Chapter

Hypopharyngeal Cancer: Staging, Diagnosis, and Therapy

Yi Huang, Yushan Liang and Weilin Zhao

Abstract

Hypopharyngeal carcinoma is uncommon in all head and neck cancers. With a synergistic reaction of each, tobacco consumption and alcohol abuse contribute to the tumorigenesis. The aerodigestive tract epithelium exposure to similar risks causing multiple cancers. Thus, a pan-endoscopic screening offers a practical approach for evaluating second primary esophageal cancer. The common symptoms of hypopharyngeal carcinoma were globus pharyngeus, sore throat, dysphagia, otalgia, neck mass, hoarseness, and dyspnoea. However, approximately 75–80% of patients are initial diagnosed with advanced-stage. Although improvements in therapy, the prognosis is still lacking. In early-stage patients, primary surgical resection and radiotherapy achieved similar survival and locoregional control rates. T1–T2 malignancies with N0–N1 can usually be treated with radiation alone, open surgery, or transoral surgery. In some people, after primary surgery or transoral approaches is often required adjuvant radiotherapy. However, most cases have been in the advanced-stage when screened. Individual therapy programs should be chosen carefully to achieve a balance between swallowing-voice rehabilitation and organ preservation in advanced-stage ones. Meanwhile, reasonable reconstruction of intraoperative defect is essential for a surgeon who seeks satisfied postoperative outcomes. Considerable treatment (surgery or non-surgery) remains the key point of improving the survival rate.

Keywords: hypopharyngeal carcinoma, etiology, staging, diagnosis, treatment

1. Introduction

Hypopharyngeal carcinoma is relatively rare in all head and neck cancers (approximately 3–5%) [1, 2]. The overall worldwide age-standardized incidence rates occur at a rate of 0.8 per 100,000 (1.4 in men and 0.3 in women) in hypopharyngeal cancer [3]. Bangladesh had the highest incidence with 4.8 per 100,000 [4]. In the past four decades, the incidence of hypopharyngeal cancer has declined smoothly in America, in part due to decreasing intake of tobacco [5–7]. Overall, it is five times greater in males than in females [8] and mainly occurs in the aged 50 to 70 years [5, 9]. However, this tumor rarely occurs at young ages [10].

Epidemiologic studies showed a series of potential environmental risk factors for hypopharyngeal carcinoma development. Tobacco consumption (> 90% of patients) and alcohol abuse (> 70% of patients) are the two well-established risk factors for hypopharyngeal squamous cell carcinoma [11–13]. Heinz Maier et al. reported a time-response correlation between tobacco intake and hypopharyngeal cancer. Besides, the amount of alcohol consumption is also related to

cancer development. Compared to non-smokers, it increased the risk by 9.5-fold (adjusted for alcohol consumption) for the long-term smoker (40–60 tobacco years). Also, alcohol drinkers increased the risk of this cancer that was up to 125.2-fold (adjusted for tobacco consumption) for alcoholics (> 100 g/day) [13]. Moreover, there is a synergistic carcinogenic effect between tobacco use and alcohol abuse [14]. Quitting smoking and refrain from drinking may reduce the risks of hypopharyngeal cancer.

Other risk factors, such as nutritional factors, diet, Plummer-Vinson syndrome, gastroesophageal reflux disease [15], and chronic infectious diseases have been reported to increase the risk of hypopharyngeal tumor. An inadequate caloric intake may lead to cancer cachexia, associated with a poor prognosis for hypopharyngeal carcinoma [16]. Plummer-Vinson syndrome is responsible for post-cricoid carcinoma, characterized by dysphagia and iron deficiency anemia. [17, 18]. It has been reported that oncogenic viral infection has a close relationship with head and neck cancers. The human papillomavirus (HPV) is involved in the malignant transformation of oropharyngeal carcinoma [7]. Epstein–Barr virus (EBV) infection is relevant to nasopharyngeal carcinoma (NPC) tumorigenesis [19]. Nevertheless, HPV and EBV infection in hypopharyngeal cancer are rare [20–22]. To date, the possible role of HPV in tumorigenesis of hypopharyngeal cancer is still controversial, EBV as well [23, 24].

In hypopharyngeal cancer, most histological types are squamous cell carcinoma (SCC) (up to 95%). That is usually represented poorly differentiated [25]. Adenocarcinoma is less frequent than in hypopharyngeal malignancies, accounted for around 5%. Other rare malignant tumors: papillary (exophytic) squamous cell carcinoma, verrucous carcinoma, and lymphoepithelial-like carcinoma, have been reported. However, the non-epithelial neoplasms that may arise in the hypopharynx include mucosal malignant melanoma, synovial sarcoma, fibrosarcoma, and liposarcoma, are not included [26]. Both histologic confirmations and histopathologic grading of squamous carcinoma should be recorded in hypopharyngeal cancers.

2. Symptoms and diagnosis

2.1 Relevant anatomy of hypopharynx

There are three parts to the pharynx: nasopharynx, oropharynx, and hypopharynx. As part of the pharynx, the hypopharynx is located behind the entire length of the larynx. It extends from the plane of the epiglottis to the lower border of the cricoid cartilage. Moreover, the pharynx is further classified into three regions (**Figure 1**): (1) the piriform sinuses, (2) the posterior pharyngeal wall, and (3) the post-cricoid area.

The pyriform sinus, a bilateral area, is bounded by the aryepiglottic fold and laterally by the esophagus's upper end. The posterior pharyngeal wall is bounded from the superior level of the epiglottis to the lower border of the cricoid cartilage and from the vertex of one pyriform sinus to the other. The post-cricoid region lies on the arytenoid cartilages' level and connecting to the plane of the inferior border of the cricoid cartilage.

In general, hypopharyngeal cancer occurs most in the piriform sinuses in 60–85% of patients, followed by the posterior pharyngeal wall up to 10–20% and rarely in the post-cricoid area in 5–15% of patients (**Figure 2**) [9, 27]. Also, during these three hypopharyngeal subsites, the tumor of the pyriform sinus and the posterior pharyngeal wall is mainly in males, while post-cricoid carcinoma is more often occurs in females [5, 9].

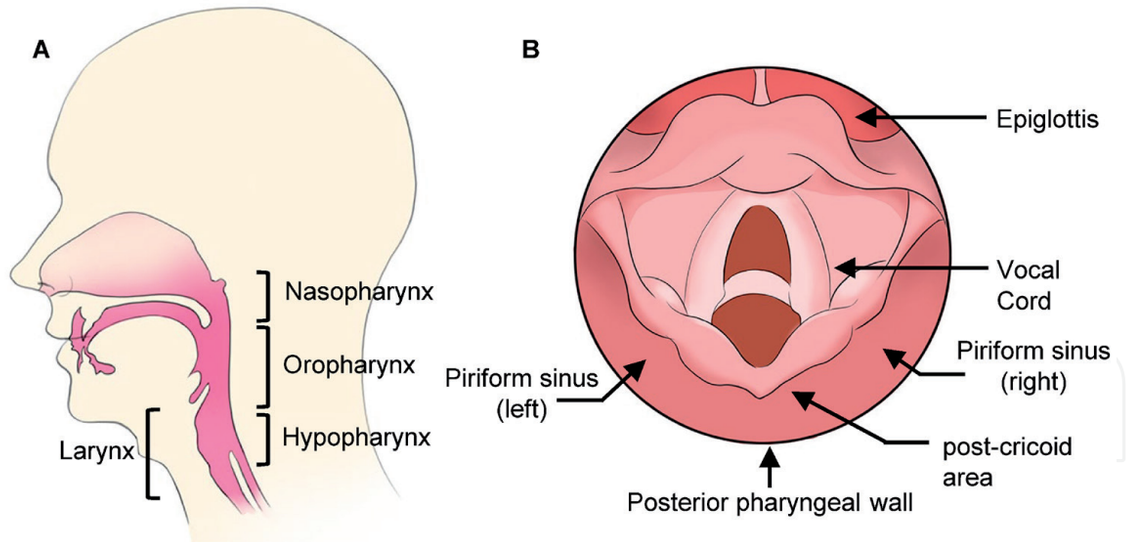

Figure 1.
Anatomical subsites of hypopharynx. (A) The pharynx includes three parts: The nasopharynx, oropharynx, and hypopharynx. (B) The hypopharynx is situated posterior to the larynx. It is further subdivided into the pyriform sinuses (left and right), posterior pharyngeal wall, and post-cricoid area.

2.2 Symptoms and signs of hypopharyngeal carcinoma

Early in hypopharyngeal cancer is not easy to be found due to the asymptomatic for an extended period. Something sticking or irritative sensation in the throat could be the early symptoms. If the tumor increases to a considerable size, sore throat, increasing dysphagia, and referred otalgia on swallowing may be present. Besides, progressive dysphagia frequently leads to significant weight loss.

A neck mass is now recognized as the typical clinical manifestation of hypopharyngeal carcinoma. There are a rich lymphatic network and vascular anatomy in the neck, allowing tumors to easily metastasize to the cervical nodal. Clinically, more than half of patients have enlarged cervical nodes at initial presentation because of the vibrant lymph nodes network in the pharynx [28]. The neck metastases rate is higher (> 75% of patients) in pyriform sinus cancers, as compared with the neck metastases rate in the posterior pharyngeal wall and post-cricoid cancers [29, 30]. Lymphatics from pyriform sinuses usually result in levels II-III and retropharyngeal node metastasis. And the posterior pharyngeal wall lymphatic metastasis area is more occurred to level II lymph node metastasis. In contrast, lymph node metastasis of the post-cricoid region prefers to levels IV-VI metastasis [31–33].

The larynx functions mainly in airway protection and respiration, which is in front of the hypopharynx. The hypopharynx configuration may allow tumor invasion or involvement of these adjacent organs, for instance, the larynx. When the throat symptoms appear, the tumor is considered significant in particular hoarseness, invading the larynx. Furthermore, some of the patients may present aggressive laryngeal invasion with life-threatening airway obstruction.

2.3 Second primary cancer

Patients with hypopharyngeal cancer have an exceptionally high risk of diagnosing a synchronous or metachronous second primary cancer, which may be associated with the prognosis's deterioration [34]. One possible mechanism causing second primary cancer in hypopharyngeal cancer is the phenomenon of "field cancerization" [35]. Anatomically, the cervical esophagus is originated at the upper esophageal sphincter, contiguous with the post-cricoid region

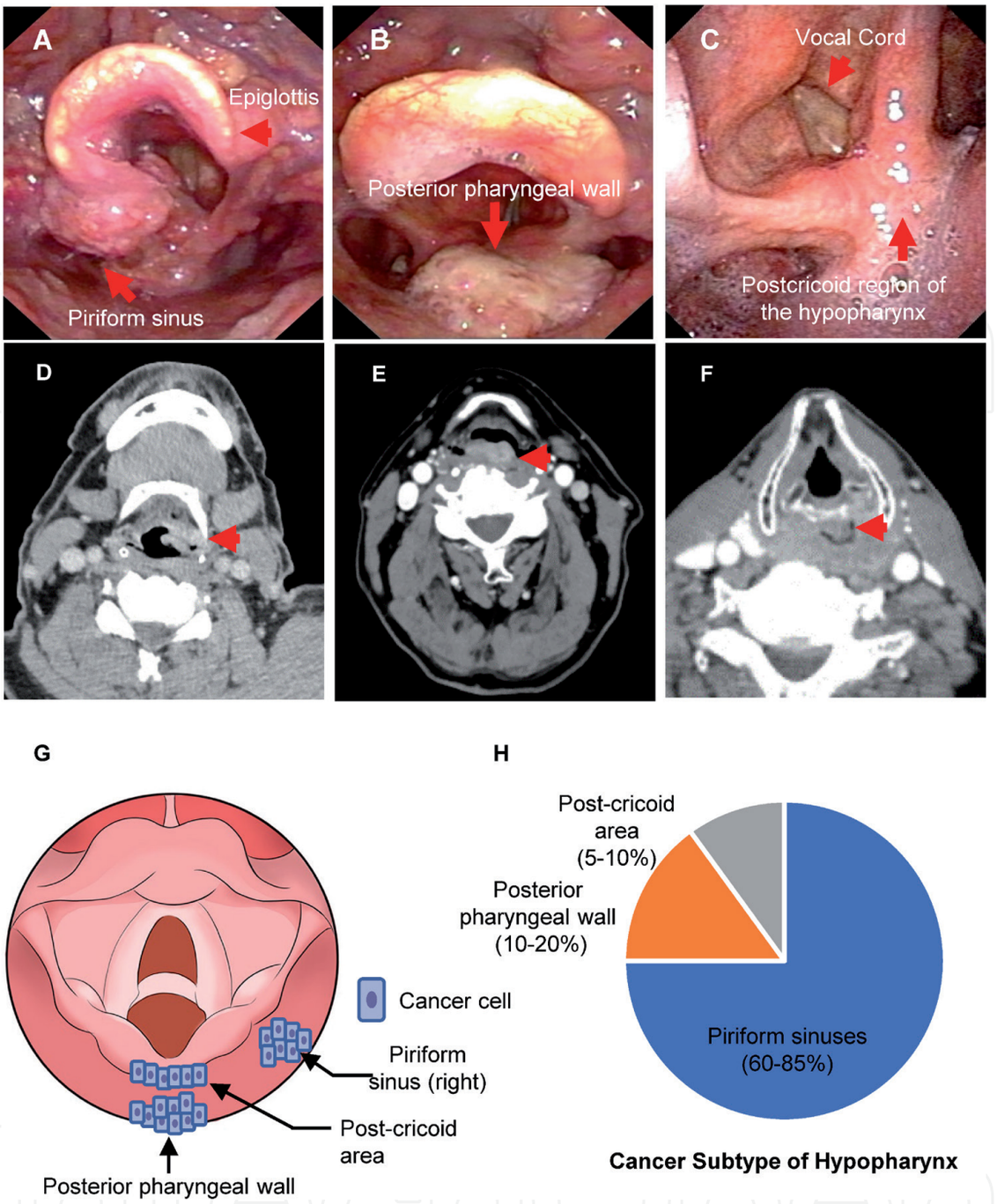

Figure 2.
Typical subtypes of hypopharyngeal carcinoma. (A, D) The pyriform sinus carcinoma (left) (red arrow) involving the left side of aryepiglottic fold in endoscopy (A) and (D) CT scan. (B, E) The posterior pharyngeal wall carcinoma (red arrow) in endoscopy (B) and (E) CT scan. (C, F) The hypopharyngeal carcinoma (red arrow) arising from the post-cricoid region in endoscopy (C) and (F) CT scan. (G) The patterns of hypopharyngeal carcinoma. (H) The percentages of hypopharyngeal carcinoma in three subtypes.

and behind the lower border of the cricoid cartilage. The aerodigestive tract mucosa, including hypopharynx and esophagus epithelium, is the squamous epithelium. During the carcinogenesis process, both hypopharynx epithelium and esophagus epithelium are exposed to similar environmental risk factors resulting in multiple cancers in the aerodigestive tract [35–37]. Tobacco use and alcohol abuse are considered as the significant risks contributing to field cancerization.

In head and neck cancers, the overall incidence of the synchronous second primary cancer was estimated to be 12% [38]. However, hypopharyngeal cancer has a high incidence of second primary cancer. The commonest sites in

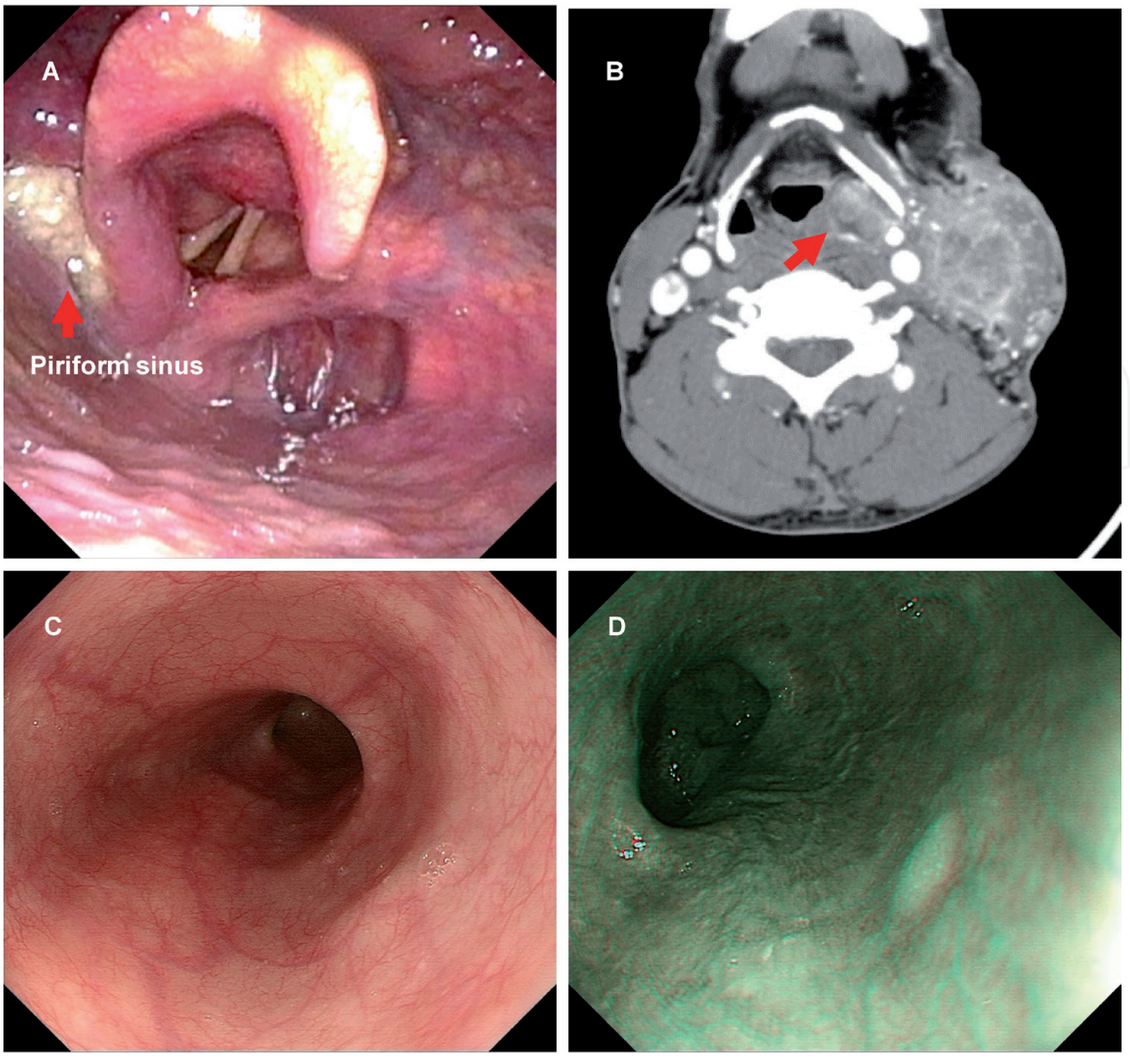

Figure 3.
The second primary cancer in hypopharyngeal cancer. (A, B) Hypopharyngeal cancer involving pyriform sinus (red arrow) by endoscopy and CT scan, respectively. (C, D) Second primary esophageal cancer of hypopharyngeal cancer, imaged with (C) white light endoscopy; (D) narrow-band imaging.

the second primary cancer [39] were the esophagus (27%) and lung (6.34%) [40–42]. Therefore, patients with hypopharyngeal carcinoma are suggested to undergo regular surveillance endoscopy (**Figure 3**) and chest CT scan to detect a second malignancy. Precancerous lesions or neoplasm are the targets of surveillance endoscopy. In case of suspected neoplasm, an endoscopic biopsy can be done to diagnose second primary esophageal cancer. The use of narrow-band imaging (NBI) shows high accuracy to screen early esophageal lesions, Lugol chromoendoscopy (LCE) endoscopy as well [43]. Most of the second primary cancer followed the hypopharyngeal cancer diagnosis within one year [34, 40].

2.4 Diagnostics of Hypopharyngeal carcinoma

2.4.1 History and physical examination

To assess the patient's condition, a thorough history of presenting symptoms must be obtained. It also is crucial to document and quantification of tobacco or alcohol use history. And then, a complete head and neck examination should be performed. Neoplasm and its extent can often be seen on indirect or laryngoscopy

tests. While the post-cricoid growths may difficult to diagnose on the laryngoscopy. The pooling of secretions in the pyriform sinus is indicated to cervical esophageal involvement. Both sides of the neck should be examined to evaluate cervical lymph nodes, and the level, number, size, and mobility of palpable lymph nodes should be carefully documented.

2.4.2 Endoscopic evaluation and pathology diagnosis

In early cases, endoscopy of the laryngopharynx is best performed in the patient under suspicion of malignancy. The panendoscopy can evaluate the entire scope of cancer and find a synchronous primary at any other site. A biopsy can be done under general anesthesia with endoscopes. It is essential for histological typing. Since lymphonodi cervical metastasis often occurs as the first symptom, a fine-needle aspiration (FNA) in the neck is recommended.

2.4.3 Imaging studies

Nowadays, the application of imaging measurement offers an efficient approach for evaluating the tumor extent, lymph nodal staging, potential laryngeal impingement, and cartilage involvement. A CT enhanced scan of the laryngopharynx and neck is exceptionally worthy in evaluating laryngeal cartilage invasion. At the same time, MRI is better for the soft-tissue extension. They are complementary examinations of each other and reveal the tumor invasive range. Due to the distant metastasis (approximately 6% of patients) in hypopharyngeal cancer, a chest CT scan or PET/CT is also recommended [44].

3. Cancer staging and prognosis

The newly updated TNM classification system (8th edition), an anatomic-based classification, was published in 2017 by The American Joint Committee on Cancer (AJCC). This cancer stage classification aims to provide information for the clinical trial, cancer control activity, therapy selection, and outcome. Compared to the previous version, the new vision reflects a better understanding of cancer therapy and research design. Here we showed an overview of modifications in cancers of pharynx: (1) the revision of TNM classifications in nasopharyngeal cancer; (2) the division of pharyngeal malignancies into HPV-related (p16+) oropharyngeal cancer, oropharynx (p16-) and hypopharynx cancer, and nasopharyngeal cancer; (3) the extranodal extension (ENE) is formulated into the N category for non-viral related head and neck cancer for the first time [45]. Besides, the TNM staging of hypopharyngeal cancer is delineated in **Figures 4** and **5**.

Generally, the cancer of hypopharynx has an abysmal prognosis in all head and neck cancers. Numerous patients (75–80%) are advanced-stage ones (stage III/IV) when initially diagnosed [46, 47]. About 60–75% of patients with cervical lymph node metastasis (N1–3) were detected [46, 47].

A population-based study reported that the five-year overall survival (OS) rate increased from 37.5% (1973–1989) to 41.3% (1990–2003) [9]. Also, Henry T. Hoffman, etc., showed the five-year disease-specific survival segregated into clinical stages increased: 63.1% (stage I), 67.6% (stage II), 41.8% (stage III), and 22% (stage IV), respectively [48]. Although the treatments have improved, the tumor

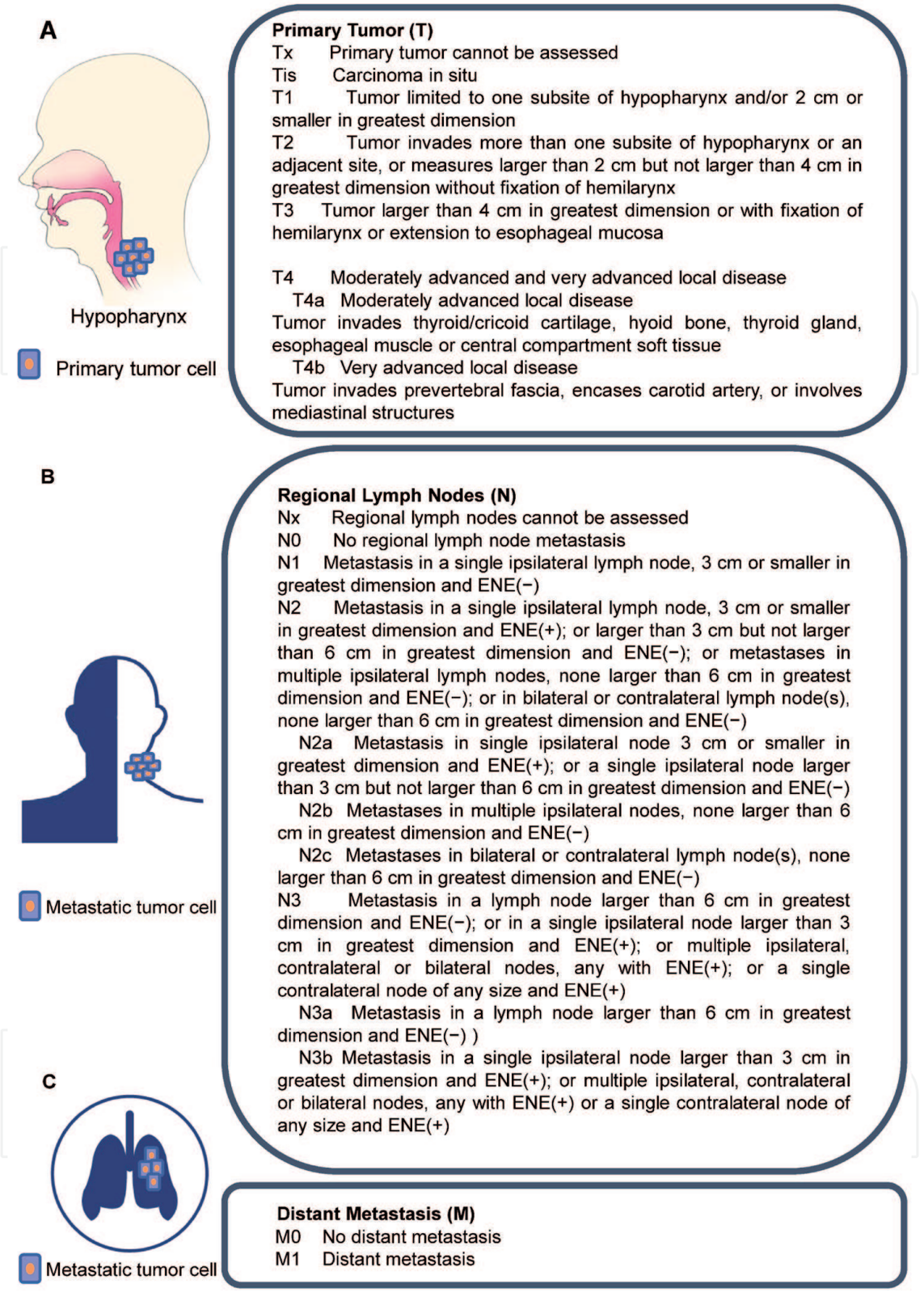

Figure 4.
TNM classification of hypopharyngeal cancer. The TNM staging system is the common language for classifying the extent of spread of cancer. Here we reveal the newest edition in hypopharyngeal carcinoma.

recurrence within one year and half of first recurrences with distance metastases [1]. Unfortunately, about 50% of the untreated cancer patients surviving within four months after the initial diagnosis, and less than 20% of patients surviving more than one year [49, 50].

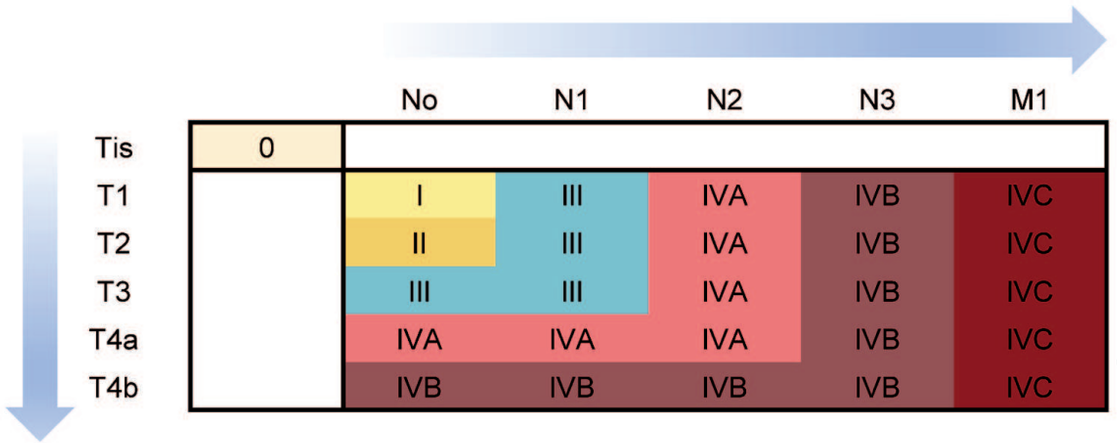

Figure 5.
Prognostic stage of hypopharyngeal cancer.

4. Treatment

Different treatment strategies, surgery, and nonoperative treatment were adopted according to the scope of the tumor. However, the existing literature has limitations due to the shortage of multicenter large sample randomized controlled tests. In the setting of unbalanced development in economic, academic, and medical conditions in different regions, remain in the effect of treatment, it is difficult to unify the mode of diagnosis and treatment, and the differences are present in curative effects. The general principle is to improve the postoperative life quality for patients on the premise of ensuring that the tumor is removed completely. Treatment selection requires optimizing swallowing and speaking functions to prevent a long-term aspiration and tracheostomy/G- tube dependence and acquire a balance between disease cure and anatomical preservation of tissue [19, 51].

In addition to taking effective measures to accurately determine the scope and clinical stage of the tumor, multidisciplinary treatment (MDT) should also run through the whole process of tumor diagnosis, treatment, and rehabilitation to gain optimal rehabilitation effect.

4.1 Early-stage tumor (T1/T2 with N0/N1)

4.1.1 Primary radiotherapy or open surgical procedures

Refinement in technology has improved radiation oncology across the past 20 years. The newer "more precise" techniques, such as intensity-modulated radiotherapy, compared with standard therapy, ameliorate locoregional control of hypopharyngeal carcinoma [52–54]. These techniques extend the concentration of dose to the primary tumor and concomitantly lower collateral injuries to normal tissues [53]. The results of the retrospective analysis showed the similarity between the long-term survival prognosis of primary radiotherapy and laryngectomy [55–57]. However, prospective evidence is limited for the similarity between locoregional control and survival rates [46, 58, 59]. Postradiation local control rate was achieved in 68–90% of patients with T1 tumors and approximately 75% cases in T2 lesions [58, 60–62]. The goal of radiation with concurrent chemotherapy is to acquire speaking and swallowing functional of invaded area and laryngeal preservation rates for five years above 70% [52, 63, 64]. Radical radiation-related injuries to the neck tissues need to be taken seriously, including substantial acute and late

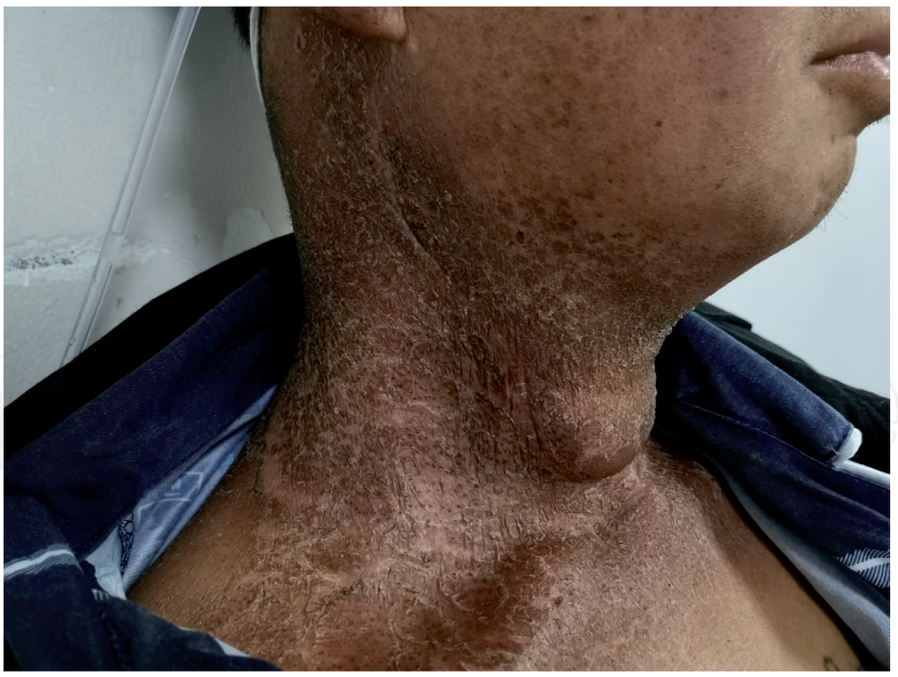

Figure 6.
Radiotherapy toxicity of neck.

toxicity (**Figure 6**). Although a majority of acute toxicities are temporary (such as radiation-related dermatitis usually alleviated within 6–12 weeks of treatment), permanent xerostomia at least partly is present invariably. Post-radiotherapy complications such as aspiration and chronic dysphagia may also occur in some cases, depending on the permanent feeding tube. The incidence is growing associated with intensive protocols (e.g., concurrent chemoradiotherapy). Therefore, effective quality assurance mechanisms and appropriate expertise are needed to be established to limit treatment-related toxicity and optimize results.

The skin injury often occurs during radiotherapy, including red swollen of skin, painful blisters, and pigmentation.

Open surgery is also an available approach for early-stage lesions compared with radiotherapy [65]. The posterior pharynx tumors can be excised through the transhyoid approach [66, 67]. Meanwhile, reservation of the internal branch of the superior laryngeal nerve is necessary. The transhyoid approach is critical for the disease that cannot be exposed transorally, especially in advanced tumors [51]. The more noticeable problem is that the postoperative T1T2 diseases with high-risk factors (e.g., positive margins, positive lymph nodes, extracapsular tumor extension) and locally advanced tumors should perform radiotherapy [68].

4.1.2 Transoral approaches

For T1/T2 tumor, minimally invasive surgery with reducing morbidity has become a surgical option for patients. In addition to open surgery, a variety of transoral surgical techniques/instrumentation, such as laser, plasma, oral robot surgery, and so on, setting primary tumor resection as a rising feasible option, with preserving laryngeal function [69, 70]. Transoral surgery (TORS/TLM) are considered as promising alternatives with better functional consequence compared with open surgery. It presents fewer complications than open surgery with nasogastric tube dependence down from 31–3% within 1 year [71]. Supporters of surgery pose that the transoral method rise the laryngeal conservation rate by over 70% through lots of single-institution series [72, 73].

Over the past few decades, with growing prevalence in a transoral path for getting into the upper aerodigestive tract, especially transoral laser surgery (TOLS), which initially was used for cancer of the larynx, gradually spread to the hypopharyngeal tumor [72–76]. Local control and cancer-free survival rates via radiotherapy and open surgery inT1/T2 diseases have been achieved through transoral routes, especially in early-stage lesions [72, 77–80]. The procedural complications of TOLS include fistula, granulation tissue formation, and fatal bleeding. [77–80]. But, in other TOLS series reported, 83% of patients were received adjuvant treatment (radiotherapy or concurrent chemoradiotherapy) after TOLS according to pathologic outcomes [77–80]. In T3, T4 cases, because of the limitation of detailed data about the use of TOLS for these lesions, the potential effects (if any) of TOLS remains poorly explained [78, 79]. Transoral robotic surgery has been considered a valid treatment for early hypopharyngeal carcinoma [81–83]. Meanwhile, it is also regarded as more appropriate for early cases without adjuvant treatment [81].

The complete resection of the tumor should be taken as the premise, with the corresponding bilateral neck dissection, combining with intraoperative frozen section examination to achieve radical procedures. If the postoperative pathological or histological examination indicates high-risk factors, postoperative adjuvant radiotherapy is required.

4.2 Advanced-stage tumor (T3/T4 or ≥ N2)

4.2.1 Non-surgical management

For the need of larynx-preservation, non-surgical treatments are considered as valid notions involved when appropriate [84]. At present, the non-operative treatment of larynx reservation is mainly combined with radiotherapy and chemotherapy (such as simultaneous radiotherapy and chemotherapy, induction chemotherapy sequential radiotherapy). Targeted therapy and immunotherapy are still being explored. The advanced patients involved postoperative adjuvant radiotherapy acquired improvement of local control, cancer-free survival rate, and overall survival [60, 85–88].

For stage IV malignancy, chemotherapy (induction therapy or concomitant therapy) heightens therapeutic efficacy, which is better in locoregional control and survival rates than radiation alone and combination therapies (surgery + radiation [84, 89–92]. A randomized trial including 202 cases indicated that chemotherapy group (induction chemotherapy +radiotherapy) achieve almost same disease survival as immediate surgery, with13.1% (the chemotherapy group) versus 13.8% (the surgery group) in a 10-year overall survival rate and with 8.5% versus 10.8% in10-year progression-free survival rates [93]. For optimizing chemotherapeutic effectiveness, organ-preservation strategies have to be abandoned in some advanced diseases in order to optimize chemotherapeutic effectiveness [94]. Pretreatment organ dysfunction, e.g., status vocal cord fixation and tracheostomy dependence, are related to posttreatment poor functional outcomes [95].

When considering organ-preservation strategy, the therapeutics must be implemented not only for saving of the anatomical units but also the return of upper aerodigestive function [96–98]. Meanwhile, the advanced patients with extensive invasion of surrounding tissue and serious decline of pharynx and larynx function present low pathologic complete response by non-operative treatment. The opinions of various disciplines should be integrated into decision-making. The American Society of Clinical Oncology (ASCO) guidelines recommend total laryngectomy for T3/T4patients with heavy tumor load and poor laryngeal function before induction chemotherapy [99].

4.2.2 Surgery

Surgery remains the preferred treatment for advanced-stage hypopharyngeal cancers [100]. Kinds of surgical manners are achieved in locally advanced cancers. Considering the possibility of aspiration after laryngeal preservation surgery, assessment of preoperative lung function is necessary. The cut margins (inferior or esophageal margin) must be extended carefully for safe boundaries. [25, 101, 102]. We should pay more attention to the extent of surgical margins, especially the inferior margin of the tumor (nearly to the esophageal part). Wide margins surgically are often considering in the skip disease and submucosal positive pathology. But researches have shown that patients did not benefit from extended edges (3–5 cm) compared with traditional (1–1.5 cm) incisal edges [103].

Partial pharyngectomy integrated with a partial laryngectomy, e.g.: vertical hemilaryngectomy, supraglottic laryngectomy, or supracricoid laryngectomy etc. is utilized in a series of hypopharyngeal cancers for hypopharyngeal cancers with small to medium lesions [104–107]. Laccourreye et share their extensive experience with the methods described above in their researches, including 135 cases with pyriform fossa lesions [104, 105]. The patients were executed supracricoid hemilaryngopharyngectomy combined with postoperative induction chemotherapy (IC) (96%). Five-year actuarial survival rates were assessed at 46.7%, with tracheostomy tubes removed in all patients (average = 9 days), and a 91.9% recovering oral intake (gastrostomy-free) at one year [105]. The conservation of competing cricoarytenoid units is important to achieve good functional outcomes. The unit comprises a single arytenoid, cricoid cartilage, ipsilateral recurrent/superior laryngeal nerves, and ipsilateral intrinsic laryngeal muscles. At least a single company should be reserved to obtain suitable swallowing function and upper respiratory function [108].

Due to roughly 10% of lesions invade the thyroid parenchyma directly, the cases with macroscopic cancer extension outside the larynx should be performed thyroid lobectomy or total thyroidectomy. In salvage treatments, considering thyroid vessel damages in response to radiation, preoperative hypothyroidism screening (routine pre- and post-operative thyroid hormone screening) is often necessary [109, 110]. In a prospective study including 137 laryngeal/hypopharyngeal patients, the incidence of hypothyroidism after treatment for laryngeal or hypopharyngeal tumors is 47.7%, especially after combination treatment [110]. Hypoparathyroidism is an important consideration in treatment, so the reservation or reimplantation of parathyroid glands must be noted during cricopharyngeal resection and/or paratracheal + mediastinal lymph node dissection [103].

4.2.3 Reconstruction

Laryngopharyngeal defect reconstruction is also an important approach for the surgeon to optimize surgery. The reconstruction presents a certain advantage in reducing the incidence of postoperative complications such as pharyngeal fistula, fatal bleeding, or infection. Meanwhile, it shows satisfactory outcomes in rehabilitating functions of speaking, swallowing, and breathing. The methods include local issue, regional flap or more vascularized free tissue transfer (**Figure 7**). Regional flaps contain the submental island flap, the supraclavicular island flap, the deltopectoral flap, the pectoralis, myocutaneous flap or latissimus dorsi myocutaneous flaps. Vascularized free tissue transfer methods include radial forearm free flap, anterolateral thigh free flap. In partial pharyngectomy with a partial laryngectomy, the small defects are repaired by local closure, and the larger defects (> 3 cm in size), regional flaps, and free tissue transfer are recommended. For

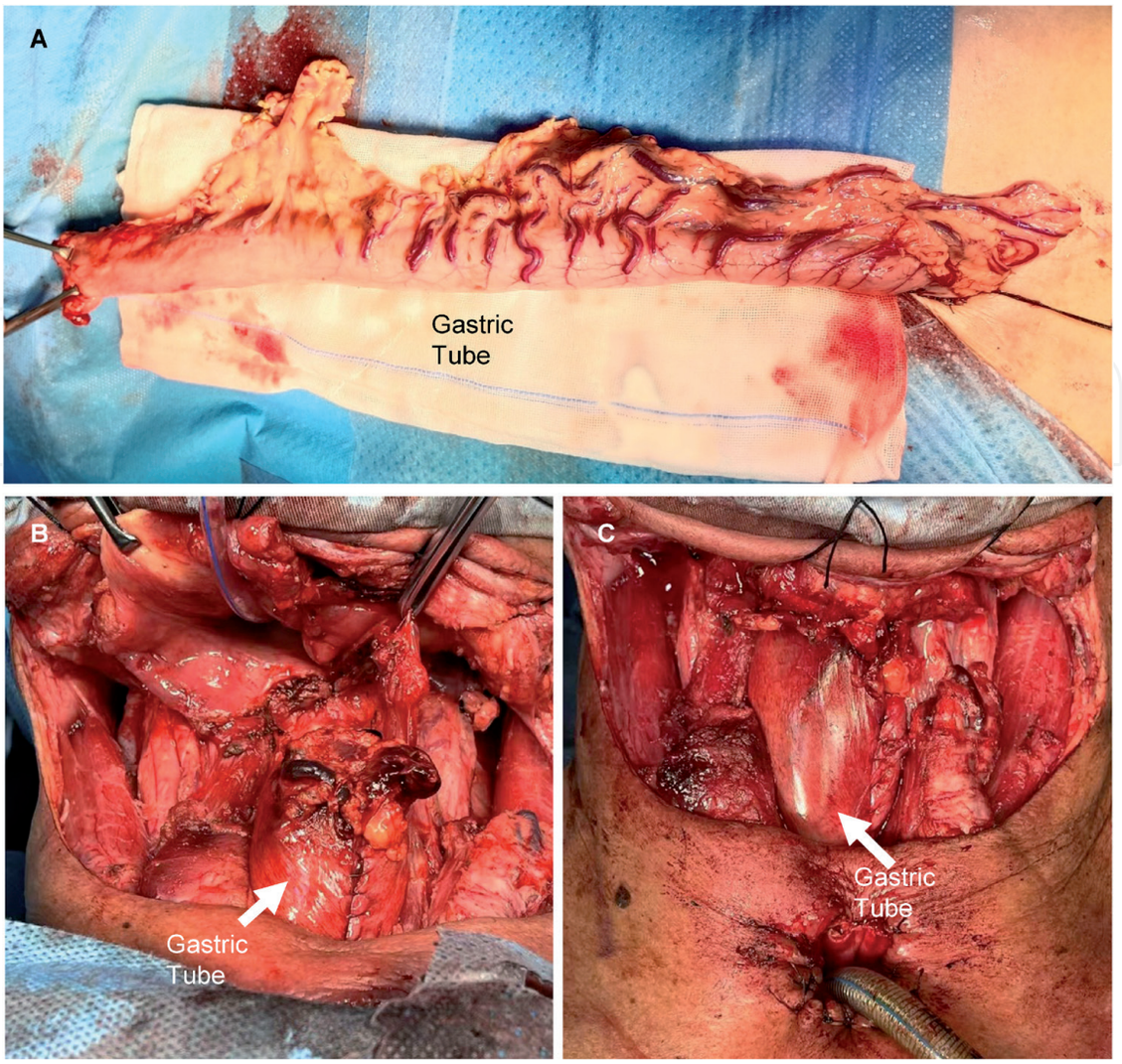

Figure 7.
Surgical reconstruction of hypopharyngeal cancer involving the larynx and esophageal. (A) The tubular gastric reconstruction was applied to repair the esophagus by video-assisted thoracoscopic surgery (VATS). (B, C) Inset of the gastric tube into the operative cavity of total laryngopharyngectomy.

partial pharyngeal defects with a total laryngectomy, despite other options, such as primary closure, primary closure with bolster flap, and regional tissue transfer, free tissue transfer has become one of the most utilized reconstructive selections. The major advantages of free tissue transfer are donor-site tissue, healthy tissue to repair circumferential defects. It is reconstructed in a tubular shape to provide a good swallowing tract and low incidence by avoiding entrance to other body cavities for total laryngopharyngectomy defects is usually rebuilt by the approaches such as enteric flap transposition, gastric pull-up, colonic Interposition, or jejunal free flap.

4.3 Nodal metastases in neck

Almost all patients with hypopharyngeal carcinoma have a high incidence of lymph node metastasis in the neck [30, 111]. Pyriform fossa cancer has the highest cervical metastasis rate (> 75%), while the lymph node metastasis rate of the posterior pharyngeal wall and posterior ring carcinoma is currently between 30% and 60% [29, 30, 111, 112]. For clinically negative (cN0) neck, the high-risk lymph node group must be included in the scope of dissection. Bilateral neck dissection should be considered with the tumor across the midline and tumors located in the

posterior pharyngeal wall, medial Pyriform wall, or posterior annular region [96, 111]. In the cN0 cases, most of the lymph nodes with positive pathological examination were located in levels II and III of the lateral neck [46, 111, 113, 114]. Thus levels II to IV should be taken into consideration for elective neck dissection in the CN+ patients, despite the low incidence of metastases at levels I and V, the cutting of levels I through V is incorporated into an overall neck dissection for reducing relapses in a node. The internal jugular vein (IJV), sternocleidomastoid muscle, and accessory nerve are recommended to be preserved and attacked directly by cancer.

Paratracheal (level VI) and retropharyngeal nodes must be brought to attention because of The risk of tumor invasion [46, 115]. Paratracheal positive nodes (level VI) are frequently involved by tumors located in the pyriform apex or post-cricoid area [111, 116–119]. A series of reports by Chung et al. poses a 27.9% occult metastasis rate in IV nodes with a much worse prognosis (26% vs. 55% 5-year disease-specific survival) [119]. So paratracheal node dissection should be strongly involved in this crowd both for the thoroughness of removing all tumor and strict disease staging. The retropharyngeal nodal disease is common in lateral pyriform and posterior pharyngeal, existing in 40% of advanced patients [120]. Retropharyngeal nodes should be taken into adjuvant radiotherapy in the setting of unremovable surgically. In advanced stages, these positive nodes clinically/radiographically may be an indication for non-surgical treatment [120].

5. Surveillance, and recurrent

Due to most tumors relapse within two years after initiate treatment, rigorous surveillance should be followed three months after treatment until two years and every six months for 3–5 years to screen early local recurrence and second primary tumors [121–123]. A favorable scanning should involve a combination of history, physical, endoscope, images (CT, MRI, PET/CT), and biopsy [124]. For suspicion cases, repeated biopsies are necessary for positive results. PET/CT has been demonstrated to be more accurate than CT/MRI for screening false-positive results [125, 126]. Surgery is considered an optimal option for recurrent cases (especially small recurrent). For unresectable recurrence or metastatic, re-irradiation or re-irradiation+chemo is one selection with improving median survival. Meanwhile, related toxicities cannot be ignored, with complications range from 9 to 32% in adjuvant chemotherapy cases [127, 128]. Therefore, the multidisciplinary team must seek a balance between the serious toxic reactions and the rescue therapy while paying attention to the progress of the disease in the long term.

There are not many options available for recurrent and metastasis, so it is urgent to develop new targeted agents in this population. The innovative drugs may be proved as another promising avenue for recurrence and metastasis. A variety of molecular targeting drugs are developed in the exploratory stage. These drugs have anti-cancer affection on aberrantly expressed intracellular proteins. In recent years, immunotherapy has been proved to ameliorate overall survival over standard, single-agent therapy for platinum-refractory cases [129, 130]. Anti-programmed cell death 1 (PD-1) therapies were assessed as a treatment for platinum-refractory recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC). Meanwhile, a small number of patients with the PD-1 approach acquire lower toxic effects than traditional therapies. Immunotherapy brings hope to this subtype of treat-limited patients [130, 131].

6. Conclusion

The primary type of hypopharyngeal cancer is squamous cell carcinoma, with a poor prognosis. Approximately up to a third of patients are diagnosed with second primary esophageal cancer. The infrequent incidence of hypopharyngeal cancer limits the extensive clinical trial application. Early-stage disease achieved successful tumor management after treatment (radiation alone or surgery resection). However, despite the improvements of therapy, measures alone may not be sufficient to preserve the laryngeal function in advanced-stage ones. Formulating an accurate and useful treatment plan depends on a comprehensive assessment of the patient's general condition and tumor staging before treatment. To explore a functional tumor remission and improve survival outcomes, researchers are seeking a balance between swallowing-voice rehabilitation and organ preservation. Also, the treatment requires cooperation involved specialized expertise and a multi-disciplinary team to benefit patients. Future directions will focus on refining surgery to afford functional organ preservation and radiotherapy techniques. Furthermore, it is important to regard to influence patient outcomes; there also needs to be more emphasis on non-surgery therapy's toxicity.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Hall, S.F., et al., The natural history of patients with squamous cell carcinoma of the hypopharynx. Laryngoscope, 2008. **118**(8): p. 1362-1371. DOI: 10.1097/MLG.0b013e318173dc4a

[2] Silver, C.E., et al., Current trends in initial management of laryngeal cancer: the declining use of open surgery. Eur Arch Otorhinolaryngol, 2009. **266**(9): p. 1333-1352. DOI: 10.1007/s00405-009-1028-2

[3] Ferlay, J., et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015. **136**(5): p. E359–E386. DOI: 10.1002/ijc.29210

[4] Shield, K.D., et al., The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin, 2017. **67**(1): p. 51-64. DOI: 10.3322/caac.21384

[5] Kuo, P., et al., Hypopharyngeal cancer incidence, treatment, and survival: temporal trends in the United States. Laryngoscope, 2014. **124**(9): p. 2064-9. DOI: 10.1002/lary.24651

[6] Global Burden of Disease Cancer, C., et al., Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol, 2017. **3**(4): p. 524-548. DOI: 10.1001/jamaoncol.2016.5688

[7] Chow, L.Q.M., Head and Neck Cancer. N Engl J Med, 2020. **382**(1): p. 60-72. DOI: 10.1056/NEJMra1715715

[8] Canto, M.T. and S.S. Devesa, Oral cavity and pharynx cancer incidence rates in the United States, 1975-1998. Oral Oncol, 2002. **38**(6): p. 610-617. DOI: 10.1016/s1368-8375(01)00109-9

[9] Newman, J.R., et al., Survival trends in hypopharyngeal cancer: a population-based review. Laryngoscope, 2015. **125**(3): p. 624-629. DOI: 10.1002/lary.24915

[10] Siddiqui, F., et al., Squamous carcinoma of the larynx and hypopharynx in children: a distinct clinical entity? Med Pediatr Oncol, 2003. **40**(5): p. 322-324. DOI: 10.1002/mpo.10291

[11] Avincsal, M.O., et al., Impact of alcohol dehydrogenase-aldehyde dehydrogenase polymorphism on clinical outcome in patients with hypopharyngeal cancer. Head Neck, 2018. **40**(4): p. 770-777. DOI: 10.1002/hed.25050

[12] Maier, H., et al., Chronic alcohol consumption--the key risk factor for pharyngeal cancer. Otolaryngol Head Neck Surg, 1994. **110**(2): p. 168-173. DOI: 10.1177/019459989411000205

[13] Blot, W.J., et al., Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res, 1988. **48**(11): p. 3282-3287.

[14] Choi, S.Y. and H. Kahyo, Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Epidemiol, 1991. **20**(4): p. 878-885. DOI: 10.1093/ije/20.4.878

[15] El-Serag, H.B., et al., Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. Am J Gastroenterol, 2001. **96**(7): p. 2013-2018. DOI: 10.1111/j.1572-0241.2001.03934.x

[16] Couch, M.E., et al., Cancer cachexia update in head and neck cancer: Pathophysiology and treatment. Head Neck, 2015. **37**(7): p. 1057-1072. DOI: 10.1002/hed.23696

[17] Anderson, S.R. and J.T. Sinacori, Plummer-Vinson syndrome heralded by postcricoid carcinoma. Am J Otolaryngol, 2007. **28**(1): p. 22-24. DOI: 10.1016/j.amjoto.2006.06.004

[18] Wahlberg, P.C., et al., Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. Head Neck, 1998. **20**(8): p. 714-719. DOI: 10.1002/(sici)1097-0347(199812)20:8<714::aid-hed9>3.0.co;2-2

[19] Lee, H.M., et al., Current Perspectives on Nasopharyngeal Carcinoma. Adv Exp Med Biol, 2019. **1164**: p. 11-34. DOI: 10.1007/978-3-030-22254-3_2

[20] Pongsapich, W., et al., Prevalence of HPV infection in hypopharyngeal and laryngeal squamous cell carcinoma at Thailand's largest tertiary referral center. Infect Agent Cancer, 2017. **12**: p. 58. DOI: 10.1186/s13027-017-0167-0

[21] Dalianis, T., et al., Human papillomavirus DNA and p16(INK4a) expression in hypopharyngeal cancer and in relation to clinical outcome, in Stockholm, Sweden. Oral Oncol, 2015. **51**(9): p. 857-861. DOI: 10.1016/j.oraloncology.2015.06.002

[22] Goldenberg, D., et al., Epstein-Barr virus in head and neck cancer assessed by quantitative polymerase chain reaction. Laryngoscope, 2004. **114**(6): p. 1027-1031. DOI: 10.1097/00005537-200406000-00013

[23] Ndiaye, C., et al., HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol, 2014. **15**(12): p. 1319-1331. DOI: 10.1016/S1470-2045(14)70471-1

[24] Zhou, L., et al., Evaluation of Epstein-Barr Virus infection in hypopharyngeal carcinomas from 37 Japanese patients. Mod Pathol, 1998. **11**(6): p. 509-512.

[25] Helliwell, T.R., acp Best Practice No 169. Evidence based pathology: squamous carcinoma of the hypopharynx. J Clin Pathol, 2003. **56**(2): p. 81-85. DOI: 10.1136/jcp.56.2.81

[26] Amin, M.B., American Joint Committee on Cancer., and American Cancer Society., *AJCC cancer staging manual*. Eight edition / editor-in-chief, Mahul B. Amin, MD, FCAP ; editors, Stephen B. Edge, MD, FACS and 16 others ; Donna M. Gress, RHIT, CTR - Technical editor ; Laura R. Meyer, CAPM - Managing editor. ed. 2017, Chicago IL: American Joint Committee on Cancer, Springer. xvii, 1024 pages.

[27] Sarradin, V., et al., [WHO classification of head and neck tumours 2017: Main novelties and update of diagnostic methods]. Bull Cancer, 2018. **105**(6): p. 596-602. DOI: 10.1016/j.bulcan.2018.04.004

[28] Uzcudun, A.E., et al., Clinical features of pharyngeal cancer: a retrospective study of 258 consecutive patients. J Laryngol Otol, 2001. **115**(2): p. 112-118. DOI: 10.1258/0022215011907703

[29] Spector, G.J., Distant metastases from laryngeal and hypopharyngeal cancer. ORL J Otorhinolaryngol Relat Spec, 2001. **63**(4): p. 224-228. DOI: 10.1159/000055746

[30] Newkirk, K.A., et al., Planned neck dissection for advanced primary head and neck malignancy treated with organ preservation therapy: disease control and survival outcomes. Head Neck, 2001. **23**(2): p. 73-79. DOI: 10.1002/1097-0347(200102)23:2<73::aid-hed1001>3.0.co;2-6

[31] Chung, E.J., et al., Pattern of cervical lymph node metastasis in medial wall pyriform sinus carcinoma. Laryngoscope, 2014. **124**(4): p. 882-887. DOI: 10.1002/lary.24299

[32] Kim, S.Y., et al., Clinicopathological factors influencing the outcomes of surgical treatment in patients with T4a hypopharyngeal cancer. BMC Cancer, 2017. **17**(1): p. 904. DOI: 10.1186/s12885-017-3880-6

[33] Kotwall, C., et al., Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg, 1987. **154**(4): p. 439-442. DOI: 10.1016/0002-9610(89)90020-2

[34] Lee, D.H., et al., Second cancer incidence, risk factor, and specific mortality in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg, 2013. **149**(4): p. 579-586. DOI: 10.1177/0194599813496373

[35] Strong, M.S., J. Incze, and C.W. Vaughan, Field cancerization in the aerodigestive tract--its etiology, manifestation, and significance. J Otolaryngol, 1984. **13**(1): p. 1-6.

[36] Chang, C.C., et al., Influence of residential environment and lifestyle on multiple primary malignancies in Taiwan. Asian Pac J Cancer Prev, 2015. **16**(8): p. 3533-3538. DOI: 10.7314/apjcp.2015.16.8.3533

[37] Katada, C., et al., Alcohol Consumption and Multiple Dysplastic Lesions Increase Risk of Squamous Cell Carcinoma in the Esophagus, Head, and Neck. Gastroenterology, 2016. **151**(5): p. 860-869 e7. DOI: 10.1053/j.gastro.2016.07.040

[38] Shaha, A.R., et al., Synchronicity, multicentricity, and metachronicity of head and neck cancer. Head Neck Surg, 1988. **10**(4): p. 225-228. DOI: 10.1002/j.1930-2398.1988.tb00003.x

[39] Liu, W.S., et al., Secondary primary cancer in patients with head and neck carcinoma: the differences among hypopharyngeal, laryngeal, and other sites of head and neck cancer. Eur J Cancer Care (Engl), 2014. **23**(1): p. 36-42. DOI: 10.1111/ecc.12084

[40] Lee, K.D., et al., The incidence and risk of developing a second primary esophageal cancer in patients with oral and pharyngeal carcinoma: a population-based study in Taiwan over a 25 year period. BMC Cancer, 2009. **9**: p. 373. DOI: 10.1186/1471-2407-9-373

[41] Lien, C.F., et al., Cortactin as a potential predictor of second esophageal neoplasia in hypopharyngeal carcinoma. Auris Nasus Larynx, 2019. **46**(2): p. 260-266. DOI: 10.1016/j.anl.2018.08.002

[42] Kotarba, E., [Surgical treatment of tumors of the external ear]. Przegl Dermatol, 1990. **77**(1): p. 61-67.

[43] Lee, C.T., et al., Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy, 2010. **42**(8): p. 613-619. DOI: 10.1055/s-0030-1255514

[44] Eckel, H.E., et al., Surgical treatment for hypopharynx carcinoma: feasibility, mortality, and results. Otolaryngol Head Neck Surg, 2001. **124**(5): p. 561-569. DOI: 10.1067/mhn.2001.115060

[45] Lydiatt, W.M., et al., Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin, 2017. **67**(2): p. 122-137. DOI: 10.3322/caac.21389

[46] Takes, R.P., et al., Current trends in initial management of hypopharyngeal cancer: the declining use of open surgery. Head Neck, 2012. **34**(2): p. 270-281. DOI: 10.1002/hed.21613

[47] Olzowy, B., M. Hillebrand, and U. Harreus, Frequency of bilateral cervical metastases in hypopharyngeal squamous cell carcinoma: a retrospective analysis of 203 cases after bilateral neck dissection. Eur Arch Otorhinolaryngol, 2017. **274**(11): p.

3965-3970. DOI: 10.1007/s00405-017-4724-3

[48] Hoffman, H.T., et al., Hypopharyngeal cancer patient care evaluation. Laryngoscope, 1997. **107**(8): p. 1005-1017. DOI: 10.1097/00005537-199708000-00001

[49] Kowalski, L.P. and A.L. Carvalho, Natural history of untreated head and neck cancer. Eur J Cancer, 2000. **36**(8): p. 1032-1037. DOI: 10.1016/s0959-8049(00)00054-x

[50] Choi, H.G., B. Park, and S.H. Ahn, Untreated head and neck cancer in Korea: a national cohort study. Eur Arch Otorhinolaryngol, 2017. **274**(3): p. 1643-1650. DOI: 10.1007/s00405-016-4392-8

[51] Chan, J.Y. and W.I. Wei, Current management strategy of hypopharyngeal carcinoma. Auris Nasus Larynx, 2013. **40**(1): p. 2-6. DOI: 10.1016/j.anl.2011.11.009

[52] Mok, G., et al., Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck, 2015. **37**(5): p. 655-661. DOI: 10.1002/hed.23649

[53] Lin, A., et al., Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. Int J Radiat Oncol Biol Phys, 2003. **57**(1): p. 61-70. DOI: 10.1016/s0360-3016(03)00361-4

[54] Eisbruch, A., et al., Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys, 2004. **59**(1): p. 28-42. DOI: 10.1016/j.ijrobp.2003.10.032

[55] Pracy, P., et al., Hypopharyngeal cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol, 2016. **130**(S2): p. S104-S110. DOI: 10.1017/S0022215116000529

[56] Martin, A., et al., Organ preserving transoral laser microsurgery for cancer of the hypopharynx. Laryngoscope, 2008. **118**(3): p. 398-402. DOI: 10.1097/MLG.0b013e31815aeda3

[57] Rabbani, A., et al., Definitive radiotherapy for T1-T2 squamous cell carcinoma of pyriform sinus. Int J Radiat Oncol Biol Phys, 2008. **72**(2): p. 351-355. DOI: 10.1016/j.ijrobp.2008.01.003

[58] Garden, A.S., et al., Early squamous cell carcinoma of the hypopharynx: outcomes of treatment with radiation alone to the primary disease. Head Neck, 1996. **18**(4): p. 317-322. DOI: 10.1002/(SICI)1097-0347(199607/08)18:4<317::AID-HED2>3.0.CO;2-0

[59] Amdur, R.J., et al., Organ preservation with radiotherapy for T1-T2 carcinoma of the pyriform sinus. Head Neck, 2001. **23**(5): p. 353-362. DOI: 10.1002/hed.1044

[60] Amdur, R.J., et al., Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys, 1989. **16**(1): p. 25-36. DOI: 10.1016/0360-3016(89)90006-0

[61] Fein, D.A., et al., Pharyngeal wall carcinoma treated with radiotherapy: impact of treatment technique and fractionation. Int J Radiat Oncol Biol Phys, 1993. **26**(5): p. 751-757. DOI: 10.1016/0360-3016(93)90488-h

[62] Mendenhall, W.M., et al., Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surg, 1987. **10**(2): p. 88-92. DOI: 10.1002/hed.2890100205

[63] Nakamura, K., et al., Multi-institutional analysis of early squamous cell carcinoma of the hypopharynx treated with radical radiotherapy. Int J Radiat Oncol Biol Phys, 2006. **65**(4): p. 1045-1050. DOI: 10.1016/j.ijrobp.2006.02.001

[64] Edson, M.A., et al., Outcomes for hypopharyngeal carcinoma treated with organ-preservation therapy. Head Neck, 2016. **38 Suppl 1**: p. E2091–E2099. DOI: 10.1002/hed.24387

[65] Wei, W.I., The dilemma of treating hypopharyngeal carcinoma: more or less: Hayes Martin Lecture. Arch Otolaryngol Head Neck Surg, 2002. **128**(3): p. 229-232. DOI: 10.1001/archotol.128.3.229

[66] Julieron, M., et al., Surgical management of posterior pharyngeal wall carcinomas: functional and oncologic results. Head Neck, 2001. **23**(2): p. 80-86. DOI: 10.1002/1097-0347(200102)23:2<80::aid-hed1002>3.0.co;2-3

[67] Spiro, R.H., et al., Squamous carcinoma of the posterior pharyngeal wall. Am J Surg, 1990. **160**(4): p. 420-423. DOI: 10.1016/s0002-9610(05)80557-4

[68] Cooper, J.S., et al., Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med, 2004. **350**(19): p. 1937-1944. DOI: 10.1056/NEJMoa032646

[69] Park, Y.M., et al., The long-term oncological and functional outcomes of transoral robotic surgery in patients with hypopharyngeal cancer. Oral Oncol, 2017. **71**: p. 138-143. DOI: 10.1016/j.oraloncology.2017.06.016

[70] Weiss, B.G., et al., Transoral laser microsurgery for treatment for hypopharyngeal cancer in 211 patients. Head Neck, 2017. **39**(8): p. 1631-1638. DOI: 10.1002/hed.24814

[71] White, H., et al., Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. JAMA Otolaryngol Head Neck Surg, 2013. **139**(8): p. 773-8. DOI: 10.1001/jamaoto.2013.3866

[72] Steiner, W., et al., Organ preservation by transoral laser microsurgery in piriform sinus carcinoma. Otolaryngol Head Neck Surg, 2001. **124**(1): p. 58-67. DOI: 10.1067/mhn.2001.111597

[73] Vilaseca, I., et al., CO2 laser surgery: a larynx preservation alternative for selected hypopharyngeal carcinomas. Head Neck, 2004. **26**(11): p. 953-959. DOI: 10.1002/hed.20074

[74] Werner, J.A., Transoral resection of laryngeal and hypopharyngeal cancer is an established surgical procedure. Eur Arch Otorhinolaryngol, 2015. **272**(1): p. 1-2. DOI: 10.1007/s00405-014-3359-x

[75] Bernal-Sprekelsen, M., I. Vilaseca-Gonzalez, and J.L. Blanch-Alejandro, Predictive values for aspiration after endoscopic laser resections of malignant tumors of the hypopharynx and larynx. Head Neck, 2004. **26**(2): p. 103-110. DOI: 10.1002/hed.10363

[76] Imanishi, Y., et al., Clinical outcomes of transoral videolaryngoscopic surgery for hypopharyngeal and supraglottic cancer. BMC Cancer, 2017. **17**(1): p. 445. DOI: 10.1186/s12885-017-3396-0

[77] Rudert, H.H. and S. Hoft, Transoral carbon-dioxide laser resection of hypopharyngeal carcinoma. Eur Arch Otorhinolaryngol, 2003. **260**(4): p. 198-206. DOI: 10.1007/s00405-002-0520-8

[78] Suarez, C., et al., Laser surgery for early to moderately advanced glottic, supraglottic, and hypopharyngeal cancers. Head Neck, 2012. **34**(7): p. 1028-1035. DOI: 10.1002/hed.21766

[79] Vilaseca, I., J.L. Blanch, and M. Bernal-Sprekelsen, Transoral laser surgery for hypopharyngeal carcinomas. Curr Opin Otolaryngol Head Neck Surg, 2012. **20**(2): p. 97-102. DOI: 10.1097/MOO.0b013e32834fa8fe

[80] Karatzanis, A.D., et al., T1 and T2 hypopharyngeal cancer treatment with laser microsurgery. J Surg Oncol, 2010. **102**(1): p. 27-33. DOI: 10.1002/jso.21550

[81] Lorincz, B.B., et al., Feasibility and safety of transoral robotic surgery (TORS) for early hypopharyngeal cancer: a subset analysis of the Hamburg University TORS-trial. Eur Arch Otorhinolaryngol, 2015. **272**(10): p. 2993-2998. DOI: 10.1007/s00405-014-3259-0

[82] Lorincz, B.B., N. Jowett, and R. Knecht, Decision management in transoral robotic surgery: Indications, individual patient selection, and role in the multidisciplinary treatment for head and neck cancer from a European perspective. Head Neck, 2016. **38 Suppl 1**: p. E2190–E2196. DOI: 10.1002/hed.24059

[83] Park, Y.M., et al., Feasiblity of transoral robotic hypopharyngectomy for early-stage hypopharyngeal carcinoma. Oral Oncol, 2010. **46**(8): p. 597-602. DOI: 10.1016/j.oraloncology.2010.05.003

[84] Lagha, A., et al., Larynx preservation: what is the best non-surgical strategy? Crit Rev Oncol Hematol, 2013. **88**(2): p. 447-458. DOI: 10.1016/j.critrevonc.2013.05.005

[85] Peters, L.J., et al., Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys, 1993. **26**(1): p. 3-11. DOI: 10.1016/0360-3016(93)90167-t

[86] Vikram, B., et al., Failure at the primary site following multimodality treatment in advanced head and neck cancer. Head Neck Surg, 1984. **6**(3): p. 720-3. DOI: 10.1002/hed.2890060303

[87] Frank, J.L., et al., Postoperative radiotherapy improves survival in squamous cell carcinoma of the hypopharynx. Am J Surg, 1994. **168**(5): p. 476-480. DOI: 10.1016/s0002-9610(05)80105-9

[88] Tupchong, L., et al., Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. Int J Radiat Oncol Biol Phys, 1991. **20**(1): p. 21-28. DOI: 10.1016/0360-3016(91)90133-o

[89] Bourhis, J., et al., Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol, 2012. **13**(2): p. 145-153. DOI: 10.1016/S1470-2045(11)70346-1

[90] Rosenthal, D.I. and K.K. Ang, Altered radiation therapy fractionation, chemoradiation, and patient selection for the treatment of head and neck squamous carcinoma. Semin Radiat Oncol, 2004. **14**(2): p. 153-166. DOI: 10.1053/j.semradonc.2004.01.001

[91] Pignon, J.P., et al., Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol, 2009. **92**(1): p. 4-14. DOI: 10.1016/j.radonc.2009.04.014

[92] Cohen, E.E., M.W. Lingen, and E.E. Vokes, The expanding role of systemic therapy in head and neck cancer. J Clin Oncol, 2004. **22**(9): p. 1743-1752. DOI: 10.1200/JCO.2004.06.147

[93] Lefebvre, J.L., et al., Laryngeal preservation with induction

chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol, 2012. **23**(10): p. 2708-2714. DOI: 10.1093/annonc/mds065

[94] Rosenthal, D.I. and A.I. Blanco, Head and neck squamous cell carcinoma: optimizing the therapeutic index. Expert Rev Anticancer Ther, 2005. **5**(3): p. 501-514. DOI: 10.1586/14737140.5.3.501

[95] Staton, J., et al., Factors predictive of poor functional outcome after chemoradiation for advanced laryngeal cancer. Otolaryngol Head Neck Surg, 2002. **127**(1): p. 43-47. DOI: 10.1067/mhn.2002.124473

[96] Gourin, C.G. and D.J. Terris, Carcinoma of the hypopharynx. Surg Oncol Clin N Am, 2004. **13**(1): p. 81-98. DOI: 10.1016/S1055-3207(03)00122-4

[97] Eisbruch, A., et al., Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2002. **53**(1): p. 23-28. DOI: 10.1016/s0360-3016(02)02712-8

[98] Vokes, E.E., et al., Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol, 2000. **18**(8): p. 1652-1661. DOI: 10.1200/JCO.2000.18.8.1652

[99] Forastiere, A.A., N. Ismaila, and G.T. Wolf, Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update Summary. J Oncol Pract, 2018. **14**(2): p. 123-128. DOI: 10.1200/JOP.2017.027912

[100] Pfister, D.G., et al., Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, 2020. **18**(7): p. 873-898. DOI: 10.6004/jnccn.2020.0031

[101] Joshi, P., et al., Thyroid gland involvement in carcinoma of the hypopharynx. J Laryngol Otol, 2014. **128**(1): p. 64-67. DOI: 10.1017/S0022215113003277

[102] Kraus, D.H., et al., Salvage laryngectomy for unsuccessful larynx preservation therapy. Ann Otol Rhinol Laryngol, 1995. **104**(12): p. 936-941. DOI: 10.1177/000348949510401204

[103] Clark, J.R., et al., Primary and salvage (hypo)pharyngectomy: Analysis and outcome. Head Neck, 2006. **28**(8): p. 671-677. DOI: 10.1002/hed.20428

[104] Laccourreye, O., et al., Supracricoid hemilaryngopharyngectomy in selected pyriform sinus carcinoma staged as T2. Laryngoscope, 1993. **103**(12): p. 1373-1379. DOI: 10.1288/00005537-199312000-00010

[105] Laccourreye, O., et al., Supracricoid hemilaryngopharyngectomy in patients with invasive squamous cell carcinoma of the pyriform sinus. Part I: Technique, complications, and long-term functional outcome. Ann Otol Rhinol Laryngol, 2005. **114**(1 Pt 1): p. 25-34. DOI: 10.1177/000348940511400106

[106] Chevalier, D., et al., Supraglottic hemilaryngopharyngectomy plus radiation for the treatment of early lateral margin and pyriform sinus carcinoma. Head Neck, 1997. **19**(1): p. 1-5. DOI: 10.1002/(sici)1097-0347(199701)19:1<1::aid-hed1>3.0.co;2-a

[107] Lecanu, J.B., et al., Conservative surgery in T3-T4 pharyngolaryngeal squamous cell carcinoma: an alternative to radiation therapy and to total laryngectomy for good responders to induction chemotherapy. Laryngoscope, 2000. **110**(3 Pt 1): p. 412-416. DOI: 10.1097/00005537-200003000-00015

[108] Chawla, S. and A.S. Carney, Organ preservation surgery for laryngeal

cancer. Head Neck Oncol, 2009. **1**: p. 12. DOI: 10.1186/1758-3284-1-12

[109] Thorp, M.A., et al., Parathyroid and thyroid function five years after treatment of laryngeal and hypopharyngeal carcinoma. Clin Otolaryngol Allied Sci, 1999. **24**(2): p. 104-108. DOI: 10.1046/j.1365-2273.1999.00214.x

[110] Lo Galbo, A.M., et al., A prospective longitudinal study on endocrine dysfunction following treatment of laryngeal or hypopharyngeal carcinoma. Oral Oncol, 2013. **49**(9): p. 950-955. DOI: 10.1016/j.oraloncology.2013.03.450

[111] Buckley, J.G. and K. MacLennan, Cervical node metastases in laryngeal and hypopharyngeal cancer: a prospective analysis of prevalence and distribution. Head Neck, 2000. **22**(4): p. 380-385. DOI: 10.1002/1097-0347(200007)22:4<380::aid-hed11>3.0.co;2-e

[112] Lefebvre, J.L., et al., Lymph node invasion in hypopharynx and lateral epilarynx carcinoma: a prognostic factor. Head Neck Surg, 1987. **10**(1): p. 14-18. DOI: 10.1002/hed.2890100104

[113] Candela, F.C., K. Kothari, and J.P. Shah, Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. Head Neck, 1990. **12**(3): p. 197-203. DOI: 10.1002/hed.2880120302

[114] Wu, A.J., et al., Radiotherapy after surgical resection for head and neck mucosal melanoma. Am J Clin Oncol, 2010. **33**(3): p. 281-285. DOI: 10.1097/COC.0b013e3181a879f5

[115] de Mones, E., et al., Initial staging of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding nasopharynx). Part 2: Remote extension assessment and exploration for secondary synchronous locations outside of the upper aerodigestive tract. 2012 SFORL guidelines. Eur Ann Otorhinolaryngol Head Neck Dis, 2013. **130**(2): p. 107-112. DOI: 10.1016/j.anorl.2012.09.003

[116] Timon, C.V., M. Toner, and B.J. Conlon, Paratracheal lymph node involvement in advanced cancer of the larynx, hypopharynx, and cervical esophagus. Laryngoscope, 2003. **113**(9): p. 1595-9. DOI: 10.1097/00005537-200309000-00035

[117] Martins, A.S., Neck and mediastinal node dissection in pharyngolaryngoesophageal tumors. Head Neck, 2001. **23**(9): p. 772-9. DOI: 10.1002/hed.1110

[118] Clayman, G.L., et al., Laryngeal preservation for advanced laryngeal and hypopharyngeal cancers. Arch Otolaryngol Head Neck Surg, 1995. **121**(2): p. 219-223. DOI: 10.1001/archotol.1995.01890020081015

[119] Chung, E.J., et al., Pattern of lymph node metastasis in hypopharyngeal squamous cell carcinoma and indications for level VI lymph node dissection. Head Neck, 2016. **38** Suppl 1: p. E1969–E1973. DOI: 10.1002/hed.24361

[120] Hasegawa, Y. and H. Matsuura, Retropharyngeal node dissection in cancer of the oropharynx and hypopharynx. Head Neck, 1994. **16**(2): p. 173-180. DOI: 10.1002/hed.2880160212

[121] Kirchner, J.A., Pyriform sinus cancer: a clinical and laboratory study. Ann Otol Rhinol Laryngol, 1975. **84**(6): p. 793-803. DOI: 10.1177/000348947508400611

[122] Terhaard, C.H., et al., F-18-fluoro-deoxy-glucose positron-emission tomography scanning in detection of local recurrence after radiotherapy for laryngeal/ pharyngeal cancer. Head Neck, 2001. **23**(11): p. 933-941. DOI: 10.1002/hed.1135

[123] Ho, C.M., et al., Squamous cell carcinoma of the hypopharynx--analysis of treatment results. Head Neck, 1993. **15**(5): p. 405-412. DOI: 10.1002/hed.2880150507

[124] Lowe, V.J., et al., Surveillance for recurrent head and neck cancer using positron emission tomography. J Clin Oncol, 2000. **18**(3): p. 651-658. DOI: 10.1200/JCO.2000.18.3.651

[125] Conessa, C., et al., FDG-PET scan in local follow-up of irradiated head and neck squamous cell carcinomas. Ann Otol Rhinol Laryngol, 2004. **113**(8): p. 628-635. DOI: 10.1177/000348940411300806

[126] Bataini, J.P., et al., Significance and therapeutic implications of tumor regression following radiotherapy in patients treated for squamous cell carcinoma of the oropharynx and pharyngolarynx. Head Neck, 1990. **12**(1): p. 41-49. DOI: 10.1002/hed.2880120106

[127] Chmura, S.J., M.T. Milano, and D.J. Haraf, Reirradiation of recurrent head and neck cancers with curative intent. Semin Oncol, 2004. **31**(6): p. 816-821. DOI: 10.1053/j.seminoncol.2004.09.003

[128] Creak, A.L., K. Harrington, and C. Nutting, Treatment of recurrent head and neck cancer: re-irradiation or chemotherapy? Clin Oncol (R Coll Radiol), 2005. **17**(3): p. 138-147. DOI: 10.1016/j.clon.2004.10.008

[129] Leemans, C.R., P.J.F. Snijders, and R.H. Brakenhoff, The molecular landscape of head and neck cancer. Nat Rev Cancer, 2018. **18**(5): p. 269-282. DOI: 10.1038/nrc.2018.11

[130] Ferris, R.L., et al., Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med, 2016. **375**(19): p. 1856-1867. DOI: 10.1056/NEJMoa1602252

[131] Cramer, J.D., et al., The changing therapeutic landscape of head and neck cancer. Nat Rev Clin Oncol, 2019. **16**(11): p. 669-683. DOI: 10.1038/s41571-019-0227-z