Head and Neck Cancer: An Overview

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ABSTRACT

Ablative surgery for malignancies of the upper aerodigestive tract is the most common reason why the reconstructive surgeon is called upon to reconstruct adult head and neck defects. An understanding of the pathophysiology and treatment of head and neck malignancy is vital to the reconstructive surgeon so that restoration of both form and function can be achieved. It is important to understand the behavior of cancers of each head and neck subsite, as staging and ultimately the treatment of tumors from each subsite is different. Historically, the standard treatment of head and neck cancer was surgery and/or primary radiation therapy with surgical salvage for failure. Beginning in the 1980s, advances in chemotherapy and concurrent delivery with radiation offered new options to standard surgical therapy. Over the past two decades, the concept of organ preservation using chemotherapy together with radiation therapy has been definitively established. Yet, even with the strides made over these two decades with chemoradiation, surgical treatment of head and neck cancer and reconstruction thereof will be an important treatment option for the foreseeable future. Therefore, the relationship between the extirpative and reconstructive surgeon is vital, and a clear understanding of the biology and behavior of head and neck malignancy is crucial to successful patient outcomes.

KEYWORDS: Head, neck, cancer

Ablative surgery for malignancies of the upper aerodigestive tract is the most common reason why the reconstructive surgeon is called upon to reconstruct adult head and neck defects. Squamous cell carcinoma is responsible for more than 90% of the malignancies of the upper aerodigestive tract and is the most common cause of death among patients with head and neck cancer. Overall, it accounts for more than 40,000 new cancer cases and 11,000 deaths annually in the United States.¹ As important as the mortality associated with head and neck cancer is the associated morbidity experienced by the head and neck cancer patient. Structures vital for the functions of speech, mastication, and swallowing are frequently affected by malignancy. Additionally, many

head and neck cancer patients require intervention to secure and maintain a patent and protected airway secondary to an obstructive and/or destructive process. Therefore, an understanding of pathophysiology and treatment of head and neck malignancy is vital to the reconstructive surgeon so that restoration of both form and function can be achieved.

The evaluation of head and neck malignancy, its staging system, and ultimately its treatment have evolved over many years. Even with the advances made in surgical technique and the development of chemotherapeutic and radiation regimens, little improvement in survival has been made over the past 25 years.¹ The structure of the upper aerodigestive system can be broken

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Advances in Head and Neck Reconstruction, Part I; Guest Editors,

Samir Mardini, M.D., Christopher J. Salgado, M.D., and Hung-Chi Chen, M.D., F.A.C.S.

Semin Plast Surg 2010;24:107–116. Copyright © 2010 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI: <http://dx.doi.org/10.1055/s-0030-1255328>.

ISSN 1535-2188.

down into different subsites, as the behavior of tumors of these different subsites differs. These subsites include:

- the oral cavity
- the nasopharynx and paranasal sinuses
- the oropharynx
- the hypopharynx
- the larynx.

To be complete, cutaneous malignancies that arise on the face and scalp should be considered in any discussion of head and neck reconstruction, but only those malignancies arising in the upper aerodigestive tract will be discussed in this overview of head and neck cancer.

It is important to understand the anatomy and embryology of each subsite, as staging and ultimately the treatment of tumors from each subsite is different. An understanding of the lymphatic drainage of each subsite is also important, so that the lymph nodes of the neck are appropriately treated along with the primary lesion.

PATIENT EVALUATION

A thorough medical workup is the first step in the evaluation and treatment of a patient with a head and neck cancer. The key elements of a good patient evaluation go beyond the history and office physical examination. Examination under anesthesia with direct laryngoscopy, bronchoscopy, and esophagoscopy, along with computed tomography (CT) and/or magnetic resonance imaging of the neck are key elements of a complete workup. Though not yet the “gold standard,” there are accumulating data supporting use of 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}FDG -PET/CT) not only as a means for oncologic surveillance after definitive treatment but also as a primary survey tool in the initial evaluation of these patients.²

The main goal of all these elements is to accurately assess and stage the primary lesion, assess for regional nodal metastasis, and determine if there are synchronous primary and/or metastatic lesions at distant sites. The history and office physical examination should assess the patient's overall health status and should determine if the patient is fit to undergo surgery and/or chemoradiation. Office examination usually includes flexible fiberoptic laryngoscopy, at which time the mobility of the vocal cords should be assessed and documented. Examination under general anesthesia (EUA) is one of the next important steps to take after initial history and physical examination. During EUA, all aspects of the above-mentioned subsites should be inspected, paying close attention to the floor of the mouth, the base of the tongue, the tonsillar pillars, the piriform sinuses, and the post-cricoid region. The size and

location of the lesion should be noted, as well as any exposure, involvement, or overt invasion of bone (i.e., the hard palate or mandible), cartilage (i.e., the thyroid cartilage, arytenoids, or cricoid cartilage), or vascular structures. After inspection, it is important to palpate the neck for nodal metastasis and the subsites of the oral cavity and the base of the tongue. When the primary lesion is apparent and within reach of digital palpation, it should be determined whether the lesion is mobile or fixed to underlying structures (i.e., the mandible, extrinsic musculature of the tongue, or prevertebral fascia), and also the size and extent of the submucosal component of the lesion should be assessed.

These physical examination findings directly influence the staging of the lesion and subsequently the type of treatment that will be recommended. After inspection of the oral cavity and oropharynx and direct laryngoscopy, a flexible bronchoscopy and esophagoscopy are performed. As most head and neck patients have a significant history of tobacco and alcohol abuse, it is important to rule out any synchronous primary lesions of the lung and esophagus during EUA. In patients with primaries of the oral cavity and oropharynx, one should not overlook other upper aerodigestive tract sites, as the most common site of a second primary is within the head and neck region, followed by the lungs. Almost universally, a CT scan of the neck with contrast is performed to better assess nodal status. In addition, the extent of the primary lesion can be accurately defined with CT, and this tool is useful in defining bony erosion, cartilage invasion, and submucosal extension. A PET scan can be used to locate and define the primary lesion, regional and distant metastasis, and synchronous primaries, although the role of PET scanning differs from institution to institution. Diagnostic PET scanning can also be performed in conjunction with PET imaging for radiation therapy planning. An example of a diagnostic PET/CT scan is shown in Fig. 1.

STAGING

The stage of the head and neck lesion is critical in planning the type of therapy that will be offered/recommended to the patient. For each subsite of the head and neck, there is a different staging schema outlined by the American Joint Committee on Cancer, which follows the standard tumor, node, metastasis (TNM) staging system for malignancy. A complete review of the staging criteria is beyond the scope of this article, but in general, staging elements for each subsite depend upon the size of the lesion and/or involvement of other subsites, extension to or erosion through surrounding structures, status of regional lymph nodes, and the presence of distant metastasis. For example, for lesions of or near the larynx, staging is determined based on assessment of vocal cord movement. Tumor that involves the superficial mucosal

Figure 1 PET/CT scan of a patient who had resection of right maxillary sinus carcinoma, showing malignant left neck adenopathy not appreciated on clinical examination. Upper panes show axial, sagittal, and coronal plane CT images. Middle panes show PET images in the same planes. Lower images show fused images highlighting multiple PET-avid lymph nodes in the left neck corresponding with malignant adenopathy.

surface of the cord and allows free movement of the cord would be staged T1. A lesion that completely impairs the motion of the cord is T3, and a T4 lesion is one that invades surrounding cartilage. As with other sites outside the head and neck region, the larger the tumor and/or the more involved the tumor is with underlying structures, the higher the T stage.

The staging of regional metastases in the neck is based on the size, number, laterality, and fixation of the involved nodes. Larger nodes, multiple nodes, fixed nodes, and nodes contralateral to the primary lesion carry a worse outcome in terms of survival, and thus carry a higher N classification and therefore a higher stage. For example, patients with an oropharyngeal lesion larger than a T1 carry a 20 to 30% chance of harboring occult metastatic disease in an otherwise N0 neck. This fact alone decreases the 5-year survival rate by 50%.³ Therefore, it is vital that the correct assessment and staging of disease be made at the time of diagnosis.

The nodes in the neck are divided into different levels and compartments for ease of classification. Level I is composed of the submental and submandibular triangles and is bounded posteriorly by the posterior belly of the digastric muscle. Level I is divided into two compartments: Ia and Ib. Level Ia contains the fibrofatty tissue in the midline of the neck between the two

anterior borders of the digastric muscle and is bounded by the mandible superiorly. Level Ib contains the contents of the submandibular triangle. Level II contains the upper cervical nodes, extending from the skull base to the inferior border of the hyoid bone. The posterior limit for level II (as well as levels III and IV) is the posterior border of the sternocleidomastoid muscle (SCM). Level II is further subdivided by the spinal accessory nerve (IX) into levels IIa and IIb, with nodes anterior to the nerve considered to be in level IIa, whereas those posterior to it are in level IIb. Level III lymph nodes are found from the inferior border of the hyoid down to the inferior border of the cricoid cartilage. Level IV extends from the inferior border of the cricoid to the superior border of the clavicle. Level V nodes are found in the posterior triangle, bounded by the posterior border of the SCM anteriorly, the anterior border of the trapezius posteriorly, and the clavicle inferiorly. Although less commonly described, levels VI and VII designate the nodes in the central paratracheal region and the central substernal area, respectively.

The third component of the assessment of stage is whether or not there are distant metastases. A designation of M1 is given to those patients with distant metastases; regardless of their T and N stage, these patients have a dramatically decreased survival and are designated as stage IV.

OVERVIEW BY SUBSITE

Oral Cavity

The oral cavity is defined as the region from the vermillion of the lips anteriorly to the junction of the hard and soft palates posteriorly. Laterally, the oral cavity includes the anterior palatoglossal pillars and buccal mucosa. The subsites of the oral cavity are the lips, the buccal mucosa, the upper and lower alveolar ridges, the floor of the mouth, the anterior two-thirds of the tongue, and the hard palate. It is estimated that there are 363,000 new cases of oral cavity malignancy worldwide each year, and oral cavity malignancy accounted for 3% of all cancers in the United States in 2007. As with other upper aerodigestive tract cancers, patients with oral cavity cancers usually have a significant history of tobacco use and alcohol intake. Both smoking and drinking contribute to the development of lesions within the oral cavity, and, together, patients have a 15-fold increased risk of developing an oral cavity malignancy.⁴ Another risk factor highly correlated with the development of head and neck cancer is viral infection, specifically human papilloma virus (HPV). HPV-16 is the most common of the HPV subtypes associated with oral and laryngeal malignancies.

Traditionally, carcinomas of the oral cavity are treated with either surgery and/or radiation therapy; more advanced lesions will require combination therapy. Oral cavity malignancy is amenable to early detection and treatment. Early-stage lesions of the lip, anterior tongue, and cheek can all be treated by excising them surgically followed by local repair/closure, if needed. When appropriate, surgery as the sole modality of therapy avoids the comorbidities associated with radiation therapy. However, more extensive lesions will require a combination of both therapies. Another important consideration is the functional impairment that may occur as a result of surgical resection, especially with larger lesions of the tongue and mandible. Before a treatment plan is devised, it is critical to accurately stage the lesion in question. Small lesions (those <4 cm) that do not involve underlying bone or the extrinsic muscles of the tongue are generally amenable to surgical resection without the need for adjuvant radiation therapy. The goal of the ablative surgeon is to obtain clear surgical margins with the resection, as it has been shown that local control rate of disease drops from 90 to 62% when surgical margins are close or positive.⁵ Advanced lesions (those >4 cm in their greatest dimension or that invade critical structures) require larger resections to clear margins and will usually require postoperative radiation therapy. The defect left by such a resection is large and will usually require some sort of tissue transfer to achieve optimal reconstruction (Figs. 2 and 3).

The lymphatic drainage of the oral cavity occurs in a predictable fashion. In general, the nodes most at

Figure 2 Squamous cell carcinoma of the mandibular gingiva (with mandible invasion).

risk for metastasis from oral cavity malignancy are in levels I, II, and III. The specific subsite of the lesion within the oral cavity helps to predict the nodes at most risk. The lips, in general, drain to the submental and submandibular nodes, with some drainage to the preauricular nodes. The anterior tongue has several lymphatic pathways, with the tip draining to level I and the lateral tongue draining to levels I and II. It should also be noted that the lateral tongue has pathways that can sometime “skip” levels II and III and metastasize directly to level IV. The buccal mucosa and retromolar trigone tend to drain to level I and to levels I to III, respectively. The lymphatic drainage of the floor of the mouth is important in that the anterior aspect can drain to the contralateral levels I, II, and III as well as to the ipsilateral nodes. Posterior lesions, though, tend to drain to the ipsilateral upper cervical chain nodes.

Oropharynx

The oropharynx is situated just posterior to the oral cavity and is an important and dynamic region for the functions of speech and swallowing. The oropharynx is bounded superiorly by a horizontal line through the

Figure 3 Resection specimen including segmental anterior mandible resection with bilateral neck dissections.

superior surface of the soft palate and inferiorly by the superior border of the hyoid bone. Laterally, it is bounded by the tonsillar pillars and posteriorly by the posterior pharyngeal wall. Anteriorly, the oropharynx ends at the most anterior extent of the soft palate, anterior tonsillar pillars, and the base of the tongue (that portion of the tongue posterior to the foramen cecum). The oropharynx is further subdivided into four subsites: the palatine tonsils and tonsillar pillars, the base of the tongue, the soft palate, and the mid-posterior pharyngeal wall. A large amount of lymphoid tissue can be found in the oropharynx within Waldeyer's ring, which includes the tonsils bilaterally, the lingual tonsils, and the adenoid pad within the nasopharynx.

Because of the abundant lymphoid tissue, lymphoma is the second most common malignancy found in the oropharynx, after squamous cell carcinoma. Also, minor salivary glands within this region can give rise to advanced salivary gland malignancies such as adenoid cystic or mucoepidermoid carcinoma. The likelihood of a second primary lesion within the oropharynx is relatively high. Lesions of the oropharynx can produce minimal symptomatology early in their development and therefore usually present at an advanced stage. Small and sometimes even larger lesions can be difficult to detect by the untrained examiner. It has been reported that anywhere from 50 to 75% of patients presenting with oropharyngeal malignancy also present with regional nodal metastasis. Often, a neck mass is the only presenting sign.

The tonsil and tonsillar fossa are the most common sites for squamous cell carcinoma of the oropharynx. Presenting symptoms may include throat pain, pain or difficulty swallowing, and referred pain to the ipsilateral ear. Tonsillar lesions can grow inward toward deeper musculature or in an outward, exophytic fashion. The base of the tongue is where these lesions most commonly extend, but they may also involve the posterior pharyngeal wall or the oral cavity. Even to the trained examiner, small tonsil lesions can be very difficult to see on office examination. The tonsil and tonsillar fossa are the most common sites for squamous cell carcinoma of the oropharynx (Fig. 4). One must suspect tonsillar cancer in patients presenting with a cervical nodal metastasis with an otherwise unknown primary, and a tonsillar biopsy or tonsillectomy must be performed to rule out malignancy as one searches for the primary.

Base of tongue lesions, like the tonsil, can be difficult to detect when they are small to moderate size and may be palpable but not visible. These lesions can present as an exophytic lesion or can grow deeply into the musculature of the tongue. These endophytic lesions are among the most difficult to detect because there may be no mucosal ulceration or defect present. It should be reiterated, therefore, that a critical part of the head and

Figure 4 CT scan showing typical appearance of advanced carcinoma of the tonsil with early base of tongue involvement.

neck examination is palpation of the base of the tongue, which can yield the first clues to a developing lesion. Base of tongue lesions can spread to the glossopharyngeal sulci, to the vallecula and epiglottis, and more advanced lesions can involve the floor of the mouth and the mandible.

Although not intuitively obvious, lesions of the posterior pharyngeal wall can also be difficult to visualize on physical examination. Often these cancers will present as advanced lesions, and often as cervical metastasis. Posterior pharyngeal wall lesions can extend into other areas of the oropharynx or superiorly into the nasopharynx or inferiorly into the hypopharynx. Evaluation of invasion into surrounding structures, in particular the prevertebral fascia, becomes critical to evaluate resectability.

Lesions of the soft palate are usually easier to manage, as they tend to present early because they are often painful and are more accessible and easily seen on office examination.

As mentioned above, cervical metastases can occur early with oropharyngeal cancers and are sometimes the presenting sign. More than 60% of patients with malignant tongue base neoplasms will present with adenopathy, and ~20% will have bilateral disease.⁶ The oropharynx has a rich lymphatic drainage system to levels II to IV and also drains to the retropharyngeal nodes, which cannot be overlooked on diagnostic workup. With some posterior pharyngeal wall lesions with retropharyngeal extension, it can be difficult to delineate between the lesion and nodal involvement. When evaluating cervical metastasis, it is important to remember that all sites of the oropharynx, especially the tongue base, can and will metastasize bilaterally.

The oropharynx is a region of the head and neck of great functional importance, both for maintaining a stable airway and for maintaining normal swallowing function. As organ preservation has become more important over the past two decades, primary treatment of many of these lesions with chemotherapy and radiation therapy has become the preference of many centers. Surgery, in general, is usually reserved for chemoradiation failures. Because of the propensity for early cervical metastasis, the neck must be addressed early and aggressively. Early-stage lesions of the oropharynx (T1 and T2) respond well to radiation therapy alone, with the addition of chemotherapy for nodal involvement.⁷ Advanced lesions (T3 and T4) are best treated with combination chemotherapy and radiation. Many patients have bulky nodal disease upon presentation with an advanced oropharyngeal cancer, and the neck historically has been addressed with a planned neck dissection after primary chemoradiation. Emerging data suggest that, even with patients who have had bulky nodal disease, a negative PET scan (in patients who appear to have had a complete response) performed ~10 to 12 weeks after completion of chemoradiation reliably predicts which patients may need a neck dissection and which patients can be observed.

For chemotherapy and radiation failures and for small, selected oropharyngeal lesions, surgery is the treatment of choice. Surgical resection within the oropharynx can be challenging because of difficulties with exposure; however, various maneuvers such as mandibular splitting can make resection possible. For early-stage lesions of the tonsil, soft palate, and even of the posterior pharyngeal wall, transoral resection can be very effective. Tonsillectomy, partial lateral pharyngectomy, mucosal resection of the soft palate and posterior pharyngeal wall, and even small lesions of the base of the tongue can be performed with the oral cavity held open with a McIvor or Crowe-Davis mouth gag. For T3 and T4 lesions, an open transcervical approach usually is necessary.

There are three primary approaches for wide exposure to the oropharynx:

- lateral pharyngotomy
- transhyoid pharyngotomy
- mandibular split.

Usually, neck dissection is performed first, immediately followed by resection of the tumor. Lateral pharyngotomy provides access to the base of the tongue and the inferolateral pharyngeal wall. This is an excellent approach for lesions that are difficult to expose, especially after neck dissection has already been performed. Suprahyoid pharyngotomy allows access to midline lesions of the tongue base. Some surgeons are critical of this approach, though, and believe that it risks blind entry into the lesion with disruption of margins. The lip/mandibular split with mandibular swing allows the

widest access to virtually all aspects of the oropharynx and is the approach of choice for total glossectomy. The main disadvantages of this approach are the possibility of conspicuous lip/chin scars and the possibility of bony malunion or nonunion. With a properly designed incision, however, the resultant scar will heal very well and may be quite acceptable.

As has already been mentioned, large extirpative defects of the oropharynx have great consequence with respect to the function of swallowing, especially after resection of the base or all of the tongue. Therefore, reconstruction after large resection is the rule, rather than the exception. Certain small, select defects of the base of the tongue or lateral or posterior pharyngeal wall can be allowed to granulate, closed primarily, or skin grafted. However, reconstruction is usually accomplished with a pedicled myocutaneous flap or with free tissue transfer such as with a radial forearm flap, a rectus flap, or an anterior lateral thigh flap to provide bulk and support where it had been previously present. Along with reconstruction after total glossectomy, it is sometimes necessary to perform a total laryngectomy to prevent chronic aspiration.

Larynx

The primary function of the larynx as a valve is to provide an airway for respiration and to protect the airway when swallowing. Its secondary function is to produce sound, which, in humans, we know as voice. The larynx is divided into three distinct anatomic divisions: the supraglottis, the glottis, and the subglottis. The supraglottis is composed of the epiglottis, the aryepiglottic folds, the arytenoid cartilages, and the false vocal cords. The glottis proper includes the superior and inferior surfaces of the true vocal folds and the anterior and posterior commissures. It extends from the lateral margin of the ventricle to 1 cm inferiorly. The subglottis extends from the lower border of the glottis to the inferior border of the cricoid cartilage. Once again, the main risk factors for development of laryngeal malignancy are smoking and alcohol consumption. There are also some data that support HPV as a risk factor for laryngeal carcinoma, but there is no conclusive evidence for this.

More than 95% of laryngeal malignancy is squamous cell carcinoma. Even very small true cord lesions cause symptoms (voice changes) and, combined with a paucity of lymphatic drainage, these lesions are often detected early and are amenable to treatment before they become large or metastasize. Patients can present with sore throat, otalgia, and voice changes. Changes in voice that last more than 4 weeks should prompt evaluation for laryngeal malignancy. A full head and neck examination includes both a mirror examination or visualization of the larynx with a flexible endoscope or rigid laryngeal telescope. Vocal cord mobility should be assessed at the

Figure 5 Endoscopic view of T1 squamous cell carcinoma of the vocal cord.

time of office examination, as impairment or fixation of the cord signifies invasion of the vocal musculature. One must be sure to visualize the anterior and posterior commissures, although these two areas are often better visualized with direct laryngoscopy under general anesthesia.

Lesions of the glottis are usually well-differentiated squamous cell carcinoma and usually present at an early stage (T1 and T2) (Figs. 5 and 6). Because of the relative paucity of lymphatics draining the glottis proper, regional and distant metastases are usually not seen at initial presentation. This is not the case for supraglottic lesions. For advanced lesions, in which nodal metastasis is more likely, levels II to IV are most frequently involved. Early detection is possible with glottic lesions as the phonatory surface of the vocal cord is disrupted, resulting in a raspy or hoarse voice. Radiation therapy is probably the most common treatment for early-stage glottic lesions without the need for treatment of the neck. With advances that have been made in both endoscopic and laser-assisted surgery, local resection can also be achieved with good phonatory results. For early glottic lesions, neither radiation therapy nor surgery offers a distinctly superior rate of cure. There are no clear advantages to either radiation therapy or surgery in the literature for early glottic lesions. For T3 and *advanced* T2 lesions, it may not be possible to clear margins with endoscopic resection techniques. These advanced lesions are more amenable to partial laryngectomy procedures, such as a vertical partial laryngectomy or a supracricoid laryngectomy with cricohyoidoepiglottomy. Although conservative procedures are designed to preserve some function of the larynx, they should not be performed in patients with poor lung function and those unable to tolerate aspiration. In these patients, total laryngectomy should be performed. Advanced lesions of the larynx (T3 and T4) have historically been treated with total laryngectomy (Fig. 7) with postoperative radiation therapy. However, many of these

Figure 6 Endoscopic view of T2 squamous cell carcinoma of the vocal cord.

lesions can be treated with combination chemoradiation with surgery reserved for salvage. Standard external beam radiation with concurrent chemotherapy provides an opportunity to cure laryngeal cancer while preserving the larynx. Before recommending chemoradiation, however, the clinician should be aware of the potential functional results of therapy because, especially for bulky lesions with advanced cartilage destruction that extend into soft tissues, structural organ preservation may occur, but patients may have dysphagia, aphagia, poor voice, and/or tracheostomy tube dependence.

Figure 7 Total laryngectomy specimen (with pharyngectomy and neck dissections) for carcinoma of the piriform sinus with larynx involvement.

The potential for morbidity as a result of cancers of the supraglottis should not be underestimated. Lesions of the supraglottis require close attention, as the supraglottis has a rich lymphatic drainage, and regional metastases are common. Therefore, the neck must be addressed with every supraglottic lesion. One important determinant of regional and distant spread is involvement of the pre-epiglottic space, which is outside the confines of the cartilaginous supraglottis. This space encompasses the region from the hyoepiglottic ligament superiorly, the hyoid bone and thyroid cartilage anteriorly, and the epiglottis posteriorly. Early lesions of the suprahoid epiglottis (the portion above the pre-epiglottic space) are amenable to endoscopic resection with the laser. More advanced lesions, which involve the pre-epiglottic space, do not fare as well with endoscopic surgery alone. Many of these patients will require re-biopsy under general anesthesia along with bilateral neck dissection after initial resection. Open supraglottic laryngectomy is an oncologically safe procedure for select T1 to T3 lesions. Patients who undergo this procedure must have bilateral vocal cord mobility, without anterior commissure or thyroid cartilage involvement. As aspiration is the main comorbidity of removal of the supraglottis, young, motivated patients with good pulmonary function fare best with this operation. The time-tested treatment for T4 carcinomas of the supraglottis is a total laryngectomy with postoperative radiation. With all lesions of the supraglottis, definitive radiation therapy with surgery reserved for salvage is always an option.

True subglottic lesions are unusual: one focused report found that, in 2180 laryngeal cancers, 1.6% occurred below the vocal cords.⁸ Patients usually present with symptoms of airway obstruction and do not respond to standard treatments for asthma and chronic obstructive pulmonary disease. Lesions begin at below the conus elasticus, which is 1 cm below the true edge of the vocal fold, and can invade surrounding cricoid and thyroid cartilages. Definitive treatment is total laryngectomy as these lesions usually involve the laryngeal framework of the larynx. The paratracheal nodes should also be removed at the time of surgery as they are commonly involved.

UPDATE ON CHEMOTHERAPY AND RADIATION THERAPY

The treatment of head and neck squamous cell carcinoma is a field that has undergone significant changes over the past 50 years. One such dramatic change is the role of radiation therapy and chemotherapy in the treatment of head and neck cancer. Historically, the standard treatment of head and neck cancer was surgery and/or primary radiation therapy with surgical salvage for failure. Although extirpative procedures such as total laryngectomy and total glossectomy offer a chance for cure

from head and neck cancer, they obviously offer little in the way of organ preservation. Beginning in the 1980s, advances in chemotherapy and concurrent delivery with radiation offered new options to standard surgical therapy.

In 1991, the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group reported the first landmark study comparing patients treated with chemotherapy and radiation against those treated surgically with postoperative radiation therapy.⁹ This phase III, multicenter trial examined patients with resectable stage III or IV squamous cell carcinoma of the larynx. These patients were randomized into two treatment arms. The experimental arm consisted of patients who received three cycles of induction cisplatin and 5-fluorouracil (5-FU) followed by radiation; the control arm consisted of patients who underwent surgical resection followed by radiation therapy. The experimental patients underwent two rounds of chemotherapy, followed by an assessment of tumor response. Those who responded to the first two cycles went on to receive a third cycle of cisplatin and 5-FU followed by radiotherapy to a dose of 66 to 76 Gy. Those who did not respond underwent total laryngectomy followed by postoperative radiation. The control group underwent total laryngectomy followed by postoperative radiation therapy. A total of 332 patients enrolled, and 64% of patients in the experimental arm ultimately were able to retain their larynges. There was no statistical significance between the two arms in 2-year survival at the median follow-up of 33 months. Those who underwent induction chemotherapy followed by radiation reported better communication scores. The conclusion of this study was that chemotherapy plus definitive radiation therapy was "effective in preserving the larynx." One comparison that was not made in the study, however, was the use of chemotherapy with radiation versus radiation therapy alone, leaving the exact role of chemotherapy for this disease unexplained. Most importantly, this study opened the door to a new era of organ-preservation treatment modalities. Finally, inadequate evaluation was made of patients who failed chemotherapy and radiation who then required extirpation and reconstruction. Surgical intervention in this group is typically plagued with high morbidity because of the chemoradiated field that a surgeon will have to operate on, which are typically tissues that exhibit properties far worse than those of tissues treated with radiation alone.

The next seminal study of organ preservation was reported in 1996 by the European Organization for Research and Treatment of Cancer (EORTC).¹⁰ This study enrolled patients with T2 to T4 squamous cell carcinoma of the piriform sinus and aryepiglottic folds, with N0 to N2b nodal status. Patient controls underwent surgery followed by radiation therapy, whereas experimental arm patients underwent induction chemotherapy followed by radiation therapy. Similar to the VA

study, the chemotherapeutic agents used were cisplatin and 5-FU, given in three cycles. In contrast with the VA study, patients were evaluated for tumor response after each cycle of chemotherapy administration, and those with no response or progressive disease at each evaluation underwent surgical resection. Those with a complete response went on to radiation therapy. Of the 194 patients enrolled, 52 patients underwent full induction chemotherapy followed by radiation, and 64% of these patients reported a functional larynx at 3 years (identical to the VA study). Five-year survival rates were not statistically significant between the two groups: 30% in the induction chemotherapy arm and 35% in the surgery arm. Despite this lack of statistical difference, the EORTC "accepted the use of induction chemotherapy followed by radiation as the new standard treatment" against which future treatments would be compared.

From these initial studies, the concept of organ preservation using chemotherapy together with radiation therapy was definitively established. However, the exact contribution of chemotherapy to radiation treatment had yet to be determined. Therefore, the Radiation Therapy Oncology Group (RTOG) conducted a three-arm randomized trial, RTOG 91-11, to better delineate the role of chemotherapy and to discover the optimal timing of the different therapeutic options. Briefly, this three-arm trial randomized 547 patients with stage III and IV squamous cell carcinoma of the glottis and supraglottic larynx into three treatment groups: induction chemotherapy followed by definitive radiation therapy, concurrent chemoradiation, and radiation therapy alone. Chemotherapeutic agents used were cisplatin and 5-FU, identical to the VA laryngeal cancer study, and the radiation dose was 70 Gy, delivered in 35 fractions. Salvage laryngectomy was performed in those patients who did not respond to their assigned treatment protocol, followed by radiation therapy. Among the three arms, salvage laryngectomy was performed in 28% of patients receiving induction chemotherapy, 16% receiving concurrent chemoradiation, and 31% of patients receiving radiation therapy alone. Results also showed that the rate of organ preservation in those receiving concurrent chemoradiation was significantly higher (84%) than that in those receiving induction chemotherapy or radiation therapy alone. Survival at 2 and 5 years was not statistically significant among the three arms; however, local and regional metastases were better controlled in the concurrent chemotherapy arm, and a lower rate of distant metastasis was shown in those patients receiving chemotherapy. It should also be added that the toxicity was worse in the concurrent chemotherapy arm, with 77% of patients experiencing a grade 3 or higher mucositis.

Since these studies were published, many others have shown the benefit of concurrent chemoradiation as an organ-preserving alternative to extirpative

surgery. Clinical trials are being designed or are in progress that investigate the role of newer chemotherapeutic agents, with general overall goals of either reducing toxicity or improving survival. One such trial, RTOG 0234, found that postoperative chemoradiation with cetuximab (a chimeric monoclonal antibody epidermal growth factor inhibitor) increased disease-free survival rates in patients with high-risk head and neck cancer.¹¹ This has been the only trial of chemoradiation with cetuximab targeting the epidermal growth factor receptor in both arms in the postoperative setting with patients who had positive resection margins and/or two or more nodal metastases and/or extracapsular spread.

Needless to say, treatment options must be individualized for each patient, and there are cases in which primary concurrent chemoradiation is not considered to be the treatment of choice. Such cases include tumor involvement of bone and large lesions with extensive cartilage destruction, which are better cleared by surgical resection rather than chemoradiation therapy. The one subsite of the head and neck in which surgery still tends to be the first-line treatment choice is the oral cavity. Even in the oral cavity, however, postoperative radiation therapy is indicated for most advanced-stage lesions. The future of organ-preserving modalities is very promising, as cetuximab and newer agents gefitinib and erlotinib are added to the treatment protocols. Of course, the goal of all clinical trials is to improve the quality of life and overall survival of patients.

CONCLUSION

The treatment of head and neck cancer patients requires the multidisciplinary involvement of the head and neck surgeon, the reconstructive surgeon, radiation and medical oncologists, and a variety of others including radiologists, pathologists, nurses, dietitians, dentists, speech and swallowing therapists, and social workers. The role of each of these specialties is being redefined as new advances in treatment are made. Even with the strides made over the past two decades with chemotherapy and radiation, surgical treatment of head and neck cancer and reconstruction thereof will be an important treatment option, either for primary or salvage therapy, for the foreseeable future. Therefore, the relationship between the extirpative surgeon and the reconstructive surgeon is vital, and a clear understanding of the biology and behavior of head and neck malignancy is crucial to successful patient outcomes.

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