Disease outcome in T1 glottic carcinoma

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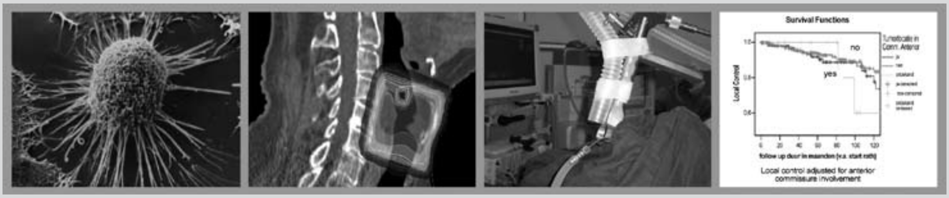
Chapter 1

Introduction

- an infamous case
- basic anatomy and physiology of the larynx
- definition and treatment of “early glottic carcinoma”
- scope of this thesis



An infamous case

Much has been written about the early stages of glottic carcinoma. Probably one of the most famous, if not the first, accounts is the case history of Crown Prince Frederich III of Prussia, who died of pneumonia after having suffered a tracheo-oesophageal fistula caused by a fausse-route created during the changing of his tracheal canula. It was published as *Die Krankheit Kaiser Friederich des Dritten* in July 1888, soon to be followed by a second report by Morell Mackenzie in *The Fatal Illness of Frederick the Noble* in October of that same year. A bitter dispute about the best treatment had arisen amongst the attending physicians during the illness of the Crown Prince, which was now being fought out in the press. More than a year earlier, a small swelling had been discovered on the posterior part of the left vocal cord after the Crown Prince begun complaining of hoarseness in January 1887. His German physicians, led by Von Bergmann, regarded this as highly suggestive for a malignancy and advised removing the tumor through an external approach (laryngofissure), a new and decidedly risky operation at that time. They were days away from performing the surgery in May 1887, when Morell Mackenzie, the renowned British laryngologist was called in, probably at the insistence of the Crown Prince's wife, Crown Princess Victoria, who was herself British.

Mackenzie examined the Kaizer and confirmed a "pea sized swelling" on the posterior part of the left vocal cord which he considered to have a benign appearance. He also reported that the movement of the left vocal cord was impaired. It is unclear if he realized the ominous implications of this last finding. Mackenzie advised against an operation until malignancy could be microscopically confirmed. Instead, he removed the tumor in three separate sittings through an endoscopic approach. In all three instances the material was examined by Dr Rudolph Virchow who proclaimed them all free of cancer.

Figure 1 | Crown Prince Frederich III of Prussia, Artist: Heinrich von Angeli 1874

In the end this turned out to be a mistake. After examining the Crown Prince again in November 1887 and seeing that the swelling had returned, this time showing ulcerations and sub-glottic spread, when asked by the Crown Prince if it was cancer, Mackenzie had to admit: "I am sorry to say, sir, it looks very much like it". But by this time it was too late. The Crown Prince refused to undergo the proposed laryngectomy and died on the 15th of June 1888 after the dramatic incident with the trachea canula.

The sad irony of the missed diagnosis is that Morell Mackenzie was one of the first physicians who insisted on working by systematic methods and making use of pathological examination. Frederick was succeeded by Kaiser Wilhelm II, who along with Otto van Bismark militarized Germany and led them into the First World War. The question will always remain: could modern laryngology have prevented WWI?

Background

More than one hundred years have passed since the unfortunate history of Kaiser Frederich the III. The majority of laryngeal carcinomas are now diagnosed at an early stage and with modern treatment methods patients with early vocal fold cancer have close to 100% disease specific survival. But even so there are still unresolved dilemmas around the treatment of these tumors. The discussion on optimal management of early glottic carcinoma in literature is still strong. The purpose of this thesis is to contribute to this discussion by providing data on treatment outcome and prognostic factors to support better decision-making in early glottic carcinoma. In this introductory chapter, the basic anatomy and physiology of the larynx is reviewed, early glottic carcinoma is more closely defined and current treatment methods as well as relevant outcome parameters are described. Finally, the scope of the thesis is presented.

Basic anatomy and physiology

Many textbooks give detailed descriptions of laryngeal anatomy and physiology such as Hirano and Sato (1993), Titze (1994) and Sataloff (1997). The present section includes only the most essential information that is necessary to understand the influence of tumors and their treatment on voice production, and is therefore a summary of information selected from the textbooks mentioned above.

Gross anatomy of the larynx

The larynx, colloquially known as “the voice box”, is shaped like a hollow tube and is located between the base of the tongue and the top of the trachea, at the point where the food and airway divide (fig 2). It has a cartilaginous skeleton consisting of five separate cartilages: the thyroid cartilage, the cricoid cartilage, the epiglottis and the two arytenoid cartilages. The thyroid and cricoid cartilages are positioned one on top of the other to form the main framework of the larynx. The two arytenoid cartilages are localized within this framework, resting on the posterior border of the cricoid cartilage (fig 3). The cartilaginous skeleton is lined by muscle and mucosa to give it the aspect of a hollow tube (fig 4).

The larynx has three main functions: to keep the airway open, to seal the airway when necessary and to produce voice. To this end, it contains the vocal folds which are sus-

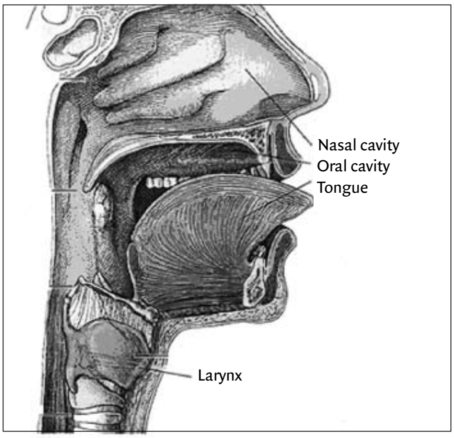


Figure 2 | Position of the larynx between the base of the tongue and the top of the trachea.
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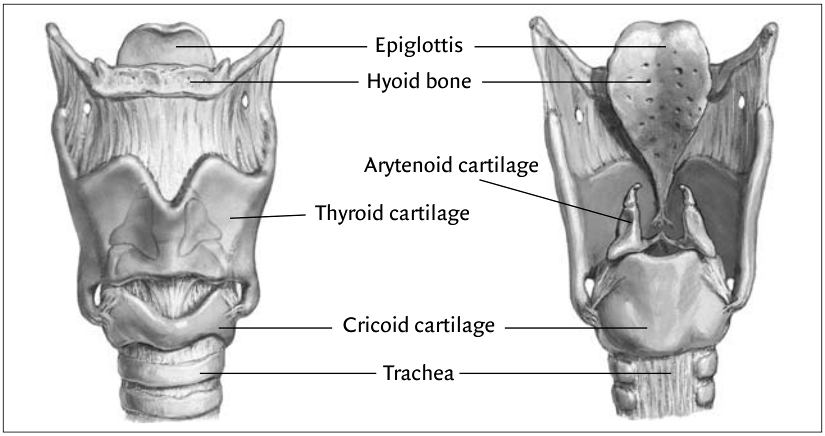

Figure 3 | Cartilaginous skeleton of the larynx connected by ligaments.
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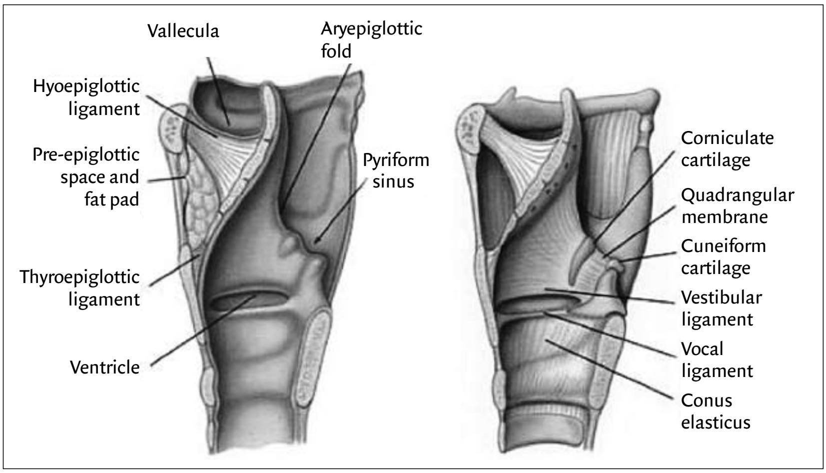

Figure 4 | Interior of larynx, with and without mucosa (sagital view).
Image from The Larynx by Tucker, 1992. Used with the permission of Thieme publishing.

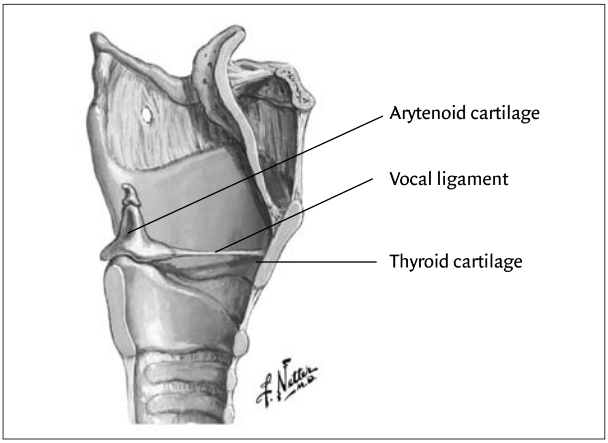

**Figure 5 | ** Vocal ligament suspended between arytenoid cartilage and the thyroid cartilage.
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**Figure 6a | ** Anatomy of the vocal cords viewed from above.
Image from Anatomy by Henry Gray, 1858.
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**Figure 6b | ** Vocal cords as viewed from above during examination.

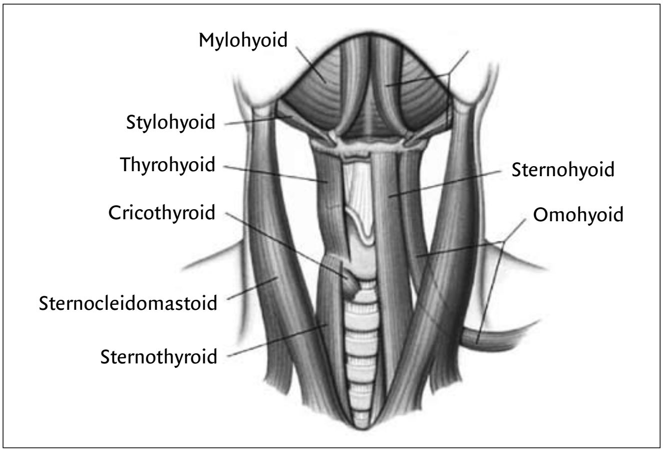

**Figure 7 | ** Extrinsic musculature.
Image from The Larynx by Tucker, 1992. Used with the permission of Thieme publishing.

pended midway in its structure. At its core, each vocal fold has a central vocal ligament anchored to an arytenoid cartilage posteriorly (fig 5). The vocal ligaments, also lined by muscle and mucosa, join and attach in the midline to the inside of the thyroid cartilage anteriorly, forming a v-shape known as the anterior commissure. Seen from above, the vocal folds thus appear as two whitish bands that stretch across the airway in a V-shape inside the framework of the larynx (fig 6). The opening between the vocal folds is called the glottis. The region of the larynx above this level is called the supraglottis and the region below this level is called the subglottis.

The laryngeal cartilages are all connected by pliable ligaments that allow changes in their relative angles and distance. This is accomplished by the extrinsic and intrinsic laryngeal musculature. The extrinsic laryngeal muscles such as the strap muscles and the omohyoid muscle attach to the outer surface of the laryngeal skeleton and act on the larynx as a whole, by depressing or elevating the entire framework (fig 7). The intrinsic musculature are small muscles mainly located within the larynx which act to abduct, adduct and tension the vocal folds by changing the relative positions of the laryngeal cartilages (mainly the arytenoids) (fig 8). In this way the length and position of the vocal folds are constantly changing which is in turn essential for the control of the airway and the production of voice. During breathing, the air can pass freely through abducted vocal folds. During phonation, the pressure of the air stream from the lungs will cause the vocal folds to vibrate (cyclic ad- and abduction) (fig 9). However, vocal fold vibration, and therefore voice, is not only dependent on the intrinsic muscle activity and airstream, but on the biomechanical properties of the vocal folds as well. The microscopic structure of the vocal folds is therefore briefly discussed below.

Structure of the vocal folds

The cross-section in figure 10 shows that the vocal fold is composed of several orderly layers of tissue. The bulk of the vocal fold consists of the thyroarytenoid or “vocalis” muscle that runs along its length and forms the inner “body”. The surface, or the “cover”, consists of epithelium at the vocal fold edge. Between these two layers, a network of parallel fibers form a transitional layer called the lamina propria. The character of the fibres in the lamina propria gradually changes from a loose, almost fibreless tissue in the superficial lamina propria (Reinke’s space) to more elastic fibres in the intermediate lamina propria and then to more collagenous fibres in the deep lamina propria. This deep layer is known as the vocal ligament. This layered structure in which the “cover” is able to move loosely over the “body”, like the skin over the back of one’s hand, gives the vocal folds their biomechanical properties essential for vibration and voice production.

Voice production

The basic waveform, which is the raw material for what we perceive as voice, is produced by the vibration of the vocal folds within the larynx in what is called “the glottal cycle”.

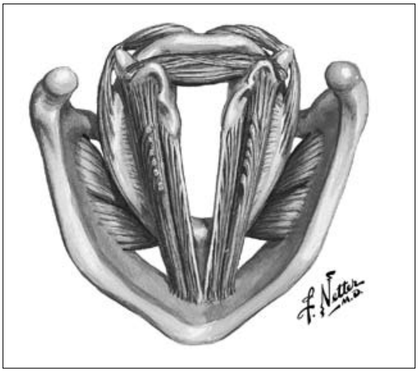

Figure 8 | Intrinsic musculature.
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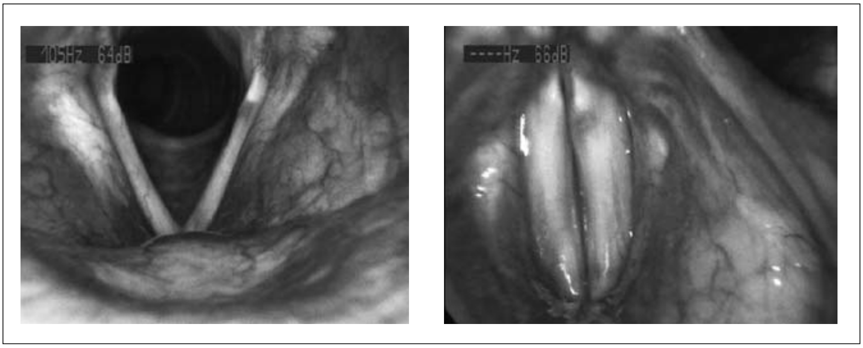

Figure 9 | Abduction (open for breathing) and adduction (voicing) of the vocal folds.

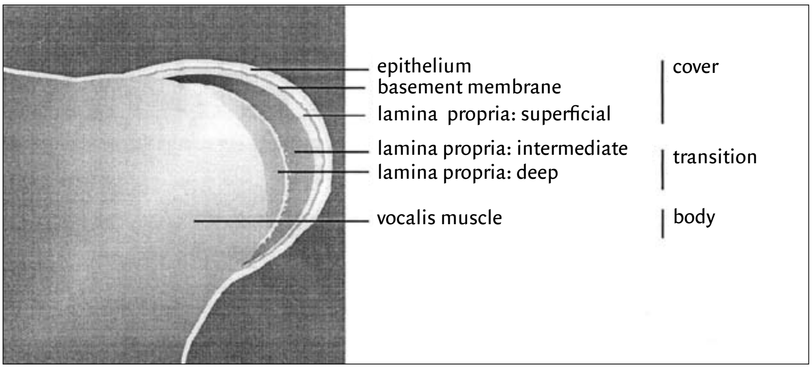

Figure 10 | Schematic layers of the vocal fold.
From the thesis “Voice characteristics following radiotherapy: the development of a protocol”.
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The net outcome of the glottal cycle is to "chop" the air stream from the lungs into short bursts or puffs of air by the rapid opening and closing of the vocal folds. The frequency with which this occurs is called the fundamental frequency (Fo) and lies around 125 Hz in males and 210 Hz in females. This process, governed by both aerodynamics and biomechanics, is described below.

Glottic cycle

At the beginning of the glottic cycle, the vocal folds are adducted, closing off the airway. Driven by the air in the lungs, pressure builds up under the vocal folds forcing them apart, first the lower margins and then the upper margins, and airflow through the open vocal folds begins. The glottal opening is narrower than the regions directly above and below, causing the speed of the airflow within the glottic region to increase and the air pressure inside the glottis to decrease (Bernoulli's law*). This relatively negative pressure has the effect of "sucking" the lower margins of the glottis back towards the midline while the upper margins are still being blown apart. At this point the biomechanical properties of the vocal folds come into play. As the upper margins are now pushed far away from the midline, the highly elastic edge of the vocal ligament has been stretched. Like a rubber band, the more it is stretched, the stronger the tendency for it to snap back to its original shape. When the airflow starts to decline because the lower margins have been closed, this restorative force overcomes the outward-pushing force of the air pressure and snaps the upper margin back towards the midline. It is the sharp cut off of airflow occurring from the quick retraction of the upper margins of the vocal folds that is the true raw material of voice. The vocal folds are now restored to their adducted position and the cycle is ready to repeat.

Mucosal wave

The "wave-like" movement of the "cover" over the "body" of the vocal fold during the glottic cycle is termed the "mucosal wave". The pliability of the vocal folds, based on the layered structure discussed above, is essential in maintaining the propagation of the mucosal wave and therefore for normal voice production. The characteristics of this system, which can be partly altered by varying the tension in the vocal folds, are responsible for the quality and the variations in the voice produced. Anything that severely disrupts the characteristics of this system, such as a tumor, will therefore affect voice quality and ultimately voice function. Figure 11 shows how a tumor can disrupt various layers of the vocal fold, depending on the depth of infiltration. Eventually the "cover" can become anchored to the "body" in which case the mucosal wave will be completely absent. It is important to realize that not only the tumor, but also the treatment of the tumor in the form of radiotherapy or laser surgery will have consequences for the voice due to defects and/or scarring of the tissues of the vocal fold.

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* Bernoulli's law: the velocity of flow of a gas or fluid through a tube is inversely related to its pressure against the side of the tube; i.e., velocity is greatest and pressure lowest at a point of constriction.

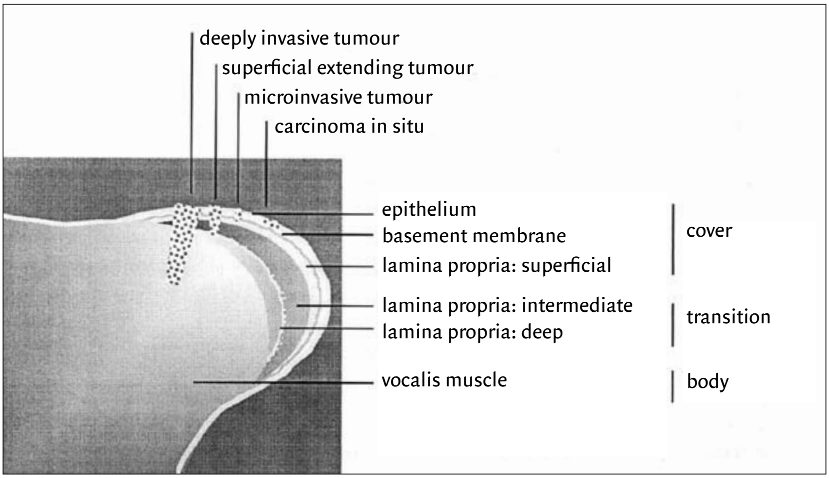

Figure 11 | Tumor infiltration disrupting layered structure of vocal fold.
From the thesis "Voice characteristics following radiotherapy: the development of a protocol".
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Definition and treatment of "early glottic carcinoma"

Laryngeal cancer

Approximately 95% of all cancers of the larynx originate from the thin, flat cells called squamous epithelium that make up the mucosal lining of the larynx. Cancers originating from these cells are called squamous cell carcinomas, or carcinomas for short. Laryngeal carcinomas can arise from all three levels of the larynx and are defined as supraglottic, glottic or subglottic according to their region of origin. This thesis is devoted to early carcinomas of the vocal folds, or "early glottic carcinomas".

Definition of "early glottic carcinoma"

"Early glottic carcinoma" is often used as a collective term for early stages of squamous cell carcinomas originating from the vocal folds. According to Ferlito early glottic cancer should be defined as a minimally invasive tumor that does not yet invade the vocal muscle or cartilage (1). Vocal fold mobility has to be normal. However, there is no absolute consensus as to which tumor stages should be included and studies on "early glottic carcinoma" therefore have varying tumor populations ranging from in situ (Tis) to T2-stage carcinomas. The definitions for Tis, T1, and T2 glottic carcinomas according to the sixth edition of the UICC TNM classification are shown in table 1 and are graphically portrayed in figure 12 and 13.
Most "early glottic carcinomas" are T1-stage tumors. Giving early signs of hoarseness, 56% of glottic carcinomas are diagnosed at this stage (see chapter 2). T1 lesions are confined to the true vocal folds and relatively superficial (no fold fixation). Whereas lymphatics in the supraglottis and subglottis are plentiful, lymphatics in the glottic region

Table 1 | Definition of TNM classification (Tis-T2) for glottic carcinoma.

Tumor stage	Definition (TNM 6th edition)
Tis (in situ)	Intra-epithelial tumorcells with intact basal membrane
T1	Tumor limited to vocal cord(s) with normal mobility, may involve anterior or posterior commissure T1a: tumor limited to one vocal cord T1b: tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

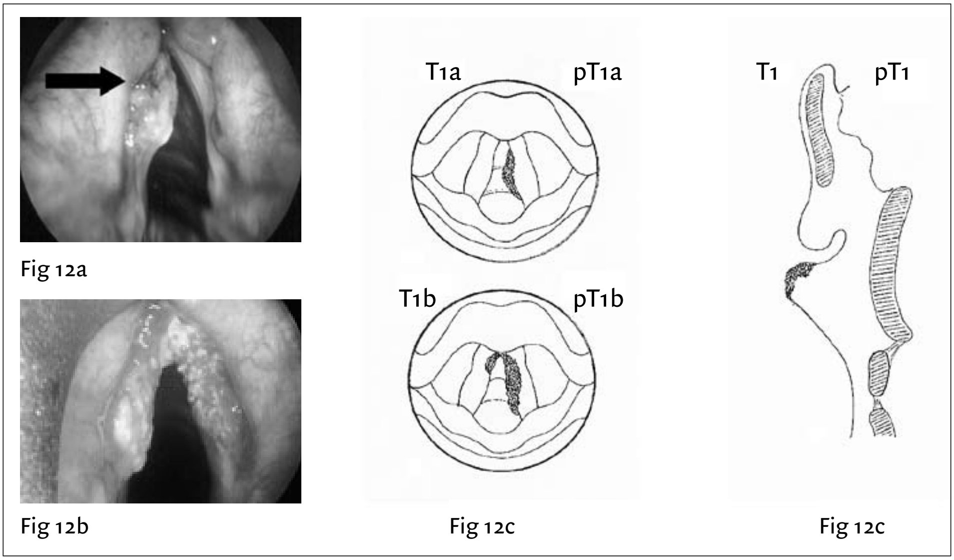

Figure 12 | Illustration of T1 glottic carcinoma:
a. T1a glottic carcinoma confined to one vocal cord
b. T1b glottic carcinoma located on both vocal cords
c. schematic representation of T1a and T1b carcinomas as seen from above
d. schematic representation of T1 carcinoma, coronal view

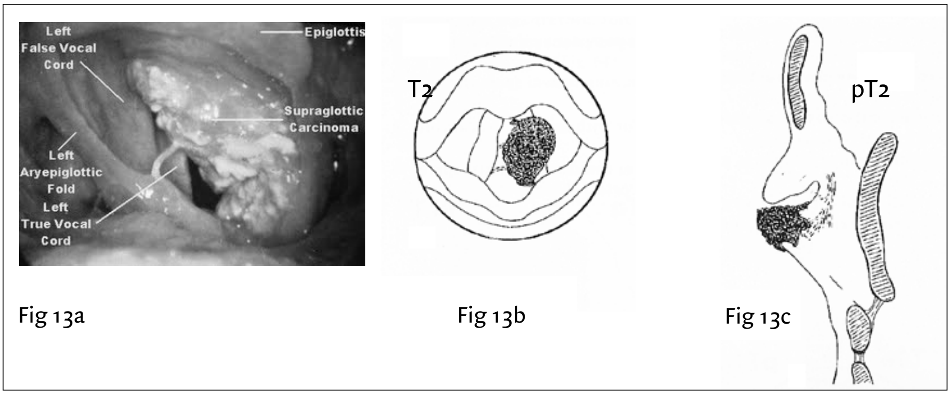

Figure 13 | Illustration of T2 glottic carcinoma:
a. T2 glottic carcinoma with spread to the false vocal cord
b. schematic representation of T2 a carcinomas as seen from above
c. schematic representation of T2 carcinoma, coronal view

are sparse to non-existent. Therefore, T1 stage tumors, as a rule, do not have regional metastasis. Management can therefore be confined to the primary tumor. The superficial character and the absence of metastasis are the reasons for the high rates of local control (85-90%), larynx preservation (93-97%) and the extremely high rates of disease specific survival (97-100%) in T1 stage patients (see chapter 9). T2 carcinomas are more extensive than T1 lesions, either by having spread outside the confines of the vocal folds to the supra and / or subglottis, or having infiltrated deeper in the vocalis muscle, decreasing vocal fold mobility – or both. Five to ten percent of T2 lesions also have regional metastasis at diagnosis (2). This is reflected in disease outcome which is less favorable than in T1 lesions, with an average 5-year local control rate of 71%, larynx preservation of 75% and disease specific survival of 81% (see chapter 9). That these lesions are not comparable and do not belong under one heading is reflected by the fact that the difference in outcome is mostly found to be significant in multivariate analysis.

Therefore, we would advocate minimizing the use of the term "early glottic carcinoma" and instead to specify TNM classification for all lesions and all results. This thesis will focus on T1N0M0 glottic carcinoma; two studies include patients with in situ carcinomas (chapter 4 and 5).

Treatment modalities

The two main treatment modalities for T1 glottic carcinoma are radiotherapy and endoscopic CO_2 laser surgery. They are used both in primary treatment and in the treatment of recurrent disease. Vocal fold stripping or microsurgery, chemotherapy, partial external laryngeal surgery and photodynamic therapy are alternative treatments and are less widely used. Treatment strategy depends on surgeon and patient preference and varies between countries, institutions and individual surgeons although total laryngectomy is unanimously considered a last resort. A brief summary of the trend in the Netherlands is presented below. In addition, although not the main topic of this thesis, it is important to state that in the Netherlands, both in situ carcinoma and severe dysplasia are treated in the same way as T1 glottic carcinoma.

External beam radiotherapy has traditionally been the gold standard for treatment of T1 glottic carcinoma. Although the Dutch guideline for the treatment of laryngeal carcinoma (3;4) does not give a definite advice on treatment schedules 30 x 2 Gy was a prevailing schedule until around 2000. Due to the positive impact of shorter treatment times on local control, (5-8) accelerated schedules such as 25 x 2.4 Gy have now become more common. Both schedules are still in use in the Netherlands today.

Endoscopic excision of glottic carcinomas by CO_2-endoscopic laser surgery was first introduced by Strong and Jako in 1972 and was brought into prominence by the work of Steiner and other European pioneers in the '80s and early '90s. Since September 1996 it has been used in Leiden as an alternative to radiotherapy in superficial, midcord T1a carcinomas, which make up about 50% of all T1 lesions. In the year 2000, it was classified as a possible alternative to radiotherapy in superficial, midcord T1a lesions in the Dutch guideline for the treatment of laryngeal carcinoma. In the recent revision of the guideline (2009), laser surgery was officially "upgraded" to "treatment of choice" in these tumors.

Outcome parameters

Disease outcome

As almost all patients survive T1 glottic carincoma, survival is not the main outcome parameter in this disease. Although local control is also high, the 10-15% (see chapter 9) of patients who do develop a recurrence may eventually face a laryngectomy with all the associated impacts on daily life. Therefore, these last two parameters (local control and larynx preservation) are the most important for determining and comparing treatment results.

Voice outcome

Any treatment affecting the vocal folds is potentially harmful to the voice. As the chance of local control and survival is very high, any long-term handicap experienced by the patient after treatment is a major concern. Measuring voice outcome is complex and largely subjective. It may be described in terms of three major dimensions: *voice quality*; *voice function* and *voice impact*, which in turn have different rating instruments.

Voice quality is defined as everything in the acoustic signal that is not pitch (F0) or loudness (dB), in accordance with the ANSI Standard (9). Auditory-perceptual analysis and acoustic analysis are the most common instruments used clinically. Acoustically, perturbation measures are customary ("jitter" - the variation in length of successive cycles of F0, "shimmer" – the variation in amplitude of successive cycles of F0, and the "harmonic-to-noise ratio"). Auditory perceptual evaluation, in which (expert) listeners rate the perceived dysphonia, relies on VAS ratings or other rating systems such as the GRBAS (Grade Roughness Breathiness Asthenia Strain) (10). Patient's self-rating of perceived voice quality is usually in the form of the VAS or simple grades.

Voice function is defined in accordance with the WHO ICF framework's impairment (11). If the vocal apparatus no longer works or operates properly, in this case production of voice (sound), its function is impaired. Stroboscopy, phonetography (voice profile) and aerodynamic measurements are typically used to assess vocal function, as well as the patient's subjective rating about his or her vocal capability.

Voice impact is based on the WHO ICF components of disability and handicap, the first results in changes in performance, the latter results in disadvantages in relation to others. The Voice Handicap Instrument is the most widely used instrument to measure impact (12).

Voice assessment protocols

Although the dimensions and the measurement instruments above seem clear, there is no standard voice assessment protocol in literature. In the year 2000, the European Laryngological Society (ELS) identified the need for a standardized assessment and proposed a multidimensional approach that consists of a set of basic tests, covering the three dimensions described above. They do however acknowledge that the development of new techniques is to be encouraged. The components that they included all provide quantitative data (13-15).

Voice quality

AUDITORY-PERCEPTUAL ANALYSIS: the severity of the perceived dysphonia, (Grade), as well as the presence of Breathiness (audible impression of turbulent air) and Roughness (audible impression of aperiodic vibration) is rated on a four-point scale.
ACOUSTIC ANALYSIS of the voice signal (see above): perturbation measures (%jitter and % shimmer) are measured on a sustained vowel (/a:/)

Voice function

AERODYNAMIC function during phonation: for an impression of the efficiency of voicing, maximum phonation time is the most basic measurement, consisting of a maximally sustained /a:/ after maximum inhalation.
VIDEOSTROBOSCOPY: during phonation the vocal fold structure is observed under normal light and vocal fold vibration under stroboscopic light. Visual parameters such as glottal closure, regularity of vibration, the quality and extent of the mucosal wave and symmetry ("mirror" motion) are evaluated.
Voice impact
SUBJECTIVE PATIENT RATING: as part of the *basic* protocol, patients give a minimal subjective impression of their voice quality and the repercussions that the voice problem has on everyday life, on 100 mm VAS. The Voice Handicap Index, or a similar validated questionnaire may also be computed.

The two studies in this thesis on voice quality (chapter 7 and 8) used a multidimensional protocol that covers the three dimensions mentioned above and closely resembles the quantitative measures proposed by the ELS.

Scope of this thesis

When work on this thesis was begun in 1998, radiotherapy was still the main treatment for T1 glottic carcinoma in the Netherlands. Laser surgery had just recently been introduced and was considered an experimental therapy in selected, superficial T1a lesions. There was, as there is still, uncertainty over tumor related prognostic factors for local control. Furthermore, little was known about the voice outcome (voice quality and voice function) and how this compared between the two treatment modalities: laser surgery and radiotherapy. There was no guideline to aid in treatment decisions. Two central dogmas were however already established:

1. When comparing radiotherapy and laser surgery, laser surgery should theoretically have the advantage, even if local control would be assumed to be equal for the two modalities. This is because in the case of a local recurrence, there are more secondary treatment options for patients who were primarily treated with laser surgery, as they can still undergo repeated laser resections or irradiation. Patients who have been primarily treated with radiotherapy cannot be re-irradiated, and achieving a radical laser resection is more difficult in an irradiated larynx. Therefore, these patients should theoretically have a higher risk of undergoing a laryngectomy.

2. Laser surgery, although possibly superior in local control, is commonly held to be more harmful to the voice, especially in larger lesions.

There was, and unfortunately still is, little data available that could reliably support or refute these two beliefs (see chapter 9: review of the literature). However, as will become apparent in this thesis the trade-off they present plays a central role in defining the optimal treatment strategy for T1 glottic carcinoma. Against this background, the aims of this thesis were to:

- describe the epidemiology of laryngeal carcinoma
- determine disease outcome and prognostic factors for T1 glottic carcinoma treated with radiotherapy
- determine disease outcome in T1a glottic carcinoma following laser surgery
- compare the voice outcome following radiotherapy and laser surgery
- identify problems and gaps in current research and suggest areas and strategies for further studies

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