6 Oropharyngeal and Hypopharyngeal Tumours and Their Treatment

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6.1 Benign Oropharyngeal Tumours

6.1.1 Lingual Thyroid

Lingual thyroid, an abnormal ectopic thyroid tissue, is commonly found within the base of the tongue. Lingual thyroid was initially reported by Hickman in 1869 [1]. Apart from tongue base, lingual thyroid can be located at the floor of the mouth [2]. It is noteworthy that lingual thyroid has been reported as the sole functioning thyroid tissue in nearly 75% of individuals [3], which necessitates thorough investigation and management. Lingual thyroid occurs ensuing failure of thyroid gland during embryogenesis to descend from ventral floor to its original location, which is over the thyroid cartilage. Lingual thyroid is said to arise from thyroglossal duct epithelium, which is unobliterated.

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6.1.2 Epidemiology

Female predominance has been reported with a female-to-male ratio of 7:1 [3]. Lingual thyroid is mostly seen amongst females when the plasma thyroid-stimulating hormone (TSH) level increases in body causing hypertrophy of the thyroid tissue, especially during puberty, pregnancy or menopause [4]. Ectopic thyroid can be found in more than one location in the body. It has been reported that 70% of patients with lingual thyroid are hypothyroid [5] and nearly 10% of patients may suffer cretinism. Incidence of lingual thyroid, albeit unknown, has been reported around the third decade of life [5]. Ectopic thyroid tissue is traditionally located within lingual, sublingual, thyroglossal, laryngotracheal and lateral cervical region. Albeit rare, other sites of involvement include submandibular, prelaryngeal, tracheal, oesophageal and substernal [3].

6.1.3 Clinical Presentation

Clinical presentation may vary and ranges from dysphagia, odynophagia, foreign-body sensation, bleeding, choking, dysphonia and snoring to upper airway obstruction. A small group of patients may remain asymptomatic until late adolescence. Additionally, acute symptoms may manifest locally in relation to the size of the lingual thyroid [6]. Clinically, lingual thyroid located at the base

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of the tongue appears as smooth-surfaced lobulated mass with bluish to reddish colour.

6.1.4 Histology

Lingual thyroid histologically resembles normal thyroid parenchyma. It is noteworthy that within the ectopic thyroid tissue, other benign as well as malignant conditions may arise such as thyroid adenoma, hyperplasia, inflammation and carcinoma [5].

6.1.5 Imaging

Neck ultrasonography is an important imaging modality, especially to detect thyroid tissue at the thyroid gland region. Technetium-99 (99mTC) is the gold standard to diagnose lingual thyroid as it demonstrates radionuclide activity at the base of the tongue and not at the thyroid gland level.

6.1.6 Blood Investigation

Thyroid function test is prudent as hypothyroidism is present in approximately 70% of patients with lingual thyroid.

6.1.7 Treatment

Treatment for lingual thyroid includes both surgical and medical treatment.

6.1.8 Surgical Treatment

Surgical treatment comprises excising the lingual thyroid or autotransplantation of lingual thyroid into the muscle. Surgical approach varies and depends on the location of the lingual thyroid including transoral, transhyoid and lateral pharyngotomy. Although surgical excision is ideal, it is important that radionuclide scan is performed to confirm the presence of functioning thyroid tissue at the thyroid gland level. If the lingual thyroid is found to be the only functioning thyroid, the lingual thyroid can be autotransplanted into the neck post-excision [7].

6.1.9 Non-surgical Treatment

Non-surgical treatment includes hormonal therapy as well as radionuclide ablation. Levothyroxine is used to suppress thyroid-stimulating hormone to correct hypothyroidism as well as to prevent the ectopic tissue to increase in size while preventing local symptoms [6]. Interestingly, usage of levothyroxine in paediatric age group has revealed symptom improvement in addition to reduction of the size of lingual thyroid [8]. Radioactive iodine ablation is another alternative amongst patients who are found unsuitable for surgical excision.

6.2 Pleomorphic Adenoma

Pleomorphic adenoma (PA) is the most prevalent non-cancerous tumour of the salivary gland. PA constitutes epithelial and myoepithelial cells arranged in various patterns. It is noteworthy that minor salivary gland is vastly located within the oropharyngeal region.

Minor salivary gland PA comprises only 10% [9]. Minor salivary gland tumours traditionally appear from the palate, upper lips, gums, cheek, floor of mouth, pharynx and even trachea. Palate is the predominant site of PA amongst the minor salivary gland tumour followed by upper lip.

Patients' presenting symptoms depend on the site and size of oropharynx involvement. Patients may occasionally remain asymptomatic and may be discovered incidentally. The most common symptom of oropharynx PA is non-ulcerative submucosal mass followed by dysphonia, dyspnoea, hoarseness [10] and rarely sleep apnoea [11].

6.2.1 Diagnosis

Computed tomography is ideal in assessing the nature of the mass, site and size as well as for surgical planning.

6.2.2 Biopsy and Histology

Incisional biopsy is a preferred method to obtain diagnosis, which can be performed in the clinic setting or in operating theatre if the mass is not reachable. PA comprises epithelial, myoepithelial and fibromyxoid tissue. PA arising from the minor salivary gland demonstrates superior cellular element with lesser mesenchymal element [12].

6.2.3 Treatment

Surgery is the gold standard modality of choice. Surgical approach depends on the size, locality as well as structures located in the vicinity. As the oropharyngeal region is narrow, it is prudent for the surgeons to choose the right approach for optimal resection. Amongst the approaches available include transoral, transhyoid, transcervical, transpharyngeal, transmandibular as well as combined approaches. Additionally, with the advent of instrumentations, endoscopic as well as robotic assisted surgery is being rapidly used, especially in tongue base tumours [13]. Enucleation is not advised following risk of recurrence [14]. Recurrence rate of approximately 6% has been reported in minor salivary gland PA [15].

6.2.4 Case Illustration 1

This is a case of a Myanmar lady, 30 years old, presented with a history of neck swelling associated with odynophagia and voice change (Fig. 6.1). There is no history of loss of appetite or loss of weight. Other history was insignificant. Clinical examination revealed a left parotid swelling measuring 8.0 cm × 6.0 cm, firm in consistency, mobile and non-tender, with well-defined border.

Intraoral examination showed extensive medialization of the lateral pharyngeal wall and soft palate (Fig. 6.2). The opening of Stenson's duct is normal, with no discharge or calculi debris seen. Other ENT examinations are unremarkable. CT scan of neck is performed, and it revealed a heterogenous mass of both superficial and deep lobe of the parotid glands. Oropharyngeal mass caused partial oropharyngeal obstruction. FNAC of the parotid suggests that it is a benign tumour which corresponds to the clinical diagnosis of pleomorphic adenoma.

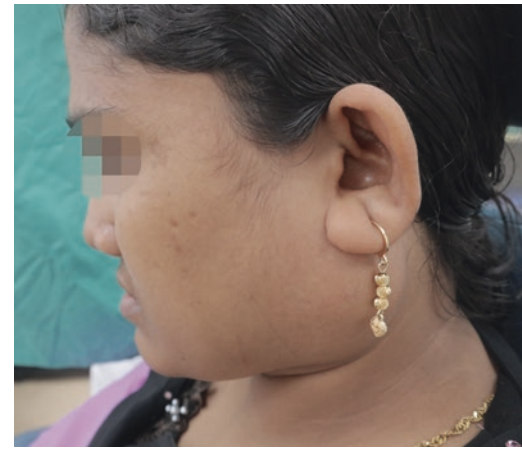

Fig. 6.1 Neck examination shows a diffuse left neck mass, around the parotid area and extending inferiorly to the level of angle of mandible. The mass has pushed the ear lobule anterosuperiorly. The displacement of ear lobule is a significant finding of mass that originates from the parotid glands

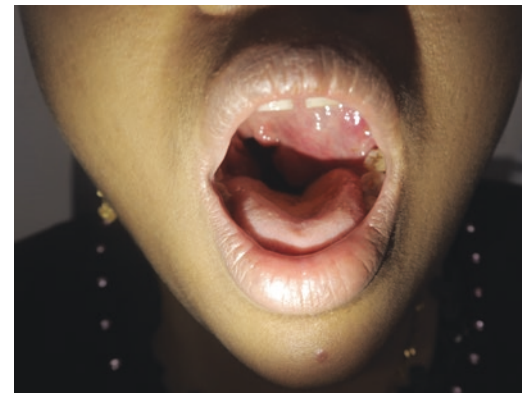

Fig. 6.2 Oral cavity examination showed the medialization of left soft palate and lateral pharyngeal wall

She was planned for total parotidectomy with preservation of the facial nerve, owing to the benign nature of the tumour. In case of malignant tumour, if the evidence of facial nerve palsy is observed preoperatively, and intraoperatively the facial nerve is adherent to the mass, then the facial nerve needs to be resected to achieve better oncologic outcomes.

Fig. 6.3 The facial nerve leads to facial nerve function monitoring during parotidectomy. This is vital as the facial nerve runs between the superficial lobes and deep lobes of parotid glands. The facial nerve monitor allows the identification of the nerve and thus avoids injury to the facial nerve. Otherwise, the patient will suffer from facial asymmetry due to the facial nerve injury

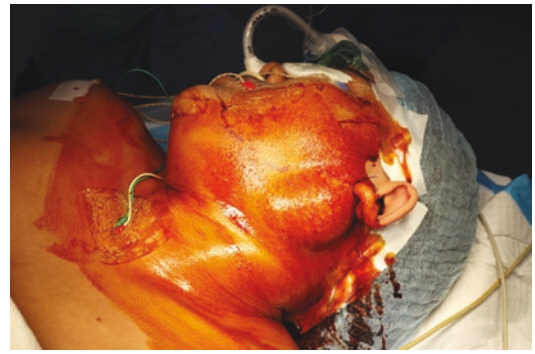

Fig. 6.4 The patient is intubated via a nasal intubation tube, which is seen in situ. The parotid mass is visualized clearly below the left-ear lobule. Facial nerve needles have been secured on the patient's face. Blue needle is for orbicularis oculi, and red needle is for orbicularis oris

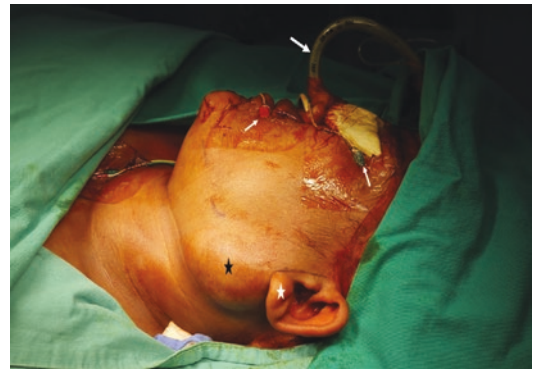

Fig. 6.5 The patient is intubated via a nasal intubation tube, which is seen in situ. The parotid mass is visualized (black star), and the displacement of ear lobule anterosuperiorly is seen (white star). The nerve needles are secured (small arrows)

Intraoperatively, the facial nerve monitor is applied (Fig. 6.3). This consists of four-channel electrodes, where the pin needle is inserted into frontalis, orbicularis oculi, orbicularis oris and mentalis. The short muscle relaxant is used to facilitate contraction of the muscle during dissection of the parotid tissues, neighbouring the facial nerve trunk and its branches.

The skin is cleaned with a diluted povidone iodine solution (Fig. 6.4), and the draping is done. Importantly, the draping should be done on the other half of the face, exposing the eye corner and oral commissure for the observation of contraction during dissection (Fig. 6.5). This will give clues if the nerve trunk or its branches are nearby. Thus, the surgeon needs to be more careful with the dissection.

The skin incision should be marked accordingly, which includes the mass (Fig. 6.6), the angle of mandible, the midline neck and the outline of SCM muscle. The modified Blair skin incision is done. Importantly, the inferior limb of this incision should be extended more inferiorly to facilitate dissection for deep lobe removal. Ideally, in selected cases, mandibulotomy is required to provide access to the deep lobe. In most cases, if the deep lobe tumour is small-to-moderate size, mandibulotomy is not required. With good dissection and correct techniques, deep lobe tumour can be removed successfully.

Surgical steps are similar with superficial parotidectomy, which is covered in Chap. 8 of this book. For deep lobe approach, it is important to do deep dissection medial to the digastric muscles, to access the parapharyngeal space. Extra precaution needs to be exercised to avoid injury to hypoglossal nerve, which is located just near to the muscle, but more anteriorly. The facial nerve and its branches need to be skeletonized, isolated and retracted superolaterally. Continuous dissection will expose the mass, which most of the time is well encapsulated. Blunt dissection around this mass will facilitate tumour removal.

Post-operatively, the patient had marginal mandibular nerve paresis with other branches intact. The patient was prescribed intravenous dexamethasone for 3 days and was discharged at 5 days post-operatively. The Redivac drain is

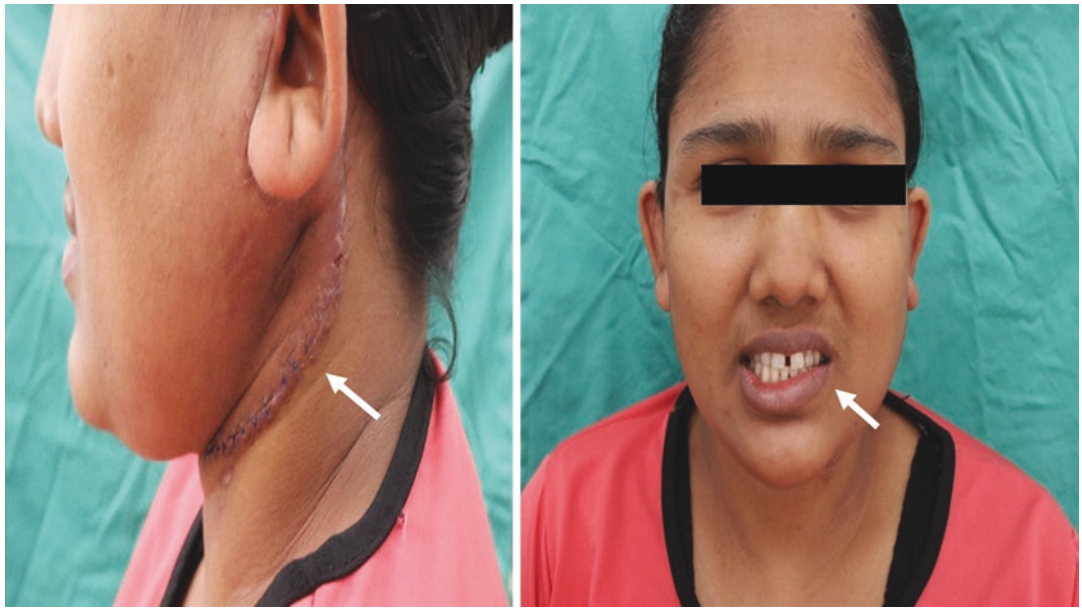

Fig. 6.6 The post-operative wound has dried out; some small suture is still visible in blue. The left marginal mandibular nerve paresis is evident

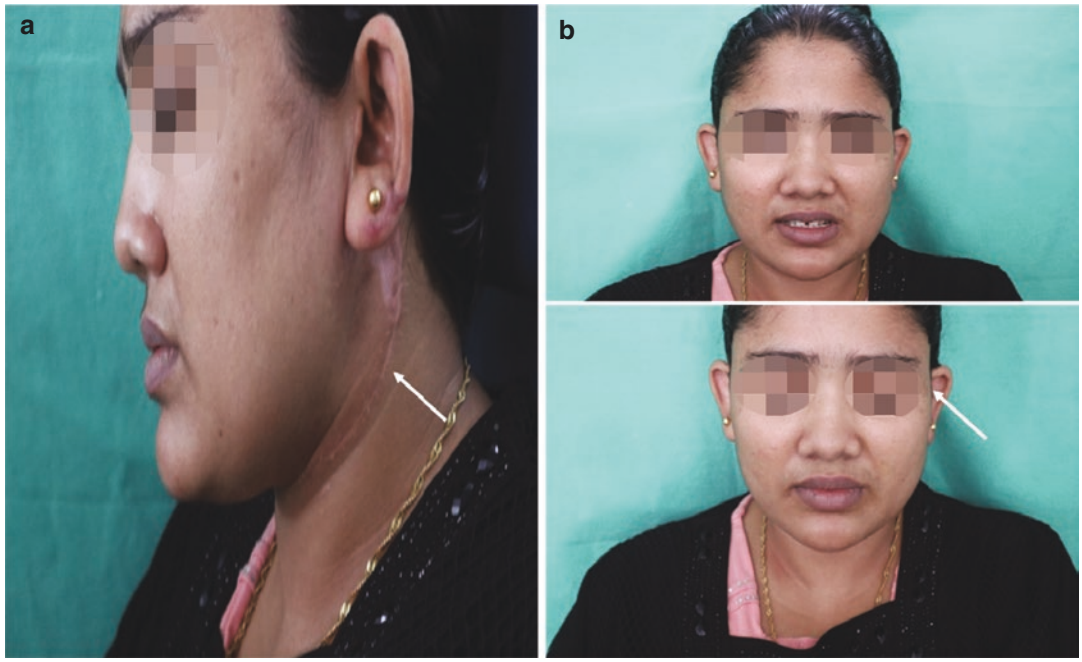

Fig. 6.7 The post-operative wound completely healed (**a**). The facial nerve function has recovered, wherein the patient was able to close the eye fully and had oral commissure symmetry (**b**)

removed if drainage is less than 20 cc over 24 h. At a follow-up at 2 weeks post-operatively, the wound has healed and the marginal mandibular nerve paresis has improved (Fig. 6.6).

At 3-month follow-up, the nerve has improved to near normal. The patient hand good eye closure and symmetry of oral commissure during smiling. There is no loss of depression of lower lips (Fig. 6.7).

6.3 Papilloma

Papilloma is a benign epithelial mass which comprises fingerlike projections involving squamous epithelium. Squamous papilloma is an exophytic mass which involves soft palate, tonsils [16] or uvula.

6.3.1 Epidemiology

Oropharyngeal papilloma is common amongst adults [17]. Female predominance is noted with a male-to-female ratio of 1:1.5 [16]. Mean age of patients with oropharyngeal papilloma is 33 years of age [16]. The most common location is palate and tongue [18]. Oral papilloma is associated with human papillomaviruses 6 and 11 in almost 50% of cases [19].

6.3.2 Clinical Presentation

Oral papilloma may present with varying symptoms depending on its location and size. Most common symptoms include dysphagia and foreign-body sensation [20]. However, amongst immunosuppression patients, papillomas may be larger and multifocal and appear more aggressive [21]. Yet, it is noteworthy that the majority of patients remain asymptomatic.

6.3.3 Histology

Papilloma histologically appears as fingerlike projections of squamous epithelium with evidence of hyperkeratosis and parakeratosis [22]. The fibrovascular core is covered by stratified squamous epithelium.

6.3.4 Treatment

Surgical excision of papilloma is regarded the gold standard. Recurrence is rare.

6.4 Oropharyngeal Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most prevalent oropharyngeal malignancy (Figs. 6.8, 6.9 and 6.10), which comprises 90% of malignancy within the oropharyngeal region [23]. The numbers of cases of oropharyngeal squamous cell carcinoma (OSCC) have burgeoned over the past decade, especially amongst the Western countries [24]. Despite the reported decreasing trend within the overall head and neck malignancy, human papillomavirus (HPV)-related OSCC has been steadily increasing [25, 26]. It is interesting that the prevalence of OSCC is increasing both in male and female [27]. HPV-related OSCC has demonstrated a distinct manifestation as compared to the traditional

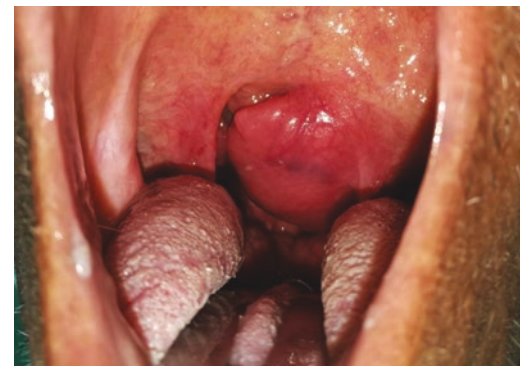

Fig. 6.8 Unilateral tonsillar enlargement whereby the left tonsil is filling the entire oropharyngeal region

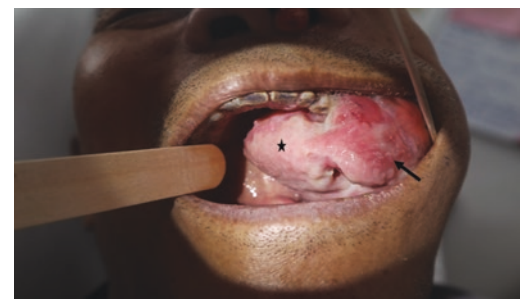

Fig. 6.9 The palatal malignant mass (star) has extended laterally to involve the dentition and gingivobuccal sulcus (arrow) and also invaded to the oropharyngeal area

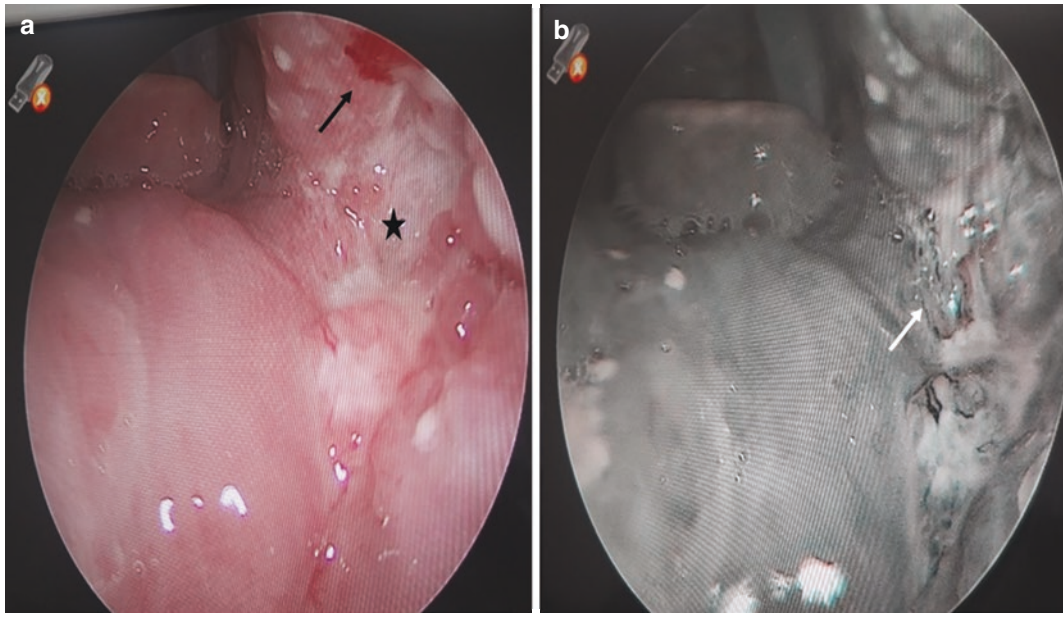

Fig. 6.10 (**a**) The friable tissue at left retromolar trigone area is suspicious of malignancy. (**b**) The narrowband image-enhanced endoscopy showed the changes in the vessel pattern that signify malignancy

Table 6.1 Subtypes of squamous cell carcinoma

Subtypes	Description
Verrucous SCC	Verrucous carcinoma has better prognosis than traditional OSCC. It appears as dull projections and invaginations of well-differentiated squamous epithelium. Additionally, prominent surface keratinization with occasional abnormal mitoses is seen. Verrucous carcinoma is able to invade stroma with well-defined pushing border.
Basaloid SCC	Basaloid SCC comprises rounded nests with smooth borders, and peripheral palisading, basophilic myxoid or mucoid material along with gland-like foci are present. Nuclear pleomorphism, high mitotic activity, apoptosis and necrosis are seen. Basaloid SCC is claimed to have worse prognosis than the traditional OSCC.
Papillary SCC	Papillary SCC demonstrates papillary growth pattern along with thin fibrovascular core blanketed by cancerous epithelial cells. Surface of epithelium can be of two types: High-grade keratinizing epithelial dysplasia or immature and basaloid epithelial cells with no evidence of maturation or keratinization. Papillary SCC has a better prognosis compared to traditional OSCC.
Spindle SCC	Spindle SCC appears as an exophytic mass with ulcerated surface with remnants of dysplastic squamous epithelium with areas of transition from squamous cells to malignant spindled or pleomorphic tumour cells with hypercellularity, necrosis and abnormal mitosis. The prognosis of this tumour is similar to traditional OSCC.
Adenosquamous SCC	Adenosquamous carcinoma demonstrates characteristics of squamous and glandular differentiation. This subtype is rare in oropharynx. Prognosis is worse than traditional OSCC.
Lymphoepithelial SCC	Lymphoepithelial carcinoma is morphologically similar to non-keratinizing nasopharyngeal carcinoma, undifferentiated type. However, unlike the nasopharyngeal carcinoma, it is not related to Epstein-Barr virus. It comprises large cells with round-to-oval vesicular nuclei, and scanty eosinophilic and amphophilic cytoplasm.

OSCC. HPV-related OSCC afflicts younger patients, white females, non-smokers and promiscuous behaviour [28–30]. Non-HPV-related OSCC on the other hand afflicts elderly male notably amongst heavy smokers and high alcohol consumers [31, 32]. Subtypes of OSCC (Table 6.1) include verrucous carcinoma, basaloid SCC, papillary SCC, spindle cell SCC, adenosquamous SCC and lymphoepithelial carcinoma [33].

6.4.1 Risk Factors

Smoking or tobacco consumption and alcohol are considered by far the highest risk factors to develop OSCC.

1. Smoking

   The International Agency for Research on Cancer (IARC) groups tobacco smoking as group 1 carcinogen for both oral cavity and oropharynx [34]. Relative risk for OSCC based on a meta-analysis is 6.76 amongst current tobacco smokers compared to non-smokers [35]. It is noteworthy that smoking-associated risk is dose dependent, and it is based on total or cumulative cigarette usage. The risk for OSCC reduces over time amongst patients who stop smoking and may even reach to a non-smoker status after 10 years [36].
2. Alcohol

   Heavy alcohol consumption is associated with high risk of developing oropharynx malignancies, especially when consumed >60 g or 4 drinks per day or more than 4–7 drinks per week [37]. Besides that, alcohol is reported as an independent risk factor. Relative risk for head and neck SCC is 1.3 for 10 g of ethanol per day compared with 13.0 for 125 g of ethanol per day, whereby superior risk is noted for OSCC as compared to oral cavity SCC [38].
3. HPV

   HPV has been discovered as a major aetiologic risk factor for numerous head and neck cancers, notably OSCC. HPV-16 accounts as the most common subtype in nearly 95% of the HPV-related OSCC [39]. HPV-related OSCC has been reported to be more common amongst people who are younger, white and of higher socioeconomic status as well as in those with increased lifetime sexual or oral sexual partners.

Other additional risk factors include oral microbiome, nutritional deficiencies, poor immune status, environmental pollutants, occupational exposure as well as genetic factors.

6.4.2 Clinical Presentation

OSCC traditionally manifests as an ulcerative non-healing tumour or appears as an irregular mucosal change frequently in the tonsils and base of tongue (Figs. 6.11 and 6.12) [40]. OSCC is known for its ability to remain asymptomatic for a long period as well as metastasis propensity. Non-healing extraction socket is also a telltale sign of OSCC. Presence of persistent neck mass, sore throat and dysphagia are the most common complaints. However, it is worth noting that pre-

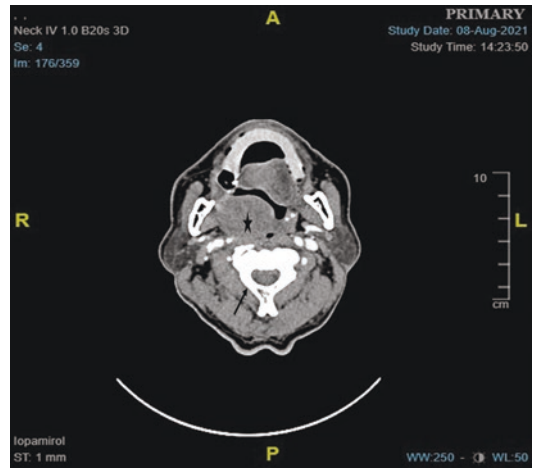

Fig. 6.11 The oropharyngeal mass (star) is visualized with some obstruction of the oropharyngeal airway. Patient may complain of dysphagia and voice change

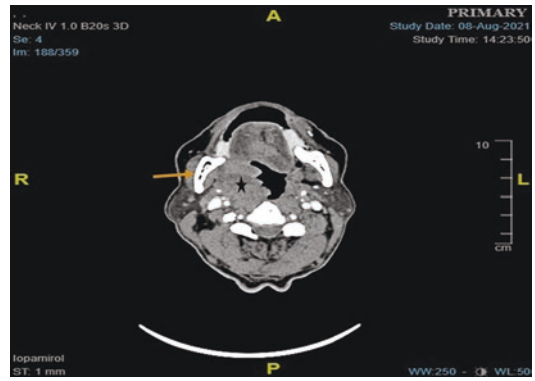

Fig. 6.12 The irregular border of the oropharyngeal mass (star). The mass has occluded the airway to 50%. The mass is very close to the mandible (arrow)

sentation may differ according to the HPV status of the mass. Among HPV-related OSCC, neck mass is the most common presentation (51%), followed by sore throat (28%) and dysphagia (10%). It is worth noting that humongous metastatic node may emerge with a tiny primary tumour.

Neck swelling was reported to be more common amongst the HPV-related OSCC as compared to the non-HPV-related OSCC, whereby sore throat was more common in the latter group of patients.

Patients with OSCC are reported to present with symptoms until tumour becomes large enough (>2 cm) and invades other structures [41], as patients usually remain asymptomatic when the primary tumour is <2 cm [42]. As primary tumour of OSCC enlarges, it leads to dysphagia, odynophagia, sore throat, pain, referred otalgia and obstructive symptoms, especially when the tumour is obstructing the airway as well as constitutional symptoms [43].

6.4.3 Diagnosis

Endoscopic examination under general anaesthesia enables assessment of the primary tumour size along with its extension, for biopsy in a controlled setting to obtain histological diagnosis as well as to detect the presence of secondary tumour or synchronous lesion.

6.4.4 Histology

HPV-related OSCC appears to be non-keratinizing with basaloid features reiterating tonsillar crypt epithelium [44]. HPV status is determined using several methods including reverse transcriptase polymerase chain reaction for high-risk HPV E6 and E7 mRNA, DNA or RNA in situ hybridization test as well as p16 immunohistochemistry [45]. p16 has become a favoured biomarker for HPV status and is utilized mainly for oropharyngeal carcinoma as well as non-keratinizing tumours [46]. Additionally, the College of American Pathologists favours usage of p16 immunohistochemistry or in situ hybridization to predict oropharyngeal origin when investigating the metastatic node of known primary.

6.4.5 Imaging

Imaging is necessary as a diagnostic modality to assess staging, extension of tumour, presence of synchronous tumour, metastatic and regional lymph node spread, as well as recurrence or residual disease (Figs. 6.11 and 6.12). Chest radiograph is a valuable diagnostic modality to assess metastasis, and lung is the most prevalent location for the spread of OSCC as well as a possible site for second primary. Additionally, chest radiograph is an important part of preoperative evaluation to identify the presence of pulmonary or airway disease.

Ultrasound is used as a diagnostic tool for guiding fine needle aspiration cytology/biopsy as well as to detect the presence of occult primary tumour sites in patients with metastatic cervical lymph node [47, 48].

Contrasted computed tomography is crucial to delineate the tumour size, extension, staging, and bone or cartilage involvement. CT enables rapid image acquisition as well as excellent resolution of bony involvement. It is worth noting that the presence of cystic metastatic lymph node has been associated with HPV-related OSCC [49]. Magnetic resonance imaging (MRI) is the preferred modality to evaluate soft-tissue, perineural, intravascular and marrow involvement [50].

Positron emission tomography (PET)/CT is effective to evaluate the site of the occult tumour as it has superior sensitivity and specificity in comparison to the traditional CT. Additionally, PET/CT is deemed superior to assess the effectiveness of treatment. PET/CT has been reported to be an excellent modality when performed 12 weeks post-chemoradiation to assess response following treatment. Surveillance imaging should be carried out at an optimal timing which is vital. Surveillance PET/CT, if carried out at earlier stages, may lead to false positives and false negatives [51, 52]. A retrospective study performed

revealed that PET/CT carried out 2 months post-treatment provides accurate results [53], although to date there is yet any consensus on the ideal timing for imaging to assess post-treatment outcome [54, 55].

6.4.6 Staging

Staging for oropharyngeal carcinoma is based on the TNM staging of carcinomas originating in the oropharynx. TNM staging pertains to SCC as well as other epithelial malignancies originating in the oropharynx. The most recent TNM staging system is the 8th edition of the American Joint Committee on Cancer (AJCC).

6.4.7 Treatment

Multidisciplinary discussion should include oto-rhinolaryngologists, oncologists, dieticians, nurses and speech pathologists as well as social workers. Despite the variation noted across the causative factors, clinical behaviour, outcome of treatment as well as molecular pattern of HPV-positive compared to HPV-negative tumours, the choice of treatments remains similar [56]. Treatment is based on tumour, node and metastasis (TNM) staging, patient's age, general conditions, patient's preference as well as facilities available at the medical centre [57]. Generally, single mode of treatment is advocated at the early stage of disease, whereas advanced stage of the OSCC is treated with dual-modality treatment [58].

6.4.8 Early Stage

Early-stage tumour can be treated either surgically or via radiation therapy. Early-stage OSCC can be treated surgically via either open or transoral/endoscopic approach with a margin of 1–2 cm. Neck dissection is carried out when there is evidence of neck disease or in an N0 neck as occult cervical neck disease has been reported to be nearly 30–40% in OSCC.

6.4.9 Advanced Stage

Multimodality treatment is traditionally carried out in advanced OSCC (stages III and IV). Combined mode of treatment comprises surgical resection in the initial stage with subsequent adjuvant radiotherapy or chemoradiotherapy [59]. Surgery addresses both primary sites as cervical node. In a clinically negative node, elective neck dissection should be performed. Generally, the functional as well as curative outcome of both surgery and chemoradiation is difficult to predict [60]. Surgical techniques which are performed include open resection, transoral robotic surgery as well as transoral laser microsurgery. Regardless of the surgical techniques, the surgical principle is the same: removal of tumour with at least 1–2 cm margins. Extensive resection requires reconstruction.

6.4.10 Non-surgical Treatment

Radiation therapy can be given primarily or combined with chemotherapy or post-surgical resection. Radiation therapy has been reported to show promising results notably at the earlier stage of the disease. Five-year loco-regional control rate has been reported to be 98% with the overall survival rate of 90% [61]. Following surgery, radiation therapy is prescribed in patients in advanced stage of disease, nodal involvement, close margin, perineural invasion as well as lymphovascular invasion [62]. Also, chemotherapy, when combined with radiation therapy in post-surgery patients with extranodal extension and/or in patients with positive margins, has demonstrated promising results [59].

Standard radiation dose to treat OSCC with gross tumour is 66–70 Gy in 33–35 daily fractions over a period of 6.5–7 weeks. As for radiation therapy post-surgery, the dose is 60 Gy in 30 fractions over 6 weeks. In patients with positive extranodal extension or close or positive margin, the dose comprises an additional 3–6 Gy. In an unoperated neck, dosage of 50–54 Gy is used. Radiation therapy is traditionally given within a 6-week period to reduce the chances of repopulation [62].

Since its introduction in the early 2000s, intensity-modulated radiotherapy (IMRT) has been a favoured form of radiation therapy, which permits the oncologist to manipulate the radiation dose to increase accuracy to the targeted region while reducing radiation to the neighbouring vital structures. IMRT has been extensively used with excellent outcomes of chemoradiation OSCC [58]. Recent study on survival outcome with primary IMRT of which 90% had locally advanced disease who received concurrent chemotherapy showed a 3-year overall survival rate of 77.2%. GORTEC group reported the first OSCC-specific trial, whereby 266 patients in this study were randomized to concurrent chemoradiotherapy or radiotherapy alone [63]. The 3-year overall survival rate was 51% in the chemoradiotherapy group in comparison to 31% in the radiotherapy group. This regime has become a standard therapy for loco-regionally advanced disease of OSCC [64].

1. Chemotherapy

   It is noteworthy that the current treatment regime of curative treatment of the loco-regionally advanced HPV-related p16-positive as well as non-HPV-related p16-negative OSCC is concurrent chemoradiotherapy with IMRT plus cisplatin, a platinum-based chemotherapy agent given every 3 weeks [65]. In patients with locally advanced stage III–IV SCC of the oral cavity, oropharynx, larynx or hypopharynx, standard fraction rate of radiotherapy with cisplatin at 100 mg/m^2 × 3 or accelerated fractionation and a concomitant boost with cisplatin at 100 mg/m^2 × 2 demonstrated similar overall survival rate [66].
2. Immunotherapy

   Usage of immune checkpoint inhibitors, notably nivolumab, pembrolizumab, durvalumab, atezolizumab and avelumab, as an adjunct therapy for head and neck malignancies has shown promising results. Pembrolizumab and nivolumab are FDA approved amongst patients with recurrent and metastatic disease. It is worth noting that these drugs principally target programmed cell death protein 1 (PD-1)/PD-L1 axis, and oropharynx has been regarded as a known immune-privileged site.

   Cetuximab, a monoclonal antibody against human epidermal growth factor receptor, has demonstrated promising results amongst patients with advanced head and neck SCC [67]. Cetuximab has demonstrated lower toxicity as compared to the standard chemotherapy agents such as paclitaxel, cisplatin and methotrexate.

6.4.11 Case Illustration 1

A 45-year-old Chinese lady initially presented with tonsillar mass and was diagnosed with adenoid cystic carcinoma. She underwent bilateral tonsillectomy and had adjuvant radiation in 2012. On subsequent follow-up, oral cavity and oropharyngeal examination revealed a residual mass at the inferior pole of right tonsils (Fig. 6.13). The biopsy of the mass confirmed recurrent ACC. Subsequently, CT scan was performed, which showed mass at the right parapharyngeal space region. She was counselled for excision of the recurrent tumour and neck dissection but refused. In the following years of follow-up, the

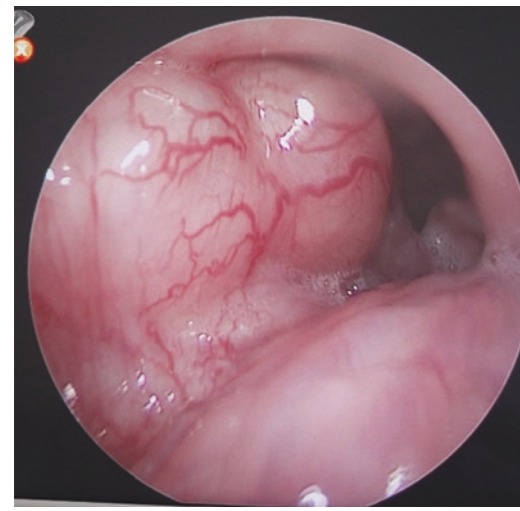

Fig. 6.13 Oral cavity examination showed a vascularized mass at right tonsillar region. This is a recurrent adenoid cystic carcinoma as the patient had bilateral tonsillectomy previously

mass increased in size with prominent vascularity seen. Repeated CT scan was performed, which showed that the mass has increased in size. The patient however refused for further treatment.

6.4.12 Case Illustration 2

A 30-year-old Malay lady presented with a history of globus, odynophagia and voice change. Clinical examination revealed a unilateral tonsillar hypertrophy (Figs. 6.14 and 6.15). Cervical palpation revealed a small neck node at left level II region. Other systems' examination is unremarkable. FNAC of neck nodes shows lymphoproliferative changes. The diagnostic tonsillectomy was performed and suggestive leukaemic infiltration. Further investigations showed that she had lymphoblastic leukaemia. Subsequently, she was referred to haemato-oncology for chemotherapy treatment.

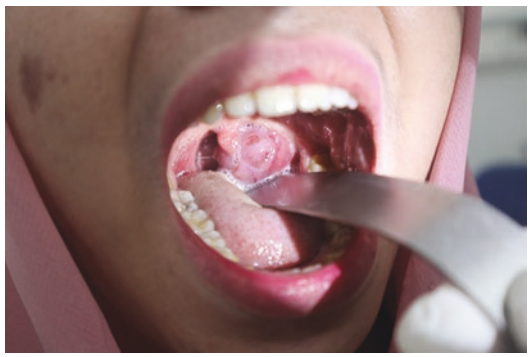

Fig. 6.14 Oral cavity examination showed grade 4 left tonsillar enlargement with minimal ulcerative mucosa. The ulcerative mucosa is a sign of sinister pathology like malignancy. A common tonsillar hypertrophy has intact mucosa

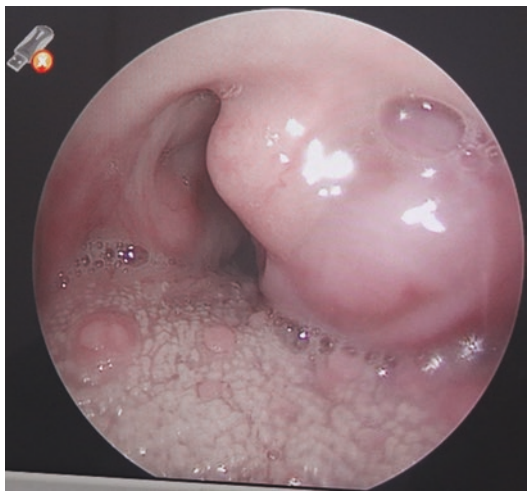

Fig. 6.15 Left oropharyngeal mass

6.5 Benign Hypopharyngeal Tumours

6.5.1 Fibrolipoma

Fibrolipoma is a pedunculated benign tumour. It is amongst two most common benign hypopharyngeal tumours including leiomyoma [68]. Fibrolipomas are encapsulated, smooth and pedunculated. Male predominance was reported [69]. Clinical presentations are commonly dysphagia, discomfort, irritation and cough [69]. Albeit rare, if lipoma enlarges, it may obstruct the airway and cause hoarseness, asphyxia and even death [70]. Having said that, clinical manifestations rely chiefly on the location and size of the mass.

Computed tomography is able to diagnose the mass although magnetic resonance imaging (MRI) is usually favoured [69]. MRI is deemed superior owing to its multiplanar imaging potential, which enables precise delineation of the soft-tissue mass apart from the avoidance of ionizing radiation exposure.

Surgical resection via suspension laryngoscope and carbon dioxide laser is the ideal choice of treatment. Although malignant transformation of solitary lipoma has not been reported, malignant transformation of multiple lipomata of the larynx as well as pharynx has been reported [71].

6.6 Hypopharyngeal Squamous Cell Carcinoma

Hypopharyngeal carcinoma comprises malignant tumours occurring at the hypopharynx subsites: pyriform sinus, postcricoid or posterior pharyngeal wall. Over 95% of hypopharyngeal carci-

noma arises from the epithelial mucosal lining of the hypopharynx leading to squamous cell carcinoma (SCC). Hypopharynx carcinoma comprises 7% of all malignancy of the aerodigestive tract. Hypopharynx SCC involves 5% of all head and neck cancers [72]. The most common site of malignancy is pyriform sinus, with posterior pharyngeal wall and postcricoid being the least common [73]. Pyriform sinus SCC represents 70% of cases [72–74].

6.6.1 Epidemiology

Overall male predominance is found in hypopharynx carcinoma [75] predominantly amongst patients with a history of heavy usage of alcohol and smoking [76]. Long-term exposure results in progressive cellular dysregulation by alteration of tumour suppressor gene such as TP53, amplification of proto-oncogenes such as cyclin D1 as well as damage to regulatory factors including transforming growth-beta (TGF-beta) and retinoic acid receptors. Additionally, transformation from normal mucosa to malignancy is related to genetic anomaly. Yet, women predominance is found amongst postcricoid SCC following Plummer-Vinson syndrome. Interestingly, postcricoid SCC amongst female patients is unrelated to alcohol consumption or smoking [76]. It is noteworthy that hypopharyngeal carcinoma is associated with an overall poor prognosis with an overall 5-year survival rate of 30–35% [77, 78]. National cancer database (NCDB) revealed epidemiologic data of hypopharyngeal cancer averages at 63 years of age, of which 75% are male patients involving over 70% of Caucasians [79].

6.6.2 Risk Factor

Heavy smoking and alcohol consumption have been predominantly linked to head and neck cancers. Other predominant causative factors are poor nutrition, Plummer-Vinson syndrome (especially in females) and gastroesophageal reflux disease. Effect of human papillomavirus in the pathogenesis of hypopharyngeal cancer remains a debate to date [80]. Asbestos is found to be an independent causative factor leading to the occurrence of hypopharyngeal cancer [81]. Genetic factors as a risk factor are still under research. Presence of heritable polymorphisms of expression of enzymes that activate tobacco-related proto-oncogenes such as aryl hydrocarbon hydroxylase and detoxifying carcinogens such as glutathione S-transferase is linked with head and neck malignancy. Detection of polymorphisms in alcohol dehydrogenase genes increases the risk of oral and pharyngeal malignancy associated with alcohol.

6.6.3 Clinical Presentation

It is noteworthy that patients with hypopharyngeal carcinoma have traditionally shown delayed presentation with loco-regional or distant metastasis, hence accounting for a poor prognosis [82]. Patients typically remain asymptomatic until the mass grows large, extending into the laryngeal region or following cervical nodal metastasis [83]. Early clinical manifestations may be non-typical and mimic benign conditions such as laryngopharyngeal reflux. Dysphagia is the most common presentation followed by sore throat, hoarseness or globus sensation [78]. Referred otalgia is another presentation of hypopharyngeal cancer. Following the extensive lymphatic network of the hypopharynx, early cervical nodal metastasis has been reported [78]. Approximately 6% of patients exhibit metastasis upon presentation, and the number increases as the disease progresses as metastasis is said to be present up to 60% during the disease course [79].

6.6.4 Diagnosis

A meticulous history taking is imperative followed by physical examination with a thorough head and neck assessment. Additionally, underlying medical illness or comorbidities, presence of unexplained weight loss, nutrition status and performance status of the patient are deemed necessary. Flexible fibre-optic laryngoscopy is

mandatory to assess the site, size and extension of the tumour; presence of synchronous lesion; and vocal cord mobility. Yet, the patient needs to be under direct laryngoscopy and oesophagoscopy to assess the tumour spread, length, involvement of oesophagus mucosa and presence of synchronous lesion as well as for biopsy to determine the pathological diagnosis. Presence of narrowband imaging (NBI) with or without autofluorescence enables a clearer delineation of the tumour compared to the standard white-light endoscopy [84, 85]. It is noteworthy that synchronous tumours are present in 1–6% of patients newly diagnosed with head and neck SCC [86].

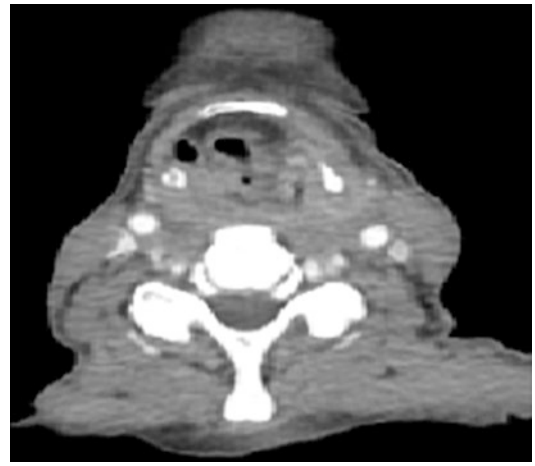

Fig. 6.16 Hypopharyngeal tumoural mass

6.6.5 Blood Investigations

Blood investigations are necessary to evaluate the presence of anaemia notably iron deficiency anaemia due to its association with Plummer-Vinson syndrome. Additionally, presence of macrocytic anaemia directs towards alcohol abuse. Thrombocytopenia and hypoalbuminemia, on the other hand, suggest nutritional deficiency. It is mandatory to assess the thyroid function as the patient may need to be assessed for hypothyroidism as radiation may lead to this condition in nearly 40% of individuals, which may be worst in patients with underlying hypothyroidism.

6.6.6 Imaging

Imaging is a mandatory part of tumour assessment. It is noteworthy that imaging should be done prior to biopsy as to avoid false positives, which overestimates the tumour following post-biopsy oedema. Chest radiograph is mandatory as a preoperative assessment in addition to assessing for the presence of lung metastasis. Barium swallow is carried out to delineate the inferior border of the lesion and to look for the presence of involvement of oesophageal inlet.

Computed tomography (CT) with contrast is essential for staging of the tumour, to assess the size, extension and presence of cervical and distant metastasis in addition to the presence of secondary or synchronous tumour (Fig. 6.16). Thickness slice for CT should be 0.625–1.25 mm, and the reformatted is to be no greater than 2.5 mm. It is imperative that CT scan needs to be carried out upon quiet respiration with patients instructed not to swallow [87].

Magnetic resonance imaging (MRI) is superior to delineate the soft-tissue involvement [87]. Multiplanar MRI enables a three-dimensional assessment of the tumour as well as assessment of the prevertebral involvement. CT or MRI has been the recommended imaging for hypopharynx by the Royal College of Radiologists, 2014 [88]. MRI requires an axial, sagittal and coronal T1W and T2W sequence with contrast enhancement as well as fat suppression to visualize soft-tissue and cartilage invasion [87]. PET is deemed ideal amongst patients with locally advanced disease and nodal involvement to evaluate unknown primary site involvement and to evaluate the outcome of therapy. PET/CT is ideal in advanced cases of hypopharyngeal carcinoma, in residual or recurrent cases [87].

6.6.7 Endoscopic Examination Under General Anaesthesia

Endoscopic examination under general anaesthesia enables thorough assessment of the primary tumour along with its extension, for biopsy in a

controlled setting to obtain histological diagnosis as well as to detect the presence of secondary tumour or synchronous lesion. It is mandatory to perform oesophagoscopy as involvement of oesophagus is discovered frequently due to its close proximity of the hypopharynx especially postcricoid malignancy.

6.6.8 Histology

Overexpression of epidermal growth factor receptor (EGFR) has been reported in approximately 100% of head and neck malignancies.

6.6.9 Staging

Staging for hypopharyngeal carcinoma is based on TNM staging of carcinomas originating in the hypopharynx. TNM staging system applies to squamous cell carcinoma as well as other epithelial malignancies originating in the hypopharynx. The most recent TNM staging system is the 8th edition of the American Joint Committee on Cancer.

6.6.9.1 Primary Tumour (T)

- **TX**: primary tumour cannot be assessed
- **Tis**: carcinoma in situ
- **T1**:
  - Tumour limited to one subsite of hypopharynx (left or right pyriform sinuses, posterior hypopharyngeal wall, or postcricoid region) and/or
  - Tumour ≤2 cm in greatest dimension
- **T2**:
  - Tumour extends into adjacent subsite of hypopharynx or adjacent site (larynx, oropharynx) and/or
  - Tumour >2 and ≤4 cm without fixation of hemilarynx
- **T3**:
  - Tumour >4 cm or
  - Clinical fixation of hemilarynx or
  - Extension to oesophageal mucosa
- **T4**: moderately advanced and very advanced local disease
  - **T4a**: moderately advanced local disease in which tumour invades one or more of the following:
    Thyroid cartilage
    Cricoid cartilage
    Hyoid bone
    Thyroid gland
    Oesophageal muscle
    Central compartment soft tissue (prelaryngeal strap muscles and subcutaneous fat)
  - **T4b**: very advanced local disease in which tumour encases carotid artery or invades one or more of the following:
    Mediastinal structures
    Prevertebral fascia

6.6.9.2 Regional Lymph Node (N)

Regional nodal status is defined the same as for most other cancers of the head and neck. See the main article, cervical lymph node (staging).

6.6.9.3 Distant Metastasis (M)

The terms pM0 and MX are not valid TNM categories. The following categories may be used:

- **cM0**: no evidence of metastases
- **cM1**: distant metastasis
- **pM1**: distant metastasis, microscopically confirmed

6.6.9.4 Stage Groups

The prognostic stage groups are defined the same as for most other cancers of the head and neck:

- **Stage 0**
  - Tis, N0, M0
- **Stage I**
  - T1, N0, M0
- **Stage II**
  - T2, N0, M0
- **Stage III**
  - T3, N0, M0
  - [T1, T2, T3], N1, M0

- **Stage IVA**
  - T4a, [N0, N1], M0
  - [T1, T2, T3, T4a], N2, M0
- **Stage IVB**
  - [Any T], N3, M0
  - T4b, [Any N], M0
- **Stage IVC**
  - [Any T], [Any N], M1

6.6.10 Treatment

Treatment option is based on the staging of the tumour, age, patients' performance status, facility availability in the medical centre as well as patients' preference. Ideally, a multidisciplinary meeting should be carried out involving the surgical and radiation oncologists, speech and language therapists as well as patients and their family prior to commencement of treatment. Favoured treatment options available include surgery, radiotherapy or chemotherapy. Single-mode therapy is advocated for early-stage, localized tumour (T1 and T2 N0), whereas multimodality treatment is opted for the advanced stage of disease.

6.6.10.1 Surgical

Myriad surgical techniques as well as approaches are available today including both transoral and open techniques depending on the tumour extension and structures involved [89]. Transoral surgical approach is associated with superior ability in localized smaller tumour, whereby complete surgical resections can be achieved successfully with negative margin.

1. Early-stage tumour

   Early stage is managed either surgically or via radiation therapy [90]. Surgical approaches include transoral resection or partial open laryngopharyngectomy with or without reconstruction. Occult nodal metastasis is reported to be present in nearly 30–40% of hypopharyngeal carcinoma patients. Hence, neck dissection should be carried out in all cases electively during the surgical resection of the primary tumour.

2. Late stage of tumour

   Nearly 80% of patients with hypopharyngeal carcinoma patients are at stage III and IV during their first visit. It is noteworthy that more than 60% of patients have demonstrated submucosal extension [91], with histological studies reporting 1–2 cm of submucosal extension warranting minimal resection margin of 1.5 cm superiorly, 3 cm inferiorly and 2 cm laterally [87]. Approximately 80% of macroscopical submucosal extensions are demonstrated in patients with previous radiotherapy [87].

3. Recurrent disease

   Salvage surgery carried out in patients with recurrence post-radiation has reported a lower success rate, with larynx preservation rarely possible [74]. Additionally, patients with recurrence post failed radiation therapy require greater resection margin causing difficulty for reconstruction.

6.6.10.2 Non-surgical: Chemotherapy and Radiotherapy

Radiotherapy has been utilized as organ-sparing modality as compared to surgery in treating early-stage hypopharyngeal SCC. Locally advanced hypopharyngeal SCC can be treated with radiotherapy when combined with systemic therapy. Post-operative radiotherapy or chemoradiotherapy demonstrated improved loco-regional disease control as well as overall survival rate even with the presence of positive margin or extra-capsular nodal extension or extra-capsular nodal disease [92]. Prospective trials have revealed equal rate of local control and survival when surgery and adjuvant treatment are compared with primary non-surgical therapy in advanced cancers. It is noteworthy that there is scarcity of trials including randomized controlled trials involving primary tumour of hypopharyngeal carcinoma. Hence, most of the referred clinical trials have been for laryngeal cancer.

Addition of concomitant systemic therapy, notably cisplatin, has demonstrated moderate improvement of the overall survival rate. Combination therapy in the advanced stage of hypopharyngeal carcinoma has been reiterated.

Yet, in elderly patients aged 71 years and above, the benefit of systemic therapy has been deemed doubtful [93, 94].

As for induction chemotherapy, several large trials have been performed which revealed its potential as an organ preservation modality, which has been shown to be in par with the survival outcome of surgery in laryngeal cancer. Induction chemotherapy has demonstrated the possibility to reduce distant metastasis [95]. Primary radiotherapy with subsequent salvage surgery showed poorer survival rate in comparison to primary surgery followed by post-operative radiotherapy, especially in advanced stage [74]. Whereas the outcome of primary radiotherapy [95, 96] in patients with early-stage hypopharyngeal carcinoma is comparable to primary total-laryngectomy or larynx-conserving surgery [97–99].

In a phase III trial of hypopharyngeal carcinoma patients, induction chemotherapy followed by radiotherapy as compared to primary surgery followed by radiotherapy revealed no difference in local or regional recurrence as well as 5-year disease-free survival rate [100]. In the induction chemotherapy group, disease-free survival rate was 25%, and it was 27% in the primary surgery group. Additionally, survival rate of patients with a functional larynx amongst the chemoradiation group was 35% [101]. Based on a recent Surveillance, Epidemiology, and End Results (SEER) program study regarding survival outcome amongst hypopharyngeal cancer patients, non-surgical organ preservation study was favoured for hypopharyngeal carcinoma management [77].

Intensity-modulated radiation therapy enables precisely targeted therapy to minimize the risk of radiation to the vital structures located at the vicinity, for example the parotid gland. Intensity-modulated radiation therapy enables target volume delineation, which has demonstrated local control as well as functional outcomes.

Targeted therapy is rapidly developing in the management of head and neck carcinoma. Immunotherapy, especially the one with targeted therapies against programmed death ligand pathway [PD-1, PD-L1], is currently under investigation for various tumour types [102]. Randomized clinical trials of these targeted therapies known as immune checkpoint inhibitors including pembrolizumab and nivolumab have demonstrated improvement in head and neck cancers and are currently approved in recurrent as well as metastatic head and neck cancers [103, 104]. p53 and ERCCI, a host of molecular targets of interest to head and neck cancer including hypopharyngeal cancer, have been associated with providing response to treatment, notably chemotherapy and laryngeal preservation [105].

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