Advanced larynx cancer. Trends and treatment outcomes

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

STAGING AND TREATMENT OF ADVANCED LARYNX CANCER

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

In view of the ongoing discussion about the status of the (chemo)RT-based larynx preservation approach in both T3 and T4 cancer, and its possible impact on survival, in Chapter 2 we describe a retrospective analysis assessing whether the commonly found difference in survival between T3 and T4, obviously also depending on neck node status, still exists despite the fact that T3 disease was not treated surgically since over 15 years in our Institute. In this cohort of 182 patients treated with TL, RT or concomitant chemoradiation (CCRT) between 1999 and 2008 in the Netherlands Cancer Institute no significant differences in OS were observed between T3 and T4 larynx cancer, nor between stage III and stage IV disease. The dominating prognostic factors in this study were nodal status and co-morbidity, as has been found in many other studies in head and neck cancer. The lack of a difference in survival between T3 and T4 was an unexpected finding since generally T3 tumors are considered to have a better prognosis than T4 disease, when corrected for nodal status. The fact that the majority of T3 larynx cancers were treated with RT or CCRT and the majority of T4 with TL
(+/-PORT) was a possible explanation for this finding. Variation in the staging system over time would be an unlikely explanation for this, because we uniformly restaged (based on the available radiology reports) all cases according to the latest (7th) 2010 UICC edition. However, tumor volume was not available for inclusion in that analysis. Therefore, tumor volume as possible prognostic parameter was addressed in Chapter 3. For 166 of 182 patients, imaging of sufficient quality was available for radiological tumor volume assessment. In this patient cohort, we found that tumor volume was not significantly associated with local control, loco-regional control or overall survival in the surgically treated group. In the group treated with radiotherapy there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with CCRT a significant impact of tumor volume on local control was found. In the literature studies are conflicting regarding these results (6-11). The reason why we did not find an influence of tumor volume on oncological outcome –except for the association with local control in the CCRT-group—remains unclear, but maybe it is not that surprising after all, considering our initial finding that there was also no difference in prognosis between (the smaller volume) T3 and (the larger volume) T4. It is thus probably due to a selection bias: patients with the higher tumor volumes were selected for TL (median volume T4 15.8 cc; median volume TL 19.7 cc), leaving the smaller tumors for organ preservation treatment (median volume T3 8.1 cc; median volume RT 7.4 cc; median volume CCRT 13.5 cc). And this lack of the full range of tumor volumes thus might have obscured a possible significant volume effect in the RT only group, although a trend was noted in this group as well. Another explanation might be the small number of patients in this study as illustrated by Knegjens et al. (2011). These authors found that in 360 patients treated with chemoradiation for advanced head and neck cancer, tumor volume was more powerful for predicting outcome after chemoradiation than the TNM classification (10). However, when 10 random samples of 75 patients in this cohort of 360 patients were assessed, in only 5 out of 10 samples this significant effect of tumor volume on local control could be found (see Table below (12)).

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

<table>
<thead>
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<th>No of series with p &lt; 0.05</th>
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Apart from volume, for patients treated with (C)RT other parameters may be of more predictive value, like gene expression signatures, hypoxia and radio-sensitivity in general (12, 13). It has been postulated that tumor control after RT depends on killing all clonogenic cells in the tumor and that the number of clonogenic cells increases linearly with tumor volume and thus influences local control (14, 15). That possibly explains why we and others found that tumor volume was significantly associated with local control in the CCRT-group.
The above-mentioned studies included patients that were treated in the Netherlands Cancer Institute. However, to learn more about the treatment results in the Netherlands, and to assess the impact of the afore-mentioned 1999 national consensus, a population-based study was conducted, described in Chapter 4. The aim of is this study was to determine time trends for primary treatment modalities in advanced larynx cancer, overall survival and laryngectomy-free interval (LFI) over the last two decades in the Netherlands. This study comprised all Dutch patients diagnosed with squamous cell larynx cancer between 1991 and 2010. We found that for both T3 and T4 larynx cancer, the use of primary TL as a proportion of all patients diagnosed with T3 and T4 larynx cancer decreased, whereas the use of RT increased. Hoffman et al. (2006) studied patterns of care and survival after larynx cancer between 1985 and 2001 in the United States in 158.426 patients. These authors also observed a decrease in number of TLs as primary treatment for larynx cancer and an increase in RT and CRT, but that study included all larynx cancer cases and not only the advanced cases as in the present study (16). The decrease in TLs and increase in RT for T3 larynx cancer in our study is not unexpected, since the Dutch guidelines for treating larynx cancer changed in 1999 as described above.

We also found that overall survival of T3 and T4 larynx cancer differs significantly (44% and 39% respectively after 5 years). When analyzed per treatment, overall survival is similar for T3 larynx cancer after treatment with TL, RT or CRT. For T4 larynx cancer however, patients treated with RT or CRT have poorer survival compared to patients treated primarily with TL and adjuvant RT. The respective roles of organ preservation (CRT) treatment and organ sacrificing surgical treatment for advanced larynx cancer have been extensively addressed in the recent literature. Hoffman et al. (2006), previously mentioned, reported a decreasing trend in survival from the mid-80s to the mid-90s and, in the same period, an increase of CRT as primary treatment with a decrease in surgery. For T3NOM0 larynx cancer specifically, a significantly better 5-year relative survival was found for those patients treated with surgery and irradiation compared to patients treated with irradiation (with or without chemotherapy; 64.4% versus 49.4%). It should be noted however, that specific data regarding RT and chemotherapy were not available. Also, ‘surgery’ was not further specified in TL, endoscopic surgery or other surgery. In a population-based study in the Province Alberta, Canada, Dziegielewski et al. (2012) also found superior survival rates after treatment with TL for T4 larynx cancer (17). Furthermore, Chen et al. (2007), analyzing the NCDB database, reported HRs for death of 1.61 and 1.43 for RT and CRT respectively when compared to TL for stage IV larynx cancer, which are in line, but slightly higher than found in our Dutch 20-year population-based study. It has to be kept in mind, though, that stage IV in the Chen-study also includes T3N+ cancers and thus not solely T4 cancers (18).

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

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

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

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

In the retrospective cohort study in the Netherlands Cancer Institute, we reported a 5-year LFI of 72% after RT and 83% after CCRT. In the population-based study we found a 5-year LFI of 77% or higher in patients with T3 or T4 larynx cancer after RT or CRT. These findings are in agreement with the literature. In the VA-study the larynx was preserved in 64% of the
patients after 2 years for patients initially treated with induction chemotherapy combined with RT (27). The RTOG 91-11 study reported larynx preservation rates after 10 years of 82% and 64% after treatment with CCRT and RT alone, respectively (28).

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

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

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

Although TN classification, sex and age are important in predicting survival and larynx preservation, many other factors play a role in decision making and patient counseling for treatment selection. Among these are co-morbidity and general condition, tumor volume, and patient and physician preferences.
THE OUTCOME AFTER TOTAL LARYNGECTOMY IN A CHANGING TREATMENT LANDSCAPE

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

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

In Chapter 5, the results of a retrospective analysis of all relevant clinical and functional characteristics of 25 patients who underwent TL for a dysfunctional larynx were presented. In these 25 patients, representing 11% of the total 10-year TL cohort in the Netherlands Cancer Institute, the indication for TL is made relatively late. Most patients already had experienced several life-threatening complications, as well as the need for a permanent tracheotomy in 13 patients and for permanent tube feeding in 20 patients, before the decision for TL was made. The severe weight loss and the inherent loss of condition (with half of the patients having a BMI < 18) also suggest that the indication for surgery in most cases was postponed for a long time. This is not surprising, because all patients were in complete remission, and apparently both the patients and the health care professionals had to “grow” toward the belief that TL was the only option left for resolving the patients’ intolerable situations and for restoring at least some quality of life. Unfortunately, we found a relatively high incidence of major complications (56%) and mortality (8%). This, however, is quite comparable to the report by Van der Putten et al., who also found postoperative complications in 56% of the
patients treated with salvage laryngectomy for residual or recurrent larynx cancer after prior treatment with (C)RT (32). In their study, the postoperative mortality rate was 3% (3 of 120 patients), but this is not significantly different from the 8% (2/25) we found (unpaired t test, P=0.17). Five-year overall survival in the series of van der Putten and colleagues was 50%, a percentage that is somewhat higher than the 35% in the present study, which also suggests that our patients were in poorer condition at the time of TL. However, the main eliciting functional problems (aspiration, recurrent pneumonia, and dyspnea) did not recur after TL. Dysphagia requiring pre-TL tube feeding was not completely eliminated in 20 of the 25 patients (80%), though, leaving 4 of 14 patients (29%) dependent on tube feeding after 2 years.

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

Next to (C)RT, some studies suggest early oral intake (EOI) as a possible predisposing factor for the development of PCF (43, 44). Therefore, oral intake after TL is mostly delayed until postoperative day 10–12, under the assumption that this limits the incidence of PCF. However, early oral intake could be advantageous from a psychological perspective: early oral intake can be encouraging for patients in that they seem to be returning to normalcy (more) quickly. It may reduce costs, providing that it does not lead to increased PCF. Therefore, in Chapter 7, in a consecutive series of 247 TL patients over a 12-year period we compared PCF incidence in a traditional ‘late’ oral intake protocol (start at postoperative day 10–12; LOI-group) and in an early oral intake protocol (start at postoperative day 2–4; EOI-group). We found that the incidence of PCF was not significantly different between the
two groups. This study thus suggests that EOI is safe and does not increase PCF. This is in concordance with several other studies, although in most of these studies some selection bias was apparent (45-47). Concerning reconstruction simultaneously to TL, patients who underwent standard TL started significantly earlier with oral intake than patients who were reconstructed. Similar results were found when analyzing the LOI and EOI groups separately or when patients with PCF were excluded. This was to be expected, since patients with reconstruction usually start later with oral intake than patients after standard TL. However, it is still interesting to note that in the reconstructed group the EOI protocol could also be adopted successfully, leading to an earlier start of oral intake at (median) day 4 instead of day 12 under the LOI protocol. The historical paradigm has been to start oral intake not earlier than on postoperative day 7–10, and although recent studies have shown that EOI is a safe clinical practice, there is still no consensus among head and neck surgeons worldwide when to start oral intake after TL. It is believed that EOI delays the healing process of the pharyngeal suture line, and this is considered the main reason for surgeons not to start oral intake too early (48, 49). Interestingly, however, most sutured skin incisions heal within 1–2 days in a watertight manner; apparently, the pharyngeal mucosa suture line does not behave differently in this respect (45, 50). To some degree ‘oral intake’ still takes place, because one can never fully prevent patients from swallowing saliva, and the subsequent movement of the pharyngeal suture line could then also contribute to the occurrence of PCF (45). Another argument in favor of EOI is that with LOI the movements of the NGT are stressing the pharyngeal suture line longer, and therefore the NGT might achieve the opposite from what is intended with respect to PCF (46, 51). Seven et al. and Aswani et al. (47, 52) compared patients, who started oral intake on day 1 and day 2, respectively, with patients who were fed via a NGT through the tracheoesophageal puncture (TEP) until the seventh postoperative day. Despite the fact that feeding through the TEP eliminates the possible negative role of the NGT in the pharynx, both studies did not observe differences in PCF rates. Aprigliano, in a retrospective study on 625 total laryngectomies, reported that patients experienced the NGT as highly unpleasant. This was the reason to abandon the use of a NGT and to start oral intake on the 3rd postoperative day, with a reported PCF incidence of 9.1 % (57/625) (53). From a psychological perspective, it could be valuable to start oral intake early in the postoperative period, because this is encouraging for patients in that they seem to be returning to normalcy (more) quickly. The only downside of this approach, however, is that, if at a later stage PCF is diagnosed and the patient already has commenced oral intake, its interruption will certainly be a disappointment. This was the case in some 60% of the PCF cases in the EOI group; at the same time, this was also not uncommon in the LOI group, where it occurred in roughly one-third of the PCF patients. Nevertheless, for the simple reason that oral intake is started earlier, under an EOI protocol more patients will have to deal with a discontinuation of already resumed oral intake—something to take into account in patient counseling. Aside from the advantages already mentioned, the possible additional advantage of an early start with oral intake is that it could potentially shorten
hospital stay, thus reducing costs. Aswani et al. reported a significantly shorter hospital stay for the subgroup of patients who were fed from day 2 after TL, but this was after exclusion of PCF patients in both the EOI and LOI group (47). Overall, however, these authors did not find a significant difference in hospital stay between both groups. Medina and Khaff found a significant decrease in hospital stay from 12 days in the LOI group to 7 days in the EOI group (45). In the present study, however, no significant difference in hospital stay between the two groups was found, nor after exclusion of patients with PCF, as in the study of Aswani et al. The reason for this is that resumption of oral intake is not the only factor determining discharge in our institute; successful restoration of oral communication is also considered relevant. Patients start with voice and speech rehabilitation not sooner than day 10–12, and are only discharged if speech proficiency is satisfactory. In future this may change, however, since capacity for providing the necessary (outpatient) rehabilitation support recently has increased.

SPEECH REHABILITATION

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

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

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

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

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

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

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

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

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

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

**Future prospects**

In the future, possibly markers or assays predicting response and larynx preservation will become more important (82). Throughout the world many researchers have studied molecular markers, short term cultures, imaging characteristics, chemoselection and other approaches to predict response. Nomograms, two-dimensional diagrams that permit the estimated graphical computation of a function, might become more useful especially when
incorporated in a web based prediction model (83, 84). With data from the population-based study as presented in Chapter 4 we are planning to build a nomogram that might help physicians in the outpatient clinic in treatment decision-making in patients with advanced larynx cancer. Nevertheless, physicians should always take the patient’s wishes and individual characteristics of the patient into account since in a nomogram only a selection of parameters is included.

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

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


Chapter 11


