



UNIVERSITÀ DEGLI STUDI DELL'AQUILA
DIPARTIMENTO DI SCIENZE CLINICHE APPLICATE E BIOTECNOLOGIE

Dottorato di Ricerca in Medicina Sperimentale
Curriculum Scienze cliniche, mediche e chirurgiche
XXXVIII ciclo

Titolo della tesi
TRANSORAL LASER SURGERY (TML) VERSUS RADIOTHERAPY (RT) IN
EARLY GLOTTIC CARCINOMA

SSD MEDS-06/A

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a.a. 2024/2025

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INTRODUCTION

Laryngeal carcinoma is the 11th commonest form of cancer in men world-wide.¹ It is one of the most common malignancies in Europe, with about 52.000 new cases per year²; approximately 9.500–11.000 new cases of laryngeal cancer are estimated to occur yearly in the United States.^{3,4}

The yearly incidence rate for men in southern and northern Europe is between 18 per 100.000 and 6 per 100.000, respectively. For women, incidence rate is not higher than 1.5 per 100.000 per year.²

Laryngeal carcinoma is the most frequent cancer of the upper aero-digestive tract (28%), accounting for 2.5% of all malignancies in men and 0.5% in women. It is prevalent in males than females, in Italy the male: female ratio is 10 to 1 and the age of incidence is between 50 and 60 years.

The most frequent head and neck cancers sites are the larynx, the pharynx, and the oral cavity.⁵

In 56–75 % the disease is diagnosed in an early stage (T1 and T2), most frequently arising from the glottis ⁶.

Significant variations in the distribution of carcinoma at different sites within the larynx have been observed.

In southern Europe, supraglottic carcinoma is more common than glottic carcinoma, whereas the reverse is true for north-western Europe.⁷ Carcinomas of the glottis are predominant in Anglo-Saxon populations; in the Black populations of the United States, the number of glottic and supraglottic tumours are approximately equal.⁸ The most important functions of the larynx are to provide airway patency, protect the tracheo-bronchial tree from aspiration, and allow phonation. Tumours that involve the larynx may impair these function in a variable degree depending on location, size and depth of invasion.

The presence of hoarseness, sore throat, shortness of breath, dysphagia or “lump in throat” sensation are all symptoms observed in early or moderately advanced stages of laryngeal cancers.⁷

Glottic cancers are usually detected because of hoarseness occurrence, airway obstruction occurs later in disease progression. Cancers arising in the subglottic area are rare and present with airway obstruction or vocal fold immobility.

It is recommended that patients with hoarseness persisting longer than three weeks or with persisting sore throat, dysphagia, odynophagia lasting for more than six weeks are referred from a general practitioner to an otolaryngologist.⁹

More than 95% of all laryngeal malignancies are squamous cell carcinomas (SCC).^{10,11}

Less common phenotypic expressions of this malignancy can occur.

Tobacco is the predominant risk factor in laryngeal carcinogenesis.

Alcohol is generally regarded as the second major risk factor. In most series, >95% of patients with SCC of the larynx have a background of tobacco and/or alcohol consumption prior to tumour diagnosis. The appearance of laryngeal cancer has been related to other factors, such as environmental exposure, gastroesophageal and biliary reflux, viral infection (oncogenic types of human papilloma virus), dietary factors, radiation and individual predisposition.

When it rarely occurs in childhood and adolescence, laryngeal carcinoma seems to be a genetic disease associated with specific chromosomal damage.¹²

The staging for laryngeal cancers is based on laryngeal subsites invasion, vocal cord mobility, and neck involvement.

The staging system estimates the extent of disease before (cTNM) and after treatment (pTNM).¹³

Although early stage glottic carcinoma (T1–T2) is accepted to have a low incidence of lymph node metastasis (0–10%), the reported incidence with more advanced stage disease (T3–T4), varies between 10% and 35%.¹⁴

The overall prevalence of lymph node metastases in laryngeal cancers proportionally increased with T category from 10% in pT1, 29% in pT2, 38% in pT3 to 57% in pT4.¹⁵

The subdivision of the larynx into supraglottic region, glottic region and subglottic region is not only important for descriptive reasons but has clinical implications which affect both prognosis and therapeutic strategy. The supraglottic structures have a rich lymphatic network and drain in levels II, III and IV while the lymphatic network is less developed in the subglottic region and the drainage is predominantly towards lymph nodes III and IV and towards the tracheal lymph nodes. The glottic is devoid of lymphatic capillaries, so that metastatic lymph nodes spread of glottic tumors occurs only in the case of supra or subglottic extension.

Status T and N proved to be the most relevant prognostic factors. Other prognostic factors are sex, age, patient performance status and disease sub-site. The survival of patients with glottic tumor varies from 75% to 95% depending on the site, size, degree of infiltration, " involvement of commissures and paraglottic spaces.¹⁶ Tis, T1, T2 laryngeal carcinomas have an 80–90% probability of cure, whereas for more advanced tumours this is approximately 60%.

Treatment indications in cancer of the larynx are often controversial, since there are few comparative studies of the different available therapeutic approaches.^{7,17} Early glottic carcinomas can be treated using transoral laser surgery (TLM), radiotherapy (RT), or open partial horizontal laryngectomy (OPHL).¹⁸

The choice of treatment should be based on the cure rate, larynx preservation rate, functional preservation and the total expenses¹⁹.

TLM and RT have undergone significant advancement in the past few years leading to a decrease in open procedures.

Since the survival rates are almost equivalent (87–98 %)²⁰, treatment modality is usually decided on the basis of post-treatment voice quality, treatment duration, cost, patient's general medical condition, and patient's preference for surgery or radiation.²¹

As a general rule, early stage laryngeal tumours should be approached by a single modality of treatment.^{23, 24}

RT offers good control rates, but the prolonged time of the treatment (6–7 weeks), mucosal radiation damage, and long-term side effects such as xerostomia are deterrents for selecting RT as the treatment of choice and it's reserved for further treatments²⁵.

TLM provides an excellent alternative to the others in the treatment of early stage glottic cancer.^{26–29}

Since its introduction by Strong and Jako in 1972³⁰, it has found wide acceptance in the treatment of laryngeal diseases.

This technique offers intra- and post-operative advantages: reduced traumatism, lack of tracheostomy, low bleeding, fast functional recovery (deglutition and speech), brief hospital stay, and low management costs³¹.

Another advantage of TLM is that it can be easily repeated in case of histologically proven close or positive resection margins; indeed re-resections can be applied several times until tumor-free margins are obtained³².

At the same time, the respect of the European Laryngological Society (ELS) classification allows to perform excisions that achieve a complete removal of the tumor and good functional outcomes too.^{33, 34}

A lot of published studies have demonstrated the effectiveness of TLM for Tis, T1 and selected T2 glottic cancer^{35–38}.

The success of this kind of surgery depends anyway on two important factors:

- Meticulous pre-operative endoscopic evaluation with the use of innovative diagnostic methods;
- Surgical planning based on the ELS guidelines^{33, 34}.

The principal aim of any type of treatment is oncological radicality preserving organ functionality.

Our study is a retrospective one and it is the only one in the literature that evaluate oncological and functional outcomes for T1 and T2 glottic carcinomas.

The sample of this study is composed of twenty (20) patients affected by early stage glottic cancer: in the first group there are 10 subjects from Otorhinolaryngology Department, 1 woman and 9 men and in the second one from Radiation Oncology Department are 10 people, 1 female and 9 males.

The 4-years overall survival (OS) and disease-free survival (DFS) are respectively in the first group 88% and 90 % and in the second group are 78% and 71%, but this difference of OS and DFS between the two groups is not statistically significant (p= 0.50 and p= 0.59 respectively).

Our study was only based on subjective patient evaluation because in our opinion the patients' own evaluation takes into account their expectations as to the results of treatment, with possibly a more favorable outlook on functional outcomes like voice and swallowing.

Considering the two groups both had moderate dysphonia.

We noted a significant lower subjective perception of disability related to voice disfunction among patients over 70 years old (Mann- Whitney U test, $p= 0.03$).

For the majority of patients life remained unchanged, but the subjects with bigger negative impact of their voice had a tendency to be younger.

We achieved a good satisfactory degree of laryngeal functionality, without statistically significant difference for TLM or RT and none of patients of the sample reported swallowing disorders.

ANATOMY OF LARYNX

The larynx is located in the anterior third of the neck and is linked to the bone hyoid and mandible by means of the digastric, stylohyoid, geniohyoid and mylohyoid muscles. Below, it is connected to the trachea.

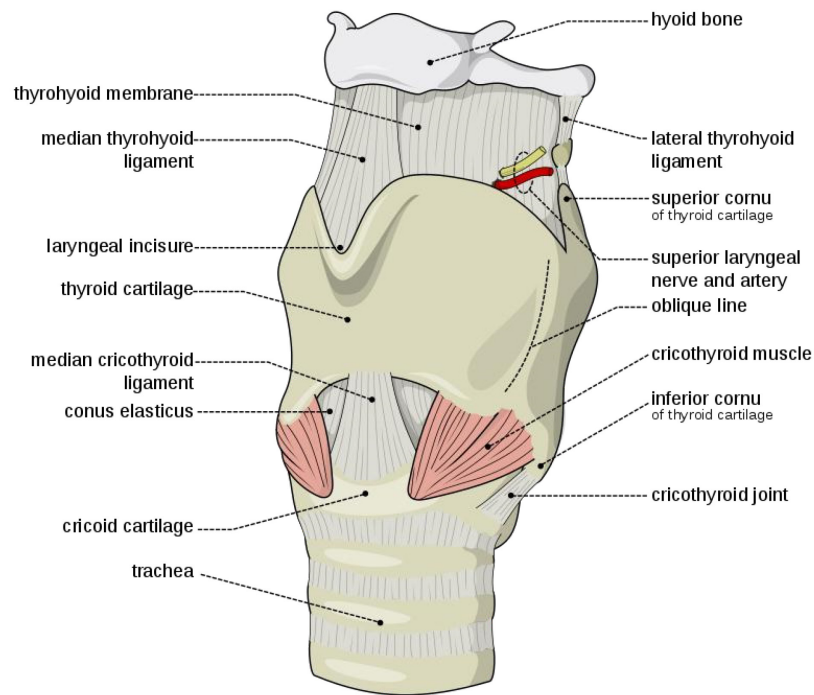


Figure 1 The larynx

The larynx varies its position in the neck depending on the age of the subject. In the sagittal section, in childhood, it is located at the level of the third-fourth cervical vertebra, and then progressively descends around 2 years of age and reach the level of the sixth-seventh cervical vertebra in age adult ^{39,40}.

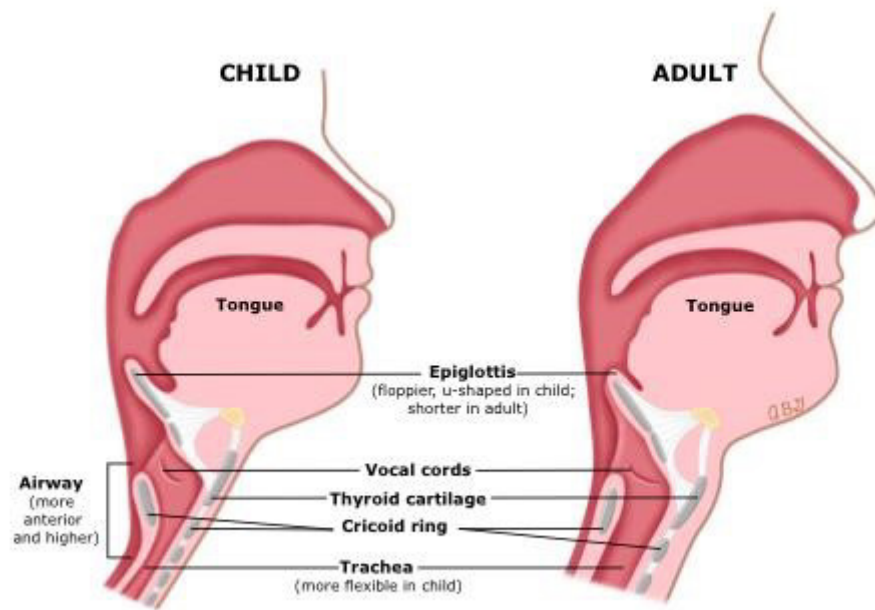


Figure 2 Comparison between a larynx of a child and a adult larynx

The descent of the larynx continues in the elderly patient, resulting in an elongation of the vocal tract (6-8 mm in the infant, 12-17 mm in the female adult, 17-23 mm in the male adult), with a consequent progressive reduction of the vocal pitch.⁴¹ The number of tracheal rings in the cervical position, to which it is connected, decreases proportionally with the age of the patient (approximately eight in the young adult patient, six in the elderly patient). For the fewer cervical tracheal rings available, surgical resections of the upper airways become progressively less simple to be performed in the older patient.

The larynx is divided into three regions: supraglottic, glottic and subglottic.

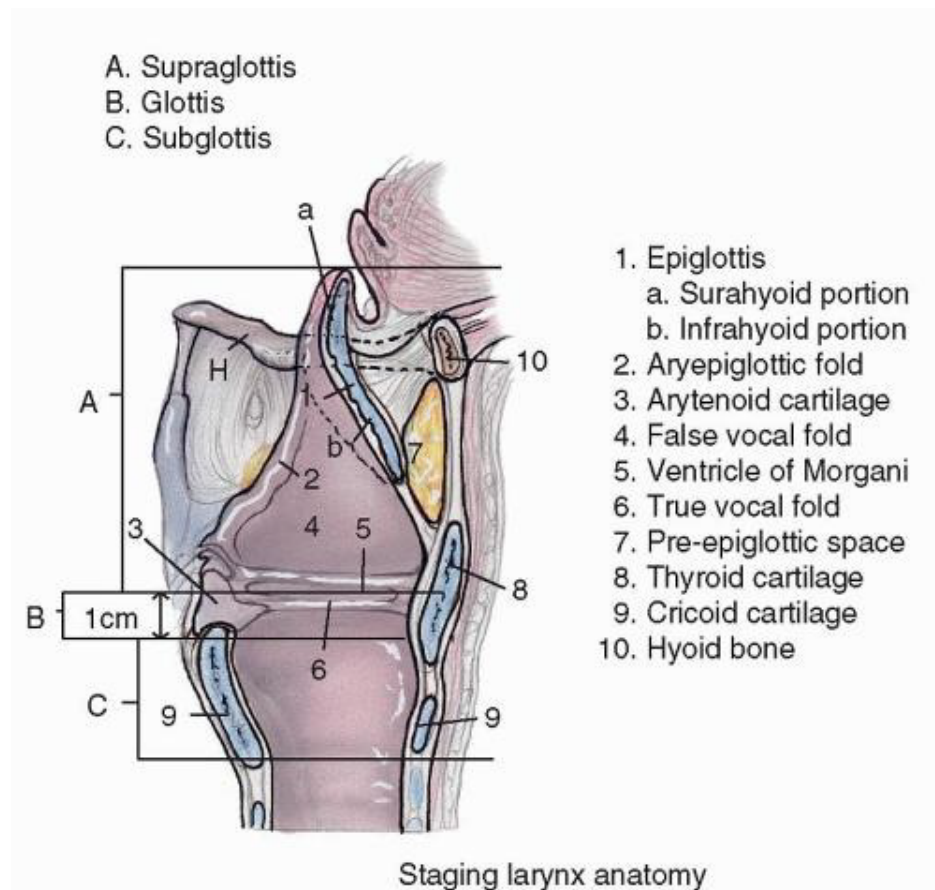


Figure 3 Subsites of larynx

The supraglottic region is divided into 5 segments: suprahoid epiglottis, infrahoid epiglottis, laryngeal face of the aryepiglottic folds, arytenoids and false cords. A horizontal plane extends from the lateral edge of the ventricle to mark the inferior surface of the supraglottic region.

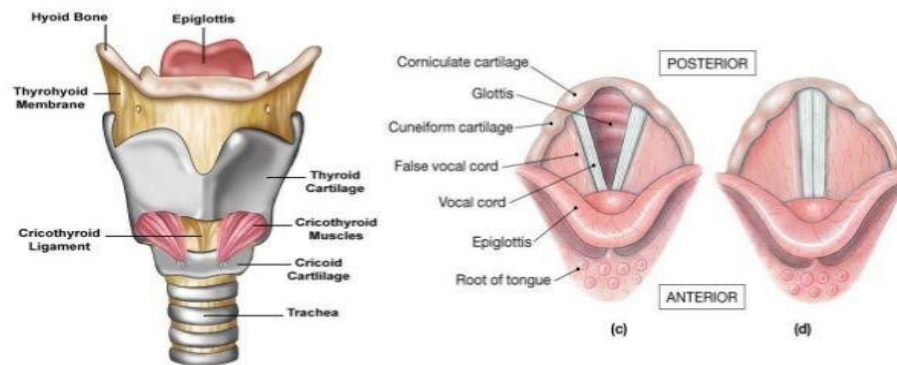
Below this plane, the glottic region is identified, made up of the true vocal cords and the space between them.

True vocal cords consist of epithelium, superficial lamina propria, vocal ligament (intermediate and deep lamina propria), vocal muscle.

The glottic plane extends anteriorly from the anterior commissure (AC), the junction of the vocal cords and vocal ligaments with the thyroid cartilage, until they reach posteriorly the vocal process of arytenoid cartilage.

Immediately below the inferior border the glottic region develops the hypoglottic region that extends to the lower edge of the cricoid cartilage.

STRUCTURE OF LARYNX



Figure

4: Structure of the larynx

The laryngeal structure is devoid of bone structures. Although it is connected to the hyoid bone that guarantees its stability, the latter does not belong to laryngeal structures.

It consists exclusively of hyaline and elastic cartilages. Three unpaired cartilages are recognized (epiglottis, thyroid, cricoid) and three paired cartilages (arytenoids, corniculate and cuneiform cartilage).

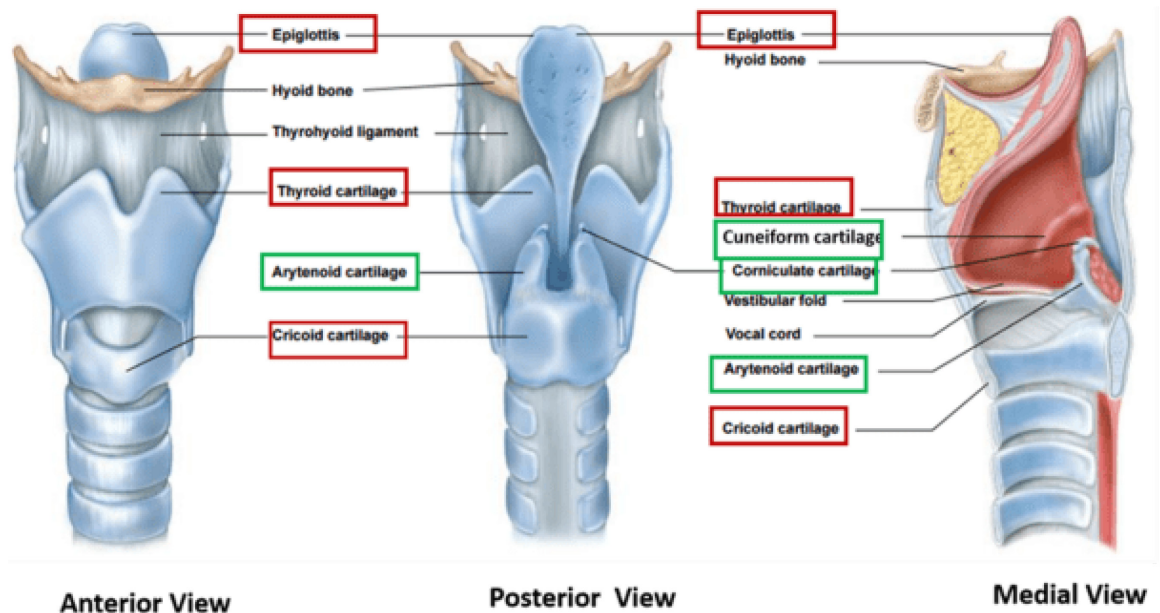


Figure 5: Different views of laryngeal cartilages

The epiglottis is the only one, among them, to be made up of elastic cartilage and does not undergo progressive ossification processes that instead affect the entire larynx

(except for the corniculate and cuneiform cartilages) and complete around 65 years of age, reducing the mobility of the laryngeal and tracheal tract during surgical treatment. It is attached by its stalk to the inner aspect of the angle formed by the laminae of the thyroid cartilage via the thyroepiglottic ligament in the midline. The epiglottis is also attached to the hyoid bone by the hyoepiglottic ligament which extends from the anterosuperior surface of the epiglottis to the body of the hyoid bone. The epiglottis projects superiorly into the pharynx, with its upper margin just behind the root of the tongue.

During swallowing, as the larynx moves up and forwards, the epiglottis swings downward to close off the laryngeal inlet, and thus prevents materials from entering the airway.

A thin layer of connective tissue, the quadrangular membrane extends between the lateral borders of the epiglottis and the anterolateral margins of the arytenoid cartilage. Its free lower edge is thickened and forms the vestibular ligament. This ligament is enclosed by a fold of mucous membrane to form the vestibular fold (false vocal cord) which extends from the thyroid cartilage to the arytenoid cartilage.

The cuneiform cartilages are the two small club-shaped cartilages that lie superior and anterior to the corniculate cartilages. They do not directly attach to any other laryngeal cartilage but are suspended within and strengthen a fibro-elastic membrane called the aryepiglottic membrane. This membrane forms the free superior edge of the quadrangular membrane, which as described earlier, connects the arytenoid cartilages to the lateral borders of the epiglottis. It is covered by mucosa to form the aryepiglottic fold. On the posterior aspect of the aryepiglottic folds both the corniculate and cuneiform cartilages are seen as small nodules surrounding the laryngeal inlet.

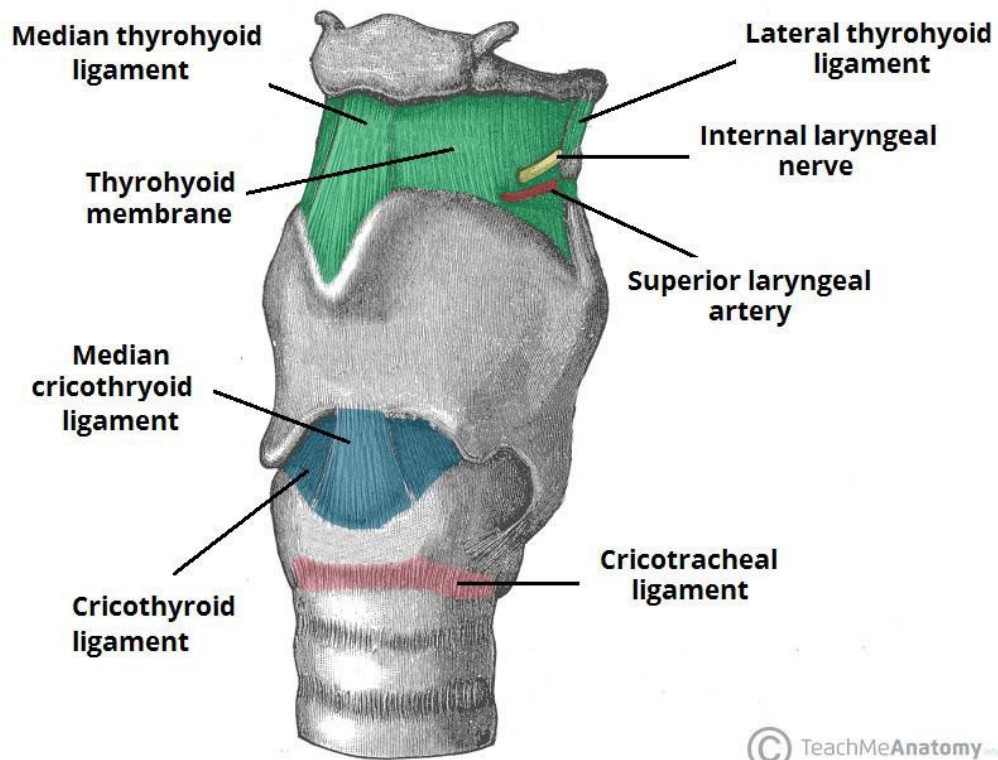


Figure 6: Laryngeal ligaments

Thyroid cartilage has two laminae that come together to join anteriorly at the laryngeal prominence, popularly known as the "Adam's apple". Posteriorly, the two laminae of the thyroid cartilage remain open. The posterior aspect of each thyroid cartilage lamina extends superiorly and inferiorly forming both the superior and inferior horns. The superior horn of the thyroid cartilage makes an attachment to the hyoid bone via the thyrohyoid membrane and the lateral thyrohyoid ligament. Within this thyrohyoid membrane lies a foramen in which both the superior laryngeal vessels and the internal branch of the superior laryngeal nerve reside. The lateral thyrohyoid ligament may contain triticeous cartilage that is often mistaken for a foreign body when it calcifies. The inferior horn attaches to the cricoid cartilage via the cricothyroid membrane.

The cricoid cartilage is the only full cartilage ring within the larynx. It is composed of hyaline cartilage and often referred to as having a "signet ring" appearance. The posterior aspect of the cricoid cartilage, known as the lamina, is much wider than the anterior portion of the cartilage, referred to as the arch of the cricoid. The wider posterior portion serves as a base for the arytenoid cartilages to articulate via a ball and socket joint. Each arytenoid cartilage has two important processes that extend from it: the first is the vocal process, responsible for serving as an attachment for the vocal ligament and the second process is the muscular process and serves as an attachment for intrinsic laryngeal muscles. These two processes, combined with the unique ball and socket articulation with the cricoid, allow the arytenoid to rotate within the facet causing adduction or abduction of the vocal ligament and vocal folds required for airway protection and phonation.

The laryngeal cavity is divided into three regions:

- Vestibule: between the laryngeal inlet and the vestibular folds
- Middle part: between the vestibular folds above and vocal folds below
- Infraglottic cavity: between the vocal fold and the trachea

Laryngeal cavity divisions

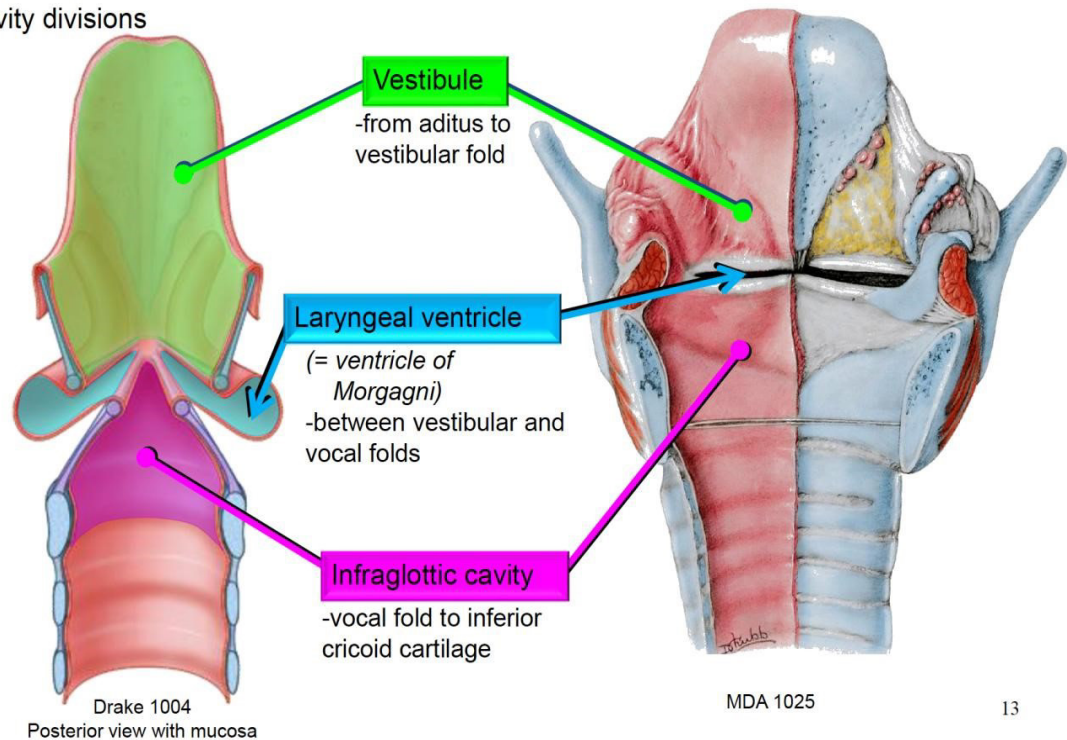


Figure 7: Laryngeal cavity

The lateral walls of the middle part of the laryngeal cavity bulge outward to form lateral recesses (laryngeal ventricle) between the vestibular fold and the vocal fold. Each ventricle has an elongated blind tubular extension, the laryngeal saccule, that projects anterosuperiorly between the vestibular fold and the thyroid cartilage. Each saccule is lined with mucus glands that produce mucus to lubricate the vocal folds.

The vocal apparatus of the larynx is called the glottis and consists of two vocal folds (true vocal cords) and the rima glottidis. Each mucous membrane-covered vocal fold contains a vocal ligament that extends from the inner surface of the thyroid cartilage to the vocal process of the corresponding arytenoid cartilage. Running parallel to each vocal ligament is the vocalis muscle which is responsible for adjusting the tension of the vocal folds. The vocal folds are the “true” structures that produce sound as air passes over them, whereas the vestibular folds (false vocal cords) have no role in sound production but protect the vocal cords.

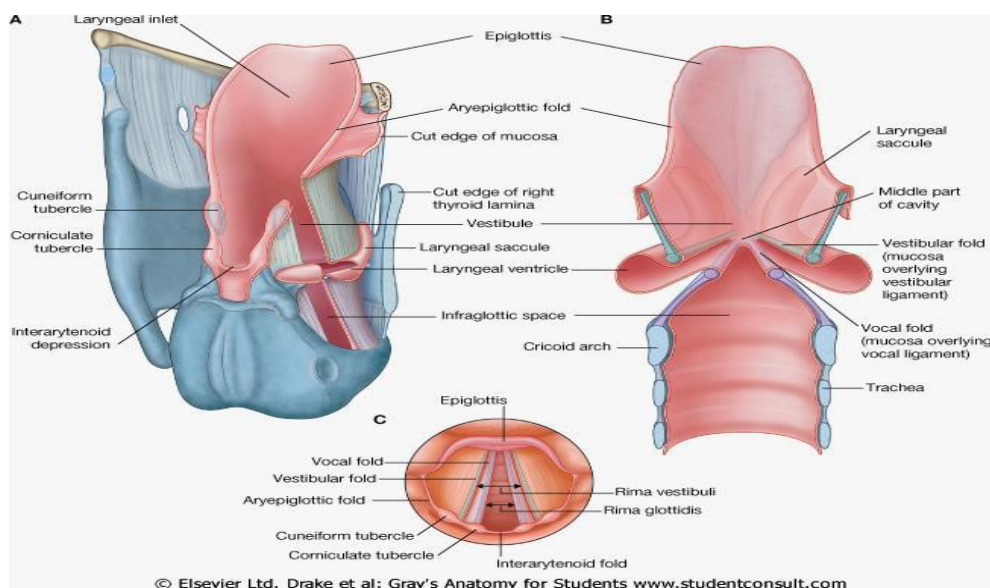


Figure 8: Vocal apparatus

The opening between the vocal cords is referred to as the rima glottidis. The shape of this opening depends on the position of the vocal folds. Rotational movements of the arytenoid cartilages at the cricoarytenoid joints can separate (abduct) the vocal folds, widening the rima glottidis or appose (adduct) the vocal folds and narrow the rima glottidis. Typically, during breathing, the vocal cords are abducted however, during swallowing, they are adducted to close the rima glottidis. The qualities of the sound produced depends on the length, tension, and position of the vocal folds. Normally, during phonation, the vocal cords are closely apposed resulting in a slit-like rima glottidis. As expired air passes over the cords, it causes them to vibrate, producing sound. The sound is then modified by tongue, jaw and lip movements into speech.

The vocal fold comprises five layers (deep to superficial layers): thyroarytenoid muscle, deep lamina propria, intermediate lamina propria, superficial lamina propria, and the squamous epithelium. The deep and intermediate lamina propria both are grouped to form the vocal ligament mentioned above. The superficial layer of the lamina propria provides a gelatinous surface upon which the vocal folds to vibrate.

The laryngeal ventricle is both an outpouching the laryngeal wall and potential space. It lies between the supraglottic and glottic larynx. It extends laterally as an outpouching that is known as the laryngeal saccule because of its ability to collapse upon itself. It is difficult to assess the laryngeal ventricle in its entirety when examining the patient via nasopharyngeal endoscopy; therefore, it must be in the mind of the clinician when ruling out cancer and to monitor the progression of malignancy.

Two structures within the larynx are important to prevent the spread of malignancy. The first is the quadrangular membrane. It houses the ventricular ligament. The other structure is the conus elasticus. This membrane spreads from the cricoid cartilage to the vocal ligament within the true vocal folds.

Intrinsic Laryngeal Muscles

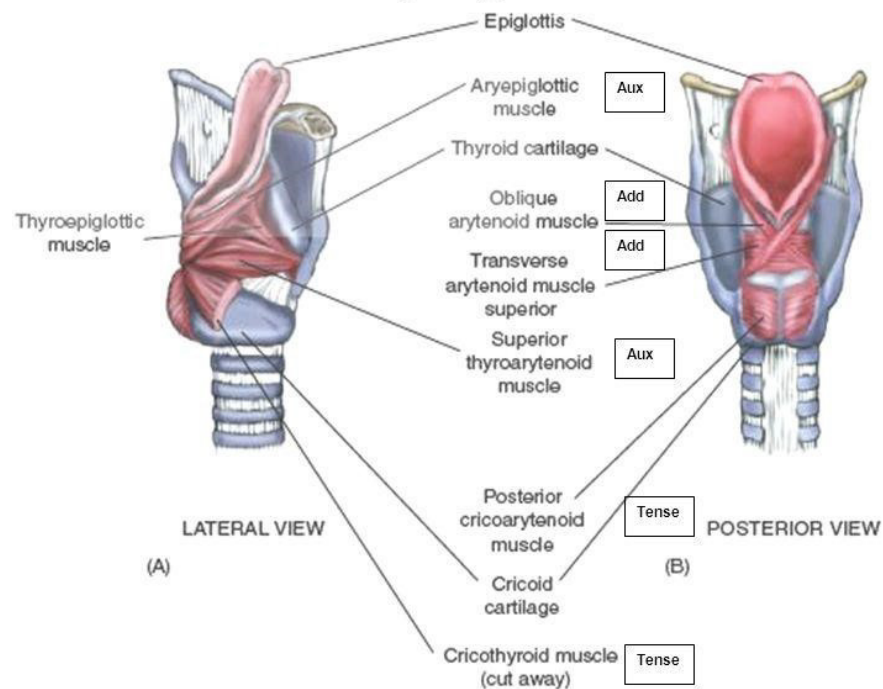


Figure 9: Intrinsic Laryngeal muscles (A) Lateral and (B) Posterior views

The larynx is also made up of six fibrous membranes and ligaments: aryepiglottic ligament, thyroid ligament, thyroid membrane, quadrangular membrane, elastic cone, cricothyroid membrane.

With the exception of the thyroepiglottic ligament, the laryngeal cartilages and the fibrous membranes constitute a natural barrier to the extension of a new pathology. The intrinsic laryngeal musculature is responsible for mechanisms of glottic opening, protection of the lower respiratory tract and production voice.

Abductor muscles: posterior cricoarytenoid.

Adductor muscles: lateral cricoarytenoid, interarytenoid.

Tensor muscles: cricothyroid, thyroarytenoid.

The function of each individual muscle varies slightly according to the position of the vocal cords.

The posterior cricoarytenoid muscle, traditionally identified as a single muscle, is actually, according to some authors ⁴², consisting of three muscular components (vertical, oblique and horizontal).

The vertical and oblique components are responsible for the abduction of vocal folds, while the horizontal component is responsible for the arytenoid stabilization in phonation. The action of the posterior cricoarytenoid muscle counteracts the tensor function of the thyroid muscle during phonation to stabilize arytenoid cartilage.

This type of interaction between agonist and antagonist muscles it is essential to balance laryngeal muscle function. Other small muscles, such as the thyroepiglottic and aryepiglottic muscles play minor roles: they improve the sphincter effect of the laryngeal vestibule by reducing ligament vocal, and produce a lowering of the vocal pitch.

The muscles in the supraglottic region consist of the extension of the intrinsic laryngeal muscles. The oblique arytenoid muscles originate from the posterior portion of the arytenoid muscular process and cross medially to insert at the apex of the contralateral arytenoid cartilage. Some of the fibers continue like aryepiglottic muscles, whose function is mainly to determine the narrowing of the laryngeal vestibule. Similarly, some fibers of the thyroarytenoid muscle extend into the lateral aspect of the aryepiglottic fold and epiglottis. These fibers constitute the thyroepiglottic muscle and are involved in the enlargement of the laryngeal vestibule. The extrinsic musculature supports the larynx in the movements of raising (by the suprahyoid muscles) and lowering (by the subhyoid muscles) which occur primarily during swallowing.

Suprahyoid muscles: digastric, stylohyoid, mylohyoid, geniohyoid and hioglossus. Subhyoid muscles: thyroid, sternothyroid, homohyoid, sternohyoid.

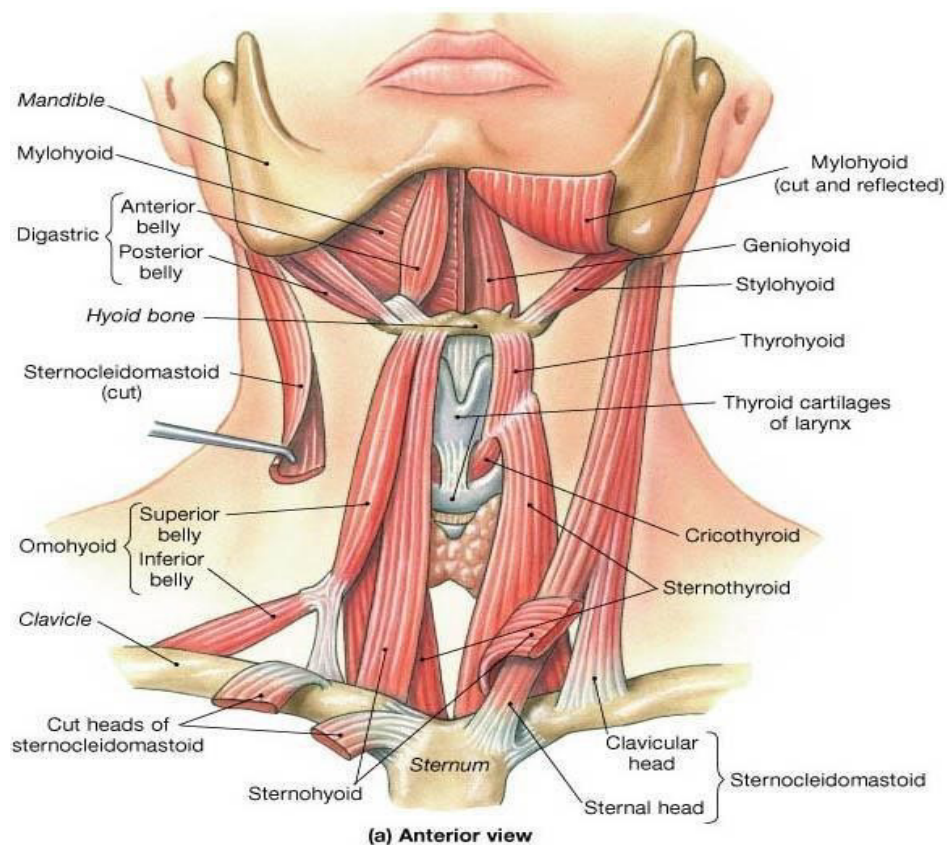


Figure 10: Extrinsic musculature of the larynx

The sensory and motor innervation of the larynx originates from the vagus nerve and from it originates the superior laryngeal nerve (SLN) and the inferior laryngeal nerve or recurrent (RLN).

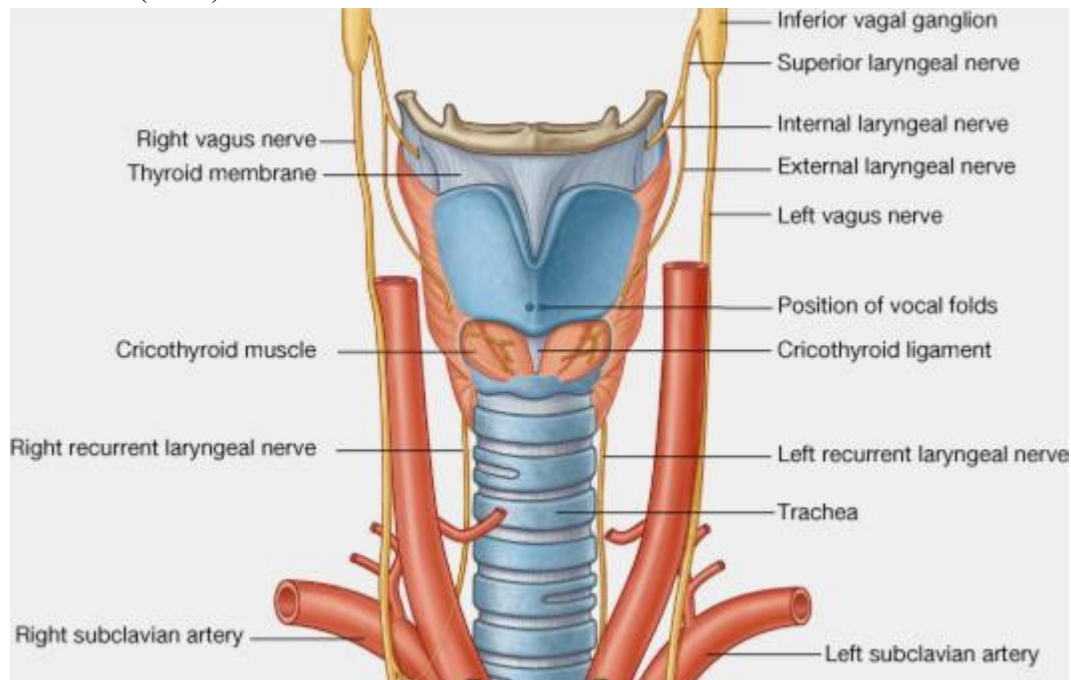


Figure 11: sensory and motor innervation of the larynx

The SLN mainly provides the sensory supplying of the glottic and supraglottic region, but its external branch also provides the motor innervation of the cricothyroid muscle. The RLN provides the sensory innervation of the hypoglottic region, but its main function is to provide motor innervation to the intrinsic laryngeal muscles. Galen loop, an anastomosis between the branch internal of the SLN and one of the branches of the RLN, provides motor innervation and the sensory innervation of the endolaryngeal structures.

The SNL leaves the vagus nerve trunk at the level of the nodose ganglion. It runs transversely behind the carotid artery, it approaches the larynx with the branch upper laryngeal artery of the upper thyroid artery, to then penetrate through the anterior thyroid membrane into the thyroid ligament between the superior rim of thyroid and hyoid bone⁴³.

Before entering the larynx, the SLN provides a smaller external motor branch for the cricothyroid muscle that flows on the external surface of the constrictor muscle, where it is at risk of injuries during surgery⁴⁴.

The RLN arises from the vagus nerve. On the left, in the chest, it separates from the vagus, it passes around the aortic arch, returns cranially to the tracheo-esophageal sulcus, and reaches the larynx behind the cricothyroid joint.

On the right, however, it passes under the subclavian artery, runs cranially in the tracheo-esophageal sulcus, goes on the opposite side and enters the larynx behind the cricothyroid joint⁴⁵. Due to the length, the RLN is subjected to insults of iatrogenic

origin during intrathoracic surgery (left), laryngo-tracheal, pharyngo-esophageal and thyroid (bilaterally).

The point entrance of the RLN into the larynx is placed exactly behind and below the crico-thyroid cartilage. At this level the nerve is protected by the muscle inferior constrictor and the cricothyroid muscle.

In about 90% of cases, the RLN divides into two or three branches a few millimeters before entering the larynx under the inferior constrictor muscle⁴⁶. The branch posterior goes behind the mucosa of the posterior cricoarytenoid muscle, where it comes into close contact with the lower edge of the cricoid ring.

The vascularity of the larynx is supported by the branches of the upper and lower thyroid arteries.

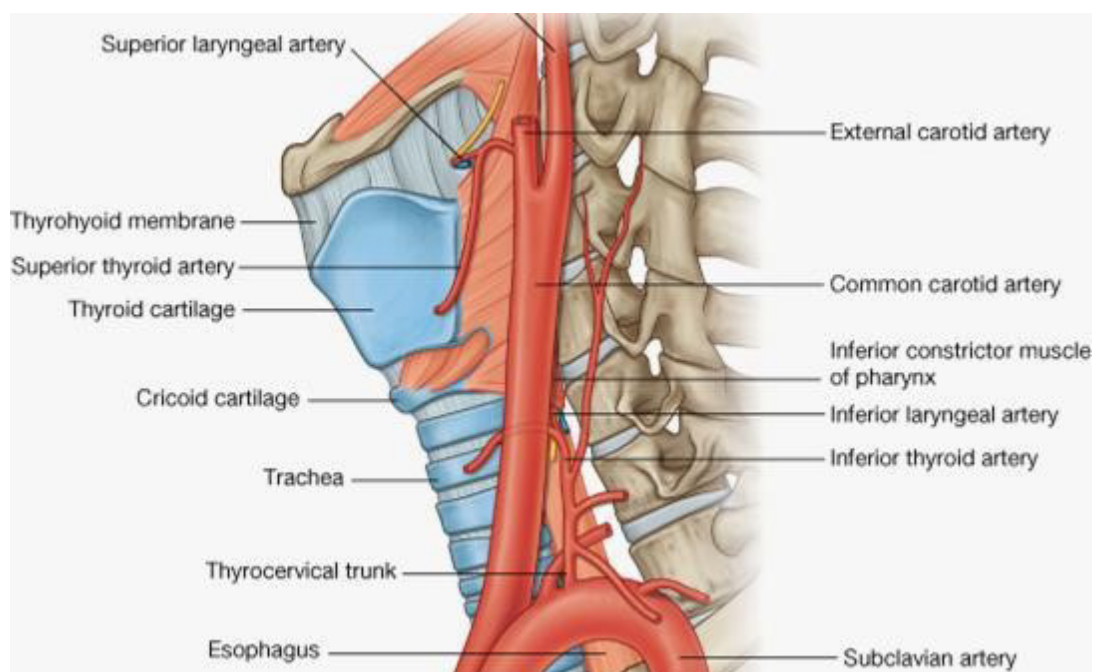


Figure 12: Arterial vasculature of the larynx

The superior laryngeal artery, branch of the superior thyroid artery, penetrates the thyrohyoid membrane together with the SLN, anteriorly to the lateral thyroid ligament, providing for the circulation of the glottic and supraglottic regions^{47,48}. The inferior laryngeal artery, branch of the lower thyroid artery, reaches the larynx at the level of the cricothyroid cartilage and supplies the cricothyroid muscles and inferior constrictor muscles, of the glottic and hypoglottic region, where it anastomoses with the vessels of the superior laryngeal artery.

The superior thyroid artery does not reach directly with its branches the cervical trachea, but anastomosed with branches of the lower thyroid artery in correspondence with the thyroid gland, indirectly supplying the adjacent tracheal wall through the gland capsule itself.

In its cervical segment the trachea is supplied by the inferior thyroid artery, and in its thoracic segment instead by the subclavian system and bronchial arteries ⁴⁹. The inferior thyroid artery ⁵⁰ passes posteriorly to the carotid sheath and in most cases gives rise to three branches which reach the tracheoesophageal junction laterally, traveling anterior or posterior to the RLN.

The rich endotracheal submucosal vascular network originates from the intercartilaginous transverse arteries derived from the lateral longitudinal anastomosis.

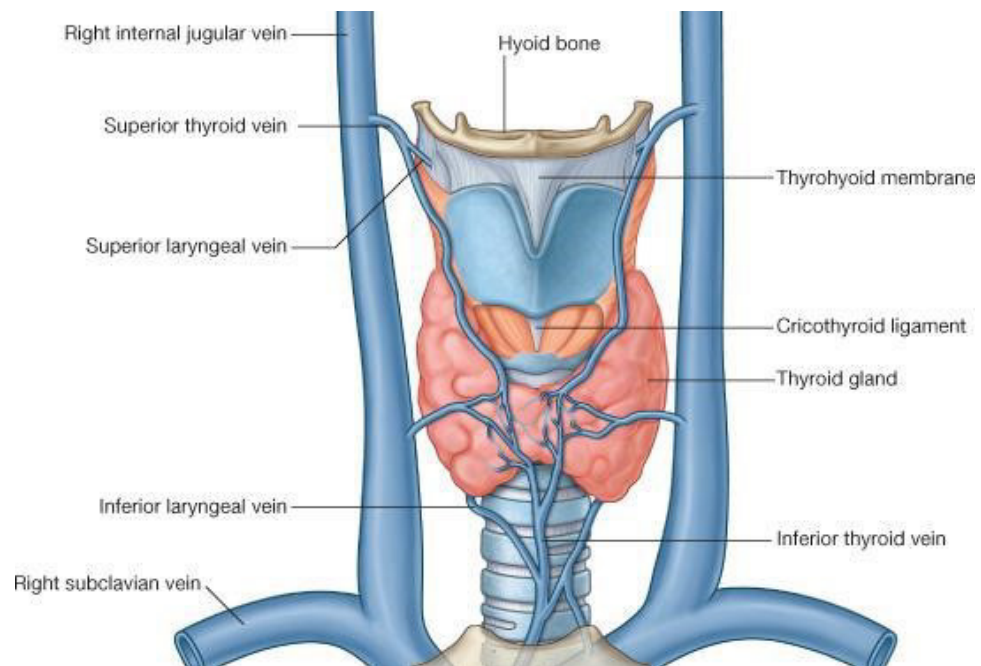


Figure13: Venous vascularization of the larynx

The superior and middle thyroid veins both drain into the internal jugular vein. The inferior thyroid vein drains directly into the subclavian vein. Meanwhile, lymph drainage goes to the deep cervical, paratracheal, pre-tracheal, and pre-laryngeal nodes.

PHYSICAL PROPERTIES OF LASERS

Laser is light.

The term being an acronym for *light amplification by stimulated emission of radiation*.

Light occupies one region of the electromagnetic spectrum. Because of the dual nature of light, it can behave both as an electromagnetic wave and as a type of particle radiation (photon).

Light is described as a wave or a particle depending on the specific contest.

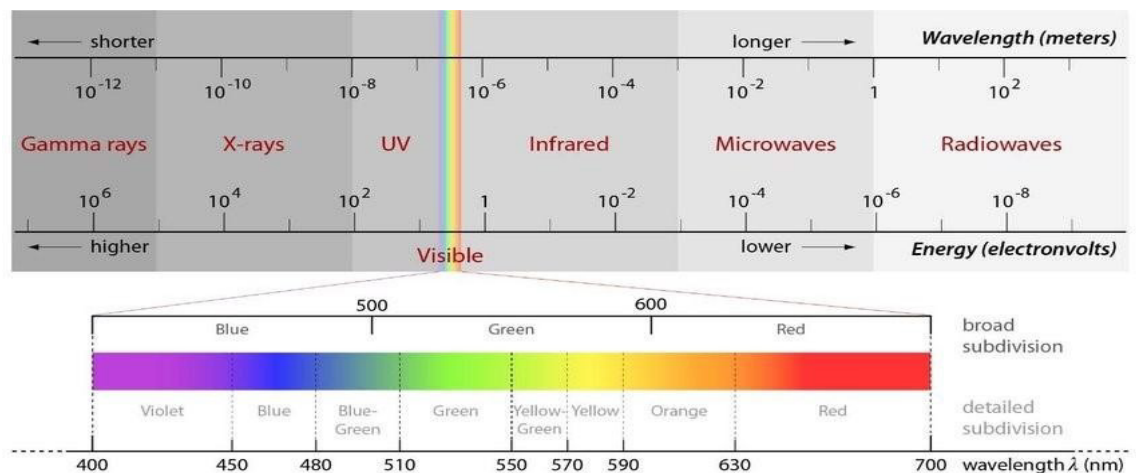


Figure 14: Electromagnetic spectrum

The classical laser machine is an optical resonator, first described by Einstein and the name of Maiman is linked to the invention of the ruby laser on May 16, 1960 at the laboratories of Hughes Research in Malibu (California). Developing Albert Einstein's theory of stimulated radiation emission (1917), the American physicist first created a handmade ruby crystal laser, the invention that gave rise to all subsequent laser applications. As early as 1962, the laser found its first practical application for microwelding during retinal surgery.

A cavity contains the laser material (gas, doped glasses, or crystals), at the end a 100% mirror is mounted, and at the other end some portion of the light is transmitted and escars the system through a partially reflecting mirror. This is an emitted laser beam. The largest portion is again reflected into the system and continues the laser process. The laser material is pumped with energy (e.g. radiofrequency, light, electric discharge) and electrons are excited into a higher orbital shell. This unstable condition ends when the electron returns to its ground state and a photon with a certain amount of energy is emitted. This is called spontaneous emission. All photons will be similar in energy (wavelength, color, etc) as long as they are generated from identical atoms. If an already excited atoms struck by a photon emitted from another like atom, two identical photons will be emitted. This is referred to as stimulated emission.

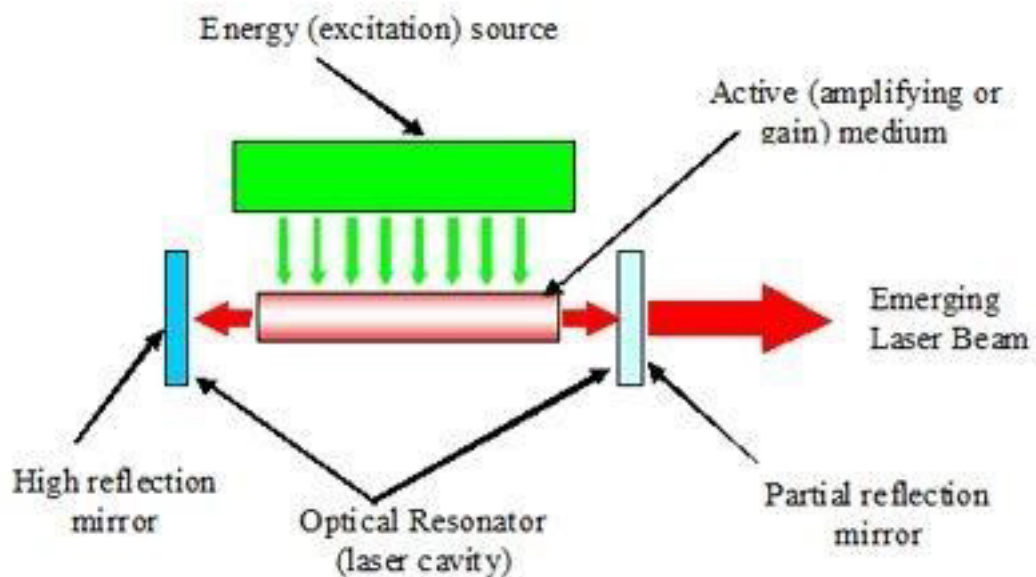


Figure 15: Laser machine

Both photons have identical energy (wavelength), direction (collimation), and phase (coherence). Photons traveling in the axis of the laser material will encounter other atoms, excite them, and a cascade will develop. Via the mirrors the path is endless and the laser process continues as long as pumping energy is supplied.

A laser combines:

- Monochromasia: all photons in a laser beam exhibit the same color or wavelength
- Collimation: negligible divergence of the laser beam and photons travel in parallel fashion with no significant divergence
- Coherence: photons travel in the same direction and synchronously, both spatially and temporally (in phase).

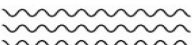
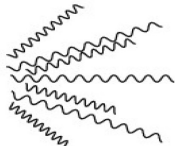
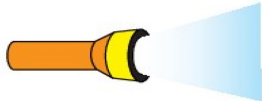
Laser light	Non-laserlight (e.g. flashlight)
Monochromatic 	Polychromatic 
Coherent 	Incoherent 
Collimated 	Divergent 

Figure 16: Combination of laser light

A combination that does not exist in nature.

The high collimation of the laser beams is responsible for the high amount of energy and the ability to focus in small localized spots with high power densities, unimaginable with conventional sources.⁵¹

Laser functionality is controlled by four variables: wavelength, energy, spot size and duration:

1. Light is a part of the electromagnetic spectrum. The longer its wavelength, the lower its frequency and the lower the energy of the individual photons. As the wavelength increases, the waves become less numerous. Thus the terms photon energy, frequency, wave number, wavelength, and colors are synonyms for the same property described from different perspectives. We approach the range of the wavelengths in visible light region and especially in the ultraviolet (UV) and x-ray regions of the spectrum, the single-photon energy becomes more important.

2. On adding together all the single-photon energies in a laser beam, we obtain the total energy of the laser beam in joules. The joule (J) is widely used because it permits comparison of different forms of energy, including the conversion of radiant energy to heat.

The J energy of lasers is frequently measured by aiming the laser beam at an absorber that converts the light energy into thermal energy. But the term “laser beam” also refers to spatial and temporal propagation and velocity (the velocity of light). Thus, the distribution of laser energy within a laser beam can be equated with the corresponding photon density.

When we calculate the energy delivered by a laser beam to a particular spot in 1 second, we obtain the power, $P = J/s$, in watts (W). The laser beam and focal point must be considered as occupying a specific area. From this the concepts of power density (W/m^2) and energy density (J/m^2) are derived when considering the total duration of laser exposure or a single energy pulse.

3. Spot size is crucial for the power or energy density and subsequently for the tissue effect with vaporization, coagulation, or heating in thermal laser interaction.

It is possible to obtain different surgical effects by keeping the power and the exposure time constant and only changing the spot size.

4. Duration:

-continuous beam: continuous wave (cw) lasers emit beams in an uninterrupted continuous fashion. During the emission, the energy delivered per time unit is stable. The appropriate unit to describe the beam are power/area in W/cm^2 short: power density (W/cm^2).

The continuous mode gives the advantage of having a full average power output from the laser tube with the most homogeneous irradiation of the tissue. -pulsed beams: pulses are temporal sequences of laser beams with on and off cycles. The tissue effect depends on the length of the single pulse, the temporal and spatial beam profiles, and the frequency. A single pulse is described by its energy (J) and the diameter of the incident beam (cm^2) or energy density (J/cm^2) and the pulse width. A train of pulses requires the frequency to describe it completely. With increasing pulse width and frequency, the time between the pulses gets smaller and it may make sense to add the average power (W) to describe the beam. The average power is calculated by multiplying the single-pulse energy by the frequency in seconds.

Pulse frequency is set at a value between 0.5 and 1.6 Hertz (hz).

Note that a 20 W emitted by a pulsed laser may produce an entirely different effect from that produced by 20 W emitted by a cw laser.

In this operating mode, the system provides a constant power peak for a certain average power. The system produces the average power required by varying the emission time and keeping constant frequency.

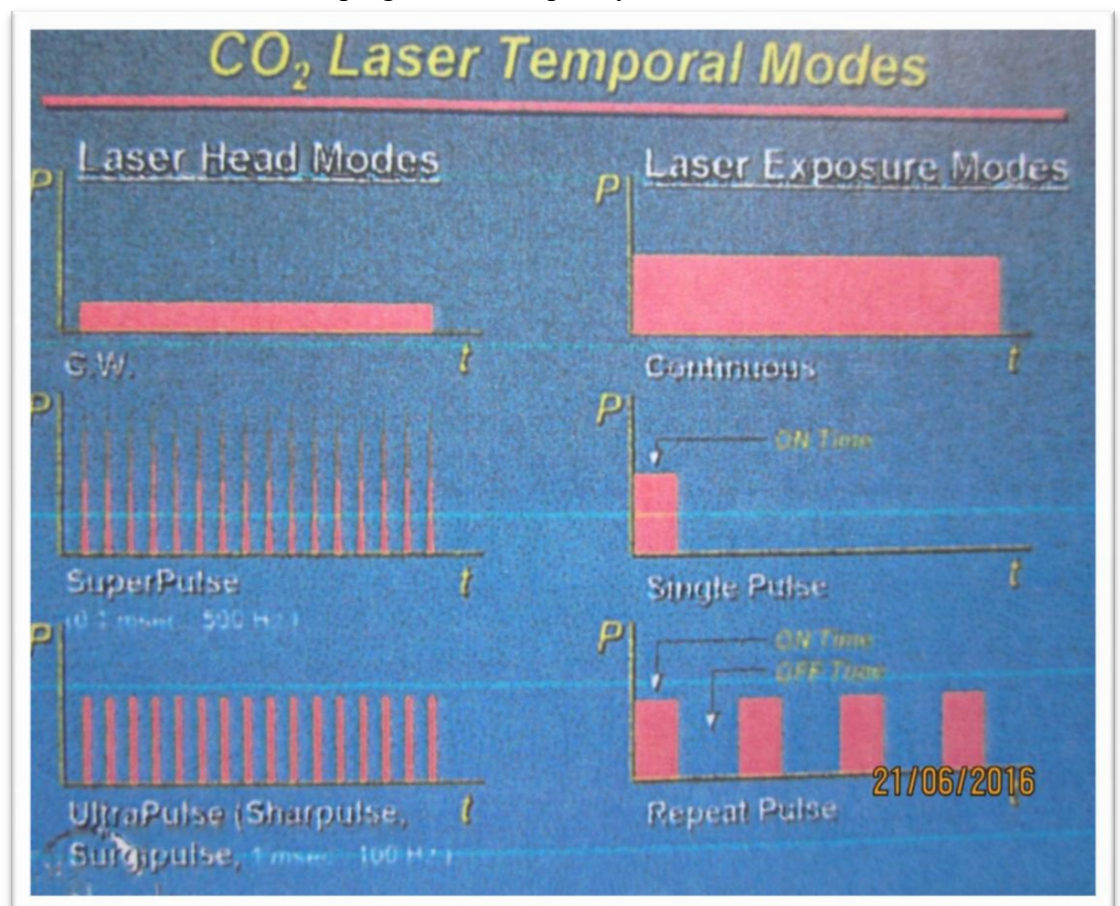


Figure 17: carbon dioxide laser (CO₂ laser) temporal modes

The term "superpulse" is used in pulsed lasers and means that the peak power during the pulse is at least one order of magnitude higher than the

corresponding average power within a very short time period, usually within microsecond range.

The current in the tube is pulsed to a level 5-10 times greater than in cw levels. The typical pulse parameters therefore have a frequency of 1 khz, a duration of 0.1 ms and a peak power 7-8 times greater than the normal cw power.

In superpulse mode the average power is sacrificed.

The pulsed mode gives the advantage of full average power while reducing the thermal effect on the adjacent tissue.

The superpulsed mode gives the advantage of an higher peak power, minimizing the thermal effects on the adjacent tissue but with a reduced average power.

The term “ultrapulse” is used by companies to point out that the superpulse of their laser is even shorter and has even higher peak power compared with common superpulse.⁵²

INTERACTION OF LASER BEAM WITH TISSUE

When a laser beam encounters tissue, it is usually scattered and then absorbed. Only absorbed radiation can be transformed into other kinds of energy. The optical properties of tissues are determined by the scattering at interfaces such as cell membranes, cell nuclei etcetera (etc) and also by absorption by tissue chromophores such as melanin, hemoglobin, water etc. These properties can vary considerably with the wavelength of the radiation due the different chromophores present in tissues. At UV wavelengths shorter than 300nm, the laser radiation is chiefly absorbed by cellular proteins and nucleic acid. Visible light radiation and near-infrared (NIR) wavelengths (400-1200 nm) are absorbed mainly by chromophores such as hemoglobin, flavin, cytochromes and carotinoids. In the far-infrared range (>1200 nm) water is the most efficient absorber.

The scattering coefficient (μ_s) is the probability that a photon will undergo a scattering event while traveling over a certain path length. Scattering, too, varies with the wavelength. It is greatest with short wavelengths and decreases with increasing wavelength.

The absorption coefficient (μ_a) is the probability that a photon will be absorbed over a certain path length.

Both are stated in units of reciprocal length (cm^{-1} or mm^{-1}).

The probability that a photon will be scattered at the angle θ may be equal for all angles (isotropic scattering) or may favor a particular scattering axis (anisotropic scattering). The degree of anisotropy is expressed by the anisotropic factor g. When $g=1$, scattering occurs almost exclusively in a forward direction. When $g=0$, scattering is isotropic and the photons are scattered with equal probability in all directions.

The g value for tissues in vitro is between 0.7 and 0.99, and increases with the wavelength of light, being high for the CO₂ laser.

The albedo (a) is calculated by dividing the scattering coefficient by the sum of the scattering and absorption coefficients:

$$a = \mu_s / (\mu_s + \mu_a).$$

With an albedo of 0, all radiation is absorbed by the medium and is not scattered.

A completely transparent medium does not scatter or absorb.

An albedo of 1 means that all the radiation is scattered and none is absorbed.

The optical depth τ is defined as the distance from the tissue surface (z) multiplied by the sum of the absorption and scattering coefficients

$$(\tau = (\mu_s + \mu_a) z).$$

With a value of 1, z is equal to mean free path. This is an average distance that a photon can travel before it is scattered or absorbed by interacting with the tissue.

The possible tissue effects depends on the wavelength of the laser light, the power and duration of a single pulse, the repetition rate and the spot diameter. Besides these properties of emission, specific tissue reactions and perifocal reaction are critical determinants of penetration depth and effect.

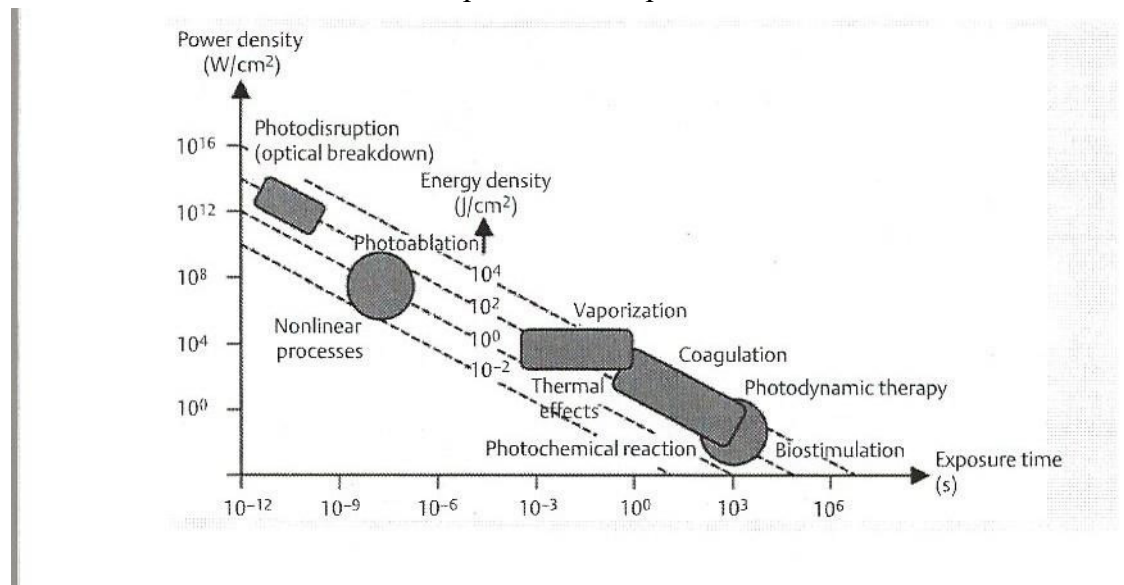


Figure 18: Tissue interaction depends on power density and pulse duration

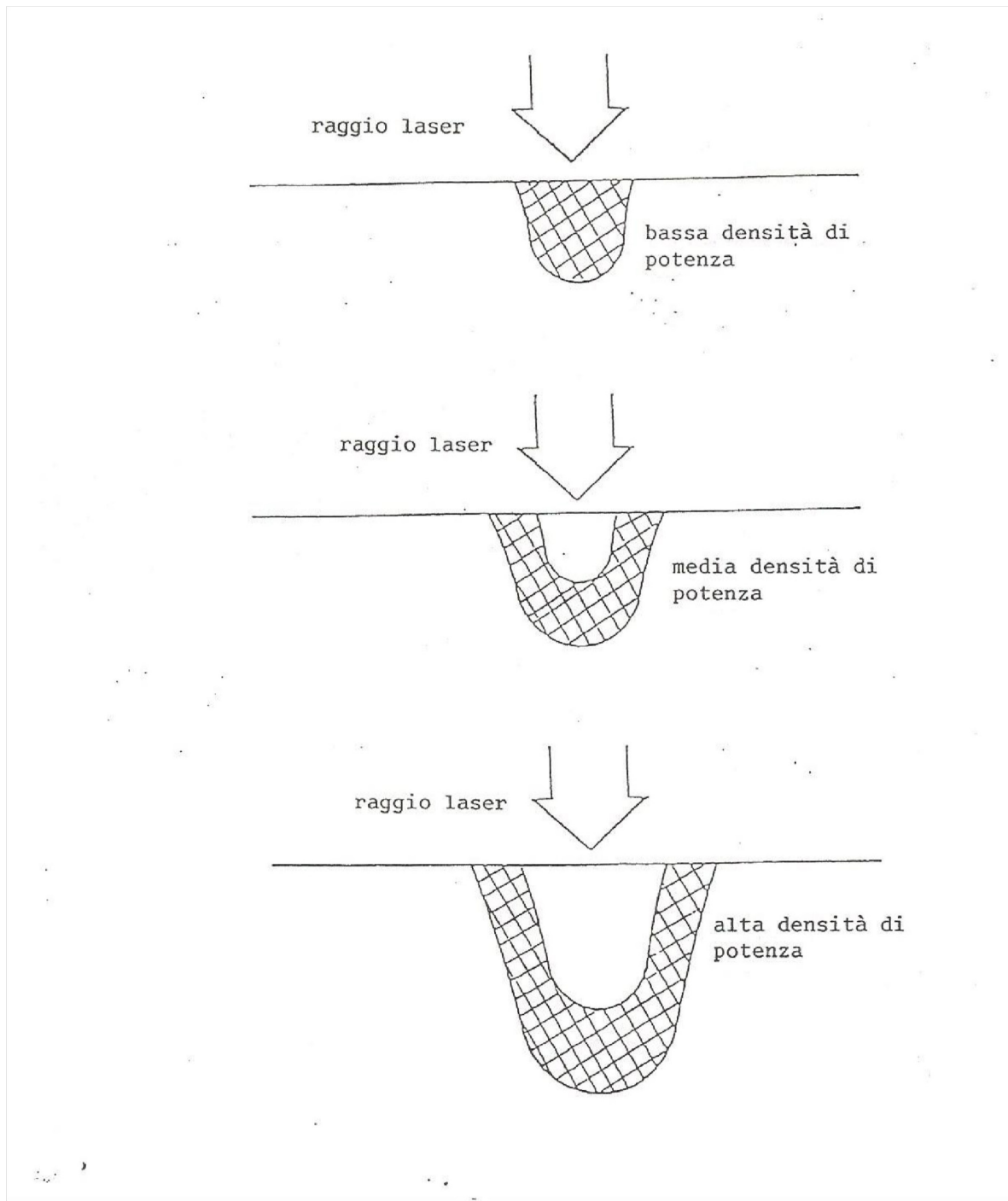


Figure 19: Interaction of laser beam with tissue depending on power density

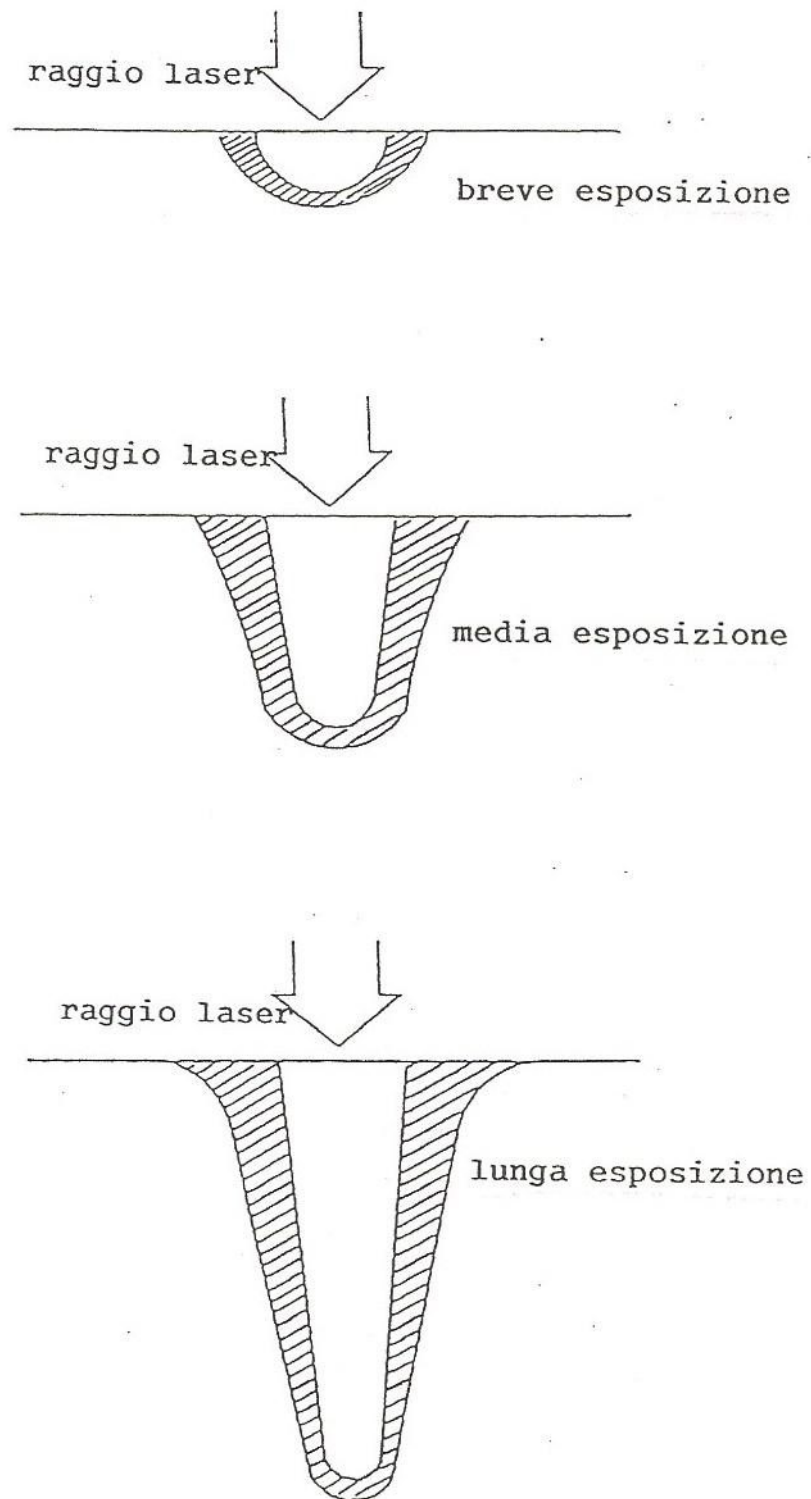


Figure 20: Interaction of laser beam with tissue depending on exposure time

With exposures in the microsecond (ms) range, heating is confined largely to the absorbing structure. With a longer exposure time or with continuous exposure, heat diffusion assumes major importance. Heat conduction from the absorbing tissue into the environment causes damage to the surrounding

tissues. The extent of this damage depends on the magnitude and duration of the temperature increase. Beyond the optical penetration depth, thermal effects are determined entirely by the thermal properties of the tissue such as heat conduction, heat capacity and heat dissipation. In tissues with a high rate of perfusion, heat is efficiently removed by transport along the vessels and this can reduce the local thermal effect.

The photons of the CO₂ laser beam are absorbed in a small depth or volume of the tissue exposed by the presence of water. Human tissues in general have high water content (75-90%). For about 80% water content an optical penetration of 100 μm is reasonably assumed. Coagulated tissues responds with higher scattering and less absorption and, thus, lowers the vaporization effectiveness and promotes diffuse heating of the tissue by thermal diffusion with shrinkage and carbonization. Thermal diffusion is the reason why a time-dependent coagulation seam between 100 μm and 1 mm around the incision is possible with a laser of 100 μm optical penetration depth, which equals the minimal coagulation seam.

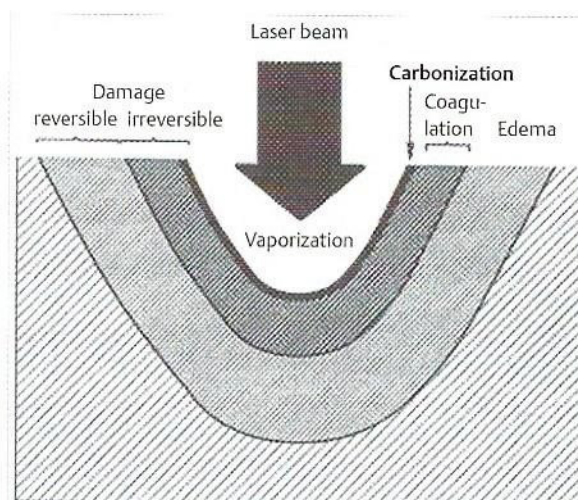


Figure 21: Thermal damage zones

Because of the small absorbing volume and high water absorption, tissue interaction with the CO₂ laser is dominated by vaporization. The amount of coagulation is influenced mainly by the pulse duration with longer exposures leading to more coagulation. Using high fluence combined with short exposure time may lead to an immediate vaporization but favor bleeding. Lower power densities lead to larger coagulation volumes and less vaporization and bleeding maybe prevented. Pulse duration and exposure time are important as the coagulation is mainly propagated by thermal diffusion (heat conduction). The edema volume is reversible tissue damage and its amount depends on the total energy not used for vaporation or coagulation.

Best cutting properties are achieved with a small focus and very high power densities. For ablation, high power densities with a large focal point are

requested and for coagulation purposes, lower power densities are needed, which can be reached by focusing the beam.

High power density, small spot size, and short pulse duration in the focus of the beam leads to high vaporization efficacy. Defocusing the beam by increasing distance will produce more coagulation and thermal stress to surrounding tissues.

This makes the CO₂ laser a unique surgical tool.⁵¹

LASERS SYSTEMS

Various laser media are available: gases, dye solutions, crystals, glasses, fibers and semiconductors.

Microlaryngoscopy was an essential prelude to the subsequent development of laser surgery.

In the early 1960s the introduction of laser systems into laryngeal surgery marks an important milestone in the development of this operative approach. By coupling a CO₂ laser to the operating microscope and controlling the invisible treatment beam with a micromanipulator, guided by a visible wavelength coaxial aiming beam, a relatively stationary, noncontact technique was achieved for dividing endolaryngeal tissues while simultaneously coagulating smaller blood vessels. The laser beam does not obstruct the surgeon's view of the confined operating field, it provides adequate tissue hemostasis for greater visibility and it facilitates the surgical dissection. TLM combines a minimally invasive approach with the special advantages of the laser: surgical precision, ease of control, optimum tissue effect, and noncontact technique. This permits an organ- and function- conserving mode of surgery. The obvious advantages of TLM were not appreciated at first. A major objection was that laser incisions always caused thermal tissue damage (burns) and therefore did not meet the requirement of clean, atraumatic tissue division with margins that could be histologically evaluated.

The necessary ingredients for successful TLM include:

- A refined operating technique,
- Appropriate anesthesia and ventilation,
- A complete instrumentation set for endolaryngeal surgery

Surgical lasers can be used in various ways for treatment of laryngeal and tracheal lesions:

- Tissue ablation: precise cutting with minimal coagulation for resection of abnormal tissue with absolute precision with a

focused beam, without causing clinically thermal damage to normal surrounding tissue;

- Coagulation of blood vessels;
- Vaporization of tissues;
- Induction of photochemical precosses in photodynamic therapy⁵²

COMPONENTS OF THE LASER CO₂

The Laser

The CO₂ laser is a classical gas laser with a tube filled with a gas mixture of usually 5% CO₂, 15% nitrose gas (N₂) and 80% helium (He) under a pressure of 15 to 20 mbar. Two mirrors, one of which is only partially reflective at the ends, form the light-amplifying resonator. Pumping energy is either supplied by direct electric discharge or radiofrequency. In the current CO₂ laser the tube is sealed. Medical needs poker are between 20 and 100 watts.

The CO₂ laser produces a beam of infrared light with the principal wavelength bands centering around 9.4 and 10.6 μ m. The typical wavelength is 10.6 μ m and this wavelength is strongly absorbed by water and makes the CO₂ laser a very predictable tool, as optical penetration into the tissue is limited.

It is a very good surgical tool with nontouch technique.

Depending on anatomical site, laser light with a power 1 to 15 W is used for surgery. Superpulsing allows for a deeper penetration than a laser of the same wavelength that is not superpulsed because ultimately short pulses allow for quick absorption at the cellular level. For TLM, the laser light is delivered to the microscope through an articulated arm and under the use of micromanipulators coupled to the surgical microscope. To precisely direct the laser beams onto the tissue site, a micromanipulator with a gambale mirror is located in the beam path that can be moved by the surgeon with a joystick.

Microscopes

The CO₂ laser is attached to an operating microscope with a recommended working range of 400 mm. Furthermore a steady suspension system is obligatory for a good visualization and the head should be balanced over the entire range of motion to allow the surgeon single-handed repositioning.⁵³

HD IMAGING WITH OPERATING MICROSCOPES

A solution to upgrade any surgical microscope with state-of-art full HD (High Definition) imaging technology. To achieve optimal results, all components in the video chain- from camera system to the monitor- must be of the highest quality.⁵⁴



Figure 22: Camera HD attached to an operating microscope

Articulated arms

Most CO₂ laser employ articulated arms with reflecting mirrors inside for beam delivery. The primary beam of the laser keeps its typical properties (collimation and coherence) during its pathway inside the articulated arm. Because of this, the lens or mirror system in the final applicator can easily focus the beam down to diameters in the micron range for cutting or widened up to a very homogeneous field for ablation or coagulation.

The articulated arm itself is weightless as counter-weights are used to keep it in a neutral position.⁵³



Figure 23: Articulated arms

Handpiece

One property of the laser beam is its straight forward propagation after leaving the last optical component, usually the lens of the handpiece or micromanipulator, usually with a certain distance to the tissue and a focal point. After the focal plane, the beam is divergent as it is with fibers- here the

highest power density is very close to the tip. Handpiece can be easily directed according to the surgical needs. A focusing handpiece usually consists of a connector that mounts on the articulated arm and, at the same time, holds a lens or lens system. These lenses are made of zinc selenide (ZnSe) which is transparent to CO₂ laser beam. In contact with water the crystal structure takes up H₂O molecules and transmission of the CO₂ laser beam is hampered. An insert of gas (usually air) is mounted on one side, which always should be used to keep the lenses clean and provide some cooling.

The distal tube covers the focusing part of the beam for protection and better handling. At the very end of the tube a distance guide indicating the focal point may be mounted. As tube and distance guide usually contain no optical parts, both may be sterilized by steam. Because the lens could be damaged on contact with water, sterilization with steam is not possible. Usually clearing and disinfection is done with alcohol-based disinfectants.

Micromanipulators

In endoscopy micromanipulators attached to operation microscopes have been in use for decades in otorhinolaryngology with typical long beam paths, usually between 250 and 400 mm.

The micromanipulator is attached to the operation microscope and coupled with the articulated arm. Both the CO₂ laser and the pilot beam are reflected usually by a dichroic mirror into the field of vision, leaving the mirror in a free beam path with focal lengths between 250 and 400 mm.

Both pilot laser and CO₂ laser have to match at the operation plane locally and in diameter at every space of the operation plane. During every set up and in advance of every use this has to be tested and verified by the user. The beam is directed by manipulating the mirror with a small joystick. Proper alignment and adjustments are important.

During the operation additional instruments are used and may block the path of the beam leading to unwanted reflection and heating with potential risks.⁵⁴



Figure 24: Micromanipulator attached to operating microscope

For some application hand-driven movements are replaced by optomechanical devices to improve reproducibility and speed. These devices are referred to as scanners.

The focus remains only for a short time at a certain space, resulting in very defined and small coagulation, down to optical penetration of CO₂ laser beam. The beam is moved over the area by the scanner, in a spiral or linear fashion, and produces shallow vaporization with a controlled coagulation and edema zone.

Endoscopes

Obligatory for diagnosis, surgery and postoperative treatment. These scopes are available in different angles of view (0°, 30°, 70°).

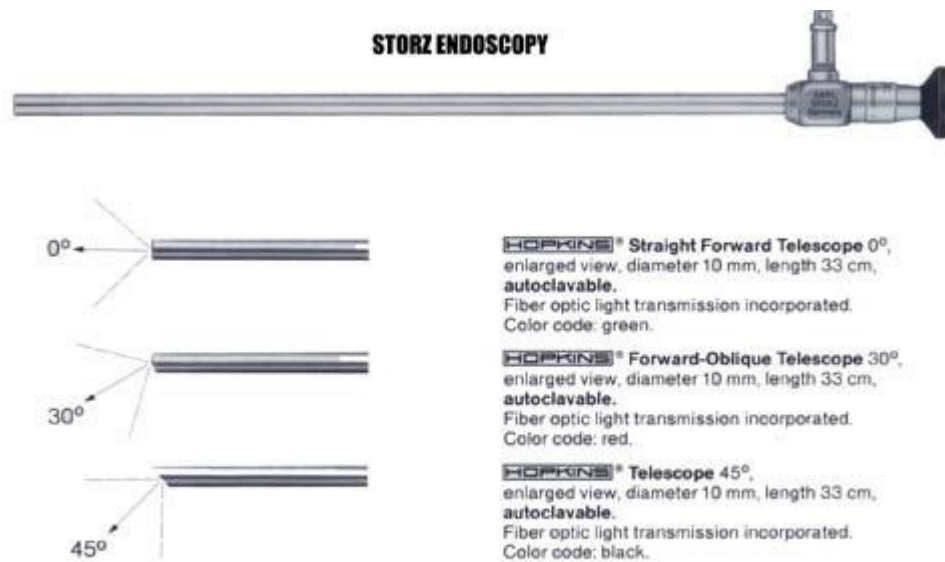


Figure 25: Telescopes are available in different angles of view



Figure 26: Basic laryngoscopy set for adults

Laringopharyngoscopes

All laryngoscopes should be modified to meet the special requirements of TLM. A matt finish reduces light reflection, an integrated suction channel can evacuate vapor, and different lengths and inner diameters should be available.

Distending operating laryngoscopes

The distending operating laryngoscopes has an integrated suction channel and is used in adults mainly in supraglottic larynx and hypopharynx surgeries. Advantages of the distending laryngopharyngoscopes are a widely accessible

operating field, imprecise orientation, and an easier manipulation with instruments.

Closed operating laryngoscopes

Medium- to- large closed operating laryngoscopes are especially used for endolaryngeal surgery particularly of the glottis and in adults. Longer (19 cm) and, in diameter, smaller operating laryngoscopes are more suitable for adults where the anatomical exposure is more difficult and where the medium- sized laryngoscope is inappropriate. It is particularly useful for the anterior glottis, the interarytenoid area, and for the subglottis when often considerable pressure onto the larynx is necessary from the outside to gain adequate access to the inner larynx and especially to the anterior commissure. It is also applicable in children.



Figure 27: Selection of various laryngoscopes used in TLM for tumor exposure

Laryngoscope Holder, Supporting Table and Chest Support

The introduced laryngo(pharyngo)scope is fixed with a holder on the support table, which is a very important and helpful device in transoral laser microsurgery. It has an adjustable platform that can be secured in any three- dimensional position which allows effortless changes in the position of the laryngoscope or the laryngopharyngoscope. Even in cases from very lateral introduction, the laryngoscope can be maintained in its positions due to the extremely wide range of possible adjustments.

A special chest support system has been designed to meet the requirements of transoral tumor surgery in the pharynx and larynx, together with an adjustable platform that can be secured in any of three dimensional position of the

laryngopharyngoscope during tumor surgery. Extremely lateral angles are easily achieved and maintained.



Figure 28: Laryngoscope Holder and Chest Support

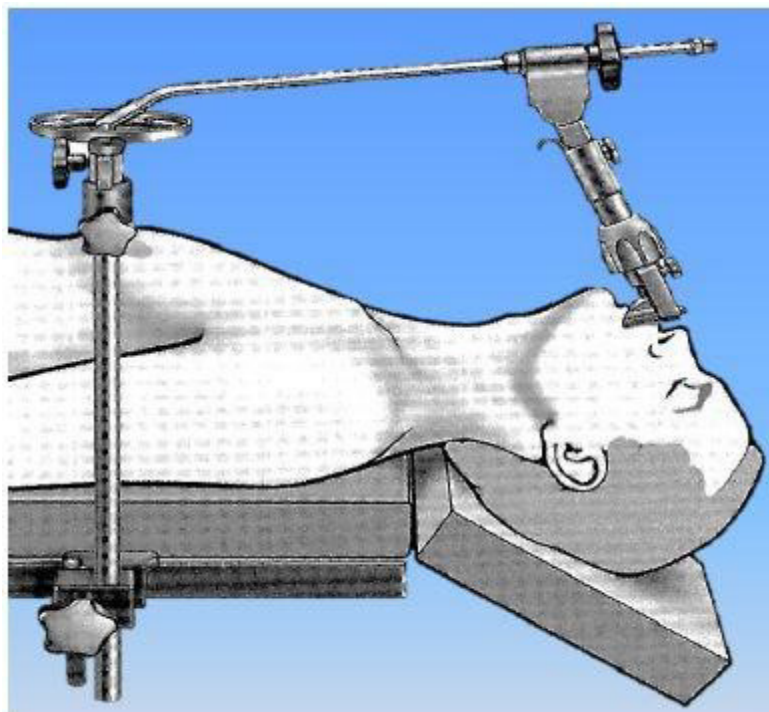


Figure 29: Intraoperative set of TLM

Coagulation Forceps

Grasping forceps, curved to the right or to the left, that have an insulated shaft and can be used for unipolar coagulation. A bipolar coagulation device is useful if available.

Grasping instruments

The grasping forceps, serrated jaws, and alligator type forceps are available in different sizes and allow gentle but also firm hold of the tissue. The tumor may be retracted and manipulated in multiple directions using these specialized grasping forceps. The grasping forceps can have an integrated suction channel to remove vapor. It is recommended to have all instruments with a matte finish that effectively absorbs the laser energy. This is particularly advantageous during photo or video documentation due to the elimination of interfering reflections.

Clipping instruments

Clipping forceps, with right or left curved jaws, are obligatory to avoid or stop bleeding of the large vessels. It is recommended to use two clips, especially to the proximal portion of larger vessels such as the superior laryngeal artery pedicle.

Suction

Suction tube is also insulated and can be used for unipolar coagulation. Routinely it is useful to keep the suction in the left hand during removal of larger tumors because it enables the surgeon to stop bleeding immediately, to manipulate tissue and additionally to evacuate vapor.

Suction tubes have different sizes with insulated sheath for unipolar coagulation.



Figure 30: Specially designed microlaryngeal instrumentation for the use in TLM.
A. Forceps and scissors. B. Insulated cannula for suction and unipolar coagulation

Protecting Shields

Different types of varying size and shape with incorporated suction tubes can be placed during laser surgery to protect the distal tissue. Examples are protection of the vocal fold during operating on false cord, or retraction of a healthy contralateral cord in patients with exophytic lesions of anterior glottis.

ANESTHESIA FOR TLM

All varieties of ear, nose and throat (ENT) CO₂ laser surgery are performed with the patient under general anesthesia. Cooperation between the anesthesiologist and the surgeon is essential because both work in the same surgical field and share the same problems.⁵⁵

The observed incidence of difficulty of intubation in laryngeal microsurgery is of 12% to 28%, quite higher than in other kinds of surgery (0.4%)⁵⁶⁻⁵⁷ The anesthetic technique must ensure patient safety and the best exposure of the glottis. Curarization is essential to keep the vocal cords abducted and immobile.

Tracheal intubation allows to work safely if protective measures are taken that minimize the risk of airway burns. Ventilation must be carried out with a gaseous mixture that does not maintain combustion in the event of a fire caused by the laser: the best choice is an air-O₂ mixture with FiO₂ <30%. The tracheal tube is made of fireproof material that is impenetrable by the laser beam, non-reflective and in any case biologically well tolerated, transparent to allow immediate recognition of intraluminal combustion phenomena, reasonably small external caliber to allow greater visualization of the glottic plane and internal caliber sufficient to guarantee patient ventilation; so rigid that it is not compressed and occluded by the maneuvers of the operative laryngoscope.

Laryngeal microsurgery forces the anesthesiologist to attend to various tasks, such as airway management, ventilation modalities, and the control of the hemodynamic response caused by laryngeal manipulation.

Risky situations are diverse: glottic exposition will be difficult when the anatomic distortion caused by the tumors does not allow for the recognition of laryngeal structures; endolaryngeal obstruction might complicate the passage of the intubation tube; exophytic tumors can bleed during laryngoscopy; and respiratory insufficiency implies a risk of hypoxia and worsen intubation and ventilation strategies. Additionally, the patients might have sequelae of prior surgeries and radiotherapy, such as retraction and stiffness of the head and neck region.

The ASA algorithms establish the steps to take in case of a difficult airway as well as the use of auxiliary systems that allow for ventilation and tracheal intubation⁵⁸. In laryngeal pathology, before completing anesthetic induction and muscle relaxation, it is convenient to perform a direct laryngoscopy with the patient under sedation and topical pharyngolaryngeal anaesthesia, in order to establish the position of the glottic space with the help of the breathing movements. Hence, maintenance of spontaneous ventilation is required. The upper airway remains permeable thanks to dilatator muscles of the pharynx, whose action would be suppressed under general anaesthesia. The loss of muscle tone in the tissues, due to the use of muscle relaxants, may precipitate

the occlusion of the tumoral airway, making it impossible to ventilate with face mask.

The Mallampati score is a graded 4-level pictorial scale created to predict difficult intubation before general anesthesia and is now routinely used for this purpose in operating rooms worldwide.⁵⁵⁻⁵⁹

The score has subsequently been extrapolated outside of the operating room to procedural sedation, with a number of specialty societies recommending it as a routine screening element.⁶⁰⁻⁶⁴

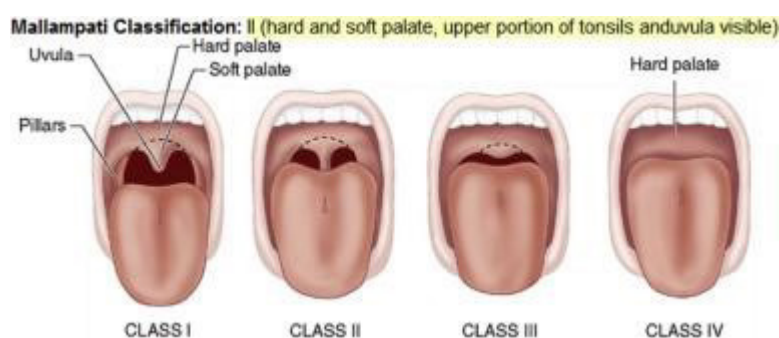


Figure 31: Mallampati classification

In 1983, Mallampati described the Mallampati score that might similarly predict airway and respiratory adverse events during procedural sedation and the score contains 3-level expansion of this evaluation with numeric values:

- 1=normal visualization,
- 2=obscured uvula but visible faucial pillars,
- 3=obscured uvula and faucial pillars.⁵⁵

In 1987, Samsoon and Young⁵⁹ expanded this evaluation to the 4-level pictorial classification now in widespread use.

The Mallampati score is intended to supplement, but not replace, the baseline clinical judgment of a general multidimensional airway evaluation.⁵⁷ This standard airway assessment includes a history and physical inspection of the craniofacial structure to identify risk factors such as short neck, obesity, obstructive sleep apnea, long upper incisors or overbite, restricted mouth opening, micrognathia, macroglossia, laryngomalacia, tonsillar hypertrophy, airway edema, blood or vomit in the airway, cervical immobility, and facial or neck trauma. The quality and reliability of this general airway evaluation will at times be hindered or limited by emergency situations, impaired patient cooperation, and unavailable medical history.

Although the Mallampati has 4 possible scores, it has been customary in clinical practice and in research to dichotomize it into classes I and II (low risk) versus classes III and IV (higher risk). This binary risk assessment is then used to predict a research outcome of either difficult laryngoscopy or of difficult intubation.

In order to derive a clinically practical predictive model, each preoperative airway assessment variable was stratified into “risk” categories in El-Ganzouri score⁶⁵

Score was measured calculating a lot of variables:

1. Mouth opening in patients with anterior teeth was recorded as the interincisor gap measured with the mouth fully open and was categorized as >4 cm or <4 cm. In edentulous patients, the intergingival distance with the mouth fully opened was recorded.
2. Thyromental distance was measured along a straight line from the thyroid notch to the lower border of the mandibular mentum with the head fully extended and categorized as >6.5 cm, 6.0- 6.5 cm, or <6.0 cm.
3. The visibility of oropharyngeal structures was assessed in the sitting position. Assignment was made to class I when faucial pillars, soft palate, and uvula could be visualized, class II when faucial pillars and soft palate could be visualized but uvula was masked by the base of the tongue, or class III when only the soft palate could be visualized. The fourth oropharyngeal class described by Samsoon and Young was not used.
4. Head and neck movement was measured by asking the patient to fully extend the head and neck. The range of motion from full extension through full flexion was categorized as >90°, 80-90°, or ~80°.
5. Ability to prognath was graded as capacity to bring the lower incisors in front of the upper incisors or the inability to perform this maneuver. Edentulous patients were assigned to the first of the latter categories.
6. Body weight was categorized as <90 kg, 90-110 kg, or > 110 kg.
7. History of difficult intubation was quantified as absent, questionable, or definite.

Variable	Score
Mouth opening	
≥4 cm	+0
<4 cm	+1
Thyromental distance	
>6.5 cm	+0
6.0-6.5 cm	+1
<6.0 cm	+2
Mallampati class	
I	+0
II	+1
III	+2
IV	+2
Neck movement	
>90°	+0
80-90°	+1
<80°	+2
Teeth prognath	
Patient is able to prognath	+0
Patient is not able to prognath	+1
Body weight	
<90 kg	+0
90-110 kg	+1
>110 kg	+2
Previous difficult intubation	
Absent	+0
Questionable	+1
Definite	+2

Table1: El- Ganzouri score

The laryngeal view can be classified according to the method of Cormack and Lehane as Grade I when there is full view of the glottis, as Grade II when at least the posterior commissure is visualized, as Grade III when none of the glottis but part or all of the epiglottis can be seen or as Grade IV when neither the laryngeal structures nor the epiglottis are visualized.⁶⁶⁻⁷⁰

When conventional intubation is used, there are zones of the larynx that remain hidden under the tube (posterior commissure, arytenoids, subglottis). Consequentially, the lesions that lie on these areas might be hard to reach, complicating the surgery.

Different methods of intubation and ventilation have been evaluated in anesthesiology that would help for the surgical exposure of the larynx.⁷¹ These ventilation techniques use jet ventilation. Their main characteristic is manual or automatic high pressure

injection of gas through a small-gauge injector introduced through the upper airway. The main risk of jet ventilation is barotrauma, which may happen if the outflow of insufflated gas is blocked due to an upper airway obstruction. Hypoventilation and hypercapnia could also happen in chronic obstruction pulmonary disease (COPD) or obese patients, since only low FiO_2 (0.3-0.4) are allowed in laser surgery.⁷²

Jet ventilation requires the use of specific material, both for air injection as for ventilation, which must per force include a device that measures tele-inspiratory pressure, in order to avoid pulmonary overdistension.

The use of a manual injector increases the risk of barotrauma. Jet ventilation requires the glottis to remain open, with a free upper airway, in order to allow for the air outflow.

High frequency jet ventilation (HFJV) requires a specific ventilator that can administer air at high frequencies. Just as in manual jet ventilation, the air injection can be administered above the glottis with the catheter attached to the suspension laryngoscope; below the glottis after intubation with a specially commercialized tube (Mon-Jet tube)⁷³, or with two 2.2 mm Teflon catheters- one for administering air and the other for measuring pressure inside the airway. These catheters are attached to one another so as to avoid diverging trajectories during intubation and ventilation, but they are loose inside the trachea.⁷²

A third invasive technique is to ventilate via a transtracheal approach, puncturing the cricothyroid membrane and a 14 gauge, 7 mm catheter is used. This last option has two indications: 1) in laryngeal endoscopy when there is a severe difficulty for intubation or when it is necessary to fully expose the glottic aperture^{74,75}; and 2) when one cannot ventilate/cannot intubate in an emergency scenario.⁷⁶ Transtracheal ventilation is associated with a 9% incidence of subcutaneous emphysema of the head and neck area, and 1.9% in the mediastinal area.⁷⁷

If jet ventilation is unavailable, in some rare cases and as an option to reach laryngeal areas otherwise hidden by the orotracheal tube and always in close collaboration with the surgical team, the patient can be extubated for a short period of time (1 to 2 minutes, and always keeping oxygen saturation >90%) in order to allow for the surgery to be performed. During infrequent occasions and within a short period of time, the patient can maintain spontaneous ventilation with a deep enough sedation that allows for suspension laryngoscopy to be performed for surgical access on laryngeal lesions. Nonetheless, this is a risky technique because it is hard to keep an adequate level of sedation and the upper airway is left unprotected.

TNM STAGING CLASSIFICATION FOR GLOTTIC CANCER¹³

VIIIth Edition of TNM staging of the UICC/ AJCC (Union for International Cancer Control /American Joint Committee on Cancer) is a universally accepted system to define the extent of a tumor and is based on the evaluation of three elements:

T: extension of the primary tumor;

N: absence or presence and extension of metastases to regional lymph nodes; M: absence or presence of distant metastases.

The addition of numbers to these 3 components indicates the extent of the tumor, that is:

- T0, T1, T2, T3, T4
- N0, N1, N2, N3
- M0, M1

All cases must be confirmed histologically.

Two classifications are defined for each site clinical (cTNM) and pathological (pTNM).

After having defined the categories T, N and M these they can be grouped into stages. If there are doubts, the clinic must assign the lower grade category.

In case of simultaneous multiple tumors in one organ must classify the tumor with the highest category and indicate in brackets the number of tumors, e.g. T2.

ADDITIONAL SYMBOLS

- m symbol: indicates the presence of tumors multiples; y symbol: indicates that the classification is carried out during or after the start of a multimodal therapy; r: indicates relapsing tumors staged later a
 - disease-free interval;
 - a: indicates that the classification is determined for the first time with an autopsy; R
 - indicate the absence or presence of tumor residues:
- RX: cannot be ascertained;
- R0: there are no tumor residues; -
- R1: microscopic tumor residues; -
- R2: macroscopic tumor residues.

T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumour limited to one vocal cord

T1b Tumour involves both vocal cords

T2 Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

T3 Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of the thyroid cartilage

T4a Tumour invades through the outer cortex of the thyroid cartilage, and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus

T4b Tumour invades prevertebral space, encases carotid artery, or mediastinal structures.

N – Regional Lymph nodes

NX regional lymph nodes can not be evaluated

N0 No evidence of lymph nodes metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension N2 Metastasis described as:

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

N3b Metastasis in a single or multiple lymph nodes with clinical extranodal extension*

* The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extra nodal extension. Midline nodes are considered ipsilateral nodes.

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

pTNM Pathological Classification

The pT and pM categories correspond to the clinical T and M categories.

pN – Regional Lymph Nodes

Histological examination of a selective neck dissection specimen will ordinarily include 10 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 15 or more lymph nodes. pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension pN2 Metastasis described as: pN2a Metastasis in a

single ipsilateral lymph node, less than 3 cm in greatest dimension with extranodal

extension or more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

pN2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
pN3b Metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension or multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension

Stage

Stage 0 Tis N0 M0

Stage I T1 N0 M0

Stage II T2 N0 M0

Stage III T3 N0 M0

T1,T2,T3 N1 M0

Stage IVA T4a N0, N1 M0

T1,T2,T3,T4a N2 M0

Stage IVB T4b Any N M0

Any T N3 M0

Stage IVC Any T Any N M1

DIAGNOSTIC WORK UP IN THE CANCER OF LARYNX

Patients must be counseled with regard to the disease and the stepwise technique of the endoscopic surgery. Ideally, they should be cooperative, motivated, and willing to change their smoking and alcohol habits. They must be able to attend regular follow-up visits and should be made to understand the potential need for re-resection if there is subsequent debate with regard to margins.

Careful selection of appropriate patients with an excellent probability of preserving function is essential to TLM.

Panendoscopy is undertaken as an initial procedure in order to define the extent of the primary tumor and to detect any possible second primary lesions.

The philosophy of TLM is to try, wherever possible, to unify the diagnostic and curative procedures into one operation.

In order to optimize the oncological and functional results in the transoral treatment of laryngeal carcinomas using CO₂ laser, careful pre- and intraoperative work up is necessary in order to evaluate the superficial extension of the tumor by endoscopy and the deep extension of the cancer by imaging.⁷⁸⁻⁸⁰

Born in the mid-nineteenth century by Manuel Garcia⁷⁸, the modern endoscopic exploration of the larynx makes use of a very rich set of tools and technologies. Endoscopic staging undoubtedly represents the most important and sensitive examination of the diagnostic path of laryngeal neoplasms.

The diagnostic strategy involves two distinct phases:

1. indirect examination with dynamic assessment of the patient, prepared with local anesthesia (contact anesthesia with 10% lidocaine spray, gargling for a long time, in the oropharynx and in both nasal fossas, asking the patient to inhale deeply); this step allows the vision of all the explorable parts of the larynx;
2. direct examination of the larynx with the patient in narcosis, completing the diagnostics on the "less visible" parts such as the ventricle, the commissure of the true and false vocal cords, the hypoglottic cone, using endoscopes at different angles and concludes the process with the biopsy assessment of the lesion.

Intraoperative endoscopic evaluation using 0 ° and angled optics has already been demonstrated as an indispensable tool in the definition of the surface extension and in the planning of surgical excision.⁸⁰

It is necessary to ascertain the indirect signs of extension in depth essentially represented by the reduction and absence of mobility of the vocal cord, of mobility of the arytenoid and of the glottic mucosa wave.

The first two parameters allow to differentiate the deep infiltration in the middleanterior paraglottic space (fixity of the vocal cord), from the deep infiltration of the posterior paraglottic space (fixity of the arytenoid). The reduction or absence of a mucous glottic wave can only be evaluated with laryngostroboscopy.

HD TECHNOLOGY in the preoperative, intraoperative and post-operative phases with 0 °, 30 ° and 70 ° angled telescopes allows to obtain a good diagnostic gain, highlighting the surgical margins for a better tumor staging, without requiring tissue manipulations.

NEW ENDOSCOPIC INSTRUMENTS:

- AUTOFLUORESCENCE ENDOSCOPY
- NBI (narrow band imaging)
- HD SPIES
- CONTACT ENDOSCOPY

AUTOFLUORESCENCE ENDOSCOPY

Autofluorescence of laryngeal tissues, normal and pathological, has been studied since the 1980s.

In 1984 Alfano, exploiting the principle that the biochemical composition and histomorphological architecture of the tissue profile determine their spectral fluorescence characteristics, demonstrated that the autofluorescence technique could effectively differentiate normal tissue from pre-neoplastic and neoplastic tissue. It is based on the principle that all our tissues contain molecules, endogenous fluorophores (porphyrins, NADH, flavins, collagen fibers, elastic fibers), capable of increasing their internal energy when they absorb electromagnetic waves, passing into an excited state. The excited state is, by definition, unstable and has a very short average life (10^{-9} - 10^{-8} s). These molecules therefore have a tendency to return to a state of rest. This occurs partly by dissipating heat (internal conversion), partly by the release of photons (fluorescence). The latter represent the emission of fluorescence which, according to Plank's law, is characterized by a lower frequency and a longer wavelength than that of ionizing radiation⁸¹⁻⁸³.

The degree of fluorescence of biological tissues essentially depends on three factors:

1. Tissue content of endogenous fluorophores;
2. Tissue architectural structure: the fluorescence spectrum of the tissues is the resultant of the spectra of its components; therefore it depends on the morphological structure and on the spatial distribution of the tissue constituents;
3. Characteristics of the stimulation light: the phenomenon of fluorescence occurs with exciting electromagnetic waves having a wavelength between 370 and 430 nm capable of making the molecules described above perform one of the possible energy transitions.

Fluorophores are present in reduced quantities in preneoplastic or tumor lesions. The lack of autofluorescence of pre-neoplastic and neoplastic lesions allows to draw more precisely the limits of the lesion, to obtain greater resolution on multifocal lesions and to make a prediction on the pathological degree of the same.
and distribution.

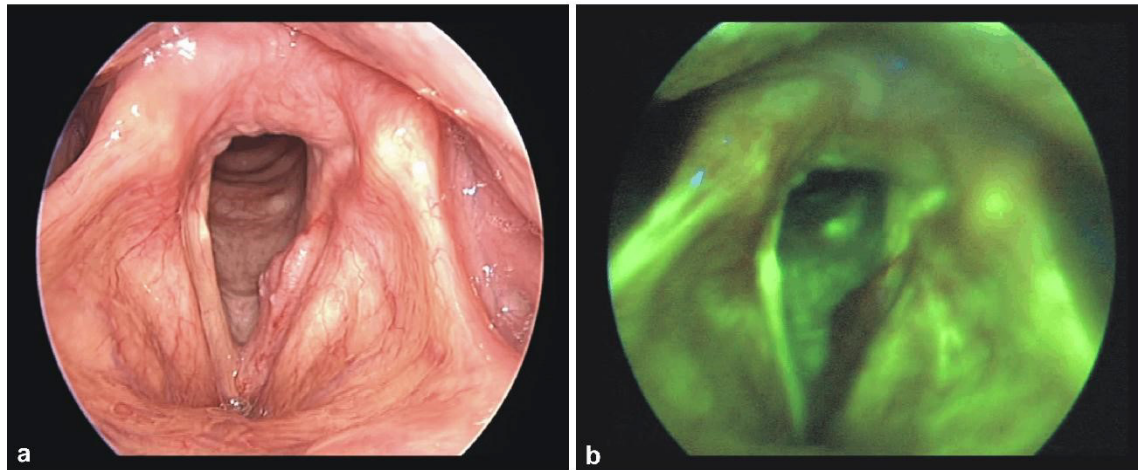


Figure 3 – Invasive carcinoma (pT1a): White light endoscopy (a) demonstrates a bulging tumor of the left vocal fold;

Figure 32:

- a) White light endoscopy demonstrating a lesion on left vocal cord
- b) Autofluorescence endoscopy shows a marked loss of autofluorescence of the lesion of the left vocal cord

Also this technique can be used both in the clinic and in the operating room and can be combined with HD technology, improving its sensitivity.

Autofluorescence with respect to NBI shows good sensitivity but poor specificity. Specificity improves when used intraoperatively because you can get closer to the lesion with the rigid telescope having fewer positive margins in the post-operative.

NBI

The introduction of NBI, which has already proved to be a useful screening method in other fields of endoscopy, has recently demonstrated its diagnostic potential in the early identification of carcinomas of the head-neck^{84,85}.

NBI is an innovative optical technology system that uses a double filter that selects only two wavelengths equal to 415 and 540 nm, corresponding to blue light and green light. The light filtered by the NBI corresponds to the absorption peak of hemoglobin (it absorbs the blue and green color while reflecting the red color), which is then particularly emphasized within the blood vessels which appear dark blue, if located at the level very superficial, or green, if located submucosally. In fact, the wavelength corresponding to blue light (between 400 and 430 nm) is able to penetrate the mucosa only on the surface, highlighting the vascularization contained in the surface layers; the wavelength corresponding to green light (between 525 and 555 nm), on the other hand, penetrates more deeply, highlighting the blood vessels of the submucosa.

It can be performed in the clinic with a rigid or flexible instrument and intraoperatively.

The NBI technique combines the potential of two methods:

1. Magnification and image processing capacity, typical of video endoscopy;
2. Evaluation of the content of hemoglobin by varying the spectrometric characteristics of the illumination light, obtained through an optical filter. The potential of the NBI is even more amplified if a HD camera system (HDTV) is used, capable of providing a signal 4.62 times higher than traditional systems. The advantage of NBI-HDTV technology is to emphasize the vascular architecture, ensuring the detection of lesions and precancerous epithelial cells thanks to their characteristic neoangiogenic hypervascularization.⁸⁵ The "satellite vessel" leading to the lesion is highlighted.

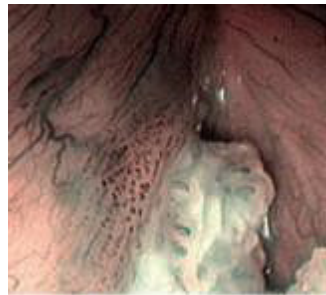


Figure 33: HDTV-NBI intraoperative endoscopy with rigid optic 30 ° showing the characteristic afferent hypertrophic vessel that branches into small ed irregular vascular loops in the context of the lesion

This technology permits a more accurate definition of the neoplastic superficial diffusion with a consequent improvement of the control of the surgical margins, tumoral staging and an "ad hoc" modulation of the endoscopic treatment and also allows an early diagnosis of persistence, relapses and metachron lesions without significantly increasing the time required for endoscopic evaluation and requiring no additional staining or tissue manipulation.

In 2011, the Chinese school of X-G Ni highlighted 5 vascular patterns:

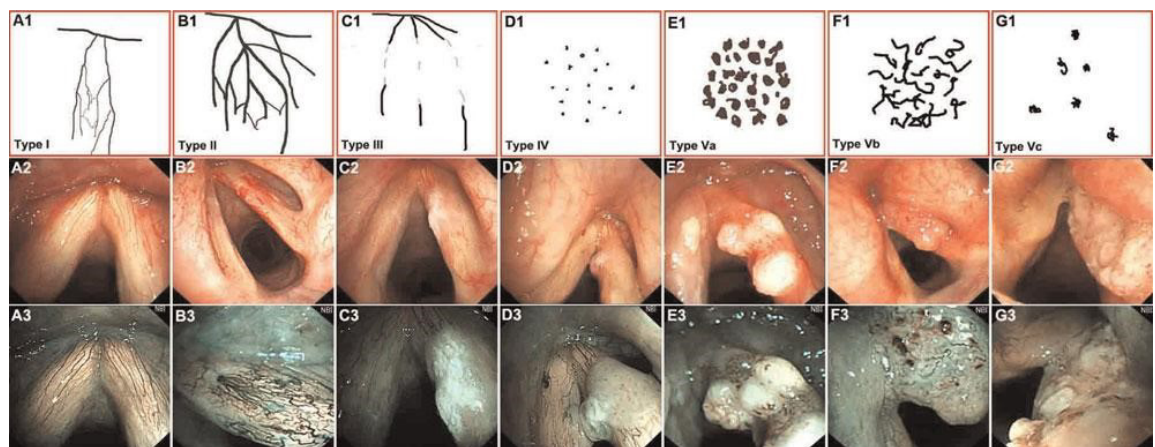


Figure 34 NBI vascular pattern

Type I (A1, A2 and A3): thin, oblique and arborescent vessels are interconnected and intraepithelial papillary capillary loops are almost invisible.

Type II (B1, B2 and B3): diameter of oblique and arborescent vessels is enlarged, and intraepithelial papillary capillary loops are almost invisible.

Type III (C1, C2 and C3): intraepithelial papillary capillary loops are obscured by white mucosa.

Type IV (D1, D2 and D3): intraepithelial papillary capillary loops can be recognized as small dots.

Type Va (E1, E2 and E3): intraepithelial papillary capillary loops appear as solid or hollow, with a brownish, speckled pattern and various shapes.

Type Vb (F1, F2 and F3): intraepithelial papillary capillary loops appear as irregular, tortuous, line-like shapes.

Type Vc (G1, G2 and G3): intraepithelial papillary capillary loops appear as brownish speckles or tortuous, line-like shapes with irregular distribution, scattered on the tumor surface.

Types I-II-III are suggestive of benign lesions;

Type IV the vascular network is interrupted by the lesion; Type

V indicates carcinoma in situ or invasive tumor lesion.

HD SPIES

Method that allows us to view a lesion in 5 different ways using an HD camera system:

1) STANDARD therefore white light (WL)

2) CLARA in which there is an increase in lighting and eliminates shadow areas

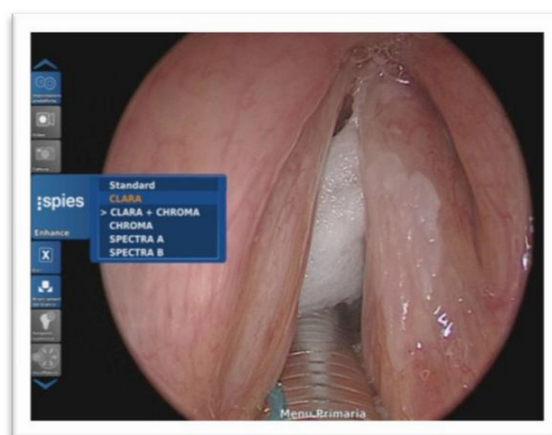


Figure 35: visualization of the lesion with CLARA way

- 3) CHROMA in which the vascular network is highlighted as it enhances the color contrast by emphasizing the detail of the vascular structures without altering the normal color perception.

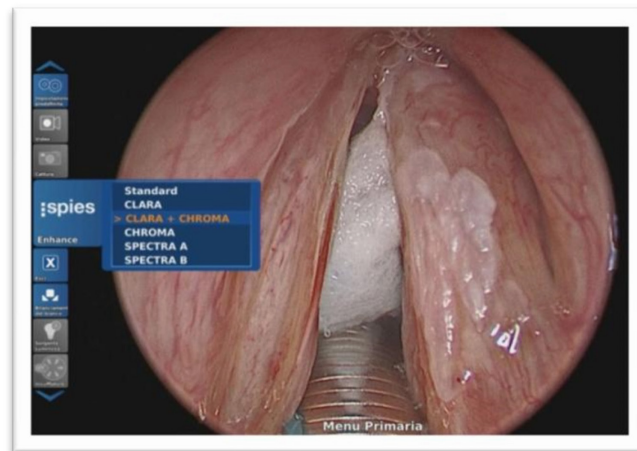


Figure 36: visualization of the lesion with CLARA + CHROMA way

- 4) SPECTRA A similar to NBI and is obtained by removing the red component from the traditional light spectrum. Thanks to the medium-low depth of penetration of green and blue, this modality emphasizes the contrast between capillaries and vessels of the mucosa and submucosa.

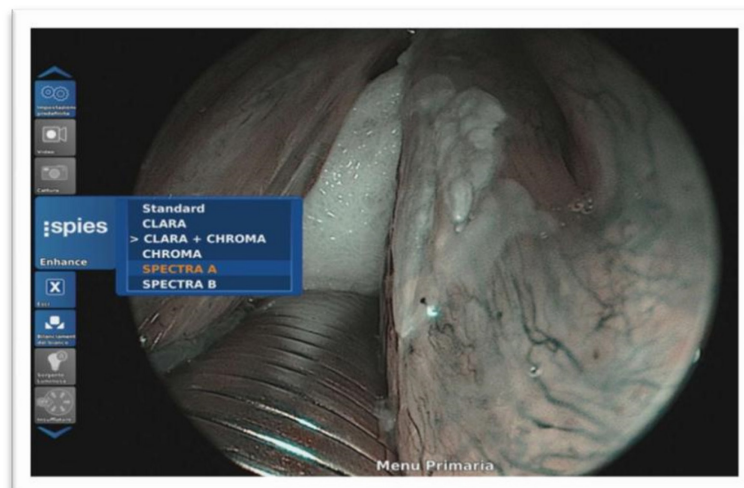


Figure 37: visualization of the lesion with SPECTRA A way

- 5) SPECTRA B is like spectra A but with greater highlighting of the red spectrum: this guarantees to highlight the vessels of the mucosa and submucosa without losing the information of the deeper layers that are visible only with red.

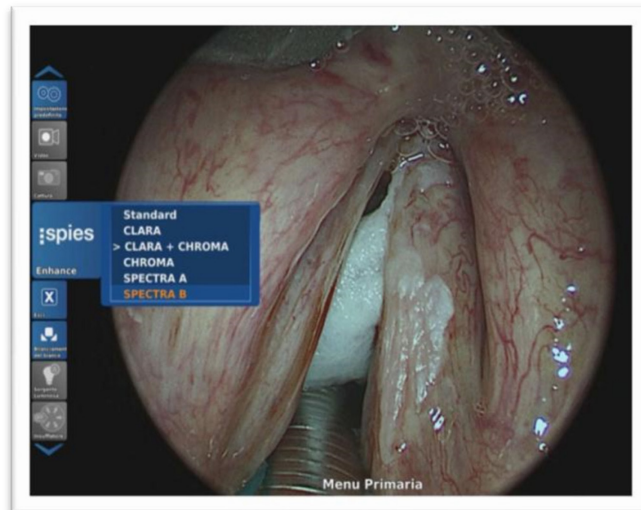


Figure 38: visualization of the lesion with SPECTRA B way

CONTACT ENDOSCOPY

It allows the clinician to evaluate the microvascular net in the healthy patient and in the pathological mucosa of the larynx and hypopharynx.⁸⁶

Numerous studies have shown that the structure and organization of vessels undergoes dynamic changes along the process leading from dysplasia to invasive cancer.

5 types: type 0 normal mucosa: thin and regular subepithelial vessels connecting with a thicker and deeper arborescent vascular network running parallel to the epithelium; type 1 inflammation: the subepithelial vessels are increase in number and size, with irregular and sometimes crossing directions; type 2 hyperplasia: when it is at the initial stage, intra-capillary loops are visible running toward the surface. In this phase, capillary loops are generally still very thin and short arising from the underlying inflammatory vasculature, with a scattered distribution but in case of mature hyperplasia, the deeper inflammatory vascular network is not visible, and only the elongated capillary loops can be easily seen. In the case of vegetating keratosis, the deeper inflammatory vascular network is often not visible and the elongated capillary loops are difficult to see.



Figure 39: vascular changes in case of hyperplasia

type 3 mild to moderate dysplasia: vascular changes become progressively more consistent, with elongated small vessels, but some arborescence appears at the end of the capillary loops.

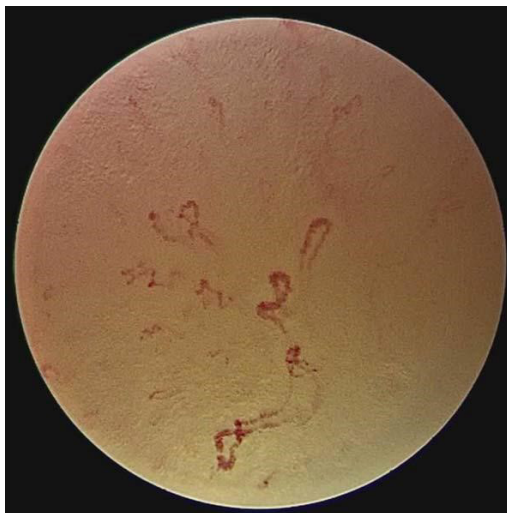


Figure 40: vascular changes in case of mild-moderate dysplasia

type 4 severe dysplasia-carcinoma in situ: the vascularity of the chorion is more evident and capillary loops appear significantly dilated, with various shape and a wide range of vascular architectural changes.

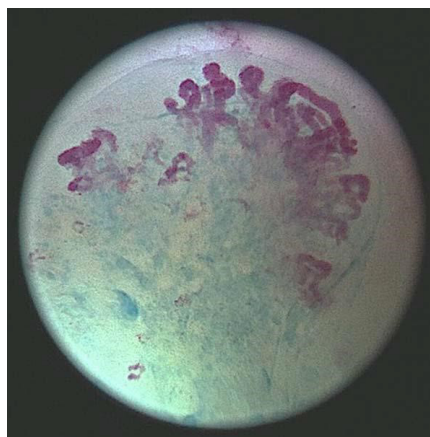


Figure 41: vascular changes in case of severe dysplasia and carcinoma in situ

In the operating room you must avoid bleeding to make bioendoscopy and always ask the anesthetist to use the glade to avoid injury or lacerations. These methods pay duty in all patients pretreated with both TLM and RT. Bioendoscopy becomes increasingly important so much so that in 2016 the ELS marks the descriptive guidelines by delineating only two vascular patterns divided into LONGITUDINAL (not suspected of lesions) and PERPENDICULAR (with identification of intraepitealy papillary capillary loops, a sign of preneoplastic or tumor lesion).

The perpendicular forms are three from a first dilated form, to an initial anarchic structure up to a bizarre course.

COMPUTED TOMOGRAFY (CT)

Compared to the clinical examination, CT plays a complementary role in the stage and follow-up of cancers of the larynx: it allows to determine the submucosal extension of the tumor, including any invasion of the adjacent structures, locoregional or systemic metastases, synchronous tumors, or persistence / relapse of disease. The possibility of a conservative surgical approach is confirmed or excluded by best evaluating some critical anatomical areas that influence the preferential pathways of neoplastic diffusion. Fundamental for the radiologist is therefore an adequate anatomical knowledge of the investigated district, of the infiltration and diffusion patterns of the neoplasm for each site and sub-site considered. The larynx, from the anatomo-topographical point of view, is composed of an external cartilaginous skeleton connected by fibrous ligaments and joints, and by an internal elastic skeleton that follows the profile of the mucous surface. The elastic skeleton chondrisates in some regions and forms the epiglottis, the cuneiform and corniculate cartilages and the vocal process of the arytenoid. The laryngeal mucosa arises superficially to the elastic skeleton, while the submucosa is between the elastic skeleton and the cartilage. Internal and external skeleton in some sites are very close (anterior commissure, vocal cords) making the presence of the submucosa minimal or virtual. The latter, in the front macrosections, appears as an hourglass; abundant in supraglottis and hypoglottis, poor at glottic level. The submucosa corresponds to the paraglottic spaces, rich in loose

connective tissue, glands and lymphatics. They include the preepiglottic space, the upper and lower paraglottic spaces. These spaces communicate with each other and condition the pathways of tumor diffusion.^{87,88}

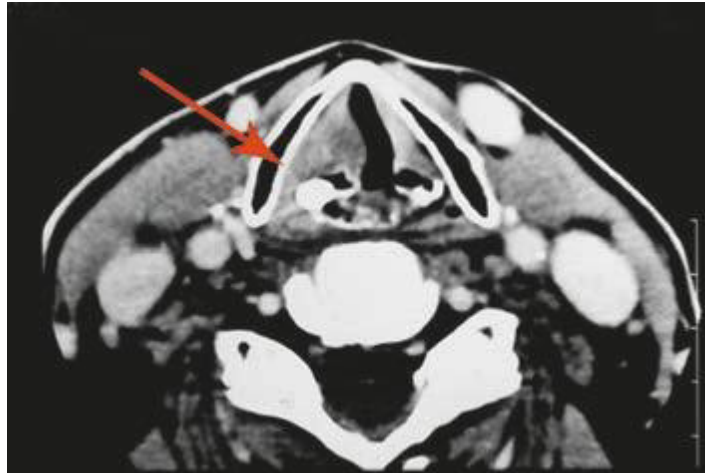


Figure 42: Axial CT image that shows glottic cancer on the left vocal cord with the involvement of the inferior paraglottic space

CT is the main imaging method used for the staging of hypopharyngeal-laryngeal neoplasia: the data is justified by the greater operational availability of CT equipment, by the limited experience of nuclear magnetic resonance (MRI) operators and by the short duration of the examination. MRI is typically used as a diagnostic complement in cases where CT does not provide the information necessary for therapeutic planning.⁸⁹

The patient is placed on his back and instructed not to swallow or cough and to maintain a calm breath. Axial scans are obtained, extended from the upper dental arch to the thorax, in the pre- and post-contrast phase and with a layer thickness of 1 mm. The acquired volume is then reformatted in postprocessing in the oblique axial planes, with orientation parallel to the true vocal cords, coronal (for a better evaluation of the paraglottic spaces and the laryngeal ventricle) and sagittal (to better investigate the preepiglottic space and the lingual base). In selected cases, additional dynamic scans are performed during speech with the letter "E" or Valsalva maneuver to enhance the visibility of some anatomical areas such as the laryngeal ventricle or hypopharynx.

CT in the staging phase plays a key role in the evaluation of submucosal tumor spread: the predominantly adipose content of these spaces offers towards the tumor tissue a natural contrast that can be further emphasized by the intravenous injection of iodized contrast medium.

Proper preoperative work up, supported by CT imaging, is therefore essential to plan the most appropriate surgical approach for the patient.

The questions that the surgeon and radiologist must answer are:

1. What is the real submucosal extension of the neoplasm?

2. Does it involve critical sites from the point of view of T staging (preepiglottic space, paraglottic space, cartilages, lingual base, etc.)?
3. Is there associated lymph node disease?
4. Coexists a second proximal or pulmonary, esophageal synchronous tumor?
5. Is conservative surgery still feasible?
6. And, among the conservation possibilities, which one to propose?

CT provides key information about the submucosal extension of the disease, the tumor volume, the extra-laryngeal extension and the staging of N. In addition, by extending the CT study to the chest in the staging phase, it is also possible to obtain additional information about the presence of any synchronous pulmonary neoplasms, playing a key role in therapeutic planning.

MRI

MRI has the ability to discriminate different tissues much more precisely than CT through the use of T2 and T1 weighted sequences; this attitude is enhanced by the use of paramagnetic contrast media.

MRI is usually reserved to particular cases, in which the information provided by the CT is not considered sufficient to resolve clinical questions on the presence of submucosal lesions or on the infiltration of cartilage.⁹⁰ The greatest limits to the use of MRI in the study of the larynx are of a technical nature: spatial resolution and long acquisition times. The latter results in an incidence of movement artifacts (breathing and swallowing) higher than that of CT, often with significant degradation of image quality. These disadvantages actually represent two sides of the same coin: in fact, spatial resolution and duration of the acquisition are directly dependent on each other. In recent years, thanks to the development of new sequences, new coils and dedicated study protocols, the MRI study of the larynx has become faster. This allowed to improve the spatial resolution of the images and minimize the presence of artifacts. Furthermore, the use of functional studies like diffusion-weighted magnetic resonance (DWI) and dynamic MRI has become possible, opening up new scenarios in the field of characterization of neoplasms from the point of view of biological aggression, early control of response to treatment and differential diagnosis between post-treatment alterations and relapses.

1. Improvement of signal and spatial resolution

The phased-array coils, made up of many small elements that simultaneously and independently acquire the signal from the volume under examination, combine the advantages of small coils (high signal) and those with larger dimensions (wide field of view).

Another method to maximize the signal provided by a coil is to minimize the distance between it and the volume to be studied: for this purpose, coils with reduced dimensions and particular designs have been designed, suitable to be applied directly

to the patient's neck. These surface coils provide a very high signal within a limited field of view. They express their maximum potential when used individually. They have the disadvantage of limiting the useful field of view to a few centimeters in depth with respect to their position. However, if there is a need to view larger or deeper volumes, they can be combined with traditional coils.

2. Reduction of acquisition times and motion artifacts

The use of surface coils makes the sequences more sensitive to movement and can reduce the patient's comfort during the examination, due to the positioning on the neck that is not always tolerated. Movement artifacts caused by breathing, pulsation of the vessels and swallowing represent, in fact, the major problem in MRI imaging of the larynx.

It is therefore necessary to obtain the essential information as quickly as possible, to avoid the risk of producing non-diagnostic images.

However, if the breaths are regular and not too deep, they do not generate artifacts. Furthermore, to reduce the pulsation artifacts of the carotid arteries, it is useful to place pre-saturation bands caudally to the acquisition volume, with the aim of canceling the signal of the protons that quickly enter the field of view, following the flow of blood. It is necessary that imaging provides detailed information about the anatomy of the paraglottic space and the signs of its possible infiltration. To do this, the paraglottic space must be displayed both on the plan axial than coronal. MRI better distinguishes the fat signal (hyperintense in T2 and T1) of the para-glottic space compared to that of intrinsic musculature (hypointense in T2, with intermediate density in T1) and that of tumor tissue (generally hyperintense compared to muscle) than CT in T2 but constantly hypointense with respect to adipose tissue.⁹¹

It is also important to study the pre-epiglottic space. Because of its median arrangement, with prevalent vertical development, and of the anatomical communications with the surrounding spaces, the ideal planes for the study of preepiglottic space are the axial and sagittal planes.⁹² MRI is able to clearly visualize the signal of the adipose tissue contained in this space, although its evaluation can sometimes be denied from the movement of the epiglottis and cyclic deformation during breathing.

The presence of cartilage invasion influences both the choice of surgery and the outcome of RT, with an increased risk of relapse and radionecrosis.^{93,94} Laryngeal cartilages comprise three components: non-ossified hyaline cartilage, cortical bone, and medullary bone. Epiglottis and vocal process of the arytenoid cartilages usually remain non-ossified, while the other cartilages undergo a process of enchondral ossification of varying degrees during growth. The presence of nonossified areas in adults is usually, but not always, symmetrical in the thyroid cartilages. CT allows an excellent visualization of the ossified components of the cartilages (high attenuation of the cortical bone, minor attenuation in the trabecular bone of the medulla); the hyaline component, on the other hand, has a density similar to that of soft tissues and therefore cannot be discriminated from them. MRI provides a better distinction of

these three histological components: very low signal in T1 and T2 for the cortical bone, high signal in T1 and T2 for the medulla (due to the presence of adipose tissue between the bone trabeculae), low signal in T1 and T2 for hyaline cartilage. Under physiological conditions there is no enhancement after administration of contrast medium. The neoplastic invasion of the cartilages occurs preferentially where the collagen fibers are inserted on the perichondrium; this condition occurs in specific locations: the anterior commissure, the junction between the anterior and posterior three quarters of the thyroid lamina, the posterior border of the thyroid cartilage, the crico-arytenoid joint and the insertion of the cricothyroid membrane. The ossified components of the cartilage seem to be more predisposed to neoplastic invasion.

Tumors of the anterior commissure⁹⁵ are characterized by a higher incidence of relapses, therefore imaging must provide targeted indications. MRI with surface coils could be superior to CT in determining cartilage invasion, the presence of tumor within Broyle's ligament, consisting of fibrous tissue and therefore more hypointense than the tumor in T2 images; moreover, MRI can demonstrate early spread to prelaryngeal tissues through the gap existing between the anterior margins of the thyroid laminae. MRI in the follow-up is fundamental.

Imaging must be able to differentiate the neoplastic tissue of any recurrence or persistence from inflammatory changes secondary to surgical or chemo-radiotherapy treatments: edema, granulation tissue /scar/granuloma, radionecrosis of the mucosa and cartilage.⁹⁶ The high contrast resolution of MRI allows the complex pattern of signals present within an anatomical field altered and distorted by the treatment to be better classified than CT. However, performing an MRI exam in patients prostrate from treatment, sometimes dyspnoic and suffering and therefore not very cooperative, is not easy and in some cases it is not even feasible.

The presence of edema is a common condition after TLM and RT. In the latter case, the edema can persist for many months after the end of the therapy. In the MRI study, edema is characterized by a high signal in the T2-weighted sequences. Although the edema consists of exudate in the interstitial space and therefore by definition is not vascularized, it is accompanied by an increase in the vascular permeability of arterioles and capillaries and can cause a compression of the venules, preventing the normal flow of blood: for this reason within the edematous tissues a modest enhancement can be recognized, which is usually lower and less homogeneous than that of the mucosa but can make it difficult to recognize small neoplastic residues. The edema resulting from the RT or TLM usually involves the mucosa, however it can also be present within the vocal muscles.

The presence of scar tissue is the typical outcome of surgical treatment. The appearance of the scar is that of a retracting tissue, without a nodular appearance, with poor enhancement, recognizable along the course of the resection. In the outcome of cordectomy, the scar usually has a linear appearance, involves the vocal muscle and/or the para-glottic space and can lead to a cancellation of the adipose signal of the latter (type IV and V cordectomy). There are hypertrophic scars, which modify the profiles of the mucosa, in the staging and follow-up of laryngeal neoplasms, simulating a submucosal neoplasm on endoscopic examination. Scar tissue has a very low MRI

signal in T2-weighted sequences; this feature makes the distinction between scar and neoplastic recurrence / persistence easier than with CT, in which the densities of tumor and scar tissue are similar. However, the surgical wound repair process consists of several phases, of which the formation of a mature, that is stable, scar is only the last. Granulation tissue, which precedes fibrosis, is characterized by angiogenesis, just like neoplasms. It is therefore intuitive that the differential diagnosis with tumor tissue is very difficult.

In about 1% of patients, RT is followed by a serious complication, consisting of necrosis of the mucosa and laryngeal cartilages. The peak incidence of radionecrosis is around twelve months from the end of treatment, comparable to that of neoplastic relapses; however, cases are described in which radionecrosis follows the term of radiotherapy for many years (late radionecrosis). The mechanism of radionecrosis consists in endothelial fibrosis caused by actinic damage, which in turn generates ischemic necrosis of the mucous membranes. Cartilages are more resistant than mucous membranes to radiation damage, however if the perichondrium is damaged, it is possible for microorganisms to infect the irradiated cartilage, triggering the mechanism of necrosis. Mucosal changes consist in the formation of ulcers and fistulas. On MRI, mucosal necrosis is recognized as the presence of nonenhancement tissue, which is usually well differentiated from the surrounding mucosa with enhancement even higher than normal, due to the presence of inflammatory changes and granulation tissue. The signs of cartilage necrosis are detectable adjacent to and within the cartilages, in the sites where the greatest number of persistence/relapses is found. CT is better able to detect the presence of bone fragments of destroyed cartilage and the presence of air bubbles in the surrounding tissues than MRI. MRI is superior to CT in visualizing inflammatory changes within the cartilages (loss of the adipose signal of the medulla in T1 weighted sequences without contrast medium; enhancement of the bone marrow after contrast medium). Effusion can be found around necrotic cartilages, especially adjacent to the thyroid laminae.

Both methods correctly identify sclerosis which is often present at the level of the arytenoid cartilages and the cricoid; the presence of sclerosis cannot however be considered as a sign of radionecrosis. The differential diagnosis between (chondro) radionecrosis and neoplastic persistence/relapse is among the most difficult and the presence of the described signs cannot exclude the coexistence of tumor residues. Signs of perichondritis and chondritis can also follow TLM, when the resection techniques involve exposure or resection of the perichondrium. It is therefore of fundamental importance to be aware of the resection techniques used in the treatment of primary cancer.⁹⁷

In relation to the above, MRI is considered as the first choice for the follow up of laryngeal neoplasms with suspected recurrence in collaborating patients. MRI could also be used to accurately classify tumors extending to the anterior commissure. For the other studies, e.g. the staging of almost all primary neoplasms, CT can still be considered as the technique of choice, by virtue of its practicality and availability.

ADVANTAGES OF TLM

- Rapidity of treatment,
- Repeatability of treatment
- Good compliance by the patient,
- Low morbidity,
- Preservation of intrinsic musculature and cartilagenous skeleton,
- Sporadic need of tracheostomy,
- Short hospitalization,
- Limited costs.

CONTRAINDICATIONS FOR TLM

Keep attention to pattern of spread of laryngeal cancer.

Contraindications for TLM are spread of cancer to cartilagenous skeleton, to posterior commissure and to lower paraglottic space and the crico-thyroid joint. The growth of laryngeal cancers depends a great deal on the site of onset and take place along preferential route. The knowledge of anatomy of the larynx and the study of the spread of tumours are the basis of the concepts of functional laryngeal surgery. The correct staging of the tumor is the basis of a correct therapy and, consequently, of an optimal oncological result. At the origin of the local recurrences there is probably a staging error that ignores the true extent of the tumor and leaves residues of the disease after surgical resection.

The attention of the surgeon and radiologist must focus on the study of the critical points of the larynx which is carried out by performing endoscopy and CT and MRI evaluating the natural ways of spreading the laryngeal tumor.

Whether or not these areas are involved will lead us to the most suitable surgical proposal.

- 1) Thyroid cartilage: in glottic and transglottic tumors its infiltration contraindicates TLM and points towards an OPHL, not necessarily towards a total laryngectomy.

The AC is a critical area for the larynx surgeon. The epithelium is only 1-2 mm from the cartilage, there is no perichondrium and of the entire larynx is the area of most difficult exposure. T1a vocal cord tumor reaching the AC is easily tamed and CT is rarely required. Instead the primary carcinoma of the AC, fortunately much rarer eventuality, is a more risky situation for transglottic and transcartilagenous diffusion and it is mandatory to perform a CT scan.

- 2) Pre-epiglottic space and superior paraglottic spaces;
- 3) Lower paraglottic space and the crico-thyroid joint: they are anatomical spaces in continuity with each other and their possible infiltration excludes TLM;
- 4) Lateral crico-thyroid space: from the lower paraglottic space the neoplasm can insinuate laterally into the crico-thyroid space and emerge from the larynx.

It is necessary to evaluate the cause of hypomobility or fixity of the vocal cord which can be caused by the mass effect due to the volume of the tumor, by infiltration of the vocal muscle or deeper by involvement of the lower paraglottic space and the cricoarytenoid joint.

It should be borne in mind that a deep anterior tumor infiltration is well dominated with a type IV cordectomy while a posterior extension gives worse results in terms of local control.

- 5) Anterior crico-thyroid space: palpatory evident along the anterior profile of the larynx, between the thyroid and cricoid cartilages. Any infiltration of this space indicates that the tumor has emerged from the larynx;
- 6) the subglottis.

The surgeon must know and know how to manage all therapeutic options; the possibility of a more conservative approach with acceptable oncological results must always be taken into consideration.

The pattern of spread of chordal tumors is of three types:

- a) Horizontal spread. More frequently it occurs in the anterior direction, towards the AC: this virtual space is in fact a critical point from which the tumor can invade the thyroid cartilage, the anterior subglottis, the inferior pre-epiglottic space and spread to the extralaryngeal site through the cricothyroid membrane.

The neoplasm can also spread in a posterior direction, towards the posterior commissure, and from here extend to the arytenoid and cricoid cartilages or to the crico-arytenoid joint, with possible submucosal involvement of the apex of the piriformis sinus (and access to the lymphatic drainage): the posterior diffusion towards the crico-arytenoid joint contraindicates TLM. The last escape route is in the lateral direction, along the mucosa – vocal ligament – vocal muscle – paraglottic space – perichondrium – cartilage. Particularly critical is the invasion of the lower paraglottic adipose space, which determines the transition to stage T3 contraindicating laser resection or cordectomy: CT and MRI at this level have equal diagnostic accuracy (80%).

- b) Cranial diffusion. The growth pattern, typically submucosal, makes these tumors often misrecognized at endoscopic investigation (unless they cause a bulging of the mucosa) or underestimated: CT and MRI are therefore essential to define their real extent before surgery. Tumor can spread vertically along the anterior midline and have a tendency to invade the laryngeal structure and crico-thyroid membrane. In these infiltration patterns the risk of lymph node metastases increases⁹⁸.
- c) Caudal diffusion. In chordal tumors, subglottic involvement is relatively common. The lower diffusion can occur superficially or submucosally, therefore it can be difficult to highlight endoscopically with the risk of understage if imaging is not associated with the clinical examination. The hypoglottic cone, in the CT and MRI axial sections, is a perfect oval: a thickening of the soft parts at the level of the lower cricoid margin should be interpreted as a neoplastic extension until proven otherwise. The contribution of CT and MRI to the neoplastic invasion of the cricothyroid membrane is critical: at this level the soft tissues are invaded through the neurovascular foramina of this membrane or at the level of its insertion at the lower surface of the thyroid cartilage.

LIMITS OF TLM- EXPOSURE-

In the last decades, TLM has become a widely accepted surgical procedure for definitive diagnosis and treatment of selected benign and malignant laryngeal diseases. Good exposure and visualization of the glottic plane, especially at the level of the anterior one-third of the vocal cords and AC, should be always regarded as an essential prerequisite for an effective operative microlaryngoscopy. In fact, if the entire glottis

is not appropriately visualized through direct laryngoscopy due to suboptimal laryngeal exposure, misdiagnosis, incomplete resection, or inadvertent injury to teeth and pharyngolaryngeal soft tissues can be easily encountered.⁹⁹ Anesthesiologists first defined the concept of the difficult airway and suggested the importance of an accurate preoperative evaluation in order to avoid potential difficulty during orotracheal intubation and reduce the incidence of life-threatening complications.¹⁰⁰

The surgeon's main aim during microlaryngoscopy is to obtain optimal exposure affording complete visualization of the larynx. This is required to maximize functional outcome during phonosurgery and, importantly, to completely resect the tumor and lessen the risk of local recurrence during laryngeal cancer removal. Indeed, a retrospective study recently demonstrated a 4.6-fold higher rate of local recurrence in patients with difficult laryngeal exposure (DLE)¹⁰¹ but at the same time underlined the difficulty predicting it preoperatively.

The basis for performing a safe transoral surgery is adequate exposure of the area to be treated to minimize the risk of damage to surrounding tissue or incomplete resection, which is especially important in oncologic surgery.¹⁰²

The Laryngoscore¹⁰³ is a reliable and easily reproducible score to preoperatively detect the occurrence of DLE before operative microlaryngoscopy.

It is a preoperative assessment protocol including 11 parameters: interincisors gap (IIG), thyro-mental distance (TMD), upper jaw dental status, trismus, mandibular prognathism, macroglossia, micrognathia, degree of neck flexion-extension, history of previous open-neck and/or RT of the head and neck, Mallampati's modified score, and body mass index (BMI).

Interincisors gap	≥ 4 cm	0
	< 4 cm	1
Thyromental distance	> 6.5 cm	0
	6–6.5 cm	1
	< 6 cm	2
Upper jaw dental status	Edentulous	0
	Partially edentulous	1
	Normal teeth	2
	Prominent teeth	3
Trismus	No	0
	Yes	1
Mandibular prognathism	Absent or reducible	0
	Present or not reducible	1
Macroglossia	No	0
	Yes	1
Micrognathia	No	0
	Yes	1
Degree of neck flexion– extension	$> 90^\circ$	0
	80° – 90°	1
	$< 80^\circ$	2
Previous treatments (RT, open-neck surgery)	No	0
	Yes	1
Mallampati modified classes	I. Hard and soft palate, uvula, and pillars visible	0
	II. Hard and soft palate, and base of uvula visible	1
	III. Hard and soft palate visible	2
	IV. Only hard palate visible	3
BMI	≤ 25	0
	> 25	1

Table 2: Laryngoscore

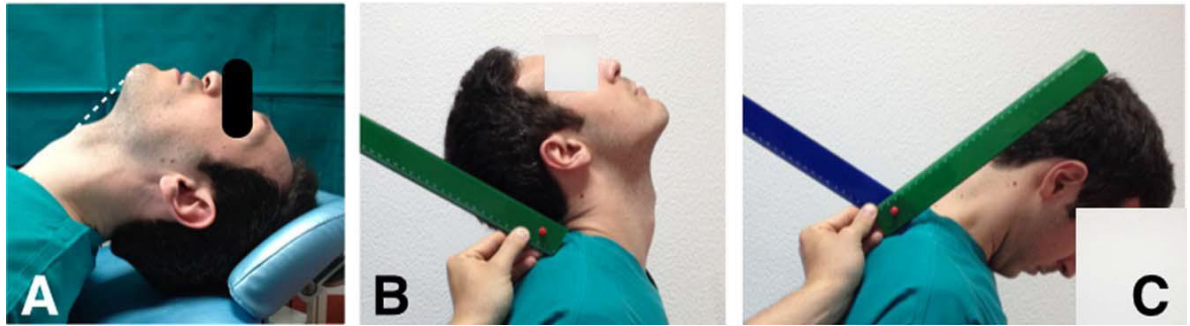


Figure 43: A How to calculate TMD
B and C How to calculate the degree of neck flexion-extension

Each parameter was assessed and scored as follows:

- IIG was measured, with the mouth fully open, between the upper and lower teeth when present, and between the upper and lower gums in edentulous patients. It was then categorized as ≥ 4 cm (score 0) or <4 cm (score 1);
- TMD was measured along a straight line from the thyroid notch to the lower border of the mandibular symphysis with the head fully extended, and categorized as >6.5 cm (score 0), between 6 and 6.5 cm (score 1), or <6 cm (score 2);
- Upper jaw dental status was scored 0 in edentulous subjects, 1 in partially edentulous, 2 in presence of normal teeth, and 3 in case of prominent superior teeth;
- Trismus was scored 0 if absent and 1 when present;
- Mandibular prognathism was considered as the position of the lower incisors in front of the upper ones, and was scored 0 when absent or reducible, and 1 when present and not reducible;
- Macroglossia was considered as the situation in which patient's tongue fills the entire oral cavity, and was scored 0 if absent and 1 when present;
- Micrognathia was scored 0 when absent and 1 if present;
- Degree of neck flexion-extension was measured as described by asking the patient to extend the neck and then measuring the arc from this position to that of full flexion of the neck on chest. The range of motion was categorized as, $>90^\circ$ (score 0), between 80° and 90° (score 1), or $<80^\circ$ (score 2);
- Previous open-neck surgery and/or RT on the head and neck were scored 0 if never performed and 1 in treated patients;
- Evaluation of oral and oropharyngeal structures was assessed in the sitting position, without phonation, leaving the tongue inside the mouth, by the modified Mallampati's score assigning score 0 to class I, score 1 to class II, score 2 to class III, and score 3 to class IV;
- BMI was scored 0 when <25 kg/m² and 1 when >25 kg/m².

The scores of each parameter were added to obtain a sum potentially ranging from 0 to 17.

When the score was <6 it was a condition of good laryngeal exposure (GLE); this situation can be considered the ideal for treating “difficult” lesions and teaching operative microlaryngoscopy to residents and junior staff members. Conversely, when the Laryngoscore was >6 40% of patients had DLE, an aspect that should be always discussed with patients during preoperative counseling.

In fact, better surgeon–patient and surgeon–anesthesiologist counseling are two of the most important outcomes expected from the routine application of such a clinical tool. The Laryngoscore herein presented is easy to use, reliable, and reproducible.

It allows identifying GLE with a great confidence, while alarming about possible DLE (especially in the presence of high scores and alteration of specific parameters). The entire Laryngoscore evaluation typically required 3 to 4 minutes to be fully accomplished.

An adequate AC exposure is an indicator of an ideal condition. In the case of a therapeutic microlaryngoscopy, a DLE could represent a contraindication and the patient should be referred for open surgery or nonsurgical treatment.

Considering that the surgeon’s strength, dexterity, and expertise could influence the efficacy of a surgical procedure, and that adequate experience in handling the instruments is important especially during TLM.

Glottic Exposure for Transoral Laser Microsurgery: Proposal of a Mini-Version of the Laryngoscore (mLS)

However, one of the main disadvantages of the Laryngoscore was the presence of inherently subjective variables that may hamper its reliability and general applicability increasing the inter- and intraobserver variabilities. In particular, variables such as macroglossia, micrognathia, prognathism, and trismus, although useful to obtain comprehensive evaluation of the individual patient, do not represent objective and absolute measures.

In consideration of the main drawbacks observed in its original version, mLS¹⁰⁵ is a revised and abbreviated version that can grant even quicker, yet sufficiently accurate and less subjective, preoperative evaluation of laryngeal exposure prior to TLM.

It has been confirmed a significant impact of IIG, TMD, and upper jaw dental status. This has been performed in keeping with the general principles of surgical scoring systems, focusing on minimization of intra- and interobserver variabilities and optimization of its predictive potential.¹⁰⁶

The rationale for this choice, supported by multivariate analysis, was to select the most predicting criteria adhering to the above mentioned principles. In general, mLS may be viewed as a quick evaluation potentially substituting the purely subjective impression upon which most surgeons rely when evaluating a patient before TLM. Indeed, IIG and upper jaw dental status are the first characteristics that both surgeons and anesthesiologists assess when thinking about transoral access to the airways.

Although upper jaw dentition retained a certain degree of subjectivity due to the differentiation between “normal” and “prominent teeth,” this had been improved routinely classifying those with a class II dentition or upper jaw dental implants as “prominent teeth”.

Interestingly, Rose and Cohen also reported that IIG and TMD were the most significant clinical variables predicting difficult access to the airways in 18,500 patients, with a relative risk of 10.3 and 9.7, respectively.¹⁰⁷

In keeping with the original intent of the Laryngoscope, evaluation of IIG, TMD, and upper jaw dental status does not need specific instruments (except for a ruler) and can be performed in an office setting in few seconds, even by relatively unexperienced transoral surgeons having an appropriate knowledge of such a preoperative scoring system.

With a score of mLS=0, TLM may be safely planned and DLE should only be regarded as a rare inconvenient. The patient should always be informed about this rare event, while assuring a high probability of being able to adequately perform

TLM.

With mLS = 1, patient is characterized by a high likelihood of obtaining GLE (85%) with, however, a 15% incidence of poor or impossible visualization of the glottic plane. In this regard, patient counseling is essential, and the surgeon should consider alternative procedures as a secondline approach in case of major limitations for TLM. The characteristics of the lesion to be removed play an important role when evaluating their ideal management. In particular, small lesions involving only the posterior third of the vocal fold may usually be effectively approached by TLM, even in case of suboptimal exposure. On the other hand, larger lesions and those involving the anterior third of the glottis and/or the AC may sometimes require a second-line option that should always be considered preoperatively.

Considering the third situation (mLS = 2), a high chance of DLE (45%) should prompt to carefully review the indications for TLM. The patient should be informed about the possibility to stop the transoral procedure without being able to remove the lesion or to shift intraoperatively toward different treatment options.

Finally, the fourth group (mLS $\geq$ 3) represents the absolute minority of patients and is characterized by a highly unfavorable anatomic conformation that seldomly allows a GLE. In these cases, purely diagnostic laryngoscopy by angled telescopes should be planned to allow examination and, when needed, biopsy of the lesion itself. Different approaches according to the nature of disease should be considered as the first-line indication, reserving TLM only for rare cases in which GLE should be serendipitously found.

This preoperative algorithm may greatly improve patient management by identifying various categories that could benefit from different approaches in everyday clinical practice.

Interincisors gap	≥ 4 cm	0
	< 4 cm	1
Thyromental distance	> 6.5 cm	0
	6–6.5 cm	0
	< 6 cm	1
Upper jaw dental status	Edentulous	0
	Partially edentulous	0
	Normal teeth	1
	Prominent teeth	2

Total 0–4

Table 3: The Three Parameters and Related Scoring System of mini-Laryngoscore

SURGICAL TECHNIQUE

Complete oncological radical removal of the tumor is essential.

TLM follows the spread of the tumor under microscopic control, adjusting resection to the operative findings.

TLM is custom-tailored to the individual tumor with an excellent view of the limits and maximal preservation of normal tissue and function. The tumor is divided into manageable units with the laser beam and removed stepwise until excision is complete. It is shown that transecting tumors is not producing an increase rate of regional or distant metastasis.^{108,109}

The extent of the tumor must be clearly distinguishable under the operating microscope.

The lesion must be resected until healthy tissue is found, and an appropriate safety margin is obtained. Sometimes, resection of healthy tissue, such as the false vocal cord, is indicated to approach the tumor located in the ventricle or true vocal fold.

The tumor will be excised in more than one section.

The laser incisions into and through the tumor enable the surgeon to identify the real extension of the cancer and to estimate the depth of tumor penetration.

The concept of piecemeal resection of larger tumors can be explained showing that:

- a) Unsatisfactory approach to tumor removal that makes it difficult to assess the deep margins;
- b) The tumor is transected to assess the depth of infiltration
- c) Debulking is performed initially, followed by trasection of the tumor to identify the depth of infiltration.

An important benefit of transecting the primary tumor is the intraoperative clarification of the third dimension, the exact depth of infiltration, and the meticulous evaluation under high magnification to determine clearly the deep margin, which is crucial to a complete excision. A small spot size and superpulse mode on the laser lessen carbonization and aid the contrast between tumor and normal tissue. In doubtful cases, confirmation of clear surgical margins can be obtained by frozen section.

TLM can be easily repeated if inadequate resection margins are proven by postoperative pathology. Positive margins should rather be submitted to resection to improve overall survival.

An excision margin of 1 to 2 mm is appropriate at the laryngeal glottis.

With TLM, R0 resection can be attained with margins as small as 1–2 mm. For early glottic cancer, the scarce glottic submucosal lymphatic network suggests that surgical margins can be narrower than required in other head and neck cancers; if surgical margins are surely close or positive, further treatments should always be given; even if the percentage of histologically confirmed neoplastic tissue in the specimen of the laser re-resection can be low. This leads to minimal morbidity, good phonatory outcome and good oncological outcomes.

The disease is eradicated with maximal preservation of the normal layered structure of the vocal folds.¹¹⁰

However, the relationship between resection margin status and relapse rate is still controversial.^{36,111}

If any suspicious areas are detected, additional tissue can be excised and sent for frozen sections. All resection specimens must be properly marked for orientation in order to enable the pathologist to make a valid assessment.

Frozen sections may be required intraoperatively and the pathologist should be encouraged to attend the operating theater and made to understand the issues of the postoperative examination of the resected tumor bulk and the specimens obtained from the margins. A meticulous synopsis of clinical and histological findings during and after surgery is essential.

After each vertical incision through the tumor to the area of normal tissue has been made, the tissue portion harboring the tumor is removed and the deep resection margin of this specimen is marked with a pen.

Video documentation of the procedure is very helpful.

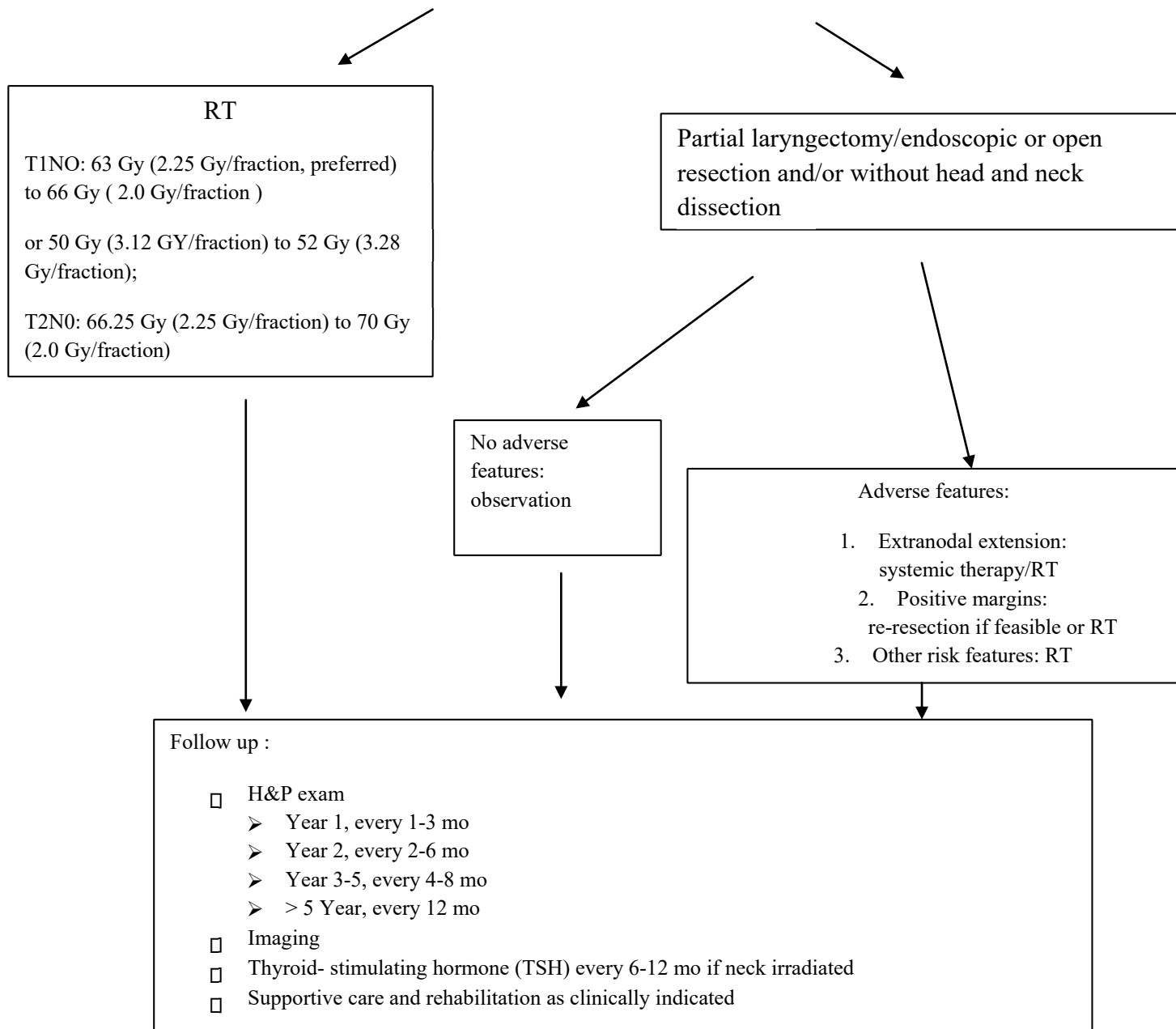
**NCCN (NATIONAL COMPREHENSIVE CANCER NETWORK)
GUIDELINES VERSION 2. 2020 for early glottic cancer ¹⁷**

Carcinoma in
situ



Endoscopic resection preferred or RT (60.75 Gy/fraction)

Amenable to larynx-preserving (conservation) surgery (T1-T2, N0 or select T3,N0)



Adverse features: extranodal extension, positive margins, close margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion and lymphatic invasion.

ELS CLASSIFICATION OF CORDECTOMIES

Since its introduction in laryngeal surgery, TLM has been widely adopted for the treatment of early stage malignant tumors of the larynx.

Lynch¹¹² first introduced the technique of endoscopic cordectomy in 1920. Lillie and De Santo¹¹³ in 1973 and Kleinsasser¹¹⁴ in 1974 reported excellent results for a series of endoscopic cordectomies that were performed using cold instruments. However, it has only been since Strong's work¹¹⁵ and use of the CO₂ laser that the present technique of cordectomy began to develop. There is no uniformity between the classifications proposed by the various authors.¹¹⁶⁻¹²²

In 2000, the working committee of the ELS proposed a simple, easy-to-use classification for cordectomies³³ based on the depth and extent of surgical resection in order to ensure better definitions of postoperative results, to reach better agreement and uniformity and to offer reproducibility to the majority of laryngologists to allow relevant comparisons with the literature when presenting/publishing the results of cordectomies. This classification was revised in 2007³⁴. A common classification of cordectomies is necessary in order to understand and to compare postoperative results following different types of cordectomies that are based on each surgeon's own indications. Furthermore, this system improves the teaching and training of inexperienced laryngologists.

Based on the extent of surgical resection, cordectomies can be classified into six types with the fifth type divided into four subtypes^{33,34}. Each type of cordectomy is defined by a name and a number. The numerical classification is shorter to enumerate and therefore more practical in everyday practice.

Type 1 cordectomy or subepithelial cordectomy consists of the resection of the epithelium, passing through the superficial layer of the lamina propria, sparing the deeper layers and thus the vocal ligament.

Subepithelial cordectomy is performed for cases of vocal fold lesions suspected of premalignant or malignant transformations.

As the entire epithelium is generally affected in various degrees of severity, it is usually necessary to resect it completely.

This is undertaken in order to avoid leaving in place a dysplastic or even carcinomatous area.

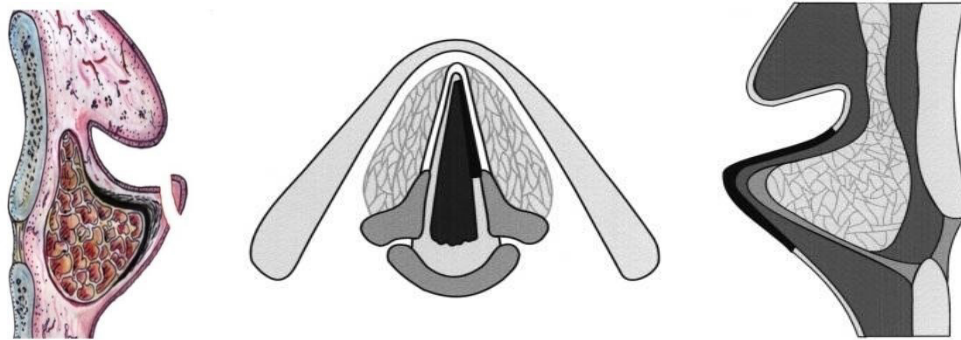


Figure 44: type 1 cordectomy

Type 2 cordectomy or subligamental cordectomy consists of the resection of the epithelium, Reinke's space and the vocal ligament.

Subligamental cordectomy is performed by cutting between the vocal ligament and the vocal muscle. The vocal muscle is preserved as much as possible. The resection may extend from the vocal process to the AC.

At a therapeutic level, subligamental cordectomy is indicated for cases of microinvasive carcinoma or severe carcinoma in situ with possible microinvasion.

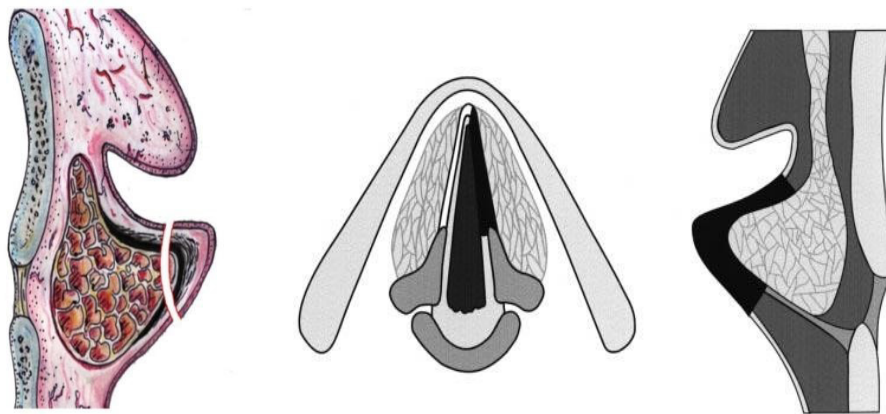


Figure 45: Type 2 cordectomy

Type 3 cordectomy or transmuscular cordectomy is performed by cutting through the vocalis muscle. The resection encompasses the epithelium, lamina propria, and part of the vocalis muscle. The resection may extend from the vocal process to the AC. In order to expose the entire vocal fold, partial resection of the ventricular fold may be necessary.

At a therapeutic level, a transmuscular cordectomy is indicated for cases of small superficial cancer of the mobile vocal fold. The technique may be indicated for cases of cancer, where cancer reaches the vocalis muscle without deeply infiltrating it.

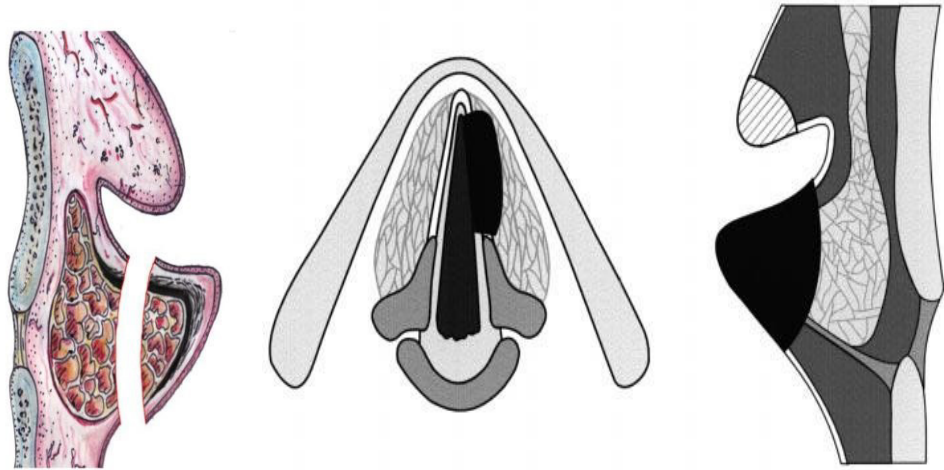


Figure 46: Type 3 cordectomy

Type 4 cordectomy or total cordectomy extends from the vocal process to the AC. The depth of the surgical margins reaches the internal perichondrium of the thyroid ala. Sometimes the perichondrium is included with the resection. Anteriorly, the incision is made in the AC. It is important that the attachment of the vocal ligament to the thyroid cartilage is cut. Complete cordectomy is indicated for cases of T1a cancer, where cancer infiltrates the vocal fold and is diagnosed prior to surgery. The procedure, which does therefore not serve any diagnostic purpose, but it is purely curative.

Extension of a neoplasm may spread as far as the AC, but without involving it.

At the AC, the distance between mucosa and cartilage is at maximum 2–3 mm. Although there is no internal perichondrium to resist tumoral invasion of the thyroid cartilage, Broyle's tendon may act as a barrier to the further spread of these carcinomas.

Complete cordectomy can be extended when it is necessary to remove partially or totally the ipsilateral ventricular fold in order to ensure complete resection of the vocal fold.

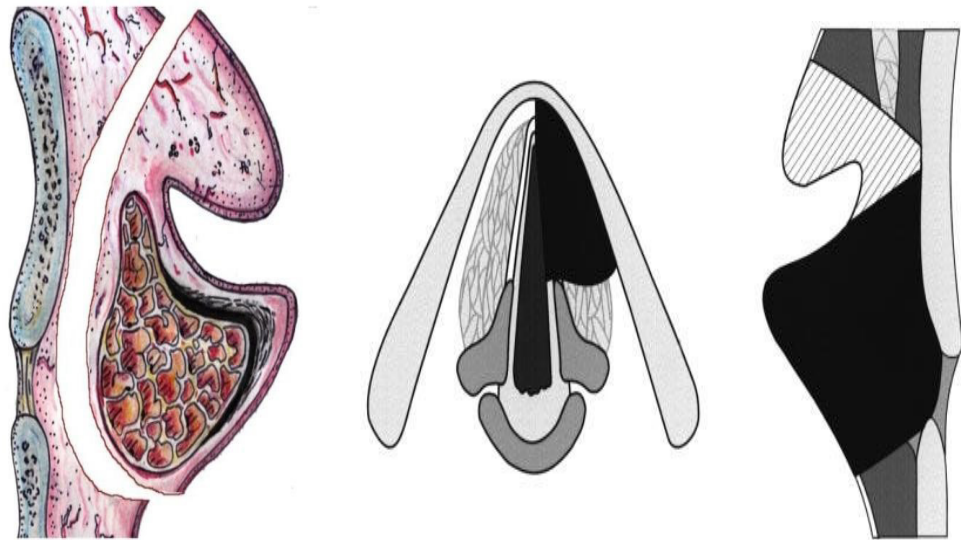


Figure 47: Type 4 cordectomy

Type 5 cordectomy or extended cordectomy is divided into four subtypes depending on the additional structure that is removed.

Type 5a or extended cordectomy encompassing the contralateral vocal fold.



Figure 48: Type 5a cordectomy

The resection includes the AC and, depending on the extent of the tumour, either a segment or the entire contralateral vocal fold. The resection must continue along the cartilage at the height of the AC, thereby removing Broyle's ligament. To achieve this, the incision starts above the insertion plane of the vocal folds, at the base of the epiglottic insertion, and then passes through Broyle's ligament. To achieve this extend of resection, it may be necessary to resect the petiole of the epiglottis to ensure sufficient visualization.

If necessary, the incision is continued towards the subglottis.

In order to ensure a good exposure of the contralateral vocal fold, resection of the contralateral ventricular fold may also be necessary.

The extent of this resection may vary.

According to some surgeons,^{123,124} a T1b tumor involving the AC can be managed by this procedure. In this case, the resection must include the subglottic mucosa and the cricothyroid membrane because cancers of the AC tend to spread towards the lymphatic vessels of the subglottic area¹²⁵.

Type 5b or extended cordectomy encompassing the arytenoid

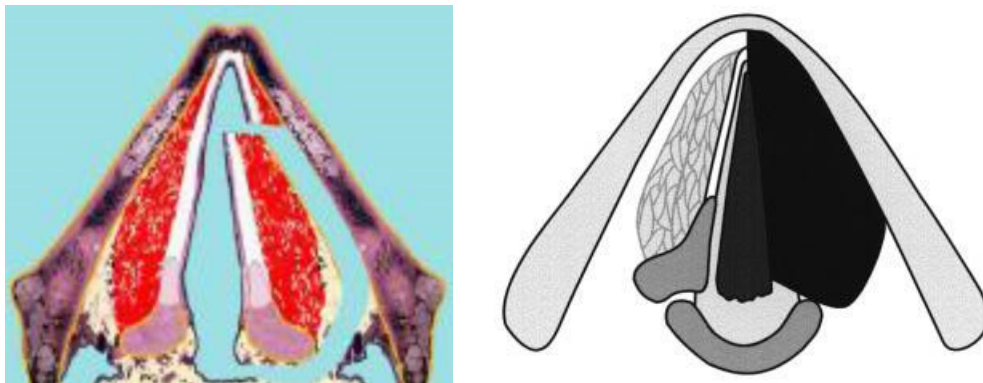


Figure 49: Type 5b cordectomy

It includes the ipsilateral cartilage of the arytenoid partially or totally with preservation of the cover mucosa. This technique is indicated for cases of vocal fold carcinoma involving posteriorly the vocal process but sparing the arytenoid. The arytenoid is mobile. The cartilage is partially or totally resected and the posterior arytenoid mucosa is preserved.

Type 5c or extended cordectomy encompassing the subglottis.

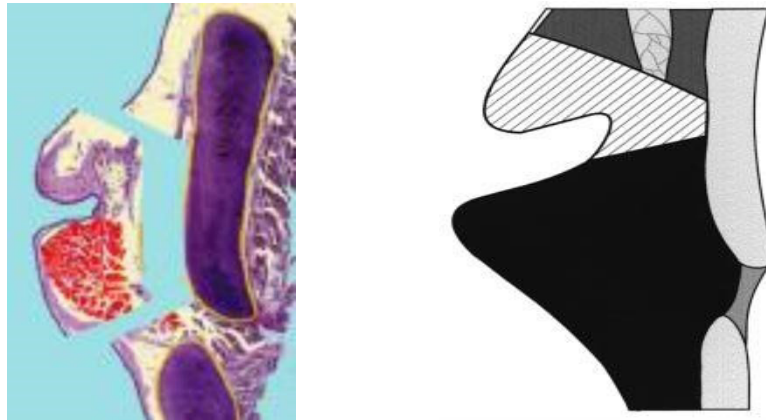


Figure 50: Type 5c cordectomy

If necessary, cord resection can be continued as deep as 1 cm under the glottis in order to expose the cricoid cartilage.

Type 5d or extended cordectomy encompassing the ventricular fold.



Figure 51: Type 5d cordectomy

This procedure is indicated for ventricular cancers or for transglottic cancers that spread from the vocal fold to the ventricle.

The specimen encompasses the ventricular fold and Morgani's ventricle.

Type 6 cordectomy concerns tumors originating at the AC, which have extended or not to one or both of the vocal folds, without infiltration of the thyroid cartilage and it

consists of the resection of the AC and the anterior third of the two vocal folds. In other words it is an anterior commissurotomy with bilateral anterior cordectomy.

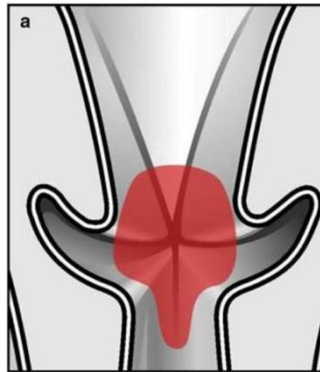


Figure 52: Type 6 cordectomy

If necessary, the anterior angle of the thyroid cartilage, as well as the subglottis mucosa and the cricothyroid membrane, can also be removed.

If the tumor is in close contact with the cartilage, resection can encompass the anterior angle of the thyroid cartilage. To remove the Broyle's ligament, the incision has to be started above the insertion plane of the vocal folds, at the base of the epiglottic insertion, and is extended through the Broyle's ligament.

To achieve this resection, it may be necessary to resect the petiole of the epiglottis to ensure sufficient visualization.

Resection of the AC may include the subglottic mucosa and the cricothyroid membrane,¹¹⁸ because cancers of the AC tend to spread towards the lymphatic vessels of the subglottic area.¹²⁶ In order to expose properly the anterior part of the vocal folds, partial resection of the ventricular folds may be necessary.

The difference between type 5a and type 6 cordectomies is the origin of the tumor that has been resected. In type 5a cordectomy the origin is the vocal fold whereas in type 6 cordectomy the origin is the AC.

The AC has been recognized as the subsite in the larynx that is more frequently at risk to give rise to local treatment failures than others.¹²⁷

For this reason, TLM, usually, has repeatedly been discouraged for AC carcinoma, because of inadequate exposure and close proximity to underlying cartilage. Anatomically, the AC is characterized by the lack of perichondrium on the inner surface of the thyroid cartilage. Traditionally, it has been thought that this anatomical feature facilitates the spread of carcinoma arising from the AC into the thyroid cartilage and beyond the laryngeal framework. However, the tight fibrous tissue of the AC tendon, known as Broyle's ligament, should be as solid a barrier to the spread of cancer as a layer of perichondrium. The main peculiarity of the AC probably is that the supraglottic, glottic and subglottic compartments of the larynx are only 2–4 mm apart from one another. Therefore, even very small tumors of the AC gain access to the lymphatic system of the supraglottic and the subglottis, allowing a further spread of cancer cells within these lymphatic vessels.¹²⁸

In TLM, proper and complete exposition of the AC can be particularly difficult due to the narrow-angled and V-shaped configuration of the thyroid alae (particularly in male patients). In addition, the petiole of the epiglottis frequently obstructs a complete visualization of the most anterior portion of the AC.

These peculiarities of tumors originating from the AC has prompted the authors to revise the ELS classification of different laryngeal endoscopic cordectomies first published in 2000,¹²⁹ confirming, as previously observed, that anterior commissural involvement at the glottic level does not negatively influence oncologic outcomes after endoscopic resection and does not require a two-staged surgery as it was proposed. 130-134

Indication of each type of cordectomy:

- Type 1: lesion limited to the epithelium (carcinoma in situ without signs of microinvasion);
- Type 2: microinvasive carcinoma;
- Type 3: Small superficial cancer of the mobile vocal fold, reaching the vocal muscle without deeply infiltrating it;
- Type 4: T1a cancer with deep infiltration of the vocal muscle;
- Type 5a: cancer of one vocal fold superficially reaching the AC without infiltrating it;
- Type 5b: cancer invading the arytenoid without fixation of the cricoarytenoid articulation;
- Type 5c: ventricular cancers or transglottic cancers that spread from the vocal fold to the ventricle;
- Type 5d: glottic cancer with limited spread from the vocal fold to the subglottis;
- Type 6: lesion originating at the AC without infiltrating of the thyroid cartilage.

To describe more extensive procedures, terms may have to be combined. For example, a resection of a transglottic tumor with infiltration of the AC and the arytenoid may be operated on with a type V a,b,c resection.

At a terminology level, the term “cordectomy” has been maintained even for partial resections while in fact, according to etymology, the word “cordectomy” can only apply to a total resection of the vocal fold.

ELS working committee classification for endoscopic cordectomies is being widely adopted by European and non-European teams in reporting oncologic and functional outcomes in TLM for early glottic cancer. It has reached its goal to standardize the reported results of TLM for glottic cancer.

MATERIALS AND METHODS

PATIENTS

This retrospective study was conducted on twenty (20) consecutive cases of previously untreated pT1-pT2 glottic carcinomas (18 men and 2 women) in the period from March 2015 to May 2019 .

A total of 20 people, age- and sex-matched comparison subjects, gave fully informed consent to take part in this study, before sampling.

Selected patients for this study were from 2 groups:

1. The first group, coming from the Otorhinolaryngology Department, San Salvatore Hospital, L'Aquila and it was composed of patients affected by early stage glottic cancer treated by TLM.
2. The second group, coming from the Radiation Oncology Department, San Salvatore Hospital, L'Aquila and it was composed of patients affected by early stage glottic cancer treated by RT.

Patients age is ranged from 40 to 89 years old (mean age 68.45 ± 13.54), and all people had at least one year of follow-up (range, 13-60 months; mean 34.55).

Inclusion criteria were patients over 18 years old affected by glottic pT1 and pT2 SCC previously untreated and over one year after surgical or not surgical treatment. All patients underwent to preoperative flexible videolaryngoscopy to assess tumor volume and superficial tumor margins under WL.

Deep neoplastic extension was evaluated using CT or MRI performed by dedicated head and neck radiologists.

Patients of the first group were evaluated intraoperatively with rigid endoscopy with 0°, 30°, and 70° telescopes under WL and HD SPIES during microlaryngoscopy to obtain better definition of superficial surgical margins.

TLM was not indicated in :

1. Patients with primary carcinoma of the AC with clear transglottic extension;
2. Patients with suspected thyroid cartilage carcinoma infiltration;
3. Patients with carcinoma significantly involving paraglottic spaces;
4. Patients with unsatisfactory glottic exposure.

All tumors were restaged according to the eighth edition of TNM of the UICC-AJCC staging system¹³ and the clinical staging of primary laryngeal lesions was T1a in 11 cases, T1b in 5 and T2 in 4.

The pathological diagnosis of the glottic lesion was achieved after bioptic microlaryngoscopy under general anesthesia performed in ENT Unit.

CO2 LASER ASSISTED EXCISION TECHNIQUE

All surgical procedure were performed under general anesthesia after oro-tracheal intubation with Laser Oral Tracheal Dual Cuffed Tubes (Covidien, Ireland) with internal diameters ranging from 4.5 to 5.5 mm. Laryngeal exposure was obtained with different laryngoscopes.

The microscope Carl Zeiss OMPI 1-FC (Germany) with 400 mm focal lens coupled with an Acupulse Duo Surgitouch with an Acuspot 712 micromanipulator (Lumenis Ltd, Yokneam, Israel) has been used. Pulsed energy, mean power in W and excision depth were tailored to carcinoma localization and cordectomy type.

The classification of cordectomies was performed according to the “Proposal for revision of the ELS classification of endoscopic cordectomies”³⁴.

Endoscopic resection were performed by the same surgeon (G-P dM) using en bloc or piecemeal techniques depending on the number of variables including tumor localization, tumour dimensions, and laryngeal exposure. Surgical specimens were sent to the pathologist after making one designed edge with blank ink en bloc excision. Considering the resections could be performed the piecemeal technique, a diagram of the larynx with detailed indications of the procedure was sent together with the specimen in which critical margins were precisely indicated. Deep and superficial margins were also considered.

From a pathological viewpoint, the excision margins were classified as negative, close (< 1 mm from carcinoma), positive, or with artefacts. In case of close surgical margins, a close endoscopic follow-up with monthly controls was chosen. Surgical endoscopic

revision was performed in cases of positive margins involved. Therapeutic options were clearly explained to the patients: the wishes of the patients were also considered.

RADIOTHERAPY PROCEDURE

All patients treated with RT underwent to the preliminary simulation CT.

Treatment planning CT scan was performed having the patient in the treatment position, preferably using an I.V. contrast liquid. The patient is usually set up on the treatment table in supine position. For head and neck treatments the immobilization device is a thermoplastic mask for head and shoulders.

The position of head is usually neutral and the patient is instructed to breath normally.

CT-scan thickness should be 0.3cm.

All patients were treated in the supine position using a fixation device for the neck.

The target volume encompassed the laryngeal cartilage, including the thyroid and cricoid cartilage.

Treatment portals were assessed by direct simulation.

Typically, the field size was 5cm X 5cm for T1N0 or 6 cm X 6 cm for T2N0, but in some cases, this was adjusted to anatomical structures.

The upper border was located between the hyoid bone and upper border of thyroid cartilage.

The lower border was chosen just below the cricoid cartilage.

The elective nodal areas were not included in the radiation portals.

RT was delivered using 2 opposing lateral fields.

Hypofractionated radiotherapy was locally applied in 25 fractions of 2.4 Grey (Gy) (5 days a week) delivered daily to a total dose of 60 Gy.

Patients, subject to informed consent, are subjected to questionnaires for the evaluation of functional outcomes about dysphonia,¹³⁵⁻¹³⁹ performance status of larynx¹⁴⁰ and swallowing disorders.^{141,142}

CONSENSO AL TRATTAMENTO DEI DATI CLINICI

Dò il mio consenso alla utilizzazione per scopi scientifici dei dati anamnestici e clinici a me riferiti e raccolti presso l'Ospedale San Salvatore dell'Aquila, sui quali verrà mantenuto l'anonimato secondo la Normativa vigente in materia di Privacy.

Nome Cognome

Data

Firma

1. ITALIAN VERSION OF VOICE HANDICAP INDEX (VHI) AND VHI-10

Impatto delle problematiche vocali sulle normali attività quotidiane

Mai: 0

Quasi Mai:

Qualche Volta: 2

Quasi Sempre:3 Sempre:4

- 1 Mi sentono con difficoltà a causa della mia voce
- 2 Mi capiscono con difficoltà in un ambiente rumoroso
- 3 Mi capiscono con difficoltà anche in ambiente silenzioso
- 4 I membri della mia famiglia fanno fatica a sentirmi
- 5 Telefono meno spesso di quanto vorrei
- 6 Tendo ad evitare i gruppi numerosi per la mia voce
- 7 Parlo poco con amici e parenti a causa della mia voce
- 8 I miei problemi di voce limitano la mia vita sociale
- 9 Mi sento escluso/a dalle conversazioni per la mia voce
- 10 Se parlo a lungo mi gira la testa

Punteggio: _____ (punteggio massimo: 40)

0 MAI

1-10 QUASI MAI

11-20 QUALCHE VOLTA

21-30 QUASI SEMPRE

31-40 SEMPRE

Impatto psicologico

Mai: 0

Quasi Mai: 1

Qualche Volta: 2

Quasi Sempre: 3

Sempre: 4

- 1 Sono teso quando parlo con gli altri per la mia voce
 - 2 La gente sembra irritata dalla mia voce
 - 3 Trovo che gli altri non comprendano il mio problema
 - 4 I miei problemi di voce mi innervosiscono
 - 5 Sono meno socievole a causa dei miei problemi di voce
 - 6 Mi sento handicappato a causa della mia voce
 - 7 Sono infastidito/a quando la gente mi chiede di ripetere
 - 8 Sono imbarazzato/a quando la gente mi chiede di ripetere
 - 9 A causa della mia voce mi sento incompetente
 - 10 Mi vergogno del mio problema di voce
- Punteggio: _____ (punteggio massimo: 40)

Percezione delle caratteristiche dell'emissione vocale

Mai: 0

Quasi Mai: 1

Qualche Volta: 2

Quasi Sempre: 3

Sempre: 4

- 1 Quando parlo rimango a corto di fiato
- 2 La mia voce varia nel corso della giornata
- 3 La voce mi sembra soffiata e flebile
- 4 La voce mi sembra rauca
- 5 Ho l'impressione di dover forzare per produrre la voce
- 6 Mentre parlo la voce varia in modo imprevedibile
- 7 Cerco di modificare la mia voce perché sia migliore
- 8 Faccio molta fatica a parlare
- 9 Alla sera la mia voce è più brutta
- 10 Nel corso di una conversazione rimango senza voce

Punteggio: _____ (punteggio massimo: 40)

PUNTEGGIO GLOBALE:

Nella Norma: 0

Alterazione Lieve: 1- 40

Alterazione Moderata: 41- 80

Alterazione Grave: 81- 120

VHI-10

Mai: 0

Quasi Mai: 1

Qualche Volta: 2

Quasi Sempre³

Sempre: 4

- 1 La mia voce rende difficile farmi sentire dalla gente
- 2 La gente ha difficoltà a capirmi in una stanza rumorosa
- 3 Le mie difficoltà vocali restringono la mia vita personale e sociale
- 4 Mi sento escluso/a dalle conversazioni a causa della mia voce
- 5 Il mio problema vocale mi causa perdita di entrate economiche
- 6 Sento che devo fare sforzo per produrre la voce
- 7 La chiarezza della mia voce è imprevedibile
- 8 Il mio problema di voce mi sconvolge
- 9 La mia voce mi fa sentire handicappato/a
- 10 La gente mi chiede “cosa c’è che non va nella tua voce?”

Punteggio: _____ (punteggio massimo:40)

PUNTEGGIO GLOBALE:

0 Nella norma

1-13 Alterazione lieve

14-27 Alterazione moderata

28-40 Alterazione Grave

The VHI assesses patients' perception of disability related to voice disfunction.

The self-assessment of dysphonia is a subjective investigation in which the patient evaluates, through a questionnaire, the degree of severity of his vocal handicap.

Such an investigation of fundamental importance to know the degree of patient satisfaction with the treatment performed.

VHI provides, in its full version,¹³⁵ administering a questionnaire with 30 questions, which in the Italian version¹³⁶ have been divided in three groups of ten questions regarding:

- Impact of speech problems on normal daily activities
- Psychological impact
- Perception of the characteristics of voice output

Each question must be answered in five degrees of severity (0,1,2,3,4). The score obtained is calculated according to an "analytical" evaluation for each group of ten questions and an evaluation of a "global" type in four degrees of severity (0,1,2,3).

A total score (possible range, 0-120 points) and subscales' score (possible range, 0-40) are given; the higher the score, the greater the voice handicap.

It was proposed by Rosen and Coll,¹³⁷ a version of the VHI, using the ten questions that statistically are most significant: VHI-10.

This questionnaire does not allow a specific evaluation for each of the three fields to which they belong the questions, but it is easier and faster to fill in, so it is progressively replacing internationally the VHI.

The Italian version of the VHI-10^{138,139} provides for the evaluation of the score obtained in four degrees of severity (normal, alteration mild, moderate, severe).

2. PERFORMANCE STATUS SCALE:

Laryngeal functional status was quantified at the end of the first year posttreatment by the same doctor (M.P.) in each department using the Performance Status Scale (PSS), as reported by List et al.¹⁴⁰

This a simple, practical, clinical-rated assessment tool consisting of three subscales: speech compresion, normalcy of diet and eating in public.

MANGIARE IN PUBBLICO

100 Nessuna limitazione di luogo, cibo o compagnia (mangia fuori in ogni occasione)

75 Nessuna restrizione di posto, ma limita la dieta in pubblico (mangia ovunque, ma può limitare l'assunzione di alimenti meno "disordinati", ad es. liquidi)

50 Mangia solo in presenza di persone selezionate in luoghi selezionati

25 Mangia solo a casa in presenza di persone selezionate

0 Mangia sempre da solo

COMPENSIBILITÀ DEL DISCORSO

100 Sempre comprensibile

75 Comprensibile per la maggior parte del tempo; ripetizione occasionale necessaria

50 Di solito comprensibile; contatto faccia a faccia necessario

25 Difficile da capire

0 Mai comprensibile; può usare la comunicazione scritta

NORMALITA' DELLA DIETA

100 Dieta completa (nessuna restrizione)

90 Arachidi

80 Tutta carne

70 Carote e sedano

60 Pane secco e crackers

50 Alimenti morbidi e masticabili (ad es. pasta, frutta in scatola / frutti di bosco, verdure cotte, pesce, hamburger, piccoli pezzi di carne)

40 Alimenti morbidi che non richiedono masticazione (ad es. purè di patate, salsa di mele, budino)

30 Alimenti frullati (nel frullatore)

20 Liquidi caldi

10 Liquidi freddi

0 Alimentazione non orale (PEG o SNG)

3. ITALIAN M.D. ANDERSON DYSPHAGIA INVENTORY - MDADI

Dysphagia- related disability was investigated through a reliable and clinically valid dysphagia-specific Quality of Life (QoL) questionnaire for Italian- speaking patients with head and neck cancer, divided into a global, an emotional, a physical, and a functional subscale.^{141,142}

Fortemente d'accordo: 0

D'accordo: 1

Non so: 2

In disaccordo: 3

Fortemente in disaccordo: 4

LA MIA DIFFICOLTA DEGLUTITORIA LIMITA LE MIE ATTIVITA QUOTIDIANE.

- E2. SONO IMBARAZZATO DAL MIO MODO DI MANGIARE.
F1. LE PERSONE HANNO DIFFICOLTA A CUCINARE PER ME.
P2. LA DEGLUTIZIONE E PIU DIFFICOLTOSA LA SERA.
E7. NON MI SENTO SICURO DI ME QUANDO MANGIO.
E4. SONO ARRABBIATO PER LE MIE DIFFICOLTA DEGLUTITORIE.
P6. DEGLUTIRE MI RICHIEDE UN GRANDE SFORZO.
E5. NON ESCO A CAUSA DEI MIEI PROBLEMI DEGLUTITORI.
F5. I MIEI DISTURBI DEGLUTITORI MI HANNO CAUSATO UNA PERDITA DI REDDITO.
P7. CI METTO PIU TEMPO A MANGIARE A CAUSA DEI MIEI PROBLEMI DEGLUTITORI.
P3. LE PERSONE MI CHIEDONO: "PERCHE NON PUOI MANGIARE QUESTO?". E3.
ALTRE PERSONE SONO IRRITATE DAI MIEI PROBLEMI DEGLUTITORI.
P8. TOSSISCO QUANDO CERCO DI BERE LIQUIDI.
F3. I MIEI PROBLEMI DEGLUTITORI LIMITANO LA MIA VITA SOCIALE E PRIVATA. F2.
MI SENTO LIBERO DI ANDARE A MANGIARE FUORI CON I MIEI AMICI, VICINI I CASA
O PARENTI.
P5. LIMITO LA QUANTITA DI CIBO CHE MANGIO A CAUSA DEI MIEI PROBLEMI
DEGLUTITORI.
P1. NON RIESCO A MANTENERE IL MIO PESO A CAUSA DEI MIEI PROBLEMI
DEGLUTITORI.
E6. HO UNA BASSA AUTOSTIMA A CAUSA DEI MIEI PROBLEMI DEGLUTITORI. P4.
QUANDO MANGIO, AD OGNI BOCCONE MI SEMBRA DI INGOIARE UN'ENORME
QUANTITA DI CIBO.
F4. MI SENTO ESCLUSO PER LE MIE ABITUDINI ALIMENTARI.

The total score and each subscale's score ranged from 20 (extremely low functioning) and 100 (high functioning).

Two scores are obtained: a Global Score and a Composite Score.

All questions except for E7 and F2:

Strongly Agree = 1 point

Agree = 2 points

No Opinion = 3 points

Disagree = 4 points

Strongly Disagree = 5 points

E7 and F2

Strongly Agree = 5 points

Agree = 4 points

No Opinion = 3 points

Disagree = 2 points

Strongly Disagree = 1 point

Global Score: first question (not numbered)

Global Score ranges from 1 (extremely low functioning) to 5 (high functioning)

Composite Score: 19 numbered questions

Calculate total points: add scores for the 19 questions

Calculate the mean point score: Divide total points by 19

Calculate final score: Multiply the mean by 20

Composite Score ranges from 20 (extremely low functioning) to 100 (high functioning)

STATISTIC ANALYSIS

The discrete and nominal variables will be described with frequencies and percentages and the differences will be evaluated through the χ^2 test for the comparison between the two treatments.

Quantitative variables will be expressed in terms of mean and standard deviation (SD) and the significance of mean comparisons will be evaluated with the Mann – Whitney test for the comparison of continuous variables for independent samples.

The average local and remote relapse times between the initial presentation and the date of the relapse will be calculated.

The Kaplan-Meier method will be used for the analysis of overall and disease-free survival (OS and DFS).

The level of significance established will be $p < 0.05$.

Statistical analysis will be performed using the Stata software package 12. (Stata Corp, College Station, Texas, 77845 USA)

OBJECTIVES

The aims of the study is to evaluate:

- OS overtime;
- DFS overtimr;
- functional outcomes: dysphonia, laryngeal functional status and swallowing disorders in patients treated with TLM or RT.

RESULTS

The sample of this study is composed of twenty (20) patients affected by early stage glottic cancer, enrolled between September 2022 and October 2025, divided into two group: in the first group there are 10 subjects from Otorhinolaryngology Department, 1 woman and 9 men; in the second one from Radiation Oncology Department are 10 people, 1 female and 9 males.

Individuals were ranged in age from 40 to 89 years old: mean age for the first group is 69 ± 15.22 ; in the second group is 67.9 ± 12.45 years old.

There is no significant differences between the study groups with regards to sex and age.

	SEX		AGE	
	F	M	MEAN	ST
Group 1	1	9	69	15.22
Group 2	1	9	67.9	12.45

Table 4: Sex and mean age of the two groups of the sample

The pT classification in our series was in the first group pT1a in 6 patients, pT1b in 2 and pT2 in 2; in the second group pT1a in 5 patients, pT1b in 3 and pT2 in 2.

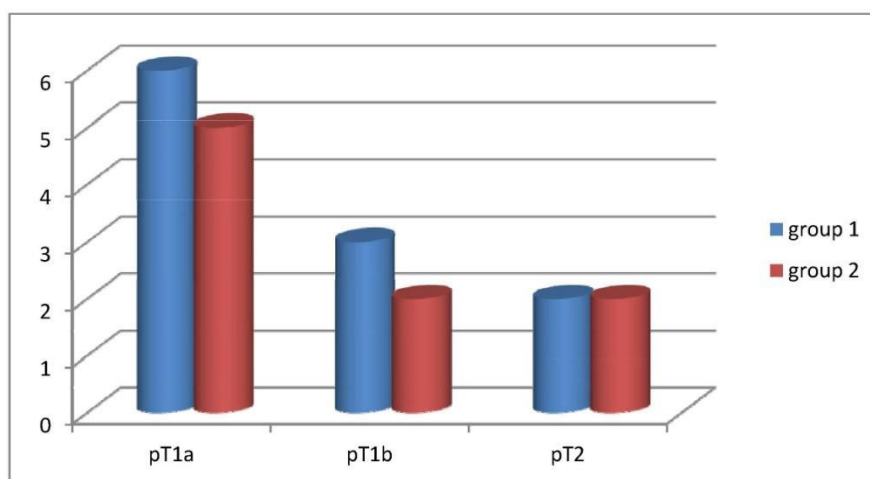


Figure 53: pT classification in our series

70% of the first group are current or former smokers and in the second one are 90%.

There is no significant differences between the study groups with regards to clinical stage and smoke.

The TLM procedures were classified as: type I cordectomies (0 cases); type II (2 cases); type 3 (4 cases); type 4 (0 cases); type 5 (2 cases) and type 6 (2 cases).

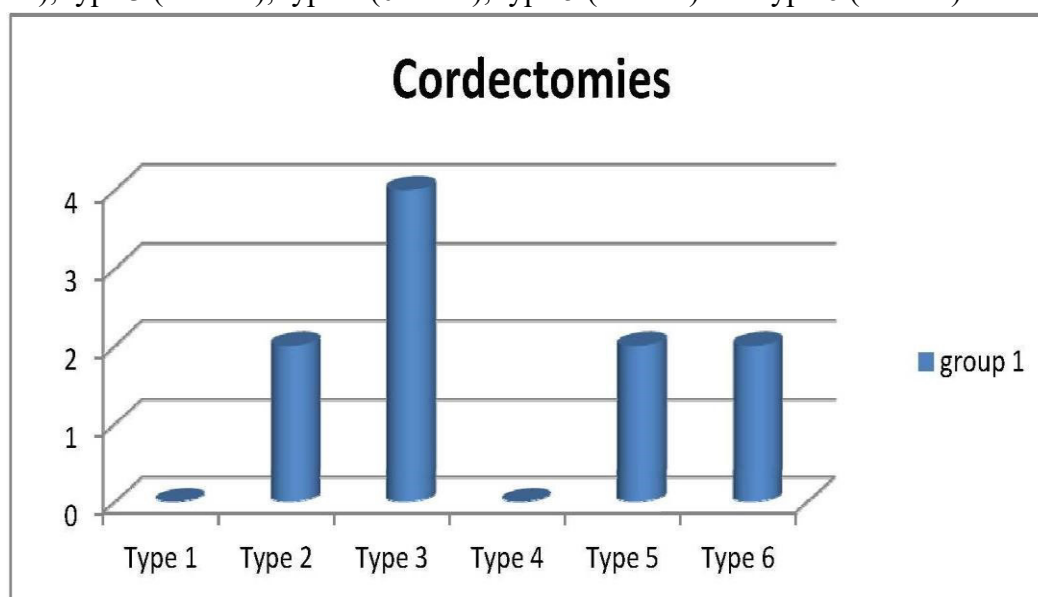


Figure 54: TLM cordectomies according to ELS classification

The mean follow up was 34.55 ± 13.87 months. At latest follow up in the first group 9 patients were alive and disease- free and one had died of other cause; in the second group 8 patients were alive and disease free and two had died of other causes.

The 4-years OS and DFS are respectively in the first group 88% and 90% and in the second group are 78% and 71%, but this is not statistically significant ($p= 0.50$ and $p= 0.59$ respectively).

OS 4 years

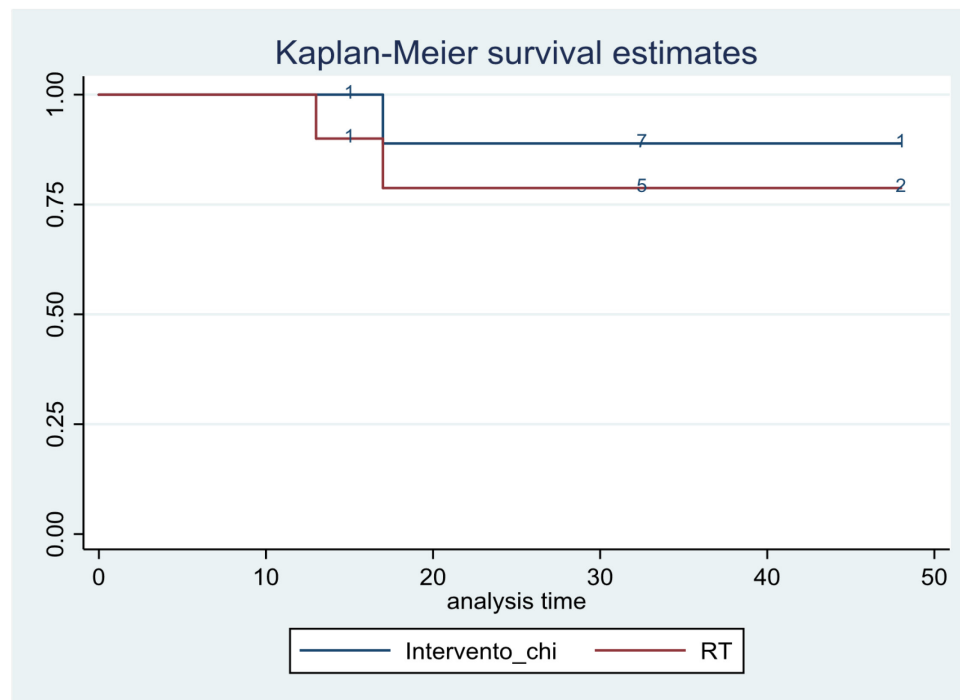


Figure 55: OS 4 years ($p=0.50$)

OS 4 YEARS VARIABLE AGE

We noted slight difference, statistically significant, in OS in patients under 70 years old (100%) versus patients over 70 years old (63%) ($p=0.03$).

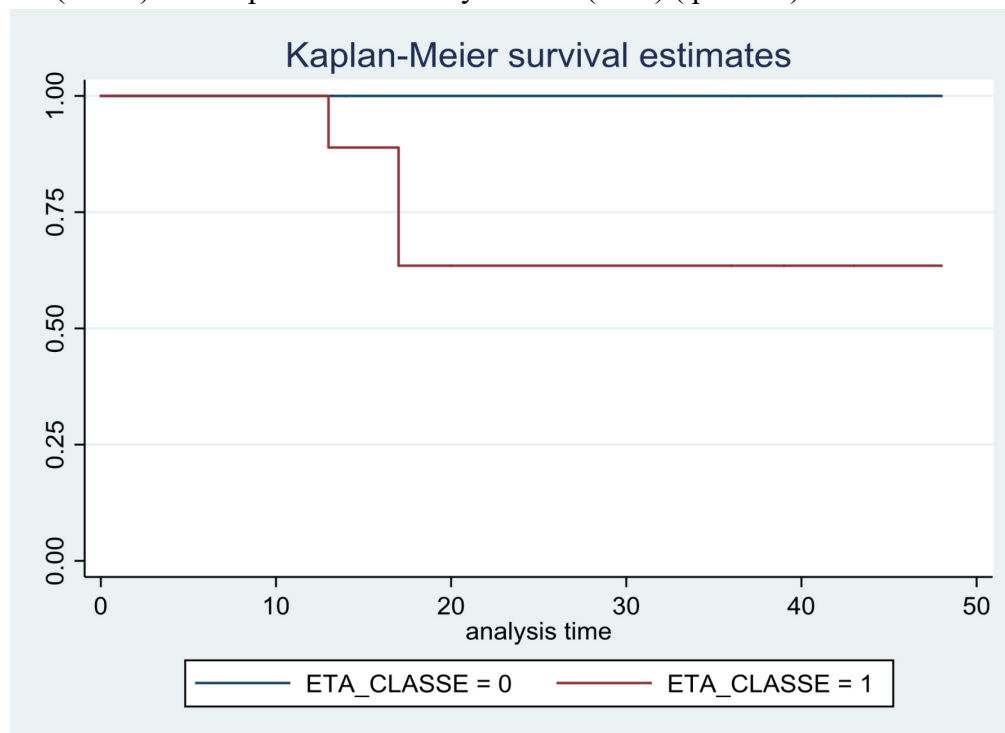


Figure 56: OS 4 years and variable age ($p=0.03$)

DFS 4 years

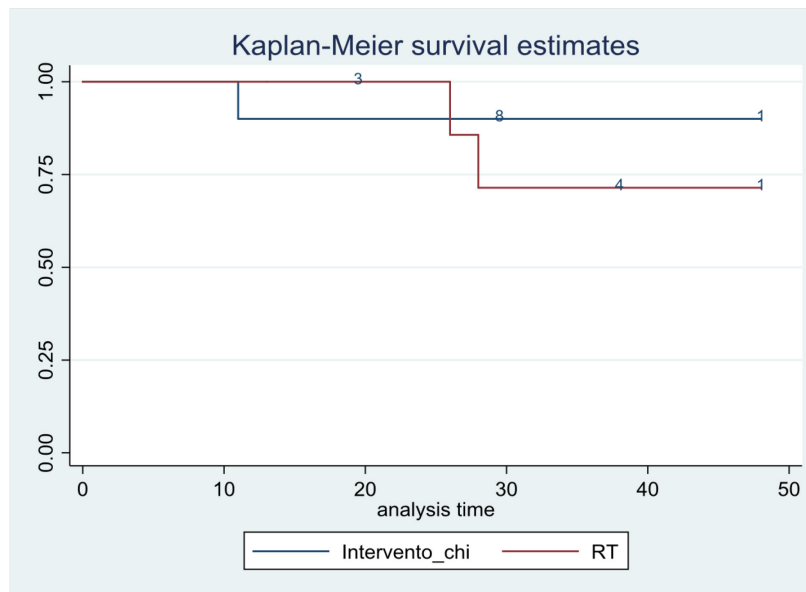


Figure 57: DFS 4 years ($p=0.59$)

One patient of the first group had a local recurrence and was managed by RT and two patients of the second group had local recurrences and were managed by total laryngectomy.

DFS 4 YEARS VARIABLE T

We noted slight difference in DFS in T1a patients vs T1b and T2, although not statistically significant ($p=0.08$)

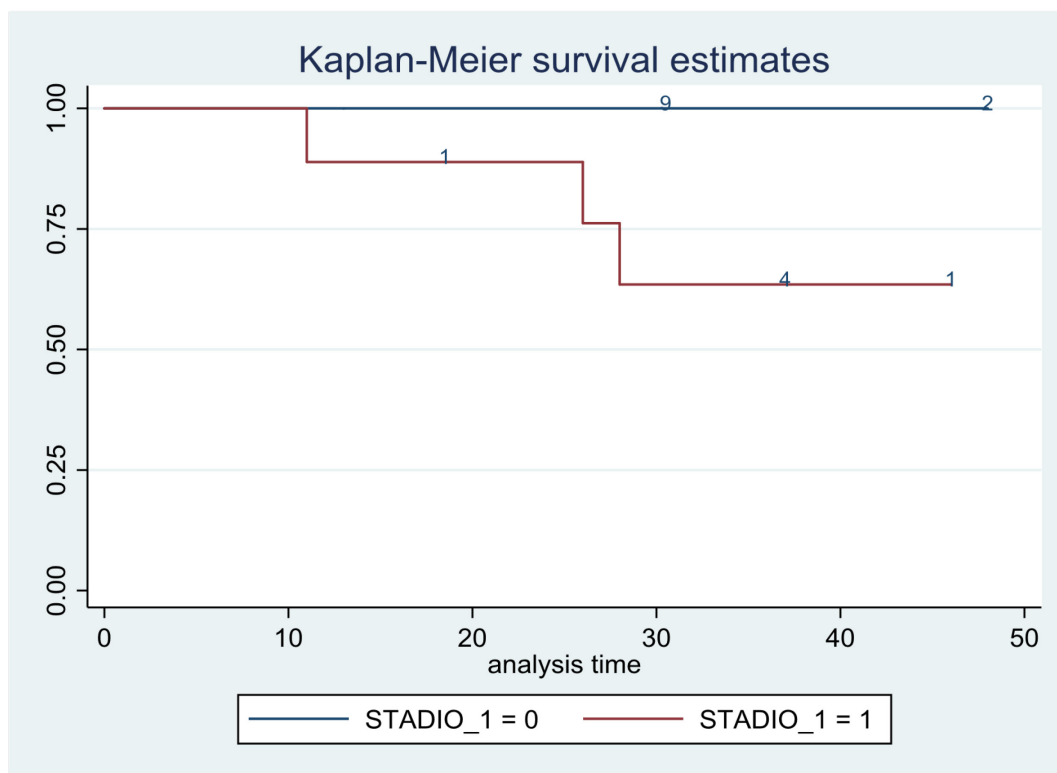


Figure 58: DFS 4 years variable T ($p=0.08$)

The results of VHI and VHI 10 are detailed in Table 2.

	GROUP 1		GROUP 2		P VALUE
	MEAN	SD	MEAN	SD	
VHI functional subscale	9.78	± 8.19	8.5	± 9.23	0.62
VHI emotional subscale	6.22	± 4.94	6.0	± 8.16	0.36
VHI physical subscale	15.33	± 8.90	11.5	± 9.15	0.33
VHI total score	31.33	± 10.36	26	± 24.14	0.81
VHI 10	11.11	± 9.96	9.75	± 10.75	0.73

Table 5: VHI and VHI-10 results and p value in group 1 and group 2

Considering the two groups both had moderate dysphonia and there was not significant differences emerged between two groups about VHI total score and about each subscale of it and about VHI10 questionnaire.

About VHI 10 we noted a significant lower subjective perception of disability related to voice disfunction among patients over 70 years old ($p= 0.03$).

	UNDER 70 YEARS		OVER 70 YEARS OLD		P VALUE
	MEAN	SD	MEAN	SD	
VHI 10	14	±10.51	4.0	± 4.90	0.03

Table 6: VHI 10 mean score and p value in patients under 70 years old and over 70 years old

We noted a significant lower subjective perception of disability related to voice disfunction evaluated by VHI 10 and VHI among patients without recurrences (VHI 10 Mann- Whitney U test, $p= 0.026$; VHI total score Mann- Whitney U test, $p= 0.008$; VHI functional subscale Mann- Whitney U test, $p= 0.0021$; VHI emotional subscale Mann- Whitney U test, $p= 0.012$).

	WITH RECURRENCES		WITHOUT RECURRENCES		P VALUE
	MEAN	SD	MEAN	SD	
VHI functional subscale	20.67	± 6.03	6.71	± 6.71	0.021
VHI emotional subscale	15.33	± 5.68	4.14	± 4.70	0.012
VHI physical subscale	14.66	± 2.51	13.29	± 9.86	1
VHI total score	24.14	± 2.30	5.67	± 2.31	0.08
VHI 10	24.33	± 11.02	7.5	± 7.18	0,026

Table 7: VHI and VHI-10 results and p value in patients with recurrences and without recurrences

We reported a satisfactory degree of laryngeal function status measured by PSS, a better score for the first group (100%) instead of the second one(90%), even if non statistically significant.

None of patients of our sample referred swallowing disorders measured by MDADI.

DISCUSSION

RT and TLM are widely accepted and effective modalities for the treatment of early stage glottic cancer.

Therapeutic protocols are moving towards approaches that allow better organ and function preservation, low morbidity rate and low cost.^{21, 143-147}

TLM is the gold standard in the treatment of early glottic carcinoma because of high local control rates with laser alone, day surgery modality, very low morbidity, good post-operative voice quality in most of the cases, and low costs.

A multidisciplinary team (MDT) management is now the accepted standard of care.¹⁴⁸⁻¹⁵⁰

For a MDT to reach an evidence-based consensus on recommended treatment in circumstances in which different treatment options offer similar chances of cure, the estimated end-organ function and quality of life that will be achieved after each treatment must be taken into consideration.

TLM and RT have undergone significant advancement in the past few years leading to a decrease in open procedures.

Many studies indicate that TLM shows an OS of 90–99% and a 5-year diseasespecific survival of 90–98%. On the other hand, RT shows OS of 83–95% and a 5-year disease-specific survival of 95–98%.²⁰

In our study OS and DFS were estimated at 4 years using Kaplan-Meier curves.

The end-points considered were obtained as the length of time from the date of diagnosis to :

OS= the date of death or last control and DFS= the date of the first recurrence.

The 4-years OS and DFS are respectively in the first group 88% and 90% and in the second group are 78% and 71%, but this difference of OS and DFS between the two groups is not statistically significant ($p= 0.50$ and $p= 0.59$ respectively).

Since the survival rates are almost equivalent, treatment modality is usually decided on the basis of post-treatment voice quality, treatment duration, cost, patient's general medical condition, and patient's preference for surgery or radiation.²¹⁻²²

RT offers good control rates, but the prolonged time of the treatment (6–7 weeks), mucosal radiation damage, and long-term side effects such as xerostomia are deterrents for selecting RT as the treatment of choice and it's reserved for further treatments.²⁵

TLM cordectomy provides an excellent alternative to the others in the treatment of early-stage glottic cancer,²⁷⁻³⁰ because IT is characterized by rapidity of treatment, low morbidity, good compliance by the patient, short hospitalization and limited costs.

TLM is custom-tailored to the individual tumor with an excellent view of the limits and maximal preservation of normal tissue and function. The tumor is divided into manageable units with the laser beam and removed stepwise until excision is complete. It is shown that transecting tumors is not producing an increase rate of regional or distant metastasis.¹⁰⁸

The laser incisions into and through the tumor enable the surgeon to identify the real extension of the cancer and to estimate the depth of tumor penetration.

The extent of the tumor must be clearly distinguishable under the operating microscope. The lesion must be resected until healthy tissue is found, and an appropriate safety margin is obtained. Sometimes, resection of healthy tissue, such as the false vocal cord, is indicated to approach the tumor located in the ventricle or true vocal fold.

The tumor will be excised in more than one section. TLM can be easily repeated if inadequate resection margins are proven by postoperative pathology. Positive margins should rather be submitted to resection to improve OS and DFS.

An excision margin of 1 to 2 mm is appropriate at the laryngeal glottis.

The disease is eradicated with maximal preservation of the normal layered structure of the vocal folds.¹⁰⁹

At the same time, the respect of the ELS classification allows to perform excisions that achieve a complete removal of the tumor and good vocal quality too. In 2000, the working committee of the ELS proposed a simple, easy-to-use classification for cordectomies³³ based on the depth and extent of surgical resection in order to ensure better definitions of post-operative results, to reach better agreement and uniformity and to offer reproducibility to the majority of laryngologists to allow relevant comparisons with the literature when presenting/publishing the results of cordectomies. This classification was revised in 2007.³⁴

Based on the extent of surgical resection, cordectomies can be classified into six types.^{33,34}

In TLM, the operator skills play a crucial role in the achieved oncological results, probably more than in other approaches. A single surgeon for a high number of patients

is likely to be an important index of high quality treatment. Patients of the first group were treated consecutively by the same laser surgeon.

When compared with RT, TLM allows equivalent oncological results^{21, 147} similar functional results and cost reduction of about 50%.^{151,152}

In the both group we noted slight difference in OS in patients under 70 years old (100%) versus patients over 70 years old (63%) ($p= 0.03$).

Three patients, all over 70 years old, in our sample had died for cardiac causes.

In western societies, there is evidence of an increase in head and neck cancers in the geriatric population,¹⁵³ making the question of whether age should be one of the factors determining the treatment strategy for head and neck carcinoma increasingly relevant.¹⁵⁴

In laryngeal carcinoma, tumor- related factors and patient- related factors play a crucial part in the therapeutic decision-making process.

Colasanto et al¹⁵⁵ found that age did not significantly correlate with local recurrence rates in patients with T1 and T2 laryngeal SCC. Sakata et al¹⁵⁶ studied T1 and T2 glottic carcinomas and concluded that age did not significantly affect DFS. Nowadays a patient's general conditions are considered more important than their age when it comes to selecting patients for conservative laryngeal surgery. Our results confirm that TLM is also an effective treatment for selected glottic carcinomas in elderly patients because very high local control rates are achieved with the laser alone , with a very low morbidity as well as a good patient compliance and a very short hospital stay.

The functions of the larynx are to provide airway patency, protect the tracheobronchial tree from aspiration, and allow phonation.⁷

One of the aims of our study was to evaluate functional outcomes in patients affected by early stage glottic cancer treated with TLM or RT.

Quantitative acoustic measurements¹⁵⁷ are more regularly studied. These are obtained from tools that digitize and analyze the voice being investigated and quantify the characteristics that deviate from normality, understanding normality to mean when the voice is uniform in both amplitude and tone periodicity. Although all these measurements are important parameters but they fail to provide information on the patient's perceived voice quality.

The VHI^{135, 136} assesses patients' perception of disability related to voice disfunction.

The self-assessment of dysphonia is a subjective investigation in which the patient evaluates, through a questionnaire, the degree of severity of his vocal handicap.

Such an investigation of fundamental importance to know the degree of patient satisfaction with the treatment performed.

VHI allows a specific evaluation for each of the three fields of the questionnaire to which they belong the questions and to calculate a total score.

VHI-10¹³⁷ is easier and faster to fill in, so it is progressively replacing the version internationally complete with the VHI.

Considering the two groups both had moderate dysphonia and there was not significant differences emerged between two groups on VHI total score and for each subscale and VHI10 questionnaire.

We noted a significant lower subjective perception of disability related to voice disfunction evaluated by VHI 10 and VHI among patients without recurrences (VHI 10 Mann- Whitney U test, $p= 0.026$; VHI total score Mann- Whitney U test, $p= 0.008$; VHI functional subscale Mann- Whitney U test, $p= 0.0021$; VHI emotional subscale Mann- Whitney U test, $p= 0.012$).

Combined approaches are always associated with worse functional outcome.²³ About VHI 10 we noted a significant lower subjective perception of disability related to voice disfunction among patients over 70 years old (Mann- Whitney U test, $p= 0.03$).

For the majority of patients life remained unchanged, but the subjects with bigger negative impact of their voice had a tendency to be younger.

Most likely, the impact of any grade of dysphonia in older patients is easier to cope with because they have reduced professional and social voice requirements than younger patients.

However, there are fewer published works that include patient opinions with regard to the impact the illness and the treatment has had on their quality of life.¹⁵⁸⁻¹⁶⁰

VHI and its short version (VHI-10) are a post-treatment global result evaluation method, from the point of view of the patient. Although they permit only a subjective evaluation based on the patient's own perception, it can provide valuable data as to the reasons why patients with similar dysphonia characteristics can have different handicap severity indices.¹⁶¹

Our study was only based on subjective patient evaluation and not on objective acoustic measurements, aerodynamic measurements, or stroboscopy.

The patients' own evaluation takes into account their expectations as to the results of treatment, with possibly a more favorable outlook on voice quality because the patients were "relieved" to have a voice after treatment. The longer follow-up in these patients may also have influenced their appreciation of their voice handicap; these patients may have had more time to "get used to" their voices.

In the early days of TLM, many publications considered voice quality to be superior with RT. With increasing experience, progressive introduction of scanner technology, and more accurate micromanipulators (160 μ m spot diameter), the quality of the laser cut dramatically improved, reducing thermal damage and allowing a more precise

resection. Presently, margins of 1 to 3 mm are considered sufficient in the treatment of early stage glottic tumors, allowing a more functional resection.

Voice quality after TLM has been directly correlated with the amount of tissue resected.¹⁶²⁻¹⁶⁶

The photomicrosurgical approach to early glottic cancer minimizes vocal sequelae in case of endoscopic resections up to the subligamental cordectomy and achieves a postoperative conversational voice comparable to that of controls.¹⁶⁴

For larger excision, or in those involving the AC, more vocal difficulties are to be expected after surgery than after RT ^{33, 164-166,168, 169}

A lot of authours reviewed about different treatment modalities for early glottic cancer with respect to vocal outcomes and they concluded that vocal outcomes were comparable for both groups.^{170,171}

About functional outcomes, we evaluated also laryngeal functional status and it was quantified at the end of the first year post-treatment by the same doctor (M.P.) in each department using the Performance Status Scale, as reported by List et al.¹⁴⁰, and agreeing with a review of eleven studies ¹⁷² we reported a better score for the first group (100%) instead of RT(90%), even if non statistically significant.

Performance Status Scale is a simple, practical, clinical-rated assessment tool consisting of three subscales: speech compresion, normalcy of diet and eating in public and patients from both group gained a satisfactory degree of laryngeal function, lower for group of RT but there was not a statistically difference.

We evaluated also swallowing disorders in patients affected by early glottic cancer.

Small glottic tumours usually display no problems with the deglutition^{131, 173, 174} .

We agree with these studies because in our study none of patients from the two groups referred swallowing disorders through MDADI questionnaire.

CONCLUSION

The aim of this study was to investigate about oncological and functional outcomes in patients affected by early stage glottic cancer treated with TLM or RT.

This research has attempted to examine and appraise the available literature on the subject, but evidently more work is needed to further clarify this area because literature is many times controversial.

This study focuses on survival outcomes and voice quality, laryngeal functional status and swallowing disorders post treatment, surgical or not in T1 and T2 glottic cancers.

Our results agree with other studies that refer that the survival rates are almost equivalent between RT and TLM and so the cure has to be decided on the basis of post-treatment functional outcomes, treatment duration, cost, patient's general medical condition, and patient's preference for surgery or radiation.

RT offers good control rates, but the prolonged time of the treatment, mucosal radiation damage, and long-term side effects such as xerostomia are deterrents for reserving it for further treatments.²⁵

TLM is characterized by rapidity of treatment, repeatable surgery, low morbidity, good compliance by the patient, short hospitalization and limited costs.²⁷⁻³⁰

TLM is custom-tailored to the individual tumor with an excellent view of the limits and maximal preservation of normal tissue and function. The tumor is divided into manageable units with the laser beam and removed stepwise until excision is complete.

In TLM, the operator skills play a crucial role in the achieved oncological results, probably more than in other approaches. A single surgeon for a high number of patients is likely to be an important index of high quality treatment. Patients of the first group were treated consecutively by the same laser surgeon.

We noted slight difference in OS in patients under 70 years old versus patients over 70 years old.

In western societies, there is evidence of an increase in head and neck cancers in the geriatric population, making the question of whether age should be one of the factors determining the treatment strategy for head and neck carcinoma increasingly relevant.

We think that TLM is an effective treatment for selected glottic carcinomas in elderly patients because very high local control rates are achieved with the laser alone, with a very low morbidity as well as a good patient compliance and a very short hospitalization stay.

We evaluate also functional outcomes in patients affected by early glottic cancer treated with TLM or RT.

Considering the two groups both had moderate dysphonia and there was not significant differences emerged between two groups on VHI total score and for each subscale and VHI10 questionnaire.

We noted with our results a significant lower subjective perception of disability related to voice disfunction among patients over 70 years old.

We think that the answer is that for the majority of patients life remained unchanged, but the subjects with bigger negative impact of their voice had a tendency to be younger.

Most likely, the impact of any grade of dysphonia in older patients is easier to cope with because they have reduced professional and social voice requirements than younger patients.

In our sample we achieved a satisfactory degree of laryngeal functional status and none of patients referred swallowing disorders.

A multidisciplinary team (MDT) management is now the accepted standard of care¹⁴⁸⁻¹⁵⁰ and we are hopeful that in the future a MDT could reach an evidencebased consensus on recommended treatment in circumstances in which different treatment options offer similar chances of cure.

In our opinion TLM is the gold standard for the treatment of early stage glottic cancer for its high local control rates; repeatability in reverse of RT, low morbidity, good patient compliance and short hospitalization stay.

ABBREVIATIONS

a: albedo absorption

coefficient (μ_a)

AC: Anterior Commissure

BMI: Body Mass Index cm:

centimeter

CO₂ laser: carbon dioxide laser

COPD: Chronic Obstruction Pulmonary Disease

CT: computed tomography

cTNM: clinical TNM cw:

continuous wave

DFS: Disease-Free Survival

DLE: Difficult Laryngeal Exposure DWI:
diffusion-weighted magnetic resonance e.g.:
for example

ELS: European Laryngological Society energy
density (J/m²)

ENT: Ear, Nose and Throat

Etc: etcetera FiO₂: inspired

fraction of O₂ g: anisotropic
factor

GLE: Good Laryngeal Exposure

HD: High Definition

HDTV :HD camera system He:
Helium

HFJV: High Frequency Jet Ventilation

hz: hertz

IIG: interincisors gap

J= Joule

L.A.S.E.R. : Light Amplification by Stimulated Emission of Radiation;

M: absence or presence of distant metastases;

MDADI: M.D. Anderson Dysphagia Inventory

MDT: multidisciplinary team mLS:

mini-version of the Laryngoscore mm:

millimeter

MRI: nuclear magnetic resonance ms:

millisecond

N: absence or presence and extension of metastases to regional lymph nodes

N₂: nitrose gas

NBI: Narrow Band Imaging

NIR: near-infrared

OPHL: Open Partial Horizontal Laryngectomies;

OS: Overall Survival

P = Power

Power density (W/m²)

PSS: Performance Status Scale

pTNM: pathological TNM

QoL: Quality of Life

RNL: Recurrent Laryngeal Nerve

RT: RadioTherapy s:

second scattering

coefficient (σ_s)

SCC: squamous cell carcinoma;

SD: standard deviation

SNL: Superior Laryngeal Nerve

T: extension of the primary tumor

TLM: Trans-oral Laser Surgery

TMD: thyro-mental distance

UV: ultraviolet

VHI: Voice Handicap Index

W= watts WL: white light z :
distance from the tissue surface

ZnSe: zinc selenide

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