Advanced larynx cancer. Trends and treatment outcomes
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CHAPTER 1

General Introduction

In part based on a publication in Dutch.

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[New developments in the treatment and rehabilitation of head and neck cancer in the Netherlands].

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EPIDEMIOLOGY OF LARYNX CANCER

In the Netherlands, head and neck cancer is diagnosed in about 3000 patients annually, of whom 700 suffer from larynx cancer (1). The most important risk factors for developing larynx cancer are alcohol and smoking (2). For glottic tumors smoking behavior is determinative whereas in supraglottic cancers the combination of smoking and alcohol abuse is risk enhancing. More men than women develop larynx cancer. However, incidence of supraglottic and glottic cancer in men is slightly decreasing, whereas the incidence for women stays stable over the years (period 1989-2010). The incidence-curves of men and women are converging, due to smoking and drinking behavior of men and women, which are more similar nowadays. In 65-70% of the patients the tumor is originating from the vocal cords (glottic) and in 30% at supraglottic level. Tumors are rarely found at the subglottic level (Figure 1).

Figure 1. Anatomy of the larynx, (A) anterior view of the larynx and (B) top view of the larynx.
STAGING AND TREATMENT OF ADVANCED LARYNX CANCER

Decisions about treatment of larynx cancer are based on tumor staging according to the Union Internationale Contre le Cancer (International Union Against Cancer) (UICC) or the American Joint Committee on Cancer (AJCC) TNM classification (3), functionality of the larynx, the general condition of the patient and patient as well as doctor preferences. To determine T and N classification, physicians rely on clinical examination, laryngoscopy, imaging, ultrasound-guided fine-needle aspiration cytology, and biopsy. T1 and T2 larynx cancers are generally considered ‘early’ tumors and T3 and T4 larynx cancer ‘advanced’ tumors. The distinction between T3 and T4 is mainly based on thyroid cartilage destruction and extralaryngeal spread (3). Primary treatment options for advanced (T3-T4) larynx cancer are radiotherapy (RT), concurrent chemoradiotherapy or total laryngectomy (TL) with or without adjuvant RT. In the Netherlands Cancer Institute, T3 larynx cancer is usually treated with accelerated RT and T4 larynx cancer with TL and adjuvant RT. In case of extensive nodal disease (for both T3 and T4 tumors), chemotherapy is given concurrently to RT. Thus, T classification plays a major role in the treatment decision and should be of predictive value. However, some studies suggest that T classification is not sufficient to predict outcome and several authors identified tumor volume as a substitute/additional prognostic factor for local and loco-regional control and for survival (4-7). Other authors, however, did not identify tumor volume as a useful prognostic factor in advanced larynx cancer (8, 9).

Of the primary treatment modalities for advanced larynx cancer, TL with adjuvant RT has long been considered the gold standard. However, since this organ-sacrificing surgery often results in significant morbidity leading to psychosocial, vocal, pulmonary and olfactory problems, other options for treatment, e.g. partial laryngectomy and RT, have gained in popularity. After the publication of two randomized studies, organ-preserving (chemo-)RT treatment protocols are increasingly being used as alternative to TL (10, 11). The first randomized study, conducted by the Department of Veterans Affairs (VA) Larynx Cancer Study Group (1991) showed that 2-year survival rates in patients treated with induction chemotherapy (cisplatinum and fluorouracil) followed by RT were similar to those treated with TL, except for T4N0 disease, which showed a significantly better survival in the TL arm. Moreover, the larynx was preserved in 64% of patients receiving organ preservation treatment, in contrast to the obvious 0% in the TL arm of the study (10). The second, purely RT-based organ preservation study was the Radiation Therapy Oncology Group (RTOG) 91-11 trial, which assessed in a three-arm design the effects of the addition of chemotherapy to RT, either induction with cisplatinum and fluorouracil, or concurrent with cisplatinum only. At 2-years posttreatment, larynx preservation and loco-regional control rates in this study were significantly higher in the concurrent chemoradiotherapy arm than in the other two arms. Overall survival in the three arms, however, did not differ significantly (11).
Recently, the 10-year results of this RTOG 91-11 trial were published. Similar as in the 2-year report, loco-regional control and larynx preservation still were highest in the concurrent chemoradiotherapy arm. However, also at 10-years the addition of chemotherapy to the radiation treatment did not provide any overall survival benefit (12).

In 2005 Carvalho et al. published the results of a population-based study based on the SEER (Surveillance, Epidemiology, and End Results) database of the National Cancer Institute and reported improved survival for most head and neck cancer sites, except for larynx cancer (13). In 2006, Hoffman et al. studied changes in demographics, treatment patterns and survival based on the NCDB (a hospital-based oncology data set) and reported decreasing survival for larynx cancer patients from the mid-80s to the mid-90s in the US (14). They found an increase in the use of organ-preserving treatment modalities and a decrease in the use of surgery in the same period. The shift towards organ-preserving treatment protocols has been postulated as a possible cause of the lack of gradual survival improvement for larynx cancer, when compared to other head and neck sites (13, 14). In 2007, Chen et al. aimed to determine factors predictive for survival in patients with advanced larynx cancer. The authors reported a hazard ratio for death of 1.6 for RT and 1.3 for RT combined with chemotherapy when compared to treatment with TL (15). Since then, there has been a debate on whether or not TL should be performed more often in (a selection of) patients with advanced larynx cancer (16).

The above-mentioned studies were based on patients from the United States. In the Netherlands, the Dutch Head and Neck Society (former Dutch Cooperative Head and Neck Oncology Group) published a consensus document on larynx cancer diagnostics and treatment in 1999 (17). This document contained evidence-based protocols on all stages of larynx cancer and was in part based on the results of earlier national studies on treatment modalities and results in all participating centers (18). Whereas before, T3 and T4 larynx cancers in most centers preferably would be treated with TL, from then on patients with T3 larynx cancer received RT, in line with the consensus protocol then drafted. For T4 larynx cancer, TL plus adjuvant RT remained the preferred treatment modality. Van Dijk et al. (2013) recently published a study reporting a declining incidence and a stable relative survival of around 70% for all larynx cancer cases from 1989 to 2010 (19). Thus, although no decreasing survival was seen as in the US, survival rates did not increase either.

**Goals of this thesis are to study the changing treatment landscape in the Netherlands and its consequences for treatment outcomes in terms of survival, surgical sequels, and some of the voice rehabilitation aspects.**
In the 1st part of this thesis, oncological outcome after treatment for advanced larynx cancer was assessed in a retrospective cohort study in the Netherlands Cancer Institute. Subsequently, the prognostic role of tumor volume in this cohort was evaluated. In a population-based cohort study in the Netherlands, primary treatment trends and survival were determined.

OUTCOME AFTER TOTAL LARYNGECTOMY IN A CHANGING TREATMENT LANDSCAPE

Since the introduction of RT and RT combined with chemotherapy as primary treatment modalities for patients with advanced larynx cancer, TL (plus adjuvant RT in case of T4) is thus no longer considered the only curative option. However, recurrent or residual disease is not uncommon (e.g. 23-36% after treatment with RT for T3-T4 larynx cancer (4, 20)) requiring salvage TL with an accompanying higher risk of complications (21, 22). Furthermore, the function of the larynx, especially its vital role in swallowing/aspiration prevention, can become impaired to such an extent that some patients require TL because of a dysfunctional larynx after prior RT or RT combined with chemotherapy. In these cases, TL seems the only resolution for restoring some function and thus quality of life for patients.

Pharyngocutaneous fistulization (PCF) is the most frequent complication in the early postoperative period after TL. The reported incidences vary widely, ranging from 2.6% to 65.5% (23). PCF increases morbidity, prolongs hospitalization, raises costs, possibly necessitates additional surgery, and delays oral feeding (23-25). Various predictive factors for PCF have been identified—most prominently, preoperative RT (26, 27). In an era with an increase in the use of organ-preserving treatments, the addition of chemotherapy to RT has further increased the incidence of PCF (21). Other predictive factors for PCF are the extent of the pharyngeal resection, comorbidities such as hypothyroidism and diabetes, poor nutritional status, and an index tumor that originated in the hypopharynx (25, 26, 28-31).

Besides these factors, the postoperative day of initiating oral feeding is a topic of discussion, and there is no consensus concerning the timing of oral intake. Most head and neck surgeons, however, tend to delay oral intake until 10-12 days postoperatively in order to prevent or limit the chance of PCF (32, 33). However, evidence that late oral intake (LOI) reduces the incidence of PCF is quite weak, whereas there are several arguments supporting EOI as a preferable and beneficial approach. First, EOI could have a positive psychological effect by increasing the patient’s feeling of earlier return to ‘normalcy’ (34). Also, the presence of a nasogastric feeding tube moving across the pharyngeal suture line, which can be painful or irritating and might promote PCF more than LOI does. Furthermore, early return to oral feeding saves costs and may facilitate earlier hospital discharge. Finally, quite some studies
suggest that EOI is a safe approach in clinical practice (32, 33, 35, 36). In this respect, it could be interesting to consider developments in other areas of alimentary tract surgery, where a worldwide trend can be seen towards EOI in patients undergoing gastro-intestinal surgery (37-39).

In the 2nd part of this thesis, functional outcomes after TL for a dysfunctional larynx are evaluated. Moreover, incidence of PCF, predictive factors and the influence of timing of oral intake after a TL on the development of PCF are described.

VOICE REHABILITATION AFTER TOTAL LARYNGECTOMY

Another important aspect in this changing landscape concerns post TL voice rehabilitation. Prosthetic voice rehabilitation is considered the present gold standard. We were interested in which clinical and surgical characteristics were related to speech and voice outcomes in these patients. Further, the question arose whether technological improvements can be helpful in maintaining the advances of prosthetic tracheoesophageal voice.

Voice quality and surgical characteristics
After TL, the vocal tract and upper digestive tract are separated and the trachea is attached to the base of the neck, forming a permanent stoma (Figure 2). Because the voice box is removed, an alternative sound source has to be found in order to restore oral communication. Options are an external sound source in the form of an electrolarynx or using the reconstructed pharynx as the new sound source (called pharyngoesophageal (PE) segment, also called neoglottis), either enabling esophageal speech with air injected into and then expelled from the esophagus, or tracheoesophageal speech using air inhaled during breathing. In the latter case, a voice prosthesis containing a one-way valve mechanism is implanted into a tracheoesophageal puncture tract to allow pulmonary air to be diverted into the esophagus. Previous research has demonstrated that tracheoesophageal speech, utilising a prosthesis acting as a valve, is superior in terms of quality and intelligibility. Op de Coul et al. (2000), for instance, reported fair to excellent voice quality in 88% of the patients (40). Because of its high success rate and ease of acquisition, tracheoesophageal prosthetic voice has become the method of choice for restoring oral communication after TL.
Figure 2. The normal anatomy (A) and the anatomy after a total laryngectomy and speech rehabilitation with a voice prosthesis (B).

Nevertheless, TL still has a major impact on speech, swallowing, and psychosocial wellbeing (41-43). For TE speech, significant correlations were found between voice quality and quality of life measures, fatigue, sentence duration, anxiety to speak, and the frequency of making telephone calls. Female patients exhibit a greater voice handicap and significantly lower quality of life scores than males (43-45).

Voice quality and speaking effort differ widely within the TE population (44, 46, 47). The tonicity of the PE segment, and therewith voice quality, is based on the adaptation and vibration dynamics of the pharyngeal mucosa (48). Dependent on the individual anatomy, the surgical procedures performed and possibly radiotherapy, variation occurs in muscular control, position and length of the vibrating segment, and mass and stiffness of the PE segment. Each of these characteristics can affect voice (and swallowing) function.

In comparison to the quasi-symmetric vocal folds, the vibrating neoglottis consists of amorphic vibrating elements in the wall of the PE segment. The whole vibrating segment is in general larger (more mass) and neurologically less controllable than the vocal folds are. Furthermore, in view of the fact that air pressure control is needed to initiate and extend vibration, it seems a ‘drawback’ that the PE segment below and at the neoglottic region is expandable, while the (sub)glottic larynx and trachea are stabilized through their cartilage framework. After TL, the laryngeal differences between the sexes are lost and the limited neurological control, the myo-elastic properties, mass, size, and diameter of the neoglottis and its surrounding tissues bring about a lower frequency and more irregular voice, decreased dynamic range, and less aerodynamic voice and f0 control (49-52).
Although post-TL voice quality and control are known to differ substantially between patients, studies discussing the morpho-physiology and surgical characteristics and their (interacting) effects on post-TL functioning are still sparse. In the literature various variables were found to affect functional outcomes. Among these, besides the extent of the resection, are the surgical method of pharynx closure and reconstruction (muscle closing techniques, donor site tissue properties), the conservation of the posterior pharyngeal wall, the degree and level of neoglottic closure during phonation (presence and place of the neoglottic bar and distance and intensity of contact between posterior and anterior wall), the pressure built up below the neoglottic bar during phonation (intraluminal pressure), the diameter of the pharynx (pharyngeal and esophageal volume and extension), previous or post-operative (chemo-)radiotherapy, and (the extent of) neck dissections (50, 52-64). Although the extent of the surgical resection is primarily dictated by tumor extent, surgical techniques, such as neurectomy and upper esophageal myotomy, and the technique of pharynx (muscle) closure and type of reconstruction thus seem important phonosurgical aspects of TL.

Biofilm formation on voice prostheses

As already mentioned, prosthetic tracheoesophageal voice rehabilitation has become the gold standard in the Netherlands. The lifespan of voice prostheses varies from a few weeks to several years. In most cases, voice prostheses have to be replaced because of transprosthetic leakage (40). The main reason for this leakage is microbial biofilm formation on the valve causing failure of the valve mechanism, and sometimes also blockage and/or an increased airflow resistance (65). The biofilm consists of a mixture of bacteria and fungi and starts to develop from the moment the voice prosthesis is implanted into the tracheoesophageal puncture. In particular, Candida species grow into and subsequently build up on the silicone rubber (66).

To solve this problem in a material-technical way, a special voice prosthesis was developed: the Provox ActiValve (Atos Medical AB, Horby, Sweden) (67). The valve and valve seat of this voice prosthesis are solely made out of fluoroplastic, which is deemed insusceptible to ingrowth of Candida species. The lack of a destructive effect of Candida species on the fluoroplastic material has so far not been visualized in appropriate studies. Furthermore, the composition and diversity of the biofilm on fluoroplastic valves have not been described before. Buijssen et al already showed that the biofilm on silicone rubber voice prostheses is composed of lactobacilli as the predominant bacterial genus and Candida as the main fungal component (66). The composition and diversity of the biofilm on the fluoroplastic valve of the Provox ActiValve, however, have not yet been studied, and increasing insight in the behavior of Candida species and the composition of the biofilm on fluoroplastic material could be helpful to further improve durability of voice prostheses in a material-technical way.
In the 3rd part of this thesis, voice and speech outcome of TL speakers will be related to surgical and medical details. Moreover, we aim to determine the composition and diversity of the biofilm of both the silicone and the fluoroplastic material of the Provox ActiValve and to confirm the hypothesis that the fluoroplastic material is not susceptible to destruction by Candida-species.
OUTLINE OF THIS THESIS

**Part I** of this thesis describes treatment and survival trends in patients with advanced larynx cancer. In **chapter 2** the 10-year treatment results for T3-T4 larynx cancer in the Netherlands Cancer Institute are presented. In **chapter 3** the prognostic value of CT- and MRI-based tumor volume in the same cohort as in Chapter 2 is reported. **Chapter 4** will address trends in treatment and survival of advanced larynx cancer in a 20-year population-based study in the Netherlands.

In **part II** outcomes after total laryngectomy in a changing treatment landscape are described. In **chapter 5** the results of a retrospective analysis of all relevant clinical and functional characteristics of 25 patients who underwent TL for a dysfunctional larynx are reported. In **chapter 6** the incidence of PCF and predictive factors for the development of PCF after total laryngectomy are assessed. In **chapter 7** the timing of oral intake after total laryngectomy and its influence on PCF is presented.

In **part III**, postlaryngectomy rehabilitation facets are presented. **Chapter 8** provides an introduction to voice and speech rehabilitation following total laryngectomy. In **chapter 9** voice and speech outcomes in laryngectomized speakers will be related to surgical and medical details. In **chapter 10** we will address the composition and diversity of the biofilm of both the silicone and the fluoroplastic material of the Provox ActiValve and test the hypothesis that the fluoroplastic material is not susceptible to destruction by Candida species.

Finally, in **chapter 11**, the results obtained in this thesis are discussed and suggestions for future research projects are given.
REFERENCES

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