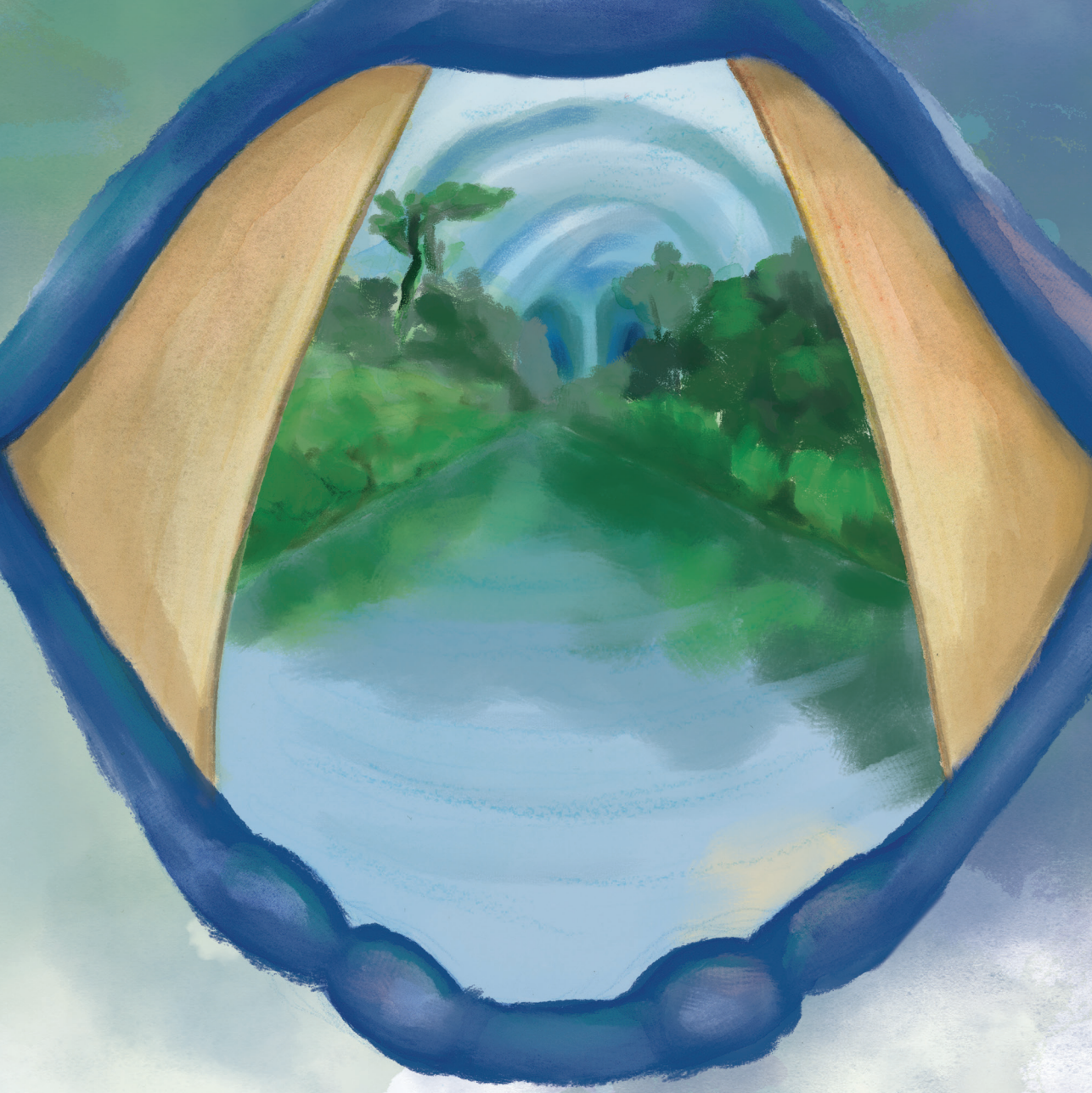

LARYNX AND HYPOPHARYNX CANCER

educated choices in treatment and rehabilitation

J.F. Petersen

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Japke Frieda Petersen

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1

General introduction

INTRODUCTION

ETIOLOGY AND EPIDEMIOLOGY OF LARYNX AND HYPOPHARYNX CANCER

In the Netherlands, at present, 700-750 patients are diagnosed annually with larynx cancer, and some 160 patients with hypopharynx cancer.[1] The larynx, or voice box, consists of the supraglottic, glottic and subglottic area, and is involved in breathing and generation of sound. Furthermore, by closure of the vocal cords and sealing off the larynx entrance with the epiglottis, food is prevented from entering the trachea, which allows swallowing. The hypopharynx consists of the pyriform sinus, post-cricoid region and the posterior pharyngeal wall.[2] Cancers developing in the larynx and hypopharynx are usually squamous cell carcinomas (SCC) and the main risk factors are smoking and alcohol consumption.[3] Excessive alcohol consumption seems to play a bigger role in the development of hypopharynx cancer, and patients with hypopharynx cancer typically have more comorbidities.[4] In the Netherlands, Northern European countries and the US, most patients are around 60 years of age and the male to female ratio for the incidence of larynx and hypopharynx cancer is 4 to 1.[5, 6]

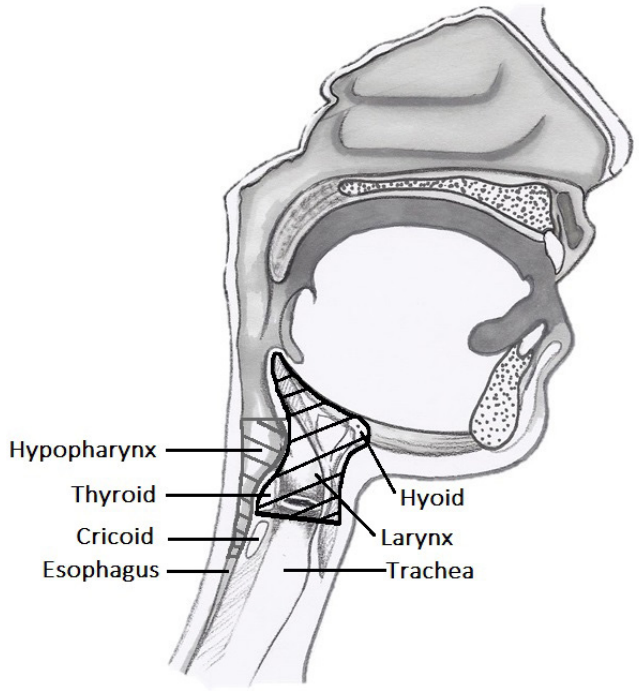

Figure 1. Sagittal view of the head and neck area, depicting the larynx and hypopharynx

Due to early symptoms such as hoarseness and/or throat irritation, glottic larynx cancer is typically diagnosed in an early stage (T1-T2), whereas the more advanced stages of larynx cancer (T3-T4) are usually located in the supraglottic area, which often lead to a later onset of symptoms.[7] The hypopharynx is frequently called the 'silent area' because tumors arising here often give symptoms in a very late stage, or early signs, such as referred earache, are not recognized early on.[4] The supraglottic and hypopharynx have a rich submucosal lymphatic network, enabling early spread of cancer cells towards the lymphatic network. Most patients with hypopharynx cancer have lymph node metastases at time of diagnosis.[8, 9]

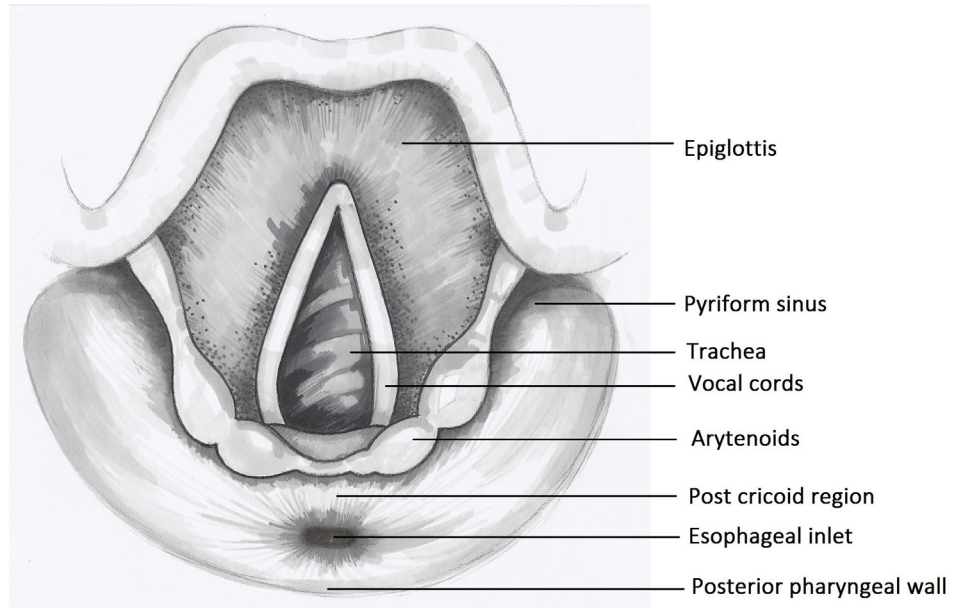

Figure 2. Axial view on the larynx and hypopharynx

EVOLUTION OF TREATMENT STRATEGIES

Total laryngectomy and vocal rehabilitation

The gold standard in treatment for advanced larynx and hypopharynx cancer used to be total laryngectomy (TL) with or without partial pharyngectomy and neck dissection. The first laryngectomy for cancer was performed by the famous Viennese surgeon Theodore Billroth in 1873, although years earlier, in 1866, the first total laryngectomy ever was performed by Watson in Edinburgh, for a case of syphilis.[10] Despite some improvements in the operating technique, peri-operative mortality rates were high, up to 50%, and survival following TL

was poor. This was mainly due to the surgical technique that was used to enable applying an artificial larynx, as even in those early days, vocal rehabilitation was considered a major challenge after total laryngectomy. Several different types of artificial larynxes were created in order to maintain means of communication after surgery, in part based on experiments in canines.[11] Although many different types of artificial larynxes were presented, none of them became widely accepted.[11] Around 1888, Gluck changed the original laryngectomy, where a pharyngostoma was created to allow the use of the artificial larynx device, and showed that *closing* the pharynx dramatically lowered the mortality rate, to below 5%.[12] Around 1920, Seeman showed that esophageal speech was an alternative substitute voicing option. He claimed that he could teach each patient to have an intelligible voice, making them independent from artificial larynxes, and he even claimed that '*the artificial larynx belongs to the past*'.[11] However, the technique of esophageal speech, further explored in the Netherlands by Burger and Kaiser (1925) and later on by Molenaar-Bijl and Damsté, could not be mastered by all patients. Viable alternatives to TL were still very much sought after.[13]

At the turn of the century, radium was discovered. The first medical use of radium was for diagnostic procedures, in 1901. In 1922, Coutard and Regaud were the first to describe the treatment of 6 larynx cancer patients with X-rays.[10] Radiotherapy (RT) treatment gradually became widely accepted. From 1940 onwards, small larynx tumors were increasingly being treated with radiotherapy, and surgery was reserved for the more advanced lesions. Because the prognosis of advanced (T4) larynx cancer remained poor, a few decades later, laryngectomy was combined with adjuvant radiotherapy for these tumors.[14, 15]

Another few decades later, the invention and acceptance of the modern voice prostheses gave a new impulse to the use of TL as primary treatment option. Mozolewski et al. reported on the first functional voice prostheses in 1973.[16] A few years later, the first commercially available voice prostheses were introduced by Singer and Blom.[17] Since then, several different types of voice prostheses have been developed, contributing to improved vocal rehabilitation and thereby improved quality of life after TL.[18-23] Currently, prosthetic vocal rehabilitation is widely accepted in most Western countries and reported to be highly successful. With this technique, around 90% of patients are now able to achieve fair to excellent voice quality.[24]

Chemoradiotherapy

Despite the highly improved vocal rehabilitation, alternative options to total laryngectomy were still sought after. The chemotherapeuticum cisplatinum, now widely used in head and neck cancer, was accidentally discovered by dr. Rosenberg in 1965.[25] After its first successful use in the treatment for testicular cancer, it was tested in numerous other solid cancers, including head and neck cancer.[26] In 1990, the department of Veterans Affair (VA) published the results of a randomized controlled trial (RCT) in which they compared induction chemotherapy with cisplatinum and fluorouracil (PF) followed by radiotherapy to a total laryngectomy. The results of this VA study demonstrated equal OS rates of 68% after 2 years, and 64% of the organ preservation group was able to maintain their larynx.[27] A subsequent study - the RTOG 91-11 trial - assessed the addition and timing of chemotherapy in a three-arm design, comparing the outcomes of single modality radiotherapy, induction chemotherapy with cisplatin plus fluorouracil (PF) followed by RT, and concurrent chemoradiotherapy (CRT) with cisplatin. In this study, a superior local control and larynx preservation rate was found in the concurrent CRT arm with no difference in toxicities. However, based on the results from the VA study, large T4 tumors were excluded in this RCT.[28]

Lefebvre et al. performed one of the few RCTs specifically with hypopharynx cancer patients only, comparing the outcomes of TL plus adjuvant radiotherapy to induction chemotherapy with PF followed by definitive RT.[29, 30] The two treatment arms were considered to be equal in terms of overall survival. In the induction CT arm, the larynx preservation rate at 5 years was 17%, which was considerably lower than reported in the VA study.[27] However, the authors initially defined larynx preservation as 'survival without any local disease, a tracheotomy, feeding tube or gastrostomy'. When analyzing only 'death from local disease progression', any local disease, a tracheotomy, feeding tube or gastrostomy, the 5-year estimate was 35%.[29]

The landmark trial of Lefebvre et al. demonstrated the feasibility of organ preservation treatment in hypopharynx cancer, but oncological outcome remained poor. Subsequent studies have evaluated the addition of taxanes to the regular treatment protocol, to further improve oncological outcome. In 2009, Pointreau et al. published the results of an RCT comparing induction chemotherapy with PF to induction chemotherapy with TPF (docetaxel, cisplatin and 5-FU). They included both advanced larynx and hypopharynx cancer patients and reported a significant higher overall response rate and larynx preservation rate in the TPF arm versus the PF arm at 3 years.[31] In the same year, Posner et al. reported on a similar study comparing induction TPF versus induction PF, followed in both arms by concurrent chemoradiotherapy with weekly carboplatin in locally advanced larynx, hypopharynx, oropharynx and oral cavity cancer. The authors reported an increased OS in the TPF group.[32] Two years later, a subgroup analysis of only the larynx and hypopharynx cancer patients demonstrated that besides superior OS in the TPF group (57% vs. 40% at 3 years), also larynx preservation was significantly higher in the TPF group (52% vs. 32%).[33] In the Netherlands, a phase II study was conducted in which patients received induction TPF followed by either concomitant CRT with cisplatin (100mg/m^2 every 3 weeks) and

conventional RT, or CRT with cisplatin (weekly 40mg/m^2) and accelerated RT. This study was however ended prematurely, because only 32% of patients were able to receive the planned dose of cisplatin due to toxicity[34].

Although the addition of chemotherapy to single modality RT yielded successful results in terms of OS, the resulting extra toxicity has always been a great concern. In an attempt to lower toxicities, Bonner et al. evaluated the effect of the IgG1 monoclonal antibody cetuximab in combination with RT.[35] In their phase III study, patients with loco-regionally advanced larynx, hypopharynx or oropharynx cancer received radiotherapy with or without cetuximab. The first results reported increased loco-regional control in the cetuximab arm, although this benefit seemed to be most applicable to oropharynx cancer patients[35]. A later publication reported that the 5-year OS rate in the cetuximab group was 46% versus 36% in the RT only group, but again the benefit was most pronounced in the oropharynx group.[36] However, another 6 years later, a subgroup analysis in the larynx and hypopharynx cancer patients revealed a non-significant difference in OS and laryngectomy free-survival between the two treatment arms.[37] A comparison of RT with cetuximab versus chemoradiotherapy or TL in a RCT has however never been made.

Although there is quite some heterogeneity in the RCTS described above, the results of these studies within advanced larynx and hypopharynx cancer offered patients an opportunity to preserve the larynx and reserve TL for salvage, in case of recurrence of tumor or when the larynx would become dysfunctional. Since these publications, the treatment paradigm shifted towards favoring organ preservation with (chemo)radiotherapy. This approach was further supported by the results of a meta-analysis by Pignon et al., who demonstrated an absolute survival benefit of 6.5% for concomitant chemoradiotherapy, compared to radiotherapy only, in the treatment of head and neck cancer. This effect however decreases with increasing age, and in general, in patients over 70 years of age the addition of chemotherapy is questionable.[38]

A CHANGING LANDSCAPE

After some steady years of favoring organ preservation for advanced larynx and hypopharynx cancer, an alarming report came from a population-based study in the US, which demonstrated a decrease in survival for advanced larynx cancer.[39] Since this phenomenon was paired with an increase in the use of non-surgical techniques, certain groups started to question the presumed equality of TL and organ preservation in the more advanced T4 tumors.[39] These concerns were amplified when a late report on the first RCT in larynx cancer demonstrated that patients with a T4N0 tumor in fact had better overall survival rates following TL.[40]

To evaluate whether these trends in treatment and survival could also be witnessed in the Dutch population, Timmermans et al., performed an institutional[6] and a national database study[7] among patients with advanced larynx cancer. And indeed, in the Netherlands, a similar trend towards more CRT and less upfront surgery was witnessed, although it was not coupled with a decreasing overall survival rate for the group as a whole. However, in this national larynx cancer study, the superiority of TL over CRT in terms of OS in T4 larynx cancer was again confirmed.[7] In recent years, more retrospective studies have demonstrated a superior OS for patients with T4 larynx cancer treated with TL. In 2017, Dyckhoff et al. reported a two-fold risk on death when treated with CRT vs. TL.[41] Stokes et al. analyzed all T4N0 larynx cancer patients in the US National Cancer Data Base and reported superior OS for TL compared to concurrent CRT, but demonstrated no significant difference in survival between TL and induction CRT.[42] Although the evidence of superior OS among T4 cancer patients in the TL group seems compelling for larynx cancer[43], fewer studies have investigated this effect in hypopharynx cancer patients or only with limited patient numbers.[44]

PREDICTING SURVIVAL

In the Netherlands, the vast majority of larynx and hypopharynx cancer patients are treated in a multidisciplinary setting in one of the dedicated head and neck cancer centers. Based on the studies described above, most patients with advanced larynx or hypopharynx cancer are offered one of the three available curative treatment options, i.e. single modality radiotherapy, concurrent chemoradiotherapy with cisplatin, or total laryngectomy with adjuvant radiotherapy.[45, 46] Other possible treatment strategies such as induction CT followed by (concurrent chemo)radiotherapy or Transoral Robotic Surgery (TORS), are currently rarely applied in the Netherlands.[47] Following adequate diagnostic procedures and staging, each patient is discussed within the multidisciplinary group meetings. In case of perceived equal overall survival rates, guidelines in the Netherlands advice to use organ preservation for advanced larynx or hypopharynx cancer.[46, 48]

When discussing estimates of OS, currently, the TNM classification plays a central role. There are however many more patient, treatment and tumor-related aspects that are predictive of survival. This includes, for example, age, gender, comorbidity, gross tumor volume, various peripheral blood parameters, and/or genetic markers.[49-53] During multidisciplinary meetings, physicians will implicitly incorporate numerous tumor and patient specific variables into their decision, but the cognitive capacity of the human mind is limited, and capable of consciously weighing only a few variables at a time in each decision.[54] Furthermore, ‘specialty bias’ might play a role in advising on treatment. Specialty bias refers to the phenomenon in which physicians are more likely to recommend the treatment they are trained to deliver[55]. Large studies have shown that when there

is no optimal treatment strategy, physicians will have stronger belief in the efficacy of their 'own' treatment.[55, 56] The development and implementation of prediction models that incorporate multiple prognostic variables into an easy to use statistical model, can aid medical decision-making by generating numerical probabilities on an event for clinical subgroups, based on large numbers of data without leaving room for elements such as specialty bias. In the past years, various studies have demonstrated the superiority of these models over the estimations made by physicians.[57, 58]

Several clinical prediction models (CPM) have been developed for head and neck cancer sites.[59, 60] In order to use a prediction model in clinical practice, the accuracy of the model-based predictions should be proven to be sufficient. Internal and external validation are important steps to assess the predictive strength of the model, which can be expressed in terms of discrimination and calibration.[61] Discrimination refers to the ability of the model to distinguish patients experiencing an event from those who will not, and is represented by the C statistic, which ranges from 0.5 (no discrimination) to 1.0 (a perfect model).[62] A C statistic of 0.75 means the model can distinguish a patient who will experience an event from a patient who will not experience this event 75% of the time. Calibration refers to the agreement between observed and predicted outcomes (i.e. survival time).[63] Before using clinical prediction models, it is important to assess whether these validation steps have been taken, and if discrimination and calibration are within the acceptable range. An important consideration is that a model with good discrimination but flawed calibration can still be useful in distinguishing clinical subgroups based on high or low risk on an event. When proven to be adequate, these models have great capacity to improve patient specific survival predictions and thereby aid clinical decision making.[64]

QUALITY OF LIFE AND REHABILITATION AFTER TREATMENT

Although survival is an important consideration when counseling patients on their cancer treatment, the expected quality of life following treatment and the available rehabilitation options, deserve a comprehensive discussion as well. Currently, there are three adequate treatment options for advanced larynx and hypopharynx cancer, but these options all have significant effects on the quality of life or self-esteem of patients, as they interfere with important functions such as breathing, swallowing and the production of speech.[65, 66]

Radiotherapy and chemoradiotherapy

Radiotherapy uses ionizing radiation to induce DNA damage, which causes apoptosis or mitotic cell death. Since its first clinical use in cancer treatment in the early 20th century, radiotherapy has witnessed numerous technological advancements. Currently, the large majority of cancer patients will be treated with radiotherapy at some point during the course of their disease.[67, 68] The effect of radiotherapy partly relies on the fact that cancer cells have less capacity to repair radiotherapy induced DNA damage than normal cells. By delivering several fractions of radiotherapy over a set course of time, the tumor will be eradicated whereas the healthy cells will repair. The standard definitive radiotherapy in the Netherlands is 70 Gy in 35 daily fractions of 2 Gy over 7 weeks to the primary tumor and involved nodes, although altered fractionation regimens have been widely used. A dose of 46 Gy in 23 fractions or 54.25 Gy in 35 fractions, in simultaneous integrated boost technique, is a standard dose to electively treat lymph node region. Intensity-modulated radiotherapy (IMRT) of volumetric modulated arc therapy (VMAT) is the accepted standard radiotherapy technique for primary or adjuvant treatment. In case of more advanced disease and nodal involvement, platinum-based concurrent chemoradiotherapy is considered for fit patients under the age of 70. In the Netherlands, most head and neck patients will be treated with the radiosensitizer cisplatin. By forming crosslinks between DNA strands, cisplatin will alter the DNA structure and DNA replication is inhibited. As already mentioned, a meta-analysis of the added effect of chemotherapy to radiotherapy demonstrated an absolute survival benefit of 6.5% at 5 years.[38]

Although radiotherapy is an effective treatment strategy, it also can produce significant toxicity within the head and neck area. Reported side effects of radiotherapy on the short term are pain, swallowing problems and mucositis, and toxicities on the long-term can be xerostomia, dysphagia, dysphonia, fibrosis, radionecrosis, atherosclerosis or edema.[69] The addition of cisplatin is also related to significant extra toxicities, both on the short term and on the long term. Nephrotoxicity is the most important dose-limiting side effect of cisplatin. Other reported toxicities are severe nausea, vomiting, myelosuppression, ototoxicity and neurotoxicity.[70, 71]

Although many patients have been successfully treated with organ preservation treatment, a number of patients will suffer from tumor recurrence necessitating salvage laryngectomy. Furthermore, in 11% of cases, patients are left with a dysfunctional larynx after treatment, in which case a functional total laryngectomy often is the only solution.[72] Among patients that are treated with TL for a dysfunctional larynx or for salvage reasons, higher rates of pharyngocutaneous fistulas, wound healing problems and swallowing difficulties have been observed.[72]

In the VA trial organ preservation was defined as 'the larynx being in situ'. However, this does not always mean that the patient survives with a functional larynx. Several retrospective studies have demonstrated that patients may suffer from severe dysphagia necessitating a (permanent) feeding tube, frequent aspiration pneumonias, or even from

having a tracheotomy in situ years after treatment.[69] A new endpoint called 'laryngo-esophageal dysfunction free survival rate' has therefore been proposed by a consensus panel on larynx preservation, to provide a better understanding of the actual success of organ preservation treatment.[73]

TOTAL LARYNGECTOMY

Total laryngectomy entails the surgical removal of the larynx and the creation of a stoma in the neck, see Fig. 3A and B. Depending on the size of the tumor, a partial, near total or circumferential pharyngectomy is performed. In case of limited pharyngectomy, the pharynx can be closed primarily, but in more extensive resections, reconstruction of the lost tissue is necessary. This can be achieved with well-vascularized tissue, e.g. a pectoralis major myocutaneous flap to reconstruct the resulting pharyngeal defect. Other frequently used flaps are the free radial forearm flap or the anterolateral thigh flap, especially in case of a circumferential pharyngectomy, for which also a gastric pull up procedure can be applied. Usually, the laryngectomy is accompanied with a unilateral or bilateral (selective) neck dissection and a primary tracheoesophageal puncture to create a tract in which a voice prosthesis can be placed. In case of a primary T4 tumor, adjuvant radiotherapy is advised to start within 4-6 weeks after surgery, to allow for maximum tumor control and prevent stoma recurrences.[15, 74]

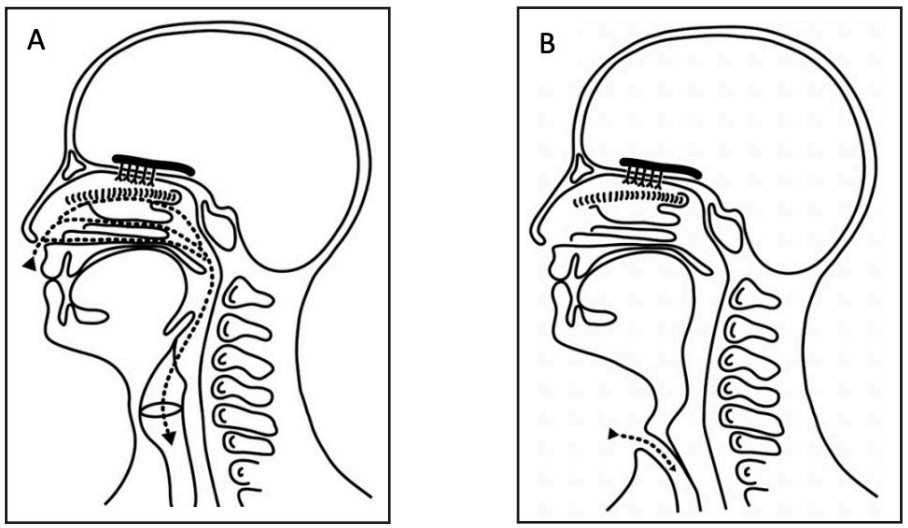

Figure 3. A) Normal anatomy; B) Changed anatomy after total laryngectomy (without primary puncture and voice prosthesis)

During laryngectomy, certain surgical refinements can improve the quality of life after TL. Dissection of the sternal heads of the sternocleidomastoid muscle will create a flatter stoma, facilitating inspection and cleaning of the stoma and subsequent replacements of voice prostheses. Myotomy of the cricopharyngeal muscle is performed to improve voicing and swallowing function.[75] Whenever possible, a primary puncture of the TEP tract is advised to start early vocal rehabilitation after surgery. Only in case of a gastric pull up, a secondary puncture in a later stadium is preferred.[24] Most frequent complications following total laryngectomy on the short term are delayed wound healing, infection, and pharyngocutaneous fistulas.[76] When looking at long-term complications and rehabilitation challenges after total laryngectomy, it becomes clear that the larynx is more than a voice box alone.[77] On the long-term, patients are faced with many vocal, pulmonary, olfactory, and swallowing changes and challenges.

Over the past years, a plethora of studies have increased our insight into the problems encountered after TL and provided possible solutions. Pulmonary rehabilitation focuses on diminishing the complaints related to loss of function of the upper respiratory tract. To this end, heat and moisture exchanger (HMEs) have been developed, which have been proven to lead to reduced respiratory problems and improved quality of life.[78-80] The permanent disconnection of the upper and lower airways also results in impaired ability to smell. To restore olfaction, the 'nasal airflow-inducing maneuver' (NAIM technique) has been developed.[81] This technique aims at generating under-pressure in the oral cavity, which induces airflow across the olfactory epithelium, thus reestablishing the sense of smell. The other two issues, vocal and swallowing rehabilitation, subjects of this thesis, will be discussed in more detail below.

VOCAL REHABILITATION FOLLOWING TOTAL LARYNGECTOMY

The removal of the vocal cords means that the patient will need other means to produce speech. The three main methods of restoring oral communication are tracheoesophageal speech, esophageal speech and the use of an electrolarynx, see Fig. 4A-C. In most Western countries, tracheoesophageal speech is most widely used after TL.

For the production of speech, three components are essential: air supply, tissue that can be brought into vibration, i.e. a sound box, and a cavity in which the sounds are modified into intelligible speech, i.e. the vocal tract. By placing a voice prosthesis in the tracheoesophageal wall through which pulmonary air can be redirected from the lungs into the pharynx, all three prerequisites are met. The combination of 1) the oral (and nasal) cavity being the vocal tract; 2) the mucosa of the pharyngoesophageal segment forming the vibrating tissue/sound box; and 3) the air passing through the voice prosthesis being

the air supply, gives the patient the ability to produce pulmonary driven speech again. Thus, just like laryngeal voicing, tracheoesophageal voicing is pulmonary driven, which makes this substitute communication method the closest to normal.[82] Esophageal speech is not pulmonary driven, but using this technique, the air supply that can be brought into the esophagus to produce speech ranges between 60-80ml. Compared to the average tidal volume of 500-600 ml which can be used during tracheoesophageal voicing, esophageal speech results in reduced phonation time, loudness and intelligibility.[82]

As mentioned before, since the introduction of the first voice prosthesis in in 1973, several new prostheses have been developed.[16, 17] In The Netherlands Cancer Institute, in 1990 the first Provox voice prosthesis was developed in collaboration with Atos Medical in Sweden.[18] In the meantime, several improvements to the first Provox voice prosthesis have been made resulting in improved airflow characteristics, more comfortable anterograde replacement, reduction of the formation of a biofilm on the VP and the introduction of a small magnet controlling inadvertent valve opening.[20, 83, 84]

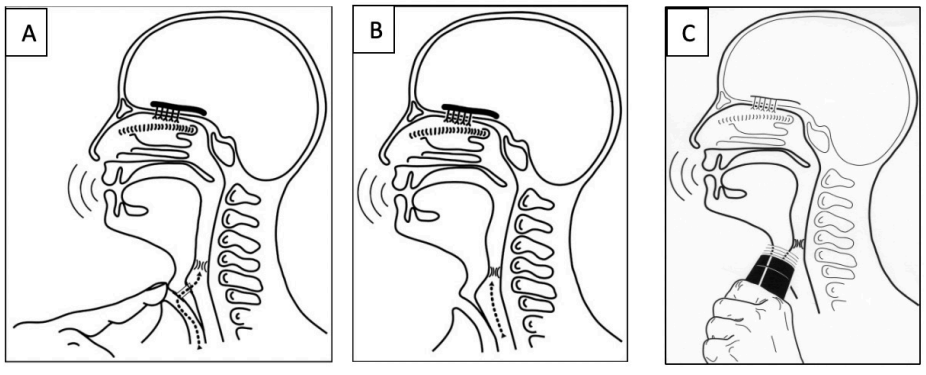

Figure 4. Three main methods of oral communication after TL: A) Tracheoesophageal speech; B) esophageal speech; and C) electrolarynx speech.

In 2000, Op de Coul et al. published the results of vocal rehabilitation following TL in a consecutive cohort of laryngectomized patients in The Netherlands Cancer Insitute.[24] In this cohort, a median device lifetime of 89 days was observed. Most patients from this cohort underwent primary total laryngectomy, whereas 45% of patients were treated for recurrent disease after prior radiotherapy. In light of the increasing use of salvage TLs following (chemo)radiotherapy, concerns were raised whether vocal rehabilitation using voice prostheses was still a safe and sound option.[85] The combined effect of chemotherapy and radiotherapy on the tissues in the neck can result in further increased fibrosis and impaired wound healing, complicating vocal rehabilitation. Indeed, recent publications on device lifetime in cohorts from Germany and the US showed a decreased device lifetime in patients treated with salvage TL.[85, 86] Currently, one can now expect a median device lifetime of regular VPs to be around 2 months instead of the historical 3 months.

SWALLOWING REHABILITATION FOLLOWING TOTAL LARYNGECTOMY

Following TL, little attention is paid towards swallowing rehabilitation. However, up to 50% of patients complain of swallowing difficulties after TL. Dysphagia in these patients can be multifactorial, since the majority of patients are treated both with surgery and (chemo)radiotherapy. The pharyngeal closure technique, denervation, myotomies, the extent of pharynx resection, the occurrence of a stenosis or a pseudodiverticulum are surgical aspects that might contribute to this swallowing problem, while effects such as xerostomia, fibrosis, (lymph)edema or sensorial neuropathy more likely result from (chemo) radiotherapy.[87] Although this did not specifically concerned TL patients, long-term follow-up of patients treated for advanced head and neck cancer with CRT alone has shown that 10-years after CRT, up to 50% of patients complain of dysphagia, and 14% is still dependent on tube feeding.[69]

When a patient complains of dysphagia later in follow-up after TL, first, recurrent disease has to be ruled out. Apart from flexible nasopharyngoscopy, there can be an indication for an X-ray swallowing study or CT scan, and in certain more severe cases, examination under general anesthesia can be indicated. When modifications to diet and exercises from the speech language pathologists are unsuccessful, and the diagnosis of a non-suspicious stenosis is established, patients can be treated with (repeated) dilatation of the stenosis. Dilatation can be carried out with silicon bougies using the Savary Guillard technique[88] or using balloon dilatations.[89] Dilatation of a benign esophageal stenosis in non-laryngectomized patients is successful in 80-90% of strictures, but recurrence of dysphagia within the first year is common. The complication rate is low: around 0.8% for benign and 4.6% for malignant strictures.[88] Little is known, however, about the success rate of dilatation procedures in laryngectomized patients, who represent a distinct patient group, often treated with both surgery and (chemo)radiotherapy.[89] A recent systematic review on dysphagia following TL reported that only 4 studies described dilatation procedures following TL.[87] Only one of these studies was a thorough evaluation of success and safety of dilatation procedures for dysphagia in a consecutive cohort. However, this cohort consisted of only 20 patients, and all patients were dilated with balloon dilatations.[89]

COUNSELING PATIENTS - SHARED DECISION MAKING

There is a growing body of evidence on epidemiology[5, 7, 90], survival[7], and pulmonary[79], swallowing[91], olfactory[81] and vocal rehabilitation[24, 82] following treatment for advanced larynx and hypopharynx cancer. When counseling new patients, it obviously is important to try to give accurate predictions on expected overall survival, but also, to give the patients a clear image on what to expect after treatment in terms of quality of life and rehabilitation possibilities. Only when patients are counseled on all these aspects, and can comprehend and reproduce them, they are able to participate in shared decision making.

Current research on the counseling process and shared decision making among patients with advanced larynx cancer shows that there is ample room for improvement. A recent review reported that the majority of patients in the UK considered pre-operative TL counseling to be inadequate.[92] Zeine et al. reported that in their study of 153 laryngectomees in the US, 21% had been unaware that loss of normal voice would occur after surgery.[93] Similarly, in a more recent US study, only 40% of patients had been seen by a speech and language pathologist pre-operatively, and again 20% of patients reported not to be aware of the loss of voice.[94] Pre- and perioperative knowledge on treatment and treatment outcomes is essential for patients. Not only to lower decisional regret, improve their overall satisfaction, and improve shared decision making, but also because it may lead to lower postoperative readmission rates.[95-97] Graboyes et al. performed a pilot study evaluating the effect of a perioperative education program and demonstrated a lower readmission rate and higher preparedness for TL in the patients who followed the program and had a better knowledge on TL.[96] To empower patients in shared decision-making, in the Netherlands, the Dutch Patient Federation and the Federation of Medical Specialist have launched a campaign 'Better care starts with a good conversation' (Betere zorg begint met een goed gesprek).[98] This campaign aims to involve patients in the decisional process, and gives health care professionals advice on how to incorporate this in clinical practice, as there are quite some challenges in shared decision-making.

CHALLENGES IN SHARED DECISION-MAKING

Despite the increased attention to shared decision-making as reflected in the launch of a national campaign, the concept of shared decision-making has not yet been universally implemented in clinical practice. Shared decision making refers to the process in which patient and healthcare professionals make health-related choices in which the best available evidence regarding the treatment options is considered, as well as the patients' personal values.[99, 100]

Differences in personal values between patients and healthcare providers are a challenging aspect in shared decision-making.[101] Physicians often tend to provide counseling based on a personal preference for the treatment option that is associated with the highest overall survival rate, or can have a tendency to have a stronger belief in the treatment they are trained to deliver; the specialty bias[55]. Patients, on the other hand, may value quality over quantity of life and are therefore sometimes prefer a treatment that is expected to result in poorer survival but also in what they consider to be a better quality of life.[101-103] For example, a study among firefighters and business executives, in which participants were asked to make a trade-off between e.g. radiotherapy with a lower OS rate versus TL with higher OS rate but loss of normal voice, convincingly demonstrated that overall survival is not the only consideration patients might have.[104] Later studies by Laccourreye et al. demonstrated clear differences in opinion when both patients from a COPD clinic (a patient group that bares similarities to larynx cancer patients) and members of the head and neck team were asked to rate treatment outcomes for advanced larynx cancer.[105, 106] This study also demonstrated that physicians underestimate the effect their treatment will have on the daily life of a patient.[55]

Shared decision making in clinical practice thus seems to be challenging to implement. Transferring all the advantages and disadvantages of different treatment options is a difficult and time-consuming task. Especially in the head and neck cancer patient group, patients might be less outspoken, making it more of a challenge to discover their actual needs and preferences. Furthermore, 'health literacy' can be a significant problem in this group characterized by its relative lower social-economic status and educational levels.[107] Health literacy reflects 'the capacity that patients have to obtain, process and understand basic health information and services in order to make appropriate health decisions'.[108] On the other hand, physicians can be hampered by a busy clinic, which can limit their time counseling patients. Another barrier to adequate shared decision making is the fact that patients diagnosed with cancer often experience difficulties in grasping all the information they will receive during counseling, a logical consequence of the emotions associated with such a diagnosis.[100]

PATIENT DECISION AIDS

Patient decision aids (PDAs) can provide support in these issues, and aim to involve patients in the decisional process by providing objective, clear and concise treatment information and by helping patients to clarify their needs and values.[109] Numerous advantages of using a PDA in clinical practice have already been reported. It has been shown to improve the knowledge of patients and improve the participative role of a patient in the decisional talk.[100] Furthermore, by providing objective information, it may partly eliminate the potential issue of 'specialty bias'. A recent Cochrane review has evaluated the effect of numerous

PDAs and reported less decisional conflict, better adherence to treatment regimes, and possibly even better patient outcomes in patients that have used a PDA.[100]

Several PDAs have now also included a section with questions that helps patients reflect on their norms and values. Discussing the outcomes of these 'reflective exercises' with their treating physician will make it easier for the physician to understand the needs and preferences of the patient. Especially in a setting where there is no 'best treatment option', a PDA could offer patients welcome guidance in the difficult process of medical decision-making. In this way, all the information gathered during decades of research can be directed at those for whom it all was meant: *the patient*.

OUTLINE OF THIS THESIS

Larynx cancer data, both institutional and national, are well known since the studies of Timmermans et al, but similar data on hypopharynx cancer were missing. National data on hypopharynx cancer are presented in **Chapter 2**, which is an epidemiologic study to explore trends in treatment, incidence and survival of this malignancy in the Netherlands. **Chapter 3** describes the development and external validation of a clinical prediction model to give a more accurate estimation on prognosis for patients with advanced larynx cancer. In **Chapter 4,** an assessment of predictive factors for survival in hypopharynx cancer is presented, resulting in the development and validation of a clinical prediction model. In **chapter 5**, we evaluated the laryngo-esophageal dysfunction free survival rate hypopharynx cancer patients in the Netherlands Cancer Institute and describe a propensity score matched analysis of survival. **Chapter 6** reports on the outcome of prosthetic voice rehabilitation in a consecutive cohort of laryngectomized patients over a time period of 13 years. In **chapter 7**, we discuss the management of recurrent periprosthetic leakage, and report the results of a prospective study evaluating a novel prosthetic device. **Chapter 8** focuses on swallowing rehabilitation following TL and reports the cumulative incidence, outcome and complication rate of dilations following TL in two centers in the Netherlands. Finally, in **Chapter 9** we describe the development of an online patient decision aid for advanced larynx cancer, in which all the above described data is presented in an easy to understand way, to empower patients in shared decision making. In **Chapter 10** the results described in this thesis are discussed and suggestions for future research are given. Lastly, in **Chapter 11** a summary of this thesis in Dutch and English is presented.

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Trends in treatment, incidence and survival of hypopharynx cancer: a 20-year population based study in the Netherlands

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2 Trends in treatment, incidence and survival of hypopharynx cancer: a 20-year population based study in the Netherlands

Japke F Petersen, Adriana J. Timmermans, Boukje A.C. van Dijk, Lucy I.H. Overbeek, Laura A. Smit , Frans J.M. Hilgers, Martijn M. Stuiver, Michiel W.M. van den Brekel

ABSTRACT

Background: *Hypopharynx cancer has the worst prognosis of all head and neck squamous cell cancers. Since the 1990s a treatment shift has appeared from a total laryngectomy towards organ preservation therapies. Large randomized trials evaluating treatment strategies for hypopharynx cancer, however, remain scarce, and frequently this malignancy is evaluated together with larynx cancer. Therefore, our aim was to determine trends in incidence, treatment and survival of hypopharynx cancer.*

Materials and Methods: *We performed a population-based cohort study including all patients diagnosed with T1-T4 hypopharynx cancer between 1991 and 2010 in the Netherlands. Patients were recorded by the national cancer registry database and verified by a national pathology database.*

Results: *2999 patients were identified. The incidence increased significantly with 4.1% per year until 1997 and decreased non-significantly afterwards. For women, the incidence increased with 1.7% per year during the entire study period. Total laryngectomy as primary treatment significantly decreased, whereas radiotherapy and chemoradiation increased. The five-year overall survival significantly increased from 28% in 1991-2000 to 34% in 2001-2010. Overall survival for T3 was equal for total laryngectomy and (chemo)radiotherapy, but for T4-patients the survival was significantly better after primary total laryngectomy (± adjuvant radiotherapy).*

Conclusion: *This large population-based study demonstrates a shift in treatment preference towards organ preservation therapies. The 5-year overall survival increased significantly in the second decade. The assumed equivalence of organ preservation and laryngectomy may require reconsideration for T4 disease.*

INTRODUCTION

Despite improvements in radiotherapy (RT) techniques and the advent of chemoradiation (CRT), hypopharynx cancer has the poorest prognosis of all head and neck squamous cell cancers (SCC).[1] In the US and Europe, it represents approximately 3-14% of all head and neck SCC's and up to 75% of newly diagnosed patients present in stage III or IV.[1-4] This is in part due to the 'silent' anatomical location, resulting in late presentation of symptoms.[4] Furthermore, the hypopharynx has a rich submucosal lymphatic network, which promotes early spread towards lymph nodes.[2, 5, 6] Since the majority of patients are heavy smokers and drinkers, they generally present with multiple co-morbidities.[7]

Historically, total laryngectomy (TL) with (partial or total) pharyngectomy used to be the gold standard in hypopharynx cancer treatment. However, since the introduction of CRT in the 1990s there has been a shift towards the use of organ preservation strategies.[8,9] Randomized controlled trials comparing organ preservation treatment strategies to TL for hypopharynx cancer remain scarce, probably due to the relatively low incidence.[1] Therefore, presently population-based studies give the highest level of evidence to gain insight in the epidemiology and survival. In this study we investigate the national trends in treatment, incidence and survival for hypopharynx cancer in the period 1991-2010.

MATERIALS AND METHODS

We conducted a retrospective population-based cohort study based on data retrieved from the databases of the Netherlands Cancer Registry (NCR) and PALGA (the nationwide network and registry of histo- and cytopathology in the Netherlands).[10] We included all patients diagnosed with T1-T4N0-N3M0 SCC of the hypopharynx in the Netherlands between 1991 and 2010. The following data were retrievable: age at incidence, sex, subsite of tumor according to the International Classification of Disease for Oncology (ICD-0-3)[11], TNM classification[12-16], primary treatment (surgery, RT, chemotherapy (CT)), patient

vital status (alive, deceased, lost to follow-up), and follow-up time. The NCR coded type of treatment as RT, CT, surgery or a combination of these. Timing of radiotherapy and chemotherapy was unknown. However, as induction chemotherapy in the Netherlands has never been a standard outside trials, the great majority has been treated with concomitant chemoradiation. By examining the pathological report from the PALGA database we were able to verify the type of surgery performed and the date. To comply with privacy legislation, both databases were anonymized by a trusted third party; therefore we were unable to extent our database with additional clinical variables such as comorbidity, intoxications and exact dose of chemotherapy and radiotherapy, a limitation most population-based studies have.

Our main outcome measures were trends in incidence expressed by European Standardized Rates (ESR), trends in primary treatment and trend in 5-year OS rates. The ESR are rates standardized for the age distribution of a population, which allows for a better comparison between the various European countries and time periods.[17]

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

Statistical analysis

We analyzed incidence rates for the period 1989-2013. Using the Joinpoint Regression Program (version 3.5.3. May 2012; Statistical Research and Applications Branch, National Cancer Institute), the estimated annual percentage change (EAPC) of the ESR was calculated using the log-linear model, allowing for a maximum of four joinpoints. To assess changes in treatment and 5-year OS, patients were divided into patients diagnosed in the first decade (1991-2000) or the second decade (2001-2010). We used the Chi square to assess trends in treatment between the two decades. Kaplan-Meier analysis was used to analyze 5-year OS rates. Univariable comparisons were tested using the Log Rank Test. Using the R package cmprsk[18], a competing risk survival analysis was conducted to calculate the cumulative incidence of salvage laryngectomy and death, respectively. Cox Regression analysis was used for multivariable analyses. SPSS ® Statistics 20.0 (IBM, Armonk, NY) and R-3.2 [19] were used to perform all the statistical analyses.

RESULTS

Combining the two national databases resulted in 3016 patients diagnosed with T1-T4N0-N3M0 SCC of the hypopharynx in the Netherlands during the period 1991-2010. We excluded 17 (0.6%) patients because the pathology reports showed that the main location of the tumor was outside the hypopharynx (*n*=16) or because the pathology report questioned the presence of malignancy (*n*=1). This left 2999 patients for further analyses. Patient characteristics are shown in table 1. Most tumors were located in the pyriform sinus (71%), followed by the posterior pharyngeal wall (8%) and the postcricoid area (6%).

Table 1. Patient characteristics

	Total	TL	RT	CRT	CT	Local Sugery	No treatment
Total	**2,999**	**567**	**1311**	**752**	**48**	**50**	**271**
Sex							
Male	**2373 (79)**	465 (82)	1010 (77)	614 (82)	37 (77)	38 (76)	209 (77)
Female	**626 (21)**	102 (18)	301 (23)	138 (18)	11 (23)	12 (24)	62 (23)
Age in categories							
<50	**385 (13)**	83 (15)	140 (11)	119 (16)	9 (19)	10 (20)	24 (9)
50-59	**948 (32)**	175 (31)	365 (28)	309 (41)	20 (42)	17 (34)	62 (23)
60-69	**970 (32)**	191 (34)	424 (32)	245 (33)	15 (31)	13 (26)	82 (30)
>70	**696 (23)**	118 (21)	382 (29)	79 (11)	4 (8)	10 (20)	103 (38)
TNM classification							
T1N0	**136 (5)**	18 (3)	85 (7)	6 (0.8)	0 (0)	17 (34)	10 (4)
T1N+	**180 (6)**	8 (1)	128 (10)	27 (4)	1 (2)	6 (12)	10 (4)
T2N0	**305 (10)**	44 (8)	194 (15)	36 (5)	4 (8)	12 (24)	15 (6)
T2N+	**497 (17)**	48 (9)	273 (21)	145 (19)	5 (10)	4 (8)	22 (8)
T3N0	**187 (6)**	48 (9)	75 (6)	39 (5)	3 (6)	5 (10)	17 (6)
T3N+	**528 (18)**	107 (19)	189 (14)	183 (24)	9 (19)	2 (4)	38 (14)
T4N0	**337 (11)**	101 (18)	111 (9)	69 (9)	6 (13)	3 (6)	47 (17)
T4N+	**829 (28)**	193 (34)	256 (20)	247 (33)	20 (42)	1 (2)	112 (41)
Stage grouping							
Stage I	**136 (5)**	18 (3)	85 (7)	6 (0.8)	0 (0)	17 (34)	10 (4)
Stage II	**305 (10)**	44 (8)	194 (15)	36 (5)	4 (8)	12 (24)	15 (6)
Stage III	**506 (17)**	108 (19)	255 (20)	90 (12)	4 (8)	8 (16)	41 (15)
Stage IV	**2052 (68)**	397 (70)	777 (59)	620 (8)	40 (83)	13 (26)	205 (76)

Abrreviations: TL = Total laryngectomy (with/without (partial) pharyngectomy, RT = radiotherapy, CRT = chemoradiotherapy, CT = chemotherapy
Values in parentheses are percentages.

Trends in incidence

Incidence and mortality rates in the Netherlands were analyzed for the period 1989-2013. The total number of patients diagnosed with hypopharynx cancer in the Netherlands increased from 116 in 1989 to 208 in 2013, resulting in an increase in ESR from 0.81 (per 100,000) to 0.95 (per 100,000), respectively. The male incidence declined non-significantly since 1997 but the female incidence rose with 1.7% EAPC since 1989 ($p < 0.05$, Fig 1).

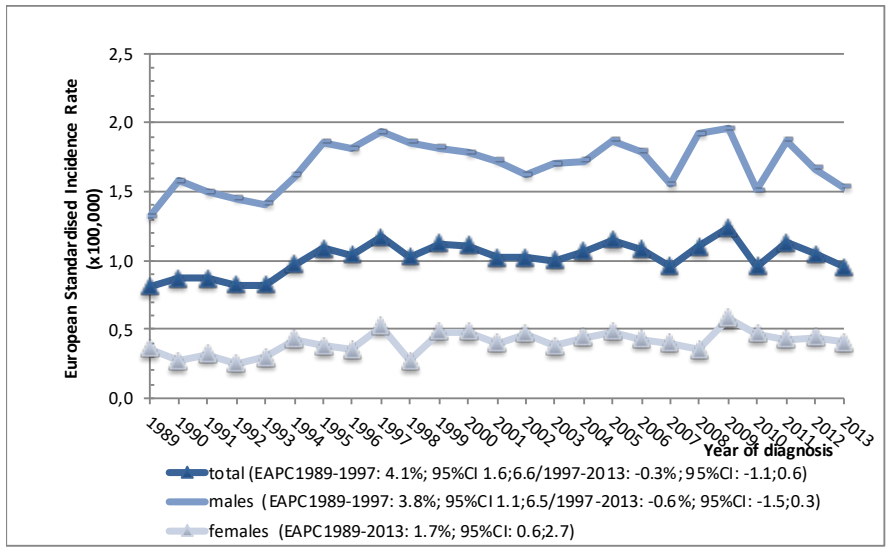

Figure 1. The estimated annual percentage change over the standardized incidence and mortality rates (ESR) was calculated with the log-linear model, allowing for a maximum of four joinpoints.

Trends in treatment

Overall, the majority of patients were treated with RT (44%), followed by CRT (25%) and primary TL with or without post-operative RT (19%). There was a small and heterogeneous group of patients, who were treated with surgery other than TL (2%). Furthermore, 2% of patients received CT only and 9% of patients were not treated at all.

Figure 2 shows the trends in treatment. During the first decade, 20% of all patients with T1-T2 hypopharynx cancer were treated with TL, which decreased significantly to 4.8% in the second decade ($p < 0.001$). The use of RT in T1-T2 increased significantly from 60% in the first decade to 73% in the second decade ($p < 0.001$). CRT remained more or less stable (20% and 22%, respectively;$p = 0.27$).

For patients diagnosed with T3-T4 hypopharynx cancer, the use of TL decreased significantly from 38% during the first decade to 20% during the second ($p < 0.001$). The largest decline was seen in T3 patients, from 39% to 14%, versus a decline from 38% to 23% for T4 patients (both$p < 0.001$). For T3-T4 patients, RT and CRT both showed a significant increase in the second decade from 34% to 43% for RT ($p = 0.007$) and 28% to 38% for CRT ($p < 0.001$). The number of not-treated patients remained the same, as did the distribution of TNM-classification.

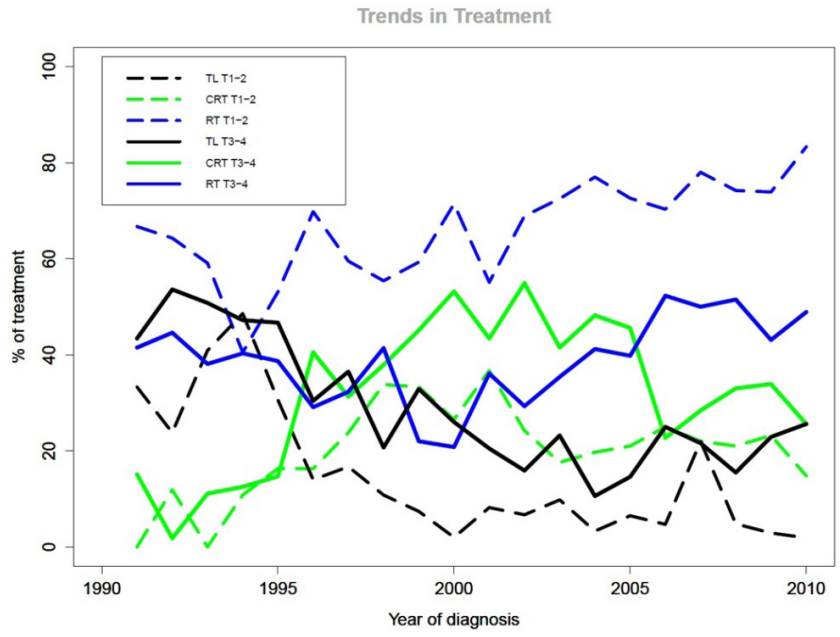

Figure 2. The X-axis depicts the year of diagnosis; the Y-axis depicts the primary treatment divided by the total number of patients treated with CRT (green), RT (blue) or TL (black) that year, for T1T2 (dotted lines) and T3T4 (straight lines) in percentages.

Total laryngectomy

Of the patients, who received TL as primary treatment, 78% received adjuvant RT. There was no significant difference in use of adjuvant RT between the two decades and no significant difference in 5-year OS after TL compared to TL+RT (36% and 34%, respectively; p=0.76). However, the TL+RT group included more T3-T4 (83%) than T1-T2 tumors (27%) as compared to the TL alone group (T3T4 64%, T1T2 36%). In the further analyses, no distinction was made between these two TL subgroups.

Overall survival

The 5-year overall survival for the entire group (*n*=2999) was 29%, including patients, who were not treated. When analyzed separately for patients who received RT, CRT or TL (± RT) (*n*=2630), this was 31%. The 5-year OS for CRT (34%) and TL (34%) was significantly higher than RT (28%,$p < 0.001$), and there was no statistical significant difference in 5-year OS between CRT and TL for the total group. For the treated patients, 5-year OS increased significantly from 28% in the first decade to 34% in the second decade ($p = 0.002$). The small number of patients, who did not receive oncological treatment, had a 5-year OS rate of 3%. The patients who received only CT had a 5-year OS of 15%, and for the patients treated with surgery other than TL this was 46%. eTable 1 shows the 5-year OS rate stratified per treatment and TNM classification.

Trends in overall survival for T1-T2 hypopharynx cancer

When stratified by treatment modality and TNM classification, the 5-year OS of T1-T2 patients treated with TL, CRT and RT was 40%, 44%, and 39%, respectively ($p = 0.268$). There was no significant difference in 5-year OS after TL or CRT between the two decades (TL 41% for 1991-2000 and 37% for 2001-2010,$p = 0.92$; CRT 40% and 46%,$p = 0.353$). For patients receiving primary RT, the 5-year OS increased significantly from 34% in the first to 42% in the second decade ($p = 0.007$).

Trends in survival for T3 hypopharynx cancer

For patients with T3 hypopharynx cancer, the 5-year OS for TL and CRT did not differ significantly (40% and 39%, respectively;$p = 0.475$). The 5-year OS following radiotherapy (24%) was significantly poorer than for TL and CRT ($p < 0.001$). When comparing the two decades, 5-year OS following TL and CRT increased, but was not significantly better in the second decade (TL 38% for 1991-2000 and 43% for 2001-2010;$p = 0.736$, CRT 39% and 40%, respectively,$p = 0.664$). The OS following RT increased significantly from 12% in the first decade to 31% in the second ($p = 0.008$). Kaplan-Meier curves of 5-year OS for T3 per decade are shown in Fig. 3a, b.

Trends in survival for T4 hypopharynx cancer

For patients with T4 hypopharynx cancer, the 5-year OS was significantly better following a TL (29%) when compared to CRT (24%) ($p = 0.039$). Radiotherapy had the lowest 5-year OS of 13%. When comparing the two decades, there was a trend towards an improved 5-year OS after TL, which increased from 24% (1991-2000) to 36% (2001-2010) ($p = 0.050$)). For RT and CRT, OS was not significantly different between the two decades (RT: 12% and 13%,$p = 0.491$; CRT: 23% and 25%,$p = 0.682$). Kaplan-Meier curves of 5-year OS for T4 per decade are shown in Fig. 3c, d.

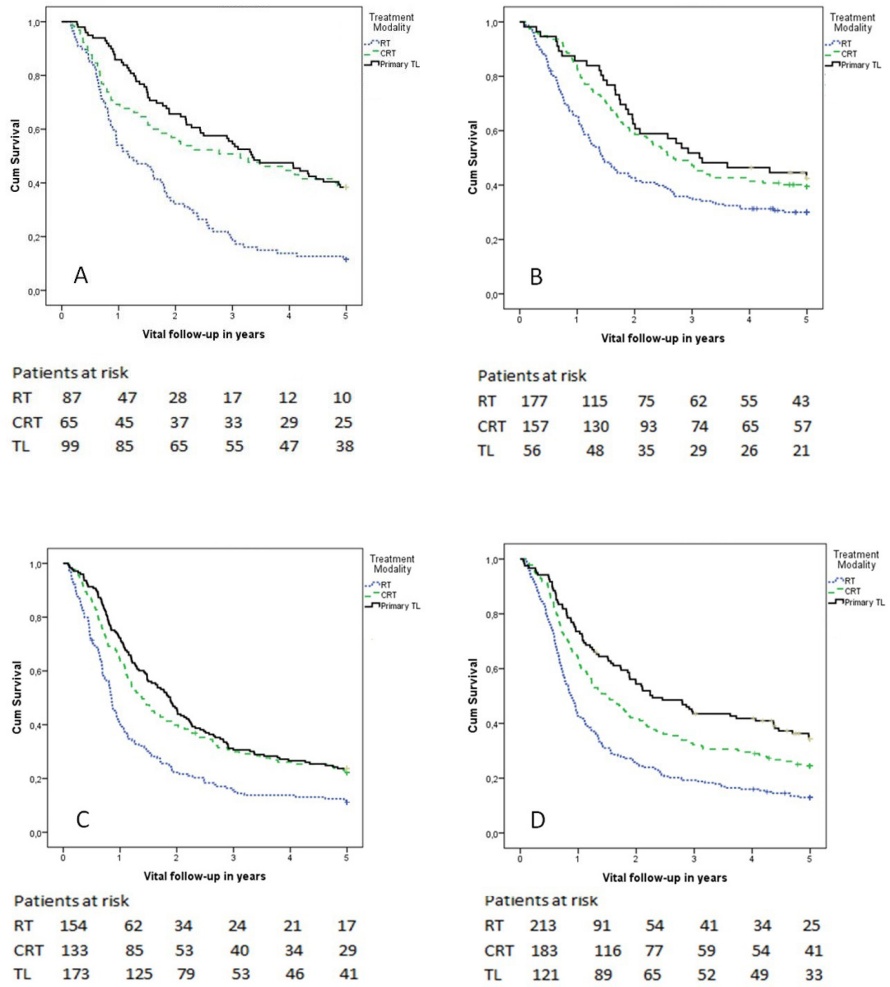

Figure 3 a-d. Kaplan-Meier overall survival rates for T3 hypopharynx cancer diagnosed in the first decade (a) or second decade (b), and T4 hypopharynx cancer diagnosed in the first (a) or second (b) decade.

Supplementary table. 5-Year OS rate per treatment modality and TNM classification

TNM classification	Treatment Modality	5-year OS 1991-2010	Number of patients	P value
T1N0	RT	46%	85	0.736
	CRT	50%	6	
	TL	56%	18	
T1N+	RT	39%	128	0.959
	CRT	41%	27	
	TL	38%	8	
T2N0	RT	44%	194	**0.025**
	CRT	69%	36	
	TL	50%	44	
T2N+	RT	32%	273	0.091
	CRT	37%	145	
	TL	25%	48	
T3N0	RT	36%	75	**0.024**
	CRT	59%	39	
	TL	42%	48	
T3N+	RT	20%	189	**<0.001**
	CRT	35%	183	
	TL	39%	107	
T4N0	RT	20%	111	**<0.001**
	CRT	38%	69	
	TL	38%	101	
T4N+	RT	9%	256	**<0.001**
	CRT	20%	247	
	TL	24%	193	

N = number of patients, P value was calculated between the three treatment options per TNM-classification (Log Rank)

Salvage laryngectomy

During the study period, 706 TLs were performed: 567 primary TLs, 119 salvage TLs, 19 TLs for a dysfunctional larynx. One patient developed a second primary hypopharynx cancer 9 years after RT for a T2N0 posterior pharyngeal wall tumor that occurred in the same subsite, for which she underwent TL.

For the calculation of cumulative incidence of salvage laryngectomy, time in days was used starting from date of incidence until salvage/functional TL, death or date of last FU (cut off at 5-year), and patient status at 5-year (alive, dead, lost to follow-up). The cumulative incidence of salvage/functional TL at 5-year is 7% for RT and 4% for CRT (p = 0.02). The cumulative incidence of death at 5-year is 68% for RT and 64% for CRT (p = 0.006), see eFigure 1 for the cumulative incidence plot of TL and death, stratified by treatment (RT or CRT).

Of the 2063 patients initially treated with RT or CRT, 119 TLs were performed within 5 years after diagnosis; 87 for patients treated with RT and 32 for patients treated with CRT. The median time in days until salvage TL was 423 days, 400 days after RT and 469 days after CRT (p = 0,78).

eFigure 1. Cumulative incidence of incidence of salvage/functional TL or death. The X-axis depicts the time in years since diagnosis, the Y-axis depicts the cumulative probability on a salvage/functional TL or death.

Multivariable analysis

We conducted a multivariable analysis to estimate the Hazard Ratio (HR) for death controlling for age, sex, TNM classification, treatment and subsite (Table 2). Receiving RT as primary treatment was associated with a significant higher risk of death when compared to TL (HR 1.59, 95% CI 1.40-1.81,p < 0.0001), which was not confirmed for CRT compared to TL in the total group (HR 1.07, 95% CI 0.93-1.23). We subsequently analyzed whether the time period (1991-2000 versus 2001-2010) had an impact on 5-year OS. Corrected for age, sex, TNM-stage, treatment (TL, RT or CRT) and subsite, the HR for death in the second decade was significantly lower than in the first decade both for T1-T2 tumors (HR 0.82, 95% CI 0.71-0.96,p = 0.01), and for T3-T4 tumors (HR 0.84, 95% CI 0.76-0.94,p = 0.002). In the previously described Kaplan-Meier analyses, we saw an increased 5-year OS rate for T4 tumors, increasing from 24% in the first to 36% in the second decade. When analyzing only T4 tumors treated in the second decade by a multivariate analysis, we found a significantly higher HR for death for CRT as compared to TL (HR 1.41, 95% CI 1.06-1.87,p = 0.02) when corrected for age, sex, TNM classification and subsite.

Table 2. Multivariable analysis for overall survival using Cox Regression analysis including all patients treated with RT, CRT or TL. The given hazard ratios are hazard ratios for death.

	T1-T4			T1-T2			T3-T4		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age									
<50	REF			REF			REF		
50-59	0.95	0.81-1.11	.50	0.94	0.71-1.24	.67	0.95	0.78-1.14	.57
60-69	0.97	0.83-1.13	.67	1.15	0.88-1.51	.31	0.87	0.73-1.06	.17
>70	1.34	1.14-1.57	**<.0001**	1.71	1.29-2.26	**<.0001**	1.18	0.97-1.44	.11
Sex									
Female	REF			REF			REF		
Male	1.17	1.04-1.32	**.01**	1.23	1.00-1.52	.05	1.15	0.96-1.34	.06
TNM classification									
T1N0	REF			REF			-	-	-
T1N+	1.36	0.98-1.88	.07	1.50	1.07-2.09	**.02**	-	-	-
T2N0	1.01	0.75-1.38	.93	1.03	0.76-1.41	.84	-	-	-
T2N+	1.67	1.25-2.22	**<.001**	1.75	1.30-2.34	**<.001**	-	-	-
T3N0	1.43	1.02-1.99	**.04**	-	-	-	REF		
T3N+	2.14	1.61-2.86	**<.0001**	-	-	-	1.47	1.16-1.85	**.001**
T4N0	2.12	1.57-2.87	**<.0001**	-	-	-	1.49	1.16-1.91	**.002**
T4N+	3.36	2.54-4.44	**<.0001**	-	-	-	2.28	1.83-2.85	**<.0001**
Treatment									
TL	REF			REF			REF		
RT	1.59	1.40-1.81	**<.0001**	1.05	0.82-1.36	.69	1.80	1.55-2.08	**<.0001**
CRT	1.07	0.93-1.23	.34	0.85	0.63-1.15	.28	1.10	0.94-1.28	.22
Subsite									
Pyriform Sinus	REF			REF			REF		
Post-cricoid region	1.29	1. 06-1.58	**.01**	1.58	1.12-2.22	**.008**	1.18	0.92-1.51	.20
Aryepiglottic fold	0.95	0.72-1.26	.72	0.83	0.58-1.21	.33	1.19	0.77-1.81	.43
Posterior wall	1.31	1.10-1.56	**.002**	1.46	1.10-1.92	**.008**	1.23	0.98-1.54	.08
Hypopharynx OL	1.43	1.13-1.79	**.003**	0.83	0.47-1.48	.53	1.56	1.21-2.01	**.001**
Hypopharynx NOS	1.20	1.01-1.43	**.04**	0.76	0.52-1.12	.16	1.36	1.12-1.66	**.002**

Abbreviations: HR hazard ratio, CI confidence interval, REF reference, TL total laryngectomy, RT radiotherapy, CRT chemoradiotherapy, OL overlapping, NOS not otherwise specified

DISCUSSION

This population-based study is one of the largest surveys on hypopharynx cancer published in the literature. With it, we were able to answer the three main research questions posed in the introduction. First, we found that after an initial increase in ESR incidence from 1989 until 1997, there was a non-significant decline from 1997 to 2013. Second, we established that there was a significant decline in the use of TL for both T1-T2 and T3-T4 tumors over the two decades. Last, we found that the 5-year OS for all patients treated with RT, CRT and TL significantly improved in the second decade when compared to the first decade (28%-34%, respectively). Moreover, we observed that T4 patients had the highest 5-year OS rate when treated with TL, followed by CRT and RT (29 versus 24 and 13%).

The trend towards a declining incidence in hypopharynx cancer observed in our cohort since 1997 is in line with international trends[20, 21], as are the changing treatment trends.[9] Lefebvre et al. were one of the first to evaluate organ preservation therapies for hypopharynx cancer in an RCT. The authors found no significant difference in OS, and concluded that organ preservation is the preferred treatment when the tumor is chemo-sensitive.[22] Although since then CRT was routinely used in clinical practice, controversy remained. Meta-analyses specifically comparing TL to CRT for hypopharynx cancer are not available. In 2000, Pignon et al. described a meta-analysis on larynx preservation based on 3 RCTs of which only one RCT included hypopharynx cancer patients. They demonstrated a reduced survival in the CRT arm of 6% at 5 years when compared to TL.[23] In 2011, a meta-analysis analyzing the addition of chemotherapy to locoregional treatment was published in which hypopharynx cancer was analyzed separately. Loco-regional treatment could be: standard/hyperfractionated RT, surgery (with or without RT) or 'other'. For patients with hypopharynx cancer, an overall survival benefit at 5 years of 4% was observed when chemotherapy was added to any loco-regional treatment.[24] However, again there was no direct comparison between CRT and TL in this meta-analysis.

Despite the improved prognosis in the last decade, OS for patients with hypopharynx cancer remains poor.[4, 21, 25] Up to 95% of all recurrences occur in the first 36 months and over half of the first recurrences are distant metastases.[26] Our National Cancer Registry database did not collect data regarding (logo-regional) recurrences and the development of distant metastasis, precluding us from drawing conclusion on these issues. In other cohorts, the incidence of distant metastases constitutes a large problem among hypopharynx cancer patients affecting between 9-40% of patients during follow-up.[4, 26-29] Another issue among hypopharynx cancer patients is the low number of salvage TLs performed after failed RT or CRT. The low cumulative incidence of 4-7% of salvage/functional TL at 5-year mainly reflects the incurability of most recurrences, reflected by the low 5-year OS (RT 28%, CRT 34%), and supported by low OS rates after salvage TL for hypopharynx cancer.[30] Furthermore, as patients diagnosed and treated with (C)RT before 1990 were not included in our database, the patients at risk for salvage TL or TL for a dysfunctional larynx in the first few years are not representative of the actual number of patients at risk in those years.

In concordance to other studies concerning hypopharynx cancer we demonstrated an increased OS for female patients.[21] Possibly a combination of biological and medical behavior plays a role; however, with the results from our study, this remains speculation.

In 2010, a matched pair analysis of patients treated for head and neck cancer in the Memorial Sloan Kettering center was performed to evaluate gender survival disparities. After matching 286 men and 286 women on 6 known prognostic variables the authors concluded that there is no difference between men and women in recurrence-free, disease-specific or overall survival.[31]{Roberts, 2010 #224} Possibly, female patients in our cohort indeed had favorable prognostic variables that contributed to their superior OS.

In our cohort we found no significant difference in OS between TL and CRT for T3 tumors, whereas both treatments had higher OS rates when compared to RT alone. For T4 tumors, we did find a significant difference, where TL was associated with the highest 5-year OS rates when compared to CRT and RT. Several other authors have reported higher 5-year OS rates following TL as compared to RT.[7, 21, 25] Furthermore, a large epidemiological study in the USA reported worse outcomes for CRT compared to TL.[4] Due to the observational nature of all retrospective studies, the results, in part, can be confounded by indication. Yet, given the lack of robust evidence for equivalence of organ preservation compared to TL in patients with T4 tumors, and the observed better survival after TL in epidemiological cohort studies, the assumed equivalence of CRT and TL for T4 tumors is questionable. In our opinion, TL should not be restricted to those patients who carry a high risk on a dysfunctional larynx after (C)RT, but all T4 patients should be counseled on the potentially better chance for survival using TL, as compared to (C)RT.

Limitations

The results of our study have to be interpreted with caution. Despite the fact that we used data collected by trained cancer registry administrators, the accuracy of the NCR data as such cannot be tested. However, by combining the NCR database with the national Pathology database, we were able to verify the histopathology of the tumors and the treatment modalities. However, details regarding treatment, patient- and tumor characteristics are lacking in this national database. Some patients, especially in the T4 group, might have received RT with palliative intent. Despite these considerations, the conclusions on the trends in incidence, treatment and OS of hypopharynx cancer from this large population-based database seem valid.

CONCLUSION

This population-based study demonstrates a shift in treatment preference towards organ preservation therapies in the Netherlands, with a significant decline in TL and a significant increase in RT and CRT since 2001. At the same time, the 5-year OS of patients treated with RT, CRT or TL increased significantly. Based on our results, the assumed equivalence of CRT and TL for T4 disease may require reconsideration.

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3

Development and external validation of a risk prediction model to predict 5-year overall survival in advanced larynx cancer

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3 Development and external validation of a risk prediction model to predict 5-year overall survival in advanced larynx cancer

Japke F. Petersen, Martijn M. Stuiver, Adriana J. Timmermans, Amy Chen, Hongzhen Zhang, James Paul O'Neill, Sandra Deady, Vincent Vander Poorten, Jeroen Meulemans, Johan Wennerberg, Carl Skroder, Andrew T. Day, Wayne Koch, Michiel W.M. van den Brekel

ABSTRACT

Objective: *TNM classification inadequately estimates patient specific overall survival (OS). We aimed to improve this by developing a risk prediction model for patients with advanced larynx cancer.*

Study design: *Cohort study*

Methods: *We developed a risk prediction model to estimate the 5-year OS rate based on a cohort of 3,442 patients with T3T4N0N+M0 larynx cancer. The model was internally validated using bootstrapping samples and externally validated on patient data from five external centers (n=770). Main outcome was performance of the model as tested by discrimination, calibration and the ability to distinguish risk groups based on tertiles from the derivation dataset. The model performance was compared to a model based on T- and N classification only.*

Results: *We included age, gender, T and N classification, and subsite as prognostic variables in the standard model. After external validation the standard model had a significantly better fit than a model based on T- and N classification alone (C statistic 0.59 vs. 0.55,p < 0.001). The model was able to distinguish well between three risk groups based on tertiles of the risk score. Adding treatment modality to the model did not decrease the predictive power. As a post-hoc analysis, we tested the added value of comorbidity as scored by American Society of Anesthesiologists score in a subsample, which increased the C statistic to 0.68.*

Conclusion: *A risk prediction model for patients with advanced larynx cancer, consisting of readily available clinical variables, gives more accurate estimations of the estimated 5-year survival rate when compared to a model based on T and N classification alone.*

INTRODUCTION

Larynx cancer is among the most frequently diagnosed head and neck squamous cell cancers (SCC), and approximately 40% of patients present with advanced disease.[1-3] The 5-year overall survival (OS) of the advanced (T3T4) tumors varies between 34% and 49%, depending on patient-related factors, tumor-related factors and treatment.[3, 4] Historically, patients with advanced larynx cancer were treated with a total laryngectomy (TL) with adjuvant radiotherapy (RT). In 1991, the randomized controlled VA trial demonstrated equal OS for organ preservation (induction chemotherapy [CT] followed by chemoradiotherapy [CRT]) compared to TL plus adjuvant RT.[5] In 2003, the results of the Radiation Therapy Oncology Group (RTOG) 91-11 study confirmed the value of CT added to RT; however, large T4N0 larynx cancer patients were excluded.[6] Furthermore, in a later publication on the VA data, OS for T4N0 patients was significantly higher after TL.[7] Recently, several other retrospective studies have reported significantly higher OS rates for TL when compared to organ preservation protocols.[2, 4, 7-10]

Adequate information regarding the prognosis is crucial in communicating with patients and in clinical decision-making. The mixed results regarding the best treatment for advanced larynx cancer have made the decision process, however, a complex task. Currently, the TNM classification is often used when talking about the estimated prognosis of patients. Although the TNM classification effectively prognosticates at a population level, it works less well on the individual level.[11, 12] Furthermore, the influence of variables such as age and subsite on OS is difficult to assess in the individual patient. Several studies have demonstrated that OS predictions based on clinical prediction models (CPM) are superior to those made by experienced clinicians.[11, 13-15] The availability of a quantitative prediction model may therefore enhance the quality of the decisional process.

In this study we aimed to develop a CPM to aid decision making in advanced larynx cancer

care. We hypothesized that the model would give more accurate predictions on OS than the TNM classification alone gives us now. Because of the absence of decisive evidence from randomized controlled trials on the best treatment choice for advanced larynx cancer, a secondary objective of this large observational study was to estimate the effect of treatment on expected survival.

METHODS

Derivation data

We collected patient data from a cohort of the Netherlands Cancer Registry covering all patients that have been diagnosed with advanced SCC of the larynx in the Netherlands (1991-2010). Timmermans et al. recently published the trends in treatment, incidence and survival of this cohort in which a detailed description is given of the selection and characteristics of the patients[4]. For the development of the CPM, we included all patients with primary T3T4N0N+M0 SCC of the larynx who were treated with a primary TL, CRT or primary RT. The derivation dataset initially consisted of 3,794 patients with T3T4N0N+M0 SCC of the larynx diagnosed between 1991 and 2010 in the Netherlands. We excluded patients without follow-up (n = 7), patients who had emigrated (n = 12) and patients who were not treated with primary RT, CRT or TL (n = 333). Thus, 3,442 patients were included in the study.

Validation data

External validation of a CPM is crucial to evaluate its performance. We collected data of five independent patient cohorts: 390 patients from an Irish National Cancer Registry, 91 patients from Johns Hopkins, 89 from Emory University Hospital, 100 from Lund Medical Center and 100 from the University Hospitals Leuven (total = 770). All centers received permission from their institutional review board to participate in this study.

Statistical analysis

We used descriptive statistics to summarize patient characteristics and compared the pooled validation group and the derivation group by means of the χ^2 or Student t tests. Five-year OS rates were compared by means of the log-rank test, and a multivariable Cox proportional hazard analysis was used to estimate the influence of treatment modality on OS.

Clinical prediction model

For the risk-prediction model, we used the Cox proportional hazards model.[16] The model was fully pre-specified, with exception of year of treatment, which was subject to selection based on statistical significance (to control for changes in survival probability due to changes in treatment trends over time if necessary). The predictors included in the model were chosen based on current knowledge, availability and biological plausibility, and included age (using a restricted cubic spline), gender, subsite within the larynx (*International Classification of Diseases for Oncology, Third Revision*), T classification and N classification.

Model performance

We assessed model performance using discrimination and calibration. Discrimination is the ability of a prediction model to distinguish between patients who experience an event from those who do not and can be measured by means of the C statistic.[16] The C statistic can range from 0.5, which means equal to chance, to 1.0, which means a perfect model. In a Cox proportional hazard model, a C statistic of 0.60 implies that at any point in time, a random patient with an event has a higher risk score than a random patient without an event 60% of the time.[16, 17]

Calibration relates to the agreement between estimated and observed probabilities and is depicted in a calibration plot. In a perfect calibration plot the lines of the estimated and observed probabilities would follow a 45° line, which implies that the predicted probability is identical to the observed probability.[16-18]

Internal validation was performed by taking 200 bootstrapping samples. Based on the results of the bootstrap validation, we applied uniform shrinkage to adjust the coefficients. We then performed external validation of the shrunken model and calculated the C statistic and calibration curves.

As a third measure of model performance we divided the validation data into 3 risk categories based on tertiles derived from the derivation data. We then plotted the observed Kaplan-Meier (KM) curve of the validation data over the expected KM curve of the derivation set based on the predicted risks, to visually inspect the agreement between observed and expected survival in each of the risk groups.
All models were built using the RMS package in R Software.[19, 20]

RESULTS

Derivation and validation dataset

The derivation dataset consisted of 3,442 patients. Mean age was 64 years, the majority of patients were male (79%) and the 5-year OS rates were 44% for RT, 45% for CRT and 49%

for TL. All included variables (age, gender, subsite T- and N classification and treatment) had a significant effect on OS ($p < 0.001$ for all variables except gender: $p < 0.03$).

Patient characteristics from the derivation and validation dataset can be found in Table 1. Patients in the derivation dataset were significantly older than the validation dataset ($p < 0.001$) and had less male patients (79% *vs*. 85%). In the derivation data, more tumors were located in the supraglottic, and more patients were treated with primary RT (58% *vs*. 37%) and less with CRT (8% *vs*. 28%) or primary TL (34% *vs*. 40%). Furthermore, there were significant differences in T and N classification ($p < 0.001$) and 5-yr OS rates ($p < 0.001$).

Table 1. Patient characteristics from the derivation and validation datasets.

	Derivation dataset	Pooled validation dataset	Leuven, Belgium	NCR Ireland	Baltimore, US	Atlanta, US	Lund, Sweden
Age							
Mean (range)	64 (28-100)	62 (16-92)	64 (40-90)	62 (35-85)†	60 (38-92)	59 (16-83)	66 (35-89)
Gender							
Male	2705 (78.6)	652 (85)	92 (92)	339 (86.9)	72 (79.1)	64 (74.1)	85 (85)
TN classification							
T3N0	1237 (35.9)	282 (36.6)	34 (34)	159 (40.8)	28 (30.7)	25 (28.1)	36 (36)
T3N+	681 (19.8)	145 (18.8)	17 (17)	72 (18.5)	21 (23.1)	21 (23.6)	14 (14)
T4N0	887 (25.8)	174(22.6)	28 (28)	73 (18.7)	17 (18.7)	18 (20.2)	38 (38)
T4N+	637 (18.5)	169 (21.9)	21 (21)	86 (22.1)	25 (27.5)	25 (28.1)	12(12)
Sublocation							
Glottis	1074 (31.2)	335 (43.5)	55 (55)	157 (40.3)	43 (47.3)	37 (41.6)	43 (43)
Supraglottis	2172 (63.1)	313 (40.6)	38 (38)	147 (37.7)	45 (49.5)	36 (40.4)	47 (47)
Subglottic	88 (2.6)	26 (3.4)	3 (3)	16 (4.1)	2 (2.2)	2 (2.2)	3 (3)
Larynx NNO	108 (3.1)	96 (12.5)	4 (4)	70 (17.9)	1 (1.1)	14 (15.7)	7 (7)
Treatment							
TL	1168 (33.9)	311 (40.4)	54 (54)	120 (30.8)	55 (60.4)	40 (44.9)	42 (42)
RT	2009 (58.4)	281 (36.5)	15 (15)	164 (42.1)	1 (1.1)	9 (10.1)	57 (57)
CRT	265 (7.7)	213 (27.7)	31 (31)	106 (27.2)	35 (38.5)	40 (44.9)	1 (1)
Total	3442	770	100	390	91	89	100

† After transformation to continuous variable using midpoint of given age category, median = 63
Abbreviations: Larynx NNO = Larynx not otherwise specified.
Values in parentheses are percentages.

Model performance - Internal validation

Our main objective was to compare the discriminative power of a multivariable prediction model with a model based on T classification and N classification alone. As a second objective, we evaluated the effect of treatment on OS, for which we added treatment modality as a prognostic variable in a third model containing the same variables as the prediction model. First, internal validation was performed taking bootstrapping samples ($n = 200$). This demonstrated that the prediction model including age, gender, T classification, N classification and subsite as predictors had significantly better discrimination (C statistic 0.65) than the model based on T- and N classification alone (C statistic 0.57) (likelihood ratio test$p < 0.001$).

Model performance - External validation

After external validation on the combined validation dataset ($n = 770$), discrimination proved to be significantly better for the full model (C statistic 0.59, 9% better) compared to the model based on T-and N classification alone (C statistic 0.55) (likelihood ratio test$p < 0.001$). Calibration of the two models is depicted in Figure 1A and B, which show a slight degree of miscalibration in both models as they do not exactly follow the 45° line. As a third measure of strength, the observed KM curves of the validation sets were plotted over the KM curves estimated from the derivation dataset for the two models (Fig. 2) to test whether a distinction can be made between high-, medium- and low-risk patients. The plots show that the models are able to distinguish between the three different risk categories, although OS in the medium and low risk groups of the validation set was lower compared to these risk groups in the derivation set.

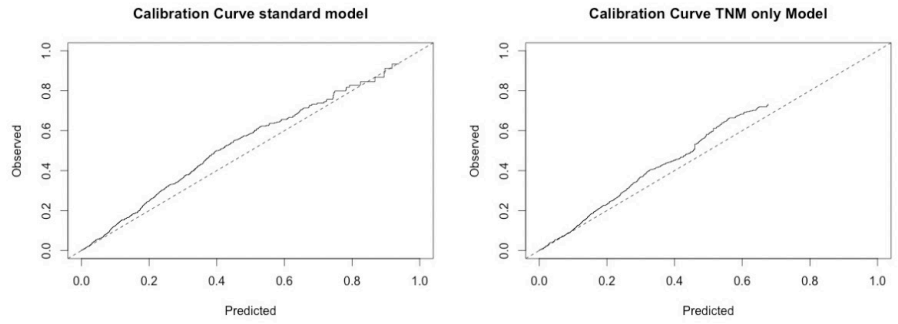

Figure 1 a-b. Calibration curves for the model based on the combined dataset (a) and the model based solely on T- and N classification as a prognostic variable (b)**.** A perfect calibration would exactly follow the 45° line (dashed curve).

Influence of treatment modality

Treatment modality was significantly related to OS in the validation database ($p < 0.0001$). The hazard ratio for death adjusted for age, gender, subsite, T classification and N

classification was 1.56 for RT compared to TL ($p < 0.001$), and 0.95 for CRT compared to TL ($p = 0.71$). With treatment modality as a prognostic variable added to the prediction model, the C statistic was 0.60.

Exploratory analysis

*A*lthough the prediction model was able to distinguish well between the three risk groups and performed better compared to a model based on TNM classification alone, the C statistic was still relatively low. We hypothesized that adding comorbidity as a prognostic variable might further improve model performance. However, this variable was not recorded in our derivation database since it was retrieved from a national cancer registry. We therefore performed an exploratory post-hoc analysis on a subset of the derivation dataset including 181 patients with T3T4N0N+M0 SCC of the larynx, diagnosed and treated with RT, CRT or TL in the Netherlands Cancer Institute between 1999-2008,[4] for which we were able to collect American Society of Anesthesiologists (ASA) scores as a substitute measure for comorbidity. The majority of the external centers had not systematically recorded ASA scores in the patient files, thus we were unable to perform external validation on this model. After shrinkage by internal validation the C statistic was 0.68.

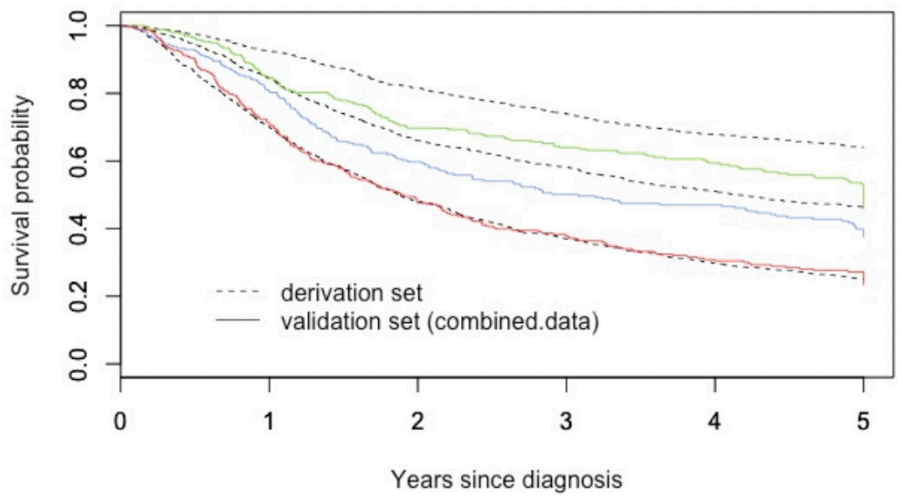

Figure 2. Kaplan Meier curve of the expected overall survival as estimated by the derivation set (dashed line) and the observed overall survival as seen in the validation set, divided in three risk groups. Gree*n* = low risk, blue = intermediate risk, red = high risk on death.

DISCUSSION

The results of our study confirm our hypothesis that a validated multivariable risk prediction model gives more accurate OS predictions for advanced larynx cancer compared to a model based on T and N classification alone. According to estimated and observed KM curves, the model distinguishes adequately between the three risk categories. Yet, with a C statistic of 0.59, the predictive accuracy leaves rooms for improvement in the context of clinical decision making for individual patients.

As a secondary objective, we aimed to investigate the effect of treatment on expected OS. Estimating the effect of treatment modality in an observational study is troublesome, since this incorporates a bias by indication. However, because a new, large, randomized controlled trial comparing TL with organ preservation strategies may never be performed, we investigated the influence of treatment modality when accounting for the other prognostic variables included in the prediction model. This analysis suggested that survival after TL is better than after CRT or RT, as was suggested by the results published by Timmermans et al.[4]

As also was reported by Timmermans et al., the derivation data contained more supraglottic tumors than the validation data. Interestingly they demonstrated how this distribution was reversed in the T1T2 tumors, in which they found more glottic (78.6%) than supraglottic tumors (19.9%).[4] The RTOG 91-11 study, with mainly advanced tumors, found a similar rate of supraglottic tumors (69%).[6, 21]

In recent years, several risk-prediction models have been published. In 2001, Baatenburg de Jong et al. developed a risk-prediction model for T1-T4 SCC occurring in all subsites of the head and neck except the esophagus.[22] The model was based on 1,396 patients diagnosed between 1981 and 1998, and included the prognostic predictors age, gender, tumor site, prior tumor and TNM classification. In 2013, the model was updated, and the Adult Comorbidity Evaluation-27 was added as a prognostic variable and external validation was performed. After external validation, the model showed a good C statistic of 0.69, but the validation dataset did not include hypopharynx and nasopharynx cancer.[23] In their model, the impact of severe comorbidity appeared comparable to the impact of a T4 tumor or N3 neck on OS. We were not able to include comorbidity in our original model, which might explain why our model was less accurate. The exploratory post-hoc analysis that included ASA score as an indicator of comorbidity improved the discriminative ability.

Another risk-prediction model has been developed by Egelmeer et al., who developed

and externally validated a model for T1 to T4 larynx cancer receiving RT, based on a cohort of 994 patients. In concordance with our findings, they reported male gender, older age, higher T classification and nodal involvement to be negative predictive factors for OS. Furthermore, they included hemoglobin level and radiotherapy dose as prognostic factors. The performance of their model ranged from 0.68 to 0.74.[24] More recently, another CPM for T3T4 larynx cancer patients was published based on a cohort of 615 patients. In this model, the authors included age, Eastern Cooperative Oncology Group (ECOG) performance status, N classification and treatment modality, but excluded variables such as T classification, subsite and smoking status using a stepwise selection procedure. Such a data-driven approach for variable selection results in a model that might not be accurate when used for new patients.[25] External validation was not performed, and the authors note that the model needs external validation first and might not be generalizable.[26]

In the literature, several different patient-specific and tumor-specific factors have been investigated as prognostic variables for head and neck cancer, indicating that factors such as albumin (<4 g/dL), alcohol intake[27], insurance status, race[8], tumor volume[28], tumor hypoxia[29], and several different biomarkers[30, 31] can have a prognostic influence on overall survival. In order to help distinguish the actual predictors for OS and creating a more accurate RPM, a large prospective cohort should be kept in which multiple parameters are collected or this data could be extracted from electronic patient files. Currently, in the Netherlands a national prospective audit is being conducted which in the future could be used to further improve our model.

Next to OS, another frequently used endpoint in clinical studies is larynx preservation. Predicting which patients benefit from organ preservation strategies and which do not could be of great value for avoiding unnecessary toxic treatment with added morbidity after salvage surgery. A well-known model to predict this is the TALK score: a prognostic model developed to facilitate the treatment decision making in larynx preservation.[27] TALK is an acronym for T status, Albumin, Alcohol (or liquor) use and Karnofsky Performance score, which were the predictors used. In an external validation on the VA larynx cancer study dataset, a C statistic of 0.57 was obtained for predicting larynx preservation. The TALK score however does not indicate which patients suffer from a non-functioning larynx after organ preservation, such as those who have a tracheotomy or nasogastric feeding tube in situ. In our derivation cohort, larynx preservation was scored as not having had a laryngectomy after organ preservation. However, information regarding a tracheotomy or feeding tube was missing, due to the fact that it was based on a national cancer registry cohort. We therefore chose not to predict larynx preservation based on these data.

In survival predictions, comorbidity scores can be of great value. However, in our cohort comorbidity scores were missing. ASA score was available, however, for a subgroup of the derivation dataset. In the ASA score the burden of comorbidity is incorporated, thus it could potentially serve as a proxy for an actual comorbidity scale. In 2015, Young et al. compared the ASA score with the ECOG/World Health Organization performance scale as a measure of functional status in a predictive model and demonstrated equal performance in predicting length of stay after cancer surgery.[32] In our exploratory post hoc analysis, adding ASA score as a prognostic variable increased our C statistic to 0.68. We recommend that future studies determine which comorbidity scale might be of most value for prediction of survival outcomes in head and neck cancer, and assess the added value of this scale in a multivariable prediction model.

There are certain limitations to our study. In multivariable prediction modeling, a generally accepted rule of thumb is that a minimum of *m*/10 predictors should be used in a model, where *m* is the number of uncensored event times (e.g. death)).[33] With 2,180 uncensored events times in our cohort, we could have included many more predictors without risking overfitting. However, our choice of predictors was limited to those available in the population-based database. Because the database was anonymized we were unable to extend our database with variables such as comorbidity, intoxications, tumor volume, race and insurance status that might have improved the predictive value of the model for OS.

CONCLUSION

We have developed a ready-to-use prediction model based on a large systematically coded database on advanced-stage larynx cancer. The model gives significantly more accurate predictions on OS than compared to a model based on T and N classification alone. All of the variables included in the model are readily available in clinical practice. Although it should not be used as a replacement for clinical reasoning, it may aid the decision-making process for patients with advanced larynx cancer.

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Optimizing survival predictions of hypopharynx cancer: Development of a clinical prediction model

Submitted

4 Optimizing survival predictions of hypopharynx cancer: Development of a clinical prediction model

Japke F. Petersen, Coralie R. Arends, Vincent van der Noort, Adriana J. Timmermans, C. René Leemans, Remco de Bree, Michiel W.M. van den Brekel, Martijn M. Stuiver

** JF Petersen and CR Arends contributed equally to this manuscript*

ABSTRACT

Objectives: *To develop and validate a clinical prediction model (CPM) for survival in hypopharynx cancer, thereby aiming to improve individualized estimations of survival.*

Methods: *Retrospective cohort study of hypopharynx cancer patients. We randomly split the cohort into a derivation and validation dataset. The model was fitted on the derivation dataset and validated on the validation dataset. We used a Cox's proportional hazard model and least absolute shrinkage and selection operator (LASSO) selection. Performance (discrimination and calibration) of the CPM was tested.*

Results: *The final model consisted of gender, subsite, TNM classification, ACE27, BMI, hemoglobin, albumin and leukocyte count. Of these, TNM-classification, Adult Comorbidity Evaluation-27 score (ACE27), BMI, hemoglobin and albumin had independent significant associations with survival. The C Statistic was 0.62 after validation. The model could significantly identify clinical risk groups.*

Conclusions: *ACE27, BMI, hemoglobin and albumin are independent predictors of overall survival. The identification of high-risk patients can be used in the counseling process and tailoring of treatment strategy or follow-up.*

INTRODUCTION

Hypopharynx cancer is a rare disease and has the worst overall survival (OS) of all head and neck squamous cell (SCC) malignancies.[1-3] Due to the anatomical location of the hypopharynx, tumors can progress relatively far before giving rise to any clinical symptoms, and the majority of patients have lymph node metastases at time of diagnosis.[4] Survival rates are gradually improving, but remain low, with 5-year OS rates of 28-41%.[1, 4, 5] Oncological management usually consists of either primary radiotherapy (RT), chemoradiotherapy (CRT), laser surgery or a total laryngectomy (TL) with partial or circumferential pharyngectomy.[6] The TNM classification is an important tool to describe tumor characteristics and estimate prognosis on a population level, but does not translate well to survival predictions made on the individual level.[7] To estimate prognosis on the individual level, physicians need to consider numerous patient specific variables, such as age, gender, comorbidity and results from imaging, pathology reports and possibly peripheral blood tumor markers.[8, 9] Based on a combination of all these factors, the 'best treatment option', usually defined in terms of survival, is selected and discussed with the patient. However, the human cognitive capacity is limited, and capable only of taking into account a few variables at a time when making a decision.[10] Several studies have already demonstrated the superiority of statistical decisional models over clinical expertise-based predictions of physicians.[11, 12]

In order to improve survival estimations for individual patients with hypopharynx cancer, the objectives of this study are to examine clinical predictors of survival in hypopharynx cancer, and develop and validate a clinical prediction model (CPM) based on these readily available variables. The resulting improved survival estimates might enable tailoring of treatment strategies or follow-up regimen.

MATERIALS AND METHODS

Study design and participants

We performed a retrospective study in which we collected data of patients diagnosed and treated for squamous cell carcinoma (SCC) of the hypopharynx in three dedicated head and neck centers in The Netherlands: the Netherlands Cancer Institute (1990-2013), the University Medical Center Utrecht (1990-2012) and Amsterdam University Medical Center, location VUmc (2003-2010). Data of patients in these cohorts were provided by the research information department of each hospital. We excluded patients with distant metastases at time of diagnosis, patients who were not treated with curative intent, patients who were primarily treated in another hospital, and patients who had revision of diagnosis

after additional medical evaluation, mostly because of a different tumor localization.
This study does not fall under the scope of the Medical Research Involving Human Subjects Act. The institutional review boards of all hospitals approved this study.

Predictor variables

We build the model using a limited number of candidate variables, which were preselected based on clinical expertise, scientific evidence and practical feasibility.[13, 14] The preselected variables were age at diagnosis, gender, T classification, N classification, subsite, the Adult Comorbidity Evaluation-27 (ACE27) score, packyears, alcohol consumption, BMI and the baseline peripheral blood values hemoglobin (mmol/L), albumin (g/L) and leukocyte count (10E9/L). Leukocyte count was dichotomized into low-normal (<10,5*10^9/L) and high (≥10,5*10^9/L). ACE27 was scored in retrospect by one researcher (J.P.) for all patient cohorts based on the comorbidities registered in the medical files at time of diagnosis.

Statistical analysis

To obtain two datasets that were representative of the Dutch population of patients with hypopharynx cancer, we first combined all three cohorts into one dataset, and then randomly split the cohort into two datasets, one of which was used for the model derivation while the other was used for the validation. Descriptive statistics were used to report patient characteristics and to assess whether there were relevant differences between the derivation dataset and the validation dataset. The samples were compared by means of the independent T-test (continuous variables), and Linear-by-Linear test or Fisher exact test (categorical variables). Missing data of the predictors under consideration in our cohort was considered to be missing at random. Multiple imputation was used to complete the data in the derivation dataset, using the Multiple Imputation by Chained Equations procedure (MICE package in R).[15] We generated 20 imputed datasets from our dataset.

Model derivation

On each of the 20 imputed datasets, a least absolute shrinkage and selection operator (LASSO) penalized cox proportional hazards model was fitted using the penalized package in R studio.[16] In this method, variables are not selected based on p-values, but shrinkage is applied to the regression coefficients in such a way that coefficients of the least contributing predictors become exactly zero. Non-zero coefficients are retained in the model and are therefore considered significant predictors. In this way, LASSO regression strives to balance two competing objectives: optimize the prognostic accuracy versus minimizing the number of predictors contributing to the model, in order to reduce the risk of overfitting. The resulting model thus in part depends on the relative 'strength' of these opposing forces, as expressed by a parameter 'lambda', which can be set by the user. In our case, we chose the optimal value of the lambda coefficient (for each imputed dataset separately) for a set of 12 candidate values by internal cross-validation, using the leave-one-out method. Afterwards, the regression coefficients of the models fitted on the imputed datasets were pooled into the final CPM by averaging them.

Model performance and validation

Performance of the CPM was assessed in the derivation and validation dataset using discrimination and calibration. Discrimination of the prognostic model is defined as its accuracy to distinguish a patient who died from a patient who survived, and is expressed in the C statistic. A C statistic of 0.5 indicates no discriminative ability, whereas a C statistic of 1.0 indicates perfect discrimination[14]. Calibration reflects the similarity between the probabilities of the event for each patient as predicted by the model and the outcomes observed in the sample, and is visually depicted in a calibration plot. A 45° line indicates perfect agreement between predicted and observed outcome.[17]

After internal validation in the derivation data, we assessed discrimination and calibration of the model in the validation dataset to assess its performance when used in new patients. This step is essential to test the strength of the model before it can be used in clinical practice.[14] To assess the model performance in a more clinically interpretable way, we created three risk strata of equal size, based on the distribution of linear predictors in the derivation dataset. Survival rates of these strata in the derivation dataset and the external validation dataset were plotted with Kaplan-Meier curves, to assess whether the model accurately discriminates between the risk strata. We used a cox proportional hazard analysis to compare hazard ratios (HRs) and 95% confidence intervals (CI) for these risks groups.

To compare the accuracy of the CPM to a model containing only the TNM classification as clinical predictors, we used the C statistic to estimate the performance of a model containing only TNM classification. The TNM classification model was similarly built using a LASSO-penalized cox proportional hazards model. Furthermore, using a likelihood-ratio test, we tested whether our model performed significantly better that the model with the TNM classification only. For this test, a p-value <0.05 was considered to indicate statistical significance.

Table 1. Patient characteristics of the derivation and validation datasets

Characteristics	Total cohort	Derivation dataset	Validation dataset	p-value
	768	**384**	**384**	
Age, mean [sd]	63 [10.1]	63 [10.1]	63 [10.2]	.803*
Sex				.287***
Female	161 (21)	87 (23)	74 (19)	
Male	607 (79)	297 (77)	310 (81)	
T classification				.838**
T1	81 (10)	43 (11)	38 (10)	
T2	204 (27)	99 (26)	105 (27)	
T3	213 (28)	109 (28)	104 (27)	
T4	268 (35)	133 (35)	135 (35)	
Missing	2 (0.3)	0	2 (0.5)	
N classification				.895**
N0	251 (33)	130 (34)	121 (32)	
N1	138 (18)	59 (15)	79 (21)	
N2	305 (40)	158 (41)	147 (38)	
N3	73 (9)	37 (10)	36 (10)	
Missing	1 (0.1)	0	1 (0.3)	
Subsite				.862***
Pyriform Sinus	599 (78)	298 (78)	301 (78)	
Other	169 (22)	86 (22)	83 (22)	
ACE27				.511**
0	261 (34)	126 (33)	135 (35)	
1	299 (39)	152 (39)	147 (38)	
2	167 (22)	84 (22)	83 (22)	
3	41 (5)	22 (6)	19 (5)	
Packyears, median [IQR]	37 [25-47]	38 [26-47]	36 [25-47]	.442*
Missing	29 (4)	16 (4)	13 (3)	
Alcohol consumption, median [IQR]				.492*
	21 [14-42]	21 [14-42]	21 [14-42]	
Missing	15 (2)	7 (2)	8 (2)	
BMI, mean [sd]	23 [4.3]	22.9 [4.3]	22.9 [4.3]	.617*
Missing	73 (10)	38 (10)	35 (9)	
Leukocytosis				.609***
Yes	485 (63)	242 (63)	243 (63)	
No	190 (25)	99 (26)	91 (24)	
Missing	93 (12)	43 (11)	50 (13)	
Hemoglobin, median [IQR]	8.6 [7.9-14.5]	8.6 [7.9-9.1]	8.6 [7.9-9.2]	.132*
Missing	19 (6)	6 (2)	13 (3)	
Albumin, median [IQR]	40.6 [36.5-44]	40.1 [37-45]	40 [34.7-44]	.423*
Missing	222 (29)	117 (30)	105 (27)	

Abbreviations: n, number of patients: sd, standard deviation; ACE27, Adult Comorbidity Evaluation-27; IQR, interquartile range; BMI, Body Mass Index.
Leukocytosis was expressed as a level of ≥10.5 10E9/L.
Values in parentheses are percentages unless otherwise indicated.
*independent T-test, ** linear by linear test & *** Fisher exact test

RESULTS

Derivation and validation datasets

The research information departments provided us with data on 1077 patients that had been diagnosed with hypopharynx cancer in the respective hospitals. We subsequently excluded 309 patients (see Figure 1). This left us with 768 patients for analysis. An analysis of the data revealed that there were no significant differences in all variables between the two datasets, thus the random split could be considered successful. There were predictors without missingness, with a maximum of 29% missing data of the peripheral blood value albumin. Patient characteristics are shown in Table 1.

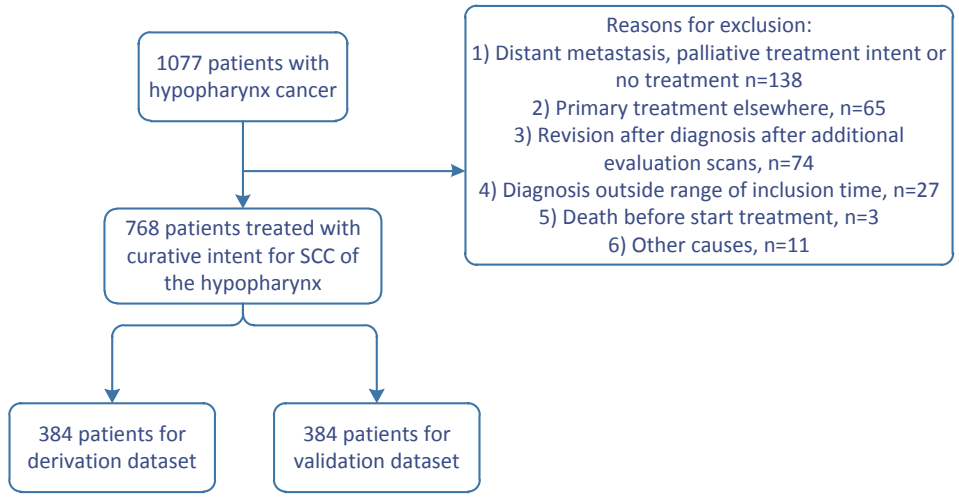

Figure 1. Inclusion of patients.

Development and internal validation

First, we examined the univariable association of each predictor under consideration with survival. The regression coefficients for alcohol consumption and the amount of packyears had a wrong sign, showing a small protective effect with increasing exposure. Because of the unreliability of this data, and the biologically implausible association, these variables were excluded as candidate predictors.

Next, we included the remaining candidate predictors in the LASSO model. The distinctions between T4 and T3, between N3 and N2, between N2 and N1, and between all four levels

of ACE27, as well as values of BMI, hemoglobin and albumin contributed significantly to the models on all 20 imputed datasets. In all but one of the datasets there was a significant difference in the survival of T3 vs. T2 patients. By contrast, in none of the imputed datasets a significant distinction between N0 and N1 (in their effect on survival) was observed, nor a significant contribution of age. T2 and T1 patients had significantly differing survival in only one dataset. Gender and leukocyte count contributed significantly only in 2 of 20 cases. Because gender is widely accepted as predictor for survival, we forced this variable into the model. A location in the pyriform sinus proved relevant in 13 out of 20 models. This model had a discrimination (C statistic) of 0.66.

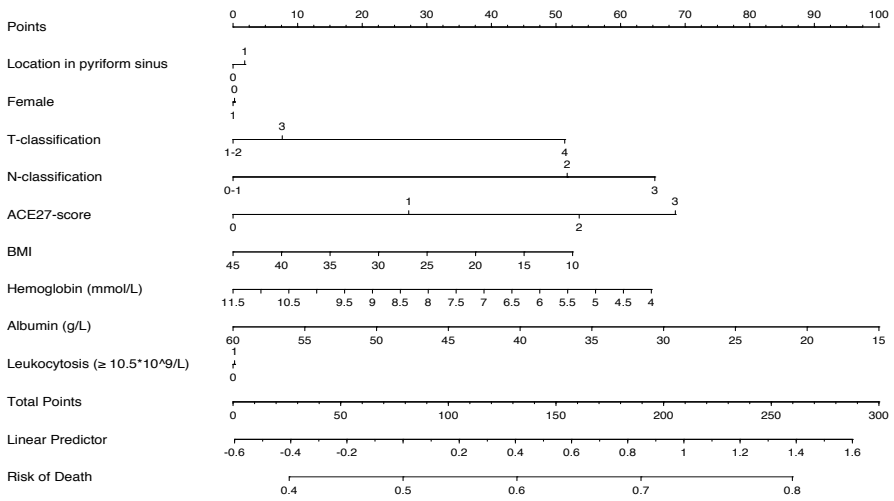

Figure 2. Nomogram of the final model. Combining the amount of points that correspond with each variable on the top scale will lead to a total amount of points. Drawing a straight line from the total points to the bottom scale will identify the linear predictor and risk of death for each patient.

Validation

In the validation, the discriminative ability of the CPM showed a C statistic of 0.62. The CPM is shown in Table 2 and a nomogram of this model is presented in Figure 2. The CPM showed excellent calibration as depicted in Figure 3.

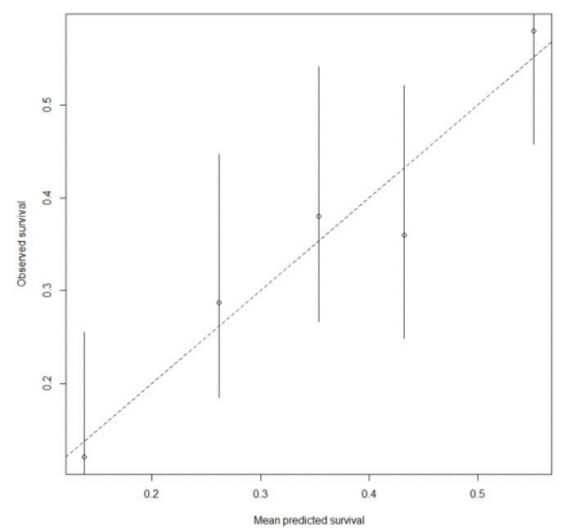

Figure 3. Calibration plot of the CPM model after validation. A 45-degree line (dashed line) indicates perfect agreement between predicted and observed outcome[17]. Calibration of our model is depicted in the straight line, and closely follows the 45-degree line.

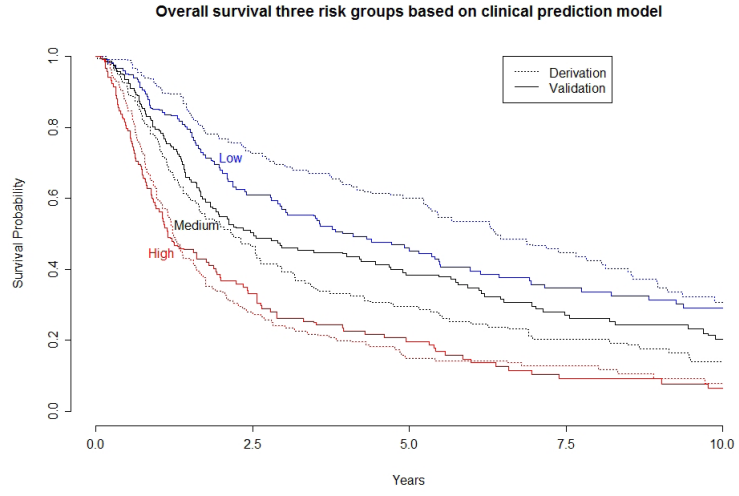

Figure 4. Kaplan Meier curves for three risk groups based on the derivation dataset. The Kaplan Meier curve of the derivation dataset is plotted using the straight line, and the validation dataset with the dashed line. Blue represents low risk, black medium risk and red represents high risk on death.

Based on the distribution of the linear predictors in the derivation dataset, we created three risk strata: low-, medium- and high-risk on death. The Kaplan Meier curves for the three risk strata of the original model showed good discrimination in the derivation dataset. Also, in the validation dataset, discrimination was good for all three risk groups, especially the high-risk group showed excellent discrimination. The survival curves for medium- and low-risk groups are closer together, but still clearly separated (see Figure 4). The hazard ratio of patients in the low-risk versus medium-risk group was 0.76, 95% CI 0.71-0.81. For the high-risk versus medium-risk group this was HR 1.77, 95% CI 1.67-1.88.

We compared the results of this CPM to a model based on the TNM classification only. The CPM using only the TNM classification had a C statistic of 0.61 in both the derivation and validation data.The model fit of the original CPM was significantly better compared to the TNM model (likelihood ratio test$p < 0.0001$).

DISCUSSION

This article describes the development and validation of a CPM for hypopharynx cancer containing gender, subsite, TNM classification, ACE27, BMI, albumin, hemoglobin and leukocyte count. The model showed better discrimination compared to a model based on TNM classification alone and was especially good in distinguishing high-risk patients that might benefit from more intensive treatment strategies and/or follow-up regimen. Using the LASSO technique, we identified the variables ACE27, BMI, albumin and hemoglobin levels to significantly contribute to a predictive model for survival, in addition to the expected TNM classification.

In our model, comorbidity scores, as measured by the ACE27, appeared to be one of the strongest predictors of survival. The ACE27 score is regularly used measure for comorbidity, especially in the setting of (head and neck) cancer and incorporates 27 ailments in 9 organ systems plus the presence of a malignancy, substance abuse and bodyweight. The ACE27 score can range from 0 (no comorbidity) to 3 (severe comorbidity). Although hypopharynx cancer patients are known to have relatively more comorbidity compared to other patients with head and neck cancer, it still has an important prognostic value. The independent prognostic value of comorbidity has indeed been confirmed by other authors and should therefore always be accounted for when estimating prognosis in the frail head and neck cancer patient group.[9, 18-20]

Table 2. Variables used in the final developed CPM with their associated regression coefficient and hazard ratio

Variables	Regression coefficient B	HR
Sex (female vs. male)	-0.00176	0.998
Age	0.00	1
Subsite (pyriform sinus vs. other)	0.01385	1.014
T-classification		-
T2vsT1	0.00033	1
T3vsT2	0.5807	1.060
T4vsT3	0.33530	1.398
N-classification		
N1vsN0	0	1
N2vsN1	0.39662	1.487
N3vsN2	0.104	1.11
ACE27	-	-
1vs0	0.220853	1.232
2vs1	0.20235	1.224
3vs2	0.11411	1.121
BMI	-0.01552	0.989
Hemoglobin*	-0.0662	0.936
Albumin*	-0.01704	0.983
Leukocytosis	0.00182	1.002

Abbreviations: HR, hazard ratio; ACE27, Adult Comorbidity Evaluation-27; BMI, Body Mass Index. Leukocytosis was expressed as a level of ≥10.5 10E9/L

*For hemoglobin and albumin expressed coefficients represent the added effect of every mmol/L or g/L increase.

In the current ACE27 scoring system, a high BMI is incorporated as one of the 27 ailments.[21] However, in our prediction model, a lower BMI and higher ACE27 were both independent predictors of worse OS, a finding that has been reported by others studying patients with head and neck cancer.[22, 23] In the current ACE27 scoring system, BMI results in a positive score when a patient has a BMI >38, which is an infrequent finding in our cohort and in other studies on head and neck cancer patients.[22, 24] Yet, there was little correlation between the two variables. Thus, since multicollinearity was not a concern, we chose to consider BMI as a separate variable in the CPM, and this variable was retained by the LASSO model.

Besides ACE27 and BMI, the peripheral blood parameters hemoglobin and albumin level both demonstrated an independent prognostic effect on survival. The association between pretreatment anemia and worse OS has been well established in head and neck cancer and is likely a result of the resulting hypoxia of the tumor micro-environment, which is associated with decreased radiosensitivity.[25, 26] Low albumin level as a proxy for reduced nutritional status has similarly been widely reported as a predictor of cancer survival and

possibly even functional outcome.[27, 28] Sherman et al. used the VA-dataset to report on the TALK score, incorporating the variables T-stage, Albumin, Liquor intake and the comorbidity index Karnofsky score into a prognostic model to estimate functional outcome in terms of larynx preservation[28] In terms of predicting oncological survival, the Glasgow prognostic score, incorporating low albumin and high CRP levels, has been shown to be predictive of outcome in several different tumor sites[29, 30] The original publication on the Glasgow score however also investigated other variables such as age, gender, stage, type of tumor (SCC or adenocarcinoma), performance status (ECOG), hemoglobin level and leukocyte level. The authors analyzed several combinations, each containing two of these variables, and although they reported that the combination of stage and comorbidity was considered to have a comparable prognostic value to the combination albumin and CRP, still they did not include these variables into their scoring system. Possibly, a more extensive model would have led to an increased predictive value.

In recent years, several easy to obtain serum inflammatory markers have been shown to have predictive value in cancer survival.[31] Although the inflammatory response should obviously be directed against the tumor, it is clear that inflammatory cells can influence tumor growth, stimulate DNA damage and promote angiogenesis and lymphangiogenesis.[32] The association between leukocytosis and OS is a relatively new concept in head and neck cancer, but has gained increasing interest in the past years, especially in the context of neutrophil to lymphocyte ratio (NLR).[33-35] A recent meta-analysis analyzed by Tham et al. demonstrated that an elevated pre-treatment NLR is associated with significant poorer OS and disease free survival in head and neck cancer.[35] The presence of leukocytosis was however unrelated to OS in our analysis. In our cohort, only leukocyte level was available and further differentiation allowing NLR calculation was lacking. Possibly, the NLR is more informative than leukocytosis alone. If proven to be predictive of survival in hypopharynx, such easy to obtain and inexpensive biological bio-markers are welcome new discoveries that could improve risk stratification for patients, and possibly tailor (neo) adjuvant treatment.

Apart from tumor-specific and patient-specific variables, the choice of treatment obviously also affects survival. However, we did not include treatment in our model, as recommended previously, since the estimate of effect would likely be confounded by indication.[14]

This is not the first study to report on a prediction model for head and neck cancer but to the best of our knowledge this is the first prediction model including hypopharynx cancer patients only. This distinct subgroup is often analyzed together with larynx cancer, although hypopharynx cancer is known to have 5-yr OS almost half of the expected OS for patients with larynx cancer.[4, 36, 37] Thus, when aiming to optimize individual estimations of prognosis through the development of a prediction model, it is important that patients are selected based on type of tumor to create more accurate estimations.

There are certain limitations to this study. Inherent to the retrospective design of our study, there is a weakness in data collection which resulted in a certain degree of missing variables, although we tried to correct this by performing multiple imputation. We were unable to collect variables that might have played an important prognostic role in survival, such tumor volume, the presence of sarcopenia or low skeletal muscle mass, or several peripheral blood tumor markers.[23, 35, 38, 39] However, considering the relatively low incidence of this tumor and the lack of prospective databases which can be used to develop or improve prediction models, large retrospective databases like ours still provide valuable information regarding survival. Our clinical prediction model is based on patients treated with curative intent with TLP, RT or CRT in three dedicated head and neck centers in The Netherlands. One has to be careful in extrapolating survival estimates from this model to a different geographical setting, where possibly different treatment strategies or patient care is delivered. Constructing a model on more heterogeneous group in terms of geographical location and treatment strategies would probably allow for better clinical use around the world.

CONCLUSION

In conclusion we have been able to identify a high ACE27 score, the presence of low BMI, low hemoglobin and albumin levels as independent prognostic variables for hypopharynx cancer in addition to several patient and tumor specific characteristics. The developed clinical model is better for estimating survival, compared to estimations based on TNM-classification only. Although predictions at the individual level remain uncertain, the model adequately distinguishes between risk groups. These results can be used during the counseling process and possibly tailor treatment strategy or intensify follow-up regimen, but should never replace clinicians' judgment. Further research is needed to investigate which variables, other than those considered to date, can further improve predictions of survival for individual patients with hypopharynx cancer.

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5

Laryngo-esophageal dysfunction free survival and propensity score matched analysis comparing organ preservation and total laryngectomy in hypopharynx cancer

Submitted

5 Laryngo-esophageal dysfunction free survival and propensity score matched analysis comparing organ preservation and total laryngectomy in hypopharynx cancer

Japke F. Petersen, Coralie R. Arends, Vincent van der Noort, Abrahim Al-Mamgani, Jan Paul de Boer, Martijn M. Stuiver, Michiel W.M. van den Brekel

ABSTRACT

Aims: *To assess the functional outcomes of patients treated for hypopharynx cancer and to obtain an unbiased estimate of survival difference between patients treated with chemoradiotherapy (CRT) or total laryngectomy (TL).*

Methods: *Retrospective cohort study of all patients treated with curative intent for T1-T4 squamous cell carcinoma of the hypopharynx in The Netherlands Cancer Institute (1990-2013). Functional outcome following radiotherapy (RT) or CRT was measured using laryngo-esophageal dysfunction free survival rate (LDFS). Using propensity score (PS) matched analysis, we compared survival outcome of TL to CRT in T2-T4 patients.*

Results: *We included 343 patients with T1T4 hypopharynx cancer. LDFS 2 and 5-years following CRT was respectively 44 and 32%. Following RT this was 39 and 30%. Patients were matched on the following variables: age, gender, TNM classification, subsite of tumor, decade of diagnosis, prior cancer, smoking, ACE27 score, BMI hemoglobin, albumin, and leukocyte level. With PS matching, we were able to match 26 TL patients with 26 CRT patients. The OS rates for TL and CRT in this matched cohort were respectively 56% and 46% at 5 years and 35% and 17% at 10 years.*

Conclusion: *In conclusion, functional outcomes following RT or CRT are suboptimal and require improved treatment strategies or rehabilitation efforts. The OS results challenge the preposition that CRT and TLE are equivalent in terms of survival.*

INTRODUCTION

Each year, an estimated 3,000 people in the US will be diagnosed with hypopharynx cancer and face one of the worst prognoses of all head and neck squamous cell malignancies.[1] Intensive treatment protocols yield limited success in terms of overall survival (OS). The average 5-year OS rate varies between 28-41%, although this rate is improving.[1-3]

While there is little doubt about organ preservation therapy in smaller tumors, for advanced T4 tumors there is no consensus whether organ preservation with chemoradiotherapy (CRT) versus a total laryngectomy (TL) yields higher OS rates. Recently, several publications have demonstrated the superiority of TL vs. CRT in advanced T4 larynx cancer[4, 5], but there is a paucity of studies reporting on the effect of TL versus CRT on survival in advanced hypopharynx cancer.[3, 6, 7] Currently, most national guidelines advise to use organ preservation whenever possible, and as a consequence, the rate of primary TLs for hypopharynx cancer is gradually declining.[8]

In light of the increasing use of organ preservation therapy, optimizing functional outcomes has become more important. Although CRT aims to spare the larynx surgically, laryngeal function can be severely hampered on the long term; patients can experience dysphonia, swallowing complaints, require repeated dilatations because of pharyngeal stenosis, be tube-feeding dependent, or can become tracheotomy dependent years after treatment.[9, 10] Around 11% of patients are left with a non-functioning larynx after organ preservation treatment and require a TL for functional reasons.[11] On the other hand, following a TL, patients can also have severe functional problems and will have to master pulmonary, vocal and swallowing rehabilitation.[12] Furthermore, they might experience surgical complications on the short term, and social distress or loss of self-esteem on the long-term.[13]

Given the lack of consensus as to whether TL or CRT is the optimal treatment for advanced hypopharynx cancer and the scarcity of RCTs on this topic, population-based observational studies provide the best possible evidence regarding oncological and functional survival. However, in these studies, confounding by indication can produce a significant risk of

bias. Confounding by indication arises when (prognostic) baseline variables that influence choice of treatment are not properly accounted for. To control for this issue in the comparison of OS, a propensity score (PS) matched analysis can be performed. Therefore, the aim of this study was to assess the functional outcomes in patients treated with organ preservation (RT or CRT), by describing the laryngo-esophageal dysfunction free survival rate (LDFS), and to obtain an unbiased estimate of survival difference between patients treated with CRT or TL, using PS matching. Laryngo-esophageal dysfunction free survival rate is defined as the proportion of patients surviving without a local recurrence, and do not have a feeding tube or a tracheostomy in situ.

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients diagnosed and treated with curative intent for hypopharynx cancer in The Netherlands Cancer Institute between February 1990 and February 2013, allowing for a minimum follow-up of 5 years for all patients. Patient numbers were received from the scientific information department, who record all patients treated in our institute with the tumor location according to the International Classification of Disease for Oncology (ICD-0-3), date of diagnosis, status and last date of follow-up. Patient and tumor specific variables were retrospectively collected from the (scanned) patient files to assess their impact on overall survival and LDFS. Events for the composite endpoint LDFS were death from any cause, recurrence, TL, and presence of a tracheotomy or feeding tube2-years or 5 years following treatment.[14]

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Differences between groups (TL and (C)RT) were calculated using students' T test, Pearson's Chi Square test or linear-by-linear as appropriate. Analysis of the LDFS rate was conducted in the original unmatched cohort of (C)RT patients with T1-T4 hypopharynx cancer, using Kaplan-Meier (KM) analysis; the log rank test was used to test differences in LDFS rates between patients treated with RT or CRT.

Propensity score matching

To obtain an unbiased estimate of treatment effect we used propensity score matching to compare TL with CRT.[15] Based on knowledge from literature and clinical expertise, biological plausibility of prognostic value, and availability[15], we used the following variables to construct the propensity score model: age at diagnosis, gender, TNM classification, subsite of tumor, prior cancer, smoking (current smoker, stopped >5 years ago, never smoked), alcohol (current user, stopped > 5 years ago, never used alcohol), ACE 27 comorbidity score, and levels of BMI and the peripheral blood parameters hemoglobin (mmol/L), albumin (g/L) and leukocyte(10E9/L). Additionally, we included decade of diagnosis as a predictor, to account for the time trends in treatment choice. The propensity score for each patient, representing the estimated probability that this patient will receive TL treatment based on the observed baseline covariates, was calculated using a logistic regression model. We used "greedy matching" to match TL patients 1:1 to similar CRT patients.[15] We set the caliper (the maximum acceptable difference in propensity score in a matched pair) at 0.25 standard deviation (SD), and used complete cases only. To evaluate the success of our matching procedure, we visually compared the distribution of the propensity scores between the matched groups, and we calculated standardized mean differences (SMD) of baseline characteristics.[16] To assess whether the results were sensitive to hidden bias as a result of misspecification of the propensity score model, we performed a sensitivity analysis as described by Olmos et al.[17] This sensitivity analysis results in a Gamma value, indicating by how much the odds of hidden treatment bias needs to change before the statistical significance of the outcome shifts. The larger the value, the more robust the results will be to hidden treatment bias. Gamma values close to 1 indicate that a study is sensitive to such bias.[18] Finally, survival analysis in the matched cohort was performed using KM analysis and a Cox-proportional hazards model. The latter employed a cluster term and robust standard errors, to account for the matched nature of the sample. All analyses were performed using the packages 'matching' and 'survival' in R software.[19-21]

Ethics

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

RESULTS

Patients

We initially retrieved a database with 441 patients. After exclusion of 98 patients (see Fig. 1), we were left with 343 patients diagnosed with squamous cell carcinoma (SCC) of the hypopharynx who were treated with curative intent in The Netherlands Cancer Institute, between February 1990 and February 2013. Mean age was 61 years (sd 10, range 32-91), 81% was male and the majority of patients received CRT (54%), followed by TL (26%) and RT (19%). Three patients were treated with primary laser surgery (0.9%). The first patient was treated with CRT in 1997. Before 1997, 75% of patients (n = 79) were laryngectomized and 25% received primary RT. This changed to 17% RT, 70% CRT and 11% TL from 1997 and

onwards (*n* = 264). The majority of patients were diagnosed in an advanced stage: 21% in stage III, 45% in IVA and 15% in IVB. Patient characteristics are shown in Table 1.

Most patients were current smokers (85%), 8% were former smokers and the median amount of pack years of both groups was 40. Alcohol was consumed by 85% of patients, who drank a median amount of 28 units per week. Seventeen percent of patients had a history of cancer other than basal cell carcinoma, and half of these carcinomas were located in the head and neck area. Nine percent of patients were diagnosed with a synchronous tumor (89% in the head and neck area), 22% developed a second primary during follow-up and 6% a third primary.

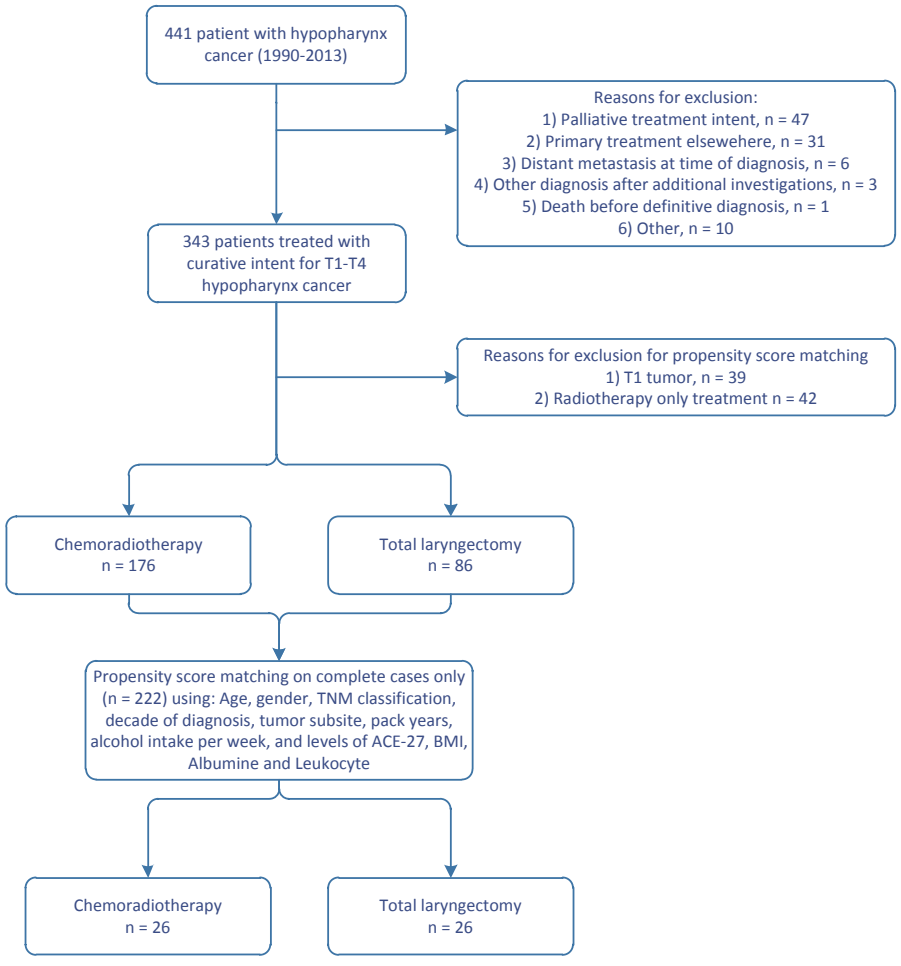

Figure 1. Inclusion of patients in total cohort and propensity score matched analysis of chemoradiotherapy and total laryngectomy patients.

Table 1. Patient characteristics

	Total group	(C)RT original cohort	TL original cohort	P value	CRT matched cohort	TL matched cohort	SMD
No. patients	343*	251	89		26	26	
Age at diagnosis (mean, SD)	61 (10.4)	60.1 (9.5)	63.3 (12.1)	**0.013**	59 (9.4)	59 (12.1)	0
Male gender	276 (81)	202 (80)	72 (81)	1.00	20 (77)	23 (88)	0.29
T classification				**0.001**			
T1	39 (11)	33 (13)	3 (3.4)		-	-	
T2	106 (31)	82 (33)	24 (27)		8 (31)	9 (35)	0.08
T3	85 (25)	65 (26)	20 (23)		5 (19)	8 (31)	0.28
T4	108 (31)	70 (28)	38 (43)		13 (50)	9 (35)	0.30
TX	5 (1.5)	1 (0.4)	4 (4.5)				
N classification				**0.001**			
N0	107 (31)	66 (26)	38 (43)		8 (31)	9 (35)	0.08
N1	70 (20)	46 (18)	24 (27)		6 (23)	8 (31)	0.18
N2	125 (36)	105 (42)	20 (23)		9 (35)	6 (23)	0.26
N3	39 (11)	33 (13)	6 (7)		3 (12)	3 (12)	0
NX	2 (0.6)	1 (0.4)	1 (1.1)				
Subsite				**0.005**			
Pyriform sinus	263 (77)	203 (81)	57 (64)		20 (77)	21 (81)	0.10
Posterior wall	34 (10)	19 (8)	15 (17)		2 (8)	1 (4)	0.90
Postcricoid region	22 (6)	16 (6)	6 (7)		1 (4)	2 (8)	0.90
Other	24 (7)	13 (5)	11 (12)		3 (12)	2 (8)	0.13
ACE27				0.139			
0	110 (32)	84 (34)	25 (28)		9 (35)	9 (35)	0
1	130 (38)	91 (37)	38 (43)		10 (39)	11 (42)	0.06
2	84 (25)	58 (23)	25 (28)		6 (23)	6 (23)	0
3	17 (5)	16 (6)	1 (1)		1 (4)	0 (0)	0.4
Unknown	2 (0.6)	2 (0.8)					
Prior cancer: yes	59 (17)	23 (9)	25 (39)	**<0.001**	7 (27)	5 (19)	0.18
Smoking				0.219			0.44
Never	25 (7)	16 (6)	9 (10)		3 (12)	2 (8)	0.13
Yes	290 (85)	217 (87)	70 (79)		21 (81)	24 (92)	0.33
Stopped >5yrs ago	28 (8)	18 (7)	10 (11)		2 (8)	0 (0)	0.58
Alcohol				0.564			
Never	39 (11)	29 (12)	9 (10)		2 (8)	3 (12)	0.13
Yes	291 (85)	214 (85)	75 (84)		24 (92)	22 (85)	0.22
Stopped >5yrs ago	13 (4)	8 (3)	5 (6)		0 (0)	1 (4)	0.40
BMI (mean, SD)	23 (4.4)	23 (4.4)	23 (4.5)	0.685	23 (4.1)	24 (5.6)	0.21
Hb (mean, SD)	8.7 (1.0)	8.8 (1.07)	8.5 (0.9)	0.069	8.3 (0.9)	8.6 (0.9)	0.33
Albumin (mean, SD)	43 (4.9)	43.5 (4.8)	42 (5.2)	**0.033**	44 (6.1)	43 (4.6)	0.19
Leukocyte (mean, SD)	9.9 (4.2)	9.7 (4.1)	10.2 (4.0)	0.306	9.6 (3.4)	9.5 (3.4)	0.03

*There were 3 patients in our cohort treated with laser surgery that were not analyzed separately. Values in parentheses are percentages unless indicated otherwise.
Abbreviations: SD standard deviation, SMD standardized mean difference, BMI body mass index, Hb Hemoglobine.

Functional outcomes

We assessed the functional outcomes in the original (unmatched) cohort of patients treated with RT (*n* = 66), CRT (*n* = 185) or TL (*n* = 89). Function of the larynx and feeding status for all treatment options at 6 months, 2- and 5-years following treatment are reported in table 2. Of the patients that were alive and not lost to follow-up two years following treatment, respectively 82, 89 and 94% of patients treated with RT, CRT and TL were able to consume full oral intake. This changed to 92, 89 and 91% at 5 years. The percentage of patients that required one of more dilatation procedures during follow-up was respectively 14%, 8% and 36% following treatment with RT, CRT or TL.

In the total cohort, 251 patients were treated with CRT or RT. Of these patients, the LDFS rate at 2-years and 5-years was respectively 42% and 31%. The LDFS rates in patients treated with RT at 2-years was 39% vs. 44% in the CRT group (p = 0.90), at 5-years this was 30% for RT vs. 32% for CRT patients (p = 0.96). To compare, the unadjusted 2- and 5 year OS rates in the RT group were 39% and 30%, and in the CRT group 44% and 32%.

Propensity score matching

To create an unbiased comparison of survival rates between CRT and TL we used propensity score matching. For propensity score matching we excluded patients with a T1 tumor (*n* = 39) since these patients are rarely treated with CRT or TL. Furthermore, patients treated with radiotherapy only (*n* = 42) were excluded as this is convincingly proven to be inferior to CRT and TL in terms of survival[2, 22]. After excluding patients with missing data on predictors for the propensity score model (*n* = 40, 15%), 68 TL patients were available for matching. Based on the variables age at diagnosis, gender, TNM classification, subsite of tumor, decade of diagnosis, prior cancer, smoking, alcohol, ACE27 and levels of BMI and the peripheral blood parameters albumin, and leukocyte count, we were able to match 26 TL patients to 26 CRT patients with similar propensity scores (see Table 1 for their clinical characteristics). Sensitivity analysis resulted in a Gamma value of 2.7, indicating that the results of matching were not very sensitive to hidden bias.

Before matching, patients in the TL group were significantly older and had a lower nodal stage. After matching there were relatively more T4 patients in the CRT group (13 vs. 9) but due to the small sample size, this difference was considered acceptable. Other than that, there were no clinically relevant differences between groups (see Table 1).

Survival

In the matched cohort, the HR for death in the TL group compared to CRT was 0.65 (95% CI 0.34-1.24,p = 0.19). The 5-year overall survival rate for the patients treated with TL was better compared to CRT: 56% (95% CI 40-79) versus 46% (95% CI 31-70), but the difference was not statistically significant (p = 0.19). The 10-year OS rate was 35% (95% CI 20-60) for TL versus 17% (95% CI 7-41) (see Figure 2).

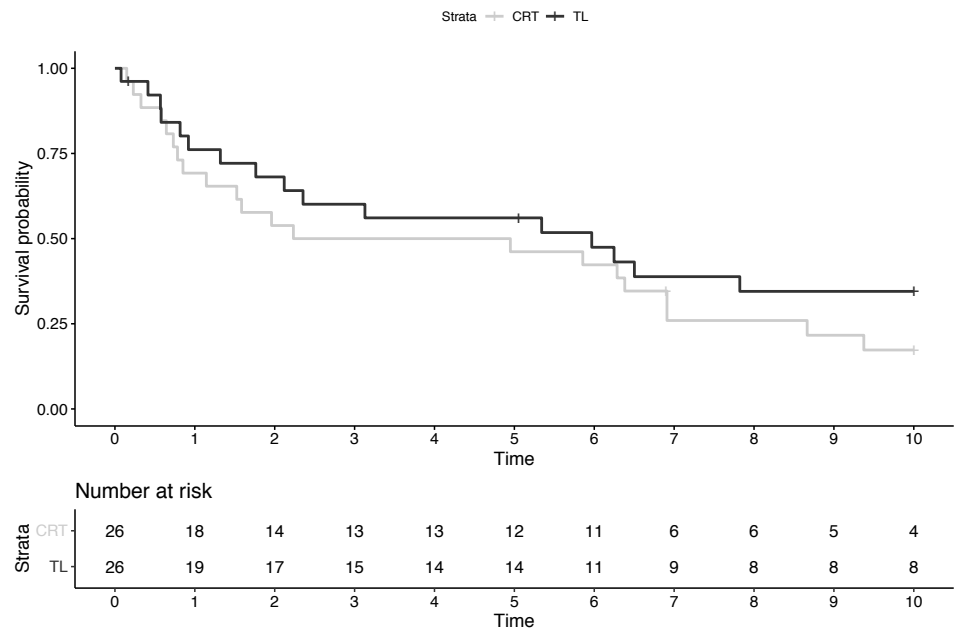

Figure 2. Kaplan Meier curve of the matched cohort demonstrating the 10-year overall survival for the CRT (light grey) and TL (black) patients

Table 2. Functional outcomes measured 6 months, 2- and 5-years post treatment

	6 months post treatment						5 years post treatment		
	RT	**CRT**	**TL**	**RT**	**CRT**	**TL**	**RT**	**CRT**	**TL**
Initial cohort	66	185	89	66	185	89	66	185	89
Censored*	9	24	12	31	69	37	42	105	55
Patients in FU	57	161	77	35	116	52	24	80	34
Larynx function									
Larynx in situ	51 (89)	152 (94)	-	31 (89)	106 (91)	-	18 (75)	68 (85)	-
Tracheotomy	4 (7)	7 (4)	-	0	4 (3)	-	0	4 (5)	-
Salvage TL	2 (4)	2 (1)	-	4 (11)	6 (7)	-	6 (25)	8 (10)	-
Feeding status									
Normal	38 (67)	108 (67)	58 (75)	29 (82)	103 (89)	49 (94)	22 (92)	71 (89)	31 (91)
Pureed food only	8 (14)	7 (4)	9 (12)	1 (3)	4 (3)	1 (2)	1 (4)	2 (2.5)	0
NG feeding tube	5 (9)	12 (7)	3 (4)	2 (6)	1 (1)	1 (2)	1 (4)	1 (1)	1 (3)
PRG/PEG/ jejunostomy	6 (11)	33 (20)	7 (9)	3 (9)	8 (7)	1 (2)	0	6 (7.5)	2 (6)
TPN	0	1 (0.6)	0	0	0	0	0	0	0

*Censored patients were died or lost to follow-up at the respecting point in time. Percentages are calculated over the number of patients that were alive and not lost follow-up for each treatment and point in time.
Values in parentheses are percentages.
Abbreviations: FU follow-up, NG nasogastric (feeding tube), PRG Percutaneous radiologic gastrostomy (feeding tube), PEG Percutaneous endoscopic gastrostomy (feeding tube) , TPN total parenteral nutrition

DISCUSSION

In this consecutive cohort of T1-T4 hypopharynx cancer patients treated with RT or CRT the LDFS rate was respectively 39% vs. 44% ($p = 0.90$), and 30% vs. 32% ($p = 0.96$), 2- and 5 years following treatment. In the PS matched pair cohort of T2-T4 patients treated with TL or CRT, we observed a higher 5-year OS rate (56%) in the TL group compared to the CRT group (46%), although the difference was not statistically significant.

In line with other studies, we report an increase in the use of (C)RT at the expense of TL as primary treatment.[8] Therefore, in recent years, functional outcomes and long term toxicity following organ preservation have received more focus. However, heterogeneity in patients, treatment protocols, outcome measurements and definitions make direct comparisons between studies difficult and reported LDFS rates in literature vary widely.[23-27]

The first RCT in hypopharynx cancer reported a LDFS of 17% at 5 years, although when only death from local disease was used as endpoint instead of death from any cause, this rate was 35%.[28] Much higher LDFS rates were reported in the long-term results of the GORTEC-2000-01 comparing induction CT with cisplatin (P) and 5-fluorouracil (F) with or without docetaxel (T) followed by RT. They reported an LDFS of 67% in the TPF group versus 47% in the PF group at 5 years.[29] However, their LDFS rate included 'the presence of natural speech, absence of a tracheostomy, absence of a feeding tube for ≥2 years after treatment or recurring pneumonia that required hospitalization'. Despite the improved results following induction CT with TPF, concerns regarding dose limiting toxicity compromising the concurrent component have prevented this from becoming standard of care.[30] While a recent meta-analysis analyzing induction CT followed by concurrent CRT in head and neck cancer demonstrated a significant improved disease control and complete response rate, they were unable to demonstrate significant improved OS rate in patients treated with induction CT.[31]

In a subset of patients, significant long term toxicity can be expected following organ preservation treatment. The GORTEC 2000-01 study reported most late toxicities to occur in the mucous membrane, salivary gland, larynx and subcutaneous tissues. In their cohort, significantly fewer grade III-IV toxicities of the larynx were observed in the TPF regimen versus PF (9 vs. 17%), but the cisplatin and 5-FU dose was lower in the TPF treatment arm.[29] Rütten et al. reported on a cohort of 77 stage III-IV head and neck cancer patients treated with CRT and reported long-term toxicity rates at 5 years of 52% grade III and 25% grade IV.[10] Only 15.6% of patients were able to consume a normal diet. Kraaijenga et al. reported that 10 years after treatment with CRT, 50% of patients had impaired swallowing and 14% were tube feeding dependent.[9] Meanwhile, hypopharyngeal dose has been reported as a prognostic factor for severe late toxicity following CRT.[32, 33]

Although organ preservation can lead to significant long term toxicity following treatment, a TL will, on the other hand, likewise interfere with important basic life functions such as breathing, swallowing and the production of speech, and can lead to significant short and long-term toxicity or complications.[34] The percentage of patients that needed dilatations for dysphagia was highest in the TL group with a crude incidence of 36%, versus 14 and 8% in patients treated with RT or CRT. Granting that vocal rehabilitation is quite successful with modern day voice prostheses, only few are genuinely satisfied with their altered voice, many patients still suffer from pulmonary complaints, have difficulty swallowing and experience social distress.[12, 13, 23, 35]

Although less pronounced than in our study, the first RCT comparing organ preservation with TL in hypopharynx cancer reported a similarly better but also non-significant higher OS rate in the TL group versus CRT. In their cohort, the 5-year OS was reported to be 35% for surgery versus 30% for CRT, and the final results showed a 10-year OS of 13.8% in the surgery arm versus 13.1% in the CRT arm.[28, 36] Later, several retrospective studies have reported a significant survival benefit for surgery versus radiotherapy.[3, 7, 37, 38] In 2014, Kuo

et al. analyzed 3,958 patients from a SEER database and reported a survival benefit in the surgery plus radiotherapy arm over radiotherapy, with 5-yr OS rates of 34.5% vs. 22.6%.[7] A later study by Newman et al., analyzing 6,647 patients from the SEER database, similarly reported a survival benefit in the surgery plus radiotherapy arm versus radiotherapy, with 5-yr OS rates of 49% versus 37.8%.[8] Both SEER studies are however limited by the fact that important details regarding the use of chemotherapy, the type of surgery and the functional outcomes are missing and a subset of the radiotherapy arm in both studies will have been treated with chemoradiotherapy. As demonstrated by Blanchard et al., the addition of concomitant chemotherapy leads to an absolute benefit of 3.9% at 5 years among patients with hypopharynx cancer.[39] This benefit does not fully explain the observed OS difference between surgery and radiotherapy in the SEER cohorts, suggesting TL is indeed superior in terms of OS.

In a subsequent analysis, Kuo et al. reported on the effect of chemotherapy, but in this study the number of patients treated with surgery plus chemotherapy that were used for analysis represented only 4.9% of the total cohort. While they reported no significant difference in OS between TL and CRT, the small sample of the surgical subgroup limits interpretability of the results.[7] In 2019, Tassler et al. performed a propensity score adjusted analysis, controlling for year of diagnosis and T-stage. In their retrospective cohort of 137 hypopharynx cancer patients treated with CRT or TL, a significant survival benefit in favor or TL was observed.[40]

With the increasing amount of evidence questioning the presumed equality between TL and CRT, there clearly is no consensus on the 'best treatment option'. However, since both options significantly impact a patients' life, it is extremely important to counsel future hypopharynx cancer patients about all the associated risks and possible consequences of the treatment options, so they can make a well informed decision on treatment.[41] Laccourreye et al. demonstrated how improved knowledge about the potential risk on a tracheotomy or feeding tube following organ preservation therapy shifted the treatment preferences of patients.[41] Improving patient counseling and shared decision making has been shown to lead to improved patient outcomes.[42] Therefore, especially in a setting with no 'best treatment' and/or treatment options with will have a significant effect on quality of life such as for hypopharynx cancer, optimal shared decision making should be the standard of care.

There are certain limitations to this study. Inherent to the retrospective nature and the long inclusion time of patients, certain prognostic variables that could affect oncological or functional outcomes could not be retrieved. While we tried to equalize treatment groups by performing a propensity score matched pair analysis, variables that were not included in our PS-model due to unavailability might have potentially influenced the outcome. The sensitivity analysis suggested that the analysis was robust for such bias, however. Although there is low risk of bias due to confounding, after matching, we were not able to match all TL patients, and only 26 patients per group were left for analysis. This makes the observations relatively vulnerable to sample idiosyncrasies, and left us with low power to detect statistical significance, as reflected in the wide CI for the hazard ratio.

CONCLUSION

In conclusion, we report a laryngo-esophageal dysfunction free survival rate at 5 years of 31% for RT and CRT, and a 5-year OS rate of 56% following TL as compared to 46% for CRT. Although these results should be interpreted with caution, they are in in line with results from previous studies, and challenge the preposition that CRT and TLE are equivalent in terms of survival. Moreover, the disappointing LDFS rate demands improved treatment strategies or rehabilitation efforts.[43] Until better alternative treatment strategies are found, counseling the patients about the expected outcome and quality of life should be a major point of focus of physicians treating these patients.

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

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6 Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period

Japke F. Petersen, Liset Lansaat, Adriana J. Timmermans, Vincent van der Noort, Frans J.M. Hilgers, Michiel W.M. van den Brekel

** Japke F Petersen and Liset Lansaat contributed equally to this manuscript*

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, 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. 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 (VP).[2, 3] With a success rate of around 90%, tracheoesophageal 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® voice prosthesis (VP) (InHealth Technologies, Carpinteria, CA, USA), a variety of prosthetic devices have been developed, e.g. in the Netherlands the Groningen button, the Nijdam VP and Provox VP's (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 tracheoesophageal wall (TEP tract)-related problems and possibly a lower device lifetime of VPs.[9-11]

In 2000, Op de Coul et al. published the long-term results of voice rehabilitation with the first Provox VPs in the Netherlands Cancer Institute.[4] 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 TL patients. 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: gender, age at TL, primary tumor site, TNM classification, primary treatment, indication for TL (primary, salvage, second primary, dysfunctional larynx), surgical characteristics (e.g. 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 (e.g. ActiValve vs. normal) on this hazard is the same across patients.

For estimating the influence of *patient and treatment characteristics* (e.g. age) we address the fact that each patient can have multiple events (i.e. 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 05, 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 due to 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 ActiValve during follow-up. Variables with known correlations between them (e.g. 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 twelve patients (5%) did not receive radiotherapy 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%) of 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

	No. of patients
Sex	
Male	185 (79)
Female	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
Primary tumor site	
Larynx	167 (72)
Hypopharynx	31 (13)
Oropharynx	21 (9)
Miscellaneous	13 (6)
Primary treatment	
RT	119 (51)
CRT	38 (16)
Other†	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)
Bilateral during TL	103 (44)
Unknown	12 (5)

Table 1 continued.

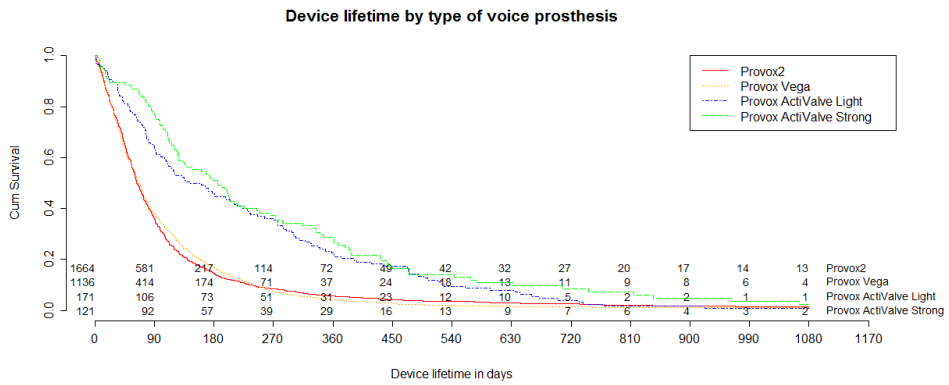
	No. of patients
Reconstruction	
None (primary closure)	143 (61)
PM flap for reconstruction lumen	46 (20)
PM flap for reinforcement	15 (6)
FRFF	9 (4)
Gastric pull-up	9 (4)
ALT	5 (2)
LD	1 (0.4)
Unknown	4 (2)

Abbreviations CCRT, concomitant chemoradiation; RT, radiotherapy; TL, total laryngectomy, PM: pectoralis major muscle, FRFF: Free radial forearm flap, ALT: Antero-lateral thigh flap, LD: Latissimus dorsi flap.
†One patient underwent C02 laser therapy prior to TL and one patient was treated for thyroid cancer with radioactive iodine therapy.
Variables in parentheses are percentages unless otherwise indicated.

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 due to immediately noticed sizing errors. We excluded VPs replaced for developmental study purposes (n = 86), and sporadically used types of VPs: Provox Vega XtraSeal (n = 16; introduced at the end of the study period), Provox1 (n = 4), 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, five were lost to follow-up with the first VP in situ, and in one 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 (i.e. the regular Provox2 (n = 1664), and 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).



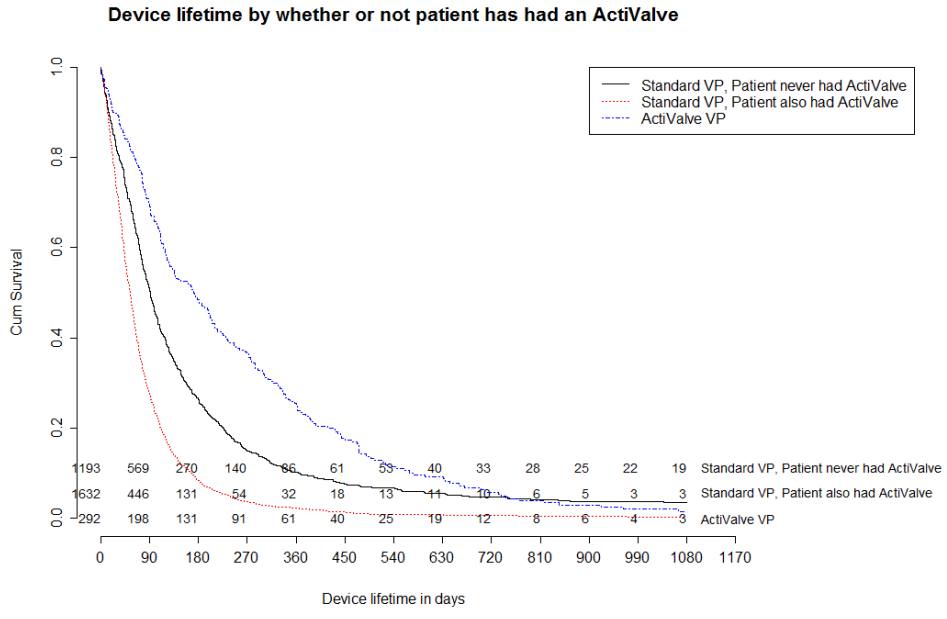


Figure 1 a). Kaplan Meier curve of device lifetime analyzed separately for the different VPs. **b**) The device lifetime for the standard VPs (Provox2 and Vega) grouped by whether or not these patients have ever had an ActiValve VP during follow-up and the device lifetime of the ActiValve VPs together.

Table 2. Univariate and multivariate analysis for device lifetime

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**P value**	**HR**	**95%**	**P value**
Age (per 10yr increase)	0.96	0.93-0.99	0.013*	0.94	0.91-0.98	<0.001*
Age (per 10 incr) within patients with indication for:						
Primary TL				0.91	0.86-0.97	0.002 ‡
Salvage TL				0.95	0.90-0.99	0.03 ‡
Second primary				0.99	0.89-1.11	0.87 ‡
Dysfunctional larynx				1.21	1.02 – 1.42	0.03 ‡
Gender (ref=male)	1.00	0.90-1.11	1.00			
Origin tumor (ref=larynx)						
Hypopharynx	0.84	0.73-0.97	0.020*			
Oropharynx	0.98	0.86-1.12	0.79			
Micellaneous	1.25	1.08-1.45	0.003*			
T classification (Ref=T1)						
T2	0.95	0.85-1.07	0.42			
T3	1.03	0.92-1.15	0.65			
T4	0.78	0.70-0.87	<0.001*			
N classification (Ref=N0)						
N1	0.92	0.80-1.06	0.24			
N2	1.05	0.95-1.15	0.35			
N3	0.55	0.40-0.74	<0.001*			
Indication TL (Ref = primary TL)						
Salvage TL	1.29	1.19-1.41	<0.001*	1.38	1.26-1.50	<0.001 †
2nd primary	1.06	0.94-1.21	0.33	1.28	1.13-1.46	<0.001 †
Dysfunctional larynx	1.26	1.10-1.45	0.001*	1.31	1.14-1.51	<0.001 †
Pharyngectomy type (ref = partial)						
Near total	0.91	0.82-1.00	0.04*			
Circumferential	0.95	0.81-1.10	0.49			
(Neo)-adjuvant treatment (ref = RT)						
None	0.86	0.72-1.03	0.10			
CRT	0.93	0.84-1.04	0.19			
Driving time to hospital (standard VPs)						
Per 15 minutes increase	0.92	0.90-0.94	<0.001*	0.90	0.88-0.92	<0.001 ‡

Abbreviations HR Hazard ratio, ref Reference variable. Note: HR > 1 means a shorter device lifetime; HR < 1 means a longer device lifetime. * = p-value < 0.05. Note that in the multivariate analysis we present the results from 2 multivariate models: We first constructed a simple model containing age at TL, indication for TL and driving distance to the hospital (marked with †). In a subsequent cox model we have used an interaction term between indication and age, to assess the effect of aging (marked with ‡).

The indication for using the 'problem solving' ActiValve in our institution was a device lifetime of less than two 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 ActiValve. 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 ActiValve 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;$p < 0.0001$), 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 hazard ratio (HR) of 0.90 (95% CI 0.88 – 0.92,$p < .0001$).

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,$p = .03$), 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,$p = .87$).

Table 3. Indications for replacement of 3133 VPs in 232 patients

Indication for replacement	Voice prosthesis	Patients
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**	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)

* Patients could have multiple indications for replacement of their voice prosthesis therefore the numbers add up to 3201 indications in 3133 VP replacements. Sometimes, it was difficult to determine the main indication for VP replacement, e.g. 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.
** 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).
Variables in parentheses are percentages unless otherwise indicated.

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 voice prosthesis 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.

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. 20 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 six patients twice and in three 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.

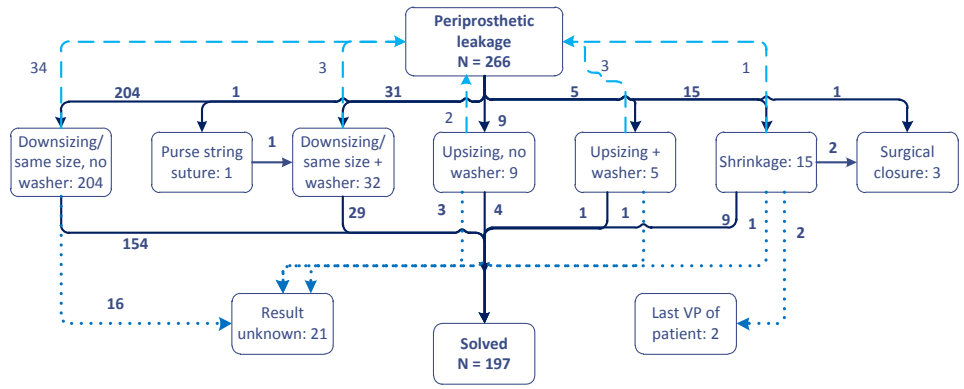


Figure 2. This figure illustrates the complex pathways of VP problem solving, in this case, periprosthetic leakage. As can be seen in this figure, 204 VPs were replaced with either the same or a smaller size, which was effective in 154 and not effective in 34 replacements. The result was undocumented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

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), 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 two 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. who showed a median device lifetime of 61 days and a study by Kress at al., who observed a median of 74 days (including ActiValve VPs, which figure in our cohort was 70 days).[11, 19] Interestingly, if we compare the device lifetime of the non-ActiValve group of 91 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 under-pressure 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. there was no significant effect of the extent of surgery or RT on device lifetime in the multivariable analysis.[11] 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 non-radiated patients and patients ever receiving RT[4], but in the present study the number of non-irradiated 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., the uncomfortable method of retrograde placement was still used.[4] 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, however, 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 six years in our historical cohort.[4] This figure compares favorably with the 12% after one 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 ActiValve cohort apparently also suffers significantly more from TEP tract hypertrophy/infection, as was found in the multivariable 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 comorbidity, just like TEP tract-related issues, I.e. reflux and pharyngeal stenosis.[10, 23, 24] Since these comorbidities are treatable, shortening of the device life might be a reason to start an intervention (dilation or proton pump inhibitor (PPI) treatment). Especially of interest in this respect is the study of Lorenz et al., where these authors found that device lifetime was significantly associated with reflux.[25] Likewise, Boscolo-Rizzo et al. demonstrated a mean device lifetime of 127 days for patients with endoscopic evidence of gastroesophageal reflux disease, versus 216 days for patients without.[10] Due to 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 co-morbidities 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 e.g. 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 voice prosthesis. 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 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 radiotherapy versus 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 total laryngectomy.

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How I do it?

Solving periprosthetic leakage with a novel prosthetic device

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How I do it? Solving periprosthetic leakage with a novel prosthetic device

Japke F. Petersen, Liset Lansaat, Frans J.M. Hilgers, Michiel W.M. van den Brekel

INTRODUCTION

Total laryngectomy (TL) is still an indispensable surgical procedure for advanced and recurrent larynx and hypopharynx cancer. Tracheoesophageal prosthetic voice rehabilitation is the method of choice for restoring oral communication in most Western countries, with success rates of around 90%.[1] However, with an increasing rate of salvage TLs performed after failed chemo(radiotherapy), more attention is needed to maintain durable results.

Voice prostheses (VPs) have a median device lifetime of around 2-3 months and the main indication for replacement is transprosthetic leakage, solvable by replacing the VP.[2-4] Recurrent periprosthetic leakage is however a problem requiring more attention.[3-6] It can be caused by normal, gradual subsiding of postsurgical edema, making the VP too long and thereby permitting periprosthetic leakage, solvable by downsizing the VP.[1] Later in time, co-morbidities such as gastric reflux, local infection, radiation effects, or recurrence of tumor can have a profound effect on the surrounding tissue, that can lead to atrophy and/or widening of the TEP tract, also resulting in periprosthetic leakage.[6, 7] Therefore, first of all co-morbidities such as reflux should be treated adequately were possible, in order to prevent periprosthetic leakage on the long-term.

The easiest short-term solution often is placing a thin silicone washer on the tracheal side of the VP, if the VP is still functioning properly. This is a simple, effective and cheap solution, as there is no need to replace the current VP. It is however obvious that in case of periprosthetic leakage the fluids originate from the esophageal side. A washer at that side is more effective than a washer on the tracheal side, because otherwise the fluids are still able to penetrate the TEP tract up to the tracheal side.. However, this means replacement of the VP and thus higher costs. Patients known with recurrent periprosthetic leakage could benefit from instantly placing a VP with an enlarged esophageal flange. Thus, a new VP with an extra esophageal flange ((Provox Vega XtraSeal; PVX) was developed, which we tested in our institute.

MATERIALS AND METHODS

We performed a prospective evaluation on the efficacy, satisfaction and ease of placement of the PVX among a consecutive cohort of patients seen in the outpatient clinic with periprosthetic leakage. After placement of the PVX, patients and physicians were asked to fill in a study-specific questionnaire regarding the satisfaction of (placement of) the PVX with regards to the handling of the insertion device, and procedure. Patients were excluded from FU if they had received two successive VPs other than a PVX.

Prosthesis

The PVX is an adjustment of the regular Provox Vega with an additional enlarged esophageal flange, glued to the VP at the flange-shaft crossing, see Figure 1. The flange is angled, thin and flexible, which should enhance its adherence to the surface around the TEP-tract to prevent leakage around the VP. The prosthesis is inserted with the regular insertion device, with special attention to the proper unfolding of the enlarged esophageal flange by inserting the entire VP into the esophagus (overshooting) and pulling the tracheal flange back in position.

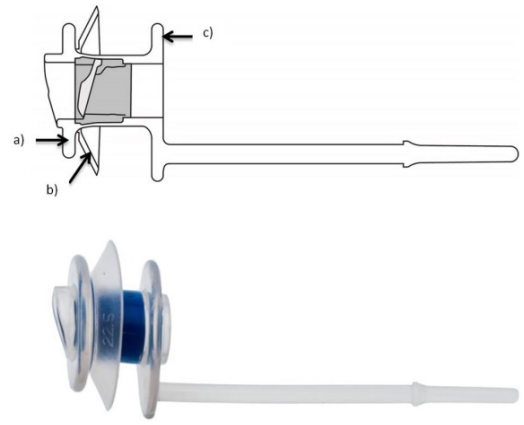

Figure 1. Schematic drawing and actual photo of the Provox Vega XtraSeal showing the location of the normal esophageal flange (a), the extra thin, angled esophageal flange (b), and the tracheal flange (c).

Statistics

Descriptive statistics were used to report patient characteristics and Kaplan Meier analysis to assess device lifetime. All analyses were done in SPSS ® Statistics 20.0 (IBM, Armonk, NY).

This study does not fall under the scope of the 'Medical Research Involving Human Subjects Act', which was confirmed by the institutional review board (MREC16.1202).

RESULTS

We included 13 patients (85% male), mean age at TL was 59 years, and median follow-up time after TL was 117 months, see Table 1. Reason for placement of the first PVX in each patient was periprosthetic leakage (*n* = 11), a too wide TEP tract (*n* = 1) or a lost VP (*n* = 1). These latter two patients were known with recurrent leakage around the VP and therefore included in this study. In these 13 patients, 26 PVXs were placed. Five patients received multiple PVXs during follow-up, with a maximum of seven in one patient, see Table 2.

After replacement, the seal was checked by the patient drinking water. The seal was sufficient in 25/26 placements. In the remaining replacement, Calcium-Hydroxyapatite (Radiesse®; Merz Pharmaceuticals, Germany) was injected at the oval shaped TEP-tract, which solved the persistent periprosthetic leakage.

Results from the study specific questionnaire indicated that loading of the PVX in the insertion device went well in all cases except one, where more force than usual was needed during the overshooting phase. All but one patient reported no difference in ease and discomfort during placement, this latter patient favored placement of the new VP.

Table 1. Patient characteristics

	No.	Percentage
Gender		
Male	11	85
Female	2	15
Mean age at TL (range)	59	40-79
Median FU in months† (range)	117	7-227
Indication TL		
Primary	5	39
Salvage	5	39
Dysfunctional	2	15
Second primary	1	8
Origin tumor		
Larynx	10	77
Hypopharynx	1	8
Other	2	15

†FU in months was calculated from date of TL to date of removal of final VP

Device lifetime

Median device lifetime of the PVX was 68 days (95% CI 56-80). Median device lifetime of the former VP before placement of the first PVX was 38 days (95% CI 1-76). One patient died 3 days after placement of the PVX from a metastasized esophageal cancer. Former VPs led to aspiration problems, with the PVX he was aspiration-free. A second patient with an irresectable tracheal recurrence also died with his third PVX in situ. He was free from periprosthetic leakage since the insertion of the first PVX, the first two PVXs lasted respectively 79 and 62 days.

Table 2. Device lifetime, size and reason for removal of PVX and former VP for all replacements.

Pt.	Indication TL	Type old VP	Size old VP	DLT old VP	Reason removal old VP	Size PVX	DLT PVX in days	Reason removal PVX
1	Salvage	ActiValve Light	4,5	147	PP leakage	10	3	Pt died
2	Second primary	Vega	8	7	PP leakage	8	22	TP leakage
3.1	Salvage	Vega	6	31	PP leakage	8	68	TP leakage
3.2	Salvage	PVX	8	NA	TP leakage	8	44	TP leakage
3.3	Salvage	Vega	8	NA	TP leakage	8	70	Unknown
3.4	Salvage	Vega	8	NA	PP leakage	8	232	Leakage NOS
3.5	Salvage	PVX	8	NA	Leakage NOS	8	42	TP leakage
3.6	Salvage	PVX	8	NA	TP leakage	8	92	TP leakage
3.7	Salvage	PVX	6	NA	TP leakage	6	27	TP leakage
3.8	Salvage	PVX	8	NA	TP leakage	8	504	NA, still in situ
4.1	Salvage	Vega + XtraFlange	10	105	PP leakage	10	133	TP leakage
4.2	Salvage	PVX	10	NA	TP leakage	10	223	TP leakage
4.3	Salvage	PVX	10	NA	TP leakage	10	835	NA, still in situ
5	DF larynx	Vega	8	99	PP leakage	8	34	Leakage NOS
6.1	Primary	Vega	10	28	PP leakage	10	63	Leakage NOS
6.2	Primary	PVX	10	NA	Leakage NOS	6	41	Leakage NOS
7.1	Salvage	Vega + XtraFlange	6	25	PP leakage	6	79	TP leakage
7.2	Salvage	PVX	8	NA	Unknown	8	62	TP leakage
7.3	Salvage	PVX	8	NA	Unknown	8	39	Pt died
8	Salvage	Vega	6	246	PP leakage	6	91	TP leakage
9	Primary	Vega	8	4	VP lost	8	15	PP leakage
10	Primary	Vega	8	38	PP leakage	8	156	TP leakage
11.1	Primary	Vega	8	20	Wide TEP tract	8	4	VP lost
11.2	Primary	PVX	8	NA	VP lost	8	28	Surgical revision
12	DF larynx	ActiValve Light	8	60	PP leakage	8	36	TP leakage
13	Primary	Vega	8	222	PP leakage	8	232	Voice problems

Abbreviations used: DF larynx = dysfunctional larynx, PP leakage = periprosthetic leakage, TP leakage = transprosthetic leakage, PVX = Provox Vega XtraSeal, DLT = Device lifetime. Old VP is the VP that was replaced with the PVX.

Reason for removal

Main reason for removal of the PVX was transprosthetic leakage in 50% (13/26) followed by leakage not otherwise specified in 15% (4/26), probably also cases of transprosthetic leakage. In one patient (4%) the PVX had to be removed because of periprosthetic leakage. For the other reasons, see table 2. Two patients still had PVX in situ at last date of follow-up (June 2018), with device lifetime of respectively 504 and 835 days. No adverse events occurred during the study period.

During follow-up, in seven patients the PVX was replaced with a Provox Vega, in three cases combined with a washer at the tracheal side. One patient went back to his usual ActiValve Light. The median in situ time of the subsequent non-PVX VP was 62 days. Reasons for removal of these non-PVX VPs were periprosthetic leakage (n = 3), transprosthetic leakage (n = 3), surgical revision (n = 1). Of the 5 remaining patients, 2 still had a PVX in situ at last date of FU, 2 died and in one patient the TEP-tract was closed.

DISCUSSION

In this prospective evaluation of the Provox Vega XtraSeal, we were able to test the device lifetime, efficacy, and ease of placement. Median device lifetime was 68 days, this is comparable to the median device lifetimes of the Provox2 (63 days) or Provox Vega (66 days), which we recently found in a consecutive cohort of patients for over 13 years and which is in line with other literature.[2-4] Only one PVX needed replacement due to periprosthetic leakage, although in one patient the reason for removal was unknown and in four patients the leakage problem was not otherwise specified.

A recent meta-analysis reported an average rate of 7.2% of patients suffering from an enlarged TEP tract and/or periprosthetic leakage.[8] The most commonly used treatments were temporary removal of the VP and injections at the TEP tract. Temporary removal and placement of a nasogastric feeding tube and cuffed canula is however quite cumbersome for the patient and it might take several days before sufficient shrinkage is observed.[8] Placement of a silicone washer is usually an elegant and conservative solution to manage periprosthetic leakage, especially when the VP is still functioning properly.[9] If the insertion of a washer fails, other strategies such as injection of a filler like hydroxy-apatite, fat or collagen, the application of a purse string suture or temporary removal of the VP to allow for shrinkage could be tried, all aiming to prevent unwanted surgical closure of the TE fistula.

Earlier studies have reported success rates of 77-88% in managing periprosthetic leakage with an enlarged flange on the tracheal side.[6, 9-11] Kress et al described 76 patients with periprosthetic leakage who were managed with custom fit VPs with an enlarged flange on the esophageal side and were highly successful (97%).[12] Choussy et al evaluated 28 Blom-Singer large esophageal and tracheal flange VPs in 18 patients and reported success in all patients, with a median device lifetime of 70 days (range 24-219).[13] It indeed seems logical that an extra flange on the esophageal side is more successful than a flange on the tracheal side, as it provides a better seal to the mucosa. However, a tracheal flange can be placed on an existing VP, whereas an esophageal flange usually necessitates replacement of the VP and thus higher costs.

Due to local reimbursement differences and costs of VPs in various countries, it is difficult to give exact numbers, but on average the costs of a Provox Vega combined with a silicone washer is quite comparable with that of a PVX, ranging from 90-110% of the costs of a PVX (personal communication with ATOS Medical). If there is need for replacement of the VP, a washer on the esophageal side/PVX is most effective, but if there is no need for replacement, a washer on the tracheal side is most cost-efficient.

CONCLUSION

With this prospective study, we have demonstrated that the new Provox Vega XtraSeal adds a valuable new tool to solving periprosthetic leakage, diminishing the burden of this uncomfortable adverse event both for the patient and the clinician. We were able to solve almost all cases of periprosthetic leakage and were able to reach an adequate median device lifetime of 68 days, comparable to current device lifetime of modern voice prostheses.

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Dilation after laryngectomy: incidence, risk factors and complications

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8 Dilation after laryngectomy: incidence, risk factors and complications

Japke F. Petersen, Thomas F. Pézier, Jolanda M. van Dieren, Vincent van der Noort, Tom van Putten, Sandra I. Bril, Luuk Janssen, Richard Dirven, Michiel W.M. van den Brekel, Remco de Bree

Japke F. Petersen and Thomas F. Pézier contributed equally to this manuscript

ABSTRACT

Background: *Neopharyngeal stenosis is a recognized sequela of total laryngectomy (TL). We aim to investigate the incidence of stenosis requiring dilation, risk factors for stenosis and complications of dilation.*

Methods: *Retrospective cohort study of patients undergoing TL in two dedicated head and neck centers in the Netherlands.*

Results: *A total of 477 patients (81% men, median age of 64 at TL) were included. Indication for TL was previously untreated primary tumor in 41%, salvage following (chemo)radiotherapy (CRT) in 44%, dysfunctional larynx in 9% and a second primary tumor in 6%. The cumulative incidence of dilation at 5 years was 22.8%, and in total 968 dilations were performed. Median number of dilations per patient was 3 (range 1-113). Female gender, a hypopharynx tumor, and (C)RT before or after the TL were significantly associated with stenosis requiring dilation. We observed 8 major complications (0.8%), predominantly occurring during the first dilation procedures. Use of general anesthesia is a risk factor for complications. The most frequent observed major complication was severe esophageal perforation (n = 6 in 5 patients).*

Conclusion: *The cumulative incidence of pharyngeal stenosis needing dilation was 22.8% at 5 years. Roughly half of these patients could be treated with a limited number of dilations, the rest however needed ongoing dilations. Major complications are rare (0.8%) but can be life threatening. General anesthetics is a risk factor for complications, and complications occurred predominantly during the first few dilations procedures. This should alert the physician to be extra careful in new patients.*

INTRODUCTION

Total laryngectomy (TL) with or without (partial) pharyngectomy and adjuvant radiotherapy (RT) is often recommended for bulky advanced stage cancer of the larynx or hypopharynx whilst less bulky disease is often treated with (chemo)radiotherapy (CRT) for organ preservation.[1-5] However, despite initial organ preservation, TL is subsequently still performed in roughly a third of advanced stage patients, either as salvage procedure for a recurrence, treatment of a second primary or for functional reasons.[4, 6, 7]

Rehabilitation following TL largely focuses on speech rehabilitation. Most Western countries use indwelling voice prostheses (VP) and with this, up to 90% of patients achieve satisfactory speech.[8, 9] Less attention however is paid to swallowing function after TL. The majority of patients are expected to return to a normal diet, but some find that swallowing becomes difficult.[10, 11] This can be due to anatomical reasons such as narrowing of the neopharyngeal lumen (a lumen <12mm invariably leads to dysphagia[12]), pseudo-diverticulum formation[13], or due to functional problems caused by changes in the quality/quantity of saliva, poor pressure built up at the base of tongue or loss of coordinated muscular contraction in the neopharynx. Rates of anatomical pharyngeal stenosis have been reported as high as 33% in surgically treated patients[14] and over 50% in patients treated with CRT.[15] Severe dysphagia negatively effects patients' quality of life and can lead to nutritional deficiencies and increased healthcare costs.[16]

The diagnosis of dysphagia is almost entirely from the patient's self-reported symptoms and the threshold for intervention depends on whether a patient's nutritional status is affected and/or their perceived quality of life. Stepwise interventions can involve dietary advice/modification, the use of supplementary nutritional drinks, dental rehabilitation, proton pump inhibitors, tube feeding, dilation or surgical reconstruction of the neo-pharynx.

Not all patients with dysphagia are suitable for dilation. Some patients have no clear radiographic or endoscopic evidence of a stricture. In these patients, it is thought that the dysphagia is more "functional/physiological" than "anatomical".[17, 18] Other patients have

clear radiographic evidence of a diverticulum or pseudo-epiglottis[19] which is also not amenable to dilation.

Dilation for benign esophageal strictures caused by inflammation of the esophagus or post-operative stenosis of the anastomosis after esophagectomy is reported to be highly successful.[12, 20-22] However, among TL patients who are often treated with chemo-radiotherapy before or after the TL and thereby represent a distinct patient group, only small case series have described the effect of dilation procedures in this group of patients.[23]

In this paper we aim to investigate in a cohort of patients having undergone TL:

i. The cumulative incidence of pharyngeal stenosis requiring dilation
ii. Risk factors for stenosis requiring dilation
iii. The incidence and risk factors for complications following dilation

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients undergoing total laryngectomy in two dedicated Head and Neck Centres in The Netherlands: the University Medical Center Utrecht, Utrecht (Jan 2008 to Dec 2016) and The Netherlands Cancer Institute, Amsterdam (Jan 2000 to Dec 2012). Patients' demographic, staging, treatment and outcome data were collected using (scanned) electronic patient records. We recorded TNM classification according to the then applicable AJCC manual, (5th, 6th and 7th editions). All patients underwent total laryngectomy with or without (partial) pharyngectomy either as a primary treatment, salvage treatment, treatment for a second primary or as a functional treatment for a dysfunctional larynx. TLs were performed by a variety of surgeons during the study period and details on the surgical techniques could not be found in all patients. Specifically, myotomy of the cricopharyngeal muscle and neurectomy of the pharyngeal plexus, as well as the method of closure vertical, T, horizontal, suture type, stitch type) were not well documented and differed between surgeons.

For each dilation procedure we recorded the maximum size of dilation (in mm), type of dilator, type of anesthetic, which physician group performed the dilation (head and neck surgeon or gastroenterologist) and whether any complications occurred. We excluded dilation procedures where the stenosis was due to tumor recurrence. Complications following dilation were grouped into minor or major. Major complications were defined as complications for which the patient had to be admitted to the ward for >24 hours and received medical treatment other than analgesics, anti-emetics, and antipyretics. Minor complications were defined as complications which resolved within <24hours after dilation, for which no medical treatment was necessary (other than replacement of a dislocated voice prosthesis).

Dilation technique

In our institutes, dilation is performed either by a gastroenterologist or a head and neck surgeon. The gastroenterologist generally uses procedural sedation (using a combination of fentanyl and midazolam or propofol) whereas the head and neck surgeon dilates under general anesthesia. The gastroenterologists routinely use a flexible endoscope to inspect the esophagus and stomach and place a guidewire for Savary bougies (Savary Gilliard technique).[12] The head and neck surgeons use the same bougies but without placing a guidewire and generally visualize only the upper esophagus with a rigid oesophagoscope. For both physician groups, the stenosis is dilated by passing bougies of increasing diameter through the stenosis until either the maximum diameter is reached (18mm) or until too much resistance is felt by the operator. Whilst achieving small mucosal tears is necessary to treat the stenosis, an esophageal perforation is a well-known major complication of this procedure that has to be avoided.

Statistical analysis

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY) and R studio. Descriptive analysis was used to summarize patient and treatment characteristics. We used a cumulative incidence technique to assess the effect (expressed as a hazard ratio) of patient and treatment characteristics on dilation, which is a time dependent outcome, using the R-package 'cmprsk'.[24] Death was treated as a competing risk and patients were censored when lost-to-follow-up. The same technique was used to assess the cumulative incidence of dilation with death as a competing risk. To calculate the cumulative incidence, we used time in days since TL to date of first dilation procedure.

Using this technique we performed univariate and multivariate regression analyses to identify patient and treatment characteristics that correlate with the patient having a dilation. Odds ratios on a complication following a dilation procedure, which was not considered time dependent, were calculated using univariate and multivariate logistic analyses.

Ethical considerations

This study does not fall under the scope of the Medical Research Involving Human Subjects Act and the institutional review boards of both centers approved this study.

RESULTS

Patients

A total of 477 patients (81% men) with a median age at TL of 64 (range 38-91) were included in this study. Median follow-up time in months since TL was 81 months (95% CI 69-96). Indication for TL was salvage surgery in 211 (44%), primary surgery in 193 (41%), a dysfunctional larynx in 45 (9%) and second primary tumor in 28 (6%), see Table 1 for patient characteristics.

Dilations

In our cohort 111/477 (23%) patients underwent a total of 968 dilations for symptomatic pharyngeal stenosis. The cumulative incidence of dilation (with death as a competing risk) increased over time. At 5, 10 and 15 years this was respectively 22.8%, 26.5% and 29.0%, see Figure 1. for a plot of the cumulative incidence. The median number of dilations performed per patient was 3 (range 1-113). Median time to first dilation was 9 months after TL (95% CI 7-11). Twenty-seven (27/111=24%) patients underwent one dilation, 23 (21%) required two dilations, 13 (12%) three dilations and the remaining 48 patients (43%) had more than 3 dilations.

The gastroenterologists performed 91% of all dilations, 9% was performed by the head and neck surgeons, though there was considerable cross-over with patients being dilated by both types of specialists. On a patient level, 43 patients (39%) underwent their first dilation procedure by the head and neck surgeon. Of these 43 patients, 13 patients were also dilated by the gastroenterologists at a later time point. Of the 68 patients who were initially dilated by gastroenterologists, 8 patients were also dilated by the head and neck surgeon at a later time point.

The stenosis was dilated to a mean maximal diameter of 13mm (range 6-18 mm) which was similar among dilation procedures by the head and neck surgeons and gastroenterologists. All patients were dilated using silicon bougie dilatators. In 67% of procedures a combination of fentanyl and midazolam for sedation was used, in 18% propofol , 8% was performed under general anesthetics and in 7% the type of sedation was not reported. One patient performed self-dilations at home. Because the frequency and complication rate of these dilations were unknown, we did not include these dilations in our analysis.

Risk for stenosis requiring dilation

We performed a univariate analysis to assess risk factors for dysphagia requiring dilation using the cumulative incidence technique described in the methods section (see Table 1).

Statistically significant variables on univariate analysis included female gender, a hypopharynx tumor (ref = larynx), TL for a dysfunctional larynx or for a second primary (ref = primary TL), (C)RT before, after or before and after TL (ref = no (C)RT), a pectoralis major (PM) flap to reconstruct a mucosal defect (i.e. not as overlay reinforcement), a free radial forearm flap (FRFF (ref = no flap)), and the development of a pharyngo-cutaneous fistula <30 days after TL.

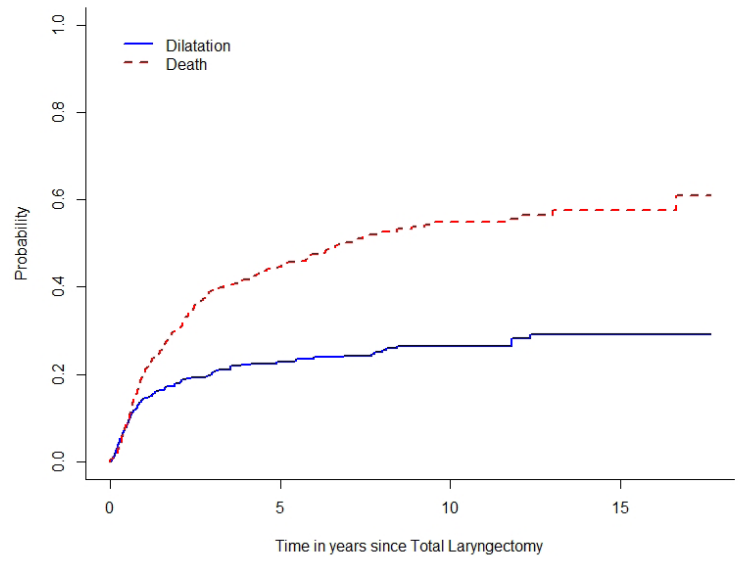

Figure 1. Cumulative incidence of dilation. The X-axis depicts the time in years since total laryngectomy, the Y-axis depicts the cumulative probability on a dilation procedure (blue straight line) or death (red, dashed line).

We subsequently performed a multivariate analysis including the parameters that showed significant interaction with stricture formation on univariate analysis. Using a binary logistic backwards regression model the following parameters remained statistically significantly associated with stricture formation necessitating dilation: female gender (HR 1.87, p = 0.006), a hypopharynx tumor (ref = larynx) (HR 2.12, p = 0.001), (C)RT before TL (HR 6.13, p = 0.003), (C)RT after TL (HR 3.65, p = 0.04), and (C)RT before as well as after the TL (HR 25.09, p<0.0001) (ref = no (C)RT) (see Table 2).

Table 1. Characteristics of dilation vs. non-dilation groups and univariable analysis presented in hazard ratios with corresponding p-values.

	Total	Non-dilation group	Dilation group	Univariate analysis, OR (95% CI)	P value
Total	**477**	**366**	**111**		
Mean age at TL (SD)	64 (10.0)	64 (10.2)	64 (9.4)	1.00 (0.98-1.02)	0.890
Gender					**0.004**
Male	385 (81)	306 (84)	79 (71)	1.00	
Female	92 (19)	60 (16)	32 (29)	2.07 (1.26-3.39)	
Tumor site					**0.008**
Larynx	344 (72)	277 (76)	67 (60)	1.00	
Hypopharynx	98 (21)	66 (18)	32 (29)	2.01 (1.22-3.30)	**0.006**
Other	35 (7)	23 (6)	12 (11)	2.16 (1.02-4.55)	0.044
Initial T-stage					0.654
Tis/T1	71 (15)	52 (14)	19 (17)	1.00	
T2	106 (22)	79 (22)	27 (24)	0.94 (0.47-1.85)	0.848
T3	102 (21)	81 (22)	21 (19)	0.71 (0.35-1.45)	0.345
T4	189 (40)	149 (41)	40 (36)	0.74 (0.39-138)	0.338
Unknown	9 (2)	5 (1)	4 (4)	-	-
Initial N-stage					
N0	294 (62)	234 (64)	60 (54)	1.00	
N positive	178 (37)	129 (35)	49 (44)	1.48 (0.96-2.29)	0.076
Unknown	5 (1)	3 (0.8)	2 (1.8)	-	-
Indication TL					**<0.001**
Primary	193 (41)	158 (43)	35 (32)	1.00	
Salvage	211 (44)	167 (46)	44 (40)	1.19 (0.73-1.95)	0.492
2nd primary	28 (6)	14 (4)	14 (13)	4.51 (1.98-10.32)	**<0.001**
Dysfunctional	45 (9)	27 (7)	18 (16)	3.01 (1.50-6.06)	**0.002**
Neck dissection during TL					0.744
None	183 (38)	137 (37)	46 (41)	1.00	
Unilateral	142 (30)	111 (30)	31 (28)	0.83 (0.50-1.40)	0.487
Bilateral	152 (32)	118 (32)	34 (31)	0.86 (0.52-1.42)	0.554
Primary puncture					
No	65 (14)	48 (13)	17 (15)	1.00	
Yes	412 (86)	318 (87)	94 (85)	0.84 (0.46-1.52)	0.554
(Chemo)radiotherapy					**0.001**
Never	56 (12)	53 (15)	3 (3)	1.00	
Before TL	310 (65)	227 (62)	83 (74)	6.35 (1.93-20.89)	**0.002**
After TL	104 (22)	82 (23)	22 (20)	4.47 (1.27-15.72)	**0.020**
Before and after TL	7 (1.5)	2 (0.5)	5 (4)	44.17 (5.92-329.79)	**<0.001**
Flap type					**0.030**
None	295 (62)	240 (66)	55 (49)	1.00	
PM to reconstruct	105 (22)	71 (20)	34 (30)	2.14 (1.29-3.54)	**0.003**
PM to overlay	24 (5)	18 (5)	6 (5)	1.49 (0.56-3.92)	0.422
FRFF	14 (3)	8 (2)	6 (5)	3.35 (1.12-10.04)	**0.031**
ALT	13 (3)	8 (2)	5 (4)	2.79 (0.88-8.86)	0.082

Table 1 continued.

	Total	Non-dilation group	Dilation group	Univariate analysis, OR (95% CI)	P value
Total	**477**	**366**	**111**		
Flap type					**0.030**
Gastric pull up	10 (2)	7 (2)	3 (3)	1.91 (0.48-7.64)	0.359
Other	8 (2)	7 (2)	1 (0.9)	0.64 (0.08-5.29)	0.677
Unknown	8 (2)	5 (1)	3 (3)	-	-
Post-operative clinical fistula <30 days after TL					
None	347 (73)	275 (75)	72 (65)	1.00	
Yes	126 (26)	87 (24)	39 (35)	1.71 (1.08-2.71)	**0.021**
Unknown	4 (0.8)	4 (1)	-	-	**-**

Bold faced p-values are significant. Values in parentheses are percentages unless otherwise indicated.

Complications following dilation

On a procedure level we observed 27 complications during the 968 dilations (2.8%), of which 19 minor (2.0%) and 8 major (0.8%). On a patient level, 7 patients (6%) suffered 8 major complications.

The major complications were: anaphylactic shock caused by NSAIDs taken before the dilation procedure (n = 1), a voice prosthesis dislodged into the bronchus causing severe cardiac stress, intensive care stay and a Tsako-Tsubo cardiomyopathy (n = 1) and transmural esophageal perforations (n = 6 in 5 patients).

Two proximal perforations caused leakage laterally to the carotid artery (n = 1) and leakage posteriorly to the pre-vertebral space (n = 1). The former developed a pharyngo-cutaneous fistula which was managed conservatively with wound dressings. The latter underwent multiple surgeries including stabilization of the vertebral column by the spinal surgeons. One distal perforation required intensive care admission (n = 1) and another distal perforation necessitated laparotomy (n = 1) and direct repair. One patient suffered two major complications at dilation number 1 and 2, both involving proximal perforations which could be managed conservatively.

Five of the 8 major complications occurred in the first or second dilation procedure of this patient. The other three occurred during respectively the 8th, 12th and 31st dilation procedure. Of note, two of these “late” complications were unusual in that one was a distal esophageal perforation in a patient with a hiatus hernia and one was the dislodged voice prosthesis. We observed only one ‘late’ proximal esophageal perforation in a patient during his 31st dilation.

Minor complications were: loss of voice prosthesis during dilation or <24h due to edema (*n* = 6), suspected mucosal tear/hematemesis for which the patient was observed but that resolved spontaneously <24h after dilation (*n* = 7), edema temporarily worsening dysphagia (*n* = 3), fever with unknown cause which resolved <24h after dilation (*n* = 1), exacerbation COPD (*n* = 1) and transient but significant desaturation during the procedure without any further consequences (*n* = 1).

Table 2. Multivariate analysis demonstrating hazard ratio for development of stricture formation necessitating dilation after total laryngectomy.

		OR (95% CI)	P-value
Gender			
	Male	1.00	
	Female	2.31 (1.35-3.95)	**0.002**
Tumor site			**0.034**
	Larynx	1.00	
	Hypopharynx	2.04 (1.19-3.51)	**0.010**
	Other	1.37 (0.61-3.08)	0.453
Indication TL			**0.020**
	Primary TL	1.00	
	Salvage TL	0.74 (0.35-1.54)	0.415
	2nd primary	2.38 (0.85-6.71)	0.101
	Afunctional	1.60 (0.66-3.86)	0.299
(Neo-)adjuvant (Chemo)radiotherapy			**0.002**
	Never	1.00	
	Before TL	7.12 (1.92-26.42)	**0.003**
	After TL	4.49 (1.25-16.12)	**0.021**
	Before and after TL	61.16 (7.08-528.37)	**<0.0001**

Risk factors for complications

We performed a univariate analysis to assess risk factors for major complications. The following variables were entered into univariate analysis: age, gender, T-stage, N-stage, tumor localization, indication for TL, (C)RT pre- or post TL, clinical fistula after TL, flap reconstruction, maximum size of bougie used (6-12mm, 12.5-14mm or 14.5-18mm), dilation performed by head and neck surgeon or gastroenterologists, type of anesthetic used, and first dilation versus subsequent dilation. The following variables were significantly related to a higher risk on a major complication: first dilation procedure (OR 4.7, 95% CI 1.12-20.1, $p = 0.04$), general anesthetic (OR 9.15, 95% CI 1.81-46.10, $p = 0.007$, ref = other anesthetics (fentanyl, midazolam) and dilation performed by the head and neck surgeon (OR 5.95, 95% CI 1.40-25.30, $p = 0.016$, ref = gastroenterologist).

We subsequently entered the variables into a multivariate analysis, except for type of physician. Since only head and neck surgeons perform dilations under general anesthesia, these two variables are overlapping, thus the variable type of physician was barred from entering the multivariate model. Using a binary logistic backward regression model, only a dilation procedure under general anesthetics remained significantly associated with a higher risk on a major complication (OR 9.15 95% CI 1.81-46.10, $p = 0.007$).

Gastric pull-up

During follow-up, two patients with symptomatic stenosis underwent a gastric pull up reconstruction of the stenotic segment following failed dilations. One of the patients suffered a heart attack intra-operatively and died, the other made an unremarkable recovery although his swallowing function remained impaired, as the jejunostomy tube could not be removed.

DISCUSSION

In this consecutive cohort of 477 patients who underwent a laryngectomy, almost a quarter of all patients underwent one or more dilations for dysphagia, with a median of 3 procedures per patient. The cumulative incidence of dilation increased over time from 22.8% at 5 years to 29% 15 years after TL. Risk factors for dysphagia requiring dilation were female gender, a hypopharynx tumor, and (chemo)radiotherapy before or after TL. On a procedure level, we observed a major complication rate of 0.8%, which was significantly higher among patients dilated under general anesthesia.

The cumulative incidence of 22.8% requiring dilation at 5 years means that dysphagia is one of the most common sequela of a TL.[25] Indeed, other studies found (dilation and non-dilation necessitating) rates of dysphagia as high as 50-72% after TL[17] and stricture formation rates of 13-50%.[26-31] Due to the retrospective nature of the cohort, we were unable to reliably evaluate the incidence of dysphagia not necessitating dilation. Therefore, the actual incidence of dysphagia in our cohort is probably higher.

Not surprisingly, (C)RT before or after the TL was the most important risk factor for dysphagia requiring dilation besides female gender and a hypopharynx tumor. Dysphagia as a complication after CRT for head and neck cancer has been described by Kraaijenga et al. in a long term follow-up study. In their cohort, at a median follow-up time of 11 years, 54% had moderate to serious swallowing problems, and 14% was still tube feeding dependent.[15] In another retrospective study of 199 patients receiving CRT mainly for T3/T4 larynx,

hypopharynx and oropharynx cancer, 21% of patients developed symptomatic strictures. Similarly to our data set, risk factors for stricture formation in their cohort were female gender and a hypopharynx tumor, but also patients receiving twice daily radiotherapy showed an increased risk for stenosis.[32]

In our cohort, patients were laryngectomized in the time period 2000-2016 and received RT before (66%) or after (22%) the TL. Only 12% was not treated with RT. Given the time frame in which patients were included and the fact that patients might have had radiotherapy several years before their TL, patients in this cohort were treated with several different radiotherapy techniques. Details regarding type of radiotherapy and dosage were missing not at random, rendering an analysis based on radiotherapy details impossible. The incidence of dysphagia and the necessity for dilations in future patients treated with Intensity Modulated Radiotherapy (IMRT) or Volumetric Arc Therapy (VMAT) might be lower, as this technique aims to spare organs at risk.[33] Christianen et al. recently demonstrated how swallowing sparing IMRT (SW-IMRT) with dose constraints for both parotid glands and the swallowing organs at risk, can indeed lead to reduced swallowing dysfunction 6 months after completion of treatment.[34] It is however important to note that also preventive swallowing therapy and a dedicated rehabilitation program following (C)RT might further decrease the incidence of dysphagia and necessity for dilation in future patients.[35]

Due to the retrospective nature of our study we were unable to reliably analyze closure technique and its relation to dysphagia. The specific stich technique used (eg. Conley, interrupted, stapler), the suture material (monofilament, polyfilament, barbed), and the closure form (vertical, T, horizontal) are all of particular interest, and have their proponents in the surgical community. Furthermore, whether the pharynx could be primarily closed or whether partial reconstruction with for example a pectoralis major skin island flap or full 360 degree reconstruction should intuitively impact on dysphagia post-operatively. Indeed in univariate analysis the PM to reconstruct was statistically significant, as was the free fore-arm flap but these did not remain significant on multivariate analysis.

In the literature, the most important risk factor for a complication of dilation, is the presence of a malignant or complex stricture, or a caustic induced stricture.[12, 36, 37] Complex strictures are described as narrower, or more angulated strictures. Piotet et al. described their experience in 1,826 endoscopic dilations in which they observed a complication rate of 0.8% for benign strictures and 4.6% for malignant strictures.[12] These figures have been indeed reported by other studies[38, 39], and the 0.8% is similar to our major complications rate.

In our cohort, 7 patients (6%) suffered 8 major complications, of which 6 perforations. Five of the 6 perforations occurred during the first or second dilations. This should alert the operator to be particularly careful with new patients. On multivariate analysis, dilation under general anesthesia was associated with the highest OR for a complication. It is possible that the muscle relaxant used during anesthesia mitigates feedback from the patient, leading to overly ambitious dilation and a higher risk on an esophageal perforation. Furthermore, the indication for the first dilation is invariably given by the head and neck surgeon, who then chooses whether this will be done by a head and neck surgeon under general anesthesia or as an endoscopic procedure by the gastro-enterologist. Reasons to perform the dilation under general anesthesia by the head and neck surgeon may be to exclude recurrent tumor in the neopharynx or to evaluate severe stenosis for other treatment options like surgical reconstruction of the neo-pharynx. It can be anticipated that these cases are more difficult and harbor a higher risk of complications.

In our data set, 57% of patients who were dilated required 1-3 dilations. The remaining 43% underwent repeated dilations due to ongoing dysphagia (one patient had >100 dilations). In these patients, surgical reconstruction of the stenotic segment (for example with a flap or gastric pull up) can be offered. It must however be noted that our experience with gastric pull-up as a functional procedure to treat dysphagia was limited to two patients, making the numbers too small for any meaningful conclusions.

CONCLUSION

With an cumulative incidence rate of 22.8% at 5 years, dysphagia necessitating dilation is a common sequela following laryngectomy, and is more common in female patients, patients with hypopharynx tumors and in association with (chemo)radiotherapy before or after the TL. Roughly half the patients requiring dilation could be treated with a limited number of dilations, the others however needed serial dilations. Major complications such as perforations are rare, and occur almost exclusively in the first and second dilations. This should alert the physician to be extra careful in new patients.

8

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Improving decision making in larynx cancer by developing a decision aid - a mixed methods approach

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9 Improving decision making in larynx cancer by developing a decision aid - a mixed methods approach

Japke F. Petersen, Adriana Berlanga, Martijn M. Stuiver, Olga Hamming-Vrieze, Frank Hoebers, Philippe Lambin, Michiel W.M. van den Brekel

ABSTRACT

Objective: *Patients diagnosed with advanced larynx cancer face a decisional process in which they can choose between radiotherapy, chemoradiotherapy or a total laryngectomy with adjuvant radiotherapy. Clinicians do not always agree on the best clinical treatment, making the decisional process for patients a complex problem.*

Methods: *Guided by the International Patient Decision Aid Standards, we followed three developmental phases in which we held semi-structured in-depth interviews with patients and physicians, thinking out loud sessions and a study specific questionnaire. Audio recorded interviews were verbatim transcribed, thematically coded and analyzed. Phase one consisted of an evaluation of the decisional needs and the regular counseling process. Phase two tested the comprehensibility and usability, and phase three beta tested the feasibility of the PDA.*

Results: *Patients and doctors agreed on the need for development of a PDA. Major revisions were conducted after phase one to improve the readability and replace the majority of text with video animations. Patients and physicians considered the PDA to be a major improvement to the current counseling process.*

Conclusion: *This study describes the development of a comprehensible and easy to use online patient decision aid for advanced larynx cancer, found satisfactory by patients and physicians (available on www.treatmentchoice.info). The outcome of the interviews underscores the need for better patient counseling. The feasibility and satisfaction among newly diagnosed patients as well as doctors will need to be proven. To this end, we started a multicenter trial evaluating the PDA in clinical practice (ClinicalTrials.gov Identifier: NCT03292341).*

INTRODUCTION

A major shift from current population/guidelines based medicine to personalized and participative medicine is underway. This transition is being supported by the development of clinical decision support systems based on prediction models of treatment outcome.[1, 2] In parallel, shared decision making (SDM) is gradually taking over the traditional paternalistic patient-doctor relationship. SDM represents the process in which patients and healthcare professionals make healthcare choices in which both the best available evidence regarding risks and benefits of the possible options is taken into account, as well as the patients' personal values and his or her situation.[3, 4] There is level 1 evidence that SDM improves patient satisfaction and patient-doctor communication and leads to better patient outcomes.[5-9] However, SDM is challenging: doctors have limited consultation time and physicians find it difficult to assess patients' treatment preferences.[10-12] Especially for patients diagnosed with advanced cancer for whom there is no 'best choice', making a shared decision can be difficult.

An example of a condition in which there is not always a 'best choice' is the treatment decision for advanced larynx cancer. Historically, patients were treated by a total laryngectomy (TL). This leads to loss of normal voice, social and adaptation problems and associated distress. In the last decades, concurrent chemoradiotherapy (CRT) or radiotherapy (RT) alone, have been shown to be successful in sparing the larynx in the majority of patients whilst reaching almost similar overall survival (OS) rates.[13] Recent publications however demonstrated that in more advanced tumors, TL still seems to give the best OS rates.[14, 15] These publications have led to an update in the ASCO guidelines in 2018, in which is stated that extensive T3 or large T4a lesions might achieve better survival rates following total laryngectomy.[16] Despite these results, organ preservation is still widely applied[14, 15, 17], and patients sometimes are willing to trade off survival in order to preserve their larynx.[18] However, (C)RT sometimes fails, necessitating salvage surgery, and in these cases rehabilitation is even more complicated and less successful.[19] It therefore seems difficult – if not impossible – for a doctor to transfer all this information and the associated uncertainty to patients, while at the same time helping them to capture all the information and make a well-balanced treatment choice.

A patient decision aid (PDA) can support this decisional process by transferring medical information in an easy to understand way. PDAs aim to inform patients about the different treatment options and help them to clarify their personal preferences. A recent Cochrane review reported that patients using a PDA had more knowledge about the treatment options and expected benefits and harms, experienced less decisional conflict and became less passive decision makers.[7]

To empower patients and improve shared decision making, we developed a comprehensive, interactive web-based PDA for patients with primary T3-T4 larynx cancer receiving curative treatment. In this article, we describe the development process and evaluation of the PDA among patients and doctors in two dedicated head and neck cancer centers.

MATERIALS AND METHODS

The development of the PDA was based on the quality criteria as set out by the International Patient Decision Aid Standards (IDPAS) collaboration.[20, 21] We followed three phases in the development process, see Figure 1. In phase 1, we reviewed relevant literature on advanced larynx cancer and compared this to currently used counseling papers. Furthermore, we held semi-structured in-depth interviews with patients and doctors to evaluate patients' decisional needs and the regular counseling process. We stopped inclusion of participants after reaching data saturation, meaning additional participants did not contribute anything new to our knowledge as obtained by previous interviews. Based on these results, a hospital based web designer constructed the first version of the PDA.

In phase 2, we alpha tested the comprehensibility and usability of the first version using a mixed method approach. Similar to phase 1, we interviewed patients and doctors. Next, we demonstrated the PDA using a 'thinking-out-loud' session, during which the research assistant guided the participant through the PDA while asking for feedback. Participants then filled in a study specific questionnaire containing 38 statements regarding the satisfaction with the PDA, the effectiveness, the comprehensibility, the usability and the value of the information (see online appendix). Each statement was phrased in a positive way, ranging from 1 (totally disagree) to 5 (totally agree), therefore agreement conferred a positive evaluation of the PDA. Furthermore, participants were asked to rank the tool on overall satisfaction, ranging from 0 (very unsatisfied) to 10 (very satisfied).
In phase 3, we beta tested the feasibility of the second and last version of the tool by using the same mixed method approach as described for phase 2.

All patients participating in this study were recruited by their treating physician or by the "Dutch Patient Society for Head and Neck Cancer", had been treated with TL, CRT or RT for larynx cancer and gave written informed consent. Interviews were audio recorded, verbatim transcribed without personal data and thematically coded using MAXQDA software (MAXQDA, software for qualitative data analysis, 1989-2018, VERBI Software - Consult - Sozialforschung GmbH, Berlin, Germany). Thematically coding the interviews enabled us to identify patterns with respect to decisional needs, the counseling process and the PDA. These developmental steps allowed us to identify critical flaws in the PDA, and supplement missing information after discussions within the developmental team.

Ethics

This study does not fall under the scope of the Medical Research Involving Human Subjects Act, which was confirmed by the institutional review board. The institutional review board of both hospitals approved this study.

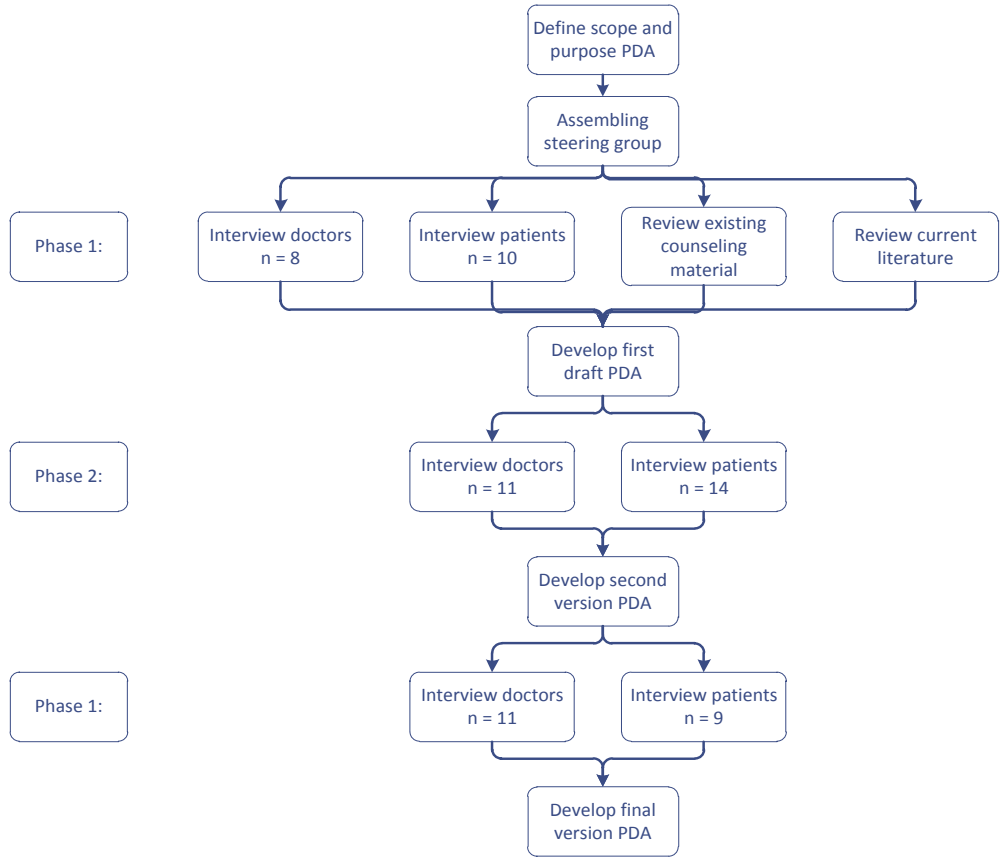

Figure 1. Developmental process showing the flowchart of the developmental process of the PDA (analogy of IPDAS checklist)[21].

RESULTS

PHASE 1 - NEEDS ASSESSMENT AND BARRIERS TO THE COUNSELING PROCESS

Doctors

Characteristics of participants are to be found in table 1. All doctors agreed that the need for a PDA is increasing. In terms of development of the PDA, doctors indicated it should be as complete and objective as possible, clear, and contain easy to understand numbers or figures regarding survival and possible side effects for different treatments. It should not push the patient in a particular direction by asking them questions like 'Is OS most important to you?' or 'Do you want to preserve your larynx at any costs?'. Regarding the layout, the optimal PDA should be visually supported by images, and be easy to navigate through.

> *'Yes, I believe there is a need for something like that, if everything is nicely illustrated for patients and can be explained in a simple way'. HNS1*

Perceived barriers for good patient counseling for advanced larynx cancer were the relatively low average educational level of the typical patient. Most doctors doubted that patients would remember the information provided during the counseling process. Another experienced barrier was difficulty gaining insight into personal values and coping strategies of the patient:

> *'In a conversation it is often difficult to understand what is most important for the patient. That is where I see the biggest challenge'. HNS3*

Patients

Most patients were positive about the intended development of a PDA and would have wanted to use it if it would have been available to them. One patient however did not want to know any details regarding his treatment, although he agreed it could be useful for other patients. Most patients had searched for more information on the Internet during their counseling process. The majority of patients indicated repetition of information as useful to reconfirm the received information, and said they often did not remember information received during counseling. Reasons for not remembering were the amount of information given at once, and the impact of the diagnosis, which made them forget about the rest.

> *'You are occupied with the disease. Not with the information; that you do not remember. When you are told it is that serious, it is almost like you are numb. The whole thinking process does not work anymore'. PtTL04*

Development PDA

After combining the information found in the literature, existing patient counseling flyers, and the interviews, the first version of the online PDA was constructed, see figure 2.

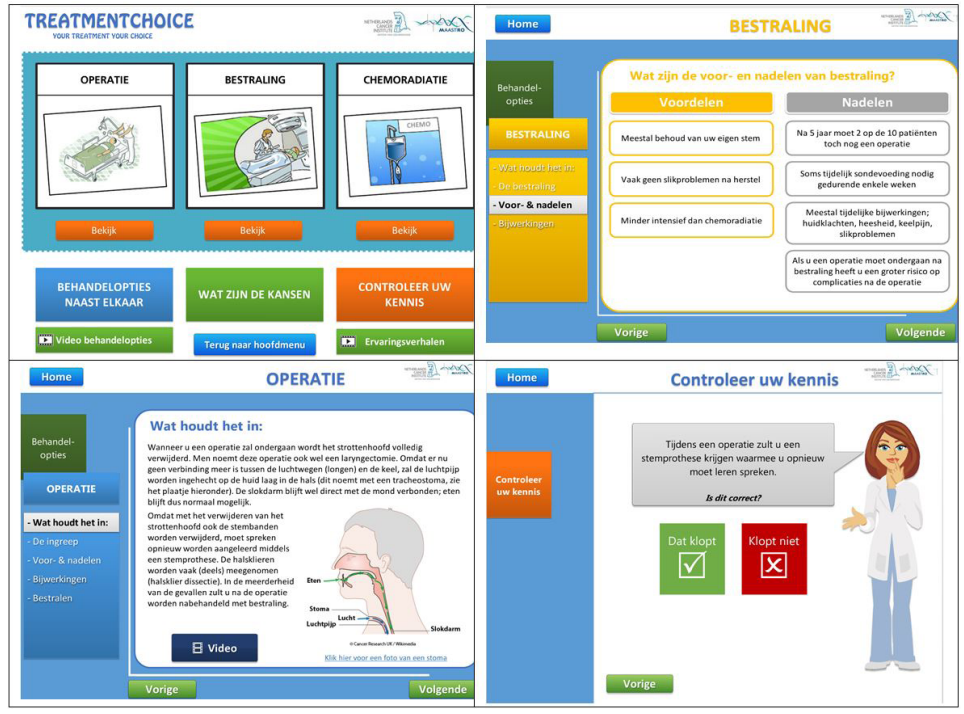

Figure 2. Lay-out of the first version of the PDA

(a) Home page of the PDA. For each treatment option we included videos of doctors explaining the treatment and videos of patients who are interviewed on their decisional process, the treatment and their quality of life. **(b)** The PDA contains a short summary with the risks and benefits of each option laid out next to each other and estimated overall survival rates per treatment and tumor characteristics (based on the TNM-classification). **(c)** All the treatment options are explained using text, pictures and videos **(d)** At the end, patients can fill in a knowledge and preference test. They are encouraged to take the results of these tests to their physician, to identify potential gaps in their knowledge and discuss personal preferences.

PHASE 2 - ALPHA TESTING OF COMPREHENSIBILITY AND USABILITY

Doctors

Due to time restraints, most doctors only thoroughly evaluated the medical information of their own specialty and recommended on the usability of the PDA in general. They estimated it would take patients a median of 60 minutes to complete the PDA. In general, the feedback was positive, with a median mark of 7/10. Yet several, mostly small, adjustments were suggested by all participants. The participants were generally satisfied with the medical information given, although several participants made some corrections to the text. Furthermore, almost half of them were afraid there was too much text. Also, two participants felt that the treatment from their specialty was described too negatively, but the other 9 other participants did not consider this to be the case. With regards to navigation, improvements were suggested to add a homepage with an index of all the chapters, and alter the use of colors.

Patients

Fourteen patients evaluated the first draft and filled in a study specific questionnaire. All statements were ranked with a median score of 4 (out of 5), and the PDA got a median 8/10 score for overall satisfaction. The patients identified several strong points of the tool. They expected it would provide future patients with a clear picture of the different treatment options and the diagnostic procedures, which would improve communication with the doctor. They considered the information as very reliable as compared to information on the internet that they would otherwise have searched for. Furthermore, patients were happy that they could consult all this information at home again, also during the process, instead of waiting for a doctor's appointment to answer a simple question.

> *'Yes, but indeed it is sometimes easier to not...err... if you think you have to consult the doctor to ask a simple question, this is a more accessible tool' PtRT01*

Regarding improvements to be made to the PDA, the most important issue was that some patients were concerned that low-educated patients might have difficulty interpreting the abundance of text in the PDA. They suggested summarizing the text or looking for other ways to present the information.

Improvements to the PDA

Based on the findings from the alpha testing, the PDA underwent major revisions, see figure 3. We replaced almost all text slides with animation videos, we drastically changed the lay-out and made some usability adjustments.

PHASE 3 – BETA TESTING OF THE FEASIBILITY

Doctors

All doctors were satisfied with the new PDA and thought of it as an effective tool for new patients. All items in the questionnaire were scored with a median score of either 4/5 or 5/5. The median time that doctors indicated would be necessary to use the tool was 60 minutes, and their median mark for overall satisfaction was 8/10. In the interviews, they indicated that the PDA gave a good and detailed overview of the different treatment options, that the interface was clear, and the simple structure used in the PDA made navigating through the different treatment options an intuitive process.

Contrary to how the majority of doctors evaluated the PDA, two of them commented that it took them too long to go through all the options. Also, interestingly one doctor said it should be made clearer that sometimes patients do not have a choice in treatment. Another suggestion was to quantify the frequency and incidence of certain side effects. Overall, the doctors agreed it was a good tool that would aid the regular counseling process, and thereby improve the quality of patient care.

Patients

The new version of the PDA was tested again among patients from both clinics. All patients were very satisfied, the median score of all items in the study specific questionnaire was 4/5, the usability and comprehensibility questions scored a median of 5/5.

> *'Fantastic, yes I really mean it, I really think it is fantastic, I believe it's fantastic counseling. And I tell you, they have failed the counseling in my case.' PtTL02*

Patients indicated that they could complete the whole tool in 60 minutes and gave the PDA a median score 8/10. The animations were considered a good improvement, as they made it easier to understand and visualize, for example, the changed anatomy after TL. Other improvements mentioned were the easy navigation and the leaner lay-out with less bright and flashy colors.

To the question of what could be improved in the tool, one patient answered he missed information about expressing your emotions such as the inability to make sound while you laugh or cry after a TL. Also, a comparison of speech rehabilitation methods was suggested, as well as the desire for information on other related care, such as physical therapy or dentistry. TL patients expressed concern that the patient in the TL video seemed to have above average quality of life which might give unrealistic expectations regarding rehabilitation after TL. Other than that, all patients would advise new patients to use the

tool. They indicated that the information provided is easy to understand and gives enough details to make a well-reasoned treatment choice.

Final corrections to the tool

Final corrections to the tool were made, with the most important change being the addition of a new video of a TL patient to manage expectations of recovery after a TL. Furthermore, minor editorial changes were made, for example in the representation of the OS rates. The final version of the tool will be accessible on http://www.treatmentchoice.info/.

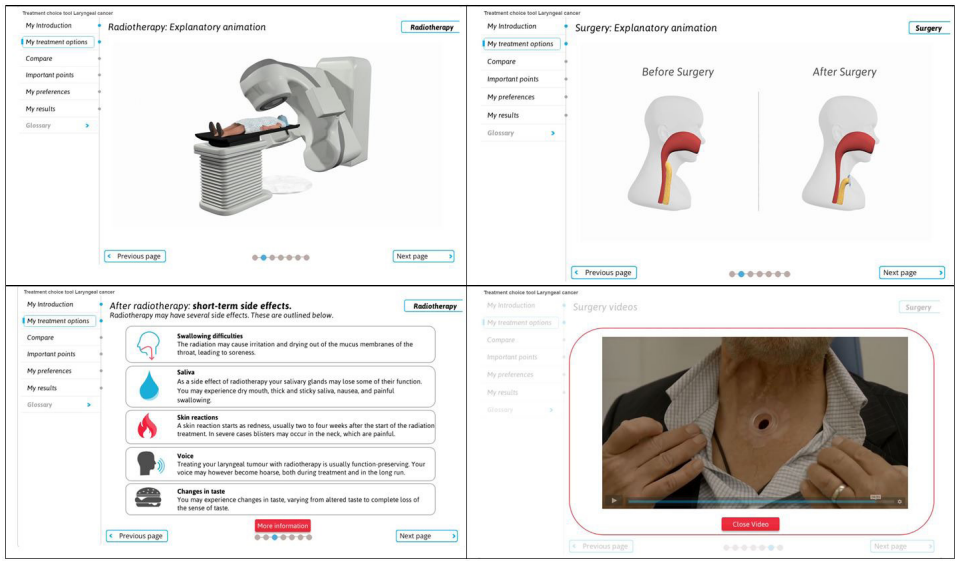

Figure 3. Lay-out of the final version of the PDA.

With the results of the interviews major changes were made. The majority of text was replaced by animation videos (a, b) explaining the details of all the different treatment options, and textual corrections suggested by the physicians were adjusted. We added a voice-over so patients would not have to read the text, and the structure of the PDA is now explained at the homepage with an 'introduction' animation video. (c) Large texts were summarized, but the more comprehensive text was still available on request via an 'extra information' button. (d) Furthermore, bright colors were replaced with blue and white tones. An extra patient video was added.

Table 1. Participant characteristics

Phase	No. participants	Mean age	Male/female	Treatment/type physician
Phase 1	9 Patients	74	2 female/7 male	2 CRT, 1 TL, 6 RT
Phase 1	8 Physicians	-	1 female/7 male	4 HNS, 4 RTO
Phase 2	14 patients	70	2 female/12 male	2 CRT, 2 CRT and salvage TL, 8 RT, 2 RT and salvage TL
Phase 2	11 Physicians	-	2 female/9 male	4 HNS, 4 RTO, 3 MO
Phase 3	9 Patients	66	1 female/8 male	3 TL, 1 RT, 4 RT and salvage TL, 1 CRT and salvage TL
Phase 3	11 Physicians	-	2 female/9 male	4 HNS, 4 RTO, 3 MO

Abbreviations used: CRT = chemoradiotherapy, TL = total laryngectomy, RT = radiotherapy, HNS = head and neck surgeon, RTO = radiation oncologists, MO= medical oncologist

DISCUSSION

In this article we have described the developmental process and qualitative evaluation of a web based PDA for advanced larynx cancer using a mixed methods approach. We followed the process as outlined out by the IPDAS guidelines and performed several semi-structured interviews with patients and doctors.[21] All participants who evaluated the last version agreed on the usefulness and quality of the tool and thought it would make a great contribution to the process of medical decision making. Patients agreed it would clarify the possible outcomes of treatment, improve communication with the doctor, and help them make a choice. These results are in line with studies evaluating PDAs developed for other medical decisions.[7]

The necessity for improvement of the regular counseling process seems evident. Stafford et al. performed a national survey among surgeons in the UK and revealed that 84% gave the diagnosis and discussed TL at the same consultation, which lasted approximately 15 minutes.[22] Perhaps not surprisingly, a recent review on pre-operative counseling for TL patients demonstrated that the majority of patients and their spouses considered the current pre-operative counseling inadequate. Up to 20% of patients were unaware that loss of normal voice would occur and up to 41% noted that they had not received any counseling at all.[11] Although this might have been forgotten by the patients, as patients from our study also indicated that they often did not remember information received during counseling, the implications for improvements are clear.

Evaluation of patients' preferences is a difficult task, and is quite often overlooked or forborne in the era of national guidelines and results from multidisciplinary meetings, in which strong emphasis is placed on survival outcomes. Patients however, may have

other considerations and might not always prefer the treatment option with the highest expected OS.[18, 23, 24] Furthermore, treatment choices can be highly dependent on the type of information provided during counseling. In 2014, Laccourreye et al. evaluated how giving more specific information regarding the risk on a feeding tube or tracheotomy after primary radiotherapy altered the treatment decision made by patients, and demonstrated significant changes in their preferred treatment after obtaining more specific information.[25]

In order to make a medical decision on treatment that is in line with personal values and preferences of the patient, there are certain conditions that need to be met. First, a sufficient amount of decisional needs have to be fulfilled. These are, for example, adequate knowledge, realistic expectations and clear information regarding the risks and benefits of each treatment. If patients lack one or more of these basic decisional needs, this leads to decisional conflict. When less decisional needs are met, patients are more likely to postpone decisions, feel regret and/or blame others for their potential poor outcome.[26-28] Indeed, patients from our study who had not been informed about the different treatment options at the time of their treatment felt they had been mistreated by their physician and some even felt resentful to them.

Focusing on the head and neck cancer patient group, lack of health literacy might be a problem; a concern which was also expressed during the interviews. Health literacy is defined as the 'degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions'.[29] Low health literacy is associated with increased hospital rates and even mortality[30] and related to the educational level of patients, which is relatively low among head and neck cancer patients.[31, 32] Yet, Narwani et al. evaluated online available patient information for larynx cancer and demonstrated that it was written at an advanced level, similar to that of Times Magazine.[30] Indeed, also after the first evaluation of our PDA, participants recommended to simplify the PDA to make it more readable and understandable. These findings underscore the value of a simple and understandable PDA for this population.

Limitations

There are certain limitations to our study. Patients who participated in our study were recruited by their treating physician and the National patient society. Although we tried to get a mix of patients, some bias is almost unavoidable as patients who are not interested in improving counseling were not participating in this study. Furthermore, as the developmental team conducted the majority of the interviews, patients and doctors might have hesitated to give too much negative feedback on the tool. However, by following the steps as set out by the IPDAS and interviewing several different patients and doctors, we have reached a saturation level in the feedback that gives us confidence in the usability of the tool.

CONCLUSION

The results of our study suggest that a web based PDA for advanced larynx cancer can be a valuable addition to the regular counseling process. The feasibility and actual satisfaction among newly diagnosed patients as well as doctors or trained paramedics has yet to be proven. To this end, a multicenter trial has now started in the Netherlands comparing regular care to patients receiving the PDA (ClinicalTrials.gov Identifier: NCT03292341). Results are expected in 2020.

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APPENDIX 1.

The following terms were used in PubMed.

The following terms were used in PubMed;
'laryngeal neoplasm' (MESH), or laryngeal or larynx and neoplasm or cancer or tumour or tumor or maligna* or carcinoma*, advance* or stage III/IV or stage IV or stage 3 or stage 4 or T3/T4 or T3T4 or T 3/ T 4 or T3 or T4 or T 3 or T 4 or T3-T4, radiotherapy or radiotherapy or radiotherapy*, chemoradiotherapy or chemo-radiotherap* or chemoradiotherap* or chemo-radiotherap* or chemo-radiotherap* or chemoradiation or chemo-radiation, laryngectomy or laryngectom* or larynx or laryngeal* and excis* or remov* or resect* and total.*

APPENDIX 2.

During the developmental phase several questionnaires were used for the patient interviews. Section A. was used during the needs assessment of phase 1. Sections B-E. Were used during phases 2 and 3 for alpha and beta testing of the patient decision aid.

A. OPEN QUESTIONS

Medical History

1. Can you tell me something about larynx cancer?
2. Can you tell me something about your treatment of larynx cancer?
3. Can you tell me something about you current state of health?
4. Can you describe to me the people involved in your treatment process and your relationship with them?

Impact on daily life.

1. How has larynx cancer changed your daily life?
2. What is it you missed the most from the time before being diagnosed with l larynx cancer?

Diagnosis and information

1. Did you understand all the information your doctor gave you?
   a. Regarding larynx cancer, what would you have liked to have known more about before the treatment?
   b. Which doctor was important during this process? Example given: your general practitioner, the head and neck-surgeon, medical oncologist or the radiotherapist.
   c. Did you receive contradicting information from doctors?
2. Which parts of the information where the most important for you and why? Example given: The advantages, disadvantages of treatment, the duration of the treatment, the side effects etcetera.
   a. Did you think certain information was missing? Would you have liked more technical information or emotional support?
3. Did you research extra information about larynx cancer?
   a. Why did you or why didn't you?
   b. Which information did you look up and why?
   c. What did you like about the information you looked up?
   d. Did you get in contact with a patient organization?
4. In which way would you prefer to get your information? Example given: text, video, animation, game, etcetera.

Treatment choice

1. Where you involved in choosing a treatment?
   a. If yes, how did this process work?
   b. If not, why didn't you participate in making a treatment decision?
2. What was the hardest part of being involved in making a treatment decision?
3. What was the role of your family when making a decision.
4. If you could improve 3 things of the decision making process, what would you change?
5. What made you choose for your treatment?
6. What advice would you give someone who has just been diagnosed with larynx cancer?

Computer skills

1. Would you like access to a computer program which you can use in the process of making a treatment decision? Why?

B. THINKING OUT LOUD SESSION - PATIENT DECISION AID

Give a short introduction to the patient and then show him or her the tool. Ask the patient to use the tool, while the tool is being used, all comments and questions of the patient should be written down. During this time these three general questions should be asked.

General

1. What is your first impression of the Patient Decision Aid?

2. Is the Patient Decision Aid easy to use?

3. Can you clearly understand the text of the tool?

C. QUESTIONS ABOUT THE USE OF THE PATIENT DECISION AID.

With these questions you will find two opposites ("Strongly disagree" en "Strongly agree"). Please mark to what extent you agree with the following statements.

	Strongly Disagree	Dis-agree	No Opinion	Agree	Strongly Agree
1. I needed no help from others to go through the tool.	1	2	3	4	5
2. The instructions in the patient decision aid are clear.	1	2	3	4	5
3. The aim of to use this patient decision aid is clear.	1	2	3	4	5
4. This tool is good for giving information.	1	2	3	4	5
5. This tool is nicely designed.	1	2	3	4	5
6. The written information of the tool is clear.	1	2	3	4	5
7. The videos about the treatments are clear.	1	2	3	4	5
8. The written information about the treatments is useful.	1	2	3	4	5
9. The videos about the treatments are useful.	1	2	3	4	5
10. The information about the side effects is clear.	1	2	3	4	5
11. The information about the side effects is useful.	1	2	3	4	5
12. The tool clearly shows the advantages and disadvantages of a total laryngectomy.	1	2	3	4	5
13. The tool clearly shows the advantages and disadvantages of chemoradiotherapy.	1	2	3	4	5
14. The tool clearly shows the advantages and disadvantages of radiotherapy.	1	2	3	4	5
15. The tool helps me to make a decision for a treatment.	1	2	3	4	5
16. The tool helped me see what is important for me in a treatment.	1	2	3	4	5
17. I would recommend this tool to every patient with larynx cancer.	1	2	3	4	5
18. The tool takes too much time to finish.	1	2	3	4	5
19. The information about the different treatments was comforting.	1	2	3	4	5
20. I would watch this tool at home on my computer.	1	2	3	4	5
21. How much time did you need to go through the tool?	..... Minutes				
22. On a scale from 1 to 10, which grade would you give this tool.	..... Grade (1-10)				

D. TREATMENTCHOICE

With these questions you will find two opposites ("Strongly disagree" en "Strongly agree"). Please mark to what extent you agree with the following statements.

		Strongly Disagree	Disagree	No Opinion	Agree	Strongly Agree
1.	In general, I am satisfied with this Patient Decision Aid.	1	2	3	4	5
2.	I believe Patient Decision Aids can improve the healthcare quality.	1	2	3	4	5
3.	I believe this Patient Decision Aid can motivate patients to participate in their treatment.	1	2	3	4	5
4.	The tool works well.	1	2	3	4	5
5.	In general the tool is easy to use.	1	2	3	4	5
6.	It is easy to learn how to use the Patient Decision Aid.	1	2	3	4	5
7.	Navigating in the Patient Decision Aid is easy.	1	2	3	4	5
8.	It is clear how the tool should be used.	1	2	3	4	5
9.	I believe the tool is a useful Patient Decision Aid.	1	2	3	4	5
10.	I believe this tool will help me learn more about treatment options.	1	2	3	4	5
11.	I believe this tool will help me to make an informed decision.	1	2	3	4	5
12.	I would recommend this tool to others.	1	2	3	4	5
13.	I would have liked to use this tool before I was treated.	1	2	3	4	5
14.	I believe every patient in my hospital should be able to use a decision aid when possible.	1	2	3	4	5
15.	The tool gives enough details about the treatments to make a decision.	1	2	3	4	5
16.	The content of the tool is clear and easy to follow.	1	2	3	4	5
17.	The information presented in the tool is correct.	1	2	3	4	5
18.	The Patient Decision Aid will make a doctor's visit take longer.	1	2	3	4	5

E. GENERAL FEEDBACK - COMMENTS

Name the aspects of the Patient Decision Aid which you liked.

1.

2.

3.

Name the aspects of the Patient Decision Aid which you disliked.

1.

2.

3.

Do you have any improvement suggestions? These can be changes, additions or functionalities.

1.

2.

3.

10

General discussion and
future perspectives

10 General discussion and future perspectives

Over the past decades, the field of advanced larynx and hypopharynx cancer has witnessed several important changes in terms of treatment, survival and rehabilitation. Since the publication of the landmark randomized controlled trials (RCTs) evaluating organ preservation therapy in advanced larynx and hypopharynx cancer, an increasing number of patients were treated with organ preservation protocols instead of total laryngectomy (TL).[1-3] For larynx cancer, the first (Veterans Administration; VA) trial in 1991, demonstrated an equal overall survival (OS) rate of 68% at 2 years.[1] The subsequent RTOG 91-11 trial demonstrated the superiority of concurrent chemoradiotherapy over induction chemoradiotherapy or single modality radiotherapy.[2] In 1996, Lefebvre et al. demonstrated the safety and efficacy of induction chemotherapy followed by radiotherapy in hypopharynx cancer.[3] Several subsequent RCTs have focused on the type of chemotherapy[4, 5], the use of cetuximab[6] or the effect on larynx preservation[5], but none of these studies have however specifically compared concurrent CRT with TL in hypopharynx cancer patients.

One and a halve decade after the VA trial, in 2006, Hoffman et al. raised concerns about a decreasing overall survival rate for advanced larynx cancer, which seemed to coincide with the increasing application of organ preservation protocols.[7] To assess whether such trends could be witnessed in the Netherlands as well, Timmermans et al. performed a population-based study evaluating all patients treated for T3-T4 squamous cell carcinoma (SCC) of the larynx between 1991-2010. This study did not show a decrease in OS rates over time in the Netherlands[8], despite the fact that similar to the results from Hoffman et al., also here a clear trend towards more organ preservation strategies was noted. However, patients with T4 larynx cancer showed better OS rates when treated with TL compared to CRT[8], something that in hindsight also was observed in the first VA study.[9]

Because of the close anatomical proximity of the larynx to the hypopharynx, treatment strategies for larynx cancer are often one-to-one translated to patients with hypopharynx cancer. The first RCT demonstrating the safety of chemoradiotherapy in hypopharynx cancer was published in 1996, but around the world, many patients with hypopharynx cancer were already treated with CRT years before this publication. We were interested in evaluating whether similar trends in treatment for hypopharynx cancer could be witnessed in The Netherlands, and what the effect of this possible trend would be on survival. Similar to the national larynx cancer study, we performed a population-based study evaluating the trends in treatment, incidence and survival of hypopharynx cancer, described in chapter 2. We combined a national database from the Netherlands Cancer Registry (NCR) with the national pathology database (PALGA), and evaluated all patients treated for T1-T4 SCC of the hypopharynx in the period 1991-2010. Incidence and mortality rates were assessed for the period 1989-2013. We found that the incidence of hypopharynx cancer in the overall population showed an initial increase from 1989 to 1997, but has been slowly decreasing since then. Among female patients, who accounted for 18% of the total hypopharynx cancer population, a significant increase was observed however, with an annual percentage change (APC) of 1.7% over the years 1989-2013.[10] Possibly, this latter finding is related to the increased smoking behavior of women; the proportion of smokers among women increased from 29% in 1958, to its highest level of 42% in 1970. Since then, it has decreased again to 26% in 2010. The smoking behavior of males, on the other hand, continued to decline drastically; the proportions of smokers among men was 90% in 1958 and 28% in 2010.[11] This could explain the decreasing incidence of hypopharynx cancer among males since 1997.

Similar to trends observed regarding the treatment of larynx cancer[8], we witnessed a decrease in use of primary TL and an increase in the use of CRT and RT. In the period 1991-2000, 38% of patients with T3T4 hypopharynx cancer were treated with TL, which decreased to 20% in the period 2001-2010 ($p<0.001$). Interestingly, also in the Netherlands, the number of patients treated with CRT started to increase years before the feasibility of CRT was demonstrated by the publication of Lefebvre et al.[3]

THE BALANCE BETWEEN CRT AND TL IN T4 HYPOPHARYNX CANCER

An important finding of this national study is the superior OS rate for patients with T4 hypopharynx cancer treated with TL versus CRT (29% vs. 24% at 5 years, $p=0.039$), similar to results obtained for T4 larynx cancer.[8] Patients treated with single modality radiotherapy had a significantly worse OS at 5-years of 13%. Large population-based studies from the US have pointed towards a possible survival benefit in the surgical group as well.[12, 13] However, the results of these studies have to be interpreted with caution, as treatment results from population-based studies bear a risk of bias by indication. Furthermore, most large (national) databases do not include detailed information regarding type of treatment and/or report on other specific patient or tumor related variables. For example, in our national study, intent of treatment (curative versus palliative) was not recorded. While chemoradiotherapy is rarely applied as palliative treatment, single modality radiotherapy on the other hand can be given as a palliative treatment. This might in part explain the low OS of patients treated with single modality radiotherapy in our cohort.

Despite a lack of RCTs, evidence supporting the superior OS rate following TL in T4 hypopharynx cancer now seems to be accumulating. In 2014, Kuo et al. reported on 3,958 patients from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI), and demonstrated superior OS at 5-years in the surgical arm of 34.5% vs. 22.6% in the radiotherapy arm.[13] A year later, Newman et al. reported on 6,637 hypopharynx cancer patients, also from the SEER database, and reported OS rates of 49% versus 37.8% for surgery versus radiotherapy at 5 years.[12] Both SEER based studies however lacked information on the use of chemotherapy, which is likely applied in a part of the radiotherapy group. If these CRT patients would have been analyzed separately, a higher OS rate would probably have been reported for this subgroup.[14] In the meta-analysis on the addition of chemotherapy by Blanchard et al., the 5-year absolute benefit for patients with hypopharynx cancer was estimated to be 3.9%, which does not fully explain the survival difference observed between TL and CRT in these two studies.[15] Kuo et al. were able to assess the use of chemotherapy in a subsequent study, and in this analysis, survival rates were similar between CRT and TL (33.6% vs. 34.4%). However, the subgroup of patients treated with chemoradiotherapy for whom information was available, represented just 4.9% of the total study population.[16]

PREDICTING SURVIVAL

In current practice, when patients are counseled and ask for estimations on prognosis, most often the expected overall survival is presented based on their TNM classification and weighed against the proposed treatment. The TNM classification gives good estimations on a population level, but translates less well to the individual level. We aimed to optimize individual estimations on survival by developing risk prediction models for advanced larynx and hypopharynx cancer. Improved individualized risk estimations can aid the decisional process and possibly tailor treatment strategies, where for example high-risk patients might benefit from more intense (adjuvant) treatment strategies or follow-up regimens.

In chapters 3 and 4, we describe the development of two risk prediction models for advanced larynx and hypopharynx cancer. For both types cancer we succeeded in categorizing patients in low-, medium- or high-risk groups. The prediction model for advanced larynx cancer was based on a Cox proportional hazards model, constructed using a national database covering all patients with advanced T3T4 larynx cancer on which Timmermans et al. have published before[8]. We validated the model using data from 5 external centers: Lund Medical Center, Sweden, University Hospital Leuven, Belgium, The Irish National Cancer Registry, and the Johns Hopkins and Emory University Hospitals from the US. Discriminative power was assessed using the C statistic; a C statistic of 0.50 equals chance and a C statistic of 1.0 indicates a perfect model. Discriminative capacity of our model was average with a C statistic of 0.65 after internal and 0.59 after external validation. Because the model left room for improvement with regard to individual risk predictions for advanced larynx cancer, we performed an additional exploratory analysis, which demonstrated that the addition of comorbidity data increased the discriminative ability of the model to 0.68. Although comorbidity information was limited to the patients treated in our own institute, the results in this subgroup suggests that adding comorbidity information might further improve the discriminative capacity of the model.

Based on the knowledge gained during the construction of the larynx model, we subsequently build a model to predict survival in hypopharynx cancer. In order to include more patient specific variables such as comorbidity, we used retrospectively collected data from the Netherlands Cancer Institute and 2 other dedicated head and neck centers in the Netherlands: University Medical Center Utrecht and Amsterdam Medical Center, Location VUmc. The model was build using the least absolute shrinkage and selection operator (LASSO) technique and consisted of the variables gender, subsite, TNM classification, Adult Comorbidity Evaluation score 27 (ACE27), body mass index (BMI), hemoglobin, albumin and leukocyte count. The model performed better than a model based on TNM classification alone, and yielded a slightly higher discriminative power of 0.62 after validation. Building further on recent data from Bril et al., the hypopharynx cancer model will likely be improved using data on sarcopenia, another relevant factor for OS that has been studies by several authors in recent years[17, 18]. Other improvements can be expected from the addition of certain biomarkers, for example the neutrophil-to-lymphocyte ratio (NLR)[19], or features such as tumor volume[20] or radiomics[21]. Adding such information to clinical prediction models may help to further improve robust individualized estimations of surival[19, 22-24]. Ideally, these models should not only predict survival but also predict treatment response and toxicity, and are continuously re-evaluated and updated to maintain its clinical applicability.

FUNCTIONAL OUTCOMES

Besides providing individualized risk estimations, another aspect of great importance to patients is counseling about the expected quality of life following treatment. In our national cohort, we analyzed the cumulative incidence of salvage or functional TL following (chemo) radiotherapy with death as a competing endpoint. The cumulative incidence at 5-year was 7% for RT and 4% for CRT, with a cumulative incidence of death of respectively 68% and 64%. The low rate of salvage/functional TLs might reflect the fact that most recurrences in the hypopharynx region are considered to be inoperable. Although the term ‘laryngectomy free survival’ is often used to measure success of organ preservation, a more informative endpoint is however the term ‘laryngo-esophageal dysfunction free survival rate’ (LDFS)[25]. This definition is a composite endpoint combining time to local recurrence, death or

salvage TL and the presence of a feeding tube or tracheotomy at 2- or 5-years[26], and gives a better reflection of the functional success of organ preservation.

Driven by the limitations of our national study in which information on LDFS was missing, we performed an analysis of all patients treated for hypopharynx cancer in our institute between 1990-2013, described in chapter 5. In this retrospective study, we report an LDFS rate of 31% at 5-years. The first RCT by Lefebvre et al. reported a similar LDFS of 35% at 5 years, but in this endpoint, only death from local disease was used. When they used 'death from other causes than local disease progression' in this composite endpoint, it appeared to be 17% at 5 years[3].

A subsequent RCT reported even higher LDFS rates in patients treated with induction cisplatin (P), 5-fluorouracil (F) with docetaxel (T) followed by RT versus patients treated with induction PF followed by RT; respectively 67% versus 47% at 5-years[5]. These authors however used a different definition of LDFS: 'the presence of natural speech, absence of a tracheostomy, absence of a feeding tube for ≥2 years after treatment or recurring pneumonia that required hospitalization'. Despite the superior results obtained following the induction TPF regimen, the increased toxicity resulting from the addition of docetaxel has limited the widespread acceptance of this regimen[27]. Despite the fact that both RCTs used induction chemotherapy, the standard of care in The Netherlands is concurrent chemotherapy. In a meta-analysis comparing induction CT to concurrent CRT, the authors were unable to demonstrate a significant OS benefit in the patients treated with induction CT[28].

In our institutional study, we also reported on OS rate using a propensity score matched pair analysis of patients with T2-T4 hypopharynx cancer treated with TL versus CRT. As mentioned before, several tumor and patient related factors used implicitly or explicitly by physicians to indicate patients for a certain treatment, can confound the estimate of effect of treatment choice. Since the treatment paradigm has shifted towards favoring CRT instead of TL, year of diagnosis might also influence treatment choice and thus confound effect estimates. Using the propensity score matching approach, we aimed to control for these biases. In our cohort, we reported 5-year OS rate of 56% following TL versus 46% following CRT. This result was not statistically significant, possibly due to the low number of patients that remained after matching, and consequently the low power to detect statistical significance. Yet, the result is in line with that of previous observational studies.In a similar study, Tassler et al performed a propensity score adjusted analysis in a retrospectively collected cohort of 137 hypopharynx cancer patients treated at the University of Pittsburgh[29]. Their propensity score model was based on T-classification (T4 patients were more likely to receive surgery) and year of diagnosis (patients in earlier years were more likely to be laryngectomized), and in the adjusted analyses these authors found a significant survival benefit in the surgical group over the CRT group[29].

In light of the increasing evidence favoring TL in terms of survival in patients with T4 hypopharynx cancer, the treatment choice between CRT and TL becomes even more difficult. How many survival years are patients willing to sacrifice in order to maintain their larynx? With this in mind, more attention should be paid to expected quality of life following treatment; especially since each patient might value the outcome differently[30, 31]. The treatment decision between TL and CRT is a very personal one, and before making a choice, patients should be aware of the functional outcomes following TL and CRT, and should be counseled that each option can have a profound effect on quality of life. Kraaijenga et al. evaluated the long term toxicities following CRT and reported that 10-years after CRT, 54% had moderate to severe swallowing complaints and 14% was tube feeding dependent[32]. On the other hand, TL has a significant impact on a patients' quality of life and patients will have to cope with speech- and swallowing rehabilitation, issues we discussed in chapters 6,7 and 8.

REHABILITATION FOLLOWING TL

Although the use of TL as primary treatment is decreasing over the past decades, it still remains a cornerstone in the treatment for head and neck cancer, although nowadays more often as salvage TL or TL for functional reasons. The three principal techniques to restore oral communication after TL are tracheoesophageal speech, esophageal speech and/or the use of an electrolarynx. Tracheoesophageal speech is the most frequently used method of speech rehabilitation in most Western countries. Although tracheoesophageal speech is associated with higher costs due to the need for recurrent replacements of voice prostheses (VPs), this method is reported to be associated with the best acoustic and perceptual outcomes.[33]

In chapter 6 we studied the prosthetic vocal rehabilitation of a cohort of 232 consecutive TL patients over a period of 13 years. This is one of the larger reports available in literature. Similar to other studies[34, 35], we reported a declining device lifetime of now approximately 2 months in contrast to the 3 months reported in older studies.[36, 37] Several explanations for the declining device lifetime have been suggested, such as the increased use of (chemo) radiotherapy in the adjuvant or neo-adjuvant setting, changes in diet and/or in biofilm composition on the VP[38], or the more comfortable antegrade replacement as compared to the old retrograde replacement method of the Provox1.[39] In countries such as Australia or the US, distance to the hospital is often perceived as another barrier for replacement.

Although the driving distance to a hospital in the Netherlands is almost never beyond 30-45 minutes, surprisingly, even with a median driving distance of 26 minutes in our cohort, we observed a significant effect of driving distance on device lifetime; the longer the driving distance, the longer the device lifetime. This effect was more pronounced in the non-standard replacements for TEP-tract related problems such as hypertrophy or infection of the TEP-tract. This suggests that patients recognize these issues less well as a reason to visit the hospital as compared to the standard leakage through.

Another aspect that might play a role in the relatively low device lifetime is the fact that all patients receive reimbursement for voice prostheses. Since patients in The Netherlands or for example Germany are not challenged by financial constraints, average device lifetimes of up to 17 months as reported in a Turkish cohort[40] are a rare phenomenon in the Netherlands. However, in light of the increasing health care costs, physicians have a social responsibility in this aspect to manage these costs, determine whether there is a solid reason for replacement, and to adequately determine which patients might benefit from more expensive devices such as the Provox ActiValve.

In 2003, Hilgers et al. first reported on the Provox ActiValve. This prosthetic device is equipped with Candida-resistant fluoroplastic material and has a small magnet that prevents inadvertent valve opening[41]. This device appeared to have a highly significant average 14-fold increase in device lifetime. The authors therefore suggested that using this (more expensive) VP would be cost-effective in patients known with relative low device lifetime due to Candida related transprosthetic leakage or inadvertent valve opening caused by swallowing and inhalation-related underpressure in the esophagus. Graville et al. evaluated the device lifetime and cost-effectiveness of the ActiValve in patients with below average device lifetime. They estimated that use of this device could be considered cost-effective and reported an average increase in device lifetime of more than 500% to an average of 10.3 months with the ActiValve[42]. In our recent study cohort, we were similarly able to demonstrate a significant increased device lifetime when using the ActiValve. During follow-up, 30% of patients (n = 69) received an ActiValve, generally given to patients that show a device lifetime < 2 months. Within these 69 patients, the device lifetime of a regular VP was 54 days, whereas the device lifetime of an ActiValve in this group was respectively 143 and 186 days for the ActiValve Light and Strong. A cost-effective analysis on the use of different VPs in our institute will be undertaken in a future study.

While the ActiValve was designed in order to improve device lifetime of patients experiencing mostly transprosthetic leakage problems and/or underpressure issues, the Provox Vega XtraSeal was designed to address recurrent periprosthetic leakage. This prosthesis has an additional thin and extended esophageal flange to provide a better mucosal seal. Periprosthetic leakage is a less frequently observed problem than transprosthetic leakage, but it appears to be difficult to solve. In our device lifetime study we described several solutions for this problem[36]. In general, first the underlying problems causing periprosthetic leakage should be addressed in order to achieve long-term success, for example by prescribing proton pomp inhibiters for gastroesophageal reflux, often encountered in TL patients[43]. For the short-term solution, temporary removal of the VP to allow for natural shrinkage and/or downsizing of the VP can be tried, with or without placing a washer on the tracheal or esophageal side[44]. If the problem persists, either a purse string suture or injection of bio-material can be tried, and finally surgical closure followed by a secondary TEP puncture[45, 46]. In chapter 7 we analyze the success of this new prosthetic device. The median device lifetime increased from 38 to 68 days when using the XtraSeal, and only in 1/26 cases the XtraSeal had to be removed because of periprosthetic leakage. Despite the small sample size, it seems reasonable to conclude that this novel device is a valuable new tool to solve periprosthetic leakage, further improving the long-term durability of tracheoesophageal speech.

SWALLOWING REHABILITATION

Rehabilitation following TL focusses mainly on vocal, pulmonary, and olfactory rehabilitation[47], but swallowing rehabilitation for dysphagia following TL is another aspect that requires special attention. A recent review reported a prevalence of dysphagia after TL to range from 35-89%.[48] Since most TL patients have been treated with radiotherapy, and in certain cases with chemotherapy as well, dysphagia following TL can be multifactorial. Dysphagia in laryngectomized patients can result from anatomical changes following surgery creating strictures or a narrowed lumen, functional problems due to (chemo)radiotherapy induced xerostomia, fibrosis or stricture formation following (C)RT or reduced coordination of swallowing muscles (REF).

After TL, especially when also (chemo)radiotherapy has been part of the treatment protocol, pharyngoesophageal stenosis is the main culprit of dysphagia, and often dilatation is required to resolve this issue.[48, 49] In chapter 8 we focused on swallowing complaints following TL that necessitated one or more dilatation procedures. Although dilatation procedures are well described in literature, there are very few studies describing the incidence, success rate and complications of dilatation in TL patients. In our cohort of 477 consecutive patients laryngectomized for any indications (primary, salvage, dysfunctional) in two major Head and Neck Cancer Centers in the Netherlands, we found a cumulative incidence of 22.8% at 5-years for dysphagia necessitating dilatation. In total, we analyzed 968 dilatation procedures. The median number of procedures per patient was 3 (range

1-113). Risk factors for a dilatation procedure were female gender, a hypopharynx tumor and chemoradiotherapy before or after TL. Chemoradiotherapy before or after the TL appeared to have the strongest effect on dysphagia following TL, which is not surprising as several studies have demonstrated a high incidence of dysphagia following CRT[32]. Lee et al. specifically evaluated risk factors for stricture formation following CRT and reported female gender and a hypopharynx tumor to be significant predictive factors for stricture formation, besides twice-daily radiation fractionation.[50] The crude incidence of stricture formation in their cohort was 21%.

The main risk factor for a major complication appeared to be a dilatation procedure under general anesthesia. In our cohort, most patients who complain of dysphagia following TL are first subjected to an endoscopic examination under general anesthesia in order to rule out a possible recurrence. When this examination is combined with the first dilatation, the physician will not get feedback from the patient, indicating pain/irritation from a (too) large dilator. Possibly this imposes a higher risk on a transmural perforation. Although we cannot exactly point out the underlying cause for the increased risk of major complications following dilatation under general anesthesia, physicians should be extra careful in dilating new patients, who suffer from stenosis following TL.

Our cohort was more or less evenly split between patients that required 1-3 dilatations versus patients that required serial dilatations. The need for serial dilatation implies repeated hospital visits and associated health care costs. One of the patients in our TL cohort had learned how to self-dilate. This could be a valuable alternative to the repeated hospital visits, if proven to be safe. Because we could not retrospectively assess the number of dilatations and the success rate of this patient, he was excluded from analysis. Some small retrospective case studies (ranging from 16-32 patients) evaluating the safety and efficacy of this procedure, however, suggest that self-dilatation can be the treatment of choice for selected patients with refractory esophageal strictures[51-53]. While these studies seem promising and complication rates following dilatation procedures are reported to be low, complications can be life threatening. In our cohort, we observed 27 complications of which 19 minor (2.0%) and 8 major (0.8%). Minor complications were loss of VP <24h after dilatation (n=6), suspected mucosal tear/hematemesis, which resolved spontaneously within 24hours after dilatation (n=7), temporary edema (n=3) and not further specified (n=3). Six out of the 8 major complications were transmural esophageal perforations, which occurred mainly in the first or second dilatation procedure. The two other major complications in our cohort were an anaphylactic shock caused by NSAIDs, and dislodgement of the VP towards the bronchus causing severe cardiac distress, a cardiomyopathy, and intensive care admission. Although the complications rates are low, patients need to be aware of the possible life-threatening risks they can impose before they are taught how to self-dilate. Furthermore, the presence of a VP should alert physicians performing the dilatation procedure in a TL patient with a VP in situ, as well as patients who self-dilate, to always check the proper position of the VP and confirm there is no aspiration at the end of the procedure.

SHARED DECISION MAKING

As discussed above, even though TL might be superior in terms of OS of advanced T4 larynx and hypopharynx cancer, there is a quite difficult trade-off in terms of survival and quality of life following the different treatment options, and each patient might value these options differently.

Counseling cancer patients on treatment options is difficult and becomes even more challenging in a setting where there is no 'best treatment' option, or when all options interfere significantly with quality of life. In order to improve patient counseling and shared decision making concerning the treatment options TL, CRT or RT, the availability of a patient decision aid (PDA) for patients with advanced larynx cancer would be of great value. There is ample evidence that shared decision-making and improved health communication improves patient outcomes and leads to more patient satisfaction.[54-57] A Cochrane review has evaluated the use of such PDAs in clinical practice and reported that patients experience less decisional conflict, had more knowledge on the treatment options and became less passive decision makers.[57]

In chapter 9 we describe the development of such a PDA for advanced larynx cancer patients, who we hope to empower by giving them more knowledge on the different treatment options. Based on the guidelines as set out by the International Patient Decision Aid Standards (IPDAS), we conducted several semi-structured and in-depth interviews with patients and physicians during three developmental phases. Patients and doctors agreed to the need for such a PDA. Several studies have indeed indicated that counseling of TL patients is in need for improvement. In a UK national survey, 84% of surgeons reported to discuss the diagnosis of cancer and the treatment option TL in the same consultation, which, on average, lasted 15 minutes.[58] A review on the current counseling in the UK reported that the majority of patients considered counseling to be inadequate; up to 20% of patients were not aware of the consequence of loss of normal voice.[59] Similarly, van de Sluis et al. who interviewed several female laryngectomees, reported that patients were often unaware of, or unprepared for, the challenges they would experience following their TL. Some of them reported they barely captured any of the information provided during the counseling process.[60]

The results of our study described in chapter 9, indicate that an online PDA for advanced larynx cancer can be a valuable addition to the current counseling process. Head and neck cancer patients on average have a relatively low level of education, and most physicians in our study indicated that they perceived this as a barrier to good patient counseling. The interviewed patients, also those with a high level of education, indicated that they often could not remember the information given during the counseling process, and that repetition of information would be very useful. To test the feasibility of and satisfaction with our newly developed PDA in clinical practice, we started a prospective multicenter trial in The Netherlands.

FUTURE PERSPECTIVES

While the studies described in this thesis have improved our knowledge on survival in hypopharynx cancer following different treatments, robust overall survival figures are preferably derived from randomized trials. However, in current practice, setting up an RCT comparing TL with CRT seems near to impossible. An important issue in this respect, is the recent emergence of immunotherapy in (head and neck) cancer treatment. While most advancements in immunotherapy have been made in targeting melanoma[61, 62], several institutes around the world are now exploring the possibilities of treating head and neck cancer patients with immunotherapy.[63] Currently, in our institute, the neo-adjuvant administration of nivolumab and ipilimimab before surgery is being tested in a phase II single arm design (Clinical trials number NCT03003637). It seems that immunotherapy has great potential to alter the current treatment dogmas, but for head and neck cancer, until now, these antibodies are administered only in experimental settings. It remains speculative how TL and/or CRT will be replaced by this new discovery, and whether TL eventually can be abandoned or if it will always remain necessary, either as salvage treatment or possibly even as a primary treatment. It certainly will take several years before the results of the first large phase III trials are published and we might witness a shifting treatment paradigm again. In light of the current poor overall survival rate for hypopharynx cancer, any improvement to the current treatments options would be most welcome.

The above-mentioned studies offer great potential to alter the standard of care in advanced larynx and hypopharynx cancer on the long-term. Meanwhile, on the short term a focus on prospective, standardized data collection will greatly attribute to our current understanding of this disease. The Dutch Head and Neck Working group has recently set up a cooperation with the DICA (Dutch Institute for Clinical Auditing), which will facilitate a national monitoring of a pre-specified set of quality criteria. Based on this planned data collection, covering several medical aspects and patient reported outcome measurements (PROMS), the working group will internally evaluate the quality of care. Being able to compare not only oncological, but also functional outcomes and PROMS, is of great value. Especially in the study of rare tumors, where most studies report on small, heterogeneous patient groups, and the risk of selection or treatment bias is high, such national databases will greatly improve our knowledge.

Whatever the outcome of the above described studies will be, adequate patient counseling should always be a cornerstone of treatment. Building on the experiences of the PDA for advanced larynx cancer, we are now developing PDAs targeting other types of head and neck cancer. An important consideration in these PDAs is that, after successful introduction in clinical care, they should be checked and updated regularly to maintain its validity. Likewise, the above described clinical prediction models for advanced larynx and hypopharynx cancer should be updated using new data whenever this becomes available. Hopefully we will witness several important changes in the coming decade, and further improve survival and quality of life of patients with advanced larynx and hypopharynx cancer.

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11

Summary

Nederlandse samenvatting

11 Summary

Chapter 1 provides a general introduction into the historical background of treatment for advanced larynx and hypopharynx cancer. We discuss the evaluation and surgical refinements of total laryngectomy and give an introduction to speech rehabilitation. The paradigm shift over the last three decades towards organ preservation therapy is subsequently addressed, and we focus on the functional outcomes following treatment, and discuss speech and swallowing rehabilitation following TL. Finally, we suggest capturing all this information in a patient decision aid, in order to improve patient counseling and shared decision making.

In **chapter 2** we describe an epidemiological study in which we present the trends in treatment, incidence and survival of all patients diagnosed with squamous cell carcinoma (SCC) of the hypopharynx in the Netherlands in the period 1991-2010. This large population-based study was conducted using data from The Netherlands Cancer Registry (NCR), which provided information on patient, tumor and treatment characteristics. We combined this data with the national data from PALGA (the nationwide network and registry of histo- and cytopathology in the Netherlands) to verify the type of surgical treatment of these patients by examining the pathology reports. In total, 2,999 patients were identified. First of all, we reported a decrease in TL as primary treatment and an increase in the use of single modality radiotherapy (RT) and chemoradiotherapy (CRT). Although the results were expected because national guidelines advise to use organ preservation therapy whenever possible, interestingly, treatment with CRT started to increase several years before the first publication on the feasibility and efficacy on CRT in hypopharynx cancer. Overall, we reported a non-significant decrease in incidence since 1997, although for women the incidence rose 1.7% per year. OS rate increased from 28% in the first, to 34% in the second decade. Despite the decreasing use of TL as primary treatment, in our cohort, patients with a T4 tumor showed a significantly higher OS when treated with TL versus CRT (29% versus 24%). Among T3 tumors both treatments resulted in the same OS rate (TL 40%, CRT 39%). For both T3 and T4 tumors, RT was associated with a significantly worse OS of respectively 24% and 13% at 5 years. Overall survival estimates for future patients based on TNM classification have proven to be useful on a population-based level, on the individual level they are, however, suboptimal. Therefore, we have tried to improve individualized survival estimates for advanced larynx and hypopharynx cancer in **chapters 3 and 4**, by developing clinical prediction models. Similar to the national hypopharynx study, Timmermans et al. evaluated trends in treatment and survival for advanced larynx cancer. We used this national database covering 3,442 patients with T3T4 larynx cancer, to develop a clinical prediction model using a Cox proportional hazards model in **chapter 3**. After internal validation, the model was externally validated on patient data from five external centers: The Irish National Cancer Registry, Lund Medical Center, Sweden, University Hospital Leuven, Belgium and the Johns Hopkins and Emory University Hospitals from the US. The clinical prediction model performed better than a model based on TNM classification alone, and was able to distinguish well between low-, medium-, and high-risk groups. The national database did not include variables such as comorbidity, but a post-hoc analysis on data from our own institute revealed that adding comorbidity to the model increased the discriminative capacity. Based on this knowledge, in **chapter 4**, we subsequently developed a clinical prediction model for hypopharynx cancer based on institutional data. We included all patients diagnosed and treated with curative intents for SCC of the hypopharynx in the Netherlands Cancer Institute in (1990-2013), the Amsterdam Medical Center, location VUmc (2003-2010), and the University Medical Center Utrecht, the Netherlands (1990-2012). Patient information was retrospectively collected, which allowed us to include more patient specific variables such as comorbidity and certain peripheral blood values. We used a Cox proportional hazard modal and least absolute shrinkage and selection operator (LASSO) technique. The final model consisted of gender, subsite, TNM classification, Adult Comorbidity Evaluation 27 score (ACE27), body mass index (BMI), hemoglobin, albumin and leukocyte count, and again the model performed better than a model based on TNM classification alone. Furthermore, the model was well able to identify clinical risk groups. The results of these clinical prediction models can help in counseling patients to make a well-informed treatment choice and possibly tailor (adjuvant) treatment strategies or follow-up regimens.

While OS estimates are an important aspect when comparing treatment strategies, almost equally important is the expected quality of life following treatment. Therefore, we focus on functional outcomes following treatment in **chapters 5, 6, 7 and 8**. In **chapter 5**, we evaluate functional and oncological outcomes of patients with SCC of the hypopharynx treated with curative RT, CRT or TL in the period 1990-2013. Functional outcomes were reported using the laryngo-esophageal dysfunction free survival rate (LDFS). The events considered for this composite endpoint were death, local recurrence, (salvage) TL, and presence of a tracheotomy or feeding tube at 2- or 5-years. Of the 251 patients treated with curative organ preservation, the LDFS rate at 2- and 5-years was respectively 42% and 31%. Oncological outcome was assessed using a propensity score (PS) matched pair analysis, which aims to control for confounding by indication. The PS matched pair analysis

demonstrated that in the patients with a T2-T4 hypopharynx tumor, TL yielded a 5-year OS estimate of 56% versus 46% in the CRT group. The 10-year OS estimates for TL and CRT were respectively 35% and 17%. Due to the small number of patients “surviving” the matching procedure, however, the study had limited power and the difference was not statistically significant. Nevertheless, these results add to the growing body of evidence that questions the presumed equality between TL and CRT.

In **chapter 6**, we evaluated vocal rehabilitation following TL in a consecutive cohort of patients laryngectomized between 2000 and 2012 and seen for vocal rehabilitation in the Netherlands Cancer Institute. This is one of the larger cohorts in literature with 232 patients using 3,117 voice prostheses. We reported a median device lifetime of 63 and 66 days for the regular Provox2 and Vega VPs, and 143 and 186 days for the Provox ActiValve Light and Strong. In our cohort, 69 patients (30%) received an ActiValve during follow-up, which, as a general rule of thumb, is given to ‘problematic’ patients that shows a device lifetime of less than 2 months. Within this group of patients that received an ActiValve during follow-up, the device lifetime of a regular VP was 54 days. Patients that never required an ActiValve reported a median device lifetime of 90 days, which was statistically significant. When compared to historical cohorts, the device lifetime is decreasing. Probably this is a result of the currently larger proportion of TL patients receiving their surgery for salvage reasons after (chemo)radiotherapy. In multivariable analysis, salvage TL and TL for a dysfunctional larynx were associated with a decreased device lifetime. The median driving distance of all patients to our institute was 26 minutes, but interestingly, we noted a significant effect between increasing driving distance and increasing device lifetime. This effect was more pronounced in the non-standard replacements for leakage around the VP, caused by hypertrophy or infection. Almost half of our patients (48%) experienced occasional problems related to the tracheoesophageal puncture tract (TEP-tract). When compared to an historical cohort from our institute, this issue was not occurring more frequently but affected more patients. Similar to historical data, transprosthetic leakage was the main reason for replacement (70%), while periprosthetic leakage accounted for 9% of all replacements.

While periprosthetic leakage is not occurring very frequently, it can be difficult to tackle this problem. Therefore, we evaluated a novel voice prosthesis designed to control for this problem in **chapter 7**. This VP, the Provox Vega XtraSeal (PVX) was tested in consecutive patients who presented themselves at the outpatient clinic with recurrent periprosthetic leakage. The PVX is an adjustment of the Provox Vega, but has an enlarged thin angled flange underneath the esophageal flange. With this adjustment, good adhesion to the surface of the esophageal mucosa is more likely, which should prevent periprosthetic leakage. Of the 26 instances in which the PVX was placed, the seal was immediately sufficient in 25 placements. Where median device lifetime of the former VP before placement of the first VP was 38 days, median device lifetime of the PVX appeared to be 68 days. Based on these results, we believe that in selected patients with recurrent periprosthetic leakage, the placement of a PVX can adequately diminish the burden of repeated replacement for leakage around the VP.

While rehabilitation following TL often focusses on vocal rehabilitation, swallowing can become a significant problem, which we evaluated in **chapter 8**. Using the same TL cohort described in chapter 6 combined with a similar consecutive cohort of laryngectomized patients from the University Medical Center Utrecht (2008-2016), we evaluated the cumulative incidence of dysphagia necessitating one or more dilatation procedures, risk factors for dilatation and complications following dilatation procedures. We observed a cumulative incidence of 22.8% at 5-years. Roughly half of our patients required 1-3 dilatation procedures, whereas the other half required repeated dilatation procedures. Risk factors for stenosis were female gender, a hypopharynx tumor and CRT before or after the TL. The latter effect was most pronounced, which is not surprising since stenosis is frequently observed as a late complication following CRT. We reported a major complication rate of 0.8%, with 6/8 major complications being transmural esophageal perforations. Despite the low incidence of complications, they can be life threatening. After multivariable analysis, dilatation procedure under general anesthesia was associated with the highest risk on a complication.

In **chapter 9**, we describe the development of an online patient decision aid (PDA) for advanced larynx cancer patients in which the pros and cons of the three treatment-options RT, CRT and TL are extensively discussed. We followed the guidelines as set out by the International Patient Decision Aid Standards (IPDAS) and during three phases we conducted several semi-structured in-depth interviews, thinking out loud sessions and used a study specific questionnaire evaluating the usability and satisfaction of the PDA. Participants in our study were patients treated for larynx cancer and physicians working as a head and neck surgeon, radiotherapist or medical oncologist. Patients and physicians agreed there is a need for an online PDA. Physicians’ perceived barriers to adequate patient counseling were difficulties in understanding the personal values of patients, and the relatively low educational level of head and neck cancer patients, which made them doubt whether information was remembered adequately. Patients, also those with a high level of education, confirmed they often did not remember information given during counseling and considered repetition, for example by means of a PDA, useful. During the final phase, both physicians and patients expressed that the introduction of this tool would

aid the regular counseling process and improve the quality of patient care. To test the feasibility of and satisfaction with the tool, we started a multicenter trial in the Netherlands comparing the use of a PDA with usual care.

Finally, **chapter 10** is a general discussion of the results described in this thesis and future perspectives are discussed.

Nederlandse samenvatting

Hoofdstuk 1 is een algemene introductie waarin de historische ontwikkelingen rondom de behandeling van keelkanker in een gevorderd stadium worden beschreven, voor zowel het larynx- als het hypofarynx carcinoom. We beschrijven de ontwikkeling en chirurgische verfijning van een totale laryngectomie (TL) (een operatie waarbij het gehele strottenhoofd wordt verwijderd en een stoma in de hals wordt gemaakt) en de verschillende methodes van stemrevalidatie. Ook hiervan wordt de historische ontwikkeling beschreven. In de afgelopen 30 jaar lijkt de voorkeur van een totale laryngectomie als primaire behandeling voor een larynx- of hypofarynx carcinoom af te zwakken, en wordt in toenemende mate orgaan sparende therapie toegepast, middels radiotherapie, eventueel in combinatie met chemotherapie. We bespreken de functionele uitkomsten na de verschillende behandelingen, en bespreken stem- en slikrevalidatie na een TL. Uiteindelijk wordt de suggestie gedaan dat al deze informatie moet worden samengevat in een keuzehulptool, om zo de voorlichting aan de patiënt en gezamenlijke besluitvorming te optimaliseren.

Hoofdstuk 2 bestaat uit een epidemiologische studie waarin we de trends in behandeling, incidentie en overleving beschrijven van alle patiënten die gedurende de periode 1991-2010 in Nederland zijn gediagnosticeerd met een plaveiselcelcarcinoom (PCC) van de hypofarynx. Deze populatie studie werd uitgevoerd met data van de Nederlandse Kanker Registratie, die ons voorzag van informatie over patiënt-, tumor- en behandelingskarakteristieken. Deze data hebben wij gecombineerd met nationale data van PALGA (het pathologisch-anatomisch landelijk geautomatiseerd archief) om door middel van de pathologie verslagen onderscheid te kunnen maken in het type chirurgische behandeling. In totaal werden 2,999 patiënten geïdentificeerd. Als eerste uitkomstmaat rapporteerden wij een daling in het aantal uitgevoerde laryngectomieën als primaire behandeling, en een toename in het gebruik van primaire radiotherapie (RT) of de gecombineerde behandeling middel chemoradiotherapie (CRT). Hoewel de resultaten enigszins in de lijn der verwachting lagen, gezien het feit dat landelijke richtlijnen orgaan preservatie middels RT of CRT aanbevelen, werd de toename in CRT al geobserveerd voordat internationale studies de veiligheid en effectiviteit van CRT hadden aangetoond voor het hypofarynx carcinoom. Voor incidentie observeerden we in totaal een niet-significante daling sinds 1997. Het aandeel van vrouwen is wel toegenomen; voor vrouwen steeg de incidentie met 1.7% per jaar. De algehele 5-jaars overleving steeg van 28% in de periode 1991-2000, tot 34% in de periode 2001-2010. Ondanks het dalende gebruik van een TL als primaire behandeling, zagen we dat patiënten met een T4 tumor de beste 5-jaars overleving lieten zien wanneer zij behandeld werden middels een TL versus CRT (29% vs. 24%). Onder T3 tumoren bleek er geen significant verschil in overleving tussen de

twee verschillende behandelingen (TL 40%, CRT 39%). Bij zowel T3 als T4 tumoren bleek dat een behandeling met radiotherapie alleen was geassocieerd met een significant slechtere 5-jaars overleving van respectievelijk 24% en 13%. Schattingen van de verwachte overleving op basis van de TNM-classificatie zijn succesvol gebleken op populatieniveau, maar op het individuele niveau laten zij ruimte over voor verbetering. In **hoofdstuk 3 en 4** hebben wij daarom een poging gedaan om individuele schattingen van de overleving van het larynx en hypofarynx carcinoom te verbeteren door het ontwikkelen van klinische risico predictie modellen. Net als de landelijke hypofarynx studie hebben Timmermans et al. de nationale trends in behandeling en overleving van het larynxcarcinoom onderzocht. We hebben deze database gebruikt met 3,442 larynxcarcinoom patiënten om een klinisch predictie model te ontwikkelen middels een Cox proportional hazards model in **hoofdstuk 3.** Na interne validatie werd het model extern gevalideerd op patiënten data van 5 externe centra: de Ierse Nationale Kanker Registratie, het Lund Medisch Centrum uit Zweden, het Universiteitsziekenhuis Leuven uit België, en het Johns Hopkins en het Emory Universiteitsziekenhuis uit de VS. Het ontwikkelde predictie model bleek beter in het voorspellen van de overleving dan een model gebaseerd op de TNM-classificatie, en kon een goed onderscheid maken tussen patiënten met een laag-, medium-, of hoog risico op overlijden. Hoewel de nationale database geen informatie bevatte over co-morbiditeit, toonde een post-hoc analyse op een subset van de data uit ons eigen instituut aan dat het toevoegen van co-morbiditeit een positief effect had op de accuratesse van het model. Aan de hand van de kennis opgedaan in hoofdstuk 3, beschrijven we in **hoofdstuk 4** de ontwikkeling van een klinisch predictie model voor hypofarynx kanker, gebaseerd op institutionele data. We hebben alle patiënten geïncludeerd die met curatieve intentie zijn behandeld voor een plaveiselcelcarcinoom van de hypofarynx, in het Antoni van Leeuwenhoek (1990-2013), het Amsterdam Universitair Medisch Centrum, locatie VUmc (2003-2010), of het Universitair Medisch Centrum Utrecht (1990-2012). De patiënten informatie werd retrospectief verzameld waardoor het mogelijk was om meer patiënt specifieke informatie te verzamelen zoals co-morbiditeit en een aantal bloedwaarden. We hebben een Cox proportional hazards model gebruikt en de 'least absolute shrinkage and selection operator' (LASSO) techniek. Het uiteindelijke model bestond uit de variabelen geslacht, subsite van de tumor, TNM-classificatie, co-morbiditeit gescoord aan de hand van de Adult Comorbidity Evaluation 27 score (ACE27), BMI, en hemoglobine, albumine en leukocyten waarden. Het model bleek wederom beter in het voorspellen van de overleving dan een model gebaseerd op alleen de TNM-classificatie, en het kon een goed onderscheid maken in klinische risico groepen. De resultaten van deze klinische predictie modellen kunnen worden gebruikt tijdens de voorlichting van toekomstige patiënten, en kunnen mogelijk helpen bij het individualiseren van de behandeling en bijvoorbeeld leiden tot een meer of minder strikte follow-up.

Hoewel schattingen van de overleving een belangrijk aspect zijn wanneer behandelstrategieën worden vergeleken, is ook de verwachte kwaliteit van leven na de behandeling een zeer belangrijk aspect dat moet worden meegewogen in het besluit omtrent de behandeling. Daarom focussen we ons in **hoofdstukken 5, 6, 7 en 8** op de functionele uitkomsten na behandeling. In **hoofdstuk 5** evalueren we de functionele en oncologische uitkomsten van patiënten met een hypofarynxcarcinoom, die in de periode 1990-2013 curatief behandeld zijn in het Antoni van Leeuwenhoek, met radiotherapie, chemoradiatie of een totale laryngectomie. De functionele uitkomst werd gemeten aan de hand van de 'laryngo-oesophageale dysfunctie-vrije overleving'. Eindpunten voor deze samengestelde uitkomstmaat zijn overlijden, een lokaal recidief, (salvage) laryngectomie en/of aanwezigheid van een tracheotomie of een neusmaagsonde 2- of 5-jaar na behandeling. Van de 251 patiënten die behandeld zijn met in opzet curatieve orgaan preservatie was de laryngo-oesophageale dysfunctie-vrije overleving op 2- en 5-jaar respectievelijk 42% en 31%. We hebben de oncologische uitkomsten geëvalueerd met behulp van een propensity score (PS) "matched pair" analyse, wat als doel heeft om bias veroorzaakt door *confounding by indication* te minimaliseren. Uit de gepaarde PS analyse kwam voort dat, in de groep patiënten met een T2-T4 hypofarynx tumor, een TL leidde tot een geschatte 5-jaars overleving van 56%, versus 46% in de CRT groep. De geschatte 10-jaars overleving voor TL en CRT was respectievelijk 35% en 17%. Vanwege het lage aantal patiënten dat de matching procedure 'overleefde', had de studie beperkte power en het verschil niet statistisch significant. Desondanks is het een belangrijke bevinding die bijdraagt aan het oplopende bewijs dat de veronderstelde equivalentie tussen TL en CRT voor T4 tumoren zou moeten worden heroverwogen.

In **hoofdstuk 6** hebben we de stemrevalidatie na een TL beschreven van een cohort patiënten die tussen 2000 en 2012 een laryngectomie ondergingen en in het Antoni van Leeuwenhoek werden gezien voor de stemrevalidatie. Dit is een van de grootste cohorten in de literatuur, waarin 232 opeenvolgende patiënten worden beschreven die gezamenlijk 3,117 stemprotheses (SPs) hebben gebruikt. We vonden een mediane levensduur van de SP van 63 en 66 dagen voor de 'reguliere' Provox2 en Vega SPs, en 143 en 186 dagen voor de Provox ActiValve Light en Strong. In ons cohort kregen 69 patiënten (30%) gedurende de follow-up een ActiValve, die vooral wordt toegepast bij patiënten bij wie de mediane levensduur van hun SP korter dan 2 maanden wordt. Binnen deze groep 'probleem' patiënten die een ActiValve heeft moeten gebruiken, bleek de mediane levensduur van de 'reguliere' stemprotheses 54 dagen. Bij patiënten die nooit een ActiValve nodig hadden tijdens de follow-up was de mediane levensduur van de SP 90 dagen, wat significant langer is dan in de ActiValve groep. Wanneer we onze getallen vergelijken met historische cohorten, is de mediane levensduur van de SPs gedaald. Waarschijnlijk is dit een gevolg van een groter aantal patiënten dat alsnog

een laryngectomie moet ondergaan na (chemo)radiatie. Na multivariabele analyse bleek een laryngectomie voor een recidief na (C)RT en een laryngectomie voor een dysfunctionele larynx significant geassocieerd met een kortere levensduur.

Een interessante bevinding was dat, hoewel de mediane reisduur naar het Antoni van Leeuwenhoek 26 minuten was, wij een significant effect zagen tussen toenemende reisduur naar het AvL en toenemende levensduur van de stemprothese. Dit effect was duidelijker aanwezig bij de SPs die vervangen werden voor lekkage rondom de SP veroorzaakt door hypertrofie of infecties dan bij reguliere indicaties voor wisseling, zoals lekkage door de SP heen. Ongeveer de helft van het aantal patiënten (48%) in ons cohort ervoer klachten gerelateerd aan problemen rondom het tracheoesofageale fistel. Vergeleken met historische data komen deze klachten niet vaker voor op stemprothese niveau, maar betreft het wel meer patiënten. Net als in historische data was lekkage door de stemprothese heen de meest voorkomende aanleiding voor vervanging van de SP (70%), terwijl lekkage rondom de SP verantwoordelijk was voor 9% van alle vervangingen.

Hoewel lekkage rondom de stemprothese niet de meest frequente oorzaak is voor een wisseling, kan het wel een probleem zijn dat moeilijk op te lossen is. Daarom hebben we in **hoofdstuk 7** een nieuwe stemprothese geëvalueerd, die ontworpen is om dit probleem aan te pakken. We hebben deze SP, de Provox Vega XtraSeal (PVX) getest in een cohort patiënten die op de polikliniek werden gezien in verband met lekkage rondom de SP. De PVX is een aanpassing van de Provox Vega, waarbij er een extra grote flexibele flens onder de oesofagiale flens is bevestigd. Door middel van deze aanpassing wordt er gestreefd naar een goede adhesie van de flens aan het mucosale oppervlak waardoor lekkage rondom moet worden voorkomen. Van de 26 gevallen waarin wij een PVX hebben geplaatst bleek dit in 25 gevallen de lekkage rondom direct te verhelpen. De mediane levensduur van de SP die was geplaatst voorafgaand aan de PVX was 38 dagen, en de mediane levensduur van de PVX was 68 dagen. Op basis van deze resultaten denken wij dat bij geselecteerde patiënten die frequent worden gezien met lekkage rondom de SP, de plaatsing van de PVX kan bijdragen aan het verminderen van het aantal wisselingen vanwege lekkage rondom de SP.

Hoewel revalidatie na een TL zich vooral focust op stem revalidatie, kan slikken na een TL eveneens een significant probleem zijn, wat we hebben uitgezocht in **hoofdstuk 8**. Hierin hebben we gebruik gemaakt van hetzelfde TL-cohort als in hoofdstuk 7, en dit vervolgens gecombineerd met een gelijkwaardig cohort van patiënten die in de periode 2008-2016 gelaryngectomeerd zijn in het Universitair Medisch Centrum Utrecht. In dit samengestelde cohort hebben we de cumulatieve incidentie onderzocht van een of meer dilatatie procedures vanwege een stenose, evenals de risicofactoren voor het ondergaan van een dilatatie en de incidentie van complicaties na dilatatie procedures. We vonden een cumulatieve incidentie van 22.8% voor dilataties, in de 5 jaar na de TL. Ongeveer de helft van de patiënten had 1-3 dilataties nodig, terwijl de andere helft vaker werd gedilateerd. Vrouwelijk geslacht, een tumor in de hypofarynx en CRT voor of na de TL bleken risicofactoren voor een stenose waarvoor dilatatie nodig was. CRT was de sterkste risicofactor, wat niet verassend is aangezien stenose zich ook kan ontwikkelen als complicatie van CRT alleen. Bij 0.8 procent van de dilataties trad een grote complicatie op, en zes van de in totaal acht grote complicaties bleek een transmurale slokdarm perforatie. Hoewel het risico op grote complicaties laag is, kunnen deze levensbedreigend zijn. Dit moet duidelijk worden gecommuniceerd met de patiënt. Na multivariabele analyse bleek een dilatatie procedure onder algehele anesthesie geassocieerd met het hoogste risico op een complicatie.

In **hoofdstuk 9** beschrijven we de ontwikkeling van een online keuzehulptool voor patiënten met een gevorderd larynxcarcinoom. In deze keuzehulptool worden de drie opties voor behandeling (RT, CRT en TL) uitgebreid besproken, en kunnen patiënten video's bekijken van patiënten die hun ervaringen delen of van artsen die de behandeling nogmaals toelichten. Voor de ontwikkeling van de keuzehulptool hebben we internationale richtlijnen gevolgd (IPDAS). In drie fases hebben wij verschillende semigestructureerde diepte interviews en 'thinking out loud' sessies uitgevoerd en een studie-specifieke vragenlijst afgenomen om de bruikbaarheid en tevredenheid met de keuzehulptool te evalueren. Deelnemers aan deze studie waren patiënten die behandeld waren voor keelkanker en artsen die deze patiënten behandelen en werken als hoofd-hals chirurg, radiotherapeut of medisch oncoloog. Patiënten en artsen waren het erover eens dat er een noodzaak is voor een online keuzehulptool. Artsen gaven de volgende mogelijke barrières aan voor adequate patiëntenvoorlichting; moeite met het verhelderen van de persoonlijke normen en waarden van de betreffende patiënt, en het relatief lage opleidingsniveau van de gemiddelde hoofd-hals patiënt, waardoor zij twijfelden of alle informatie wel goed werd begrepen. Patiënten, ook die met een hoog opleidingsniveau, bevestigden dat ze zich de gegeven informatie vaak niet goed konden herinneren en gaven aan dat herhaling van de informatie, bijvoorbeeld door middel van een keuzehulptool, zeer nuttig is. Zowel artsen als patiënten gaven aan dat de introductie van een keuzehulptool de huidige voorlichting zou verbeteren en de kwaliteit van patiënten zorg ten goede zou komen. Om de klinische toepasbaarheid en tevredenheid van de keuzehulptool te testen zijn we gestart met een multicenter studie, waarin de toegevoegde waarde van de keuzehulptool aan de huidige voorlichting wordt geëvalueerd.

Hoofdstuk 10 is een algemene discussie van de resultaten beschreven in dit proefschrift, waarin eveneens mogelijkheden voor toekomstig onderzoek wordt beschreven.

Appendices

Authors and affiliations

Author contributions

PhD Portfolio

List of publications

Curriculum Vitae

Dankwoord

AUTHORS AND AFFILIATIONS

AA Abrahim Al-Mamgani, Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

AB Adriana Berlanga, Department of Radiation Oncology (MAASTRO), Research Institute GROW, Maastricht University, Maastricht, The Netherlands

AC Amy Chen, Department of Otolaryngology Head and Neck Surgery, Emory University, Atlanta, Georgia, USA

AD Andrew T Day, Department of Head and Neck Surgery and Oncology, Johns Hopkins Medical Center, Baltimore, USA

AT Adriana J Timmermans, Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands, Department of Head and Neck Oncology and Surgery, Amsterdam UMC, location VUmc Amsterdam, The Netherlands

BD Boukje AC van Dijk Comprehensive Cancer Organization The Netherlands (IKNL), Department of Research, Utrecht, The Netherlands and University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands

BT Bernard Tijink, Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

CA Coralie R Arends, Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands, Department of Clinical Epidemiology Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

CL C René Leemans, Department of Head and Neck Oncology and Surgery, Amsterdam UMC, location VUmc Amsterdam, The Netherlands

CS Carl Skroder, Department of ENT / Head and Neck Surgery, Lund University Hospital, Sweden

FH Frans JM Hilgers, Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

FHs Frank Hoebers, Department of Radiation Oncology (MAASTRO), Research Institute GROW, Maastricht University, Maastricht, The Netherlands

GH Gyuri Halmos, Department of Head and Neck Oncology and Surgery, University Medical Center Groningen, Groningen, The Netherlands

HZ Hongzhen Zhang, Department of Otolaryngology Head and Neck Surgery, Emory University, Atlanta, Georgia, USA

JB Jan Paul de Boer, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

JD Jolanda M van Dieren, Department of Gastroenterology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

JN James P O'Neill, Department of Head and Neck Surgery and Oncology, Dublin, Ireland

JM Jeroen Meulemans, Department of Oncology, section Head and Neck Oncology, University Hospitals Leuven, KU Leuven, Belgium

JW Johan Wennerberg, Department of ENT / Head and Neck Surgery, Lund University Hospital, Sweden

LJ Luuk M Janssen, Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

LL Liset Lansaat, Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

LO Lucy IH Overbeek, PALGA (the Dutch Nationwide network and registry of histopathology and cytopathology), Houten, The Netherlands

LS Laura A Smit, Department of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

MB Michiel WM van den Brekel, Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands, Institute of Phonetic Sciences-Amsterdam Center of Language and Communication, University of Amsterdam, Amsterdam, The Netherlands and Department of Oral and Maxillofacial Surgery, Academic Medical Center, Amsterdam, The Netherlands

MS Martijn M Stuiver, Department of Clinical Epidemiology Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

OH Olga Hamming-Vrieze, Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands

PL Philippe Lambin, Department of Radiation Oncology (MAASTRO), Research Institute GROW, Maastricht University, Maastricht, The Netherlands

RB Remco de Bree, Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

RD Richard Dirven, Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

SB Sandra I Bril, Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

SD Sandra Deady, National Cancer Registry, Ireland

TP Thomas F Pézier, Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

TvP Tom van Putten, Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

VN Vincent van der Noort, Biometrics department, The Netherlands Cancer Institute, Amsterdam, The Netherlands

VP Vincent Vander Poorten, Department of Oncology, section Head and Neck Oncology, University Hospitals Leuven, KU Leuven, Belgium

WK Wayne Koch, Department of Head and Neck Surgery and Oncology, Johns Hopkins Medical Center, Baltimore, USA

AUTHOR CONTRIBUTIONS PER CHAPTER

CHAPTER 2

Trends in Treatment, incidence and survival of hypopharynx cancer: a 20-year population based study in the Netherlands

Study concepts and design | JP, AJ, BD, FH, MB
Data acquisition | BD, LO, AJ, JP
Data analysis and interpretation | JP, AT, FH, BD, MS
Statistical analysis | JP, AT, BD, MS
Manuscript preparation | JT, AT, FH
Manuscript editing and review | JP, AT, BD, LO, LS, FH, MS, MB

CHAPTER 3

Development and external validation of a risk-prediction model to predict 5-year overall survival in advanced larynx cancer

Study concepts and design | JP, AT, MS, MB
Data acquisition | JP, AT, AC, HZ, JN, SD, VP, JM, JW, CS, AD, WK
Data analysis and interpretation | JP, MS, AT, MB
Statistical analysis | JP, MS, AT
Manuscript preparation | JP, MS, AT, MB
Manuscript editing and review | JP, MS, AT, AC, HZ, JN, SD, VP, JM, CS, AT, WK, MB

CHAPTER 4

Optimizing survival predictions of hypopharynx cancer: development of a clinical prediction model

Study concepts and design | JP, CA, MB, MS, VN
Data acquisition | JP, CA, JT, RB, RL
Data analysis and interpretation | JP, CA, VN, MS
Statistical analysis | JP, CA, VN, MS
Manuscript preparation | JP, CA, VN, MS
Manuscript editing and review | JP, CA, VN, AT, CL, RB, MB, MS

CHAPTER 5

Laryngo-esophageal Dysfunction Free Survival and Propensity Score Matched Analysis comparing organ preservation and total laryngectomy in hypopharynx cancer

Study concepts and design | JP, MB
Data acquisition | JP, CA
Data analysis and interpretation | JP, CA, VN, MS
Statistical analysis | JP, CA, VN, MS
Manuscript preparation | JP, CA, VN, MS
Manuscript editing and review | JP, CA, VN, AA, JB, MS, MB

CHAPTER 6

Post-laryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period

Study concepts and design | JP, LL, AT, FH
Data acquisition | JP, LL, AT
Data analysis and interpretation | JP, LL, VN, FH
Statistical analysis | JP, LL, VN
Manuscript preparation | JP, LL, FH
Manuscript editing and review | JP, LL, AT, VN, FH, MB

CHAPTER 7

How I do it? Solving periprosthetic leakage with a novel prosthetic device

Study concepts and design | LL, FH
Data acquisition | LL, JP
Data analysis and interpretation | JP
Statistical analysis | JP
Manuscript preparation | JP, FH
Manuscript editing and review | JP, LL, FH, MB

CHAPTER 8

Dilation after laryngectomy: incidence, risk factors and complications

Study concepts and design | JP, FH, TP,RB
Data acquisition | JP, TP, SB, TPu
Data analysis and interpretation | JP, TP, VN, JD
Statistical analysis | JP, VN
Manuscript preparation | JP, TP, VN
Manuscript editing and review | JP, TP, JM, VN, TPu, SB, LJ, RD, MB, RB

CHAPTER 9

Improving decision making in larynx cancer by developing a decision aid: a mixed methods approach

Study concepts and design | JP, AB, FH, MB, PL
Data acquisition | JP, AB
Data analysis and interpretation | JP, AB
Statistical analysis | JP
Manuscript preparation | JP, AB, MS
Manuscript editing and review | JP, AB, MS, OH, FH, PL, MB

PhD PORTFOLIO

PhD period	April 2015 – March 2019
PhD supervisors	Prof. dr. MWM van den Brekel, prof. dr. F.J.M. Hilgers, dr. M.M. Stuiver

COURSES

2014	GPRA Post-laryngectomy Rehabilitation course, NKI-AVL, Amsterdam
2014	Fundamental Critical Care Support, Houten
2015	Practical biostatistics, AMC Graduate School
2015	Basiscursus regelgeving klinisch onderzoek (BROK), AMC Graduate School
2015	Introduction to R and statistics, NKI-AVL
2015	Scientific writing, AMC Graduate School
2016	Clinical Data Management, AMC Graduate School
2016	Clinical Epidemiology: Observational Epidemiology, AMC Graduate School
2016	Medical Business Masterclass
2017	Clinical prediction models, Free University, Amsterdam
2017	Scientific Integrity, ACTA
2017	How to write high impact articles and what to do when your paper is rejected, AMC Graduate School
2018	Dentistry for non-dentists, ACTA
2018	Basis Cursus Oncologie, Nederlandse Vereniging voor Oncologie

(INTER)NATIONAL CONFERENCES ATTENDED

2015-2019	KNO voor- en najaarsvergadering, Nieuwegein
2016-2018	NWHHT-vergadering, several locations in the Netherlands
2016-2019	Jonge onderzoekersdag van de NWHHT, several locations in the Netherlands
2016-2017	OOA retraite, Renesse
2015	12th International Head and Neck Symposium, Antoni van Leeuwenhoek, Amsterdam
2015	VMTI Congres, Haarlem
2016	22e AVL symposium voor Oncologie VPK en (para)medici
2016	AHNS 9th International Conference on Head and Neck Cancer, Seattle, VS
2016	7th European Congres on Head and Neck Oncology, ECHNO, Budapest, Hongarije
2016	Samen Beslissen Symposium, ETZ Tilburg
2015	13th International Head and Neck Symposium, Antoni van Leeuwenhoek, Amsterdam
2017	World ENT congres – IFOS, Parijs, Frankrijk
2018	SCCHN Head and Neck symposium, UMC Utrecht
2018	International PhD Student Cancer Conference, Londen, VK
2018	6th World Congress IFHNOS, Buenos Aires, Argentinië
2019	14th International Head and Neck Symposium, Antoni van Leeuwenhoek, Amsterdam

SUPERVISING

2015-2016	E. Gelissen, scientific internship, master student Medische Beelvormende Radiotherapeutische Technieken
2018-2019	C. Arendsen, scientific internship, master student Evidence Based Practice

LIST OF PUBLICATIONS

JF Petersen, TF Pézier, JM van Dieren, V van der Noort, T van Putten, SI Bril, LM Janssen, R Dirven, MWM van den Brekel, R de Bree. Dilation after laryngectomy: incidence, risk factors and complications. Oral Oncology 2019;91;107-112

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JF Petersen, MM Stuiver, AJ Timmermans, A Chen, H Zhang, JP O'Neill, S Deady, V Vander Poorten, J Meulemans, J Wennerberg, C Skroder, AT Day, W Koch, MWM van den Brekel. Development and external validation of a risk prediction model to predict overall survival in advanced larynx cancer. Laryngoscope 2018;128(5);1140-1145

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SA de Boer, DJ Mulder, **JF Petersen**, JD Lefrandt, K Hoogenberg. The effects of GLP-1 analogues in obese, insulin-using type 2 diabetes in relation to eating behaviouw. Int j Clin Pharm 2016;38(1)144-51

JF Petersen, PA Borggreven, N Kuck, MJAM Tegelberg, PJFM Lohuis. Paradigm change in the treatment of non-melanoma skin cancer of the auricle: reconstruction with full thickness skin grafting instead of wedge excision. Eur Arch Otorhinolaryngol 2015;272(7);1743-8

JF Petersen, LE Smeele, AJM Balm. Een routine lokale infiltratie anesthesie als ongebruikelijke oorzaak voor trismus. NTvKNO Heelkunde, 2015;21(2);71-73

S Kruijff, **JF Petersen**, P Chen, AM Aniss, RJ Clifton-Bligh, SB Sidhu, LW Delbridge, A Gill, D Learoyd, MS Sywak. Patterns of Structural Recurrence in Papillary Thyroid Cancer. World J Surgery 2014;38(3);653-9

BOOK CHAPTERS

MWM van den Brekel, **JF Petersen**. Locally advanced glottic larynx cancer. Book chapter in Laryngeal Cancer: Clinical Case-Based Approaches. Editors: RA. Dedivitis, G Peretti, E Hanna, CR Cernea. Publisher: Thieme Medical Publishers, Inc., New York, 2019; pp 108-113. ISBN 978-1684200016

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CURRICULUM VITAE

Marije Petersen werd op 25 maart 1988 geboren in Zoetermeer en groeide op in Bennekom met haar ouders en oudere broer Dirk-Jan. Zij doorliep het Tweetalig VWO aan het Marnix College te Ede en liep tijdens haar middelbare schooltijd een maand mee op een highschool in Maryland, in de VS. Zij slaagde in 2006 en ging vervolgens Internationale Organisaties en Internationale Betrekkingen studeren in Groningen. Na het behalen van haar propedeuse maakte ze de overstap naar de studie Geneeskunde, eveneens in Groningen. Daar ging ze werken bij het Prometheus nier(transplantatie)team waardoor haar liefde voor een chirurgisch vak al snel was ontstaan. Zij volgde een coschap chirurgie in Trujillo, Peru en endocriene chirurgie in Sydney, Australië. Haar oudste coschap liep zij op de afdeling Hoofd-hals chirurgie in het Antoni van Leeuwenhoek, waar ze na het behalen van haar artsenbul startte als ANIOS Heelkunde/Hoofd-hals chirurgie. Op 1 april 2015 begon zij aan haar promotietraject met als promotor prof. dr. Michiel van den Brekel en copromotoren prof. dr. Frans Hilgers en dr. Martijn Stuiver. Naast haar promotietraject was zij verantwoordelijk voor de intake van nieuwe patiënten op de polikliniek hoofd-hals chirurgie. Marije houdt erg van reizen en wielrennen en heeft in 2016 samen met een groep van meer dan 20 collega's de Stelvio in Italië beklommen om geld in te zamelen voor onderzoek naar kanker in het kader van de 'Stelvio for life'. In 2017 heeft zij een pauze ingelast om een maand mee te lopen op de afdeling hoofd-hals chirurgie van het Rajavithi Hospital in Bangkok, Thailand, gevolgd door een reis door verschillende landen in Azië.

Na haar promotietraject start Marije met de studie Tandheelkunde aan de ACTA, gevolgd door de opleiding tot MKA-chirurg in het Amsterdam UMC, locatie VUmc onder leiding van prof. dr. Schulten en prof. dr. Forouzanfar.