ADVANCED LARYNX CANCER

TRENDS AND TREATMENT OUTCOMES

A.J. Timmermans

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Faculteit der Tandheelkunde

Lieve opa van Bezooijen,

waar u het niet kon afmaken, ben ik verder gegaan.

CONTENTS

CHAPTER 1

General Introduction

In part based on a publication in Dutch.

A.J. Timmermans
M.W.M. van den Brekel
L. van der Molen
A. Navran
T.F. Nijssen
F.J.M. Hilgers

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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).

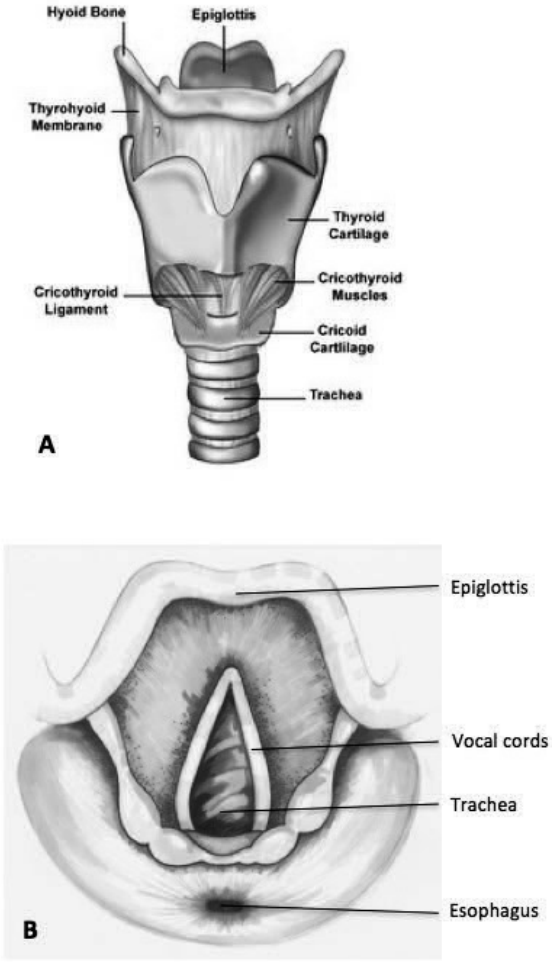

Figure 1. Anatomy of the larynx, (A) anterior view of the larynx and (B) top view of the larynx.

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.

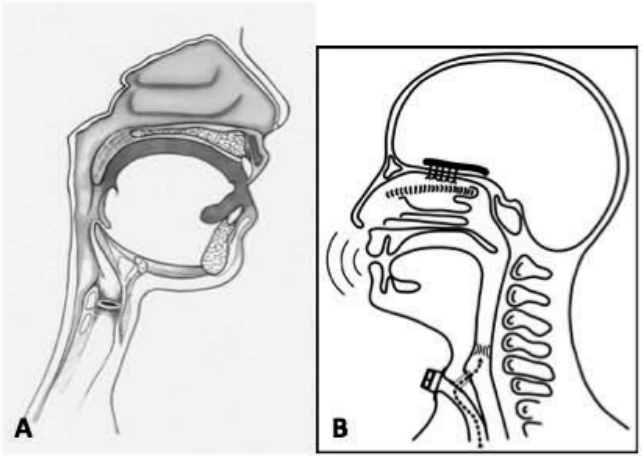

Figure 2. The normal anatomy (A) and the anatomy after a total laryngectomy and speech rehabilitation with a voice prosthesis (B).

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.

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PART I

TREATMENT AND SURVIVAL TRENDS

CHAPTER 2

T3-T4 larynx cancer in the Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol

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ABSTRACT

Background: Both organ-preserving (concurrent chemo)radiotherapy ((CC)RT) and organ sacrificing surgery (total laryngectomy; TL) are used for treatment of advanced larynx cancer. The purpose of this study was to present the assessment of our treatment protocol for T3 ((CC)RT) and T4 disease (TL+postoperative RT).

Methods: We conducted a retrospective cohort study in 182 consecutive patients (1999-2008). The primary outcome was overall survival (OS) in relation to stage and treatment.

Results: One hundred two patients received RT (82.4% T3), 20 patients CCRT (60.0% T3), and 60 patients TL+RT (91.7% T4). Five-year OS: T3 52%, T4 48%, for RT 50%, for CCRT 43% and for TL+RT 52%. Five-year laryngectomy-free interval was 72% after RT, 83% after CCRT.

Conclusions: There were no differences in survival according to T classification or treatment modality. Because the majority of T3 larynx cancers were treated with (CC)RT and the majority of T4 with TL+RT, this gives food for thought on whether the present protocol for T3 larynx cancer is optimal.

INTRODUCTION

Over the last two decades, several studies have shown an overall increase of survival in head and neck cancer. Unfortunately, however, this does not seem to apply to all subsites and especially survival of larynx cancer seems to have decreased in the United States and to have remained stable in other countries, e.g. the Netherlands and Canada (1-4).

Historically, the advanced stages of larynx cancer have been treated with total laryngectomy (TL) with or without postoperative radiotherapy (RT). However, in an attempt to preserve the larynx, organ preservation (chemo)radiotherapy ((CC)RT) protocols increasingly are being applied. This is mainly based on the results of two "landmark" studies. The first was the Department of Veterans Affairs (VA) Larynx Cancer Study Group (1991) showing 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. 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 (5-7). 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 (CCRT) only. At 2-years posttreatment, larynx preservation and loco-regional control rates in this study were significantly higher in the CCRT arm than in the other two arms. Overall survival (OS) in the three arms, however, did not differ significantly (8). 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 CCRT arm. However, also at 10-years the addition of chemotherapy to the radiation treatment did not provide any OS benefit (9).

Based on the results of the VA study, patients with large-volume T4 lesions with cartilage invasion or extending more than 1 cm into the tongue base were excluded from the RTOG 91-11 study. This means that only selected cases of advanced larynx cancer were studied and that the outcomes of this study cannot be generalized for all advanced larynx cancers, as often has been suggested (8). Hoffmann et al., as already mentioned, suggested that the decreased survival in the United States was in parallel with the declining use of surgery in favor of organ-preserving treatment modalities. Since then, there is a growing concern about the decreasing survival in advanced larynx cancer because of this shift in the therapeutic approach.

In 1999 the Dutch Head and Neck Society (former Dutch Cooperative Head and Neck Oncology Group) published a consensus document on larynx cancer diagnostics and treatment (10). 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 the treatment

modalities and results in all participating centers (11). Since then, the therapeutic approach in the Netherlands Cancer Institute followed the national consensus protocols and remained unchanged over the last 10 years. For advanced (T3 and T4) larynx cancer this protocol consisted of accelerated RT for T3 disease, supplemented with concurrent chemotherapy in case of extensive neck disease, and of TL with planned postoperative RT in case of T4 disease. This protocol remained unchanged also after the publication of the RTOG 91-11 results in 2003.

In view of the ongoing discussion about the status of the (CC)RT-based larynx preservation approach in both T3 and T4 cancer, and its possible impact on survival, a retrospective analysis was conducted to assess whether the commonly found difference in survival between T3 and T4 (12), obviously also depending on neck node status, still exists despite the fact that T3 disease was not treated surgically any longer in our Institute.

MATERIALS AND METHODS

A total of 635 patients with larynx cancer were treated at the Netherlands Cancer Institute between January 1999 and December 2008. Of these, 197 patients with T3 and T4 tumors were selected for this study. In total, 182 patients were eligible for further analysis, and the reasons for the exclusion of 15 patients are given in the flow chart in Figure 1.

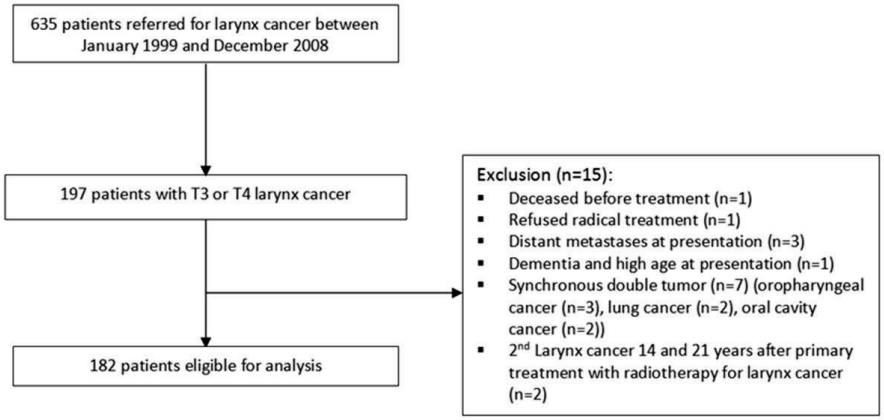


Figure 1. Flowchart of patient inclusion and exclusion.

The following data were collected for each patient, if available: age and sex, American Society of Anesthesiologists (ASA) classification, staging according to the 7th edition of the Union for International Cancer Control (UICC) TNM staging manual (2009), primary tumor site, tracheotomy and/or debulking before primary treatment (yes/no), treatment characteristics, recurrences, outcome and last date of follow-up.

Tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009). As patients treated before 2002 were staged following the 5th edition, restaging was necessary since the 5th edition differs from the 6th and 7th edition, especially for the delineation between T3 and T4. For restaging, clinical records, computed tomography-scans and pathology examinations were reviewed by 2 of the authors in consensus.

The primary endpoint was OS. Although we do provide information on recurrences, disease free survival was not calculated, because information about the cause of death in our database was deemed not to be reliable enough, since most patients died at home. OS was defined as the period of time the patients were diagnosed with larynx cancer until the last follow-up or death. The last follow-up date was defined by the last visit to the outpatient clinic of our institute. The last follow-up date and survival status were updated on August 1, 2012.

Statistical analysis

Descriptive statistics were performed. To find differences between the groups we used the Pearson Chi-Square, one-way ANOVA and linear-by-linear. Univariate analysis was performed by Cox regression analysis to reveal factors associated with a higher likelihood of mortality in patients with T3 or T4 larynx cancer. Furthermore, for multivariable analysis, Cox regression analysis was performed using backward elimination with a significance level of 10% (2-sided) to eliminate parameters. Hazard ratios (HRs) and 95% confidence levels (CIs) were estimated. For OS, loco-regional control and laryngectomy free interval Kaplan Meier curves were plotted. To determine loco-regional control, local, regional and loco-regional recurrences were included. In case of a second primary or distant metastasis only, the date of diagnosis was used as moment of censoring. Other cases were censored at date of last follow-up or date the patient deceased. For laryngectomy free interval, patients at risk (treated with RT or CCRT) were included. Date of TL was the date of the event. Other cases were censored at date of last follow-up or at date the patient deceased. To compare groups Log-Rank tests were performed. Variables with a p-value < 0.05 were considered statistically significant. Analyses were performed with IBM® SPSS® Statistics 20.0.

RESULTS

Patients

Patient and treatment data are shown in Table 1. Of the 182 primary T3 and T4 larynx cancer cases, 137 were males and 45 were females. There were 104 supraglottic, 31 glottic, 44 transglottic and 3 subglottic tumor and 101 were T3 lesions and 81 T4 lesions. As a result of restaging to the 2009 UICC classification, 10 of the 182 patients were down-staged from T4 to T3 and 5 patients were up-staged.

Table 1. Patient and tumor characteristics listed according to primary treatment (Total laryngectomy, radiotherapy and chemoradiotherapy); TL = Total laryngectomy; RT = Radiotherapy; CRT = Chemoradiotherapy; ASA = American Society of Anesthesiologists; BMI = Body Mass Index (calculated as weight in kilograms divided by height in meters squared)

	TL	RT	CCRT	*p*-value
n	60	102	20	
Sex (n, %)				0.022 *
Male	51 (85.0)	75 (73.5)	11 (55.0)	
Female	9 (15.0)	27 (26.5)	9 (45.0)	
Age at diagnosis (range)	Mean 64.1 years (44-85)	Mean 62.1 years (36-87)	Mean 57.2 years (43-72)	0.053 †
ASA (n, %)				0.297 ‡
1	11 (18.3)	22 (21.6)	1 (5.0)	
2	26 (43.3)	47 (46.1)	16 (80.0)	
3 or 4	23 (38.3)	25 (24.5)	3 (15.0)	
Missing	0	8 (7.8)	0	
BMI (n, %)				0.250 ‡
< 18	7 (11.7)	3 (2.9)	4 (20.0)	
18-25	39 (65.0)	55 (53.9)	10 (50.0)	
25-30	10 (16.7)	30 (29.4)	4 (20.0)	
30-40	2 (3.3)	6 (5.9)	1 (5.0)	
> 40	1 (1.7)	1 (1.0)	0	
Missing	1 (1.7)	7 (6.9)	1 (5.0)	
Tracheotomy before primary treatment (n, %)				0.014 *
No	53 (88.3)	97 (95.1)	15 (75.0)	
Yes	7 (11.7)	5 (4.9)	5 (25.0)	
Debulking before primary treatment (n, %)				0.287 *
No	49 (81.7)	82 (80.4)	19 (95.0)	
Yes	11 (18.3)	20 (19.6)	1 (5.0)	
Origin tumor (n, %)				0.001 *
Supraglottic	21 (35.0)	64 (62.7)	19 (95.0)	
Glottic	11 (18.3)	19 (18.6)	1 (5.0)	
Subglottic	2 (3.3)	1 (1.0)	0	
Transglottic	26 (43.3)	18 (17.6)	0	
T classification of origin tumor (following criteria of 7th edition) (n, %)				0.001 ‡
T3	5 (8.3)	84 (82.4)	12 (60.0)	
T4a	54 (90.0)	18 (17.6)	6 (30.0)	
T4b	1 (1.7)	0	2 (10.0)	
N classification of origin tumor (n, %)				0.006 ‡
N0	33 (55.0)	62 (60.8)	3 (15.0)	
N1	5 (8.3)	21 (20.6)	0	
N2a	2 (3.3)	0	0	
N2b	6 (10.0)	9 (8.8)	1 (5.0)	
N2c	13 (21.7)	9 (8.8)	12 (60.0)	
N3	1 (1.7)	1 (1.0)	4 (20.0)	
Stage (n, %)				0.001 ‡
Stage III	2 (3.3)	68 (66.7)	2 (10.0)	
Stage IV	58 (96.7)	34 (33.3)	18 (90.0)	

* Pearson Chi-Square; † one-way ANOVA; ‡ Linear-by-Linear

Primary TL followed by planned postoperative RT was employed in 60 patients. Of these 60, 9 patients did not undergo the planned postoperative RT, because of the following reasons: refusal of the additional treatment (n=6), a very favorable histology (no extra-larynx spread, i.e. T3 instead of T4; n=1), or interfering co-morbidity (n=2). Primary single modality RT was given to 102 and CCRT to 20 patients.

According to T classification, 82.4% of the patients treated with RT had a T3, 60.0% of patients treated with CCRT had a T3, and 91.7% of the patients treated with TL had a T4 lesion. According to treatment (RT, CCRT, or TL+/-RT), there were significant group differences with respect to sex (more females in the CCRT group (45.0%) compared to the TL (15.0%), and RT group (26.2%); p = 0.020), and tumor origin (more supraglottic lesions in the RT and CCRT groups; 62.7% and 95.0%, respectively compared to 35.0% in the TL group; p = 0.001).

Moreover, obviously as a result of the prevailing protocol, there were significant group differences for T classification (T3 larynx cancer was mainly treated with RT or CCRT, whereas T4 larynx cancer was treated with TL), N classification (patients in the CCRT group had more often positive lymph nodes (85.0% compared to 39.2% in the RT group and 45.0% in the TL group; p = 0.006)), and tracheotomy prior to primary treatment (CCRT more often than TL+RT and RT; p = 0.014). The treatment groups were comparable with respect to age, ASA classification, BMI and debulking prior to primary treatment.

Radiotherapy

In 102 patients, primary treatment consisted of single modality RT. Two protocols were in place during this period:

(1) In eighty-five out of 102 patients (83.3%) RT consisted of 46 Gy in 23 fractions to the primary tumor and the elective bilateral neck. A boost of 24 Gy was given to the tumor-bearing areas, to a total dose of 70 Gy in 35 fractions. In 34 patients also the pathologic lymph nodes in the neck received a total dose of 70 Gy. The vast majority (78 patients) received accelerated RT according to the DAHANCA protocol with 6 fractions per week with a reduced overall treatment time of 6 weeks (13), and four patients received conventional RT with 5 fractions per week (overall treatment time of 7 weeks). Data on the remaining 3 patients were missing. In 61 patients of these 85 patients the RT was delivered with 3D conformal RT (3D-RT) or intensity-modulated RT (IMRT), and in 22 with two lateral fields and these data were missing in 2 patients. One patient did not finish treatment and died 21 days after the start of treatment.

(2) Fourteen patients (13.6%) were treated in another accelerated/hyperfractionated RT national study protocol (69.5 Gy, in 40 fractions in 5 weeks). The primary tumor received 69.5 Gy (10x2.0Gy + 15x1.8Gy + 15x1.5Gy), the elective bilateral neck 47 Gy (10x2.0Gy + 15x1.8Gy). In 2 (14%) patients a total dose was delivered on pathologic lymph nodes in the neck as well.

Three patients (2.9%) could not be assigned to one of these two protocols. Two patients received 74 and 80 Gy in respectively 7 and 10 weeks to compensate for too many 'lost' RT days during the treatment time. One patient received a total dose of 70 Gy on the tumor-bearing area, but 54.25 Gy on the elective bilateral neck following simultaneous integrated boost approach.

Concomitant chemoradiation

Twenty patients received CCRT, 17 on the indication of N2 or N3 neck disease, one because of inoperable disease. The remaining two patients had T3N0 disease, and thus were protocol violations in hindsight. The RT protocols for these 20 patients were similar to those described above. In 14 (70.0%) patients the pathologic lymph nodes in the neck also received a total dose of 70 Gy. Nine patients underwent conventional RT, 11 patients the DAHANCA schedule. In 10 patients the RT was delivered in two lateral fields, in 10 patients with 3D-RT or IMRT. All patients received cisplatinum in high- or low-doses. High-dose three weekly cisplatinum consists of 100 mg/m^2, 3 courses (n=9). Low-dose daily cisplatinum consists of 6 mg/m^2, 25 courses (n=11).

The deviation from application of the Institute's protocol (T3 primary RT, inoperability or N2c/N3 CCRT; T4 primary TL+RT) over the study period was as follows (see Table 1). There were 5 T3 patients treated with TL and 18 T4 patients treated with RT. The 5 patients with a T3 lesion receiving TL initially all were classified as T4 according to the 5th or 6th UICC edition, which explains the choice for surgery at that time. In the group of 18 patients with T4 larynx cancer, in 4 patients the tumor was upstaged for this study (original T3 classification), which explains the choice for RT. Of the remaining 14 T4 patients treated with RT, the indication was refusal of TL in 3 patients. In one T4 patient there was inoperable disease (where CCRT would have been indicated), and in the remaining 10 patients the reason to use RT instead of TL could not be deducted from the charts in retrospect. This means that together with the 2 T3N0 patients receiving CCRT, 16 patients (9%) should be considered protocol violations, whereas 166 (91%) were treated according to protocol.

Survival

Figure 2 shows the OS of T3 and T4 larynx cancer separately, and for the total group categorized by treatment. Five-year OS for T3 larynx cancer was 52%, for T4 larynx cancer 48% (Log Rank p = 0.528). Five-year OS after TL was 52%, after RT 50% and after CCRT 43% (Log Rank: p = 0.828).

In figure 3A and figure 3B the OS is analyzed per primary treatment for T3 larynx cancer respectively T4 larynx cancer. Figure 4 shows the OS analyzed per stage (stage III and stage IV). For stage III the OS was 58% and for stage IV 44% (p=0.126), the latter having a significant larger proportion of patients with positive nodal status compared to stage III

(figure 4). Figure 5 shows the influence of nodal status on OS when analyzed separately for T3 and T4 larynx cancer. Patients with T3N0 larynx cancer had a 5-year OS of 65% compared to 35% for patients with T3N+ larynx cancer (p = 0.005). Patients with T4N0 larynx cancer and T4N+ larynx cancer had 5-year OS of 58% respectively 35% (p = 0.026). Five-year OS between T3N0 and T4N0 larynx cancer was not significant (Log Rank p = 0.549).

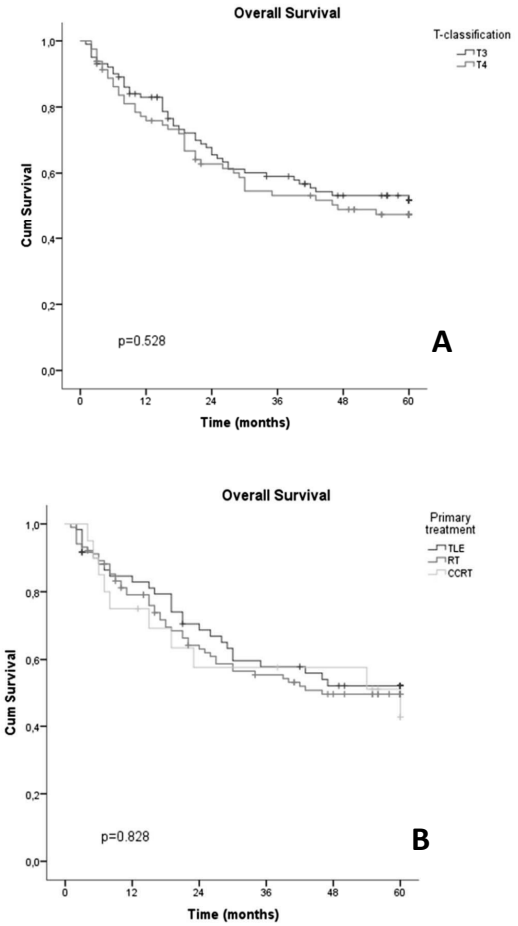


Figure 2. (A) Overall survival of T3 and T4 larynx cancer and (B) overall survival categorized by the 3 treatment groups.

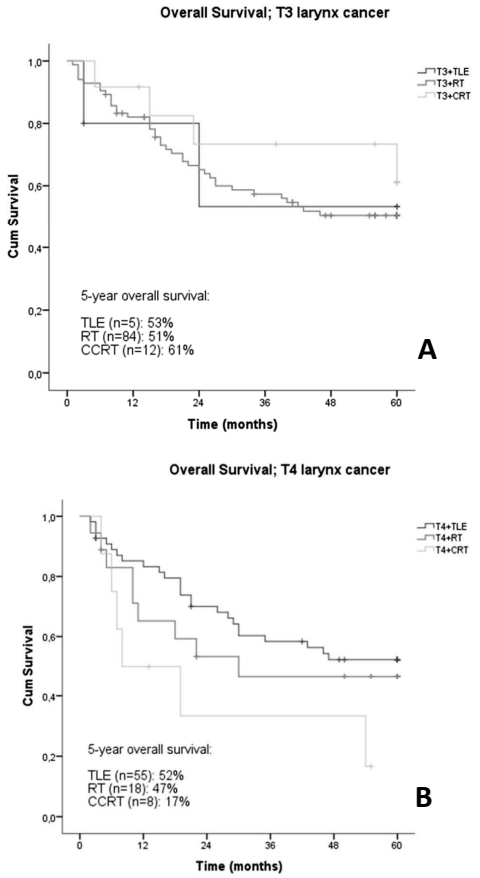
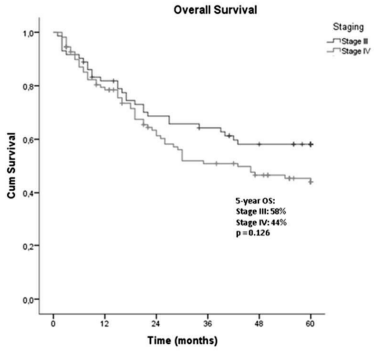


Figure 3. Overall survival analyzed per treatment-group for (A) T3 larynx cancer and (B) T4 larynx cancer.



	N0	N+	Total
Stage III	54	18	72
Stage IV	44	66	110
	98	84	182
Chi-square: p=0.001			

Figure 4. Overall survival analyzed for stage III and stage IV.

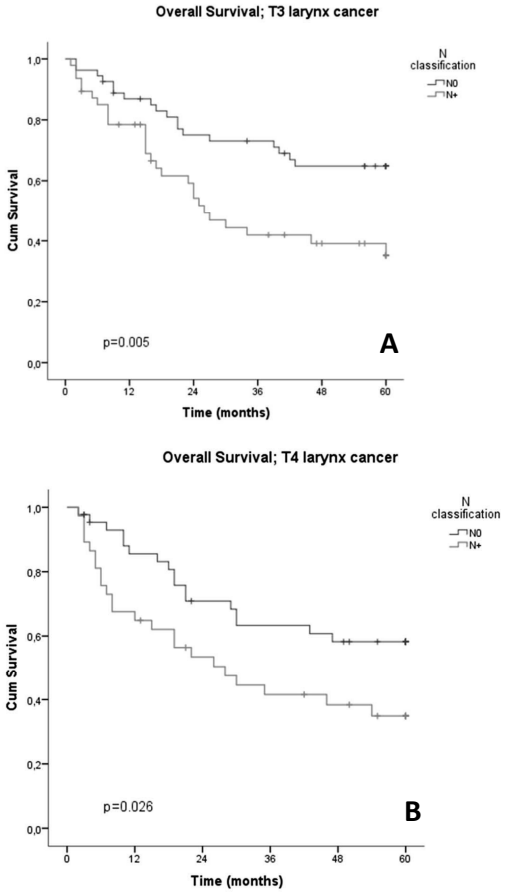


Figure 5. The influence of nodal status on overall survival analyzed for (A) T3 larynx cancer and (B) T4 larynx cancer.

Univariate analysis was performed to reveal factors associated with a higher likelihood of mortality (Table 2). Patients with a positive N classification were 2.16 (HR: 95% CI 1.40-3.33; p = 0.001) more likely to die than patients with N0. Also, patients with higher ASA scores had worse survival. In multivariable analysis N classification and ASA score remained significant (Table 3).

Table 2. Univariate analysis for factors influencing overall survival in patients with T3/T4 larynx cancer. Hazard ratios (HR) and *p*-values were calculated using Cox regression. TL = Total laryngectomy; RT = Radiotherapy; CRT = Chemoradiotherapy; ASA = American Society of Anaesthesiologists

	No. of patients	HR (95% CI)	*p*-value
Primary treatment *(n=182)*			0.831
TL	60	Ref	
RT	102	1.11 (0.69-1.78)	0.664
CRT	20	1.23 (0.60-2.55)	0.570
Sex *(n=182)*			0.066
Male	137	Ref	
Female	45	1.55 (0.97-2.47)	
ASA *(n=174)*			***0.015***
ASA 1	34	Ref	
ASA 2	89	2.26 (1.11-4.63)	***0.026***
ASA 3 or ASA 4	51	3.02 (1.43-6.38)	***0.004***
Origin tumor *(n=182)*			0.551
Supraglottic	104	Ref	
Glottic	31	0.65 (0.34-1.24)	0.193
Subglottic	3	0.00 (0.00-2.04[237])	0.966
Transglottic	44	1.09 (0.66-1.79)	0.747
T classification (following criteria of 7th edition) *(n=182)*			0.532
T3	101	Ref	
T4	81	1.15 (0.75-1.75)	
N classficiation *(n=182)*			***0.001***
N0	98	Ref	
N+	84	2.16 (1.40-3.33)	

Table 3. Multivariable analysis to reveal factors influencing overall survival in patients with T3/T4 larynx cancer. Hazard ratios (HR) and *p*-values were calculated using Cox regression; ASA = American Society of Anesthesiologists

	No. of patients	HR (95% CI)	*p*-value
ASA *(n=174)*			***0.013***
ASA 1	34	Ref	
ASA 2	89	2.23 (1.09-4.56)	***0.029***
ASA 3 or ASA 4	51	3.08 (1.45-6.50)	***0.003***
N classification *(n=174)*			***0.001***
N0	94	Ref	
N+	80	2.09 (1.35-3.24)	

Loco-regional control and laryngectomy-free interval

After TL, single modality RT, and CCRT 13.3%, 32.4% and 30.0% of the patients respectively developed one or more recurrences (Chi Square Test: p = 0.025). The first recurrence was local in 50%, 72%, and 33%, respectively. Five-year loco-regional control was 73% for the total group and 87%, 65% and 76% for patients after treatment with TL, RT respectively CCRT. Five-year laryngectomy-free interval was 72% after RT and 83% after CCRT. Of the in total 25 patients that underwent a TL after RT or CCRT, 20 had the TL for recurrent disease and 5 for a dysfunctional larynx.

DISCUSSION

In this retrospective cohort of 182 consecutive patients no significant differences in OS were observed between T3 and T4 larynx cancer, nor between stage III and stage IV disease. The dominating prognostic factors in this study still were nodal status and co-morbidity, as has been found in many other studies in head and neck cancer. The survival rates for stage III (58%) and stage IV disease (44%) in our institute are in line with the recently published survival figures from the Netherlands Cancer Registry over the period from 1999 to 2009: the 5-year relative survival rates for stage III and IVa larynx cancer are 56% respectively 41% (1999-2002), and 55% respectively 42% (2003-2009) (14). However, it is important to note that T2N1-2 disease, also part of the 'stage III-family', and T2N3 disease (stage IV) was not included in the present study.

Historically, survival of T3 larynx cancer has been better than that of T4 larynx cancer (12, 15). E.g. Robin et al (1991) found that of all patients treated with TL, T3 larynx cancer had better survival than T4 larynx cancer (supraglottis T3N0: 83% (total of 22 cases); T4N0: 45% (total of 10 cases); glottis: T3N0 50% (total of 107 cases); T4N0 39% (total of 9 cases)) (12). And Groome et al. (2002), comparing different TNM based stage groupings in larynx cancer using data from Canada and Norway, reported a hazard ratio for death of larynx cancer of 5.4 and 7.5 for T3N0, and of 10.5 and 9.0 for T4N0 larynx cancer (for Canada and Norway, respectively) (15). The authors did however not report on treatment but, including all T, N, M classifications, >80% of the patients in both countries were irradiated. It is thus noteworthy that such difference in survival was absent in our cohort.

The treatment protocol consistently used in this patient cohort is based on a consensus document on larynx cancer diagnostics and treatment of the Dutch Head and Neck Society (former Netherlands Cooperative Head and Neck Tumor Group) published in 1999 (10). That document, in part, was based on an earlier national study reporting on the treatment results of T3 larynx cancer (11, 16-17). That study showed that planned combined treatment (consisting of surgery and RT) significantly increased corrected survival. Primary surgery and primary RT had similar effects. With the improved RT protocols (i.e. reduction of the overall treatment time in the DAHANCA protocol) emerging at that time, it was expected that loco-regional control and survival would improve, and the need for TL with or without adjuvant RT, at that time the standard treatment for T3 larynx cancer in most head and neck services in the Netherlands, would decrease.

The respective roles of organ preservation ((chemo-)RT) treatment and organ sacrificing surgical treatment for advanced larynx cancer have been extensively addressed in the recent literature (2,7,18-22). Gourin et al (2009) found that patients with T4 disease had significantly better survival after TL (55%) than after CCRT (25%) or RT alone (0%). Also after

controlling for nodal status, organ-preserving treatment was still a significant predictor of worse survival (18). Furthermore, Hoffman et al (2006) studied patterns of care and survival after larynx cancer between 1985 and 2001 in the United States in 158.426 patients (2). These authors reported a decreasing trend in survival from the mid-80s to the mid-90s and, in the same period, an increase of chemoradiation as primary treatment with a decrease in surgery. For T3N0M0 larynx cancer specifically, a significant better 5-year relative survival was found for those patients treated with surgery and irradiation compared to patients treated with irradiation (with or without chemotherapy; 64.4% versus 49.4%). It should be noted however, that specific data regarding RT and chemotherapy were not available. Also, 'surgery' was not further specified in TL, endoscopic surgery or other surgery. Recently, Dziegielewski et al (2012) found better survival for patients with T3 and T4a larynx cancer treated with TL (with (CC)RT) compared to RT and CCRT and suggest reassessment of current treatment guidelines (20). Also, Chen and Halpern (2007) found TL to be superior to RT and CCRT as primary treatment in patients with stage IV larynx cancer in terms of OS (21). For stage III disease TL had better survival than RT in their series. The findings of a decreased survival for the advanced stages of larynx cancer are serious and warning. Several authors already have expressed their concerns about this issue (7, 22).

Especially in T3 larynx cancer there is discussion about what treatment modality is best for which patient. Besides (CC)RT and TL, other treatment options for T3 disease are partial open laryngeal surgery or transoral laser microsurgery (TLM). E.g. with respect to the latter approach, recently Canis et al (2013) published the results of a cohort of 226 patients with pT3 larynx cancer treated with TLM. Sixteen percent of patients also underwent selective neck dissection and postoperative RT, and postoperative RT only was given in another 2% of the patients. Five-year OS was 64.4%. The functional results were also quite favorable, 6 patients (2.7%) required a temporary tracheotomy and 2 patients (0.9%) needed a permanent tracheotomy. Percutaneous endoscopic gastrostomy tubes were temporarily necessary in 6 patients (2.7%) and permanently in 3 patients (1.3%). Unfortunately, no data on the voice quality were available. The authors concluded that the results of transoral laser microsurgery are satisfactory, but they also address that the data are only of 1 institution and that further prospective studies should be done (23). For carefully selected cases, it may be a good alternative.

In the multivariable analysis in the present study N classification and ASA score were found to be associated with mortality. Both findings are in line with the literature. Various studies reported that patients with positive neck nodes have worse prognosis (18, 24). Also, ASA scores have been reported to be predictive for morbidity and mortality as well as chance for successful organ preservation (25-27).

Next to survival, quality of life, toxicity and larynx preservation are important parameters in the decision-making process. Both organ sacrificing and preserving treatments for advanced larynx cancer significantly affect quality of life. Finizia et al (1998) studied voice and quality of life of patients treated for larynx cancer with RT with or without TL as salvage surgery. They found that irradiated patients and listeners rated their voices higher than that of laryngectomized patients using tracheoesophageal speech. In most studies, however, scores for quality of life were similar regarding most functions and symptoms (28-30). Moreover, one has to keep in mind that in the last two decades major progress has been made with respect to vocal, pulmonary, and olfactory rehabilitation, making the functional deficits of TL less debilitating than ever before (31). Toxicity after (CC)RT can be considerable, resulting in swallowing problems, difficulties with speech and a dysfunctional larynx. Fortunately, the reduction of the radiation dose to the surrounding tissues achievable with IMRT has decreased RT side effects. Especially through preservation of the salivary glands, the reduction of xerostomia leads to less severe dysphagia. Nevertheless, in some cases a TL is still deemed to be the only solution to resolve the sequels of (CC)RT, as recently published from our institute, where 11% of the TLs over the last decade was indicated for a 'dysfunctional larynx' (32). It should be noted that in that study all patients previously treated with RT or CCRT for any head and neck cancer site were included. In the present study, the 5-year laryngectomy-free interval was 72% after RT and 83% after CCRT. Of these patients 20 underwent TL for recurrent disease and 5 for a dysfunctional larynx. This however gives no complete information on how severe toxicity was in our (CC)RT study population. Unfortunately we could not retrieve reliable data on these aspects from the medical records.

An obvious shortcoming of this study is its retrospective character. Also, the relative small sample size precludes drawing far-reaching conclusions. An aspect to stress is that retrospective (and this obviously also counts for prospective) studies like the one presented here should to be based on uniform staging. Since the larynx cancers in this study originally were staged according to the 5th, 6th and 7th edition of the UICC TNM staging manual, the necessity of restaging all tumors according to the 7th edition of the UICC TNM staging manual (2009) was obvious. A disadvantage of re-staging is that comparison with literature based on earlier editions of the UICC TNM staging becomes difficult. In the 6th edition the criterion 'minor thyroid cartilage erosion' was added to the T3 classification of supraglottic and glottic larynx cancer. This means that tumors staged as a T4 in editions before the 6th edition, will be classified as a T3 now, resulting in a higher chance of treatment with (CC)RT for a tumor that would have been treated surgically years ago. The move of the 'minor cartilage erosion' cases from T4 to T3 means that the T3 category now might be more unfavorable than in the past, but on the other hand, it is likely that the T4 category has 'lost' its most favorable subgroup, so that the remaining T4s are the relatively more unfavorable cases, neutralizing the potential effects on survival this restaging has for both categories. An additional point

to make with regards to the present study is that we did include all T3 and T4 tumors, also the large-volume tumors invading the larynx and with extralaryngeal spread, which means that there was no selection bias for the larger tumors in this cohort, something that has not always been the case in prospective studies and is a concern with regards to generalizing results for all larynx cancers (8).

In conclusion, in this cohort, representing a single institution's treatment outcome based on a consistent application (91%) of treatment protocols over a 10-year period, survival according to staging (T3 versus T4 larynx cancer), and according to treatment modality (TL + RT versus (CC)RT) showed no differences for either of the two. Considering that the majority of T3 larynx cancers were treated with organ-preserving modalities and the majority of T4 larynx cancers with TL+RT this gives food for thought on whether the present treatment protocol for T3 larynx cancer is optimal.

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CHAPTER 3

Tumor volume as prognostic factor for local control and overall survival in advanced larynx cancer?

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ABSTRACT

Objective: Tumor volume has been postulated to be an important prognostic factor for oncological outcome after radiotherapy or chemoradiotherapy. This postulate was retrospectively investigated in a consecutively treated cohort of T3-T4 larynx cancer patients.

Study design: Retrospective cohort study.

Methods: For 166 with T3-4 larynx cancer (1999-2008), pre-treatment CT and MRI scans were available for tumor volume delineation. Patients were treated with radiotherapy, chemoradiotherapy or total laryngectomy with postoperative radiotherapy. Both a dedicated head and neck radiologist and the first author determined all tumor volumes. Statistical analysis: Kaplan-meier plots, Cox proportional hazard models.

Results: Patients with T3 larynx cancer had significantly smaller tumor volumes than patients with T4 larynx cancer (median: 8.1 cc respectively 15.8 cc; $p<0.0001$). In the group treated with total laryngectomy and postoperative radiotherapy no association was found between tumor volume and local, loco-regional control or overall survival. In the group treated with radiotherapy a non-significant trend was observed between local control and tumor volume. In the chemoradiotherapy group however, a significant impact of tumor volume was found on local control (HR 1.07 (95% CI 1.01-1.13; $p=0.028$)).

Conclusion: Tumor volume was not significantly associated with local control, loco-regional control or overall survival in the surgically treated group. In the group treated with radiotherapy there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with CCRT a significant impact of tumor volume on local control was found.

INTRODUCTION

Advanced larynx cancer can be treated with radiotherapy (RT) alone, RT with concurrent chemotherapy (CCRT) or with total laryngectomy (TL) with or without postoperative RT (PORT) (1-3). Decisions about treatment are based upon 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 (4), functionality of the larynx, the general condition of the patient and patient as well as physicians preferences. In the Netherlands Cancer Institute, patients with T3 larynx cancer generally receive organ-preserving treatment (RT, or CCRT in case of extensive nodal disease), and to patients with T4 larynx cancer TL+PORT is advised, a protocol based on the consensus protocol of the Dutch Head and Neck Society (5). To determine T and N classification, physicians rely on clinical examination, laryngoscopy, CT or MRI, ultrasound-guided fine-needle aspiration (cytology), and biopsy. The distinction between T3 and T4 is mainly based on thyroid cartilage destruction and extralaryngeal spread (4). Thus, T classification plays a major role in the treatment decision. 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 (6-9). Other authors, however, did not identify tumor volume as a useful prognostic factor in advanced larynx cancer (10, 11).

Recently, we published the results on 182 patients with T3 or T4 larynx cancer treated in the Netherlands Cancer Institute with TL+PORT, RT or CCRT (12). No difference in overall survival (OS) was found between T3 and T4 larynx cancers, or between the three treatment modalities applied. This was an unexpected finding since generally T3 tumors are considered to have a better prognosis than T4 disease, when corrected for nodal status. The fact that the majority of T3 larynx cancers were treated with RT or CCRT and the majority of T4 with TL (+/-PORT) was a possible explanation for this finding (12). In that study all cases were uniformly restaged (based on the available radiology reports) according to the latest (7th) UICC edition, because of the classification has changed over time. However, tumor volume was not available for inclusion in that analysis. In view of the lack of discriminatory role for T classification for local, loco-regional control and/or survival, the question arose whether tumor volume could play such a role in this patient cohort. Therefore, the aim of the present study was to measure tumor volume and to assess its prognostic value for local, loco-regional control and OS.

MATERIALS AND METHODS

Patients

From a total of 635 larynx cancer patients treated at the Netherlands Cancer Institute between January 1999 and December 2008, 182 patients had biopsy-proven T3 or T4 larynx cancer and were treated with curative intent with RT, CCRT or TL+PORT, as extensively described earlier (12). Patient and treatment specific data collected included age, sex, American Society of Anesthesiologists score for comorbidity (ASA score), TNM classification (4), subsite, treatment, local and regional recurrences, distant metastases and survival status. In order to achieve uniform staging in this cohort, because T3-T4 classification had undergone (mainly imaging-based) changes during the study period, tumors were re-staged according to the 7th edition of the UICC TNM staging manual (2009) based on the available radiology reports. We will further refer to this re-staged T-classification as the original or "T_{org} classification" (12).

Tumor volume assessment

Sixteen patients had to be excluded from tumor volume assessment because imaging was of insufficient quality for adequate volume measurements (n=9) or imaging could not be traced (mostly performed in other hospitals; n=7) leaving 166 patients for this assessment. In 151 patients a diagnostic CT scan was used; in 10 patients a diagnostic MRI scan. A treatment planning CT scan was used in 5 patients, because no diagnostic scan was available. Both hard-copy scans and digital scans were used. Hard-copy scans were first digitized and transferred to a delineation system where 3D volumes were (re)created. Digital scans were directly transferred. Tumors were manually delineated on the axial slices of the 3D volumes using delineation tools and software developed at our institute. Both a dedicated head and neck radiologist (C.A.H.L.) and the first author (A.J.T.) evaluated the scans and delineated all tumor volumes separately and in consensus. Tumor volumes were measured in cubic centimeter (cc). All images were classified following the UICC TNM staging manual (2009). We will further refer to this revision radiological T classification as "T_{radrev} classification". However, since the T_{org} classification was based on clinical examination, laryngoscopy and the original imaging report and the T_{radrev} classification was based on revision of the imaging only, and also treatment decisions obviously were based on T_{org}, only the T_{org} classification was used in the multivariable analysis. Using the original T classification also makes comparison with earlier published results possible (12). Pathological lymph nodes were not included in these volume measurements and revisions. Instead, the original medical records, imaging and fine-needle aspiration were used to determine the presence (N+) or absence (N0) of pathologic lymph nodes.

Outcome measures

Outcome measures were local control, loco-regional control and OS. Local or loco-regional control was defined as time from date of diagnosis until (histopathologic) confirmation of local or loco-regional failure. To assess local control, the first local recurrence was recorded. To assess loco-regional control, the first recurrence (local, regional or loco-regional) was recorded. In case of residual disease, date of primary treatment was used as date of event. In case of a second primary in the head and neck area, TL for a dysfunctional larynx (or regional) or distant metastasis, the date of diagnosis was used as moment of censoring. Other cases were censored at date of last follow-up or date the patient deceased. OS was defined as time from date of diagnosis until last follow-up or death. The last follow-up date was defined by the last visit to the outpatient clinic in our institute. The last follow-up date and survival status were updated on the 1st of April 2014.

Statistical analysis

Descriptive statistics were performed. To find differences between groups the Pearson Chi-Square, Fisher's exact test, independent *t*-test, one-way ANOVA, Mann-Whitney U and Kruskal Wallis were used. The latter two tests were used in case of non-parametric distribution of data. Univariable analysis was performed by Cox regression analysis to reveal factors associated with a higher likelihood of local failure, loco-regional failure, and mortality. Furthermore, for multivariable analysis, Cox regression analysis was used and hazard ratios and 95% confidence levels were estimated. We also tested for a possible interaction between primary treatment and tumor volume for local control. For local and loco-regional control and overall survival Kaplan Meier curves were plotted. Maximally selected log-rank statistics were used to look for possible cut-points of volume as prognostic factor. Variables with a p-value < 0.05 were considered statistically significant. Analyses were performed with *IBM® SPSS® Statistics* 21.0 and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and treatment

In total, 166 patients were included in this study. There were no significant differences between the included cohort and the 16 patients that had to be excluded from this tumor volume assessment study because of absence or insufficient quality of the imaging (Table 1). Patient and tumor characteristics of the remaining 166 patients are shown in Table 2a and 2b.

Table 1. Patient and tumor characteristics of the included and excluded patients

	Total	Included	Excluded	*p*-value
Total	182	166	16	
Gender (n (%))				0.764¥
Male	137	124 (74.7)	13 (81.2)	
Female	45	42 (25.3)	3 (18.8)	
Age at date of diagnosis (mean (SD))	182	61.9 (11.3)	65.1 (9.5)	0.276^
T_{org} classification (n (%))				0.119¥
$T3_{org}$	101	89 (53.6)	12 (75)	
$T4_{org}$	81	77 (46.4)	4 (25)	
N classification (n (%))				1.00¥
N0	99	90 (54.2)	9 (56.3)	
N+	83	76 (45.8)	7 (43.8)	
Subsite (n (%))				0.297#
Supraglottis	104	93 (56.0)	11 (68.8)	
Glottis	31	27 (16.3)	4 (25.0)	
Subglottis	3	3 (1.8)	0	
Transglottis	44	43 (25.9)	1 (6.3)	

Abbreviations: SD = standard deviation; T_{org} = tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009) based on the diagnostic work-up including clinical examination, laryngoscopy, imaging reports, fine-needle aspiration and biopsy.
Pearson Chi-Square; ¥ Fisher's exact test; ^ independent *t*-test

Table 2a. Patient and tumor characteristics categorized per treatment group

	Total	TL+/-PORT	RT	CCRT	*p*-value*
Total***	166	56	92	18	
Gender (n (%))					
Male	124	48 (38.7)	66 (53.2)	10 (8.1)	0.023#
Female	42	8 (19.0)	26 (61.9)	8 (19.0)	
Age at date of diagnosis (mean (SD))	61.9 (11.3)	64.1 (11.9)	61.4 (11.5)	58.1 (6.4)	0.111$
T_{org} classification (n (%))					
$T3_{org}$	89	5 (5.6)	74 (83.1)	10 (11.2)	0.0001#
$T4_{org}$	77	51 (66.2)	18 (23.4)	8 (10.4)	
T_{radrev} classification (n (%))					
$T3_{radrev}$	90	8 (8.9)	68 (75.6)	14 (15.6)	0.0001#
$T4_{radrev}$****	76	48 (63.2)	24 (31.6)	4 (5.3)	
N classification (n (%))					
N0	91	31 (34.1)	57 (62.6)	3 (3.3)	0.0001#**
N+	75	25 (33.3)	35 (46.7)	15 (20.0)	
Subsite (n (%))					
Supraglottis	93	18 (19.4)	58 (62.4)	17 (18.3)	0.0001#
Glottis	27	10 (37.0)	16 (59.3)	1 (3.7)	
Subglottis	3	2 (66.7)	1 (33.3)	0	
Transglottis	43	26 (60.5)	17 (39.5)	0	
Tumor volume in cc (median (IQR))	11.6 (5.7-21.3)	19.7 (11.8-30.8)	7.4 (4.3-12.4)	13.5 (5.7-25.2)	0.0001%

Abbreviations: TL = total laryngectomy; PORT = postoperative radiotherapy; RT = radiotherapy; CCRT = concomitant chemoradiation; SD = standard deviation; T_{org} = tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009) based on the diagnostic work-up including clinical examination, laryngoscopy, imaging, fine-needle aspiration and biopsy; T_{radrev} = radiological T classification; IQR = interquartile range.

* Differences were calculated between the three treatment groups

** Difference between TL and RT was not significant (p=0.491#), whereas differences between CCRT versus RT and TL were significant (TL vs CCRT=0.006#; RT vs CCRT=0.001#).

*** Due to rounding not all percentages total exactly 100%.

**** Only two patients were radiologically classified as a T4b tumor, with tumor volumes 10.7 and 49.8 cc, respectively.

Pearson Chi-Square; $ One-way ANOVA; % Kruskal Wallis

Table 2b. Patient and tumor characteristics categorized per T_{org} classification

	Total	$T3_{org}$	$T4_{org}$	*p*-value*
Total (n (%))	166	89	77	
Gender (n (%))				
Male	124	61 (49.2)	63 (50.8)	0.073¥
Female	42	28 (66.7)	14 (33.3)	
Age at date of diagnosis (mean (SD))	61.9 (11.3)	60.9 (11.3)	63.2 (11.2)	0.195^
T_{radrev} classification (n (%))				
$T3_{radrev}$	90	75 (83.3)	15 (16.7)	0.0001#
$T4_{radrev}$**	76	14 (18.4)	62 (81.6)	
N classification (n (%))				
N0	91	49 (53.8)	42 (46.2)	1.000¥
N+	75	40 (53.3)	35 (46.7)	
Subsite (n (%))				
Supraglottis	93	63 (67.7)	30 (32.3)	0.0001#
Glottis	27	12 (44.4)	15 (55.6)	
Subglottis	3	1 (33.3)	2 (66.7)	
Transglottis	43	13 (30.2)	30 (69.8)	
Tumor volume in cc (median (IQR))	11.6 (5.7-21.3)	8.1 (4.9-13.7)	15.8 (8.0-29.8)	0.0001&
Primary treatment (n (%))				
TL+/-PORT	56	5 (8.9)	51 (91.1)	0.0001#
RT	92	74 (80.4)	18 (19.6)	
CCRT	18	10 (55.6)	8 (44.4)	

Abbreviations: T_{org} = tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009) based on the diagnostic work-up including clinical examination, laryngoscopy, imaging, fine-needle aspiration and biopsy; SD = standard deviation; T_{radrev} = radiological T classification; TL = total laryngectomy; PORT = postoperative radiotherapy; RT = radiotherapy; CCRT = concomitant chemoradiation; IQR = interquartile range.

* Differences were calculated between T subgroups

** Only two patients were radiologically classified as a T4b tumor, with tumor volumes 10.7 and 49.8 cc, respectively.

¥ Fisher's exact test ; ^ independent *t*-test; # Pearson Chi-Square; & Mann-Whitney U test.

In the previous publication on this patient cohort a more detailed description of the treatment characteristics can be found (12). The mean age at diagnosis was 61.9 (SD 11.3). The male to female ratio was 3:1. When compared to TL (mean age: 64.1 years (SD 11.9)), patients primarily treated with CCRT were significantly younger (mean age: 58.1 years (SD 6.4; independent *t*-test: $p < 0.008$)). Eighty-nine patients were originally diagnosed with $T3_{org}$ larynx cancer, whereas 77 patients were diagnosed with $T4_{org}$ larynx cancer. After the current radiological revision 14 patients (8.4%) were upstaged from T3 to T4 and 15 (9.0%) were down-staged from T4 to T3.

Of in total 166 patients, primary TL with or without planned postoperative RT was employed in 56 (33.7%) (51/77 T4; 5/89 T3) patients. Primary single modality RT was given to 92 (55.4%) (18/77 T4; 74/89 T3) and CCRT to 18 (10.8%) (8/77 T4; 10/89 T3) patients. Most patients with $T4_{org}$ larynx cancer (51/77: 66.2 %) underwent TL, whereas most patient with $T3_{org}$ larynx cancer (74/89: 83.1%) underwent RT (for details see table 2a).

Tumor volume

Table 3 shows tumor volumes per T and N classification, per subsite and primary treatment. Median tumor volume for the total study population was 11.6 cc (interquartile range (IQR): 5.7-21.3). Median tumor volume for $T3_{org}$ larynx cancer was 8.1 cc (IQR: 4.9-13.7), for $T4_{org}$ 15.8 cc (IQR: 8.0-29.8) (Mann-Whitney U: p<0.0001). Median tumor volume for $T3_{radrev}$ larynx cancer was 8.7 cc (IQR: 5.0-15.9) and for $T4_{radrev}$ 14.2 cc (IQR 6.8-28.5; Mann-Whitney U: p=0.001). Patients that were treated with TL +/- PORT had significantly higher tumor volume (19.7 cc (IQR: 11.8-30.8)) when compared to RT (7.4 cc (IQR: 4.3-12.4); Mann-Whitney U: p<0.0001), but not when compared to CCRT (13.5 cc (IQR: 5.7-25.2); Mann-Whitney U: p=0.42).

Table 3. Tumor volumes per T and N classification, subsite and primary treatment

	Tumor volume in cc (median (IQR))	*p*-value
Total	11.6 (5.7-21.3)	N/A
T_{org} classification		
$T3_{org}$	8.1 (4.9-13.7)	<0.0001[&]
$T4_{org}$	15.8 (8.0-29.8)	
T_{radrev} classification		
$T3_{radrev}$	8.7 (5.0-15.9)	0.001[&]
$T4_{radrev}$*	14.2 (6.8-28.5)	
N classification**		
N0	10.7 (4.7- 17.0)	0.35[&]
N+	13.0 (6.4- 23.4)	
$Subsite_{org}$		
$Supraglottis_{org}$	12.0 (6.6- 22.4)	0.42[%]
$Glottis_{org}$	5.4 (3.0-15.8)	
$Subglottis_{org}$	3.1 (2.1-16.1)	
$Transglottis_{org}$	11.8 (5.8- 23.4)	
Primary treatment		
TL+/-PORT	19.7 (11.8-30.8)	
RT	7.4 (4.3-12.4)	TL vs RT: <0.0001[&]
CCRT	13.5 (5.7-25.2)	TL vs CCRT: 0.42[&]

Abbreviations: T_{org} = tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009) based on the diagnostic work-up including clinical examination, laryngoscopy, imaging, fine-needle aspiration and biopsy; T_{radrev} = radiological T classification; TL = total laryngectomy; PORT = postoperative radiotherapy; RT = radiotherapy; CCRT = concomitant chemoradiation; IQR = interquartile range.

[&] Mann-Whitney U test; [%] Kruskal Wallis.

* Only two patients were radiologically classified as a T4b tumor, with tumor volumes 10.7 and 49.8 cc, respectively.

** Referring to the primary tumor volumes specified per N subroup.

Local control and loco-regional control and tumor volume

Median follow-up for all patients was 37 months (IQR: 13.8-74.0). Five-year local control for the total group was 77%, after TL +/- PORT 88%, after RT 70% and after CCRT 72%. Five-year loco-regional control rates were 70% (overall), 84% (TL+PORT), 61% (RT), and 68% (CCRT). No associations between tumor volume and local and loco-regional control (data not shown) were found with univariable and multivariable analysis (Table 4). No significant

cut-off point was found by a systematic search over the range of possible volumes. In the multivariable analysis we found that primary treatment was associated with local control. When compared to TL +/- PORT, patients undergoing RT have higher hazards to develop local recurrences (HR 5.47 (1.61-18.60); p=0.006). The interaction between "primary treatment" and "tumor volume" with local control as endpoint was tested and found to be significant (p=0.036, Figure 1).

Table 4. Univariable and multivariable analysis of local control in patients with T3/T4 larynx cancer. Hazard ratios (HR) and p-values were calculated using Cox regression

			Univariable analysis		Multivariable analysis	
	No. of patients	No. of events	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary treatment				0.080		0.024
TL+/-PORT	56	5	Ref		Ref	
RT	92	22	3.01 (1.14-7.96)	0.026	5.47 (1.61-18.60)	0.006
CCRT	18	4	2.90 (0.78-10.79)	0.113	3.13 (0.73-13.51)	0.126
Age (per year)	166	31	0.99 (0.96-1.02)	0.413	1.00 (0.96-1.04)	0.89
Sex				0.638		0.46
Male	124	25	Ref		Ref	
Female	42	6	0.81 (0.33-1.97)		0.70 (0.27-1.79)	
ASA				0.744		0.675
ASA 1	32	6	Ref		Ref	
ASA 2	80	18	1.36 (0.54-3.42)	0.519	1.53 (0.57-4.12)	0.400
ASA 3/ASA 4	47	7	1.05 (0.35-3.13)	0.931	1.18 (0.38-3.63)	0.776
T_{org} classification				0.362		0.395
$T3_{org}$	89	19	Ref		Ref	
$T4_{org}$	77	12	0.72 (0.35-1.47)		1.48 (0.60-3.63)	
T_{radrev} classification				0.434		
$T3_{radrev}$	90	19	Ref			
$T4a_{radrev}$ and 4b	76	12	0.75 (0.36-1.55)	0.434		
N classification				0.361		0.380
N0	91	16	Ref		Ref	
N+	75	15	1.39 (0.69-2.82)		1.44 (0.64-3.23)	
Tumor volume (per cc)	166	31	1.00 (0.98-1.02)	0.821	1.01 (0.98-1.03)	0.548

Abbreviations: TL = total laryngectomy; PORT = postoperative radiotherapy; RT = radiotherapy; CCRT = concomitant chemoradiation; ASA = American Society of Anesthesiologists; T_{org} = tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009) based on the diagnostic work-up including clinical examination, laryngoscopy, imaging, fine-needle aspiration and biopsy; T_{radrev} = radiological T classification.

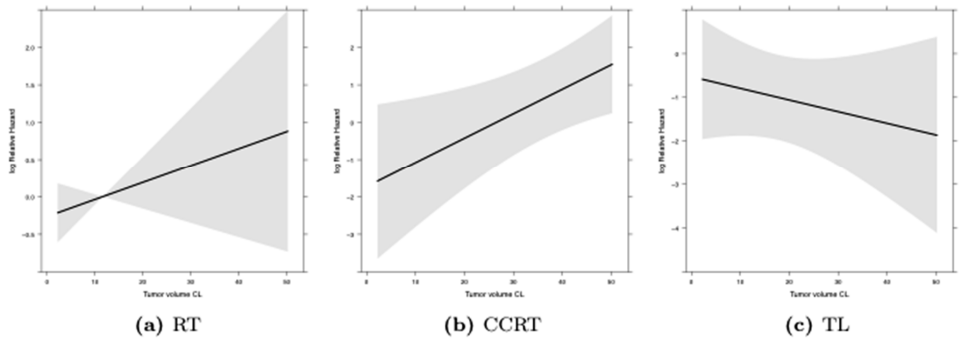

Figure 1. Estimated log relative hazards (black line) with 95% confidence interval (shaded area) for local control from a model with interactions between volume and primary treatment. RT = radiotherapy; CCRT = chemoradiotherapy; TL = total laryngectomy.

Subsequently, subgroup analyses were performed for the separate treatment groups. In univariable analysis, we found that patients treated with CCRT had a HR of 1.07 (95% CI 1.01-1.13; p=0.028) per 1 cc increase in tumor volume to develop a local recurrence. It should be noted that this was a small subgroup with 18 patients, of whom 4 developed a local recurrence. For the RT- and TL-group no significant association was found. In the group treated with RT there was a non-significant trend of HR=1.03 per cc (95% CI 0.98–1.07, p=0.24), whereas in the subgroup that had a TL+PORT a non-significant inverse trend was seen HR=0.97 (95% CI 0.91–1.04, p=0.39). Further subgroup analyses (T3/RT and T4/TL subgroups) did not reveal any associations between tumor volume and one of the outcome measures (data not shown).

Overall survival and tumor volume

Five-year OS for $T3_{org}$ and $T4_{org}$ was similar: 49% respectively 46% (Log Rank: p=0.597). Five-year OS per T_{radrev} classification was also similar: for $T3_{radrev}$ it was 49%, for $T4_{radrev}$a 46% and for $T4_{radrev}$b 50% (Log Rank: p=0.754). Five-year OS analyzed per treatment also showed similar survival figures: after TL it was 51%, after RT 49% and after CCRT 36% (Log Rank: p=0.586). With univariable and multivariable analysis no association between tumor volume and overall survival was found (Table 5). Per treatment group (TL, RT, CCRT) and in subgroup analyses (T3/RT and T4/TL), no prognostic value of tumor volume was found for OS (data not shown). In the multivariable analysis we found (again) that patients with higher ASA score and positive lymph nodes have higher hazards for mortality.

Table 5. Univariable and multivariable analysis of overall survival in patients with T3 or T4 larynx cancer. Hazard ratios (HR) and p-values were calculated using Cox regression

			Univariable analysis		Multivariable analysis	
	No. of patients	No. of events	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary treatment				0.65		0.23
TL+/-PORT	56	33	Ref		Ref	
RT	92	51	1.06 (0.68-1.65)	0.79	1.67 (0.89-3.14)	0.11
CCRT	18	13	1.35 (0.71-2.58)	0.36	1.15 (0.53-2.51)	0.73
Age (per year)	166	97	1.03 (1.01-1.05)	0.005	1.04 (1.01-1.06)	0.003
Sex				0.03		0.057
Male	124	68	Ref		Ref	
Female	42	29	1.60 (1.04-2.48)		1.63 (0.99-2.68)	
ASA				0.04		0.041
ASA 1	32	12	Ref		Ref	
ASA 2	80	47	1.89 (1.00-3.57)	0.05	2.11 (1.09-4.09)	0.028
ASA 3/ASA 4	47	34	2.98 (1.54-5.76)	0.001	2.40 (1.20-4.80)	0.014
T_{org} classification				0.63		0.38
$T3_{org}$	89	50	Ref		Ref	
$T4_{org}$	77	47	1.10 (0.74-1.64)		1.28 (0.74-2.20)	
T_{radrev} classification				0.20		
$T3_{radrev}$	90	47	Ref			
$T4_{radrev}$ a and 4b	76	50	1.38 (0.94-2.01)	0.099		
N classification				0.002		0.001
N0	91	46	Ref		Ref	
N+	75	51	1.86 (1.25-2.78)		2.27 (1.42-3.64)	
Tumor volume (per cc)	166	97	1.002 (0.99-1.01)	0.758	1.009 (1.00-1.02)	0.18

Abbreviations: TL = total laryngectomy; PORT = postoperative radiotherapy; RT = radiotherapy; CCRT = concomitant chemoradiation; ASA = American Society of Anesthesiologists; T_{org} = tumors were clinically staged according to the 7th edition of the UICC TNM staging manual (2009) based on the diagnostic work-up including clinical examination, laryngoscopy, imaging, fine-needle aspiration and biopsy; T_{radrev} = radiological T classification.

DISCUSSION

In this study, including 166 patients with T3-T4 larynx cancer treated with TL+PORT, RT or CCRT, tumor volume was not significantly associated with local and loco-regional control or OS, except for the CCRT-group, wherein tumor volume was significantly associated with local control. Further, T4 tumors were significantly larger than T3 lesions and tumor volumes (in part) were significantly different between the three treatment groups (TL > CCRT > RT).

In the literature studies are conflicting regarding these results. Recently, Janssens et al (2014) prospectively investigated the impact of tumor volume on outcome in 270 patients with cT2-4 larynx cancer treated with accelerated RT with or without carbogen breathing and nicotinamide (ARCON). These authors found no correlation between primary tumor volume and local control. They also reported the presence of a correlation between primary tumor volume and T classification (10). Bernstein et al (2014) concluded that in 114 patients

with advanced larynx or hypopharynx cancer treated by organ preservation strategies tumor volume was not an independent prognostic factor for loco-regional control. However, these authors did find that a higher tumor volume was an independent prognostic factor for disease-specific mortality (11). On the other hand, there are several studies that identified tumor volume as a prognostic factor for oncological outcome. Hoebers et al (2013) reported on 117 patients with cT3-4 larynx cancer treated with primary RT only and found that gross tumor volume was an independent prognostic factor for both overall survival (HR 1.016 (95% CI 1.006-1.026); p=0.001) and local relapse free survival (HR 1.017 (95% CI 1.007-1.027); p=0.001), whereas cT and cN classification were not significant prognostic factors for overall survival (6). Also Pameijer et al (1997) found in 42 patients with T3 larynx cancer treated with RT alone that tumor volume significantly influenced local control (13). Knegjens et al. (2011) found that in 361 patients treated with chemoradiation for advanced head and neck cancer tumor volume was more powerful for predicting outcome after chemoradiation than the TNM classification. However, in that study no patients with larynx cancer were included (8). Finally, Yang (2013) found that in 182 patients with larynx and hypopharynx cancer treated with either surgery or organ-preserving treatment primary tumor volume was of significant influence on OS in univariate analysis. Because of multi-colinearity between total tumor volume (also including metastatic neck lymph nodes), primary tumor volume and other variables only total tumor volume was included in multivariate analysis, where total tumor volume at a cut-off value of 8.38 cc remained a significant predictor (9).

It should be noted, however, that most studies focused on irradiated patients (with or without chemotherapy) and that studies focusing on surgery are scarce (9, 14). Gallo et al (2003) studied 327 T3N0 larynx cancer patients treated with TL and reported that a tumor size of more than 2 cm resulted in a higher risk of tumor recurrence. However, these authors used (2-dimensional) tumor size instead of (3-dimensional) tumor volume as outcome measure (14). Lo et al (1998) studied 55 patients with T2-T3 larynx cancer treated with either primary RT (n=39) or primary TL (n=16). The authors did not identify tumor volume as a predictor of loco-regional control in the surgically treated patients (15).

The reason why we did not find an influence of tumor volume on oncological outcome –except for the association with local control in the CCRT-group- remains unclear, but maybe it is not that surprising after all, considering our initial finding that there was also no difference in prognosis between (the smaller volume) T3 and (the larger volume) T4. It is thus probably due to a selection bias: patients with the higher tumor volumes were selected for TL (median volume T4 15.8 cc; median volume TL 19.7 cc), leaving the smaller tumors for organ preservation treatment. And this lack of the full range of tumor volumes thus might have obscured a possible significant volume effect in the RT only group, although a trend was noted in this group as well (figure 1).

Tumor volume measurements are still time consuming despite the progress in digital/ software evaluation tools, and are still not routinely used in every day practice. In the future this might become easier when automated volume measurement become available (16). Nevertheless, since T3-4 classification is associated with tumor volume and there seems not to be a significant association between tumor volume and local control in the laryngectomy group, in these cases volume measurement is not indicated. If, on the other hand CCRT is considered as a treatment modality, volume measurement might help in decision-making and patient counseling as local control in larger tumors might be impaired.

The limitations of the present study are inherent to any retrospective analysis, where treatment selection biases are unavoidable and difficult to unravel from the patient charts. Further, in this study only patients from one institution were analyzed. However, the fact that our study comprises of an unselected cohort of consecutively treated patients in any case means that there is no other selection bias than the one mentioned, as might not be the case in clinical trial cohorts.

In conclusion, in this retrospective cohort study including 166 patients with T3-T4 larynx cancer, tumor volume was not significantly associated with local control, loco-regional control or overall survival in the surgically treated group. In the group treated with RT there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with CCRT a significant impact of tumor volume on local control was found.

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CHAPTER 4

Trends in treatment and survival of advanced larynx cancer: a 20-year population-based study in the Netherlands

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ABSTRACT

Background: Determining time trends for primary treatment modalities in advanced larynx cancer (LC), overall survival (OS) and laryngectomy-free interval (LFI) over the last two decades in the Netherlands.

Methods: Analysis of T3-4 LC data from two combined national (population-based, and pathology-based) cancer registries.

Results: 2,072 (14.7%) T3, and 1,722 (12.2%) T4 cases were identified. Total laryngectomy (TL) as primary treatment modality decreased, whereas radiotherapy (RT) increased. For T3 disease, 5-year OS after primary TL (+/- adjuvant-RT), RT and chemoradiotherapy (CRT) was 49%, 47% and 45% respectively. For T4 this was 48%, 34% and 42% (overall $p<0.0001$) respectively. 5-year LFI for T3 were 81% (RT) and 77% (CRT), and for T4 81%, and 87%, respectively.

Conclusions: From 1991-2010 TL as primary treatment modality for advanced LC decreased and RT increased. T3 disease showed similar survival rates for all primary treatment modalities. For T4 disease TL (+adjuvant-RT) showed the best survival.

INTRODUCTION

Primary treatment options for advanced larynx cancer are radiotherapy (RT), concomitant chemoradiotherapy or total laryngectomy (TL) with or without adjuvant RT. Of these treatments, 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-)radiotherapy treatment protocols are increasingly being used as alternative to TL (1, 2).

The first of these studies was published in 1991 by the Veterans Affairs Study Group (VA study) (1). The authors concluded that patients treated with either TL or induction chemotherapy combined with RT had similar survival rates. Moreover, in the latter group the larynx could be preserved in 64% of the patients. It is worthy to note that, in a revision of the data of this study, patients with T4N0 cancer had a statistically significant (p=0.05) higher survival rate after treatment with TL (3). A decade later, the RTOG 91-11 study (2003) assessed whether any, and if so, which chemotherapy regimen had added value over RT alone. Patients with large-volume T4N0 larynx cancer were excluded because of their better survival after TL in the VA study. The RTOG 91-11 study concluded that concurrent chemoradiation was superior to induction chemotherapy combined with RT or RT alone in terms of larynx preservation and loco-regional control, but similar in terms of overall survival (2, 4).

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 (5, 6). E.g., in 2006, Hoffman et al. reported decreasing survival for larynx cancer patients from the mid-80s to the mid-90s in the US (6). They also found an increase in the use of organ-preserving treatment modalities and a decrease in the use of surgery in the same period. 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 CRT when compared to treatment with TL (7). 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 (8).

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 (9). 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 (10). 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 (11). Thus, although no decreasing survival was seen as in the US, survival rates did not increase either.

Since the introduction of RT and CRT 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 and still often requires salvage TL with an accompanying higher risk of complications (12, 13). Furthermore, the function of the larynx, especially its vital role in aspiration prevention, can become so impaired that some patients require a TL because of a dysfunctional larynx after prior RT or CRT (14).

In the Netherlands, there are two unique databases for cancer: the Netherlands Cancer Registry (NCR) and the PALGA foundation database ('the nationwide network and registry of histo- and cytopathology in the Netherlands' (15)). Combining these two databases now makes it possible to conduct a population-based cohort study on advanced larynx cancer with the following research questions: (1) What is the trend in proportion of TLs for T3-T4 larynx cancer in the period from 1991 to 2010? (2) What is the trend in primary treatment (primary TL (+/- adjuvant RT), RT and CRT) for T3-T4 larynx cancer? (3) What is the 5-year overall survival (OS) of patients with T3-T4 larynx cancer? (4) What is the laryngectomy-free interval (LFI) after RT or CRT for T3-T4 larynx cancer?

MATERIALS AND METHODS

This study does not fall under the scope of the Medical Research Involving Human Subjects Act (WMO), which means that it does not have to be reviewed by an accredited MREC. The privacy committees of the NCR and the PALGA foundation approved this study.

Study design

A population-based cohort study with NCR data and PALGA was conducted. The NCR receives data from PALGA, from the registry of hospital discharges, and through trained administrators reviewing patient related medical records. The NCR covers at least 95% of all malignancies. The PALGA foundation manages a database covering all pathology reports in the Netherlands. All pathology laboratories collaborate and send in their pathology reports on a daily basis. Data from the latter database were used to verify the histopathology of the larynx cancer, to identify whether "surgery" meant TL and whether TL was conducted for salvage or for a dysfunctional larynx.

Patient selection

The database from the NCR included 14,080 patients diagnosed with invasive larynx cancer between 1991 and 2010. Patient-specific information retrievable was: patients' age (at incidence) and sex, TNM classification/staging, site of the tumor (supraglottic, glottic, subglottic or larynx not otherwise specified; according to the International Classification of Disease for Oncology (ICD-O-3)(16)), primary treatment (surgery/RT/CT), follow-up status (alive, emigrated, deceased), and follow-up time. Follow-up time was defined as time from date of incidence to date of last follow-up (31 December 2013). Date of incidence was defined as date of first histological or cytological confirmation of the tumor, or first admission in relation to this tumor.

PALGA delivered all pathology records (free text conclusion of the report) possibly reporting a TL. The pathology records dated from 1 January 1991 until 1 October 2012. These pathology records were manually screened to identify TLs. Subsequently, the NCR and PALGA databases were merged.

Clinical staging was used, since the pathological stage is unavailable in case of primary treatment with RT and/or CRT. cT1A and cT1B were grouped as T1 and cT4A and cT4B as T4. cNX/missing was coded as N0 in case a cT-classification was known. cT0 or cTis larynx cancer were included in the T1 group (N=10). One patient was scored as having a cT0 or cTis, but had a pT4 and was subsequently scored as having a T4. cT-classification will be referred to as T-classification. Patients with T1 larynx cancer (N=5,573), T2 larynx cancer (N=4,008), distant metastases prior to primary treatment (N=150), cTX (N=499), non-squamous cell cancer (N=56) were excluded leaving 3,794 patients with T3-4N0-3M0 larynx cancer for analysis.

Treatment

Merging the databases enabled identifying primary treatment coded as "surgery" in the NCR database as a primary TL or partial laryngectomy. In case primary treatment was not a TL or a partial laryngectomy, "surgery" was coded as "treatment NOS". In case surgery, RT or CT were not coded as primary treatment, treatment was coded as "no treatment/treatment NOS". By merging the databases we were also able to identify TLs that were not part of the primary treatment. To determine the indication for a TL, a cut-off value was chosen of 120 days between date of incidence and date of TL. TL performed within these 120 days was considered a primary TL. In case the TL was performed at least 120 days after the incidence date, the TL was coded as salvage procedure, or as TL for a dysfunctional larynx. The distinction between salvage TL and TL for a dysfunctional larynx was made based on the presence of malignancy (salvage) or not (dysfunctional larynx) in the pathology report. We chose a cut-off value of 120 days because we felt confident that the primary treatment would be finished within this time window, also because the time delay between date of incidence and onset of (mostly centralized) primary treatment in the Netherlands rarely exceeds 40 days.

Outcome measures

Outcome measures were trends in primary treatment (TL (+/-RT), RT and CRT), laryngectomy-free Interval (LFI) (sometimes also referred to as larynx preservation rate) after primary RT and CRT and OS per T-classification and treatment. LFI was determined using follow-up time, which was calculated starting from date of incidence until TL or censoring (death or last date of follow-up). Patients at risk were defined as patients that were primarily treated with either RT or CRT. For OS the follow-up of vital status was calculated as the time from incidence to death, emigration or until 31 December 2013. Patients without follow-up (date of incidence and date of loss-to-follow-up were equal or negative (N=7)), were excluded from the survival analysis.

Statistical analysis

Descriptive statistics were performed. The independent t-test was used to calculate if mean ages between treatment groups were significantly different (age was normally distributed). Linear-by-Linear was used to assess the association between T-classification and incidence years. Linear regression was used to calculate the trends in TLs over the years (1993-2010). The percentage of TLs (total numbers and per indication) was calculated counting the number of TLs divided by the number of patients diagnosed with T3 or T4 larynx cancer. The percentage of TL, RT and CRT was calculated counting the number of treatments divided by the number of all patients diagnosed with T3 or T4 larynx cancer. For OS and LFI, Kaplan Meier curves were plotted. Log-Rank tests were used to compare groups. For multivariable analysis, Cox regression analysis was applied. The variables: primary treatment, age, sex, T- and N-classification and subsite were included in the model. The continuous variable age was categorized in 5 groups. Hazard ratios and 95% confidence levels were estimated. Variables with a p-value < 0.05 were considered statistically significant. Analyses were performed using *IBM® SPSS® Statistics* 20.0.

RESULTS

Patient, tumor and treatment characteristics

Detailed information on patient, tumor and treatment characteristics is shown in Table 1. The male to female ratio was 3.7:1 and the mean age was 64.1 years (range 28-100 years). Overall, most T3-4 patients had supraglottic cancer (63.1%), followed by glottic cancer (31.0%). A minority had subglottic cancer (2.6%) or larynx not otherwise specified (3.3%). Noteworthy is that the distribution of subsite was reversed for patients with T1-T2 larynx cancer (N=9581): glottic cancer occurred in 78.6% of the patients, followed by supraglottic cancer (19.9%) (Figure 1).

Over this 20-year period, the number of patients with T3 larynx cancer increased (Linear-by-Linear: p=0.001) and with T4 larynx cancer decreased (Linear-by-Linear: p=0.003) (Figure 2).

Table 1. Patient and tumor characteristics at time of primary treatment (N=number; NOS=not otherwise specified; TL=total laryngectomy; RT=radiotherapy; CRT=chemoradiotherapy)

	Total (N, %)	Primary TL (N, %)	RT (N, %)	CRT (N, %)	Partial laryngectomy (N, %)	CT (N, %)	No treatment/ treatment NOS (N, %)
	3794 (100)	1172 (30.9)	2018 (53.2)	265 (7.0)	27 (0.7)	14 (0.4)	298 (7.9)
Sex							
Male	**2991 (78.8)**	971 (82.8)	1554 (77.0)	191 (72.1)	19 (70.4)	13 (92.9)	243 (81.5)
Female	**803 (21.2)**	201 (17.2)	464 (23.0)	74 (27.9)	8 (29.6)	1 (7.1)	55 (18.5)
Mean age (range)	**64.1 (28-100)**	62.8 (31-89)	64.7 (28-100)	58.4 (34-80)	59.0 (39-71)	58.4 (44-71)	70.8 (40-98)
Subsite							
Supraglottic	**2394 (63.1)**	651 (55.5)	1307 (64.8)	220 (83.0)	26 (96.3)	13 (92.9)	177 (59.4)
Glottic	**1175 (31.0)**	420 (35.8)	625 (31.0)	35 (13.2)	1 (3.7)	1 (7.1)	93 (31.2)
Subglottic	**98 (2.6)**	44 (3.8)	39 (1.9)	5 (1.9)	-	-	10 (3.4)
Larynx NOS	**127 (3.3)**	57 (4.9)	47 (2.3)	5 (1.9)	-	-	18 (6.0)
TN							
T3N0	**1329 (35.0)**	177 (15.1)	1011 (50.1)	53 (20.0)	8 (29.6)	2 (14.3)	78 (26.2)
T3N+	**743 (19.6)**	147 (12.5)	447 (22.2)	89 (33.6)	5 (18.5)	5 (35.7)	50 (16.8)
T4N0*	**983 (25.9)**	495 (42.2)	362 (17.9)	35 (13.2)	7 (25.9)	5 (35.7)	79 (26.5)
T4N+*	**739 (19.5)**	353 (30.1)	198 (9.8)	88 (33.2)	7 (25.9)	2 (14.3)	91 (30.5)

* The total of 1722 patients with a T4 larynx cancer, there were 1208 non-specified T4 cases, 489 T4a cases and 25 T4b cases (of which 4 underwent a TL).

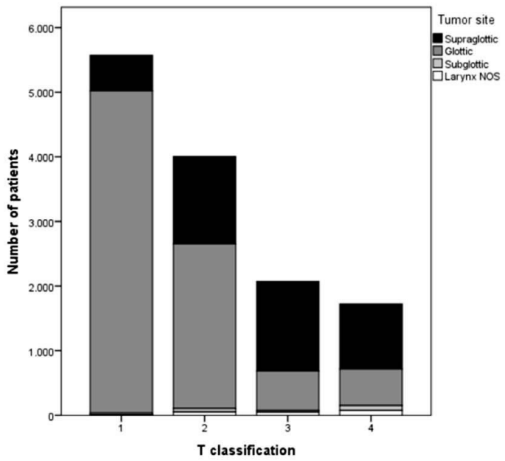

Figure 1. The distribution of tumor site per T-classification

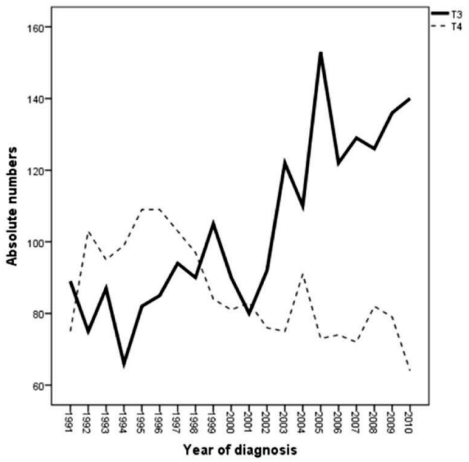

Figure 2. Number of patients diagnosed with T3 larynx cancer and T4 larynx cancer from 1991 to 2010. Over this 20-year period, the number of patients with T3 larynx cancer increased (p=0.001) and with T4 larynx cancer decreased (p=0.003)

Trends in total laryngectomy

Figure 3 shows the total number of TLs and per indication (primary TL, salvage TL and TL for a dysfunctional larynx) as a percentage of all patients with T3-T4 larynx cancer over the years 1991-2010 (N=3,794). There was a decrease of 3.07 TLs per year ($p < 0.0001$; calculated from 1993 to 2010). The use of a TL as primary treatment declined (-3,30 TLs per year; $p < 0.0001$), whereas numbers of salvage TLs and TLs for a dysfunctional larynx remained stable.

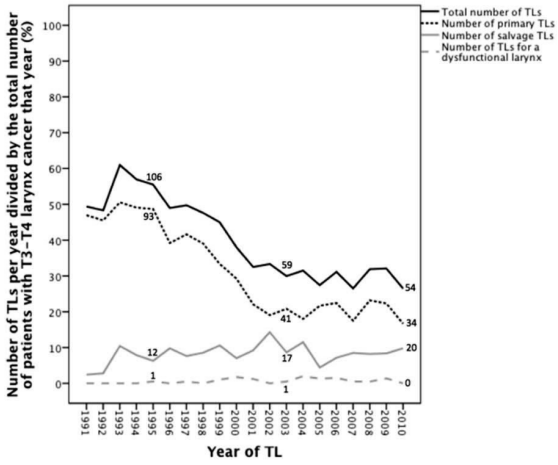

Figure 3. Number of total laryngectomies (TL). Lines indicate total number of TLs and per indication (primary TL, salvage TL and TL for a dysfunctional larynx) as percentage of patients with T3-T4 larynx cancer over the years 1991-2010 (N=3,794; absolute numbers for the years 1995, 2003 and 2010)

Trends in treatment of advanced larynx cancer

When compared to TL (mean age: 62.8 years (range 31-89)), patients primarily treated with CRT were significantly younger (mean age: 58.4 years (range 34-80 years; $p < 0.0001$)) and patients undergoing RT significantly older (mean age: 64.7 years (range 28-100 years; $p=0.001$)).

Figures 4a and b show the trend in primary treatment for T3 and T4 larynx cancer patients from 1991 to 2010. For both T3 and T4 larynx cancer the use of primary TL as proportion of all patients with T3 or T4 larynx cancer decreased, whereas the use of RT increased. In both figures, the trend appears to change in 2000-2002 with an increase in RT and a decrease in TL which levels off a few years later.

Over the study period from 1991 to 2010 the main treatment modality for T3N0 and T3N+ larynx cancer was RT (76.1% respectively 60.2%). Only 13.3%, respectively 19.8%, underwent TL as primary treatment. Of these patients, 76.9% received postoperative RT. For patients with T4N0 and T4N+ larynx cancer the main treatment modality was TL (50.4% respectively 47.8%), followed by postoperative RT in 82.5% of the cases. RT as a primary treatment for T4N0 and T4N+ larynx cancer was administered in 36.8%, respectively 26.8% of the patients. Only 3.6% and 11.9% of these patients received CRT as primary treatment.

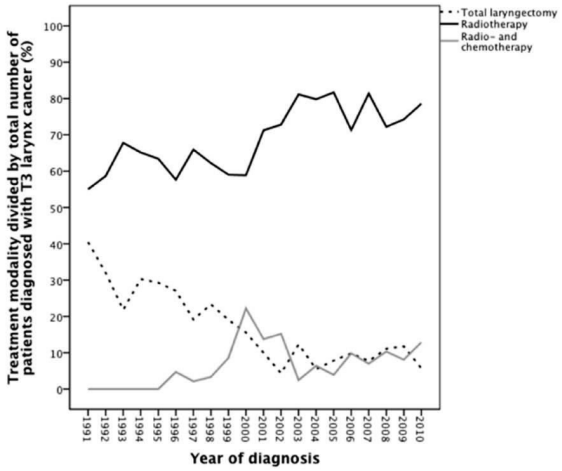

Figure 4a. Treatment modalities for T3 larynx cancer from 1991 to 2010 (primary treatment divided by total number of patients diagnosed with T3 larynx cancer that year, in %).

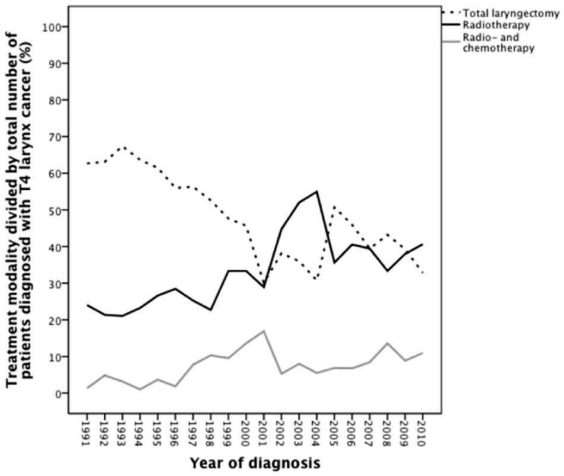

Figure 4b. Treatment modalities for T4 larynx cancer from 1991 to 2010 (primary treatment divided by total number of patients diagnosed with T4 larynx cancer that year, in %).

Overall survival

The OS for T3 and T4 larynx cancer after 5 years for T3 larynx cancer was 44% and for T4 39% (Log-Rank: p<0.0001; including *all* treatment modalities). Median OS was 3.81 years for T3 (95% CI: 3.42-4.20) and 2.83 years (95% CI: 2.51-3.15) for T4 larynx cancer.

Figure 5a shows the OS for patients with T3 larynx cancer. OS rates after TL, RT and CRT were similar: 49%, 47% and 45% respectively after 5 years (Log-rank: overall p=0.539). No significant differences were found between the patients that did and did not receive adjuvant RT after TL (47% and 56% respectively; Log-Rank: p=0.442) (Figure 5b). When analyzed for supraglottic and glottis tumors separately, no significant differences were found between tumor site.

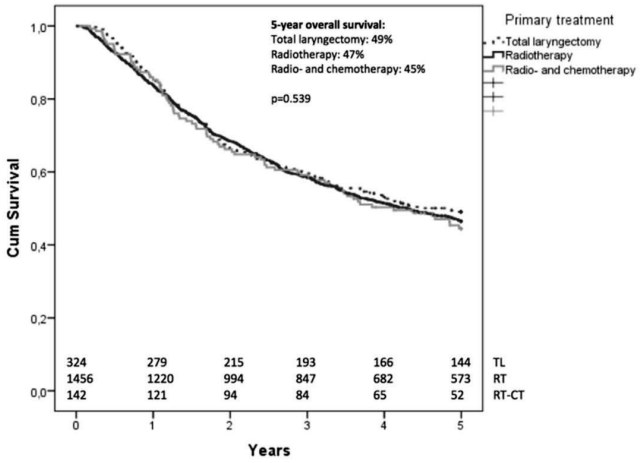

Figure 5a. Overall survival for T3 larynx cancer for total laryngectomy (TL; n=324), radiotherapy (RT; n=1456) and radiotherapy combined with chemotherapy (CRT; n=142) separately.

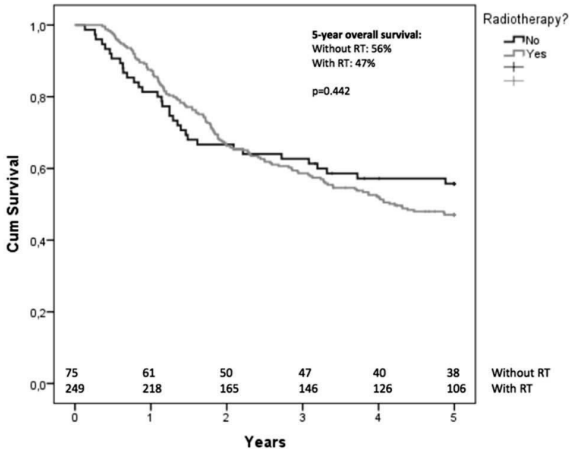

Figure 5b. Overall survival for T3 larynx cancer for total laryngectomy (n=324) without radiotherapy (RT; n=75) or with RT (n=249).

Figure 6a shows the OS for patients with T4 larynx cancer. For these patients, 5-year OS after TL (48%) was better than after RT (34%) or after CRT (42%) (Log-Rank: overall p<0.0001). Patients who received adjuvant RT after TL had significant better survival than patients not undergoing RT (49% and 42% respectively; Log-Rank: p=0.047) (Figure 6b). When analyzed for supraglottic and glottis tumors separately, no significant differences were found between tumor site.

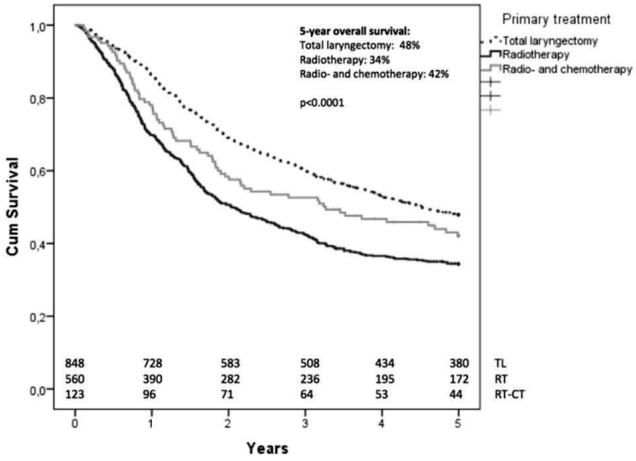

Figure 6a. Overall survival for T4 larynx cancer for total laryngectomy (TL; n=848), radiotherapy (RT; n=560) and radiotherapy combined with chemotherapy (CRT; n=123) separately.

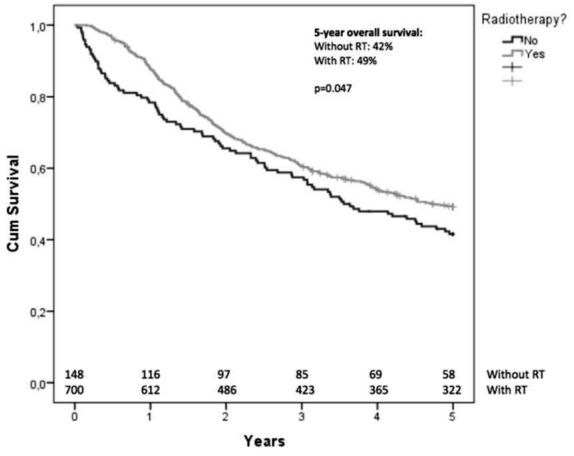

Figure 6b. Overall survival for T4 larynx cancer for total laryngectomy (n=848) without radiotherapy (RT; n=148) or with RT (n=700).

Table 2 shows a multivariable analysis for OS of primarily treated T3 or T4 larynx cancer patients. Patients with T4 larynx cancer have a higher hazard ratio (HR) for dying when compared to patients with T3 larynx cancer (HR 1.21 (95% CI 1.11-1.32; p<0.0001)). This was also the case for patients with positive lymph nodes when compared to patients without positive lymph nodes (HR 1.62 (95% CI 1.49-1.77; p<0.0001). Primary treatment with RT or CRT resulted in poorer survival (HR 1.33 (95% CI 1.21-1.47; p<0.0001) respectively HR 1.26 (95% CI 1.07-1.49; p=0.006)) compared to treatment with TL+adjuvant RT. HRs for dying increased with increasing age. Females had a lower hazard ratio for dying when compared to males (HR 0.88 (95% CI 0.80-0.97; p=0.01).

Table 2. Multivariable analysis calculating overall survival using Cox regression analysis including all patients with T3 or T4 larynx cancer and separately for T3 and T4 larynx cancer (HR = hazard ratio; TL = total laryngectomy; adj RT = adjuvant radiotherapy; CRT = chemoradiotherapy; NOS = not otherwise specified). The given hazard ratios are hazard ratios for death

	T3+T4 larynx cancer			T3 larynx cancer			T4 larynx cancer		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Primary treatment									
TL+adj RT	1.00			1.00			1.00		
TL alone	1.09	0.93-1.29	0.29	0.94	0.70-1.26	0.66	1.12	0.92-1.37	0.25
RT	1.33	1.21-1.47	<0.0001	1.09	0.93-1.28	0.28	1.50	1.33-1.71	<0.0001
CRT	1.26	1.07-1.49	0.006	1.11	0.86-1.43	0.41	1.27	1.01-1.59	0.04
Age									
< 50	1.00			1.00			1.00		
50-59	1.34	1.14-1.58	<0.0001	1.55	1.22-1.97	<0.0001	1.20	0.96-1.49	0.11
60-69	2.00	1.71-2.33	<0.0001	2.22	1.76-2.79	<0.0001	1.81	1.46-2.24	<0.0001
70-79	3.01	2.56-3.55	<0.0001	3.62	2.85-4.59	<0.0001	2.52	2.01-3.17	<0.0001
≥ 80	5.20	4.28-6.35	<0.0001	6.92	5.21-9.18	<0.0001	4.06	3.08-5.37	<0.0001
Sex									
Male	1.00			1.00			1.00		
Female	0.88	0.80-0.97	0.01	0.85	0.75-0.97	0.02	0.91	0.78-1.05	0.20
T-classification									
T3	1.00								
T4	1.21	1.11-1.32	<0.0001						
N-classification									
N0	1.00			1.00			1.00		
N+	1.62	1.49-1.77	<0.0001	1.66	1.48-1.87	<0.0001	1.56	1.37-1.76	<0.0001
Subsite									
Supraglottic	1.00			1.00			1.00		
Glottic	0.92	0.84-1.01	0.09	0.92	0.82-1.05	0.22	0.92	0.80-1.05	0.21
Subglottic	1.01	0.79-1.29	0.96	1.09	0.66-1.83	0.73	0.98	0.73-1.30	0.87
Larynx NOS	1.45	1.18-1.78	<0.0001	1.16	0.83-1.61	0.38	1.71	1.31-2.24	<0.0001

When analyzed separately by T-classification, patients with T3 larynx cancer had higher HRs for dying in case of positive lymph nodes (HR 1.66 (95% CI 1.48-1.87; p<0.0001)), in case they were male, and with increasing age. For patients with T4 larynx cancer, HRs for dying were higher in case of positive lymph nodes (HR 1.56 (95% CI 1.37-1.76; p<0.0001)), primary treatment with RT or CRT (when compared to TL+adjuvant RT: HR 1.50 (95% CI 1.33-1.71; p<0.0001) respectively HR 1.27 (95% CI 1.01-1.59; p=0.04)) and with increasing age.

In figure 4a and 4b it appears that there is a change in treatment around 2000-2002 with an increase in RT and a decrease in TL, which levels off a few years later. As mentioned earlier in the Introduction, a consensus document on larynx cancer diagnostics and treatment was published in 1999 and implemented in 2000 (9). Therefore, in multivariable analysis, separately for T3 and T4 larynx cancer, we also compared the first with the second decade, adding an interaction term for the two decades and primary treatment (because of their changes over time). This additional analysis revealed that there is no significant difference in survival between the two decades based on treatment (data not shown).

Laryngectomy-free interval

Eighty-one percent of the T3 larynx cancer patients treated with RT retained their larynx at 5 years (5-year LFI: 81%) and 78% at 10 years (10-year LFI: 78%). After treatment with CRT these rates were similar: both 77% after 5 and 10 years (Figure 7a). LFI for patients with T4 larynx cancer and primary treatment with RT were 81% and 75% after 5 and 10 years respectively. After treatment with CRT these numbers were higher: 87% and 82% after 5 and 10 years respectively (p=0.076; figure 7b).

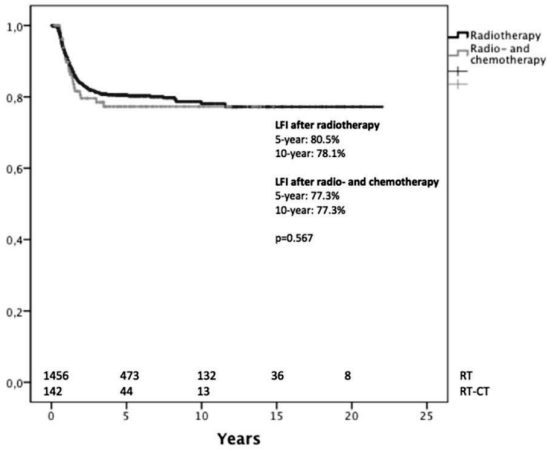

Figure 7a. Laryngectomy-free interval (LFI) for patients with T3 larynx cancer (N=1598) primarily treated with radiotherapy (N=1456) or radio- and chemotherapy (N=142) using Kaplan-Meier survival analysis (LFI was determined using follow-up time, which was calculated starting from date of incidence until total laryngectomy or censoring (death or last date of follow-up))

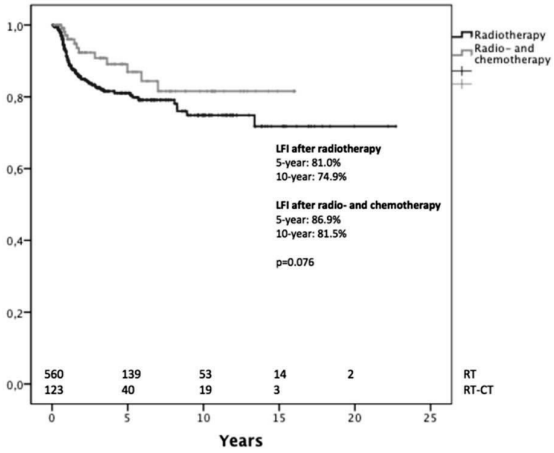

Figure 7b. Laryngectomy-free interval (LFI) for patients with T4 larynx cancer (N=683) primarily treated with radiotherapy (N=560) or radio- and chemotherapy (N=123) using Kaplan-Meier survival analysis (LFI was determined using follow-up time, which was calculated starting from date of incidence until total laryngectomy or censoring (death or last date of follow-up))

DISCUSSION

This population-based study, comprising all Dutch patients diagnosed with squamous cell larynx cancer between 1991 and 2010 present in two national cancer registries, indeed enabled answering the 4 research questions raised at the end of the introduction (trends in proportion of TL for T3 and T4, time trends for all treatment modalities, 5-year OS rates, and 5-year LFI).

For both T3 and T4 larynx cancer, the use of primary TL as a proportion of all patients diagnosed with T3 and T4 larynx cancer decreased, whereas the use of RT increased. Hoffman et al. (2006) also observed a decrease in number of TLs as primary treatment for larynx cancer and an increase in RT and chemotherapy (1985-2001), but that study included all larynx cancer cases and not only the advanced cases as in the present study (6). The decrease in TLs and increase in RT for T3 larynx cancer in our study is not unexpected, since the Dutch guidelines for treating larynx cancer changed in 1999 after the publication of a consensus document by the Dutch Head and Neck Society (DHNS, former Dutch Cooperative Head and Neck Oncology Group) (9, 17). Until that time, patients with T3 and T4 larynx cancer in most centers preferably were treated with TL with or without adjuvant RT. After the publication of this consensus document, which was also based on published data from the Netherlands (10), patients with T3 larynx cancer were preferably irradiated and patients with T4 larynx cancers in most centers were still laryngectomized and received adjuvant RT. This policy in essence did not change after the publication of the RTOG 91-11 study in 2003 although CRT became more popular in the Netherlands as well.

OS of T3 and T4 larynx cancer differs significantly (44% and 39% respectively after 5 years). When analyzed per treatment, OS is similar for T3 larynx cancer after treatment with TL, RT or CRT. For T4 larynx cancer however, patients treated with RT or CRT have poorer survival compared to patients treated primarily with TL and adjuvant RT. In a population-based study in the Province Alberta, Canada, Dziegielewski et al. (2012) also found superior survival rates after treatment with TL for T4 larynx cancer (18). Furthermore, Chen et al. (2007) reported HRs for death of 1.61 and 1.43 for RT and CRT respectively when compared to TL for stage IV larynx cancer, which are in line, but slightly higher than found in the present study. It has to be kept in mind, though, that stage IV also includes T3N+ cancers and thus not solely T4 cancers (7).

A possible explanation for the inferior survival after RT for T4 larynx cancer may be due to unknown selection biases, such as co-morbidity, the patient and physician preferences, intent of the treatment, and tumor characteristics, such as tumor volume and operability of the tumor. Possibly, a subgroup of patients, who underwent RT for T4 larynx cancer had inoperable disease or had significant co-morbidity and was treated with palliative intent.

The majority of the T4 cases who were primarily treated with TL, received postoperative RT. These patients had superior survival rates when compared to those not undergoing RT. In the Dutch consensus document on larynx cancer (1999) it is recommended to add RT in case surgery is the treatment of choice (9). This recommendation was based on several studies that suggest that RT in the postoperative setting improves oncological outcome (19, 20), which is underlined (again) in the present study.

As reported earlier by Van Dijk et al. (2013) the decrease in survival that was seen in the United States does not seem to apply for the Netherlands (11). Hoffman et al. (2006) attributed their decrease in survival to the increase of the use of organ-preserving treatment modalities, such as RT and CRT. That we do not see a difference in survival for T3 larynx cancer after treatment with TL, RT or CRT might be due to several factors. Firstly, head and neck cancer care is highly centralized in the Netherlands in the 8 centres participating in the DHNS, which guarantees treatment by dedicated head and neck specialists. This possible centralisation effect (bigger volume - better outcome) is underlined by the comparatively favorable survival figures for larynx cancer achieved in the Netherlands according to the European cancer statistics published by Sant et al. in 2009 (21). Secondly, since the late nineties in the Netherlands altered fractionated RT is widely used for advanced larynx cancers in most centers, which seems to be superior to conventional schemes of RT regarding local control and survival in head and neck cancer (22). In some centers the ARCON protocol was used for many years involving accelerated RT in combination with carbogen inhalation and nicotinamide (23). The clinical relevance of the similar survival figures for T3 larynx cancer in this study is that patients should be extensively counseled about the various pro's and con's of the three options, i.e. TL, RT and CRT, in order to be able to take a well-informed choice.

As expected, patients with positive lymph nodes in the neck have poorer survival when compared to patients without positive lymph nodes, which is in concordance with the literature (24, 25).

LFI for patients with T3 or T4 larynx cancer after RT or CRT was 77% or higher after 5 years. This finding is in agreement with the literature. In the VA-study the larynx was preserved in 64% of the patients after 2 years for patients initially treated with induction chemotherapy combined with RT (1). The RTOG 91-11 study reported larynx preservation rates (a synonymous term for LFI) after 10 years of 82% and 64% after treatment with concurrent chemoradiation and RT alone, respectively (4).

An interesting and noteworthy finding is the reversed distribution of subsite for patients with T3-T4 larynx cancer, when compared to T1-T2 larynx cancer. In the advanced stages, supraglottic cancer occurred twice as often as glottic cancer. These numbers are in concordance with the distribution of patients in the RTOG 91-11 study (2, 4).

Although TN classification, sex and age are important in predicting survival and larynx preservation, many other factors play a role in decision making and patient counseling for treatment selection. Among these are co-morbidity and general condition, tumor volume, and patient and doctor preferences. In the future possibly, markers predicting response and larynx preservation will become more important (26). Nomograms, as developed by Egelmeer et al. and Sherman et al. might become more useful (27, 28).

Limitations

In the NCR and PALGA database, data regarding co-morbidity, treatment intentions, loco-regional control, functional outcome, toxicity, patient and physician preferences, tumor characteristics such as tumor volume and operability of the tumor and quality of life are not recorded. These data are also important in evaluating and understanding treatment results.

Another limitation of this study is that in 2003 the definition of T-classification changed (5^{th} to 6^{th} edition of TNM-staging of the UICC). This is probably (in part) the explanation of the fact that patients with T3 larynx cancer increased over the study period, whereas the number of patients with T4 larynx cancer decreased. In the description for T3 and T4 larynx cancer in the 5^{th} edition, the presence of cartilage erosion or invasion was reserved for T4. In the 6^{th} edition however, (minor) cartilage erosion was de-classified as a T3 larynx cancer, with extra-laryngeal spread being required for T4 classification. The T3 category now might be more unfavorable than before, but at the same time the T4 category has "lost" its most favorable subgroup, and thus also would be more unfavorable. Furthermore, incidence of larynx cancer decreased, most likely as a result of a decrease in smoking.

In 1991 and 1992, there was a smaller number of TLs than expected. This can be explained by the fact that only patients were included that were *diagnosed* with larynx cancer between 1991 and 2010. Patients diagnosed in the years preceding 1991 and laryngectomized in 1991 and 1992 for recurrent disease, were thus not included in this study.

In conclusion, TL as primary treatment for advanced larynx cancer decreased and RT increased between 1991 and 2010 in the Netherlands. T3 larynx cancer showed similar survival with all three primary treatment modalities (TL, RT or CRT). After RT or CRT 4 out of 5 larynges are preserved both in T3 and T4 cancers after 5 years. Patients with T4 larynx cancer treated with TL and adjuvant RT have a better survival than after RT or CRT.

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PART II

ADVERSE EVENTS AND TREATMENT FACETS

CHAPTER 5

Total laryngectomy for a dysfunctional larynx after (chemo)radiotherapy

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ABSTRACT

Objective: To evaluate the functional outcomes after total laryngectomy (TL) for a dysfunctional larynx in patients with head and neck cancer that is in complete remission after (chemo)radiotherapy.

Design: Retrospective cohort study.

Setting: Tertiary comprehensive cancer center.

Patients: The study included 25 patients from a cohort of 217 consecutive patients with TL who were treated between January 2000 and July 2010. The inclusion criteria for this subgroup analysis were complete remission and functional problems for which TL was considered to be the only resolution. Quality of life assessment was carried out using the European Organization for Research and Treatment of Cancer Quality of Life C30 and Head and Neck Module 35 questionnaires and an additional study-specific questionnaire covering functional aspects, such as swallowing and dyspnea, in more detail.

Intervention: Total laryngectomy.

Main Outcome Measures: Morbidity, mortality, and functional outcomes.

Results: The indication for TL was chronic aspiration with or without recurrent pneumonia (n=15 [60%]), debilitating dyspnea (n=8 [32%]), and persistent profuse hemorrhage (radiation ulcer) (n=2 [8%]). After TL, 14 of the 25 patients (56%) had 20 major postoperative complications, including 11 pharyngocutaneous fistulas, requiring additional treatment. Tube feeding and recurrent pneumonia incidence had decreased from 80% and 28% to 29% and 0%, respectively, 2 years after surgery. Prosthetic voice rehabilitation was possible in 19 patients (76%). Two years after surgery, 10 of 14 patients (71%) still reported TL-related pulmonary problems despite the consistent use of a heat and moisture exchanger. The 5-year overall survival rate was 35%.

Conclusions: TL for a dysfunctional larynx tends to have a high complication rate. However, in this study, the initial functional problems (aspiration, recurrent pneumonia, and dyspnea) did not recur. Tube feeding was significantly reduced, and the quality of life of the surviving patients appeared to be reasonable.

INTRODUCTION

Radiotherapy (RT), either as a single-modality treatment or as an adjuvant to surgery, plays a central role in the curative treatment of head and neck cancer (1). In advanced head and neck cancer, in the last 2 decades RT increasingly has been combined with chemotherapy (CT) (mainly cisplatin based), which either has been added as induction before radiation or has been administered concurrently. This treatment has led to improvements in loco-regional control and overall survival in many head and neck cancer sites, especially in oropharyngeal cancer, with improvement between 8% and 15% (2). Nowadays, therefore, organ preservation cisplatin-based chemoradiation therapy (CRT) has become the treatment of choice for anatomically and functionally inoperable advanced-stage cancer of the head and neck, probably with the exception of stage IV laryngeal cancer (3,4). However, one of the challenges organ preservation treatment has created is that although more cases of cancer seem to be curable, the function of the target organ is not always preserved. Also, although RT as a single-treatment modality can result in serious adverse effects and complications, the addition of CRT has caused them to become more prominent and more serious (5). According to the National Cancer Institute's Common Terminology Criteria for Adverse Events(6), the most severe (grade 3-4) adverse effects due to CRT for laryngeal and pharyngeal carcinoma are stridor, severe (throat) pain, swallowing difficulty (dysphagia and/or aspiration), neurotoxic reactions, renal failure, and airway compromise. Dysphagia and aspiration can become so severe that permanent tube feeding is often required, and airway compromise due to laryngeal edema can become so problematic that permanent tracheotomy is unavoidable. These complications can become life threatening and severely compromising for the quality of life (QoL) of patients. In an attempt to reduce these adverse effects by reoxygenating damaged tissues, the use of hyperbaric oxygen therapy (HBO) has been recommended, but the results of HBO are rather limited and, to our knowledge, have never been substantiated in randomized trials (7). In some instances, despite complete remission, removal of the dysfunctional organ, eg, total laryngectomy (TL), is the only resolution for controlling severely disabling and potentially life-threatening aspiration and for restoring at least some QoL for patients. Interestingly, although there are many series published on salvage TL for residual and/or recurrent disease, there is rarely any literature discussing TL for a dysfunctional larynx in patients with head and neck cancer that is in complete remission after (C)RT. Therefore, the aim of this study was to obtain more insight in the clinical outcomes and QoL aspects among this increasing subgroup of patients with TL. Consequently, we performed a retrospective analysis of all relevant clinical and functional characteristics of 25 patients who underwent TL for a dysfunctional larynx.

METHODS

Study design

The study patients were selected from a cohort of 217 consecutive cases of TL performed at The Netherlands Cancer Institute, Amsterdam, over a period of slightly more than 10 years (January 2000 to June 2010). Primary TL was performed in 84 patients (39%); salvage TL was performed in 108 patients (50%) with residual or recurrent cancer after (C)RT; and TL was performed in 25 patients (11%) with a dysfunctional larynx after (C)RT. The latter 25 patients were all in complete remission based on imaging results, findings of examination with the patient under general anesthesia, and pathologic findings, but they had serious, often life-threatening adverse effects, such as inspiratory dyspnea, intolerable dysphagia, and/or recurrent aspiration pneumonia, after (C)RT, and TL was considered to be the only resolution. One treatment choice was narrow-field TL; however, in view of the clinical and pathologic findings in all of these patients and the relatively high chance of a sampling error in the biopsy specimens, narrow-field TL would result in irradical resection in case of false-negative biopsy results. Therefore, wide-field TL was performed in all cases. There were 20 male and 5 female patients, with a mean age of 63 years (age range, 48-77 years) at the time of TL. The index tumor was laryngeal cancer in 14 patients (6 glottic, 8 supraglottic), hypopharyngeal cancer in 4 patients, cervical esophageal cancer in 1 patient, oropharyngeal cancer in 4 patients, and nasopharyngeal cancer in 2 patients. Table 1 shows all the relevant pre-TL data. The study was approved by the institutional review board. Informed consent was obtained from the 11 patients who participated in the QoL part of the study.

Prior treatment

Fourteen patients had received RT as a single-modality treatment and 11 had been treated with concurrent CRT. In the majority of the patients, the RT protocol consisted of 46 Gy in 23 fractions to the primary tumor and the bilateral aspect of the neck, with a boost to the tumor-bearing areas (additional 24 Gy in 12 fractions), to a total dose of 70 Gy in 7 weeks. Different RT schedules were used in 3 cases of laryngeal cancer: (1) hyperfractionation and accelerated fractionation consisting of 70 Gy in 40 fractions; (2) hypofractionation consisting of 60 Gy in 25 fractions in 5 weeks; and (3) a total dose of 68 Gy in 34 fractions. In the esophageal cancer case, the total dose was 60 Gy in 30 fractions. In the patients who underwent CRT, the RT schedule was similar to that in the RT-only group, with the exception of 1 patient (with T3N2c supraglottic carcinoma) who was treated according to the accelerated Danish Head and Neck Cancer study schedule (8). The concurrent CT regimen consisted of intravenous cisplatin therapy (100 mg/m2) on days 1, 22, and 43 of the RT, with the exception of the patient who was treated with the accelerated fractionation schedule. This patient received daily concomitant intravenous cisplatin therapy (6 mg/m2) for 5 weeks. In 3 patients, the larynx was previously irradiated because of head and neck cancer. The dose delivered to the larynx was approximately 70 Gy in all 3 patients (Table 1).

Table 1. Patient characteristics preceding the decision for total laryngectomy (N=25)

No	Sex	Age	Tumor Site	Stage	Prior treatment	Larynx dose (Gy/Fr)	HBO	(C)RT-TL (yrs)
1	Male	48	Glottic	T2N1	RT	60/25	Yes	1
2	Male	69	Glottic	T3N1	RT	70/40	-	1
3	Female	67	Glottic	T1N0	RT	70/35	Yes	3
4	Male	64	Glottic	T1N0	RT	70/35	-	6
5	Male	71	Glottic[1]	T3N0	RT	68/34 +51/18	-	3
6	Male	65	Glottic	T3N0	RT	70/35	Yes	11
7	Male	55	Supraglottic	T1N1	RT	70/35	-	6
8	Male	77	Supraglottic	T3N0	RT	70/35	-	2
9	Female	56	Supraglottic	T3N2c	CRT	70/35	Yes	2
10	Male	62	Supraglottic	T2N0	RT	70/35	-	1
11	Male	60	Supraglottic[2]	T4N2	CRT	70/35 + 70/35	-	1
12	Male	70	Supraglottic	T1N2c	RT	70/35	-	6
13	Male	64	Supraglottic	T3N2	CRT	70/35	-	5
14	Male	64	Supraglottic	T3N3	CRT	70/35	-	7
15	Male	54	Hypopharynx[3]	T4bN2b	CRT	70/35 + 70/35	-	1
16	Male	50	Hypopharynx	T4N2c	CRT	70/35	-	3
17	Male	67	Hypopharynx	T2N0	CRT	70/35	-	7
18	Female	73	Hypopharynx	T4N0	CRT	70/35	-	1
19	Male	56	Oesophagus	T3N1	RT	60/30	Yes	10
20	Male	63	Oropharynx	T3N0	RT	70/35	-	19
21	Male	63	Oropharynx	T4N2	CRT	70/35	-	4
22	Female	59	Oropharynx	T4N2c	RT	70/35	-	1
23	Male	76	Oropharynx	T1N1	RT	70/35	-	6
24	Male	55	Nasopharynx	T3N2	CRT	50/35	-	20
25	Female	59	Nasopharynx	T2N2	CRT	70/35	Yes	8

Abbreviations: RT = Radiotherapy; CRT = Chemoradiotherapy; Gy/Fr = total dose of radiation on the larynx in Gray / number of fractions it is delivered in; HBO = Hyperbaric Oxygen Therapy; TL = Total Laryngectomy

[1] Additional radiotherapy for high mediastinal lymph node metastasis with an overlapping dose of 51 Gy delivered to the larynx

[2] Two courses of CRT for supraglottic cancer and a recurrence in the base of tongue, treated elsewhere; and an emergency laryngectomy for a bleeding ucer on the base of the tongue

[3] Patient refused surgery for hypopharynx cancer, but ultimately accepted TL for functional reasons

Table 2. Patient characteristics at time of decision to perform total laryngectomy

No	Tracheotomy	Tube feeding	Smoking*	Alcohol*	BMI#	ASA	Fistula	Deceased
1	Yes	-	+ / +	+ / +	< 18	1	Yes	-
2	-	Yes	+ / -	+ / +	< 18	1	Yes	-
3	Yes	Yes	- / -	+ / -	< 18	3	Yes	Yes
4	-	-	+ / -	+ / +	ow	1	-	-
5	Yes	Yes	+ / -	+ / -	n	2	Yes	Yes
6	-	-	+ / +	+ / +	n	2	-	Yes
7	Yes	Yes	+ / +	+ / +	< 18	2	-	Yes
8	-	Yes	+ / +	+ / +	ow	3	Yes	Yes
9	Yes	Yes	+ / -	+ / +	n	2	Yes	Yes
10	-	Yes	+ / +	+ / +	< 18	3	-	-
11	Yes	Yes	+ / -	+ / -	< 18	2	Yes	Yes
12	-	Yes	+ / +	+ / +	n	2	-	Yes
13	-	Yes	+ / -	+ / +	ow	2	-	-
14	-	Yes	+ / +	+ / +	< 18	3	-	Yes
15	Yes	Yes	+ / +	+ / +	n	3	Yes	Yes
16	Yes	Yes	+ / +	+ / -	< 18	3	-	-
17	-	Yes	+ / -	+ / -	< 18	2	Yes	-
18	Yes	Yes	+ / -	+ / -	n	2	Yes	-
19	-	Yes	+ / -	- / -	< 18	2	-	Yes
20	Yes	Yes	+ / +	+ / +	n	3	-	Yes
21	Yes	Yes	+ / +	+ / -	< 18	3	-	Yes
22	Yes	Yes	+ / +	+ / -	< 18	2	-	Yes
23	-	-	+ / -	+ / +	< 18	3	Yes	-
24	Yes	-	- / -	+ / -	n	3	-	-
25	-	Yes	+ / -	- / -	n	2	-	Yes

* Smoking or alcohol usage in the past / at time of TL.
# BMI = Body Mass Index: normal (n) = 18-25; overweight (ow)= 25-30
Abbreviations: ASA = American Society of Anesthesiologists

Quality of life

Of the 11 patients who were still alive at the start of this analysis, the QoL assessment was carried out using the European Organization for Research and Treatment of Cancer Quality of Life C30 and Head and Neck Module 35 (EORTC QLQ-C30/H&N35) questionnaires (9,10). The questionnaires were administered at the end of 2010. Also, to obtain more detailed information about functional aspects, such as swallowing and dyspnea, an additional study-specific questionnaire was administered based on earlier research in The Netherlands Cancer Institute (11).

Statistical analysis

The data were entered in a database of SPSS version 15 (SPSS Inc). The statistics were mainly descriptive. The EORTC scale and item scores were linearly transformed to a scale of 0 to 100. The scores were calculated according to the EORTC QLQ-C30 Scoring Manual (12). For overall survival, a Kaplan-Meier curve was plotted.

RESULTS

Patient, tumor, and treatment characteristics are shown in Tables 1 and 2. The median time between (C)RT and TL was 4 years (range, 1-20 years). In 13 patients (52%), there was clinically relevant comorbidity, including cardiovascular disease, chronic obstructive pulmonary disease, cerebrovascular disease, and diabetes mellitus. Thyroid-stimulating hormone values were available for 19 of the 25 patients (76%), and 8 of the 19 patients (42%) had hypothyroidism. At the time of TL, 13 patients (52%) had a body mass index (BMI) of less than 18 (calculated as weight in kilograms divided by height in meters squared). Before the TL, the patients were classified according to the American Society of Anesthesiologists (ASA). Three patients (12%) were classified as ASA 1, 12 (48%) as ASA 2, and 10 (40%) as ASA 3. Twenty-three patients (92%) were cigarette smokers before the treatment of the index tumor (median [range], 35 [10-76] pack-years), and 12 (48%) of them were still smoking at the time of the TL. Twenty-three patients (92%) had a history of alcohol use, and 14 (56%) of them still were using alcohol at the time of surgery. Six patients (24%) had been treated with HBO in attempt to prevent TL.

Indications for surgery

The decisive indication for TL was chronic aspiration with recurrent pneumonia in 12 patients (48%), persistent profuse hemorrhage of a radiation ulcer in the base of tongue/vallecula despite arterial embolization in 2 patients (8%), aspiration problems without recurrent pneumonia in 3 patients (12%), and debilitating dyspnea in 8 patients (32%). The indications were often overlapping, and, in total, 20 patients (80%) were dependent on tube feeding and 13 patients (52%) had a tracheotomy before surgery. Most indications were semi elective. Therefore, the clinical condition of all patients, except the 2 with acute TLs for intractable hemorrhage, was optimized as well as possible, but in most cases, stabilizing the malnutrition and correcting the hypothyroidism were the best outcomes that could be achieved. Of the 12 patients with recurrent pneumonia, 2 with nasopharyngeal carcinoma were severely aspirating 20 and 8 years after CRT because of constrictor pharyngeal muscle dysfunction and a lack of laryngeal elevation; they had also had several life-threatening episodes of pneumonia before the TL decision. At the time of TL, all patients were in complete remission, which was confirmed by postoperative pathologic findings revealing that no recurrent or residual tumor was present in any of the laryngectomy specimens. In 1 of the specimens (4%), overt chondroradionecrosis was found. In 2 specimens (8%), no histologic abnormalities were seen. The other 22 specimens (88%) showed typical post-RT soft-tissue alterations such as reactive and degenerative changes, fibrosis, and/or necrosis.

Surgery and complications

In 9 patients (36%), the pharynx could be closed primarily, and in 16 patients (64%), reconstruction was required; 13 pectoralis major (PM) flaps and 3 microvascular flaps (2 free radial forearm flaps and 1 anterolateral thigh flap) were used for closure. Fourteen patients (56%) had a total of 20 major postoperative complications. There were 11 cases of pharyngocutaneous fistulas requiring additional interventions; 2 cases of wound infection without fistula formation, which were treated conservatively; and 1 case of bilateral permanent hypoglossal nerve damage. Other major complications in these 14 patients were postoperative hemorrhage (n=1), which had to be controlled surgically; pneumonia (n=2); carotid blowout (n=2) (managed with ligation and PM flap reconstruction); and perioperative cerebrovascular accident (n=1). In the 9 primary closed cases, 3 patients developed a pharyngocutaneous fistula, which required 3 surgical interventions in 2 patients. The median total healing time was 10 weeks. Of the 13 patients with PM flap reconstruction, 5 developed a pharyngocutaneous fistula. In 2 of these 5 patients, the fistula healed spontaneously, 1 needed a second intervention with an additional PM flap, and 2 died with a persistent fistula. The median total healing time in the 3 spontaneously healing cases was 4 weeks (Table 3). All 3 patients who underwent reconstruction with a microvascular flap developed a pharyngocutaneous fistula, and 1 patient required an additional PM flap; the median healing time of these patients was 7 weeks. The use of a PM flap did not significantly improve healing time ($P = 0.59$). There were no statistically significant correlations between the complications and the comorbidity factors assessed (eg, BMI <18, hypothyroidism, and ASA < 1) ($p > 0.10$ in all cases). Two patients (8%) died shortly after surgery: one developed a sudden nocturnal metabolic encephalopathy due to hypoglycemia despite 15 days of stable glucose blood values with insulin and antidiabetic medications (BMI, 26-30), and the other (BMI <18) had a cerebrovascular accident during his emergency TL for persistent profuse hemorrhage. After surgery, the latter patient developed a non-healing pharyngocutaneous fistula and pneumonia and subsequently died. After discharge from the hospital, there were a total of 27 readmissions in 14 patients (56%). The median time between discharge and first readmission was 5.5 weeks (range, 0-36 weeks). The reasons for readmission were pulmonary infection requiring intravenous antibiotics (8 times in 6 patients); neck abscess requiring drainage (3 times in 2 patients); stenosis of the pharyngoesophageal segment requiring dilatation (2 times in 2 patients); hypopharyngeal hemorrhage requiring embolization (2 times in 1 patient); suspicion of tumor recurrence requiring examination with the patient under general anesthesia (3 times in 3 patients); trismus requiring surgical intervention (1 time in 1 patient); and osteoradionecrosis of the mandible requiring repeated sequestrectomy (3 times in 1 patient). Finally, there were 5 readmissions for voice prosthesis (VP) problems in 2 patients (eg, a too-wide tracheoesophageal fistula, leakage, and replacements). In 4 patients, there were overlapping indications.

Table 3. Pharynx closure/reconstruction and postoperative fistula rate, additional reconstructions and healing time of pharyngocutaneous fistula (in weeks)

Reconstruction during TL	N	Fistula (%)	Postoperative PM flap	Healing timing of fistula (in weeks)
PM flap	13	5 (38)	1	3,4,4[1]
FRFF Flap	2	2 (100)	0	6,10
ALT Flap	1	1 (100)	1	4
Primary closure	9	3 (33)	3[2]	2,10,12
Total	25	11	5[3]	

Abbreviations: PM = Pectoralis Major; FRFF =Free Radial Fore arm; ALT = Antero Lateral Thigh

[1] Three patients, as one patient died during admission with a fistula, one patient refused any further surgery for fistula

[2] Two patients received PM-flap reconstruction after 2 weeks, one of whom received a 2nd PM-flap after 12 weeks

[3] In 4 patients

Follow-up

The median survival was 30.0 months (95% CI, 17.0-NA (not applicable)). The 5-year overall survival rate was 35% (Figure 1). At the time of the final analysis (November 2011), 15 patients (60%) had died. Four patients developed recurrent cancer: 1 regional recurrence in the neck (at 4 months), 1 stoma recurrence in the patient with esophageal cancer (at 12 months), 1 local recurrence in a patient with oropharyngeal cancer (at 24 months), and 1 case of lung metastases (at 1 month). Three other patients developed a second primary cancer in the lung (at 7, 14, and 18 months, respectively). All patients with recurrent disease, metastases, or a second primary cancer died of their disease. Of the other 8 patients, 2 died after surgery and 6 died of other causes, eg, kidney failure or pulmonary decompensation.

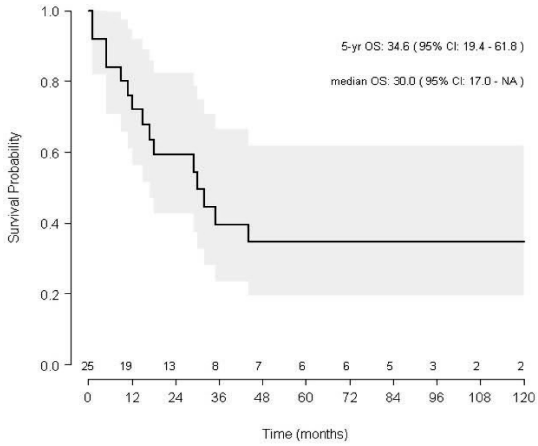

Figure 1. Overall survival (OS) after total laryngectomy for a dysfunctional larynx. NA indicates not applicable.

Functional outcomes

Table 4 shows the functional outcomes of the TL. Inspiratory stridor, present in 8 patients (32%) before TL, did not recur after surgery. Recurrent penumonia, which occurred in 12 patients (48%) before TL, also did not recur. Pulmonary problems related to TL were

seen frequently in more than half of the patients, despite the consistent use of a heat and moisture exchanger. Swallowing problems, which occurred in all but 1 patient (96%) before TL, decreased considerably, with 4 of 14 patients (29%) having persistent dysphagia at 2 years. In concordance, tube feeding decreased from 80% prior to surgery to 29% at 2 years after TL. Changes in diet consistencies are also shown in Table 4. With respect to the BMI of the patients, weight gain was reported in 62% of the patients, but precise weight data were not recorded. Twenty-two patients (88%) underwent primary tracheoesophageal puncture, with immediate insertion of an 8-mm Provox VP, and 1 patient (4%) underwent a secondary tracheoesophageal puncture (13). In 3 of these 23 cases, the VP was removed because of poor voicing due to fibrosis of the neoglottis (n=1) or unmanageable periprosthetic leakage (n=2). One patient died early after surgery and never had the opportunity to use his VP. Two patients (8%) did not receive a VP because of the complexity of the surgery. Therefore, in total, 19 patients (76%) could be rehabilitated with a VP and 6 could not. With respect to TL voice quality, the patients were grouped as having a good/reasonable voice or a moderate/ poor voice, and, over time, there was an improvement in this respect, with most patients having a good/ reasonable voice, as shown in Table 4.

Table 4. Functional outcomes over time

	Preoperative N=25 (%)	3 months N=23 (%)	1 year N=19 (%)	2 year N=14 (%)	5 year N=7 (%)
Airway compromise					
Inspiratory stridor	8 (32)	0	0	0	0
Recurrent pneumonia	12 (48)	0	0	0	0
TL-related pulmonary problems	NA	15 (65)	11 (57)	10 (71)	3 (43)
None	5 (20)	8 (35)	8 (42)	4 (28)	4 (57)
Swallow					
Aspiration	15 (60)	0	0	0	0
Dysphagia	6 (24)	8 (35)	8 (42)	4 (29)	5 (71)
Odynophagia	3 (12)	2 (9)	0	3 (21)	0
Regurgitation	0	4 (17)	3 (16)	0	0
None	1 (4)	9 (38)	7 (37)	6 (43)	2 (29)
Diet					
Tube feeding	20 (80)	12 (52)	6 (32)	4 (29)	0
Liquid diet	0	1 (4)	3 (16)	1 (7)	0
Pureed diet	2 (8)	2 (9)	2 (11)	1 (7)	1 (14)
Normal diet	3 (12)	8 (35)	8 (42)	8 (57)	6 (86)
Voice (larynx)					
Moderate / poor voice	2 (8)	NA	NA	NA	NA
Acceptable voice	23 (92)				
Voice (TL)					
Moderate / poor voice	NA	12 (52)	11 (58)	3 (21)	1 (14)
Reasonable / good voice	NA	11 (47)	8 (42)	11 (78)	6 (86)

Abbreviations: TL = total laryngectomy; NA = not applicable

QoL Questionnaires

At the start of the retrospective analysis, October 2010, a total of 11 patients (44%) were available for QoL assessment. The mean follow-up of this subgroup was 5 years (range [median], 1-10 [6] years). Results of the EORTC QoL C-30/H&N35 questionnaires are shown in Table 5. The mean score for global health in general was 63, and the mean scores on the functional scales ranged from 66 to 85 (scale, 0-100; a higher score represents better QoL). On the symptom scales (a higher score means a higher level of symptoms), the highest scores on the EORTC QLQ-C-30 questionnaire were seen for fatigue, dyspnea, and insomnia (34, 24, and 24, respectively; scale, 0-100). On the H&N35 symptom scales (here a higher score also means a higher level of symptoms), most problems were seen in speech (score 60), followed by senses, eg, smell and taste (score 56), mouth opening (score 52), and sticky saliva (score 49). On the additional study-specific questionnaire, the patients were asked to grade their current swallowing and dyspnea complaints (good, fair, moderate, or poor) and to compare their current complaints with those before surgery. Overall, most patients graded their current swallowing and dyspnea complaints as fair to good. In comparing their current complaints with complaints before TL, roughly half of the patients reported an improvement and half a deterioration of the swallowing and dyspnea complaints. All patients considered their voice quality and sputum production to be worse than before TL.

Table 5. Results obtained from the EORTC QLQ-C30 and H&N35 questionnaire (N=11), administered in October and November 2010

Qlq-C30	Mean Scores (Sd)	H&N 35**	Mean Scores (Sd)
*Global Health**	63 (15)	Pain	9 (15)
*Functional Scales**		Swallowing	35 (25)
Physical Functioning	83 (16)	Senses Problems (Smell & Taste)	56 (23)
Role Functioning	74 (24)	Speech Problems	60 (26)
Emotional Functioning	66 (32)	Trouble With Social Eating	35 (24)
Cognitive Functioning	85 (16)	Trouble With Social Contact	18 (28)
Social Functioning	68 (26)	Less Sexuality	15 (32)
*Symptom Scales **		Teeth	21 (34)
Fatigue	34 (23)	Opening Mouth	52 (35)
Nausea And Vomiting	5 (15)	Dry Mouth	21 (40)
Pain	14 (27)	Sticky Saliva	49 (41)
Dyspnea	24 (26)	Coughing	24 (33)
Insomnia	24 (30)	Felt Ill	24 (30)
Appetite Loss	3 (10)	Pain Killers	27 (47)
Constipation	9 (22)	Nutritional Supplements	27 (47)
Diarrhea	6 (13)	Tube Feeding	18 (40)
Financial Difficulties	15 (31)	Weight Loss	18 (40)
		Weight Gain	21 (40)

All Scale And Item Scores Are Linearly Transformed To A Scale Of 0-100

*A Higher Score Represents A Better Qol

** A Higher Score Means A Higher Level Of Symptoms

DISCUSSION

The main indications for TL are advanced (stage IV) laryngeal and/or hypopharyngeal cancer and residual/recurrent disease after organ preservation (C)RT. Much less frequently, this surgical procedure is required for a dysfunctional larynx after organ preservation treatment. Our series of 25 patients, representing 11% of the total 10-year TL cohort in a tertiary comprehensive head and neck cancer center, shows that the indication for TL in this case is made relatively late. The mean time of 4 years between CRT and TL certainly seems longer than that in most series of salvage laryngectomy. Most patients already had experienced several life-threatening complications, such as the need for a permanent tracheotomy in 13 patients and for permanent tube feeding in 20 patients, before the decision for TL was made. The severe weight loss and the inherent loss of condition (with half of the patients having a BMI < 18) also suggests that the indication for surgery in most cases was postponed for a long time. This is obviously not surprising, because all patients were in complete remission, and apparently both the patients and the health care professionals had to "grow" toward the belief that TL was the only option left for resolving the patients' intolerable situations and for restoring of at least some QoL. In view of that, and taking into account the frequent presence of significant comorbidities, the results in this patient cohort seem acceptable. Of course, there were many complications and frequent readmissions that the patients had to deal with, and there were 2 postoperative fatalities, but, still, most patients recovered reasonably well. In hindsight, it could be said that the decision to perform a TL should have been made earlier, while the patient was still in a better condition, but, as stated, it is obviously a difficult dilemma to sacrifice a "disease-free" organ only for functional reasons. Moreover, for 7 patients, an even longer delay would have meant that the tumor had recurred or that a second primary cancer had become apparent in the mean time, thereby overruling the indication for TL. It could be interesting, though, to compare this cohort of the 25 patients considered to have a vital indication for the TL with other patients who have had similar severe adverse effects of (C)RT but in whom the decision for TL was not made because tracheotomy and/or gastrostomy had solved the main "vital issues." Such a comparison was not in the scope of this study but is certainly worthwhile looking into in the near future. With respect to complications, it can be concluded that since 11 of our study patients (44%) developed an orocutaneous fistula, our results are in line with those published for the Radiation Therapy Oncology Group trial 91-11 (14). Meta-analysis of the risk factors that contribute to the development of a fistula after TL has shown that these risk factors include prior tracheostomy, concurrent neck dissection, and preoperative radiotherapy (15). All patients in the present study had at least 1 of these risk factors, and more than half of them had a tracheotomy. It should be stressed that treatment of comorbity issues, such as substitution of thyroid-stimulating hormone in case of hypothyroidism (42% in our series), and preoperative improvement of the nutritional status (more than half of our patients had a BMI < 18) remain imperative for the reduction of complications, even

though we did not find significant correlations in this respect. However, the small number of patients does not allow adequate statistical analysis of the association of comorbidities and complications. A possible strategy to reduce fistula rates after TL is treatment with HBO. The efficacy of HBO has been suggested in only a few case reports and series (7). In our study, 6 patients were treated with HBO before TL, but no differences were seen in the development of postoperative fistulas. Another fistula-preventive strategy is the insertion of nonirradiated, well-vascularized tissue; therefore, many authors have described the use of PM flap reconstruction in a salvage setting. Righini et al performed a study examining the use of the PM flap and noted a substantial reduction in fistula rate, from 50% to 23%. This difference, however, did not reach statistical significance (16). Patel and Keni concluded that the PM flap is a safe, reliable means of preventing pharyngocutaneous fistula at the time of salvage laryngectomy (17). In their study, 17 patients underwent a salvage laryngectomy; 10 were also treated with a PM flap reconstruction, and none of them developed a fistula. On the other hand, 4 of the 7 patients who did not receive a PM flap developed a fistula. Gil et al concluded that in a selected population of patients undergoing salvage TL who were at high risk for fistula because they had already undergone prior CRT, PM flap reconstruction could be a valuable adjunct for decreasing the risk of complications, morbidity, and the potential need for revision surgery (18). In the present study, a similar number of fistulas were seen after PM flap reconstruction or primary closure (38% and 33%, respectively). Also, all 3 patients who underwent a free-flap reconstruction developed a fistula after TL. Healing time seemed somewhat shorter after PM flap reconstruction (4 and 10 weeks, respectively), but this difference was statistically not significant ($P > 0.10$) and does not allow any definite recommendations in this respect. Van der Putten et al found postoperative complications in 56% of the patients treated with salvage laryngectomy for residual or recurrent laryngeal carcinoma after prior treatment with (C)RT, a percentage that is identical to the 56% in the present study. In their study, the postoperative mortality rate was 3% (3 of 120 patients), and we observed a mortality rate of 8% (2 of 25 patients) (19). The difference in mortality rate in both studies, however, is not significant (unpaired t test, $P=0.17$). Overall survival in the series of van der Putten and colleagues was 50%, a percentage that is somewhat higher than the 35% in the present study, which also suggests that our patients were in poorer condition at the time of TL. The results of the present study are also comparable to those of the rather similar retrospective study that was just published online by Hutcheson et al, who stated: "*Salvage TL [total laryngectomy] may improve health status by significantly decreasing the rate of pneumonia and improve quality of life by restoring oral intake in patients with refractory laryngopharyngeal dysfunction after head and neck cancer treatment. TE [tracheoesophageal] voice restoration may enhance functional outcomes in select patients treated with elective TL for dysfunction.*" (20).

The QoL interviews taken from 11 patients to compare their QoL before and after TL show an acceptable overall QoL of 63 on a scale of 0 to 100. These results are comparable to the results of Hanna et al, who compared the QoL of patients treated with CRT or TL and found mean scores of overall QoL of 63.6 and 65.8, respectively (21). Van der Putten et al studied functional outcomes, including speech. Within 1 year after TL, 87% of the patients were able to speak with a VP (19); in our study population, acceptable voice was achieved in 86% of the patients after 5 years. The limitations of this retrospective study include the small number of patients and the heterogeneity of the study population. A case-control study comparing the present patient cohort with the salvage TL subgroup could have given additional information. Such a study is planned as part of the analysis of the total 10-year TL cohort at our institution (The Netherlands Cancer Institute). However, we believe that the present results are already clinically important and can guide future counseling of patients for informed consent. The patients should understand that the surgery is not without major risks. Furthermore, some patients will still have dysphagia after TL, and although debilitating and life-threatening aspiration is "cured" by the TL, the patients should also be informed of this potential remaining dysphagia issue, even though 16 of the 25 patients (62%) in our study showed an increase in body weight. In this patient population, there are not many alternatives for treatment. Laryngotracheal separation (ie, separation of the esophagus and trachea with a permanent tracheostomy) is mostly performed in patients with intractable aspiration due to neurologic disease (22). After CRT, laryngotracheal separation most likely is also complication prone and often has the added disadvantage of leaving behind an organ in which cancer is still suspected. In conclusion, this study showed that TL for a dysfunctional larynx after (C)RT is accompanied by a relatively high incidence of major complications (56%) and mortality (8%). However, the main eliciting functional problems (aspiration, recurrent pneumonia, and dyspnea) did not recur. Dysphagia requiring pre-TL tube feeding was not completely eliminated in 20 of the 25 patients (80%), however, leaving 4 of 24 patients (29%) dependent on tube feeding. The QoL of the patients who survived appeared to be reasonable.

ADDITIONAL CONTRIBUTIONS

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CHAPTER 6

Predictive factors for pharyngocutaneous fistulization after total laryngectomy

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ABSTRACT

Objectives: Postoperative complications, especially pharyngocutaneous fistulization (PCF), are more frequent after total laryngectomy (TL) performed for salvage after (chemo) radiotherapy than after primary TL. The aim of this study was to identify the incidence of PCF, predictive factors for PCF, and the relationship of PCF to survival.

Methods: We performed a retrospective chart review of 217 consecutive patients treated with TL between 2000 and 2010. Univariate and multivariable analysis with logistic regression was used to identify factors associated with PCF. We used a Kaplan-Meier survival analysis.

Results: The overall incidence of PCF was 26.3% (57 of 217 cases). The incidence of PCF after primary TL was 17.1% (12 of 70), that after salvage TL was 25.5% (25 of 98), that after TL for a second primary was 37.5% (9 of 24), and that after TL for a dysfunctional larynx was 44.0% (11 of 25). The predictive factors for PCF were hypopharynx cancer (odds ratio [OR], 3.67; 95% confidence interval [CI], 1.74 to 7.71; P = 0.001), an albumin level of less than 40 g/L (OR, 2.20; 95% CI, 1.12 to 4.33; P = 0.022), previous chemoradiotherapy (OR, 3.38; 95% CI, 1.34 to 8.52; P = 0.010), more-extended pharyngeal resection (P = 0.001), and pharynx reconstruction (P = 0.002). The median duration of survival was 30 months (95% CI, 17.5 to 42.5); the 2-year overall survival rate was 54%. The median duration of survival of patients with PCF was 23 months (95% CI, 9.4 to 36.6), and that of those without PCF was 31 months (95% CI, 15.0 to 47.0; P = 0.421). The 2-year overall survival rate was 48% in patients with PCF and 57% in those without PCF (P = 0.290).

Conclusions: Incidence of PCF after TL is significantly higher in patients with hypopharynx cancer, previous chemoradiotherapy, a low albumin level, more-extended pharyngeal resection, or pharynx reconstruction. The occurrence of PCF does not influence the rate of survival.

INTRODUCTION

Pharyngocutaneous fistulization (PCF) is the most frequent complication in the early postoperative period after total laryngectomy (TL). The reported incidences vary widely, ranging from 2.6% to 65.5% (1). PCF increases morbidity, prolongs hospitalization, raises costs, possibly necessitates additional surgery, and delays oral feeding (1-3). Various predictive factors for PCF have been identified—most prominently, preoperative radiotherapy (RT) (4,5). In an era with an increase in the use of organ-preserving treatments, the addition of chemotherapy to RT (chemoradiotherapy; CRT) has further increased the incidence of PCF (6). The physiological basis for this setback most likely is the decreased tissue vascularization due to radiotherapy with or without chemotherapy ((C)RT). Russell et al, for example, found changes in arteries similar to early stages of atherosclerosis in patients who underwent irradiation for head and neck (HN) or breast cancer (7). 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 (3,4,8-11). 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 HN surgeons, however, tend to delay oral intake in order to prevent or limit the chance of PCF (12,13). Many studies have tried to identify predictive factors for PCF. However, thus far, no consensus has been achieved on which factors are most relevant and which of these could be influenced in order to decrease the risk of PCF. The aim of this retrospective cohort study was to identify the incidence of PCF, and the relevant predictive factors for PCF, in a 10-year cohort of TL patients in our comprehensive cancer center for whom we took into account all available patient, tumor, and treatment characteristics. Also, we assessed the influence of PCF on survival with a minimum follow-up of 2 years.

METHODS

Patient selection

The medical records of all 219 consecutive patients who underwent TL between January 2000 and May 2010 were retrospectively reviewed. Two patients were excluded from the analysis—in 1 case because of thyroid carcinoma that was treated with thyroidectomy and iodine 131 and then by TL for a local recurrence that invaded the larynx. In the other patient, information about the dependent variable (PCF) was missing. Thus, in total, 217 patients were included in the descriptive, univariate and multivariable logistic regression analyses.

Data collection

The data collection concerned the following patient characteristics: gender, age at TL, body mass index (BMI), ASA (American Society of Anesthesiologists) score, origin of index tumor, and T and N category. The surgical data collected concerned the indication for TL, mode and dose of (C)RT prior to TL, surgeon, extent of pharyngectomy, extent of neck dissection, extent of thyroidectomy, upper esophageal myotomy (yes/no), pharyngeal reconstruction method, indication and extent of pectoralis major (PM) flap reconstruction, tracheoesophageal puncture (TEP; primary/secondary), and fistula-related data, including time to clinical occurrence of PCF and its management. Because of the retrospective character of the study, not all data that are possible predictors for PCF were traceable and/or available in the medical records.

Normal course of preoperative and postoperative care

The preoperative care in our institution consists of a specific smoking cessation program for all patients with head and neck cancer (14). The nutritional status of all patients is evaluated and optimized, when indicated, before the surgery (eg, more than 10% weight loss in the 6 months prior to surgery) (15). All patients routinely receive 24 hours of perioperative prophylactic antibiotics. (The most recent protocol consists of 1,000 mg cefazolin and 500 mg metronidazole, repeated after every 4 hours of additional operation time.) All patients receive nonsteroidal anti-inflammatory drugs for pain relief, combined with antireflux medication (proton pump inhibitors). Patients were started on oral intake between days 10 and 12 until 2006, but in 2006, the policy was changed so that oral intake is started between days 2 and 4. Since the timing of oral intake in this patient cohort was not a significant factor for PCF, as elsewhere noted, this issue is not further addressed in the present report (16).

End points

The primary end point for this study was the clinical occurrence of PCF within 31 days after the operation. (Routine barium swallow assessment was not part of the protocol during the study period.) If PCF occurred, the time from TL to the first day of the diagnosis of PCF was recorded. The second end point was overall survival, defined as the time from TL to the last day of follow-up or death.

Follow-up

The last follow-up date was defined as the last visit to the outpatient clinic at the institution. The follow-up date and survival status were updated on June 1, 2012.

Statistical analysis

Analyses were performed with IBM SPSS Statistics 20.0. In addition to the descriptive statistics, univariate and multivariable analysis using binary logistic regression analysis was carried out to determine factors associated with the occurrence of PCF. Furthermore, logistic

regression analysis was performed by backward elimination with a significance level of 10% (2-sided) to eliminate parameters. Odds ratios (ORs) and 95% confidence levels (CIs) were estimated. In order to find differences in hospitalization (not a normal distribution), we used the nonparametric Mann-Whitney U test. We used Fisher's exact test to find differences in PCF incidence in several subgroups. For overall survival, Kaplan-Meier curves were plotted. In order to find differences in survival between patients with and without PCF, a P value was calculated with a log rank test. Variables with a p-value of less than 0.05 were considered statistically significant.

RESULTS

Patients

The cohort of 217 patients consisted of 175 men and 42 women (80.6% and 19.4%, respectively) with a mean age at the time of TL of 63.2 years (range, 38 to 87 years). The index tumor was located in the larynx in 154 patients (71.0%; 65 supraglottic, 58 glottic, 7 subglottic, and 24 transglottic), and in the hypopharynx in 38 patients (17.5%). Furthermore, there were 25 patients with "miscellaneous cancers": 19 (8.8%) with oropharynx cancer, 2 (0.9%) with nasopharyngeal cancer, 2 (0.9%) with cervical esophageal cancer, 1 (0.5%) with thyroid cancer, and 1 (0.5%) with oral cavity cancer. Table 1 shows a detailed overview of patient and tumor characteristics. Seventy patients (32.3%) underwent primary TL: 60 with larynx cancer, 9 with hypopharynx cancer, and 1 with thyroid cancer (with massive invasion and destruction of the thyroid cartilage). Salvage TL was performed in 98 patients (45.2%) for recurrent disease after (C)RT. Twenty-four patients (11.1%) underwent TL for a second primary because prior treatment for an earlier primary in the HN left surgery as the only curative option. The remaining 25 patients (11.5%) underwent TL for a larynx that was dysfunctional after (C)RT (results published earlier (17)).

Surgical aspects

In 86 of the 217 patients (39.6%) bilateral (selective or comprehensive) neck dissection was performed at the time of TL. In 89 (41.0%), some form of pharyngeal reconstruction was necessary (PM flap with or without a skin island, free flap reconstruction, or gastric pull-up). The indications for a PM flap (63 patients) were reconstruction of the pharyngeal lumen in 52 patients (82.5%) and reinforcement of the pharynx suture line in 11 patients (17.5%). Primary TEP with immediate insertion of an indwelling voice prosthesis (Provox2) was carried out according to protocol in 197 of 217 patients (90.8%). Secondary TEP at a later date was performed in 13 patients (6.0%). This was done according to protocol in cases of gastric pull-up (8 patients) or because of other unforeseen circumstances (eg, too-extensive tracheal resection; 5 patients). In 7 patients, no TEP was performed (3.2%): 3 cases of gastric pull-up, 2 cases with TL and total glossectomy, and 2 cases with flap reconstruction at the TEP site. The other surgical characteristics assessed are shown in Table 2.

Table 1. Patient and tumor characteristics; within brackets the number of patients for whom data were available

	N	*%*
Gender (n=217)		
Male	175	80.6
Female	42	19.4
*Age at TL (n=217)**	Mean 63.2 years Range 38-87 years	
BMI (n=213)*		
< 18	60	28.2
18-25	104	48.8
> 25	49	23.0
ASA* score *(n=216)*		
1	47	21.8
2	121	56.0
3	48	22.2
Origin of index tumor (n=217)		
Larynx *(n=154)*		
Supraglottic	65	30.0
Glottic	58	26.7
Subglottic	7	3.2
Transglottic	24	11.1
Hypopharynx	38	17.5
Miscellaneous *(n=25)*		
Oropharynx	19	8.8
Nasopharynx	2	0.9
Cervical oesophagus	2	0.9
Thyroid	1	0.5
Oral cavity	1	0.5
T stage of origin tumor (n=217)		
T1	24	11.1
T2	46	21.2
T3	51	23.5
T4	96	44.2
N stage of origin tumor (n=217)		
N0	131	60.4
N1	26	12.0
N2	54	24.9
N3	6	2.8

*** Abbreviations:** TL = Total laryngectomy; BMI = Body mass index (calculated as weight in kilograms divided by height in meters squared); ASA = American Society of Anesthesiologists

Table 2. Total laryngectomy – surgical characteristics

	N	*%*
Indication for TL (n=217)*		
Primary[1]	70	32.3
Salvage	98	45.2
Second primary[2]	24	11.1
Functional	25	11.5
(C)RT prior to TL (n=217)*[1]		
No	70	32.3
RT*	113	52.1
CRT*	34	15.7
Pharyngectomy (n=217)		
Partial[3]	139	64.1
Near total[4]	54	24.9
Circumferential	24	11.1
Neck dissection (n=217)		
No	80	36.9
Yes, unilateral	51	23.5
Yes, bilateral	86	39.6
Thyroidectomy (n=216)		
No	54	25.0
Hemithyroidectomy	143	66.2
Total thyroidectomy	19	8.8
Upper esophageal myotomy (n=214)		
No	17	7.9
Yes	185	86.4
N/A*	12	5.6
Pharynx reconstruction (n=217)		
No	128	59.0
PM flap* (with or without skin or SSG*)	63	29.0
Free flap[5]	16	7.4
Gastric pull-up[6]	10	4.6
Indication PM flap reconstruction (n=63)		
Reconstruction pharyngeal lumen	52	82.5
Reinforcement of the pharynx	11	17.5
TEP (n=217)*		
No	7	3.2
Yes, primary	197	90.8
Yes, secondary[‡]	13	6.0

[1] Seven patients in the primary TL group received prior treatment in or outside the HN area: 2 patients received low dose RT several decades ago (1 for tuberculosis and 1 for hyperthyroidism), 2 patients had prior curative treatment for cervical cancer (radical hysterectomy) and 1 patient for renal cancer (nephrectomy). Another 2 patients received CRT outside the HN area, 1 for lung cancer, and 1 for non-Hodgkin lymphoma.

[2] All second primaries were preceded by HN malignancies leaving TL as the only curative treatment option

[3] Primary closure still possible

[4] Not enough pharyngeal mucosa left for primary closure making reconstruction necessary

[5] Free flap reconstruction includes free radial fore arm flap, anterolateral thigh flap, lateral upper arm flap, free latissimusdorsi flap and free fibula flap

[6] One patient received a PM flap together with the gastric pull-up

[‡] Mean day of insertion was 47.69 days (27-92) postoperatively

*** Abbreviations:** TL = Total laryngectomy; (C)RT = (Chemo)radiotherapy; RT = Radiotherapy; CRT= Chemoradiotherapy; N/A = Not applicable; PM flap = Pectoralis major flap; SSG = Split skin graft; TEP = Tracheo-esophageal puncture; HN = head and neck.

Pharyngocutaneous fistulization

The overall incidence of PCF during admission was 26.3% (57 of 217 patients), and the median time from TL to the diagnosis of PCF was 12 days (range, 1 to 31 days). In patients treated with a primary TL, the incidence of PCF was 17.1% (12 of 70). The incidence was 25.5% (25 of 98) after salvage TL, 37.5% (9 of 24) after TL for a second primary, and 44.0% (11 of 25) after TL for a larynx that was dysfunctional after (C)RT (Table 3). Twenty-six of these 57 patients (45.6%) could be treated conservatively, and in 31 (54.4%), additional surgery was needed. The conservative treatment involved delaying or cessation of oral intake and, in some patients, administration of antibiotics. The additional surgery included PM flap reconstruction (28 patients), a sternocleidomastoid muscle flap (1 patient), necrotectomy and resuturing (1 patient), and latissimus dorsi free flap reconstruction (1 patient). Most patients remained in the hospital until the fistula was healed, but 16 patients were discharged with a fistula (16 of 217; 7.4%) and a feeding tube. In 12 of these 16 patients, the fistula ultimately closed spontaneously (9 patients) or with additional surgery (3 patients, all with a PM flap). In 3 patients, oral intake and speech rehabilitation could be resumed by inserting a second voice prosthesis in the shrunken remaining fistula (cranial to the primarily inserted voice prosthesis) in the following period (59, 59, and 60 days after clinical occurrence of PCF). In the 1 remaining patient, the fistula persisted until death. For the patients with PCF who left the hospital with restored oral intake, the median PCF healing time was 30 days (range, 3 to 120 days). With respect to hospitalization, patients with uneventful wound healing were hospitalized for 18 days (median), in contrast to 47 days for patients with PCF (Mann-Whitney U test, p=0.001). Regarding the patients with PCF, there was a significant difference in hospitalization between the group with conservative treatment and the group that needed additional surgery (median, 36 days and 58 days, respectively; Mann-Whitney U test, p=0.001; Table 4).

Table 3. Incidence and treatment of pharyngocutaneous fistulization (PCF) per TL group

Indication	**Incidence of PCF**	**Treatment of PCF formation**	
		Spontaneous closure	*Additional surgery needed*
Primary TL*	12/70 (17.1%)	6/12 (50.0%)	6/12 (50.0%)
Salvage TL	25/98 (25.5%)	7/25 (28.0%)	18/25 (72.0%)
TL for a second primary	9/24 (37.5%)	6/9 (66.7%)	3/9 (33.3%)
TL for a dysfunctional larynx	11/25 (44.0%)	7/11 (63.6%)	4/11 (36.4%)
Overall	57/217 (26.3%)	26/57 (45.6%)	31/57 (54.4%)

*** Abbreviations**: TL = Total laryngectomy.

Table 4. Hospitalization per group

	Hospitalization in days; median	*p* – value[1]
Overall	*20*	***0.001***
Patients without PCF*	18	
Patients with PCF	47	
Patients with PCF	*47*	***0.001***
Treated conservatively	36	
Required additional surgery	58	

*** Abbreviations**: PCF = Pharyngocutaneous fistula.
[1]*p* – value was calculated with the Mann-Whitney U test.

The following variables were included in the univariate analysis to identify possible predictive factors for PCF: gender, age, origin of index tumor, diabetes, BMI, preoperative tube feeding, preoperative albumin level, duration of surgery (in minutes), surgeon, ASA score, RT or CRT prior to TL, extent of pharyngectomy, extent of neck dissection, pharynx reconstruction, thyroidectomy, and timing of TEP (Table 5). The factors significant for PCF were hypopharynx cancer (OR, 3.67; 95% CI, 1.74 to 7.71; p=0.001), an albumin level of less than 40 g/L (OR, 2.20; 95% CI, 1.12 to 4.33; p=0.022), CRT prior to TL (OR, 3.38; 95% CI, 1.34 to 8.52; p=0.010), more extensive pharyngeal resection (near-total versus partial pharyngectomy OR, 3.21; 95% CI, 1.58 to 6.51; p=0.001), and pharynx reconstruction (PM flap versus no reconstruction OR, 2.59; 95% CI, 1.29 to 5.17; p=0.007). No correlations were found with the other variables—most prominently, not with RT as prior single modality treatment (OR, 1.83; 95% CI, 0.87 to 3.85; p=0.113). The incidence of PCF was lower in those with primary TEP (borderline significance of p=0.052). Analysis of the duration of surgery showed that there was a significant correlation between the duration of the surgery and PCF (data not shown). Since the time necessary for the procedure, for the most part, is a variable that is possibly confounded by other variables and influenced by the additional surgical procedures besides the TL, a subgroup analysis was performed for the 120 patients who were treated with TL (primary or salvage after RT) and did not require additional reconstruction. Table 6 shows that in this subgroup there was a significant influence of operation duration, with an increased PCF incidence in patients in whom the surgery lasted longer than 240 minutes (17 of 74 patients, or 23.0%, versus 2 of 46 patients, or 4.3%; p=0.009). Also, the 240 minutes seems to be the cutoff point for an increase in PCF for both patients with and patients without neck dissection (Table 6). Multivariable analysis using logistic regression revealed that preoperative albumin level (p=0.04) and pharyngectomy (near-total versus partial OR, 3.63; 95% CI, 1.36 to 9.72; p=0.01) were significant predictive factors for PCF (Table 7).

Table 5. Univariate analysis of possible risk factors for fistula formation. Odds ratios (OR) and *p*-values were calculated using logistic regression

	No. of patients (%)	PCF* (%)	OR (95% CI)	*p*-value
Gender	217			0.055
Male	175 (80.3)	41 (23.4)	Ref	
Female	42 (19.7)	16 (38.1)	2.01 (0.99-4.11)	
Age at TL	217			0.978
≤ 54	50 (23.0)	13 (26.0)	Ref	
55-61	50 (23.0)	13 (26.0)	1.00 (0.41-2.44)	1.000
62-71	64 (29.5)	18 (28.1)	1.11 (0.48-2.57)	0.800
72-87	53 (24.2)	13 (24.5)	0.93 (0.38-2.25)	0.864
Origin of index tumor	217			***0.002***
Larynx	154 (71.0)	33 (21.4)	Ref	
Hypopharynx	38 (17.5)	19 (50.0)	3.67 (1.74-7.71)	***0.001***
Miscellaneous	25 (11.5)	5 (20.0)	0.92 (0.32-2.63)	0.871
Diabetes	216			0.300
No	200 (92.6)	51 (25.5)	Ref	
Yes	16 (7.4)	6 (37.5)	1.75 (0.61-5.10)	
BMI*	213			0.537
< 18	60 (28.2)	19 (31.7)	1.46 (0.72-2.97)	0.289
18-25	104 (48.8)	25 (24.0)	Ref	
> 25	49 (23.0)	12 (24.5)	1.03 (0.47-2.26)	0.951
Tubefeeding pre-operative	216			0.080
No	176 (81.5)	42 (23.9)	Ref	
Yes	40 (18.5)	15 (37.5)	1.91 (0.92-3.96)	
Albumin pre-operative	174			***0.022***
< 40 g/L	70 (40.2)	26 (37.1)	2.20 (1.12-4.33)	
≥ 40 g/L	104 (59.8)	22 (21.2)	Ref	
ASA*score	216			0.074
1	47 (21.8)	8 (17.0)	Ref	
2	121 (56.0)	30 (24.8)	1.61 (0.68-3.82)	0.283
3	48 (22.2)	18 (37.5)	2.93 (1.12-7.63)	0.028
(C)RT prior to TL	217			***0.035***
Primary TL	70 (32.2)	12 (17.1)	Ref	
Prior RT	113 (52.1)	31 (27.4)	1.83 (0.87-3.85)	0.113
Prior CRT	34 (15.7)	14 (41.2)	3.38 (1.34-8.52)	***0.010***
Pharyngectomy	217			***0.001***
Partial[1]	139 (64.1)	23 (16.5)	Ref	
Near total[2]	54 (24.9)	21 (38.9)	3.21 (1.58-6.51)	***0.001***
Circumferential	24 (11.0)	13 (54.2)	5.96 (2.38-14.94)	***0.001***
Neckdissection	217			0.882
No	80 (36.9)	22 (27.5)	Ref	
Yes, unilateral	51 (23.5)	14 (27.5)	1.00 (0.45-2.19)	0.995
Yes, bilateral	86 (39.6)	21 (24.4)	0.85 (0.43-1.71)	0.651
Pharynx reconstruction	217			***0.002***
No reconstruction	128 (59.0)	22 (17.2)	Ref	
PM flap* (with or without skin or SSG*)	63 (29.0)	22 (34.9)	2.59 (1.29-5.17)	***0.007***
Free flap[3]	16 (7.4)	8 (50.0)	4.82 (1.63-14.22)	***0.004***
Gastric pull-up[4]	10 (4.6)	5 (50.0)	4.82 (1.29-18.07)	***0.020***
Thyroidectomy	216			0.284
No	54 (25.0)	16 (29.6)	Ref	
Yes, hemi-thyroidectomy	143 (66.2)	38 (26.6)	0.86 (0.43-1.72)	0.668
Yes, total thyroidectomy	19 (8.8)	2 (10.5)	0.28 (0.06-1.35)	0.113
TEP*	217			0.052
Primary puncture	197 (90.8)	48 (24.4)	Ref	
Secondary or no puncture	20 (9.2)	9 (45.0)	2.54 (0.99-6.50)	

[1] Primary closure still possible

[2] Not enough pharyngeal mucosa left for primary closure making reconstruction necessary

[3] Free flap reconstructions include free radial fore arm flap, anterolateral thigh flap, lateral upper arm flap, free latissimusdorsi flap and free fibula flap

[4] One patient received gastric pull-up and PM flap

*** Abbreviations**: PCF = Pharyngocutaneous fistula; TL = Total laryngectomy; RT = Radiotherapy; CRT = Chemoradiation; ASA = American Society of Anesthesiologists; BMI = Body mass index (calculated as weight in kilograms divided by height in meters squared); PM = Pectoralis major flap; SSG = Split skin graft; TEP = Tracheo-esophageal puncture.

Table 6. Subgroup-analysis representing all patients who underwent primary TL or TL after RT** and primary pharyngeal mucosa closure. In total, and after categorization by neck dissection**

	No. of patients	PCF**(%)	*p*-value*
Duration of surgery (minutes)	120		***0.009***
< 240	46	2 (4.3%)	
≥ 240	74	17 (23.0%)	
No neckdissection			0.072
< 240	32	2 (6.3%)	
≥ 240	15	4 (26.7%)	
Uni- or bilateral neckdissection			0.061
< 240	14	0 (0%)	
≥ 240	59	13 (22.0%)	

**p* – value was calculated with the Fisher's Exact test.
*** **Abbreviations**: TL = Total laryngectomy; RT = Radiotherapy; PCF = Pharyngocutaneous fistulization

Table 7. Multivariable analysis using logistic regression by backward elimination method

	OR* (95% CI)	*p*-value
Origin of index tumor		0.10
Larynx	1.00	
Miscellaneous	0.37 (0.09-1.56)	0.18
Hypopharynx	1.74 (0.56-5.38)	0.34
Albumin pre-operative		***0.04***
< 40 g/L	2.23 (1.03-4.83)	
≥ 40 g/L	1.00	
(C)RT* prior to TL*		0.21
Primary TL	1.00	
Prior RT*	2.15 (0.85-5.44)	0.11
Prior CRT*	2.51 (0.72-8.70)	0.15
Pharyngectomy		***0.01***
Partial	1.00	
Near total	3.63 (1.36-9.72)	***0.01***
Circumferential	6.37 (1.52-26.63)	***0.01***

* **Abbreviations**: OR = Odds Ratio; (C)RT = (Chemo)radiotherapy; TL = Total Laryngectomy; RT = Radiotherapy; CRT = Chemoradiotherapy.

Follow-up and survival

The median follow-up was 24 months (range, 0 to 144 months). The median survival was 30 months (95% CI, 17.5 to 42.5). The 2-year overall survival was 54% (Figure 1). At the time of analysis, 135 patients (61.6%) had died. Figure 2 shows the differences in survival rates for patients with and without PCF. Patients with PCF had a median survival of 23 months (95% CI, 9.4 to 36.6), and those without PCF had one of 31 months (95% CI, 15.0 to 47.0; p=0.421). The 2-year overall survival rates were 48% and 57%, respectively (p=0.290).

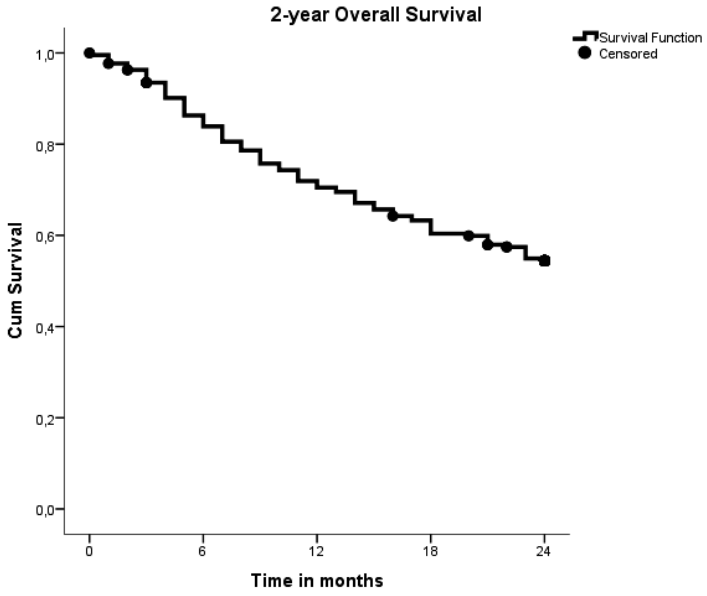

Figure 1. Two-year overall survival rate according to Kaplan-Meier analysis

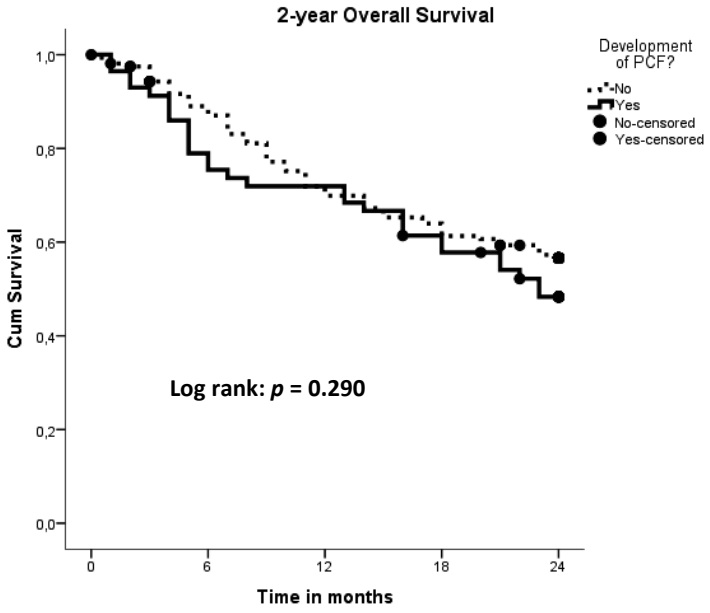

Figure 2. Differences in survival between patients with and without a pharyngocutaneous fistula (PCF) according to Kaplan-Meier analysis

DISCUSSION

This 10-year cohort study of a consecutive series of 217 patients shows an overall incidence of PCF of 26.3%. As expected, the PCF incidence was lower for primary TL (17.1%) than for salvage TL, TL after prior treatment for another HN malignancy, or TL for a larynx that was dysfunctional after (C)RT, which had incidences of 25.5%, 37.5%, and 44.0%, respectively. The overall incidence of 26.3% is quite high, but is comparable to those of many other studies in the literature. Also, the higher incidences for the various "salvage" procedures are in line with the literature (3,5,6,11). The use of organ-preserving treatments such as RT and CRT for advanced HN cancer is increasing, and therefore TL nowadays is most often used as a salvage procedure (in this study, two thirds of the procedures). Thus, the incidence of complications such as PCF after TL has also increased (6). However, the literature regarding the role of (C)RT prior to TL as a predictive factor for PCF formation is still ambiguous. In contrast to CRT, previous RT did not increase the incidence of PCF in the present study. This finding is in concordance with those of some other studies, which also indicated RT as a nonsignificant contributor and CRT as a significant contributor to PCF (11,19). With respect to the role of RT alone, several studies reported higher incidences of PCF in patients treated with single-modality RT before TL, (3-6,10,18) whereas other studies reported that RT prior to TL had no influence (8,11,21). With respect to the other predictive factors in the present study, univariate analysis did reveal a hypopharynx primary, a low preoperative albumin level (less than 40 g/L), a longer duration of surgery, a more extensive pharyngeal resection, and flap reconstruction as significant predictive factors for PCF. A hypopharynx primary has previously been described by some authors as a predictive factor (8,22). A low preoperative albumin level was also reported earlier as a predictive factor (8,23,24). However, one should keep in mind that different cutoff values were in use; ie, Qureshi et al and Boscolo-Rizzo et al used 35 g/L as a cutoff value, and Tsou et al used 25 g/L (8,23,24). The cutoff value of 40 g/L in the present study was based on the values recently applied by Sherman et al (25). Those authors identified 4 parameters, including a preoperative level of albumin below 40 g/L, that predicted the chance of larynx preservation after (C)RT (25). It is fair to mention, though, that if a cutoff value of 35 g/L had been used in the present study, the group with a lower albumin level would have been too small for a meaningful statistical analysis. The role of two other possible factors in PCF mentioned in the literature, prophylactic perioperative antibiotics and postoperative antireflux therapy, could not be evaluated, since both are part of the standard clinical path in our center (26). As has also been reported by others, in the present study more-extensive pharyngeal resection and flap reconstruction, representing the extensiveness of surgery, were significant predictive factors for PCF (8,22,27). Also, a longer duration of surgery was a significant predictive factor. However, the duration of surgery is a variable that is possibly confounded by other variables. Obviously, flap reconstruction and neck dissection require more surgery time. Therefore, subgroup analysis was performed to identify whether time was an independent

predictive factor for PCF. This, indeed, seems to be the case; in the subgroup of patients who were treated with primary TL and with single modality RT before TL and primary pharyngeal mucosa closure, a significantly higher PCF rate was found in the group operated on for more than 240 minutes. Also, after categorization by neck dissection, patients operated on for more than 240 minutes had a higher PCF rate, although the difference was not significant.

The difference may be due to experience, as senior HN surgeons can usually operate more quickly than surgeons in training. However, "surgeon" was not a significant factor in this study. Only a few reports have discussed this topic; some authors found a significant increase in PCF if the patient was treated by a surgeon in training, whereas others could not confirm this difference (5,8). In any case, it seems reasonable to take operation time into account when (salvage) TL has to be performed.

Another issue debated in the literature is whether in cases of salvage TL, the use of a PM flap reconstruction can prevent PCF (28-31). The hypothesis is that the transposition of well-vascularized healthy tissue could improve wound healing, and thus could prevent postoperative complications such as PCF. Sousa et al reported on 31 patients with salvage TL in whom the pharyngeal mucosa was either closed primarily or additionally reinforced with a PM flap (29). They found a significant incidence of PCF in patients whose pharynges were closed primarily without reinforcement. However, their study included a limited number of patients, and the choice of using a flap or not was not randomized (29). Righini et al reported, in a series of 60 consecutive patients treated with RT prior to TL, a significantly lower incidence of PCF—23%, as opposed to 50%—when PM flap pharyngeal suture reinforcement was used (31). Fung et al did not find any advantage of free flap reconstruction in preventing PCF (32).

In the present study, these findings could not be confirmed or invalidated, as it was not possible to retrieve these data retrospectively in enough detail for a meaningful analysis. In the present study, the vast majority of patients underwent primary TEP with immediate insertion of an indwelling voice prosthesis (Provox2). The results of the statistical analysis that indicated a lower PCF incidence in the primary TEP subgroup thus should be interpreted with caution. They should also be interpreted with caution because the TEP may have been either deemed too risky by the surgeon or delayed or not applicable according to the protocol (as in gastric pull up). Nevertheless, the lower incidence of PCF in the patients who underwent prosthetic surgical voice restoration still suggests that this method to restore oral communication and thus the quality of life after TL is relatively safe and probably has no relationship to PCF even in salvage surgery.

This study shows once more that the duration of hospitalization in patients with PCF is significantly longer than that of patients without PCF. Moreover, patients who required additional surgery were discharged significantly later than were patients in whom the PCF could be managed conservatively. These results underline that PCF indeed substantially lengthens hospitalization and considerably raises costs.

It should be noted that PCF is not known to be a predictor for overall survival, as the survival rates were not significantly different for patients with and without PCF in the present study, and the only other study in the literature to assess this issue found similar results (5).

Obviously, a retrospective study always has its limitations. Cause-and-effect relations are difficult to establish, and thus, the results should be interpreted with caution. Furthermore, the present study had a small sample size. However, the validity of the findings is strengthened by the facts that the study concerned a consecutive group of patients from a single institution, all data on the indications for TL were included, and only a few exclusions from the analysis were necessary because of missing data. Most factors predictive for PCF cannot be influenced in order to reduce the incidence of this dismal complication after TL. However, optimizing local wound healing potential by optimizing the patient's preoperative nutritional status and condition, using well-vascularized reconstructive flaps, and reducing the surgery time as much as possible are factors that potentially can decrease PCF incidence, and therefore warrant special attention.

In conclusion, in the present study, previous CRT, hypopharynx malignancy, low preoperative albumin level (less than 40 g/L), longer duration of surgery, more-extensive pharyngeal resection, and flap reconstruction were identified as the main predictive factors for PCF.

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CHAPTER 7

Early oral intake after total laryngectomy does not result in increased pharyngocutaneous fistulization

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ABSTRACT

Objective: Timing of oral intake after total laryngectomy (TL) is mostly delayed until postoperative day 10–12, under the assumption that this limits the incidence of pharyngocutaneous fistulization (PCF). However, early oral intake could be advantageous and could reduce costs, providing that it does not lead to increased PCF. Comparison of PCF incidence in traditional 'late' oral intake protocol (start at postoperative day 10–12; LOI) and in early oral intake protocol (start at postoperative day 2–4; EOI).

Methods: Retrospective cohort study comparing two different oral intake protocols in 247 consecutive patients laryngectomized between early 2000 until mid 2006 (LOI; N = 140), and mid 2006 until mid 2012 (EOI; N = 107).

Results: Both groups were comparable in terms of sex, age, origin of tumor, and TL indication, except for the American Society of Anesthesiologists score (ASA), which was slightly more favorable in the LOI group (p = 0.047). Compliance with the oral intake protocols during both periods was good: the median day of starting oral intake was day 11 (range 6–103) in the LOI group vs. day 3 (range 2–84) in the EOI group (p = 0.001). The incidence of PCF was not significantly different between the two groups (25% for LOI and 32% for EOI; Fisher's exact: p = 0.255). In addition, no association was observed between the timing of oral intake and PCF (HR = 0.995; CI 0.98–1.01; p = 0.364).

Conclusion: This study suggests that early oral intake is safe and does not increase pharyngocutaneous fistulization.

INTRODUCTION

Pharyngocutaneous fistulization (PCF) is a common and serious complication after total laryngectomy (TL) (1). It is one of the most frequent postoperative adverse events, substantially increasing morbidity (2), potentially necessitating additional surgery (3), considerably prolonging hospitalization (4), delaying voice rehabilitation and oral intake (3), and increasing costs (5). The reported incidence of PCF varies widely, ranging from 2.6 to 65.5% (6). Various studies have identified factors associated with PCF, such as previous radiotherapy and/or chemoradiotherapy (7), (older) age at the time of the surgery (8), origin of the tumor (hypopharynx more than larynx) (9), simultaneous neck dissection (4), extensiveness of surgery (1), low postoperative hemoglobin levels and diabetes (3). Moreover, some studies suggest early oral intake (EOI) as a possible predisposing factor (10,11). Therefore, surgeons have been delaying oral intake until 10–12 days postoperatively as a means to lower PCF incidence. 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' (12). Also, the presence of a nasogastric feeding tube (NGT) moving alongside the pharyngeal suture line, which can be painful or irritating and might promote PCF more than LOI, prevents it (13). 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 (14-17). 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 (18 –20).

In 2006, these considerations led to the introduction of an EOI protocol (starting oral intake on day 2–4) at our tertiary comprehensive cancer center. This change in protocol has since been monitored continuously. In this clinical study, PCF incidence and duration during the EOI protocol used over the last 6 years are compared to those occurring with the traditional LOI protocol used over the preceding 6 years.

METHODS

The patient population of this retrospective cohort study consisted of all 247 patients who were laryngectomized at a tertiary comprehensive cancer center between January 2000 and July 2012. Indications for TL were primary treatment for advanced (T4) laryngeal cancer, salvage surgery after (chemo-) radiotherapy, treatment for a second primary head and neck tumor, or treatment for a dysfunctional larynx after (chemo-) radiotherapy. One additional patient, on whom no data on PCF and oral intake had been reported, was excluded from

further analysis. The study cohort consisted of two groups: one comprising 140 patients in whom oral intake according to the prevailing protocol started on day 10–12 postoperatively (LOI group) and one comprising 107 patients in whom, oral intake (liquid) started on day 2–4 postoperatively and water on the first postoperative day (EOI group). In both groups, intravenous fluids were stopped once the patient's oral intake was adequate, and in case PCF was diagnosed patients were fed through a (reinserted) NGT. Before March 2006 the LOI protocol was used. The EOI protocol was introduced in April 2006 and, under continuous monitoring, has remained in effect since then. Patients' sex, age at TL, ASA score, diabetes, origin of the tumor, indication of TL, neck dissection, pharyngectomy, type of reconstruction, PCF during hospitalization, day of occurrence of PCF, day of starting oral intake, and total duration of hospitalization were recorded.

Statistics

Statistical analyses were conducted using IBM ® SPSS ® Statistics 20.0. Descriptive statistics were used to characterize the variables in both the LOI group and EOI group. Chi square tests and an independent t test were carried out to determine whether the two oral intake groups were comparable. The Mann–Whitney U test was used to compare the median days of starting oral intake. To study the association between oral intake and PCF formation a Cox regression was applied. Start of oral intake was included in this model as a time dependent variable. A Kaplan–Meier analysis was performed to compare the duration of hospitalization in the LOI group to that in the EOI group. To estimate a p value for the difference between the survival curves of the two groups, a log-rank test was used. A p value < 0.05 was used to indicate significance.

RESULTS

Patient and tumor characteristics for both the LOI group and the EOI group are summarized in table 1. No significant differences were found between the two groups regarding any of the known risk variables, except for the ASA score (p=0.047). In the LOI group 23.7% of the patients were classified as having an ASA 1 score, compared to 14.0% in the EOI group. ASA 2 scores were comparable in both groups (56.1 and 58.9%, respectively), but in the LOI group 20.1% of the patients were classified as ASA 3 versus 27.1 % in the EOI group. In the LOI group, 11 patients never started oral intake during hospitalization compared to seven patients in the EOI group. Compliance of the medical and nursing staff with the oral intake protocol during both periods was good. The median day of starting oral intake was day 11 (range 6–103 days) in the LOI group, versus day 3 (range 2–84 days) in the EOI group, a significant difference (p=0.001). Patients who underwent standard TL started significantly earlier with oral intake than patients who needed additional reconstructive surgery. In the total group, the median start of oral intake for patients undergoing standard TL was day

9 (range 2–84 days) compared to day 11 (range 2–103 days) in the reconstruction group (Mann–Whitney U test: p=0.001). In the LOI group, patients started at day 10 (range 6–72 days) and day 12 (range 8–103 days), respectively (Mann–Whitney U test: p=0.001). In the EOI group, standard TL patients started oral intake at day 3 (range 2–84 days) compared to day 4 (range 2–70 days) in case of reconstruction (Mann–Whitney U test: p=0.009) (table 2). After exclusion of patients with PCF, the differences in timing of oral intake in patients with standard TL compared to patients with additional reconstructive surgery were still significant (data not shown). The median duration of hospitalization in the LOI group was 20 days (range 12–115) vs. 21 days (range 2–147) in the EOI group. During hospitalization, five patients in the LOI group died, on postoperative day 12, 53, 53, 65 and 90, respectively. Data on one additional deceased patient in the LOI group was missing. In the EOI group one patient died during hospitalization (on day 2). As shown in figure 1, there is no difference in duration of hospitalization between the two groups (Chi square 2.584; p=0.108). Subgroup analysis for patients without PCF also showed no significant difference in hospitalization duration between the LOI and the EOI groups (median 18 days versus 17 days, respectively; p=0.815).

PCF occurred in 35 patients (25.0%) in the LOI group and in 34 patients (31.8%) in the EOI group; statistically not a significant difference (p=0.255). The mean day of occurrence of PCF was 13.7 days (range 1–31) in the LOI group and 12.2 days (range 2–37) in the EOI group. With respect to the occurrence of PCF after start of oral intake, necessitating reinsertion of the NGT, this happened in 12 of the 35 PCFs (34.3%) in the LOI group, and in 21 of the 34 PCFs (61.8%) in the EOI group, a significant difference (p=0.014). For the LOI and EOI groups overall, this means that oral intake had to be discontinued for 9% (12/140), and 20% (21/107) of the patients, respectively. The difference in ASA scores between the LOI and EOI groups did not correlate with the occurrence of PCF (p=0.417).

There was also no association between PCF formation and the timing of oral intake (HR=0.995; CI 0.98–1.01; p=0.364).

Table 1. Patient characteristics and tumor characteristics for both the LOI-group and the EOI-group

	Late Oral Intake Group	%	Early Oral Intake Group	%	*p*-value
Sex					0.942†
Male	112/140	80.0	86/107	80.4	
Female	28/140	20.0	21/107	19.6	
Age at TL	Mean 63.1 years Range 38-87 years		Mean 63.5 years Range 41-85 years		0.774*
ASA					0.047†
1	33/139	23.7	15/107	14.0	
2	78/139	56.1	63/107	58.9	
3	28/139	20.1	29/107	27.1	
Diabetes					0.887†
Yes	11/139	7.9	9/107	8.4	
No	128/139	92.1	98/107	91.6	
Origin tumor					0.899†
Hypopharynx	24/140	17.1	17/107	15.9	
Larynx	97/140	69.3	77/107	72.0	
Miscellaneous	19/140	13.6	13/107	12.1	
Indication of TL					0.985†
Primary	40/140	28.4	30/107	28.0	
Salvage	66/140	46.8	49/107	45.8	
2nd primary	19/140	14.2	15/107	14.0	
Functional	15/140	10.6	13/107	12.1	
Neck dissection					0.324†
None	28/140	20.0	27/107	25.2	
Ipsilateral	29/140	20.7	19/107	17.8	
Bilateral	83/140	59.3	61/107	57.0	
Pharyngectomy					0.592†
Partial	126/140	90.0	94/107	87.9	
Total	14/140	10.0	13/107	12.1	
Reconstruction					0.704†
No	81/140	57.9	65/107	60.7	
PM flap	20/140	14.3	10/107	9.3	
PM flap + skin or SSG	21/140	15.0	23/107	21.5	
Free flap + gastric pull-up	18/140	12.9	9/107	8.4	

† Chi-square was used to determine if the 2 groups were statistically different

* The independent t-test was used to determine if the 2 groups were statistically different

Abbreviations: TL = Total laryngectomy; ASA = American Society of Anesthesiologists; PM = Pectoralis Major; SSG = Split Skin Graft

Table 2. Timing of oral intake in patients with standard TL compared to patients with additional reconstructive surgery

	Standard TL	**Reconstruction**	***p*-value***
Total group**	9 (2-84)	11 (2-103)	0.001
LOI-group**	10 (6-72)	12 (8-103)	0.001
EOI-group**	3 (2-84)	4 (2-70)	0.009

* *p*-value is based on the Mann-Whitney U test

** Median day oral intake was initiated (range)

Abbreviations: TL = Total Laryngectomy; PCF = Pharyngocutaneous fistula; LOI = Late Oral Intake; EOI = Early Oral Intake

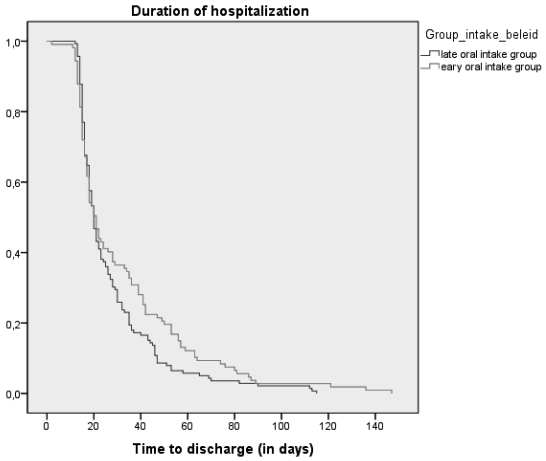

Figure 1. Kaplan-Meier analysis regarding duration of hospitalization between the LOI-group and the EOI-group
Chi-square: 2.584; $p = 0.108$

DISCUSSION

This retrospective study in a consecutive series of 247 patients over a 12-year period, comparing a traditional LOI protocol (postoperative day 10–12) with EOI (day 2–4), suggests that EOI is safe and does not increase PCF. This is in concordance with several other studies, although in most of these studies some selection bias was apparent. Medina and Khafif concluded that starting oral intake after 48 h is a safe clinical practice, but unfortunately they excluded patients with previous radiotherapy (except patients with T1–T2 glottic carcinoma treated with radiotherapy including just the larynx), and partial pharyngectomy (15). Boyce et al. studied the data of 94 patients who underwent TL with primary pharyngeal closure (14). Patients were excluded if they had undergone more extensive pharyngeal reconstruction. No differences in PCF rates were observed between the patients who started oral intake on day 5 or sooner compared with patients who started oral intake from day 6 onwards (14). Aswani et al. recommended starting oral intake on day 2 based on their results (21). However, they excluded patients who needed pharyngeal reconstruction with myocutaneous flaps.

In the present study, all patients who underwent TL, irrespective of whether this procedure was combined with neck dissection and/or reconstruction, or of the indication (primary treatment, salvage procedure, second primary treatment, or dysfunctional larynx after (chemo) radiotherapy), were included. Thus, the results presented cover an unselected consecutive group of laryngectomized patients. This also explains the rather high total incidence of PCF (28%) compared to other studies discussing effects of the timing of oral

intake. Concerning reconstruction simultaneously to TL, patients who underwent standard TL started significantly earlier with oral intake than patients who were reconstructed. Similar results were found when analyzing the LOI and EOI groups separately or when patients with PCF were excluded. This was to be expected, since patients with reconstruction usually start later with oral intake than patients after standard TL. However, it is still interesting to note that in the reconstructed group the EOI protocol could also be adopted successfully, leading to an earlier start of oral intake at (median) day 4 in stead of day 12 under the LOI protocol.

The historical paradigm has been to start oral intake not earlier than on postoperative day 7–10 (14,15), and although recent studies have shown that EOI is a safe clinical practice, there is still no consensus among head and neck surgeons worldwide when to start oral intake after TL. It is believed that EOI delays the healing process of the pharyngeal suture line, and this is considered the main reason for surgeons not to start oral intake too early (22,23). Interestingly, however, most skin incisions heal within 1–2 days in a watertight manner; apparently, the pharyngeal mucosa suture line does not behave differently in this respect (15,16). To some degree 'oral intake' still takes place, because one can never fully prevent patients from swallowing saliva, and the subsequent movement of the pharyngeal suture line could then also contribute to the occurrence of PCF (15). Another argument in favor of EOI is that with LOI the movements of the NGT are stressing the pharyngeal suture line longer, and therefore the NGT achieves the opposite from what is intended with respect to PCF (4,14). Seven et al. and Aswani et al. compared patients who started oral intake on day 1 and day 2, respectively, with patients who were fed via a NGT through the tracheoesophageal puncture (TEP) until the seventh postoperative day (17,21). Despite the fact that feeding through the TEP eliminates the possible negative role of the NGT in the pharynx, both studies did not observe differences in PCF rates. Aprigliano (24), in a retrospective study on 625 total laryngectomies, reported that patients experienced the NGT as highly unpleasant. This was the reason to abandon the use of a NGT and to start oral intake on the 3rd postoperative day, with a reported PCF incidence of 9.1 % (57/625) (24).

From a psychological perspective, it could be valuable to start oral intake early in the postoperative period, because this is encouraging for patients in that they seem to be returning to normalcy (more) quickly. The downside of this approach, however, is that, if at a later stage PCF is diagnosed and the patient already has commenced oral intake, its interruption will certainly be a disappointment. This was the case in some 60% of the PCF cases in the EOI group; at the same time, this was also not uncommon in the LOI group, where it occurred in roughly one-third of the PCF patients. Nevertheless, for the simple reason that oral intake is started earlier, under an EOI protocol more patients will have to deal with a discontinuation of already resumed oral intake—something to take into account in patient counseling. A possible advantage of an early start with oral intake is that it could potentially shorten hospital stay, thus reducing costs. Aswani et al. reported a significantly

shorter hospital stay for the subgroup of patients who were fed from day 2 after TL, but this was after exclusion of PCF patients in both the EOI and LOI group (21). Overall, however, these authors did not find a significant difference in hospital stay between both groups. Medina and Khafif found a significant decrease in hospital stay from 12 days in the LOI group to 7 days in the EOI group (15). In the present study, however, no significant difference in hospital stay between the two groups was found, nor after exclusion of patients with PCF, as in the study of Aswani et al. The reason for this is that resumption of oral intake is not the only factor determining discharge in our institute; successful restoration of oral communication is also considered relevant. Patients start with voice and speech rehabilitation not sooner than day 10–12, and are only discharged if speech proficiency is satisfactory. In future this may change, however, since possibilities for providing the necessary (outpatient) rehabilitation support have recently increased.

Obviously, a retrospective study with a historical comparison such as this will always have its limitations. However, one of the strengths of the present study is that a consecutive group of patients was included with exclusion of only one patient because of missing postoperative data.

Moreover, there were no changes in surgical techniques and/or aftercare during a 12-year period, except for the timing of oral intake. In addition, the two patient cohorts did not differ with respect to known risk factors, such as (chemo-) radiotherapy, origin of the primary tumor, and extent of the disease, the resection and/or the reconstruction, with the exception of the ASA score, which was actually more unfavorable in the EOI group. Also, the fact that the study was performed in a single institute, thus precluding possible differences between hospitals, speaks for the validity of the study.

In conclusion, the results of this retrospective study in a consecutive series of 247 patients over a 12-year period suggest that the timing of oral intake does not influence the occurrence of PCF and that resuming oral intake early postoperatively is safe.

ACKNOWLEDGMENTS

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PART III

POSTLARYNGECTOMY REHABILITATION FACETS

CHAPTER 8

An introduction to speech rehabilitation following total laryngectomy

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[*Speech rehabilitation following a total laryngectomy*].
Ned Tijdschr Tandheelkd. 2012;119:357-361 (English translation)

ABSTRACT

Total laryngectomy is performed on patients with advanced larynx or hypopharynx cancer, or due to a relapse after prior radiotherapy or chemoradiation. Speech rehabilitation is vital for the functioning of patients. Voice prostheses or an electrolarynx can be used for speech rehabilitation. Oesophageal speech can also be used. In recent decades, voice prostheses in particular have undergone significant development. They can be considered the standard technique for rehabilitation. For dentists, it is important to realize that the anatomy in these patients has changed. In addition, many have a prior history of radiotherapy and thus an increased risk of xerostomia and osteoradionecrosis. In cases where maxillofacial surgery is indicated, the chance of osteoradionecrosis is higher. If extraction is being considered, consultation with a head and neck oncology centre is necessary.

ANATOMY AND FUNCTION OF THE LARYNX

The larynx is composed of several cartilages that are interconnected by ligaments and muscles. The cartilaginous skeleton is composed of cricoid, thyroid, epiglottis and arytenoids cartilages (Figure 1). It receives its blood supply from the superior thyroid artery and vein and the inferior thyroid artery and vein. Motor and sensory innervation of the larynx and trachea is provided by the inferior laryngeal nerves (recurrent laryngeal nerve) and superior laryngeal nerves (branches of the vagus nerve.) The hypopharynx is part of the pharynx and is divided at the top by an imaginary plane, which passes through the hyoid bone. The lower border is formed by the base of the cricoid.

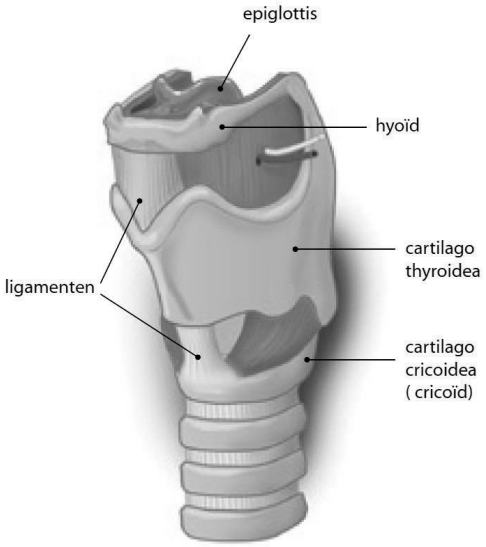

Figure 1. Anatomy of the larynx.

The primary function of the larynx is to work as a sphincter. The sphincter function is vital: the larynx protects the lower airway during swallowing and prevents aspiration. Its secondary function is phonation, which is vital for communication. To produce sound, air is forced through closed vocal cords that vibrate to create a voiced sound. The sound is converted into intelligible speech through coordination with breathing, vocal cord closure and movement of the mouth and throat cavities (articulation). The final function of the larynx is its role during coughing.

LARYNX TUMORS

Epidemiology

In the Netherlands, approximately 2800 patients are diagnosed with head and neck cancers every year. The largest group, involving approximately 700 patients, has larynx cancer, mostly originating in the vocal cords. Hypopharynx cancer is diagnosed in 190 patients every year. A total of 95% of all larynx and hypopharynx tumors are squamous cell carcinomas. The primary risk factors are alcohol and smoking (1). Glottic tumors are caused by smoking habits, while supraglottic cancers and hypopharynx cancers are caused by a combination of smoking and drinking. Men are more likely to develop larynx cancer than women. However, the incidence of supraglottic and glottic cancers in males is gradually decreasing, while the number of cases in females has been stable or has shown a slight increase during two decades (1989-2009) (Figure 2). The incidence curves for males and females seem to be converging. This is primarily because smoking and drinking habits among men and women are becoming increasingly similar. The mortality rate for larynx and hypopharynx cancers is an average of 223 for the years 2000-2010 and 100 for the years 1989-2003 respectively (Netherlands Cancer Registry, 2012; Oncoline, 2012) (2,3). The tumor was at a glottic level for 65-70% of patients and at a supraglottic level for 30% of patients. Subglottic tumors are rare.

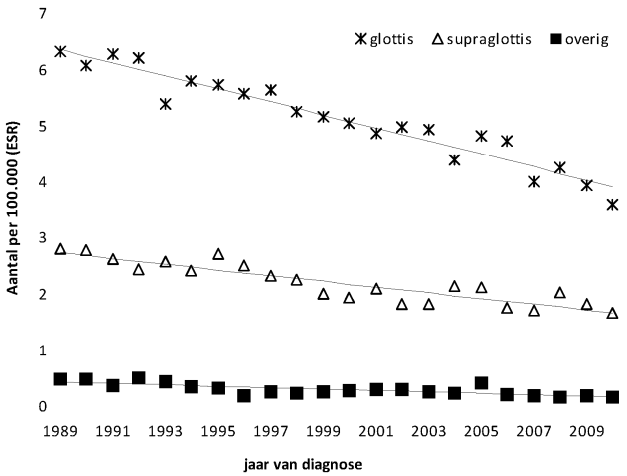

Figure 2A. Incidence of larynx cancer in males per subsite (Netherlands Cancer Registry 2012).

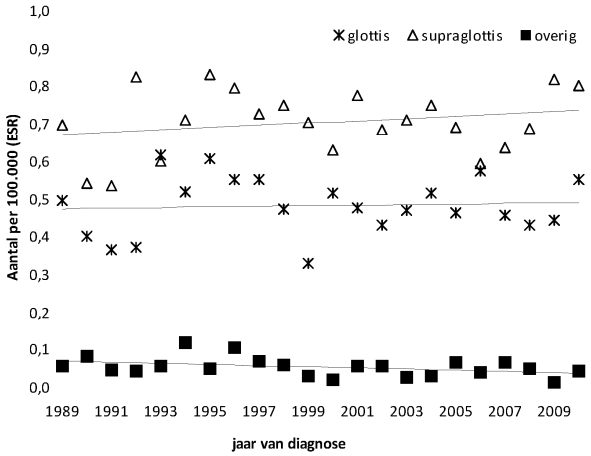

Figure 2B. Incidence of larynx cancer in females per subsite (Netherlands Cancer Registry 2012).

Symptomatology, diagnosis and staging

The symptomatology depends on the location of the tumor. In case of primary glottic cancer the patient usually presents with hoarseness. Patients with supraglottic cancer or hypopharynx cancer generally present later because the tumor does not give any symptoms until a late stage. Patients subsequently present with a sore throat, pain and difficulty when swallowing, a lump in the throat, halitosis or pain that radiates to the ear. Shortness of breath occurs when the tumor obstructs the larynx. Some patients do not have any symptoms and present with a swelling in the neck, which upon further examination turns out to be a cervical lymph node metastasis of larynx cancer.

The diagnosis and staging are based on (endoscopic) examination of the throat, nose and ear region, computed tomography (CT) imaging and/or magnetic resonance imaging (MRI) and histological analyses of biopsies usually performed under general anaesthesia. In the centre in Amsterdam, where the authors of this article work, all patients are referred to a dentist for a focus examination prior to treatment and a panoramic x-ray is performed. Periapical abnormalities are usually followed by extraction in order to prevent osteoradionecrosis after radiotherapy.

Treatment

Depending on the stage of the tumor, the treatment of larynx and hypopharynx cancer consists of (chemo)radiotherapy or surgery. The advantage of (chemo)radiotherapy treatment is that it preserves the larynx. The functional results are usually better as a result. The surgical procedure for stage 3 or 4 larynx cancer involves a total laryngectomy, alone or in combination with a (selective) neck dissection - often bilateral. In other cases, a total laryngectomy may also be performed due to functional considerations (for example, in the event of recurrent aspiration pneumonia).

After total laryngectomy, the vocal tract and upper digestive tract are separated and the trachea is attached to the base of the neck, forming a permanent stoma. After removal of the larynx and the hyoid bone, the patient is no longer able to speak. In the Netherlands, larynxes are removed in this way approximately 150 times each year. The survival rates after a total laryngectomy or after (chemo)radiotherapy are probably similar. However, recent literature shows that the survival rates for patients with larynx cancer have decreased over the past decades (4). This is partly due to the fact that the survival rate is lower for large tumors treated with (chemo)radiotherapy than for a total laryngectomy with postoperative radiotherapy (5).

Changes after a laryngectomy

After a laryngectomy the air and food passages are separated. Patients breathe through a stoma in the throat and continue to eat normally through the mouth. Aspiration is no longer possible. Because breathing occurs through a stoma, the air no longer passes through the oral and nasal cavities and is therefore no longer filtered, humidified and heated before entering the lungs. As a result, the lungs are exposed to cold, dry, unfiltered air and this causes the patient to cough up tough mucus more often, develop respiratory tract infections, tiredness and other symptoms. Fortunately, better equipment has been developed in recent years, such as heat and moisture exchangers that are able to mimic part of the nose function (Figure 3). This significantly reduces the gravity of the symptoms.

A second result of the change in respiration is that patients no longer have a normal sense of smell. However, a technique has been developed to teach patients to smell by lowering the tongue and floor of the mouth in a yawning movement that induces the nasal airflow. Many patients benefit from this.

In order to swim with a stoma, aids are necessary and showering can cause problems. Many patients also develop psychological and social problems arising from this mutilating surgery.

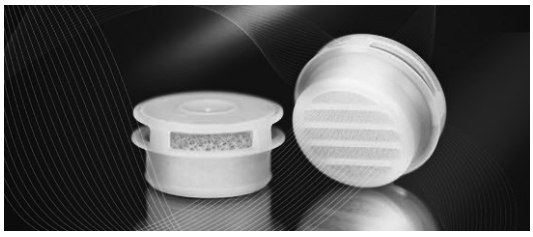

Figure 3. Heat- and moisture exchanger (HME). A HME heats and moisturizes the air.

SPEECH REHABILITATOIN

Physiological speech

Normal speech requires airflow, a sound source and a cavity in which the sound can be formed into an intelligible voice. In a healthy situation, the lungs, vocal cords, oral cavity and pharynx perform this function. After a total laryngectomy the vocal cords are removed and the anatomy of the oral cavity and pharynx is different. This affects the voice and speech (6). Figure 4 shows the anatomy before and after a total laryngectomy. Figure 4B also shows the respiratory tract after voice rehabilitation using a voice prosthesis.

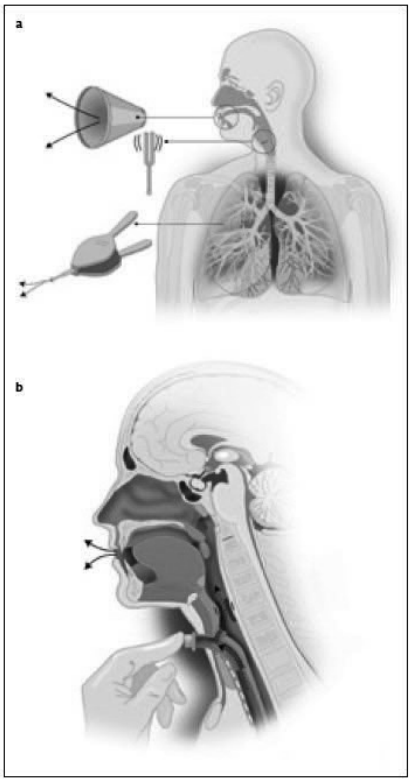

Figure 4. The normal anatomy (A) and the anatomy after a total laryngectomy and speech rehabilitation with a voice prosthesis (B).

History of speech rehabilitation

Since Billroth performed the first laryngectomy in 1873, postoperative speech rehabilitation has been of major concern. His colleague Gussenbauer described in 1874 how the first patient rehabilitated using a large artificial larynx, which was actually a tracheostomy cannula that forced air from the lungs to form speech using a valve (7). It was said that the patient's speech was audible at the other end of the hospital ward. The method was not

very long lived owing to the many complications involved in wound healing and aspiration (8).

Since the 1970s, speech rehabilitation has undergone a major change. A number of surgical techniques have been developed to make tracheoesophageal speech possible. This involves the creation of a fistula between the trachea and oesophagus. Air can then be propelled from the lungs into the oesophagus, which in turn vibrates the pharynx wall to produce a voice. Interestingly, aspiration occurred in patients who spoke well using this method while aspiration did not occur in patients who did not speak. The Polish doctor Mozolewski developed the first silicon valve, which was placed in the tracheoesophageal fistula (Figure 5)(9). With the aid of a single-valve mechanism in the prosthesis, pulmonary air can be diverted into the oesophagus but food in the oesophagus cannot get into the lungs.

The first commercial voice prosthesis was introduced by Singer and Blom in 1980. Many voice prostheses have since been introduced on the market, such as the Groningen voice prosthesis in 1984, followed by the Nijdam voice prosthesis (10). Currently, the Netherlands and many other European countries primarily use the Provox (Figure 6).

Figure 5. The voice prosthesis designed by the Polish doctor Mozolewski.

Figure 6. Provox® voice prosthesis.

Speech rehabilitation following total laryngectomy

Speech rehabilitation can be attained using 3 options: an external sound source in the form of an electrolarynx, or using the reconstructed pharynx as the new sound source, either enabling esophageal speech with air injected into and then expelled from the esophagus, or tracheo-esophageal speech with a voice prosthesis.

Oesophageal speech is difficult to learn and only 50% of patients successfully develop a voice using this method. Developing a good voice and the ability to articulate multiple syllables requires intensive speech therapy. Only a third of patients achieve this successfully. Patients are taught how to swallow air and then regurgitate it to create a vibration in the oesophagus that sounds similar to burping. One disadvantage of this method is that up to only 80 ml of air can be regurgitated, which makes the phonation time very brief (1-2 seconds, as opposed to 20 seconds for normal speech). The method also takes many months to learn. It requires a great deal of effort from patients and results in a great deal of frustration. However, the advantage is that after the rehabilitation period it is an inexpensive speech technique that does not require the stoma to be closed.

An electrolarynx, which patients hold under the chin, can be used to generate speech by creating vibrations in the throat that can then be converted into intelligible speech by articulation (Figure 7). One major disadvantage is that the voice is extremely monotone and sounds robotic. The advantage of this method is that patients can grasp it very quickly. For this reason, it is mainly used temporarily when the other methods do not work.

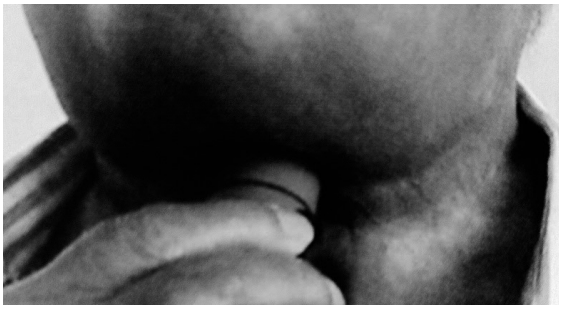

Figure 7. An electrolarynx.

The tracheo-oesophageal voice prosthesis has become the gold standard in speech rehabilitation with success rates as high as 90%. There are various methods for fitting voice prostheses. In Europe, a tracheo-oesophageal fistula is usually created during a total laryngectomy and a voice prosthesis is fitted immediately afterwards. Patients usually start speech rehabilitation 14 days after a surgical procedure. Voice prostheses are usually made of silicone. Although this material is well tolerated it has a limited life span. After a period of 3 - 6 months, most prostheses start leaking and need to be replaced. In order to produce a voice, patients must pinch their stoma closed so that when they breathe out the air is forced into the oesophagus via the prosthesis. This creates the vibrations that in turn form the sound of the voice. Many patients wear an easy to close heat and moisture exchanger for the stoma, which makes it fairly simple to close the stoma. However, one disadvantage is that patients always need a hand free when speaking and are forced to draw attention to their handicap in order to speak. Fortunately, automatic speech valves with a built-in heat

and moisture exchanger have also been available for several years and these allow some patients to speak without using a finger.

POSTOPERATIVE REHABILITATION

After a total laryngectomy the sense of smell is no longer present and patients must learn to take care of their tracheostomy and voice prosthesis. Patients must learn to brush their prostheses regularly in order to prolong the life span. They also have to learn to fit and change their heat and moisture exchanger. Sometimes a cannula is necessary.

Postoperative rehabilitation takes a long time. Good cooperation between nursing specialists, head and neck surgeons, speech therapists and medical social workers is vital. In addition, patient information workers (patients who have undergone a total laryngectomy and have completed the rehabilitation protocol) visit patients to help prepare them for life after the surgical procedure.

ORAL CARE

Patients who have undergone radiotherapy in the head and neck area often experience side effects that can damage the salivary glands, jawbone and teeth. Hyposialia is a common side effect. Radiotherapy can cause irreversible damage to the salivary glands, reducing saliva production. The salivary glands suffer irreversible hyposialia when subjected to a dose of 40 Gy. The curative dose of radiation for larynx cancer is in most cases 70 Gy on the primary tumor. Nowadays, intensity modulated radiotherapy is also used and the resulting hyposialia is less severe. This is due to the fact that this type of radiotherapy irradiates the tumor more precisely than conventional radiotherapy, thereby sparing the salivary glands. Another important side effect of radiotherapy is osteoradionecrosis. It presents spontaneously in 35% of cases, but the most frequent cause is after haemorrhage trauma, such as a tooth extraction.

It is also important that oral care providers take into account the presence of a tracheostomy both in terms of communication as well as psychologically and physically.

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CHAPTER 9

Voice quality and surgical detail in post-laryngectomy tracheoesophageal speakers

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Submitted.

ABSTRACT

Objective: To assess surgical parameters correlating with voice quality after total laryngectomy (TL) by relating voice and speech outcomes of TL-speakers to surgical details.

Method: Seventy-six tracheoesophageal patients' voice recordings of running speech and sustained vowel were assessed in terms of voice characteristics. Measurements were related to data retrieved from surgical reports and patient records.

Results: In standard TL (sTL), harmonics-to-noise-ratio (HNR) was more favorable after primary TL+postoperative RT than after salvage TL. Pause/breathing time increased when RT preceded TL, after extensive base of tongue resection, and after neck dissections. Fundamental frequency (f0)-measures were better after neurectomy. Females showed higher minimum f0 and higher second formants. While voice quality differed widely after sTL, gastric pull ups and non-circumferential pharyngeal reconstructions using (myo-) cutaneous flaps scored worst in voice and speech measures and the two tubed free flaps best. Formant/resonance-measures in /a/ indicated differences in pharyngeal lumen properties and cranio-caudal place of the neoglottic bar between pharyngeal reconstructions, and indicate that narrower pharynges and/or more superiorly located neoglottic bars bring with them favorable voice quality.

Conclusion: Ranges in functional outcome after TL in the present data, and the effects of treatment and surgical variables such as radiotherapy, neurectomy, neck dissection, and differences between partial or circumferential reconstructions on different aspects of voice and speech underline the importance of these variables for voice quality. Using running speech, next to sustained /a/, renders more reliable results. More balanced data, and better detail in surgical reporting will improve our knowledge on voice quality after TL.

INTRODUCTION

Tracheoesophageal (TE) speech presently is the preferred method of restoring oral communication after total laryngectomy (TL), because in many aspects it considerably outperforms esophageal (E) and electrolarynx (EL) speech (1). A major advantage over E speech is the speed of acquisition and the close to normal phonation time and speaking rate of TE speech, whereas its wider intonation/pitch variability and speech intelligibility also outperform EL speech (1). Nevertheless, TL still has a major impact on speech, swallowing, and psychosocial wellbeing (2-4). 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 (4-6). In studies on the relationship between acoustic measures and patient-experienced voice quality, self-assessed voice-related quality of life correlated with acoustic measures of intensity and temporal aspects of speaking (pauses, duration) (7, 8). Studies that matched professional listeners' judgments of voice quality of sustained /a/ with acoustics or visual signal typing of the spectrogram pointed out the importance of harmonics and formants, also in higher spectral regions (9, 10).

Voice quality and speaking effort differ widely within the TE population (5, 8, 11). The tonicity of the pharyngoesophageal (PE) segment (also called neoglottis), and therewith voice quality, is based on the adaptation and vibration dynamics of the pharyngeal mucosa (12). 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 (13-16).

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 (14, 16-28). 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.

In this retrospective study, we aim to identify patient and surgical parameters that correlate with voice quality after TL. Therefore, voice and speech outcomes of TL speakers were assessed and related to their patient and surgical details.

METHODS

Patient data

Over time, voice and speech recordings of 86 TE speakers of sufficient quality and extent were collected. For 76 of these, sufficient surgical detail could be retrieved for meaningful analyses. The vast majority of the 76 patients participated between 2007 and 2014 in voice prostheses studies at the Netherlands Cancer Institute (NKI). The included patients underwent TL between 1983 and 2013. Almost all patients underwent TL at the NKI. In 13 cases, with the patient's informed consent, surgical reports were retrieved from other Dutch hospitals. At the NKI, common procedures during TL include the creation of a separate tracheostoma in the inferior skin flap, sectioning of the sternal head of the SCM muscles to obtain a flatter stoma area, a short myotomy of the upper esophageal sphincter, T-shaped closure of the pharyngeal defect, and a primary TE puncture (TEP) with direct fit of the voice prosthesis (VP) (29). Between 1990 and 2002, unilateral neurectomy of the pharyngeal plexus was performed on a regular basis.

Medical records were assessed for demographic and surgical information, e.g. sex, age, site and TNM classification of the tumor, indication for TL, and prior and postoperative treatments in the head and neck area, staff surgeon performing the TL, surgical extent (indicated by surgical details such as the level of the trachea resection, base of tongue resection and tumor location), remaining pharyngeal mucosa and reconstruction procedure, pharyngeal mucosa and muscle closure technique, neck dissection, myotomy of the upper esophagus,

and plexus pharyngeus neurectomy. Since mass properties play a large role in voicing, as a general indicator of tissue properties, Body Mass Index (BMI) was assessed. The later VP lengths were used as a possible surrogate marker for the tracheoesophageal wall thickness and its potential effect on voicing.

Outcome measure to assess voice and speech

Voice and speech recordings included a read aloud standard Dutch text (length: 151 words) and sustained /a/. The read aloud text allows analysis of speech (including f0, %voiced and %unvoiced speech) and no-speech (%pause and/or breathing time). The chosen outcome measures are based on the available literature on voice quality, and have importance for laryngectomized patients in view of perceptual and experienced voice quality.

1. Speaking fundamental frequency (f0): We assessed f0 in terms of its minimum, maximum, mean/median, and range across the read aloud text. The mean indicates the height of he normal speaking frequency; the range of f0 indicates the possibility to produce variation in intonation.

2. %voiced and %unvoiced speech: TE speech is generally less voiced than laryngeal speech; higher amounts of %voiced indicate better TE speech.

3. %pause/breathing time (calculated from the ratio of pause and breathing time to the overall reading time (7): %pause/breathing time was assessed to measure the ease of reading a whole piece of text. Comparable to laryngeal speakers, TE speakers tend to pause/breathe at phrase ends indicated by the text (e.g. at comma's, points). Therefore the total percentage of pause was assessed and not e.g. the number.

4. Band energy difference (BED; between 0-500Hz and 4000-5000Hz, according to van As-Brooks et al. (10); dB) in sustained /a/ as a measure for spectral tilt (further referred to as "spectral tilt"). The tilt of the spectrum is related to the pressure build-up and the force of (neo-)glottic closure during vibration; it indicates effort. Spectral tilt has been shown to correlate with perceived voice quality in laryngectomized patients (30).

5. Harmonics-to-noise ratio (in dB; HNR) in sustained /a/, indicating the degree of acoustic periodicity. HNR has been found to correlate with perceived voice quality, pleasantness, and intelligibility (9,10).

6. Presence of formants and harmonics in the area of the third and fourth formant (HNR F3/F4); in sustained /a/ (9, 10), which were found to correlate with intelligibility and voice quality.

7. The position of and the distance between the first two formants (spectral peaks) were assessed in sustained /a/ as indicator for differences in the vocal tract resonance cavities (lumen). Higher formants indicate shorter vocal tracts (less distance from voice source to lips). The formant distance was found to correlate with intelligibility and pleasantness (9).

All analyses were performed with Praat (31).

Statistics

Descriptive statistics were performed. For pairwise comparisons between groups on the continuous acoustic variables we used Mann-Whitney U-tests, for three samples the Kruskal-Wallis (alpha = 0.05/3) followed by Mann-Whitney U-tests. Pearson's correlation was applied for relationships between voice measures. Spearman's correlation was applied for relationships between prosthesis size and acoustic measures or age. The Fisher's exact test was applied between categorical variables. Analyses were performed with IBM SPSS Statistics 22.0.

RESULTS

Patient and surgical characteristics

The 76 included patients underwent a TL for the following indications: 24 as primary cancer treatment, and 52 after RT (N=47) or chemoradiation (CCRT; N=5). Of these latter 52, 38 concerned salvage treatment, 5 a second primary, and 9 a dysfunctional larynx after prior (chemo-) radiotherapy. Of the 24 primary TL patients, 16 underwent postoperative RT and 3 postoperative CCRT. Five patients were not irradiated at all. The patients' demographic, medical and surgical characteristics are shown in Table 1.

The majority of patients had a glottic or supraglottic carcinoma with tumor-negative lymph nodes. Mean age at TL was 59 years. Simultaneously with the TL, 39 patients (52%) underwent a neck dissection (ND), including at least levels 2 to 4. The vast majority underwent a primary TEP (90%) with insertion of a Provox2 VP. The most common VP length at primary TEP was 8mm, and during follow-up 6mm or 8mm (36% and 30% respectively).

Forty-seven patients were treated with standard TL (sTL) without reconstruction (62%), and 35 (75%) underwent short myotomy of the upper esophageal musculature. Fifteen of the sTL patients (32%) had a neurectomy of the pharyngeal plexus. Only in 8 patients (10%), a significant part of the base of the tongue was resected. In 30 patients, the trachea was transected above the third ring (64%).

Besides the 47 patients with a sTL, 10 underwent a sTL with PM-muscle flap reinforcement of the pharyngeal suture line or closure of a pharyngocutaneous fistula. Pharyngeal closure techniques, such as layers and to what extent the constrictor pharyngeal muscle remnants were sutured together, were not consistently reported in detail. Nineteen patients underwent an extended pharyngeal resection requiring reconstruction of the lumen. There were two circumferential reconstructions with a free flap, four with a tubed gastric pull-up, and one with a full gastric pull-up. There were twelve partial reconstructions of the pharyngeal wall; one with a free radial forearm flap and eleven with a PM-myocutaneous flap. Sixteen different surgeons/surgical teams were involved in the surgeries in this patient cohort.

Table 1. Patient and surgical characteristics; * in "Extent of TL" refers to details in "Lumen reconstruction"

	N	%
Total	76	(100)
Male	66	(90)
Mean age at TL (range)	59	(29-85)
Mean age at recording (range)	66	(42-88)
Primary site		
Supraglottic	20	(26)
Glottic	37	(49)
Subglottic	4	(5)
Oropharynx	4	(5)
Hypopharynx	9	(12)
Proximal esophagus	2	(3)
T classification (initial)		
Tis-T1	20	(26)
T2	17	(22)
T3	11	(15)
T4	28	(37)
N classification (initial)		
N0	54	(71)
N+	22	(29)
Indication TL		
Primary	24	(32)
Salvage	38	(50)
Second primary	5	(7)
Dysfunctional larynx	9	(12)
BMI at TLE		
< 18	5	(7)
18-25	33	(43)
25-30	28	(37)
> 30	5	(7)
unknown (TL elsewhere)	5	(7)
TL timing in relation to RT		
TL for RT failure	44	(58)
TL for CCRT failure	5	(7)
TL for RT failure + postoperative RT	3	(4)
TL + postoperative RT	16	(21)
TL + postoperative CCRT	3	(4)
No RT	5	(7)

Extent of TL		
Standard TL	47	(62)
Standard TL with PM flap reinforcement	10	(13)
Extended TL with non-circumferential resection*	12	(16)
Extended TL with circumferential pharyngeal resection*	7	(9)
Lumen reconstruction*		
PM myocutaneous flap	11	(58)
Free flap	3	(16)
Gastric pull-up	5	(26)
Neck dissection ≥ level 2 to 4		
No	37	(49)
Unilateral	18	(24)
Bilateral	21	(28)
Extended resection base of tongue		
No	68	(90)
Yes	8	(10)
Neurectomy (standard TL, N=47)		
Yes	15	(32)
No	32	(68)
Short myotomy (standard TL, N=47)		
Yes	35	(75)
No	12	(25)
Neurectomy (standard TL, including PM flap for reinforcement, N=57)		
Yes	16	(28)
No	39	(68)
unknown	2	(4)
Short myotomy (standard TL, including PM flap for reinforcement, N=57)		
Yes	42	(74)
No	13	(23)
unknown	2	(4)
Transection trachea (standard TL, N=47)		
< 3rd ring	17	(36)
> 3rd ring	30	(64)
Tracheoesophageal puncture (TEP)		
Primary TEP	69	(91)
Secondary TEP	7	(9)

Voice and speech outcomes

Standard TL

There were several interactions between various treatment parameters: statistical analyses confirmed differences in the frequency of ND and pre- or post- (C)RT treatment (Fisher's exact test, p=0.005) as well as the frequency of neurectomy (p=0.027). Patients with a bilateral ND were predominantly treated by postoperative (C)RT (60%) and all but one underwent neurectomy. Patients with a unilateral ND were predominantly treated by (C) RT before TL (62%), and had no neurectomy (67%). In patients without ND, most had (C) RT prior to TL (83%) and only half of them underwent neurectomy. Next to differences in subcategory frequencies, these correlations between treatment groups limited an analysis of relationships with voice.

Within the sTL speakers (N=47), speaking f0 and the percentage of voicedness in the read aloud text were significantly correlated (r=.666, p<0.001): the higher f0, the more voicing during speech. The voicedness in the read aloud text correlated significantly with the harmonics-to-noise ratio (HNR) measured in sustained /a/: the more voicing in the text, the better the harmonics-to-noise ratio, (r=.492, p<0.001). Spectral tilt (BED) correlated marginally with the f0-range in the text (r=.297, p=0.045): the higher the range of f0 in the text, the more tilt in the spectrum of sustained /a/. Speaking fundamental frequency correlated significantly with other f0-measures: the higher the speaking mean, the higher the minimum, maximum, and range were (r=.665, maximum r=.874, range r=.705, p<0.001). There was no significant correlation with pause/breathing time.

Speakers' sex

The median speaking f0 across the read aloud text was lower for males (median 108 Hz, ranging from 49 to 238 Hz) than for females (140 Hz, range 33-277 Hz). The minimal f0 in running speech was higher for females (71 Hz vs. 41 Hz, p=0.009, U=40,0). All other differences in voice outcome between male (N=40) and female (N=7) speakers were insignificant.

Age, BMI and thickness of the tracheoesophageal wall

There was a significant decline in prostheses lengths in older speakers (p=0.018, r=-.343, N=47), but there were no associations between voice measures and age, prosthesis length (tracheoesophageal party wall thickness), and/or BMI.

Pharyngeal closure

The variety of surgical teams (N=16) and their muscle closure techniques as well as underspecified procedure descriptions precluded evaluations of an effect of pharyngeal closure technique or the extent of the residual pharyngeal wall.

Short myotomy and neurectomy

Most patients in the sTL group underwent a short myotomy (35/47) and had no neurectomy (32/47). There were no significant main effects of myotomy on voice measures, only a trend towards increased pause/breathing time during speech in TE speakers with myotomy compared to those without myotomy (24% vs. 20%, p=0.057, U=132,0). TL speakers with neurectomy showed significantly more voicing during speech (55% vs. 33%, p=0.035, U=129,5), and higher speaking f0 (122 Hz vs. 103 Hz, p=0.058, U=157,0).

(Chemo-)radiotherapy

In view of the subsample sizes, for effects of (C)RT (salvage surgery after (C)RT failure) versus primary TL with postoperative (C)RT), we excluded the smallest subgroups: three patients with no history of (C)RT, and one patient with pre- and post (C)RT, leaving a subset

of 43 patients. While the harmonics-to-noise ratio was significantly better after primary TL with postoperative (C)RT when compared to those patients receiving pre-operative (C)RT (p=0.042, U=118,0), pause/breathing time during the reading task was longer (21% vs. 24%, p=0.048, U=120,5).

Neck dissection of at least level 2 to 4

Neck dissection (no/unilateral/bilateral) had a significant effect on the percentage of pause/breathing time in running speech, and this effect increased from no- to uni- to bilateral ND (20% vs. 24% vs. 29%, $\chi^2(2)=8,216$, p=0.016). Post-hoc tests showed significantly higher percentage of pause/breathing time after bilateral ND than without ND (p=0.004, U=77,5).

Extensive base of tongue resection

Significantly lower first formants were found after extensive tongue resection (589 Hz vs. 656 Hz, p=0.033, U=69,5) and higher percentage of pause/breathing time during the reading task (25% vs. 21%, p=0.039, U=71,5). Extensive base of tongue resections were equally distributed in terms of ND and timing of (C)RT, the factors found to affect pause/breathing time as well.

Standard TL with PM flap for reinforcement

In sTL group with PM-flap reconstructions for reinforcement (10 patients), speech and voice measures were comparable to the sTL group without such additional flap (table 2, figures 1-3). In the whole sTL group including the 10 reinforcement flaps (N=57) analysis of the influence of myotomy, neurectomy, neck dissection, RT, and base of tongue resection rendered similar results as in the sTL group without PM-flap reinforcement. Several effects were even more evident in this larger group: again, females (9/57) had a higher minimum f0 and significantly higher second formants (F2 1452 Hz vs. 1398 Hz, p=0.030, U=117,0). In this larger group, next to an effect of age on tracheoesophageal party wall thickness, prosthesis length tended to be shorter when (C)RT preceded TL ($\chi2(1)=5,610$, p=0.018). After neurectomy, next to more voicing during the running speech task, the median (131 Hz vs. 101Hz, U=201,0, p=0.040), maximum (204 Hz vs. 172 Hz, U=191,5, p=0.033) and range (162 Hz vs. 122 Hz, U=197,0, p=0.043) of the speaking f0 were significantly higher.

Table 2. Mean and standard deviation of acoustic voice measures per subgroup. Two of five of the gastric pull up's had to be excluded from the f0 analyses due to the absence of voicing during the reading task

	Standard TL		Standard TL + PM for reinforcement		Partial reconstruction (PM/RFF)		Tubed free flap		Gastric pull up +/- PM		Full gastric pull up + PM	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
text												
f0 median	119	(50)	134	(73)	61	(20)	135	(8)	67	(39)	.	.
f0 min	48	(32)	59	(36)	26	(11)	38	(0)	43	(19)	.	.
f0 max	197	(72)	206	(94)	93	(35)	225	(23)	149	(32)	.	.
f0 range	148	(59)	147	(71)	67	(23)	187	(23)	106	(19)	.	.
% voiced	40	(21)	38	(18)	23	(12)	41	(18)	8	(6)	4	.
% pause	23	(9)	25	(11)	24	(6)	17	(4)	28	(6)	20	.
% unvoiced	36	(21)	37	(20)	53	(18)	43	(14)	65	(11)	79	.
/a/												
HNR	1,8	(3,9)	0	(2,4)	-,1	(1,5)	4,4	(2,5)	-1,2	(1,4)	-3,7	.
HNRF3/4	78	(16)	82	(14)	81	(12)	101	(0)	78	(26)	52	.
Spectral tilt	-16	(8)	-17	(8)	-12	(8)	-31	(6)	11	(10)	0,4	.
F1 Hz	644	(39)	636	(37)	657	(31)	592	(88)	668	(44)	672	.
F2 Hz	1393	(68)	1427	(76)	1440	(86)	1498	(27)	1433	(102)	1367	.
F3 Hz	2853	(178)	2896	(205)	2908	(252)	2481	(222)	2845	(87)	2924	.

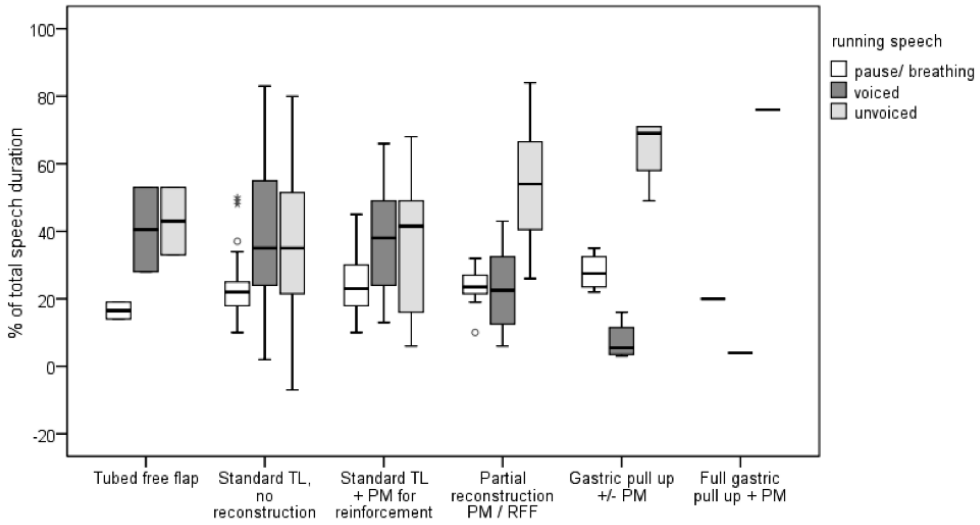

Figure 1. Amount of voiced and unvoiced speech, and pause /breathing time as a percentage of the duration of the running speech task. Percentage voiced speech as box-plots (representing the median, 95% CI and interquartile range). Most favorable groups/outcomes to the left, least normal to the right.

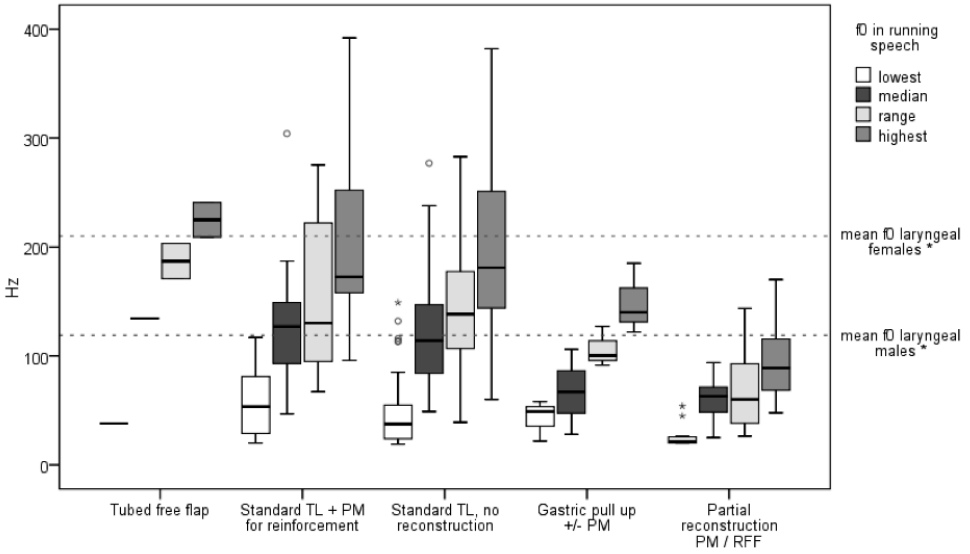

Figure 2. Boxplots of lowest, median, and highest fundamental frequency (f0) during the running speech task. Three patients had to be excluded from the f0 analyses due to less than 5 percent of voicing during the running speech task. The broken horizontal lines depict mean f0 values for groups of laryngeal female and male speakers according to Traunmüller & Eriksson (1995). From left to right: most to least favorable speaking frequency and range.

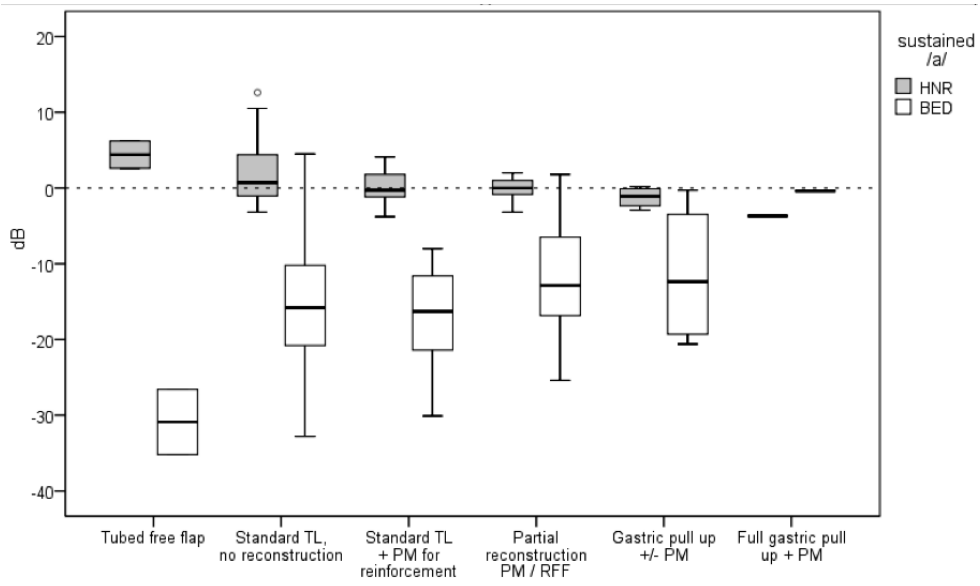

Figure 3. Boxplots of harmonics-to-noise ratio (HNR) and spectral tilt, both from sustained /a/. To the left: most favorable (signal type I; (10)), to the right: least favorable (signal type IV; (10)).

Extended TL with reconstruction

Several voice measures differed significantly between sTL speakers (N=57) and the group with TL plus (near-)total pharyngectomy with lumen reconstruction (N=19). Three speakers showed less than 5 percent of voicing during the running speech task, including two of the five total pharyngectomies with a gastric pull up (one full and one tubed). These three speakers were excluded from f0-analyses.

In running speech, compared to the sTL group, for this reconstruction group, we found significantly lower values for: the median f0 (67 Hz vs. 117 Hz, $p<0.001$, U=195,5), the lowest and highest f0 (22 Hz vs. 39 Hz, p=.011, U281,0 and 114 Hz vs. 179 Hz, $p<0.001$, U=183,5), the f0 range (81 Hz vs. 136 Hz, $p<0.001$, U=205,0), and voicedness (18% vs. 37%, $p<0.001$, U=245,0) (see figure 1 (including laryngeal f0-means according to Traunmüller and Eriksson (32)). Moreover, in this group, the 2nd formant of /a/ was slightly higher (1426 Hz vs. 1400Hz, p=0.048, U=376,5). There were no significant differences in measures of harmonics-to-noise ratios and spectral tilt.

Sample sizes in the pharyngeal reconstruction subgroups were small. However, there was a clear trend in measures across running speech as well as in sustained /a/: overall, there was a trend for two tubed free flap reconstructions to show more favorable results of f0 (median, maximum, minimum and range), as well as voicedness across the read aloud text (table 2, figure 1), pause/breathing time and spectral tilt (figure 1 and 3), harmonics-to-noise ratio (figure 3), as well as the harmonics-to-noise ratio in the region of the 3rd and 4th formant (not plotted). Speakers with PM myocutaneous flap reconstruction and those with gastric pull-up reconstruction showed the least favorable outcome (depicted in figures 1-3). The two tubed free flap reconstruction were comparable to or even better than the best sTL voices. In comparison to the other TL speakers, vocal tract resonance cavity measures (formants) showed rather high 2nd formant and low 1st formant values (large F2-F1 distance) for these 2 patients (table 2).

DISCUSSION

The aim of the present retrospective study is to identify surgical parameters that correlate with voice quality after TL by relating voice and speech outcomes of TL speakers to details of their surgical procedure.

In the sTL speakers there are several interesting correlations: higher speaking f0 correlates with more voicedness, and voicedness correlates with a better harmonics-to-noise ratio. Moreover, in running speech, there is a trend towards a higher f0 in females, with significant higher minimum f0 in running speech. Females also differed in formants (vocal tract cavities)

with higher second formants. These f0- and formant differences might be due to gender-dependent behavior, with females trying to produce a higher pitch (by using more tension and changing the height of the neoglottis). Yet, differences between the sexes in the average vocal tract/esophageal lumen size can not be ruled out.

Other studies did not find f0 differences between the sexes, when assessing f0 in sustained /a/ (6). In sustained /a/, however, f0 is not necessarily representative for normal speaking f0.

One of the effects of surgical detail present in this cohort of sTL speakers is that pause/breathing time increases from no- to uni- to bilateral neck dissections, and is more pronounced after extensive tongue resection, and when postoperative (C)RT is used. Another interesting finding is that patients with primary TL and postoperative (C)RT showed better harmonics-to-noise ratios than patient who had a salvage laryngectomy after prior (C)RT, suggesting that the 'condition' of the PE segment is more favorable for voicing after primary TL than after salvage surgery.

Next to longer pause and breathing time, TL speakers with extensive base of tongue resection presented with lower first formants in /a/, possibly the result of ratio changes in the front versus back cavity and compensatory strategies to still reach the perceptual impression of /a/. The base of tongue plays a major role in speech, as is the case for swallowing. After TL, swallowing deficiencies, especially with solid food, are reported regularly (4, 23, 33, 34). This dysphagia usually presents in pharyngeal clearance problems and prolonged (oro) pharyngeal transit times, which are the result of both the decreased control of the base of tongue and the pharyngeal wall (35, 36).

To prevent spasm of the neoglottis, most of our sTL speakers underwent a short myotomy of the upper esophageal segment (37). The need for this short myotomy to prevent spasm is controversial in literature, and several (early) studies supported pharyngeal neurectomy (19, 28, 38, 39), with good PE pressure and higher voices, presumably by the maintenance of some residual pressure in the neoglottis as a function of the contralateral plexus. This was reason why between 1990 and 2002, neurectomy was favored. However, in view of the favorable effects of a short myotomy of the upper esophageal sphincter in one of our studies (37) neurectomy was abandoned. Interestingly, we now find that, in line with literature, speaking pitch is higher and f0 measures are more favorable after neurectomy.

Due to the various details in surgical reporting, the limited number of patients per subgroup, selection biases and the diverse surgical teams over the 30 years the surgical data were collected, an analysis of pharyngeal closure technique on voice and speech outcome was not possible retrospectively. Literature on speech failure, intraluminal pressure, fistulae, and swallowing, however, clearly favors muscle closure over non-muscles closure (19, 27, 40, 41).

Our results confirm previous studies in showing worse functional scores for speakers with (partially) reconstructed pharynges (42), although the voice outcome was more favorable for the two tubed free radial forearm flaps (RFF). This could be a selection bias. The worse voice quality after circumferential reconstruction coincides with the literature (25). Yet, other than in our study, after partial pharyngeal reconstruction, voice (and swallowing) was reported to be comparable to standard TL (25). Including electro-larynx speakers, a different subset of donor sites, and other voice quality scoring in that study, however, a direct comparison of voice outcome is difficult.

In pharyngeal reconstructions, (full) gastric pull-ups and non-circumferential reconstructions scored worst across running speech as well as in sustained /a/ measures. In 3 of the 5 (tubed) gastric pull-up patients a measurable f0 was present (however, minimally voicing), which suggests an occasionally sufficient diameter and closure of its lumen. The other 2 had no voicing (f0).

For sTL, voice measures showed no significant effect of age, BMI or TEP length. With the TEP being well below the PE segment, it is a too imprecise indicator of pharyngeal wall thickness. Nonetheless, in line with previous studies on pharyngeal wall or tissue thickness, TEP length showed a significant effect of age. The fact that age, in contrast to earlier findings (43) is not correlated with any of the acoustic voice parameters studied, might be a selection bias, since the better/fitter patients are probably overrepresented in this cohort of voice recordings. More precise measures to assess tissue properties might lead to a better interpretation of the role of (changes) in tissue properties in TE voice and speech quality.

Next to differences in voice quality, formants (resonance cavity measures) in /a/ indicate differences in pharyngeal lumen properties and cranio-caudal place of the neoglottic bar between pharyngeal reconstruction procedures. While the vocal folds in normal adult laryngeal speakers are at the height of C5-C6, imaging of TL speakers during phonation suggests that the neoglottic bar is located higher than the vocal folds (middle of C3-C5) (6, 42). Roughly speaking, formant frequencies are inversely proportional to the vocal tract length (the ratio of pharynx length to mouth length) with small formant dispersion (F2-F1 distance) indicating larger body size and shape (44). According to the effect of shortening of the vocal tract (from lips to the neoglottic bar) after laryngectomy, overall, higher formant values were found in TL speakers than in laryngeal speakers (45). Whereas in sTL speakers the neoglottic bar is usually around the level of C4, this level was found to differ widely in TL speakers with pharyngeal reconstructions (C3-C7) (42). In our dataset, the second formant and the formant dispersion were highest in tubed RFF, and lowest in full gastric pull up, explainable by different locations of the neoglottic bar caused by different lumen diameters and tissue characteristics of the reconstruction. Overall, the voice outcome and formants in our data suggest that smaller diameter pharynges and/or more superiorly located neoglottic

bars are associated with favorable voice quality and more effortless speech. To compensate for a wide pharynx, external pressure (e.g. by PM flap) might be useful to compensate for a low tonicity. These findings are confirmed in previous studies using videofluoroscopy in which it has been shown that smaller pharyngeal diameters and optimization of the intraluminal pressures favor voicing (14, 16, 24, 37, 42, 46).

As shown on videofluoroscopy, for vibration after TL, pulmonary airstream is sent through the PE segment, and the walls are pushed up until the walls form a neoglottic bar (pharyngeal closure) leading to a Bernoulli-effect, and the walls starts to vibrate. Positioning and muscular control of the vibratory segment play a significant role in f0-alterations, and in some patients there is a striking pharyngeal control, leading to a good control over loudness and dynamic range (47, 48). Dynamic range of the TL voice has been reported to correlate with the contraction amplitude in the neoglottis (14), and air pressure with esophageal expansion (16). Although ideally we would like to create the narrowest point at the optimal level with maximal muscular control, we do not have enough knowledge and data to determine the optimal creation of the pharynx and neoglottic bar. A very wide 'pharynx', as in full gastric pull-up has the worst outcome, but a too narrow pharynx, although not necessarily bad for voicing, can interfere with swallowing, and a too muscular pharynx can cause hypertonicity-related voicing problems.

Strength and Limitations

Studies discussing the direct impact of surgical detail in TL procedures on functioning are sparse. Much of the literature regarding voice functioning focuses on sustained vowels, which ignores the patient perspective as Kazi et al. (6) pointed out. In contrast, running speech covers different aspects of voice and speech and consequently, next to sustained /a/, predominantly running speech was used in the present study. Although we were able to compare patients with various surgical procedures, the present retrospective study had limited power due to the unbalanced dataset, the limited numbers of patients in various subgroups and the impossibility to carry out meaningful multivariable analyses. In this study, patients of whom voice recordings were available, were mostly patients that participated in voice prosthesis studies and were thus possibly the "better/fitter" TL speakers. This might have caused an unbalanced dataset.

Also, the presumed effect of pharyngeal closure technique could not be assessed because surgical reports were not always clear. Prospective data collection and structured reporting of surgical detail is needed to draw more definitive conclusions.

For the future, imaging data during voicing and data on muscle activity during phonation would help to disentangle relationships between pharyngeal properties, vibrating mass, and surgical procedures, including muscle closure techniques, myotomy and neurectomy, and the role of speaker behavior in voice outcome after TL.

CONCLUSION

The ranges in voice outcome after TL are related to variables like radiotherapy, neurectomy, neck dissection, and reconstruction procedures. In this patient cohort gender/speaker behavior appears to have an influence on the f0 in running speech. Overall, our results suggest that narrower pharynges and/or more superiorly located neoglottic bars are associated with more favorable voice quality. Patients with pharyngeal lumen reconstructions (i.e. by PM myocutaneous flaps and (tubed) gastric pull-ups) have the poorest voices. In sTL, neurectomy may be favorable.

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CHAPTER 10

Biofilm formation on the Provox ActiValve: Composition and ingrowth analyzed by Illumina paired-end RNA sequencing, fluorescence in situ hybridization and confocal laser scanning microscopy

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ABSTRACT

Background: The most frequent cause of voice prosthesis failure is microbial biofilm formation on the silicone valve, leading to destruction of the material and transprosthetic leakage. The Provox ActiValve valve is made of fluoroplastic, which should be insusceptible to destruction. The purpose of this study was to determine if fluoroplastic is insusceptible to destruction by Candida-species.

Methods: 33 dysfunctional Provox ActiValves (collected: 2011-2013). Biofilm-analysis: Illumina paired-end sequencing (IPES); assessment of biofilm-material interaction with fluorescence in situ hybridization (FISH) and confocal laser scanning microscopy (CLSM).

Results: IPES (n=10) showed that Candida albicans and Candida tropicalis are dominant populations on fluoroplastic and silicone. Microbial diversity is significantly lower on fluoroplastic. L. gasseri is the prevalent bacterial strain on most voice prostheses. FISH and CLSM (n=23): in none of the cases was ingrowth of Candida-species present in the fluoroplastic.

Conclusions: Fluoroplastic material of Provox ActiValve seems insusceptible to destruction by Candida-species, which could help improve durability of voice prostheses.

INTRODUCTION

Total laryngectomy (TL) is still an important treatment option for advanced stage larynx cancer and is often the only remaining curative choice for recurrence after (chemo) radiotherapy. 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. 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, either enabling esophageal speech with air injected into and then expelled from the esophagus, or tracheoesophageal speech. 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 silicone prosthesis is superior in terms of quality and intelligibility. Op de Coul et al. (2000), for instance, reported a success rate with respect to voice quality (fair to excellent rating) of 88% (1). Because of its high success rate and ease of acquisition, tracheoesophageal prosthetic speech has become the method of choice for voice and speech rehabilitation after TL (1). A variety of voice prostheses, mostly made out of silicone rubber, have been developed in the past few decades, e.g. Blom-Singer, Groningen, Nijdam, and Provox (2, 3). The lifespan of these devices varies from a few weeks to several years. A retrospective study conducted at the Netherlands Cancer Institute reported a mean lifespan for the Provox2 of 163 days and a median of 89 days. In most cases, voice prostheses have to be replaced because of transprosthetic leakage (1).

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 (4). The biofilm consists of a mixture of bacteria and fungi and starts developing 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 (5). To extend the lifespan of the device, the use of oral and/or topical fungicidal drugs on a regular basis is proposed. To date, however, this has not been substantiated in properly conducted clinical studies, and regular use of antifungals might induce resistance or cause side effects (6). Other options that could extend the lifespan of the device are flushing water or air through the lumen of the prosthesis under light pressure or using a dedicated brush to clean the inside of the prosthesis (7). Some studies reported the reduction of biofilm formation by the use of certain dairy products, such as probiotics, which also extends the clinical device lifespan (8).

To solve this problem in a material-technical way, a special voice prosthesis was developed: the Provox ActiValve (Atos Medical AB, Hörby, Sweden; Figure 1) (9). The valve and valve seat

of this voice prosthesis are solely made out of fluoroplastic, which is deemed insusceptible to ingrowth of Candida-species (Figure 2). Closure of the valve is achieved “actively” with 2 magnets (one in the valve and one in the valve seat), when the tracheoesophageal airflow stops. The Provox ActiValve is available in three versions depending on magnet strengths (Light, Strong and XtraStrong), which are applied according to the “underpressure” in the esophagus. Although the clinical effectiveness of the Provox ActiValve has been substantiated in several retrospective and prospective studies (10-12), 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 (5). 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.

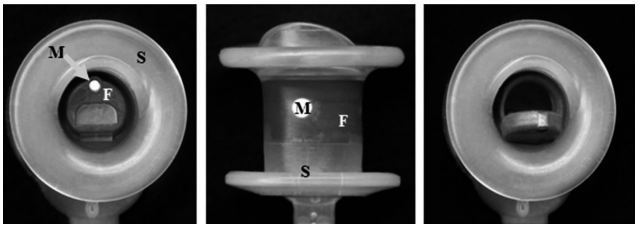

Figure 1. Overview of the Provox ActiValve voice prosthesis (S: silicone material; F: Fluoroplastic –blue-material; M: magnets).

Figure 2. Macroscopic image of a Provox ActiValve, which was 364 days in situ, illustrating the amount of biofilm on the silicone material and on the fluoroplastic valve.

The first purpose of this study, therefore, was to determine the composition and diversity of the biofilm of both the silicone and the fluoroplastic material of the Provox ActiValve. This was done by analyzing both the bacterial and fungal communities on these samples using Illumina paired-end sequencing (IPES) (13). This is the first time IPES will be used to analyze

microbial communities by combining amplicons sequencing of the bacterial 16S rRNA gene and the eukaryotic ITS regions on these voice prostheses. The second purpose was to confirm the hypothesis that the fluoroplastic material is not susceptible to destruction by Candida-species. For this purpose, fluorescence in situ hybridization (FISH) and a confocal laser scanning microscopy (CLSM) were used (5). FISH is especially suitable for the identification of multiple species in a biofilm. CLSM has the ability to control the depth of the field, to reduce background information and to collect serial optical sections from thick samples.

MATERIALS AND METHODS

The study period lasted from November 2011 to June 2013. During this 19-month period, we collected 33 consecutive dysfunctional Provox ActiValve prostheses of patients visiting the outpatient clinic of the Department of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute (Amsterdam, the Netherlands), or of the Department of Otorhinolaryngology of the University Medical Center Groningen (Groningen, the Netherlands). Of these 33 prostheses, the first 23 prostheses were used for FISH and CLSM after fixation within 24 hours and storage at 4°C. The subsequent 10 prostheses were analyzed using IPES and stored at -20°C, both numbers being sufficient for the envisaged analyses.

Composition and diversity of the biofilm using IPES

Composition and diversity of the biofilm were determined by the IPES method (13). The explanted prosthesis was cut into cross-sections using a surgical blade. Cross-sections of the fluoroplastic part of the valve and of the silicone material of the esophageal flange were stored at -20°C. When all 10 prostheses were collected, cut and stored, DNA was isolated and purified from both the fluoroplastic part of the valve and of the silicone material of the esophageal flange. We added a lysis buffer (500 mM NaCl, 50 mM Tris-HCl (pH 8), 50 mM EDTA, 4% sodium dodecyl sulfate (SDS)) to the samples and heated the samples at 70 °C. To disrupt cell walls in order to obtain DNA, zirconium beads (0.1 mm) and glass beads (3 mm) were added and the samples were mechanically disrupted at room temperature at 5.5 ms^{-1} for 3 times 1 minute. In between, the samples were cooled on ice. Then the samples were heated at 95 °C for 15 minutes and shaken by hand every 5 minutes. Samples were centrifuged for 5 minutes at 4 °C to collect the supernatant. Fresh lysis buffer was added to the lysate tube and the samples underwent the same steps of mechanical disruption again in order to obtain a higher yield. Afterwards, the corresponding supernatants were pooled. Then, 10 M ammonium acetate was added to each lysate tube, mixed and incubated on ice for 5 minutes. After centrifugation at 4 °C for 10 minutes the pellet was discarded. Samples were mixed 1:1 with isopropanol and were incubated on ice for 30 minutes. After centrifugation for 15 minutes, the supernatant was removed by decanting. The pellet was

washed with 500 ml 70% ethanol for 2 minutes and was air-dried after removal of most of the ethanol. The nucleic acid pellet was dissolved AE buffer (200 ml per sample) overnight at 4 °C. DNA purity was measured on the NanoDrop 2000, a UV-Vis Spectrophotometer.

The extracted DNA was subsequently amplified with ITS2 primers for eukaryotic (fungal) DNA (ITS3 and ITS4) (14). For bacteria, primers covering the hypervariable V3 and V4 region of bacterial 16S rRNA genes were used (15, 16). The length per read was around 465 bases for bacteria and around 345 bases for fungi.

Visualization of the biofilm using FISH and CLSM

The biofilm of the fluoroplastic part of the valve and of the silicone hinge was visualized using FISH and CLSM. The explanted prosthesis was transferred into sterile PBS (phosphate buffered saline, 0.15M, pH 7.3), fixed within 24 hours in 4%-paraformaldehyde solution in PHEM-buffer (0.2M, pH 6.9) and stored at 4°C. After 24 hours the prosthesis was conserved in an ethanol/PBS (1:1) solution until the time of analysis. During this procedure, the prosthesis was stored at -20°C. For analysis, the valve of the prosthesis was cut in four thin slices using a surgical blade and glued onto glasses with a silicone gel. A plastic ring was glued around each slide to enclose the later applied probe and buffer. Subsequently, the glass slides were fixed in 96% ethanol for 10 min. To increase permeability of the bacterial cell membrane Labmix enzyme mixture was used prior to hybridization (17). Subsequently, FISH was performed with two DNA probes, i.e. a rhodamine-labeled EUB338 probe and a fluorescein-isothyocyanate (FITC)-labeled EUK516 probe. The EUB338 probe is specific for bacteria and provides a red signal. The EUK516 probe is specific for eukaryotes and provides a green signal. The slices on the glass slides were hybridized in 50 µl of pre-warmed hybridization buffer (0.9M NaCl, 20 mM Tris, pH 7.2, and 0.01% SDS) containing both probes (5 ng/µl each). Subsequently, the slides were incubated at 50°C in a dark chamber and hybridized overnight. To remove unbound probes, the slides were washed in a washing buffer (50°C; 0.9 M NaCl, 20 mM Tris, pH 7.2) for 15 minutes. Then, the slides were cleaned with Millipore water and dried with compressed air. Vectashield (Vector Laboratories, Burlingame, CA, USA) was applied for fluorescence. To visualize Eukaryotes (Candida) and bacteria after hybridization we used a confocal laser scanning microscope (model LEICA TCS SP2; Leica Microsystems Heidelberg GmbH, Heidelberg, Germany).

Statistical analysis

For the description of patients, tumor and prosthesis characteristics, descriptive statistics were performed. Software that was used to analyze the data received from IPES, included PANDAseq (18), QIIME and ARB (19). Principal component analysis (PCA) was performed to find clusters of similar groups of samples or species. PCA is an ordination method based on multivariate statistical analysis that maps the samples into a reduced number of relevant dimensions of variability. The Simpson index was used as a measure of microbial diversity.

Non-parametric tests were used, as microbial abundances are never or rarely normally distributed. Mann-Whitney *U*, Spearman ρ or Wilcoxon tests were used as indicated. All tests were two-tailed and a $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using *IBM® SPSS® Statistics* 20.0.

RESULTS

Thirty-three voice prostheses were analyzed of 22 patients (18 males and 4 females). Some patients had multiple replacements during the study period and were thus included two (n=5) or three times (n=3) in this study. The mean age at time of TL was 56.5 years (± 10.1 years) and at time of the (first) Provox ActiValve prosthesis replacement 68.8 years (± 9.7 years). Patients underwent a TL for several indications: 8 patients underwent a TL as primary treatment of larynx cancer, 17 patients as a salvage procedure after primary treatment with radiotherapy for larynx or hypopharynx cancer or after total thyroidectomy for a papillary thyroid cancer (n=1). In 6 patients a TL was performed because of a second primary tumor and in 1 patient for a dysfunctional larynx after primary treatment with chemoradiotherapy. The following Provox ActiValve prostheses were used: Light (n=17), Strong (n=15) and XtraStrong (n=1) in the sizes 4.5, 6, 8, 10 and 12.5 mm. The median device lifespan was 168 days (range 5 to 738). All patient and prostheses characteristics are shown in Table 1a and 1b. In the majority of patients the prosthesis was removed because of leakage through the prosthesis (see Tables 1a and 1b for all reasons). Median follow-up time from TL until (last) replacement was 161 months (range 3 to 249).

Table 1a. Patient and prostheses characteristics (Illumina paired-end sequencing)

No.	Gender	Age[1] at TL[2]	TN-classification primary tumor[3]	Primary tumor	Indication for TL	RT[4] pre- or postoperatively?	Magnetic force in PAV[5]	Size of PAV	Device lifetime (days)	Reason of replacement
1	Male	69	T4N0	Transglottic	Primary	Yes, post-TL	Light	4.5 mm	260	Leakage through the prosthesis
2	Male	64	T1N0	Hypopharynx	2nd primary	Yes, pre-TL	Strong	12.5 mm	301	Overgrowth of biofilm
3	Male	42	T1bNX	Glottic	Salvage	Yes, pre-TL	Strong	10 mm	332	Demonstration during Provox course
4	Male	47	T2N0	Glottic	Salvage	Yes, pre-TL	Strong	12.5 mm	251	No leakage*
5	Male	62	T4N0	Transglottic	Primary	Yes, post-TL	Strong	6 mm	106	Leakage around the prosthesis
6	Female	56	T3N0	Supraglottic	Primary	Yes, post-TL	Strong	8 mm	132	Overgrowth of biofilm
7	Male	65	T2aN0	Glottic	Salvage	Yes, pre-TL	Strong	6 mm	157	Inadequate sizing
8	Male	43	T4N2a	Supraglottic	2nd primary	Yes, pre-TL	Strong	6 mm	20	Leakage around the prosthesis
9	Male	43	T4N2a	Supraglottic	2nd primary	Yes, pre-TL	Strong	6 mm	< 10**	Leakage through the prosthesis
10	Male	41	T2N0	Glottic	2nd primary	Yes, pre-TL	Light	8 mm	5	Leakage through the prosthesis

[1] Age was calculated at time of TL

[2] TL = Total laryngectomy

[3] TNM classification according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging manual

[4] RT = Radiotherapy

[5] PAV = Provox ActiValve

* No leakage, this patient went abroad and received a free Provox ActiValve XtraStrong

** The exact date of insertion of the voice prosthesis remained unknown. We knew however that the device lifetime was within 10 days. For calculating the median device lifetime we used a device lifetime of 9 days for this patient

Table 1b. Patient and prostheses characteristics (Fluorescence In Situ Hybridization and Confocal Laser Scanning Microscopy)

No.	Gender	Age[1] at TL[2]	TN-classification primary tumor[3]	Primary tumor	Indication for TL	RT[4] pre- or postoperatively?	Magnetic force in PAV[5]	Size of PAV	Device lifetime (days)	Reason of replacement
1	Male	57	T4N0	Glottic	Salvage	Yes, pre-TL	Light	6 mm	168	Leakage through/around the prosthesis
2	Male	47	T2N0	Glottic	Salvage	Yes, pre-TL	Strong	12.5 mm	137	Leakage through/around the prosthesis
3	Male	50	T2N0	Supraglottic	Salvage	Yes, pre-TL	Light	6 mm	177	Leakage around the prosthesis
4	Male	64	T1N0	Hypopharynx	2nd primary	Yes, pre-TL	Strong	12.5 mm	148	Unknown
5	Male	43	T2N2c	Hypopharynx	Salvage	Yes, pre-TL	Light	8 mm	311	Leakage through/around the prosthesis
6	Male	69	T4N0	Transglottic	Primary	Yes, post-TL	Light	4.5 mm	518	Leakage through/around the prosthesis
7	Male	50	T1bNX	Glottic	Salvage	Yes, pre-TL	Strong	10 mm	543	Leakage through the prosthesis
8	Female	59	T4N0	Supraglottic	Primary	Yes, post-TL	Strong	6 mm	731	Leakage through the prosthesis
9	Male	48	T2N0	Glottic	Salvage	Yes, pre-TL	Light	10 mm	26	Leakage through/around the prosthesis
10	Female	56	T3N0	Supraglottic	Primary	Yes, post-TL	Light	8 mm	136	Prosthesis distorted
11	Female	78	T2N0	Glottic	Salvage	Yes, pre-TL	Light	4.5 mm	70	Leakage through/around the prosthesis
12	Male	44	T4N0	Glottic	Salvage	Yes, pre-TL	XtraStrong	4.5 mm	388	Infected fistula
13	Male	47	T2N0	Glottic	Salvage	Yes, pre-TL	Strong	12.5 mm	180	Leakage through the prosthesis
14	Male	64	T2N0	Glottic	Salvage	Yes, pre-TL	Light	8 mm	311	Leakage through the prosthesis
15	Male	55	T4N0	Transglottic	Salvage	Yes, pre-TL	Light	6 mm	280	Unknown
16	Male	64	T1N0	Hypopharynx	2nd primary	Yes, pre-TL	Strong	10 mm	14	Inadequate sizing
17	Female	78	T2N0	Glottic	Salvage	Yes, pre-TL	Light	4.5 mm	136	Leakage through the prosthesis
18	Male	58	T4aN1	Supraglottic	Primary	Yes, post-TL	Light	8 mm	21	Unknown
19	Female	61		Papillary thyroid	Salvage	No	Light	6 mm	43	Leakage through the prosthesis
20	Male	57	T4N0	Glottic	Salvage	Yes, pre-TL	Light	6 mm	189	Unknown
21	Male	55	T3N2	Nasopharynx	Dysfunctional larynx	Yes, pre-TL*	Strong	6 mm	334	Leakage through/around the prosthesis
22	Male	73	T2N0	Glottic	Salvage	Yes, pre-TL	Light	6 mm	738	Leakage through the prosthesis
23	Female	56	T3N0	Supraglottic	Primary	Yes, post-TL	Light	8 mm	112	Leakage through the prosthesis

[1] Age was calculated at time of TL
[2] TL = Total laryngectomy
[3] TNM classification according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging manual
[4] RT = Radiotherapy
[5] PAV = Provox ActiValve
* This patient also received chemotherapy concomitant with radiotherapy

Composition and diversity of the biofilm using IPES

A total of 10 Provox ActiValve voice prostheses were analyzed.

Fungal populations

Figure 3 shows an overview of the proportion per fungus of all fungal species. Six species in total were found: *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida tropicalis*, *Candida xylopsoci* and *Saccharomyces cerevisiae*. Both on the fluoroplastic and on the silicone material, *Candida albicans* and *Candida tropicalis* were the dominant populations. Figure 4 shows the Simpson index for fluoroplastic and silicone material respectively as a measure of microbial diversity. An increasing Simpson Index indicates increasing microbial diversity. For almost all prostheses, the microbial diversity is higher on the silicone material. Microbial diversity is significantly lower on the fluoroplastic material ($p = 0.017$, Wilcoxon test); *Candida albicans* or *Candida tropicalis* are the main species present on the fluoroplastic material, as is depicted in Figure 3.

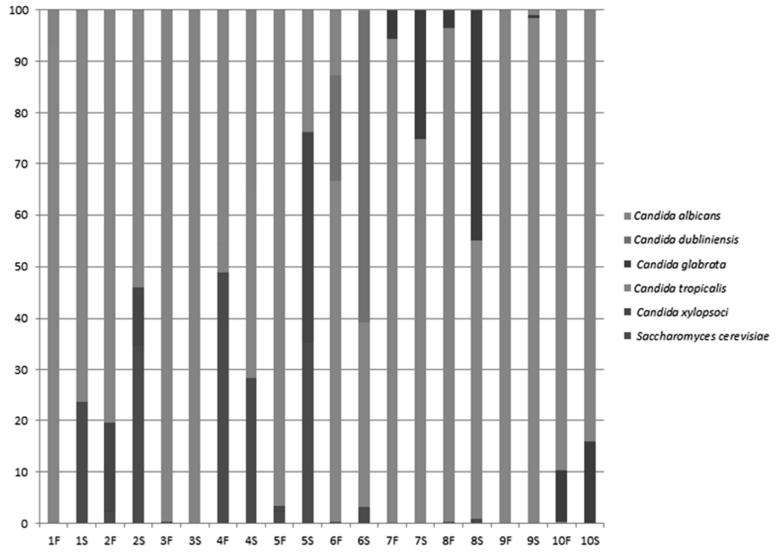

Figure 3. Histogram of all the fungal populations on the fluoroplastic and silicone material. F indicates fluoroplastic and S indicates silicone material. The number in front of F or S indicates the number of the voice prosthesis. These numbers correspond with the numbers in Table 1a. Both on the fluoroplastic and on the silicone material, *Candida albicans* and *Candida tropicalis* were the dominant populations.

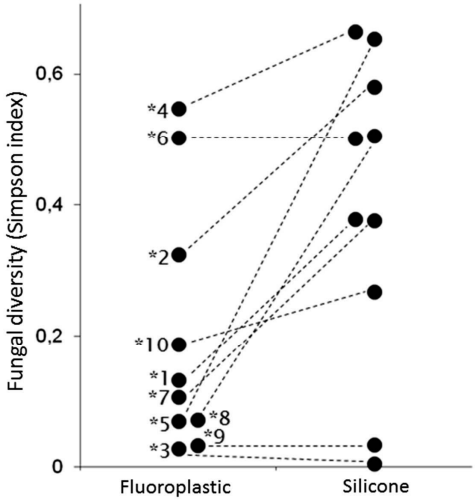

Figure 4. Simpson index of the fungal species on fluoroplastic and silicone material. An increasing Simpson index indicates a higher diversity and more equal distribution of fungal species. For almost all prostheses, the microbial diversity is higher on the silicone material. Each number in the graph represents a voice prosthesis.

Bacterial populations

The most dominant bacterial species are presented in Figure 5. Especially *L. gasseri* is highly prevalent on most prostheses. *L. gasseri* and *L. johnsonii* were grouped together as they cannot be distinguished from one another using 16S rRNA sequencing. The *Streptococcus* genus colonized the fluoroplastic material to a lesser extent than the silicone material ($p = 0.047$, Wilcoxon test). On most prostheses *L. gasseri* tended to be relatively abundant on the fluoroplastic material when compared to the silicone material ($p = 0.059$, Wilcoxon test). Similarly, bacterial diversity usually tended to be lower on the fluoroplastic material ($p = 0.14$). PCA analysis clearly shows the inverse relationship between the abundance of *L. gasseri* and microbial diversity (Figure 6). It should furthermore be noted that PCA analysis demonstrates that one sample pair (sample 6) represented an extreme outlier. Removal of this outlier results in all of the above described patterns reaching statistical significance; $p = 0.008$ for the increase of *L. gasseri*, $p = 0.011$ for the decrease in streptococcal abundance and $p = 0.038$ for the decrease in diversity.

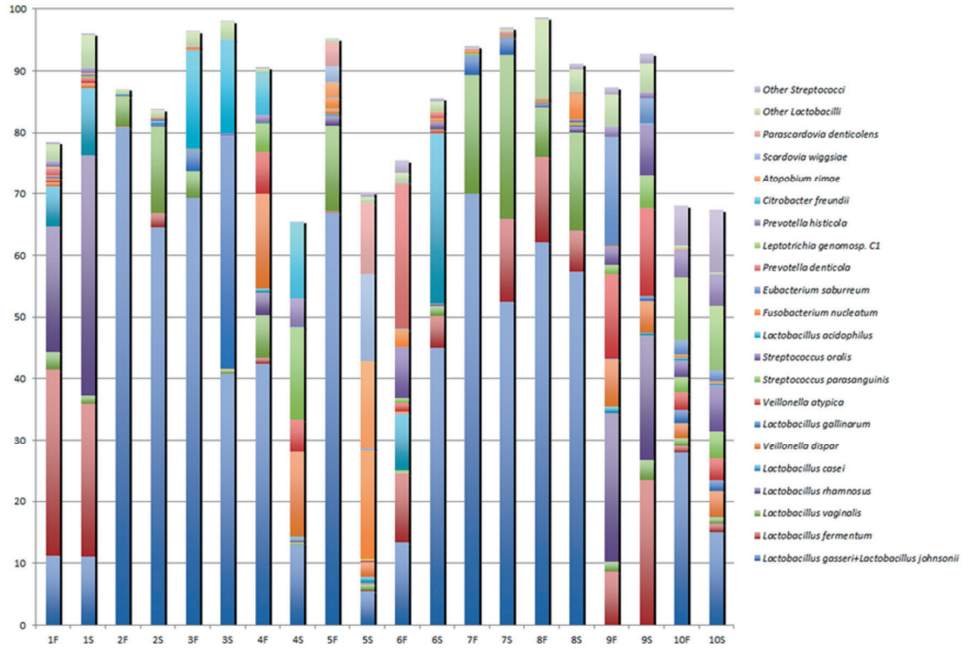

Figure 5. Histogram of the dominant bacterial populations. F indicates fluoroplastic and S indicates silicone material. The number in front of F or S indicates the number of the voice prosthesis. Note that numbers do not count to 100% because we only show the most dominant bacterial populations. These numbers correspond with the numbers in Table 1a. Especially *L. gasseri* is highly prevalent on most prostheses. The *Streptococcus* genus colonized the Fluoroplastic material to a lesser extent than the silicone material.

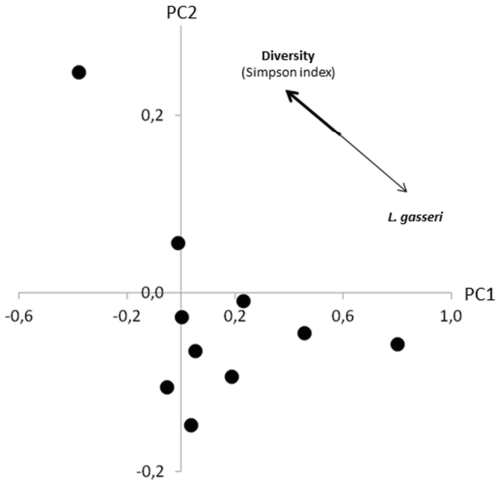

Figure 6. Difference in diversity between fluoroplastic and silicone material analysed with the principal component analysis. The biofilm on fluoroplastic material of most prostheses is less diverse, with a subsequent increase in the proportion of *L. gasseri* and *L. Johnsonii* together. PC = principal component.

Visualization of the biofilm using FISH and CLSM

A total of 23 Provox ActiValve voice prostheses were analyzed. In 11 out of 23 voice prostheses the biofilm on the fluoroplastic material was visualized. It was not possible to visualize the biofilm of the other 12 voice prostheses because there was too little biofilm (7 prostheses), the valve in the prosthesis was lost (probably during processing; 3 prostheses) or the prosthesis was frozen (2 prostheses). Because it has already been shown by several authors that Candida-species grow into the silicone material (4,5), we focused on the fluoroplastic material. To allow comparison with earlier reported results, visual analysis of the biofilm formation on silicone material was performed in two of the Provox ActiValve prostheses.

The median lifespan of the 23 voice prostheses was 177 days (range 14 to 738 days). On most prostheses, the biofilm on the valve was visible to the naked eye. Figures 7 and 8 show images of the biofilm on the fluoroplastic valve and the silicone material after different prosthesis lifespans. In both figures the bacteria (red signal) are located 'on' the yeasts (green signal). In the fluoroplastic material no ingrowth of the biofilm was found in any of the specimens (Figure 7). In contrast, the silicone material does show ingrowth of Candida-species as in-growing bags of yeast colonies without visual hyphae, as can be seen in Figure 8.

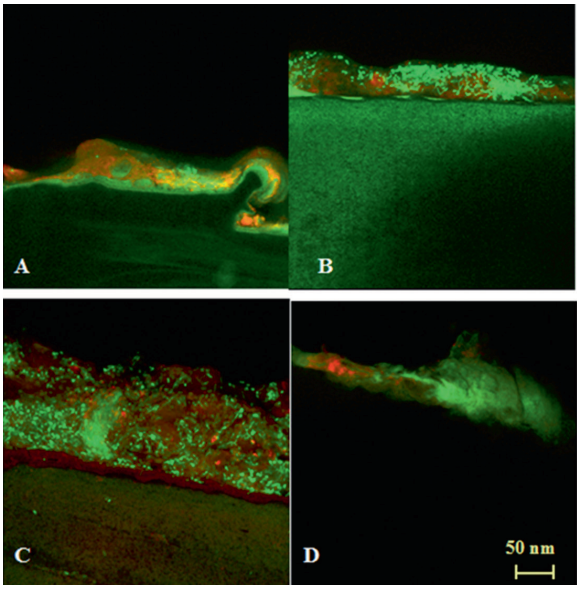

Figure 7. Confocal laser scanning microscopy images of the fluoroplastic material of the Provox ActiValve after fluorescence in situ hybridization with the rhodamine-labeled EUB338 probe (red signal, specific for bacteria) and a fluorescein-isothyocyanate (FITC)-labeled EUK516 probe (green signal, specific for eukaryotes). A-D: no ingrowth of the Candida-species was observed for any of the fluoroplastic material-samples. A: a 311 (prosthesis 5) day old biofilm. B: a 112 (prosthesis 23) day old biofilm without ingrowth of Candida-species. C: a 136 (prosthesis 10) day old biofilm. D: a 543 (prosthesis 1) day old biofilm.

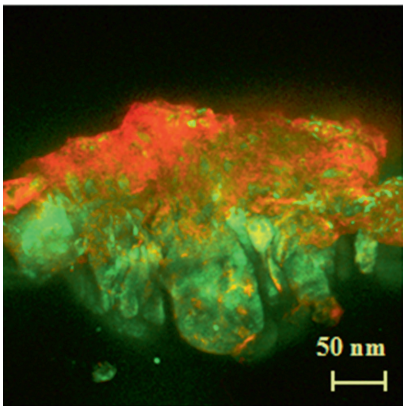

Figure 8. Confocal laser scanning microscopy image of the silicone material of the Provox ActiValve after fluorescence in situ hybridization with the rhodamine-labeled EUB338 probe (red signal, specific for bacteria) and a fluorescein-isothyocyanate (FITC)-labeled EUK516 probe (green signal, specific for eukaryotes). A 311 (prosthesis 5) day old biofilm.

DISCUSSION

The Provox ActiValve is “a problem-solving device” for those patients requiring frequent replacements (every few weeks) because of biofilm overgrowth or inadvertent opening of the valve during swallowing or inhalation (9). As already clinically proven, the Provox ActiValve has a longer device lifespan than the Provox2 (10, 11). In the present study, we could confirm the hypothesis that Candida-species do not destroy the fluoroplastic valve material of the Provox ActiValve. This is most likely due to the nature of the material, which, as has been shown in this study, is not permeable by Candida-species. Thus, patients requiring frequent replacements of their usual voice prosthesis because of leakage through the prosthesis can benefit from the Provox ActiValve. Nevertheless, the silicone material of the body and hinge of the Provox ActiValve prosthesis can still be damaged or destroyed by Candida-species, as has been published before (5), ultimately leading to failure of the valve mechanism and transprosthetic leakage, which in this series also proved the main reason for its replacement.

We further found that, although the overall composition of the biofilm on both material components is about the same, the diversity of bacterial and fungal species is lower on the fluoroplastic material. On both the fluoroplastic and the silicone material the predominant bacterium was *L. gasseri* and the predominant fungi were *Candida albicans* and *C. tropicalis*. With regard to the bacteria, the abundance of *L. gasseri* had increased on the fluoroplastic material relative to other bacterial species - or, more precisely, the other bacterial species had decreased in abundance. The fungal diversity was also lower on the fluoroplastic material and usually only *C. albicans* or *C. tropicalis* can be found. Buijssen et al also found that *L.*

gasseri was the predominant bacterium on silicone material (5). Lactobacilli are common bacteria in the normal oral cavity and account for about 1% of cultivable oral microbiota (20). Their presence on voice prostheses is thus not surprising. This also holds for Candida-species, which are normal commensals of humans and have already been identified as the most important causative species for failure and/or destruction of the silicone valve (5).

The head and neck region is a non-sterile environment. Bacteria and fungi belonging to the oral microbiota include lactobacilli, streptococci, staphylococci and Candida. Voice prostheses become rapidly colonized by these organisms that subsequently develop into a biofilm. The species in the biofilm are embedded within a self-produced matrix of extracellular material. *C. albicans* in particular is a dominant fungus in the biofilm. Candida species however do not exist alone in a biofilm and are thought to interact with the dominant bacteria: streptococci, staphylococci and lactobacilli. Candida changes morphologically and forms hyphae. These hyphae form the organisms' virulence and invasiveness. It has been suggested that lactobacilli in combination with Candida reduce the thickness of the biofilm in vitro, which possibly extends the lifespan of the device (5).

To visualize the biofilm we used FISH and CLSM. These methods have already been used by Buijssen et al (2012) to visualize the biofilm on silicone material (5). FISH is especially suitable for the identification of multiple species in a biofilm. For visualization of the biofilm it was logical to opt for CLSM, an optical microscope with a laser beam; CLSM has the ability to control the depth of the field, to reduce background information and to collect serial optical sections from thick samples. The latter was very useful in the present study, because the fluoroplastic material was difficult to cut into thin slices.

For the identification of bacterial and fungal species IPES was used. This is the first time this technique was used to analyze microbial communities by combining amplicons sequencing of the bacterial 16S rRNA gene and the eukaryotic ITS regions on these voice prostheses. In the present study, the combined analysis in a single Miseq run turned out to be quite successful and is now preferred for analysis of microbial diversity.

This study clearly shows that fluoroplastic material is not susceptible to destruction by Candida-species. This might be useful in the further improvement of the durability of voice prostheses.

In conclusion, the fluoroplastic valve components of the Provox ActiValve appear not to be susceptible for ingrowth and destruction by Candida-species. Furthermore, although the composition of the biofilm on both material components of the Provox ActiValve is not significantly different from the composition of the biofilm on silicone voice prostheses, there is less diversity in the biofilm on the fluoroplastic material. These findings provide evidence of material-technical progress in voice prosthesis development.

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CHAPTER 11

General Discussion

In the last decades, the treatment landscape for patients with advanced larynx cancer has changed. Whereas patients with advanced larynx cancer used to be treated with organ-sacrificing total laryngectomy (TL), the last decades patients increasingly were treated with organ-preserving modalities, i.e. radiotherapy (RT) alone, or RT combined with chemotherapy (CRT). This thesis describes and discusses institutional and national oncological treatment outcomes, surgical sequels and postlaryngectomy voice rehabilitation aspects.

STAGING AND TREATMENT OF ADVANCED LARYNX CANCER

In 1999, the Dutch Head and Neck Society (former Netherlands Cooperative Head and Neck Tumor Group) published a consensus document on larynx cancer diagnostics and treatment (1). That document was, as much as possible, based on the evidence present in the literature and in part, based on an earlier national study reporting on the treatment results of T3 larynx cancer (2-4). That study showed that planned combined treatment (consisting of surgery and RT) significantly increased corrected survival. Primary surgery and primary RT had similar outcomes. With the improved RT protocols (i.e. reduction of the overall treatment time in the DAHANCA protocol) emerging at that time, it was expected that loco-regional control and survival would improve, and the need for TL with or without adjuvant RT, at that time the standard treatment for T3 larynx cancer in most head and neck services in the Netherlands and worldwide, would decrease in spite of the outcome of that retrospective study. Patients with T4 larynx cancers on the other hand are still laryngectomized and receive adjuvant RT in most centers. This policy in essence also did not change after the publication of the RTOG 91-11 study, that reported a better loco-regional control for advanced larynx cancer after concurrent chemoradiotherapy as compared to induction chemotherapy and RT or single modality RT (5). However, in this study large-volume T4 cases were excluded.

In view of the ongoing discussion about the status of the (chemo)RT-based larynx preservation approach in both T3 and T4 cancer, and its possible impact on survival, in Chapter 2 we describe a retrospective analysis assessing whether the commonly found difference in survival between T3 and T4, obviously also depending on neck node status, still exists despite the fact that T3 disease was not treated surgically since over 15 years in our Institute. In this cohort of 182 patients treated with TL, RT or concomitant chemoradiation (CCRT) between 1999 and 2008 in the Netherlands Cancer Institute no significant differences in OS were observed between T3 and T4 larynx cancer, nor between stage III and stage IV disease. The dominating prognostic factors in this study were nodal status and co-morbidity, as has been found in many other studies in head and neck cancer. The lack of a difference in survival between T3 and T4 was an unexpected finding since generally T3 tumors are considered to have a better prognosis than T4 disease, when corrected for nodal status. The fact that the majority of T3 larynx cancers were treated with RT or CCRT and the majority of T4 with TL

(+/-PORT) was a possible explanation for this finding. Variation in the staging system over time would be an unlikely explanation for this, because we uniformly restaged (based on the available radiology reports) all cases according to the latest (7th) 2010 UICC edition. However, tumor volume was not available for inclusion in that analysis. Therefore, tumor volume as possible prognostic parameter was addressed in Chapter 3. For 166 of 182 patients, imaging of sufficient quality was available for radiological tumor volume assessment. In this patient cohort, we found that tumor volume was not significantly associated with local control, loco-regional control or overall survival in the surgically treated group. In the group treated with radiotherapy there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with CCRT a significant impact of tumor volume on local control was found. In the literature studies are conflicting regarding these results (6-11). The reason why we did not find an influence of tumor volume on oncological outcome –except for the association with local control in the CCRT-group- remains unclear, but maybe it is not that surprising after all, considering our initial finding that there was also no difference in prognosis between (the smaller volume) T3 and (the larger volume) T4. It is thus probably due to a selection bias: patients with the higher tumor volumes were selected for TL (median volume T4 15.8 cc; median volume TL 19.7 cc), leaving the smaller tumors for organ preservation treatment (median volume T3 8.1 cc; median volume RT 7.4 cc; median volume CCRT 13.5 cc). And this lack of the full range of tumor volumes thus might have obscured a possible significant volume effect in the RT only group, although a trend was noted in this group as well. Another explanation might be the small number of patients in this study as illustrated by Knegjens et al. (2011). These authors found that in 360 patients treated with chemoradiation for advanced head and neck cancer, tumor volume was more powerful for predicting outcome after chemoradiation than the TNM classification (10). However, when 10 random samples of 75 patients in this cohort of 360 patients were assessed, in only 5 out of 10 samples this significant effect of tumor volume on local control could be found (see Table below (12)).

Table 4
Random series of $N = 75$ from $N = 360$. Ten series of 75 patients, all randomly selected from a larger series of 360 patients. Five of the ten randomly generated series had a p-value < 0.05 for tumor volume in a cox proportional hazards model.

Series	1	2	3	4	5	6	7	8	9	10	No of series with $p < 0.05$
p-value for volume	0.004	0.3	0.02	0.08	0.002	0.008	0.04	0.2	0.07	0.2	5

Apart from volume, for patients treated with (C)RT other parameters may be of more predictive value, like gene expression signatures, hypoxia and radio-sensitivity in general (12, 13). It has been postulated that tumor control after RT depends on killing all clonogenic cells in the tumor and that the number of clonogenic cells increases linearly with tumor volume and thus influences local control (14, 15). That possibly explains why we and others found that tumor volume was significantly associated with local control in the CCRT-group.

The above-mentioned studies included patients that were treated in the Netherlands Cancer Institute. However, to learn more about the treatment results in the Netherlands, and to assess the impact of the afore-mentioned 1999 national consensus, a population-based study was conducted, described in Chapter 4. The aim of is this study was to determine time trends for primary treatment modalities in advanced larynx cancer, overall survival and laryngectomy-free interval (LFI) over the last two decades in the Netherlands. This study comprised all Dutch patients diagnosed with squamous cell larynx cancer between 1991 and 2010. We found that for both T3 and T4 larynx cancer, the use of primary TL as a proportion of all patients diagnosed with T3 and T4 larynx cancer decreased, whereas the use of RT increased. Hoffman et al. (2006) studied patterns of care and survival after larynx cancer between 1985 and 2001 in the United States in 158.426 patients. These authors also observed a decrease in number of TLs as primary treatment for larynx cancer and an increase in RT and CRT, but that study included all larynx cancer cases and not only the advanced cases as in the present study (16). The decrease in TLs and increase in RT for T3 larynx cancer in our study is not unexpected, since the Dutch guidelines for treating larynx cancer changed in 1999 as described above.

We also found that overall survival of T3 and T4 larynx cancer differs significantly (44% and 39% respectively after 5 years). When analyzed per treatment, overall survival is similar for T3 larynx cancer after treatment with TL, RT or CRT. For T4 larynx cancer however, patients treated with RT or CRT have poorer survival compared to patients treated primarily with TL and adjuvant RT. The respective roles of organ preservation ((C)RT) treatment and organ sacrificing surgical treatment for advanced larynx cancer have been extensively addressed in the recent literature. Hoffman et al. (2006), previously mentioned, reported a decreasing trend in survival from the mid-80s to the mid-90s and, in the same period, an increase of CRT as primary treatment with a decrease in surgery. For T3N0M0 larynx cancer specifically, a significantly better 5-year relative survival was found for those patients treated with surgery and irradiation compared to patients treated with irradiation (with or without chemotherapy; 64.4% versus 49.4%). It should be noted however, that specific data regarding RT and chemotherapy were not available. Also, 'surgery' was not further specified in TL, endoscopic surgery or other surgery. In a population-based study in the Province Alberta, Canada, Dziegielewski et al. (2012) also found superior survival rates after treatment with TL for T4 larynx cancer (17). Furthermore, Chen et al. (2007), analyzing the NCDB database, reported HRs for death of 1.61 and 1.43 for RT and CRT respectively when compared to TL for stage IV larynx cancer, which are in line, but slightly higher than found in our Dutch 20-year population-based study. It has to be kept in mind, though, that stage IV in the Chen-study also includes T3N+ cancers and thus not solely T4 cancers (18).

A possible explanation for the inferior survival after RT for T4 larynx cancer may be due to unknown selection biases, such as co-morbidity, the patient and physician preferences,

intent of the treatment, and tumor characteristics, such as tumor volume and operability of the tumor. Possibly, a subgroup of patients, who underwent RT for T4 larynx cancer had inoperable disease or had significant co-morbidity and was treated with palliative intent.

The majority of the T4 cases, who were primarily treated with TL, received postoperative RT. These patients had superior survival rates when compared to those not undergoing postoperative RT. In the Dutch consensus document on larynx cancer (1999) it is recommended to add RT in case surgery is the treatment of choice (1). This recommendation was based on several studies that suggest that RT in the postoperative setting improves oncological outcome (3, 19), which is underlined (again) in this population-based study.

As reported earlier by Van Dijk et al. (2013) the decrease in survival that was seen in the United States does not seem to apply for the Netherlands (20). Hoffman et al. (2006) attributed their decrease in survival to the increase of the use of organ-preserving treatment modalities, such as RT and CRT. That we do not see a difference in survival for T3 larynx cancer after treatment with TL, RT or CRT might be due to several factors. Firstly, head and neck cancer care is highly centralized in the Netherlands in the 8 centres participating in the Dutch Head and Neck Society, which guarantees treatment by dedicated teams. This possible centralisation effect (bigger volume - better outcome) is underlined by the comparatively favorable survival figures for larynx cancer achieved in the Netherlands according to the European cancer statistics published by Sant et al. in 2009 (21). Secondly, since the late nineties altered fractionated RT is widely used for advanced larynx cancers in most centers in the Netherlands, which seems to be superior to conventional schemes of RT regarding local control and survival (22).

Next to survival, quality of life, toxicity and larynx preservation are important parameters in the decision-making process. Both organ sacrificing and preserving treatments for advanced larynx cancer significantly affect quality of life. Finizia et al (1998) studied voice and quality of life of patients treated for larynx cancer with RT with or without TL as salvage surgery. They found that irradiated patients and listeners rated their voices more favorable than that of laryngectomized patients using tracheoesophageal speech. In most studies, however, scores for quality of life were similar regarding most functions and symptoms (23-25). Moreover, one has to keep in mind that in the last two decades major progress has been made with respect to postlaryngectomy vocal, pulmonary, and olfactory rehabilitation, making the functional deficits of TL less debilitating than ever before (26).

In the retrospective cohort study in the Netherlands Cancer Institute, we reported a 5-year LFI of 72% after RT and 83% after CCRT. In the population-based study we found a 5-year LFI of 77% or higher in patients with T3 or T4 larynx cancer after RT or CRT. These findings are in agreement with the literature. In the VA-study the larynx was preserved in 64% of the

patients after 2 years for patients initially treated with induction chemotherapy combined with RT (27). The RTOG 91-11 study reported larynx preservation rates after 10 years of 82% and 64% after treatment with CCRT and RT alone, respectively (28).

With respect to reporting outcomes, in our studies, we used LFI calculated with the Kaplan-Meier method wherein we censored for death or last date of follow-up. Forastiere et al. reported, next to the larynx preservation rate, which is more or less similar to LFI, on laryngectomy-free survival (5, 28). With laryngectomy-free survival both laryngectomy and death are accounted for as an event. However, in their 2013-report they write, "*Evaluating each end point separately (e.g. survival, larynx preservation, loco-regional control) provides the clearest information and does not equally weight death and loss of one's larynx.*" This is a valid conclusion, reason not to report on this in our study.

Since the introduction of organ-preserving treatment modalities the decision in treatment of advanced larynx cancer has become more complicated. Especially in T3 larynx cancer there is discussion about what treatment modality is best for which patient. Organ-preserving treatments not only comprise RT or CCRT but also conservation laryngeal surgery, like transoral laser microsurgery (TLM) or open approach partial laryngectomies. Canis et al (2013) published the results of a cohort of 226 patients with pT3 larynx cancer treated with TLM. Five-year OS was 64.4%. The functional results were also quite favorable, 6 patients (2.7%) required a temporary tracheotomy and 2 patients (0.9%) needed a permanent tracheotomy. Percutaneous endoscopic gastrostomy tubes were temporarily necessary in 6 patients (2.7%) and permanently in 3 patients (1.3%). Unfortunately, no data on the voice quality and dietary restrictions were available. The authors concluded that the results of transoral laser microsurgery are satisfactory, but they also underline that the data are only of 1 institution and that further prospective studies should be done (29).

From the similar survival figures for T3 larynx cancer in the population-based study we might conclude that patients should be extensively counseled about the various pros and cons of the three options, i.e. TL, RT and CRT, in order to be able to take a well-informed choice. Moreover, it remains interesting to speculate about the observation that the overall survival for the T4 TL+RT group is similar than that for all T3 subgroups.

Although TN classification, sex and age are important in predicting survival and larynx preservation, many other factors play a role in decision making and patient counseling for treatment selection. Among these are co-morbidity and general condition, tumor volume, and patient and physician preferences.

THE OUTCOME AFTER TOTAL LARYNGECTOMY IN A CHANGING TREATMENT LANDSCAPE

Both in head and neck cancer in general, and in larynx cancer in particular, organ-preserving treatment modalities are increasingly applied. However, one of the challenges organ-preservation treatment has created is that the function of the target organ is not always preserved. Also, although RT as a single-treatment modality can result in serious adverse effects and incidence of complications may be higher, the addition of CRT has caused these to become more prominent and more serious (30). According to the National Cancer Institute's Common Terminology Criteria for Adverse Events (31), the most severe (grade 3-4) adverse effects due to CRT for larynx and pharynx cancer are stridor, severe (throat) pain, swallowing difficulty (dysphagia and/or aspiration), neurotoxic reactions, renal failure, and airway compromise. Dysphagia and aspiration can become so severe that permanent tube feeding is required, and airway compromise due to laryngeal edema can become so problematic that permanent tracheotomy is unavoidable. These complications can severely compromise the quality of life of a subgroup of patients and even become life threatening. In some instances, despite complete remission, removal of the dysfunctional organ, i.e. TL, is the only resolution for controlling severely disabling and potentially life-threatening aspiration and for restoring at least some quality of life for patients.

Chapter 5, 6 and 7 describe a cohort of consecutive patients that were treated with TL within the period from 2000-2012 in the Netherlands Cancer Institute. Within this cohort, first, we focused on those patients that underwent a TL for a dysfunctional larynx and second, we assessed predictive factors for the development of pharyngocutaneous fistula (PCF) and evaluated if the timing of oral intake influenced the development of PCF.

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 were presented. In these 25 patients, representing 11% of the total 10-year TL cohort in the Netherlands Cancer Institute, the indication for TL is made relatively late. Most patients already had experienced several life-threatening complications, as well as the need for a permanent tracheotomy in 13 patients and for permanent tube feeding in 20 patients, before the decision for TL was made. The severe weight loss and the inherent loss of condition (with half of the patients having a BMI < 18) also suggest that the indication for surgery in most cases was postponed for a long time. This is not surprising, because all patients were in complete remission, and apparently both the patients and the health care professionals had to "grow" toward the belief that TL was the only option left for resolving the patients' intolerable situations and for restoring of at least some quality of life. Unfortunately, we found a relatively high incidence of major complications (56%) and mortality (8%). This, however, is quite comparable to the report by Van der Putten et al., who also found postoperative complications in 56% of the

patients treated with salvage laryngectomy for residual or recurrent larynx cancer after prior treatment with (C)RT (32). In their study, the postoperative mortality rate was 3% (3 of 120 patients), but this is not significantly different from the 8% (2/25) we found (unpaired t test, P=0.17). Five-year overall survival in the series of van der Putten and colleagues was 50%, a percentage that is somewhat higher than the 35% in the present study, which also suggests that our patients were in poorer condition at the time of TL. However, the main eliciting functional problems (aspiration, recurrent pneumonia, and dyspnea) did not recur after TL. Dysphagia requiring pre-TL tube feeding was not completely eliminated in 20 of the 25 patients (80%), though, leaving 4 of 14 patients (29%) dependent on tube feeding after 2 years.

Besides studying the clinical and functional characteristics of 25 patients that underwent a TL for a dysfunctional larynx, we studied the entire cohort of patients that underwent a TL in this period and assessed predictive factors for the development of PCF, described in Chapter 6. As mentioned above, a common complication after TL is the postoperative occurrence of a PCF. In the entire 10-year cohort of a consecutive series of 217 TL patients an overall incidence of PCF of 26.3% was found. The PCF incidence was lower for primary TL (17.1%) than for salvage TL, TL after prior treatment for another HN malignancy, or TL for a larynx that was dysfunctional after (C)RT, which had incidences of 25.5%, 37.5%, and 44.0%, respectively. The overall incidence of 26.3% is quite high, but is comparable to those of many other studies in the literature. Also, the higher incidences for the various “salvage” procedures are in line with the literature (33-36). The literature regarding the role of (C)RT prior to TL as a predictive factor for PCF formation is still ambiguous. In contrast to CRT, previous RT did not increase the incidence of PCF in the present study. This finding is in concordance with those of some other studies, which also indicated RT as a non-significant contributor and CRT as a significant contributor to PCF (36, 37). With respect to the role of RT alone, several studies reported higher incidences of PCF in patients treated with single-modality RT before TL (33-35, 38-40), whereas other studies reported that RT prior to TL had no influence (36, 41, 42).

Next to (C)RT, some studies suggest early oral intake (EOI) as a possible predisposing factor for the development of PCF (43, 44). Therefore, oral intake after TL is mostly delayed until postoperative day 10–12, under the assumption that this limits the incidence of PCF. However, early oral intake could be advantageous from a psychological perspective: early oral intake can be encouraging for patients in that they seem to be returning to normalcy (more) quickly. It may reduce costs, providing that it does not lead to increased PCF. Therefore, in Chapter 7, in a consecutive series of 247 TL patients over a 12-year period we compared PCF incidence in a traditional ‘late’ oral intake protocol (start at postoperative day 10–12; LOI-group) and in an early oral intake protocol (start at postoperative day 2–4; EOI-group). We found that the incidence of PCF was not significantly different between the

two groups. This study thus suggests that EOI is safe and does not increase PCF. This is in concordance with several other studies, although in most of these studies some selection bias was apparent (45-47). Concerning reconstruction simultaneously to TL, patients who underwent standard TL started significantly earlier with oral intake than patients who were reconstructed. Similar results were found when analyzing the LOI and EOI groups separately or when patients with PCF were excluded. This was to be expected, since patients with reconstruction usually start later with oral intake than patients after standard TL. However, it is still interesting to note that in the reconstructed group the EOI protocol could also be adopted successfully, leading to an earlier start of oral intake at (median) day 4 instead of day 12 under the LOI protocol. The historical paradigm has been to start oral intake not earlier than on postoperative day 7–10, and although recent studies have shown that EOI is a safe clinical practice, there is still no consensus among head and neck surgeons worldwide when to start oral intake after TL. It is believed that EOI delays the healing process of the pharyngeal suture line, and this is considered the main reason for surgeons not to start oral intake too early (48, 49). Interestingly, however, most sutured skin incisions heal within 1–2 days in a watertight manner; apparently, the pharyngeal mucosa suture line does not behave differently in this respect (45, 50). To some degree 'oral intake' still takes place, because one can never fully prevent patients from swallowing saliva, and the subsequent movement of the pharyngeal suture line could then also contribute to the occurrence of PCF (45). Another argument in favor of EOI is that with LOI the movements of the NGT are stressing the pharyngeal suture line longer, and therefore the NGT might achieve the opposite from what is intended with respect to PCF (46, 51). Seven et al. and Aswani et al. (47, 52) compared patients, who started oral intake on day 1 and day 2, respectively, with patients who were fed via a NGT through the tracheoesophageal puncture (TEP) until the seventh postoperative day. Despite the fact that feeding through the TEP eliminates the possible negative role of the NGT in the pharynx, both studies did not observe differences in PCF rates. Aprigliano, in a retrospective study on 625 total laryngectomies, reported that patients experienced the NGT as highly unpleasant. This was the reason to abandon the use of a NGT and to start oral intake on the 3rd postoperative day, with a reported PCF incidence of 9.1 % (57/625) (53). From a psychological perspective, it could be valuable to start oral intake early in the postoperative period, because this is encouraging for patients in that they seem to be returning to normalcy (more) quickly. The only downside of this approach, however, is that, if at a later stage PCF is diagnosed and the patient already has commenced oral intake, its interruption will certainly be a disappointment. This was the case in some 60% of the PCF cases in the EOI group; at the same time, this was also not uncommon in the LOI group, where it occurred in roughly one-third of the PCF patients. Nevertheless, for the simple reason that oral intake is started earlier, under an EOI protocol more patients will have to deal with a discontinuation of already resumed oral intake—something to take into account in patient counseling. Aside from the advantages already mentioned, the possible additional advantage of an early start with oral intake is that it could potentially shorten

hospital stay, thus reducing costs. Aswani et al. reported a significantly shorter hospital stay for the subgroup of patients who were fed from day 2 after TL, but this was after exclusion of PCF patients in both the EOI and LOI group (47). Overall, however, these authors did not find a significant difference in hospital stay between both groups. Medina and Khafif found a significant decrease in hospital stay from 12 days in the LOI group to 7 days in the EOI group (45). In the present study, however, no significant difference in hospital stay between the two groups was found, nor after exclusion of patients with PCF, as in the study of Aswani et al. The reason for this is that resumption of oral intake is not the only factor determining discharge in our institute; successful restoration of oral communication is also considered relevant. Patients start with voice and speech rehabilitation not sooner than day 10–12, and are only discharged if speech proficiency is satisfactory. In future this may change, however, since capacity for providing the necessary (outpatient) rehabilitation support recently has increased.

SPEECH REHABILITATION

Another important aspect in this changing landscape concerns post TL voice rehabilitation. Prosthetic tracheoesophageal voice rehabilitation has become the gold standard for restoring oral communication in the Netherlands, as described in a review article in Chapter 8. Although post TL voice quality and control are known to differ substantially between patients, studies discussing the morphophysiology and surgical characteristics and their (interacting) effects on post-laryngectomy functioning are still sparse. Therefore, in Chapter 9, we describe a retrospective study on the assessment of post-laryngectomy voice and speech quality and their possible correlations with the speakers' surgical and medical detail in a cohort of 76 laryngectomized patients. In the standard TL (sTL) speakers there are several interesting correlations: higher speaking f0 correlates with more voicedness, and voicedness correlates with a better harmonics-to-noise ratio. Moreover, in running speech, there is a trend towards a higher f0 in females, with significant higher minimum f0 in running speech. Females also differed in formants (vocal tract cavities) with higher second formants. These f0- and formant differences might be due to gender-dependent behavior, with females trying to produce a higher pitch (by using more tension and changing the height of the neoglottis). Yet, differences between the sexes in the average vocal tract/esophageal lumen size cannot be ruled out.

One of the effects of surgical detail present in this cohort of sTL speakers is that pause/breathing time increases from no to uni- to bilateral neck dissections, and is more pronounced after extensive tongue resection, and when postoperative (C)RT is used. Another interesting finding is that patients with primary TL and postoperative (C)RT showed better harmonics-to-noise ratios than patient who had a salvage laryngectomy after prior (C)RT, suggesting

that the 'condition' of the PE segment is more favorable for voicing after primary TL than after salvage surgery.

Next to longer pause and breathing time, TL speakers with extensive base of tongue resection presented with lower first formants in /a/, possibly the result of ratio changes in the front versus back cavity and compensatory strategies to still reach the perceptual impression of /a/. The base of tongue plays a major role in speech, as is the case for swallowing. After TL, swallowing deficiencies, especially with solid food, are reported regularly (54-57). This dysphagia usually presents in pharyngeal clearance problems and prolonged (oro) pharyngeal transit times, which are the result of both the decreased control of the base of tongue and the pharyngeal wall (58, 59).

To prevent spasm of the neoglottis, most of our sTL speakers underwent a short myotomy of the upper esophageal segment (60). The need for this short myotomy to prevent spasm is controversial in literature, and several (early) studies supported pharyngeal neurectomy (61-64), with good PE pressure and higher voices, presumably by the maintenance of some residual pressure in the neoglottis as a function of the contralateral plexus. This was reason why between 1990 and 2002, neurectomy was favored. However, in view of the favorable effects of a short myotomy of the upper esophageal sphincter in one of our studies (60) neurectomy was abandoned. Interestingly, we now find that, in line with literature, speaking pitch is higher and f0 measures are more favorable after neurectomy.

Due to the various details in surgical reporting, the limited number of patients per subgroup, selection biases and the diverse surgical teams over the 30 years the surgical data were collected, an analysis of pharyngeal closure technique on voice and speech outcome was not possible retrospectively. Literature on speech failure, intraluminal pressure, fistulae, and swallowing, however, clearly favors muscle closure over non-muscles closure (63, 65-67).

Our results confirm previous studies in showing worse functional scores for speakers with (partially) reconstructed pharynges (68), although the voice outcome was more favorable for the two tubed free radial forearm flaps. This could be a selection bias. The worse voice quality after circumferential reconstruction coincides with the literature (25). Yet, other than in our study, after partial pharyngeal reconstruction, voice (and swallowing) was reported to be comparable to standard TL (69). Including electro-larynx speakers, a different subset of donor sites, and other voice quality scoring in that study, however, a direct comparison of voice outcome is difficult.

In pharyngeal reconstructions, (full) gastric pull-ups and non-circumferential reconstructions scored worst across running speech as well as in sustained /a/ measures. In 3 of the 5 (tubed) gastric pull-up patients a measurable f0 was present (however, minimally voicing),

which suggests an occasionally sufficient diameter and closure of its lumen. The other 2 had no voicing (f0).

Next to differences in voice quality, formants (resonance cavity measures) in /a/ indicate differences in pharyngeal lumen properties and cranio-caudal place of the neoglottic bar between pharyngeal reconstruction procedures. While the vocal folds in normal adult laryngeal speakers are at the height of C5-C6, imaging of TL speakers during phonation suggests that the neoglottic bar is located higher than the vocal folds (middle of C3-C5) (68, 70). Roughly speaking, formant frequencies are inversely proportional to the vocal tract length (the ratio of pharynx length to mouth length) with small formant dispersion (F2-F1 distance) indicating larger body size and shape (71). According to the effect of shortening of the vocal tract (from lips to the neoglottic bar) after laryngectomy, overall, higher formant values were found in TL speakers than in laryngeal speakers (72). Whereas in sTL speakers the neoglottic bar is usually around the level of C4, this level was found to differ widely in TL speakers with pharyngeal reconstructions (C3-C7) (68). In our dataset, the second formant and the formant dispersion were highest in tubed free radial forearm flaps, and lowest in full gastric pull up, explainable by different locations of the neoglottic bar caused by different lumen diameters and tissue characteristics of the reconstruction. Overall, the voice outcome and formants in our data suggest that smaller diameter pharynges and/or more superiorly located neoglottic bars are associated with favorable voice quality and more effortless speech. To compensate for a wide pharynx, external pressure (e.g. by PM flap) might be useful to compensate for a low tonicity. These findings are confirmed in previous studies using videofluoroscopy in which it has been shown that smaller pharyngeal diameters and optimization of the intraluminal pressures favor voicing (60, 68, 73-76). Ranges in functional outcome after TL in the present data, and the effects of treatment and surgical variables such as radiotherapy, neurectomy, neck dissection, and differences between partial or circumferential reconstructions on different aspects of voice and speech underline the importance of these variables for voice quality. More balanced data, and better detail in surgical reporting will improve our knowledge on voice quality after TL.

In post-laryngectomy tracheoesophageal voice rehabilitation the material-technical properties of the voice prosthesis (VP) play an important role. These VPs are not permanent implants and require regular replacement, which mostly is a simple outpatient clinic procedure without local anesthesia. As already introduced in the General Introduction, the main reason for VP replacement is transprothetic leakage, which is caused by microbial biofilm formation on the device causing failure of the valve mechanism. This biofilm consists of a mixture of bacteria and fungi, and in particular: Candida species that grow into and subsequently build up on the silicone rubber (79). The Provox ActiValve (Atos Medical AB, Horby, Sweden) was developed to solve this problem in a material-technical way (80). 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. Therefore, as described in Chapter 10, we collected 33 dysfunctional Provox ActiValves and performed biofilm-analysis by Illumina paired-end sequencing (IPES) and assessment of the biofilm-material interaction with fluorescence in situ hybridization (FISH) and confocal laser scanning microscopy (CLSM). With IPES we found that the composition of the biofilm on both material components of the Provox ActiValve is not significantly different from the composition of the biofilm on silicone voice prostheses, but there is less diversity in the biofilm on the fluoroplastic material. On both the fluoroplastic and the silicone material the predominant bacterium was *L. gasseri* and the predominant fungi were *Candida albicans* and *C. tropicalis*. With regard to the bacteria, the abundance of *L. gasseri* had increased on the fluoroplastic material relative to other bacterial species - or, more precisely, the other bacterial species had decreased in abundance. The fungal diversity was also lower on the fluoroplastic material and usually only *C. albicans* or *C. tropicalis* can be found. Buijssen et al also found that *L. gasseri* was the predominant bacterium on silicone material (79). Lactobacilli are common bacteria in the normal oral cavity and account for about 1% of cultivable oral microbiota (81). Their presence on voice prostheses is thus not surprising. This also holds for Candida-species, which are normal commensals of humans and have already been identified as the most important causative species for failure and/or destruction of the silicone valve (79).

With FISH and CLSM we found that in none of the cases ingrowth of Candida-species was present in the fluoroplastic material. We subsequently concluded that the fluoroplastic material of the Provox ActiValve appears to be insusceptible to destruction by Candida-species. This is most likely due to the nature of the material. Thus, patients requiring frequent replacements of their usual voice prosthesis because of leakage through the prosthesis can benefit from the Provox ActiValve. Nevertheless, the silicone material of the body and hinge of the Provox ActiValve prosthesis can still be damaged or destroyed by Candida-species, as has been published before (79), ultimately leading to failure of the valve mechanism and transprosthetic leakage, which in this series also proved the main reason for its replacement. This finding might be useful in the further improvement of the durability of voice prostheses.

Future prospects

In the future, possibly markers or assays predicting response and larynx preservation will become more important (82). Throughout the world many researchers have studied molecular markers, short term cultures, imaging characteristics, chemoselection and other approaches to predict response. Nomograms, two-dimensional diagrams that permit the estimated graphical computation of a function, might become more useful especially when

incorporated in a web based prediction model (83, 84). With data from the population-based study as presented in Chapter 4 we are planning to build a nomogram that might help physicians in the outpatient clinic in treatment decision-making in patients with advanced larynx cancer. Nevertheless, physicians should always take the patient's wishes and individual characteristics of the patient into account since in a nomogram only a selection of parameters is included.

With regard to the development of PCF: presently, the day of initiating oral intake after TL differs between the head and neck services in the Netherlands. In Chapter 7 we found that an EOI-protocol in this cohort did not lead to a significantly increased number of PCF. However, duration of hospitalization was not significantly different between the two groups, possibly explained by the fact that patients, in general, receive speech rehabilitation clinically 12 days postoperatively. Duration of hospitalization will possibly be shortened if patients receive speech rehabilitation in the outpatient clinic. Therefore, a multicenter randomized controlled trial is under planning to evaluate if EOI (and speech rehabilitation in the outpatient clinic) will shorten duration of hospitalization without an increased complication rate and decrease of quality of life when compared to LOI and speech rehabilitation clinically.

Finally, further improvements of the durability of voice prostheses remain important in order to maintain quality of life for patients after TL in a changing treatment landscape where an increasing number of patients undergo TL after (C)RT. This is something that also goes for the new surgical voice prosthesis implantation device, the Provox Vega Puncture Set. This recently developed device has made tracheoesophageal puncture with direct voice prosthesis insertion easier and seemingly also less traumatic than the former standard procedure, using a relatively crude, non-disposable instrument. This lesser trauma aspect is very relevant in this changing landscape, and studies to evaluate this are under way.

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SUMMARY

In the last two to three decades, the treatment landscape for patients with advanced larynx cancer has changed. Whereas for long patients with advanced larynx cancer were treated with organ-sacrificing total laryngectomy (TL), the last decades an increasing number of patients are treated with organ-preserving modalities, i.e. radiotherapy (RT) alone, or RT combined with chemotherapy (CRT). This thesis describes and discusses institutional and national treatment outcomes of advanced larynx cancer, and some of the surgical sequels and voice rehabilitation aspects of TL. **Chapter 1** provides a general introduction into the epidemiology, staging and treatment outcomes of (advanced) larynx cancer. Moreover, an overview is given on (prosthetic) voice rehabilitation after TL with focus on possible relations between voice quality and surgical details, and on biofilm growth of voice prostheses, the main reason for failure of these semi-permanent implants.

Part I focused on treatment and survival trends in advanced larynx cancer. **Chapter 2** presents a retrospective cohort study of 182 consecutive patients treated for advanced (T3-T4) larynx cancer between 1999 and 2008 in the Netherlands Cancer Institute. The aim was to assess overall survival (OS), loco-regional control and laryngectomy-free interval (LFI) after treatment with RT, concomitant CRT (CCRT) or TL for T3 and T4 larynx cancer. Of the 182 patients, 102 patients received RT (82.4% T3), 20 patients CCRT (60.0% T3), and 60 patients TL+RT (91.7% T4). The 5-year OS was 52% for T3 larynx cancer, 48% for T4 larynx cancer, 50% after RT, 43% after CCRT and 52% after TL+RT. The 5-year LFI was 72% after RT and 83% after CCRT. Thus, neither survival according to staging (T3 versus T4 larynx cancer), nor according to treatment modality (TL + RT versus (CC)RT) showed differences for either of the two. In view of this somewhat unexpected finding of a lack of the usual discriminatory role of T classification for survival, but also for loco-regional control, the question arose whether tumor volume could play such a role in this patient cohort. This subsequent study is presented in **Chapter 3**. For 166 of 182 patients, imaging of sufficient quality was available for radiological tumor volume assessment. In this patient cohort, which despite the 9% missing tumor volumes was not significantly different from the total cohort of 182 patients, we found that tumor volume was not significantly associated with local control, loco-regional control or OS in the surgically treated group. In the group treated with RT there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with CCRT a significant impact of tumor volume on local control was found, meaning that in this subgroup the larger tumors fared worse. The reason why we did not find an influence of tumor volume on oncological outcome –except for the association with local control in the CCRT-group- remains unclear, but maybe it is not that surprising after all, considering our initial finding that there was also no difference in prognosis between (the smaller volume) T3 and (the larger volume) T4. The reason for this absence of a clear volume effect probably is selection bias: patients with the higher

tumor volumes were selected for TL (median volume T4 15.8 cc; median volume TL 19.7 cc), leaving the smaller tumors for organ preservation treatment (median volume T3 8.1 cc; median volume RT 7.4 cc; median volume CCRT 13.5 cc). And this lack of the full range of tumor volumes thus might have obscured a possible significant volume effect in the RT only group, although a trend was noted in this group as well. Another explanation might be the small numbers included in this study.

In **Chapter 4**, the results of a 20-year population-based study in the Netherlands are presented. The aim of this study was to determine time trends for primary treatment modalities in advanced larynx cancer, OS and LFI over the last two decades in the Netherlands. This study comprised all Dutch patients diagnosed with squamous cell larynx cancer between 1991 and 2010, data were provided by two unique databases in The Netherlands: the Netherlands Cancer Registry (NCR) and the PALGA foundation database ('the nationwide network and registry of histo- and cytopathology in the Netherlands'). We found that over these two decades for both T3 and T4 larynx cancer, the use of primary TL as a proportion of all patients diagnosed with T3 and T4 larynx cancer decreased, whereas the use of RT increased. The decrease in TLs and increase in RT for T3 larynx cancer in our study is not unexpected, since in 1999 the evidence-based consensus guidelines of the Dutch Head and Neck Society (former Dutch Cooperative Head and Neck Oncology Group) for treating larynx cancer were changed, mainly with respect to T3, for which (single modality, accelerated) RT became the preferred treatment modality. Overall survival of T3 and T4 larynx cancer in this large cohort of 3,794 patients differs significantly (44% and 39% respectively after 5 years). When analyzed per treatment modality, overall survival is similar for T3 larynx cancer after treatment with TL, RT or CRT. For T4, overall survival after TL with postoperative RT was significantly better than after RT and CRT (HR for death TL: 1.00 (reference value), RT: HR 1.50 (95% CI 1.33-1.71; $p<0.0001$) and CRT: 1.27 (95% CI 1.01-1.59; $p=0.04$)). These survival figures in the population-based study can help in counseling patients about the various pros and cons of the three options, i.e. TL, RT and CRT, in order to be able to take a well-informed choice.

In **Part II** outcomes after TL in this changing treatment landscape are presented. **Chapter 5, 6 and 7** describe a cohort of consecutive patients that were treated with TL within the period 2000-2012 in the Netherlands Cancer Institute. We focused on patients who underwent a TL for a dysfunctional larynx after prior organ preservation treatment, assessed predictive factors for the development of pharyngocutaneous fistulization (PCF), and evaluated if the timing of oral intake influenced the development of PCF. **Chapter 5** describes the results of a retrospective analysis of the relevant clinical and functional characteristics of 25 patients who underwent TL for a dysfunctional larynx. In these 25 patients, representing 11% of the total 10-year TL cohort in the Netherlands Cancer Institute, the indication for TL is made relatively late. Most patients already had experienced several life-threatening complications, such as

pneumonia and the need for a permanent tracheotomy in 13 patients and for permanent tube feeding in 20 patients, before the decision for TL was made. The severe weight loss and the inherent loss of condition (with half of the patients having a BMI < 18) also suggest that the indication for surgery in most cases was postponed for a long time. In hindsight, this is not surprising, because all patients were in complete remission, and apparently both the patients and the health care professionals had to "grow" toward the belief that TL was the only option left for relieving the patients' intolerable situations and for restoring of at least some quality of life. Unfortunately, we found a relatively high incidence of major complications (56%) and mortality (8%). Nevertheless, most of the surviving patients regained a decent quality of life and were saved from their debilitating aspiration problems. Subsequently, in **Chapter 6** we studied the entire cohort of patients that underwent a TL in this period (2000-2010) and assessed predictive factors for the development of PCF. PCF is a common complication after TL. In the entire 10-year cohort of a consecutive series of 217 patients an overall incidence of PCF of 26.3% was found. The PCF incidence was lower for primary TL (17.1%) than for salvage TL, TL after prior treatment for another HN malignancy, or TL for a larynx that was dysfunctional after (C)RT, which had incidences of 25.5%, 37.5%, and 44.0%, respectively. Predictive factors for PCF were hypopharynx cancer, an albumin level of less than 40 g/L, previous CRT, more extended pharyngeal resection and pharynx reconstruction. In contrast to CRT, previous RT did not increase the incidence of PCF in the present study. The effect of the timing to resume postoperative oral intake on PCF was addressed in **Chapter 7**. Some studies suggest early oral intake (EOI) as a possible predisposing factor for the development of PCF. Therefore, oral intake after TL is mostly delayed until postoperative day 10–12, under the assumption that this limits the incidence of PCF. However, EOI could be advantageous from a psychological perspective: EOI can be encouraging for patients in that they seem to be returning to normalcy (more) quickly. It may reduce costs, providing that it does not lead to increased PCF. This effect of oral intake timing on PCF incidence was retrospectively assessed in a consecutive series of 247 patients over a 12-year period. During the first 6 years the traditional 'late' oral intake protocol (start at postoperative day 10–12; LOI-group) was applied, whereas in the subsequent period an EOI protocol (start at postoperative day 2–4; EOI-group) was in place. We found that the incidence of PCF was not significantly different between the two groups. This study thus suggests that EOI is safe and does not increase PCF.

In **Part III** postlaryngectomy rehabilitation facets are presented. Prosthetic tracheoesophageal voice rehabilitation has become the gold standard for restoring oral communication in the Netherlands, which is reviewed in **Chapter 8**. In **Chapter 9**, we describe a retrospective study on the assessment of post-laryngectomy voice and speech quality and their possible correlations with the speakers' surgical and medical detail in a cohort of 76 laryngectomized patients. We found that the ranges in voice outcome after TL are related to variables like radiotherapy, neurectomy, neck dissection, and reconstruction procedures. In this patient

cohort gender/speaker behavior appears to have an influence on the f0 in running speech. Overall, our results suggest that narrower pharynges and/or more superiorly located neoglottic bars are associated with more favorable voice quality. Patients with pharyngeal lumen reconstructions (i.e. by PM myocutaneous flaps and (tubed) gastric pull-ups) have the poorest voices. In sTL, neurectomy may be favorable.

Finally, in **Chapter 10**, we present a study on biofilm growth of voice prostheses, the main reason for failure of these semi-permanent implants. We studied the Provox ActiValve, in which we focused on the composition and ingrowth of the biofilm on the two material components of this prosthesis, i.e. silicone and fluoroplastic. The techniques used to identify the various bacterial and fungal species in the biofilm were Illumina paired-end RNA sequencing (IPES), fluorescence in situ hybridization (FISH) and confocal laser scanning microscopy (CLSM). Thirty-three dysfunctional Provox ActiValves were collected from patients. With IPES we found that the composition of the biofilm on both material components of the Provox ActiValve is not significantly different from that on purely silicone voice prostheses, but that there is less diversity in the biofilm on the fluoroplastic material. With FISH and CLSM we found that in none of the cases ingrowth of Candida-species was present in the fluoroplastic material. We therefore can conclude that the fluoroplastic material of the Provox ActiValve is insusceptible to destruction by biofilm/Candida-species. This might have implications for future voice prosthesis developments.

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

SAMENVATTING

In de laatste 20-30 jaar is er veel veranderd wat betreft de behandeling van patiënten met een voortgeschreden (T3 en T4) larynx carcinoom (strottenhoofdkanker). Tot circa 30 jaar geleden werden patiënten met een voortgeschreden larynx carcinoom vrijwel uitsluitend behandeld met een totale laryngectomie, waarbij het gehele strottenhoofd verwijderd wordt. Meer recent echter, worden patiënten steeds vaker orgaan sparend behandeld met bijvoorbeeld radiotherapie, al dan niet gecombineerd met chemotherapie. In dit proefschrift beschrijven we zowel de behandelresultaten in het Antoni van Leeuwenhoek als de landelijke behandelresultaten van het voortgeschreden larynxcarcinoom na orgaan offerende (totale laryngectomie) en orgaan sparende ((chemo)radiotherapie) behandeling. Daarna gaan we in op een aantal aspecten die (kunnen) spelen na een totale laryngectomie, zoals het ontwikkelen van een faryngocutane fistel (verbinding tussen keelholte en huid) en de spraakrevalidatie na een totale laryngectomie.

In **hoofdstuk 1** geven we een introductie tot de epidemiologie, stadiering en oncologische resultaten van (voortgeschreden) larynx carcinoom. Daarnaast wordt kort ingegaan op spraak revalidatie na een totale laryngectomie waarin we focussen op mogelijke relaties tussen stemkwaliteit en chirurgische karakteristieken en op biofilm groei op de klep van een stemprothese. Groei van een biofilm op de klep is een belangrijke reden van lekkage door een stemprothese.

Deel I gaat in op de behandel- en overlevingstrends voor het voortgeschreden larynx carcinoom. Doel van **hoofdstuk 2** was het in kaart brengen van de oncologische resultaten van patiënten met een voortgeschreden (T3-T4) larynx carcinoom in het Antoni van Leeuwenhoek (1999-2008). De algehele overleving, locoregionale controle en het laryngectomie-vrije interval (LVI) na behandeling met radiotherapie, chemoradiatie of totale laryngectomie voor een T3 of T4 larynx carcinoom werden bepaald. Van de 182 patiënten, die in die periode behandeld zijn, ondergingen 102 radiotherapie (82.4% T3), 20 chemoradiotherapie (60.0% T3), en 60 patiënten een totale laryngectomie meestal met postoperatief radiotherapie (91.7% T4). De 5-jaars algehele overleving per tumor classificatie was 52% voor patiënten met een T3 larynx carcinoom en 48% voor patiënten met een T4 larynx carcinoom, en uitgesplitst per behandelmodaliteit 50% na radiotherapie, 43% na chemoradiotherapie en 52% na totale laryngectomie met/zonder radiotherapie. De 5-jaars LVI was 72% na RT en 83% na chemoradiotherapie. De overleving bleek dus niet verschillend, niet per T-classificatie (T3 versus T4), en niet per behandelmodaliteit (totale laryngectomie versus (chemo) radiotherapie). Dat er geen verschil werd gezien in overleving (maar ook niet in locoregionale controle) per T-classificatie was een onverwachte bevinding, omdat de T-classificatie over het algemeen een prognostische waarde heeft. De vraag rees daarom of het tumor volume een rol heeft in ons patiënten cohort. Die vraag onderzochten we vervolgens in

hoofdstuk 3. Voor 166 van de 182 patiënten was beeldvorming beschikbaar van voldoende kwaliteit voor radiologische beoordeling van het tumor volume. Dit patiënten cohort was niet significant anders dan het totale cohort van 182 patiënten, ondanks dat 9% van de tumor volumina niet berekend kon worden. Tumor volume bleek echter ook niet significant geassocieerd te zijn met lokale controle, locoregionale controle en algehele overleving in de chirurgisch behandelde groep. In de groep behandeld met radiotherapie was er ook geen statistisch significante associatie, maar er werd wel een trend gezien tussen lokale controle en tumor volume. Alleen in de groep patiënten behandeld met chemoradiotherapie werd een significante invloed van tumor volume op lokale controle gevonden, wat betekende dat in deze kleine subgroep de grotere tumoren het slechter deden. De reden waarom wij geen invloed van tumor volume op oncologische uitkomst vonden –behalve voor de associatie met lokale controle in de chemoradiotherapie-groep- is onduidelijk. Misschien is het echter toch niet zo verrassend gezien onze initiële bevinding, waar wij ook geen verschil in prognose vonden tussen de (kleinere) T3 tumoren en de (grotere) T4 tumoren. Waarschijnlijk heeft selectie bias een belangrijke rol gespeeld in het uitblijven van een volume-effect: de patiënten met een groter volume werden behandeld met een totale laryngectomie (mediaan volume T4 15.8 cc; mediaan volume totale laryngectomie 19.7 cc), waardoor de kleinere tumoren orgaan sparend behandeld werden (mediaan volume T3 8.1 cc; mediaan volume radiotherapie 7.4 cc; mediaan volume chemoradiatie 13.5 cc). Daardoor hadden we geen volledig 'arsenaal' aan tumor volumes en heeft dat mogelijk een significant volume effect in de radiotherapie groep versluierd (alhoewel we wel een trend vonden). Een andere reden zou het kleine aantal patiënten kunnen zijn. In **hoofdstuk 4** worden de resultaten van een landelijke studie gepresenteerd. Het doel van deze studie was om de trends te bepalen voor primaire behandeling van voortgeschreden larynx carcinoom, algehele overleving en laryngectomie-vrije interval in de laatste 20 jaar in Nederland. Alle Nederlandse patiënten die werden gediagnosticeerd met een plaveiselcelcarcinoom van het strottenhoofd tussen 1991 en 2010 werden geïncludeerd. Twee unieke Nederlandse databases vormden de basis voor deze studie: de database van de Nederlandse Kanker Registratie (NKR) en van PALGA ("Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief"). We vonden dat in deze 2 decennia voor zowel T3 als T4 larynx carcinoom de toepassing van totale laryngectomie als proportie van alle met T3 of T4 gediagnosticeerde patiënten daalde, terwijl de toepassing van radiotherapie toenam. De afname in het aantal totale laryngectomieën was niet geheel onverwacht, aangezien in 1999 een consensus document verscheen van de Nederlandse Werkgroep Hoofd-Hals Tumoren waarin de behandelrichtlijn werd veranderd, met name voor T3 larynx carcinoom. Voor het T3 larynx carcinoom werd toen geaccelereerde radiotherapie de behandeling van eerste keus. De algehele overleving van patiënten met T3 of T4 larynx carcinoom in dit grote cohort van 3794 patiënten verschilde significant (44% en 39% respectievelijk na 5 jaar). Wanneer we per behandelmodaliteit keken, was de algehele overleving voor patiënten met een T3 larynx carcinoom hetzelfde na een totale laryngectomie, radiotherapie of chemoradiotherapie. Voor T4 tumoren was de algehele

overleving na een totale laryngectomie met postoperatief radiotherapie significant beter dan na radiotherapie of chemoradiotherapie (hazard ratio (HR) voor overlijden; totale laryngectomie: HR 1.00 (referentie), radiotherapie: HR 1.50 (95% betrouwbaarheidsinterval (BI) 1.33-1.71; p<0.0001) en chemoradiotherapie: HR 1.27 (95% BI 1.01-1.59; p=0.04)). De overlevingscijfers uit deze landelijke studie kunnen de arts helpen om de patiënt beter voor te lichten over de voor- en nadelen van de drie behandelopties (totale laryngectomie, (chemo)radiotherapie), zodat de patiënt een meer weloverwogen besluit kan nemen.

In **deel II** bespreken we de uitkomsten na een totale laryngectomie in het voor het voortgeschreden larynx carcinoom veranderde 'behandellandschap'. **Hoofdstuk 5, 6 en 7** beschrijven een cohort patiënten die behandeld zijn met een totale laryngectomie in de periode van 2000-2012 in het Antoni van Leeuwenhoek. In dit cohort ging onze aandacht uit naar de patiënten die een totale laryngectomie ondergingen vanwege een disfunctioneel strottenhoofd na een eerdere orgaan sparende behandeling. Daarna onderzochten we welke factoren voorspellend zijn voor het ontwikkelen van een faryngocutane fistel (FCF) en evalueerden we of de timing van het starten van orale intake na een totale laryngectomie het ontwikkelen van een FCF beïnvloed. **Hoofdstuk 5** beschrijft de resultaten van een retrospectieve analyse van de relevante klinische en functionele karakteristieken van 25 patiënten die een totale laryngectomie ondergingen in verband met een disfunctioneel strottenhoofd. Voor deze 25 patiënten, die 11% van het totale 10-jaars cohort betreffen, werd de indicatie tot operatieve behandeling relatief laat gesteld. De meeste patiënten hadden daarvoor al verschillende ernstige complicaties, zoals een aspiratie pneumonie. Dertien en 20 patiënten waren afhankelijk van respectievelijk een permanente tracheotomie en permanente sondevoeding. Ook ernstig gewichtsverlies en de daarmee slechtere conditie (de helft van de patiënten had een BMI van < 18) wijst erop dat de keuze voor chirurgie relatief laat gesteld werd. In retrospect is dat niet verrassend aangezien alle patiënten in complete remissie waren en waarschijnlijk zowel patiënt als arts er naar toe moest 'groeien' dat een totale laryngectomie onvermijdelijk was geworden om enige kwaliteit van leven te behouden. Helaas vonden we een relatief hoge incidentie complicaties (56%) en mortaliteit (8%), wat overigens in overeenstemming bleek te zijn met de literatuur. Wel hadden de meeste overlevende patiënten een redelijke postoperatieve kwaliteit van leven en hadden zij geen aspiratie problemen meer. Daarna bestudeerden we in **hoofdstuk 6** het gehele cohort van patiënten die een totale laryngectomie ondergingen tussen 2000 en 2010. We onderzochten welke factoren voorspellend waren voor het ontwikkelen van een faryngocutane fistel (FCF). Een FCF is een veel voorkomende complicatie na een totale laryngectomie. In 217 opeenvolgende patiënten vonden wij een incidentie van FCF van 26.3%. De FCF-incidentie was lager na een primaire totale laryngectomie (17.1%) dan na een totale laryngectomie voor een recidief carcinoom na voorgaande (chemo)radiotherapie, na eerdere behandeling voor een andere hoofd-hals maligniteit, of na totale laryngectomie voor een disfunctionele larynx na (chemo)radiotherapie (incidenties waren respectievelijk

25.5%, 37.5% en 44.0%). Voorspellende factoren voor het ontwikkelen van een FCF waren hypofarynx carcinoom, een albumine van 40 g/L of minder, eerdere behandeling met chemoradiotherapie, een meer uitgebreide farynx resectie en farynx reconstructie. In tegenstelling tot chemoradiotherapie, zorgde eerdere behandeling met radiotherapie niet voor een toename in incidentie FCF in deze studie. Het effect van de timing van starten met postoperatieve orale intake op het ontwikkelen van een FCF werd onderzocht in **hoofdstuk 7**. Sommige studies suggereren dat vroeg starten met orale intake mogelijk een predisponerende factor is voor het ontwikkelen van een FCF. Daarom wordt het starten van orale intake meestal tot de 10^{e}-12^{e} postoperatieve dag uitgesteld met als achterliggende gedachte dat dit de FCF-incidentie beperkt. Echter, vroeg starten met orale intake kan ook voordelig zijn vanuit een psychisch perspectief: het kan de patiënt het gevoel geven dat hij/zij het 'normale leven' eerder kan oppakken. Daarnaast kan het kosten reduceren, mits het niet tot een hogere incidentie FCF leidt. Het effect van timing van orale intake op de incidentie FCF is retrospectief onderzocht in 247 opeenvolgende patiënten die binnen een periode van 12 jaar werden gelaryngectomeerd in het Antoni van Leeuwenhoek. Gedurende de eerste 6 jaar was er sprake van het 'late' orale intake protocol (start op 10^{e}-12^{e} postoperatieve dag), in de daarop volgende periode was het 'vroege' orale intake protocol (start op 2^{e}-4^{e} postoperatieve dag) van kracht, waarbij de FCF-resultaten continue gemonitord werden. We vonden dat de incidentie van FCF niet significant verschilde tussen de twee groepen. Deze studie suggereert daarmee dat vroeg starten met orale intake na een totale laryngectomie veilig is en niet zorgt voor een stijging in het aantal FCF.

In **deel III** bespreken we postlaryngectomie revalidatie aspecten. Tracheoesofageale spraakrevalidatie met een stemprothese is in Nederland de gouden standaard geworden. In **hoofdstuk 8** wordt een overzicht gegeven over spraakrevalidatie na een totale laryngectomie. In **hoofdstuk 9** beschrijven we in een retrospectieve studie de postlaryngectomie stem- en spraakkwaliteit en bespreken we mogelijke correlaties tussen stem- en spraakkwaliteit en chirurgische en medische karakteristieken in een cohort van 76 gelaryngectomeerde patiënten. We vonden dat de variatie in stemuitkomsten na een totale laryngectomie gerelateerd is aan variabelen zoals radiotherapie, neurectomie, halsklierdissectie en reconstructies. In dit patiënten cohort leek het geslacht invloed te hebben op de f0 in lopende spraak (in tegenstelling tot de heersende opvattingen blijken vrouwen toch een hogere minimale f0 te hebben dan mannen). Alles bij elkaar genomen, suggereren onze resultaten dat een nauwere farynx en/of een hoger gelegen neoglottis geassocieerd zijn met een gunstigere stem kwaliteit. Patiënten met een reconstructie van het faryngeale lumen (zoals door een PM spier-huidlap of een (gebuisde) maag transpositie) hebben de minst goede stem. In een standaard totale laryngectomie, lijkt een neurectomie mogelijk gunstiger. Tot slot, presenteren we in **hoofdstuk 10** een studie over groei van biofilm op de (klep van de) stemprothese. Biofilm-groei is een belangrijke oorzaak van falen van deze semipermanente implantaten. We bestudeerden de Provox ActiValve, waarin we focusten

op de samenstelling en ingroei van de biofilm op de 2 verschillende materialen die deze prothese bevat, namelijk silicone en fluoroplastic. De technieken die gebruikt worden om verschillende bacteriën en schimmels in een biofilm te identificeren zijn *Illumina paired-end RNA sequencing* (IPES), *fluorescence in situ hybridization* (FISH) en *confocal laser scanning microscopy* (CLSM). Drieëndertig disfunctionele Provox ActiValves van patiënten werden verzameld. Met IPES vonden we dat de samenstelling van de biofilm op beide materialen van de Provox Activalve niet significant verschillend was dan dat op een enkel siliconen stemprothese, maar er was wel minder diversiteit in de biofilm op het fluoroplastic materiaal. Met FISH en CLSM vonden we dat in geen van de stemprothesen ingroei was van Candida in het fluoroplastic materiaal. Daarmee concludeerden wij dat het fluoroplastic materiaal bestand is tegen destructie door de biofilm/Candida. Dit heeft mogelijk consequenties voor toekomstige ontwikkelingen van stemprothesen.

In **hoofdstuk 11** worden de resultaten van dit proefschrift bediscussieerd en wordt een voorstel voor verder onderzoek geformuleerd.

AUTHOR CONTRIBUTIONS

Chapter 1 **General Introduction**

In part based on a publication in Dutch: [New developments in the treatment and rehabilitation of head and neck cancer in the Netherlands].
Timmermans A.J., van den Brekel M.W.M., van der Molen L., Navran A., Nijssen T.F., Hilgers F.J.M. Ned Tijdschr Geneeskd. 2012;156(40):A505

Regarding the General Introduction: AT wrote the text, FH and MB were involved in reviewing the text.
Regarding the publication: AT wrote the manuscript. AT, MB, LM, AN, TN and FH rewrote the text into its final version.

Chapter 2 **T3-T4 larynx cancer in the Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol.**

Timmermans A.J., de Gooijer C.J., Hamming-Vrieze O., Hilgers F.J.M., van den Brekel M.W.M. Head Neck, online October 10, 2014

AT, FH, MB were responsible for the study design. AT, CG and OH collected the data. AT performed the statistical analysis. AT, OH, FH and MB took part in data interpretation. AT and CG took part in writing the manuscript and all authors were involved in reviewing the manuscript.

Chapter 3 **Tumor volume as prognostic factor for local control and overall survival in advanced larynx cancer?**

Timmermans A.J., Lange C.A.H., de Bois J.A., van Werkhoven E., Hamming-Vrieze O., Hilgers F.J.M., van den Brekel M.W.M. Accepted, Laryngoscope 2015.

AT, CL, FH and MB were responsible for the study design. JB collected and digitized hard-copy scans and transferred these and the digital scans to a delineation system. AT and CL evaluated the scans and delineated all tumor volumes separately and in consensus. AT and EW performed the statistical analysis. AT, EW, FH and MB took part in data interpretation. AT wrote the manuscript. All authors were involved in reviewing the manuscript.

Chapter 4 **Trends in treatment and survival of advanced larynx cancer: a 20-year population-based study in the Netherlands.**

Timmermans A.J., van Dijk B.A.C., Overbeek L.I.H., van Velthuysen M.L.F., van Tinteren H., Hilgers F.J.M., van den Brekel M.W.M. Accepted for publication in Head Neck 2015

AT, BD, HT, FM, MB were responsible for the study design. BD and LO were involved in the data collection. AT manually screened the pathology records to identify total laryngectomies. In case of doubt regarding the pathology, AT consulted MV. BD merged the two databases. AT, BD and HT performed the statistical analysis. AT, BD, HT, FH and MB took part in data interpretation. AT wrote the manuscript and all authors were involved in reviewing the manuscript.

Chapter 5 **Total laryngectomy for a dysfunctional larynx after (chemo)radiotherapy.**

Theunissen E.A.R., Timmermans A.J.*, Zuur C.L., Hamming-Vrieze O., de Boer J.P., Hilgers F.J.M., van den Brekel M.W.M. *Equal contribution. Arch Otolaryngol Head Neck Surg. 2012; 138: 548-555*

ET, CZ, FH and MB were responsible for the study design. ET and AT were involved in the data collection. ET performed the statistical analysis. ET, FH and MB took part in data interpretation. ET and AT wrote the manuscript and all authors were involved in reviewing the manuscript.

Chapter 6 **Predictive factors for pharyngocutaneous fistulization after total laryngectomy.**

Timmermans A.J., Lansaat L., Theunissen E.A.R., Hamming-Vrieze O., Hilgers F.J.M., van den Brekel M.W.M. Ann Otol Rhinol Laryngol. 2014; 123: 153-161

AT, LL, FH and MB were responsible for the study design. AT and ET were involved in the data collection. AT performed the statistical analysis. AT, LL, FH and MB took part in data interpretation. AT and LL wrote the manuscript and all authors were involved in reviewing the manuscript.

Chapter 7 **Early oral intake after total laryngectomy does not result in increased pharyngocutaneous fistulization.**

Timmermans A.J., Lansaat L.*, Kroon G.V.J., Hamming-Vrieze O., Hilgers F.J.M., van den Brekel M.W.M. *Equal contribution. Eur Arch Otorhinolaryngol. 2014; 271: 353-358.*

AT, LL, FH and MB were responsible for the study design. AT, LL and GK were involved in the data collection. AT and LL performed the statistical analysis. AT, LL, FH and MB took part in data interpretation. AT and LL wrote the manuscript and all authors were involved in reviewing the manuscript.

Chapter 8 **An introduction to speech rehabilitation following total laryngectomy.**
Timmermans A.J., Krap M., Hilgers F.J.M., van den Brekel M.W.M. Ned Tijdschr Tandheelkd. 2012; 119: 357-361
AT, MK and MB wrote the manuscript. AT, MK, FH and MB rewrote the text into its final version.

Chapter 9 **Voice quality and surgical detail in post-laryngectomy tracheoesophageal speakers.**
Jacobi I., Timmermans A.J.*, Hilgers F.J.M., van den Brekel M.W.M. *Equal contribution. Submitted, Eur Arch Otorhinolaryngol.*
All authors were responsible for the study design. IJ and AT were responsible for the data collection and IJ performed voice and speech assessment. IJ and AT wrote the manuscript and all authors were involved in reviewing the manuscript.

Chapter 10 **Biofilm formation on the Provox® ActiValve: composition and ingrowth analyzed by Illumina paired-end RNA sequencing, fluorescence in situ hybridization and confocal laser scanning microscopy.**
Timmermans A.J., Harmsen H.J.M., Bus-Spoor C., Buijssen K.J.D.A., van As-Brooks C., de Goffau M.C., Tonk R.H., van den Brekel M.W.M., Hilgers F.J.M., van der Laan B.F.A.M. Head Neck. Online Jan 12, 2015
AT, CA, MB, FH, BL were responsible for the study design. AT collected the voice prostheses and was involved in the data collection. CB and HH prepared the voice prostheses for the analyses and performed the analyses. AT performed the descriptive statistics. MG and RT performed the statistical analysis. AT, HH, CA, MG, RT, MB, FH and BL took part in data interpretation. AT wrote the manuscript and all authors were involved in reviewing the manuscript.

Chapter 11 **General Discussion**
AT wrote the text, FH and MB were involved in reviewing the text.

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PHD PORTFOLIO

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PhD supervisors	Prof. dr. M.W.M. van den Brekel
	Prof. dr. F.J.M. Hilgers

Courses

2011	BROK ('Basiscursus Regelgeving Klinisch Onderzoek')
2011	Good Clinical Practice (Netherlands Cancer Institute)
2012	Access Gevorderd 2003 NL
2012	Writing and Presenting in Biomedicine
2012	Clinical Epidemiology
2012	Practical Biostatistics
2012	Clinical Data Management
2012	Scientific Writing in English for Publication
2013	Advanced Topics in Biostatistics
2013	Systematic reviews
2014	Fundamental Critical Care Support Provider Course
2014	TIAS-MBE Summer Academy
2014	Advanced Topics in Clinical Epidemiology
2015	Herregistratie BROK

Seminars, workshops and master classes

2011-2015	Monthly Werkgroep Hoofd-Hals Tumoren (WHHT)
2011-2015	Monthly Heelkundige Oncologische Disciplines (HOD) department seminars (Sectie XI)
2014	Medical Business Masterclass
2015	Verdieping financieel jaarverslag Jeroen Bosch Ziekenhuis

(Inter)national conferences attended

2011-2015	KNO voor- en najaarsvergadering, Nieuwegein, Maastricht, Groningen
2012-2014	De Jonge Onderzoekersdag, Groningen, Utrecht, Amsterdam
2013-2014	NWHHT-vergadering, Utrecht, Amsterdam
2012	IFHNOS, Amsterdam
2013	IFOS, Seoul, South Korea
2013	European Head & Neck Course, Amsterdam
2013	AAO-HNSF Annual Meeting, Vancouver, Canada
2014	Skin Cancer of the Head and Neck Course, Utrecht
2014	Intercontinental Rhinoplasty course, Utrecht

2014 IFHNOS 5th World Congress, New York, USA
2015 World Congress on Larynx Cancer, Cairns, Australia

Publications

2015 **Timmermans AJ**, Lange CA, de Bois JA, van Werkhoven E, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. *Tumor volume as prognostic factor for local control and overall survival in advanced larynx cancer?* Accepted for publication in Laryngoscope, July 2015.

Paulides TJ, **Timmermans AJ**, Lange CA, Visser BC, Hamming-Vrieze O, Lohuis PJ. [*Nekpijn bij een oncologische patiënt - een diagnostische dwaling]*. Accepted for publication in Nederlands Tijdschrift KNO-heelkunde, May 2015.

Timmermans AJ, van Dijk BA, Overbeek LI, van Velthuysen ML, van Tinteren H, Hilgers FJ, van den Brekel MW. *Trends in treatment and survival of advanced larynx cancer: a 20-year population-based study in the Netherlands.* Accepted for publication in Head Neck, April 2015.

2014 **Timmermans AJ**, Harmsen HJ, Bus-Spoor C, Buijssen KJ, van As-Brooks C, de Goffau MC, Tonk TH, van den Brekel MW, Hilgers FJ, van der Laan BJ. *Biofilm formation on the Provox® ActiValve: composition and ingrowth analyzed by Illumina paired-end RNA sequencing, fluorescence in situ hybridization and confocal laser scanning microscopy*. Head Neck. 2015 Jan.

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Timmermans AJ, van Harten MC, Remmelts AJ, Hamming-Vrieze O, Klop WM, Lohuis PJ, van den Brekel MW. *Complications after transoral excision in previously irradiated head and neck cancer patients: a retrospective cohort study of 52 patients*. Clin Otolaryngol. 2014;39(4):245-51.

2013 **Timmermans AJ**, Lansaat L, Theunissen EA, Hamming-Vrieze O, van den Brekel MW, Hilgers FJ. *Predictive factors for pharyngocutaneous fistulization after total laryngectomy*. Ann Otol Rhinol Laryngol. 2014;123(3):153-61.

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2012 Indrasari SR, **Timmermans AJ**, Wildeman MA, Karakullukcu MB, Herdini C, Hariwiyanto B, Tan IB. *Remarkable response to photodynamic therapy in residual T4N0 nasopharyngeal carcinoma: a case report*. Photodiagnosis Photodyn Ther. 2012;9(4):319-20.

Timmermans AJ, van den Brekel MW, van der Molen L, Navran A, Nijssen TF, Hilgers FJ. [*New developments in the treatment and rehabilitation of head and neck cancer in the Netherlands*]. Ned Tijdschr Geneeskd. 2012;156(40):A5059.

Timmermans AJ, Krap M, Hilgers FJ, van den Brekel MW. [*Speech rehabilitation following a total laryngectomy*]. Ned Tijdschr Tandheelkd. 2012;119(7-8):357-61.

Theunissen EA*, **Timmermans AJ***, Zuur CL, Hamming-Vrieze O, Paul de Boer J, Hilgers FJ, van den Brekel MW. *Total laryngectomy for a dysfunctional larynx after (chemo)radiotherapy*. Arch Otolaryngol Head Neck Surg. 2012;138(6):548-55 (*equal contribution).

2010 Groeneveld E, Kouijzer IJ, **Timmermans AJ**, Schats R, Hompes PG. *Effectiveness of highly purified human menopausal gonadotropin (HP hMG) in intra-uterine insemination (IUI)*. Eur J Obstet Gynecol Reprod Biol. 2011;154(2):182-6.

Presentations

Presentation of over 15 poster and oral presentations at (inter)national conferences

Supervising

2011-2013	C.J. de Gooijer (medical student), scientific internship (Bachelorthesis)
2013-2014	T.J.C. Paulides (medical student), scientific internship
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