Evidence-Based Management for Head and Neck Cancers

Paranasal sinuses, Nasopharynx, Parapharyngeal space, anterior and lateral skull base

Vol XV

(Part A)

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Dedicated to
all our patients at
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Contents

Preface

In the 16th Evidence Based Management meeting of Tata Memorial Hospital the theme is Head and Neck Cancers, Immunotherapy and Pediatric Solid Tumors. The previous years have witnessed several changes in the way we manage these cancers today. However, it is important to take stock of the evidence so far and also to look at what the future may possibly have in store.

Head and neck cancers comprise 25% of all cancers in India and are one of the common causes for mortality and morbidity in males. However, the subsites that we have chosen to cover this year are relatively uncommon. We will be addressing malignancies of the nasopharynx, paranasal sinuses and nasal cavity, external auditory canal, paragangliomas and salivary gland neoplasms. These are niche areas even within the head and neck region and besides being uncommon, do not have overwhelming high level evidence for their management except for the nasopharynx. Most of the management is based on large retrospective

studies, single arm institutional experience and systematic reviews.

The locational complexity and proximity of these subsites to critical normal structures like the optic and auditory apparatus, temporal lobes and other neurological structures pose a challenge for the treating oncology team. It therefore becomes mandatory to achieve an optimal therapeutic ratio trying to attain good tumor control with acceptable toxicity. Fortunately, there have been advances in imaging, surgical techniques, radiation therapy planning and delivery, more effective chemotherapy schedules and supportive care, which have resulted in improvements in outcomes in these complex tumor subsites.

The present EBM book aims to address the management of these tumors in our part of the world giving an overview of the disease with options of management of these subsites in the head and neck region based on current available evidence.

The purpose of this book is to act as a ready reference in the clinic and will serve as a useful tool for the practicing oncologist in our setup.

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February 2018
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General principles and outline of management:

It is important to understand that the above sites within the head and neck contribute to < 10% of head and neck cancers. They are a complex group of cancer sites characterized by varying histopathology, each with its own distinct natural history and clinical behavior. Owing to their small numbers and diverse behavior most of the evidence for the management for cancers of these subsites comes from case series, systematic reviews and meta-analyses. But for the nasopharynx which has a large body of level I evidence to support the management of common cancers arising from this region, none of the other sites have such evidence and it is unlikely to happen soon. However, it may be possible to have multicentric collaboration with central pathology review and pooling of clinical data to arrive at some form of consensus in management.

1. All patients with suspected carcinoma of these sites in the head and neck region should be evaluated by a

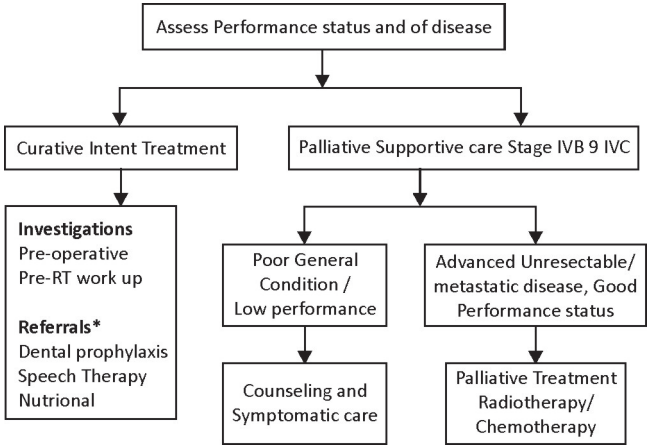
specialist head and neck oncologist who should record the following:

A. History
   - Disease related information
   - Detailed history of habits, addictions and occupation
   - Medical and Family history, including any prior malignancy
   - Comorbidity

B. Clinical Examination
   - Performance and Nutrition status assessment
   - Histological diagnosis – FNAC/Biopsy/ Slide review
   - Imaging for extent of disease and assessment for resectability
   - Clinical staging and documentation of the subsite(s) involved

C. Investigations
   - X-Ray Chest
   - CT Scan / MRI for extent of disease (Appropriate sequences, with and without contrast are paramount for optimal management. Greater details are provided in the chapter on Imaging)
   - EUA / Endoscopy for mapping of disease
   - USG for N0 neck in select cases
   - PET-CECT whenever indicated.

Treatment decisions for all patients should be made in a multidisciplinary joint clinic with the goal for maximizing survival and preservation of form and function.



General guidelines for selecting a treatment modality:

- Stage I / II disease - Single modality (Surgery or Radiotherapy)
- Stage III & IV disease - Combined modality
  - Surgery + Radiotherapy ± chemotherapy
  - Chemotherapy + radiotherapy

Selection of modality depends on the subsite of cancer.

- When different modalities are available, the modality that gives maximum chance of cure should be used.

- When different modalities have similar results, a modality that gives better quality of life, with organ / function preservation is preferred.

Surgery is preferred over radiotherapy as a single modality in

1. Sites where surgery is not morbid (cosmetically and functionally)
2. Lesions involving or close to bone - to prevent radionecrosis.
3. Young patients – possibility of a subsequent second primary
4. Presence of sub mucous fibrosis (SMF).

Radiotherapy is preferred over surgery as a single modality, where

1. Severe impairment of function / cosmesis with surgery, e.g. base tongue, glottis.
2. Surgery is technically difficult with high morbidity and poor results e.g. nasopharyngeal carcinoma.
3. Patient refuses surgery
4. High risk of surgery

For patients undergoing planned surgery,

- A plan should be developed for a tumour free resection margin and appropriate reconstruction for restoration of form and function
- No modification of this plan should be done based on response to any prior chemotherapy

- Modify plan for wider resection, if there is disease progression while waiting.

Assessment of resectability

A. Tumour involvement of the following structures are considered technically unresectable:
   - Erosion of pterygoid plates, sphenoid bone, widening of foramen ovale
   - Extension to superior nasopharynx or deep extension into Eustachian tube or lateral nasopharyngeal wall
   - Encasement of internal carotid artery, defined radiologically as tumor surrounding the carotids > 270 degrees.
   - Involvement of prevertebral fascia or cervical vertebrae

Principles of resection

1. En bloc resection of primary tumor whenever feasible
2. In continuity neck dissection when direct extension of primary into neck
3. Third dimension (the base) should be taken carefully into account before excision
4. Adequate margin: 1.5 – 2 cm
5. Clear margin: > 0.5 cm
6. Close margin < 0.5 cm
7. Frozen section confirmation for margins may be done if the facility is available
8. Addressing the neck for tumors of these sites is a function of the site, extent of disease and histology.

Contralateral neck should be addressed when the probability of bilateral / contralateral metastases is high. Eg. Tumours crossing the midline / midline tumours.

Reconstruction options:

1. Mucosal defects:
   - Small defect –Primary closure/local flap / SSG / leave raw according to the site involved
   - Large defect –Try to replace tissue loss with similar kind of tissue.
2. Soft tissue loss: (Pedicled Flaps Eg. PMMC) or Free tissue transfer
   - Skeletal defects +/- Soft tissue and Skin loss
     a. Anterior or Midline:
        i. Free fibula / Deep Circumflex Illiac Artery (+/- Skin paddle)
        ii. Regional osteo myocutaneous flaps
        iii. Plate
     b. Posterior Segment
        i. PMMC
        ii. Free Fibula
   - Skin defects can be covered with
   - Local flaps /forehead flap
   - Deltopectoral flap / PMMC
   - Free flaps

Indications for postoperative radiotherapy

Primary:

- Large primary – T3/T4
- Deep infiltrative tumour
- High grade tumour
- Lymphovascular and perineural invasion

Lymph nodes:

- Bulky nodal disease N2/N3
- Extra nodal extension
- Multiple level involvement
- Multiple nodes

Chemo-radiotherapy

- Positive or close margin after curative resection
- Nodes with perinodal extension
- Unresectable disease, certain histologies and sites like nasopharynx

Dose for radical radiotherapy

- T1-4 N0-2
    - o Concomitant chemoradiation: 66-70Gy/33-35#/ 6-7 wks + concomitant Cisplatin, 30mg/m2 for 6-7 wks or 3 weekly Cisplatinum, 100mg /m2 x 3 cycles

      Or
    - o External RT: 66-70Gy/33-35#/6-7wKS (reducing fields).

Doses and Volumes in adjuvant setting

- Primary and involved nodal disease: 56-60 Gy/28-30#/ 6 weeks, using reducing fields.
- Site of residual disease, positive cut margins: 4-10 Gy Boost
- Uninvolved nodal stations: 45 -50 Gy

Dose of chemotherapy in the adjuvant setting in combination with radiotherapy: 30mg/m2 weekly with hydration and antiemetic prophylaxis

Specific to these subsites there is a need for pre-treatment assessment of ophthalmologic and auditory functions over and above the nutritional assessment, dental prophylaxis, speech and swallowing assessment that also have to be carried out.

Rehabilitation

- Abstinence from tobacco/alcohol
- Oral hygiene
- Shoulder physiotherapy in all cases of neck dissections
- Bite guide prosthesis following mandibulectomy
- Jaw stretching exercises to prevent post-operative trismus
- Swallowing and speech rehabilitation
- Ophthalmologic and auditory

Follow up

- Every 2-3 months in first 2 years
- Six monthly for next 3 years

- Annually thereafter
- On every follow up thorough head and neck examination for loco-regional control, second primary tumour and late sequelae of treatment. Investigation only if indicated by symptoms and positive clinical findings.
- Serum T3, T4 & TSH annually for all patients receiving RT.
- Imaging at follow-up is necessary

Participation in clinical trials is encouraged.

Imaging in Head & Neck Cancers

Why Imaging?

Imaging plays an indispensable role in

- delineating the deeper extent of disease
- guides the clinicians in deciding appropriate management strategy, assessing resectability and estimating precise extent of resection.
- Image guidance can be used for targeting difficult/ multiple negative biopsies and to plan radiation therapy (Image guided radiotherapy dose-painting)
- Imaging features can also help prognosticate disease
- evaluate for residual / recurrent disease.

Imaging provides information regarding the following that's helps in planning the therapy.

- to differentiate benign from malignant tumours,
- to detect the location and extension of the mass,
- to evaluate perineural spread.

- to look for resectability; meningeal or brain parenchymal invasion, invasion of orbit, cavernous sinus or vascular structures,

Which Modality to be used?

General principle-

- MR imaging is the modality of choice for tumors of the PNS, nasopharynx, base skull, salivary gland and parapharyngeal space.
- Bone detail is a major strength and make CT scanning a complimentary imaging modality for temporal bone and paranasal malignancies.
- *In certain instances, multi-modality approaches are complementary to each other but should not adversely impact on the speed of the diagnostic pathway.*
- US is used for
    - o evaluating salivary glands
    - o lymphadenopathy in the neck.
- Imaged guided fine needle aspiration cytology
- PET-CECT is valuable
    - o for evaluation in the staging work-up
    - o planning radiotherapy portals.
    - o evaluation of malignant cervical adenopathy from an unknown primary
    - o Port-therapy setting for response assessment and differentiating treatment changes versus residual disease.

- Chest imaging is advocated for metastatic work-up of the patient and at least chest radiograph must be performed as a part of staging work-up of patients. However, there is more and more evidence supporting chest CT is far superior for staging work-up especially in patients that have a high risk of pulmonary metastasis at presentation and include the following.

Resectability issues and Imaging

Perineural spread: Perineural spread is usually associated with cavernous sinus, cranial nerve infiltration, skull base invasion, and has bad prognosis.Perineural spread occurs commonly along cranial nerves V, III, IV, and VI through foramen rotundum, foramen ovale, superior and inferior orbital fissures. Perineural spread in parotid malignancies occurs along the facial nerve via stylomastoid foramen. Perineural spread along the cranial nerves IX, X, XI, and XII with intracranial extension occurs along the jugular foramen and hypoglossal canal.

Orbital invasion: Sinus lesions may easily infiltrate the orbit wall through the lamina papyracea, which is the weakest of all orbital walls. However, the Central skull base lesions invade the orbit through the orbital fissures or orbital apex. Loss of fat and abnormal enhancement within these neural foramina indicate invasion, which can be better appreciated on MRI. Strong fibrous periorbita is attached along the superior and inferior aspect of the medial wall and limits the tumor spread. Tumors invading the periorbita and extending into the orbital apex require orbital exenteration with sacrifice of the optic nerve. Both

CT and MRI are equivocal for invasion of periorbita. Tumor spreading to the orbital apex can enter into the middle cranial fossa through the superior orbital fissure.

Cavernous sinus invasion: Invasion of the cavernous sinus usually is contraindicated for complete resection of a lesion. Imaging signs of cavernous sinus invasion include compression, encasement, stenosis, or irregularity of the cavernous carotid artery; loss of contrast enhancement of the cavernous sinus, which is best depicted on a dynamic coronal MR imaging study; and bulging of the lateral sinus wall, which is concave under normal conditions.

Dural invasion: Nodular dural enhancement and linear dural enhancement thicker than 5 mm when seen indicate dural invasion. Dural enhancement less than 5 mm may be seen in reactionary fibrovascular changes and may not suggest dural invasion.

Specific tumor sites

This section highlight specific tumor sites and important radiological findings that have therapeutic implications.

Temporal Bone Cancers

CT and MRI are complimentary to each other and together can provide the vital information to the surgeon to decide the possibility of resectability and best surgical approach.

CT imaging:

- CT should always be using intravenously administered iodinated contrast medium.

- The data set should be acquired in soft tissue and by means of a high-resolution bone algorithm
- Submillimetric acquisition should performed.
- Multiplanar reconstructions provide additional information regarding the exact extension of the tumor and the invasion of vascular structures, nerve channels, and the membranous labyrinth.

CT helps in

- Delineation of soft-tissue abnormalities against a background of air (middle ear cavity, EAC, mastoid air cells).
- Defining the bony anatomy of the skull base, allows assessment of bone changes and/or involvement.
- Detecting fibro osseous skull base lesions, calcification, and sclerosis.

Aggressive infections and malignant lesions show permeative and erosive patterns of bone involvement while smooth cortical expansion and remodeling with cortical thinning is associated with benign slow growing processes. Phlebolith formation is associated with vascular tumors while bone sclerosis is associated with meningiomas.

MR imaging offers more detailed characterization of soft tissue and fluid, allows better visualization of enhancement in small structures, and aids in distinction between soft tissues of different nature (eg, granulation tissue versus tumor).

An MR imaging protocol

- Should start with an entire brain examination using a
  - T2-weighted fast spin echo (FSE),
  - turbo spin echo (TSE) sequence,
  - fluid-attenuated inversion recovery sequence to exclude associated brain pathologic processes.
- A heavily T2-weighted sequence, usually a submillimetric three-dimensional (3D) TSE/FSE T2-weighted sequence, to evaluate the fluid content and signal intensity characteristics in the membranous labyrinth.
- T1-weighted sequences before and after intravenous administration of gadolinium: a 1-mm (or even submillimetric) axial 3D T1-weighted gradient echo sequence or a thin-slice (2 mm or less) axial and coronal SE T1-weighted sequence. Fat saturation techniques should be applied in one direction after contrast administration.

In general, inflammatory lesions have high water content and have high T2W signal intensity. Benign and low-grade tumors of minor salivary glands, schwannoma, hemangioma, and meningioma have high T2W signal. Malignant neoplasms are cellular and have intermediate signal intensity on T2W images. MRI has an edge over CT scan to depict intracranial extent (dural, leptomeningeal and brain parenchyma invasion), perineural and perivascular spread, and bone marrow involvement.

Nasopharynx

Nasopharyngeal cancer (NPC) is a unique disease that shows clinical behaviour, epidemiology and histopathology that is different from that of other squamous cell carcinomas of the head and neck.

Magnetic resonance imaging is the preferred imaging modality and give better:

- soft tissue contrast,
- demonstrate perineural tumour spread,
- Parapharyngeal space involvement (For the evaluation of parapharyngeal extension, CT is inferior to MRI in distinguishing compression as a large bulging tumor still confined within the mucosal space resulting from direct invasion.)
- Extension of disease to the nasal cavity is well demonstrated on multiplanar MRI, especially around the superior meatus and sphenoethmoidal recess. MRI can help in distinguishing direct tumoral extension from retropharyngeal nodes in the evaluation of oropharyngeal involvement.
- Involvement of the skull base. Although cortical erosion is often diagnosed more confidently with CT than with MRI, MRI better depicts bone marrow infiltration, which appears as moderately low signal intensity against the high signal intensity of fatty bone marrow on T1-weighted images without gadolinium enhancement. However, after the administration of contrast agent, the enhancing tumor may have signal intensity similar to that of bone marrow, rendering

interpretation more difficult. Contrast-enhanced and fat-saturated T1-weighted sequences have been used to overcome this problem.

- In the evaluation of intracranial extension of disease, MRI is superior to CT because MRI provides better contrast between the tumor and brain tissue and because MRI is multiplanar. MRI is also superior to CT for detecting retropharyngeal lymph nodes<4mm.

FDG PET/CT imaging, with its added functional information, helps in

- Nodal staging
- Helps plan adaptive radiation therapy during treatment so as to minimize complications.
- Provide the GTV that needs to be irradiated
- Treatment response assessment during the early treatment and post-treatment periods,

A combination of EBV DNA levels and FDG PET can effectively monitor patients during follow-up to detect recurrence and can help in planning treatment and assessing prognosis in recurrent cases.

Paranasal sinuses

- CT and MRI play complementary roles. It is not about the histology but about answering the question 'is it tumor or not?' and then determining the extent of the disease, for example intracranial or orbital extension.

- Findings typically associated with benign tumors include bony remodeling or thickening of the adjacent bone, whereas malignant tumors tend to destroy bone. Additional findings suggestive of malignancy include ill-defined tumor margins, perineural spread, and presence of cervical lymphadenopathy.
- CT is not the best modality for characterizing neoplasms and mapping extent of disease, CT can help define the site of origin, depict bony remodeling vs. bony destruction, and detect internal calcifications and tumor matrix.
- If MR is not available, post-contrast CT imaging must be acquired in soft tissue windows and reconstructed bone algorithms must be available for assessment of bony anatomic landmarks and identifying erosive processes and acquired developmental deficiencies of the bone.
- Scanning down to the hyoid bone allows for examination of the levels I and II lymph nodes: about 10% of paranasal neoplasms have nodal metastases at presentation.
- CT is also excellent for determining whether there is intraorbital extension of sino-nasal disease in the ventral 2/3 of the orbit. When pathology approaches the orbital apex, an MRI study is necessary to assess spread to the cavernous sinus and intracranial compartment.

MR imaging helps in

- Characterize the soft tissue components of the tumour and to evaluate the extent of tumour invasion

beyond the bony sinus walls. It can differentiate adjacent tumor from soft tissue (eg, gadolinium enhances tumor diffusely to an intermediate degree, whereas inflamed mucosa enhances more intensely in a peripheral fashion),

- Differentiating inspissated secretions from neoplasms. Apparent Diffusion Coefficient (ADC) mapping shows potential as an additional MRI tool to effectively differentiate benign/inflammatory lesions from malignant tumors in the sinonasal area.
- Demonstrating skull base invasion, intracranial, intraorbital and perineural spread. Invasion of the orbital apex, dura, brain, middle cranial fossa and clivus are specific features that constitute T4b disease. Unenhanced T1 is also optimal for evaluating tumour interruption of the signal void (black) cortical bone or low tumour signal into the high signal fatty bone marrow of the skull base. Around the sinuses, the normal bone may be too thin for proper evaluation by MR.

Perineural spread is a manifestation of advanced disease and indicates a poor prognosis. MRI can give direct visualization of perineural extension or spread such as nerve enlargement and enhancement as well as indirect signs mentioned above. MRI can correctly predict the presence of perineural spread with 95% sensitivity but can only map the entire extent of spread in approximately 60% of cases. The MRI evaluation of perineural spread should utilize gadolinium enhanced, spin echo T1-weighted sequences with a slice thickness of <3 mm and with special

attention to the trigeminal and facial nerve branches, the two most commonly involved nerves.

On MRI, features of perineural tumor involvement are:

- indirect signs including effacement of fat planes, enlargement of neuroforamina or muscular atrophy due to nerve denervation
- an increase in nerve diameter,
- enhancement of the nerve due to disruption of the blood–nerve barrier
- loss or obliteration of fat around a nerve below a neural foramen.
- In addition, nerve enhancement, while a sensitive sign of perineural involvement, is nonspecific.
- Replacement of normal CSF signal in Meckel's cave or convexity of the lateral aspects of the cavernous sinus may also suggest perineural disease.

Angiography with carotid flow study is not routinely performed and is only reserved for surgical candidates presenting with tumors that surround the carotid artery or when sacrifice of the vessel is anticipated to obtain clear margins. Balloon occlusion test of the ICA, offers a reasonable estimate of the risk of ischemic brain infarction if the internal carotid artery is sacrificed. This test however, cannot predict ischemia at marginal ("watershed") areas or embolic phenomena.

Metastatic workup should be performed should an extensive resection be considered in a patient with advanced stages, especially those with tumors that have

invaded the soft tissues of the face and in tumors with a propensity for hematogenous metastasis, such as sarcomas. This may include CT scans of the neck, chest, and abdomen and bone scan. This extensive work up is necessary should an extensive resection be considered. FDG PETCT is increasingly being used to evaluate for metastases and for surveillance.

Salivary glands

Superficial glands:

- For lesions in the superficial parotid and submandibular gland, ultrasound is an ideal tool for initial assessment.
- These are superficial structures accessible by high resolution ultrasound which provides excellent resolution and tissue characterization without a radiation hazard.
- US can be used to distinguish focal from diffuse disease, assess adjacent vascular structures and vascularity, distinguish solid from cystic and perform nodal staging.
- Ultrasonography can guide fine-needle aspiration to increase the likelihood of getting a good sample, and it can precisely guide core needle biopsies 97% of the time in an outpatient setting, lessening the need for intraoperative biopsies.

For deep glands:

- Ultrasound has limited visualization of the deep lobe of parotid gland which is obscured by the mandible.

Minor salivary gland lesions in the mucosa of oral cavity, pharynx and tracheo-bronchial tree, are also not accessible by conventional ultrasound.

- The role of CT in assessing salivary gland tumors is limited. CT evaluates cortical mandibular involvement better and the presence of calculus disease in sialadenitis (which may mimic a tumor).
- For lesions of the deep lobe of parotid gland and the minor salivary glands, MRI is the modalities of choice.
- If deep tissue extension is suspected or malignancy confirmed on cytology, an MRI is mandatory to evaluate tumor extent, local invasion and perineural spread. For all tumors in the sublingual gland, MRI should be performed as the risk of malignancy is high.

MRI helps in predicting

- exact localization and extent of the lesion,
- invasion of neighboring structures,
- perineural spread, bone invasion and meningeal infiltration
- MRI is also useful for evaluating residual or recurrent disease.

Axial T1- and T2-weighted sequences allow the exact extent of the tumor, tumor margins and growth patterns to be determined, whereas T1-weighted sequences in the axial and coronal plane after gadolinium administration and with fat suppression allow determination of perineural spread along the cranial nerve VII (stylomastoid foramen), the cranial nerve V-3 (foramen ovale) or the cranial nerve

V-2 (foramen rotundum) as well as tumor margins (sharp, fuzzy). Bone invasion can also be detected as a hypointense signal on T1-weighted sequences and contrast enhancement on post-contrast fat-suppressed images.

Recently, new MR technologies such as dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DW-MRI) and proton MR spectroscopy (MRS) have shown promising results in the differentiation between benign and malignant salivary gland tumours. Malignant salivary gland tumours can be differentiated from pleomorphic adenomas but not from Whartin tumours using DCE-MRI at a time of peak enhancement of 120s. A washout ratio of 30% enabled the additional differentiation between malignant and Whartin tumours. Using time-signal intensity curves on the basis of time to peak enhancement of 120s and a washout ratio of 30% had high sensitivity (91%) and specificity (91%) in the differentiation between benign and malignant tumours. The apparent diffusion coefficient (ADC) as the quantitative parameter of DW-MRI is found to be significantly smaller in lymphomas than in carcinomas. The mean ADC of carcinomas has been shown to be significantly smaller than that of benign solid tumours; however the ADC value of Whartin tumours is even smaller than that of malignant tumours.

Parapharyngeal space and paragangliomas

Parapharyngeal space is divided into

a) the prestyloid compartment that consists of the parapharyngeal fat and deep lobe of parotid. The lesions of the prestyloid compartment are

pleomorphic adenomas from the cell rests in the fat and a range of tumors from the deep lobe.

b) the poststyloid compartment that consists of the carotid sheath, with the nerves and paraganglionic tissue posterior to the vessels. The common post styloid compartment lesions are the schwannomas and paragangliomas (PGLs).

The location of the ICA and IJV are important clues in the diagnoses. Prestyloid lesions displace the vessels posteriorly while the post styloid masses displace the vessels anterolaterally. Vagal schwannomas can also splay the ICA and IJV. Carotid body tumors splay the bifurcation of the CCA.

Evaluation by an imaging procedure is absolutely necessary to establish the diagnosis of a head and neck PGLs and for treatment planning. Diagnostic imaging can be considered in two clinical situations:

- Patients who present with clinical symptoms suggestive of a paraganglioma, and
- Individuals from families with hereditary PGLs. Patients with a positive family history are at a higher risk of having multicentric disease.

The preoperative classification of jugular and tympanic paragangliomas is essential, since the operative approach will be chosen depending on the tumor stage. The patterns of spread of the glomus jugulare paragangliomas tumors are predictable and follow the paths of least resistance.

Role of Imaging

- MRI is frequently the imaging study of choice for primary diagnosis.
- It provides superior definition of location, extent, and characterization of paragangliomas,
- It better demonstrates tumor involvement of the ICA and IJV
- MR imaging can depict paragangliomas that are smaller than 5 mm, whereas CT demonstrates only lesions greater than 8 mm.
- CT is excellent for evaluating the integrity of the temporal bone and aids in defining the surgical anatomy of glomus jugulotympanicum tumors.
- Use of CT may obviate additional imaging for most small glomus tympanicum tumors. The extent of temporal bone destruction is important to classify those tumors.
- High resolution CT of the temporal bone will show expansion and a moth eaten pattern of erosion of the jugular foramen in case of jugular paragangliomas.
    - Tumor expansion will occur superiorly and subsequently into the tympanic cavity, causing destruction of the ossicular chain.
    - Further extension laterally will destroy the bony canal of the facial nerve with infiltration of the nerve itself.
    - Finally, intracranial posterior fossa extension along jugular foramen.

Contrast-enhanced MR imaging can show intense tumor enhancement, which again is a key finding in the diagnosis. In addition, a salt-and-pepper fine vascular pattern can be seen in the tumors; this finding is suggestive of intrinsic tumor neovascularity and is particularly well demonstrated on T2-weighted images. Dynamic imaging can reveal rapid enhancement and washout of paragangliomas while schwannomas reveal delayed persistent enhancement. Flow voids are seen on T1 and T2W MR images in paragangliomas while large schwannomas show necrosis. MRI can help predict the Shamblin grouping of the tumor which can help plan surgical resection.

The circumferential degree of contact of the tumor with the ICA is used to classify the tumor radiologically into 3 types

Type I: less than or equal to 180°;

Type II: greater than 180° and less than 270°;

Type III: greater than or equal to 270°.

Functional imaging using 18F-FDOPA PET imaging agent has been found to have promising role for localization and diagnosis of head and neck PGLs in SDHx-mutation carriers. Furthermore, DOTA-peptides are used for peptide receptor radionuclide therapy (PRRT), a potentially new treatment option in patients with HNPGLs, especially those around the foramen jugulare that are rarely suitable for surgical removal. This is important, because therapeutic approaches for surgically nonremovable tumors are limited and most of these patients are not eligible for 131I-metaiodobenzylguanidine (131I-MIBG) treatment because

of their lack of 123/131I-MIBG uptake. More recently, PET/CT imaging with 68Ga-labeled somatostatin analogues (68Ga-DOTA-SSAs) has rapidly evolved, since it does not require a cyclotron to make the radiotracer. All 68Ga-DOTA-SSAs (DOTATOC, DOTATATE, and DOTANOC) effectively target somatostatin receptor subtype 2 (SST2), which is the most overexpressed subtype in PGLs.

Angiography remains of paramount importance if the diagnosis is obscure or if embolization is contemplated. The typical angiographic appearance of a paraganglioma is that of a hypervascular mass with enlarged feeding arteries, intense tumor blush, early draining veins and the patency of the IJV (which is frequently thrombosed in larger paragangliomas). Rarely, avascular paragangliomas may occur. Digital subtraction angiography is the most reliable preoperative imaging study for assessing ICA invasion, which is characterized by vessel narrowing and irregularity. An aortic arch study with four-vessel cerebral angiography is suggested as the ideal workup for affected patients when screening for multicentric tumors. Angiography is also very sensitive in the detection of small lesions.

Embolization is a common technique used as the lone treatment option or as a precursor to surgical excision. As a result of the highly vascular nature of these neoplasms, embolization is an effective technique that is aimed at starving the lesion of its blood supply and inducing necrosis. This is the primary and, at times, the only treatment option for glomus jugulare tumors because of the difficulty in excising many of the tumors. In

combination with surgical excision, embolization is often used to reduce blood loss, and it has been proven to be highly effective.

Cervical Nodes

CT and MRI are the usual modalities to assess metastatic nodes and rely on size criteria, and specific feature such as necrosis. PETCT is superior in nodes that are subcm, but both false negative and false positive results are also known. US guided FNAC has the highest accuracy in detecting metastatic nodes and can be used in centres where expertise is available. DW MRI and dynamic contrast enhanced MRI have an emerging role.

Post treatment issues

MR and PETCT has a major role in the post treatment setting for differentiating between post treatment changes and recurrent / residual disease. PETCT is useful for long term surveillance. Diffusion weighted (DW) MRI has a promising role.

Suggested reading

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Malignancy of External Auditory Canal

Background:

Squamous cell carcinoma (SCC) is the most common primary malignant tumor of the External auditory canal (EAC) however, it accounts for less than 0.2% of all head and neck tumors. The patient usually presents in 5th to 7th decade. The reported mean interval between symptoms and diagnosis is 10 months. Majority of the patients present late and facial paralysis at presentation is seen in 20% of the cases.

Malignancy of external auditory canal presents in advanced stages and have guarded prognosis. There are no rational diagnostic/ therapeutic guidelines for management of temporal bone squamous cell carcinoma (TBSCC) due to the rarity of this disease and varied histologies in this site. Various histological types of neoplasm arising from temporal bone are as follows

Epithelial Malignancy	Squamous cell carcinoma
	Basal cell carcinoma
	Adenocarcinoma
	Carcinoid tumor

Soft tissue neoplasms	Rhabdomyosarcoma Malignant paraganglioma Malignant schwannoma Hemangiopericytoma
Tumors of bone and cartilage	Osteosarcoma Chondrosarcoma
Miscellaneous	Malignant germ cell tumor Malignant lymphomas Metastatic neoplasms

Staging system

The International Union against Cancer and the American Joint Committee on Cancer have not yet endorsed any of the several staging classifications proposed to date. University of Pittsburgh TNM staging system for carcinomas of the external auditory canal (EAC) is the most commonly employed staging system and has often been validated by numerous case series showing good survivals for T1 and T2 tumors and overall poor prognosis for T3 and T4 tumors.

T Stage

T1 Tumor limited to the EAC without bony erosion or evidence of soft tissue involvement

T2 Tumor with limited external auditory canal bone erosion (not full thickness) or limited (< 0.5cm) soft tissue involvement

T3 Tumor eroding the osseous bone EAC (full thickness) with limited (< 0.5cm) soft tissue involvement or tumor involving the middle ear and/or mastoid

T4 Tumor eroding the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura, or with extensive soft tissue involvement (>0.5cm), or evidence of facial paresis

N Stage

N0 No regional lymph node metastasis

N1 Single regional metastatic lymph node < 3 cm

N2a Single ipsilateral metastatic lymph node measuring 3-6 cm

N2b Several ipsilateral metastatic lymph nodes < 6 cm

N2c Contralateral metastatic lymph node, ≤ 6 cm

N3 Metastatic lymph node > 6 cm

M Stage

M0 Distant metastasis

M1 Metastasis to distant sites

Overall stage

Stage I T1N0M0

Stage II T2N0M0

Stage III T3N0M0

Stage IV T4N0M0, T1–4N1M0, T1–4N0–3M1

Etiology

The most common etiological factor as per literature appears to be Chronic Suppurative Otitis Media which is seen in 90% of patients. This may be due to chronic irritation which might be the reason for its carcinogenic

potential. Exposure to Radiation for nasopharyngeal or other intracranial malignancies has also been implicated as an aetiological factor. The latency between radiation exposure and the tumor has been reported between 5-30 years.

Clinical signs and symptoms

Symptoms: Otorrhea, Pain, Facial weakness, Facial numbness, Hearing loss, Vertigo, imbalance, Trismus, Hoarseness, Dysphagia

Signs: EAC mass, Bloody otorrhea, Facial paralysis, Other cranial nerve deficits, Parotid mass, Cervical mass, Middle ear mass, Middle ear effusion, Conductive hearing loss, Sensorineural hearing loss

Routes of spread are given in figure 1

Imaging:

All patients undergo High Definition CT scans. In addition, Contrast enhanced MRI gives details about soft tissue involvement and is complementary to CT scan. MRI is usually performed in all cases unless the tumor is limited to the EAC and CT does not show any bone erosion.

There are some advantages of MRI over CT:

1. MRI can differentiate tumor from mastoiditis and cholesteatomas. The tumor commonly shows isointensity on T1WI, T2WI and DWI and obvious enhancement. While mastoiditis shows

hyperintensity on T2WI and cholesteatomas shows heterogenous intensity on T1WI and hyperintensity both on T2WI and DWI, which helps to differentiate them from the tumor.

2. The tumor shows isointensity similar to muscle on T1WI. The soft tissue of subcutaneous and parapharyngeal space shows hyperintensity due to the presence of fat.
3. Muscle, dura and cerebral involvement can be evaluated with contrast-enhanced T1W imaging. If tumor is involving carotid vessels, then angiography and balloon occlusion test should be performed, to assess the adequacy of cerebral blood flow from the contralateral carotid artery. Venous outflow phase is important to determine the adequacy of the torcula and contralateral drainage pathway, in case the surgery requires the sacrifice of the sigmoid sinus or internal jugular vein. PET CT is usually reserved for extremely advanced or recurrent cases. In addition to imaging, all patients will undergo pure tone audiogram, routine investigations, and fitness for surgery.

Treatment plan:

Most of the treatment is based on retrospective studies. There is no level I evidence for treatment of Squamous cell carcinoma of the external auditory canal.

Treatment protocol

Stage	Treatment
T1	Lateral temporal bone resection (LTBR), consider superficial parotidectomy (SP) or primary radiation
T2	Lateral temporal bone resection (LTBR),consider SP plus postoperative radiation
T3	Subtotal temporal one resection (STBR) or Total temporal bone resection (TTBR),consider SP plus postoperative radiation
T4	STBR or TTBR plus postoperative radiation, consider SP
N0	May consider SP and SND
N+	Add radical parotidectomy and SND to the above
M1	Palliation

Sleeve resection

It should only be considered for low-grade lesions of the EAC skin that do not involve bone. It involves the removal of the cartilaginous portion of the EAC, the skin of the bony EAC, and possibly the tympanic membrane, leaving the bony EAC intact. However, SCC of the EAC requires LTBR as the minimum extent of surgery.

Lateral temporal bone resection (LTBR)

LTBR is indicated in a tumor involving the bony external auditory canal and involves removal of the cartilaginous and bony EAC, tympanic membrane, malleus, and incus lateral to the facial nerve. However, inner ear are preserved.

Subtotal temporal bone resection(STBR)

STBR is indicated for malignant tumors extending to the middle ear. This surgery involves en bloc removal of the temporal bone and involves craniotomy, exposure of arcuate eminence, sigmoid sinus and sinodural angle, glenoid fossa and stylomastoid foramen. The facial nerve is sacrificed in this procedure.

Modified Subtotal Temporal Bone Resection (MSTBR)

MSTBR is indicated in malignant tumors involving the middle ear. Surgery begins with an en bloc LTBR. Further dissection is dictated by the extent of tumor spread. The facial nerve is resected if there is disease along its path in the temporal and extratemporal component of the nerve. All involved bone is drilled out (otic capsule, petrous temporal bone) preserving uninvolved important structures until negative margins are obtained.

TTBR(Total temporal bone resection) includes the resection similar to STBR along with resection of the petrous apex, sigmoid sinus, and possibly the petrous segment of the internal carotid artery.

The issue in standard en-bloc resection versus sequential or piecemeal resection is the philosophy of oncologic resection. The philosophy of sequential or piecemeal resection is the preservation of uninvolved and functional aspects such as facial nerve and labyrinth. This involves removal of the soft tissue components followed by the bony component by sequential drilling until tumor free margins are reached. The philosophy of en-bloc resection is complete removal of the organ without tumor spillage.

En-bloc resection follows an anatomical plane of dissection through normal tissues.

The en-bloc resection is being challenged in various other areas of head neck including larynx. In most cases, a mid-way between the two procedures is adopted. The goal of surgical treatment is to remove all malignancy while minimizing damage to or sacrifice of vital structures and to remain functional as far as possible without compromising on oncologic safety.

Contraindications for surgery:

1. Massive intracranial extension
2. Internal carotid Artery involvement
3. Inner ear involvement
4. Dural and cranial nerve enhancement
5. Unresectable neck disease
6. Distant metastases
7. Poor general health

Dural involvement is not a contraindication in itself since it can be resected without further morbidity, but the prognosis remains guarded.

Role of radiotherapy:

Radical Radiation for T1 tumors has shown comparable results as compared to surgery in retrospective studies.

Adjuvant postoperative RT is commonly indicated for TBSCC (T3–T4) and in cases with aggressive pathological features such as perineural/vascular invasion, close

(<5 mm) or positive surgical margins, lymph node metastases or extracapsular spread. Considering aggressive nature of the disease, adjuvant radiation is also advocated by some in T2 tumors.

Dose of External Beam Radiotherapy (EBRT):

Radical: 66 – 70 Gy/ 33 – 35#/ 6.5 – 7 weeks to the gross tumor, with adequate margins.

Adjuvant: 60 – 64 Gy/ 30 – 32#/ 6-6.2 weeks to the tumor bed with adequate margins

Lymph node radiation to be undertaken depending on the extent of disease

Technique of EBRT: Conformal techniques with image guidance

Role of chemotherapy:

Mainly in inoperable, residual and metastatic disease. Chemotherapy has been used in a neoadjuvant setting by Joshi et al in patients who were deemed unfit for surgery due to extensive disease involving occipital bone with soft tissue infiltration (n = 2), temporal dura (n = 1), left temporal lobe, and extensive soft tissue involvement (n =1). Surgery was possible in 2 patients and the other 2 patients underwent chemo-radiation(10).

The role of chemoradiation(CCRT) in SCC of EAC was studied in a recent meta-analysis by Takenaka et al who concluded that preoperative CCRT may improve the survival of surgically treated patients with external auditory canal SCC and that definitive CCRT may be equivalent to

surgical resection(11). This meta-analysis included retrospective studies.

Neck dissection and Parotid surgery:

The EAC and middle ear are drained by the parotid and peri-parotid, pre- and post-auricular, upper deep cervical and retropharyngeal lymph nodes. The incidence of lymph node involvement in TBSCC is relatively low (10–23%)(12). For a clinically node positive disease, it is mandatory to do a superficial parotidectomy and modified neck dissection. However, in a clinically node negative patients there is no evidence for elective neck dissection. Parotid surgery is mainly indicated when parotid is involved by the tumor or if there are intra-parotid nodal metastasis. Total parotidectomy is considered if tumor is involving the parotid. Superficial parotidectomy as a part of en-bloc resection is advocated by few surgeons in all cases. However, others showed no survival benefit by performing routine superficial parotidectomy.(13,14)

Follow-up: Every 1–3 months in the first year after treatment; every 2–4 months in the second; every 3–6 months in the third; every 4–6 months in the fourth and fifth; and yearly thereafter. As for follow-up imaging studies, yearly head, neck, and chest CT is recommended

Prognosis:

Patient with higher T stage, nodal metastasis, dura involvement and facial nerve involvement have a poor prognosis.

Survival: Morita et al(15) reported 5 years overall survival(OS) to be 100% in T1 disease, 76.2% in T2, 55.6% in T3 and 36.7% in T4 stage. Thus, T stage is an independent marker for OS rate. A meta-analysis from 2006 to 2013(16) reported 5 years OS to be 72.5% for T3 ad 35.8% for T4 disease, as compared to another meta-analysis from 1976 to 2008 (11) where 5 years OS was reported as 57.5% for T3 and 22.9% for T4 tumors. Although treatment outcome has improved but they still have a dismal prognosis, especially in T4 cancers. Survival outcomes following definitive radiation(RT)/ CCRT vs. surgery + adjuvant treatment is given below:

Author	**Number of patients (CCRT)**	**Radiation(RT)/ chemo-radiation**	**Surgery + Adjuvant treatment**
Ogawa et al	87- T1 T2 T3	83% 45% 0%	75% 75% 46%
Takenaka et al	274	Definitive CCRT- 43.6% Preoperative CCRT- 85.7%	53.5%
Choi et al	32	42.4%	64.8%

Survival difference as per En bloc and piece meal resection is given below:

	Number of patients	En bloc removal / Piecemeal removal	Survival of T3,T4 tumors
Wierzbicka et al(2017)	89	Not mentioned	58.7% (3-year OS)
De silva et al(2016)	18	En bloc removal	57.1% (5- year OS)
Mazzoni et al(2014)	51	En bloc removal	48% (5- year DSS)
Bacciu et al(2013)	45	Enbloc removal	62% (5-year DFS)
Xie et al(2013)	39	En bloc removal	22.3% (2- year OS)
Chi et al(2011)	72	Enbloc removal	17.5% (5-year OS)
Gidley et al(2010)	124	Enbloc removal	28% (5-year OS)
Bibas et al(2008)	17	Enbloc removal	40% (5- year OS)
Kunst et al (2008)	28	Enbloc removal	46% (5- year OS)
Nagakawa et al (2006)	25	En bloc removal	57.5% (5-year OS)
Moffat et al(2005)	39	Enbloc removal	44% (5-year OS)
Okada(2008)	18	En-bloc removal	78% (5- year OS)
Dean et al(2010)	65	Piece meal removal	50.4% (5-year DFS)
Lassig et al(2013)	30	Piece meal removal	59% (5 –year DFS)

Suggested Reading

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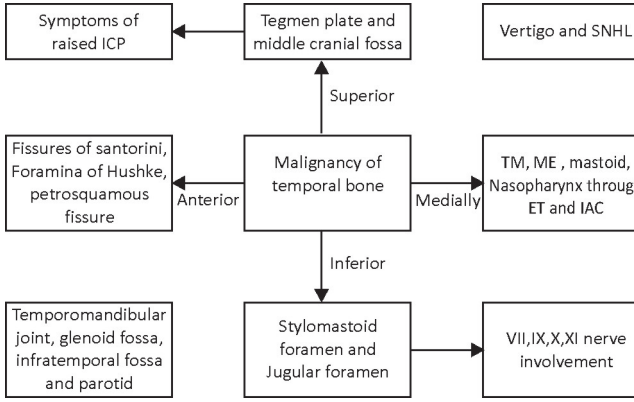
Figure 1: Route of spread in carcinoma of External auditory canal.

ICP: Intracranial pressure, SNHL: Sensineural Hearing loss, TM: Tympanic membrane, ME: Middle ear, ET: Eustachian Tube, IAC: Internal auditory canal



Para Nasal Sinus & Paranasal Cavity

Introduction:

Sinonasal malignancies are relatively less common lesions, accounting for < 5 % of all head neck malignancies. They are a heterogenous group of lesions with different sites and originating from different histopathologic components including Schneiderian mucosa, minor salivary glands, neural tissue, and lymphatics. The commonest pathologies are carcinomas (adenocarcinomas, squamous cell carcinomas, olfactory neuroblastomas etc) and the commonest site of involvement is the maxillary sinus (60%), whereas approximately 20% arise in the nasal cavity, 5% in the ethmoid sinuses, and 3% in the sphenoid and frontal sinuses. This heterogeneity and the small numbers in each group make it difficult to obtain a high level of evidence in their management. There is an increasing role of endoscopy in the surgical management of these cases. Newer advances in surgery and radiotherapy like IMRT have improved survival in these cancers.

Sites

- Nasal Cavity
- Maxilla
- Ethmoids
- Frontal Sinus
- Sphenoid

Investigations / Procedures

1. Biopsy

Endoscopic biopsy is preferred. Biopsy should be taken taking care to avoid necrotic areas. Immunohistochemistry forms a mainstay in the histopathological diagnosis after biopsy.Mucosal biopsy from the palate is to be avoided as far as possible. The Caldwell – Luc procedure should be usedfor biopsy only in select cases.

2. Imaging (mandatory) to assess the extent of disease

A combination of both CT scan and MRI is ideal for the assessment of local extent of disease.

- CT scan - preferred for osseous involvement, floor of anterior cranial fossa and orbital walls
- MRI preferred for
  - Soft tissue extent
  - Intracranial extension
  - Perineural Spread
  - Differentiation between retained secretions and tumour tissue
  - Post surgery setting

- PETCT scans should be done in aggressive histologies with a high incidence of distant metastasis at presentation

3. Prosthetic / Dental Workup

Pre-operative dental impression for post-op prosthesis whenever the alveolus is to be resected without bony reconstruction.

4. Ophthalmologic examination

Documentation of visual acuity, fundoscopy and visual field (perimetry) is important both in management of the disease as well for comparison post-treatment especially when combined with radiation therapy.

5. Documentation of cranial nerve involvement

6. Pretreatment pituitary hormone level evaluation in select cases where radiation is required and would have possible impact on the hormone levels.

Staging: TNM (AJCC) 2018 (used for all Paranasal sinus pathologies except mucosal melanomas which are separately staged)

Tumor (T)

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis : Carcinoma in situ

Maxilla

T I Tumor limited to maxillary sinus mucosa with no erosion or destruction o f bone

T2 Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates

T3 Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues,floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses

T4 Moderately advanced or very advanced local disease

T4a Moderately advanced local disease

Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses

T4b Very advanced local disease

Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Nasal cavity and Ethmoid Sinus

TI Tumor restricted to any one subsite, with or without bony invasion

T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion

T3 Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate

T4 Moderately advanced or very advanced local disease

T4a Moderately advanced local disease

Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses

T4b Very advanced local disease

Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus

Regional nodes

Clinical N (cN)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

NI Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension andENE(-)

N2 Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)

N2a Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)

N2b Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)

N2c Metastasis in bilateral or contralateral lymphnodes, none larger than 6 cm in greatest dimension and ENE(-)

N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or metastasis in any node(s) with clinically overt ENE(+)

N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

N3b Metastasis in any node(s) with clinically overt ENE (ENEC)

Pathological N (pN)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

NI Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)

N2 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+);or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)

N2a Metastasis in single ipsilateral or contralateral node 3 cm or less in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)

N2b Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)

N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)

N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+);or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

N3b Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

Distant Metastasis (M)

M0 No distant metastasis (no pathologic MO; use clinical M to complete stage group)

MI Distant metastasis

Treatment Options

Nasal Cavity & Ethmoid sinus

Considerations for surgery:

The standard of care for treatment of malignancies of the paranasal sinus is craniofacial resection.1However, recently the role of endoscopic endonasal resection in the management of these tumors has come to the fore.The endoscopic techniques whether endonasal alone in case

of limited disease or combined with open craniotomy have shown encouraging oncological results which are comparable or better to open craniofacial approaches, with significantly reduced morbidity and hospital stay. However, there are definite limitations to the endoscopic approaches. In addition, it is imperative that surgeons who are well versed and competent with both endoscopic as well as open surgical approaches to these tumors carry out endoscopic resections. Appropriate multilayer reconstruction of the dural defects should be carried out.

Treatment of Primary:

T1, T2:

1. Surgery ± post-operative radiotherapy

   Approaches-Midfacial degloving or Lateral rhinotomy or Endoscopic Transnasal

   Medial maxillectomy with ethmoidal clearance may be adequate for localised ethmoidal and nasal cavity tumors.

   RT in case of margin positivity or perineural spread

   RT technique: Conventional/3DCRT/IMRT with IGRT. IMRT with IGRT preferred. Postoperative doses of 54-60Gy depending on the tolerance of critical structures.

2. Radical Radiotherapy preferred if surgical resection morbid/patients unfit or unwilling for surgery.

   RT technique: Conventional/3DCRT/IMRT with IGRT. IMRT with IGRT preferred. Radical doses of 60-66Gy depending on the tolerance of critical structures.

T3, T4a

Surgery + Adjuvant RT (Concurrent chemo as per indication)

- Total Maxillectomy with ethmoidectomy
- Combined Craniofacial approach for lesions reaching / involving the cribriform plate.
- Orbital exenteration if eye involved.

T4b

1. Palliative - RT or CT
   Concurrent CTRT may be considered in-patient with good performance status.
2. Resection in very select group with favourable histology with low biologically aggressive tumours for eg. Adenoid cystic carcinoma, basal cell carcinoma.

Treatment of Neck:

N0

Observe

N+

Appropriate neck dissection and post-operative radiotherapy to both necks.

Maxillary Sinus

Treatment of Primary:

T1, T2:

Surgery + Post-op Radiotherapy

- Infrastructure maxillectomy
- Maxillectomy with orbital plate preservation
- RT in case of margin positivity or perineural spread or adenoid cystic histology

T3:

Surgery + Post op Radiotherapy (Primary and neck)

- Total Maxillectomy with Ethmoidectomy
- Orbital exenteration if eye involved. NACT X2 cycles can be considered if orbital preservation is attempted in selected indications.

T4a:

I. Combined craniofacial resection + Post op Radiotherapy12 (Primary +/- neck)

II. Borderline resectable or technically unresectable : NACT X2 followed by reassessment for surgery + CTRT

NACT regimen : 3 drug regimen of TPF (Docetaxel 75 mg/m2 D1, Platinum (Cisplatin 75 mg/m2 D1 or Carboplatin AUC 5-6 on D1)and infusional 5FU 750 mg/m2 CVI from D1-D5 : Total dose 3750 mg/m2)

III. CT+RT in unresectable tumours

Concurrent chemotherapy: Cisplatin preferably 100 mg/m2 3 weekly D1, D21 and D43 or 40 mg/m2 weekly 6-7 cycles.

T4b:

I. Palliative - RT or CT

Concurrent CTRT may be considered in patient with good performance status.

II. Resection in very select group with favourable histology tumours for eg. Adenoid cystic carcinoma, basal cell carcinoma.

III. PS 3-4: Best supportive care

Treatment of Neck:

N0 Observe

N+ Appropriate neck dissection and post-operative radiotherapy.

Management of the orbit

Special consideration must be given to the management of tumors involving the orbit. The orbital periosteum is a relatively strong barrier to early invasion by tumor. Orbital preservation can be attempted in certain cases where there is no invasion of the orbital fat, intraorbital muscles or orbital apex. One way to plan orbital preservation is to biopsy the orbital fat near tumor and preserve the orbit only if fat is negative for tumor infiltration on frozen section. However, in case of any doubt, it may be oncologically prudent to resect the orbit.

Criteria of Unresectibility

- Gross infiltration of infratemporal fossa.
- Pterygoplatine fissure involvement
- Involvement of dura and intra-cerebral extension of squamous carcinoma.
- Cavernous sinus involvement
- Involvement of sphenoid.
- Extensive soft tissue and skin infiltration.
- Bilateral orbital involvement

Absolute contraindications for Endoscopic resection:

- Skin involvement
- Anterior wall of maxilla

- Gross brain invasion
- Involvement of floor of nasal cavity
- Involvement of lateral or posterior nasopharyngeal walls
- Involvement of lateral wall of maxilla
- Involvement of posterior wall of frontal sinus

Post- Maxillectomy Reconstruction:

- If palatal defect less than one third obturator preferred.
- Sling if orbital floor excised, to prevent post-op diplopia. Fascial sling preferred over muscle. Titanium mesh may be used.
- Micro vascular Free tissue transfer for
    1. Extensive skin and soft tissue defect
    2. More than half of palatal loss
    3. Orbit resection
    4. Skull Base Reconstruction
- Temporary obturator for 2 –3 months till complete contracture occurs.
- Final maxillary prosthesis after 2-3 months

Follow up Policy:

- Regular follow up as usual for all head neck malignancies.
- Surveillance to be done using endoscope.
- Baseline post – treatment imaging (MRI preferred) to be done 3 months after completion of treatment.
- Follow up imaging with MRI recommended annually for at least 2 years, thereafter when symptomatic.

- In case of cavity closed by free flap, surveillance with MRI recommended.

Suggested reading

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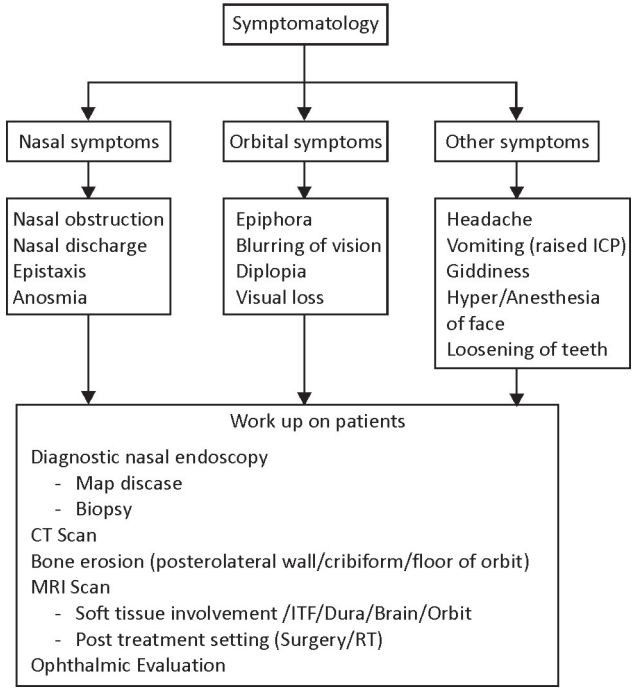
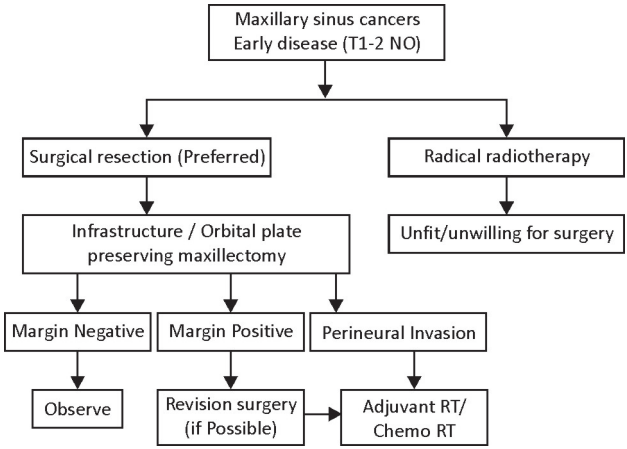
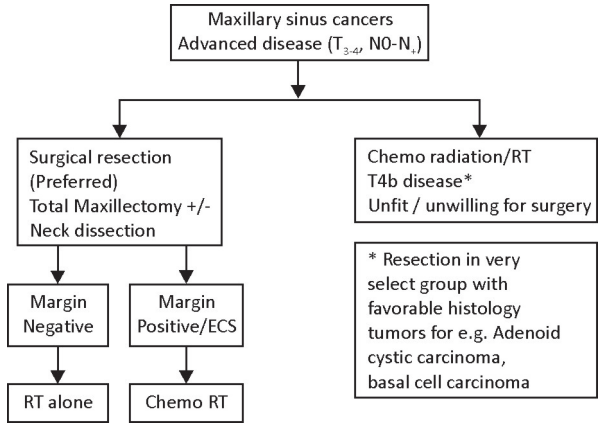
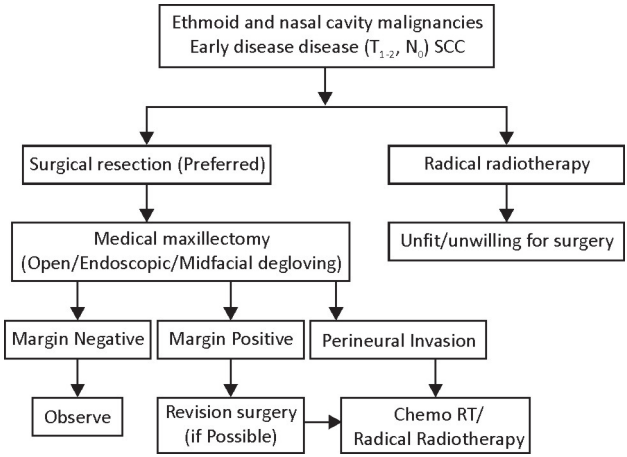
13. Hanna E, DeMonte F, Ibrahim S, Roberts D, Levine N, Kupferman M. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. Arch Otolaryngol Head Neck Surg. 2009 Dec;135(12):1219-24.

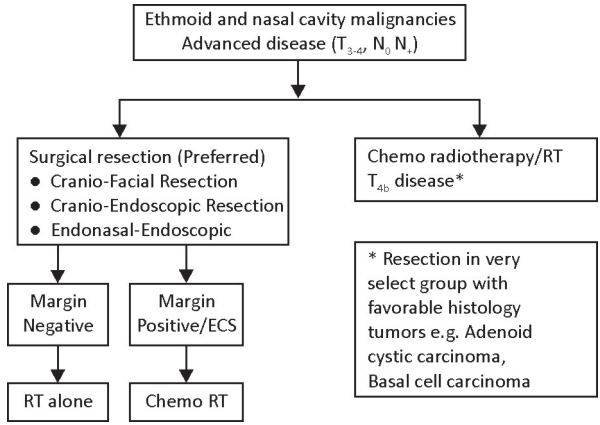
PARANASAL SINUS AND NASAL CAVITY MANAGEMENT ALGORITHM

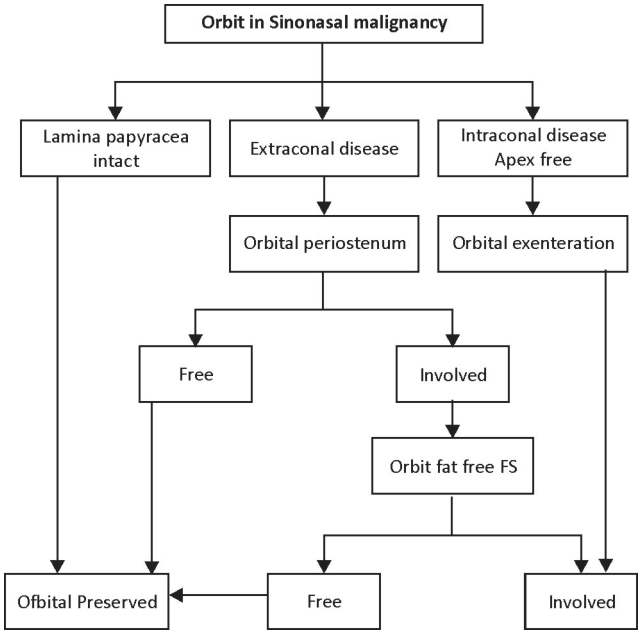



Maxillary sinus cancers
Early disease (T1-2 NO)
Surgical resection (Preferred)
Radical radiotherapy
Infrastructure / Orbital plate preserving maxillectomy
Unfit/unwilling for surgery
Margin Negative
Margin Positive
Perineural Invasion
Observe
Revision surgery (if Possible)
Adjuvant RT/ Chemo RT


Maxillary sinus cancers
Advanced disease (T_{3-4}, N0-N_+)
Surgical resection (Preferred)
Total Maxillectomy +/-
Neck dissection
Chemo radiation/RT
T4b disease*
Unfit / unwilling for surgery
* Resection in very select group with favorable histology tumors for e.g. Adenoid cystic carcinoma, basal cell carcinoma
Margin Negative
Margin Positive/ECS
RT alone
Chemo RT


Ethmoid and nasal cavity malignancies
Early disease disease (T_{1-2}, N_0) SCC
Surgical resection (Preferred)
Radical radiotherapy
Medical maxillectomy
(Open/Endoscopic/Midfacial degloving)
Unfit/unwilling for surgery
Margin Negative
Margin Positive
Perineural Invasion
Observe
Revision surgery
(if Possible)
Chemo RT/
Radical Radiotherapy


Ethmoid and nasal cavity malignancies
Advanced disease (T_{3-4}, N_0 N_+)
Surgical resection (Preferred)
• Cranio-Facial Resection
• Cranio-Endoscopic Resection
• Endonasal-Endoscopic
Chemo radiotherapy/RT
T_{4b} disease*
* Resection in very select group with favorable histology tumors e.g. Adenoid cystic carcinoma, Basal cell carcinoma
Margin Negative
Margin Positive/ECS
RT alone
Chemo RT


Orbit in Sinonasal malignancy
Lamina papyracea intact
Extraconal disease
Intraconal disease Apex free
Orbital periostenum
Orbital exenteration
Free
Involved
Orbit fat free FS
Ofbital Preserved
Free
Involved

Nasopharynx

Nasopharyngeal carcinomas are relatively radio and chemosensitive tumours. Radiotherapy forms the mainstay of treatment of nasopharyngeal carcinomas. Surgery has a very limited role to play in management of nasopharyngeal carcinomas. Chemotherapy in combination with radiotherapy has shown to improve survival in advanced nasopharyngeal carcinomas. However, there has been a lack of consensus regarding the optimal sequencing of chemotherapy with radiotherapy. Earlier meta-analysis showed that concurrent chemoradiation definitely contributes the most towards disease control. However, a significant proportion of patients develop distant metastases after concurrent chemoradiation necessitating intensification of systemic treatment. Owing to poor compliance to adjuvant chemotherapy after chemoradiation, neoadjuvant chemotherapy is emerging as a preferred means of treatment intensification. A recent randomized trial of neoadjuvant chemotherapy has shown a survival benefit with addition of neoadjuvant chemotherapy to standard chemoradiation.

- Specific Investigations before definitive treatment Nasopharyngeal examination, endoscopy & biopsy Imaging:
  - PET- CECT (if available), with MRI of the face, including PNS and base of skull or
  - CECT (thorax),
  - CT scan / MRI face, neck, including PNS. MRI scan is preferred when there is definite evidence to suggest intracranial extension, extension into the PNS.
  - Bone scan especially in WHO type IIb, especially with advanced T and N stage

As both the pre-treatment and post treatment plasma/ serum load of Epstein–Barr viral DNA have been shown to be of prognostic value it is suggested that it be integrated in work up whenever possible.

All patients being planned for Chemoradiotherapy/ radiotherapy should undergo

a. Dental checkup and prophylaxis
b. Nutritional counselling and swallowing evaluation
c. Baseline Thyroid function
d. Audiometry and Ophthalmologic evaluation.

TNM Staging (AJCC Eighth Edition)

Primary Tumor (T)	
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle
Regional Lymph Node (N)	
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the cauda! border of cricoid cartilage

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

Stage Grouping			
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0, N1	M0
Stage III	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Nasopharyngeal carcinoma differs from other head and neck squamous cell carcinomas in following aspects à

- Classified into 3 types
  a) WHO type I – Keratinising Sq. Ca
  b) WHO type IIa – Non-keratinising Sq. Ca
  c) WHO type IIb – Undifferentiated Carcinoma
  d) WHO type III- Basaloid Carcinoma
- Radiosensitive tumours, even with large volume nodal disease respond well to radiotherapy.
- WHO type IIb (Undifferentiated carcinoma) responds better than keratinising variety.
- Surgery has a very limited role as en bloc surgical resection of the primary tumour is difficult and

severely morbid. Surgery is usually reserved for elective/ salvage of residual neck nodes.

Staging Workup	**Other Workup**
• Endoscopic examination & biopsy • PET-CT OR • Chest X-Ray • CT scan / MRI face, neck, including PNS. • Bone scan especially in WHO type IIB	• EBV Titers Dental prophylaxis • Audiometry & visual field testing • Nutritional counselling • Thyroid function

Treatment			
T1N0M0	**T2N0M0**	**T3-T4N0M0/ Any T N+**	**Any T/N M1**
RT alone	CTRT + ACT CTRT 2 – 3 # NACT + CTRT	2 – 3 # NACT + CTRT CTRT + ACT CTRT CTRT	2 – 3 # NACT f/b consolidative eCTRT Palliative RT

Treatment options

T1 N0 :

- Radical Radiotherapy alone with or without Intraluminal Brachytherapy
- IMRT or 3-DCRT should be the preferred technique when facilities are available.
- Bulky T1 or lesions classified as T2a by previous staging (6th edition of AJCC) should be treated with Concurrent chemoradiotherapy.

T2 N0-

- Concurrent chemoradiotherapy
- Neo Adjuvant CT x 2-3 cycles + Concurrent CT + RT

T3 - 4 N0 / Any T N+

- Neo Adjuvant CT x 2-3 cycles + Concurrent CT + RT
- Concurrent chemoradiotherapy followed by adjuvant chemotherapy.
- Concurrent chemoradiotherapy

ANY T ANY N M1

- Platinum based chemotherapy should be used as 1st line
- RT or Chemoradiotherapy should be used in patients with good/complete response to chemo as clinically indicated.
- Palliative radiotherapy may also be offered to the symptomatic metastatic site or for palliation of progressive locoregional disease

Radiotherapy schedule for Undifferentiated Ca Nasopharynx:

Intensity Modulated Radiation Therapy is the preferred technique. It offers excellent disease control and normal tissue sparing in this setting. Radiation therapy should be targeted to the primary tumour and nodal volumes based on Pre Chemo Imaging. Gross disease and High risk volumes should receive doses biologically equivalent to 70 Gy/35#/ 7weeks, conventional. Hypofractionated schedules using simultaneous integrated boost technique maybe employed. Low risk areas should receive doses

biologically equivalent to 50 Gy/ 25 fr/ 5 weeks. An intermediate risk volume may also be defined.

Chemotherapy in the Radical Setting:

1. Neo-adjuvant Chemotherapy:

Regime (i)

DCF Protocol:Docetaxel (75 mg/m2 Day 01), Cisplatin (75 mg/m2 Day 01) and 5-FU (750 mg/m2 /day continuous IV infusion through PICC Day 01 to Day 05. Total dose in 5 days 3750 mg/m2) X 2 - 3 Cycles

Regime (ii)

TIP Protocol:Paclitaxel (175 mg/m2 Day 01),Cisplatin (20 mg/m2 Day 01 to Day 05),Ifosfamide (1200 mg/m2 Day 01 to Day 05) and Mesna (400 mg/m2 at 0 4, 8 hrs Day 01 to Day 05) X 2 - 3 Cycles

Regime (iii)

Cisplatinum (33mg / m2 / day x 3 days) + Ifosfamide (2gm /m2 / day x 3 days) + Mesna rescue X 2 - 3 Cycles

Regime (iv)

Cisplatin (100 mg/m2 day 01 and 5 FU 1000 mg/m2/day continuous IV infusion through PICC Day 01 to Day 05) X 2 -3 cycles.

2. Adjuvant Chemotherapy:

Cisplatin (100 mg/m2 day 01 and 5 FU 1000 mg/m2/day continuous IV infusion through PICC Day 01 to Day 05) X 3 cycles or Docetaxel (75 mg/m2 Day 01), Cisplatin (75 mg/ m2 Day 01) and 5-FU (750 mg/m2 /day continuous IV

infusion through PICC Day 01 to Day 05. Total dose in 5 days 3750 mg/m2) X 3 Cycles.

3. Concurrent Chemotherapy with Radiotherapy:

Regime (i):

Cisplatin (30-40 mg/m^2 weekly for 06 to 07 Cycles with RT)

Regime (ii):

Cisplatin (100 mg/m2 Day 01, 22 and 43 with RT)

For bulky T2 tumors and if stage is T3N0 and higher at presentation, neo-adjuvant chemotherapy, followed by concurrent chemoradiotherapy warrants trial in view of the recent phase III randomized trials showing its benefit over concurrent chemoradiotherapy.

Chemotherapy schedules in the Palliative setting:

Author	Drugs	PFS in months	OS in months
Single drug			
Foo et al	Gemcitabine	3.6 (pre-treated) 5.1 (un treated)	7.2 (pre-treated) 10.5 (untreated)
Ma et al	Gemcitabine	1 month-31%	1year-48%
Ngeow et al	Docetaxel	5.3 months	12.8 months
2-Drug combination			
Zhang et al	Cisplatin -5FU	5·6 months	20·9 months
Zhang et al	Gemcitabine cisplatin	7·0 months	29·1 months
Tan et al	Paclitaxel-Carboplatin	7.0 months	12 months

Author	Drugs	PFS in months	OS in months
3-drug combination			
Siu et al	Cisplatin, methotrexate, bleomycin, cyclophosphamide, and doxorubicin	NR	14 (M)- 16(R) months
Hasbini et al	5FU, Mitomycin, Epirubicin Cisplatin,	9 months	14 months

Table: Selected studies reporting on palliative chemotherapy in first line setting. M-metastatic patients, R-recurrent

Second line chemotherapy:

In nasopharyngeal cancer second line and beyond chemotherapy regimens provide clinically meaningful outcomes and hence should be used in fit patients.

Author	Drugs	PFS in months	OS in months
Dugan et al	Mitoxantrone	4.5	13
Au et al	Paclitaxel	7.5	12
Poon et al	Irinotecan	3.9	11.4
Chua et al	Capecitabine	4.9	7.6
Ngeow et al	Docetaxel	5.3	12.8
Zhang et al	Pemetrexed	1.5	13.3
Chi et al	P+F+LV	NR	14-R 34-M
Chua et al	I+F+LV	6.5	1 year-51%
Altundag et al	I+D	7	NR
Wang et al	G+V	5.6	11.9

P- Cisplatin, F-5FU, LV-Leucovorin, I-Ifosfamide. D-Docetaxel, G-Gemcitabine, V-Vinorelbine

Table depicting second line and beyond benefit with systemic therapy

Surgery:

- Role of surgery is minimal: No neck dissection upfront even for large nodes. Neck dissection is reserved for palpable nodes persisting 8 weeks after radiotherapy and when the primary is controlled.
- Treatment of recurrence: surgery in selected cases.

Recurrent/Persistent NPC

An overall loco-regional failure after initial treatment is approximately 10%. An early detection of loco-regional failure can provide a better chance of salvage. Therefore regular follow up of patients is recommended. Nasopharyngoscopy and SOS biopsy, imaging (CT/MRI/PET-CT) and EBV titers/EBV DNA levels are routinely used methods for early detection of recurrent/persistent NPC.

PET-CT is superior to CT/MRI in differentiating tumor recurrence from radiation fibrosis. Plasma EBV DNA levels is another useful biomarker for early detection of recurrence, plasma EBV DNA levels may be elevated up to 6 months prior to a clinical recurrence.

Recurrent NPC could be treated either by surgical salvage or re-irradiation.

Role of surgery:

Surgery provides a good local control with 5-year survival rates ranging between 30% - 50% in recurrent/persistent

NPC, especially with early lesions. Surgery also plays a significant role in the treatment of radio-resistant malignancies. Surgery is usually performed through open approaches (Lateral approach, transpalatal, mandibular swing and maxillary approaches) which require translocation of maxillofacial skeleton or the transposition of critical neurovascular structures. These approaches are associated with significant morbidity especially due to associated risk of cranial nerve injuries. This has led to the evolution of minimal access, minimally invasive procedures.

Endoscopic endonasal nasopharyngectomy is a feasible minimal access technique indicated for the resection of select recurrent and radio-resistant nasopharyngeal malignancies. It bestows the advantages of lack of external incisions or scars, decreased trauma to adjacent soft tissues and bone, reduced risk of neurological damage, and superior postoperative quality of life.

Chen et al. carried out an endoscopic nasopharyngectomy in 37 recurrent NPC, almost all of them with rT1–T2 tumours. No severe complications or deaths resulting from the operation were observed. The 2-year overall survival rate, local relapse-free survival rate, and progression free survival rate were 84, 86, and 83%, respectively. Robotic assisted endoscopic nasopharyngeal resection may also play a very important role in these difficult situations

Role of Re-Irradiation:

Endocavitory brachytherapy, Intersititial brachytherapy, Stereotactic radiosurgery, Intensity modulated

radiotherapy and particle beam radiotherapy are various modalities used for Re-irradiation in recurrent NPC.

A judicious case selection taking into account previous radiation dose, previous radiation volume, interval after previous RT and current tumor bulk is essential for success of Re-Irradiation.

Promising results are seen, with local control and survival equivalent to nasopharyngectomy in rT1-rT3 lesions. IMRT has emerged as a promising technique of re-irradiation with low complication rates. The complications commonly reported after re-irradiation for NPC include massive epistaxis, nasopharyngeal necrosis, cranial nerve palsies, temporal lobe necrosis, and osteoradionecrosis of skull base.

Follow-Up

- PET-CT/MRI should be used to evaluate the response to RT or chemoradiotherapy.
- Follow-up should include examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis.
- For T3 and T4 tumours, PET-CT/MRI might be used on a yearly basis for atleast 5 years.
- Evaluation of thyroid function in patients with irradiation to the neck is recommended at 1, 2 and 5 years.
- Audiometry
- EBV titres

Suggested Reading:

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Salivary Gland Tumors

Salivary gland tumors are relatively rare and constitute 3% to 4% of all head and neck neoplasms. The majority (70%) of salivary gland tumors arise in the parotid gland. Of the tumors of the parotid gland, 75% are benign and 25% are malignant. However in the submandibular gland, nearly 40% of tumors have a malignant etiology. Although there is no single predominant factor known to be associated with the development of salivary gland cancer, a number of factors have been implicated as potential causes: Radiation exposure has been associated with the development of both benign and malignant salivary gland tumors. Warthin's tumor has a strong association with smoking, in contrast to other salivary gland tumors for which there is no clear relationship. Viral infections may be associated with an increased risk of salivary gland cancers. Environmental factors and industrial exposure to factors such as rubber manufacturing, hair dressers, beauty shops, and nickel compounds have been reported to be associated with the development of salivary gland tumors.

Histology:

Histologically, the most common type of benign salivary gland tumor is the pleomorphic adenoma, which comprises about half of all salivary tumors. Other rarer benign salivary gland tumors include Warthin tumor, basal cell adenoma, and canalicular adenoma. The most common malignant salivary gland tumors are mucoepidermoid carcinoma and adenoid cystic carcinoma, which together comprise approximately one-half of all malignant salivary gland tumors. Salivary gland cancers vary in their aggressiveness and their propensity to recur and metastasize. A histologic grading system has been proposed, in which salivary gland malignancies are classified as high-grade or low- to intermediate-grade based upon clinical behaviour and outcomes. A higher tumor grade appears to correlate with more aggressive behaviour in mucoepidermoid carcinoma and adenocarcinoma not otherwise specified, but there are conflicting data on the importance of grading according to histological pattern in adenoid cystic carcinoma.

Who Classification

Malignant Epithelial Tumors	Benign Epithelial Tumours
• Malignant epithelial tumours	• Pleomorphic adenoma
• Acinic cell carcinoma	• Myoepithelioma
• Mucoepidermoid carcinoma	• Basal cell adenoma
• Adenoid cystic carcinoma	• Warthin tumour
• Polymorphous low-grade adenocarcinoma	• Oncocytoma
• Epithelial-myoepithelial carcinoma	• Canalicular adenoma

Malignant Epithelial Tumors	Benign Epithelial Tumours
• Clear cell carcinoma, not otherwise specified • Basal cell adenocarcinoma • Sebaceous carcinoma • Sebaceous lymphade nocarcinoma • Cystadenocarcinoma • Low-grade cribriform cystadenocarcinoma • Mucinous adenocarcinoma • Oncocytic carcinoma	• Sebaceous adenoma • Lymphadenoma - Sebaceous - Non-sebaceous • Ductal papillomas - Inverted ductal papilloma - Intraductal papilloma - Sialadenomapapilliferum • Cystadenoma
• Salivary duct carcinoma • Adenocarcinoma, not otherwise specified	Soft Tissue Tumours Haemangioma
• Myoepithelial carcinoma • Carcinoma ex pleomorphi c adenoma • Carcinosarcoma • Metastasizing pleomorphi c adenoma • Squamous cell carcinoma • Small cell carcinoma	Haematolymphoid Tumours Hodgkin lymphoma Diffuse large B-cell lymphoma Extranodal marginal zone B-cell lymphoma
• Large cell carcinoma • Lymphoepithelial carcinoma • Sialoblastoma	Secondary Tumour

Histologic grades of salivary gland cancers

High-grade	Low- to intermediate-grade
High-grade mucoepidermoid ca	Low-grade mucoepidermoid carcinoma
Salivary duct carcinoma	Acinic cell carcinoma
Adenoid cystic carcinoma adenocarcinoma (PLGA)	Polymorphous low-grade
Carcinoma ex-pleomorphic adenoma	Epithelial-myoepithelial carcinoma
Squamous cell carcinoma	
Anaplastic or undifferentiated carcinoma	
Malignant mixed carcinoma	

Clinical Presentation:

The clinical presentation of a salivary gland neoplasm depends upon its specific site of origin and the extent of involvement of adjacent organs. Patients with a tumor of a major salivary gland typically present with a painless mass or swelling of the parotid, submandibular, or sublingual gland. The presence of a parotid mass in combination with signs or symptoms indicative of facial nerve involvement (eg, facial nerve paralysis) is generally indicative of a malignant rather than a benign tumor. Minor salivary gland tumors arising within the oral cavity may present with a painless submucosal mass or mucosal ulceration in the palate, lips, or buccal mucosa, with an appearance similar to sialometaplasia (squamous metaplasia of salivary glands) or squamous cell carcinoma. Symptoms due to more advanced minor salivary gland tumors are a function

of the location of the tumor and can include nasal obstruction, congestion, vision changes, or trismus when present in the nasal cavity or maxillary sinus. Minor salivary gland tumors involving the nasopharynx usually present at an advanced stage; invasion of the skull base, intracranial extension, or involvement of cranial nerves is common.

Initial Assessment:

History and physical examination — The initial history should evaluate the duration the mass has been present, the rapidity of its growth, and the presence of pain, numbness, or any subtle asymmetry of facial motion. In addition, the patient should be questioned for a history of previous skin cancers such as squamous cell carcinoma or melanoma of the scalp or facial region.

Physical examination should document the size of the mass, its mobility, fixation to overlying skin or to deep structures, any limitation in jaw opening, pharyngeal asymmetry or buccal involvement, pain with palpation, skin or scalp lesions suggestive of primary malignancy, and detailed facial nerve examination that details specific branch involvement if present. Examination of the neck should include assessment for cervical lymphadenopathy.

Investigations:

A. Fine Needle Aspiration Cytology (FNAC):

- FNAC is safe, simple to perform, inexpensive and has minimal morbidity. The overall sensitivity ranges from 85.5% to 99%, and the overall specificity ranges from 96.3% to 100%.

- Results of a recent meta-analysis regarding utility of FNAC are:

Utility	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive value
Neoplastic (benign & malignant) vs. Non-neoplastic	96%	98%	81%	100%
Benign vs. Malignant	80%	97%	94%	90%

- Preoperative FNAC is recommended, because it can change the clinical approach in up to 35% of patients
- FNAC should be considered in all patients with salivary gland tumors
- Allows betterpreoperative counselling of patients regarding the nature of the tumor, the likely extent of resection, management of the facial nerve, and thelikelihood of a neck dissection

B. USG:

- Advantage: inexpensive, noninvasive, simple to perform.
- It can be used to differentiate solid from cystic masses;
- Ultrasound guidance may increase the accuracy of FNAC in non palpable tumors or those with a highly heterogeneous architecture.
- Not comprehensive enough for assessing deep lobe of parotid or parapharyngeal space

C. CT and MRI Scans:

- All patients do not routinely require CT or MRI scans
- Indications of CT scan:
  - Where bone destruction is suspected at skull base
  - Suspected involvement of the mandible
  - To assess neck nodes
- Indications of MRI:
  - MRI is better in soft tissue delineation and in delineating the interface between tumor and normal salivary gland
  - For better imaging of the parapharyngeal space
  - For evaluating perineural spread, e.g. in adenoid cystic carcinomas
  - Facial nerve status may be better appreciated in the MRI scan
- PET scan:
  - Although not routine in the evaluation of all malignant salivary gland tumors, 18Ffluorodeoxyglucose (FDG) positron emission tomography (PET) has good diagnostic accuracy in the assessment of regional lymph nodes and distant metastases in patients with salivary gland malignancies. However, PET is not able to distinguish benign from malignant parotid tumors.

D. USG Guided Core Needle Biopsy:

- Relatively new modality in diagnosis of salivary gland lesions

- More invasive: requires local anesthesia. But morbidity is minimum in experienced hands.
- In a meta-analysis, found to be more accurate than FNAC: sensitivity 92%, specificity 100%, inadequacy rate 1.2%
- Yields more tissue, but on current evidence should be limited to cases where:
    - o FNAC is equivocal
    - o To assess certain lymphoid lesions
    - o To perform immunohistochemistry on sample

E. Role of Frozen Section:

Frozen section , though not available at all centres , has a unique advantage over FNAC in being more sensitive . It can be used in the following scenarios :

- o To refine the diagnosis of malignancy obtained on FNAC
- o To identify nodal metastases
- o To confirm/ rule out involvement of the facial nerve or its divisions/ branches, when these have been resected (to confirm a negative proximal/ distal margin).

A recent meta analysis has shown that Frozen section has similar specificity as FNAC (97 %) but a higher sensitivity (90%) , which provides us with the opportunity to refine the presurgical diagnosis .

Staging:

Cancers of the major glands are staged according to the eighth edition (2017) of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control

(UICC) tumor, node, metastasis (TNM) system (table 1). Tumors arising in minor salivary glands are staged similar to squamous cell carcinoma, according to their anatomic site of origin.

Major salivary gland tumors TNM pathologic staging AJCC UICC 2017.	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension without extraparenchymal extension*
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor larger than 4 cm and/or tumor having extraparenchymal extension*
T4a	Moderately advanced or very advanced disease
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.

N and M stage are similar to head neck squamous cell carcinoma

Treatment:

Treatment recommendations are based upon retrospective reviews of clinical experience, and there are almost no data from randomized trials to guide treatment decisions.

I. Surgery: Mainstay of treatment is surgery.

A. Parotid Gland:

- *Superficial parotidectomy:* Implies complete removal of the parotid gland superficial to the plane of the facial nerve
  - It is the minimum standard surgical procedure.
  - It is the "treatment of choice" for tumors in the superficial lobe, which are not involving the facial nerve.
  - Every effort is made to preserve the facial nerve.
  - It is important to avoid enucleation and excision biopsy because it greatly increases the likelihood of recurrence (up to 80%)and nerve damage.
- *Adequate parotidectomy:* Implies removing the tumor completely, taking care to avoid capsular rupture or nerve damage, with approximately 0.5–1-cm tumor-free margins.
  - Requires very careful and stringent case selection
  - Should be done only in: benign tumors, limited to superficial lobe, preferably small pleomorphic adenomas in tail parotid
  - In properly selected benign tumors, adequate parotidectomy is as safe as and less morbid than superficial parotidectomy.

- *Total Conservative parotidectomy:*Implies excision of entire parotid gland (superficial and deep lobes), while preserving the facial nerve. Done for:
    - tumors involving the deep lobe, with intact facial nerve functions
    - high-grade malignant tumors with a high risk for metastasis
    - any parotid malignancy with an indication of metastasis to intraglandular or cervical lymph nodes
    - any primary malignancy originating within the deep lobe itself
    - Positive margin (base) after superficial parotidectomy
- *Total Parotidectomy with the excision of facial nerve:*indications as above, when the nerve is involved by the tumor.
- *Radical parotidectomy:*Implies excision of other structures than the parotid gland and facial nerve. Done when tumor involves:
    - Skin
    - Infra-temporal fossa
    - Mandible
    - TM joint
    - Petrous bone
- *Extracapsular Dissection:* This technique of resection is described only for benign lesions. It implies the excision of a small,benign, superficial tumour using careful microdissection around itscapsule, without a prior planned identification of the facial nerve.

Branches of the nerve might be identified during dissection and are carefully dissected away. A large meta-analysis comparing Superficial parotidectomy and Extracapsular dissection has shown this technique to have lower incidence of temporary facial nerve impairment and Frey's syndrome, while that of Permanent Facial nerve impairment remains the same.

B. Submandibular Gland:

Excision of the submandibular gland with supraomohyoid neck dissection to stage the neck is advised. The presence of positive lymph nodes in the neck necessitates comprehensive clearance of Levels I-V.

C. Neck Dissection:

1. Node negative (N0) neck:

- No consensus regarding management of node negative neck.
- Some recommendations based on retrospective studies for elective neck dissection are:
  - o T3, T4 tumors
  - o Size > 4 cm
  - o High grade
  - o Extraparenchymal spread
- Alternate approach: Routine sampling of level II nodes → Frozen section → if positive, Modified Neck Dissection is done.
- For submandibular gland tumors: Supra Omohyoid Neck Dissection is performed

2. Node positive (N+) neck:

- Consensus well established. A comprehensive modified neck dissection (Levels I-V) should be performed in N+ necks.

D. Management of Facial Nerve:

- Sacrifice of the facial nerve or other structures is generally best guided by findings at surgery. Therefore, appropriate consent should be taken before surgery.
- If nerve is non-functioning pre-operatively due to tumor involvement: excision must be done
- Facial nerve branches should be sacrificed only if the tumor is adherent to or surrounds the nerve, and if margins around the nerve are involved.
- In case of adenoid cystic carcinoma, if the sectioned nerve is involved, drilling of the temporal bone must be done till a free proximal stump is confirmed on frozen section
- Role of intra operative nerve monitoring:

Facial nerve monitoring is a useful aid to identify the nerve during surgery. However, practice varies widely across the world and it is yet to be considered as a standard of care. A recent meta-analysis of 546 patients has shown that there is significant reduction in immediate post-operative paralysis but not in permanent facial nerve impairment. Also, the benefit of using the nerve monitor is greater in recurrent cases.

II. Adjuvant Radiotherapy:

- Early stage, low-grade malignancies including low-grade mucoepidermoid carcinomas, acinic cell carcinomas, and low-grade adenocarcinomas are well controlled with complete surgical resection, with control reaching 85 percent at 10 years. Adjuvant RT generally is not indicated if adequate margins are obtained.
- No level I or level II evidence to support use of adjuvant RT
- Large number of prospective and retrospective studies are the guidelines for use of PORT
- Indications are as follows:
    1. T3/T4 cancers
    2. Close or positive margins
    3. Lymph node metastasis
    4. Adenoid cystic carcinoma
    5. High or intermediate grade tumors
    6. Deep lobe cancers
    8. Peri-neural involvement
    9. Recurrent tumors

The optimal adjuvant radiation dose for a malignant salivary gland tumor depends upon the fractionation scheme utilized, but most use doses of 60 to 66 Gy at 2 Gy per fraction. The radiation treatment volume encompasses the original tumor bed and regional lymph nodes only if involved or thought to be at high risk. For adenoid cystic carcinoma, neural pathways to the skull base are also included. Conformal RT techniques are preferred.

III. Radical Radiotherapy for Unresectable Primary:

- Role of definitive radical RT is restricted to unresectable tumors. This form of treatment is usually of palliative in intent.
- Fast neutron beam therapy has been shown to be beneficial than standard photon therapy in a RCT. However, its use is limited by the extremely scarce availability of fast neutron RT units.

IV. Chemotherapy:

The role of chemotherapy in salivary gland tumours is limited to upfront or recurrent locally advanced inoperable tumours (where the intent is usually palliation rather than cure) and as adjuvant treatment along with radiation in selected cases. There has been a lot of research with respect to biomarkers and targeted agents designed against the same. This has generated vast amounts of literature that needs to be critically analysed and interpreted before being incorporated into clinical practice. We shall broadly discuss the role of chemotherapy in light of the available evidence.

- Concurrent Chemoradiation in the Adjuvant setting

  Adjuvant chemoradiation has been offered for the following indications :

- T3-4, or N1-3 disease
- Intermediate or High grade tumours
- T1-2 N0 patients with positive or close (< = 1mm) microscopic margins of resection

Benefit

Level 1 evidence regarding benefit of postoperative radiation or chemoradiation does not exist. Both therapies have been administered on the basis of retrospective series.

Hsieh et al compared the long-term outcomes in patients with salivary gland adenoid cystic carcinoma (SGACC) treated with postoperative chemoradiotherapy (POCRT) versus postoperative radiotherapy (PORT). Their study showed significantly improved Locoregional control in those who had received adjuvant chemoradiation as compared to those with radiation alone. However, the rates of distant control, Disease free survival and Overall survival were comparable between the two groups.

In a large retrospective analysis using records from the National Cancer Database (NCDB),patients undergoing chemoradiation were seen to have poorer outcomes than those receiving adjuvant radiation alone .It is to be noted that there was significant heterogeneity amongst the two groups with reference to adverse prognosticators like histology , grade and TNM stage , rendering the evidence unreliable. This controversy surrounding the role of adjuvant chemoradiation will remain unanswered till the results of RTOG 1008 are reported. (The RTOG 1008 is a RandomizedStudy of Adjuvant Concurrent Radiation and Chemotherapy versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors).

- **Palliative Chemotherapy**

Indications:

- Locally advanced incurable tumors
- Recurrent or progressive advanced tumours

Benefit:

The natural history of metastatic salivary gland tumours disease is variable, and some patients remain asymptomatic for long periods. The goal of treatment is palliation, since there is no clear evidence that survival is prolonged by systemic therapy.

1. Watchful waiting (surveillance) is the most appropriate strategy for patients with indolent disease and few or no symptoms.
2. Systemic therapy may be reserved for those with symptoms and/or rapid disease progression and for those whom local therapy, is not appropriate

Biomarkers:

Certain biomarkers are detected in salivary gland tumours. The incidence varies with histology (Table 1).

Table 1: Biomarker distribution in salivary gland tumors

Histological subtype	Her-2	EGFR	c-Kit	AR	ER	PR
Adenoid cystic	R	V	C (80%)	R	R	R
Adenocarcinoma	UC (20-25%)	UC (10-25%)	V	UC (10-20%)	R	R
Mucoepidermoid	UC (25-30%)	C (35-40%)	R	R	R	R
Salivary duct	C (>50%)	C (40%)	R	C (40-50%)	R	R

AR-Androgen receptor, ER-Estrogen receptor, PR-Progesterone receptor, R-rare, UC-Uncommon, C-Common, V-Variable.

Her-2 Neu Expression

HER2 overexpression and/or HER2 gene amplification are seen in Mucoepidermoid, adenocarcinoma and Salivary duct carcinoma.

Evidence for use of Trastuzumab

Mucoepidermoid carcinomas and salivary duct cancers are seen to over express Human epidermal growth factor receptor 2. Expression of the same is rarely encountered in adenoid cystic carcinomas and adenocarcinomas. Patients with recurrent salivary duct carcinoma may be given the option of HER2 testing, and when possible, those positive may receive trastuzumab in combination with chemotherapy, such as carboplatin plus paclitaxel or the same agents given sequentially. Series with small numbers (Limaye et al) have shown some promise of adding Trastuzumab to Adjuvant therapy in advanced disease and as palliative treatment in the metastatic setting with a median duration of response being 18 months .This approach need to be further validated in larger cohorts before being recommended in routine clinical practice .

EGFR (Epidermal Growth Factor Receptor)

Although EGFR overexpression is seen in a certain subset of patients, the results with Gefitinib and cetuximab in salivary gland are disappointing. There are no objective responses seen with these drugs in their respective phase 2 single arm studies.

C-KIT

C-Kit overexpression and not mutation is mostly seen in adenoid cystic carcinoma. Two phase 2 single arm trials have explored the benefit of imatinib in these patients. However, both trials failed to demonstrate and objective response rate with imatinib. In a phase II trial of the combination of imatinib and cisplatin in 28 patients with advanced ACC, 19 patients had stable disease and median time to progression and overall survival of 15 months and 35 months, respectively.

AR (Androgen Receptor)

No phase 2 trial has systematically evaluated the role of androgen receptor blockers in salivary gland tumours. However, case reports suggest that AR blockade with tamoxifen or bicalutamide can be useful in view of the lower side effects of targeted therapy

Systemic chemotherapy

1. Multiple regimens have been used in salivary gland tumors.
2. In general responses rates are higher in polychemotherapy regimens as opposed to single agent regimen. (Table 2)
3. Selection of chemotherapy should take into consideration the histology and ability to tolerate chemotherapy.

Table 2: Monotherapy and Poly chemotherapy response rates. ACC- Adenoid cystic carcinoma. ADC-Adenocarcinoma, MEC-Mucoepidermoid carcinoma.

Regimen	Histology	Response rate
Monotherapy		
Cisplatin	ACC, MEC and ADC	Upfront : 16-21%, Recurrent : 7-18%
Mitoxantrone	ACC	12.5%
Epirubicin	ACC	10%
Vinorelbine	ACC and ADC	20%
5-Fluorouracil	ACC	46%
Methotrexate	MEC	40%
Paclitaxel	MEC and ADC	21-29%
Docetaxel	MEC	100%
Polychemotherapy		
Cyclophosphamide/ Doxorubicin/Cisplatin	ACC, MEC and ADC	46%
Cisplatin/Doxorubicin/5FU	ACC, MEC and ADC	35%
Cyclophosphamide/ Doxorubicin/Cisplatin/5FU	ACC, MEC and ADC	50%
Cisplatin/Epirubicin/5FU	ACC and ADC	29%
Cyclophosphamide/ Doxorubicin	ACC and ADC	35%
Cisplatin/5FU	ACC	0%
Carboplatin/Paclitaxel	ACC	20%
Gemcitabine/Cisplatin	ACC, MEC and ADC	24%

Follow Up and Prognosis:

Regular posttreatment follow-up is employed to detect early recurrences and to monitor for complications. For patients with malignant salivary gland tumors, the intensity of follow-up is generally greatest in the first two to four years since approximately 80 to 90 percent of all recurrences occur within this timeframe. However, continued follow-up is generally suggested as there is a risk of recurrence even beyond the first five years. Locoregional recurrence rates were higher in patients with malignant submandibular or minor salivary gland primaries. For patients with adenoid cystic carcinoma, distant metastases are of particular concern and may occur even 20 to 30 years after successful treatment of the primary tumor. Chest imaging is useful to monitor for metastatic disease in these patients.

The 10-year disease free survival of salivary gland tumors ranges from 47 to 74%; and 10-year overall survival was 50% in one large study.

Some prognostic factors associated with poor outcomes are:

- Extent of disease (Advanced T & N-status)
- Positive or close resection margins
- Named nerve involvement
- Peri-neural invasion
- Grade: high-grade mucoepidermoid carcinoma, high grade adenoid cystic carcinoma, undifferentiated carcinoma, squamous cell carcinoma, adenocarcinoma NOS, salivary duct carcinoma

- High Ki-67 and low p27expression: associated with shorter disease-freesurvival in adenoid cystic and mucoepidermoid carcinoma

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Head and Neck Paragangliomas

Introduction

Amongst paragangliomas (PG), only 3% are located in the Head and Neck region and they comprise ~0.6% of head and neck tumours. Among head and neck paraganglioma, carotid body tumours constitute nearly 60%, tympanojugular 40% and vagal <5%.

Paraganglia are cells of neural crest origin and occur throughout the body associated with vascular and neuronal adventitia, related to autonomic nervous system. PGs are tumours formed from these cells and grow slowly whilst being locally invasive. Sympathetic PG occur in the sympathetic paravertebral ganglia of thorax, abdomen and pelvis and secrete catecholamines e.g. phaechromocytoma. Most parasympathetic PGs are nonchromaffin tumours seen along the glossopharyngeal and vagal nerves in the neck and skull base as well as around the carotid. These are non-functional.

Traditional management of head and neck PG involved surgery with resultant high morbidity due to proximity to the neurovascular structures in the skull base. There has

been a paradigm shift in their management with a more conservative approach which includes wait and scan as well as non-surgical approaches with stereotactic radiation therapy in some specific situations.

Epidemiology:

There is equal gender affinity peaking between the 4th and 5th decade with female preponderance seen in carotid body tumours. The sporadic tumours are more common in comparison to inherited tumours.Hereditary PGs are linked to mutations of the succinate dehydrogenase (SDH) enzyme complex and may form part of syndromes such as multiple endocrine neoplasia types 2A and 2B (MEN2), neurofibromatosis type 1 (NF1), von Hippel Lindau (VHL) and Carney-Stratakis dyad.

Sporadic carotid body PGs are frequently seen in 1 out 10 patients living at high altitudes in comparison to less than 1 in 500,000 people living at low-altitude again more common in females.

WHO CLASSIFICATION EXTRAADRENAL PARAGANGLIOMA OF HEAD AND NECK
CAROTID BODY TUMOUR
JUGLOTYMPANIC
VAGAL
LARYNGEAL
AORTICOPULMONARY
ORBITAL NASOPHARYNGEAL

Pathophysiology

PG contain 2 cell types: chief cells or type I cells with cytoplasmic granules containing catecholamines and Schwann -like satellite cells or type II cells. A classic *zellballen* (cell ball) configuration is observed, consisting of chief cells surrounded by fibrovascular stroma with thin -walled capillaries and sustentacular cells.

Head and neck PGs cannot produce epinephrine as they lack phenylethanolamine -*N*- methyltransferase in comparision to adrenal medulla. They are however functional in up to 4% and if catecholamine excess is identified, further investigation should rule out an abdominal or thoracic PG before attributing this to a head and neck PG.

Genetic Testing

PGs can arise either as sporadic or familial entities. Sporadic tumours are usually solitary. In sporadic cases, somatic and germ line mutation have been detected in 25-30% and 8–24% respectively. Familial tumours are usually multicentric (80%) and multiple (80%). Majority of PGs are solitary, while approximately 10% are multiple.

Inheritance is related to SDH (succinate dehydrogenase) genes, which is a mitochondrial enzyme complex involved in kreb's cycle, transmitted in an autosomal dominant fashion (Fig1). SDHA, SDHB, SDHC, and SDHD are four nuclear genes that encode the four subunits (A, B, C, D) of the SDH mitochondrial enzyme and are believed to function as tumor suppressor genes. Five hereditary paraganglioma syndromes have been described with

different mutations in each type including SDH complex assembly factor 2 (SDHAF2). Among patients with familial paraganglioma syndrome, the most commonly mutated gene is SDHD. In SDHD linked PG the paternally transmitted mutation manifests clinically. Tumor risk and malignancy rates vary by type of mutation, however SDHB mutations are associated with a higher malignancy rate

- PGL1 Paraganglioma syndrome 1 with mutations in SDHD at gene locus 11q23 and is the most common type of familial paraganglioma syndrome.
- PGL2 – Paraganglioma syndrome 2 is associated with mutations in the gene for SDH complex assembly factor 2 (SDHAF2), which is located at gene locus 11q12.2 and occurs rarely.
- PGL3 –Paraganglioma syndrome 3 is associated with mutations in SDHC at locus 1q21. SDHC mutations are rare
- PGL4 –Paraganglioma syndrome 4 with mutations in SDHB at gene locus 1.p36.1-35 is the second most common type of familial paraganglioma. PGs with SDHB mutations are most likely to be metastatic and are associated with renal cell carcinoma
- PGL5 – Paraganglioma syndrome 5 is associated with mutations in SDHA, which comprises 15 exons and encodes a 2390-bp transcript.

Clinical Presentation

Carotid Body PG

Present as an asymptomatic, slowly enlarging pulsatile neck mass located below the angle of mandible. Typically,

they are mobile in the horizontal but not vertical plane (Fontaine sign). Rarely a bruit or thrill may be present on auscultation or palpation, suggesting significant arterial compression. High altitude increases the incidence of carotid body tumour. The carotid body is involved in the reflex regulation of arterial pH, pO_2 and pCO_2.

Tympanic and Jugulotympanic PG

The most common presentationas are hearing loss, pulsatile tinnitus, features of lower cranial nerve palsy.Classically described blanching of the middle ear component (Brown's sign) is present in 20%. Tumours invading the tympanic cavity from the jugular fossa can show the classic "rising sun" sign. Any vascular mass seen on otoscopy, if the margins are not seen in their entirety, involves the jugular bulb until proven otherwise.

Patients presenting with palpitation, sweating, flushing, hypertension should be screened for serum and urine catecholamine levels which if elevated further imaging should be done to rule out pheochromocytoma or multiple PGs.

Malignant PGs occur in 2% to 5% cases of tympanojugular PG. Vagal paraganglioma have high incidence of malignancy (19%) followed by Carotid body tumours (up to 12%). Commonly metastasizing to regional lymph nodes, distant metastases may occur in bone, liver and lung. Histopathologic confirmation is necessary to prove malignant PGs. Malignant PG is more common in SDHB mutations in comparison to other SDH mutations or with sporadic disease.

Diagnostic Work Up

Thorough history, family history, local physical examination, cranial nerve examination as well as catecholamine evaluation (24 hour urine metanephrine, VMA) is mandatory. In functioning PGs serum epinephrine level is checked. Genetic testing for PGL genetic mutation is important. All head and neck PGL patients and first degree relatives of patients with genetic mutations should be offered genetic counselling and regular screening. A fine-needle biopsy is not indicated in most tumours because the radiographic studies are virtually diagnostic.

Multidetector computed tomography and magnetic resonance imaging is widely used in initial evaluation. Carotid body PGs display splaying of the internal and external carotid arteries (Lyre Sign) on MR angiography. Vagal lesions typically displace the ICA anteriorly and occupy the high parapharyngeal space. Jugular PG causes erosion of caroticojuglar spine (Phlep's sign), enlargement of the jugular foramen with bone destruction (moth eaten appearance) and can involve the middle ear and mastoid.

MRI shows low to intermediate on T1W and hyperintense on T2W. Intense enhancement on postcontrast T1W is seen and the salt pepper pattern due to high flow voids is characteristic. Dynamic contrast enhanced MRI could potentially differentiate PGs from schwannoma when doubtful.MR angiograms facilitate detection of paragangliomas, their multicentricity as well as to determine feeding vessels preoperatively. Three-dimensional time of flight (TOF) MRA allows detection of vessel displacement, gross tumour involvement and

compromised blood flow. MR venogram determines the patency of the contralateral sigmoid sinus and internal jugular vein.

Functional imaging with [123I]-MIBG and [18FDG] PET/CT is useful in localizing HNPGLs in whole body. PET seems to be the imaging of choice scoring over MIBG. Imaging of somatostatin receptors using [68Ga]- DOTATATE PET/CT which emphazises a possible functional dedifferentiation of the large amino acid transporter in *SDHx* mutations. Current studies advocate [68Ga]-DOTATATE PET/CT compared to [18F]-FDA, [18F]-FDOPA, [18F]-FDG, and CT/MRI in localizing *SDHB*-related metastatic sympathetic PHEOs/PGLs and may become the new standard in imaging of PGs.

Classification

SHAMBLIN Classificationof Carotid Body Tumour

Type 1 Relatively small tumor with minimal attachment to the carotid vessels

Type 2 Large tumor with moderate attachment to carotid vessels but resectable with preservation of carotid vessels

Type 3 Tumor encases the carotid vessel requiring arterial sacrifice with reconstruction

Glasscock Jackson classification of Glomus Tympanicum

Type 1 Mass limited to promontary

Type 2 Tumor completely filling the middle ear

Type 3 Tumor filling the middle ear and mastoid

Type 4 Tumor completely filling middle ear, extending to the mastoid o through the external auditory canal. May also extend anteriorly to involve internal carotid artery

Modifed Fisch classification of Juglotympanic paraganglioma

Class A Tumors arising on tympanic plexus confined to middle ear

Class B Tumors arising from inferior tympanic canal in hypotympanum with middle ear/mastoid invasion but jugular bulb and carotid canal intact

Class C Tumors arising in dome of jugular bulb and involving overlying cortical bone

- C1 Tumor eroding carotid canal but not involving carotid artery
- C2 Tumor involving the vertical petrous carotid artery
- C3 Tumor involving the horizontal carotid canal but not foramen lacerum
- C4 Tumor involving the foramen lacerum and cavernous sinus

CLASS D Tumor with intracranial extension, e –extradural, i – intradural

- De1 Extradural extension of <2 cm medial dural displacement
- De2 Extradural extension of >2 cm medial dural displacement
- Di1 Intradural extension of < 2 cm
- Di2 Intradural extension of > 2 cm
- Di3 Neurosurgically unresectable tumor

Treatment

Tympanic PG

All Class A and B tumours

Surgical resection

Jugulo Tympanic PG

The various options include surgical resection, waiting and scanning for increase in rate of growth and radiation therapy depending on the age of the patient, comorbidities of the patient, symptoms and lower cranial nerves involvement.

Surgical Resection options include

- Total surgical removal
- Planned subtotal removal aiming to preserve neurovascular structures with or without postoperative radiotherapy
- Partial resection for symptomatic control

Wait and Scan

This should be the initial approach in most patients to determine the tumour biology. The patients should be evaluated with imaging to determine location and potential for morbidity following treatment and assess the need for treatment in these benign tumours. Once the need is ascertained decision making becomes clear to both the physician as well as the patient. Generally these are the indications for observing the patient.

- Small tumours in elderly patients with intact cranial nerves
- Tumour in elderly patients with poor general health
- Small tumours with insufficient venous circulation
- Patient with a contralateral lower cranial nerve palsy

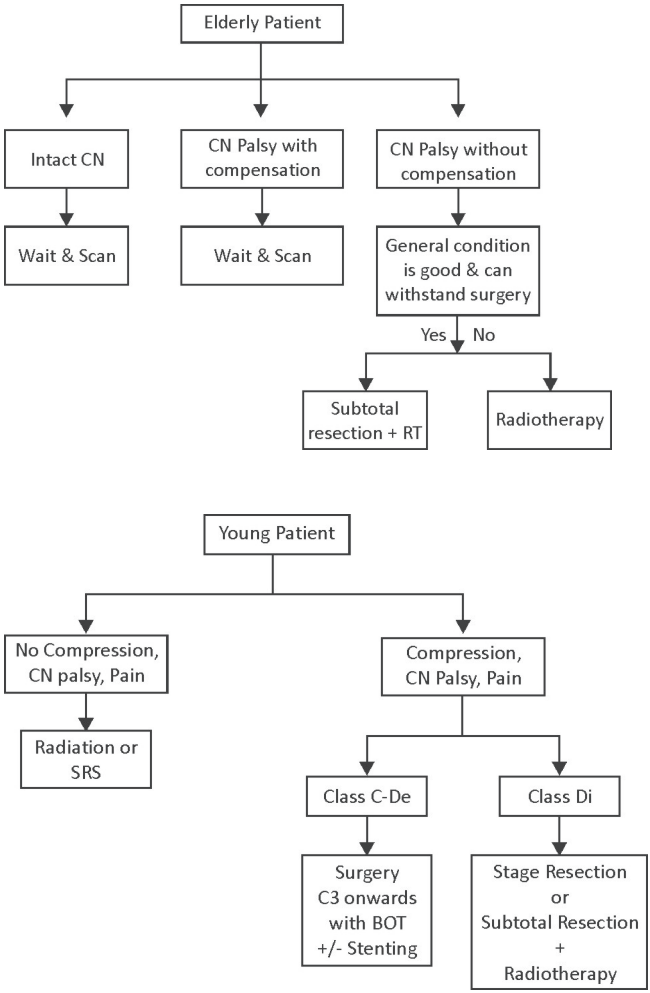
Radiotherapy

PGs being benign tumours which are slow growing, radiation therapy with either stereotactic single dose modality (Radiosurgery), stereotactic fractionated radiation, charged particle therapy and are suitable in these conditions:

- Refusal of surgery
- Significant co-morbidity
- Elderly Patients with intact lower cranial nerve function
- Following planned subtotal resection in C4 tumour
- Carotid artery involvement with insufficient collateral, in which stenting is impossible

Peptide receptor radionuclide therapy

There is an emerging role of the PRRT using (177)Lu-DOTATATE PRRT in symptomatic metastaticparaganglioma with uptake seen with DOTATATE PETCT scan.



Algorithm for Jugulotympanic Paragangliomas Class C and D.

Carotid Body Tumour

Surgery is preferred modality of treatment for carotid body tumours via transcervical approach. Those extending to the skull base might require a transmandibular approach via mandibulotomy. The key in CBT surgery is the proximal and distal control of carotid artery initially followed by microdissection in periadventitial plane (plane of Gordon Taylor) with bipolar cautery in the cleavage plane which facilitates surgery.

Single CBT

Shamblin I and II – Distance of more than 3cm from Skull Base

1. Angiography / Embolisation
2. Surgery

Shamblin III – Distance of more than 3 cm from Skull Base

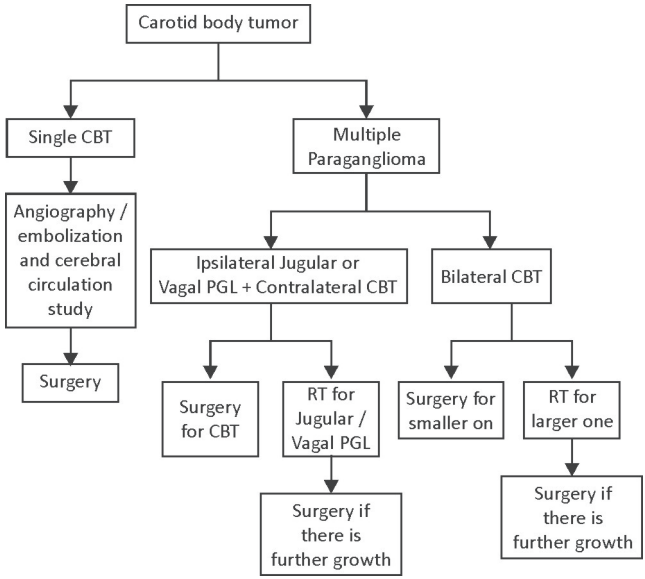
1. Angiography / Embolisation & Cerebral circulation study
2. Carotid artery resection with replacement if withstanding Balloon Test Occlusion
    a. Vein Graft
    b. PTFE graft

Shamblin III – Distance less than 3 cm from Skull Base

1. Angiography / Embolisation & Cerebral circulation study
2. Carotid artery resection with replacement if withstanding Balloon Test Occlusion
3. If Cerebral Cross circulation absent
    a. Intracranial – Extracranial bypass

Multiple PGs

- Bilateral CBT
  - Surgery for smaller one first, followed by other side if Cranial nerves spared.
  - Non surgical option RT for larger one if symptomatic
- Ipsilateral Jugular or Vagal PG with Contralateral CBT
  - Surgery for CBT
  - Jugular or Vagal PG to be planned depending on carotid involvement, cranial nerve involvement and age of patient.



Management of Neck

Level II or III lymph nodes sampling is advocated during the removal of jugolotympanic and vagal PG and carotid body tumour. If sample node turns out to be positive, a comprehensive neck dissection is performed.

Postoperative Follow Up

A long term post treatment follow -up is necessary, since majority of the recurrences are seen at a mean of 7 years. A contrast enhanced, fat -suppressed magnetic resonance imaging is indicated at 1, 3, 5, 7, and 10 years from the surgery.

Suggested Reading

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14. Van der Mey AG, Jansen JC, van Baalen JM. Management of carotid body tumours. Otolaryngol Clin North Am 2001;34(5):907–924.

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Synoptic Reports: Datasets for Histopathology Reporting

Introduction:

Synoptic histopathology reports summarize all data elements required for accurate cancer staging in order to provide optimum treatment to patient. They are used by pathologists as proforma for reporting pathology specimens and are useful to oncologists to interpret histopathology reports. The standard datasets consist of:

- Core data elements: Essential data elements that must be reported in all reports
- Conditional data elements: Reported only if applicable
- Optional data elements: May be reported as required by local practice standards

The data elements must be represented in synoptic report format and should be answered (including "not applicable" or "cannot be determined").

Standard Dataset for Cancers of Nasal Cavity, Paranasal Sinuses and Pharynx:

Core and conditional data elements -

1. Procedure / Type of specimen
2. Tumor Site, Laterality and extension of tumor into adjacent organs
3. Tumor focality (number of tumor foci – unifocal / multifoal / cannot be determined)
4. Tumor size: All three dimensions including greatest dimension
5. Histologic type of cancer including subtypes / variants (as per WHO Classification of Head-Neck Tumors, 2017)
6. Degree of differentiation / Grade: Most commonly used grading systems are:
   - Well differentiated / Moderately differentiated / Poorly differentiated
   - Two tier system – Low grade / High grade or Three tier system – Low grade / Intermediate grade / High grade
   - Specific grading systems are used for certain tumors including adenoid cystic carcinoma, mucoepidermoid carcinoma, olfactory neuroblastoma and neuroendocrine carcinoma
   - Oropharyngeal squamous cell carcinoma are divided into HPV-mediated (positive) and HPV-unrelated (negative) carcinoma
   - Histologic typing alone is sufficient and grading is not required for certain tumor types / variants

including sinonasal undifferentiated carcinoma (SNUC) as well as squamous cell carcinoma variants such as verrucous carcinoma, basaloid carcinoma.

7. Margins:
   - Distance of margins from the tumor (if applicable; cannot be assessed if any of the margins sent separately)
   - Involved by tumor (specify) / not involved by tumor / cannot be assessed
8. Lymphovascular invasion:
   - Not identified / Present / Cannot be assessed
9. Perineural invasion:
   - Not identified / Present / Cannot be assessed
10. Bone invasion:
    - Not identified / Present / Cannot be assessed
11. Pathologic stage classification (pTNM, AJCC 8th edition)
12. Frozen section diagnosis (if applicable): It should accompany final report, including any additional findings recorded on paraffin sections.

Other Conditional as well as Non-core / Optional data elements:

- Macroscopic / Gross appearance of tumor: Exophytic / polypoidal / ulcerative / endophytic
- Carcinoma in situ
- Dysplasia (Grade – Mild / Moderate / Severe)
- Inflammatory response – Type and intensity

- Changes related to prior treatment or surgery
- Associated pathology – Such as presence of papilloma, fungal infection etc.
- ICD-10 Code / Snowmed T, P and M codes

Molecular Marker / Biomarker Reporting in Sinonasal and Pharyngeal Cancers:

1. **HPV testing (for oropharyngeal cancer):**
   - Method of testing: p16 IHC / HPV-DNA ISH / HPV-mRNA ISH / HPV-DNA PCR / HPV-mRNA RT-PCR
   - Results interpreted as:
     - p16 – Positive / Equivocal / Negative / Indereminate
     - Other tests – Positive / Negative / Indeterminate
2. **EBV testing (Nasopharyngeal carcinoma)**
   - EBV early mRNA (EBER) by ISH –
     - Positive (nuclear signal) / Negative (no signal) / Indeterminate
3. **NUT Midline carcinoma – molecular tests**
   - NUT expression by IHC / NUT rearrangement by FISH / *BRD4-NUT* fusion by RT-PCR
4. **INI-1 Deficient Carcinoma: INI-1 by Immunohistochemistry (IHC)**
5. **Biphenotypic Sinonasal Sarcoma:**
   - PAX3 rearrangement by FISH
   - PAX3-MAML3 Fusion by RT-PCR
6. **Paraganglioma**
   - SDHB expression by IHC

Standard Datasets for Carcinoma of Major Salivary Glands

Core and conditional data elements -

1. Procedure / Type of specimen
2. Tumor Site, Laterality and extraparenchymal extension of tumor
3. Tumor focality (number of tumor foci – unifocal / multifoal / cannot be determined)
4. Tumor size: All three dimensions including greatest dimension
5. Histologic type of cancer including subtypes / variants (as per WHO Classification of Head-Neck Tumors, 2017)
6. Degree of differentiation / Grade: Most commonly used grading systems are:
   - Well differentiated / Moderately differentiated / Poorly differentiated
   - Two tier system – Low grade / High grade or Three tier system – Low grade / Intermediate grade / High grade
   - Specific grading systems are used for certain tumors including adenoid cystic carcinoma and mucoepidermoid carcinoma
   - High grade transformation (if applicable) – Present / Not identified
7. Margins:
   - Distance of margins from the tumor (if applicable; cannot be assessed if any of the margins sent separately)

- Involved by tumor (specify) / not involved by tumor / cannot be assessed

8. Lymphovascular invasion:
   - Not identified / Present / cannot be assessed
9. Perineural invasion:
   - Not identified / Present / cannot be assessed
10. Lymph nodes
    - As per standard datasets for Lymph nodes in Head Neck Cancer
11. Pathologic stage classification (pTNM, AJCC 8th edition)
12. Frozen section diagnosis (if applicable): It should accompany final report, including any additional findings recorded on paraffin sections.

Other Conditional as well as Non-core / Optional data elements:

- Macroscopically (Grossly):
  - Nature of tumor circumscription and tumor-host interface: Encapsulated / well-defined / ill-defined / infiltrative
  - Appearance of cut surface: Solid / Cystic / Necrotic / Hemorrhagic / Any other
- Microscopically:
  - Sialadenitis if present
  - Tumor associated inflammatory response – Type and intensity
  - Associated any other pathology (specify)
- ICD-10 code / Snowmed T, P and M codes

Molecular Marker / Biomarker Reporting in Salivary Gland Cancers:

1. Hyalinizing Clear Cell Carcinoma
   - *EWSR1* Rearrangements: FISH / *EWSR1-ATF1* fusion by RT-PCR
2. Mammary Analogue Secretory Carcinoma
   - *ETV6* Rearrangements: FISH / *ETV6-NTRK3* fusion by RT-PCR
3. Mucoepidermoid Carcinoma
   - *MAML2* Rearrangements: FISH / *CRTC1-MAML2* or *CRTC3-MAML2* fusion by RT-PCR
4. Adenoid Cystic Carcinoma
   - *MYB* expression by IHC or *MYB* Rearrangements (FISH / *MYB-NFIB* fusion by RT-PCR)
5. Carcinoma-ex-Pleomorphic Adenoma
   - *HMGA2* rearrangement by FISH
   - *PLAG1* expression by IHC or *PLAG1* Rearrangements by FISH
6. Salivary Duct Carcinoma
   - *HER2* expression by IHC or *HER2/neu* amplification by FISH
   - Androgen Receptor (AR) expression by IHC

Standard Dataset for Lymph nodes in Head Neck Cancers

- Reported only if lymph nodes are included in specimen
- For each lymph node group –
  - Level / Group of lymph nodes and laterality

- No lymph nodes identified
- If lymph nodes are identified –
    a) Total number of nodes involved / Number cannot be determined
    b) Total number of nodes examined / Number cannot be determined
    c) Cross-sectional diameter / greatest dimension of largest metastatic deposit (if metastasis identified)
    d) Micrometastasis: Metastatic focus measuring > 0.2 mm, but < 2 mm in size.
    e) Isolated tumor cells: Defined as metastatic focus measuring < 0.2 mm or < 200 cells. The significance is not known yet.
    f) Isolated tumor nodule in connective tissue: For Head and Neck Cancers, any isolated tumor nodule, discontinuous with main tumor, more than 10 mm away and in the region of lymphatic drainage is regarded as lymph node metastasis.
    g) Extranodal extension (ENE) if metastasis identified –
    o) Present (> 2mm or < 2mm) / Absent / Cannot be determined

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