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Hypopharyngeal cancer: A state of the art review

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ABSTRACT

Cancer of the hypopharynx is relatively rare and accounts for roughly 3% of all head and neck cancers. Unfortunately, hypopharyngeal carcinoma has one of the worst prognosis of all head and neck cancers with a reported 5-year overall survival rate of approximately 30–35%. Toxicity related to therapy, and the need for surgical salvage continue to dominate the landscape in this disease. In this article, we set out to discuss a comprehensive overview of the current management principles, recent literature and evidence based therapeutic options surrounding treatment for hypopharyngeal squamous cell carcinoma, with a special focus on the evolution of an organ sparing paradigm.

Introduction

Cancer of the hypopharynx is relatively rare and accounts for roughly 3% of all head and neck cancers. Unfortunately, hypopharyngeal carcinoma has one of the worst prognosis of all head and neck cancers with a reported 5-year overall survival rate of approximately 30–35% [1,2]. Anatomically, the hypopharynx is commonly defined by its subsites, which include the lateral pharynx, posterior pharyngeal wall, piriform sinuses, and the post-cricoid region leading to the esophageal inlet. In clinical practice, hypopharyngeal cancers frequently present at advanced stage and warrant aggressive treatment regimens that drastically impact a patient's quality of life. Despite medical advancements in overall oncology treatment for head and neck cancer, outcomes for hypopharyngeal carcinoma have remained relatively poor and have demonstrated only marginal improvement in survival over the years [1]. Recurrence is quite common, as nearly 50% of patients recur within the first year after diagnosis and are frequently diagnosed with distant metastasis [2]. Treatment for hypopharyngeal cancer remains a challenge and a multidisciplinary approach is required in order to develop an optimal treatment regimen. The overarching goal is to optimize survival and provide functional organ preservation when feasible from an oncological standpoint. In this article, we set out to discuss a comprehensive overview of the current management principles, recent literature and evidence based therapeutic options surrounding treatment for hypopharyngeal squamous cell carcinoma, with a special focus on the evolution of an organ sparing paradigm.

Epidemiology and pathophysiology

From a histologic perspective, the overwhelming majority of hypopharyngeal tumors are squamous cell carcinoma. Patients with hypopharyngeal squamous cell carcinoma (HSCC) are predominantly male and commonly have a history of tobacco (90%) and heavy alcohol use (50%) [3] Epidemiologic data from the National Cancer Database (NCDB) reports that patients with hypopharyngeal cancer are on average 63 years of age, 75% male, and over 70% Caucasian [4]. In addition to tobacco and alcohol intake, other reported risk factors include Plummer-Vinson syndrome and gastroesophageal reflux. At the present time, the human papilloma virus (HPV) has not been found to play a significant role in the pathogenesis of hypopharyngeal squamous cell carcinoma [5].

The anatomy of the hypopharynx informs the natural progression of disease, mainly by its unique lymphatic and vascular anatomy, which allows tumors to easily metastasize to cervical nodal basins as well as distant sites. The rich lymphatic network in the region primarily drains to cervical jugular nodes (levels II-IV) and retropharyngeal nodes [6–9]. In the upper aerodigestive tract, the hypopharynx is closely related to nearby structures such as the oropharynx, larynx, and cervical esophagus. However, the configuration of the hypopharyngeal subsites (posterior and lateral pharyngeal walls, piriform sinuses, and post cricoid region) may allow for substantial tumor growth before causing impingement or invasion of these nearby structures. Furthermore, many of the signs and symptoms of hypopharyngeal cancer may be delayed due to substance abuse, or be confused with other benign issues

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such as reflux, upper respiratory infections, or smoking related irritation. These factors make early identification of hypopharyngeal tumors challenging and increase the likelihood of advanced stage disease upon initial presentation.

Clinical presentation

Patients afflicted with hypopharyngeal tumors may remain asymptomatic until laryngeal invasion or nodal metastasis occurs. Symptoms in early stage disease are nonspecific and may imitate benign conditions such as laryngopharyngeal reflux or globus sensation. Tumors positioned within the piriform sinus are challenging to visualize on flexible fiberoptic laryngoscopy exams and may be missed on routine imaging such as computed tomography (CT) or magnetic resonance imaging (MRI). There is a tendency for hypopharyngeal primary tumors to exhibit submucosal extension owning to difficulty identifying their location on clinical and even gross pathologic examination [10]. The most common presenting symptom is dysphagia, which occurs in 50% of patients along with sore throat, hoarseness, or globus sensation [2]. The hypopharynx has a robust lymphatic network allowing tumors to demonstrate early dissemination to the nodal basins of the neck and retropharynx as well as increasing the chance for distant metastasis [2]. It has been reported that approximately 6% of patients with hypopharygneal cancer have distant metastasis on initial presentation, and up to 60% develop metastasis at some time throughout their treatment or surveillance period [4].

Diagnosis and prognosis

The management of hypopharyngeal carcinoma is highly dependent on prompt diagnosis and accurate staging. A complete history and physical examination with a comprehensive head and neck exam including flexible fiberoptic laryngoscopy is indicated, as with other head and neck cancers. As previously mentioned, fiberoptic laryngoscopy exam may be inadequate when there is a clinical suspicion for hypopharyngeal cancer. Therefore, examination under anesthesia with direct laryngoscopy and biopsy is needed to provide a comprehensive assessment. The overwhelming majority of hypopharyngeal malignancies are of squamous cell carcinoma origin, but pathologic diagnosis with biopsy is required to entertain the wide differential of possibilities including inflammatory, infectious, benign, and malignant neoplasms. Since a majority of hypopharyngeal cancers are locally advanced at the time of diagnosis, high resolution imaging such as CT with contrast or MRI is recommended for assessment of the primary site and regional lymphatics. Some favor MRI as the preferred imaging modality given the chance of submucosal spread [11]. Ultrasound is another imaging modality that has been recommended as a cost effective, non-invasive assessment of cervical lymph nodes, but not preferred for assessment of the primary tumor site [12]. Given the increased chance for distant metastasis, chest imaging is recommended, which generally is performed with chest CT, or PET/CT when available. Multidisciplinary care is a routine part of pre-treatment counseling and consultations for nutritional services, speech and swallow specialists, and dental evaluation should be considered in all patients.

Despite medical advancements, and oncologic improvements in the treatment of many head and neck cancers, outcomes for hypopharyngeal carcinoma have remained relatively poor and have demonstrated only marginal improvement in survival over the years [1]. Recurrence is quite common, as nearly 50% of patients recur within the first year after diagnosis and are frequently diagnosed with distant metastasis. For example, autopsy studies in patients with hypopharyngeal cancer have demonstrated the presence of distant metastasis in 60% of patients [8]. Negative prognostic factors for survival include male gender, advanced age, advanced clinical stage, comorbid conditions, and poor performance scores [13,14].

Treatment

Available treatment options for HSCC include the potential use of surgery, radiotherapy (RT), or chemotherapy depending on the clinical stage and co-morbid conditions. The current NCCN guidelines are stratified by the feasibility of surgical resection for the primary tumor and offer various surgical and non-surgical treatment options. However, there is not a clear preference for a primary treatment modality. In general, single modality treatment is reserved for select early stage disease (T1 and certain T2 lesions, without nodal metastasis) and multimodality treatment is required for the remainder of advanced stages. The guiding principle of attempting organ preservation without compromising oncologic outcome has led to both important refinements in chemoradiotherapy regimens and innovative surgical techniques over the years.

Organ preservation studies

In 1991, the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) published the seminal article investigating the role of induction chemotherapy (IC) followed by radiotherapy (RT) in order to spare patients who demonstrated a good response to cisplatin and 5-FU a total laryngectomy [15]. The study comprised of patients with stage III and IV laryngeal cancer, mostly located in the supraglottic subsite. The trial demonstrated that 64% of patients assigned to the IC arm were able to preserve their larynx and avoid surgical resection. In addition, the two-year OS was 68% for the IC and surgical arm, with no significant difference between the two treatment arms when grouped by tumor stage or laryngeal cancer sub-site. Of note, the OS analysis included those patients who were non-responders and subsequently went on to have a total laryngectomy. The results of the trial established the role of IC followed by RT and the concept of laryngeal preservation in the treatment of advanced stage laryngeal cancer. Although this study set in motion major landmark trials that confirmed the feasibility of a non-surgical chemoradiotherapy based regimen for advanced laryngeal cancer, the emerging paradigm of laryngeal preservation was not yet validated for cancer of the hypopharynx.

Interestingly, according to a recent SEER study on survival trends in hypopharyngeal cancer, Newman et al. identified that a non-surgical, organ preservation strategy became adopted for treatment of hypopharyngeal cancer around the time of VALSG study, but prior to the hypopharynx equivalence studies performed by Lefebvre et al. [1,16,17]. A historical analysis suggests that physicians were extrapolating VALSG regimens and outcomes to primary tumors of the hypopharynx before analogous evidence based medicine studies had been published and widely accepted [1]. Only a limited subset of the major trials that corroborated the feasibility of laryngeal preservation after the VA trial in 1991 included patients with primary tumors of the hypopharynx. For instance, the pivotal RTOG 91-11 trial that demonstrated superiority of IC and concomitant chemoradiotherapy (CCRT) compared to RT alone with CCRT having a significantly increased laryngeal preservation rate for laryngeal cancer did not enroll any patients with a hypopharyngeal primary tumor [18]. Also, a major consideration worth noting is the variability of the definition of “laryngeal preservation” across various studies published in the existing literature. The definition of laryngeal preservation can range from a patient who retains their larynx (i.e. whether or not the larynx is functional) to patients with a functional larynx without tracheostomy, feeding tube, or residual tumor. In the current literature, studies pertaining to laryngeal preservation do not universally include hypopharyngeal tumors. In fact, there is a limited amount of evidence based, randomized controlled trials that restrict patient enrollment to patients with hypopharyngeal primary tumors.

One of the earliest studies to include hypopharyngeal tumors was the EORTC 24,891 trial published in 1996 [19]. This trial was developed as a phase III randomized control trial comparing IC followed by