

Review Article

Laryngeal Cancer Update: A Review

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Submitted: 22 June 2017

Accepted: 10 August 2017

Published: 12 August 2017

ISSN: 2379-948X

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Abstract

Laryngeal cancer is the second most frequent tumor of the upper aerodigestive tract. The most common type is squamous cell carcinoma, accounting for 85-95% of neoplasms. The most important risk factors are alcohol and tobacco consumption. The diagnosis is made by histopathology; however a complete medical history and physical examination should be performed. The direct visualization by direct or indirect laryngoscopy, or videostroboscopy are fundamental in the diagnosis process. The mass should be evaluated completely by extension imaging studies such as a computed tomography or nuclear magnetic resonance. Staging of the patient is vital for the correct treatment approach.

Keywords

- Laryngeal carcinoma
- Squamous cell carcinoma
- Supraglottis
- Glottis
- Sub glottis

INTRODUCTION

Laryngeal cancer is the second most common neoplasm of the upper aerodigestive tract after oral cavity carcinoma. There are approximately 110,000 to 130,000 new cases diagnosed annually in the world [1]. Most of these tumors are squamous cell carcinomas, accounting from 85 to 95% of all neoplasms of the larynx [2]. There are multiple treatment modalities and for this to be successful, it must be appropriately selected by personalizing the patient's approach. It is based primarily on the clinical stage of the patient, their desires, the patient's medical conditions and the prognosis of survival. The present paper is based on the squamous cell carcinoma of the larynx because it is the most common variety of these tumors.

Laryngeal sub-sites

Supraglottis: It consists of the epiglottis (lingual and laryngeal surface), aryepiglottic folds (laryngeal surface only), arytenoids, and ventricular bands (false vocal cords). The lower limit of the supraglottis is a horizontal plane passing through the lateral margin of the ventricle and its union with the upper surface of the true vocal cord.

Glottis: The glottis is composed of the true vocal cords (upper and lower surface) in addition to anterior and posterior commissures. The upper limit of the glottis is marked by a line drawn through the larynx ventricle to its lower limit which is a horizontal plane 1 cm below the upper limit of the glottis.

Sub glottis: It does not present any division in sub-sites. It extends from the lower border of the glottis to the lower border of the cricoid cartilage.

Risk factors

Alcohol and tobacco are the two main risk factors for laryngeal cancer. The risk is proportional to the intensity and duration of consumption and the risk decreases after cessation of intake.

There is insufficient evidence to support the causal role of laryngopharyngeal reflux and laryngeal cancer, mainly due to confusion of the tobacco and alcohol effects and inaccuracies in the diagnosis of reflux [3].

An increased intake of fruits and vegetables is associated with a lower risk of head and neck cancer in all subtypes, which means that this could be a protective factor for laryngeal cancer [4].

The influence of human papilloma virus on laryngeal cancer has also been associated, most frequently with subtypes 16 and 18. It has been detected in 21% of advanced laryngeal cancers, most commonly detected in women compared to men [5].

Diagnosis

An accurate diagnosis is based on a complete medical history and an adequate physical examination. Risk factors such as tobacco and alcohol, use of medications, and diseases that may affect the patient's choice of treatment should be questioned.

The presentation of laryngeal cancer is highly variable and depends on the location and size of the tumor. Tumors of glottis, typically presents in hoarseness early stages. Supraglottic tumors are more common with late symptoms of pain, hoarseness or difficulty swallowing [6].

Direct visualization of the larynx should be performed to identify the lesions through indirect laryngoscopy, flexible laryngoscopy with fiber optics or stroboscopy.

The sensitivity and specificity of videostroboscopy in predicting the invasive nature of lesions based on absence or mucosal reduction was 96.8% and 92.8%, respectively [7].

It is extremely important to perform biopsy of the primary site or by fine needle aspiration of the affected lymph node if possible.

It is recommended to perform imaging studies that support staging, such as computed axial tomography, which is a very useful resource for assessing affection of bone structures. Positron emission tomography combined with computed tomography are useful in evaluating recurrences and can identify areas of local and nodular recurrence and distant metastases [8]. Computerized axial tomography sensitivity was 60% and specificity was 85.7% and the nuclear magnetic resonance showed 80% sensitivity and 92.9% specificity [9]. Nuclear magnetic resonance surpasses the computerized axial tomography in the detection when cartilaginous and soft tissues are affected.

In a meta-analysis performed in 2017 by De Vito and colleagues where the identification of laryngeal cancer and its precursor lesions was studied, the NBI (narrow band image) showed a high sensitivity of 97% (CI, 84.2 % -99.9%), specificity of 92.5% (CI, 79.6% -98.4%) [10].

Staging

For the staging of malignant tumors, the AJCC and the International Union against Cancer use the TNM classification system. The TNM system takes into account the extent of the tumor, the presence of metastases to cervical lymphadenopathy and the absence or presence of distant metastases, as shown in (Table 1, 2).

Treatment

The goals in the treatment of laryngeal cancer are:

1. Healing the patient
2. Preserving the function of the larynx
3. Minimize treatment morbidity

Patient selection:

Patient factors: The predictive factors of a good treatment outcome are non-smokers, who have stopped smoking habit, with good general condition, minimal comorbidities, a good psychological state, adequate family support, those married and with religious or spiritual beliefs [11].

Tumor factors: Patients who present better treatment results are those with localized tumors, who are in the early stages of the disease, without metastatic disease in the neck, without nodular extracapsular dissemination, with no recurrence in more than 12 months after termination of the treatment.

Stage 1:

3.5.2.1. Supraglottis: Standard treatment options are radiation therapy or any surgical treatment options such as supraglottic laryngectomy or transoral surgery. The use of radiotherapy has been studied with a local control of up to 70 ± 10.07% and a survival rate of 63% in 5 years for T2 lesions.

Table 1: American Joint Committee of Cancer (AJCC) TNM Staging System for the Larynx. Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone and cartilage are not included. Classification of Laryngeal Carcinoma:

| Clinical Stage | |
|----------------|--|
| Primary Tumor | |
| TX | The primary tumor cannot be assessed. |
| T0 | No evidence of a primary tumor. |
| Tis | Carcinoma <i>in situ</i> . |
| Supraglottis | |
| T1 | Tumor limited to one subsite of supraglottis with normal vocal cord mobility |
| T2 | The tumor invades the mucosa of more than one adjacent subsite of the supraglottis or glottis, or a region outside the supraglottis (eg, the mucosa of the base of the tongue, the vallecula, the medial wall of the piriform sinus) without fixation of the larynx. |
| T3 | The tumor is confined in the larynx, with fixation of a vocal cord or invades any of the following sites: postcricoid area, preepiglottic space, paraglottic space or internal cortex of the thyroid cartilage |
| T4a | Moderately advanced local disease. The tumor spreads through the thyroid cartilage or invades tissues beyond the larynx (eg, the trachea, soft tissues of the neck, including the extrinsic deep muscle of the tongue, spindle muscles, thyroid, or esophagus). |
| T4b | Very advanced local disease. The tumor invades the prevertebral space, wraps the carotid artery or invades the mediastinal structures. |
| Glottis | |
| T1 | The tumor is confined to the vocal cord (s) (may involve anterior or posterior commissure), with normal mobility. |
| T1a | The tumor is confined to a vocal cord. |
| T1b | The tumor involves both vocal cords. |
| T2 | The tumor has spread to supraglottis or subglottis, or there is deterioration of the mobility of a vocal cord. |
| T3 | The tumor is confined to the larynx, with fixation of a vocal cord, or invasion of the paraglottic space or the internal cortex of the thyroid cartilage. |
| T4a | Moderately advanced local disease. The tumor spreads through the outer cortex of the thyroid cartilage or invades the tissues beyond the larynx (eg, the trachea, soft tissues of the neck, including the deep extrinsic muscle of the tongue, spindle muscles, thyroid or the esophagus). |
| T4b | Very advanced local disease. The tumor invades the prevertebral space, wraps the carotid artery or invades the mediastinal structures. |
| Subglottis | |
| T1 | The tumor is confined in the subglottis |
| T2 | The tumor spreads to the vocal cord (s) with normal or impaired mobility. |
| T3 | The tumor is confined to the larynx, with fixation of a vocal cord. |
| T4a | Moderately advanced local disease. The tumor invades the cricoid or thyroid cartilage, or invades the tissues beyond the larynx (eg, the trachea, soft tissues of the neck, including the extrinsic deep muscle of the tongue, spindle muscles, thyroid, or esophagus) |
| T4b | Very advanced local disease. The tumor invades the prevertebral space, wraps the carotid artery or invades the mediastinal structures. |

| Regional lymphnodes | |
|------------------------|--|
| NX | Regional lymph nodes cannot be assessed. |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension. |
| N2 | Metastasis in a single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, no more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, no more than 6 cm in greatest dimension. |
| N2a | Metastasis in a single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension. |
| N2b | Metastasis in multiple ipsilateral lymph nodes, no more than 6 cm in greatest dimension. |
| N2c | Metastasis in bilateral or contralateral lymph nodes, no more than 6 cm in greatest dimension. |
| N3 | Metastasis in a lymph node, more than 6 cm in greatest dimension. |
| Distant metastasis (M) | |
| M0 | No distant metastasis. |
| M1 | Distant metastasis. |

| Table 2: Classification of Metastases. | | | |
|--|-------|-------|----|
| Anatomic Space | | | |
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T3 | N0 | M0 |
| | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage IVA | T4a | N0 | Mx |
| | T4a | N1 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N2 | M0 |
| | T4a | N2 | M0 |
| Stage IVB | T4b | Any N | M0 |
| | Any T | N3 | M0 |
| Stage IVC | Any T | Any N | M1 |

Endolaryngeal surgery for T1 and T2 lesions has excellent local control, even better than radiotherapy alone [12].

Glottis: In a study by Chung et al., it was found that radiotherapy has a 3-year local control of 91.9% and a 5-year local control of 89.9% compared to 82.8% and 73.2% control in the cordectomy group. [13] The healing opportunities are extremely good with any of the following options: radiotherapy, transoral laser microsurgery and open partial laryngeal surgery. A systematic review has found insufficient evidence to determine which of these options is most effective in early carcinoma [6].

Surgical treatment of early glottic SCC also aims to preserve the larynx and is referred to as conservation laryngeal surgery or partial laryngectomy. Traditionally, these limited laryngeal resections were performed via an external approach:

Cordectomy and vertical hemilaryngectomy (VHL) are the two classic open procedures for the treatment of early glottic carcinoma. Cordectomy is the removal of the diseased true vocal cord via a laryngofissure. Vertical hemilaryngectomy removes the ipsilateral true and false vocal cords, extending laterally to the perichondrium of the thyroid cartilage.

Subglottis: Lesions can be successfully treated by radiotherapy alone with preservation of the normal voice. Surgery is reserved for cases of radiotherapy failure or for patients who cannot be easily assessed for radiation therapy.

Stage 2:

Supraglottis: Radiation therapy can be used as the only treatment option for small lesions. [14] Supraglottic laryngectomy or total laryngectomy with bilateral neck dissection may be performed depending on the location of the lesion, the clinical condition of the patient and the expertise of the surgical team. Careful selection should be made to ensure postoperative pulmonary and lingual functions. Radiotherapy is indicated for compromised or narrow surgical margins or other adverse pathological risk factors.

Glottis: In Stage I, radiation therapy can be considered as the only treatment. [15] In a study by Tateya et al., a 5-year survival rate of 93% and a laryngeal preservation rate of 90% was observed. [16] Partial hemilaryngectomy or total laryngectomy may be performed. In some circumstances, transoral laser microsurgery may be appropriate [17].

Subglottis: Lesions can be successfully treated by radiotherapy alone with preservation of a normal voice. Surgery is reserved for radiotherapy failure or for patients in whom follow-up is likely to be difficult.

Stage 3:

Supraglottis: Chemotherapy given in conjunction with radiation therapy may be an option to be taken into account in those patients who would require a total laryngectomy for control of the disease. Laryngectomy is reserved for patients with less than 50% response to chemotherapy or for those with persistent disease after radiation. Definitive radiotherapy alone with modified fractionation for patients who are not suitable for chemotherapy and surgery (total laryngectomy). Surgery may be performed with or without post-surgical radiotherapy [18].

Glottis: Chemotherapy given in combination with radiation therapy may be considered for the patients who need a total laryngectomy to control the disease. Induction chemotherapy followed by concurrent chemotherapy and radiation are indicated. Laryngectomy is reserved for patients with less than 50% response to chemotherapy or for those who have persistent disease after radiation. Definitive radiotherapy alone with modified fractionation is indicated in patients who are not able to receive simultaneous chemotherapy and surgery (total laryngectomy) for failures of radiation. Also, surgery with or without postoperative radiotherapy is a treatment option.

Subglottis: Among the treatment options, laryngectomy with isolated thyroidectomy and cervical dissection of tracheoesophageal ganglia followed by postoperative radiotherapy may be performed [19].

Radiation therapy alone is indicated for patients who are not eligible for surgery. Careful monitoring of patients should be done and rescue surgery must be performed in case of local or advanced recurrence. Definitive radiotherapy alone with modified fractionation is recommended in patients that are not suitable for simultaneous chemotherapy and surgery (total laryngectomy). In patients treated with induction chemotherapy followed by simultaneous chemotherapy and radiation, laryngectomy is indicated for patients with less than 50% response to chemotherapy or for those who present persistent disease after radiation [15].

Stage 4:

Supraglottis and glottis: Chemotherapy given together with radiotherapy may be considered for patients who require total laryngectomy to control the disease, including those with T4a disease without a large tumor mass. It is possible to select induction chemotherapy followed by concurrent chemotherapy and radiation. Laryngectomy is reserved for patients with less than 50% response to chemotherapy or for those who have persistent disease after radiation. Definitive radiotherapy alone is preferred in patients who are not eligible for simultaneous chemotherapy and surgery (total laryngectomy) to rescue radiation failures [20].

Subglottis: Total laryngectomy together with thyroidectomy and dissection of bilateral tracheoesophageal ganglia usually followed by postoperative radiotherapy are indicated. Radiation therapy alone is indicated for patients who are not eligible for surgery [15,18].

According to the pathological findings after primary surgery, postoperative radiotherapy or postoperative chemoradiotherapy is used as an adjuvant treatment when the following histological features are present:

1. T4 disease.
2. Perineural invasion.
3. Lymphovascular invasion.
4. Margins compromised or less than 5 mm.
5. Extracapsular extension in a lymph node.
6. Commitment of two or more lymph nodes.

Follow-up

The follow-up should include a complete physical examination that evaluates the head and neck with direct visualization of the larynx. In the first year the revisions must be every month to 3 months, in the second every 2 to 6 months and between the 3rd and 5th year the follow-up should be every 4 to 8 months. After five years, the patient should be checked every year.

Post treatment baseline imagin is recommended within 6 months of treatment. Further reimagin as indicated based on signs and symptoms; no routinely indicated in asymptomatic patients [21].

DISCUSSION & CONCLUSION

For a successful treatment it is very important to take into

account all factors of the patient and tumor. As previously mentioned, the general conditions of the patient, their family support, clinical staging of the disease and even socioeconomic status are determining factors for the evolution of laryngeal cancer.

A close follow-up during and after treatment with periodic visits to the consultation, complete laryngeal exploration with studies such as flexible laryngoscopy and NBI are very useful in determining relapses.

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Cite this article

Cavazos LC, Soto-Galindo GA, Treviño González JL (2017) Laryngeal Cancer Update: A Review. *Ann Otolaryngol Rhinol* 4(6): 1184.