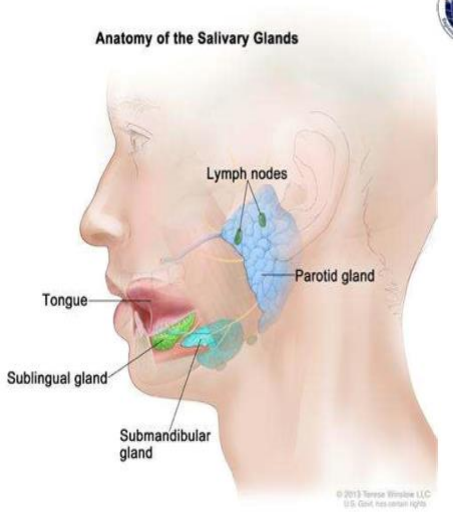

Adjuvant Radiotherapy Of Salivary Gland Tumors

Dr. Arpana Shukla

4/09/2022

Content

- Introduction
- Natural History
- Diagnostic workup and Staging
- Pathologic classification
- Prognostic factors
- Indications for RT
- RT Techniques
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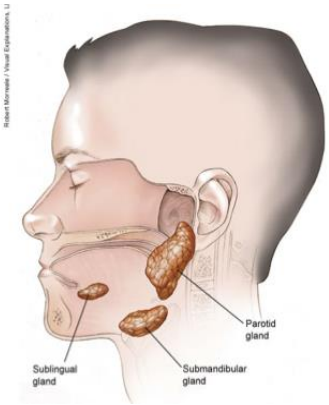
- Sequalae of treatment

Salivary Gland Tumors



- 3 large paired glands-Parotid, submandibular and sublingual.
- Minor smaller glands located throughout the upper aerodigestive tract.
- 1-5% of all H&N Cancers.
- ¾ parotid masses are benign.
- 70% of all salivary tumors arise in the parotid gland,22% in minor salivary gland and 8%in submandibular gland.
- Two third of the cancers are located in the Major salivary glands(parotid 53%, SMG 12%, sublingual 1.5%)and one third in the minor salivary glands.

Salivary Gland Tumors

- The proportion of malignant tumor increases from parotid (25%),.to submandibular (43%),minor salivary glands(65%).
- Most common salivary gland tumor Pleomorphic adenoma .
- Most common malignant tumor Mucoepidermoid cancer.
- Risk Factors :
  - Diet deficient in VitA and Vit C
  - Radiation exposure
  - Women employed in saloons
- Rarity and Heterogenity of tumor poses a management problem.

TABLE 46.2 DISTRIBUTION OF PRESENTING SITES OF INTRAORAL MINOR SALVARY GLAND TUMORS

Site	No. of Patients (%)	Percentage Malignant
Palate	206 (54)	43
Upper lip	64 (17)	9
Buccal mucosa	54 (14)	37
Retromolar region	20 (5)	95
Lower lip	18 (5)	56
Floor of mouth	13 (3)	69
Tongue	5 (1)	60
Total	380	41

Adapted from Buchner A, Merrell P, Carpenter W. Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. *J Oral Pathol Med* 2007;36:207–214.

Widely distributed in upper aerodigestive tract pharynx,trachea
Nasal cavity & PNS , Nasopharynx

Clinical Presentation

- A lump on the face, neck, or mouth that is usually painless.
- Numbness in the face.
- Pain or swelling in the face, chin, jawbone area, or neck.
- A difference between the size and/or shape of the left and right sides of the face or neck .
- Sign and symptom of minor salivary gland tumor depends on location .

Natural History

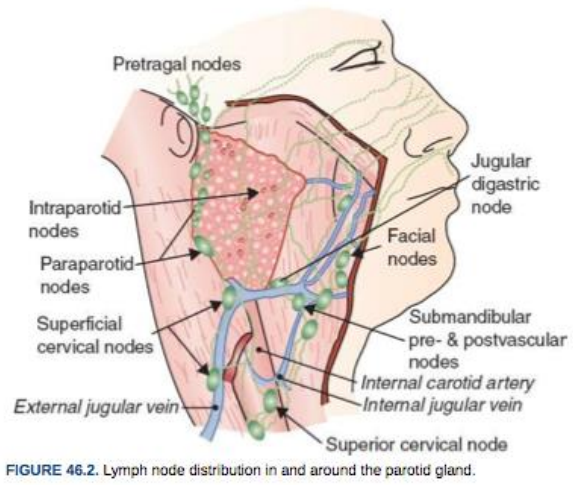


FIGURE 46.2. Lymph node distribution in and around the parotid gland.

- Local invasion is the initial route.
- 18 to 25% with malignant parotid salivary gland tumor present with facial palsy from cranial nerve invasion.
- Nodal involvement depends upon tumor loction, histology and T STAGE.

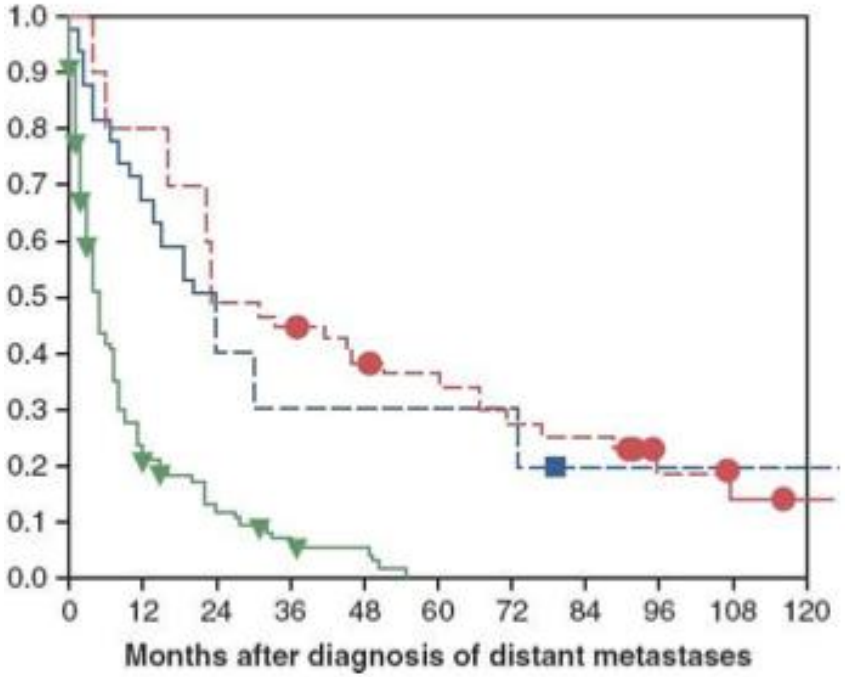
TABLE 46.1 RISK ESTIMATION (%) FOR POSITIVE NECK NODES

Summation: T Score + Histologic Type Score	Parotid Gland	Submandibular Gland	Oral Cavity	Other Locations
2	4	0	4	0
3	12	33	13	29
4	25	57	19	56
5	33	60	—	—
6	38	50	—	—

T1 = 1; T2 = 2; T3-T4 = 3; acinic/adenoid cystic/carcinoma ex pleomorphic adenoma = 1; mucoepidermoid = 2; squamous/undifferentiated = 3.

Decision to treat neck will be indicated by a score of atleast 4.

Distant metastasis



RE 46.3. Survival after diagnosis of distant metastases depending on histology, e of the nationwide Dutch study. (•) adenoid cystic carcinoma[35]; (■) acinic cel noma[11]; (▲) others[36]; $P < .001$. (From Terhaard CHJ, Lubsen H, Van der Tweel Salivary gland carcinoma: Independent prognostic factors for locoregiona l, distant metastases, and overall survival: results of the Dutch Head and Neck logy Cooperative Group. *Head Neck* 2004;26[8]:681–693. Copyright © 2004 Periodicals, Inc. Reprinted by permission of John Wiley & Sons, Inc.)

- 3-4% of pt at presentation and 33% after 10 years.
- Fairly common with adenoid cystic, salivary duct, squamous cell and undifferentiated Ca.
- 5 year after diagnosis of DM 1/3 pts are still alive, 10% alive after 10 years.

Survival Stage Wise

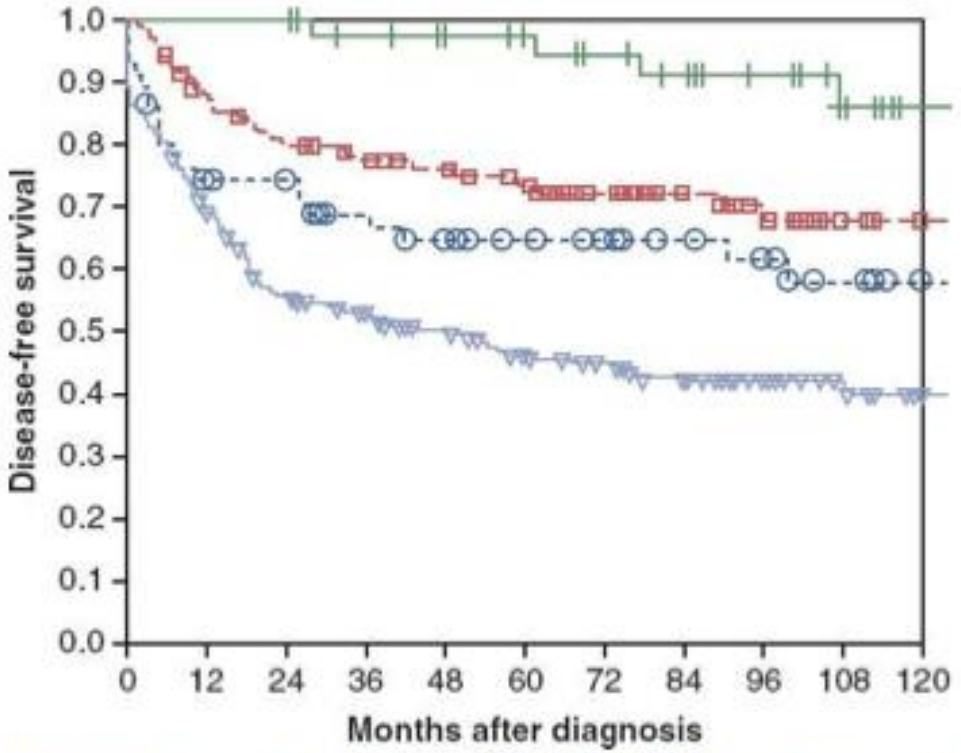


FIGURE 46.6. Disease-free survival for major salivary glands according to the 2002 classification of the American Joint Committee on Cancer. Results of the nationwide Dutch study: +, stage I; □, stage II; ○, stage III; ∇, stage IV.

Management Of Parotid Tumors Diagnosis-Level Of Evidence

Diagnostics		
Clinical examination	Important for the differentiation between benign and malignant tumor: fast growing, facial palsy, pain, fixation are signs of malignancy	Cohort studies
Ultrasound and fine-needle aspiration cytology	Accurate for benign superficial tumors	Cohort studies, meta-analysis of cohort studies
MRI	Accurate for large tumors, deep lobe tumors, malignant tumors	Cohort studies
Core needle biopsy	Alternative if fine-needle aspiration cytology is not available of if the cytopathologist suggests that fine-needle aspiration cytology is not sufficient for diagnosis	Cohort studies
Frozen sections	Alternative if fine-needle aspiration cytology is not available or if fine-needle aspiration cytology was not conclusive	Cohort studies, meta-analysis of cohort studies
Treatment		

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

- Was developed by an international consortium of experts and endorsed by the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC)
- The effort started in September 2015 and the atlas was published in 2018
- Aims to standardize reporting terminology in order to replace the conventional, descriptive interpretation for salivary gland fine needle aspirations (FNA) for better communication between clinicians and between institutions
- Main outputs useful for clinical decisions and lab quality control are risk of malignancy (ROM) and frequency of each diagnostic category

- Consists of 6 diagnostic categories:

1. Nondiagnostic

2. Nonneoplastic Atypia of undetermined significance (AUS)

3. Neoplasm (benign)

4 . salivary gland neoplasm of uncertain malignant potential [SUMP])

5 . Suspicious for malignancy (SM)

6. Malignant

Table 1 Diagnostic categories and ROM in the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC).

Diagnostic category	% ROM
I. Nondiagnostic	25
II. Non-neoplastic	10
III. Atypia of Undetermined Significance (AUS)	20
IV. Neoplasm	
IVA. Neoplasm: Benign	<5
IVB. Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)[e]	35
V. Suspicious for Malignancy	60
VI. Malignant	90

Abbreviation: ROM, risk of malignancy.

TABLE 3 | TNM Stages for parotid cancer.

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1, T2, T3 N1 M0
Stage IVA	T1, T2, T3 N2 M0
	T4a N0, N1, N2 M0
Stage IVB	T4b Any N M0
	Any T N3 M0
Stage IVC	Any T Any N M1

Most Histologically Heterogenous Group

TABLE 4 | WHO histological classification of salivary gland tumors 2017 (42, 43).

Benign epithelial tumors	Malignant epithelial tumors
Pleomorphic adenoma 8940/0	Acinic cell carcinoma 8550/3
Myoepithelioma 8982/0	Mucoepidermoid carcinoma 8430/3
Basal cell adenoma 8147/0	Adenoid cystic carcinoma 8200/3
Warthin tumor 8561/0	Polymorphous adenocarcinoma 8525/3
Oncocytoma 8290/0	Epithelial-myoepithelial carcinoma 8562/3
Canalicular adenoma and other ductal adenomas 8149/0	Clear cell carcinoma 8310/3
Sebaceous adenoma 8410/0	Basal cell adenocarcinoma 8147/3
Lymphadenoma	Sebaceous adenocarcinoma 8410/3
Sebaceous 8410/0	Secretory carcinoma 8502/3
Non-sebaceous 8410/0	
Ductal papillomas 8503/0	Intraductal carcinoma
	Oncocytic carcinoma 8290/3
Sialadenoma papilliferum 8406/0	Salivary duct carcinoma 8500/3
Cystadenoma 8440/0	Adenocarcinoma, NOS 8140/3
	Myoepithelial carcinoma 8982/3
Soft tissue tumors	Carcinoma ex pleomorphic adenoma 8941/3
Hemangioma 9120/0	Poorly differentiated carcinoma 8020/3
	Carcinosarcoma 8980/3
Hematolymphoid tumors	Squamous cell carcinoma 8070/3
Hodgkin lymphoma	
Diffuse large B-cell lymphoma 9680/3	
Extranodal marginal zone	Lymphoepithelial carcinoma 8082/3
B-cell lymphoma 9699/3	
Hodgkin lymphoma	Sialoblastoma 8974/1
	Secondary tumors

WHO Classification 2020

Key changes in the 2017 WHO classification of salivary gland tumours[8]

Key changes	Explanatory notes
New entities	
Secretory carcinoma	First described in 2010.[14] Formerly known as mammary analogue secretory carcinoma (MASC)
Sclerosing polycystic adenosis	First described in 1996.[15] There is controversy over its status as a neoplasm
New names	
Polymorphous adenocarcinoma	Formerly polymorphous low-grade adenocarcinoma
Intraductal carcinoma	Formerly low grade cribriform cystadenocarcinoma, low grade salivary duct carcinoma, salivary duct carcinoma *in situ*
Poorly differentiated carcinoma	Single category includes undifferentiated carcinoma, large and small cell neuroendocrine carcinoma
Clarifications, changes	
Adenocarcinoma NOS	Definition broadened to include rare entities, including: cystadenocarcinoma, mucinous (cyst) adenocarcinoma, papillary cystadenocarcinoma
Cystadenocarcinoma	Cystadenocarcinoma is removed as a separate entity (see above)
Mucinous adenocarcinoma	Mucinous adenocarcinoma is removed as a separate entity (see above)
Metastasising pleomorphic adenoma	Moved from malignant category to a variant of benign pleomorphic adenoma
Carcinoma ex-pleomorphic adenoma	Clarifications on diagnostic terminology: should explicitly state the histological type of malignant component. Definition of minimally invasive changed from 1.5 mm to "<4—6 mm"
Sialadenoma papilliferum	Given its own category. No longer a "ductal papilloma"
Ductal papilloma	A single name for two variants: inverted ductal papilloma and intraductal papilloma
Lymphadenoma	A single category replacing sebaceous and non-sebaceous lymphadenomas. Sebaceous-type is regarded as a simple variant
Non-neoplastic epithelial lesions	New category, includes sclerosing polycystic adenosis, nodular oncocytic hyperplasia, lymphoepithelial sialadenitis, intercalated duct hyperplasia

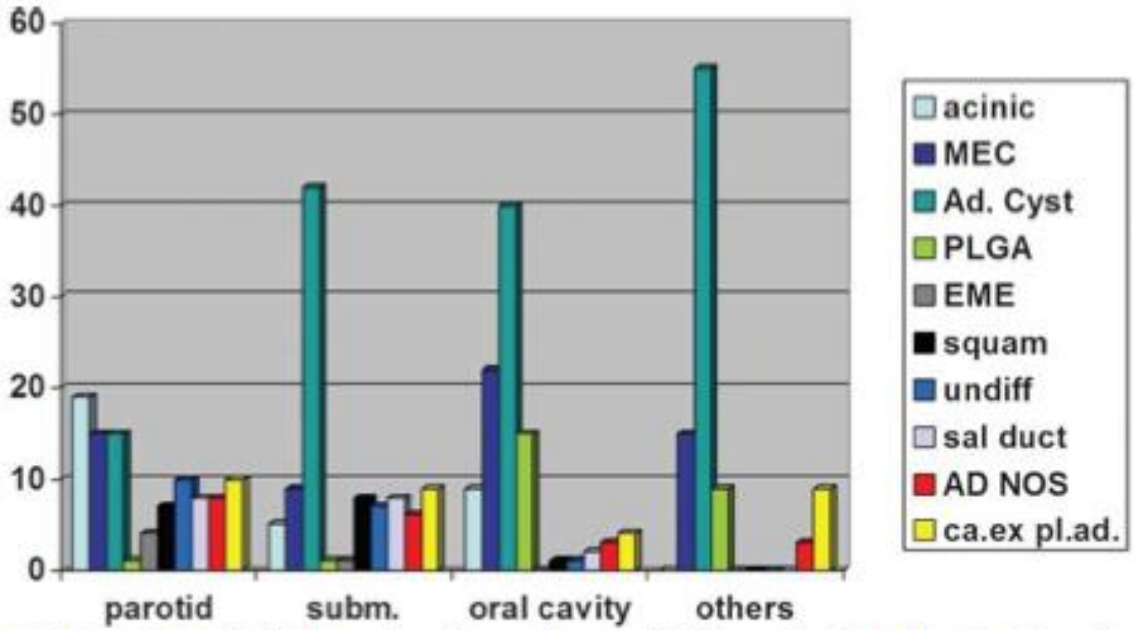


FIGURE 46.7. Distribution of various cell types (%) in series from the Dutch study, depending on site. Ad. Cyst, adenoid cystic; AD NOS, adenocarcinoma not otherwise specified; ca. ex pl. ad., carcinoma ex pleomorphic adenoma; EME, epithelial myoepithelial carcinoma; MEC, mucoepidermoid cancer; PLGA, polymorph low-grade adenocarcinoma; sal duct, salivary duct carcinoma; squam, squamous cell carcinoma; subm, submandibular. undiff, undifferentiated.

Prognostic Factors – Associated With Poor Outcome

– Extent of disease (advance T and N status)

– Positive or close resection margins

– Nerve involvement , Perineural invasion ,Preoperative facial nerve dysfunction

– Grade: high-grade mucoepidermoid Ca,high grade adenoid cystic Ca, undifferentiated Ca, adenoCa NOS, SCC, salivary duct Ca.

– High Ki67 and low p27 expression: associated with shorter DFS in adenoid cystic and mucoepidermoid Ca.

- HER2/neu overexpression in salivary gland carcinoma

- DNA Aneuloploidy

- Older age, male sex, smoking history

with the solid type and thus with poor prognosis.

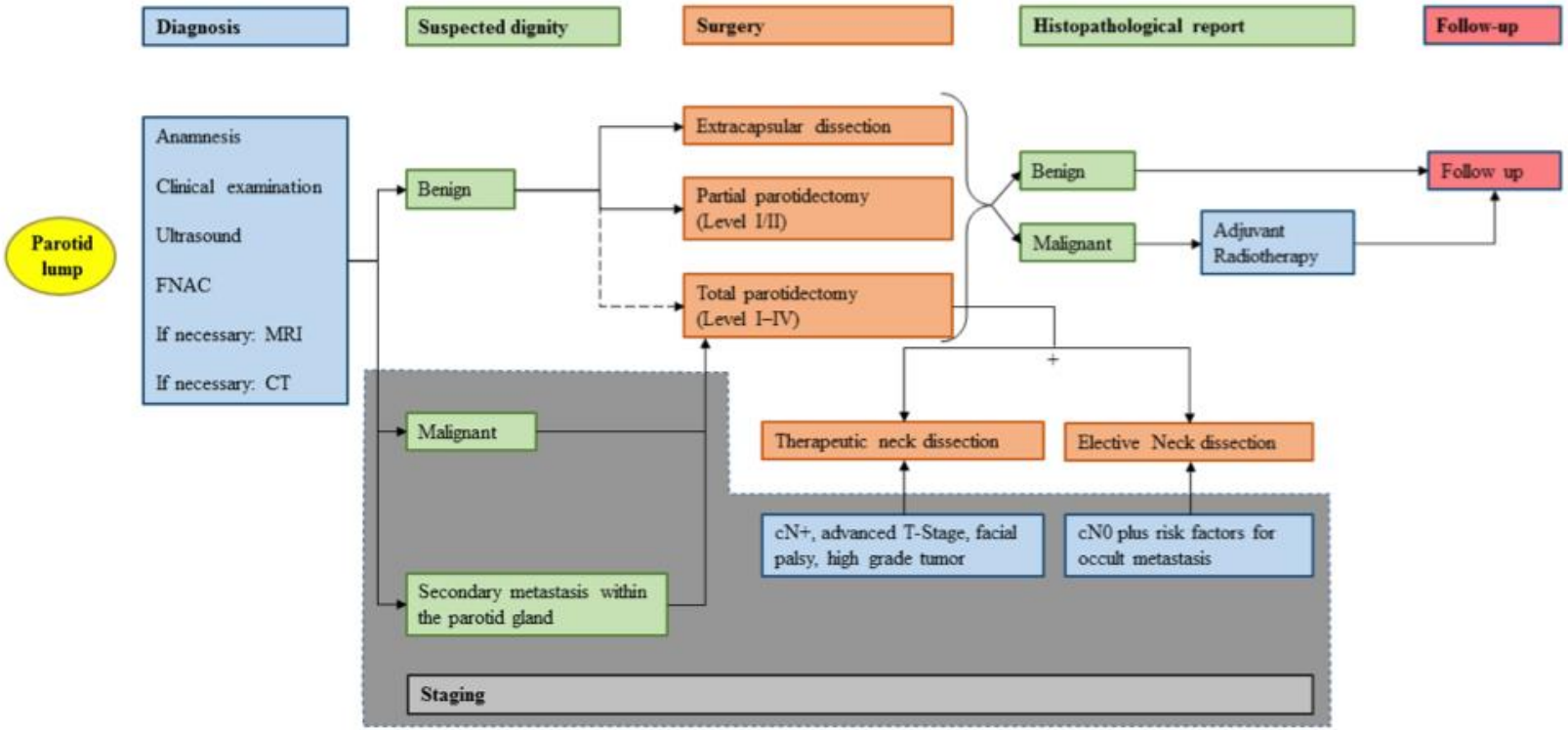
TABLE 46.5 PROGNOSTIC FACTORS FOR SALIVARY GLAND CANCER—SELECTION OF MULTIVARIATE ANALYZED STUDIES

Study (by Name of First Author)	No.	Locoregional Control	Distant Meta-Analyses	Survival
General				
Terhaard[20,60]	565	L: T, site, bone inv. R: N VII dysfunction, N L + R: Margin, therapy[a]	Gender, T, N, skin, histology, perineural inv.	OS: Gender, age, T, skin inv., bone inv., comorbidity
Holtzman[74]	291	L: T, therapy[b]	Stage	DFS + OS: Stage, clinical nerve invasion, therapy[a]
Bjorndal[75]	871	L + R: Stage, therapy[b]		
Chen, adenoid cystic[76]	140	L + R: Stage, margin, vasc. invasion, grade		
Chen, S alone[93]	207	L + R: T4, perineural inv., major nerve involvement, therapy[a] L + R: pN+, grade, margin, T3-T4		OS: Age, latency, stage, margin, vasc. invasion
Major				
Yun Li[78] (SEER)	4218			OS + DFS: Age, gender, grade, site (par > subm), T,N, therapy[a]
Parotid				
Spiro[57]	470			OS: Stage, age, histology, site
Bhattacharryya[55]	903			OS: Age, T, N, extraglandular extension
Van der Poorten[21]	237			DFS: Age, pain, T, N, perineural + skin inv., N VII dysfunction
Poulsen[77]	209	L: Age, N, margin, grade		
Submandibular				
Bhattachatyya[35]	370			OS: Age, grade
Storey[50]	83	Grade, histology, margin, early years		DS: Early years
Minor				
Jones[7]	103	L: T, N		OS: T, general condition
Lopes[29]	128	R: Stage N, histology, bone invasion		DFS: Stage, therapy[b]
	116			DFS: Grade, T, margin

Management Of Parotid Tumors-Level Of Evidence

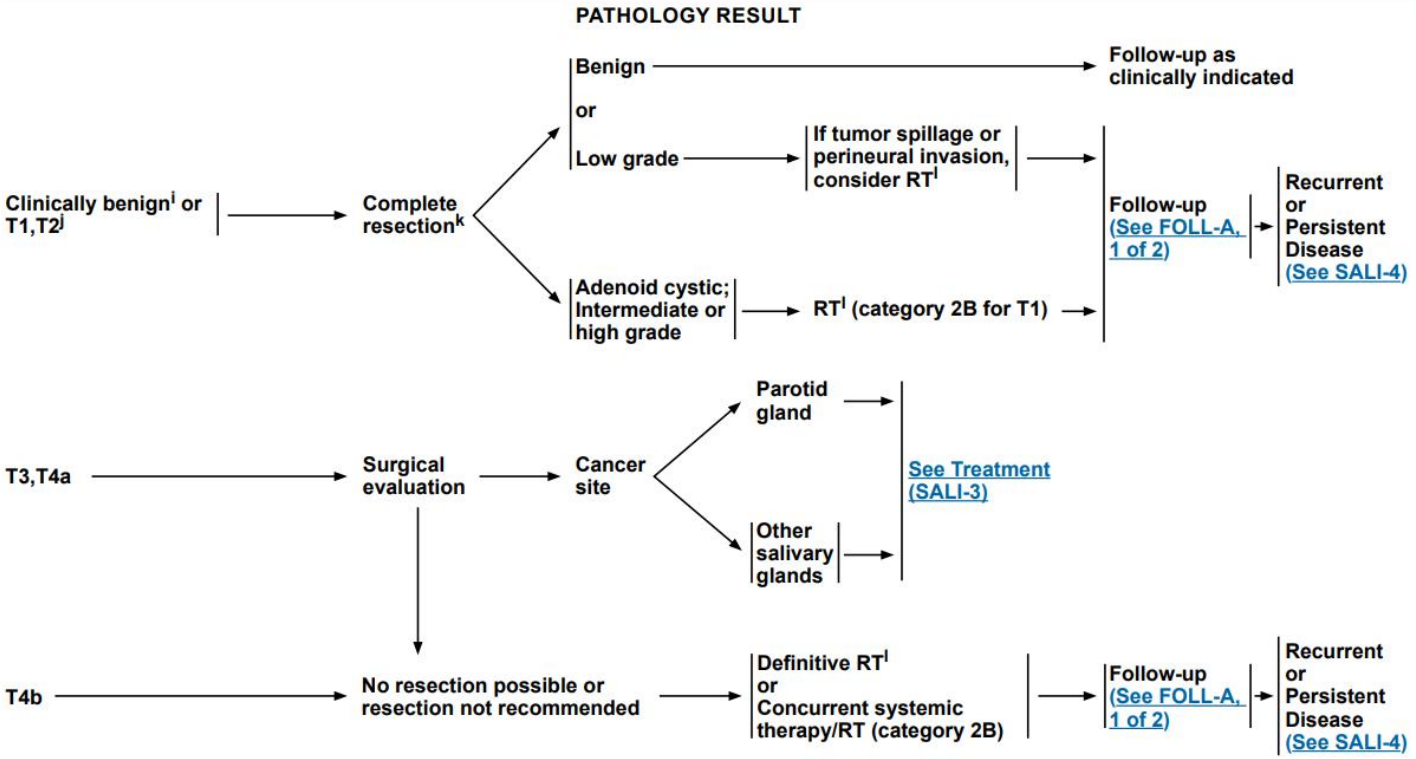
Treatment		
	conclusive	
Wait-and-scan	For selected cases of Warthin tumors	Descriptive studies
Partial or superficial parotidectomy	For benign tumors in the superficial lobe	Cohort studies, meta-analysis of cohort studies
Extracapsular dissection	For selected benign tumors in the superficial lobe	Cohort studies, meta-analysis of cohort studies
Total parotidectomy	For benign tumors of the deep lobe, extension into the parapharyngeal space, malignant tumor without facial nerve infiltration	Cohort studies
Radical parotidectomy	For malignant tumor with facial nerve infiltration	Descriptive studies
Curative neck dissection	For cN +parotid cancer including level I-V	Cohort studies
Elective neck dissection	For cN +parotid cancer, at least level I-III	Cohort studies
Facial nerve rehabilitation	If reconstruction is possible in case of parotid cancer with facial nerve infiltration as single stage procedure	Descriptive studies
Radiotherapy, adjuvant	For all cases of advanced-stage disease (T3/T4), high-grade tumors, always for adenoid cystic carcinoma, close or positive margins, bone invasion, lymph node metastases (more than three metastatic nodes), perineural and/or vascular invasion	Cohort studies
Radiotherapy, definitive	For non-resectable parotid cancer	Mainly cohort studies, a few non-randomized controlled trials
Chemotherapy, adjuvant	No effectivity is adjuvant therapy together with radiotherapy, compared to adjuvant therapy alone	Cohort studies
Chemotherapy, palliative	Low effectivity	Descriptive studies
Biologicals	No clear demonstration of effectivity in metastatic/ recurrent parotid cancer	Small controlled non-randomized phase I-II trials

Heterogenous nature of tumor with various histopathological types and rarity
Limits study size and ability to do phase III TRIALS


Diagnosis
Suspected dignity
Surgery
Histopathological report
Follow-up
Parotid lump
Anamnesis
Clinical examination
Ultrasound
FNAC
If necessary: MRI
If necessary: CT
Benign
Malignant
Secondary metastasis within the parotid gland
Extracapsular dissection
Partial parotidectomy (Level I/II)
Total parotidectomy (Level I–IV)
Therapeutic neck dissection
Elective Neck dissection
cN+, advanced T-Stage, facial palsy, high grade tumor
cN0 plus risk factors for occult metastasis
Benign
Malignant
Adjuvant Radiotherapy
Follow up
+
Staging

Indications for adjuvant Radiotherapy

- T3/T4 cancer
- Close or positive margine
- Lymph node metastasis
- Adenoidcystic Carcinoma
- High or intermediate grade
- Deep lobe involvement
- Perineural involvement
- Recurrent tumor



[i] Characteristics of a benign tumor include mobile superficial lobe, slow growth, painless, V and/or VII intact, and no neck nodes.
[j] If incidental N+ disease is present go to SALI-3.
[k] Resection of a clinically benign tumor includes: no enucleation of lateral lobe and intraoperative communication with pathologist if indicated.

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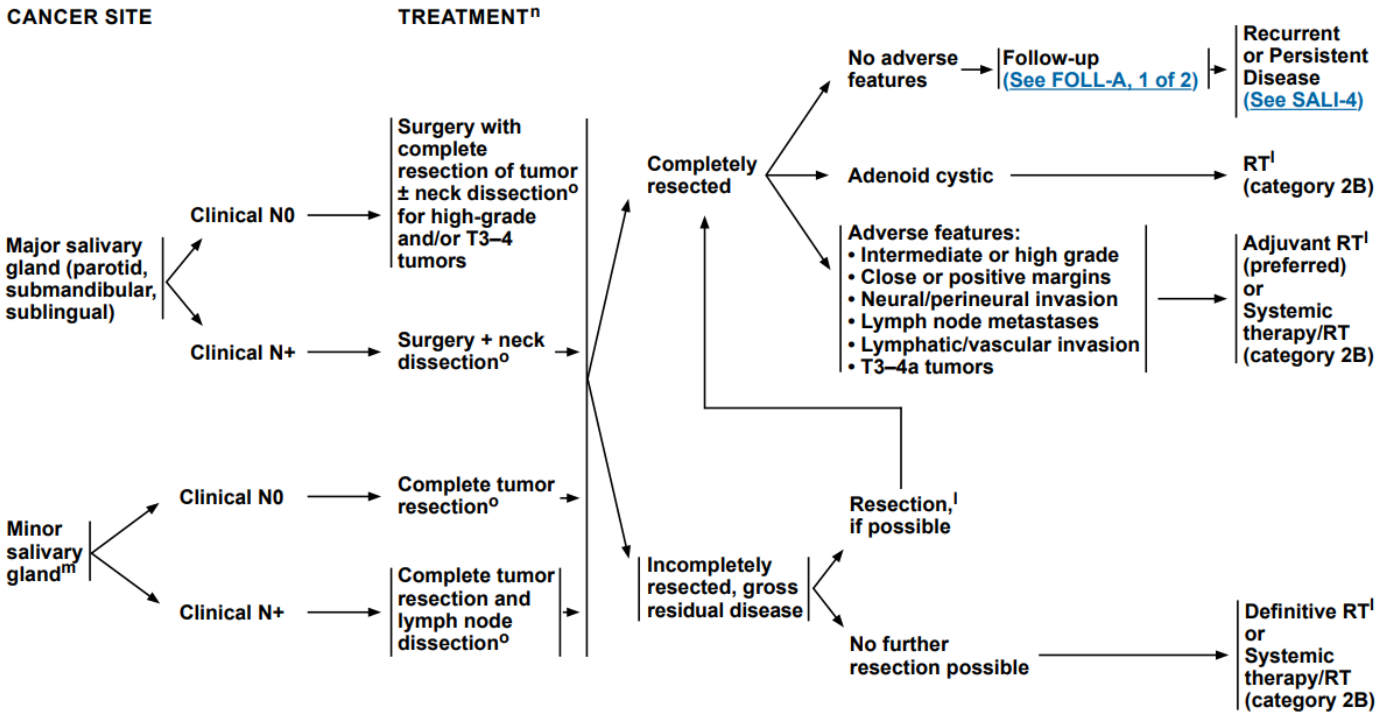

[l] See Principles of Radiation Therapy (SALI-A).
[m] For submandibular and sublingual gland tumors, complete gland and tumor resection is recommended.
[n] The facial nerve should be preserved if possible; strongly consider referral to a specialized center with reconstructive expertise.

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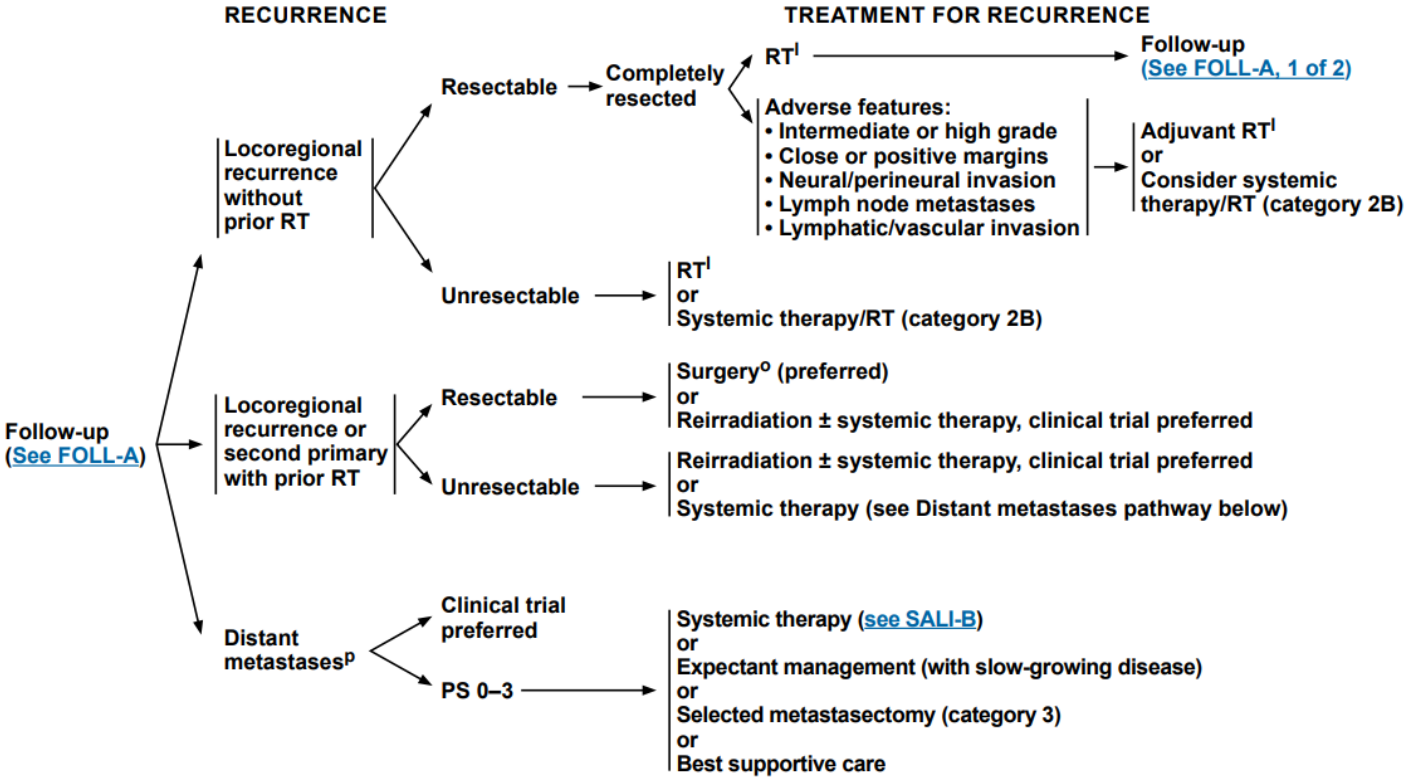


TABLE 46.6 INDICATIONS FOR RADIOTHERAPY: SALIVARY GLAND CANCER

Local Port	Regional Port	Primary RT (≥70 Gy)	High LET RT Consider if Available
AJC Stage T3-T4	pN_+ (60 Gy)	Med. inoperable	R2 resection
High grade	ENE (66 Gy)	Funct. inoperable	Primary RT: T4
Perineural invasion	Elective (Table 46.1) 50 Gy	Irresectable	Reirradiation
Close Res. (1–5 mm) (60 Gy)		Recurrent	
Incomplete Res. (66 Gy)			

ENE, extranodal extension; Funct, functional; Med, medical; PORT, postoperative radiotherapy; Res, resection; RT, radiotherapy.

For Benign disease- PORT improves LC in cases with incomplete excision, involved surgical margins or multi-focal disease recurrence

4 Grading system for MEC

Table 1:

Comparison of Mucoepidermoid Carcinoma Histologic Grading Systems

	Modified Healey[5,6]	AFIP[7,8]	Brandwein[9]	Katabi[10]
Intracystic Component	L: macro + micro cysts I: micro cysts + solid H: solid +/− micro cysts	2 (<20%)	2 (<25%)	L: predominantly cystic (>80%) I: predominantly solid H: any (usually solid)
Perineural Invasion	H: present	2	3	n/a
Necrosis	n/a	3	3	L: absent I: absent H: present
Mitosis	L: rare I: few H: many	3 (4/10 HPF)	3 (5/10 HPF)	L: 0–1/10 HPF I: 2–3/10 HPF H: 4+/10 HPF
Nuclear Anaplasia / Pleomorphism	L: absent/minimal I: slight/moderate H: considerable (including nucleoli)	4	2	L: no significant I: no significant H: any
Border / Invasive Front	L: broad/circumscribed I: uncircumscribed H: soft tissue/perineural/vascular invasion	n/a	2 (small nests & islands)	L: well circumscribed I: well circumscribed or infiltrative H: any (usually infiltrative)
Lymphovascular Invasion	H: present	n/a	3	n/a
Bony Invasion	n/a	n/a	3	n/a
Intermediate Cells	L: rare I: more common H: predominant	n/a	n/a	n/a
Stroma	L: extravasated mucin + fibrosis + CI I: fibrosis separating nests + CI H: desmoplasia, minimal CI	n/a	n/a	n/a
Architecture	L: daughter cysts from larger I: large duct less conspicuous H: variable architecture/cell morphology	n/a	n/a	n/a
Low		0–4	0	
Intermediate		5–6	2–3	
High		7–14	4+	

Key: L=low grade, I=intermediate grade, H=high grade, n/a=not applicable, CI=chronic inflammation.

CONVENTIONAL EBRT

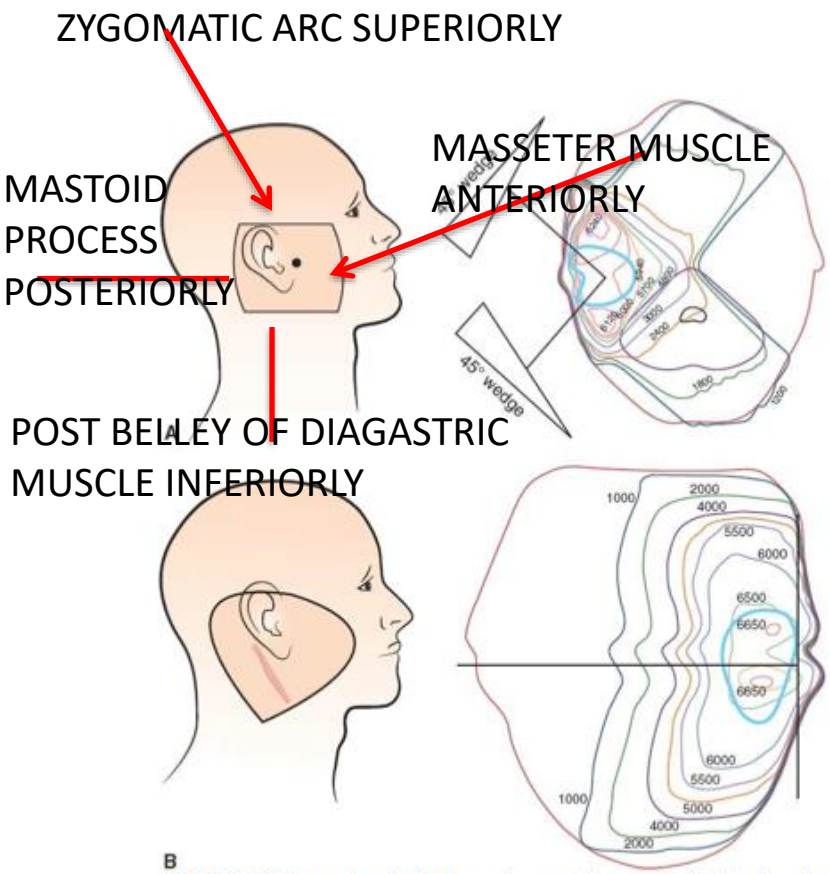


FIGURE 46.10. Conventional radiotherapy for parotid cancer. **A:** Unilateral wedge arrangement and isodose distribution using wedged pair. **B:** Ipsilateral 16-MeV electrons plus ^{60}Co (4:1) electron beam field.

- Positioning: patient lies in supine cast, head should be extended as much as possible, operation scar and any palpable disease should be marked with the wire.
- I/L anterior and posterior wedge pair fields using 60 cobalt or 4 to 6 MV Photons.
- Inferior angutlaion of beam to avoid dose to c/l eye.
- Homolateral field with electron, proton combination to spare the contralateral parotid gland, reduce mucositis and decrease the skin reactions.
- Conventional technique does not allow for tissue heterogeneity.

3DCRT AND IMRT

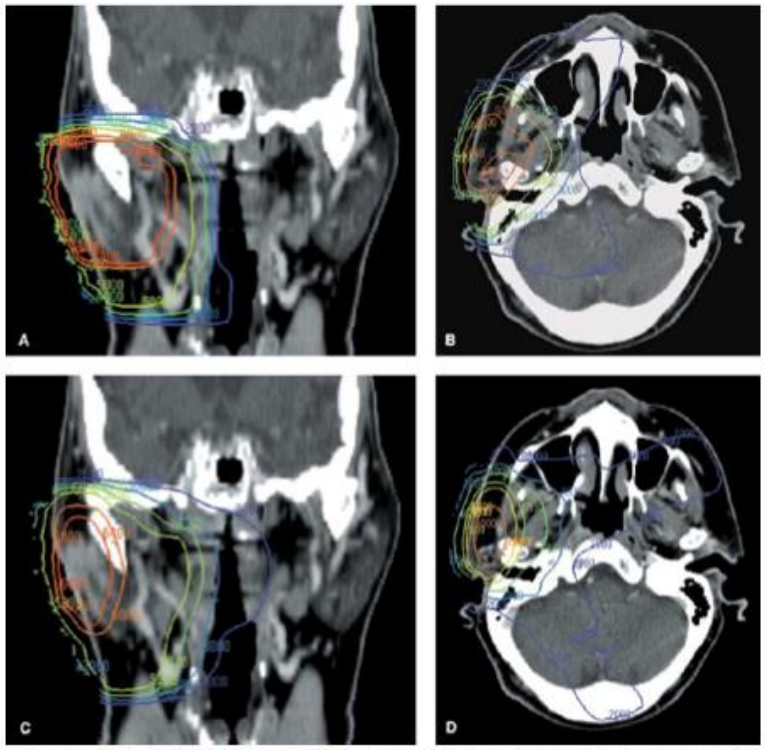
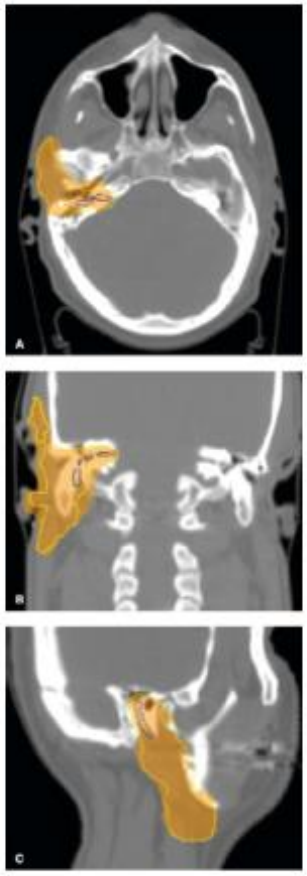


FIGURE 46.11. Postoperative radiation therapy of a parotid cancer, microscopically incomplete resected. Coronal **(A** and **C)** and transversal **(B** and **D)** dose distribution for three-dimensional conformal radiation therapy (25 × 2 Gy primary field, 8 × 2 Gy boost) **(A** and **B)** and intensity-modulated radiation therapy (inverse, 7 fields and 39 segments; simultaneously moderated accelerated radiotherapy (SMART): 33 × 1.6 Gy primary field, 33 × 2 Gy boost) **(C** and **D)**.

- Better coverage of PTV and sparing of OAR.
- Compared to 3DCRT ,IMRT spares the cochlea, Inner ear better.
- In the National cancer data base ,5 year OS with IMRT OR 3DCRT was 84.7% and 80.7% respectively.
- ENI is indicated in clinically facial nerve involvement and recurrent tumor .
- PORT has no negative effect on facial nerve function.
- Intraparotideal-level II,III,IV- I&V
- No need to treat the scar to full dose, bolus required only if skin is involved.
- Parapharyngeal space, RPLN and ITF needs to be incorporated in case of involvement of deep lobe.

Parotid Carcinoma With Named Nerve Involvement



- Recurrent adenoca of the parotid gland with named perineural involvement –total parotidectomy was performed.
- Resection was incomplete.
- The facial nerve was delineated based on MRI.
- 50 Gy isodose was depicted in yellow colour.

Submandibular Gland - PORT

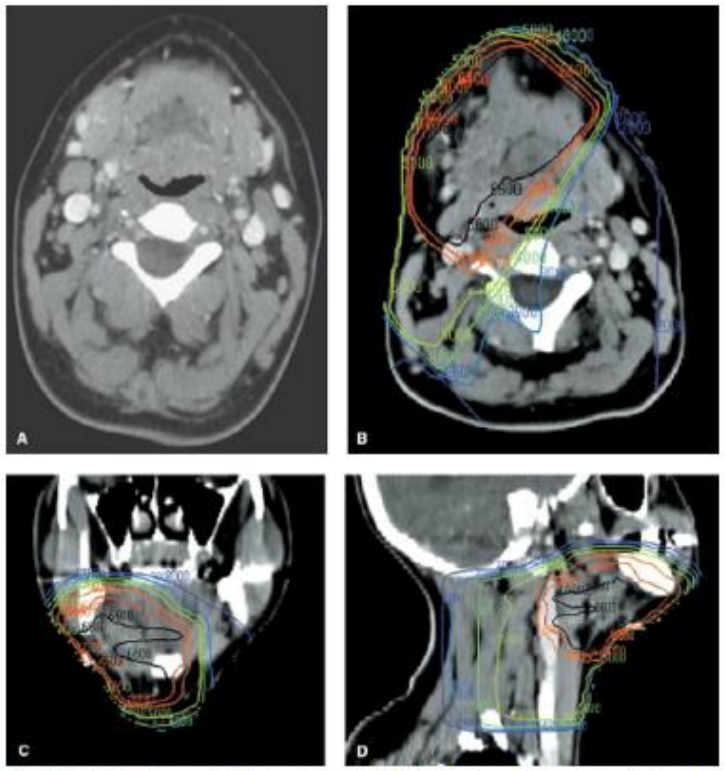


FIGURE 46.13. Dose distribution for a T2N0 adenoid cystic cancer of the right submandibular gland. Computed tomography performed before microscopically incomplete local excision **(A)**. Three-dimensional conformal radiation therapy, three fields (one right and two left oblique): 25 × 2 Gy, 5 × weekly primary tumor and level I to III nodes, 8 × 2 Gy boost; transversal **(B)**, coronal **(C)**, and sagittal **(D)** planes. Mean dose to contralateral submandibular gland is 27 Gy.

- Except for small acinic cell and adenoid cystic cancer neck node level I –IV should be treated.
- If there is named PNI of a major nerve , a tumor dose of 60 to 66 is recommended and the nerve path to the base of skull should be treated.
- Adenoidcystic carcinoma with focal PNI NO NEED TO TRACE THE NERE TO SKULL BASE.

Sublingual Gland

- Mostly adenoidcystic carcinoma
- Mostly advanced disease and high grade
- Low risk of positive neck nodes.
- Aggressive surgery with PORT.
- Elective nodal tratment level I-III.
- In case of name nerve involvement it should be included in Radiation Portal.

Minor Salivary Gland

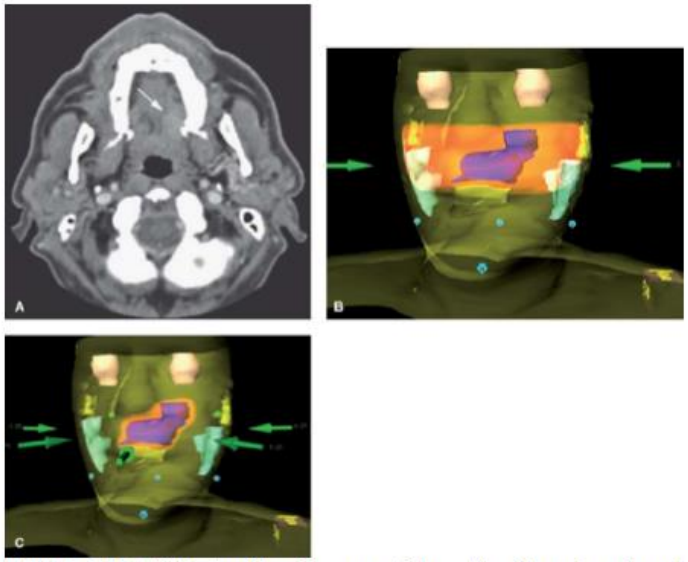


FIGURE 46.14. T2NO adenoid cystic cancer of the palate with major perineural invasion. Computed tomography performed before local excision (**A**, *arrow:* tumor); target includes right palatinus major nerve until base of skull. Dose distribution (25 × 2 Gy primary field) in transversal planes; conventional bilateral opposed fields **(B)**; intensity-modulated radiation therapy (7 fields, 40 segments) **(C)**; 95% isodose of 50 Gy in *red*.

- T/t varies with location
- risk of +ve neck nodes depend upon 4 prognostic factors
- Male gender, T3-T4, pharyngeal site and histology.
- Ipsilateral level I-III NODES
- For PNS base of skull should b included

Table 1: PORT *vs.* RT alone

Study	Year	Neck treatment		Treatment	Median dosage	*n*	Survival rate	*P*
		RT	ND					
Liu et al. [11]	2008	9	-	S+RT RT	69.7 Gy 71.4Gy	10 10	54.8% (5-year OS) 0%	0.024
Cianchetti et al. [12]	2009	-	21	S+RT RT	69.6 Gy 74.3 Gy	76 64	55% (10-year OS) 35%	0.027
Mendenhall et al. [13]	2005	120	59	S+R RT	66 Gy 74.0Gy	160 64	48% (10-year OS) 35%	0.0482
Mendenhall et al. [14]	2004	55	13	S+RT RT	67.8 Gy 72.4 Gy	59 42	77% (5-year AS) 57%	NS
Terhaard et al. [15]	2005	120	-	S+RT	62.6 Gy 63 Gy	386 40	94% (5-year LC) 50%	<0.0005
Schramn et al. [16]	2001	-	15	S+RT	52-66 Gy	23	67% (5-year DFS)	NS
Iseli et al. [17]	2009	-	-	S+RT RT	62.0 Gy 66.0 Gy	93 10	75.5% (10-year LRFS) 24.6%	0.001

Abbreviation: n, the number of patients; RT, radiotherapy; S, surgery; OS, overall survival; DFS, disease-free survival; AS, absolute survival; LC, local control; LRFS: local recurrence-free survival; NS, not stated.

Table 2: PORT *vs.* surgery alone

Study	Year	Treatment	Median dosage	*N*	Survival rate	*P*	LC/RC rate	*p*
Armstrong et al. [22]*	1990	PORT S	56.6 Gy	46 46	51% (5-year DS) 10%	0.015	51.3% (5-year LC) 16.8%	0.14
Terhaard et al. [15]	2005	PORT S	62.6 Gy	386 112	NS		91% (10-year LC) 76%	0.0005
Storey et al. [23]	2001	PORT S	60.0 Gy	83 83	NS		88% (5-year LRC) 50%	<0.05
North et al. [24]	1990	PORT S	60.0 Gy	50 19	75% (5-year AS) 59%	0.014	NS (10-year LC)	<0.001
Le et al. [26]	1999	PORT	60.0 Gy	52	63% (10-year OS)	NS	88% (10-year LC)	NS
Terhaard et al. [27]#	2003	PORT S	62.0 Gy	385 113	NS	NS	89%(10-year RC) 67%	0.03

Dutch Head and neck oncology cooperative group (NHNOCG) Trial 2005→ 538 cases

- Parotid gland in 59 %, submandibular gland in 14%, oral cavity in 23% and elsewhere in 5%.
- All with surgery and 78% (386) with post op RT
- Mean RT dose 62 Gy.
- Adjuvant RT significantly increased local control in T3-T4 tumours, close surgical margins, incomplete resection, bone invasion and perineural infiltrations
- PORT improved 10 yr. local control significantly
  - in T3-T4 tumours (84% vs. 18%)
  - in patient with close(95% vs. 55%)
  - incomplete resection (85 % vs. 60%)
  - in bone invasion (86% vs. 54%)
  - perineural invasion (88% vs. 60%)
  - N+ neck (86% vs. 62%) for surgery alone

DEFINITIVE RT

USCF 2006

- Retrospective analysis of 45 patients with malignant salivary gland tumours treated with RT alone done.
  - Median primary dose 66Gy (57-74 Gy).
  - Distribution of T-stage was: 24% T1, 18% T2, 31% T3, and 27% T4.
  - Histology: Mucoepidermoid (31%), Adenocarcinoma (22%), Adenoid cystic (18%), Undifferentiated (9%), Acinic (9%), Malignant mixed (4%), Squamous (4%), and Salivary duct carcinoma (2%).
  - No patient has clinical or pathological evidence of clinical disease.
  - 5 year local control with RT: 70%
  - 10 year local control with RT: 57%
  - Local recurrences are frequent in T3-T4 tumours (p value 0.004) and for RT doses <66 Gy (p value 0.001).
- Conclusion :
  - Radiotherapy alone is a reasonable alternative for surgery in the definitive management of Salivary gland tumours resulting in significant long term survival.
  - Radiation doses in excess of 66 Gy is recommended

Elective Nodal RT

University of California and San Francisco Trial (2007)

- 251 cases with N0 malignant salivary gland tumours was analysed retrospectively. [Surgery(120) vs. Surgery + ENI(131)]
- Adenocystic 33% ,Mucoepidermoid 24%, Adenocarcinoma 23%.
- Gross total resection R0 44%, R1 56%.

- Adjuvant RT, Median primary RT dose 63 Gy (45-72 Gy), Median Neck RT dose 50Gy (40-66 Gy).
  - Elective neck RT: Ipsilateral 69%, bilateral 31%
  - Crude rate of nodal relapse without ENI: squamous 67%,undifferentiated 50%, adenocarcinoma 34%, mucoepidermoid carcinoma 26%.
  - Nodal relapse : 10 yr. actuarial rate of nodal relapse T1 7%,T2 5%,T3 12%, T4 16%.
  - Elective nodal RT: 10 yr. nodal relapse risk decreased from 26% to 0% (p value 0.0001)
  - Whether or not elective nodal RT was given, no nodal relapse was observed in adenocystic (0/84) and acinic cell(0/21)tumors .

- Conclusion : Elective nodal RT is required for high grade tumours, but not for adenoid cystic and acinic cell tumours.

ACC of Parotid Gland treated with Sx and PORT: long-term outcomes, QoL assessment and ROL

- Between 1995 and 2010, 46 patients with PGACC were treated with Sx followed by **RT**.
- Endpoints were LRC, DMFS, DFS, CSS, and OS,late toxicity.
- After a median follow-up of 58 months (range 4-171), the 5-year LRC, DMFS, DFS, CSS, and OS were 88%, 78%, 75%, 80%, and 67%, respectively and the 8-year rates were 88%, 75%, 72%, 77%, and 64%, respectively
- On multivariate analysis, T-stage, N- stage, **tumor** grade, and perineural invasion correlate significantly with DMFS and DFS.
- The overall 5-year cumulative incidence of grade ≥2 late toxicity was 9%
- ***QoL-scores deteriorate during and shortly after treatment but returned in all scales to almost baseline levels within 6 months***.

Oral Oncol. 2012 Mar;48(3):278-83.

Proton Therapy

Stephen R. et al (2015):

- Retrospective analysis of 24 paediatric patient treated with adjuvant RT, 13 received proton therapy and 11 received photon/electron therapy.
  - Mean prescribed dose in each cohort: 60Gy
  - Follow up 49 months
  - Grade 3 mucositis and dermatitis 18% and 27% vs. 0%
  - No disease recurrence or deaths were observed in each cohort.
  - Reduced doses to OARs. In proton arm

- Conclusion: Proton therapy significantly reduced doses to multiple normal tissues. Moreover, clinically, no grade 3 toxicities were observed in the proton group vs. 45% in the photon/electron cohort.

stephenR. Grant BS. Et al (P086) proton vs Photon/electron based therapy in the treatment of paediatric salivary gland tumours : A comparison of dosimetric Data and Acute Toxicities

Impact of Adjuvant Radiotherapy for Malignant Salivary Gland Tumors.

- Results
- During the study period, 4068 patients met the inclusion criteria for this analysis, of which 2728 (67.1%) received PORT and 1340 (32.9%) did not.
- With a median follow-up of 49.1 months, there was a significant > in OS associated with those receiving PORT (5 years, 56% vs 50.6%).
- On multivariable analysis, PORT ($P < 0.001$) and female sex were associated with > survival. When the analysis was limited to patients ≤65 years old, the survival benefit was persistent .
- Conclusion : PORT was associated with > OS.

Otolaryngol Head Neck Surg. 2017 Dec;157(6):988-994.

Results of standard therapy for ca parotid

Bhattacharyya[55]	903	S ± R	67	50	NA
Sp					
Te					
Ga					
Nc					
Po					
Rc					
Ponar[13]	56	S	65	50	63 (locoreg.)
	91	S + R	55	40	89 (locoreg.)
Chen (carc, ex pl. ad.)[95]	23	S	44	NA	49 (5-y)
	40	S + R	59	NA	75 (5-y)

Best prognosis is shown for acinic cell and mucoepidermoid cancer after 10 year and with a 15% risk of distant metastasis and 10 year LRC OF 85%.

SCC & undifferentiated tumor 10 years OS of 35% or less

Adenoidcystic carcinoma and cancer ex pleomorphic adenoma –distant failure after 10 years is around 35%. PORT is indicated in almost all cases.

TABLE 46.8 RESULTS OF STANDARD THERAPY FOR CANCER OF THE SUBMANDIBULAR GLANDS

Study (by Name of First Author)	No. of Patients	Treatment	% 5-Year Survival	% 10-Year Survival	% Local Control
Spiro[6]	129	S	31	22	40 (loreg.)
Terhaard[20]	68	S + R	57	45	91 (10 y)
Storey[50]	83	S + R	60 (DFS)	53 (DFS)	88 (loreg.)
Bhattacharyya[49]	370	S ± R	60	NA	NA
Mallik[129]	39	S + RT	59 (DFS)	NA	59 (loreg.)
	25	RT≤56Gy	77 (FDS)	NA	100 (loreg.)
	14	RT>56 Gy			

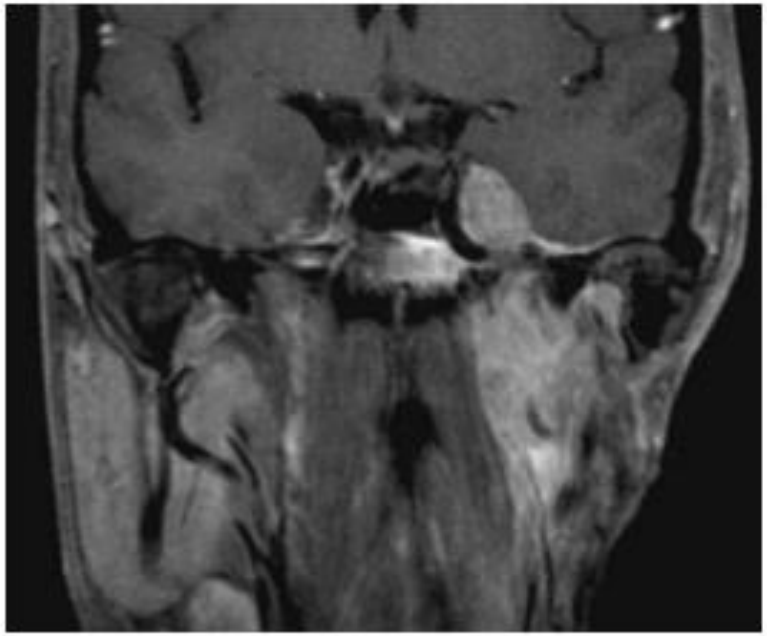
DFS, disease-free survival; loreg., locoregional; NA, not available; R, irradiation; S, surgery.

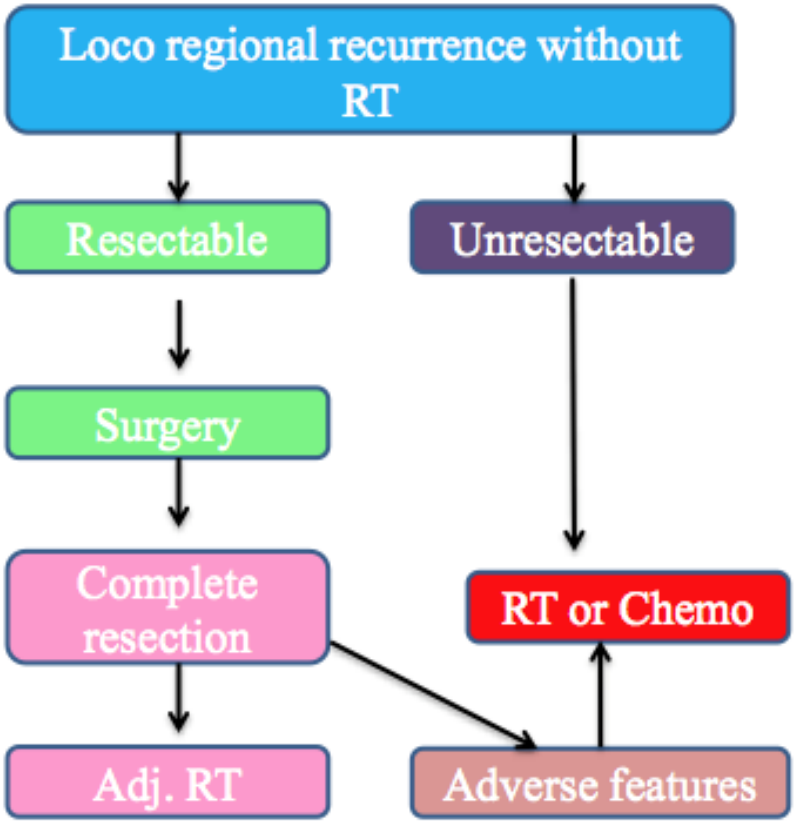
TABLE 46.9 RESULTS OF STANDARD THERAPY FOR MINOR SALIVARY GLANDS

Study (by Name of First Author)/Site	No. of Patients	Treatment	% 5-Year Survival	% 10-Year Survival	% Local Control
Spiro[6]	526	S	48	37	35 (locoreg.)
Garden[112]	160	S + R	81	65	88 (15 y)
Terhaard[20] (oral cavity)	67	S	87	76	91
	54	S + R	85	72	98
Lopes[29] (oral cavity)	59	S	86	83	90 (locoreg.)
	32	S + R	88	56	78 (locoreg.)
	15	R	46	—	13 (locoreg.)
Beckhardt[37] (palate)	79	S	90 (DSS)	80 (DSS)	NA
	35	S + R	87 (DSS)	83 (DSS)	NA
Ali[52] (adenoid cystic, 59 minor)	28	S			42 (10 y)
	58	S+R			90 (10 y)
Salgado[132]	98	S + R	82	58	81 (10 y)
Zeidan[36]	90	S + R	76	63	88 (10 y)

DSS, disease-specific survival; locoreg., locoregional; NA, not available; R, irradiation; S, surgery.

Recurrent Ca of Salivary Gland





Sequelae of treatment

- Facial nerve palsy
- Frey syndrome- gustatory sweating
- Xerostomia
- Trismus
- Chronic otitis media and chronic otitis externa leading to conducting hearing loss.
- Minor slavary gland depending on locations
- Can be minimised with modern RT Techniques.

Conclusion

- Surgery remains the standard of care for resectable SG cancer.
- Adjuvant RT improves DFS &OS in high risk group. IG-IMRT is the standard.
- Promising role of particle RT particularly Carbon Ion Therapy.
- CT still has no defined place in the t/t of SG cancer. Molecular targeted therapy is investigational..
- RTOG 1008 Ongoing trial for PORTCCT
- CCT based on genetic testing in patients with high-risk salivary gland tumors needs further evaluation in long term prospective trials.

Multidisciplinary Approach

- Surgical oncologist
- Radiation oncologist
- Radiologist
- Pathologist
- Maxillofacialprosthodontist
- [illegible]ologist
- [illegible]dentist or oral oncologist
- Physiotherapist
- Speech pathologist
- Psychiatrist
- Psychologist
- Medical oncologist