FUNCTIONAL OUTCOME OF EARLY GLOTTIC CANCER

The author gratefully acknowledges the financial support for printing this thesis by: Chip-Soft B.V., Mediq Tefa, Olympus Nederland B.V., Meda Pharma B.V., Specsavers, PENTAX Medical, Beter Horen B.V., ZEISS, Daleco Pharma B.V., DOS Medical B.V.

Printed by Ipskamp Drukker B.V., Enschede

Cover-design: Jornt van Dijk - www.persoonlijkproefschrift.nl

Lay-out: Jornt van Dijk - www.persoonlijkproefschrift.nl

Afbeelding cover: uit 'Atlas d'Anatomie Descriptive du Corps Humain', C. Bonamy & P. Broca. Parijs, 1860. Met dank aan mijn 'roomy' Jochen Bretschneider.

ISBN

VRIJE UNIVERSITEIT

Functional outcome of early glottic cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op vrijdag 4 december 2015 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

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geboren te Budel

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voor Lieve en Roos

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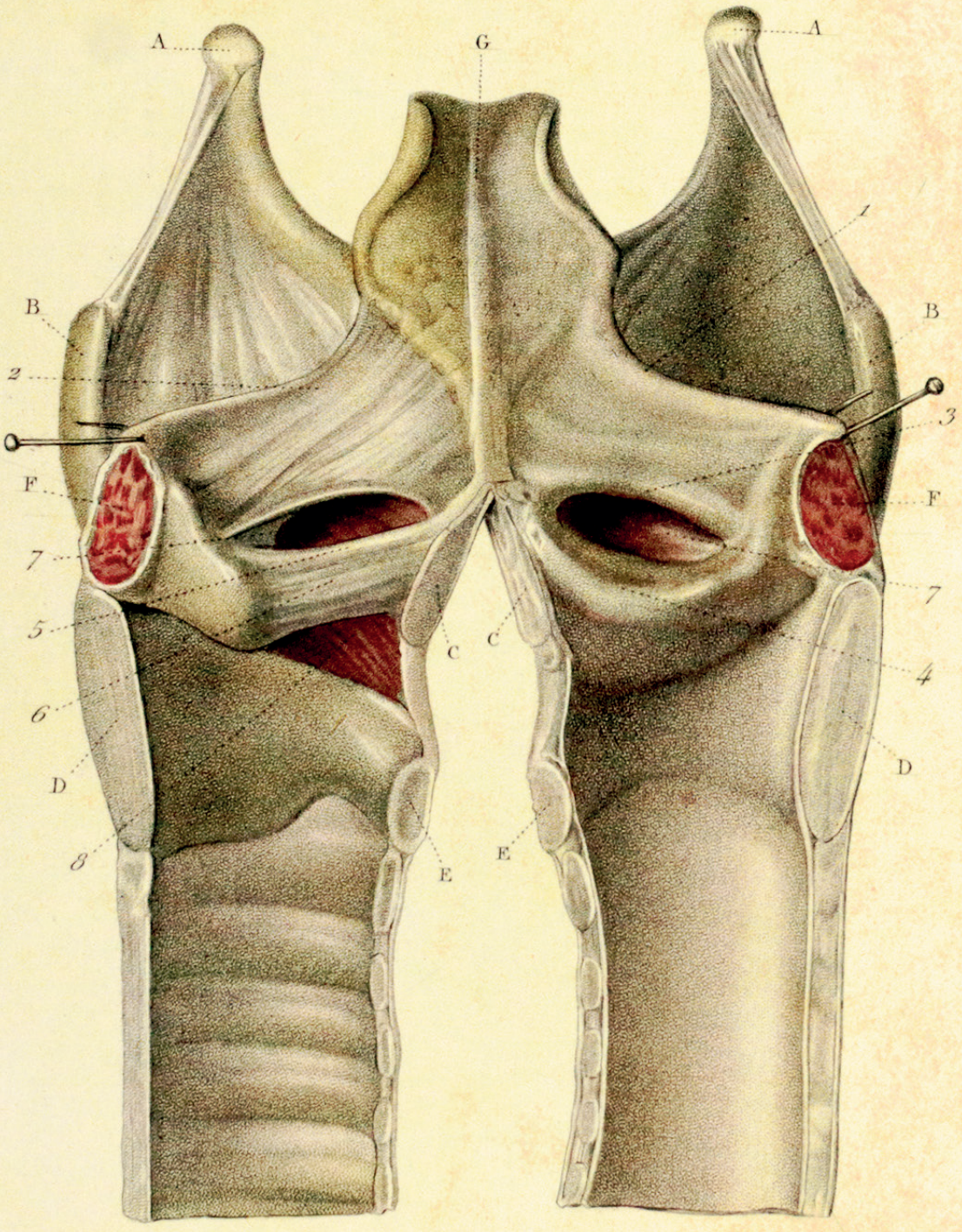

CHAPTER

GENERAL INTRODUCTION

GENERAL INTRODUCTION

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 female[1].

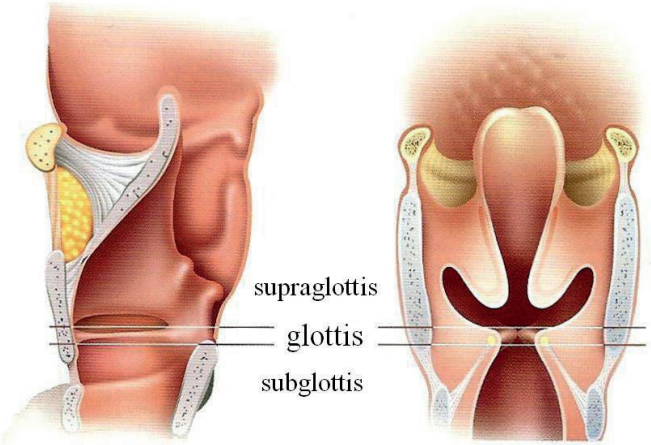

Figure 1. Laryngeal sub sites. Image from Cirurgia da Laringe by Olias, 2004 (with permission).

Of these laryngeal carcinomas in the Netherlands approximately 65% are from glottic origin[1]. 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[2]). 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[3]. 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[1].

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.

Tumor	Definition
Tis	Carcinoma in situ; Intra-epithelial tumor cells with intact basal membrane.
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility.
T1a	Tumor limited to one vocal cord.
T1b	Tumor involves both vocal folds.
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility.
T3	Tumor limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of the thyroid cartilage.
T4a	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.
T4b	Tumor invades prevertebral space, encases carotid artery, or mediastinal structures.

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[4], 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[5]. 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[3]. 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, T1and 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[5]. For all early glottic carcinomas it can be stated that metastases to regional lymph nodes or distant metastases, are extremely rare[6].

Figure 2. Example of T1a glottic carcinoma (confined to one vocal fold).

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

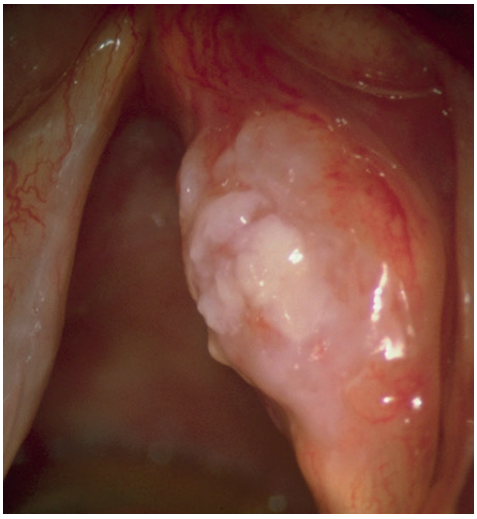

Figure 4. Example of a superficial T2 glottic carcinoma with slight invasion of the supraglottis (ventricle).

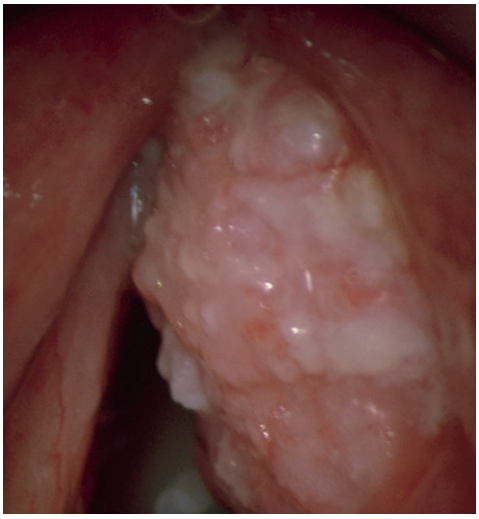

Figure 5. Example of a bulky T2 glottic carcinoma with impaired vocal fold mobility and invasion of the supraglottis.

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[10]. Leroux-Robert (1956) propagated the so called sandwich-procedure: preoperative radiotherapy - excision - postoperative radiotherapy[11]. In the following years full course preoperative radiotherapy became common practise after having been introduced by Goldman and Silverstone (1961)[12]. In 1974 Lindberg promoted postoperative radiotherapy as the most successful treatment procedure[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[14]. Chemoradiotherapy did not result in a better survival, but much more patients retained their larynx[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[15].

CO2 endoscopic laser surgery as a treatment modality for laryngeal carcinomas was first introduced by Strong and Jako in 1972[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[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[22]. The revision of this guideline, accepted in 2010, states that laser surgery is the treatment of choice for these midcord T1a laryngeal carcinomas[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[23-24]. 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 2Gy (6 times a week).

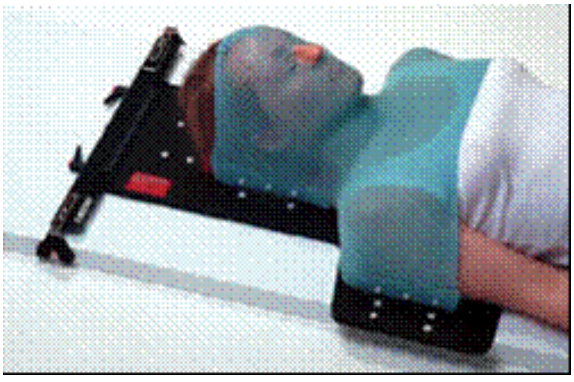

Figure 6. Fixation mask

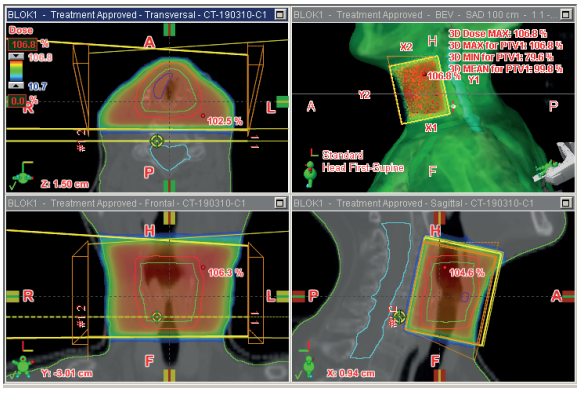

Figure 7. Planning CT-scan of a T1a glottic carcinoma.

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 CO_2-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[25]. 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.

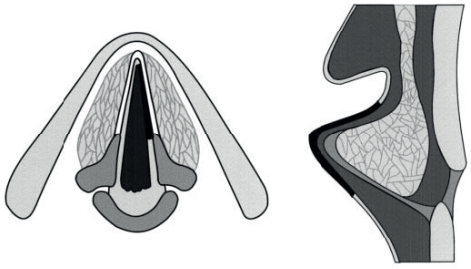

Figure 9. Subepithelial cordectomy (Type I). Image from the European Laryngological Society (ELS) (with permission).

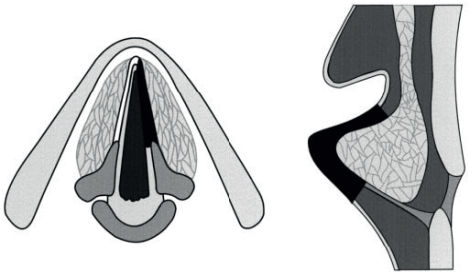

Figure 10. Subligamental cordectomy (Type II). Image from the European Laryngological Society (ELS) (with permission).

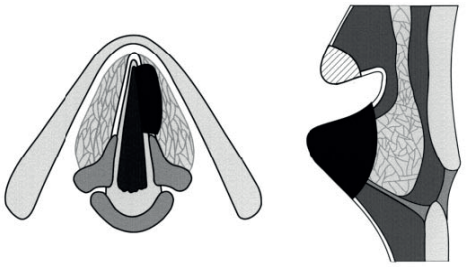

Figure 11. Transmuscular cordectomy (Type III) . Image from the European Laryngological Society (ELS) (with permission).

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[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[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

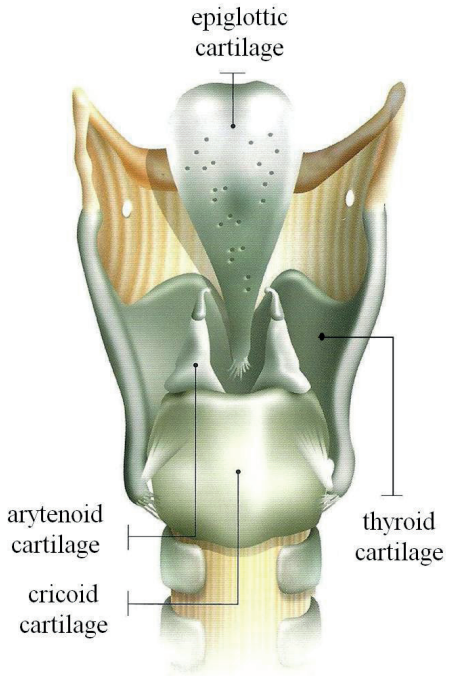

Figure 12. Laryngeal skeleton posterior view. Image from Cirurgia da Laringe by Olias, 2004 (with permission).

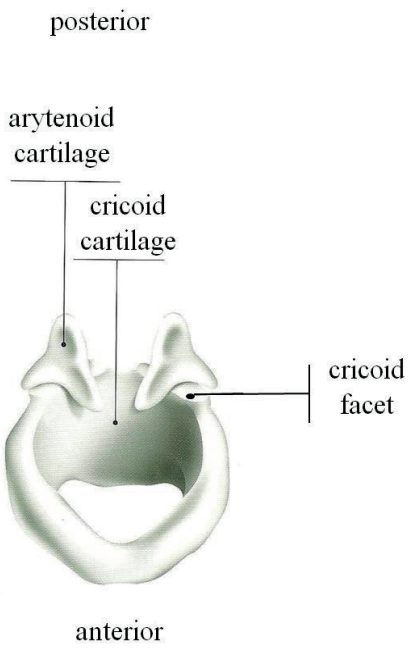

Figure 13. Cricoid and arytenoids cartilages and cricoid facet. Image from Cirurgia da Laringe by Olias, 2004 (with permission).

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 commis-

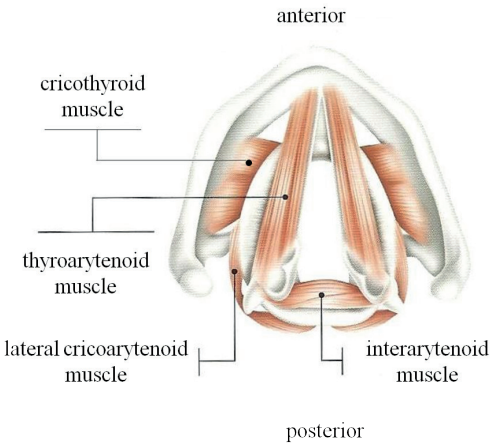

Figure 14. Intrinsic laryngeal muscles. Image from Cirurgia da Laringe by Olias, 2004 (with permission).

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,

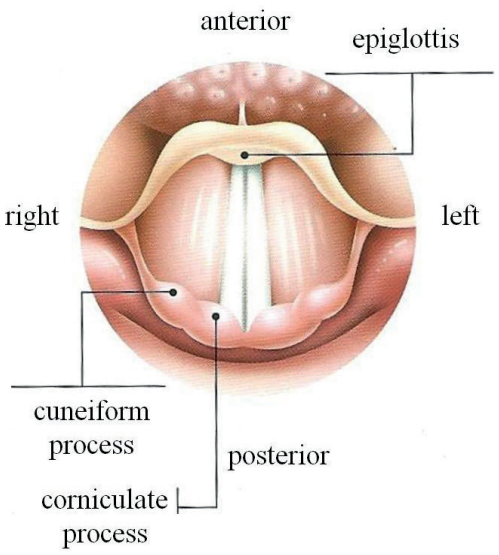

Figure 15. Vocal folds in adducted position. Image from Cirurgia da Laringe by Olias, 2004 (with permission).

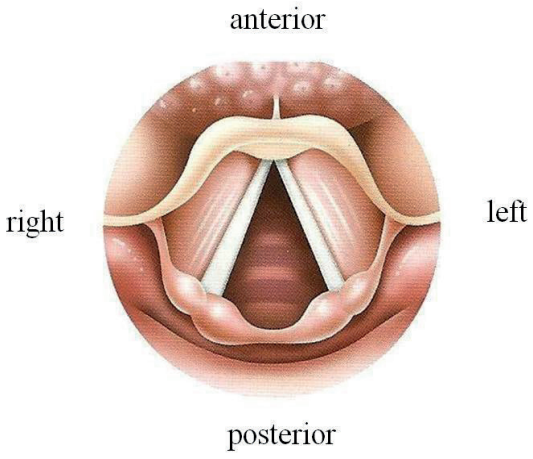

Figure 16. Vocal folds in abducted position. Image from Cirurgia da Laringe by Olias, 2004 (with permission).

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].

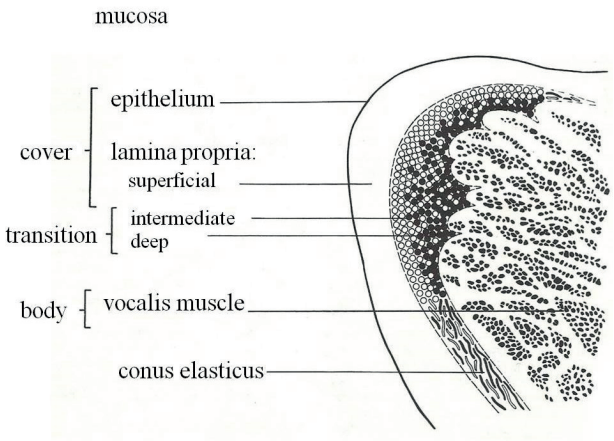

Figure 17. Schematic illustration of a frontal section of the vocal fold: typical layered structure. For details see text. Images based on the original images by Hirano, 1977.

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

(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.

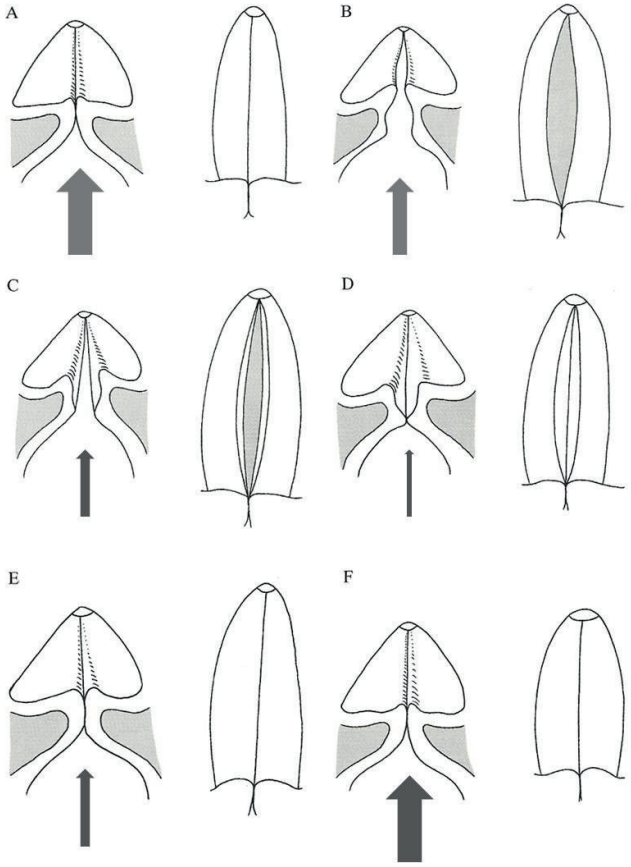

Figure 18. Schematically simplified illustration of the vocal folds during a glottic cycle, with changes in subglottic air pressure. Images based on the original images by Schönharl, 1952.

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[29].

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 strobe light source 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)**[30]. 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[31]. Extensive description of these latter two methods is beyond the scope of this thesis.

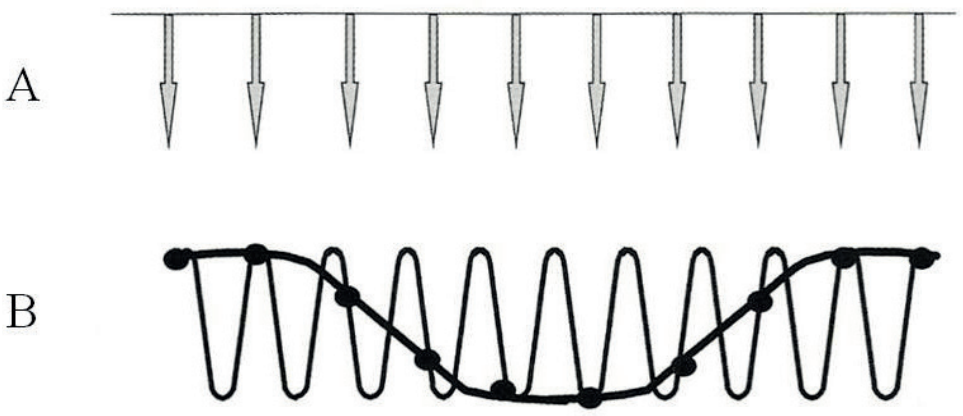

Figure 19. Principle of videolaryngostroboscopic imaging. A: the stroboscopic light flashes occurring in a marginally lower frequency than the glottic cycle, B: actual vibratory cycle of the vocal cords and the line between the dots depicting the slow motion image as illuminated by the stroboscopic light flashes.

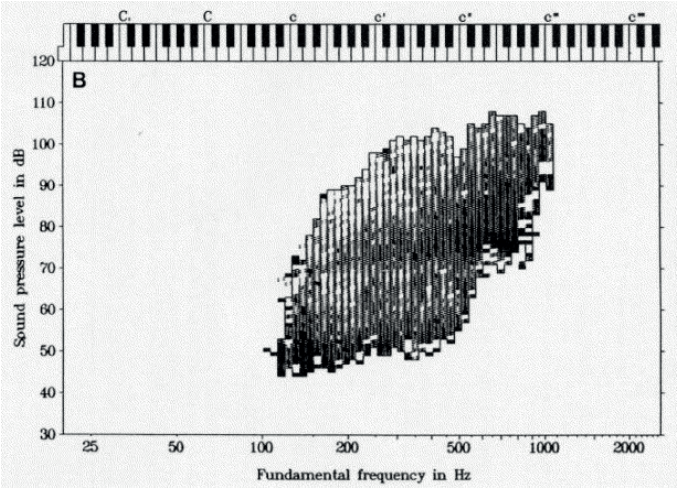

Figure 20. Example of a Voice Range Profile.

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)[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, rhythmicality, and diplophonia[31].

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[32].

Communicative suitability

The concept of communicative suitability was initially developed by Franken, for stuttering patients[33]. 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[34] *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)(**Appendix 1)**.

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[35]. 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) (**Appendix 2)**.

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[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[19,20,49-61] and 17-70% after endoscopic laser surgery[19,53-65]. These findings could lead to the conclusion that there is no clear difference in voice outcome following both treatment modalities[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*.[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[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

1. Nederlandse kankerregistratie. http://www.ikcnet.nl/
2. Sobin L., Gospodarowicz M., Wittekind C. TNM Classification of Malignant Tumours. UICC 2009 (seventh edition).
3. Streefkerk JG., Verhey ThJM. Kleine kwalenin de huisartsenpraktijk. Utrecht:Bunge;1997.
4. Ferlito A., Carbone A., DeSanto LW., Barnes L., Rinaldo A., D'Angelo L., Devaney KO. "Early" cancer of the larynx: the concept as defined by clinicians, pathologists, and biologist. Ann OtolRhinolLaryngol. 1996;105:245-250.
5. Kwaliteitsinstituut voor de Gezondheidzorg CBO, Vereniging van Integrale Kankercentra, en Nederlandse Werkgroep Hoofd-Halstumoren. RichtlijnLarynxcarcinoom 2010; versie: 3.0.
6. Principles and practice of head and neck oncology. PH. Rhys Evans, PQ. Montgomery, PJ. Gullane, M. Dunitz (Taylor & Francis). London 2003.
7. Delavan DB. A history of thyrotomy and laryngectomy. Laryngoscope. 1933;43(2):81-96.
8. Gussenbauer. Archiv. FurKlin Chirurg.1874:343.
9. Coutard H. Roentgen therapy of epitheliomasof the tonsillair region, hypopharynx, and larynx from 1920 to 1926. Amer J Roentgen. 1932;28:313-331.
10. Portmann G., Bisch X., Pardes P.. Combination of radiotherapy and surgery in the treatment of cancer of the larynx. Rev LaryngolOtolRhinol. 1968;89(1):3-27.
11. Leroux-Robert J. Indications for radical surgery, partial surgery, radiotherapy and combined surgery and radiotherapy for cancer of the larynx and hypopharynx. Ann OtolRhinolLaryngol. 1956;65(1):137-53.
12. Goldman JL., SilverstoneSM.. Combined radiation and surgical therapy for cancer of the larynx and laryngopharynx. Trans Am AcadOphtalmolOtolaryngol. 1961;65:496-507.
13. Lindberg R. Radiotherapy in the sectorial cancer of the larynx. Tumori. 1974; 60(6):497 -502.
14. Ackerstaff AH, Rasch CR, Balm AJ, *et al*. Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck. 2012;34:974-80.
15. Dziegielewski PT, O'Connell DA, Klein M, *et al*. Primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer: a population-based analysis of survival. J Otolaryngol Head Neck Surg. 2012;41(1):S56-64.
16. StrongMS., Jako GJ. Laser surgery in the larynx. Early clinical experience with continuous CO 2 laser. Ann OtolRhinolLaryngol. 1972;81(6):791-798.
17. Jones AS, Fish B, Fenton JE, Husband DJ. The treatment of early laryngeal cancers (T1–T2N0): surgery or irradiation? Head Neck. 2004;26:127-135.
18. Goor KM, Mahieu HF, Langendijk JA, Leemans CR, Verdonck-de Leeuw IM, van Agthoven M.

Cordectomy by CO2 laser or radiotherapy for small T1a glottis carcinomas: costs, local control, survival, quality of life, and voice quality. Head Neck. 2007; 29(2):128-36.

19. Mendenhall WM, Werning JW, HinermanRW, Amdur RJ, Villaret DB. Management of T1-T2 Glottic carcinomas. Cancer. 2004;100:1786-1792.

20. Krengli M, Policaro M, Manfredda I, Aluffi P, Gambaro G, Panella M, Pia F. Voice quality after treatment for T1a glottic carcinoma. ActaOncologica.2004;43:284-289.

21. Mlynarek A, Kost K, Gesser R. Radiotherapy versus surgery for early T1-T2 glottic carcinoma. J Otolaryngol. 2006;35(6):413-419.

22. Kwaliteitsinstituut voor de Gezondheidzorg CBO, Vereniging van Integrale Kankercentra, en Nederlandse Werkgroep Hoofd-Halstumoren. Richtlijn Larynxcarcinoom 2000.

23. Sakata K., Someya M., Hori M., Nakata K., Takagi M., Hareyama M. Hyperfractionatedacceleratedradiotherapyfor T1,2 glottic carcinoma. StralentherOnkol. 2008;184(7):364-369.

24. Haugen H., Johansson KA., Mercke C. Hyperfractionated-accelerated or conventionally fractionated radiotherapy for early glottic cancer. Int J RadiatOncolBiol Phys. 2002;52(1):109-119.

25. Remacle M, Eckel HE, Antonelli A, *et al*. Endoscopic cordectomy. A proposal for a classification by theWorking Committee, European Laryngological Society. Eur Arch Otorhinolaryngol. 2000;257(4):227-31.

26. Hartl DM., Ferlito A., Brasnu DF., Langendijk JA., Rinaldo A., Silver CE., Wolf GT. Evidence-based review of treatment options for patients with glottic cancer. Head Neck. 2011;33:1638-1648.

27. World Health Organization. International Classification of Functioning, Disability and Health. 2003.

28. Hirano M. Structure and vibratory behavior of the vocal folds. In: Dynamic Aspect of Speech Production. Tokyo:1977;13–27.

29. DeJonckere PH., Crevier-Buchman L., Marie JP., Moerman M., Remacle M., Woisard V.; European Research Group on the larynx. Implementation of the European Laryngological Society (ELS) basic protocol for assessing voice treatment effects. Rev LaryngolOtolRhinol (Bord). 2003;124(5):279-283.

30. Head and Neck Cancer. Treatment, Rehabilitation, and Outcomes. Ward EC., Van As-Brooks CJ. Chapter 2: Evaluating the impact of cancer of the Head and Neck. Plural Publishing.

31. Laver J, Wirz S, MacKenzie J, *et al*. A perceptual protocol for the analysis of vocal profiles. In: Work in progress. Edinburgh: 1981;14:139-155.

32. Hirano M. Psycho-acoustic evaluation of voice. In: Clinical examination of voice. New York: 1981;81-84.

33. Franken MC, van Bezooijen R, Boves L. Stuttering and communicative suitability of speech. J. Speech Lang. Hear. Res. 1997;40(1):83-94.

34. Van der Torn M, Verdonck-de Leeuw IM, Kuik DJ, Mahieu HF. Communicative suitability of voice following radiotherapy for T1a glottic carcinoma: testing the reliability of a rating instrument. Journal of Voice 2002;16:398-407.

35. Jacobson BH, Johnson A, Grywalski C, *et al*. The voice handicap index (VHI): development and validation.Am J Speech Lang Pathol. 1997;6:66-70.

36. Brandenburg JH. Laser cordectomy versus radiotherapy: an objective cost analysis. Ann Otol Rhinol Laryngol 2001;110:312-318.

37. Motta G, Esposito E, Cassiano B, *et al*. T1-T2-T3 GlotticTumors: Fifteen years experience with CO2 laser. ActaOtolaryngol (Stockh) 1997;suppl. 527:155-159.

38. Cragle SP, Brandenburg JH. Laser cordectomy or radiotherapy: cure rates, communication, and cost. Otolaryngol Head Neck Surg 1993;108:648-654.

39. Smith JC, Johnson JT, Myers EN. Management and outcome of early glottic carcinoma. Otolaryngol Head Neck Surg 2002;26:356-364.

40. Eckel HE, Thumfart W, Jungehülsing M, *et al*. Transoral laser surgery for early glottic carcinoma. Eur Arch Otorhinolaryngol 2000;257:221-226.

41. Pukander J, Kerälä J, Mäkiti A, *et al*. Endoscopic laser surgery for laryngeal cancer. Eur Arch Otorhinolaryngol 2001;258:236-239.

42. Mahieu HF, Patel P, Annyas AA, *et al*. Carbon dioxide laser vaporisation in early glottic carcinoma. Arch Otolaryngol Head Neck Surg 1994;120:383-387.

43. Rosier JF, Grégoire V, Counoy H, *et al*. Comparison of external radiotherapy, laser microsurgery and partial laryngectomy for the treatment of T1N0M0 glottic carcinomas: a retrospective evaluation. Radiotherapy and Oncology 1998;48:175-183.

44. Mohanti BK, Tandon DA, Bahadur S, *et al*. Results of definitive radiotherapy in T1 and T2 glottic carcinoma: Institute of Rotary Cancer Hospital experience (Abstr). Australas Radiol 1996;40(3):287-290.

45. Franchin G, Minatel E, Gobitti C, *et al*. Radiotherapy for patients with early-stage glottic carcinoma. Cancer 2003;98:765-772.

46. Fein DA, Mendenhall WM, Parsons JT, *et al*. T1-T2 squamous cell carcinoma of the glottic larynx treated with radiotherapy: a multivariate analysis of variables potentially influencing local control. Int J Radiat Oncol Biol Phys 1993;25(4):605-611.

47. Peretti G, Piazza C, Balzanelli C, *et al*. Vocal outcome after endoscopic cordectomies for Tis and T1 glottic carcinomas. Ann OtolRhinolLaryngol 2003;112(2):174-179.

48. Goor KM, Mahieu HF, Leemans CR, Peeters AJ, Langendijk JA, van Agthoven M. CO2-laser decortication: an efficient alternative to radiotherapy in the treatment of T1a carcinomas of the glottis. Ned TijdschrGeneeskd 2003;147(24);1177-1181.

49. Aref A, Dworkin J, Devi S, Denton L, Fontanesi J. Objective evaluation of the quality of voice following radiation therapy for T1 glottic cancer. RadiotherOncol. 1997;45(2):149-153.

50. Verdonck-de Leeuw IM, Keus RB, Hilgers FJM, *et al*. Consequences of voice impairment in daily life for patients following radiotherapy for early glottic cancer: voice quality, vocal function, and vocal performance. Int J RadiatOncolBiolPhys. 1999;44:1071-1078.

51. Verdonck-de Leeuw IM, Hilgers FJM, Keus RB, *et al*. Multidimensional assessment of voice characteristics after radiotherapy for early glottic cancer. Laryngoscope.1999;109:241-248.

52. Honocodeevar – Boltežar I, Žargi M. Voice quality after radiation therapy for early glottic cancer. Arch Otolaryngol Head Neck Surg. 2000;126:1097-1100.

53. Lehman JJ, Bless DM, Brandenburg JH. An objective assessment of voice production after radiation therapy for stage I squamous cell carcinoma of the glottis. Head Neck Surg. 1988;98:121129.

54. Elner Å, Sören F. Carbon dioxide laser as primary treatment of glottic T1s and T1a Tumours. ActaOtolaryngol (Stockh). 1988;449:135-139.

55. Hirano M, Hirade Y, Kawasaki H. Vocal function following carbon dioxide laser surgery for glottic carcinoma. Ann OtolRhinolLaryngol. 1985;232-235.

56. Rydell R, Schalen L, Fex S, Elner Å. Voice evaluation before and after laser excision vs. radiotherapy of T1a glottic carcinoma. ActaOtolaryngol (Stockh). 1995;115:560-565.

57. Wedman J, Heimdal JH, Elstad I, Olofsson J. Voice results in patients with T1a glottic cancer treated by radiotherapy or endoscopic measures. EurArch Otorhinolaryngol.2002;259:547-550.

58. McGuirtWF, Blalock D, Koufman JA, *et al*. Comparative voice results after laser resection or irradiation of T1 vocal cord carcinoma. Arch Otolaryngol Head Neck Surg.1994;120:951-955.

59. Epstein BE, Lee DJ, Kashima H, Johns ME. Stage T1 glottic carcinoma: results of radiation therapy or laser excision. Radiology. 1990;175:567-570.

60. Delsuphe KG, Zink I, Lejaegere M, Bastian RW. Voice quality after narrow-margin laser cordectomy compared with laryngeal irradiation. Otolaryngol Head Neck Surg. 1999;21:528-533.

61. Ott S, Klingholz F, Willich N, Kastenbauer E. Die bestimmung der qualität der sprechstimme nach therapie von T1- und T2-stimmlippenkarzinomen. Laryngorhinootologie. 1992;71:236-241.

62. Höfler H, Bigenzahn W. Die stimmqualität nach CO2-laserchordektomie. Laryngorhinootologie. 1986;65:655-658.

63. Koufman JA. The endoscopic management of early squamous carcinoma of the vocal cord with the carbon dioxide surgical laser: clinical experience and a proposed subclassification. Otolaryngol Head Neck Surg. 1986;95:531-537.

64. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. Otolaryngol Head Neck Surg. 1998;19:418-424.

65. McGuirt WF, Blalock D, Koufman JA, Feehs RS. Voice analysis of patients with endoscopically treated early laryngeal carcinoma. Ann OtolRhinolLaryngol.1992;101:142-146.

66. Tamura E, Kitahara S, Ogura M, Kohno N. Voice quality after laser surgery or radiotherapy for T1a glottic carcinoma. Laryngoscope 2003;113:910-914.

67. Loughran S, Calder N, MacGregor FB, Carding P, MacKenzie K. Quality of life and voice following endoscopic resection or radiotherapy for early glottic cancer. ClinOtolaryngol. 2005;30:42-47.

68. Cohen SM, Garrett CG, Dupont WD, Ossoff RH, Courey MS. Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. Ann OtolRhinol Laryngol. 2006;115:581-586.

69. Sjögren EV, Van Rossum MA, Langeveld TPM, Voerman MS, Van de Kamp VAH, Friebel MOW, Wolterbeek R, Baatenburg de Jong RJ. Voice outcome in T1a MidcordGlottic Carcinoma. Arch Otolaryngol Head Neck Surg 2008;134:965-972.

70. Fex S. and Henriksson B. Phoniatric treatment combined with radiotherapy of laryngeal cancer for the avoidance of radiation damage. Acta Otolaryng. 1970;263:128-129.

71. Zwirner P, Michaelis D, Kruse E. Akustische stimmanalysen zur dokumentation der stimmrehabilitation nach laserchirurgischer larynxkarzinomresektion. HNO. 1996;44:514-520.

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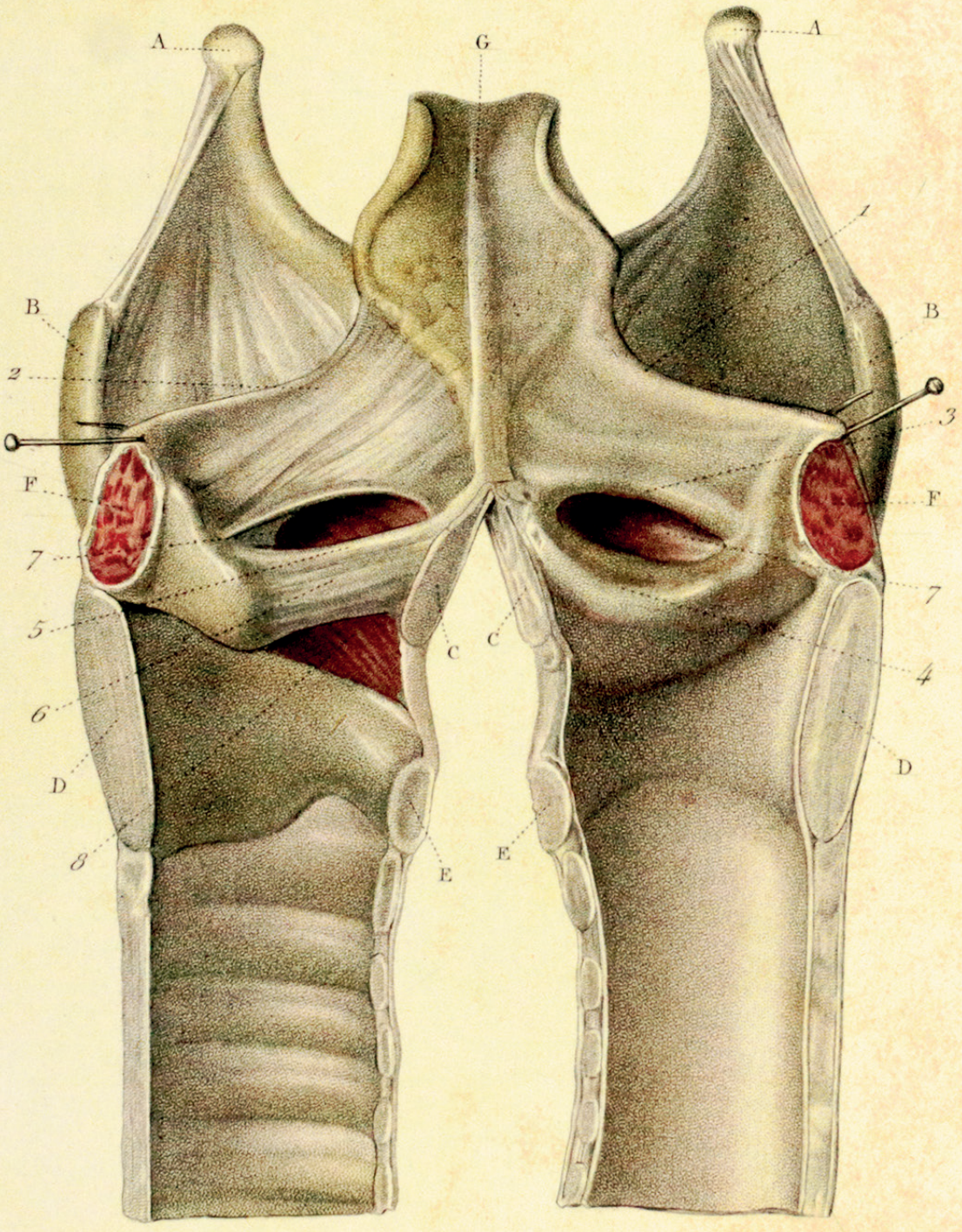
Fig. I.



CHAPTER

A SCREENING QUESTIONNAIRE FOR VOICE PROBLEMS AFTER TREATMENT OF EARLY GLOTTIC CANCER

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Int. J. Radiation Oncology Biol. Phys 2005;62(3). 700–705.

ABSTRACT

Purpose: After treatment for early glottic cancer, a considerable number of patients end up with voice problems interfering with daily life activities. A 5-item screening questionnaire was designed for detection of voice impairment. The purpose of this study is to assess psychometric properties of this questionnaire in clinical practice.

Methods and Materials: The questionnaire was completed by 110 controls without voice complaints and 177 patients after radiotherapy or laser surgery for early glottic cancer.

Results: Based on normative data of the controls, a score of 5 or less on at least 1 of the 5 questions was considered to state overall voice impairment. Reliability of the questionnaire proved to be good. Voice impairment was reported in 44% of the patients treated with radiotherapy vs. 29% of the patients treated with endoscopic laser surgery.

Conclusions: The questionnaire proved to be a reliable, valid, and feasible method to detect voice impairment in daily life. The questionnaire is easy to fill in, and interpretation is straightforward. It is useful for both radiation oncologists and otorhinolaryngologists in their follow-up of patients treated for early glottic cancer.

INTRODUCTION

Because the aim of cancer treatment is directed primarily at achieving cure and secondarily at preventing or restoring major functional deficits, the mainstream of research has not been focused on the outcome of early glottic cancer treatment. Early glottic cancer has excellent cure rates, irrespective of the treatment modality, of which radiotherapy and endoscopic laser surgery are the most widely used, and the voice outcome is often said to be "functionally" normal, usually without a definition of functionality being given. Local control rates range from 82% to 96% after endoscopic laser surgery[1–8] to 67% to 96% after radiotherapy[1, 8–12], and rates of ultimate preservation of the larynx range from 93% to 100% after initial endoscopic laser surgery[1, 4, 5, 7, 13, 14] to 85% to 97% after initial radiotherapy[1, 12, 14]. Those few studies that did define functionality unfortunately often used different definitions and described an abnormal voice outcome ranging from14% to 92% after radiotherapy[15–19] and 17% to 61% after laser surgery[20–23]. Comparative studies show either no difference between both treatment modalities or a slightly better voice quality after radiotherapy[9, 24–31].

The most important question, however, is whether deteriorated voice quality affects the ability to communicate and thereby results in limitations in social participation. Such studies on voice problems in daily life or communicative suitability of patients after their treatment for laryngeal cancer are scarce and the results contradictory[16, 17,32–36].

Smith *et al.*[32] reported that patients primarily treated for early glottic cancer either with endoscopic excision or radiotherapy were satisfied with their speech and understandability, which did not impede daily life activities. Other studies focusing more on voice than on speech revealed more voice-related problems in daily life. Verdonck-de Leeuw *et al.*[16, 17] found that only 55% of the patients treated with radiotherapy regained normal voice quality, whereas in 45% of the patients, voice quality remained abnormal with negative consequences in daily life. Van der Torn *et al.*[33] showed that communicative suit- ability of patients after radiotherapy as judged by "naïve" listeners improved but did not approach normal communicative suitability. They also found that with increasing vocal demand, the communicative suitability decreases. Stoeckli *et al.*[34] reported an increased difficulty in communication (hoarseness, trouble talking to other persons or on the telephone) for patients after both endoscopic laser surgery and radiotherapy, without significant differences between both treatment modalities. Jepsen *et al.*[35] used the Voice Handicap Index (VHI) to compare consequences of voice outcome after treatment for laryngeal cancer. They suggested greater voice impairment (mean VHI = 42.2) by patients treated for glottic laryngeal cancer than by patients treated for supraglottic laryngeal cancer (mean VHI = 27.2). Patients with combination therapy of laser surgery and radiotherapy did worse (mean VHI = 34.9) than patients treated with laser surgery alone (mean VHI =

22.5). Peeters *et al*. [36] compared voice problems in daily life as judged by the patients themselves (VHI) 2 years after radiotherapy or laser surgery for T1aN0M0 glottic carcinoma. They found a deviant VHI score in 40% of the patients treated with laser surgery vs. 58% of the patients treated with radiotherapy.

It can be concluded from these studies that, despite the generally held belief to the contrary, a considerable number of patients end up with deteriorated voice quality after treatment for early glottic cancer, with an impact on daily life function.

Not only can a deviant voice quality lead to limitations in social life, but it can also be an early sign of tumor recurrence[11,37]. A standardized easy and brief questionnaire to detect voice impairment or deterioration is therefore mandatory. In earlier studies, a 12-item questionnaire on voice problems was designed and validated: High correlations were found with perceptual voice quality evaluation by trained raters and vocal function[16,38]. Though very useful in a study setting, this 12-item questionnaire was considered too extensive for routine use in a busy clinic. Therefore, a shorter and more robust questionnaire was developed. The Dutch Cooperative Head and Neck Oncology Group[39] recommends this 5-item questionnaire for the assessment of the voice on a regular basis after treatment of glottic cancer.

The purpose of the present study is to assess psychometric properties and value of this brief questionnaire to be used in daily clinical practice, in terms of internal consistency, reliability, predictive validity, and normative data.

PATIENTS AND METHODS

Patient group

During a 1-year period, 177 patients visiting the outpatient clinic for their follow-up visit after initial radiotherapy or endoscopic laser surgery for early glottic cancer were requested to participate. All patients were treated 6–120 months before inclusion. At the time of inclusion, there were no indications of tumor recurrence or other organic laryngeal disorders. Tumor classification ranged from severe dysplasia/carcinoma in situ to squamous cell glottic carcinoma stage T1N0M0 or T2N0M0 (according to the UICC staging system[40]). An overview of patient data is given in **Table 1**.

Of the 126 patients treated with radiotherapy (9 females, 117 males), 2 (1.6%) were diagnosed with severe dysplasia/carcinoma in situ, 52 (41.3%) with T1aN0M0, 32 (25.4%) with T1bN0M0, and 40 (31.7%) with T2N0M0 glottic carcinoma. All patients were locally irradiated with the Varian CLINAC 2300, a linear 6-MV accelerator (Varian Medical Systems Inc., Palo Alto, CA, USA). The total radiation was 57.5 to 60.0 Gy in case of T1a and T1b tumors (2.5 Gy per fraction, 5 times a week), whereas T2 tumors were generally ir-

radiated with an accelerated schedule to a total dose of 70 Gy (2 Gy per fraction, 6 times a week). All T1 patients were treated with two opposing lateral fields, generally, with a standard field size of 6 x 6 cm, using 6-MV photons. In case of a T2 tumor with supraglottic extension beyond the false cords and/or subglottic extension < 1 cm, the radiation portals were extended to levels II to IV on both sides and/or the paratracheal lymph node areas, respectively. Mean posttreatment time was 46 months (range, 6–135 months). The mean age of the patients treated with radiotherapy at inclusion was 66 years (range, 39 – 80 years).

Of the 51 patients (6 females, 45 males) primarily treated by endoscopic laser surgery, 25 (49%) were diagnosed with severe dysplasia/carcinoma in situ and 23 with T1 tumors (18 T1aN0M0 [35.3%], 5 with T1bN0M0 [9.8%]), and 3 (5.9%) with T2N0M0. All patients had been selected for endoscopic laser surgery by means of videolaryngostroboscopic evaluation, using the presence of mucosal undulation as an indication for superficial tumor spread. A Sharplan-CO2-laser (with ACU-spot micromanipulator; Sharplan Laser Industries, Tel Aviv, Israel) in a super-pulse mode was used. Patients in the laser surgery group had a mean posttreatment time of 24 months (range, 6 to 127 months). The mean age of the patients treated with endoscopic laser surgery at the time of inclusion was 66 years (range, 40 – 81 years).

Table 1. Overview of patient data on treatment modality and tumor stage

	Total group N=177	Radiotherapy N=126	Endoscopic laser surgery N=51
Severe dysplasia/ Carcinoma in situ	27	2	25
T1aN0M0	70	52	18
T1bN0M0	37	32	5
T2N0M0	43	40	3

Control group

To collect normative data on the questionnaire, 110 persons without apparent voice complaints were asked to complete the questionnaire. The control group consisted of 55 males and 55 females; 85 persons were current smokers. Subjects were matched for age group of 40 to 80 years with a mean of 61 years.

Questionnaire

All 177 patients and 110 controls were asked to fill out a screening questionnaire concerning voice problems in daily life. The questionnaire is composed of 5 questions on a 10-point scale covering vocal abilities and social situations. An overview is given in **Appendix 1**.

Statistical analyses

Cronbach's alpha was calculated to determine internal consistency of the questionnaire. Spearman correlation coefficients were calculated to determine interrelations between the 5 items of the questionnaire.

Normative criterion values were set based on the 95% central range (2.5% at each end of the distribution) for each separate question of the control group.

To investigate test-retest reliability of the questionnaire, all 177 patients were asked by mail to fill in the same questionnaire again after a period of time. The mean time between the completion of the two questionnaires was 5.3 months (range, 1–10 months, median: 5 months). During this period, none of these patients underwent any intervening medical or surgical treatment. Two extra questions were attached to exclude overall health problems and recent voice problems that could cause voice changes and thereby influence the results. To evaluate each item's test-retest reliability, intraclass correlation coefficients were computed.

To test predictive validity of the questionnaire in clinical practice, the number of patients with self-reported voice impairment either treated by radiotherapy or laser surgery for early glottic cancer was determined. Voice impairment was defined by the criterion value obtained from the control group as described above. To test whether the screening questionnaire could differentiate between controls and patients, Mann-Whitney tests were carried out. Next, the ratings of the radiotherapy group and the laser group were compared to test whether a difference in voice impairment could be detected between the two treatment modalities. For this purpose, chi-square and Mann-Whitney tests were carried out.

In the patient group, Spearman correlation coefficients were calculated to determine the relation between voice impairment, age, tumor stage, and posttreatment time. In the control group, Spearman correlations were determined between score per question, gender, and current smoking habit.

RESULTS

Internal consistency and interrelations

The internal consistency of the screening questionnaire as a whole was assessed by Cronbach's alpha and seemed to be 0.88 for the control group and 0.89 for the patient group. Interrelations between the five items were assessed by Spearman correlation coefficient. Spearman correlation coefficients between the five items ranged from 0.59 to 0.73 for the patient and control group as a whole (**Table 2**). Because of the moderate Spearman

correlation coefficients, the five items on the screening questionnaire were regarded separately; a composite score was not calculated.

Table 2. Interrelations (Spearman correlation coefficients) of the five items on the questionnaire for the patient and control group as a whole

	Item 1	Item 2	Item 3	Item 4
Item 1	1.000			
Item 2	0.616	1.000		
Item 3	0.590	0.691	1.000	
Item 4	0.639	0.671	0.640	1.000
Item 5	0.601	0.727	0.699	0.688

Normative data

Based on the control data, normative data were determined. The 95% central range was assessed for each of the five questions; results are shown in **Table 3**. For each separate question, a score less than the 2.5th centile was regarded as signifying voice impairment. To facilitate the interpretation of the questionnaire in clinical practice, one criterion value valid for all five questions was determined. Based upon these 2.5th centiles from the separate questions and the 10-point grading scale commonly used in the educational system, in which 5 or less is evaluated as insufficient and 6 or more as sufficient, the criterion value for all five questions was set at the score of 5. This means that patients scoring 5 or less on at least one of the five questions were considered to have overall voice impairment.

Table 3. Results of the 95% central range for each individual question based on the control group

	2.5^{th} percentile	97.5^{th} percentile
1. Does your voice sounds deviant (e.g. breathy or rough)?	5.00	10.00
2. Do you encounter problems holding conversation due to your voice?	5.78	10.00
3. Do you encounter problems making a telephone call due to your voice?	4.78	10.00
4. Do you encounter problems shouting?	4.78	10.00
5. Do you have to strain to produce voice	6.00	10.00

Reliability of the screening questionnaire

In total, 104 respondents completed the second questionnaire (59% return rate). None of the respondents were excluded based on the two additional questions on recent voice changes. The test-retest intraclass correlation coefficients are shown in **Table 4**. Correlation coefficients were good to very good, varying from 0.67 to 0.76.

Table 4. Intraclass correlation coefficients (ICC) for the relationship between test and retest scores

	ICC
1. Does your voice sounds deviant (e.g. breathy or rough)?	0.71
2. Do you encounter problems holding conversation due to your voice?	0.67
3. Do you encounter problems making a telephone call due to your voice?	0.76
4. Do you encounter problems shouting?	0.69
5. Do you have to strain to produce voice	0.69

Predictive validity

Patient group vs. control group

Regarding overall voice impairment (score of 5 or less on at least 1 of the 5 items), 40% of the patients vs. 9% of the controls had overall voice impairment, which difference proved to be significant ($p > 0.0005$). The number of persons with voice impairment, based on each individual question (score of 5 or less) was significantly higher for the patient group when compared with the control group ($p \leq 0.001$ for all five p values). An overview is given in **Figure 1**.

Patient group

Radiotherapy vs. laser surgery

The study was not designed to compare the two treatment modalities, particularly because baseline information was not available. Regarding overall voice impairment (score of 5 or less on at least one of the five items), 44% percent of the patients treated with radiotherapy vs. 29% of the patients treated with endoscopic laser surgery had overall voice impairment. This difference between both treatment modalities was not found to be significant ($p = 0.079$). The number of patients with voice impairment on the separate questions showed no statistical differences between both treatment modalities ($0.069 \leq p \geq 0.89$ for all five p values). An overview is given in **Figure 2**.

Age, gender, current smoking habit, tumor stage, and posttreatment time

In the control group, no correlation was found between score per question, age, gender, and current smoking habit (Spearman correlation coefficients varied from -0.15 to -0.03).

For both treatment modalities, no correlations were found between overall voice impairment, age, tumor stage, and posttreatment time (Spearman correlation coefficients varied from -0.003 to 0.165).

Patients were not asked to fill in a question on smoking habit, because the relationship between the occurrence or recurrence of laryngeal cancer and smoking habit is well known to the patients, and they might be reluctant to answer truthfully such a question from

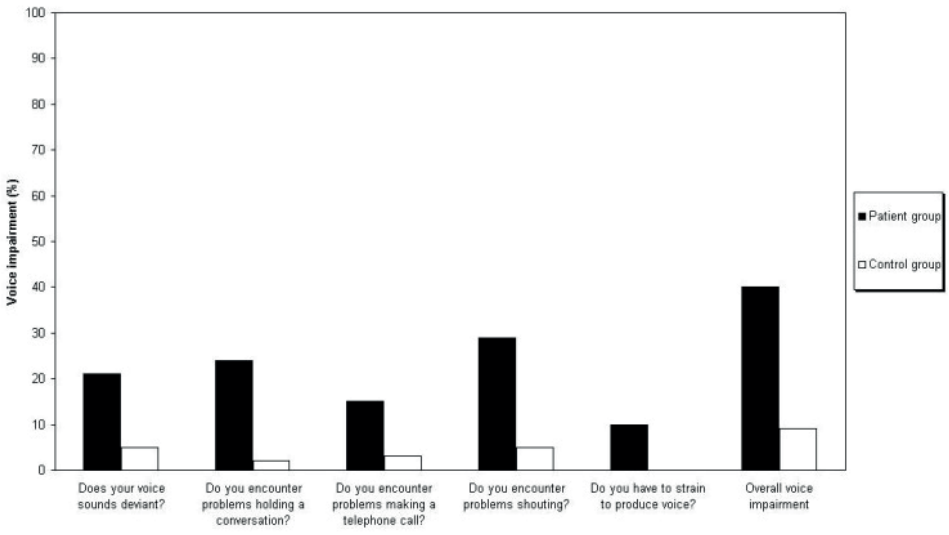


Figure 1. Voice impairment (score of 5 or less) for each individual question and overall voice impairment (score of 5 or less on at least one of the five questions) for patient vs. control group. All differences are significant.

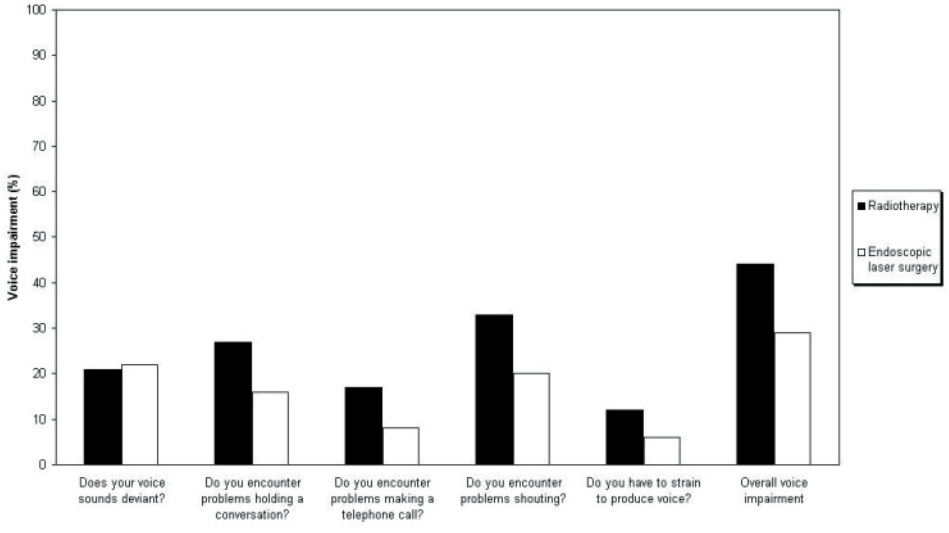


Figure. 2. Voice impairment (score of 5 or less) for each individual question and overall voice impairment (score of 5 or less on at least one of the five questions) for radiotherapy vs. endoscopic laser surgery group. None of the differences are significant.

their attending physician. Furthermore, the smoking habit proved to be without con- sequence for the questionnaire in the control group. It should be kept in mind that this questionnaire has been developed as a screening tool and not as a sophisticated tool to evaluate voice quality.

DISCUSSION

To assess health-related quality of life outcome or functional status, several specific validated instruments are available for head-and-neck cancer patients, among which the EORTC QLQ-H&N35[41] (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 35 with a 3-item speech subscale), the HNPSS[42] (Head and Neck Performance Status Scale with a 1-item speech subscale), and the UWQOL[43] (University of Washington Quality of Life Head and Neck Questionnaire with a 2-item speech sub- scale) are most widely used. More recently, the HNHSAI[44] (Head and Neck Health Status Assessment Inventory with a 14-item speech subscale) and the Voice Handicap Index have been introduced. However, for voice screening purposes, these instruments are inappropriate either because of speech/intelligibility rather than voice-related items (the UWQOL, the HNHSAI, and the HNPSS) or because of the length of the questionnaire (the EORTC QLQ-H&N module with 35 items including a 3-item speech subscale and the Voice Handicap Index with 30 items). The aim of the present study was to assess the psychometric properties of using a 5-item screening questionnaire to detect voice problems in daily life after treatment of early glottic cancer. The screening questionnaire can be used easily in clinical settings: The questions are simple, patients do not need help completing the questions, completion of the questionnaire takes less than 2 min, and interpretation of the results is straightforward. Reliability, internal consistency, and predictive validity proved to be good. Based on normative data, overall voice impairment was defined as a score of 5 or less on any of the five items, which corresponds to the common Dutch educational grading scale.

The questionnaire proved to be very useful in the differentiation between normal and abnormal voices. In this study a relatively high number of patients report voice problems in daily life after treatment for early glottic cancer: 44% of the patients treated with radiotherapy reported vocal impairment vs. 29% of the patients treated with endoscopic laser surgery. This difference is not significant.

As every experienced clinician knows, a poor voice or deterioration of voice can be the first sign of recurrence of laryngeal cancer[11, 37]. During the study period, 4 out of 5 patients with local recurrence of the tumor had impairment of the voice according to the screening questionnaire at the time or even before this recurrence was clinically apparent. Using this 5-item screening questionnaire on a routine basis can help the clinician

in the early detection of tumor recurrence. Detmar and Aaronson[45] suggested that use of such questionnaires might facilitate the doctor-patient communication; some patients hesitate to "burden" their doctor with problems, whereas other patients find it difficult to elicit relevant information. The questionnaire might in- crease efficiency of a follow-up visit: It enables the physicians to focus quickly on issues that require further attention.

The present study supports the recommendation by the Dutch Cooperative Head and Neck Oncology Group[39] to use this reliable and validated 5-item questionnaire on a regular basis after treatment of glottic cancer. If this questionnaire indicates the existence of voice impairment, a more extensive voice analysis, including acoustic measurements and laryngostroboscopy, is recommended.

CONCLUSION

The 5-item questionnaire proved to be a reliable and feasible quick method to detect voice impairment in daily life. The questionnaire is easy to fill in, and interpretation is straightforward. It is useful for both radiation oncologists and otorhinolaryngologists in their follow-up of patients treated for early glottic cancer. When used on a regular basis, the questionnaire can easily detect voice deterioration, and results of the questionnaire can help clinicians in deciding whether to perform a more extensive voice assessment protocol and medical examination.

REFERENCES

1. Brandenburg JH. Laser cordectomy versus radiotherapy: An objective cost analysis. Ann Otol Rhinol Laryngol 2001;110:312–318.
2. Motta G, Esposito E, Cassiano B, *et al*. T1-T2-T3 glottic tumors: Fifteen years experience with CO2 laser. Acta Otolaryngol (Stockh) 1997;527:155–159.
3. Cragle SP, Brandenburg JH. Laser cordectomy or radiotherapy: Cure rates, communication, and cost. Otolaryngol Head Neck Surg 1993;108:648 – 654.
4. Smith JC, Johnson JT, Myers EN. Management and outcome of early glottic carcinoma. Otolaryngol Head Neck Surg 2002;26:356 –364.
5. Eckel HE, Thumfart W, Jungehülsing M, *et al*. Transoral laser surgery for early glottic carcinoma. Eur Arch Otorhinolaryngol 2000;257:221–226.
6. Pukander J, Kerälä J, Mäkiti A, *et al*. Endoscopic laser surgery for laryngeal cancer. Eur Arch Otorhinolaryngol 2001;258:236 –239.
7. Mahieu HF, Patel P, Annyas AA, *et al*. Carbon dioxide laser vaporisation in early glottic carcinoma. Arch Otolaryngol Head Neck Surg 1994;120:383–387.
8. Rosier JF, Grégoire V, Counoy H, *et al*. Comparison of external radiotherapy, laser microsurgery and partial laryngectomy for the treatment of T1N0M0 glottic carcinomas: A retrospective evaluation. Radiother Oncol 1998;48:175–183.
9. Jones AS, Fish B, Fenton JE, *et al*. The treatment of early laryngeal cancers (T1–T2N0): Surgery or irradiation? Head Neck 2004;26:127–135.
10. Mohanti BK, Tandon DA, Bahadur S, *et al*. Results of definitive radiotherapy in T1 and T2 glottic carcinoma: Institute of Rotary Cancer Hospital experience (Abstr). Australas Radiol 1996;40:287–290.
11. Franchin G, Minatel E, Gobitti C, *et al*. Radiotherapy for patients with early-stage glottic carcinoma. Cancer 2003;98:765–772.
12. Fein DA, Mendenhall WM, Parsons JT, *et al*. T1-T2 squamous cell carcinoma of the glottic larynx treated with radio- therapy: A multivariate analysis of variables potentially influencing local control. Int J Radiat Oncol Biol Phys 1993;25:605– 611.
13. Peretti G, Piazza C, Balzanelli C, *et al*. Vocal outcome after endoscopic cordectomies for Tis and T1 glottic carcinomas. Ann Otol Rhinol Laryngol 2003;112:174 –179.
14. Goor KM, Mahieu HF, Leemans CR, Peeters AJ, Lange- ndijk JA, van Agthoven M. CO2-laser decortication: An efficient alternative to radiotherapy in the treatment of T1a carcinomas of the glottis. Ned Tijdschr Geneeskd 2003;147:1177–1181.
15. Aref A, Dworkin J, Devi S, *et al*. Objective evaluation of the quality of voice following radiation therapy for T1 glottic cancer. Radiother Oncol 1997;45:149 –153.

16. Verdonck-de Leeuw IM, Keus RB, Hilgers FJM, *et al*. Con- sequences of voice impairment in daily life for patients fol- lowing radiotherapy for early glottic cancer: Voice quality, vocal function, and vocal performance. Int J Radiat Oncol Biol Phys 1999;44:1071–1078.

17. Verdonck-de Leeuw IM, Hilgers FJM, Keus RB, *et al*. Multidimensional assessment of voice characteristics after radiotherapy for early glottic cancer. Laryngoscope 1999;109:241–248.

18. Honocodeevar-Boltežar I, Žargi M. Voice quality after radiation therapy for early glottic cancer. Arch Otolaryngol Head Neck Surg 2000;126:1097–1100.

19. Lehman JJ, Bless DM, Brandenburg JH. An objective assessment of voice production after radiation therapy for stage Isquamous cell carcinoma of the glottis. Head Neck Surg 1988;98:121–129.

20. Höfler H, Bigenzahn W. Die stimmqualität nach CO2-laser-chordektomie. Laryngol Rhinol Otol 1986;65:655– 658.

21. Koufman JA. The endoscopic management of early squamous carcinoma of the vocal cord with the carbon dioxide surgical laser: Clinical experience and a proposed subclassification. Otolaryngol Head Neck Surg 1986;95:531–537.

22. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. Otolaryngol Head Neck Surg 1998;19:418 – 424.

23. McGuirt WF, Blalock D, Koufman JA, *et al*. Voice analysis of patients with endoscopically treated early laryngeal carci- noma. Ann Otol Rhinol Laryngol 1992;101:142–146.

24. Elner Å, Sören F. Carbon dioxide laser as primary treatment of glottic T1s and T1a tumours. Acta Otolaryngol (Stockh) 1988;449:135–139.

25. Hirano M, Hirade Y, Kawasaki H. Vocal function following carbon dioxide laser surgery for glottic carcinoma. Ann Otol Rhinol Laryngol 1985;232–235.

26. Rydell R, Schalen L, Fex S, *et al*. Voice evaluation before and after laser excision vs. radiotherapy of T1a glottic carcinoma. Acta Otolaryngol (Stockh) 1995;115:560 –565.

27. Wedman J, Heimdal JH, Elstad I, *et al*. Voice results in patients with T1a glottic cancer treated by radiotherapy or endoscopic measures. Eur Arch Otorhinolaryngol 2002;259:547–550.

28. McGuirt WF, Blalock D, Koufman JA, *et al*. Imperative voice results after laser resection or irradiation of T1 vocal cord carcinoma. Arch Otolaryngol Head Neck Surg 1994;120:951–955.

29. Epstein BE, Lee DJ, Kashima H, *et al*. Stage T1 glottic carcinoma: Results of radiation therapy or laser excision. Radiology 1990;175:567–570.

30. Delsuphe KG, Zink I, Lejaegere M, *et al*. Voice quality after narrow-margin laser cordectomy compared with laryngeal ir- radiation. Otolaryngol Head Neck Surg 1999;21:528 –533.

31. Ott S, Klingholz F, Willich N, *et al*. Die bestimmung der qualität der sprechstimme nach therapie von T1- und T2- stimmlippenkarzinomen. Laryngorhinootologie 1992;71:236 –241.

32. Smith JC, Johnson JT, Cognetti DM, *et al*. Quality of life, functional outcome, and costs of early glottic cancer. Laryngoscope 2003;113:68 –76.

33. Van der Torn M, Verdonck-de Leeuw IM, Kuik DJ, *et al*. Communicative suitability of voice following radiotherapy for T1a glottic carcinoma: Testing the reliability of a rating instrument. J Voice 2002;16:398 – 407.

34. Stoeckli SJ, Guidicelli M, Schneider A, *et al*. Quality of life after treatment for early laryngeal carcinoma. Eur Arch Otorhinolaryngol 2001;258:96 –99.

35. Jepsen MC, Gurushanthaiah D, Roy N, *et al*. Voice, speech, and swallowing outcomes in laser-treated laryngeal cancer. Laryngoscope 2003;113:923–928.

36. Peeters AJGE, Van Gogh CDL, Goor KM, *et al*. Health status and voice outcome after treatment for T1a glottic carcinoma. Eur Arch Otorhinolaryngol 2004;261:534 –540.

37. Agrawal A, deSilva BW, Buckely BM, *et al*. Role of the physician versus the patient in the detection of recurrent disease following treatment for head and neck cancer. Laryngoscope 2004;114:232–235.

38. Verdonck-de Leeuw IM, Mahieu HF. Vocal aging and the impact in daily life: A longitudinal study. J Voice 2004;18:193–202.

39. Kaanders JHAM, Hordijk GJ. Carcinoma of the larynx: The Dutch national guideline for diagnostics, treatment, supportive care and rehabilitation. Radiother Oncol 2002;63:299 –307.

40. Union Internationale Contre le Cancer (UICC). Manual of clinical oncology. Berlin: Springer-Verslag; 1987.

41. Sprangers MA, Cull A, Bjordal K, *et al*. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: Guidelines for developing questionnaire modules - EORTC Study Group on Quality of Life. Qual Life Res 1993;2:287–295.

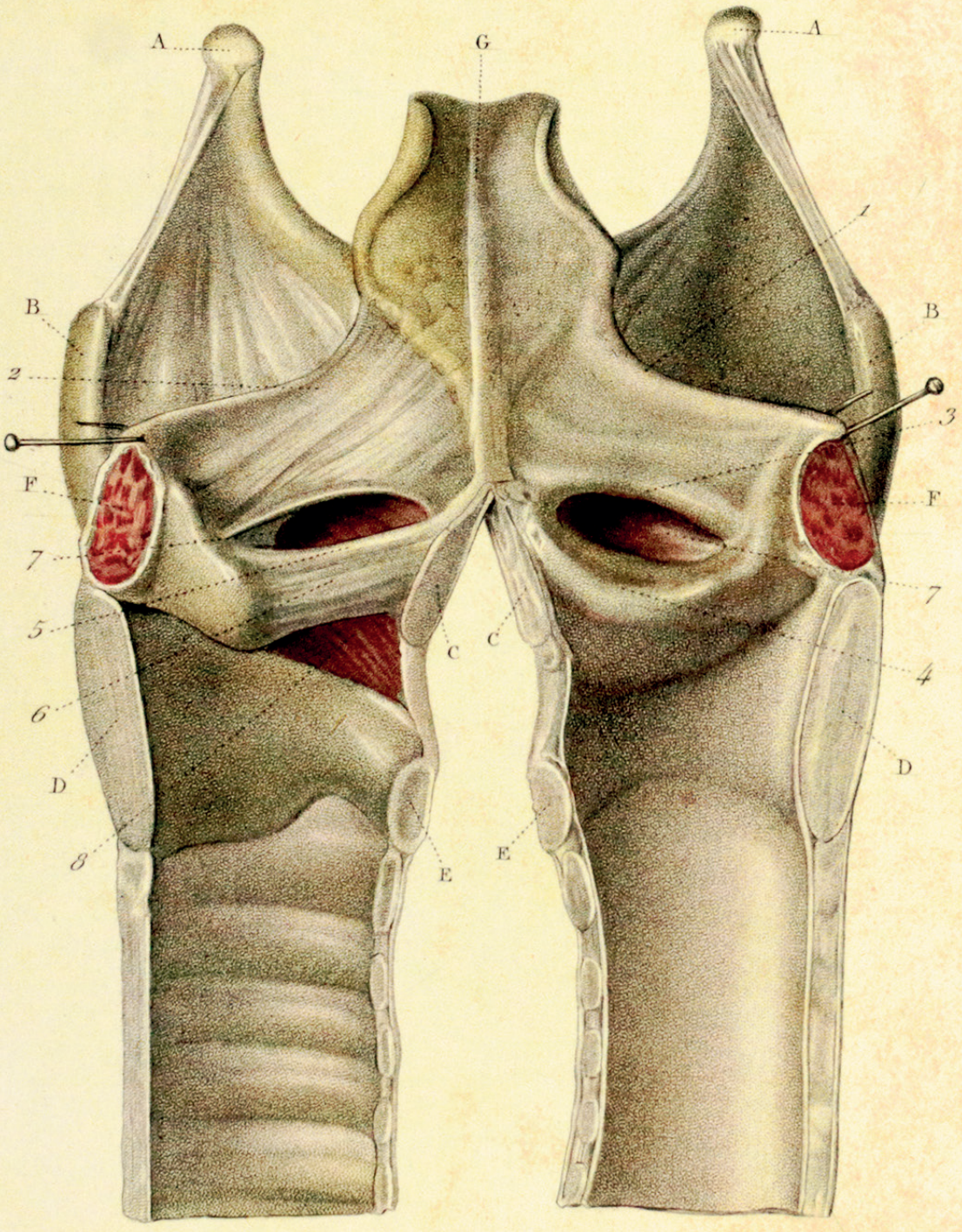
42. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Head Neck 1990;14:218 –223.

43. Hassan SJ, Weymuller EA. Assessment of quality of life in head and neck cancer patients. Head Neck 1993;15:485– 496.

44. Karnell LH, Funk GF, Tomblin JB, *et al*. Quality of life measurements of speech in the head and neck cancer patient population. Head Neck 1999;21:229 –238.

45. Detmar SB, Aaronson NK. Quality of life assessment in daily clinical oncology practice: A feasibility study. Eur J Cancer 1998;34:1181–1186.

Fig. I.



CHAPTER

HEALTH STATUS AND VOICE OUTCOME AFTER TREATMENT FOR T1A GLOTTIC CARCINOMA

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European Archives of Ototrhinolaryngology 2004;261:534-540.

ABSTRACT

Radiotherapy as well as endoscopic laser surgery as the most widely used treatment modalities for T1a glottic carcinoma cause minor morbidity and negligible mortality and result in more or less comparable, excellent cure and larynx preservation rates. Therefore, other outcome measures such as voice-related problems and health status are important factors in the choice of treatment for T1a glottic cancer. The present study focuses on voice- related problems in the daily life of patients treated by radiotherapy or endoscopic laser surgery for T1a glottic cancer. Self ratings on health status assessed by means of COOP/WONCA health status charts and voice problems evaluated with a validated voice-specific questionnaire (the Voice Handicap Index) and overall judgment on voice quality were obtained. A total of 102 patients (56 treated by endoscopic laser surgery and 46 treated by radiotherapy) with at least 1-year follow-up were included. Response scores were high: 52 (93%) patients after endoscopic laser surgery versus 40 (87%) patients after radiation therapy completed and returned the questionnaires. A high percentage of patients reported voice problems in daily life: 58% of the patients following radiotherapy and 40% of the patients following endoscopic treatment had abnormal VHI scores. The difference between both treatment modalities proved to be significant. No significant differences were found concerning health status or overall judgment of voice quality. Moderate correlations were found between total VHI score and voice quality judgment and the COOP/WONCA social activities chart. This study reveals that treatment for T1a glottic cancer often does result in voice problems in daily life, negatively influencing patients social activities. Patients selected for endoscopic laser surgery on average report fewer voice-related problems than those who underwent radiotherapy.

INTRODUCTION

In many centers the preferential treatment for early glottic carcinoma is still radiotherapy, although endoscopic laser surgery has gained in popularity since the first description in the 1970s[25]. As in any cancer, the choice of treatment depends on cure rates, treatment morbidity and mortality, organ preservation rate, quality of life, functional outcome and costs.

Cost studies reveal that objective and hidden costs (such as traveling time or work missed) for T1a glottic cancer are substantially greater in patients treated with radiotherapy than in patients treated with endoscopic laser surgery [2,3,8,17,23]. Of course, cost aspects are of influence in treatment decision strategy only if cure and laryngeal preservation rates, treatment morbidity, voice quality and health-related quality of life outcomes are comparable for both treatment modalities.

Although scarcely objectively evaluated in the literature, most authors consider both radiotherapy as well as endoscopic surgery for T1a glottic cancer to cause only minor treatment morbidity and negligible mortality. High cure rates and larynx preservation are reported in studies on radiotherapy[2,3,6,12,13,20] or endoscopic laser surgery[2,3,6,15,17,20,26] for T1 glottic carcinoma, ranging from 66–95% after radiotherapy versus 76–96% after endoscopic laser surgery; larynx preservation rates range from 89–99% after radiation versus 93–100% after endoscopic laser surgery. Despite comparable cure and larynx preservation rates and lower costs for endoscopic laser surgery, radiotherapy is often the treatment of choice because of the generally held opinion that voice quality is poor after endoscopic laser surgery. A review of the literature on studies comparing voice outcome after radiotherapy or endoscopic laser surgery for T1a glottic carcinoma, however, reveals substantial methodological and intersubject variation precluding adequate comparison **(Table 1)**. Studies either reported no significant differences in voice outcome between both treatment modalities[3,4,16,18,20] or a better voice quality after radiotherapy[5,6,21]. Although Hirano *et al*. in 1985[9] and Wedman *et al*. in 2002[27] reported a significant difference on videostroboscopic evaluation of the mucosal wave of the affected vocal fold in favor of radiotherapy, both treatment modalities were comparable in these two studies as far as conversational voice quality was concerned.

Recently, two studies[23,24] reported on the health-related quality of life of patients after radiotherapy versus endoscopic laser surgery for early glottic cancer **(Table 1)**. No significant differences were found between both treatment modalities on generic or cancer-specific questionnaires (as the UW-QOL-R or the EORTC QLQ-C30): all patients had excellent scores on overall quality of life in both studies. Contradictory results were found on domain-specific questionnaires on head and neck cancer. Smith *et al*.[23] revealed excellent scores on the PSS-HN (eating in public, how well speech could be understood and normalcy of

Table1. Overview of comparable studies on voice outcome and quality of life assessment after endoscopic surgery and radiotherapy for early glottic carcinoma. Therapy: ES endoscopic surgery, RT radiotherapy. Time schedule: m months, yrs years, n.i. no information, * significantly better voice outcome after radiotherapy.

	Therapy	*n*/stage	Moment of assessment	Voice outcome	Quality of life
Hirano, 1985 [9]	ES	17 T1a	3 m	Yes*	No
	RT	14 T1a	3 m		
Elner, 1988 [5]	ES	10 T1a	12 m	Yes*	No
	RT	15 T1a	12 m		
Epstein, 1990 [6]	ES	13 T1a	31 m	Yes*	No
	RT	42 T1a	59 m		
Ott, 1992 [18]	ES	15 T1	1 to 8 yrs	Yes	No
	RT	13 T1/T2	1 to 8 yrs		
Cragle, 1993 [3]	ES	11 T1	5 to 58 m	Yes	No
	RT	20 T1	1 to 7 yrs		
McGuirt, 1994 [16]	ES	11 T1a	>6 m	Yes	No
	RT	13 T1a	>6 m		
Rydell, 1995 [21]	ES	18 T1a	3 and 24 m	Yes*	No
	RT	18 T1a	3 and 24 m		
Rosier, 1998 [20]	ES	6 T1a	>4 yrs	Yes	No
	RT	7 T1a	>4 yrs		
Delsupehe, 1999 [4]	ES	30 T1/T2	6 and 24 m	Yes	No
	RT	12 T1/T2	6 and 24 m		
Wedman, 2002 [27]	ES	15 T1a	2 to 15 yrs	Yes*	No
	RT	9 T1a	2 to 15 yrs		
Stoeckli, 2001 [24]	ES	40 T1/T2	>4 yrs	No	No
	RT	16 T1/T2	>4 yrs		
Smith, 2003 [23]	ES	30 Tis/T1	n.i.	No	Yes
	RT	11 Tis/T1			

diet). Stoeckli *et al.*[24], however, found elevated scores for the three speech-related items on the head and neck specific EORTC QLQ-H&N35 (hoarseness and trouble talking to other persons or on the phone) for patients both after radiotherapy and after endoscopic laser surgery.

Reviewing all previously mentioned studies, one can only conclude that voice outcome following treatment of T1a glottic cancer is contradictory: head and neck-specific questionnaires show no differences (although elevated scores) on speech-related items, while voice analyses show no differences between the two treatment modalities (radiotherapy and endoscopic laser surgery) in half of the studies, but a better voice outcome after radiotherapy in the other half.

The goal of the present study is to gain more insight into voice-related problems in daily life by obtaining self ratings on overall voice quality and on a validated voice-specific questionnaire (the Voice Handicap Index) in a large cohort of patients treated by radiotherapy

or endoscopic laser surgery for T1a glottic cancer. These self-reported voice outcome results are compared with self ratings on the COOP/WONCA, a generic questionnaire on functional health, to investigate relations between specific voice outcome and overall status of functional health of patients treated for T1a glottic cancer.

SUBJECTS AND METHODS

Patients

In this retrospective study, the medical charts of 1,082 patients treated for a laryngeal carcinoma between 1992 and 2001 in the VU medical center in Amsterdam were reviewed. Inclusion criteria for the present study were: (1) T1a glottic carcinoma treated either by subepithelial or subligamental CO2-laser cordectomy[19] or radiotherapy, (2) a follow-up period of at least 12months after initial treatment, (3) primary site controlled and free of disease at time of inclusion, (4) not suffering from or recently treated for another disease interfering with vocal function or general health at the time of inclusion and (5) alive and still in the follow-up program. The inclusion criteria were met by 102 patients (56 treated by endoscopic CO2-laser surgery and 46 treated by radiotherapy). They all received an information letter, a letter requesting their consent and the questionnaires. Response scores were high: 52 (93%) patients after endoscopic CO2-laser surgery versus 40 (87%) patients after radiation therapy completed and returned the questionnaires **(Table 2)**.

The choice between radiotherapy or endoscopic laser surgery was based on pretreatment videolaryngostroboscopic evaluation of mucosal undulation on the affected vocal fold. In case of an absent mucosal undulation, indicating possible tumor infiltration in deeper layers of lamina propria or vocalis muscle, radiation therapy was the treatment of choice. Curative doses of radiation ranged from 5,000 to 7,000cGy in 20 to 35 daily fractions. In case of a present mucosal undulation, indicating superficial tumor growth, CO2-laser cordectomy was performed.

Table 2. Patient characteristics

	Inclusion	Responders	Gender	Mean age (range)
Endoscopic surgery	*n*=56	*n*=52 (93%)	♂=47 ♀= 5	66 yrs (34–87)
Radiotherapy	*n*=46	*n*=40 (87%)	♂=38 ♀= 2	64 yrs (44–83)

Quality of voice

To assess voice-related problems in daily life, the Voice Handicap Index (VHI) was used, a standardized and validated questionnaire to assess a person's level of handicap resulting from a voice disorder or voice disorder treatment[10]. The VHI has been translated into Dutch and validated. The VHI consists of an overall question on the quality of the voice (with four response levels) and 30 statements on voice-related aspects in daily life (with five response levels). Summarizing the scores on the 30 statements leads to a total VHI score ranging from 0 to 120. A higher score corresponds to a worse voice-related functional status (see **appendix 2**). Total VHI scores were collected from a control group of 16 males and 19 females (mean age 38years, range 17–72) without voice problems and judged by a trained speech pathologist to have a normal voice quality. Mean total VHI score in this control group was 2.3 (S.D. 2.7, range 0–9) with a prediction interval of 7.7. Total VHI scores of 10 or lower are therefore considered as normal.

Functional health status

Functional health as an aspect of quality of life was assessed by means of COOP/WONCA charts, which are widely used in primary health care to determine the functional health status of groups of patients with chronic diseases[28]. COOP/WONCA charts represent six dimensions: physical fitness, mental well-being, daily activities, social activities, change in health and overall health. Each chart consists of a question referring to the status over the past 2 weeks and five response levels, supported by simple drawings. In all charts, lower scores refer to better functioning, except for the chart 'change in health,' where a middle score represents no change in health, a higher score represents better and a lower score worse health. These charts were validated for many languages, including Dutch (see **appendix 3**).

Statistical analyses

Independent Mann-Whitney tests were carried out to assess the effect of treatment modality on self ratings of the VHI and the COOP/WONCA charts. Spearman correlation coefficients were calculated to determine relations between VHI and COOP/WONCA scores.

RESULTS

COOP/WONCA charts

No statistical differences concerning functional health status were found between both treatment modalities on the COOP/WONCA charts (**Table 3**).

Table 3. Percentages of patients on COOP/WONCA score categories after treatment for T1a glottic carcinoma. *ES* endoscopic surgery, *RT* radiotherapy

	% of subjects scoring				
	1	2	3	4	5
Physical fitness					
ES	15	17	39	23	6
RT	23	25	30	10	13
Mental well-being					
ES	67	17	10	6	0
RT	58	20	15	8	0
Daily activities					
ES	52	17	19	10	2
RT	48	23	21	3	5
Social activities					
ES	79	15	0	4	2
RT	73	10	8	8	3
Change in health					
ES	10	6	77	6	2
RT	8	5	83	5	0
Overall health					
ES	12	17	58	14	0
RT	10	23	53	15	0

VHI

A significant difference between treatment modalities was found for the total VHI score ($p < 0.05$) with a lower (better) score for the patients treated with endoscopic surgery (mean VHI score 12) as compared to the radiated patients (mean VHI score 18). Based on the normal VHI score of 10 or lower, 60% of the patients treated with endoscopic surgery had a normal VHI score vs. 42% of the patients treated with radiation, illustrated in **Figure 1**.

Analysis of the separate VHI statements (see **appendix 2**) reveals that patients after radiotherapy have significantly higher (worse) scores ($p<0.05$) than patients after endoscopic surgery on 5 of the 30 VHI statements. On intelligibility (F3) 39% of the patients after endoscopic surgery report problems vs. 60% of the patients after radiotherapy. After endoscopic surgery 4% of the patients mentioned that they spoke less to friends, neighbors or relatives because of their voice (F11) vs. 17% of the radiated patients. A creaky and dry voice (P13) was mentioned in 43% of the patients after endoscopic surgery vs. 70% after radiotherapy. In 49% of the endoscopically treated patients the voice deteriorated in the evening (P21) vs. 70% of the irradiated patients. The voice gave out in the middle of speaking (P26) in 18% of the patients after endoscopic surgery vs. 37% of the patients after radiotherapy.

Regarding the statement on overall voice quality, no differences between treatment modalities was found (70% of all patients report overall good voice quality).

Relations between VHI and COOP/WONCA

Spearman correlation coefficients were calculated between the total VHI score, the score on the statement on voice quality and on the COOP/WONCA charts (**Table 4**). A significant strong correlation was found between total VHI score and the statement on quality of the voice (rho = 0.67). Significant correlations were found between the total VHI score and the COOP/WONCA charts for social activities (rho = 0.27), mental well being (rho = 0.23) and overall health (rho = 0.21).

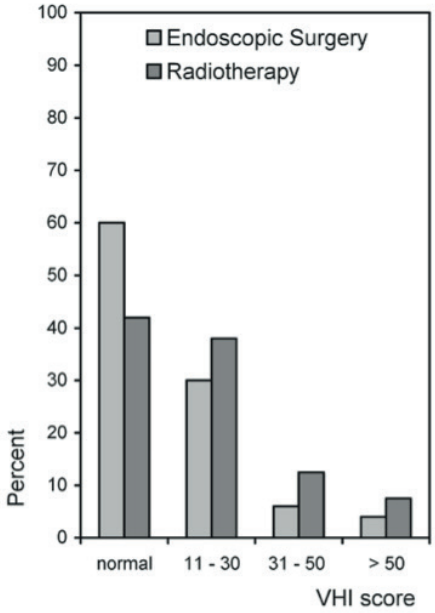


Figure 1. Distribution of VHI scores of patients treated for T1a glottic carcinoma as related to treatment modality

Table 4. Spearman's rank correlations between VHI and COOP/WONCA charts
Results are given only in the case of significant correlations, $p < 0.01$, $p < 0.05$.

	Voice quality	Overall health	Health change	Social activities	Daily activities	Mental well-being	Physical fitness
VHI	0.67	*0.21*		0.27		*0.23*	
Physical fitness		0.59		0.28	0.49		
Mental well-being		0.35		0.47	0.48		
Daily activities	*0.23*	0.54		0.49			
Social activities	0.30	0.39					
Health change		0.30					
Overall health	0.27						

DISCUSSION

In this retrospective study a large number of patients reported voice-related problems in daily life following treatment for T1a glottic cancer. There proved to be a significant difference between both treatment modalities: 58% of the patients treated with radiotherapy had an abnormal VHI score versus 40% of the patients treated with endoscopic surgery. Fung *et al*.[7] reported slightly better VHI scores (mean VHI score 13) in 13 patients treated with radiotherapy for T1a glottic cancer than were found in our radiotherapy group. Behrman *et al*.[11] assessed worse VHI scores (mean VHI score 29) in 20 patients (13 T1a and 7 T1b) after radiotherapy.

Several studies comparing voice outcome following radiotherapy or endoscopic treatment by means of response scores on a single statement on voice quality revealed no differences between treatment modalities[16,20,23,24,27]. However, voice problems in daily life comprise more than just the quality of voice. Next to static physical voice aspects (e.g., "my voice sounds creaky") and dynamic physical voice aspects (e.g., "my voice is worse in the evening" or "my voice gives out on me"), the VHI also includes aspects such as intelligibility (e.g., "people have difficulty understanding me") and avoidance of social contacts (e.g., "I speak less often with friends"). There can be little doubt that a structured, validated instrument such as the VHI gives more insight into voice-related problems in daily life of patients treated for early glottic cancer than single statement evaluation of voice quality.

Just like the studies of Stoeckli *et al*. [24] and Smith *et al*.[23] on generic quality of life questionnaires, we were unable to find differences between both treatment modalities on functional health status (COOP/WONCA). Because norm scores on the COOP/WONCA charts are lacking, data were compared with those from Kinnersley *et al*.[14], who compared the

Table 5. Median COOP/WONCA chart score after treatment for T1a glottic carcinoma compared with data from the literature (Kinnersley *et al*.[14]. *ES* endoscopic surgery, *RT* radiotherapy

	Median COOP/WONCA chart score			
	ES	RT	Patients	Controls
n	52	40	100	74
Physical fitness	3	3	3	2
Mental well-being	1	1	3	2
Daily activities	1	1	2	1
Social activities	1	1	2	1
Change in health	3	3	3	3
Overall health	3	3	3	2

COOP/WONCA charts of 100 patients who consulted primary health care, irrespective of disease or complaints, and 73 controls **(Table 5)**.

It seems that most patients after treatment for T1a glottic cancer have comparable scores with the control group from Kinnersley's study on daily activities, social activities and change in health. Concerning physical fitness and overall health, our patients following T1a laryngeal cancer treatment resemble more the patient group from Kinnersley's study. Striking high scores were found for the mental well-being of patients treated for T1a glottic cancer as compared with patients and controls of Kinnersley's study. High levels of happiness and mental well-being have been reported before in patients treated for head and neck cancer[11,22], and the high scores in our study might be explained by the fact that the patients were cured from cancer and had organ preservation, which are among the highest outcome priorities of patients with laryngeal cancer.

Examination of relations between voice-related problems in daily life and general health status revealed significant correlations between scores on the VHI and the COOP/WONCA charts for social activities, mental well-being and overall health, indicating that many patients after treatment for early glottic cancer do encounter voice problems that can lead to problems in their social life, mental well-being and overall health. However, more (prospective) studies are needed to investigate these specific side effects of treatment on general health status and quality of life.

From this study, it could be concluded that more T1a laryngeal cancer patients treated with radiotherapy encounter voice-related problems in daily life than patients who have been selected for endoscopic surgery. However, it has to be taken into consideration that patient selection was based on laryngo-stroboscopic findings with implications concerning the depth of tumor invasion (superficial tumors treated with endoscopic surgery and deeper infiltrating tumors treated with radiotherapy), and therefore this possibly also influenced the voice outcome. Nevertheless, for this selected group of patients with superficial T1a glottic carcinoma, endoscopic surgery proves to be a good alternative for radiotherapy from the voice outcome point of view.

REFERENCES

1. Behrman A, Abramson AL, Myssiorek D. A comparison of radiation-induced and presbylaryngeal dysphonia. Otolaryngol Head Neck Surg 2001;125:193–200.
2. Brandenburg JH. Laser cordotomy versus radiotherapy: an objective cost analysis. Ann Otol Rhinol Laryngol 2001;110:312–318.
3. Cragle SP, Brandenburg JH. Laser cordectomy or radiotherapy: cure rates, communication, and cost. Head Neck Surg 1993;108:648–654.
4. Delsupehe KG, Zink I, Lejaegere M, Bastian RW. Voice quality after narrow-margin laser cordectomy compared with laryngeal irradiation. Otolaryngol Head Neck Surg 1999;121:528-533.
5. Elner A, Fex S. Carbon dioxide laser as primary treatment of glottic T1S and T1a tumours. Acta Otolaryngol [Suppl] 1988;449:135–139.
6. Epstein BE, Lee DJ, Kashima H, Johns ME. Stage T1 glottic carcinoma: results of radiation therapy or laser excision. Radiology 1990;175:567–570.
7. Fung K, Yoo J, Leeper HA. Vocal function following radiation for non-laryngeal versus laryngeal tumors of the head and neck. Laryngoscope 2001;111:1920–1924.
8. Goor KM, Mahieu HF, Leemans CR, Peeters AJGE, Langendijk JA, Agthoven van M. Decorticatie met behulp van de CO2-laser, een doelmatig alternatief voor radiotherapie in de behandeling van kleine T1a carcinomen van de glottis. Ned Tijdschr Geneeskd 2003;147:1177–1181.
9. Hirano M, Hirade Y, Kawasaki H. Vocal function following carbon dioxide laser surgery for glottic carcinoma. Ann Otol Rhinol Laryngol 1985;94:232–235.
10. Jacobson G, Johnson A, Grywalski C, Sibergleit A, Jacobson G, Benninger MS, Newman CW. The Voice Handicap Index (VHI): development and validation. Am J Speech Lang Pathol 1997;6:66–70.
11. Katz MR, Irish JC, Devins GM, Rodin GM, Gullane PJ. Psychosocial adjustment in head and neck cancer: the impact of disfigurement, gender and social support. Head Neck 2003;25:103–112.
12. Kaiser TN, Sessions DG, Harvey JE. Natural history of treated T1N0 squamous carcinoma of the glottis. Ann Otol Rhinol Laryngol 1989;98:217–219.
13. Kelly MD, Hahn SS, Spaulding CA, Kersh CR, Constable WC, Cantrell RW. Definitive radiotherapy in the management of stage I and II carcinomas of the glottis. Ann Otol Rhinol Laryngol 1989;98:235–239.
14. Kinnersley P, Peters T, Stott N. Measuring functional health status in primary care using the COOP-WONCA charts: acceptability, range of scores, construct validity, reliability and sensitivity to change. Br J Gen Pract.1994; 44:545–549.

15. Koufman JA. The endoscopic management of early squamous carcinoma of the vocal cord with the carbon dioxide surgical laser: clinical experience and a proposed subclassification. Otolaryngol Head Neck Surg 1986;95:531–537.

16. McGuirt WF, Blalock D, Koufman JA, Feehs RS, Hilliard AJ, Greven K, Randall M. Comparative voice results after laser resection or irradiation of T1 vocal cord carcinoma. Arch Otolaryngol Head Neck Surg 1994;120:951–955.

17. Myers EN, Wagner RL, Johnson JT. Microlaryngoscopic surgery for T1 glottic lesions: a cost-effective option. Ann Otol Rhinol Laryngol 1994;103:28–30.

18. Ott S, Klingholz F, Willich N, Kastenbauer E. Die bestimmung der qualität der sprechstimme nach therapie von T1-und T2- stimmlippenkarzinomen. Laryngol Rhinol Otol 1992;71:236–241.

19. Remacle M, Eckel HE, Antonelli A, Brasnu D, Chevalier D, Friedrich G, Olofsson J, Rudert HH, Thumfart W, Vincentiis DM, Wustrow TPU. Endoscopic cordectomy, a proposal for a classification by the working committee, European Laryngological Society. Eur Arch Otorhinolaryngol 2000;257:227–231.

20. Rosier JF, Gregoire V, Counoy H, Octave-Prignot M, Rombaut P, Scalliet P, Vanderlinden F, Hamoir M. Comparison of external radiotherapy, laser microsurgery and partial laryngectomy for the treatment of T1N0M0 glottic carcinomas: a retrospective evaluation. Radiother Oncol 1998;48:175–183.

21. Rydell R, Schalén L, Fex S, Elner A. Voice evaluation before and after laser excision vs. radiotherapy of T1a glottis carcinoma. Acta Otolaryngol 1995;115:560–565.

22. Sharp HM, List M, MacCracken E, Tenson K, Stocking C, Siegler M. Patients' priorities among treatment effects in head and neck cancer: evaluation of a new assessment tool. Head Neck 1999;21:538–546.

23. Smith JC, Johnson JT, Cognetti DM, Landsittel DP, Gooding WE, Cano ER, Myers EN. Quality of life, functional outcome and costs of early glottic cancer. Laryngoscope 2003; 113:69–76.

24. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schmid S. Quality of life after treatment for early laryngeal carcinoma. Eur Arch Otorhinolaryngol 2001;258:96–99.

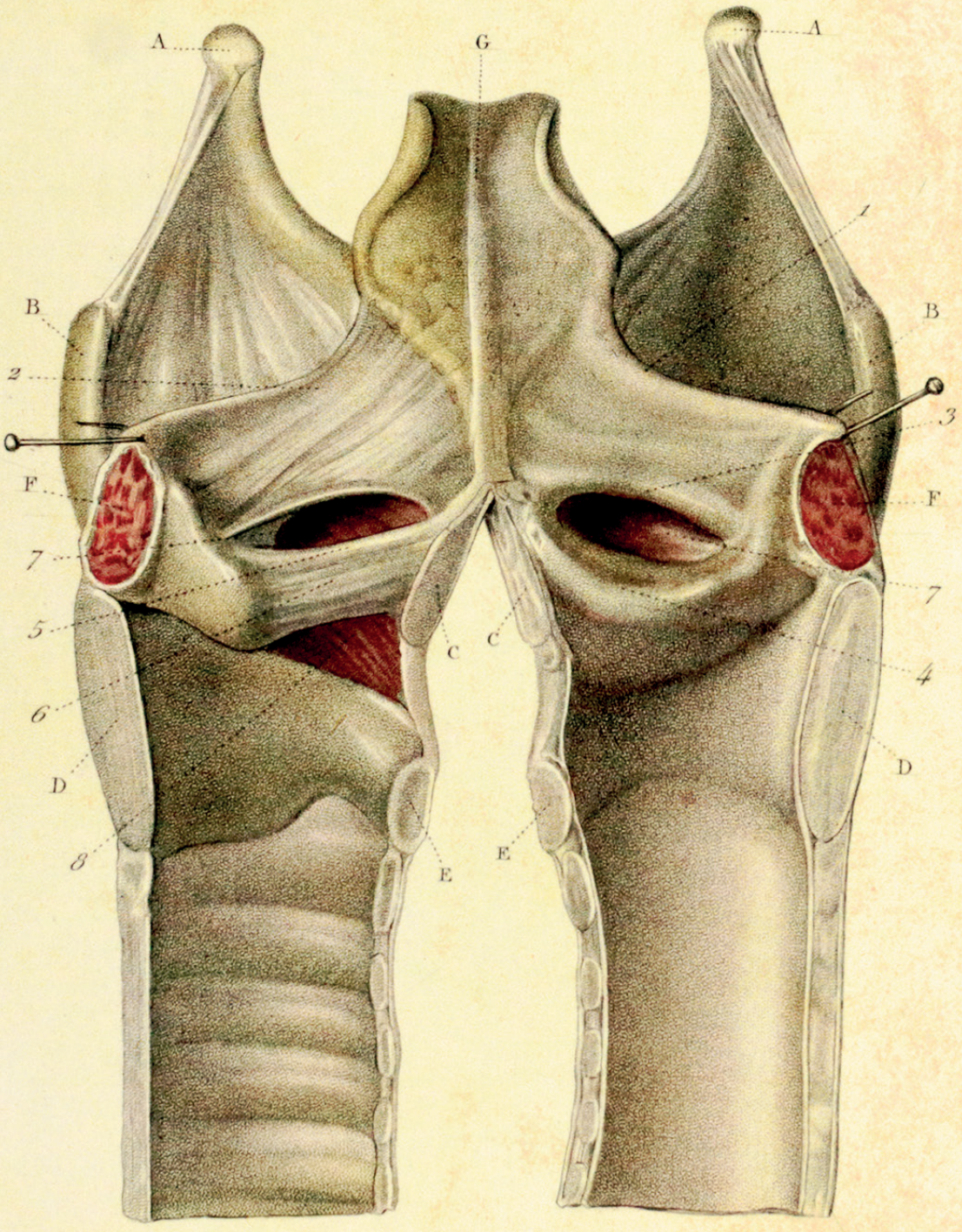
25. Strong MS, Jako GJ. Laser surgery in the larynx: early clinical experience with continuous CO2 laser. Ann Otol 1972;81:791–798.

26. Thomas JV, Olson KD, Neel HB III, DeSanto LW, Suman VJ. Recurrences after endoscopic management of early (T1) glottic carcinoma. Laryngoscope 1994;104:1099–1104.

27. Wedman J, Heimdal J-H, Elstad I, Olofsson J. Voice results in patients with T1a glottic cancer treated with radiotherapy or endoscopic measures. Eur Arch Otorhinolaryngol 2002;259:547–550.

28. Weel van C. Functional status in primary care: COOP/WONCA charts. Disabil Rehabil 1993;15:96–101.

Fig. I.



CHAPTER

VOICE IN EARLY GLOTTIC CANCER COMPARED TO BENIGN VOICE PATHOLOGY

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European Archives of Otorhinolaryngology 2007;264:1033-1038.

ABSTRACT

The purpose of this study is to compare (Dutch) Voice Handicap Index (VHIvumc) scores from a selected group of patients with voice problems after treatment for early glottic cancer with patients with benign voice disorders and subjects from the normal population. The study included a group of 35 patients with voice problems after treatment for early glottic cancer and a group of 197 patients with benign voice disorders. Furthermore, VHI scores were collected from 123 subjects randomly chosen from the normal population. VHI reliability was high with high internal consistency and test–retest stability. VHI scores of glottic cancer patients were similar to those of patients with voice problems due to benign lesions. Both groups of patients were clearly deviant from the normal population. Within the normal population, 16% appeared to have not-normal voices. Based on ROC curves a cut-off score of 15 points was defined to identify patients with voice problems in daily life. A clinical relevant difference score of 10 points was defined to be used for individual patients and of 15 points to be used in study designs with groups. Patients with voice problems after treatment for early glottic cancer encounter the same amount of problems in daily life as the other voice-impaired patients. The VHI proved to be an adequate tool for baseline and effectiveness measurement of voice.

INTRODUCTION

Voice impairment in patients after treatment for early glottic cancer has been reported in several studies, ranging from 14 to 92% of the patients[1,6,9,16,24,25]. Furthermore, several studies on the influence of voice problems on quality of life revealed that in 27 up to 58% of the patients experienced difficulties in communication abilities leading to a disrupted social life[3,8,12,17,19-22,25]. To enable quick screening on voice problems, a short 5-item voice-screening questionnaire was developed and validated, which proved to be feasible in clinical practice[22]. A more detailed multidimensional voice analysis protocol is however recommended for monitoring voice intervention and for research purposes[24], including a structured questionnaire such as the Voice Handicap Index (VHI). The VHI is a validated 30-item questionnaire measuring psychosocial handicapping effects of voice disorders[7] and is used in several studies on patients after treatment for early glottic cancer with mean VHI scores ranging from 12 to 34 points[3,8,12,19]. Most of these studies include patients with and without deviant voice quality and mean VHI data are therefore not informative on the amount of problems that patients with voice impairment after oncological treatment encounter in daily life. In a study on 23 patients with voice problems after oncological treatment, Van Gogh *et al*.[23] reported a mean VHI score of 35. However, interpretation of how cancer patients cope with voice problems compared to patients with voice problems due to benign laryngeal lesions and compared with the normal population is difficult because of some underexposed psychometric characteristics of the VHI: data from the normal population are limited, no clear clinical cut-off score is available, and information on clinical relevant difference scores is scarce.

The purpose of this study is to compare voice problems of patients after treatment for early glottic cancer with voice problems as reported by patients with benign voice disorders and subjects from the normal population. The study will also provide psychometric information of the VHI regarding internal consistency, reliability, normative data and a clinical cut-off score, and clinical relevant difference scores for use in individual patients and group study designs.

MATERIALS AND METHODS

Patients

The patient sample consisted of 232 subjects: 35 patients with voice problems after treatment for early glottic cancer and 197 patients with voice problems due to benign voice disorders.

Patients after treatment for early glottic cancer (carcinoma in situ, T1 and T2 tumors) were selected based on a validated voice-screening questionnaire; having a voice problem was defined as a score of 5 or higher (on a 10-point scale) on one of the 5 voice items[22]. Of these 35 patients, 33 were males, 2 females; the median age was 62 years (range: 41–81); mean post-oncological treatment time was 32 months (range: 6–135). Treatment included radiotherapy (n = 24) or endoscopic laser surgery (n = 11); mean VHI scores regarding treatment modality were comparable (37 vs. 36 points).

Patients with voice problems due to benign voice disorders were randomly selected from the patient population at our voice clinic. This cohort of 197 patients included 44 patients with vocal fold paresis, 84 with structural lesions (polyps, nodules, scarring, granuloma), 10 patients with Reincke' oedema, 55 patients with laryngitis, and 5 patients with laryngeal trauma. Of these 197 patients, 82 were males and 115 females; median age was 46 years (range 18–90).

Controls

The group of 123 randomly selected controls from the normal population (employees from the hospital and (acquaintances of) relatives and neighbors of the researchers) consisted of 54 males and 58 females (gender was not indicated by 11 subjects); median age was 55 years (range 23–87).

Voice Handicap Index

The VHI is a validated questionnaire measuring psychosocial handicapping effects of voice disorders and was translated and validated in Dutch. The VHI consists of 30 statements on voice-related aspects in daily life (with 5 response levels, scored 0 to 4). Summarizing the scores on the 30 statements leads to a total VHI score, ranging from 0 to 120. A higher score corresponds to a worse voice-related functional status. Furthermore, the VHI includes an overall question on the quality of the voice with four response levels ranging from 0 (good), 1 (reasonable), 2 (moderate), 3 (poor)(**Appendix 2)**. All VHI questionnaires were collected at baseline (i.e. before logopedic, surgical or medical voice treatment).

To assess test–retest reliability, a subset of 30 patients (11 cancer, 13 structural lesion, 2 Reincke's oedema, 2 laryngitis, and 2 pareses) Filled out the VHI twice, with a mean interval period of 3.5 months (range 1–6 months) without any voice intervention.

Statistical analyses

Because of the skewed distribution of the VHI scores of the control group (the patient group showed normal distribution), independent Mann–Whitney tests (U test) and Kruskal–Wallis analysis-of-variance-by-ranks tests (H test) were used with a two-sided probability level of ≤ 0.05 to compare subject groups and to assess the association of VHI scores with age, gender, and self-reported voice quality.

The relations between VHI scores and case of voice impairment was evaluated with Receiver Operating Characteristics (ROC) analyses, using the area under the curve (AUC) as a summary measure of the overall discriminative ability of the VHI. In addition to ROC analyses, the sensitivity and specificity were calculated at various cut-off scores.

Internal consistency of the VHI was assessed by Cronbach's alpha. Test–retest stability was determined by Spearman's correlation coefficient between the first and the second (repeated) ratings. The clinical relevant difference score to be used in individual patients was defined as the maximum deterioration or improvement between test and retest scores. The clinically relevant difference score to be used in group study designs was defined based on an effect size (ES) of 0.80, being defined as the difference between the experimental group mean minus the control group mean divided by the standard deviation of the control group.

RESULTS

Reliability

Internal consistency of the VHI proved to be good with Cronbach's alpha ranging from 0.87 (123 subjects from the normal population), 0.90 (35 glottic cancer patients), to 0.92 (196 voice-impaired patients), and 0.96 for the total group. Test–retest scores of the 30 patients who filled in the VHI twice over a mean period of 3.5 months (range 1–6 months) attested high test-retest stability with Spearman's rho of 0.95 ($p < 0.01$).

Voice-impaired patients and the normal population

Within the normal population 16% subjects judged their own voices as not good (score > 0 on the overall question on the quality of the voice) versus 93% of the patients with benign voice disorders and 94% of the cancer patients.

Voice handicap index scores of glottic cancer patients were similar to those of patients with voice problems due to benign lesions ($p = 0.64$), but clearly deviant from the normal population ($p < 0.01$) as were the scores of the total group of patients with benign voice disorders ($p < 0.01$). An overview is given in **Figure 1**. Because of this similarity between voice patient groups, further analyses were carried out on the total group of voice-impaired patients (n = 232).

Sensitivity and specificity of the VHI in detecting voice-impaired patients using a range of cut-off points is shown in **Table 1**. The AUC was 0.98 (95% CI: 0.97–0.99) indicating good overall discriminative ability of the VHI. **Table 2** shows that sensitivity and specificity is good with a cut-off point between 13 and 17. A cut-off point of 15 (or higher) on the VHI scale is proposed to identify patients with voice problems in daily life, because of a good degree of sensitivity and a sound (16% of the normal population judged their own voices as not-good) degree of specificity.

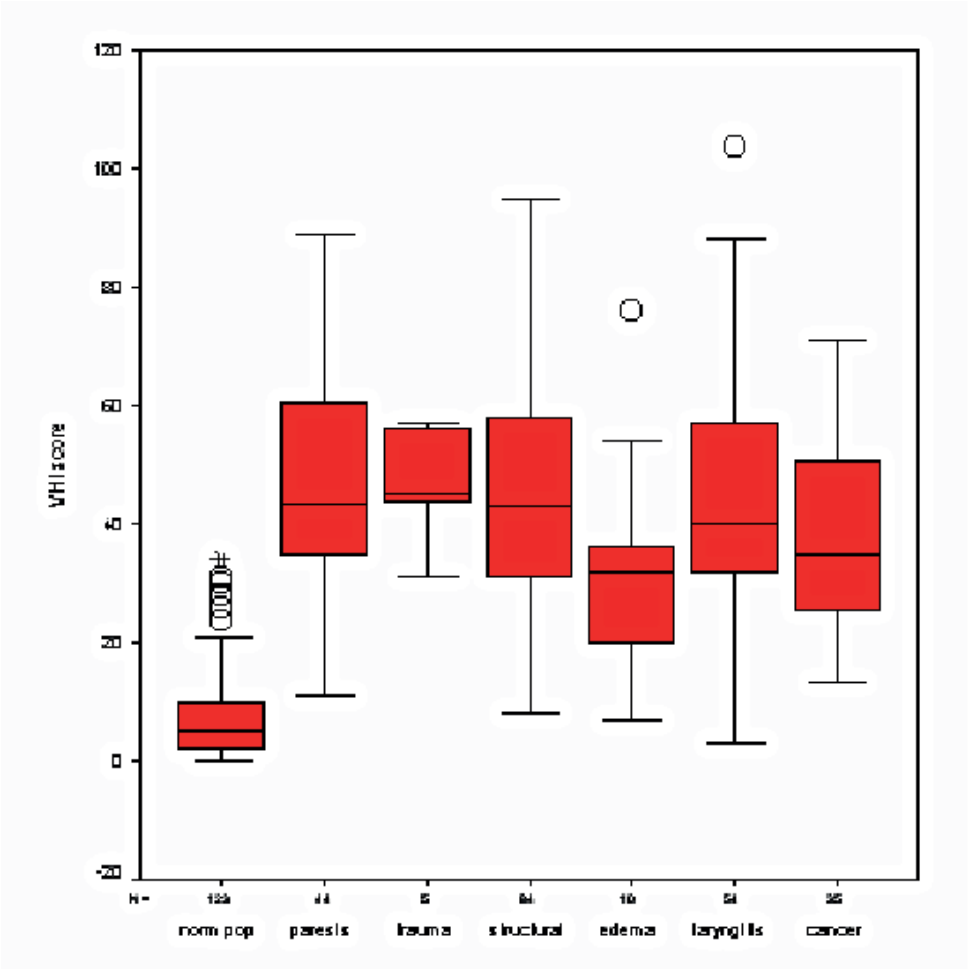

Figure 1. Boxplots presenting Voice Handicap Index scores for various subjects groups: normal population, patients with vocal fold paresis, larynx traumata, structural vocal fold lesions, Reincke's oedema, laryngitis, and patients with voice problems after treatment for early glottic cancer.

Table 1. Overview of various Voice Handicap Index cut-off points regarding sensitivity and specificity.

Cut-off point	Sensitivity (%)	Specificity (%)
12	98	79
13	97	82
14	97	84
15	**97**	**86**
16	96	88
17	95	92
18	94	92
19	92	93
20	89	94

In bold, the proposed cut-off point of 15 points or lower, which combines good Positive Predictive Value with high sensitivity and sound specificity.

Table 2. Overview of various Voice Handicap Index difference scores regarding effect size (with standard deviation of 19.40 as found in the total group of voice patients).

Difference score	Effect size
10	.51
11	.56
12	.62
13	.67
14	.72
15	**.77**
16	.82
17	.88
18	.93

In bold, the proposed clinical relevant difference score of 15 points or more to be used in group study designs.

Age, gender, and voice quality

No association between the VHI scores with gender was found for the normal population ($p = 0.86$) or for the voice-impaired patients ($p = 0.59$).

Regarding age, no clear associations were present either in the normal population ($r = 0.03$, $p = 0.97$) or the voice-impaired patients ($r = 0.01$, $p = 0.99$).

Self-ratings of voice quality appeared to be clearly related to VHI scores with Spearman's

rho ranging from 0.32 for the normal population to 0.48 for the voice-impaired patients ($p < 0.001$).

Difference scores for individuals

The difference score between the first and second rating appeared not to be dependent (Spearman's r = -0.005, p = 0.98) on the height of the VHI score (**Figure 2**). Individual difference scores between the first and second ratings remained within ten points, ranging from -9 to +10 points. Therefore a 10-point shift can be defined as a clinical relevant difference score to be used for single individual patients.

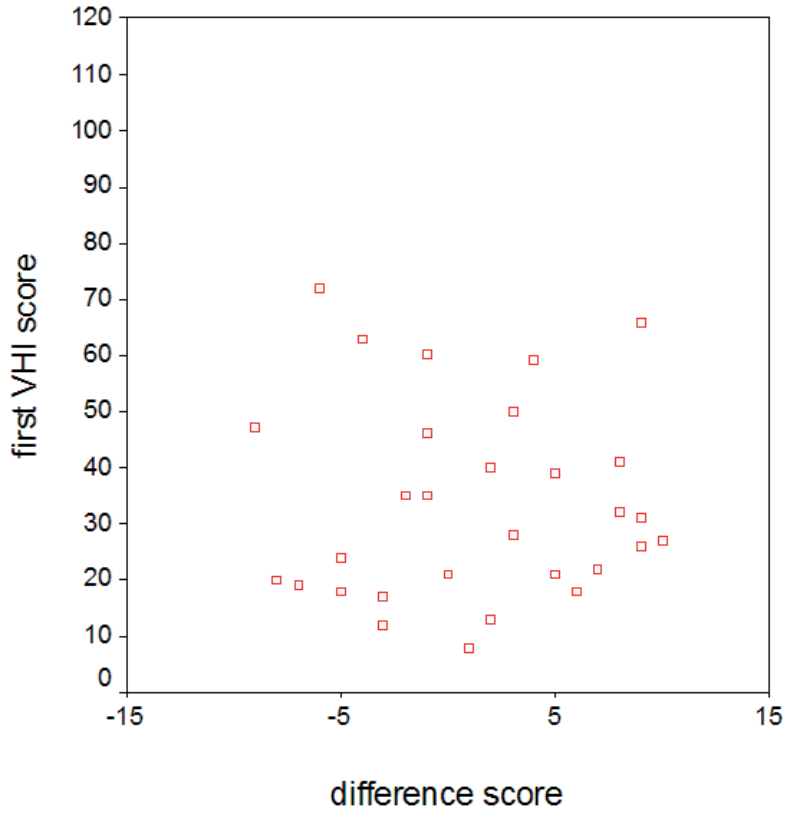

Figure 2. Scatter plot showing the (absent) relation between the first VHI score and the difference score between the first and second repeated VHI score as reported by 30 patients (Spearman's r=-.005).

Difference scores for study designs

To define a relevant difference score for study designs with groups, determination of the effect size (ES) was used. ES above 0.80 represents a large statistical and clinical difference. From this study, standard deviations of the groups of voice-impaired patients at baseline ranged from 10.60 (trauma), 15.98 (early glottic cancer), 18.43 (paresis), 19.78 (structural lesions), to 20.50 (oedema and laryngitis); the standard deviation of the total group of voice-impaired patients (n = 232) was 19.40. **Table 2** represents an overview of effect sizes regarding various difference scores with a standard deviation of 19.40 as representative for the total group of voice-impaired patients. The results show that a difference score of 15 points or more is clinically relevant in comparing groups of patients.

DISCUSSION

The results of this study demonstrated a significant difference in mean VHI scores between patients with either benign voice pathology or voice pathology following treatment for glottic malignancy as compared to the normal population, which is in concordance with various previous studies. These studies, all about benign organic and/or functional voice disorders reported mean VHI scores varying from 11 to 47 which were found to differ significantly from controls with normal voices[4,5,11-13]. Nawka[11] was the first to report a significant difference between 9 patients with voice problems due to a malignant tumor (mean VHI score 34 points) and 16 normal control subjects (mean VHI score 7 points); moreover they also did not find a difference in VHI score between various diagnosis groups (benign organic or functional voice disorders (n = 159), neurogenic voice disorders (n = 32) or malignant voice disorders (n = 9)). From our results and the results as reported by Nawka *et al*., it is clear that voice problems in daily life of cancer patients are similar to those of patients with benign voice impairment. One could find this result remarkable because it might be expected that patients being cured of a malignancy experience the inherent voice impairment in a less negative way than patients cured of a benignancy. The secondary aim of this study was to assess some underexposed psychometric characteristics of the VHI. Internal consistency proved to be good, as was test–retest stability. Regarding identification of voice-impaired patients, several authors used controls (subjects from the normal population without voice problems) in their randomised controlled studies on VHI change and reported mean **"**normal**"** values varying from 2.3 to 10.5 points but neither of them made a reliable effort to define a cut-off point[4,5,11-13]. The present study revealed a cut-off point of 15 to identify patients with voice problems in daily life.

Regarding clinical relevant difference scores, we found a difference score of 10 points to be useful for individuals in clinical practice and 15 points to be useful in study group designs. Jacobson *et al*. reported a shift of 18 points as a valuable difference score to measure ef-

ficacy of specific voice treatment techniques, but no clear analysis description was given[7]. Another non-statistical approach to define a clinically relevant difference score to be used in group design studies is to line up published studies on the efficacy of voice treatment and assess difference score appearing to be significant or non-significant. Four studies on the efficacy of voice therapy in patients with several benign voice pathologies or voice pathologies following treatment for glottic malignancy, showed significant improvement of the mean VHI with a range of 12 to 18 points[10,14,15,23]. On the contrary, Speyer[18] reported a non-significant median improvement of 6 points after voice therapy in patients with a diversity of chronic benign voice disorders. Other studies on the effect of several medical treatment modalities for different benign voice disorders show a mean VHI improvement ranging from 13 to 46 points[2,13,26]. All these studies on the efficacy of voice intervention on various voice patient groups reveal that a statistical difference score is at least 12 points. A meta-analysis could provide further information but it seems too early to perform such as study because of the limited number of studies on efficacy of voice treatment at this moment. In the mean time, we propose a difference score of 15 points signifying a statistical and clinical high effect size.

The proposed cut-off point and the clinical difference scores in this study are not meant to be conclusive, mainly because of the Dutch origin of the data, which may have influenced the results. Currently, an European VHI Study Group is working on comparison of various translations of the VHI to assess equivalence. The first preliminary results reveal that there are only minor differences between the included versions, but further data exploring is ongoing.

CONCLUSION

Patients with voice problems after treatment for early glottic cancer encounter the same amount of problems in daily life as other voice-impaired patients and therefore require the same attention and care for this sequel to their initial cancer treatment. Furthermore, the VHI proved to be an adequate tool for baseline and effectiveness measurement of voice.

REFERENCES

1. Aref A, Dworkin J, Devi S, Denton L, Fontanesi J. Objective evaluation of the quality of voice following radiation therapy for T1 glottic cancer. Radiother Onco 1997;45(2):149–153.
2. Benninger MS, Gardner G, Grywalski C. Outcomes of botulinum toxin treatment for patients with spasmodic dysphonia. Arch Otolaryngol Head Neck Surg 2001;127:1083–1085.
3. Fung K, Yoo J, Leeper HA, Hawkins S, Heeneman H, Doyle PC, Venkatesan VM. Vocal function following radiation for non-laryngeal versus laryngeal tumors of the head and neck. Laryngoscope 2001;111:1920–1924.
4. Guimares I, Abberton E. An investigation of the voice handicap index with speakers of Portuguese: preliminary data. J Voice 2004;18(1):71-82.
5. Günther S, Rasch T, Klotz M, Hoppe U, Eysholdt U, Rosanowski F. Voice related quality of life and voice handicap index in dysphonic patients. A comparison (German) HNO 2005;53(10):895–904.
6. Hocevar -Bolteqar I, Largi M. Voice quality after radiation therapy for early glottic cancer. Arch OtolaryngolHead Neck Surg 2000;126:1097–1100.
7. Jacobson BH, Johnson A, Grywalski C, Sibergleit A, Jacobson G, Benninger MS, Newman CW. The voice handicap index (VHI): development and validation. Am J Speech Lang Pathol 1997; 6:66–70.
8. Jepsen MC, Gurushanthaiah D, Roy N, Smith ME, Gray SD, Davis RK. Voice, speech, and swallowing outcomes in laser-treated laryngeal cancer. Laryngoscope 2003;113:923–928.
9. Lehman JJ, Bless DM, Brandenburg JH. An objective assessment of voice production after radiation therapy for stage I squamous cell carcinoma of the glottis. Head Neck Surg 1988;98:121–129.
10. Machulla R, Hacki T, Hoppe U, Rosanowski F. Voice Handicap Index in rehabilitation. HNO 2006;54(1):52-8.
11. Nawka T, Wiesmann U, Gonnermann U. Validierung des voice handicap index in der deutschen fassung. HNO 2003;51:921–929.
12. Peeters AJGE, Van Gogh CDL, Goor KM, Verdonck-de Leeuw IM, Langendijk JA, Mahieu HF. Health status and voice outcome after treatment for T1a glottic carcinoma. Eur Arch Otorhinolaryngol 2004;261:534–540.
13. Rosen CA, Lee AS, Osborne J, Zullo T, Murry T. Development and validation of the voice handicap index-10. Laryngoscope 2004;114(9):1549–1556.
14. Rosen CA, Murry T, Zinn A, Zullo T, Sonbolian M. Voice handicap index change following treatment of voice disorders. J Voice 2000;14:619–623.

15. Roy N, Gray SD, Simon M, Dove H, Corbin-Lewis K, Stemple JC. An evaluation of the effects of two treatment approaches for teachers with voice disorders: a prospective randomized clinical trial. J Speech Lang Hear Res 2001;44:286–296.

16. Rydell R, Schalen L, Fex S, Elner Å. Voice evaluation before and after laser excision vs. radiotherapy of T1a glottic carcinoma. Acta Otolaryngol (Stockh) 1995;115:560–565.

17. Smith JC, Johnson JT, Cognetti DM, Landsittel DP, Gooding WE, Cano ER, Myers EN. Quality of life, functional outcome, and costs of early glottic cancer. Laryngoscope 2003;113:68–76.

18. Speyer R, Wieneke GH, Dejonckere PH. Self-assessment of voice therapy for chronic dysphonia. Clin Otolaryngol 2004;29(1):66–74.

19. Stewart MG, Chen AY, Stach CB. Outcomes analysis of voice and quality of life in patients with laryngeal cancer. Arch Otolaryngol Head Neck Surg 1998;124:143–148.

20. Stoeckli SJ, Guidicelli M,Schneider A, Huber A, Schmid S. Quality of life after treatment for early laryngeal carcinoma. Eur Arch Otorhinolaryngol 2001;258:96–99.

21. Van der Torn M, Verdonck-de Leeuw IM, Kuik DJ, Mahieu HF. Communicative suitability of voice following radiotherapy for T1a glottic carcinoma: testing the reliability of a rating instrument. J Voice 2002;16:398–407.

22. Van Gogh CDL, Verdonck-de Leeuw IM, Boon AB, Langendijk JA, Kuik DJ, Mahieu HF. A screening questionnaire for voice problems after treatment for early glottic cancer. Int J Radiat Oncol Biol Phys 2005;62:700–705.

23. Van Gogh C, Verdonck-de Leeuw I, Boon-Kamma A, Rinkel RN, de Bruin MD, Langendijk JA, Kuik DJ, Mahieu HF. Efficacy of voice therapy in patients after treatment of early glottic cancer. Cancer 2006;106(1):95–105.

24. Verdonck-de Leeuw IM, Hilgers FJM, Keus RB, Koopmans-van Beinum FJ, Greven AJ, de Jong JM, Vreeburg G, Bartelink H. Multidimensional assessment of voice characteristics after radiotherapy for early glottic cancer. Laryngoscope 1999;109:241–248.

25. Verdonck-de Leeuw IM, Keus RB, Hilgers FJM, Koopmans-van Beinum FJ, Greven AJ, de Jong JM, Vreeburg G, Bartelink H. Consequences of voice impairment in daily life for patients following radiotherapy for early glottic cancer: voice quality, vocal function, and vocal performance. Int J Radiat Oncol Biol Phys 1999;44:1071-1078.

26. Wingate JM, Ruddy B, Lundy DS, Lehman J, Casiano R, Collins SP, Woodson GE, Sapienza C. Voice handicap index results for older patients with adductor spasmodic dysphonia. J Voice 2005;19(1):124-131.

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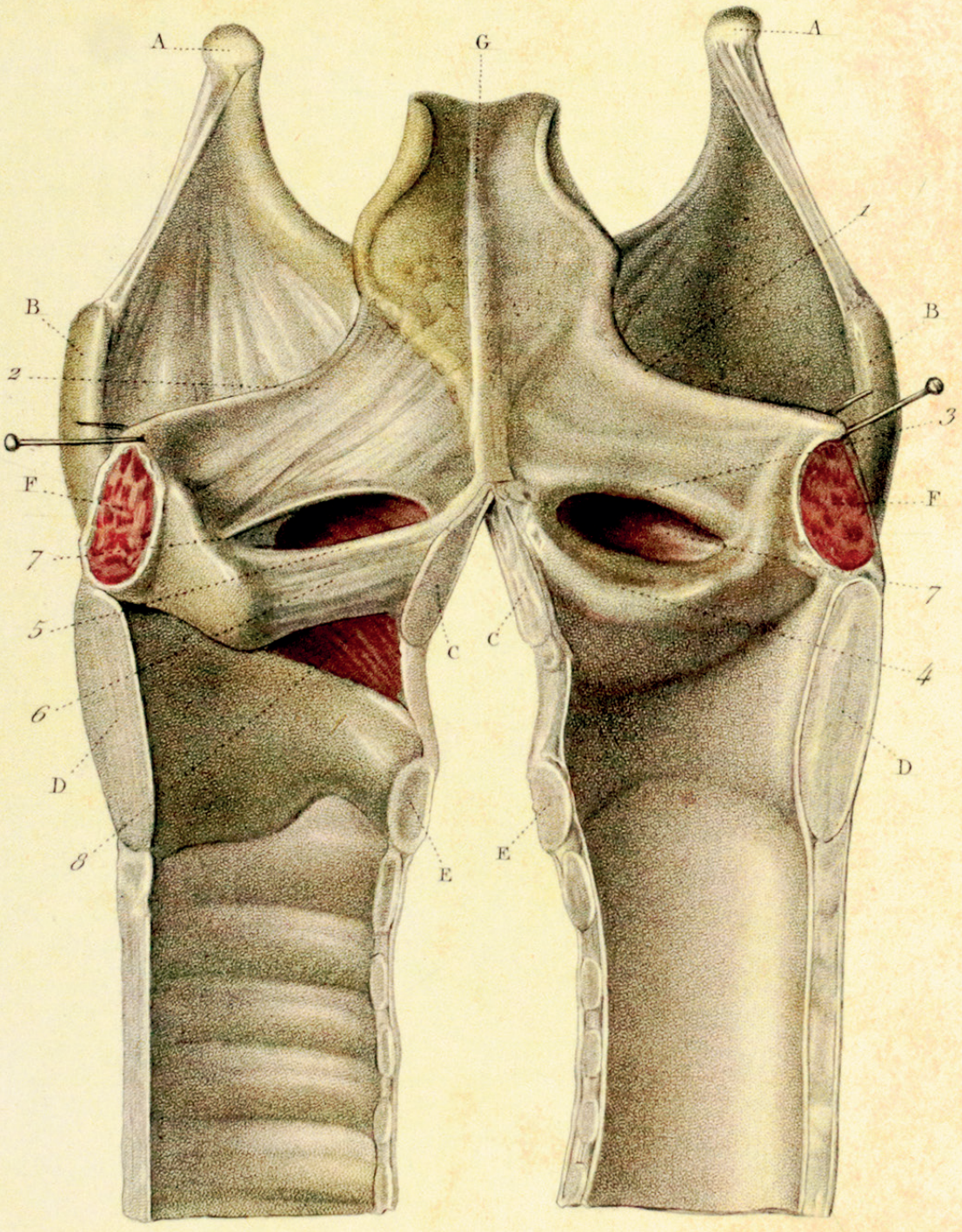
Fig. I.



CHAPTER

PROSPECTIVE EVALUATION OF VOICE OUTCOME DURING THE FIRST TWO YEARS IN MALE PATIENTS TREATED BY RADIOTHERAPY OR LASER SURGERY FOR T1A GLOTTIC CARCINOMA

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European Archives of Otorhinolaryngology 2012;269(6):1647-52.

ABSTRACT

In this prospective cohort study, we assessed voice outcome in patients before and up to 2 years after treatment for early glottic cancer either by radiotherapy or by laser surgery; 106 male patients, treated for T1aN0M0 glottic cancer either by endoscopic laser surgery (n = 67) or by radiotherapy (n = 39), participated in the study. Patients' voices were recorded and analyzed pre-treatment and 3, 6, 12 and 24 months post-treatment at their routine visit at the outpatient clinic. Average fundamental frequency (F0), percent jitter, percent shimmer and normalized noise energy (NNE) were determined. After 2 years, local control rate was 95% in the radiotherapy group and 97% in the laser surgery group. Larynx preservation rate was 95% after radiotherapy and 100% after laser surgery. Voice outcome recovers more quickly in patients treated with laser surgery in comparison to radiotherapy: 3 months after laser surgery there is no longer a difference with regard to normal voices except for the fundamental frequency, which remains higher pitched, even in the longer term. For patients treated with radiotherapy it takes longer for jitter, shimmer and NNE to become normal, where jitter remains significantly different from normal voices even after 2 years. According to these results, we believe that laser surgery is the first treatment of choice in the treatment of selected cases of T1a glottic carcinomas with good functional and oncological results.

INTRODUCTION

Until about a decade ago, radiotherapy was the first choice of treatment for patients with early glottic cancer. Currently, it has been widely accepted that for these early stages endoscopic laser surgery can be a safe and valid alternative for radiotherapy. Cure rates are the major criterion in determining the treatment of choice. Since both treatment modalities provide good local control of approximately 90%, other criteria become important in determining the first treatment of choice[1-6].

One of these other criteria is the consideration that radiotherapy can be delivered only once at the same target area, while laser surgery can be performed repeatedly. Furthermore, radiotherapy takes a much longer period of treatment and recovery as compared to laser surgery. Therefore, in shared decision making in clinical practice, patients often prefer laser surgery. Another argument against radiotherapy is that laser surgery is much more cost-effective than radiotherapy[7-9].

Another important outcome measure is voice quality. Several cross-sectional studies have shown that voice outcome seems similar after both treatment modalities[10-17]. However, in most of these studies, information on tumor size, time of follow-up, and type of voice analyses is lacking. Moreover, prospective studies on voice outcome comparing both treatment modalities for comparable T1a lesions are scarce.

Therefore, the main purpose of this prospective cohort study was to assess voice outcome in patients before and up to 2 years after treatment for early glottic cancer either by radiotherapy or laser surgery. This study was approved by the local medical ethics committee.

PATIENTS AND METHODS

Patients

During a period of 9 years, 106 male patients were treated for T1aN0M0 (T1a: tumor limited to one vocal fold with normal mobility; N0: no regional lymph node metastasis; M0: no distant metastasis, according to the UICC staging system) glottic cancer. Staging was based on direct laryngoscopy and was proven by biopsy. Sixty-seven patients were treated by endoscopic laser surgery (mean age 66 years; range 34–87 years) and 39 by radiotherapy (mean age 65 years; range 44–85 years).

Twenty-one age-matched (mean age 64 years; range 50–81 years) males (spouses of patients visiting the outpatient clinic) without voice problems were used as controls.

Endoscopic laser surgery

Patients treated with endoscopic laser surgery were selected by means of videolaryn-

gostroboscopic evaluation using the presence of mucosal undulation as an indication for superficial tumor spread only. A Sharplan CO_2-laser (with ACU-spot micromanipulator; Sharplan Laser Industries, Tel Aviv, Israel) in a superpulse mode was used for a chordectomy Type II (according to the European Laryng- ological Society (ELS) classification[18]), involving resection of the epithelium, Reinke's space and typically continuing the resection just into the deeper parts of the lamina propria. Because of this slight extension into the deeper parts of the lamina propria, this resection does not qualify as a type I resection, which is limited to Reinke's space, the superficial part of the lamina propria.

Radiotherapy

Patients not selected for laser surgery were locally irradiated with the Varian CLINAC 2300, a linear 6 MV accelerator (Varia Medical Systems Inc., Palo Alto, CA, USA). The total radiation was 57.5–60.0 Gy (2.5 Gy per fraction, five times a week). All patients were treated with two opposing lateral fields, generally, with a standard field- size of 6 × 6 cm, using 6 MV photons.

Methods

Patients' voices were recorded and analyzed pre-treatment and 3, 6, 12 and 24 months post-treatment at their routine visit at the outpatient clinic. Only patients were included in the present study of whom voice assessments of at least three of the assessment periods were completed and who had at least one voice assessment at 12 or 24 months. Patients who were treated for recurrence or suspicion of recurrence of the tumor during the follow-up period were excluded from the study.

Acoustic voice analyses

Digital recordings of a sustained vowel /a/ at comfortable loudness and pitch were performed using Dr. Speech, developed by Tiger Electronics (Seattle, WA). A mouth-to- microphone distance of approximately 30 cm was held constant throughout all samples. Acoustic signal typing according to Behrman revealed that all recordings were suitable for further acoustic analyses[19]. Average fundamental frequency (F0), percent jitter, percent shimmer and normalized noise energy (NNE) were determined. The percentage of jitter represents the relative period-to-period variability. The percentage of shimmer represents the relative variability of the peak-to-peak amplitude. The normalized noise energy is the degree of noise produced by turbulent air escaping through the glottis during vocal emission.

Statistical analyses

Independent t tests were used to compare the patient data versus the controls for all five assessment periods. Independent t test were also used in the comparison of voice results between the two different therapy groups. To investigate the longitudinal results for both

treatment groups independently, paired t tests were used between the voice data of consecutive assessment periods.

RESULTS

Patients

In total, 106 patients participated in the study. During the follow-up period, 10 patients underwent a complementary biopsy for suspicion of recurrence of the tumor and were excluded from further voice analyses. Three of them had been primary treated by radiotherapy, including two who had to be laryngectomised because of recurrence of tumor. The other patient who had no recurrence but merely moderate dysplasia was treated by laser surgery. Of the other seven patients, primary treated by laser surgery, two had tumor recurrence. One underwent radiotherapy, and the other one, laser surgery once more. The other five patients, primarily treated with laser surgery, suffered from light to moderate dysplasia and were treated once more by laser surgery **(Table 1).** None of the patients succumbed to their disease during the follow-up period. Another five patients were excluded for further analyses because they failed to complete the required number of at least three voice assessment moments even though they were not lost to oncological follow-up.

Of the remaining 91 patients, 55 patients had been treated by endoscopic laser surgery (mean age 66 years; range 34–87 years) and 36 had been treated by radiotherapy (mean age 66 years; range 44–85 years). Median time of follow-up was comparable for patients treated with radiotherapy or laser surgery **(Table 2).**

Table 1. Treatment outcome after 2 years.

	Radiotherapy (n=39)	**Laser surgery** (n=67)	**Total** (n=106)
Recurrence	2 (5%)	2 (3%)	4 (4%)
Larynx preservation	37 (95%)	67 (100%)	104 (98%)

Table 2. Median time of follow up voice assessments in months after treatment.

	3rd month assessment	6th month assessment	12th month assessment	24th month assessment
Radiotherapy				
Median	3.3	7.1	12.4	24.7
Laser surgery				
Median	3.6	6.8	12.4	24.5

Voice outcome

Prospective voice outcomes are shown in **Figures 1-4** of patients treated with radiotherapy (green lines) or laser surgery (red lines). Mean values of acoustic voice analyses of controls were jitter 0.30 (SD = 0.18), shimmer 5.20 (SD = 1.69), NNE −9.10 (SD = 3.21), and F0 111 Hz (SD = 24) and are represented by a blue line in **Figures 1–4**.

In patients 3 months after radiotherapy, NNE was significantly better and the fundamental frequency was significantly lower compared to pre-treatment ($t = 2.5$, $p = 0.021$ and $t = 4.2$, $p = 0.000$ respectively). No significant voice changes occurred in the longer term at 6th, 12th and 24th month assessment. In patients 3 months after laser surgery, jitter and shimmer were significantly better compared to pre-treatment ($t = 3.2$, $p = 0.003$ and $t = 3.1$, $p = 0.004$ respectively). No significant voice changes occurred in the longer term at 6th, 12th and 24th month assessment. **Figures 1 to 4** represent the prospective results for jitter, shimmer, NNE and fundamental frequency.

Patients versus controls

Before radiotherapy, patients scored significantly worse compared to controls regarding jitter ($t = -3.1$, $p = 0.001$), shimmer ($t = -3.1$, $p = 0.003$), and NNE ($t = -4.3$, $p = 0.000$) and fundamental frequency was significantly higher ($t = -6.4$, $p = 0.000$). Three months after radiotherapy, patients scored significantly worse regarding jitter, shimmer, and NNE ($t = -3.0$, $p = 0.006$; $t = -2.1$, $p = 0.041$ and $t = -2.1$, $p = 0.042$ respectively). Six and 12 months after treatment, patients scored significantly worse regarding jitter ($t = -2.0$, $p = 0.050$ and $t = -2.4$, $p = 0.022$ respectively) and fundamental frequency ($t = -2.5$, $p = 0.016$ and $t = -2.4$, $p = 0.022$ respectively) remained significantly higher compared to controls. Twenty-four months post treatment, jitter remained significantly worse in patients compared to controls ($t = -2.8$, $p = 0.007$).

Patients before laser surgery scored significantly worse compared to controls regarding jitter ($t = -3.1$, $p = 0.003$), shimmer ($t = -2.5$, $p = 0.015$), and NNE ($t = -2.4$, $p = 0.21$) and fundamental frequency was significantly higher ($t = -6.0$, $p = 0.000$). At 3, 6, 12 and 24 months after treatment, the fundamental frequency remained significantly higher in comparison with controls ($t = -5.2$, $p = 0.000$; $t = -5.4$, $p = 0.000$; $t = -4.9$, $p = 0.000$ and $t = -4.2$, $p = 0.000$ respectively); at these time points, all other voice outcome parameters were not significantly different between patients and controls. See also **Table 3** and **Figures 1–4**.

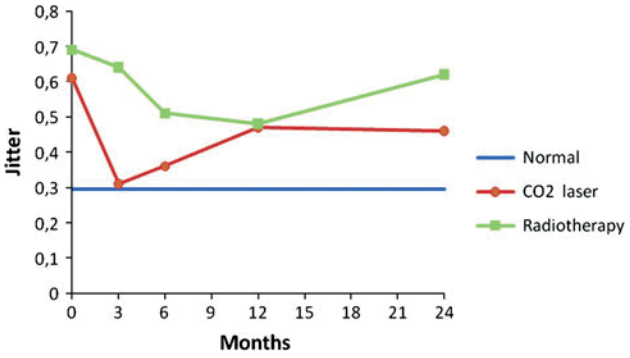


Figure 1. Prospective results of jitter for patients with T1a glottic carcinoma treated with either laser surgery or radiotherapy, compared with normal controls

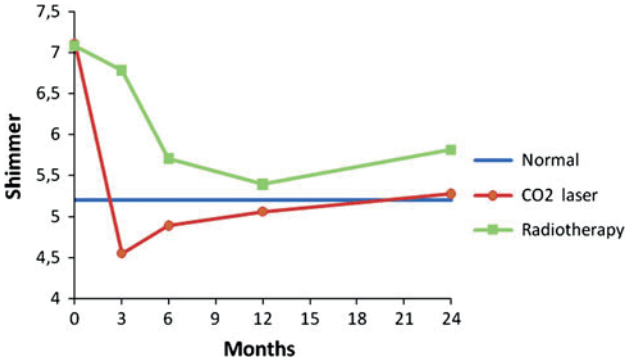


Figure 2. Prospective results of shimmer for patients with T1a glottic carcinoma treated with either laser surgery or radiotherapy, compared with normal controls.

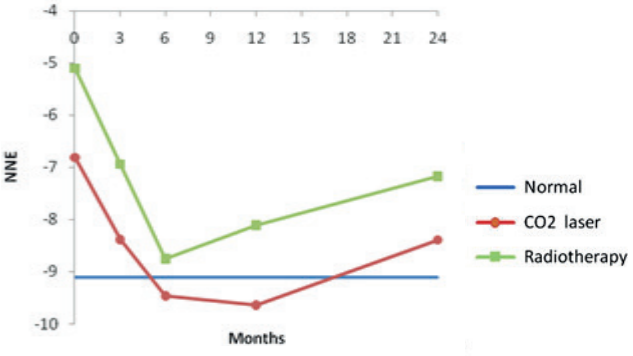


Figure 3. The prospective results of the Normalized Noise Energy for both treatment modalities and the controls.

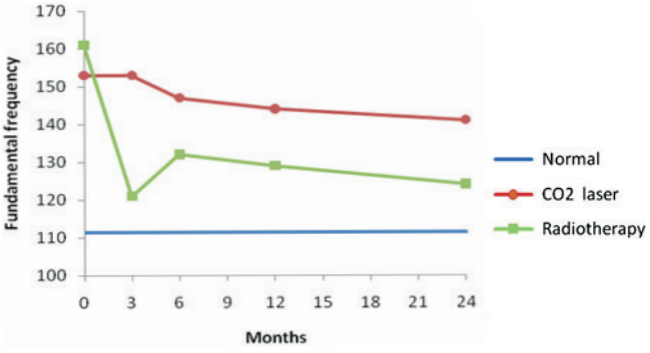


Fig. 4. Prospective results of fundamental frequency for patients with T1a glottic carcinoma treated with either laser surgery or radiotherapy, compared with normal controls

Table 3. Differences between treatment modalities regarding voice outcome. Mean and (standard deviation); significant different outcomes are printed bold.

	Pre treatment assessment		3rd month assessment		6th month assessment		12th month assessment		24th month assessment	
	RT	Laser	RT	Laser	RT	Laser	RT	Laser	RT	Laser
Jitter	.69 (68)	.61 (.65)	**.64** (.55)	**.31** (.22)	.51 (.54)	.36 (.30)	.48 (.41)	.47 (.75)	.62 (.62)	.46 (.49)
Shimmer	7.08 (2.73)	7.11 (4.76)	**6.78** (3.26)	**4.55** (1.98)	5.70 (2.54)	4.89 (2.75)	5.39 (2.66)	5.06 (4.46)	5.81 (3.75)	5.28 (3.19)
NNE	-5.10 (3.38)	-6.81 (4.77)	-6.94 (3.79)	-8.38 (3.90)	-8.57 (3.92)	-9.46 (4.43)	-8.11 (4.45)	-9.64 (5.09)	-7.17 (4.00)	-8.39 (4.23)
F0	161 (32)	153 (33)	**121** (29)	**153** (40)	132 (37)	147 (28)	**129** (32)	**144** (31)	**124** (29)	**141** (33)

Radiotherapy versus laser surgery

Before treatment there was no significant difference for all four voice outcome parameters between patients treated with radiotherapy or laser surgery **(Table 3)**.

Three months after treatment there was a significant difference between the two treatment modalities with better scores for patients treated with laser surgery regarding jitter and shimmer ($t = -2.9$, $p = 0.007$ and $t = -3.1$, $p = 0.004$ respectively) and higher fundamental frequency for patients treated with laser surgery ($t = 3.8$, $p = 0.000$). At 6, 12 and 24 months there were no significant differences any longer between the two treatment modalities except for the fundamental frequency. Voices of patients treated with laser surgery were significantly higher pitched compared to patients treated by radiotherapy at 12 and 24 months after treatment ($t = 2.3$, $p = 0.027$ and $t = 2.4$, $p = 0.018$ respectively) **(Table 3)**.

DISCUSSION

In this study, four out of the 106 patients developed a recurrence, resulting in an overall local control of 96%. Overall larynx preservation rate was 98%. When comparing both treatment modalities local control rate after 2 years was 95% in the radiotherapy group and 97% in the laser surgery group. Larynx preservation rate was 95% after radiotherapy and 100% after laser surgery. Although it must be kept in mind that there is some selection bias because of the deliberate selection of tumors treatable by laser surgery (which implies the more superficial and less extensive tumors), it can be concluded that laser surgery for T1a glottic carcinomas results in excellent treatment outcome. Comparable

results were found by other studies also including only T1a glottic laryngeal carcinomas as a homogenous study group. For example Sjögren *et al*.[2] reported 5-year local control rates of 75% for patients after radiotherapy respectively 89% after laser surgery of T1a glottic carcinomas. In their study group, larynx preservation was also 100% for the laser treated patients versus 83% for the patients who received radiotherapy. Schrijvers *et al*.[20] also published a better larynx preservation rate of 95% for patients treated by laser surgery versus 77% for patients treated by radiotherapy after a follow-up of at least 41 months for T1a glottic carcinomas.

This paper describes a study investigating voice outcome prospectively from baseline to 2 years after treatment of patients treated with radiotherapy or laser surgery for T1a glottic carcinoma. Earlier studies most often involved retrospective analysis comparing measurements in a wide range of time intervals. The present study shows that recovery of the voice is dependent upon the time interval since the treatment, and that both treatment modalities result in a different recovery time regarding voice outcome. It appears that voice outcome recovers more quickly in patients treated with laser surgery in comparison to radiotherapy: 3 months after laser surgery there is no longer a difference with regard to the normal voices except for the fundamental frequency, which remains higher pitched, even in the longer term. For patients treated with radiotherapy it takes longer for jitter, shimmer and NNE to become normal, where jitter remains significantly different from the normal voices even after 2 years.

This current study provides evidence that, except from the fundamental frequency, in the longterm follow up there is no lasting difference in voice outcome between radiotherapy and laser surgery. After laser surgery the voices remain significantly higher pitched than after radiotherapy. This is in accordance with several other studies where the fundamental frequency also tends to be higher after laser surgery[11-13,17]. This may be explained by increased stiffness of the vocal cord due to scar tissue after laser surgery and by a combination of scar tissue and edema after radiotherapy. Even before treatment the fundamental frequency is higher in both treatment groups than in normal male controls (F0 = 111 Hz, as found in present study) which can be attributed to a combination of increased vocal fold stiffness as a result of the tumor in combination with compensatory hyperkinetic voicing. This finding of a higher mean fundamental frequencies in patients with early glottic cancer has been demonstrated in other studies as well with mean fundamental frequencies varying from 151 to 204[21-23].

It seems logical to expect that following endoscopic laser surgery the voice quality outcome highly depends on the extend and depth of the resection. Roh *et al*. [21] divided his patients with early glottic cancer in different groups depending on the extent of laser surgery. He found that larger tumors and tumors involving the anterior commissure had poor voice quality. In our study, we only included T1a mid vocal cord tumors and pre treatment

there were no significant differences in the voices between both treatment groups. In the light of this, it may very well be that patients with more extensive tumors, requiring more extended laser resections, are not better off after laser surgery in comparison to radiotherapy from a voice out- come point of view. Therefore, multidimensional decision making also taking into account the experience of the surgeon and the radiation oncologist remains an important issue.

Based on this study and supported by others in literature we believe that laser surgery is the first treatment of choice in the treatment of selected cases of T1a glottic carcinomas with good functional and oncological results.

REFERENCES

1. Sjögren EV, Wiggenraad RGJ, Le Cessie S, Snijder s, Pomp J, Baatenburg de Jong RJ. Outcome of radiotherapy in T1 glottic carcinoma: a population based study. Eur Arch Otorhinolaryngol 2009;266:735–744
2. Sjögren EV, Langeveld APM, Baatenburg de Jong RJ. Clinical outcome of T1 glottic carcinoma since the introduction of laser surgery as a treatment option. Head Neck 2008;30:1167–1174.
3. Sigston E, de Mones E, Babin E, Hans S, harti DM, Clement P, Brasnu DF. Early-staged glottic cancer: oncological results and margins in laser corctomy. Arch Otolaryngol Head Neck Surgery 2006;132:147–152.
4. Jones AS, Fish B, Fenton JE, Husband DJ. The treatment of early laryngeal cancers (T1–T2N0): surgery or irradiation? Head Neck 2004;26:127–135.
5. Franchin G, Minatel E, Gobitti C, Talamini R, Vaccher E, Sartor G, Politi D, Trovò MG, Barzan L. Radiotherapy for patients with early-stage glottic carcinoma. Cancer 2003;98:765–772.
6. Peretti G, Piazza C, Balzanelli C, Cantarella G, Nicolai P. Vocal outcome after endoscopic cordectomies for Tis and T1 glottic carcinomas. Ann Otol Rhinol Laryngol 2003;112(2):174–179.
7. Goor KM, Mahieu HF, Leemans CR, Peeters AJ, Langendijk JA, van Agthoven M. CO_2-laser decortication: an efficient alternative to radiotherapy in the treatment of T1a carcinomas of the glottis. Ned Tijdschr Geneeskd 2003;147(24):1177–1181.
8. Cragle SP, Brandenburg JH. Laser cordectomy or radiotherapy: cure rates, communication, and cost. Otolaryngol Head Neck Surg 1993;108:648–654.
9. Brandenburg JH. Laser cordectomy versus radiotherapy: an objective cost analysis. Ann Otol Rhinol Laryngol 2001;110:312–318.
10. Peeters AJGE, Van Gogh CDL, Goor KM, Verdonck-de Leeuw IM, Langendijk JA, Mahieu HF. Health status and voice outcome after treatment for T1a glottic carcinoma. Eur Arch Otorhinolaryngol 2004;261:534–540.
11. Rydell R, Schalen L, Fex S, Elner Å. Voice evaluation before and after laser excision versus radiotherapy of T1a glottic carcinoma. Acta Otolaryngol (Stockh) 1995;115:560–565.
12. Wedman J, Heimdal JH, Elstad I, Olofsson J. Voice results in patients with T1a glottic cancer treated by radiotherapy or endoscopic measures. Eur Arch Otorhinolaryngol 2002;259:547–550.

13. McGuirt WF, Blalock D, Koufman JA, Feehs RS, Hilliard AJ, Greven K, Randall M. Comparative voice results after laser resection or irradiation of T1 vocal cord carcinoma. Arch Otolaryngol Head Neck Surg 1994;120:951–955.

14. Tamura E, Kitahara S, Ogura M, Kohno N. Voice quality after laser surgery or radiotherapy for T1a glottic carcinoma. Laryngoscope 2003;113:910–914.

15. Loughran S, Calder N, MacGregor FB, Carding P, MacKenzie K. Quality of life and voice following endoscopic resection or radiotherapy for early glottic cancer. Clin Otolaryngol 2005;30:42–47.

16. Cohen SM, Garrett CG, Dupont WD, Ossoff RH, Courey MS. Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. Ann Otol Rhinol Laryngol 2006;115:581–586.

17. Sjögren EV, Van Rossum MA, Langeveld TPM, Voerman MS, Van de Kamp VAH, Friebel MOW, Wolterbeek R, Baatenburg de Jong RJ. Voice outcome in T1a midcord glottic carcinoma. Arch Otolaryngol Head Neck Surg 2008;134:965–972.

18. Remacle M, Eckel HE, Antonelli A, Brasnu D, Chevalier D, Friedrich G, Olofsson J, Rudert HH, Thumfart W, de Vincentiis M, Wustrow TP. Endoscopic cordectomy. a proposal for a classification by the Working Committee, European Laryngological Society. Eur Arch Otorhinolaryngol 2000;257(4):227–231.

19. Behrman A, Abramson A, Myssiorek D. A comparison of radiation-induced and presbylaryngeal dysphonia. Otolaryngol Head and Neck Surg 2001;125:193–200.

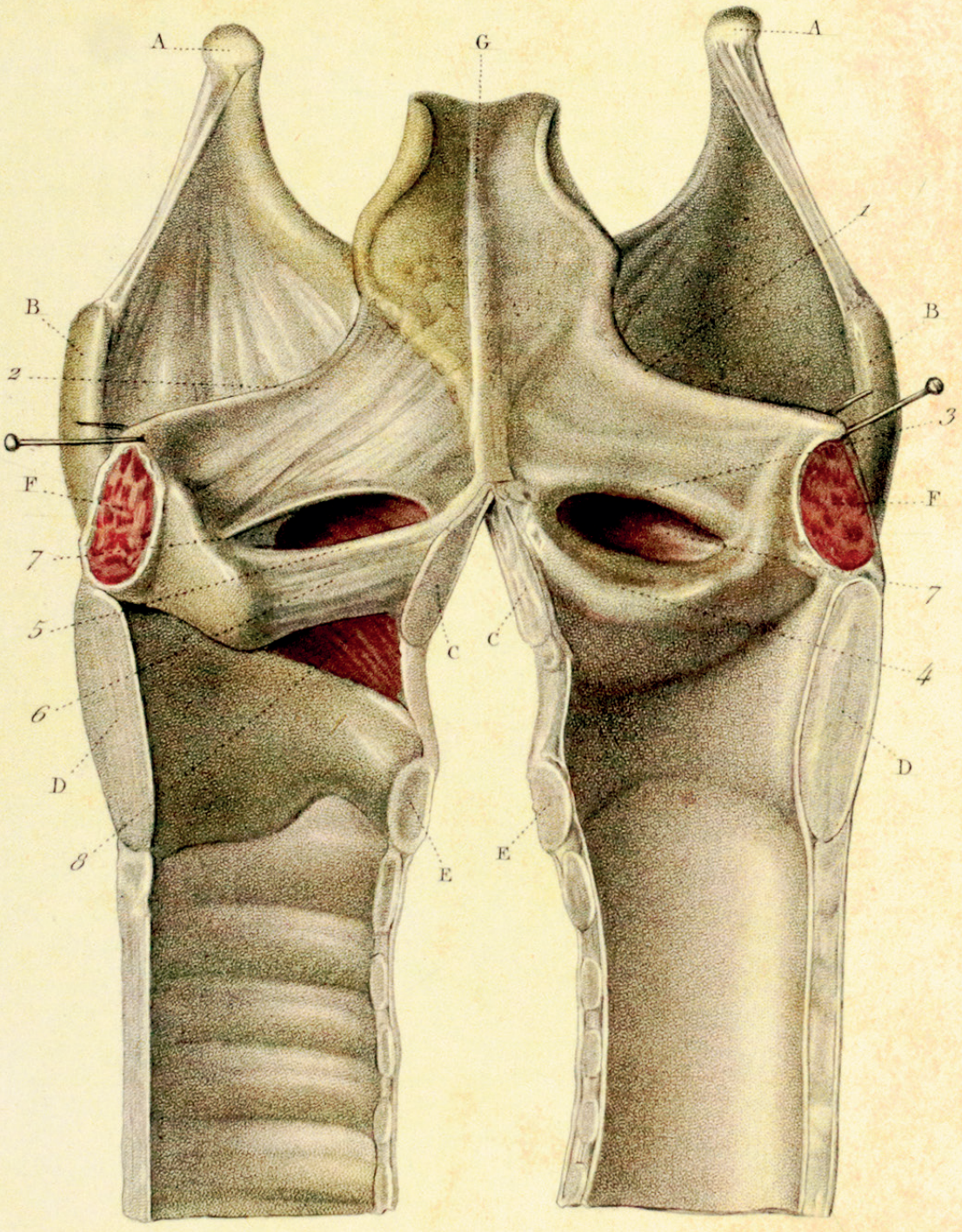
20. Schrijvers ML, Van Riel EL, Langendijk JA, Dikkers FG, Schuuring E, Van der Wiel JE, Van der Laan BFAM. Higher laryngeal preservation rate after CO_2 laser surgery compared with radiotherapy in T1a glottic laryngeal carcinoma. Head Neck 2009;31:759–764.

21. Roh JL, Kim DH, Kim SY, Park CI. Quality of life and voice in patients after laser cordectomy for Tis and T1 glottic carcinomas. Head Neck 2007;29(11):1010–1016.

22. Agarwal JP, Baccher GK, Waghmare CM, Mallick I, Ghosh-Laskar S, Budrukkar A, Pai P, Chaturvedi P, D'Cruz A, Shrivastava SK, Dinshaw KA. Factors affecting the quality of voice in the early glottic cancer treated with radiotherapy. Radiother Oncol 2009;90(2):177–182.

23. Bibby JR, Cotton SM, Perry A, Corry JF. Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck 2008; 30(5):600–610.

Fig. I.



CHAPTER

THE EFFICACY OF VOICE THERAPY IN PATIENTS AFTER TREATMENT FOR EARLY GLOTTIC CARCINOMA

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Cancer 2006;106:95–105.

ABSTRACT

Background After treatment for early glottic carcinoma, a considerable number of patients end up with voice problems that interfere with daily life activities. The objective of this randomized and controlled study was to assess the efficacy of voice therapy in these patients.

Methods Of 177 patients, 6–120 months after treatment for early glottic carcinoma, 70 patients (40%) suffered from voice impairment based on a 5-item screening questionnaire. Approximately 60% of those 70 patients were not interested in participating in the current study. Twenty-three patients who were willing to participate were assigned randomly either to a voice therapy group (n=12 patients) or to a control group (n=11 patients). Multidimensional voice analyses (the self-reported Voice Handicap Index [VHI], acoustic and perceptual voice quality analysis, videolaryngostroboscopy, and the Voice Range Profile) were conducted twice: before and after voice therapy or with 3 months in between for the control group.

Results Statistical analyses of the difference in scores (postmeasurement minus premeasurement) showed significant voice improvement after voice therapy on the total VHI score, percent jitter, and noise-to-harmonics ratio in the voice signal and on the perceptual rating of vocal fry.

Conclusions Voice therapy proved to be effective in patients who had voice problems after treatment for early glottic carcinoma. Improvement not only was noticed by the patients (VHI) but also was confirmed by objective voice parameters.

INTRODUCTION

Radiotherapy and endoscopic laser surgery are the main treatment modalities for patients with early-stage, glottic laryngeal carcinoma. Both treatment modalities provide good cure rates[1-16]. Several reports on functional results have described a wide range of incidence of abnormal voice quality in 14 –92% of patients after radiotherapy[15–29] and in 17–70% of patients after laser surgery[15,21–33]. Furthermore, studies on the influence of a deteriorated voice on quality of life revealed that 27–58% of patients with voice problems experienced difficulties in communication that led to a disrupted social life[18,34-42]. Evidently, considerable numbers of patients who are treated for early glottic carcinoma have to deal with voice problems in daily life. It is not clear whether these voice problems respond to voice therapy. Outcome studies on the efficacy of voice therapy are scarce. Fex and Henriksson[43] applied voice therapy to reduce voice damage caused by radiotherapy for laryngeal carcinoma. In their study, 15 patients received voice treatment during radiation therapy. Unfortunately, the definition of normal voice quality in that study remained unclear, and a control group was not included; therefore, it is impossible to conclude that the voice results were a consequence of voice therapy. Zwirner *et al*[44]. reported a positive acoustic effect of voice therapy in patients after laser surgery for T1–T3 laryngeal carcinomas. In that prospective study, 13 patients with substantial deterioration of voice function after laser surgery were subjected to an intensive voice rehabilitation program. After rehabilitation, the standard deviation of fundamental frequency and the noise-to-harmonics ratio (NHR) improved significantly, but it did not return to "normal" values, which were obtained from an age-matched and gender-matched control group. Sittel *et al*[45]. could not demonstrate this beneficial effect of voice therapy after laser surgery for patients with T1–T2 laryngeal carcinomas. On the contrary, those authors found that patients who did not receive voice therapy had considerably better voices than patients who did receive voice therapy. The patients after voice therapy showed a high percentage of ventricular fold phonation. According to the authors, this may have been because of a lack of information and knowledge of the speech therapists, who may have assumed that phonation on a glottic level was impossible after laser surgery.

It may be concluded that convincing evidence for the efficacy of voice therapy in patients with early glottic carcinoma is lacking. The main objective of the current randomized study was to assess the efficacy of voice therapy in patients with voice problems after they received treatment for early glottic carcinoma by using a multidimensional voice-assessment protocol.

MATERIALS AND METHODS

Study Design

During 1 year, all patients who received treatment for early glottic carcinoma (carcinoma in situ [Tis], T1N0M0, and T2N0M0, as defined according to the International Union Against Cancer staging system[46]: T1, tumor limited to the vocal folds with normal mobility; T2, supraglottic and/or subglottic tumor expansion and/or impaired mobility; N0, no regional lymph node metastasis; M0, no distant metastasis) at least 6 months previously with either radiotherapy or endoscopic laser surgery were screened regarding voice impairment during their regular follow-up visit at our outpatient department. The screening instrument consisted of a validated and standardized, 5-item, 10- point, anchored, scaled questionnaire that covered vocal abilities and social situations[38,47].

According to the questionnaire, patients who showed voice impairment (a score ≤ 5 on at least 1 of the 5 items) were asked to participate in a study on the efficacy of voice therapy. Those who were willing to participate were divided, in the order of their presentation (i.e., random), into either a voice-therapy group or a control group.

Radiotherapy

Patients who were treated with radiotherapy received local irradiation with the Varian CLINAC 2300, a linear 6 MV accelerator (Varia Medical Systems Inc., Palo Alto, CA). The total radiation dose was 57.5– 60.0 grays (Gy) in patients with T1a and T1b tumors (2.5 Gy per fraction, 5 times per week), whereas patients with T2 tumors generally received an accelerated schedule to a total dose of 70 Gy (2 Gy per fraction, 6 times per week). All patients with T1 tumors were treated with 2 opposing lateral fields, generally with a standard field size of 6 x 6 cm and with 6-MV photons. In patients who had T2 tumors with supraglottic extension be- yond the false cords and/or subglottic extension >1 cm, the radiation portals were extended to Levels II to IV on both sides and/or to the paratracheal lymph node areas, respectively.

Endoscopic laser surgery

Patients who underwent endoscopic laser surgery had been selected by means of videolaryngostroboscopic evaluation using the presence of mucosal undulation as an indication for superficial tumor spread only. A Sharplan CO_2-laser (with an AcuSpot™ micromanipulator; Sharplan Laser Industries, Tel Aviv, Israel) in a super-pulse mode was used for a chordectomy Type II[48].

Voice Therapy

Patients in the voice-therapy group were referred to a speech-language pathologist who specialized in voice therapy (voice therapist) in their own neighborhood and were treated

with a maximum of 24 sessions. The sessions lasted for 30 minutes each and were held twice per week. The voice therapists were informed about the patient's medical history and videolaryngostroboscopic examination findings. The type of voice therapy could be chosen freely according to the patient's needs. To gather information about the kind of voice therapy used, the voice therapists kept a log.

Voice Analyses

All patients' voices were examined twice: once at baseline (study entry assessment) and once after voice therapy or after 3 months for patients in the control group (study exit assessment). Digital recordings of a standardized text that was read aloud (30 seconds) and a sustained vowel /a/ at comfortable loudness and pitch were performed using the Computerized Speech Lab and Multidimensional Voice Program developed by Kay Elemetrics (Pine Brook, NJ). A mouth-to-microphone distance of approximately 30 cm was held constant throughout all samples.

Voice Handicap Index

The Voice Handicap Index (VHI) was chosen as the primary outcome measure. The VHI is a validated questionnaire that measures psychosocial handicapping effects of voice disorders[49] and was translated and validated in Dutch[50]. The questionnaire consists of 30 statements on voice-related aspects in daily life (5-point rating scale). The total score for the 30 questions ranges from 0 to 120. A higher score indicates a higher level of voice handicap (**Appendix 2**).

Communicative suitability

The concept of communicative suitability developed by Franken *et al*[51]. for stuttering patients was adapted by van der Torn *et al*[34]. for patients after treatment for early glottic carcinoma. A panel of 10 untrained volunteers judged the voice samples on communicative suitability in 3 different, demanding speaking situations on a 10-point, anchored scale that ranged from extremely poor (score 1) to excellent (score 10). The three speaking situations ranged from low demanding (talking about everyday events with a friend), medium demanding (asking a passer-by for directions), to highly demanding (giving a lecture) (**Appendix 1)**. The raters assessed communicative suitability of text samples that were read aloud in a computerized-rating protocol. Voice samples from all patients (the voice-therapy group and the control group; study entry and exit assessments) were presented in random order for both study groups and for study entry or exit assessments. To test reliability, 10 randomly chosen voice samples were rated twice. The raters were blinded to the clinical data.

Perceptual voice-quality assessment

The same voice samples (text read aloud) that were used to assess communicative suit-

ability were used to assess voice quality. Two trained raters, both voice therapists experienced with patients who had laryngeal carcinoma but not familiar with the study patients, assessed voice quality perceptually in a computerized rating protocol. Voice samples from all patients (the voice-therapy group and the control group; study entry and exit assessments) were presented in random order for both study groups and for study entry or exit assessment. To test reliability, 10 randomly chosen voice samples were rated twice. The raters were blinded to the clinical data. An adapted and limited version of the Vocal Profile Analysis Protocol by Laver *et al*[52]. was used. The following 10 items were judged on a 4-point-scale based on a consensus reached by the 2 raters: breathiness, roughness, tension/strain, unsteadiness, asthenia, aphonia, falsetto, vocal fry, diplophonia, and tremor.

Acoustic voice analyses

Acoustic analyses of voice quality were performed by using samples of a sustained vowel /a/. Acoustic signal typing according to Behrman *et al*[53]. revealed that all recordings were suitable for further acoustic analyses. Average fundamental frequency (F0), the percentage jitter, the percentage shimmer, and the NHR were determined. The percentage of jitter represents the relative period-to-period variability. The percentage of shimmer represents the relative variability of the peak-to-peak amplitude. The NHR is an average ratio of energy of the inharmonic components in the range 1500 – 4500 Hz to energy of the harmonic components in the analyzed signal.

Videolaryngostroboscopy

Vocal fold anatomy and movement were assessed by means of videolaryngostroboscopy (stroboscopy). Digital recordings were obtained by using a Strobo- view 2000 ACLS digital system (developed by Alphatron Medical and Microwave Systems BV, Rotterdam, The Netherlands). Each individual was asked to produce the sustained vowels /u/ and /i/ and two vowel glides (from high to low frequency, and vice versa). Two raters, both experienced laryngologists, participated in a randomized, blinded rating protocol. The 16-item rating form was adapted from Hirano and Bless[54] and consisted of scales relating to overall laryngeal anatomy, vocal fold movement, mucosal wave pattern, irregularity, periodicity and glottic closure. Judgments were performed by the two raters reaching consensus. To test the reliability of the raters, 10 randomly chosen samples were rated twice.

Voice Range Profile

The Voice Range Profile (VRP) or phonetogram was obtained using the automatic VRP, which was developed by Kay Elemetrics, to assess the pitch and intensity ranges of the speakers' voices. The speakers were asked to produce a sustained /a/ as loud and soft as possible at selected frequencies and to produce several vowel glides. Two parameters were determined for each patient: the pitch range in semitones (highest frequency minus

lowest frequency) and the intensity range in decibels (loudest level minus softest level).

Statistic Analyses

Interrater reliability of the communicative suitability test was determined by calculating the intraclass correlation coefficients (ICC) between the 10 raters. Intrarater reliability of each rater of the communicative suitability test was determined by calculating the ICC between the first and second (repeated) ratings. Test- retest reliability of perceptual and stroboscopic ratings was determined by calculating weighted values between the first and second (repeated) ratings. Because of the small number of patients who underwent endoscopic laser surgery compared with the number of patients who were treated with radiotherapy, statistic analyses were performed for both treatment groups together. Independent Mann–Whitney U tests (perceptual and stroboscopic evaluation) and independent Student t tests (VHI, communicative suitability, acoustical analyses, VRP) were used to compare the study entry data between the two different study groups. The efficacy of voice therapy was assessed by independent Student t tests on the mean difference scores, which were defined as the study exit assessment score/value minus the study entry assessment score/value.

RESULTS

Study Group Composition

In total, 177 patients (162 men and 15 women; mean age, 66 yrs; age range, 39 – 80 yrs), including 126 patients who received radiotherapy and 51 patients who underwent endoscopic laser surgery, completed the screening questionnaire. Of these 177 patients, 70 patients (40%; 67 men and 3 women) suffered from voice impairment based on their answers in the questionnaire, including 55 patients who were treated with radiotherapy and 15 patients who underwent endoscopic laser surgery. Thus, 44% percent of the patients who received radiotherapy and 29% of the patients who underwent endoscopic laser surgery had overall voice impairment. This difference between the 2 treatment modalities was not significant ($p = 0.079$).

Forty-one of 70 patients (58%) who had voice complaints did not wish to participate in the study. Twenty-nine patients (41%) were willing to participate and were included in the study after they provided written informed consent. There were no significant differences concerning the questionnaire scores between patients who were willing or unwilling to participate in the study.

None of the patients who were included in the study had received previous voice therapy, and none suffered from neurologic diseases that could influence speech or voice.

The 29 patients who were included were assigned randomly to either the voice-therapy group (n = 16 patients) or the control group (n = 13 patients). During the course of the study, 6 of 29 patients dropped out of the study, four patients dropped out because of a biopsy that was suspicious for recurrent tumor, 1 patient developed myocardial infarction, and 1 patient withdrew from the study because of lack of motivation.

Of the remaining 23 patients, 12 patients formed the voice-therapy group, including 9 patients who received radiotherapy and 3 patients who underwent laser surgery. The other 11 patients formed the control group, which included 8 patients who received radiotherapy and 3 patients who underwent laser surgery. Patients in the control group did not receive voice therapy during the study period.

The average posttreatment time was 31 months (range, 6 – 81 mos) for the voice-therapy group and 42 months (range, 6 –120 mos) for the control group; this difference was not significant (Student t = 0.73; p = 0.47). Both the voice-therapy group and control group consisted of only men with a mean age of 67 years (age range, 55– 80 yrs) for the voice-therapy group and 58 years (age range, 40 – 80 yrs) for the control group; this age difference proved to be statistically different (Student t = -2.13; p = 0.048). There was no difference in tumor stage between the 2 treatment groups (chi-square statistic, 6.33; p = 0.097).

Voice Therapy

The patients in the voice-therapy group attended 4 –24 sessions of voice therapy (mean, 16 sessions). The main part of the therapeutic sessions consisted of voice and breathing exercises and vocal hygiene. Specific voice exercises took up > 50% of the treatment time.

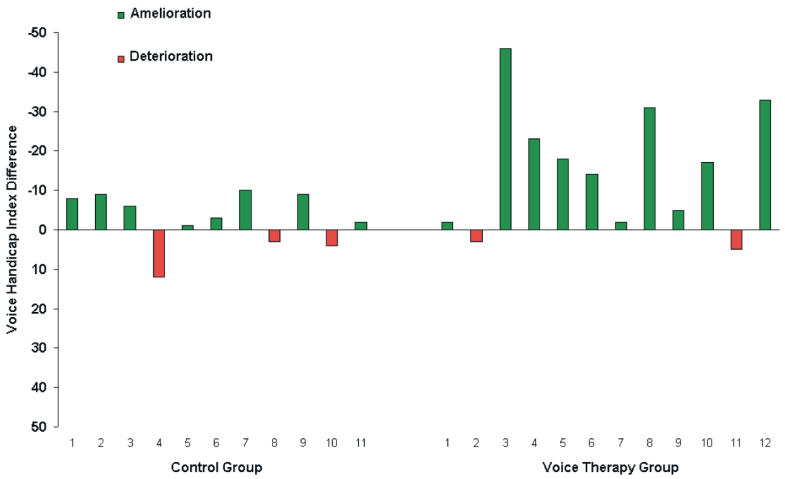


Figure 1. Differences in Voice Handicap Index scores are illustrated per patient for both study groups (difference postmeasurement -premeasurement score).

Self-Ratings of Vocal Performance

The mean VHI scores for patients in both the voice- therapy group and the control group are presented in **Table 1**. At the start of the study, there was no significant difference in the total VHI score between the control group and the voice-therapy group (Student t = 1.66; p = 0.11). The mean improvement in VHI was significantly better (Student t = 2.51; p = 0.024) in the voice-therapy group (15.25 points) than the mean VHI improvement in the control group (2.64 points). The VHI difference scores per patient in the 2 study groups are illustrated in **Figure 1**.

Table 1. Mean Scores/Values with Standard Deviations on the Voice Handicap Index, Acoustic Analyses, and Voice-Range Profile Parameters for Both Study Groups

	Control group		Voice therapy group	
	Study entry assessment	Study exit assessment	Study entry assessment	Study exit assessment
Voice Handicap index				
Total VHI score	29.45 (13.34)	26.82 (15.04)	39.67 (16.17)	24.42 (10.26)
Acoustic analyses				
Fundamental frequency	131 (27)	127 (19)	118 (44)	124 (33)
NHR	0.18 (0.042)	0.18 (0.057)	0.20 (0.064)	0.14 (0.021)
Jitter	1.39 (0.59)	1.70 (1.15)	2.20 (1.50)	1.39 (1.32)
Shimmer	8.56 (5.82)	7.48 (2.09)	7.26 (3.20)	5.094 (1.12)
Voice Range Profile				
Intensity range	28.4 (6.6)	30.4 (6.3)	32.2 (8.02)	31.8 (7.9)
Pitch range	20.7 (6.1)	21.9 (4.8)	23.7 (5.2)	21.9 (3.3)

Communicative Suitability

Interrater reliability was high: The ICC was 0.85, 0.84, and 0.90, respectively, for the low demanding, medium demanding, and highly demanding speaking situations. Intrarater reliability appeared to be equally high with ICCs ranging from 0.70 to 0.93. Given this high reliability, the means of the ratings of all judges were calculated and were used for further analyses.

The mean communicative suitability scores for patients in the voice-therapy group and the control group are presented in **Table 2**. At the start of the study, the suitability scores for all 3 speaking situations showed no significant differences between the 2 study groups (low demanding: Student t = 0.51 [p = 0.61]; medium demanding: Student t = 0.47 [p = 0.65]; and highly demanding: Student t = 0.25 [p = 0.80]). After voice therapy, none of the 3 speaking situations improved significantly compared with patients in the control group (low demanding: Student t = 0.43 [p = 0.67]; medium demanding: Student t = -0.09 [p = 0.93]; and highly demanding: Student t = 0.41 [p = 0.69]).

Table 2. Mean Communicative Suitability Scores with Standard Deviations and Median Perceptual Voice-Quality Scores for Both Study Groups

	Control group		Voice therapy group	
	Study entry assessment	Study exit assessment	Study entry assessment	Study exit assessment
Communicative suitability				
Talking with a friend	6.45 (1.15)	6.37 (1.51)	6.19 (1.23)	6.26 (1.53)
Asking a passer-by	6.44 (1.11)	6.53 (1.30)	6.23 (1.07)	6.29 (1.31)
Giving a lecture	5.85 (1.31)	5.65 (1.53)	5.71 (1.30)	5.64 (1.50)
Perceptual voice quality				
Breathiness	1.00	1.00	.50	.00
Roughness	1.00	1.00	1.00	1.00
Vocal fry	2.00	2.00	3.00	2.00

Perceptual Voice Quality

Of the 10 voice-quality items, 6 items appeared to be noninformative for the study group: unsteadiness, asthenia, aphonia, falsetto, diplophonia, and tremor were absent in all or all but 1 of the voice samples. Reliability of the 4 relevant items proved to be good for breathiness, roughness, and vocal fry with weighted values of 0.83, 0.92, and 0.70, respectively. Reliability of the item tension/strain was low with a weighted value of 0.074. Given these considerations, the ratings on breathiness, roughness, and vocal fry were taken into account for further analyses. The median perceptual voice quality scores are presented in **Table 2**. At the beginning of the study, there was no significant difference between the 2 study groups regarding roughness ($Z = -0.46$; $p = 0.70$) and breathiness ($Z = -1.05$; $p = 0.32$); however, vocal fry was present significantly more often ($Z = -2.14$; $p = 0.04$) among patients in the voice-therapy group. After voice therapy, vocal fry decreased significantly compared with patients in the control group (Student $t = 2.66$; $p = 0.015$) (**Figure 2**). The items roughness and breathiness did not change significantly after voice therapy (roughness: Student $t = 0.0005$ [$p = 1.00$] and breathiness: Student $t = -0.91$ [$p = 0.38$]).

Acoustic Voice Analyses

Table 1 shows the mean values of the acoustic parameters. At the beginning of the study, there were no significant differences between the 2 study groups regarding F0 (Student $t = 0.83$; $p = 0.42$), jitter (Student $t = -1.74$; $p = 0.10$), shimmer (Student $t = 0.65$; $p = 0.52$), or the NHR (Student $t = -1.17$; $p = 0.26$).

After voice therapy, a significant improvement was observed in the NHR (Student $t = 2.70$; $p = 0.013$) and in jitter (Student $t = 2.76$; $p = 0.012$). **Figures 3 and 4** show the difference scores for NHR and jitter.

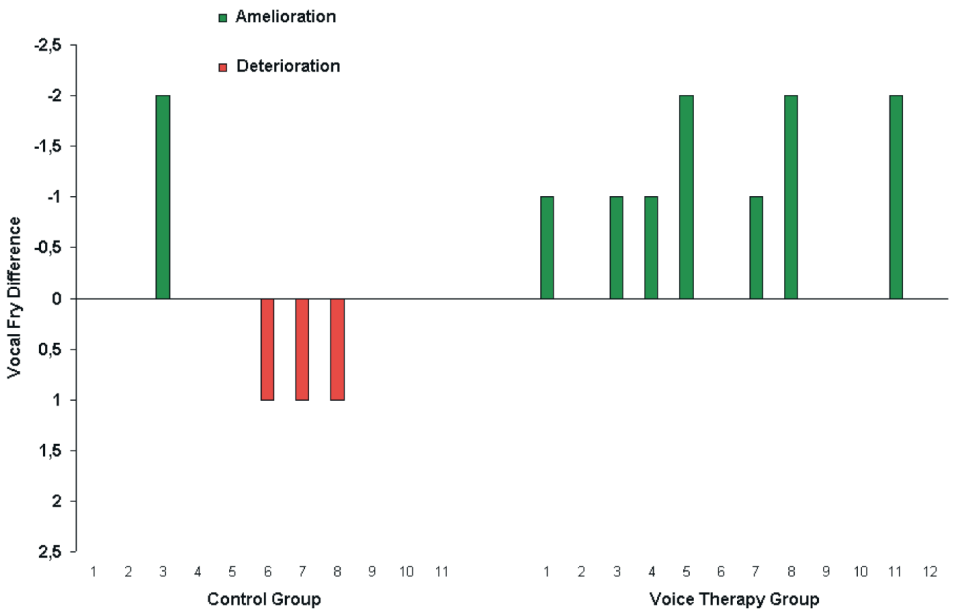


Figure 2. Differences in vocal fry scores are illustrated per patient for both study groups.

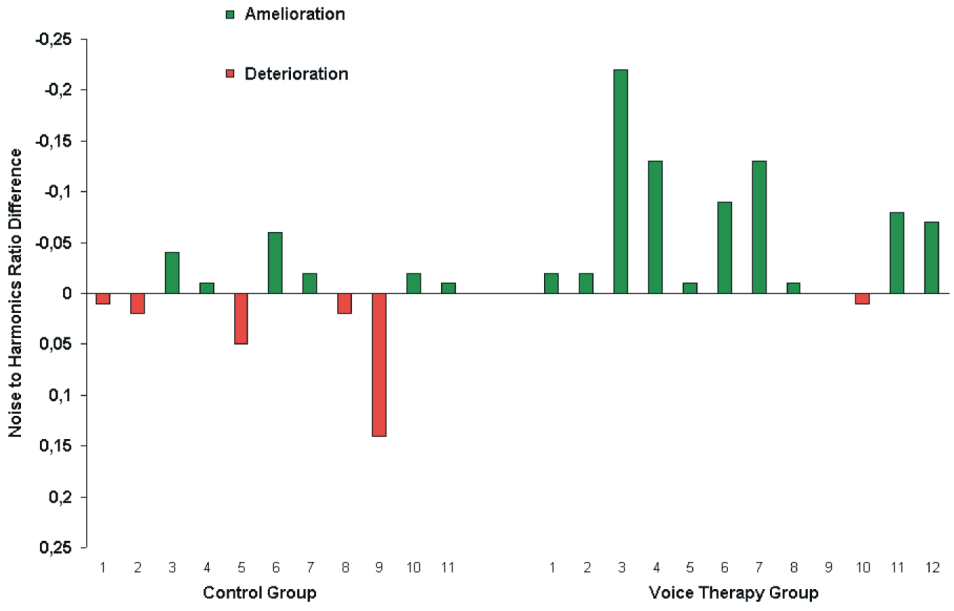


Figure 3. Differences in noise- to-harmonics ratio scores are illustrated per patient for both study groups.

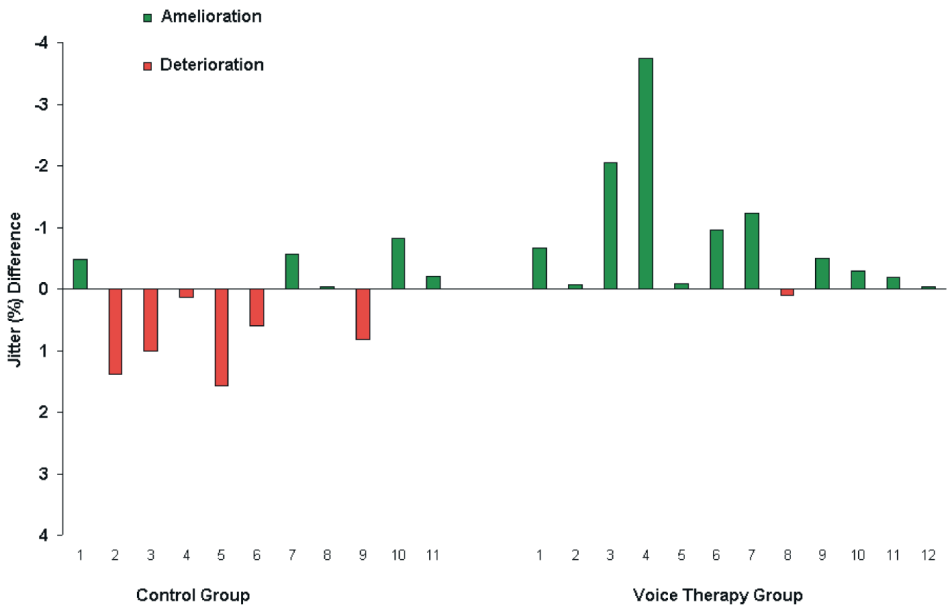


Figure 4. The percentage differences in jitter are illustrated per patient for both study groups.

Laryngostroboscopy

Although all arytenoids were mobile both at study entry and study exit, there was one patient whose arytenoids showed a minor asymmetry (the left arytenoid started to move slightly earlier than the right arytenoid, but the range of movement was identical) at study entry. At study exit, this finding was identical. Because it was judged that the mobility of the arytenoids itself was normal, and there was no difference in symmetry of the arytenoids between study entry compared with study exit, these two items were not included in the statistical analyses. Test-retest reliability of the remaining 14 items was moderate to good, with weighted κ values ranging from 0.46 to 0.88 for all items except phase symmetry, which had a poorly weighted κ value of 0.098. Therefore, the item phase symmetry was discarded for further analyses.

At the beginning of the study there were no significant differences noted in the laryngostroboscopic findings between the voice-therapy group and the control group (Z ranges between -1.89 and -0.036; p values between 0.079 and 0.98). No significant changes were observed after voice therapy on any of the stroboscopic items, except for the item “regularity of vocal fold edge.” After voice therapy, the vocal fold edge became more irregular ($Z = -2.67$; $p = 0.008$). When the left and right vocal folds were observed separately, it became clear that the left vocal fold edge became more irregular ($Z = -2.12$; $p = 0.034$), whereas the right vocal fold edge did not change ($Z = -0.38$; $p = 0.71$).

Voice Range Profile

Table 1 illustrates the mean values of the VRP parameters. At the start of the study, there were no significant differences between both study groups in pitch (Student t = 1.30; p = 0.21) or in intensity range (Student t = 1.25; p = 0.23). Posttreatment, the difference score of pitch and intensity range did not differ significantly between both study groups (pitch: Student t = -1.78, p = 0.092; intensity: Student t = -1.16, p = 0.26).

DISCUSSION

The current study provides evidence of the efficacy of voice therapy in patients with voice problems after treatment of early glottic carcinoma. The voice complaints of the patient, as assessed by the VHI, improved significantly, with an ample score of 15 points, which is comparable to the results from other studies concerning the efficacy of voice therapy. Roy *et al*[55]. reported that results from a randomized, controlled study showed a significant mean improvement of 11.63 points on the VHI after voice therapy in teachers who had voice problems. Rosen *et al*[56]. found that patients who had muscular tension dysphonia improved significantly after voice therapy on the VHI, with a mean improvement of 18 points. More recently, Speyer *et al*[57]. reported a median improvement of 6 points after voice therapy in patients who had a diversity of chronic, benign voice disorders.

In the current study, the primary outcome measure consisted of voice impairment, as assessed by the patients using the VHI. A beneficial effect of voice therapy also was observed in the secondary voice-quality outcome measures (NHR, jitter, and perceptual rating of vocal fry). Other randomized, controlled studies of the efficacy of voice therapy in patients with a diversity of chronic, benign voice disorders produced more or less similar improvements in acoustic and/or perceptual analyses[58–63].

Stroboscopic examination in the current study did not show an improvement after voice therapy. The minor but significant increase of irregularity of the left vocal fold edge after voice therapy cannot be explained easily. It is noteworthy that such a change in regularity of the vocal fold edge was not observed for the right vocal fold. It is our educated guess that this difference in regularity of the left vocal fold edge is based on a coincidence. It also may be argued that voice therapy could lead to a temporary overloading of the vocal fold in a fragile laryngeal mucosal condition after radiotherapy or laser surgery. In such a patient, however, a similar finding also would be expected in the right vocal fold.

Nearly 60% of patients, all of whom met the inclusion criteria for the study, were not willing to participate in the study despite their self-reported voice problems. This high percentage may be explained by the time-consuming nature of voice therapy and the fact that many patients accepted their voice problem as a logical consequence of their treat-

ment for a potentially life-threatening disease. Despite the randomization, baseline data from the voice-therapy group seemed slightly worse than data from the control group (but there was no significant difference, with the exception of the perceptual rating on vocal fry).

Although a significant improvement was observed in the VHI scores, the mean total VHI score of 24 points after voice therapy remains above the range of normal voices, which varies from a VHI score < 7 points for a sample of individuals from the general population with good voices, as assessed by an expert[50], to 12–17 points for a sample of individuals who were chosen randomly from the general population[64–66]. In other studies regarding voice after treatment for head and neck tumors, VHI scores ranged from 12 points to 45 points[37,39,40,42,67–72]. In those studies, patients were not selected with regard to voice problems or site of head and neck tumor. The current study involved patients who were treated for early glottic carcinoma only, and they were selected on the basis of their voice problems. It is our considered opinion that regular assessment of voice quality after treatment for early glottic carcinoma, for example, using the screening questionnaire employed in this study, is helpful to select patients who may benefit from voice therapy.

REFERENCES

1. Brandenburg JH. Laser cordectomy versus radiotherapy: an objective cost analysis. Ann Otol Rhinol Laryngol. 2001;110:312–318.
2. Motta G, Esposito E, Cassiano B, *et al*. T1–T2–T3 glottic tumors: fifteen years experience with CO2 laser. Acta Otolaryngol (Stockh). 1997;(Suppl 527):155–159.
3. Cragle SP, Brandenburg JH. Laser cordectomy or radiotherapy: cure rates, communication, and cost. Otolaryngol Head Neck Surg. 1993;108:648 – 654.
4. Smith JC, Johnson JT, Myers EN. Management and outcome of early glottic carcinoma. Otolaryngol Head Neck Surg.2002;26:356 –364.
5. Eckel HE. Local recurrences following transoral laser surgery for early glottic carcinoma: frequency, management, and outcome. Ann Otol Rhinol Laryngol. 2001;110:7–15.
6. Pukander J, Kerala J, Makiti A, *et al*. Endoscopic laser surgery for laryngeal cancer. Eur Arch Otorhinolaryngol. 2001;258:236 –239.
7. Mahieu HF, Patel P, Annyas AA, *et al*. Carbon dioxide laser vaporisation in early glottic carcinoma. Arch Otolaryngol Head Neck Surg. 1994;120:383–387.
8. Rosier JF, Gregoire V, Counoy H, et al. Comparison of external radiotherapy, laser microsurgery and partial laryngectomy for the treatment of T1N0M0 glottic carcinomas: a retrospective evaluation. Radiother Oncol. 1998;48:175–183.
9. Jones AS, Fish B, Fenton JE, et al. The treatment of early laryngeal cancers (T1–T2N0): surgery or irradiation? Head Neck. 2004;26:127–135.
10. Mohanti BK, Tandon DA, Bahadur S, *et al*. Results of definitive radiotherapy in T1 and T2 glottic carcinoma: Institute of Rotary Cancer Hospital experience [abstract]. Australas Radiol. 1996;40:287–290.
11. Franchin G, Minatel E, Gobitti C, et al. Radiotherapy for patients with early-stage glottic carcinoma. Cancer. 2003;98:765–772.
12. Fein DA, Mendenhall WM, Parsons JT, et al. T1–T2 squamous cell carcinoma of the glottic larynx treated with radiotherapy: a multivariate analysis of variables potentially influencing local control. Int J Radiat Oncol Biol Phys. 1993;25:605– 611.
13. Peretti G, Piazza C, Balzanelli C, *et al*. Vocal outcome after endoscopic cordectomies for Tis and T1 glottic carcinomas. Ann Otol Rhinol Laryngol. 2003;112:174 –179.
14. Goor KM, Mahieu HF, Leemans CR, Peeters AJ, Langendijk JA, van Agthoven M. CO2-laser decortication: an efficient alternative to radiotherapy in the treatment of T1a carcinomas of the glottis. Ned Tijdschr Geneeskd. 2003;147;1177–1181.
15. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1–T2 glottic carcinomas. Cancer. 2004;100:1786 –1792.
16. Krengli M, Policaro M, Manfredda I, *et al*. Voice quality after treatment for T1a glottic carcinoma. Acta Oncol. 2004;43:284 –289.

17. Aref A, Dworkin J, Devi S, Denton L, Fontanesi J. Objective evaluation of the quality of voice following radiation therapy for T1 glottic cancer. Radiother Oncol. 1997;45:149 –153.

18. Verdonck-de Leeuw IM, Keus RB, Hilgers FJM, *et al*. Consequences of voice impairment in daily life for patients following radiotherapy for early glottic cancer: voice quality, vocal function, and vocal performance. Int J Radiat Oncol Biol Phys. 1999;44:1071–1078.

19. Verdonck-de Leeuw IM, Hilgers FJM, Keus RB, *et al*. Multidimensional assessment of voice characteristics after radiotherapy for early glottic cancer. Laryngoscope. 1999;109:241–248.

20. Honocodeevar Boltezar I, Zargi M. Voice quality after radiation therapy for early glottic cancer. Arch Otolaryngol Head Neck Surg. 2000;126:1097–1100.

21. Lehman JJ, Bless DM, Brandenburg JH. An objective assessment of voice production after radiation therapy for Stage I squamous cell carcinoma of the glottis. Head Neck Surg. 1988;98:121–129.

22. Elner A, Soren F. Carbon dioxide laser as primary treatment of glottic T1s and T1a tumours. Acta Otolaryngol (Stockh).1988;449:135–139.

23. Hirano M, Hirade Y, Kawasaki H. Vocal function following carbon dioxide laser surgery for glottic carcinoma. Ann Otol Rhinol Laryngol. 1985;94:232–235.

24. Rydell R, Schalen L, Fex S, Elner A. Voice evaluation before and after laser excision vs. radiotherapy of T1a glottic carcinoma. Acta Otolaryngol (Stockh). 1995;115:560 –565.

25. Wedman J, Heimdal JH, Elstad I, Olofsson J. Voice results in patients with T1a glottic cancer treated by radiotherapy or endoscopic measures. Eur Arch Otorhinolaryngol. 2002;259:547–550.

26. McGuirt WF, Blalock D, Koufman JA, *et al*. Imperative voice results after laser resection or irradiation of T1 vocal cord carcinoma. Arch Otolaryngol Head Neck Surg. 1994;120:951–955.

27. Epstein BE, Lee DJ, Kashima H, Johns ME. Stage T1 glottic carcinoma: results of radiation therapy or laser excision. Radiology. 1990;175:567–570.

28. Delsuphe KG, Zink I, Lejaegere M, Bastian RW. Voice quality after narrow-margin laser cordectomy compared with laryngeal irradiation. Otolaryngol Head Neck Surg. 1999;21:528 –533.

29. Ott S, Klingholz F, Willich N, Kastenbauer E. Die bestimmung der qualitat der sprechstimme nach therapie von T1- und T2-stimmlippenkarzinomen. Laryngorhinootologie. 1992;71:236 –241.

30. Hofler H, Bigenzahn W. Die stimmqualita¨t nach CO2-laser- chordektomie. Laryngorhinootologie. 1986;65:655– 658.

31. Koufman JA. The endoscopic management of early squamous carcinoma of the vocal cord with the carbon dioxide surgical laser: clinical experience and a proposed subclassification. Otolaryngol Head Neck Surg. 186;95:531–537.

32. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. Otolaryngol Head Neck Surg. 1998;19:418 – 424.

33. McGuirt WF, Blalock D, Koufman JA, Feehs RS. Voice analysis of patients with endoscopically treated early laryngeal carcinoma. Ann Otol Rhinol Laryngol. 1992;101:142–146.

34. van der Torn M, Verdonck-de Leeuw IM, Kuik DJ, Mahieu HF. Communicative suitability of voice following radiotherapy for T1a glottic carcinoma: testing the reliability of a rating instrument. J Voice. 2002;16:398 – 407.

35. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schmid S. Quality of life after treatment for early laryngeal carcinoma. Eur Arch Otorhinolaryngol. 2001;258:96 –99.

36. Smith JC, Johnson JT, Cognetti DM, et al. Quality of life, functional outcome, and costs of early glottic cancer. Laryngoscope. 2003;113:68 –76.

37. Peeters AJGE, van Gogh CDL, Goor KM, et al. Health status and voice outcome after treatment for T1a glottic carcinoma [review]. Eur Arch Otorhinolaryngol. 2004;261:534 –540.

38. van Gogh CDL, Verdonck-de Leeuw IM, Boon AB, *et al*. A screening questionnaire for voice problems after treatment of early glottic cancer. Int J Radiat Oncol Biol Phys. 2005;62:700 –705.

39. Jepsen MC, Gurushanthaiah D, Roy N, *et al*. Voice, speech, and swallowing outcomes in laser-treated laryngeal cancer. Laryngoscope. 2003;113:923–928.

40. Fung K, Yoo J, Leeper HA, et al. Effects of head and neck radiation therapy on vocal function. J Otolaryngol. 2001;30:133–139.

41. Behrman A, Abramson A, Myssiorek D. A comparison of radiation-induced and presbylaryngeal dysphonia. Otolaryngol Head Neck Surg. 2001;125:193–200.

42. Stewart MG, Chen AY, Stach CB. Outcomes analysis of voice and quality of life in patients with laryngeal cancer. Arch Otolaryngol Head Neck Surg. 1998;124:143–148.

43. Fex S, Henriksson B. Phoniatric treatment combined with radiotherapy of laryngeal cancer for the avoidance of radiation damage. Acta Otolaryngol. 1970;263:128 –129.

44. Zwirner P, Michaelis D, Kruse E. Akustische stimmanalysen zur dokumentation der stimmrehabilitation nach laserchirurgischer larynxkarzinomresektion. HNO. 1996;44:514 –520.

45. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. Otolaryngol Head Neck Surg. 1998;19:418 – 424.

46. Union Internationale Contre le Cancer (UICC). Manual of clinical oncology. Berlin: Springer-Verlag, 1987.

47. Kaanders JHAM, Hordijk GJ. Carcinoma of the larynx: the Dutch national guideline for diagnostics, treatment, supportive care and rehabilitation. Radiother Oncol. 2002;63:299 –307.

48. Remacle M, Eckel HE, Antonelli A, et al. Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society. Eur Arch Otorhi- nolaryngol. 2000;257:227–231.

49. Jacobson BH, Johnson A, Grywalski C, et al. The Voice Handicap Index (VHI): development and validation. Am J Speech Lang Pathol. 1997;6:66 –70.

50. Verdonck-de Leeuw IM, Boon-Kamma AB, van Gogh CDL, *et al*. Het meten van stemkarakteristieken van patiënten met een klein larynxcarcinoom [in Dutch]. Logopedie en Fonia- trie. 2002;12:340 –345.

51. Franken MC, van Bezooijen R, Boves L. Stuttering and communicative suitability of speech. J Speech Lang Hear Res.1997;40:83–94.

52. Laver J, Wirz S, Mackenzie J, *et al*. A perceptual protocol for the analysis of vocal profiles. In: Work in Progress. University of Edinburgh, Linguistics Department, Edinburgh, Scot- land: 1981;14:139 –155.

53. Behrman A, Agresti CJ, Blumstein E, Lee N. Microphone and electroglottograhic data from dysphonic patients: type 1, 2 and 3 signals. J Voice. 1998;12:249 –260.

54. Hirano M, Bless DM. Videostroboscopic examination of the larynx. London: Whurr Publishers, 1993.

55. Roy N, Gray SD, Simon M, *et al*. An evaluation of the effects of two treatment approaches for teachers with voice disorders: a prospective randomised clinical trial. J Speech Lang Hear Res. 2001;44:286 –296.

56. Rosen CA, Murry T, Zinn A, Zullo T, Sonbolian M. Voice handicap index change following treatment of voice disorders. J Voice. 2000;14:619 – 623.

57. Speyer R, Wieneke GH, Dejonckere PH. Self-assessment of voice therapy for chronic dysphonia. Clin Otolaryngol. 2004;29:66 –74.

58. Speyer R, Wieneke GH, Dejoncere PH. Documentation of progress in voice therapy: perceptual, acoustic and laryngostrobic findings pre- and post-therapy. J Voice. 2004;18:325–340.

59. Carding PN, Horsley IA. An evaluation study of voice therapy in non-organic dysphonia. Eur J Disord Commun. 1992;27:137–158.

60. Carding PN, Horsley IA, Docherty GJ. The effectiveness of voice therapy for patients with non-organic dysphonia. Clin Otolaryngol. 1998;23:310 –318.

61. Carding PN, Horsley IA, Docherty GJ. A study of the effectiveness of voice therapy in the treatment of 45 patients with nonorganic dysphonia. J Voice. 1999;13:72–104.

62. MacKenzie K, Millar A, Wilson JA, *et al*. Is voice therapy an effective treatment for dysphonia? A randomised controlled trial. BMJ. 2001;323:1– 6.

63. Verdolini-Marston K, Burke MK, Lessac A, *et al*. Preliminary study of two methods of treatment for laryngeal nodules. J Voice. 1995;9:74 – 85.

64. Weigelt S, Krischke S, Klotz, *et al*. Voice handicap in patients with organic and functional dysphonia. HNO. 2004;52:751–756.

65. Guimaraes I, Abberton E. An investigation of the Voice Handicap Index with speakers of Portuguese: preliminary data. J Voice. 2004;18:71– 82.

66. Gunther S, Rasch T, Klotz M, Hoppe U, Eysholdt U, Rosanowski F. Determination of subjective impairment in dysphonia. A methodological comparison. HNO. 2005;53(10):895-900, 902-4.

67. Fung K, Yoo J, Leeper HA, et al. Vocal function following radiation for non-laryngeal versus laryngeal tumors of the head and neck. Laryngoscope. 2001;111:1920 –1924.

68. Trussart C, Lawson G, Remacle M. Voice prostheses: long- term follow-up retrospective study (three- to sixteen-year follow-up of 22 patients). Rev Laryngol Otol Rhinol (Bord).2003;124:299 –304.

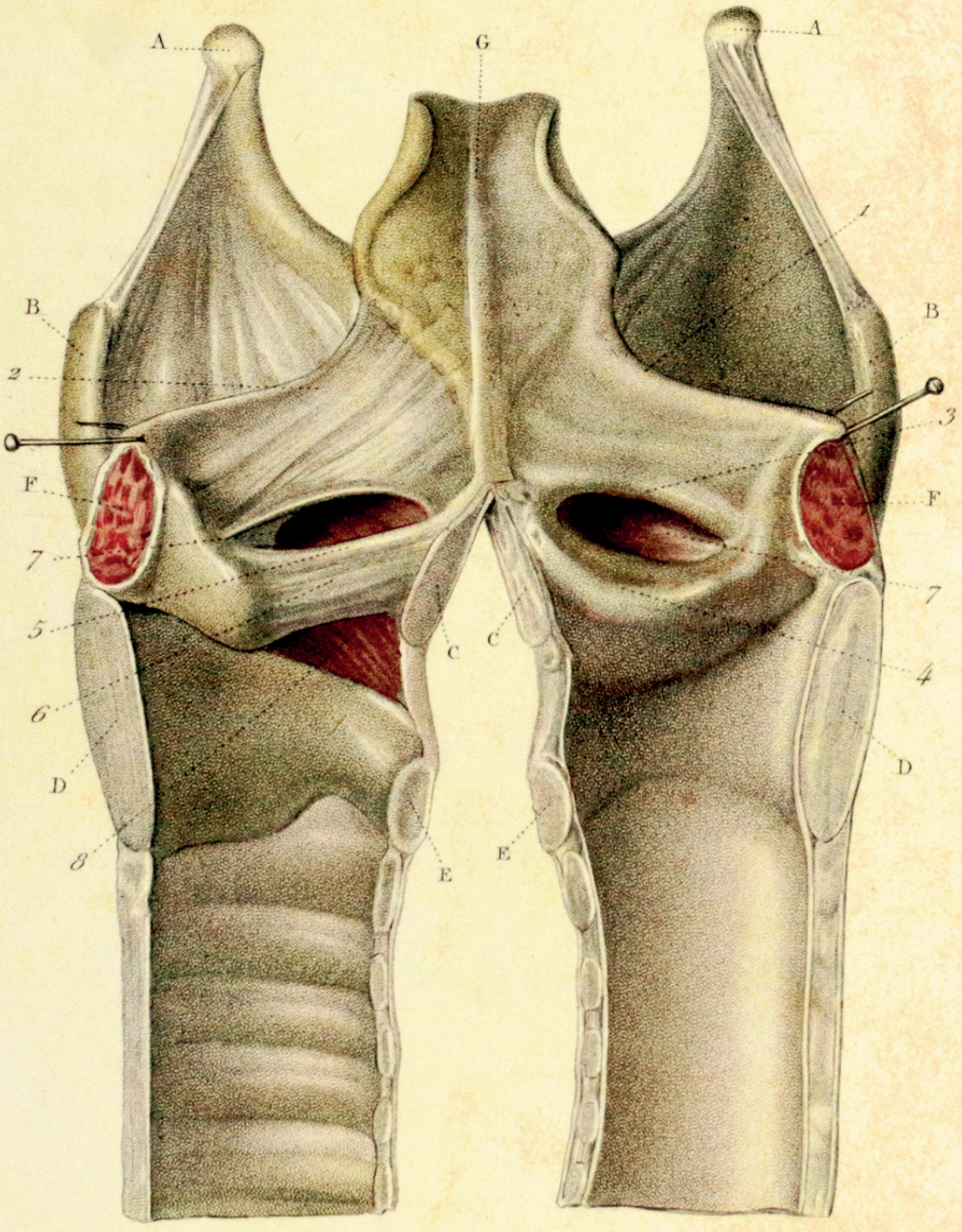
69. Moerman M, Martens J-P, Dejonckere P. Application of the Voice Handicap Index in 45 patients with substitution voicing after total laryngectomy. Eur Arch Otorhinolaryngol.2004;261:423–428.

70. Meleca RJ, Dworkin JP, Kewson DT, Stachler RJ, Hill SL. Functional outcomes following nonsurgical treatment for advanced-stage laryngeal carcinoma. Laryngoscope. 2003;113:720 –728.

71. Schuster M, Lohscheller J, Hoppe U, Kummer P, Eysholdt U, Rosanowski F. Voice handicap of laryngectomies with tracheoesophageal speech. Folia Phoniatr Logop. 2004;56:62–67.

72. Brondbo K, Benninger MS. Laser resection of T1a glottic carcinomas: results and postoperative voice quality. Acta Otolaryngol. 2004;124:976 –979.

Fig. I.



CHAPTER

LONG-TERM EFFICACY OF VOICE THERAPY IN PATIENTS WITH VOICE PROBLEMS AFTER TREATMENT OF EARLY GLOTTIC CANCER

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Journal of Voice 2012; 26(3):398-401.

ABSTRACT

Objective The purpose of the present pilot study is to investigate whether the beneficial short-term effects of voice therapy in patients with voice problems after treatment of early glottic cancer as reported in our earlier study remain present on the long term.

Study Design In this prospective study, 12 patients, selected based on a screening questionnaire about voice problems and randomly assigned for treatment with voice therapy (vs no treatment), were evaluated with a mean of 13 months after finishing voice therapy to evaluate the long-term voice effects.

Methods Voice assessment consisted of the Voice Handicap Index (VHI) and acoustic analyses (percent jitter, percent shimmer, and noise-to-harmonics ratio).

Results Statistical analysis showed that the beneficial short-term effect on the mean VHI, percent jitter, and shimmer remained stable after more than a year of follow-up.

Conclusions The present study provides initial evidence that the beneficial effect of voice therapy is not just a short-lived voice improvement but may result in a better voice for a period of at least 1 year. Future long-term randomized controlled trials are needed to confirm our findings.

INTRODUCTION

Early staged glottic cancer can be successfully managed by either radiotherapy or endoscopic laser surgery, both providing high local control rates and long-term cure rates[1-5]. Reports on voice outcome are generally less favorable and more contradictory concerning both treatment modalities. Recent studies on functional results describe a wide range of incidence of abnormal voice quality 14–92% after radiotherapy and 17–70% after laser surgery, respectively[6-12]. Furthermore, studies on the influence of deteriorated voice on quality of life revealed that 27–58% of patients with voice problems experienced difficulties in communication leading to a disrupted social life[8,13-22]. Evidently, a considerable number of patients treated for early glottic cancer have to deal with voice problems in daily life. Until recently, it was not clear whether these voice problems are amenable to voice therapy. Earlier research provided evidence of short-term efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer[23]. In this randomized prospective study, immediate beneficial effect of voice therapy was not only found in the primary outcome measure, the Voice Handicap Index (VHI), but also in some of the other voice quality outcome measures (noise-to-harmonics ratio[NHR], jitter, and the perceptual rating of vocal fry)[23]. Outcome studies on efficacy of voice therapy in general are scarce and usually only report short-term effects. To the best of our knowledge, only three studies have reported on Long-term results of voice therapy involving patients treated for laryngeal cancer, and their results were contradictory[24-26]. Fex and Henriksson[24] applied voice therapy to reduce voice damage caused by radiotherapy fork laryngeal cancer. In their study, 15 patients received voice treatment during radiation therapy. Unfortunately, the definition of normal voice quality in that study remained unclear, and a control group was lacking. Therefore, it is impossible to conclude that the voice results were a consequence of voice therapy. Zwirner *et al*.[25] reported a positive acoustic effect of voice therapy in patients after laser surgery for T1–T3 laryngeal carcinomas. In this prospective study, 13 patients with substantial deterioration of voice function after laser surgery were subjected to an intensive voice rehabilitation program. After rehabilitation, the standard deviation of fundamental frequency and the NHR improved significantly but did not return to ''normal'' values as obtained from an age-and gender-matched control group. Sittel *et al*.[26] could not demonstrate this beneficial effect of voice therapy after laser surgery for T1–T2 laryngeal carcinomas. On the contrary, they found that patients who did not receive voice therapy had considerable better voices than patients who did receive voice therapy. The patients after voice therapy showed a high percentage of ventricular fold phonation. According to the authors, this might have been because of lack of information and knowledge of the speech therapists, who may have assumed that phonation on glottic level was impossible after laser surgery.

The purpose of the present study is to determine whether the beneficial short-term effects of voice therapy in patients with voice problems after treatment of early glottic cancer as reported in our earlier study remain present on the long-term.

PATIENTS AND METHODS

Patients

During a period of 1 year, all patients visiting the head and neck oncology outpatient clinic for their regular follow-up after previous treatment with either radiotherapy or endoscopic laser surgery for early glottic cancer (Tis, T1N0M0, and T2N0M0 tumors; Tis: carcinoma in situ; T1: tumor limited to the vocal folds with normal mobility; T2: tumor expands supra- and/or subglottic, and/or impaired mobility; N0: no regional lymph node metastasis; M0: no distant metastasis, all according to the International Union Against Cancer staging system) at least 6 months before their visit had been screened regarding voice impairment. The screening instrument consisted of a validated and standardized 5-item 10-point anchored scaled questionnaire covering vocal abilities and social situations[27].

Patients who, according to this questionnaire, showed voice impairment (score of 5 or less on at least one of the five items) had been asked to participate in a study on the efficacy of voice therapy. Those who were willing to participate had been divided, in order of appearance (random), into a voice therapy group(n = 12) or a control group(n = 11). Short-term results of this controlled study on efficacy of voice therapy have been reported earlier[23].

The present pilot study focuses on the long-term results among the 12 patients in the voice therapy group. These patients were followed up for an average of 13 months (range, 6–20 months) after completion of the voice therapy. Their mean age, at the initial inclusion, was 58 years (range, 40–80). At the time of initial inclusion, the average time elapsed since the cancer treatment had been 31 months (range, 6–81). None of the 12 patients in the voice therapy group underwent any intervening medical or surgical treatment during the study period.

Radiotherapy

Patients treated with radiotherapy (n = 9) had been locally irradiated with the Varian CLINAC 2300, a linear 6 MV accelerator (Varian Medical Systems Inc., Palo Alto, CA). The total radiation was 57.5–60.0 Gy in case of T1a and T1b tumors (2.5 Gy per fraction, five times a week), whereas T2 tumors were generally irradiated with an accelerated schedule to a total dose of 70 Gy (2 Gy per fraction, six times a week). All T1 patients had been treated with two opposing lateral fields, generally, with a standard field size of 6 x 6 cm, using 6 MV photons. In case of a T2 tumor with supraglottic extension beyond the false cords and/or subglottic extension >1 cm, the radiation portals had been extended to levels II to IV on both sides and/or the paratracheal lymph node areas, respectively.

Endoscopic laser surgery

Patients treated with endoscopic laser surgery (n = 3) had been selected by means of videolaryngostroboscopic evaluation, using the presence of mucosal undulation as an indication for superficial tumor spread only. A Sharplan CO2 laser (with ACUspot micromanipulator; Sharplan Laser Industries, Tel Aviv, Israel) in a superpulse mode had been used for a chordectomy type II[28].

Methods

Voice therapy

Patients were referred to a speech-language pathologist specialized in voice therapy (voice therapist) in their own neighborhood and treated with a maximum of 24 sessions; 30 minutes each, with a frequency of twice a week. The voice therapists informed about the patient's medical history and videolaryngostroboscopic examination findings. The type of voice therapy could be freely chosen according to the patient's needs and the therapists' preference.

Voice analyses

All patients' voices were examined three times: once at baseline (study entry assessment), once directly after finishing voice therapy (short-term assessment), and once after a longer period of time (follow-up assessment) at a moment that coincided with the normal follow-up in the head and neck oncology outpatient clinic. Multidimensional voice analysis (VHI questionnaire, acoustic and perceptual voice quality analysis, videolaryngostroboscopy, and voice range profile) was performed. As previously reported, the results of short-term efficacy proved to be good (p = 0.024) with a mean improvement of 15 points on the VHI (the main outcome measure)[23]. A beneficial short-term efficacy of voice therapy had also been found regarding the secondary voice quality outcome measures: NHR, jitter, and perceptual rating of vocal fry[23].

To assess long-term efficacy of voice therapy, follow-up assessment was performed 6 months or more after finishing voice therapy. The follow-up voice assessment was restricted because of logistic reasons and included the VHI and acoustical voice analyses, which had shown the most distinct beneficial immediate effects of voice therapy[23]. The study period was defined as the time between short-term and follow-up assessment.

Voice Handicap Index.

The VHI had been chosen as primary outcome measure. The VHI is a validated questionnaire measuring psychosocial handicapping effects of voice disorders[29] and was translated and validated in Dutch[30]. The questionnaire consists of 30 statements on voice-related aspects in daily life (5-point rating scale), which can be divided in a functional, a physical, and an emotional subscale. The total score of the 30 questions ranges from 0 to 120. A higher score indicates a higher level of voice handicap (**Appendix 2)**.

Acoustic Analyses.

Digital recordings of a sustained vowel /a/ at comfortable loudness and pitch were performed using the Computerized Speech Lab and Multidimensional Voice Program, developed by Kay Elemetrics (Pine Brook, NJ). A mouth-to-microphone distance of approximately 30 cm was held constant throughout all samples. Acoustic signal typing according to Behrman et al.31 revealed that all recordings were suitable for further acoustic analyses. Percent jitter, percent shimmer, and NHR were determined. The percentage of jitter represents the relative period-to-period variability. The percentage of shimmer represents the relative variability of the peak-to-peak amplitude. The NHR is an average ratio of energy of the inharmonic components in the range 1500–4500 Hz to the harmonic components energy in the analyzed signal.

Statistical analysis

The maintenance of the beneficial short-term efficacy of voice therapy in the long term was assessed by independent t tests on the mean voice analyses scores between short-term and follow- up assessments.

RESULTS

The mean time between short-term and follow-up assessments (study period) was 13 months (range, 6–20).

Voice Handicap Index

Table 1 shows the total VHI score per individual patient for the three different voice assessment periods (study entry, short-term, follow-up). The mean VHI scores improved significantly immediate after completion of voice therapy from 40 to 24 ($t = 2.76$, $p = 0.013$)[23]. During the study period, there was no additional significant change in VHI ($t = 0.533$, $p = 0.600$), and the mean VHI score at follow-up assessment stayed significantly better as compared with the initial study entry assessment ($t = .3.10$, $p = 0.006$).

Acoustic analyses

Table 2 shows the mean scores of the acoustical parameters per voice assessment period. Immediately after completion of voice therapy, the acoustical parameters NHR ($t = 3.142$, $p = 0.009$), jitter ($t = 2.513$, $p = 0.029$), and shimmer ($t = -2.653$, $p = 0.022$) had improved significantly. During the study period, none of the acoustical parameters changed significantly with exception of the NHR, which ($t = -4.185$, $p = 0.002$)deteriorated. The mean values of the NHR and jitter at follow-up assessment showed no significant difference as compared with the initial study entry assessment ($t = 1.307$, $p = 0.221$ and $t = 2.082$, $p = 0.064$, respectively). However, the mean value of shimmer at follow-up assessment stayed significantly better as compared with the initial study entry assessment ($t = 2.250$, $p = 0.048$).

Table 1. Voice Handicap Index scores per assessment for each individual patient, and mean total scores (Standard deviation) per assessment

N	Study entry	Short term	Follow up	Study- period (months)
1	30	25	14	12
2	61	28	17	6
3	21	26	32	6
4	25	23	16	15
5	22	4	9	14
6	38	15	10	11
7	33	36	27	12
8	57	11	11	12
9	51	37	21	14
10	68	37	34	20
11	43	26	44	12
12	27	25	30	18
Mean Total	40 (16.17)	24 (10.26)	22 (11.19)	13

Table 2. Mean values (Standard Deviation) for the acoustical parameters of the patients per assessment

	Study entry	Short term	Follow up
NHR	.20 (.06)	.14 (.02)	.17 (.02)
Jitter	2.20 (1.50)	1.39 (1.32)	1.24 (1.03)
Shimmer	7.26 (3.20)	5.10 (1.12)	4.94 (2.95)

DISCUSSION

Our previous report already demonstrated the beneficial short-term effect of voice therapy in patients with voice problems after treatment of early glottic cancer[23]. The present study provides initial evidence that this beneficial effect of voice therapy is not only just a short-lived voice improvement but also results in a better voice for a period of at least a year, and there is no reason to suspect a spontaneous voice deterioration after a longer period of time. The mean VHI score (the main outcome measure) improved from 40 at baseline to 24 post voice therapy and remained stable (score 22) after more than a year.

Recent studies revealed equivalence of various European translations and the original American VHI and confirmed the validity of a Dutch translation of the VHI in Dutch[32,33].

In the previous study, we confirmed that the VHI is an adequate tool for baseline and effectiveness measurement of voice problems in daily life. Regarding clinical relevant difference scores, a difference score of 10 points was found to be useful for individuals in clinical practice and 15 points to be useful in study group designs[33]. Applied to the results of this former study, we see that immediately after completion of voice therapy in 7 of the 12 patients, the improvement on the VHI was clinically relevant with an amelioration of more than 10 points. Two of them even managed to obtain a VHI score well within the normal range (below 15) immediately after completion of voice therapy[33]. Even more, another three patients showed further improvement into the VHI range of normal voices during the study period in the long term.

Findings in this study indicate that the beneficial short-term effect of voice therapy in patients who experience voice problems after treatment of early glottic cancer usually lasts in the long term and that even some time after completion of voice therapy further improvement can be found. Obviously, these results must be interpreted with some precaution, as a consequence of the relatively small number of patients included in the present study. Another point of concern is the low motivation rate noted during the initial inclusion phase of this study: almost 60% of the patients with self-reported voice problems after treatment for early glottic cancer did not feel the need for voice therapy and therefore did not participate[23]. The patients presently included represent a group that was selected on grounds of positive motivation to follow a voice therapy program. The results may, therefore, be less favorable if patients are urged to enroll in a voice therapy program without the proper motivation. Future large-scaled studies are needed to assess long-term efficacy of voice therapy in patients treated for early glottic cancer.

CONCLUSION

The present study provides initial evidence that this beneficial effect of voice therapy is not just a short-lived voice improvement but results in a better voice for a period of at least 1 year.

Acknowledgments

This study was financed by the Efficiency Research Program of the Association of Academic Hospitals (VAZ) and the Dutch Health Insurance Council (CVZ).

REFERENCES

1. Jones AS, Fish B, Fenton JE, Husband DJ. The treatment of early laryngeal cancers (T1–T2N0): surgery or irradiation? Head Neck. 2004;26:127–135.
2. Goor KM, Mahieu HF, Langendijk JA, Leemans CR, Verdonck-de Leeuw IM, van Agthoven M. Cordectomy by CO2 laser or radiotherapy for small T1a glottic carcinomas: costs, local control, survival, quality of life, and voice quality. Head Neck. 2007;29:128–136.
3. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. Cancer. 2004;100:1786–1792.
4. Krengli M, Policaro M, Manfredda I, Aluffi P, Gambaro G, Panella M, Pia F. Voice quality after treatment for T1a glottic carcinoma. Acta Oncol. 2004;43:284–289.
5. Mlynarek A, Kost K, Gesser R. Radiotherapy versus surgery for early T1-T2 glottic carcinoma. J Otolaryngol. 2006;35:413–419.
6. Kennedy JT, Paddle PM, Cook BJ, Chapman P, Iseli TA. Voice outcomes following transoral laser microsurgery for early glottic squamous cell carcinoma. J Laryngol Otol. 2007;121:1184–1188.
7. Aref A, Dworkin J, Devi S, Denton L, Fontanesi J. Objective evaluation of the quality of voice following radiation therapy for T1 glottic cancer. Radiother Oncol. 1997;45:149–153.
8. Verdonck-de Leeuw IM, Keus RB, Hilgers FJM, *et al*. Consequences of voice impairment in daily life for patients following radiotherapy for early glottic cancer: voice quality, vocal function, and vocal performance. Int J Radiat Oncol Biol Phys. 1999;44:1071–1078.
9. Verdonck-de Leeuw IM, Hilgers FJM, Keus RB, *et al.* Multidimensional assessment of voice characteristics after radiotherapy for early glottic cancer. Laryngoscope. 1999;109:241–248.
10. Hocevar-Boltezar I, Zargi M. Voice quality after radiation therapy for early glottic cancer. Arch Otolaryngol Head Neck Surg. 2000;126:1097–1100
11. Lehman JJ, Bless DM, Brandenburg JH. An objective assessment of voice production after radiation therapy for stage I squamous cell carcinoma of the glottis. Otolaryngol Head Neck Surg. 1988;98:121–129.
12. RydellR, SchalenL, Fex S, Elner A. Voice evaluationbeforeandafter laser excisionvs. radiotherapyofT1aglotticcarcinoma.ActaOtolaryngol.1995;115:560–565.
13. CohenSM,GarrettCG,DupontWD,OssoffRH,CoureyMS.Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. Ann Otol Rhinol Laryngol. 2006;115:581–586.
14. RohJL,KimDH,Yoon KimS,ParkCI.Qualityoflifeandvoice inpatients after lasercordectomy for Tis and T1 glottic carcinomas.Head Neck. 2007;29:1010–1016.
15. Van der Torn M, Verdonck-de Leeuw IM, Kuik DJ, Mahieu HF. Communicative suitability of voice following radiotherapy for T1a glottic carcinoma: testing the reliability of a rating instrument. J Voice. 2002;16:398–407.

16. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schmid S. Quality of life after treatment for early laryngeal carcinoma. Eur Arch Otorhinolaryngol. 2001;258:96–99.

17. SmithJC, JohnsonJT, Cognetti DM, Landsittel DP,GoodingWE, Cano ER, Meyers EN. Quality of life, functional outcome, and costs of early glottic cancer. Laryngoscope. 2003;113:68–76.

18. Peeters AJGE, Van Gogh CDL, Goor KM, Verdonck-de Leeuw IM, LangendijkJA, Mahieu HF.Health status and voice outcome after treatment for T1a glottic carcinoma. Eur Arch Otorhinolaryngol. 2004;261:534–540.

19. Van Gogh CDL, Verdonck-de Leeuw IM, Boon AB, Langendijk JA, Kuik DJ, Mahieu HF. A screening questionnaire for voice problems after treatment for early glottic cancer. Int J Radiat Oncol Biol Phys. 2005;62:700–705.

20. Jepsen MC, Gurushanthaiah D, Roy N, Smith ME, Gray SD, Davis RK. Voice, speech, and swallowing outcomes in laser-treated laryngeal cancer. Laryngoscope. 2003;113:923–928.

21. Fung K, Yoo J, Leeper HA, *et al.* Effects of head and neck radiation therapy on vocal function. J Otolaryngol. 2001;30:133–139.

22. Stewart MG, Chen AY, Stach CB. Outcomes analysis of voice and quality of life in patients with laryngeal cancer. Arch Otolaryngol Head Neck Surg. 1998;124:143–148.

23. Van Gogh CDL, Verdonck-de Leeuw IM, Boon-Kamma BA, *et al*. Efficacy of voice therapy in patients after treatment of early glottic cancer. Cancer. 2006;106:95–105.

24. Fex S, Henriksson B. Phoniatric treatment combined with radiotherapy of laryngeal cancer for the avoidance of radiation damage. Acta Otolaryngol Suppl. 1969;263:128–129.

25. Zwirner P, Michaelis D, Kruse E. On documentation of voice rehabilitation after laser surgery laryngeal carcinoma resection. HNO. 1996;44:514–520.

26. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. Otolaryngol Head Neck Surg. 1998;119:418–424.

27. Kaanders JHAM, Hordijk GJ. Carcinoma of the larynx: the Dutch national guideline for diagnostics, treatment, supportive care and rehabilitation. Radiother Oncol. 2002;63:299–307.

28. Remacle M, Eckel HE, Antonelli A, *et al.* Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society. Eur Arch Otorhinolaryngol. 2000;257:227–231.

29. Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G, Benninger MS, Newman CW. The voice handicap index (VHI): development and validation. Am J Speech Lang Pathol. 1997;6:66–70.

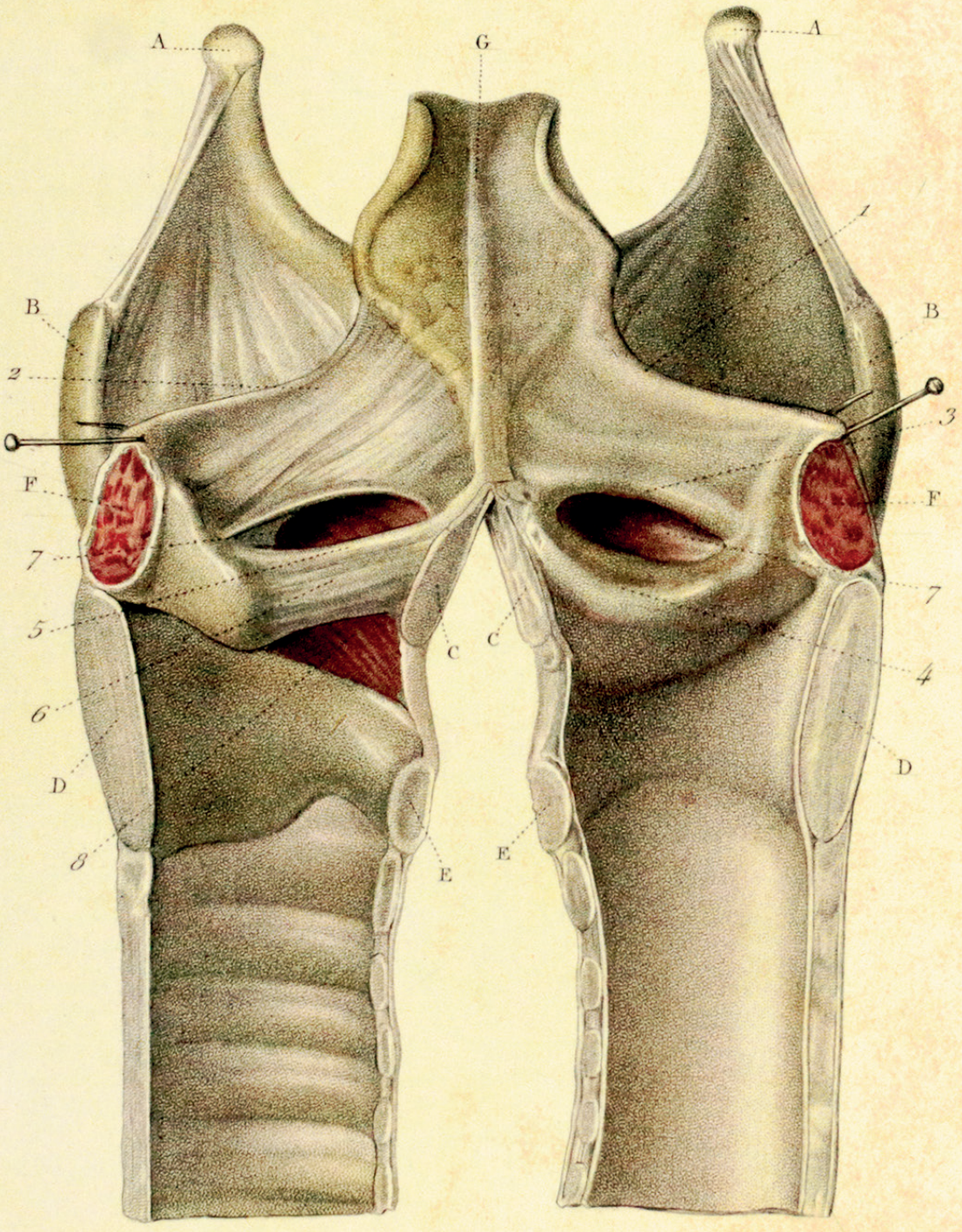
30. Verdonck-de Leeuw IM, Boon-Kamma AB, van Gogh CDL, Greven AJ, Peeters AJGE, Mahieu HF. Measurement of voice quality of patients with early glottic cancer. Logopedie en Foniatrie. 2002;12:340–345 [in Dutch].

31. Behrman A, Agresti CJ, Blumstein E, Lee N. Microphone and electroglottograhic data from dysphonic patients type1, 2 and 3 signals. JVoice.1998;12:249–260.

32. Verdonck-de Leeuw IM, Kuik DJ, De Bodt M, *et al*. Validation of the Voice Handicap Index (VHI) by assessing equivalence of European translations. Folia Phoniatr Logop. 2008;60:173–178.

33. Van Gogh CDL, Mahieu HF, Kuik DJ, Rinkel RNPM, Langendijk JA, Verdonck-de Leeuw IM. Voice in early glottic cancer compared to benign voice pathology. Eur Arch Otorhinolaryngol. 2007;264:1033–1038.

Fig. I.



CHAPTER

CONCLUSIONS, DISCUSSION AND RECOMMENDATIONS

CONCLUSIONS

Identification of voice problems after treatment of early glottic cancer is important, especially since so many patients with early glottic cancer can be cured of their disease, and voice problems have an important impact in daily life activities.

The purpose of this thesis was to enhance our knowledge regarding voice outcome in patients after treatment of early glottic cancer, to investigate the relation 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. In order to achieve this goal, 8 research questions were formulated as described in the introduction and can be addressed based on the studies reported on in this thesis.

Research questions

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?*

The study described in Chapter 2 demonstrated that voice problems after treatment of early glottic cancer frequently occur: 44% of the patients treated with radiotherapy and 29% of the patients treated with endoscopic laser surgery experience voice problems (no significant difference p= 0,079). Patients with voice problems following treatment of early glottic cancer can be identified in clinical practice using a short 5-item screening questionnaire.

2. *To assess the impact of voice problems after treatment of early glottic cancer on daily life activities.*

The study described in Chapter 3 demonstrated that many patients (58% of the patients following radiotherapy and 40% of the patients following endoscopic laser surgery (p= <0,05) experience voice problems after treatment of early glottic cancer, leading to restrictions in their social life, mental well-being and overall health, as was shown by significant correlations between the VHI (tool to assess patient reported voice problems) and COOP/WONCA charts (tool to assess patient reported functional health status).

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

The study described in Chapter 4 demonstrated the VHI to be an adequate tool for detailed assessment of perceived voice problems after treatment of early glottic cancer. A validated cut-off point of 15 (or higher) on the total VHI score was recommended to identify patients with voice problems in daily life. To interpret significant changes or differences, a validated difference score of 10 points for individuals in clinical practise and 15 points for study group designs was recommended.

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.*

The study described in Chapter 4 demonstrated that voice problems among patients after treatment of early glottic cancer are comparable to voice problems perceived by patients with benign vocal fold pathology as was demonstrated by similar VHI scores in both groups.

5. *To investigate 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.*

The study described in Chapter 5 demonstrated that, except for fundamental frequency, no significant long-term (24 months) differences in voice outcome between radiotherapy and laser surgery treated patients with early glottic cancer were identified, as measured by acoustic analyses. Fundamental frequency remained higher pitched in patients treated by laser surgery.

However, voice recovery following treatment, as determined by acoustic analysis, occurred more rapidly in patients treated with laser surgery than in patients treated with radiotherapy. Moreover, long term voice outcome (one year or more following treatment), as reported by the patients themselves as assessed with the VHI, significantly favours laser surgery above radiotherapy as described in Chapter 3 with a mean VHI for the laser surgically treated group of 12,0 and a mean VHI of the radiotherapy treated group of 18,2.

6. *To investigate whether voice outcome following treatment for early glottic cancer differs from normal voices.*

The study described in Chapter 5 demonstrated that compared to normal voices, in the long-term (24 months) the patients treated with laser surgery had a higher than normal vocal pitch and the patients treated with radiotherapy had a higher than normal jitter value. Based on the new validated cut-off point for voice impairment as determined in Chapter 4 (considering a VHI score lower than 15 as normal instead of a score lower than 10), 50% of the patients after radiotherapy achieve normal VHI-scores, whereas 70% of the patients after laser surgery achieve normal VHI scores (significant difference, $p<0,05$) (as recalculated using the data from Chapter 3) .

7. *To assess the efficacy of voice therapy for voice problems after treatment of early glottic cancer.*

The study described in Chapters 6 and 7 demonstrated that, compared to a randomized control group without voice therapy, voice therapy has a beneficial effect on voice quality of the patients with voice problems following treatment of early glottic cancer. This

positive effect was found with respect to patient reported voice outcome (VHI) as well as to acoustic voice quality assessment. These beneficial effects of voice therapy on voice outcome persisted for at least 1 year after completing voice therapy.

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.*

The studies described in Chapters 3 and 5 demonstrated that there are differences in voice outcome between radiotherapy and laser surgery for early glottic cancer, especially during the first period following treatment, and that patients treated with laser surgery demonstrate an earlier recovery of normal voice values and more patients (70%) achieve normal VHI scores than patients following radiotherapy (50%). Therefore voice outcome can be considered an important factor in deciding on a preferred treatment modality.

DISCUSSION

Treatment of choice for early glottic cancer

Obviously cure remains the most important factor for patients who are diagnosed with a malignancy. But when primary cure rates of different treatment options are equal, this is no longer a factor determining the primary choice of treatment. This thesis revealed that it is worth considering to include (speed of) recovery of voice outcome in (shared) decision making on treatment choice.

Besides voice outcome, other factors such as morbidity, remaining options for salvage therapy, treatment options for a regional second primary malignancy, quality of life, patient's general health and costs also play a prominent role in the decision making for the individual patient concerning cancer treatment as well as post treatment supportive cancer care. In the following section we will discuss the factors determining the choice of preferred treatment modality in more detail.

Oncological outcome in broader perspective

Recent data support the generally held opinion that both laser surgery as well as radiotherapy have good local control rates for early glottic carcinoma of 71-94% and 73-94% respectively[1-3]. However, oncological outcomes of laryngeal cancer are not only determined by the local control rates, but also by the salvage treatment options in case of a recurrence of the primary tumor, preferably without sacrificing the larynx or its functions. Literature reports larynx preservation rates of 95-98% and 77-95% for respectively primary laser surgery and primary radiotherapy[1-3]. Although this was not the main purpose of this thesis, similar results as in the above mentioned studies were found in our own study group described in Chapter 5 (including 106 patients; 67 treated with endoscopic laser surgery and 39 patients treated with radiotherapy) with local control rates of 97% and 95%, and larynx preservation rates of 100% and 95% for respectively laser surgery and radiotherapy 2 years after treatment of T1a glottic cancer.

Given the excellent and almost identical primary local control rates of both treatment modalities it makes sense to take the salvage options into account when trying to determine a preferred treatment of choice.

Given the fact that patients, who have once developed a head and neck malignancy[4], have a higher risk of developing a second primary tumor, the above mentioned also holds true for taking into account how previous treatment of an early glottic cancer will influence the possibilities of treating a regionally developed second primary tumor.

Salvage treatment after primary radiotherapy

In case of radiotherapy as primary treatment, Kasperts[5] *et al*. demonstrated, in a systematic review, that re-irradiation for recurrent and second primary head and neck cancer has a relatively high risk of both acute and late complications. Soft tissue necrosis and osteonecrosis are the most frequently occurring complications but also (fatal) haemorrhages and fistulas are described.

This can be expected to hold true for re-irradiation of a recurrent cancer as well as for irradiation of a second primary tumor, should that second primary tumor develop within a previously irradiated area. Kasperts *et al*. conclude that salvage surgery, when feasible, is the treatment of choice for recurrences or second primaries following primary radiotherapy. We have to bear in mind that this study was not restricted to cases of early glottic cancer, usually treated with lower over-all doses of radiotherapy than more extensive head and neck tumors. In contrast with Kasperts, Wang *et al*.[6], who studied the possibilities of re-irradiation following recurrences of early glottic cancer, concluded that re-irradiation is a good alternative for laryngectomy.

Without any doubt total laryngectomy remains an oncological safe salvage procedure but it severely compromises quality of life[7]. Several studies report good results with external partial laryngectomy as organ preserving salvage therapy for limited recurrences (T1-T2) after primary radiotherapy[8-12]. However, these procedures performed as salvage therapy after radiotherapy carry an increased risk of postoperative complications, like chondritis, chondronecrosis and fistulas. Furthermore quality of life can be compromised by temporary or permanent tracheostomy and swallowing problems[13].

Several studies proved laser surgery to be an adequate organ preserving salvage procedure for selected recurrences after primary radiotherapy for early glottic cancer[14-16]. In spite of the occasional (17-19%) need for repetition of salvage laser surgery this can eventually result in 5-year disease-specific survival rates of 68% to 94%, local control rates of 42% to 84%, and larynx preservation rates of 74% to 87% for treatment of recurrent cancer[14,15].

To our knowledge only Del Bon[14] *et al*. studied voice outcome after salvage laser surgery. In a small series they found no significant differences in VHI and acoustical analyses between 10 patients following primary laser surgery for early glottic cancer as compared to 10 patients following laser salvage treatment for irradiation failure.

Salvage after primary laser surgery

In case of recurrence after primary laser surgery for early glottic carcinoma many retreatment options are available[17,18]. First of all repeated laser surgery proves to be a good salvage treatment for recurrences after primary laser surgery for early glottic cancer[19,20]. Both Huang[19]*et al*. and Roedel[20] *et al*. justify salvage laser surgery for the less advanced re-

currences (rTis-T2) with a 5-year disease-specific survival rate of 97.9% and 81%, a larynx preservation rate of 86% and 91% and a 5-year local control rate of 70% and 64% respectively (16% and 34% required repeated laser surgery). Both authors stress the importance of experience with salvage laser surgery, good exposure of the tumor and patients who are closely followed-up. Furthermore they state that advanced recurrences, infiltration of both arytenoids, and/or deep cervical tumor spread are not suitable for laser salvage.

Salvage radiotherapy, is also a reliable therapeutic option for recurrences after initial laser surgery[17,18].

Furthermore partial laryngectomies (for the less advanced recurrences) and total laryngectomies (for the more advanced recurrences) are oncological safe salvage procedures for laser failures, with less morbidity than when performed after primary radiotherapy[18,21].

Voice outcome

When endoscopic laser treatment came "en vogue", the initially by many authors held opinion was that voice outcome following laser treatment was worse compared to voice outcome than following radiotherapy[22-27]. Since then many studies addressed voice outcome after laser surgery and radiotherapy for early glottic cancer, but results remained contradictory[28-45]. Our studies clearly demonstrate that voice problems indeed occur in patients after treatment of early glottic cancer, either following laser surgery or radiotherapy, and that this may interfere with the daily life activities of patients.

The most important differences between both treatment options that we found, were more rapid voice recovery, less often patient reported voice problems in daily life, and higher pitched voice, in patients after laser surgery in comparison to patients after radiotherapy.

The persisting higher pitched fundamental frequency of the voice following endoscopic laser surgery (Chapter 5), is in accordance with recent literature[46,47]and may be explained by loss of mass and increased stiffness of the vocal fold, which both can result in an increase of the fundamental frequency. Cheng[46] *et al*. compared acoustical voice outcome (fundamental frequency, jitter, shimmer and harmonics to noise ratio) between patients treated by radiotherapy or endoscopic laser surgery for early glottic cancer (Tis-T2). Measured at least one year after treatment no difference was found between both groups concerning jitter, shimmer and harmonics to noise ratio. Only fundamental frequency was significantly higher in the patients of the endoscopic laser group. Unfortunately, their study had a cross-sectional (not longitudinal) design and their data can therefore not support nor deny our finding that voices of patients recovered more rapidly after laser surgery than after radiotherapy. The study by Cheng *et al*. as well as other studies[36,37,46] supported our finding that fundamental voice frequency in irradiated patients does not differ significantly from normal controls. It may be that the changes in structure of the vocal folds follow-

ing radiotherapy, such as radiation-induced tissue fibrosis, atrophic changes, and mucosal dryness on the one hand and post radiation oedema on the other hand, compensate each other, with respect to vocal fundamental frequency outcome, but future physiological studies are needed to investigate this hypothesis.

Although we did not find a significant difference for jitter between radiotherapy and laser surgery 6 months after treatment, jitter remained (even after 24 months) significantly higher after radiotherapy in comparison to normal speakers.

Although voice quality of patients following treatment for early glottic cancer over-all differs from the standard, especially in the first months following treatment, this does not mean that all patients indeed experience a voice problem in daily life. Voice problems six months or more after either radiotherapy or endoscopic laser surgery were reported by 44% and 29% respectively in a group of 177 patients with early glottic cancer as determined by a voice screening questionnaire (Chapter 2). In Chapter 3, among a group of 92 patients, at least 12 months after radiotherapy or laser surgery, these percentages were respectively 58% and 40% as determined by the VHI questionnaire with a cut-off point taken at that time at 10 points. In the more recent study as described in Chapter 4 the new, validated cut-off point of the VHI changed to 15 points. If the results presented in Chapter 3 are re-calculated taking into account the validated cut-off point of 15, 50% and 30% of the patients experience voice problems following respectively radiotherapy and endoscopic laser surgery. The results support the screening questionnaire (5 items) to be a good tool to identify voice problems, comparable with the slightly more elaborate VHI (30 items). Contrary to the sometimes still held opinion that radiotherapy[25-27] is the most voice preserving therapy for early glottic cancer, our results demonstrated that voice recovery after laser surgery is faster and it is less likely that patients treated with laser surgery experience voice problems in daily life compared to patients following radiotherapy.

Morbidity of primary treatment of early glottic cancer

Radiotherapy is more time consuming for patients than laser surgery: patients undergoing radiotherapy have to go the clinic (depending on the radiation schedule) five days a week for 6 weeks on a row, while laser surgery can be performed in a one day clinical admission. Furthermore patients treated with radiotherapy often experience discomfort during and several weeks following the irradiation due to localized mucositis.

As a consequence of the narrow field of irradiation and the relatively low over-all dose of irradiation in cases of early glottic cancer, the incidence of major or long-term complications due to primary radiotherapy, such as glottic fibrosis and/or stenosis, cervical myelitis, laryngeal cartilage necrosis and hypothyroidism is low[48-50]. However, minor complications and discomforts, such as laryngitis, laryngeal dryness, swallowing disorders, radiation dermatitis or moderate oedema, not resolving within several weeks following the end of irradiation are reported to occur in up to 18% of patients[48-51].

Major complications after laser surgery for early glottic carcinoma are also rare[52,53]. Complications such as post-operative haemorrhaging, synechia of the anterior commissure, thermal tissue damage and oedema are described[52,54,55]. Ellies[52]*et al* treated 337 T1a and 30 T1b vocal fold carcinomas by endoscopic laser excision, with a low complication rate of 1.2% and 6.7% respectively. Postoperative hemorrhaging, requiring microlaryngoscopic hemostasis occurred in 3 cases. Furthermore they described 1 patient who developed a synechia, requiring treatment and 2 patients with laryngeal edemas which were managed conservatively. None of the cases required tracheotomy. In order to prevent synechia in the anterior commissure after laser surgery, Roh and Yoon[55] suggest application of mitomycin C to the wound defect. Thermal tissue damage can be minimized by using proper laser settings of energy, pulse, time and focus.

Treatment costs

Treatment of early glottic cancer by radiotherapy is a time-consuming procedure lasting several weeks and mainly because of that the one day visit endoscopic laser surgery is much more cost-effective than radiotherapy[42,56-59]. In our department Goor[57] *et al*., studying patients with T1a glottic cancer, found the total costs of treatment to be 8322 euros for radiotherapy and 4434 euros for endoscopic laser surgery in the period 1995 to 1999. This amount included the costs of the treatment of a recurrence, should it occur. In addition to the above mentioned actual costs, Smith[42] *et al*. showed that the hidden costs for radiation therapy versus endoscopic excision of early glottic cancer were all significantly higher for radiotherapy in terms of total number of hours of work missed, total travel time, and total travel distance.

Voice therapy

While voice therapy is commonly accepted as intervention in selected patients with benign voice disorders, patients with voice problems after treatment of early glottic cancer are usually not referred for voice therapy. This thesis revealed that patients after treatment of early glottic cancer encounter the same voice problems as patients with benign voice disorders and that voice therapy is beneficial for patients with voice problems following either radiotherapy or endoscopic laser surgery. The beneficial effect was observed not only immediately following voice therapy, but also in the long term (Chapter 6 and 7).

The prerequisite for effectiveness of voice therapy of course must be that a patient is sufficiently motivated to enter a voice therapy programme. It must be taken into consideration that the patients included in this study were motivated to follow a voice therapy program. The results may, therefore, be less favourable if patients are urged to enrol in a voice therapy program without clear motivation. A striking finding in our study was that nearly 60% of the patients with voice problems in daily life, did not express the need to be enrolled in a voice therapy program. This may be caused by the time-consuming nature of

voice therapy and the fact that patients may accept their voice problem as an unavoidable consequence of the treatment for a potentially life-threatening disease (adaptive coping strategy). To our knowledge there are no further recent studies about the efficacy of voice therapy in patients after treatment of early glottic cancer. Future research is needed to obtain more insight into the need and motivation for voice therapy. Nevertheless, based on the beneficial effect of voice therapy, it is recommended to offer patients with voice problems after treatment for early glottic cancer voice therapy as evidence based intervention.

Shortcoming

The results as reported in this thesis would have been methodologically stronger if randomized treatment allocation of patients to either radiotherapy or surgery could have been performed. We have to take into consideration that our research as presented in this thesis started in a period that radiotherapy was the recommended treatment modality for these early glottic cancers, and a randomized controlled trial was not an option at that time.

Also, even if a RCT would have been an option, comparison of functional outcome of different treatment modalities for early glottic cancer is difficult and challenging, and multicentre studies are needed to guarantee adequate subject numbers[60]. I agree with van Loon[60] *et al*., who mentioned that a standardized method is needed to accurately measure tumor extent and depth in order to allow comparison of laser surgery versus radiotherapy. Also, agreement on functional outcome measures is a requirement for comparison of functional results of types of treatment and resection.

The initial Dutch national guideline on laryngeal cancer (2000) adopted laser surgery only as a possible alternative for radiotherapy in superficial midcord T1a lesions[61]. The more recent Dutch guideline (2010) on laryngeal cancer recommends laser surgery as the treatment of choice for these T1a lesions, where a sufficient margin can be obtained within the affected fold, by either a subligamental or subepithelial resection which does not extend into the anterior commissure (type I and II cordectomy according to ELS classification)[62-64].

Regarding surgical treatment, although achievement of local control is paramount, the ability to perform radical resection, while preserving adequate voice quality, has been an important consideration in treatment decision making and in the design of current guidelines.

Deep T1a lesions or lesions extending into the anterior commissure requiring a transmuscular, total, or extended cordectomy or a resection of the anterior commissure (type III, VI and V of the ELS classification) are commonly regarded as less suitable for laser surgery, because poor voice quality is expected after these procedures[39]. Involvement of the anterior commissure can be considered slightly challenging because of its allegedly easy

local tumor spread. The anterior commissure is located very near to the thyroid cartilage: because of the absence of perichondrium or conus elasticus and early ossification of the cartilage at this level there is a poor local defence against for tumor spread once the tumor has infiltrated more deeply in the vocal fold. Clearly this is not a big issue in case of only superficial tumor spread. Adequate radiological staging at this level, especially invasion of the cartilage can be challenging[65]. Because of this and the fact that deep infiltration of tumor in the anterior commissure can occur without impairment of vocal cord mobility leads to a risk of understaging or overstaging in 25% to 50% of the cases[65-70]. The more extensive the tumor, the more extended the endoscopic laser resection, the more extensive the scarring of the vocal folds and consequently the worse voice outcome is anticipated. Roh[39] *et al*. indeed found that the extent of laser resection for Tis or T1 glottic carcinomas can affect the vocal function by influencing a patient's QOL associated with social activities. The early glottic cancers with a limited extent and infiltration depth (type I and II cordectomies) had significantly better results on VHI as well as on GRBAS as on acoustic analysis, compared to those lesions requiring extensive laser resection (type III, IV and V cordectomies). Also both Ledda[71] and Peretti[72,73] found worse voice quality from type III and more extensive resections in comparison to the smaller resection types I and II.

Despite many studies concerning cure rates and functional outcomes, international consensus on the choice of treatment for early glottic cancer is still an utopia. In the United Kingdom, the ENT-UK Head and Neck Group achieved consensus that trans oral laser assisted microsurgical resection should be offered as a treatment modality to all patients with early glottic cancer[74]. In Germany and Spain also more extensive tumor stages are treated by laser surgery[75-79].

Although treatment allocation in our studies was not randomized and conclusions therefore should be regarded with caution, it is important that no significant difference in the voice analyses was found before treatment between both patient groups (undergoing either laser resection or radiotherapy) with early glottic cancer, to be treated by laser surgery or radiotherapy. Therefore no patient selection has occurred on basis of voice quality. In the study on the effectiveness of voice therapy, we did perform a randomised controlled trial targeting patients with voice problems after treatment. This RCT involved a relatively small study sample and is therefore considered as a proof of principle.

RECOMMENDATIONS

Recommendation regarding treatment of choice for early glottic cancer

Taking into account the above mentioned considerations, it is our considered opinion that laser surgery should be recommended as the treatment of choice for most early glottic carcinomas. Although radiotherapy offers the same excellent oncological outcomes as laser surgery does, the morbidity as well as the options for salvage therapy in the unlikely event of recurrence, are less favourable. Moreover, voice quality recovers more rapidly following laser resection and patients less often report voice problems in daily life. Furthermore radiotherapy is less cost effective than laser surgery. In clinical practice however there may be individual reasons, e.g. co-morbidity precluding general anaesthesia or other factors which favour radiotherapy as a good alternative.

Recommendation regarding voice screening and voice therapy

Based upon this thesis we recommend active screening for voice impairment after treatment of early glottic cancer in clinical practise and, if indicated, to carry out a more extensive voice assessment. Patients experiencing voice problems after treatment for early glottic cancer (laser surgery or radiotherapy) should be offered the option of voice therapy, an evidence based intervention, as proven in this thesis.

Recommendation for future research

Future studies on the (cost-) effectiveness of the optimal choice of treatment and (early) rehabilitation of patients diagnosed with early glottic cancer are needed and can be designed as randomized controlled trials, but other designs such as case–control and cohort studies may also be considered suitable for “personalized medicine” approaches. In any case, choice of outcome measures should be based on consensus and existing evidence, such as provided in the present thesis.

REFERENCES

1. Schrijvers ML, van Riel EL, Langendijk JA, Dikkers FG, Schuuring E, van der Wal JE, van der Laan BF. Higher laryngeal preservation rate after CO2 laser surgery compared with radiotherapy in T1a glottic laryngeal carcinoma.Head Neck. 2009;31(6):759-64.
2. Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int J RadiatOncolBiol Phys. 2010;78(2):461-6.
3. Lucioni M, Marioni G, Bertolin A, Giacomelli L, Rizzotto G.Glottic laser surgery: outcomes according to 2007 ELS classification. Eur ArchOtorhinolaryngol.2011;268(12):1771-8.
4. Lee DH, Roh JL, Baek S, Jung JH, Choi SH, Nam SY, Kim SY. Second cancers incidence, risk factor, and specific mortality in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg. 2013;149(4):579-586.
5. Kasperts N, Slotman B, Leemans CR, Langendijk JA. A review on re-irradiation for recurrent and second primary head and neck cancer. OralOncol. 2005;41(3):225-43.
6. Wang CC, McIntyre J. Re-irradiation of laryngeal carcinomatechniques and results. Int J RadiatOncolPhys 1993;26(5):783-5.
7. Piazza C, Peretti G, Cattaneo A, Garrubba F, De Zinis LO, Nicolai P. Salvage surgery after radiotherapy for laryngeal cancer: from endoscopic resections to open-neck partial and total laryngectomies. ArchOtolaryngol Head NeckSurg. 2007;133(10):1037-43.
8. Nibu K, Kamata S, Kawbata K, Nakamizo M, Nigauri T, HokiK.Partiallaryngectomy in the treatment of radiation-failure of earlyglottic carcinoma. Head Neck. 1997;19:116–120
9. Spirano G, Pellini R, Romano G, Muscatello L, Roselli R. Supracricoid partial laryngectomy as salvage surgery after radiation failure. Head Neck. 2002;24:759–765
10. Toma M, Nibu KI, Nakao K, Matsuzaki M, Mochiki M, Yuge T, *et al.* Partial laryngectomy to treat early glottic cancer after failure of radiation therapy. Arch Otolaryngol Head Neck Surg. 2002;128:909–912
11. Sewnaik A, Meeuwis CA, van der Kwast TH, Kerrebijn JDF. Partial laryngectomy for recurrent glottic carcinoma after radiotherapy. Head Neck. 2005;27:101–107
12. León X, López M, García J, Viza I, Orús C, Quer M. Supracricoidlaryngectomy as salvage surgery after failure of radiation therapy. Head Neck. 2007;29:809–814
13. Bradley PJ, Ferlito A, Suárez C, Werner JA, Genden EM, Shaha AR, *et al.* Options for salvage after failed initial treatment of anterior vocal commissure squamous carcinoma. Eur Arch Otorhinolaryngol. 2006;263:889–894.
14. Del Bon F, Piazza C, Mangili S, Redaelli De Zinis LO, Nicolai P, Peretti G.Transoral laser surgery for recurrent glottic cancer after radiotherapy: oncologic and functional outcomes. ActaOtorhinolaryngol Ital. 2012;32(4):229-37.

15. Roedel RM, Matthias C, Wolff HA, Schindler P, Aydin T, Christiansen H. Transoral laser microsurgery for recurrence after primary radiotherapy of early glottic cancer.Auris Nasus Larynx. 2010;37(4):474-81.

16. Han YJ, Lee HS, Kim SW, Hong JC, Kim ST, Park HS, Lee KD. Transorallaser microsurgery of recurrent early glotticcancer after radiation therapy: clinical feasibility and limitations. Ann OtolRhinolLaryngol. 2012;121(6):375-82.

17. Mortuaire G, Francois J, Wiel E, Chevalier D. Local recurrence after CO2 laser cordectomy for early glottic carcinoma. Laryngoscope. 2006;116(1):101-5.

18. Eckel HE. Local recurrences following transoral laser surgery for early glottic carcinoma: frequency, management, and outcome. Ann OtolRhinolLaryngol. 2001;110(1):7-15.

19. Huang J, Yu Z, Fang J, Chen X, Chen X, Huang Z. Salvage transoral laser microsurgery for early recurrent glottic carcinoma after primary laser treatment. ActaOtolaryngol. 2013;133(5):531-537.

20. Roedel R.M.W., Matthias C, Wolff H.A., Christiansen H. Repeated transoral laser microsurgery for early and advanced recurrence of early glottic cancer after primary laser resection. AurisNasus Larynx 2010;37:340-346.

21. Ganly I, Patel SG, Matsuo J, Singh B, Kraus DH, Boyle J. Analysis of postoperative complications of open partial laryngectomy. Head Neck. 2009;31:338-45.

22. Jones AS, Fish B, Fenton JE, Husband DJ.The treatment of early laryngeal cancers (T1-T2 N0): surgery or irradiation? Head Neck. 2004;26(2):127-35.

23. EpsteinBE, Lee DJ, Kashima H, Johns ME. Stage T1 glottic carcinoma: results of radiation therapy or laser excision. Radiology. 1990;175(2):567-70.

24. Rydell R, Schalén L, Fex S, ElnerA.Voice evaluation before and after laser excision vs. radiotherapy of T1A glottic carcinoma. ActaOtolaryngol. 1995;115(4):560-5.

25. Dinapoli N, Parrilla C, Galli J, Autorino R, Miccichè F, Bussu F, Balducci M, D'Alatri L, Marchese R, Rigante M, Di Lella G, Liberati L, Almadori G, Paludetti G, Valentini V. Multidisciplinaryapproach in the treatment of T1 glotticcancer. The role of patient preference in a homogenous patient population. StrahlentherOnkol. 2010;186(11):607-13.

26. Kerr P, Mark Taylor S, Rigby M, Myers C, Osborn H, Lambert P, Sutherland D, Fung K. Oncologic and voice outcomes after treatment of early glottic cancer: transoral laser microsurgery versus radiotherapy.JOtolaryngol Head Neck Surg. 2012;41(6):381-8.

27. Kujath M, Kerr P, Myers C, Bammeke F, Lambert P, Cooke A, Sutherland D. Functional outcomes and laryngectomy-free survival after transoral CO_2 laser microsurgery for stage 1 and 2 glottic carcinoma.JOtolaryngol Head Neck Surg. 2011;40Suppl 1:S49-58.

28. Al-Mamgani A, van Rooij PH, Woutersen DP, Mehilal R, Tans L, Monserez D, Baatenburg de Jong RJ. Radiotherapy for T1-2N0 glottic cancer: a multivariate analysis of predictive factors for the long-term outcome in 1050 patients and a prospective assessment of quality of life and voice handicap index in a subset of 233 patients.ClinOtolaryngol. 2013;38(4):306-12.

29. Remmelts AJ, Hoebers FJ, Klop WM, Balm AJ, Hamming-Vrieze O, van den Brekel MW. Evaluation of lasersurgery and radiotherapy as treatment modalities in early stage laryngeal carcinoma: tumour outcome and quality of voice.Eur Arch Otorhinolaryngol. 2013;270(7):2079-87.

30. Bajaj Y, Uppal S, Sharma RK, Grace AR, Howard DM, Nicolaides AR, Coatesworth AP. Evaluation of voice and quality of life after transoral endoscopic laser resection of early glotticcarcinoma. JLaryngol Otol. 2011;125(7):706-13.

31. Lester SE, Rigby MH, MacLean M, Taylor SM. How does that sound?': objective and subjective voice outcomes following CO_2 laser resection for early glottic cancer.JLaryngol Otol. 2011;125(12):1251-5.

32. Kennedy JT, Paddle PM, Cook BJ, Chapman P, Iseli TA. Voice outcomes following transoral laser microsurgery for early glottic squamous cell carcinoma. J Laryngol Otol. 2007;20:1-5.

33. Aref A, Dworkin J, Devi S, Denton L, Fontanesi J. Objective evaluation of the quality of voice following radiation therapy for T1 glottic cancer. RadiotherOncol1997;45(2):149-153.

34. Verdonck-de Leeuw IM, Keus RB, Hilgers FJM, *et al.* Consequences of voice impairment in daily life for patients following radiotherapy for early glottic cancer: voice quality, vocal function, and vocal performance. Int J RadiatOncolBiol Phys. 1999;44:1071-1078.

35. Verdonck-de Leeuw IM, Hilgers FJM, Keus RB, *et al.* Multidimensional assessment of voice characteristics after radiotherapy for early glottic cancer. Laryngoscope. 1999;109:241-248.

36. Hocevar – Boltežar I, Žargi M. Voice quality after radiation therapy for earlyglottic cancer. Arch Otolaryngol Head Neck Surg. 2000;126:1097-1100.

37. Lehman JJ, Bless DM, Brandenburg JH. An objective assessment of voiceproductionafter radiation therapy for stage I squamous cell carcinoma of the glottis. HeadNeck Surg. 1988;98:121-129.

38. Cohen SM, Garrett CG, Dupont WD, Ossoff RH, Courey MS. Voice-related qualityof life in T1 glottic cancer: irradiation versus endoscopic excision. Ann OtolRhinolLaryngol. 2006;115(8):581-586.

39. Roh JL, Kim DH, Yoon Kim S, Park CI. Quality of life and voice in patientsafterlasercordectomy for Tis and T1 glottic carcinomas. Head Neck. 2007;29(11):1010-1016.

40. Van der Torn M, Verdonck-de Leeuw IM, Kuik DJ, Mahieu HF. Communicativesuitability of voice following radiotherapy for T1a glottic carcinoma: testing the reliabilityof a rating instrument. J Voice. 2002;16:398-407.

41. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schmid S. Quality of life aftertreatment for early laryngeal carcinoma. Eur Arch Otorhinolaryngol. 2001;258:96-99.

42. Smith JC, Johnson JT, Cognetti DM, Landsittel DP, Gooding WE, Cano ER, Meyers EN. Quality of life, functional outcome, and costs of early glottic cancer. Laryngoscope. 2003;113:68-76. 20.

43. Jepsen MC, Gurushanthaiah D, Roy N, Smith ME, Gray SD, Davis RK. Voice,speech, and swallowing outcomes in laser-treated laryngeal cancer. Laryngoscope. 2003:113:923-928.

44. Fung K, Yoo J, Leeper HA, *et al.* Effects of head and neck radiation therapy on vocal function. J Otolaryngol. 2001;30:133-139.

45. Stewart MG, Chen AY, Stach CB. Outcomes analysis of voice and quality of life in patients with laryngeal cancer. Arch Otolaryngol Head and Neck Surg. 1998;124:143-148

46. Cheng-Ming Luo, Tuan-Jen Fang, Chien-Yu Lin, Joseph Tung-Chieh Chang, Chun-Ta Liao, I-How Chen, Hsueh-Yu Li and Hui-Chen Chiang. Transoral laser microsurgery elevates fundamental frequency in early glotticcancer. J of Voice. 2012;26(5):596-601.

47. Jotic A, Stankovic P, Jesic S, Milovanovic J, Stojanovic M, Djukic V. Voice quality after treatment of early glottic carcinoma. J Voice. 2012;26(3):381-9.

48. Mantravadi RV, Liebner EJ, Haas RE, Skolnik EM, Applebaum EL. Cancer of the glottis: prognostic factors in radiation therapy.Radiology. 1983;149(1):311-4.

49. Chatani M, MatayoshiY, Masaki N. Radiation therapy for larynx carcinoma: long-term results of stage I glotticcarcinoma.StrahlentherOnkol. 1993;169(2):102-6.

50. Bron LP, Soldati D, Zouhair A, Ozsahin M, Brossard E, Monnier P, Pasche P. Treatment of early stage squamous-cell carcinoma of the glottic larynx: endoscopic surgery or cricohyoidoepiglottopexy versus radiotherapy.Head Neck. 2001;23(10):823-9.

51. Khan MK, Koyfman SA, Hunter GK, Reddy CA, Saxton JP. Definitive radiotherapy for early (T1-T2) glottic squamous cell carcinoma: a 20 year Cleveland Clinic experience. RadiatOncol. 2012;7:193.

52. Ellies M, Steiner W.Peri- and postoperative complications after laser surgery of tumors of the upper aerodigestivetract.Am J Otolaryngol. 2007;28(3):168-72.

53. Peters TT, van der Laan BF, Plaat BE, Wedman J, Langendijk JA, Halmos GB. The impact of comorbidity on treatment-related side effects in older patients with laryngeal cancer. OralOncol. 2011;47(1):56-61.

54. Koo HJ, Burns JA, Kobler JB, Heaton JT, Zeitels SM. Novel device for tissue cooling during endoscopic laryngeal laser surgery: thermal damage study in an ex vivo calf model. Ann OtolRhinolLaryngol. 2012;121(7):485-9.

55. Roh JL, Yoon YH.Prevention of anterior glottic stenosis after transoralmicroresection of glottic lesions involving the anterior commissure with mitomycin C. Laryngoscope. 2005;115(6):1055-9.

56. Myers EN, Wagner RL, Johnson JT. Microlaryngoscopic surgery for T1 glottic lesions: a cost-effective option. Ann OtolRhinolLaryngol 1994;103:28–30.

57. Goor KM, Peeters AJ, Mahieu HF, Langendijk JA, Leemans CR, Verdonck-de Leeuw IM, van Agthoven M. Cordectomy by CO2 laser or radiotherapy for small T1a glottic carcinomas: costs, local control, survival, quality of life, and voice quality. Head Neck. 2007;29(2):128-36.

58. Brandenburg JH.Lasercordotomy versus radiotherapy: anobjectivecost analysis. Ann

OtolRhinolLaryngol 2001;110:312–318.

59. Cragle SP, Brandenburg JH. Laser cordectomy or radiotherapy:cure rates, communication, and cost. Head Neck Surg 1993;108:648–654.

60. van Loon Y, Sjögren EV, Langeveld TP, Baatenburg de Jong RJ, Schoones JW, van Rossum MA.Head Neck. Functional outcomes after radiotherapy or laser surgery in early glottic carcinoma: A systematic review. Head Neck.2012;34(8):1179-89.

61. Kwaliteitsinstituut voor de Gezondheidzorg CBO, Vereniging van Integrale Kankercentra, en Nederlandse Werkgroep Hoofd-Halstumoren. Richtlijn Larynxcarcinoom 2000.

62. Kwaliteitsinstituut voor de Gezondheidzorg CBO, Vereniging van Integrale Kankercentra, en Nederlandse Werkgroep Hoofd-Halstumoren. RichtlijnLarynxcarcinoom 2010; versie: 3.0.

63. Remacle M, Eckel HE, Antonelli A, Brasnu D, Chevalier D, Friedrich G, Olofsson J, Rudert HH, Thumfart W, de Vincentiis M, Wustrow TP. Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society.Eur Arch Otorhinolaryngol. 2000;257(4):227-31.

64. Remacle M, Van Haverbeke C, Eckel H, Bradley P, Chevalier D, Djukic V, de Vicentiis M, Friedrich G, Olofsson J, Peretti G, Quer M, Werner J. Proposal for revision of the European Laryngological Society classification of endoscopic cordectomies.Eur Arch Otorhinolaryngol. 2007;264(5):499-504.

65. Hartl DM, Ferlito A, Brasnu DF, Langendijk JA, Rinaldo A, Silver CE, Wolf GT. Evidence-based review of treatment options for patients with glottic cancer. Head Neck. 2011;33(11):1638-48.

66. Nakayama M, Brandenburg JH. Clinical underestimation of laryngeal cancer. Predictive indicators. Arch Otolaryngol Head Neck Surg. 1993;119(9):950-7.

67. Bradley PJ, Rinaldo A, Suárez C, Shaha AR, Leemans CR, Langendijk JA, Patel SG, Ferlito A. Primary treatment of the anterior vocal commissure squamous carcinoma. Eur Arch Otorhinolaryngol. 2006;263(10):879-88. Review.

68. Fernandes R, Gopalan P, Spyridakou C, Joseph G, Kumar M. Predictive indicators for thyroid cartilage involvement in carcinoma of the larynx seen on spiral computed tomography scans. JLaryngolOtol. 2006;120(10):857-60.

69. Becker M, Zbären P, Casselman JW, Kohler R, Dulguerov P, Becker CD. Neoplastic invasion of laryngeal cartilage: reassessment of criteria for diagnosis at MR imaging.Radiology. 2008;249(2):551-9.

70. Becker M.Neoplasticinvasion of laryngeal cartilage: radiologic diagnosis and therapeutic implications.Eur J Radiol. 2000;33(3):216-29. Review.

71. Ledda GP, Grover N, Pundir V, Masala E, Puxeddu R. Functional outcomes after CO2 laser treatment of early glottic carcinoma. Laryngoscope;116(6):1007-11.

72. Peretti G, Piazza C, Balzanelli C, Mensi MC, Rossini M, Antonelli AR. Preoperative and postoperative voice in Tis-T1 glottic cancer treated by endoscopic cordectomy: an additional issue for patient counseling. Ann OtolRhinolLaryngol. 2003;112(9):759-63.

73. Peretti G, Piazza C, Balzanelli C, Cantarella G, Nicolai P. Vocal outcome after endoscopic cordectomies for Tis and T1 glottic carcinomas. Ann OtolRhinolLaryngol. 2003;112(2):174-9.

74. Bradley PJ, Mackenzie K,Wight R, Pracy P, Paleri V.– On behalf of ENT-UK Head & Neck Group. Consensus statement on management in the UK: Transoral laser assisted microsurgical resection of early glottic cancer. Otolaryngol. 2009;34:367–373.

75. Hinni ML, Salassa JR, Grant DG, Pearson BW, Hayden RE, Martin A, Christiansen H, Haughey BH, Nussenbaum B, Steiner W. Transoral laser microsurgery for advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg. 2007;133(12):1198-204.

76. Christiansen H, Hermann RM, Martin A, Florez R, Kahler E, Nitsche M, Hille A, Steiner W, Hess CF, Pradier O. Long-term follow-up after transoral laser microsurgery and adjuvant radiotherapy for advanced recurrent squamous cell carcinoma of the head and neck. Int J RadiatOncolBiol Phys. 2006;65(4):1067-74.

77. Olthoff A, Ewen A, Wolff HA, Hermann RM, Vorwerk H, Hille A, Rödel R, Hess CF, Steiner W, Pradier O, Christiansen H. Organ function and quality of life after transoral laser microsurgery and adjuvant radiotherapy for locally advanced laryngeal cancer. Strahlenther Onkol. 2009;185(5):303-9.

78. López-Álvarez F, Rodrigo JP, Llorente-Pendás JL, Suárez-Nieto C.Transoral laser microsurgery in advanced carcinomas of larynx and pharynx.Acta Otorrinolaringol Esp. 2011;62(2):95-102.

79. Blanch JL, Vilaseca I, Caballero M, Moragas M, Berenguer J, Bernal-Sprekelsen M. Outcome of transoral laser microsurgery for T2-T3 tumors growing in the laryngeal anterior commissure. Head Neck. 2011;33(9):1252-9.

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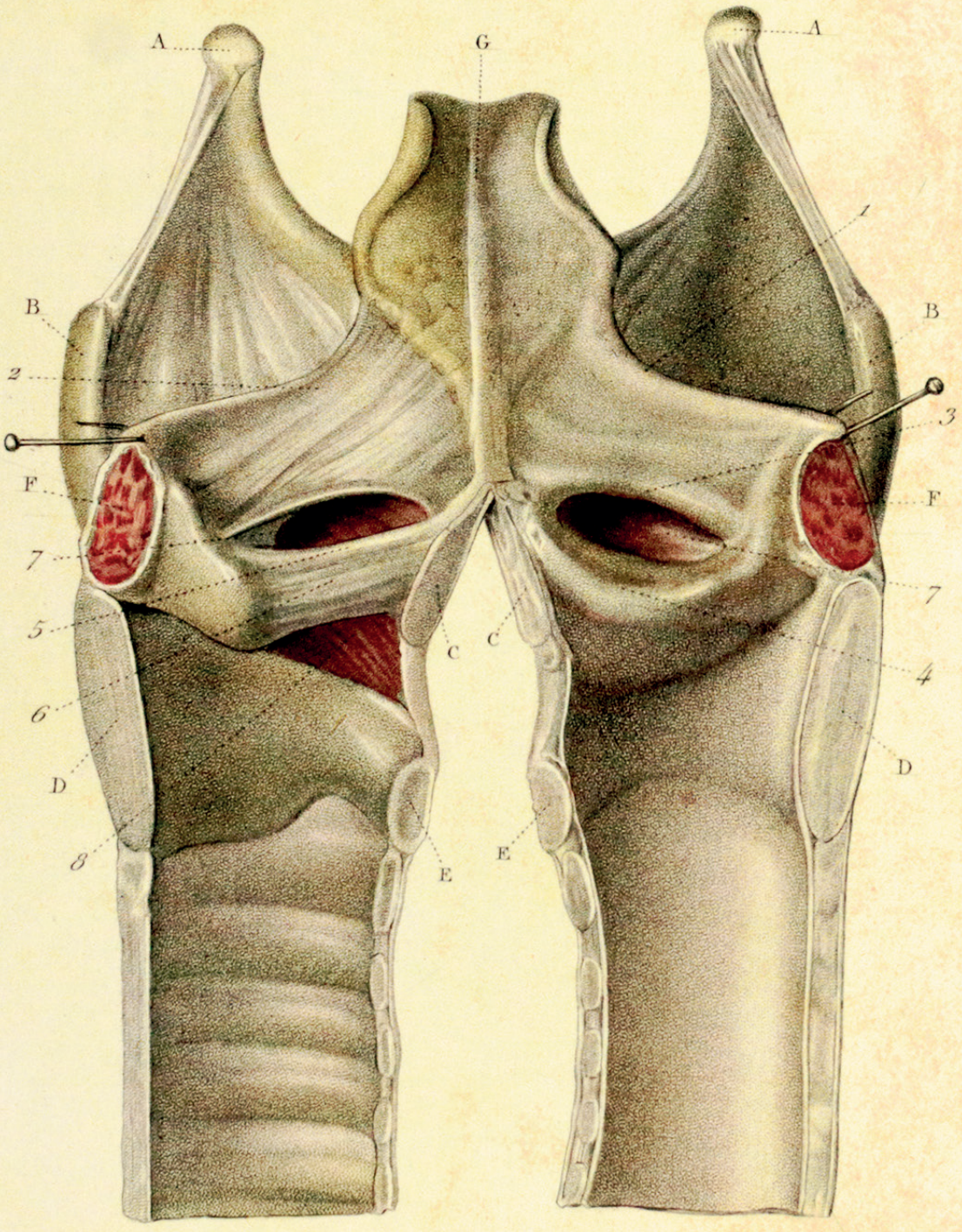
Fig. I.



SUMMARY

SUMMARY

When someone is diagnosed with cancer, obviously the prognosis regarding cure and survival is the most important issue. However, other factors, such as functional outcome and quality of life following treatment, can also play an important role in determining the treatment of choice. In early glottic cancer cure rates are very high with percentages of more than 90%, irrespective of type of treatment (endoscopic laser surgery or radiotherapy). Voice outcome, being at risk in glottic cancer and its treatment, is generally considered to be the most important functional outcome measure, with expected high impact on the quality of life, and therefore forms the prominent theme of this thesis.

Chapter 1

This Chapter provides a general introduction of voice production, and the anatomy and physiology of the larynx in relation to phonation. Several methods of voice assessment are described. Furthermore a description of the staging of laryngeal carcinomas and more specifically early glottic carcinomas (Tis, T1 and T2) is given. These early glottic laryngeal carcinomas were traditionally treated by radiotherapy or even open surgery. But the last decades laser surgery has gained its place as an alternative to radiotherapy in the treatment of early glottic carcinomas. Based on the literature review in this Chapter, specific research goals are formulated:

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?
2. To assess the impact of voice problems after treatment of early glottic cancer on daily life activities.
3. To investigate the applicability of the Voice Handicap Index (VHI) as a tool to assess patient reported voice problems in laryngeal cancer patients.
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.
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.
6. To investigate whether the voice outcome following treatment for early glottic cancer differs from normal voices.
7. To assess the efficacy of voice therapy for voice problems after treatment of early glottic cancer.

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 2

Even though there are several studies concerning 'voice quality' after treatment of early glottic cancer, the results are difficult to compare and sometimes even contradictory, most likely as a result of differences in patient selection, voice assessment tools and study designs. Nevertheless, it seems that a considerable number of patients end up with deteriorated voice quality after treatment of early glottic cancer. In order to detect voice problems, a 5-item questionnaire on a 10 point scale (1 = very much 10 = not at all) was developed. The assessment of the psychometric properties and value of this 5-item questionnaire is described in this chapter. In total, 177 patients after treatment of early glottic cancer (51 treated by laser surgery vs 126 by radiotherapy) filled in the questionnaire. 104 patients responded to our request to complete the questionnaire a second time after at least one month (median interval period 5 months; range1-10 months). Furthermore the same questionnaire was completed by 110 healthy, age and sex matched, controls. The psychometric properties of the questionnaire, as specified by the reliability, the internal consistency and the predictive validity, were good. The questionnaire therefore proved to be a reliable screening instrument resulting in a useful differentiation between normal and abnormal voices. Patients scoring a 5 or less on at least one of the five questions were considered to have overall voice impairment. In this study a relatively high number of patients report voice problems after treatment of early glottic cancer: 44% of the patients treated by radiotherapy vs. 29% of the patients treated with laser surgery (not significant; p=0.079).

Chapter 3

This chapter describes a cross-sectional study to gain more insight concerning the impact of voice problems after treatment of early glottic cancer on daily life activities. The self-reported outcome measure Voice Handicap Index of patients was used to assess voice-related problems in daily life and COOP/WONCA charts were used to assess their functional health status. The VHI is a 30-item questionnaire measuring voice-related quality of life and the COOP/WONCA charts represent self-assessment in six domains: physical fitness, mental well-being, daily activities, social activities, change in health, and overall health. Results show that voice-related problems in daily life (VHI) were significantly related to social activities, mental wellbeing, and overall health (COOP/WONCA). In this study 58% of the patients following radiotherapy and 40% of the patients following endoscopic laser surgery for early glottic cancer, experience voice problems, leading to restrictions in their social life, mental well-being and overall health. It must be mentioned that these results

were calculated with the initially presumed cut-off point of 10 on the VHI. Where a VHI-score below 10 was considered a normal score without self-assessed voice impairment. In Chapter 4 the psychometric properties of the VHI were re-evaluated and the cut-off point was validated at 15. Recalculation lead to voice problems in 50% of the patients treated with radiotherapy versus 30% of the patients treated with endoscopic laser surgery.

Chapter 4

This Chapter describes (psychometric) research on the Voice Handicap Index. The VHI scores of patients with voice problems after treatment of early glottic cancer were compared to the VHI scores of patients with voice problems caused by benign voice disorders, and to VHI scores of a sample of the Dutch general population, without voice problems. Patients were asked to fill out the questionnaire twice with an interval period of mean 3,5 months. Reliability of the VHI was proven by good internal consistency and high test-retest stability. A cut-off point of 15 (or higher) on the total VHI scale was defined to identify patients with voice problems in daily life. A difference score of 10 points was defined for use in individual patients in clinical practise, and of 15 points for use in study group research designs. Overall the VHI proved to be a reliable, validated tool to assess voice problems in daily life, in clinical practice and for research purposes. Furthermore results showed that patients after early glottic cancer have comparable voice problems to patients with benign voice disorders with similar scores on the VHI.

Chapter 5

In Chapter 5 the difference in voice outcome and voice recovery after treatment of early glottic cancer either by radiotherapy or endoscopic laser surgery was evaluated. A prospective cohort study investigated acoustical voice outcome from baseline (before treatment) to 2 years after treatment in a group of patients treated with radiotherapy or endoscopic laser surgery for T1a glottic carcinomas. Voice parameters, jitter, shimmer, and normalised noise energy (NNE), recovered sooner in patients treated with laser surgery than those of patients treated with radiotherapy. Already 3 months after endoscopic laser surgery voices were comparable to normal voices except for the fundamental frequency, which remained higher pitched, even after 24 months. Three months after radiotherapy pathological results were obtained for jitter, shimmer and NNE. Six and twelve months after radiotherapy pathological results were still obtained for jitter and fundamental frequency. Two years after radiotherapy, no difference as compared to normal voices was found except for the jitter, which remained on a pathological level.

Six months after treatment there was no longer a difference between the two treatment modalities, except for the fundamental frequency, which remained higher pitched, even after 24 months, in patients treated with laser surgery.

Given the fact that widely reported oncological outcome is excellent following both treatment modalities, these voice results favour endoscopic laser surgery as the first treatment of choice in T1a glottic carcinoma.

Chapter 6

Chapter 6 describes a randomized controlled trial to assess the efficacy of voice therapy in a group of patients with voice problems at least 6 months after treatment of early glottic cancer (by radiotherapy or endoscopic laser surgery). Patients were included following an abnormal score on the 5-item screening questionnaire described in Chapter 2, and their consent to enter the study with the possibility that they would be assigned to voice therapy. Included patients were randomly assigned into the voice therapy group or control group. To assess the effect of voice therapy, a multidimensional voice assessment protocol, with the VHI as primary outcome measure, was performed. All patients' voices were examined twice: once at baseline (study entry assessment) and once after voice therapy or after 3 months for patients in the control group (study exit assessment). The voice complaints of the patient, as assessed by the VHI, improved significantly in the voice therapy group, with a mean improvement of 15 points. In the control group a mean VHI difference of 3 points was found between the two measurements. A beneficial significant effect of voice therapy was also observed on secondary voice quality outcome measures (acoustical measures: Noise to Harmonics Ratio and jitter, and perceptual rating of vocal fry).

A striking finding in this study was that nearly 60% of the patients, all of whom reported voice problems in daily life on the 5 item screening questionnaire, were not willing to participate in the study. This high percentage may be explained by the time-consuming nature of voice therapy and the fact that many patients accepted their voice problem as an inevitable consequence of their treatment for a potentially life-threatening disease, but more research is needed to obtain insight in possible barriers and facilitators of referral to voice therapy. The study described in this Chapter provides evidence that voice therapy is effective for patients with voice problems after treatment of early glottic carcinoma.

Chapter 7

While the previous chapter provided evidence of short-term efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer, it is of course also of interest to determine whether this positive result of voice therapy is long lasting. In this study we focussed on the VHI, as the primary outcome measure. Patients were re-evaluated at least 6 months after completing voice therapy. Results showed no significant change in VHI measured after 6 months or more as compared to the VHI score measured directly after voice therapy. The mean VHI score at follow-up assessment (6 months or more after voice therapy) remained significantly better than the baseline assessment measured be-

fore voice therapy. The findings in this study prove that the beneficial short-term effect of voice therapy in patients who experienced voice problems after treatment are long lasting (at least 6 months or more).

Chapter 8

In Chapter 8, the outcomes of the initially formulated research goals are summarized and discussed and put into broader perspective. Furthermore some recommendations were made, based upon the literature and the results presented in this thesis.

The overall conclusion of this thesis is that voice problems are prevalent and interfere with daily life activities, in patients after treatment of early glottic cancer, either following endoscopic laser surgery or radiotherapy.

Recommendation regarding treatment of choice for early glottic cancer

It is our considered opinion that endoscopic laser surgery should be recommended as the treatment of choice for most early glottic carcinomas. Although radiotherapy offers the same excellent oncological outcomes as endoscopic laser surgery, the morbidity as well as the options for salvage therapy in the unlikely event of recurrence, are less favourable. Moreover, voice quality recovers more rapidly following laser resection and patients less often report voice problems in daily life. Furthermore radiotherapy is less cost effective than endoscopic laser surgery. In clinical practice however there may be individual reasons, e.g. co-morbidity precluding general anaesthesia or other factors which favour radiotherapy as a good alternative.

Recommendation regarding voice screening and voice therapy

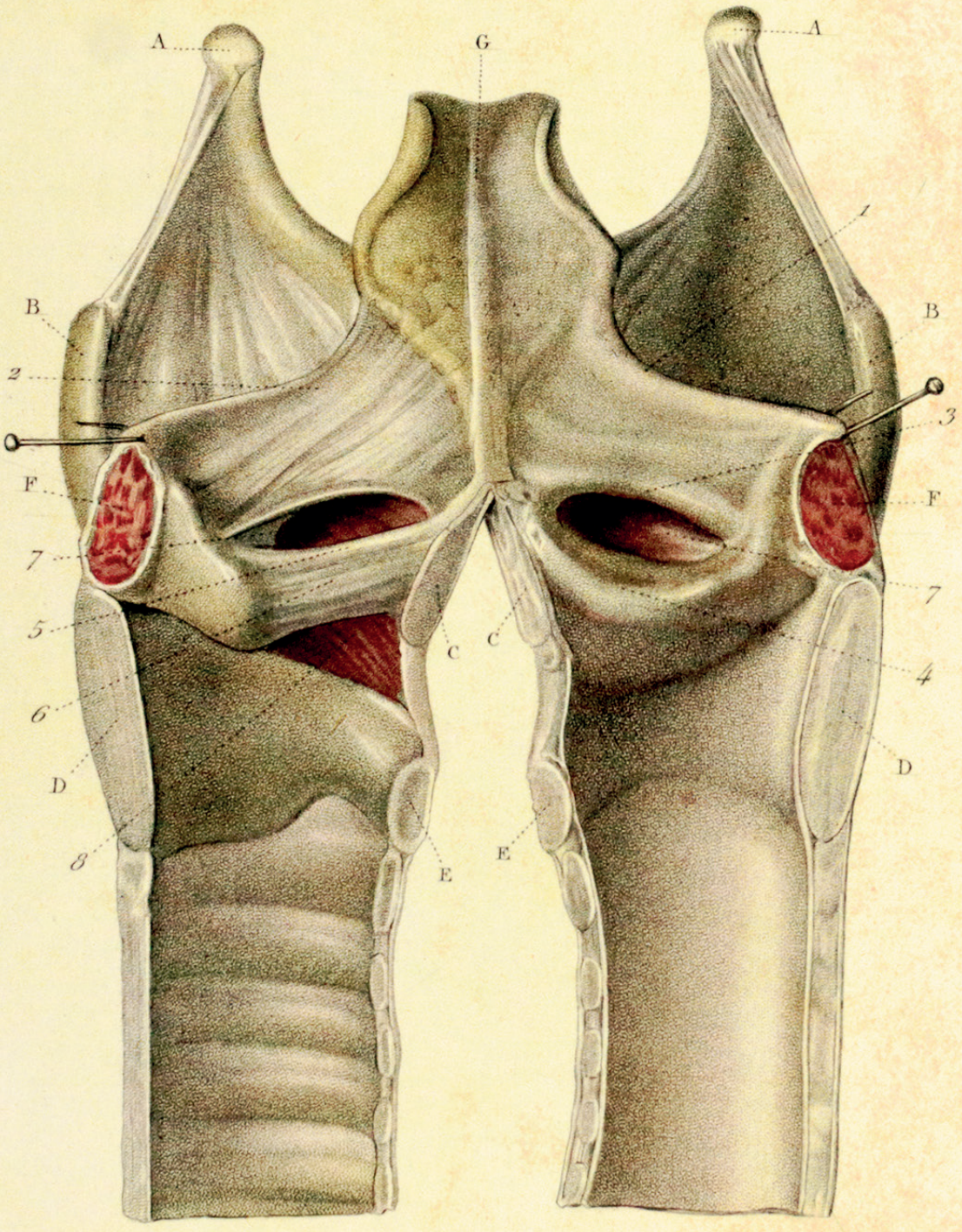
Based upon this thesis we recommend active screening for voice impairment after treatment of early glottic cancer in clinical practise and, if indicated, to carry out a more extensive voice assessment. Patients experiencing voice problems after treatment for early glottic cancer (endoscopic laser surgery or radiotherapy) should be offered the option of voice therapy, an evidence based intervention, as proven in this thesis.

Recommendation for future research

Future studies on the (cost-)effectiveness of the optimal choice of treatment and rehabilitation of patients diagnosed with early glottic cancer are needed and can be designed as randomized controlled trials, but other designs as case–control and cohort studies may also be considered to be more suitable for “personalized medicine” approaches. In any case, choice of outcome measures should be based on consensus and existing evidence, such as provided in the present thesis.

S

Fig. I.



SAMENVATTING

SAMENVATTING

Wanneer de diagnose kanker gesteld is gaat de aandacht eerst uit naar een behandeling met de beste prognose op genezing en overleving. Echter ook andere factoren, zoals functionele resultaten en kwaliteit van leven, kunnen een rol spelen bij de keuze van een behandeling. Het klein glottisch larynxcarcinoom kan behandeld worden middels radiotherapie of endoscopische laserchirurgie en beiden kennen een zeer hoge kans op genezing met percentages boven de 90%. Het belangrijkste functionele resultaat van een klein glottisch larynxcarcinoom en de behandeling daarvan is de stem; stemproblemen kunnen een grote negatieve impact hebben op de kwaliteit van leven. Het onderzoek in dit proefschrift richt zich op verschillende aspecten van stemkwaliteit bij patiënten die behandeld worden voor een klein glottisch larynxcarcinoom.

Hoofdstuk 1

Dit hoofdstuk geeft een algemene inleiding over de stadiering van larynxcarcinomen en in het bijzonder het klein glottisch larynxcarcinoom (Tis, T1, T2). Het klein glottisch larynxcarcinoom werd traditioneel behandeld middels radiotherapie of zelfs open chirurgie. De laatste decennia heeft endoscopische laserchirurgie zijn plaats verworven als een goed alternatief voor radiotherapie in de behandeling van klein glottische larynxcarcinomen. Verder wordt in dit hoofdstuk de stemproductie, haar fysiologie en haar anatomische relatie met het strottenhoofd beschreven. De stem kan beoordeeld worden op meerdere facetten en de verschillende methoden hiertoe worden uiteengezet.

Op basis van de literatuurstudie in dit hoofdstuk, worden de specifieke onderzoeksvragen geformuleerd:

1. Ervaren patiënten stemproblemen na de behandeling van een klein glottisch larynxcarcinoom? En zo ja, hoe kunnen we deze patiënten identificeren?
2. Wat voor impact hebben stemproblemen na de behandeling van een klein glottisch larynxcarcinoom op het dagelijks functioneren?
3. Is de Voice Handicap Index (VHI) een klinisch toepasbaar instrument om stemproblemen aan te tonen bij patiënten met een larynxcarcinoom?
4. Zijn de stemproblemen die patiënten ervaren na behandeling van een klein glottisch larynxcarcinoom vergelijkbaar met de stemproblemen die patiënten met goedaardige stempathologie ervaren?
5. Is er een verschil in stemresultaat en herstelperiode tussen patiënten behandeld voor een klein glottisch larynxcarcinoom met radiotherapie of endoscopische laser chirurgie?

6. Verschilt het stemresultaat na behandeling van een klein glottisch larynxcarcinoom met een normale stem?
7. Is logopedische behandeling effectief bij patiënten met stemproblemen na behandeling van een klein glottisch larynxcarcinoom?
8. Kan, gezien het feit dat de kans op genezing voor zowel radiotherapie als voor laserchirurgie zeer hoog is, het stemresultaat een rol spelen in de therapie van keuze?

Hoofdstuk 2

Alhoewel er verscheidene studies zijn gepubliceerd over de 'stemkwaliteit' na behandeling van een klein glottisch larynxcarcinoom, zijn de resultaten van deze studies vaak lastig met elkaar te vergelijken en soms zelfs tegenstrijdig. Dit mede door verschillen in de studieopzet, in de wijze van patiënten selectie, of in de methode van stemevaluatie. Desalniettemin lijkt het erop dat een aanzienlijk aantal patiënten een verminderde stemkwaliteit ervaren na de behandeling van een klein glottisch larynxcarcinoom. Voor het herkennen van stemproblemen werd een 5-item vragenlijst op een schaal van 10 punten ontwikkeld. In deze studie werd deze vragenlijst beoordeeld op haar psychometrische eigenschappen en haar klinische relevantie.

In totaal vulden 177 patiënten, behandeld voor een klein glottisch larynxcarcinoom (51 middels laserchirurgie, 126 middels radiotherapie) de vragenlijst in. Honderd en vier patiënten reageerden op ons verzoek om de vragenlijst ten minste één maand later nog eens in te vullen (mediane interval periode van 5 maanden met een range van 1-10 maanden).

Daarnaast werd de vragenlijst beantwoord door 110 gezonde mensen gelijkwaardig in geslacht en leeftijd.

De psychometrische eigenschappen van de vragenlijst, zoals de betrouwbaarheid, de voorspellende waarde, en de interne consistentie waren goed. Op basis hiervan werd geconcludeerd dat de vragenlijst een betrouwbaar instrument is om te screenen op een onderscheid tussen normaal ervaren en afwijkende stemmen. Patiënten die een 5 of minder scoren op ten minste één van de vijf vragen van de vragenlijst worden beschouwd als het hebben van een stemprobleem. In deze studie bleek dat een groot aantal patiënten een stemprobleem ervaart na de behandeling van een klein glottisch larynxcarcinoom: 44% van de patiënten behandeld door radiotherapie vs. 29% van de patiënten behandeld met laserchirurgie ($p = 0.079$).

Hoofdstuk 3

Dit hoofdstuk beschrijft een cross-sectioneel onderzoek om duidelijkheid te krijgen over de mate van impact van het hebben van een stemprobleem na behandeling van een klein

glottisch larynxcarcinoom op het dagelijks functioneren.

De Voice Handicap Index (VHI) over zelf-gerapporteerde stemklachten werd gebruikt om stem- gerelateerde problemen in het dagelijks leven op te sporen en COOP/WONCA kaarten om de functionele gezondheidstoestand van een patiënt te evalueren. De VHI is een vragenlijst bestaande uit 30 items die de psychosociale consequenties op het dagelijks leven van stemproblemen kwantificeert (score 0-120 punten). De COOP/WONCA kaarten beoordelen de functionele gezondheidstoestand van patiënten op zes domeinen: lichamelijke fitheid, mentaal welzijn, dagelijkse activiteiten, sociale activiteiten, verandering in gezondheid, en algemene gezondheid.

De resultaten toonden aan dat de stem gerelateerde problemen in het dagelijkse leven (VHI) sterk correleren met het mentale welzijn, de sociale activiteiten en de algemene gezondheid (COOP/WONCA). In deze studie ervaarden 58% van de patiënten na radiotherapie en 40% van de patiënten na laserchirurgie voor een klein glottisch larynxcarcinoom stemproblemen, welke lijden tot restricties op het mentale welzijn, het sociale leven en de algemene gezondheid.

Belangrijk te vermelden is dat deze resultaten gebaseerd zijn op een aanvankelijk veronderstelde afkapwaarde van 10 punten op de VHI, waarbij een score van 10 punten of hoger werd beschouwd als indicatief voor een stemprobleem. In hoofdstuk 4 werden de psychometrische eigenschappen van de VHI gerevalueerd en werd de gevalideerde afkapwaarde vastgelegd op 15 punten. Herberekening met deze afkapwaarde toonde stemproblemen aan bij 50% van de patiënten na radiotherapie en 30% van de patiënten na laserchirurgie.

Hoofdstuk 4

Dit hoofdstuk beschrijft het onderzoek naar de psychometrische eigenschappen van de Voice Handicap Index (VHI) bij patiënten behandeld voor een klein glottisch larynxcarcinoom. De VHI scores van patiënten met een stemprobleem na behandeling van een klein glottisch larynxcarcinoom werden vergeleken met die van patiënten met een stemprobleem veroorzaakt door goedaardige stempathologie en met de scores van personen zonder stemproblemen. De patiënten werden gevraagd om de vragenlijst een tweede maal in te vullen met een interval periode van gemiddeld 3,5 maanden (reikwijdte 1-6 maanden).

De VHI werd gevalideerd als een betrouwbaar instrument met bewezen goede interne consistentie en een hoge test-hertest stabiliteit. Een score van 15 punten of hoger op de VHI werd vastgesteld om patiënten met stemproblemen in het dagelijkse leven te identificeren. Een verschilscore van 10 punten op de VHI werd beschouwd als klinisch relevant voor individuele patiënten, een verschil van 15 punten voor groepen patiënten in studieverband.

Over het geheel genomen bewijst de VHI dat ze een betrouwbaar en gevalideerd hulpmiddel is, zowel in de klinische praktijk als in studieverband, om stemproblemen in het dagelijks leven aan te tonen. Bovendien werd aangetoond dat de stemproblemen in het dagelijkse leven ervaren door patiënten na behandeling van een klein glottisch larynxcarcinoom vergelijkbaar zijn met stemproblemen bij patiënten met een stemaandoening veroorzaakt door goedaardige stempathologie.

Hoofdstuk 5

In hoofdstuk 5 wordt een studie beschreven die het verschil in herstelperiode en uiteindelijke stemresultaat onderzoekt na behandeling middels radiotherapie of laserchirurgie van een klein glottisch larynxcarcinoom. In een prospectieve cohort studie onderzochten we het akoestische stemresultaat vanaf het moment van de diagnose (vóór de behandeling) tot en met 2 jaar na behandeling van een T1a glottisch larynxcarcinoom. De akoestische stemparameters: jitter, shimmer en de genormaliseerde ruisenergie herstelden sneller na laser chirurgische behandeling dan na radiotherapie.

Al 3 maanden na laserchirurgie waren alle akoestische parameters vergelijkbaar met normaalwaarden, behalve de fundamentele frequentie, welke hoger bleef zelfs na 24 maanden.

Drie maanden na radiotherapie waren de jitter, shimmer en de genormaliseerde ruisenergie afwijkend in vergelijking met normaalwaarden. Zes en 12 maanden na radiotherapie werden nog steeds afwijkende waarden gevonden voor jitter en de fundamentele frequentie. Twee jaar na radiotherapie waren alle akoestische parameters vergelijkbaar met normaalwaarden behalve jitter, welke afwijkend bleef.

Zes maanden na behandeling was er akoestisch geen verschil meer tussen beide behandelmodaliteiten, behalve wat betreft de fundamentele frequentie welke hoger bleef zelfs 24 maanden na laserchirurgie.

Gezien het feit dat het oncologische resultaat voor beide behandelingen uitstekend is, pleiten bovengenoemde resultaten voor laserchirurgie als eerste keuze bij een T1a glottisch larynxcarcinoom.

Hoofdstuk 6

Hoofdstuk 6 beschrijft een gerandomiseerde gecontroleerde studie naar het effect van stemtherapie bij patiënten met stemproblemen ten minste 6 maanden na behandeling (radiotherapie of laserchirurgie) van een klein glottisch larynxcarcinoom.

Patiënten werden geselecteerd op het ervaren van een stemprobleem op basis van een afwijkende score op de eerder beschreven 5- item vragenlijst. Na informed consent werden patiënten gerandomiseerd ingedeeld in de stemtherapie- dan wel controle groep.

Om het effect van stemtherapie te achterhalen werd een multidimensionaal stemanalyse protocol opgesteld met de VHI als primaire uitkomstmaat. De stemmen van alle patiënten werden tweemaal onderzocht: eenmaal aan het begin van de studie en eenmaal na stemtherapie of na 3 maanden voor patiënten in de controlegroep.

De stemklachten, zoals aangetoond op de VHI, verbeterden aanzienlijk in de groep na stemtherapie, met een gemiddelde verbetering van 15 punten. Ter vergelijking werd in de controlegroep een verschil van 3 punten gezien tussen de 2 metingen.

Ook verschillende secundaire uitkomstmaten lieten een significante verbetering zien na stemtherapie: akoestisch verbeterden de jitter en de signaal-ruis verhouding, en op perceptueel gebied de krakerigheid van de stem.

Een opvallende bevinding was dat bijna 60% van de patiënten, die allen op basis van de 5-item vragenlijst aangaven een stemprobleem te ervaren, niet wilden deelnemen aan de studie. Dit hoge percentage zou mogelijkerwijs verklaard kunnen worden door de tijdrovende aard van stemtherapie of dat patiënten hun stemprobleem aanvaarden als een onvermijdelijk gevolg van de kanker behandeling. Al met al bewijst deze studie dat stemtherapie effectief is bij patiënten met stemproblemen na behandeling van een klein glottisch larynxcarcinoom.

Hoofdstuk 7

Het vorige hoofdstuk toonde een positief effect van stemtherapie bij patiënten met stemproblemen na behandeling van een klein glottisch larynxcarcinoom op de korte termijn. Nu is het natuurlijk ook van belang om te weten of dit positieve effect op de lange termijn stand houdt. In deze studie hebben we ons gericht op de VHI als eerdere primaire uitkomstmaat. Patiënten werden ten minste 6 maanden na het voltooien van de stemtherapie opnieuw geëvalueerd. Na 6 maanden of langer werd geen significante verandering gemeten in de VHI in vergelijking met de score direct na beëindiging van de stemtherapie.

De gemiddelde score van de VHI bij deze follow-up beoordeling bleef significant beter dan de meting voor de start van de stemtherapie. De bevindingen van deze studie bewijzen dat het gunstige effect van stemtherapie, voor stemproblemen na behandeling van een klein glottisch larynxcarcinoom, aanhoudt op langere termijn.

Hoofdstuk 8

In hoofdstuk 8, worden de primaire onderzoeksvragen beantwoord, bediscussieerd en in een breder perspectief uiteengezet. Daarnaast worden, gebaseerd op de literatuur en de bevindingen in dit proefschrift, aanbevelingen gedaan welke toepasbaar zijn in de klinische praktijk. De basisconclusie van dit proefschrift is dat 30-50% van de patiënten stemproblemen ondervinden na behandeling van een klein glottisch larynxcarcinoom en dat deze stemproblemen interfereren met het mentale welzijn, het sociale leven en de algemene gezondheid.

Aanbeveling betreffende de keuze van behandeling van het klein glottisch larynxcarcinoom

Het is onze weloverwogen mening dat endoscopische laserchirurgie aanbevolen moet worden als eerste keuze van behandeling voor een klein glottisch larynxcarcinoom. Hoewel radiotherapie dezelfde uitstekende oncologische resultaten heeft, leggen de morbiditeit, en de opties voor behandeling bij het weliswaar onwaarschijnlijke geval van een residu/recidief, het af tegen de laser chirurgische behandeling. Daarnaast is het herstel van de stemkwaliteit sneller na laserchirurgie en rapporteren deze groep patiënten ook minder vaak stemklachten in het dagelijkse leven. Bovendien brengt radiotherapie meer kosten met zich mee. Toch kunnen er verschillende individuele redenen zijn, zoals een hoog narcose risico, die in de klinische praktijk doen kiezen voor radiotherapie.

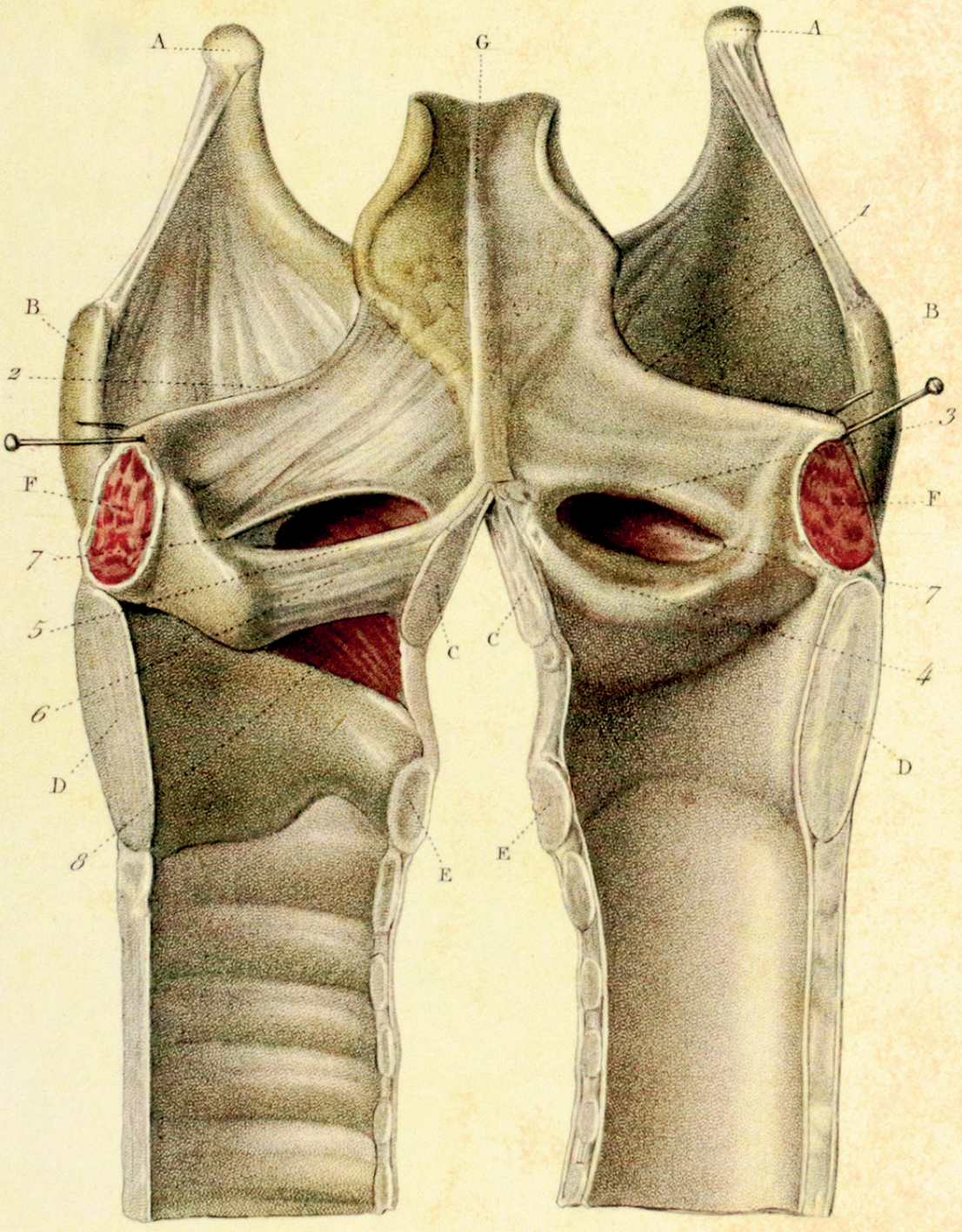
Aanbeveling met betrekking tot stem screening en stemtherapie

Op basis van de bevindingen in dit proefschrift adviseren wij om patiënten na behandeling van een klein glottisch larynxcarcinoom actief te screenen op ervaren stemproblemen, en indien aangegeven, een meer uitgebreide stemevaluatie uit te voeren. Ook wordt aanbevolen om patiënten met stemproblemen stemtherapie aan te bieden, als wetenschappelijk bewezen zinvolle interventie.

Aanbeveling voor toekomstig onderzoek

Toekomstige studies naar de kosteneffectiviteit van de juiste behandeling en revalidatie van patiënten met een klein glottisch larynxcarcinoom verdienen aanbeveling. Groot opgezette gerandomiseerd en gecontroleerde studies zouden het meest verdienstelijk zijn. Maar wellicht zijn patiënt gecontroleerde of cohort studies geschikter voor de meer patiëntgerichte resultaten. In ieder geval zal de keuze van uitkomstmaten gebaseerd moeten zijn op consensus en wetenschappelijk bewijs, zoals geleverd in dit proefschrift.

Fig. I.



DANKWOORD

DANKWOORD

Tot slot wil ik iedereen bedanken die op een of andere manier aan dit proefschrift heeft bijgedragen.

Prof. dr. H.F. Mahieu, beste Hans, aan jou ben ik de eerste dank verschuldigd. Hans, ik heb veel waardering en respect voor je, jij zit vol kennis en ideeën en kan dit vol passie en enthousiasme overbrengen. Als jij wetenschap bedrijft spreid je je armen uit en verzamelt alles wat mogelijk is, ook als het buiten de inclusie valt, “Chris, je weet nooit of we het nog ergens anders voor kunnen gebruiken!”. Ook waardeer ik de avonden bij je thuis, waar ik me altijd welkom heb gevoeld, ook mede door je vrouw, Margriet. Iedere keer kwam ik weer vol enthousiasme thuis met frisse moed om aan de slag te gaan. We hebben de tijd “genomen” maar het is ons gelukt, jihoe!

Prof. dr. I.M. Verdonck-de Leeuw, beste Irma, ook jou ben ik veel dank verschuldigd. Toen ik aan mijn onderzoeksperiode begon was ik één van de eersten onder jou begeleiding. Nu heb je een hele onderzoeksgroep onder je. Respect! Jij keek altijd nog vanuit een andere invalshoek naar een manuscript en wist deze dan aan te scherpen. Dank dat ik ook altijd bij je terecht kon als ik weer eens een schop onder mijn kont nodig had!

Prof. dr. C.R. Leemans, beste René, dank voor je vertrouwen in me. Niet alleen wat dit manuscript betreft en tijdens mijn opleiding tot KNO-arts, maar ook als staflid van onze afdeling.

Mede-auteurs, prof. dr. J.A. Langendijk, Rico Rinkel, Brigitte Boon-Kamma, Jeanne Wedler-Peeters, Joop Kuik, Diana de Bruin en Kim Goor, dank voor jullie bijdragen.

Alle patiënten, die meegedaan hebben in mijn studies, zonder hen zou dit alles niet mogelijk zijn geweest.

Leden van de promotiecommissie, Prof. dr. N.K. Aaronson, Prof. dr. A.J.M. Balm, Prof. dr. ir. J.M. Festen, Prof. dr. G.J. Ossenkoppele, hartelijk dank dat u het manuscript heeft willen beoordelen.

Jaqueline en Ton, dank voor jullie hulp als ik weer eens in gevecht was met een apparaat en het niet zelf kon oplossen met behulp van de stekker of de aan/uit knop.

Drs. P.A.H. Doornaert, beste Patricia, dank voor het redigeren van de radiotherapeutische stukjes in mijn proefschrift.

Collega’s en oud-collega’s in het VU medisch centrum. Collega stafleden, AIOS, dames van het secretariaat, verpleegkundigen van de poli en verpleegafdeling, dames van de “balie en opnameplanning”, collega’s van het audiologisch centrum, collega’s van het schisisteam, collega’s op en van het operatiecomplex, collega’s van de kinderafdeling/IC en eenieder die ik vergeten ben, dank voor de dagdagelijkse samenwerking, collegialiteit, vertrouwen en gezelligheid.

Mijn paranimfen Jantien en Willem.

Jantien, Lieve Tinus, volgens mij begon je een aantal weken na mij als onderzoeker op de afdeling KNO. We hadden direct een klik en al snel waren we “de jut en jul” onder de onderzoekers. Tinus we delen lief en leed en sinds een jaar het dorp Breukelen. Jouw vanzelfsprekendheid om naast me te staan tijdens mijn verdediging waardeer ik zeer. Xx!

Willem, lieve grote broer, we zien elkaar minder dan zou moeten, maar ik weet dat het altijd goed zit. Ik ben er trots op dat je weer naast me wil staan op een belangrijke dag zoals deze.

Mijn schoonfamilie Hoomans, dank voor de gezelligheid, die bij jullie vanzelfsprekend is.

Alle vrienden en vriendinnen, sommigen van oudsher, dank voor de nodige ontspanning en gezelligheid. Dat we nog veel leuke dingen met elkaar mogen beleven!

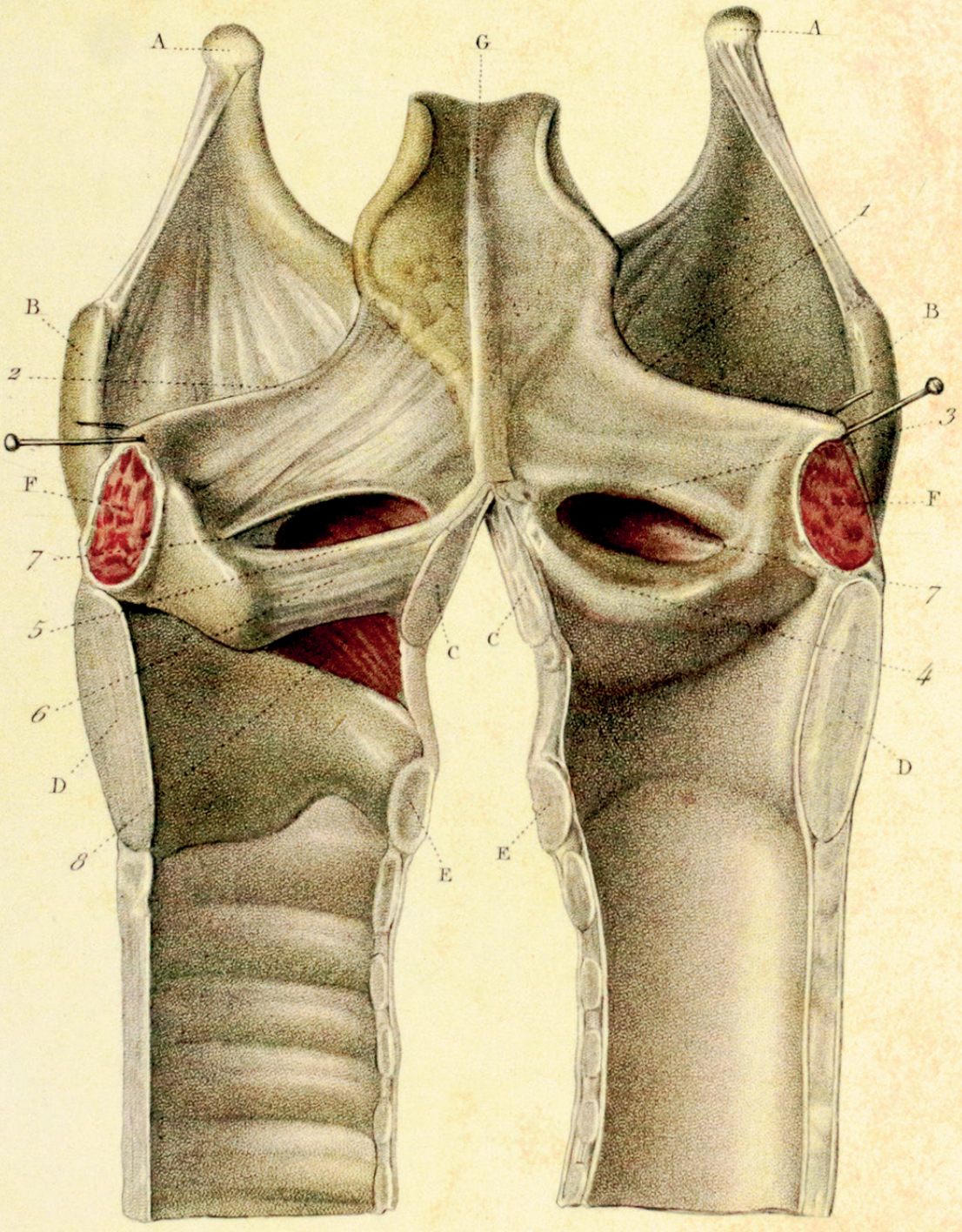
Mijn twee andere broers, lieve Geert “Kees” en Poel, wat vond ik het vroeger vervelend om het enige meisje te zijn. Nu ben ik er trots op 3 stoere broers te hebben en zou ik het niets anders willen! Onze familie wordt groter en groter en stiekem geniet ik toch van de chaotische, drukke en vooral luide familiebijeenkomsten.

Lieve pa en ma, jullie “no nonsens” opvoeding hebben me gemaakt tot wie ik ben. Het is fijn gestimuleerd te worden om eruit te halen wat er in zit zonder echt gepusht te worden. Pa: “die lege zakken zijn nu echt wel rechtgezet”. Dank!

Mijn meisjes, lieve “kaboutertjes” iedere dag worden jullie slimmer en ondeugender. Jullie verbazen mij keer op keer, maar wat geniet ik van jullie! Lieve en Roos, dit boekje is dan ook voor jullie, niet om uit voorgelezen te worden en al helemaal niet om zelf ooit uit te lezen, maar gewoon om jullie mee te geven dat je moet afmaken waar je aan begonnen bent, hoe lastig dit soms ook kan zijn. Oh ja, Lieve ik hoop dat het formaat van mijn boekje niet tegenvalt, de Cummings is toch echt niet door mama geschreven…!

Liefste Bart, “B”, beter dan jou worden ze niet gemaakt. We did it: VOLDEMORT is verslagen! Wat geef jij een rust in ons hectische bestaan en wat een top pa ben je! Dat we nog lang van elkaar mogen genieten! Dikke kus.

Fig. I.



LIST OF PUBLICATIONS

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Van Gogh CDL, Verdonck-de Leeuw IM, Boon AB, et al. A screening questionnaire for voice problems after treatment for early glottic cancer. Int J Radiat Oncol Biol Phys. 2005 Jul 1;62(3):700-705.

Van Gogh CDL, Verdonck-de Leeuw IM, Boon-Kamma AB, Rinkel RNPM, Langendijk JA, Kuik DJ, Mahieu HF. The efficacy of voice treatment in patients after treatment of early glottic cancer. Cancer. 2006 Jan;106(1):95-105.

Van Gogh CD, Mahieu HF, Kuik DJ, Rinkel RN, Langendijk JA, Verdonck-de Leeuw IM. Voice in early glottic cancer compared to benign voice pathology. Eur Arch Otorhinolaryngol. 2007 Sep;264(9):1033-1038.

Van Gogh CDL, Verdonck-de Leeuw IM, Langendijk JA, Kuik DJ, Mahieu HF. Long term efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer. J Voice.2012 May;26(3):398-401.

Van Gogh CDL, Verdonck-de Leeuw IM, Wedler- Peeters J, Langendijk JA, Kuik DJ, Mahieu HF. Prospective evaluation of voice outcome during the first two years in patients treated by radiotherapy or laser surgery for T1a glottic carcinoma. Eur Arch Otorhinolaryngol.2012 Jun;269(6):1647-1652.

Van Gogh CDL, Verdonck-de Leeuw IM, Boon-Kamma AB, Langendijk JA, Rinkel RNPM, Mahieu HF. Onderzoek naar het effect van logopedische behandeling bij patiënten met stemproblemen en communicatiebeperking na behandeling van een klein glottisch larynxcarcinoom. Hoofd-Hals Journaal. 2004; 32:5-6.

Van Gogh CDL, Festen JM, Verdonck-de Leeuw IM, Parker AJ, Traissac L, Cheesman AD, Mahieu HF. Acoustical analysis of tracheoesophageal voice. Speech Communication. 2005;47:160-168.

Van Gogh CDL, Verdonck-de Leeuw IM, Boon-Kamma AB, Langendijk JA, Rinkel RNPM, de Bruin MD, Mahieu HF. Onderzoek naar het effect van logopedische behandeling bij patiënten met stemproblemen en communicatiebeperking na behandeling van een klein glottisch larynxcarcinoom. Eindrapportage ten behoeve van VAZ en CVZ, 2004.

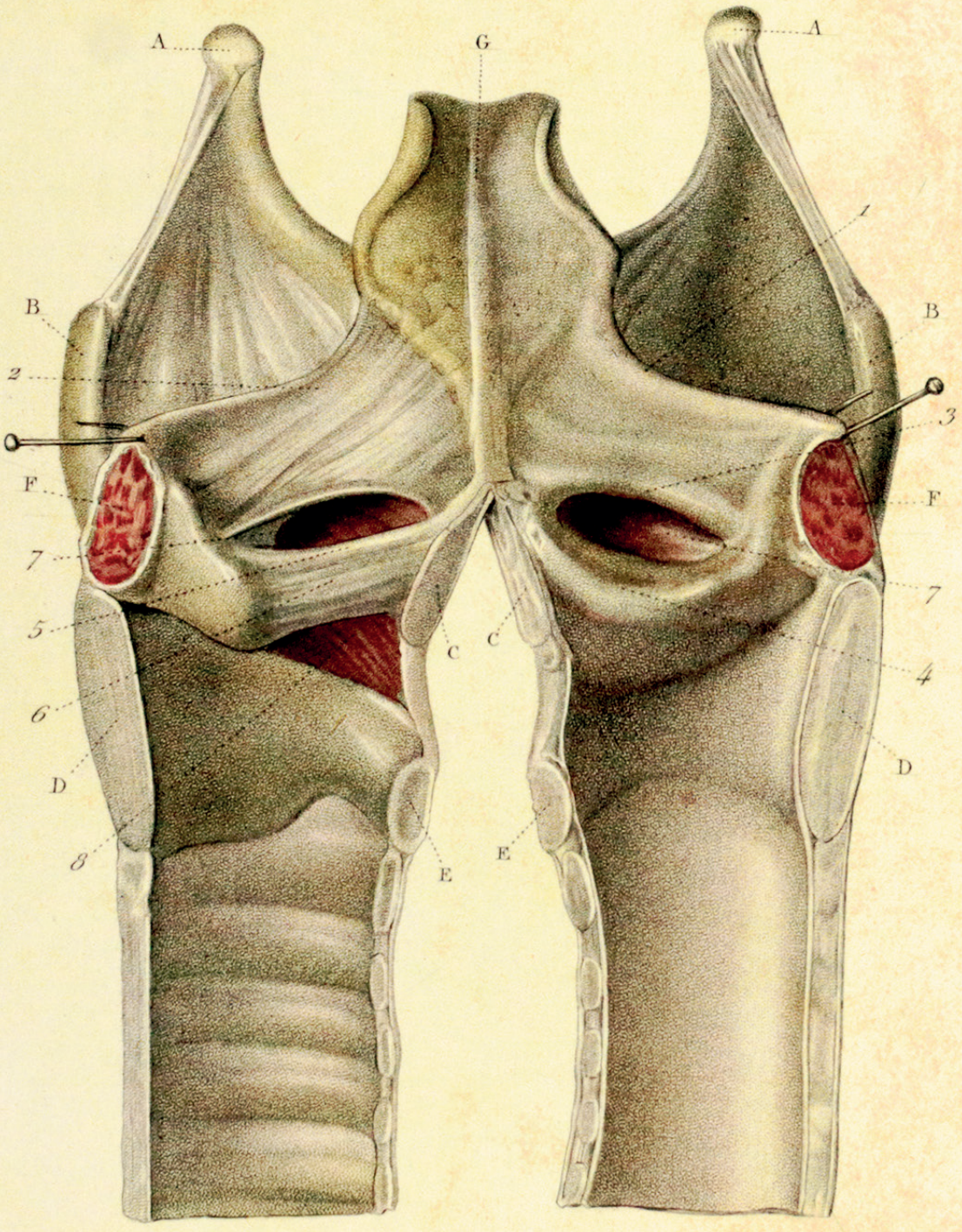
Peeters AJGE, **Van Gogh CDL**, Goor KM, Verdonck-de Leeuw IM, Langendijk JA, Mahieu HF. Health status and voice outcome after treatment for T1a glottic carcinoma. Eur Arch Otorhinolaryngol. 2004; 261(10):534-540.

Verdonck-de Leeuw IM, Boon-Kamma AB, **van Gogh CDL**, Greven AJ, Peeters AJGE, Mahieu HF. Een multidimensioneel stemonderzoeksprotocol: het meten van stemkarakteristieken van patiënten met een klein larynxcarcinoom. Logopedie en Foniatrie. 2002; 74:340-345.

Van der Torn M, **Van Gogh CD**, Verdonck-de Leeuw IM, Festen JM, Verkerke GJ, Mahieu HF. Assessment of alaryngeal speech using a sound-producing voice prosthesis in relation to sex and pharyngoesophageal segment tonicity. Head Neck. 2006 May;28(5):400-412.

Van der Torn M, **Van Gogh CD**, Verdonck-de Leeuw IM, Festen JM, Mahieu HF. Analysis of failure of voice production by a sound-producing voice prosthesis. J Laryngol Otol. 2006 Jun;120(6):455-462.

Fig. I.

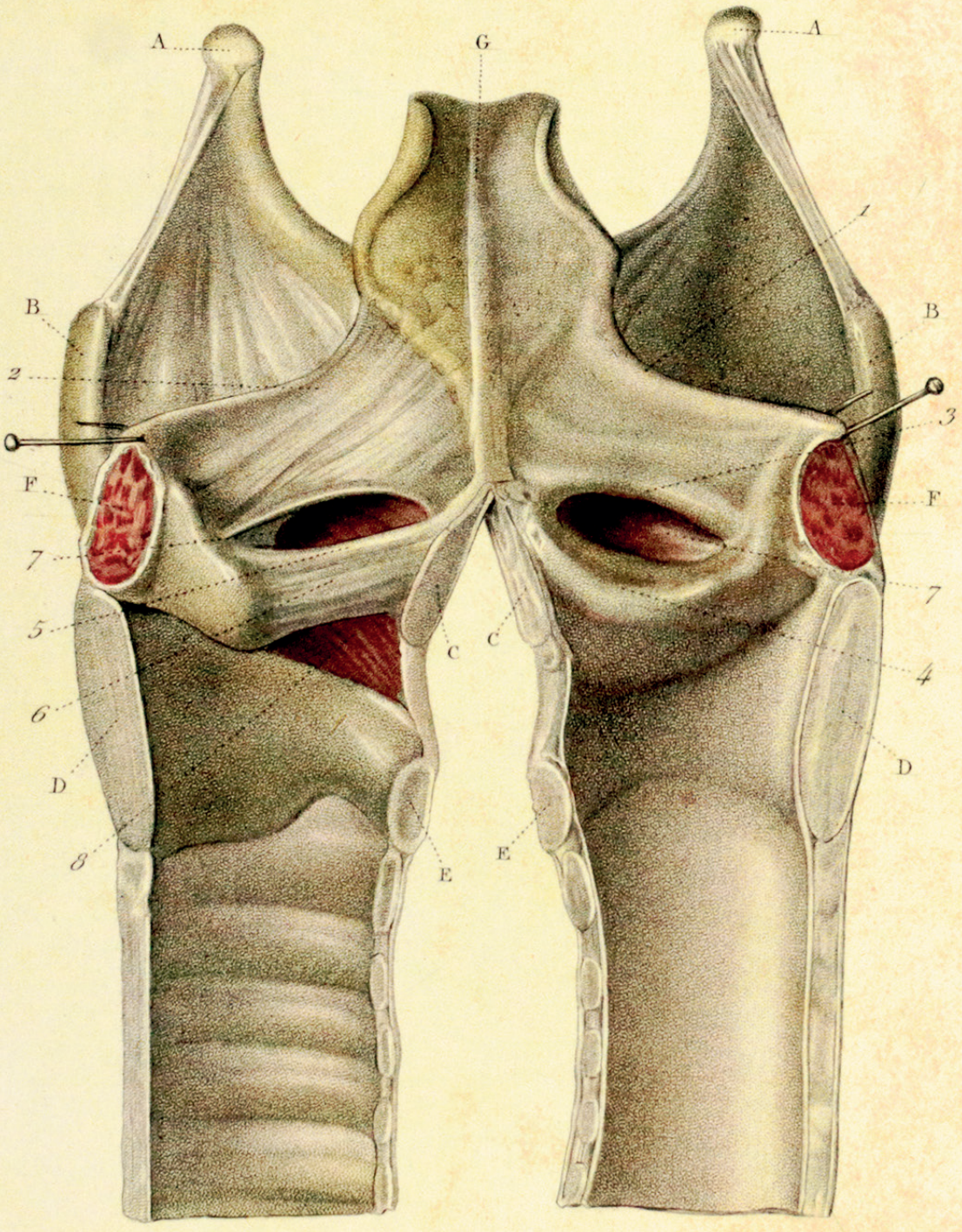


CURRICULUM VITAE

CURRICULUM VITAE

Christine van Gogh werd in Budel geboren op 13 april 1977. Na haar eindexamen VWO aan het Bisschoppelijk college te Weert, begon zij in 1995 haar studie geneeskunde aan de KU Leuven te België. Haar artsexamen werd behaald in 2002. In datzelfde jaar begon zij als onderzoeker op de afdeling Keel-, Neus- en Oorheelkunde / Hoofd-Halschirurgie (KNO) van VU medisch centrum Amsterdam onder begeleiding van Prof. Dr. H.F. Mahieu en Prof. Dr. I.M. Verdonck-de Leeuw. In juni 2005 begon zij aan haar opleiding tot KNO arts eveneens aan het VU medisch centrum Amsterdam met als opleiders Prof. Dr. C.R. Leemans en Prof. Dr. R. de Bree. Haar perifere stages werden doorlopen in het Spaarne Ziekenhuis te Hoofddorp (opleider: Dr. E.J.B. van Nieuwkerk) en in het Tergooi Ziekenhuis te Hilversum (opleider: Dr. M.J. Middelweerd). In oktober 2010 rondde ze haar opleiding af. Hierna bleef ze als staflid verbonden aan de afdeling KNO Hoofd-Halschirurgie van het VU medisch centrum met als aandachtsgebieden laryngologie en pediatrische KNO. Ze is getrouwd met Bart Hoomans en samen hebben ze twee dochters, Lieve (2009) en Roos (2011).

Fig. I.



APPENDICES

APPENDIX 1

Overview of the screening questionnaire covering vocal abilities and social situations

1. Does your voice sounds deviant (e.g. breathy or rough)?	Very Much	1	2	3	4	5	6	7	8	9	10	Not at all
2. Do you encounter problems holding conversation due to your voice?	Very Much	1	2	3	4	5	6	7	8	9	10	Not at all
3. Do you encounter problems making a telephone call due to your voice?	Very Much	1	2	3	4	5	6	7	8	9	10	Not at all
4. Do you encounter problems shouting?	Very Much	1	2	3	4	5	6	7	8	9	10	Not at all
5. Do you have to strain to produce voice?	Very Much	1	2	3	4	5	6	7	8	9	10	Not at all

APPENDIX 2 - THE VOICE HANDICAP INDEX (VHI)

Instructions: These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience:
never = 0, almost never = 1, sometimes = 2, almost always = 3, always = 4.

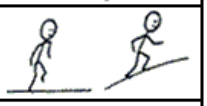
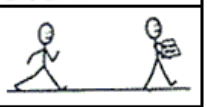
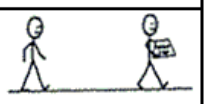
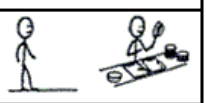
	0	1	2	3	4
F1. My voice makes it difficult for people to hear me.					
P2. I run out of air when I talk.					
F3. People have difficulty understanding me in a noisy room.					
P4. The sound of my voice varies throughout the day.					
F5. My family has difficulty hearing me when I call them throughout the house.					
F6. I use the phone less often than I would like.					
E7. I'm tense when talking with others because of my voice.					
F8. I tend to avoid groups of people because of my voice.					
E9. People seem irritated with my voice.					
P10. People ask, "What's wrong with your voice?"					
F11. I speak with friends, neighbors, or relatives less often because of my voice.					
F12. People ask me to repeat myself when speaking face-to-face.					
P13. My voice sounds creaky and dry.					
P14. I feel as though I have to strain to produce voice.					
E15. I find other people don't understand my voice problem.					
F16. My voice difficulties restrict my personal and social life.					
P17. The clarity of my voice is unpredictable.					
P18. I try to change my voice to sound different.					
F19. I feel left out of conversations because of my voice.					
P20. I use a great deal of effort to speak.					
P21. My voice is worse in the evening.					
F22. My voice problem causes me to lose income.					
E23. My voice problem upsets me.					
E24. I am less out-going because of my voice problem.					
E25. My voice makes me feel handicapped.					
P26. My voice "gives out" on me in the middle of speaking.					
E27. I feel annoyed when people ask me to repeat.					
E28. I feel embarrassed when people ask me to repeat.					
E29. My voice makes me feel incompetent.					
E30. I'm ashamed of my voice problem.					

Please select the word that matches how you feel your voice is today: Normal Mild Moderate Severe

APPENDIX 3 - COOP WONKA

PHYSICAL FITNESS

During the past 4 weeks...
What was the hardest physical activity you could do for at least 2 minutes?

Very heavy (for example) • Run, fast pace • Carry a heavy load upstairs or uphill (25lbs/10kgs)		1
Heavy (for example) • Jog, slow pace • Climb stairs or a hill moderate pace		2
Moderate (for example) • Walk, fast pace • Carry a heavy load on level ground (25lbs/10kgs)		3
Light (for example) • Walk, medium pace • Carry light load on level ground (10lbs/10kgs)		4
Very light (for example) • Walk, slow pace • Wash dishes		5

FEELINGS

During the past 4 weeks...
How much have you been bothered by emotional problems such as feeling anxious, depressed, irritable or downhearted and blue?

Not at all		1
Slightly		2
Moderately		3
Quite a bit		4
Extremely		5

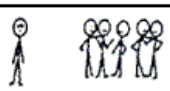
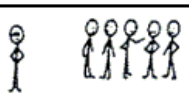
DAILY ACTIVITIES

During the past 4 weeks...
How much difficulty have you had doing your usual activities or task, both inside and outside the house because of your physical and emotional health?

No difficulty at all		1
A little bit of difficulty		2
Some difficulty		3
Much difficulty		4
Could not do		5

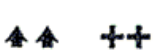
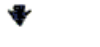
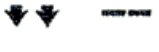
SOCIAL ACTIVITIES

During the past 4 weeks...
Has your physical amd emotional health limited your social activities with family, friends, neighbors or groups?

Not at all		1
Slightly		2
Moderately		3
Quite a bit		4
Extremely		5

CHANGE IN HEALTH

How would you rate your overall health now compared to 4 weeks ago?

Much better		1
A little better		2
About the same		3
A little worse		4
Much worse		5

OVERALL HEALTH

During the past 4 weeks...
How would you rate your health in general?

Excellent		1
Very good		2
Good		3
Fair		4
Poor		5