Traitement des carcinomes du larynx par radiothérapie radicales avec ou sans chimiothérapie: résultats et facteurs pronostiques

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TRAITEMENT DES CARCINOMES DU LARYNX PAR RADIOTHÉRAPIE RADICALE AVEC OU SANS CHIMIOTHÉRAPIE: RESULTATS ET FACTEURS PRONOSTIQUES

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Résumé :

Le but de cette étude est d'examiner l'impact de l'envahissement des différents sous-sites du larynx sur les résultats oncologiques lors du traitement de cancers laryngés avec la radiothérapie ± chimiothérapie. Pour cela, une étude rétrospective de patients consécutifs traités aux HUG entre 1996-2005 par cette modalité a été entreprise.

Nos résultats montrent que les stades T avancés, une atteinte de la commissure antérieure et de la sous-glotte sont associés à une survie et contrôle local moindres. La présence de troubles de la mobilité cordale et d'œdème laryngé à 3 mois après la fin du traitement sont associés à une augmentation des récidives.

En conclusion, la radiochimiothérapie permet de guérir des cancers modérément avancés du larynx, mais les résultats pourraient être améliorés en excluant des patients avec invasion de certains sites à mauvais pronostic. Une comparaison avec d'autres modalités permettant une préservation des fonctions du larynx est discutée.

Signature du doctorant :

Visa du directeur de thèse :

This work is dedicated to:

My mother.

My late father.

My wife.

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At last, I hope this work can add a little step forward to improve the cancer larynx management, and it will open the way for future relevant studies to improve the survival results. Thanks for our cancer patients they suffer much and we offer them our limited knowledge about this disease.

RESUME

Buts de l'étude: Examiner l'impact de l'envahissement tumoral de différents sous-sites anatomiques du larynx sur le control local et la survie dans les cancers laryngés traités avec une radiothérapie radicale ± chimiothérapie.

Méthode: Étude rétrospective de patients consécutifs avec carcinome épidermoïde du larynx résécable traités aux HUG entre 1996 and 2005 avec une radiothérapie radicale ± chimiothérapie et dont le suivi minimal est de deux ans. Les patients avec un carcinome non-invasif, des cancers synchrones, des cancers métachrones de moins de deux ans, des dossiers cliniques et radiologiques incomplets ou traités chirurgicalement ont été exclus.

Les variables analysées comportaient une liste exhaustive des sous-sites anatomiques du larynx, ainsi que les stades T, la mobilité cordale, l'œdème laryngé. Une classification des régions de la commissure antérieure (AC) pouvant être envahies est proposée. Ces variables ont été analysées en termes de survie globale, survie spécifique lié au cancer, les contrôles local et régional et la préservation anatomique et fonctionnelle du larynx.

Résultats: Stades T: le contrôle local estimé à 5 ans pour les stades T1, T2, T3 and T4 est de 82%, 75%, 66%, et 0/1 respectivement: La survie spécifique estimée à 5 ans pour les stades T1, T2, T3 and T4 stages est de 100%, 77%, 44%, and 0/1 respectivement. Ces différences sont significatives (p=0.02).

SITES ANATOMIQUES: une association significative avec le contrôle local était retrouvée pour l'atteinte de la sous-glotte (p= 0.002), la sous-glotte antérieure (p< 0.001), la commissure antérieure (p= 0.001), l'atteinte de la mobilité cordale post-traitement (p< 0.001), l'œdème laryngé persistent (p= 0.003).

LA COMMISSURE ANTERIEURE: le contrôle local estimé à 5 ans pour l'extension tumorale à AC, AC1, AC2, and AC3 était de 57%, 47%, 40% et 45% respectivement. La survie spécifique estimée à 5 ans pour AC, AC1, AC2, and AC3 était de 70%, 76%, 40% et 54% respectivement.

PRESERVATION LARYNGEE: le taux de préservation anatomique du larynx à 5 ans est de 73% et le taux de survie avec préservation d'un larynx fonctionnel de 67%.

Conclusions: La radiothérapie radicale ± chimiothérapie donne de bons résultats oncologiques dans le traitement des carcinomes laryngés modérément avancés. Le volume tumoral ne semble pas être un facteur pronostique, puisque l'atteinte de la mobilité cordale et une extension sous-glottique latérale ne diminue pas la survie. L'atteinte de sous-sites spécifiques du larynx comme la commissure antérieure (surtout une extension verticale) et de la sous-glotte (surtout une extension antérieure) est associée avec de moins bons contrôle local et survie. La présence d'une atteinte de la mobilité cordale et d'une œdème laryngé après traitement sont des facteurs prédictifs importants pour une récidive tumorale.

SUMMARY

Aim of the work: To examine, the impact of the different anatomical laryngeal subsites on the local control and disease specific survival in primary cases of laryngeal squamous cell carcinoma treated with radical radiotherapy ±chemotherapy.

Methods: Retrospective consecutive cohort study, including all the patients with primary invasive resectable squamous cell carcinoma of the larynx (SCC-L) diagnosed between 1996 and 2005 at HUG, and treated with radical (chemo)radiotherapy at our hospital with a minimum 2 years follow-up. Patients with synchronous malignancy, and /or previous non-cured malignancy, incomplete records (clinical and radiological) were excluded.

The variables analysed included laryngeal anatomical sites that might be involved by the SCC-L, as well as T stage, vocal cord mobility, laryngeal oedema, and anterior commissure (AC). For the AC, a classification of different areas is proposed. Outcome measurements included overall, local, and regional control and survival, as well as anatomical and functional laryngeal preservation.

Results: FOR T STAGES: the estimated 5 years local control rates for the T1, T2, T3 and T4 stages were 82%, 75%, 66%, and 0/1 respectively; the estimated 5 years disease specific survival rates for T1, T2, T3 and T4 stages were 100%, 77%, 44%, and 0/1 respectively. These differences were significant (p=0.02).

SIGNIFICANT ANATOMICAL SUBSITES: an association of poor the local control was found with the involvement of the subglottis (p= 0.002), anterior subglottis (p< 0.001), anterior commissure involvement (p= 0.001), post-treatment impairment of vocal fold mobility (p< 0.001), persistent laryngeal oedema (p= 0.003).

ANTERIOR COMMISSURE INVOLVEMENT: the estimated 5 years local control rates for tumour extension to AC, AC1, AC2, and AC3 positive were 57%, 47%, 40%, and 45% respectively. The estimated 5 years disease specific survival rates for involvement of AC, AC1, AC2, and AC3 were 70%, 76%, 40%, and 54% respectively.

LARYNGEAL PRESERVATION: the adjusted 5 years laryngectomy free rate was 73% and the adjusted 5 years survival rate with a preserved laryngeal function was 67%.

Conclusions: Radical (chemo)radiotherapy in the treatment of SCC-L give good oncologic outcome for moderately advanced SCC-L. Tumour volume in itself might not be an important prognostic factor, since vocal cord fixation and lateral subglottic extensions do not decrease the survival. Involvement of specific locations, such as the anterior commissure (especially with vertical extension) and the subglottis (especially an anterior extension) are associated with poor local control and / or survival. Post-treatment vocal fold mobility impairment and/or persistent laryngeal oedema are strong predictors of tumour recurrence.

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Cancer larynx is the most common head and neck mucosal cancer in Geneva as well as throughout the world, and every year about 40 patients are presented to the head and neck tumour board of Geneva University Hospitals with this disease. Total laryngectomy which is a highly mutilating procedure often followed by postoperative radiotherapy remained the main treatment until the last three decades, when several partial laryngectomies and radiotherapy became established as a treatments for most of the early lesions. The situation remained more or less unchanged for locally advanced lesions until the 1990s, when new radical radiotherapy protocols ± chemotherapy were established to become within the last 10 years one of the main treatments for many advanced lesions of cancer larynx.

In Geneva University Hospitals we were from the beginning (early 1990s) applying these "organ preservation" protocols to offer the best outcome for our patients, and we have now about 18 years of experience with these new modalities in the field of cancer larynx.

In recent years a slight overall deterioration in the specific survival of cancer larynx was observed in the US national cancer statistics, especially for the advanced glottic lesions, which were treated with similar protocols. Thus, it was important to conduct a research reviewing our results for cancer larynx treated with radical radiotherapy and to study the different anatomical prognostic factors. While the different anatomical subsites of the larynx are paramount for studies of cancer progression, the staging of laryngeal cancer in term of TNM, and the choice of the type of partial surgical resection, these subsites have seldom been addressed in studies of radiotherapy and even less in chemoradiation publications.

Our results with (chemo)radiation treatment of cancer larynx are compared with other publication using similar protocols, as well as with those of other available surgical treatment modalities. The ultimate goal is to update our recommendations for treatment selection for future patients. In the process, more unanswered questions arise and should be addressed by future research in order to improve the survival and function of our patients.

I. INTRODUCTION

1.1. ANATOMY

The larynx is located anteriorly in the midline of the neck, with its long axis vertically aligned with the trachea at the level of the third to sixth cervical vertebrae. It articulates with the hyoid bone anterosuperiorly, and its inlet is nearly at the level of the base of the tongue where it communicates superiorly and dorsally with both the oropharynx and the hypopharynx (laryngopharynx). It is attached to the muscular walls of the pharynx dorsally, and connects with the trachea inferiorly. The laryngeal skeleton is composed of three unpaired cartilages joined to each other, and to the hyoid bone above and the trachea below, by synovial joints, ligaments, membranes, and muscles [1]. The larynx is closely related to the hyoid bone and the average distance between the upper border of hyoid bone and the lower border of cricoid cartilage at the anterior midline is about 63 mm in the male and 51 mm in the female [2].

1.1.1. LARYNGEAL SKELETON

The laryngeal skeleton (Figure 1-5) is composed of three unpaired cartilages (epiglottic, thyroid, and cricoid) and three paired cartilages (arytenoid, corniculate, and cuneiform). The main cartilages are the thyroid cartilage, cricoid cartilage, and the two arytenoid cartilages. The most superior cartilage is the epiglottis, and the most inferior cartilage is the cricoid. The anterior aspect is largely occupied by the thyroid cartilage and also includes the epiglottis superiorly and the cricoid inferiorly while the posterior aspect is composed mostly of the cricoid cartilage, and the arytenoids cartilages [1,3,4].

1.1.2. HYOID BONE

Hyoid bone (Figures 1) is a C-shaped bone situated in the upper part of the anterior neck, between the third and fourth cervical vertebrae; it consists of a central body with greater and lesser horns (cornua) on each side. It is attached superiorly to base of the tongue, inferiorly to the larynx, and it is maintained in its position by numerous muscular, ligamentous, and membranous attachments [4].

1.1.3. THYROID CARTILAGE

The thyroid cartilage is the largest and most prominent laryngeal cartilage. It is a shield shaped structure (Figure 1) that serves to protect the inside of the larynx from anterior trauma. It is composed of two lateral wings (Figure 2) the alae (laminae) which are fused anteriorly in the midline and are opened posteriorly. In the male, the alae fuse by an angle nearly about 90 degrees, while in females, this fusion angle is more obtuse and it is nearly about 120 degrees. The superior most point of anterior fusion line projects ventrally and is called the laryngeal prominence, which is more apparent in males, the so-called Adam's apple. Superiorly, the fusion of the alae is deficient, accounting for the thyroid notch (Figure 1). Each lamina has a pair of projections (cornua or horns) from the dorsal edge (Figure 2): one long extending superiorly (superior horn) and one short extending inferiorly (inferior horn) [1,5].

Superiorly, the thyroid cartilage attaches to the hyoid bone via the thyrohyoid membrane and each superior cornu attaches to the ipsilateral greater horn of the hyoid bone by the lateral thyrohyoid ligament, which often contains a small, round triticeal cartilage (Figure 1). The thyroid and cricoid cartilages are attached ventrally by a median cricothyroid ligament and laterally by the lateral cricothyroid membrane (Figure 1). Each inferior cornu articulates with the cricoid cartilage to form the cricothyroid joint [1,4,5].

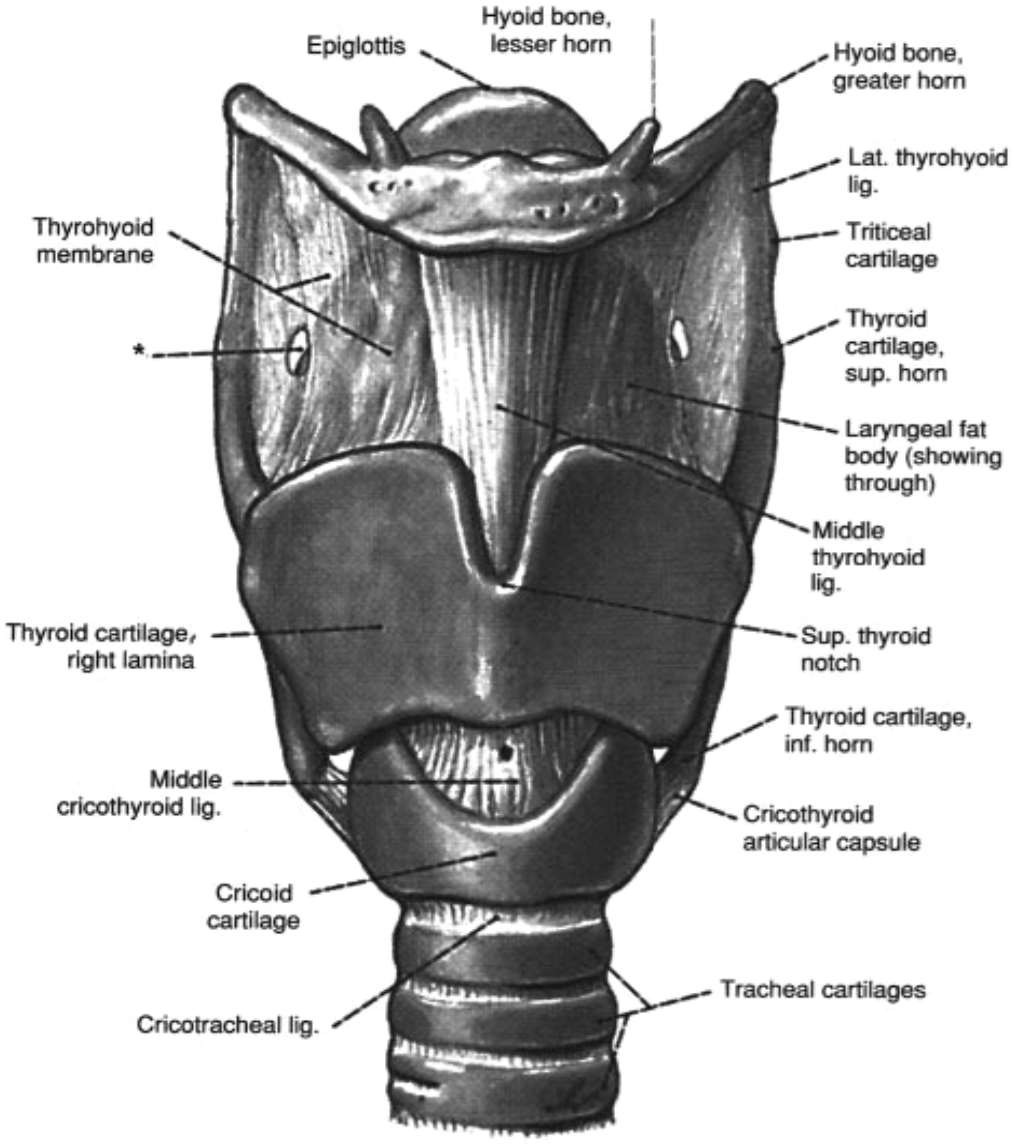


Figure 1: Anatomy of the larynx - front view.
From: Sasaki CT, Kim YH. Anatomy and Physiology of the Larynx. In: Snow JB, editor. Ballenger's otorhinolaryngology head and neck surgery. Ontario, BC Decker Inc, 2003 [5]. Figure 47-1A. Reproduced with permission.

At the attachment of the superior cornu to the alae of the thyroid, a protuberance called the superior tubercle is found, while the inferior thyroid tubercle is found in the middle of the inferior border [5,6]. Running obliquely from the superior tubercle to the inferior tubercle, a ridge called the oblique line is described (Figure 2), serving as the attachment point for the thyrohyoid, sternothyroid, and inferior constrictor muscles [4-6].

The dimensions of the thyroid cartilage have been studied extensively, especially in regard to the external projection of the vocal cords [2,7-10]. There is an agreement between studies that the height of the thyroid cartilage at the anterior midline (from the thyroid notch to the lower border in the midline) is usually around 20 mm in men and 14 mm in women. The level of the vocal cords projects externally at or very close to the anterior midpoint of the thyroid cartilage in males and slightly above the anterior midpoint in females [2,7-10].

The thyroid cartilage is lined by a thick layer of perichondrium on all surfaces except the inner surface of

the area immediately above the anterior commissure, where the attachment of the anterior commissure ligament is found [5].

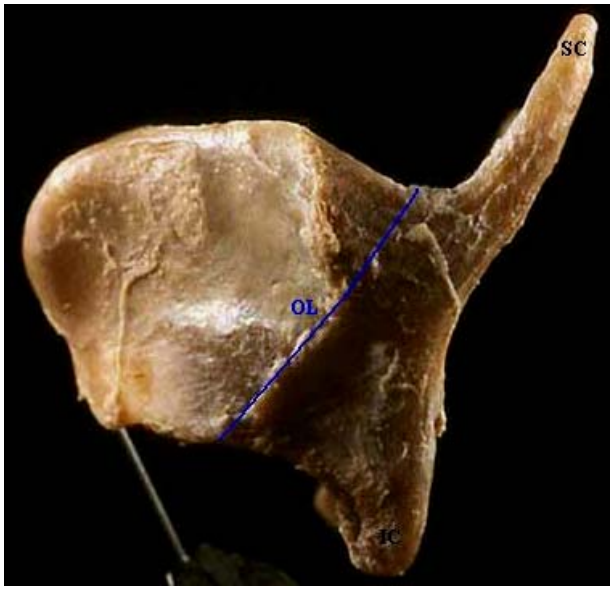


Figure 2: Thyroid cartilage - lateral view.
SC: superior cornu, IC: inferior cornu, OL: oblique line. Modified from the W.R. Zemlin Memorial Web Page: http://zemlin.shs.uiuc.edu/larynx1/default.htm

1.1.4. CRICOID CARTILAGE

The cricoid cartilage (Figures 1, 3-5) is the only complete ring in the airway and is considered as the major support for the functioning larynx. Its shape is classically described as that of a signet ring with wider flat quadrangular lamina posteriorly and narrow arch anteriorly (Figure 3). The inferior border is nearly horizontal and is attached to the first tracheal cartilage by the cricotracheal ligament(Figures 1, 5), while its' broad lamina extends much more cranially above the level of the arch making the superior border slopping up in the anteroposterior line (Figure 3). At the line where the arch joins the lamina, the cricoid cartilage articulates with the inferior cornu of thyroid cartilage (Figure 4-A). The cranial border of the cricoid lamina supports a pair of arytenoid cartilages, forming the cricoarytenoid articulation, a true synovial joint (Figure 4-A). The lamina shows on its posterior surface a thick midline ridge which gives the attachment to the longitudinal fibers of the suspensory ligament of the oesophagus (cricopharyngeal ligament); this ridge also separates two wide depressions that give the origin of posterior cricoarytenoid muscles (Figure 3-B) [1,4,5].

The height of the cricoid arch at the midline is widely ranging between 3.5-6.9 mm and it is longer in men, while the height of the posterior lamina at the mid line shows less variation and is roughly around 21 mm in women and 24 mm in men. [8,11].

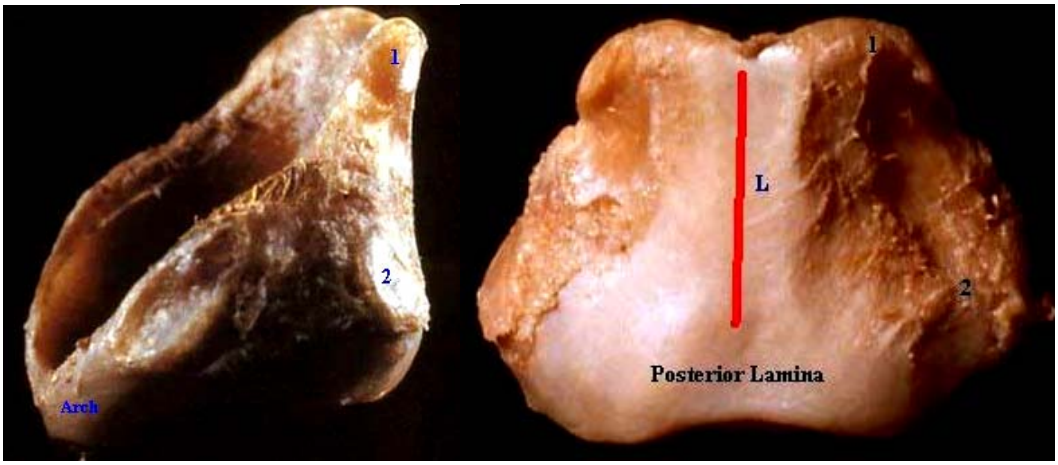


Figure 3: Cricoid cartilage. LEFT - lateral view; RIGHT - posterior view.
1: facet for articulation with the arytenoid, 2: facet for articulation with thyroid cartilage, L: line for the attachment of the oesophagus. Modified from the W.R. Zemlin Memorial Web Page: http://zemlin.shs.uiuc.edu/larynx1/default.htm.

1.1.5. ARYTENOID CARTILAGES

The arytenoids (Figure 4, 5) are paired cartilages that articulate with the posterosuperior portion of the cricoid cartilage. Each is shaped like a tetrahedron (roughly pyramidal in shape), with the apex directed cranially where the corniculate cartilage is sitting. The apex gives attachment to the aryepiglottic fold, while the base articulates with the cricoid cartilage lamina by the cricoarytenoid synovial [1,4,5].

Each arytenoid has three surfaces (medial, posterior, and anterolateral) and two processes originating from the base. The thin anterior process (vocal process) gives attachment to the vocal ligament, which in turn, supports the medial edge of the vocal fold. The thick lateral process (muscular process) receives many muscular attachments. The posterior surface receives also muscular attachments, while the medial surface is covered by the mucosa that constitutes the lateral border of the posterior (intercartilaginous) part of the glottis [5,12]. The anterolateral surface gives strong attachments to the thyroarytenoid muscle near the base and it is attached to the vestibular ligament near its apex [12].

Figure 4: Arytenoid cartilage. 4A: Posterior view of the laryngeal skeleton; 4B: Posterior view of the left arytenoid; 4C: Posterior view of the right arytenoid.
1: muscular process, 2: corniculate cartilage. Modified from the W.R. Zemlin Memorial Web Page

(http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.6. EPIGLOTTIC CARTILAGE

The epiglottic cartilage (Figures1, 5) is positioned in the midline and is the most superior cartilage of the larynx, as implied by its name. The cartilage and its coverings are collectively termed the epiglottis. It is a leaf-shaped highly elastic fibrocartilage, with a very narrow stalk-like base (petiole), which is attached inferiorly to the anterior luminal aspect of the thyroid cartilage by the thyroepiglottic ligament. Superiorly, it is attached to the hyoid bone by the hyoepiglottic ligament or membrane [1,4,5].

The epiglottis may be divided into a suprahyoid and an infrahyoid portion. The suprahyoid portion (Figure 1) is free on both of its laryngeal and lingual surfaces and forms the anterior margin of the laryngeal inlet. The mucosa is more adherent to the underlying cartilage on the laryngeal surface than the lingual one. As the mucosa of the laryngeal surface is reflected back onto the base of the tongue, three folds result: two lateral glossoepiglottic folds and a median glossoepiglottic fold. The two depressions formed by these folds are known as the valleculae, a part of the oropharynx. Laterally the epiglottic cartilage is attached to a membrane extending to the arytenoid and corniculate cartilages, the quadrangular membrane which constitutes the main support of the aryepiglottic folds. The infrahyoid portion is free only on its laryngeal or posterior surface, where it contains a small protuberance known as the tubercle. Between the anterior surface of the infrahyoid epiglottis, the thyrohyoid membrane, and the thyroid cartilage, a fat containing space exists: the pre-epiglottic space. The posterior surface of the epiglottic cartilage has multiple pits (perforations) (Figure 5) filled with mucous glands [5].

The mean height of the epiglottis is 34.6 mm in men and 28.2 mm in women, while the mean width at the level of hyoid bone, where the epiglottis is the largest, is 25.2 mm in men and 19.9 mm in women [8].

1.1.7. MINOR CARTILAGES OF THE LARYNX

The corniculate or cartilage of Santorini are housed on the apex of the arytenoid cartilage. The cuneiform or cartilage of Wrisberg, when present, are lateral to the corniculate cartilages and are embedded in the aryepiglottic fold. These are fibroelastic cartilages that appear to add rigidity to the aryepiglottic fold, although some feel that these cartilages are vestigial [5]. The list is completed by the small triticeal cartilage, often found in the lateral thyrohyoid ligament [4,5].

1.1.8. OSSIFICATION OF THE LARYNGEAL CARTILAGES

The thyroid, the cricoid, and most of the arytenoid cartilages (except the tip and superior part of the vocal process) are composed of hyaline cartilage and thus will undergo ossification. It should be noted that the hyoid bone is completely ossified at 2 years of age and is generally not a point of radiologic confusion. The thyroid cartilage begins to ossify in the male around the age of 18- 20 years and in the female a few years later [5]. The ossification begins in the small area situated posteroinferiorly on the lamina and just superior to the inferior horn, it then extends anteriorly on the inferior border and superiorly at the posterior border [4,5,13]. The last to ossify is a small tongue shaped area just below the thyroid notch [13].

The cricoid and arytenoid cartilages undergo ossification somewhat later than the thyroid cartilage; ossification of the arytenoid cartilages begins at its base, while the cricoid cartilage generally begins at the inferior border and at the superior margin of the quadrate lamina [4,5,13,14]. Unlike the thyroid cartilage, the ossification of the cricoid cartilage begins nearly at the same age for men and women (in the third decade), but after that it proceeds more rapidly in men. The ossification process is mostly bilaterally symmetrical, but shows high individual variability especially in cricoid cartilage [13,14].

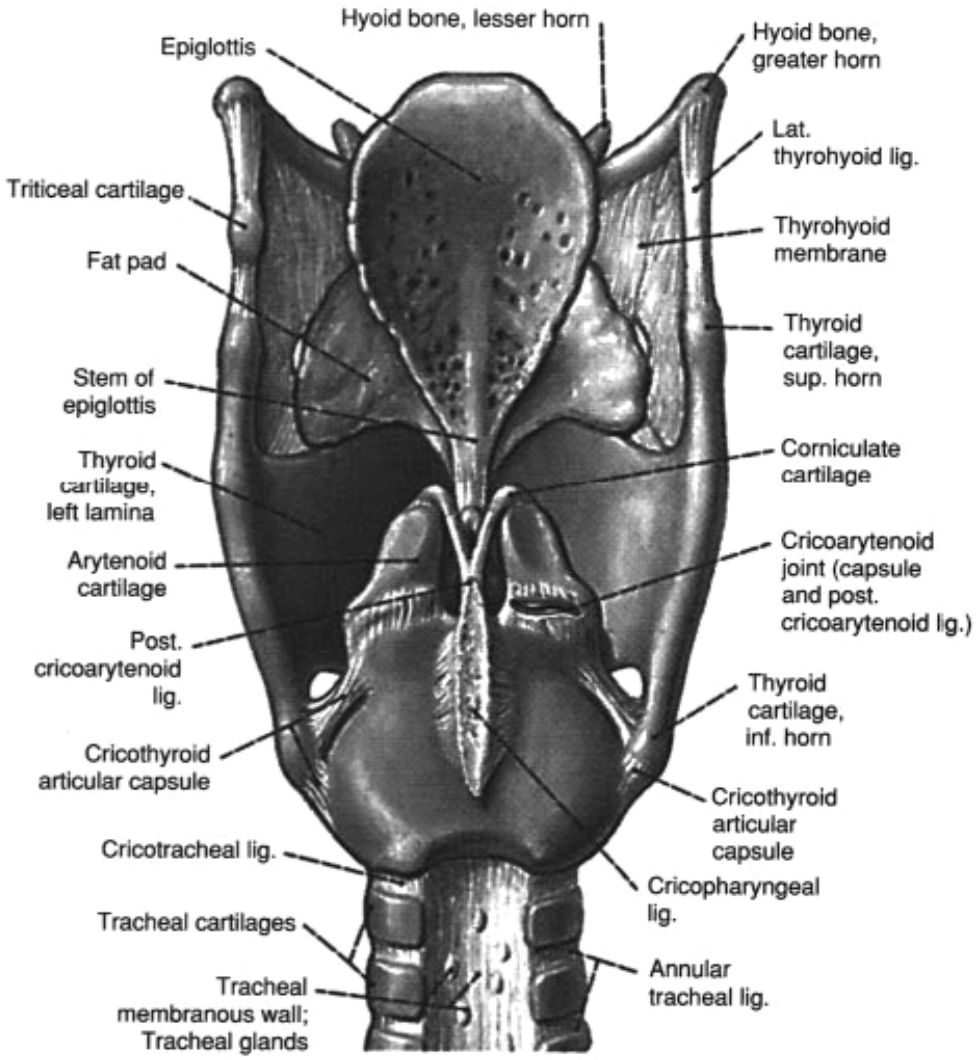


Figure 5: Anatomy of the larynx - posterior view.
From: Sasaki CT, Kim YH. Anatomy and Physiology of the Larynx. In: Snow JB, editor. Ballenger's Otorhinolaryngology - Head and Neck Surgery. Ontario: BC Decker Inc, 2003. Figure 47-1B.[5] Reproduced with permission.

1.1.9. LARYNGEAL JOINTS

The cricoarytenoid joint is a synovial joint between each arytenoid and the superior part of the cricoid lamina. The articular surface of the cricoid cartilage is convex throughout its length, along its short axis (which runs in an oblique anteroposterior plane), while its long axis runs in oblique lateral plane giving the articular surface - a tear-drop shape with the larger end situated posterolateral. This contour of the cricoid cartilage facet allows for an inferior and medial rotation of the vocal process toward the end of adduction. The long axis of the arytenoid cartilage facet rests nearly perpendicular to the cricoid cartilage facet long axis [15].

The complex changes in the relation between the two articular facets of the joint with the different muscular, ligamentous and membranous attachments allow a wide range of movements. The main types of cricoarytenoid joint motions that could be identified are 1) rocking (sliding) along the sagittal short axis of the cricoid facet, 2) twisting or rotating along the axis of the joint, and 3) gliding motion in an oblique lateral to

medial plane. It is important to realize that these movements cannot be individualized, but must be viewed together since they occur more or less simultaneously [15,16].

The second intralaryngeal articulation is the cricothyroid joint, which is a synovial articulation between the inferior cornu of the thyroid cartilage and the side of the cricoid cartilage. It has a strong capsule which is strengthened posteriorly by a fibrous band. The joint has two movements: rotation and gliding. The primary (main) movement is rotation, with the cricoid rotating up around a transverse access passing through both joints and the thyroid cartilage tilting forwards and downwards [4,17].

1.1.10. LARYNGEAL MUSCLES

1.1.10.1. EXTRINSIC MUSCLES

The extrinsic muscles of the larynx are those muscles having attachment outside the laryngeal cartilage and moving the whole larynx. These muscles serve to elevate, lower, or to stabilize the larynx. The muscles that elevate the larynx are the suprahyoid muscles that elevate the hyoid bone and thus the closely attached larynx during swallowing; they also help to suspend the larynx, via the hyoid bone, from the skull base and mandible. The laryngeal elevators include the stylohyoid, digastric, geniohyoid, mylohyoid, and stylopharyngeus muscles. To these should be added the thyrohyoid muscle which elevates the thyroid cartilage towards the hyoid bone [4,5].

The principal depressors of the larynx (Figure 6) are the sternothyroid, omohyoid, and sternohyoid muscles. The sternothyroid muscle displaces the larynx directly downward during inspiration, while the omohyoid, and sternohyoid muscles depress the larynx indirectly by putting pressure on the entire larynx [4,5].

The middle constrictor, inferior constrictor, and cricopharyngeus muscles are also important extrinsic laryngeal muscles; the functioning of these muscles is mainly related to swallowing [5].

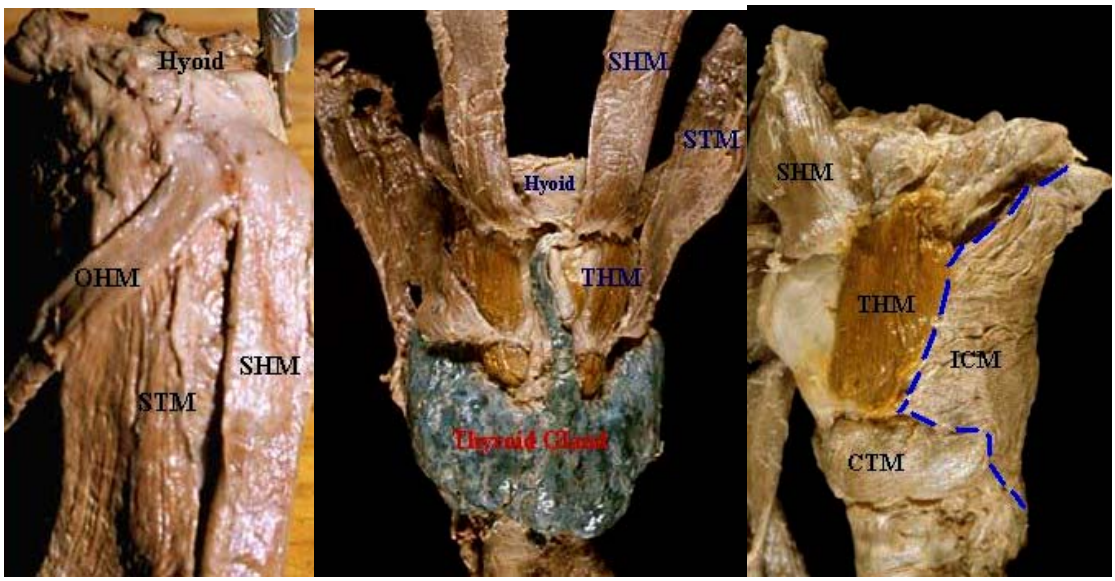


Figure 6: External laryngeal muscles, from left to right: 6A: lateral view; 6B: anterior view; 6C: anterolateral view. SHM: sternohyoid muscle, OHM: omohyoid muscle, STM: sternothyroid muscle, THM: thyrohyoid muscle stained with yellow colour, ICM: inferior constrictor muscle, and CTM: cricothyroid muscle. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.10.2. INTRINSIC MUSCLES

The intrinsic muscles of the larynx attach only between the different cartilages of the larynx. With the exception of the cricothyroid muscle, intrinsic laryngeal muscles are behind the thyroid cartilage shield and are covered by the laryngeal mucosa [1,5]. With the exception of the interarytenoid, the intrinsic laryngeal muscles are paired (left and right) and each muscle pair appears to act synchronously [1,5].

There are multiple adductors, but only a single abductor. Most of the intrinsic muscles act to protect the larynx by narrowing the laryngeal inlet (additus) and closing the glottis (the space between the vocal folds). The origin, development, and circumferential arrangement around the laryngeal inlet of these muscles suggest that they act mainly as a sphincter to narrow the laryngeal inlet. In addition, they modify the size of the glottic opening along with the length and tension of the vocal folds [1,5].

- *POSTERIOR CRICOARYTENOID MUSCLE*

The posterior cricoarytenoid muscle (Figure 7) is the only abductor of the vocal folds. It originates from the dorsal laminae of the cricoid cartilage and its' fibers run obliquely in a superior and lateral direction, to be inserted in the lateral aspect of the muscular process of each arytenoid. It is composed of two compartments: a horizontal and a vertical belly (Figure 7). Contraction of these fibers brings the muscular process medially, posteriorly, and inferiorly so the arytenoid is rotated laterally along its axis. These actions abduct, elongate, and thin the vocal folds and thereby open the laryngeal lumen [5,18]. It is proposed that the vertical and oblique bellies normally cause vocal fold abduction during respiration, whereas the horizontal belly is primarily used to adjust the position of the vocal process during phonation [18].

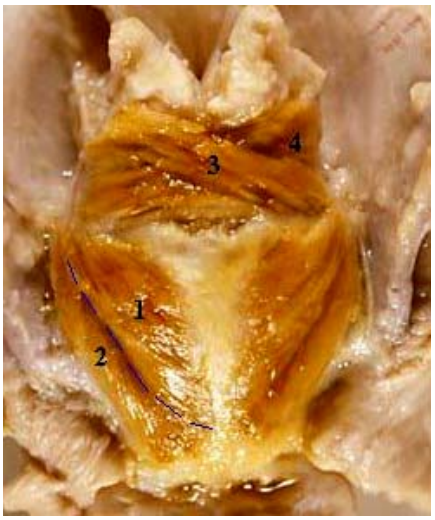


Figure 7: Posterior view of the larynx demonstrating the posterior cricoarytenoid muscles.
1: horizontal part, 2: vertical part, 3 and 4: interarytenoid muscles. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

- *LATERAL CRICOARYTENOID MUSCLE*

The lateral cricoarytenoid muscle (Figure 8) is the main antagonist of the posterior cricoarytenoid and represents the main adductor of the vocal folds. It attaches along the superior border of the lateral part of the arch of the cricoid cartilage and then sends its fibers posteriorly to insert on the anterolateral portion of the muscular process of the arytenoid. Contraction of this muscle brings the muscular process anterolaterally, while internally rotating the arytenoid and thereby adducting and lowering the vocal process. This results in

adduction, elongation, and thinning of the vocal folds (e.g. the edge of the vocal fold becomes sharper) [5].

- *INTERARYTENOID AND ARYEPIGLOTTIC MUSCLES*

The interarytenoid is the only unpaired intrinsic muscle, consisting of two types of muscle fibers (Figure 7); the bulk of the muscle consists of transverse fibers (transverse interarytenoid) passing from the posterior surface of one arytenoid cartilage to the posterior surface of the other. It is known that this muscle receives rich innervations bilaterally from both the recurrent laryngeal nerves, as well as some fibers from the internal branch of the superior laryngeal nerves. This muscle contracts to bring together the arytenoid cartilages, thus assisting in closing the posterior portion of the glottis, although this does not significantly affect the mechanical properties of the vocal folds. Along with these transverse fibers there are oblique fibers (Figure 7). These oblique fibers pass from the posterior portion of the arytenoid on one side to the apex of the arytenoid on the other side, thus crossing in the midline (X-shape). Some of these fibers insert at the apex, whereas others travel along the quadrangular membrane, in the aryepiglottic fold) constituting the aryepiglottic muscle (Figure 10). The contraction of the aryepiglottic fibers narrows the laryngeal additus [1,5,19].

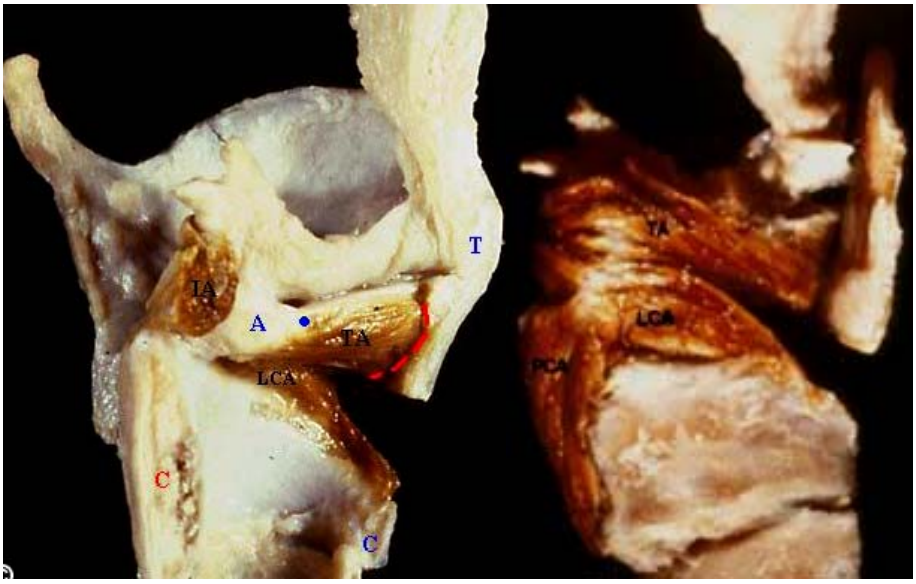


Figure 8: Paramedial sagittal views of the larynx.
C: cricoid, T: thyroid, A: arytenoid, LCA: lateral cricoarytenoid muscle, TA: thyroarytenoid muscle. Note that the attachment of the TA muscle to the thyroid in the subglottis (interrupted line). Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

- *THYROARYTENOID MUSCLE*

The thyroarytenoid muscle (Figures 8-10) is classically divided into the medial (internal) thyroarytenoid muscle (vocalis muscle) and lateral (external) thyroarytenoid muscle (Figure 10). All fibers have the same attachments, but the internal lie deep to the external. The external thyroarytenoid muscle arises from the inner surface of the thyroid cartilage in the midline, close to the anterior commissure, and inserts onto the lower part of the anterolateral surface of the arytenoid cartilage (Figures 8, 9). It contracts to bring the vocal process and anterior commissure closer to each other, thus adducting and shorting the vocal folds. It also contracts to adduct the false cords. The external muscle sends up a few slips of muscle fibers onto the quadrangular membrane (Figure 10) to establish the thyroepiglottic muscle. This muscle, like the aryepiglottic muscle, acts to narrow the laryngeal inlet [5,20].

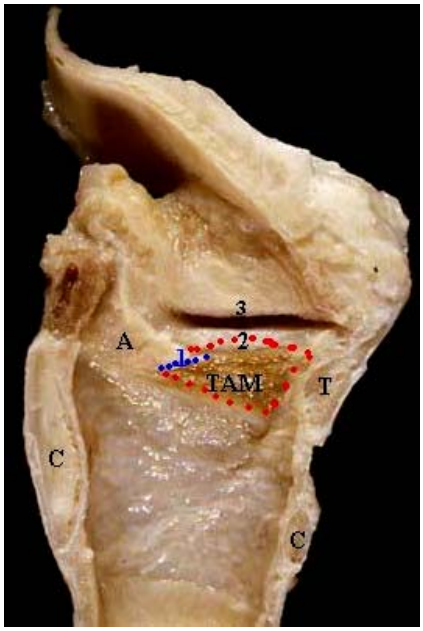


Figure 9: Midsagittal view of the larynx demonstrating the thyroarytenoid muscle.
The thyroarytenoid muscle (TAM) inside the red dotted line, with (1) its attachment to the vocal process of arytenoid. 2: vocal fold, 3: false vocal fold, C: cricoid cartilage, T: thyroid cartilage, A: arytenoid cartilage. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

The internal thyroarytenoid or vocalis muscle attaches at the anterior commissure and inserts onto the vocal process, sending a few slips of fibers below the vocal ligament onto the conus elasticus and it runs adjacent to the lateral aspect of the vocal ligament [5,20,21]. It contracts to adduct, shorten, thicken, and lower the vocal fold while rounding its edge [5]. In addition, it can be divided into superior and inferior compartments; the superior compartment is uniquely well-developed in humans and it contains a very high concentration of muscle spindles, collagen fibers, and slow-twitch muscle fibers. These concentrations are mainly located in the area adjacent to the vocal ligament, in the same location; the vocalis muscle is separated into small and physically separate fascicles. The remaining part of the thyroarytenoid muscle and the inferior vocalis compartment have much fewer muscle spindles and low-twitch fibers and an entirely different morphology. These facts support the hypothesis that the different sub-compartments are designed for different functions, the lateral thyroarytenoid and the inferior compartment of the vocalis muscle acting mainly as adductors for the vocal fold, while the superior compartment of the vocalis muscle is concerned with phonation [21].

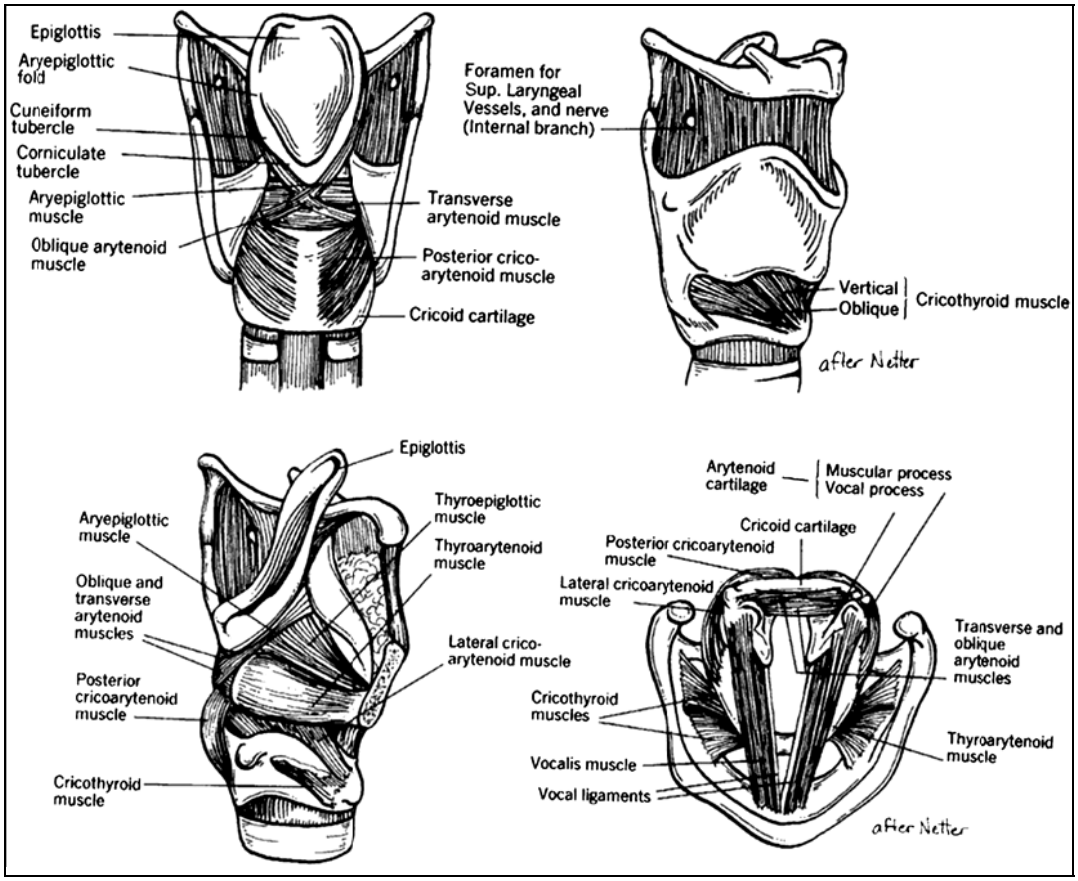


Figure 10: Drawings of the intrinsic muscles of the larynx.
From Sataloff RT, Heman-Ackah YD, Hawkshaw MJ: Clinical anatomy and physiology of the voice. Otolaryngol Clin North Am 40:909-29,2007[3]. Reproduced with permission.

- *CRICOTHYROID MUSCLE*

The human cricothyroid muscle is located on the anterolateral external surface of the laryngeal cartilages; it does not attach to the arytenoid cartilages and thus can act only indirectly on the vocal folds. It is composed of three bellies (rectus, oblique, and horizontal). The rectus portion (Figure 11) attaches the lateral portion of the anterior arch of the cricoid cartilage to the inferior border of the thyroid cartilage in a fairly vertical direction. The second belly, the oblique part, also extends from the anterolateral border of the cricoid arch, travels obliquely upward to insert on the anterior portion of the inferior cornu (Figure 11). The horizontal belly is a small deep belly originating from the top surface of the posterior cricoid arch, immediately anterior to the origin of the lateral cricoarytenoid muscle, and courses posterosuperiorly to insert onto the posterior one third of the medial surface of the inferior margin of the thyroid lamina and the thyroid inferior horn. The external branch of the superior laryngeal nerve supplies all the bellies but gives more nerve branches to the rectus belly than to the oblique and horizontal bellies [22].

When the right and left cricothyroid muscles contract, they rotate the cricoid at the cricothyroid joint. This action brings the anterior arch of the cricoid superiorly toward the inferior border of the thyroid laminae while displacing the posterior cricoid lamina (and the arytenoid cartilages) inferiorly. In the same time, the thyroid lamina is rotated and displaced anteroinferiorly. These movements increase the distance between the vocal processes and the anterior commissure, the result of this action is to lower, stretch, and thin the vocal folds while bringing them into a paramedian position. The stretching of the vocal fold also sharpens the edge of the vocal fold and passively stiffens the component layers of the vocal fold. Biomechanically, this translates

into a higher fundamental frequency produced by the vocal folds [5,22].

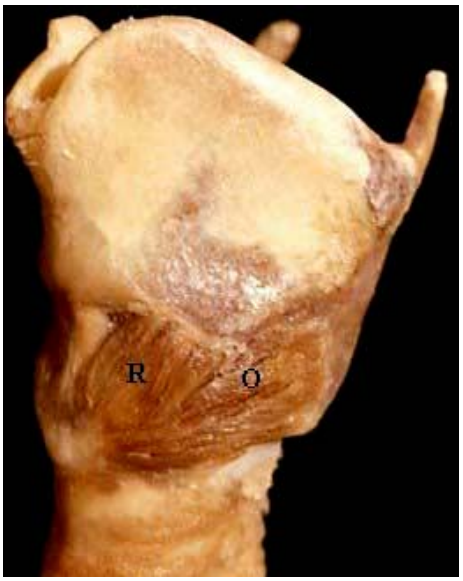


Figure 11: Oblique lateral view of the larynx.
Rectus (R) and oblique (O) part of the cricothyroid muscle. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.11. INTERNAL ANATOMY OF THE LARYNX

1.1.11.1. LARYNGEAL INLET

The entrance of the laryngeal (Figure 12) cavity is called the laryngeal additus or laryngeal inlet. Superiorly and dorsally, this opening connects the laryngeal vestibule with the oropharynx and laryngopharynx. The edge of the opening is defined ventrally by the epiglottis, laterally by the aryepiglottic folds, and dorsally by the mucosa over the arytenoids and the transverse mucosal fold between the arytenoid cartilages. The ventral aspect rises further superiorly than the dorsal aspect due to the height differences between the tall epiglottic and the short arytenoid cartilages, making the larynx inlet oblique [1,4,5].

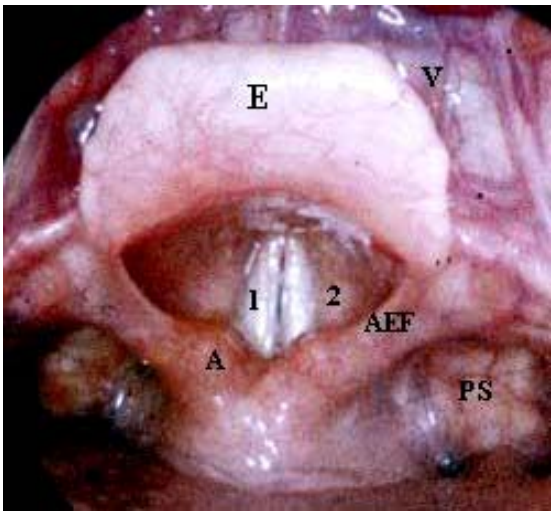


Figure 12: The larynx as seen from above during vocal fold adduction.

1: left vocal fold, 2: right false fold, E: epiglottis, A: left arytenoid apex, AEF: right aryepiglottic fold, V: right vallecula, PS: right piriform sinus. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.11.2. LARYNGEAL OUTLET

Inferiorly, the subglottic lumen of the laryngeal cavity is continuous as the tracheal lumen, at the lower border of the cricoid cartilage. This smooth transition between the lining of the cricoid cartilage and the trachea is called the cricotracheal membrane [1,4].

1.1.11.3. LARYNGEAL CAVITY

The internal cavity of the larynx (Figures 12-14) consists anatomically of three compartments separated by two folds; the vestibular fold above, also called the false vocal fold or the ventricular band, and the true vocal fold below. The three compartments are the vestibule, the ventricle, and the subglottic or infraglottic cavity. The region bounded by the vocal folds is called the rima gottidis or glottis and the region bounded by the vestibular folds is called rima vestibulum [4,5].

1.1.11.4. THE VESTIBULE

The vestibule of the larynx is that portion of the larynx extending from the laryngeal inlet above to the vestibular folds below. Thus, it is bounded anteriorly by the epiglottis and the thyroepiglottic ligament in the lower part, laterally by the aryepiglottic folds and the fat of the peri-epiglottic space, posteriorly by the arytenoid and corniculate cartilages and the interarytenoid muscle [23].

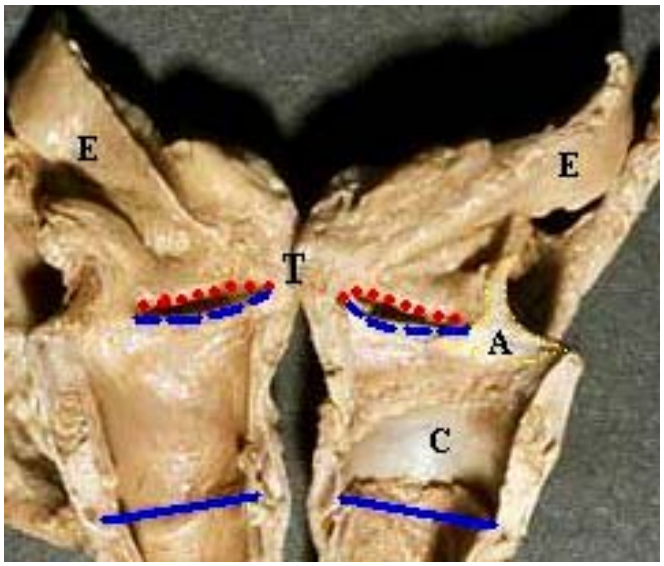


Figure 13: Larynx cut in the midsagittal plane, demonstrating the internal cavities.
In the right hemilarynx one distinguish the cricoid (C), arytenoid (A), thyroid (T), epiglottic (E) cartilages. The red dotted line is the level of false cord, the blue interrupted line is the vocal fold and the ventricle opening is in between. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.11.5. THE VENTRICLE

The ventricle (Figures 13, 14) or sinus of Morgagni is the small space between the false and true vocal folds. The ventricle is often hidden during laryngoscopic examination of the larynx unless exposed by lateralization of the false vocal fold. At the anterior end of the ventricle is a diverticulum known as the laryngeal saccule (of Hilton) which is lined with mucous glands, acting to lubricate the vocal folds. The size of

the saccule is quite variable, in some histological sections it extends up to the upper border of the thyroid lamina. The musculature surrounding the laryngeal ventricle comprises the thyroarytenoid (the main paraventricular muscle), the thyroepiglotticus, and the ventricularis muscles (which consists of small fibers running medial to the ventricular band and represents an upper extension of the thyroarytenoid muscle). With the exception of the thyroarytenoid muscle, all other muscles are small, variable in size and orientation, and may even be absent [4,24].

1.1.11.6. THE VESTIBULAR FOLD

The vestibular folds (false vocal folds), are composed of the mucous membrane, adipose and connective tissue, numerous groups of mucous glands. A weak and often deficient ligamentous skeleton for these tissues is provided by the thickened caudal margin of the quadrangular membrane (the vestibular ligament). The region bounded by the vestibular folds is called rima vestibulum [6,25].

In addition to the craniolateral extension of the thyroarytenoid muscle, the superior thyroarytenoid and ventricularis muscles are small, variable muscles present in the lateral border of the vestibular fold and the upper part of the ventricle [24]. This non-thyroarytenoid muscular tissue of the vestibular fold is ill developed anteriorly, and better observed at the posterolateral margin of the vestibular fold (near the arytenoid), where occasionally some muscle fibers extend beyond the lateral margin of the arytenoid cartilage to join the transverse arytenoid muscle [25].

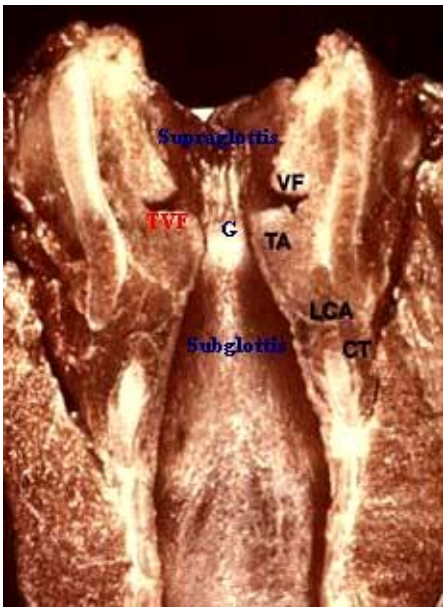


Figure 14: Laryngeal cavity, coronal section at the posterior end of the vocal fold.
G: glottis, TVF: vocal fold, VF: vestibular fold, LCA: lateral cricoarytenoid, TA: thyroarytenoid muscle. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.11.7. THE VOCAL FOLDS AND THE GLOTTIS

The vocal fold (Figures 12-15) is commonly considered as the structure extending from the anterior commissure to the vocal process of the arytenoid (the anterior glottis), but the glottic plane extends also posteriorly to involve all the area lined laterally by the medial surface of the arytenoid. The vocal folds and the medial surfaces of the arytenoids constitute a slit (rima glottidis) known as the glottis [5,26].

The average glottic length in adults (defined as the distance between the insertions of the vocal cords in

the thyroid cartilage and the dorsal mucosa-walled border of the glottis) is 22.1 mm in men and 17.6 mm in women. The glottis can be divided by a horizontal line between the tips of the vocal processes. This imaginary line divides the glottis into an intermembranous portion and an intercartilaginous portion. The average membranous glottic length (defined as the distance between the insertions of the vocal cords in the thyroid cartilage and the attachment to the tip of vocal process of arytenoid) is 13.2 mm in men and 10.6 mm in women, while the average cartilaginous glottic length (defined as the distance of the glottis lined by the arytenoid) is 8.6 mm in men and 6.9 mm in women. Thus, anterior to posterior (length) ratio of the intermembranous portion to the intercartilaginous is about 3 to 2 [5,26].

The cross sectional area of the intercartilaginous portion during the neutral position of the vocal folds is about 56% in men and 60% in women of the total area at the level of the vocal folds, while during the abduction it accounts for 59% in both. So the cross-sectional areas ratio of the intermembranous portion to the intercartilaginous position is about 2 to 3 [5,27].

The vocal fold (Figure 15) consists of three well-defined structural layers: the cover, the transition zone, and the body. These in turn correspond histologically to five distinct layers[3,5,28].

The cover consists of: 1) the squamous epithelium layer of the mucosa which is very thin and helps holding the shape of the vocal fold, there are no mucous glands located within this epithelium; and 2) the superficial layer of the lamina propria, clinically referred to as Reinke's space. Reinke's space is composed primarily of extracellular matrix supported by few loose fibers and can be thought of as a soft gelatinous mass. It offers the least resistance to vibration and this layer is vital for proper phonatory function[3,5,28].

The transition zone consists of: 1) the intermediate layer of the lamina propria exhibiting higher concentration of elastic and collagenous fibers; 2) the deep layer of the lamina propria made up of collagen bundles in high concentration. This deep layer is dense and fibrous and together with the intermediate layer forms the vocal ligament. Some collagenous fibers of the deep layer of the lamina propria insert into the muscle fibers of the vocalis muscle. The intermediate and deep layers are not easy to separate[3,5,28].

The body of the vocalis muscle provides the main mass of the vocal fold. The muscle fibers run parallel to the free edge of the vocal fold [3,5,28].

According to this multilayered concept, the membranous part of each vocal fold consists of a multilayered vibrator with increasing stiffness from the cover to the body. Thus, the cover is responsible for most of the vibratory action of the vocal folds [5,28].

At the anterior and posterior ends of the membranous vocal folds exists a thickening of the intermediate layer of the lamina propria, called the anterior and posterior macula flava, respectively. These are histologically unique structures, composed of dense masses of cells and extracellular matrix. The role of the maculae flava is still debated, but it is thought that they are involved in the metabolism of the vocal cord extracellular matrix, which maintains the viscoelasticity of the lamina propria, and, also function as "cushions" protecting the ends of the vocal folds from vibratory damage [28,29].

In addition to that the hypothesis of the sub-compartmentalization of the thyroarytenoid muscle into medial and lateral parts and each part further divided into superior and inferior, with the upper medial part containing very high concentration of muscle spindles, collagen fibers, and slow-twitch muscle fibers [5,21]. All these micro-anatomical descriptions support the ideas that the most superomedial part of the vocal fold is mainly responsible for phonation [5,21,28,29].

On the other hand, the posterior (intercartilagenous) part of the glottis is related bilaterally to the medial surface of the arytenoids and posteriorly to the lamina of the cricoid. Histologically it is formed of mucosa which has pseudostratified ciliated epithelium, with many glandular structures. The posterior glottis is larger, accounting for 50-65% of the glottic area and, thus, playing an important role in respiration. The term of

posterior glottis is more accurate than posterior commissure as the vocal folds never meet posteriorly, and during the abduction, the arytenoids mucosa meets immediately above the glottic plane to close the posterior glottis leaving a small conic space at the glottic level [27].

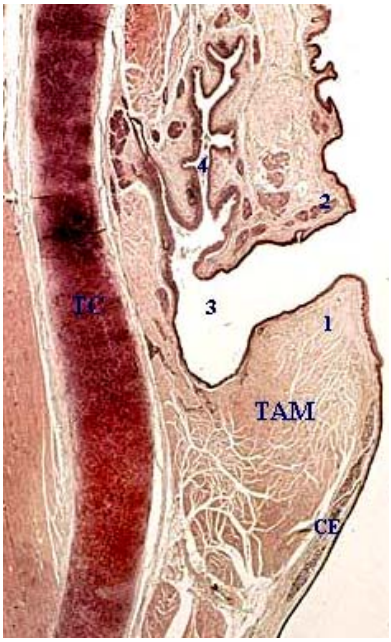


Figure 15: Midcoronal section of the left larynx.
The vocal fold (1) and the vestibular fold (2) surround the ventricle (3) and saccule (4). CE: conus elasticus, TAM: thyroarytenoid muscle, TC: thyroid ala. Modified from the W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

1.1.11.8. THE SUBGLOTTIC OR INFRAGLOTTIC CAVITY

The subglottic cavity (Figures 13, 14), extends from the glottis down to the inferior border of the cricoid cartilage. The superior border of the subglottis is identified histologically by the change from the flat stratified squamous epithelium into the folded respiratory epithelium at the lower surface of the vocal fold. In addition, the submucosa beneath the respiratory epithelium contains numerous glands while no glands are found beneath the squamous epithelium. In the adult, the respiratory epithelium begins 5 -10 mm caudally from the free edge of the vocal cord, and only after 1-2 mm at the area of the anterior commissure. The exact identification of the superior border of the subglottic region is thus histological, and it remains difficult to describe it clearly by clinical methods. Anteriorly, the subglottic cavity is bordered, from cranial to caudal, by the inferior rim of the thyroid cartilage cranially, the median cricothyroid ligament, and the cricoid arch. Posteriorly, the subglottic cavity is bordered by the thick cricoid lamina. The lateral boundary is constituted by the conus elasticus cranially and the cricoid arch caudally [5,6,30].

1.1.12. LARYNGEAL MEMBRANES AND LIGAMENTS

The larynx is lined by a fibroelastic membrane beneath the mucous membrane. This membrane, which runs just under the mucosa, begins superiorly as a tissue spanning between the epiglottis and the arytenoid cartilages and ends inferiorly at the cricoid cartilage. The fibroelastic membrane is divided into an upper section called the quadrangular membrane and a lower section called the conus elasticus (cricothyroid membrane) [1,6].

1.1.12.1. THE CONUS ELASTICUS (CRICOTHYROID MEMBRANE)

The conus elasticus (Figures 16, 17) consists of an anterior and two lateral portions. The anterior part is made of the middle (median) cricothyroid ligament, a thick and strong layer of dense fibrous tissue, and by the firm attachment to the inner perichondrium of the thyroid cartilage. The lateral portions are thinner and lie close under the mucous membrane of the larynx; caudally they attach firmly to the cricoid arch and are covered externally in the middle part by the cricothyroid muscles and then posteriorly by the cricoid cartilage. Cranially this lateral part is formed of a fibrous sheet which attaches anteriorly to the inner thyroid perichondrium and at the anterior end of the vocalis muscle, at the area of anterior commissure, then extends along the superior and most medial part of the vocalis muscle up to the vocal process of arytenoids (this thickened uppermost part is called the vocal ligament). Near the inferior thyroid margin (close to the inferior border of the thyroarytenoid muscle), this fibrous sheet in the middle and posterior thirds is separated into medial very thin part that tapers and ends with the submucous fibrous tissue, and lateral part that border the postero-medial surface of the lateral cricoarytenoid muscle, where it may send a very thin fibrous layer between the thyroarytenoid and lateral cricoarytenoid muscle. At the most posterior part these fibers taper and end in the adipose tissue between the arytenoid and cricoid cartilages, with many neurovascular structures piercing the fibrous tissue at this area, also at the arytenoids attachment it is not easy to separate the attachments of the thyroarytenoid from the lateral cricoarytenoid muscles. The small paramedian area between the lateral borders of the median cricothyroid ligament and the anterior borders of the cricothyroid muscles is formed by thin fibrous sheet and pierced in many case with blood vessels [5,6,31-33].

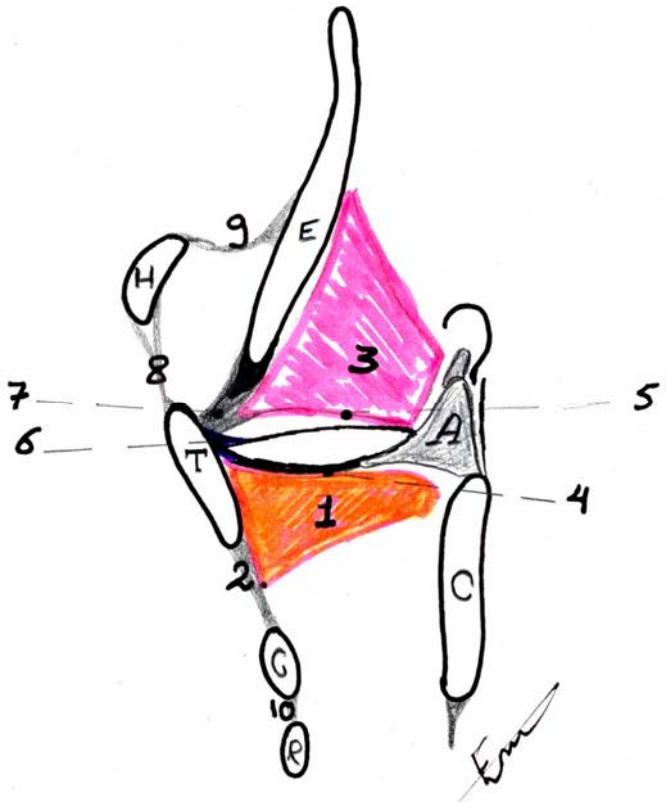


Figure 16: Drawing of the laryngeal ligaments and membranes.
1: conus elasticus, 2: median cricothyroid ligament, 3: quadrangular membrane, 4: vocal ligament, 5: vestibular ligament, 6: anterior commissure tendon, 7: thyroepiglottic ligament, 8: thyrohyoid ligament, 9: median hyoepiglottic ligament, 10: cricotracheal ligament.

1.1.12.2. THE QUADRANGULAR MEMBRANE

The quadrangular membrane (Figures 16, 17) represents the upper portion of the internal fibroelastic membrane of the larynx. It is less developed than the cricothyroid membrane and is pierced by more vessels. It

attaches anteriorly to the lateral margin of the epiglottis and curves posteriorly to attach to the arytenoid and corniculate cartilages. This structure and the overlying mucosa constitute part of the aryepiglottic folds. The thickened inferior edge of the quadrangular membrane constitutes the vestibular ligament [5,6,20,26].

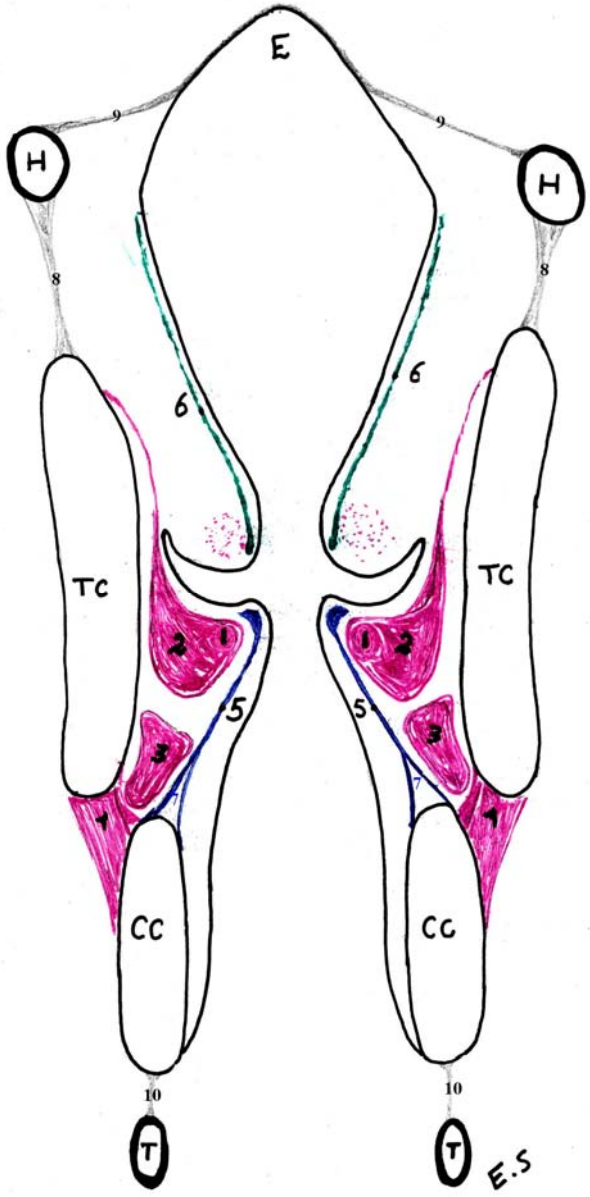


Figure 17: Drawing of the larynx - midcoronal section.
1: vocalis muscle, 2: lateral part of the thyroarytenoid muscle, 3: lateral cricoarytenoid muscle, 4: cricothyroid muscle, 5: conus elasticus with the upper thickened part representing the vocal ligament, 6: quadrangular membrane with the lower thickened part representing the vestibular ligament, 7: cricoid area, 8: lateral thyrohyoid ligaments, 9: lateral hyoepiglottic ligaments, 10: cricotracheal ligament.

1.1.12.3. THE HYOEPIGLOTTIC LIGAMENT

The hyoepiglottic ligament (Figures 16, 17) extends from the anterior surface of the epiglottis to the upper border of the body of the hyoid bone. After the removal of the fascia lining the valleculae, a fibrous, fan-shaped band of tissue running in the midline from the hyoid bone to the anterior surface of the epiglottis (the median hyoepiglottic ligament) is seen. In addition to the median hyoepiglottic ligament, two short, fibrous

bands of tissue pass from the lateral edges of the epiglottis to the greater cornua of the hyoid bone (the lateral hyoepiglottic ligaments). These three folds correspond to the three mucosal glossoepiglottic folds that cover them [6,33].

1.1.12.4. THE CRICOTRACHEAL LIGAMENT

The cricotracheal ligament (Figures 1, 5, 16, 17) connects the cricoid cartilage with the first ring of the trachea; it resembles the fibrous membrane, which connects the cartilaginous rings of the trachea to each other [6].

1.1.12.5. THE THYROHYOID MEMBRANE

The thyrohyoid membrane (Figures 1, 5, 16, 17) is a broad, fibro-elastic layer, stretched from the upper border of the thyroid cartilage to the upper margin of the posterior surface of the body and greater cornua of the hyoid bone. The thyrohyoid membrane thus passes behind the posterior surface of the body of the hyoid, being separated from it by a mucous bursa, which facilitates the upward movement of the larynx during deglutition [6]. The middle part is thicker and termed the middle thyrohyoid ligament (Figure 1), while the lateral thinner portions are pierced by the superior laryngeal vessels and the internal branch of the superior laryngeal nerve. The lateral thyrohyoid ligament is a round elastic cord, which forms the posterior border of the thyrohyoid membrane and passes between the tip of the superior cornu of the thyroid cartilage and the extremity of the greater cornu of the hyoid bone (Figure 5). Numerous connective tissue septa subdividing the infrahyoid muscles are attached to the thyrohyoid membrane. Only a few collagenous fibers originate from the membrane to radiate into the pre-epiglottic fat pad [6,34].

1.1.12.6. THE THYROEPIGLOTTIC LIGAMENT

The thyroepiglottic ligament (Figures 16, 18-20) consists of several parallel collagenous strata, which are arranged sagittally and separated by layers of adipose tissue. Ventrally, the collagenous fibers radiate into two cartilaginous spines which extend backward from the lateral rims of the thyroid notch. Near the airway lumen, the thyroepiglottic ligament includes groups of glands. The lateral collagenous layers of the ligament are continuous with the quadrangular membrane dorsally and converge towards the median sagittal plane caudally [34].

1.1.12.7. THE ANTERIOR COMMISSURE TENDON (BROYLES' LIGAMENT)

The anterior commissure tendon (Broyles' ligament) (Figures 16, 18-20) is formed by the anterior fusion of the vocal ligaments at the midline in close relation to the thyroid cartilage. Broyle's ligament forms the apex of the subglottic region [35].

At the midline area of the inner surface of the thyroid cartilage that begins from the anterior fusion of the vocal ligaments up to the thyroid notch there is a dense fibrous tissue [35,36], This fibrous zone contains different anatomical structures which are not described in older anatomical studies, but other authors have described the micro-anatomical details studies of it [36-38].

At the level of the anterior end of the vocal ligaments, the two ligaments fuse and attach firmly to the inner perichondrium of the thyroid cartilage, and there is small vascular and glandular structure separated by the arrangement of the dense fibrous band (section 4 in figure 19). Immediately above this plane there is a very dense layer of fibrous bands completely filling the gap between the mucosa of the anterior end of the ventricle and the thyroid cartilage, its length is about 1.5-2 mm and it attaches firmly to the cartilage (section 3 in figure 19), the fibers of this layer have X shaped arrangement in the cross section so called "X-space", and devoid

from any vascular or glandular structure so called “Plane zero” [36-40].

Immediately above this avascular zone the anterior part of this ligament only remains devoid of vessels and tapers superiorly while the inner part (towards the laryngeal lumen) regains vascular and glandular structures (section 2 in figure 19). Above this level, at the level of the false vocal fold the new arrangement of the fibrous and vascular tissue appears (the thyroepiglottic ligament fibers running to the petiole of the epiglottis could be easily detected) (section 1 in figure 19) [36-38].

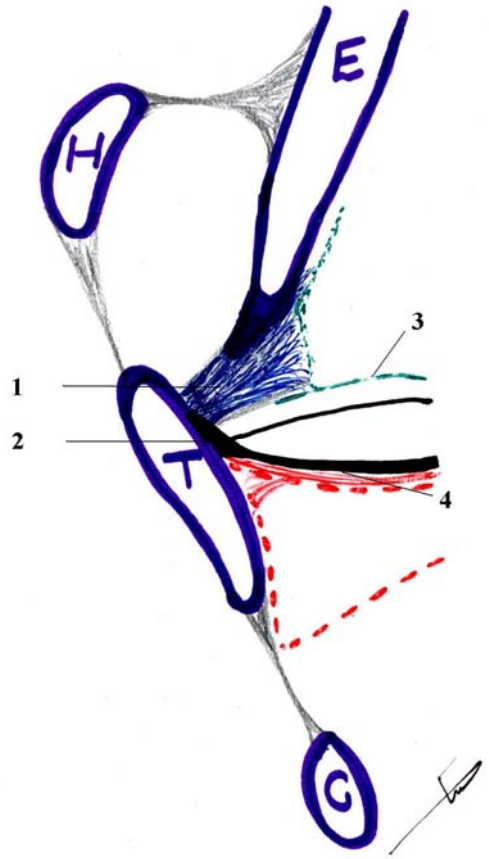


Figure 18: Drawing of the anterior commissure.
1: the thyroepiglottic ligament 2: anterior commissure tendon, 3: vestibular ligament, 4: vocal ligament.

The anterior commissure ligament has also muscular attachments and components which are mainly from the anterior ends of the vocalis muscles, and these share in the confluence of fibers that come from the vocal ligaments, conus elasticus, and the perichondrium. In addition, a small commissural muscle has been described and thought to act as a tensor for the vocal ligaments [31,38-40].

The anterior commissure tendon separates anteriorly the supraglottic region from the glotto-subglottic area and this separation with the exception of the mucosa is complete at the level of the X-space (immediately above the glottic level) [36,38,39]. While it is difficult to separate the glottic plane from the subglottic cavity anteriorly [36].

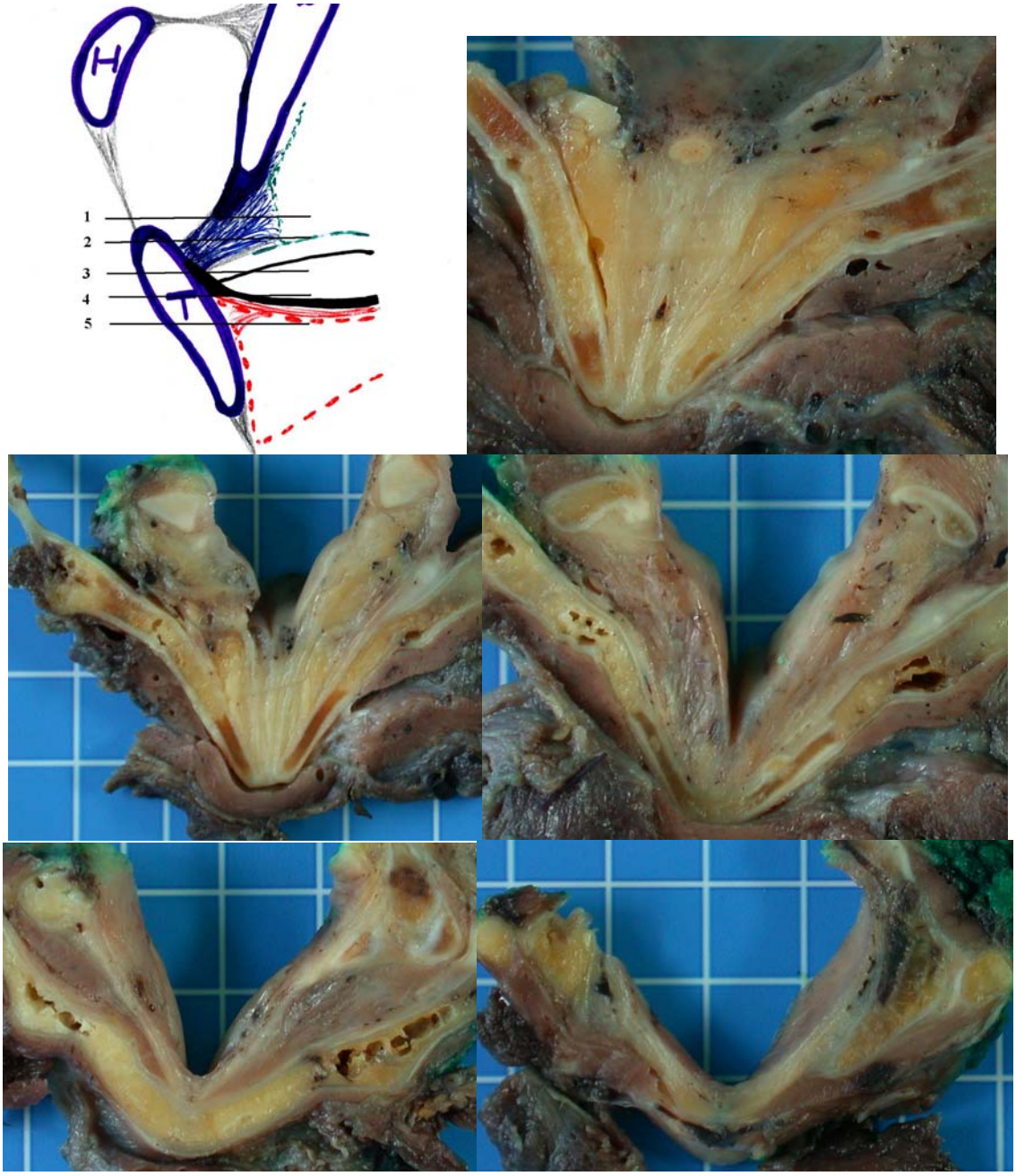


Figure 19: Horizontal sections of a plastinated male larynx at the level of the anterior commissure area.
Top right: coronal drawing indicating the level of the sections. Section 1 on the top-right then the sequence of sections 2-5 from up downwards and from left to right.

1.1.13. LARYNGEAL PARALUMINAL SPACES

1.1.13.1. THE PRE-EPIGLOTTIC (PERI-EPIGLOTTIC) SPACE

The pre-epiglottic space (Figures 20, 21) was described as the space in front and along the sides of the epiglottis [41,42]. However, a detailed analysis of the borders and the posterolateral and inferior extensions of this space suggests that the term peri-epiglottic space is more adequate [34,43].

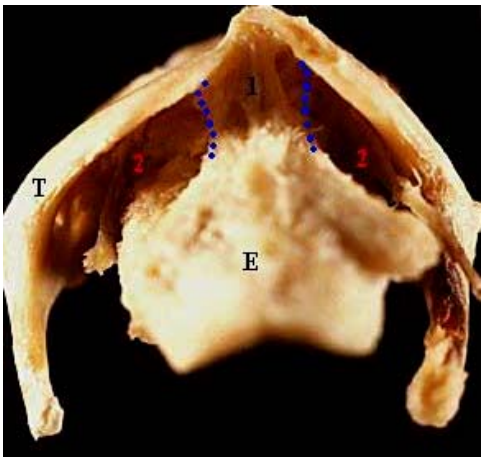


Figure 20: Superior view of the pre-epiglottic space.
E: epiglottis, T: thyroid cartilage, 1: thyroepiglottic ligament, 2: the lateral extensions of the pre-epiglottic space. Modified from W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

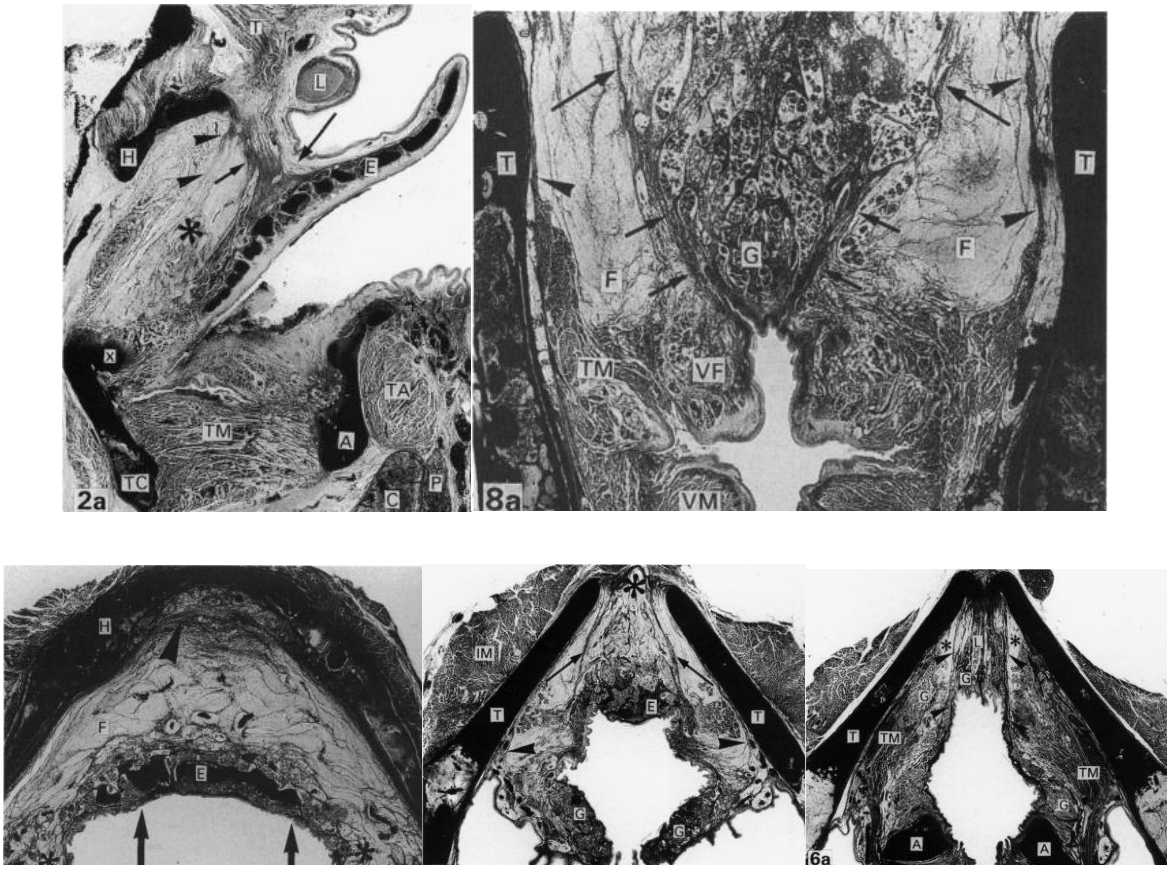


Figure 21: Laryngeal sections explaining the extensions of the pre-epiglottic space. 2a - paramedian sagittal section; 8a - coronal section at the petiole of epiglottis, BOTTOM - three transverse sections at the levels of hyoid, upper border of thyroid, and thyroepiglottic ligament.
T and TC: thyroid cartilage, E: epiglottis, A: arytenoid cartilage, C: cricoid cartilage, H: hyoid bone, TM: thyroarytenoid muscle, F: fat, VF: ventricular band, VM: vocalis muscle, G: groups of glands . Reproduced with permission from Reidenbach MM. The peri-epiglottic space: topographic relations and histological organisation. J Anat 188:173-82,1996 [34].

Superiorly, the peri-epiglottic space is bordered by several layers of collagen fibers that form the hyoepiglottic membrane and ligaments. These fibers extend in an anteroposterior direction from the hyoid

bone and base of the tongue anteriorly to the lingual surface of the epiglottis posteriorly [33,34].

Anteriorly, the peri-epiglottic space is bordered by the thyrohyoid membrane [6,34]. Inferiorly, the peri-epiglottic space is bordered by the thyroepiglottic ligament [34]. Posteriorly, the peri-epiglottic space extends beyond the lateral margins of the epiglottis into the aryepiglottic folds beneath the mucosal lining. The aryepiglottic folds contain increasing amounts of irregularly arranged collagen and muscle fibers and groups of glands, a different histological appearance than the pre-epiglottic fat pad [34].

Lateral, posterolateral borders of the peri-epiglottic space and histological organisation of its contents:

Superiorly, the greater cornua of the hyoid bone constitute the lateral borders of the peri-epiglottic space followed inferiorly by the thyrohyoid membrane; at this level the adipose tissue is lobulated by collagen fibers with a wavy arrangement and contains conspicuous blood vessels, especially near the midline. More caudally, at the level of the thyroid cartilage, the fat pad is subdivided into a medial and two lateral regions by two sagittal collagenous fibrous septa. They originate from the connective tissue at the lateral margins of the epiglottic cartilage where a confluence of upperlateral fibers from the thyroepiglottic ligament and anteroinferior fibers of the quadrangular membrane is found. Posteriorly, the septa join the quadrangular membrane; anteriorly they are attached to the rims of the thyroid notch and downward are continuous with the lateral collagenous layers of the thyroepiglottic ligament. Between these two septa the medial part exists (actual pre-epiglottic space), and are bordered by the epiglottis dorsally, and stopped inferiorly by the thyroepiglottic ligament, it contains adipose tissue and numerous collagen fibers, and blood vessels. It is immediately adjacent to the thyroid vessels and groups of glands. The lateral parts lie on each side of the medial part and bordered anterolaterally by the perichondrium of the thyroid cartilage, while posteriorly and posterolaterally, it is bordered by a thin collagenous layer extends towards the thyroid cartilage and continuous with the fibrous sheet of the thyroarytenoid muscle that extends anterosuperiorly from it, to be attached to the perichondrium of the thyroid cartilage in some cases. The fibrous sheet of the thyroarytenoid muscle constitutes the medial boundary of a triangular space extending to the thyroid cartilage laterally and the mucosal lining of the piriform sinus dorsally, and contains areolar tissue and groups of blood vessels and nerves. More often, at the anterior area of the thyroid ala this fibrous tissue splits into several incomplete layers, which radiate into the pre-epiglottic fat pad cranially, leading to narrow connection between the peri-epiglottic space posterolaterally and the anterosuperior part of the paraglottic space [34].

But this description for the incomplete separation between the two spaces is opposed in other study, that consider this fibrous sheet is a constant finding with constant attachment to the thyroid cartilage thus, separating the two spaces and so called the thyroglottic ligament [43].

Also it is important to mention that the laryngeal surface of the infrahyoid epiglottis communicates with the prepiglottic space as mentioned above [4-6].

1.1.13.2. THE PARAGLOTTIC SPACE

The paraglottic space (Figures 22, 23) was described classically in 1962 [41] as the connective tissue compartment bounded by the thyroid cartilage anterolaterally, the conus elasticus inferomedially, the laryngeal ventricle and the quadrangular membrane medially, and the mucosal lining of the piriform sinus dorsally [41,42].

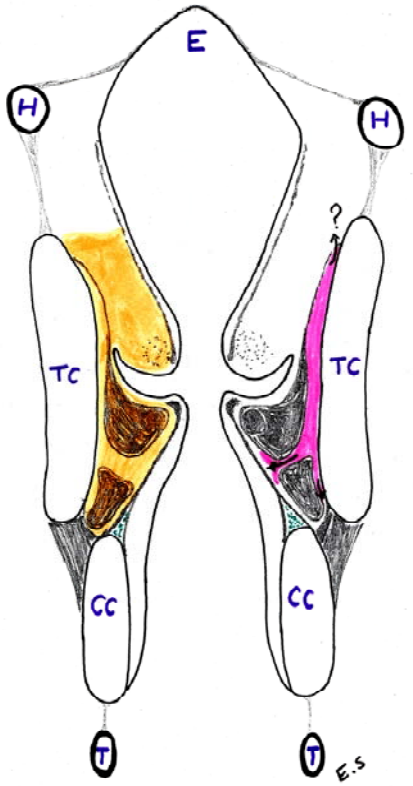


Figure 22: Drawing of a midcoronal section of the larynx explaining the paraglottic space.
The paraglottic space according to Tucker and Smith [41] is delineated in orange (left), while on the right, in rose, is the paraglottic space extension according to Sato et al. [43].The dotted green area represents the cricoid area.

According to the above description by Tucker and Smith [41], the paraglottic space includes the thyroarytenoid muscle and the small triangular region mainly composed of adipose and areolar tissue located between the thyroid cartilage laterally, the thyroarytenoid muscle medially, and the pyriform sinus dorsally (yellow-coloured area in figure 22). More recently, Sato et al.[43] excluded the thyroarytenoid muscle from the paraglottic space and this description was echoed by others [34,44].

Organ section studies of the human larynx explain that the paraglottic space extends into all three levels of the larynx (Figure 23), being located medial to the thyroid ala. The paraglottic space is very narrow anteriorly, at the area adjacent to the anterior commissure, where it is reduced to a small region of adipose tissue included between the thyroid cartilage laterally and the anterior insertion of the thyroarytenoid muscle medially (at this level the mucosa of the larynx is 2-3 mm medial to the thyroid cartilage). In this area, it is confined to the glottic level. Dorsally, the paraglottic space becomes larger in width and extends beyond the superior and inferior borders of the thyroarytenoid muscle [44-46].

At the mid vocal cord level (membranous cord), the paraglottic space (Figure 23) extends to the three levels of the larynx. Superiorly, the continuity with the peri-epiglottic space is controversial [43,44]. Inferiorly, it extends into the subglottis in an inferomedial direction, between the lateral part of the thyroarytenoid muscle superomedially and the cricothyroid muscle inferolaterally (Figure 23), where it is bordered by the conus elasticus. At the angle between the anterior surface of the cricothyroid muscle and the inferior border of the thyroid cartilage, a tiny area of the paraglottic space is in contact with the extralaryngeal tissues where some small vessels enter the larynx at that site. This is the first dehiscence allowing paraglottic lesions to escape into extralaryngeal tissue [30,44,46].

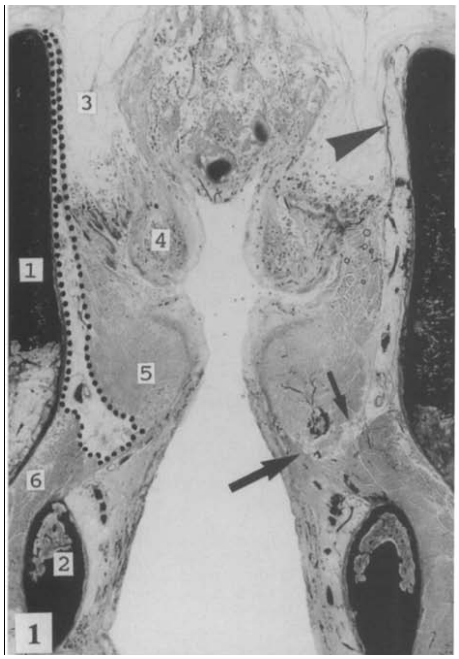


Figure 23: Midcoronal section of a larynx illustrating the paraglottic space.
The dotted line delineates the paraglottic space. 1: thyroid cartilage, 2: cricoid cartilage, 3: peri-epiglottic space, 4: false vocal fold, 5: thyroarytenoid muscle, 6: cricothyroid muscle. Arrows indicate the inferomedial extension of the paraglottic space, the arrow head explains the separation between the pre-epiglottic and paraglottic space. Reproduced with permission from Reidenbach MM. Borders and topographic relationships of the paraglottic space. Eur Arch Otorhinolaryngol. 254:193-5, 1997 [44].

Posteriorly, at the glottic and subglottic levels the paraglottic space is stopped by the lateral cricoarytenoid muscle. After that, at the most posterior area the space is bordered posteriorly by the submucosal tissue of the pyriform sinus and compressed into a line located between the thyroid cartilage laterally and the intrinsic muscles medially in its posteroinferior end. While at the supraglottic level the paraglottic space is really a triangular space, it tapers down to end in the posterosuperior part of the subglottis as a small slit [44,46]. At the area between the cricoid lamina and the inferior cornu of the thyroid cartilage the big neurovascular structure is located which may give a root to the extramucosal tissue between oesophagus, larynx and trachea. This is the second dehiscence area of the paraglottic space, along its posterior border [44,46]. Posterosuperiorly, the paraglottic space is stopped by the tissues of the aryepiglottic fold [43,44,46].

According to this new detailed description of the paraglottic space, it is constantly lateral to the thyroarytenoid muscle but not separated from it, also there is no anatomic structures suggesting any horizontal subdivision [43,44,46].

The paraglottic space is filled with adipose and loose connective tissue and contains numerous blood vessels that have mainly a vertical orientation; nerves are mostly located within the posterior region of the paraglottic space [44,46].

Although there is nearly agreement that the lateral border of the paraglottic space is the thyroid cartilage [41-44,46], some investigators limit the inferior part of the space (at the glottic and upper supraglottic areas), to a small slit between the medial and lateral thyroarytenoid muscles. This description is based on their embryological and anatomical findings [39,40].

1.1.13.3. THE CRICOID AREA

Tucker and Smith [41] described a small region of areolar tissue medial to the internal perichondrium of the cricoid cartilage as the cricoid area (Figures 17, 22), although the exact boundaries were not precisely

studied [41]. Subsequent studies confirmed that the cricoid space is a fixed anatomical finding in all the larynges studied, and it is located on the superomedial portion of the cricoid arch (Figures 17, 22) [47].

The cricoid area is located along the superomedial border of the cricoid arch and extends to a short distance anteromedial to the cricoid lamina. It is found bilaterally and no inter-communication between the two sides. It is enclosed between outer lateral and inner medial fibroelastic layers of the conus elasticus, which are fused near the inferomedial surface of the thyroarytenoid muscle (Figures 17, 22). It is bordered laterally by the cricothyroid muscle anteriorly then the superior part of the cricoid lamina posteriorly, where it is related to the adipose tissue around the cricoarytenoid region. Inferiorly, the cricoid area is usually separated from the subglottic submucous glands. This area contains loose adipose tissue and blood vessels, few nerve twigs and no glands [32,47].

1.1.13.4. REINKE'S SPACE

Reinke's space is the subepithelial space related to the free edge (superomedial surface) of the membranous vocal fold [3,48].

1.1.14. BLOOD SUPPLY OF THE LARYNX

1.1.14.1. ARTERIAL SUPPLY

The larynx is supplied by the superior and inferior thyroid arteries (Figures 24, 25). The superior thyroid artery is a branch of the external carotid artery, and the inferior thyroid artery is a branch of the thyrocervical trunk, itself originating from the subclavian artery. The superior laryngeal artery is the main arterial supply of the larynx (Figures 24, 25), with the blood supply from one side sufficient to perfuse the entire larynx[49].

Traditionally, the superior laryngeal artery is described as emerging from the superior thyroid artery and, accompanied by the internal laryngeal nerve, piercing the lower part of the thyrohyoid membrane, to anastomose with its fellow and as well as with the inferior laryngeal artery . Variations of the origin of the superior laryngeal artery have been found in other anatomical studies, with a direct takeoff from the external carotid artery, just above the level of the superior thyroid artery, in 16%-32% of cases. [50,51]

When coursing normally, the superior laryngeal artery is directed anteriorly, over the superior horn of the thyroid cartilage and the superior fibers of the inferior constrictor muscle of the pharynx, below the internal branch of the superior laryngeal nerve. It pierces the thyrohyoid membrane at a variable distance from its origin, continues immediately above the superior margin of the thyroid cartilage (transverse segment), prior to descend deep to the thyroid cartilage lamina (descending segment). The point where the superior laryngeal artery changes its course is located anterior to the base of the superior horn of the thyroid cartilage, at the superior border of this cartilage. The mean distance of this point from the base of the superior horn of the thyroid cartilage is 1.3 cm (1.1-1.8 cm). [51] The descending segment of the superior laryngeal artery continues deep to the thyroid cartilage lamina, in the paraglottic space; this segment was projected on the thyroid cartilage lamina on a line parallel and anterior to the oblique line at a mean distance of 1.3 cm (1.1 and 1.5 cm) [51]. Rarely, the superior laryngeal artery traverses the thyroid cartilage through the foramen thyroideum, located at the upper area of the oblique line of the thyroid cartilage, and directly enters the paraglottic space[51,52].

The branching pattern of the normal superior laryngeal artery inside the larynx includes five fixed and named branches: the superior, anterior, postero-medial, antero-inferior, and postero-inferior branches. Beside these, there are some small and variable branches to the epiglottis, piriform sinus and pharynx[51]. The superior laryngeal artery gives also a small caliber branch (the inferior laryngeal artery) that travels external to the thyroid cartilage in close relation to the external laryngeal nerve supplying the adjacent structures along its

course. Then, it ends in the anastomotic network in front of the cricothyroid membrane[50].

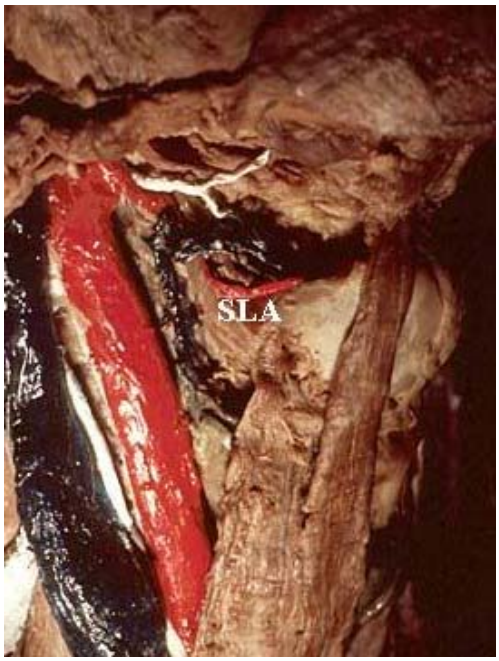


Figure 24: Dissection of the right side of the neck demonstrating the laryngeal vessels.
The carotid system is colored in red and the internal jugular vein is colored with blue. SLA: indicated the right superior laryngeal artery where it enters the larynx at the thyrohyoid membrane. Modified from W.R. Zemlin Memorial Web Page (http://zemlin.shs.uiuc.edu/larynx1/default.htm).

The inferior thyroid artery comes off the thyrocervical trunk, itself a branch of the subclavian artery. The inferior thyroid artery gives a terminal small caliber artery that accompanies the terminal segment of the recurrent laryngeal nerve. This branch is called the posterior laryngeal artery and it gives many small branches to the mucosa of the pharynx, inferior constrictor muscle, cricothyroid joint, and after coursing posteriorly to the cricothyroid joint, it gives two small branches. The first branch supplies the posterior cricoarytenoid muscle, and the second one passes along the lower border of the cricoid cartilage. Both of the two terminal branches give many anastomotic arteries to the terminals of the superior laryngeal artery[50].

The anteroinferior laryngeal arteries are small arteries (usually three on each side) that pierce the cricothyroid membrane near the lower border of the thyroid cartilage. Usually there are three on each side, one medial and two paramedial, and they originate from the anastomotic network which is done mainly by the two terminal ends of the inferior laryngeal arteries with other some tiny arteries[37,50]. These anteroinferior laryngeal arteries supply the anterolateral area of the glottosubglottic region and they join with the other systems inside the larynx[37].

The posterior part of the larynx especially at the glottic level shows wide anastomosis between the different systems[37,50,51].

1.1.14.2. VENOUS DRAINAGE

The venous drainage of the larynx is parallel to the arterial supply, the larynx being drained by the superior and middle thyroid veins, which join the internal jugular vein, and the inferior thyroid vein, which empties into the left brachiocephalic vein [1,5].

1.1.14.3. LYMPHATIC DRAINAGE

The lymphatics of the larynx are divided into superficial (intramucosal) and deep (submucosal) groups. The deep network is further divided into right and left halves, with little communication between them. These two halves can be further divided into supraglottic, glottic, and subglottic, with special consideration given to the ventricle in the supraglottic region. Although the superficial network is richly anastomotic throughout the larynx, it is the deep network that is important in the spread of the malignant tumours [5,48]. The drainage of the supraglottic structures (aryepiglottic folds and false cords) follows the superior laryngeal and superior thyroid vessels. Thus, the lymphatics flow from the piriform sinus through the thyrohyoid membrane to end primarily in the deep jugular chain around the carotid bifurcation. It should be noted that the epiglottis is a midline structure; thus, its lymphatic drainage is bilateral [5]. The lymphatic drainage of the ventricle is different from the other supraglottic structures. Dye injected into the ventricle enters the paraglottic space and is quickly spread by the lymphatic system through the cricothyroid membrane and also into the ipsilateral lobe of the thyroid [5]. The subglottic larynx has two lymphatic drainage systems. One system follows the inferior thyroid vessels to end in the lower portion of the deep jugular chain as well as the subclavian, paratracheal, and tracheoesophageal chains. The other system pierces the cricothyroid membrane. This system appears to receive lymphatics from both sides of the larynx and disseminate bilaterally to the middle deep cervical nodes as well as to the prelaryngeal (Delphian) [5]. The Delphian (cricothyroid) or (prelaryngeal) nodes are part of the anterior cervical glands of group VI which receives drainage from the subglottic larynx and the thyroid gland, and its efferent vessels pass to the lowest of the superior deep cervical glands [5,53].

The true vocal folds are classically devoid of lymphatics [5], but a recent anatomical study demonstrate that the inferior border of the vocal fold contains a rich lymphatic network especially near the area of the posterior glottis with many communications with the other levels of the larynx[54].

1.1.15. NERVE SUPPLY

Each hemilarynx is supplied by the ipsilateral superior laryngeal nerve and the ipsilateral recurrent laryngeal nerve (Figure 25), these two nerves being branches from the tenth cranial nerve (the vagus), and each carrying motor and sensory fibers [4,5,55].

Classically the nerve supply of the larynx is described as follows [1,4-6,55]: the superior laryngeal nerve carries the sensory fibers from all the mucosa of the supraglottis and the upper surface of the glottis and sends the motor nerve for the cricothyroid muscle, while the recurrent laryngeal nerve carries the sensory fibers from the mucosa of the subglottis and lower surface of the vocal folds, and is the motor nerve to all the intrinsic muscles of the larynx except the cricothyroid. In addition, the nerve supply is highly unilateral since each side is supplied only by the ipsilateral nerves and the superior and recurrent laryngeal nerve innervation is mostly sharply demarcated [1,4-6,55].

More recent anatomical and clinical studies have demonstrated multiple anastomotic areas in the larynx between the two sides and between the superior and recurrent laryngeal nerves. The interarytenoid muscle is now known to be bilaterally supplied by the recurrent and superior laryngeal nerves [55-57]. This muscle and the closely related area of the posterior glottis show a rich anastomosis between the four laryngeal nerves with ipsilateral predominance [55-57]. The internal branch of the superior laryngeal nerve also connects with the ipsilateral recurrent nerve with the Galen's anastomosis, which is observed in all the cases [55,56]. Other area of anastomosis between laryngeal nerves include: 1) a cricoid anastomosis (located just in front of the cricoid lamina) has been found in 60% of the cases 2) thyroarytenoid muscle anastomosis (within the muscle fibers) (only in 14%), 3) along the mucosa of the vocal fold shows 4) between the recurrent laryngeal nerve and the external branch of the superior laryngeal at the area between the cricothyroid, lateral cricoarytenoid, and posterior part of thyroarytenoid muscle, and each of these muscles may receive nerve supply from this anastomosis [56]. These studies explained that; the interarytenoid muscle is bilaterally supplied by both the laryngeal nerves, the anastomosis of Galen is almost often a fixed anatomical finding, in addition to that

another second anastomosis is found in about 80% of the cases. So these finding should be used to update knowledge about the pathologies related to laryngeal nerve paralysis and its managements, especially the post paralysis vocal fold positions which is not so clear up till now. [55-57]

1.1.15.1. THE SUPERIOR LARYNGEAL NERVE

The superior laryngeal nerve branches from the inferior vagal (nodose) ganglion just caudal to the pharyngeal branches of the vagus and descends toward the thyrohyoid membrane. The superior laryngeal nerve crosses anterior to the superior sympathetic cervical ganglion where it receives sympathetic contribution from it, and posterior to the internal carotid artery where the nerve contributes to the innervation of the carotid body. Then it descends medially toward the thyrohyoid membrane. Posterior to the internal carotid artery, the superior laryngeal nerve branches into the internal (sensory) and external (motor) laryngeal branches. The internal superior laryngeal nerve descends inferior to the greater horn of the hyoid bone, in the angle between the middle and inferior constrictors and the upper lateral border of the omohyoid muscle, where it approaches the thyrohyoid membrane along with the superior laryngeal artery. The nerve is a few millimeters above the artery. Both the nerve and the artery pierce the external surface of the thyrohyoid membrane at a point anterior to the base of the superior cornu of the thyroid cartilage and above the superior end of the oblique line. At their entrance the nerve and the artery create several branches that interdigitate with each other [4,51,57,58].

The internal superior laryngeal nerve is subdivides into three branches: the superior branch supplies the epiglottis and a small section of the anterior wall of the vallecula, the middle branch supplies the aryepiglottic and the ventricular folds, and the inferior branch supplies the mucosa of the piriform sinus and send also fibers to the interarytenoid muscle. The internal laryngeal nerve connects with the ipsilateral recurrent laryngeal nerve by the Galen's anastomosis prior to terminating in the inferior constrictor muscle [58,59].

The external superior laryngeal nerve, after its origin, crosses posterior and medial to the common carotid or the internal carotid artery towards the cricothyroid muscle. During its descent, it innervates the inferior pharyngeal constrictor, and it runs superior to the superior thyroid artery, lateral to the thyroid cartilage and within the pretracheal fascia superficial to the inferior pharyngeal constrictor muscle and deep to the thyrohyoid muscle, along their attachments to the oblique line of the thyroid cartilage [58,60,61].

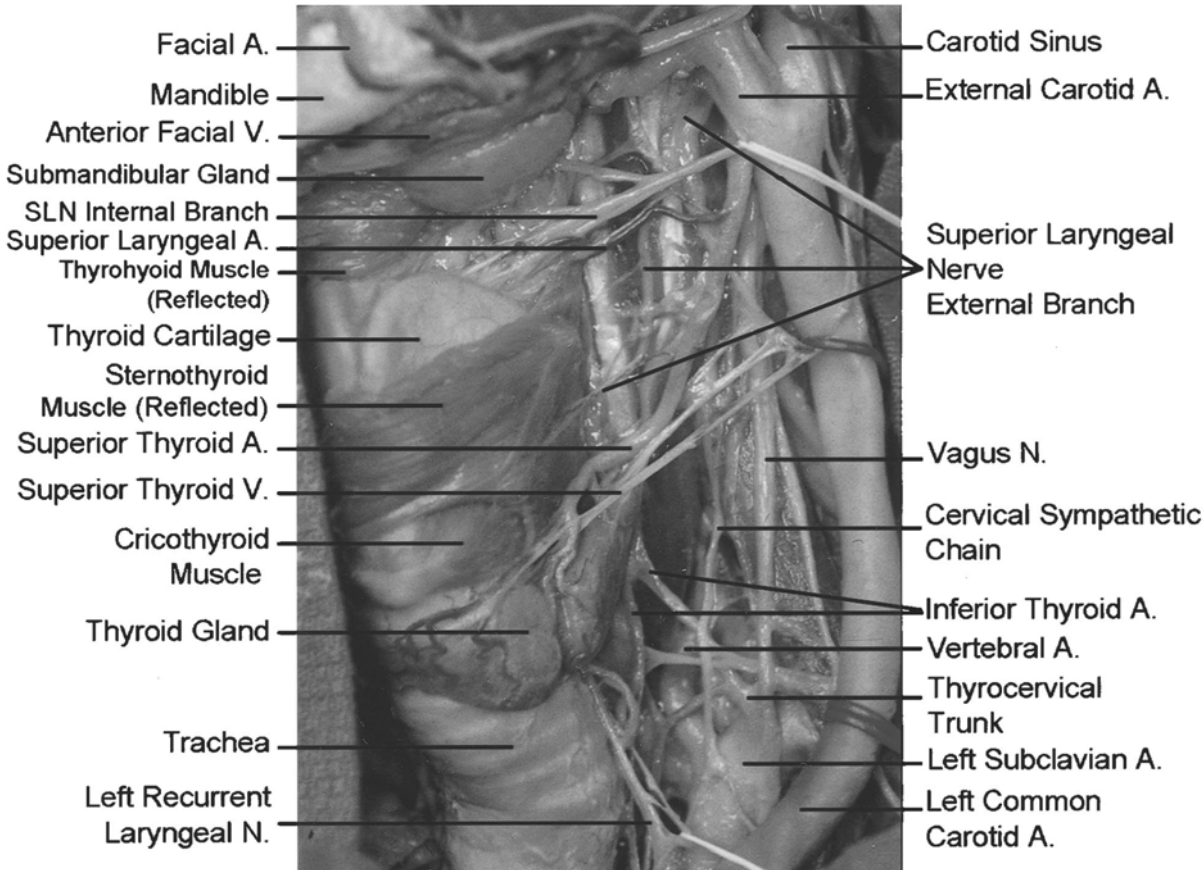


Figure 25: Lateral dissection of the neck demonstrating the left superior and recurrent laryngeal nerves.
Reproduced from Monfared A, Gorti G, Kim D. Microsurgical anatomy of the laryngeal nerves as related to thyroid surgery. Laryngoscope. 112:386-92, 2002 [58] with permission.

1.1.15.2. THE RECURRENT LARYNGEAL NERVE

- *THE EXTRA LARYNGEAL COURSE*

The right and left recurrent laryngeal nerves originate from the vagus at different levels. The right recurrent laryngeal nerve branches from the vagus at the level of or just superior to the subclavian artery. The nerve creates a loop by travelling inferior and medial to the subclavian artery and then ascends medially toward the tracheoesophageal groove. As the right recurrent laryngeal nerves travels inferior to the subclavian artery, it gives off one or two cardiac branches that join sympathetic branches and create the deep cardiac plexus. The proximal part of the right recurrent laryngeal nerves is crossed anteriorly by the proximal common carotid artery. The right recurrent laryngeal nerve, except for its most distal part, does not reside in the tracheoesophageal groove and is separated from it by fat and connective tissue[58].

The left recurrent laryngeal nerves departs from the vagus as it enters the thorax passing anterior to the branching point of the common carotid and the subclavian arteries, immediately posterior to the brachiocephalic vein. The nerve is anterolateral to the arch of the aorta and is crossed anteriorly by the left superior intercostal vein. Then it descends medially, passes left of the ligamentum arteriosum (the remnant of the fetal ductus arteriosus), and ascends medially toward the tracheoesophageal groove, thus creating a loop under the arch of the aorta. Similar to the right side, the left recurrent laryngeal nerves contributes to the deep cardiac plexus by one or two cardiac branches that come off the left recurrent laryngeal nerves at the midpoint of its loop. During its lengthy ascent, the nerve is found residing on the trachea, lying in the tracheoesophageal

groove, or is separated from it by fat and connective tissue. During their ascent toward the larynx, both right and left recurrent laryngeal nerves give off numerous esophageal and tracheal branches to the longitudinal and circular muscles of esophagus, along with the trachealis muscles[58].

- *THE ENTRANCE TO THE LARYNX*

The distal part of the right and left recurrent laryngeal nerves (inferior laryngeal nerves) enters the larynx at the level of the inferior fibers of the cricopharyngeus muscle, coming from the tracheoesophageal groove to continue anteromedially between the cricoid and the hypopharynx. On the right side 66% pass deep to the muscle and the 34% penetrate it, while in left side 72% passes deep to the muscle and 28% penetrate it[62]. The diameter of the nerve just before entering the larynx is about 1.8–2.2 mm[63].

The inferior laryngeal nerve branching pattern before the entrance is not fixed, it may passes as a single trunk under the lower border of the inferior constrictor muscle and behind the cricothyroid joint where the branching occurs under the inferior constrictor muscle, or more commonly it is divided into anterior and posterior branches before passing under the muscle. The anterior branch is closely passing behind the cricothyroid joint, while the posterior branch is located more medially being closely related to the posterior cricoarytenoid muscle, and the branching point is also variable it may be just at the lower border of the of the cricopharyngeus muscle or more commonly at a distance 1.5-3 cm below it. In rare condition the nerve may enter the larynx by three branches [63,64].

The line by which the nerve enters the larynx makes an angle with the tracheooesphageal groove, this angle is usually around 30 degrees and very rare to be more than 45 degrees [65].

- *THE RELATION WITH THE INFERIOR THYROID ARTERY*

The inferior thyroid artery comes off the thyrocervical trunk, a branch of the first part of the subclavian artery. The inferior thyroid artery ascends medial to the anterior scalene muscle, deep to all structures of the neck, residing on the prevertebral fascia. Posterior to the thyroid gland the artery has a distinct loop at the C6–7 vertebral level and begins its anteromedial ascent toward the inferior pole of the thyroid gland. Then the inferior thyroid artery pierces the posterior layer of the pretracheal fascia to enter a compartment created by the splitting of this fascia. The inferior thyroid artery branches in this compartment, and each branch enters the anterior layer of pretracheal fascia separately. There are two significant branches: an anterior and a posterior branch. These branches supply the thyroid gland, the upper esophagus, and trachea. The relationship between these branches and the recurrent laryngeal nerve is highly variable and complex and should not be used as a landmark to identify the nerve [58,64,66,67].

- *THE RELATION WITH THE LIGAMENT OF BERRY*

The pretracheal fascia that covers the thyroid gland splits on the posterior aspect of the gland. One layer anchors the gland at or above the isthmus, and from the medial part of the back of each thyroid lobe; it continues to attach the gland to the trachea by its thickening, called the lateral ligament, also known as the ligament of Berry. The relation of the distal part of the recurrent laryngeal nerve to this ligament is important, especially at its lateral part where the ligament is closely related to nerve and the vascular structures near the inferior pole of the thyroid. According to several anatomical and clinical studies the nerve is most often found posterolateral to the ligament, but sometimes it can be posteromedial and rarely can pierce the ligament [58,68-70].

- *NON-RECURRENT LARYNGEAL NERVE*

The non-recurrent laryngeal nerve is a very rare condition found in 0.21%- 1.6% in different series [58,64,71], usually on the right side. Generally, the nerve passes behind the carotid artery. [71]

1.1.16. BRIEF ANATOMY OF THE PIRIFORM SINUS

Although the piriform sinus is anatomically a part of the hypopharynx, understanding its anatomy and its relationship to the larynx is essential. The piriform sinus is a gutter formed by the aryepiglottic fold, arytenoid, and superior cricoid medially and the thyrohyoid membrane and internal surface of the thyroid lamina laterally. Superiorly, it begins at the level of lateral glossoepiglottic fold. Inferiorly, the apex of the sinus blends with the esophageal inlet at about the superior border of the cricoid. There are two important markings within the piriform sinus. Anteriorly in the floor of the sinus, a small fold can be seen, which marks the course of the superior laryngeal nerve. This submucosal course of the nerve makes it possible to anesthetize the nerve topically in the piriform sinus. The second, more variable landmark is the protrusion made into the sinus from the superior cornu of the thyroid cartilage, which is more often seen in the elderly [1,5].

1.2. EMBRYOLOGY

Human prenatal development is divided into embryonic and foetal periods. The embryonic period, which comprises the first 8 weeks, is subdivided into 23 stages according to the Carnegie staging system, while the foetal period comprises the last 32 weeks of gestation[72,73].

1.2.1. EMBRYONIC PERIOD

By the end of the third week and the beginning of the forth week (stage 10), the first sign of the respiratory system development is seen as an epithelial thickening along the ventral surface of the foregut: the respiratory primordium [72,73]. The respiratory primordium is shaped as a ridge externally and as a sulcus internally (laryngotracheal sulcus). It continues to grow caudally and acquires a diverticulum, which would by stage 12 give the bronchopulmonary buds, followed by the trachea (stage 13), the growth and elongation of which will eventually give the lungs[72,73].

The future infraglottis develops from the cephalic portion of the respiratory diverticulum, while the future supraglottis develops from the primitive laryngopharynx which is a segment of the foregut separating the pharyngeal floor at the level of the fourth pharyngeal pouch from the respiratory diverticulum. [73]

During the fifth week (stages 15 and 16), the primitive laryngopharynx becomes compressed bilaterally by the developing mesoderm of the laryngeal cartilages, muscles, and branchial arch arteries leading to obliteration of its lumen by an epithelial lamina. At the dorso-cranial portion of the epithelial lamina, the median pharyngeal floor gives rise to two elevations posteriorly, the arytenoid swellings. In addition, a third small elevation develops from the most posterior aspect of the hypopharyngeal eminence and by opposing the arytenoid swellings creates a 'T' shaped entrance of the primitive laryngopharynx [72,73].

The obliteration of the lumen of the primitive laryngopharynx by the epithelial lamina is almost complete except for a narrow duct which communicates the uppermost caudal area of the infraglottic cavity with the pharyngeal lumen behind, and below the arytenoid swellings and called the pharyngoinfraglottic duct. In addition, a depression called the laryngeal cecum begins to develop between the arytenoid swellings [72,73].

By 6 weeks age (stages 17 and 18), the laryngeal cecum continues caudally in the ventral area of the epithelial lamina with lateral expansions at its cephalic portion forming the embryonic vestibule, which corresponds only to a portion of the adult vestibule. In the same time, the hyoid condensation begins to

appear, and the cricoid can be identified in the mesenchyme, followed by the appearance of a single cartilaginous cricoid center. By the end of the 6th week, laryngeal muscles are beginning to develop, the hyoid condensation is undergoing chondrification, and condensations for the thyroid laminae begins to appear[72].

During the seventh and eighth weeks (stages 19-23), the laryngeal cecum continues to deepen caudally until it reaches the glottic level without continuation with it. In the same time the epithelial lamina begins to recanalize in adorsocephalic to ventrocaudal direction, joining the infraglottic cavity, so that the pharyngeal lumen becomes again in a wide contact with the larynx and hence with the trachea [72-74].

At the same time the ventricles begin to develop from the caudal part of the epithelial lamina cephalic to the glottic level as two lateral epithelial buds that continue to grow in a ventrolateral direction, although they remain mostly solid by the end of the embryonic period [72,74,75].

By the end of the embryonic period (stage 23), the hyoid cartilage consists of the body and greater horns, the lesser horns being as distinct nodules separated from the styloid processes. The cartilaginous thyroid laminae, which may show a foramen, are united by mesenchyme, and the thyroid superior horns may or may not be continuous with the laminae. The cricoid cartilage is a continuous ring that comprises an arch and a lamina. Each arytenoid cartilage possesses a cartilaginous muscular process and a mesenchymal vocal process which are the last to undergo chondrification. The epiglottis is the last laryngeal cartilage to develop; it arises from an area of the pharyngeal mesoderm in contact with the palate. The primitive T shaped inlet of the embryonic larynx is still very high, with an upper border located at the level of nasopharynx. Most of the major laryngeal muscles (cricothyroid, posterior and lateral cricoarytenoids, thyroarytenoid, transverse arytenoid) are now present (although not yet striated), and their innervations follows the adult pattern. Motoneurons penetrate the muscles [72,74,76].

The laryngeal cavity now comprises (as in the adult) the vestibule, the ventricles, and the part between them, and the infraglottic cavity. The ventricles are not at the level of the future glottis, which lies more caudally. The sensory innervation is well established, with receptors in the epithelium, although nerve fibers do not yet reach the epithelium [72,74].

1.2.2. FOETAL PERIOD

During the human foetal period, the length of the human larynx increases from about 3 mm to reach up 20 mm by the end of the third trimester, and the inlet of a full term foetus is about 5 mm in diameter[72]. During the foetal period the larynx descents in its position in relation to the cervical vertebrae. This descent is done by the effects of the unfolding of the neck beside the general elongation of the foetal length due to its growth. This descending process moves the epiglottis from the level of the upper border of C1 to the level of C2 and the cricoid cartilage from the level of the C2 up to the lower border of C4 by the end of the foetal period. [72,73,77,78]

The intrinsic muscles of the larynx show two different maturation times and patterns. The interarytenoids, posterior cricoarytenoids, lateral cricoarytenoids, and lateral thyroarytenoid muscles, together with the internal cricoarytenoid ligaments (all the structures related to the sphincteric function) show an early maturation from the beginning of the fetal period. On the other side, the maturation of the vocal process of the arytenoid, vocalis muscles, vocal ligaments, and Reinke's space (structures related to phonatory functions) begins late and remains incomplete at birth. The maturation begins posteriorly around the arytenoids to proceed in a fan-like orientation in a postero-lateral-ventral direction [38,39].

At the beginning of the foetal period the two lateral laminae of the thyroid cartilage are still connected anteriorly by a band of mesenchyme that extends along the entire length of thyroid cartilage from the caudal portion of the supraglottis to the cephalic portion of the subglottis[79]. This mesenchyme will differentiate into a ventral part which give rise to the intermediate lamina of the thyroid cartilage which joins later its two lateral laminae, and a dorsal part called the median process which give rise to several structures, including: the

anterior commissure ligament, the fibrous ligaments and muscle fibers which are in close relation to the anterior commissure ligament and attach to it[79].

The larynx is largely derived from the fourth through sixth branchial arches and its embryology is unique. The development follows a craniocaudal progression, with the more superior thyroid cartilage arising from the fourth arch, and the more caudal cricoid cartilage arising from the sixth arch. The hyoid bone is derived from the cartilaginous elements of second and third pharyngeal arches, while the cartilaginous tissues from the fourth and sixth pharyngeal arches fuse and form the arytenoid, thyroid, cricoid, corniculate, and cuneiform cartilages, except the epiglottis which comes from the third arch. The laryngeal cartilages, including the epiglottis, originate from the mesenchymal tissue adjacent to both entoderm and endoderm. In this tissue, small foci of cells showing a trend towards chondroitic differentiation emerge. Complete confluence of these foci and formation of the definitive cartilages occur mostly postnatally. Thyroid, cricoid, and arytenoid (except the vocal processes) cartilages consist of hyaline cartilage; the other cartilages consist of elastic cartilage. Hyaline cartilages tend to ossify after the age of 18 years, earlier in men than in women. In contrast to hyaline cartilages, ossification does not occur in elastic cartilages. The intrinsic muscles of the larynx also originate from the fourth to sixth arches[72,73,78,80].

Finally, it is thought that the fifth branchial arch may play a role in the origin of the arytenoid and corniculate cartilages, and the intrinsic muscles of the larynx. However, due to its rapid degeneration during the human development, its role is still unclear [1,77].

1.3. PHYSIOLOGY

The human larynx has three basic functions: respiration, airway protection, and phonation. It coordinates and optimizes the airway during respiration. Most importantly, the larynx protects the airway from swallowed matter through several mechanisms. Finally, the larynx provides controlled phonation, which, in conjunction with the pharynx, oral cavity, and nose, allows for detailed vocal communication [81]. From the earliest studies of laryngeal physiology, the main conclusion is that the larynx should be described as the valve of the pulmonary tract[82].

1.3.1. IMPORTANT STRUCTURAL POINTS

1.3.1.1. RECEPTORS OF THE LARYNX

The larynx is a highly reflexogenic organ, thus it contains a variety of receptors which can be divided physiologically into: 1) mucosal receptors (pressure receptors, cold receptors, and irritant- or chemoreceptors), 2) mechanoreceptors located mainly in laryngeal muscles and joints, and 3) C-fiber receptors the exact function of which is still uncertain [83,84].

Regarding the morphology at least four types have been described: (1. free nerve endings, 2. taste buds, 3. glomerular, corpuscular, and lamellar receptors, and 4. muscle spindles). In spite of the large number of physiological and morphological studies of laryngeal sensory receptors, one cannot say with confidence which receptor is responsible for specific recorded afferent nerve discharge patterns and thus reflexes [83,84].

The distribution of the sensory nerve fibers in the mucosa of the larynx shows that there are large amounts of sensory nerve fibers on the laryngeal surface of the epiglottis, the aryepiglottic fold, and the arytenoid cartilage. Therefore, the sensory nerve supply is much higher in the inlet of the larynx and laryngeal vestibule, if compared with the subglottic area[57]. Also the sensory fibers on the dorsal aspect of the posterior cricoarytenoid muscle and the overlaying mucosa are dense, forming a sensory nerve plexus. Similar sensory nerve plexuses are observed also in the lateral and posterior walls of the hypopharyngeal mucosa[57].

Taste-bud-like structures were also observed in the arytenoid eminence, the aryepiglottic fold and the laryngeal aspect of the epiglottis[57,83,84]. The laryngeal response to water which was believed to be initiated by water receptors is proved now to be initiated by the chemoreceptors [83,84].

1.3.1.2. THE AFFERENT AND EFFERENT SYSTEMS

The sensory and motor nerve supply of the larynx has been discussed in details in the anatomy.

1.3.2. THE PROTECTIVE FUNCTIONS OF THE LARYNX

1.3.2.1. THE GLOTTIC (LARYNGEAL) CLOSURE REFLEX

As mentioned above, the larynx should be described as the valve of the pulmonary tract: the closure of the larynx during deglutition is the most important function of the larynx[82].

A multilevel description of the sphincteric function of the larynx, with the indication to the glottic level as the most important level, is described even in the earliest laryngeal studies[82]. The detailed description of the three levels of the laryngeal sphincter was discussed thereafter: the first at the laryngeal inlet mainly due to the closure of the aryepiglottic folds with the epiglottis; the second at the level of false vocal folds, and the third at the true vocal folds' level[85]. The most important closure level in Man is the true vocal cord level, while the role of the epiglottis in Man is rudimentary, if compared to other species[82,85].

So the normal laryngeal (glottic) closure reflex is defined as a simple polysynaptic reflex that allows the larynx to protect the lower airway from penetration and aspiration [81,85,86]. Protective closure of the larynx occurs in three tiers. In the first tier, the laryngeal inlet is contracted by collapsing the aryepiglottic folds medially. The anterior and posterior gaps are filled by the epiglottic tubercle and the arytenoid cartilages, respectively. In the second tier, the false vocal folds are brought together [81,85]. The final and most important tier occurs at the level of the true vocal folds where the contraction of the laryngeal adductors, specially the lateral cricoarytenoid and the thyroarytenoid muscles are responsible for the glottic closure[81,85,86].

This reflex is initiated and maintained by various stimuli to the mucosal areas of the laryngeal margin and supraglottic larynx, especially by mechanical and chemical stimuli. The impulses are then carried along the superior laryngeal nerve to the brainstem (tractus solitarius) [81]. Unlike the commonly used animal models in physiology research, humans do not possess a crossed adductor reflex: thus stimulation of one superior laryngeal nerve does not produce simultaneous action potentials in the contralateral adductor musculature. It is therefore possible that unilateral superior laryngeal nerve injury in humans may result in the failure of an ipsilateral vocal fold closure, a condition predisposing to aspiration despite anatomic integrity of both recurrent laryngeal nerves [81,86]. Reflex action potentials in the recurrent laryngeal nerve can be elicited by electrostimulation of the optic, acoustic, chorda tympani, trigeminal, splanchnic, vagus, radial, and intercostal nerves. The susceptibility of this reflex response to such a variety of sensory stimuli is unique and emphasizes its primitive role in respiratory protection of the organism from a wide variety of potentially noxious influences [81,86].

The approximated true cords serve as a relatively adequate valve to prevent the ingress of air, fluids, or solids into the trachea, but their closure is inadequate to prevent the egress of air. The anatomy of the larynx in a coronal section explains why the true vocal cords can more strongly act as an inspiratory valve (their free border is directed slightly up), while the false vocal folds are better suited for stopping the egress of air outside the larynx(their free borders are directed down) [85].

The Laryngospasm which is an exaggerated laryngeal closure reflex results usually from abnormal prolongation of the laryngeal closure in response to normal stimulation, or less commonly as an abnormal initiation of the reflex. The laryngospasm occurs more frequently in the infants in comparison to the adults, and

with the cerebral cortical growth during the infancy this reflex maturates in humans, so this may explains the higher incidence of the exaggerated reflex in patients with multiple system atrophy and among infants [81,87,88].

As the glottic closure reflex is controlled by the cerebral cortex, any condition disturbing the consciousness, like the use of general anaesthesia and strong sedatives depresses this reflex. This reflex, as well as the laryngospasm, is inhibited by the inspiratory phase of respiration, hypercapnia, hypoxia and positive intrathoracic pressure, while the expiratory phase, hypocapnia, increased arterial pO2 and negative intrathoracic pressure facilitate them [81,89,90].

The glottic closure reflex is part of the reflexes occurring during swallowing to protect the airway, as well as one of the laryngeal chemoreflexes that protect against aspiration. This reflex is involuntary and is integrated in the brain stem, closely related with the integration of the pharyngeal and oesophageal phases of swallowing [91-93].

Finally, in spite of the many studies, the exact central connections in the brainstem are not completely clear. , It is known, however, that this reflex is composed of several ultrarapid movements in the intrinsic and extrinsic muscles of the larynx that occurs in a rapid sequence and integrates with the propagation of food during the pharyngeal phase and the beginning of oesophageal phase of swallowing [94-96].

1.3.2.2. THE COUGH REFLEX

The cough is a complex airway defensive reflex consisting of several phases (cycles). It begins with an inspiratory phase, followed by a forced expiratory effort initially against a temporary closed glottis, followed by active sudden glottal opening and rapid expiratory flow; it is mainly a laryngeal reflex. The expiration reflex also is a reflex for airway protection but it differs from cough in the lack of a preparatory inspiration, and it is not mainly a laryngeal reflex. Coughing reflex has many afferents, can be both voluntarily induced and involuntarily initiated by activation of vagal afferent nerves innervating the airways and lungs, but mainly it is induced by laryngeal irritation or penetration. Centrally, cough is regulated at the level of the brainstem through integration of vagal afferent nerve input by relay neurones in the nucleus tractus solitarius. Projections to and from the nucleus tractus solitarius add further complexity to cough regulation, as do the profound influences of psychological and social factors known to regulate cough. Peripherally, both neuronal and non-neuronal elements in the airways regulate the excitability of the vagal afferent nerve terminals regulating cough. These multiple levels of integration and encoding of the cough reflex may render this defensive respiratory response highly susceptible to modulation both by disease processes and through therapeutic intervention. The sudden egress of a large quantity of air under great pressure carries with it whatever foreign matter is to be expelled from the lower airway and trachea. The respiratory reflex is different in its function and neurological pathway and control from the cough reflex [85,97-99].

1.3.2.3. THE LARYNGEAL CLOSURE RELATED TO OTHER REFLEXES

The laryngeal closure also occurs in relation to other reflexes to ensure air-trapping with the accompanying increases in intrathoracic and / or intra-abdominal pressure. This is an essential mechanism in the physiology of urination, defecation, childbirth, cough, and vomiting. It is brought about directly by contraction of the muscles. The false vocal fold plays an important role in that by its suitable anatomical orientation to prevent egress of air from the respiratory tract [85].

Laryngeal closure occurs also in the mid inspiratory phase during hiccup. This reflex represents a violent and sudden contraction of one or both copulae of the diaphragm and an expansion of the thoracic cage, while the vocal cords remain widely opened at the beginning of the act. The first phase therefore represents the beginning of a deep inspiration. In the midst of this inspiratory effort, however, the vocal cords sharply close and the inspiratory effort is abruptly terminated producing the characteristic sound of this reflex [85,100].

1.3.3. THE RESPIRATORY FUNCTIONS OF THE LARYNX

Although the main function of the larynx is to protect the airway, laryngeal muscles act to help inspiration by opening the glottis. Besides that, laryngeal muscles are affected by the different respiratory phases and have a controlling role especially in expiration[101-106]. The movement of the vocal folds can be easily seen during the quit breathing. Different studies in the last two decades tried to observe the movements of the laryngeal muscles in relation to the respiratory cycle under different conditions [101-106]. At the beginning of inspiration or in response to hypercapnia or hypoxia the posterior cricoarytenoid muscle is highly active, while the adductors of the larynx are less active; on the contrary condition the tone and activity of the adductors are increased, these changes are limited in the thyroarytenoid and cricothyroid muscles [101-104]. In one of this study [105], which was conducted in humans during non rapid eye movement sleep, it was found that the posterior cricoarytenoid muscle, the vocal cord abductor, appears to respond in a manner very similar to the inspiratory pump muscles of respiration, this would help ensure glottic patency in the presence of subatmospheric intraluminal pressure [105]. The study of these activities during sleep also proved the involuntary control of these changes [105], also it is found the voluntary hyperventilation can increase and prolong the activity of the posterior cricoarytenoid to help increasing the pulmonary capacity [105,106].

One of the reflexes related to larynx is yawning, which is similar to the respiratory reflex, it is involuntary act accomplished by the rapid inhalation of large quantities of air with the mouth widely opened and both the pharynx and the glottis are markedly dilated [85].

1.3.4. THE PHONATORY FUNCTIONS OF THE LARYNX

The phonatory performance of the larynx, although the most studied, is probably the least well understood among the three basic functions.[81] It is generally agreed from long time that larynx participates in the production of speech sound by the production of a fundamental tone which is thereafter modified by resonating chambers of the upper aerodigestive tract. Intelligible speech, therefore, represents the combined effects of the larynx, tongue, palate, and related structures of the oral and nasal cavities, under higher cortical and subcortical control [81,85,107]. Thus intelligible speech depends on the combined function of the larynx, tongue, palate, oral vestibule and other related structures and their higher control and not a pure function of the larynx [81,85].

The larynx (and more specifically the vocal fold) is the organ responsible for the production of our tones, and two main theories are described to explain this process. The passive theory which suggests that: the vocal fold vibration is a passive process occurring at its border with no active role for the vocal folds in the voice production. The main changes in the tones in this theory is explained by the changes in the air pressure and power when passing between the vocal fold, and this theory is supported by the ability of the paralyzed larynx to produce voice and the capability of production of sounds by blowing through a cadaver larynx [5,81].

The other theory suggests that: the sound production occurs at the vocal fold level by an active process of vocal fold rhythmic vibrations produced by the contractions of the thyroarytenoid muscles as a result of beat-by-beat impulses centrally generated then transmitted through the recurrent laryngeal nerve. This theory is less accepted now as a mechanism of voice production [81]. Also the old studies explained that the different animals are capable of production of different sounds in spite of its ill-developed vocal folds [82,85]. It seems that the active role of the vocal fold vibration is more related to the refinement of our sound by sharing in the production of different pitches (frequencies), adjusting the different degrees of loudness (amplitudes), and fluctuation between these different parameters thus giving us the different acoustic spectrum that we have [5,81]. The vocal fold vibration depends on the vibratory mass of the vocal folds, their anteroposterior tension, and the changes in the subglottic pressure, and these factors result in the different forms and positions of the vocal fold during phonation [5,81].

The actions of the intrinsic muscles is explained above in the anatomy, but generally in man the

electromyographic studies showed that the thyroarytenoid muscle is the most active one in the modulation of our sound frequencies and amplitudes [5,81,108], and more specifically its most superomedial part which is highly developed to serve this fine phonatory functions [21]. The second role is played by cricothyroid muscles which tense the vocal folds and play a role in increasing the pitch of the voice [5,22,81,108]. Other possible contribution in the sound control may come from the other intrinsic muscles, especially the posterior cricoarytenoid [18], but this role minimally affects the phonation [5,81].

Beside the role of the vocal folds, changes in the subglottic pressure plays also an important role in the adjustment of our voice parameters especially the intensity [109-111]. Changes in the voice loudness is correlated by a parallel changes in the subglottic and tracheal air pressure. Moreover it was observed that the increase in the tracheal pressure is markedly correlated with the increase in the intra-alveolar pressure, thus the intensity of the voice could be controlled by the changes in the intra-alveolar pressure in addition to the active role of the intrinsic laryngeal muscles (mainly by increasing the resistance to airflow during phonation) [109,110].

Finally the fine mechanisms responsible for the production of our different voicing outputs are still unclear and needs further investigations, and the human adults and children have a high capability to produce enormous number of changes in the shape and size of the vocal folds in relation to each letter, voice output[111].

1.3.5. CENTRAL CONTROL OF LARYNGEAL MUSCLES

The laryngeal muscles have many and complex functions. They are controlled at different level in the brain. Phonatory functions are mainly controlled at the cortical level while the respiratory and protective functions are mainly controlled at the brain stem [112].

1.4. PATHOLOGY OF LARYNGEAL SQUAMOUS CELL CARCINOMA

1.4.1. EPIDEMIOLOGY OF CANCER LARYNX

Cancer is a major health problem all over the world, with a tendency of an increasing incidence, mainly explained by the improvement in diagnostic methods more than an actual rise in incidence. This tendency was noted in earlier studies and is still observed in recent large studies in the USA and Europe [113-115].

In a global epidemiological study for cancer incidence in the year 2002 [116], 159,000 new cases of cancer larynx were diagnosed. The global cancer larynx incidence among the malignant tumours in men was 2.4 %[116].

Slightly higher incidence of cancer larynx is observed in the European countries with a global incidence of 3% among men[117].

There is a large geographic variability in the disease frequency, with the highest incidence in south Europe (Spain, France, and Italy), followed by Eastern Europe (Russia, Ukraine), and South America (Uruguay, Argentina, Brazil) [116,117].

Cancer larynx is a rare cancer in women, with a global sex ratio about 7:1 [116], the sex ratio shows also a great variability and interestingly the increase in incidence is almost proportional to the increase in sex ratio [116,117], especially in Spain where the ratio reaches 49:1 in some statistics [117].

Laryngeal cancer is the most common mucosal head and neck cancer[115-117]. Like the other head and neck carcinoma, it is a disease of the old adults and elderly, with 90% of the cases occurring after 45 years[118].

1.4.2. AETIOLOGY OF CANCER LARYNX

The risk for cancer larynx is greatly increased by tobacco smoking and alcohol consumption, an effect which is multiplicative [119-127]. Smoking is the most dangerous risk factor to cancer larynx (average relative risk is about 10 in most of the studies [119-121]), with the risk proportionally related to the smoking rate and duration. [119-121]Cessation of the smoking may reduce the risk up to 60% after a delay of 10-15 years. [121]

Alcohol is identified also as a major risk factor for cancer larynx, the relative risk range being between 1.3 and 4.6 [122-126]. Like the smoking, the risk is dose- and duration dependent [122-126]. Combination of both smoking and alcohol multiplies the total risk, which may reach 100 with the high levels of consumption of these two risk factors [123,126].

Also the pattern and type of alcohol beverage consumption proved to have a role in the subsite affected within the larynx [123,125,126]. For example, higher wine consumption in southern Europe (France, Italy, and Spain) is associated with an increased frequency of carcinoma of the epilarynx and supraglottis, while the glottic cancer incidence increases in areas where the smoking is the main risk factor [123-126].

The occupational exposure, dietary factors, gastroesphageal reflux, human papilloma virus, and genetic susceptibility are discussed as minor risk factors, especially in the absence of the major other factors. Their exact implication even as a minor risk factors for laryngeal cancer remains controversial [127].

The history of neck irradiation was discussed also as a minor risk factor, but this is usually described as a rare condition, and related to history of irradiation in young patients [128].

1.4.3. HISTOLOGICAL TYPES OF PRIMARY LARYNGEAL MALIGNANCIES

Primary malignant tumours of the larynx include wide variety (Table 1), but squamous cell carcinoma (SCC) represents the vast majority of the cases [127].

1.4.4. LARYNGEAL SQUAMOUS CELL CARCINOMA

Laryngeal squamous cell carcinoma represents at least 95% of the cases of cancer larynx [129,130]. Although it is one of the head and neck SCC the comparative genomic studies, especially regarding p53 polymorphism suggest that it might be more related to lung SCC than to head and neck SCC [130].

Epithelial tumours	Typical squamous cell carcinoma	
	Variants of squamous cell carcinoma	Verrucous squamous cell carcinoma
		Basaloid squamous cell carcinoma
		Spindle (Sarcomatoid) cell carcinoma
		Adenosquamous carcinoma
		Papillary squamous cell carcinoma
		Acantholytic (Adenoid) squamous cell carcinoma
	Lymphoepithelial carcinoma (Undifferentiated squamous carcinoma nasopharyngeal type)	
	Giant cell carcinoma (Anaplastic carcinoma)	
	Malignant salivary gland –type malignancies	Mucoepidermoid carcinoma
		Adenoid cystic carcinoma
		Carcinoma ex pleomorphic adenoma
		Acinic cell carcinoma
		Epithelial-myoepithelial carcinoma
		Salivary duct carcinoma
		Clear cell carcinoma
		Adenocarcinoma
Neuroendocrine tumours	Typical carcinoid tumour (Grade I)	
	Atypical carcinoid tumour (Grade II)	
	Small cell carcinoma (Grade III)	
	Combined (Composite) small cell carcinoma	
	Malignant paraganglioma	
Soft tissue malignancies (extremely rare)	Fibrosarcoma ,Malignant fibrous histiocytoma, Liposarcoma, Leiomyosarcoma, Rhabdomyosarcoma, Angiosarcoma, Kaposi sarcoma, Malignant hemangiopericytoma, Malignant nerve sheath tumour, Alveolar soft part sarcoma, Synovial sarcoma, Ewing sarcoma.	
Bone and cartilage malignancies (extremely rare)	Chondrosarcoma, Osteosarcoma	
Malignant primary haematolymphoid tumours		
Mucosal malignant melanoma		
Malignant germ cell tumours		
Unclassified tumours		

Table 1: Histological types of primary laryngeal malignancies.

1.4.4.1. MACROSCOPY

The macroscopic appearance of the SCC of the larynx is variable; it usually appears as exophytic circumscribed lesion or flat plaque with well defined raised edges, but it may also exhibit a diffuse, endophytic, or a big exophytic polypoid appearance. The colour also may be white, red, or gray and may differ within the

same lesion. The surface is usually irregular and granular, but may be smooth, or ulcerated. Different clinical (macroscopic) terms are used to define abnormalities in the epithelium which help in the description of the tumour or may be present in the precancerous lesions (Table 2) [127,131].

Leukoplakia	white patch on the mucous membrane surface.
Hyperplasia	thickening and irregularity in the surface epithelium
Leukoplasia	1+2
Erythroplakia	red patch on the mucous membrane surface.
Erythroplasia	2+4
Keratosis	presence of keratin plaques on the surface
Papillary and verrucous	extensive irregular epithelial outgrowth (warty like)
Ulcer formation	Areas of break down in the surface epithelium of the tissue or the lesion

Table 2: Pathological descriptive terms.

The supraglottic SCC usually presents with exophytic mass with an ulcerated surface. Early glottic SCC presents usually with a limited epithelial lesion, while in advanced cases different aspects are possible: exophytic, endophytic, or ulcerative mass. Subglottic SCC are rare and resemble the glottic one, while transglottic tumours which involve vertically the three subdivisions of the larynx, tends to be big aggressive and more infiltrative[127,131].

1.4.4.2. MICROSCOPY

Invasive laryngeal SCC microscopically resembles other mucosal SCC: the invasion is manifested by the disruption of the basement membrane; keratinisation is present in glottic and subglottic lesions while the degree of keratinisation decreases in supraglottic lesions. The tumours are graded traditionally according to the cellular parameters (the degree of nuclear pleomorphism, mitotic activity, and maturity of cells and nuclei) into well, moderately, and poorly differentiated SCC. The keratinisation usually decreases from well to the poorly differentiated tumours. Most of the laryngeal carcinomas are moderately differentiated [127,131].

Often, one tumour may contain more than one component of differentiation, especially in glottic tumours, which contain commonly a component of in situ or microinvasive carcinoma [131]. The role of the differentiation degree is limited as a prognostic factor [127,131,132].

Laryngeal SCC is almost always accompanied by stromal reaction, extracellular matrix deposits, cellular proliferation, and sometimes it is associated with inflammatory reaction. Neovascularisation is frequently seen [127]. The invasive front or (tumour border growth) is more important, the growth may be expansive or infiltrative or both [127,131,132].

Infiltrative borders are more dangerous and more common with the transglottic tumours[131]. In addition; endophytic lesions with infiltrative borders, with less marked or no distinct margins tend to metastasize to regional lymph nodes more frequently and rapidly [132].

Perineural, vascular and higher depth of the invasion may increase the risk of lymph node metastases and may be associated with higher incidence of local recurrence [131-134].

1.4.4.3. GENETICS AND MOLECULAR BIOLOGICAL ASPECTS

In the continuous search to improve the survival in head and neck SCC, several biological markers appeared in the last years [127,130,135-138]. The overexpression of p53 (the name of the tumour suppressor gene located on the short arm (p) of chromosome 17, as well as the protein encoded by this gene) is studied as a prognostic factor in a number of cancer localizations, but till now its prognostic role for laryngeal tumours remains to be demonstrated [130,135]. The estimation of the markers Ki-67 or (MIB1) index and the proliferating cell nuclear antigen (PCNA) as indicators for survival has been widely studied recently but again with contradictory results in laryngeal SCC [135,136]. In a similar manner, the overexpression of the epidermal growth factor receptor (EGFR) is investigated in head and neck SCC, as a significant factor in the choice of the treatment and in the prediction of locoregional relapse [137], but in laryngeal SCC the use of this marker still remains debatable [138].

1.4.5. LOCAL SPREAD

The results of the early studies of the injections of dyes and radioactive isotopes, introduced the hypothesis of compartmentalization and submucosal subsites of the larynx [48]. Furthermore, embryological data of the development of the submucosal connective tissue layers and compartments of the larynx explain this hypothesis and point to submucosal barriers which may affect tumour spread in the larynx especially in early cases [41]. In 1961 a detailed histological study of serial sections of the laryngeal cancer cases was introduced as a basis to observe the behaviour of cancer of the larynx [139].

A big review [140] of the experimental and clinical anatomical studies of the spread of cancer larynx, concluded that [140]:

- cancer of the larynx mainly spreads by direct extension, prior to lymphatic spread and more rarely follows the vascular and neurological routes;
- the larynx should be considered as a highly compartmentalized organ in which, five compartments on each side are identified;
- the submucosal compartments on each side are completely separated from those of the other side, and both are sharply demarcated from the submucosal tissue of the trachea;
- laryngeal cancer spread follows the line of least resistance, and thus, the growth tends to be limited to the compartment of origin by the fibers bounding the compartment;

1.4.5.1. GLOTTIC AND TRANSGLOTTIC TUMOURS

Laryngeal SCC originating from the glottis accounts for close to 60% of all laryngeal cancer cases [141,142], with the exception of south Europe, where supraglottic carcinoma including epilarynx are more common than glottic carcinoma [125,127].

Glottic carcinoma originates from the epithelium of the vocal fold in the vast majority of the cases (more than 95%), especially the anterior two thirds [131,142]. Initially it usually spreads along the vocal fold mucosa without deep infiltration, and tumours tend to go anteriorly towards the anterior commissure rather than posteriorly (Figure 26) to the area of the arytenoid [38,142,143].

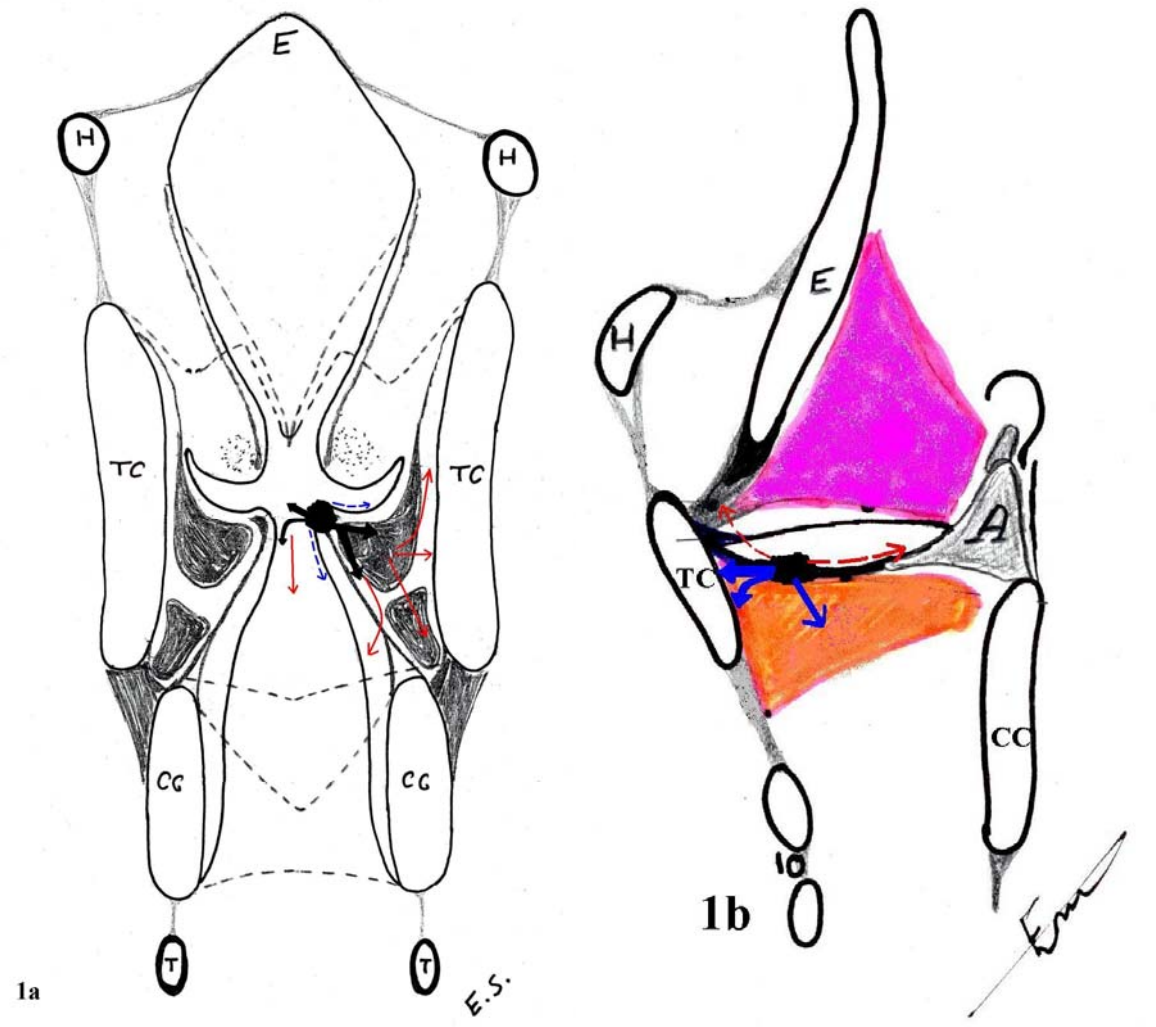


Figure 26: Diagrams of the larynx: midcoronal section (1a) and midsagittal section (1b) showing glottic tumour spread.
Tumour spread is represented by the black spot at the vocal cord level. H: hyoid bone, TC: thyroid cartilage, CC: cricoid cartilage, E: epiglottis, A: arytenoid, T: trachea. In figure 1a the thick black arrows indicate the common routes of spread in early glottic cancer, while the red thin arrows show the next steps when the cancer becomes more advanced, the thin blue interrupted arrows indicate the less common routes in early cases. In figure 1b the thick arrows indicate the common routes of spread in early glottic cancer, while the red interrupted thin arrows show the less common routes.

- *ANTERIOR COMMISSURE EXTENSION*

While pure carcinoma originating from the anterior commissure is a rare condition (1%) [38,142], extension of glottic cancer to the area of the anterior commissure is common, ranging from 20% to 50% in different studies [38,142,144,145]. When the cancer reaches the anterior commissure it becomes very close to the subglottis [38,45,144], and to the thyroid cartilage (the distance between the vocal cord mucosa and the thyroid cartilage is about 2-3 mm) [38,45].

When the tumour reaches the anterior commissure: 1) it can pass along the mucosa to the opposite side, usually slightly at a subcommissural level; 2) it can spread down or less commonly up [143,144].

After anterior commissure invasion, deep invasion is limited superiorly and superolaterally by the very strong anatomical fibrous arrangement of the anterior commissure ligament layers and the thyroepiglottic ligament which act like a basket to stop cancer extension. In rare cases, when cancer invades into this area it invades easily the thyroid cartilage and rapidly the preepiglottic space [36,79,143-147]. Therefore, anterior

commissure invasion is more commonly associated with a downwards extension to the subglottic area immediately below the anterior commissure, where no fibrous barriers are present [38,143,144]. From this site the tumour usually spreads in the anterior subglottis and becomes easily in contact with the thyroid cartilage, which becomes at a higher risk [143,144,147].

Thus, most glottic tumours extend anteriorly and inferiorly in the anterior subglottic area which is a weak zone, with a thin submucosa adherent to an ossified cartilage [30,31,79,144,147]. Invasion of this zone is associated with a high incidence of cartilage invasion and extralaryngeal extension (Figure 27) though the cricothyroid membrane [30,31,143,147]. The weakest spot in this zone is the narrow paramedian area between the median cricothyroid ligament and the anterior border of the cricothyroid muscle where the tumour faces only a delicate fibrofatty tissue pierced by the vascular structures [30,31].

- *LATERAL EXTENSION*

Less commonly, glottic tumours can spread to the subglottis directly along the mucosa without deep infiltration [143,144,146,147]. Commonly invasion proceeds first through the vocal ligament, followed by the medial and lateral parts of the thyroarytenoid muscle, up to the fat of the paraglottic space which is adjacent to the thyroid cartilage [143,144,146]. These different degrees of invasion can be inferred from the clinical examination of vocal fold mobility, from the early disturbance of the cordal mobility, up to the complete fixation of the vocal fold [39,143].

Less commonly the cancer can extend along the ventricular mucosa to reach laterally the paraglottic space[143]. Whatever the route of the spread, when cancer larynx reaches the paraglottic space it becomes rapidly a transglottic cancer [39,46,143]. Transglottic cancers usually invade the thyroarytenoid muscle and fix or severely impair the vocal fold mobility [39,143,146]. In addition, they spread down to the upper part of the subglottis, between the conus elasticus and the thyroid perichondrium, usually causing a bulge in the lateral infraglottic cavity [46,143,146,147]. Since no barriers are found in this location, the cancer can easily pass anteriorly to extralaryngeal tissues [31,44,46] or proceed posteroinferiorly to the area of the cricoarytenoid joint and the surrounding muscular attachments, causing fixation of the arytenoid [31,39,44,46]. Finally, tumours can spread superiorly (less frequent), lateral to the ventricle and the ventricular band, causing bulging of the aryepiglottic fold and, rarely, breaking through the supraglottic mucosa, this extension usually occurs late with a highly advanced glottic tumour [46,143].

When transglottic tumours (Figure 27) reach the thyroid cartilage, the thyroid perichondrium restricts cartilage invasion for the vast majority of the tumours until a very advanced stage (transglottic tumours 3 cm or larger, or glottic tumours with more than 1 cm subglottic spread) [143].

The lateral barrier separating the anterosuperior part of the paraglottic space from the preepiglottic space is still a matter of debate [33,44,46].

At the glottic level the posterior extension along the paraglottic space is limited early by the attachments of thyroarytenoid and lateral cricoarytenoid muscles (where they come nearly in contact with each other), however with the advancement of the invasion the cancer invades deeply these muscles fixing both the vocal fold and the arytenoid. Moreover, the cancer becomes so close to the submucous tissue of the angle of the piriform sinus which becomes at risk for invasion [31,39,44,46].

Extension of the glottic tumors to the mucosa of the posterior glottis is not common and occurs usually in advanced cases and transglottic tumours. The invasion proceeds through the vocalis muscle, lateral to the vocal process of the arytenoid rather than by direct posterior extension along the mucosa [144,146].

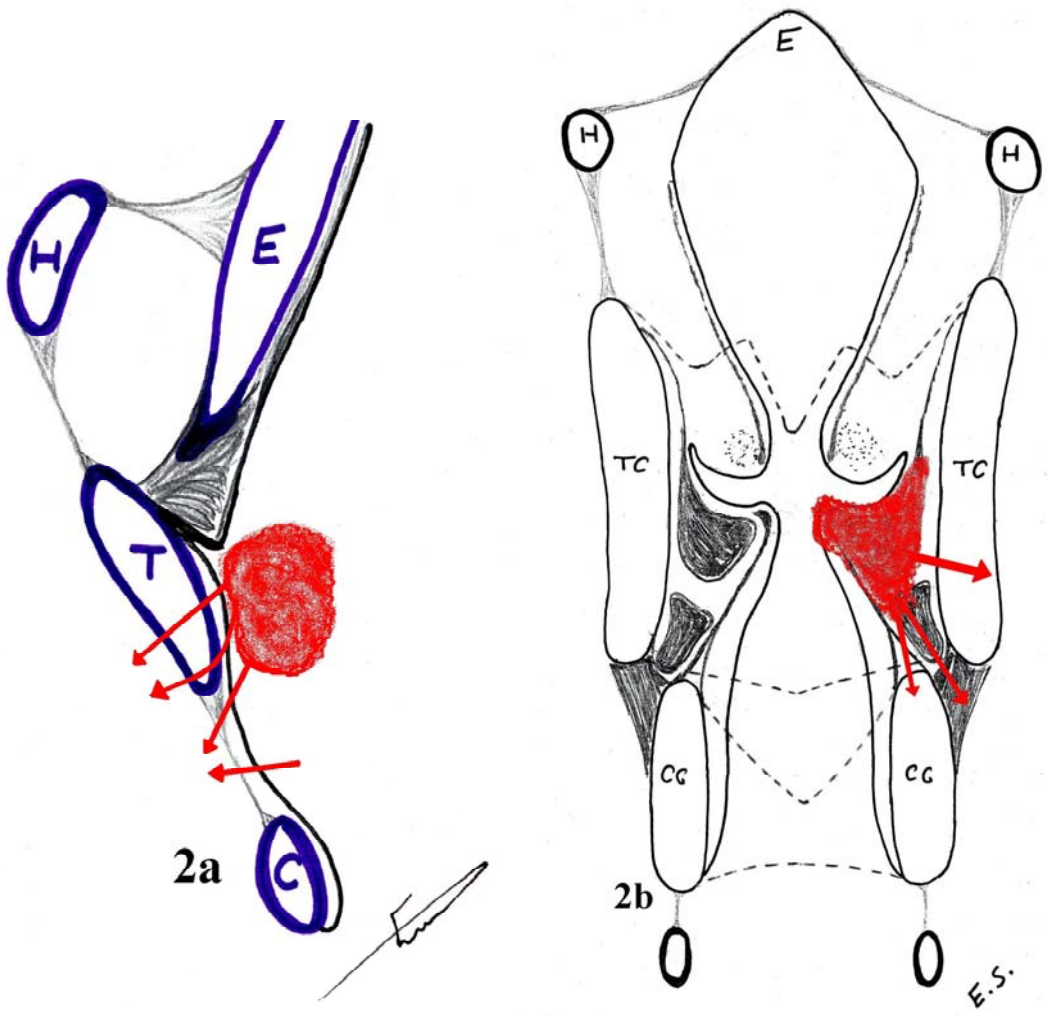


Figure 27: Diagrams for the larynx midsagittal section (2a) and midcoronal section (2b) showing the transglottic tumour spread and the common routes for cartilage invasion and extralaryngeal spread.
H: hyoid bone, TC: thyroid cartilage, CC: cricoid cartilage, E: epiglottis. In figure 2a, the red arrows indicate the common routes of spread anteriorly, usually at the lower part of the thyroid cartilage or through the cricothyroid membrane. In figure 2b, the red arrows indicate the common routes of extralaryngeal spread and cartilage invasion, usually at the postero-inferior areas of the thyroid cartilage and the adjacent area of the cricoid cartilage.

1.4.5.2. SUPRAGLOTTIC TUMOURS

As discussed above (§4.5.1), supraglottic SCC exhibits high variation in incidence: in North America it accounts for 30-40% of all laryngeal cancers [141,142], while it is nearly equally distributed in Europe [125,127]. The primary site of origin is globally the same, the supraglottic endolarynx accounts for most cases, while epilaryngeal or laryngeal margin lesions are less common [125,127,141,142]. In regions with high incidence of supraglottic carcinoma, such as southern Europe, the relative incidence of the epilaryngeal lesions increases. [125,127]

In supraglottic endolaryngeal SCC, the laryngeal surface of the epiglottis is the most common site of origin, followed by the false vocal fold, while the ventricle is a rare site of origin. In epilaryngeal lesions, the aryepiglottic fold is the more common site of origin, followed by the tip and lingual surface of the epiglottis, and finally the arytenoids, which are the rarest site [141-143].

Supraglottic SCC spreads more up than down and more anteriorly than posteriorly. Anteroinferiorly, the

thyroepiglottic ligament stops the vast majority of the lesions except in the rare cases of big ulcerative lesions. Along the inferolateral margins, supraglottic tumours routinely pushes the ventricles inferomedially, giving the wrong impression of a transglottic mass but it rarely invade the ventricles or the glottis itself [143,146-149].

The basis of this clinico-pathological finding is not completely clear and the presence of lateral glotto-supraglottic barrier has been debated. 150 However, the clinical and pathological observations in addition to the high success rate of supraglottic laryngectomy provide a relative evidence that the supraglottic tumours do not invade the glottis until late stage [143,144,147,149].

As tumours extend cranially, an anterior growth into the preepiglottic space occurs easy through the pits in the epiglottis, followed by an extension to the mucosa and muscles of the base of the tongue. The hyoid bone, hyoepiglottic membrane, and thyrohyoid membrane are rarely invaded, even in advanced cases involving the base of tongue and preepiglottic space [143,146,149-151].

Thus the supraglottic cancer remains limited to the supraglottis until very advanced stage and thyroid cartilage invasion in supraglottic cancer is extremely rare [143,146,147,149]. Cartilage invasion usually occurs in rare conditions, when a transglottic lesion develops from a supraglottic tumour (which travel along the lateral wall of the paraglottic space to invade the intrinsic laryngeal muscles, the glottis, and behaving like the transglottic tumours), or in big ulcerative lesions eroding the anterior commissure tendon [146,149,150].

Carcinoma that originates from the epilarynx tends to creep over the mucosa to the surrounding extralaryngeal structures, like base of tongue, oropharynx and piriform sinus. Generally they are more aggressive than the typical endolaryngeal supraglottic cancer, the worst being lesions originating from the aryepiglottic fold because they tend to extend towards both larynx and piriform sinus [143,149,150].

1.4.5.3. SUBGLOTTIC TUMOURS

Carcinoma originating from the subglottis is a rare entity, representing about 2 % of all laryngeal SCC [141,142,152]. When the lower surface of the vocal fold is included the incidence increases to 5% [152].

Subglottic carcinoma usually presents late, and spreads mainly circumferentially along the subglottic mucosa and towards the vocal fold muscles. When it advances it has a high tendency to spread to the cartilages, extralaryngeal soft tissue, trachea and thyroid gland [142,152,153].

1.4.5.4. CARTILAGE (FRAMEWORK INVASION)

Cartilage invasion in cancer larynx usually occurs in advanced cases. Transglottic tumours have the highest incidence, around 50%, while in glottic tumours cartilage invasion is found in 20% of cases [146,154].

The perichondrium and the cartilage itself are very strong barriers to invasion, while the ossified cartilage is a weak spot [154,155]. Invasion usually occurs at the areas with advanced ossification thus framework invasion is a better term than cartilage invasion [145,155]. The most common sites for framework invasion are the lower margin of the thyroid ala, and the upper surface of the cricoid arch (Figure 27) [143,146,147,154,155].

Whatever the supraglottic cancer size, it never invades the framework when confide to the supraglottis [146,154].

Cartilage invasion can occur as a single one or combination, thyroid cartilage is affected in the most cases, also it is the most cartilage affected alone [155].

The anterior part of the lower border of thyroid ala is the most affected part by invasion, transglottic tumours usually invades the lower border of thyroid and or the upper border of cricoid [143,146,147,154,155]. The invasion can take different forms from erosion up to growing through, but a rare form of growth can occur also which includes small erosion followed by intracartilaginous spread when the perichondrium is intact over an

ossified cartilage and this also supports that the perichondrium is a strong barrier against spread [154,155].

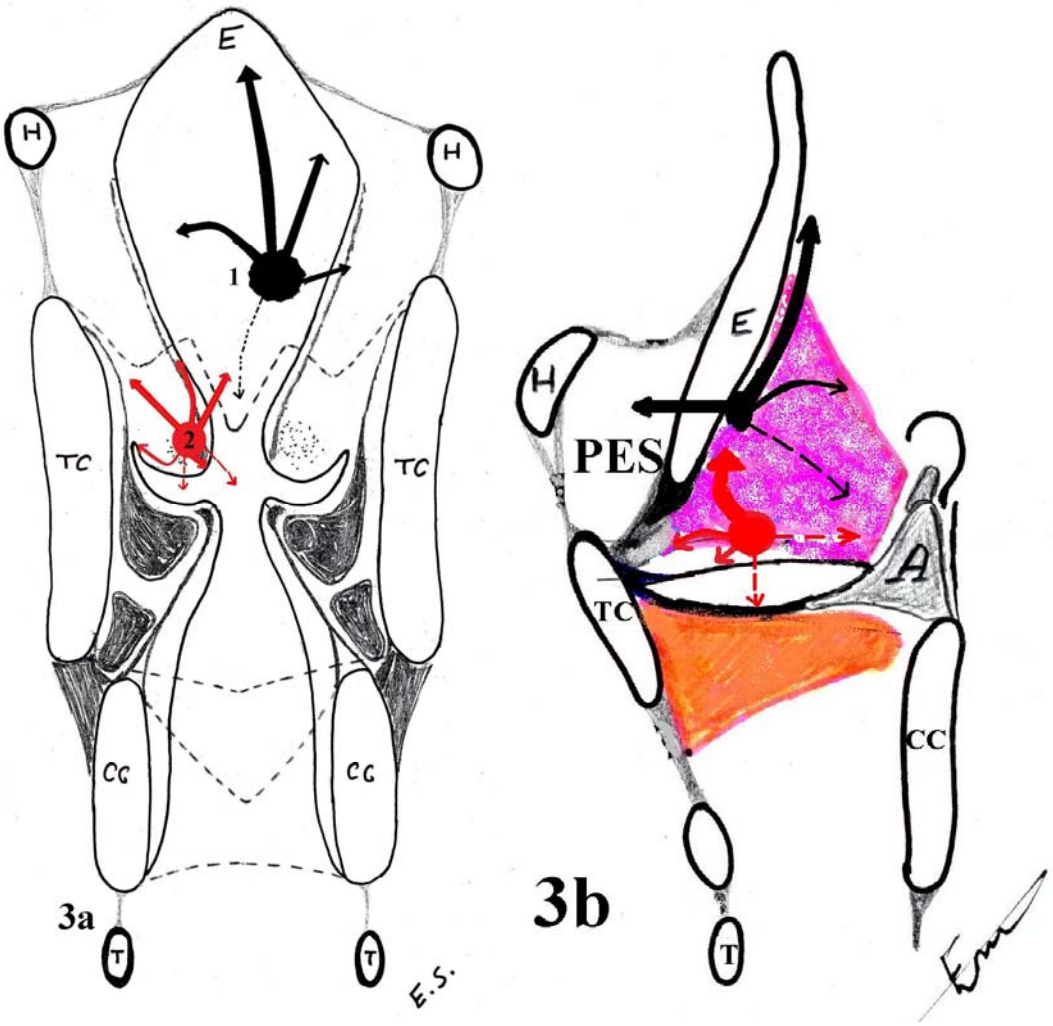


Figure 28: Diagrams for the larynx midcoronal section (3a) and midsagittal section (3b) showing supraglottic tumour spread. Supraglottic tumour spread is represented by the black spot (1) at the epiglottis and red spot (2) at the ventricular band. H: hyoid bone, TC: thyroid cartilage, CC: cricoid cartilage, E: epiglottis, A: arytenoid, PES: pre-epiglottic space, T: trachea. The thick arrows indicate the common routes of spread, while the thin interrupted arrows indicate the less common routes.

1.4.6. LYMPHATIC SPREAD

Different experimental studies of dyes and isotopes injected in the larynx demonstrate that lymphatic spread in the larynx follows a specific ipsilateral (with the exception of the epiglottis, and the lowermost part of the infraglottic cavity) compartmental pattern. Moreover, the lymphatic drainage of the larynx is often carried unilaterally in a cephalic direction, with lymphatics exiting through the thyrohyoid membrane except for the lowermost part of the subglottis where the lymphatics form a small plexus on the cricothyroid membrane. However, when the efferent lymphatics are obstructed the spread can be carried to the contralateral side [48,140,156,157].

In a large study analyzing the lymph node dissection specimens of 1400 patients of cancer larynx, the overall incidence was 32.9%. Among the positive cases 75.6% were ipsilateral, 19% were bilateral and 5.4% were contralateral [158]. Also it was observed that positive nodes percentages were 0%, 23.8%, 34.3% and 44.2% in T1, T2, T3 and T4 cases, respectively [158].

The incidence of the lymph node metastases in cancer larynx is also highly influenced by the site of origin and the extent of the tumour [142,159], at the time of the diagnosis 50% of the supraglottic carcinomas have suspected lymph nodes [142], and about 40% of the surgical specimens of supraglottic carcinomas have pathologically positive nodes, with increase the incidence up to 47% when the lesion is situated in the laryngeal margin [159]. While, only 8% of the glottic carcinomas have a metastatic nodes at the time of the diagnosis [142], and in the operated cases of glottic origin the incidence ranges from 10% in T1 (1 case from 10) up to 57% (60 cases from 105) in T4 [159]. In the transglottic carcinoma the incidence is about 26% ranging from 15% in T2 up to 40% in T4 [160].

The incidence of the occult metastases in cancer larynx generally is relatively low, about 13% [158], and most of these cases are advanced cases and supraglottic in origin [158]. In supraglottic carcinoma, the incidence of the occult metastases is 0% for T1 cases and increases to 40% in T4 patients [159,161,162].

Levels II and III account at least for 80% of the pathologically positive nodes [158,159,161,163]. Moreover, isolated positive nodes in other levels, without positive levels II and or III, are extremely rare [158,159,161,163].

The contralateral positive nodes are not uncommon in supraglottic lesions where the incidence is around 20% [158,159,163], while in glottic SCC it is less than 5% [159,163]. Controlateral nodes are more frequently encountered when supraglottic lesions are central and when the ipsilateral nodes are positive[158,159,163].

1.4.6.1. DELPHIAN (CRICOTHYROID LYMPH NODE)

The detailed role of the delphian lymph node in the spread of cancer larynx and its effect on the locoregional control is completely unclear, because of the rarity of the studies addressing the issue. The incidence of the positive delphian node in surgically treated cases is less than 10% [164], and when a positive delphian node is present the risk of positive lateral nodes is nearly doubled [53,164,165].

In one study of the specimens of the total laryngectomy including excision of the tissues in this area, positive delphian nodes were detected in 8.7% of cases, none of the cases were T1, and in the majority of the cases anterior subglottis and/or the cricoid cartilage invasion was present [53]. The positivity of these nodes doubled the incidence of both the lateral positive nodes and stomal recurrence in that review[53].

1.4.7. DISTANT METASTASES

Distant metastases from laryngeal SCC are defined as tumour spread to other organ systems. The tumour spread may be of two types: (1) non-lymphatic metastases (hematogenous spread) to other organs, or (2) metastases to lymph nodes other than the regional neck lymph nodes, the most common being mediastinal, abdominal, and axillary node metastases [166].

In one study reporting the distant metastases for 2,550 patients of SCC of the larynx and hypopharynx (75% of the cases was laryngeal SCC) the distant metastases rate was about 4.4% from glottic and 3.6% from supraglottic SCC. Curiously, SCC from the aryepiglottic fold or subglottis metastasize in 16.1% and 14.2%, respectively [166]. In other studies done for all head and neck sites, the incidence of the distant metastatic lesions in glottic carcinoma is usually lower than other head and neck sites (1% and 3.1%), while in supraglottic SCC including laryngeal margin the incidence is (8% and 15%) which is higher than glottic SCC but still lower than hypopharyngeal SCC [167,168].

Distant metastases lesions usually manifest clinically in the first 2 years and in 80% of the cases, they are diagnosed in the first year. The incidence is correlated with an advanced local (T) stage and more obviously with an advanced regional (N) stage. Higher rates of metastases are associated with N2-N3 stages (the risk is increased three folds), larger numbers of pathologically positive nodes, and extracapsular spread within involved lymph nodes [166-168]. 50%-70% of the distant metastatic lesions are pulmonary, either isolated or

accompanied by other sites, followed by the bone and the liver [166-168].

Generally, in the head and neck SCC when the primary locoregional control is achieved this decreases the rate of distant metastases to 5%, instead of 18% if the locoregional control failed [167].

1.4.8. SECOND PRIMARY MALIGNANCY IN LARYNGEAL CARCINOMA

The incidence of second primary malignancy (non recurrent and non metastatic malignant tumour) is ranging from 5.5% up to 28%.[169,170] This large variation might result from large differences in patient selected and follow up periods, but in the large series of laryngeal SCC the range is reduced to 8.2-14% [169-173].

In two large series the incidence of synchronous cases, i.e. cases diagnosed simultaneously with or within 6 months of the cancer larynx diagnosis, is 1.55% [170] and 2.6% [173], while metachronous malignancy, i.e. SCC diagnosed after 6 months from the diagnosis of cancer larynx, is 6.61% [170] and 7.4% [173].

In the different studies the common features of the second primary malignancy in laryngeal SCC were: (1) most of the cases present with one second tumour; (2) the upper aerodigestive tract is the site of the most of the second malignancies, especially the lung which account for 40% of the cases; (3) most of the cases are diagnosed in the first year but patients remain at risk for their lifetime; (4) there is no direct relation between T or N stage at the time of the diagnosis and the incidence of the second localisation; and (5) a slightly higher incidence is observed in supraglottic cases[169-173].

The higher incidence observed with T1-2N0 cases is normal as these cases carry very good prognosis and the patients live for longer periods so they become at high risk to develop a second malignancy, and it was observed that the risk increases when the primary treatment is radiation[169,170,173].

Second primary malignancies has a major impact on the survival of laryngeal SCC, especially in early cases which exhibit a high cure rate and long survival after the primary treatment [169-174].

1.5. PRETREATMENT DIAGNOSIS AND WORK-UP

1.5.1. HISTORY AND GENERAL EVALUATION

1.5.1.1. CANCER LARYNX PATIENT

Typical patients with laryngeal SCC (90% at least) are males, over 45 years, and heavy smokers. Heavy alcohol abuse is the second important risk factor for cancer larynx and is commonly expected in supraglottic carcinoma [115-127].

1.5.1.2. SYMPTOMS

Hoarseness, voice changes, dysphagia, odynophagia, neck mass, dyspnoea, referred otalgia, and aspiration are the symptoms seen in laryngeal carcinoma. As any minor pathology affecting the mucosa of the vocal fold produces hoarseness, glottic carcinomas usually are diagnosed earlier and hoarseness is the most common typical symptom, while hoarseness is a late sign in supraglottic primaries. Supraglottic SCC tend to manifest at first with dysphagia, voice changes odynophagia and finally otalgia, a reason why some of these cases present to the general clinics before reaching the otorhinolaryngologist. In addition, palpable cervical nodes and loss of weight are not uncommon at the time of presentation of supraglottic carcinomas. Subglottic carcinomas are rare and usually present late with stridor and hoarseness, often as an emergency requiring tracheotomy[175,176]. It is recommended that patients with persistence of any of the above symptoms, but

especially hoarseness, for more than 1 month have their larynx evaluated by an otolaryngologist[175,176].

1.5.1.3. MEDICAL HISTORY AND GENERAL EVALUATION

General medical and oncologic history and evaluation are important to decide if the patient can tolerate surgery and the postoperative rehabilitation. Thus, in addition to the routine work the surgeon should give extra-effort to verify the pulmonary status and especially the ability of the patient to tolerate postoperative aspiration. As most of the patients are heavy smokers, pulmonary function test can be used as a routine preoperative evaluation, but the most important is the ability of the patient to walk up 2 flights of stairs without stopping due to shortness of breath and the integrity of the cough reflex [175,177].

Previous head and neck malignancy is not uncommon and requires a detailed review of the previous tumour management including radiotherapy portals and doses and chemotherapy drugs and doses[169-175]. The previous treatment with (chemo)radiation of neck and especially laryngeal tissues has a major impact on early and late tissue healing, complications, and fibrosis [178]. Moreover, the diagnosis of the persistent or recurrent tumour is not easy and the exact assessment of the tumour extension is a challenging process[178,179].

1.5.1.4. SOCIAL HISTORY

Finally, the patient social and economic status is one of the most important factors that affect the choice of the treatment [175,180-184]. Beginning from the specific voice needs of the patient [177], his capability to work and transportation to the centre where the treatment and follow-up will be done [180], his psychological background, and family support, especially in the absence of advanced governmental protocols to support patients with low educational and financial levels [181-183]. In this setting, non compliance with radiotherapy regimens are proved to significantly increase the failure rates of radio(chemo)therapy protocols [175,180-184].

1.5.2. LARYNX AND HEAD AND NECK EXAMINATION

The aims of patient examination are determine as exactly as possible the local and regional extent of the tumour, to obtain a pathological proof and diagnosis of the SCC, as well as the early detection of other synchronous malignancy in the upper aerodigestive tract. The surgeon should be able to predict confidently the three dimension extension of the tumour, allowing for precise treatment selection of organ conservation modalities without local control impairment [175,177,185].

1.5.3. OUTPATIENT (OFFICE) EXAMINATION

Routine otorhinolaryngologic examination includes a careful examination of all the accessible mucosal sites in the upper aerodigestive tract and palpation of the neck, especially the lymph nodes. Complete laryngeal visualisation is mandatory using laryngeal mirrors, rigid telescopes (90^{o} or 70^{o}), and/or flexible nasoendoscopes, with or without local anaesthesia depending on patient toleration. Examination by mirror or rigid scopes provides better colour and image quality, while flexible nasoendoscopy is better tolerated ensuring a greater chance of visualizing the anterior commissure and subglottis [175,177,185].

Whatever the method used, geographic description of the affected subsites and nature of the lesion should be described [175,177,186,187]. A dynamic description of laryngeal movements should be done by vocalisation of sustained (e) at normal (Figure 29) and high pitch, as well as slight cough used to detect active arytenoid mobility in vocal fold fixation cases [175,177]. The description of laryngeal movements should includes comments on vocal fold mobility (mobile, impaired, fixed), and arytenoid mobility (mobile, sluggish, fixed) as two separate items aiming to give a good impression on the depth of the invasion in the muscles at the paraglottic space and the cricoarytenoid joint [177,186,187]. While fixed vocal folds with and without loss of active mobility

(pseudofixation) of the arytenoids is not a contraindication for SCPL, bilateral fixed arytenoids are a contraindication to any organ preservation surgery [175,177].

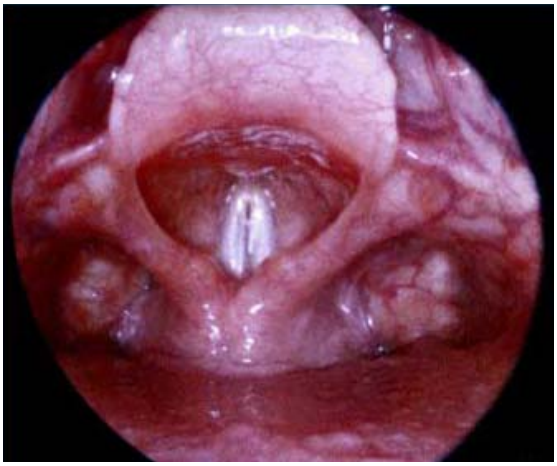


Figure 29: Photo of normal larynx during the vocalization of a sustained (e).

Stroboscopic assessment of the mucosal wave may help to detect early grades of invasion in superficial glottic lesions, although the difference between these grades is highly subjective [188]. The videotaping helps in the documentation and the use of TV monitors facilitates the visualisation to others and helps explanations and discussions with the patient [189].

None of these methods provides a secure evaluation of the depth of invasion such as cartilage infiltration. During this office clinical examination, potential problems with intubation during general anaesthesia should be evaluated [175,190].

1.5.4. DIRECT LARYNGOSCOPY

Endoscopic examination under general anaesthesia in cases of cancer larynx should be done in a systematic, smooth, and professional manner to obtain a precise mapping of the lesion, especially in the difficult parts such as the anterior commissure, posterior glottis, anterior and lateral subglottis, and the ventricles [190,191]. Further goals include directed biopsy(ies) for pathological diagnosis at different areas and possible debulking of the tumour to avoid the tracheotomy which diminishes the chance of local control[175,177,185,190,191].

This could be done by systematic examination of the larynx by 0^{o} and 30^{o} or 70^{o} telescopes at the beginning of the procedure under apnoea without intubation, a step requiring discussion with the anaesthesiologist and precise planning [177,190]. The aims of this examination are to have a panoramic view of the larynx and the surrounding structure in normal position, to obtain an excellent view of posterior commissure, to detect any fine mobility of the arytenoid, and finally the angled telescopes can be passed under the vocal folds to examine the anterior commissure and subglottis [175,177,190].

After that, the patient is intubated and the larynx examined usually with the use of suspension microlaryngoscopy. It is important to choose the appropriate type and size of the laryngoscope to expose the endolarynx [191]. Re-evaluation with the angled telescopes is performed again evaluating precisely the subglottic extension of the tumour [190-193]. External pressure on the cricoid and manipulation of the larynx may be needed [190]. Instruments should be used to palpate the larynx and to test the passive mobility of the arytenoid in order to differentiate between false and true fixation, which is a contraindication to SCPL [175,177,190].

Biopsy must be done in the tumour to ascertain the diagnosis but several directed biopsies may be needed to exclude tumour extensions to areas that contraindicate partial laryngectomy [190,191]. Debulking is

done if needed with the CO_2 laser or a microdebrider [177,190].

At the end, hypoharyngoscopy should be done to evaluate the pyriform sinuses, postcricoid area, valleculae, and the entire hypopharynx. In addition, palpation of the base of tongue, pre-epiglottic space, and the neck should be performed while the patient is under general anaesthesia [177,190].

Data from both the office examination and the direct laryngoscopy are used to obtain a detailed schematic drawing in different plans (Figure 30) with the site of the biopsies indicated and the mobility of the cord and the arytenoid mentioned, allowing for the prediction of the three dimensional extension of the cancer larynx [190].

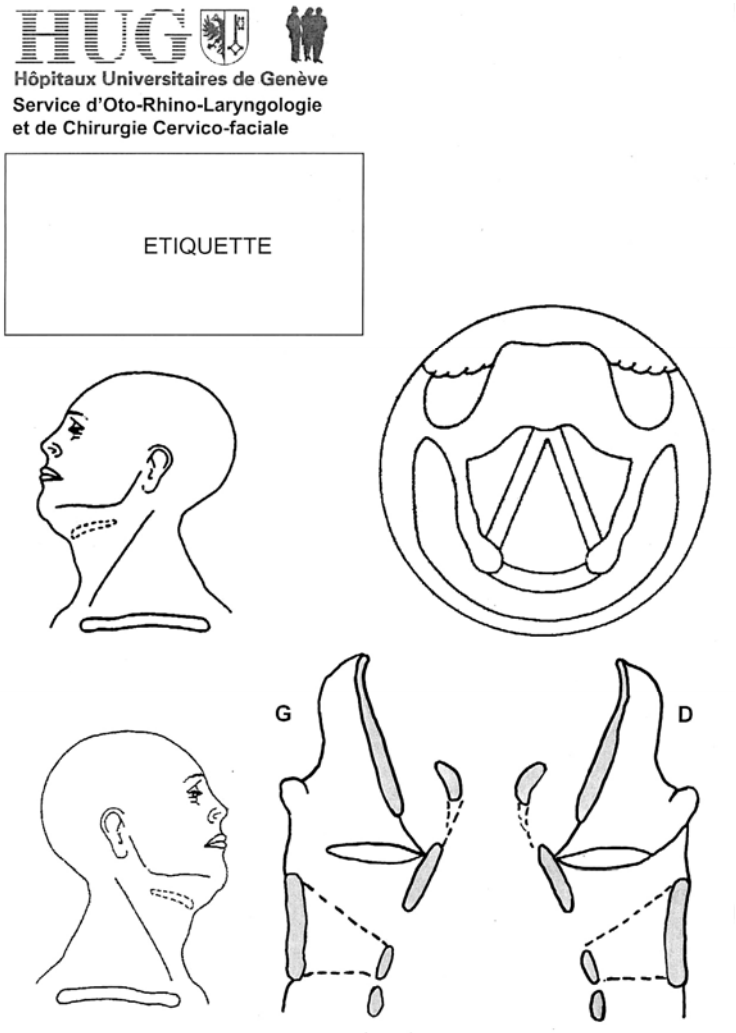


Figure 30: The scheme used for tumour mapping in cancer larynx at the Otorhinolaryngology - head and neck surgery department, University Hospitals of Geneva.

1.5.1. IMAGING

Imaging is highly recommended to complete the pretherapeutic assessment in all cases of cancer larynx

beyond early small vocal fold carcinomas, not reaching the anterior commissure [176].

Images are done to optimise the local tumour mapping by detection of cancer spread in the submucosal spaces (pre-epiglottic, paraglottic) which are usually underevaluated with the clinical tools, as well as to detect and evaluate the degree of cartilaginous invasion [194,195].

In addition imaging is needed to evaluate and stage the metastatic nodal spread and it could be used to obtain the pathological diagnosis of lymph node metastatic involvement by image guided aspiration cytology [176,194-196].

Imaging is also useful in highly advanced cancers to see the degree of carotid involvement and the tumour fixation to the prevertebral fascia [197-199].

Finally, imaging is a commonly used tool in the follow up, especially when non-surgical treatment has been used [176,194,195].

1.5.1.1. WHAT TYPE OF IMAGES TO USE CT VERSUS MRI?

As a role whatever CT or MRI will be used to evaluate the case, the examined field should extend from the skull base down to the superior mediastinum, and the examination should be done with contrast and in different planes beside the usual axial plane [175,194,195].

The MRI has the advantage of delivering slightly better results than modern CT regarding tumour staging and extension, while the CT is quicker, widely available, less coasty, can be done in specific conditions like claustrophobia or in patients with metal devices, and finally less affected by respiratory and deglutition movements or by the intravascular flow. Thus CT is the routine examination in many centers and MRI is kept for specific questions [194-196].

The state-of-the-art CT examination is done using a multidetector CT (MDCT). The images obtained with the patient in the supine position, with neck slightly extended, during quit breathing while he is instructed to refrain from swallowing or coughing. Dynamic maneuvers like prolonged phonation and or modified Valsalva may be used to obtain better visualisation of the tumour in certain areas [195,196].

Slice thickness is about 3mm in the neck and 1-2 mm in the area of the larynx to allow better visualisation and reconstruction [195,196].

1.5.1.2. CANCER SPREAD IN THE SUBMUCOSAL SPACES

Cancer invasion is usually determined in both pre-epiglottic and paraglottic spaces, by presence of altered density or signals replacing the characteristic fat in these spaces, and these changes or masses should enhance with the contrast injection [194-196].

Pre-epiglottic space is ideally examined in the sagittal plane but it can be well seen also in the axial one. Regarding tumour detection in the pre-epiglottic space, MRI reaches 100% sensitivity and 85% specificity, thus it is very accurate in detection and description of the cancer invasion [195,200].

Regarding paraglottic space it can be examined in coronal and axial planes, both CT and MRI carry high sensitivity to exclude invasion (93-95%) but unfortunately they have limited specificity (50-75%), to differentiate the cancer from the surrounding peritumoural reaction, leading to overestimation of the tumour extension in this area [195].

In the CT the shape and volume of the fat in both pre-epiglottic and paraglottic spaces varies and usually they are evaluated together at the lower part of pre-epiglottic space and anterosuperior part of the paraglottic space where it is difficult to separate them[201].

For the involvement of the subglottis, it is easy to evaluate it in the midcoronal plane but also it can be evaluated well in the axial one. Imaging is a good tool to evaluate the deep lateral subglottic extension, especially when the tumour touches the upper border of the cricoid cartilage and the organ preservation surgeries becomes contraindicated, an area which is difficult to evaluate clinically [194,195].

Finally, as the evaluation of tumour extension in the paraglottic space is not very specific, the adjacent sign (tumour adjacent to the thyroid cartilage) is proposed as an independent prognostic factor in patients with glottic carcinoma, and it was correlated with higher failure rates in patients treated with radiotherapy [202].

1.5.1.3. FRAMEWORK (CARTILAGE) INVASION

On CT, ossified cartilage has a high-attenuating cortex and a central low-attenuating medullary space, whereas non-ossified hyaline cartilage and non-ossified fibroelastic cartilage have attenuation values of soft tissue. On MRI, non-ossified hyaline cartilage has an intermediate to low signal intensity on T1-weighted and T2-weighted images. Normal ossified and normal non-ossified hyaline cartilages show no enhancement after intravenous administration of contrast material on CT or MRI [195].

Cartilage invasion is important in selecting the treatment for the individual patient. The vast majority of studies determine the cartilage invasion as a bad prognostic factor when radiotherapy is the treatment selected, in addition to increasing the risk of chondronecrosis [194-196,203,204]. Thyroid or cricoid or bilateral arytenoid cartilage invasion contraindicate all the conservation laryngeal surgery except SCPL, which can be done safely in minimal thyroid and or unilateral arytenoid cartilage invasion [177,194,195]. Moreover SCPL can be done in extensive thyroid cartilage invasion when the tumour does not go out through the outer cortex to the extralaryngeal tissue [205].

The ability of CT to diagnose framework invasion is well demonstrated in comparison studies of CT to histopathological sections of laryngectomy specimens. From these studies, one can conclude that CT has a low sensitivity (46-66%) and a high specificity (88-94%) to diagnose cartilage invasion [204,206-208]. CT generally is not very reliable to detect early cartilage invasion, especially of the thyroid cartilage, however the use of a combination of criteria (lysis, erosion, sclerosis but not in thyroid cartilage, extralaryngeal spread) improves the sensitivity somewhat [204]. The use of sclerosis as a diagnostic sign for thyroid cartilage invasion carries high sensitivity (around 85%)[204,206,207]but on the other hand it has a low specificity (usually around 40%) [204,208], which translate that many cases will be overestimated and overstaged. [204,206,208] The use of erosion and lysis alone in the thyroid cartilage improves much the specificity to 86% but with moderate sensitivity (about65%)[204,208,209].

Similar studies for the MRI concluded that the sensitivity is high, with negative predictive values usually above 90%, allowing to exclude cartilage invasion [195]; with the exception of one study which reported a limited sensitivity of the MRI (67 %)[210]. The specificity of MRI in the diagnosis of early cartilage invasion is limited (under 70%) because many changes, such as reactive inflammation, oedema, fibrosis, and ectopic red bone marrow in the vicinity of the tumour may display similar diagnostic features as cartilage infiltration by tumour [195,204,210,211]. The specificity is even lower (56%) in the thyroid cartilage [204]. Therefore, MRI has a high sensitivity to exclude early cartilage invasion, but it tends to overestimate and overstage the tumour, especially regarding thyroid cartilage invasion [195,204,210,211].

Recently new promising criteria to assess intensity changes on MRI were proposed to improve the specificity of the MRI in detecting cartilage invasion [211], and the results are promising especially for the thyroid cartilage (the specificity increases from 54% to 75%). But widespread practical application of these criteria is still unclear because of the high experience in laryngeal MRI knowledge needed to use these criteria [212-214].

1.5.1.4. ANTERIOR AND POSTERIOR COMMISSURE

Extension of the carcinoma to the anterior commissure affects staging and treatment planning in cancer

larynx, making determination of cancer extension and the degree of the involvement at this site extremely important [194,215].

From the radiological point of view, the anterior commissure level is identified in the axial plane at the same level as the vocal process of arytenoids and as the anterior confluence of the two vocalis muscles. In this area and immediately below it (the beginning of the anterior subglottis), the mucosa is nearly in direct contact with the cartilage and the average thickness during vocal fold abduction is 1-2 mm [216,217]. Any thickness more than 2 mm should be suspicious of invasion by cancer [216,217].

Recently, another method is introduced to evaluate the cancer extension at the anterior commissure in both axial and mid sagittal views: the examiners used helicoidal CT 1mm slice thickness and identified the anterior commissure by the methods described above [218]. They defined the involvement by what they called "gross radiologic anterior commissure involvement" (GRACI) recognized by the following: (1) in the horizontal plane, presence of anterior commissure thickening greater than 1.0 mm detected in at least two contiguous tomographic slices; and/or (2) in the vertical plane on sagittal reconstruction, presence of anterior commissure tumor volume growing superiorly into the preepiglottic space, anteriorly into the thyroid cartilage, or inferiorly into the cricoid cartilage [218].

Cancer extension to the mucosa of the posterior commissure is a rare finding [144,146]. As the mucosa is adherent to the cartilage at this site, detection of tissue thickness is easy by the imaging tools, and the diagnosis of cancer at this site contraindicate all the partial surgeries, including SCPL [194].

1.5.1.5. METASTATIC CERVICAL LYMPH NODES

Clinical palpation of the neck carries accuracy around 65% to detect metastatic lymph node[219,220], but has a low sensitivity in N0 necks [219], a reason why imaging is now used routinely in head and neck cancer evaluation [194]. Since imaging is often necessary for the primary lesion in cancer larynx, detection of the metastatic nodes is performed in the same setting with the radiological evaluation of the local lesion [149,220]. CT examination is more accurate than palpation reaching an accuracy in the range of80%-90% [219,220].

MRI also has the same or slightly higher accuracy and a higher sensitivity to detect early lymph node metastasis. Ultrasound is a cheaper and very sensitive examination but carries a low specificity [185,194,219,220]. The main advantage of ultrasound is the frequently combined fine needle aspiration cytology of suspected nodes, allowing for an excellent specificity and accuracy (usually more than 90%)[219,220].

Criteria that suggest metastatic involvement of a lymph node on all imaging modalities include enlarged size, abnormal shape, necrosis, enhancement, and extracapsular spread [185,194,219,220].

1.5.1.6. METASTATIC WORK-UP

Chest X-ray, examination of the mucosa of the upper aerodigestive tract during panendoscopy, and liver enzymes constitute routine steps in the pretreatment evaluation of cancer larynx in many centres[175,176,185].

The CT of the chest is usually kept for the advanced cases with positive large nodes or when abnormalities are detected by chest X-ray. In some centers, chest CT is used routinely to screen the lungs and is also viewed as a substitute for the routine panendoscopy, a debatable point of view [175,176]. Although panendoscopy has a low rate of detection of other non-clinical lesions, it is justified by many because lesions are diagnosed at an early stage and the procedure is excellent opportunity for residents to acquire training and knowledge in the endoscopy of the upper aerodigestive tract [221,222].

The role of positron emission tomography and the fused modality positron emission tomography/computed tomography is still under investigation, but up till now it is mainly indicated for diagnosing and staging of the patients with primary metastasis and recurrent unclear cases when both

endoscopy and routine images fail to clarify the diagnosis [175,179].

1.5.2. STAGING

Since survival of cancer larynx greatly depends of the size and extension of the tumour at the time of the diagnosis, efforts were directed to classify the cancer into stages. Since the development of the system of (Tumor (T), Node (N), and Metastasis (M) system) in the 1940s by Pierre Denoix of France, the International Union Against Cancer (UICC) tried to improve the accuracy of the staging system. A few years later, the American Joint Committee on Cancer (AJCC) sharing this goal of improving the accuracy of the TNM system joined forces with the UICC in the unique TNM system we presently have[223-225]. The TNM system has been standardised since the fourth edition, allowing for a worldwide approach and a common language in cancer care. Its objectives are to:

- to aid clinicians and investigators in planning of the treatment,
- to assess the prognosis,
- to stratify the patients for therapeutic studies,
- to evaluate the results of treatment,
- to contribute to the continuing investigation of human cancer,
- to facilitate communication and provide a formwork for discussion with cancer patient,
- to encourage more accurate recording of clinical assessment.[223-225]

Currently the sixth edition (2002) [226,227] of the TNM system is used to classify the cancer, for the carcinoma of the larynx. Clinical TNM (cTNM) is obtained by using the following modalities:

- T categories: Physical examination, laryngoscopy, and imaging.
- N categories: Physical examination and imaging.
- M categories: Physical examination and imaging.

The TNM system is based on anatomical sites and subsites which for the larynx include the following [226-230]:

1.5.2.1. SUPRAGLOTTIS

The supraglottis is itself divided into the following subsites:

- Epilarynx (including marginal zone);
  - Suprahyoid epiglottis (including tip, lingual surface, and laryngeal surface),
  - Aryepiglottic fold, laryngeal aspect,
  - Arytenoids,
- Supraglottis excluding epilarynx;
  - Infrahyoid epiglottis.
  - Ventricular bands (false cords).

1.5.2.2. GLOTTIS

The glottis is itself divided into the following subsites:

- Vocal cords.
- Anterior commissure.
- Posterior commissure.

1.5.2.3. SUBGLOTTIS

As a trial to clarify the borders:

- The limit between the glottis and supraglottis is defined according to Kleinsasser [228], which is a plane running horizontally through the opening of the ventricle, posteriorly over the vocal process of the arytenoid cartilage and then rising between the cuneiform and the corniculate cartilage to end over the upper edge of the posterior commissure.
- The limit between the glottis and subglottis is a horizontal plane 1 cm inferior to the level of the upper surface of the vocal cords[226-230].

1.5.2.4. THE SIXTH EDITION OF TNM CLASSIFICATION FOR CANCER LARYNX 226,227

- *T - PRIMARY TUMOUR*

TX: Primary tumour cannot be assessed.

T0: No evidence of primary tumour.

Tis: Carcinoma in situ.

Supraglottis:

T1: Tumour limited to one subsite of supraglottis with normal vocal cord mobility.

T2: Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, or medial wall of piriform sinus) without fixation of the larynx.

T3: Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).

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

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

Glottis:

T1: Tumour limited to the vocal cord(s), which 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 the larynx with vocal cord fixation and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).

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

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

Subglottis:

T1: Tumour limited to the subglottis.

T2: Tumour extends to vocal cord(s) with normal or impaired mobility.

T3: Tumour limited to larynx with vocal cord fixation.

T4a: Tumour invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep (extrinsic) muscles of the tongue, strap muscles, thyroid, or oesophagus).

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

- *N - REGIONAL LYMPH NODES*

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in a single ipsilateral lymph node 3 cm or smaller in greatest dimension.

N2: Metastasis in a single ipsilateral lymph node larger than 3 cm but 6 cm or smaller in greatest dimension, or in multiple ipsilateral lymph nodes 6 cm or smaller in greatest dimension, or in bilateral or contralateral lymph nodes 6 cm or smaller in greatest dimension.

N2a: Metastasis in a single ipsilateral lymph node larger than 3 cm but 6 cm or smaller in greatest dimension.

N2b: Metastasis in multiple ipsilateral lymph nodes 6 cm or smaller in greatest dimension.

N2c: Metastasis in bilateral or contralateral lymph nodes 6 cm or smaller in greatest dimension.

N3: Metastasis in a lymph node larger than 6 cm in greatest dimension.

Midline nodes are considered homolateral nodes.

- *M – DISTANT METASTASIS*

MX: Distant metastasis cannot be assessed.

M0: No distant metastasis.

M1: Distant metastasis.

- *NOTES FOR THE PATHOLOGICAL TNM*

For pathological classification (pTNM), concerning impaired mobility or fixation of vocal cords the information from the clinical T is used for the pathologic T.

For (pN), in pN0 histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes, and histological examination of a radical or modified radical neck dissection specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node.

Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.

Cases with micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of "(mi)", e.g., pN1(mi) or pN2(mi).

Isolated tumour cells (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest dimension that are usually detected by immunohistochemistry or molecular methods, but which may be verified with H and E stains and they have 5 subcategories.

Histopathological grading of the primary tumour is determined as:

- GX: Grade of differentiation cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated.

For residual tumours (rT) classification, the following are used:

- RX: Presence of residual tumour cannot be assessed.
- R0: No residual tumour.
- R1: Microscopic residual tumour.
- R2: Macroscopic residual tumour.

- *STAGE GROUPING*

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1,T2,T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Table 3: Global stage grouping

1.5.2.5. PROSPECTIVE CHANGES IN THE TNM STAGING SYSTEM:

Although the TNM anatomical system is the best available tool in cancer larynx staging till now, it is criticized in several aspects, especially the lacking of a definite definition for some anatomical subsites [225,228,231,232], and its shortage when choosing in between the conservation laryngeal surgeries like SCPL [177].

1.6. OVERVIEW OF TREATMENT OF CANCER LARYNX WITH EMPHASIS ON THE NON-SURGICAL TREATMENT

1.6.1. HISTORICAL BACKGROUND

One hundred years ago Doctor George Brewer stated in his article (the operative treatment of cancer of the larynx); "four methods of radical surgical treatment of cancer larynx have been proposed. First, intralaryngeal removal; secondly, thyrotomy, allowing exposure of the diseased area and removal of the lesion with subsequent closure of the laryngeal cavity; thirdly, partial laryngectomy; and fourthly, total laryngectomy" [233].

The introduction of the indirect laryngoscopic examination by Manuel Garcia in 1855 [234] and the detailed anatomical description of the larynx by Van Luschka in 1871 helped much to develop the different approaches to cancer larynx treatment [235].

Total laryngectomy was first performed on human cadaver by Watson of Edinburgh in 1866 [233]. Then Theodore Billroth of Vienna on the 31/12/1873 performed the first total laryngectomy for laryngeal cancer, but his patient died 7 months later from a fatal recurrence [233]. This is followed by several trials by Heine, Maas, Czerny, and others, but the first oncologically successful laryngectomy was that of Enrico Bottini of Turin, whose patient lived six years after the surgery [233]. In the 19th century, total laryngectomy was associated with very high mortality in the different reports (range 10-50%) and an extremely high local recurrence rate (80-90 %)[233].

In 1908, Gluck reported 128 total laryngectomies among which 20 patients were alive and free from recurrence at the end of three years [233]. Actually Gluck and his school, especially Sorensen, made two important steps to standardise the technique by performing the surgery as one stage and by the routine creation of a tracheostoma[236].

The concept of a localised excision of the tumour through a laryngofissure or thyrotomy was described prior to that of total laryngectomy. It was first performed by Brauers in 1833. Von Bruns in 1878, forty-five years later, reported 19 cases done by this approach but all cases died from recurrence within the first year. Thus, this technique was not recommended until good results were reported by Butlin and Semon in the beginning of the 20th century [233], and by George Stewart in 1915 [237].

The open partial laryngectomy was also introduced early. Trotter described a partial pharyngolaryngectomy for epilaryngeal tumours in 1913 [235]. The horizontal supraglottic, supracricoid, and reconstructive laryngectomies were born and developed in Europe and south America during and after the second world war [235]. Both supraglottic and supracricoid laryngectomy are considered as a major advance in the field of cancer larynx treatment, and they were popularised and performed widely in Europe (especially southern Europe) before the US and UK [235]. The concept of vertical surgery for the early unilateral glottic carcinoma reported successfully by George Monks in 1895 (he did a hemilaryngeal excision but with permanent tracheotomy) [235,238]. But actually the modern vertical surgery for cancer larynx was initiated by Leroux-Robert in France and Som in t USA [235]. Generally, the three decades after the Second World War were the era for the development of open partial laryngeal surgeries[235].

The concept of the transoral resection of the cancer larynx was first reported in 1886, but the real development of the endoscopic cancer larynx resection belongs to both Kleinsasser and Jako in the middle of the 20th century, following the development of the operating microscope[235]. In 1972 Jako and Strong and Jako presented the use of the CO_2 laser, but the actual development of this surgery was mainly done in the 1980s and 1990s in the European countries, especially in Germany by Wolfgang Steiner and his colleges[235].

The history of radiation therapy for cancer larynx follows the discovery of the X-rays in 1895 and early trials to treat cancer larynx in the beginning of the 20th century. The early trials were done by using the curietherapy technique, followed by teletherapy, which was developed later on. The real advance in modern radiotherapy was made during the same period that saw of the development of open partial laryngectomies (1950s-1970s) [239]. In 1961, and 1975 Lederman the famous British radiotherapist recommended the use of the radiotherapy as a primary treatment for early and moderate laryngeal carcinomas especially in N0 cases. He ascertained that better functional results were achieved with radiotherapy in comparison to total laryngectomy, while the oncologic results were comparable when the laryngectomies are done to the failed cases [240,241].

1.6.2. CURATIVE TREATMENT MODALITIES IN THE LAST 30 YEARS

Total laryngectomy remained the standard curative treatment for cancer larynx for about one hundred years [235], until the successful development of surgical and non-surgical laryngeal preservation protocols[235,242]. From the early 1990s until now, many authors [235,242-244] described this period as a new era in the treatment of cancer larynx. Their description is based on three landmark changes in the treatment options:

- The introduction of new non-surgical (chemo)radiation protocols, which can be used as an alternative to total laryngectomy in many cases [235,242-244].
- The maturation and dissemination of the supracricoid laryngectomy technique, which added a new option to treat the intermediate and selected advanced cases of cancer larynx, with conservation of the laryngeal functions [235,242-244].
- The development and advances in the endoscopic CO_2 laser treatment which added a new approach for the treatment protocols [235,242-244]. [235,242-244]

So it is now possible to treat most of the cases of the laryngeal carcinoma with more than one laryngeal preservation modality, reserving total laryngectomy to a minority of primary cases and, more commonly, as a salvage surgery after (chemo)radiation failure [235,242-244].

1.6.2.1. CURATIVE TREATMENT OF EARLY GLOTTIC CARCINOMA

Early invasive glottic carcinomas (T1-T2 N0) represent a very important group in the treatment of head and neck cancer since:

- It accounts for a large portion of laryngeal cancer cases [125,127,141,142].
- The risk of nodal disease is minimal as only 8 % of glottic carcinomas present with clinically positive lymph nodes [142], and this usually occurs in advanced T stages [245,246].
- Distant metastasis at the time of presentation and after achieving local control is very rare, with an incidence of about 2% [166,167].

Thus, the treatment of the early glottic carcinoma is directed to local control using one treatment modality, while the management of neck is not necessary, and the aim of the treatment is to cure the patient with the preservation of a high level of laryngeal functions, without decreasing his long-term survival [247,248].

- *RADIOTHERAPY*

Radiotherapy is widely used in the management of the early invasive glottic carcinoma, with many authors [248-255] reporting 5 years local control rates around 90% for T1 lesions and 70% for T2 lesions. In failure cases, salvage surgery further increases the 5 years disease-specific survival to 95% for T1 and to 80% for T2 lesions [248-255]. In T2 carcinomas, the published results show wide variations in the survival and laryngeal preservation rates [248-255]. In T1 lesions, the 5 years disease-specific survival with laryngeal preservation is usually above 90% and salvage surgery is possible in most cases, usually in the form of partial laryngectomy, while in T2 lesions the salvage procedure is usually a total laryngectomy and it is possible only in approximately half of the failures [248-255].

The technical details in the radiotherapy protocols also show a wide variability [248-255], but generally for T1 lesions the radiation field is a small one (5×5 cm) and is formed of two laterally opposed fields, while for T2 lesions the fields are larger and depend on the tumour extension [248,250-252,255,256]. Cobalt 60 and 4 to 6 megavoltage photons can achieve a similar therapeutic effect [248,250-252,255,256], but the 6 megavoltage photons may deliver lower doses in the anteriorly located tumours specially in thin patients.[255] The doses administered also vary widely, from 56Gy up to 78Gy [248,250-252,255], but several authors recommended a 66Gy dose for the T1 lesions, observing that doses below 60Gy increase the local failure rate and doses above 66Gy add no benefit [248-250,252-256]. For T2 cases, it is recommended to increase the dose up to 70 Gy to the tumour site [248-250,255,257].

The radiotherapy scheme in T1 lesions is almost always a monofractionation with a daily dose of 1.8-2.2 Gy. It is also recommended not to lower the daily dose below 1.8 Gy [248-257], while some authors reported a mild benefit from increasing the dose up to 2.25Gy per day [256]. The treatment is done usually 5 days per week over a total period of 40-60 days and it is better to deliver the total dose over a period of 6 weeks or less [248-257].

T2 lesions in the last two decades are commonly treated by new schemes to improve the local control, either by acceleration of the treatment (delivering the same dose over a shorter time) or by hyperfractionation of the daily dose (delivering several smaller doses during the same day), for a larger total dose (usually two doses of 1.2Gy with 6 hours treatment intervals every treatment day). In some centers, the altered combined scheme combining both is used, usually it is bifractionated and accelerated with a high dose (70Gy or above) over a short period [250,257,258]. Although the altered schemes increase the tissue toxicity especially during treatment (acute toxicity), they are widely used nowadays in most T2 and in all advanced laryngeal carcinomas to improve the local control rate [255]. The computed tomography (CT) based planning is recommended in all the lesions to improve the assessment and distribution of the dose [255].

Intensity modulated radiotherapy (IMRT) which enables a more effective distribution of the dose to the tumour with sparing of the normal structures (especially the salivary glands), is not widely recommended in glottic carcinoma until now, because the submandibular glands are not included in the radiation field and more locoregional recurrences were observed [255]. In addition, this technique is quite expensive and not yet supported by randomised trials to justify its routine use in the larynx [255].

Several factors are claimed to decrease the local control rate obtained by radiation therapy in early glottic carcinoma: anterior commissure involvement [248,251-255,257], impairment of the vocal fold mobility [248,252-255], involvement of many anatomical subsites [252], and finally the subglottic involvement [248,252-255,257]. The tumour extension to the anterior commissure is a point of major debate, with many authors describing it as a bad prognostic factor which reduces local control and survival rates [248,251-255,257], while other authors refused this hypothesis [250,256].

- *TRANSORAL ENDOSCOPIC EXCISION*

In the last two decades, endoscopic microsurgical resection of the early glottic carcinomas by using the CO_2 laser has gained popularity and it has become a widely performed procedure [259-266]. For the T1 lesions, the

5 years local control rate in different large series is ranging between 85%-100%, depending on the lesion extension. The reported 5 years disease-specific survival and laryngeal preservation rates are over 95% in all the series [248,259-266]. In the T2 lesions, the 5 years local control rate is ranging between 66% and 85%, also depending on the lesion extension in addition to the mobility status of the vocal cord. The 5-year disease-specific survival and the laryngeal preservation rates are about 85% [248,259-266].

These excellent survival and laryngeal preservation results reported by this line of treatment reflects that most of the recurrences can be treated successfully and the need for total laryngectomy is minimal, since beginning of the treatment with the microlaryngeal laser resection leaves all other treatment options open in the rare case of local failure, being radiotherapy, endoscopic re-resection, or partial open laryngectomy [248,259,261,265]. Besides that, the laser resection is superior to both radiotherapy and open partial laryngectomies regarding the postoperative morbidity and the total cost [248,259,264,265,267].

The main limitation of the endoscopic laser treatment is to obtain an adequate exposure of the lesion especially at the anterior commissure which can be overcome in most of the cases by the proper positioning of the patient, selection of the appropriate laryngoscope, and finally by the manipulation of the larynx [261,263,265-267]. Another limitation is to obtain a definite negative pathological result regarding the margins which is a real problem in some cases, especially when the piecemeal resection is used. This can be handled by a re-resection with frozen section examination or by meticulous observation of the patient and doing a second look endoscopy with the possibility of re-resection if needed [265,266,268,269].

The treatment of the early glottic carcinomas (especially T1) by the CO_2 laser is now considered as an established procedure, thus trials were conducted in the last 10 years to standardize the types of the resection into several types of cordectomies (I-VI) [270,271]as the following: type I: subepithelial cordectomy: limited to the superficial layer of the lamina propria, type II: subligamental cordectomy: limited to the mucosa, Reinke's space, the vocal ligament, and the very superficial part of the vocal muscle, type III: transmuscular cordectomy: limited to the medial portion of the vocal muscle, type IV: total cordectomy: involving the entire vocal cord together with the inner perichondrium, type V: extended cordectomy (a; extended to the contralateral vocal cord , b; extended to the arytenoid cartilage , c; extended to the supraglottic region and d; extended to the subglottic region) [270]. Recently type VI is proposed and it involves anterior bilateral cordectomy and anterior commissurectomy [271]. This standardisation helps also in the indication of the treatment e.g. in T1 mid-cordal lesions the excision biopsy techniques is usually done by using type II, or III cordectomies, while in the big T1a lesions, T1b and T2 the cordectomies types IV, V, and VI are used and the resection is usually done by using the piecemeal technique [261,264,265,270,271].

The voice quality after the laser resection of early glottic carcinoma is generally believed to be inferior to that of radiation therapy and better than that of open partial surgery, but generally the analysis of voice parameters is comparable to radiotherapy [248,259,264,265,272]. In T1a midcordal lesions the voice is similar to radiation with no or minimal difference [272,273]. But, in other early glottic lesions vocal results depend on the extension of the resection, with more pronounced dysphonia and more breathy voice with type IV and V cordectomies, bilateral resection of the anterior parts of both vocal folds (e.g. when the anterior commissure area is involved) [264,271,274-276]. In these extensive resections, especially at the anterior part, some authors suggested the reconstruction of the completely resected vocal fold to improve the phonatory functions [271,275,276].

Although anterior commissure and subglottic extensions do not decrease much the local control and survival rates contrary to the radiation therapy, these extensions tend to have worse success rates, especially in the local control of the tumour [248,259,265,266,277]. Because of all these shortcomings, some authors do not encourage the endoscopic resections of the lesions showing extensive anterior commissure involvement and / or subglottic extension [265].

Finally, it is known that the oncologic results after endoscopic CO_2 laser surgery are affected by the

learning curve and the personal skills of the surgeon [248,265,278], as well as the experience for the entire operative team[278].

- *OPEN PARTIAL SURGERY*

Vertical partial laryngectomies were developed mainly in the three decades following the Second World War by the efforts Som and co-worker in the US and Leroux-Robert in Europe, although numerous techniques have been described [279-281]. Initially, these procedures were adopted mainly as a treatment option for T1a vocal cord carcinoma, followed by different extensions to address limited contralateral vocal cord extension, and impaired vocal fold mobility, very limited subglottic extension. Nowadays, vertical procedures are most often indicated for T1 and T2 glottic lesions, with a large number of variations from the simple unilateral cordectomy up to the extended hemilaryngectomy (near-total laryngectomy) with epiglottic reconstruction. This marked heterogeneity in the resection and reconstruction techniques make the extraction of the exact results for every variant a difficult process [177,248,279-282].

Nevertheless, in general all these procedures [177,279-284],share the following common principles:

- Vertical thyrotomy (laryngofissure) at the midline or paramedian.
- Surgical removal of thyroid cartilage, from a small strip (except the simple cordectomy) up to the entire homolateral alae.
- Complete removal of at least one vocal cord, with partial removal of the paraglottic space.
- Bilateral sparing of the arytenoids, however the vocal process is sometimes removed on the affected side (total arytenoid resection is extremely rarely performed).
- Reconstruction is obligatory after the resection[177,279-284].

The most frequently performed variants during the last 30 years are: the frontolateral laryngectomy, the classical hemilaryngectomy, and the cordectomy; the reconstruction of the gap after vocal fold resection is commonly done by using either the false vocal fold, an imbrication laryngoplasty, or less commonly the infrahyoid muscles; prior to thyroid cartilage closure with primary sutures [177,281,283-285]. The extended frontolateral laryngectomy (near-total laryngectomy) with epiglottic reconstruction is a variant that includes a more wide removal of the anterior third of the thyroid cartilage with downward mobilisation of the epiglottis to be used in the reconstruction [177,281-284].

The indications of all vertical laryngectomies are T1 and T2 glottic carcinomas [177,248,279-286]. The unilateral cordectomy (glottectomy) and the classical hemilaryngectomy are almost exclusively used in T1a lesions [281,283], the frontolateral is done when the lesion reaches the anterior commissure in T1a lesions, T1b lesions and in small T2 lesions [281,285,286], while the extended resection is preferred for extensive lesions at the anterior commissure or in big T2 lesions or in T2 with impaired vocal fold mobility [282,284]. All the open vertical procedures share many oncologic and general contraindications making their clinical use not common [177,279-286]. In addition, the recent advances in endoscopic laser resection offering comparable results with less morbidity further limit their use, as can be deduced from the low number of patients included in the recent publications [279,286].

In the non extended vertical laryngectomies done for T1 lesions the reported 5 year local control rate is about 90 %, with a 5 years disease specific survival ranging about 80%-90%. Anterior commissure involvement significantly increases the risk of local failure from about 5% up to 25% [281,285,286]. While in T2 lesions (usually with minimal extensions and mild impairment of the cord mobility) the local control rates are around 70% and the 5 years disease specific survival ranging between 67%-80%. Impairment of cord mobility significantly decreases the control rate [281,282,285,286], The worst results being reported for T2 lesions with both anterior

commissure involvement and vocal fold mobility impairment (5 years local failure rate about 45%) [281,285,286].

The oncologic results of the extended hemilaryngectomy (near-total laryngectomy) with epiglottic reconstruction show a 5 year local control rate ranging between 83-97% and they are not affected by anterior commissure involvement and T2 lesions, while impaired cord mobility and subglottic extension(>5mm) increase the risk of failure. But these better results are obtained on the expense of prolonged postoperative rehabilitation such as the tracheotomy needed usually for about 10 days, and the nasogastric feeding tube for about 2 weeks, beside that long hospitalisation and phoniatric rehabilitation are essential [282,284].

The SCPL-CHEP is another option for the treatment of the early glottic carcinomas. It is usually indicated in more risky lesions such as T1b and T2 with important anterior commissure involvement (the reported 5 years local control rate is about 98% with 100% 5 years disease specific survival) [287,288], and T2 with impaired mobility (the 5 years local control and disease specific survival rates are 95% or more) [288,289]. So, as the SCPL achieves better control rates and avoid the risk of pathological surprises, it is preferred by some authors to vertical procedures [177,288]. Another reason to prefer SCPL is the standardized reconstruction if compared to the vertical procedure, which remains quite variable after the vertical procedures [177].

While the morbidity after the open surgical approaches depends mainly on the procedure [248], in the SCPL, the frontolateral laryngectomy, and the epiglottic reconstruction techniques the long term functional results and morbidity are more or less similar [282,284,288].

1.6.2.2. CURATIVE TREATMENT FOR ADVANCED GLOTTIC CARCINOMA

According to the TNM system, advanced glottic carcinoma treated with curative intent include: T3-4N0 lesions and any T with N positive nodes, with no distant metastases (M0). While "respectable lesions" is the term usually given to stages III and IV-A excluding the T4b and / or N3 lesions (stage IV-B) in which the cancer usually manifest with a huge tumour volume and is commonly incurable[226,230].

Among T3-4 glottic carcinomas, the incidence of nodal metastases is usually around 20%, and the lymphatic spread is often to the ipsilateral levels II and III, a pattern that is the least aggressive among the upper aerodigestive SCC [142,158-163]. In addition, the distant metastatic incidence in glottic carcinomas is low (1%-3%) and mainly related to the advanced nodal disease [167,168].

Therefore, despite an advanced stage, the treatment of advanced glottic carcinoma should be curable in most cases and it should include both the larynx and the neck. Classically the treatment plane was total laryngectomy with or without neck dissection followed by postoperative radiotherapy in many cases, but recently it became possible in many cases to preserve the larynx without an impairment of the survival rates. Two main interventions are identified by many authors to allow this change in the treatment strategy: the SCPL and the chemoradiation organ preservation protocols [235,242-244,290].

- *THE NON-SURGICAL TREATMENT*

After the establishment of radiotherapy as a treatment modality for the early cancer larynx, several trials accessed the treatment of advanced glottic carcinomas with exclusive radiotherapy: these trials were done mainly in the 1970s and 1980s and were mainly targeting selected T3 lesions (fixed vocal fold) which are unilateral and low volume (e.g. not obstructing the airway). The results of these trials were not so encouraging since the 5 year local control rates reported were about 40% and total laryngectomy was the routine salvage surgery in case of failure with a 5 year disease specific survival of 50%-70%. Despite that, these studies demonstrated that the larynx could be preserved in some advanced glottic carcinomas using non surgical modalities [244,249,291-295]. In these trials, only few T4 lesions were included and the local failure rate was high (about 75%)[249,291,292].

Mendenhall in 1998, reported an encouraging 5 years local control rate of 63% for T3 glottic lesions and

he recommended the use of the altered radiotherapy scheme to increase the control rate. In addition, his series also presented better results in T4 lesions (radiological,) although the number of cases was very small. Among T3 lesions the incidence of severe complications requiring tracheotomy or laryngectomy was 7 % and the incidence of severe complications after salvage total laryngectomy was 33% [296].

The usual conventional scheme used in the treatment of advanced cancer larynx often delivers for both the primary tumour and the positive neck nodes a dose of 70 Gy by using a daily monofraction of 2-Gy, 5 times per week, over a period of 7 weeks, whereas the non involved nodes at moderate and low risk of disease receive 60Gy and 50 Gy respectively, commonly by a shrinking field technique. If the treatment of the involved nodes can increase the risk of complications at the spinal cord level, electrons can be used instead of photons as they have low penetration power [255].

In the last two decades, new radiotherapy trials were introduced to improve the local control for the advanced laryngeal lesions [297-301]. In 1997, a randomised multicenter trial investigated a continuous hyperfractionated accelerated radiotherapy (CHART) scheme (three 1.5 Gy daily doses over 12 days) with a reduction of the total dose (54Gy) versus conventional radiotherapy (66 Gy) in 918 cases of head and neck cancer. Among the included cases, the T1 lesions were less than 4% and the T3-4 lesions represented about 50% of the cases, beside that 46% were laryngeal cases. This trial showed a trend but not a significant improvement in the short term local control rate, no change regarding the survival rates, and an elevated acute toxicity. However the subgroup analysis suggested that T3-4 laryngeal carcinomas could be better controlled by this accelerated scheme [297]. Similarly, the randomised trials 6 & 7 of the Danish Head and Neck Cancer Group (DAHANCA) compared a moderately accelerated radiation protocol (conventional scheme plus an additional dose given during the week-end or as an extra dose with 6 hours interval, for a total of 6 doses per week) versus the conventional radiotherapy in head and neck carcinomas with similar total dose in both arms. The trial contained 690 cases of glottic SCC but only 30% of the studied cases were locally advanced carcinomas and the anatomical and stage details of each group were not mentioned. The 5-years loco-regional control for all groups was significantly improved with the use of the accelerated radiotherapy (70 vs. 60%) as well as the disease specific survival, at the expense of a significant increase in acute toxicity [298]. The radiation therapy oncology group (RTOG) presented in 2000 the results of a randomised trial including three schemes of altered radiation versus the conventional radiotherapy (70Gy over 50 days) in head and neck carcinoma. More than 60 % of the cases were locally advanced, and the results showed about 8% (54.5 vs. 46%) and 6% improvements in the 2 year local-regional control and disease-specific survival respectively, but these improvements were only with a hyperfractionated scheme delivering a total extra dose of 81.6 Gy over 50 days or with an accelerated scheme with concomitant boost to the tumour site delivering 72 Gy over 43 days. In addition, both the acute and late toxicity were increased, both in incidence and severity. In this trial, the number of the laryngeal cases was limited and most cases were supraglottic carcinomas [299]. Several other trials studied the hyperfractionated or accelerated radiotherapy but unfortunately with a broad heterogeneity in the radiation protocols and the tumour sites (e.g. the trials were not exclusive for glottis or even the larynx) [300,301]. Overall from the review of these studies, it is possible to conclude to a significant improvement in the local control rate and some improvement in the disease specific survival by using a hyperfractionated scheme with an increase in total dose or by delivering the same dose as conventional protocols by an accelerated scheme [300,301]. A significant increase in the radiation morbidity is usually observed and few details are mentioned about the functional evaluation of the preserved larynx or the detailed anatomical extension of cancer larynx [297-301].

During the same period, parallel efforts were exploring the role of the chemotherapy in the advanced laryngeal carcinoma [302-306]. In 1991, the Veterans Affairs (VA) landmark study opened a new gate for the treatment of advanced cancer larynx: the study compared the induction chemotherapy (two cycles of cisplatin and 5-fluorouracil) followed by conventional radiotherapy with a total dose of 66-76 Gy in one arm versus total laryngectomy with post operative radiotherapy in the other arm. Each group involved 166 patients with a mean age of 62 years and a good performance status. For each group, glottic cases accounted for 36% of the

patients, nearly 56% of the cases were N0, vocal cord fixation was observed in 58%, and cartilage invasion incidence was 9%. T1-2 lesions were 9.5%, T3 lesions were 65%, T4 lesions were 25.5% and finally all cases were respectable laryngeal SCC and the distribution in both groups were similar. In the chemoradiotherapy group, a salvage total laryngectomy was performed for progressive tumours (no or poor response to chemotherapy) in 30 cases and as treatment failure in 29 cases. Up to the time of the analysis (about 40 months from the randomisation) in the chemoradiotherapy group 65 deaths (39%) were reported with 42 cases due to cancer and 6 cases of unknown cause, while in the surgical group 58 deaths (35%) were reported with 38 cases due to cancer and 2 cases of unknown cause. The failure rates (local, regional, distant, and overall) were (20:4, 14:5, 18:29, and 52:42) for the chemoradiotherapy: surgery groups, respectively. The salvage total laryngectomy was needed in 36% and there was 10% increase in the incidence (but did not reach a statistical significance) usually when comparing (glottic: supraglottic, fixed cord: mobile cord, cartilage invasion: free cartilage). No details were mentioned about the detailed anatomical subsites, methods for evaluation of cartilage invasion or staging (e.g. clinical versus radiological). The short term overall survivals for both groups were comparable 68 % but at the time of the study writing (about 40 months), for the chemoradiotherapy group; 101(61%) were alive with no evidence of disease and among these patients 36(22%) had total laryngectomies, while 65(39%) retained their larynges, for an overall survival with preserved larynx rate of 39% at the time of publication. No data were mentioned about the rates and durations of tracheotomy, feeding tubes, feeding habits, voice parameters, and the morbidity and hospitalisations in the salvage cases. Long term disease specific survival (5 years or more) was not mentioned clearly in the study, but from the disease free survival curve at 5 years, it was about 64% for surgery and 52% for chemoradiotherapy. The authors mentioned that in this protocol a careful and high standard follow up is necessary to diagnose the failure early and optimise the results of the chemoradiotherapy [302].

These good results were opposed by another randomised French trial involving only 68 patient of resectable primary SCC of the larynx, also randomized between induction chemotherapy and radiation versus total laryngectomy and postoperative radiotherapy. While this trial included a smaller number of patients, all epilaryngeal lesions were excluded and all included cases were clinically T3 with a fixed vocal fold. The incidence of N0 was 78%, and among the 54 patients (79%) in whom neck dissection was done only 16(30%) were positive; thus all the patients of this trial were advanced endolaryngeal cancers and most of the lesions were extensively involving the glottic level. All survival and locoregional control rates were significantly better with surgery and the disease specific survival percentage at 5 years in the surgical group was about twice the chemoradiation group. Again, detailed data about the function of the preserved larynges were not available[303].

Following these initial studies, the role of chemotherapy in the treatment of laryngeal cancer was subjected to several extensive reviews and analysis[301,304-306]. The landmark meta-analyses of the role of chemotherapy in the head and neck cancer published in 2000, showed that the use of chemotherapy adds a minimal significance in the overall survival of 4% at 2 years (from 50 to 54%) and at 5 years (from 32 to 36%). This study used the original individual patients' data and updated the survival follow up for the patients, allowing for several sub-analysis showing that the benefit was mainly in concomitant chemotherapy with about 8% improvement in survival ($p<0{\cdot}0001$), and mainly in the studies using non conventional radiotherapy protocols, while in the adjuvant and in the new-adjuvant chemotherapy studies there was no significant survival improvement. This study also contained a meta-analyses for the laryngeal preservation randomised trials for the larynx and hypopharynx, and it showed an overall decrease in the survival at 5 years of 6% (from 45 to 39%), with significant heterogeneity ($p=0{\cdot}05$) especially regarding the anatomical subsites. However the morbidity, especially delayed, quality of life, and cost-benefit were not well studied. Due to the negative impact on the survival in the larynx preservation (23% alive with intact larynx at 5 years), the authors recommended the discussion of this percentage against the decreased local control obtained by this protocol when compared with the total laryngectomy. The authors addressed the importance of the description of the detailed anatomical subsite, morbidity especially late one, quality of life, and cost-benefit in the future studies to

decrease the heterogeneity and to improve the clinical values of these trials[304]. In another meta-analysis of concomitant chemoradiotherapy a significant benefit of the platinum based concomitant chemoradiotherapy on the survival rates was found. Although this study addressed late toxicities and morbidity in these trials, the trials again included head and neck malignancies as a group, with inclusion of only a limited number of cancer larynx[305]. Similar limitations can be found in other recent reviews[301,306].

In 2003, another landmark randomised study (the RTOG study 91-11) attempted to explore the best regimen for the non surgical treatment for advanced laryngeal SCC. This study compared three groups of resectable primary stages III and IV SCC of the larynx. The groups included were: group 1 receiving two cycles of induction chemotherapy followed by radiotherapy with the salvage laryngectomy kept for the poor responders, group 2 receiving a concomitant chemoradiotherapy, and group 3 receiving exclusive radiotherapy. The radiotherapy given in all cases was conventional with a dose of 70 Gy to the primary tumour and the positive nodes and at least 50 Gy to the whole neck. The groups included 173, 172, and 173 patients respectively and there was no surgical group. The T stages were 12% T2, 78% T3, and 10% low volume T4 (all cases with large volume T4 or penetrating through the thyroid cartilage were excluded), only 46% of the patients had a fixed vocal fold. The N stages were 50% N0, 19% N1, 29% N2, and 2% N3, also all the cases of N2 and N3 were subjected to elective neck dissection, although the results of the salvage surgery and neck dissection was not mentioned in details. Only 31% of the cases were glottic. Stage III accounted for 65% of the cases while 35% were stage IV, and the distribution of the patients was similar in the three groups. The mortality rate related to the treatment modalities was 4%, the overall severe toxicity rates were 81%, 82%, 61% for groups 1,2 and 3, respectively, the severe late toxicity were around 30 %, and the concomitant chemoradiotherapy was the arm with the highest mortality and morbidity. The 2 years local control rates were 64%, 80%, and 58%, the 2 years disease free survival rates were 52%, 61%, and 44%, and the 5 years disease free survival rates were 38 %, 36%, and 27% for the groups 1, 2, and 3 respectively. For the composite end point of laryngectomy free survival (either laryngectomy or death from any cause constituted the treatment failure), the two year and five-year estimated rates of this end point were 59 % and 43 %, respectively, for patients assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 66 % and 45 % for those assigned to radiotherapy with concurrent cisplatin, and 53 % and 38 % for those assigned to radiotherapy alone. The tracheotomy and feeding tube incidences and durations were not discussed and the short term speech and swallowing evaluation were not mentioned. However after one year, about 15 % of the survivors reported significant dysphagia, and in the concomitant chemoradiotherapy group 23% were able to swallow only fluids and soft diet, 3% not being able to swallow at all. At two years dysphagia were reported in 15% of the patients. No voice analysis was done and at one year about 10% of the patients reported moderate difficulties in speech intelligibility, especially "during phone usage." The authors reported that; only 77% of the patients were available for the swallowing and speech description and concluded that; concurrent chemoradiotherapy therapy is the most superior form of non-surgical management of cancer larynx, despite a doubling in the rate of the mucosal morbidities. The authors stated that; concurrent chemoradiotherapy should be considered as the standard care for patients desiring laryngeal preservation whose cancer is stage II or IV and laryngectomy should be kept only for salvage or for patients with "significant" invasion of the tongue base, "significant" invasion the laryngeal cartilages[307]. These results are the base for the recent American guidelines which recommend concomitant chemoradiation for the advanced cancer larynx [247].

Recently the use of taxane-based chemotherapeutic agents in combination with the platinum based protocols seems to improve the short term control rates and saves more larynges, but it is still under investigation. Again, there is a tendency to increase the complications and no data about the long term results are available for laryngeal cancer [308-310] Similarly, targeted therapy in cancer larynx is under investigation, either used alone or associated with the traditional chemotherapeutic agents, but the primary results concerning the larynx and hypopharynx is not as promising as for other head and neck sites [310-313].

Functional evaluation in the big organ preservation trials of cancer larynx is usually missing, or

incomplete, or depending on rough patients data [302,303,307], but several following studies showed that; the complications and the functional disabilities (especially the dysphagia and the aspiration) were usually underestimated in these treatment modalities [314-321]. The long term dependency on a feeding gastrostomy (more than 6 months after the treatment) in these organ preservation protocols is around 30%, the aspiration rate is also high when radiologically evaluated, and at one year nearly 10-20% of the patients report moderate to severe aspiration [314-316,318]. The larynx and hypopharynx are the head and neck sites most frequently showing these complications [314-316,318]. In one study, reporting only on laryngeal cases, the incidence of aspiration during videofluoroscopy was 84%, and up to one year post-treatment half of the patients expressed symptoms related to aspiration[320]. Other authors similarly reported 29% of gastrostomy, 29% of tracheotomy, and 10% of both at 6 months in a series of cancer larynx treated with organ preservation protocols, reflecting that many patients may retain a free but non-functioning larynx after the treatment [321].

Finally, the radiotherapy protocols involving the lower neck carry a high risk to induce a hypothyroidism, the risk at 2 or more years after the treatment being around 40%. So, a long term monitoring of the thyroid function is recommended to avoid the underestimation of this complication [255,322,323].

- *TRANSORAL ENDOSCOPIC EXCISION*

The good oncologic results, the excellent laryngeal preservation rate and finally the limited morbidity of CO_2 laser approach in many cases of T2 glottic carcinomas encouraged surgeons to use this modality in selected cases of advanced glottic carcinoma [259,261]. Up till now there is no enough data to establish the definite results for advanced glottic SCC, but in large series the incidence of T3 glottic carcinomas is increasing [259].

Ambrosch in her review, reported a 5 years local control rate of 68% and a 5 years disease specific survival of 62% for 70 cases of pathologically T3 lesions [259]. Motta et al., reported 51 cases of T3 lesion with 64% and 72% 5 years local control and disease specific survival rates respectively [261]. Hinni et al., reported a multicenter study including 117 patients with advanced cancer larynx (only 42 cases were glottic with 27 cases pathologically T3) with a 74% five years local control and 68% five years disease free survival [324]. The resection of these advanced lesions is done by a piece meal technique [259,261,324], and the complete exposure of the lesion and the pathological evaluation of the margin become more difficult than in early lesions [265,266]. In addition, the risk of having residual tumour is increased with a direct impaction on the control and survival rates [325]. Moreover, the reported mortality and morbidity rates are higher with these advanced cases [261,324]. Hinni et al., reported 3% treatment related mortality, 5% postoperative bleeding that mandates surgical interventions, and 7% of cases with permanent tracheotomy and or feeding tube among the disease-free survivors [324]. Motta et al., reported 5% of penetration of the cricothyroid membrane when resecting these large lesions with development of severe emphysema, and 43% of granulation tissue formation which needs frequent removal in the early weeks until healing (these extensive granulations were associated with extensive resections, especially when involving the perichondrium). They reported also a longer period of recovery with T3 lesions with a mean hospitalisation period of 11 days [261].

It was explained above that voice quality depends on the extent of resection [271,274-276], thus the evaluation of voice after these lesions is usually directed to measure the overall speech intelligibility. 90% or more of the patients can communicate normally but severe to moderate dysphonia is usually present [324]. Also, it is important to know that neck dissection is needed in the advanced cases, which can be done in the same sitting or after, and postoperative radiotherapy is used for about one third of the cases [261,324].

- *OPEN PARTIAL SURGERY*

Extensive vertical resection even the subtotal (near-total) laryngectomy with epiglottic reconstruction

carry unfavourable oncologic results in T3 glottic carcinoma with fixed vocal fold and even in the T2 lesions with unfavourable extensions, thus it is not recommended in the recent reports outlining the indication of these surgeries [279,282,284-286]. Chevalier et al., compared the results of the vertical laryngectomy (in the literature) against the SCPL-CHEP in the T3 fixed cord and T2 with severely impaired cord mobility, a strong significant difference in all the control and survival rates were observed favoring the more use of the SCPL [289]. Similar results were reported in a study for the T2 lesions including 204 patients [288].

The SCPL is an alternative to total laryngectomy in many cases of advanced laryngeal carcinoma [289,326-329]. Chevalier et al., reported a 94% five years disease specific survival rate in T3 glottic SCC with fixed cord [289]. Similar to this result, a report of 118 T3 endolaryngeal carcinomas showed 91.4% 5 years local control with 89.8% laryngeal preservation rate [326]. Lima et al., reported 53 cases of T3-4 glottic cancer with definite cartilage infiltration in 11 cases and they obtained 85% and 78% 5 years local control and disease specific survival rates respectively [327]. Gallo et al., reported 57.6% of overall survival at 16 years in a cohort with 253 patients operated by SCPL (36% of the patients were advanced laryngeal carcinoma and among this group 75% of them were glottic lesions) [328]. SCPL is effective even in the advanced cancer cases with thyroid cartilage invasion whatever the type of this invasion, since SCPL offers a monoblock resection of the thyroid cartilage with the cricothyroid membrane, the results regarding the thyroid cartilage invasion is only affected when the tumour reaches the prelaryngeal soft tissue [190,205]. Finally, nasal breathing, near normal oral feeding and highly intelligible speech are achieved in about 95% of the patients [190,205,330].

- *RADICAL SURGERY*

Total laryngectomy with or without neck dissection was the treatment for most of the primary advanced curable laryngeal carcinomas from the early 20th century up to the last 20 years when the non-surgical methods become more popular. [144,235]However, total laryngectomy was not popularised and practiced widely before the 1950s, when the procedure disseminated all over the world [331], and become the standard care for advanced cancer larynx [129,332,333].

Sessions et al., reported a 68% 5 years diseases specific survival for T3N0 glottic carcinomas, and the neck dissection had a trend to improve the results for about 10% [334]. Spector et al., reported a 59% 5 years disease specific survival for T3N1 glottic carcinomas [335]. For the above two reports, the post-operative radiotherapy did not improve the survival rate [334,335]. De Santo., reported 6% local failure and 9% mortality from the glottic carcinoma in the T3N0 sub-stage [336]. Yuen et al., reported an 82% locoregional control in 155 patients with T3 glottic carcinoma, treated with surgery alone [337]. Foote et al., obtained a 74% 5 years locoregional control and disease specific survival in 81 patients of T3 glottic carcinoma treated with total laryngectomy without radiotherapy [338]. Hall et al., obtained a 67% 5 years disease specific survival in a cohort of 64 patients having advanced laryngeal carcinomas, one third of the patients being T4; subgroup analysis showed marked deterioration of the specific survival with the advanced T stage (at 5 years T3 survival percentage was nearly double the T4 percentage) [339]. Spector et al., reviewed 96 patients with stage IV glottic SCC including 61 patients classified clinically as T4 and they reported about 39% 5 years disease specific survival, moreover only 25 patients were N+ which reflects the unfavourable long term results of such lesions[340].

Beside the complete loss of the laryngeal functions, total laryngectomy for locally advanced laryngeal carcinomas is associated with a high rate of local (wound) complications, 20%-30% of the patients developing a pharyngeal fistula [341,342]. Makitie et al., reviewed the reports of pharyngocutaneous fistula and found a large variation in its incidence (5-65%), with an incidence of 9-23% in recent reports. They mentioned that the risk is higher in salvage cases with an increasing incidence with the new aggressive protocols of non-surgical treatment [342], a finding confirmed by others [343,344]. In addition to all of the above, a recent survey showed that the swallowing troubles seem to be underestimated after total laryngectomy as about 70% of the patients

complain of different grades of dysphagia which forced them to alter their dietary habits [345].

1.6.2.3. CURATIVE TREATMENT OF EARLY SUPRAGLOTTIC CARCINOMA

Early invasive supraglottic carcinomas (T1-T2 N0) are less common than the glottic one since supraglottic carcinomas do not produce early symptoms [175,176]. Supraglottic carcinoma is more frequently associated with a lymphatic spread than glottic SCC [142,159,161,162]. On the other hand, most early supraglottic carcinomas remain confined to the supraglottic region and rarely involve the glottic level [146,149,150].

Early supraglottic carcinoma should be treated also with a unimodality treatment, with the conservation of the laryngeal functions like the early glottic carcinoma [247,248]. But the elective neck management is widely recommended in T2 lesions and bilateral treatment for the neck is preferred when the carcinoma originates from or near the midline [246].

- *RADIOTHERAPY*

Exclusive radiotherapy became more widely used in the management of the early invasive supraglottic carcinoma in the recent three decades, with most recent reports achieving comparable survival rates to conservative laryngeal surgery but unfortunately the detailed functional results are usually not mentioned. [247,255,346] Sykes et al., in a study including 331 cases of T1-4N0 supraglottic carcinomas (staged according to the TNM system of 1992) reported 92% and 81% five years local control rates for T1 and T2 lesions respectively, the 5 years ultimate regional control was 91% and 88 %, and the 5 years disease specific survival was of 83% and 78%, respectively for T1 and T2 lesions. The average organ preservation rate was 90% among the controlled cases, and a meticulous follow up schedule in the first 2 years was deemed essential to pick up early failure cases [346]. The morbidity was high, however, as the investigator used a protocol to deliver a dose of 52.5-55 Gy to most of the cases in 16 fractions over a total 21 days [346,347]. Nakfoor et al., obtained 95% and 88% 5 years local control rates for T1N0 and T2N0 lesions (staged according to the TNM system of 1992), with about 85% 5 years disease specific survival for both. They used a bifractionated accelerated scheme of two 1.6 Gy daily doses to deliver a mean of 70 Gy over 41 days[348]. Hinerman et al., reported 100 % 5 years locoregional control and disease specific survival results for T1N0 (17 cases), as well as 86% and 93% 5 years locoregional control and disease specific survival results for T2N0 cases (with about 88 % laryngeal preservation rate) [349]. Moreover, both Sykes et al., and Hinerman et al., reviewed the results of large cohorts of supraglottic carcinomas treated with radiotherapy: the 5-year local control rates were ranging between 60-100 %, with an average of 90% and 80% for T1 and T2 lesions respectively. The use of the altered (fractionated and accelerated schemes) improved the control rate especially in T2 lesions, unfortunately associated with an increase in acute morbidity [346,349].

The treatment field for the early supraglottic carcinoma must involve the whole larynx up to the upper border of the cricoid cartilage and at least the cervical node groups IIA and III. Different extensions of the fields according to the subsites affected, when the conventional technique is used a dose of 66 Gy for T1 lesions and 70 Gy for T2 lesions are usually delivered [255]. More recently, altered fractionation schemes and the use of CT-based treatment planning are widely recommended and these altered radiotherapy schemes become now the standard radiotherapy for T2 supraglottic carcinomas in many centers [255,346,348,349].

- *TRANSORAL ENDOSCOPIC EXCISION*

Although there are few large series reporting on the endoscopic CO_2 laser resection of the supraglottic carcinomas, this concept is becoming more popular and is changing from the concept of a big biopsy into a real oncologic resection[259,350-354].

Ambrosch et al., reported 46 cases (12 pathological T1N0, 36 pathological T2N0) with 100% and 89% 5

years local control rate for the T1 and T2 lesions respectively; postoperative radiotherapy was done only in 4 cases. The 2 and 5 years overall survival rates were 89% and 76%, and the laryngeal preservation rate among the controlled cases was 100%. The mean time for feeding tube was 6 days; tracheotomy was done only in one patient (some patients needed a prolonged intubation). Only 4 patients developed major complications (2 of them had a haemorrhage that mandated surgical control) [350]. Iro et al., reported 141 cases of early supraglottic carcinomas (staged according to the TNM system of 1987) with 5 years local control rates of 86% and 75% for T1N0 and T2N0 lesions; neck dissection was done for most of the cases, negative margins were obtained in about 85%, and about one third of the patients had postoperative radiotherapy [351]. Davis et al., reported the results of extensive supraglottic resection for 46 cases classified clinically and radiologically as T2 lesions, however postoperative radiotherapy (66 Gy) was carried out in 38 cases; 5 years local control was 98 %, aspiration pneumonia was reported in 5%, vocal fold paralysis in 5%, and severe postoperative bleeding in 1 patient [352]. Agrawal et al., used a similar combined treatment and reported 97% 3 years local control rate and 88% 3 years overall survival for 34 T1-2 patients. The functional results were described in detail: 4 temporary tracheotomies (less than one week), on the other hand only 71% retained early oral feeding, 21% had a long feeding tube time (3-10 months), and 9% became gastrostomy dependent. All swallowing problems were mainly related to the extensive resection, except in one patient in whom it was mainly due to radiotherapy [353]. Similar to the last two report, Grant et al., pointed to the need for a prolonged feeding tube in some patients (34%), especially with the use of postoperative radiotherapy, as well as a higher rates of tracheotomy (42%) and postoperative laryngeal stenosis; they were able to obtain a comparable control results with less use of the radiotherapy to the primary site [354].

Recently Rodrigo et al., reviewed the laser surgery results for early supraglottic cancer and they reported 5 years local control rates of 88.4% for T1 lesions (77 cases), and 85% for T2 lesions (138 cases). Most of the reports reviewed used the old TNM systems (earlier than 1997) where the extension to the medial wall of pyriform sinus is considered T3. For the functional results the authors mentioned that the tracheotomy rate, the recovery time, and hospital stay is significantly better with endoscopic supraglottic resection than with open supraglottic laryngectomy, however, the long-term functional results and complications are similar in both approaches and the swallowing recovery depended mainly on the extent of the resection[355].

- *OPEN PARTIAL SURGERY*

Open horizontal (subtotal) supraglottic laryngectomy is a landmark advance in the oncologic surgery of supraglottic carcinoma, by the radical excision of the supraglottic compartment and approximation of the glottis to the base of the tongue [149,177,356-365]. It achieves local control rates comparable to total laryngectomy for most supraglottic lesions, with the conservation of the laryngeal functions. It was first described and developed by Alonso in Montevideo and then popularised all over the world, especially in Europe and South America [356].

Earlier reports on standard or the extended supraglottic laryngectomy proved the excellent efficacy of the procedure in T1-2 supraglottic carcinoma [149,358-360]. Bocca., presented a very large series of supraglottic laryngectomy and neck dissection, including 537 cases. He reported 5 years local control rates of 93.5% and 82% for T1N0 and T2N0 lesions, and 5 years locoregional control rates of 91.5% and 79.5% for the same groups. The main interest of his report is that it reflects mainly the surgical results as postoperative radiotherapy was infrequently used [361]. Gonzalez et al., reported the results of 110 cases treated with supraglottic laryngectomy and neck dissection, 62 cases were early stages with about 95% 3-year local control rate [362]. Adamopoulos et al., reported 97% and 91% 3 years local control rates for T1 lesions (33cases) and T2 lesions (46 cases), respectively [363]. These last two studies reported complication rates of 20%, with a fistula rate of about 5% and aspiration pneumonia in 6% of the patients. Decanulation was possible in 94% of the patients, supraglottic stenosis or arytenoid oedema being the causes of permanent tracheotomy. Long standing (6-12 months) mild swallowing problems (mainly aspiration) were found in about 40% of patients, with 7% reporting severe

troubles and became gastrostomy dependent. The mean feeding tube time and hospitalisation period were about three weeks and the feeding tube was present in 15% of the patients by the end of the first month [362,363]. Bron et al., obtained 93% and 91% 5 years disease specific survival for T1 (16 cases) and T2 (43 cases) lesions respectively; the functional results were slightly better if compared to other reports as they were able to decanulate all their patients and a long standing feeding gastrostomy was reported only in one patient [364]. Sevilla et al., published recently a large report of 267 cases of primary supraglottic laryngectomies with neck dissection, post operative radiotherapy was used in 47% of the cases but rarely for the early stages. The 5 years disease specific survival rates were 92% and 71% for the stages I and II, respectively [365].

SCPL is another conservation technique that can be used in early supraglottic carcinomas extending to the petiole of the epiglottis, the anterior commissure, or the vocal fold, as well as supraglottic carcinoma originating from the ventricle or in cases of impaired vocal fold mobility [190,366,367]. However, these indications represent rare conditions in early supraglottic carcinomas as explained previously, since most supraglottic tumours extend to the glottic level very late [146,149,150,361], and since the ventricles are rarely encountered as the primary site of origin of the laryngeal carcinoma [142,143,349].

1.6.2.4. CURATIVE TREATMENT OF ADVANCED SUPRAGLOTTIC CARCINOMA

Similarly to glottic carcinoma, supraglottic carcinoma is also classified as a curable advanced tumour either because of local (T3-4) and/or lymphatic (N+) extensions, except for T4b and N3 lesions which are identified as indicators for very difficult or impossible surgical resectability [226,230]. However, contrary to glottic SCC, advanced supraglottic carcinoma (T3-4) is more common than the early one (T1-2) [142,175,176]. In addition, supraglottic carcinoma exhibit a higher rate of lymph node spread, since at least 50% of T3-4 lesions is combined with positive nodes[142,349,361,363,365]. It is not only the higher incidence of nodal disease but also the advanced nodal extensions which are observed among the supraglottic carcinoma, if compared to the glottic one [159,161,163], with the impact of the nodal state on survival rates of supraglottic carcinoma being obvious [361-363,365]. Contrary to that aggressive nodal behaviour commonly the T3-4 supraglottic lesions remains confined to the supraglottic region without extensive glottic extensions [146,149,150,360,361], or cartilage invasion [146,154].

In order to achieve good control and survival rates in advanced supraglottic carcinoma, the neck should be addressed in all cases: by an elective neck treatment for all the N0 lesions and combining neck dissection with postoperative chemoradiation in most of the N2-3cases [302,307,348,349]. In the mean time, the larynx should be treated with a conservation basis to prevent unnecessary total laryngectomy in most advanced supraglottic lesions [190,247,302,307,361].

- *NON-SURGICAL TREATMENT*

Several trials were made to treat supraglottic carcinoma by exclusive radiotherapy, keeping salvage surgery for the recurrence [346,348,349,368,369]. Sykes et al., reported 5 years local control rates of 67% and 73% for the T3N0 and T4N0 lesions respectively and 5 years disease specific survivals of 53% and 61% for the same groups. These good results were associated with higher nodal failure for N0 carcinomas, despite including groups IIA and III in the radiotherapy fields. High morbidity was reported with the extremely accelerated hypofractionated technique used in this study [346]. Nakfoor et al., reported 83% and 67% 5 years local control rates for the T3N0 and T4N0 by using a bifractionated accelerated radiotherapy protocol (mean total dose of 70 Gy). The 5 years local control rates were 76% and 43% for T3 and T4, 74% and 46% for N1 and N2-3, and finally 79% and 55% for stages III and IV, respectively. The results were favourable for the moderately advanced lesions on the expense of higher complication rate, the salvage surgery was almost often total laryngectomy, and the failure rate for the salvage surgery among the T3-4 lesions was high [348]. Other studies reported unfavourable survival results with exclusive radiotherapy treatment for the T3-4 supraglottic lesions (12-38% for the T3, and 14-29% for the T4) but the radiotherapy protocols used in these studies were suboptimal if

compared with the new regimen [368,369]. Improvement of the control rates, when using the new altered radiotherapy protocols was reported also by Hinermann et al., [349], and the various other recent prospective trials and reviews [298-301].

As mentioned above, the role of the chemotherapy in the treatment of the advanced cancer larynx either with conventional radical radiotherapy or with the new altered protocols was established in the last 2 decades, and combined chemoradiotherapy is now the standard treatment, when a non-surgical approach is favored [242,255,302,304-307].

The two landmark laryngeal preservation studies (the Veterans Affairs in 1991 and the RTOG study 91-11 in 2003) reported good control and survival results, as mentioned in previously. In these two trials, 67% of the cases included were advanced supraglottic SCC, making the non-surgical treatment a good alternative to the radical surgery in advanced supraglottic carcinoma. The subgroup analysis mentioned in these trials pointed to inferior results when dealing with the locally aggressive tumours, deeply invading the tongue and / or the laryngeal cartilages, notwithstanding the markedly low number of T4 compared to T3 lesions included in these studies [302,307].

In addition, other studies show a decrease in the control and survival rates with non-surgical treatments if the vocal fold is fixed [302,303,349].

Finally, as mentioned above, in laryngeal carcinoma a preserved larynx does not translate in a preservation of laryngeal function, many authors reporting long-term functional troubles after the organ preservation protocols [314-321].

- *TRANSORAL ENDOSCOPIC EXCISION*

The use of the endoscopic CO_2 laser resection as a line of treatment for the T3-4 supraglottic carcinomas is reported in some series within the last years [324,325,351,353,354]. The resection was usually done in some selected cases of T3 lesions and highly selected cases of T4 as a substitute for open supraglottic laryngectomy, associated with neck dissection in most and postoperative radiotherapy in about one half of cases [324,325,351,353,354]. So the indications for endoscopic CO_2 laser surgery should be done with marked caution, due to the limited number of reported cases, the high selection in these series, the T3-4 was made n pathological basis and the marked difference in functional results in advanced cases versus early supraglottic lesions [244,325,351,355].

Hinni et al., reported 58% 5 years disease specific survival and 51% 5 years of laryngectomy free survival for 117 cases of advanced cancer larynx (65 cases were pathologically supraglottic T3-4 - 1992 TNM system), but with high mortality and morbidity and worse functional (especially the swallowing) results [324]. Iro et al., reported 72 cases of advanced supraglottic carcinomas (staged according to the TNM system of 1987) associated with postoperative radiotherapy in two thirds of the patients. The authors reported the inability to resect the lesion endoscopically in about 20% of the cases with intraoperative conversion into an open approach and more positive margins with the more locally advanced lesions. The 5 years local control rate was 77% [351]. Similar conclusions were drawn by Blanch et al., [325]. Rodrigo et al., reviewed the use of the endoscopic CO_2 laser to treat T3 supraglottic lesions, finding a 5 years local control rate of 81.5% (70 cases). Most of these cases were classified T3 due to minimal pre-epiglottic space invasion and the incidence of vocal fold fixation among the cases was very low. The authors concluded that with wide resections in advanced lesions many of the advantages of the endoscopic CO_2 laser approach are lost, especially regarding the post-treatment swallowing troubles[355].

- *OPEN PARTIAL SURGERY*

Bocca., reported 5 years local and locoregional control rates of 80.5% , 71% for stage III supraglottic carcinoma (205 patients) and 66.5%, 51.5% for stage IV supraglottic carcinomas (33 patient) treated with supraglottic laryngectomy and neck dissection. Among the stage III cases, 107 patients were classified clinically as T3 lesions and extended supraglottic laryngectomy was almost always the treatment [361]. Other authors also reported the feasibility of supraglottic or extended supraglottic laryngectomy to obtain good local control and laryngeal preservation rates in selected cases of locally advanced supraglottic carcinoma [244,362-365]. Sevilla et al., reported 5 years disease specific survival of 80% for stage III supraglottic lesions (59 cases) and 61% for stage IV supraglottic lesions (90 cases), the 5 years local control rates for pathological T3 (49 cases) and pathological T4 (31 cases) were 92% and 87% respectively. But the authors reported also increases in the positive margins, the need for postoperative radiotherapy, and the incidence of permanent tracheotomy among the T3 and T4 lesions [365].

SCPL-CHP is a good alternative to total laryngectomy in many cases of advanced supraglottic carcinomas which are not suitable to supraglottic laryngectomy. SCPL-CHP is reported by many authors to be safer oncologically when the tumour extends to the glottic level (even when the vocal fold is totally fixed), to the paraglottic space, and associated with thyroid cartilage invasion [205,326,366,370,371]. Schwaap et al., reported a 5 years overall survival rate of 88% for 146 cases of supraglottic carcinoma treated with SCPL-CHP with a 85% laryngeal preservation rate. Seventy two cases were advanced with 57 cases T3-4, 22 cases showed thyroid cartilage invasion, 63 cases showed pre-epiglottic space invasion and the subglottis was involved in 11 cases. All these extensions were not significant regarding the control or survival rates achieved by this surgery [370]. These extensions were also studied by other authors with similar results, reflecting the safety of SCPL-CHP in locally advanced endolaryngeal supraglottic carcinoma [326,371]. Moreover, Hassmann and Skotnikca, examined the pathological specimens of 90 cases of advanced cancer larynx (70% T4) treated with total laryngectomy and found that many supraglottic cases could be resected safely with SCPL [372]. Thus SCPL-CHP arose as a surgical procedure of choice for selected advanced supraglottic carcinomas not suitable for supraglottic laryngectomy [190,367].

- *RADICAL SURGERY*

Sessions et al., pointed to the difficulties to extract and compare the results of the primary total laryngectomy as a treatment for supraglottic carcinomas due to the rarity of the reports concentrating on this title and the heterogeneity between the TNM editions used [373]. Goepfert et al., reviewed 144 supraglottic carcinomas treated with total laryngectomy ± neck dissection: the 2 and 5 years non corrected local control rates were 87% and 62% for stage III and 32% and 23% for stage IV respectively, but the staging system was quite different from the present TNM system [374]. Myers and Alvi, reported the results of 103 cases of supraglottic carcinomas treated with surgery (total laryngectomy used in 68% of the cases) with or without post-operative radiotherapy (stages I:3%, II:34%, III:37% and IV:26%). All locally advanced lesions extending beyond the medial wall of the pyriform sinus and / or the tongue base were excluded. The 2 years overall survival rates were 68% and 52% for stages III and IV respectively, the survival was better among the non-irradiated cases, and a positive neck or extracapsular spread were associated with a significant lowering in the survival rates [375]. Recently Sessions et al. reported the treatment results for 653 primary supraglottic SCC. Total laryngectomy was the local treatment in about 32% % of the patients and was followed by postoperative radiotherapy in about 20.8 % of the cases. Total laryngectomy was done for most of the T3-4 lesions. In the 1950s and the 1960s but after that the supraglottic laryngectomy begun to dominate the treatment even in the advanced cases and neck dissection was done for most of the cases. The 5 years non-corrected disease specific survival rates were 72% for the cases treated with total laryngectomy and 50% for the cases treated with total laryngectomy and postoperative radiotherapy. Among the total laryngectomy subgroups the survival was about

15 % higher in the N0 patients [373].

II. AIM OF THE WORK

The broad aim of this study is to examine the impact of the different anatomical laryngeal subsites on the local control and disease-specific survival in primary cases of laryngeal squamous cell carcinoma treated with radical radiotherapy with and without chemotherapy.

In a more specific manner, we will study the effect of:

- The different clinical T stages according to the last TNM edition [226].
- The detailed anatomical subsites of the larynx.
- The involvement of the anterior commissure globally and in detailed manner, according to a new proposed classification.
- The pre-treatment and post-treatment vocal fold mobility status.
- The presence of persistent laryngeal oedema after the end of the radiotherapy.

The results from the patients series treated with radiotherapy ± chemotherapy are compared to previous publications using similar treatment protocols. Furthermore, a critical evaluation of the literature is conducted in order to attempt a concise summary of the optimal treatment for each TNM stage.

III. PATIENTS AND METHODS

3.1. PATIENTS

It is important to give a background on the treatment strategy at the Geneva University Hospitals during the study period. Most of the carcinoma in situ, microinvasive SCC, T1 supraglottic, T1a glottic were treated by endoscopic resection. Most supraglottic lesions (early T2 and some of T3) were treated by supraglottic laryngectomy. Partial laryngectomy was not widely performed for glottic lesions and most of these cases were treated by non-surgical methods.

Usually, for cases with definite radiologic cartilage invasion, or extensive subglottic involvement, or with huge tumour volume obstructing the airway the recommended treatment was total laryngectomy followed by postoperative radiotherapy, chemoradiotherapy being used mainly if the patient refused the surgery.

3.1.1. TARGETED POPULATION

Our target population in this clinical study was the primary cases of cancer larynx presented to the head and neck tumour board of Geneva University Hospitals during the period between 01.01.1996 - 31.12.2005. During this period 222 patients with primary (non-recurrent, and not a metastasis from another primary) laryngeal squamous cell carcinoma were presented to the tumour board, 194 were men and 28 were women.

Unfortunately, it was not possible to treat all patients with curative intent (8 patients treated with palliative measures) and 11 patients did not accept the treatment proposed by the multidisciplinary tumour board team.

Thus 203 patients (91.4%) of the patients presented to the tumour board) had been treated with a curative intent, 199 patients (89.6%) were treated at the Geneva University Hospitals and only four patients were treated in other centers outside Geneva (Figure 31).

Surgery was included in the treatment regimen in 62 patients (40 cases surgery only, 22 cases surgery followed by post-operative (chemo) radiotherapy), bringing the final number of cases matching the inclusion criteria to 137.

3.1.2. EXCLUSION CRITERIA

All the electronic and original paper files of the above 137 patients were reviewed, and 54 cases were further excluded because of:

- Non squamous histology (7 cases)
- Synchronous malignancy at the time of presentation (2 cases)
- History of previous malignancy within the last 2 years (8 cases)
- Carcinoma in situ (6 cases)
- Microinvasive carcinoma (7 cases)
- Patients with follow-up less than 2 years (6 patients - 4 died due to causes not related to the cancer or its treatment, and 2 returned to the country of origin and were lost to follow-up).
- Patients without pre-treatment radiological evaluation of the larynx (7 cases all classified as T1a glottic SCC).

- Clinical and or radiological reports that do not contain enough detailed data for the evaluation, or inappropriate radiological evaluations (11 cases, with 7 early and 4 advanced cases).

All the following criteria regarding the radiologic examination and reports were exclusion criteria: absence of actual images, imaging performed within a week after the biopsy, CT with slice thickness greater than 2 mm, no usage of radiological contrast material, incomplete or poor radiological report, and insufficient quality of the radiological examination.

Most of the excluded cases were non-invasive or T1 SCC and 83 patients (69.2% of the intended sample) met the criteria of inclusion and exclusion. Thus, the final studied sample subjected to the statistical analysis included 83 patients and all of them were primary invasive SCC of the larynx treated with (chemo)radiotherapy, with detailed clinical and radiological reports and a minimum 2 years follow-up (Figure 31).

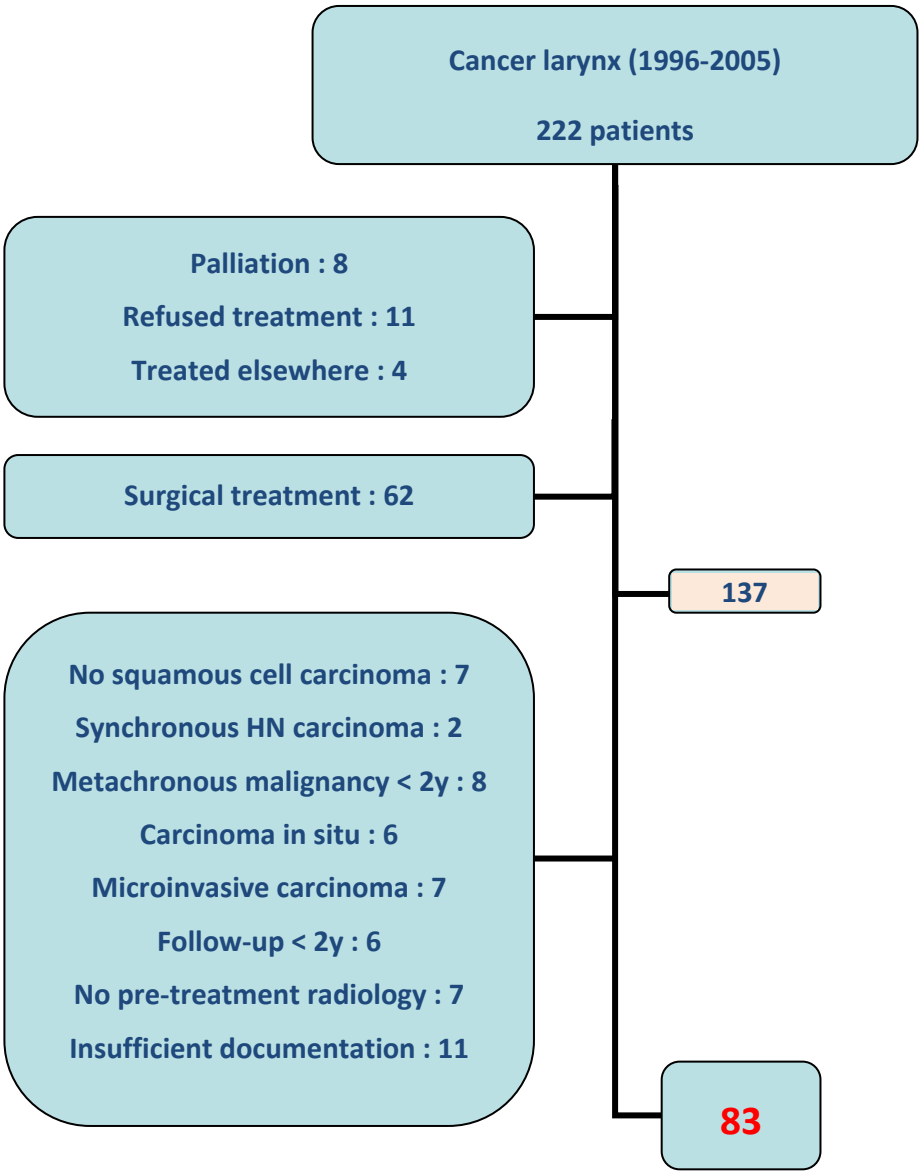


Figure 31: Diagram of patient exclusion criteria.

3.2. METHODS

3.2.1. TREATMENT

3.2.1.1. RADIOTHERAPY

The radiotherapy dose and protocol delivered to the patients were depending mainly on the tumour staging. The tumour volume within the larynx and the cervical nodes (whether positive or at high risk) received a dose of radiotherapy ranging from 62.4Gy to 74.4 Gy with a mean dose of 70.3Gy. The rest of the neck including the spinal (posterior) lymph node chain, and the supraclavicular lymph nodes received a total dose of 50.4 Gy in almost all cases with the exception of stage I carcinoma.

The radiation source was 6 MeV photons in all cases except in the majority of the stage I glottic cases, where Cobalt 60 photons was used.

The shielding of the spinal cord was done routinely from the 40Gy dose when irradiating the supraclavicular lymph nodes. In addition, at the level of the spinal lymph node chain from 40Gy up, 9 MeV electrons was used to avoid the injury of the spinal cord.

A monofractionated scheme was used in all the cases of stage I glottic carcinomas, while in all other cases (except three) an accelerated bifractionated schemes was used (Table 4). The most commonly used altered scheme (48 cases) delivered a dose of 50.4 Gy to the whole neck and the tumour sites through 28 fractions with a dose of 1.8Gy per fraction, the treatment being administered five days per week. Additionally, a concomitant boost scheme was used to deliver 19.5Gy to the macroscopic tumour site and the positive lymph nodes during the last 13 treatment days (1.5Gy per fraction) through a bifractionated daily scheme with an interval of at least 6 hours between the two fractions. Therefore, the total dose was increased up to 69.9 Gy in a mean treatment period of 40 days [376].

Another altered scheme was also used (14 cases) especially in the early years of this study. This scheme was delivering doses of 74.4 Gy to the larynx and the positive nodes, and 50.4 Gy to the negative lymph node groups II-VI by a continuous bifractionated protocol with 1.2 Gy per fraction with a mean overall treatment time of 44 days.

The radiation was delivered through two lateral opposed fields in most cases, while in some cases kicked out fields or non-opposed oblique fields were attempted. The fields encompassed the whole larynx, the positive lymph nodes, and the lymph nodes at risk; except in stage I carcinoma when a small field (6×6 cm) was used. A pretreatment CT with the patient in treatment position was usually performed. Carbogen inhalation during the radiotherapy was used as a radiosensitizer only in three cases.

Number of the cases treated by each scheme	Monofractionated traditional scheme	Altered (accelerated bifractionated scheme)	Total dose (Gy) to the tumour site (mean)	Treatment days (mean)
T1a Glottic (6 cases)	6	0	66	45
T1a Glottic (1 case) T1b Glottic, (11 cases)	12	0	70	49
T2-T4 (65 cases)	3	62	70.6	41.5

Table 4: The summary of the radiotherapy treatment.

3.2.1.2. CHEMOTHERAPY

At the time of the tumour board decision, chemotherapy was planned for 38 patients, but only 36 patients actually received the chemotherapy treatment (Table 5). Concurrent (concomitant) chemotherapy was used in all the patients, and two patients had additional induction chemotherapy (2 cycles in one patient and 3 cycles in the other) because the radiotherapy had to be delayed to complete the pre-radiotherapy dental treatment.

Intravenous infusion of cisplatin (100 mg per square meter of body surface area – 100 /m^2) divided on five days per week (20mg/m^2/d) was given to all the patients except two patients who received carboplatin due to cardiac troubles.

Cisplatin was the only used drug in 20 cases. The first dose was delivered on the first day of radiotherapy, a second dose was routinely given at the beginning of the fifth week of radiotherapy in 13 patients and at the beginning of the fourth week in 6 patients. One patient did not have the second course due to severe agranulocytosis.

Taxotere (10mg / m^2 / day) was given as a concomitant therapy with cisplatin in 10 cases; in these cases chemotherapy was administered every week during the radiotherapy and the daily dose of the cisplatin was usually reduced to 15 mg/m2/day.

5 fluorouracil (5-FU) was also administrated in 5 cases in combination with cisplatin at the first and fourth weeks of radiotherapy, and in 3 of these cases a third course was given after the end of the radiotherapy. It was administrated through a continuous intravenous infusion over 5 days / week with a dose of 1200 mg / day.

Chemotherapy was used only in advanced cases and it was combined with altered radiotherapy in 34 cases, while it was used with the traditional scheme only in two cases (total dose: 70.4 Gy).

		Platin-based chemotherapy alone	Combined cisplatin + Taxotere	Combined cisplatin + 5-FU	Type of radiotherapy scheme used
Concomitant chemotherapy	34	19	10	5	33 altered scheme
					1 traditional scheme
Induction + concomitant chemotherapy	2	1	1	0	2 traditional scheme

Table 5: The chemotherapy treatment.

3.2.1.3. SURGERY

During the evaluation panendoscopy, some patients presented with bulky laryngeal carcinoma protruding in the lumen. In order to avoid a tracheotomy, debulking the tumor was performed in some patients. This was performed with the biopsy forceps in the majority and using the laser in few patients.

Neck dissection was not done after the end of the treatment in this study, but in two cases with large lymph nodes (more than 3 cm) neck dissection was done prior to the scheduled chemoradiation treatment [376].

Salvage surgery for local failure cases was possible only in 12/21 cases: wide field total laryngectomy or total laryngopharyngectomy were performed for nine patients, while conservation surgery was possible only in

three cases (all three cases initially classified as early cases). Six free or pediculated myocutaneous flaps were needed for the reconstruction and / or the treatment of a pharyngocutaneous fistula in these cases.

Among the neck failure cases neck dissection was possible only in 5/9 cases, it was done alone in two cases and in combination with the salvage surgery for the local failure in the other three cases.

3.2.2. STUDY DESIGN

3.2.2.1. TYPE OF THE STUDY

Retrospective cohort study of primary invasive SCC of the larynx treated by (chemo)radiotherapy at Geneva University Hospitals with a two years minimum follow up after the end of the treatment.

3.2.2.2. DATA ACQUISITION AND DESCRIPTION

All the clinical data regarding the anatomical extensions of the tumour were obtained from the original microlaryngoscopic report and the schematic drawing of the tumour mapping (Figures 32 and 33) done by the surgeons at the time of the panendoscopic examination. The presence of these two drawings was mandatory to include the case in our study population. This description was used as the basis for the clinical T description done in this study. The cancer involvement of following subsites was analysed: right vocal fold, left vocal fold, right arytenoid (anterior surface), left arytenoid (anterior surface), right ventricle, left ventricle, right false vocal fold, left false vocal fold, infrahyoid epiglottis, suprahyoid epiglottis, right aryepiglottic fold, left aryepiglottic fold, right arytenoid (superior surface), left arytenoid (superior surface), mucosa of the oropharynx, pyriform sinus, postcricoid area, subglottis globally, anterior subglottis, right lateral subglottis, left lateral subglottis, posterior commissure, palpation suspicious for a huge laryngeal lesion, and tracheal mucosa.

In addition, tumour extension at the anterior commissure was classified as explained in figure 34 into: 1) bilateral anterior commissure involvement along the horizontal axis (AC1); 2) superior extension along the vertical axis (AC2); 3) inferior extension along the vertical axis (AC3), and 4) combined superior and inferior extensions (AC4). This detailed classification is based on embryological and anatomical findings describing this area as a complex and not as a line. The aim of this detailed description was to characterize the impact of these anterior commissure extensions on the oncologic outcome.

The vocal cord mobility (normal, hypomobile, fixed) was reported according to the pre-endoscopic evaluation and the examination done during the tumour board; if there is a contradiction in the evaluation, the endoscopic examination during the tumour board was used.

The clinical cervical node description was also based on the clinical report of the case.

All the radiological data describing the laryngeal tumour and the lymph nodes were extracted from the original radiological report of the case. The variables studied were similar, but not identical to the clinical ones: right and left vocal fold, right and left thyroarytenoid muscle, right and left ventricle, right and left false vocal fold, infrahyoid epiglottis, suprahyoid epiglottis, right and left aryepiglottic fold, right and left paraglottic space, pre-epiglottic space, mucosa of the oropharynx, pyriform sinus, postcricoid area, subglottis globally, anterior subglottis, right lateral subglottis, left lateral subglottis, and posterior commissure. Cartilage invasion is a parameter that cannot be assessed clinically and we tabulated laryngeal framework invasion into global, thyroid cartilage invasion, cricoid cartilage invasion, arytenoid cartilages invasion, as well as an extralaryngeal spread through the anterior and/or lateral laryngeal surfaces, invasion of cricothyroid membrane, and invasion of thyrohyoid membrane. Paraglottic space invasion and pre-epiglottic space invasion were also extracted from the original reports of the images. In addition, like for the clinical assessment, tumour extension at the anterior commissure was classified as explained in figure 34 into: 1) bilateral anterior commissure involvement along the horizontal axis (AC1); 2) superior extension along the vertical axis (AC2); 3) inferior extension along the

vertical axis (AC3), and 4) combined superior and inferior extensions (AC4).

Extraction of the clinical and radiological data was not performed at the same time: all the clinical data were extracted first, followed by the radiological data.

The pathological data regarding the differentiation grades were based on the original pathology report for the biopsy results.

The TNM system was reported as mentioned in the tumour board; in addition, it was adjusted both clinically and radiologically to the fifth edition (1997) and the sixth edition (2002) to unify the systems for all patients. Because of the previous discussion about the anatomical extension of paraglottic space, the difficulties associated with the diagnosis of its involvement by imaging, and its classification as T3 in TNM 2002, we divided the T3 according to TNM 2002 into T3a (only paraglottic space invasion) and T3b (vocal cord fixation and/or cartilage erosion).

The treatment data regarding the radiotherapy and the chemotherapy were obtained from the final treatment reports. If some data were missing, the original detailed treatment protocol describing the doses was reviewed to obtain the data. The radiomucosal and radioepithelial toxicities were extracted from the final report of the radiotherapy treatment.

The follow up of the patients was done routinely every month in the first year, every two months in the second year, every 3-4 months in the third year, every 4-6 months up to the fifth year, and every year up to the tenth year. Patients were followed by both the otolaryngology team and the chemoradiotherapy team but not simultaneously. The ORL-HNS follow up was performed in the hospital clinic for most patients, except few patients followed by their private otolaryngologist.

The post-treatment vocal cord mobility and oedema were reported and studied; the data for these variables were obtained from the reports at 3 months after the end of radiotherapy.

The basic laryngeal functions were evaluated at 6-12 months post-treatment by reporting the rates of the tracheotomy, and / or tube feeding dependency. The patient was considered as tracheotomy dependent if the tracheotomy stayed in place for at least 6 months after the end of the treatment. Similar characteristics were used for the feeding gastrostomy and the feeding nasogastric tube.

A treatment failure was considered only when confirmed by a pathological result, and the indicated time of the positive biopsy was considered as the time of the failure.

The follow-up data were updated for all the patients to obtain the long term results, the mean follow up duration for all the patients being about 5 years. No patient was lost during the follow-up in the first 30 months post treatment. All the causes of death were clear in the reports.

3.2.2.3. STUDY BEGINNING POINT

The study beginning point for the calculation of the control and survival durations was the first day after the end of the radiotherapy.

3.2.2.4. STUDY END POINTS

The final end point for all the calculated durations was 31.12.2008, when the data collection closed and preparation of the data analysis begun.

- *PRIMARY END POINT- CONTROL RATES*

The primary end point for the control rates (local, regional, metastatic, and overall) was the pathological proof of cancer recurrence. Any patient alive with no previous reported recurrence or dead with no previous evidence of the disease, were considered as successfully controlled at the given calculated duration.

- *PRIMARY END POINT - SURVIVAL*

For overall survival, death due to any cause at a given duration is considered.

For the disease specific survival, death from the laryngeal cancer or as a direct complication to its treatment is considered. So, any patient alive or dead with no evidence of disease (e.g. controlled either by the primary treatment or after the salvage surgery) was considered as a successful survival at the calculated duration.

- *THE COMPOSITE END POINT - LARYNGECTOMY SPECIFIC SURVIVAL*

The composite end points for the laryngectomy specific survival at a given duration (e.g. disease specific survival with organ preservation rate) were death attributed to the laryngeal cancer as explained above or total laryngectomy to treat the cancer recurrence.

- *THE COMPOSITE END POINT - LARYNGEAL FUNCTION SPECIFIC SURVIVAL*

The basic laryngeal functions were considered lost if any of the following conditions occurred: 1) the patient became tracheotomy, 2) the patient became feeding tube dependent, or 3) a definitive surgical procedure to treat persistent aspiration such as laryngeal diversion or total laryngectomy was performed.

The composite end points for the laryngeal function specific survival at a given duration were death attributed to the laryngeal cancer as explained above, or total laryngectomy to treat the cancer recurrence, or loss of the basic laryngeal functions as explained above.

3.2.3. STATISTICAL ANALYSIS

All the data were first entered into Excel sheet, and then all the data description and analysis were done by SPSS version 15.

Descriptive statistics were used to describe age distribution, incidence, and the different doses of the radiotherapy treatment. The incidence of the different variables, treatment modalities, and complications were calculated directly.

The control and survival durations were estimated by the Kaplan-Meier method. The comparison of the control and survival curves was done by the Log Rank (Mantel-Cox) test.

All the variables were analysed against the control and survival with the p value is considered significant if ≤ 0.05.

All the mentioned percentages of the control and survival represent the median value between the superior and inferior limit for each measurement which is estimated with 95% confident interval.

Other duration regarding the (laryngeal preservation, tracheotomy dependent, feeding tube dependent, duration to metastatic recurrence …etc) were calculated by the cumulative percentage.

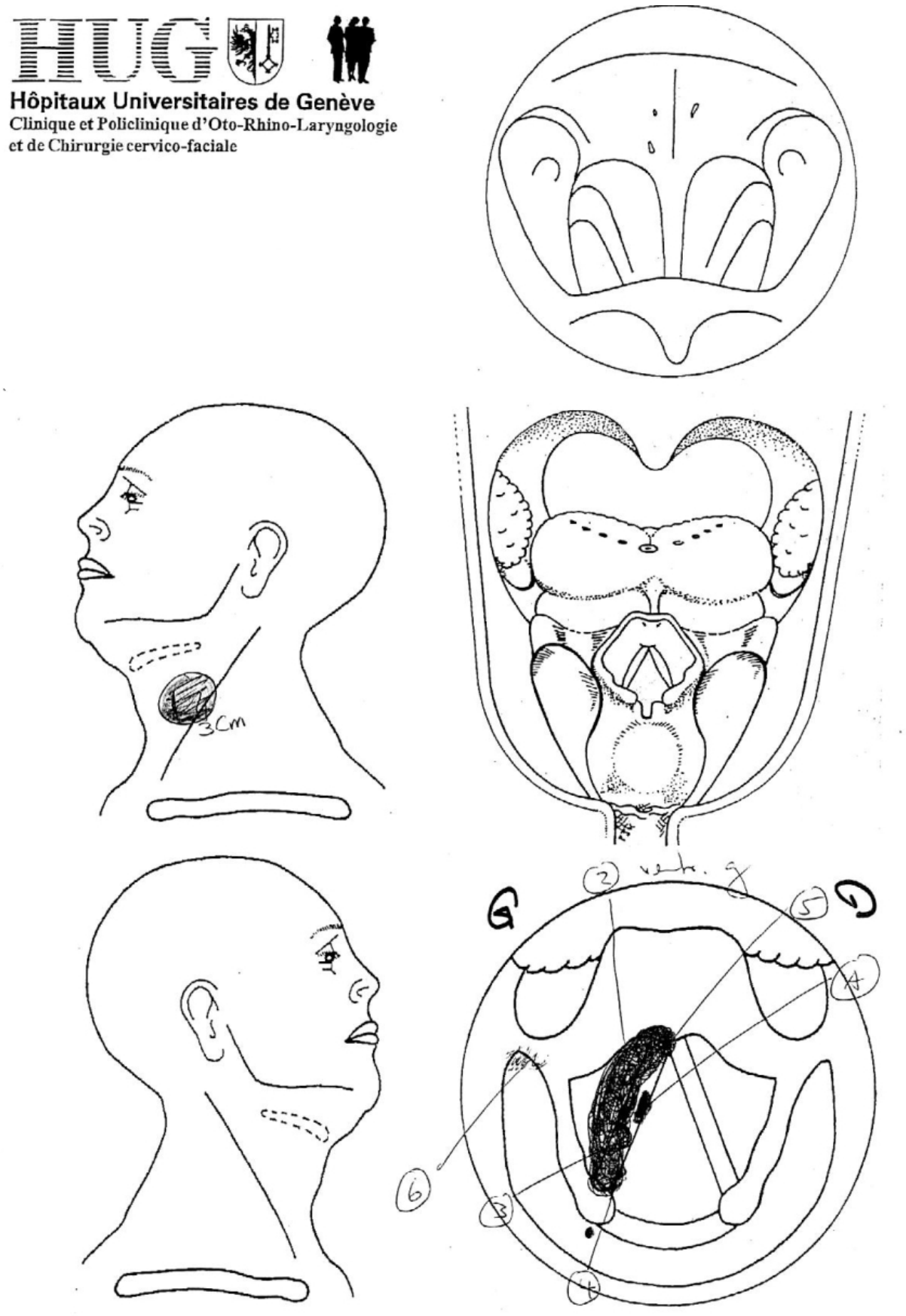


Figure 32: Schematic tumour mapping illustrating the tumour extension in one of the patients included in the study.

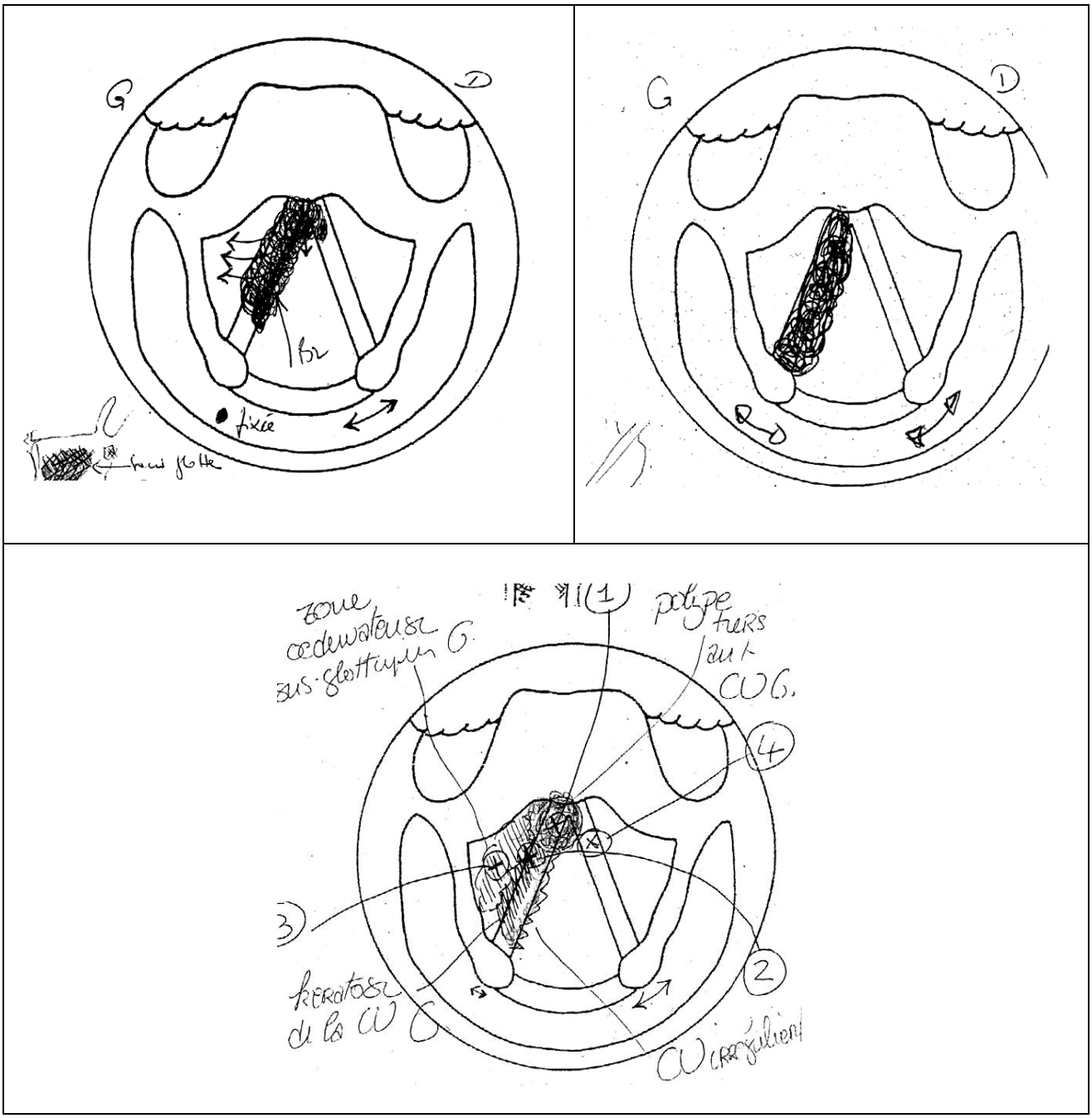


Figure 33: Three examples for the tumour mapping of the tumours included in the study.

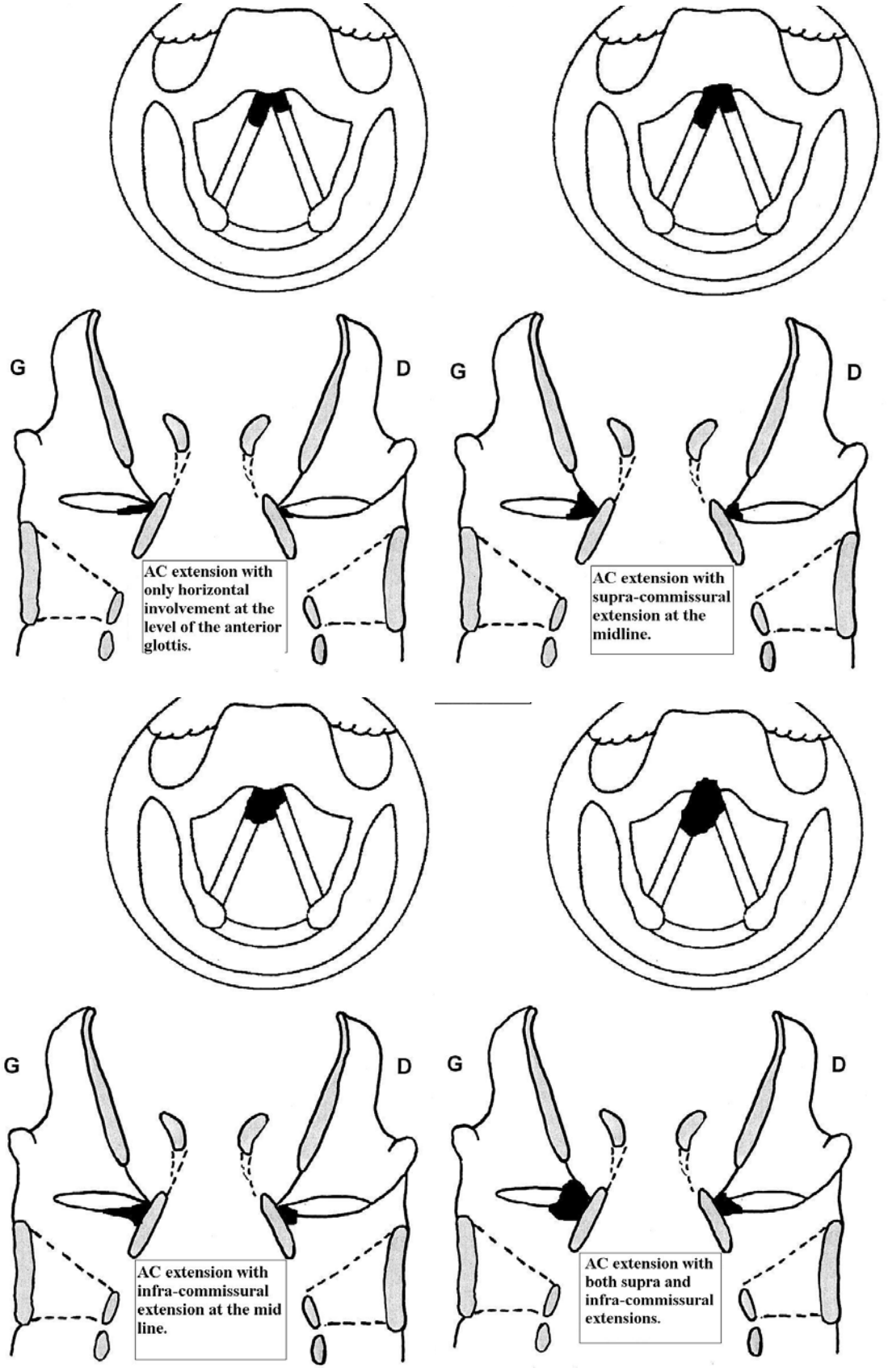


Figure 34: The different types of anterior commissure involvement by the cancer.

IV. RESULTS

4.1. PATIENTS

This study included 83 patients, 76 males and 7 females with a sex ratio (11:1). The patients' age was ranging between 37 and 89 years with the mean age 61.8 years.

4.2. THE SITE OF ORIGIN

In 68% of the cases included the site of origin was glottic (Table 6 and Figure 35), while 24% of the cases were originating from the supraglottic region and only 1 case (1%) was subglottic in origin. At the time of the diagnosis 7% of the cases were transglottic, i.e. involving all the three regions with difficulty to determine the exact subsite of origin.

Site of origin	Number of cases	Percentage
Glottic	56	67.5
Subglottic	1	1.2
Supraglottic	20	24.1
Transglottic	6	7.2
Total	83	100

Table 6: Site of origin.

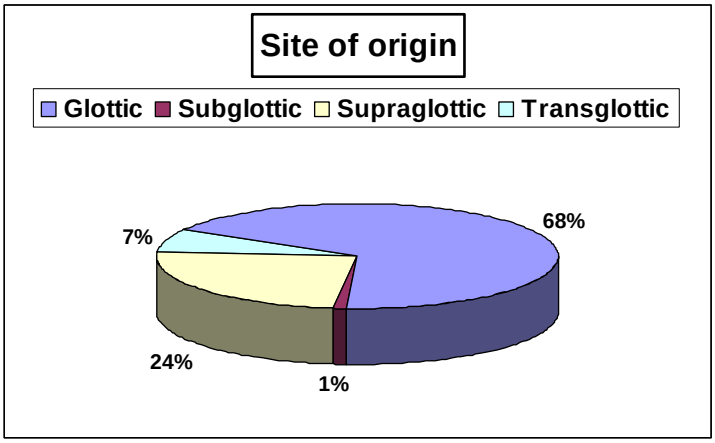


Figure 35: Site of origin.

4.3. DESCRIPTION OF THE CLINICAL VARIABLES

4.3.1. TNM DISTRIBUTION

All the cases were curable (e.g. M0) and resectable (e.g. no T4b and or N3). The cases were classified according to both the fifth and sixth editions of the TNM, but since both systems are identical regarding the clinical description, only one description is given here. The distribution according to T stage is shown in table 7 and figure 36, to N stage is shown in table 8 and figure 37, and to oncologic stage in table 9 and figure 38.

T stage	Number of cases	Percentage
T1	25	30.1
T2	39	47.0
T3	18	21.7
T4	1	1.2
Total	83	100.0

Table 7: The clinical T distribution according to the TNM stages of UICC 2002.

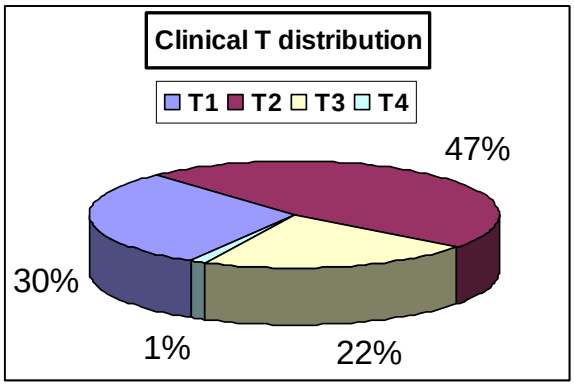


Figure 36: The clinical T distribution according to the TNM stages of UICC 2002.

N stage	Number of cases	Percentage
N0	72	86.7
N1	7	8.4
N2b	2	2.4
N2c	2	2.4
N3	0	0
Total	83	100.0

Table 8: The clinical lymph node extensions according to the TNM stages of UICC 2002.

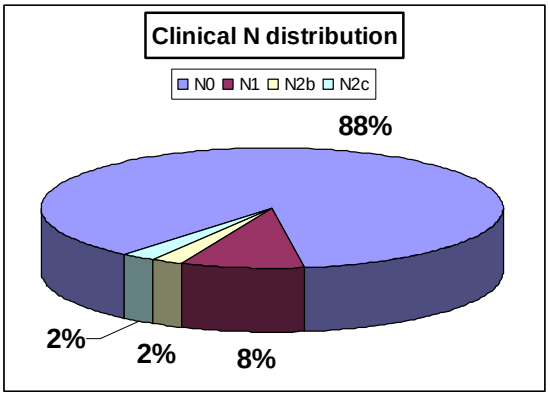


Figure 37: The clinical lymph node extensions according to the TNM stages of UICC 2002.

Grouped stages	Number of cases	Percentage
Stage 1	24	29
Stage 2	36	43
Stage 3	18	22
Stage 4A	5	6
Stage 4B	0	0
Stage 4C	0	0
Total	83	100.0

Table 9: The clinical grouped stages according to the TNM stages of UICC 2002.

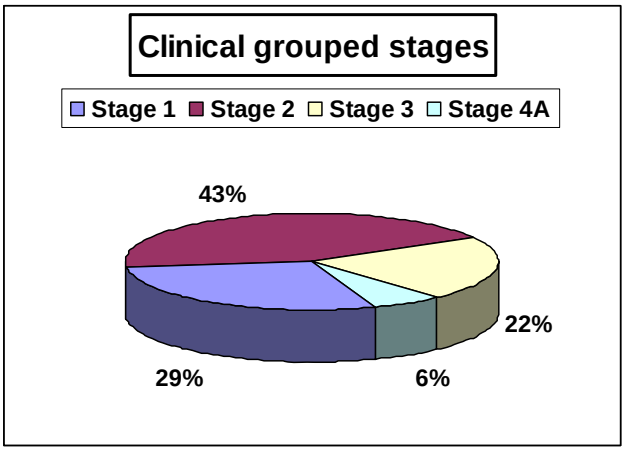


Figure 38: The clinical grouped stages according to the TNM stages of UICC 2002.

4.3.2. PATHOLOGICAL GRADING

The pathology grades were reported as described in the pathology report, i.e. G1-mild, G2-moderate and G3-poorly differentiated. Most cases were classified as mild to moderate differentiated (Table 10).

Pathological grading	Number of cases	Percentage
Well differentiated, G1	60	72.3
Moderately differentiated, G2	19	22.9
Poorly differentiated, G3	4	4.8
Total	83	100.0

Table 10: Pathological grades of the cases.

4.3.3. ANATOMICAL SUBSITES OF THE LARYNX

The incidences and percentages of all the anatomical sites which were studied are described in table 11. The involvement of the glottic anatomical subsites dominate as during the period of the study the supraglottic cases were managed usually by surgery ± postoperative radiotherapy, while the glottic cases was usually treated with the non-surgical modalities except high volume T4 cases needing combined treatment (e.g. T4 with extensive cartilage invasion, and or airway obstruction and or extensive subglottic involvement).

The anatomical site	Number of patients	Percentage
Right vocal fold	45	54.2
Left vocal fold	46	55.4
Right arytenoid (anterior surface)	10	12.0
Left arytenoid (anterior surface)	9	10.8
Right ventricle	16	19.3
Left ventricle	21	25.3
Right false vocal fold	9	10.8
Left false vocal fold	25	30.1
Infrahyoid epiglottis	18	21.7
Suprahyoid epiglottis	13	15.7
Right aryepiglottic fold	8	9.6
Left aryepiglottic fold	10	12.0
Right arytenoid (superior surface)	7	8.4
Left arytenoid (superior surface)	10	12.0
Mucosa of the oropharynx	8	9.6
Pyriform sinus	8	9.6
Postcricoid area	0	0
Subglottis globally	13	15.7
Anterior subglottis	6	7.2
Right lateral subglottis	4	4.8
Right left subglottis	8	9.6
Anterior commissure globally	37	44.6
Anterior commissure bilateral glottic involvement	17	20.5
Anterior commissure with supracommisural vertical extension	10	12.0
Anterior commissure with subcommisural vertical extension	11	13.3
Posterior commissure	4	4.8
Huge laryngeal lesion suspected by palpation	1	1.2
Extension to the tracheal mucosa	0	0

Table 11: Involvement of the various anatomical subsites by clinical assessment

4.3.4. THE ANTERIOR COMMISSURE

The incidence of the anterior commissure (AC) involvement is 45% (Figure 39). Anterior commissure involvement was present in 44% of T1, 46% of T2, 41% of T3, and 1/1 T4 cases. There is no correlation between T stage (Figure 40) and grouped stages (Figure 41) and involvement of the AC.

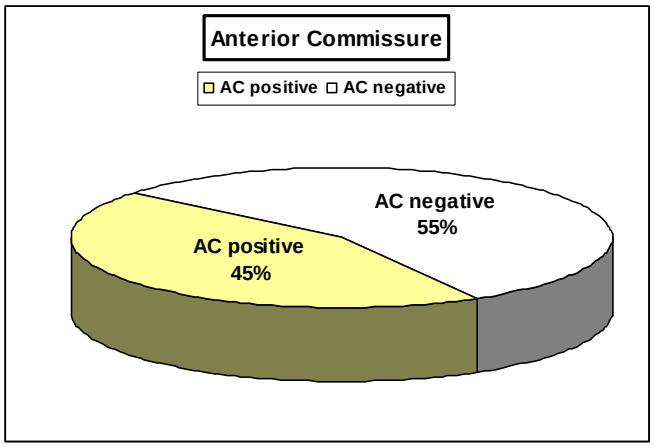


Figure 39: The general incidence of the anterior commissure involvement.

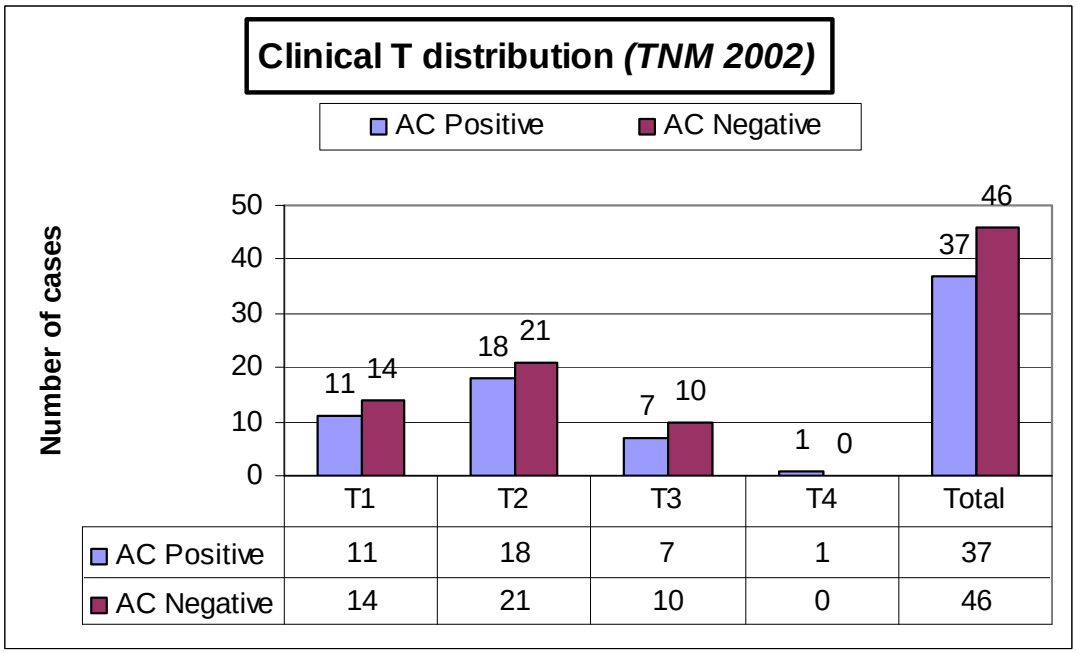


Figure 40: Comparison of the T distribution between the AC positive and AC negative cases.

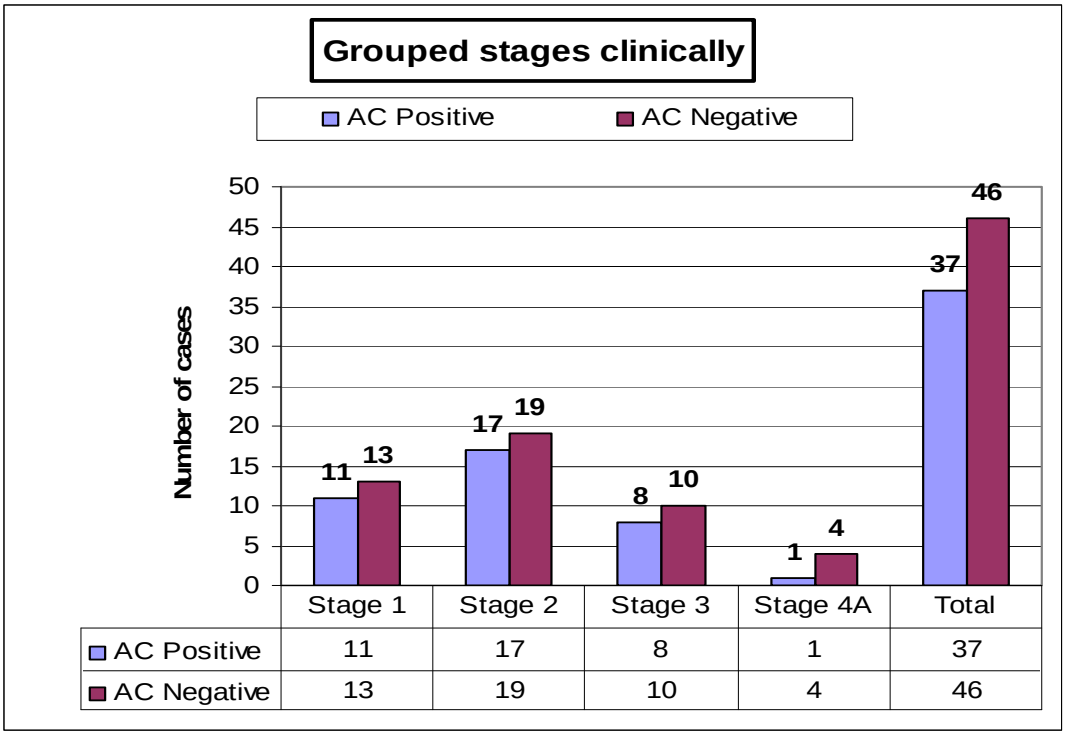


Figure 41: Comparison of the grouped stages between the AC positive and AC negative cases.

The incidence of the subgroups of the anterior commissure (AC1, AC2, and AC3) is described in figure 42. It is important to mention that one case may affect both vocal folds (AC1) and in the same time it show up (AC2) or down extension (AC3) at the anterior commissure, so it could be mentioned twice (e.g. the total number is not the sum of the subgroups but the total number of the AC cases).

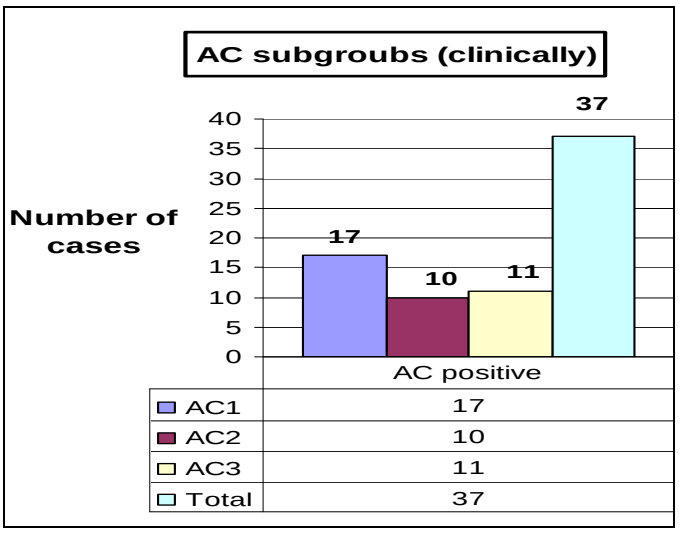


Figure 42: The anterior commissure subgroups.

4.3.5. VOCAL FOLD MOBILITY

The vocal fold mobility variables which are subjected to the analysis are described in table 12. Beside the classical analysis of the pre-treatment mobility status, we also analysed the mobility status reported in the third post treatment follow-up report.

Vocal cord mobility variables	Number of patients	Percentage
Right vocal fold (Hypomobile)	4	4.8
Right vocal fold (Fixed)	6	7.2
Right vocal fold - post treatment impaired mobility	9	10.8
Left vocal fold (Hypomobile)	7	8.4
Left vocal fold (Fixed)	6	7.2
Left vocal fold - post treatment impaired mobility	5	6.0
Vocal fold mobility impairment (global)	22	26.5
Post treatment affected vocal fold mobility impairment	15	18.1
Post treatment fixed vocal fold	4	4.8
Pre and post treatment persistent vocal fold mobility problems	6	7.2

Table 12: The incidences and the percentages of the vocal fold mobility variables.

4.3.6. LARYNGEAL OEDEMA

Laryngeal oedema was studied before and three months after the end of radiotherapy. Pre-treatment oedema was mild in all the cases and reported only in nine cases while the post-treatment oedema was mild to moderate in several cases and severe in two cases as described in table 13.

Laryngeal oedema 3 months post-treatment	Number of patients	Percentage
None	56	67.5
Mild to Moderate	24	28.9
Severe	2	2.4

Table 13: Laryngeal oedema three months post-radiotherapy.

4.4. DESCRIPTION OF THE RADIOLOGICAL VARIABLES

4.4.1. TNM DISTRIBUTION

All the cases were curable (e.g. M0) and resectable (e.g. no T4b and or N3). The cases were classified according both the fifth edition (TNM system 1997) as shown in tables 14, 16, and 17 and figures 43, 45, and 46 and the sixth editions (TNM system 2002) as shown in tables 15, 16, and 18 and figures 44, 45, and 47.

Radiological T stage 1997	Number of cases	Percentage
*Tx & *T1	24	28.9
T2	21	25.3
T3	22	26.5
T4	16	19.3
Total	83	100.0

Table 14: The radiological T distribution according to the TNM stages of UICC 1997.

*Three cases were not visible at the imaging, thus classified as radiological TX and analysed with the T1 as all these cases were clinically T1a.

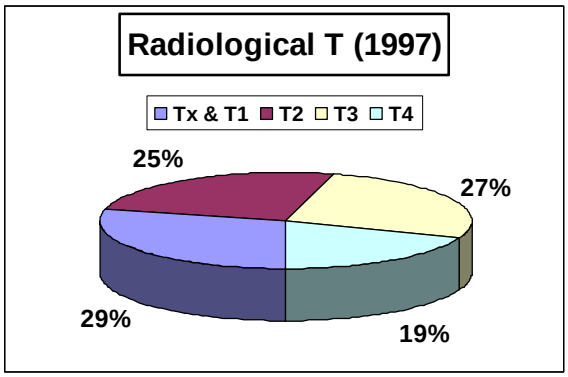


Figure 43: The radiological T distribution according to the TNM stages of UICC 1997.

Radiological T stage 2002	Number of cases	Percentage
*Tx & *T1	23	27.7
T2	8	9.6
T3	48	57.9
T4	4	4.8
Total	83	100.0

Table 15: The radiological T distribution according to the TNM stages of UICC 2002.

*Three cases were not visible at the imaging, thus classified as radiological TX and analysed with the T1 as all these cases were clinically T1a.

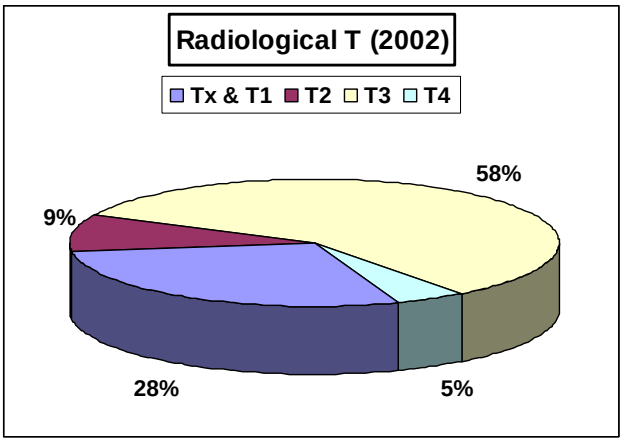


Figure 44: The radiological T distribution according to the TNM stages of UICC 2002.

N stage	Number of cases	Percentage
N0	66	79.5
N1	7	8.4
N2a	2	2.4
N2b	2	2.4
N2c	6	7.2
N3	0	0
Total	83	100.0

Table 16: The radiological lymph node extensions according to the TNM stages of UICC 1997 and 2002.

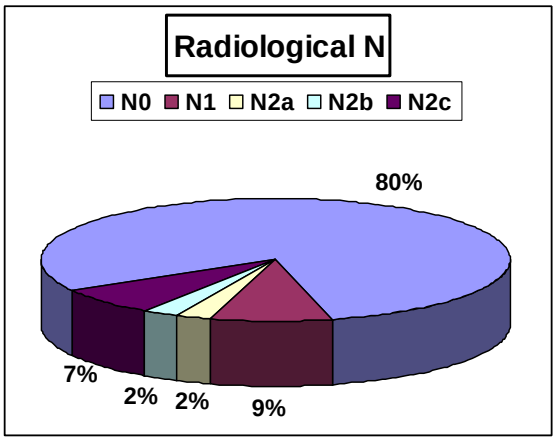


Figure 45: The radiological lymph node extensions according to the TNM stages of UICC 1997 and 2002.

Grouped stages	Number of cases	Percentage
Stage 1	23	28
Stage 2	20	24
Stage 3	17	20
Stage 4A	23	28
Stage 4B	0	0
Stage 4C	0	0
Total	83	100.0

Table 17: The radiological grouped stages according to the TNM stages of UICC 1997.

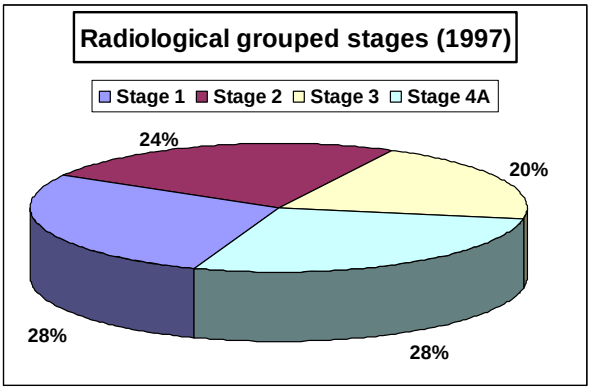


Figure 46: The radiological grouped stages according to the TNM stages of UICC 1997.

Grouped stages	Number of cases	Percentage
Stage 1	22	27
Stage 2	8	10
Stage 3	40	47
Stage 4A	13	16
Stage 4B	0	0
Stage 4C	0	0
Total	83	100.0

Table 18: The radiological grouped stages according to the TNM stages of UICC 2002.

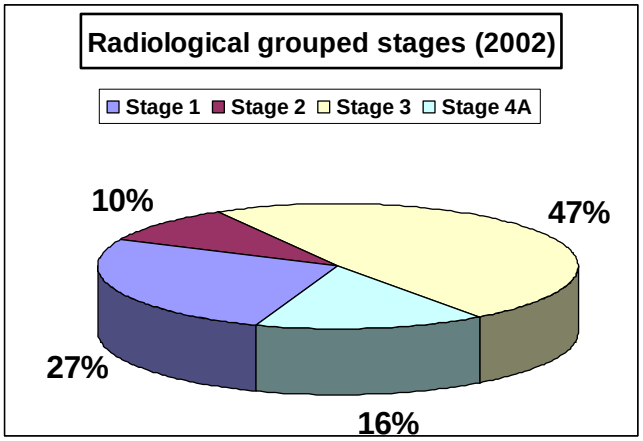


Figure 47: The radiological grouped stages according to the TNM stages of UICC 2002.

		Radiological T stage UICC2002										Total
		T1	T1a	T1b	T2	T3	T3a	T3b	T4	T4a	Tx	
Radiological T stage UICC1997	T1	1	0	0	0	0	0	0	0	0	0	1
	T1a	0	10	0	0	0	0	0	0	0	0	10
	T1b	0	0	9	0	0	1	0	0	0	0	10
	T2	0	0	0	8	1	12	0	0	0	0	21
	T3	0	0	0	0	13	9	0	0	0	0	22
	T4	0	0	0	0	0	0	12	1	3	0	16
	Tx	0	0	0	0	0	0	0	0	0	3	3
Total		1	10	9	8	14	22	12	1	3	3	83

Table 19: Correlation between radiological stages according to TNM-1997 and TNM-2002

The shift of patients between the two TNM classifications is summarized in table 19: 24 patients (29%) changed T stages, the majority of patients shifting towards T3: 12 patients shifting from T2 to T3 and 12 patients shifting from T4 to T3.

An even more important shift of patients can be seen between the clinical (UICC 2002) and the radiological (UICC 2002) T staging. Less than half of the patients remained in the same T stage, with 50 patients (60%) changing T stages. The main shift concerned T2 clinical cases which were upstaged to T3 and the majority because of paraglottic space involvement (16 patients) and a minority because of cartilage erosion (6 patients), the remaining being supraglottic cases with preepiglottic space involvement (Table 20).

		Radiological T stage UICC2002				Total
		T1	T2	T3	T4	
T clinical by UICC2002	T1	20	1	4	0	25
	T2	2	7	29	1	39
	T3	1	0	15	2	18
	T4	0	0	0	1	1
Total		23	8	48	4	83

Table 20: Correlation between clinical and radiological T stages (UICC 2002)

4.4.2. DETAILED ANATOMICAL SUBSITES

The incidences and percentages of all the anatomical sites are described in table 21. Similarly to clinical variables, the majority of involved sites are glottic. The low incidence of cartilage invasion and especially of extensive growth through the cartilage (only 4 cases) should be noted. As previously discussed these cases

were usually treated with total laryngectomy followed by post-operative radiotherapy.

Large percentage of patients had an involvement of the anterior commissure (see below) and the paraglottic space.

The anatomical site	Number of patients	Percentage
Right vocal fold	43	51.8
Left vocal fold	37	44.6
Right Thyroarytenoid Muscle	19	22.9
Left Thyroarytenoid Muscle	20	24.1
Right ventricle	17	20.5
Left ventricle	25	30.1
Right false vocal fold	20	24.1
Left false vocal fold	23	27.7
Infrahyoid epiglottis	15	18.1
Suprahyoid epiglottis	14	16.9
Right aryepiglottic fold	6	7.2
Left aryepiglottic fold	12	14.5
Paraglottic space grouped	43	51.8
Right paraglottic space	18	21.7
Left paraglottic space	25	30.1
Pre-epiglottic space	19	22.9
Mucosa of the oropharynx	12	14.4
Pyriform sinus	14	16.8
Postcricoid area	0	0
Subglottis globally	16	19.3
Anterior subglottis	7	8.4
Right lateral subglottis	8	9.6
Right left subglottis	5	6.0
Anterior commissure globally	44	53.0
Anterior commissure bilateral glottic involvement	19	22.9
Anterior commissure with supracommisural vertical extension	17	20.5
Anterior commissure with subcommisural vertical extension	15	18.1
Posterior commissure	6	7.2
Laryngeal framework invasion (global)	19	22.8
Extralaryngeal spread through the anterior and /or lateral laryngeal surfaces	4	4.8
Invasion of cricothyroid membrane	1	1.2
Invasion of thyrohyoid membrane	0	0
Extension to the tracheal mucosa	0	0

Table 21: The anatomical subsites involvement according to imaging.

4.4.3. THE ANTERIOR COMMISSURE

The incidence the anterior commissure (AC) involvement can be found in table 21 and distribution of the cases involving the anterior commissure (AC) against the TNM UICC 2002 in figures 48 and 49.

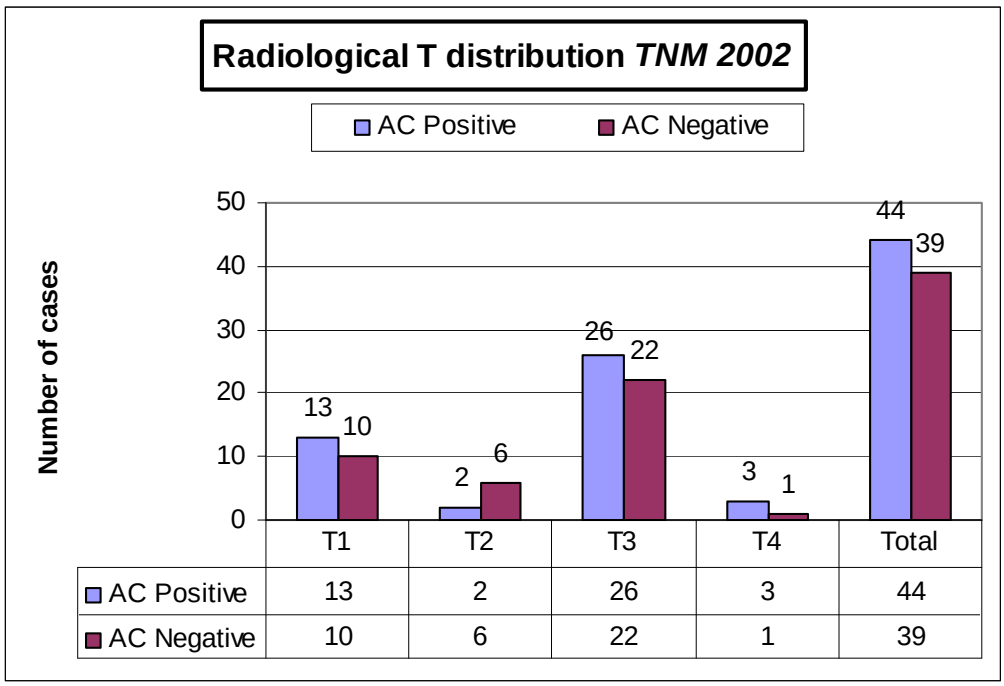


Figure 48: Comparison of the T distribution between the radiological AC positive and AC negative cases (TNM UICC 2002).

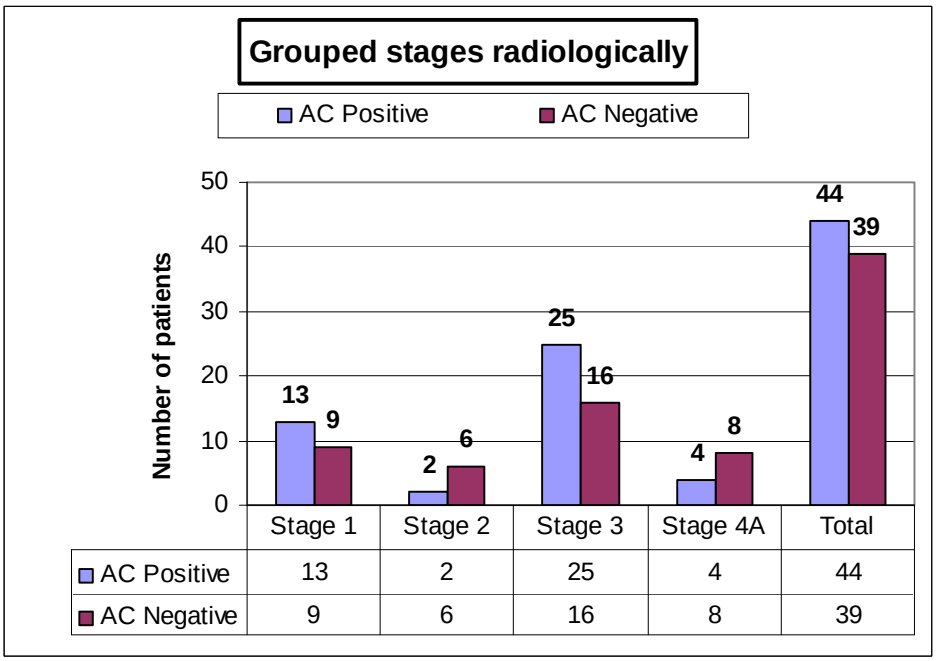


Figure 49: The comparison of the grouped stages distribution between the radiological AC positive and AC negative cases regarding the TNM UICC 2002.

4.4.4. DETAILED DATA OF CARTILAGE INVASION

All the variants of the suspected cartilage invasion reported in the images are described in table 22. The overall incidence of the cartilage invasion was not high, and the incidence of both extensive cartilage invasion or cricoid cartilage affection were minimal since almost all these cases were subjected to total laryngectomy and were not treated with organ preservation protocols.

Variants of cartilage invasion	Number of patients	Percentage
Laryngeal framework invasion (thyroid and /or cricoid cartilage invasion)	19	22.8
Thyroid cartilage invasion	16	19.3
Cricoid cartilage invasion	3	3.6
Arytenoid cartilages invasion	17	20.5
Combined thyroid + cricoid + arytenoid cartilages invasion	0	0
Combined thyroid + cricoid cartilages invasion	0	0
Combined cricoid + arytenoid cartilages invasion	2	2.4
Combined thyroid + arytenoid cartilages invasion	6	7.2
Isolated arytenoid cartilage invasion	9	10.8
Sever destruction or lyses of the arytenoid cartilage	2	2.4
Other variants of arytenoid cartilage invasion	15	18.1
*Thyroid cartilage invasion at the anterior area (the intermediate lamina)	8	9.6
*Thyroid cartilage invasion at the lateral areas (the lateral thyroid ala)	10	12
*Wide area of thyroid cartilage invasion =†(anterior and lateral)	2	2.4
Thyroid cartilage invasion (transverse through the cartilage e.g. with extralaryngeal spread)	3	3.6
Thyroid cartilage invasion other variants	13	15.6
Cricoid cartilage invasion at the anterior area	0	0
Cricoid cartilage invasion at the lateral area	1	1.2
Cricoid cartilage invasion at the near the cricoarytenoid joint	2	2.4
Cricoid cartilage invasion (transverse through the cartilage e.g. with extralaryngeal spread)	0	0
Cricoid cartilage invasion other variants	3	3.6

Table 22: The different variables of suspicious cartilage invasion.

***One case may involve both anterior and lateral invasion. † One case was invading anterior and bilaterally in the same time.**

4.5. TREATMENT MODALITIES

Different treatment modalities used were detailed previously (§3.2.) and summarised for radiotherapy in tables 4 and for chemotherapy in table 5.

4.5.1. DEBULKING

Debulking was reported in almost one third of the patients (Table 23).

Debulking	Number of patients	Percentage
No	59	71.1
Yes	24	28.9

Table 23: The incidence of debulking.

4.6. FOLLOW-UP

No cases were lost during the first two years. The mean follow-up for all the patients included in this study was 49.84 (1-138) months (Figure 50) and the mean follow up for the survivors at the time of the analysis was 65.2 (1-138) months. Moreover, at seven years post treatment only (23%) patients were lost in follow up. Thus, it was feasible to describe the control and survival rates at both 2 and 5 years post treatment.

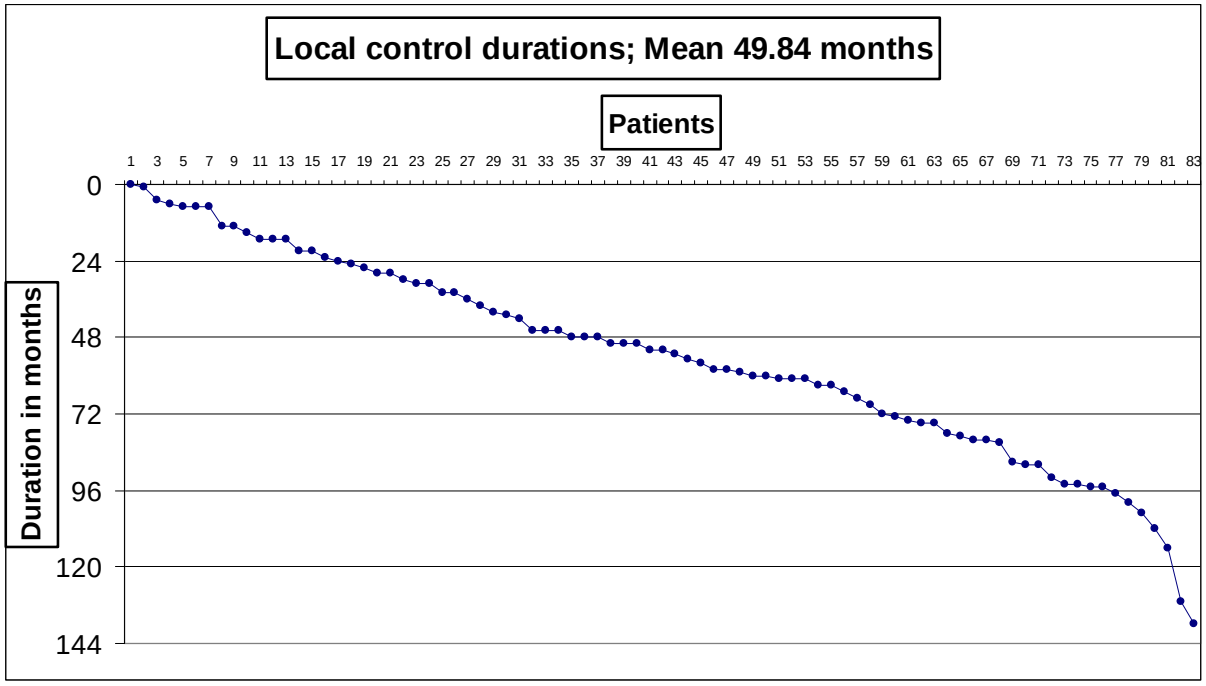


Figure 50: Follow-up duration

4.7. GLOBAL SURVIVAL AND CONTROL RATES

4.7.1. THE CONTROL RESULTS

The estimated local control, locoregional control and overall control rates at 50 months post treatment (the mean follow-up for all the patients) were 75.9%, 74.6%, and 71.1%, thus the overall tumour control was mainly dependent on the local control as shown in figure 51. One case only failed after the date of the mean follow-up and it was a locoregional failure. Overall survival and local control probabilities are shown in figure 52.

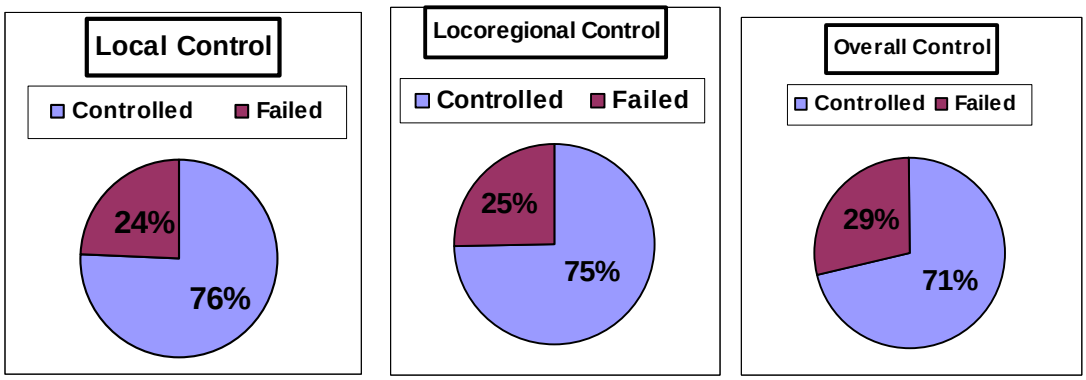


Figure 51: Pie-chart of (from left to right) local, locoregional, and overall crude control rates.

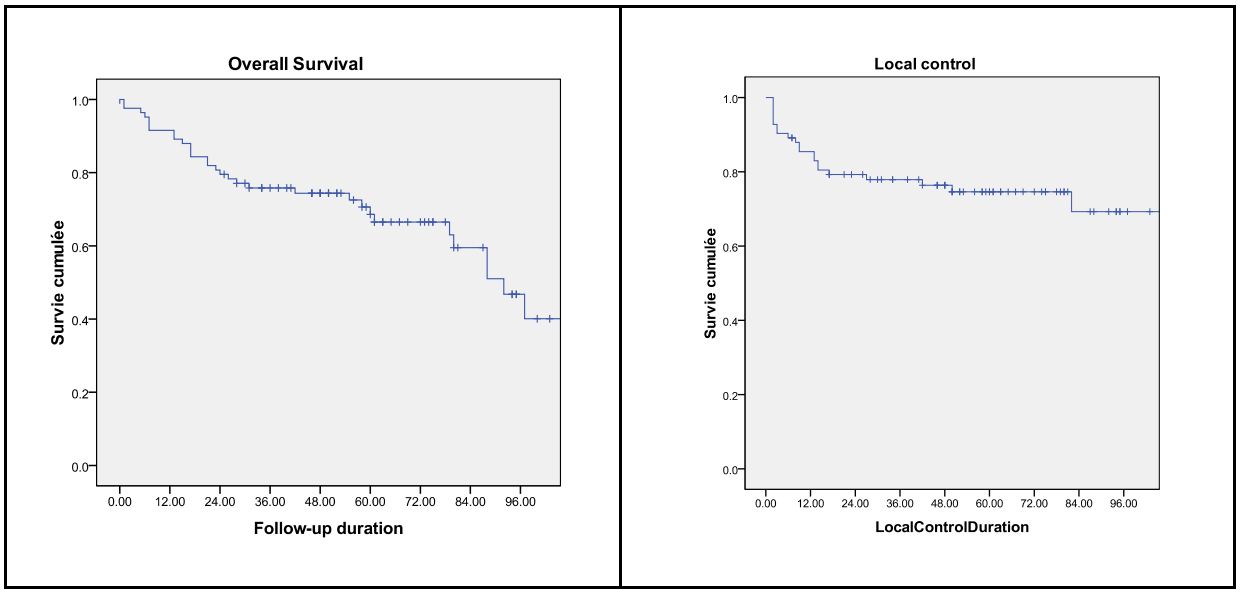


Figure 52: Overall survival (Left) and local control (Right) according to the Kaplan-Meier method.

Twenty-one cases failed locally with a mean delay to local failure of 15.3 (1-82) months. The two, five

and seven years local control rates were 79.5%, 75.9% and 74.6% respectively.

Nine cases showed regional failure with a mean delay of 23.3 (2-82) months. The two, five and seven years locoregional control rates were 79.5%, 74.6% and 73.5% respectively.

Distant metastatic failure was detected in six cases with a mean delay of 17.3 (4-45). Among these six cases, three was not accompanied with local or regional failure but it the biopsy results from these larynges showed severe dysplasia. The two, five and seven years overall control rates were 77.1%, 71.1%, and 69.8% respectively.

Finally, recurrent cancer was diagnosed in 25 of the cases of this study during the follow up periods, and the different variants of failure are explained in figure 53.

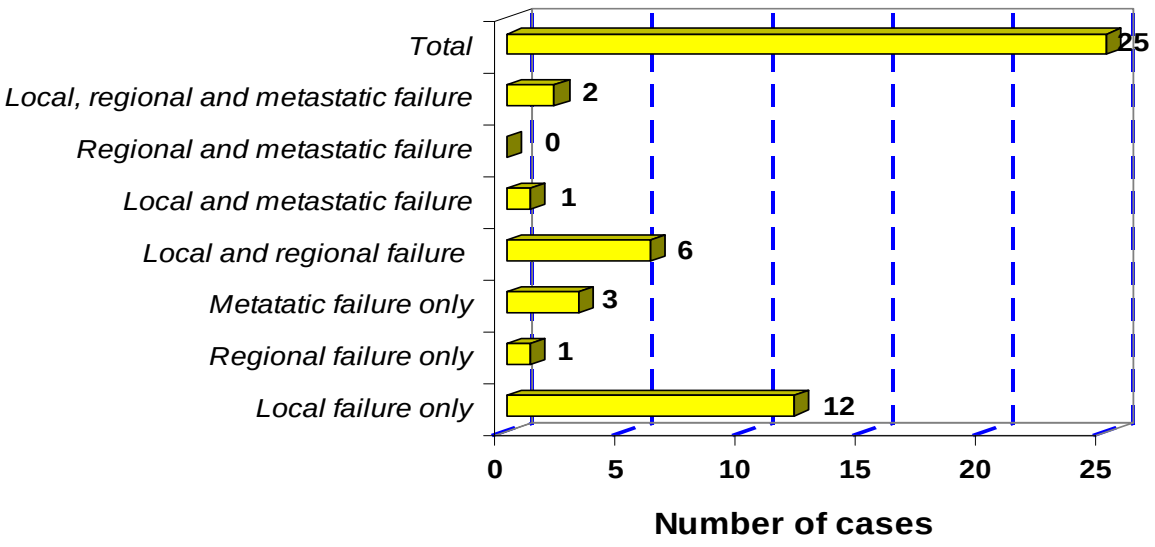


Figure 53: Variants of tumour failure reported in this study.

4.7.2. CAUSES OF DEATH

All causes of death were known in this study, thus no case was reported as died due to unknown cause. At the time of the analysis, 31 deaths were reported, and in 62% of cases, the cause of death was related to cancer larynx. The causes and percentages of the deaths are summarised in table 24 and figure 54.

Cause of death	Number
Cancer larynx	20
Upper aerodigestive tract cancer	3
Other malignancy	3
Other disease	5
Alive at the analysis	52
Total	83

Table 24: Causes of death

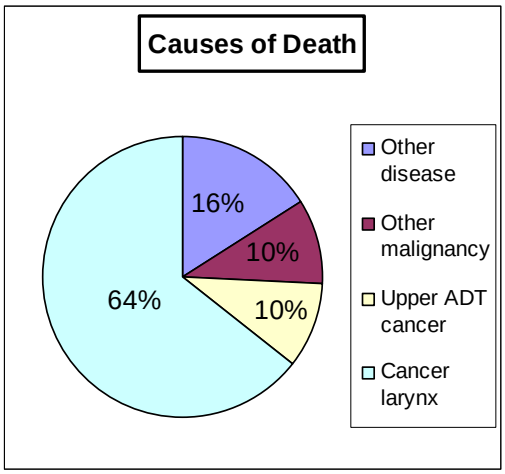


Figure 54: Diagram explaining the different causes of death.

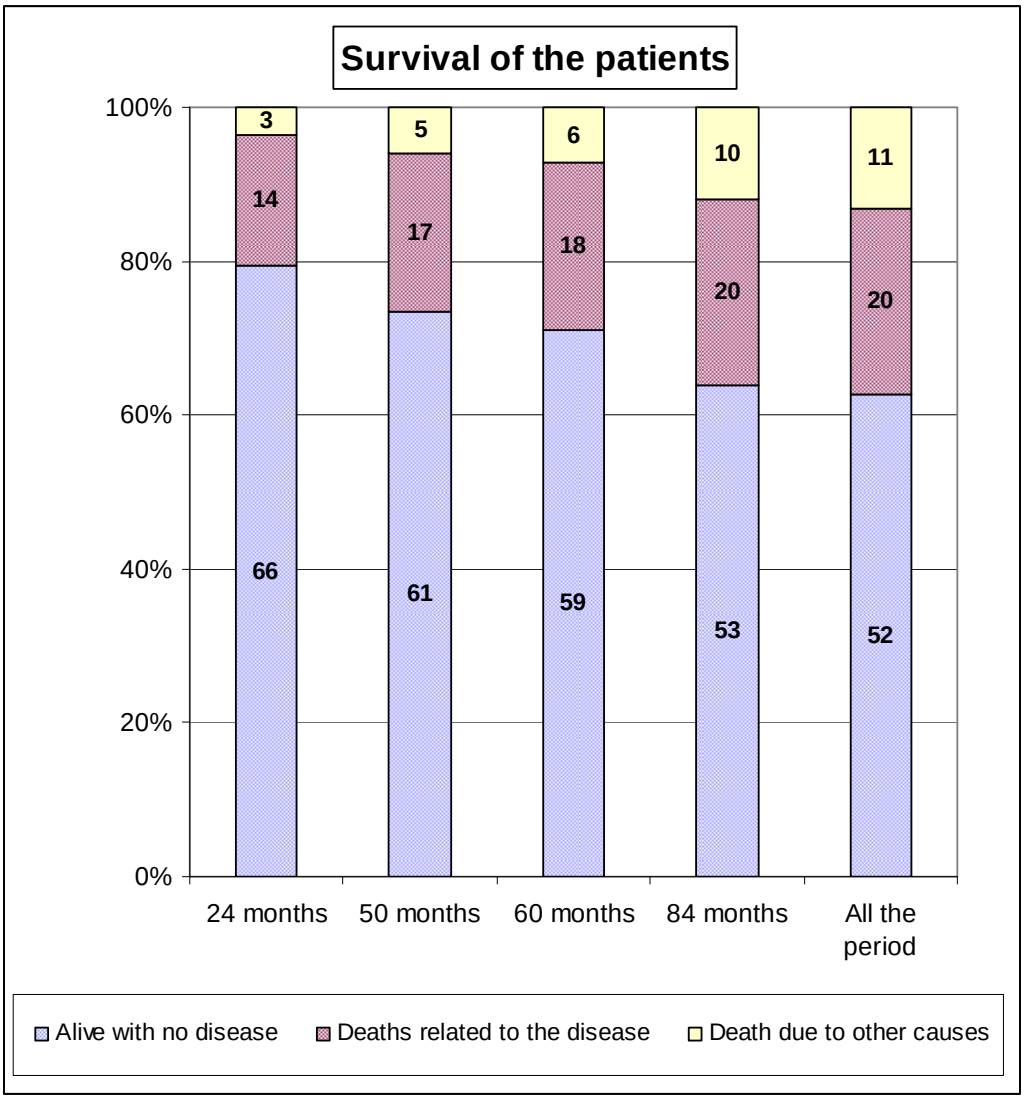


Figure 55: Diagram of the different causes of death and various time intervals.

4.7.3. SURVIVAL RESULTS

The precise outcome, i.e. alive with no disease (cured), dead due to cancer larynx, or dead from other causes at various times is shown in figure 55. At 50 months (the mean follow-up for the cohort) the disease specific survival and the overall survival rates were 80 % and 73 % respectively.

The overall survival probability at two, five and seven years were 80%, 71% and 64%, respectively (Figure 56).

The disease specific survival probability at two, five and seven years were 83%, 78% and 76%, respectively (Figure 57).

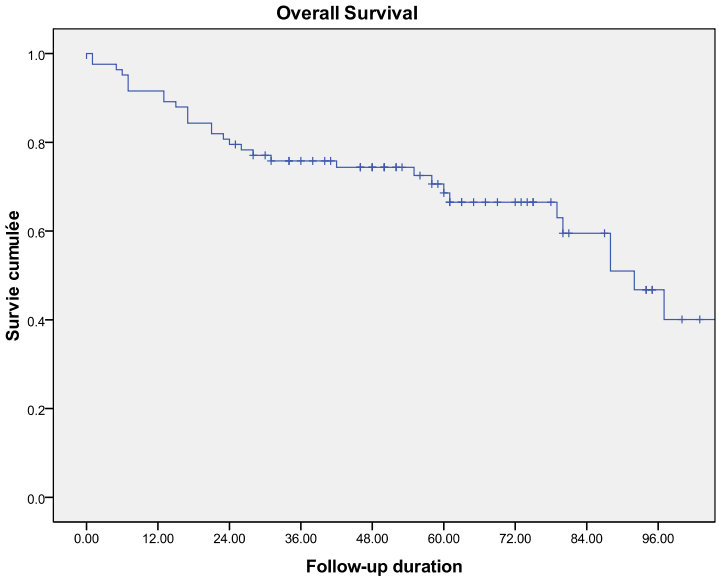


Figure 56: Overall survival

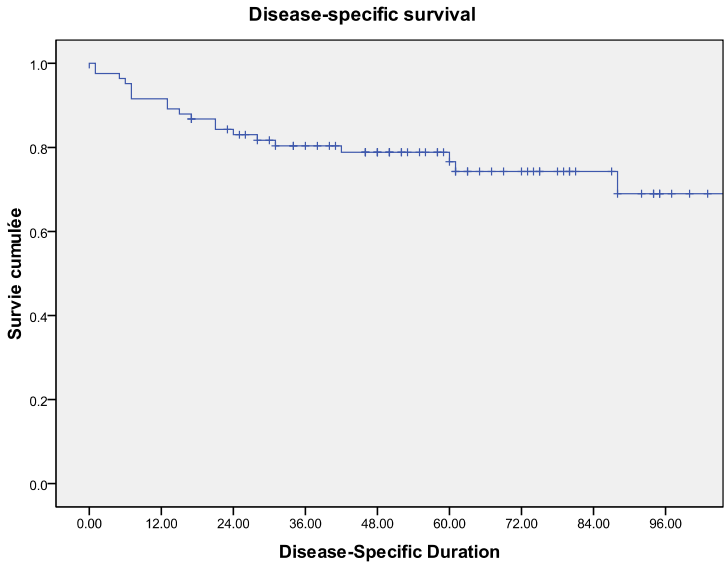


Figure 57: Disease-specific survival

4.8. ONCOLOGIC RESULTS FOR DIFFERENT VARIABLES

4.8.1. ANALYSIS OF THE DIFFERENT VARIABLES

All the variables were analysed against the control and survival to detect the most unfavourable extensions that affect the local control and survival when treating the patients with the (chemo)radiotherapy. Only statistically significant variables are summarized here: in table 25 for the clinical variables, and table 26 for the radiological variables.

Variables	Local Control	Disease Specific Survival	Overall Survival
Site of origin	0.1020	0.0000	0.0020
Pathological grades	0.0380	0.0010	0.0130
Treatment strategy	0.7150	0.0890	0.7780
Debulking	0.9110	0.1280	0.5410
T clinical by UICC2002	0.0200	0.0000	0.0000
N clinical by UICC2002	0.7320	0.0000	0.0010
AC Involvement globally	0.0010	0.2620	0.3410
AC bilateral glottic involvement (AC1)	0.0020	0.8620	0.4140
AC Superior extension (AC2)	0.0040	0.0010	0.0050
AC Inferior extension (AC3)	0.0060	0.0270	0.0070
VC Mobility	0.4780	0.8800	0.8920
VC mobility 3 months post-treatment	0.0000	0.0000	0.0000
Suprahyoid epiglottis	0.1660	0.0000	0.0020

Infrahyoid epiglottis	0.2040	0.0000	0.0020
Oropharynx	0.0340	0.0000	0.0000
Right ary-epiglottic fold	0.8880	0.0000	0.0100
Left ary-epiglottic fold	0.1850	0.0020	0.0390
Subglottis anterior - involvement	0.0000	0.0000	0.0000
Subglottic extension	0.0020	0.0140	0.0010
Pyriform sinus	0.349	0.005	0.05
Laryngeal oedema 3 months post-treatment	0.0030	0.0000	0.0010
Clinically palpable lymph nodes	0.7990	0.0000	0.0050

Table 25: The significant p-values for clinical variables.

The boxes of the highly significant variables are coloured in green, while in the other significant variables the background is yellow. The variable is considered significant if the p value is ≤ 0.05, and is considered highly significant if the p value is ≤ 0.001.

Variables	Local Control	Disease Specific Survival	Overall Survival
Radiological T stage UICC1997	0.8030	0.0130	0.0410
Radiological T stage UICC2002	0.2690	0.0040	0.0150
Radiological N stage UICC2002	0.6780	0.0000	0.0030
Radiological suprahyoid epiglottic cartilage invasion	0.2760	0.0000	0.0130
Radiological Preepiglottic Space	0.4120	0.0010	0.0070
Radiological Oropharynx global	0.4000	0.0000	0.0140
Radiological Piriform Sinus	0.2310	0.0000	0.0060
Radiological Thyroid or Cricoid Cartilage Involvement	0.6040	0.0390	0.0050
Radiological Thyroid Cartilage Involvement AC	0.8580	0.7360	0.0460

Table 26: The significant p-values radiological variables

The boxes of the highly significant variables are coloured in green, while in the other significant variables the background is yellow. The variable is considered significant if the p value is ≤ 0.05, and is considered highly significant if the p value is ≤ 0.001.

4.8.2. CLINICAL (TN) STAGES

The estimated 2 years local control for T1, T2, T3 and T4 cases were 93%, 77%, 71%, and 0/1 respectively (Figure 58). The estimated 5 years local control for T1, T2, T3 and T4 cases were 82%, 75%, 66%, and 0/1 respectively (Figure 58).

The estimated 2 years disease specific survival for T1, T2, T3 and T4 cases were 100%, 90%, 57%, and 0/1

respectively (Figure 59). The estimated 5 years disease specific survival for T1, T2, T3 and T4 cases were 100%, 77%, 44%, and 0/1 respectively (Figure 59).

The estimated 2 years disease specific survival for the clinically N negative and the clinically N positive cases were 89%, and 56% respectively The estimated 5 years disease specific survival for the clinically N negative and the clinically N positive cases were 82%, and 35% respectively (Figure 60).

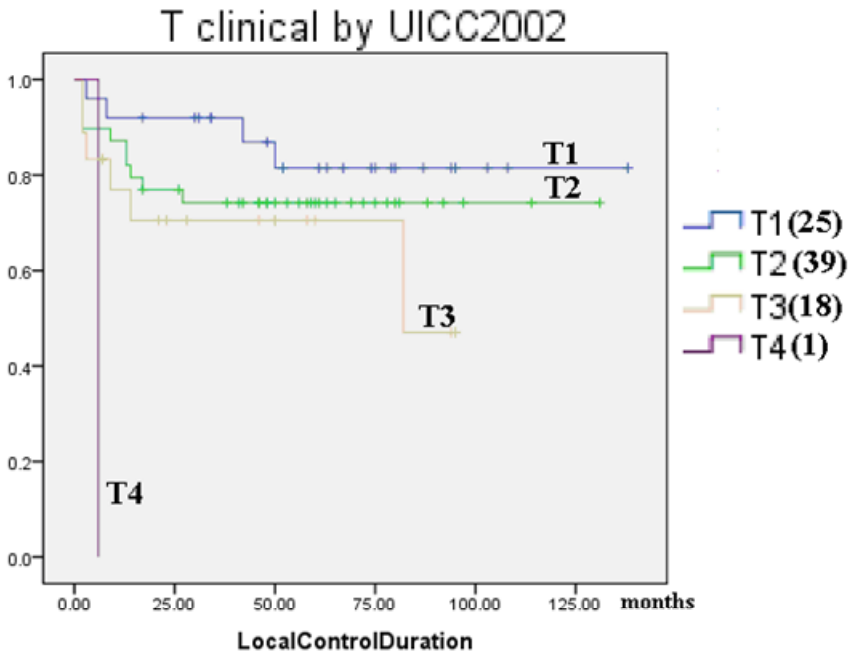


Figure 58: The local control according to the T stages.

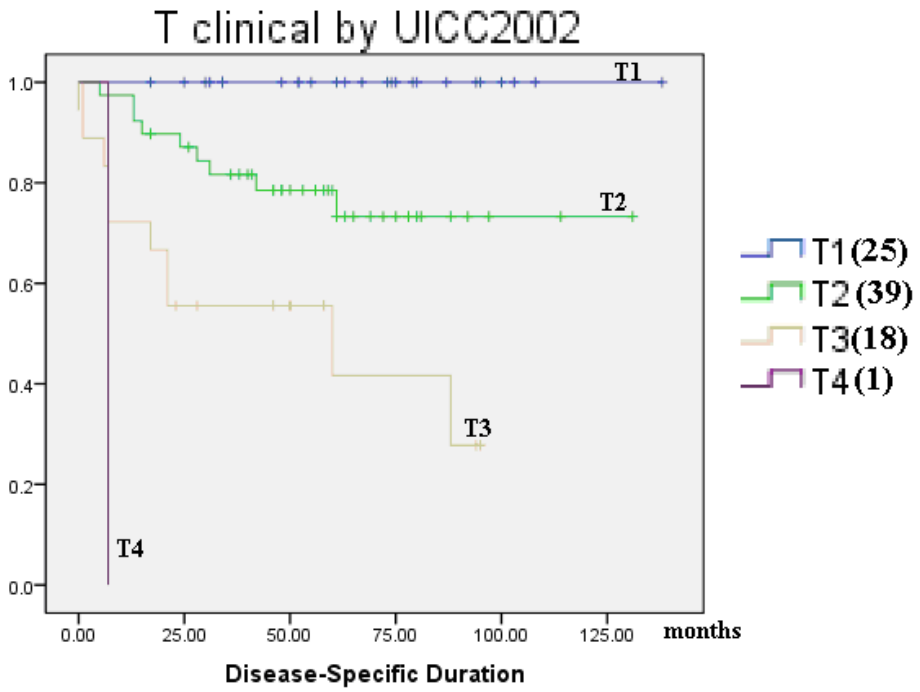


Figure 59: The disease specific survival according to the T stages.

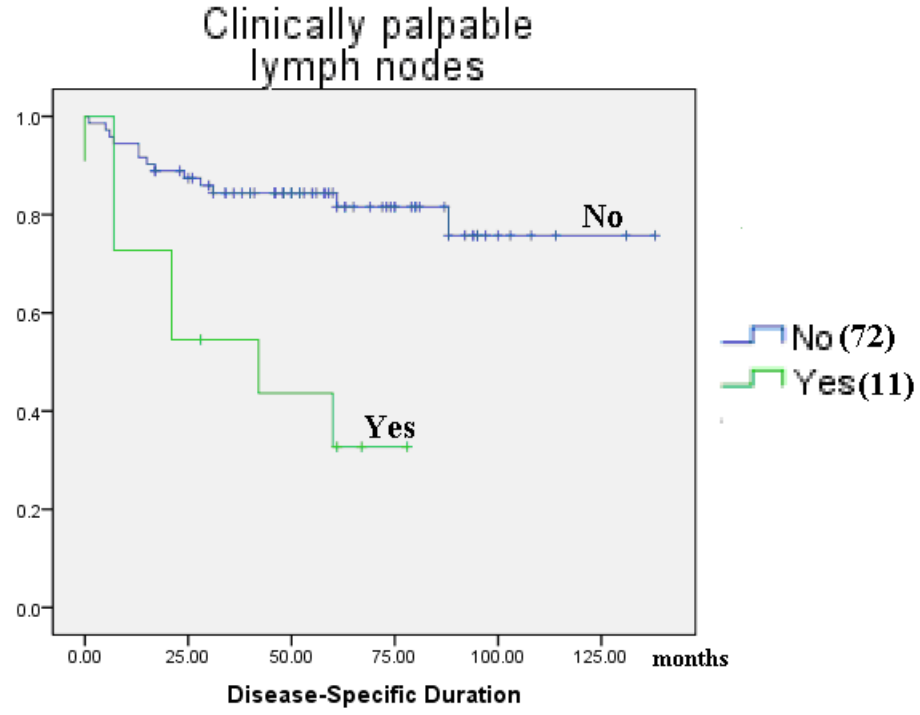


Figure 60: The disease specific survival in the presence of clinical lymph nodes.

4.8.3. RADIOLOGICAL (T) STAGES

The estimated 5 years local control for the radiological T1, T2, T3, T4 according to the TNM UICC 1997 were 87.5%, 76.2%, 71.4%, and 68.7%, respectively (Figure 61). The estimated 5 years local control for the same categories according to the TNM UICC 2002 were 82.6%, 50%, 77.1% and 50% (2/4), respectively (Figure 62).

The estimated 5 years disease specific survival for the radiological T1, T2, T3, T4 according to the TNM UICC 1997 were 100 %, 80.9%, 60%, and 56.2% respectively (Figure 63). The estimated 5 years local control for the same categories according to the TNM UICC 2002 were 100%, 62.5%, 79.1% and 25% (3/4), respectively (Figure 64).

In figures 62 and 64 the T3a cases are that cases classified as T3 due to the radiological paraglottic space invasion and the T3b were the cases with suspected minimal cartilage invasion in the images.

The estimated 5 years disease specific survival for the N stages (N0, N1, N2a, N2b, and N2c) were 83.3%, 3/7, 0/2, 2/2, and 3/6, respectively (Figure 65). One case classified as N2a and other case classified as N2b were treated with neck dissection followed by (chemo)radiotherapy for the primary site and post-operative for the neck dissection site.

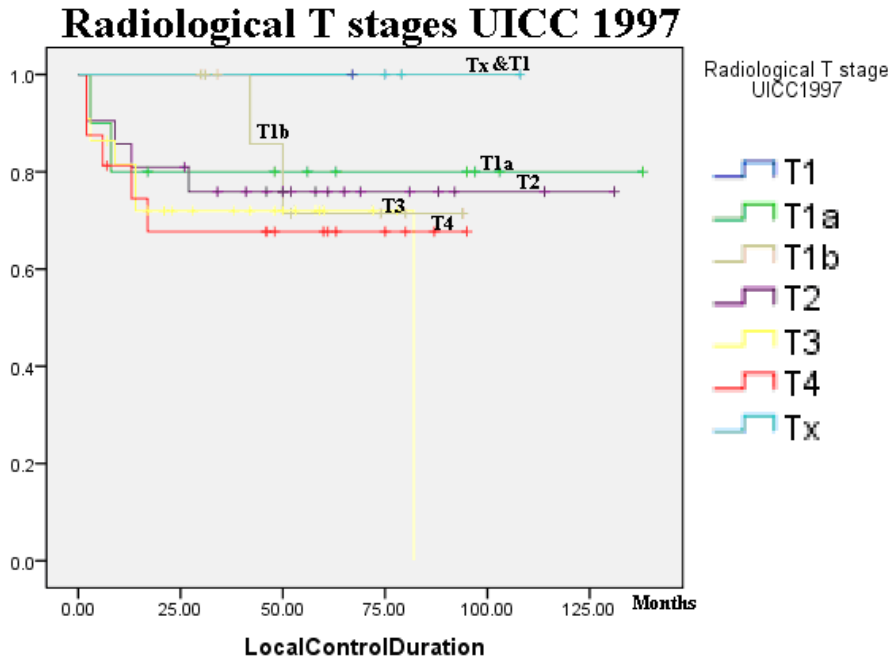


Figure 61: The local control according to the T stages UICC 1997.

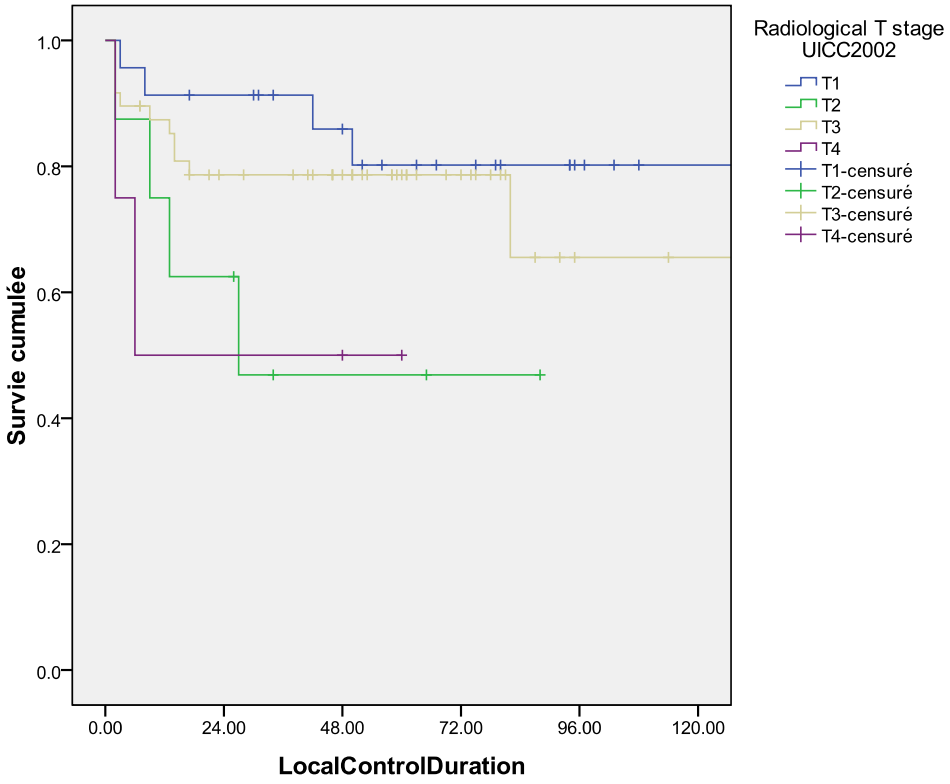


Figure 62: The local control according to the T stages UICC 2002.

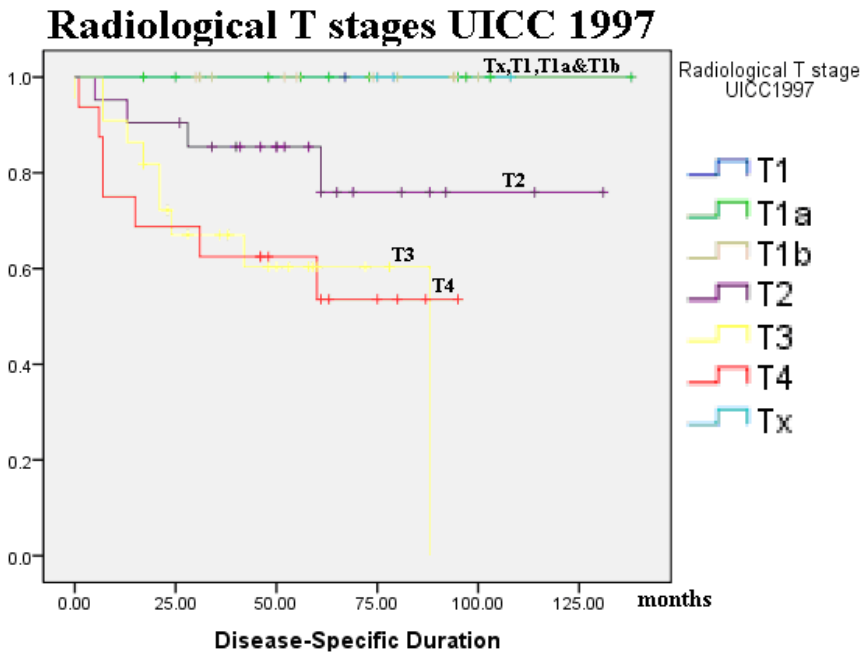


Figure 63: The disease specific survival according to the T stages UICC 1997.

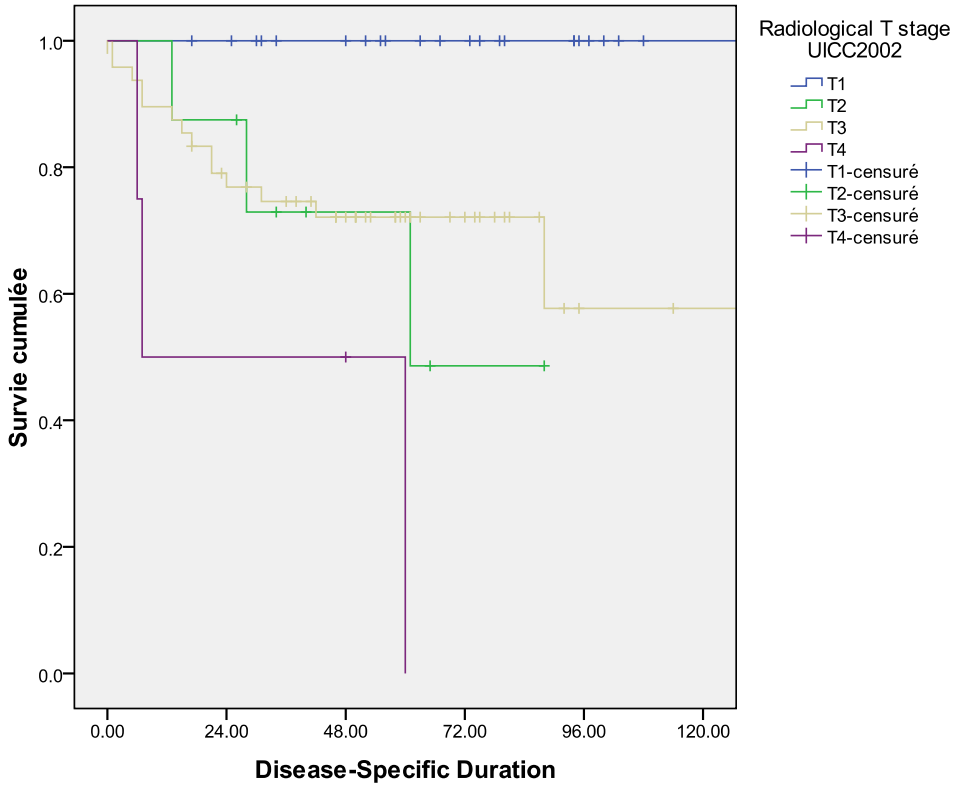


Figure 64: The disease specific survival according to the T stages UICC 2002.

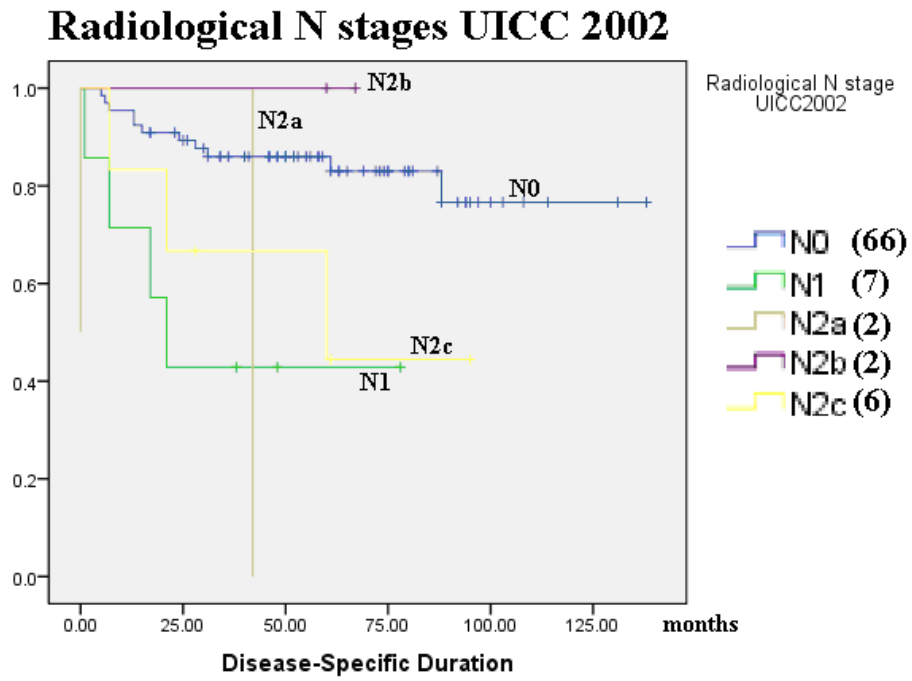


Figure 65: The disease specific survival according to the N stages UICC 2002.

4.8.4. THE EFFECT OF ANTERIOR COMMISSURE INVOLVEMENT

The calculated local control and failure rates referred to the mean follow-up time of the study (49.84) months are summarised in table 27 regarding the different clinical T stages.

Clinical T	Locally controlled	Locally failed	Total
T1 AC +ve	7 (64%)	4	11
T1 AC -ve	14 (100%)	0	14
T2 AC +ve	11 (61%)	7	18
T2 AC -ve	18 (86%)	3	21
T3 AC +ve	3 (43%)	4	7
T3 AC -ve	9 (82%)	2	11
T4 AC +ve	0	1	1
T4 AC -ve	0	0	0
Total	62 (75%)	21 (25%)	83

Table 27: Effect of anterior commissure involvement on local control in different clinical T stages.

According to the clinical evaluation the estimated 5 years local control rate of the clinical AC positive cases were 57% while it was 89% in the clinical AC negative cases (Figure 66). However, the 5 years disease

specific survival rates were 80% and 70% for the AC negative and AC positive cases, respectively (Figure 67).

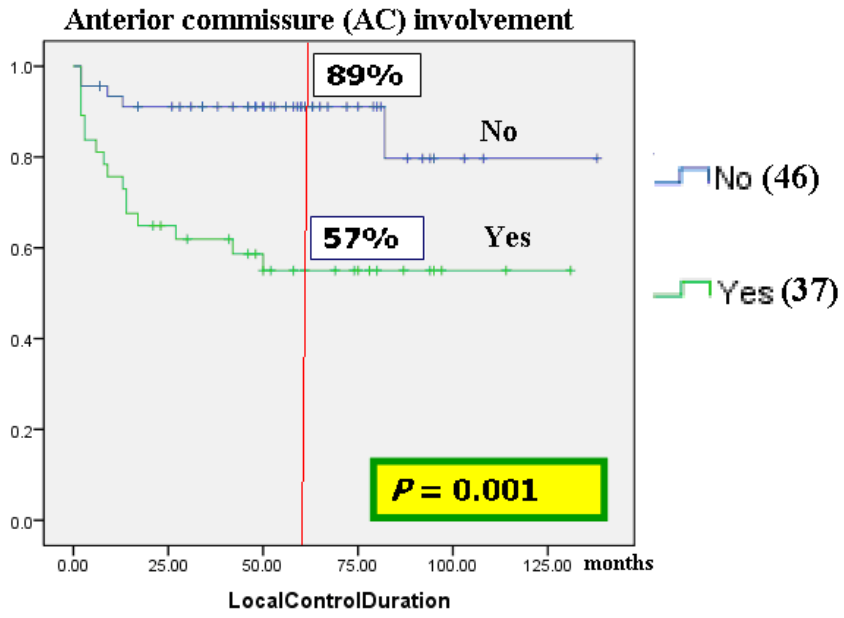


Figure 66: The 5 years local control regarding the anterior commissure involvement.

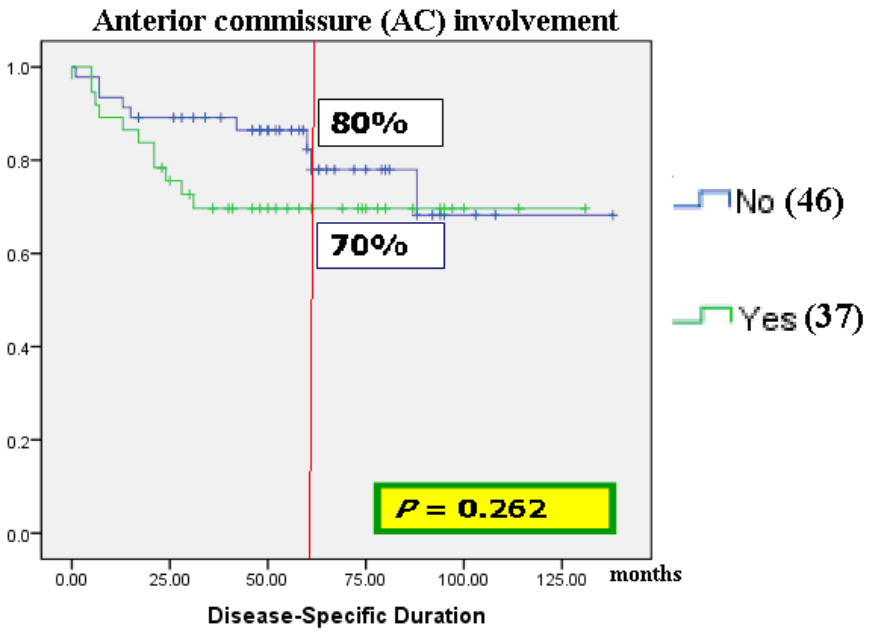


Figure 67: The 5-year disease specific survival regarding the anterior commissure involvement.

4.8.5. THE SUB-ANALYSIS OF THE ANTERIOR COMMISSURE

4.8.5.1. ANTERIOR COMMISSURE 1 (AC1)

Seventeen cases were reported to have extension along the horizontal plane at the anterior commissure involving the anterior parts of both vocal folds. The distribution of the T stages, the control and survival results are detailed in figures 68 and 69. Only one case has positive nodal disease (1/17).

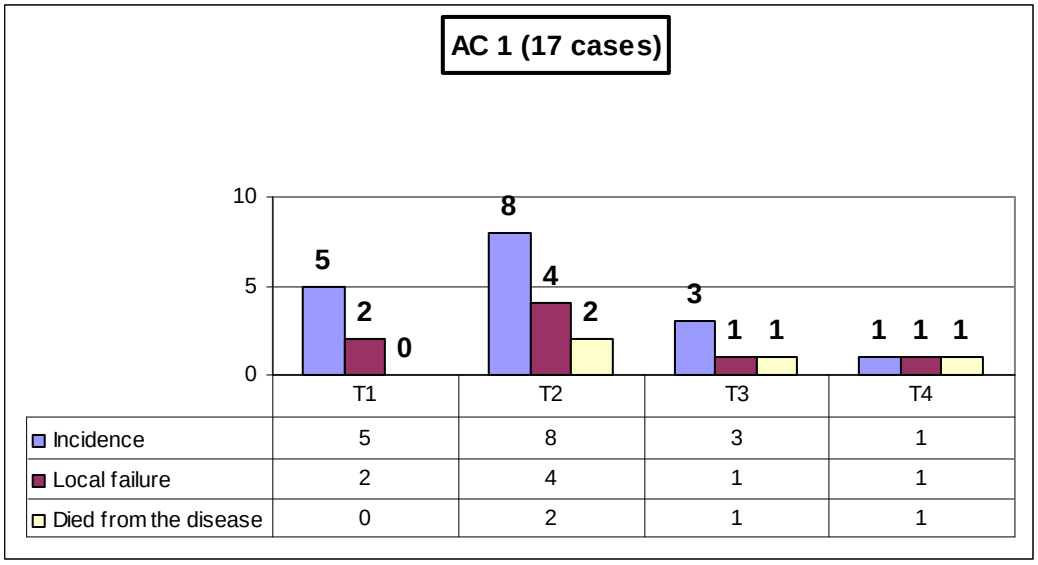


Figure 68: The T distribution and control results of the AC 1 regarding the different clinical T stages.

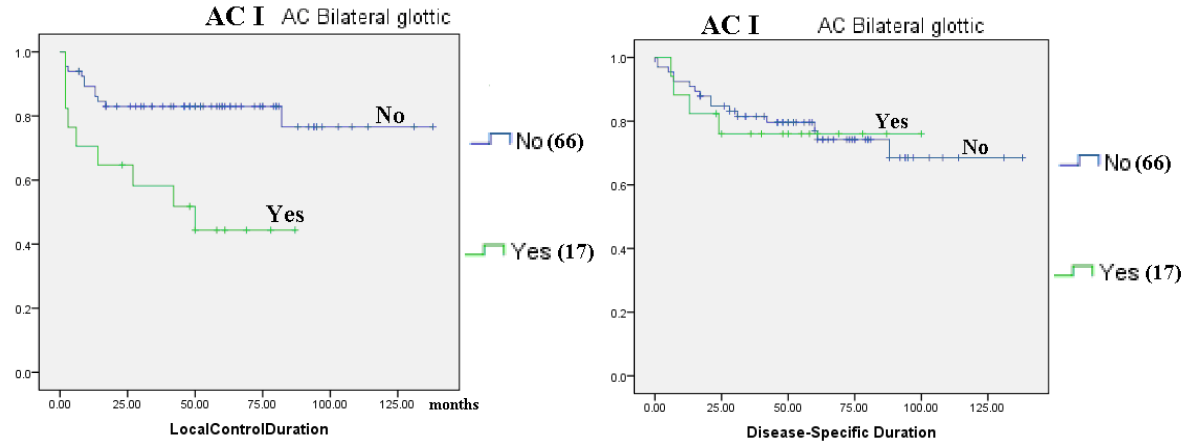


Figure 69: The local control curve (left) and the disease specific survival curve (right) for AC1.

4.8.5.2. ANTERIOR COMMISSURE 2 (AC2)

Ten cases were reported to have up extension along the vertical plane at the anterior commissure involving the supra-commissural area. The distribution of the T stages, the control and survival results are detailed in figures 70 and 71. Three cases had a positive nodal disease.

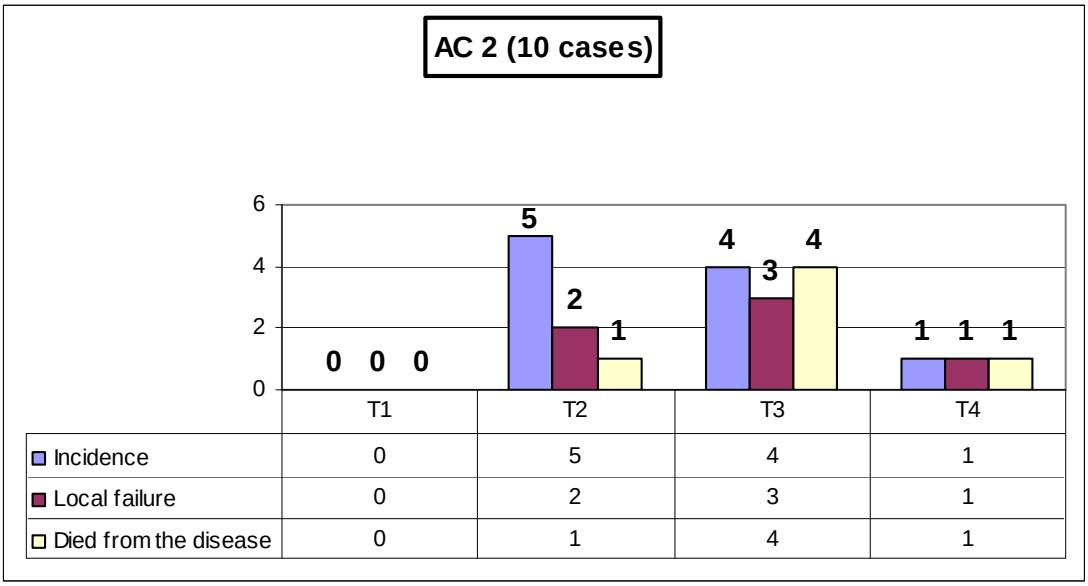


Figure 70: The T distribution and control results of the AC2 regarding the different clinical T stages.

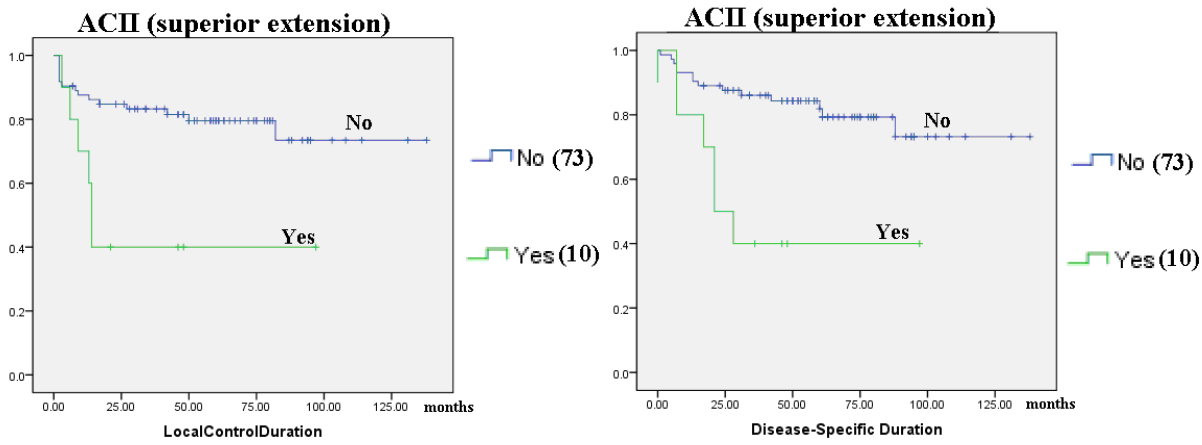
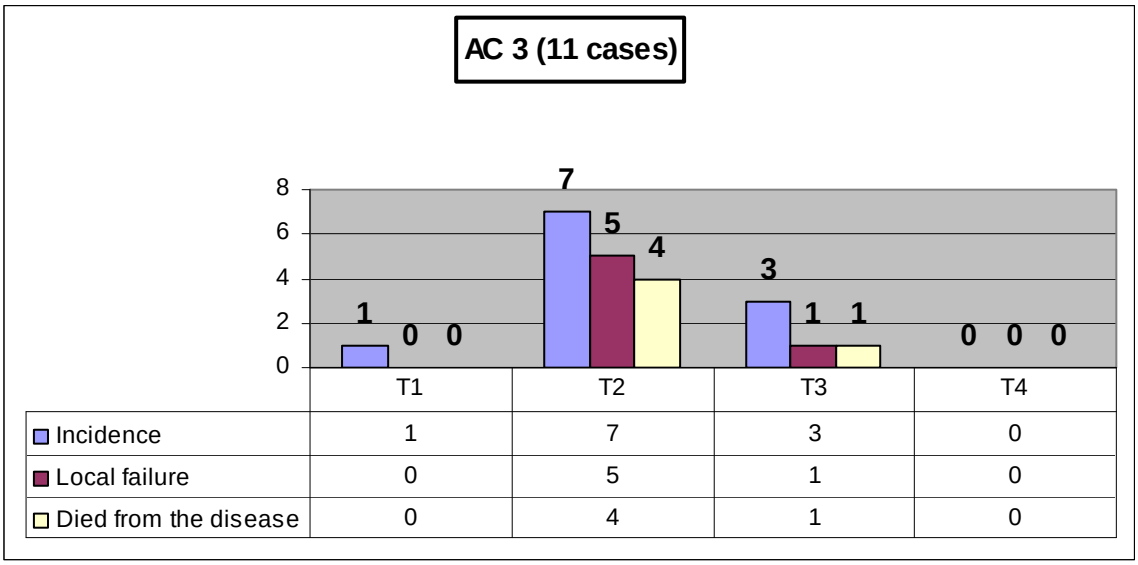


Figure 71: The local control curve (left) and the disease specific survival curve (right) for the AC2.

4.8.5.3. ANTERIOR COMMISSURE 3 (AC3)

Eleven cases were reported to have down extension along the vertical plane at the anterior commissure involving the infra-commissural area. The distribution of the T stages, the control and survival results are detailed in figures 72 and 73. All the cases were N0.

Only two cases had both up and down extension, thus it was not feasible to analyse these two cases as a separate group.



	T1	T2	T3	T4
Incidence	1	7	3	0
Local failure	0	5	1	0
Died from the disease	0	4	1	0

Figure 72: The T distribution and control results of the AC3 regarding the different clinical T stages.

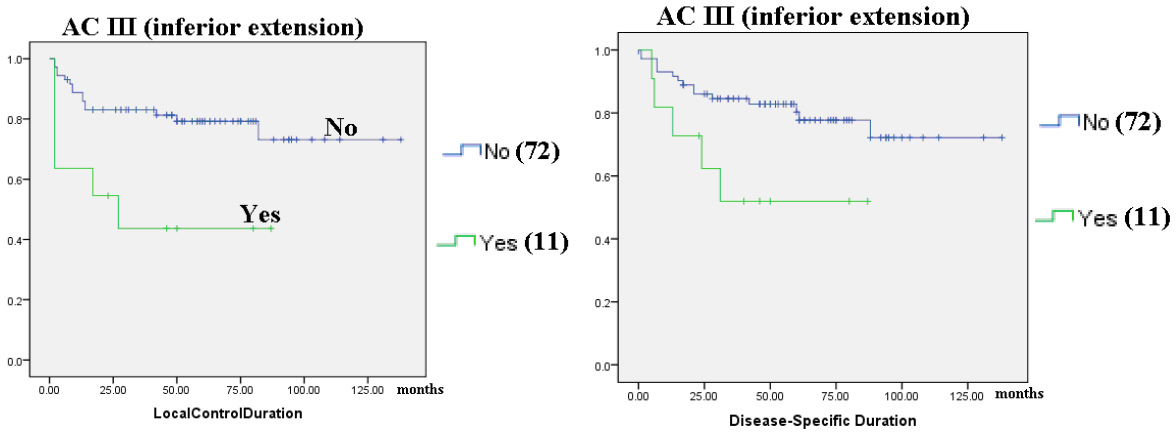


Figure 73: The local control curve (left) and the disease specific survival curve (right) for the AC3.

4.8.6. VOCAL FOLD MOBILITY

Although the vocal cord mobility changes either impaired or fixed were not significant for both control and survival (Table 25), but the persistence or the development of mobility impairment or fixation after the end of radiotherapy were highly significant for both local control and survival (Figure 74). Fifteen cases were reported to have vocal fold mobility impairment or fixation three months after the end of the radiotherapy.

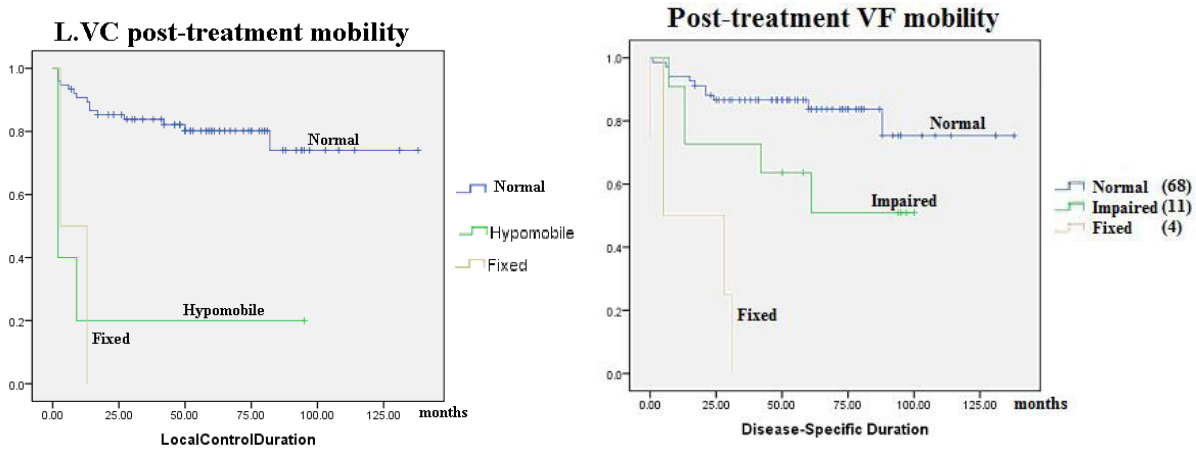


Figure 74: The local control curve (left) and the disease specific survival curve (right) for the cases that reported to have post-radiotherapy VC mobility impairment.

4.9. FUNCTIONAL RESULTS

4.9.1. TRACHEOTOMY

Temporary tracheotomy was done during or immediately after the end of the treatment in 10 cases and lasted for a period of three months or more for all the patients (Figure 75). Among these ten cases, six died from cancer larynx recurrence. Five of these cases presented with local failure, four died from the disease and one was salvaged successfully with total laryngectomy.

Three cases only had a long-standing tracheotomy for more than one year; two of them had a permanent tracheotomy (Figure 76).

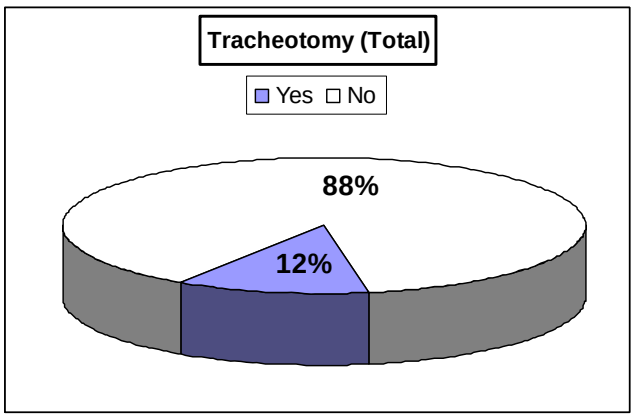


Figure 75: The incidence of tracheotomy.

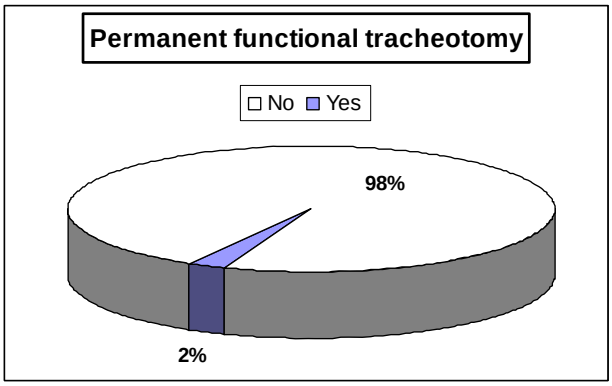


Figure 76: The incidence of the permanent functional tracheotomy.

4.9.2. FEEDING TUBES

Twenty cases remained dependent on the nasogastric feeding tube after the end of the treatment, six of these cases died from the disease and five of them presented with local failure. Eighteen of these cases stayed 3 months or more with the nasogastric tube or a feeding gastrostomy (Figure 77). Three cases had a permanent feeding gastrostomy (none of them had a permanent tracheotomy) (Figure 78).

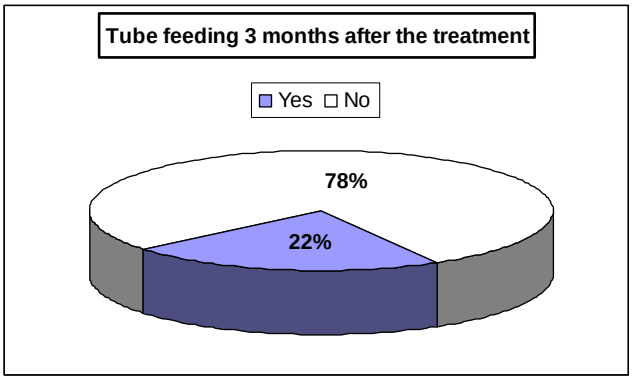


Figure 77: The incidence of feeding tube ≥ 3 months after the end of radiotherapy

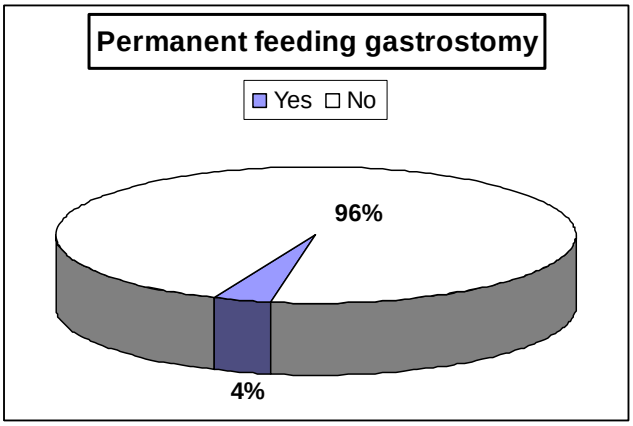


Figure 78: The incidence of the permanent feeding gastrostomy

4.9.3. LOST LARYNGEAL FUNCTIONS

Among the successfully controlled patients, five patients retained their larynges but with permanent tracheotomy or gastrostomy, thus we considered these patients as functional failure.

4.10. THE COMPOSITE FUNCTIONAL SURVIVAL RESULTS

4.10.1. SALVAGE SURGERY

Among the 21 local failures, it was possible to perform a salvage laryngectomy in 12 cases: 3 partial and 9 total (pharyngo)laryngectomies. Salvage surgery was more frequently attempted in the recurrent cases 8/11 patients, than the persistent cases 3/9, moreover the results were more successful (Table 28). The outcome was successful in 2/3 cases with conservation of the larynx and in 4/9 cases treated with total laryngectomy.

Among the nine regional failures, neck dissection was possible in five cases, in four cases it was done at the same time of laryngectomy and in one case, it was the only treatment.

In six cases, either a microvascular or a myocutaneous flap was used to reconstruct the pharyngeal defect or to treat a persistent salivary fistula.

In one case, a partial laryngectomy was attempted but due to the extensive positive margin total laryngectomy was done after the pathological results. Similar to that, two cases with extensive positive margins after total laryngectomy mandated completion pharyngectomy and reconstruction of the pharynx.

	Palliative treatment	Total (pharyngo)laryngectomy		Partial laryngectomy	
		Successful	Failed	Successful	Failed
Persistent	6	0	2	1	0
Recurrent	3	4	3	1	1
Total	9	4	5	2	1

Table 28: The details of the salvage laryngectomy.

4.10.2. THE COMPOSITE LARYNGECTOMY FREE SPECIFIC SURVIVAL

In this parameter, all the cases with death from the disease and or successful salvage total laryngectomy were considered as failure otherwise all the other cases alive or died with free and intact larynx are considered as success. The main aim of this parameter to present the percentage of cases controlled with retained larynx at specific duration.

At two years post-treatment, 14 cases were died from the disease and two cases were controlled successfully with salvage total laryngectomy, while at five years post-treatment 18 cases were died from the disease and 4 cases were controlled successfully with total laryngectomy. Thus, the approximated two and five years composite laryngectomy free specific survivals were 81 % (67/83) and 73 % (61/83) respectively.

4.10.3. THE COMPOSITE LARYNGEAL FUNCTION FREE SURVIVAL

This parameter is similar to the above one and in addition, all the cases with intact larynx but with permanent tracheotomy and or gastrostomy are considered as failure (e.g. loss of the basic laryngeal function).

Five cases in this study were controlled successfully with the non-surgical treatment but remained dependent on the tracheotomy or the feeding gastrostomy. The approximated composite intact laryngeal function laryngectomy free survival at two and five years were 75% (21/83) and 67 % (56/83).

4.11. COMPLICATION OF (CHEMO)RADIOTHERAPY

The complication of the treatment was not extensively studied in this report, but we reported the main grades of the acute mucosal and epithelial toxicities.

One case died due to the direct complications related to the treatment and was considered as death related to the disease. The different degrees of the mucosal and epithelial toxicities, as reported in the first follow-up report after the end of the treatment (2-4 weeks after the end of the radiotherapy), are illustrated in figures 79, and 80. In 10 cases, there were no clear definite data about the degree of post treatment mucosal and epithelia toxicities.

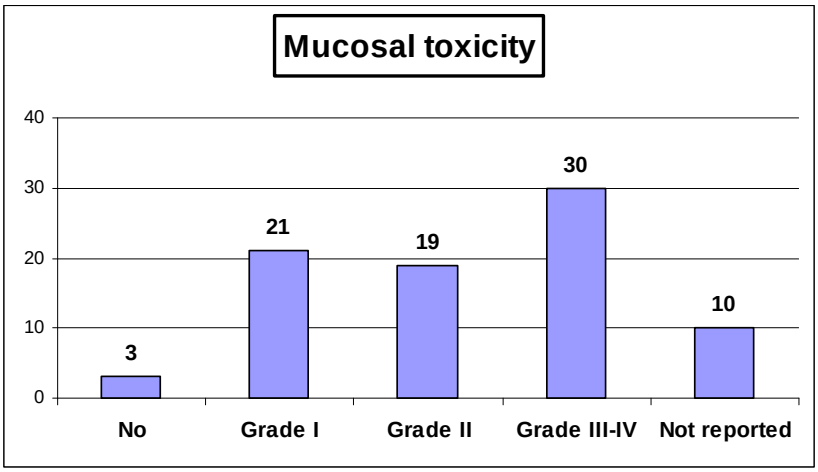


Figure 79: The incidence of the different grades of the mucosal toxicity.

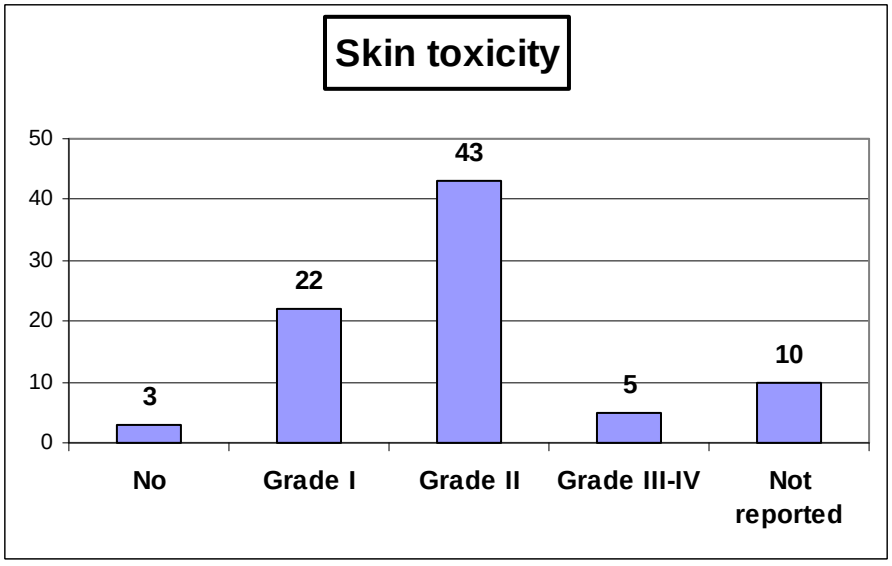


Figure 80: The incidence of the different grades of the radioepithelial toxicity.

V. DISCUSSION

5.1. THE METHODS

''You can tell whether a man is clever by his answers. You can tell whether a man is wise by his questions.''

Proverb by author Naguib Mahfouz, Nobel Prize for Literature 1988.

The main goal of physicians managing laryngeal cancer is to provide the best curative treatment and whenever possible to preserve the larynx [242,243,377]. Aiming to reach this goal, several conservation techniques either surgical or non-surgical were introduced to the field of cancer larynx treatment.[235]

Radiotherapy was introduced more than one hundred years ago as a treatment for cancer larynx targeting its preservation [241] and, by the 1970s, was established as a good curative treatment for early laryngeal carcinomas[235,241,249-253]. Radiotherapy was also attempted in advanced stages but the results were not as promising [249,255,291-295]. Thus, several trials were performed to improve the results in advanced stages either by modifying the traditional schemes of radiotherapy and the introduction of the new altered protocols [297-301], or by using chemotherapy as an adjunctive modality [302,303,307]. In the last 15 years, the use of chemoradiotherapy, especially the concomitant protocol, is preferred as a management strategy for the advanced laryngeal carcinomas in many centers, with surgery reserved in case of failure [242,302-312]. Moreover, the concomitant chemoradiotherapy is recommended now as the standard management of the advanced laryngeal carcinoma in the recent American guidelines of the American Society of Clinical Oncology, published in 2006 [247].

Since the early 1990s, a similar attitude in the management of the head and neck SCC was practiced in the Geneva University Hospital [376,378], and the non-surgical treatment is extensively used in the treatment of advanced head and neck carcinomas with the surgery mainly directed to failure cases [376,379-381]. Most laryngeal carcinoma T2 cases and all the T3-4 cases are treated with hyperfractionated accelerated radiotherapy with a total dose of 70 Gy or more [376,379-381]. In addition, concomitant platin-based chemotherapy is routinely used in the advanced cases. During the period included in our study, 59% of the patients diagnosed with primary cancer larynx and treated with curative intent received (chemo)radiotherapy: 1) all patients included in this study were treated with radical radiotherapy; 2) 95% of the T2-4 and or N positive cases were treated by a hyperfractionated accelerated radiotherapy protocols; and 3) 43% of the patients received a concomitant chemotherapy (all the advanced stages except three patients).

So, the first relevant point in our study is that the included sample reflects the results of an optimum protocol of the (chemo)radiotherapy treatment for cancer larynx. Moreover, all the included patients had begun their first dose within the first 4 weeks after the treatment decision and no patient dropout occurred during the treatment, so factors related to treatment interruption do not have an impact on the control and survival results in this study.

The second interesting point is that the studied population is typical for cancer larynx and allows extraction of a treatment decision for SCC of the larynx. This follows from our inclusion and exclusion criteria: 1) only cancer larynx cases were included, contrary to many studies on head and neck chemoradiation; [297,299,300,304] 2) only cases of SCC were included, since SCC accounts for at least 90% of all laryngeal carcinomas

and represents a homogenous group; [127,129,130] 3) all patients presenting with synchronous malignancy or previous non-cured carcinoma were excluded, avoiding heterogeneity in the studied sample and a false negative impact on the survival results; [169-173,382,383] 4) all the cases of carcinoma or situ or microinvasive carcinomas were excluded, avoiding a false positive impact on the results.

The inclusion of only patients of one site in head and neck cancer studies (e.g. laryngeal cases) is an important step to allow meaningful conclusions, as discussed by others[304,384]. Including all head and neck SCC patients during the same period at our hospital would have brought the sample population to about 1000, but at the expense of an extremely heterogeneous sample that would require several sub-grouping and multiple sub-analyses, possibly increasing the probability of false results. Most importantly, treatment results obtained on other head and neck localisations (oral cavity, pharynx) would be applied to the larynx, as in several recent randomized trials dealing with the chemoradiotherapy for head and neck cancer [297,299,300,304,308,309,311]. Pignon et al. [304], in their landmark metanalysis of the chemotherapy effect in head and neck carcinomas, observed this extreme heterogeneity. The study included 10741 patients, coming from 63 trials, most of the trials being multicentric and including all head and neck sites. Because of the high and significant heterogeneity (p=0.005), the authors did not perform sub-analyses for specific anatomical sites and recommended more site-specific future studies [304]. Similar observations about the weaknesses of trials involving all head and neck sites was mentioned also by Higgins et al [384].

In our opinion, large mixed-population studies in the field of head and neck cancer research are excellent to introduce new treatment strategies, to study treatment complications, or the cost of a specific treatment protocol[297,299,308,309,311]. However, the results cannot be generalized to targeted populations, as the patients are usually drawn from many centers, over long periods, and the population included in these studies represents a fraction of the cases treated at a given center.

The major limitation in our study is its retrospective nature, which makes the extraction of definitive conclusions more difficult, but on the other hand the approach we took from the targeted population up to the final sample subjected to the analysis minimizes the heterogeneity and probability effects. And this was obtained by three main steps.

The first one is made by avoiding the inclusion of every laryngeal cancer patient whatever his clinical or histological diagnosis is, as explained above. This approach resulted in a relatively small sample (only 83 patients) which is specific, dealing with the primary invasive curable SCC with no second localization and treated with (chemo)radiotherapy. This precise sample accounts for 80% of invasive laryngeal cancer cases treated with curative intent by (chemo)radiotherapy during this period at our department, so the exclusion of the remaining subcategories not only avoids heterogeneity but also helps studying the impact of the different variables on control and survival.

Should we study cancer larynx separately from the other head and neck groups? There are several arguments favoring such an approach. First of all, cancer larynx is one of the most common head and neck mucosal cancers [115-117], it carries a better prognosis than other sites [115,116], its metastatic rate remains low[142,158,166-168] reflecting that it remains a loco-regional disease and thus its treatment is mainly related to local control. Furthermore, the new promising non-surgical treatments for advanced head and neck cancer showed no or minimal improvement in laryngeal cancer when compared to the other head and neck sites[309,311,312]. In addition, advances in the field of tumour markers in head and neck cancers seem less applicable in cancer larynx in comparison to other areas and their role in the management of cancer larynx is not clear yet [135-138]. Finally, clear differences are present even at the aetiology level: while cancer larynx remains mainly related to smoking [385], oral and pharyngeal carcinomas are more related to excessive alcohol use and other aetiological factors [386], especially the HPV virus [386-388]. So cancer larynx seems different from the other mucosal head and neck cancer sites and should be studied separately from other head and neck carcinomas.

The third point that strengths the validity is that the sample population includes all patients treated

during the study period, thus are consecutive, non-selected, and from the same geographical area. This is at opposition to the majority of randomised trials, as previously discussed [302,303,307,310,311]. While these studies are excellent, being randomised and prospective, the difficulties in applying their results directly to patients are highlighted by the recent deterioration in the survival observed among the advanced cancer larynx stages (especially T3) which are nowadays mostly treated with chemoradiotherapy [141].

While the TNM staging system represents a common language and the major tool to compare oncologic outcome[223,225], the TNM staging system of cancer larynx had undergone several changes that allow a wide shift of a given lesion between different stages. As an example, for supraglottic lesions up to the 4th edition of the TNM staging system, any extension to the pyriform sinus mucosa or the mucosa of the base of the tongue is considered as T3 and deep involvement of the tongue base is considered as T4 (exact criteria not specified)[389]. In the 5th TNM edition, the above mucosal extensions are moved to T2 and the deep tongue base involvement to T3 (exact criteria not specified)[229]. Finally in the 6th TNM edition, deep tongue base involvement is specified as being invasion of the extrinsic muscles of the tongue and becomes T4[226]. Possibly a more important issue is cartilage invasion, that used to be staged as T4 in all the old editions[229,389], and with the 6th TNM [226] is considered T3, while T4 is restricted to tumours that extend outside the larynx through the cartilage. This would downstage the majority of T4 lesions reported in radiotherapy studies to T3, as these lesions are exclusion criteria for these trials [296,307,390]. Therefore, reporting the TNM system alone as the only measurements of cancer extension limits the reproducibility of research results and makes the comparison of these results by different review methods a difficult process because of the potential of inclusion of non-comparable groups.

For this reasons, we adopted a detailed anatomical description of cancer extension to study the control and survival in addition to the TNM staging system. The goal is to explore the different anatomical prognostic factors related to chemoradiotherapy treatment outcome and to compare to other surgical reports [289,391], which use many anatomical parameters beyond the TNM. Moreover, studying the sub-anatomical extensions of cancer larynx is supported by their role as one of the important prognostic factors in cancer larynx [227] and the fact that T stages for cancer larynx depend mainly on the anatomical extensions, contrary to oral and pharyngeal sites which depend mainly on the size of the tumour [226,227].

Although precise anatomical tumour extensions can greatly influence the results, it is seldom to see an article dealing with cancer larynx explaining exactly how the anatomical sites are defined. If T staging of larynx depends mainly on the detailed anatomical extensions, what is the exact definition or limits of these anatomical sub-sites? In addition, what is the best available tool to evaluate these areas? Unfortunately, the TNM system lacks precise definitions for many important parameters such as paraglottic space invasion, cartilage invasion, subglottic extension …etc [203,231,232].

Besides that, many of these extensions are based on radiological evaluation with no uniform definition of their boundaries and of the precise radiological criteria that signal their invasion. For example, paraglottic space invasion is now staged as T3 [226], and this could be achieved by a very small anterior vocal cord carcinoma where the vocal cord mucosa is about 2 mm from the thyroid perichondrium. Modern imaging tools carry a high sensitivity to exclude this extension but a low specificity to confirm it [195], a reason why some radiologists suggested to limit the positive reading of this extension to cancers reaching the perichondrium or what is called the adjacent sign[202]. To increase the complexity, the paraglottic space has two anatomical definitions [41,43]. Another good example is cartilage invasion, diagnosed in earlier reports by the detection of sclerosis of the thyroid cartilage on CT [296,307,390], a radiological sign found more recently to carry a very low specificity (about 40%) [204,208]. With MRI, many of the intensity changes which were interpreted before as cartilage invasion are considered in the last two years as signs of peritumoral inflammation and not cartilage invasion [211,212]. The increasing role of imaging in defining the staging of cancer larynx is not without problems since the final pathological verification of the exact extension is lacking in chemoradiotherapy treatment protocols.

A detailed clinical description of the extensions of cancer larynx and a standardization of the definition and methods of evaluation of each subsite is of paramount importance. Conducting a prospective trial measuring the survival of T3 laryngeal carcinomas without defining precisely paraglottic space and cartilage and its radiological characterization appears of relatively low value.

In our study, the detailed clinical description of cancer extensions encompasses vocal mobility evaluation by nasoendoscopy, followed by a detailed microlaryngoscopic evaluation of the lesion with the use of telescopes in some areas[177,190]. To this should be added detailed CT ± MRI imaging read by a head and neck radiology expert. These steps are routinely done and should not be solely used as a basis for conservation laryngeal surgery.

The end point in any research question is the outcome [392,393]. Although some changes are observed for the survival of head and neck carcinomas in the last two decades, cancer larynx still has the best prognosis among the mucosal sites of head and neck region [394,395]. Generally the estimated five year survival rates for cancer larynx (including all the stages) in recent epidemiologic studies is about 64% [141,395]. Logically, by excluding all palliatively treated cases and the huge non-resectable tumours the survival would be improved. Therefore, it seems essential for us when measuring the different control and survival rates of resectable cases of laryngeal carcinoma to refer mainly to in intermediate or long time outcome e.g. five up to 10 years after the end of the treatment. In the same time, cancer larynx is typically a disease of elder men with positive history of excessive smoking ± alcohol use [115-127,385] and thus we find a cancer with relatively good prognosis in a population of moderate life expectancy, resulting in significant differences between the overall and the disease specific survivals. This difference of survival is already observed in most studies at five years, and, after exclusion of stage IV cancer larynx, 15% difference or more can be easily detected, reflecting the high incidence of non-cancer related mortality on the long run [249-252,296,346,348,396]. In our study we measured the control and survival estimates at 2 and 5 years and for the discussion and comparison we adopted the control and disease specific survival at 5 years which seems to be the most specific tool to measure the curative probability of our treatment on the intermediate and long run. In addition, it is not wise to depend only on the overall survival measurement on the long run when evaluating laryngeal conservation strategies, as these strategies include mainly stages I-III carcinomas [242-244].

Coming to the functional outcome measurement, as discussed in previous studies [314-321] preservation of the larynx does not translate in the preservation of laryngeal function. This should be put in perspective with the removal of most of the larynx while maintaining laryngeal functions, as obtained in 95% of patients operated by the reconstructive surgeries [282,397-399]. This difference between preservation of the laryngeal function and preservation of the laryngeal framework was also was highlighted in the landmark metanalysis of chemotherapy done by Pignon et al [304].

Thus, we reported the incidences of the tracheotomy and feeding tube in our patients, and from the beginning of the study we decided to consider the long standing (one year or more) tracheotomy and or gastrostomy as indicators for a loss of the laryngeal functions. Therefore, we estimated a composite survival outcome with the laryngeal preservation rates to deliver clear data about the composite outcome of our treatment. Similar detailed reporting for the laryngeal basic functions in addition to the laryngeal preservation rate were reported in a very recent trial done for laryngeal preservation in laryngeal and hypopharyngeal carcinomas. The authors expressed the importance to measure the rate of functioning larynges instead of measuring the retained organs after the treatment [400].

Finally our research is not industry supported, another good point of our study, since it was observed that industrial funding is usually associated with more positive results in both medical and surgical research [401]. A recent review of the clinical cancer research observed that the relation between the industry and cancer research is increasing and becoming very complex. Trials containing chemotherapeutic agents most often report an industrial funding, with more reported positive outcomes supporting the new interventions [402].

5.2. CHARACTERISTICS OF THE PATIENTS

Our study included 83 patients, 76 males and 7 females with male: female ratio of 11:1. The patients' age ranged between (37-89) years with the mean age 61.8 years. These data are nearly identical with the previous reported data for cancer larynx in Geneva during the period 1973-1977. In this previous multicentric study including many cities from middle and southern Europe, the male: female ratio for cancer larynx in Geneva was 10.2:0.8 and the mean age of the patients was 61 for glottic carcinoma and 60 years for supraglottic carcinoma [125].

In this previous survey, the supraglottis lesions represented 47% of the primary laryngeal carcinomas while the glottis (including subglottic primaries) represented 53%, these percentages being generally similar to reports coming from central and south Europe where the supraglottic larynx account for about 50-60% of all primary laryngeal carcinomas[116,117,125]. In the current study, however, glottic carcinoma accounted for 69% of the cases while the supraglottis was the site of origin in only 24% and 7% of the cases were extensive and classified as transglottic. This larger proportion of glottic primaries does not reflect a change in the distribution but results from the treatment policy of cancer larynx in Geneva where T1-3 supraglottic carcinomas were treated surgically, while most T1b-T3 glottic carcinomas usually underwent a non-surgical treatment and finally all large T4 lesions are treated by total laryngectomy and postoperative chemoradiotherapy. Thus, the sample included in the current study is biased towards intermediate glottic carcinomas (T2-3 N0-1M0).

5.3. TREATMENT RESULTS ACCORDING TO THE TNM STAGING SYSTEM

5.3.1. TREATMENT OF T1-2 CARCINOMA

Early glottic carcinoma is an important and peculiar subgroup in head and neck cancer, being common in incidence [125,127,141,142], representing nearly always a local problem because of the rarity of regional [142,245] and distant metastasis[166,167]. Early glottic carcinoma is a highly curable disease by several modalities, including radiotherapy, transoral surgery, and open conservation surgery with high and comparable survival results (§1.6.2.1).

Early supraglottic carcinoma is less frequent than the early glottic one [125,127,141,142], but generally it exhibits similar characteristics except a higher incidence of occult neck disease, especially in T2 lesions [142,159,162] and a slightly worse survival rates when treated by either radiotherapy or conservation surgical techniques (§1.6.2.3).

Despite these differences, experts agree that the treatment decision for early laryngeal carcinomas is mainly targeting at the highest rate of laryngeal preservation with high quality laryngeal functions, with consideration for other factors like patient's age, his voice needs, the cost of the treatment, and the experience of the managing team [243,247].

5.3.1.1. RADIOTHERAPY TREATMENT OF T1 CARCINOMA

In our study, the estimated 5 years local control rate for T1 lesions was 82%, and the estimated 5 years disease specific survival was 100%. Four patients failed locally but none of the patients had regional or distant failure. These results are comparable with different series of T1 lesion as shown in table 29 [250,254,256,257,403-408]: with the exception of two reports [250,256], all the authors reported a 5 years local control rate around 84%. Our local control rate is nearly identical to Cellai et al [251] and Johansen et al [403], these two reports being large retrospective reports of consecutive patients from centers draining all the population of their surroundings and, in our opinion, are good examples of cohorts comparable to ours. Relative to other series, our control results might be affected by the relatively high incidence of clinical T1b lesions and by the fact that some

lesions are upstaged radiologically. If T1 lesions are considered according to the radiological criteria, our estimated 5 years local control rate was 88% (§4.8.2).

None of our clinical T1 patients presented with regional or distant failure, which is normally expected (§1.1.6.1) due to the non-aggressive behaviour in T1 laryngeal SCC. This behaviour could be observed also in the series of table 29, since all the authors report no or rare regional disease and the disease specific survival rates at 5 years are usually over 95%.

	Year	TNM	N	5-LC	5-DSS	5-OAS	NC	5-LP
Le et al.[257]	1997	1992	T1a: 260 T1b: 55	All: 85%	All: 97%	All: 63%		
Marshak et al.[254]	1998	1992	188	88%				
Warde et al.[253]	1998	1992	T1a: 403 T1b: 46	91% 82%				
Mendenhall et al.[250]	2001	1998	T1a: 230 T1b: 61	94% 93%	95% 95%	82% 79%	99%	
Johansen et al. [403]	2002	1982	T1a: 396 T1b: 81	85% 83%	95% 93%	76% 86%	97% 100%	85% 83%
Franchin et al. [405]	2003	2002	T1a: 267 T1b: 56		All: 90%	All: 80%		
Colasanto et al.[408]	2004		119	91%		76%		
Cellai et al.[251]	2005	2002	831	84%	95%	77%		
Yamazaki et al.[256]	2006	1992	T1a: 144 T1b: 36	83% 91%	99% 100%	All: 88%		
Reddy et al.[406]	2007	2002	T1a: 159 T1b: 49	86% 84%	All: 92%	All: 77%		84%
Nomiya et al. [407]	2008	2002	T1a: 115 T1b: 48	92% 85%	97% 93%	85% 89%		
Sjogren et al.[404]	2009		T1a: 210 T1b: 99	86% 84%	All: 97%	All: 80%		

Table 29: Results of T1 glottic carcinoma treated with exclusive radiotherapy.

N: number of patients included, 5-LC: 5-year local control rate, 5-DSS: 5-year disease specific survival, 5-OAS: 5-year overall survival, NC: nodal control, 5-LP: 5-year laryngeal preservation rate, All: the entire study population. NB: The percentages are approximated to facilitate the reading. Some articles lack some outcomes or use other measurements so the entries are left empty to avoid multiple measurements.

These excellent long-term disease-specific survival rates not only reflect the limited regional and distant failure, but also imply that most, if not all, T1 failures could be salvaged successfully. Among the four failure cases, two cases were salvaged successfully with total laryngectomy and two cases were salvaged with partial procedures (cordectomy and frontolateral laryngectomy). Our probability of laryngeal preservation at 5 years was 92%. Total laryngectomy was the main procedure used for the failure cases in our study and this was observed in the other series (Table 30) [250,251,257,403-406]. The use of conservation laryngeal surgeries, especially

the supracricoid laryngectomy as salvage procedure is another option that may increase the laryngeal preservation rate [177,190,409] but has not yet gained popularity.

	Year	N	5-F	Salvage	TL	PL	ND	Ultimate Failure
Le et al.[257]	1997	315	51 (16%)	51	32	19	7	13%
Mendenhall et al.[250]	2001	291	19 (7%)	18	11	7		2%
Johansen[403] et al.	2002	477	76 (16%)	54	4/5			28 (6%)
Franchin[405] et al.	2003	323	47 (15%)	46	18	26	1	
Cellai et al.[251]	2005	831	121(15%)	70	48	19	3	51(6%)
Reddy et al.[406]	2007	208	29 (14%)	20	14	6		
Sjogren[404] et al.	2009	319	45 (14%)	43	35	8		

Table 30: Salvage surgery used in T1 glottic carcinoma treated with exclusive radiotherapy.

N: number of patients included; 5-F: 5 years failure cases; TL: total laryngectomy; PL: partial laryngectomy; ND: neck dissection.

Our T1 lesions included only three supraglottic carcinomas, so we compared our results to glottic series (Tables 31 and 32). The results of the 5 years local control and survival of representative supraglottic T1 series are summarised in table 33 for comparison. With the exception of Johansen et al [396]. The control results are comparable to T1 glottic lesions. In that report [396], the doses and schemes of radiotherapy seem suboptimal when compared to other protocols [348,349] using either hyperfractionated accelerated scheme with high doses, or an extremely hypofractionated accelerated scheme [346]. Although the survival for T1 supraglottic cases remains good, it is lower than for T1 glottic lesions due to the higher incidence of occult nodal disease [346,348,349,396]. Another problem with T1 supraglottic carcinoma is that salvage surgery was almost always a total laryngectomy, which has a negative impact on the laryngeal preservation rate [346,348,349,396].

	Year	TNM	N	5-LC	5-DSS	5-OAS	NC	5-LP
Sykes et al.[346]	2000	1992	65 - T1N0	92%	83%		91% Ultimate control	† 90% Deaths excluded
Nakfoor et al.[348]	1998	1992	21 - T1N0	95%			95%	
Hinnerman et al.[349]	2002	1998	17 - T1N0	100%	100%	65%	100%	
Johansen et al.[396]	2002	1982	156 – T1 131 - T1N0	63% 62%	71% 74%	56% 53%	55% *LR : 53% 57% *LR: 54%	

Table 31: Results of T1 supraglottic carcinoma treated with exclusive radiotherapy.

N: number of patients included; 5-LC: 5 years local control rate; 5-DSS: 5 years disease specific survival; 5-OAS: 5 years overall survival; NC: nodal control; 5-LP 5 years laryngeal preservation rate; *LR loco-regional control; † Laryngeal preservation in survivors. NB: The percentages are approximated to facilitate the reading. Some articles lack some outcomes or use other measurements so the entries are

left empty to avoid multiple measurements.

5.3.1.2. OTHER TREATMENT MODALITIES IN T1 CARCINOMA

Transoral laser resection is another good alternative for T1 laryngeal carcinoma. In T1a glottic carcinoma the reported 5 years local control rates are: 85% [261], 87% [263], 88% [265], 92% [410], 94% [264], 96% [411] , and 100% [262],. The reported 5 years local control rates for the T1b lesions are: 80% [266],80% [410], 84% [261], 91% [263], and 100% [262],. The overall control results are comparable to radiotherapy, however the survival rates are better since all these series reported 96%-99% 5 years disease specific survival [261-264,410,411]. In addition, the laryngeal preservation rates are higher than with radiotherapy 94%-97% [261-264,410-412]. In the T1 supraglottic carcinoma this approach is not as widely reported in the literature, but in several reports the local control rate range between 86%-100% [350-355]. These excellent control rates, the high disease specific survival, and laryngeal preservation rates around 95% [350-353] are promising but larger studies are still needed to establish this approach. A difficulty in interpreting the data is the extensive use of postoperative radiotherapy in some of these reports. [352,353]

The higher survival and laryngeal preservation rates with transoral laser resection reflect the easy management of failure cases as the diagnosis of recurrence is not difficult and all the possibilities remain available for treatment, with a limited need of total laryngectomy [259-266,350,351,410]. On the other hand, good endoscopic exposure is not always possible [261,265,267] and all patients are not candidates for laser resection. Voice outcome remains comparable to radiotherapy when type I-III cordectomies are used [264,272,273] but with more extended resections voice parameters become inferior to radiotherapy [264,273-276]. Brandenburg[412], compared the cost of laser resection and radiotherapy for T1No glottic carcinoma and pointed to the cost benefit of endoscopic laser treatment.

Finally, open surgical techniques were one of the established treatment options for T1 glottic carcinoma before the era of the transoral laser resection, especially cordectomy and hemilaryngectomy for T1a and frontolateral laryngectomy mainly for T1b [177,281,283-285,413]. Leroux-Robert, in 1975 reported 84% and 95% 5 years local control and diseases specific survival for 88 T1a patients treated with open cordectomy [413]. Laccourreye et al. [281] reviewed the open surgical procedures for the early glottic carcinoma in 286 patients, finding a 5 years control rate for T1a lesions of 100% when the lesion is limited to the mid cord, while in bigger lesions the rate dropped to 91%. In T1b lesions a frontolateral laryngectomy is mandatory and the control rate further dropped to 84% [281]. The drop of control rate of these limited vertical procedures in T1b lesions is also highlighted by other authors [285]. Furthermore, these open techniques have more morbidity, longer postoperative rehabilitation course, and less optimal vocal outcome [248]. Recently Karatzanis et al, compared open and endoscopic procedures for T1 glottic carcinoma and found no significant difference between both approaches in terms of control and survival [414]. Thus, the role of open conservation surgeries in the management of T1 glottic carcinoma seems to be shrinking, especially with the growing experience with endoscopic laser resection.

Our results for T1 laryngeal SCC and the review of the literature support our attitude: this group is mainly treated either by exclusive radiotherapy or endoscopic laser resection, with small T1a glottic and limited T1 supraglottic lesions usually resected with laser, while the bigger lesions are treated by radiotherapy to avoid the poor voice outcome associated with extensive resections. The patient needs and age are a prime consideration during the decision: for younger patients, surgery should be preferred to save the radiotherapy as a treatment option for a future second localisation.

5.3.1.3. RADIOTHERAPY TREATMENT OF T2 CARCINOMA

The T2 lesions in our study represent the largest subgroup of patients (47%, 39 patients). The glottis was the site of origin in 28 patients (including, one subglottic tumour extending to the glottic level), while in only nine patients did the lesion originate from the supraglottis (six of them were extending to the vocal cord), and

two cases were transglottic. This distribution results from our treatment policy, as we mentioned previously (§3.1), with surgery being the main treatment of supraglottic lesions.

In this group, 3 patients had clinically palpable lymph nodes, while radiologically positive nodes were suspected in 6 patients. This rate of nodal disease (15%) is more or less comparable with the incidence of neck metastases in the other reports, keeping in mind that 25% of our lesion diagnosed clinically as T2 were supraglottic in origin [158-160,163].

The effect of imaging on the staging of this group is highly interesting. According to the 1997 TNM version [229], while most of these cases remained in the same stage, 9 patients were upstaged to T4 lesions (8 due to detection of thyroid cartilage sclerosis or minimal erosion, and one due to a large lysis of the cartilage) and 11 others upstaged to T3 lesions (invasion the pre-epiglottic space or extension to the pharyngeal mucosa). Two cases were understaged to T1, bringing the agreement rate to less than 50%. This stage migration effect, with a high tendency to upstage the tumours by imaging was also reported by other authors [415,416]: it is observed more often with MRI, especially regarding the evaluation of cartilage invasion [204,415].

These mainly imaging-defined points were reviewed by the TNM committee in 2002 and the definition of T4 was changed to become limited to definite trans-cartilaginous cancer extension [226,227]. Unfortunately, an upstaging of T3 was associated, with any paraglottic space invasion being now considered T3. We discussed earlier the problematic definition of the paraglottic space (1.1.13.2) and the fact compounded by the TNM committee avoiding to exactly define exactly this extension or the parameters of its radiological evaluation, which are not very specific even in the most recent studies [195]. Thus, according to the TNM-2002 [226,227], 30 of our clinically T2 lesion moved to T3 (77%) while 8 patients were downstaged from T4 to T3 (Table 20). These large shifts in staging between the clinical and radiological assessment resulted in a loss of correlation between the radiological T staging system and the oncologic outcome with non-significant values regarding the control, and limited significant values regarding the disease specific survival (Tables 25, 26). The need to upstage every paraglottic space invasion to T3 or to limit that to cancers deeply invading up to the thyroid perichondrium is an urgent question to address, as eluded to be others [202].

	Year	TNM	N	N0 stage	5-LC	5-DSS	5-OAS	NC	5-LP
Mendenhall et al.[250]	2001	1998	T2a 146 T2b 82	100%	80% 72%	95% 90%	82% 79%	95% 87%	82% 76%
Frata et al.[252]	2005	2002	256	100%	73%	86%	59%		76%
Warde et al.[253]	1998	1992	286	100%	69%				
Marshak et al.[254]	1998	1992	25	100%	69%				
Le et al.[257]	1997	1992	T2a 60 T2b 23	100%	70%	91%	*10-years 61%		
Garden et al.[258]	2002	1997	230	100%	72%	92%	73%		
Johansen [403] et al.	2002	1982	225	100%	61%	83%	64%	95%	60%
Franchin[405] et al.	2003	2002	T2a 70 T2b 17	100%		79%	76%		
Colasanto et al [208]	2004		71	100%	72%		76%		

Table 32: Results of T2 glottic carcinoma treated with exclusive radiotherapy.

N: number of patients included, N0 stage: percentage of N0 patients, 5-LC: 5-year local control rate, 5-DSS: 5-year disease specific survival, 5-OAS: 5-year overall survival (*results at 10 years), NC: nodal control, 5-LP: 5-years laryngeal preservation rate. NB:

The percentages are approximated to facilitate the reading. Some articles miss some outcomes or use other measurements thus these entries are left empty to avoid multiple measurements within each column.

All the patients of this group were treated with radical radiotherapy using an altered scheme except one, and 17 of them had concomitant chemotherapy. The estimated 5 years local control rate was 75%, and the estimated 5 years disease specific survival was 77%. Over the whole period of follow up, 10/39 patients failed locally, while only one patient had an isolated regional failure with a loco-regional failure of 11/39, two patient developed distant metastases and died soon from their disease.

The exact role of chemotherapy in this setting is controversial: 21 patients were treated with exclusive radiotherapy and 18 patients treated with chemoradiotherapy, with local failure rate of 6/21 and 4/18, respectively.

Our control and survival results are comparable with the results summarised for T2 glottic carcinoma (Table 32), and T2 supraglottic carcinoma (Table 33), but as mentioned before it was impossible to separate our patients according to the site to avoid very small groups, so we preferred to compare our results to the glottic studies since the majority was classified as of glottic origin.

With one exception (Johansen et al. [403]) the 5 years local control rate of T2 glottic carcinoma ranges between 69-78% [250,252-254,257,405]. The altered radiotherapy has been identified as one of the factors that improve the control results in this subgroup [250,258,298,301]. The results reported by Johansen et al. [403], could be possibly accounted for by an suboptimal radiotherapy protocol used at this period, since the same authors reported later a 10% of loco-regional improvement in their results when using an accelerated protocol of radiotherapy and a total dose increase up to 68 Gy [298]. In studies using similar radiation techniques to ours, i.e. a bifractionated accelerated radiotherapy and a mean total dose to the tumour site of 70 Gy [250,258], the local control for T2 glottic lesions is nearly identical to ours.

However, some studies reported a better disease specific survival, possibly explained by all their patients being N0 while we had six patients (15%) N positive. On the other hand, we had only one patient with regional failure among these six patients, meaning that elements beyond the TNM stage might be responsible [250,258]. This is highlighted by the reported wide range of 5 years disease specific survival in T2 glottic lesions treated with radiotherapy (72%-94%) even in the recent studies [248,250,252-254,257,403,405].

	Year	TNM	N	5-LC	5-DSS	5-OAS	NC	5-LP
Sykes et al. [346]	2000	1992	136 - T2N0	81%	78%		88%	90%All deaths excluded
Nakfoor et al. [348]	1998	1992	59 - T2N0	88%			80%	
Hinnerman et al. [349]	2002	1998	74 T2N0	86%	93%	59%	86%	
Johansen et al.[396]	2002	1982	86-T2 73-T2N0	62% 63%	74% 78%	52% 53%	81% *LR : 52% 85% *LR : 55%	

Table 33: Results of T2 supraglottic carcinoma treated with exclusive radiotherapy.

N: number of patients included, 5-LC: 5 years local control rate, 5-DSS: 5 years disease specific survival, 5-OAS: 5 years overall survival, NC: nodal control, 5-LP; 5 years laryngeal preservation rate. *LR: loco-regional control. NB: The percentages are approximated to facilitate the reading. Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple

measurements.

For the T2 supraglottic carcinoma (Table 33) radiotherapy has a slightly lower control results than for glottic ones, especially in the absence of nodal disease, but it is clear that the major difference in survival between T2 supraglottic and glottic carcinomas is mainly attributed to regional element of the disease as easily observed in table 33 [346,348,390,396].

Among our 10 patients that failed locally, salvage surgery was attempted in 5 patients (one partial and four total procedures) and unfortunately at 5 years post radiotherapy it was successful in only 1 patient, for a 2- and 5-year disease specific survival of 90% and 77%, respectively. No larynx was saved by partial laryngectomy and the corrected laryngeal preservation probability at 5 years was 77%. Total laryngectomy accounts also for about 80% of the salvage procedure in ours and other studies (Table 34). Similarly, in T2 supraglottic failure it is rare to salvage the case with a partial procedure [346,348,390,396].

	Year	T 2	5-F	Salvage	TL	PL	ND	Ultimate Failure
Mendenhall et al. [250]	2001	248	51	49	43	6		4%
Frata et al. [252]	2005	256	62	28	25	2	1	34 (13%)
Le et al.[257]	1997	83	24	24	19	4		
Garden et al. [258]	2002	230	67	57	50	7		
Johansen et al.[397]	2002	225	87	60	4/5			28 (6%)

Table 34: Salvage surgery used in T2 glottic carcinoma treated with exclusive radiotherapy.

N: number of patients included, 5-F: 5 years failure cases, TL: total laryngectomy, PL: partial laryngectomy, ND: neck dissection

5.3.1.4. OTHER TREATMENT MODALITIES IN T2 CARCINOMA

Open conservation laryngeal surgery is another alternative to treat T2 laryngeal carcinomas. For glottic lesions, vertical procedures (frontolateral laryngectomy, and subtotal laryngectomy with epiglottoplasty) were used to treat selected T2 patients. [177,280-286,413] SCPL-CHEP was also used but usually in patients with unfavourable criteria (extensive anterior commissure involvement, impairment of vocal cord mobility, subglottic extension not reaching the cricoid) [288,289]. The reported 5 years local control rate for frontolateral laryngectomy is around 75%, and the risk of failure is increased by both impairment of vocal cord mobility and involvement of the anterior commissure [281,285,286,413]. Leroux-Robert reported 5 years disease specific survival of 86% for 215 T2 cases but with normal vocal fold mobility [413]; Laccourreye et al. reported 81% of adjusted 5 years laryngeal preservation rate [281]. The extended frontolateral laryngectomy with epiglottic reconstruction could achieve the same control results like the classical technique even with anterior commissure involvement or impaired vocal cord mobility, but on the expense on a longer period of postoperative rehabilitation, especially when the arytenoid is included in the resection. However, it does address several problems like extensive anterior commissure involvement, subglottic extension, and risk of cartilage invasion [282,284] with an excellent 5 years local control, disease specific survival, and laryngeal preservation rates (95%) [287-289]. However, enthusiasm about its excellent oncologic outcome is tempered by 3-4 weeks of postoperative hospitalization and 1-3 months of postoperative rehabilitation that are essential to obtain its good functional results [330].

Open supraglottic laryngectomy was performed widely since the 1970s as a treatment for early

supraglottic carcinoma but these early reports use tumour description parameters difficult to compare to the present ones [149,358,359]. The estimated 5 years local control rate is ranging between 82% and 91% [361,364,417].

	Type of surgery	T2	5-LC	5-DSS	5-OAS	5-LP
Leroux-Robert. [413] 1975	Frontolateral laryngectomy	T2a -215	77%	86%		
Laccourreye et al. [281] 1988	Frontolateral laryngectomy	T2a -32 T2b -33	75% 72%		79% 70%	82% 80%
Brumund et al.[285] 2005	Frontolateral laryngectomy	35	60%		40%	
Fiorella et al.[286] 1997	Frontolateral laryngectomy	69	85%			
Mallet et al.[282] 2001	Epiglottoplasty	19	79%			
Giovanni et al.[284] 2001	Epiglottoplasty + ipsilateral arytenoidectomy	65	92%	94%	86%	
Laccourreye et al. [288] 2000	Frontolateral laryngectomy SCPL-CHEP	85 119	74% 94%		10 years 46% 66%	
Chevalier et al. [289] 1997	SCPL-CHEP	T2b - 90	95%	96%	81%	95%
Bocca.[361] 1991 TNM 1982	Supraglottic laryngectomy + Neck dissection	T2N0 - 252	82% *R 97%		78%	
Heranz-Gonzalez et al. [362] 1996 - TNM 1982	Supraglottic laryngectomy + Neck dissection	37	3 year 95%	† 78%		
Adamopoulos et al.[363] 1997 - TNM 1987	Supraglottic laryngectomy + Neck dissection	47	3 year 87%			
Bron et al. [364] 2005 TNM 1982	Supraglottic laryngectomy + Neck dissection	43	91%	91%		
Scola et al. [417] 2001 - TNM 1998	Supraglottic laryngectomy + Neck dissection	T2N0 - 252		† 81%		

Table 35: Large series using conservation laryngectomies in T2 carcinoma with no or minimal postoperative radiotherapy.

N: number of patients included, 5-LC: 5-year local control rate, 5-DSS: 5 year disease specific survival, 5-OAS: 5-year overall survival, NC: nodal control, and 5-LP: 5-year laryngeal preservation rate. *R regional control. † Non-corrected value (e.g. all non-disease events excluded). Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple measurements.

Transoral endoscopic surgery for T2 glottic carcinoma is gaining popularity in the last two decades due to the good reported results in selected cases. The reported 5 years local control rates are: 66% [261], 82% [263], 91%[265], and 84% (T2a) [410]. The 5 years disease specific survival is also variable and ranges between 86%-98% [261,263,265,410]. Beside the inability to do this approach for every T2 patient, the reported rate of granulations is

high when the resection is wide and usually ranges between 30-40% [261,262,265]. In addition, some authors reported high failure rates, reaching 37%, when the anterior commissure is extensively involved [263], while others recommended against endoscopic resection in this condition [265]. Moreover, it is advised to select the patient well if vocal cord mobility is impaired e.g. T2b [260,263,265,410]. Finally, most of the advantages of the endoscopic resection, like better voice quality and short hospitalisation are lost when the resection is large [264,265,274-276].

Excellent results have been reported with endoscopic resection of supraglottic T2 lesions, with 3- and 5-year of local control rates of 97% [353] and 98% [352], but these reports included a limited number of patients that underwent postoperative radiotherapy. Other authors reported 5 years local control rates without radiotherapy of: 89% [350] and 75% [351], but the reports used older version of T staging and reported the T stage according to the pathology with a possible overestimation of the results. The endoscopic technique was usually introduced because of its higher functional results if compared to the open supraglottic laryngectomy but without true comparative study. Rodrigo et al., found that when a wide resection is needed to control the disease, the functional results are comparable to the open surgery [355] Cabanillas et al. [418], compared open partial and laser endoscopic resection and reported a non-significant difference regarding the swallowing and functional recovery, except shorter periods of nasogastric tube with the endoscopic technique. In a recent report for endoscopic supraglottic laryngectomy including mainly clinical T2 lesions, tracheotomy was needed in 45% of the primary cases and in 100% of the salvage cases [419]. In our opinion, the reports of endoscopic laser resection in T2 supraglottic lesions suffer from numerous shortcomings: the number of included patients in each study was small (< 40), radiotherapy was always or usually used in the clinical T2 cases, the reported results show a wide range of variability, the technique is linked to specific names with each surgeon recommending his indications. Finally, for supraglottic cases if the neck is not open for the laryngectomy it will opened for the neck dissection.

In conclusion, endoscopic laser resection in T2 lesions (both glottic and supraglottic) should be used in highly selected cases and the surgery should not be done by beginners to avoid positive margins and optimize outcome.

The above-discussed results of T2 carcinoma, suggest a slight change in our attitude of treatment reported during the period involved in the study. For the glottic cases, the radiotherapy could be used in most patients but it should be avoided if unfavorable extensions, such as extensive growth in the anterior commissure are present. The SCPL-CHEP is the most suitable technique for these unfavorable cases, since, although the vertical procedures have comparable oncologic outcome to radiotherapy, they are associated with worse functional outcomes. In such situation a dilemma remains when conservation techniques are contraindicated, whether to offer chemo-radiotherapy or total laryngectomy to the patient. For supraglottic lesions, both open supraglottic laryngectomy and radiotherapy have a comparable outcome, thus the main factor is the patient age and the need of post-operative radiotherapy should be considered: younger patients should be directed more to surgery except if postoperative radiotherapy will be needed (like N2-3 and or mucosal involvement of base of tongue).

5.3.2. TREATMENT OF T3 AND RESECTABLE T4 CARCINOMA

5.3.2.1. CHEMO-RADIOTHERAPY TREATMENT OF T3-4 CARCINOMA

Wide field total laryngectomy ± radiotherapy was the only treatment option for T3-4 laryngeal carcinomas, until some studies suggested that it is possible to treat highly selected cases with radiotherapy [291,292,294], or conservation surgical techniques[149,358-360,366,420-422] without significant difference in the survival

outcome.

Four main differences outline the oncologic and functional outcome between T1-2 lesions and resectable T3-4 lesions:

- The nodal stage at the time of the diagnosis is the main predictor for survival whatever the treatment used [158,303,335,337,340,396,403,417,423,424].
- Multimodality treatment is usually needed, especially in T4 and / or N positive patients [302,303,307,335,340,365].
- When laryngeal conservation is attempted, either by non-surgical [307]or surgical approaches [190,282,330,362,363] a good functional recovery needs longer time especially regarding swallowing.
- Whatever the type of the laryngeal conservation technique used, the main voice outcome is to enable the patients to speak with more intelligible and understandable speech than total laryngectomy, the results of the different conservation modalities used in T3-4 carcinomas suggesting that normal voice quality is beyond the reach of available standard conservation modalities [190,307,330,425-428].

So the aim of the treatment of resectable T3-4 laryngeal SCC is to cure the patient and, whenever possible, to preserve his basic laryngeal functions and his ability to have an intelligible speech [243,247]. Because the changes in the T4 definition between the different TNM editions were carried without specific standardised criteria to diagnose cartilage invasion, a fact not discussed in most (chemo)radiotherapy studies, we group these two stages in a common discussion.

Our study included 18 patients reported clinically as T3: 8 glottic, 2 transglottic, and 8 supraglottic clinically classified as T3 due to the extensive involvement of the base of the tongue and or the pharyngeal mucosa, and only one patient reported clinically as T4. Only two of the supraglottic patients had impaired mobility of the vocal fold.

The effect of the imaging tools on the clinical staging is interesting. According to the TNM fifth edition [229] the images upstaged 6 of these patients into T4, understaged two into T2, and 10 patients remained T3. According to the sixth edition (TNM 2002) [226,227], only two of them are upstaged to T4. Thus, the last TNM edition seems to allow better concordance between the clinical and radiologic staging for T3-T4 lesions.

Seven patients of this group (T3-4) had clinically palpable nodes, and in another three patients, the images detected metastatic nodal disease, which could be accounted for by the presence of 10/18 lesions with extensive invasion of the supraglottis and the higher incidence on nodal disease in advanced carcinomas.

The estimated 5 years local control rate was 66 % (the case died from the complication was excluded from this estimate); the estimated 5 years disease specific survival was 44% and the estimated 5 years overall survival was 38%. Six of the patients (33%) of this group failed locally, of which four patients had also a recurrent nodal disease (4/18) - no patient had an isolated nodal recurrence.

Finally, three patients were diagnosed with distant lesions before their death without locoregional recurrence despite multiple endoscopies and neck imaging procedures. This problem of difficult detection of the local recurrence is addressed by other authors [179] and is now considered a major challenge after the extensive use of the radical radiotherapy with or without the chemotherapy

One patient only in our study had a big transglottic cancer invading through the thyroid cartilage and the cricothyroid membrane (suspected by palpation and the prelaryngeal invasion was confirmed by imaging). Patients having lesions such like that are not recommended for organ preservation protocols [243,247,307], but the patient refused total laryngectomy and underwent curative chemoradiotherapy. Unfortunately the tumour

persisted and the patient died from the disease.

The results of published series of the non-surgical treatment for T3-4 laryngeal carcinoma are reported in tables 36-38 which are restricted to large studies specifically addressing laryngeal T3-4 cases and published after 1990 to avoid results due to suboptimal doses of radiotherapy.

Our results are comparable with the French trial [303], which was done for the laryngeal preservation in the endolaryngeal clinical T3 carcinomas, with similar patient characteristics to ours: mainly T3 glottic carcinomas, most of the patients (69%) had a fixed cord, all the lesions were endolaryngeal, and a long follow-up. In addition, our results are comparable to other retrospective non-selected studies [396,403,429], however these studies reported the results of radical radiotherapy as a treatment for T3-4 with only few patients receiving chemotherapy.

	TNM	N	Evaluation of T4	5-LC	5-DSS	5-OAS	5-LRC	5-LP
Mendenhall et al.[296] 1998	1992	T3:89	Preepiglottic space Minimal medial wall of pyriform sinus	68%				
Johansen et al.[397] 2002	1982	T3 :85 T4 :76 IV:101		45% 42% 47%	52% 43% 39%	45% 33% 31%	51% 43% 38%	36% 29% 28%
Sykes et al.[346] 2000	1992	T3N0 : 83 T4N0 : 47		67% 73%	53% 61%			
Nakfoor et al. [348] 1998	1992	T3.51 T4:16 IV:29		76% 43% 55%	†64% †40% †42%			
Hinnerman et al.[349] 2002	1998	T3 : 99 T4 : 28 III : 75 IVA : 87 IVB : 17		62% 62%	 81% 50% 13%		 64% 61% 28%	68% 68%
Finizia et al.[429] 1996	1987	T3 : 65 T4 : 35 T3N0 : 54 T4N0 : 24			59% 32% 61% 31%		44% 26% 47% 25%	

Table 36: Results of T3-4 glottic carcinoma treated with exclusive radiotherapy.

N: number of patients included, 5-LC: 5-year local control rate, 5-DSS: 5-year disease specific survival, 5-OAS: 5-year overall survival, NC: nodal control, 5-LP: 5-year laryngeal preservation rate. †: the percentages are not corrected for deaths from e.g. alive with no evidence of disease. Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple measurements.

Hinerman et al., [390] reported better control and survival results (Table 36), but their cases were highly selected (the included patients are mainly low volume tumour with non obstructed airway, and unilateral lesions not passing or minimally affecting the contralateral side). These selection criteria de facto exclude cases with extensive anterior commissure involvement, opening the discussion about the effect of the anterior commissure on the oncologic outcome in T3-4 carcinoma treated by (chemo)radiotherapy. Another bias in this study is the use of low specific signs to classify the lesions as T4 [204,208] (cartilage sclerosis) and thus an usual

overestimation of the lesion [204,206,208]. Possibly this explains the reported 81% 5-year local control for T4 cases, which is about 20% higher than published rates for T3 lesions included in the same study and higher than the results of the new trials of chemoradiotherapy [302,303,307]. The results of the same center[296] regarding T3-4 supraglottic lesions are also higher than ours, but this 1998 publication reported the results according to TNM 1992 which considers any affection of the medial wall of the pyriform sinus as T3. The population seems again to be highly selected by mainly including lesions with low volume tumour and unfixed vocal folds. The effect of the use of the older T staging system editions (before the 5th - 1997) should be kept in mind in interpreting the results of other studies [346,348,396,429], as any extension to the mucosa of the medial wall of the pyriform sinus was considered as T3. Finally, most of the studies included in tables 36 and 37 did not specify the role of the imaging in their report although the T4 cancer is mainly staged radiologically.

	TNM	N	Evaluation of T4	5-LC	5-DSS	5-OAS	5-LRC	5-LP
Hinermann et al.[390] 2001	1998	T3:87 T4:22	Cartilage sclerosis on CT	63% 81%	83% 87%	52% 67%	62% 78%	
Johansen et al. [403] 2002	1982	T3:128 T4:17 IV:21	No data	48% 38% 44%	63% 40% 43%	43% 24% 24%	43% 33% 46%	43% 33% 39%
Finizia et al.[429] 1996	1987 Glottis:47 SupraG:44	T3 :65 T4 :35 T3N0 : 54 T4N0 : 24			59% 32% 61% 31%		44% 26% 47% 25%	

Table 37: Results of T3-4 glottic carcinoma treated with exclusive radiotherapy.

N: number of patients included, 5-LC: 5-year local control rate, 5-DSS: 5-year disease specific survival, 5-OAS: 5-year overall survival, NC: nodal control, 5-LP: 5-year laryngeal preservation rate. Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple measurements.

Chemoradiotherapy (especially the concomitant regimen) is now considered the gold standard for the treatment of T3-4 laryngeal carcinomas [242,247]. Actually our results were not promising if compared with the main two trials in that field [302,307], but are comparable to other randomised studies with a group of patient having similar characteristics to our group [303].

These trials [302,307] are landmark studies, as they gave a new hope for the advanced cancer cases of cure with laryngeal conservation, however they carry common week points that should be examined carefully in light of the decreasing survival of advanced laryngeal cancer, especially glottic lesions [141,430]:

1. The patients come from several specialized tertiary centers where patient received meticulous follow-up to detect and treat the failure cases [302,307]. This may explain the differences between the reported results and the general population results of this approach, as published in the annual reports of cancer larynx statistics [141,430]. Therefore, the external validity of these trials should be further investigated.
2. Regarding the patients' characteristics for the trials under discussion, [302,307] as reported in table 38 most of the patients were supraglottic (63% and 69%) so real conclusion for advanced glottic lesions cannot be drawn from these trials.
3. These trials did not study the different anatomical extensions of the lesions (e.g. no data about the

subglottic extension, anterior commissure, and internal spaces of the larynx). Moreover the authors did not specify the role of imaging in their staging system and what criteria were used to stage their patients. Some criteria like cartilage sclerosis, and the old parameters to judge tumour extension are proved recently to upstage patients [204,208,211-214]. This could translate in a tendency to overestimate the lesions in these trials, especially in the RTOG trial [307] where nearly all the T4 lesion would be now considered as T3.

4. The oncologic outcome description usually were not reported clearly especially on the long run, e.g. the disease specific survival at 5 years were not reported although it measures the probability of these modalities to cure the patients without the effect of the death from other non related causes.

The VALCSG study [302] reported mainly the short term results, the local control results were not given at a specific duration, the basic functional outcome (tracheotomy and feeding tube incidences) was not mentioned. Beside that they have 4% unexplained mortality in the chemotherapy arm in addition to 2% mortality related to the treatment.

The GETTEC trial [303] in our opinion is a good study to examine the long term outcome of this protocol in the clinically T3 glottic carcinoma with fixed vocal cords: there are strong significant results favouring the surgery in these lesions.

The RTOG trial [307], tried to access the best chemoradiation protocol for advanced laryngeal cancers, but unfortunately there was no surgical arm for comparison. In addition, the included cases in this study should be considered as T2-3 according to the most recent TNM staging system [226]. Moreover, in our opinion the concept of the authors during the discussion is based on total laryngectomy only, while many of their patients with minimal cartilage invasion or low volume advanced cases could be resected successfully with SCPL, as highlighted by other authors [431]. The study also has 4% mortality with concomitant chemoradiotherapy, 82% acute severe toxicity, and about 20% long- term dysphagia and tubal feeding dependency after one year. These high morbidity and poor functional outcome in anatomically retained larynges has been observed by many authors [314-321,432] and should bring a reconsideration of the definition of a "preserved larynx" [400,433]. A follow-up study of the surgical results for salvage cases in the RTOG trial [434] reported 5% of total laryngectomy due to functional reasons (aspiration) or toxicity. In these laryngectomies a 59% complication rate was reported with 30% of fistula rate.

In our opinion all the above observation should be examined carefully before drawing a definite conclusion from these trials. Recently, several trials [308,400,435,436] examined different protocols of chemoradiotheray to preserve the larynx in laryngeal and hypopharyngeal cancers, but unfortunately these trials combine the larynx with the hypopharynx and usually examine different protocols of non-surgical treatment with no surgical arm. Again, the included cases are mainly supraglottic with minimal numbers of glottic lesions, making these trials partially useful for supraglottic lesions but not for glottic carcinoma [308,400,435,436].

	TNM	Patients	Evaluation of T4	Follow- up	LC	DSS	OAS	LP
VALCSG Trial 1991.[302] More than 5 centers.	1985	332 K score > 80 SG:G = 63:37 T1,2: 9%; T3: 65%; T4: 26% N0: 54%; N+: 46% Cartilage invasion 9% Fixed VF 57% Stage III: 57%; IV: 43% Surgery arm CRT arm	???	Median 33 months 2% lost in the first 33 months			2y: 68% 2y: 68%	2y: 64% & 4y:39%
GETTEC Trial [303] 1998 5 centers 1986-1989	1986	68 clinical T3 with fixed VF N0 = 78% N+ = 22% Surgery arm ICRT arm	???	Median 99 months		*AND 62% 33%	2y: 84%; 5y :70% 2y: 69%; 5y: 45%	
RTOG Trial 2003.[307] More than 10 centers. 1992-2000		332 SG:G = 69:31% T2:12%; T3:78%; T4:10% Mild tongue involvement <1cm Minimal cartilage invasion N0: 50%; N+: 50% Fixed VF 32% Stage III: 65%; IV 35% ICRT arm CCRT arm RT arm	CT	Median 44 months	2y: 64% 2y: 80% 2y: 58%	2y: 52%; 5y: 38% 2y: 61%; 5y: 36% 2y: 44%; 5y: 27%	2y: 76%; 5y: 55% 2y: 74%; 5y: 54% 2y: 75%; 56%	2y: 84%; 5y-LFS: 43% 2y: 72% 5y-LFS: 45% 2y: 67% 5y-LFS: 38%

Table 38: Results of the main randomised trials of laryngeal preservation (trials including larynx only).

LC: local control rate, DSS: disease specific survival, OAS: overall survival, NC: nodal control, LP: laryngeal preservation rate, ICRT: induction chemoradiotherapy, CCRT: concomitant chemoradiotherapy, RT: radiotherapy, *AND: alive with no evidence of disease, LFS: laryngectomy free survival, 2y: 2years, 5y: 5 years. Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple measurements

In our study, seven of our T3-4 patients failed locally and, unfortunately, it was possible to salvage only three patients (all were clinically T3 lesions) by radical surgical procedures. We observed that the salvage surgery improves the survival on the short run, with a 57% two years disease specific survival for the T3 stage, but at five years this rate dropped to 44%, an effect also observed by others [302,303,307].

The difficulty to salvage failure cases after (chemo)radiotherapy and the low success rate of salvage surgery are two of the difficulties of this approach. Johansen et al.,[396,403] pointed to the relation between the advanced T stages and the need for total laryngectomy as salvage procedure; their success rate of salvage surgery was around 45%. Nakfoor et al., [348] were able to salvage 41% of their failures (all laryngeal T stages) and their success rate of salvage at five years for T3 and T4 cases were 45% and 20%, respectively. In the VA trial salvage total laryngectomy was needed in 36% of the patients (29% persistent tumours, and 7% local failure), with unfavourable lesions (e.g. fixed vocal cord, big volume, T4 stage IV) the rate of failure was higher and the salvage more prone to failure [302]. In the RTOG trial [307] 26 % of the patients included needed salvage laryngectomy [434]. With these protocols of radical non-surgical treatment the observed complications when attempting salvage laryngectomy are prohibitive, especially the fistula rate [342,343]. Johansen et al., reported 80% fistula rate with a 70 Gy dose of radiotherapy [437] and Relic et al., reported 73% fistula rate after a treatment protocol similar to ours [438].

In other words, the patient with T3-4 cancer larynx choosing chemoradiation as treatment should be made aware that the salvage is total laryngectomy, that recurrence might not be detected early enough to allow for such surgical salvage, that the success rates are lower than for the initial lesion, and that total laryngectomy in this setting is associated with significant complications.

5.3.2.2. SURGICAL TREATMENTS OF T3-4 CARCINOMA

Chemoradiotherapy is dealing with resectable cases in the vast majority of the patients. Thus, these lesions could be treated also with surgery.

For both transoral laser surgery and vertical partial surgery the characteristics of the lesions reported and the rarity of T3-4 cases treated by these approaches make their use as treatment in T3-4 lesions limited to extremely selected lesions (see above, 1.6.2.2, and 1.6.2.4).

Open supraglottic laryngectomy is an alternative for selected cases of T3 supraglottic carcinomas and it could achieve a 5 years local control rate ranging around 80%, associated with classical postoperative radiotherapy which is needed in 30-50% of patients [365,417]. SCPL is oncologically safer than supraglottic laryngectomy for these extended lesions [190,205,326,328,329,366,367,439,440] and could also be used with high degree of safety in many cases of advanced glottic and transglottic lesions [289,327,328,391,441]. With SCPL a wide monoblock resection, similar to total laryngectomy is performed, allowing the procedure to mange fixed vocal cords and or thyroid cartilage invasion [190,205,289,327,328,367,372,391,441,442]. The results of open conservation surgery for T3-4 lesions are summarised in table 39.

Although the SCPL looks a feasible alternative for excellent oncologic control with laryngeal preservation in advanced cancer larynx, it is contraindicated in extensive subglottic involvement, with fixation of the arytenoid, with invasion of the posterior commissure, and when the pulmonary status is poor [190,366,367,443]. Another shortcoming is the need for a long hospitalisation period (3-4 weeks) to rehabilitate the patient [190,330,427]. SCPL has undergone very slow dissemination in US centers until now [444], which could be attributed to

failed trials of managing these patients with a short hospitalisation period and to transfer the main part of the rehabilitation to the outpatient setting [445,446].

	Type of surgery	N	5 LC	5 DSS	5 OAS	5 LP
Bocca.[361] 1991 TNM 1982	Supraglottic laryngectomy + Neck dissection	T3: 107 III: 205 IV: 33	80% 77%		87% 80%	
Sevilla et al. 2008 [365] TNM 2002	Supraglottic laryngectomy + Neck dissection + radiotherapy in 50% of the cases	T3: 49 T4: 31	92% 87%			
Scola et al. [417] 2001 - TNM 1998	Supraglottic laryngectomy + Neck dissection 903 cases	III: 14.8% IV: 19%		†76% †55%	71% 52%	
Chevalier et al. [289] 1997 - Fixed VF	SCPL-CHEP+ Neck dissection	T3: 22	94%	94%	86%	94%
Dufour et al. [326] 2004 - TNM 2002	SCPL+ Neck dissection	T3: 118 N0: 90 N+: 28	91%	98%		90%
Lima et al.[327] 2006 - TNM 2002	SCPL+ Neck dissection	T3-4: 53	†85%	†83%		
Laccourreye et al. [439] 1998 - TNM 2002	Induction chemotherapy+ SCPL+ Neck dissection	T3: 54 T4: 6	92%	98%	73%	92%
Laudadio et al. [440] TNM 2002	SCPL+ Neck dissection	T3: 46 T4: 5		†78% †54%		98% 92%

Table 39: Large series using conservation techniques in T3-4 carcinoma

N: number of patients included for each stage, 5LC: 5 years local control rate, 5DSS: 5 years disease specific survival, 5 OAS: 5 years overall survival, N control: nodal control, 5: LP 5 years laryngeal preservation rate, and 10 OAS: 10 years overall survival. † Non-corrected value (e.g. all non-disease events excluded). Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple measurements.

Finally, total laryngectomy ± neck dissection ± postoperative radiotherapy is the last option for the treatment of the T3 and resectable T4 laryngeal carcinomas. The reported control and survival rates are variable, but in the VA surgical arm only 2% of local failure and 5% of regional failure were reported [302]. The reported five years locoregional control of this procedure for the T3 cases is usually around 75% and it is about 5-10% better when there are no positive cervical nodes [334-339,373,375], the 5 years disease specific survival being around 70% [334,338]. In T4 lesions the control and survival rates drop about 20% and usually range around 50% [337,340]. When evaluating these results, it is important to keep in mind the evolution the laryngeal surgery and

other conservative treatment modalities in the last 20 years and the fact that total laryngectomy is nowadays offered only for advanced cases with the worse anatomical extensions. In two recent trials comparing chemoradiotherapy to the total laryngectomy, at 5 years from randomisation the surgery arm was better by 10% in terms of control and the relapse free survival [302,303].

Interesting approaches could combine the benefits of induction chemotherapy to surgery in advanced cases: Laccourreye et al. [439] tested induction chemotherapy with SCPL. Leon et al.[447] also studied this approach with total laryngectomy and they reported 80% 5-year adjusted survival for a group of patients treated with total laryngectomy after incomplete response to chemotherapy. The chemotherapy is proved to decrease minimally the rate of the distant metastatic lesions [304], has some effect on the tumour volume in laryngeal cancers [302,303,439,448], and in rare conditions it can cure the lesion[448]. This combined treatment should be explored in T4 cases.

From the results of our chemoradiotherapy protocol used in T3-4 patients and the above mentioned studies, it possible to infer that for the T3-4 supraglottic cases chemoradiotherapy is a real alternative to surgery with comparable short-term and slightly decreased long-term survival. Conservation surgery (supraglottic or SCPL) could be only used in selected cases, keeping in mind the need of postoperative radiotherapy in about 30% of the patients.

In T3-4 glottic and transglottic lesions, chemoradiotherapy has not proved to be an alternative to surgery until now, due to the low numbers of such patients in the laryngeal trials, the observed deterioration of survival of cancer larynx in the last decades in these subgroups, and finally because of the need for salvage total laryngectomy in failure cases. If the patient's laryngeal function could be saved by SCPL it should be attempted. When SPCL is contraindicated, total laryngectomy should be considered. In the most unfavorable lesions, i.e. high cancer volume and definitive extralaryngeal spread, total laryngectomy combined with postoperative chemoradiotherapy is the only option to cure the patient.

All the main radiotherapy studies of cancer larynx included in the discussion are mentioned in the next table 40 to give a complete background about the radiotherapy used in these studies and the main methodology of each one.

	Design	N	Source (main)	Dose (main)	Scheme	D/F (main)
Cellai et al. 2005	Retrospective Non-selected 1970-1999 2 centers	T1	Co60	65	Monofractionated	2
Frata et al. 2005	Retrospective Non-selected 1970-1999 2 centers	T2	Co60 4MV	65	Monofractionated	2-2.4 (2.2)
Mendenhall et al. 2001	Retrospective Non-selected 1964-1998 1 center	T1-2	Co60 2MV	T1: 63 T2 66 or 74	Monofractionated Monofractionated Bifractionated accelerated	2.25 2.25 74
Warde et al.1998	Retrospective Non-selected 1981-1989 1 center	T1-2	Co60	50	Hypofractionated accelerated	2.5
Marshak et al. 1998	Retrospective Non-selected 1974-1994 1 center	T1-2	Co60	66-72	Monofractionated	1.8-2
Yamazaki et al. 2006	Prospective Randomised	T1	4MV	Multiple doses used	Monofractionated	2 Vs 2.25
Le et al. 1997	Retrospective Non-selected 1956-1995 1 center	T1-2	4 MV Co60 1 MV	(median) 63	Monofractionated	1.8
Garden et al. 2002	Retrospective Non-selected 1970-1998 1 center	T2	4 MV Co60	70 64	Monofractionated Bifractionated accelerated	2 1.2
Hinermann et al.390 2001	Retrospective highly-selected 1966-2002 1 center	T3-T4	Co60 2-4MV	74	Bifractionated accelerated.	1.2
Johansen403 et al. 2002	Retrospective Non-selected 1963-1991* 1 center	T1-T4 Mainly T1-3				

Sjogren404 et al. 2009	Retrospective Non-selected 1982-1993 1 center	T1	4-6 MV Co60	60	Monofractionated	
Franchin405 et al. 2003	Retrospective Non-selected 1985-2001 1 center	T1-2	6 MV	63-68	Monofractionated	2-2.25
Reddy et al.4062007	Retrospective Non-selected 1976-2003 1 center	T1	Co60	66	Monofractionated	2
Colasanto et al. 2004	Retrospective	T1-2	2-6 MV	66	Monofractionated	2
Nomiya et al. 40 2008	Retrospective Non-selected 1976-2002 1 center	T1	4 MV	T1a 64 T1b 66	Monofractionated	2
Sykes et al. 346 2000	Retrospective selected 1982-1992 1 center	T1-4N0	4 MV	52.5	Hypofractionated accelerated	3.5
Nakfoor et al. 348 1998	Retrospective Non-selected 1981-1992 1 center	All stages	Co60 4MV	67-72	Bifractionated accelerated	1.6
Hinnerman et al. 349 2002	Retrospective Non-selected 1964-1998 1 center	All stages		32% 68%	Monofractionated Bifractionated accelerated	2 1.2
Johansen et al.410 2002	Retrospective Non-selected 1963-1991 1 center	All stages	Co60	55-66 66-72 (27%)	Monofractionated Monofractionated Split course	2 2
Mendenhall et al.296 1998	Retrospective highly-selected 1964-1992 1 center	T3-4	Co60 2-4MV	74	Bifractionated accelerated.	1.2
Finizia et al.429 1996	Retrospective Non-selected 1986-1990** 1 center	All stages	Co60 4-6MV	61-74 T3-4 68-74	Monofractionated	2-2.4

Table 40: Criteria and protocols of the important radiotherapy studies included in the discussion.

Some articles miss some outcomes or use other measurements so the blocks left empty to avoid multiple measurements.

5.4. ANATOMICAL FACTORS BEYOND THE TNM

Several authors reported many tumour factors beyond the TNM staging system as bad prognostic factors for control and survival of cancer larynx [38,202,212,215,231,232,248,251-255,257,449,450]. In our study one of the main aim was to detect the serious anatomical extensions that can impair the local control and affect the patients' survival.

5.6.1. THE ANTERIOR COMMISSURE (AC)

The effect of AC involvement on local control and survival has been extensively studied in T1-2 glottic carcinoma treated by radiotherapy. Most of the authors reporting this extension concluded to a significant decrease in local control survival [248,251-255,257], while few authors reported no significant changes [250,256].

In our study, the anterior commissure involvement was a significant factor for local control, the 5 years local control rate decreasing from 89% with no involvement to 57% with AC involvement (p=0.001), however it was not significant for the disease specific survival with only 10% difference at 5 years (p=0.262), both groups being comparable regarding the number of patients, the TN stages and the vocal cord fixation. This finding reflects globally that extension to the anterior commissure impairs the local control when a non-surgical treatment is chosen, but failures could be salvaged in most cases at the expense of the laryngeal preservation, since the needed procedure is usually total laryngectomy.

Bradley et al. [215] reviewed the results of the treatment of cancer larynx regarding the anterior commissure extension and reported a general agreement with few exception between studies about the negative impact of the anterior commissure in cases treated with radiotherapy. Trying to explain why the anterior commissure is a bad prognostic factor, they pointed at the probability of the underdosage with radiation sources based on 6 MeV photons or the essential limitation of traditional schemes to treat cases with anterior commissure extension. We observed that in the literature, high failures rates in cases with AC extension were associated with the use of Cobalt 60 and 2-4 MeV photons [248,251-255,257]. Another radiotherapy regimen was studied by Yamazaki et al.[256] in a randomized prospective study for T1 lesions treated with radiotherapy and they recommended hypofractionated radiotherapy with a daily dose of 2.25 Gy. They observed that, by increasing the dose per fraction in their monofractionated scheme an improvement in the local control could be achieved, but the majority of included cases were T1a.

In the second step in our evaluation of the AC, we divided this area to assess extensions that might be associated with poorer outcome. This classification is based on the anatomical and embryological description of the AC [36-40,79]. We had 17 cases with bilateral glottic involvement (13 cases were early stages and 4 cases were advanced) with positive lymph nodes in one case only. The reported 5 years local control was 47% while the 5 years disease specific survival rate was 76% with the adjusted 5 years laryngeal preservation rate of 65%. These results suggest that a pure horizontal extension at the AC could impair the control rate (p=0.002) but the survival remains unaffected (p=0.86) because of salvage total laryngectomy.

Superior extension at the AC was found in only 10 cases (5 were early and 5 were advanced), with 3 patients having nodal disease. The 5 years local control, disease specific survival and laryngeal preservation rates were all 40%, with (p=0.004) for the local control, and (p=0.001) for the survival. This poor outcome suggests that supracommissural extension is a danger zone, an observation already mentioned by Kirchner in his excellent studies on the behavior of cancer larynx [143,146,147]. However, in our study, we cannot exclude an

impact of the advanced disease on the poor outcome in this group.

Eleven patients had infracommissural extension (8 were early and 3 were advanced), all these patients were glottic in origin and were classified as N0. The reported 5 years local control was 45% (p=0. 0.006) while the 5 years disease specific survival rate was 54% (p=0. 0.027) with the adjusted 5 years laryngeal preservation rate of 45%. The results of this group are poor and both control and survival rates were severely impaired although the lesions were early, reflecting that the infracommissural extension can decrease the control and survival results even in T2 lesions.

Different anatomical and pathological studies suggested that glottic carcinoma reaching the anterior commissure can grow easier in a downward direction because of the anatomical arrangement of the fibrous structures [36-40,79,143,144,147,451] In our opinion, the T2-3 glottic or glotto-subglottic tumours can easily invade this area with increased risk of early extralaryngeal spread. The importance of the evaluation of the vertical extension along the AC and its impact on the control rates of the tumour were mentioned by other authors, in particular when transoral resection is considered [265,452].

Although expert centers (Mendenhall et al. [250] and Hinermann et al. [390]) report excellent with radiotherapy in selected T3 glottic carcinomas, they recommended the exclusion of patients with actual crossing at the anterior commissure or extensive bilateral anterior vocal folds involvement.

The low numbers of these subgroups in our study do not allow us to reach a clear conclusion. However, our study strongly suggests that the vertical extension along the AC should be specifically investigated and a non-surgical treatment could have a poor prognosis with this extension. In our opinion, this area should be evaluated carefully with the angled telescopes during microlaryngoscopy and in pure horizontal involvement radiation could be used with meticulous care to salvage the recurrence early with partial surgery. But in cases with vertical extension, SCPL should be considered to have a monoblock resection of this area as pointed by many authors [190,205,215,287,289,327,391,398].

5.6.2. VOCAL CORD MOBILITY

This study involved 22 (26.5%) cases with vocal cord mobility impairment: in 11 patients the mobility was reported as impaired, while in the other 11 patients the vocal cord was reported as completely immobile. Among these 22 patients, 17 had chemoradiotherapy and the other 5 had altered radiotherapy. We analyzed the vocal cord mobility globally and separately for each side in grades and all the analyzed variables regarding the mobility were non-significant (table 25).

Recent meta-analysis performed to study the effect of the vocal cord mobility on the control and survival in T2 patients treated with radiotherapy concluded that impaired vocal cord mobility has a negative effect on the control and survival of the patients [453]. Although this meta-analysis provides good evidence for vocal fold mobility impairment as a bad prognostic factor, its conclusion are hampered by a large number (15/21) of studies published prior to 1995 and thus using traditional monofractionated protocols and the lack of details on the total radiation dose in each study. We used in all our cases of mobility affection altered radical radiotherapy, and different authors reported similar results to ours with the use of the altered radiotherapy [250,258]. Medini et al, [454] concluded that a high total dose was associated with improved local control in T2 cases with impaired mobility. Thus, in our opinion the results of this meta-analysis could be mainly attributed to the traditional schemes of radiotherapy or to a suboptimal dose. Another variable, not well studied, is the role of chemoradiotherapy treatment on the outcome of patients with impaired vocal cord mobility.

As in our results, the previously mentioned chemoradiotherapy randomized trials [302,307] did find a significant effect of cordal fixation on the survival. Although the number of the patients with fixed vocal cord in our study was limited, it seems that impaired or fixed vocal fold alone does not affect much the survival when an optimum protocol of (chemo)radiotherapy is used. Again, this issue should be further investigated.

On the other hand one of the most significant predictors for local control and survival in our study is the post treatment vocal cord mobility status (p=0.0000). At three months after treatment, 15 of our patients either developed vocal fold mobility impairment or presented with persistent impairment of the vocal fold. Among these 15 cases, 10 recurred: 9 of them with local failure and 9 of these patients died from the disease.

With the increasing use of chemoradiotherapy to treat the advanced laryngeal carcinomas, this parameter is becoming a subject of investigation [455,456]. Iloabachie et al, [455] explored the return of vocal fold mobility in T2-3 laryngeal carcinomas as a prognostic factor after non-surgical treatment and they reported the post-treatment mobility impairment as an independent highly significant predictor for local failure (100% Vs 0%). Solares et al, [456] evaluated the return of normal mobility in T3-4 patients with fixed vocal fold treated with chemoradiotherapy and they reported also a highly significant decrease in the local control (from 87% to 30%) and survival outcome with persistent vocal cord fixation or hypomobility. Moreover, their conclusions are identical to ours, meaning that chemoradiotherapy is a feasible treatment in many cases of vocal fold fixation but post-treatment persistent vocal fold mobility impairment is a very poor prognostic factor. These recent data from the literature should be carefully evaluated to establish the indications of salvage laryngectomy.

5.6.3. SUBGLOTTIC EXTENSION

Subglottic extension has been traditionally treated with total laryngectomy, but there was no clear evidence in the literature for the effect of subglottic extension on the outcome of patients treated with (chemo)radiotherapy. We had in our study only 13 patients with clinical subglottic extension and 16 cases reported radiologically to have subglottic involvement.

The clinical subglottic extension was found to be significant regarding local failure and survival, and more specifically the anterior subglottic extension was highly significant for local failure, while the lateral one was not significant. We found no studies that tested this variable in a similar manner to compare with ours, however, some authors reported the detection of subglottic extension on MRI to be highly significant for local failure in cases treated with radiotherapy [457].

5.6.4. PERSISTENT POST TREATMENT OEDEMA

Similar to the post-treatment mobility status we tested the persistent oedema three months after the end of the treatment. Although this variable was significant for local failure and survival in our study, these results are limited by the subjective assessment of this parameter.

The presence of severe persistent oedema is described by many authors as independent factor for local recurrence, especially if associated with signs of radionecrosis of the laryngeal cartilages [179,458,459]. The problem in these situations is that the diagnosis of recurrence is very difficult [179] as illustrated in our three cases with oedema, two of them subjected to multiple biopsies that ended with distant metastases.

An interesting question is whether patients with persistent vocal cord fixation and oedema after the end of the radiotherapy should be offered laryngectomy without pathological proof of recurrence? What if the patient is also tracheotomy dependent? We can obviously not answer these questions because of the small number of patients but the issue should be addressed in future studies.

5.5. FUNCTIONAL OUTCOME

5.7.1. FEEDING TUBE AND TRACHEOTOMY

In our study, no patient had a feeding tube before treatment which is expected when dealing with a population cancer larynx composed mainly of early and intermediate lesions. In previous publications of our

hospital, 20 % [376] and 37% [379] of the patients treated with (chemo)radiotherapy needed insertion of the feeding tube for nutritional support during and/or shortly after the treatment. Also, 15% [376] and 18% [379] required hospitalization for the nutritional and general support. In our study at a cutting line three months after the end of the radiotherapy, the total rate of feeding tube was 22%. Permanent gastrostomy (one year or more) was needed only in 4% (three patients).

In our study the total tracheotomy rate during and after the end of radiotherapy was 12% while 2 patients only (2%) had a permanent tracheotomy. Finally 5% of the patients lost their basic laryngeal functions due to permanent tracheotomy and or gastrostomy but none of the patients needed total laryngectomy for functional reasons.

Unfortunately the RTOG trial [307], did not report clearly the feeding tube and tracheotomy tube rates but at one year 23% of the patients treated with concomitant chemoradiotherapy were able to swallow fluids only, and 3% were not able to swallow at all, which is close to our results. While in the VA trial [302] the functional results were not reported, in other chemoradiotherapy studies, involving all head and neck sites, the long-term dependency on feeding gastrostomy after chemoradiotherapy (6-12 months after the end of the treatment) was reported to be 20-30% [314-319,321,432]. Nguyen et al,. reported 10% of feeding gastrostomy and tracheotomy at 6 months after the treatment in cases treated with (chemo)radiotherapy [318]. After radiotherapy alone, Mendenhall [296] reported 3% loss of larynx and Johansen et al., [396] reported 51 tracheotomies in a series of 410 patients (12%).

Caudell et al. [314] found that after concomitant chemoradiotherapy, laryngeal and hypopharyngeal primaries were associated with the worse functional outcome and long need for a feeding tube, similarly to the RTOG trial [307]. Staton et al. [321] analyzed the factors associated with poor functional outcome after chemoradiotherapy protocols for laryngeal cancer and found that patients with fixed vocal fold, T4 lesions, prior tracheotomy, and massive cartilage destruction are associated with very poor functional outcome.

Recently it was highly recommended to describe the details of the functional results following chemoradiotherapy and it was recommended to exclude cases with pretreatment tracheotomy or poor laryngeal functions from the trials as these groups carry a high risk of extremely poor functional outcome with the non-surgical treatment [433].

Our results and the reported rates in the different studies mentioned above [296,307,314-319,321,348,376,379,396,432,433], point to an important concept for the new protocols of non-surgical laryngeal preservation modalities. We have to accept that recovery of the laryngeal functions, especially swallowing, is not immediate and most of the patients will need a temporary feeding tube which will remain for at least three months in about 20% and for a minority (2-4%) more than one year. These global results are more or less comparable to the subtotal reconstructive laryngectomies used to treat advanced laryngeal carcinomas with preservation of the laryngeal functions [190,205,326,328-330,362-364,366,367,391,417,439,440]. This concept should be clear for the management team and fairly explained to the patient and his family. In other words, when dealing with intermediate and advanced laryngeal carcinoma the recovery and long term laryngeal functions are almost the same whatever the conservation treatment modality used (surgical or not). A related issue is whether we should use a swallowing rehabilitation program as a routine during and after the organ preservation protocols, as we do after the conservation laryngeal surgeries?

Thus, the multidisciplinary team managing cancer larynx should remember the swallowing dysfunction (20% for 3 months and 2-4% permanent), the need for a tracheotomy (12% temporary and 2% permanent), the need for a temporary (1-2 weeks) hospitalization in 15%, the difficulty of an early diagnosis of recurrence, the poor outcome and significant morbidity after salvage total laryngectomy when offering chemoradiation "organ preservation" protocols to the patient. It is up to future studies to add the cost of all these events and to compare them to the prolonged hospitalisation and rehabilitation after conservative partial laryngectomies.

5.7.2. THE COMPOSITE OUTCOME

The composite laryngectomy free survival at five years in our study is 73%. This parameter was reported by the RTOG trial [307] to translate the survival outcome and the laryngeal preservation, and they reported 45% laryngectomy free survival for the patients assigned to concomitant chemoradiotherapy. Our study contains many cases of T1, which account for this high difference, but another factor is the exclusion of non cancer related deaths, which, should be excluded to improve the validity of this measurement. In our opinion, it is not logic to consider a patient three years free of disease with an intact larynx but dead from other causes as a treatment failure.

In addition, we proposed to measure a composite parameter that measure the specific survival with the real conservation of the laryngeal function that could be obtained considering patients with permanent tracheotomy and or gastrostomy as failures. Similar recommendations for calculating the laryngeal preservation was reported recently [400,433]. The composite functioning larynx free survival at 5 years in our study was 67%.

5.6. MORTALITY

Our study contained only 1% treatment related mortality, which is comparable to our previous publications [376,379] and is similar to different reports of radiotherapy using altered radiotherapy techniques [296,349,390]. This rate is also comparable to the surgical techniques that can be used in these lesions[190,397,399]. In the VA trial the reported mortality was 2%, however 4% in the non-surgical arm was reported as deaths from unknown aetiology [302]. In the RTOG trial concomitant chemoradiotherapy arm, higher rates of treatment related mortality were reported (4%) [307].

VI. CONCLUSIONS

The following factors should be considered when using the radical (chemo)radiotherapy in the treatment of primary laryngeal SCC:

1) Anterior commissure involvement is a poor prognostic factor for local control and laryngeal preservation but it does not impair disease specific survival.
2) Vertical extension along the anterior commissure impairs both local control and disease specific survival.
3) Lesions that show subcommissural extension and/or anterior subglottic extension give poor results and a treatement by supracricoid laryngectomy or total laryngectomy ± radiotherapy should be considered.
4) Pre-treatment vocal cord fixation, lateral subglottic extensions do not decrease the disease specific survival to a significant level.
5) Both post-treatment vocal fold mobility impairment, and/or persistent laryngeal oedema are strong early predictors to the treatment failure.

The detailed clinical description of the anatomical extensions (tumour mapping) by the routine use of the microlaryngoscopy and the use of the angled telescopes when needed is the milestone for the accurate T staging, allowing for a tailored treatment for every patient.

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