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. 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. Cancers developing in the larynx and hypopharynx are usually squamous cell carcinomas (SCC) and the main risk factors are smoking and alcohol consumption. Excessive alcohol consumption seems to play a bigger role in the development of hypopharynx cancer, and patients with hypopharynx cancer typically have more comorbidities. 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.

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. 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. 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.

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. 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. Although many different types of artificial larynxes were presented, none of them became widely accepted. 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%. 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.” 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.

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. 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.

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. M poisonedewski et al. reported on the first functional voice prostheses in 1973. A few years later, the first commercially available voice prostheses were introduced by Singer and Blom. Since then, several different types of voice prostheses have been developed, contributing to improved vocal rehabilitation and thereby improved quality of life after TL. 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.

**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. After its first successful use in the treatment for testicular cancer, it was tested in numerous other solid cancers, including head and neck cancer. 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. 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.

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. 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. 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%.

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. 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. 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%). In the Netherlands, a phase II study was conducted in which patients received induction TPF followed by either concomitant CRT with cisplatin (100mg/m² every 3 weeks) and
conventional RT, or CRT with cisplatin (weekly 40mg/m²) 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.

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. 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, advanced larynx, hypopharynx or oropharynx cancer received radiotherapy with or without cetuximab in combination with RT. 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. 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.

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. 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.

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. 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. 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.

To evaluate whether these trends in treatment and survival could also be witnessed in the Dutch population, Timmermans et al., performed an institutional and a national database study 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. 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. Stokes et al. analyzed all T4NO 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. Although the evidence of superior OS among T4 cancer patients in the TL group seems compelling for larynx cancer, fewer studies have investigated this effect in hypopharynx cancer patients or only with limited patient numbers.

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. Other possible treatment strategies such as induction CT followed by (concurrent chemoradiotherapy or Transoral Robotic Surgery (TORS), are currently rarely applied in the Netherlands.

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.

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. 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. 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. Large studies have shown that when there...
is no optimal treatment strategy, physicians will have stronger belief in the efficacy of their ‘own’ treatment. 53, 54 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.53, 54

Several clinical prediction models (CPM) have been developed for head and neck cancer sites.53, 54 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.53, 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.57, 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.61

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.63 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.62, 73

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.73

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...
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. 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. Most frequent complications following total laryngectomy on the short term are delayed wound healing, infection, and pharyngocutaneous fistulas. 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. 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. 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. 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.

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. 

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.\textsuperscript{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.\textsuperscript{82}

As mentioned before, since the introduction of the first voice prosthesis in 1973, several new prostheses have been developed.\textsuperscript{16, 17} In The Netherlands Cancer Institute, in 1990 the first Provox voice prosthesis was developed in collaboration with Atos Medical in Sweden.\textsuperscript{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.\textsuperscript{20, 83, 84}

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 Institute.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, lymphedema or sensorial neuropathy more likely result from (chemo)radiotherapy.\textsuperscript{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.\textsuperscript{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\textsuperscript{88} or using balloon dilatations.\textsuperscript{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.\textsuperscript{89} 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.\textsuperscript{89} A recent systematic review on dysphagia following TL reported that only 4 studies described dilatation procedures following TL.\textsuperscript{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.\textsuperscript{89}
COUNSELING PATIENTS • SHARED DECISION MAKING

There is a growing body of evidence on epidemiology, survival, and pulmonary, swallowing, olfactory and vocal rehabilitation 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. 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. 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. 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. 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. 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). 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. Differences in personal values between patients and healthcare providers are a challenging aspect in shared decision-making. 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. 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. 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. 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. This study also demonstrated that physicians underestimate the effect their treatment will have on the daily life of a patient.

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. 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. 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.

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. 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. 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 periprosthesis 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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1. **CHAPTER 1 GENERAL INTRODUCTION**


