Outcomes for advanced salivary gland disease are unsatisfactory, so novel, systemic, therapeutic strategies should be determined through future research.

Multidisciplinary Management of Salivary Gland Cancers
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Background: Salivary carcinomas are a rare group of biologically diverse neoplasms affecting the head and neck. The wide array of different histological entities and clinical presentations has historically limited attempts to establish well-defined treatment algorithms. In general, low-risk lesions can be managed with a single treatment modality, whereas advanced lesions require a more complex, multidisciplinary approach.

Methods: The relevant literature was reviewed, focusing on diagnostic and treatment algorithms for salivary malignancies.

Results: Salivary carcinomas with high-risk features require an aggressive treatment approach with complete surgical resection, neck dissection to appropriate cervical lymph-node basins, and postoperative radiotherapy.

Conclusions: The heterogeneity of salivary neoplasms represents a unique clinical challenge. Despite the multidisciplinary management paradigm detailed in this review, outcomes for advanced disease are unsatisfactory. Future progress will likely require the addition of novel systemic therapeutic strategies.

Introduction
Salivary carcinomas are a rare collection of neoplasms that account for roughly 3% to 5% of all head and neck malignancies.1-3 In the United States, 2,500 new cases are diagnosed each year, and salivary carcinoma has an estimated incidence rate of 2.2 to 3.0 cases per 100,000 people per year.1,4,5 A broad array of unique clinical entities comprises this group of salivary carcinomas. From a pathological perspective, the World Health Organization identified 24 well-defined malignant histologies that can arise within major or minor salivary tissue.4,6 The spectrum of biological behavior expressed is diverse, ranging from indolent, low-grade tumors that almost mimic a benign process to aggressive, high-risk lesions with a propensity for early disseminated metastasis.5

Approximately 70% of these lesions originate within the parotid glands, often presenting as a painless but slowly enlarging preauricular mass.1 A distinct feature of these carcinomas is their wide anatomical distribution.7,8 The remaining 30% of tumors can arise throughout the upper aerodigestive tract, particularly affecting the oral cavity, pharynx, larynx, nose/paranasal sinuses, and middle ear space.9 The initial presentation and potential morbidity depend on the site of involvement, which necessitates a nuanced and individualized treatment strategy.1,6,9

A well-defined treatment algorithm has long been lacking for salivary carcinomas due to their clinical and biological heterogeneity. Research is further confounded by a known propensity for late treatment fail-
ure, with 25% to 50% of all disease recurring more than 5 years after initial management.\textsuperscript{10} In general, tumors can be stratified into low- or high-risk categories on the basis of clinicopathological risk features. Some key features include patient age, tumor size, cervical lymph-node metastasis, grade/histology, American Joint Committee on Cancer (AJCC) tumor stage, and gross perineural invasion.\textsuperscript{11-13}

For low-risk tumors, a single-modality treatment approach is likely to yield a high rate of locoregional disease control (88%-95%) with a correspondingly high 5- to 10-year survival rate.\textsuperscript{14-16} By contrast, neoplasms with high-risk features tend to have an aggressive clinical course and 5-year survival rates ranging from 30% to 40%.\textsuperscript{1,15,17,18}

**Diagnostic Challenges**

The difficulty distinguishing benign tumors from malignancies is a key management challenge for salivary gland carcinomas, particularly those within the parotid glands. They commonly present as a painless and slowly evolving neck mass. “Worrisome” clinical symptoms (eg, pain, hard consistency, rapid tumor growth, cranial nerve deficits, cervical adenopathy) may be utilized to identify a malignancy in approximately 30% of cases.\textsuperscript{7} Imaging studies (eg, ultrasonography, computed tomography, magnetic resonance imaging [MRI]) are often utilized in this setting to better define the neoplastic lesion. The soft-tissue definition afforded by MRI makes this imaging modality the most useful for characterizing salivary pathology.\textsuperscript{19,20} MRI can also be utilized to discriminate between benign and malignant tumors because certain findings on MRI, including T2 hypointensity, ill-defined tumor margins, diffuse growth pattern, and invasion of subcutaneous tissue, are strongly supportive of a malignant process.\textsuperscript{19} However, a certain subset of salivary cancers will have a relatively benign appearance on imaging, potentially leading to misdiagnosis in select patients if pathological analysis is not performed.\textsuperscript{20}

The role of routine pretreatment biopsy for salivary masses remains a controversial topic.\textsuperscript{21} Fine needle aspiration biopsy (FNAB) is considered by some to be an important diagnostic tool to assist with initial treatment planning and patient counseling.\textsuperscript{7,22} The sensitivity rates of FNAB for distinguishing malignant from benign lesions range from between 80% and 98%, and this technique is particularly accurate at differentiating high-grade from less-aggressive lesions.\textsuperscript{7,21-23} However, FNAB is poor at clearly defining tumor pathologies, and it has a relatively low specificity rate and a potentially high false-negative rate.\textsuperscript{22,24} Cytological assessment of salivary pathology by FNAB can also be challenging to interpret, potentially leading to inaccurate interpretations at low-volume centers. Ultrasonographic-guided core biopsy may be an improvement over FNAB, but it can cause patient discomfort, comes with risk of facial nerve injury, and the theoretical (though clinically unproven) risk of tumor seeding.\textsuperscript{21} Therefore, the initial approach to salivary neoplasms must combine data obtained from the clinical examination as well as imaging, biopsy, and potentially intraoperative findings to ensure patients receive optimal first-line treatment.

**Surgical Considerations**

Regardless of tumor location, histology, or stage, the first-line treatment approach for salivary malignancies should be curative surgical resection, when feasible.\textsuperscript{1,6,7} Other first-line treatment modalities have been studied, but those modalities have generally been reserved for patients with either unresectable disease or medical comorbidities preventing a surgical approach.\textsuperscript{25} Preoperative decision-making is challenging in these cases because the operative strategy must take into account the anatomical tumor localization, the extent of locoregional disease, the cosmetic/functional morbidity of tumor extirpation, and need for reconstruction of the postoperative defect.\textsuperscript{26,27} Another important consideration is a tendency of certain tumor histologies (eg, adenoid cystic carcinomas) for perineural invasion.\textsuperscript{28,29} In this scenario, the operative strategy may require extensive nerve dissection (eg, trigeminal or facial nerve branches) toward and through the skull-base foramina in an attempt to achieve tumor clearance.\textsuperscript{28,30}

Because the parotid location is the most common site, many of these tumors will be addressed with some form of parotid surgery. Conservative resection (superficial parotidectomy) with facial nerve dissection and preservation is considered to be appropriate in most cases.\textsuperscript{7,27,31,32} Nerve sacrifice is considered necessary only when gross nerve adherence/invasion is intraoperatively observed. When possible, nerve grafting should be considered at the time of resection to theoretically optimize long-term functional outcomes.\textsuperscript{7,27,31,32} Rarely, lateral temporal bone resection or parapharyngeal space dissection/mandibulectomy may also be required for complete excision of gross disease in extensive tumors. For lesions outside of the parotid tissue, a broad array of surgical strategies may be applicable, ranging from traditional open ablative approaches to transoral, endoscopic, or robotic-assisted techniques.\textsuperscript{9,33,34} Regardless of the approach, the operative management of salivary carcinomas should be to attempt complete tumor eradication, with the goal being microscopically negative surgical margins.\textsuperscript{6,7,9,32}

**Role of Adjuvant Radiotherapy**

Despite an adequate surgical resection, locoregional treatment failure is common for advanced tumors.
Chen et al\textsuperscript{16} observed a 10-year locoregional disease control rate of 80\% for T1 to T2 lesions vs 63\% for T3 to T4 lesions. Postoperative radiotherapy (RT) has been utilized, in particular, to enhance locoregional control in this setting. Armstrong et al\textsuperscript{14} presented a matched-pair analysis of salivary malignancies treated with surgery alone (n = 46) vs surgery plus adjuvant RT (n = 46). Although no difference was seen in locoregional disease control rates in low-stage disease, the 5-year rate of locoregional disease control improved from 17\% to 51\% when RT was added for treatment of advanced lesions (stages 3/4).\textsuperscript{14} A review by Chung et al\textsuperscript{35} of multiple retrospective series published between 1989 and 2012 further supports the benefit of adjuvant RT. In that series for which surgery and adjuvant RT were combined, 5-year locoregional control rates of RT ranging from 73\% to 96\% were achieved vs 66\% to 84\% for surgery alone.\textsuperscript{35}

The decision as to when postoperative RT should be recommended for salivary carcinomas generally depends on the presence/absence of “high-risk” clinical/pathological features. This timing is derived from study authors who have identified the most predictive variables of locoregional treatment failure.\textsuperscript{26,36,37} Of these characteristics, tumor size (> 4 cm), cervical lymph-node metastases, high-grade histopathology, and positive surgical margins are considered the most significant.\textsuperscript{26,36,37} Conversely, a small series of 58 study patients conducted by Zbären et al\textsuperscript{38} suggested a potential benefit of adjuvant RT, even in the setting of low-risk disease (T1 and T2 and N0). However, this series is considered by some authors to be an outlier and, consequently, adjuvant RT may be of little benefit for small (< 4 cm), low-grade lesions without additional adverse pathological features.\textsuperscript{6,14,16,26}

Terhaard et al\textsuperscript{16} conducted the largest institution- al series to address the use of postoperative RT for salivary malignancies. Of 498 study patients with major/minor salivary carcinoma, 386 received a combined treatment approach (surgery in combination with RT).\textsuperscript{16} With a mean follow-up period of 76 months, multivariate analysis indicated a locoregional control benefit of adjuvant RT only in the settings of T3 to T4 tumors, node-positive disease, positive/close margins, bone invasion, or perineural invasion.\textsuperscript{16} The most recent guidelines from the National Comprehensive Cancer Network reflect these findings, advocating use of RT for patients with major or minor salivary malignancies and these particular adverse features.\textsuperscript{39} Optimal results may be achieved with a radiation dose of 60 Gy, increased to between 66 and 70 Gy for those with gross residual disease.\textsuperscript{16,25,36}

**Treatment of the Neck**

Management of the cervical lymph nodes warrants particular discussion. There is little debate on the approach to node-positive disease, with a neck dissec- tion advocated at the time of primary surgery followed by adjuvant RT.\textsuperscript{7,9,10} In particular, for major salivary tumors, when node-positive disease is present, multiple ipsilateral neck levels are often involved. In 31 parotid malignancies with node-positive disease, Ali et al\textsuperscript{40} identified the risk of nodal involvement to be greater than 70\% for levels 2 and 3, greater than 50\% for levels 1 and 4, and 40\% for level 5. Lim et al\textsuperscript{41} further confirmed these findings in their review of 39 primary parotid malignancies with node-positive necks at presentation. In these cases, pathologically positive nodal metastases were uniformly found across all neck levels when dissected.\textsuperscript{41} Thus, when a therapeutic neck dissection is undertaken, comprehensive clearance of all major nodal basins in the involved side of the neck is advocated.\textsuperscript{40,42}

Elective treatment of the N0 neck is a controversial topic. Some authors propose node sampling (neck dissection) in all patients with salivary carcinoma, because current methods of predicting the presence of lymphatic metastasis (in N0 necks) can be imprecise.\textsuperscript{43} However, the literature is also suggestive of a more selective management algorithm on the basis of clinicopathological risk features. A retrospective series of 363 cases by Yoo et al\textsuperscript{42} helps to elaborate on patterns of cervical lymph-node metastasis in major/minor salivary tumors. The total rate of nodal involvement was 20.1\%, including 51 study patients with clinically node-positive disease at presentation.\textsuperscript{42} Of the 312 N0 cases, 110 study patients underwent elective neck dissection and had a 15.5\% rate of occult metastasis.\textsuperscript{42} The other 202 study patients underwent surgical resection of the primary lesion without neck dissection (with or without RT) and experienced a 2.5\% rate treatment failure within the cervical lymph-node basins.\textsuperscript{42}

Of the literature series reviewed, most indicated that high tumor grade, adverse histology, and potentially tumor size (> 4 cm or T3/T4 tumors) are the most important predictors for cervical lymph-node metastasis.\textsuperscript{16,42,44-46} When positive nodes are identified in these cases after elective neck dissection, they are clustered within levels 1 to 3 in both major and minor salivary malignancies.\textsuperscript{42,46} Consequently, elective neck management is generally advocated only in these high-risk scenarios to the most likely affected nodal basin.\textsuperscript{16,42,44} A paucity of evidence exists to distinguish the optimal treatment modality in this setting. Because these high-risk patients meet the criteria for adjuvant RT, elective neck irradiation would seem appropriate. An elective neck irradiation approach, generally with a dose of 46 to 50 Gy for N0 disease, has also been employed in select patients with a high degree of regional disease control (> 90\%).\textsuperscript{16,45} However, in most cases, a
combined benefit of pathological nodal staging and the potential therapeutic benefit of identifying these occult nodal metastases.\textsuperscript{16,42,46}

An alternative approach for the N0 neck in patients at high risk is selective level 2 nodal sampling.\textsuperscript{7} The approach is performed at the time of primary surgery with frozen section analysis: Patients with positive nodal disease undergo comprehensive lymphadenectomy plus adjuvant RT, whereas those with negative findings on biopsy receive elective neck irradiation alone. Such an approach still requires validation, but it could offer a more selective approach with diminished morbidity.\textsuperscript{7} However, we continue to recommend elective neck dissection (generally incorporating levels 1–3) followed by adjuvant RT for patients with high-grade or locally advanced (T3 or T4) salivary carcinoma.

**Management of Inoperable Disease**

For patients who present with metastatic disease, extensive locoregional disease deemed to be unresectable, or with medical comorbidities that make them inappropriate surgical candidates, nonsurgical treatment strategies can be considered.\textsuperscript{25} In these settings, high-dose RT (> 66 Gy) may be reasonable to promote durable disease control.\textsuperscript{7,16,17,26} For example, a series of 64 cases attained a 10-year locoregional disease control rate of 40% rate with RT alone.\textsuperscript{26} In a series of 40 study patients, Terhaard et al\textsuperscript{16} further elaborated on the dose-response relationship between radiation and treatment effect. They found that a 5-year locoregional disease control rate of 50% could be achieved at a radiation dose of at least 66 Gy vs 0% for lower than 66 Gy.\textsuperscript{16}

High linear energy transfer neutron RT has been explored in this patient population (particularly for adenoid cystic carcinomas) due to presumed radio-resistance.\textsuperscript{7,48} A randomized trial completed during the 1980s compared neutron beam RT vs photon beam therapy in unresectable disease.\textsuperscript{49} At 10 years, a significant benefit in locoregional control was seen with neutron RT vs photo beam therapy (56% vs 17%; \(P = .009\)).\textsuperscript{7,48,49} Some retrospective series have confirmed this finding, with 5- to 6-year locoregional control rates as high as 75% after particle beam therapy.\textsuperscript{48} This has led some authors to conclude that neutron beam RT could be considered the treatment of choice for unresectable salivary malignancies or in those with gross residual disease following attempted surgical extirpation.\textsuperscript{7,49,50}

Despite the potential benefits afforded by neutron beam RT (compared with conventional RT) in this population, few barriers have prevented its wide utilization. It is an expensive technology and available in limited centers worldwide.\textsuperscript{48} Relatively high rates of severe late toxicity (in particular, cranial neuropathy and soft-tissue/brain necrosis) have been reported with neutron beam RT when compared with conventional RT.\textsuperscript{7,16,48} Neutron beam RT has also failed to improve survival rates (despite its improved rates of locoregional control) due to the likelihood of disease dissemination.\textsuperscript{48,50}

**Prognostication and Survival Outcomes**

Given the varying range of tumor histologies and disease presentation, surrogate clinicopathological factors are used as a means of stratifying the presumed biological aggressiveness of each individual case.\textsuperscript{10,37,51-53} Bhattacharyya et al\textsuperscript{54} reviewed 903 study patients with parotid gland carcinomas identified by the Surveillance, Epidemiology and End Results database. Patient age, tumor histology, extraglandular spread, tumor grade, and cervical lymph-node status (N stage) were all found to have an impact on rates of survival.\textsuperscript{54}

Other authors have attempted to synthesize these data into clinical nomograms to theoretically predict the likelihood of disease recurrence and patient survival.\textsuperscript{12,13} Carillo et al\textsuperscript{55} describe a 3-tiered risk-stratification scheme utilizing patient and tumor-specific features, including age and tumor stage, grade, and margin status. In their single institution experience, disease recurred in 71.4% of high-risk and 8.8% of low-risk cases.\textsuperscript{55} Therefore, a multidisciplinary treatment approach is advocated for those with intermediate- or high-risk disease, whereas single-modality (surgical) management is considered acceptable for low-risk cases.\textsuperscript{55} Although nomograms may be of benefit for patient counseling, none have been widely adopted or validated for routine clinical use.\textsuperscript{56}

A risk-stratification scheme that incorporates current AJCC tumor, node, and metastasis guidelines and tumor histological grading (for appropriate entities such as mucoepidermoid or salivary duct carcinomas) can be used to guide treatment decisions and for reasonably accurate prognostication.\textsuperscript{57} A multimodality treatment approach with primary tumor resection — likely elective neck dissection — and adjuvant RT is advocated for high-stage (AJCC stage 3/4), high-grade salivary carcinomas, or both. This approach has been proven successful in a number of series because durable rates of locoregional disease control within the head and neck have been achieved.\textsuperscript{7,16,17,37,35}

However, this aggressive multimodality treatment approach has not had a robust impact on survival rates among patients with advanced salivary malignancies.\textsuperscript{26,55} Bjørndal et al\textsuperscript{37} reported a 5-year crude survival rate of 30% for stage 4 tumors (\(n = 251\)), despite 60% of study patients receiving adjuvant RT. A meta-analysis of parotid adenocarcino-
ma, which included 19 series (n = 4,631), did identify a modest improvement in survival with use of adjuvant RT; however, the 5-year rate of overall survival among those with high-grade lesions was 35%, often despite a multimodality approach. A multivariate analysis of Surveillance, Epidemiology and End Results data reported a statistically significant improvement in overall survival with adjuvant RT in cases of salivary malignancies classified as high-risk, locally advanced (T3/T4 or node-positive), or both (hazard ratio = 0.76; P < .001). However, squamous cell carcinomas (likely metastatic cutaneous neoplasms) were included, making these data somewhat less applicable to tumors of true salivary origin. Overall, a poor prognosis is generally attributed to advanced salivary malignancies. The presumed mechanism for this is a biological propensity for distant metastasis, which thus far has been unchanged by locoregional management strategies.

Systemic Therapy

Applying effective systemic treatment approaches presumably will be necessary to improve outcomes for patients with high-risk salivary malignancies due to their likelihood of distant disease dissemination. The appropriate use of chemotherapy has not been confirmed and is generally studied only in the setting of palliation of metastatic disease. Some barriers exist that prevent the appropriate use of systemic treatment strategies for salivary malignancies, including historically low response rates to standard chemotherapeutic agents, biological tumor diversity (which theoretically necessitates use of a histologically specific drug regimen), and a paucity of literature mostly comprised of small, nonrandomized phase 2 studies.

In the palliative setting, a wide array of conventional chemotherapeutic agents can be used (both single- and poly-drug regimens); partial and complete response rates range from 25% to 60%. These responses are also generally of a short duration, as demonstrated by a median 7-month partial response rate of 27% achieved in a single phase 2 trial of cisplatin, doxorubicin, and cyclophosphamide. Because these study results are not promising for the palliative setting, conventional chemotherapeutic agents have not generally been considered for the adjuvant management of advanced salivary malignancies; however, the exception has been a group of exploratory studies that have employed concurrent chemoradiotherapy. Rationale exists for use of chemotherapy as a radiosensitizer against salivary malignancies, which could theoretically impact the risk of distant disease dissemination. At present, the research base is too small to advocate for a standard approach involving use of chemoradiotherapy for these carcinomas, but chemoradiotherapy is being explored for the treatment of advanced salivary tumors.

The failure of most conventional chemotherapeutic agents has led to the use of targeted agents to treat salivary neoplasms. Preliminary studies of agents, including tyrosine kinase inhibitors (eg, cetuximab, gefitinib, imatinib) and appropriate monoclonal antibodies (eg, trastuzumab, lapatinib), had mixed results, with no agent showing clear antitumor activity. However, other drug targets continue to be identified, ranging from key cell-surface receptors (eg, epidermal growth factor, C-kit, human epidermal growth factor receptor 2, androgen receptors) to histologically specific oncogenic gene fusions. How this exploratory phase into the molecular genomics of salivary malignancies will evolve into new systemic treatment paradigms remains uncertain.

Conclusions

The optimal management of salivary malignancies requires combining accurate diagnostic pathology with an understanding of key patient- and tumor-specific clinicopathological features to facilitate risk stratification. Although low-risk tumors can be controlled in most situations with surgery alone, a more complex multidisciplinary approach is necessary in cases of intermediate- to high-risk disease. In this setting, aggressive surgical extirpation, neck dissection, and postoperative radiotherapy (to resection bed and at-risk cervical lymph-node basins) are advocated. Treatment escalation with concurrent chemoradiotherapy is also under investigation as a potential means of improving management outcomes. However, in the absence of a more robust evidence base, this approach cannot be routinely recommended.

It is our belief that future progress in this field will require the innovative use of systemic therapeutic agents. This may include the use of newer, targeted therapies or the novel use of conventional agents in either the adjuvant or neoadjuvant setting. Regardless, the biological diversity of salivary gland malignancies will likely continue to pose both unique and fascinating clinical challenges.

References

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