, liver, and brain and are also associated with the histologic grade.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Most patients presenting with SGTs are asymptomatic and present typically with a solitary, painless mass. Low-grade SGTs tend to be slow-growing tumors that rarely invade local structures. Symptoms are largely related to the anatomic location from which it originates. Symptoms may include local pain with involvement of the parotid gland, and facial paralysis with involvement of cranial nerve VII. Local obstructive symptoms and possibly drainage from the ipsilateral ear can result from extension to involve the external auditory canal. Trismus may develop with involvement of the deeper parapharyngeal space or pterygoid muscles. Involvement of the skull base can result in other cranial nerve deficits, including symptoms of dysphagia. Minor salivary gland MSGTs commonly involve the palate where they are typically asymptomatic or cause a vague sensation of a mass. SGTs may also present with mass effect symptoms in the submandibular gland, maxillary sinus, oropharynx and larynx. Tumor involvement of functionally sensitive sites, like the larynx, is more likely to lead to symptoms and an earlier disease presentation.

PNI may result in symptoms of pain and numbness but more commonly presents as a painless mass with an indolent history of growth. Clinical symptoms are more likely to be associated with radiologic evidence of PNI (Figure 37-1). Extension through the skull base with intracranial growth can also occur and result in mass effect symptoms. Because ACCs commonly occur in the palate, spread along the palatine nerves through the greater and lesser palatine foramen is an important route of local spread.

Patient Evaluation

As with any patient with a suspected or documented malignancy, proper evaluation begins with a detailed history and physical (Box 37-2). Presence of a new mass in the face, neck, or mouth should be investigated for associated symptoms based on the surrounding anatomic structures that may be affected by disease extension. This should also include symptoms that may relate to perineural spread of the cancer. Physical examination should include a full oral cavity inspection

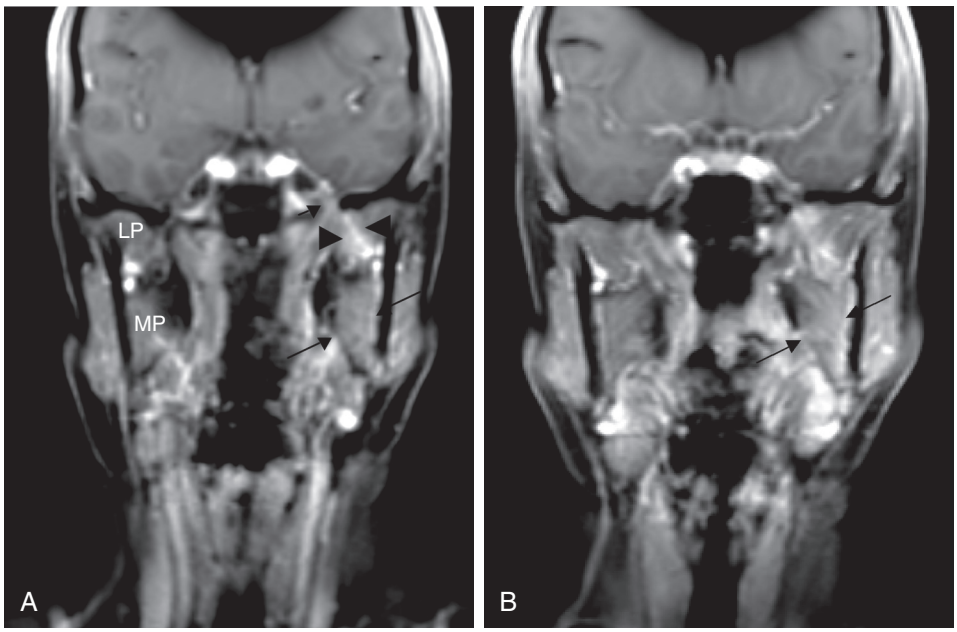

Figure 37-1 Preoperative T1 postcontrast **(A)** coronal images demonstrating an adenoid cystic carcinoma of the left submandibular gland with clinical perineural invasion (PNI) extending along the thickened mandibular branch of the cranial nerve V *(between arrow heads)* between the medial pterygoid (MP) and the lateral pterygoid (LP) muscles to involve the foramen ovale *(short arrow)*. There is also abnormal signal intensity and tissue in the region of the mandibular foramen along the left ascending ramus of the mandible and in the adjacent medial pterygoid muscle *(between long arrow heads)* **(A** and **B)**.

BOX 37-2 Diagnostic Algorithm for MSGTs

GENERAL

History
Physical examination

RADIOGRAPHIC STUDIES

Chest radiograph or CT
CT scan of the head and neck with contrast or MRI of the head and neck with contrast
PET-CT scan for high-grade aggressive histologies

LABORATORY STUDIES

Liver function tests (lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase)

CT, *Computed tomography;* MRI, *magnetic resonance imaging;* PET, *positron emission tomography.*

TABLE 37-3 Primary Tumor Staging Criteria

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumor ≥2 cm but <4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor ≥4 cm or tumor having extraparenchymal extension*
T4a	Tumor invades skin, mandible, ear canal, or facial nerve
T4b	Tumor invades base of skull or pterygoid plates or encases the carotid artery

**Extraparenchymal extension is defined as the presence of any clinical or macroscopic evidence of invasion of the adjacent soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.*

and bimanual palpation of structures that are or may be involved. Minor salivary gland tumors typically appear as a submucosal mass and commonly involve the palate. The proximity of the mass and any changes to the greater and lesser palatine foramina should be noted. Flexible fiberoptic nasopharyngolaryngoscopy should be performed to assess for the location and extent of any mucosal lesions in the pharynx or to assess the function of critical cranial nerves that may be suspected to be involved due to a mass at the skull base.

Fine needle aspiration or ultrasound-guided core needle biopsy of suspicious lesions may be useful to distinguish a malignant from benign processes. In a recent retrospective study of 879 patients, fine needle aspiration demonstrated a sensitivity of 83% and specificity of 99%, with overall accuracy of 93%.[67] However, other studies have demonstrated false negative rates as high as 33% and 43% for adenoid cystic carcinoma and low-grade mucoepidermoid carcinoma, respectively.[68] FNA is strongly preferred for the diagnosis of parotid gland masses as it is associated with minimal risk of tumor seeding along the biopsy tract or facial nerve injury. This is particularly important as benign tumors such as pleomorphic adenomas can be very difficult to control after local tumor seeding.

Both CT and MRI are necessary to assess the extent of the disease though the later may be particularly helpful. MRI provides better delineation of soft-tumor infiltration, PNI, and intracranial spread.[69] Bony destruction and regional lymph node metastases are better visualized with CT. CT with contrast may be complementary to MRI for minor SGTs.[69] Both pre- and postcontrast images are needed for optimal evaluation. Recently, MRI techniques such as diffusion-weighted MRI (DW-MRI), dynamic contrast-enhanced MRI (DCE-MRI), and MR spectroscopy (MR) have shown potential for discriminating malignant from benign SGTs.[70] Although the role of PET-CT imaging for salivary gland cancers has yet to be established, early studies have demonstrated an accuracy of more than 90% for detection of the primary tumor and an increased ability in identifying unrecognized local, nodal, and distant metastases.[71,72] The role of sentinel lymph node biopsy for parotid MSGTs remains a promising method to evaluate the risk of nodal metastases but warrants further evaluation before its routine recommendation.[73,74]

Staging of Major and Minor Salivary Gland Malignancies

Unlike minor salivary gland tumors, which are staged according to the anatomic site of origin, major salivary gland cancers have their own staging system. In general, tumors of the major salivary glands are staged according to the tumor size, and whether there is any extraparenchymal extension (Table 37-3). Extraparenchymal extension is described as either clinical or macroscopic evidence of invasion of the soft tissues. Microscopic extension does not constitute extraparenchymal extension. For parotid tumors, the prognostic significance of facial nerve involvement is also considered. Although tumor grade does affect outcome, the current AJCC seventh edition does not incorporate tumor grade as a component of the staging system.

Nodal staging and group staging for major salivary gland tumors follows other head and neck cancer sites and are described here.[75]

PRIMARY THERAPY

The treatment approach for SGTs continues to be based on a surgical resectability paradigm. The therapeutic dilemma occurs when there is significant involvement of a functional region in the head and neck involved in the speech or swallow function or if there is unresectable disease. Therapeutic advancements in recent years include the development of novel organ-preserving surgical approaches (Figures 37-2 and 37-3). Radiotherapy advancements include the development of more conformal radiotherapy techniques and the advent of particle beam therapy. Advancements in systemic agents have included the translation of molecular therapeutics, offering a potentially more favorable therapeutic ratio.

Surgery

The surgical treatment of salivary malignancies can be divided into categories based on the gland involved. The most common site for salivary malignancy is the parotid gland. The submandibular gland and the minor salivary glands have a lower absolute number of cancers; however, the risk of a neoplasm being malignant is higher in submandibular and minor salivary glands than it is in the parotid gland.[76]

Parotid Gland Malignancy

The mainstay of surgical management of parotid malignancies is the parotidectomy, and the extent of the surgery is dictated by the tumor extent. The gland itself is divided into superficial and deep lobes by the seventh cranial nerve (facial nerve), and tumors can exist and arise in either or both lobes of the gland. Although there is no embryologic boundary between the two components of the gland, most tumors arise from the superficial lobe.

eFigure 37-1 This demonstrates a modified Blair incision used for a surgical access for a left parotid salivary gland tumor. The incision includes a preauricular incision that transitions under the ear into a postauricular and upper neck incision.

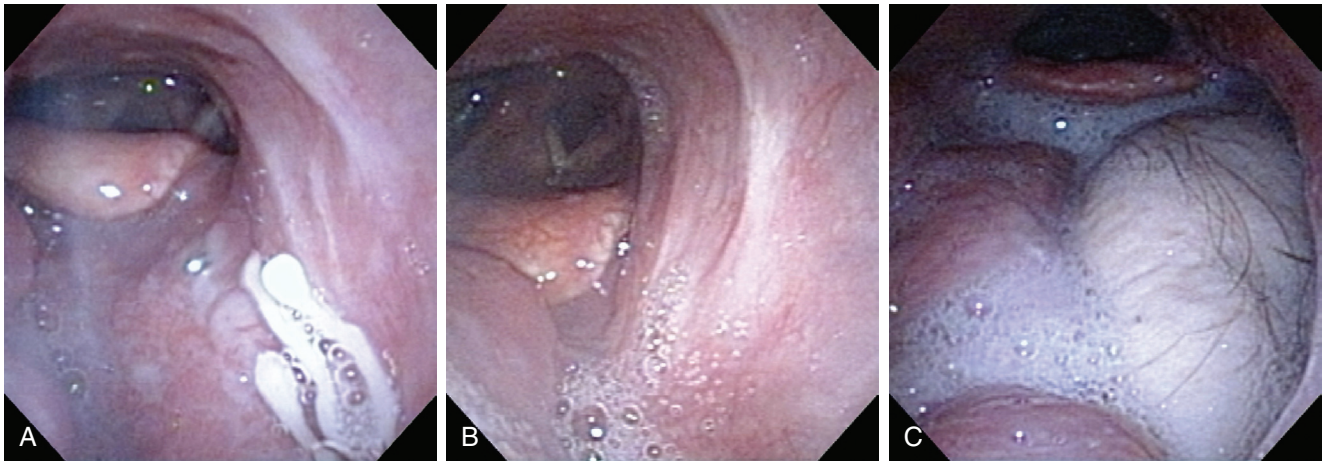

Figure 37-2 Transoral robotic resection (TORS) for an adenoid cystic carcinoma of the base of tongue. The patient was swallowing a full oral diet in the early postoperative setting **(A)** and did not require a mandibulotomy. Very good swallow function can be seen with no pooling of secretions in the vallecula with further wound healing **(B)**. In contrast, a second patient was treated with a traditional mandibulotomy and a radial forearm free-flap reconstruction in the left base of tongue demonstrating more limited swallow function with pooling of secretions in the vallecula **(C)**.

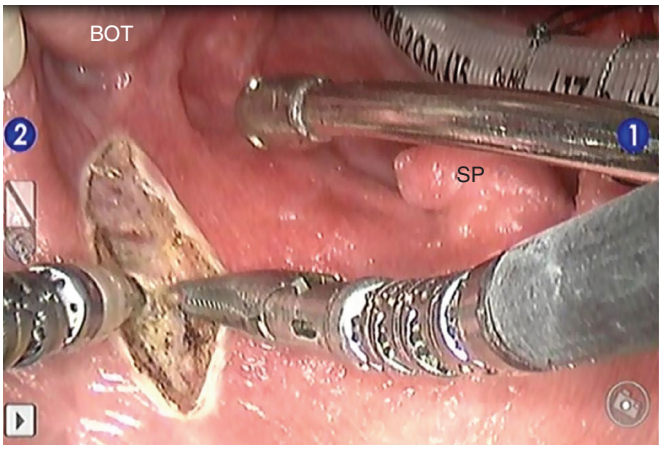

Figure 37-3 Transoral robotic surgery (TORS) of a parapharyngeal space pleomorphic adenoma. This demonstrates the robotic wristed instruments performing the early incision and dissection through the left lateral oropharyngeal wall adjacent to the base of tongue (*BOT*) and soft palate (*SP*). Excellent visualization can be demonstrated through the magnified optics.

Surgery involves an incision in the preauricular crease extending postauricularly and then into the upper neck (eFigure 37-1). This incision, known as the modified Blair incision, gives access to the facial nerve as it comes out of the stylomastoid foramen. A facelift incision is an alternative for select patients. The goal of the surgery is to identify and protect the facial nerve, trace it out along its main branches, and then manage the tumor once its relationship to the nerve has been clarified. In cases where the nerve is compromised by the tumor, or in which the tumor abuts the stylomastoid foramen, it may be necessary to identify the nerve before it comes out of the mastoid bone. This can be accomplished by drilling out the mastoid bone and identifying the nerve before it comes out of the foramen.

Once the appropriate branches of the nerve have been identified, the tumor is removed. Great care is taken to avoid entry into the tumor, and attempts are made to avoid residual positive margins as this is a known poor prognostic indicator.[77,78] Because most tumors involve only the superficial lobe of the parotid, dissecting the tumor carefully off the facial nerve is appropriate surgical care. Tumors that involve the deep lobe of the parotid gland or that involve the parapharyngeal space just medial to the parotid gland may require extended procedures to perform complete resections. These procedures are often possible through the same parotid incision but occasionally require extension of the neck incision or a mandibulotomy.[79] Excision of soft tissue, skin, muscle, and neurovascular structures in the region is appropriate if they are involved with tumor.

All attempts should be made to preserve the facial nerve during parotid surgery. Complete paralysis of the facial nerve will not only cause a significant cosmetic deficit but has the potential to affect many aspects of a patient's outcome. Corneal abrasion, nasal congestion, poor oral competence, and slurred speech are some of the common complaints after this event. Most surgeons would agree that tumor proximity to the nerve is not adequate justification for its sacrifice. However, there are circumstances under which most surgeons would agree that sacrifice of all or a part of the nerve is reasonable. Complete or partial paralysis of the face preoperatively often heralds an intraoperative finding of direct invasion of the facial nerve by tumor. If the tumor extends into the nerve, or grossly encases the nerve, then sacrifice of the nerve is warranted.

Submandibular Gland Malignancy

Although the absolute number of malignancies of the submandibular gland is far less than the parotid gland, the chance of a lesion being malignant is much higher, nearing 50%.[80] For this reason, a high level of vigilance must be in place when managing masses in the submandibular region. Most commonly, patients present with a painless mass in the region. Less commonly, painful masses or neck adenopathy may occur. Any of these presentations warrants a workup of the area, including possibly a CT or MRI and a fine-needle aspiration biopsy.

As with parotid cancers, SGT of the submandibular gland is a surgical disease. Definitive treatment often includes a combination of therapies but almost always begins with surgical excision. The surgical approach should include, at the minimum, a complete submandibular gland excision with clear margins. There is no role for enucleation of the tumor because this has been clearly associated with a higher rate of local recurrence.[81] In patients who have undergone subtotal

surgery, only to be diagnosed with cancer postoperatively, imaging studies should be performed and reoperation performed if there is residual gross tumor to obtain negative margins before considering further therapy.[54]

Sublingual and Minor Salivary Malignancy

Malignancies of the sublingual gland and minor salivary glands are rare. Minor salivary glands are present throughout the upper aerodigestive tract, and SGTs can occur at any of the sites. The oral cavity and oropharynx are the most common sites of disease, but the nasal cavity, paranasal sinuses, hypopharynx, larynx, nasopharynx, and parapharyngeal space (PPS) are all at risk for these cancers.[82]

As is the case with other salivary cancers, surgical therapy with negative margins is the mainstay of therapy. Depending on the site of the cancer, this may include a variety of surgical approaches. The challenge for these MSGTs is the functional impact that surgery can have on the speech-and-swallow function. Unlike the more common squamous carcinomas of the head and neck, the role of nonsurgical therapy has not been well established.

The role of organ-preserving surgical approaches that do not use transcervical exposure techniques are valuable in limiting the swallowing complications resulting from surgery. These include various transoral approaches including the TORS approach (Figures 37-2 and 37-3).[83] TORS has several advantages including the improved visualization of the tumor resection in three dimensions avoiding sight-line limitations with magnified optics. Its application has included function preserving resection of SGTs in the base of tongue[84,85] and in the PPS (Figure 37-3).[86]

Management of the Neck

Patients who present with clinically palpable or radiologically evident disease in the neck lymph nodes require management of this disease. This generally involves planned neck dissection at the time of the primary surgery with or without radiation.[87] What remains more controversial is the role of treatment in patients with no clinicoradiologic evidence of disease in the neck.

Some studies have demonstrated that all high-grade malignancies, (regardless of histology) would benefit from elective management of the neck.[88] Other studies have suggested elective management of the neck based on histologic type or size. This includes elective neck surgery for all squamous cell carcinomas, adenocarcinomas, high-grade MECs, undifferentiated carcinomas, and all T2 or higher tumors.[62,89,90] Still, other groups have suggested either nodal sampling of the upper neck lymph nodes at the time of the primary surgery, or including the neck in the primary treatment field for certain cancers.[91,92] What does appear clear is that high-grade, high-stage cancers benefit from aggressive multimodality therapy, including treatment of the primary site and the lymphatic drainage pathway for the tumors.

Radiotherapy

Postoperative Radiotherapy

At present no randomized studies have been conducted to establish the value of postoperative radiotherapy. Tables 37-4, 37-5, and 37-6 summarize the treatment results from modern series comparing surgery with surgery and postoperative, adjuvant radiation therapy for malignant major salivary gland, submandibular gland, and minor salivary gland cancers, respectively. These demonstrate that the addition of postoperative radiation therapy, when indicated, appears to be associated with improved local control rates and survival in patients with malignant salivary gland cancers. Frequent pathologic indications reported for the use of postoperative radiotherapy include the presence of a positive or close surgical margin (not well defined in the scientific literature), PNI, high-grade histology, extraglandular extension, bone invasion, tumor size, T category, and the presence of nodal metastases (Box 37-3). Because these pathologic indications have not been prospectively evaluated, the absolute risk of relapse and the incremental risk reduction with adjuvant radiotherapy cannot be determined. Recently, a postoperative nomogram predicting for survival in the individual patient with MSGTs of the major glands was developed further confirming the importance of these pathologic risk factors.[93]

TABLE 37-4 Results of Surgery Alone and Combined Surgery and Postoperative External Irradiation for MSGTs

Institution (Reference)	No. of Patients	Median Follow-up (yrs)	Prognostic Factors	Disease Outcomes, 5-yr (%)			
				Local Control		Survival	
				S	S + RT	S	S + RT
MSKCC[73]	92	S: 10.5 S + RT: 5.8	Stage I/II	79	91	96	82 (det.)
			Stage III/IV	17	51 $p = 0.14$	9.5	51 (det.) $p = 0.015$
			Positive Nodes	40 (LRC)	69 $p = 0.05$	19	49 (det.) $p = 0.015$
			High-grade	44	63	28	57 (det.)
Johns Hopkins[74]	87	—	All patients	58	92 $p = 0.001$	59	75 (det.) $p = 0.01$
MDACC[71]	155	7.5	All patients	58	86	50-56*	66-72*
PMH[75]	271	10	All patients	—	—	60	75 (CSS) $p = 0.039$
						29	69 (RFS) $p = 0.0005$
MGH[76]	62	5.5	All patients	—	95	—	77 (DFS)

CSS, *Cause-specific survival;* det, *determinate;* DFS, *disease-free survival;* LRC, *locoregional control;* MDACC, *M. D. Anderson Cancer Center;* MGH, *Massachusetts General Hospital;* MSKCC, *Memorial Sloan Kettering Cancer Center;* PMH, *Princess Margaret Hospital;* RFS, *relapse-free survival;* S, *surgery alone;* S + RT, *surgery and postoperative radiation therapy;* yr, *year.*

**Survival varies by presence of high-grade or perineural invasion*

TABLE 37-5 Results of Surgery and Surgery with Postoperative, Adjuvant Radiation Therapy for Malignant Tumors of the Submandibular Gland

Institution (Reference)	No. of Pts	Minimum Follow-up	Prognostic Factor	Local Control (%)		Survival, 5-yr (%)	
				S	S + RT	S	S + RT
PMH[77]	91	—	All patients	30 (5 yr LRC)	69 $p < 0.05$	60 27	65 (CSS) 52 (RFS) $p < 0.1$
MDACC[78]	86	24 mo	All patients	— Crude	—	71	60
			Soft tissue extension	48	85 $p < 0.034$	—	—
			Perineural invasion	62	92	—	—
			Adenoid cystic CA*	29	100 $p < 0.01$	—	—

CSS, *Cause-specific survival;* det, *determinate;* LRC, *locoregional control;* MDACC, *M. D. Anderson Cancer Center;* PMH, *Princess Margaret Hospital;* RFS, *relapse-free survival;* S, *surgery alone;* S + RT, *surgery and postoperative radiation therapy;* yr, *year.*
**With soft tissue and perineural invasion*

TABLE 37-6 Results of Surgery and Surgery with Postoperative, Adjuvant Radiation Therapy for Malignant Minor Salivary Gland Tumors

Institution (Reference)	No. of Patients	Median Follow-up	Treatment	Local Control (%)	Survival (5-yr) (%)
MSKCC[79]	434	—	S	53 (crude)	42 44.5 det
UF[80]	87	≥2 yr	S + RT	87.5 (crude)	63-100 CSS 56-100 OS 50-93 RFS
			RT	51.3 (crude)	38-90 CSS 39-82 OS 25-73 RFS
MDACC[81]	160	110 mo	S + RT	96 (5-yr)	81
Stanford[82]	54	7.8 yr	S + RT	88 (10-yr)	81 10-yr CSS 63 10-yr OS

CSS, *Cause-specific survival;* det, *determinate;* MDACC, *M. D. Anderson Cancer Center;* MSKCC, *Memorial Sloan Kettering Cancer Center;* OS, *overall survival;* RFS, *relapse-free survival;* RT, *radiation therapy;* S, *surgery;* UF, *University of Florida.*

BOX 37-3 Indications for Postoperative, Adjuvant Radiation Therapy for MSGTs

- Close or microscopically positive surgical margins or gross residual disease
- High-grade cancer
- Involvement of skin, bone, nerve (gross invasion or extensive perineural involvement), and tumor extension beyond the capsule of the gland with periglandular and soft-tissue invasion
- Lymph node metastases
- Large tumors (T3 or T4 disease) requiring radical resection
- Tumor spillage during operation
- Recurrent cancer (including benign histologies such as recurrent pleomorphic adenoma)

In general, the use of postoperative radiotherapy doses typically to 60 Gy appear to be sufficient for MSGTs with PNI of unnamed nerves.[64] In a retrospective review of 140 patients, skull-base relapses may be reduced from 15% to 5% with elective skull-base irradiation especially for T4 disease.[94] Patients with skull-base relapses had a poorer survival when compared to those who did not experience a relapse. For MSGTs with PNI of a major named nerve, elective skull-base irradiation has also been shown to be effective.[95]

Doses between 50 Gy and 60 Gy have also been used for elective irradiation of the neck with relapses less than 5%.[96] Terhaard et al observed a trend to a lower rate of neck control with elective irradiation <46 Gy compared ≥46 Gy ($p = 0.07$).[64] Again, patients with neck relapses have been associated with a poorer survival compared to those patients without neck relapses. When a higher burden of microscopic disease is suspected based on the presence of a positive margin or PNI of a major named nerve, doses <56 Gy are insufficient and doses >60 Gy may be associated with improved local control rates.[97]

With surgery and postoperative radiotherapy to the doses described, long-term locoregional control rates on the order of 80% to 90% may be expected for patients with T1-3 with N0-1 disease. With T4 or multiple nodes, locoregional control rates are significantly lower on the order of 60% to 70%.

Definitive Radiotherapy

Definitive radiotherapy is used primarily for patients with locally unresectable SGTs and will be discussed in the next section.

LOCALLY ADVANCED DISEASE AND PALLIATION

Definitive Radiotherapy: Conventional Fractionation

With locally unresectable salivary gland malignancies, the use of definitive radiotherapy on the order of 70 Gy with

conventionally fractionated schedules typically results in locoregional control rates on the order of ≤20% to 30%.[86-88] These results are also limited by the inherent biases seen with retrospective institutional reviews but are significant in their independent verification of a consistently poor outcome for unresectable salivary gland malignancies when treated with photon radiotherapy alone. These results are also consistent with the standard arm (photon) in a randomized trial of neutron versus photon radiotherapy for unresectable salivary gland malignancies.[98]

Altered Fractionation

Although RTOG 9003 demonstrated that altered fractionation improves locoregional control in other sites of the head and neck,[99] its role in salivary gland tumors is unclear. Wang and Goodman reported results using high-dose, accelerated, hyperfractionated photon beam therapy in patients with inoperable and unresectable major and minor salivary gland cancers.[100] All patients were treated with 1.6 Gy per fraction, twice a day, combined with various boost techniques to obtain a total dose of 65 Gy to 70 Gy. Local control and survival rates were promising, with a 5-year 100% local control and 65% survival rate for parotid gland lesions, and a 5-year 78% local control and 93% survival rate for minor salivary gland lesions. Late complications were minimal. However, the follow-up was relatively short, and thus far, no update has been reported.

Although this suggests a potential role for altered fractionation, it should be regarded as investigational until further data adequately addresses this issue.

Neutrons and Heavy Charged Particle Therapy

High linear energy transfer (LET) radiation from neutrons and heavy charged particles causes direct damage to DNA and is characterized by a reduced oxygen enhancement factor (OER). Compared to low LET radiation from standard photon therapy, damage from high LET radiation is less repairable, and less dependent on cell cycle state. These characteristics make high LET potentially suitable for MSGTs, which are thought to be radioresistant due to a low growth fraction and a long doubling time.

The only randomized trial comparing neutron radiation to conventional photon irradiation was conducted by the Radiation Therapy Oncology Group (RTOG) and the Medical Research Council (MRC) for patients with locally unresectable primary and recurrent MSGTs.[98] The study closed early as a result of ethical concerns because an interim analysis performed at 2 years of 25 patients demonstrated significantly better local control with neutron compared with photon irradiation (67 versus 17%, $p < 0.005$) and a trend toward improved survival (62 versus 25%, $p = 0.1$). The local control rate of 67% was consistent with prior single-institution reports associated with the use of fast neutrons.[101-103] A median survival of 2.97 years with neutrons versus 1.23 years with photons was initially reported. With longer follow-up, the overall survival curves showed no difference. The majority of failures in the neutron arm were systemic. In contrast, the major relapse pattern in the photon arm was predominantly locoregional failures. The incidence of severe or life-threatening toxicity was greater in patients treated with neutrons, with 9 patients treated with neutrons having at least one "severe or greater" complication, compared to 4 patients in the photon arm. This finding of a relatively high rate of severe complications from neutrons has been observed in another comparative series.[104]

Overall, the lack of survival difference from the randomized trial, and the high rate of severe complications coupled with the lack of institutions with available treatment capabilities, limited the broad use of fast neutron therapy. However, mature uncontrolled, single-institution studies continue to demonstrate impressive results, with lower rates of toxicity. Douglas et al published a retrospective study of 148 patients with major salivary gland tumors treated at the University of Washington with a 5-year actuarial locoregional control rate of 100% for tumors <4 cm in size, and only a 6% grade 3 or 4 complication rate.[105] An updated larger series of 279 patients from the same institution demonstrated a 6-year actuarial locoregional control rate of 59% with a grade 3 or 4 toxicity rate of 10%.[66] Neutrons have also been used in the postoperative setting for microscopic residual disease with a 100% 5-year actuarial locoregional control rate reported.[106]

In part, the increased complication rates are the result of the use of neutrons at the skull base and the adjacent CNS. The sensitivity of the CNS structures to high LET radiation often precludes safe delivery of therapeutic doses of high LET radiation to tumors with skull-base involvement. Despite this, it is interesting to observe that neutron radiation does not appear to be associated with an increased risk of facial nerve palsy as a treatment complication.[102,107] Complicating the risk of CNS injury is the recognition that skull-base involvement is associated with a poorer prognosis, local control, and survival in a group of 159 patients with unresectable ACCs.[106]

To address this technical limitation of neutrons, investigators from the University of Washington have been investigating the role of boosting the superior portion of the tumor with stereotactic radiosurgery, after reduced dose neutron beam radiotherapy, in patients with skull-base disease. In 34 patients with skull-base disease treated with a Gamma Knife boost (for details, see discussion), the 40-month actuarial local control was 82%, compared to a historical control rate of 39% in patients with skull-base disease treated with neutrons alone ($p = 0.04$).[108] Heavy charged particle radiation may also hold promise because it combines the biologic qualities of high LET with rapid Bragg Peak dose fall-off. Limited data with carbon ion radiation suggests similar tumor control as neutron beam, with less late effects.[109]

In summary, for patients with locally advanced, unresectable disease of the salivary glands, neutrons offer superior locoregional control compared to standard photon radiation, but with a potential increased risk of severe toxicity. For postoperative radiation, it is not clear that the therapeutic ratio is improved upon given the potential for increased late normal tissue toxicities. Techniques to improve the therapeutic ratio, such as those seen with stereotactic boost or with heavy charged particle radiation therapy, are warranted and are the subject of ongoing investigations.

Stereotactic Radiosurgery

Whether or not the use of hypofractionated doses of radiotherapy in the form of stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (SRT) can overcome the radioresistance associated with conventionally fractionated photon therapy has not been clearly established. There have been two main indications that are relevant for MSGTs and have been the subject of clinical investigations.

The first is the study of SRS at the skull base as a treatment strategy to more safely escalate the effective biologic radiotherapy dose delivered. This largely reflects the experience reported by the University of Washington as described previously. Douglas et al used a Gamma Knife radiosurgery boost as a strategy to reduce the relative biologic neutron dose to the skull base and minimize the risk of CNS injury while improving on the local control rates.[108] The median prescribed Gamma Knife dose was 12 Gy to the 50% isodose line resulting in a median neutron dose of 19.2 nGy to the isocenter. The

median number of isocenters was 17. The median target volume treated was 12.4 cm^3 (range, 1.9 cm^3 to 28.9 cm^3) with a median total volume treated of 18.3 cm^3 (range, 5.9 cm^3 to 53.9 cm^3). This resulted in a median dose of 11.98 nGy to the adjacent tip of the temporal lobe. In total, 34 patients were treated. With a median follow up of 20.5 months, the actuarial 24-month and 40-month local control rates were 82% and 82% compared to 81% and 39% in historical patients not receiving SRS boost. A total of four failures in the SRS group were described with two in-field and two out-of-field relapses. Noteworthy complications included three cases of radionecrosis with only one third of cases with symptomatic headaches responsive to steroids. Comparable risk of brain necrosis (i.e., <10%) has recently been reported by Owen et al in a retrospective analysis of 184 patients with head and neck cancers treated with SRS alone or in combination with external beam radiotherapy.[110]

The other major indication for SRS or SRT has been for *palliative indications*. The rationale for the use of an SRT approach is twofold. First, the stereotactic approach affords greater confidence in the accuracy of the target lesion to be irradiated allowing a smaller margin of uncertainty and thus reducing the volume of normal tissues that receive both unnecessary entry and exit radiation. The second is the potential greater therapeutic benefit that *may* be achieved with higher doses delivered over a single fraction or just a few fractions. To date, the reported experiences are limited and largely amount to small case reports and heterogeneous cohorts for the use of SRS or SRT for head and neck cancers including some recurrent salivary gland malignancies.[111-113] These observations limit the ability to draw any definitive generalized conclusions about the risks and benefits of SRS and SRT at this time including the optimal prescribed dose. The range in prescribed dose includes single fractions of 11 Gy to 18 Gy and hypofractionated schedules including 30 Gy in 6 fractions. In the only series reporting sole on MSGTs, effective palliation of pain was achieved with durable responses including freedom from local tumor progression ranging from 10 months to 35 months.[113] In general, the major serious but infrequent risk associated with this palliative treatment approach includes the risk of optic, facial, and trigeminal nerve injury. At this time, the use of SRS or SRT for MSGTs should be limited to treatment on a clinical protocol or treatment at institutions with a broad stereotactic experience at the skull base for other malignancies where the risks are well defined.

Proton Radiotherapy

There is limited published experience with the use of proton therapy for salivary gland tumors, although the sharp dose fall-off at depths beyond the Bragg peak may potentially allow for safer dose escalation. The Paul Scherrer Institute in Switzerland published a comparative dosimetry study of intensity-modulated photon and proton therapy in the treatment of head and neck tumors.[114] The primary endpoint was the risk of secondary cancers based on the risk estimated using the organ equivalent dose model. For proton plans, both the scatter and the neutron dose contributions were accounted for. Their modeling demonstrated that the risk of secondary malignancies may be reduced with the use of intensity-modulated proton therapy (IMPT) compared to intensity-modulated radiation therapy (IMRT) with photons. The risk was particularly reduced when the number of proton fields was limited.

Pommier et al at the Francis H. Burr Proton Center in Boston have treated 23 patients with ACCs of the skull base with a combination of proton and photon radiotherapy.[115] Only 2 of 23 patients had a complete gross resection but with residual positive margins. The mean total dose to the primary tumor was 75.9 cobalt-gray equivalent (CGE). With a median follow-up of 64 months, the 5-year actuarial local control rate was 93%. The 5-year disease-free survival (DFS) and OS rates were 56% and 77%, respectively. Multivariate analysis demonstrated that tumor involvement of the sphenoid sinus and the clivus and the presence of vision change at presentation were significant adverse risk factors for overall survival. No grade-4 or grade-5 ocular toxicities were reported. Significant grade-3 neurologic toxicities were observed in 10 patients and 2 patients developed grade-5 toxicity. These findings suggest that radiotherapy dose-escalation with protons may result in improved local control rates beyond the historic 20% to 30% local control rates with photons.[116] Recently, with a median follow-up of 25 months (7 months to 54 months), Linton et al reported similar findings using passive scatter proton radiotherapy in 26 patients with ACCs treated to a median dose of 72 Gy (CGE) with or without surgery.[117] The 2-year local control rate was 95% for previously untreated patients with two grade-3, one grade-4, and one grade-5 toxicity observed. The single case of grade-5 toxicity was observed in a patient who previously was irradiated with IMRT and SRS boost for a nasopharyngeal ACC with the prior treatment plan not archived digitally limiting reconstruction and proton planning considerations.

Chemoradiation

The data for concurrent chemoradiation (chemoRT) is scant (typically case reports and small series) and the subject of an extensive review by the French Rare Head and Neck Cancer Network. These investigators concluded that cisplatin-based chemoRT chemoradiation was the most common regimen typically used for adverse pathologic high-risk situations with low evidence to support its efficacy.[118] In the adjuvant context, a single case-control study compared 12 patients with a variety of histologies treated with chemoRT to 12 matched controls treated with radiation alone.[119] This analysis showed a significant survival and local control advantage with chemoRT, with a 3-year OS and DFS survival of 83% and 77% compared to 44% and 52% for radiotherapy alone. However, in addition to the small number of patients analyzed, several other key caveats must be noted. Performance status and comorbidity of the two groups were not reported, IMRT was used more frequently in the chemoradiation group, and a variety of histologies were treated. Thus, adjuvant chemoRT must be considered experimental. However, in the absence of level I data to support its efficacy, it is commonly used for patients with aggressive disease, positive margins, extracapsular extension, and other factors associated with a high risk of recurrence. This practice is largely based on the extrapolated experience in patients with head and neck squamous cell carcinoma (HNSCC). Hence, in the absence of established efficacy, its use should be limited to the use of chemotherapy agents in dose ranges and with schedules of administration where the toxicity spectrum and risks have been well established if it is being considered.

Much of the available literature on chemoRT for SGTs involves small single-institution series. One case report describes definitive concurrent chemoRT with intraarterial cisplatin and docetaxel in 2 patients.[120] A retrospective study of 13 patients treated with cisplatin chemoRT demonstrated complete response to initial therapy in all patients.[121] A single patient developed delayed local failure at 39 months (but achieved successful surgical salvage) and a second patient developed distant metastases; 5-year OS was 83%. Although also experimental, definitive chemoradiation is reasonable for patients who are not candidates for surgery, either based on

anatomic constraints or medical inoperability. Finally, a case series of 14 patients with recurrent MSGTs reported a 3-year locoregional control rate of 51.6% and a 3-year actuarial survival of 35.7% with 5-fluorouracil and hydroxyurea chemoRT following a median radiation treatment interval of 48 months.[122]

Palliation: Role of Chemotherapy

Data on the efficacy of chemotherapy for salivary gland malignancies is limited to case reports, retrospective reviews, and small Phase II studies.

Once metastatic, salivary gland malignancies are not curable. Nonetheless, their course can frequently be indolent, especially for ACC with metastatic disease limited to the lung. Median survival with metastatic disease with ACC is approximately 3 years[123] with some patients living substantially longer. Results with systemic agents, both chemotherapeutic and molecular-targeted agents, have been disappointing. Therefore, careful consideration must be given to administration of supportive care, with systemic therapy reserved for rapid or symptomatic progression.

Chemotherapeutic agents are of limited efficacy in salivary gland malignancies, with particularly poor responses in adenoid cystic histology. A variety of single-agent chemotherapies have been studied in the Phase II setting. Limited responses have been observed with cisplatin, vinorelbine, mitoxantrone, epirubicin, methotrexate, and paclitaxel. For example, ECOG1394 evaluated paclitaxel, given at 200 mg/m^2 every 3 weeks.[124] No responses were seen in 14 patients with ACC, whereas a 26% response rate was seen in patients with mucoepidermoid or adenocarcinoma histologies.

The best studied combination regimen is cyclophosphamide, doxorubicin and cisplatin (CAP).[125] Although CAP has demonstrated good response rates across histologies, there is no clear evidence for superior efficacy as compared to single-agent chemotherapy. Only a single randomized study compared single agent therapy to a platinum-based doublet. Airoldi et al compared vinorelbine (given at 30 mg/m^2 on days 1 and 8 every 3 weeks) to cisplatin plus vinorelbine (with cisplatin administered at 80 mg/m^2 on day 1 and vinorelbine at 25 mg/m^2 on days 1 and 8).[126] This study showed a doubling of response rate from 20% to 44% and a strong trend toward improved median survival (8.5 months versus 11 months, $p = 0.058$) with use of the doublet. Of particular note was the 44.4% response rate in the typically chemoresistant ACC. Many oncologists consider cisplatin plus vinorelbine as the standard of care when cytotoxic chemotherapy is chosen, with paclitaxel as a reasonable consideration in non-ACC disease.

Malignant salivary gland tumors commonly over express a variety of molecular targets. Given the success of targeted agents in other cancers overexpressing these markers[127-130] and the relative tolerability of the agents targeting these markers, investigators have sought to apply these agents to the MSGTs (see eTable 37-1).

Given the paucity of data, no regimen may be considered a standard of care for any histology of MSGT. Thus, when therapy is required, the authors consider a clinical trial to be the preferred option. When no Phase II trial is available, Phase I studies with agents directed at relevant targets, with low expected toxicity should be considered. In the absence of available trials and the need for therapy, it is reasonable to evaluate for molecular markers of interest (ER, EGFR, HER2, AR, and c-Kit) and consider treatment targeting any biomarker that is present. Although response rates are low for targeted agents, multiple studies suggest the possibility of prolonged stable disease. For rapidly progressive disease, especially in the patient with good functional status, good renal function, and good bone marrow function, the combination of cisplatin plus vinorelbine may be considered. Additional clinical trials are desperately needed, but the rarity of these tumors will likely require novel cooperative strategies to promote successful accrual. Ideally, studies of targeted agents aimed at promoting stable disease would be tested using creative study designs, such as a randomized discontinuation design, but the rarity of these tumors may make such definitive trials impossible.

TECHNIQUES OF IRRADIATION

Target Volume Delineation

Parotid Gland

Target volumes include the location of the primary tumor or the surgical bed for SGTs meeting the indications for radiation. The ipsilateral neck should be included in the setting of cervical lymph node metastases or high-grade primary tumor histology (especially for MEC and adenocarcinoma–NOS). It is unclear whether a primary tumor recurrence increases the risk of cervical nodal metastases. Involvement of the facial nerve requires coverage of the course of the nerve, via the facial canal, to the base of skull through the stylomastoid foramen. This should be a consideration for ACC. A boost should be considered to areas at high risk of incomplete resection.

Anatomic landmarks for the parotid should include the zygoma superiorly, styloid process medially, the soft tissues of the neck laterally, including possibly the skin and the surgical scar if there was evidence of tumor spillage or direct tumor infiltration, the masseter muscle anteriorly, the hyoid bone inferiorly, and the mastoid bone posteriorly. Careful review of preoperative imaging and the intraoperative findings are also important to consider in delineating the parotid surgical bed as is noting the location of the contralateral parotid gland.

For the cervical neck, anatomic landmarks for the N0 neck have been referenced. Briefly, cervical levels II to IV are located along the course of the sternocleidomastoid anterolaterally and the scalenus muscles posteromedially. The nodal levels at risk typically include levels II to IV but may require consideration of level V in the setting of known cervical nodal metastases or evidence of metastases to level V.

Submandibular Gland

The primary target volume includes the location of the primary tumor or surgical bed for SGTs meeting indications for radiotherapy. A boost is given to areas of unresected disease. When PNI is present, but limited to small, unnamed nerves, the target volumes are enlarged in the area of the postoperative bed, but the nerve pathways are not treated comprehensively. If named nerves are involved, such as the lingual or hypoglossal nerves, their course should be treated to the base of skull. This involves delineation of the course of the mandibular (V3) branch of cranial nerve V to the foramen ovale. The V3 branch runs from the submandibular space extending into the parapharyngeal and masseter space medial to the course of the medial pterygoid muscle to the foramen ovale (Figure 37-4). Review of preoperative imaging and intraoperative and pathologic findings are imperative in treatment planning.

Indications for treatment of the elective neck are similar to those described previously in the section for the parotid gland. However, because of the proximity of the submandibular gland to the midline of the neck, irradiation of the adjacent and contralateral upper cervical nodal regions should be a consideration when treatment of the ipsilateral neck is indicated.

eTABLE 37-1 Summary Table of Clinical Trials of Molecular Targeted Agents for MSGTs

Agent	Molecular Target	Response Rate for Adenoid Cystic Carcinoma (%)	Response Rate for Nonadenoid Cystic (%)
Imatinib mesylate	c-kit, Bcr-Abl, PDGF-R	0/16[131] 0/14[132] 0/5*[133]	N/A N/A
Trastuzumab	HER2	0/2[39,134]	1/11†
Lapatinib	HER2, EGFR	0/19[35]	0/17
Gefitinib	EGFR	0/19[135]	0/2
Cetuximab	EGFR	0/19[136]	0/9
Bortezomib	26S proteosome NF-kappa-B (indirectly)	0/23[137]	N/A

N/A, *Not applicable.*

**Study closed early because three fifths of patients had rapidly progressive disease.*

†*One of three patients with mucoepidermoid histology had a durable response out to 45 months of follow-up.*

As c-kit is expressed by the majority of ACC, imatinib mesylate, an inhibitor of the c-kit, Bcr-Abl and PDGF-R tyrosine kinases was studied. Although responses were noted in three case reports[138,139] there were no responses in 30 patients with ACC treated in two Phase II studies.[131,132] KIT was assessed only by immunohistochemistry with no mutational analysis performed. Stable disease was common in these studies, including stable disease longer than 6 months. However, the lack of a control group and the indolent behavior of many ACC leave unclear whether this stability was the result of the activity of imatinib or the underlying indolent nature of the tumors. Pending more effective therapies, many clinicians still consider imatinib for c-kit expressing ACC because of its lack of toxicity relative to cytotoxic therapies. An ongoing Phase II study is evaluating the more potent c-kit inhibitor dasatinib.[123,140]

The anti-HER2 antibody trastuzumab and the tyrosine kinase inhibitor lapatinib have demonstrated efficacy in HER-2 overexpressing breast cancer. All histologies of MSGTs have been reported to overexpress HER2 at rates from 24% to 56%, depending on the histology, leading to a Phase II study of trastuzumab with planned accrual of 50 patients.[119,141] A total of 137 tumors were screened for HER2/neu with 17% found to be overexpressed at 2+ or 3+.[39] This result was substantially lower than previously reported in smaller series and the study was closed early with only 14 patients treated. A single patient with MEC histology achieved a long-lasting partial response (PR).[134] It is relevant to note for future investigations of HER2 as a therapeutic target, that HER2 overexpression in ACC was rare at 4%, but common in secretory duct cancers, with 21% in MEC, 83% in salivary duct, and 60% in squamous histologies.[39] A SWOG trial of trastuzumab also closed early as a result of poor accrual. In this trial, 3 patients were enrolled and treated; 1 had stable disease for almost a year and the other progressed on therapy.[129,142]

Lapatinib is an oral tyrosine kinase inhibitor (TKI) that targets both HER2 and EGFR. A Phase II study of this agent enrolled 29 patients with ACC and 28 patients with non-ACC MSGT.[35] In total, 88% of patients with ACC and 97% of patients with non-ACC expressed EGFR or erbB2. There were no responses in either group, but 47% of patients with ACC and 24% of patients with non-ACC had stable disease (SD) lasting at least 6 months. Although the indolent nature of the disease itself likely contributed to some of this stability, biologic activity of lapatinib was likely greater than that represented by the response rate. To meet response criteria, a tumor must shrink by 30%. Many patients classified as having SD experienced reductions in tumor volumes that failed to meet this threshold but nonetheless are suggestive of activity. Further, 36% of the patients with SD for more than 6 months were progressing before starting therapy, suggesting that although the therapy may not have been sufficiently active to shrink the cancer, it could at least stop its growth.

Similar results were found with the TKI gefitinib, which targets primarily EGFR. At the time of presentation, 21 patients were assessable for response, with 0 of 21 responses.[135] Thirteen of 14 patients with SD had ACC, but the median duration of SD was only 13 weeks, again raising concerns that the SD was secondary to the indolent nature of the cancer, rather than efficacy of therapy. Similarly, a Phase II study of cetuximab failed to achieve any responses. However, 20 of 23 (87%) of patients with ACC achieved SD, with 12 of these 23 (52%) achieving stability lasting at least 6 months.[136] Of note, 11 patients with ACC were actively progressing at the time of study entry; all of these patients achieved SD for at least 6 months.

Bortezomib inhibits the 26S proteosome, indirectly inhibiting NF-KB activity. A Phase II study treated 25 patients with ACC.[137] Again, no responses were seen. Patients with progressive disease were treated with the combination of bortezomib and liposomal doxorubicin based on preclinical data for synergy. Four patients were treated with this combination; one achieved a PR and 2 had SD. A Phase II study of the combination of bortezomib and doxil just closed secondary to poor accrual.[130,143]

Data for the efficacy of the hormonal agent tamoxifen is limited to three case reports of long-term SD.[144,145] Case reports also describe responses, including a complete response, to luteinizing hormone–releasing hormone analogues in patients with androgen-receptor–positive adenocarcinoma.[146]

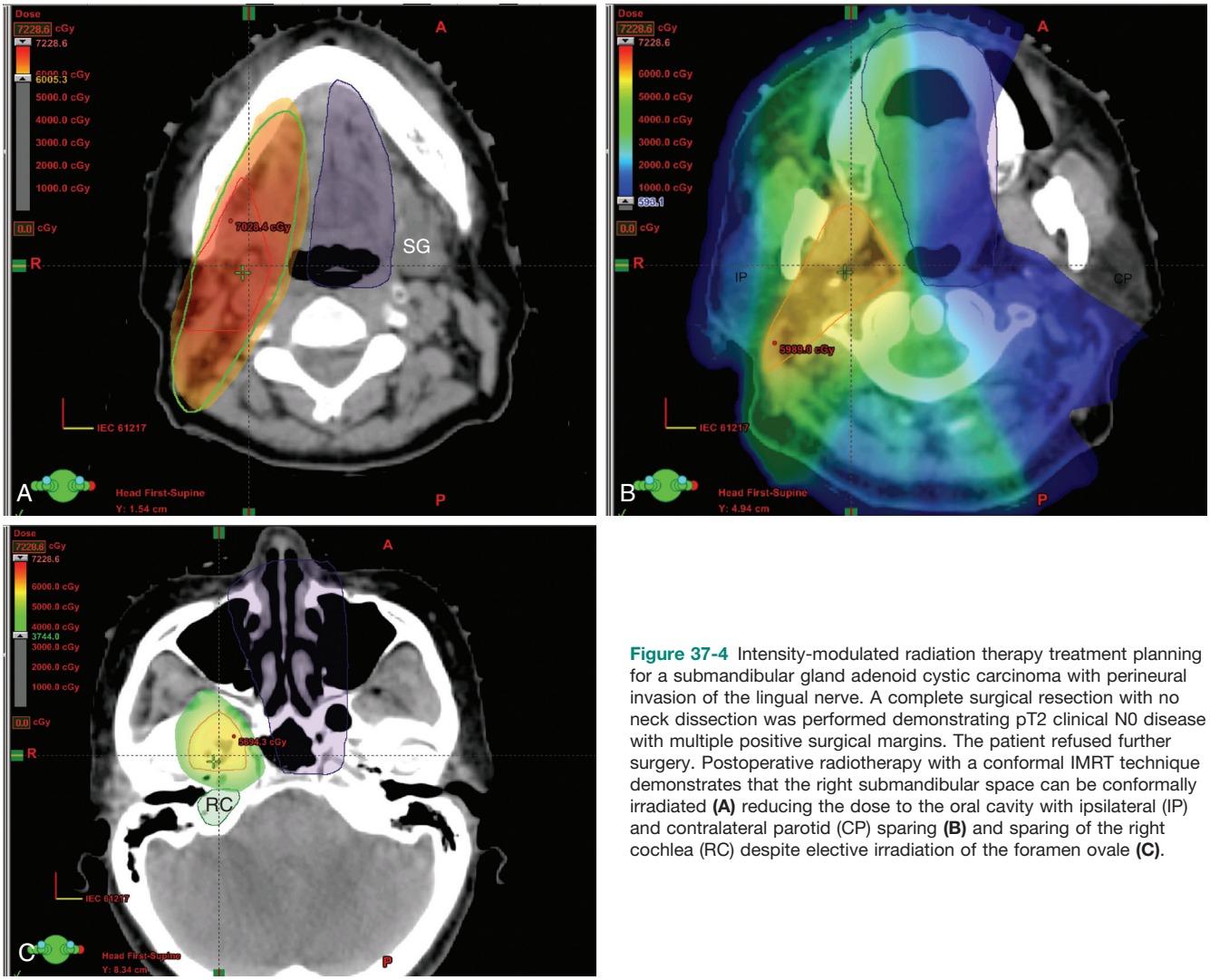

Figure 37-4 Intensity-modulated radiation therapy treatment planning for a submandibular gland adenoid cystic carcinoma with perineural invasion of the lingual nerve. A complete surgical resection with no neck dissection was performed demonstrating pT2 clinical N0 disease with multiple positive surgical margins. The patient refused further surgery. Postoperative radiotherapy with a conformal IMRT technique demonstrates that the right submandibular space can be conformally irradiated **(A)** reducing the dose to the oral cavity with ipsilateral (IP) and contralateral parotid (CP) sparing **(B)** and sparing of the right cochlea (RC) despite elective irradiation of the foramen ovale **(C)**.

Minor Salivary Glands

Target volumes include the primary tumor or surgical bed for small or low-grade cancers meeting indications for radiation therapy. These areas are determined by preoperative imaging and intraoperative and pathologic findings. Areas of unresected disease are given a boost.

Elective neck treatment varies with the histology, grade, T category, anatomic site, and nodal category.[63] Lloyd et al analyzed the SEER database identifying 2667 cases of minor salivary gland cancers with known lymph node status from 1988 to 2004. Although there are inherent limitations with SEER database analyses, the results are consistent with smaller clinical series that in turn lack the size for a multivariate analysis. Analysis demonstrated that male sex, T3-T4 category, primary site involving the pharynx and high-grade adenocarcinoma or high-grade MECs were independent risk factors for the development of nodal metastasis for minor salivary glands.

Although these findings suggest that the biology of salivary gland malignancies influences the risk of nodal metastases, they also suggest that lymphatic-rich anatomic sites may have higher rates of nodal metastases, as seen with squamous carcinomas. For ACCs, Mendenhall et al reported that this was a significant consideration in their institutional approach. They reported a 10-year neck control rate of 90% when the neck was observed compared with 98% with elective irradiation.[96] Other relevant but unestablished anatomic factors that have been well described for squamous carcinomas can also be considered during treatment planning for malignant SGTs. These include the presence of mucosal disease at the coronal midline, increasing the risk for contralateral nodal metastases,[147] and the involvement of the posterior pharyngeal mucosa, increasing the risk of retropharyngeal lymph node metastases.[148]

Simulation and Field Arrangements

A CT scan is obtained in the treatment position. Patients are typically positioned supine, with arms down, and the head and neck in the hyperextended position to move the orbits out of the radiation field. A thermoplastic face mask is used for immobilization. For cases with skull-base or intracranial involvement, a MRI can be obtained and fused to the CT to assist in target delineation. The target volumes and normal critical structures are defined on the representative CT or MRI axial images.

Traditional standard techniques used to treat parotid tumors include wedged pair or mixed beam techniques, whereas IMRT is now commonly used as well. It is our preference to use either a wedged pair technique or an IMRT

technique (allows for comprehensive coverage of the parotid bed and cervical lymph nodes, while avoiding the potential impact on the mandible of electron beam dosimetry). IMRT also allows for improved conformality at the skull base, especially when the surgical bed and scar extends superiorly above the plane of the middle and inner ear complex and may lie adjacent to the temporal lobe. Traditional radiotherapy techniques have often relied on matched fields typically with electrons to treat the course of the surgical scar if it was deemed to be at risk. This results in potential dosimetric uncertainties with a photon-electron match with the potential for a dosimetric hotspot that may lie in the temporal lobe.

IMRT may also allow for additional sparing of structures such as the cochlea, semicircular canal, mastoid air cells, and temporal lobes. Historically, hearing deficits, and soft-tissue and bone necrosis have been observed in approximately 20% of patients treated with a traditional beam arrangements especially with wedge-pair fields.[149] Using these techniques to treat the tumor bed with or without the ipsilateral neck, mean doses to the contralateral salivary glands can be effectively limited to less than 10% of the prescription dose, thereby preventing any grade-3 symptoms of xerostomia during and after treatment.

Dose, Fractionation and Pathologic Considerations

Frequent pathologic indications reported for the use of postoperative RT include the presence of a close if not positive surgical margin, PNI, high-grade histology, extraglandular extension, bone invasion, tumor size, T category, and the presence of nodal metastases. It is important to recognize that these pathologic indications have not been prospectively evaluated to determine what the absolute risk level is and the incremental risk reduction with adjuvant radiotherapy.

The typical postoperative dose to the surgical bed that has been reported has typically ranged from 60 Gy to 66 Gy with a conventional daily fractionated schedule. For a positive or close surgical margin, localization of the area of concern based on preoperative imaging and intraoperative findings for a boost dose of radiation typically of 6 Gy to a total dose of 66 Gy is an important consideration. Other risk stratified radiotherapy dose recommendations have not been clearly established. Hence, it is unclear if areas involved with extraglandular extension (i.e., T3 and T4) or nodal metastases necessitate a dose higher than 60 Gy.

PNI has been correlated with an increased risk of locoregional relapse, especially for ACCs. Recent detailed histologic studies of serial sections suggest that the mechanism in which PNI may be contributing to relapse is the result of the direct contiguous spread of cancer along the branches of the nerves.[65] Hence, a judicious clinical target volume (3 cm to 5 cm) surrounding the primary tumor bed should be created, to reflect the potential subclinical extent of cancer. The use of postoperative radiation therapy appears to be effective in reducing the risk of local relapse resulting from PNI (10-year local control rates of tumors with PNI treated with surgery compared with surgery and postoperative RT was 60% versus 88%, $p = 0.01$).[64]

For more extensive PNI resulting in clinical symptoms or radiologic nerve abnormalities, there is a further increased risk of locoregional relapse, especially with ACCs.[96] This observation is consistent with other cancer sites in which the size of the involved nerve appears to increase the risk of relapse.[150] With involvement of major named nerves, there is an increased risk of relapse including spread to the skull base and increased risk of distant relapses. Hence, elective irradiation along the course of the nerve is recommended.

For elective nodal irradiation, the anatomic draining lymphatics should be encompassed. The usual dose has ranged from 50 Gy to 54 Gy with a conventional daily fractionated schedule. However, it should be recognized that the optimal elective nodal irradiation dose for MSGTs is unknown.

Gross, unresectable disease has typically been treated to 70 Gy again with a conventional daily fractionated schedule. It is important to note that the optimal dose and fractionation schedule has not been clearly defined especially for unresectable gross disease. This is important to consider in light of evidence suggesting that radiotherapy dose escalation with photons[108] and protons[115] may offer additional improvements in local control rates. Unknown at this time is whether or not there may be incremental gains in locoregional disease control rates with the practice of a simultaneous in-field boost ("dose painting") that is now possible with the use of IMRT.

Treatment Side Effects

The side effects associated with radiation therapy are dependent on several factors: the site and volume treated, the dose fractionation regimen, and total dose delivered, whether treatment is delivered definitively or adjuvantly, the type of radiation used (low LET versus high LET), and whether concomitant chemotherapy is used.

In the treatment of salivary gland tumors, acute phase reactions (within first 90 days of completion of RT) are generally limited to rapidly proliferating tissues, such as the skin, and the oral and pharyngeal mucosa. Skin reactions can range from a mild erythema to moist desquamation, which would require aggressive skin care and antibiotic treatment. Xerostomia and dysgeusia may also occur during RT, but the risk of long-term xerostomia can be minimized with appropriate field arrangements and treatment planning, by excluding the contralateral parotid and submandibular gland. Acute mucositis is commonly observed if the oral cavity or pharyngeal mucosa is in the field. The risk of developing severe mucositis is increased with approaches such as accelerated fractionation, concurrent chemotherapy, or high LET radiation. Attention to pain control, close monitoring for the development of oral candidiasis, and aggressive nutritional support (with the placement of a percutaneous gastrostomy [PEG] tube, if needed) are required with severe mucositis.

Late complications (occurring >90 days after completion of treatment) are associated with slower proliferating tissues, with side effects limited to the particular region treated. In treatment of the base of skull, careful treatment planning is required to limit the dose delivered to critical structures, thereby minimizing the risks of side effects such as pituitary dysfunction, temporal lobe necrosis, optic neuropathy, keratitis, and hearing loss. With conventional 1.8 Gy to 2 Gy fractionation, the dose to the spinal cord should be limited to 45 Gy (maximum [max]), cochlea to 45 Gy (mean), lacrimal gland to 30 Gy (mean), optic nerves and chiasm to 54 Gy (max), temporal lobes to 65 Gy (max), and brainstem to 60 Gy (max). These doses need to be appropriately adjusted if nonstandard approaches (concurrent chemotherapy, altered fractionation, high LET radiation) are used. Every patient should undergo preradiation dental evaluation, with any necessary extractions to be done before initiation of radiation, and if dentition is to be preserved, custom fluoride trays should be applied daily using custom trays. If extractions or oral surgery needs to be done following radiation therapy, hyperbaric oxygen therapy is recommended to minimize the risk of developing osteoradionecrosis. Another common late side effect in patients receiving neck radiation therapy is hypothyroidism. In patients receiving unilateral radiation therapy, the risk of xerostomia can be minimized through conformal delivery (via

TABLE 37-7 Treatment Algorithm for Malignant Major and Minor Salivary Gland Cancers

Clinical Situation	Standard Therapy	Proposed Clinical Trial
Complete resection, adjuvant therapy	Postoperative, adjuvant EBRT when indicated (see Box 37-3)	Intergroup trial of surgical resection plus postoperative adjuvant EBRT versus surgical resection plus postoperative adjuvant EBRT with concomitant and maintenance chemotherapy
Locally advanced (primary or recurrent; unresectable or resected but residual)	1. High-dose conventional photon irradiation (consider altered fractionation) 2. Maximal surgical resection, IOERT, or brachytherapy and conventional EBRT 3. Neutron beam therapy with or without SRS boost	1. Neoadjuvant chemotherapy followed by resection (with or without IOERT or brachytherapy), and EBRT (photons or protons) with concomitant and maintenance chemotherapy 2. High-dose conventional or altered-fractionation EBRT (photons or protons) with concomitant and maintenance chemotherapy 3. Carbon ion therapy
Locally recurrent, prior irradiation	Low- to moderate-dose EBRT plus hyperthermia Palliative chemotherapy	Low to moderate dose CCRT, resection, IORT (electrons or HDR brachytherapy)

CCRT, *Concurrent chemoradiation;* EBRT, *external beam irradiation;* IOERT, *intraoperative electron beam irradiation.*

three-dimensional conformal radiation therapy, IMRT, proton therapy, or heavy charged particle therapy). Limiting the mean dose to contralateral major salivary glands to <10% of the prescription dose has commonly been recommended.

TREATMENT ALGORITHM, CONCLUSIONS, CONTROVERSIES, AND FUTURE POSSIBILITIES

In summary, SGTs are characterized by their rare incidence, diverse histology, and the potential for an indolent natural history. It is this heterogeneity that has hampered clinical progress in the management of SGTs. In recent years, progress has been made in further understanding the genetic and molecular characteristics of these tumors, but this has not yet yielded any significant therapeutic insights. However, the favorable survival associated with expression of the *CRTC1-MAML2* fusion oncogene in MECs is an important advancement toward improved classification of MECs. Therapeutic progress has been made with technical advances in surgical techniques such as the transoral robotic technique, and in radiation oncology, with the maturation of the use of fast neutron radiotherapy. The increasing study of charged particle beam radiotherapy, both protons and heavy ion beams offer the potential to further reduce toxicities with improved locoregional control rates. Although various molecular targeted therapeutics have been introduced into clinical trials, none have yet realized the goal of significantly decreasing the risk of distant metastasis. However, the toxicities associated with these systemic approaches are acceptable and manageable, and disease stabilization may be possible with several targeted agents.

In conclusion, the treatment options for patients with SGTs have significantly improved in recent years offering the potential for more effective function preserving locoregional therapy. Our preferred treatment algorithm is seen in Table 37-7. Major survival gains will likely only be realized with the development of more effective systemic therapy.

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