

Diplomarbeit

CLINICAL OUTCOME OF PATIENTS AFTER TOTAL
LARYNGECTOMY

A retrospective study

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Graz, am 26.09.2018

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Glossar und Abkürzungen

CI	confidence interval
CLS	conservation laryngeal surgery
CT	chemotherapy
CTM	cricothyroid muscle
DG	digastric muscles
ECOG	Eastern Cooperative Oncology Group (ECOG)
ELS	electrolaryngeal speech
ES	esophageal speech
H&N	head and neck
HNC	head and neck cancer
HPV	human papillomavirus
IA	interarytenoid muscle
IMRT	intensity-modulated radiation therapy
iSLN	interior branch of the superior laryngeal nerve
KPS	Karnofsky Performance Status
LCA	lateral cricoarytenoid muscle
LN	lymph nodes
LP	larynx preservation
OR	odds ratio
PCA	posterior cricoarytenoid muscle
QOL	quality of life
RCT	radiochemotherapy
RLN	recurrent laryngeal nerve
RR	relative risk
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SCC	squamous cell carcinoma
SCM	sternocleidomastoid muscle
SLN	superior laryngeal nerve
STL	salvage total laryngectomy
TA	thyroarytenoid muscle

TES	tracheoesophageal speech
TL	total laryngectomy
TLP	total laryngopharyngectomy
TO	tracheo-esophageal
VA	Department of Veteran Affairs
VP	voice prosthesis

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Zusammenfassung

Einleitung: Bei der totalen Laryngektomie (TL) wird der Larynx vollständig entfernt, was zu einer Trennung des Luft- und Speiseweges sowie zum Verlust der Stimme führt. Die häufigste Indikation stellen fortgeschrittene Karzinome des Larynx und Hypopharynx dar. In den letzten Jahren wurden für diese PatientInnen zunehmend organerhaltende Therapieansätze mittels Radio- und Chemotherapie angewandt. Das Ziel dieser Studie war es, Komplikations-, Rezidiv- und Überlebensraten nach TL zu ermitteln und einen Einblick in die aktuellen Standards der Stimmrehabilitation zu geben.

Methoden: PatientInnen, bei denen zwischen 01.01.2002 und 16.01.2018 an der HNO-Universitätsklinik Graz eine TL durchgeführt wurde, wurden mittels der elektronischen Datenbank "MEDOCS" identifiziert. Allgemeine und klinische Parameter wurden erhoben und ausgewertet.

Ergebnisse: Insgesamt erfüllten 103 PatientInnen die Einschlusskriterien. 101 davon waren KrebspatientInnen, 2 wurden aufgrund von Aspirationsproblematik operiert. 88 der KarzinompatientInnen waren Männer und 13 Frauen mit einem medianen Alter von 63 Jahren. 72 PatientInnen hatten ein Larynxkarzinom und 22 ein Hypopharynxkarzinom. 13 PatientInnen unterzogen sich einer Salvage-Laryngektomie nach Versagen einer Radio- bzw. Chemotherapie. Die Komplikationsrate lag bei 58%. Als häufigste Komplikation trat eine pharyngokutane Fistelbildung auf, welche bei 29 Fällen beobachtet wurde. Die Überlebensrate betrug 83% nach einem und 64% nach drei Jahren. 30 PatientInnen entwickelten ein Rezidiv nach einer mittleren Dauer von 6 Monaten. 48 PatientInnen wurde eine Stimmprothese implantiert, die im Mittel nach 148 Tagen gewechselt werden musste. Kehlkopflose Stimmgebung erfolgte bei 43 PatientInnen mittels Ruktusstimme, bei 32 mittels Stimmprothese und bei 8 mittels Elektrolarynx. 28 PatientInnen verwendeten mehr als eine Methode.

Konklusion: TL bleibt die Therapie der Wahl bei PatientInnen mit Karzinomen im Stadium T4a. Die Überlebens- und Komplikationsraten waren vergleichbar mit den Ergebnissen der aktuellen Literatur. Obwohl Stimmgebung mittels Stimmprothese den derzeitigen Goldstandard in der Stimmrehabilitation darstellt, können auch mit der Ruktussprache gute Ergebnisse erzielt werden, ohne Komplikationsrisiko der Prothesenimplantation und ohne Notwendigkeit eines Prothesenwechsels.

Abstract

Introduction: Total laryngectomy (TL), the procedure in which the larynx is completely removed, results in total separation of respiratory and upper digestive tract and loss of voice. It is most commonly used in the treatment of advanced cancer of the larynx and hypopharynx. These patients are increasingly being treated with organ-preserving protocols using radiotherapy and chemotherapy. The purpose of this study was to review complication, recurrence and survival rates following TL and gain insight into the recent standards of voice rehabilitation.

Methods: In a retrospective study, patients who had undergone TL between 01.01.2002 and 16.01.2018 were identified and reviewed via the electronic database "MEDOCS" of the Department of Otolaryngology, University Hospital of Graz. Clinicopathological data was collected and evaluated.

Results: A total of 103 patients met the inclusion criteria. 101 patients had been treated due to cancer, and 2 due to chronic aspiration. 88 of the cancer patients were men and 13 women, with a median age of 63 years. Primary cancer involved the larynx in 72 and the hypopharynx in 22 cases. 13 patients were treated with salvage laryngectomy. Overall complication rate was 58%, and the most common complication was development of pharyngocutaneous fistula in 29 patients. Survival rate was at 83% after one year and 64% after three years. Recurrence developed in 30 patients after a median of 6 months. In 48 patients a voice prosthesis was implanted, with a mean time range of 148 days between replacements. Alaryngeal speech was achieved by use of esophageal speech in 43 patients, of tracheoesophageal speech in 32, of an electrolarynx in 8 and of more than one method in 28.

Conclusion: TL remains the preferred initial approach to treat T4a laryngeal and hypopharyngeal cancer. We found survival and complication rates comparable to results found in current literature. While tracheo-esophageal speech by voice prosthesis is considered the gold standard, esophageal speech can achieve good results without the risk of complications and the frequent prosthesis replacements.

1. Introduction

1.1. History

Laryngeal cancer has been a known and feared entity since antiquity, and treatment used to be almost impossible due to a lack of knowledge in anatomy and physiology combined with the limited methods of anesthesia and instrumentation.(1) Reports show that the first tracheotomies were done on dyspnoeic patients in ancient Egypt.(2) First accounts of a TL performed on corpses by Watson(3) in the United States stem from 1866. Around 1870, Czerny(4), one of Billroth's assistants, conducted experimental laryngectomies on dogs. The results were questionable, and as 80% of the dogs died, the experiments were terminated.(2,5) The first known successful laryngectomy was carried out by Billroth(6–8) on a human cancer patient in 1873 in Vienna. The 36-year old patient had suffered from dysphonia for three years. Upon examination, a subglottic tumor, located mainly on the left side, was found. Conservative treatment proved ineffective and the tumor continued to grow, causing stridor and dyspnea. Billroth practiced a median cricothyroidotomy and endolaryngeal excision of the tumor in November. One month later, on December 31, an examination showed extensive recurrence of the tumor, which required Billroth to perform a TL. The procedure was complicated by pronounced bleeding, intermittent awakening of the patient from anesthesia and coughing, but was ultimately successful. The hyoid bone and epiglottis were left in situ. The patient resumed oral nutrition on the eighth postoperative day, even though he suffered from a large pharyngocutaneous fistula. The patient was then fitted with a T-shaped device, which is said to have prevented food from entering the trachea and also succeeded in giving the patient a clear, if monotonous, voice. The patient was discharged in March of 1874 and survived for seven months. (1,2,6,9) It was Gussenbauer(8), one of Billroth's students, that reported the details of the procedure to the German Surgical Society in 1874, as Billroth was absent at the time.(6,8,9)

In 1875 in Italy, Enrico Bottini from Turin performed a TL on a patient who survived for 10 years after the operation.(10) In a retrospective study published in 1880,

Gluck and Soerensen found the intraoperative and immediate postoperative mortality following TL to be at 50%. To decrease postprocedural mortality, he proposed to perform the procedure in two stages.(10,11) First, larynx and trachea were separated, followed by TL after a recovery period of two weeks. Soerensen developed a new technique in 1890 conducting a total TL in a single procedure, which was very similar to the method of retrograde laryngectomy currently in use. The American surgeon Crile implemented the radical neck dissection to be done in the same procedure with TL after understanding the connection between the lymphatic system and metastasis.(12) Martin and Ogura succeeded in creating a standardized TL with neck dissection after continuous improvements in technique and equipment around 1950.(5,13,14)

1.2. Anatomy

1.2.1. The Larynx

The important role of the larynx in airway protection, swallowing and speech production complicates the therapeutic management of cancers of this structure. The larynx is comprised of a cartilaginous framework, and the vocal folds divide it vertically into the supraglottic, glottic, and subglottic subsites.(15)

The larynx is located at the anterior aspect of the neck, suspended from the hyoid bone and continuing inferiorly into the trachea. Spanning between C5 and C6 vertebrae, it conjoins the hypopharynx with the trachea and facilitates the separation of the upper respiratory and digestive tract. Laterally, it is blanketed by the lobes of the thyroid gland and related closely to the major blood vessels of the neck in the course of their ascent to the head. The infrahyoid muscles cover the larynx anteriorly, and at its back and to the side the hypopharynx and the cervical part of the oesophagus are situated. The hypopharynx contains the pyriform sinuses, the postcricoid area and the posterior pharyngeal wall. The larynx is fixated by its connection to the hyoid and the trachea through the thyrohyoid membrane and cricotracheal ligament, respectively, as well as by muscular attachment connecting it to the hyoid and mandibule and the sternum and clavicle. Physiologically, it is susceptible to considerable movement along the longitudinal axis during swallowing and phonation axis due to the elasticity of the

trachea. The most important functions of the larynx are control of ventilation and phonation, but also encompass coughing, the Valsalva maneuver and protection of the airway during passage of food to avoid aspiration.(16–18)

The larynx is built up by a cartilaginous skeleton, connected by joints, ligaments and membranes, as pictured in Figure 1. The laryngeal skeleton is composed mostly of hyaline cartilages: the thyroid, the cricoid, the paired arytenoid, corniculate and cuneiforme cartilages as well as the unpaired epiglottis which consists of fibroelastic cartilage.(19)

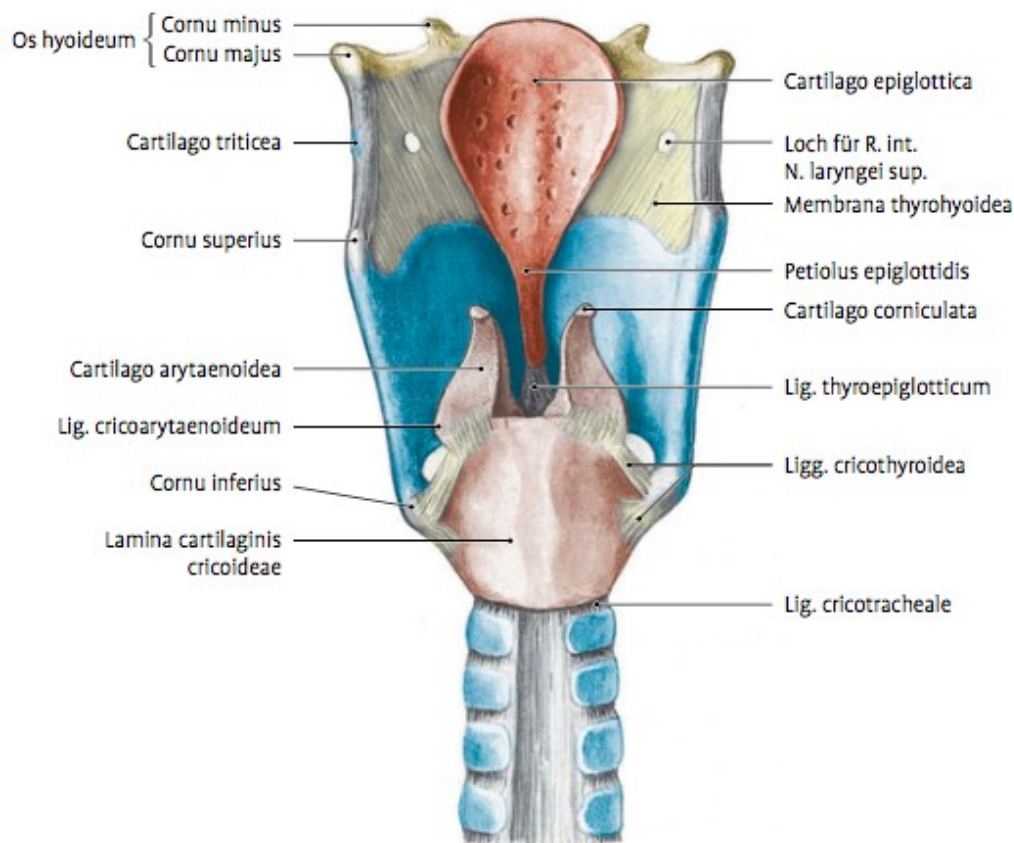


Figure 1: Cartilaginous skeleton and ligaments of the larynx, viewed from behind. Picture from Waldeyer - Anatomie des Menschen, 19th Edition.(20)

The external form of the larynx can be compared to a three-sided pyramid with one posterior and two anterolateral walls, its apex positioned at the transition to the trachea. The aditus laryngis is located at the top of the posterior wall, followed inferiorly by the cricoid lamina.(17,20)

The cavity of the larynx can be divided into three anatomic subsites. The supraglottis or vestibule begins from the laryngeal aditus to the vestibular bands and includes the epiglottis, the laryngeal aspect of the aryepiglottic folds,

arytenoids and ventricular bands. The glottis extends from the vestibular folds to the vocal folds and contains the true vocal folds including the anterior and the posterior commissures. The region below the vocal folds to the inferior margin of the cricoid represents the subglottis. The endolaryngeal anatomy is illustrated in Figure 2. The mucous membrane lining the inside of the larynx is pseudostratified, ciliated columnar epithelium, except for the vocal folds, which are lined with a stratified squamous epithelium.(15,17,20)

The spatula-shaped plate of the epiglottis marks the entrance to the larynx. Its stalk is called petiolus epiglottidis, which is connected to the median back of the thyroid by the thyroepiglottic ligament. Three glosso-epiglottic plicae connect the epiglottis to the tongue. On each side of the epiglottis the stylopharyngeus muscle raises the pharyngoepiglottic plica. Inferiorly, the paired aryepiglottic plicae limit the entrance to the larynx. Lateral to the plicae, the mucosa of the pharynx bulges into the pyriform sinuses. The anterior part of the epiglottis attaches to the corpus of the hyoid bone via the hyoepiglottic ligament. The preepiglottic fat body is situated inferiorly to this ligament, bordered anteriorly by the thyroid and the median thyroepiglottic ligament and posteriorly by the epiglottis itself. This fat pad, as well as the tongue move backwards during the act of swallowing, shifting the epiglottis backwards and moving it toward the arytenoid cartilages. This action leads to endolaryngeal closure, thus preventing aspiration.(16–19)

The thyroid is a prominent structure, which consists of two laminae meeting at an anterior median peak called the laryngeal prominence or the Adam's apple. In the midline of this peak are the superior and inferior thyroid notches. The posterior borders of each laminae form superior and inferior horns. The superior horns and superior margin of the thyroid attach to the major horns and the body of the hyoid bone via the thyrohyoid membrane at C4 and C5 vertebrae. This membrane is internally covered by mucosa of the pyriform sinus and pierced laterally by the the internal branch of the superior laryngeal nerve and the superior laryngeal vessels. The anteromedial and posterolateral thickening of the thyrohyoid membrane represent the median thyrohyoid and lateral thyrohyoid ligament, respectively. The inferior horns are shorter and contain small articular facets to conjoin with the cricoid cartilage.(16,17,19,20)

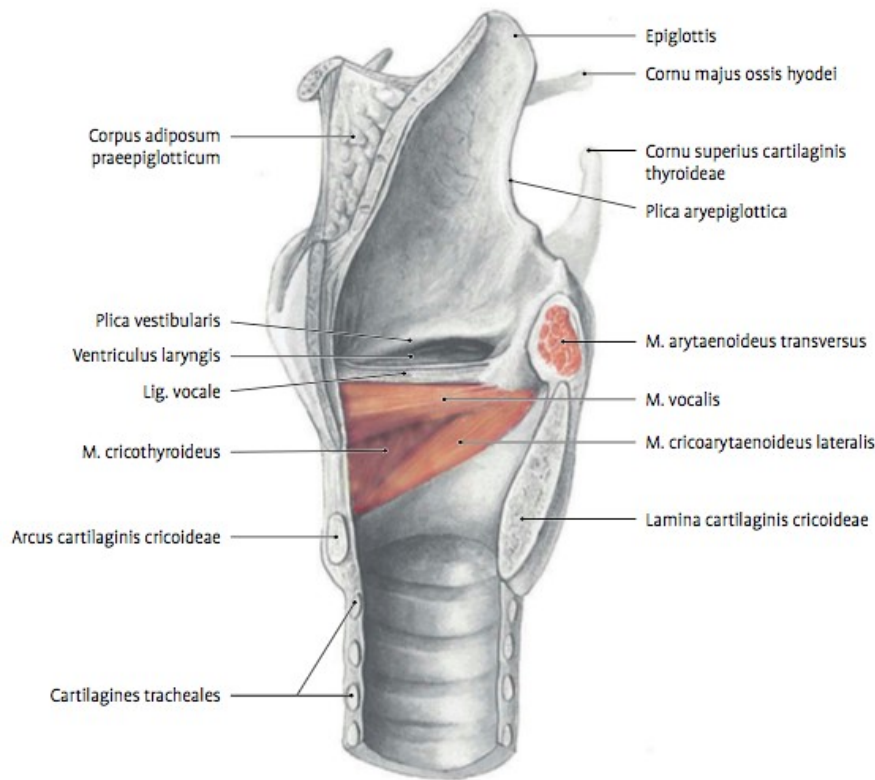


Figure 2: View of the endolaryngeal anatomy. Picture from Waldeyer - Anatomie des Menschen, 19th Edition.(20)

The cricoid is a complete ring of cartilage that marks the inferior border of the larynx at the lower level of C6 vertebra just below the thyroid. It is said to resemble a signet ring, as it consists of a narrow anterior arch and a broader posterior lamina. It is connected to the thyroid by the median cricothyroid ligament and the cricothyroid joints, and it articulates with the arytenoid cartilages posterosuperiorly. Inferiorly, it attaches to the first tracheal ring of cartilage by the cricotracheal ligament. The cricothyroid ligament originates from the cricoid cartilage and is composed of two parts, the median cricothyroid ligament, which attaches to the thyroid, and the lateral cricothyroid ligament or conus elasticus. The paired lateral cricothyroid ligaments extend superiorly, where they end with an unattached upper margin forming the vocal ligaments. The vocal ligaments extend from the vocal processes to the arytenoid cartilages in the back. The quadrangular membrane spans between the anterolateral arytenoid cartilage and the lateral part of the epiglottis and has a free upper and lower margin. The lower margin thickenes into the vestibular ligament.(16,17,19,20)

The pyramidal shaped arytenoid cartilages sit on the cricoid cartilage. They each have two processes, and provide attachment points for several key structures in

the larynx. The apex of the arytenoid articulates with the corniculate cartilage, while the base connects to the upper border of the cricoid. The posterior and lateral cricoarytenoid muscles attach to the muscular process, while the vocal process provides attachment for the vocal ligament. The corniculate cartilages are small structures that articulate with the apices of the arytenoid cartilages. (16–18,20) The paired aryepiglottic folds extend from the epiglottic framework to the arytenoid cartilages in the back and consist of muscle, connective tissue and mucous membrane. Both the corniculate and the cuneiform cartilages are located within the aryepiglottic folds. While the cuneiform cartilages do not have direct attachment, they act to strengthen the folds and add support and stiffness.(19)

1.2.2. Laryngeal Musculature

Muscles that attach to the larynx either move it as a whole (extrinsic muscles), or alter the position of the cartilages against each other (intrinsic muscles). The extrinsic muscles move the larynx along the frontal axis superiorly and inferiorly.(16) The extrinsic group is comprised of the suprahyoid and infrahyoid muscles, and the stylopharyngeus, which is a pharyngeal muscle. Elevation of the larynx is achieved by the suprahyoid muscles and the stylopharyngeus, whilst the infrahyoid muscles depress the larynx.(17,20) In the act of swallowing an elevation of the larynx happens, facilitating the closure of the laryngeal aperture by the epiglottis, as well as during voice production. Elevation of the larynx changes the angle between the cricoid and thyroid cartilage, lengthening the vocal folds.(22) Phonation and ventilation are controlled by movement of the intrinsic laryngeal muscles, which alter the position of the muscular and vocal processes of the arytenoids. This alters the length, tension, shape, and spatial position of the vocal folds and the shape of the opening between the vocal folds and the arytenoids, which is called the rima glottidis.(19)

The posterior cricoarytenoid (PCA) is the only muscle capable of widening the rima glottidis, attaching to the muscular process of the arytenoid and inserting on the middle and lateral section of the posterior cricoid.(22) It rotates the arytenoids outward and therefore abducts the vocal folds. The cricothyroid (CTM) muscle elongates and tenses the vocal folds, controlling forceful speech. The thyroarytenoid (TA) muscle acts to shorten and relax the vocal folds, allowing for a softer voice, and also to narrow the rima glottidis. It forms the body of the vocal

fold, connecting the arytenoid cartilage to the anterior inner commissure of the thyroid while enveloping the vocal processes. The lateral cricoarytenoid (LCA) muscle rotates the arytenoid cartilages to approximate their vocal processes, which adducts the vocal folds and narrows the rima glottidis, which modulates the volume and tone of speech. The interarytenoid (IA) muscles act to adduct the arytenoids, resulting in closure of the posterior part of the rima glottidis.(16,17,20)

1.2.3. Main vessels of the larynx

The main vessels of the larynx are the superior and inferior laryngeal artery and the accompanying veins. The superior laryngeal artery is a branch of the superior thyroid artery, which derives from the external carotid artery. It follows the internal branch of the superior laryngeal nerve into the larynx. The superior laryngeal vein drains into the superior thyroid vein and then the internal jugular vein. They supply the larynx above the level of the vocal folds, while the inferior laryngeal vessels supply the area below the vocal folds. The inferior laryngeal artery derives from the inferior thyroid artery, which arises from the thyrocervical trunk. It follows the recurrent laryngeal nerve into the larynx. The inferior laryngeal vein drains to the inferior thyroid vein, which then joins the brachiocephalic vein.(16,17,20)

1.2.4. Innervation of the larynx

The vagus nerve and sympathetic nerve provide innervation to the larynx, the vagus nerve sending two branches, the superior and recurrent laryngeal nerve. The superior laryngeal nerve (SLN) divides into an external and internal branch. The internal branch (iSLN) is almost entirely sensory, entering the larynx by passing through the hyothyroid membrane. It then divides into three branches, supplying the epiglottis, the aryepiglottic fold and the mucous membrane along the posterior part of the larynx, where it communicates with the recurrent nerve. The external branch innervates the CT muscle. Beneath the lower margin of the inferior pharyngeal constrictor muscle, the recurrent nerve (RLN) ascends, providing sensory innervation to the infraglottis and to all remaining intrinsic muscles of the larynx via its inferior laryngeal nerve. The mucous membrane is supplied by subepithelial plexuses formed by sensory branches of both laryngeal nerves.(16,17,20)

1.2.5. Lymphatic system of the larynx

The lymphatic vessels consist of a superficial and a deep network of vessels. Both of these networks communicate with each other and with the lymphatic network of the pharynx and trachea. The superior lymphatic vessels collecting the lymph fluid of the supraglottis and glottis accompany the superior laryngeal artery, passing through the hyothyroid membrane. They drain mainly to the upper and middle deep cervical lymph nodes (LN) located cranio- and mediojugularly, along with lymph fluid from the cranial hypopharynx. Subglottic lymph fluid flows in ventral direction mainly through the conic ligament and in posterior direction through the cricotracheal ligament. It is drained to the deep cervical LN, the LN of the recurrent chain, the prethyroidal LN, the pre- and paratracheal and sporadically also to prelaryngeal LN. The laryngeal lymphatic plexus continues into the tracheal lymphatic network without interruption. Lymphatic drainage of the larynx is characterized by a high degree of variability.(20,23)

In the past, LN of the neck were classified into chains surrounding important vascular and nervous structures of the neck and divided into superficial, deep, lateral and medial chains. (16,17) It was Lindberg in 1972 that first described the distribution of lymphatic metastases related to localization of the primary head and neck (H&N) tumor.(24) He developed the concept of anatomically correlated groups of cervical LN, describing nine lymphatic levels on each side of the neck plus LN of the parotid gland. His studies form the basis for our current knowledge, allowing to a certain degree of probability the prediction of the direction of lymphatic spread.(23,25) In 1982, Shan et al. developed a simplified version of Lindberg's LN classification, dividing the LN regions into seven levels.(25) This basic structure has not changed significantly since, although it was modified several times.(23)

The level system describing the location of LN of the neck now consists of seven levels (Table 1).(15)

Table 1: Anatomical structures defining the boundaries of the neck levels and sublevels. Table adapted from the Paleri et al.(26) and 7th edition AJCC(27)

Level	Clinical location	superior	inferior	anterior (medial)	posterior (lateral)
IA	Submental triangle	Symphysis of mandible	Hyoid bone	Left anterior belly of digastric	Right anterior belly of digastric
IB	Submandibular	Body of mandible	Posterior belly of digastric	Anterior belly of digastric	Stylohyoid muscle

	triangle				
IIA	Upper jugular	Skull base	Inferior border of the hyoid bone	Stylohyoid muscle	Vertical plane defined by the accessory nerve
IIB	Upper jugular	Skull base	Inferior body of the hyoid bone	Vertical plane defined by the accessory nerve	Lateral border of the sternocleidomastoid (SCM)
III	Mid jugular	Inferior body of hyoid	Inferior border of the cricoid cartilage	Lateral border of the sternohyoid muscle	Lateral border of SCM or sensory branches of cervical plexus
IV	Lower jugular	Inferior border of cricoid cartilage	Clavicle	Lateral border of the sternohyoid muscle	Lateral border of SCM or sensory branches of cervical plexus
VA	Posterior triangle	Convergence of SCM and trapezius muscles	Horizontal plane along inferior border of cricoid cartilage	Posterior border of SCM muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VB	Posterior triangle (supraclavicular)	Horizontal plane along inferior border of cricoid cartilage	Clavicle	Posterior border of the SCM muscle	Anterior border of the trapezius muscle
VI	Anterior compartment	Hyoid bone	Sternal notch	Common carotid artery	Common carotid artery
VII	Superior mediastinum	Sternal notch	Innominate artery	Common carotid artery	Common carotid artery

Level I is divided into level IA and IB. Metastases to level IA are most likely due to cancers of the floor of mouth, anterior tongue and lower lip. Resection of level IB includes the submandibular gland. Metastases to level IB are most likely due to cancers of the oral cavity, anterior nasal cavity, mid face and submandibular gland. A vertical plane along the accessory nerve divides level II in sublevel IIA anteriomedially, and the sublevel IIB posteriolaterally.(27) Metastases to level II most commonly stem from cancers arising in the oral or nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx and parotid gland. Metastases to level III most likely arise from cancers of the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. Level IV includes Virchow's node. Cancers of the hypopharynx, larynx and cervical esophagus are the most likely to metastasize to level V. Level V is divided by a horizontal plane at the arch of the cricoid into sublevels VA and VB. Sublevel VA contains the spinal accessory LN, and sublevel VB contains the LN around the transverse cervical vessels as well as the supraclavicular LN. Cancers of the nasopharynx and oropharynx may metastasize

into LN of sublevel VA, while cancers of the thyroid gland may metastasize into LN of sublevel VB. A plane defined by the sensory branches of the cervical plexus constitutes the surgical landmark that marks the lateral border of levels II, III, and IV and the medial border of level V. Level VI includes the pre- and paratracheal LN, the precricoid and the prethyroidal LN.(27) Metastases to these levels most commonly come from cancers of the thyroid gland, glottic and subglottic larynx, pyriform sinuses and cervical esophagus.(15) Level VII encompasses the pretracheal, paratracheal, and esophageal groove LN. Metastases to these LN are most likely due to cancer of the thyroid and of the esophagus. (15,26,27)

1.3. Physiology

The larynx serves as a valve in the upper airway, maintaining the opening of the vocal folds for respiration and closing during deglutition to prevent aspiration of foreign matter into the lower airway or to stabilize the chest by building up intrathoracic pressure.(22)

In humans, the larynx serves three important functions: protection of the airway, control of respiration and phonation.(19) The primary function of the larynx is that of a sphincter, guarding the lower respiratory tract from the intrusion of foreign matter. Its secondary function centers around its role in respiration by active dilatation of the laryngeal aperture. Phonation, the third function of the larynx, appears to be a late phylogenetic acquisition. Humans alone have developed complex sound production by using the sphincter of the larynx as a vibratory source.(21,28)

The upper airway crosses the digestive tract in the region of the pharynx. This common passageway complicates the sphincteric function of the larynx and also compromises its respiratory performance by creating ventilatory turbulence and resistance. The anatomic configuration in adult humans that enables phonation simultaneously compromises the sphincteric and respiratory function of the larynx, creating a functional dilemma. This is resolved on a laryngopharyngeal level by structural adaption and exact coordination of the laryngeal functions by precisely organized brainstem reflexes, called laryngeal reflexes.(21) The larynx constantly controls life supporting processes such as breathing, swallowing and coughing by specific laryngeal reflexes or responses.(22) Basic functions are controlled by

complex interactions of polysynaptic brainstem reflexes. The protective function is involuntary and reflexive, as opposed to the respiratory and phonatory functions that can be initiated voluntarily but are regulated through an array of involuntary feedback reflexes.(17,21)

1.3.1. Swallowing

The act of swallowing is elicited by stimulation of mechanoreceptors in the larynx and pharynx. Deglutition actively suppresses respiration while the upper airway closes to allow for passing of the bolus into the esophagus. The respiratory apnea during deglutition is an active cessation, which usually happens on expiration and resets the respiratory rhythm.(22) During the pharyngeal phase of swallowing, a sequence of events works to transport the bolus from the oropharynx into the esophagus without aspiration. The flat configuration of the epiglottis in adults directs swallowed matter away from the median laryngeal aperture into the pyriform sinuses. The aryepiglottic folds act as embankments, guiding food boli to pass laterally of the epiglottis along the gutter between the fold and the pharyngeal wall on each side.(21) The larynx and hyoid bone are elevated and moved anteriorly by extrinsic laryngeal muscles. This elevation as well as the descent of the epiglottis facilitate closure of the vestibule, with simultaneous closure of the vocal folds.(22,29) Deglutition is a semireflectory process.(29) The pharyngeal phase of swallowing is regulated by a central pattern generator in the medulla oblongata. This phase of swallowing is considered reflexive and can be initiated by stimulation of sensory triggers in the oropharynx, but it can also be initiated volitionally.(30) Deglutition depends on feedback of the SLN to execute and coordinate the pharyngeal phase of swallowing. Loss of this feedback has not only shown to induce a sensation of being unable to initiate deglutition but also to increase the occurrence of aspiration in human adults.(22)

1.3.2. Respiration

To facilitate respiration, the upper airway is dilated for inspiration(31) and relaxes on expiration. The PCA, which works to open the rima glottidis(32), is constantly active but tone increases during inspiration to keep the vocal folds apart.(33) This muscle is essential to life support(34), as bilateral paralysis of the PCA can result

in negative pressure between the vocal folds during inspiration, sucking them toward the midline and thus obstructing air flow.

During expiration, air flow is modulated by muscles closing the vocal folds, including the TA(35) and the LCA, which actively adducts the vocal folds. The LCA is most active for phonation and deglutition.(36)

During inspiration, a chain of muscles actively dilate the upper respiratory tract from the nasal cavity and to the larynx.(37) The laryngeal muscles act to open the vocal folds to enhance air intake. In tidal breathing, laryngeal muscular activity is generally low during expiration, with the TA activating to partially close the vocal folds to reduce air flow.(30,38) Hypoxia or hypercapnia cause stress on the respiratory system, which activate the laryngeal muscles to a higher degree to support air flow intake with opening of the vocal folds and activation of the adductor muscle to reduce expiratory air flow.(39,40) This demonstrates that respiratory reflexes actively control the laryngeal musculature in adult humans.(40)

1.3.3. Phonation

The most complex and specialized laryngeal function is voice production. Human speech, phonation, articulation and resonance require precise coordination and specific mechanical properties of the laryngeal musculature, brainstem reflexes and high-level cortical control. Lung capacity, thoracic wall compliance, anatomy of the pharynx, nasal and oral cavity, and mental status also play a role, and expiratory flow from the lungs must provide sufficient subglottic pressure.(19)

The process begins with inhalation and activation of the laryngeal muscles to create glottic closure as well as the adequate length, tension and closure of the vocal folds.(22) Expiratory flow increases subglottic pressure until it overcomes the glottal closure force and opens the posterior part of the vocal folds. Expiratory airflow passes between the vocal folds, inducing vibration due to the pliability and vibratory capacity of the mucosa. This wave-like motion of loose mucosa of the vocal folds over the denser tissue of the vocal ligaments and vocalis muscles is described by the body-cover theory. The mucosal wave begins infraglottically and moves superiorly toward the free edge of the vocal fold. Due to the decrease in pressure and elastic recoil of the tissue, the inferior edges eventually become reapproximated. The closure phase is propagated toward the front. Subglottic

pressure builds again when the vocal folds are fully approximated, and the cycle can be repeated.(19,22)

The role of the laryngeal muscles during phonation is to achieve an appropriate posture the vocal folds. This requires adequate contraction of the TA to shorten the vocal folds and lower them into the midline. The opposing action of the CTM lengthens and tenses the vocal folds.(22,41) The ratio of contraction levels of these muscles changes the fundamental frequency of vibration and thereby the pitch of the voice. The intrinsic muscles of the larynx are highly specialized for their specific vector of action during phonation, for the degree of recruitment and the timing of contraction.(19)

1.4. Laryngeal and Hypopharyngeal Cancer

1.4.1. Epidemiology

Head and neck cancer (HNC) is common all over the world, with large geographic variations of the incidence and primary site. Chronic exposure of the mucosa of the upper aero-digestive tract to carcinogenic substances can lead to dysplastic and ultimately malignant lesions. Primary risk factors for development of HNC are consumption of tobacco and alcohol as well as human papillomavirus (HPV) infection.(42) At least 75% of HNC diagnosed in industrialized regions can be attributed to cigarette smoking and alcohol consumption or a combination of both.(43) The relative prevalence of these risk factors as well as ethnic and genetic diversity contributes to observed differences in distribution of HNC.(42)

Worldwide, HNC accounts for more than 550,000 cancer cases and 380,000 deaths annually.(44) In the United States, HNC makes up 3 percent of malignancies, which correspond to approximately 63,000 Americans developing HNC and 13,000 HNC related deaths annually.(45) About 14,000 cases of laryngeal cancer and 3600 laryngeal cancer related deaths occur annually in the United States.(45,46)

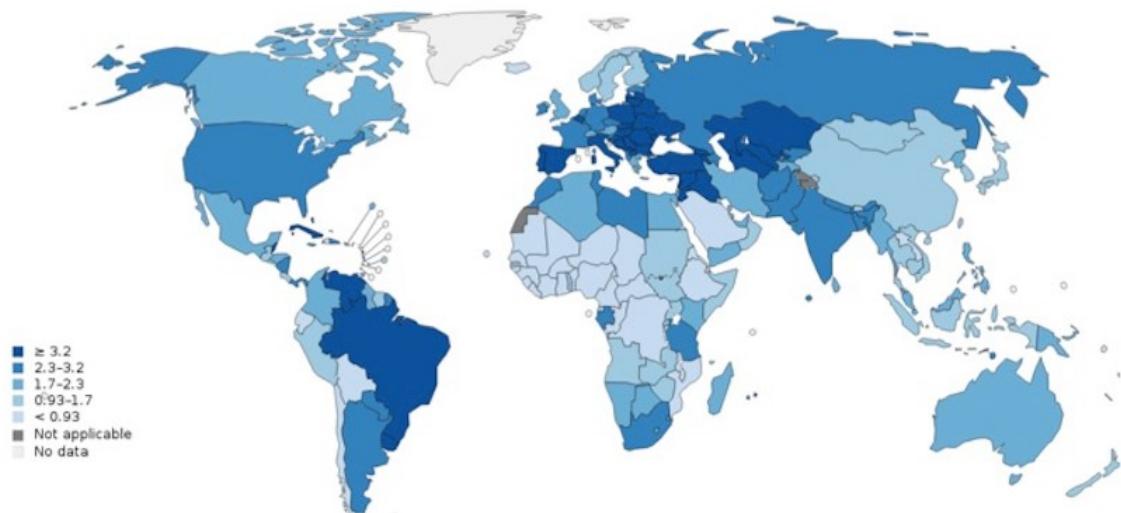


Figure 3: Estimated age-standardized rates (World) of incident cases, both sexes, laryngeal cancer, worldwide in 2012. Data source: GLOBOCAN 2012, Graph production: IARC, World Health Organization(47)

In Europe, approximately 250,000 cases of HNC in 2012 were reported, which correspond to an estimated 4 percent of the incidence of all malignancies, and 63,500 deaths.(48) Estimated by IARC approximately 36,000 cases of laryngeal cancer were diagnosed in 2012, which account for 1.98% of overall cancer incidence in Europe. The approximate incidence rate for 22 European countries is 4.8/100 000 in 2002 and 4.7/100 000 in 2012.(47,49) A total of 18,069 cases died from laryngeal cancer in Europe in 2012, accounting for 1.85% of all cancer deaths.(50) Figure 3 from IARC and GLOBOCAN 2012(47) shows estimated incident cases of laryngeal cancer in both sexes worldwide in 2012.

A slight downward trend in both the incidence and mortality rates of laryngeal cancer could be observed in the last years in most of the European Union (EU) in men and women.(51,52) Hypopharyngeal cancer is a relatively uncommon disease, with an incidence of less than 1/100 000 in the United States.(53,54)

Males are affected significantly more often than females, with an incidence rate ratio of 4,5 (M/F).(42,45) The highest incidence of HNC is found in older males, though the rate ratio has been decreasing due to an increasingly higher incidence of HNC in women(55), and in young non-smoking individuals with HPV infection. The incidence of laryngeal cancer is approximately 50% higher in African American males.(56) In African American men there is also a significantly higher mortality rate associated with both laryngeal and oropharyngeal cancer, which maybe a reflection of the lower prevalence of HPV infection among this

population.(57) Incidence and mortality of laryngeal and hypopharyngeal cancers is low in people under 40 years of age. Incidence increases rapidly in patients over 40 years old and finally peaks in subjects of 60-75 years. Mortality also increases with age, peaking at 85 years old.(49,58)

1.4.2. Risk factors

Squamous cell carcinomas (SCC) of the H&N develop from the squamous mucosal lining of the upper aero-digestive tract mainly in patients with risk factors like tobacco consumption, alcohol abuse, or HPV infection in their personal history. However, SCC arise in only 20% of individuals with a history of these risk factors.(59,60) Squamous carcinogenesis is caused when molecular genetic changes accumulate in the squamous epithelial lining of the upper aero-digestive tract. Dysplasia progresses to invasive carcinoma in a complex process, in which the interaction of epithelium and of host stromal elements trigger the dysregulation of key pathways which lead to cellular and structural changes.(59,60)

1.4.2.1. Tobacco products

Smoking tobacco products is the most important risk factor for the development of HNC.(61) Some evidence suggests a genetic predisposition to carcinogenic effects of tobacco use. Heavy cigarette smokers suffer from a 5- to 25-fold increased risk of cancer compared with nonsmokers.(42,61,62) There also appears to be a dose-response relationship, with relative risk (RR) increasing with frequency, duration and pack-years of cigarette smoking.(42) Cessation of smoking is associated with a significant decrease in RR, with no excess risk after 20 years.(63) This suggests that smoking primarily affects at a later stage in the process of carcinogenesis.(43) Cigarette smoking is strongly associated with higher risk of developing laryngeal and hypopharyngeal cancer, while the association to oral cavity or pharyngeal cancers is not as strong.(61,64)

Tobacco consumption other than cigarette smoking also increases the risk of developing HNC. Smoking of pipes and cigars is associated with a higher risk, even in patients who never smoked cigarettes.(61) Secondhand smoke exposure may also result in increased risk. Tan et al.(65) evaluated 59 patients with HNC who did not consume tobacco and did not abuse alcohol. Non-smoking patients

with HNC stood out as predominantly white, female and presented with significantly more tongue primaries. When compared with the control population without cancer, these patients showed a significantly higher risk of being exposed to environmental tobacco smoke.(65)

Evidence showing the association of the development of HNC and marijuana usage is somewhat conflicting, as the outcome of observational studies is often limited by reporting and selection bias and confounded by alcohol and tobacco consumption.(66,67)

1.4.2.2. Alcohol

Consumption of alcohol independently increases the risk of developing cancer in the upper aero-digestive tract, although the effects of smoking and alcohol are often confounded.(43) The RR of developing HNC due to alcohol appears to be dose-dependent.(63,64,68)

While no correlation with duration of alcohol use and risk for HNC is apparent in the absence of tobacco use, high doses and high frequency of alcohol use does increase the risk. Hashibe et al.(64) found that consumption of three or more alcoholic drinks per day was associated with approximately twice the risk of HNC than for never-drinkers. Increased frequency of alcohol consumption results in an increased risk to develop pharyngeal cancer when drinking one to two drinks per day, and laryngeal cancer when drinking five or more drinks per day.(64) The increase in risk is higher among those consuming hard liquor or beer than those consuming wine.(43) Similarly, Lewin et al.(63) reported that alcohol intake of 50 grams or more daily versus less than 10 grams daily led to a RR of 5.5%. Moderate alcohol consumption of 10-19 grams per day had little or no effect among nonsmokers.(63)

Alcohol intake combined with tobacco smoking appear to have an interactive and multiplicative effect on the risk of developing HNC.(43,63,69) The risk is increased more than 35-fold when two or more packs of cigarettes and more than four alcoholic drinks were consumed per day according to Blot et al.(43)

1.4.2.3. Human papillomavirus infection

HPV infection is associated with increased risk to develop HNC, particularly oropharyngeal cancer.(57,70) HPV-16 seropositivity was twice as high among HNC patients as among a control population, while no increased risk was observed for HPV-18, HPV-33 or HPV-73 by Mork et al.(71) Significantly elevated OR was detected for cancer of the tonsils and base of tongue. HPV associated HNC are typically seen in younger, white nonusers of tobacco and alcohol that present with local T category tumors and poor differentiation at histologic examination.(42) There is conflicting evidence whether HPV-associated risk of HNC is different in males and females.(71,72) It is also associated with significantly better outcome and improved survival in the subsites oropharynx, hypopharynx, larynx and oral cavity, with the largest benefit in survival in cancers of the oropharynx and hypopharynx.(72)

Immunohistochemical staining is used to distinguish HPV-related from non-HPV related cancers, as overexpression of p16, a tumor suppressor protein, is a surrogate biomarker for HPV-mediated carcinogenesis and also a positive prognostic factor regarding oropharyngeal carcinomas.(70,73) Overexpression of p16 is typically localized in tumor cell nuclei and cytoplasm. The cutoff point for positive p16 expression is at least moderate (+2/3) staining intensity and diffuse ($\geq 75\%$) tumor expression.(73)

1.4.2.4. Occupational exposure

Multiple occupational or environmental toxins have been studied for a potential relationship with HNC. These include the exposure to the dry cleaning agent perchloroethylene(74), asbestos, pesticides, man-made mineral vitreous fibers (MMMF)(75), polycyclic aromatic hydrocarbons (76), and cement(77).(42)

1.4.2.5. Diet

An increased intake of fruits and vegetables is associated with a decreased risk for HNC.(78)

1.4.2.6. Genetic factors

Genetic predisposition plays a modulating role in developing HNC, as not all

individuals exposed to the main etiologic factors experience the disease. Multiple genetic factors and pathways contribute to an increase in the risk of HNC, and these factors interact with other known risk factors.(79) These factors include metabolic polymorphisms that affect exposure to the carcinogens in tobacco smoke, polymorphisms of DNA repair genes, and variations in other pathways contributing to carcinogenesis.(42)

1.4.3. Pathology

Head and neck squamous cell carcinomas often develop from premalignant entities caused by carcinogen exposure, such as leukoplakia and erythroplakia.(80) Histopathologically, dysplasia is defined by the presence of mitoses and prominent nucleoli. Progression to invasive cancer happens in 15 to 30% of cases of dysplasia.(81) Leukoplakia is a descriptive clinical term for grey to white lesions characterized by hyperparakeratosis and often associated with hyperplasia of the underlying epithelium.(80) In the absence of underlying dysplastic alterations, leukoplakia is associated with malignant change in less than 5%.(82) Erythroplakia describes red patches adjacent to normal mucosa. It is less common than leukoplakia but more often associated with malignancy.(80) It is typically associated with epithelial dysplasia and with the presence of carcinoma in situ or invasive cancer in up to 40% of cases.(81,82)

SCC account for more than 90 percent of the lesions in the hypopharynx and larynx. In hypopharyngeal lesions, a general pattern is that the more posterior and the more inferior the site, the worse the prognosis. This is not true for laryngeal lesions, possibly because of differences in the type and the extent of SCC at the different locations. Also, anatomical differences between the sites influence prognosis. The less abundant lymphatic drainage of the larynx compared to the hypopharyngeal lymphatics may explain the higher metastatic rate and worse prognosis for hypopharyngeal cancer.(58,83)

SCC are graded depending on their keratinization using the World Health Organization's standard grading system, although there are distinct grading schemes used for cancers of different morphologic and anatomic site groupings.(83,84)

Histopathological grade is reported in registry systems by the grade value (Table 2).

Generally, the following grading system is used:

Table 2: Grading system. Table adapted from AJCC 7th edition(27)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Less common histologies of H&N malignancies include verrucous carcinoma, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinomas and chondrosarcomas.(85) Head and neck chondrosarcomas (HNCS) are the most common malignant mesenchymal tumors of the larynx, but they are rare occurrences, making up only 0.2% of H&N cancers and 1% of laryngeal cancers. They are defined as malignancies characterized by the formation of cartilage, but not of bone. Laryngeal chondrosarcomas typically affect the cricoid and thyroid cartilages, and are very rarely occur in the epiglottis.(60) They are more common in males and present at a mean age of 60 to 64 years.(60,86)

1.4.4. Clinical manifestation

Larynx

Cancers of the larynx are divided horizontally by the vocal folds into glottic, supraglottic and subglottic lesions. Glottic lesions are the most common and account for about 59% of laryngeal cancers, supraglottic lesions account for about 40% and subglottic lesions are rare, making up about 1%.(80,87,88)

The spread and pattern of growth of laryngeal tumors are influenced by the membranes and ligaments within the larynx. This confines the tumor to anatomic compartments and enables adequate margins when performing partial laryngectomies in early cancers. The quadrangular membrane and the conus elasticus have been described as the superior and inferior barriers of periventricular extension, respectively.(87)

Glottic cancers typically develop from the vocal folds and often show infiltrative growth patterns resulting in ulcerations and destruction of the surrounding laryngeal structures.(80,87,88) The majority of glottic lesions are located in the anterior two thirds of the vocal folds.(87) Glottic tumors typically show unilateral metastasis, and regional spread is less common than with supraglottic

cancers.(87,88) In continuation of the preglottic space, the paraglottic space lies between the vocal folds and the thyroid cartilage. This enables transglottic spread, a submucosal spread of tumor from the glottis to the supraglottis and/or the subglottis.(15) Supraglottic cancers arise from the vestibular folds, the epiglottis, the arytenoid cartilages and the aryepiglottic folds and often spread locally. They typically become symptomatic at a larger size than glottic tumors, and are associated with LN metastases upon initial presentation in 50% of the cases.(80,88) The preepiglottic space lies anteriorly to the supraglottis. Due to its rich lymphatic network it contributes to the typical early and bilateral spread of supraglottic tumors to the LN of the upper, middle and lower jugular chain, which correlates to levels II-IV.(15) Subglottic cancers tend to be poorly differentiated and to infiltrate the cricoid at an early stage of the disease.(80,87) Initial development of subglottic lesions is rare, but tumors arising from the supraglottis or glottis may spread in a transglottic fashion to involve the subglottis. Subglottic cancers commonly metastasize to the middle or lower jugular and paratracheal LN groups, representing levels III, IV and level VI, respectively.(15)

Symptoms differ depending on the location, but dysphonia and hoarseness represent the most common symptoms regardless of tumor site. In glottic tumors, persistent hoarseness is the typical initial symptom. Later symptoms may include dysphonia, dysphagia, referred otalgia, dyspnea, neck mass, hemoptysis and stridor.(81,88) Airway obstruction and chronic sore throat are typical initial symptoms, as well as palpable metastatic LN in supraglottic cancers.(81,88) Patients affected by subglottic tumors may present with stridor or complaints of dyspnea and exertion.(81) The number of symptoms at presentation has been found to correlate with cancer stage.(88)

Hypopharynx

The hypopharynx extends superiorly to the hyoid bone where it continues into the oropharynx, and is limited inferiorly by the cricopharyngeus muscle, continuing into the cervical esophagus. The pyriform sinuses, the postcricoid region and the pharyngeal wall are the major subsides of the hypopharynx. Hallmarks of hypopharyngeal cancers include skip areas of spread and submucosal spread.(15) Patients often present at advanced stages, as hypopharyngeal tumors remain asymptomatic for a longer period and the time between occurrence of initial

symptoms and diagnosis is typically longer than for other HNC.(89) Due to their location, they can impact swallowing and phonation adversely.(15) One of the most common symptoms is chronic sore throat, typically on one side, well localized and with possible referred otalgia. Other symptoms include odynophagia and varying degrees of dysphagia. A unilateral neck mass can be the initial symptom, as spread to the upper, middle and lower jugular LN, which represent levels II-IV, as well as the retropharyngeal LN is typical.(15,89) Even in early tumors, incidence of clinically positive LN upon initial examination is high. In very advanced tumors, hoarseness induced by direct extension of the tumor into the larynx or by RLN involvement as well as dyspnea may occur. As hypopharyngeal tumors are often advanced at presentation, many patients suffer from malnutrition and weight loss at the time of diagnosis.(81)

1.4.5. Staging

Cancer staging plays a pivotal role in the battle against cancers. The extent of cancer at the time of diagnosis defines prognosis and is essential in deciding upon an appropriate treatment based on the outcomes and experiences of previous patients with similar stage.(27) It is therefore an important component of patient care across the world, and a key factor in the successful management of HNC patients.(15,73)

The tumor, node, metastasis (TNM) staging system allows for the categorization of HNC to enable the assessment of disease status, prognosis, and therapeutic management. The staging systems are clinical stagings and are based on the best possible estimate of tumor extent before primary treatment.(15) All available clinical information is used to stage tumors, including the physical exam, medical imaging, intraoperative and pathologic findings and histopathologic analysis. T characterizes tumor extent at the primary site, N specifies the degree of regional LN involvement; and M indicates the absence or presence of distant metastases.(15,27)

The T classification are generally similar for H&N regions, but differences in specific details for each site allow for anatomic considerations.(27) Accordingly, each subdivision of the larynx is staged using individual T criteria, as presented in Table 3.(87,88)

Table 3: TNM Staging for the Larynx and Hypopharynx. Table from AJCC Cancer Staging Manual, 7th Edition(27)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
(T) Supraglottis	
T1	Tumor limited to one subsite of the supraglottis with normal vocal fold mobility
T2	Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to the larynx with vocal fold fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease Tumor 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 esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
(T) Glottis	
T1	Tumor limited to the vocal fold(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal fold
T1b	Tumor involves both vocal folds
T2	Tumor extends to the supraglottis and/or subglottis, and/or with impaired vocal fold mobility
T3	Tumor limited to the larynx with vocal fold fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4	Moderately advanced local disease Tumor invades the outer cortex of 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 esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
(T) Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to the vocal cord(s) with normal or impaired mobility.
T3	Tumor limited to the larynx with vocal fold fixation.
T4a	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
(T) Hypopharynx	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of the hypopharynx and is 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of the hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of the hemilarynx or extension to the esophagus
T3	Tumor more than 4 cm in greatest dimension or with fixation of the hemilarynx or extension to the esophagus
T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue (Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat)
T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodes metastasis
N1*	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2*	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none greater than 6 cm in greatest dimension
N2a*	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b*	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c*	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3*	Metastasis in a lymph node more than 6 cm in greatest dimension.
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

A numerical status of Stage I, II, III or IV is then achieved by tabulating the TNM status of each patient. For each stage, possible specific subdivisions may be denoted with an a, b, or c status (Table 4). (15)

In general, Stage I or II disease is denoted as early-stage disease, while Stage III or IV disease is denoted as advanced-stage disease. Any positive LN metastases, which correlate to N1 or N2 status, will classify as advanced disease. T4a disease is staged as IVa. T4b disease correlates as Stage IVb, and the presence of any distant metastasis constitute Stage IVc. T4a disease indicates advanced disease that is still considered resectable. T4b disease indicates very advanced disease with findings that determine it to be unresectable, such as prevertebral fascia or skull base involvement or carotid artery encasement.(15,27)

Table 4: AJCC Staging of HNC. Table from AJCC Cancer Staging Manual, 7th edition(27)

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

1.4.6. Treatment options

The treatment goal for laryngeal cancers is using available treatment options to achieve a cure while preserving functionality. For T1 and T2 larynx cancers, organ-preserving treatment such as radiotherapy (RT) and transoral endoscopic excision is recommended as the initial treatment approach.(88,90) While both options yield good locoregional control, proponents of each modality often disagree on the functional sequelae of each option.(91) Appropriate treatment protocols should be decided using a multidisciplinary approach.(88)

Definitive treatment for advanced stage cancer of the larynx consists of either TL or organ preserving RCT. The objective of organ preserving therapy in cases of advanced laryngeal cancer is to offer improved function and quality of life (QOL) without compromising survival.(92) With the publication of the Department of Veteran Affairs (VA) Laryngeal Cancer Study(93) and the Radiation Therapy Oncology Group (RTOG) 91-11 study(94), a major shift in treatment for patients occurred, as it was indicated that organ preservation could be achieved in locally advanced disease when using concurrent radiochemotherapy (RCT) without compromising survival. This led to a fall in primary TL and a corresponding rise in nonoperative larynx-preservation (LP) treatments.(87,92,95) RTOG protocol 91-11 showed that concurrent RCT achieved higher rates of organ preservation than RT alone or induction CT followed by definitive RT. Primary RCT can achieve high rates of organ preservation and no decline in survival compared with RT alone or TL even in advanced laryngeal cancer.(87,95) Primary RT is reserved for patients with substantial comorbidity who are unsuitable for the safe administration of RCT or TL.(92) Concurrent RCT is regarded as the gold standard of care for patients with T3 cancer who prefer LP.(92) Guideline recommendations specify TL as the initial treatment of choice for T4a larynx cancer, as T4 patients showed lower rates of successful LP and higher complication rates.(92,96) Concerns have been raised that LP is being offered too broadly to patients, as a decline in survival and concurrent rise of LP and the decrease of TL has been demonstrated.(95,96) Furthermore, an improved overall survival rate was reported for patients with stage IV disease treated with TL compared with LP.(95,97) The selection of treatment is complex and multifactorial. In addition to institutional factors including support systems and surgical expertise, it is also influenced by individual factors such as

functional performance status and personal preference of the patient. The choice of treatment regimen also depends on the overall health of the patient. Comorbidity can be classified by specific measures of additional medical illnesses. General performance measures are helpful in predicting survival.(27) To assess this, the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale is used, as it is a standard functional classification in oncology practice. Each patient is allocated a score on a linear scale between 0 (fully active) and 5 (dead) according to their physical activity. (98,99)

1.4.6.1. Radiotherapy

Radiotherapy (RT) alone and in combination with LP surgery is accepted as an effective treatment for T1 tumors and also, to a lesser degree, for T2 tumors. Radiation doses typically range from 60 to 70 Gy. Accelerated regimens using higher daily fractions and shorter treatment durations have been associated with improved outcomes in local control.(88)

Complications from RT can be divided into early and late subgroups. Early complications include mucositis, edema, hoarseness and dysphagia. Fibrosis, stenosis, xerostomia and hypothyroidism are late complications. Incidence of xerostomia and dysphagia has been shown to be reduced using intensity-modulated radiation therapy (IMRT).(88)

In a 2014 study by O'Neill et al. comparing treatment-related complications, RCT patients suffered from mucositis, xerostomia and dysphagia significantly more often than TL patients.(92) There was no significant difference in the rates of patients who experienced esophageal stricture requiring dilation, esophagitis, pneumonia, sepsis or thrombosis between the groups. While the number of patients requiring hospital or ER admissions did not differ significantly, RCT patients required feeding tubes more often and for longer periods of time than TL patients. Some patients undergoing RCT experience acute, often severe treatment-related toxicities, which can lead to interruption or modification of RT delivery. This compromises RCT especially among older patients, patients with coexisting medical conditions or lower PS.(92)

Ideally, adjuvant RT should begin within 4–6 weeks after primary surgery and neck dissection, unless wound healing is delayed by postoperative complications. A delay in administering adjuvant therapy has been shown to significantly decrease

ther rate of locoregional control.(15) Concurrent RCT increases local tumor control, but it does so at the expense of high toxicity. Several clinical and pretreatment factors were associated with the development of severe late toxicity. In a study by Machtay et al., 46% of evaluable patients showed symptoms of severe late toxicity. Development of severe late toxicity correlated most significantly with older age and also with radiation dose received to the inferior hypopharynx.(100)

1.4.6.2. Chemotherapy

Chemotherapy (CT) has been evaluated as a monotherapy, which is not the standard of care, and in combination with either surgery or RT.(88) In concurrent RCT regimens, CT is given on days 1, 22 and 43 of RT.(15) Concurrent RCT has been shown to significantly ameliorate local control and LP in advanced cancers. It has also been shown to significantly increase organ preservation in T1 and T2 cancers.(101) Concomitant RCT used in the postoperative setting should be instituted within six weeks of the primary surgery. It has been shown to yield improved disease control, overall survival in patients with positive margins, positive LN and/or extracapsular spread in cervical LN.(15) Neoadjuvant CT before TL or induction CT before definite RT are used to decrease tumor volume.(102) TL is performed after two cycles of ICT when restaging shows a partial remission of less than 50% of tumor volume.

Typical agents used for CH are cisplatin, carboplatin and 5-fluorouracil. Recurrent and/or metastatic HNC are incurable, but palliative CT can result in delaying cancer progression and modestly improve survival.(87)

Epidermal growth factor receptor (EGFR) overexpression is associated with more advanced tumor and nodal stage, and worse rates of locoregional control and overall survival. Multiple compounds are the subjects of ongoing research evaluating their effect on tumor progression. The most widely studied in the treatment of HNC is the monoclonal antibody cetuximab, which inhibits EGFR.(15)

1.4.6.3. Larynx Preservation Surgery

Options for LP surgery are mostly used in T1 and T2 stage laryngeal cancers and include transoral endoscopic resection and open procedures. Transoral laser

microsurgery (TLM) has similar outcomes to other larynx-preserving modalities in T1 and T2 glottic tumors.(88) Open procedures include laryngofissure with cordectomy, vertical hemilaryngectomy, supraglottic laryngectomy and supracricoid laryngectomy. In a supracricoid laryngectomy, both the true and false vocal folds are resected, as well as the thyroid cartilage, one partial or full arytenoid and both paraglottic spaces.(87,88)

In a supraglottic laryngectomy the resection occurs between the preepiglottic space and the ventricles, which allows for preservation of the true vocal folds, the arytenoids and the hyoid.(88) Supraglottic laryngectomy is also available for T3 and T4 supraglottic cancers and has shown a local control rate of 70-85%, but poor predictability for recurrence. Elective bilateral neck dissection should be considered in T3N0 settings to spare the patient postoperative RT. Supraglottic laryngectomy is not recommended in patients whose pulmonary function is too low to tolerate aspiration, or in patients who previously underwent RT due to associated wound healing complications.(87)

1.4.7. Total Laryngectomy

For many patients with advanced tumors who are not suitable for organ preservation treatment options, TL remains the standard of care, possibly combined with partial pharyngectomy and cervical esophagectomy.(87,89) Primary total laryngectomy is typically performed in T4a tumors, and smaller tumors in which the functional outcome of primary RCT is expected to be poor.(89) TL can also become necessary for patients with intractable dysphagia and aspiration as an ultima ratio treatment approach.(103)

TL describes a complete resection of the larynx, including all laryngeal cartilages, the intrinsic muscles, hyoid bone as well as the upper tracheal rings. TL results in a complete separation of the pharynx and the respiratory tract. Subsequently, the trachea is brought out through the front of the neck and a permanent tracheostoma is created, through which patients breathe.(104)

The skin incision used for traditional TL is a U-shaped or "apron" incision in the anterior neck. The incision starts at the apex of the mastoid and continues on the anterior border of the SCM muscle, and runs symmetrically to the mastoid on the other side.(5,87) It can encompass a planned stoma located just above the sternal notch in line with the incision, or a separately created tracheostoma below the

incision line.(105) Through this single skin incision the visceral compartment of the neck as well as LN can be accessed for neck dissection (ND) on both sides. A flap consisting of skin, subcutaneous tissue and platysma, is dissected up to the hyoid bone. The blood vessels and nerves supplying the larynx are then separated from the trachea and hyoid bone, allowing for separation of the visceral compartment of the neck.(87) The anterior jugular vein is ligated and the dissection plane between carotid, larynx and thyroid is entered. Infrahyoid muscles are sectioned at the hyoid and mobilized. After the thyroid isthmus is divided, the thyroid lobes are dissected off the trachea and cricoid, and the RLN, superior laryngeal artery and vein and SLN are divided and ligated.(106) After the disinsertion of prelaryngeal cervical muscles from the surface of the thyroid cartilage, the pharyngeal constrictor muscles are cut from the posterior edge of the cartilage. The inferior thyroid artery is identified and ligated at the level of the cricoid cartilage. The suprahyoid muscles are dissected from the hyoid bone. The hyoid bone will be dissected along its superior margin. Depending on the superior limit of the tumor, the aerodigestive tract is typically incised at the vallecula, which allows anterior retraction of the larynx to provide tumor visualization and enables mucosal cuts around the lesion with adequate margins.(87) The incision line follows the aryepiglottic fold along the superior border of the cricoid cartilage on both sides. The trachea is entered using a horizontal incision below the inferior limit of the tumor, and a tracheostoma is created.(5,87,106) A study by Feng et al. suggests that a mid-neck apron incision and tracheostoma separated from the neck incision decrease stress on the incision lines, and consequently reduce risk of peristomal wound dehiscence.(105) When the posterior wall of the larynx and the anterior wall of the oesophagus are dissected, en bloc resection of the larynx, tracheal rings, pharyngeal mucosa and sometimes the hyoid bone can be performed. The delivery of the specimen is achieved using mucosal cuts along the postcricoid region.(87)

Retrograde laryngectomy can also be performed. The hyoid bone and thyroid cartilage are dissected and mobilized, and an incision into the trachea is made. After transecting the posterior tracheal wall, lifting the larynx and superjacent tracheal rings allows for dissection between the tracheal and the esophageal wall. A transverse incision of the pharyngeal mucosa below the upper border of the cricoid lamina allows entrance into and dissection of the hypopharynx and pyriform

sinuses. Upward traction on the epiglottis allows for inspection of the pharynx to ensure sufficient tumor resection. The base of the tongue is cut and sutured and en bloc resection of the larynx, trachea and pharyngeal mucosa occurs.(5,106) Figure 4 shows the operating field after resection of the larynx.

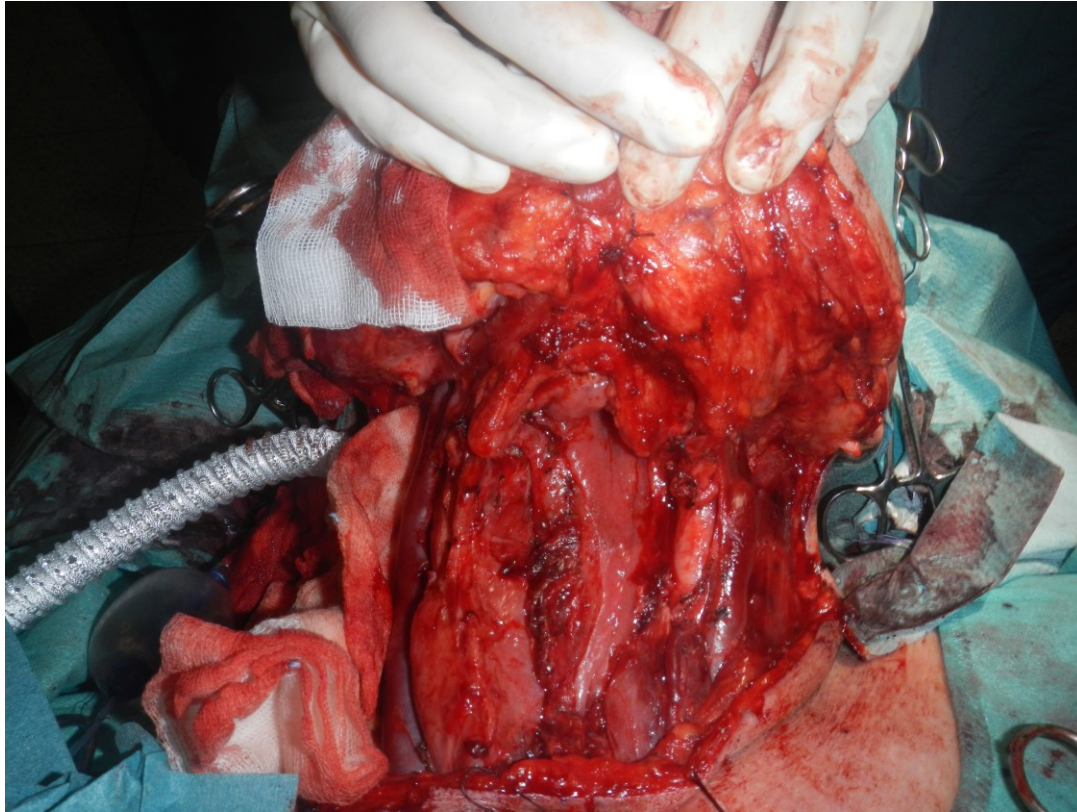


Figure 4: Operating field of a TL after en bloc resection of the larynx, trachea and pharyngeal mucosa. Photo used with permission from the Department of Otorhinolaryngology, University Hospital Graz.

A pharyngoesophageal myotomy is typically performed to prevent hypertonicity and optimize speech and swallowing. A tracheoesophageal voice prosthesis can be placed by creating a fistula about 5-10mm below the upper margin of the tracheostoma. Then, pharyngeal mucosal sutures are placed with care as tension sutures can lead to stenosis, and too loose sutures can lead to pharyngocutaneous fistula. A nasogastric feeding tube should be inserted and stitched to the nasal septum to allow feeding until oral nourishment can be resumed.(5,106)

Concurrent neck dissection is performed in case of clinically positive LN or high possibility of nodal metastasis in laryngeal cancers. Selective ND of levels II-IV is likely adequate in advanced disease for clinically N0 necks, while modified or

radical ND is performed in clinically positive necks.(5,87) As hypopharyngeal tumors have a high risk for LN metastases, even in clinically N0 necks selective ND is appropriate. In most cases, levels II-IV should be resected. Level VI LN should be included for tumors that show esophageal extension or invasion of the apex of the pyriform sinus.(89)

Hypopharyngeal cancers can be resected by TL with partial pharyngectomy. The pharyngeal defect can usually be closed by primary closure, but as the submucosal spread of hypopharyngeal cancers requires wide margins, a pedicle flap or free-tissue transfer can become necessary. This can also be required in salvage total laryngectomy (STL) after failure to achieve disease control using RCT. Single stage closure can then be achieved by using a pectoralis major or a radial forearm myocutaneous flap.(89)

TL is one of the most feared surgical procedures by patients, as swallow function and speech as well as body image are significantly influenced by the procedure. QOL is profoundly and adversely affected if treatment is associated with dysfunction and disfigurement, making body image reintegration postsurgically critical to ensure subsequent QOL.(87) TL safely prevents aspiration, but also significantly alters swallow function. Resection of the larynx leads to weaker bolus propulsion and higher resistance to bolus clearance. The pharyngeal phase of swallowing is prolonged. Postsurgically, swallowing soft foods poses less problems, but patients may progress to a general diet.(104)

As the treatment of cancers of the larynx has moved away from primary TL towards organ preserving modalities, the use of initial RCT has become more popular in recent years. In case of subsequent disease recurrence, STL can become necessary.(107,108) STL constitutes a final curative treatment strategy, but can be technically complex and can significantly impact patient morbidity.(92)

1.4.8. Neck dissection

Radical neck dissection (RND) refers to the resection of all ipsilateral cervical LN groups from Levels I through V. The spinal accessory nerve, internal jugular vein, and SCM muscle are also removed. Modified radical neck dissection (MRND) describes RND where one or more non-lymphatic structures are spared from resection. Selective neck dissection (SND) refers to a cervical lymphadenectomy in which one or more of the LN groups that are routinely removed in RND are

preserved. The LN groups resected are based on the patterns of metastasis that are predictable according to the primary site of tumor (Table 5).(15,26,91)

Table 5: Recommended neck levels to be dissected based on primary site. Table from Paleri et al.(26)

Supraglottis	IIa–III; IIb and IV can be spared. Contralateral SND not indicated for lateralised tumors
Glottis	IIa-III, IIb can be spared. Include IV for T3 and T4 primaries
Subglottis	II-IV, VI
Hypopharynx	II-IV

In a clinically N0 neck the choice for elective treatment lies between MRND and SND. SND seems to be as effective as MRND for most primary sites with decreased morbidity. In laryngeal and hypopharyngeal tumors, the procedure of choice is SND of levels II–IV.(26) This refers to the resection of the upper, middle and the lower jugular LN.(91) Incidence of metastasis is less than two percent at level IIb LN. Therefore, level IIb resection may be excluded for the majority of patients, and the designated procedure would be SND of levels IIa, III, IV.(26,91) Patients with central tumors or tumors involving both sides of the larynx require bilateral ND.(109) This is especially true for supra- and subglottic tumors.(91) Tumors of only one side of the larynx are more likely to show lymphatic spread to the ipsilateral LN, but occult metastatic spread may be found on contralateral LN. This suggests that elective bilateral ND should always be performed, even if this increases the number of unnecessary ND.(109)

Elective neck irradiation has been shown to be as effective as elective ND in controlling subclinical regional disease.(26) Elective ND during salvage laryngectomy is beneficial in patients with advanced local disease at recurrence for both disease-free and overall survival.(110)

1.4.9. Complications of total laryngectomy

The overall mortality rate for TL was 0.5% in a 2005 study by Ganly et al.(111), and 40% of all patients developed postoperative complications after TL. Local complications occurred most frequently, in 28% of all patients.

TL in the era of the principle of organ preservation has increasingly taken the role of salvage surgery. Primary RCT has been shown to be an independent predictor of both local wound complication and PCF. STL following RCT was more frequently associated with any postoperative complication than PTL due to wound

healing difficulties.(92,111) The complication rates following STL are not consistently reported in the literature. The most common complication of STL is development of a pharyngocutaneous fistula (PCF), which was found to occur in 28.9% of all patients who undergo STL in a review by Hasan et al.(112) The overall complication rate was 67.5%, but complications such as wound infection, dehiscence and bleeding are likely under-reported.(112) Ganly et al.(111) found that in the group of STL after RCT, a greater number of patients developed local wound and fistula complications compared to the PTL group. In STL patients, the most common postoperative complications were local wound healing problems and the development of PCF.(111)

1.4.9.1. Early Postoperative Complications

The most common early postoperative complications include wound infection, pharyngeal stenosis, bleeding and dysphagia. Overall complication rate was 67.5% according to the review of Hasan et al.(112)

1.4.9.2. Pharyngocutaneous Fistula

Development of a pharyngocutaneous fistula (PCF) is a common complication in the early postoperative period after TL. Many predisposing factors to fistula formation have been identified, including preoperative RT, surgical technique, concurrent ND, tumor stage, preoperative tracheostomy, early oral feeding, presence of systemic diseases, and nutritional status.(113)

Pooled incidence of PCF was 28.9% in the meta-analysis of 50 studies by Hasan et al.(112), and rates varied in individual series between 5.6-73%. In the study by Ganly et al.(111), PCF occurred in 17% patients. Multivariate analysis showed that primary RT and RCT were independent predictors of PCF, with no significant difference in PCF incidence between patients who received RCT compared to RT only.(111,112) There seems to be no association of ND and elevated incidence of PCF.(112) Fung et al.(114) showed that free vascularized tissue reinforcement of primary pharyngeal closure in STL could help prevent major wound complications by but did not reduce the overall rate of PCF development.

1.4.9.3. Pharyngeal stenosis

A typical late complication following TL is stenosis of the neopharynx due to scar tissue, resulting in difficulty clearing food and liquid to the esophagus. Nasal regurgitation of liquids can occur in severe cases.(104) Pharyngeal stenosis was reported in 14.3% of patients in the study by Hasan et al.(112) Stricture formation was typically located around the pharyngeal anastomosis or the thoracic esophagus. Flap reconstruction shows an increased risk of stenosis compared to primary pharyngeal closure.(112) Relief can be provided by serial dilatation, which can be required to be performed periodically for the rest of the affected patients' lives. Pharyngoesophageal myotomy is another option to prevent stenosis.(104)

1.4.10. Voice rehabilitation

Achieving alaryngeal voice is the most challenging of post-TL rehabilitations, as the ability to speak and communicate vocally is a unique human characteristic that is fundamental to many aspects of daily life.(104,115) Nowadays, three options to achieve voice restoration are in common use: esophageal speech (ES), tracheo-esophageal speech (TES) using a voice prosthesis and use of an electrolarynx (ELS). All three methods have potential benefits, but TES is usually described as the gold standard.(115) Articulation is only affected if the surgery involves base of tongue resection, which can lead to reduced tongue range of motion, resulting in distorted articulation.(104) Both adjuvant RT and definite RT which then requires STL have a significantly negative effect on phonatory and swallowing outcome. This should be taken into consideration for patients with advanced laryngeal cancer when deciding upon laryngectomy or organ preservation treatments.(116) To achieve ES speech, vibration of the pharyngoesophageal segment is used to create sound, which travels through the pharynx and oral cavity and can be articulated into speech. Patients must learn to swallow air and to use a process called glossopress, in which the tongue is used as a pumping mechanism. This can make this method of voice rehabilitation difficult to learn. The ES voice sounds natural, but is often lower in pitch.(87,104)

The introduction of TES in 1979 made it possible for many patients to rapidly recover high quality speech. This facilitates quick rehabilitation of TL patients as it allows them to return to normal activities of life and work and subsequently to

maintain satisfactory QOL.(87,117) Shunting air from the lungs, TES also utilizes vibration of the pharyngoesophageal segment to create a voice. A surgeon performs a tracheoesophageal puncture (TEP) and a voice prosthesis (VP) is implanted. This can happen primarily or secondarily to TL.(115) The VP is a one-way valve, which lets air travel anterior-posteriorly, but stops food or liquid to travel posterior-anteriorly. The VP does require periodic replacement and leakage around the prosthesis is possible. To achieve efficient stoma occlusion and exhalation strategies, speech therapy is usually required following placement of the VP.(104) TES has been shown to confer significant benefit in terms of self-reported voice outcome in a study by Robertson et al.(116)

The electrolarynx is a device that is held against the neck or cheek. Sound is created by a piston rapidly striking a fixed diaphragm, which travels through the pharynx and oral cavity and is articulated into speech. Pitch and loudness can be adjusted. ELS is a very effective mode of communication, but it does require speech and language therapy. The voice created has a mechanical sound, which puts off some patients of using ELS.(104)

2. Purpose

Total laryngectomy (TL) is the operation in which the larynx is completely removed, which results in a total and permanent separation of respiratory and digestive tract and consequent loss of voice and sense of smell. For much of the 20th century, TL was widely regarded as the gold standard of treatment for advanced laryngeal and hypopharyngeal cancers. In the last years, organ preservation has become the principle of therapeutic approaches for advanced lesions that would previously have been treated with TL.(5,118) This was encouraged by the results of studies that found that larynx preserving treatment using concurrent radiotherapy and chemotherapy did not reduce survival in patients with even advanced cancer of the larynx and hypopharynx.(93,94) As there have only been few reports on the clinical outcome following TL, the purpose of the present study was to analyse complication, survival and recurrence rates after TL and to gain insight into postoperative voice rehabilitation.

3. Materials and methods

The study population consisted of patients who underwent total laryngectomy between 01.01.2002 and 15.01.2018 at the Department of Otorhinolaryngology, at the University Hospital Graz. The patients' clinical data and medical history were collected from medical files in the computerized database MEDOCS. Ethical approval was obtained from the Ethics committee at the University Hospital Graz. The Institute for Medical Informatics, Statistics and Documentation at the Medical University of Graz provided a table of patients who had received the medical service "total laryngectomy" at the Department of Otorhinolaryngology in the last 16 years. Of 106 patients who were identified, 103 could be included in the study.

The following parameters were assessed:

- Age
- Sex (female, male)
- Common comorbidities
- Date of diagnosis
- Location of tumor
- T-, N-, M-stage
- Pathological type
- Grade
- First-line therapeutic approach
- Positive LN metastasis
- Surgical technique
- Median postoperative stay
- Occurrence of early and late complications
- Recurrence
- Overall survival (OS)
- Disease-free survival (DFS)
- Methods of alaryngeal voice rehabilitation

Date of laryngeal biopsy was considered as the time of diagnosis. The location of the tumor was classified according to the patient's pathology report into three main categories, laryngeal, hypopharyngeal and other location (including oral, cervical esophagus and tracheal). Subcategories for laryngeal cancer were defined as

supraglottic, glottic, subglottic, and transglottic (tumor extending beyond the larynx). The TNM stage system was applied to determine the stage of cancer using the AJCC Cancer Staging Manual, 7th edition.(27) The first-line therapeutic approaches were divided into four categories: TL alone, TL plus adjuvant RT/RCT, neoadjuvant RCT plus TL and STL. Surgical treatment included TL with or without neck dissection. Removal of the hyoid bone and methods of closure (primary closure, closure using a flap) were assessed. Recurrent disease was classified into four categories, namely local recurrence, regional lymphatic recurrence, distant recurrence and second primary tumors. Disease free survival was calculated from the date of diagnosis to the date of recurrence. Overall survival was calculated from the date of diagnosis to the date of death. For patients who were still alive at the cut-off date, survival time was defined as the duration from the date of diagnosis until January 2018. Effectiveness of speech and quality of life were not evaluated

The required variables were collected using the medical databank "MEDOCS". They were then processed in a tabular manner using Microsoft Excel.

Recurrence and survival data were calculated using the Kaplan–Meier method, and compared using the log–rank test. The significance level in this study was $p < 0.05$. The data was analyzed using Microsoft Excel and SPSS software.

4. Results

4.1. Patient characteristics

A total of 103 patients were included in the study. Of these, 101 patients presented with laryngeal or hypopharyngeal cancer. Two patients were operated on due to chronic aspiration as an ultima ratio treatment.

Of the 101 cancer patients, 13 (13%) were women and 88 (87%) were men. The median age at diagnosis was 63 years (range 44-79 years). 91 patients (90%) used to or were smoking cigarettes at time of diagnosis, while 10 patients (10%) did not report any tobacco consumption. A mean of 34 packyears (range 8-156 packyears) was found among the 68 patients who reported packyears. While alcohol consumption was not assessable in 12 cases (12%), 25 patients (25%) had no alcohol abuse in their history, 23 (23%) were abusing alcohol at time of

diagnosis and 7 (7%) reported having had problems with abuse in the past. 37 (37%) reported occasional alcohol consumption. ECOG scale was assessable in 67 patients, 36 (54%) of who had a score of 0 and 28 (42%) a score of 1.

The most common comorbidities were chronic pulmonary disease in 25 (25%) and liver disease in 15 (15%) patients. Diabetes was present in 12 (11%) patients and chronic kidney disease in 7 (7%). Peripheral vascular disease and congestive heart failure affected 9 (9%) patients, respectively, while 8 (8%) had cerebrovascular disease. 5 (5%) had suffered from a myocardial infarction.

Of the 101 patients, 72 (71%) presented with laryngeal cancer, 22 (22%) with hypopharyngeal cancer, 3 (3%) had cancers that affected both the larynx and hypopharynx and 4 (4%) had tumors of the oropharynx, trachea or proximal esophagus.

18 of laryngeal tumors (25%) were located in the glottis, 29 (40%) in the supraglottis, 3 (4%) in the subglottis and 15 (15%) showed transglottic spread at time of diagnosis. Figure 5 illustrates the distribution of tumor locations.

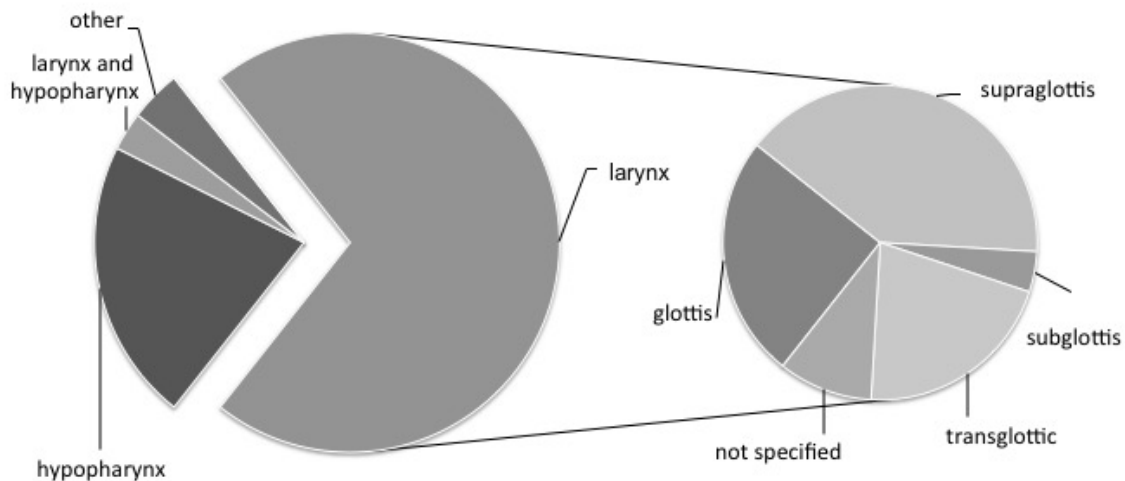


Fig. 5: Location of primary tumors

All but one of the tumors were found to be SCC, the one being a chondrosarcoma of the larynx. Grading was based on biopsies to confirm diagnosis or on the surgery specimen. 3 (3%) SCC were found to be grade 1, 56 (56%) were found to be grade 2 and 42 (42%) grade 3.

The 7th edition AJCC staging system(27) was used to determine cancer stage according to TNM status. Of all 101 cancer patients, 1 (1%) presented at stage I, 9 (9%) at stage II, 26 (26%) at stage III and 49 (49%) at stage IVa. 2 (2%) were found to be at stage IVb, 4 (4%) at stage IVc, 6 (6%) were classified as Mx, 1 (1%) as Nx and 3 (3%) patients could not be classified. An overview of the characteristics of the study population is presented in Table 6.

Table 6: Characteristics of study participants. SCC= squamos cell carcinoma, DM= diabetes mellitus, CHF=congestive heart failure, OS=overall survival, DFS= disease-free survival

Age at diagnosis (year)	63 (44-79)		
Sex (n=101)			
Male	88		
Female	13		
Primary site			
Larynx	72		
Glottis	18	Supraglottis	29
Subglottis	3	Transglottic	15
Hypopharynx	22		
Other	7		
Risk Factors			
Smoker	91	Packyears	38 (8-156)
Non-smoker	10	Alcohol consumption	67
Stage			
II	9	IVb	2
III	26	IVc	4
IVa	49	Mx	6
Histology			
SCC	100	Chondrosarcoma	1
Comorbidities			
Pulmonary disease	25	DM	12
Myocardial infarct	5	CHF	9
Peripheral vascular disease	9	Cerebrovascular disease	8
Liver disease	15	Renal disease	7
ECOG scale			
0	36	1	28
2	1	3	2
Survival rates			
1-year OS (%)	83	1-year DFS (%)	82
3-year OS (%)	64	3-year DFS (%)	64

4.2. Treatment regimen

First-line treatment regimen included TL and adjuvant RT in 35 patients (35%). TL and adjuvant RCT was implemented in 29 patients (29%), while 21 patients (21%) underwent only TL. 3 patients (3%) were treated with neoadjuvant RCT. On 13 patients (13%), STL following primary RCT or induction CT and RT was

performed. Prior LP surgery had been performed on 14 patients (14%). The incidence of first-line therapeutic approaches is illustrated in Figure 6.

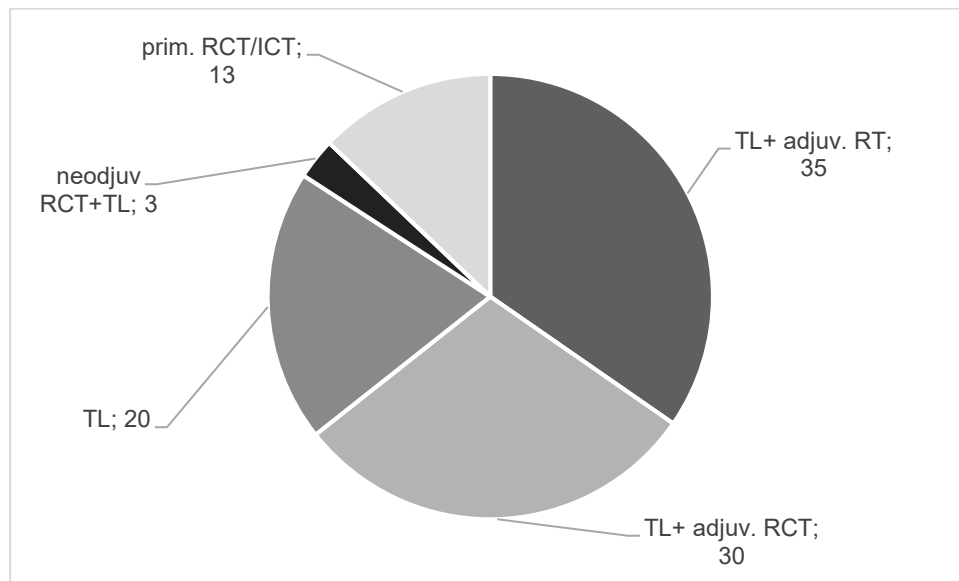


Figure 6: Primary treatment regimen of all 101 cancer patients. TL= total laryngectomy. RT= radiotherapy. RCT= radiochemotherapy. ICT= induction chemotherapy.

4.3. Surgical techniques

In 68 patients, surgical reports specified whether the hyoid bone had been removed during the procedure. Of these, removals of the hyoid bone were performed in 21 cases (31%), while it was left in situ in 47 cases (69%). In 6 cases (6%) of all 103 TL, surgical closure was performed using a flap - a pectoralis flap in 5 cases, and a radialis flap in 1 case. Neck dissection was performed in 88 of the 101 cancer patients (87%). In the majority of the cases, levels II to IV were resected. Upon pathohistological examination, 46 of these cases were shown to have positive LN metastasis. Median postoperative stay was 19 days (range 11-88 days). Implantation of a PEG-probe was necessary in 38 patients (37%), while a jejunal probe was implanted in 9 patients (9%). PEG-probe implantation was performed before surgery or before RT in 22 of these patients, due to dysphagia as a result of complications such as a PCF or stenosis in 10 patients and in a palliative setting in 2 patients.

4.4. Postoperative complications

24 patients (23%) experienced early postoperative complications, the most common being wound infection (12 patients), bleeding (9 patients), lymphatic

fistula (2 patients) and impaired wound healing (1 patient). Figure 7 shows the occurrence of early complications.

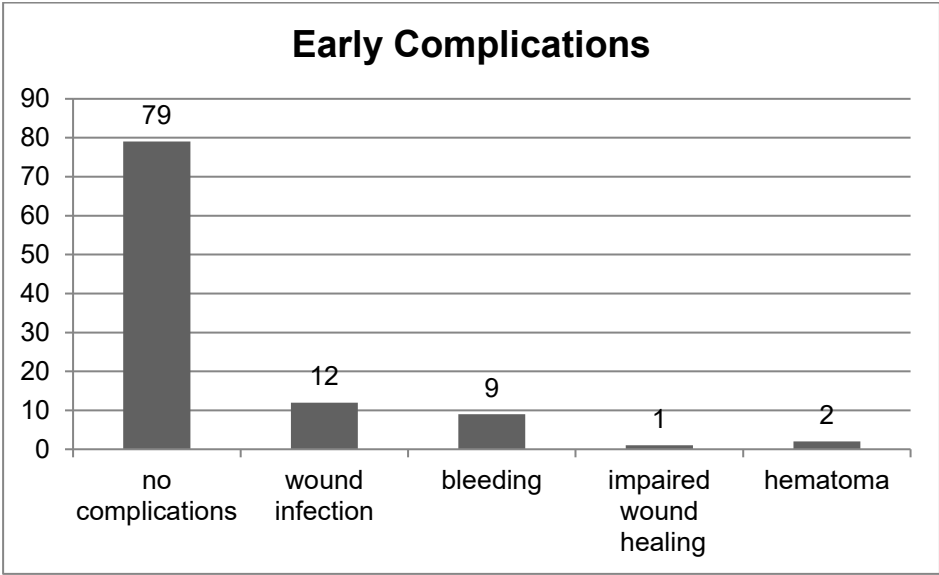


Figure 7: Prevalence of observed early complications

52 patients reported late postoperative complications. 29 (56%) of these 52 patients developed PCF, 9 of which required surgical intervention to achieve closure of the PCF. 25 patients (48%) developed stenosis, and 24 of these underwent surgical intervention, either bougienage dilatation or relaxation through botox injection. 2 patients were affected by both PCF and stenosis. Prevalence of late complications is presented in Figure 8.

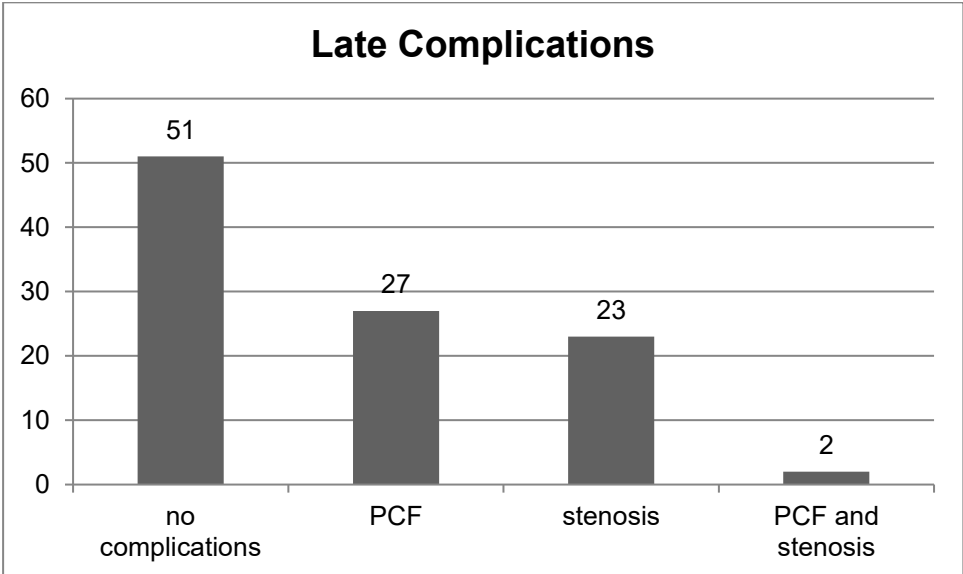


Figure 8: Prevalence of observed late complications. PCF= Pharyngocutaneous fistula

68 patients (66%) reported no problems with the tracheostoma, however in 11 cases (11%) it was not possible to find information about tracheostoma complications. Of the 24 patients (23%) who experienced problems, most commonly reported were inflammation of the tracheostoma (6 cases) and occurrence of metastasis (4 cases) as well as redness, tracheostomal stenosis and bleeding.

4.5. Survival rates

OS was at 83% after one year, and 64% after three years. The overall survival rate of patients after TL until the cut-off time is presented in Figure 9.

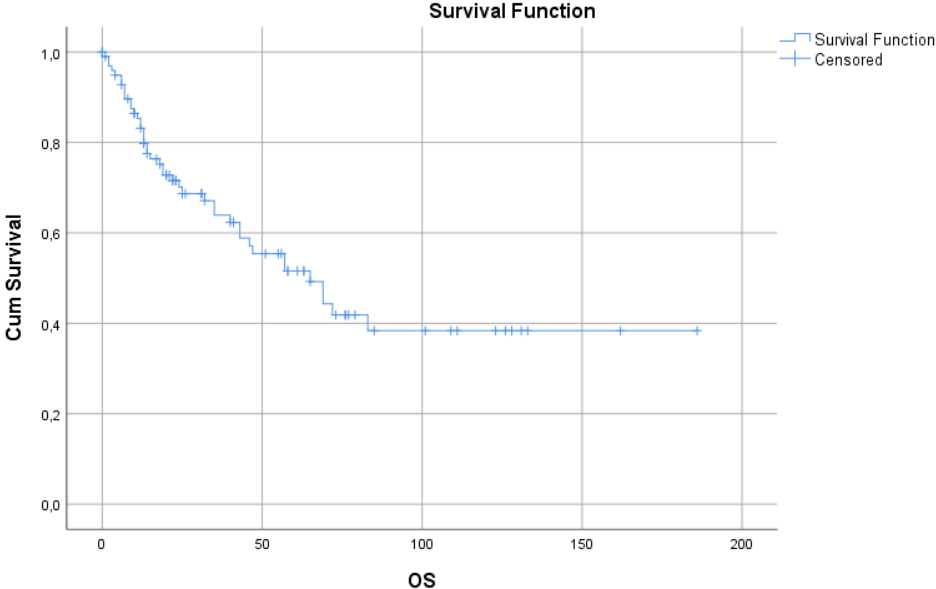


Figure 9: Overall-survival curve

Figure 10 compares the survival rates of the two most common first-line treatment regimen, TL and TL plus adjuvant RT or RCT.

The survival distributions for the different first-line treatment regimen were not statistically significant (p=0,835). There was also no statistically significant difference (p=0.367) between survival rates of early (stages I and II) and advanced (stages III and IV) cancer. DFS was 82% after one year and 64% after three years.

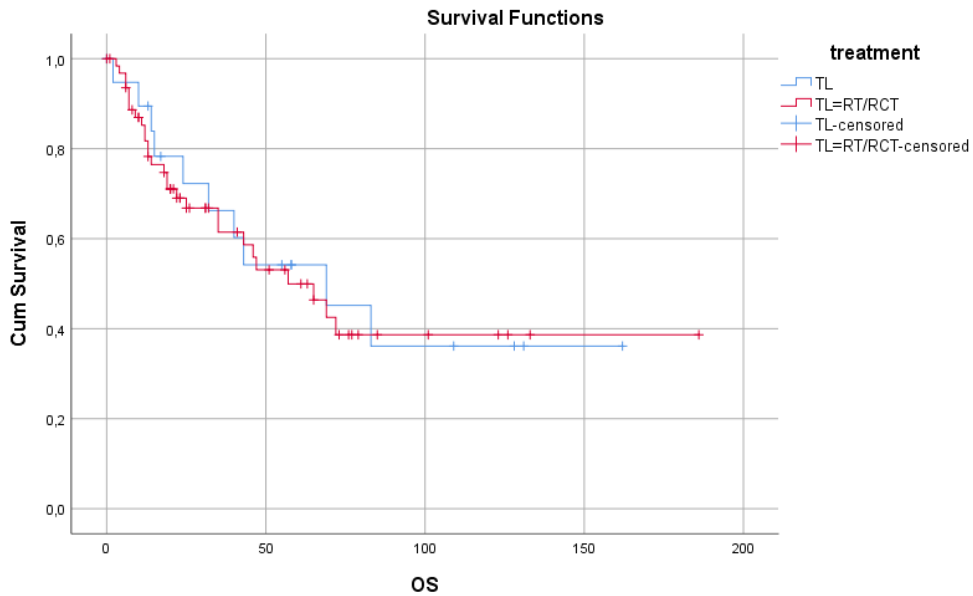


Figure 10: Comparison of overall survival rates of first-line therapeutic approach. ($p=0,835$). RT= radiotherapy, RCT= radiochemotherapy, OS= overall survival

4.6. Recurrence rates

30 patients showed tumor recurrence after TL, with a mean of 6 months between TL and diagnosis of recurrence (range 1-61 months).

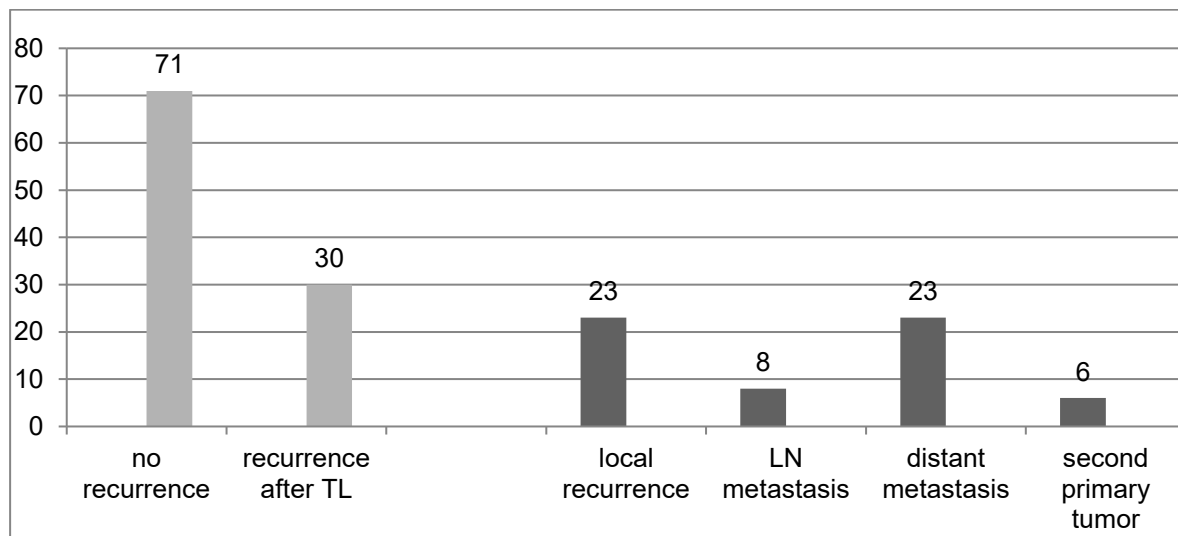


Figure 11: Number and distribution of tumor recurrence after TL. Note that 15 patients (50%) of the 30 showed tumor recurrence at more than one site

Of these 30, 15 patients (50%) showed recurrence at more than one location. 23 patients experienced local tumor recurrence. In 8 patients, LN metastasis was

found, while distant metastasis occurred in 23 patients. 6 patients presented with or developed a secondary tumor. 18 patients (18%) progressed into a palliative setting and were treated with immuno-polychemotherapy or RCT. Figure 11 shows the occurrence and distribution of recurrent disease.

4.7. Voice rehabilitation

Out of the 103 patients observed, 48 patients (47%) were implanted with a voice prosthesis (VP) at primary surgery or postoperatively, while 55 patients (53%) did not receive a VP. The mean time range between changes of a VP was 143 days among all patients (range 27 - 349 days). Not included in this calculation were durations of more than 365 days, as that hinted at faulty documentation of VP change.

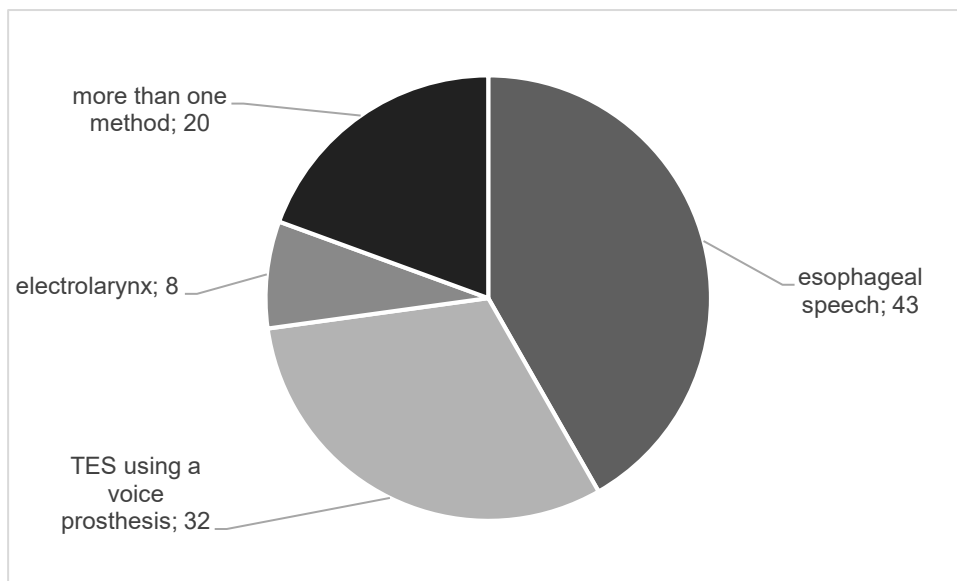


Figure 12: Prevalence of alaryngeal voice rehabilitation methods

The primary method to achieve voice rehabilitation was esophageal voice in 43 patients (42%), usage of VP in 32 patients (31%) and usage of an electrolarynx in 8 patients (8%), while 28 patients (27%) were using two or more of these methods. The prevalence of methods to achieve voice rehabilitation is presented in Figure 12.

5. Discussion

The aim of the study was to examine the clinical outcome of patients who were treated with TL. Of the 103 patients who fit the study criteria, 101 patients presented with laryngeal or hypopharyngeal cancer. Two patients were operated on due to chronic aspiration as an ultima ratio treatment.

The typical demographic of laryngeal and hypopharyngeal cancer patients are males over 65 who have a history of tobacco and or alcohol consumption.(43,45,58) This fact was represented in our study population of 101 patients with laryngeal or hypopharyngeal cancer. Median age at diagnosis was 63 years. 87% of the patients were males, and 13% were females. The discrepancy in incidence in men and women can be expected to shrink as women nowadays smoke and drink alcohol at the same rate as men, and as HPV as an etiologic factor is on the rise. We were not able to conclusively assess prevalence of HPV-positive cancers, as HPV status was not recorded in a large number of patients.

90% of patients reported tobacco consumption with a mean of 34 packyears, and 67% disclosed alcohol consumption, ranging from occasional consumption to abuse. Accordingly, the most common comorbidities were chronic pulmonary disease in 25% and liver disease in 15% of patients. Diabetes, chronic kidney disease and peripheral and cerebro-vascular disease were also common.

Laryngeal cancer was most common, affecting 71% of the patients. Hypopharyngeal cancer is a less common entity, and occurred in 22% of patients. When classifying the tumors according to the 7th Edition AJCC Cancer Staging Manual(27) and compartmentalizing stage I and II as early disease and stage III and IV as advanced disease, only 10% of patients presented with early disease. 81% presented with advanced disease tumors at diagnosis.

Neck dissection was performed in 87% of patients, and 52% of these were shown to have positive LN metastasis at histological examination.

Median postoperative stay was 19 days (range 11-88 days). Hall et al.(118) also reported a median of 19 days postoperative stay in their 2003 study.

Overall, the incidence of any postoperative complication was at 58%. Early postoperative complications occurred in 23% of all patients, most commonly

wound infection, bleeding and lymphatic fistula. 51% of all patients reported late postoperative complications. The 2017 systematic review of complications after STL by Hasan et al.(112) found overall complication rates of 67.5%. It is difficult to compare overall complication rates because many studies focus on a specific complication, such as occurrence of PCF or pharyngeal stenosis, and do not report incidence of overall complications.

Incidence of development of PCF was 26% of all patients, constituting 56% of late postoperative complications, 31% of which required surgical closure. Galli et al.(113) found a 16% rate of PCF development following TL in their study. The incidence of PCF was 17.7% in the study by Hall et al.(118) Sayles and Grant(119) found the incidence of PCF to be 14.3% after primary TL, 22.8% after previous RT and 34.1% after previous RCT in their 2014 review. We did not assess whether treatment methods influenced incidence of complications. Since multiple studies showed an association of PCF to previous RT or RCT, this would be an interesting aspect to examine in further studies. Incidence of pharyngeal stenosis was 22%, occurring in 48% of late complication cases. 96% of these had to undergo either bougienage dilatation or relaxation through Botox injection to regain oral feeding. Hasan et al.(112) found a 14.3% incidence of pharyngeal stenosis or stricture with a range of 2.3-43.9% in their review.

Comparing survival rates among different studies is complicated by different methods of recruitment, study design, and assessment of the patients in different studies. We found OS to be at 83% after one year, and 64% after three years. The cutoff time for the study was January 2018, which means time of observation differed massively between patients. There was no statistically significant difference between early and advanced stage disease, however only a small fraction of patients in our study population presented with early stage disease. Daneshi et al.(120) reported the 1-year, 3-year and 5-year year survival rates in patients with laryngeal carcinoma were 81%, 62% and 53%, respectively. Hall et al.(118) described a 67% 5-year survival for patients with laryngeal cancer and a significantly worse 37% 5-year survival for hypopharyngeal cancer. They also found a correlation of survival with clinical and pathological stage of laryngeal cancer, while prognosis for hypopharyngeal cancer was poor irrespective of stage. A study by Ho et al.(121) found that stage influenced outcome, reporting a decline in survival from 74% to 14% for stages I to IV. Wolf et al.(93) reported a 2-year

survival rate of 68% among patients with advanced cancers of the larynx who were treated with surgery and RT. Foote et al.(122) reported a 5-year survival rate of 74% among patients with T3 laryngeal cancer treated by surgery only.

Laryngeal and hypopharyngeal cancer constitute a diverse disease, and preferred therapeutic management is influenced by anatomic subsite, stage of disease, and patient preference. Organ preserving treatments have been persistently popular for T1 to T3 disease following the publication of RTOG 91-11(94) and the VA Laryngeal Cancer(93) studies, but TL is still regarded as standard of care for individuals with more locally advanced disease. Recent analyses of care patterns show a trend of LP protocols for patients with T4 disease.(95–97) Many studies were conducted on the impact of treatment methods on patients' survival, but did not reach conclusive results, possibly due to differences in study design and population. Timmermans et al.(123) and Karlsson et al.(124) found no significant difference in survival between surgical and organ-preserving treatment modalities. However, Hoffman et al. showed that the survival rate of patients with advanced laryngeal cancer declined between 1985 to 1996, following the increase in nonsurgical definite treatment.(96) Carvalho et al. also found a declining 5-year survival rate. Although the causal factors for this decline were not specified, evidence suggests that the decline of TL and a consequent increase in organ preserving treatments occurred during the same time period.(125) A study by Megwalu and Sikora(126) showed that patients who received surgical treatment had significantly better survival compared to non-surgically treated patients, regardless of gender or stage. Chen and Halpern(97) reported higher survival rates in patients with stage IV laryngeal cancer that had been treated with TL compared to other methods of treatment. The study by Grover et al.(95) showed a significant association of TL and survival rate in patients with T4a disease. This suggests that surgical treatment should remain the standard of care for T4a cancers as opposed to organ preserving methods, and highlights the risk of broadly applying results from studies that included a specific patient population, but were not limited to it.(95)

It was not a purpose of this study to evaluate speech rehabilitation or QOL, but reports on outcome measures that are not strictly clinical are increasingly

appreciated. QOL is an outcome measure whose results sometimes defy clinical impressions and biases. While TL results in greater measurable dysfunction, especially of speech, Morton(127) found no major QOL differences in overall QOL between patients treated with TL or definite RT in his 1997 study. Similarly, Deleyiannis et al.(128) reported no significant difference in pre- and post-laryngectomy QOL scores. Though the loss of voice is disabling, the functional limitations caused by TL may not necessarily translate into a worse overall QOL.(128)

As TL represents a challenging change in physiology for all patients, proper rehabilitation is essential to restore functionality and QOL, which relies on continuous speech and language counselling and therapy. A pre-treatment assessment of swallowing has been found to significantly improve post-laryngectomy swallow function and should be implemented in all HNC patients.(87,129) Continued speech and language therapy is crucial to regain and optimize voice and swallow function after TL. Krishnan and Maclean also found dysphagia to be common following TL, compounded by the use of adjuvant RT and CT.(130) Arenaz Búa et al.(131) reported problems with swallowing in 89% of patients, and moderate-to-severe voice handicap in 66%. 62% of patients required additional therapeutic interventions to help with problems with voice and swallowing.(131) Van Sluis et al.(132) found that all speaker groups after TL report a degree of voice handicap. Attendance of rehabilitation was associated with better functional outcome in speech intelligibility in the study by Singer et al.(133); they also found considerable improvements in intelligibility between 6 months and 1 year after TL.

Out of the 103 patients observed, 47% underwent TEP and placement of a VP at primary surgery or secondarily, while 53% of patients did not receive a VP. The mean time range between replacements of a VP was 143 days among all patients (range 27 - 349 days). Mayo-Yáñez et al. found a mean time range between VP replacements to be between 106 and 124 days in their study.(134)

It is important to note the challenges faced in assessing mean time range between VP replacements, which has not been documented in a uniform manner. Several patients received speech and language therapy and medical attendance at other

medical centers, which made a thorough documentation of the VP changes impossible. These patients, as well as cases reporting durations of more than 365 days, were excluded from calculations.

The primary method to achieve voice rehabilitation was ES in 42% of patients, TES in 31% and ELS in 8%, while 27% of patients were using two or more methods. When comparing international figures, TES is the most common form of voice rehabilitation and considered gold standard in developed countries.(5) Krishnan and Maclean(130) and Xi et al.(135) described TES as the primary alaryngeal voice rehabilitation method in their respective studies. Singer et al.(133) reported the best results regarding subjective and objective speech intelligibility in patients using TES compared to ES and ELS. Van Sluis et al.(132) reported significant better outcomes for TES compared to ES for acoustic parameters and maximum time and intensity of phonation, but no significant difference in patient-reported outcomes in their review.

We did not investigate intelligibility or quality of speech after TL, but looked at complications with and mean duration of VP, and found that many patients reported problems, most importantly leakage around the VP, and consequent VP replacements. Occurrence of complications and high replacement frequency can result in numerous hospital visits, which negatively influence QOL while also constituting a financial burden on the health care system. Furthermore, it is important to consider that TEP is an interventional procedure with a risk of complications. Overall complication rate related to TEP and the VP was 42.6% during a mean follow-up of 15.3 months in a study by Imre et al.(136) Mostly minor complications were reported, the most common being TEP enlargement and leakage around prosthesis, which was also the most common cause of complete closure of TEP. Of three observed major complications, two were life-threatening; a mediastinitis and paraesophageal abscess.(136)

ES was the main form of vocal rehabilitation in our study population. While this is the most difficult to learn and requires practice and extensive vocal rehabilitation training, very good results in intelligibility can be achieved without the risk of complications of TES.

Limitations of the study were due to its retrospective design and method of data collection, as database analysis has inherent limitations. This includes the

potential for miscoding of variables and selection bias that is not accounted for by variables available in the database. Many variables were not uniformly documented, which impeded data collection significantly.

To make a statement about which treatment of advanced cancer of the larynx and hypopharynx yields better results at the Department of Otorhinolaryngology at the University Hospital Graz, the clinical outcome of patients treated with organ preserving protocols must be reviewed and the results compared. Furthermore, prospectively assessing subjective and objective outcomes of speech rehabilitation and QOL following TL would provide valuable insight into the impact TL has on patients' life.

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