INTRODUCTION

Epidemiology

Oral cavity, oropharyngeal and hypopharyngeal cancers represent approximately 3% of all cancers worldwide.[1] In the united states, an estimated 42,440 new cases of cancer of the oral cavity and pharynx were expected in 2014, and the estimated deaths were about 8,390.[2] In Egypt, The most recent national cancer registry program report of Damietta Governorate in 2010 showed that the incident cases of oral cavity and pharyngeal cancer were about 4% of all cancer cases. The incident cases in other governorates in 2008 and 2009 ranged between 3% and 15% of all cancer cases.[3]

These cancers are more than twice as high in men as in women. They are diagnosed more often among people over age of 50 years than they are among younger people.[2]

Etiology and pathogensis

Tobacco use and heavy alcohol consumption are major independent predisposing factors for oral and pharyngeal cancers. In addition, alcohol use appears to enhance the effect of smoking.[4] It has been suggested that alcohol consumption suppress DNA repair following exposure to nitrosamine compounds, despite that the exact mechanism is still unknown.[5] These cancers in most cases share a common carcinogenetic pathway of surface mucosal exposure to carcinogens originating from betel nut, cigarettes, and alcohol. This led to the notorious phenomenon called ‘‘field cancerization’’ of the upper aerodigestive tract.[6, 7] Carcinogens tend to disperse along the aerodigestive tract and result in multifocal cancerous lesions.[8] Several studies have recently demonstrated the significant role of genetic instability in the etiology of cancers of the oral cavity and pharynx.[9] Genetic data revealed the involvement of multiple tumor suppressor pathways, e.g. p53 in tumor initiation, progression, and maintenance.[10]

Oral human papillomavirus (HPV), particularly HPV 16, contribute strongly to the etiology of oropharyngyeal cancers, responsible for 40–80% of oropharyngeal squamous cell cancers.[11, 12] Rising incidence rates for certain subsites, notably the base of tongue, tonsil, and oropharynx related to HPV infection, have been reported in the US particularly among young white men.[12-15] Poor dental hygiene and chronic mechanical irritation have also been associated with the development of cancer of the oral cavity.[16] Dietary factors, particularly consumption of fruits and vegetables, have been consistently associated with reduced risks of oral cavity and pharyngeal cancers.[17, 18]

Other environmental factors associated with hypopharyngeal cancer include iron and vitamin C deficiencies, occupational exposure to asbestos, coal dusts, wood, crop residue.[19, 20] Plummer-Vinson syndrome (the triad of dysphagia, glossitis, and iron deficiency anemia) has been associated with postcricoid hypopharyngeal cancers, especially in women from Scandinavian countries. However, improved nutrition, and iron and vitamin dietary fortification have dramatically reduced the incidence of Plummer-Vinson syndrome in developed countries and thus its role in the etiology of hypopharyngeal cancers.[21]

Pathology

Approximately 90% of cases are squamous cell carcinomas (SCCs), while the remaining 10% represent rare malignancies (unusual forms of squamous cell carcinoma, minor salivary gland tumors, melanomas, lymphomas, and sarcomas) and a variety of malignant tumors of odontogenic origin.[5, 22]

Patterns of Spread

Local spread

SCCs usually begin as surface lesions, but occasionally originate below the surface of the mucosa. Very early surface lesions may show only erythema and a slightly elevated mucosa. Local spread varies by each site. Muscle invasion is common, and tumor may spread along muscle or fascial planes away from the palpable or visible lesion. Tumor may attach early to the periosteum or perichondrium, but bone or cartilage invasion is usually a late event. Tumor extension into the parapharyngeal space allows superior or inferior spread from the skull base to the low neck. Perineural invasion may be observed in SCCs which predicts a poorer rate of local control when managed by surgery. Vascular space invasion is associated with an increased risk for regional and distant metastases.[23]

Lymphatic Spread

The differentiation of the tumor, size of the primary lesion, presence of vascular space invasion, and density of capillary lymphatics predict the risk of lymph node metastasis. The relative incidence of clinically positive lymph nodes on admission is determined mainly by primary site and T stage.[23]

Distant Spread

The risk of distant metastasis is related more to the nodal stage, and location of involved nodes in the low neck, than T stage. The lung is the most common site, accounting for half of the first recognized distant metastases.[23]

Diagnostic Evaluation

A general medical evaluation is performed, including a thorough head and neck examination. The location and extent of the primary tumor and any clinically positive lymph nodes should be documented.

Imaging studies:

Contrast enhanced computed tomography (CT) is typically used as the initial imaging modality to assess local tumor extent and any pathologic lymphadenopathy.[23] It can help determine the extent of tumor infiltration into deep tongue musculature and if there is cortical bony involvement of the mandible.[24, 25] In addition, cartilage invasion, a criterion for stage T4 disease, can be more readily detected.[26]

Magnetic resonance imaging (MRI): MRI provides superior soft tissue definition and gross perineural spread compared with CT and can often provide complementary information to CT.[27] MRI is also better than CT for discriminating tumor from mucus and

in detecting bone marrow invasion.[28] Ideally the scan(s) should be obtained prior to biopsy so that biopsy changes are not confused with tumor.[23]

Combined positron emission tomography (PET/CT) scans: It can help to evaluate the primary site, identify occult nodal involvement, and detect distant metastasis or synchronous primary tumors that are missed by conventional imaging.[29-31]

A chest radiograph is obtained to determine the presence of distant metastases and/or a synchronous primary lung cancer. Patients with N3 neck disease, as well as those with N2 disease with nodes below the level of the thyroid notch, have a 20% to 30% risk of developing distant metastases and are considered for a chest CT or positron emission tomography (PET).[23]

Biopsy:

Tumors amenable to transoral biopsy may be biopsied using local anesthetics in the clinic. Otherwise, direct laryngoscopy under anesthesia is performed to determine the extent of the tumor and to obtain a tissue diagnosis. Given the risk of synchronous cancers, some advocate routine triple endoscopy (i.e., laryngoscopy /pharyngoscopy, bronchoscopy, and esophagoscopy). The additional yield is low, unless diffuse mucosal abnormalities or a malignant lymph node without an identified primary site, particularly in the low neck, are present.[23]

Before initial treatment, the patient should be evaluated by the team who may be involved in the initial management as well as possible salvage therapy, head and neck surgeons, radiation oncologists, medical oncologists, diagnostic radiologists, plastic surgeons, pathologists, dentists, speech, swallowing, and nutritional therapists. The treatment options are discussed and presented to the patient who makes the final decision.[32]

Cancer of the Oral Cavity:

The oral cavity includes the following subsites: floor of mouth, anterior two-thirds of the tongue, buccal mucosa, upper and lower alveolar ridges, hard palate, and retromolar trigone. The area is rich in lymphatic supply, and its initial regional nodal spread is primarily to nodal group I-III.[32]

Regional nodal involvement is evident in 30% of patients at presentation, but the risk varies according to site. For example, primaries of the hard palate and alveolar ridge infrequently involve the neck, whereas occult neck metastases is common (50-60%) in patients with anterior tongue cancers (figure 1.A).[32]

Clinical presentation:

Many patients with oral cavity tumors present with advanced stage disease as initial symptoms may be vague and painless. Presenting symptoms may include Non-healing ulcer, pain, bleeding, or ill-fitting dentures. More advanced lesions may present with speech difficulties, dysphagia, otalgia, hypersalivation, and neck mass.[23]

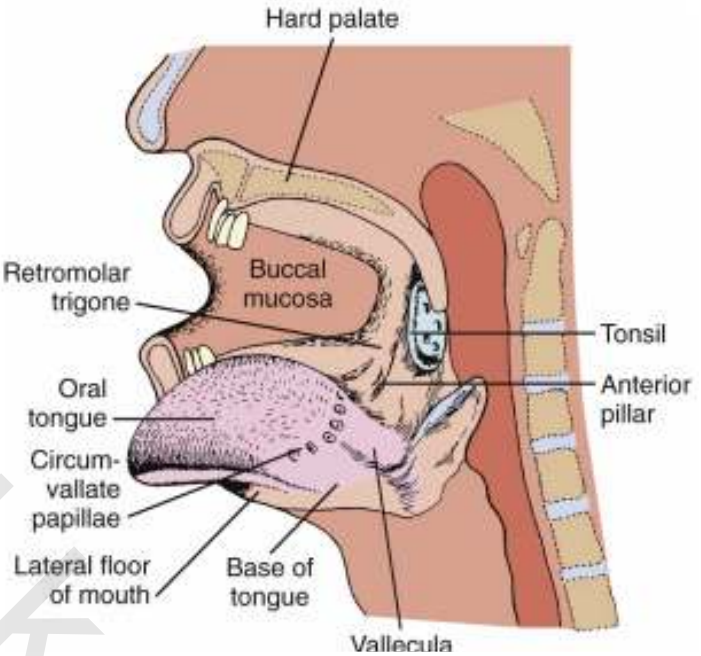

Figure (1.A): lateral view of the oral cavity.

Staging

The tumor node metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC)(7^{th} edition) and the International Union for Cancer Control (UICC) is used to classify oral cavity carcinoma.[33]

Tumor node metastases (TNM) staging system for cancer of the oral cavity

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease*
	Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose
	Oral cavity: Tumor invades adjacent structures only (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced local disease
	Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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

General management

Cancers of the oral cavity may be treated with either radiation therapy, surgery or combined therapy. Single modality treatment is usually attempted for early stage tumors. Multimodality therapy is usually reserved for more advanced tumors.

Management of the primary tumor

Early stage disease

By definition, patients with early (stage I and II) disease have tumors <4 cm in greatest dimension without deep invasion into surrounding structures and have no evidence of lymph node involvement.[33] Early tumors of the oral cavity can be treated with

equivalent excellent cure rates with either radiation therapy (RT) or surgical excision. Surgery is often preferred for management of early cancers of the oral cavity, as surgical cures can often be achieved rapidly and with modest morbidity. While a course of radiation therapy can require several weeks of daily therapy followed by an interstitial implant. Moreover, the risk of associated xerostomia, osteoradionecrosis and dysphagia may renderRT less convenient choice. Therefore, RT is usually reserved for those patients who are unable to undergo surgery or in whom surgical resection would result in significant functional loss.[5]

As regards the postsurgical adjuvant treatment options depend on whether adverse features are present or not. For patients with resected oral cavity cancers who have adverse pathologic features of extracapsular nodal spread with or without positive mucosal margin postoperative chemoradiotherapy is the preferred recommended adjuvant treatment. For patients with positive margins options include re-resection if feasible, RT or chemoradiotherapy.[32]

Advanced stage disease

Advanced disease of the oral cavity is best managed with multimodality therapy. Surgery with or without reconstruction [34] coupled with preoperative or postoperative chemoradiation therapy is often utilized for advanced disease. Although preoperative chemoradiation has been employed in selected cases to decrease the tumor mass and, therefore, improve respectability of the tumor, it is common practice to surgically resect the tumor based on the pre-radiation margins. In addition, preoperative radiation is associated with a higher rate of postoperative complications. For these reasons, most centers perform surgery followed by postoperative radiation.[35]

Although primary surgical management has been advocated for advanced oral cavity cancers due to concerns of safety and efficacy of non-surgical approaches, particularly with cancers that involve bone, recent evidence suggests that primary chemoradiotherapy may be an effective treatment approach for selected patients with T4 lesions. Rates of locoregional control, survival and complications are comparable to those associated with primary surgical management and postoperative radiotherapy.[36] Another reason to choose chemoradiotherapy as a primary treatment may be functional irresectability, which is vague and may differ among surgeons, [37] for example, to avoid total glossectomy.[5]

Functional organ preservation approaches has not been widely applied to patients with oral cavity cancer, and no survival advantage has been demonstrated for patients with stage III or IV primary tumors of the oral cavity.[38-40] However Data are limited; there are concerns about increased toxicity.[41]These approaches are generally more widely used for patients with locoregionally advanced oropharyngeal and hypopharyngeal cancers.

For resected tumors with high-risk pathologic features of extracapsular nodal spread and/or positive mucosal margins the adjuvant treatment options include chemoradiotherapy (preferred), re-resection of positive margins if feasible or RT.[42-45] Other risk features include T3 ,T4 primary ,N2 N3 nodal disease, level 4, 5 nodal involvement, perineural invasion, vascular tumor emboli.[32]

Surgery

Surgical approaches to cancers of the oral cavity may either be transoral, transcervical (pull-through), or alternatively via mandibulectomy, which is sometimes necessary to obtain the exposure required to achieve adequate margins.

Tumors that approximate the gingiva should be resected with the gingiva and periosteum as an additional deep margin, while those that appear to involve the periosteum should be resected with an additional deep margin of bone, which is called marginal mandibulectomy.[46] It has been suggested that tumor invasion of the periosteum or cortical bone, without invasion of the medullary cortex, can be appropriately managed with a marginal resection. Tumors that erode into the medullary canal (T4 lesions) require a segmental resection. [5]

The goal of a surgical excision is to achieve a complete resection of the tumor with free margins, since positive margins are associated with a worse prognosis.[47] Clear margins are defined as the distance from invasive tumor front that is 5 mm or more from the resected margin.[32]

Regarding reconstruction, small surgical defects may not require reconstruction and often allowed to heal by secondary intention. Larger defects may be reconstructed by primary closure, skin graft, regional flap, or free tissue transfer from different site. [46]

Postoperative management of high risk disease

Postoperative RT with or without concurrent chemotherapy should be standard of care for patients with locoregionally advanced oral cavity cancer since these patients are at significant risk for local recurrence after surgery.[32]

The role of postoperative chemotherapy/RT in the management of patients with high risk prognostic features has been clarified by 2 separate multicenter randomized trials [42, 43] and a combined analysis of data from the 2 trials for patients with high risk disease including patients with oral cavity cancer, oropharynx, hypopharynx and larynx [44].

The US intergroup trial (RTOG 9501) randomly assigned patients with 2 or more involved nodes, positive margins and extracapsular nodal spread of tumor to standard postoperative RT alone or the same RT plus cisplatin (100mg/m2 every 3 weeks for 3 doses). The trial showed statistically significant improvement in loco-regional control, disease free survival but not overall survival for concurrent postoperative chemotherapy and radiotherapy [43]. Long term results from the RTOG 9501 trial have been recently published, the results concluded that the subgroup of patients who had either microscopically involved resection margins and/or extracapsular spread of disease showed improved local-regional control and disease-free survival with concurrent administration of chemotherapy. The subgroup of patients who were enrolled only because they had in 2 or more involved lymph nodes did not benefit from the addition of chemotherapy [48]. The European trial (EORTC 22931) was designed using the same chemotherapy and similar RT dosing but also included patients with perineural or perivascular invasion, and nodal involvement at levels 4 and 5 from oral cavity or oropharyngeal cancer. This trial revealed improvement in overall survival in addition to loco-regional control and DFS [42]. In

another randomized trial a schedule using cisplatin 50mg intravenously weekly has been revealed survival advantage in this setting [45].

For a better risk identification a combined analysis of prognostic factors and outcomes from the 2 trials was done. This analysis showed that patients in both trials with extracapsular nodal spread and/or microscopically positive margins benefited from the addition of cisplatin to postoperative RT provided that they are medically fit to receive chemotherapy. There was also a trend towards improvement with chemo-radiotherapy in patient with stage III-IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. For those with multiple enlarged regional lymph nodes without ECS there was no survival benefit [44].

When postoperative radiation is used, the most common dose fractionation in the United States is 1.8 to 2.0 Gy per day. High risk regions that harbored adverse pathologic features should generally receive on the order of 60-66 Gy in 6-6.5 weeks.[32] However, if there is gross residual disease, either further surgical resection or focal boosting up to 70 Gy is advisable. Regions of somewhat lesser risk (i.e., clinically or pathologically uninvolved necks) should receive 44-50Gy (2Gy/fraction) with 3D conformal RT and sequentially planned IMRT or 54-63Gy (1.6 to 1.8Gy/fraction) using IMRT dose painting technique.[32]

If concomitant chemoradiotherapy is indicated, cisplatin 100mg/m2 every 3 weeks for 3 doses is recommended.[42-44, 48]

Radiation therapy

Conventional external beam RT techniques and/or brachytherapy using either interstitial implants or intracavitary techniques can be used in the management of cancers of the oral cavity. The choice of technique depends upon the site of a tumor and the goal of therapy.

For early oral tongue, and floor of the mouth tumors, radiation therapy is an effective method of achieving tumor control.[5] Retrospective studies suggest that control rates at the primary site of early oral cavity lesions treated with brachytherapy alone or a combination of brachytherapy plus external beam radiation range from approximately 70% to >95%.[49, 50] Involvement of the mandible is a contraindication to definitive radiotherapy because it compromises control and increases the risk of osteoradionecrosis.[23]

The outcomes for advanced lesions of the oral cavity (T3 and T4) are less than satisfactory with either surgery or radiation alone. Definitive RT is an alternative for patients who are medically inoperable or refuse surgery.[32]

When definitive radiation is used for oral cavity cancer, boosting the primary tumor with either interstitial implantation, submental, or intraoral cone therapy can result in increased tumor control and decreased complications, particularly osteoradionecrosis.[51] In situations where EBRT is used as the sole treatment modality, the high risk region (the primary tumor and involved nodes including the possible local subclinical infiltration at primary tumor and high risk lymph nodes) require doses in the range of 66 Gy(2.2Gy /fractions) to 70Gy (2 Gy/fraction) in 6 -7 weeks, While low to intermediate risk sites

should receive doses in the range of 44 -50 Gy (2Gy/fraction) using 3D conformal RT and sequentially planned IMRT. When using hyperfractionation regimen, high risk sites generally require up to 81.6 Gy (1.2Gy/fraction). Elective irradiation to low and intermediate risk sites can require up to 54 - 60 Gy (1.6 – 1.8 Gy/fraction) using IMRT dose painting technique.[32, 46]

External beam RT may be delivered with 3D conformal technique or intensity-modulated radiation therapy (IMRT) to produce a homogenous dose distribution and to reduce the dose to the normal tissues.[52, 53] The usual indication for IMRT is to reduce the dose to the contralateral parotid gland and thus limit long-term xerostomia.[23] IMRT dose painting refers to the technique that deliver different dose levels to different structures within the same treatment fraction.[54, 55] Hot spots associated with higher toxicity can occur.[54] Sequential delivery of separate dose plans for low versus high dose plans can also be used.[32]

Brachytherapy

Brachytherapy has been used to boost the primary site in the oral cavity before or following external beam radiation (EBRT). Brachytherapy can be used as a single modality in the treatment of selected (early stage) tumors of the oral cavity with good results.[32] When it is used as a sole treatment modality, doses of 60 to 70 Gy are commonly prescribed over 6 to 7 days using low-dose rates of 0.4 to 0.5 Gy per hour to the target volume.[56, 57] However, there has been recent interest in high-dose rate (HDR) brachytherapy at centers where there is expertise in this modality. Doses of 45 to 60 Gy at 3-6 Gy/fraction are considered if using HDR brachytherapy as a sole treatment.[32] The interval between HDR fractions should be a minimum of 6 hours. Brachytherapy can be accomplished with either rigid cesium needles or with iridium-192 (^{192}Ir) sources afterloaded into angiocaths. If lesions exceed 2.5 cm, it is difficult to avoid significant cold spots in the implant volume. For this reason, it is recommended that for lesions larger than 2.5 cm to be treated with combined treatment plan. In this setting, plan typically gives 50 Gy over 5 weeks with EBRT followed by 30 Gy with a low dose rate brachytherapy implant.[46]

Intraoral Cone RT

Intraoral orthovoltage or electron cone RT requires daily positioning and verification by the physician. This technique is generally best suited for anterior oral cavity lesions in edentulous patients. Intraoral cone treatment should be delivered before EBRT so that the lesion can be adequately visualized. A major advantage of cone therapy is that it is highly focal to the tumor bed but noninvasive. For this reason, when available it may be preferable to interstitial RT because there is little or no irradiation of the mandible.[23, 46]

Cancer of the Oropharynx

The main sites of the oropharynx are base of the tongue, tonsils, soft palate and posterior pharyngeal wall. The oropharynx is highly enriched with lymphatics. According to the subsite involved, 15% to 75% of patients present with lymph node disease.[32] The lymphatic spread pattern is first to the level II nodes and then along the jugular chain to level IV nodes. The level IB and level V nodes are less commonly involved.[23] level I or level V involvement was found more commonly associated with metastases at other levels. Tumors in the midline or of the posterior pharyngeal wall exhibit a higher propensity for bilateral lymphadenopathy.[58, 59] Retropharyngeal lymph node involvement is frequent in posterior pharyngeal wall tumors. but can also occur from other subsites, particularly with advanced disease.[23, 26]

Clinical Picture

Base of the tongue: early symptoms may include mild sore throat. As early disease is relatively silent, a level II neck mass is often the first sign. Dysphgia, a nasal quality of voice, and ear pain occur with disease progression. Advanced lesions can result in tongue fixation. Ulceration and necrosis result in foul odour breath.[23]

Tonsillar lesions: may present with pain, sore throat, dysphagia, trismus, and ipsilateral neck mass.[26]

Soft Palate: the earliest symptom is usually a mild ill-defined sore throat. More advanced lesions can result in dysphagia, voice change and regurgitation of food and fluid into the nasopharynx. Also trismus, temporal pain, and otitis media can occur due to nasopharynx and parapharyngeal space extension.[23]

Posterior pharyngeal wall lesions: can present with dysphagia, sore throat, and pain.[23]

Staging

Tumor node metastases (TNM) staging system for cancer of the oropharynx [33]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease
	Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b	Very advanced local disease
	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Regional lymph nodes (N)•			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.
• Metastases at level VII are considered regional lymph node metastases

Treatment of primary tumor

General principles

Early squamous cell carcinomas of the oropharynx can often be treated with either surgery or radiation therapy (RT) as a single modality. Surgery and RT produce similar cure rates.[23] Because the morbidity is generally higher after surgery and because of the significant high risk of bilateral lymphatic involvement and primary drainage into the

retropharyngeal nodes which are not typically addressed surgically, radiation therapy or chemo-radiotherapy are chosen more often than surgery for either early or advanced lesions.[23, 59]

Treatment of Early-Stage (T1–2, N0–1) oropharyngeal cancers:

Treatment may be 1) primary surgery with or without neck dissection, or 2) definitive radiotherapy.

For lateralized lesions involving the tonsils, the risk for contralateral lymph node metastases is low unless there is tongue invasion, soft palate invasion within 1 cm of midline, or extensive ipsilateral positive nodes.[23, 60] The preferred treatment for these lesions is ipsilateral radiation therapy to avoid irradiation of the contralateral parotid decreasing the incidence of xerostomia.[23]

However, early stage tumors arising near the midline (eg, base of tongue, soft palate, pharyngeal wall) are usually associated with high risk bilateral neck metastases and retropharyngeal nodal involvement.[23, 32] For these lesions bilateral neck treatment is required. Patients managed with definitive RT, bilateral neck irradiation is generally used. Those who initially undergo resection of their primary tumor, a selective neck dissection is usually performed if postoperative radiation is not already planned.[32, 58, 61]

Treatment of locally advanced resectable disease (T3–4a, N0–1) (any T, N2–3) may be either:

1) Concurrent systemic chemo-radiotherapy with high dose cisplatin is preferred (salvage surgery is used for managing residual or recurrent disease)[32, 62]
2) Surgery with appropriate adjuvant chemoradiotherapy or radiotherapy.
3) Induction chemotherapy followed by radiotherapy or chemoradiotherapy.

Surgical Treatment

Soft Palate: primary surgery is generally associated with greater functional impairment, particularly velopharyngeal insufficiency.[63] Small, discrete lesions can be managed by transoral excision and repaired by a pharyngeal flap to prevent any velopharyngeal incompetence. Tonsillectomy may also be necessary in order to achieve an adequate margin. If full thickness resection is done, prosthesis is often required.[23]

Tonsillar Area: Surgery for early cancers of the tonsillar pillars consists of a transoral wide local excision, including a tonsillectomy. If surgery is used for more extensive tumors that extend beyond the tonsil itself, the pharyngeal wall and/or soft palate and/or the tongue should be included in the resection. Depending on the size of the defect, a tongue, deltopectoral, or osteomyocutaneous flap may be required. A prosthesis may be needed for the palatal defect.[23] For these tumors, there are several surgical approaches, including an anterior approach (a combined lip splitting incision coupled with an anterior midline or lateral mandibulotomy) and a transhyoid approach.[23, 64]

Transoral laser microsurgery (TLS) and transoral robotic surgery (TORS) avoids the morbidity associated with the anterior approach and have been associated with significantly improved outcomes.[65, 66] Recent reports suggest that TORS alone provides

high local control and is associated with low surgical morbidity in patients with early stage tumors.[67]

Base of Tongue: patients with a low-volume T1 or early T2 cancer may be suitable for transoral laser excision in combination with a neck dissection.[68] Transoral laser microsurgery uses an endoscope to view the pharynx through the mouth and a laser to excise the tumor. For appropriately selected patients with base of tongue cancers, transoral laser microsurgery may improve local control and functional results.[68, 69] Surgery for early unilateral base of tongue cancer consists of hemiglossectomy. These tumors have been traditionally removed by resecting the mandible or using a translabial transmandibular approach. However, these procedures involve significant morbidity including lip and chin scars, malocclusion, compromised swallowing, chronic aspiration, and altered speech articulation.[70] Surgical treatment of a large tumor requires simultaneous removal of part or the entire larynx.[23]

With either RT or surgery, primary tumors of the base of tongue are associated with lower disease-specific survival compared with other oropharyngeal cancers (65 and 54 percent, for stages I and II, respectively).[71, 72]

When early primary stage is accompanied by advanced nodal staging, controversy exists over the best treatment approach. Since many of these patients will require adjuvant chemoradiation for their advanced nodal stage disease, the question arises whether transoral approaches add benefit to those patients who may be cured by chemoradiation alone and which approaches offer the best functional results. Excellent overall survival and swallowing results have also been reported with chemoradiation approaches for advanced oropharyngeal cancer.[73]

Postoperative Adjuvant Radiation Therapy

Patients managed primarily with surgery should receive the appropriate postoperative RT with or without concurrent chemotherapy for positive or close resection margins, extracapsular nodal extension, or other high risk features.[32]

The postoperative RT suggested dose is 60 - 66 Gy (2Gy/fraction) for 6 - 6.5 weeks for high risk region as positive margin, extracapsular nodal spread, T3 or T4 primary, N2 or N3 nodal disease, nodal spread to level 4 or 5, perineural invasion, and vascular embolism. While other intermediate to low risk regions should receive 44 – 50Gy (2Gy/fraction) to 54 – 63Gy (1.6 – 1.8Gy/fraction). Adjuvant RT treatment should start within 6 weeks after surgical resection.[32] If chemotherapy will be administered concurrently, cisplatin 100mg/m^2 every 3 weeks is preferred.[42-44, 48]

Radiation Therapy

Primary RT is the preferred definitive treatment for most T1–2, N0–1 oropharyngeal tumors because the results are excellent and the functional outcome is better.

Patients with early cancer of the soft palate are usually treated with RT to the primary tumor and the neck to avoid functional impairment associated with surgery.[63] RT is also preferred as the primary therapy for most T1, T2, and many T3 (exophytic) base of tongue tumors. For infiltrative or endophytic T3 or T4 lesions, an organ-preservation

approach using RT and chemotherapy should be used. Most T1 to T2 tonsillar lesions in patients with an N0 or N1 neck can be treated with ipsilateral fields. The target volume of the ipsilateral treatment should include the primary lesion with at least 2-cm margins, the ipsilateral jugular vein, and retropharyngeal lymph nodes.[26]

Radiation therapy doses and fractionation:

In general standard conventional fractionation is preferred for definitive RT treatment of T1-2, N0 lesions. Altered fractionation is appropriate for more advanced lesions particularly if concomitant chemotherapy is not used. Recent data indicated that the use of IMRT may be helpful to minimize the toxicity and the risk of xerostomia.[74, 75]

High risk sites (primary tumor and involved lymph nodes) require a total of 66 to 72 Gy in 6.5 - 7 weeks using conventional fractionation (1.8 to 2.0 Gy / fraction) for definitive treatment. As doses greater than 75 Gy using conventional fractionation may lead to unacceptable normal tissue damage, doses greater than 70 Gy should be slightly modified (less than 2 Gy /fraction) for at least part of the treatment to minimize toxicity. When using hyperfractionation regimen, high risk sites require up to 81.6 Gy (1.2 Gy/ fraction). While elective irradiation to low and intermediate risk sites requires 44 (2 Gy / fraction) to 60 Gy (1.6 Gy /fraction) suggesting 44 to 54 Gy for 3D conformal technique and 44 to 60 Gy using IMRT.[32]

Two large randomized trials from Europe have reported better locoregional control when either accelerated or hyperfractionated regimens are used. EORTC protocol 22791 compared conventional fractionation of 70 Gy / 35-40 fractions in 7- 8weeks, to pure hyperfractionation of 80.5 Gy / 70 fractions in 7 weeks using 2 fractions of 1.15 Gy daily, in T2-T3 oropharyngeal carcinoma (excluding base of tongue), N0,N1 of less than 3 cm. At 5 years analysis there was significant improvement in local control in the hyperfactionation arm (56% compared to 38% in the conventional Fractionation arm, $p = 0.01$). The superiority of HF was demonstrated in patients staged T3N0,T3N1 but not in T2. There was no significant difference in late normal tissue damage between the 2 modalities.[76] Long term follow up analysis has also shown small survival benefit ($p = 0.05$) for hyperfractionation.[77]

EORTC trial 22851 compared accelerated fractionation of 1.6 Gy 3 times daily or 72 Gy /5 wks to conventional fractionation 70 Gy /7 wks in T2 T3 T4 head & neck cancers (hypopharynx was excluded). The AF arm is significantly better for locoregional control ($p = 0.017$) and for time to progression ($p = 0.012$) resulting in a 15% locoregional gain at 5 years. Acute and late toxicity were higher in the AF arm. Specific survival shows a non significant improvement ($p = 0.06$) for the AF arm.[78]

The RTOG 9003 phase III 4 armed randomized study compared the leading US altered fractionated regimens for multiple head and neck cancer sites, including oropharynx cancers (60%). Patients were randomized to four arms:

1. Conventional fractionation (CF) 70 Gy (2 Gy/ fraction), 5 days / week in 7 weeks,
2. Split-course accelerated fractionation (S-AF) with 1.6 Gy twice daily to 67.2 Gy in 6 weeks with an intentional 2-week break after 38.4 Gy and an interfraction interval of 6 hours,

3. Delayed concomitant boost (DCB) to a total dose of 72 Gy during 6 weeks with daily morning 1.8 Gy treatments and a 1.5 Gy afternoon concomitant boost for the last 12 days of treatment with a 6-hour interfraction interval,

4. Pure hyperfractionation (HF) to a dose of 81.6 Gy/ 1.2 Gy twice daily in 7 weeks with an interfraction interval of 6 hours.

After 2 years of follow up, Patients treated with hyperfractionation and accelerated fractionation with concomitant boost had significantly improved local-regional control and trend toward improved disease-free survival than those treated with standard fractionation, although there was no significant difference in overall survival. Acute side effects were significantly higher for all three altered fractionation groups but not late effects. Long term analysis after a median of 8.5 years confirmed a significant local-regional control benefit with hyperfractionation and accelerated fractionation with concomitant boost. No significant improvement was reported for either disease free survival or overall survival.[79, 80] Final results of local-regional control and late toxicity have been recently published showed that at 5 years, only the hyperfractionation improved locoregional control and overall survival for patients with locally advanced SCC without increasing late toxicity.[81]

A meta-analysis analyzing the effect of HF and AF radiation therapy on survival of patients with head and neck squamous cell carcinoma was published using updated individual patients' data from 15 randomized trials. There was a significant survival benefit with altered fractionated radiotherapy to an absolute benefit of 3.4% at 5 years (hazard ratio 0.92, 95% CI 0.86-0.97; p=0.003). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy. However, this benefit was limited to patients less than 60 years of age.[82]

Recently, the RTOG 0129 trial compared standard fractionation RT and concurrent cisplatin with accelerated fractionation RT and cisplatin and found that the two treatment schedules were nearly equivalent to one another.[83]

GORTEC 99-02 trial recently reported that altered fractionation did not improve outcomes when compared with conventional fractionation chemoradiotherapy, suggesting that chemotherapy has a substantial treatment effect when given concomitantly with CF radiation therapy, and that accelerated fractionation may not be beneficial in concomitant chemoradiotherapy schedules.[84, 85]

Concurrent Chemoradiotherapy

For patients with locally advanced oropharyngeal tumors, concurrent chemoradiotherapy is the standard treatment particularly for fit patients.[32] As extensive surgery with or without total laryngectomy has often been associated with suboptimal results with a significant impact on the functional, psychological, and cosmetic consequences.[26]

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) included 63 randomized trials, all of which compared loco-regional treatment without or with chemotherapy either as a neoadjuvant, concurrently with RT, or as an adjuvant following definitive locoregional therapy.[86] This analysis confirmed that regimens that included both chemotherapy and RT significantly decreased the risk of death in 5872

patients with oropharyngeal carcinoma compared with RT alone (hazard ratio [HR] 0.88, 95% CI 0.82-0.93). This corresponded to an absolute improvement of 5 percent in overall survival at five years.[87] The benefit observed in this meta-analysis was limited to concurrent chemoradiotherapy. In the MACH-NC meta-analysis, platinum-based chemotherapy was superior to non-platinum based regimens; there was no significant difference between single-agent and multiagent concurrent chemotherapy.[86]

Cisplatin (100 mg/m every 21 days for three doses) is the preferred chemotherapy regimen for use in combination with conventionally fractionated RT.[42-44, 48] More recent trials have explored alternative schedules for combined chemoradiotherapy, including weekly or daily cisplatin, as has carboplatin in combination with 5-fluorouracil.[84] Weekly carboplatin or cetuximab given concurrently with RT may be a particularly useful option for patients who received cisplatin as a part of an induction chemotherapy regimen.[88-90]

Induction chemotherapy

Neoadjuvant chemotherapy impact on survival of oropharyngeal cancer patients was demonstrated in a French trial in which 318 patients were randomly assigned to three cycles of cisplatin plus infusion of 5-fluorouracil for 5 days or definitive locoregional therapy without neoadjuvant chemotherapy. Overall survival was significantly better in those given neoadjuvant chemotherapy compared with those treated with definitive locoregional therapy alone (median survival 5.1 versus 3.3 years).[91]

Two other trials, TAX 324 and TAX 323 provide evidence for the role of induction chemotherapy. Approximately one-half of the patients in these two trials had oropharyngeal cancer. In these trials the addition of docetaxel to an induction regimen of cisplatin plus 5-fluorouracil was more effective than cisplatin plus 5-fluorouracil alone.[92, 93] However, the optimal role of induction chemotherapy is currently controversial. Residual toxicity after induction chemotherapy may interfere with the appropriate delivery of subsequent definitive RT or chemoradiotherapy. Meta-analyses demonstrated that induction chemotherapy was less efficacious than concurrent chemotherapy treatment.[86, 94]

Tumor HPV status has emerged as an important predictor of favorable treatment response and survival.[95] This observation is well illustrated in the analysis of ECOG 2399, patients received induction paclitaxel and carboplatin followed by weekly paclitaxel during RT. Most patients enrolled had oropharynx cancer. Response to chemotherapy, to all protocol treatment, progression free-survival, and overall survival were all improved in the HPV-positive group.[95]

Cetuximab

Concurrent cetuximab plus RT was evaluated in a multinational randomized study of patients with locoregionally advanced head and neck cancer, in which approximately 60 percent of patients had oropharyngeal cancer. The addition of cetuximab improved both locoregional control and overall survival compared with RT alone.[96]

Preliminary results from an Italian randomized trial of chemoradiotherapy using a platinum compound versus cetuximab plus RT suggest no significant differences in progression-free survival or in-field toxicities. Half of these patients had oropharyngeal cancer. Surprisingly, the chemoradiotherapy regimen had better compliance and fewer RT

interruptions than the cetuximab plus RT group.[97] Also, data indicate that combining cetuximab plus a platinum as concurrent therapy during RT is no better than treatment with a platinum alone.[98]

Cancer of the Hypopharynx:

Tumors arising in the hypopharynx have their own specific and unique characteristics and considerations regarding treatment. Hypopharyngeal cancers show a tendency to spread submucosally and are often asymptomatic until they have reached advanced stages, contributing to higher rates of advanced and distant metastatic disease.[99-101] Approximately 70% to 85% of the patients reported in large series have stage III or IV disease at presentation, and the 5-year overall survival rate is reported to be around 15% to 45%.[22, 102-105] The anatomic proximity of the larynx, advanced stage of disease at presentation, and higher rates of regional and distant metastasis portend a worse prognosis compared with other head and neck cancer sites and are factors that require consideration when making treatment decisions.[106]

Anatomically the Hypopharynx extends from superior border of the hyoid bone to the lower border of the cricoid cartilage. The hypopharynx is divided into 3 areas: 1) the pyriform sinus (the most common site of hypopharyngeal cancer), 2) the lateral and posterior pharyngeal walls, 3) the postcricoid area.[23, 32] The primary echelon drainage is to the jugular chain (levels II to IV), it also has a rich bilateral lymphatic plexus, and thus is prone to early occult metastatic disease. Moreover, hypopharyngeal malignancies are more likely to spread to the retropharyngeal and level VI lymph nodes.[106, 107]

Clinical Picture

Lateralized tumors of the lateral pharyngeal wall or pyriform sinus produce a unilateral sore throat. Dysphagia, weight loss, foreign body sensation, ear pain, blood-streaked saliva, and a change of voice can occur later. A neck mass may be the presenting complaint.

Lesions of the apex of the pyriform sinus or postcricoid area produce pooling of secretions, arytenoid edema, asymmetry of the posterior tonsillar pillars and inability to see into the apex of the pyriform sinus may be observed. An extensive postcricoid tumor may push the larynx anteriorly and the thyroid click is lost.[23]

Staging

Tumor node metastases (TNM) staging system for cancer of the hypopharynx. [33]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx

T3	Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus		
T4a	Moderately advanced local disease		
	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue*		
T4b	Very advanced local disease		
	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures		
Regional lymph nodes (N)•			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

*Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.
• Metastases at level VII are considered regional lymph node metastases.

Treatment of primary tumor:

Accurate determination of tumor size and extent of invasion is critical for selection of appropriate treatment modality. In patients with early-stage hypopharyngeal cancer, overall and disease-specific survival following definitive radiotherapy is comparable to radical surgery (total laryngopharengectomy) or larynx-conserving surgery.[106, 108] Local recurrences are the most frequent pattern of progression after definitive radiotherapy. In contrast, distant metastases are more common with surgery. However, the incidence of neck recurrences is similar with both RT and surgery[102]

Regarding advanced staged disease, the results of primary chemoradiotherapy or primary radiotherapy followed by salvage surgery if tumor persists or recurs are inferior to those after initial surgery with post-operative adjuvant radiotherapy.[109, 110]

Patients with resectable cancer are divided into 2 groups based on the indicated surgical options;

1) Those with early stage disease (T1N0, selected T2N0 cases) amenable for larynx preserving surgery, may be managed with either:
   a. Definitive RT with salvage surgery (with or without neck dissection) when indicated for any residual disease.
   b. Surgery (partial laryngopharyngectomy with ipsilateral or bilateral neck dissection) with or without postoperative RT or CRT as indicated by the adverse pathologic features.[32]

2) And those with advanced resectable cancer ($T1N^{+}$,T2 – 4a, any N) requiring total laryngectomy with partial or total pharyngectomy, may be managed with 3 approaches:
   a. Induction chemotherapy followed by definitive radiotherapy if complete response was achieved at primary site. Other options for those patients achieved partial response after induction chemotherapy include surgery or concurrent chemoradiotherapy, patients with less than partial response at the primary site should undergo surgery.[111]
   b. Surgery with postoperative RT or CRT as indicated by the pathological risk features.
   c. Concurrent chemoradiotherapy (with high dose cisplatin is the preferred systemic agent) with surgery and/or neck dissection for any residual disease at the primary site or the neck.

In addition to the option of participation in multimodality clinical trials.[32]

Primary surgery

In early stage hypopharyngeal cancer, surgery is a treatment option for patients with a disease that is technically resectable via a laryngeal sparing approach. Also, in cases of extensive disease, surgery with adequate reconstruction followed by adjuvant therapy may have both the best functional and oncologic outcomes for patients with seriously impaired laryngeal and hypopharyngeal function,.[106]

Three surgical options can be used for treatment of hypopharyngeal cancer: total laryngopharyngectomy (TLP) or total laryngectomy with partial pharyngectomy, partial laryngopharyngectomy, and partial transoral (or minimally invasive) surgery.[110]

1) Total laryngopharyngectomy (TLP):

Total laryngopharyngectomy removes the larynx and varying amounts of pharyngeal wall. Advanced lesions require excision of nearly the entire circumference. Pharyngeal reconstruction may be done by primary closure after a partial pharyngectomy, reconstruction with a pectoralis major myocutaneous flap or radial forearm free flap is typically required.

Total laryngopharyngectomy procedures are typically reserved for T3 and T4 tumors, may also be required for small lesions that involve the pyriform sinus apex or postcricoid region.[23]

2) Partial laryngopharyngectomy :

A wide range of larynx-conservative surgical approaches that aim to preserve speech and swallowing have been used in appropriately selected patients with early (T-stage) hypopharyngeal cancer.[112-115]

A partial laryngopharyngectomy removes the false cords, epiglottis, aryepiglottic fold, and pyriform sinus; one arytenoid may be removed when necessary. The vocal cords are preserved. Early stage patients with transglottic tumor extension, postcricoid invasion, extension to the apex of the pyriform sinus, fixed cord, extension to contralateral arytenoid, poor pulmonary function, and large, fixed lymph nodes are contraindications for partial laryngopharyngectomy .[23, 110]

3) Transoral (Minimally Invasive) Procedures:

The oncologic results of transoral laser surgery (TOLS) appear comparable with open approaches, with a 5- year overall survival rate of around 50% to 70% in stage I and II disease and 40% to 50% in stage III and IV disease. The disease-specific survival rate with TOLS is on the order of 60% and is associated with high rates of larynx preservation in these selected cases. However, most patients continue to require postoperative radiotherapy.[106]

Adjuvant RT or chemoradiotherapy is indicated following surgery for patients who have positive resection margins, lymphovascular or perineural invasion, extranodal extension, or pathologically positive lymph nodes identified after neck dissection. Patients with close margins may also need additional treatment.[42-44, 48]

Definitive RT

Definitive radiation therapy (RT) with a median dose of 70 Gy (2 Gy / fractions) to the primary tumor and 44 to 50 Gy to elective nodal regions is feasible for T1 and small T2 hypopharyngeal cancers. Definitive RT has resulted in variable rates of laryngeal preservation, ranging from 41 to 100 percent for T1 tumors and from 41 to 86 percent for T2 tumors.[116]

Specific considerations are needed when irradiating early stage hypopharyngeal cancers include elective coverage of bilateral neck, paratracheal, and retropharyngeal nodes, because of the small but real risk of retropharyngeal lymph node failure.[107, 117] Additionally, tumors extending to or arising from the posterior hypopharyngeal wall require a more posterior border splitting the vertebral body when using conventional, non conformal fields. For those treated with three-dimensional conformal RT or intensity-modulated radiotherapy (IMRT), doses to the spinal cord in this region are typically higher given the proximity of planning volumes.[23]

For patients with an incomplete response to RT and for those with a local recurrence without evidence of distant metastasis, surgery can be considered for salvage therapy.[108, 118] Surgery following irradiation may be associated with increased frequency of complications compared with initial surgery.

Combined modality treatment:

Chemoradiotherapy and induction chemotherapy can be used as functional organ preserving alternatives in the treatment of potentially resectable locally advanced cancer of the hypopharynx for good performance status patients. These approaches require that the patient be able to withstand the prolonged course of treatment and associated toxicities, in addition to participation in rehabilitation from the radiation.[119]

Induction chemotherapy

Although this approach may not be as effective as concurrent chemoradiotherapy in initial control of locoregional disease without salvage laryngectomy, induction therapy may decrease the incidence of distant metastases compared with concurrent chemoradiotherapy alone and had a better, although not statistically significant, survival outcome.[120]

The feasibility of functional organ preservation using induction chemotherapy followed by definitive RT was established by the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group larynx trial. Similar results were seen in a European cooperative group trial (EORTC 24891) that included patients with cancers of the hypopharynx as well as the larynx.[111, 121]

In the European trial, 194 eligible patients with stage II through IV squamous cell carcinoma of the pyriform sinus or aryepiglottic fold were randomly assigned to receive induction chemotherapy with cisplatin 5fu to a maximum of 3 cycles followed by definitive RT (70 Gy) or surgery (total laryngectomy with partial pharyngectomy) followed by postoperative RT (50 to 70 Gy). Patients who failed to achieve a complete response at the primary site to induction chemotherapy underwent salvage surgery and postoperative RT. At a median follow-up of 10.5 years, there were no significant differences in survival or patterns-of-failure outcomes. The 10-year progression-free survival probabilities for the chemotherapy plus definitive RT and for the surgery arms were 10.8% and 8.5%, respectively. Overall survival probabilities at 10 years were 13.1% and 13.8%, respectively. In the chemotherapy arm, the 10-year probabilities of being alive with a functional larynx were about 8.7 %.[121]

In earlier reports of the MACH-NC meta-analysis, there was no statistically significant survival benefit for induction chemotherapy in general versus definitive locoregional therapy alone, although there was a benefit for induction chemotherapy in the subset of trials using induction with cisplatin plus 5-fluorouracil (hazard ratio (HR) 0.88, 95% CI 0.79-0.97).[87, 94] Furthermore, the subsequent TAX 323 trial found that a three-drug combination that added a taxane to cisplatin plus 5-fluorouracil regimen significantly improved overall survival compared with cisplatin plus 5-fluorouracil alone, when both were followed by definitive RT.[93]

The responsiveness of the tumor to induction therapy provides predictive and prognostic information that may be useful in deciding whether functional organ preservation is feasible or whether surgical resection is indicated or whether more intensive chemoradiotherapy might be given. Three or four cycles of docetaxel, cisplatin, and fluorouracil (TPF) chemotherapy are typically used for induction therapy.[93, 122]

Concurrent chemoradiotherapy

Concurrent chemoradiotherapy administers systemic chemotherapy at the same time as definitive RT to improve the likelihood of disease control and laryngeal preservation. This approach is more effective in achieving locoregional control of disease. However, concurrent chemoradiotherapy is less effective in preventing the development of distant metastases compared with induction chemotherapy followed by definitive RT and is associated with more unexplained deaths.[120]

Data supporting the role of concurrent chemotherapy come from the 2011 update of the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group, which conducted a comprehensive analysis by tumor site.

For the 2767 patients with hypopharyngeal cancer, a survival benefit with chemotherapy was observed (HR 0.88, 95% CI 0.80-0.96). However, there was no statistically significant difference between those given concomitant chemoradiotherapy (HR 0.85) and those given neoadjuvant chemotherapy (HR 0.88), although the authors cautioned that the study may not have adequate power to detect a difference in this disease site.[87]

Based upon these results, concurrent chemoradiotherapy is widely recommended for good performance status patients with resectable locally advanced (stage III and carefully selected stage IV) hypopharyngeal cancer, with a platinum-based chemotherapy regimen, such as cisplatin (100 mg/m every three weeks).

Sequential chemoradiotherapy:

Sequential therapy incorporates induction chemotherapy followed by concurrent chemoradiotherapy. In theory, sequential therapy combines the reduction in distant metastases afforded by induction chemotherapy with improvements in locoregional control achieved with concurrent chemoradiotherapy.

The most extensive data on sequential chemoradiotherapy in squamous head and neck cancer come from the TAX 324 trial, which demonstrated improved effectiveness of induction with docetaxel, cisplatin, plus 5-fluorouracil (TPF) rather than cisplatin plus 5-

fluorouracil alone, with both regimens followed by concurrent chemoradiotherapy using weekly carboplatin.[92, 122] In addition to patients with unresectable oral cavity, oropharyngeal, hypopharyngeal, or laryngeal cancer, patients considered to be candidates for organ preservation were also included. Laryngectomy-free survival was significantly greater with docetaxel-cisplatin fluorouracil: at 3 years 52% vs 32%. Fewer patients treated with docetaxel cisplatin-fluorouracil underwent surgery (22% vs 42%). In this study there was also a significant benefit regarding overall survival in favor of docetaxel-cisplatin-fluorouracil induction chemotherapy.[123]

Sequential therapy was studied specifically in patients with laryngeal and hypopharyngeal cancers in the randomized phase II TREMPLIN study. In that trial, 153 enrolled patients were treated with induction chemotherapy (three cycles of docetaxel, cisplatin, and 5-fluorouracil). Overall, 126 patients (82 percent) responded, and 116 were randomly assigned to RT plus cisplatin or RT plus cetuximab. Local control was superior in the cisplatin arm, but laryngeal preservation, laryngeal function, and overall survival were similar for the two treatment groups (95 versus 93 percent, 87 versus 82 percent, and 92 versus 89 percent), for the cisplatin and cetuximab arms, respectively.[90]

Patients who might benefit the most from sequential therapy are those with large primary tumors (bulky T3 and select T4) and/or advanced nodal presentations (large N2a, N2b, N2c, and N3), who are at high-risk for distant metastases. Although, randomized trials have yet to confirm a survival benefit for these indications. When sequential therapy approach is chosen, TPF induction chemotherapy followed by concurrent therapy with carboplatin is applied as used in the TAX 324 trial.[92, 122]

Sequential therapy has not been compared with concurrent chemoradiotherapy alone in adequately powered randomized trials. It may be concluded from the data of these studies that intensifying treatment may increase the rate of larynx preservation but survival benefit has been reported less consistently.[106, 124, 125]

Management of neck nodes

The risk of residual occult disease in the neck nodes must be balanced against the complications of treatment, which may be neck dissection and/or irradiation.

Both elective nodal irradiation and elective neck dissection are approximately 90% efficient in controlling subclinical regional deposits.[126] A policy of close observation may be an alternative for the clinical N0 neck to avoid unnecessary treatment, and the neck can be managed by surgery and/or RT if cervical metastases develop. The salvage rate for patients developing clinically positive lymph nodes with the primary lesion controlled is 50% to 60%.[23]

Clinically Negative Neck

When the primary tumor is to be treated surgically, an elective neck dissection should be performed when the risk of regional lymph node metastasis is 10% to 15% or greater. Radical or modified radical neck dissections, which remove lymph node levels I through V, are comprehensive neck dissections with the modified type sparing certain structures (e.g. the internal jugular vein, and/or sternocleidomastoid muscle, and/or spinal

accessory nerve). Selective neck dissections are more limited and include the resection of lymph node levels that are at highest risk for nodal metastatic spread.[23, 32]

Elective treatment of the neck in patients with clinically N0 neck stage I and II oral cavity Cancer remains controversial.[127] Rates of occult deposits are as high as 45% in patients with early stage oral cavity cancer, particularly for cancers of the oral tongue and floor of mouth. [128-130] Depth of invasion is currently the most reliable indicator for predicting subclinical nodal spread in patients with oral cavity squamous-cell carcinoma especially the oral tongue. For tumors with more than 4 mm depth of invasion, elective neck dissection should be strongly considered if RT is not already planned. For lesions between 2 – 4 mm depth of invasion, clinical judgment should be utilized to decide if it is appropriate to undergo elective dissection. Superficial tumors with less than 2 mm depth of invasion elective neck dissection is only indicated in selected situations.[32, 131, 132]

To remove lymph nodes at greatest risk of subclinical disease from oral cavity tumors, a selective neck dissection should include level I-III with sometimes superior parts of level V which is called the supraomohyoid neck dissection.[23, 32] Patients with advanced lesions of the anterior tongue or floor of the mouth that approximate or cross the midline should undergo bilateral neck dissection.[32]

Prophylactic selective neck dissection involve at least lymph node levels II to IV for oropharyngeal and hypopharyneal tumors with N0 neck disease, but the retropharyngeal and level VI nodes are all at risk,[107, 117] As well as the high rate of contralateral metastasis.[133] Partial neck treatment is suboptimal for primary lesions of the base of tongue, soft palate, and hypopharynx; treatment of the entire neck is advised for sites with a high rate of subclinical disease. Patients with lateralized T1–T2 tonsillar cancers do not require elective treatment for the contralateral N0 neck.[60] Those with significant extension into the tongue and/or soft palate, as well as those with T3 or T4 cancers, should receive bilateral neck treatment to the entire neck.[23]

Patients who are found to have multiple positive nodes or extracapsular extension (ECE) are then referred for postoperative RT.[134] Concurrent chemotherapy is recommended in ECE.[42-44] If the primary lesion is to be treated with EBRT, elective nodal irradiation adds relatively little cost and modest morbidity.[23]

Clinically Positive Neck Nodes

For patients who will be managed primarily with surgery, comprehensive neck dissection is sufficient treatment for the ipsilateral neck for patients with N1 or N2a disease without ECE. RT, often combined with concurrent chemotherapy, is added for N2b and N3 disease, control of contralateral subclinical disease, ECE, and/or multiple positive nodes.[23, 134]

If the primary lesion is to be managed by RT or chemoradiotherapy, observation is usually sufficient for patients in whom the nodes regresses completely as documented on CT obtained 4 weeks after RT.[135, 136] RT is followed by a neck dissection for patients with residual nodes that are 1.5 cm or larger, as well as those that demonstrate focal defects, enhancement, and/or calcification.[136] A PET scan obtained 12 weeks after RT is completed is often helpful in assessing whether there is persistent disease.[137] Controversy exists as to whether or not a post treatment neck dissection is indicated for all patients with

initial N3 disease who achieve a complete response or whether observation is appropriate in the presence of a PET and/or CT based complete response.[138]

Although the role of selective versus comprehensive neck dissection after chemoradiation therapy is controversial, selective neck dissection has been found to be feasible, safe and oncologically sound.[139]

Very advanced oral cavity, oropharyngeal, and hypopharyngeal cancer:

Generally, Very advanced cancers include:

1. Newly diagnosed locally advanced T4b (M0).
2. Newly diagnosed unresectable nodal disease.
3. Metastatic disease.
4. Recurrent or persistent disease.
5. Patients unfit for surgery.

Enrollment in clinical trials is encouraged for all patients with very advanced head and neck cancers.[32]

Newly diagnosed advanced disease:

Goal of treatment is cure for patients with newly diagnosed unresectable cancers. Many randomized trials and meta-analysis of clinical trials showed significantly improved overall survival, disease free survival, and local control when concurrent or alternating chemotherapy combined with RT regimen is compared with RT alone for advanced disease.[140-142] For patients with good performance status (PS) 0 to 1, standard treatment is concurrent chemoradiation typically using conventional fractionated RT 2 Gy / fraction to 70 Gy or more with high dose cisplatin every 3 weeks is the preferred systemic treatment[140], other chemotherapeutic options include: carboplatin/5-FU or cetuximab.[84, 143] Induction chemotherapy (TPF) followed by radiotherapy or chemoradiation is another controversial treatment option for those patients with good performance status.[93, 122]

Other patients with PS 2, treatment may be definitive RT with or without chemotherapy, patients with PS 3 options include palliative RT, single agent chemotherapy, and best supportive care.[32]

Recurrent or persistent disease:

Surgery is recommended for resectable recurrent or persistent disease with adjuvant postoperative RT is recommended based upon adverse pathologic risk features. For unresectable disease, if patient didn't receive previous irradiation then concomitant chemoradiotherapy is recommended based upon patient's PS. Patients with unresectable recurrent disease who are not candidates for RT with curative intent should be managed as metastatic disease.[32]

Metastatic disease:

For those patients with M1 disease, prognosis is dismal; the median survival times are usually less than a year.[106] The results of studies testing a new treatment paradigm combining immunotherapeutic and conventional chemotherapeutics look promising.[144]

Palliative measures include palliative RT to symptomatic disease areas, analgesics, single and combination regimens chemotherapy both can be used.[32, 145] The most active single agent chemotherapeutic agents include cisplatin, carboplatin, paclitaxel, docetaxel, methotrexate, 5fu, ifosfamide, bleomycin, capecitabine, vinorelbine, and cetuximab.[145-147] Response rate to single agents chemotherapy are ranging from 15 to 35%.[146, 148, 149] Combination regimens generally result in doubled response rate when compared to single agent regimens but no improvement in overall survival.[150-152] Active combination regimens include cisplatin or carboplatin plus 5FU with cetuximab,[144] cisplatin or carboplatin with a taxane,[150, 153] cisplatin with cetuximab,[154] or cisplatin plus 5FU.[150, 151]