Evidence Based Management of Cancers in India
(Two Parts)

Guidelines for Head and Neck Cancers
(Part A)

Tata Memorial Hospital
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Guidelines for Head and Neck Cancers
Vol XI

PART A

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Guidelines for Head and Neck Cancers
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Guidelines for Hodgkin’s Lymphoma

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Dedicated to
all our patients at
The Tata Memorial Hospital
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Preface

It is the 10th year of the “Evidence Based Management” meetings as Tata Memorial Hospital. This decade has seen a perceptible change in the academic lingo with off repeated use of terms “randomized evidence”, “meta-analysis and “levels of evidence”. Probably it has also induced uniform patterns to care across India reducing unnecessary long distance travel for patients to seek better patient care.

This year the theme of the conference is Head and Neck Cancers, Hodgkin’s Lymphoma and Infections and Cancer. Head and neck cancers comprise of 25% of all cancers in India and are one of the common causes for mortality and morbidity in males. In addition due to lack of screening programs many patients present with advanced disease. Fortunately there have been advances in chemotherapy and radiation which have resulted improvements in the overall survival of these patients. Recent developments in the management of head and neck cancer also include use of targeted therapies which have become an important option for a select group of patients.

The present EBM book aims to address the management of this common problem in our part of the world and is an update on the earlier one. It has updates on areas where there have been changes in management since the last
book published in 2005, giving an overview of the disease with options of management of the various 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. Every section is also followed by suggested reading and abstracts. This handbook together with the book on algorithms will serve as a useful tool for practicing oncologists in our setup.

February 2012
Mumbai

R A Badwe
Director,
Tata Memorial Centre
General Principles and Outline of Management

1. All patients with suspected carcinoma of head and neck should be evaluated by a head and neck surgical oncologist and should record the following:

A. History
   - Disease related information
   - Detailed history of habits and addictions
   - 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 of operability
Clinical staging and documentation of the subsite(s) involvement

C. Investigations

- X-Ray Chest
- CT Scan / MRI for extent of disease
- EUA / Endoscopy for mapping of disease
- USG for $N_0$ neck in select cases
- Ba swallow + PC film
- PET - CT 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 mediastinal structures
   - 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
4. ""
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. 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

**Role of Brachytherapy (BRT)**
• Accessible lesions
• Small (preferable < 3 cm) tumours
• Lesions away from bone
• N0 nodal status
• Superficial lesions
Dose for radical radiotherapy

**Tumours suitable for brachytherapy**

- **T1-2 N0:**
  - Radical BRT: 60-70Gy low dose rate $^{192}$Iridium or equivalent doses with fractionated high dose rate.
- **T1-3 N0-1**
  - External RT: 56 -60Gy/28-30#/6wks
  - Boost BRT: Low dose rate $^{192}$Iridium: 15-20 Gy or High Dose rate: 14Gy in 4 fractions over 2 days (4-3-3-4 Gy)

**Tumours not suitable for brachytherapy**

- **T1-4 N0-2**
  - 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
  - External RT: 66-70GY/33-35#/6-7weeks (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/m$^2$ weekly with hydration and antiemetic prophylaxis
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

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.

*Participation in clinical trials is encouraged.*
Imaging in Head & Neck Cancers

Why Imaging?
About 20% of the neoplasms in the head and neck region may be small and superficial and imaging may not be needed. However in the remaining 80%, the primary role of imaging is to evaluate the deep extent of disease. This can provide an anatomic map of the disease to help plan therapy and assess resectability. Imaging features can also help prognosticate and evaluate for residual / recurrent disease. Imaging can be used for guided biopsies and to plan radiation therapy.

Which Modality to be used?
General principle—MRI in the suprahypoid neck and CT in the infrahyoid neck (with exceptions as below)
MRI sections must extend from above the base skull to the root of the neck. Both noncontrast and postgadolinium scans are essential. MRI is the preferred modality for imaging suprahypoid neck which includes the nasopharynx, oropharynx, base of tongue, anterior tongue and hard
palate, salivary glands, paranasal sinuses, cavernous sinuses, dura, and brain. *Perineural and dural involvement are best seen on MRI.*

CT scanning is preferred for gingivobuccal cancers for evaluating bone erosion. CT also has a complementary role for evaluating the sinonasal region. CT scanning is now widely performed with 16 slice or 64 slice multidetector CT (MDCT) scanners. For imaging of the infrahyoid neck, MDCT is preferred. For the larynx, MRI can be used as a problem solving modality (for cartilage involvement).

PET CT is valuable for evaluation in the post treatment setting, for radiotherapy planning, has a role in evaluating an unknown primary and is the best modality for metastatic workup.

**Resectability issues in Head & Neck Cancers**

The AJCC in 2002 has revised the T stage classification into T4a and T4b, where T4a indicated advanced but resectable disease while T4b indicated unresectable tumors. The terms resectable and unresectable though have now been replaced by “moderately advanced” and “very advanced”. The three major T4B issues common to all head neck cancers are carotid artery invasion, mediastinal invasion and prevertebral fascial infiltraton. Circumferential involvement of the artery more than 270° by the tumor on imaging indicates an inability to strip the vessel off the tumor, while circumferential contact less than 180 degrees suggests high likelihood of peeling vessel off the tumor. Imaging criteria for mediastinal invasion too are fairly accurate while prevertebral fascial involvement is the only
feature which may not be successfully detected with imaging.

**ORAL CAVITY**

**Subsites**

**Gingivobuccal region, lips, retromolar trigone (RMT).** Cancers of these regions often erode adjacent bone. Extent of mandibular erosion is important for planning resection as well as a prognostic criterion.

MDCT is the preferred imaging technique with “Puffed cheek technique”. 16 slice and 64 slice MDCT scanners yield high resolution coronal and sagittal reformations that can demonstrate subtle bone erosion with high accuracy. Puffed cheek technique improves visualization of lesion epicenter (gingival or buccal mucosa) and precise extent. RMT lesions are often not amenable to clinical inspection and imaging often reveals the true deep extent. Masticator space involvement is considered T4b, but when the invasion is relatively low in this space, resection maybe feasible with or without neoadjuvant chemotherapy. On the other hand, high masticator space (infratemporal fossa) invasion above the mandibular notch carries poor prognosis.

**Tongue and Hard palate** MRI preferred as it has superior soft tissue characterization. MRI can show involvement of extrinsic and intrinsic muscles, tumor thickness, posterior extent including involvement of base tongue, and mandibular invasion (involvement of all of which constitute T4a disease) and neck nodes. DW MRI can help differentiate between metastatic and uninvolved nodes.
Extensive involvement of masticator space, pterygoid plates, skull base and ICA which constitutes T4b disease are also well demonstrated. MDCT though has insufficient characterization for accurate delineation of the tumor extent.

**LARYNX** MDCT has the advantage of speed of scanning, universal acceptance, thin sections with high resolution reformations, and high specificity for cartilage erosion. The major disadvantage with MRI is lack of uniform patient acceptance, image degradation by swallowing and long duration of scanning.

The revised AJCC classification classifies minor cartilage invasion (inner perichondrium) as T3 which can be treated with chemoradiation while through and through cartilage invasion is T4A and requires surgery. MRI has high sensitivity for cartilage invasion, but lower specificity with resultant false positives while CT has lower sensitivity and higher specificity.

The most problematic cartilage is the thyroid cartilage as it ossifies patchily. Moreover sclerosis of the cartilage has only a 50% positive predictive value for tumor invasion. Hence if CT is used for primary imaging and is equivocal for cartilage invasion, MRI can be reserved for problem solving, particularly if tumor is adjacent to unossified cartilage or if cartilage sclerosis is present. Recently Becker et al have reported that presence of intermediate signal intensity within the thyroid cartilage on T2W images that enhance on postcontrast images is highly specific for tumor invasion while reactive inflammation has bright signal intensity on T2W images. Sclerosis of the arytenoid
or cricoid cartilages on CT is more in favor of tumor invasion.

Imaging features in squamous cancers of the larynx also have a strong prognostic significance. Tumor volume > 3.5cc in the glottis or > 6cc in the supraglottis, multiple / significant cartilage involvement, pre-epiglottic and paraglottic space invasion are poor prognostic factors with poor local control.

**PARANASAL SINUSES**. Imaging with MRI is preferred although CT is often the baseline investigation. Imaging is primarily of value in assessing disease extent rather than suggesting specific diagnoses. MRI is superior for 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.

**THYROID**

Ultrasound is the primary modality of investigation for thyroid nodules. Ultrasound is highly sensitive for nodule detection, but nonspecific in nodule characterization. Certain features of nodules such as microcalcification with increased vascularity have the highest specificity for malignancy requiring needling. As per the revised ATA (American Thyroid association) guidelines 2009, a solid nodule > 1.5cm and a nodule > 1cm with microcalcification should be subjected to FNA. In the presence of abnormal nodes, any ipsilateral thyroid nodule should be needled. CT scanning is required for staging in confirmed cases of thyroid cancer with extrathyroidal spread.
SALIVARY GLANDS. MRI is the optimal modality of investigation due to superior soft tissue characterization. Perineural and intracranial spread are demonstrated with high accuracy. Invasion of the skull base, ICA and pterygoid plates contraindicate resection. MRI is also useful for evaluating residual or recurrent disease.

PARAPHARYNGEAL SPACE LESIONS. Parapharyngeal space is divided into a) the prestyloid compartment that consists of the parapharyngeal fat and deep lobe of parotid and b) the poststyloid compartment that consists of the carotid sheath, with the nerves and paraganglionic tissue posterior to the vessels. 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. The common post styloid compartment lesions are the schwannomas and paragangliomas.

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. 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.

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 is used in centres where expertise is available. DW MRI and dynamic contrast enhanced MRI have an emerging role.

**Post treatment issues** 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**

1. **D.M. Yousem, K. Gad, and R.P. Tufano**
   
   *Resectability Issues with Head and Neck Cancer*
   

   
   *A Potential Pitfall of MR Imaging for Assessing Mandibular Invasion of Squamous Cell Carcinoma in the Oral Cavity.*
   

   
   *Tumor Thickness and Paralingual Distance of Coronal MR Imaging Predicts Cervical Node Metastases in Oral Tongue Carcinoma*
   
   AJNR Am J Neuroradiol 2008 29: 45-50
4. Suresh K. Mukherji, Ilona M. Schmalfuss, Jonas Castelijns, and Anthony A. Mancuso

Clinical Applications of Tumor Volume Measurements for Predicting Outcome in Patients with Squamous Cell Carcinoma of the Upper Aerodigestive Tract


Fluorodeoxyglucose—Positron-Emission Tomography Imaging of Head and Neck Squamous Cell Cancer

6. Ryuji Murakami, Mitsuhiro Furusawa, Yuji Baba, Ryuichi Nishimura, Fumihiro Katsura, Masao Eura, Keisuke Masuyama, and Mutsumasa Takahashi

Dynamic Helical CT of T1 and T2 Glottic Carcinomas: Predictive Value for Local Control with Radiation Therapy

7. WR Nemzek, S Hecht, R Gandour-Edwards, P Donald, and K McKennan

Perineural spread of head and neck tumors: how accurate is MR imaging?


**Carotid Body Tumors: Objective Criteria to Predict the Shamblin Group on MR Imaging**  

**Discrimination of Metastatic Cervical Lymph Nodes with Diffusion-Weighted MR Imaging in Patients with Head and Neck Cancer.**  

**Role of Diffusion-Weighted Echo-Planar MR Imaging in Differentiation of Residual or Recurrent Head and Neck Tumors and Posttreatment Changes**  
Protocol for Histopathological Examination and Reporting
H & N Cancer (Synoptic Reporting)
(Including lip, buccal mucosa, tongue, mandible and maxilla)

Introduction
There are some common guidelines for the histopathological examination procedure, despite the diverse sites of origin and complex anatomy resulting in the varied types of resections in Head and Neck mucosal malignancy. The synoptic reporting style captures these guidelines and at the same time remains concise, praise and user-friendly.

A. Specimen details:
1. Anatomic site with laterality
2. Type of specimen:
3. Biopsy: Incision or Excision biopsy
4. Resection – Type of surgery performed
   a) Tongue: Wide excision, Hemiglossectomy, Near total glossectomy, Total Glossectomy
b) Lip: Wide excision, Bite resection

c) Mandible: Composite resection with – Hemimandibulectomy, Segmental Mandibulectomy (including Middle Third Mandibulectomy), Marginal Mandibulectomy

d) Maxilla: Palatectomy, Partial Maxillectomy (Including suprastructure, infrastructure, medial maxillectomy), Total Maxillectomy with or without Orbital exenteration

e) Wide excision: Buccal mucosa, Floor of Mouth – Specify whether oriented or not.

f) Lymph nodes: Specify type of neck node dissection
   i) Individual levels, if sent separately
   ii) Selective node dissection (including).
      • Supra-omohyoid neck dissection
      • Modified neck dissection: Type I, II or III
      • Radical neck dissection

g) Other specimens accompanying with main specimen including separately sent or revised margins.

5. Received fresh / in formalin
6. Received intact / fragmented

B. Frozen section examination, if performed:

1. Type of specimen sent for frozen section with relevant gross details
2. Nature of tissue submitted for freezing (closest margin, base, inked margin, node etc.)

3. Frozen section interpretation (Including name of pathologist reporting it)

C. Gross / Macroscopic Examination:

1. Specimen of ____ with dimensions: ____ X ____ X ____ cm
   OR for Mandibulectomy – measuring ____ cm along lower alveolar border overlying skin measuring ____ X ____ cm

2. Number of tumor foci

3. Location and extent of tumor: Enumerate all the structures involved by tumor.

4. Size of tumor: ____ X ____ X ____ cm. Specify maximum thickness of tumor especially for tongue specimen as well as wide excision, after cutting through the tumor.

5. Type of tumor: Polypoidal / Sessile / Ulceroproliferative / Ulcerative / plaque like

6. Distance of tumor from mucosal, bony and soft tissue cut margins (including base) as well as from overlying skin if present

7. Underlying mandibular / maxillary bone: Whether involved by tumor or free of tumor

8. Neck nodes: For each specimen / level, specify – Number of nodes dissected with size of largest node and appearance on cut surface, extra nodal spread if any

10. Any other specimen sent separately: Dimension, appearance

D. Sections: Check-list for sections:
   1. Tumor (2-4 sections) with adjacent soft tissue
   2. Tumor with underlying bone (if present)
   3. Tumor with overlying skin (if present)
   4. All margins, labeling each mucosal, bony and soft tissue margin separately
   5. Neck nodes – All nodes at individual levels or as per type of neck node dissection
   6. Salivary gland one section
   7. Other specimens sent separately
   8. Frozen section tissue submitted entirely

E. Microscopic Examination:
   1. Type of tumor:
      a) Squamous carcinoma and variants
      b) Minor salivary gland carcinoma: Specify type
   2. Grade of tumor:
      a) For squamous and adenocarcinoma: Well, Moderate or Poorly differentiated
      b) For mucoepidermoid carcinoma: Low, Intermediate or High grade
      c) For adenoid cystic carcinoma: Grade I, II or III
3. Stromal response: Lymphoplasmacytic or desmoplastic
4. Lymphovascular emboli: Present or Absent
5. Perineural invasion: Present or Absent
6. Underlying bone / bones: Involved by tumor / free of tumor; when involved, specify periosteum cortex and / or medulla involvement
7. Overlying skin: Involved by tumor / free of tumor
8. Status of all margins:
   a) All free of tumor
   b) Close to tumor but free (specify margin and its distance from the tumor)
   c) Involved by tumor (specify the margin / margins involved)
9. Neck nodes: For each level or type of neck node dissection, specify
   a) Number of total nodes dissected
   b) Number of nodes showing metastasis
   c) Perinodal extension present or absent
   d) Any other findings (Granuloma, Treatment related changes etc.)
10. Separately sent specimen: Relevant microscopic _____ X _____ cm findings (involved by tumor or not etc.) or synchronous lesion, if any.

F. Final Diagnosis:
Primary site, type of carcinoma, grade and extent, cut margin status and regional node involvement.

TNM Stage: P T_N_M_
References:

1. Synoptic Reports: “Mandibulectomy and Tongue”, by Department of Pathology, Tata Memorial Center, Mumbai.

2. College of American Pathologists: Protocol for Examination of Specimens from Patients with Carcinomas of Lip and Oral Cavity, November 2011

3. Kane SV, Patil A: “Grossing Head and Neck Specimen”, Grossing of Surgical Oncology Specimens, Edited by Dr. Saral Desai et al, Department of Pathology, Tata Memorial Hospital, 2011.
Oral Cavity

Introduction
The annual incidence of oral cancer worldwide is 2,63,000 and every year 1,27,000 people die because of oral cancer. Oral cancers are more common in Southeast Asia particularly India. India accounts more than one-fourth of world’s burden. The two most important etiological factors of oral cancers are tobacco use (smoking and smokeless) and alcohol consumption. In India, the use of smokeless tobacco is an important cause of oral cancer.

Subsites:
- Lip
- Buccal mucosa
- Lower alveolus
- Retro molar trigone
- Oral tongue
- Floor of mouth (FOM)
- Upper alveolus
- Hard palate
Specific Investigations:

- USG neck for clinically N0 neck when neck is to be observed or neck evaluation is difficult. USG with FNAC increases the specificity.
- CT scan/ MRI for suspected bony/vascular/maxillary infiltration and extension of tumor in infratemporal fossa.
  - CT scan is most commonly used to detect mandibular invasion. It is preferred over the OPG as it gives information about soft tissue extent along with bony invasion. It is used to assess early bone involvement, in midline lesions and in sites as buccal mucosa, upper & lower alveolus, RMT & hard palate.
  - MRI is preferred for tongue and floor of mouth lesions and for extension in oropharynx or parapharyngeal space.

<table>
<thead>
<tr>
<th>Imaging Modality for bony invasion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Scan</td>
<td>82.6%</td>
<td>86.9%</td>
<td>82.6%</td>
<td>86.9%</td>
</tr>
<tr>
<td>MRI Scan</td>
<td>100%</td>
<td>71%</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- PET-CT scan for evaluation of post treatment residual/recurrent disease.
- EUA (Examination under anesthesia) for mapping of lesion.
TNM Staging (AJCC, 2010)

Primary tumor:
TX Primary tumor cannot be assessed.
T0 There is no evidence of primary tumor.
Tis Carcinoma is *in situ*.
T1 Tumor is 2 cm or less in greatest dimension.
T2 Tumor is more than 2 cm but not greater than 4 cm in greatest dimension.
T3 Tumor is more than 4 cm in greatest dimension.
T4 Moderately advanced local disease.
   (Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose (Oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone, [mandible or maxilla] into deep [extrinsic] muscle of tongue [Genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b Very advanced local disease.
   Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery, skull base and/or encases the internal carotid artery.

*Note:* Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.

Regional lymph nodes
Nx Regional LN cannot be assessed
N0 No regional LN metastasis
N1 Ipsilalateral Single node < 3cm
N2a Ipsilalateral Single node 3-6cm
N2b  Ipsilateral multiple nodes <6cm
N2c  Bilateral/Contralateral nodes<6cm
N3   Lymph node > 6cm

Metastasis
M0   No metastasis
M1   Distant metastasis

Surgical margins: Refer to general principles for details.

MANAGEMENT OF PRIMARY:
(Lip/Buccal Mucosa/Oral Tongue/Floor of mouth/Lower alveolus /Retro Molar Trigone)

LIP
T1, T2 Tumors: Surgery or RT
Surgery: Wide excision
Radiotherapy: Radical Radiotherapy / Brachytherapy.

T3, T4 Tumors: Surgery + Post operative RT/ CT-RT
Surgery: Wide excision with marginal/ segmental / hemimandible resection with appropriate reconstruction.

BUCCAL MUCOSA
T1, T2 Tumors: Surgery or RT
Surgery: wide excision +/- marginal mandibulectomy with appropriate reconstruction.
Radiotherapy: Radical RT/ Brachytherapy.

T3, T4 Tumors: Surgery + Post operative RT/ CT-RT
Surgery: Composite resection of the buccal mucosa with mandible or upper alveolus or overlying skin with reconstruction.
ORAL TONGUE & FLOOR OF MOUTH

**T1, T2 Tumors:** Surgery or RT

Surgery: Wide excision Glossectomy / Hemiglossectomy with appropriate reconstruction.

Radiotherapy: Radical RT/ Brachytherapy.

**T3, T4 Tumors:** Surgery + Post operative Radiotherapy/ CT-RT

Surgery: Appropriate wide excision glossectomy with mandibular swing or pull through along with lingual plate / segmental / hemimandibular resection, if required (based on extent of involvement) with reconstruction.

LOWER ALVEOLUS & RETRO MOLAR TRIGONE

Mandible uninvolved or minimally involved

Surgery: Wide Excision with marginal mandibulectomy (avoided in RMT disease, edentulous mandible, paramandibular disease, post radiotherapy) if required with reconstruction.

Indication for Marginal Mandibulectomy:

1) Whenever tumor is close to the mandible to achieve adequate margin (5 mm-10mm)

2) Limited superficial bony erosion

3) Limited periosteal invasion

**Mandible grossly involved**

Surgery + Post operative/ CT-RT

Surgery: Wide Excision (cheek flap) with segmental/ hemimandible resection with reconstruction.
Indication for Segmental Mandibulectomy:
1) Gross tumor invading the mandible
2) Prior radiotherapy
3) Edentulous mandible
4) Gross paramandibular disease
5) Whenever inferior soft tissue and bony margin of 1 cm is not possible (Eg. Retro Molar Trigone, gross periosteal invasion)

MANAGEMENT OF NECK NODES:
(Lip/Buccal Mucosa/Oral Tongue/Floor of mouth/Lower alveolus /Retro Molar Trigone)

T1, T2 Tumors
N0: Observe or SOHD (if cheek flap is raised, USG suspicious, thick tumor>3-4mm, high grade tumor or poor follow up expected) followed by FS, if positive nodes MND is required

N+: MND / RND
Note: Post op RT as per earlier guidelines.

T3, T4 Tumors
N0: SOHD followed by FS, if positive nodes MND is required

N+: MND / RND
Note: Bilateral neck needs to be addressed if the primary disease is in midline or extending across midline (including middle third mandible).
Post op RT/CT-RT as per earlier guidelines.
UPPER ALVEOLUS & HARD PALATE

Primary:

Maxillary antrum not involved
Surgery: Upper alveolectomy / Partial maxillectomy
Radiotherapy: Radical RT / Brachytherapy for selected early T1-2 Hard palate lesions

Maxillary antrum involved
Surgery: Orbital floor preserving total maxillectomy with reconstruction.

Nodes:
Neck needs to be addressed if the neck is clinically positive, if there is extension of the primary disease to the buccal mucosa or there is soft tissue infiltration or radiological suspicion of metastatic node.

Post operative RT/ CT-RT as per guidelines mentioned earlier.

Reconstructive options for oral cavity-

Objectives:
Achieve primary healing
Maintain oral competence
Facilitate swallowing
Prevent aspiration
Preserve speech
Cosmesis
Based on the size and composition of defect, the options are:

**Mucosal defects** –
- Leave raw
- Primary closure
- Split thickness skin graft (STSG)
- Mucosal grafts

**Full thickness defects** –
- Local Flaps: Abbe-Estlander’s flap, Gille’s Flap (for lip)
- Regional flaps: Tongue flap, Nasolabial flap, Facial artery myomucosal flap, Masseter flap, Platysmal flap, , Forehead flap
- Distant Flaps: Pectoralis major myocutaneous flap, Deltopectoral flap, Latissimus dorsi myocutaneous flap
- Free Flaps: Radial forearm flap, Lateral arm flap, Antero-lateral thigh flap

**Mandibular Defects**
Anterior mandibular defect needs to be reconstructed by
- Free osteocutaneous flaps-
  Fibular osteocutaneous flap (preferred because of long bone length, easy contouring and dual blood supply), Radial osteo-cutaneous flap, Scapular osteocutaneous flap
- Distant flaps-
  Pectoralis major myocutaneous flap, Latissimus dorsi osteocutaneous flap, Trapezius osteocutaneous flap
Lateral mandibular defects may be reconstructed with adequate soft tissue replacement, complemented by proper use of guide bite prosthesis and appropriate post-operative isometric exercises.

Criteria for Inoperability:
Primary disease: Adequate surgical clearance is not achievable.

- Extensive Infratemporal Fossa involvement
- Extensive involvement of base skull.
- Extensive induration /soft tissue disease till zygoma or hyoid.

Nodal Disease:
- Clinically fixed nodes.
- Infiltration of Internal /Common carotid artery.
- Extensive infiltration of prevertebral muscles, skull base.

These patients are usually treated with palliative intent with chemotherapy or radiotherapy. If general condition is good, then concurrent chemo radiotherapy can be offered. If general condition is poor, then only best supportive care.

Prognosis:

**Oral cavity**

<table>
<thead>
<tr>
<th>stage</th>
<th>5 year relative survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>69.5% - 73.5%</td>
</tr>
<tr>
<td>II</td>
<td>55.5% - 60.4%</td>
</tr>
<tr>
<td>III</td>
<td>41.8% – 47.3%</td>
</tr>
<tr>
<td>IV</td>
<td>40.3% – 33.6%</td>
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</table>
**Lip**

<table>
<thead>
<tr>
<th>stage</th>
<th>5 year relative survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>86.5% - 92.7%</td>
</tr>
<tr>
<td>II</td>
<td>75.5% - 91.5%</td>
</tr>
<tr>
<td>III</td>
<td>39.8% - 69.8%</td>
</tr>
<tr>
<td>IV</td>
<td>34.2% - 60.1%</td>
</tr>
</tbody>
</table>

**Suggested reading:**


15. Totsuka Y, Usui Y, Tei K, et al. Mandibular involvement by squamous cell carcinoma of lower alveolus:


**Oral Cancers**


Walvekar RR, Chaukar DA, Deshpande MS, Pai PS, Chaturvedi P, Kakade A, D’Cruz AK
The purpose of our study was to analyze the indicators of loco-regional failure in a large cohort of patients with gingivobuccal complex tumors treated at a single institution. A retrospective review of 2275 patients diagnosed with tumors of the gingivobuccal complex was conducted from January 1997 to December 1999; 642 patients who fulfilled our inclusion criteria were analyzed. A univariate analysis, multivariate analysis, and disease-free survival are reported. During a median follow up of 2.51 years, there were 228 (35.5%) recurrences with a median post-recurrence survival of 2.7 months. The incidence of occult neck metastasis was 29%. The 2- and 5-year DFS rates were 63.8% and 53.3%, respectively. On multivariate analysis, tumor depth and metastatic lymphadenopathy were found to be independent prognostic factors for disease-free survival. Advanced gingivobuccal cancers fail loco-regionally. Cervical metastasis and tumor depth influence disease-free survival. Elective neck dissection due to a high incidence of occult neck disease is recommended.

2. Squamous cell carcinoma of the superior gingival-buccal complex.

Pathak KA, Mathur N, Talole S, Deshpande MS, Chaturvedi P, Pai PS, Chaukar DA, D’Cruz AK.


Squamous cell carcinoma of the superior gingival-buccal complex are rare and few English-language data have been published on their biological behaviour. Reported in this
paper are the clinical behaviour and treatment outcomes of squamous cell carcinoma of the upper gingival-buccal complex. We reviewed the charts of 110 patients with squamous cell carcinoma restricted to the upper gingiva, superior gingival-buccal sulcus and adjoining buccal mucosa, seen between 1997 and 2001. Separate outcome analyses were carried out among 86 patients who had undergone surgery, and 24 patients treated by radiotherapy or chemo-radiation. Disease-free survival at 2 and 5 years was 48.9% and 36%, respectively, and was independent of epicentre of disease. Five-year, disease-free survival was 48.8% and 0% for surgical treatment and non-surgical treatment groups. T stage (p=0.024) and extra-capsular spread of disease (p=0.036) were independent predictors of disease-free survival on multivariate analysis. Adequate surgical resection and adjuvant treatment, in the first instance, offers the best chance of disease control.

3. Patterns of invasion and routes of tumor entry into the mandible by oral squamous cell carcinoma.

*Brown JS, Lowe D, Kalavrezos N, D’Souza J, Magennis P, Woolgar J.*


**Background:**
An understanding of the patterns, spread, and routes of tumor invasion of the mandible is essential in deciding the appropriate level and extent of mandibular resection in oral squamous cell carcinoma.
Methods:
A prospective study of histologic patterns of tumor invasion and routes of tumor entry into the mandible was performed in a consecutive series of 100 previously untreated patients.

Results:
The pattern of tumor invasion of the mandible depended on the depth of invasion both in the hard (p = .001) and soft tissues (p = .001). There was evidence that the pattern of invasion was related to histologic prognostic indicators of the disease, such as extracapsular spread from invaded lymph nodes (p = .03). The route of tumor entry was at the point of abutment to the mandible (direct) in all 13 cases, invading the dentate part of the mandible. Fifty-five percent (23 of 42) of tumors invading the edentulous ridge entered through the occlusal (superior) surface. Direct entry to the mandible in the edentulous ridge was more likely for tumors arising in the tongue, floor of the mouth and the buccal mucosa compared with alveolar or retromolar sites (p = .003).

Conclusions:
Larger or more deeply invading tumors in the soft tissue are more likely to invade the mandible and show the more aggressive (invasive) form of tumor spread, reducing the options of a more conservative (rim) resection. Tumors tend to enter the mandible at the point of abutment, which in both the dentate and edentulous jaw is often at the junction of the reflected and attached mucosa. A point of tumor entry below the occlusal ridge or gingival crest should be assumed when planning rim or marginal resections of the mandible.
Purpose:
Prognosis of patients with advanced oral cavity cancer is worth improving. Chemotherapy has been reported to be especially active in oral cavity tumors. Here we repeat the results of a randomized, multicenter trial enrolling patients with a resectable, stage T2–T4 (> 3 cm), N0–N2, M0 untreated, squamous cell carcinoma of the oral cavity.

Patients and Methods:
Patients were randomly assigned to three cycles of cisplatin and fluorouracil followed by surgery (chemotherapy arm) or surgery alone (control arm). In both arms, postoperative radiotherapy was reserved to high-risk patients, and surgery was modulated depending on the tumor’s closeness to the mandible. Patients’ accrual was opened in 1989 and closed in 1999. It included 195 patients.

Results:
In the chemotherapy arm, three toxic deaths were recorded. No significant difference in overall survival was found. Five-year overall survival was, for both arms, 55%. Postoperative radiotherapy was administered in 33% of patients in the chemotherapy arm, versus 46% in the control arm. A mandible resection was performed in 52% of patients in the control arm, versus 31% in the chemotherapy arm.
**Conclusion:**
The addition of primary chemotherapy to standard surgery was unable to improve survival. However, in this study, primary chemotherapy seemed to play a role in reducing the number of patients who needed to undergo mandibulectomy and/or radiation therapy. Variations in the criteria used to select patients for these treatment options may make it difficult to generalize these results, but there appears to be room for using preoperative chemotherapy to spare demolitive surgery and/or radiation therapy in patients with advanced, resectable oral cavity cancer.

5. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck.

_Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM._


There is still no consensus on the optimal treatment of the neck in oral cavity cancer patients with clinical N0 neck. The aim of this study was to assess a possible benefit of elective neck dissection in oral cancers with clinical N0 neck. A comprehensive search and systematic review of electronic databases was carried out for randomized trials comparing elective neck dissection to therapeutic neck dissection (observation) in oral cancer patients with clinical N0 neck. A meta-analysis of the studies which met our defined selection criteria was performed using disease-specific death as the primary outcome, and the relative risk (RR) of disease-specific death was calculated for each
of the identified studies. Both fixed-effects (Mantel-Haenszel method) and random-effects models were applied to obtain a combined RR estimate, although between-study heterogeneity was not found to be significant as indicated by an I(2) of 8.5% (p=0.350). Four studies with a total of 283 patients met our inclusion criteria. The results of the meta-analysis showed that elective neck dissection reduced the risk of disease-specific death (fixed-effects model RR=0.57, 95% CI 0.36-0.89, p=0.014; random-effects model RR=0.59, 95% CI 0.37-0.96, p=0.034) compared to observation. This reduction in disease-specific death rate supports the need to perform elective neck dissection in oral cancers with clinical N0 neck.

**Summary**

Stage I and II are treated with surgery or radiotherapy as a single modality. There no randomized control trials comparing surgery with radiotherapy in early stage disease. Combined modality in the form of surgery with post-operative radiotherapy is used in operable stage III & IV disease. There is a controversy regarding management of N0 neck in oral cancers.
**Oropharynx**

**Introduction:**
The treatment of oropharyngeal carcinoma is aimed at maximizing cure with minimal functional morbidity. Radical radiotherapy is the treatment of choice in early T1, T2 tumors and chemoradiotherapy is the treatment of choice in advanced T3, T4 tumors. IMRT is preferred modality of radiotherapy for tumors of Oropharynx (1).

Surgery is preferred in select early cases where surgical resection is associated with reasonable functional outcome. It is also preferred with postoperative radiotherapy in select advance cases eg. Infiltrative lesions of base tongue, tonsil and lesions involving the mandible and as a salvage procedure for residual neck nodes following chemoradiotherapy.

**Oropharynx Subsites**
- Base of Tongue
- Tonsil
- Soft palate
- Uvula
- Pharyngeal wall

**Specific Investigations:**
- Clinical evaluation including per-oral examination, indirect laryngoscopy and neck examination.
- Imaging:
  - MRI: investigation of choice for soft tissue extent.
  - CT scan: preferred in suspected bony erosion (mandible, pterygoid plates, base skull)
  - PET-CT: for post-treatment residual or recurrent disease
- Examination under general anaesthesia (EUA) for
  - Extent of tumour,
  - Biopsy / FNAC of neck nodes.
  - Assessment for operability (If surgery is contemplated).

HPV testing suggested (2)

Chest imaging

**Treatment options:**

**Stage I & II (T1-2 N0)**
- Radical Radiotherapy: In most cases.

RT: External beam RT +/- Brachytherapy.

Radiotherapy techniques: Conventional radiation therapy/3DCRT/IMRT (1)
Doses: Primary tumor with involved nodes: 70Gy/35 fractions equivalent, High risk nodal region: 60Gy equivalent, Low risk nodal region: 50Gy equivalent. Tolerances of critical structures to be respected. Simultaneous integrated boost may also be considered. Breaks in treatment should be minimized (As per RTOG H0022).

**Brachytherapy:**
Radical brachytherapy: Can be considered for accessible tumors: T1 tumors of tonsil, soft palate, uvula. Doses: 50-60Gy of low dose rate equivalent.

**Boost brachytherapy:**
For T2 oropharyngeal tumors and T1 base tongue tumors. Generally considered after 46-50Gy of Ext RT. Doses: 20-30Gy low dose rate equivalent

- Surgery: Open Surgery / Transoral Laser microsurgery / Transoral Robotic Surgery
  In selected cases eg. Lateralised lesion, infiltrative disease.
  (Criteria: Patient’s preference, institutional practice and complexity of procedure).

**Stage III & IV**
T1-2, N2-3
- Concurrent Chemoradiotherapy, followed by salvage neck dissection if residual nodes lymphadenopathy (3)
  Altered fractionation schedules may be considered as an alternative option (4)
Chemotherapy: 3 weekly single agent cisplatin/weekly cisplatin

- Split therapy: (In selected cases of large nodes with small radio-curable primary) Node mass excision followed by RT / CT+RT (5)

**T3-4, NO, N+**

- Concurrent Chemoradiotherapy (3): In most cases.
- Surgery: (if low peri-op risk & reasonable functional outcome) Composite resection + appropriate neck dissection + Adjuvant therapy

**Note:** Post-op RT / CT+RT as per general guidelines.

**Suggested Reading**


PARSSPORT trial management group.Head and Neck Unit, Royal Marsden Hospitals NHS Foundation Trust, London, UK.

**Background:**

Xerostomia is the most common late side-effect of radiotherapy to the head and neck. Compared with conventional radiotherapy, intensity-modulated radiotherapy (IMRT) can reduce irradiation of the parotid
glands. We assessed the hypothesis that parotid-sparing IMRT reduces the incidence of severe xerostomia.

**Methods:**
We undertook a randomised controlled trial between Jan 21, 2003, and Dec 7, 2007, that compared conventional radiotherapy (control) with parotid-sparing IMRT. We randomly assigned patients with histologically confirmed pharyngeal squamous-cell carcinoma (T1-4, N0-3, M0) at six UK radiotherapy centres between the two radiotherapy techniques (1:1 ratio). A dose of 60 or 65 Gy was prescribed in 30 daily fractions given Monday to Friday. Treatment was not masked. Randomisation was by computer-generated permuted blocks and was stratified by centre and tumour site. Our primary endpoint was the proportion of patients with grade 2 or worse xerostomia at 12 months, as assessed by the Late Effects of Normal Tissue (LENT SOMA) scale. Analyses were done on an intention-to-treat basis, with all patients who had assessments included. Long-term follow-up of patients is ongoing. This study is registered with the International Standard Randomised Controlled Trial register, number ISRCTN48243537.

**Results:**
47 patients were assigned to each treatment arm. Median follow-up was 44.0 months (IQR 30.0-59.7). Six patients from each group died before 12 months and seven patients from the conventional radiotherapy and two from the IMRT group were not assessed at 12 months. At 12 months xerostomia side-effects were reported in 73 of 82 alive patients; grade 2 or worse xerostomia at 12 months was
significantly lower in the IMRT group than in the conventional radiotherapy group (25 [74%; 95% CI 56-87] of 34 patients given conventional radiotherapy vs 15 [38%; 23-55] of 39 given IMRT, p=0.0027). The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which was more prevalent in the IMRT group (18 [41%; 99% CI 23-61] of 44 patients given conventional radiotherapy vs 35 [74%; 55-89] of 47 given IMRT, p=0.0015). At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy (20 [83%; 95% CI 63-95] of 24 patients given conventional radiotherapy vs nine [29%; 14-48] of 31 given IMRT; p<0.0001). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival.

Conclusion:
Sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life, and thus strongly supports a role for IMRT in squamous-cell carcinoma of the head and neck.

Background:
Oropharyngeal squamous-cell carcinomas caused by human papillomavirus (HPV) are associated with favorable survival, but the independent prognostic significance of tumor HPV status remains unknown.

Methods:
We performed a retrospective analysis of the association between tumor HPV status and survival among patients with stage III or IV oropharyngeal squamous-cell carcinoma who were enrolled in a randomized trial comparing accelerated-fractionation radiotherapy (with acceleration by means of concomitant boost radiotherapy) with standard-fractionation radiotherapy, each combined with cisplatin therapy, in patients with squamous-cell carcinoma of the head and neck. Proportional-hazards models were used to compare the risk of death among patients with HPV-positive cancer and those with HPV-negative cancer.

Results:
The median follow-up period was 4.8 years. The 3-year rate of overall survival was similar in the group receiving accelerated-fractionation radiotherapy and the group receiving standard-fractionation radiotherapy (70.3% vs. 64.3%; P=0.18; hazard ratio for death with accelerated-fractionation radiotherapy, 0.90; 95% confidence interval
[CI], 0.72 to 1.13), as were the rates of high-grade acute and late toxic events. A total of 63.8% of patients with oropharyngeal cancer (206 of 323) had HPV-positive tumors; these patients had better 3-year rates of overall survival (82.4%, vs. 57.1% among patients with HPV-negative tumors; P<0.001 by the log-rank test) and, after adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment, had a 58% reduction in the risk of death (hazard ratio, 0.42; 95% CI, 0.27 to 0.66). The risk of death significantly increased with each additional pack-year of tobacco smoking. Using recursive-partitioning analysis, we classified our patients as having a low, intermediate, or high risk of death on the basis of four factors: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage.

**Conclusions:** Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer. (ClinicalTrials.gov number, NCT00047008.)


Pignon JP, le Maître A, Maillard E, Bourhis J;
MACH-NC Collaborative Group. Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France.

**Background:**
Our previous individual patient data (IPD) meta-analysis showed that chemotherapy improved survival in patients
curatively treated for non-metastatic head and neck squamous cell carcinoma (HNSCC), with a higher benefit with concomitant chemotherapy. However the heterogeneity of the results limited the conclusions and prompted us to confirm the results on a more complete database by adding the randomised trials conducted between 1994 and 2000.

**Methods:**
The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment+chemotherapy in HNSCC patients and conducted between 1965 and 2000. The log-rank-test, stratified by trial, was used to compare treatments. The hazard ratios of death were calculated.

**Results:**
Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 (p<0.0001) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction (p<0.0001) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 (p<0.0001) and the absolute benefit 6.5% at 5 years. There was a decreasing effect of chemotherapy with age (p=0.003, test for trend).
Conclusion:
The benefit of concomitant chemotherapy was confirmed and was greater than the benefit of induction chemotherapy.


Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Radiation Oncology Department, Institut Gustave Roussy, Villejuif, France.

Background:
Several trials have studied the role of unconventional fractionated radiotherapy in head and neck squamous cell carcinoma, but the effect of such treatment on survival is not clear. The aim of this meta-analysis was to assess whether this type of radiotherapy could improve survival.

Methods:
Randomised trials comparing conventional radiotherapy with hyperfractionated or accelerated radiotherapy, or both, in patients with non-metastatic HNSCC were identified and updated individual patient data were obtained. Overall survival was the main endpoint. Trials were grouped in three pre-specified categories:
Results:
15 trials with 6515 patients were included. The median follow-up was 6 years. Tumours sites were mostly oropharynx and larynx; 5221 (74%) patients had stage III-IV disease (International Union Against Cancer, 1987). There was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years (hazard ratio 0.92, 95% CI 0.86-0.97; p=0.003). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1.7% with total dose reduction at 5 years, p=0.02). There was a benefit on locoregional control in favour of altered fractionation versus conventional radiotherapy (6.4% at 5 years; p<0.0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced. The benefit was significantly higher in the youngest patients (hazard ratio 0.78 [0.65-0.94] for under 50 year olds, 0.95 [0.83-1.09] for 51-60 year olds, 0.92 [0.81-1.06] for 61-70 year olds, and 1.08 [0.89-1.30] for over 70 year olds; test for trends p=0.007).

Conclusion:
Altered fractionated radiotherapy improves survival in patients with head and neck squamous cell carcinoma. Comparison of the different types of altered radiotherapy suggests that hyperfractionation has the greatest benefit.
5. Split therapy: planned neck dissection followed by definitive radiotherapy for a T1, T2 pharyngolaryngeal primary cancer with operable N2, N3 nodal metastases—a prospective study.

_D’cruz AK, Pantvaidya GH, Agarwal JP, Chaukar DA, Pathak KA, Deshpande MS, Pai PS, Chaturvedi P, Dinshaw KA._

J Surg Oncol. 2006 Jan 1;93(1):56-61

**Background:**

The management of patients with a small pharyngolaryngeal cancer (T1 and T2) with large nodal metastases is a subject of debate. We present data on the feasibility and outcome of treating these patients with surgery for the nodal metastases followed by definitive radiotherapy.

**Methods:**

Prospective study of 59 patients of small pharyngolaryngeal primary squamous carcinomas with operable (N2/N3) nodal metastasis treated with neck dissection followed by radiotherapy.

**Results:**

Complete nodal clearance was achieved in 54 (90%). The mean nodal size was 4 cm and extranodal extension was seen in 88% of patients in the study group. There were no significant postoperative complications. Median interval between surgery and radiotherapy was 23 days. Forty-nine patients (83%) started their RT within 6 weeks of surgery. With a median follow-up of 25 months, the disease free and overall survival was 54% and 60% (5 years).
Conclusion:
The management of patients with a radiocurabe pharyngolaryngeal primary with large nodes by this approach is a feasible option with adequate control and survival.
Larynx and Hypopharynx

Management of larynx & hypopharynx has seen more changes than in any other site amongst Head & Neck tumours. Since 1991, when the first randomised controlled trial was published comparing organ preservation versus the gold standard of total laryngectomy in advanced laryngopharyngeal cancers, the standards of care have been constantly evolved in the past two decades. Along the way conservative laryngeal surgery took a new dimension with acceptance of transoral laryngeal microsurgery as a now established treatment option in early laryngopharyngeal cancers. For intermediate advanced diseases supracricoid laryngectomy has shown promising results. In the past 5 years taxane based chemotherapy and biological modifiers such as cetuximab and nimotuzumab have improved on response rates bringing more moderately advanced laryngopharyngeal cancers into realm of organ preservation. New technology and altered fractionation regimes have increased radiation dosage and reduced toxicities and morbidity to the patients. These are indeed exciting times with so much to
offer to the patient. It is also sobering for us to realise the need to be more meticulous in our evaluation and documentation to offer the treatment which will attempt to give the best cure rates and at the same time try to preserve function and ultimately the larynx [organ] from the clutches of cancer.

<table>
<thead>
<tr>
<th>Larynx</th>
<th>Hypopharynx</th>
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<tbody>
<tr>
<td>Supra-glottis: Epiglottis, Ary-epiglottic folds, Arytenoids, False cord, Ventricles</td>
<td>Pyriform sinus</td>
</tr>
<tr>
<td>Glottis: True vocal cord with anterior &amp; posterior commissures</td>
<td>Posterior pharyngeal wall</td>
</tr>
</tbody>
</table>

**Subglottis**

**TNM 2010**

- **Tx** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ

**SUPRAGLOTTIS**

- **T1** Tumor limited to one subsite of supraglottis with normal vocal cord mobility
- **T2** Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
- **T3** Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage.
T4a  Moderately advanced local disease
    Tumor invades through the thyroid cartilage and / or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b  Very advanced local disease.
    Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

GLOTTIS
T1  Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords

T2  Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

T3  Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage

T4a  Moderately advanced local disease
    Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b  Very advanced local disease.
    Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
SUBGLOTTIS

T1  Tumor limited to the subglottis
T2  Tumor extends to vocal cord(s) with normal or impaired mobility
T3  Tumor limited to larynx with vocal cord fixation
T4a Moderately advanced local disease
    Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease.
    Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

HYPOPHARYNX

T1  Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2  Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
T3  Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a Moderately advanced local disease.
    Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue [includes prelaryngeal strap muscles and subcutaneous fat]
T4b Very advanced local disease.
    Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
REGIONAL LYMPH NODES (N)
Nx  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3  Metastasis in a lymph node, more than 6 cm in greatest dimension

*Note: Metastases at level VI are considered regional lymph node metastases

DISTANT METASTASIS (M)
M0  No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1  Distant metastasis

Management Guidelines:

Documentation of Disease:

- Indirect laryngoscopy / Hopkins telescope
  - Extent of mucosal disease
  - Vocal Cord Status
  - Arytenoid mobility
**Documentation of Patient Morphology:**
For Feasibility of direct and microlaryngoscopy and laser surgery

- Cervical spine disorders
- Mouth opening
- Position of teeth – buck teeth, loose teeth

**Documentation of Functional status of larynx:**
For feasibility of larynx conservation procedures

- Aspiration
- Stridor
- Dysphagia

**Specific Investigations before definitive treatment:**

- **Ba swallow:** To document passage in stricturous lesions and diagnose second primary cancers in the oesophagus.

- **Direct laryngoscopy:** Map the lesion and take biopsy

- **Microlaryngoscopy:** For lesions involving the glottis

- **CT Scan:** Disease extent, Pre and Paraglottic Spread, Exolaryngeal spread, thyroid cartilage involvement. CT preferred for cartilage involvement

- **MRI Scan:** When dealing with T3 and above to document thyroid inner perichondrial involvement. MR preferred for soft tissue extent.
Decision Making for Curative Intent

Supraglottis

*Stage I & II \([T_{1-2}N_0]\)*
- External Beam Radiotherapy
- Transoral Laser Microsurgery with evaluation of neck for occult metastasis

*Stage III \([T_{1-2}N_1]\)*
- Non Surgical Option
  - Normal creatinine clearance
    - Concurrent Chemotherapy and Radiotherapy
  - Compromised creatinine clearance
    - Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
    - Accelerated RT
- Surgical Option
  - Transoral Laser Microsurgery with ipsilateral neck dissection with adjuvant therapy*
  - Supraglottic laryngectomy with bilateral neck dissection with adjuvant therapy*

*Stage III \([T_3N_{0-1}]\)*
- Laryngeal function intact and normal creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
- Laryngeal function intact and compromised creatinine clearance

* Adjuvant Therapy as per guidelines mentioned in general guidelines.
Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT

Accelerated RT

Supraglottic Laryngectomy with bilateral neck dissection with adjuvant therapy*

Laryngeal Function Compromised

Near-Total / Total Laryngectomy with bilateral neck dissection with adjuvant therapy*

Stage IV \([T_{1-2} \, N_{2a-3}]\)

Non Surgical Option

Normal creatinine clearance

Concurrent Chemotherapy and Radiotherapy

Compromised creatinine clearance

Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT

Accelerated RT

Surgical Option

Transoral Laser Microsurgery with bilateral neck dissection with adjuvant therapy*

Supraglottic laryngectomy with bilateral neck dissection with adjuvant therapy*

Split Therapy – Neck Dissection with adjuvant therapy*

Stage IV \([T_{3} \, N_{2a-3}]\)

Laryngeal function intact and normal creatinine clearance

Concurrent Chemotherapy and Radiotherapy
• Laryngeal function intact and compromised creatinine clearance
  o Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
  o Accelerated RT
  o Supraglottic Laryngectomy with bilateral neck dissection with adjuvant therapy*

• Laryngeal Function compromised
  o Near-Total Laryngectomy / Total Laryngectomy with bilateral neck dissection with adjuvant therapy*

**Stage IV \([T_4 \text{ any } N]\)**

• Intact Laryngeal function and framework [exolaryngeal without cartilage destruction]
  o Normal creatinine clearance
    □ Concurrent Chemotherapy and Radiotherapy
    □ Near – Total laryngectomy/Total laryngectomy with bilateral neck dissection with adjuvant therapy*
  o Compromised creatinine clearance
    □ Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
    □ Accelerated RT
    □ Near-Total Laryngectomy / Total Laryngectomy with bilateral neck dissection with adjuvant therapy*
Laryngeal function and framework compromised [cartilage destruction]
  o Near-Total Laryngectomy / Total Laryngectomy with bilateral neck dissection with adjuvant therapy*

**Technical Factors**

**Neck Dissection:**
N0 - Selective Neck Dissection (SND) is performed, bilateral [Level II- IV]
N+ -Ipsilateral SND [II-V] and contralateral SND [II-IV]

**Concurrent Chemotherapy:**
Cisplatinum 100mg/m$^2$ Three weekly- Day 1, 22, 43
Cisplatinum 30mg/m$^2$ weekly for 6 cycles

**Radiotherapy:**
Radical: 66 – 70 Gy / 33-35 # / 6 – 7 weeks [5 days per week of radiation]
Accelerated: 66 – 70 Gy / 33-35 # / 5-6 weeks [5 days per week of radiation]

**Biological Modifier**
Cetuximab or Nimotuzumab

**Nutrition:**
Special Attention to weight and nutrition with Nasogastric or Percutaneous Gastrostomy tube feeding to be maintained
Post Organ Preservation Treatment Evaluation

- Direct Laryngoscopy and CT scan 6 weeks after treatment PETCT scan if ordered to be done only after 12 weeks
- Thyroid Function tests after 6 months or symptomatic whichever is earlier
- Swallowing Therapy To initiate in pre treatment setting and continue during and after radiation

Surgical Salvage

Primary Tumour

- Pectoralis major myofascial flap to cover the pharyngeal musculature after closure.

Residual Neck Node

- Appropriate Neck Dissection Levels II – V with involved structures

Decision Making for Curative Intent

Glottis

Stage I & II \( [T_1-2 \; N_0] \)

- Small field External Beam Radiotherapy either 3week or 6week
- Transoral Laser Microsurgery

Stage III \( [T_{1-2} \; N_1] \)

- Non Surgical Option
  - Laryngeal function intact and normal creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
Laryngeal function intact and compromised creatinine clearance
- Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
- Accelerated RT

Transoral laser Microsurgery with ipsilateral lateral neck dissection with adjuvant therapy*

Stage III \([T_3 N_{0-1}]\)
- Laryngeal function intact and normal creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
- Laryngeal function intact and compromised creatinine clearance
  - Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
  - Accelerated RT
  - Supracricoid Laryngectomy with ipsilateral Lateral neck dissection with adjuvant therapy*
- Laryngeal Function Compromised
  - Near-Total / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy*

Stage IV \([T_{1-2} N_{2a-3}]\)
- Non Surgical Option
  - Normal creatinine clearance
    - Concurrent Chemotherapy and Radiotherapy
  - Compromised creatinine clearance
- Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
- Accelerated RT

- Surgical Option
- Transoral Laser Microsurgery with bilateral neck dissection with adjuvant therapy*
- Vertical Partial laryngectomy with bilateral dissection with adjuvant therapy *
- Split Therapy – Neck Dissection with adjuvant therapy*

**Stage IV \([T_3 \, N_{2a-3}]\)**
- Laryngeal function intact and normal creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
- Laryngeal function intact and compromised creatinine clearance
  - Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
  - Accelerated RT
  - Supracricoid Laryngectomy with bilateral Lateral neck dissection with adjuvant therapy*
- Laryngeal Function compromised
  - Near-Total Laryngectomy / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy *

**Stage IV \([T_4 \, any \, N]\)**
- Intact Laryngeal function and framework [exolaryngeal without cartilage destruction]
Normal creatinine clearance
- Concurrent Chemotherapy and Radiotherapy
- Near – Total laryngectomy/Total laryngectomy with bilateral neck dissection with adjuvant therapy*

Compromised creatinine clearance
- Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
- Accelerated RT
- Near-Total Laryngectomy / Total Laryngectomy with bilateral neck dissection with adjuvant therapy*

- Laryngeal function and framework compromised [cartilage destruction]
- Near-Total Laryngectomy / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy*

Technical Factors:

Surgical Options
Transoral Laser Microsurgery: CO2 Laser, microspot with superpulse in continuous mode 2 to 3 watts

Open Partial Laryngectomy: Vertical Partial [Hemilaryngectomy, Extended Hemilaryngectomy]
Supracricoid Laryngectomy with epiglottotomyidopexy of cricothyroidopexy

Radical Surgery: Near-Total Laryngecomy, Total Laryngectomy

Neck Dissection: Selective Neck Dissection (SND) is performed, bilateral [Level II- IV]

- $N_0$
  - Ipsilateral SND [II-V] and contralateral SND [II-IV]

- $N^+$
  - In lesions with subglottic extension – Ipsilateral SND[II-V, VI]

**Concurrent Chemotherapy:**
- Cisplatinum 100mg/m$^2$
  - Three weekly- Day 1, 22, 43
  - OR
  - Cisplatinum 30mg/m$^2$
  - weekly for 6 cycles

**Radical Radiotherapy:**
- Small Field Radiation 62.5 Gy/ 25fr/6 weeks
  - OR
  - 55Gy/16fr/3 weeks
  - only the vocal cords with margins
- Large Field Radiation 66 – 70 Gy / 33-35 # / 6 – 7 weeks

Primary with neck
**Biological Modifier**
Cetuximab or Nimotuzumab

**Nutrition:**
Special Attention to weight and nutrition with Nasogastric or Percutaneous Gastrostomy tube feeding to be maintained

**Post Organ Preservation Treatment Evaluation**
Direct Laryngoscopy and CT scan 6 weeks after treatment
PETCT scan if ordered to be done only after 12 weeks
Thyroid Function tests after 6 months or symptomatic whichever is earlier
Swallowing Therapy To initiate in pre treatment setting and continue during and after radiation

**Surgical Salvage following chemoradiation**

**Primary Tumour**
- Pectoralis major myofascial flap to cover the pharyngeal musculature after closure.

**Neck Node residual**
- Appropriate Neck Dissection Levels II – V with involved structures

**Speech Therapy:**
Pre treatment voice evaluation is of prime importance for comparing with post treatment voice as well as for voice training and therapy.
Decision Making for Curative Intent

Subglottis

Stage I – II
- External beam radiation

Stage III
- Laryngeal function intact and normal creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
- Laryngeal function intact and compromised creatinine clearance
  - Accelerated Radiation therapy
  - Total Laryngectomy with bilateral neck dissection including central compartment on ipsilateral side with adjuvant Radiation therapy
- Laryngeal Function Compromised
  - Total Laryngectomy with bilateral central and lateral neck dissection with adjuvant therapy*

Stage IV
- Total laryngectomy with bilateral central compartment and lateral compartment neck dissection with adjuvant therapy *

*Adjuvant therapy as per guidelines mentioned in general principles.
Decision Making for Curative Intent

Pyriform Fossa

Stage I & II [$T_{1-2} N_0$]
- External Beam Radiotherapy
- Transoral Laser Microsurgery

Stage III [$T_{1-2} N_1$]
- Non Surgical Option
  - Laryngeal function intact and normal creatinine clearance
    - Concurrent Chemotherapy and Radiotherapy
  - Laryngeal function intact and compromised creatinine clearance
    - Accelerated RT
- Transoral Laser Microsurgery with ipsilateral neck dissection with adjuvant RT

Stage III [$T_3 N_{0-1}$]
- Laryngeal function intact and normal creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
- Laryngeal function intact and compromised creatinine clearance
  - Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
  - Accelerated RT
  - Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant radiotherapy
• Laryngeal Function Compromised
  o Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant radiotherapy

**Stage IV \([T_{1-2} N_{2a-3}]\)**

• Non Surgical Option
  o Normal creatinine clearance
    □ Concurrent Chemotherapy and Radiotherapy
  o Compromised creatinine clearance
    □ Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
    □ Accelerated RT

• Surgical Option
  o Transoral Laser Microsurgery with bilateral neck dissection with adjuvant radiation therapy with or without concurrent chemotherapy depending on creatinine clearance

• Split Therapy – Neck Dissection with adjuvant radiation therapy with or without concurrent chemotherapy depending on creatinine clearance

**Stage IV \([T_3 N_{2a-3}]\)**

• Laryngeal Function Intact and normal creatinine clearance
  o Concurrent Chemotherapy and Radiotherapy

• Laryngeal Function Intact and compromised creatinine clearance
Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT

Accelerated radiotherapy

Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant radiotherapy

Laryngeal Function compromised

Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant radiotherapy with or without concurrent chemotherapy depending on creatinine clearance

Stage IV \(T_4\) any \(N\)

Intact Laryngeal function and framework [exolaryngeal without cartilage destruction]

Normal creatinine clearance

Concurrent Chemotherapy and Radiotherapy

Compromised creatinine clearance

Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT

Accelerated RT

Near-Total Laryngectomy / Total Laryngectomy partial pharyngectomy with bilateral neck dissection with adjuvant radiotherapy

Laryngeal function and framework compromised [cartilage destruction]
Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant radiotherapy with or without concurrent chemotherapy depending on creatinine clearance.

Technical Factors

**Surgical Options**

Transoral Laser Microsurgery:

CO2 Laser, microspot with superpulse in continuous mode 2 to 3 watts

**Radical Surgery:**

- Near-Total / Total Laryngectomy with partial / total pharyngectomy
- Partial Pharyngeal Reconstruction:
  - Patch Pectoralis Major Myocutaneous (PMMC) Flap,
  - Total Pharyngeal Reconstruction:
  - Tube PMMC flap, Free Jejunum or Free Radial artery Fasciocutaneous Flap

**Neck Dissection:**

N₀⁻ Selective Neck Dissection (SND) is performed, bilateral [Level II- IV]

N+-Ipsilateral SND [II-V] and contralateral SND [II-IV]

**Concurrent Chemotherapy:**

Cisplatinum 100mg/m² Three weekly- Day 1, 22, 43

OR Cisplatinum 30mg/m² weekly for 6 cycles
Radical Radiotherapy:
Large Field Radiation Primary with neck
66 – 70 Gy / 33-35 # / 6 – 7 weeks

Biological Modifier
Cetuximab or Nimotuzumab

Nutrition:
Special Attention to weight and nutrition with Nasogastric or Percutaneous Gastrostomy tube feeding to be maintained

Post Organ Preservation Treatment Evaluation
- Direct Laryngoscopy and CT scan 6 weeks after treatment PETCT scan if ordered to be done only after 12 weeks
- Thyroid Function tests after 6 months or symptomatic whichever is earlier
- Swallowing Therapy To initiate in pre treatment setting and continue during and after radiation

Surgical Salvage following chemoradiation
- Primary Tumour
  - Pectoralis major myofascial flap to cover the pharyngeal musculature after closure.
- Neck Node residual
  - Appropriate Neck Dissection Levels II – V with involved structures

Speech Therapy:
Pre treatment voice evaluation is of prime importance for comparing with post treatment voice as well as for voice training and therapy.
Decision Making for Curative Intent
Post Cricoid & Posterior Pharyngeal Wall

Stage I & II $[T_{1-2}N_0]$  
- External Beam Radiotherapy

Stage III $[T_{1-2}N_1]$  
- Non Surgical Option
  - Laryngeal function intact and normal creatinine clearance
    - Concurrent Chemotherapy and Radiotherapy
  - Laryngeal function intact and compromised creatinine clearance
    - Accelerated RT
- Transoral Laser Microsurgery with ipsilateral lateral neck dissection with adjuvant RT

Stage III $[T_{3}N_{0-1}]$  
- Laryngeal function intact and good creatinine clearance
  - Concurrent Chemotherapy and Radiotherapy
- Laryngeal function intact and poor creatinine clearance
  - Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
  - Accelerated RT
  - Disease not extending to oesophagus
    - Total laryngopharyngectomy with bilateral neck dissection with pharyngeal
reconstruction with Tube PMMC or Free radial forearm flap or Free Jejunal Flap and adjuvant radiation therapy.

○ Disease extending to oesophagus
  □ Total Laryngopharyngectomy with oesophagectomy with bilateral neck dissection with gastric pullup with adjuvant radiotherapy.

● Laryngeal Function Compromised
  ○ Disease not extending to oesophagus
    □ Total laryngopharyngectomy with bilateral neck dissection with pharyngeal reconstruction with Tube PMMC or Free radial forearm flap or Free Jejunal Flap and adjuvant radiation therapy.
  
  ○ Disease extending to oesophagus
    □ Total Laryngopharyngectomy with oesophagectomy with bilateral neck dissection with gastric pullup with adjuvant radiotherapy.

Stage IV [T_{1-2} N_{2a-3}]

● Non Surgical Option
  ○ Normal creatinine clearance
    □ Concurrent Chemotherapy and Radiotherapy
  
  ○ Compromised creatinine clearance
    □ Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT
    □ Accelerated RT
• Split Therapy – Neck Dissection with adjuvant radiation therapy with or without concurrent chemotherapy depending on creatinine clearance

**Stage IV \([T_3 N_{2a-3}]\)**

• Intact Laryngeal Function and creatinine clearance
  
  o Concurrent Chemotherapy and Radiotherapy

• Intact Laryngeal Function and compromised creatinine clearance
  
  o Concurrent Targetted Therapy [ Cetuximab or Nimotuzumab] with RT
  
  o Accelerated radiotherapy
  
  o Disease not extending to oesophagus
    
    □ Total laryngopharyngectomy with bilateral neck dissection with pharyngeal reconstruction with Tube PMMC or Free radial forearm flap or Free Jejunal Flap and adjuvant radiation therapy.

  o Disease extending to oesophagus
    
    □ Total Laryngopharyngectomy with oesophagectomy with bilateral neck dissection with gastric pullup with adjuvant radiotherapy.

• Laryngeal Function compromised

  o Disease not extending to oesophagus
    
    □ Total laryngopharyngectomy with bilateral neck dissection with pharyngeal reconstruction with Tube Pectoralis Major Myocutaneous or Free radial forearm flap or Free Jejunal Flap and adjuvant radiation therapy.
o Disease extending to oesophagus
  q Total Laryngopharyngectomy with oesophagectomy with bilateral neck dissection with gastric pullup with adjuvant radiotherapy.

Stage IV \([T_4 \text{ any } N]\)

- Disease not extending to oesophagus
  o Near-Total / Total Laryngectomy with partial pharyngectomy with bilateral lateral neck dissection with adjuvant RT
  o Total laryngopharyngectomy with bilateral neck dissection with pharyngeal reconstruction with Tube Pectoralis Major Myocutaneous or Free radial forearm flap or Free Jejunal Flap and adjuvant radiation therapy.

- Disease extending to oesophagus
  o Total Laryngopharyngectomy with oesophagectomy with gastric pullup with adjuvant radiotherapy.

Technical Factors

Surgical Options

Transoral Laser Microsurgery:
CO2 Laser, microspot with superpulse in continuous mode 2 to 3 watts

Radical Surgery:

Near-Total / Total Laryngectomy with partial / total pharyngectomy
Partial Pharyngeal Reconstruction:
Patch Pectoralis Major Myocutaneous (PMMC) Flap,
Total Pharyngeal Reconstruction:
Tube PMMC flap, Free Jejunum or Free Radial artery Fasciocutaneous Flap

**Neck Dissection:**
N\textsubscript{0} - Selective Neck Dissection (SND) is performed, bilateral [Level II- IV]
N+-Ipsilateral SND [II-V] and contralateral SND [II-IV]
In lesions involving pyriform apex and Postcricoid Level VI on ipsilateral side

**Concurrent Chemotherapy:**
Cisplatinum 100mg/m\textsuperscript{2} Three weekly- Day 1, 22, 43
OR Cisplatinum 30mg/m\textsuperscript{2} weekly for 6 cycles

**Radical Radiotherapy:**
Large Field Radiation Primary with neck
66 – 70 Gy / 33-35 # / 6 – 7 weeks

**Biological Modifier**
Cetuximab or Nimotuzumab

**Nutrition:**
Special Attention to weight and nutrition with Nasogastric or Percutaneous Gastrostomy tube feeding to be maintained

**Post Organ Preservation Treatment Evaluation**
- Direct Laryngoscopy and CT scan 6 weeks after treatment PETCT scan if ordered to be done only after 12 weeks
- Thyroid Function tests after 6 months or symptomatic whichever is earlier
- Swallowing Therapy To initiate in pre treatment setting and continue during and after radiation

**Surgical Salvage following chemoradiation**
- Primary Tumour
  - Pectoralis major myofascial flap to cover the pharyngeal musculature after closure.
- Neck Node residual
  - Appropriate Neck Dissection Levels II – V with involved structures

**Speech Therapy:**
Pre treatment voice evaluation is of prime importance for comparing with post treatment voice as well as for voice training and therapy.

**Suggested Reading:**

**Early Glottic Carcinoma:**
Cure rates are similar in early glottic cancers with radiation therapy and surgical modalities like transoral laser surgery and open partial laryngectomy. There is no conclusive evidence to support any particular modality and at this instance the treatment is still based on patient and physician preference. The possibility of running a trial to demonstrate the superiority of a particular modality is difficult.
Radiation therapy v/s Transoral endoscopic surgery v/s Open partial laryngectomy


Background: Radiotherapy, open surgery and endolaryngeal excision (with or without laser) are all accepted modalities of treatment for early stage glottic cancer. Case series suggest that they confer similar survival advantage. Opinions on optimal therapy vary across disciplines and between countries.

Objectives: To compare the effectiveness of open surgery, endolaryngeal excision (with or without laser) and radiotherapy in the management of early glottic laryngeal cancer

SEARCH STRATEGY: Electronic search of MEDLINE (from 1966 to October 2000), EMBASE (from 1980 to October 2000), CINAHL (from 1982 to October 2000) and CancerLit (from 1963 to October 2000) databases and the Cochrane Controlled Trials Register. SELECTION CRITERIA: Randomised controlled trials (RCT) comparing open surgery, endolaryngeal resection and/or radiotherapy

DATA COLLECTION AND ANALYSIS: Two reviewers independently assessed RCTs identified from the electronic searches for eligibility and methodological quality. All authors of the review discussed the results of these assessments.

Main Results: Only one RCT was identified which compared open surgery and radiotherapy among a substantial number of patients with early glottic laryngeal cancer.
Reviewer's Conclusions: There is currently insufficient evidence to guide management decisions on the most effective treatment. Interpretation of the only large scale RCT comparing open surgery and radiotherapy in patients with early glottic cancer is limited because of concerns about the adequacy of treatment regimens and deficiencies in the reporting of the study design and analysis. Endolaryngeal resection of early glottic tumours is becoming more common and a well designed multicentre RCT is warranted.

Treatment option should be customised to suit the patient depending on vocation, distance from treatment centre and availability of expertise.

LASER

Background: Transoral CO(2) laser surgery has been accepted as a valuable therapeutic option for glottic cancer.

Methods: This was a retrospective analysis of 595 patients. Five-year overall and disease-specific survivals, local control with laser, locoregional, regional control, and organ preservation rates were calculated. The impact of different variables was calculated by univariate analysis.

Results: Overall, disease-specific and disease-free survivals, local control with laser, locoregional, regional
control, and organ preservation rates were 87.5%, 99%, 81.3%, 92.7%, 98.9%, 98.2%, and 97.1%, respectively. Univariate analysis showed a significant impact of pT category on local control with laser, organ preservation, locoregional and regional control, of endoscopic re-treatment for positive deep surgical margins on local control with laser and organ preservation, and recurrence after endoscopic re-treatment on local control with laser and organ preservation.

**Conclusion:** This series confirms the good oncologic outcomes of endoscopic laser surgery for T(is), T(1), and selected T(2) and T(3) glottic tumors.

**Comparison with Radiotherapy**


**Aims:** The aim of this study was to compare laser surgery, conventional endoscopic surgery and radiotherapy in the treatment of early T1a glottic cancer.

**Methods:** We conducted a retrospective analysis of patients with early vocal cord cancer (who underwent either conventional surgery via endoscopy or laryngofissur, or primary radiotherapy) at the Medical University of Vienna. By univariate and multivariate Cox regression models the influence of treatment and other parameters on survival and locoregional control were analysed.
Results: 337 Patients were analyzed with a mean follow-up period of 133.8 months. Overall survival rates were similar in all three treatment groups. Five-year, 10-year and 15-year estimates of disease specific survival for laser-treated patients were 100%, for conventional surgery were 100%, 98% and 98%, and for radiotherapy were 96%, 92% and 91%, respectively. Locoregional recurrences were observed after laser surgery in 10%, after conventional surgery in 13% and after radiotherapy in 30% of the patients treated. According to the log-rank test, time to relapse was significantly shorter for irradiated patients compared to patients who underwent surgery (p < 0.0001). Mortality caused by the laryngeal tumour was significantly higher in the radiotherapy group (p = 0.003).

Conclusion: Patients undergoing laser or conventional surgery have a significantly lower incidence of locoregional recurrences and longer disease-free intervals when compared to patients treated by radiotherapy.

Anterior Commissure


Background: Early glottic cancer can be cured with transoral laser resection, but in cases with anterior commissure involvement, there is still controversy concerning the best treatment modality.
**Methods:** The impact of anterior commissure involvement on local control was analyzed in a retrospective review of 444 patients with early glottic cancer (pT1a-pT2a) treated between 1986 and 2004 with transoral laser microsurgical resection.

**Results:** The anterior commissure was involved in 153 cases; the 5-year local control rate with and without anterior commissure involvement was 73% versus 89% for T1a and 68% versus 86% for T1b tumors. For T2a lesions, the 5-year local control rate was 76%, irrespective of anterior commissure involvement.

**Conclusion:** In early glottic cancer treated by transoral laser microsurgery, a decrease in local control is evident in case of anterior commissure involvement for T1a and T1b but not for T2a tumors.

**Supraglottis & Hypopharynx**

Supraglottic and hypopharyngeal cancers tend to spread to the lymph nodes early on in their growth due to the rich lymphatics and vascularity in this region. More often the treatment decisions are guided by the neck node management in these sites.


The goal of treatment for supraglottic cancer is to achieve cure and to preserve laryngeal function. Organ preservation strategies include both endoscopic and open surgical approaches as well as radiation and chemotherapy. The challenge is to select the correct
modalities for each patient. Endoscopic procedures should be limited to tumors that can be completely visualized during diagnostic microlaryngoscopy. If complete resection can be achieved, the oncologic results of transoral laser surgery appear to be comparable to those of classic supraglottic laryngectomy. In addition, functional results of transoral laser resection are superior to those of the conventional open approach, in terms of the time required to restore swallowing, tracheotomy rate, incidence of pharyngocutaneous fistulae, and shorter hospital stay. The management of the neck remains of paramount importance, as survival of patients with supraglottic cancer depends more on cervical metastasis than on the primary tumor. Most authors advocate bilateral elective neck dissection. However, in selected cases (T1,T2 clinically negative [N0] lateral supraglottic cancers), ipsilateral selective neck dissection could be performed without compromising survival. The authors conclude that with careful selection of patients, laser supraglottic laryngectomy is a suitable, and often the preferred, treatment option for supraglottic cancer.

Hypopharynx:

Objective: To assess the feasibility of transoral laser microsurgery (TLM) in the treatment of hypopharyngeal
cancer, with a special focus on piriform sinus carcinomas, and to report the oncologic and functional outcomes.

**Study Design:** Prospective case-series study at a single institute, an academic tertiary referral center. Methods: A total of 172 patients with previously untreated squamous cell carcinoma of the hypopharynx were eligible for this study (1986-2003). The piriform sinus was the most common localization (n = 150). Patients with simultaneous second primaries, distant metastases, or N3 neck disease and cancers of the category pT4b were excluded. Fifteen percent of the patients had stages I and II (according to guidelines from the Union Internationale Contre le Cancer 2002/American Joint Commission on Cancer, 2002), and 85% had stages III and IVa. The median follow-up period was 45 months. All patients (n = 172) were treated by TLM, mainly by selective neck dissection (93%) and/or postoperative radiotherapy (52%). Overall survival, recurrence-free survival, organ preservation, and local control were analyzed as end points. Rate of tracheotomies, postoperative complications, and swallowing function (feeding tube dependency) were also analyzed.

**Results:** Five-year Kaplan-Meier local control was 84% for pT1; 70% for pT2; 75% for pT3; and 57% for pT4a. Five-year Kaplan-Meier recurrence-free survival was 73% for stages I and II, 59% for stage III, and 47% for stage IVa. The whole group of 172 hypopharyngeal cancer patients was analyzed, with an additional special focus on the homogenous group of piriform sinus carcinomas (n = 150).
Conclusions: Our data support the conclusion that TLM is a valid option to standard radical surgery or standard conservation treatment. Oncologic and functional results compare favorably, while morbidity and complication rates tend to be lower.

Organ preservation protocol:
Organ preservation in laryngeal / hypopharyngeal cancers seemed a reality with the landmark VA trial, However the meta analysis of the various organ preservation trials does not seem to warrant concurrent chemoradiation as a standard treatment as of now. Outside clinical trials surgery followed by radiation therapy remains the standard of care in advanced operable laryngeal and hypopharyngeal cancers and concurrent chemoradiation is to be followed only in a controlled trial setting.

Landmark trial: Induction CT v/s Total Laryngectomy

Background: We performed a prospective, randomized study in patients with previously untreated advanced (Stage III or IV) laryngeal squamous carcinoma to compare the results of induction chemotherapy followed by definitive radiation therapy with those of conventional laryngectomy and postoperative radiation.
Methods: Three hundred thirty-two patients were randomly assigned to receive either three cycles of chemotherapy (cisplatin and fluorouracil) and radiation therapy or surgery and radiation therapy. The clinical tumor response was assessed after two cycles of chemotherapy, and patients with a response received a third cycle followed by definitive radiation therapy (6600 to 7600 cGy). Patients in whom there was no tumor response or who had locally recurrent cancers after chemotherapy and radiation therapy underwent salvage laryngectomy.

Results: After two cycles of chemotherapy, the clinical tumor response was complete in 31 percent of the patients and partial in 54 percent. After a median follow-up of 33 months, the estimated 2-year survival was 68 percent (95 percent confidence interval, 60 to 76 percent) for both treatment groups (P = 0.9846). Patterns of recurrence differed significantly between the two groups, with more local recurrences (P = 0.0005) and fewer distant metastases (P = 0.016) in the chemotherapy group than in the surgery group. A total of 59 patients in the chemotherapy group (36 percent) required total laryngectomy. The larynx was preserved in 64 percent of the patients overall and 64 percent of the patients who were alive and free of disease.

Conclusions: These preliminary results suggest a new role for chemotherapy in patients with advanced laryngeal cancer and indicate that a treatment strategy involving induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high
percentage of patients, without compromising overall survival.

**Landmark Trial: Hypopharynx Induction CT versus TL**


**Background:** As a general rule, surgery whenever possible, followed by irradiation is considered to be the standard treatment for cancer of the hypopharynx, thus sacrificing natural speech. In most patients, surgery includes removal of the larynx.

**Purpose:** A prospective, randomized phase III study was conducted by the European Organization for Research and Treatment of Cancer (EORTC) starting in 1990 to compare a larynx-preserving treatment (induction chemotherapy plus definitive, radiation therapy in patients who showed a complete response or surgery in those who did not respond) with conventional treatment (total laryngectomy with partial pharyngectomy, radical neck dissection, and postoperative irradiation) in previously untreated and operable patients with histologically proven squamous cell carcinomas of the pyriform sinus or aryepiglottic fold, but free of other cancers.

**Methods:** Patients were randomly assigned to one of two treatment arms: 1) immediate surgery with postoperative radiotherapy (50-70 Gy) or 2) induction chemotherapy (cisplatin [100 mg/m²] given as a bolus intravenous injection on day 1, followed by infusion of fluorouracil
[1000 mg/m2 per day] on days 1-5). An endoscopic evaluation was performed after each cycle of chemotherapy. After two cycles, only partial and complete responders received a third cycle. Patients with a complete response after two or three cycles of chemotherapy were treated thereafter by irradiation (70 Gy); nonresponding patients underwent conventional surgery with postoperative radiation (50-70 Gy). Salvage surgery was also performed when patients relapsed after chemotherapy and irradiation. The trial was designed to test the equivalence of the two treatment arms; i.e., the induction chemotherapy treatment would be judged equivalent to immediate surgery if the relative risk of death for induction chemotherapy compared with immediate surgery was significantly less than 1.43 using a one-sided hypothesis test at the .05 level of significance.

**Results:** Two hundred two patients entered the trial and were randomly assigned; only 194 were eligible for treatment (94 in the immediate-surgery arm and 100 in the induction-chemotherapy arm). In the induction-chemotherapy arm, complete response was seen in 52 (54%) of 97 patients with local disease (primary tumor) and in 31 (51%) of 61 patients with regional disease (involvement of the neck). Treatment failures at local, regional, and second primary sites occurred at approximately the same frequencies in the immediate-surgery arm (12%, 19%, and 16%, respectively) and in the induction-chemotherapy arm (17%, 23%, and 13%, respectively). In contrast, there were fewer failures at distant sites in the induction-chemotherapy arm than in the immediate-surgery arm (25% versus 36%, respectively;
P = .041). The median duration of survival was 25 months in the immediate-surgery arm and 44 months in the induction-chemotherapy arm and, since the observed hazard ratio was 0.86 (logrank test, P = .006), which was significantly less than 1.43, the two treatments were judged to be equivalent. The 3- and 5-year estimates of retaining a functional larynx in patients treated in the induction-chemotherapy arm were 42% (95% confidence interval = 31%-53%) and 35% (95% confidence interval = 22%-48%), respectively.

Conclusions and Implications: Larynx preservation without jeopardizing survival appears feasible in patients with cancer of the hypopharynx. On the basis of these observations, the EORTC has now accepted the use of induction chemotherapy followed by radiation as the new standard treatment in its future phase III larynx preservation trials.

Landmark: RTOG 91-11 Induction CT v/s Concurrent CTRT v/s RT


Background: Induction chemotherapy with cisplatin plus fluorouracil followed by radiotherapy is the standard alternative to total laryngectomy for patients with locally advanced laryngeal cancer. The value of adding chemotherapy to radiotherapy and the optimal timing of chemotherapy are unknown.
Methods: We randomly assigned patients with locally advanced cancer of the larynx to one of three treatments: induction cisplatin plus fluorouracil followed by radiotherapy, radiotherapy with concurrent administration of cisplatin, or radiotherapy alone. The primary end point was preservation of the larynx.

Results: A total of 547 patients were randomly assigned to one of the three study groups. The median follow-up period was 3.8 years. At two years, the proportion of patients who had an intact larynx after radiotherapy with concurrent cisplatin (88 percent) differed significantly from the proportions in the groups given induction chemotherapy followed by radiotherapy (75 percent, P=0.005) or radiotherapy alone (70 percent, P<0.001). The rate of locoregional control was also significantly better with radiotherapy and concurrent cisplatin (78 percent, vs. 61 percent with induction cisplatin plus Fluorouracil followed by radiotherapy and 56 percent with radiotherapy alone). Both of the chemotherapy-based regimens suppressed distant metastases and resulted in better disease-free survival than radiotherapy alone. However, overall survival rates were similar in all three groups. The rate of high-grade toxic effects was greater with the chemotherapy-based regimens (81 percent with induction cisplatin plus fluorouracil followed by radiotherapy and 82 percent with radiotherapy with concurrent cisplatin, vs. 61 percent with radiotherapy alone). The mucosal toxicity of concurrent radiotherapy and cisplatin was nearly twice as frequent as the mucosal toxicity of the other two treatments during radiotherapy.
**Conclusions:** In patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control.

**RTOG 91-11 Long term results**


**Background:** The 2-year results of Intergroup RTOG 91-11 were published in 2003 (NEJM 349:2091-8,2003). We now present the 5-year results (after median follow-up for surviving patients of 6.9 years) of 515 eligible pts with resectable stage III or IV (excluding T1 and high volume T4), cancer of the glottic or supraglottic larynx.

**Methods:** Patients were randomized to induction cisplatin/5-FU (CF) with responders then receiving RT (I+RT) (n = 173); or concurrent cisplatin (100 mg/m2 q 21 days × 3) and RT (CRT) (n = 171); or RT alone (R) (n = 171). Laryngectomy was performed for < partial response to induction CF, for persistent/recurrent disease or for laryngeal dysfunction.

**Results:** At 5 years, laryngectomy-free survival (LFS) was significantly better with either I+RT (44.6%, p = 0.011) or CRT (46.6%, p = 0.011) compared to R (33.9%). There was no difference in LFS between I+RT and CRT (p = 0.98). Laryngeal preservation (LP) was significantly better with...
CRT (83.6%) compared to I+RT (70.5%, p = 0.0029) or R (65.7%, p = 0.00017). Local-regional control (LRC) was significantly better with CRT (68.8%) compared to I+RT (54.9%, p = 0.0018) or R (51%, p = 0.0005). I+RT compared to R for LP and LRC showed no significant difference (p = 0.37 and 0.62, respectively). The distant metastatic rate was low (I+RT 14.3%, CRT 13.2%, R 22.3%) with a trend (p ~0.06) for benefit from chemotherapy. Disease-free survival (DFS) was significantly better with either I+RT (38.6%, p = 0.016) or CRT (39%, p = 0.0058) compared to R (27.3%). Overall survival rates were similar for the first 5 years (I+RT 59.2%, CRT 54.6%, R 53.5%); thereafter I+RT had a non-significant lower death rate. Compared to CRT, significantly more pts in the R group died of their cancer (34% vs 58.3%, p = 0.0007); the rate for I+RT was 43.8%.

Conclusion: These 5-year results differ from the 2-year analysis by a significant improvement in LFS now seen for both I+RT and CRT treatments compared to R. For the endpoints of LP and LRC, CRT is still the superior treatment with no advantage seen to the addition of induction CF to R. There is no significant difference in overall survival

RTOG 91-11– Surgical Salvage Data

Objective: To evaluate the incidence of morbidity, mortality, and disease control for patients requiring salvage total laryngectomy (TL) following organ preservation therapy. DESIGN: Patients entered into a 3-arm
randomized prospective multi-institutional trial for laryngeal preservation who required TL following initial treatment. SETTING: The Radiation Therapy Oncology Group 91-11 trial for laryngeal preservation.

Patients: From 1992 to 2000, 517 evaluable patients were randomized to receive chemotherapy followed by radiation therapy (arm 1), concomitant chemotherapy and radiation therapy (arm 2), or radiation therapy alone (arm 3).

Results: Overall, TL was required in 129 patients. The incidence was 28%, 16%, and 31% in arms 1, 2, and 3, respectively (P =.002). Of these, 7 patients (5%) required TL for aspiration or necrosis. Following TL, the incidence of major and minor complications ranged from 52% to 59% and did not differ significantly among the 3 arms. Pharyngocutaneous fistula was lowest in arm 3 (15%) and highest in arm 2 (30%) (P>.05). There was 1 perioperative death. Local-regional control following salvage TL was 74% for arms 1 and 2 and 90% for arm 3. At 24 months, the overall survival was 69% (arm 1), 71% (arm 2), and 76% (arm 3) (P>.73).

Conclusions: Laryngectomy following organ preservation treatment is associated with acceptable morbidity. Perioperative mortality is low but up to one third of patients will develop a pharyngocutaneous fistula. Local-regional control is excellent for this group of patients. Survival following salvage TL was not influenced by the initial organ preservation treatment.

Landmark: Hypopharyngeal Cancers ICT v/s TL

Background: In 1986, the EORTC HNCCG initiated a randomized phase III trial to assess whether LP using ICT followed by radiation therapy (XRT) was as safe as the conventional treatment: total laryngectomy with partial pharyngectomy (TLP), radical neck dissection (RND) and postop XRT. Preliminary results were published in 1996; this updated analysis has been carried with a median follow-up of 10 years.

Methods: 202 patients (pts) candidates for TLP + RND + XRT were randomly assigned to receive in the surgery arm (arm 1) this treatment or in the ICT arm (arm 2) up to 3 cycles of CDDP (100mg/m² day 1) and 5FU (1000 mg/m² days 1-5) followed in case of complete response by XRT or by TPL + RND + XRT in the other cases. The endpoints were survival (OS and PFS) and LP defined as a functional larynx free of disease (larynx in place without tracheotomy, feeding tube or gastrostomy, and without evidence of local disease).

Results: this final analysis was carried out on 194 eligible pts (arm 1: 94, arm 2: 100). There were 92 males (98%) in arm 1 and 94 (94%) in arm 2. Stage II, III and IV respectively numbered 6, 51 and 37 in arm 1 and 7, 59 and 34 in arm 2. Postop courses and quality of surgical resections did not differ between both arms (ie. initial surgery in arm 1or surgery after ICT in arm 2) as well as tolerance to
XRT whatever its schedule. Ultimate disease control, including successful salvage surgeries after XRT, was not significantly different between both arms. As of December 2003, 14% of pts in arm 1 and 17% of pts in arm 2 were still alive. The hypopharynx SCC evolution was the cause of death in 43 pts in arm 1 and in 41 pts in arm 2. The 5-yr. OS was 33% in arm 1 and 38% in arm 2, the 10-yr. OS was respectively 14% and 13%. The 5-yr. PFS was 26% in arm 1 and 32% in arm 2, the 10-yr. PFS was respectively 8.5% and 11%. In arm 2 survival with a functional larynx in place was 22% at 5 years and 9% at 10 years.

**Conclusions:** this final analysis has confirmed the preliminary results. This LP strategy provided similar survival curves as compared with conventional treatment and allowed 2/3 of the survivors to retain their larynx.

**Meta Analysis of Larynx preservation from MACH-NC**


**Abstract:** The MACH-NC group performed a meta-analysis using updated individual patient data from all 3 randomized trials (1985—1993) comparing immediate surgery + radiotherapy (RT) to CT followed by RT in responders or by surgery + RT in non responders in laryngeal & hypopharyngeal carcinoma. Overall survival (OS) was the main end-point. The logrank-test, stratified
by trial, and the relative risk (RR) were calculated. The American (n = 332) and French (n = 68) trials included laryngeal tumors and the European (n = 202), pharyngeal & epilaryngeal tumors. OS and disease-free survival (DFS) results are given below for the 602 patients. The types of first events were different in the two arms with twice as many loco-regional recurrences in the CT arm as in the control arm, 35% vs 20%, less metastases/second primaries, 38% vs 54%, and similar rates of deaths not due to cancer, 27% vs 26%. In the CT group, the proportion of patients with a functional larynx was 67% and 58% among patients alive at 3 and 5 years respectively. In conclusion, no significant differences in OS or DFS were observed between the CT arm and the control arm. The larynx was preserved in 58% of patients alive at 5 years. However, organ preservation should remain experimental because of the non significant trend observed in favor of the control arm.

**Induction Therapy**


**Background:** Both induction chemotherapy followed by irradiation and concurrent chemotherapy and radiotherapy have been reported as valuable alternatives to total laryngectomy in patients with advanced larynx or hypopharynx cancer. We report results of the randomized phase 3 trial 24954 from the European Organization for Research and Treatment of Cancer.
Methods: Patients with resectable advanced squamous cell carcinoma of the larynx (tumor stage T3-T4) or hypopharynx (T2-T4), with regional lymph nodes in the neck staged as N0-N2 and with no metastasis, were randomly assigned to treatment in the sequential (or control) or the alternating (or experimental) arm. In the sequential arm, patients with a 50% or more reduction in primary tumor size after two cycles of cisplatin and 5-fluorouracil received another two cycles, followed by radiotherapy (70 Gy total). In the alternating arm, a total of four cycles of cisplatin and 5-fluorouracil (in weeks 1, 4, 7, and 10) were alternated with radiotherapy with 20 Gy during the three 2-week intervals between chemotherapy cycles (60 Gy total). All nonresponders underwent salvage surgery and postoperative radiotherapy. The Kaplan-Meier method was used to obtain time-to-event data.

Results: The 450 patients were randomly assigned to treatment (224 to the sequential arm and 226 to the alternating arm). Median follow-up was 6.5 years. Survival with a functional larynx was similar in sequential and alternating arms (hazard ratio of death and/or event = 0.85, 95% confidence interval = 0.68 to 1.06), as were median overall survival (4.4 and 5.1 years, respectively) and median progression-free interval (3.0 and 3.1 years, respectively). Grade 3 or 4 mucositis occurred in 64 (32%) of the 200 patients in the sequential arm who received radiotherapy and in 47 (21%) of the 220 patients in the alternating arm. Late severe edema and/or fibrosis was observed in 32 (16%) patients in the sequential arm and in 25 (11%) in the alternating arm.
Conclusions: Larynx preservation, progression-free interval, and overall survival were similar in both arms, as were acute and late toxic effects.


Background: Locally advanced laryngeal and hypopharyngeal cancers (LHC) represent a group of cancers for which surgery, laryngectomy-free survival (LFS), overall survival (OS), and progression-free survival (PFS) are clinically meaningful end points.

Patients and Methods: These outcomes were analyzed in the subgroup of assessable LHC patients enrolled in TAX 324, a phase III trial of sequential therapy comparing docetaxel plus cisplatin and fluorouracil (TPF) against cisplatin and fluorouracil (PF), followed by chemoradiotherapy.

Results: Among 501 patients enrolled in TAX 324, 166 had LHC (TPF, n = 90; PF, n = 76). Patient characteristics were similar between subgroups. Median OS for TPF was 59 months [95% confidence interval (CI): 31-not reached] versus 24 months (95% CI: 13-42) for PF [hazard ratio (HR) for death: 0.62; 95% CI: 0.41-0.94; P = 0.024]. Median PFS for TPF was 21 months (95% CI: 12-59) versus 11 months (95% CI: 8-14) for PF (HR: 0.66; 95% CI: 0.45-0.97; P = 0.032). Among operable patients (TPF, n = 67; PF, n = 56), LFS was significantly greater with TPF (HR: 0.59; 95% CI: 0.37-0.95; P = 0.030). Three-year LFS with TPF was 52%
versus 32% for PF. Fewer TPF patients had surgery (22% versus 42%; \( P = 0.030 \)).

**Conclusions:** In locally advanced LHC, sequential therapy with induction TPF significantly improved survival and PFS versus PF. Among operable patients, TPF also significantly improved LFS and PFS. These results support the use of sequential TPF followed by carboplatin chemoradiotherapy as a treatment option for organ preservation or to improve survival in locally advanced LHC.

Induction Chemotherapy in organ preservation setting remains investigational to be conducted only in a trial setting

**Laryngeal Cancer Survival**


**Background:** Survival has decreased among patients with laryngeal cancer during the past 2 decades in the United States. During this same period, there has been an increase in the nonsurgical treatment of laryngeal cancer.

**Objective:** The objectives of this study were to identify trends in the demographics, management, and outcome of laryngeal cancer in the United States and to analyze factors contributing to the decreased survival.

**Study Design:** The authors conducted a retrospective, longitudinal study of laryngeal cancer cases. Methods: Review of the National Cancer Data Base (NCDB) revealed
158,426 cases of laryngeal squamous cell carcinoma (excluding verrucous carcinoma) diagnosed between the years 1985 and 2001. Analysis of these case records addressed demographics, management, and survival for cases grouped according to stage, site, and specific TNM classifications.

**Results:** This review of data from the NCDB analysis confirms the previously identified trend toward decreasing survival among patients with laryngeal cancer from the mid-1980s to mid-1990s. Patterns of initial management across this same period indicated an increase in the use of chemoradiation with a decrease in the use of surgery despite an increase in the use of endoscopic resection. The most notable decline in the 5-year relative survival between the 1985 to 1990 period and the 1994 to 1996 period occurred among advanced-stage glottic cancer, early-stage supraglottic cancers, and supraglottic cancers classified as T3N0M0. Initial treatment of T3N0M0 laryngeal cancer (all sites) in the 1994 to 1996 period resulted in poor 5-year relative survival for those receiving either chemoradiation (59.2%) or irradiation alone (42.7%) when compared with that of patients after surgery with irradiation (65.2%) and surgery alone (63.3%). In contrast, identical 5-year relative survival (65.6%) rates were observed during this same period for the subset of T3N0M0 glottic cancers initially treated with either chemoradiation or surgery with irradiation.

**Conclusions:** The decreased survival recorded for patients with laryngeal cancer in the mid-1990s may be related to changes in patterns of management. Future studies are warranted to further evaluate these associations.
Future Trial Designs in Larynx and Hypopharynx Tumours
Larynx preservation clinical trial design: key issues and recommendations—a consensus panel summary.


Background: To develop guidelines for the conduct of phase III clinical trials of larynx preservation in patients with locally advanced laryngeal and hypopharyngeal cancer.

Methods: A multidisciplinary international consensus panel developed recommendations after reviewing results from completed phase III randomized trials, meta-analyses, and published clinical reports with updates available through November 2007. The guidelines were reviewed and approved by the panel.

Results: The trial population should include patients with T2 or T3 laryngeal or hypopharyngeal squamous cell carcinoma not considered for partial laryngectomy and exclude those with laryngeal dysfunction or age more than 70 years. Functional assessments should include speech and swallowing. Voice should be routinely assessed with a simple, validated instrument. The primary endpoint should capture survival and function. The panel created a new endpoint: laryngo-esophageal dysfunction-free survival. Events are death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later. Recommended secondary endpoints are overall survival, progression-free survival, locoregional control, time to tracheotomy, time to laryngectomy, time to discontinuation of feeding tube, and quality of life/patient reported outcomes. Correlative
biomarker studies for near-term trials should include EGFR, ERCC-1, E-cadherin and beta-catenin, epiregulin and amphiregulin, and TP53 mutation.

**Conclusions:** Revised trial designs in several key areas are needed to advance the study of larynx preservation. With consistent methodologies, clinical trials can more effectively evaluate and quantify the therapeutic benefit of novel treatment options for patients with locally-advanced laryngeal and hypopharyngeal cancer.
Management of Neck Nodes in SCC of Head and Neck
(Excluding nasopharyngeal cancer)

Introduction:
Neck node metastases is the single most important prognostic factor in head and neck cancer, in particular squamous cell carcinoma. Management of the neck remains controversial in view of multiple sites constituting the “head and neck” region as well as the variable lymphatic drainage and metastatic pattern. Decision to treat the neck, the modality of treatment, and the extent of dissection will depend on the primary site in the head and neck as well as the TNM staging.

Staging
Neck staging under the AJCC/TNM staging for Head and Neck cancers:
(Excluding nasopharynx and thyroid)
# Table 1: staging of neck nodes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional nodes metastasis.</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension.</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or metastasis is in multiple ipsilateral lymph nodes, none more that 6 cm in greatest dimension; or metastasis is in bilateral or contralateral lymph nodes, none greater than 6 cm in greatest dimension.</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension.</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more that 6 cm in greatest dimension.</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension.</td>
</tr>
</tbody>
</table>

**Investigations:**

- **FNAC**: Investigation of choice. FNAC should be performed in all patients for diagnosis and confirmation of any clinically/radiologically suspicious lymph node, preferably ultrasound guided.
- **Imaging**: Various modalities used for imaging the neck are ultrasonography computed tomography.
(CT), and magnetic resonance imaging (MRI), the sensitivities and specificities are outlined in the table below.

- Ultrasound guided fine needle aspiration cytology (USgFNAC) is the most accurate diagnostic modality for neck node metastases.

### Table 2: Sensitivity and specificity of various imaging modalities

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>USgFNAC</td>
<td>80%</td>
<td>98%</td>
</tr>
<tr>
<td>Ultrasound alone</td>
<td>87%</td>
<td>86%</td>
</tr>
<tr>
<td>CT scan</td>
<td>81%</td>
<td>76%</td>
</tr>
<tr>
<td>MRI</td>
<td>81%</td>
<td>63%</td>
</tr>
</tbody>
</table>

- Biopsy: Indicated only if two FNAC, at least one image guided, are inconclusive.
  - More useful when a non-squamous etiology is suspected.

**Treatment of neck nodes:**

**A) N0 neck in oral cavity cancer - Neck dissection and extent:**

*Stage I (cT1N0M0) and stage II (cT2N0M0)/ Early oral cancers:*

- Low incidence of occult metastases (cT1N0:13-33% and cT2N0:37-53%)
- Decision to treat the neck prophylactically is an ongoing area of debate
Options for treatment of N0 neck:
- Elective neck dissection
- Wait and watch policy (therapeutic dissection)
- Elective Radiotherapy

Indications for use of various treatment options:

1. Elective neck dissection
   - High risk for metastases (tumor thickness > 4 mm, poorly differentiated)
   - Regular follow up not possible

2. “Wait and watch” policy
   - Low risk for nodal metastases (tumour thickness < 4mm, well differentiated)
   - Reliable and regular follow up (3 monthly Clinical examination + USG neck)

3. Elective radiotherapy
   - If treatment to primary is EBRT or brachytherapy

*Current evidence shows that disease specific death rate is significantly lower in elective neck dissection in N0 neck as compared to observation with better regional control rates and less recurrence.*

- Extent: SND (I-III) for oral cavity cancers is adequate surgery for the node negative neck (please refer to nomenclature of neck dissections given below)

*Stage III (cT3N0) and IV (cT4N0):*
- High incidence of occult metastases
- Elective neck dissection should be performed
- Extent: SND (I-III) for oral cavity cancers

__________________________ 111
B) **N0 neck for other sites: Oropharynx, Larynx, Hypopharynx**

Management of the node negative neck in sites other than the oral cavity depends on the treatment plan for the primary site:

- RT to areas of nodal drainage of the primary if primary modality is RT/CTRT
- Selective neck dissection if surgery is the primary treatment option

C) **Management of the node positive N+ neck:** It depends on the treatment modality planned for the primary cancer. (Ref to algorithm)
If surgery is the primary modality of therapy, a neck dissection should be performed at the time of surgery. Refer to Table 3 for extent of neck dissection depending upon the primary site of cancer.

If primary treatment is by chemoradiation, the involved node levels will be treated with doses of 66-70Gy in conventional fractionation.

Treatment of the neck post chemoradiation is addressed below in special issues.

**Extent of ND:**
- Depends on the site of primary (see table 3)
- Lesser neck dissections can also be performed for node positive necks like SND (I-IV) for oral cancers, however the evidence for the same is poor. We therefore recommend the extent of neck dissection as outlined in table 3 for node positive necks

**Table 3:**
**Extent of neck dissection depending on primary site**

<table>
<thead>
<tr>
<th>Site</th>
<th>Levels to be addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>I – V</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>I – V</td>
</tr>
<tr>
<td>Larynx</td>
<td>II - V</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>II - V</td>
</tr>
</tbody>
</table>

**Nomenclature of neck dissection**

Neck dissections are classified as comprehensive/modified or selective.
1. Comprehensive neck dissection (CND) or Modified Neck Dissection includes removal of all nodes and lymphatic structures from levels I-V, independent of whether the non-lymphatic structures (spinal accessory/ XII nerve/ IJV/ SCM) are preserved.

   - Structures preserved are to be mentioned separately.
   - For example, if spinal accessory nerve alone is preserved, it will be named as: ‘CND (I-V) with preservation of the XII nerve’.

2. Selective neck dissection (SND) includes removal of one or more levels of lymph nodes draining the involved/diseased site in the head and neck.

   Types: Antero lateral (I-IV), Lateral (II-IV), Postero-lateral (II-IV), supra-omohyoid (I-III), anterior (VI)

   Levels dissected to be mentioned within brackets.

   Example- Supra-omohyoid neck dissection for oral cavity cancer is written as: SND (I-III)

C) **Sub-level II B: Indications for dissection:**

   Sub-level IIB, also known as Bocca’s space or the sub-muscular recess (SMR) is a triangular area bounded antero-medially by the spinal accessory/ XIIth cranial nerve, superiorly by the base of skull, postero-laterally by the posterior border of the sternocleidomastoid muscle.

   - Overall incidence of IIB metastases in N0 neck (any site) is very low (2-6%)
   - Occult metastases is highest for oral cavity (3.9%): mainly oral tongue
• Isolated IIB metastases is extremely rare (0.3%)

• Current recommendations for IIB dissection:
  ➢ N0 neck: not required
  ➢ N+ neck: to be dissected
  ➢ Avoid excessive traction and skeletonisation of XII nerve (SAN)

D) Special issues in neck node management:

1. Role of sentinel LN biopsy
   Sentinel lymph node is the first draining group of nodes for a particular site. SLN biopsy may potentially avoid unnecessary lymph node dissection and subsequent morbidity.

   • Current role of SLNB is still investigational and should be used only in a trial setting.

2. Management of neck in post CTRT head and neck cancer:
   Whether neck dissection post RT/ CTRT should follow as a “planned” or a “salvage” procedure is controversial. Residual microscopic disease in resected specimens with complete clinical response has been reported upto 30%. However, nodal area as the first site of failure is low.

   • Management depends on: (see algorithm above)
     1. Initial N stage
     2. Method of neck assessment / as per resource level
     3. Presence of residual disease in the neck post CTRT
- Post CTRT N+ is managed by salvage neck dissection (extent depends on the level of the node and the structures involved)
- Management of post CTRT N0 is summarized in the table below:

Table 4:
Management of the post CTRT Node negative neck

<table>
<thead>
<tr>
<th>Initial N stage (before CTRT)</th>
<th>Post CTRT N0 neck using the following method of neck assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical examination only</td>
</tr>
<tr>
<td>N1</td>
<td>Observe*</td>
</tr>
<tr>
<td>N2</td>
<td>Observe</td>
</tr>
<tr>
<td>N3</td>
<td>Observe/ planned dissection</td>
</tr>
</tbody>
</table>

* Observe means regular follow up and salvage neck dissection at recurrence

** CT scan is done at 6-8 weeks post CTRT

*** PET-CT is done at 8-12 weeks post CTRT

PETCT scan is the investigation of choice for Post-CTRT evaluation of response at primary site and neck node status. Optimal time is 8-12 week (12 weeks: More accurate for PETCT)

3. Management of large neck nodes with small primary:

Split therapy is a regimen combining two definite sequenced treatment modalities, surgery and RT, equally
important in the control of disease in patients with oropharyngopharyngeal primaries

- **Indications:**
  1. Small, radiocurable, pharyngolaryngeal tumours (cT1, T2) with
  2. Large/ bulky clinically resectable neck nodes (cN2, N3)

- **Prerequisites:**
  1. Good Patient compliance to complete treatment and reliable follow up
  2. Accurate clinico- radiological assessment to ensure complete nodal resection

```
T1/T2, N2a-N3
Oropharynx, larynx, hypopharynx
Suitable for treatment on organ preservation protocols

Upfront neck dissection

2-3 weeks

Definitive Chemoradiation to the primary and neck
```

* Algorithm for us of “Split therapy”
Suggested Reading

1. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck.

   Ayotunde J. Fasunla, Brandon H. Greene, Nina Timmesfeld, Susanne Wiegand, Jochen A. Werner, Andreas M. Sesterhenn.


There is still no consensus on the optimal treatment of the neck in oral cavity cancer patients with clinical N0 neck. The aim of this study was to assess a possible benefit of elective neck dissection in oral cancers with clinical N0 neck. A comprehensive search and systematic review of electronic databases was carried out for randomized trials comparing elective neck dissection to therapeutic neck dissection (observation) in oral cancer patients with clinical N0 neck. A meta-analysis of the studies which met our defined selection criteria was performed using diseasespecific death as the primary outcome, and the relative risk (RR) of disease-specific death was calculated for each of the identified studies. Both fixed-effects (Mantel–Haenszel method) and random-effects models were applied to obtain a combined RR estimate, although between-study heterogeneity was not found to be significant as indicated by an I² of 8.5% (p = 0.350). Four studies with a total of 283 patients met our inclusion criteria. The results of the meta-analysis showed that elective neck dissection reduced the risk of disease-specific death (fixed-effects model RR = 0.57, 95% CI 0.36–0.89, p = 0.014; random-effects model RR = 0.59, 95% CI
0.37–0.96, p = 0.034) compared to observation. This reduction in disease-specific death rate supports the need to perform elective neck dissection in oral cancers with clinical N0 neck.


To perform a meta-analysis comparing ultrasonography (US), US guided fine needle aspiration cytology (USgFNAC), computed tomography (CT), and magnetic resonance imaging (MRI) in the detection of lymph node metastases in head and neck cancer. Methods MEDLINE, EMBASE and Cochrane databases were searched (January 1990–January 2006) for studies reporting diagnostic performances of US, USgFNAC, CT, and MRI to detect cervical lymph node metastases. Two reviewers screened text and reference lists of potentially eligible articles. Criteria for study inclusion: (1) histopathology was the reference standard, (2) primary tumors and metastases were squamous cell carcinoma and (3) data were available to construct 2 × 2 contingency tables. Meta-analysis of pairs of sensitivity and specificity was performed using bivariate analysis. Summary estimates for diagnostic performance used were sensitivity, specificity, diagnostic odds ratios (DOR) (95% confidence intervals) and summary receiver operating characteristics (SROC) curves. Results
From seventeen articles, 25 data sets could be retrieved. Eleven articles studied one modality: US \((n = 4)\); USgFNAC \((n = 1)\); CT \((n = 3)\); MRI \((n = 3)\). Six articles studied two or more modalities: US and CT \((n = 2)\); USgFNAC and CT \((n = 1)\); CT and MRI \((n = 1)\); MRI and MRI-USPIO (Sinerem\textsuperscript{®}) \((n = 2)\); US, USgFNAC, CT and MRI \((n = 1)\). USgFNAC (AUC = 0.98) and US (AUC = 0.95) showed the highest areas under the curve (AUC). MRI-USPIO (AUC = 0.89) and CT (AUC = 0.88) had similar results. MRI showed an AUC = 0.79. USgFNAC showed the highest DOR (DOR = 260) compared to US (DOR = 40), MRI-USPIO (DOR = 21), CT (DOR = 14) and MRI (DOR = 7). Conclusion USgFNAC showed to be the most accurate imaging modality to detect cervical lymph node metastases.

3. **Metastases to level IIb in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis.**


**Background:** In this study, a meta-analysis of level IIb metastases in squamous cell carcinoma (SCC) of the oral cavity was conducted.

**Methods:** Two independent reviewers screened abstracts and full text papers deemed potentially relevant. Data were pooled using a random intercept model.

**Results:** In this analysis, 729 abstracts and 177 full text papers were screened (Kappa statistic 0.8 and 1.0, respectively). A total of 332 patients in 9 papers were included in the analysis. Twenty patients had level IIb
metastases (mean, 6%; range, 0% to 10.4%). The pooled percentage of level IIb metastases was 6.0% (95% CI: 3.5-8.6). Only 3 patients with level IIb metastases had isolated nodal disease. Eighty-five percent of those with level IIb metastases had additional nodal disease (95% CI: 64.0-94.8), with IIa being a common denominator among all.

**Conclusion:** Level IIb nodal metastases are relatively uncommon in previously untreated SCC of the oral cavity (6%). Furthermore, isolated level IIb nodal disease is uncommon. However, given the quality of evidence to date, it is recommended that dissection of level IIb remain the standard of care in oral cavity squamous cell cancer.

4. **Management of the neck after chemoradiotherapy for head and neck cancers in Asia: consensus statement from the Asian Oncology Summit 2009 Review Article.**

*Joseph T Wee, Benjamin O Anderson, June Corry, Anil D’Cruz, Khee C Soo, Chao-Nan Qian, Daniel T Chua, Rodney J Hicks, Christopher HK Goh, James B Khoo, Seng C Ong, Arlene A Forastiere, Anthony T Chan.*


The addition of a planned neck dissection after radiotherapy has traditionally been considered standard of care for patients with positive neck-nodal disease. With the acceptance of chemoradiotherapy as the new primary treatment for patients with locally advanced squamous-cell head and neck cancers, and the increasing numbers of patients who achieve a complete response, the role of planned neck dissection is now being questioned. The
accuracy and availability of a physical examination or of
different imaging modalities to identify true complete
responses adds controversy to this issue. This consensus
statement will address some of the controversies
surrounding the role of neck dissection following
chemoradiotherapy for squamous-cell carcinomas of the
head and neck, with particular reference to patients in
Asia.

5. Split therapy: planned neck dissection followed by
definitive radiotherapy for a T1, T2 pharyngolaryngeal primary cancer with operable
N2, N3 nodal metastases—a prospective study.

D’cruz AK, Pantvaidya GH, Agarwal JP, Chaukar DA,
Pathak KA, Deshpande MS, Pai PS, Chaturvedi P,
Dinshaw KA.


Background: The management of patients with a small
pharyngolaryngeal cancer (T1 and T2) with large nodal
metastases is a subject of debate. We present data on the
feasibility and outcome of treating these patients with
surgery for the nodal metastases followed by definitive
radiotherapy.

Methods: Prospective study of 59 patients of small
pharyngolaryngeal primary squamous carcinomas with
operable (N2/N3) nodal metastasis treated with neck
dissection followed by radiotherapy.

Results: Complete nodal clearance was achieved in 54
(90%). The mean nodal size was 4 cm and extranodal
extension was seen in 88% of patients in the study group.
There were no significant postoperative complications.
Median interval between surgery and radiotherapy was 23 days. Forty-nine patients (83%) started their RT within 6 weeks of surgery. With a median follow-up of 25 months, the disease free and overall survival was 54% and 60% (5 years).

Conclusion: The management of patients with a radiocurable pharyngolaryngeal primary with large nodes by this approach is a feasible option with adequate control and survival.
Nasal Cavity & Paranasal Sinuses

Introduction:
The 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.
Sites

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

Investigations / Procedures

1. Biopsy
   Punch / Endoscopic
   Endoscopic preferred.
   Mucosal biopsy from palate to be avoided
   Caldwell – Luc procedure for biopsy only in select cases

2. Imaging (mandatory) to assess the extent of disease
   Computed Tomography (CT) and / or Magnetic Resonance Imaging (MRI)
   * 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

3. Prosthetic / Dental Workup
   Pre-operative dental impression for post-op prosthesis

4. Ophthalmologic examination
Documentation of visual acuity, fundoscopy and visual field (perimetry) is important both in the 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

**Staging: TNM (UICC) 2010**

**Tx:** Primary tumor cannot be assessed

**T0:** No evidence of primary tumor

**Tis:** Carcinoma in situ

**Maxilla**

**T1** Tumour limited to the mucosa with no erosion or destruction of 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

**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**

T1 Tumour restricted to one subsite of nasal cavity or ethmoid sinus, with or without bony invasion

T2 Tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion.

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

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

Nx Regional LN cannot be assessed

N0 No regional LN metastasis

N1 Single node < 3cm

N2a Single node >3cm and <6cm

N2b Ipsilateral multiple nodes <6cm

N2c Bilateral/Contralateral nodes < 6cm

N3 Lymph node > 6cm
Treatment Options

Nasal Cavity & Ethmoid sinus

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. 3DCRT/IMRT 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. 3DCRT/IMRT 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.
**T4a:**

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

II. CT+RT in unresectable tumours

**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.

**Treatment of Neck:**

N0 Observe

N+ Appropriate neck dissection and post-operative radiotherapy.

**Criteria of Unresectibility**

- Gross infiltration of infratemporal fossa.
- Pterygopalatine 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**

   

   Malignant tumors of the superior sinonasal vault are rare, and, because of this and the varied histologic findings, most outcomes data reflect the experience of small patient cohorts. This International Collaborative study examines a large cohort of patients accumulated from multiple institutions experienced in craniofacial surgery, with the aim of reporting benchmark figures for outcomes and identifying patient-related and tumor-related predictors of prognosis after craniofacial resection (CFR).

   **Methods:**
   
   Three hundred thirty-four patients from 17 institutions were analyzed for outcome. Patients with esthesioneuroblastoma were excluded and are being reported separately. The median age was 57 years (range, 3-98 years). One hundred eighty-eight patients (56.3%)
had had prior single-modality or combined treatment, which included surgery in 120 (36%), radiation in 79 (23.7%), and chemotherapy in 56 (16.8%). The most common histologic findings were adenocarcinoma in 107 (32%) and squamous cell carcinoma in 101 (30.2%). The margins of resection were close or microscopically positive in 95 (30%). Adjuvant radiotherapy was given in 161 (48.2%) and chemotherapy in 16 (4.8%). Statistical analyses for outcomes were performed in relation to patient characteristics, tumor characteristics, including histologic findings and extent of disease, surgical resection margins, prior radiation, and prior chemotherapy to determine predictive factors.

**Results:**
Postoperative mortality occurred in 15 patients (4.5%). Postoperative complications occurred in 110 patients (32.9%). The 5-year overall, disease-specific, and recurrence-free survival rates were 48.3%, 53.3%, and 45.8%, respectively. The status of surgical margins, histologic findings of the primary tumor, and intracranial extent were independent predictors of overall, disease-specific, and recurrence-free survival on multivariate analysis.

**Conclusions:**
CFR for malignant paranasal sinus tumors is a safe surgical treatment with an overall mortality of 4.5% and complication rate of 33%. The status of surgical margins, histologic findings of the primary tumor, and intracranial extent are independent predictors of outcome.
2. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review.

Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T.

Cancer 2001 Dec 15;92(12):3012-29

Background:
The authors reviewed treatment results in patients with nasal and paranasal sinus carcinoma from a large retrospective cohort and conducted a systematic literature review.

Methods:
Two hundred twenty patients who were treated between 1975 and 1994 with a minimum follow-up of 4 years were reviewed retrospectively. A systematic review of published articles on patients with malignancies of the nasal and paranasal sinuses during the preceding 40 years was performed.

Results:
The 5-year survival rate was 40%, and the local control rate was 59%. The 5-year actuarial survival rate was 63%, and the local control rate was 57%. Factors that were associated statistically with a worse prognosis, with results expressed as 5-year actuarial specific survival rates, included the following: 1) histology, with rates of 79% for patients with glandular carcinoma, 78% for patients with adenocarcinoma, 60% for patients with squamous cell carcinoma, and 40% for patients with undifferentiated carcinoma; 2) T classification, with rates of 91%, 64%, 72%,
and 49% for patients with T1, T2, T3, and T4 tumors, respectively; 3) localization, with rates of 77% for patients with tumors of the nasal cavity, 62% for patients with tumors of the maxillary sinus, and 48% for patients with tumors of the ethmoid sinus; 4) treatment, with rates of 79% for patients who underwent surgery alone, 66% for patients who were treated with a combination of surgery and radiation, and 57% for patients who were treated exclusively with radiotherapy. Local extension factors that were associated with a worse prognosis included extension to the pterygomaxillary fossa, extension to the frontal and sphenoid sinuses, the erosion of the cribriform plate, and invasion of the dura. In the presence of an intraorbital invasion, enucleation was associated with better survival. In multivariate analysis, tumor histology, extension to the pterygomaxillary fossa, and invasion of the dura remained significant. Systematic review data demonstrated a progressive improvement of results for patients with squamous cell and glandular carcinoma, maxillary and ethmoid sinus primary tumors, and most treatment modalities.

**Conclusions:**

Progress in outcome for patients with nasal and paranasal carcinoma has been made during the last 40 years. These data may be used to make baseline comparisons for evaluating newer treatment strategies.

3. **Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: A 10-year experience**

Piero Nicolai, M.D., Paolo Battaglia, M.D., Maurizio Bignami, M.D., Andrea Bolzoni Villaret, M.D., Giovanni
Background:
The increasing expertise in the field of transnasal endoscopic surgery recently has expanded its indications to include the management of sinonasal malignancies. We report our experience with the endoscopic management of nasoethmoidal malignancies possibly involving the adjacent skull base.

Methods:
A retrospective analysis was performed of patients treated by an exclusive endoscopic approach (EEA) or a cranioendoscopic approach (CEA) from 1996 to 2006 managed by two surgical teams at the Departments of Otorhinolaryngology of the University of Brescia, and the University of Pavia/Insubria-Varese, Italy.

Results:
One-hundred eighty-four patients were considered eligible for the present analysis. An EEA was performed in 134 patients and the remaining 50 patients underwent the CEA. The most frequent histotypes encountered were adenocarcinoma (37%), squamous cell carcinoma (13.6%), olfactory neuroblastoma (12%), mucosal melanoma (9.2%), and adenoid cystic carcinoma (7.1%). Overall, 86 (46.7%) patients received some form of adjuvant treatment. The patients were followed up for a mean of 34.1 months (range, 2–123 months). The 5-year disease-specific survival was 91.4 _ 3.9% and 58.8 _ 8.6% (p _ 0.0004) for the EEA and CEA group, respectively.
Conclusion:
To the best of our knowledge, this is the largest series reported to date of malignant tumors of the sinonasal tract and adjacent skull base treated with pure endoscopic or cranioendoscopic techniques. A 5-year disease-specific survival of 91.4% and 58.8% for the EEA and the CEA groups, respectively, seem to indicate that endoscopic surgery, when properly planned and in expert hands, may be a valid alternative to standard surgical approaches for the management of malignancies of the sinonasal tract.


Purpose:
To report the long-term outcome of intensity-modulated radiotherapy (IMRT) for sinonasal tumors.

Methods and Materials:
Between July 1998 and November 2006, 84 patients with sinonasal tumors were treated with IMRT to a median dose of 70 Gy in 35 fractions. Of the 84 patients, 73 had a primary tumor and 11 had local recurrence. The tumor histologic type was adenocarcinoma in 54, squamous cell carcinoma in 17, esthesioneuroblastoma in 9, and adenoid cystic carcinoma in 4. The tumors were located in the ethmoid sinus in 47, maxillary sinus in 19, nasal cavity in 16, and multiple sites in 2. Postoperative IMRT was
performed in 75 patients and 9 patients received primary IMRT.

Results:
The median follow-up of living patients was 40 months (range, 8-106). The 5-year local control, overall survival, disease-specific survival, disease-free survival, and freedom from distant metastasis rate was 70.7%, 58.5%, 67%, 59.3%, and 82.2%, respectively. No difference was found in local control and survival between patients with primary or recurrent tumors. On multivariate analysis, invasion of the cribriform plate was significantly associated with lower local control (p = 0.0001) and overall survival (p = 0.0001). Local and distant recurrence was detected in 19 and 10 patients, respectively. Radiation-induced blindness was not observed. One patient developed Grade 3 radiation-induced retinopathy and neovascular glaucoma. Nonocular late radiation-induced toxicity comprised complete lacrimal duct stenosis in 1 patient and brain necrosis in 3 patients. Osteoradionecrosis of the maxilla and brain necrosis were detected in 1 of the 5 reirradiated patients.

Conclusion:
IMRT for sinonasal tumors provides low rates of radiation-induced toxicity without blindness with high local control and survival. IMRT could be considered as the treatment of choice.
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. It is shown that chemotherapy plus radiotherapy improves disease free and progression free survival compared to radiotherapy alone in advanced nasopharyngeal carcinomas. But, it is controversial whether addition of chemotherapy to radiotherapy improves overall survival. Recently published meta-analysis has shown that it does improve overall survival.

Specific Investigations before definitive treatment

- Nasopharyngeal examination, endoscopy & biopsy
- Imaging:
  - PET- CT (if available) or
  - Chest X-Ray,
  - 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

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 contemplated for Chemoradiotherapy/radiotherapy should undergo
a. Dental check up
b. Nutritional counselling and swallowing evaluation
c. Baseline Thyroid function
d. Audiological and visual acuity and field testing

**TNM STAGING (AJCC Seventh Edition)**

**Nasopharynx (T)**

T1 Tumour confined to nasopharynx, with or without extension to oropharynx, nasal cavity but without parapharyngeal extension

T2 Tumour with parapharyngeal extension

T3 Tumour invades bony structures of skull and/or paranasal sinuses

T4 Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space.

**Regional lymph node (N)**

N1 Unilateral cervical, unilateral or bilateral retropharyngeal lymph node(s), 6_cm or less in greatest dimension, above supraclavicular fossa
N2 Bilateral cervica lymph nodes, <6 cm in greatest dimension, above supraclavicular fossa

N3 Metastasis in lymph node(s), >6 cm in dimension (N3a) or in the supraclavicular fossa (N3b)

**Distant metastasis (M)**

M0 No distant metastasis

M1 Distant metastasis

**Stage grouping**

<table>
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<th>T classification</th>
<th>N classification</th>
<th>M classification</th>
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**Nasopharyngeal carcinoma** differs from other head and neck squamous cell carcinomas in following aspects

- 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.

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 should be treated with Concurrent chemoradiotherapy.

T2 N0-:
- Concurrent chemoradiotherapy
- Neo Adjuvant CT x 2 cycles + Concurrent CT + RT

T3 - 4 N0 / Any T N+:
- Neo Adjuvant CT x 2 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:**

1. **Neo-adjuvant Chemotherapy:**

   **Regime (i)**
   
   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 Cycles

   **Regime (ii)**
   
   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 Cycles
Regime (iii)
Cisplatinum (33mg / m2 / day x 3 days) + Ifosfamide (2gm /m2 / day x 3 days) + Mesna rescue X 2 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 cycles.

2. Adjuvant Chemotherap: 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.

3. Concurrent Chemotherapy with Radiotherapy:
Regime (i):
Cisplatin (30 mg/m^2 weekly for 05 to 06 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 emerging data and phase II randomized trials showing its benefit over concurrent chemoradiotherapy. However chemoradiotherapy is the minimum basic treatment recommended for locally advanced nasopharyngeal carcinomas.

Note :
- 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: Re-irradiation, chemotherapy and/or surgery in selected cases.

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 at least 5 years.

Evaluation of thyroid function in patients with irradiation to the neck is recommended at 1, 2 and 5 years.

Suggested Reading


   Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients.

   *Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, Lai M, Ho R, Cheung KY, Yu BK, Chiu SK, Choi PH, Teo PM, Kwan WH, Chan AT.*


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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.

**AJCC STAGING**

AJCC 7 (2010) staging is as follows:

**PRIMARY TUMOR (T)**

**TX:** Primary tumor cannot be assessed

**T0:** No evidence of primary tumor

**T1:** Tumor 2 cm or less in greatest dimension without extraparenchymal extension*

**T2:** Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*

**T3:** Tumor more than 4 cm and/or tumor having extraparenchymal extension*
**T4a:** Moderately advanced disease. Tumor invades skin, mandible, ear canal, and/or facial nerve

**T4b:** Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

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

**REGIONAL LYMPH NODES (N):** Same as for other head neck cancers

**DISTANT METASTASIS (M):** Same as for other head neck cancers

**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:

<table>
<thead>
<tr>
<th>Utility</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive value</th>
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<tbody>
<tr>
<td>Neoplastic (benign &amp; malignant) vs. Non-neoplastic</td>
<td>96%</td>
<td>98%</td>
<td>81%</td>
<td>100%</td>
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<td>Benign vs. Malignant</td>
<td>80%</td>
<td>97%</td>
<td>94%</td>
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<td>MALIGNANT EPITHELIAL TUMORS</td>
<td>BENIGN EPITHELIAL TUMOURS</td>
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<td>Malignant epithelial tumours</td>
<td>Pleomorphic adenoma</td>
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<td>Acinic cell carcinoma</td>
<td>Myoepithelioma</td>
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<td>Mucoepidermoid carcinoma</td>
<td>Basal cell adenoma</td>
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<td>Adenoid cystic carcinoma</td>
<td>Warthin tumour</td>
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<td>Polymorphous low-grade adenocarcinoma</td>
<td>Oncocytoma</td>
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<td>Epithelial-myoepithelial carcinoma</td>
<td>Canalicular adenoma</td>
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<td>Clear cell carcinoma, not otherwise specified</td>
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<td>Basal cell adenocarcinoma</td>
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<td>Sebaceous carcinoma</td>
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<td>lymphadenocarcinoma</td>
<td>Ductal papillomas</td>
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<td>Cystadenocarcinoma</td>
<td>- Inverted ductal papilloma</td>
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<td>Sialadenomapapilliferum</td>
<td>- Intraductal papilloma</td>
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<td>Low-grade cribriform cystadenocarcinoma</td>
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<td>Myoepithelial carcinoma</td>
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<td>Carcinoma ex pleomorphic adenoma</td>
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<td>Carcinosarcoma</td>
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<td>Metastasizing pleomorphic adenoma</td>
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<td>SOFT TISSUE TUMOURS</td>
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<td>HAEMATO-LYMPHOID TUMOURS</td>
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<td>Hodgkin lymphoma</td>
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<td>Diffuse large B-cell lymphoma</td>
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<td>Extramedullary marginal zone</td>
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<td>B-cell lymphoma</td>
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<td>SECONDARY TUMOUR</td>
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• 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 better preoperative counselling of patients regarding the nature of the tumor, the likely extent of resection, management of the facial nerve, and the likelihood 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:
  o Where bone destruction is suspected at skull base
  o Suspected involvement of the mandible
  o To assess neck nodes
• Indications of MRI:
  o MRI is better in soft tissue delineation and in delineating the interface between tumor and normal salivary gland
o For better imaging of the parapharyngeal space
o For evaluating perineural spread, e.g. in adenoid
cystic carcinomas
o Facial nerve status may be better appreciated in
the MRI scan

D. **USG GUIDED CORE NEEDLE BIOPSY:**
- Relatively new modality in diagnosis of salivary gland
  lesions
- More invasive: requires local anaesthesia. 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

**TREATMENT:**

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
  o It is the minimum standard surgical procedure.
  o 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:
  o Skin
  o Infra-temporal fossa
  o Mandible
  o TM joint
  o Petrous bone

B. **SUBMANDIBULAR GLAND:** *excision of the submandibular gland + supraomohyoid neck dissection.*

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

**E. ROLE OF FROZEN SECTION (FS):**
• FS on the operative specimen may be done for 3 purposes:
  o To clarify pre-operative diagnosis
  o To check surgical margins
  o To determine whether facial nerve or neck node involvement is present
• FS may be routinely used in cases with a presurgical malignant diagnosis to check margins and assess
nerve involvement, but its value is less certain when the presurgical diagnosis is benign or equivocal

- Recent meta-analysis showed that the overall accuracy of FS is clinically acceptable.

II. **ADJUVANT RADIOThERAPY:**

- 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

III. **RADICAL RT FOR UNRESECTABLE PRIMARY:**

- Role of definitive radical RT is restricted to unresectable tumors. This form of treatment is usually 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:
- Chemotherapy has role only in palliative setting in patients with recurrent unresectable disease or distant metastases.
- May have a palliative benefit for a small proportion of patients with recurrent/metastatic adenoid cystic carcinomas after due consideration of other therapies (palliative radiation, metastatectomy of solitary lesions)\(^\text{20}\)
- Recommendations: Single agent - Mitoxantrone and/or Vinorelbine Combination: Cisplatin + Anthracycline

V.  TARGETED THERAPY:
- Salivary gland tumors may have molecular targets like c-kit, EGFR and Her-2
- Hence, a number of molecular targeting agents have been tried in phase II studies
- However, none of these showed any benefit. Hence targeted therapy is NOT supported by evidence as of now in treatment of advanced, recurrent or metastatic salivary gland cancers.

PROGNOSIS
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 p27 expression: associated with shorter disease-free survival in adenoid cystic and mucoepidermoid carcinoma

**Suggested Reading**

1. **Surgery for major salivary gland cancer**
   

   Major salivary gland cancers are rare, with many histologic types and subtypes. The tumor stage at presentation will dictate the need for imaging, FNA, and facial nerve monitoring. Immunohistochemistry has enhanced diagnosis. In addition, precise attention to surgical landmarks and technique will reduce complications. Tumor stage, histologic type, tumor grade, surgical margin, facial nerve dysfunction, perineural involvement, extraparenchymal spread, and nodal metastasis are factors influencing the indication for neck dissection, postoperative radiation therapy, and survival rate.

2. **Salivary neoplasms: overview of a 35-year experience with 2,807 patients.**
   
   Spiro RH. Head and Neck Surgery 1986; 8 : 177-184

   We have reviewed a 35-year experience with 2,807 patients treated for salivary tumors which arose in the parotid gland (1,695 patients; 70%), submandibular gland
(235 patients; 8%), and seromucinous glands of the upper aerodigestive tract (607 patients; 22%). Pleomorphic adenomas comprised 45% of the total, most of which occurred in the parotid gland. The clinical findings and the distribution of patients according to the histology and the site of origin are summarized. Treatment was surgical and the resection was conservative when possible, depending upon the extent of the tumor. The impact of site, histology, grade, and tumor stage on the results is shown.

3. The role of radiotherapy in the treatment of malignant salivary gland tumors.


Purpose: We analyzed the role of primary and postoperative low linear energy transfer radiotherapy in 538 patients treated for salivary gland cancer in centers of the Dutch Head and Neck Oncology Cooperative Group, in search for Prognostic Factors And Dose Response.

Methods and Materials: The tumor was located in the parotid gland in 59%, submandibular gland in 14%, oral cavity in 23%, and elsewhere in 5%. In 386 of 498 patients surgery was combined with radiotherapy, with a median dose of 62 Gy. Median delay between surgery and radiotherapy was 6 weeks. In the postoperative radiotherapy group, adverse prognostic factors prevailed. Elective radiotherapy to the neck was given in 40%, with a median dose of 50 Gy. Primary radiotherapy (n = 40) was given for unresectable disease or M(1), with a dose range of 28-74 Gy.
Results: Postoperative radiotherapy improved 10-year local control significantly compared with surgery alone in T(3-4) tumors (84% vs. 18%), in patients with close (95% vs. 55%) and incomplete resection (82% vs. 44%), in bone invasion (86% vs. 54%), and perineural invasion (88% vs. 60%). Local control was not correlated with interval between surgery and radiotherapy. No dose-response relationship was shown. Postoperative radiotherapy significantly improved regional control in the pN(+) neck (86% vs. 62% for surgery alone). A rating scale for different sites, T stage, and histologic type may be applied to calculate the risk of disease in the neck at presentation, and so indicate the need for elective neck treatment. A marginal dose-response was seen, in favor of a dose $\geq$46 Gy. A clear dose-response relationship was shown for patients treated with primary radiotherapy. Five-year local control was 50% with a dose of 66-70 Gy.

Conclusions: Postoperative radiotherapy with a dose of at least 60 Gy is indicated for patients with T(3-4) tumors, incomplete or close resection, bone invasion, perineural invasion, and pN(+). In unresectable tumors, a dose of at least 66 Gy is advisable.

4. Randomized clinical trial comparing partial parotidectomy versus superficial or total parotidectomy.

Roh JL, Kim HS, Park CI.


Background: In recent decades the treatment of benign parotid tumours has shifted from superficial or total parotidectomy to partial parotidectomy. This study examined whether current surgical techniques improved
functional outcomes after surgery for benign parotid tumours.

**Methods:** One hundred and one patients were assigned randomly to conventional (49 patients) or function-preserving (52) surgery. The latter consisted of modified facelift incision, greater auricular nerve preservation, partial parotidectomy and coverage with parotid fascia.

**Results:** The mean duration of operation was 0.7 h shorter and the overall complication rate significantly lower in the functional surgery group. In this group, more patients were satisfied with their scars and facial contours, the auricular nerve sensory recovery rate was high, and transient facial paralysis and Frey’s syndrome were infrequent (12 and 6 per cent respectively). Stimulated salivary flow on the operated side decreased to 71.9 per cent after function-preserving surgery compared with 20.7 per cent after conventional operation. There was no tumour recurrence in either group during a mean follow-up of 48 months.

**Conclusion:** Compared with conventional procedures, function-preserving surgery for benign parotid tumours improved cosmetic, sensory and salivary functions, and reduced the duration of surgery and operative morbidity.

5. **Prognostic factors and outcome analysis of submandibular gland cancer: a clinical audit.**

*Mallik S, Agarwal J, Gupta T, Kane S, Laskar SG, Budrukkar A, Murthy V, Goel V, Jain S*

J Oral Maxillofac Surg. 2010 Sep;68(9):2104-10

To retrospectively review a long-term, single-institution experience of subjects with submandibular gland malignancies treated with definitive locoregional therapy.
with an aim to identify clinicopathologic variables that correlate with outcomes.

**Materials and Methods:** A comprehensive chart review of 47 patients presenting to the institute from 1993 to 2005 with a histologic diagnosis of submandibular salivary gland cancer was performed to extract demographic data, clinicopathological characteristics, and treatment details. Clinical and pathologic factors were correlated with locoregional control, distant metastases free survival, and disease-free survival using log-rank test and Cox proportional hazards model for univariate and multivariate analysis, respectively.

**Results:** With a median follow-up of 29 months (interquartile range, 13 to 64 months), the actuarial 5-year locoregional control, distant metastasis-free survival, and disease-free survivals of the entire cohort were 80.5%, 86.1%, and 71.8%, respectively. Overall stage grouping \((P = .008)\), perineural invasion \((P = .04)\), and radiotherapy dose \((P = .033)\) were significant predictors of locoregional control. Overall stage grouping \((P = .014)\) and \(T\) stage \((P = .05)\) also affected disease-free survival. Extraglandular involvement showed a trend toward poorer outcome.

**Conclusions:** Submandibular gland cancer is a rare disease with histologic diversity and variable clinical behavior. Overall stage grouping and perineural invasion remain the most significant predictors of outcome. Adequate doses of adjuvant radiotherapy improve locoregional control in high-risk patients.

6. **Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC**
To compare the efficacy of fast neutron radiotherapy versus conventional photon and/or electron radiotherapy for unresectable, malignant salivary gland tumors a randomized clinical trial comparing was sponsored by the Radiation Therapy Oncology Group in the United States and the Medical Research Council in Great Britain.

**Materials and Methods:** Eligibility criteria included either inoperable primary or recurrent major or minor salivary gland tumors. Patients were stratified by surgical status (primary vs. recurrent), tumor size (less than or greater than 5 cm), and histology (squamous or malignant mixed versus other). After a total of 32 patients were entered onto this study, it appeared that the group receiving fast neutron radiotherapy had a significantly improved local/regional control rate and also a borderline improvement in survival and the study was stopped earlier than planned for ethical reasons. Twenty-five patients were study-eligible and analyzable.

**Results:** Ten-year follow-up data for this study is presented. On an actuarial basis, there continues to be a statistically-significant \( p = 0.009 \) but there is no improvement in overall survival (15% vs. 25%, \( p = \text{n.s.} \)). Patterns of failure are analyzed and it is shown that distant metastases account for the majority of failures on the neutron arm and local/regional failures account for the majority of...
failures on the photon arm. Long-term, treatment-related morbidity is analyzed and while the incidence of morbidity graded “severe” was greater on the neutron arm, there was no significant difference in “life-threatening” complications. This work is placed in the context of other series of malignant salivary gland tumors treated with definitive radiotherapy.

**Conclusions:** Fast neutron radiotherapy appears to be the treatment-of-choice for patients with inoperable primary of recurrent malignant salivary gland tumors.
Thyroid Gland

1) Thyroid disorders are of common occurrence globally.
2) The majority of them are benign (95%).
3) Thyroid cancers have an excellent prognosis if detected early and treated appropriately.
4) Surgery followed by Radiiodine (RI) treatment when indicated, is the mainstay of treatment for these cancers.
5) External beam radiotherapy (EBRT) and chemotherapy have practically no role in treatment and are indicated only in select situations.
6) Thyroid cancers form 90% of all endocrine malignancies.

SOLITARY THYROID NODULE (STN)

- Most common presentation of thyroid enlargement (50%)
- Occurs in 4-8% of general population
- Low incidence of malignancy (1 in 1000), however may be as high as 5-15% in nodules presenting at referral centers
• Challenges of treatment are to identify these malignant lesions

**Investigations**

• **FNAC**
  - Investigation of choice
    - Cost effective
    - High accuracy (> 90 %)
    - Low false positive and false negative rates (<2%)

• **Ultrasound Neck**
  - To distinguish a true solitary from a multinodular goitre.
  - To differentiate between cystic and solid nodules
  - To target FNAC in cystic nodule with solid components or in small nodules that are not palpable
  - For objective assessment of nodule size and in follow up in those not offered surgery
  - To help identify malignant nodules based on characteristic features (Ref.incidentalomas below)

• **Thyroid function tests (T3, T4, TSH)**
  - Higher serum TSH is associated with increased risk of malignancy in a thyroid nodule

• **No role for Serum Tg in the initial evaluation of thyroid nodule**
Workup of thyroid nodule detected by palpation or imaging
Risk criteria for malignancy in STN

- Size > 4cm
- Extremes of age (<15yr or >45yr)
- Males
- Recent onset
- Rapid growth
- Prior history of radio therapy
- Family history of thyroid cancer
- Associated features s/o malignancy (neck nodes, adjacent structure involvement, cord fixity)

Role of FNAC

- Sensitivity 80-93.5%, specificity- 56-94%
- Conventional Papillary carcinoma of thyroid diagnosed on FNAC preoperatively in almost 90% of cases.
- The diagnosis of Differentiated follicular & hurthle cell carcinoma is largely dependent on demonstration of true capsular &/or vascular invasion on histological examination. The diagnosis of the lesions labeled as “Follicular neoplasm” on FNAC are likely to differ on final histopathologic examination

Non-diagnostic cytology:
  - Repeat the FNAC with ultrasound guidance

Indeterminate cytology in FNAC (follicular or follicular lesion of undetermined significance, atypia)
Risk of malignancy is higher with the following features

- Male sex
- Nodule size > 4cm
- Older age group
- Presence of atypia
- Use of molecular markers (e.g. BRAF, RAS, RET/PTC, Pax8-PPARα, or galectin-3) improves diagnostic accuracy.

If the report is suspicious for papillary carcinoma or Hürthle cell neoplasm, either lobectomy or total thyroidectomy is recommended, depending on the lesion’s size and other risks.

**Thyroid Incidentalomas**

- Incidental thyroid nodules are increasingly picked up due to routine use of FDG-PET for other diagnostic purposes.
- Risk of malignancy in 18 FDG –PET positive (discrete) nodules is about 33%.
- *Diffuse* 18FDG uptake is likely related to underlying autoimmune thyroiditis.

**Thyroid Cancers**
Classification of common thyroid cancers

---

**TNM STAGING (AJCC -2010)**

**Primary tumor (T)**
[Note: All categories may be subdivided into (s) solitary tumor or (m) multifocal tumor (the largest determines the classification).]

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor 2 cm or less in greatest dimension, limited to the thyroid
T1a: Tumor 1 cm or less, limited to the thyroid
T1b: Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3: Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroidal extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a: Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b: Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

All anaplastic carcinomas are considered T4 tumors.
T4a: Intrathyroidal anaplastic carcinoma
T4b: Extrathyroidal anaplastic carcinoma

**Regional lymph nodes (N)**

Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis
N1a: Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal / Delphian lymph nodes)
N1b: Metastasis to unilateral, bilateral cervical or contralateral cervical or retropharyngeal or superior mediastinal lymph nodes (level VII)
Distant metastases (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Stage grouping:
Differentiated Cancers (Papillary, follicular cancers)

Age below 45
- Only two stages
  - Stage I – No distant metastasis (M0)
  - Stage II – Distant Metastasis (M1)

Age 45 or above
- Stage I – T1N0M0
- Stage II – T2N0M0
- Stage III – T3N0M0
  - T1-3N1aM0
- Stage IVA – T4a N0M0
  - T1-4N1bM0
- Stage IVB – T4bN1M0
- Stage IVC – M1 disease

Medullary Carcinoma
All age groups
- Stage I – T1N0M0
- Stage II – T2N0M0
- Stage III – T3N0M0
  - T1-3N1aM0
Stage IVA – T4a N0-1a M0
T1-3 anyN Mo
Stage IVB – T4bN0M0
Stage IVC – anyT anyN M1 disease

Anaplastic Carcinoma
All anaplastic carcinomas are considered Stage IV

  Stage IVA – T4a Any N M0(
  Stage IVB – T4b Any N M0(
  Stage IVC – Any T Any N M1

DIFFERENTIATED THYROID CANCERS

PRE-OPERATIVE INVESTIGATIONS:

- Indirect laryngoscopy
- XRay neck- AP and lateral (in large goiter for airway assessment)
- XRay Chest
- USG neck for neck nodes and status of opposite lobe
- CT scan for assessing adjacent structures. (avoid iodinated contrast)
- Thyroid function tests when clinically indicated
- Serum thyroglobulin (Tg) – limited role with thyroid gland in situ.

RISK FACTORS AND STAGING SYSTEMS

There are a number of prognostic factors identified in the management of differentiated thyroid cancers. Most information on these prognostic indicators has been derived from large retrospective uncontrolled studies. Age, gender, tumour size, histologic grade, type, local invasion,
multicentricity and the presence of metastatic disease are found to be independent predictors of prognosis. Based on these, risk group schemes have been suggested to stratify patients into high or low risk groups. Some of the risk group staging systems has been contrasted in the Table below.

**Staging or scoring system**

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EORTC- European Organisation for Research and Treatment of Cancer  
AGES- Age, Grade of tumour, Extent of tumour (ETS or distant metastasis), Tumour Size  
AMES- Age, Distant Metastasis, Extent of tumour, Tumour Size  
U of C- University of California  
MACIS- Metastasis, Patient Age, Completeness of resection, local Invasion and Tumour Size  
OSU- Ohio State University
AGES, MACIS – Only papillary Ca.
ETS and distant metastases in all
Ohio state University + TNM use nodal metastases

However, the three most widely quoted and used scoring systems are the AMES, AGES and MACIS. The details of these three systems have been summarised in the table below.

AGES prognostic score = 0.05 x age (if age > 40 yrs) +1 (if grade 2) +3 (if grade 3 or 4) +1 (if extrathyroid) +3 (if distant spread) +0.2 x tumour size (cm in max. diameter)

Survival by AGES score (20 yr) < 3.9 = 99%
4-4.99 = 80%
5-5.99 = 67%
> 6 = 13%

AMES Low risk: younger patients (men < 40, women < 50) With no metastases
Older patients (intrathyroid papillary, minor capsular invasion, for follicular lesions) Primary cancers < 5 cm No distant mets.
High risk: All patients with distant metastasis
Extrathyroid papillary, major
capsular invasion for follicular lesions
Primary cancers ≥ 5cm in older patients

Survival by AMES risk groups (20 yr)

Low risk = 99%
High risk = 61%

MACIS score =
3.1 (if age < 40 yrs) or
0.08 x age
(if age ≥ 40 yrs)
+ 0.3 X T size (cm max diameter)
+1 (if incompletely resected)
+1 (if locally invasive)
+3 (if distant spread)
Survival by MACIS score (20 yrs)
<6 = 99%
6-6.99 = 89%
7-7.99 = 56%
> 8 + 24%
Extent of Surgery:
Surgery remains the mainstay of treatment of DTC. However, the extent of surgery (Hemi or total thyroidectomy) has been a matter of considerable debate.

Arguments in favour of total thyroidectomy:
1) 5-10% recurrence rate in the opposite lobe following lobectomy alone.
2) > 10% incidence of distant metastases with conservative surgery
3) An increased rate of local/regional recurrence (14 and 19% for lobectomy vs. 2% and 6% for total thyroidectomy)
4) The inability to use $^{131}$I therapy and thyroglobulin for follow up
5) Risk of de-differentiation (anaplastic transformation)

Arguments favouring Hemi-Thyroidectomy:
1) Differentiated thyroid cancer is an indolent disease and in a majority of patients has a very low recurrence and mortality rate.
2) Permanent hypoparathyroidism and recurrent laryngeal nerve injury (incidence- 0-25%) are potential complications of total thyroidectomy.

These may be unacceptable especially in patients with good long-term survival.

Recommendation
Hemithyroidectomy in
- All differentiated cancers < 1.0 cm in size without extrathyroidal extension (ETS)
• No distant metastasis

Total thyroidectomy in

Total thyroidectomy is recommended for
• All high-risk patients (using staging systems)
• Nodule >4cm
• Age < 15 years or >45 years
• Radiation history
• Known distant metastases
• Clinically involved cervical nodal metastases
• Unfavorable histology- Tall cell variant, columnar cell, diffuse-sclerosing, poorly differentiated
• Patient has first-degree family history of DTC

Controversy for nodules between sizes 1.0 – 4cm. However, majority of surgeons, endocrinologists and most guidelines are in favour of a total thyroidectomy. Total thyroidectomy significantly improved recurrence and survival rates for tumors > 1.0 cm. Referral to a thyroid surgeon with low complication rates should be considered whenever feasible.

**Lymph Nodes in Differentiated thyroid cancers (DTC)**

**Incidence of lymph node metastasis**
• Papillary cancer- 50%
• Follicular cancer- 10%
• Hurthle cell variant- 25%
Surgical Management
No role for ‘Berry picking’

Sample nodes in central compartment and Levels II-IV

Central-compartment (level VI) should be dissected in patients with clinically involved level VI lymph nodes. If lateral compartments (Level II – IV) are involved, dissect those levels.

Prophylactic level VI dissection
While balancing the risk and benefits for patients undergoing surgery in specialized centers, those with large papillary thyroid cancers (PTC) (T3/T4) may benefit from prophylactic central compartment dissection. However, for small (T1 or T2) noninvasive, clinically node-negative PTCs and for most follicular cancers, a total thyroidectomy may be sufficient. For less experienced surgeons, a close intraoperative inspection of the central compartment (and sampling) with compartmental dissection only in the presence of obviously involved lymph nodes will be safer

In node positive cases
• Central compartment (Level VI) clearance
• Lateral neck dissection (levels II-V), sparing the IJV, SCM and SA nerve. A radical neck dissection is rarely required.

Prognostic implications of nodal metastases in thyroid cancer.
In younger patients, it has no influence on long term overall survival. However bulky metastases have a higher incidence of distant metastasis and regional recurrence post treatment.
In older patients, presence of large lymph nodes is a poor prognostic marker.

**Postoperative radioiodine remnant ablation**

**Goals:**
- Remnant ablation
  - Facilitate early detection of recurrent disease by thyroglobulin measurement or by whole body scan by RAI.
  - To increase specificity of I-131 scanning for detection of recurrence or metastasis.
- Adjuvant therapy
  Ablation of persistent thyroid cancer cells remaining after appropriate surgery
- RAI therapy
  For treatment of known persistent disease (residual/recurrent/metastatic disease)

**Postoperative RAI adjuvant therapy is recommended for all patients with**
1) Known distant metastases,
2) Gross extra thyroidal extension of the tumor
3) Primary tumor size >4 cm even in the absence of other high risk features.
4) If tumor size is 1-4cm, a combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence.
   a. High risk histology include
      i. Tall cell
ii. Columnar
iii. Insular
iv. Solid
v. Poorly differentiated thyroid cancers
vi. Presence of intra-thyroidal vascular invasion
vii. Gross or microscopic multifocal disease

5) Follicular thyroid cancer with vascular invasion
6) Hürthle cell cancer

**Radioiodine therapy for distant metastasis**
- Mainstay of treatment to control distant metastasis for more than 50 years
- Lungs, spine, and appendicular bone: most common distant metastatic sites
- Bone metastasis generally resistant to radioiodine (May be related to the mass of bone metastasis at presentation)

**Preparation for RAI ablation**
Aim for a TSH level more than 30mU/L. This can be achieved by any of the following
- Discontinue LT4 & LT3 for 3-4 weeks.
- Stopping LT4 and switching to LT3 for 2-4 weeks followed by complete withdrawal of LT3 for 2 weeks.
- Recombinant human TSH (rhTSH).

Use of recombinant human TSH (rhTSH) is equally effective as thyroid hormone withdrawal in preparing patients for $^{131}$I remnant ablation with significantly improved quality of life.
Primarily to demonstrate $I^{131}$ uptake in the remnant tissue prior to RIA.
Pitfalls of not performing diagnostic scans:

1. Undertreating undetected disease
2. May lead to therapy in patients without significant remnant or with iodide interference.

RMC/TMH protocol – 100ìCi to prevent thyroid stunning

For dosage and regime – see later.

**Method of administration of RI**

1. Empiric dose: 100-300 mCi empiric dose
2. Dosimetry: Dose tailored according to dosimetric studies

-Whole body blood dosimetry is best reserved for therapy of widely metastatic thyroid carcinoma that exhibits radioiodine avidity.

No evidence to establish the superiority of one regime over the other. Majority protocols in favour of Empiric dose type.

**RI fixed dose protocol**

(TMH/RMC protocol)

**Papillary carcinoma**
- Only residual thyroid ablation 30-50 mCi
- No ET spread
- No capsular invasion
- ETS and or nodal metastasis 150 mCi
- Aggressive histology 150 mCi

**Follicular carcinoma**
- Only residual thyroid ablation 200 mCi
- Vascular invasion 200-250 mCi
With distant metastasis

- Skeletal metastasis 250 mCi
- Pulmonary metastasis 150-200 mCi

1) If uptakes high, then dose of I131 to be decreased
2) Total permissible cumulative dose of I131 is 1 curie
3) 5-10% thyroid cancers do not concentrate RI

STRATEGIES TO ENHANCE UPTAKE OF RADIOIODINE

1) Low iodine diet for radioiodine therapy of metastatic disease
2) Lithium (10 mg/kg/day for 7 days. To keep S. Lithium levels at 0.8-1.2 mmol/L)
3) Retinoic acid (1.2 mg/kg/day)
4) Other agents
   Histone deacetylase inhibitors
   Demethylating agents

RECOMBINANT THYROTROPIN (rTSH) VS. THYROID HORMONE WITHDRAWL (THW) FOR MONITORING & TREATMENT.

- rTSH – Approved for use in diagnostic testing by US FDA
- Sensitivity & specificity of diagnostic testing using rTSH is comparable to thyroid hormone withdrawal.
- No significant difference between Positive Predictive value and Negative predictive value.
Indications
- Alternative to thyroid hormone withdrawal to circumvent problems due to hypothyroidism (pulmonary and cardiac disease)
- Patients unable or unwilling for withdrawal
- In patients with demonstrated inability to generate endogenous TSH secretion due to hypothalamic or pituitary disease.
- to improve sensitivity of thyroglobulin during follow up
- in cases of life or limb threatening metastasis (spine, mediastnum, brain)

rTSH administration protocol
- rTSH 0.9 mg IM on 2 consecutive days
- Dosimetry on the 3rd day
- Whole body scan and Rx on 5th day

ROLE OF POST OPERATIVE EBRT:

Indications
- High grade tumours that do not concentrate radiiodine
- T4 tumours
- Evidence of gross residual disease (especially if not concentrating radiiodine).
- Palliation of locally advanced, inoperable tumours
- Palliation of metastatic disease in the bone, brain, spine

Currently, recommended doses are 50-60 Gy in 25-30 fractions over 5-6 weeks
Radiotherapy techniques and volumes

- A clinical target volume from hyoid to suprasternal notch is determined
- Technique using two anterolateral oblique wedged fields is used
- Phase I- The initial volume includes regional lymph nodes from mastoid tip to the carina including the thyroid bed. The Phase I volume may consist of parallel opposing antero-posterior/posterior-anterior fields to 40-46 Gy.
- Phase II- The volume should include the tissues considered at highest risk to a total dose of 14 Gy (cumulative total dose of 60Gy)

TSH Suppression therapy

Thyroxine therapy is required as replacement post total thyroidectomy. TSH suppression is beneficial for differentiated thyroid cancers (DTC)\textsuperscript{4}. For high-risk patients, an initial TSH suppression to below 0.1mU/L is recommended. Maintenance in the range of 0.1 – 0.5 mU/L is recommended for low risk patients. However, long-term thyroxine therapy can result in premature osteoporosis and cardiac related problems.

- Rise in TSH levels should not be permitted
- Maintain TSH levels just below normal in low risk patients
- Higher degree of suppression is recommended in high-risk patients.

Serum thyroglobulin (Tg)

- Highly specific marker for follow-up of DTC
- Not used for screening as it can be raised in thyrotoxicosis, thyroiditis, Iodine deficiency, benign thyroid adenomas and cancer
- Should be measured every 6-12 months in the same laboratory and using the same assay post surgery.

**Implications of Tg measurement post total thyroidectomy**

<table>
<thead>
<tr>
<th>Tg levels</th>
<th>TSH</th>
<th>Implication</th>
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<tbody>
<tr>
<td>Undetected</td>
<td>High</td>
<td>No residual thyroid/metastases</td>
</tr>
<tr>
<td>Raised</td>
<td>Low</td>
<td>Residual abnormal thyroid (goitrous/cancer)</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Does not exclude metastatic disease</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Highly s/o disease</td>
</tr>
<tr>
<td>&gt;10 ng/ml or rising Tg</td>
<td>Investigate for disease</td>
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</tbody>
</table>

Presence of anti-Tg antibodies (25% of cancer patients) can falsely lower serum Tg estimation, and therefore quantitative assessment of thyroglobulin antibodies should be performed with every measurement of serum Tg.

**Raised thyroglobulin in an asymptomatic patient**

**Paediatric thyroid cancers**
- Biological behavior differs from adult patients
- Nodules in children- > 50% chance of malignancy
- Advanced stage at presentation- higher incidence of lymph nodes and pulmonary metastases
- Has excellent prognosis.
– Total thyroidectomy with appropriate neck dissection recommended

– Pulmonary metastases not apparent on X-ray chest. Manifests on RAIU scan

**MANAGEMENT OF LOCOREGIONAL RECURRENCE IN DIFFERENTIATED THYROID CANCERS**

When technically feasible, surgery is recommended in combination with RAI and or external beam radiotherapy. For persistent or recurrent disease confined to the neck, a therapeutic compartmental lateral and or central neck dissection sparing uninvolved vital structures should be performed. For compartments that have been previously explored, only a more limited or targeted lymph-node resection may be possible. Outcome is related to complete resection of all gross disease.

**DTC carcinoma found post lobectomy for benign disease**

In case of papillary carcinoma – a completion thyroidectomy should be considered if any of the following:

- Tumor >1.5 cm
- Positive margins
- Gross extra-thyroidal extension
- Macroscopic multifocal disease
- Confirmed nodal metastasis
- Aggressive variant (Tall cell variant, columnar cell, or poorly differentiated features.)
Observation if any of the following:

- Tumor < 1.5 cm and margins free
- No suspicious lymph nodes
- No contralateral disease

Consider levothyroxine therapy to keep TSH low.

**MANAGEMENT OF METASTATIC DISEASE IN DIFFERENTIATED THYROID CANCERS**

- Central Nervous system
- If solitary- surgery if feasible
- If multiple- RI scan (with rTSH) and subsequent treatment.
- If no RI uptake- to treat with EBRT
- Skeletal metastasis
- RI uptake and treatment
- If no uptake to treat with EBRT
- Surgical palliation in the form of fixation for metastasis in the weight bearing areas and decompression of spine.
- Other extracervical sites
- RI scan, if uptake then treat
EBRT if feasible
Chemotherapy if non-iodine concentrating (usually in a trial setting) Consider surgical excision for solitary, enlarging masses or symptomatic disease.

PROGNOSIS OF DIFFERENTIATED THYROID CANCER
Low risk groups - recurrence rate 2%
   Mortality 0.1%
High risk groups - recurrence rate 40%
   Mortality 45%

Suggested Reading

OBJECTIVE: To assess the diagnostic accuracy of fine-needle aspiration (FNA) and frozen section (FS) in nodular thyroid disease.

SETTING: Tertiary care academic medical center.

STUDY DESIGN: Retrospective review of 139 consecutive patients undergoing surgery for nodular thyroid disease. FNA and FS sensitivity, specificity, and accuracy were calculated with respect to permanent section histology.

RESULTS: Among 63 patients with an FNA interpreted as either benign (n = 38) or malignant (n = 25), FNA was accurate (sensitivity 89%, specificity 97%, accuracy 94%). FS identified only one case of carcinoma missed by FNA. Among 76 patients with a “suspicious” FNA, FS was
reasonably accurate (sensitivity 67%, specificity 100%, accuracy 89%), but was deferred in 50% of cases. CONCLUSION: Given high FNA accuracy, more selective use of FS is suggested.

SIGNIFICANCE: The study results will assist with intra-institutional patient counseling and intraoperative decision-making with respect to FNA and FS results in patients with nodular thyroid disease. To conclude, Intraoperative FS consultation is of great diagnostic value in cases of non-follicular carcinoma and in cases of indeterminate FNAC including “suspicious” FNAC. A confident diagnosis rendered on FS assists surgeon in making therapeutic decision. However its utility is limited, when it comes to the interpretation of encapsulated follicular neoplasms including hurthle cell neoplasms because of high deferral rates, numerous false negatives and occasional false positive cases. A pathologist should be aware of the entire spectrum of thyroid neoplasia & their mimics to be able to render accurate & quick diagnosis on FS. Only the one who understands fully the scope & limitations of FS, can play a vital role in the intraoperative management of thyroid Neoplasia.


BACKGROUND: Thyroid cancer ranges from well-differentiated lesions with an excellent prognosis to anaplastic carcinoma, which is almost uniformly fatal. Thus, methods to assess the behavior of thyroid malignancies are necessary to arrive at appropriate treatment decisions.
METHODS: We discuss the factors that affect the prognosis of patients with well-differentiated thyroid malignancies, including papillary, follicular, Hurthle cell, and medullary thyroid carcinomas. We also review the presentation, therapy, and outcome of patients seen at our center over a span of 50 years. These data have identified those prognostic factors that are predictive of survival and recurrence in differentiated thyroid cancer. RESULTS: Several classifications with different variables have been developed to define risk-group categories. Three widely used systems, in addition to the TNM staging system, include AGES, AMES, and MACIS.

CONCLUSIONS: A better understanding of independently important prognostic variables will result in improved patient care and treatment.


OBJECTIVES/HYPOTHESIS: The outcome in differentiated thyroid cancer generally depends on the stage of the disease at the time of presentation; prognostic factors such as age, grade, size, extension, or distant metastasis; and risk groups (eg, low or high risk). The author has reviewed a large number of patients with differentiated thyroid cancer to analyze their hypothesis and to confirm that various risk groups have a major implication in relation to extent of the treatment and outcome. Differentiated thyroid cancers make up 90% of all thyroid tumors. The prognostic factors are well defined, such as age, size of the tumor, extrathyroidal extension, presence of distant
metastasis, histological appearance, and grade of the tumor. The author has previously divided the risk groups into low-, intermediate-, and high-risk categories based on prognostic factors. The study describes the author’s treatment approach related to the extent of thyroidectomy and adjuvant therapy based on various risk groups and the long-term survival.

**STUDY DESIGN:** Retrospective.

**METHODS:** In a retrospective review of 1038 patients with differentiated thyroid carcinoma, various prognostic factors were studied by univariate and multivariate analysis. The significant prognostic factors were studied in detail and, based on these prognostic factors, the patients were divided into low-, intermediate- and high-risk groups. The survival curves were plotted by Kaplan-Meier method.

**RESULTS:** The long-term survivals in low-, intermediate- and high-risk groups were 99%, 87%, and 57% respectively. Based on these risk groups, a decision tree was made regarding extent of thyroidectomy and adjuvant treatment. In the high-risk group and selected patients in the intermediate-risk group, aggressive surgery including removal of all gross disease and extrathyroidal extension with postoperative radioactive iodine ablation is recommended. In the low-risk group and selected patients in the intermediate-risk group, lobectomy appears to be satisfactory with excellent long-term outcome. The surgical treatment offers the best long-term results in low-risk patients, and the role of adjuvant treatment in this group is questionable.
CONCLUSION: The decisions in the management of well-differentiated thyroid cancer should be based on various prognostic factors and risk groups. The long-term survival in the low-risk group is excellent, and consideration should be given to conservative surgical resection depending on the extent of the disease. In the high-risk group and selected patients in the intermediate-risk group, total thyroidectomy with radioactive ablation is warranted. A consideration may be given to external-beam radiation therapy in selected high-risk patients. It is apparent, based on the author’s clinical experience and critical retrospective analysis, that the author’s hypothesis that risk groups are extremely important in the long-term outcome of patients with differentiated thyroid cancer is correct. Based on various risk groups, the author currently is able to guide the treatment policies for thyroid cancer.


Abstract

BACKGROUND: The extent of surgery for papillary thyroid cancers (PTC) remains controversial. Consensus guidelines have recommended total thyroidectomy for PTC > or =1 cm; however, no study has supported this recommendation based on a survival advantage. The objective of this study was to examine whether the extent of surgery affects outcomes for PTC and to determine whether a size threshold could be identified above which total thyroidectomy is associated with improved outcomes.
METHODS: From the National Cancer Data Base (1985-1998), 52,173 patients underwent surgery for PTC. Survival was estimated by the Kaplan-Meier method and compared using log-rank tests. Cox Proportional Hazards modeling stratified by tumor size was used to assess the impact of surgical extent on outcomes and to identify a tumor size threshold above which total thyroidectomy is associated with an improvement in recurrence and long-term survival rates.

RESULTS: Of the 52,173 patients, 43,227 (82.9%) underwent total thyroidectomy, and 8946 (17.1%) underwent lobectomy. For PTC <1 cm extent of surgery did not impact recurrence or survival (P = 0.24, P = 0.83). For tumors > or =1 cm, lobectomy resulted in higher risk of recurrence and death (P = 0.04, P = 0.009). To minimize the influence of larger tumors, 1 to 2 cm lesions were examined separately: lobectomy again resulted in a higher risk of recurrence and death (P = 0.04, P = 0.04).

CONCLUSIONS: The results of this study demonstrate that total thyroidectomy results in lower recurrence rates and improved survival for PTC > or =1.0 cm compared with lobectomy. This is the first study to demonstrate that total thyroidectomy for PTC > or =1.0 cm improves outcomes.


PURPOSE: To determine the long-term impact of medical and surgical treatment of well differentiated papillary and follicular thyroid cancer.
METHODS: Patients with papillary and follicular cancer (n = 1,355) treated either in U.S. Air Force or Ohio State University hospitals over the past 40 years were prospectively followed by questionnaire or personal examination to determine treatment outcomes. Outcomes were analyzed by Kaplan-Meier survival curves and Cox proportional-hazard regression model.

RESULTS: Median follow-up was 15.7 years; 42% (568) of the patients were followed for 20 years and 14% (185) for 30 years. After 30 years, the survival rate was 76%, the recurrence rate was 30%, and the cancer death rate was 8%. Recurrences were most frequent at the extremes of age (< 20 and > 59 years). Cancer mortality rates were lowest in patients younger than 40 years and increased with each subsequent decade of life. In a Cox regression model that excluded patients who presented with distant metastases, the likelihood of cancer death was (1) increased by age > or = 40 years, tumor size > or = 1.5 cm, local tumor invasion, regional lymph-node metastases, and delay in therapy > or = 12 months; (2) reduced by female sex, surgery more extensive than lobectomy, and 131I plus thyroid hormone therapy; and (3) unaffected by tumor histologic type. Following 131I therapy given only to ablate normal thyroid gland remnants, the recurrence rate was less than one third the rate after thyroid hormone therapy alone (P < 0.001). No patient treated in this way with 131I died of thyroid cancer. Following 131I therapy, whether given for thyroid remnant ablation or cancer therapy, recurrence and the likelihood of cancer death were reduced by at least half, despite the existence of more adverse prognostic factors in patients given 131I. At
30 years, the cumulative cancer mortality rate following 131I therapy, regardless of the reason for its use, was one third that in patients not so treated (P = 0.03).

CONCLUSION: Over the long term, for tumors > or = 1.5 cm that are not initially metastatic to distant sites, near-total thyroidectomy followed by 131I plus thyroid hormone therapy confers a distinct outcome advantage. This therapy reduces tumor recurrence and mortality sufficiently to offset the augmented risks incurred by delayed therapy, age > or = 40 at the time of diagnosis, and tumors that are much larger than 1.5 cm, multicentric, locally invasive, or regionally metastatic.


**Abstract**

A total of 195 patients had surgery for papillary thyroid cancer. The mean age at operation was 50 years. A microdissection technique was used for total thyroidectomy and lymph node clearance. Postoperative radioiodine tests showed no uptake or an uptake close to the background activity in 77% of the examined patients. By counting the lymph nodes removed at surgery we were able to check on the quality of the lymph node dissection. Men had a higher incidence (70%) of lymph node metastases than women (45%). Only 4% of the patients had radioiodine ablation of the thyroid remnant. The median follow-up time was 13 years. None of the patients below 45 years of age at surgery died of thyroid cancer. In the older age group eight patients died of thyroid cancer at a mean age of 75 years. Five of those who died of a
thyroid carcinoma had distant metastases at diagnosis. Among patients with resectable disease, three (1.6%) died of thyroid cancer, all of whom had lived for more than 17 years after surgery. Hence longer follow-up is needed before we know the final mortality in our series. The results suggest that surgical technique and strategy can positively influence the survival of patients with papillary thyroid cancer.


**Abstract**

Though survival for well-differentiated thyroid cancer is very good, specific populations suffer greater recurrence and mortality. Defining these cohorts can significantly influence prognosis and extent of treatment. This study, using a large, multi-institutional database, seeks to determine how the presence of lymph node disease in patients with well-differentiated thyroid cancer affects outcome. The Surveillance, Epidemiology, and End Results (SEER) database is a large-scale sample of 14 per cent of the U.S. population. It was used to identify patients with papillary and follicular thyroid carcinomas and identify the prognostic implications of lymph node metastasis. Additional factors, including presence of metastasis, age, and tumor size, were compared using multivariate and chi2 analyses. Of 19,918 patients identified, lymph node status was known for 9,904 (49.7%). On multivariate analysis, age > 45 years, presence of distant metastasis, large tumor size, and lymph node involvement significantly predicted
poor outcome. Overall survival at 14 years was 82 per cent for node negative and 79 per cent for node positive patients (P < 0.05). This study shows that the survival of patients with well-differentiated thyroid cancer is adversely affected by lymph node metastases. The optimum treatment for this cohort needs further delineation, as particular populations are at greater risk of recurrence and death.


BACKGROUND: Long-term thyroid hormone (TH) therapy aiming at the suppression of serum thyrotropin (TSH) has been traditionally used in the management of well differentiated thyroid cancer (ThyrCa). However, formal validation of the effects of thyroid hormone suppression therapy (THST) through randomized controlled trials is lacking. Additionally, the role - if any - of TSH effect at low ambient concentrations upon human thyroid tumorigenesis remains unclear. AIM: Evaluation of the effect of THST on the clinical outcomes of papillary and/or follicular ThyrCa.

METHODS: By using a quantitative research synthesis approach in a cumulative ThyrCa cohort, we evaluated the effect of THST on the likelihood of major adverse clinical events (disease progression/recurrence and death). A total of 28 clinical trials published during the period 1934-2001 were identified; only 10 were amenable to meta-analysis. Causality was assessed by Hill criteria.
**RESULTS:** Out of 4,174 patients with ThyrCa, 2,880 (69%) were reported as being on THST. Meta-analysis showed that the group of patients who received THST had a decreased risk of major adverse clinical events (RR = 0.73; CI = 0.60-0.88; P < 0.05). Further, by applying a Likert scale, 15/17 interpretable studies showed either a ‘likely’ or ‘questionable’ beneficial effect of THST. Assessment of causality between TSHT and reduction of major adverse clinical events suggested a probable association.

**CONCLUSIONS:** THST appears justified in ThyrCa patients following initial therapy. As most primary studies were imperfect, future research will better define the effect of THST upon ThyrCa clinical outcomes.


**Abstract :**
The use of radioactive iodine ((131)I) for the treatment of thyroid carcinoma has changed over the past 50 y. These changes are based on increasing awareness of the biophysical properties of (131)I and new discoveries concerning the biology of iodine handling by thyroid cells. The therapeutic administration of (131)I for thyroid remnant ablation and for metastases requires an appreciation of iodine clearance kinetics, of factors that can alter the occupancy time of (131)I within lesions, and of the role of thyroid-stimulating hormone in stimulating the sodium-iodide symporter.
The potential complications and adverse events associated with (131)I are discussed. (131)I will continue to be a major weapon in the fight against metastatic thyroid carcinoma. Its future role will be modified by expanding knowledge of its relative risks and benefits.


Abstract:
Radioactive iodine remnant ablation destroys residual thyroid tissue after surgical resection of papillary or follicular thyroid cancer. We systematically reviewed 1543 English references to determine whether remnant ablation decreases the risk of thyroid cancer-related death or recurrence after bilateral thyroideciomy for papillary or follicular thyroid cancer. In 13 cohort studies in which the analysis of thyroid cancer-related outcomes was statistically adjusted to a variable degree for prognostic factors or cointerventions, rates of recurrences of thyroid cancer-related outcomes were significantly decreased in the following: one of seven studies examining thyroid cancer-related mortality, three of six studies examining any tumor recurrence, three of three studies examining locoregional recurrence, and two of three studies examining distant metastases. Thyroid hormone suppressive therapy was not adjusted for in the majority of these analyses. In 18 cohort studies not adjusted for prognostic factors or interventions, the benefit off
radioactive iodine ablation in decreasing the thyroid cancer-related mortality and any recurrence at 10 yr was inconsistent among centers. However, pooled analyses were suggestive of a statistically significant treatment effect of ablation for the following 10-yr outcomes: locoregional recurrence (relative risk of 0.31, 95% confidence interval, 0.2, 0.49) and distant metastases (absolute decrease in risk 3%, 95% confidence interval, risk decreases 1-4%). In conclusion, radioactive iodine ablation may be beneficial in decreasing recurrence of well-differentiated thyroid cancer; however, results are inconsistent among centers for some outcomes, and the incremental benefit of remnant ablation in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppressive therapy is unclear.


**BACKGROUND:**
To detect recurrent disease in patients who have had differentiated thyroid cancer, periodic withdrawal of thyroid hormone therapy may be required to raise serum thyrotropin concentrations to stimulate thyroid tissue so that radioiodine (iodine-131) scanning can be performed. However, withdrawal of thyroid hormone therapy causes hypothyroidism. Administration of recombinant human thyrotropin stimulates thyroid tissue without requiring the discontinuation of thyroid hormone therapy.
METHODS: One hundred twenty-seven patients with thyroid cancer underwent whole-body radioiodine scanning by two techniques: first after receiving two doses of thyrotropin while thyroid hormone therapy was continued, and second after the withdrawal of thyroid hormone therapy. The scans were evaluated by reviewers unaware of the conditions of scanning. The serum thyroglobulin concentrations and the prevalence of symptoms of hypothyroidism and mood disorders were also determined.

RESULTS: Sixty-two of the 127 patients had positive whole-body radioiodine scans by one or both techniques. The scans obtained after stimulation with thyrotropin were equivalent to the scans obtained after withdrawal of thyroid hormone in 41 of these patients (66 percent), superior in 3 (5 percent), and inferior in 18 (29 percent). When the 65 patients with concordant negative scans were included, the two scans were equivalent in 106 patients (83 percent). Eight patients (13 percent of those with at least one positive scan) were treated with radioiodine on the basis of superior scans done after withdrawal of thyroid hormone. Serum thyroglobulin concentrations increased in 15 of 35 tested patients: 14 after withdrawal of thyroid hormone and 13 after administration of thyrotropin. Patients had more symptoms of hypothyroidism (P<0.001) and dysphoric mood states (P<0.001) after withdrawal of thyroid hormone than after administration of thyrotropin.

CONCLUSIONS: Thyrotropin stimulates radioiodine uptake for scanning in patients with thyroid cancer, but the sensitivity of scanning after the administration of thyrotropin is less than that after the withdrawal of thyroid
hormone. Thyrotropin scanning is associated with fewer symptoms and dysphoric mood states.


Recombinant human TSH has been developed to facilitate monitoring for thyroid carcinoma recurrence or persistence without the attendant morbidity of hypothyroidism seen after thyroid hormone withdrawal. The objectives of this study were to compare the effect of administered recombinant human TSH with thyroid hormone withdrawal on the results of radioiodine whole body scanning (WBS) and serum thyroglobulin (Tg) levels. Two hundred and twenty-nine adult patients with differentiated thyroid cancer requiring radioiodine WBS were studied. Radioiodine WBS and serum Tg measurements were performed after administration of recombinant human TSH and again after thyroid hormone withdrawal in each patient. Radioiodine whole body scans were concordant between the recombinant TSH-stimulated and thyroid hormone withdrawal phases in 195 of 220 (89%) patients. Of the discordant scans, 8 (4%) had superior scans after recombinant human TSH administration, and 17 (8%) had superior scans after thyroid hormone withdrawal (P = 0.108). Based on a serum Tg level of 2 ng/mL or more, thyroid tissue or cancer was detected during thyroid hormone therapy in 22%, after recombinant human TSH stimulation in 52%, and after thyroid hormone withdrawal in 56% of patients with
disease or tissue limited to the thyroid bed and in 80%, 100%, and 100% of patients, respectively, with metastatic disease. A combination of radioiodine WBS and serum Tg after recombinant human TSH stimulation detected thyroid tissue or cancer in 93% of patients with disease or tissue limited to the thyroid bed and 100% of patients with metastatic disease. In conclusion, recombinant human TSH administration is a safe and effective means of stimulating radioiodine uptake and serum Tg levels in patients undergoing evaluation for thyroid cancer persistence and recurrence.


BACKGROUND. The role of adjuvant external radiotherapy in the survival of patients with differentiated thyroid cancer (DTC) is controversial. To our knowledge, no attempt has been undertaken thus far to assess the impact of this therapy with respect to the papillary and follicular types of thyroid cancer as separate entities.

METHODS. Between 1979 and 1992, 238 patients with differentiated papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) with Stage pT4 have been treated and followed in our clinic. One hundred sixty-nine patients free of metastases at the final staging, which was performed after the second radioiodine therapy, were included in this study. The standard treatment comprised total thyroidectomy, ablative radioiodine therapy, and thyroid-stimulating hormone-suppressive therapy with levothyroxin. Ninety-nine patients free of disease after the
final staging received additional external radiotherapy to the neck (with a dose of 50-60 Gy), whereas the remaining 70 patients were treated with the standard treatment protocol only. Distributions of age, sex, and follow-up time were comparable in both irradiated and nonirradiated groups. Multivariate analysis of the influence of age, sex, histologic subtype, and lymph node status as well as of external radiotherapy on the time to first locoregional and distant failure (LDF), and the time to locoregional recurrence (LR), was accomplished using Cox’s proportional hazard model.

RESULTS. In patients with DTC, external radiotherapy was a predictive factor for improvement of both LR ($P = 0.004$) and locoregional and distant failure ($P = 0.0003$). When the time to first locoregional and distant failure was calculated separately for patients with PTC and FTC, there was a significant difference in the PTC group in favor of irradiated patients ($P = 0.0001$), whereas there was no effect of external radiotherapy in the FTC group ($P = 0.38$). Further analyses disclosed that this effect was significantly present only in patients with PTC and lymph node involvement ($P = 0.002$), whereas those without lymph node involvement did not benefit from an additional adjuvant radiotherapy ($P = 0.27$). Because none of the patients younger than age 40 years died due to the disease nor had progressive disease during follow-up, we reassessed our results in patients older than age 40 years. The effect of external radiotherapy could be confirmed in this subgroup of patients ($P = 0.0009$) and in the subgroup of lymph node positive patients older than age 40 years with invasive PTC ($P = 0.01$).
CONCLUSIONS. In addition to total thyroidectomy, treatment with radioiodine, and TSH-suppressive therapy with thyroid hormone, adjuvant external radiotherapy improves the recurrence-free survival in patients older than age 40 years with invasive PTC and lymph node involvement.

POORLY DIFFERENTIATED THYROID CANCERS (PDTC)
Poorly differentiated thyroid carcinomas include carcinomas of follicular thyroid epithelium that retain sufficient differentiation to produce scattered small follicular structures and some thyroglobulin, but generally lack the usual morphologic characteristics of papillary and follicular carcinoma.

Types:
- Insular
- Other (large cell)

Clinical Characteristics
- 10% of all thyroid cancers
- Intermediate aggressiveness when compared to Well differentiated and Anaplastic thyroid cancers

Prognostic Factors
- Age
- Extrathyroidal extension
- Vascular invasion
- Insular component

Treatment
- Total thyroidectomy with Central compartment dissection (VI) for all operable cancers
• Modified radical neck dissection if nodes present in level VI or other compartments.

Postoperative management
The percentage of PDTCs having sufficient RAI concentration to allow postoperative RAI therapy is unknown. However in view of their aggressive nature most authors advocate use of RAI and L-thyroxine.

Radiotherapy
EBRT is given as a local therapy to reduce the risk of local relapse.

Follow up
Close follow up is essential
• Serial monitoring of TG levels (Distinction between PDTC and Anaplastic cancers)
• Repeat RAI imaging
• Ultrasound scans, CT Scans / MRI Scans to assess the extent of disease
• 18 FDG- PET—helpful in localization and prognostic study in patients with PDTC who have negative RAI scans and elevated TG levels

Reference:
1) Poorly Differentiated and Anaplastic Thyroid Cancer
Kepal N. Patel, MD, and Ashok R. Shaha, MD, FACS
Cancer Control, April 2006, Vol. 13, No. 2

MEDULLARY THYROID CANCER
• Medullary thyroid carcinoma (MTC) constitutes 6% to 8% of thyroid cancers.
• It represents a malignant transformation of the neuroectodermally derived parafollicular C cells
• S. Calcitonin is the most specific circulating and immunohistochemical (IHC) marker.
• MTC does not concentrate RI and therefore has no role in its management
• Surgery is the mainstay of management of these cancers

**Types**

75-80% - sporadic
20-25% - familial

<table>
<thead>
<tr>
<th>Type</th>
<th>Associated lesion</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial MTC (FMTC)</td>
<td>None</td>
<td>Less aggressive</td>
</tr>
<tr>
<td>MEN II A</td>
<td>Pheochromocytoma</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism</td>
<td>Aggressiveness</td>
</tr>
<tr>
<td>MEN II B</td>
<td>Pheochromocytoma, Ganglioneuromas</td>
<td>Aggressive</td>
</tr>
<tr>
<td></td>
<td>Marfanoid habitus</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical differences between sporadic and familial MTCs**

<table>
<thead>
<tr>
<th></th>
<th>Sporadic MTC</th>
<th>Familial MTC (FMTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>4th -5th Decade</td>
<td>&lt; 30 years</td>
</tr>
<tr>
<td>Number</td>
<td>Solitary (nodular)</td>
<td>Multiple (diffuse)</td>
</tr>
<tr>
<td>Laterality</td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Less likely</td>
<td>More likely</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>--</td>
<td>Likely</td>
</tr>
<tr>
<td>Family history</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Presentation:
- Painless thyroid swelling or nodule (STN)
- Lymph node metastasis - 50% - 75% at presentation.
- Signs of local infiltration i.e. dyspnoea, dysphagia, and hoarsness may be present.
- Distant metastasis 10%-15% at presentation (lung, liver, bone)
- Rarely patients may present with symptoms of ectopic hormone production such as diarrhea, facial flushing and Cushings syndrome.

Principles of Management

1. **Detection**
   - Fine needle aspiration cytology/biopsy with IHC for calcitonin if necessary
   - Serum calcitonin – Most specific marker
     - increased in all cases of clinically palpable MTC.

2. **Staging**
   - Chest Xray.
   - Imaging
     - Ultrasonography/ CT scan of the neck – To assess the extent of cervical disease.
     - CT scans of the mediastinum and abdomen – To assess the extent of mediastinal lymphadenopathy, pulmonary metastasis, liver metastasis and the adrenal glands.
     - Laparoscopy – More sensitive in detecting liver metastasis than routine imaging, however not recommended as routine
3. **Evaluation of heritable disease**
   - Genetic screening
     - All patients should ideally undergo screening for RET proto oncogene mutations
     - Approximately 5-10% of patients with a negative family history have germ-line mutations
     - Screening for pheochromocytoma (Plasma free metanephrines and normetanephrines, or 24-hour urine metanephrines and normetanephrines, VMA, USG / CT abdomen)

4. **Other Investigations**
   - Basal Calcitonin, CEA
   - S. Calcium
   - X ray neck if large goiter
   - Indirect laryngoscopy

**TREATMENT**

Treat Pheochromocytoma before MTC

Treat hyperparathyroidism with 4 gland resection and autograft to heterotopic site, or subtotal parathyroidectomy. Consider cryopreservation.

**Sporadic MTC (Clinical T1a N0 M0)**
   - Total thyroidectomy with bilateral central neck dissection (level VI)

**T1b and Above**
   - Total thyroidectomy with bilateral central neck dissection (level VI)
- Prophylactic ipsilateral neck dissection (II-IV) for high volume disease or large / multiple central compartment nodes
- Therapeutic ipsilateral or bilateral modified neck dissection for clinically or radiologically identifiable disease (levels II–V)

Role of EBRT (Indications)
- Grossly residual disease after maximum possible surgical resection
- Gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease
- Moderate to high volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension.
- Unresectable tumours
- Recurrent disease in the neck not amenable to surgery
- Palliation of recurrent or metastatic disease in bone, cerebrum, spine and other areas

Familial MTCs (FMTC)
Familial Medullary Thyroid Carcinomas constitute 16 to 20% of medullary thyroid carcinomas (MTC). There are 4 types of Familial MTC.
- MEN II A
- MEN II B
- Non MEN FMTC
- Other FMTC
MEN II A:
MEN II A has 3 components

- MTC
- Pheochromocytoma (40-60% lifetime incidence)
- Hyperparathyroidism (10-20% incidence)

Three types of MEN II A are described

MEN II A (1): MTC + Pheochromocytoma + Hyperparathyroidism

MEN II A (2): MTC + Pheochromocytoma

MEN II A (3): MTC + Hyperparathyroidism (rare)

MEN II B:
MEN II B has 4 components

- MTC
- Pheochromocytoma
- Multiple mucosal ganglioneuromatosis (Lips, tongue, eye lids etc)
- Marphanoid features (long extremities, hyper flexible joints and epiphyseal abnormalities)

Non MEN FMTC:
Four or more patients in a family, without other features of MEN II.

Other Non MEN FMTC:
Two or 3 patients in a family, without other features of MEN II.
Indications for investigations for Familial MTC:

- Younger age group (less than 30 years)
- Bilateral / Multi-focal disease
- Family history of MTC and / or other features of MEN II
- Clinical features of MEN II

Investigations in suspected c/o FMTC

For pheochromocytoma

- Urinary Catacholamines (Epinephrine, norepinephrine & dopamine)
- 24 hr Urinary Vanillyl Mandelic Acid (VMA)
- USG abdomen
- I^{131} MIBG scan if above are doubtful.

For hyperparathyroidism

Serum calcium / phosphates

Serum PTH

RET Proto-oncogene

MEN IIA, MEN IIB and FMTC are autosomal dominant disorders. RET proto-oncogene is located on long arm of chromosome 10, band q11.2. Germline mutations in RET proto-oncogene are associated with Familial MTCs.
Table shows various mutations seen in MTC.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>RET Mutations</th>
<th>Exons</th>
<th>Codons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic MTC</td>
<td>Somatic (&gt;20%)</td>
<td>13</td>
<td>768</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>918</td>
</tr>
<tr>
<td>MEN IIA</td>
<td>Germline (95%)</td>
<td>10</td>
<td>609</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>611</td>
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<td></td>
<td>10</td>
<td>618</td>
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<tr>
<td></td>
<td></td>
<td>11</td>
<td>614</td>
</tr>
<tr>
<td>MEN IIB</td>
<td>Germline (94%)</td>
<td>16</td>
<td>918</td>
</tr>
<tr>
<td>FMTC</td>
<td>Germline (87%)</td>
<td>10</td>
<td>609</td>
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<td>768</td>
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<tr>
<td></td>
<td></td>
<td>14</td>
<td>806</td>
</tr>
</tbody>
</table>

Mutations in RET proto-oncogene are studied by PCR (polymerase chain reaction) on blood samples. Specific mutations are investigated with Restriction endonuclease analysis. Ideally, all patients of MTC (sporadic and familial) should be investigated for mutations in RET proto-oncogene.

*10- 25% of these patients have hyperparathyroidism in the MEN II B syndrome, making a case in point for parathyroid autotransplantation in the forearm at the time of total thyroidectomy.
<table>
<thead>
<tr>
<th>ATA risk level</th>
<th>Age of RET testing</th>
<th>Age of required first US</th>
<th>Age of required first serum Ct</th>
<th>Age of prophylactic surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>ASAP and within the 1st year of life</td>
<td>ASAP and within the 1st year of life</td>
<td>ASAP and within the 1st year of life</td>
<td>ASAP and within the 1st year of life</td>
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<tr>
<td>C</td>
<td>&lt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>Before age 5 years</td>
</tr>
<tr>
<td>B</td>
<td>&lt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met*.</td>
</tr>
<tr>
<td>A</td>
<td>&lt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>May delay surgery beyond age 5 years if stringent criteria are met*.</td>
</tr>
</tbody>
</table>

* Anormal annual basal stimulated serum Ct, normal annual neck US, less aggressive MTC family history, and family preference.
Role of Prophylactic total thyroidectomy

Prophylactic total thyroidectomy is advocated in all patients with germline mutations in RET proto-oncogene. The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited RET mutation (See the ATA risk level table). In MEN IIb, it should be done as early as possible. In MEN IIA and Non MEN FMTC, some advocate surgery between 5 to 10 years while others advocate early surgery.
If surgery is delayed, these patients should be monitored aggressively provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement.

**Adjuvant therapy in MTCs**

No role of RI therapy

$^{131}$I MIBG scan, Anti-CEA monoclonal antibody and human recombinant alpha interferon are still investigational

**Adjuvant Radiation Therapy**

Postoperative adjuvant external-beam RT to the neck and mediastinum may be considered for patients with

- Gross extra-thyroidal extension (T4a or T4b) with positive margins after resection of all gross disease
- Moderate to high volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension
- To palliate painful or progressing bone metastases.

**Chemotherapy:**

No role of chemotherapy in the initial management. For unresectable or metastatic MTC, the orally administered receptor tyrosine kinase inhibitor, Vandetanib is shown to be beneficial. FDA recently approved Vandetanib for adult patients with metastatic MTC who are not eligible for surgery.
Disseminated symptomatic metastases
1. Clinical trial (preferred)
2. External beam RT for focal symptoms
3. Vandetanib
4. Other small molecule kinase inhibitors (i.e., sorafenib or sunitinib) if patient progresses on vandetanib
5. Bisphosphonate therapy or denosumab can be considered for bone metastases
6. Best supportive care

Postoperative Calcitonin Levels
- Basal serum concentrations of calcitonin and CEA should be measured 2 or 3 months postoperatively.
- Patients with detectable basal calcitonin or elevated CEA may be followed if negative on imaging and asymptomatic
- For the patient with increasing serum markers, more frequent imaging may be considered.
- Bone scans, FDG-PET scan, or MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.

Prognosis in MTCs
Best to worst prognosis
- Non MEN Familial MTC
- MEN IIA
- Sporadic MTC
- MEN IIB
Abstracts


Recent advances in the diagnosis and treatment of medullary thyroid carcinoma (MTC) have been significant, but some issues remain controversial. MTC may occur either as a hereditary or a nonhereditary entity. Hereditary MTC can occur either alone—familial MTC (FMTC)—or as the thyroid manifestation of multiple endocrine neoplasia type 2 (MEN 2) syndromes (MEN 2A and MEN 2B). These hereditary disorders are due to germline mutations in the RET proto-oncogene. Early diagnosis and treatment considerably improve the prognosis in patients with MTC. Genetic testing can identify almost all affected individuals with hereditary disease and permits early thyroidectomy in gene carriers. Plasma CT is an excellent marker for postoperative follow-up. Imaging studies help delineate recurrent or metastatic lesions. Treatment of recurrent or metastatic disease is primarily surgical, including either palliative or microdissective surgery. Radiation therapy is reserved for skeletal metastasis or nonresectable metastatic MTC. Efficacy of current chemotherapy programs is not well established. Overall, the 10-year survival rates are approximately 65%.


Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy. About 75% are sporadic (sMTC) while the
remaining 25% are hereditary (hMTC). The treatment of choice for both sMTC and hMTC is surgery. An adequate initial operation provides the best chance of cure. Hence, the diagnosis of MTC should be made preoperatively. In sMTC, ultrasound, ultrasound-guided fine-needle aspiration cytology and measurement of calcitonin levels (basal and after injection of calcitonin-stimulating reagents, e.g., pentagastrin) are sensitive diagnostic tools. In hMTC, identification of a germline mutation in the proto-oncogene RET is sufficient for making the diagnosis. Total thyroidectomy is recommended in all patients, sporadic and hereditary. In addition, lymphadenectomy of the cervicocentral and both cervicolateral compartments should be performed. The only indication to perform a less extensive operation may be given in young patients with hMTC. Sufficient treatment of MTC beyond local disease is still non-existent. Future research should concentrate on this issue.


This is a consensus statement from an international group, mostly of clinical endocrinologists. MEN1 and MEN2 are hereditary cancer syndromes. The commonest tumors secrete PTH or gastrin in MEN1, and calcitonin or catecholamines in MEN2. Management strategies improved after the discoveries of their genes. MEN1 has no clear syndromic variants. Tumor monitoring in MEN1 carriers includes biochemical tests yearly and imaging tests less often. Neck surgery includes subtotal or total parathyroidectomy, parathyroid cryopreservation, and
thymectomy. Proton pump inhibitors or somatostatin analogs are the main management for oversecretion of entero-pancreatic hormones, except insulin. The roles for surgery of most entero-pancreatic tumors present several controversies: exclusion of most operations on gastrinomas and indications for surgery on other tumors. Each MEN1 family probably has an inactivating MEN1 germline mutation. Testing for a germline MEN1 mutation gives useful information, but rarely mandates an intervention. The most distinctive MEN2 variants are MEN2A, MEN2B, and familial medullary thyroid cancer (MTC). They vary in aggressiveness of MTC and spectrum of disturbed organs. Mortality in MEN2 is greater from MTC than from pheochromocytoma. Thyroidectomy, during childhood if possible, is the goal in all MEN2 carriers to prevent or cure MTC. Each MEN2 index case probably has an activating germline RET mutation. RET testing has replaced calcitonin testing to diagnose the MEN2 carrier state. The specific RET codon mutation correlates with the MEN2 syndromic variant, the age of onset of MTC, and the aggressiveness of MTC; consequently, that mutation should guide major management decisions, such as whether and when to perform thyroidectomy.


**Abstract**

**PURPOSE**: There is no effective therapy for patients with distant metastasis of medullary thyroid carcinoma (MTC). Activating mutations in the RET proto-oncogene cause
hereditary MTC, which provides a strong therapeutic rationale for targeting RET kinase activity. This open-label, phase II study assessed the efficacy of vandetanib, a selective oral inhibitor of RET, vascular endothelial growth factor receptor, and epidermal growth factor receptor signaling, in patients with advanced hereditary MTC.

**METHODS**: Patients with unresectable locally advanced or metastatic hereditary MTC received initial treatment with once-daily oral vandetanib 300 mg. The dose was adjusted additionally in some patients on the basis of observed toxicity until disease progression or any other withdrawal criterion was met. The primary assessment was objective tumor response (by RECIST [Response Evaluation Criteria in Solid Tumors]). Results Thirty patients received initial treatment with vandetanib 300 mg/d. On the basis of investigator assessments, 20% of patients (ie, six of 30 patients) experienced a confirmed partial response (median duration of response at data cutoff, 10.2 months). An additional 53% of patients (ie, 16 of 30 patients) experienced stable disease at $\geq$ 24 weeks, which yielded a disease control rate of 73% (ie, 22 of 30 patients). In 24 patients, serum calcitonin levels showed a 50% or greater decrease from baseline that was maintained for at least 4 weeks; 16 patients showed a similar reduction in serum carcinoembryonic antigen levels. The most common adverse events were diarrhea (70%), rash (67%), fatigue (63%), and nausea (63%).

**CONCLUSION**: In this study, vandetanib demonstrated durable objective partial responses and disease control with a manageable adverse event profile. These results demonstrate that vandetanib may provide an effective
therapeutic option in patients with advanced hereditary MTC, a rare disease for which there has been no effective therapy.

**ANAPLASTIC THYROID CANCERS**

- 1-2% of all thyroid cancers
- One of the most aggressive cancers in humans
- Poor survival rates (206 mths)

**Investigations:**

- FNAC for diagnosis. If diagnosis doubtful, tru cut/core biopsy with IHC
- Chest X ray
- If clinically resectable- CT scan neck to assess operability
- Consider FDG-PET / Bone Scan
- Thyroid function tests if clinically indicated

**Management**
Protocol for Histopathological Examination and Reporting Thyroid Specimen

A. Specimen details:

1. Type of specimen:
   a) Biopsy: Incision or Excision biopsy
   b) Resection – Type of surgery performed
      i) Lobectomy
      ii) Hemithyroidectomy
      iii) Total thyroidectomy
      iv) Completion thyroidectomy
   c) Lymph nodes: Specify type of neck node dissection
      i) Individual levels, if sent separately
      ii) Selective node dissection (specify laterality)
      iii) Central compartment nodes

2. Received fresh / in formalin

3. Received intact / fragmented
B. Frozen section examination, if performed:
1. Type of specimen sent for frozen section with relevant gross details
2. Frozen section interpretation

C. Gross / Macroscopic Examination:
1. Weight of specimen and dimensions: ____ X ____ X ____ cm (Dimensions of each lobe and isthmus noted separately)
2. Number of tumor/s or suspicious nodule/s (Unifocal or multifocal)
3. Location of nodule/s and laterality: right lobe, left lobe and/or isthmus
4. Size of nodules: ____ X ____ X ____ cm.
5. Extent of nodules (any gross evidence of extrathyroidal extension)
6. Cut surface of nodule and any gross capsular breach.
7. Adjacent thyroid
8. Neck nodes: For each specimen / level, specify – Number of nodes dissected with size of largest node and appearance on cut surface

D. Sections: Check-list for submitting sections:
1. Tumor / Nodule/s (Section from each tumor nodule; maximum up to 5)
2. Tumor with adjacent thyroid including capsule
3. Tumor with inked margin and adjacent structures (to look for extrathyroidal extension)
4. Rest of the thyroid
   a) Normal
   b) Goitre
   c) Nodule if any
   d) Other

5. Neck nodes – All nodes at individual levels or as per type of neck node dissection

E. Microscopic Examination:

1. Type of tumor:
   a) Papillary carcinoma (variant, if present, specify)
   b) Follicular carcinoma (variant, if present, specify, including Hurthle cell variant)
   c) Poorly differentiated carcinoma (including insular carcinoma)
   d) Medullary carcinoma
   e) Anaplastic carcinoma
   f) Other (specify)
      – Squamous cell carcinoma
      – Mucoepidermoid carcinoma
      – Mucinous carcinoma etc.

2. Tumor capsule:
   a) Capsulated / Partially capsulated / Non-capsulated
   b) Capsular invasion:
      i) Not identified
      ii) Present: Minimal invasion / Wide invasion
3. Lymphovascular invasion: Present or Not identified

4. Perineural invasion: Present or Not identified

5. Status of all margins:
   a) All free of tumor
   b) Close to tumor but free (specify margin and its distance from the tumor)
   c) Involved by tumor (specify the margin / margins involved)

6. Extrathyroidal extension:
   a) Not identified
   b) Present: Minimal / Extensive

7. Neck nodes: For each level or type of neck node dissection, specify
   a) Number of total nodes dissected
   b) Number of nodes showing metastasis
   c) Perinodal extension present or absent
   d) Any other findings (Granuloma, Treatment related changes etc.)

Suggested Reading:
1. Synoptic Reports: “Thyroid”, by Department of Pathology, Tata Memorial Center, Mumbai.

2. College of American Pathologists: Protocol for Examination of Specimens from Patients with Carcinomas of Thyroid, November 2011

3. Kane SV, Patil A: “Grossing Head and Neck Specimen”, Grossing of Surgical Oncology Specimens, Edited by Dr. Saral Desai et al, Department of Pathology, Tata Memorial Hospital, 2011.
Unknown Primary with Cervical Metastases:

Introduction:

Definition:
Includes patients in whom a detailed medical history, careful clinical examination and conventional imaging fail to identify a primary site.

Incidence:
Varies from 1.5-9% depending on the series and the diagnostic modalities used. On an average forms 2-3% of all head and neck cancers.

Squamous cell carcinoma account for 53-77% of these malignancies others being adenocarcinoma, lymphoma, melanoma and undifferentiated carcinoma

Theories postulated for cervical metastasis with an unknown primary

i) Slow growth rate
ii) Spontaneous involution (immunodestruction)

iii) Small size

iv) Hidden location (tonsillar crypts)

**Clinical Findings:**

- Detailed history of symptomatology and habits
- Examination of neck with respect to level of nodal involvement, multiplicity of nodes and bilaterality
- Thorough clinical examination to search for a primary site including oral cavity, nasopharynx, oropharynx and laryngopharynx
- Level of nodal involvement may indicate a potential primary site:
  - Oral cavity: I, II, III
  - Oropharynx, Laryngopharynx, Hypopharynx: Level II, III, IV
  - Nasopharynx: Bilateral nodes, Level II, V
  - Isolated supraclavicular / Level IV nodes: search for an infraclavicular primary
- Majority present with advanced nodal disease (N2/N3) with bilateral nodes in < 10%. Level II and Level III are the most commonly involved nodal sites.
- Subsequent manifestation of the primary site occurs in < 20-30%.

**Work up:**

**Tissue diagnosis:**

- FNAC:
  - To confirm the presence and type of malignancy
- Core biopsy:
  If repeated FNAC negative

- Image guided FNAC/Biopsy:
  If repeated FNAC negative and in case of a cystic metastasis to get an aspirate from the wall of the cyst

- IHC
  For undifferentiated neoplasms

- EBV detection:
  If high probability of nasopharyngeal carcinoma is suspected in view of ethnicity, bilateral nodes and undifferentiated histology

**Investigations to detect primary:**
Search for a primary is mandatory as it helps modulate radiation fields and hence reduce acute and long term toxicity.

- Radiology:
  - CT/MRI: scan from base skull to clavicle. Potential to detect primary ranges from 9.3-23%. Gives information regarding number and laterality of nodes and their relation to surrounding structures.
  - PET CT: Integrated PET CT is superior to PET scan alone. Studies have shown a higher yield rate of primary with PET CT and directed biopsies over CT/MRI. May play a role in patients with multiple or low neck nodes to detect distant metastases. It is a valuable tool in the diagnostic armamentarium; however its additional value
over conventional imaging is yet to be established. Expensive and not available at all centres.

- **Panendoscopy:**
  - Ideally performed after radiological investigations as it may help directed biopsies and prevent false positive radiological findings.
  - Direct laryngoscopy, Nasopharyngoscopy and careful palpation of the oropharynx and oral cavity under anesthesia
  - Blind biopsies and tonsillectomies:
    - Blind biopsies are not advocated. Imaging directed biopsies of suspicious areas are performed.
    - Tonsillectomies: small primaries of the tonsillar crypts maybe missed on routine imaging. Yield rate of ipsilateral tonsillectomy ranges between 18-44%. However contralateral yield rate <10%. Many centres advocate unilateral/bilateral tonsillectomy as part of routine workup. However, in the era of modern imaging, given their higher sensitivity, role of routine tonsillectomy is controversial and is not recommended.

- **Role of Molecular Studies:** under active research
  - HPV: In western literature, correlation of HPV in oropharyngeal cancers has been reported in young, non addicted patients. Hence recommended in such individuals.
- Role of micro RNA, microsatellite analysis, image cytometry and laser induced fluorescence endoscopy is investigational.

**Management:**

Management discussion will mainly concentrate on SCC. For all other histologies, management will depend upon the management guidelines for the suspected primary.

- **Low volume disease (N1):** Single modality treatment advocated by some. Usually radiocurable and RT alone can be used to treat the primary and the neck with the option of surgical salvage. Some retrospective studies have advocated surgery alone in N1 disease without ECE; however these are small retrospective studies.

- **High volume disease (N2/N3):** Multimodality treatment is strongly advocated. Most studies favour Surgery with adjuvant RT. Current evidence however does not prove whether CTRT followed by salvage neck dissection is comparable to Surgery followed by RT.

**Our recommendation:**

- **N1:** Selective neck dissection with adjuvant therapy (covering the potential primary sites):
  
  Preferred since histological specimen is obtained and may help in upstaging the disease. Adjuvant therapy depends on ECE (CTRT for ECE, only RT without ECE)

- **High volume disease (N2/N3):** Selective neck dissection with adjuvant therapy: in operable disease with adjuvant therapy depending on ECE
- Extent of radiation (fields):
The extent of radiotherapy remains controversial with respect to:
  i) Inclusion of the primary site
  ii) Unilateral or bilateral neck irradiation
  iii) Inclusion of nasopharynx in the field of RT

Our recommendation:

All stages:

Bilateral radiation involving the entire pharyngeal mucosa excluding the nasopharynx.

Radiotherapy Dose:

  66-70 Gy (or equivalent) to all areas of gross disease (Involved nodes if not operated)
  60 Gy to all areas of prophylactic treatment (Mucosal axis, node negative neck and post operative node-positive neck)
  50 Gy (or equivalent) may be considered for level 4 and 5 if only level 1 or 2 involved.

Inclusion of nasopharynx:

i) post triangle node, bilateral node OR
ii) Undifferentiated or lymphoepithelial malignancy OR
ii) EBV positivity

IMRT can be used to spare normal tissues without compromising local control.

**Outcome:** The 5 year overall survival is about 55%. Stage to stage comparison shows better survival in patients with unknown primaries than in whom the primary is known.
Abstracts:

1) Contemporary Management Of Lymph Node Metastases From An Unknown Primary To The Neck: I. A Review Of Diagnostic Approaches.


In an era of advanced diagnostics, metastasis to cervical lymph nodes from an occult primary tumor is a rare clinical entity and accounts for approximately 3% of head and neck malignancies. Histologically, two thirds of cases are squamous cell carcinomas (SCCs), with other tissue types less common in the neck. With modern imaging and tissue examinations, a primary tumor initially undetected on physical examination is revealed in >50% of patients and the site of the index primary can be predicted with a high level of probability. In the present review, the range and limitations of diagnostic procedures are summarized and the optimal diagnostic workup is proposed. Initial preferred diagnostic procedures are a fine needle aspiration biopsy (FNAB) and imaging. This allows directed surgical biopsy (such as tonsillectomy), based on the preliminary findings, and prevents misinterpretation of postsurgical images. When no primary lesion is suggested after imaging and panendoscopy, and for patients without a history of smoking and alcohol abuse, molecular profiling of an FNAB sample for human papillomavirus (HPV) and/or Epstein–Barr virus (EBV) is important.
Although uncommon, cancer of an unknown primary (CUP) metastatic to cervical lymph nodes poses a range of dilemmas relating to optimal treatment. The ideal resolution would be a properly designed prospective randomized trial, but it is unlikely that this will ever be conducted in this group of patients. Accordingly, knowledge gained from retrospective studies and experience from treating patients with known head and neck primary tumors form the basis of therapeutic strategies in CUP. This review provides a critical appraisal of various treatment approaches described in the literature. Emerging treatment options for CUP with metastases to cervical lymph nodes are discussed in view of recent innovations in the field of head and neck oncology and suitable therapeutic strategies for particular clinical scenarios are presented. For pN1 or cN1 disease without extracapsular extension (ECE), selective neck dissection or radiotherapy offer high rates of regional control. For more advanced neck disease, intensive combined treatment is required, either a combination of neck dissection and radiotherapy, or initial (chemo) radiotherapy followed by neck dissection if a complete response is not recorded on imaging. Each of these approaches seems to be equally effective. Use of extensive bilateral neck/mucosal irradiation must be weighed...
against toxicity, availability of close follow-up with elective neck imaging and guided fine-needle aspiration biopsy (FNAB) when appropriate, the human papillomavirus (HPV) status of the tumor, and particularly against the distribution pattern (oropharynx in the majority of cases) and the emergence rate of hidden primary lesions (<10% after comprehensive workup). The addition of systemic agents is expected to yield similar improvement in outcome as has been observed for known head and neck primary tumors.

3) Head and neck squamous cell carcinoma from unknown primary site.


Background: The purpose of this study is to present our experience treating patients with squamous cell carcinoma (SCC) from an unknown head and neck primary site and to determine whether a policy change eliminating the larynx and hypopharynx from the radiotherapy (RT) portals has impacted outcome.

Methods: One hundred seventy-nine patients received definitive RT with or without a neck dissection for SCC from an unknown head and neck primary site. RT was delivered to the ipsilateral neck alone or both sides of the neck and, usually, the potential mucosal primary sites. The median mucosal dose was 5670 cGy. The median neck dose was 6500 cGy. One hundred nine patients (61%) received a planned neck dissection.

Results: Mucosal control at 5 years was 92%. The mucosal control rate in patients with RT limited to the nasopharynx
and oropharynx was 100%. The 5-year neck-control rates were as follows: N1, 94%; N2a, 98%; N2b, 86%; N2c, 86%; N3, 57%; and overall, 81%. The 5-year cause-specific survival rates were as follows: N1, 94%; N2a, 88%; N2b, 82%; N2c, 71%; N3, 48%; and overall, 73%. The 5-year overall survival rates were as follows: N1, 50%; N2a, 70%; N2b, 59%; N2c, 45%; N3, 34%; and overall, 52%. Eleven patients (7%) developed severe complications.

**Conclusion:** RT alone or combined with neck dissection results in a high probability of cure with a low risk of severe complications. Eliminating the larynx and hypopharynx from the RT portals did not compromise outcome and likely reduces treatment toxicity.

4) **Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site.**


**Objectives/Hypothesis:** To discuss our experience with the diagnostic evaluation in patients with squamous cell carcinomas (SCCAs) of the head and neck metastatic to the cervical lymph nodes from an unknown primary site.

**Methods:** Between June 1983 and December 2008, 236 patients were evaluated with lymph node biopsy, computed tomography (CT), and/or magnetic resonance imaging (MRI) of the head and neck, and panendoscopy with directed biopsies. Additional studies included fluorodeoxyglucose–single photon emission computed tomography (FDG-SPECT) in 26 patients and FDG-positron emission tomography (FDG-PET) or FDG-PET/CT in 21
patients. Seventy nine patients underwent an ipsilateral (72) or bilateral (seven) tonsillectomy.

**Results:** An occult primary site was detected in 126 patients (53.4%); six patients had two synchronous primary cancers. The most common primary sites were in the tonsillar fossa (59 patients; 44.7%) and the base of tongue (58 patients; 43.9%). The primary site was found in 21 (29.2%) of the 72 patients with no suspicious findings on physical exam and/or radiographic evaluation compared with 105 (64.0%) of 164 remaining patients. Tonsillectomy revealed the primary cancer in 35 (44.3%) of 79 patients. FDG-SPECT and FDG-PET or FDG-PET/CT was the sole method of primary site detection in only one patient (2.1%) of 47 patients.

**Conclusions:** Diagnostic evaluation should include a thorough physical examination, CT and/or MRI of the head and neck, and panendoscopy with directed biopsies. Unilateral or bilateral tonsillectomy should be performed on patients with adequate lymphoid tonsillar tissue. FDG-PET or FDG-PET/CT should be considered for those with indeterminate findings on physical examination and/or head and neck CT and/or MRI if those sites are located outside of the Oropharynx.

5) **Utility of combined (18)F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors.**


**Summary:** 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been reported to identify
primary tumors in patients with cervical metastases from cancer of unknown primary (CUP). However, few reports have assessed the use of combined FDG-PET/ computed tomography (CT) in this setting. We therefore examined the utility of combined FDG-PET/CT in the detection of primary tumors and unrecognized metastases in these patients. Patients with previously untreated CUPs underwent head and neck CT and whole-body FDG-PET/CT before panendoscopy and guided biopsy. The diagnostic accuracy of CT and FDG-PET/CT in detecting primary tumors and cervical metastases was compared with that of histopathology. The ability of FDG-PET/CT to detect distant metastases was also tested. Of the 44 eligible patients, 16 had occult primary tumors in the head and neck. FDG-PET/CT was significantly more sensitive than CT for detecting primary tumors (87.5% vs. 43.7%, P = .016), but their specificity did not differ (82.1% vs. 89.3%, P = .500). Thirty-four of 44 patients underwent neck dissection; 67 of 182 dissected cervical levels had metastatic nodal diseases. On a level-by-level basis, FDG-PET/CT was significantly more sensitive than CT (94.0% vs. 71.6%, P < .001), but the two methods were equally specific (94.8% vs. 96.5%). FDG-PET/CT correctly detected distant metastases in 6 of 6 patients. Combined FDG-PET/CT is a useful screening method for primary tumor detection, accurate nodal staging, and distant metastases in patients with CUPs.

Suggested reading:

1) Waltonen JD, Ozer E, Hall NC, Schuller DE, Agrawal A. Metastatic carcinoma of the neck of unknown primary origin: evaluation and efficacy of the modern


Recurrent/ Metastatic Head and Neck Cancers

Of all the patients with locally advanced head and neck cancers two-third develop loco-regional recurrence while 20-30% present with distant metastasis. Final clinical outcome for this is affected by various factors.

**FACTORS AFFECTING CLINICAL OUTCOME:**

**PATIENT RELATED FACTORS**
- Performance score and co-morbidities
- Quality of life (QOL) and functional outcomes
- Treatment Cost

**DISEASE RELATED FACTORS**
- Stage and extent of disease
- Site of recurrence
- Disease free interval

(Patients with disease recurrence within one year of initial treatment have significantly worse survival than patients who recur later).
TREATMENT RELATED FACTORS
- History of prior treatment

MANAGEMENT
Surgical salvage offers best survival rates in recurrent / metastatic head and neck cancers. When the volume and location of recurrent disease are amenable to resection surgical salvage provides the best opportunity for long-term survival. Five-year overall survival rates after surgical salvage generally range from 11 to 39%.

Salvage surgery in curative setting
- Isolated recurrence in the neck where the primary has been treated but neck not treated/treated with single modality treatment.
- Neck recurrence following definite treatment in form of Chemo-radiation / Radiation (non dissected neck)
- Local/loco-regional recurrence following treatment for early stage disease (single modality treatment in form of surgery/radiation)
  eg. T1/T2 Oral cavity cancers
  T1/T2 laryngeal/ hypo-pharyngeal cancers
- When the surgery is not functionally morbid.

Salvage surgery with palliative intent
- To relieve symptoms like airway obstruction and feeding difficulty etc.
  (eg. Tracheostomy/gastrostomy)

RE-RADIATION
Re-irradiation is an option for patients who are not candidates for salvage surgery, but who have locally
recurrent disease after previous definitive treatment. Re-radiation to patients with recurrent/metastatic cancers can be offered in curative or palliative setting.

**Re-radiation with curative intent:**
1. Re-radiation is preferred in sites which have not been radiated before.
2. When surgery is extensive with functional morbidity and quality of life issues.
3. When surgery is not possible.

**Re-radiation with palliative Intent:**
1. Where surgery is not possible
2. When Radiotherapy with radical doses is not feasible eg. Short Disease Free Interval, poor general condition of the patient and extensive late sequelae of previous radiation
3. Palliation of symptoms like fungation, bleeding and pain etc.

**Systemic Chemotherapy**
Systemic chemotherapy is essentially palliative with a median survival of 6-8 months in recurrent/metastatic settings. Systemic chemotherapy can be offered as combination chemotherapy or single agent chemotherapy. Patient’s general condition and performance status plays an important role in deciding on the appropriate management.

**Factors Determining Systemic Chemotherapy**
- Performance status (ECOG) and co-morbidities
- Disease extent and stage
- History of prior chemotherapy
Depending on the performance status and general condition of the patient chemotherapy can be administered as single agent or combination chemotherapy.

\textit{a) Combination chemotherapy}

Cisplatin remains the cornerstone of treatment in recurrent and metastatic SCCHN. Platinum based Combination chemotherapy produced higher response rates than those of single-agent therapy. Addition of Cetuximab to combination has improved overall survival in this group of patients.

\textit{b) Single agent chemotherapy}

A large number of conventional single agents have been investigated in the past in patients with Recurrent/Metastatic SCCHN. The most active and most extensively used agents are methotrexate, Cisplatin and 5-fluorouracil (5-FU). Weekly Methotrexate may be considered as the accepted treatment.

**BEST SUPPORTIVE CARE**

Patients with severe co-morbidities or poor performance status may be best treated with supportive care.

**Metastatic Disease**

**OLIGOMETASTASIS**

\textit{Role of surgery}

1. Pulmonary metastatectomy

Not indicated in cases with short DFI, extensive nodal metastasis and when this first surgery not curative.
Role of Radiotherapy
Bony metastasis – pain, compression and fracture

Brain metastasis

Pulmonary metastasis - If surgery not possible Bleeding, chest pain, obstruction etc.

DISSEMINATED METASTATIC DISEASE
Systemic chemotherapy

Suggested Reading
   Vermorken JB, Mesia R, Rivera F et al.

Background
Cetuximab is effective in platinum-resistant recurrent or metastatic squamous-cell carcinoma of the head and neck. We investigated the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.

Methods
We randomly assigned 220 of 442 eligible patients with untreated recurrent or metastatic squamous-cell carcinoma of the head and neck to receive cisplatin (at a dose of 100 mg per square meter of body-surface area on day 1) or carboplatin (at an area under the curve of 5 mg per milliliter per minute, as a 1-hour intravenous infusion on day 1) plus fluorouracil (at a dose of 1000 mg per square
meter per day for 4 days) every 3 weeks for a maximum of 6 cycles and 222 patients to receive the same chemotherapy plus cetuximab (at a dose of 400 mg per square meter initially, as a 2-hour intravenous infusion, then 250 mg per square meter, as a 1-hour intravenous infusion per week) for a maximum of 6 cycles. Patients with stable disease who received chemotherapy plus cetuximab continued to receive cetuximab until disease progression or unacceptable toxic effects, whichever occurred first.

**Results**

Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum–fluorouracil) significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95% confidence interval, 0.64 to 0.99; P = 0.04). The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months (hazard ratio for progression, 0.54; P<0.001) and increased the response rate from 20% to 36% (P<0.001). The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19% and 13%, respectively), neutropenia (23% and 22%), and thrombocytopenia (11% in both groups). Sepsis occurred in 9 patients in the cetuximab group and in 1 patient in the chemotherapy-alone group (P = 0.02). Of 219 patients receiving cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths.
Conclusions
As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum–fluorouracil chemotherapy improved overall survival when given as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. (ClinicalTrials.gov number, NCT00122460.)

2. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab As a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy.

Jan B. Vermorken, José Trigo, Ricardo Hitt, Piotr Koralewski, Eduardo Diaz-Rubio, Frédéric Rolland, Rainald Knecht, Nadia Amellal, Armin Schueler, and José Baselga


**Purpose:** To evaluate the efficacy and safety of the epidermal growth factor receptor–directed monoclonal antibody cetuximab administered as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) who experience disease progression on platinum therapy.

**Patients and Methods:** An open-label multicenter study in which patients with disease progression on two to six cycles of platinum therapy received single-agent cetuximab (initial dose 400 mg/m2 followed by subsequent weekly doses of 250 mg/m2) for _6_ weeks (single-agent phase). Patients who experienced disease...
progression could receive salvage therapy with cetuximab plus platinum (combination-therapy phase). From June 2001 to December 2002, 103 patients were enrolled and treated with cetuximab, 53 of whom subsequently received combination therapy.

**Results**: In the single-agent phase, response rate was 13%, disease control rate (complete response/partial response/stable disease) was 46%, and median time to progression (TTP) was 70 days. During the combination-therapy phase, the objective response rate was zero, disease control rate was 26%, and TTP was 50 days. Median overall survival was 178 days. Treatment was well tolerated. The most common cetuximab-related adverse events in the single-agent phase were skin reactions, particularly rash (49% of patients, mainly grade 1 or 2). There was one treatment-related death due to an infusion-related reaction.

**Conclusion**: Single-agent cetuximab was active and generally well tolerated in the treatment of recurrent and/or metastatic SCCHN that progressed on platinum therapy. Response was comparable to that seen with cetuximab plus platinum combination regimens in the same setting.


Sharon A. Spencer, Jonathan Harris, Richard H. Wheeler, Mitchell Machtay, Christopher Schultz, William Spanos, Marvin Rotman, Ruby Meredith, Kie-Kian Ang

**Abstract**: Background. Our objectives were to determine the incidence of acute and late toxicities and to estimate
the 2-year overall survival for patients treated with reirradiation and chemotherapy for unresectable squamous cell carcinoma of the head and neck (SCCHN).

Methods. Patients with recurrent squamous cell carcinoma or a second primary arising in a previously irradiated field were eligible. Four weekly cycles of 5-fluorouracil 300 mg/m2 IV bolus and hydroxyurea 1.5 g by mouth were used with 60 Gy at 1.5 Gy twice-daily fractions. Toxicity was scored according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria.

Results: Seventy-nine of the 86 patients enrolled were analyzable. The worst acute toxicity was grade 4 in 17.7% and grade 5 in 7.6%. Grade 3 and 4 late toxicities were found in 19.4% and 3.0%, respectively. The estimated cumulative incidence of grade 3 to 4 late effects occurring at >1 year was 9.4% (95% confidence interval [CI]: 0, 19.7) at 2 and 5 years. The 2- and 5-year cumulative incidence for grade 4 toxicity was 3.1% (95% CI: 0, 9.3). The estimated 2- and 5-year survival rates were 15.2% (95% CI: 7.3, 23.1) and 3.8% (95% CI: 0.8, 8.0), respectively. Patients who entered the study at >1 year from initial radiotherapy (RT) had better survival than did those who were <1 year from prior RT (median survival, 9.8 months vs 5.8 months; p ¼ .036). No correlation was detected between dose received and overall survival. Three patients were alive at 5 years.

Conclusion. This is the first prospective multi-institutional trial testing reirradiation plus chemotherapy for recurrent or second SCCHN. The approach is feasible with acceptable
acute and late effects. The results serve as a benchmark for ongoing RTOG trials.

4 Pulmonary resection for metastatic head and neck cancer.

Chen F, Sonobe M, Sato K, Fujinaga T, Shoji T, Sakai H, Miyahara R, Bando T, Okubo K, Hirata T, Date H.

**Background:** Pulmonary metastasectomy has become the standard therapy for various metastatic malignancies to the lungs; however, little data have been available about lung metastasectomy for Head and Neck Cancers. To confirm a role for resection of pulmonary metastases for such tumors, we reviewed our institutional experience.

**Methods:** Between 1991 and 2007, 20 patients with pulmonary metastases from head and neck cancers underwent complete pulmonary resection. All patients had obtained or had obtainable locoregional control of their primary head and neck cancers. Various perioperative variables were investigated retrospectively to analyze the prognostic factors for overall survival and disease-free survival after metastasectomy.

**Results:** Of the 20 patients, 10 (50%) had squamous cell carcinoma, 7 (35%) had adenoid cystic carcinoma, and 3 had miscellaneous carcinomas. The median disease-free interval from the time of treatment of the head and neck primary cancers to the development of pulmonary metastases was 27 months. Overall survival rate after metastasectomy was 59.4% at 5 years and 47.5% at 10 years, respectively. Disease-free survival rate was 25.0% at 5 years after pulmonary resection. A disease-free interval equal to or longer than 12 months was a
significantly favorable prognostic factor for both overall survival and disease-free survival \((p = 0.02\) and \(0.01\), respectively). Patients with squamous cell carcinoma and male sex showed a worse overall survival \((p = 0.04\) and \(0.03\), respectively).

**Conclusion:** The current practice of pulmonary metastasectomy for head and neck cancers in our institution was well justified. A disease-free interval equal to or longer than 12 months, nonsquamous cell carcinoma, and female sex might be relevant to a better prognosis.

**Suggested Readings**

1. Phase I/II Study of Cetuximab in Combination With Cisplatin or Carboplatin and Fluorouracil in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck. *J Clin Oncol* 2006;24:2866-2872.
   
   Jean Bourhis, Fernando Rivera, Ricard Mesia, Ahmad Awada, Lionel Geoffrois, Christian Borel, Yves Humblet, Antonio Lopez-Pousa, Ricardo Hitt, M. Eugenia Vega Villegas, Lionel Duck, Dominique Rosine, Nadia Amellal, Armin Schueler, and Andreas Harstrick

   

3. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and

Forastiere AA, Metch B, Schuller DE, et al.


Notes
Evidence Based Management
of Cancers in India
(Two Parts)

Guidelines for
Head and Neck Cancers
(Part A)

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