CONSENSUS DOCUMENT FOR MANAGEMENT OF TONGUE CANCER

Prepared as an outcome of ICMR Subcommittee on Tongue Cancer

Coordinated by

Division of Non Communicable Diseases

Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
2014

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. V.M. Katoch
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for consensus document for Management of Tongue Cancer. The ICMR had constituted sub-committees to prepare this document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This Consensus Document on Management of Tongue Cancers summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in drafting cancer site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of Tongue Cancer patients and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on this topic based on available evidence and will have to be revised as we move. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of these guidelines will serve the desired purpose.

(Dr.V.M.Katoch)
Secretary, Department of Health Research &
Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as Chairperson of ICMR Task Force project on Guidelines for Management of Cancer.

The Task Force on Management of Cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and paediatric lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2009-2011) and Time Trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three-part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I, thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

Incidence of cancer in the country has been increasing over the last few decades. Most of the guidelines followed are those from the western literature. However the country does have a different spectrum of disease which may be biologically different (e.g. chewed tobacco induced oral cavity cancer and submucous fibrosis). Moreover our patient population may be different in terms of tolerability and availability of resources to implement guidelines that come from overseas. ICMR as the apex national body has taken the lead to put together national specific guidelines bringing the best experts from around the country to the table. This effort is laudable.

I wish to place on record the contribution of each and every member of the task force for their inputs and contribution in putting together this document on tongue cancer. It was not an easy job to sift through national and international literature and come to conclusions. I also place on record our appreciation to the office bearers of 'foundation of head neck oncology' (FHNO) and some leading oncologists nationally who were not part of the task force for their valuable suggestions (Dr. Kodaganur Gopinath, Dr.Arvind Krishnamurthy, Dr. Moni Kuriakose, Dr. Sanjay Kapoor, Dr.Vedang Murthi, Dr. Krishnakumar T)

(Dr. Anil D'Cruz)
Chairperson
of Subcommittee on Tongue Cancer

Preface

Cancer is a leading cause of death worldwide. Globally cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr.D.K.Shukla)
Head
NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document especially perseverance behind each subcommittee in formulating these documents. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. VM Katoch, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to help the cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. DK Shukla for his support and coordination in finalizing this document. I would also like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

(Dr. Tanvir Kaur)
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CHAPTER

1 INTRODUCTION

Cancers of the oral cavity are a significant public health problem in India. Traditionally gingivo-buccal cancers were the commonest oral cavity cancers in the country as opposed to tongue and floor of mouth cancers which were common in the developed world. However, the incidence of oral tongue cancers has been increasing in the last couple of years in India and today it is as common as gingivo-buccal cancers in most cancer registries across the country. International comparison of age adjusted rates (AAR) with that of population based cancer registries (PBCRs) in India shows that the top five positions in men were occupied by five Indian PBCRs and three Indian PBCRs, East Khasi Hills of Meghalaya state, Ahmadabad urban and Kamrup urban district followed Karachi in females as the highest incidence areas for tongue cancers[1].

While the broad principles of treatment of oral cancers are similar the majority of publications from India have focused on buccal mucosa cancers. Tongue cancers are a different entity with distinct differences in work-up and management. This write up aims to highlight the finer nuances in the treatment of tongue cancers. This proposed national consensus document has been put together by a team of national experts from all major disciplines including radiology and pathology. The document was then circulated to leading oncologists and senior members of the foundation of head neck oncology (FHNO) of India and inputs received were extensively deliberated upon and incorporated into the final document. This document represents the collective opinion and treatment philosophy of all major head and neck treating clinicians across the country.

CHAPTER

2 EXISTING GUIDELINES

There are no specific guidelines available for the management of tongue cancers. All existing guidelines include tongue cancers under the broad heading of oral cavity cancers. These include –

1) National Comprehensive Cancer Network (NCCN)[2]
2) National Health Services (NHS)[3,4]
3) European Society of Medical Oncology (ESMO)[5]
4) TMH textbook on evidence based medicine[6]

While the broad principles of management are the same, there are finer nuances in the management of individual cancers that comprise the oral cavity. It is an endeavor in these guidelines to highlight these differences to help the treating clinician to manage cancer of oral tongue.

The most widely followed guidelines are the NCCN (global) as well as the TMH textbook on evidence based medicine (national). There is a paucity of randomized controlled trials addressing various issues of tongue cancers specifically. This endeavor has tried to combine the best available evidence which has been put together by the experts on the task force. It is our belief that the information is the collation of the best available evidence and should form the basis of treatment of majority of the tongue cancers. However implementation and practice of these guidelines may be modified in the best interest of patient care given the paucity of strong level I evidence.

CHAPTER

3 REVIEW OF PUBLISHED LITERATURE

Traditionally gingivo-buccal cancers were the most common oral cavity cancers in our country while tongue cancers were more common in the western world. Majority of publication from the country therefore focused on the gingivo-buccal cancers with a paucity of published literature focusing on tongue cancers specifically. The incidence of tongue cancer has been showing an increase in the recent time and with the possible role of HPV. Analysis of Indian literature did reveal a number of seminal publications which have been reviewed and form the basis of suggested guidelines. These publications have been put into perspective along with published international literature. Relevant articles on tongue cancer are tabulated below-

Indian Literature

Author	Study group	Results
Fakhi,1989[7]	A prospective study to assess the role of elective versus therapeutic neck dissection in early tongue cancers.	No significant difference in survival between hemiglossectomy alone and hemiglossectomy with radical neck dissection group.
Fakhi,1989 [8]	Role of prophylactic neck dissection in early tongue cancers in randomized setting.	Disease free survival was better for the patients who received prophylactic neck dissection but not statistically significant.
Kuriakose MA, 2000 [9]	Role of tumor volume was studied in 20 oral tongue cancer patients.	Tumor volume was found to be an useful adjunct to TNM staging system.
Kane, 2006 [10]	Role of depth of invasion as histological parameter in cervical lymph node metastasis was studied in 48 early tongue cancer patients.	Patients with tumor depth more than 5 mm were at increased risk of developing lymph node metastasis.
Uma R, 2007 [11]	Genotypic markers in tumor to predict lymph node metastasis were studied in 54 cases.	Down regulation of epidermal fatty acid binding protein is associated with metastasis in tongue cancers.
D'cruz AK, 2009 [12]	359 patients of early tongue cancers, divided into 2 groups: elective neck dissection and wait and watch.	No difference in the 3 and 5-year disease-free survival between the two groups. Need for randomized controlled trial exist.
Bhalavat, 2009 [13]	Treatment outcomes in 57 patients of early tongue cancers treated with brachytherapy were studied.	Brachytherapy is an effective alternative treatment modality for early tongue cancers.
Elango KA, 2011 [14]	Role of HPV was studied in 60 oral tongue cancers and 46 controls.	Positive correlation of HPV with tongue cancers was found.
Chaturvedi P, 2012 [15]	Impact of frozen section in achieving adequate margins was studied in 877 patients.	Frozen section is useful in reducing rate of positive/close margins translating into clinical benefit.

Balasubramanian D, 2012 [16]	Incidence of isolated skip nodal metastasis was studied in 52 early stage tongue cancers.	Isolated skip metastasis to level IV is rare.
Thankappan K, 2012 [17]	Feasibility of lateral arm flap for reconstruction of tongue defects in 48 cases.	Lateral arm flap is suitable option for partial glossectomy defects.
Sharma P, 2013 [18]	Prognostic factors in early oral tongue cancers were studied in 60 patients.	Multiple risk factors were identified.
Krishnamurthy A, 2013 [19]	Epidemiological trend studied in 458 early tongue cancer patients attending institution.	Increasing trend of tongue cancers among nontobacco users was observed.
Singh B, 2013 [20]	Risk of contralateral lymph node metastasis in tongue cancers was studied in 243 patients.	Ipsilateral neck node metastasis is a predictor for contralateral metastasis.
Patil V, 2013 [21]	Role of induction chemotherapy was assessed in 123 patients with locally advanced technically unresectable oral cavity cancers. .	Induction chemotherapy was successful in converting 40 % of unresectable cancers into operable disease with improved overall survival.
Thiagarajan S, 2014 [22]	Prognostic factors in oral tongue cancers were studied in 586 patients.	Multiple prognostic factors were identified.

International Literature

Author	Study group	Results
Sessions DG, 2002 [23]	Results of treatment of different modalities of treatment were studied on 332 patients.	Patients with early stage, negative margins & negative nodes had better disease specific survival.
Bernier J, 2004 [24]	Randomized trial to compare concomitant cisplatin & radiotherapy and radiotherapy alone as adjuvant treatment for stage III & IV head neck cancer. 334 patients with high risk features were included in a randomized setting.	Progression free survival and loco-regional control was better in chemo-radiotherapy group.
Cooper JS, 2004 [25]	Head neck cancer patients following resection with high risk features included. 223 patients were randomized into two groups: radiotherapy alone & chemo-radiotherapy group	Chemoradiation significantly improved local & regional control and disease free survival.
Bernier J, 2005 [26]	Comparative analysis of EORTC 22931 & RTOG 9501 trials was done to define risk levels in locally advanced head neck cancers.	Positive margins and extracapsular spread were the most significant factors for poor outcome.
Vermorken, 2007 [27]	Comparison of TPF with PF as induction chemotherapy in advanced unresectable disease in randomized setting.	Docetaxal improved progression free and overall survival in unresectable head neck cancers.
Posner , 2007 [28]	Randomized trial to compare induction chemotherapy with TPF and PF followed by chemo-radiotherapy in head neck cancers.	TPF group had better overall survival than PF group.

Vermorken, 2008 [29]	Randomized controlled trial to study the efficacy of cetuximab plus platinum based chemotherapy in recurrent and metastatic SCC of head neck.	Addition of cetuximab prolonged overall survival in recurrent & metastatic head neck cancers.
Huang, 2009 [30]	A meta-analysis to study the predictive value of tumor thickness for lymph node involvement in oral cavity cancers.	Tumor thickness with cut off of 4 mm is strong predictor for cervical lymph node involvement.
Fasunla, 2011 [31]	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.	Elective neck dissection reduces the risk of disease specific death. Elective neck dissection should be done in clinically node negative neck.
D'Cruz AK, 2011 [32]	Critical analysis of the meta-analysis by Fasunla on elective versus therapeutic neck dissection.	Limitation and caveats of meta-analysis discussed. Need to conduct well designed randomized controlled trial exist.
Poling, 2014 [33]	Presence of HPV was studied in 78 lateral tongue cancers.	Routine testing of HPV in lateral tongue cancers is unwarranted.

CHAPTER

4 EPIDEMIOLOGY

Oral cancer forms the fifteenth most common type of cancer worldwide with a estimated incidence rate of 2.1%[34]. There are about 0.2 million new cases every year worldwide with 0.1 million deaths each year. On global comparison India shows high incidence rates of oral cavity cancers forming a major health burden. Age standardized incidence rate in India is 7.5 per 100,000 population while in western Europe and USA it is 4.6 and 3.8 per 100,000 population respectively [34]. A recent national representative survey of cancer mortality in India demonstrated oral cavity cancer as the leading cause of mortality in men which was responsible for cancer-related deaths in 22.9% cases [35]. Tongue forms the most common sub-site for oral cavity cancer in western world. While gingivo-buccal complex cancer was the predominant cancer in India, the incidence of tongue cancer is slowly increasing in our country as well.

Current figures for tongue cancers from the population based cancer registries data have been released by ICMR for the year 2009-2011 are as follows[1] -

Tongue (ICD-10: C01-C02)

National

Males: Ahmadabad Urban had the highest AAR (12.2) among all the PBCRs. Kamrup urban district showed highest AAR (9.4) among the North East registries.

Females: The North Eastern registry areas of Kamrup Urban district and East Khasi Hills of Meghalaya shared the top place with Ahmadabad urban for the highest AAR of 3.2 per 100,000 among all the population based cancer registries.

International

Males: Indian PBCRs had the highest AARs (given in parentheses) in cancers of the tongue in males among all the Indian and international PBCRs. [Ahmadabad Urban (12.2), Kamrup Urban District (9.4), Ahmedabad Rural (9.3), Bhopal (9.0) and Delhi (8.0)]. The top five positions were occupied by five Indian PBCRs.

Females: South Karachi in Pakistan had highest AAR (6.6). Three Indian PBCRs, East Khasi Hills of Meghalaya State, Ahmadabad Urban and Kamrup Urban District followed next with an AAR of 3.2.

In the hospital based cancer registries (HBCR), cancer of the tongue is an important site contributing a quarter of all head and neck cancers. Cancer of the tongue was among the five leading sites in all HBCRs among males, and in females it was among the ten leading sites in Mumbai, Thiruvananthapuram, Dibrugarh and Guwahati. The regional spread of the disease varied from 43.6% in Mumbai to 96.1% in Dibrugarh.

Definition

Oral tongue is an area limited posteriorly by circumvallate papillae with ICD number C 02.3 (figure 1). These cancers are a distinct clinical entity and must be differentiated from the cancers of the base of tongue. This write up is restricted to the cancers arising in oral tongue.

Most common site of involvement is lateral border of tongue accounting for 85% of cases. Dorsum, ventral surface and tip of the tongue (5% each) form rest of the cases (figure 2) [36].

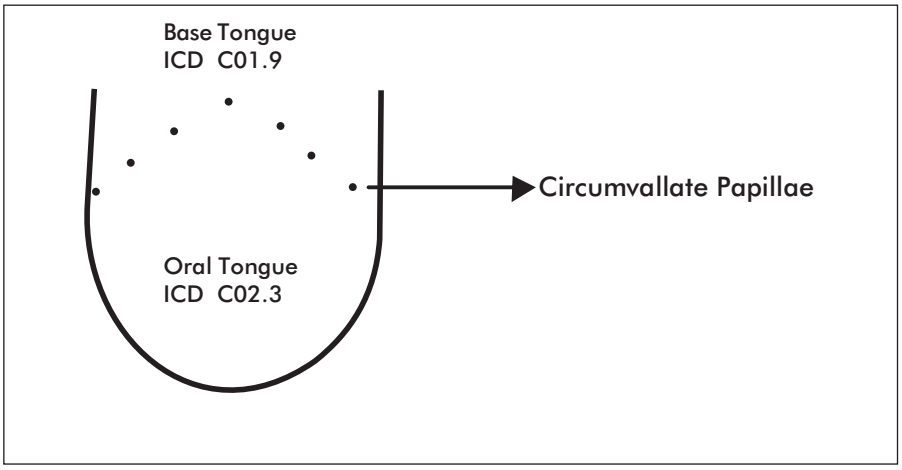


Figure 1. Oral tongue & base tongue

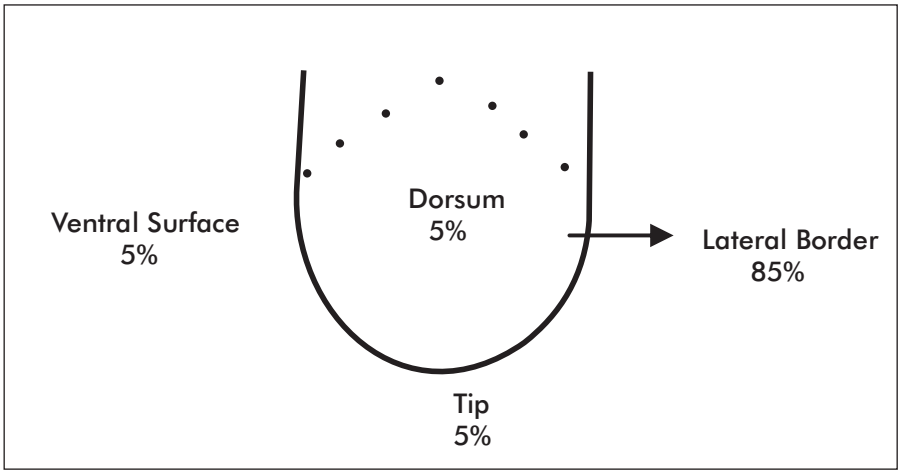


Figure 2. Distribution of oral tongue cancer.

CHAPTER

5 RISK FACTORS

1. Tobacco & Areca nut

Tobacco is the single most important risk factor for cancers of the oral cavity including tongue cancers. The use of both smoked as well as smokeless tobacco predisposes a person to cancer. Tobacco specific nitrosamines (TSNA) present in smokeless tobacco are the most harmful carcinogens which are also responsible for various precancerous lesions. Areca nut by itself is also a proven carcinogen[37].

2. Alcohol

Alcohol is a known group 1 carcinogen for oral cavity cancers[37]. It has a synergistic effect when used in combination with tobacco. Studies have reported several fold increased risk of cancer in the presence of excessive use of both the agents[38]. The use of alcohol is an important risk factor for carcinoma of oral tongue and floor of mouth.

3. Others

Human papilloma virus (HPV) is not a well established factor for oral tongue cancers. In a study done by Mulherkar et al, the incidence of HPV infection in patients with head neck cancers was 31%, majority of whom were oral cavity cancers. In this study the technique used was PCR amplification of genomic DNA extracted from tumor tissues and the corresponding adjacent normal mucosa from using 2 sets of primers in the L1 ORF of the HPV genome[39]. In another study from India HPV was detected in 48% cases of tongue cancer using PCR assay while none was detected in the control group[14]. This suggests that there may be a possibility of HPV with tongue cancers particularly in non tobacco and alcohol users.

Malnutrition or a diet lacking in chemo-protective vitamins namely A, C & E has been shown to be a predisposing factor[40-41]. Poor dental hygiene and sharp teeth are also implicated in the etiology of tongue cancers.

CHAPTER

6 DIAGNOSIS AND INITIAL WORK UP

6.1 History

- Disease related information (onset, duration, pain, difficulty in swallowing, movement of tongue, alteration in speech, dental history *etc.*)
- History of habits and addictions
- Medical and family history, including any prior malignancy
- Coexisting co morbidity
- Prior treatment with details

6.2 Examination

Important points to consider are –

- Size
- Location
- Extent
- Posterior- base of tongue / vallecula / tonsil involvement
- Lateral/ deep extent of the tumor, relationship to midline, mandible and hyoid
- Ankyloglossia
- Hypoglossal nerve palsy
- Cervical adenopathy (tongue has high propensity to contralateral metastasis particularly in larger tumors)

Examination under anesthesia may be considered in some cases when clinical examination is difficult in view of pain/trismus/previous treatment.Examination of upper aero-digestive tract is done to rule out second primary (hopkins/fiberoptic laryngoscope).

6.3 Histological Diagnosis

i. Biopsy

Biopsy of the lesion to confirm the presence of carcinoma and to know the histological type. Assessment of grading is difficult and not mandatory on a biopsy specimen.

- Punch biopsy from most representative area avoiding obviously necrotic areas
- Incisional biopsy for submucosal lesions/patch/verrucous lesions when punch biopsy is not feasible or non contributory.

ii Scrape cytology

Acts as an adjunct and not a substitute for formal biopsy. A negative scrape cytology with strong clinical suspicion warrants biopsy. Occasionally the confirmatory biopsy that follows positive scrape cytology may be negative. This is usually due to inadequate sampling of a representative area from the lesion. The biopsy needs to be repeated in such cases.

iii. Ancillary diagnostic tools/molecular techniques

At present there is no role for ancillary diagnostic tools/molecular techniques (brush biopsy, toludine blue, autoflourescence, salivary diagnostics) though there is an emerging interest.

6.4 Imaging

Imaging complements clinical examination in assessing the extent of the primary lesion and also indicates nodal involvement. This can help decide appropriate therapy, assess resectability, plan resection with reconstruction and indicates prognosis.

i. Pretreatment imaging

a. OPG

Limited role for evaluating bone erosion in tongue cancers due to low specificity owing to high incidence of periodontitis and odontogenic infections in our population. At least 30% mineral loss is required before bone erosion is detected[42-43]. It is useful for planning mandibulotomy and for dental treatment prior to radiotherapy.

b. High resolution Ultrasonography (USG) with guided FNAC

USG is performed real time with a 5- 10 MHz linear transducer and may be useful in evaluating the clinically negative neck for metastatic nodes in early tongue cancers (where imaging may not be undertaken to evaluate the primary T1 lesions). It could be used to guide fine needle aspiration of suspicious nodes and can also influence the extent of neck dissection by revealing extent of nodal disease. A meta-analysis revealed higher sensitivity of USG as compared to CT and MRI for assessing metastatic neck nodes and showed highest accuracy with USG guided FNAC[44]. However this meta-analysis was performed in both N+ and N0 necks and USG guided FNAC has reported lower accuracy in the N0 neck[44].

c. CT/MRI

Few studies exist comparing CT and MRI for imaging the oral cavity with emphasis on tongue cancers. MRI is favored over CT for T staging (better soft tissue delineation) particularly for tongue and floor of mouth squamous cancers while CT and MRI were comparable for N staging[45-51]. Diffusion weighted MR imaging is evolving and is reported to be superior to conventional MRI for detecting metastatic node[51]. A recent meta-analysis reported equivalence of CT, MRI and USG for neck nodes in the clinically negative neck[52].

Level of evidence (for MRI in T staging) - II and III

Level of evidence (for equivalence of USG, CT & MRI in N staging) - II; two meta-analyses[51-52].

- **Helical CT /Multidetector CT**

CT has the disadvantage of insufficient soft tissue characterization for imaging the tongue and preferably to be used when MRI not available. If CT is done then contrast enhanced CT is mandatory; performed after injection of 50-80 ml low osmolar non-ionic iodine containing contrast; CT images to be viewed at high contrast settings. Multidetector CT with multiplanar reformations (at least 16 slice scanner) is preferred. If helical CT is used, 3 mm sections in soft tissue and bone algorithms are needed.

MDCT- Axial images are preferably to be viewed with coronal reformation to assess extrinsic muscles and neurovascular bundle. Both soft tissue and bone algorithms are to be viewed along with axial and coronal reformations to assess the mandible.CT is most specific modality for mandibular erosion with high positive predictive value. However mandibular invasion is infrequent in tongue cancers, seen in < 10%, i.e in advanced cancers or bulky tumors reaching or involving floor of mouth.

- **MRI (Multiplanar and gadolinium enhanced)**

Imaging method of choice due to superior soft tissue characterization and when performed optimally provides accurate information regarding staging and tumor thickness[53-57]. MRI study is not optimal without post gadolinium scanning; the tumor-normal tongue contrast is maximum on contrast enhanced T1W sequences that helps achieve accurate staging[53-54]. MRI is very sensitive for mandibular erosion and has high negative predictive value, but can overestimate cortical erosion due to chemical shift artifacts[58].

Nodal status is studied with a combination of T2W, STIR and post-gadolinium sequences but adding diffusion weighted imaging (if available) can increase accuracy of nodal status evaluation[59-60].

d. PETCT

PETCT is not routinely used in the initial workup for tongue cancers[61-62]. It has an optional role for evaluating distant metastases in stage III & IV tongue cancers particularly with large nodes in the lower neck[2]. It can depict the extent of nodal involvement in the N+ neck, but has no role in the evaluation of the N0 neck.

Level of Evidence – II

ii. Recommended imaging method for different stages

1. T1 & early T2 cancers -Imaging is Desirable

Imaging may not be required for the primary; neck may be investigated for nodal metastases due to high incidence of occult metastases (27-40%)[63]. Ultrasound is cost effective and widely available, but it should be noted that both USG and USG guided FNAC have lower accuracy in the N0 neck.

2. Larger T2 , T3 &T4 cancers-Imaging is Essential

MRI—preferred *(Ideal)*

It demonstrates the deep extent (posterior and inferior) of the primary lesion and could give information on status of neck nodes.

iii. Structured reporting (to provide complete information)

Report should include the following features-

A. Primary lesion (MRI / CT)

1. Epicenter and tumor dimensions (cranio-caudal, transverse and antero-posterior) for T staging
2. Tumor thickness
3. Extent

a) Relationship to midline

b) Involvement of extrinsic muscles, invasion of lingual neurovascular bundle (perineural invasion) and muscles of floor of mouth.

c) Posterior extent to base tongue, tonsil and rest of oropharynx, pre-epiglottic space, and hyoid bone (relative contraindications to surgery).

d) Mandibular involvement and extent (to decide the need, type and site of mandibulectomy).

e) Posterior extent to masticator space and pterygoid plates (unresectable).

B. Nodes

a. MRI/CT

1. Number & size of abnormal nodes
2. Level of abnormal nodes
3. Ipsilateral, contralateral or bilateral
4. Presence of necrosis
5. Evidence of extra-capsular spread
6. Invasion of adjacent structures and vessels (circumferential contact with ICA/CCA)

b) Ultrasonography

- **Features of metastatic nodes**

1. **Abnormal echotexture -** Heterogeneity and necrosis (cystic necrosis appears as low reflective areas and coagulative necrosis may appear as brightly reflective areas).
2. **Absent hilum -** Exception; small normal nodes may not display hilum.
3. **Shape** - Rounded (exception - normal submental and submandibular nodes can be rounded). Eccentric cortical hypertrophy can indicate metastatic seeding, particularly if hypertrophied region has abnormal echotexture
4. **Size -** Criterion not reliable. Enlarged nodes can be reactive, granulomatous or metastatic. Metastatic nodes can be sub-centimeter. The nodes in the draining region of the primary –level II, IB and III need careful scrutiny as these levels are at maximum risk.
5. **Margins** - Ill defined margins in metastatic nodes are suggestive of extra-capsular spread.
6. **Doppler Features** - Used as an adjunct to gray scale and not as independent parameter

Diffuse vascularity, peripheral vascularity and absent vascularity may be seen in metastatic nodes. Normal nodes usually display central / hilar vascularity.

- **Ultrasound guided FNAC** (With 22 -23 G needle)

Ideal **-** Onsite checking of adequacy of aspirate under light microscope is preferable to avoid repeats.

iv. Imaging criteria to help distinguish between operable and inoperable locally advanced disease

Following are contraindications for surgery

a. Primary - Extension to masticator space, pterygoid plates, skull base, and ICA

b. Nodal - Disease encasing ICA / CCA more than 270 degrees (more than / equal to three fourths of the circumference)

CHAPTER 7

STAGING (ESSENTIAL)

TNM Staging (AJCC, 2010)

Staging is for oral cavity in general. No separate staging for tongue cancers, applicable for buccal cancers as well[64].

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

T4a Moderately advanced local disease

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 (ICA).

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

Regional lymph nodes

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Ipsilateral single lymph node 3 cm or less in greatest dimension
N2a	Ipsilateral single lymphnode more than 3 cm, not more than 6 cm in greatest dimension
N2b	Ipsilateral multiple lymph nodes, none more than 6cm in greatest dimension
N2c	Bilateral/contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Lymph node more than 6 cm in greatest dimension

Metastasis

M0 No metastasis

M1 Distant metastasis

Stage grouping

	N0	N1	N2	N3
T1	Stage I			
T2	Stage II			
T3	Stage III			
T4a	Stage IV A			Stage IV B
T4b				

Stage IVA - Surgically operable cancers

Stage IV B - Surgically inoperable cancers

CHAPTER

8 MULTIDISCIPLINARY TREATMENT OF TONGUE CANCERS

Treatment decisions are based on the clinico-radiological staging of the tumor. It is imperative at the beginning to decide the intention of the treatment which should be curative (stage I-IVA) or palliative (stage IVB-loco-regionally advanced and stage IVC - metastatic disease). Occasionally a stage IVB tumor may respond to treatment and subsequently be amenable for surgical salvage. However the percentage of such cases is few and should be carefully selected.

Early stage disease is treated with single modality therapy either surgery or radiotherapy. Surgery is preferred because of its simplicity, low cost, no significant functional or cosmetic deficit and that it can be repeated. Locally advanced operable cancers are treated with combined modality therapy, surgery followed by postoperative radiotherapy or chemo-radiation.

Early stage disease (Stage I & II)
• Single modality treatment (Surgery or radical radiotherapy)
• Surgery preferred

Table 1. Management of early stage disease

Advanced stage disease (Stage III & IV)
• Combined modality treatment
• Surgery followed by Radiotherapy/Chemoradiotherapy

Table.2. Management of advanced stage disease

8.1 Surgical considerations

a. Excision of primary

Wide local resection of tumor with adequate margins.

1. Resection with clear margin

Positive/close surgical margins compromise survival[65-66]. Assessment of depth of tumor by digital palpation and imaging is an essential prerequisite for obtaining appropriate deep margin. It is preferable to have a 1 cm clear margin around tumor in all dimensions at surgery as margins shrink 20-30% after resection. Any margin less than 5 mm is compromised and warrants adjuvant treatment.

8.2. Adequate surgical access is key to obtaining an en-bloc resection with clear margins

Access may be –

- Per oral
- Mandibulotomy (paramedian with preservation of mental nerve)
- Pull through technique - Combined neck and intraoral approach

Approach	Indication
Peroral	Adequate mouth opening , lesion well visualized in its entirety
Mandibulotomy	Inadequate mouth opening, larger lesions, deep tumor to ensure adequate lateral and deep clearance
Pull through	As replacement for mandibulotomy when suitable

Table.3. Various approaches for excision of primary

8.3 Management of mandible

A. General points

- Assessment for tumor involvement of the mandible is based on both clinical and radiological assessment.
- Spread occurs either through the occlusal surface or by direct erosion at the point of abutment of the tumor with mandible.

B. Indications

i. Marginal mandibulectomy

- No direct invasion of mandible by tumor, but tumor in proximity of mandible and would result in inadequate margin otherwise.
- Avoided in post radiation settings as biologically unsafe and risk of osteo-radionecrosis in remnant mandible.

ii. Segmental mandibulectomy

- Mandible invasion by tumor.
- Paramandibular soft tissue involvement that may compromise margins.

8.4 Criteria for unresectability for primary (tongue)

- Ankyloglossia signifies deep infiltration into the root of the tongue and is usually a relative contraindication for surgery as obtaining clear margins may be difficult.
- Skin involvement due to direct extension.
- Extension to infratemporal fossa / masticator space and base of skull.

b. Management of the neck

i Clinically node negative early lesions

a) Stage I (T1NOMO) and stage II (T2NOMO) early tongue cancers

Three treatment modalities are available-

A. Observation

B. Elective neck dissection

C. Elective neck irradiation

A. Observation alone

1. Tumors with low risk of metastasis (<20 % - T1, tumor thickness < 4 mm, well differentiated, no LVE, PNI)
2. Early T1/T2 low risk cancer (read above) cancers treated per orally with no violation of the neck for the approach
3. Patients with reliable follow up
4. Patients with thin neck in whom satisfactory clinical examination(palpation and ultrasonography) is possible
5. Ultrasound negative

B. Elective neck dissection

1. Thick tumor (tumor thickness more than 4 mm)
2. Entry into the neck
3. Cases with unreliable follow up
4. Patients with fat, short neck in whom satisfactory clinical examination (palpation and ultrasonography unavailable) is not possible

C. Elective irradiation

1. In cases where primary tumor is treated by radiotherapy

The need for prophylactic neck dissection is a constant area of debate. Current evidence is in favor of elective neck dissection over wait and watch policy (particularly for those tumors > 4 mm in thickness, poorly differentiated, LVE/PNI positive) as the former may be associated with significantly lower disease specific death rate with better regional control[31] (level II).

b) Extent of neck dissection

Selective neck dissection (SND) with removal of levels I-III

c) Special issues

- **Dissection of level IV**

Tongue cancers are known to harbor skip metastasis to up to 15.8%[67]. Some surgeons recommend clearing level IV as well along with level I-III - extended SOHD. No need for clearing level V as risk is <1% and dissection in this area results in compromise to accessory nerve function.

- **Level II B dissection**

Level IIB, also known as Bocca's area or submuscular recess is defined as an area bounded superiorly by skull base, antero-medially by spinal accessory nerve and postero-laterally by the posterior border of sternocleidomastoid muscle. Dissection of this area is associated with increased risk of nerve dysfunction.

Incidence of occult metastasis in IIB area in N0 neck is very low (2-6%). Isolated IIB metastasis is extremely low.

However current recommendation is to do level IIB dissection in all cases of tongue cancers when I and IIA are positive[68]. Excessive traction and skeletonisation of spinal accessory nerve should be avoided.

ii. Node positive disease

Modified neck dissection depending upon intraoperative findings. Radical neck dissection is avoided. SAN, IJV, SCM are removed only if directly involved by disease.

iii. Contralateral neck

Contaralateral neck to be addressed

- When positive – Modified neck dissection
- Tumor crossing midline – SOHD for node negative, MND if positive.

C. Reconstruction

Defect following excision of tongue cancers are usually reconstructed or closed primarily. Leaving a defect raw is usually not advisable due to the risk of infection, pain and secondary hemorrhage. However with the advent of CO_2 laser, occasionally wounds are left open and defect epithelizes.

The following are the various options used for reconstruction in order of complexity –

i. Primary closure

ii. Skin graft

iii. Local flap

iv. Regional flap

v. Distant flap

vi. Free flap

i. Primary closure

Small defects can be closed primarily. This is facilitated if excision is planned as a 'V'shape. When compromised in speech and function is anticipated, primary closure is avoided.

ii. Skin graft

- Split skin graft which consists of epidermis and part of dermis may be used for superficial defects which cannot be closed primarily without tension.
- Skin grafts are preferred for dorsal tongue defects. Thin skin grafts should be used to ensure good graft take.
- Quilting and tie over are the traditional methods described to keep the graft in place.
- Meticulous oral hygiene to be maintained to prevent graft loss.
- Grafting is usually not a preferred option for reconstruction of oral tongue.

iii. Local flaps

Inferiorly based nasolabial flaps are used in reconstruction of moderate sized tongue defects. The flap is raised along the lateral aspect of the nasolabial skin fold on a subcutaneous pedicle that contains offshoots from the facial artery and vein. Good color match, proximity to the defect, satisfactory contour and less donor site morbidity are the essential advantages of this flap[69].

iv. Regional flap

Submental artery island flap is an option for select small to moderate size tongue defects[70]. However flap necessitates the transfer of submental skin into the oral cavity and usually is not advisable due to hair growth in male patients. Moreover it may compromise nodal clearance while harvesting the flap.

v. Distant flap

Pectoralis major myocutaneous flap (PMMC) is the most frequently used myo-cutaneous flap for large defects especially when a portion of the adjacent lateral segment of the mandible also needs to be resected[71].

vi. Free flap

Radial forearm artery flap (FRAFF) is used for partial tongue defect, anterolateral thigh(ALT) flap for full tongue defects and free fibula osteo-cutaneous flap (FFOCF) is used when bone is excised[72]. Other options include parascapular flap and lateral arm flap.

- Summary

The following may be used as a practical guideline in clinical situations-

a. T1 and T2 cancers with N0 status

No reconstruction if laser excision (for superficial lesions), primary closure (e.g. wedge excision of a tongue tip lesion or excision of lesion located at the lateral border of the tongue), skin graft (not preferred, only for dorsal tongue lesions). If more than 30% of the mobile tongue needs to be resected, a free radial artery forearm flap is preferred. However optional reconstruction may be submental island flap or nasolabial flap where free flap facility is not available.

b. T1 and T2 cancers with N positive

Free radial artery forearm flap (FRAFF) or anterolateral thigh (ALT) flap are preferred. Nasolabial flap may be used as the optional reconstruction where free flap facility is not available.

c. T3 and T4 cancers

- **Free flaps** - Free radial artery forearm flap (FRAFF)or anterolateral thigh (ALT) flap. Free fibula with skin island (FFOCF) in presence of an adjacent mandibular defect that needs reconstruction
- **Pedicled flaps**- Pectoralis majormyo-cutaneous flap (PMMC) or pectoralis major myo-fascial flap (PMMF) is another option if free flap facility is not available.

D. Pathology in the management of tongue cancer

i. Synoptic pathology report for carcinoma of tongue

Pathological data is important for prognostication and in deciding the adjuvant treatment. The following module report lists the information that should be captured. Those marked in **E** are essential while those in **D** are desirable. It is advisable to have the pathology report in a synoptic form to ensure uniformity and capture of all essential data.

Demographic Data

1. Specimen (E): Primary **Primary + Neck**

2. Examination:

A] Appearance of growth (D)

Ulcero-proliferative Ulcero-infiltrative Verrucous

Plaque like Polypoidal Submucous

Length x Breadth

B] Maximum tumor size (cms) (E)

C] Cut margins (E)

Free Involved Close

D] Tumor thickness* (mm) (E)

E] Mandibulectomy(D)

Type Marginal Segmental

Measuring cm along lower alveolar border

Cut surface Free Involved

3. Histopathology Diagnosis:

A] Type of Ca(E)

a] Squamous Adeno Others

B] Type of SCC (D)

Conventional SCC(keratinizing/non keratinising) Variant

Variant – Verrucous Papillary Sarcomatoid

Basaloid Acantholytic Lymphoepithelioma like

C] WHO Grade (D)

I (Well) II (Mod) III (Poor)

D] Stromal invasion

a] Pattern of invasion#(D)

I II III IV

b] Stromal response (D)

Desmoplastic Inflammatory

E] Depth of invasion [mm] (E)

F] Perineural invasion (D)

Yes No

G] Lymphovascular invasion(D)

Yes No

4. Cut margins (E):

1] Positive Negative Close

2] Distance of tumor from the nearest margin (mm)

3] Dysplasia at margin **(D)**

No Yes Low grade High grade

5. Base of excision:(E)

Positive Negative Close mm

6. Involvement of adjacent structures (E):

Bone No Yes Skin No Yes

7. Neck Nodes dissection:

Neck nodes:

	Left		**Yes**	**No**	**Size (D)**	**Right**		**Yes**	**No**	**Size**
Level IA	a/b	ECS	☐	☐	☐		ECS	☐	☐	☐
Level IB		ECS	☐	☐	☐		ECS	☐	☐	☐
Level II		ECS	☐	☐	☐		ECS	☐	☐	☐
Level III		ECS	☐	☐	☐		ECS	☐	☐	☐
Level IV		ECS	☐	☐	☐		ECS	☐	☐	☐
Level V		ECS	☐	☐	☐		ECS	☐	☐	☐

- a =Number of positive nodes, b = Total number of nodes
- ECS- Extra-capsular spread
- Maximum dimension of the largest node in cm
- Any other findings (Treatment related changes etc.)(D)

8. Clinical Stage (D):

T N M

9. Pathological Stage (D):

p T N M

Reported by Dr (E) ---------- Date (E) ----

*Thickness is the third dimension of tumor (surface of the tumor to the deepest part)
Depth is the distance between the adjacent mucosal basement membrane & deepest part of the tumor (figure 3)

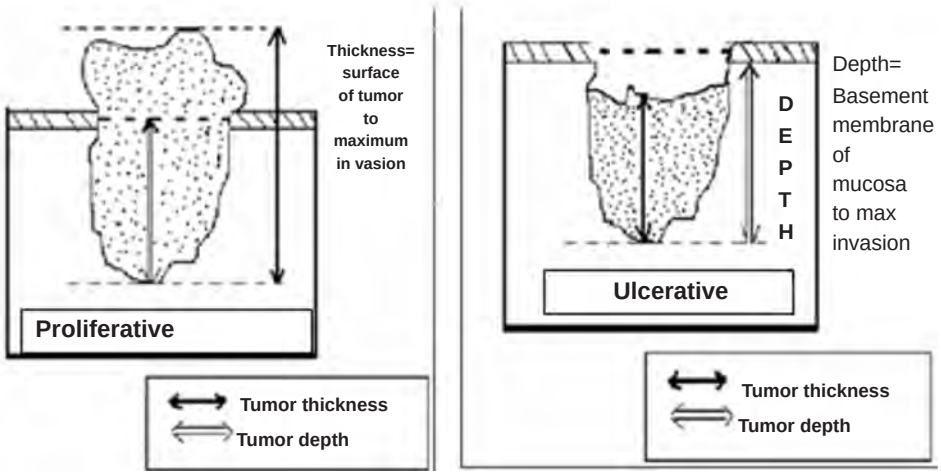


Figure 3. Tumor thickness and depth of invasion

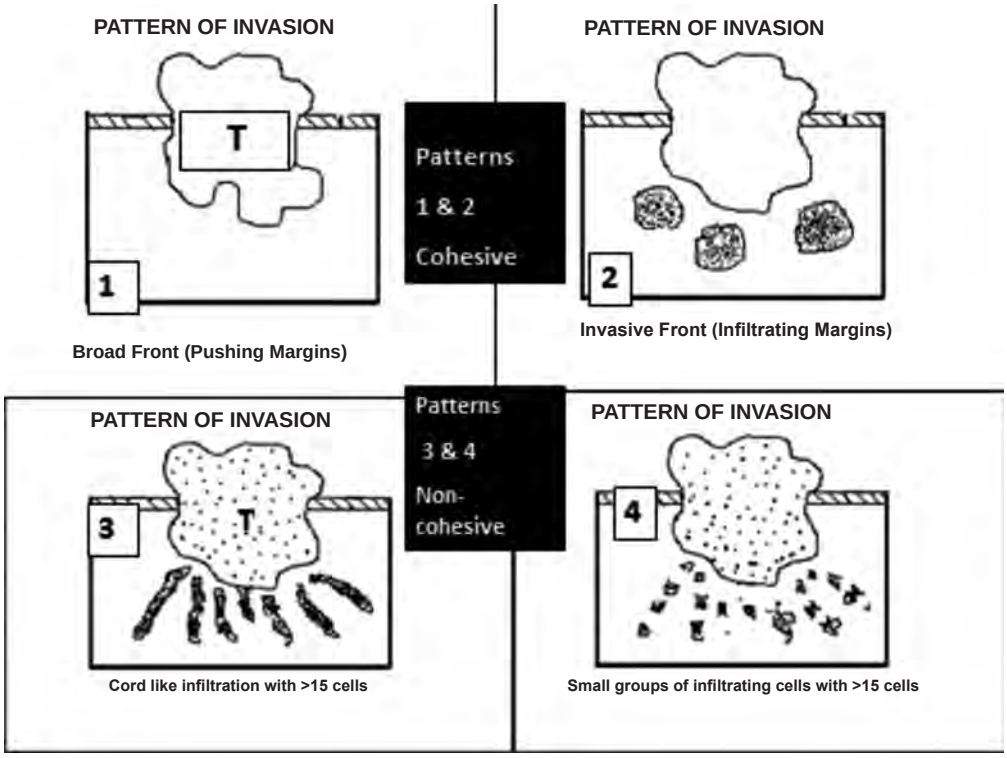


Figure 4. Patterns of invasion of tumor

ii. Role of Immunohistochemistry (IHC) in the diagnosis of Squamous cell carcinoma

Diagnosis of conventional squamous cell carcinoma–keratinising type is straightforward, if representative tissue is submitted. Diagnosis of non-keratinising SCC may be difficult in a biopsy.

The main differential diagnosis of non-keratinising SCC is high grade mucoepidermoid carcinoma (MEC). IHC is used in these cases as an ancillary technique. Diffuse CK 7 positivity is characteristic feature of MEC, in contrast diffuse p63 positivity is a characteristic feature of SCC. Mucin stain also assists in picking up mucin filled glandular cells as their presence tilts the diagnosis towards mucoepidermoid carcinoma.

When SCC is composed of basaloid cells producing extracellular matrix, then the main differential diagnosis lies between SCC which can produce myxoid & hyaline stroma and adenoid cystic carcinoma (ACC). Though squamous differentiation is the diagnostic hallmark of this variant, about 40% of basaloid SCC fail to exhibit any form of squamous differentiation in a biopsy. Basaloid SCC exhibits diffuse immunopositivity with p63 & HMWCK and negativity or focal positivity with EMA, CK7 & CKIT. ACC in contrast shows diffuse positivity with EMA, CK7 & CKIT and focal positivity with p63 & HMWCK which highlight myoepithelial cells.

Sarcomatoid carcinoma is a rare morphologic variant of oral cavity squamous cell carcinoma. These tumors pose challenge in diagnosis and management when present as pure spindle cell malignancy and lack squamous differentiation.In such a situation, immuno- positivity with epithelial markers (CK, EMA, HMWCK, CK5/6 & p63) should be carefully looked for[73]. Cytokeratin immunoreactivity is often focal or variable (40-85%). Only about 70% of cases of sarcomatoid carcinoma yield some reactivity with epithelial markers. A number of mesenchymal markers can be identified focally like smooth muscle actin, muscle-specific actin and calponin indicative of myofibroblastic differentiation. p63 immunopositivity is noted to be the most diagnostically useful.

e. Radiotherapy in management of tongue cancer

Radiotherapy can be used in the following settings-

1. Primary treatment
2. Adjuvant treatment
3. Palliative treatment

1. Primary radiotherapy

Radiotherapy can be delivered as external beam radiotherapy (EBRT) alone, brachytherapy alone or EBRT followed by brachytherapy boost.

a) Brachytherapy alone

Brachytherapy alone is a safe and short duration treatment. It has following advantages-

- Delivery of high dose is possible in a short period of time.
- Rapid dose fall off towards the periphery allows excellent normal tissue sparing.
- Decreased volume of tissue irradiated leading to better cosmetic result.
- Because of fixed relationship of sources in relation to target volume setup errors are minimized.

- Treatment interruption is uncommon as acute radiation reactions are sharply localized and usually occur after treatment completion.

i. Indications

- Early, accessible, superficial lesions preferably <2-3 cm
- Lesions situated well away from the bone
- Node negative status

ii. Brachytherapy interstitial implant

Brachytherapy may be delivered using low dose rate or high dose rate systems[74-75].

Typically dose prescription encompasses the primary with 1.0-1.5cm margins. The regional nodes are not addressed at this time of treatment.

iii. Brachytherapy dose

Low dose rate brachytherapy (LDR) 65-70Gy/6-7 days

High dose rate brachytherapy (HDR) 48Gy/12fr 4Gy 1BD x 6 days

b) EBRT alone

EBRT is delivered with megavoltage equipment with 2D conventional, 3D conformal (3DCRT) radiotherapy or intensity modulated radiotherapy (IMRT). Patient is appropriately immobilized and optimum planning is done with use of tissue compensator/wedges if required.

i. Rationale of radiotherapy

a) All histopathological variants are radiosensitive and radio responsive.

b) It has ability to treat tumor invasion beyond the gross disease with preservation of structural integrity of adjacent vital organs.

c) Least morbidity/mortality.

d) Two and five year survival equivalent (if not superior) to other modalities of treatment.

ii. Fractionation

1. Conventional fractionation:

EBRT doses of 66-70 Gy per fraction over 6-7 weeks (or biologically equivalent dose) with adequate margins all around the lesion and including level I and IV nodes[76].

2. Altered fractionation:

Altered fractionation has been used in head and neck cancers for improving loco-regional control and survival too by altering the overall time, changing the dose or dose per fractionation[77-78].

Hyperfractionation schedules though have survival advantage with least late effects but is resource demanding. However, accelerated fractionation definitely improves loco-regional control and is less resource demanding and can be easily integrated like in high precision simultaneous integrated boost.

A. Hyperfractionation

81.6 Gy in 7 weeks at 1.2 Gy b.i.d.

B. Accelerated fractionation /concomitant boost:

70 Gy in 6 weeks (6 days radiotherapy 2 Gy per fraction) or 72 Gy in 6 weeks (1.8 Gy/fraction large field; 1.5 Gy boost as second daily fraction during last 12 treatment days).

C. EBRT + brachytherapy boost

Patients who are not suitable for brachytherapy alone (i.e. large or bulky primary disease) may be treated with EBRT followed by brachytherapy boost. EBRT is delivered using conventional planning / 3DCRT/ IMRT to primary and neck. Dose of EBRT is restricted to 45-50 Gy and brachytherapy boost {dose of 20-25 Gy (LDR) or equivalent HDR} is also given.

Level I-IV neck nodes will be encompassed in the EBRT portals.

2. Adjuvant treatment

i. Post-operative EBRT +/- chemotherapy

This is part of the planned treatment in locally advanced disease. Minimum dose should be 56 Gy with 2 Gy per fraction.

The dose should be escalated to 60-66Gy in high risk areas.

Indications

Post-operative radiotherapy is indicated in following conditions[79,80]

Primary

- T3/T4
- High grade
- LVE/PNI
- Close margin

Nodal

- Node positive

ii. Post-operative chemoradiotherapy

Indications

- Extra capsular spread (ECS)
- Positive margin[24-26]

Concurrent single agent cisplatin 100 mg/m^2 every 3 weeks or 30-40 mg/m^2 per week for the entire course of radiotherapy is recommended. It is suggested that the total dose of 200 mg/m^2 needs to be maintained. Additionally anti-emetics and hydration needs to be carefully used.

3. Palliative EBRT

If the primary and /or nodal disease is symptomatic, consider palliative EBRT. Conservative portals of EBRT with smaller margins to be used: Various fractionation regimes are used. The commonly practiced regimes are 40 Gy/16Fr/4 weeks or 30 Gy/10 Fr/2 weeks or 20Gy/5 Fr/1 week, however in responders the dose may be escalated to consolidate the response[81].

i. Organ at risk dose constraints

Spinal cord <45 Gy, brainstem <54 Gy, parotid glands mean dose <26 Gy and/or attempt to keep 50% volume of each parotid <20 Gy (if possible), mandible <70 Gy, retina <45 Gy, larynx mean dose <43.5 Gy, mean (max) cochlea <37 (45) Gy, thyroid <25–35 Gy depending on adjacent adenopathy.

When possible, minimizing dose to the larynx and inferior pharyngeal constrictor muscles may reduce the risk of late swallowing dysfunction.

ii. Pre-radiotherapy evaluation

- Dental evaluation by dental experts for appropriate extraction of non-salvageable teeth and restoration of dental health with dental filling along with fluoride prophylaxis.
- Nutritional evaluation and support
- Psychosocial support
- Tobacco cessation
- Speech and swallow therapy

iii. Sequalae of RT

- **Acute:** Mucositis, skin discoloration/desquamation.
- **Late:** Skin/soft tissue fibrosis, hyperpigmentation, telangiectasias, swallowing dysfunction, voice alteration, alteration in taste, xerostomia, dental complications, chronic aspiration.

iv. Rehabilitation

- Abstinence from tobacco / alcohol
- Maintain good 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

f. Chemotherapy in management of tongue cancer

Chemotherapy is not a definitive treatment for tongue cancers and should never be given if the initial lesion is operable. The recommendations that follow are extrapolations from the results of studies enrolling the patients with head and neck cancers in general.

Chemotherapy can be given as:

i. Concurrent chemoradiation

ii. Induction/ neoadjuvant chemotherapy

iii. Chemotherapy for recurrent/metastatic disease

i. Concurrent chemoradiation

Concurrent chemoradiation is useful either as adjuvant treatment in operable tongue cancer or as definitive treatment in advanced (inoperable) tongue cancer[82,83].

a) Adjuvant treatment in operable tongue cancer

Please refer to the section on radiotherapy. Indications are-

- Extra-capsular spread
- Positive margins

The role of adjuvant CTRT for other adverse indications such as level IV/V nodes positive, perineural invasion, lymphovascular embolization and T3/T4 tumor is debatable. Current guidelines do not recommend CTRT for these indications. However when more than one of these adverse factors are present, careful considerations should be given for CTRT and patient counseled about the risk benefit ratio.

b) Definitive treatment in advanced (inoperable) tongue cancer

If the patient can tolerate CTRT, response is most durable compared to other modalities of treatment.

- Dosing

Evidence exists for 100 mg per square meter cisplatinum administered three weekly on days 1 and 22 and 43 of radiation as concurrent chemotherapy. Smaller weekly dose of cisplatinum between 30-40 mg per square meter is a widely accepted practice in India as well as elsewhere and this may also be recommended. However it is imperative to have a total dose of 200 mg/met^2 of cisplatinum.

If the patient is unsuitable for chemotherapy, biological agents (cetuximab, nimotuzimab) or carboplatin may be considered.

Concurrent chemoradiation is associated with significant short and long term toxicities. It is strongly recommended that this treatment be offered only at the high volume centers with adequate multimodality team capable of handling the toxicities. Maintenance of nutrition during therapy results in better compliance and use of tube feeding should be considered when needed.

ii. Induction/neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy is a debatable issue in tongue as well as in head neck cancers. Induction chemotherapy has been used in inoperable T4b cancers and responders considered for surgical salvage[21]. Patients most likely to benefit with such an approach are those in whom upfront surgery would have resulted in positive margins. The best regimen for induction therapy is the three drug platinum based regimen that includes taxane, cisplatinum and 5 flourouracil. Usually three cycles are given but patients are assessed after two cycles. Following induction chemotherapy, if on fresh evaluation patient is found to have resectable tumor, should be offered surgery followed by chemoradiation. This treatment needs an experienced team and a motivated patient with good performance status without co-morbidities. Alternately, definitive concurrent chemoradiation followed by surgical salvage (if possible) may be offered to these patients.

It is essential to identify the patient with large fungating nodes, orocutaneous fistula etc. who are candidates for only palliative care upfront and spare these patients from potential toxicities of definitive therapies.

iii. Chemotherapy for recurrent and metastatic disease

Please refer to the following section on "treatment of recurrent/metastatic disease".

CHAPTER 9

TREATMENT OF RECURRENT/METASTATIC DISEASE

The mainstay of the treatment of patients with recurrent/metastatic tongue cancer is palliation. Pain relief and maintaining the nutrition takes priority in the overall management of these patients. Chemotherapy may be offered to patients with good performance status. Before planning the treatment for recurrent tongue cancer, efforts should be made to identify the occasional patient who may be candidate for surgical salvage or re-radiation.

1. First line

Palliative chemotherapy is usually a two drug regimen unlike the three drug taxane based chemotherapy described in the preceding section. The most widely used and recommended doublet is cisplatinum and 5-flurouracil. The combination of carboplatin and paclitaxel or docetaxel has been described. There is little evidence that addition of a third cytotoxic agent improve the outcome and is not recommended. Addition of cetuximab has demonstrated improvement in progression free as well as overall survival[30]. The regimen is cisplatin, 5-FU and cetuximab. Cetuximab is given weekly till the progression of disease. Although there is evidence to suggest benefit of this regimen, it is costly and the cost benefit ratio is not established. Current guidelines such as NICE donot approve its use in patients who may claim reimbursement. Patients with compromised performance status or those with comorbidities may be offered single agent chemotherapy or only palliative care. The preferred single agents are cisplatinum, carboplatin, methotrexate, paclitaxel, docetaxel or 5-flurouracil. Patients with poor performance status or significant comorbidities are the candidates for only palliative care. Wherever possible, patients should be offered to participate in clinical trials.

2. Subsequent line

The outcome of patient failing first line therapy is even poorer. Patients with poor performance status or those progressing while on first line chemotherapy are best offered only palliative care. Highly selected patients with good performance status who responded to first line chemotherapy can be offered single agent chemotherapy other than the drug already used in first line. Wherever possible, patients should be offered to participate in clinical trials.

CHAPTER

10 FOLLOW UP

- Every two to three months for first 2 years
- Three to four months for the 3rd year
- Six monthly for next 2 years
- Annually thereafter
- On every follow up thorough head and neck examination for loco-regional control, second primary tumor and late sequelae of treatment. Investigation only if indicated by symptoms and positive clinical findings.
- Chest X-Ray
- Serum T3, T4, TSH annually if neck is irradiated

CHAPTER

11 PALLIATIVE CARE

11.1.1 Best symptom control (Essential)

There is a need for continuous symptom control in the overall palliative treatment.

Pain control as per the WHO protocol -

Level I - NSAIDS

Level II - Addition of weak opioids

Level III - Strong opioids

Nerve blocks may be considered if appropriate.

11.1.2 Other symptom control

- Dysphagia by nasogastric (Ryles) tube insertion for feeding which may require endoscopic assistance.In rare situations a feeding gastrostomy or jejunostomy may be required
- Airway compromise by a tracheostomy
- Anxiety and depression by psychotherapy and appropriate drugs
- Wound care - Appropriate dressing and topical antibiotics may be considered
- Bleeding by external carotid artery ligation

11.2 Definitive treatment (Desirable)

i. Palliative Radiotherapy

If the primary +/- nodal disease is symptomatic, consider palliative EBRT. (Please refer to palliative RT section)

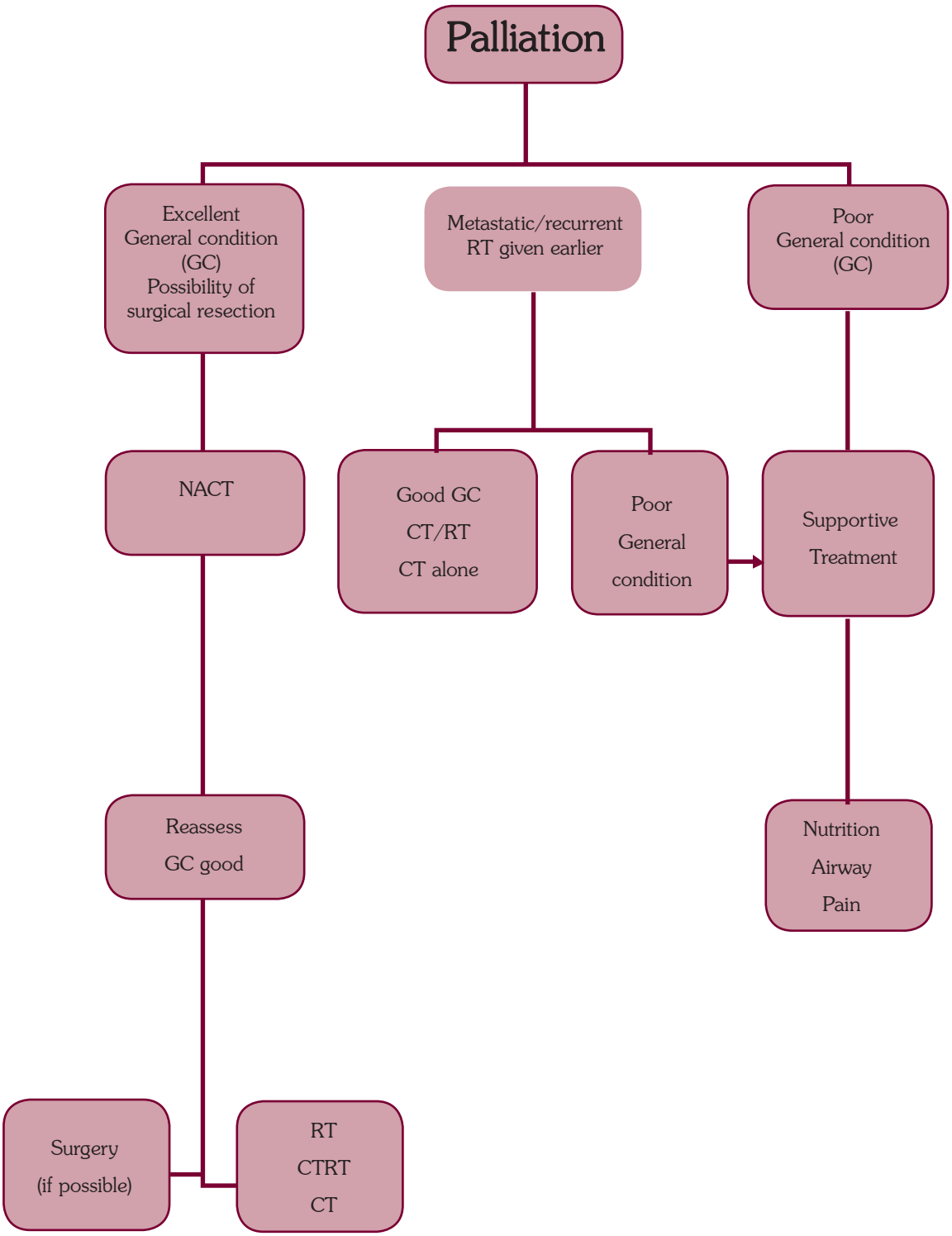
ii. Palliative Chemotherapy

Based on the performance status and affordability of the patient with single agent methotrexate or cisplatin or two drug regime with cisplatin and 5-FU may be given if the disease continues to progress after palliative RT.

In a tertiary referral institution well designed clinical trial with promising newer chemotherapeutic or biological agents may be added to the above measures.

Low dose maintenance chemotherapy may be given in patients with good disease control (stable disease). Drugs include methotrexate and geftinib.

Palliative treatment algorithm



CHAPTER

12 POTENTIALLY MALIGNANT DISORDERS (PMDS) OF TONGUE

12.1 Leukoplakia

- Leukoplakia of the tongue can be described as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"[84].
- The estimated malignant transformation rate is 1% per year[85].
- Tobacco and alcohol are the most important risk factors.

Management

Tongue is considered a high risk site for transformation into malignancy and majority are treated by excision. This is particularly so when there is –

- o A long duration of leukoplakia
- o Size > 2 cm
- o No habits
- o Idiopathic
- o Female gender
- o Non-homogeneous type
- o Presence of dysplasia

Other leukoplakias may be followed up if the patient is compliant. The role of chemopreventive and anti-oxidants has not been established in the management of leukoplakia. It is important to council patients to give up their habits in patients with premalignant lesions.

12.2 Erythroplakia

- Erythroplakia can be defined as "a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease"[84].
- If not treated, majority of the erythroplakia will undergo malignant transformation[85].
- **Management**
- o Wide excision of the lesion (margin of excision is controversial)
- o Removal of causative factor like tobacco and alcohol cessation, sharp tooth removal is mandatory.
- o Regular follow up

12.3 OSMF (Oral submucous fibrosis)

- It is premalignant condition.
- Prevalent in South-east Asia.
- Characterized by inability to open mouth, intolerance to spice, aphthous ulcers, pale blanch mucosa and inability to protrude tongue.
- High propensity for such patients to develop malignancy.
- No specific treatment but patients to be encouraged to stop habits and maintain good nutritious diet.

CHAPTER

13 RESEARCH ISSUES

1. Role of chemo-preventive agents for premalignant lesions e.g. Curcumin.
2. Establish the role for early detection of cancers - community screening programs, ancillary methods for diagnosis - autoflouroscence, salivary diagnostics.
3. Clinically N0 neck- Need for prophylactic neck dissection, extent of neck dissection, clinical and molecular markers to predict metastasis.
4. Identify patients most likely to benefit from induction chemotherapy.
5. Role of oral metronomic (low dose, low cost) chemotherapy vs. current doublet chemotherapy for recurrent/metastatic disease.
6. Identification of molecular markers to help predict response to treatment and prognosis

CHAPTER

14 BIBLIOGRAPHY

1. National cancer registry programme, Three-year report of the population based cancer registries: 2009-2011. Indian Council of Medical Research, India.
2. NCCN Guidelines Version 1.2014, Cancer of the Oral Cavity, National Comprehensive Cancer Care. Clinical Practice Guidelines in Oncology (NCCN Guidelines). Available at: http://www.NCCN.org.
3. Yorkshire Cancer Network (YCN) Head and Neck Cancer Treatment Guidelines Version 4. 2014. (NHS Guidelines). Available at: http://www.ycn.nhs.uk.
4. National Institute for Clinical Excellence (NICE) Guidance on Cancer Services: Improving Outcomes in Head and Neck Cancers 2004 (NHS): Available at http://www.nice.org.uk.
5. Pivot X, ESMO Guidelines Task Force. ESMO Mimimum Clinical Recommendations for diagnosis, treatment and follow up of squamous cell carcinoma of the head and neck. Annals on Oncology 2003; 14:1014-15.
6. D'Cruz AK, Chaukar D, Gupta T, Agarwal JP, Prabhash K, Laskar S, et al. Evidence based management of cancers in India: Guidelines for Head Neck cancers Vol XI. Mumbai: Tata Memorial Centre; 2012.
7. Fakih AR, Rao RS, Borges AM, Patel AR. Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. Am J Surg.1989;158(4):309-13.
8. Fakih AR, Rao RS, Patel AR. Prophylactic neck dissection in squamous cell carcinoma of oral tongue: a prospective randomized study. Semin Surg Oncol.1989; 5(5):327-30.
9. Kuriakose MA, Loree TR, Hicks WL, Welch JJ, Wang H, DeLacure MD. Tumour volume estimated by computed tomography as a predictive factor in carcinoma of the tongue. Br J Oral Maxillofac Surg. 2000; 38(5):460-5.
10. Kane SV, Gupta M, Kakade AC, D' Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. Eur J Surg Oncol. 2006; 32(7):795-803.
11. Uma RS, Naresh KN, D'Cruz AK, Mulherkar R, Borges AM. Metastasis of squamous cell carcinoma of the oral tongue is associated with down-regulation of epidermal fatty acid binding protein (E-FABP). Oral Oncol. 2007; 43(1):27-32.
12. D'Cruz AK, Siddachari RC, Walvekar RR, Pantvaidya GH, Chaukar DA, Deshpande MS, Pai PS, Chaturvedi P. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. Head Neck. 2009; 31(5):618-24.

13. Bhalavat RI, Mahantshetty UM, Tole S, Jamema SV. Treatment outcome with low-dose-rate interstitial brachytherapy in early-stage oral tongue cancers. J Cancer Res Ther. 2009; 5(3):192-7.

14. Elango KJ, Suresh A, Erode EM, Subhadra L, Ravindran HK, Iyer SK, et al. Role of human papilloma virus in oral tongue squamous cell carcinoma. Asian Pac J Cancer Prev. 2011; 12(4):889-96.

15. Chaturvedi P, Singh B, Nair S, Nair D, Kane SV, D'cruz A, et al. Utility of frozen section in assessment of margins and neck node metastasis in patients undergoing surgery for carcinoma tongue. Journal of cancer research and therapeutics suppl 2: 2012; S100-05.

16. Balasubramanian D, Thankappan K, Battoo AJ, Rajapurkar M, Kuriakose MA, Iyer S.Isolated skip nodal metastasis is rare in T1 and T2 oral tongue squamous cell carcinoma. Otolaryngol Head Neck Surg. 2012; 147(2):275-7.

17. Thankappan K, Kuriakose MA, Chatni SS, Sharan R, Trivedi NP, Vijayaraghavan S, Sharma M, Iyer S. Lateral arm free flap for oral tongue reconstruction: an analysis of surgical details, morbidity, and functional and aesthetic outcome. Ann Plast Surg. 2011; 66(3): 261-6.

18. Sharma P, Shah SV, Taneja C, Patel AM, Patel MD. A prospective study of prognostic factors for recurrence in early oral tongue cancer. J Clin Diagn Res. 2013; 7(11):2559-62.

19. Krishnamurthy A, RamshankarV. Early Stage Oral Tongue Cancer among Non-Tobacco Users - An Increasing Trend Observed in a South Indian Patient Population Presenting at a Single Centre. Asian Pac J Cancer Prev, 2013; 14 (9),5061-65.

20. Singh B, Nair S, Nair D, Patil A, Chaturvedi P, D'Cruz AK. Ipsilateral neck nodal status as predictor of contralateral nodal metastasis in carcinoma of tongue crossing the midline. Head Neck. 2013; 35(5):649-52.

21. Patil VM, Noronha V, Muddu VK, Gulia S, Bhosale B, Arya S,et al. Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: does it make a difference? Indian J Cancer. 2013; 50(1):1-8.

22. Thiagarajan S, Nair S, Nair D, Chaturvedi P, Kane SV, Agarwal JP, et al.Predictors of prognosis for squamous cell carcinoma of oral tongue. J Surg Oncol. 2014 Mar 12. doi: 10.1002/jso.23583.

23. Sessions DG, Spector GJ, Lenox J, Haughey B, Chao C, Marks J. Analysis of Treatment Results for Oral Tongue Cancer. The Laryngoscope 2002; 112:616-25.

24. Bernier J, Domenge C, Ozsahin M, et al. Postoperative Irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004; 350:1945–52.

25. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004; 350:1937–44.

26. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005; 27(10):843-50.

27. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007; 357(17):1695-704.

28. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007; 357(17):1705-15.

29. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008; 359(11):1116-27.

30. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies.Cancer. 2009; 115(7):1489-97.

31. Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. 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. Oral Oncol. 2011; 47(5):320-4.

32. .D'Cruz AK, Dandekar MR. Elective versus therapeutic neck dissection in the clinically node negative neck in early oral cavity cancers: do we have the answer yet? Oral Oncol. 2011; 47(9):780-2.

33. J.S. Poling a, X. J. Mab, S. Bui b, Y. Luo b, R. Li c, W.M. Koch c, W.H. Westra Human papillomavirus (HPV) status of non-tobacco related squamous cell carcinomas of the lateral tongue Oral Oncology. 2014; 50:306–10.

34. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al.GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.

35. Dikshit R, Gupta PC, Ramasundarahettige C, GajalakshmiV, Aleksandrowicz L, Badwe R, et al. Cancer mortality in India: A nationally representative survey. Lancet 2012; 379(9828):1807-16.

36. Hibbert J, Watkinson JC, Gaze MN, Wilson JA, eds. Stell and Maran's Head andNeck Surgery, 4th edn, Arnold Publishers, London; 2000 p.293.

37. International agency for research on cancer. 2012 Agents Classified by the IARC Monographs, Volumes 1–105.

38. McCoy GD, Wynder EL. Etiological and preventive implications in alcoholic carcinogens. Cancer Research 1979; 39:2844-50.R

39. Koppikar P, deVilliers EM, Mulherkar R. Identification of human papillomaviruses in tumors of the oral cavity in an Indian community. Int J Cancer 2005 1; 113(6):946-50.

40. La Vechia C, Franceschi S, Levi F, Negri E. Diet and human oral carcinoma in Europe. Oral Oncology European Journal of Cancer 1993; 29:17-22.

41. Garewal HS, Schantz S. Emerging role of B-Carotene and antioxidant nutrients in prevention of oral cancer. Archives of Otolaryngology and Head and Neck Surgery 1995; 121:141-44.

42. van den Brekel MWM, Runne RW, Smeele LE et al. Assessment of tumor invasion into the mandible: the value of different imaging techniques. Eur Radiol 1998:8:1552–57.

43. Rao LP, Das SR, Mathews A, et al. Mandibular invasion in oral squamous cell carcinoma: investigation by clinical examination and orthopantomogram. Int J Oral Maxillofac Surg. 2004:33(5):454-7.

44. de Bondt RB, Nelemans PJ, Hofman PA, et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USg FNAC, CT and MR imaging. Eur J Radiol. 2007; 64(2):266-72.

45. Sigal R, Zagdanski AM, Schwaab G, et al. CT and MR imaging of squamous cell carcinoma of the tongue and floor of the mouth. Radiographics. 1996:16(4):787-810.

46. Dammann F, Horger M, Mueller-Berg M, et al. Rational diagnosis of squamous cell carcinoma of the head and neck region: comparative evaluation of CT, MRI, and 18FDG PET. AJR Am J Roentgenol. 2005:184(4):1326-31.

47. Kimura Y, Sumi M, Sumi T, et al. Deep extension from carcinoma arising from the gingiva: CT and MR imaging features. Am J Neuroradiol. 2002: 23(3):468-72.

48. Yen TC, Chang JT, Ng SH et al. Staging of untreated squamous cell carcinoma of buccal mucosa with 18F-FDG PET: comparison with head and neck CT/MRI and histopathology. J Nucl Med. 2005:46(5):775-81.

49. Ng SH, Yen TC, Liao CT, et al. 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: a prospective study of 124 patients with histologic correlation. J Nucl Med. 2005: 46(7):1136-43.

50. Huang SH, Chien CY, Lin WC et al. A comparative study of fused FDG PET/MRI, PET/CT, MRI and CT imaging for assessing surrounding tissue invasion of advanced buccal squamous cell carcinoma. Clin Nucl Med. 2011:36(7):518-25.

51. Wu LM, Xu JR, Liu MJ, et al.Value of magnetic resonance imaging for nodal staging in patients with head and neck squamous cell carcinoma: a meta-analysis. Acad Radiol. 2012:19(3):331-40.

52. Liao LJ, Lo WC, Hsu WL, et al. Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck-a meta-analysis comparing different imaging modalities. BMC Cancer 2012; 12: 236.

53. Yasumoto M, Shibuya H, Takeda M, Korenaga T. Squamous cell carcinoma of the oral cavity: MR findings and value of T1- versus T2-weighted fast spin-echo images. AJR1995; 164: 981-87.

54. Arakawa A, Tsuruta J, Nishimura R, et al. MR imaging of lingual carcinoma: comparison with surgical staging. Radiat Med 1996; 14(91):25-9.

55. Iwai H, Kyomoto R, Ha-Kawa SK, et al. Magnetic resonance determination of tumor thickness as predictive factor of cervical metastasis in oral tongue carcinoma. Laryngoscope. 2002; 112(3):457-61.

56. Paul Lam, Kai Ming Au-Yeung, Pui Wai Cheng et al. Correlating MRI and Histologic Tumor Thickness in the Assessment of Oral Tongue Cancer. AJR 2004;182:803-8.

57. Okura M, Iida S, Aikawa T, et al. Tumor thickness and paralingual distance of coronal MR imaging predicts cervical node metastases in oral tongue carcinoma. Am J Neuroradiol 2008; 29(1):45-50.

58. Imaizumi A, Yoshino N, Yamada I et al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. Am J Neuroradiol 2006; 27(1):114-22.

59. Vandecaveye V, De Keyzer F, Poorten V, et al, Head and Neck Squamous Cell Carcinoma: Value of Diffusion-weighted MR Imaging for Nodal Staging. Radiology 2009; 25: 134-46.

60. Anna Perrone, Pietro Guerrisi, Luciano Izzo et al. Diffusion-weighted MRI in cervical lymph nodes: Differentiation between benign and malignant lesions. European Journal of Radiology 2011; 77: 281-86.

61. Quon A, Fischbein NJ, McDougall IR, et al. Clinical Role of 18F-FDG PET/CT in the Management of Squamous Cell Carcinoma of the Head and Neck and Thyroid Carcinoma. J Nucl Med 2007; 48:58S–67S.

62. HeikoScho der, Diane L. Carlson, Dennis H. Kraus, et al. 18F-FDG PET/CT for Detecting Nodal Metastases in Patients with Oral Cancer Staged N0 by Clinical Examination and CT/MRI. J Nucl Med 2006; 47:755-62.

63. Shao Hui Huang, David Hwang, Gina Lockwood, et al. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: A Meta-analysis of Reported Studies. Cancer 2009; 115(7):1489-97.

64. American Joint Committee on Cancer 7th edition. 2010; 3-1.

65. Cook JA, Jones AS, Phillips DE, Soler L, luch E. Implications of tumor in resection margins following surgical treatment of squamous cell carcinoma of the head and neck. Clin Otolaryngol Allied Sci1993; 18(1):37-41.

66. Jones AS, Bin Hanafi Z, Nadapalan V, Roland NJ, Kinsella A, Helliwell TR. Do positive resection margins after ablative surgery for head and neck cancer adverselyaffect prognosis? A study of 352 patients with recurrent carcinoma following radiotherapy treated by salvage surgery.Br J Cancer1996; 74(1):128-32.

67. Byers RM, Weber RS, Andrews T, Mcgill D, Kare R, Wolf P. Frequency and therapeutic implications of ''skip metastases'' in the neck from squamous Carcinoma of the oral tongue. Head neck 1997; 19:14-19.

68. Lea J, Bachar G, Sawka AM, Lakra DC, Gilbert RW, Irish JC, et al. Metastases to level IIb in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. Head Neck 2010; 32(2):184-90.

69. Varghese BT, Sebastian P, etal. Nasolabial flaps in Oral reconstruction an analysis of 224 cases Br. J Plast Surg 2001; 54:499-503.

70. Sebastian P, Thomas S, Varghese BT, Iype EM, Balagopal PG, Mathew PC. The submental island flap for reconstruction of intraoral defects in oral cancer patients. Oral Oncol 2008; 44(11):1014-8.

71. AriyanS. Thepectoralis major myocutaneous flap. A versatile flap for reconstruction the head and neck – plast. Reconstr. Surg 1979; 63:73-81.

72. UrkenML,OkayDJ.Reconstruction of the oral cavity following partial and total glossectomy,In Multidisciplinary Head and Neck Reconstruction;A defect oriented approach Ed by UrkenML.Wolters-Kluwer/Lippincott Williams and Wilkins 2010.

73. Lewis JS, Ritter JH, El-MoftyS.Alternative epithelial markers in sarcomatoid carcinomas of the head and neck, lung, and bladder-p63, MOC-31, and TTF-1.Mod Pathol.2005; 18(11):1471-81.

74. Grabenbauer GG, Rödel C, Brunner T, Schulze-Mosgau S, Strnad V, Müller RG, et al. Interstitial brachytherapy with Ir-192 low-dose-rate in the treatment of primary and recurrent cancer of the oral cavity and oropharynx. Review of 318 patients treated between 1985 and 1997.

StrahlentherOnkol2001; 177(7):338-44.

75. Melzner WJ, Lotter M, Sauer R, StrnadV.Quality of interstitial PDR-brachytherapy-implants of head-and-neck-cancers: predictive factors for local control and late toxicity?RadiotherOncol 2007; 82(2):167-73.

76. Dinshaw KA, Agarwal JP, Ghosh-Laskar S, Gupta T, Shrivastava SK. Radical radiotherapy in head and neck squamous cell carcinoma : an analysis of prognostic and therapeutic factors. ClinOncol (R CollRadiol). 2006;18(5):388-9.

77. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis.Lancet.2006; 368(9538):843-54.

78. OvergaardP,Mohanti BK,Begum N, Ali R, Agarwal JP, Kuddu M, et al. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study):a randomised, multicentre trial. Lancet Oncology 2010; 11(6)553-60.

79. Murthy V, Agarwal JP, Laskar SG, Gupta T, Budrukkar A, Pai P, Chaturvedi P, Chaukar D, D'Cruz A. Analysis of prognostic factors in 1180 patients with oral cavity primary cancer treated with definitive or adjuvant radiotherapy. J Cancer Res Ther. 2010; 6(3):282-9.

80. Dinshaw KA, Agarwal JP, Laskar SG, Gupta T, Shrivastava SK, Cruz AD. Head and neck squamous cell carcinoma: the role of post-operative adjuvant radiotherapy. J SurgOncol. 2005; 91(1):48-55.

81. Agarwal JP, Nemade B, Murthy V, Ghosh-Laskar S, Budrukkar A, Gupta T et al. Hypofractionated, palliative radiotherapy for advanced head and neck cancer. Radiother Oncol 2008; 89(1):51-6.

82. Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92(1):4-14.

83. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003; 21(1):92-8

84. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa J Oral Pathol Med 2007;36:575–80.

85. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncology 2009; 45:317-23.

CHAPTER

15 ABBREVIATIONS

3DCRT	3D conformal radiotherapy
5FU	5-flurouracil
AAR	Age adjusted rate
ACC	Adenoid cystic carcinoma
ALT	Antero lateral thigh
CCA	Common carotid artery
cDNA	Complementarydeoxyribonucleic acid
CK	Cytokeratin
CO2	Carbon dioxide
CT	Computed tomography
CTRT	Chemo-radiation
CXR	Chest X ray
D	Desirable
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
EMA	Epithelial membrane antigen
E	Essential
ECS	Extra capsular spread
EGFR	Epidermal growth factor receptor
FFOCF	Free fibula osteo-cutaneous flap
FNAC	Fine needle aspiration cytology
FRAFF	Free radial forearm flap
Gy	Gray
HDR	High dose rate brachytherapy
HMWCK	High molecular weight cytokeratin
HPV	Human papilloma virus
ICA	Internal carotid artery
IHC	Immunohistochemistry
IJV	Internal jugular vein
IMRT	Intensity modulated radiotherapy
LDR	Low dose rate brachytherapy
LOH	Loss of heterozygosity
LVE	Lympho-vascular emboli
MDCT	Multi detector computed tomography
MEC	Muco-epidermoid carcinoma
MRI	Magnetic resonance imaging

N	Node
NACT	Neo adjuvant chemotherapy
NICE	National institute for health and clinical excellence
NSAIDS	Non steroidal anti inflammatory drugs
OPG	Orthopantomogram
ORF	Open reading frame
OSCC	Oral squamous cell carcinoma
OSMF	Oral sub-mucous fibrosis
PBCR	Population based cancer registry
PCR	Polymerase chain reaction
PD	Poorly differentiated
PEG	Percutaneous endoscopic gastrostomy
PET CT	Positron emission tomography / computed tomography
PMMC	Pectoralis major myo-cutaneous
PNI	Peri-neural invasion
RCT	Randomized controlled trial
RT	Radiotherapy
SAN	Spinal accessory nerve
SCC	Squamous cell carcinoma
SCM	Sternocleidomastoid muscle
SND	Selective neck dissection
SOHD	Supra omohyoid neck dissection
T	Tumor
TPF	Docetaxal, Cisplatin, Flourouracil
PF	Cisplatin, Flourouracil
TSH	Thyroid stimulating hormone
TSNA	Tobacco specific nitrosamines
USG	Ultrasonography
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World health organization

*__Desirable/Ideal:__ Tests and treatments that may not be available at all centers but the centers should aspire to have them in the near future.

*__Essential:__ Bare minimum that should be offered to all the patients by all the centers treating cancer patients.

CATEGORIES OF EVIDENCE AND CONSENSUS

Levels of Evidence

Level 1: High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals. Systematic review of level I RCTs

Level 2: Lesser quality RCT (e.g. < 80% follow-up, no blinding, or improper randomization), prospective comparative study, systematic review of level II studies or level I studies with inconsistent results

Level 3: Case control study, retrospective comparative study, systematic review of level III studies. Retrospective study

Level 4: Case series

Level 5: Expert opinion

CHAPTER

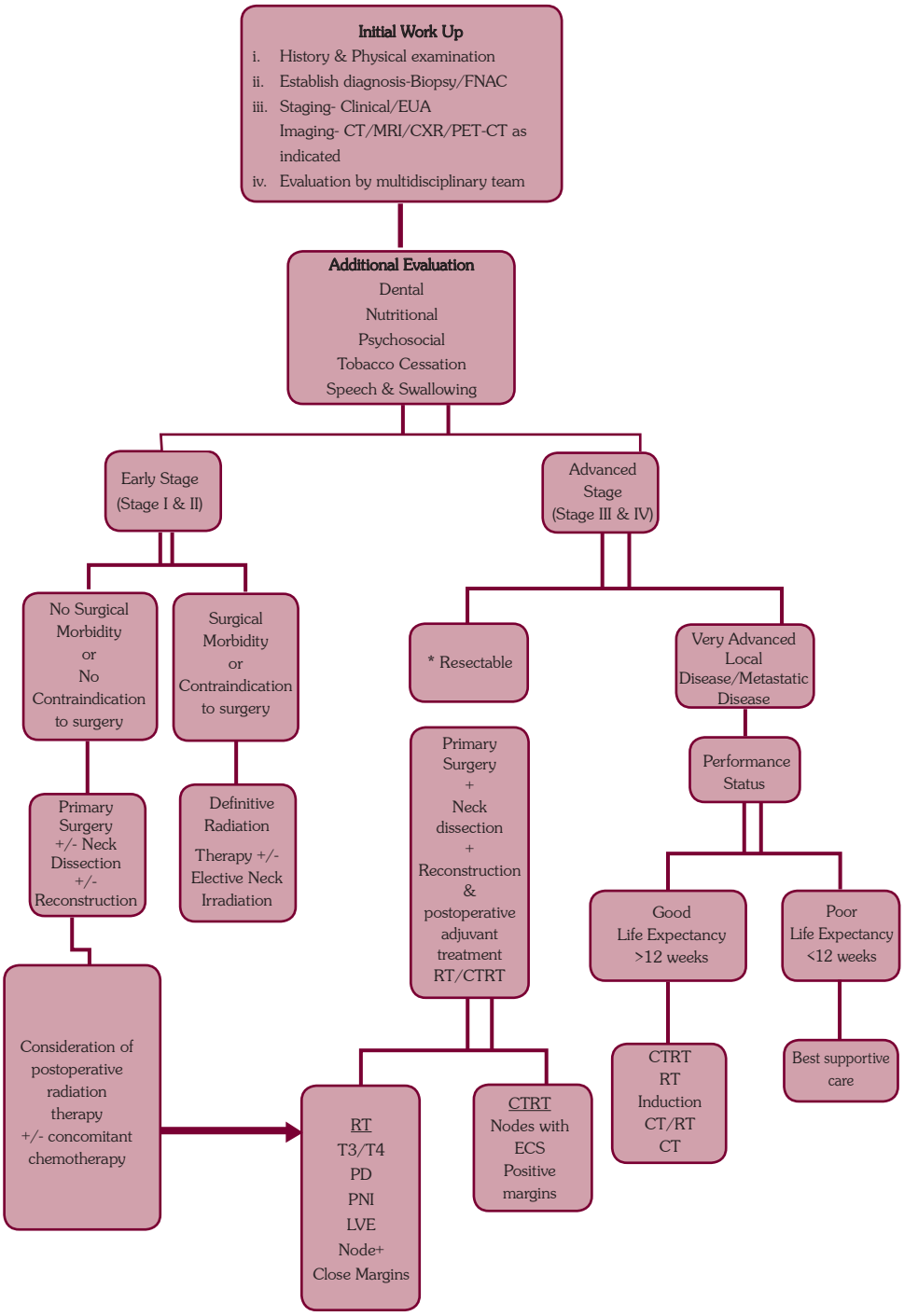
16 SUMMARY

This document has been created to put forward the best evidence that would guide practicing clinicians in the country towards the management of the tongue cancer. Evidence based practice is easily implemented when there is strong level I/II trials in the literature. Unfortunately there is a paucity of well conducted randomized trials more so focused on cancers of the oral tongue. This consensus report has been put together by an expert committee after careful consideration of the published literature. Guidelines formulated were also circulated amongst other leading head neck experts and a final document prepared. The following are the salient features of this document-

- Oral cancer is a significant health problem to the country due to widespread use of tobacco.
- There is a rising incidence of tongue cancers in the country and the problem is as acute as those with gingivo-buccal cancers.
- Early diagnosis is imperative in improving outcomes and preserving quality of life.
- Biopsy is easily established in oral cancers but a high index of suspicion is required for sub-mucosal lesions.
- Tongue is a high risk site for premalignant lesions converting to cancer and clinician should be very vigilant in following these lesions.
- MRI is the investigation of choice for visualizing the primary when available. CT scan is optional.
- In very early lesions where the primary does not require visualization, ultrasound may help guide the management of neck.
- Early stage patients (stage I&II) require single modality treatment – surgery preferred.
- Locally advanced tumors require combined multimodality treatment - surgery + adjuvant treatment.
- Radiotherapy as an adjuvant is used for all T3/T4 cancers or when there are high risk features (LVE, PNI, PD, node +, close margins).
- Adjuvant CTRT is indicated for positive margins and extranodal disease.
- The role of neoadjuvant chemotherapy is not well established in oral tongue cancers.
- A multidisciplinary approach on emphasis on proper rehabilitation (appropriate reconstruction) is necessary.
- Unresectable advanced cancers should be treated with a goal for palliation.

CHAPTER

17 MANAGEMENT ALGORITHM



*If unfit for surgery –Further treatment for locally advanced disease on the basis of performance status.