Neoplasms of the Oral Cavity and Oropharynx

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38.1 Introduction

Oral and oropharyngeal cancers (OPC) together constitute a major global public health problem with an estimated annual incidence of 354,864 and 92,887 cases worldwide, respectively [1]. Although these two sites are in close anatomical proximity and often considered a single entity, cancers affecting these areas are distinct with significant differences in disease biology as well as management protocols [2, 3].

There have been significant new data resulting in a shift in management protocols of both these cancers. This chapter attempts to highlight these details in light of the current evidence. Benign tumours of the oral cavity and oropharynx are beyond the scope of this chapter.

- Changing epidemiology, recognition of new prognostic factors and different biology of oral and oropharyngeal cancers.
- Salient clinical features, relevant diagnostic workup, and recent staging system.
- Principles of management with incorporation of new data.

38.2 Oral Cancers

Oral cavity squamous carcinomas (OSCC) are a global problem, with approximately 354,864 cases and 177,384 deaths occurring annually. The disease predominantly affects males and is strongly linked to the habits of tobacco and alcohol consumption. Two-thirds of cases occur in the developing world [1]. In India alone, there are 119,992 new cases and 72,616 deaths yearly [4]. This is primarily due to the fact that tobacco is a socially accepted custom with nearly a third of all adults and 42.4% of males addicted to this habit [5]. Moreover, there is a

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widespread use of the areca nut, and two-thirds of the tobacco consumed is in the smokeless form with its carcinogenic effects occurring locally. These habits are popular in the entire Indian subcontinent, Taiwan as well as part of Saudi Arabia and Yemen [6].

The oral cavity includes the lip, buccal mucosa, alveolus (including upper and lower gums), hard palate, retromolar trigone, anterior two-thirds of the tongue and floor of the mouth (Fig. 38.1). While each of these subsites does have variations in incidence, patterns of spread and prognosis, the general principle governing the management of these cancers is essentially the same.

38.2.1 Presentation

Despite a well-defined tumour progression model, well-established premalignant lesions (leukoplakia/erythroplakia) and ease at examination, the majority of oral cancers present at a locally advanced stage. This is due to the fact that patients are from a lower socio-economic background with a heavy dependence on tobacco and alcohol and early signs and symptoms are subtle. Locally advanced presentation is not restricted to just developing countries but is seen in the developed world as well, 55% present in the USA with locally advanced stages as seen in a large national cancer database (NCDB) study [7]. In addition prevalence of co-morbidities, which could be in as high as half the patients, compounds problems posing a challenge to appropriate treatment and compliance [8].

Attempts at early detection through population screening or the use of adjunctive aids (toluidine blue, brush cytology, fluorescent imaging, etc.) have not proven to be beneficial [9]. Three rounds of oral examination by a trained health worker every 3 years in addition to health education did not show mortality reduction in a randomized control trial (RCT) [10]. However, benefit was seen in high-risk individuals (tobacco/alcohol users). Extrapolating these findings to clinical practice there is a strong case for opportunistic screening of such high-risk populations by dentists/medical professionals during examination.

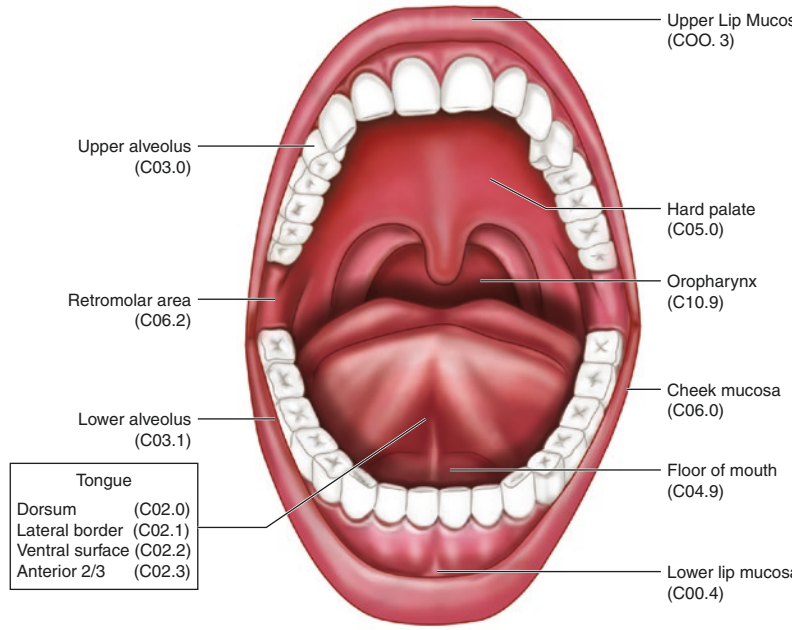


Fig. 38.1 Subsites of the oral cavity [ICD codes mentioned against each subsite in parenthesis]

38.2.2 Workup

Appropriate treatment is planned based on the clinical workup and staging of disease influenced by both patient-related and disease-related factors.

Patient-related factors include the performance status and general condition.

In addition, the presence of any co-morbidities also bears an impact on treatment planning. Disease-related factors include the tumour extent, involvement of vital structures (which may reflect inoperability) and presence of distant metastasis. This is assessed clinically as well as by appropriate imaging.

38.2.2.1 Clinical Assessment

Presentation depends on the subsite involved, classical features being a non-healing ulcer or growth, with or without pain. Pain is a feature more commonly associated with tongue lesions and hence patients present earlier than other subsites of the oral cavity. Similarly, lip cancers where the growth is readily visible, present early. Gingivo-buccal cancers present with locally advanced disease in contrast. Advanced lesions can present with pain, bleeding, or fixity to surrounding structures. Advanced tongue and floor of mouth cancers are associated with hypoglossal palsy, ankyloglossia, progressive difficulty in mastication and speech, pooling of saliva and surface bleeding. Cervical adenopathy is common given the propensity to neck node metastasis. Advanced gingivo-buccal cancers in contrast present with a large growth which may lead to subcutaneous and skin involvement, manifested by erythema, puckering or frank ulceration. In addition, there could be spontaneous loosening of teeth. Clinical signs of inoperability of tongue cancers are root of tongue involvement manifested by ankyloglossia and induration of suprahyoid musculature, while in buccal cancer, high infratemporal fossa (ITF) involvement manifested clinically with progressive trismus. Other signs of inoperability are extensive skin and subcutaneous involvement, presence of dermal skin nodules and a hard-fixed nodal mass.

38.2.2.2 Biopsy

A biopsy is required to establish the histological confirmation of malignancy. The majority of oral cancers are amenable to punch biopsy, easily performed as an office procedure. Biopsy should be performed from representative tissue avoiding obvious necrotic areas. Occasionally lesions are submucosal or infiltrative when an incisional biopsy is warranted. Similarly, for verrucous lesions, an incisional biopsy that includes deeper tissues helps the pathologist in differentiating a carcinoma from hyperplasia. Scrape cytology is not routinely used for oral lesions given the ease of a punch biopsy and lower sensitivity of this procedure.

38.2.2.3 Imaging

Imaging is important to ascertain the locoregional spread and help plan treatment. Contrast-enhanced computed tomography (CECT) scan is the workhorse and imaging modality of choice for the majority of oral cancers. It is accurate to assess the extent of disease as well as mandibular involvement. Similar diagnostic accuracy between a CECT and magnetic resonance imaging (MRI) for mandibular involvement was shown in a meta-analysis of 477 patients from 11 studies [11]. Cone-beam CT (CBCT) and single-photon emission computed tomography (SPECT) have also a high diagnostic accuracy for mandibular involvement but given the inadequate soft tissue delineation of both these modalities, they are not routinely preferred for imaging of oral malignancies [12].

Given its better soft tissue delineation, MRI is the preferred imaging modality for tongue and floor of mouth lesions. MRI has also been validated in recent studies to assess the depth of invasion (DOI) with acceptable accuracy [13, 14]. Intraoral ultrasonography (US) has also been evaluated for the assessment of DOI with similar accuracy to that of MRI [15]. However, given that it is highly operator dependent, cumbersome and could be painful, it is not used in routine practice.

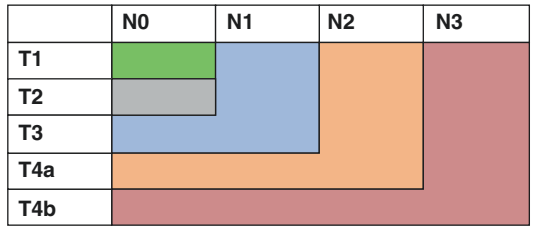
Distant metastatic workup is not routinely indicated given that these cancers even in advanced stages are largely confined

locoregionally. However, in patients with large bulky adenopathy (N2/N3), nodal involvement in the lower reaches of the neck (level IV and V), or large primary T4 tumours, it is prudent to investigate for the same. Positron emission technology (PET) scan is the investigation of choice in such situations [16]. Given that the lung is the most common site of distant spread, CT thorax is a useful alternative, especially in a cost constraint setting. It has a similar diagnostic accuracy for the detection of lung metastasis when compared to PET scan as shown in a large study [17].

All commonly used imaging modalities (CT, US, MRI, PET) have been studied for evaluating the neck. CECT and MRI have both shown comparable sensitivity to detect neck node metastasis with some studies suggesting that the CECT may have higher sensitivity [18]. Liao et al, in a meta-analysis specific to the node-negative neck, similarly showed a higher specificity of the CT scan. PET CT scan has limited application in detecting neck node metastasis especially in the node-negative setting [19]. US-guided fine-needle aspiration had the highest diagnostic odds ratio in a meta-analysis [20]. However, this modality is not extensively used given the fact that cross-sectional imaging needs to be performed in every case. The general dictum is to utilize the modality chosen for imaging of the primary tumour to image the neck as well. There is emerging data on the potential role of diffusion-weighted imaging sequences of MRI in increasing the accuracy of neck imaging [21].

38.2.3 Staging of Oral Cancers

The commonly used staging system for oral cancer is the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM system 8th edition implemented from 2018 (Fig. 38.2). Amongst the benefits of staging, the most important from a clinical standpoint is the planning of appropriate treatment and prognostication. The two main modifications for oral cancers in the current edition are the addition of depth of invasion (DOI) of the primary tumour in the T category and extranodal extension (ENE) in the N category [22]. Changes in DOI were based on the results of the International



T staging *

T1: T≤ 2 cm, DOI ≤ 5 mm
T2: Tumour ≤ 2 cm, DOI > 5 mm and ≤10 mm OR
Tumour > 2 cm but ≤ 4cm, and DOI ≤10 mm
T3: Tumour > 4 cm & DOI ≤ 10 mm OR
Tumour ≤ 4 cm and DOI >10 mm
T4a: tumour > 4 cm and DOI >10 mm OR any T with DOI > 20 mm
Local invasion into the mandible, maxilla, skin, inferior alveolar nerve
T4b: Involvement of masticator space, pterygoid plates, skull base, encasement of the ICA

N staging *

N1: Single node ≤ 3 cm, ENE negative
N2: Single node ≤ 3 cm with ENE positive OR multiple ipsilateral, bilateral and contralateral nodes, none > 6 cm and ENE negative
N3: Any node > 6 cm or any node(s) >3 cm with ENE positive

Fig. 38.2 TNM group staging for oral cancers. *For detailed TNM staging, refer to the AJCC TNM 8th edition. *DOI* depth of invasion, *ENE* extranodal extension

consortium for outcomes research (ICOR) study, which used data from 11 institutions worldwide (3149 patients). The study showed a significant difference in outcomes when DOI was incorporated into prognostication models with an incremental increase of every 5 mm translating into a higher T stage (≤5 mm as T1, 5–10 mm as T2 and >10 mm as T3/T4) [23]. For the N category, while size, number and location of lymph nodes were already part of the staging system, ENE was in addition incorporated as a prognostic factor [24–26]. Presence of ENE upstages to N2 for nodes ≤3 cm while ENE in a node >3 cm or the presence of ENE in more than one node upstages disease to N3. The relevance of the extent of ENE (microscopic vs. macroscopic) is uncertain. Wreesman et al. showed 1.7 mm to be the critical cutoff value of prognostic relevance (ENE <1.7 mm to be labelled as minor and >1.7 mm as major) [25]. While current practice necessitates both (microscopic and macroscopic) be treated similarly, it is recommended by the TNM task force that the extent of ENE be recorded (microscopic <2 mm) for subsequent modifications, should the need arise.

It should be borne in mind that the suggested changes are based primarily on pathological findings across the various studies [22, 23]. Moreover, assessment of both DOI and ENE could be subjective and difficult to evaluate clinicoradiologically. The AJCC 8th edition explicitly states that in the case of uncertainty, the lower staged group should be considered. It is important to corroborate both these findings with final histopathology for accurate assessment of prognosis and appropriate adjuvant treatment [27].

- Tobacco and alcohol are major risk factors for oral cancers.
- Majority present with locally advanced disease.
- Early detection methods and routine public screening lack evidence.
- Current staging system (8th Edition) has incorporated DOI for T Stage and ENE for N stage.
- CT is the preferred modality of imaging; MRI is the modality of choice for tongue, floor of mouth, recurrent cases and base of skull involvement.
- Definite signs for inoperability are involvement of high ITF and skull base, prevertebral fascia, carotid sheath, root of tongue with indistinct planes near the hyoid, extensive skin and soft tissue infiltration with dermal nodules.

38.2.4 Principles of Management of Oral Cancers

Management of oral cancers presents a unique challenge given that patients present late and treatment has implications on both function and cosmesis. Care of patients must be multidisciplinary with a team comprising of oncologists (surgery, radiation and medical), ancillary specialties (radiology, pathology) and reconstructive and rehabilitative services (dental, plastic reconstructive, physiotherapy, speech and swallowing) for best results. Treatment depends on the stage of cancer at presentation and broad treatment guidelines are: early-stage disease (stage I, II)-single modality therapy which could be either surgery or radiotherapy; locally advanced cancers should be triaged into those that are operable and those that are very advanced and inoperable. Locally advanced operable lesions (stage III, IVA and select IVB) are treated with combined modality treatment, surgery being the primary modality. Locally advanced inoperable tumours (Stage IVB) are treated with either radiation (RT) or chemoradiotherapy (CRT). Some of these patients can be brought into the realm of curative treatment with salvage surgery following initial treatment. Neoadjuvant chemotherapy (NACT) has also been explored in this setting with some encouraging results (discussed later). Patients with metastatic disease are treated primarily with chemotherapy. Patients with advanced/metastatic disease with a poor performance status are treated symptomatically

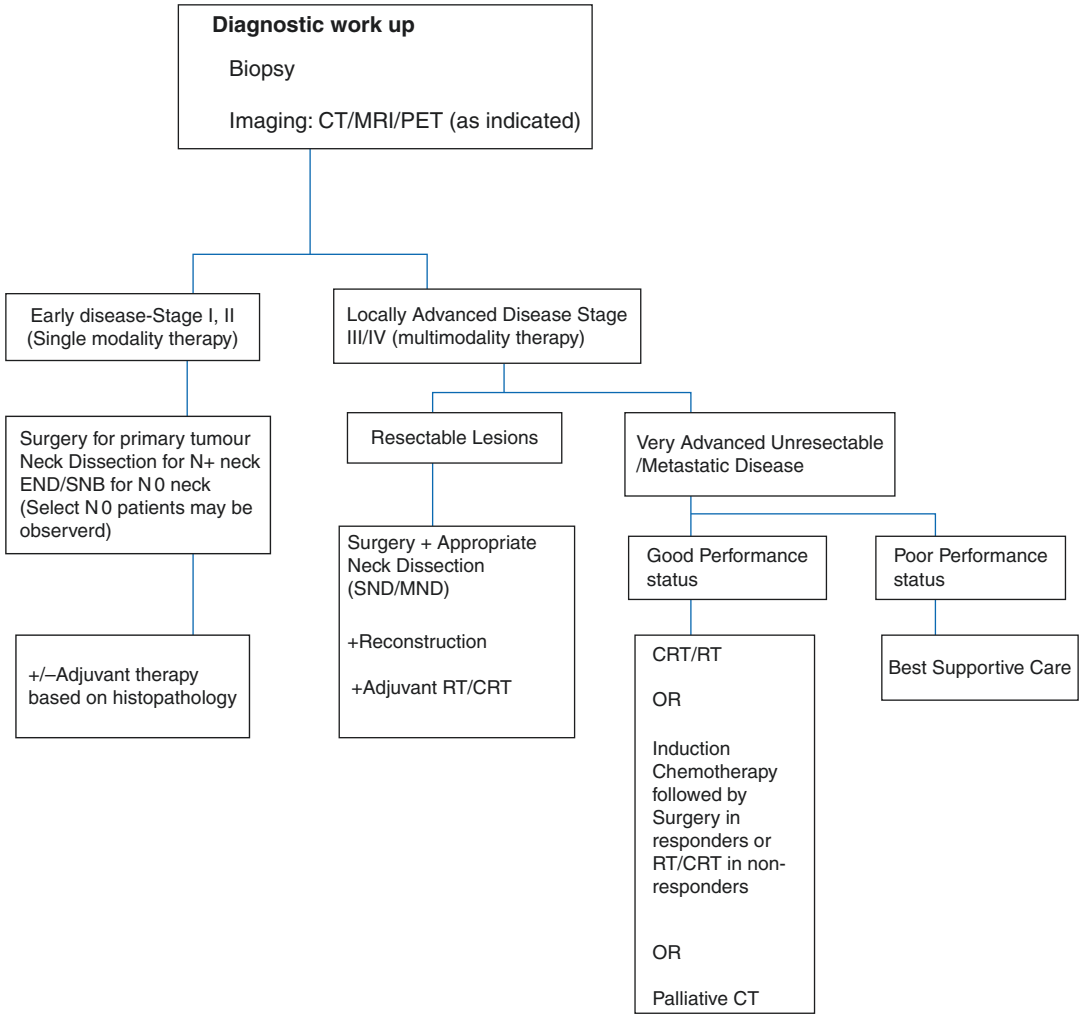


Fig. 38.3 Algorithm for oral cancer management

[16]. (Algorithm detailing the broad principles is provided in Fig. 38.3.)

38.2.4.1 Early-Stage Disease (Stage I, II)

Outcomes are essentially similar for surgery and radiotherapy for early-stage disease. While surgery has the advantage of being simple, quick, with no significant cosmetic and functional morbidity and therefore cost-effective, radiotherapy requires specialized centres and expertise, is prolonged (4–6 weeks) and with side effects of xerostomia, radiation-induced caries and occasionally osteoradionecrosis. Most importantly, radiation usually can only be given once, whereas repeated surgical procedures are possible both for recurrence and the development of a second primary. A recently published NCDB study from the USA revealed that clinicians preferred surgery over the radiotherapy in early oral cancers in 95% of cases. There was also a survival advantage in favour of surgery [28]. Brachytherapy is preferred when surgery would result in functional or cosmetic morbidity, e.g. superficially large lesions of the lip particularly with commissure involvement or superficial spreading lesions of the hard palate without bone involvement

(surface mould brachytherapy) [29]. The ideal lesion suitable for interstitial brachytherapy should be superficial, accessible, and away from bone where placement of interstitial brachytherapy catheters is possible.

38.2.4.2 Locally Advanced Operable Lesions (Stage III, IVA and Select IVB)

Surgery is the mainstay of treatment and primary modality of choice for locally advanced operable oral cancers (stage III, IVA). Results with primary surgery are better than in the salvage setting in this group of patients. There have been two randomized trials to date attempting to address this issue, one of which had to be prematurely terminated while the other was overwhelmingly in favour of surgery [30, 31]. A recent NCDB study including 6900 patients of oral cancer demonstrated that surgery followed by adjuvant RT had better overall outcomes as compared to upfront chemoradiation when analysed for the entire cohort as well as for T3, T4a tumours [32]. Stage T4b cancers (masticator space-ITF complex involvement), considered inoperable earlier, could benefit from surgery in a select subset of patients. Studies have demonstrated that low ITF involvement—described as the area below an imaginary line drawn through the sigmoid notch—could be offered surgery with acceptable outcomes [33–35]. It should be noted, however, that these studies are all focused on gingivobuccal cancers and extrapolating this concept to other subsites of the oral cavity is without scientific justification. RT/CRT with a goal at organ preservation is inadequate because of the aggressive nature of oral cancers as well as the close proximity to the mandible. There have been few reports suggesting the possibility of its use in a select subset of patients with an unacceptably high rate of complications [36].

38.2.5 Principles of Surgery

Oral cancers are a surgical disease when feasible for reasons alluded to. The aim at surgery is wide excision of the tumour, radical enough for gross tumour excision with margins, but conservative enough to preserve function and cosmesis. The broad surgical principles are as follows:

38.2.5.1 Margins

Achieving tumour free margins is of paramount importance. Clear margins have consistently shown better overall survival as compared with close or involved margins [37]. Although there have been various cut-offs proposed as the ideal tumour free margin, the consensus is in favour of 5 mm as the gold standard. A MEDLINE and EMBASE search for local recurrence following excision for oral cancer, without receipt of adjuvant therapy identified five studies. The pooled recurrence rates demonstrated a 21% absolute risk reduction when margins were more than 5 mm [38]. It should be borne in mind that there is a 20–30% shrinkage of margins after excision and fixation of the specimen and hence one should aim at placing the incision 1 cm away at surgery [39].

Tumour free margins must be achieved three-dimensionally and should be adequate for mucosa, bone and soft tissue. There have been recent reports of similar outcomes with <5 mm margin but these are retrospective single institutional studies, and therefore should not be considered as the standard of care till ratified by others [40].

The role of frozen section (FS) to guide adequacy of margin is contentious. A meta-analysis of eight studies showed that revision of positive margins to clear margins based on FS guidance does not equate to the local control achieved by adequate margins in the first instance. However, it is prudent at times to use FS control especially in complex resections and for the deep margins of excision. Analysis of margins, if done, is more accurate from the tumour specimen rather than the tumour bed [41].

38.2.5.2 Establishing Operability

There is a grey area occasionally between operability and inoperability. The decision is often subjective and based primarily on the philosophy

of the treating surgeon and centre. The ability to achieve oncologically safe margins and ensure appropriate reconstruction with early institution of adjuvant therapy is a useful guide to establish operability. While involvement of the prevertebral fascia, carotid sheath, high ITF/skull base and mediastinum are definite signs of inoperability, features such as extensive skin and subcutaneous involvement, extensive lymphoedema with dermal nodules, high-grade tumours and multiple large bilateral nodes signify aggressive tumour biology and one should be cautious to recommend surgery.

38.2.5.3 Addressing the Mandible

Gross involvement of the mandible necessitates segmental resection. For tumours close to the mandible, rim resection (marginal mandibulectomy) may be performed to achieve adequate clearance. This procedure can also be performed for superficial erosion of the bone, selecting cases judiciously. A margin of 0.5–1 cm should be achieved on bone with a minimum of 1 cm of residual mandibular height preserved to prevent postoperative fracture. Edentulous mandibles, where the vertical height is reduced (pipe stem), gross paramandibular disease (point of abutment is the site of potential spread to the mandible) [42] and the post-radiation setting (due to compromised periosteal integrity and multiple routes of tumour entry to the mandible) preclude the use of this procedure. Marginal mandibulectomy is performed in the horizontal plane for gingivobuccal cancers (horizontal mandibulectomy) or the vertical plane for tongue and floor of mouth cancers (lingual plate marginal mandibulectomy). However, performing a pure lingual plate excision is technically difficult and an oblique marginal mandibulectomy is recommended. A marginal mandibulectomy should be canoe-shaped to prevent sharp angles which predispose to fracture caused by forces of mastication.

38.2.5.4 Approaches

To ensure adequate three-dimensional clearance, there should be due diligence to the approach at the time of surgery. Peroral excision is recommended for small lesions that are anteriorly placed with ease of accessibility around its entirety. Posteriorly placed lesions or lesions requiring mandibular resection are usually approached via a lip-split incision. A pull-through approach dividing muscles in the floor of the mouth is useful for tongue and floor of mouth lesions which necessitate deep excision. Occasionally, posteriorly based tongue and floor of mouth lesions are approached by a mandibulotomy which could be median or paramedian. The paramedian position is preferred as it does not disrupt the geniohyoid complex and there is maximum divergence of roots between the canine and incisors, which helps preserve the integrity of these teeth.

38.2.5.5 Management of the Neck

Consensus today is in favour of operating the neck electively, for clinicoradiologically node-negative early oral cancers amenable to peroral excision. This is based on the results of two large randomized trials as well as numerous other meta-analyses to show the benefit of this approach [43–46]. There may be a limited role of observation in small superficial lesions in highly reliable patients willing for close surveillance though the quality of evidence to support that this recommendation is intermediate [47].

A selective neck dissection clearing levels I, II and III is adequate in the N zero setting. A minimum of 18 nodes harvested and studied ensures the adequacy and appropriateness of the procedure [47]. A modified neck dissection clearing levels I through V is recommended for node-positive cases. However, there is evidence that a selective neck dissection is a valid option in this setting when nodes are not fixed, there is an absence of metastasis in levels IV and V, nodal volume <3 cm, absence of multiple nodes or nodal involvement at multiple levels [48]. The overall incidence of metastasis to level V in oral cavity cancers is very low. Presence of metastatic nodes at the jugulodigastric area (level IIA) and

retromolar trigone disease predispose to metastasis at level V [49].

38.2.6 Adjuvant Treatment

Radiotherapy is indicated as an adjuvant for all stage III/IV cancers. Definite indications are T3/T4 tumours, N2/N3 neck status, and close margins. Literature is divided on the role of adjuvant radiotherapy for intermediate-risk factors, namely high grade, lymphovascular invasion (LVI), perineural invasion (PNI), single node-positive (without ENE) and worst pattern of invasion (WPOI). While their presence does indicate an aggressive biology, the commonly followed practice is to recommend radiotherapy when a combination of two or more of these factors are present [50, 51]. Chemotherapy is added to radiotherapy for high-risk disease, namely ENE and positive margins ≤1 mm [24].

The recommended doses of radiotherapy are 5600–6000 cGy for low-risk areas and 6000–6400 cGy for high-risk areas [52]. Early initiation of RT following surgery is beneficial. Starting within 6 weeks of surgery or a treatment package time (defined as the duration from the date of surgery till the conclusion of adjuvant therapy) <85–100 days are associated with better outcomes [50].

38.2.7 Role of Neoadjuvant Chemotherapy

Traditionally, it is believed that there is no role for chemotherapy in oral cancers except in combination with radiotherapy. However, there have been attempts to explore its role in the neoadjuvant setting. There have been two randomized trials to date addressing this question, both did not show an improvement in overall survival [53, 54]. However, the Licitra trial [53] did demonstrate the potential benefit of NACT in downsizing tumours necessitating smaller and more conservative surgeries and a decreased need for adjuvant radiotherapy. While exciting, this approach has not been ratified as others and still remains largely investigational. Patil et al. explored NACT with a similar aim of tumour downsizing but applied it to the setting of borderline operable lesions. In a large single-institution series ($n = 721$), 43% of patients could be brought into the realm of curative treatment. Median survival was 19.6 months in responders as compared to 8.16 months in non-responders [55]. While there seems to be a potential role of NACT in borderline operable tumours, its potential role in operable oral cancers needs to be established in further well-designed trials.

38.2.8 Management of Recurrent and Metastatic Disease

Oral cancer is an aggressive disease and coupled with the fact that patients present late, as high as 2/3rd of patients develop recurrences. Salvage surgery if feasible is the treatment of choice and is guided by factors such as the stage of presentation, disease-free interval (preferably >6–12 months), feasibility of achieving tumour-free margins, and performance status of the patient. These recurrent lesions are difficult to diagnose and tend to be missed out in a background of post-treatment fibrosis and distorted anatomy [56, 57]. Adjuvant re-radiotherapy, whenever feasible, is warranted as it is known to result in superior outcomes [58].

Re-irradiation should be offered to patients who are not candidates for surgery. It has been shown to have superior outcomes in a multi-institutional prospective trial (RTOG 9610) [59]. For those who are not suitable for surgery or re-radiotherapy, palliative chemotherapy should be offered to those with good performance status and symptomatic therapy for the rest. Platinum agents with 5 Fluorouracil combined with epidermal growth factor receptor (EGFR) antagonist cetuximab are considered the standard of care in this setting [60]. Recent evidence has emerged supporting the role of programmed-death-ligand

1(PD-L1) immunotherapy in platinum-resistant patients [61, 62]. However, cost constraints and lack of evidence on its role in platinum naïve patients limit its use.

- Surgery is the primary treatment modality. Patients should be triaged into operable and inoperable based on imaging and clinical assessment.
- Establishing tumour free margins in all three dimensions (minimum of 5 mm clear margins) is to be aimed for ensuring disease control.
- Elective neck dissection is recommended for clinically node-negative early oral cancers. Selective neck dissection may apply to certain node-positive patients.
- Advanced T stage, N2/N3 nodal status and close margins are definite indications for adjuvant RT. Positive margins and ENE warrant adjuvant CRT. The need for adjuvant treatment with other factors (PNI, LVE, single node-positive, WPOI) is contentious. The presence of more than one of these signifies aggressive disease and adjuvant treatment may be recommended.
- There is a potential role of NACT to downsize tumours with the role of increasing operability and organ preservation.
- Inoperable tumours are treated with radiation/chemoradiation. Salvage surgery offers the best outcomes for recurrent tumours. Chemotherapy, biologicals and immunotherapy are treatment options for other recurrent/metastatic diseases.

38.3 Oropharyngeal Cancers

38.3.1 Introduction

The oropharynx is the area bounded superiorly by an arbitrary line drawn from the soft palate to the posterior pharyngeal wall and inferiorly by a line from the hyoid to the posterior pharyngeal wall. Anteriorly it is bounded by the circumvallate papillae and the anterior tonsillar pillars, separating it from the oral cavity. It comprises four subsites: (1) base of tongue and vallecula, (2) tonsil, (3) pharyngeal wall-lateral and posterior and (4) soft palate and uvula. Tumours that arise from these subsites are predominantly squamous cell carcinomas.

Traditionally oropharyngeal cancers like other cancers of the upper aerodigestive tract were predominantly tobacco related. With a decreasing consumption of tobacco, particularly in the developed world, a paradigm shift has occurred in the etiopathogenesis of cancers affecting this subsite. Human Papilloma Virus (HPV) is now the major causative agent for the majority of cancers of the tonsil and base of tongue [63]. This has resulted in an exponential increase in the incidence of OPC. HPV-related cancers are now recognized as a distinct biological entity (reasons discussed later), with a better prognosis and are therefore currently a topic of extensive research for different and less intensive management protocols [64]. One must, therefore, establish the HPV status before counselling and initiation of treatment. This section deals with the changing epidemiology, biology of HPV tumours and principles of management of OPCs, highlighting recent advances.

38.3.2 HPV Positive OPC

38.3.2.1 Epidemiology

A sharp increase in the incidence of OPC was observed from the late 1990s in North America and Western Europe [65]. Surveillance, epidemiology and end results (SEER) database analysis demonstrated an increase in HPV prevalence in patients with OPC, from 16.3% during 1984–1989 to 71.7% in 2000–2004 with a concomitant fall in HPV negative OPC by 50% [66]. In a similar analysis of 69,592 OPCs and 113,144 OCCs across 23 countries from 1983 to 2002, a significant rise in HPV-related OPCs was seen in developed countries, mainly among young males [67].

Table 38.1 Characteristics of HPV-RELATED and HPV-unrelated tumours

	HPV positive	HPV negative
Incidence	Increasing	Declining
Age	Younger	Older
Sex ratio	3:1(Males)	3:1(Males)
Predisposing factors	High-risk sexual behaviour	Substance abuse: tobacco, alcohol
	Ethnicity—Caucasian	
Head neck sites affected	Base tongue, tonsil	All subsites
Histological features	Non-keratinizing	Keratinizing—Well to moderately differentiated
	Poorly differentiated with basaloid features	
Tumour biology	Wild type p53	Mutated p 53
	P 16 Elevated	P 16 suppressed
	EGFR downregulation	EGFR upregulation
	Lesser hypoxic areas	More hypoxic areas
Tumour presentation	Early T stages, advanced nodal stage (cystic nodes)	Variable
		Nodes are likely to be necrotic, less likely to be cystic
Response to treatment	Superior outcomes	Variable
Second primaries	Lower incidence of second primaries	Higher incidence of second primaries due to field cancerization
Metastasis	Metastasis can occur late	Metastasis occur earlier
	Disseminated—more than 1 site	Commonly to the lungs
	Associated with longer survival in some patients	Shorter median survival

HPV positive OPCs are seen to be a different disease entity (Table 38.1) [68]. A typical patient is a young Caucasian male with a history of high-risk sexual behaviour (high number of lifetime oral sex partners, vaginal sexual partners). There may be an associated history of marijuana abuse. Tumours have a non-keratinizing morphology and are poorly differentiated/undifferentiated with basaloid characteristics as opposed to HPV negative tumours. The primary tumour shows smaller T sage but a higher N stage. Nodal metastasis is often associated with a cystic component. There is an absence of field cancerization and a lower incidence of second primaries. Distant metastases occur in the same frequency as for HPV negative tumours, may occur after a longer interval and are of the disseminating type (more than one organ affected) with some patients having prolonged survival after treatment [69].

38.3.2.2 Etiopathogenesis

HPV subtypes 16 and 18 are the common strains related to cancers of the oropharynx [70]. The infection affects the palatine or lingual crypts from where the tumours arise de novo in the absence of pre-existing epithelial dysplasia. The malignant potential is attributed to the presence of two important viral oncoproteins—E 6 and E 7 which inactivate major tumour suppressor genes—p 53 and retinoblastoma (Rb), respectively. This results in an environment of uncontrolled cellular proliferation, reduced apoptosis and an increase in spontaneous and mutagen induced genomic mutations [71]. An important member of the cyclin-dependent kinase 4 (CDK4) inhibitors, the p16 molecule promotes Rb activation and subsequent G1 cell cycle arrest. The p16 and Rb molecules are known to share a reciprocal relationship and inactivation of Rb by E7 oncoprotein results in an elevation of p16 levels, which is considered as a surrogate marker for HPV infection.

38.3.2.3 Improved Outcomes

HPV positive OPCs are associated with better outcomes [64, 72, 73]. In a seminal publication looking at the association between HPV and outcomes, Ang et al. retrospectively analysed data from the RTOG 0129 [74] in which 63.8% were HPV positive. On comparing survival outcomes, HPV positive showed a significantly higher overall survival (OS) (82.4% vs. 57.1%, $p < 0.001$).When adjusted for age, race, tumour and nodal stage, tobacco exposure and treatment assignment, these tumours demonstrated a 58% reduction in risk of death (hazard ratio, 0.42; 95% CI, 0.27–0.66). Similar results were seen when survival analysis was done comparing p16 marker status (3-year OS being 83.6% [95% CI, 78.7–88.6] vs. 51.3% [95% CI, 41.5–61.0)] indicating that p 16 could be considered a reliable

surrogate marker for HPV. Recursive partitioning analysis placed patients into three groups of increasing risk of death, based on HPV status, pack-years of smoking, tumour and nodal stage. Patients with HPV-related OPC, having ≤10 pack-years and limited nodal disease (N0–N2a) constituted the low-risk group, whereas those with non-HPV related tumours, having >10 pack-years of smoking and advanced T stage (T4) formed the high-risk group. A positive history of tobacco usage was seen to mitigate the protective effect conferred by HPV on these tumours. A subsequent meta-analysis of 34 studies worldwide confirmed the superior outcomes of HPV positive tumours with a 60% reduction in risk of death [75].

38.3.2.4 Biological Explanation for Improved Survival

Various theories have been postulated to explain the improved survival. These patients are known to be younger, without addictions and hence tolerate treatment better. The tumours are biologically different, possess p53 wild type [70] and thereby proposed to have intact apoptotic response to chemotherapy-induced stress. They are also known to be associated with a decreased EGFR expression [76], and with less hypoxic areas [77].

38.3.3 Staging of Oropharyngeal Cancers

The AJCC staging system 7th edition for OPC was primarily derived from data of tobacco-related cancers. With the identification of HPV tumours as a distinct entity, there was a consensus regarding the need for a different staging system for these cancers. The Princess Margaret Hospital (PMH) studying a cohort of 573 patients using regressive partitioning analysis (RPA) proposed a new TNM stage grouping—Stage I is T1–T3, N0–N2B, Stage II: T1–T3 N2C, Stage III: T4/N3 and stage IV is M1 disease [78]. These findings were validated by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) [79] which was a multicentric cohort study of 1907 patients with HPV positive OPC. This led to the incorporation of changes in the 8th edition of the AJCC TNM wherein two different staging systems were recommended for HPV positive and negative OPCs. T staging for the former did not differentiate between T4a and T4b. The clinical N staging was simplified, with N1 indicating one or more ipsilateral nodes (none >6 cm), contralateral or bilateral nodes (none >6 cm) as N2 and any node >6 cm as N3. Metastatic disease has been placed in stage IV, with stages I–III representing local and regional disease (Fig. 38.4).

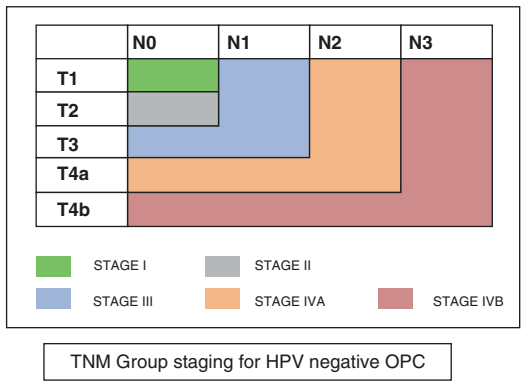


Fig. 38.4 TNM group staging for oropharyngeal cancers. *For detailed TNM staging, refer to the AJCC TNM 8th edition. *HPV* human papilloma virus, *OPC* oropharyngeal cancers

The T staging for HPV negative OPC has remained unchanged from the 7th AJCC TNM staging. The only change was the presence of ENE being incorporated into the nodal staging in keeping with other head and neck subsites.

38.3.4 Diagnostic Assessment of Oropharyngeal Cancers

Contrast-enhanced MRI is the preferred modality of imaging and has a high sensitivity for both the primary and neck. Distant metastasis are assessed with a whole-body PET CT. Chest CT may be performed for lung metastasis in the absence of the availability of PET scan. In patients who present with an unknown primary, a high index of suspicion must be maintained for an HPV related tonsil/base tongue tumour. These tumours are known to be small and within the crypts of the tonsil or the papillae of the base of tongue. Diligent, clinicoradiological evaluation must be performed. Many advocate a tonsillectomy (ipsilateral /bilateral) and surface excision of the base of tongue with a yield of the primary in as high as 89% of patients [80].

Current guidelines recommended checking the HPV status to help prognosticate and plan treatment [16, 81]. Immunohistochemistry (IHC) is widely accepted given its simplicity and ease of performance in addition to its high sensitivity (94%) [82] and cost-effectiveness. The presence of strong nuclear and cytoplasmic staining in more than 70% of malignant cells represents p16 positivity. If IHC is negative, the cancer is considered as HPV negative. The presence of HPV can be further confirmed by assessing for HPV DNA using in situ hybridization (ISH) given its higher specificity, when available. HPV DNA PCR has high specificity and along with p16 IHC has the highest sensitivity and specificity (94% and 96%), respectively [82].

HPV PCR tests on formalin-fixed tissue have their limitations and are better performed on fresh biopsy samples. DNA ISH and PCR though ideal, however, add to cost and time hence not routinely performed in clinical practice [81].

38.3.5 Principles of Management

Early-stage oropharyngeal tumours are treated with a single modality while locally advanced with combined modality therapy. Given the high rates of nodal metastasis (25–40%) [83, 84], difficulty in accessibility and functional morbidity, non-surgical treatment was the preferred option across all stages of OPC. Parsons et al. from data of 51 published series with 6400 patients showed similar control and survival rates for primary surgery compared to upfront RT [85]. Severe and fatal complications were significantly higher in the surgical group (32% vs. 3.8% for severe complications and 3.5% vs. 0.4% for fatal complications). Moreover, functional outcomes were also inferior in comparison to radiotherapy. Given the above, oropharyngeal cancers are traditionally treated with radiotherapy with surgery as salvage. The benefits of concurrent chemoradiotherapy were established through the Meta-analysis of Chemotherapy in Head Neck Cancer (MACH-NC), resulting in single modality radiotherapy being replaced by cisplatinum-radiotherapy for stage III/IV cancers [86, 87].

Radical radiotherapy prescribed in oropharyngeal cancers is 6600–7000 cGy, with or without chemotherapy, is delivered to the gross tumour volume with dose moderation to the remaining neck regions judged by the risk of disease. Intensity modulated radiotherapy (IMRT) is shown to have lesser side effects [88, 89]. Chemotherapy is administered as 100 mg/m^2 on days 1, 22 and 43 or weekly at 40 mg/m^2.

The alternate approach of cetuximab added to radiotherapy has shown to be of benefit in a trial of 424 patients, the majority of whom had oropharyngeal cancers (59.6%). The median OS was significantly in favour of cetuximab RT over RT alone [90]. The other approach is altered fractionation radiotherapy in lieu of conventional fractionation. Hyperfractionated radiotherapy was shown to have an absolute benefit of 8% over conventional RT [91], similar to the 8% benefit t of concurrent. Both these approaches of altered fractionation and adding biologicals are not standard of care at present. Cisplatinum-RT is the modality in widespread use and recommended in

day to day clinical practice. The Bonner trial was a single study while Cisplatinum-RT has stood the test of time. Also, a systematic review did show the superiority of cisplatinum-RT over cetuximab RT [92]. Replacing cisplatinum by biologicals is only recommended for platinum unsuitable patients. Altered fractionation has not gained universal acceptance being logistically difficult.

38.3.6 Management of the Neck in OPC

Since OPC is treated non-surgically, nodal disease is addressed with appropriate fields of RT. In the post-RT/CRT setting, a response assessment PET CT is advised at 12 weeks from treatment conclusion. Given its high negative predictive value, the neck may be observed if PET negative, an approach shown to be safe in a RCT [93]. It prevents the morbidity of a routinely performed neck dissection and is also cost-effective. If PET is unavailable, cross-sectional imaging is recommended and in the absence of structural nodal disease, it is safe to keep patients on observation [47].

In patients offered primary TORS (discussed later) with lateralized lesions the ipsilateral neck should be addressed, given the high incidence of nodal metastasis. While neck dissection could be concurrent or interval, the majority preference is in favour of concurrent. Ligation of feeding blood vessels to decrease the incidence of postoperative haemorrhage is also advocated by some [47]. For tumours that extend to the midline (base tongue and palate), bilateral neck dissection should be performed.

38.3.7 Transoral Robotic Surgery: An Evolving Paradigm

Transoral Robotic Surgery (TORS) revolutionized the approach to the oropharynx enabling tumours to be accessed per orally, avoiding morbidity and complications, associated with open surgery. Added to this, there was better three-dimensional magnified vision, greater dexterity of movement assuring greater precision. Node-negative T1–T2 tumours are ideal indications for TORS, though some authors have extended the approach to select T3 lesions as well. Contraindications include: (1) T4b tumours, (2) large cervical adenopathy, (3) tumours warranting excision of >50% of the base tongue and posterior pharyngeal wall, (4) retropharyngeal carotid, (5) epicentre of tumour situated in the centre of base tongue placing bilateral lingual arteries at risk and (6) technical issues such as trismus or degenerative cervical spine precluding access to the lesion [94].

Adding adjuvant radiotherapy following TORS decreases functional outcome and the ideal case, therefore, is one that can be treated with single modality TORS. Favourable oncological and functional outcomes were demonstrated in two systemic reviews by Almeida and Yeh [95, 96] giving a boost to TORS in oropharyngeal cancers. It should be kept in mind that these were retrospective reviews with inherent limitations and the ORATOR trial (described below) did not confirm the benefit of TORS [97].

38.3.8 Deintensification Approaches for HPV-Related Oropharyngeal Cancers

Chemoradiotherapy, though the standard of care, was not without associated toxicity. One-third of patients with OPC are known to be affected by toxicity post-treatment [98]. Given that HPV-related OPC has an excellent prognosis, patients are younger with more survivors, attempts were made to de-intensify treatment to avoid long-term morbidity.

Deintensification strategies are largely focused on three approaches:

1. Reducing RT doses and volumes

Trials are on, to decrease radio-curative doses for HPV cancers. Approaches include reduced total doses in low-risk patients ranging from 5400–6000 cGy with or without cisplatinum, and induction chemotherapy with response adapted RT (5400 to 6600–7000 cGy) [99].

Strictures, feeding tube dependence, aspiration and dysphagia undergo an incremental increase with higher doses of radiotherapy. The alternate approach is to limit treatment volumes. The constrictors, glottis and supraglottic larynx have been identified as the dysphagia-aspiration related structures (DARS) and a novel approach limiting the radiation dose to these structures has been proposed as Dysphagia Optimized-IMRT (DO-IMRT) [100].

2. Omitting/reducing the dose/ and replacing chemotherapy with biologics:

   The addition of chemotherapy increases toxicity to the tune of 30% [101, 102]. Approaches include omitting chemotherapy, replacing high dose chemotherapy with biologicals or weekly cisplatinum or carboplatinum in an attempt to decrease toxicity.
3. *Integrating surgery in the management* with an attempt to triage patients based on pathological findings into low or high risk and adjust adjuvant treatment accordingly.

Initial results available of trials testing the deintensification approaches have not confirmed their safety or superiority in terms of functional outcome.

1. The *ORATOR* phase II randomized trial comparing TORS with IMRT for T1–T2, N0–2 OPC demonstrated similar oncological outcomes with functional in favour of IMRT [97]. The study had limitations and further studies are needed to address this issue [103].
2. Replacing cisplatinum by cetuximab in CRT regimens explored in two trials—the *RTOG 1016* [104] and the *De-ESCALaTE* [105]. Both studies showed significantly inferior outcomes within the cetuximab arm compared to cisplatinum-RT. Postulated explanations for these results are a reduced expression of EGFR in HPV positive tumours as well as inappropriate patient selection [106].

Given these initial trial results, conventional cisplatinum-RT as in HPV negative OPC remains the standard of care in routine practice. Patients should, therefore, be treated with deintensification strategies only in the trial settings. The only accepted difference between the two groups of oropharyngeal cancers is the changes in the staging system recategorizing various TNM classifications into the different stage groupings for HPV-related tumours.

38.3.9 Management of Recurrent/Metastatic Oropharyngeal Cancers

Recurrent oropharyngeal tumours show best outcomes with surgical salvage followed by adjuvant radiotherapy (refer to Chap. 37) [56, 58] or re-irradiation, depending on the time since earlier radiation as well as sequelae of prior treatment.

Patients with metastatic disease and recurrent tumours not feasible to surgery or re-irradiation are treated with palliative intent. Those with good functional status are offered chemotherapy/palliative RT. Triplet therapy with cetuximab, 5 FU and platinum agents is the standard regimen of choice [60]. Those with poor performance status are offered symptomatic care. Recent exciting literature supporting the use of PD-L1 immunotherapy has led to the incorporation of this approach in cisplatinum resistant recurrent/metastatic patients [61, 62]. (Algorithm detailing the broad principles is provided in Fig. 38.5.)

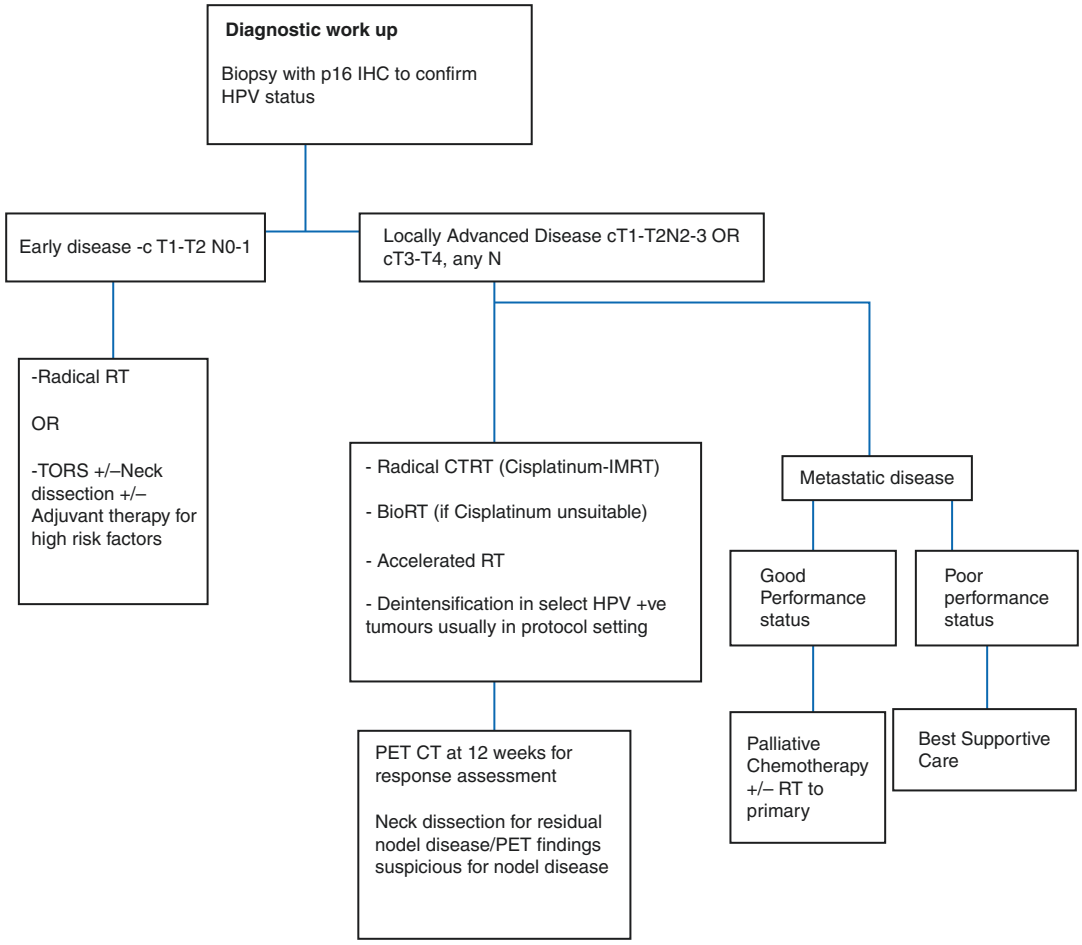


Fig. 38.5 Algorithm for oropharyngeal cancer management

38.3.10 Follow-Up of Patients with Oral and Oropharyngeal Cancer

Guidelines recommend that patients should be followed up at intervals of 1–3 months in the first year, 2–6 months in the second year, 4–8 months during the third to fifth year and annually thereafter [16, 81]. A detailed history and clinical examination of the head and neck including office-based endoscopy is warranted in all patients to rule out recurrence as well as second primary tumour. While many centres routinely perform imaging-based surveillance, others follow the practice of symptom-based imaging.

- OPC are HPV positive and negative-both being distinct entities with different etiopathogenesis, biology, staging systems and outcomes.
- Establishing HPV status is mandatory, p16 IHC is the recommended clinical test for the same.
- MRI with its better soft tissue delineation is the imaging of choice.
- Given morbidity and accessibility, treatment primarily revolves around non-surgical modalities (RT/CRT).

- TORS is emerging as an alternative for early-stage disease in an attempt to avoid the morbidity of radiotherapy.
- Given the better prognosis of HPV-related tumours, deintensification of treatment with strategies that include alterations with radiotherapy, use of biologicals, avoidance of chemotherapy and TORS are being explored.

Take-Home Messages

- Oral and oropharyngeal cancers are different disease entities.
- Oropharyngeal cancers are HPV positive and negative both being distinct.
- Oral cancers are surgically treated while oropharyngeal cancers are treated with predominantly non-surgical protocols.
- The aim of treatment is improving surgical outcomes while mitigating morbidity and maintaining the quality of life of patients.

Conflicts of Interest None of the authors have any conflict of interest with respect to the manuscript

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