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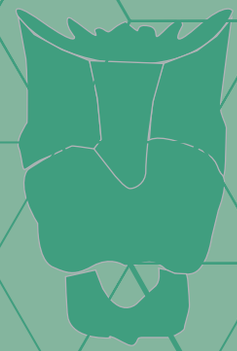

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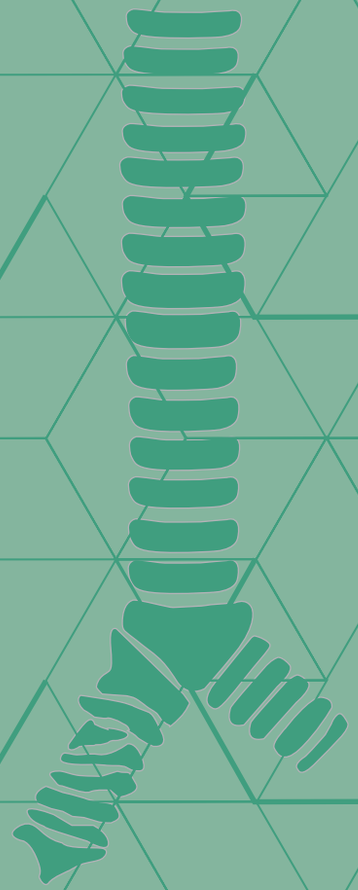

Liset Lansaat

POSTLARYNGECTOMY CARE, RECOVERY AND REHABILIATION ASPECTS

Liset Lansaat

COLOFON

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POSTLARYNGECTOMY CARE, RECOVERY AND REHABILIATION ASPECTS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

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CHAPTER 1

General introduction

TREATMENT OF ADVANCED LARYNX CANCER; THE PARADIGM SHIFT

The first total laryngectomy (TL) to treat laryngeal cancer, involving the removal of the larynx (voice box), was performed by Theodore Billroth in 1873. At that time, an operation technique with cervical diversion of the trachea and incomplete closure of the pharynx was used[1]. In the following decade, a complete pharyngeal closure was used and this adjustment of the surgical procedure significantly reduced the mortality rate and increased the percentage of long-term cures[2]. After total laryngectomy, the superior parts of the airway are permanently separated from the inferior ones and respiration has to be performed through a permanent tracheostoma. Loss of the larynx means a big life change for the patient because of the loss of the natural voice, loss of upper airway conditioning and decreased sense of smell because there is no nasal airflow any longer (Figure 1)[3,4]. Also, the deformation of the neck and all the sequels have a great psychosocial impact.

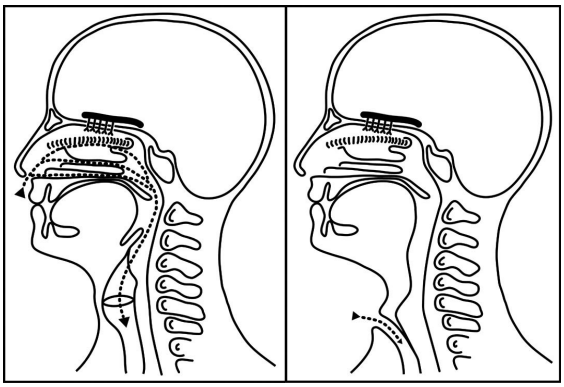

Fig. 1 Anatomical situation before and after total laryngectomy

Because of these far reaching consequences of TL, over the last 3 decades there is an increase in the use of organ-preserving (chemo-)radiotherapy ((C)RT), and a decrease in the use of primary surgery for patients with advanced larynx and hypopharynx cancer[5-7]. The underlying reasons for this paradigm shift are a high larynx retaining percentage in the organ preservation group and almost similar oncological results for organ preservation and surgery[8,9]. However, there is an increasing awareness that organ preservation is not synonymous with function preservation, which actually should be the goal of the non-surgical (C)RT treatment[10, 11].

The most important functional side effect of (C)RT applied in the head and neck region is long-term dysphagia caused by several abnormalities such as reduced retraction of the tongue base, decreased inversion of the epiglottis, reduced elevation of the larynx,

reduced opening of the oesophagus, delay in swallowing reflex, and/or bolus residue in the vallecula or piriform sinus or on the posterior pharyngeal wall after completing swallowing[12]. These swallowing abnormalities often increase during long term follow-up. When also a neck dissection (ND) is needed, this further reduces laryngeal elevation, and increases (C)RT-induced aspiration[13]. Besides these function preservation issues, in case of recurrent or residual disease after (C)RT, the patient still requires organ-sacrificing surgery (i.e. TL), which then is prone to higher complication rates and less optimal functional rehabilitation results[14]. Furthermore, survival rates for RT and CRT compared to primary TL are increasingly reported to be less similar than earlier assumed. Recently e.g., Timmermans et al., in a 20-year population based study in the Netherlands, reported similar survival rates for all primary treatment modalities (TL, RT or CRT) for T3 laryngeal cancer, but for T4 disease significantly better survival rates were observed with TL (+adjuvant RT)[15]. Petersen et al. used the same population based method to study trends in treatment, incidence and survival of hypopharyngeal cancer[16]. Also, in that study, the 5-year overall survival was significantly better for patients with T4 hypopharynx cancer treated with primary TL (+adjuvant RT) when compared to CRT. In this era of increased use of organ-preserving treatments, not only these functional and survival issues, but also several post TL-care, recovery and rehabilitation paradigms are still topics of debate and therefore relevant to remain being addressed, both at an institutional and at a national level.

POSTLARYNGECTOMY CARE AND RECOVERY

With respect to postlaryngectomy care and recovery, there are two issues that have attracted somewhat more attention in recent years. The first is the timing of postoperative oral intake. The second is the seemingly growing problem of pharyngocutaneous fistulization (PCF), attributed to the increasing incidence of salvage TL after previous unsuccessful (C)RT, or TL to solve dysfunctional larynx problems after organ preservation therapy.

ORAL INTAKE

After TL the postoperative timing of resuming oral intake is the first topic of discussion and over the years (inter)nationally there has been no consensus on this issue. Many head and neck surgeons tend to delay oral intake until day 10-12 (further called late oral intake (LOI)) because that is assumed to prevent or limit the chance of PCF. However, the evidence for this assumption is quite weak, whereas there are several arguments in favour of early oral intake (EOI) as a preferable and more beneficial approach[17]. Firstly, the nasogastric feeding tube, which is necessary when applying a LOI protocol, can be painful and irritating, and the tube moving across the pharyngeal suture line, might promote PCF more than LOI

prevents it[18]. Secondly, EOI could have a positive psychological effect by increasing the patient's feeling of earlier return to 'normalcy'[19]. Furthermore, early return to oral feeding saves costs and may facilitate earlier hospital discharge. Lastly, some studies suggest that EOI is a safe approach in clinical practice[17,20]. The results of the study conducted by Medina & Kafif e.g. indicate that oral feeding 48 hours after TL is a safe clinical practice (5% PCF rate is the early feeding group and 11% in the control group) and average hospital duration is significantly shorter in the early feeding group[21]. Aswani et al. concluded that early oral intake for TL patients is recommended in developed and developing countries (PCF rate of 20% in the late oral intake group versus 15.4% in the early oral intake group; p=0.592)[22]. In this respect, it is also interesting to note developments in other areas of alimentary tract surgery, where there is a worldwide trend towards EOI in patients undergoing gastro-intestinal surgery[23].

PHARYNGOCUTANEOUS FISTULIZATION

PCF, a complication that often occurs in the period around the planned initiation of oral intake (median day of presentation of PCF varies between day 7 and 14), can be the next challenge patient and surgeon have to deal with[24-27]. PCF increases morbidity, potentially necessitates additional surgery, considerably prolongs hospitalization, delays (and/or interrupts) voice rehabilitation and oral intake, and increases costs[28]. A PCF is characterized by saliva leaking through a defect in the pharyngeal mucosa lining, damaging the surrounding tissues (Figure 2). The reported incidence of PCF, mostly based on single institute series, varies widely, ranging from 3% to 66%[29]. Various predictive factors for PCF have been identified, most prominently preoperative (C)RT[30-32]. The general assumption is that with the more frequent use of (C)RT this common complication has further increased over the last decades. The physiological explanation for this setback most likely is decreased tissue vascularization and prolonged healing due to (C)RT. Although not substantiated by large prospective studies, PCF data of two systematic reviews papers, with some caution, support this assumption. Paydarfar et al. included observational studies about PCF published between 1970-2003 (in all studies included in this paper, RT was a studied variable as well), and Hasan et al. used relevant PCF data in salvage laryngectomy patients from studies published between 2000-2015. In figure 3, a scatterplot based on the pooled data of these two studies, shows a slight increasing trend in PCF incidence and, considering the numbers of publications, increased interest in the PCF topic over the years[29,33]. Besides (C)RT, predictive factors for PCF are the extent of the pharyngeal resection, comorbidities such as hypothyroidism and diabetes, and an index tumor originating in the hypopharynx[34,35].

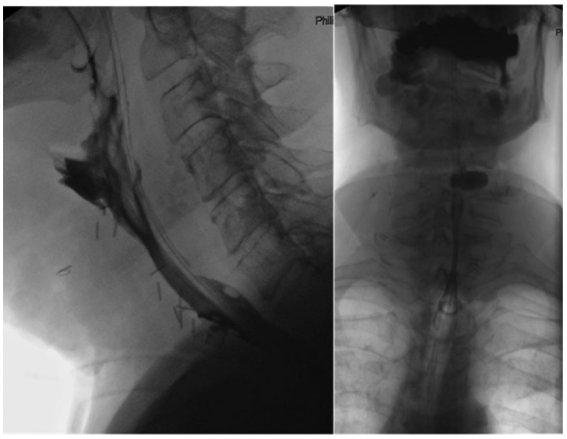

Fig. 2 Modified barium swallow. left lateral image shows defect (PCF) in anterior pharyngeal wall; right frontal image shows lateral defect (PCF) in pharyngeal wall.

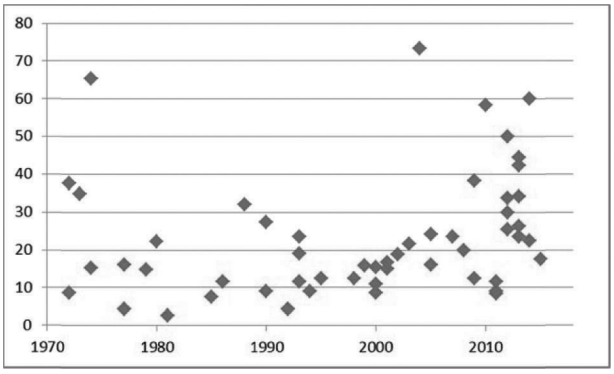

Fig. 3 Scatterplot based on the pooled pharyngocutaneous fistulization (PCF) data from studies reviewed by Paydarfar et al. and Hasan et al.; x-as: year, y-as: PCF incidence (%)

PCF data, as mentioned, usually come from single-institution series, which makes a valid interinstitutional comparison impossible. Such a comparison of complications would be relevant to gain better insight in the quality of care for patients undergoing TL on a national level but can also lead to changes in treatment protocols in individual institutes. Grau et al, using the national Danish Head and Neck Study Group dataset, did identify prognostic factors for PCF in TL patients with prior RT[36]. However, no comparisons between the different centers in their analysis were made. There is evidence in other surgical oncology disciplines in the Netherlands (e.g. colon cancer surgery), though, that multicenter comparison with proper documentation and feedback (on complications in surgery) is feasible and does lead to improved quality of the surgery and reduced costs for patients[37].

With the recent development and start of the registration of quality indicators of integrated care, this might also be achievable in the upcoming years for head and neck cancer in the Netherlands[38].

POSTLARYNGECTOMY REHABILITATION

As already mentioned, the loss of the larynx/voice box and the necessity to further breath through a permanent tracheostoma at the base of the neck has more consequences than the loss of the natural voice alone[39]. The disconnection of the upper and lower airways has significant consequences for the functions which require an intact airway, e.g. pulmonary function and the sense of smell (although a very relevant issue, the latter function is outside the scope of this thesis and will not further be addressed). All these functions have to be rehabilitated after TL and in the last several decades have received increasing attention, especially voice restoration and pulmonary rehabilitation.

VOICE RESTORATION

Restoration of voice and speech is one of the most important issues in the rehabilitation program after TL. Mostly, it can start at day 12-14 after TL if wound healing is sufficient (i.e. no occurrence of PCF) and oral intake has been initiated. The three main methods for restoring this loss of voice/speech are electrolarynx, esophageal, and tracheoesophageal (TE) voice/speech[39-41]. Since the larynx is the natural sound source for the production of speech, with pulmonary air as the driving force and the vocal tract as the "organ" where sound is modulated into speech, a substitute (external or internal) sound source is required. An electrolarynx is an external device, which produces sound that is transferred through the skin towards the vocal tract and thus can be modulated into speech (schematically shown in Figure 4). The inherent drawback is its mechanical, robotlike sound. In case of esophageal and TE voice (schematically also shown in Figure 4), the (internal) substitute sound source is the pharyngoesophageal segment, where vibrations of the mucosa produce sound. The necessary air supply to produce these vibrations is air expelled from the esophagus (60-80 ml) or the lungs (tidal volume 5-600 ml), respectively. In case of TE voice, to allow the flow of air, there needs to be a connection between the trachea and the esophagus, which is achieved by creating a puncture tract (fistula) between the two, held open by a prosthetic device. This is essentially a one-way valve, which allows the passage of pulmonary air towards the pharynx and prevents aspiration of fluids[42]. In terms of voice and speech quality there is a considerable difference between esophageal and TE voice and speech. Compared to esophageal speech, TE prosthetic speech has the advantage that acoustic outcomes are more comparable to natural speech (TE speech is pulmonary driven just like normal voicing) and better outcomes are reported in favour of

TE prosthetic speech for maximum phonation time, fundamental frequency and intensity. Moreover, in the perceptual evaluations TE prosthetic speech seems to be more pleasant and comprehensible[43]. Focusing on practicability, TE prosthetic speech requires relatively little training and the success rate is high (around 90%), whereas esophageal speech mostly takes many months to master, with considerably lower success rates (40-60%)[43-45]. The disadvantages of TE prosthetic speech compared to esophageal speech are the need of a medical device and its regular replacements, permanent dependency on the doctor/SLP, higher health costs and the possibility of fistula-related problems (i.e. hypertrophy, infection and leakage of the fistula)[43-45].

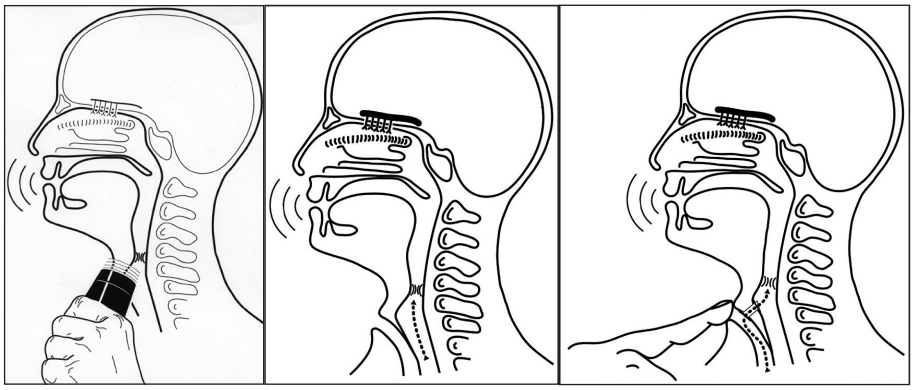

Fig. 4 Restoring the loss of voice; speech with electrolarynx, esophageal speech, and tracheoesophageal prosthetic speech (digital occlusion of the stoma to divert the pulmonary air towards the pharynx)

In 1973 Mozoleweski et al. were the first to publish the results of a prosthetic device used in 24 patients, and in 1980, Singer and Blom introduced the first commercial voice prosthesis[46,47]. With a success rate of around 90%, TE prosthetic speech is the method of choice for voice rehabilitation in most countries with an adequate health care insurance system. Besides the original Blom-Singer voice prosthesis (VP), a variety of prosthetic devices have been developed over the last decades, e.g. in the Netherlands the Groningen button, the Nijdam VP and Provox (Atos Medical AB, Hörby, Sweden)[48-51]. Other brands are Eska-Herrmann and Phonax. Median and/or mean device lifetime of these VPs have been reported to be around 3-6 months and the main reason for replacement reportedly is transprosthetic leakage. E.g. in 2000, Op de Coul et al. published the long-term results of voice rehabilitation with the first Provox VPs, developed in the Netherlands Cancer Institute[45]. These and other earlier studies, however, have been conducted in a time where primary TL was the gold standard in advanced larynx- and hypopharynx cancer treatment. The current treatment landscape, however, has been associated with more tracheoesophageal puncture-related problems and possibly a lower device lifetime

of VPs[52,53]. Moreover, since 2000, several new generations of VPs have been developed, aimed at improving patient comfort, by for example improving airflow characteristics of the device itself, and refining the puncture and replacement tools, and at reducing biofilm overgrowth or inadvertent opening of the valve during swallowing or breathing[54-56]. Thus, in an era with an increasing necessity for salvage surgery, and with the development of several new generations of VPs, it remains necessary to continuously update the status of tracheoesophageal voice and speech rehabilitation.

PULMONARY REHABILITATION

Excessive coughing and mucus production are pulmonary problems in TL patients caused by the separation of the upper and lower respiratory tracts[57]. To compensate for the functional loss of the upper respiratory tract and to prevent and/or treat these resulting/unavoidable pulmonary problems, 24/7 use of a heat and moisture exchanger (HME) has proven to be effective[57-59]. During exhalation water vapour condensates on the (mostly foam-like) material of these medical devices, and during inhalation the breathing air is humidified. An HME has to cover the tracheostoma completely in order to be optimally effective[59]. A factor to be considered hereby is that speaking with a voice prosthesis requires airtight occlusion of the stoma (with a finger; schematically shown in Figure 4) in order to divert the pulmonary air into the pharyngoesophageal segment, where mucosal vibrations produce the sound necessary for speech. This was a problem in the first generation HMEs[57,58,60]. However, after the development of specialized HMEs, airtight stoma occlusion has become easier, which improves maximum phonation time and dynamic loudness range and thus, not unexpectedly, compliance rate[61-64]. However, with these HMEs manual occlusion is still necessary and patient consider this to be a disadvantage. To overcome this problem of TE speech and to obtain handsfree speech, automatic speaking valves (ASVs) have been developed (schematically also shown in Figure 4). These medical devices contain a flexible membrane that stays open during normal calm breathing, but closes through the natural increase in air pressure when speaking is initiated[65-67]. Presently, several ASVs are available. Blom Singer and Bivona tracheostoma valves were developed in the eighties and nineties of the last century. Later, several other valves became available, such as the Eska-Herrmann and ADEVA valves[68,69]. In 2003, the Provox FreeHands HME, the first automatic speaking valve with an integrated HME, was introduced. In a long-term (6 months) study, the success rate (defined as patients using this ASV on a daily basis) was 19%. Fifty-seven percent of the patients in this study used the device on a non-daily basis at special occasions. The main reason for not using the Provox FreeHands on a daily basis was the unpredictable fixation of the adhesive to the peristomal skin; a good long-lasting seal to withstand pressure is the main drawback for all ASVs[66].

Despite all progress in this field, continuous efforts are warranted to further improve patient friendliness and compliance of automatic speech (in combination with pulmonary rehabilitation), and thus to optimize TL voice and speech outcomes.

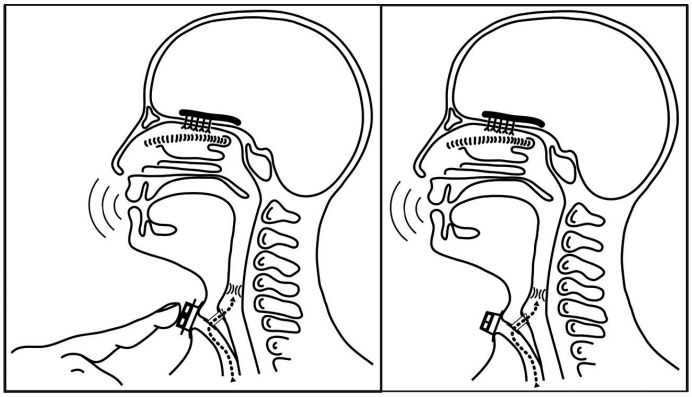

Fig. 5 Pulmonary rehabilitation using an HME (occlusion of the stoma with a finger), and an automatic speaking valve with an integrated HME

STOMA ADHESIVES

Laryngectomized patients have several options to apply HMEs and ASVs to their stoma, i.e. an intratracheal device (cannula or button), or an extratracheal device also called a stoma adhesive[70,71]. Such a peristomal adhesive, which has to create an airtight seal at the level of the stoma and provide a placeholder for the HME and/or ASV, is the most commonly used device. In 1996, Hilgers et al. found that problems, such as skin irritation, inadequate adherence and loosing of the adhesive can partly be solved by using a variety of adhesives[61]. Subsequently e.g., the Provox StabiliBase was developed and evaluated in a multicenter study in the Netherlands. This adhesive provides a more stable and more anatomically shaped conical base compared to other adhesives, which is especially important for the prolonged use of ASVs. The study showed that the majority of patients preferred this new adhesive to their usual comparator adhesive. Its device life appeared to be significantly longer, and patients with a deeper than usual stoma reported the adhesive to be more comfortable. Also, patients, who used to experience uncomfortable neck bulging during automatic speech, reported this to be less of a problem with the new device[71]. After its introduction, though, feedback from clinicians and patients revealed that some patients still experienced skin irritation with the standard adhesive material of the StabiliBase. These studies show that it is warranted to further invest in improvements of medical devices for this patient category in order to enable ever more patients to benefit of the technical advances in pulmonary and voice and speech rehabilitation.

STOMA COVERS

As an alternative for HMEs, relatively inexpensive commercial and non-commercial stoma covers can be used to improve tracheal and respiratory climate. Initial studies on the impact of HMEs almost 30 years ago, however, concerned patients, who frequently used these stoma cloths, which at that time were standard of care in many institutes. Despite the potentially relevant tracheal climate improving capacity of these cloths, these early HME studies showed highly significant clinical improvements of a wide range of respiratory problems. The observations in these studies, thus, suggested that the clinical respiratory benefits of stoma cloths in practice were limited[57,58].

Nevertheless, also stoma covers have humidifying effects, but until recently this was not a specific topic of research. In 2016, though, Quail et al, studied the humidifying effect of such stoma cloths (also called bibs) in a laboratory set-up[72]. These authors could demonstrate a positive HME effect of the locally manufactured, inexpensive stoma cloths, but they could not for commercially available HMEs, despite the fact that these medical devices through well-validated measurement technology had been proven to have clinically relevant humidifying properties[73-75]. This intriguing discrepancy with earlier published data might be due to a too short 'humidity loading time' (1 minute instead of the 10 minutes needed for properly "loading" HMEs for laboratory measurements). Moreover, they used non-validated equipment, which lacked condensation prevention technology as its most essential component. Both issues most likely hamper the precision of Quail's measurements[75]. Beside proof of humidifying concept with the use of properly validated laboratory measurement technology, patient acceptability and clinical effects of stoma covers are also very relevant outcome measures that need to be assessed. And although stoma covers undeniably have beneficial humidifying properties, more research is needed before any firm conclusions can be drawn about their place in pulmonary rehabilitation armamentarium of TL patients, especially in view of the historic observation from the early days of HME research.

OUTLINE OF THIS THESIS

In this era of increased use of organ-preserving treatments not only functional and survival issues, but also several post TL-care, recovery and rehabilitation paradigms thus remain of interest, both at an institutional and at a national level.

In the 1st section of this thesis (postlaryngectomy care and recovery), timing of oral intake after TL and its effect on PCF is presented in a retrospective cohort study in a tertiary comprehensive cancer center in the Netherlands (**chapter 2**). Subsequently, the incidence

of PCF and prognostic factors for PCF are retrospectively assessed at an institutional level (**chapter 3**) and at a national level (**chapter 4)**. Additionally, in the national cohort/audit study a prognostic model is developed predicting the percentage of PCF per center. In the 2nd section on "Postlaryngectomy rehabilitation" an institutional study on recent results of postlaryngectomy voice rehabilitation is presented and how they have been affected (or not) in the present treatment landscape with increased use of (C)RT (**chapter 5**). Next**, chapter 6** provides a prospective study on a novel automatic speaking valve, and **chapter 7** a prospective study on a novel peristomal adhesive for the application of an automatic speaking valve or an HME. Lastly in this section, in **chapter 8,** a combined in vitro and in vivo study to test stoma covers is conducted and to assess the potential of these covers and HMEs to further optimize pulmonary rehabilitation. Finally, in **chapter 9,** the results obtained in these eight studies are discussed and set into (future) perspective.

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PART I

Postlaryngectomy care and recovery

CHAPTER 2

Early oral intake after total laryngectomy does not increase pharyngocutaneous fistulization

Lansaat L*
Timmermans AJ*
Kroon GVJ
Hamming-Vrieze O
Hilgers FJM
van den Brekel MWM

**both authors contributed equally*

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ABSTRACT

Timing of oral intake after total laryngectomy (TLE) 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). 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). Both groups were comparable in terms of sex, age, origin of tumor, and TLE 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). 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 (TLE)[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 TLE 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 TLE, ASA score, diabetes, origin of the tumor, indication of TLE, 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.

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 TLE	Mean 63.1 years		Mean 63.5 years		0.774[*]
	Range 38-87 years		Range 41-85 years		
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 TLE					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	

TLE Total laryngectomy, *ASA* American Society of Anesthesiologists, *PM* pectoralis major, *SSG* Split skin graft

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

[*] The independent *t* test was used to determine if the two groups were statistically different

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 TLE 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 TLE 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 TLE 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 TLE compared to patients with additional reconstructive surgery were still significant (data not shown).

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

	Standard TLE	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

TLE Total laryngectomy, *LOI* late oral intake, *EOI* early oral intake

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

** Median day oral intake was initiated (range)

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 Fig. 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).

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[15] 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. Boyce et al.[14] studied the data of 94 patients who underwent TLE with primary pharyngeal closure. 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.[21] recommended starting oral intake on day 2 based on their results. However, they excluded patients who needed pharyngeal reconstruction with myocutaneous flaps.

In the present study, all patients who underwent TLE, 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 TLE, patients who underwent standard TLE 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 TLE. 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.

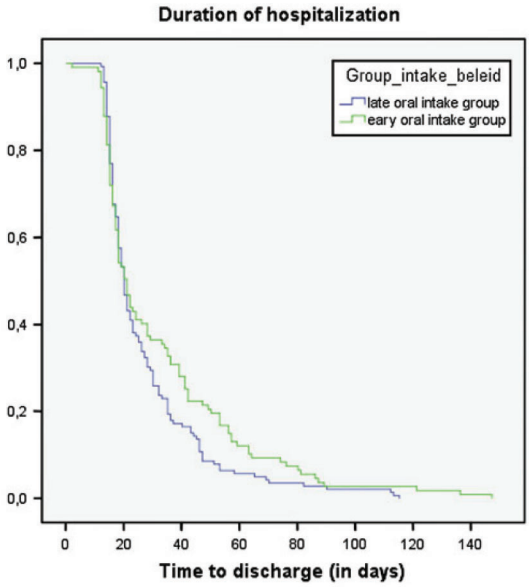

Fig. 1 Kaplan–Meier analysis regarding duration of hospitalization between the LOI group and the EOI group Chi square: 2.584; p = 0.108

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 TLE. 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.[17,21] 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[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.[21] reported a significantly shorter hospital stay for the subgroup of patients who were fed from day 2 after TLE, but this was after exclusion of PCF patients in both the EOI and LOI group. Overall, however, these authors did not find a significant difference in hospital stay between both groups. Medina and Khafif[15] found a significant decrease in hospital stay from 12 days in the LOI group to 7 days in the EOI group. 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.

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CHAPTER 3

Predictive factors for pharyngocutaneous fistulization after total laryngectomy

Timmermans AJ
Lansaat L
Theunissen EAR
Hamming-Vrieze O
Hilgers FJM
van den Brekel MWM

Annals of Otology, Rhinology & Laryngology

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 TLE 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; $P = .001$), an albumin level of less than 40 g/L (OR, 2.20; 95% CI, 1.12 to 4.33; $P = .022$), previous chemoradiotherapy (OR, 3.38; 95% CI, 1.34 to 8.52; $P = .010$), more-extended pharyngeal resection ($P = .001$), and pharynx reconstruction ($P = .002$). 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; $P = .421$). The 2-year overall survival rate was 48% in patients with PCF and 57% in those without PCF ($P = .290$).

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] Pharyngocutaneous fistulization 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,[7] 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. 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 metro-nidazole, 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,[16] this issue is not further addressed in the present report.

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 multi-variable 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 .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]).

Table 1 Patient and Tumor Characteristics.

	No.	%
Gender (n = 217[a])		
Male	175	80.6
Female	42	19.4
Age at TL (n = 217)		
Mean, 63.2 y		
Range, 38-87 y		
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
Site of origin 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 esophagus	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.

[a]Numbers in parentheses are numbers of patients for whom data were available.

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 2 Surgical Characteristics of TL Procedures.

	No.	%
Indication for TL (n = 217)		
Primary[a]	70	32.3
Salvage	98	45.2
Second primary[b]	24	11.1
Functional	25	11.5
(C)RT prior to TL (n = 217)[a]		
No	70	32.3
RT	113	52.1
(C)RT	34	15.7
Pharyngectomy (n = 217)		
Partial[c]	139	64.1
Near-total[d]	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

	No.	%
Pharynx reconstruction (n = 217)		
No	128	59.0
PM flap (with or without skin or SSG)	63	29.0
Free flap[e]	16	7.4
Gastric pull-up[f]	10	4.6
Indication for PM flap reconstruction (n = 63)		
Reconstruction of pharyngeal lumen	52	82.5
Reinforcement of pharynx	11	17.5
TEP (n = 217)		
No	7	3.2
Yes, primary	197	90.8
Yes, secondary[g]	13	6.0

Abbreviations: (C)RT, (chemo)radiotherapy; RT, radiotherapy; N/A, not applicable; PM, pectoralis major; SSG, split-skin graft; TEP, tracheoesophageal puncture; HN, head and neck; TL, total laryngectomy.

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

[b]All second primaries were preceded by HN malignancies, leaving TL as only curative treatment option.

[c]Primary closure still possible.

[d]Not enough pharyngeal mucosa left for primary closure, so reconstruction was necessary.

[e]Free flap reconstruction includes free radial forearm flap, anterolateral thigh flap, lateral upper arm flap, free latissimus dorsi flap, and free fibula flap.

[f]One patient received PM flap together with gastric pull-up.

[g]Mean day of insertion was 47.69 days (range, 27 to 92 days) after operation.

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, $P = .001$). 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, $P = .001$; Table 4).

Table 3 Incidence and Treatment of PCF by TL Group.

		Treatment of PCF	
Indication	**Incidence of PCF**	**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 second primary	9/24 (37.5%)	6/9 (66.7%)	3/9 (33.3%)
TL for 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%)

Abbreviation: PCF, pharyngocutaneous fistulization; TL, total laryngectomy

Table 4 Median Duration of Hospitalization by Group.

	Days	***P* Value[a]**
Overall	20	**.001**
Patients without PCF	18	
Patients with PCF	47	
Patients with PCF	47	**.001**
Treated conservatively	36	
Required additional surgery	58	

Abbreviation: PCF, pharyngocutaneous fistulization.

[a]Mann-Whitney U test. Boldface indicates significance.

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; $P = .001$), an albumin level of less than 40 g/L (OR, 2.20; 95% CI, 1.12 to 4.33; $P = .022$), CRT prior to TL (OR, 3.38;

95% CI, 1.34 to 8.52; *P* = .010), more extensive pharyngeal resection (near-total versus partial pharyngectomy OR, 3.21; 95% CI, 1.58 to 6.51; *P* = .001), and pharynx reconstruction (PM flap versus no reconstruction OR, 2.59; 95% CI, 1.29 to 5.17; *P* = .007). No correlations were found with the other variables—most prominently, not with RT as prior singlemodality treatment (OR, 1.83; 95% CI, 0.87 to 3.85; *P* = .113). The incidence of PCF was lower in those with primary TEP (borderline significance of *P* = .052).

Table 5 Univariate Analysis of Possible Risk Factors for Fistula Formation.

	No. of Pts (%)	PCF (%)	OR[a] (95% CI)	*P* Value[a]
Gender	217			.055
Male	175 (80.6)	41 (23.4)	1.00	
Female	42 (19.4)	16 (38.1)	2.01 (0.99 to 4.11)	
Age at TL, y	217			.978
<54	50 (23.0)	13 (26.0)	1.00	
55-61	50 (23.0)	13 (26.0)	1.00 (0.41 to 2.44)	1.000
62-71	64 (29.5)	18 (28.1)	1.11 (0.48 to 2.57)	.800
72-87	53 (24.2)	13 (24.5)	0.93 (0.38 to 2.25)	.864
Site of origin tumor	217			**.002**
Larynx	154 (71.0)	33 (21.4)	1.00	
Hypopharynx	38 (17.5)	19 (50.0)	3.67 (1.74 to 7.71)	**.001**
Miscellaneous	25 (11.5)	5 (20.0)	0.92 (0.32 to 2.63)	.871
Diabetes	216			.300
No	200 (92.6)	51 (25.5)	1.00	
Yes	16 (7.4)	6 (37.5)	1.75 (0.61 to 5.10)	
BMI	213			.537
<18	60 (28.2)	19 (31.7)	1.46 (0.72 to 2.97)	.289
18-25	104 (48.8)	25 (24.0)	1.00	
>25	49 (23.0)	12 (24.5)	1.03 (0.47 to 2.26)	.951
Preoperative tube feeding	216			.080
No	176 (81.5)	42 (23.9)	1.00	
Yes	40 (18.5)	15 (37.5)	1.91 (0.92 to 3.96)	
Preoperative albumin level	174			**.022**
<40 g/L	70 (40.2)	26 (37.1)	2.20 (1.12 to 4.33)	
≥40 g/L	104 (59.8)	22 (21.2)	1.00	
ASA score	216			.074
1	47 (21.8)	8 (17.0)	1.00	
2	121 (56.0)	30 (24.8)	1.61 (0.68 to 3.82)	.283
3	48 (22.2)	18 (37.5)	2.93 (1.12 to 7.63)	**.028**
(C)RT prior to TL	217			**.035**
Primary TL	70 (32.2)	12 (17.1)	1.00	
Prior RT	113 (52.1)	31 (27.4)	1.83 (0.87 to 3.85)	.113
Prior CRT	34 (15.7)	14 (41.2)	3.38 (1.34 to 8.52)	**.010**
Pharyngectomy	217			**.001**
Partial[b]	139 (64.1)	23 (16.5)	1.00	

	No. of Pts (%)	PCF (%)	OR[a] (95% CI)	*P* Value[a]
Near-total[c]	54 (24.9)	21 (38.9)	3.21 (1.58 to 6.51)	**.001**
Circumferential	24 (11.0)	13 (54.2)	5.96 (2.38 to 14.94)	**.001**
Neck dissection	217			.882
No	80 (36.9)	22 (27.5)	1.00	
Yes, unilateral	51 (23.5)	14 (27.5)	1.00 (0.45 to 2.19)	.995
Yes, bilateral	86 (39.6)	21 (24.4)	0.85 (0.43 to 1.71)	.651
Pharynx reconstruction	217			**.002**
No reconstruction	128 (59.0)	22 (17.2)	1.00	
PM flap with or without skin or SSG	63 (29.0)	22 (34.9)	2.59 (1.29 to 5.17)	**.007**
Free flap[c]	16 (7.4)	8 (50.0)	4.82 (1.63 to 14.22)	**.004**
Gastric pull-up[e]	10 (4.6)	5 (50.0)	4.82 (1.29 to 18.07)	**.020**
Thyroidectomy	216			.284
No	54 (25.0)	16 (29.6)	1.00	
Yes, hemithyroidectomy	143 (66.2)	38 (26.6)	0.86 (0.43 to 1.72)	.668
Yes, total thyroidectomy	19 (8.8)	2 (10.5)	0.28 (0.06 to 1.35)	.113
TEP	217			.052
Primary puncture	197 (90.8)	48 (24.4)	1.00	
Secondary or no puncture	20 (9.2)	9 (45.0)	2.54 (0.99 to 6.50)	

Abbreviations: OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; PCF, pharyngocutaneous fistulization; (C)RT, (chemo)radiotherapy; RT, radiotherapy; PM, pectoralis major; SSG, split-skin graft; TEP, tracheoesophageal puncture; TL, total laryngectomy; BMI, body mass index.

[a]Logistic regression. Bold *P* values indicate significance.

[b]Primary closure still possible.

[c]Not enough pharyngeal mucosa left for primary closure, so reconstruction was necessary.

[d]Free flap reconstructions include free radial forearm flap, anterolateral thigh flap, lateral upper arm flap, free latissimus dorsi flap, and free fibula flap.

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

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%; $P = .009$). 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 ($P = .04$) and pharyngectomy (near-total versus partial OR, 3.63; 95% CI, 1.36 to 9.72; $P = .01$) were significant predictive factors for PCF (Table 7).

Table 6 Analysis of Subgroup Without Additional Reconstruction by Duration of Surgery.[a]

	No. of Patients	PCF (%)	*P* Value[b]
Whole subgroup	120		**.009**
<240-min surgery	46	2 (4.3)	
≥240-min surgery	74	17 (23.0)	
No neck dissection			.072
<240-min surgery	32	2 (6.3)	
≥240-min surgery	15	4 (26.7)	
Unilateral or bilateral neck dissection			.061
<240-min surgery	14	0 (0)	
≥240-min surgery	59	13 (22.0)	

Abbreviation: PCF, pharyngocutaneous fistulization.

[a]Subgroup analysis represents all patients who underwent primary TL or TL after RT and primary pharyngeal mucosa closure.

[b]Fisher's exact test. Boldface indicates significance.

Table 7 Multivariable Analysis Using Logistic Regression by Backward Elimination Method.

	OR (95% CI)	*P* Value[a]
Site of origin tumor		.10
Larynx	1.00	
Miscellaneous	0.37 (0.09 to 1.56)	.18
Hypopharynx	1.74 (0.56 to 5.38)	.34
Preoperative albumin level		**.04**
<40 g/L	2.23 (1.03 to 4.83)	
≥40 g/L	1.00	
(C)RT prior to TL		.21
Primary TL	1.00	
Prior RT	2.15 (0.85 to 5.44)	.11
Prior CRT	2.51 (0.72 to 8.70)	.15
Pharyngectomy		**.01**
Partial	1.00	
Near-total	3.63 (1.36 to 9.72)	**.01**
Circumferential	6.37 (1.52 to 26.63)	**.01**

Abbreviations: OR, odds ratio; CI, confidence interval; (C)RT, (chemo) radiotherapy; RT, radiotherapy; TL, total laryngectomy.

[a]Logistic regression. Boldface indicates significance.

Follow-Up and Survival

The median follow-up was 24 months (range, 0 to 144 minutes). 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* = .421). The 2-year overall survival rates were 48% and 57%, respectively (*P* = .290).

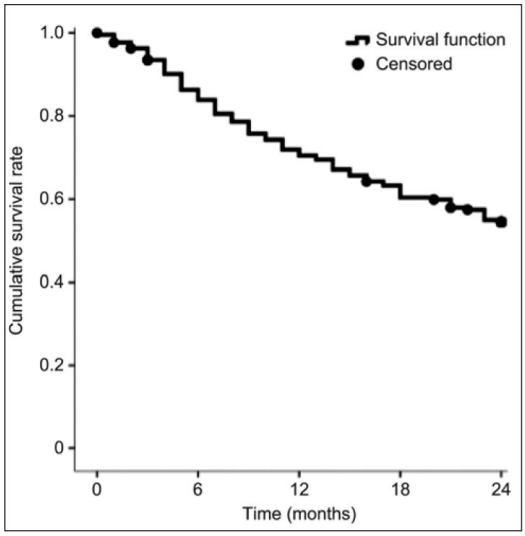

Fig. 1 Two-year overall survival rate according to Kaplan-Meier analysis.

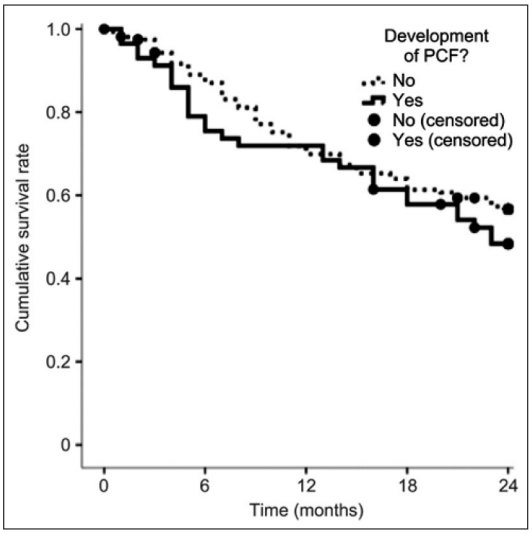

Fig. 2 Differences in 2-year overall survival rate between patients with and without pharyngocutaneous fistula (PCF) according to Kaplan-Meier analysis (log-rank test, *P* = .290).

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[8] and Boscolo-Rizzo et al[23] used 35 g/L as a cutoff value, and Tsou et al[24] used 25 g/L. 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,[26] could not be evaluated, since both are part of the standard clinical path in our center.

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 TLE, 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[29] reported on 31 patients with salvage TL in whom the pharyngeal mucosa was either closed primarily or additionally reinforced with a PM flap. 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[31] 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. Fung et al[32] did not find any advantage of free flap reconstruction in preventing PCF. 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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DECLARATION OF CONFLICTING INTERESTS

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CHAPTER 4

Predictive factors for pharyngocutaneous fistulization after total laryngectomy; a Dutch Head and Neck Society Audit

Lansaat L
van der Noort V
Bernard SE
Eerenstein SEJ
Plaat BEC
Langeveld TAPM
Lacko M
Hilgers FJM
de Bree R
Takes RP
van den Brekel MWM

On behalf of the Dutch Head and Neck Society

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ABSTRACT

Background

Incidences of pharyngocutaneous fistulization (PCF) after total laryngectomy (TL) reported in the literature vary widely, ranging from 2.6 to 65.5%. Comparison between different centers might identify risk factors, but also might enable improvements in quality of care. To enable this on a national level, an audit in the 8 principle Dutch Head and Neck Centers (DHNC) was initiated.

Methods

A retrospective chart review of all 324 patients undergoing laryngectomy in a 2-year (2012 and 2013) period was performed. Overall PCF%, PCF% per center and factors predictive for PCF were identified. Furthermore, a prognostic model predicting the PCF% per center was developed. To provide additional data, a survey among the head and neck surgeons of the participating centers was carried out.

Results

Overall PCF% was 25.9. The multivariable prediction model revealed that previous treatment with (chemo)radiotherapy in combination with a long interval between primary treatment and TL, previous tracheotomy, near total pharyngectomy, neck dissection, and BMI < 18 were the best predictors for PCF. Early oral intake did not influence PCF rate. PCF% varied quite widely between centers, but for a large extend this could be explained with the prediction model. PCF performance rate (difference between the PCF% and the predicted PCF%) per DHNC, though, shows that not all differences are explained by factors established in the prediction model. However, these factors explain enough of the differences that, compensating for these factors, hospital is no longer independently predictive for PCF.

Conclusions

This nationwide audit has provided valid comparative PCF data confirming the known risk factors from the literature which are important for counseling on PCF risks. Data show that variations in PCF% in the DHNCs (in part) are explainable by the variations in these predictive factors. Since elective neck dissection is a major risk factor for PCF, it only should be performed on well funded indication.

INTRODUCTION

Pharyngocutaneous fistulization (PCF) is a frequent and serious complication after total laryngectomy (TL). It increases morbidity, prolongs hospitalization, potentially necessitates additional surgery, delays or interrupts oral feeding and voice rehabilitation, and raises costs[1–3]. Reported incidences of PCF in the literature vary widely from 2.6 to 65.5%[4].

Many prognostic factors for PCF have been described in the literature. The main are prior (chemo)radiotherapy [(C)RT], hypopharyngeal cancer, (extensive) pharyngeal resection and reconstruction, neck dissection, and comorbidities[1,2,4–7]. It is still disputed which factors are most relevant and which could be influenced to decrease the incidence of PCF. These are important issues for pretreatment counseling and health economic decisions[7]. Furthermore, data usually come from single-institution series, which makes a valid interinstitutional comparison impossible. Such a comparison of complications would be relevant to gain better insight in the quality of care for patients undergoing TL on a national level, but can also lead to changes in treatment protocols in individual institutes. Grau et al., using the national Danish Head and Neck Study Group dataset, did identify prognostic factors for PCF in TL patients with prior radiotherapy (RT). However, no comparisons between the different centers in their analysis were conducted[8]. There is evidence though, that multicenter comparison with proper documentation and feedback on complications in surgery can lead to improved quality and reduced costs[9].

To enable such comparison on a national level, interinstitutional nationwide audits are indispensable. Recently the Dutch Head and Neck Society (DHNS) have started a prospective national audit that eventually will lead to benchmarking and hopefully further improved patient care. In the present study we performed a retrospective chart study, supported by all 8 principle Dutch Head and Neck Centers (DHNC) affiliated to the Dutch Head and Neck Society (DHNS) in a 2-year (2012 and 2013) cohort of TL patients. In this study we not only aimed to identify the incidence of PCF per center, but also to establish the factors predictive for PCF, and to develop a prognostic model predicting the PCF% per center. To provide possibly informative data not covered by the chart study, a survey among the head and neck surgeons of the participating centers was carried out as well.

METHODS

Retrospective chart study

Patient selection

All patients (*n* = 324), who underwent a total laryngectomy in the participating centers between January 2012 and December 2013 were included in the study. The total number of TL procedures per DHNC ranged from 17 to 70 (17, 22, 32, 39, 40, 50, 54, and 70, respectively). Four patients were excluded from the analysis, because they died (without PCF) on day 1, 3, 4, and 6, respectively, leaving 320 patients for further analysis.

Data collection

Patient characteristics agreed to collect in the chart review were age, gender, ASA (American Society of Anesthesiologists) score, diabetes, BMI (body mass index), smoking and alchohol history, albumin, hemoglobin, site of primary tumor, T and N classification, prior treatment [e.g., prior C(RT)] and interval between TL and prior treatment. Surgical data collected concerned the indication for TL, previous tracheotomy, extent of pharyngectomy, type of reconstruction, extent of neck dissection [no, selective; unilateral or bilateral and (modified) radical; unilateral or bilateral] use of antibiotics and tracheoesophageal puncture (TEP). Postoperative data were timing of oral intake, timing of speech rehabilitation, hospitalization time, and occurrence, timing and management of PCF. Medical records were retrospectively reviewed by the first author with supervision in each center. This study does not fall under de scope of the Medical Research Involving Human Subjects Act, which was confirmed by the institutional review board (MREC 17.0439).

Survey

Thirty-five head and neck surgeons (members of the DHNS) were invited to participate in a survey about pre-, peri-, and postoperative management concerning TL. 27 (77%) of these surgeons, representing all 8 participating centers, returned their completed questionnaires. Answers in this questionnaire were used to complete data lacking in the chart review. This concerned data on the pharyngeal closure method, because this information was not always well-documented in the surgical reports. And data on the institution's oral intake protocol, which was used in the analysis of the possible influence of early oral intake on PCF formation[3,10–12].

End points

Primary endpoints for this study were incidence of PCF (occurring within 30 days after discharge), predictive factors for PCF and predicted PCF% per DHNC[13]. As routine swallow X-ray was not performed in all centers, a PCF was recorded when clinically and/or fluoroscopically evidenced. PCF within 14 days after TL was the primary endpoint in a separate analysis pertaining to the role of the (early/late) oral intake protocol.

Statistical analyses

Identification of predictive factors for PCF

IBM SPSS Statistics 22.0 was used to conduct the analyses. Descriptive statistics were computed and additionally univariable and multivariable analyses (using binary logistic regression analysis) were carried out to assess predictive factors for PCF. Factors that were univariably predictive for PCF at a significance level of 10% (2-sided) were initially included in the multivariable logistic regression analysis, which was then further refined using backward elimination. Odds ratios (ORs) and 95% confidence intervals (CIs) of the final model were calculated. Because of multicollinearity between origin of index tumor, pharyngectomy reconstruction, and TEP, only pharyngectomy was kept in the multivariable analysis. It was decided a priori to keep BMI in the final multivariable model regardless it's predictive value in the current cohort, because its (potential) importance has been described in the literature[2,14]. Albumin level was excluded from the multivariable analysis because of missing data in 145 (45%) of the patients. As comorbidity was not routinely scored in most of the participating centers in 2012 and 2013, we used the ASA score as a surrogate[15,16]. In assessing the effect of the interval between (C)RT and TL on PCF formation, we deemed a cut-of point of 30 months clinically relevant. This resulted in one final newly created variable with five levels: no prior (C)RT, RT 0–30 months (mo) before TL, RT 31–444 mo, CRT 0–30 mo, CRT 31–444 mo[1].

Predicted PCF percentages per center

Predicted probabilities on PCF per patient were calculated from the final multivariable logistic regression model. Overall PCF% for all centers and predicted PCF% per center were compared with the observed PCF% per center. When striking differences were observed, we searched both patient data and answers to the survey question about management of pharynx closure for possible explanations.

Role of time from TL to oral intake

The possible effect of timing of oral intake on PCF was analysed univariably and multivariably using PCF within 14 days after TL as outcome variable and initiation of oral intake according to the Institutional protocol as predictor, treating the previously identified predictive factors on PCF as covariates. PCF within 14 days after TL was used as the endpoint for this analysis, because we assume that oral intake mainly can influence the development of PCF in an early postoperative stage.

Two groups were created: an early group (oral intake within 3 days after TL) consisting of all patients in hospitals D and E and late group (oral intake > 3 days after TL) consisting of the patients in the remaining hospitals. The analysis was also conducted with the cut-of point set on 6 days used in hospital H, resulting in an early group with an oral intake ≤ 6 days, and a late group with oral intake after > 6 days.

RESULTS

Retrospective chart study

Patient and tumor characteristics

The cohort consisted of 255 (80%) men and 65 (20%) women. The mean age at time of TL was 63.3 years (SD 9.8 years). Smoking data were available for 299 and missing for 21 patients. 21 patients never consumed tobacco and 278 did. Of this latter group, 143 continued until date of TL and 135 had stopped already. Alcohol abuse was reported by 125 patients, social alcohol consumption by 138, no alcohol consumption ever by 4, and for 53 patients these data were missing. In 217 patients (68%) the tumor was located in the larynx, in 73 (23%) in the hypopharynx, in 29 (9%) the primary tumor was outside these two locations (the 'miscellaneous' group), and in 1 (0.3%) the indication for TL was non-malignant disease (recurrent pneumonia). The 'miscellaneous' group consisted patients with oropharynx cancer (n = 11), larynx sarcoma (n = 6), thyroid cancer (n = 6), oral cavity cancer (n = 2), esophageal cancer (n = 1), neuroendocrine larynx tumor (n = 1), adenoid cystic carcinoma of the trachea (n = 1), and a clivus meningioma (n = 1). Primary TL was conducted in 117 patients (37%), salvage TL in 138 patients (43%), TL for a second primary in 42 patients (13%) and TL for a dysfunctional larynx in 23 patients (7%). Of the 203 'non-primary' TL patients, 140 patients had prior RT, 50 prior CRT, 12 other cancer treatments, and 1 non-malignant indication for TL. A detailed overview of patient and tumor characteristics can be found in Table 1.

Surgical aspects

Standard TL was performed in 212 patients (66%). 69 patients (22%) underwent near total pharyngectomy and 39 (12%) circumferential pharyngectomy in conjunction with TL. Reconstruction was performed in 127 patients. This concerned reinforcement of the pharynx with a pectoralis major (PM) flap without skin island in 19 patients (6%). Reconstruction of the near total pharyngeal defect with a PM-flap with skin island in 59 patients, and a free flap in 10 [radial forearm flap (RFF) 9, anterolateral thigh (ALT) 1]. The 39 circumferential pharyngeal defects were reconstructed with a tubed PM-flap with skin island (*n* = 1), a free flap (*n* = 10; RFF 4, ALT 5, internal mammary artery perforator *n* = 1), gastric pull-up (*n* = 18), or free jejunum transfer (*n* = 9). In 1 patient a planned oropharyngeal-cutaneous fistula was made, whereas this patient also had a PM-flap without skin island.

Table 1 Characteristics of study population; within brackets the number of patients for whom data were available

	n	%
Gender (*n* = 320)		
Male	255	79.7
Female	65	20.3
Age at TL (*n* = 320)	Mean 63.3 years (SD 9.8)	
Smoking history (*n* = 299)		
No	21	7.0
Yes	278	93.0
Alcohol history (*n* = 267)		
No	4	1.5
Social	138	51.7
Abusive	125	46.8
BMI (*n* = 316)		
< 18	28	8.9
18–25	170	53.8
> 25	118	37.3
ASA score (*n* = 320)		
1	24	7.5
2	159	49.7
3	132	41.3
4	5	1.6
Origin of index tumor (*n* = 320)[a]		
Larynx	217	67.8
Hypopharynx	73	22.8
Miscellaneous[b]	29	9.1
No tumor	1	0.3
T stage of index tumor (*n* = 301)[c]		
T1	35	11.6

	n	%
T2	61	20.3
T3	73	24.3
T4	132	43.9
N stage of index tumor (*n* = 301)[c]		
N0	204	67.8
N1	28	9.3
N2	68	22.6
N3	1	0.3
Prior (C)RT (*n* = 320)		
No	130	40.6
Yes, RT	140	43.8
Yes, CRT	50	15.6
Time between prior (C)RT and TL (*n* = 185)	Median 15.0 months (range 1–444)	
Time between prior (C)RT and TL dichotomized (*n* = 185)		
0–30 mo	126	68.1
31–444 mo	59	31.9
Indication TL (*n* = 320)		
Primary	117	36.6
Salvage	138	43.1
Second primary	42	13.1
Disfunctional larynx	23	7.2
Previous tracheotomy (*n* = 319)		
No	245	76.8
Yes	74	23.2

TL total laryngectomy; *BMI* body mass index; *ASA* American society of anesthesiologists; *(C)RT* (chemo)radiotherapy

[a] 294/320 (92%) were diagnosed with squamous cell carcinoma

[b] Miscellaneous: oropharynx *n* = 11; sarcoma in cricoid region *n* = 6; thyroid *n* = 6; oral cavity *n* = 2; esophagus *n* = 1; neuroendocrine tumor in larynx *n* = 1; adenoid carcinoma in trachea *n* = 1; clivus meningioma *n* = 1

[c] T and N classification is not applicable in patients with sarcoma in cricoid region *n* = 6, thyroid cancer *n* = 6, neuroendocrine tumor in larynx *n* = 1, adenoid carcinoma in trachea *n* = 1, clivus meningioma *n* = 1, no tumor *n* = 1. Data were missing *n* = 3

Selective neck dissection was performed in 110 patients (34%) and (modified) radical neck dissection in 67 patients (21%), 50 at the time of TL and 17 at an earlier date. Of the 141 patients (44%) without neck dissection, node sampling for frozen section was conducted in 36, and these patients were also categorized as 'no neck dissection'. In two patients neck dissection data were missing.

Primary TEP with insertion of an indwelling voice prosthesis was performed in 261 patients (82%), secondary TEP in 37 (12%), and in 22 (7%) no TEP was performed.

Pharyngocutaneous fistulization

The overall incidence of PCF within 30 days after discharge from the hospital was 25.9% (83/320). After these 30 days, 4 more patients developed PCF, in 3 at day 51, 58, 131, respectively, and in 1 PCF occurred in the "postoperative radiotherapy period", which we also deemed to be more than 30 days after patient's discharge at day 12 postoperatively. The incidence of PCF in patients treated with primary TL was 24.8% (29/117), with salvage TL 22.5% (31/138), with TL for a second primary 35.7% (15/42) and with TL for a dysfunctional larynx 34.8% (8/23) (P = 0.264). The median day of PCF manifestation was day 12 (range 1–48 after surgery). 66 of the 83 PCF patients were treated conservatively (79.5%) and 17 required additional surgery (20.5%). In 15 of these 17 patients, flap reconstruction was used (PM 14; ALT 1), resuturing of the pharyngeal defect (1), or surgical exploration only (1). Median time between PCF and additional surgery was 14.0 days (range 0-172). Sixty-five patients (78.3%) were discharged with a cured PCF, and 18 with a persisting PCF (21.7%). Median hospitalization time for patients without PCF was 13 days (range 7–45) and for patients with PCF 20 days (range 8–80) (P < 0.001). Median hospitalization time for conservatively treated PCF patients was 17 days (range 8–68) and for patients with surgically treated PCF this was 35.5 days (range 7–80) (P = 0.012).

Univariable analyses: prognostic factors for PCF

Univariable logistic regression analyses, to identify prognostic factors for PCF, were conducted for gender, age, site of index tumor, diabetes, BMI (n = 316), ASA score, preoperative albumin level (n = 176), preoperative hemoglobin level (n = 284), prior (C)RT, time between prior (C) RT and TL, pharyngectomy, reconstruction, neck dissection, TEP and previous tracheotomy. Factors predictive for PCF were: index tumor, i.e., hypopharynx vs larynx (OR 3.25; 95% CI 1.83–5.76; P < 0.001), BMI < 18 (OR 2.64; 95% CI 1.16-6.00; P = 0.02), albumin level ≤ 40 g/L (OR 1.79; 95% CI 0.92–3.48; P = 0.087), prior CRT (OR 2.51; 95% CI 1.26-5.00; P = 0.009), increased time between prior (C)RT and TL [OR 1.10 (per 1 year increase); 95% CI 1.02–1.17; P = 0.003], near total pharyngectomy (OR 3.86; 95% CI 2.13–6.98; P < 0.001), circumferential pharyngectomy (OR 2.96; 95% CI 1.42–6.17; P = 0.004), reconstruction (all types of reconstruction vs no reconstruction OR 3.62; 95% CI 2.15–6.11; P < 0.001), neck dissection, i.e., selective (OR 2.30; 95% CI 1.26–4.19; P = 0.007) and radical (OR 3.05; 95% CI 1.57–5.95; P = 0.001), secondary TEP and no TEP vs primary TEP (OR 3.83; 95% CI 1.58–9.31; P = 0.003, and OR 3.63; 95% CI 1.78–7.39 P < 0.001, respectively), and tracheotomy (OR 1.83; 95% CI 1.04–3.21; P = 0.036). Prior RT as single-modality treatment is not a significant prognostic factor for PCF compared to no (C)RT (OR 0.87; 95% CI 0.49–1.54, P = 0.635). Smoking (OR 2.25; 95% CI 0.63–8.06; P = 0.213) and discontinuing smoking (OR 1.86; 95%

CI 0.52–6.74; *P* = 0.342) are not predictive for PCF compared to no smoking. A history of alcohol abuse compared to no/ social drinking (OR 1.19; 95% CI 0.68–2.06; *P* = 0.542) also is not predictive for PCF. Details are summarized in Table 2. Table 3 provides an overview of the variations in the DHNC cohorts regarding these significant prognostic factors for PCF.

Table 2 Univariable analysis of possible prognostic factors for PCF

	No. of pts (%)	PCF (%)	OR[a] (95% CI)	*P* value
Gender	320			0.964
Male	255 (79.7)	66 (25.9)	1.00	
Female	65 (20.3)	17 (26.2)	1.01 (0.55–1.89)	
Age at TL	320	NA	0.61[b] (0.84–1.08)	0.454
Alcohol use	267			0.542
No/social	142 (53.2)	34 (23.9)	1.00	
Abusive	125 (46.8)	34 (27.2)	1.19 (0.68–2.06)	
Smoking	299			0.417
No	21 (7.0)	3 (14.3)	1.00	
Yes, discontinued	135 (45.2)	32 (23.7)	1.86 (0.52–6.74)	0.342
Yes, not discontinued	143 (47.8)	39 (27.3)	2.25 (0.63–8.06)	0.213
Site of origin	320			**0.000**
Larynx	217 (67.8)	42 (19.4)	1.00	
Hypopharynx	73 (22.8)	32 (43.8)	3.25 (1.83–5.76)	**0.000**
Miscellaneous	30 (9.4)	9 (30.0)	1.79 (0.76–4.18)	0.181
Diabetes	320			0.667
No	277 (86.6)	73 (26.4)	1.00	
Yes	43 (13.4)	10 (23.3)	0.85 (0.40–1.80)	
BMI	316			**0.047**
18–25	170 (53.8)	42 (24.7)	1.00	
< 18	28 (8.9)	13 (46.4)	2.64 (1.16-6.00)	**0.020**
> 25	118 (37.3)	8 (6.8)	0.95 (0.55–1.64)	0.849
ASA	320			0.664
1	24 (7.5)	6 (25.0)	1.00	
2	159 (49.7)	37 (23.3)	0.91 (0.34–2.46)	0.852
3	132 (41.3)	39 (29.6)	1.26 (0.46–3.41)	0.652
4	5 (1.6)	1 (20.0)	0.75 (0.07–8.09)	0.813
Preoperative albumin level	175			**0.087**
< 40 g/L	87 (49.7)	30 (34.5)	1.79 (0.92–3.48)	
≥ 40 g/L	88 (50.3)	20 (22.7)	1.00	
Preoperative hemoglobin level	284			0.681
Low[c]	144 (50.7)	37 (25.7)	0.90 (0.53–1.52)	
Normal	140 (49.3)	39 (27.9)	1.00	
(C)RT prior to TL	320			**0.008**
No	130 (40.6)	31 (23.9)	1.00	
RT	140 (43.8)	30 (21.4)	0.87 (0.49–1.54)	0.635
CRT	50 (15.6)	22 (44.0)	2.51 (1.26-5.00)	**0.009**
Time between prior (C)RT and TL (continuous)	185	NA	1.10[d] (1.02–1.17)	**0.003**

	No. of pts (%)	PCF (%)	OR[a] (95% CI)	*P* value
Time between prior RT/CRT and TL (≥ or < 30 months)	315			**0.000**
No prior (C)RT	130 (41.3)	31 (23.8)	1.00	
RT—0/30 mo before TL	87 (27.6)	10 (11.5)	0.42 (0.19–0.90)	**0.026**
RT—31/444 mo before TL	49 (15.5)	18 (36.7)	1.85 (0.91–3.76)	**0.087**
CRT—0/30 mo before TL	39 (12.4)	16 (41.0)	2.22 (1.04–4.73)	**0.038**
CRT—31/444 mo before TL	10 (3.2)	6 (60.0)	4.79 (1.27–18.07)	**0.021**
Indication TL				0.271
Primary	117 (36.6)	29 (24.8)	1.00	
Salvage	138 (43.1)	31 (22.5)	0.88 (0.49–1.57)	0.663
Second primary	42 (13.1)	15 (35.7)	1.69 (0.79–3.60)	0.177
Disfunctional larynx	23 (7.2)	8 (34.8)	1.62 (0.62–4.21)	0.323
Pharyngectomy	320			**0.000**
No[e]	212 (66.3)	37 (17.5)	1.00	
Near total	69 (21.6)	31 (44.9)	3.86 (2.13–6.98)	**0.000**
Circumferential	39 (12.2)	15 (38.5)	2.96 (1.42–6.17)	**0.004**
Reconstruction				**0.000**
No	193 (60.3)	31 (16.1)		
Yes	127 (39.7)	52 (40.9)	3.62 (2.15–6.11)	
Reconstruction (by type)	320			**0.000**
No	193 (60.3)	31 (16.1)	1.00	
PM-flap without skin island	20 (6.3)	6 (30.0)	2.24 (0.80–6.28)	0.125
PM-flap with skin island	60 (18.8)	28 (46.7)	4.57 (2.42–8.64)	**0.000**
Free flap	20 (6.2)	8 (40.0)	3.48 (1.32–9.22)	**0.012**
Gastric pull-up	18 (5.6)	6 (33.3)	2.61 (0.91–7.49)	**0.074**
Jejunum	9 (2.8)	4 (44.4)	4.18 (1.06–16.45)	**0.041**
Neck dissection	318			**0.002**
No/node picking	141 (44.3)	23 (16.3)	1.00	
SND	110 (34.6)	34 (30.9)	2.30 (1.26–4.19)	**0.007**
(M)RND	67 (21.1)	25 (37.3)	3.05 (1.57–5.95)	**0.001**
TEP	320			**0.000**
Primary	261 (81.6)	54 (20.7)	1.00	
No	22 (6.9)	11 (50.0)	3.83 (1.58–9.31)	**0.003**
Secondary	37 (11.6)	18 (48.6)	3.63 (1.78–7.39)	**0.000**
Previous tracheotomy	319			**0.036**
No	245 (76.8)	56 (22.9)	1.00	
Yes	74 (23.2)	26 (35.1)	1.83 (1.04–3.21)	

Bold *P* values indicate significance

PCF pharyngocutaneous fistulization; *OR* odds ratio; *CI* confidence interval; *TL* total laryngectomy; *BMI* body mass index; *ASA* American society of anesthesiologists; *(C)RT* (chemo)radiotherapy; icw in combination with; *SND* selective neck dissection; *(M)RND* (modified) radical neck dissection; *PM* pectoralis major; *TEP* tracheoesophageal puncture

[a] Logistic regression

[b] Per 5 years increase in age (higher age corresponds to lower odds of PCF)

[c] Low albumin is < 7.5 mmol/L in women and < 8.5 mmol/L in men

[d] Per 1 year increase in time between prior (C)RT and TL [longer time between prior (C)RT and TL corresponds to higher odds of PCF]

[e] Standard total laryngectomy

Table 3 Overview of variables predictive for PCF (obtained from univariable analyses) per DHNC

	Total (%)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
	***n* = 320**	***n* = 52**	***n* = 17**	***n* = 70**	***n* = 39**	***n* = 32**	***n* = 48**	***n* = 40**	***n* = 22**
Patient/tumor characteristics									
BMI									
< 18	28 (8.9)	4 (7.7)	0 (0)	11 (15.7)	3 (7.7)	5 (15.6)	1 (2.2)	0 (0)	4 (18.2)
18–25	170 (53.8)	31 (59.6)	9 (56.2)	37 (52.9)	22 (56.4)	16 (50.0)	21 (46.7)	24 (60)	10 (45.5)
> 25	118 (37.3)	17 (32.7)	7 (43.8)	22 (31.4)	14 (34.4)	11 (34.4)	23 (51.1)		
16 (40)	8 (36.4)								
Missing	4		1				3		
(C)RT prior to TL									
No	130 (40.6)	13 (25)	8 (47.1)	28 (40)	18 (46.2)	8 (25)	29 (60.4)	24 (60)	2 (9.1)
Yes, RT	140 (43.8)	35 (67.3)	8 (47.1)	29 (41.4)	17 (43.6)	12 (37.5)	17 (35.4)	10 (25)	12 (54.5)
Yes, CRT	50 (15.6)	4 (7.7)	1 (5.9)	13 (18.6)	4 (10.3)	12 (37.5)	2 (4.2)	6 (15)	8 (36.4)
Time between prior (C)RT and TL (mo)	(*n* = 185) 15.0 (1–444)	(*n* = 39) 13.0 (4–155)	(*n* = 8) 12.0 (4–32)	(*n* = 40) 30.0 (5–444)	(*n* = 21) 12.0 (1–147)	(*n* = 24) 11.0 (7–100)	(*n* = 20) 12.0 (4–234)	(*n* = 15) 16.0 (4–205)	(*n* = 19) 45.0 (4–193)
Time between prior RT/ CRT and TL (≥ or < 30 months)									
No prior (C) RT	130 (41.3)	13 (25.0)	8 (50)	28 (41.2)	18 (46.1)	8 (25)	29 (60.4)	24 (61.5)	2 (9.5)
RT—0/30 mo before TL	87 (27.6)	27 (51.9)	6 (37.5)	12 (17.6)	11 (28.2)	10 (31.3)	12 (25)	4 (10.3)	5 (23.8)
RT—31/444 mo before TL	49 (15.6)	8 (15.4)	1 (6.3)	15 (22.1)	6 (15.4)	2 (6.2)	5 (10.4)	5 (12.8)	7 (33.3)
CRT—0/30 mo before TL	39 (12.4)	4 (7.7)	1 (6.2)	9 (13.2)	4 (10.3)	10 (31.2)	2 (4.2)	5 (12.8)	4 (19.1)
CRT—31/444 mo before TL	10 (3.1)	0 (0)	0 (0)	4 (5.9)	0 (0)	2 (6.3)	0 (0)	1 (2.6)	3 (14.3)
Missing			1	2				1	1
Origin Tumor									
Larynx	216 (67.5)	38 (73.1)	17 (100)	48 (68.6)	26 (66.7)	19 (59.4)	33 (68.8)	23 (57.5)	13 (59.1)
Hypopharynx	73 (22.8)	6 (11.5)	0 (0)	18 (25.7)	11 (28.2)	7 (21.9)	12 (25)	12 (30)	7 (31.8)
Other	30 (9.4)	8 (15.4)	0 (0)	4 (5.7)	2 (5.1)	6 (18.8)	3 (6.2)	5 (12.5)	2 (9.1)
Indication TL[a]									
Primary	117 (36.6)	11 (21.2)	8 (47.1)	26 (37.1)	17 (43.6)	6 (18.8)	27 (56.3)	20 (50.0)	2 (9.1)
Salvage	138 (43.1)	37 (71.2)	9 (52.9)	23 (32.9)	15 (38.5)	18 (56.3)	12 (25.0)	12 (30.0)	12 (54.5)
Second primary	42 (13.1)	4 (7.7)	0 (0)	13 (18.6)	5 (12.8)	5 (15.6)	7 (14.6)	3 (7.5)	5 (22.7)
Disfunctional larynx	23 (7.2)	0 (0)	0 (0)	8 (11.4)	2 (5.1)	3 (9.4)	2 (4.2)	5 (12.5)	3 (13.6)
Surgical details									
Pharyngectomy									
No[b]	212 (66.3)	42 (80.8)	16 (94.1)	40 (57.1)	27 (69.2)	19 (59.4)	30 (62.5)	28 (70)	10 (45.5)
Near total	69 (21.6)	6 (11.5)	1 (5.9)	19 (27.1)	6 (15.4)	6 (18.8)	15 (31.3)	12 (30)	4 (18.2)
Circumferential	39 (12.2)	4 (7.7)	0 (0)	11 (15.7)	6 (15.4)	7 (21.9)	3 (6.3)	0 (0)	8 (36.4)
Reconstruction									
No	193 (60.3)	42 (80.8)	16 (94.1)	33 (47.1)	27 (69.2)	13 (40.6)	26 (54.2)	26 (65)	10 (45.5)
PM-flap without skin island	20 (6.3)	0 (0)	0 (0)	7 (10)	0 (0)	6 (18.8)	5 (10.4)	2 (5)	0 (0)

	Total (%)	A	B	C	D	E	F	G	H
	n = 320	*n* = 52	*n* = 17	*n* = 70	*n* = 39	*n* = 32	*n* = 48	*n* = 40	*n* = 22
PM-flap with skin island	60 (18.8)	6 (11.5)	1 (5.9)	18 (25.7)	1 (2.6)	6 (18.8)	13 (27.1)	12 (30)	3 (13.6)
Free flap	20 (6.3)	4 (7.7)	0 (0)	3 (4.3)	7 (17.9)	3 (9.4)	2 (4.2)	0 (0)	1 (4.5)
Gastric pull-up	18 (5.6)	0 (0)	0 (0)	2 (2.9)	4 (10.3)	4 (12.5)	2 (4.2)	0 (0)	6 (27.3)
Jejunum	9 (2.8)	0 (0)	0 (0)	7 (10)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9.1)
Neck dissection									
No/node picking	141 (44.3)	39 (75)	0 (0)	35 (51.5)	19 (48.7)	7 (21.9)	24 (50)	2 (5)	15 (68.2)
Selective	110 (34.6)	8 (15.4)	14 (82.4)	27 (39.7)	7 (17.9)	14 (43.8)	15 (31.3)	23 (57.5)	2 (9.1)
Radical	67 (21.1)	5 (9.6)	3 (17.6)	6 (8.8)	13 (33.3)	11 (34.4)	9 (18.8)	15 (37.5)	5 (22.7)
Missing	2			2					
TEP[a]									
No	22 (6.9)	0 (0)	0 (0)	5 (7.1)	3 (7.7)	2 (6.3)	0 (0)	0 (0)	8 (36.4)
Primary	261 (81.6)	52 (100)	17 (100)	39 (55.7)	33 (84.6)	25 (78.1)	44 (91.7)	39 (97.5)	12 (54.5)
Secondary	37 (11.5)	0 (0)	0 (0)	26 (37.1)	3 (7.7)	5 (15.6)	4 (8.3)	1 (2.5)	2 (9.1)
Previous tracheotomy									
No	245 (76.8)	46 (88.5)	11 (64.7)	57 (81.4)	31 (79.5)	18 (56.3)	38 (79.2)	29 (72.5)	15 (71.4)
Yes	74 (23.2)	6 (11.5)	6 (35.3)	13 (18.6)	8 (20.5)	14 (43.7)	10 (20.8)	11 (27.5)	6 (28.6)
Missing									1

DHNC Dutch Head and Neck Center; *PCF* pharyngocutaneous fistulization; *BMI* body mass index; *(C)RT* (chemo) radiotherapy; *TL* total laryngectomy; mo months; *PM* pectoralis major; *TEP* tracheoesophageal puncture

[a] This variable contains interesting information and is therefore presented in this table (indication of TL and TEP were not included in univariable analyses because of colinearity with other variables)

[b] Standard total laryngectomy

Multivariable analysis: final prognostic factors for PCF

The multivariable prediction model revealed that prior (C) RT combined with the time interval between TL and prior (C)RT, pharyngectomy, neck dissection and previous tracheotomy were the best predictors for development of PCF. Patients with BMI < 18 had a significantly increased risk on PCF (OR 2.70; 95% CI 1.06–6.90; *P* = 0.038). Patients with RT and CRT ≥ 31 months before TL and patients with CRT ≤ 30 months before TL were more likely to develop PCF (OR 2.34; 95% CI 1.01–5.43; *P* = 0.048/OR 5.14, 95% CI 1.13–23.42; *P* = 0.034 and OR 2.32; 95% CI 1.00–5.38; *P* = 0.049, respectively) compared to patients with no (C) RT. The other factors associated with PCF were: near total pharyngectomy (OR 2.61; 95% CI 1.33–5.15; *P* = 0.006), selective and radical neck dissection (OR 2.51; 95% CI 1.23–5.12; *P* = 0.011, and OR 2.70; 95% CI 1.18–6.15; *P* = 0.018, respectively) and previous tracheotomy (OR 2.02; 95% CI 1.07–3.79; *P* = 0.029) (Table 4).

Table 4 Final multivariable prediction model

	OR (95% CI)	*P* value
(C)RT prior to TL-time		**0.008**
No prior (C)RT	1.00	
RT—0/30 mo before TL	0.63 (0.27–1.47)	0.286
RT—31/444 mo before TL	2.34 (1.01–5.43)	**0.048**
CRT—0/30 mo before TL	2.32 (1.00-5.38)	**0.049**
CRT—31/444 mo before TL	5.14 (1.13–23.42)	**0.034**
BMI		0.093
< 18	2.70 (1.06–6.90)	**0.038**
18–25	1.00	
> 25	1.46 (0.78–2.73)	0.234
Pharyngectomy		**0.021**
No	1.00	
Near total	2.61 (1.33–5.15)	**0.006**
Circumferential	1.53 (0.62–3.81)	0.357
Neck dissection		**0.022**
No	1.00	
SND	2.51 (1.23–5.12)	**0.011**
(M)RND	2.70 (1.18–6.15)	**0.018**
Previous tracheotomy		**0.029**
No	1.00	
Yes	2.02 (1.07–3.79)	

Bold *P* values indicate significance

OR odds ratio; *CI* confidence interval; *(C)RT* (chemo)radiotherapy; *TL* total laryngectomy; *RT* radiotherapy; mo months; *SND* selective neck dissection; *(M)RND* (modified)radical neck dissection

Table 5 PCF performance per DHNC

DHNC	PCF%	Difference between PCF% and mean PCF% (25.9)	Predicted PCF%[a]	PCF performance rate[b]
A	9.6	− 16.3	14.9	− 5.3
B	17.6	− 8.3	23.6	− 6.0
C	37.1	+ 11.2	28.5	+ 8.6
D	20.5	− 5.4	23.0	− 2.5
E	25.0	− 0.9	34.9	− 9.9
F	27.1	+ 1.2	23.4	+ 3.7
G	35.0	+ 9.1	30.6	+ 4.4
H	27.3	+ 1.4	31.6	− 4.3

PCF pharyngocutaneous fistulization; *DHNC* Dutch Head and Neck Center

[a] PCF% corrected for predictive (risk) factors from the multivariable logistic regression model

[b] PCF% minus predicted PCF%

PCF performance rate

For a meaningful comparison of the differences in the PCF percentages, the clinical and surgical differences in the patient cohorts of the 8 DHNC were taken into account. Table 5 shows per DHNC the actual PCF%, the difference between this PCF% and the overall PCF%, the PCF% corrected for predictive (risk) factors found in the multivariable analysis, and the difference between the predicted PCF% and the observed PCF%, called the PCF performance rate. The mean PCF% was higher than the overall mean in centers C and G, close to the overall mean in centers E, F and H, and lower in centers A, B and D.

The predicted PCF% (correction based on the multivariable logistic regression model) was higher than the overall mean PCF% in centers C, E, G and H, indicating that these centers serve a patient population with a higher risk of developing PCF or use surgical techniques implicating a higher risk (such as elective neck dissection). In these DHNCs, patients with BMI < 18, prior CRT (and increased time between prior CRT and TL), previous tracheotomy, extensive pharyngectomy and selective or radical neck dissection occur more than average, as also can be seen in Table 3.

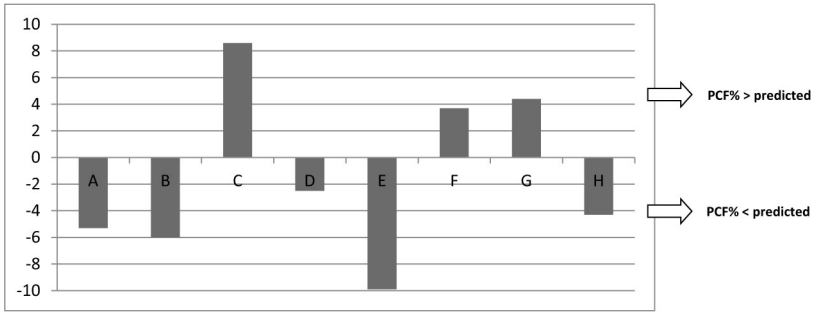

Fig. 1 PCF performance per DHNC. Gray bars: predicted probabilities per center minus observed pharyngocutaneous fistulization (PCF) rates per center (PCF performance rate); *x*-axis: Dutch Head and Neck Center (DHNC)

The last column in Table 5 shows the PCF performance rate per DHNC, which is the difference between the actual PCF% and the predicted PCF%. This shows that not all differences are explained by factors established in the prediction model. However, it is also clear that the differences corrected for the predictive (risk) factors are considerably smaller than the differences seen in the third column. Indeed, the predictive factors identified here explain enough of the differences that, compensating for these factors, hospital is no longer independently predictive for PCF (P = 0.380). The PCF performance rates are visualized in Fig. 1.

Data used from the national survey

Pharyngeal closure

Techniques for primary pharyngeal closure differ widely between centers and head and neck surgeons. Nine of 27 who filled in the survey close the pharynx vertically, 14 in a Y/T fashion, and 4 horizontally.

Oral intake

Two centers (D and E) were using an early oral intake protocol, which means initiation of oral intake within 3 days postoperatively. The remaining hospitals were using a late(r) oral intake protocol, varying from starting oral intake at day 6–12. Combining this information with data from the retrospective chart study revealed that patients who started early with oral intake according to the protocol did not have an increased risk on PCF within 14 days after TL compared to patients who started late with oral intake according to the protocol (OR 1.11; 95% CI 0.57–2.17; P = 0.752). This result was comparable in a model together with the final predictive factors (OR 1.14; 95% CI 0.54–2.41; P = 0.736). One center (H) started oral intake according to protocol on day 6 after TL. Adding this center to the 'early oral intake group according to the protocol' did not affect this result.

DISCUSSION

This nationwide 2-year audit on postoperative complications of TL showed that PCF still is a significant problem. The overall incidence of 25.9% is comparable to figures reported in the literature[1,7,17]. At first sight, there is a considerable variation in PCF% between the participating centers. The analysis based on the multivariable prediction model shows that in part these differences in PCF% are explainable by variations regarding the significant risk factors for PCF. Factors predicting PCF are prior (C)RT in combination with prolonged lead time to TL, near total pharyngectomy, selective neck dissection, radical neck dissection, previous tracheotomy, and BMI < 18. These factors are also in line with earlier studies on the risk for PCF manifestation[1,2,4,5,18].

The most interesting aspect of this study is that it allows for a detailed comparison between the participating centers. When observing the actual PCF% in the third column in Table 5, the variation is much wider than the variation in the PCF performance shown in the last column of this table. This means that in the center with the lowest incidence of PCF, this incidence is (in part) so low because the identified risk factors are more favorable. Vice versa, centers with a higher PCF% have less favorable risk factors in their population.

There are some exceptions, though, with centers showing better PCF performance than predicted (e.g., center A), and centers still less favorable than predicted (e.g., center C). This means that not all differences are explainable with the multivariable prediction model. Center C, for example, besides having a less favorable patient population more patients requiring TL for a dysfunctional larynx (11.4% vs 6.7% in the other centers) and more jejunum reconstructions (10.0% vs 0.8% in the other centers), is also the only one where the majority of the pharynx closures were done horizontally. This might be an explanation of the difference in predicted and observed fistula rate in that center. In this respect, it is somewhat disappointing that information about the closure technique was often not available in sufficient detail. Therefore we only can speculate about the relevance of pharynx closure based on the survey data. However, there are other reports showing that T-shaped closure reduces the incidence of PCF[19].

The prognostic factors found in this study are comparable with those reported in the literature. Dedivitis et al. described a 6% increase in PCF risk in patients who underwent neck dissection[5]. The underlying rationale for this increased risk is that a neck dissection further diminished the vascularity in the operation field, making the remaining tissues more susceptible for infection or poor healing just because of a lack of sufficient perfusion. We also found that both types of neck dissection, selective and radical, are associated with an increased risk on PCF. Management of the N0 neck in patients with advanced stage larynx cancer and management of the N0 neck in salvage patients (with prior N0/N + neck) is still a matter of controversy and the final choice of treatment (no neck dissection/ node sampling, or selective neck dissection) is 'surgeon and center dependent'[20,21]. According to the Dutch National Guideline on Laryngeal Carcinoma node a node sampling procedure (instead of a selective neck dissection) can be performed during a primary TL for advanced disease without clinical or radiological evidence of positive lymph nodes in case post-operative radiotherapy is planned or in case of salvage surgery with no evidence of regional metastases and no history of lymph node metastases[22]. This means that the choice for selective neck dissection should be weighed against the higher PCF risk and the option of node sampling for frozen section should be discussed[23]. Obviously, in case of suspicion or evidence of metastatic lymph node involvement there is no choice and neck dissection is indicated.

The finding that previous tracheotomy is predictive for PCF is not very surprising, since this condition forms an additional infection risk and for complicated wound healing. This means that if tracheotomy is avoidable, e.g., by performing a TL 'a chaud', that is worthwhile considering. Patients with BMI < 18 were more likely to develop PCF compared to patients with healthy BMI, which is supported by earlier studies describing poor nutritional status

as a predictive factor[14,24]. Certainly in patients in whom there is time to improve nutritional status and condition, such as in case of a TL for a dysfunctional larynx, this should be employed. Interestingly, ASA score at the time of TL had no significant correlation with PCF%. Although ASA score has been reported to be a reasonable surrogate parameter for comorbidity[15,16], it is not as representative for comorbidity as for example, the ACE-27 score, that is nowadays used in all DHNC centers[25]. However, these data were not yet available in most of the centers in 2012–2013, and hence, ASA was included in the study protocol, with the advantage that the ASA data in this study were available (from anesthesia reports) for the vast majority of the patients.

Lastly, prior (C)RT is frequently described in the literature as prognostic factor for PCF[4,5,7,8,26]. In the present study, prior CRT was a significant predictior for the development of PCF in univariable analysis[27]. RT as single-modality treatment was not significantly associated with a higher risk of PCF. Interestingly, however, when taking time since prior treatment into account (≤ 30 vs > 30 months), the multivariable analysis showed that also RT was a significant predictor for the development of PCF, as can be seen in Table 4.

The possible influence of oral intake was also examined in this study and, in accordance with other studies, we did not find an association between early oral intake and the development of PCF[3,10,11,28]. Therefore, also the present study suggests that an early oral intake protocol after TL is a safe policy enabling earlier discharge and potentially positively influences the patients' feeling of normalcy[3].

A strong aspect of this audit is that there was no selection bias as all TLs performed in the 8 centers were used in this analysis. A limitation of this study is that collection of 2-year oncologic outcome data, such as regional control and survival, was not part of the audit protocol. These data are of course indispensable for the final verdict on the best treatment strategy concerning the neck, i.e., the choice between node sampling for frozen section (associated with a decreased the risk on PCF) or selective neck dissection in the cN0 cases. It has to be kept in mind that this audit concerns a retrospective analysis and that not all surgical, clinical and comorbidity data were available. Moreover, the definition of a PCF might have caused some differences as in centers where swallow X-rays are only made in case of clinical suspicion, subclinical fistulas might have been missed. However, we did not find a difference in either the time of fistula occurrence nor in the management between centers employing routine swallow X-rays and those performing them in case of suspicion only.

In conclusion, this nationwide audit has provided valid comparative PCF data from the participating DNHCs, confirming the known risk factors from the literature. These data are

useful for counseling on PCF risks. Data show that variations in PCF% in the DHNCs (in part) are explainable by the variations in these identified predictive factors. Standardized detailed surgical reporting is important to acquire more relevant data to identify additional PCF risk factors, and future audits will hopefully lead to a reduction in the PCF rate. Based on the current analysis, the optimal approach of the neck with, especially the use of elective neck dissection, which is a major risk factor for PCF, needs further consideration. The prognostic benefit of elective neck dissection when the patient needs postoperative (C)RT has never been proven. Additionally, the need for elective neck dissection in the salvage setting of a clinically negative neck has never been proven, especially when the neck previously was irradiated electively. We therefore advise to refrain from neck dissections when the risk of occult metastases is low.

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COMPLIANCE WITH ETHICAL STANDARDS

Funding

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Conflict of interest

The Netherlands Cancer Institute receives a research grant from Atos Medical, Hörby, Sweden, which contributes to the existing infrastructure for health-related quality of life research of the Department of Head and Neck Oncology and Surgery. There are no other conficts of interest to declare.

Research involving human participants and/or animals

This study does not fall under de scope of the Medical Research Involving Human Subjects Act, which was confirmed by the institutional review board (MREC 17.0439).

Informed consent

Not applicable.

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PART II

Postlaryngectomy rehabilitation

CHAPTER 5

Postlaryngectomy prosthetic voice rehabilitation in a consecutive cohort of 232 patients over a 13-years period

Petersen JF*
Lansaat L*
Timmermans AJ
van der Noort V
Hilgers FJM
van den Brekel MWM

**both authors contributed equally*

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ABSTRACT

Background

With the increasing necessity for total laryngectomy (TL) after prior (chemo)radiotherapy, prosthetic vocal rehabilitation outcomes might have changed.

Methods

Retrospective cohort study including all patients laryngectomized between 2000 and 2012 with a voice prosthesis (VP) in the Netherlands Cancer Institute.

Results

Median device lifetimes of the standard Provox2 and Vega VPs are 63 and 66 days, respectively, and for the problem-solving ActiValve Light and Strong VPs 143 and 186 days, respectively. In multivariable analysis, salvage TL and TL for a dysfunctional larynx (compared to primary TL) were associated with a shorter device lifetime. Almost half of the patients (48%) experienced tracheoesophageal puncture tract-related problems, and this concerned 12% of all VP replacements.

Conclusions

Compared to historical cohorts, device lifetimes of regular Provox2 and Vega voice prostheses have decreased. Complications are not occurring more frequently but affect more patients. Nevertheless, the clinical reliability and validity of prosthetic voice rehabilitation is still sound.

INTRODUCTION

Since the first total laryngectomy (TL) for cancer, performed by Theodore Billroth in 1873, voice restoration has been considered the leading postlaryngectomy rehabilitation challenge.[1] The three main methods for restoring oral communication are esophageal, electrolarynx, and tracheoesophageal (TE) prosthetic speech. In 1973, Mozolewski et al[2] were the first to publish the results of a prosthetic device used in 24 patients, and in 1980, Singer and Blom[3] introduced the first commercial voice prosthesis (VP). With a success rate of around 90%, TE prosthetic speech has now become the method of choice for voice rehabilitation in most countries with an adequate health care insurance system.[4]

Besides the original Blom-Singer VP (InHealth Technologies, Carpinteria, CA, USA), a variety of prosthetic devices have been developed, for example, in the Netherlands, the Groningen button, the Nijdam VP, and Provox VPs (Atos Medical AB, Hörby, Sweden).[3,5–7] Median and/or mean device lifetime of these VPs have been reported to be around 3-6 months, and the main reason for replacement reportedly is transprosthetic leakage.[4,7] These studies have, however, been conducted in a time where primary TL was the gold standard in advanced larynx and hypopharynx cancer treatment. With the increasing use of radiotherapy (RT) and the introduction of chemoradiotherapy (CRT) in the 1990s, we have observed a decrease in primary TL and an increase in (C)RT as primary treatment modalities.[8] This has, however, also led to an increase in salvage TLs after failed (C)RT, which have been associated with more TE wall (TEP tract)-related problems and possibly a lower device lifetime of VPs.[9–11]

In 2000, Op de Coul et al[4] published the long-term results of voice rehabilitation with the first Provox VPs in the Netherlands Cancer Institute. Since then, several new generations of VPs have been developed, aimed at improving patient comfort, by, for example, improving airflow characteristics and replacement tools (Provox Vega), and at reducing biofilm overgrowth or inadvertent opening of the valve during swallowing or breathing (Provox ActiValve).[6,12–15] These new VP's have, however, not been extensively evaluated yet in a long-term fashion. Thus, in an era with an increasing necessity for salvage surgery and with the development of several new generations of VPs, the aim of this study was to evaluate our experience with the consistent use of several generations of VPs for voice rehabilitation in a large cohort of consecutively treated patients with TL. Our main outcome measures were the median device lifetime of the various VPs used in the study period, possible correlations with patient, tumor and treatment characteristics, indications for device-related and TEP tract-related VP replacement, and solutions for complications.

METHODS

Patient selection

We conducted a retrospective cohort study of all patients laryngectomized between January 2000 and December 2012 and in regular follow-up for voice rehabilitation in our hospital (n = 242). Patients, who never had a VP (n = 3) and patients whose medical files were (partially) missing were excluded (n = 7). This left 232 patients for further analysis.

We considered the following parameters: sex, age at TL, primary tumor site, TNM classification, primary treatment, indication for TL (primary, salvage, second primary, and dysfunctional larynx), surgical characteristics (eg, neck dissection and flap reconstruction), driving distance to the hospital, and survival status. To assess the driving distance in minutes by car to the hospital, we used Google Maps software and the postal codes of the patients. For each VP replacement, the following data were collected: date of insertion and replacement or removal, type and size of the VP, the reason for replacement or removal, and use of a washer for periprosthetic leakage. Last date of follow-up was set at January 05, 2017. This study does not fall under the scope of the Medical Research Involving Human Subjects Act, which was confirmed by the institutional review board (MREC 17.0793).

Statistical analysis

We consistently have described the results both on device level and on patient level. Descriptive analysis was used to summarize device and patient characteristics. Overall survival (OS) of the study population was calculated from time of TL to date of last follow-up (FU) or death, using Kaplan Meier analysis.

The main outcome measure of this study was the device lifetime of the VPs in days, measured as the time from insertion of the VP to the date of removal. Kaplan Meier analyses were used to assess the median device lifetimes. Lifetimes of the VPs ongoing at the end of the observation period were right censored as were lifetimes of VPs that were still in situ when the patient was lost to follow-up or died.

To assess the influence of several factors on the in situ time of the VPs, we used Cox proportional hazard models, with the replacement of the VP as the event of interest. For estimating the influence of *VP characteristics*, all analyzed VPs are treated as individual observations, with in situ time counted in days since insertion. However, in our Cox-model regressing the in situ time of the VP on the VP characteristic of interest, we stratify by patient. Hence, the underlying assumption is that VPs in different patients may have

different baseline hazards for replacement (depending on the patient), while the effect of the VP characteristic (eg, Acti-Valve vs normal) on this hazard is the same across patients.

For estimating the influence of *patient and treatment characteristics* (eg, age), we address the fact that each patient can have multiple events (ie, VP replacements) by adopting the "Cox models for counting processes" framework of Andersen and Gill.[16] This means that the times of insertion and replacement of each VP are measured in days since the insertion of the *first* VP of the patient using it, thus ensuring that at every time point each of the 232 patients contributes at most one VP to the estimation of the relative hazards of replacement at that time point. In both type of models, VPs are censored if they were still in situ either at January 5th, 2017 or at the date of death or lost to follow-up of the patient.

Logistic regression analysis was used to identify patient and treatment characteristics that correlate with the patient having at least one VP replacement as a result of hypertrophy or infection. In the univariable analyses, a significance level of 10% (two sided) was used to determine whether a variable would be considered for inclusion in the multivariable models. Patient characteristics considered (both for their relation to device lifetime as for their relation to hypertrophy/ infection) were age at time of TL, sex, (C)RT, origin of tumor, TNM classification, indication for TL, pharyngectomy, reconstruction, neck dissection, and driving distance to the hospital. Moreover, an additional variable was used, which was based on whether or not a patient ever required an Acti-Valve during follow-up. Variables with known correlations between them (eg, TNM classification and indication for TL) were barred from entering the multivariate models together. SPSS Statistics 20.0 (IBM, Armonk, NY) and R-3.2 were used to conduct the analyses.[17]

RESULTS

Patient characteristics

Patient, tumor, and treatment details of the 232 patients in this study are summarized in Table 1. Mean age was 64 years (SD 10.8), the majority of patients had a larynx tumor (72%) and 68% had prior (chemo)radiotherapy. Only 12 patients (5%) did not receive RT somewhere during the course of their disease. The median OS was 35.9 months (95% CI 29.7-67.8). At the end of the study period, 53 patients were still alive with the VP in situ, 7 patients were alive without a VP in situ, 141 patients were deceased with the VP in situ, and 9 patients were deceased without the VP in situ. The remaining 22 were lost to follow-up with their VP in situ. Thus, in total, in 16 (7%) patients, the VP was definitively removed. Median follow-up time was 127 months (95% CI 117-144).

Table 1 Patient, tumor and treatment details of all patients

	Number of patients (%)
Sex	
Men	185 (79%)
Women	48 (21%)
Mean age	63.5 (SD 10.8)
TNM classification	
Tis	2 (1%)
T1	34 (15%)
T2	51 (22%)
T3	49 (21%)
T4	88 (38%)
Tx	8 (3%)
N0	143 (62%)
N1	28 (12%)
N2	51 (22%)
N3	6 (3%)
Nx	4 (2%)
M0	232 (100%)
M1	0 (0%)
Primary tumor site	
Larynx	167 (72%)
Hypopharynx	31 (13%)
Oropharynx	21 (9%)
Miscellaneous	13 (6%)
Primary treatment	
RT	119 (51%)
CRT	38 (16%)
Other[a]	2 (0.9%)
TL with postoperative RT	58 (25%)
TL with postoperative CRT	5 (2%)
TL without postoperative (C)RT	10 (4.3%)
Indication TL	
Primary TL	73 (32%)
Salvage TL	107 (46%)
TL for second primary	28 (12%)
TL for dysfunctional larynx	24 (10%)
Pharyngectomy	
No (standard laryngectomy)	158 (68%)
Near total	47 (20%)
Circumferential	23 (10%)
Unknown	4 (2%)
Neck dissection during TL	
No	64 (28%)
Unilateral during TL	53 (23%)

	Number of patients (%)
Bilateral during TL	103 (44%)
Unknown	12 (5%)
Reconstruction	
No (primary closure)	143 (61%)
PM flap for reconstruction lumen	46 (20%)
PM flap for reinforcement	15 (6%)
FRFF	9 (4%)
Gastric pull-up	9 (4%)
ALT	5 (2%)
LD	1 (0.4%)
Unknown	4 (2%)

Abbreviations: ALT, Antero-lateral thigh flap; CCRT, concomitant chemoradiation; FRFF, Free radial forearm flap; LD, Latissimus dorsi flap; PM, pectoralis major muscle; RT, radiotherapy; TL, total laryngectomy.

[a]One patient underwent C02 laser therapy prior to TL and one patient was treated for thyroid cancer with radioactive iodine therapy.

Device lifetime

In total, 3319 VPs were used during the entire study period. VPs with an in situ time of 0 days (n = 92) were excluded from analysis because these mainly concerned replacements because of immediately noticed sizing errors. We excluded VPs replaced for developmental study purposes (n = 86), and sporadically used following types of VPs: Provox Vega XtraSeal (n = 16; introduced at the end of the study period), Provox1 (n = 4), and Provox ActiValve XtraStrong (n = 4), leaving 3117 VPs for the univariable and multivariable device lifetime analysis. During follow-up, 39 of the 232 patients never required VP replacement (17%): 33 died before any VP replacement was required, 5 were lost to follow-up with the first VP in situ, and in 1 patient, the first VP was removed shortly after the surgery because of a too wide TEP tract. This tract became a permanent voicing fistula, which the (gastric-feeding-tube dependent) patient refused to have closed because of her good voice.

The overall median device lifetime of the VPs used in the study period (ie, the regular Provox2 [n = 1664], Vega [n = 1136] prostheses, and the problem solving Provox ActiValve Light [n = 171] and Strong [n = 121]) together was 70 days (95% CI 67-73). The remaining 25 VPs were of "unknown type" (median device lifetime 66 days; 95% CI 27-106). Between the two regular VPs, there were no significant differences: Provox2 (median 63 days, 95% CI 61-68) and Vega (median 66 days, 95% CI 63-71). The median device lifetime of the ActiValve VPs was significantly longer than that of the regular VPs: ActiValve Light 143 days (95% CI 111-211) and ActiValve Strong 186 days (95% CI 132-245; *P* value between regular VPs and both ActiValve VPs <.0001; see Figure 1 for the Kaplan-Meier curves).

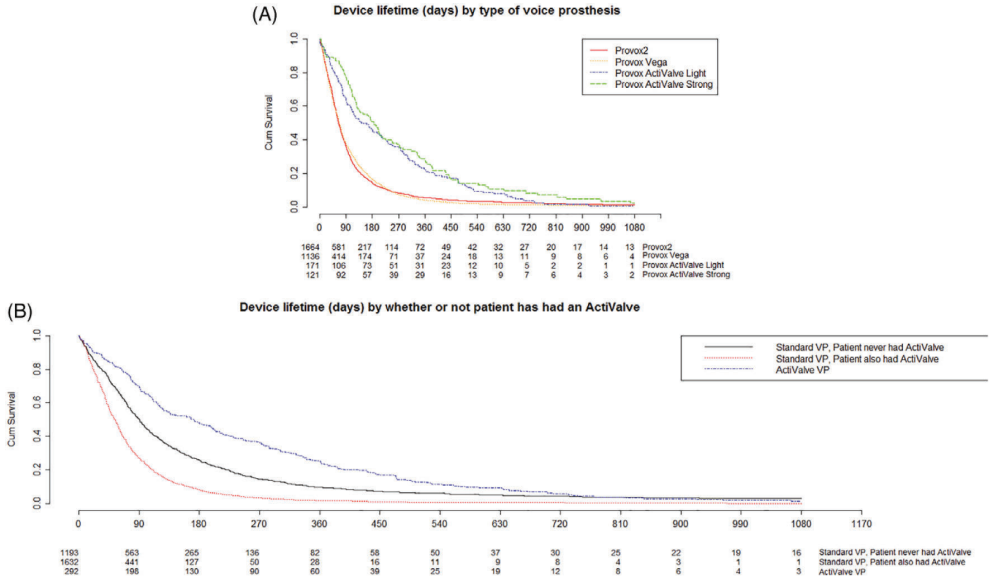

Fig. 1 A) Kaplan Meier curve of device lifetime analyzed separately for the different VPs. B) The device lifetime for the standard VPs (Provox2 and Vega) grouped by whether or not these patients have ever had an ActiValve VP during follow-up and the device lifetime of the ActiValve VPs together

5

The indication for using the "problem solving" Acti-Valve in our institution was a device lifetime of less than 2 months of the regular VPs.[14,18] There were 69 (30%) patients, who received at least one ActiValve during follow-up, and 163 (70%) patients, who never required an Acti-Valve. The median device lifetime of regular Provox2 and Vega VPs in the "non-ActiValve group" was 90 days (95% CI 84-96) and in the "ActiValve group" 54 days (95% CI 50-57; *P* value between groups < .0001; see Figure 1B). Of the 69 patients who ever received an ActiValve, 17 (25%) never had a TEP-tract-related problem, 33 (48%) had a TEP-tract-related problem prior to the first ActiValve insertion, and 19 (28%) developed such a problem after their first Acti-Valve insertion. The median time after TL of the first replacement required for a TEP-tract-related problem was 980 days (95% CI 718-1568), and the median time after TL to the first ActiValve insertion was 695 days (95% CI 537-1194).

Univariable and multivariable analyses for associations between device lifetime and clinical parameters are found in Table 2; in this analysis, a hazard ratio (HR) > 1 indicates a shorter device lifetime and a HR < 1 indicates a longer device lifetime. In univariable analysis, compared to a primary TL, salvage TL had a HR of 1.29 (95% CI 1.19-1.41; *P* < .0001), and TL for a dysfunctional larynx a HR of 1.26 (95% CI 1.10-1.45, *P* = 0.001). No significant difference in device lifetime was observed between patients with a primary TL and those with TL for a

second primary. The median driving distance to the hospital by car was 26 minutes (range 7-124 minutes). There was a significant association between driving distance and device lifetime. Among the standard VPs, every extra 15 minutes driving time resulted in a HR of 0.92 (95% CI 0.90-0.94, $P < .0001$) in which a HR < 1 indicates a longer device lifetime. This effect was more profound in the standard VPs exchanged for TEP-tract related indications for replacements than for device related indications for replacement, a HR of 0.94 (95% CI 0.88-0.99, $P = .047$) and a HR of 0.97 (95% CI 0.95-0.99, $P = .015$) respectively. Multivariable analysis was carried out with the variables age at TL, indication for TL (primary, salvage, second primary, or dysfunctional) and driving distance to the hospital in minutes. This analysis confirmed that both driving distance and indication for TL were significantly associated with device lifetime. Every 15 minutes, increase in driving time reduced the hazard of VP replacement by a HR of 0.90 (95% CI 0.88-0.92, $P < .0001$).

Table 2 Univariate and multivariate analysis for device lifetime

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (per 10 years increase)	0.96	0.93-0.99	.013*	0.94	0.91-0.98	<.001*
Age (per 10 increase) within patients with indication for:						
Primary TL				0.91	0.86–0.97	.002 ǂ
Salvage TL				0.95	0.90–0.99	.03 ǂ
Second primary				0.99	0.89–1.11	.87 ǂ
Dysfunctional larynx				1.21	1.02–1.42	.03 ǂ
Sex (ref = male)	0.9998	0.90-1.11	0.996			
Origin tumor (ref = larynx)						
Hypopharynx	0.84	0.73-0.97	.020*			
Oropharynx	0.98	0.86-1.12	.79			
Micellaneous	1.25	1.08-1.45	.003*			
T-classification (ref = T1)						
T2	0.95	0.85-1.07	.42			
T3	1.03	0.92-1.15	.65			
T4	0.78	0.70-0.87	<.001*			
N-classification (ref = N0)						
N1	0.92	0.80-1.06	.24			
N2	1.05	0.95-1.15	.35			
N3	0.55	0.40-0.74	<.001*			
Indication TL (ref = primary TL)						
Salvage TL	1.29	1.19–1.41	<.001*	1.38	1.26-1.50	<.001 ǂ
Second primary	1.06	0.94-1.21	.33	1.28	1.13-1.46	<.001 ǂ
Dysfunctional larynx	1.26	1.10-1.45	.001*	1.31	1.14-1.51	<.001 ǂ
Pharyngectomy type (ref = partial)						
Near total	0.91	0.82-1.00	.04*			
Circumferential	0.95	0.81-1.10	.49			

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
(Neo)-adjuvant treatment (ref = RT)						
None	0.86	0.72-1.03	.10			
CRT	0.93	0.84-1.04	.19			
Driving time to hospital (in minutes for standard VPs)						
Per 15 min increase	0.92	0.90-0.94	<.001*	0.90	0.88–0.92	<.001 ǂ

Abbreviations: HR, hazard ratio; ref, reference variable. Note: HR > 1 means a shorter device lifetime; HR < 1 means a longer device lifetime. Note that in the multi-variate analysis, we present the results from two multivariate models: We first constructed a simple model containing age at TL, indication for TL, and driving distance to the hospital (marked with ǂ). In a subsequent cox model, we have used an interaction term between indication and age, to assess the effect of aging (marked with ǂ).

**P* value <.05.

The predictive value of age for device lifetime differed significantly between indications for TL. Using a subsequent cox-model with an interaction term between indication and age, we find the following effects of aging. Within patients with a primary TL or a salvage TL, elder patients tend to have longer device lifetimes than younger patients: HR per 10 years age increase 0.91 (95% CI 0.86-0.97, *P* = .002) and 0.95 (95% CI 0.90-0.99, *P* = 0.03), respectively, in line with what we found in the univariable analysis. For patients with a TL for a dysfunctional larynx however younger age corresponds with better device lifetime: HR per 10 years increase in age 1.21 (95% CI 1.02-1.42, *P* = .03). For patients with a second primary, there is no significant relation: HR 0.99 (95% CI 0.89-1.11, *P* = .87).

Reasons for replacement

Reasons for replacement were assessed for 3133 VPs (the 3117 aforementioned VPs plus the 16 XtraSeal VPs, used to solve periprosthetic leakage issues; see Table 3). Patients could have multiple indications for replacement of their VP; therefore, the numbers add up to 3201 indications in 3133 VP replacements. The main reason for replacement was transprosthetic leakage: 1806 times (58%) in 174 patients (75%). For 368 VPs (12%) in 119 patients (51%), the indication for replacement was not documented; 113 of these 119 (95%) had previous replacements for transprosthetic leakage, and the reporting suggested that these replacements were quite likely standard replacements for transprosthetic leakage. This would total the replacements for transprosthetic leakage at 70%. Periprosthetic leakage was noted 266 times (9%) in 101 patients (44%). Periprosthetic leakage immediately solved by downsizing or by keeping the same size occurred in 154 VP replacements (58% of the 266 replacements for periprosthetic leakage) in 74 of the 101 patients experiencing this problem, see Figure 2. These replacements were not considered to be due to a TEP tract-related complication, but merely a result of the subsiding of the postsurgical TEP tract tissue swelling or gradual thinning of the trachea-esophageal wall.

Table 3 Indications for replacement of 3133 VPs in 232 patients

Indication for replacement	VP, N (%)[a]	Patients, N (%)[a]
Transprosthetic leakage	1805 (58%)	174 (75%)
No reason reported	368 (12%)	119 (51%)
Inaccurate size	214 (7%)	112 (48%)
Voice problems	85 (3%)	49 (21%)
Dirty VP	31 (1%)	19 (8%)
Request patient	18 (0.6%)	12 (5%)
Logistic reasons	16 (0.5%)	14 (6%)
Increased pressure	16 (0.5%)	15 (7%)
Study purposes	56 (2%)	37 (16%)
Miscellaneous[b]	13 (0.4%)	12 (5%)
Periprosthetic leakage	266 (9%)	101 (44%)
Hypertrophy/infection	177 (6%)	70 (30%)
Spontaneous VP loss	93 (3%)	41 (18%)
Shrinking TEP	34 (1%)	22 (10%)
Closure TEP tract	9 (0.3%)	7 (3%)

[a] Patients could have multiple indications for replacement of their VP; therefore, the numbers add up to 3201 indications in 3133 VP replacements. Sometimes, it was difficult to determine the main indication for VP replacement, for example, in case of transprosthetic leakage and periprosthetic leakage, both are equally compulsory indications, and therefore mentioned in this table. During follow-up, 39 patients never required VP replacement.

[b] Miscellaneous: replacements for Provox course (n = 7), second primary in the stoma region (n = 2), surgical revision of the tracheostoma (n = 2), secondary puncture (n = 1), and severe tracheitis (n = 1).

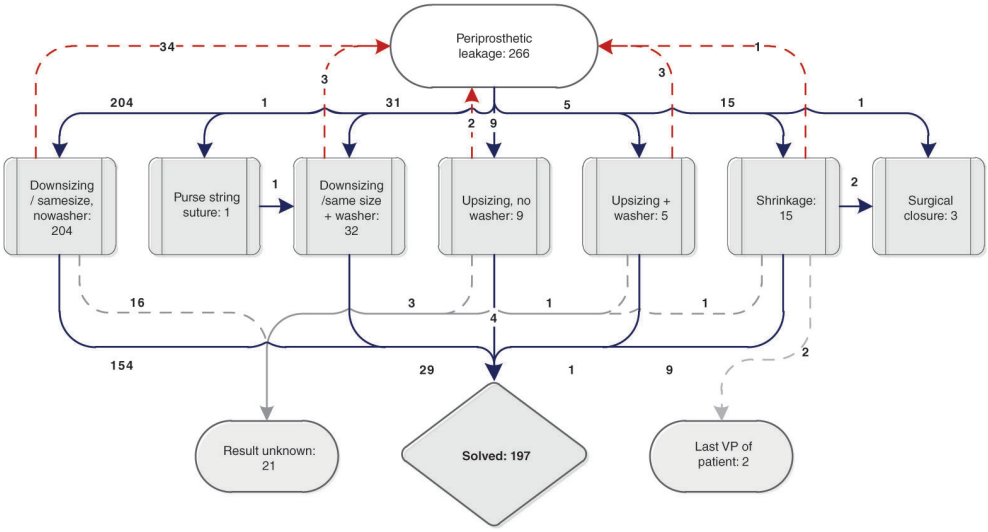

Fig. 2 This figure illustrates the complex pathways of VP problem solving, in this case, periprosthetic leakage. As can be seen in this figure, 204 VPs were replaced with either the same or a smaller size, which was effective in 154 and not effective in 34 replacements. The result was undocumented for 16 VPs. The 34 VPs entered the flowchart again. Finally, it resulted in three surgical closures

TEP tract-related reasons for replacement

The following issues were considered complicated TEP tract-related reasons for VP replacement or removal: Periprosthetic leakage not immediately solved by downsizing, TEP tract hypertrophy/infection, spontaneous VP loss, and need for shrinking and/or surgical closure of the TEP tract. The median device lifetime of VPs replaced due to TEP-tract related reasons was 48 days, which was significantly lower than replacement due to device related problems in which a median of 67 days could be observed (P = .006). However, the number of VPs replaced for TEP-tract related problems was only 371 whereas the number of VPs replaced for device related problems were 2540.

- Periprosthetic leakage not immediately solved by downsizing or keeping the same size occurred in 96 instances (36% of the 266 replacements for periprosthetic leakage) in 51 patients (22%). Twenty-five of 51 patients (49%) experienced this problem more than once. More details about VP replacement because of periprosthetic leakage and effects are summarized in Figure 2.

- Replacement of VP because of TEP tract hypertrophy/ infection occurred 177 (6%) times in 70 patients (30%). In 60% of these patients, this occurred more than once. In 137 of 177 (77%) hypertrophy/infection-related replacements, a longer VP (n = 93) or a VP with the same/shorter size (n = 44) was successfully inserted. In 24 replacements (14%), this solution was not successful. Temporary removal of the VP because of hypertrophy/ infection was needed 5 times (3%) with success n = 3, patient deceased n = 1, unsuccessful n = 1. The short-term result of insertion of a longer VP or a VP with the same/shorter size was untraceable in nine replacements. Five patients died, three VPs were still in situ at final date of data collection and data was missing in one patient. In two patients, the outcome was unknown as they were lost to follow-up after replacement for hypertrophy/infection. In multivariable analysis of the relation between patient and treatment characteristics and hypertrophy/infection, the only significant relation found was that patients ever needing an ActiValve had a significant higher risk for also having TEP tract hypertrophy/infection (OR 5.02, 95% CI 2.72-9.25, P < .0001).

- VPs replaced because of spontaneous loss occurred 93 (3%) times in 41 (18%) patients. Twenty of these 41 patients experienced this problem more than once. In three patients, the VP was lost in the lower airway and had to be removed endoscopically. In two of these patients, this happened during a dilatation procedure for a pharyngeal stenosis.

- Shrinking of TEP was a reason for VP removal 34 (1%) times in 22 (10%) patients (in 13 patients once, in 6 patients twice, and in 3 patients three times). Shrinkage of the TEP-tract entails removal of the VP to allow for natural shrinkage of its diameter. This is usually applied for a few days in which the patient requires a cuffed cannula to prevent aspiration and a feeding tube.
- Lastly, nine (0.3%) VPs, in seven (3%) patients, were removed because of definitive closure of TEP tract (two patients had a secondary puncture and surgical closure for a second time). Four of the seven patients had earlier shrinking of TEP. In the remaining three patients, closure of TEP was performed because of severe dysphagia/stenosis, failure of speech rehabilitation, and severe hypertrophy/infection.

DISCUSSION

The main outcome measure of this single institution study was the median device lifetime of all the VPs used during a 13-year assessment period in 232 consecutive TL patients. For the regular VPs Provox2 and Vega, this was 63 and 66 days, respectively, and for the problem-solving ActiValve Light and Strong VPs, this was 143 and 186 days, respectively. The finding that the device lifetime of the regular VPs in the patients never requiring an ActiValve compared to those patients having required at least one such device is significantly longer (90 and 54 days, respectively) and is a logical consequence of the fact that ActiValve VPs are indicated for patients with a (too) short device lifetime.

The main indication for replacement, transprosthetic leakage, was reported in 58% of all replacements. In 12% of replacements, the exact reason was not reported, but the way of reporting suggested that these also were standard replacements for transprosthetic leakage. Thus, the actual incidence of transprosthetic leakage most likely is 70%, which is only slightly lower than the 73% reported in the earlier study from our Institute.[4]

The observed median device lifetime of 2 months for the regular VP is noticeably lower than observed in our historical cohort.[4] This is in line with a recent study by Lewin et al[11] who showed a median device lifetime of 61 days and a study by Kress et al,[19] who observed a median of 74 days (including ActiValve VPs, which figure in our cohort was 70 days). Interestingly, if we compare the device lifetime of the non-ActiValve group of 90 days with that of our institutional historic cohort of 89 days, there is no clinically relevant difference.[4] The increase in device lifetime for the ActiValve VPs as compared to the regular VPs is, besides the active magnetic closure mechanism counteracting underpressure in the esophagus, probably also a result of the fluoroplastic material used in the ActiValve VPs, which are insusceptible to destruction by Candida species. Microbial biofilm formation on

the valve by different Candida species is thought to be the main reason for transprosthetic leakage.[15]

The increasing number of TLs after prior (chemo)radiotherapy since 1990 (68% in the present study and 45% in our historical cohort[4]), which has a profound effect on the TEP-tract, seems a likely explanation for the shorter device lifetime found in our study population. However, just like in the study of Lewin et al[11] there was no significant effect of the extent of surgery or RT on device lifetime in the multivariable analysis. On the other hand, we did find an association with the indication for TL, with the primary TL patients having a longer device lifetime than salvage TL patients. In our previous study, we found such a difference between nonradiated patients and patients ever receiving RT[4]; but, in the present study, the number of nonirradiated patients was too low for meaningful statistical analysis.

Another explanation for the shorter device lifetime found in recent studies might be the ease of replacement. In the study performed by Op de Coul et al,[4] the uncomfortable method of retrograde placement was still used. With the introduction of the Provox2 in 1997 anterograde replacement became available. This has lowered the threshold for patients to ask for a replacement in case of minor leakage, which they otherwise might have accepted somewhat longer.[20,21]

Despite the increasing number of TLs performed after prior (C)RT since 1990 the clinical reliability and validity of prosthetic voice rehabilitation is still sound. In the present cohort with a median follow-up time of over 10 years 7% of the patients were not able to keep their VP, and this figure was 5% with a median follow-up time of over 6 years in our historical cohort.[4] This figure compares favorably with the 12% after 1 year in a recent study from Germany.[22]

An interesting aspect of the present study is that we were able to analyze different types of VPs in the same patient over a prolonged period of time. This concerns the role of the special problem-solving VPs Provox ActiValve Light and Strong in comparison to the regular VPs (Provox2 and Vega). As mentioned before, the main reason to select an ActiValve somewhere during follow-up was a short device lifetime of the regular VP. Interestingly, however, this Acti-Valve cohort apparently also suffers significantly more from TEP tract hypertrophy/infection, as was found in the multi-variable analysis of these latter problems. The finding that in more than a quarter of these patients the TEP tract-related problems develop after the first ActiValve insertion is interesting. It might suggest that in some patients short device lifetime is also a sign of co-morbidity, just like TEP tract-related issues, that is, reflux and pharyngeal stenosis.[10,23,24] As these comorbidities are treatable, shortening of the device life might be a reason to start an intervention (dilatation or proton pump inhibitor (PPI) treatment). Especially of interest in this respect is

the study of Lorenz et al,[25] where these authors found that device lifetime was significantly associated with reflux. Likewise, Boscolo-Rizzo et al[10] demonstrated a mean device lifetime of 127 days for patients with endoscopic evidence of gastroesophageal reflux disease vs 216 days for patients without. Because of the retrospective nature of our study, we were unable to reliably assess presence or absence of reflux in our cohort. However, this correlation between short device lifetime/ActiValve use and TEP tract-related problems suggests that a shortened device lifetime (the first ActiValve was inserted after a median of 695 days, roughly two and a half years) as such already might be a sign of reflux. And if so, treatment with PPIs in patients not yet suffering from TEP tract-related problems could be considered to improve device lifetime before choosing an expensive specialty VP, such as the ActiValve. This comorbidity effect should be assessed in future studies, where confounding variables and possible shift in comorbidities and medication are prospectively documented.

Contrary to the decreasing device lifetime observed in our cohort and in other western countries, some studies from low-income countries report device lifetimes of up to 17-months average.[26] An explanation might be the financial challenges prosthetic voice rehabilitation imposes on patients. In our cohort, all patients received reimbursement for their VP, thus a socio-economic bias can be ruled out, similar to, for example, the study population of Kress et al. from Germany.[19] Therefore, we believe that, in the absence of economic issues, these results are more representative for the actual device lifetime of VPs. Furthermore, the relatively close distance patients have to the nearest hospital, makes a visit for a replacement less of a burden in comparison to countries such as Australia, where this might be a delaying problem and indeed longer device lifetimes are observed.[27]

However, much to our surprise even in our cohort where patients live relatively close to the hospital with a median of 26 minutes driving time, we observed a highly significant relation between longer driving time to the hospital and longer device lifetime for the standard VP. This effect was more profound in the TEP-tract related indications for replacements. This might suggest that patients recognize TEP-tract complications less easily than simple transprosthetic leakage as a reason to visit the hospital. Overall, with driving time to the hospital being a very significant factor in device lifetime, even in the multivariable analysis, when confirmed in other studies, distance to the hospital should to be taken into account when reporting device life times in future studies.

Limitations

The previous study from our institute had a prospective character, because before 2000, at each VP replacement, a special registration form was used to collect relevant data

regarding reason for replacement and voice quality.[4] After 2000, however, "registration" was done in the regular patient files. This led, as in many retrospective studies, to missing data and, for example, in 12% of cases, no reason for replacement was noted. In part, this problem could be solved by looking at the notes of the preceding and following replacement event. Another interesting piece of information missing in the present study is the voice quality assessment and use of VP for communication. This should be assessed in future studies.

CONCLUSION

In conclusion, we report the results of prosthetic vocal rehabilitation in a cohort of consecutively treated patients from one institute undergoing TL for any indication. Thereby it represents an unbiased and unselected study group and is one of the larger series in literature. In our cohort, we found an overall median device lifetime of 70 days. The median device lifetime of the regular Provox2 (63 days) and Vega (66 days) VPs was significantly shorter than that of the problem solving ActiValve Light (143 days) and Strong (186 days) VPs. The median device lifetime of the regular VPs was significantly longer in the cohort of patients never requiring an ActiValve (90 days) than that in the patients needing at least one ActiValve (54 days). This latter cohort also had a significantly higher risk for TEP tract-related problems (hypertrophy/infection). Main reason for replacement remained transprosthetic leakage (70%). However, with 12% of the replacements in almost half of the patients, TEP tract-related issues still form an important factor to take into account when performing prosthetic voice rehabilitation. Fortunately, in most patients, these TEP tract problems can be solved. We found no difference in patients treated with RT vs those treated with chemoradiation. Despite the increased numbers of patients requiring TL for salvage, with 93% of the patients maintaining their VP long term, prosthetic voice rehabilitation is still a highly successful and manageable method to restore oral communication after TL.

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CHAPTER 6

A prospective multicenter clinical feasibility study of a new automatic speaking valve for postlaryngectomy voice rehabilitation

Lansaat L
de Kleijn BJ
Hilgers FJM
van der Laan BFAM
van den Brekel MWM

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ABSTRACT

Evaluation of short- and long-term clinical feasibility and exploration of limitations and advantages of a new automatic speaking valve (ASV) for laryngectomized patients with integrated HME, the Provox FreeHands FlexiVoice (FlexiVoice). This ASV not only enables automatic, but also manual closure of the valve. A multicenter, prospective clinical study in 40 laryngectomized patients was conducted. Participants were asked to use the FlexiVoice for 26 weeks. The primary outcome measure was long-term compliance. Secondary outcome measures were: patient preference, hours of FlexiVoice use, device life of adhesive, voice and speech quality, and quality of life. After 26 weeks, 15 patients (37.5 %) were using the FlexiVoice on a daily basis, for a mean of 12.64 h/day (SD ± 5.03). Ten patients (25 %) were using the device on a non-daily basis, for a mean of 3.76 h/day (SD ± 2.07). The remaining 15 patients (37.5 %) discontinued using the FlexiVoice. Sixty percent of the 25 long-term users applied both automatic and manual closure of the valve. Unpredictable fixation of the adhesive was the main reason for discontinuing or not using the FlexiVoice on a daily basis. Overall, 18 patients (45 %) preferred the FlexiVoice, 16 patients (40 %) their usual HME, 3 patients (7.5 %) their usual ASV, 1 patient (2.5 %) preferred no device at all, and in 2 patients preference was not recorded. The minor technical issues identified could be corrected. The Provox FreeHands FlexiVoice appears to be a useful ASV, which allows for hands-free speech in a larger proportion of laryngectomized patients in the present cohort. The additional manual closure option of the device is beneficial for maintaining the adhesive seal longer.

INTRODUCTION

Total laryngectomy (TL) results in significant anatomical changes. The alimentary and respiratory tracts are separated and a permanent stoma is created in the neck[1]. To compensate for the loss of the voice box, currently primary insertion of a tracheoesophageal voice prosthesis is the gold standard for restoring pulmonary-driven speech[2]. To compensate for the functional loss of the upper respiratory tract and to prevent and/or treat pulmonary problems, such as excessive coughing and mucus production, continuous use of heat and moisture exchanger (HME) has proven to be effective[3–5]. Speaking with a voice prosthesis requires airtight occlusion of the stoma with a finger to divert the pulmonary air into the pharyngoesophageal segment or neoglottis, where mucosal vibrations produce the sound for speech. Airtight stoma occlusion has become easier after the development of specialized HMEs, which improve maximum phonation time and dynamic loudness range and thus compliance rate[6]. However, with these HMEs, it is still necessary to use a finger to occlude the stoma for speech production. To overcome this drawback of tracheoesophageal speech and to obtain hands-free speech, automatic speaking valves (ASVs) have been developed. These devices contain a flexible membrane that stays open during normal calm breathing, but closes through the natural increase in air pressure when speaking is initiated[7,8]. Several ASVs are presently available. The first were the Blom Singer and Bivona tracheostoma valves in the eighties and nineties of the last century[8–10]. Later, several other valves became available, such as the Eska-Herrmann and ADEVA valves[11,12]. In 2003, the Provox FreeHands HME (further called FreeHands; Atos Medical, Hörby, Sweden) was introduced, which was the first automatic speaking valve with an integrated HME for simultaneous pulmonary rehabilitation[7]. In a long-term (6 months) study, the success rate (defined as patients using this ASV on a daily basis) was 19 %[13]. Additionally, 57 % of patients in this study used the device on a non-daily basis at special occasions, such as during shopping or social activities[13]. The main reason for not using the FreeHands on a daily basis was the unpredictable fixation of the adhesive to the peristomal skin. This is the main drawback for all ASVs. For a considerable number of patients, it can be problematic to obtain a good and long-lasting seal of the adhesive to withstand the pressure necessary for speaking[14–17].

To further improve patient friendliness and compliance of automatic speech, a new automatic speaking valve was developed, the Provox FreeHands FlexiVoice (further called FlexiVoice; Atos Medical AB, Hörby, Sweden). This new ASV contains a renewed mechanism to lock and unlock the speaking membrane. The air pressure needed to close the membrane is lower than in the earlier FreeHands device, because the available membranes are more flexible. Moreover, there is a novel option to alternatively occlude

the device manually: a front opening also allows speech through finger occlusion of the device, even when the membrane is locked, e.g., during physical exertion. Lastly, the coughing mechanism is adapted, which also allows easy repositioning of the valve after coughing.

The objective of this prospective clinical study is to evaluate the short- and long-term feasibility of the FlexiVoice, in combination with the currently available attachments, and to explore its limitations and advantages.

METHODS

The study was carried out at two tertiary care cancer centers. Inclusion criteria were: TL, 18 years or older, use of an HME and/or ASV, use of a voice prosthesis irrespective of the voice quality, minimum of 3 months after TL and/or postoperative (chemo-) radiotherapy. Exclusion criteria were: inability to remove or operate the FlexiVoice, active recurrent or metastatic disease, inability to understand the patient information, to give informed consent, and/or to complete diaries. The study was performed according to the protocol approved by the institutional review boards and all patients were enrolled in the study between May 2014 and August 2014. Signed informed consent was obtained from all participants.

The FlexiVoice is shown in Fig. 1 (left). It combines pulmonary rehabilitation using an HME, with voice rehabilitation using an ASV, which also facilitates manual occlusion. The device is attached in front of the stoma of a laryngectomized patient, who is using a voice prosthesis for speech. There are different attachment options for the subjects to choose from (various stoma adhesives, laryngectomy tubes and buttons). The base of the device is the HME cassette and the speaking valve is anchored on top of that HME cassette. The speaking valve has a front opening and an internal flexible membrane. When the patient starts to speak, the natural increase in exhalation airflow closes the membrane. The exhaled air is thus diverted through the voice prosthesis, which allows hands-free tracheoesophageal speech. Alternatively, the patient can choose to occlude the opening in the front with his/her finger to speak. Rotating the top of the device moves the FlexiVoice into the 'locked mode', or into the 'automatic speaking mode' (Fig. 1, middle left). In 'locked mode', the membrane is prevented from closing with a hook grabbing a ring at the backside of the membrane (Fig. 1, middle right). Thereby, the patient is ensured of unrestricted and comfortable breathing during physical exertion, still allowing manual occlusion for speech. There are three versions of the speaking valve, each with a different flexibility/strength of the membrane: light, medium and strong. When coughing is needed, the membrane pops out through the front opening and the patient can push the membrane back manually.

There is an optional arch that can be attached on top of the device to prevent the front opening of being occluded by clothing (Fig. 1, right).

After inclusion, patients used the FlexiVoice for the duration of a maximum of 6 months. The primary objective was to assess long-term compliance, based on various aspects of the ASV addressed in study-specific questionnaires. Secondary outcome measures were: patient preference, hours of FlexiVoice use, device life of adhesive, voice and speech quality and quality of life. The questionnaires were completed at the time of inclusion, after 4 weeks and after 26 weeks.

Fig. 1 *Left* Provox FreeHands FlexiVoice. The heat and moisture exchanger (HME) is attached and the flexible membrane is closed. *Middle left* 'automatic speaking mode'. *Middle right* 'locked mode': the patient can rotate the top of the device and the membrane is locked by a hook that grabs a ring at the backside of the membrane. *Right* the arch is attached. It prevents the front opening being occluded by clothing (*left 3 pictures* by courtesy of Atos Medical)

The study specific questionnaires addressed the use of adhesive, effort needed to speak, noises produced by the FlexiVoice, coughing mechanism, appearance, functioning of the membrane, use of the 'locked mode'/'automatic speaking mode', manual occlusion, device life of adhesive, voice quality, speech quality and intelligibility. Additionally, patients rated satisfaction regarding the FlexiVoice, their usual ASV/HME (if applicable), the device life of their adhesive, and their voice quality on a 10-cm Numeric Rating Scale (NRS) (0 = worst and 10 = best).

Quality of life was assessed using the EuroQOL-5 Dimension-5 Level questionnaire (EQ5D5L). This instrument is validated using scores in five health-care dimensions (mobility, self-care, daily activities, pain/discomfort and anguish/depression) and a 100-mm VAS[18]. Voice and speech quality assessment consisted of reading a text, numbering breathing pauses, maximum phonation time (vowel /a/ and counting) and dynamic loudness range (with calibrated decibel meter). During the study period, patients kept a diary twice for 3 days in the week before each follow-up visit to record daily hours of FlexiVoice use. At the end of the study, patients were asked to complete comparative questionnaires. Patients were asked to compare the FlexiVoice with the usual ASV and/or HME and to

answer questions regarding preference and future use. Patients were contacted by telephone 2 weeks after inclusion and at monthly intervals until 26 weeks of follow-up. If needed, additional practical support from the speech pathologist or the study coordinator was offered. Figure 2 provides an overview of the study design.

Statistics

As this was deemed to be an uncomplicated feasibility study in patients familiar with the use of peristomal adhesives and HME devices and no risks associated with participation in the study were expected, the dropout rate was estimated to be <5 %. Statistical analyses were conducted using IBM® SPSS® 22.0. Frequencies were explored using the Kolmogorov-Smirnov test. Parametrically distributed data are shown as mean ± standard deviation and analyzed using the paired *T* test. Non-parametric data are presented as median (interquartile range) and were analyzed using the Wilcoxon signed rank test. The Likert scales rendered ordinal data from three related samples. This data was analyzed using the Friedman test. If the groups differed significantly, a Wilcoxon signed rank test was used to determine which groups were different. A p value <0.05 is considered to be significant.

RESULTS

In total, 41 laryngectomized patients were entered in the study, 21 in one institute and 20 in the other. One patient subsequently had to be excluded from the study and further analysis, because the language barrier was larger than anticipated and he did not understand the patient information. Thus, the remaining 40 patients, 36 males and 4 females, were included for analysis. Patient demographics and clinical information are provided in Table 1. At baseline, 27 patients were not using an ASV (67.5 %), 12 patients were using an ASV in combination with an HME and (30 %) 1 patient was using only an ASV (2.5 %), also during the night (all ASVs were the FreeHands[7]). Of those 13 ASV users (32.5 %), 8 patients were using the ASV on a daily basis (20 %) and 5 patients on a non-daily basis (12.5 %). The mean ASV use of the eight daily users was 13.25 h and of the five non-daily users 3.26 h. Of the 27 non-users, 19 (70 % did have experience with an ASV before entering the study and 6 (15 %) did not (data in 2 patients was missing). Most ASV users were using one of the 'stronger' adhesives, such as the Provox StabiliBase adhesive (Atos Medical AB, Horby, Sweden). The self-reported median device life of the adhesive was 19 h (range 1–168) when using an ASV (n = 12; data in 1 patient was missing). Patients' satisfaction regarding adhesive device life when using the ASV was rated 7.16 on a scale 1–10 (NRS; SD ± 2.35; n = 11). This information was missing in two patients. For the non-ASV users, the median device life of the adhesive was 24 h (range 6–168 h; n = 26, data missing in 1 patient).

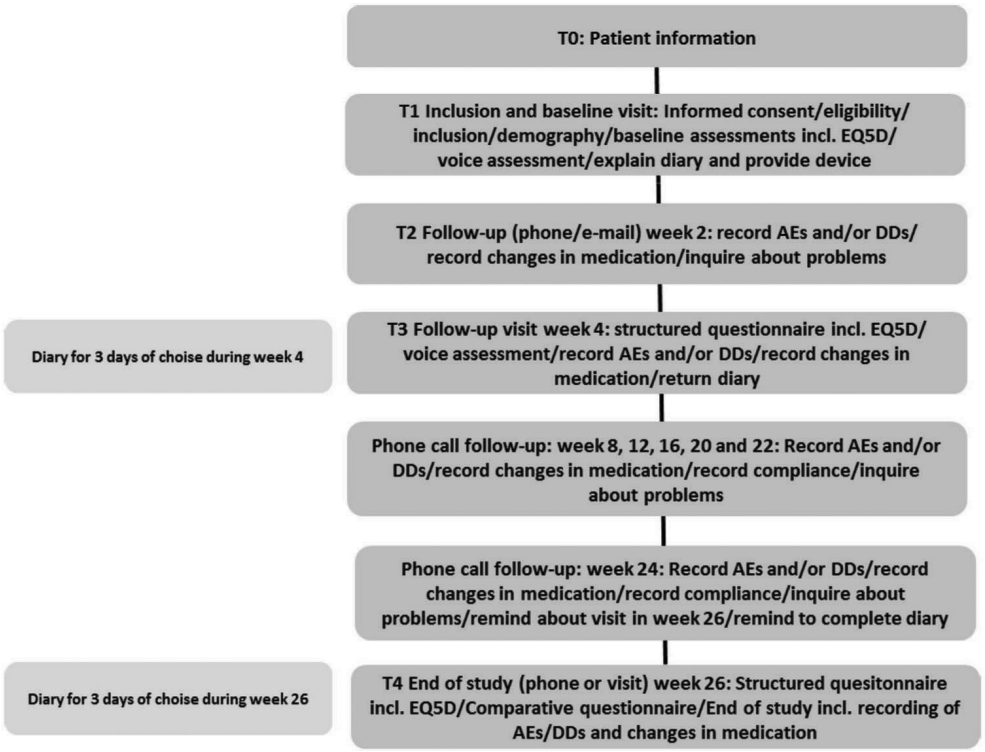

Fig. 2 Study flowchart

Table 1 Patient characteristics

Characteristics	Value	%
Gender		
Male	36	90.0
Female	4	10.0
Age at TL	Mean 56.3 years (SD ± 9.4)	
Age at entry	Median 63.5 years (SD ± 8.91)	
Post-TL	Median 74.5 months (range 3–317 months)	
TL		
Standard	32	80.0
+Reconstruction	6	15.0
Gastric pull-up	1	2.5
Information missing	1	2.5
Radiotherapy		
No	1	2.5
Preoperative	30	75.0
Postoperative	9	22.5
ASV use		

Characteristics	Value	%
No	27	67.5
Only ASV	1	2.0
ASV + HME	12	30.0
Experience with ASV		
No	6	15.0
Yes	32	80.0
Information missing	2	5.0

TL total laryngectomy, *ASV* automatic speaking valve, *HME* heat and moisture exchanger

Assessment at 4 weeks

At the 4-week follow-up, 36 patients were still in the study and 4 had stopped using the FlexiVoice. Nineteen of the original 40 patients (47.5 %) used the FlexiVoice on a daily basis, for a mean of 10.87 h/day (SD ± 4.67; *n* = 18; missing data in 1). Seventeen of the original 40 patients (42.5 %) used the FlexiVoice on a non-daily basis, for a mean of 6.82 h/day (SD ± 6.12; missing data *n* = 1). The reasons for not using the FlexiVoice on a daily basis are shown in Table 2. Most common were unpredictable fixation of the peristomal adhesive (*n* = 3) and familiarity of the usual HME/ASV (*n* = 3). Furthermore, for the four patients, who discontinued between inclusion and the 4-week follow-up, the reasons given are also summarized in Table 2.

Assessment at 26 weeks

At 26 weeks, 25 patients still used the FlexiVoice, whereas the remaining 11 patients had discontinued its use. Fifteen of these 25 patients (37.5 % of the original 40 patients) used the FlexiVoice on a daily basis, for a mean of 12.64 h/day (SD ± 5.03; *n* = 14; missing data *n* = 1). Ten patients (25 % of the original 40 patients) used the device on a non-daily basis, for a mean of 3.76 h/day (SD ± 2.07; *n* = 6; missing data *n* = 4). The type of surgery (standard TL versus pharyngeal reconstruction) did not influence ASV use. Unpredictable fixation of the adhesive was the main reason (*n* = 4) for not using the FlexiVoice on a daily basis at 26 weeks follow-up. All reasons are shown in Table 2, as well as the reasons for discontinuing between 4 and 26 weeks. Actual FlexiVoice use in the ten non-daily users was: 5–6 days/week (*n* = 1), 3–4 days/week (*n* = 4), 1–2 days/week (*n* = 2), 1–2 days/month (*n* = 1) and less than once per month (*n* = 2). Occasions when using the FlexiVoice in this non-daily user group are also given in Table 2.

Table 2 Reasons for discontinuing the study and not using FlexiVoice on a daily basis, and occasions when using FlexiVoice in the latter non-daily user group

Reasons for discontinuing the study between inclusion and 4 weeks[a]
Unpredictable adhesion of adhesive (*n* = 1); excessive mucus (already at baseline; *n* = 1); voice prosthesis problem (*n* = 1); recurrent disease (*n* = 1)
Reasons for not using FlexiVoice on a daily basis at 4 weeks[a]
Unpredictable adhesion of adhesive (*n* = 3); familiarity with usual HME/ASV (*n* = 3); less easy voicing (*n* = 3); "FlexiVoice cannot be used without HME" (*n* = 2); skin irritation with adhesive (*n* = 1); uncomfortable breathing resistance (*n* = 1); more mucus (*n* = 1); problem with voice prosthesis (*n* = 1); high T-shirt difficulty (*n* = 1); mostly using esophageal speech (*n* = 1); air leakage with manual occlusion (*n* = 1); unintentional closing membrane (*n* = 1); when home alone, ASV not necessary (*n* = 1)
Reasons for discontinuing the study between 4 and 26 weeks[a]
Unpredictable adhesion of adhesive (*n* = 6); too high breathing resistance (*n* = 6); soft voice (*n* = 2); too easy closing membrane (*n* = 2); usual ASV easier (*n* = 2); not easy with certain clothes (*n* = 1); too much speaking effort (*n* = 1); annoying sounds (*n* = 1); excessive mucus (already at baseline; *n* = 1); poor intelligibility (*n* = 1)
Reasons for not using the FlexiVoice on a daily basis at 26 weeks[a]
Unpredictable adhesion of adhesive (*n* = 4); more mucus (*n* = 2); uncomfortable breathing resistance (*n* = 2); soft voice (*n* = 2); preference for usual HME (*n* = 2); less easy voicing (*n* = 1); when home alone ASV not necessary (*n* = 1); too fast popping out membrane (*n* = 1); too loose arch (*n* = 1)
Occasions when using FlexiVoice in the non-daily user group at 26 weeks[a]
At home (*n* = 9); during social activities (*n* = 6); in special situations [e.g., when driving a car, on a quiet day, only during patient counseling (e.g., one of the less then once a month patients) (*n* = 3)]; during the whole day (*n* = 2); at the work place (*n* = 1)

HME heat and moisture exchanger, *ASV* automatic speaking valve

[a] More options per patient possible

Thus, in total, 15 patients decided to end the study earlier than planned, of whom 2 patients did use an ASV at baseline (and went back to that) and 13 patients did not use an ASV at baseline. An overview of patient numbers, compliance and rates regarding hands-free speech at different moments in the study is given in Figs. 3 and 4.

With respect to the attachment of the FlexiVoice to the stoma at 26 weeks, of the 25 FlexiVoice users 13 were using the StabiliBase adhesive to attach the FlexiVoice, 4 FlexiDerm, 3 OptiDerm, 3 StabiliBase OptiDerm, 1 Regular, 1 XtraBase, 3 LaryTube and 2 LaryButton (more options per patient possible; all adhesives/devices are from Atos Medical AB, Hörby, Sweden). The self-reported median daily device life of the adhesive was 8 h (range 0.25–168), when using the FlexiVoice (*n* = 23; 2 patients were not using an adhesive, but a laryngectomy button). Patients' satisfaction regarding adhesive device life with the FlexiVoice was rated on average 6.46 (NRS; SD 2.61; *n* = 23). Four of 11 patients (36 %), who used an ASV at baseline, changed their choice of adhesive(s), and 8 of 14 patients (57 %), who did not use an ASV at baseline, also changed their choice of adhesive(s).

With regard to the practical aspects of the FlexiVoice, patients were, e.g., asked to indicate if the membrane was popping out while coughing. Almost all patients answered

affirmative and all patients found it easy to push the membrane back. When asked if the membrane sometimes closed unintentionally, 12 patients answered in the affirmative and 13 patients answered as negative. This happened mostly when patients were physically active (*n* = 11). Seventeen of 25 patients (68 %) did use the 'locked mode' with a median of 1.5 times per day (range 0–10). All patients used automatic occlusion and 15 of 25 long-term users (60 %) used both automatic occlusion and manual occlusion. The main reasons for using manual occlusion were: loosening of the adhesive makes hands-free speech impossible, but still allows speech with manual occlusion (*n* = 8), and the voice is louder (*n* = 3). Seventeen of 25 patients indicated good intelligibility when using the FlexiVoice in automatic speaking mode, 2 found the intelligibility reasonable, 4 moderate and 2 poor. No significant differences in quality of life (according to the EQ5D5L) were found between baseline, at 4 weeks and at 26 weeks (data not shown). There were also no significant differences of the objective voice parameters assessed between baseline and 26 weeks follow-up (see Table 3).

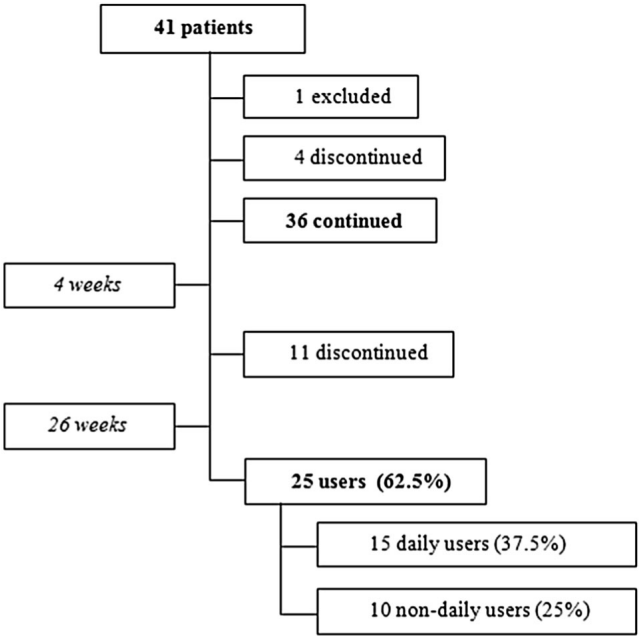

Fig. 3 Flowchart of patient compliance

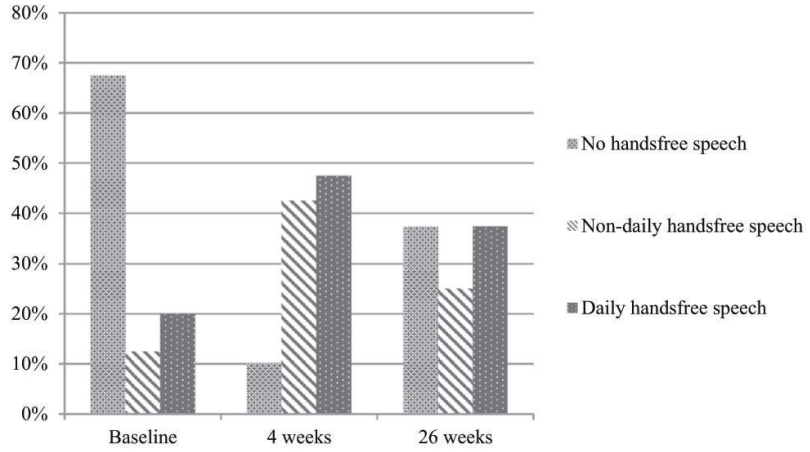

Fig. 4 Compliance rates regarding hands-free speech (*n* = 40)

Table 3 Objective voice assessment: hands-free speech parameters at baseline and 26 weeks [median (range)]

	Baseline (*n* = 13)	**26 weeks (*n* = 23*)**
Breathing pauses (*n*)	23 (16–68)	24 (9–66)
Total length of text (min)	1:19 (1.05–1.58)	1:14 (0.56–2.37)
Max phonation time (s)		
Prolonged /a/	7.30 (2.70–30.40)	7.58 (2.57–32.35)
Counting	11.1 (3.90–19.10)	11.76 (2.50–45.00)
Dynamic loudness range (dB)		
Softest	58 (42–70)	58 (51–69)
Comfortable	67.3 (62–74)	66 (55–77)
Loudest	77 (73–84)	79 (70–92)

There are no significant differences between the baseline and 26 weeks

* Two patients did not complete the voice assessment or not all items, because one could not read and the other could not read Dutch, and his adhesive did not last long

Comparison with usual ASV

At 26 weeks, 11 patients did compare the FlexiVoice with their usual ASV (in all patients, the FreeHands). Regarding the coughing mechanism, six patients preferred the coughing mechanism of the FlexiVoice and five expressed no preference. Regarding the overall voice quality, five patients preferred the FlexiVoice, five had no preference and one preferred the FreeHands. Regarding speaking effort, five patients preferred the FlexiVoice and six expressed no preference. Membrane-closing noise was reportedly less with the FlexiVoice in four patients, with the FreeHands also in four and similar in three patients. Furthermore, 4 of these 11 ASV patients reported that they could speak longer on one intake of breath with the Flex-iVoice, whereas 7 patients expressed no difference in this

respect. Regarding appearance, eight patients preferred the FlexiVoice and three had no cosmetic preference. Overall, one of these 11 patients preferred to stay with his original ASV.

With regard to overall stoma occlusion preference at 26 weeks, 18 patients preferred the FlexiVoice (45 %), 16 (40 %) their usual HME, 3 (7.5 %) their usual ASV and 1 (2.5 %) no device at all. The preference in the two patients (5 %), who stopped before the 4 weeks assessment because of recurrent disease/voice prosthesis problem, was not recorded. Figure 5 shows the preferences. Finally, regarding future use, 16 out of 40 patients (40 %) would continue to use the FlexiVoice daily, 8 patients reported that they would use the FlexiVoice on a non-daily basis (20 %) and 16 patients would not continue with the FlexiVoice.

During this study, 17 clinical and device-related events were registered. One event concerned aspiration of the voice prosthesis, which was not FlexiVoice related (voice prosthesis was retrieved from the trachea; no further morbidity). There were 13 device-related events, most of which (n = 6) concerned the arch that fitted too loosely on the FlexiVoice. Based on these reports the arch underwent a redesign, which solved this issue. Another issue (n = 3) was air leakage from the device when closed manually, which was solved by adapting the attachment of the HME to the FlexiVoice. The other four concerned membrane issues, which also led to minor design changes solving this. The remaining three registered events concerned one patient, who complained twice about excessive moisture collection in the device, and one patient, who complained about excessive mucus production (already present at baseline).

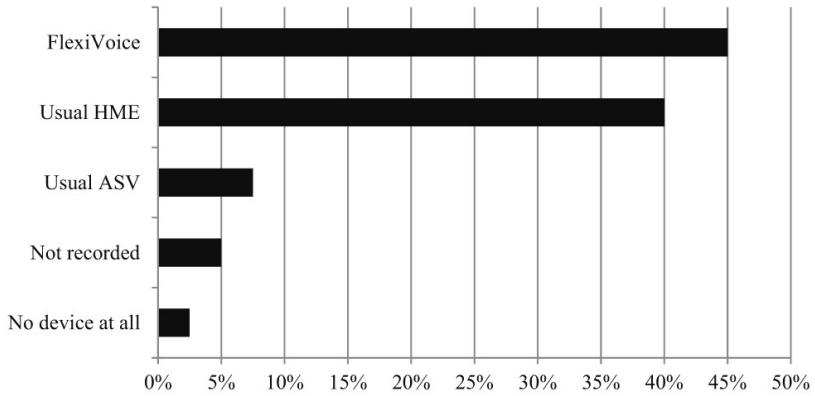

Fig. 5 Preference after 26 weeks (n = 40). *ASV* automatic speaking valve, *HME* heat and moisture exchanger

DISCUSSION

This prospective clinical feasibility study on the evaluation of the Provox FreeHands FlexiVoice, a new ASV for laryngectomized patients using prosthetic voice, shows favorable results. The daily use of hands-free speech in this cohort increased from 20 % (8/40) at baseline to 37.5 % (15/40) at 26 weeks follow-up, with 10 of the original 13 FreeHands users switching to the new FlexiVoice. Moreover, besides the original five non-daily FreeHands users, there were five additional non-daily users for a total of ten patients (12.5 % at baseline compared to 25 % at 26 weeks), who used/converted to the new FlexiVoice device. Thus, for almost two-thirds of the patients, the FlexiVoice is a valuable option, whereas one-third of the patients remain fully dependent on finger occlusion. The expectation that the new features/adaptations of this new automatic speaking valve would result in an increased proportion of patients able to use hands-free speech seems to be met. An interesting observation is that the number of hours of ASV use was not different between both devices. Daily ASV users applied the device 13.25 h per day at baseline, 10.87 h at 4 weeks and 12.64 h at 26 weeks. For the non-daily users, these numbers were 3.26, 6.82 and 3.76 h, respectively. This is in line with the fact that daily users tend to apply the ASV only during daytime and non-daily users only at special occasions.

Several factors could have contributed to this increased hands-free speaking rate. At the end of the study, 60 % of the FlexiVoice users (15 out of 25 patients) used automatic occlusion in combination with manual occlusion and the main reason for switching to manual occlusion was the unpredictable fixation of the peristomal adhesive. The advantage of this new feature of the FlexiVoice is that, when the adhesive starts loosening, it is still possible to use the device by occluding the opening in the front with a finger, which maintains the seal somewhat longer, obviating the immediate need to switch back to a normal HME and/or change the adhesive. An effective coughing mechanism is another important aspect of hands-free speech, both for relieving the tracheal pressure and maintaining a good seal of the adhesive. In almost all patients, the membrane popped out on coughing and it was easy to push the membrane back; this might have been an additional reason for patients to continue using the FlexiVoice. It cannot be excluded, though, that an important reason for this increased use might have been that the StabiliBase and StabiliBase OptiDerm adhesives, with a more stable and more anatomically shaped conical base, were popular adhesives in this study population and that these were not yet available during previous studies evaluating hands-free speech[19]. Lastly, the increased number of patients using hands-free speech, in part, also could have been an effect of the renewed attention to an ASV some time later during the follow-up, something that should be kept in mind during

regular aftercare of laryngectomized patients. A failure to acquire hands-free speech early on might still be correctable later.

There are several comparable studies on ASVs. The study of Op de Coul et al. (2005) evaluating the FreeHands device describes a higher overall compliance rate of 76 % than the 62.5 % (daily and non-daily users) in the present study[13]. However, the daily use of hands-free speech has doubled from 19 to 37.5 % in the present study, as has the number of h/day from a median of 5 h/day with FreeHands to more than 12 h/day with the FlexiVoice. In their study on the FreeHands device in 14 patients, Tervonen et al. found daily use in only 7 %, non-daily use in 86 % and non-use in 7 %[20]. These figures are again different from the ones found in the present study, but the numbers of patients in the Tervonen study are quite low, and there was a selection bias because only patients with a clear voice when using an HME were included[20]. In the present study, no such selection was made and also patients with less clear voices were represented. The heterogeneity of our patient sample (with 32 standard TLs, 6 pharynx reconstructions and 1 gastric pull-up) certainly results in a wide range of voice qualities, but this in fact did not influence long-term ASV use: reconstructed patients did as good as standard TL patients in this respect. Schwarz et al. described an acceptance rate of 62 % of patients using the device for at least 2 h per day during 4 weeks[21]. Such early results might not be that relevant, because in our study, compliance rate regarding daily use dropped from 47.5 % after 4 weeks to 37.5 % after 26 weeks, and the overall compliance dropped from 90 % at 4 weeks to 62.5 % at 26 weeks. To properly assess the compliance regarding a complicated device such as an ASV, a longer than a 4-week follow-up period is thus needed to provide relevant information. The study of Lorenz et al. on the FreeHands device in 24 patients does have a similar follow-up time as the present study (6 months), and the results are quite comparable with 42 % daily users and 29 % non-daily users[22]. However, the mean number of hours in the daily users, just like in the Op de Coul study, was also lower (8.4 h) than with the new FlexiVoice. Furthermore, the firsthand comparison of the FreeHands and FlexiVoice, possible in the present study for 11 patients, showed interesting differences, also supporting the assumption that the new design features of the FlexiVoice indeed improved its usability. The reported differences in favor of the FlexiVoice were less speaking effort, better overall voice quality, better appearance, easier and less noisy coughing mechanism and less noisy closing of the speaking membrane.

The key success factor of hands-free speech is maintaining the seal of the adhesive[7–9,19,21,23]. It is important to realize that, as reported in the results, the median device life of the adhesive among ASV users at baseline was 19 h (range 1–168), whereas this was 8 h (range 0.25–168) reported in diaries after 26 weeks using the FlexiVoice. A possible explanation

for this considerable difference in adhesive device life is that the patients, who used an ASV at baseline, were successful because of their excellent adhesive seal. Nevertheless, this study also shows once more that difficulties with adhesion of the adhesive to the skin are still a limiting factor, despite the easier closing of the more flexible/less strong membranes and the wider range of adhesives available for laryngectomized patients. More research and product development are thus needed to further improve peristomal attachment.

No significant differences in objective voice assessment were found between baseline, after 4 weeks and after 26 weeks, which shows that patients using the FlexiVoice are able to produce the same voice and speech quality compared to their baseline measurement with FreeHands as well as with HME. This is in contrast with the Op de Coul study, in which several voice parameters, such as maximum phonation time and dynamic loudness range, were significantly better when speaking with the HME[13]. The lack of such difference in the present cohort seems to further confirm the design improvements of the FlexiVoice.

The present study has some limitations. Although the only inclusion criterion was the ability to tolerate an HME, there still might have been a selection bias toward more motivated patients. Furthermore, some of the variables that (also) might influence hours of use of the FlexiVoice were not collected. In hindsight, it would have been interesting to not only let the patients report daily hours of FlexiVoice use in diaries, but also to ask the patients to give insight into the intensity of speech during the day. Also, information of stoma dimensions and local anatomy might have been of value to correlate duration of adhesive seal and thus hands-free speaking time[23]. Another limitation could be that for experienced ASV users, it is easier to handle a new ASV. However, they were willing to switch, only if the new device was really perceived as an improvement. Otherwise, they tended to stay with their original device. The fact that 10 of the original 13 ASV users did switch to the new ASV suggests that this limitation does not play a major role in this cohort.

In conclusion, the Provox FreeHands FlexiVoice is a useful ASV, which seems to allow for hands-free speech in a larger proportion of laryngectomized patients in the present cohort. The additional manual closure option of the FlexiVoice is experienced as beneficial for maintaining the adhesive seal longer.

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Medical Center Groningen also received a research grant from Atos Medical, Hörby, Sweden. The manufacturer provided the FlexiVoice devices to the patients at no charge.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The Netherlands Cancer Institute received a research grant from Atos Medical, Hörby, Sweden, which contributed to the existing infrastructure for health-related quality of life research of the Department of Head and Neck Oncology and Surgery. The University Medical Center Groningen also receives a research grant from Atos Medical, Hörby, Sweden. The manufacturer provided the FlexiVoice devices to the patients at no charge.

Research involving human participants and/or animals

The study was performed according to the protocol approved by the institutional review boards (Protocol M14VOX).

Informed consent

Signed informed consent was obtained from all participants.

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CHAPTER 7

Comparative study between peristomal patches in patients with definitive tracheostomy

Lansaat L
de Kleijn BJ
Hilgers FJM
van der Laan BFAM
van den Brekel MWM

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ABSTRACT

Introduction

To prevent or diminish pulmonary problems in laryngectomized patients, continuous use of a heat and moisture exchanger (HME) is recommended. Therefore, automatic speaking valves are also often combined with an HME to enable hands-free speech. In order to keep these devices in place, most commonly, peristomal patches are used.

Objective

This prospective clinical 2 × 2 crossover study aims at assessing the added value of a new patch for HME application, the ProvoxStabiliBase OptiDerm (SBO).The device combines the stable and conical base of the Provox StabiliBase with the skinfriendlier hydrocolloid Provox OptiDerm (OD) patch.

Methods

Thirty-two laryngectomized patients were included in this multicenter study. Participants were asked to compare SBO to OD, and to the patch they normally use. The primary outcome measure was patient preference.

Results

Overall, 60% of the participants had preference for their normally used patch, 23% preferred the SBO and 17% indicated no preference. When comparing the SBO to the OD, 43% preferred the SBO, 40% the OD and 17% had no preference.

Conclusion

Most patients preferred their normally used patch and SBO was favored by a subgroup. Provox StabiliBase OptiDerm seems to be a valuable addition to the existing patches and further increases patients' options for HME application.

INTRODUCTION

Total laryngectomy (TL) isstill an indispensable treatment option for advanced larynx and hypopharynx cancer, for recurrent disease, and a dysfunctional larynx after prior (chemo) radiotherapy (C)RT. Total laryngectomy results in significant anatomical changes. The alimentary and respiratory tracts are separated and a definitive tracheostomy is created at the base of the neck. The main disadvantage of TL is the loss of upper airway and larynx functions. This leads to pulmonary problems, such as excessive coughing and mucus production, and loss of normal speech.[1,2]

To prevent or diminish pulmonary problems, continuous use of a heat and moisture exchanger (HME) has shown to be highly beneficial.[3,4] Moreover,most automatic speaking valves (ASVs) presently are combined with an HME, so that during hands-free tracheoesophageal speech, airway protection and rehabilitation are also taken care of.[5–7] Laryngectomized patients have several options to keep these devices in place depending on their personal situation. The most commonly used device is a peristomal patch, which creates an airtight seal at the level of the tracheostoma and provides a placeholder for the HME and/or ASV.[8]

Currently, there is a wide variety of patches available to suit patients' personal needs, which is important to optimize compliance.[8-10] Recently, the Provox StabiliBase (SB) was evaluated in a multicenter study. This patch provides a more stable and more anatomically shaped conical base compared with other patches. The study showed that the majority of patients preferred this new patch to their usual comparator, and its device life appeared to be significantly longer. Also, patients with a deep stoma reported the patch to be more comfortable.[9]

After its introduction, feedback from clinicians and patients revealed that some patients experienced skin irritation with the standard adhesive material of the SB. It was felt that these patients would benefit from a patch with the same stable and conical base as the SB, but with the more skin-friendly hydrocolloid adhesive already used in the Provox OptiDerm (OD). Therefore, the Provox StabiliBase OptiDerm (SBO) was developed. To test whether this stable conical hydrocolloid SBO patch is a valuable addition to the variety of peristomal adhesive options needed to suit more laryngectomized patients, this new patch was assessed in a 2 x 2 crossover prospective multicenter clinical trial.

METHODS

This study was performed at two tertiary care cancer centers. Thirty-two laryngectomized patients were entered in the study, 16 from each center. Inclusion criteria were: 18 years

or older, use of an HME, use of a voice prosthesis, minimum of 3 months after TL and/or postoperative (C)RT. Exclusion criteria were: patient is unable to use the SBO (due to anatomical irregularities that may interfere with the stable base of the patch), medical problems prohibiting the use of HME or patch, active recurrent or metastatic disease, patient is unable to understand the patient information and/or unable to give informed consent. Skin irritation, which varies between 9 and 40% among patients,[4,10–12] was not a selection criterion. This provides us with two advantages, namely additional data on the extent of the skin irritation problem in this patient cohort, and prevention of selection bias. Moreover, it is likely that, if given more options and provided that there was no skin irritation, patients would primarily make their choice on the basis of the duration of the seal. In other words, by using an unselected patient cohort, we can get a better insight of the extent of the irritation problem and of the place of this new patch among the presently available options. The study was performed according to the protocol approved by the institutional review boards and took place between February and April of 2014. Signed informed consent was obtained from all patients. Patient characteristics are shown in **Table 1**.

The SBO is manufactured by Atos Medical AB (Hörby, Sweden). The patch is shown in **Fig. 1.** It is a single-use patch intended for laryngectomized patients. It is attached to the skin around the tracheostoma to provide a connection for HMEs and speaking valves. The SBO consists of a stable base, similar to that of the SB, but with a hydrocolloid adhesive.[9] The patch is suitable for sensitive and/or breached skin and its baseplate is designed to also accommodate deep tracheostomas.

Table 1 Patient characteristics

Characteristics	Value	%
Gender		
Male	27	84
Female	5	16
Age at TL	Mean 55.7 years (SD 9.4)	
Age at entry	Mean 64.0 years (48-82)	
Post-TL	Mean 100.7 months (SD 77.9)	
TL		
Standard	28	88
+ Reconstruction	3	9
Information missing	1	3
Origin of tumor		
Larynx	30	94
Hypopharynx	2	6
Indication of TL		
Primary	9	28
Salvage	23	72

Characteristics	Value	%
Neck dissection		
No	13	41
Unilateral	6	19
Bilateral	12	37
Information missing	1	3
Postoperative (C)RT		
No	23	72
Yes	9	28
Voice prosthesis		
Provox 2	4	13
Provox Vega	18	56
Provox ActiValve	10	31
Patch		
StabiliBase	11	34
FlexiDerm	10	31
OptiDerm	5	16
XtraBase	4	13
Other	2	6
HME		
Daily	32	100
+ ASV use	9	28

Abbreviations: ASV, Automatic Speaking Valve; (C)RT, (chemo)radiptherapy; HME, Heat and Moisture Exchanger; TL, Total Laryngectomy; SD, standard deviation.

The SBO was compared with the OD in a feasibility study with a 2 × 2 crossover design. After inclusion, the patients consecutively used 5 OD and 5 SBO patches in the order assigned by randomization. The primary outcome measure was overall patient preference, based on the various aspects of the patch addressed in the study-specific questionnaires (see below). The secondary outcome parameters were: device life, patient satisfaction (skin irritation, comfort, voice/speech), ease of application, and quality of life. Study-specific structured questionnaires were completed at baseline, after the use of the first 5 patches and after the use of the following 5 patches. Questionnaires addressed skin irritation, ease of application, ease of removal, cleanliness, mucus collection, fit, comfort, use of other devices in combination with patch, appearance, voice quality, air leakage, adherence and cleaning tracheostomy/ voice prosthesis. Answers were reported on a four-level Likert scale. Patients rated satisfaction regarding device life and voice quality using a 10-cm Numeric Rating Scale (NRS) (0 = worst and 10 = best). Quality of life was assessed using the EuroQOL-5 Dimension-5 Level questionnaire (Eq. 5D5L).[13] The Eq. 5D5L is a validated instrument using scores in five health care dimensions (mobility, self-care, daily activities, pain/discomfort and anxiety/depression) and a 100-mm visual analogue scale (VAS).

During the study period, patients kept a diary to record the device life of each patch and the number of hours per day of HME use. At the end of the study patients were asked to complete a comparative questionnaire. Patients had to compare the SBO with the OD and also with their normally used patch if different from the OD.

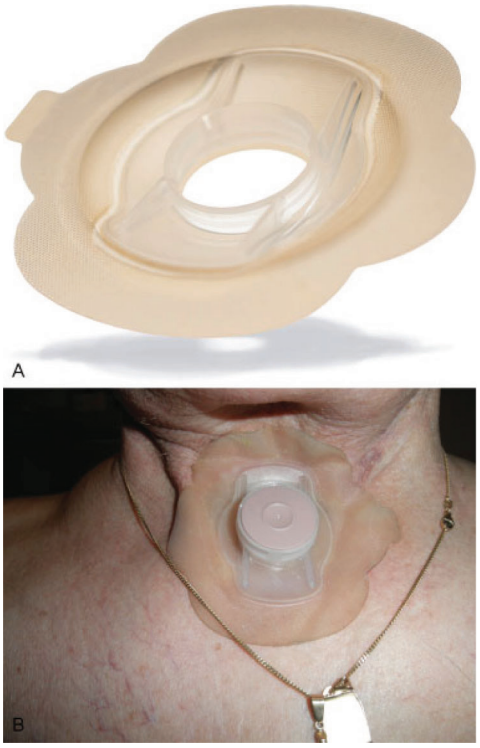

Fig. 1 StabiliBase OptiDerm (SBO); (A) a technical drawing of the SBO without liner (frontal view) showing the stable and conical base; (B) attached to a patient with the heat and moisture exchanger in situ.

The primary outcome of this study was patient preference. The goal was that 40% of the participants preferred the SBO to the OD, 5% considered the SBO to be worse, whereas the remainder considered both patches to be equally good (45%) or bad (10%). Based on earlier studies and given the assumption that in the absence of irritation, the duration of the seal is the deciding factor, this was a feasible goal to be expected and clinically relevant.[9,10,12] A sample size of 30 pairs will have 82% of power to detect a difference in proportions of 0.350, while the proportion of discordant pairs is expected to be 0.450, using a sign test of equality of paired proportions with a 0.05 two-sided level of significance. As this was a short study and no risks have been associated with participation in the study, the dropout rate was expected to be < 5%. Statistical analyses were conducted using the IBM Statistical Package for the Social Sicencessoftware (IBM Corp., Armonk, NY, US), version 22.0.

Frequencies were explored using the Kolmogorov-Smirnov test. Parametrically distributed data are shown as mean ± standard deviation and analyzed using the paired t-test. Non-parametrical data are presented as median (inter quartile range) and were analyzed using the Wilcoxon signed-rank test. The Likert Scales rendered ordinal data from three related samples. This data was analyzed using the Friedman test. If the groups differed significantly, a Wilcoxon signed-rank test was used to determine which groups were different. A p-value < 0.05 was considered significant.

RESULTS

The characteristics of the 32 patients enrolled in the study are shown in **Table 1.** One patient withdrew from the study in the first week because of recurrent disease and was excluded from further analysis. Twenty-seven males and four females remained. Four patients did not use all of the study patches. Reasons were: skin irritation after using the SBO, poor adherence of the SBO to the skin, poor adherence of the OD to the skin and painful skin after using the OD. An overview of completed questionnaires is shown in **Table 2.**

Table 2 Completed questionnaires

Questionnaire	n
Baseline	31*
OD	30**
SBO	30***
Comparative 'Normally used patch' - SBO	25***/****
Comparative OD – SBO	30***

Abbreviations: OD, OptiDerm; SBO, StabiliBase OptiDerm.

Notes: *One patient dropped out right after baseline data collection.

These data were removed from the analysis.

**One patient did not complete the OD questionnaire (poor adherence)

*** One patient did not complete the SBO questionnaire and the comparative questionnaires (poor adherence).

**** For the five patients who were already using OD at baseline, the OD-SBO comparative questionnaire was used as normally used patch-SBO comparative questionnaire.

When patients compared the OD with the SBO, 12 of 30 patients (40.0%) preferred the OD. Thirteen patients preferred the SBO (43.3%) and 5 patients (16.7%) expressed no preference. In comparison with their normally used patch, 18 patients (60.0%) indicated a preference for the normally used patch, 7 patients (23.3%) for the SBO and 5 patients (16.7%) indicated no preference. Of the 5 patients who were using the OD at baseline (preference for OD 3, for SBO 1, no preference[1]), the answers to the comparative OD-SBO questionnaire were used as 'normally used patch-SBO-data' in these analyses (**Fig. 2**).

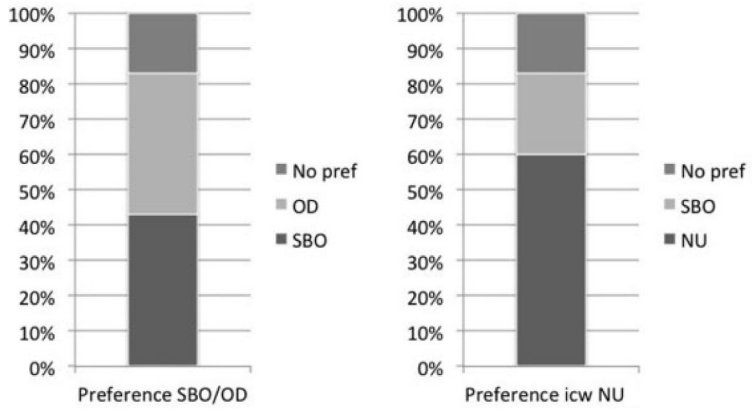

Fig. 2 To illustrate the added value of more patch choices, on the left, the preference at the end of the study for either of the 2 hydrocolloid patches (SBO = StabiliBase OptiDerm, *n* = 13; OD = OptiDerm, *n* = 12; No pref = No preference for either of the two, *n* = 5); on the right, the preference in comparison with (icw) the normally used patch (NU = normally used patch, *n* = 18; SBO, *n* = 7; No pref. *n* = 5).

Device life assessment was based on the data provided by the patients, who reported on at least 3 out of 5 OD/SBO patches. For the OD, the median device life was 18.5 hours (*n* = 26; range 0.5–109.9) and for the SBO this was 19.6 hours (*n* = 27; range 0.5–163.0) (*p* = 0.290). When data were split for patches used to apply an ASV or a HME, no significant differences were found between device life of the SBO and OD. There was an increase in device life in 15 out of 26 patients with the SBO compared with the OD, with a mean factor of 1.44. In 2 patients, there was no difference, and in 9 patients, there was a decrease of the device life with the SBO compared with the OD with a mean factor of 0.76. The overall mean factor was 1.17. The median self-reported device life in the 15 patients who had an increased device life with the SBO, was 14.47 hours (range 1.9-109.9) with the OD and 19.60 hours (range 2.35–163.01) with the SBO.

Analysis of fit, comfort, appearance, speech, air leakage and adherence, measured at baseline, after using 5 OD patches and after using 5 SBO patches, showed a statistically significantly better outcome for the normally used patch compared with the SBO and the OD. No significant differences regarding these variables were found between the SBO and OD.

With respect to skin irritation, no significant difference was found between the normally used patch, OD and SBO. When asked to compare these two patches, 17% experienced less skin irritation with the OD, 23% experienced less skin irritation with the SBO and 60% experienced no difference (*n* = 30). Compared with the normally used patch (*n* = 25), 12%

experienced less skin irritation with that patch, 32% with the SBO and 56% experienced no difference.

Participants indicated significantly less discomfort with their normally used patch compared with the SBO (p = 0.001, n = 30). When asked to compare the normally used patch with the SBO, 52% found that patch more comfortable to wear, 24% found the SBO more comfortable and 24% found no difference. When asked to compare the OD and SBO, 33% had less discomfort with the SBO, 40% with the OD and 27% indicated no difference.

Overall voice and speech was measured using a NRS. There was no statistically significant difference between the normally used patch and the SBO. Only the OD received a statistically significantly lower score compared with the normally used patch (p = 0.004, n = 30), and compared with the SBO (p = 0.007, n = 30). Furthermore, no significant differences in applying the patch and in the quality of life (according to Eq. 5D5L) between the normally used patch, OD and SBO were found.

Finally, regarding future use, 15 out of 28 patients (53.6%) reported that they would keep their normally used patch in the future. Of the 13 remaining patients answering this question, 6 (21.4%) will use the OD, 5 (17.9%) the SBO and 2 (7.1 %) a combination of the normally used patch with SBO. Data of two patients were missing. Those seven patients who will use the SBO or a combination of the normally used patch and SBO in the future consist of two former regular patch users (29%), four SB users (57%) and one tracheostomy button user (14%).

During this study, six adverse device effects were registered. There were complaints about skin irritation, painful removal of the patch and poor adherence. All reports were expected effects of using a tracheostomy patch.

DISCUSSION

This prospective clinical trial on the evaluation of the SBO, a new patch with stable conical base and hydrocolloid adhesive for peristomal attachment of postlaryngectomy pulmonary and voice rehabilitation, shows that this patch is a valuable addition to the variety of options needed to suit more laryngectomized patients.

With a quarter of the patients choosing the SBO, or a combination of the normally used patch with the SBO, it is clear that the SBO is suitable for a subgroup of patients. This subgroup might consist of patients who are using a SB as their main patch and would like to alternate with a more skin-friendly patch, keeping in mind that the median device life of the standard SB is roughly 1.8 times longer because of its stickier adhesive material.[9]

These patients may benefit when they prefer a stable base around the tracheostomy, but cannot use the SB (all day) due to sensitive/breached skin.

The results show that the device life of the SBO is not significantly increased compared with the OD (both hydrocolloid adhesives). However, for those 15 patients who had an increased device life with the SBO compared with the OD, the increase is clinically relevant. The difference (19.60 hours versus 14.47 hours) often made it possible for those patients to replace the patch only once per 24 hours. Nevertheless, a majority of the patients preferred the normally used patch, because in the absence of skin irritation, the duration of the seal is the decisive factor for their 'patch-choice'. As the mean interval between TL and participation in this study was 6.5 years, most patients have extensive experience with several peristomal attachment possibilities and found their optimal attachment modality. Still, there are patients (23.3%) who prefer the SBO to their normally used patch. These results show there are still possibilities for further innovation, despite the wide range of patches already available to laryngectomized patients which is not surprising, given the wide variations in peristomal anatomy.[14] So far, only a few clinical studies have been conducted to investigate peristomal patches. Because of the wide variety of rehabilitation options for laryngectomized patients, however, a good insight in patients' needs is necessary to find the optimal rehabilitation options. For instance, the study by Hilgers et al (2012) describes that there is no one-size-fits-all solution and emphasizes the need for a range of device options, which means that this new patch is a welcome development.[9]

In the present, relatively small study, although there was no selection based on the presence or absence of skin irritation, there still might have been some selection bias. For example, patients who were unable to use the SBO, such as patients with anatomical irregularities in the area of the patch that interfere with the stable base of the patch, were excluded. Furthermore, some variables that might influence device life were not collected. For example, we did not ask the patients to register hours of ASV use in their diaries and we did not measure tracheostomy dimensions and local anatomy, factors that obviously can influence the outcomes.[8]

The cost of these new patches was not a topic of this study. Although according to the manufacturer the periodical costs for various patches is quite comparable, to analyze costs in a meaningful way, a proper cost-effectiveness study would have been needed. This would require collecting additional data to those of a standard clinical study. Moreover, since costs and reimbursement systems vary widely between countries, even making vague suggestions about cost issues now would be speculative, at best. But this is certainly an interesting topic for studies in other countries.

CONCLUSION

Most patients preferred their normally used patch and SBO was favored by a subgroup. Therefore, SBO seems to be a valuable addition to the arsenal of devices already available and widens the options laryngectomized patients have for peristomal attachment of medical devices for pulmonary protection and rehabilitation.

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CHAPTER 8

Ex vivo humidifying capacity and patient acceptability of stoma cloths in laryngectomized individuals

Lansaat L*
van den Boer C*
Muller SH
van der Noort V
van den Brekel MWM
Hilgers FJM

*both authors contributed equally

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ABSTRACT

Background

Heat and moisture exchangers (HMEs) improve respiratory function after laryngectomy, but there is virtually no information on the benefit of traditional stoma cloths or other covers.

Methods

Two sequential studies were performed: (1) an ex vivo test was used to compare the humidifying capacity of stoma cloths to other coverings; and (2) a 4-week randomized trial was then performed to assess patient acceptability of cloths both alone and with an HME (*N*=18).

Results

The humidifying capacity of the coverings tested varied widely. For stoma cloths, a humidifying capacity of 13.7 mg/L was found to decrease to 8.5 mg/L if air-leaks around the cloth occurred. Patients who used HMEs disliked stoma cloths because they interfered with voicing, they became soiled more easily, and were less effective at reducing coughing and mucus production.

Conclusion

Although less acceptable to patients who use an HME, stoma cloths do provide significant humidifying capacity and should be encouraged when HMEs are unavailable or inappropriate.

INTRODUCTION

Total laryngectomy has a profound impact on pulmonary physiology because of the bypassing of the upper respiratory tract.[1–4] The inhalation of unconditioned air through the stoma directly into the lower airways leads to excessive mucus production, involuntary coughing, and frequent forced expectoration to clear the trachea of mucus. These predictable respiratory complaints negatively impact quality of postlaryngectomy prosthetic and/or esophageal voice and speech, and quality of life.[1] Fortunately, heat and moisture exchangers (HMEs) have been shown to help in compensating for the changes in respiratory function and to be clinically beneficial.[5,6] Since the first prospective clinical trials with such devices in the early 1990s, many studies have shown that HMEs significantly decrease coughing, phlegm production, and the need for forced stoma cleaning, whereas the reduction of these complaints also results in a decrease of tracheitis and crusting, and improvements in voice quality, pulmonary function, and quality of life.[7–12] Initial studies on the impact of HMEs some 25 years ago concerned patients who frequently used stoma cloths, which at that time were standard of care in most institutes.[5,7] In our institute, Buchanan protectors were the standard, and they were prescribed to all patients.

The relevance of postlaryngectomy humidification seems to have been intuited (even) before the first HME studies, because most institutes at that time already applied external humidification, in some cases, still with electric steam kettles, but in most already with wall-mounted, heated humidifiers.[13] The routine prescription of stoma cloths also attested to that. Nevertheless, the first HME studies, which essentially compared HMEs with the then standard of care stoma cloths, showed highly significant clinical improvements in respiratory problems after total laryngectomy. The observations suggested that the clinical respiratory benefits of stoma cloths in practice were limited. It has to be noted, however, that, despite significant respiratory, physical, and quality of life improvements, compliance initially was suboptimal with only about 50% of patients continuing HME use.[7] The reason for this was that airtight stoma occlusion, essential for prosthetic voicing, was difficult to achieve with the early HMEs. Subsequent generations of HMEs, stoma adhesives, and stoma tubes and buttons, specifically designed to be easy to use, tackled this problem.[14,15] The improved prosthetic voicing led to a significant improvement in compliance, as well as to a further appreciation of these medical devices in The Netherlands and elsewhere.[16,17]

Nevertheless, stoma covers too have humidifying effects, as do any other textiles or fabrics covering the nose and mouth; shawls, for instance, are used especially in the winter season to decrease uncomfortably large temperature and humidity differences between the environment and respiratory tract. Recently, Quail et al[18] looked into the humidifying

effects of stoma cloths. The precision of their measurements, however, is unclear as they were not able to establish the proven humidifying effect of the HMEs they included in their study.[19–21] This is probably because of the use of nonvalidated equipment, lack of essential condensation prevention technology,[22] and a "humidity loading time" of only 1 minute instead of the roughly 10 minutes, which are required for HMEs.[23]

An essential component of the clinical benefits of HMEs and stoma cloths is patient acceptability because their pulmonary protective characteristics, as is the case with the upper respiratory tract, are dependent on continuous use of the humidifying device. A clinical study assessing patient acceptability of stoma cloths in daily life, however, has, to the best of our knowledge, never been carried out.

To address these issues, we conducted 2 sequential studies. The first was to assess the humidifying capacity of various stoma cloths with the recently developed validated ex vivo technique.[23] The second was to assess patient acceptability of a stoma cloth with known ex vivo humidifying capacity in a short-term prospective randomized clinical trial.

MATERIALS AND METHODS

Ex vivo study

Ex vivo test setup. In the ex vivo test, a healthy volunteer was breathing in and out through the HME mounted on a regular spirometer (MLT300 Flowhead; ADInstruments GmbH, Oxfordshire, UK), which recorded breathing volume and frequency.[23] A fast absolute humidity sensor (response time, 0.1–0.2 seconds[24]) was integrated in the breathing circuit to monitor the humidity. A life-size mannequin of the neck and chest of a laryngectomized patient, made of plaster of Paris, was used to replicate the in vivo application of stoma cloths/HMEs as closely as possible (see Figure 1). On the back of the mannequin, the tracheostoma was connected to the spirometer, and the absolute humidity sensor was integrated in the breathing circuit as well. For optimal humidity, loading of the stoma cloths/HME before recording the data for analysis, the healthy volunteer had to breathe through the device long enough (in general at least 10 minutes) to achieve the optimal humidity loading, following the same protocol as previously described.[23,25] Before each test cycle, the mannequin was heated in an incubator to the level of human skin surface temperature (34˚C). The temperature of the mannequin was monitored with a thermocouple (MLT1402 T-type Ultra Fast Thermocouple Probe) placed in a small hole in the mannequin near the tracheostoma.

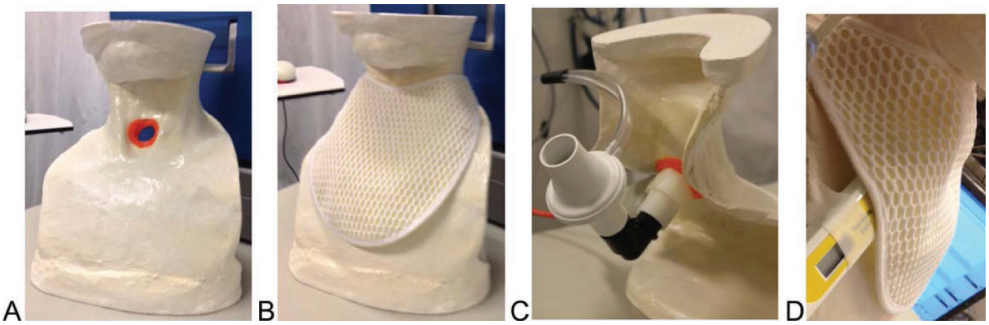

Fig. 1 Ex vivo test configuration; (A) the laryngectomy neck and chest mannequin, made out of plaster of Paris; (B) Buchanan protector covering the tracheostoma; (C) posterior view showing the connection of the tracheostoma with the spirometer and the integrated absolute humidity sensor (mounted in the black connector); and (D) Buchanan protector lifted to create a slight air leak.

The absolute humidity sensor and spirometer were calibrated as described previously, as was the temperature and humidity monitoring of the test room.[23,25] Spirometer data were recorded and analyzed using Powerlab software (ADInstruments), and humidity values were registered with data acquisition software (Acquis 2.8; Anesthesie-Technik, Göottingen, Germany). In this study, absolute humidity at end-inspiration and expiration was measured as described previously.[23] Unlike with HMEs in former studies, the weight difference between end-inspiration and end-expiration could not be measured for the stoma cloths, as these could not reproducibly be placed on the balance, making the margin of error too large. The black connector between the absolute humidity sensor and the spirometer (Figure 1C) added 70 mL to the dead space of the configuration used in the previous HME measurements (100 mL).[23,26] Therefore, in this study, the XtraMoist HME was included for comparison with the previous results.[26]

Materials/devices tested for humidifying capacity

The primary purpose of this study was the performance of the large (216 × 208 mm) Buchanan protector (Kapitex Healthcare, Whetherby, UK). Three samples of the Buchanan protectors were tested, both dry "worn" correctly and dry with an intentional small leak (Figure 1D). For comparison, a number of other materials/devices were tested once: the Tracheofix stoma cover (Servona, Troisdorf, Germany), the XtraMoist HME (HME-XM; Atos Medical, Hörby, Sweden), the Buchanan protector in combination with the HME-XM, a Buchanan protector made wet before use (2 samples), a Buchanan protector after washing, an ordinary woolen shawl, a cotton baby bib, and a standard surgical mask.

Analysis and statistical methods

Absolute humidity data were normalized to a reference environmental humidity of 5 mg/L, as described previously.[23] The association between absolute humidity and inspiratory breathing volume was determined by an exponential decay: absolute humidity = A2 + (A2-A1) exp (-V*exp(A3)), where absolute humidity is the measured absolute humidity, V the inspired volume, A1 the end-inspiratory asymptote, A2 end-expiratory intercept value, and A3 the log of the decay rate (see Ref. [26], Appendix 2, and Ref. [27]). The humidifying capacity is defined as the increase of absolute humidity in the observation with the stoma covered with a device/material over the observation without cover. Using the associations between humidity and inspiratory breathing volume, the humidifying capacity was determined at the clinically relevant breathing volumes of 0.5 and 1.0 L.

Patient study

Study purpose and design. The purpose of this segment of the study was to assess, in a prospective randomized clinical trial, the acceptability of the Buchanan protector (with now known ex vivo humidifying capacity) alone or in combination with the HME normally used by patients. The criterion for inclusion was that the patient should be at least 6 months post–total laryngectomy. Exclusion criteria were recurrent disease and difficulty understanding the purpose of the study. Patients in routine follow-up in The Netherlands Cancer Institute were invited to collaborate in the trial through a letter explaining the purpose of the study. In the letter, it was emphasized especially that the good HME capacities of the Buchanan protector, as established in the preceding ex vivo tests, made it potentially a good alternative to their regular HME. The study was approved by the protocol review board of the institute.

Ninety-one disease-free laryngectomized patients were approached by regular mail. Forty-nine patients responded (54%), 17 of whom indicated that they were not motivated for the study, 11 that they were physically and/or mentally unable to participate, and 3 that they were motivated but unable to participate because of time constraints. This left a sample of 18 motivated laryngectomized patients, who, after having given written informed consent, were enrolled in the study in April 2015.

The most important outcome measures are patient acceptability and preference for stoma cover pretrial and posttrial. Data collection consisted of study-specific structured questionnaires, patient diaries (see Appendix 1), and photographs of the stoma cover worn by the patient at baseline and after completion of the study.

At baseline, the situation with respect to HME use and voicing was assessed and patients were randomized for the order in which they were to use the Buchanan protector with and without their usual HME in weeks 2 and 3. For week 1, patients were asked to continue their usual HME use in order to collect baseline data in their diaries. For weeks 2 and 3, patients were instructed to use the Buchanan protector without the HME for 1 week and then the Buchanan protector together with their regular HME for the next week, or vice versa. In week 4, patients returned to their regular HME use. During weeks 2, 3, and 4, data were again collected in the diary. By the end of week 4, a photograph was taken once more, the diary was collected, and the final questionnaire was completed. Patients were contacted weekly by telephone for support and motivation. In Figure 2, an overview of the study design is shown.

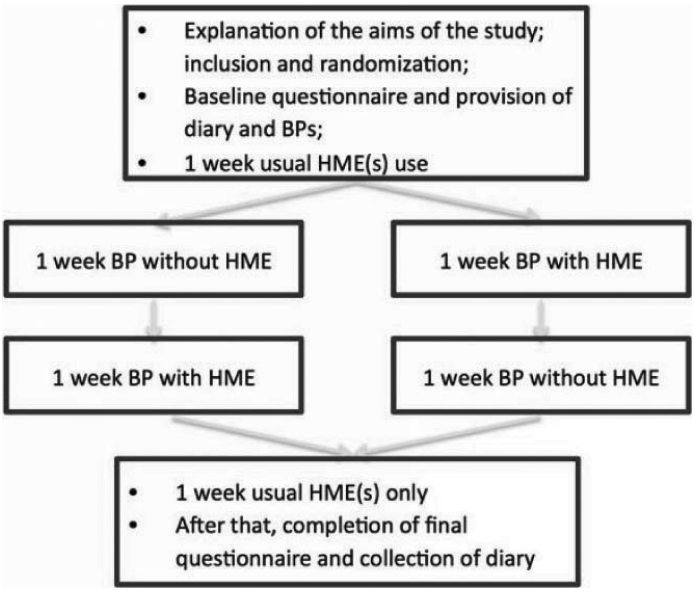

Fig. 2 Outline of short-term, prospective, randomized clinical trial. BP, Buchanan protector; HME, heat and moisture exchanger.

All patients were familiar with the daily maintenance and practical issues of their regular HMEs. Because patients were mostly unfamiliar with the daily maintenance and practical issues of the Buchanan protector, they were counseled at the start of the study, in accord with the manufacturer's recommendations. The Buchanan protector is attached by using fabric straps that are wrapped around the neck and tied in a knot; the Buchanan protector can be changed daily, or sooner if required; the Buchanan protector should be cleaned by hand in warm soapy water and rinsed thoroughly in clean water; to dry, the Buchanan

protector should be kept flat by placing it between 2 clean towels, to reduce any wrinkling effect on the foam layer; the Buchanan protector should be cleaned 3 times at the most. A total of 10 Buchanan protectors, estimated to be enough for the 2-week trial period, were provided to the patients free of charge out of the department's research budget.

Statistical analysis

Questionnaire items regarding couching, mucus production, skin irritation, stoma occlusion, and voicing (Table 2) asked patients to compare their experience during Buchanan protector use (both with and without the HME) to the situation at baseline. For these outcomes, the number of patients reporting better, similar, or worse outcomes during Buchanan protector use (as compared to baseline) were reported and tested against the null-hypothesis of no deviation from baseline in both conditions (with or without the HME) separately, using a Wilcoxon signed rank test. Questions regarding practical issues of Buchanan protector use (Table 3), on the other hand, were compared between conditions (with and without HME) again using a Wilcoxon signed rank test. All analyses were carried out in SPSS version 20.0.

RESULTS

Ex vivo study

Figure 3 shows the observations and fits for the main part of the ex vivo study and Table 1 shows the outcomes for all materials and devices. The Buchanan protector added about 14 mg/L to the end-expiratory absolute humidity at a breathing frequency of 0.5 L (typical for laryngectomized patients), even when washed. Figure 3 also shows that the repeatability with the different Buchanan protector samples is consistent. A dry Buchanan protector combined with the HME-XM and, in particular, the wet Buchanan protector added even more water. Small leaks (as shown in Figure 1D) reduced the performance of the Buchanan protector from 13.7 to 8.5 mg/L; larger leaks did so even more. The HME-XM added 6.5 mg/L, comparable to the woolen shawl and cotton baby bib (when worn without leaks). Note that without the cover the humidity increased slightly, because the entrance through the mannequin already acts as an HME (although not a very effective one). The surgical mask and the Tracheofix showed the poorest performance. Table 1 also gives some data obtained with the mannequin at room temperature instead of 34˚C, which showed that a room temperature mannequin reduced humidity only very slightly.

Table 1 Absolute humidity effect of tested materials and devices normalized to room humidity (5 mg/L).

Values for room humidity 5 mg/L	Absolute humidity mg/L	Humidifying capacity mg/L	Absolute humidity mg/L	Humidifying capacity mg/L	A1 mg/L	A2 mg/L	A3
Breathing volume	0.5 L	0.5 L	1.0 L	1.0 L	N.A.	N.A.	N.A.
Buchanan protector wet	23.8	17.9	23.5	17.7	23.5	34.7	2.0
Buchanan protector dry 1 HME-XM	20.4	14.5	19.6	13.8	19.5	33.1	1.7
Buchanan protector dry (*n* 5 3)	19.6	13.7	19.4	13.6	19.4	34.1	2.2
Buchanan protector washed	21.1	15.2	18.4	12.6	17.6	33.0	1.1
Buchanan protector cold mannequin	19.4	13.7	17.7	12.1	17.5	35.6	1.5
Shawl	16.6	10.7	15.2	9.4	15.0	31.8	1.6
Buchanan protector dry 1 small leak	14.4	8.5	13.2	7.4	13.2	35.0	1.8
HME-XM	12.3	6.5	10.9	5.1	10.7	29.5	1.6
Cotton baby bib	12.2	6.3	11.2	5.4	11.2	30.3	1.8
Tracheofix	9.0	3.1	7.5	1.7	7.4	29.1	1.7
Surgical mask	7.6	1.7	7.0	1.2	7.0	28.6	2.0
No cover	5.9	0.0	5.8	0.0	5.8	32.5	2.5
No cover/cold mannequin	5.6	0.0	5.6	0.0	5.6	33.2	2.9

Abbreviations: N.A., not applicable; HME-XM, XtraMoist heat and moisture exchanger.

All observations are for the warm mannequin (34˚C) except where marked as cold (room temperature). Data are ordered according to asymptote A1. Humidifying capacity is the difference between the value with device/material and the value without cover at an environmental humidity of 5 mg/L.

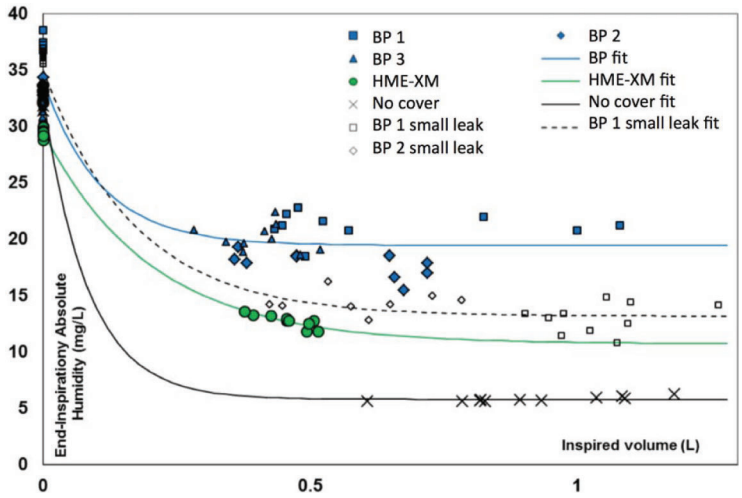

Fig. 3 Ex vivo test results for Buchanan protector (BP; 3 samples tested), XtraMoist heat and moisture exchanger (HME-XM), and Buchanan protector with a small air leak with individual data points and a fit according to the formula provided in the statistical paragraph: AHinsp (absolute humidity end-inspiration) as a function of inspiratory breathing volume. The environmental humidity was normalized to 5 mg/L.

Patient study

Baseline data. The study included 17 men and 1 woman. The mean age was 67.9 years (SD ±10.4). The average age at total laryngectomy was 58.9 years (SD ±11.0). The median follow-up since total laryngectomy was 107.9 months (SD ±84.1). Two patients underwent total laryngectomy with postoperative radiotherapy (RT), and 16 patients underwent salvage total laryngectomy for an RT failure, with 3 of them also receiving additional postoperative RT. All patients used prosthetic tracheoesophageal speech. Seventeen patients continuously used a regular HME, and 1 patient used an automatic speaking valve (ASV). Four of the regular HME users frequently switched to an ASV. The median ASV use per day was 16 hours (range, 1–24 hours). Median HME use per day was 22.0 hours (range, 10-24 hours). All but 3 patients used their HME(s) 24/7: 1 patient regularly (4/7 days) used a Tracheofix stoma cover, and 3 patients sometimes (1 day per 2 weeks) used a Buchanan protector to recover from skin irritation caused by the HME adhesive. Figure 4 shows the stoma cover situation at baseline and at the end of the 4-week trial for all patients.

Fig. 4 Pictures taken at the baseline and the 4-week consultation, grouped according to patient number (*N*=18; 2 baseline and 1 end-of-study pictures are missing).

Baseline use of heat and moisture exchanger stoma attachments and additional stoma covers

Twelve patients used a stoma adhesive all day, 4 alternated between adhesive and a LaryTube or LaryButton, whereas 2 patients used a LaryTube or LaryButton all day. Eight patients reported the additional use of a scarf, and 3 the use of their regular clothes (for example, a turtle neck), whereas 7 reported to never use anything else to cover the HME/stoma. Regarding the duration of additional stoma cover use, 5 patients reported to always using a stoma cover, all for cosmetic reasons and, in 2 cases, also for increased comfort ("less cold"), and 6 patients reported occasionally using additional cover, mostly for cosmetic reasons as well, but sometimes for extra protection in wintertime. Reasons for the 13 patients to only occasionally (6 patients) or never (7 patients) use an additional stoma cover were (more options per patient possible): cover have feeling of dyspnea (*n*=4), cover got wet (1), cover did not look good (1), unnecessary (6), too hot (2), made stoma cleaning more difficult (1), and string around neck irritated (1).

Adherence to protocol

At 4 weeks follow-up, all patients came in for their final assessment. Thirteen patients (72%) completed the study as intended. Of the remaining 5 patients, 2 used the Buchanan protector in combination with the HME for 2 weeks, because they did not want to discontinue ASV use, and 2 patients used the Buchanan protector without the HME for 2 weeks, because they misunderstood the assignment, and the fifth patient stopped after a couple of days of Buchanan protector use, because he needed a LaryTube to prevent his stoma from shrinking. This last patient also did not answer all the follow-up questions (data reported missing when applicable).

Preference and practical aspects

The practical aspects reported in relation to stoma cover use are summarized in Tables 2 and 3. As can be seen, significantly more problems were reported in the Buchanan protector-only week. An unpleasantly wet and dirty Buchanan protector and problematic stoma occlusion, voicing, and speaking were reported by 12 to 14 patients in the Buchanan protector only week and by 3 patients or fewer in the Buchanan protector + HME week. Increased coughing and mucus occurred in 7 patients in the Buchanan protector–only week, and only 1 patient in the Buchanan protector + HME week. Buchanan protector washing was needed considerably more frequent in the Buchanan protector–only period, with a median of every 24 hours as compared to 60 hours in the Buchanan protector + HME

week. The only positive aspect for Buchanan protector-only was the level of skin irritation with 5 patients reporting less skin irritation. More details can be found in the Appendices.

Table 2 Practical aspects and symptoms reported for the 2 Buchanan protector combinations "Buchanan protector + heat and moisture exchanger" and "Buchanan protector only."

Aspect/symptom (no. of patients answering the questions)	Buchanan protector + HME No. of patients	*p* value Buchanan protector + HME vs HME	Buchanan protector only No. of patients	*p* value Buchanan protector only vs HME
Coughing (increased compared to regular HME use)	0	1.000	4	.046*
(Questions 3–6; *N* = 17)				
Mucus production (increased compared to regular HME use)	1	.317	5	.025*
(Questions 7–10;*N* = 17)				
Skin irritation (less compared to regular HME use)	0	1.000	5	.025*
(Questions 19-22; *N*= 16)				
Stoma occlusion (more difficult compared to regular HME use)	3	.083	14	.000*
(Questions 23-24; *N* = 15)				
Voicing (more difficult compared to regular HME use)	2	.157	13	.000*
(Questions 25-26; *N* = 15)				

Abbreviation: HME, heat and moisture exchanger.

Questions allowing comparison between all 3 stoma cover conditions (including HME only). Although the questions allowed for patients to report less coughing, decreased mucus, etc., compared to regular HME use, these outcomes did not occur and are subsequently not represented in the table.

* One-Sample Wilcoxon signed rank test.

Table 3 Buchanan protector specific questions compared between the 2 Buchanan protector combinations.

Aspect/symptom (no. of patients answering the questions)	Buchanan protector + HME No. of patients	Buchanan protector only No. of patients	*p* value
Buchanan protector getting wet	0	12	.001*
(Questions 11–14; *N* = 16)			
Buchanan protector getting dirty	2	12	.002*
(Questions 15–18; *N* = 16)			
Buchanan protector washing needed, median hours	60 h	24 h	.028*
(Question 27; *N* = 16)			
Buchanan protector washing problematic	6		
(Question 28; *N* = 15)			

Abbreviation: HME, heat and moisture exchanger.

* One-Sample Wilcoxon signed rank test.

Future preferences

Patient's future preferences were addressed in the final 3 questions (question 29–31) of the study-specific questionnaire. For question 29 ("Which type of stoma cover do you intend to

use in the future?"), 9 patients reported that they would keep using an HME only, whereas 9 patients indicated they would use an additional stoma cover alongside the HME. Patient's reasons for this (question 30) can be found in Table 4. The answers showed a negative attitude toward the Buchanan protector–only use and were quite similar to the answers given at baseline to questions 1 and 2 (data not shown for brevity). Nighttime Buchanan protector use especially was considered dispreferable and several patients reported that, when they woke up, the Buchanan protector was often out of place. Because none of the patients had a preference for Buchanan protector-only, question 31 was not answered by any of them. Finally, comparison with baseline preference shows that 9 of the 11 patients who used an additional stoma cover beforehand (5 always, and 6 sometimes), indicated they would continue to do so in the future, whereas 2 indicated that they would only use an HME. The photographs taken at baseline and at 4 weeks were in line with the preferences expressed.

Table 4 Reasons for not wanting to use a Buchanan protector in the future, including "other reason(s)."

Reason not wearing Buchanan protector in future	No. of patients
Buchanan protector causes feeling of dyspnea	9
Buchanan protector is getting wet	6
Buchanan protector does not look good	11
Speaking/occlusion stoma more difficult	14
Less easy in everyday use	14
Other reason	13
Fabric straps are not easy to wrap around the neck/uncomfortable	4
Buchanan protector is turning around while sleeping	2
Dry cough	1
More viscous mucus	1
What to do when taking a shower?	1
More coughing	1
More mucus	1
To prevent air leak, Buchanan protector has to be wrapped uncomfortably tight around neck	1
Unhygienic	1
Scarf is lighter	1
Buchanan protector is too warm	1

Note: Question 30 of the study-specific questionnaire; for questions 29 and 31 see text; more options per patient is possible.

DISCUSSION

For a long time, stoma cloths were standard of care for postlaryngectomy stoma and airway protection in most countries. Undoubtedly, substitution of lost upper respiratory tract air conditioning was already considered necessary several decades ago, as postoperative

humidification would be applied and stoma covers would be routinely prescribed. Patient acceptability of those measures was, although, never studied. With the arrival of HMEs for laryngectomized patients in the early 1990s, the lack of evidence for the standard of care was deemed unimportant, because of the highly significant positive effects HME devices were found to have, even in patients who already use standard of care stoma cloths.[5,7–11] With additional technical improvements, patient acceptability and compliance of the HMEs increased further,[16,17] reducing stoma cloths as a means to provide humidification to second choice in many countries. Currently, stoma cloths are used for cosmetic reasons or to recover from skin irritations that can be caused by stoma adhesives.

Because of the technical difficulty in developing validated test equipment, the basic physics of humidity and temperature exchange in HMEs could only be established in the past few years.[22,23,27] One of the main early findings was that, although the HMEs tested generated a significant increase in humidity, there would at the same time be a slight but significant decrease in temperature right behind the HME at the end of inspiration because of evaporative cooling.[28,29] This finding pointed to an insufficient thermal capacity, which in the subsequent generations of HMEs was addressed by incorporating additional material and hygroscopic salt. This resulted in increased water entrapment, improving both the thermal and humidifying capacity of the HME, and diminishing the issue of temperature drop under room temperature conditions.[30] Thus, interestingly enough, the clinical evidence for the beneficial effects of HMEs preceded the physical[26,27] and physiological[31,32] evidence for those effects considerably.

Thermal capacity is presently the main limiting factor for humidifying capacity while keeping the HME small enough to be cosmetically acceptable.[33] Stoma cloths are much larger and, therefore, potentially have a good HME effect. Indeed the study by Quail et al[18] showed a large humidifying effect of several stoma cloths tested, but the validity of the results may be questioned, because they failed to measure the proven humidifying capacity of the tested HMEs.[19,20] Our study confirms that stoma cloths (and shawls etc.) can have a substantial humidifying effect. The humidifying capacity of a dry Buchanan protector without leaks is even larger than the capacity found by Quail et al[18]: the 13.7 mg/L in our study against about 8.3 mg/L for Quail et al[18] (this value had to be calculated as it is not given in the article, see Appendix 2). In our study, a wet stoma cloth, which is heavier and, thus, has a larger thermal capacity, was (not unexpectedly) found to have an even larger humidifying effect, which was not observed by Quail et al.[18] The lower values in their study may have been due to small leaks around the cloths and/or to humidity loss because of condensation in the nonheated suction tube. The values in our study are probably slightly underestimated as well, due to the somewhat larger dead space behind the HME in the

mannequin ex vivo setup. Indeed, the humidifying capacity of the HME-XM was slightly lower than previously found (6.5 instead of 6.9 mg/L).[7,25]

The question remains, however, whether the measured humidifying capacity of stoma cloths really is at the patient's full disposal in clinical practice. In view of the significant clinical benefit earlier established for HMEs in populations routinely using stoma covers,[5,7] this is quite doubtful. Both the ex vivo and the clinical study offer likely explanations.

The ex vivo study shows the impact of leakages, which enable unconditioned air to bypass the cloth. A slight lifting of the stoma cover leads to an immediate drop (from 13.7 to 8.5 mg/L at 0.5 L tidal volume) of the humidifying capacity, as shown in Figure 3 and Table 1. The leak in Figure 1D is probably small compared with the leaks that will occur in everyday life as a patient moves (and certainly during sleep). The clinical study shows a rather low patient acceptance of stoma cloths if worn without an HME, because of a variety of disadvantages reported (see Tables 2, 3, and 4), making it likely that patients will take off the stoma cloth too often. These 2 drawbacks are plausible explanations for studies on HMEs showing a clinical improvement over stoma cloths.

An interesting observation is that, although none of the patients preferred stoma cloths only, half of them still prefer covering the HME (eg, with a turtleneck or their clothes for aesthetic reasons). Again, the combination of the ex vivo study and the clinical study offers an explanation for this apparent paradox. The clinical study showed (see Table 2, 3, and 4) that with the Buchanan protector alone the vast majority of patients complained about wetting of the cloth. This complaint was completely absent in the combination with the HME. At first sight, one might conclude from the ex vivo study that (Table 1) the HME hardly has any function in the combination, because the Buchanan protector + HME combination is only slightly better than the Buchanan protector-only (humidification 14.5 vs 13.7 mg/L). However, the HME has an additional relevant effect in this combination: it prevents loss of water,[34,35] and keeps that water inside the confines of the trachea. Therefore, with the Buchanan protector + HME combination, the stoma cloth and the patient's clothes in daily practice remain dryer and the cloth requires less frequent cleaning. In addition, the combination allows for better humidifying capacity than the HME only (assuming the Buchanan protector is worn without leaks).

Adding a stoma cloth may also be beneficial during extreme situations, such as dry and cold winter conditions, as the combination has a considerably higher performance than the HME only (humidification 14.5 vs 6.5 mg/L), provided that the breathing resistance does not become too high. Furthermore, a scarf or shawl makes sense considering the performance of the woolen shawl only (10.7 mg/L). Scarfs or shawls made from natural

materials are probably to be recommended because natural materials in general have a good moisture affinity. This is also seen in our study: baby bib (cotton) and shawl (wool) perform much better than the surgical mask or Tracheofix.

Patient recruitment for the study was a challenge, with only 18 of 91 patients (20%) who received an invitation letter being willing or able to participate. The fact that all were using an HME might have biased their willingness to change their daily routines. However, all patients were highly motivated to try something new for potential further improvement of their pulmonary status, which might have compensated (partly) for potential bias in this respect.

Nevertheless, limitations of the clinical study obviously were the relatively low number of patients, and that the study population (by necessity restricted to voice prosthesis and HME/ASV users), probably has a lowered acceptability for stoma cloths, factors that have negatively skewed the results against the cloths. This possibly underestimates their value, and makes the results not fully applicable for esophageal and electrolaryngeal speakers, because some of the issues patients had concerned ease of voicing. However, the issues with the Buchanan protector becoming uncomfortably wet and soiled, and the increase in mucus would still apply to esophageal and electrolaryngeal speakers as well. It seems worthwhile, therefore, to address these aspects in a larger cohort, also including nonvoice prosthesis and non-HME users. Stoma cloths might be more acceptable to patients not yet habituated to an HME, and/or not applying tracheoesophageal prosthesis voicing. It has to be stressed that the stoma cloth used in this clinical trial provides more than just a cosmetic cover and protection against foreign bodies: it potentially has a good humidifying capacity. If patients without access to HMEs are able to wear the stoma cloth properly and accept the wet cloth against the skin, they very likely will experience better pulmonary health than without such a stoma cover at all. With respect to further technical developments, it has to be kept in mind that the solution for the main Buchanan protector issues in such patients (air leakages and wetting of the skin), likely the reasons for the limited effect of stoma cloths in the clinical studies in the past,[5,7] will probably lead to the "reinvention" of the HME, which completely eliminates these 2 issues. Maybe the use of different materials and designs (for instance, a stoma cloth with an inner water repellent layer and a fitting design) might further improve cloth-like stoma protection, but then costs might become an issue again.

In conclusion, this study shows that HMEs are the preferred choice of patients. Although a well-worn stoma cloth has a good humidifying capacity, patient acceptability in the present patient cohort seems to be low. A stoma cloth in addition to an HME can offer

additional humidification in extreme conditions and aesthetic benefits for some patients. If an HME is not an option, for instance (temporarily) because of skin irritation, a stoma cloth is a valuable alternative provided air leaks are avoided. If HMEs or commercial stoma cloths are too expensive, a simple alternative, such as a shawl or baby bib (again, worn properly without leaks), offers some protection and is better than no HME/stoma cover.

Appendix 1 . Study-specific structured questionnaires, and diary (translated from Dutch).

I. Baseline measurement (+ picture of neck to document "stoma-cover habit" of patient):

Date: dd – mm – year Patient number:

Age: dd – mm – year In years:

Sex: male – female total laryngectomy date: dd – mm – year

RT pre or post-total laryngectomy:pre – post Voice prosthesis type and size

Stoma cover (circle what is applicable): HME XtraMoist – XtraFlow – Normal – HiFlow - Micron – FreeHands (1 hours per day: . . ..) – other . . ..; HME day and night – only daytime – only nighttime; number of HMEs per day: . . ..; Adhesive preference: . . ..; number of adhesives per day: . . ..; Lary-Tube; LaryButton.

1. Besides your HME, do you use other means of covering your stoma?
   a. Yes
   b. Occasionally
   c. No, continue to question 4
2. If yes, how do you cover your stoma?
   a. With Buchanan bib
   b. With turtle neck
   c. With shawl
   d. With cloths
   e. Otherwise . . ..
3. If yes, why (more answers possible)?
   a. Provides extra comfort
   b. Breathing air less dry

c. Breathing air less cold
d. Cosmetically better
e. Other . . ..

If yes: questionnaire is completed.

4. If no or occasionally, why not or not always (more answers possible)?
   a. Causes feeling of dyspnea
   b. Gets wet
   c. Wet cloths are uncomfortable
   d. Irritating skin
   e. Does not look good
   f. Other . . ..

II. End of study (+ picture of neck to document "stoma-cover habit" of patient).

Date: dd – mm – year Patient number:

1. Which stoma cover method during these 2-week trials do you prefer?
   a. HME only, like before
   b. HME and Buchanan protector together
   c. Buchanan protector-only
   d. Other . . ..
   e. No preference
2. Can you indicate why? . . ..
3. Did you notice any difference in coughing in the past weeks?
   a. Yes
   b. No, continue to question 7
4. If yes, how
   a. More coughing
   b. Less coughing
5. If more coughing, during which period?
   a. HME only

b. HME and Buchanan protector together
c. Buchanan protector only

6. If less coughing, during which period?
   a. HME only
   b. HME and Buchanan protector together
   c. Buchanan protector only

7. Did you notice any difference in mucus production in the past weeks?
   a. Yes
   b. No, continue to question 11

8. If yes, how
   a. More mucus production
   b. Less mucus production

9. If more mucus production, during which period?
   a. HME only
   b. HME and Buchanan protector together
   c. Buchanan protector only

10. If less mucus production, during which period?
    a. HME only
    b. HME and Buchanan protector together
    c. Buchanan protector only

11. Does the Buchanan protector become wet during use?
    a. Yes
    b. No; continue to question 14

12. If yes
    a. With combination of HME and Buchanan protector
    b. With Buchanan protector only
    c. With both

13. If with both
    a. More with combination of HME and Buchanan protector
    b. More with Buchanan protector only
14. Is the Buchanan protector getting wet unpleasant for you?
    a. Very unpleasant
    b. Rather unpleasant
    c. A little unpleasant
    d. Not unpleasant
15. Is the Buchanan protector getting dirty during use?
    a. Yes
    b. No, continue to question 19
16. If yes
    a. With combination of HME and Buchanan protector
    b. With Buchanan protector only
    c. With both
17. If with both
    a. More with combination of HME and Buchanan protector
    b. More with Buchanan protector only
18. Is the Buchanan protector getting dirty unpleasant for you?
    a. Very unpleasant
    b. Rather unpleasant
    c. A little unpleasant
    d. Not unpleasant
19. Is the skin more or less irritated by wearing the Buchanan protector?
    a. More
    b. Less
    c. No effect; continue to question 23

20. If more or less
    a. More with combination of HME and Buchanan protector
    b. Less with combination of HME and Buchanan protector
    c. More with Buchanan protector only
    d. Less with Buchanan protector only

21. If with both
    a. More with combination of HME and Buchanan protector
    b. More with Buchanan protector only

22. Is this irritation unpleasant for you
    a. Very unpleasant
    b. Rather unpleasant
    c. A little unpleasant
    d. Not unpleasant

23. How does stoma closure work with the Buchanan protector covering the HME?
    a. Stoma closure is more difficult
    b. Stoma closure is easier
    c. Stoma closure is not more difficult nor easier

24. How does stoma closure work with the Buchanan protector without HME?
    a. Stoma closure is more difficult
    b. Stoma closure is easier
    c. Stoma closure is not more difficult nor easier

25. How does voicing work with the Buchanan protector covering the HME?
    a. Voicing is more difficult
    b. Voicing is easier
    c. Voicing is not more difficult nor easier

26. How does voicing work with the Buchanan protector without HME?
    a. Voicing is more difficult
    b. Voicing is easier
    c. Voicing is not more difficult nor easier

27. How long can you wear the Buchanan protector before it needs to be washed?
    a. In combination with HME: . . .. hours
    b. Without the HME also covering the stoma: . . .. hours

28. What do you think about having to wash the Buchanan protector?
    a. Not a problem
    b. A little bit of a problem
    c. Very problematic
    d. Too problematic

29. Which type of stoma cover do you intend to use in the future?
    a. HME only, like now
    b. HME in combination with Buchanan protector
    c. Buchanan protector only
    d. HME in combination with other stoma cover
    e. Do not know yet

30. If you do not want to use a Buchanan protector, what is/are the reason(s) for that (more answers possible)?
    a. Uncomfortable/too obstructive
    b. Uncomfortable/too wet
    c. Does not look good
    d. Voicing/stoma closure too difficult
    e. Daily use more cumbersome
    f. Other reason(s) . . ..
    g. Not applicable

31. If you do want to use a Buchanan protector, what is/are the reason(s) for that (more answers possible)?
    a. Breathing air feels warmer
    b. Breathing air feels more moistened
    c. Does look better
    d. Voicing/stoma closure easier
    e. Daily use easier

f. Other reason(s) . . ..

g. Not applicable

Thank you very much for your participation/cooperation. Compressed dairy and tally sheath to record stoma cover method, frequency of spontaneous coughing and deliberate mucus production, and to document any unusual events (eg, whether you have a cold or discoloration of your mucus), or any other peculiarities with respect to the use of the HME and/or Buchanan protector (* circle what is applicable).

Week 1/2/3/4* Date	Stoma cover (HME-only, Buchanan protector + HME, Buchanan protector only*	Spontaneous coughing	Deliberate mucus expectoration	Remarks
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				

Appendix 2 . Estimation of environmental corrected humidity values in Quail et al.[18]

Quail et al[18] do not provide values normalized to 5 mg/L, but clinical observations taken at different environmental humidities. The value of 8.3 mg/L at 5 mg environmental humidity was obtained from Figure 3 in their article, using the average value for the Buchanan protector/stoma cloth and the average value "without," as an estimate for the average environmental humidity. The formula used for normalization can be found in Appendix 1 of Ref.[23] of the present article.

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CHAPTER 9

General discussion and future perspectives

POSTLARYNGECTOMY CARE AND RECOVERY

Over the last 3 decades the treatment landscape for patients with advanced larynx and hypopharynx cancer has changed; there is an increase in the use of organ-preserving (chemo)radiotherapy ((C)RT), and a decrease in the use of primary surgery (total laryngectomy; TL) in these patients. Besides continued focus on functional and survival outcomes, it is also necessary to keep monitoring post TL-care, recovery and rehabilitation topics in this changed treatment landscape. This thesis describes and discusses these topics, both at an institutional and at a national level.

One of the first steps to recovery following TL is the timing of resuming oral intake. Worldwide there has been no consensus concerning timing of oral intake after TL. Many head and neck surgeons tend to delay oral intake until day 10-12 under the assumption that this prevents or limits the chance of pharyngocutaneous fistulization (PCF), one of the more serious postoperative complications. However, there is ample evidence that earlier oral intake is not related to PCF incidence and that there are more pros than cons for this practice (e.g. faster return to normalcy, lower costs), which also in other areas of alimentary tract surgery is common practice nowadays[1]. Therefore, in 2006 an early oral intake (EOI) protocol was introduced in the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL). To study if EOI indeed is successful and safe, a retrospective cohort study of 247 patients, who were laryngectomized between January 2000 and July 2012 was carried out. This study is described in **chapter 2**. We found that the protocol was adopted successfully; in the LOI group the median day of starting oral intake was day 11 (range 6-103) vs. day 3 (range 2-84) in de EOI group. With regards to the PCF incidence, the observed difference between the EOI group and LOI group (32% vs. 25%) was statistically not significant (p = 0.255) and no association was found between timing of oral intake and PCF (HR = 0.995; CI 0.98–1.01; p = 0.364). This suggests that EOI is a safe clinical practice and does not increase PCF formation. A review of Aires et al., including 8 studies (4 RCT and 4 cohort studies), supports this finding. These authors concluded that PCF rates were not increased in patients who receive oral intake < 5 days after TL compared to patient who receive oral intake > 7 days after TL and that other benefits of EOI should be kept in mind when deciding about the moment of resuming oral intake[2]. That EOI can be encouraging for patients, because they will have the feeling to return to normalcy more quickly is an important advantage of an EOI protocol. Furthermore, with an EOI protocol a nasogastric tube (NGT) (experienced as unpleasant by patients, irritating and sometimes damaging the nose and pharynx) can be removed quickly after TL leading to a shortened period of this tube stressing the pharyngeal suture line by its movements[3,4]. Additionally, EOI can possibly shorten hospital admission which leads to reduced costs and reduced

psychological stress of the patient. The only downside is that, if PCF is diagnosed at a later stage when oral intake already has started, its interruption will be disappointing and therefore this should be a discussion point in patient counseling. The argument to use a LOI protocol because of the potentially harmful effects of swallowing foods on the suture line can be downplayed by the fact that one can never prevent patients from swallowing saliva (also when using an NGT)[5]. In our study the median duration of hospitalization in the LOI protocol group was 20 days (range 12-115) vs. 21 days (range 2-147) in the group with EOI protocol (this difference was not significant). This difference can be explained by the fact that speech rehabilitation is initiated by a speech therapist on day 12-14 and patients are only discharged if speech rehabilitation is underway satisfactorily.

It should be noted that in the study period all patients were included, who underwent TL, if indicated with neck dissection and/or reconstruction, for primary or second primary treatment, salvage procedures, or for a dysfunctional larynx (after (C)RT). Thus, the results cover a consecutive and representative group of TL patients, in contrast to several other studies where only selected groups of patients were included[4-6]. All in all, this study shows that the decision to explore the possibility of changing our oral intake protocol from late (10-12 days postoperatively) to early (second day postoperatively) has worked out satisfactorily. However, it also has to be stressed that from its initiation intensive monitoring by clinical and nursing staff is mandatory to achieve acceptance for its implementation, as we also have described in this study.

PCF, as mentioned, is a serious complication after TL and can be a challenge patient and surgeon have to deal with. Given the increased patient morbidity, prolonged hospitalization, potential reoperations and costs, detailed knowledge of the incidence of PCF and its predictive factors is crucial[7]. In **chapter 3**, in a 10-year (2000-2010) consecutive cohort of TL patients in the NKI-AVL, we aimed to identify the overall incidence of PCF, and all relevant predictive factors for PCF. Oral intake was not studied again in this cohort, because we already assessed this factor in the almost completely overlapping 2000-2012 cohort, described in chapter 2. In this study we found an overall PCF% of 26%, which is substantial, but comparable to percentages reported in many other studies. As expected, the PCF% was the lowest for primary TL (17.1%). For salvage TL, TL after prior treatment for another HN malignancy, and TL for a dysfunctional larynx after (C)RT, we found incidences of 25.5%, 37.5%, and 44.0%, respectively. Higher incidences for these various salvage procedures are also in line with other studies and support the thought that PCF% have (slightly) increased in this era of increased use of organ preserving treatment modalities[7-11]. Elaborating on this, in this study previous CRT was found to be a predictive factor for PCF formation in contrast to RT as a single modality therapy. There are some other studies

were RT alone was also found to be a nonsignificant prognostic factor[12,13]. According to the multivariable analysis, other predictive factors for PCF were hypopharynx as index tumor, a low preoperative albumin level (< 40 g/L) and more-extended pharyngeal resection or pharynx reconstruction. Not surprisingly, these factors are identified as predictive factors by most authors[14-16]. It should be kept in mind that for albumin level different cutoff values are applied. Our cutoff value of 40 g/L was based on the values recently reported by Sherman et al[17]. Longer duration of surgery was also a significant predictive factor. However, this variable could possibly be confounded by other variables (e.g. (type of) reconstruction). A subgroup analysis showed that also in a non-reconstruction group a surgery time of > 240 minutes was associated with an increased PCF% (p=0.009). Prophylactic perioperative antibiotics and postoperative reflux therapy, also mentioned as possible predictive factors in the literature, could not be studied, since both are part of the standard clinical protocol in our center. In our univariable analysis we did not find neck dissection to be a possible predictive factor (p=0.882), and this is in line with the finding of Hasan et al[7]. Contrary to this, there are authors who did find higher PCF rates in patients who underwent a neck dissection[18,19]. Although surgical handling of tissues and suture techniques for closing the pharynx presumably are of importance we were not able to identify this as a predictive factor because the surgical reports were often not detailed enough. All in all, in order to reduce the incidence of PCF after TL many factors predictive for this complication cannot be influenced. Nevertheless, optimizing local wound healing by optimizing patient's preoperative nutritional status and condition (possibly leading to a higher albumin level), the use of well-vascularized reconstructive flaps, and reduction of surgery time as much as possible, are factors that can be influenced and potentially decrease PCF%.

PCF data usually come from single-institution series, which makes a valid interinstitutional comparison impossible. Such comparisons are important in view of improving quality by permanent feedback[20,21]. Therefore, we conducted a nationwide Dutch Head and Neck Society audit that did allow us to assess the magnitude of this problem in the Netherlands and to make detailed comparisons between the 8 participating centers. This study is described in **chapter 4.**

The overall PCF% of 25.9%, ranging from 9.6% to 37.1%, is comparable to figures reported in the literature and for the most equal to the PCF% found in chapter 3[7,11,16,22,23]. Factors predictive for PCF were prior (C)RT in combination with prolonged lead time to TL, near total pharyngectomy, selective neck dissection, radical neck dissection, previous tracheotomy, and BMI < 18. With use of this set of predictive factors we were able to calculate weighted PCF performance rates per center (actual PCF% in center X minus the predicted PCF% in center X) enabling us to make meaningful comparisons between

centers adjusted for case mix. In most centers, variation in PCF% could be explained by differences in the composition of the (less or more favorable) patient populations. Some exceptions were also found, i.e. in center A the predicted PCF% was higher than the actual PCF% (better performance than expected) and vice versa in center C the predicted PCF% (lesser performance than expected) was lower than the actual PCF%, meaning that not all differences were explainable with the multivariable prediction model. A possible explanation for the latter observation could be that the majority of head and neck surgeons in center C use a different, i.e. horizontal closure technique (this information was collected with use of a survey among the surgeons of the participating centers). It is somewhat disappointing to have to mention that this information and other surgical technical information was lacking in the many of the operation reports in all institutes and thus in our dataset. The negative effect of neck dissection on PCF% was also found by Dedivitis et al., who observed a 6% increase in PCF risk in patients, who underwent neck dissection[16]. The underlying meaning for this increased PCF% is that a neck dissection contributes to a further deterioration of the vascularity in the operation field, making the remaining tissues more susceptible for infection and prone to poor healing. Although we did not find this in our 10-year study described in chapter 3, in the national cohort covering 2 years of TL we found that both, selective and radical neck dissection, are associated with an increased risk on PCF formation. Because of this finding, the indications for neck dissection might have to be reconsidered. The most effective treatment approach for N0 neck patients with advanced stage larynx cancer and for N0 neck salvage patients (with prior N0/N+ neck) is still a topic of debate and the treatment of choice (no neck dissection/ node sampling or selective neck dissection) differs per center/ surgeon[19,24,25]. As an alternative for selective neck dissection, according to the Dutch National Guideline on Laryngeal Carcinoma, a node sampling procedure can be performed during primary TL for advanced laryngeal cancer without clinical or radiological evidence of positive lymph nodes, in case postoperative RT is planned. Furthermore, in case of salvage surgery with no evidence of regional metastases and no history of lymph node metastases, the choice for selective neck dissection should be weighed against this increased PCF risk and node sampling for frozen section can be considered. Obviously, in case of suspicion or evidence of metastatic lymph node involvement there is no choice, and neck dissection remains indicated. From this study, we can deduct several "take-home messages". First, our data show that variations in PCF% in the Dutch Head and Neck Society centers (in part) were explainable by the variations in the case mix. Apparently, there are centers that serve a patient population with a high risk of developing PCF and centers that serve a patient population with a lower PCF risk. Comparing these uncorrected PCF% can potentially offer a distorted interpretation and thus such comparisons can only be made after correction

for the risk factors as in our study. Furthermore, given the higher PCF risk in patients who underwent a neck dissection (both selective and (modified) radical), the choice for a selective neck dissection should be weighed against the higher PCF risk. In these cases, the option of node sampling for frozen section should be discussed. As not all differences are explained by the case mix variation, it might be wise for the surgeons with a high fistula rate, to critically look into their surgical techniques and consult the surgeons with a lower fistula rate.

POSTLARYNGECTOMY REHABILITATION

Besides resuming oral intake, resuming oral communication is the next major step in the rehabilitation program after TL. Voice and speech rehabilitation under the guidance of the speech language pathologist can usually start at day 12-14 postoperatively, if wound healing is sufficient (i.e. no occurrence of PCF). As discussed in Chapter 1, since its introduction in 1980, speaking by means of a voice prosthesis (VP) inserted in a tracheoesphageal puncture (TEP) tract has proven to be superior to esophageal and electrolarynx speech for most patients. With a high success rate, a moderate to good voice and speech quality and quality of life, TE prosthetic speech can be considered the gold standard for voice restoration in western countries nowadays[26,27].

In 2000, Op de Coul et al. published a study from the NKI-AVL, in which long-term results with use of VPs for vocal rehabilitation after TL were assessed[28]. To find out whether these positive findings obtained in the final two decades of the last century are still upholding in this era with an increasing necessity for salvage surgery, and with the development of several new generations of VPs, we assessed the postlaryngectomy prosthetic voice rehabilitation outcomes, using a dataset of 232 consecutive patients who were laryngectomized between 2000 and 2012 in the NKI-AVL (**chapter 5**). The median device lifetime for the regular VPs Provox 2 and Vega was 63 and 66 days, respectively. For the problem-solving ActiValve Light and Strong VP the median device lifetime was 143 and 186 days, respectively. Patients with a short device lifetime (less than 2 months) have an indication for these "problem solvers". Our data support the correct use of these special devices since we indeed found significant shorter device lifetimes in patients, who had been prescribed at least one ActiValve compared to patients never having required such a problem-solving device (54 days vs. 90 days; $p < 0.0001$). Transprosthetic leakage was the main reason for replacement (reported in 58% of all replacements). The exact reason for replacement was not reported in 12% of replacements, but the reporting in the medical records suggested that these were standard replacements for transprosthetic leakage too. This adds up to a 70% incidence of transprosthetic leakage, which is almost equal to the

73% incidence reported in the earlier study from our institute, which included patients who underwent TL between 1988 and 1999[28]. On the other hand, the observed median device lifetimes for the regular VPs (63 days and 66 days), which are similar to lifetimes reported in other recent studies, were lower compared to 89 days in our historical cohort[28-30]. Interestingly, when comparing this figure with the device lifetime of the subgroup of non-ActiValve users (90 days), there is no clinically relevant difference. A likely explanation for the decreased device lifetime found in our dataset compared to that reported in our historical cohort, is the higher number of TLs after prior (C)RT since 1990 (68% in the present study compared to 45% in the historical cohort). In accordance with this, we did find an association with the indication for TL, with primary TL patients having a longer device lifetime than salvage TL patients. The fact that, in our study period anterograde replacement was standard of care and uncomfortable retrograde placement became a rare, more or less obsolete technique, can also be an explanation for the decreased lifetime (patients' request for replacement with minor leakage could be increased)[27,31].

Another interesting observation in this cohort was the finding that almost half of the patients experienced TEP tract-related problems and that patients ever needing an ActiValve had a significant higher risk for having this problem. This suggests that in some patients a shortening of the device lifetime, which was the indication for using an ActiValve in the first place, in fact is also an indication to search for causative factors of TEP tract-related problems, i.e. reflux and pharyngeal stenosis, and that there thus might be an indication for starting PPIs and/or dilatation treatment(s).

Finally, much to our surprise (Dutch patients live relatively close to the hospital), and actually triggered by a question of one of the reviewers of the manuscript, we observed a relation between longer travel/ driving time to the hospital and longer device lifetime for the standard VP. This effect, also found in an Australian study of Hancock et al. (with much longer travel distances to the hospital), was more profound in the TEP tract-related indications for replacements, which might suggest that patient recognize these TEP tract-related complications less easily, or at least tend to delay their hospital visit longer[32]. With this information in mind, we suggest other authors to include the 'distance to the hospital component', in their prosthetic voice rehabilitation studies. In total 93% of the patients kept their VP long-term, also due to the technological improvements (e.g. the ActiValve VPs). From an institutional perspective, it is safe to conclude that, despite the increased use of CRT upfront, prosthetic voice rehabilitation is still a highly successful and manageable method to restore oral communication after TL.

To compensate for the functional loss of the upper respiratory tract and to prevent and/ or treat pulmonary problems in TL patients, 24/7 use of a heat and moisture exchanger (HME) has proven to be effective[33,34]. The issue an HME does not solve is that manual occlusion with a finger remains necessary for the diversion of pulmonary air into the esophagus in order to be able to speak with a VP. To overcome this drawback of TE speech, several automatic speaking valves (ASVs) enabling handsfree speech have been developed[35-38]. An important finding in several studies evaluating these devices (i.e. the FreeHands study of Op de Coul et al.), is the unpredictable (airtight) seal to the skin of the adhesives needed for the application of an ASV (and HME) in front of the stoma[36,37,39]. Considering the relatively low success rates with handsfree speech reported in the literature[26,40-44], there is room for improvement both with respect to the technical aspects of the ASV and regarding the adhesive properties of the adhesives, the topics studied in chapter 6 and 7.

With respect to handsfree speech, we conducted a prospective, multicenter, clinical feasibility study evaluating a new ASV, the Provox FreeHands FlexiVoice, which is described in **chapter 6**. This new device has the possibility to use both automatic occlusion and manual occlusion (an option which can be very helpful when the fixation of the adhesive fails), as well as an effective and convenient coughing mechanism (the membrane occluding the breathing opening is easy to push back when it has popped out when coughing). This study in a convenience sample of 40 TL patients (36 male and 4 female) from two tertiary care centers, shows that the daily use of handsfree speech increased from 20% (8/40) at baseline to 37.5% (15/40) at 26 weeks follow-up, with 10 of the original 13 handsfree users switching to the new ASV. Moreover, besides the original 5 non-daily handsfree users there were 5 additional non-daily users for a total of 10 patients (12.5% at baseline compared to 25% at 26 weeks), who used/ converted to the new ASV. For 63% of the patients the new ASV was a welcome option, whereas 27% of patients remained fully dependent on finger occlusion. At the end of the study period daily ASV users applied the device on average for 12.64 hours, which means that they apply the device for most of the daytime (ASVs are in general replaced by an HME during nighttime)[36,37]. Non-daily users applied the ASV after 26 weeks on average for 3.76 hours daily, mostly only at special occasions. The results of Lorenz et al (2006) with the FreeHands device in 24 patients with a similar follow-up time as the present study (6 months), are quite comparable with 42% daily users and 29% non-daily users[37]. However, the mean number of hours in the daily users, just like in the Op de Coul study, was also lower (8.4 hours) than with the new ASV[36]. Our data support that it is quite likely that the new features/ adaptions of this medical device as described above have contributed to the increased proportion of patients using handsfree speech. Furthermore, improved adhesives with a more stable and more anatomical shaped conical based, which were frequently used in patients included in this

study, could be another reason for this increased use[42]. All in all, this new ASV seems a valuable addition to the armamentarium of the health care providers to increase the numbers of handsfree VP speakers.

With respect to the relevance of adhesives for successful HME use and handsfree speech, a prospective clinical trial on the evaluation of the Provox StabiliBase OptiDerm (SBO) was conducted (see **chapter 7**). In this study we included 27 males and 5 females, of whom 9 patients underwent primary TL and 23 salvage TL. This new adhesive essentially is a combination of stable conical base plate of the StabiliBase, and a hydrocolloid (skin friendly) adhesive, as known from the OptiDerm (OD) adhesive[42]. In this study, the SBO turned out to be a suitable adhesive for a subgroup of patients only. Twenty-three percent preferred the SBO or a combination of the normally used adhesive with the SBO. The subgroup consists of patients who were using StabiliBase because of its stable base as their main adhesive but needed a more skin friendly adhesive as an alternative (e.g. because of a sensitive skin). The device lifetime of the SBO was somewhat better than that of the OD, with 15 patients reporting an increased device lifetime with the SBO of 19.60 hours as compared to the OD of 14.47 hours. This difference of 5 hours made it possible for those patients to replace the patch only once per 24 hours. Dirven et al. described a roughly 1.8 times longer median device lifetime of the standard StabiliBase compared to the device lifetime of the SBO established in our study[42]. The most important conclusion of this study is that the evaluated adhesive (SBO) is a valuable addition to the arsenal of devices already available. It further "customizes" the options laryngectomized patients already have for peristomal attachment of medical devices for rehabilitation purposes.

As already mentioned, after TL the functional loss of the upper respiratory tract has to be compensated for and 24/7 use of an HME has proven to be effective[33,34]. Recent advances in design, and technical layout have significantly improved the humidifying capacity which however is still not up to the level of the intact upper respiratory tract[45]. The main limiting factor for further improvement of the humidifying capacity of HMEs is the volume restrictions of functional and cosmetically acceptable HMEs. Previous studies have shown that clinically relevant HME effects are obtained in patients regularly using a stoma cloth. In theory, these stoma covers (bibs) could have a relevant humidifying effect as well, because of their potentially larger water exchange surface area. In **chapter 8** we therefore studied the place of bibs in pulmonary rehabilitation armamentarium of TL patients by means of an ex vivo test and a clinical cross-over study. In the first part of this study we found a substantial humidifying effect of stoma cloths and this effect (when using a stoma cloth without leaks) was even larger than earlier reported in the literature by Quail et al[46]. Furthermore, we found that wetting the stoma cloth further increased the

humidifying effect, contrary to that earlier report[46]. The most important reason for these discrepancies probably is the design of the equipment these authors built on the basis of our earlier research[47]: there was no condensation prevention technology incorporated in the tube sampling air from the trachea. This causes an unpredictable humidity loss due to condensation in that non-heated suction tube, making measurements quite unreliable, as documented in earlier studies from the NKI-AVL[47]. We also assume that in part these lower values are caused by air leaks around the stoma cloth, which are more likely to occur in the dynamic patient set-up than in the static in vitro test configuration. Our in vitro study indeed showed that small leaks enabling unconditioned air to bypass the cloth led to an immediate drop (from 13.7 to 8.5 mg/L at 0.5L tidal volume) of humidifying capacity.

The second, clinical part of the study showed a rather low patient acceptance of stoma cloths used without an HME, supported by a variety of disadvantages reported by the patients (more difficulties with stoma occlusion for voicing and the stoma cloths getting uncomfortably wet and fouled). It is likely that due to these disadvantages of stoma cloths, patients will take off these devices too often. It was interesting to note that half of the patients preferred to cover their HME with stoma cloths, because of cosmetic reasons. This might also be related to the finding that the best humidifying capacity in the ex vivo testing was achieved with the combination of the best available HME covered with a stoma cloth, something to keep in mind when optimal humidification is required such as in winter time. It is also important to note that the patients included in our study were all tracheoesophageal speakers using HME and/ or an ASV, which possibly lowers the acceptability of stoma cloths, and this could have biased the results. These results thus might be not fully applicable for electrolarynx and esophageal speakers. In conclusion, patients included in our study, conducted in a western country in a tertiary comprehensive cancer center, prefer using an HME for pulmonary rehabilitation and protection. When an HME is not an option (e.g. because of financial constraints or skin problems) a stoma cloth is a valuable alternative, especially when air leaks are avoided. Nevertheless, in non-western countries, where commercial stoma cloths can be too expensive, a simple shawl or non-medical stoma cloths, again worn without leaks, will offer protection and humidification of the upper respiratory tract and is still better than not covering the stoma.

FUTURE PERSPECTIVES

Continuous monitoring/ auditing of clinical events and outcomes remains important. It forms the basis of solid clinical practice (described in medical guidelines), possibly contributing to transparency and improvement of quality of healthcare. In line with this, in 2014, the DHNA (Dutch Head and Neck Audit) has been set up by the Dutch Head and

Neck Society. Automated data collection, data set generation and analysis, necessary for these audits often is an illusion and therefore, in daily practice, support of professional parties (such as DICA) is still necessary. In chapter 2, 3, 4 and 5 we conducted delineated restricted audits where data has been collected by one/ two researcher(s) (in chapter 4 with sufficient onsite support, of course). For chapter 4 (nationwide PCF audit), this has costed an estimated 250 working hours, approximately 1,935 travel kilometers, and 10 overnight stays. When electronic patient files are set up in a way that all relevant data can be extracted "with one mouse click", audits can be conducted much easier and outcomes will be available much sooner and at a lesser expense. Furthermore, chapter 4 show that there is a lot to gain with more detailed, structured reporting of surgical details. Therefore, we recommend that all head and neck surgeons explicitly describe all relevant surgical details extensively in their electronic, standardized, preferably non-narrative operation reports. This implies that e.g. with regards to the pharyngeal closure technique, this critical aspect of the surgery is no longer reported as "pharynx closure was performed in the usual manner", certainly when there is no written protocol about that "usual manner".

As described in chapter 3, EOI did not lead to shortened hospital admission. In order to gain the benefits of EOI in this respect, clinical speech rehabilitation as initiated by the speech therapist on day 12-14 should be replaced by an at least as intensive outpatient program. Whether this is feasible and results in similar success rates in terms of patient recovery and rehabilitation, this preferably should be addressed in a multicenter RCT. Such a study was already proposed by A.J. Timmermans ((co-)author) of studies described in chapter 2 and 3) in 2016, but still is pending.

One of the interesting findings of the study described in chapter 5 is that we found a significantly higher risk in patients ever needing an ActiValve for also having TEP tract hypertrophy/infection. The consequence for daily practice is that shortening of the device lifetime (< 2 months) should be considered as a warning sign for future problems and starting point for further diagnostics and treatment in these patients. The two main underlaying causes for TEP tract problems are reflux and pharyngeal stenosis, and, therefore, initiation of PPIs and/ or dilatation treatment(s) should be initiated timely, when appropriate. Furthermore, the option for using a VP with an additional enlarged esophageal flange, recently studied by Petersen et al. should be kept in mind as a new problem solver[48].

In chapter 6 a new ASV is discussed. A useful feature of this device is that it has the option to also be used manually (as a normal HME) when necessary. With this manual closure option ASV training could potentially be introduced earlier in the rehabilitation program,

making ASV use a more self-evident part of restoration of oral communication. This new ASV study and the study described in chapter 7, also show once more that difficulties with attachment of the adhesive to the skin are still limiting successful handsfree speech and that there is no one size fits all solution for peristomal attachment. An external supportive device can be a welcome addition in this respect[39]. All chapters concerning postlaryngectomy rehabilitation show that there are still quite some possibilities for further (technical) innovations of medical devices for laryngectomized patients. This is not surprising because of the wide anatomical variations of the stoma area of these patients. It seems that there is need for both (affordable) personalized, 3D printed medical devices. At this time, in the NKI-AVL medical technical students, PhD students and postdoctoral researchers are working on projects that fall within this scope. Lastly, studies on physical modeling to further improve humidifying capacity of HMEs, despite their inherent restrictions in volume, are under way.

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SUMMARY

Over the last 3 decades the treatment landscape for patients with advanced larynx and hypopharynx cancer has changed; there is an increase in the use of organ-preserving (chemo)radiotherapy ((C)RT), and a decrease in the use of primary surgery (total laryngectomy; TL) in these patients. Besides continued focus on functional and survival outcomes, it is also necessary to keep monitoring post TL-care, recovery and rehabilitation topics in this changed treatment landscape. This thesis describes and discusses these topics, both at an institutional and at a national level. **Chapter 1** provides a general introduction into the timing of resuming oral intake, incidence of pharyngocutaneous fistulization (PCF), a serious post-operative complication and its predictive factors, rehabilitation aspects such as voice and pulmonary rehabilitation and the role of some supportive medical devices in this respect.

With respect to postlaryngectomy care and recovery, there are two issues that have attracted somewhat more attention in recent years. The first is the timing of postoperative oral intake. The second the seemingly growing problem of pharyngocutaneous fistulization (PCF), attributed to the increasing incidence of salvage TL after previous unsuccessful (C)RT, or TL to solve dysfunctional larynx problems after organ preservation therapy. These topics are described in **Part I,** 'Postlaryngectomy care and recovery'. Many head and neck surgeons tend to delay oral intake until day 10-12 because that is assumed to prevent or limit the chance of PCF. However, the evidence for this assumption is quite weak, whereas there are several arguments in favor of early oral intake (EOI). In **chapter 2** a retrospective cohort study in the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL), consisting of 247 patients, was conducted to address the effect of the moment of resuming oral intake on PCF. From early 2000 until mid 2006 a late oral intake (LOI) protocol (start with oral intake at postoperative day 10-12) was used and from mid 2006 until mid 2012 an EOI protocol (start with oral intake at postoperative day 2-4) was applied. The LOI group (N=140) and EOI group (N=107), were comparable in terms of sex, age, origin of tumor, and TLE indication. ASA score was slightly more favorable in the LOI group than in the EOI group (p=0.047). This difference did not correlate with the occurrence of PCF (p=0.417). 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), which implies that compliance with the oral intake protocols was good. The difference in PCF% between the two groups (25% for LOI vs. 32 % for EOI) was statistically not significant (p=0.255). This study suggests that early resuming of oral intake after TL is safe and does not increase PCF.

Subsequently, in **chapter 3,** an institutional retrospective chart review of 217 consecutive patients treated with TL between 2000 and 2010 was performed to assess predictive factors for the development of PCF. Overall, 57 of 217 (26.3%) patients developed PCF (26.3%). The PCF% after primary TL was 17.1% (12 of 70), after salvage TL 25.5% (25 of 98), after TLE for a second primary was 37.5% (9 of 24), and after TL for a dysfunctional larynx 44.0% (11 of 25). Predictive factors 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), previous (C)RT (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). Not surprisingly, these factors are identified as predictive factors by most other authors. The median duration of survival was 30 months (95% CI, 17.5 to 42.5) and the 2-year overall survival rate was 54%. The occurrence of PCF did not influence the survival rate.

PCF data usually come from single-institution series, which makes a valid interinstitutional comparison impossible. Such a comparison of complications would be relevant to gain better insight in the quality of care for patients undergoing TL on a national level, but can also lead to changes in treatment protocols in individual institutes. Thus, in **chapter 4** a PCF audit in the 8 principle Dutch Head and Neck Centers (DHNC) is presented. Three hundred and twenty-four patients, who underwent a TL in a 2-year period (2012 and 2013) were included in this retrospective chart review. Overall PCF%, PCF% per center and factors predictive for PCF were identified. With use of the set of predictive factors weighted PCF performance rates per center were calculated (actual PCF% in center X minus the predicted PCF% in center X) and thus meaningful comparisons between centers, adjusted for case mix, could be made. A survey among head and neck surgeons of the participating centers was carried out to provide additional data. The overall PCF% was 25.9. The multivariable prediction model revealed that previous treatment with (C)RT in combination with a long interval between primary treatment and TL, previous tracheotomy, near total pharyngectomy, neck dissection, and BMI < 18 were the best predictors for PCF. PCF% varied quite widely between centers, but for a large extend this could be explained by differences in the composition of the (less or more favorable) patient populations. On the other hand, not all differences were explainable with the multivariable prediction model; e.g. in one center there was a lesser performance than expected. A possible explanation for this could be the use of a different (i.e. horizontal) closure technique, information that was collected through a survey among the surgeons of the participating centers. It is somewhat disappointing that this and other surgical technical information was lacking in many of the operation reports in all institutes and thus in our dataset. The correlation between (modified) radical neck dissection and (increased) PCF risk suggest that these

surgical procedures only should be performed when really unavoidable, and that, if permissible, the option of node sampling for frozen section should be favored.

In **Part II,** voice restoration and pulmonary rehabilitation aspects after TL are presented. A retrospective cohort study including all patients laryngectomized between 2000 and 2012 with a voice prosthesis (VP) in the NKI-AVL is described in **chapter 5**. Median device lifetimes of the standard Provox2 and Vega VPs are 63 and 66 days, respectively, and for the problem-solving ActiValve Light and Strong VPs 143 and 186 days, respectively. In multivariable analysis, salvage TL and TL for a dysfunctional larynx (compared to primary TL) were associated with a shorter device lifetime. Transprosthetic leakage was the main reason for replacement and was reported in 70% of all cases, which is almost equal to the 73% incidence reported in the earlier study from the NKI-AVL, which included patients who underwent TL between 1988 and 1999. Almost half of the patients (48%) occasionally experienced tracheoesophageal puncture (TEP) tract -related problems, and this concerned 12% of all VP replacements. Patients once needing an ActiValve VP had a significant higher risk for having this problem. This suggests that in some patients a shortening of the device lifetime, which was the indication for using an ActiValve in the first place, in fact is also an indication to search for causative factors of TEP tract-related problems, i.e. reflux and pharyngeal stenosis. Compared to historical cohorts, and in line with recent literature, device lifetimes of regular Provox2 and Vega voice prostheses have decreased, most likely due to the currently larger percentage of post (C)RT TLs. Complications are not occurring more frequently, but affect more patients. Nevertheless, the clinical reliability and validity of prosthetic voice rehabilitation is still sound.

Chapter 6 describes the results of a multicenter short- and long-term clinical feasibility study of a new automatic speaking valve (ASV) with integrated HME for laryngectomized patients (the Provox FreeHands FlexiVoice). This ASV enables automatic and manual closure of the valve. Forty participants were asked to use the new device for 26 weeks. The primary outcome measure was long-term compliance. After 26 weeks, 15/40 (37.5%) patients were using the new device on a daily basis, for a mean of 12.64 h/day (SD ± 5.03). Ten of 40 (25%) patients were using the new ASV on a non-daily basis, for a mean of 3.76 h/day (SD ± 2.07). The remaining 15 patients (37.5 %) discontinued using the new ASV. Sixty percent of the 25 long-term users applied both automatic and manual closure of the valve. Unpredictable fixation of the adhesive was the main reason for discontinuing or not using the new device on a daily basis. Overall 18/40 (45%) patients preferred the FlexiVoice, 16/40 (40%) their usual HME, 3/40 (7.5%) patients their usual ASV and 1 patient (2.5 %) preferred no device at all. Preference was not recorded in two patients. The new

ASV, with its new features/adaptions, appears to be a useful medical device, which allows for handsfree speech in an increased proportion of laryngectomized patients in this cohort.

In order to keep HMEs and ASVs in place, most commonly, peristomal adhesives are used. In **chapter 7** a prospective multicenter cross-over study in 32 patients was carried out to assess the added value of a new peristomal adhesive (StabiliBase OptiDerm (SBO)) for HME application. This device combines the stable and conical base of the Provox StabiliBase (SB) with a skin friendlier hydrocolloid adhesive as known from the OptiDerm (OD) adhesive. Participants were asked to compare SBO to the OD adhesive, and to the normally used adhesive. Overall, 60% of the participants preferred their normally used adhesive, 23% preferred the SBO and 17% indicated no preference. When comparing the SBO to the OD, 43% preferred the SBO, 40% the OD and 17% had no preference. In conclusion, most patients preferred their normally used adhesive and SBO was favored by a subgroup of patients, who were using the SB because of its stable base as their main adhesive, but needed a more skin friendly adhesive as an alternative. The study suggests that this new adhesive is a valuable addition to the existing peristomal adhesives and further increases patients' options for HME application.

In **chapter 8,** we report on studies about the place of stoma cloths in the pulmonary rehabilitation armamentarium of TL patients. These concerned an ex vivo laboratory study to assess the humidifying capacity of a wide range of potential stoma covers and a standard HME, and a clinical cross-over study to assess patients experiences and acceptability. The humidifying capacity of the tested stoma cloth varied widely. For a standard commercial stoma cover, a humidifying capacity of 13.7 mg/L was found, which decreased to 8.5 mg/L if air-leaks around the cloth occurred. The best humidifying capacity was found for the combination of this stoma cloths with a standard HME (14.5 mg/L). The clinical study revealed that patients, who use HMEs disliked stoma cloths because voicing was less easy, the cloth became more easily soiled, and was less effective at reducing coughing and mucus production. Although less acceptable to patients, who use an HME, stoma cloths can provide significant humidifying capacity, especially when air leaks are avoided, and should be used when HMEs are not an option.

In **chapter 9**, the results presented in this thesis are discussed and some potential future perspectives are outlined.

SAMENVATTING

In de laatste 30 jaar is het behandellandschap voor patiënten met een vergevorderd stadium (T3 en T4) larynxcarcinoom (strottenhoofdkanker) of hypofarynxcarcinoom (onderste keelholtekanker) ingrijpend veranderd; het gebruik van orgaansparende behandelingen (chemo)radiotherapie ((C)RT) is toegenomen en het toepassen van primaire chirurgie (totale laryngectomie; TL) is afgenomen. Temeer daar TL vaker als laatste redmiddel moet worden ingezet na voorgaande (C)RT, is het ook belangrijk om, naast aandacht voor functionele en oncologische uitkomsten, de postoperatieve zorg en het postoperatief herstel en revalidatie na een TL te blijven monitoren in dit veranderde behandellandschap. Dit proefschrift beschrijft en bediscussieerd deze onderwerpen, zowel op instituuts- als op nationaal niveau. In het inleidende **hoofdstuk 1** wordt ingegaan op het tijdstip waarop de orale voeding na de operatie wordt hervat, en op de incidentie en de voorspellende factoren van faryngocutane fistelvorming (FCF), een ernstige postoperatieve complicatie. Ook worden revalidatie aspecten zoals stem- en longrevalidatie en de positionering van bepaalde medische hulpmiddelen in dit veranderende behandellandschap besproken.

Er zijn twee kwesties met betrekking tot zorg en herstel in de periode na een totale laryngectomie waar meer aandacht naar uit is gegaan de afgelopen jaren. De eerste kwestie is het moment van het hervatten van de orale voeding na de operatie. De tweede kwestie is het ogenschijnlijk groeiende probleem van FCF dat wordt toegeschreven aan de groeiende incidentie van "salvage" TL. Deze operatie wordt uitgevoerd na eerdere niet succesvolle (C)RT, of ter verwijdering van een disfunctionele larynx na orgaansparende behandeling. **Deel I** van dit proefschrift gaat in op bovenstaande twee kwesties. Veel hoofd-halschirurgen stellen het moment van starten met orale voeding uit tot dag 10-12 na de operatie omdat gedacht wordt dat FCF hierdoor kan worden voorkomen of de kans op deze complicatie afneemt. Er is weinig bewijs ter ondersteuning van deze veronderstelling terwijl er verschillende argumenten zijn ten gunste van het vroeg hervatten van de orale voeding. In **hoofdstuk 2** wordt een retrospectieve studie bij 247 patiënten van het Antoni van Leeuwenhoek beschreven. In deze studie hebben we gekeken naar het effect van het moment van starten met orale voeding op FCF. In de periode begin 2000 tot halverwege 2006 werd een protocol toegepast waarin "laat" werd begonnen met orale voeding (start op postoperatieve dag 10-12; de late groep). In de periode halverwege 2006 t/m halverwege 2012 was een protocol van kracht waarin "vroeg" werd gestart met orale voeding (start op postoperatieve dag 2-4; de vroege groep). Beide groepen waren vergelijkbaar wat betreft geslacht, leeftijd, locatie van de tumor en de indicatie voor de TL. Patiënten in de late groep (N=140) hadden een iets gunstigere ASA-score dan de vroege groep (N=107) (p=0.047).

Dit verschil was niet geassocieerd met het ontstaan van FCF (p=0.417). De mediane dag van starten met orale voeding was dag 11 (range 6-103) in de late groep en dag 3 (range 2-84) in de vroege groep (p=0.001), wat impliceert dat de verschillende protocollen in de praktijk goed nageleefd zijn. Het verschil in FCF% tussen de twee groepen (25% in de late groep versus 32% in de vroege groep) was statistisch niet significant (p=0.255). Deze studie suggereert dat vroeg starten met orale intake na een totale laryngectomie veilig is en niet leidt tot een significante toename van FCF.

In **hoofdstuk 3** wordt vervolgens een retrospectief status onderzoek gepresenteerd betreffende 217 opeenvolgende patiënten die tussen 2000 en 2010 behandeld zijn middels een TL. Het doel van deze studie was het identificeren van voorspellende factoren voor FCF. Uit deze studie is naar voren gekomen dat 57 van 217 (26.3%) patiënten na een TL te maken hadden met FCF. Dit percentage was 17.1% (12 van 70) bij patiënten na een TL als primaire behandeling van een larynx- of hypofarynxcarcinoom, 25.5% (25 van 98) bij patiënten die geopereerd moesten worden voor een recidief, 37.5% (9 van 24) na een TLE ter behandeling van een tweede primaire tumor en 44.0% (11 van 25) na een TL ter verwijdering van een disfunctionele larynx. Voorspellende factoren voor het ontstaan van FCF waren hypofarynxkanker (OR, 3.67; 95% CI, 1.74-7.71; p=0.001), een albumine waarde van minder dan 40 g/L (OR, 2.20; 95% CI, 1.12 tot 4.33; p=0.022), voorafgaande (C)RT (OR, 3.38; 95% CI, 1.34 tot 8.52; p= 0.010), meer uitgebreide farynxresectie (p=0.001) en farynxreconstructie (p=0.002). Deze voorspellende factoren zijn niet verrassend, want zijn ook al eerder beschreven door veel andere onderzoekers. De mediane overleving was 30 maanden (95% CI, 17.5-42.5) en de tweejaars overlevingskans was 54%. Het ontstaan van FCF had geen invloed op de overlevingskans van de patiënten.

Het ontstaan van FCF wordt vaak onderzocht in studies waarbij slechts één centrum betrokken is. Dit maakt het maken van valide vergelijkingen tussen verschillende centra onmogelijk, wat relevant kan zijn om de kwaliteit van zorg, op nationaal niveau, inzichtelijk te maken. Ook kunnen deze inzichten ervoor zorgen dat behandelprotocollen in de individuele centra worden aangepast. In **hoofdstuk 4** hebben we daarom een audit opgezet waaraan alle 8 primaire Nederlandse hoofd hals centra (NWHHT) hebben deelgenomen. Driehonderdvierentwintig patiënten die in 2012 en 2013 een TL hebben ondergaan zijn geïncludeerd in dit retrospectieve status onderzoek. De incidentie van FCF is onderzocht in de gehele populatie, maar ook in de individuele centra. Het identificeren van voorspellende factoren was ook onderdeel van deze studie. Middels deze set voorspellende factoren konden voor elk afzonderlijk centrum FCF 'prestatie cijfers' (FCF% in centrum X minus het 'voorspellende' FCF% in centrum X) berekend worden. Met behulp van deze cijfers was het mogelijk om een zinvolle vergelijking tussen centra te maken,

omdat er rekening kan worden gehouden met een verschil in patiënten samenstelling in de verschillende centra. Naast het verzamelen van data is er ook een vragenlijst verspreid onder de leden van de NWHHT ter ondersteuning van de data. Uit de audit kwam naar voren dat 25.9% van de gehele studiepopulatie na een TL te maken had met FCF. Het multivariabele predictiemodel wees uit dat een eerdere niet-succesvolle (C)RT behandeling gecombineerd met een lange periode tussen deze behandeling en de uiteindelijk noodzakelijke TL, eerdere tracheotomie, subtotale faryngectomie, nekdissectie en een BMI < 18 de beste voorspellers waren voor de ontwikkeling van FCF. Er waren vrij grote verschillen in FCF% tussen de deelnemende centra, die voor het grootste deel echter verklaard konden worden door de verschillen in de (gunstigere of ongunstigere) samenstelling van de patiëntenpopulaties. Anderzijds moet ook vermeld worden dat niet alle verschillen verklaard konden worden met behulp van het multivariabele model; zo presteerde een centrum qua FCF% duidelijk minder goed dan verwacht. Een mogelijke verklaring hiervoor zou kunnen zijn dat de chirurgen in dit centrum een andere (horizontale) farynxsluitingstechniek hanteerden. Deze laatste informatie werd verkregen uit de vragenlijsten die we terugkregen van de verschillende centra. Het was enigszins teleurstellend dat dit gegeven en andere chirurgische details frequent afwezig waren in de operatieverslagen en daarom niet meegenomen kon worden in onze data analyse. De samenhang tussen een (gemodificeerde) radicale nekdissectie en een (toegenomen) risico op FCF suggereert dat deze chirurgische handeling alleen toegepast moet worden wanneer dit echt onvermijdelijk is, en dat, indien oncologisch verantwoord, de optie om alleen klieren voor vriescoupe onderzoek te verwijderen de voorkeur verdient.

In **deel II** van dit proefschrift, wordt er aandacht besteed aan stem- en longrevalidatie na een TL. Een retrospectieve cohortstudie over alle patiënten die in de periode 2000-2012 in het Antoni van Leeuwenhoek een TL hebben ondergaan, inclusief de plaatsing van een stemprothese (SP), wordt besproken in **hoofdstuk 5**. We hebben gekeken naar de mediane levensduur van de standaard Provox 2 en de Vega stemprothese. Die was respectievelijk 63 dagen en 66 dagen. Voor de 'probeemoplossende' ActiValve Light en Strong SP was dit respectievelijk 143 en 186 dagen. Uit een multivariabele analyse kwam naar voren dat 'salvage' TL en een TL ter behandeling van een disfunctionele larynx (in vergelijking met een primaire TL) geassocieerd waren met een kortere levensduur van een SP. Lekkage door de SP heen was de meest voorkomende reden voor het wisselen ervan en dit werd in 70% van de gevallen gerapporteerd. Dit percentage is vergelijkbaar met de 73% gerapporteerd in een eerdere studie over de periode 1988-1999 uit ons centrum. Bijna de helft van de patiënten (48%) hadden af en toe te maken met problemen gerelateerd aan de tracheoesofageale punctie (TEP) waarin de SP geplaatst is. Dit betrof 12% van de stemprothesewisselingen. Het bleek dat patiënten die ooit een ActiValve SP

hadden gehad een significant hoger risico hadden op dit probleem. Dit suggereert dat men bij patiënten die een verkorte levensduur van de SP ontwikkelen, de primaire reden voor het plaatsen van een ActiValve, mogelijke oorzaken voor deze TEP problematiek, zoals reflux en vernauwing van de farynx, moet opsporen. Als we de vergelijking maken met het eerdergenoemde historische cohort, en ook recente literatuur raadplegen, wordt duidelijk dat de levensduur van standaard SP (Provox 2 en Vega) is afgenomen, hetgeen waarschijnlijk veroorzaakt is doordat relatief meer patiënten een TL hebben ondergaan na eerdere niet succesvolle (C)RT. Ook lijkt het er op dat complicaties niet vaker voorkomen, maar dat er wel meer patiënten zijn geweest die te kampen hadden met deze complicaties. Desalniettemin, is de klinische betrouwbaarheid en validiteit van stemrevalidatie met behulp van een SP nog steeds gedegen.

Hoofdstuk 6 beschrijft te resultaten van een multicenter korte- en lange termijn studie naar de klinische haalbaarheid van een nieuwe automatische spreekklep (ASK) met geïntegreerde warmte- en vochtwisselaar (HME) voor gelaryngectomeerden (de Provox FreeHands FlexiVoice). Deze spreekklep maakt het mogelijk om zowel 'automatisch' (handenvrij) als middels het afsluiten van het tracheostoma met een vinger te kunnen spreken. Aan veertig patiënten werd gevraagd om dit nieuwe medische hulpmiddel gedurende een half jaar te gebruiken. De primaire uitkomstmaat was lange termijn therapietrouw. Uit de studie bleek dat 15/40 (37.5%) patiënten het nieuwe hulpmiddel, met een gemiddelde gebruiksduur van 12.64 uur per dag (SD ± 5.03), dagelijks hadden gebruikt. Tien van de 40 patiënten (25%) hadden het hulpmiddel wel gebruikt, maar niet dagelijks. De gemiddelde gebruiksduur voor deze groep was 3.76 uur per dag (SD ± 2.07). De resterende 15 patiënten (37.5%) besloten te stoppen met het gebruik van de ASK. Zestig procent van de 25 lange termijn gebruikers gebruikten beide mogelijkheden om te kunnen spreken (automatisch en handmatig). Onvoorspelbare kleefkracht van de stomapleister was de belangrijkste reden om te stoppen met het gebruik of om de ASK niet dagelijks te gebruiken. Uit de studie kwam naar voren dat 40 (45%) patiënten de voorkeur hadden voor de FlexiVoice, 16/40 (40%) voor hun gebruikelijke HME, 3/40 (7.5%) liever hun gebruikelijke ASK gebruikten en 1 patiënt (2.5%) aangaf geen voorkeur te hebben. Bij 2 patiënten ontbrak deze informatie. Deze studie laat zien dat deze nieuwe ASK, met zijn nieuwe mogelijkheden en betere HME functie, een bruikbaar medisch hulpmiddel lijkt te zijn en het voor meer gelaryngectomeerde patiënten in dit cohort mogelijk heeft gemaakt om 'handenvrij' te kunnen spreken.

Om HMEs en/ ASKs te bevestigen gebruiken de meeste patiënten peristomale pleisters. In **hoofdstuk 7** wordt een prospectieve multicenter cross-over studie bij 32 patiënten om de toegevoegde waarde van een nieuwe stomapleister vast te stellen gepresenteerd. In

dit hulpmiddel (StabiliBase Optiderm; SBO) is de stabiele conische basis van de Provox StabiliBase (SB) gecombineerd met het huidvriendelijke hydrocolloid materiaal van de OptiDerm (OD) pleister. Deelnemers aan de studie werd gevraagd om de SBO te vergelijken met zowel de OD als met hun gebruikelijke pleister. Zestig procent van de patiënten had een voorkeur voor hun gebruikelijk stomapleister, 23% had een voorkeur voor de SBO en 17% gaf aan geen voorkeur te hebben. Er werd gevraagd aan de patiënten om de SBO te vergelijken met de OD en 43% van de patiënten gaf aan een voorkeur te hebben voor de SBO, 40% voor de OD en 17% had geen voorkeur. Concluderend kan gezegd worden dat de meeste patiënten een voorkeur hadden voor hun gebruikelijke pleister. Toch was er een subgroep patiënten die een voorkeur had voor de SBO. Dit waren patiënten die de SB pleister, vanwege de stabiele basis, als standaard pleister gebruikten, maar op zoek waren naar een meer huidvriendelijk alternatief. De studie suggereert dat dit nieuwe medische hulpmiddel een waardevolle toevoeging is aan het al bestaande assortiment van peristomale pleisters en een bijdrage levert aan de verdere verbetering van de opties voor de bevestiging van een HME/ASK.

In **hoofdstuk 8** wordt een studie beschreven ten aanzien van de rol die textiele stoma bedekkers (bef) in het bestaande arsenaal van producten voor pulmonaire revalidatie voor TL patiënten kunnen spelen. Dit onderzoek bestond uit een ex vivo laboratorium studie om de bevochtigingscapaciteit van een groot aantal potentiële befs en een standaard HME vast te stellen. Daarnaast werd een klinische cross-over studie uitgevoerd om de ervaringen van patiënten ten aanzien van een bef in kaart te brengen en of zij een dergelijk hulpmiddel in de praktijk (willen) gebruiken. De ex vivo studie wees uit dat de bevochtigingscapaciteit van de geteste befs erg verschillend was. De beste waarde van 13.7 mg/L werd gevonden voor een standaard commerciële bef, die echter zakte naar 8.5 mg/L indien lucht kon weglekken vanonder de bef. De beste bevochtigingscapaciteit werd bereikt indien de bef werd gecombineerd met een standaard HME (14.5 mg/L). Uit de klinische studie kwam naar voren dat patiënten die standaard een HME gebruikten, befs niet prettig vonden vanwege het feit dat spreken minder makkelijk was, het hulpmiddel snel vies werd en dat een bef minder effectief was ten aanzien van het verminderen van hoestprikkels en slijmproductie. Alhoewel patiënten die standaard een HME gebruikten een bef dus minder prettig vonden, kan zo'n textiele stoma bedekker toch zorgen voor een significante bevochtiging van de lucht, vooral als luchtlekkage vanonder de bef wordt voorkomen. Dit hulmiddel is dan ook zeker aan te raden als het dragen van een HME geen optie is.

In **hoofdstuk 9** worden alle resultaten van dit proefschrift bediscussieerd en worden ideeën voor mogelijke toekomstig onderzoek geformuleerd.

AUTHOR CONTRIBUTIONS

Chapter 1 **General introduction.**
Writing the text | LL
Editing and reviewing the text | LL, FH, MB

Chapter 2 **Early oral intake after total laryngectomy does not increase pharyngocutaneous fistulization.**
Study concepts and design | LL, AT, FH, MB
Data collection | LL, AT, GK
Statistical analysis | LL, AT
Data interpretation | LL, AT, FH, MB
Manuscript preparation | LL, AT
Manuscript editing and review | LL, AT, GT, OH, FH, MB

Chapter 3 **Predictive factors for pharyngocutaneous fistulization after total laryngectomy.**
Study concepts and design | LL, AT, FH, MB
Data collection | AT, ET
Statistical analysis | AT
Data interpretation | LL, AT, FH, MB
Manuscript preparation | LL, AT
Manuscript editing and review | LL, AT, ET, FH, MB

Chapter 4 **Predictive factors for pharyngocutaneous fistulization after total laryngectomy; a Dutch Head and Neck Society Audit.**
Study concepts and design | LL, FH, MB, RT, RB
Data collection | LL, RT, RB, SB, SE, BP, TL, ML
Statistical analysis | LL, VN
Data interpretation | LL, VN, FH, MB
Manuscript preparation | LL, FH, MB
Manuscript editing and review | LL, VN, FH, MB, RT, RB, SB, SE, BP, TL, ML

Chapter 5 **Postlaryngectomy prosthetic voice rehabilitation in a consecutive cohort of 232 patients over a 13-years period.**
Study concepts and design | LL, JP, AT, FH, MB
Data collection | LL, JP, AT
Statistical analysis | LL, JP, VN
Data interpretation | LL, JP, VN, FH, MB
Manuscript preparation | LL, JP, FH
Manuscript editing and review | LL, JP, AT, VN, FH, MB

Chapter 6	**A prospective multicenter clinical feasibility study of a new automatic speaking valve for postlaryngectomy voice rehabilitation.**
	Study concepts and design | LL, BK, BL, FH, MB
	Data collection | LL, BK
	Statistical analysis | LL
	Data interpretation | LL, FH, MB
	Manuscript preparation | LL, BK
	Manuscript editing and review | LL, BK, BL, FH, MB
Chapter 7	**Comparative study between peristomal patches in patients with definitive tracheostomy.**
	Study concepts and design | LL, BK, BL, FH, MB
	Data collection | LL, BK
	Statistical analysis | LL
	Data interpretation | LL, FH, MB
	Manuscript preparation | LL
	Manuscript editing and review | LL, BK, BL, FH, MB
Chapter 8	**Ex vivo humidifying capacity and patient acceptability of stoma cloths in laryngectomized individuals.**
	Study concepts and design | LL, CB, SM, FH, MB
	Data collection | LL, CB
	Statistical analysis | LL, CB, SM, FH
	Data interpretation | LL, CB, SM, FH, MB
	Manuscript preparation | LL, CB, FH
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Chapter 9	**General discussion and future perspectives.**
	Writing the text | LL
	Editing and reviewing the text | LL, FH, MB

AUTHORS AND AFFILIATIONS

A.J. Timmermans, MD, PhD
Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

G.V.J. Kroon
Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

O. Hamming-Vrieze, MD
Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

F.J.M. Hilgers, MD, PhD
Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands. Institute of Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands.

M.W.M. van den Brekel, MD, PhD
Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands. Institute of Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands. Department of Oral and Maxillofacial Surgery, Academic Medical Center, Amsterdam, The Netherlands.

E.A.R. Theunissen. MD, PhD
Department of Otorhinolaryngology, Amsterdam University Medical Center, location AMC, Amsterdam, The Netherlands.

V. van der Noort, PhD
Biometrics Department, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

S.E. Bernard, MD
Department of Otorhinolaryngology-Head and Neck Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

S.E.J. Eerenstein, MD, PhD
Department of Otolaryngology-Head and Neck Surgery, University Medical Center location VU, Amsterdam, The Netherlands.

B.E.C. Plaat, MD, PhD
Department of Otorhinolaryngology-Head and Neck Surgery, University of Groningen, University Medical Center, Groningen, Groningen, The Netherlands

T.A.P.M. Langeveld, MD, PhD
Department of Otolaryngology-Head and Neck Surgery, Leiden University Medical Center, Leiden, The Netherlands

M. Lacko, MD, PhD
Department of Otolaryngology-Head and Neck Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

R. de Bree, MD, PhD
Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

R.P. Takes, MD, PhD
Department of Otorhinolaryngology-Head and Neck Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

J. F. Petersen, MD
Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

B. J. de Kleijn, MD
Department of Otorhinolaryngology-Head and Neck Surgery, University of Groningen, University Medical Center, Groningen, Groningen, The Netherlands

B.F.A.M. van der Laan, MD, PhD
Department of Otorhinolaryngology-Head and Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

C. van den Boer, MD, PhD
Department of Otorhinolaryngology-Head and Neck Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

S.H. Muller, MD, PhD
Department of Clinical Physics and Instrumentation, The Netherlands Cancer Institute, Amsterdam, The Netherlands

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ABOUT THE AUTHOR

Liset Lansaat was born on the 8th of May 1984 in Heesch, the Netherlands. After graduation from secondary school (higher general secondary education) at the Titus Brandsma Lyceum in Oss in 2002, she continued her education with Food & Business at the 'Hanze Hogeschool' in Groningen and obtained her propaedeutics degree. In 2003 she started Dental hygiene at the 'Hanze Hogeschool' in Groningen. She conducted her internship at the department of Oral & Maxillofacial surgery at the University Medical Center of Groningen and graduated in 2007. Her bachelor thesis reported on DPSI (Dutch Paradontal Screening Index) and preeclampsia. After her graduation she worked first as dental hygienist in a dental practice in Amsterdam and between 2008 and 2011 in the Erasmus MC at the department of Oral & Maxillofacial surgery, where she was responsible for treating patients with several complex diseases. In this period, she also started a master study Health Sciences at the Free University in Amsterdam. She graduated in 2011 and the topic of her master thesis was: "Misperception of body weight among recipients of the Dutch Food Bank". After her graduation she worked as a research assistant at the same university for three months. From November 2011 till July 2017 she was employed as a research coordinator at the department of Head and Neck Oncology and Surgery at the Netherlands Cancer Institute, Amsterdam. In this position she was responsible for the organization, patient inclusion and follow-up of several prospective physician-initiated pilot studies and trials in collaboration with an international medical device manufacturer. Mid 2013, she also started her PhD project at the same department. Daily supervisors were prof. dr. F.J.M. Hilgers and prof. dr. M.W.M. van den Brekel. While finishing her thesis, she started working (mid May 2018) as Advisor at het 'Kennisinstituut' van de 'Federatie Medisch Specialisten'.