CHAPTER

GENERAL INTRODUCTION
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This thesis focuses on voice related problems in patients treated by radiation or laser surgery for early glottic cancer.

The first chapter comprises four paragraphs as a general introduction. The first paragraph is a brief description of laryngeal cancer and more specifically early glottic cancer. The second paragraph describes the (history of) different treatment modalities for early glottic cancer. The third paragraph encompasses the voice, its implications, its production (by a simplified description of the anatomy of the larynx and of the physiology of phonation), and its assessment. The fourth and last paragraph narrows down to the main theme of this thesis: voice related issues in patients treated for early glottic cancer.

LARYNGEAL CANCER

Most cancers of the larynx are squamous cell carcinomas which originate from the mucosa of the larynx. According to their localization in the larynx they are divided in supraglottic, glottic or subglottic carcinomas (Figure 1). In the Netherlands the number of newly diagnosed laryngeal carcinomas has remained stable over several years at about 700 patients a year. However, given the fact that the population has increased, the incidence of laryngeal carcinoma has actually decreased. The European standardized rate (ESR) per 100.000 men, has decreased by approximately one third between 1989 and 2003 (9,5 in 1989 and 6,6 in 2003). During this same period the ESR for women has remained almost stable (1,3 in 1989 and 1,2 in 2003), so that presently approximately 16% of the newly diagnosed patients with a laryngeal cancer are female1.

Figure 1. Laryngeal sub sites. Image from Cirurgia da Laringe by Olias, 2004 (with permission).
Of these laryngeal carcinomas in the Netherlands approximately 65% are from glottic origin. According to the size and extent of these tumors it is agreed by the International Union Against Cancer (UICC) to subdivide them in a system taking into consideration the extent of the tumor, the number and size of regionally involved lymph nodes, and the existence of distant metastasis (TNM system). Glottic laryngeal cancers are subdivided in T1 to T4 tumors, as shown in Table 1. A higher stage indicates a more extensive tumor “T”. The “N” describes the involvement of the regional lymph nodes and the “M” the involvement of distant metastasis. Most glottic carcinomas in the Netherlands are diagnosed in early stages, approximately 60% as T1 tumors and approximately 30% as T2 tumors, because they already cause vocal complaints in an early stage and among general practitioners it is generally agreed to refer a patient for laryngoscopic evaluation if dysphonia persists for a period longer than 3 weeks. Laryngeal carcinomas are more common in men than in women, with a male: female ratio of 6:1. Ninety-one percent of the laryngeal carcinomas are diagnosed in patients over the age of 50 years.

The present study focuses specifically on the less extensive tumors of the vocal folds, also known as “early glottic carcinomas”.

Table 1. Classification of glottic laryngeal cancer according to TNM system by UICC (seventh edition). In bold, ‘early glottic carcinomas’ the focus of the present thesis.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Definition</th>
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<tr>
<td>Tis</td>
<td>Carcinoma in situ; Intra-epithelial tumor cells with intact basal membrane.</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility.</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor limited to one vocal cord.</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor involves both vocal folds.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of the thyroid cartilage.</td>
</tr>
<tr>
<td></td>
<td>Tumor invades through the outer cortex of the thyroid cartilage, and/or invades tissue beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue, strap muscles, thyroid, esophagus.</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades prevertebral space, encases carotid artery, or mediastinal structures.</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades prevertebral space, encases carotid artery, or mediastinal structures.</td>
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Early glottic carcinoma

The term “early glottic carcinoma” is often used to describe a glottic squamous cell carcinoma which is limited in growth concerning depth as well as extension. Nevertheless there is no consensus concerning which specific UICC tumor stages are encompassed in the group of early glottic cancers. According to Ferlito, early glottic cancer should be defined as a minimal invasive tumor that does not invade the vocal fold muscle or cartilage. By this definition, carcinoma in situ as well as deeply infiltrating carcinoma are excluded from early glottic cancer. However in most studies concerning early glottic cancer carcinoma in situ (Tis), T1 (T1a, T1b) and T2 tumors (printed in bold in Table 1) are included.

The Dutch guideline for treatment of laryngeal cancer (2010) states that a carcinoma in situ should be treated with the same treatment modalities as are used for T1 glottic carcinoma, because the risk of conversion into a true malignancy is high. Since there is no difference in treatment between carcinoma in situ and invasive carcinoma, it makes sense to indeed include Tis tumors in the group of early glottic carcinoma. T1 glottic laryngeal cancers are divided in T1a and T1b, according to their localization on one vocal cord (T1a) or both vocal cords (T1b) (Figures 2 and 3).

One can question if T2 tumors should be included in the group of early glottic carcinomas, but, as already mentioned, most studies do. According to the definition of the UICC; tumors “extending to the supraglottis and/or subglottis, and/or with impaired vocal cord mobility” are classified as T2. This results in a large range of T2 tumors with respect to tumor mass and size. A superficial T2 tumor of the glottis with slight invasion of the supra- or subglottis without impairment of the vocal fold mobility (Figure 4) is more readily accepted as an early glottic carcinoma than a bulky T2 tumor with slight invasion of the supra- or subglottis and impaired vocal fold immobility (Figure 5) not to mention bulky T2 tumors with extensive supraglottic involvement, which will definitely not be considered as early glottic cancers, but are still T2 tumors. In this thesis, the term early glottic cancer is used for Tis, T1 and T2 carcinomas with only minor supraglottic extension and no impairment of mobility.

Prognosis of glottic cancer

The prognosis with respect of survival of patients diagnosed with glottic cancer is usually good, especially in cases without regional lymph node involvement (N0). The more advanced the tumor, the higher the risk of regional lymph node involvement or distant metastasis and consequently the less favourable the survival. Five-year survival rate for patients with T1 tumors (without involvement of regional lymph nodes or distant metastasis) is 96% and for patients with T2 tumors (without involvement of regional lymph nodes or distant metastasis) 80%. For patients with the more advanced T3 and T4 tumors prognosis is mainly determined by involvement of regional lymph nodes or distant metastasis. For all early glottic carcinomas it can be stated that metastases to regional lymph nodes or distant metastases, are extremely rare.
Figure 2. Example of T1a glottic carcinoma (confined to one vocal fold).

Figure 3. Example of T1b glottic carcinoma (involvement of both vocal folds).

Figure 4. Example of a superficial T2 glottic carcinoma with slight invasion of the supraglottis (ventricle).

Figure 5. Example of a bulky T2 glottic carcinoma with impaired vocal fold mobility and invasion of the supraglottis.
TREATMENT MODALITIES

Presently the main treatment options for early glottic carcinomas are radiotherapy and endoscopic surgery, the latter usually performed with a laser (mostly CO2 laser). However, the first treatment efforts, more than one and a half century ago, entailed external surgical procedures.

History

The first surgical treatment of a laryngeal carcinoma is accredited to Buck in 1851. He performed the first laryngeal fissure approach in order to excise laryngeal carcinoma\(^7\). The patient survived almost a year. In 1868 Solis-Cohen performed a laryngeal fissure approach for laryngeal carcinoma and reported that his patient was still in excellent health with a fair voice in 1887\(^7\). In those days the results of such treatments were however usually not so good, due to a combination of poor diagnostic tools, surgical and anesthesiological limitations and limited perioperative care.

The first laryngectomy for laryngeal carcinoma was performed by Billroth in 1873\(^8\). Initially mortality was high\(^8\). Foulis reported in 1881 that of the 27 patients, who underwent laryngectomy, more than half died within a week. Another 25% died within 10 months due to residual tumor. The high mortality dropped significantly after Gluck (1881) decided to operate in two tempi. First he severed the trachea from the larynx and sutured it to the skin to secure the airway and in a second operation, a few weeks later, the larynx was removed\(^7\).

In the first quarter of the twentieth century the diagnostic procedures became the more and more sophisticated, allowing for a better evaluation of the tumor extension and it became general practise to confirm the diagnosis histologically before treatment. This was an important step forward, as in earlier times, surgeons did not bother to take biopsies and usually relied only on their experience and clinical impression to decide whether a lesion was cancerous or not.

Around approximately 1925, radiotherapy was introduced as a treatment option and became very popular. Many authors reported good results (Portmann, Coutard)\(^9\). But also severe side effects like necrosis of the cartilage were described\(^7\). During this period there was a tendency to select patients with smaller tumors for laryngectomy, while radiotherapy was used to treat the patients with more extensive tumors.

In the early fifties of the last century this policy was reversed, so that patients with smaller tumors were preferably treated by radiation whereas patients with more advanced tumors were treated surgically. During that period also the options of partial laryngectomies as opposed to total laryngectomy were further developed and came into vogue.
In the late fifties and early sixties of 20th century the combination of radiotherapy and surgery was introduced\textsuperscript{10}. Leroux-Robert (1956) propagated the so called sandwich procedure: preoperative radiotherapy - excision - postoperative radiotherapy\textsuperscript{11}. In the following years full course preoperative radiotherapy became common practise after having been introduced by Goldman and Silverstone (1961)\textsuperscript{12}. In 1974 Lindberg promoted postoperative radiotherapy as the most successful treatment procedure\textsuperscript{13}.

In the nineteen-nineties as a result of the successful use of combinations of radiotherapy and chemotherapy (chemoradiotherapy) the tendency towards total laryngectomy in the more extensive tumors diminished\textsuperscript{14}. Chemoradiotherapy did not result in a better survival, but much more patients retained their larynx\textsuperscript{14}. The fact that the larynx was preserved did not per se mean that the laryngeal functions remained adequate. Many patients experienced persistent swallowing, respiratory or phonatory limitations\textsuperscript{15}.

CO\textsubscript{2} endoscopic laser surgery as a treatment modality for laryngeal carcinomas was first introduced by Strong and Jako in 1972\textsuperscript{16}. Technical improvements, such as the development of the Acuspot improved the precision and efficacy of laser treatment.

Primary radiation therapy remained the traditional treatment modality of early glottic cancer in the Netherlands for a long time. Over the last two decades endoscopic laser surgery has gradually gained a prominent position in the treatment of early glottic carcinomas\textsuperscript{17-21}. In the first Dutch guideline for treatment of laryngeal cancer of 2000, laser surgery was adopted as an alternative to radiotherapy in superficial, midcord T1a glottic laryngeal carcinomas\textsuperscript{22}. The revision of this guideline, accepted in 2010, states that laser surgery is the treatment of choice for these midcord T1a laryngeal carcinomas\textsuperscript{5}.

**Radiotherapy**

External beam radiation therapy uses high-energy ionising radiation (called X-rays or γ-rays) to destroy cancer cells. High-energy radiation damages the genetic material, deoxyribonucleic acid (DNA) of cells. When the damage is extensive, this will result in immediate (apoptosis) or delayed cell death (reproductive cell death). Although radiation inflicts damage in normal cells as well as in cancer cells, normal cells are usually able to repair this damage at a faster rate and retain their normal function better than cancer cells. This results in a preferential destruction of the cancer cells.

Before the first actual administration of radiotherapy patients undergo CT-scanning for optimal planning of the field of irradiation and a fixation mask is tailored. This mask provides excellent immobilisation in the treatment position that is reproducible every following treatment session (Figure 6). On the planning CT-scan, the tumor and organs at risk are delineated (Figure 7). Based on this contouring, a treatment plan is made. In order to preserve as much normal tissue as possible, radiation by two lateral opposed beams is most commonly used for early glottic cancer to concentrate the radiation dose in the
target field. Radiation dose is expressed in Gray (Gy). The required total dose of radiation depends on tumor volume, the dose per fraction, and the normal tissue tolerance. For laryngeal carcinoma, the commonly used total radiation dose varies from 50 Gy to 70 Gy. To allow for preferential repair of normal tissue damage, the total dose is delivered in smaller doses, called fractions. Many different treatment schedules for external beam radiotherapy are described. Alternative fractionation schedules like hyperfractionated and accelerated radiotherapy have been investigated; these schedules seek to improve local control and overall survival rate without increasing late complications as compared to conventional schedules. In our hospital (VUmc, Amsterdam) a total dose of 60.0 Gy is usually applied for Tis and T1 glottic carcinomas with a schedule of 24 fractions of 2.5 Gy (5 times a week). T2 tumors are mostly irradiated to a total dose of 70 Gy with a schedule of 35 fractions of 2 Gy (6 times a week).

Figure 6. Fixation mask

Figure 7. Planning CT-scan of a T1a glottic carcinoma.
Endoscopic Laser surgery

Endoscopic laser surgery is usually performed under general anaesthesia after orotracheal intubation using a laser-safe endotracheal tube. The endolarynx (structures inside the larynx) is exposed by laryngoscopes of different sizes and shapes. Before treatment, accurate tumor extension can be assessed by visual evaluation of the larynx using an operating microscope as well as rigid endoscopes with 0°, 30°, and 70° angles of view. Under the accuracy of a microscope a so called cordectomy can be performed, using a CO₂-laser under the precision of an Acu-spot micromanipulator (Figure 8). Pulsed energy, mean power in Watts, and depth of excision can be tailored to tumor extension and type of cordectomy. Type I (subepithelial cordectomy, resection of the epithelium) and Type II (subligamental cordectomy, resection of the epithelium, Reinke’s space and the vocal ligament) as defined by the Working Committee of the European Laryngological Society (ELS) are mostly used in the treatment of early glottic cancer. Sometimes more extensive resections are performed: Type III (transmuscular cordectomy, resection of the epithelium, Reinke’s space, vocal ligament and part of the vocal muscle). Figures 9 to 11 give schematic illustrations of these three different types of cordectomy used for treatment of early glottic cancer.

Figure 9. Subepithelial cordectomy (Type I). Image from the European Laryngological Society (ELS) (with permission).

Figure 10. Subligamental cordectomy (Type II). Image from the European Laryngological Society (ELS) (with permission).

Figure 11. Transmuscular cordectomy (Type III). Image from the European Laryngological Society (ELS) (with permission).
Other treatment modalities

Cordectomies by cold steel microsurgery or by laryngeal fissure approach and partial laryngectomies are all described as alternative primary treatment options for early glottic carcinomas but are not routinely used in the Netherlands\textsuperscript{26}.

VOICE

The World Health Organization (WHO) classified voice as one of the major body functions. According to the International Classification of Functioning, Disability and Health (ICF) any disease leading to impaired body function can lead to a disturbed function in daily life\textsuperscript{27}. Loss or deterioration of vocal function leads to an impairment which limits an individual’s ability to speak and consequently results in a restriction of communication and consequently a limitation in the participation of daily life activities.

Anatomy of the larynx in relation to phonation

In order to explain hoarse or breathy voice quality as a consequence of pathology of the vocal folds mucosa, a simplified description of laryngeal anatomy and voice production is provided in this paragraph.

The Larynx

The laryngeal skeleton is composed of 5 cartilages: the thyroid cartilage, the cricoid cartilage, the epiglottic cartilage and two arytenoid cartilages (Figure 12). The cricothyroid joints are the articulations of the thyroid cartilage with postero-lateral facets on both sides of the cricoid cartilage. The two major actions at this joint are antero-posterior sliding and rotation of the thyroid upon the cricoid cartilage. The arytenoid cartilages are located on top of the cricoid cartilage and articulate with the cricoid by means of a joint which allows a very complex gliding, rotating and tilting movement of the arytenoids along the cricoid facet (Figure 13).

The intrinsic laryngeal muscles

The intrinsic laryngeal muscles (Figure 14); lateral cricoarytenoid muscle, posterior cricoarytenoid muscle, thyroarytenoid muscle (of which the vocalis muscle in the vocal fold is a part), interarytenoid muscle and cricothyroid muscle are all paired muscles, with the exception of the interarytenoid muscle, which is a single muscle running between the medial surfaces of both arytenoids. All intrinsic laryngeal muscles with the exception of the cricothyroid muscles are innervated by the recurrent laryngeal nerve, which branches off of the vagal nerve low in the neck on the right side and in the thorax on the left side. This nerve has a complicated function considering the fact that it activates muscles with opposing activity, such as the lateral cricoarytenoid muscles which act as the main laryngeal
adductors, as well as the posterior cricoarytenoid muscles which act as the main abductors. The cricothyroid muscles are innervated by the superior laryngeal nerve originating directly from the vagal nerve.

All intrinsic laryngeal muscles, with the exception of the cricothyroid muscles, attach to the arytenoid cartilages. These muscles are responsible for moving the arytenoids and with them the vocal folds which are attached to the vocal process, towards or away from the midline, depending upon the function the larynx has to fulfil at that moment.

The vocal folds
The vocal folds (Figure 15 and 16) are paired structures situated in the larynx which are posteriorly connected to the arytenoids at the vocal process and anteriorly to the inner surface of the thyroid cartilage. The space between both vocal folds is termed glottis and consist of a membranous part (anterior two thirds) and a cartilagenous part (posterior one third). The space between the bilateral articulation of the arytenoids with the cricoid cartilage, the so called cricoarytenoid joints, forming the posterior limit of the larynx, is termed posterior commissure. Anteriorly both vocal folds meet in the anterior commiss-
sure, where they are tightly fixed to the inner surface of the thyroid cartilage by a strong ligament called Broyle’s ligament. The action of moving the arytenoids and vocal folds towards the midline is called adduction and is completed by both vocal folds meeting each other in the midline, thus closing the glottis. The action of moving the arytenoid and the vocal folds away from the midline is called abduction and results in a separation of both vocal folds posteriorly, thus enlarging the glottis.

Anteriorly both vocal folds remain in contact in the anterior commissure. For phonation, coughing, swallowing, weight lifting, exerting abdominal pressure during bowel movement or giving birth, the vocal folds are adducted (Figure 15), whereas for respiration they are abducted (Figure 16), to allow a free passage of air into or out of the windpipe and lungs.

Membranous part of the vocal folds
The membranous part of the vocal folds consists of the vocalis muscle, the vocal ligament and the overlying mucosa with stratified squamous cell epithelium. It is at this membranous part of the vocal folds where the voice originates. To enable the generation of vibration of the vocal folds required for phonation, the microstructure of the vocal folds consists of several specific layers (Figure 17). From superficial to deep, the layers of the vocal folds consist of epithelium which is anchored to the lamina propria by the basement membrane and the lamina propria which is anchored to the vocalis muscle by the lateral part of the vocal ligament. The lamina propria is subdivided in three layers namely the superficial, intermediate and the deep layer.

The superficial layer consist of loosely connected fibrous tissue with extra cellular matrices, resulting in a gel-like consistency. This superficial layer, also called Reinke’s space,
is highly pliable and together with the overlying epithelium it forms the part of the vocal folds which is most capable of vibration during phonation. The intermediate layer is formed by the medial part of the vocal ligament and consists of elastic fibers. The deeper layer is formed by the lateral part of the vocal ligament and consists of collagenous fibers which interconnect with the muscle fibres of the vocalis muscle.28
From a functional point of view, based on their vibratory characteristics, these different layers can be divided into three sections: the cover, consisting of the epithelium and the superficial layer of the lamina propria; the transitional layer, consisting of the intermediate and deep layer of the lamina propria; the body, consisting of the vocalis muscle (Figure 17). The deeper the layer, the stiffer the tissue and the less contribution to the vibratory mucosal wave.

Phonation
The larynx produces a basic vocal sound, which is further modified and amplified in the throat and mouth, eventually resulting in intelligible speech.

The frequency and volume of the voice is regulated by interaction between the myo-elastic properties and condition of the vocal folds in the larynx, the subglottic and transglottic air pressures and the modulation in the throat. The vocalis muscle on contraction, shortens and thickens the vocal folds and reduces the tension of the vocal folds, thus lowering the pitch of a voice. Contraction of the cricothyroid muscles pulls the thyroid cartilage anteriorly with respect to the cricoid cartilage and so lengthens and thins the vocal folds, and even more important increases the tension of the vocal folds, resulting in increasing the pitch of a voice.

Glottic cycle
Prior to phonation, air is inhaled into the lungs. Phonation is typically produced during exhalation. At the onset of phonation the glottis is closed by adduction of the vocal folds. Exhaled air slightly forces the pliable medial part of the closed vocal folds apart (open phase) and while passing through the small opening between both vocal folds the airflow generates a vibratory wave in the membranous part of the vocal folds. The elastic properties of the vocal folds and the decrease of air pressure due to the outward flow of air

Figure 17. Schematic illustration of a frontal section of the vocal fold: typical layered structure. For details see text. Images based on the original images by Hirano, 1977.
(Bernoulli effect) result in a renewed closure of the small opening between the vocal folds (closed phase) (Figure 18).

The cycle of opening and closing of the glottis is called the glottic cycle and repeats itself periodically as a result of the increasing air pressure below the vocal folds (subglottic pressure) which, once having overcome the resistance of the closed vocal folds will again force the closed vocal folds slightly apart. As a result of this periodically slightly and briefly opening and closing of the glottis, the exhaled air escapes in small puffs, resulting in vibrations of air which is perceived as sound. Basically, sound is no more than vibrating air.

It is essential to realise that the separation and approximation of both vocal folds during the open phase of phonation is not a consequence of abductory and adductory activity of the intrinsic vocal muscles, but a combination of aerodynamic and myo-elastic forces. So, during phonation the vocal folds remain in the adducted position.

![Figure 18. Schematically simplified illustration of the vocal folds during a glottic cycle, with changes in subglottic air pressure. Images based on the original images by Schönharl, 1952.](image)
Mucosal wave
The passive vibration of the vocal folds, resulting in a mucosal wave, and responsible for the basic vocal sound, is only possible because of the above described layered structure of the vocal folds, each layer having specific mechanical properties.

The quality of the voice is largely dependent on the integrity of these vocal fold layers as well as on adequate closure of the glottis. Inability to close the glottis e.g. as a result of vocal fold pathology or recurrent laryngeal nerve palsy, will allow the escape of unmodulated exhaled air and will result in a breathy voice or in extreme conditions inability to generate voice (aphonic). Furthermore, one can imagine that any pathology which stiffens the vocal fold layers, will affect the quality of the voice by influencing the mucosal wave. For instance a tumor on the vocal fold will, depending on the depth of infiltration, impair or even completely dampen the mucosal wave and will thus interfere with the above mentioned glottic cycle. Irregularity of the vocal fold mucosal wave leads to irregularities in frequency and amplitude of vocal fold vibration, resulting in a hoarse voice quality. A tumor of the vocals fold can also lead to an insufficient closure of the glottis resulting in a breathy voice quality.

Voice assessment
Both tumor infiltration as well as treatment (surgery as well as radiotherapy) induced changes in vocal fold tissue affect the functioning of the layered structure of the vocal fold and consequently affect the voice. Several methods for assessment of voice outcome exist and it is widely recommended to use multidimensional voice assessment protocols to describe voice outcome following treatment of laryngeal pathology.

Assessment of voice can theoretically be divided into examination of vocal function (e.g. videolaryngostroboscopy, voice range profile [VRP], aerodynamic assessment), examination of vocal quality (e.g. acoustical assessment, GRBAS-scale [Grade, Roughness, Breathiness, Asthenia and Strain]) and examination of vocal impact on daily life (e.g. VHI, Voice screening questionnaire). Many different voice assessment protocols are being advocated by many different authors and consensus is lacking. Most protocols contain an overlap of the above mentioned vocal dimensions. The most commonly employed assessment tools are described below. Aero-dynamic voice assessments (subglottic air pressure and transglottic air pressure gradients, airflow measurements) are occasionally employed for scientific purposes, but were not used in the studies of which this thesis is comprised and are therefore not further elaborated.

Vocal fold examination
The possibilities of examination of the vocal folds has been very much improved over the last decades. Traditional mirror investigation of the vocal folds, available to us since the days of Manuel Garcia (1854) gives only a global impression of their function. Flexible
laryngoscopy yield more detailed information of the vocal folds, especially since the introduction of “chip-on-the-tip” camera facilities incorporated in the flexible endoscopes, but analysis of the vibratory function of the vocal folds remains limited without the use of stroboscopic or high-speed imaging techniques.

Nowadays videolaryngostroboscopy is considered the standard imaging tool for analysis of vocal fold function. It supplies information about the vocal fold anatomy and vibratory pattern. Laryngostroboscopy uses a stroboscope in combination with a direct laryngoscope (either rigid or fiberoptic). The stroboscopic light flashes intermittently, proportional to the frequency of the vocal fold vibration. If the frequency of these flashes of light is regulated in such a way that they occur just slightly slower than the frequency of the glottic cycle, the vibrating vocal folds are illuminated in such a manner that vocal fold motion appears as a slow-motion image by the optical illusion of stroboscopic light (Figure 19). This gives an opportunity for more accurate examination of the vocal folds and its mucosal wave. Furthermore, because of the interference of vocal fold pathology on the layered structure of the vocal fold and the resulting vibratory characteristics, it can yield information concerning the depth of tumor infiltration into the vocal fold.

Other methods to evaluate vocal fold vibratory characteristics are high-speed imaging and video-kymography. Extensive description of these latter two methods is beyond the scope of this thesis.

![Figure 19. Principle of videolaryngostroboscopic imaging. A: the stroboscopic light flashes occurring in a marginally lower frequency than the glottic cycle, B: actual vibratory cycle of the vocal cords and the line between the dots depicting the slow motion image as illuminated by the stroboscopic light flashes.](image)
Voice range profile
The voice range profile (VRP), also called phonetogram, assesses the pitch (rendered on the axis) and intensity range of the speakers’ voices (rendered on the abscissa) (Figure 20). VRP is a technique for the examination of vocal function.

Acoustic voice analyses
Acoustic analyses of voice quality can be performed quickly and objectively. Average fundamental frequency (F0), percent jitter, percent shimmer and noise-to-harmonics ratio (NHR) are the parameters most commonly determined. The percentage of jitter represents the relative period-to-period variability (variations in the pitch domain). The percentage of shimmer represents the relative variability of the peak-to-peak amplitude (variations in the loudness domain). Values of jitter and shimmer above a certain threshold are associated with pathological voices, such as breathy, rough or hoarse voices. The noise-to-harmonic ratio is an average ratio of energy of the inharmonic components (for example in the range 1500-4500 Hz) to the harmonic components energy in the analyzed signal. The noise-to-harmonics ratio is an objective and quantitative evaluation of the degree of hoarseness. Speech material for voice analyses usually consist of sustained vowels with or without variations in loudness and fundamental frequency (pitch)\textsuperscript{30}.

Perceptual Voice Ratings
Several protocols have been developed to assess perceptual voice quality. Speech material usually compromises standardized text or sentences. Global ratings include ratings on overall voice quality, intelligibility, acceptability, or communicative suitability.
**Perceptual voice quality ratings**

Perceptual voice quality ratings are performed by trained listeners on standardized text or sentences. Several rating protocols have been developed for these purposes. The Vocal Profile Analysis Protocol (VPAP) developed by Laver, for instance, is a phonetically based system consisting of four sections: vocal quality, prosody (pitch, consistency, and loudness), temporal organization (continuity, and rate), and comments (breath support, rhythmicity, and diplophonia).

Another example is the GRBAS protocol, proposed by the Japanese Society of Logopedics and Phoniatrics, which is one of the most widely used voice rating scores. It can be used by clinicians to categorize the voice using five descriptive perceptual parameters: overall grade or severity (G), roughness (R), breathiness (B), asthenia (A), and strain (S), giving a score between 0 and 3 depending upon the severity of each parameter.

**Communicative suitability**

The concept of communicative suitability was initially developed by Franken, for stuttering patients. It is a rating instrument to determine the communicative suitability of speech/voice by untrained listeners and therefore the functionality of voice. Van der Torn et al. developed an adapted version for patients after treatment for early glottic cancer. Untrained listeners judge the voice samples on communicative suitability in 3 different demanding speaking situations on a 10-point anchored scale ranging from extremely poor (score 1) to excellent (score 10). The 3 speaking situations range from low demanding (talking about everyday events with a friend), medium demanding (asking a passer-by for directions), to highly demanding (giving a lecture).

**Patient reported voice outcome**

There are several Quality of life questionnaires specifically related to voice outcome. In laryngeal cancer studies The Voice Handicap Index (VHI) is the most widely used patient reported voice outcome measure. The VHI is a validated questionnaire and consists of 30 statements (See Chapter 3 Figure 2) on voice related aspects in daily life (5 point-rating scale). Summarizing the scores on the 30 statements leads to a total VHI score, ranging from 0 to 120. A higher score corresponds with a lower voice-related functional status. Furthermore, the VHI includes an overall question on the quality of the voice with four response levels including 0 (good), 1 (reasonable), 2 (moderate) and 3 (poor).

**CONCLUSION**

This paragraph illustrates the importance of voice for our daily life functioning. The production of voice is very susceptible to even minor structural changes of the vocal folds. The many different ways to assess voice underlines the multidimensional character of voice.
PURPOSE OF THIS THESIS

Until about a decade ago radiotherapy was the preferred treatment modality for early glottic cancer in North-Western Europe. Over the last years endoscopic laser surgery gained in popularity. Many studies concerning early glottic cancer are focused on treatment outcome in terms of local control rate and overall survival. Without any doubt the aim of cancer treatment should primarily be directed at achieving cure. The results of all studies on this topic are remarkably uniform: early glottic cancer has good to excellent cure rates, irrespective of the treatment modality. Local control rates range from 82% to 96% after endoscopic laser surgery to 67% to 96% after radiotherapy, and rates of ultimate preservation of the larynx range from 93% to 100% after initial endoscopic laser surgery to 85% to 97% after initial radiotherapy\textsuperscript{36-48}. Studies concerning voice outcome after treatment of early glottic cancer show less uniform results, describing a wide range of abnormal voice quality post treatment: 14-92% after radiotherapy\textsuperscript{19,20,49-61} and 17-70% after endoscopic laser surgery\textsuperscript{19,53-65}. These findings could lead to the conclusion that there is no clear difference in voice outcome following both treatment modalities\textsuperscript{56,57,58,66-69}. However, in most of these studies information regarding tumor size, time of follow-up, and type of voice analyses is not available. Moreover, prospective studies on voice outcome comparing both treatment modalities for comparable early glottic cancers are scarce. Therefore definite conclusions concerning voice outcome are not available.

Also the role of voice therapy in patients with voice problems following treatment of early glottic cancer is unclear and studies on its efficacy are scarce. In the study by Fex et al.\textsuperscript{70}, patients received voice therapy during radiotherapy for early glottic cancer. Unfortunately, the definition of what is considered a normal voice quality as well as a control group were not available in this study, making it impossible to conclude that the voice results were a direct consequence of the voice therapy. In two other studies patients were admitted to voice therapy after endoscopic laser surgery\textsuperscript{64,71}. The results were contradictory: one study reported a positive effect of voice therapy, while the other even reported deteriorated voice after voice therapy.

The general purpose of the present thesis is to enhance our knowledge regarding voice outcome in patients after treatment of early glottic cancer, to investigate the relationship between voice outcome and quality of life, and to assess the efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer.

More specifically, the aims of the study are:

1. To assess whether or not patients experience voice problems after treatment of early glottic carcinomas. And if so, how can we identify these patients? (Chapter 2)
2. To assess the impact of voice problems after treatment of early glottic cancer on daily life activities. (Chapter 3)

3. To investigate the applicability of the Voice Handicap Index (VHI) as a tool to assess patient reported voice problems in laryngeal cancer patients. (Chapter 4)

4. To assess whether voice problems perceived by patients after treatment of early glottic cancer are comparable to the voice problems perceived by patients with benign vocal fold pathology. (Chapter 4)

5. To investigate the differences in voice outcome and voice recovery after treatment of early glottic cancer by radiotherapy as compared to voice outcome and voice recovery after endoscopic laser surgery. (Chapter 5)

6. To investigate whether the voice outcome following treatment for early glottic cancer differs from normal voices. (Chapter 5)

7. To assess the efficacy of voice therapy for voice problems after treatment of early glottic cancer. (Chapter 6 and 7)

8. To investigate whether voice outcome can be an indicator of preferred treatment modality for early glottic cancer, given the fact that the cure rates of both treatment modalities (radiotherapy and endoscopic laser surgery) are excellent. (Chapter 5 and Discussion)
REFERENCES


