Chapter 10
Salivary Gland Tumors

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III

PEARLS

- Salivary gland neoplasms account for ~3–5% of H&N cancers.

ANATOMY

- Major salivary glands consist of the paired parotid, submandibular, and sublingual glands.
- Minor salivary glands located throughout oral cavity, pharynx, and paranasal sinuses.
- Parotid glands located lateral to the mandibular ramus and masseter muscle.
  - Facial nerve divides parotid gland into superficial and deep lobes.
  - Parotid gland drains into oral cavity through Stensen's duct adjacent to upper second molar.
  - Lymphatic drainage from parotid gland is to intraparotid and periparotid nodes, followed by ipsilateral level I, II, and III nodes.
- Submandibular gland is located under the horizontal mandibular ramus.
  - Submandibular gland is lateral to and abuts lingual (V3) and hypoglossal nerves and is medial to mandibular and cervical branches of CN VII.
  - Submandibular glands drain into oral cavity through Wharton's duct.
  - Submandibular lymphatic drainage is to levels I, II, III.
  - Drainage from parotid and submandibular glands to contralateral nodes is rare.
- Sublingual gland located superior to mylohyoid muscle and deep to mucous membrane.
  - Sublingual glands drain into oral cavity through Rivinus ducts or Bartholin's duct.

- Incidence of LN involvement varies according to histology and site.
- Overall risk of lymph node involvement is less common than for SCC.
- Adenoid cystic carcinoma has the lowest frequency of cervical node metastasis (5–8%), but the highest propensity for perineural spread.
- LN metastases are most common with minor salivary gland tumors followed by submandibular gland tumors followed by parotid tumors.

HISTOLOGY

- Majority of salivary gland neoplasms are benign.
- Inverse relationship exists between size of parotid gland and ratio of malignant to benign cancer.
- For tumors of the parotid gland, 80% are benign and 20% malignant.
- Most parotid tumors present as painless swelling.
- Pleomorphic adenoma is most common benign salivary gland neoplasm.
- Salivary gland cancer is notable for its remarkable histologic diversity.
- Most common malignant histology of parotid gland is mucoepidermoid carcinoma.
- Most common malignant histology of submandibular and minor salivary glands is adenoid cystic carcinoma.
- Acinic cell carcinoma usually occurs only in the parotid gland.

OTHER

- Prognostic variables include grade, postsurgical residual disease, and LN status.
- Larger tumor size and cranial nerve involvement associated with poor prognosis.
- Patterns of failure generally dominated by high rates of distant metastases.
- Most likely sites for DM is lung, followed by bone and liver.
- Adenoid cystic, ductal, and undifferentiated carcinoma have highest rates of DM.
- Loss of salivary function is permanent and complete after 35 Gy with standard fx.

- Despite high DM rate, there is generally no role for chemotherapy.

WORKUP

- H&P with bimanual palpation. Carefully examine cranial nerves and for trismus.
- CT and/or MRI of head and neck. PET scan is still investigational for salivary gland cancers.
- Fine-needle aspiration biopsy.
- Chest X-ray.
- Dental evaluation prior to the start of RT.
- Note that minor salivary gland cancer is staged according to systems for the anatomic site of origin (e.g., oral cavity, sinuses, etc.)

STAGING: MAJOR SALIVARY GLAND

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

(AJCC 6TH ED., 2002)

Primary tumor (T)

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 more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3: Tumor more than 4 cm and/or having extraparenchymal extension
T4a: Moderately advanced disease. Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b: Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

**Note*: Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph nodes metastasis
N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
N2a: Metastasis in single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

(AJCC 7TH ED., 2010)

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
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Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension

continued

N2b: Metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
N3: Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis present

Stage grouping		~2/5-Year OS	
I:	T1N0M0	I:	88/75%
II:	T2N0M0	II:	77/59%
III:	T3N0M0, T1-3N1M0	III:	68/47%
IVA:	T4aN0-2M0, T1-3N2M0	IV:	47/28%
IVB:	T4b any N M0, any T N3 M0		
IVC:	Any T, any N, M1		

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N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
N3: Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Anatomic stage/prognostic groups

I:	T1 N0 M0
II:	T2 N0 M0
III:	T3 N0 M0
	T1-T3 N1 M0
IVA:	T4a N0 M0
	T4a N1 M0
	T1-T3 N2 M0
	T4a N2 M0
IVB:	T4b Any N M0
	Any T N3 M0
IVC:	Any T Any N M1

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TREATMENT RECOMMENDATIONS

GENERAL POINTS

- Surgery forms the mainstay of definitive treatment for salivary gland malignancies.
- Complications of surgery include facial nerve dysfunction and Frey's syndrome.
- Frey's syndrome consists of gustatory flushing, sweating, auriculotemporal syndrome.
- Superficial parotidectomy can generally be performed for low-grade parotid tumors.
- Facial nerve-sparing approaches can often be performed to preserve function, cosmesis.
- Neck dissection recommended for clinically + LN or high-grade histology.
- Indications for post-op RT are currently controversial as there is no randomized data analyzing the role of post-op RT.
- Consider post-op RT for PNI, close/+ margins, high-grade tumors, and T3-4 tumors.
- Patients with pathological LN involvement should receive post-op RT.
- RT alone is indicated for medically inoperable and unresectable tumors. LC rates with RT alone range from 20 to 80%.
- Neutron therapy may achieve better LC for unresectable or inoperable tumors.
- Brachytherapy or intraoperative RT can be considered for recurrent tumors.
- IMRT reduces mean doses to normal structures and allows dose-escalation to tumor.
- Chemotherapy is considered investigational.

2002 Stage	Recommended treatment
Resectable T1-2N0, superficial	■ Surgery followed by observation if low-grade. ■ Consider post-op RT if adenoid cystic or intermediate to high grade
Resectable, T3-4 or N+	■ Surgery with neck dissection for LN+ or high grade followed by post-op RT for close/+ margins, intermediate–high grade, adenoid cystic, PNI, LVSI. RT to neck for pN+, T3-4, and/or high grade to reduce local/regional failure (>20–50% down to 5–10%)

continued

Unresectable	■ Definitive RT. LRC may be higher with neutrons than photons
Pleomorphic adenoma	■ If total parotidectomy, LR <1 vs. ~20% after simple enucleation. Post-op RT controversial and sometimes indicated if multifocal, PNI, or residual disease. Post-op RT LRC is 90–95%

STUDIES

- Fu et al. (1977): retrospective analysis of 100 cases of major and minor salivary gland cancer treated with surgery or surgery + RT. The addition of post-op RT significantly improved LC for patients with adenoid cystic carcinoma, locally advanced (stage III/IV) disease, and + margins.
- Garden et al. (1997): retrospective analysis of 166 patients with parotid gland malignancies treated with surgery + RT. On multivariate analysis, facial nerve sacrifice and pathologic cervical nodal disease were associated with LF. The actuarial 5-, 10-, and 15-year LC rates were 92, 90, and 90%, respectively.
- Garden et al. (1995): retrospective analysis of 198 patients with adenoid cystic carcinoma of the H&N treated with surgery + RT. Five- and 10-year LC was 95 and 86%, respectively. Patients with positive margins and major (named) nerve involvement were at significantly increased risk of LR.
- Armstrong et al. (1990): matched-pair analysis of 92 patients treated with surgery vs. surgery and post-op RT. The addition of post-op RT improved outcome for patients with stage III/IV disease and for patients with pathological + LN.
- Armstrong et al. (1992): retrospective review of 474 previously untreated patients with major salivary gland cancers in an attempt to define indications for elective treatment of the neck. Overall, clinically occult, pathologically + LN occurred in only 12% of patients. On multivariate analysis, only primary tumor size and grade were significant risk factors.
- Chen et al. (2007a, b): retrospective analysis of 251 patients with clinically N0 salivary gland carcinomas treated with surgery and postoperative radiation therapy. Ten-year regional (neck) failure was 13%. Median time to neck relapse was 1.4 year. Ten-year actuarial rates of nodal failure for T1, T2, T3, and T4 disease were 7, 5, 12, and 16%, respectively. ENI reduced 10-year estimated nodal failure from 26 to 0%.
- North et al. (1990): retrospective analysis of 87 patients with major salivary gland cancer treated with surgery or surgery +

post-op RT. The addition of post-op RT significantly improved 5-year OS (59→75%) LF (26→4%).

- Storey et al. (2001): retrospective analysis of 83 patients treated with surgery and postoperative RT for submandibular gland malignancies. Actuarial 10-year LRC was 88%, 10-year DFS was 53%, and OS was 55%.
- Terhaard et al. (2005): retrospective analysis of 538 patients treated for major salivary gland tumors. Post-op RT improved 10-year LC compared with surgery alone for patients with T3-4 tumors (18→84%), close (55→95%) and incomplete resection (44→82%), bone invasion (54→86%), and PNI (60→88%).
- Chen et al. (2007a, b): retrospective analysis of 207 patients with major salivary gland carcinomas treated with definitive surgery without postoperative radiation therapy. Five and 10-year LRC were 86 and 74%, respectively. Pathologic lymph node metastasis, high histologic grade, positive margins, and T3-4 disease were independent predictors of LRR. Presence of any one of these factors had associated 10-year LRC of 37–63%.
- Spiro et al. (1993): retrospective analysis of 62 patients with parotid gland malignancies treated with surgery and post-op RT. Actuarial 5/10-year LC was 95/84%. Patients with larger tumors, recurrent disease, or facial nerve involvement had lower DFS.
- Boahene et al. (2004): retrospective analysis of 89 patients with mucoepidermoid carcinoma of parotid gland treated predominantly with surgery alone. DFS at 5, 15, and 25 years were 99, 97, and 97%, respectively.
- Garden et al. (1994): retrospective analysis of 160 patients treated with surgery and post-op RT for minor salivary gland cancer. Fifteen-year LC, DFS, and OS were 78, 54, and 43%, respectively. On multivariate analysis, paranasal primary site associated with increased risk of LF.
- Loh et al. (2009): retrospective analysis of 171 patients treated by surgery alone (30.7%), surgery and post-op RT (30.7%), or RT alone (38.6%) for minor salivary gland cancer. Ten-year DFS, DSS, and OS were 48, 67, and 58%, respectively. LR and DM were 27 and 19%, respectively. On multivariate analysis, grade of tumor associated with DSS.
- RTOG/MRC (Laramore et al. 1993): randomized trial of 32 patients with inoperable primary or recurrent salivary gland cancer compared fast neutron RT vs. conventional RT with photons and/or electrons. Trial was stopped early due to advantage

with neutrons [improved 10-year LRC, but not OS (15–25%)]. Distant metastases accounted for most failures.

- Wang and Goodman (1991): retrospective analysis of 24 patients treated with RT alone for salivary gland malignancies. All lesions were irradiated by accelerated hyperfractionated photons (bid) with 1.6 Gy per fraction, intermixed with various boost techniques including electron beam, intraoral cone, interstitial implant, and/or submental photons for a total of 65–70 Gy. Five-year LC for parotid gland lesions was 100% with 65% OS. For minor salivary gland tumors, the 5-year LC was 78% and OS was 93%.
- Mendenhall et al. (2004): retrospective analysis of 101 patients treated with RT for adenoid cystic carcinoma of the H&N. Ten-year LC was 43% for patients treated with RT alone compared to 91% for patients treated with surgery and post-op RT. On multivariate analysis, T stage and clinical nerve invasion influenced CSS.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Simulate supine with customized immobilization devices.
- Head secured in holder with face mask and neck hyperextended.
- All incisional scars and masses are wired for visualization.
- Bite block used to facilitate immobilization and reduce amount of normal tissue in field.
- Shoulder pull board can be employed to maximally depress shoulders.
- CT-planning allows for more accurate dose distribution.
- Various techniques have been described for salivary gland radiation.
- Post-op tumor volume includes operative bed with at least 2 cm margin.
- Mixed photon/electron beam can be used en face to cover target volume with margin. Weighting is generally 50–80% weighting toward electrons. Electron energy depends on distance from skin of ipsilateral cheek to oral mucosa. Typically, 12–16 MeV electrons are used in combination with 4–6-MV photons.
- Wedge pair technique with photons can also be used with anterior/posterior obliques. To avoid exit dose through contralateral eye, slightly angle beams inferiorly. Include entire surgical bed in irradiated tumor volume with bolus over the scar.

- Consider neutron therapy for unresectable or medically inoperable tumors.
- IMRT may be used to spare normal tissues and dose-escalate.
- Elective RT to the neck depends on histology, primary site, and presentation.
- Treatment of contralateral lymph nodes is unnecessary since failure there is rare.
- Using photons, AP/PA, or direct AP fields can be used.
- Neck field is angled obliquely to keep off spinal cord.
- With neck RT, attention to geometric match with primary field is essential.
- Half-beam block is used for the cranial edge of the neck field to eliminate divergence.
- For adenoid cystic carcinoma, irradiate pathways of cranial nerves to base of skull.

DOSE PRESCRIPTIONS

- Post-op RT, negative margins: 60–63 Gy at 1.8–2 Gy/fx
- Post-op RT, +margins 66 Gy at 1.8–2 Gy/fx
- RT alone or post-op RT for gross residual disease: 70 at 1.8–2 Gy/fx
- Elective neck RT: 50–54 Gy at 1.8–2 Gy/fx

DOSE LIMITATIONS

- Spinal cord ≤45 Gy, brainstem ≤54 Gy, optic chiasm and nerves ≤54 Gy, cochlea ≤50 Gy, mandible ≤60–70 Gy, temporal brain ≤60 Gy, uninvolved salivary glands ≤24 Gy.

COMPLICATIONS

- Xerostomia, trismus, otitis media, hair loss, skin erythema and desquamation, dental problems, taste loss, hypothyroidism, mucositis, oral candidiasis, esophagitis, CN palsy, second malignancy.

FOLLOW-UP

- H&P every 1–3 months for 1 year, every 2–4 months for second year, every 4–6 months for years 3–5, and annually thereafter. Regular head imaging with MRI and CXR as indicated. TSH every 6–12 months if neck irradiated.

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