15 ■ SALIVARY GLAND TUMORS

Sarah S. Kilic, Martin C. Tom, Shlomo A. Koyfman, and Nikhil P. Joshi

QUICK HIT: ■ Salivary gland tumors are an uncommon group of benign and malignant neoplasms with natural histories that vary by histology. The most common benign histology is pleomorphic adenoma. The most common malignant histology depends on location: parotid gland, mucoepidermoid carcinoma; submandibular and minor salivary glands, adenoid cystic carcinoma. Surgery is the standard of care for all histologies; the facial nerve should be preserved if possible. Postoperative RT should be considered for those at high risk of recurrence (Table 15.1). No benefit to CHT has been demonstrated prospectively.

Table 15.1 General Treatment Paradigm for Malignant Salivary Cancer

Surgical Resection With Consideration of Adjuvant RT as Follows

Primary Site		**Ipsilateral Neck**	
Stage I to stage II and no risk factors	Observation	cN0 or pN0 and low risk	Observation
T3–4, PNI, deep lobe involvement, bone involvement, high grade, or recurrent disease	60 Gy	Pathologic node-negative with risk factors (*see Terhaard and RTOG 1008*): T3–4, high grade, facial nerve deficit, recurrent disease	50 to 54 Gy levels II to IV
		Node-positive, resected	60 Gy levels Ib to V
Margin-positive or close margins (<1 mm)	66 Gy	ECE	66 Gy
Gross disease	70 Gy	Gross nodal disease	70 Gy

EPIDEMIOLOGY: Salivary gland tumors are rare neoplasms that represent approximately 6% of H&N cancers[1], with roughly 2,500 cases in the United States annually.[2] Benign histologies are more common in young females (median age 46).[3,4] Malignant histologies are more common with older age (median age 54) and have an increasing male predilection with increasing age.[2,4] Histology is classified according to the WHO 2005 system, with over 40 different histologies defined.[2] The parotid gland is the most common site (70% of all tumors, 75% of which are benign), with 22% in minor glands and 8% in submandibular glands.[4]

RISK FACTORS: Risk factors are not clearly defined. Strongest evidence is for RT exposure, as shown among Hiroshima/Nagasaki survivors.[5] Smoking is not a risk factor (except in Warthin's tumor; see Table 15.2). EBV has been implicated in lymphoepithelial carcinomas,[6] and other viruses are under investigation.

ANATOMY: Major salivary glands consist of parotid, submandibular, and sublingual gland (between mylohyoid and floor of mouth mucosa). Borders of parotid are second maxillary molar (anterior), zygomatic arch (superior), internal jugular vein (deep), mastoid tip (posterior), and posterior digastric muscle (inferior). Parotid contributes primarily to stimulated serous saliva production, and submandibular to unstimulated mucous/serous saliva (and, therefore, RT-induced xerostomia).[7] Parotid lies behind ramus of mandible and is separated into superficial and deep lobes by facial nerve. Retromandibular vein is common radiographic landmark for facial nerve. Stensen's duct drains to buccal mucosa. Facial nerve (CN VII) courses through parotid after exiting stylomastoid foramen. There are five branches of CN VII: temporal, zygomatic, buccal, marginal mandibular, and cervical. CN VII controls facial muscles and taste to oral tongue. Auriculotemporal nerve originates

From: Essentials of Clinical Radiation Oncology
DOI:10.1891/9780826169099.0015

from V3, innervates parotid (salivation/parasympathetic), and can be route of perineural spread; if damaged during surgery, this can aberrantly regenerate to innervate skin, causing auriculotemporal syndrome (preauricular sweating and flushing), also called Frey's syndrome after Dr. Lucie Frey, one of the first female European neurologists, who characterized it in 1923.[7] Submandibular is innervated by chorda tympani, and perineural spread can be to CN XII, to CN V via lingual nerve, or to CN VII via chorda tympani. Minor salivary glands are distributed throughout aerodigestive epithelium. Multiple contouring guides are available to aid in anatomy of cranial nerves when PNI is present.[8,9]

Table 15.2 Characteristics of Salivary Tumors

	Parotid	Submandibular	Sublingual	Minor Glands
Pathology[4,10]	75% benign, 25% malignant	50% benign, 50% malignant	75% malignant	
Frequency[4]	70%	8%	22%	
Salivary fluid[3,10]	Serous	Mixed	Mucous	
Associated nerves	CN VII (facial) with spread to V3 via chorda tympani	V3 (lingual) and XII (hypoglossal)	V3 (lingual)	Location dependent

PATHOLOGY: Most common histologies listed in Tables 15.3 and 15.4, in order of decreasing incidence. Grade is prognostic for mucoepidermoid carcinoma, adenocarcinoma, salivary duct carcinoma, and acinic cell carcinoma.[2] Adenoid cystic carcinoma is graded by percentage of solid component (high grade if >30% solid).

Table 15.3 Benign Salivary Tumor Histologies

Pleomorphic adenoma	Most common salivary gland tumor, two thirds of parotid tumors, two thirds are females in their 40s. Treatment is surgery, with <5% risk of recurrence, but beware of tumor spillage, in which case recurrence can be up to 45%. Risk of second recurrence is 46%. Can transform into carcinoma *ex* pleomorphic adenoma (CExP). Rate of transformation is <1% in patients without recurrence; 4% with recurrence.[3] Consider RT to 50 to 60 Gy for multiple recurrences, deep involvement, or large tumors.[11]
Warthin's tumor	Often of parotid, often bilateral (6%).[12] Associated with smoking, more common in men.[13] Can be highly PET-avid and is often an incidental finding on PET. Malignant degeneration is rare (<1%)[10]; observation is reasonable.
Basal cell adenoma	Approximately 2% of salivary tumors.[10] May be confused with basal cell of skin metastatic to parotid lymph nodes.
Oncocytoma	1% of salivary tumors. Slowly progressive parotid tumor in older patients.

Table 15.4 Malignant Salivary Tumor Histologies

Mucoepidermoid	Most common parotid malignancy. Grade is prognostic. Most are curable with surgery alone.
Adenoid cystic carcinoma	Almost always demonstrates PNI and can track along cranial nerves. Tubular pattern is most favorable, cribriform is intermediate, and solid is least favorable. Greater than 30% solid pattern is considered high-grade. Long natural history. Risk of nodal involvement classically thought to be <5%, but recent data as high as 37% in oral cavity and 19% in major glands.[14,15] Indolent distant metastases to lungs in up to 50%.[10] Late recurrences (>20 years) can be seen. Most benefit from adjuvant RT.[16]
Adenocarcinoma, NOS	Grade is prognostic, nodal metastases seen in 50% to 60% of high-grade lesions.[15]
Acinic cell carcinoma	Low-grade, slowly progressive tumors, 80% within parotid. Submandibular tumors are uncommon and most aggressive.[10]
Carcinoma *ex* pleomorphic adenoma	4% of salivary tumors, 12% of malignancies. Degenerated pleomorphic adenoma. More than 80% of patients do not have history of known pleomorphic adenoma.[10]

(*continued*)

Table 15.4 Malignant Salivary Tumor Histologies (*continued*)	
Salivary duct carcinoma	9% of salivary malignancies. Males more common (4:1). Aggressive, high grade, similar to high-grade breast ductal carcinoma.[10] Androgen receptor and HER2 amplification common.
Metastasis to salivary gland	5% of salivary malignancies,[10] incidence varies by region based on frequency of skin cancer. Mostly squamous cell carcinoma of skin followed by melanoma.
Epithelial–myoepithelial	Only 1% of salivary tumors, twice as common in women, 60% parotid, typically slow growing.

GENETICS: EGFR, c-kit, HER2, NTRK fusion, and androgen receptor positivity have all been described, most commonly in salivary duct carcinomas,[17] but no standard role for targeted agents in the non-metastatic setting.

CLINICAL PRESENTATION: Most present initially as slowly progressive painless mass. Adenoid cystic carcinoma may present initially as neuropathic pain (misdiagnosis as trigeminal neuralgia) and progress to facial nerve motor deficit.

WORKUP: H&P, including H&N exam with cranial nerve exam. Ultrasound can be helpful to differentiate between benign vs. malignant prior to biopsy. FNA sensitivity and specificity are 80% and >95%, respectively.[11] Contrast-enhanced MRI is critical for evaluation of perineural spread in malignant histologies. CT chest for malignant histologies. PET is not standard. Dental, nutrition, speech, and swallow evaluation as indicated.

PROGNOSTIC FACTORS: Stage, grade, histology, recurrence, positive margins, bone invasion, positive lymph nodes, facial nerve palsy.[11,18,19]

TREATMENT PARADIGM

Observation: Observation can be appropriate for benign histologies other than pleomorphic adenoma. Pleomorphic adenoma should be treated upfront in healthy patients due to risk of malignant transformation. Malignant histologies should always be treated.

Surgery: Surgical resection of the primary tumor is the standard of care for all technically resectable salivary gland tumors warranting treatment. Care should be taken to minimize risk of tumor spillage; enucleation should not be performed. Preservation of functional cranial nerves should be attempted. Microscopic margins preferred over facial nerve sacrifice, although not at the expense of residual gross disease.[20] Consider nerve grafting for reconstruction of sacrificed cranial nerve. For all locations and histologies, clinically node-positive neck should be dissected. For parotid tumors, elective nodal dissection of levels II to III, and possibly IV, may be recommended, and is surgeon dependent based on risk factors (size, stage, grade, histology, location). For submandibular tumors, elective dissection of levels I to III, again surgeon dependent. For parotid tumors, levels I and V may be at risk only if levels II to IV are involved.[11]

Table 15.5 AJCC 8th ed. (2017): Staging for Salivary Gland Cancer (Note that minor salivary cancers are staged according to their site of origin)

<table>
<tr><th colspan="2">N
T/M</th><th>cN0</th><th>cN1</th><th>cN2a</th><th>cN2b</th><th>cN2c</th><th>cN3a</th><th>cN3b</th></tr>
<tr><td>T1</td><td>• ≤2 cm</td><td>I</td><td rowspan="3">III</td><td rowspan="3" colspan="3">IVA</td><td rowspan="4"></td></tr>
<tr><td>T2</td><td>• 2.1 to 4 cm</td><td>II</td></tr>
<tr><td>T3</td><td>• >4 cm and/or extraparenchymal extension</td><td rowspan="2"></td></tr>
<tr><td>T4a</td><td>• Invasion[1]</td><td colspan="5"></td></tr>
<tr><td>T4b</td><td>• Invasion[2]</td><td colspan="6">IVB</td></tr>
<tr><td>M1</td><td>• Distant metastasis</td><td colspan="6">IVC</td></tr>
</table>

Notes: Invasion[1] = Invasion of skin, mandible, ear canal, or facial nerve. Invasion[2] = Invasion of skull base, pterygoid plates and/or encasing carotid artery. Nodal category definition is similar to other non-HPV-associated head and neck cancers; see Table 11.4 for clinical and pathologic nodal categories.

Chemotherapy: Addition of CHT for high-risk lesions is investigational, and retrospective data are inconsistent.[21–23] *RTOG 1008 is an ongoing phase II/III study of adjuvant RT 60–66 Gy vs. adjuvant RT 60–66 Gy with concurrent cisplatin 40 mg/m² weekly. Included are patients with resected intermediate- or high-grade adenocarcinoma, intermediate- or high-grade mucoepidermoid carcinoma, high-grade salivary duct carcinoma, high-grade acinic cell carcinoma, and high-grade (>30% solid component) adenoid cystic carcinoma with any of the following risk factors: T3–T4, or N+, or T1–T2 AND positive/close (≤1 mm) margins.* Regarding targeted therapies, many e*arly studies (imatinib,[24] lapatinib,[25] and dasatinib[26]) for salivary tumors have had disappointing results. Notably, the tyrosine kinase inhibitors larotrectinib and entrectinib have shown encouraging response rates (>75%) for NTRK fusion-positive tumors across various primary sites, including salivary gland.[27] Phase I/II studies of combined androgen blockade (for androgen receptor-positive salivary duct carcinomas),[28] lenvatinib (for adenoid cystic carcinoma),[29] and pembrolizumab (for any PD-L1-positive histology)[30] have shown some promise.*

Radiation

Indications and dose: Consider RT for pT3–4 disease, close or positive margins, high-grade, recurrent disease, positive lymph nodes, PNI, LVSI, or bone invasion. Adenoid cystic carcinomas typically display significant PNI and are treated with RT. Role of RT for T1 lesions with risk factors is unclear (NCCN category 2B):[20] 60 Gy to primary site and 54 Gy to elective neck (if included) is recommended. Dose should be escalated to 66 Gy for positive margins or extracapsular extension, and to 70 Gy for gross disease.[11,20] Treatment of ipsilateral neck for pathologically node-positive disease is required, and elective nodal coverage should be considered for pT3–4, high-grade, facial nerve deficits, or recurrent disease.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 4.[31]

Complications: Oral mucositis, odynophagia, skin erythema, altered taste, partial xerostomia, trismus, hypothyroidism, and ear complications (secretory otitis media or partial hearing loss). Limit contralateral parotid to mean 26 Gy if possible. TD 5/5 of parotid is 32 Gy.

Neutrons: Higher LC, but more late effects than photons. RBE is >2.6. Neutrons lack skin sparing, are less affected by hypoxia, and are less cell cycle dependent than photons. Consider for unresectable or recurrent tumors, particularly adenoid cystic. In one small series of tumors involving base of skull, 3-year LC doubled (39%–82%) with SRS boost following neutron treatment, without increased toxicity.[32] Complications include osteoradionecrosis, fibrosis, cervical myelopathy, CNS necrosis, optic neuritis, palatal fistula, retinopathy, and glaucoma.

■ EVIDENCE-BASED Q&A

■ What are the indications for postoperative RT?

Because salivary cancer is relatively rare, no prospective trials have been performed. Therefore, indications for postoperative RT are based on retrospective evidence. In general, adjuvant RT indications include pT3–4 disease, close or positive margins, high-grade, recurrent disease, positive lymph nodes, PNI, LVSI, or bone invasion.

Terhaard, Netherlands (*Head & Neck* 2005, PMID 15629600): RR of 498 patients treated for salivary cancers between 1984 and 1995; 386 patients received RT to median dose of 62 Gy (60.7 Gy for negative margins, 62.4 Gy for close, and 64 Gy for positive). Forty percent received elective nodal RT. Ten-year LC improved for those with T3–4 tumors, close (<5 mm) and positive margins, PNI, and bone invasion. Unresectable patients showed dose response, with 5-year LC of 0% for <66 Gy, and 50% for ≥66 Gy. **Conclusion: Postoperative RT indicated for T3–4 disease, close or positive margins, bone invasion, and PNI. Risk of nodal disease was defined using T-stage and histology.**

Armstrong, Memorial Sloan Kettering (*Arch Otolaryngol Head Neck Surg* 1990, PMID 2306346): Matched-pair analysis of 46 patients treated with postoperative RT after 1966 matched to those treated with surgery alone prior to 1966. Median RT dose was 56.64 Gy. For entire cohort, 5-yr CSS and LC were not statistically significantly different between surgery alone and surgery plus RT groups. However, RT did improve CSS (51% vs. 10%, $p = .015$) and LC (73% vs. 66%, p = NS) for stages III–IV patients. Node-positive patients also had CSS (49% vs. 19%, $p = .015$) and local control (69% vs. 40%, $p = .05$) benefits. **Conclusion: Stages III to IV and node positivity are indications for postoperative radiotherapy.**

Table 15.6 Results of Terhaard et al, 2005							
			Risk of Positive Neck Nodes (%) by Score and Primary Location				
10-Year Local Control	**No RT**	**RT**	**T Score + Histology Score***	**Parotid**	**Submandibular**	**Oral Cavity**	**Other**
T3–4 tumor	18%	84%	2	4%	0%	4%	0%
			Risk of Positive Neck Nodes (%) by Score and Primary Location				
10-Year Local Control	**No RT**	**RT**	**T Score + Histology Score***	**Parotid**	**Submandibular**	**Oral Cavity**	**Other**
Close margins	55%	95%	3	12%	33%	13%	29%
Positive margins	44%	82%	4	25%	57%	19%	56%
Bone invasion	54%	86%	5	33%	60%	–	–
PNI	60%	88%	6	38%	50%	–	–
All results statistically significant.			*Scoring: T1 = 1, T2 = 2, T3-4 = 3. Acinic/adenoid cystic/CExP = 1, MucoEp = 2, Squamous/Undifferentiated = 3.				

North, Johns Hopkins (*IJROBP* 1990, PMID 2115032): RR of 87 patients with major salivary gland tumors treated from 1975 to 1987 with surgery with or without RT. Thirty-four percent had neck dissection. Seventy-four percent received RT (60 Gy for negative margins, 66 Gy for close or positive margins, and 72 Gy for gross disease). Postoperative RT improved local recurrence for untreated and recurrent patients and improved 5-yr OS (75% vs. 59%, $p = .014$). Negative prognostic factors included facial nerve palsy, undifferentiated histology, male gender, skin involvement, and no RT. **Conclusion: RT should only be omitted for patients with low-grade T1–2 tumors with negative margins.**

Cho, Korea (*Ann Surg Oncol* 2016, PMID 27342828): RR of 179 patients with low-grade salivary gland cancers (LGSGC). Ten-year OS was 96.6% and RFS was 89.6%. Adjuvant RT improved RFS for patients with node positivity, PNI, LVSI, extraparenchymal extension, positive margin, or T3–4. Close margins (<5 mm) did not increase risk of recurrence. T1–2 patients without risk factors had low risk of recurrence after surgery alone. **Conclusion: Adjuvant RT improves RFS for high-risk LGSGC. Low-risk LGSGC (T1–2 without risk factors) have good outcomes after surgery alone.**

■ Which patients are at higher risk of nodal metastasis?

High-grade, vascular invasion, facial nerve palsy, histology, and higher T stage appear to predict risk for nodal metastases.

Xiao, NCDB Analysis (*Otolaryngol Head Neck Surg* 2016, PMID 26419838): NCDB analysis of 22,653 cases of primary parotid cancer with pathologic LN evaluation. N0 patients had improved 5-yr OS compared to N+ (79% vs. 40%, $p < .001$). Patients with low-grade tumors had improved 5-yr OS vs. high grade (88% vs. 69%, $p < .001$). Incidence of N+ independently predicted by high grade (50.9% vs. 9.3% in low grade) and high T stage. **Conclusion: Incidence of occult nodal disease varies by histology. High T stage and grade predict nodal disease in most histologies.**

Table 15.7 Incidence of Nodal Metastases in Parotid Malignancies			
Primary Parotid Cancer Histology	**cN+ (%)**	**Occult N+ (%)**	**Occult N+ (High Grade % N+ /T4 % N+)**
Salivary ductal carcinoma	53.5	23.6	36/40
Adenocarcinoma NOS	45.2	19.9	31.6/31.6
Carcinoma ex-pleomorphic adenoma	23.9	11.8	19.2/35.5

(*continued*)

Table 15.7 Incidence of Nodal Metastases in Parotid Malignancies (*continued*)			
Primary Parotid Cancer Histology	**cN+ (%)**	**Occult N+ (%)**	**Occult N+ (High Grade % N + /T4 % N+)**
Mucoepidermoid carcinoma	20.2	9.3	21.8/21.6
Adenoid cystic carcinoma	14.2	7.0	9.6/13
Acinar cell carcinoma	10	4.4	24.5/11.5
Basal cell adenocarcinoma	9.4	6.3	6.7/22.2
Epithelial–myoepithelial carcinoma	4.8	1.5	0/0
Average	**24.4**	**10.2**	

Can salivary cancer be treated with RT alone?

Based on retrospective evidence, surgery is essential for local control and is the accepted standard of care for medically operable and technically resectable patients.

Mendenhall, University of Florida (*Cancer* 2005, PMID 15880750): RR of 224 patients treated between 1964 and 2003 with RT alone ($n = 64$) or surgery with RT ($n = 160$). Median dose was 74 Gy for RT alone and 66 Gy for postoperative. LRC was significantly worse with RT alone (stages I–III 89% vs. 70%, $p = .01$; stage IV 66% vs. 24%, $p = .002$; overall 81% vs. 40%, $p < .0001$). In patients with technically unresectable disease treated with RT alone, 10-yr LRC was 20%. **Conclusion: RT alone is inferior to surgery combined with RT in terms of LRC.**

Does neutron therapy offer improved control or survival outcomes?

Local control is improved without survival benefit. Cost and toxicity are significant.

Laramore, RTOG 8001-MRC Trial (*IJROBP* 1993, PMID 8407397): PRT in England and the United States of 25 patients with inoperable or unresectable salivary cancer randomized to photon/electron therapy or neutron therapy. CR was more frequent in neutron arm. LC was significantly improved in neutron arm (56% vs. 17%, $p = .009$), leading to early closure of trial. No difference in OS (15% vs. 25%, p = NS). However, severe late complications were seen in 69% of neutron patients vs. 15% of photon patients ($p = .07$). **Conclusion: Neutron RT improves local control, but does not improve survival, and has a much higher rate of long-term toxicity.**

Douglas, University of Washington (*Arch Otolaryngol Head Neck Surg* 2003, PMID 12975266): RR of 279 patients treated with fast neutrons for salivary gland cancers, 263 of whom had evidence of gross disease at time of treatment. MFU of 36 months. Total dose delivered was between 17.4 and 20.7 nGy, with fractions given 3 to 4 times per week. CSS and LRC were 67% and 59% at 6 years, respectively. Grades 3–4 RTOG toxicity at 6 years was 10%. **Conclusion: For gross residual disease, neutrons offer modest local control and good survival outcomes**.

Is modern RT as effective as neutron therapy with less toxicity?

This was suggested by a small RR from MSKCC, though data are limited.

Spratt, MSKCC (*Radiol Oncol* 2014, PMID 24587780): RR of 27 patients with unresectable salivary cancer treated with photons to median dose of 70 Gy with IMRT or 3D-CRT. Eighteen patients also received CHT. At MFU 52 months, 5-yr LRC was 47%, which compared favorably to neutron arm of RTOG 8001. **Conclusion: Modern photon therapy with or without CHT may be a reasonable alternative to neutrons with less toxicity.**

Is there a role for carbon ion therapy in the treatment of salivary gland tumors?

Jensen, COSMIC Trial (IJROBP 2015, PMID 26279022): *German prospective phase II trial of 53 patients with malignant salivary gland tumors. All patients treated with 24 Gy (RBE) C12 followed by IMRT 50 Gy. MFU 42 months. At 3 years, LC 82%, PFS 58%, and OS 78%. High rates of long-term hearing impairment*

(25%) and "adverse events of the eye" (20%). **Conclusion: Carbon ion + IMRT treatment offered good control outcomes, but with significant late toxicities**.

■ **Does the addition of adjuvant chemoRT improve outcomes compared to adjuvant RT alone?**

Several small retrospective analyses have demonstrated promising control rates.[21–23] Conversely, an NCDB analysis actually revealed inferior survival with adjuvant chemoRT compared to RT alone.[33] RTOG 1008 is a phase II/III RCT that aims to answer this question in high-risk salivary gland cancer.

Amini, NCDB (*JAMA Otolaryngol Head Neck Surg* 2016, PMID: 27541166): NCDB analysis of 2,210 patients with salivary gland cancer s/p resection comparing adjuvant chemoRT to adjuvant RT alone. Included grade 2 or 3 with ≥1 adverse feature (T3–4, N+, or margin 83% received RT, 17% received chemoRT). At MFU of 39 months, 5-yr OS was inferior with chemoRT compared to RT alone (39% vs. 54%, $p < .001$). OS with chemoRT was inferior on MVA (HR: 1.22, $p = .02$) and trended to inferiority on propensity score matched analysis (HR: 1.20, $p = .08$). **Conclusion: In high-risk salivary gland cancer, adjuvant chemoRT was not associated with improved OS compared to adjuvant RT alone, and may actually worsen outcomes.**

REFERENCES

1. Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinoma of the major salivary glands according to the WHO classification, 1992 to 2006: a population-based study in the United States. *Cancer Epidemiol Biomarkers Prev.* 2009;18(11):2899–2906. doi:10.1158/1055-9965.EPI-09-0638
2. Guzzo M, Locati LD, Prott FJ, et al. Major and minor salivary gland tumors. *Crit Rev Oncol Hematol.* 2010;74(2):134–148. doi:10.1016/j.critrevonc.2009.10.004
3. Andreasen S, Therkildsen MH, Bjorndal K, Homoe P. Pleomorphic adenoma of the parotid gland 1985–2010: a danish nationwide study of incidence, recurrence rate, and malignant transformation. *Head Neck.* 2016;38 Suppl 1:E1364–E1369. doi:10.1002/hed.24228
4. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg.* 1986;8(3):177–184. doi:10.1002/hed.2890080309
5. Saku T, Hayashi Y, Takahara O, et al. Salivary gland tumors among atomic bomb survivors, 1950–1987. *Cancer.* 1997;79(8):1465–1475. doi:10.1002/(SICI)1097-0142(19970415)79:8<1465::AID-CNCR4>3.0.CO;2-A
6. Leung SY, Chung LP, Yuen ST, et al. Lymphoepithelial carcinoma of the salivary gland: in situ detection of epstein-barr virus. *J Clin Pathol.* 1995;48(11):1022–1027. doi:10.1136/jcp.48.11.1022
7. Motz KM, Kim YJ. Auriculotemporal syndrome (Frey Syndrome). *Otolaryngol Clin North Am.* 2016;49(2):501–509. doi:10.1016/j.otc.2015.10.010
8. Gluck I, Ibrahim M, Popovtzer A, et al. Skin cancer of the head and neck with perineural invasion: defining the clinical target volumes based on the pattern of failure. *Int J Radiat Oncol Biol Phys.* 2009;74(1):38–46. doi:10.1016/j.ijrobp.2008.06.1943
9. Ko HC, Gupta V, Mourad WF, et al. A contouring guide for head and neck cancers with perineural invasion. *Pract Radiat Oncol.* 2014;4(6):e247–e258. doi:10.1016/j.prro.2014.02.001
10. Fang P. Internal mammary misfortune. *Int J Radiat Oncol Biol Phys.* 2017;97(3):447. doi:10.1016/j.ijrobp.2016.10.032
11. Halperin EC, Brady LW, Perez CA, Wazer DE. *Perez & Brady's Principles and Practice of Radiation Oncology.* LWW; 2013.
12. Maiorano E, Lo Muzio L, Favia G, Piattelli A. Warthin's tumour: a study of 78 cases with emphasis on bilaterality, multifocality and association with other malignancies. *Oral Oncol.* 2002;38(1):35–40. doi:10.1016/S1368-8375(01)00019-7
13. Pinkston JA, Cole P. Cigarette smoking and warthin's tumor. *Am J Epidemiol.* 1996;144(2):183–187. doi:10.1093/oxfordjournals.aje.a008906
14. Amit M, Binenbaum Y, Sharma K, et al. Incidence of cervical lymph node metastasis and its association with outcomes in patients with adenoid cystic carcinoma. An International Collaborative Study. *Head Neck.* 2015;37(7):1032–1037. doi:10.1002/hed.23711
15. Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of nodal metastasis in parotid malignancies: a national cancer data base study of 22,653 patients. *Otolaryngol Head Neck Surg.* 2016;154(1):121–130. doi:10.1177/0194599815607449
16. Lee A, Givi B, Osborn VW, et al. Patterns of care and survival of adjuvant radiation for major salivary adenoid cystic carcinoma. *Laryngoscope.* 2017;127(9):2057–2062. doi:10.1002/lary.26516
17. Can NT, Lingen MW, Mashek H, et al. Expression of hormone receptors and her-2 in benign and malignant salivary gland tumors. *Head Neck Pathol.* 2018;12(1):95–104. doi:10.1007/s12105-017-0833-y

18. Carrillo JF, Vazquez R, Ramirez-Ortega MC, et al. Multivariate prediction of the probability of recurrence in patients with carcinoma of the parotid gland. *Cancer.* 2007;109(10):2043–2051. doi:10.1002/cncr.22647
19. Storey MR, Garden AS, Morrison WH, et al. Postoperative radiotherapy for malignant tumors of the submandibular gland. *Int J Radiat Oncol, Biol, Phys.* 2001;51(4):952–958. doi:10.1016/S0360-3016(01)01724-2
20. Douglas JG, Koh WJ, Austin-Seymour M, Laramore GE. Treatment of salivary gland neoplasms with fast neutron radiotherapy. *Arch Otolaryngol Head Neck Surg.* 2003;129(9):944–948. doi:10.1001/archotol.129.9.944
21. Pederson AW, Salama JK, Haraf DJ, et al. Adjuvant chemoradiotherapy for locoregionally advanced and high-risk salivary gland malignancies. *Head Neck Oncol.* 2011;3:31. doi:10.1186/1758-3284-3-31
22. Schoenfeld JD, Sher DJ, Norris CM Jr, et al. Salivary gland tumors treated with adjuvant intensity-modulated radiotherapy with or without concurrent chemotherapy. *Int J Radiat Oncol Biol Phys.* 2012;82(1):308–314. doi:10.1016/j.ijrobp.2010.09.042
23. Tanvetyanon T, Qin D, Padhya T, et al. Outcomes of postoperative concurrent chemoradiotherapy for locally advanced major salivary gland carcinoma. *Arch Otolaryngol Head Neck Surg.* 2009;135(7):687–692. doi:10.1001/archoto.2009.70
24. Hotte SJ, Winquist EW, Lamont E, et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a princess margaret hospital phase II consortium study. *J Clin Oncol.* 2005;23(3):585–590. doi:10.1200/JCO.2005.06.125
25. Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol.* 2007;25(25):3978–3984. doi:10.1200/JCO.2007.11.8612
26. Wong SJ, Karrison T, Hayes DN, et al. Phase II trial of dasatinib for recurrent or metastatic c-KIT expressing adenoid cystic carcinoma and for nonadenoid cystic malignant salivary tumors. *Ann Oncol.* 2016;27(2):318–323. doi:10.1093/annonc/mdv537
27. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol.* 2018;15(12):731–747. doi:10.1038/s41571-018-0113-0
28. Fushimi C, Tada Y, Takahashi H, et al. A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. *Ann Oncol.* 2018;29(4):979–984. doi:10.1093/annonc/mdx771
29. Tchekmedyian V, Sherman EJ, Dunn L, et al. Phase II study of lenvatinib in patients with progressive, recurrent or metastatic adenoid cystic carcinoma. *J Clin Oncol.* 2019;37(18):1529–1537. doi:10.1200/JCO.18.01859
30. Cohen RB, Delord JP, Doi T, et al. Pembrolizumab for the treatment of advanced salivary gland carcinoma: findings of the phase 1b KEYNOTE-028 study. *Am J Clin Oncol.* 2018;41(11):1083–1088.
31. Videtic GMM WN, Vassil AD. *Handbook of Treatment Planning in Radiation Oncology.* 2nd ed. Demos Medical; 2015. doi:10.1891/9781617051975
32. Douglas JG, Goodkin R, Laramore GE. Gamma knife stereotactic radiosurgery for salivary gland neoplasms with base of skull invasion following neutron radiotherapy. *Head Neck.* 2008;30(4):492–496. doi:10.1002/hed.20729
33. Amini A, Waxweiler TV, Brower JV, et al. Association of adjuvant chemoradiotherapy vs radiotherapy alone with survival in patients with resected major salivary gland carcinoma: data from the national cancer data base. *JAMA Otolaryngol Head Neck Surg.* 2016;142(11):1100–1110. doi:10.1001/jamaoto.2016.2168