Changing of Quality of Life in patients with laryngeal and hypopharyngeal carcinoma undergoing primary (chemo)radiation or primary surgery followed by postoperative (chemo)radiation

Research report

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# LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

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<thead>
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<tr>
<td>CT</td>
<td>Chemotherapy</td>
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<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
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<tr>
<td>EORTC HN35</td>
<td>European Organization for Research and Treatment of Cancer Head and Neck Module</td>
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<tr>
<td>EORTC-QLQ-C30</td>
<td>European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module 30</td>
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<tr>
<td>HNC</td>
<td>Head and neck cancer</td>
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<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
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<tr>
<td>MDADI</td>
<td>MD Anderson Dysphagia Inventory</td>
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<tr>
<td>PLE</td>
<td>Partial laryngectomy</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SF-36</td>
<td>Disease-unspecific short-form-36 health-survey</td>
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<tr>
<td>TLE</td>
<td>Total laryngectomy</td>
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<tr>
<td>VoISS</td>
<td>Voice Symptom Scale</td>
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Summary

**Introduction:** Organ preservation protocols are preferred as better QoL is assumed. This assumption is not yet thoroughly investigated.

**Objective:** The primary aim is to compare QoL of patients with stage III and IV laryngeal- and hypopharyngeal cancer treated with (C)RT and those treated with TLE and postoperative (C)RT.

**Study design and study population:** A retrospective observational cohort study performed on a prospectively built database containing stage III and IV laryngeal- and hypopharyngeal cancer treated with primary (C)RT and those treated with primary TLE and postop (C)RT.

**Main study parameters:** The questionnaires, EORTC QLQ-H&N35 and QLQ-C30, which have been used for collecting quality of life data at the time points: baseline, 1, 2, 3, 4, 5, 6, 7 and 12 weeks, and 6, 12, 18 and 24 months.

**Results:** 33 patients were excluded. No difference in global QoL score was found in the EORTC QLQ-C30 questionnaire. However, the EORTC QLQ-H&N35 questionnaire showed difference during the (C)RT treatment period, in the favor of the (C)RT only patients.

**Discussion/conclusion:** there were some limitations, more investigations is needed.

Samenvatting

**Introductie:** Orgaansparende behandeling heeft de voorkeur, omdat daarbij een betere QoL wordt verwacht. Deze assumptie is nog niet grondig onderzocht.

**Doelstelling:** Het primaire doel is om de kwaliteit van leven van patiënten te vergelijken met stadium III en IV laryngeal- en hypofarynxcarcinoom behandeld met (chemo)radiotherapie en degenen behandeld met TLE en postoperatieve (chemo) radiotherapie.

**Studie opzet en studie populatie:** Een retrospectieve observationele cohort studie gebaseerd op een prospectief gemaakte database bevattend patiënten met stadium III en IV laryngeal- en hypofarynxcarcinoom behandeld met Primary (chemo)radiotherapie en degenen behandeld met Primary TLE en postop (chemo) radiotherapie.

**Hoofd parameters:** de vragenlijsten, EORTC QLQ-H&N35 and QLQ-C30, gebruikt voor het verzamelen van de kwaliteit van leven data op de tijdspunten: uitgangswaarde, 1, 2, 3, 4, 5, 6, 7 and 12 weken, en 6, 12, 18 and 24 maanden.

**Resultaten:** 33 patiënten waren geëxcludeerd. Er was geen verschil in de globale QoL score volgens de EORTC QLQ-C30 vragenlijst. Volgens de EORTC QLQ-H&N35 wel verschil tijdens de (C)RT behandeling, in het voordeel van de (C)RT alleen patiënten. Ook was er verschil tussen de groepen in een aantal variabelen.

**Discussie/conclusie:** Er waren een aantal limitaties aan het onderzoek, meer onderzoek is nodig.
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1: Introduction and rationale

1.1 General aspects (epidemiology, anatomy, etiology, symptoms)

Head and neck cancer (HNC) is the sixth most common solid malignancy. (Schutter) In 2012, approximately 157,000 new cases of laryngeal cancer were diagnosed worldwide. According to the Dutch Cancer Register the annual incidence of pharyngeal and laryngeal cancer in 2012 was 680 and 709, respectively. Laryngeal cancer is the most common form of HNC. (Pulte D, Brenner H.) However, the incidence rates are decreasing, very likely due to decreasing number of smokers. (Trivedi NP, Swaminathan DK, et al. 2008) Hypopharyngeal cancer accounted for 7% of HNC (Parkin MD, Whelan SL et al. 2002) The most common histological type of HNC is squamous cell carcinoma, being responsible for more than 90% of head and neck cancers (Sanderson RJ, Ironside 2002).

Figure 1. The incidence of laryngeal cancer.

Figure 2. Anatomy of the larynx
The larynx is located within the anterior aspect of the neck, anterior to the inferior portion of the pharynx and superior to the trachea. Its functions include preventing aspiration by closing abruptly upon mechanical stimulation or swallowing, phonation, coughing, the Valsalva maneuver, facilitation of respiration, and acting as a sensory organ. (Standring S. 2008, Barnes L, Eveson JW, et al. 2005 and Merati AL, Bielamowicz SA. 2006). The hypopharynx, also referred to as laryngo-pharynx, is the lowest part of the pharyngeal cavity, positioned behind and lateral to (piriform sinus) the entire length of the larynx. It comprises the posterolateral pharyngeal wall, the postcricoid region and piriform sinuses. Its primary function is the passage of food towards the esophagus (Million RR, Mancuso AA. 1994).

Laryngeal and hypopharyngeal cancers are more common in African American and white men. Typically, hypopharyngeal cancer patients are aged between 55 and 70 years and over half of the patients with these cancers are 65 years of age or older at diagnosis. The two most important risk factors for both laryngeal as hypopharyngeal cancer are smoking and alcohol consumption. This risk increases with the smoking and alcohol quantity. The increase caused by alcohol use is less than the increase caused by smoking. Combining these two habits multiplies the risk of getting these cancers. (Garden AS. 2001, Cooper JS, Porter K et al. 2009, Saleh EM, Abdullwahab AA, Kammal MM. 1995, Pignon JP, Bourhis J, et al. 2000, Sturgis, Erich M., and Paul M. Cinciripini. 2007, Radosievich JA. 2013)

Other but less important risk factors include poor nutrition, genetic syndromes like Fanconi anemia and congenital dyskeratosis, and workplace exposure to wood dust, paint fumes, and certain chemicals used in the metalworking, petroleum, plastics, and textile industries. There is also an association between asbestos dusts and fibers exposure, and inorganic acid mists and laryngeal cancer. The reason why poor nutrition may increases the risk of getting these cancers, is still unknown. (Cooper JS, Porter K et al. 2009, Barnes L, Eveson JW, et al. 2005, Merati AL, Bielamowicz SA. 2006, Marchand JL, Luce D.)

The two most important symptoms caused by laryngeal or hypopharyngeal cancer are voice and swallowing symptoms. A change in voice or hoarseness can be an early symptom of laryngeal cancer originating at the vocal cords (glottis). For cancers starting at a location other than the glottis, hoarseness may occur at a later stage. Hypopharyngeal cancers more often present with swallowing problems. The swallowing symptoms include dysphagia and odynophagia. Other symptoms with which these patients can present are permanent sore throat, persistent coughing, referred pain or otalgia, aspiration, weight loss and a mass in the neck. (Ferlay J, et al. 2010, Radosievich JA. 2013)

### 1.2 Survival

The prognosis of laryngeal and hypopharyngeal depends on stage and subsite. Staging ranges from stage 0 (carcinoma in situ) to stage IVc: Stage 0 (Tis, N0, M0), Stage I (T1, N0, M0), Stage II (T2, N0, M0), Stage III (T3, N0, M0, or T1 to T3, N1, M0), Stage IVA (T4a, N0 or N1, M0, or T1 to T4a, N2, M0), Stage IVB (T4b, Any N, M0, or Any T, N3, M0) and Stage IVC (Any T, Any N, M1) (American Joint Committee on Cancer. Larynx. 2010, American Joint Committee on Cancer. Pharynx. 2010 and Pulte D, Brenner H.) An increase in stage is associated with poorer prognosis (Table 3). In supraglottic laryngeal cancer prognosis is worse compared to the glottic cancer. Hypopharyngeal cancer has even worse prognosis compared to the laryngeal cancers.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Supraglottic (%)</th>
<th>Glottic (%)</th>
<th>Hypopharynx (%)</th>
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<tr>
<td>I</td>
<td>59</td>
<td>90</td>
<td>53</td>
</tr>
<tr>
<td>II</td>
<td>59</td>
<td>74</td>
<td>39</td>
</tr>
<tr>
<td>III</td>
<td>53</td>
<td>56</td>
<td>36</td>
</tr>
</tbody>
</table>
Table 3. 5-year relative survival rate

1.3 Treatment
The primary treatment strategy in laryngeal and hypopharyngeal carcinoma is either non-surgical (i.e., chemoradiotherapy (CRT) or radiotherapy alone (RT)) or surgery with or without adjuvant RT or CRT. The choice of treatment depends on tumor stage and local extension, the tumor location and patient-related factors.

1.3.1 Surgery
For the treatment of laryngeal and hypopharyngeal cancer, different surgical approaches are available, including: transoral laser surgery (TLS), total laryngectomy (TLE), partial laryngectomy (PLE) and laryngo-pharyngectomy. The type of surgery depends on the local tumor extension.

Endoscopic CO2 laser surgery is an effective form of treatment for early glottic carcinoma (ELS), in which the tumor is completely resected (Prgromet D, Bacić A, Prstacić R, Janjanin S., 2013). The functionality is preserved in the largest amount possible, by for example conservation of the cartilaginous skeleton.

PLE is the surgical removal of only a part of the larynx. PLE includes supraglottic laryngectomy or hemilaryngectomy and there are several modifications. In the Netherlands, PLE is only performed in a very small selected group of patients.

TLE means the surgical removal of the entire larynx, dividing the airway and the digestive system. A persistent tracheostomy is made, creating an opening of the trachea in the anterior part of the neck to maintain an open airway.

Laryngo-pharyngectomy is the surgical removal of the pharynx and the larynx. This procedure is applied in case of hypopharynx cancers (Takes RP, Strojan P, et al. 2012.). In case of laryngo-pharyngectomy, the pharynx is removed completely or partially. If it is completely removed, the pharynx has to be reconstructed, usually by using free tissue transfer. In case of partial removal of the pharynx the remaining pharyngeal wall can be primary closed or can be reconstructed, depending on the size of the defect. (Moyer JS, Wolf GT. 2009 and Mendenhall WM, Werning JW, Pfister DG. 2011)

Proper treatment of the neck is essential. Occult nodal neck metastasis is a well-known phenomenon and has a negative impact on survival. Therefore the treatment of the neck can be elective or therapeutic in the form of neck dissection or radiation therapy (Byers RM, Clayman GL, et al. 1999). Elective treatment means that the lymphatic system of the neck is treated without evidence of metastasis. Generally, elective treatment is applied if the chance of neck metastasis is higher than 20%.

1.3.2 Radiotherapy with or without chemotherapy
Based on the results of a number of randomized trials, the current standard technique for radiation therapy for head and neck cancer is intensity modulated radiotherapy (IMRT), but 3D conformation-radiotherapy (3D-CRT) is also used (Nutting CM, Morden JP, Harrington KJ, et al. 2011).

IMRT is a more advanced technique than 3D-CRT which allows for better sparing of normal tissues, in particular the parotid glands, while the same therapeutic dose to the tumor can be administered. In the first era of IMRT, it took more time to deliver the radiation. (Teh BS et al. 1999). However, with new technologies like Volumetric Arc Therapy (VMAT), the time per fraction is only a few minutes.
CRT is the combined treatment of chemotherapy and radiation. There are different chemotherapeutic agents. The most commonly used in head and neck cancer are platinum based. Chemotherapy can be combined with radiotherapy in different ways, including, concurrent, neoadjuvant or adjuvant. Concurrent CRT means that chemotherapy and RT are given at the same time, which induces maximal tumor control, because of the additive effect.
Neoadjuvant chemotherapy means that chemotherapy is given before RT to increase the success rate while in case of adjuvant chemotherapy, the chemotherapy is given after completion of RT.

At present, concurrent CRT is considered standard treatment as the results of a large meta-analysis has shown that the addition of chemotherapy to radiotherapy results in a significant improvement of the overall survival, but only when these two modalities are given concurrently (Pignon JP et al. 2009).

When patients are not fit enough to receive concurrent chemoradiation, an alternative is RT in combination with cetuximab (humanized monoclonal antibody directed against the epidermal growth factor). A randomized trial (Bonner JA et al. 2010, Bonner JA et al. 2006) showed that RT with cetuximab compared to RT alone significantly improved locoregional control and overall survival at 5 years.

It should be noted that both concurrent chemotherapy and cetuximab are only beneficial in patients younger than 70 years of age. (Pignon, Bonner). When systemic therapy is not possible, RT as single modality can be considered as alternative larynx preserving treatment approach.

1.3.3 Treatment choice

The choice of treatment is based on tumor location, tumor extension (stage) and patient preference.

Stage I laryngeal cancer is mostly treated by TLS or if not feasible by RT alone or partial open surgery.

Stage II laryngeal cancer is mostly treated with RT, but in well selected cases PLE may be a better option.

In stage III/IV laryngeal cancer, both primary surgery followed by adjuvant RT or CRT can be considered as well as a larynx preserving approach, consisting of concomitant CRT or RT alone. A larynx preservation strategy can be considered in case function preservation of the larynx can be expected after treatment. In very advanced tumor stages, when no cure can be expected from (C)RT, e.g. due to large tumor volume, no functional larynx and or extensive cartilage invasion, then primary TLE may be a better choice. (Wolf GT, Hong WK, Gross Fisher S, et al. 1991 and Forastiere AA, Goepfert H, et al. 2003)

Stage I hypopharyngeal cancer can either be treated with RT, TLS or open partial laryngo-pharyngectomy, but in practice it is rarely seen. Patients usually present with more advanced stages of the disease.

The principals in the treatment of stage II/III/IV hypopharyngeal cancers are comparable to those described for advanced stage laryngeal cancer. (Takes RP, Strojan P, Silver CE, Bradley PJ, Haigentz M Jr, Wolf GT, et al. 2012). Organ preservation protocols are used if functional larynx can be expected after (C)RT, otherwise total laryngectomy with partial or total pharyngectomy is applied. (20, 21)

As previously mentioned, the treatment of the neck is crucial. In case of clinically manifest neck node metastases, radical treatment by either surgery or RT is indicated. Because of the high probability of occult nodal metastases, in most patients the ipsi- and contralateral necks are treated electively, in particular in case of hypopharyngeal cancer.

When surgery is used as primary treatment, adjuvant treatment, i.e. postoperative RT of CRT is indicated in case of more than one lymph node metastases, cT3/cT4, close or positive resection margins, lymph node metastases with extracapsular tumor spread, and perineural tumor growth. (Strojan P, Haigentz M Jr, Bradford CR, Wolf GT, Hartl DM,
In case of positive surgical resection margins and/or extracapsular spread, adjuvant concurrent CRT is indicated when patients are younger than 70 years of age.

In general, treatment protocols do not take comorbidity, the general condition (physical, psychological, social), and patient preferences into account. However, differences in these aspects can influence the success of treatment. A better awareness of these aspects and a more personalized approach may result in a better and perhaps safer treatment.

For decades, the golden standard for treating locally advanced laryngeal and hypopharyngeal squamous cell carcinoma was TLE. This operation can cure patients but also causes significant impairment of QoL of these patients. With the development of more advanced radiation techniques and the addition of new chemotherapeutic and biological agents (e.g. cetuximab), organ preservation protocols became the standard choice of treatment for advanced stage laryngeal and hypopharyngeal cancer. Therefore, at present TLE is reserved for cases when the risk of local recurrence is considered too high (e.g. in case of massive cartilage invasion), of no functional larynx can be expected after (chemo) radiation or as a salvage procedure in case of recurrent or residual disease after non-surgical treatment. (Olsen KD. 2010). The survival rates of both treatments are broadly comparable (Sessions DG. 2005), with some studies finding a slightly better survival rate in TLE patients compared to (C)RT. There is a difference in survival rates dependend on the stage of the cancer (McNeill BJ. 2013, Bussu F. 2013. Grover S. 2015). Patients with stage T4a (cartilage invasion or extralaryngeal tumor extension) and/or N0 have better survival rate when treated with TLE compared to (C)RT.

1.4 Outcome

There are different types of outcomes, like survival, recurrence, early and late toxicity, voice rehabilitation and QoL. TLE includes the removal of the vocal cords, persistent tracheostomy, often swallowing problems and sensory complications. RT may result in early and late side effects. An example of an early side effect (starting during RT up to until 3 months after RT) is mucositis, resulting in painful sores in the mouth and throat, difficulties with eating and drinking and subsequent weight loss and malnutrition. The most common late side effect is xerostomia, although this may recover over time when new radiation techniques like intensity modulated radiotherapy (IMRT) are used. Other side effects are dermatitis, hoarseness, odyno-dysphagia, loss of taste, shortage of breath due to swelling of the larynx, and fatigue.

Xerostomia can also lead to subsequent late side effects (after 3 months of RT treatment), such as tooth decay and swallowing problems.


After TLE, patients are unable to communicate using vocal cords, therefore voice rehabilitation with the help of speech therapist is needed. Different voice rehabilitation devices can be used including esophageal speech, tracheo-esophageal puncture (TEP) and electrolarynx. With esophageal speech some people learn to swallow air and consequently force it burp through their mouth. As the air passes through the throat it will cause waves in the mucosa of the pharyngeal wall, which, with training, can be turned into speech.

At present, TEP is the most commonly used method for speech rehabilitation. It creates a connection between the trachea and the esophagus through a small puncture at the
posterior wall of the stoma. A small one-way valve is placed into this puncture site restoring the ability to force air from the lungs into the mouth. During phonation the patients has to cover their stoma to force air out of their mouth. Sound is generated by mucosal waves, just like in case of esophageal speech. By electrolarynx a device is placed in either the corner of the mouth or against the skin of the neck. After pressing a button on the device, a vibrating sound is made. By moving the mouth and tongue, this sound can be turned into words. All of these techniques require training by a speech therapist (Teh BS et al. 1999, Bonner JA et al. 2006, Forastiere AA et al. 2013).

1.5 Quality of life
Quality of life (QoL) is considered a multidimensional concept and refers to the satisfaction and well-being that a patient experiences on a daily basis. The European Organization for Research and Treatment of Cancer (EORTC) has developed several QoL instruments. The Quality of Life Questionnaire, Core Module 30 (EORTC QLQ-C30) is developed to assess the health related (HR)QoL of all cancer patients. The Head and Neck Module (EORTC QLQ HN35) is the most commonly used questionnaire to measure site-specific QoL and is specifically developed for head and neck patients. It consists of 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality (Trivedi NP, et al. 2008, EORTC QLQ-C30 Scoring Manual, QL Coordinator, Quality of Life Unit, EORTC Data Center 2001).


Some authors found that radiation-induced dysphagia, xerostomia and severe weight loss during and after radiotherapy has a significant impact on social eating, social contact, and QoL in head and neck cancer. These studies also found that the course of QoL of patients with head and neck cancer during the first 2 years after CRT is different for survivors compared to non-survivors and is associated with comorbidity and tumor subsite (patients with oral or oropharynx carcinoma have more problems than patients with hypopharynx or larynx). (Langius JA et al. 2013)

The difference in the impact of the treatment modalities on the QoL of laryngeal and hypopharyngeal carcinoma patients has not been determined yet. It is difficult to compare complications and QoL after (C)RT and surgery. Knowledge of post-treatment QoL could be
important in routine daily practice, being a decisive factor in choosing between different treatment modalities, especially when survival rates are more or less similar. Organ preservation protocols are preferred to radical surgery as better QoL is assumed in case the larynx is preserved. This assumption is more based on prejudices rather than facts. In clinical practice there are several patients seen with satisfactory QoL after TLE and also patients with poor QoL with preserved voice box.

Therefore, the primary aim of the present study was to compare QoL, measured at different time points during and after radiation treatment in patients with stage III and IV laryngeal and hypopharyngeal cancer between patients treated with primary (chemo)radiotherapy and those treated with primary TLE and postoperative (chemo)radiation. Our hypothesis was that primary (chemo)radiotherapy results in lower QoL than patients treated with primary TLE and postoperative (chemo)radiation.
2. Methods

2.1 Study population

2.1.1 Population
The study population was composed of patients with T3-T4 laryngeal or hypopharyngeal carcinoma or T stage I and T stage II with lymph node involvement (N2a to N3), who were either treated with primary (chemo)radiation or primary surgery followed by postoperative (chemo)radiation in the UMCG between 2007 and 2014. The data for this analysis was extracted from the database of the Department of Radiation Oncology of the UMCG.

2.1.2 Inclusion criteria
Stage III and IV laryngeal- and hypopharyngeal carcinoma (either T3-T4, any N, or T1-T2, N2a-N3), treated with either primary (chemo)radiation or primary total laryngectomy (-pharyngectomy) followed by postoperative (chemo)radiation

2.1.3 Exclusion criteria
- Other modalities of treatment
- Patients with other malignancies than the HNC during treatment.
- Patients with previous RT in the HN area
- Patients treated with palliative intention

2.2 Study design
This was a retrospective analysis based on the data from a prospective cohort study. In 2007, the department of Radiation Oncology started a prospective data collection program for all patients with head and neck cancer referred for RT either or not combined with other treatment modalities, such as surgery, chemotherapy and/or biological agents. In this program, acute and late toxicity, patient-rated outcome measures and treatment efficacy endpoint are prospectively and systemically scored prior, during and after completion of treatment.

The data for the present analysis was extracted from the database of this program, including results from the EORTC QLQ-C30 and EORTC QLQ-H&N35 quality of life questionnaires, assessed at baseline (before start (C)RT treatment), in week 1 2, 3, 4, 5, 6, 7 (during radiation) and at 12 weeks, and 6, 12, 18 and 24 months after completion of treatment. Other variables, including patient characteristics, tumor characteristics, treatment and follow-up data were also included in the analysis (details follow later).

All efforts were made to complete missing data by searching in electronic patient’s dossier (Poliplus) and contacting the general practitioner. To ensure legal regulations and privacy, data were transferred to the TARGET platform in which a protected workspace was created with anonymised data.

2.2.1 Interventions
Patients were primarily treated by either TLE and postoperative RT or CRT or with definitive (CH)RT for their advanced stage laryngeal or hypopharynx carcinoma. The choice of treatment was always made by the Head and Neck Oncology Multidisciplinary Team and according to Dutch guidelines.

According to the national guidelines, in both hypopharyngeal and cancer, organ preservation using RT (in small tumors) or CRT (in more advanced tumours) was the
preferred treatment, provided that adequate local control and post-treatment function can be expected (*Oncoline richtlijn hypopharynxcarcinoom en richtlijn larynxcarcinoom*).

### 2.3 Methods

#### 2.3.1 QoL assessment

QoL of patients was assessed by the Dutch version of the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires (the full questionnaires can be found in the appendix).

#### 2.3.1.1 EORTC QLQ-C30 questionnaire

The EORTC QLQ-C30 (version 3.0) contains 30 questions organized into five functional scales (physical, role, emotional, cognitive, and social), three symptoms scales (fatigue, pain, and nausea and vomiting), a global health/QoL scale, a single items assessing additional symptoms (dyspnea, sleep disturbance, constipation, and diarrhea), and perceived financial impact. This questionnaire has already been validated in a wide range of cancer patient populations (*EORTC QLQ-C30 Scoring Manual, QL Coordinator*). It has been translated and validated for use with Dutch patients.

#### 2.3.1.2 EORTC QLQ-H&N35 questionnaire

The EORTC QLQ-H&N35 contains 35 questions assessing symptoms and side effects of treatment, social function in and body image/sexuality. It consists of only one scale, the symptom scale, which consist questions regarding pain, swallowing, sense problems, trouble with social eating, trouble with social contact, and less sexuality. There are also single items assessing additional symptoms and problems; teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, painkillers, nutritional supplements, weight loss, and weight gain. (*EORTC QLQ-C30 Scoring Manual, QL Coordinator*)
As recommended by the EORTC, scores were linearly converted to a scale ranging from 0 to 100. For the functional and global health status/QoL scales, higher scores represent a better level of functioning. For the symptom scales, higher scores represent a greater degree of symptoms. (*EORTC QLQ-C30 Scoring Manual, QL Coordinator*)

### 2.4 Variables

The QoL data were extended by gathering variables, such as patients’ characteristics, tumor characteristics, treatment and follow-up data (for the detailed list of the variables, see the table below), from the electronic patient dossier of the UMCG. In case of missing data the paper based charts were also reviewed.

<table>
<thead>
<tr>
<th>Variables</th>
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<td><strong>Sociodemographic</strong></td>
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<td><strong>Clinical Variables</strong></td>
<td></td>
</tr>
<tr>
<td>o Tumor site</td>
<td></td>
</tr>
<tr>
<td>o Tumor subsite</td>
<td></td>
</tr>
<tr>
<td>o Nodal status</td>
<td></td>
</tr>
<tr>
<td>o Localization of the metastasis</td>
<td></td>
</tr>
<tr>
<td>o TNM classification and stage</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>o Histological type</td>
<td></td>
</tr>
<tr>
<td>o Differentiation grade</td>
<td></td>
</tr>
</tbody>
</table>
- Extracapsular spread
- Perineural growth
- Angiovasion
- Resection margin

**Treatment**
- Therapy intention
- Therapy modality
- Date of therapy
- (C)RT dose

**Follow-up data**
- Follow-up time
- Date of recurrence
- Type of recurrence
- Survival status
  - No evidence of disease (NED)
  - Alive with disease (AWD)
  - Dead of disease (DOD)
- Dead of other cause (DOC)

### 2.5 Statistical analysis
First, descriptive statistical analysis was used to describe the population and QoL outcome. QQ plots were used to check for normality, and if needed (log) transformations were performed to correct for problems with normality and the assumption of homogeneity of variance. Frequency tables were made for every question separately and displayed in histograms. In addition, according to EORTC guidelines for handling QoL questionnaires, the questions were transformed into scales ranging from 0 to 100. For the functioning and global QoL scales, higher scores represent better function/QoL. For the symptom scales, higher scores represent more symptoms.

QoL changes over time in the different treatment groups were analyzed first by comparing means, using the Mann-Whitney test or T-test for continuous variables whenever appropriate and Wilcoxon-Mann Whitney test for ordinal variables.

Logistic regression was applied to identify predictors for QoL changes. The categorical variables were analyzed using the Chi-Square test and when <80% of the tables had an expected count of less than 5, the Fisher’s exact test was used. Furthermore baseline differences were corrected for using significant predictors at univariate test were further analyzed by ANOVA mixed model analysis to determine independent predictors for QoL change.

### 2.6 Ethical consideration
#### 2.6.1 Regulation statement
The study was conducted according to the principles of the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, latest amendment 59th WMA General Assembly, Seoul, Korea, October 2008) and in accordance with the Medical Research Involving human Subjects Act (WMO) and other guidelines, regulations and Acts.
Regarding the observational and retrospective nature of this study, it is not needed to obtain approval from the Ethics Committee. Only anonymized data were used during statistical analysis, to secure the privacy of the patients.
3: Results

3.1 Patient population
Initially, 278 patients were identified in the database. Based on the eligibility criteria, 33 patients were excluded. Patients were excluded for the following reasons: there was one patient with a tongue base carcinoma instead of a larynx or hypopharynx carcinoma. Two patients had stage II instead of stage III-IV. From three patients, no QoL results were available in the database, while in 23 patients therapy data were missing. Two patients had a histology other than squamous-cell carcinoma (SCC) or large cell undifferentiated carcinoma, one patient had small-cell carcinoma and one patient had carcinoma ex pleomorphic adenoma.

Eventually, the study population was composed of 247 patients that met all eligibility criteria.

3.2 Descriptive analysis
Patients’ age at start of radiotherapy ranged from 41-95 years. The most relevant patient’s characteristics are listed in Table 4, while the remainder of these results is included in the appendix.

Most patients (82.0%) were primarily treated with non-surgical treatment modalities (Table 4). The majority of patients were male (79.4%) and had SCC carcinoma (96.4%). Most tumors were considered resectable (78.3%), including 36.0% who were regarded as functionally irresectable (meaning the tumor is resectable from a technical point of view, but is considered not acceptable when the remaining function is taken into account).

<table>
<thead>
<tr>
<th>Categorical variable</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy modality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>73</td>
<td>29.6</td>
</tr>
<tr>
<td>RT</td>
<td>125</td>
<td>50.6</td>
</tr>
<tr>
<td>TLE + (C)RT</td>
<td>49</td>
<td>19.8</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>196</td>
<td>79.4</td>
</tr>
<tr>
<td>Female</td>
<td>51</td>
<td>20.6</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>238</td>
<td>96.4</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Undifferentiated cell carcinoma (UCC)</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Resectability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resectable</td>
<td>144</td>
<td>58.3</td>
</tr>
<tr>
<td>Functional irresectable</td>
<td>89</td>
<td>36.0</td>
</tr>
<tr>
<td>Technical irresectable</td>
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<td>5.3</td>
</tr>
<tr>
<td><strong>Differentiation grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (good)</td>
<td>7</td>
<td>2.8</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>152</td>
<td>61.5</td>
</tr>
<tr>
<td>Grade 3 (bad)</td>
<td>22</td>
<td>8.9</td>
</tr>
<tr>
<td>Grade 4 (undifferentiated)</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Not Otherwise specified</td>
<td>62</td>
<td>25.1</td>
</tr>
<tr>
<td><strong>RT location</strong></td>
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<td></td>
</tr>
<tr>
<td>Locale RT</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Locale RT + ipsilateral neck 4 1.6
Locale RT + neck both sides 239 97.6
Ipsilateral neck 1 0.4

WHO Score
WHO 0 125 50.6
WHO 1 85 34.4
WHO 2 21 8.5
WHO 3 7 2.8
WHO missing 9 3.6

T Stage
T1 12 4.9
T2 29 11.7
T3 113 45.7
T4 93 37.7

N Stage
N0 83 33.6
N1 33 13.4
N2a 3 1.2
N2b 53 21.5
N2c 67 27.1
N3 7 2.8
Nx 1 0.4

Localization
Postcricoid 3 1.2
Sinus Piriformis 52 21.1
Hypopharyngeal wall 32 13.0
Supraglottic 93 37.7
Glottic 58 23.5
Subglottic 6 2.4
Transglottic 3 1.2

Table 4. Frequency and percentage of categorical variables.

3.2.1 Analysis of the categorical data
We analyzed the relevant categorical data using Fisher’s exact test of the chi-square test whenever appropriate (table 5).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-surgical treatment</th>
<th>Surgical treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>Ns</td>
</tr>
<tr>
<td>Male</td>
<td>157 79.3%</td>
<td>39 79.6%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 20.7%</td>
<td>10 20.4%</td>
<td></td>
</tr>
<tr>
<td>T-stage</td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>T1</td>
<td>10 5.0%</td>
<td>2 4.1%</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>28 14.1%</td>
<td>1 2.0%</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>105 53.0%</td>
<td>8 16.3%</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>55 27.8%</td>
<td>38 77.6%</td>
<td></td>
</tr>
<tr>
<td>N-stage</td>
<td></td>
<td></td>
<td>Ns</td>
</tr>
<tr>
<td>-----------</td>
<td>---</td>
<td>---</td>
<td>-------</td>
</tr>
<tr>
<td>N0</td>
<td>65</td>
<td>32.8%</td>
<td>18</td>
</tr>
<tr>
<td>N0</td>
<td>23</td>
<td>11.6%</td>
<td>10</td>
</tr>
<tr>
<td>N0</td>
<td>21</td>
<td>1.0%</td>
<td>1</td>
</tr>
<tr>
<td>N0</td>
<td>40</td>
<td>20.2%</td>
<td>13</td>
</tr>
<tr>
<td>N0</td>
<td>61</td>
<td>30.8%</td>
<td>6</td>
</tr>
<tr>
<td>N0</td>
<td>6</td>
<td>3.0%</td>
<td>1</td>
</tr>
<tr>
<td>Nx</td>
<td>1</td>
<td>0.5%</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>Histology</th>
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<th></th>
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</thead>
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<tr>
<td>SCC</td>
<td>191</td>
<td>96.5%</td>
<td>44</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>0</td>
<td>0.0%</td>
<td>2</td>
</tr>
<tr>
<td>OGC</td>
<td>4</td>
<td>2.0%</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1.5%</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resectability</th>
<th></th>
<th></th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>96</td>
<td>48.7%</td>
<td>44</td>
</tr>
<tr>
<td>Functional irresectable</td>
<td>88</td>
<td>44.7%</td>
<td>0</td>
</tr>
<tr>
<td>Technical irresectable</td>
<td>13</td>
<td>6.6%</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Differentiation grade</th>
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<th>p&lt;0.05</th>
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</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>5</td>
<td>2.5%</td>
<td>2</td>
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<td>Grade 2</td>
<td>115</td>
<td>58.1%</td>
<td>37</td>
</tr>
<tr>
<td>Grade 3</td>
<td>16</td>
<td>8.1%</td>
<td>6</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4</td>
<td>2.0%</td>
<td>0</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>58</td>
<td>29.3%</td>
<td>4</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>WHO-score</th>
<th></th>
<th></th>
<th>p&lt;0.05</th>
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</thead>
<tbody>
<tr>
<td>WHO 0</td>
<td>109</td>
<td>55.1%</td>
<td>16</td>
</tr>
<tr>
<td>WHO 1</td>
<td>62</td>
<td>31.3%</td>
<td>23</td>
</tr>
<tr>
<td>WHO 2</td>
<td>16</td>
<td>8.1%</td>
<td>5</td>
</tr>
<tr>
<td>WHO 3</td>
<td>6</td>
<td>3.0%</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>2.5%</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th>Target area</th>
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</thead>
<tbody>
<tr>
<td>Local RT</td>
<td>1</td>
<td>0.5%</td>
<td>0</td>
</tr>
<tr>
<td>Local RT + ipsilateral neck</td>
<td>4</td>
<td>2.0%</td>
<td>0</td>
</tr>
<tr>
<td>Local RT + both sides of neck</td>
<td>190</td>
<td>96.9%</td>
<td>48</td>
</tr>
<tr>
<td>Ispilateral neck</td>
<td>0</td>
<td>0.0%</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Localization</th>
<th></th>
<th></th>
<th>Ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcricoid</td>
<td>3</td>
<td>1.5%</td>
<td>0</td>
</tr>
<tr>
<td>Sinus Piriformis</td>
<td>29</td>
<td>19.7%</td>
<td>13</td>
</tr>
<tr>
<td>Hypopharyngeal wall</td>
<td>26</td>
<td>13.1%</td>
<td>6</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>Supraglottic</td>
<td>78</td>
<td>39.4%</td>
<td>15</td>
</tr>
<tr>
<td>Glottic</td>
<td>45</td>
<td>22.7%</td>
<td>13</td>
</tr>
<tr>
<td>Subglottic</td>
<td>4</td>
<td>2.0%</td>
<td>2</td>
</tr>
<tr>
<td>Transglottic</td>
<td>3</td>
<td>1.5%</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5. Results of the Fisher’s exact test and chi-square test performed on the categorical variables.

Only the variables T-stage, resectability and differentiation grade differed significantly between the surgical and non-surgical patients. In addition, a significant difference was found with regard to WHO performance status, with more favorable WHO-scores in the non-surgical treatment group. For the other pre-treatment variables, the two treatment groups were well balanced.

3.3 Head and neck cancer symptoms

The EORTC QLQ-H&N35 was used to assess patient-rated head and neck cancer symptoms. The relevant results of the comparison between the two treatment groups are listed below. Other results are included in the appendix (table 6 – 37)

3.3.1. Cough

The results with regard to patient-rated cough in the two treatment groups are summarized in Figure 3.1.

The univariate analysis showed that patients treated with the non-surgical approach had significantly higher scores for cough at baseline than those treated with primary (CH)RT (p=0.008). Significant differences were also found at week 6 during treatment and at 6 and 12 months after completion of treatment.

Figure 3.1: Mean scores for patient-rated COUGH between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.

The repeated measures ANOVA corrected for baseline cough for week 1 to 12 revealed a significant increase of cough over time (p=0.004) but this change over time did not depend on the treatment strategy. Similar results were found for cough at later time points (M6 to M24).
3.3.2. Dysphagia

The results with regard to patient-rated dysphagia in the two treatment groups are summarized in Figure 3.2.

The univariate analysis showed no significant difference for dysphagia at baseline (p=0.173) between the two treatment groups.

![Figure 3.2: Mean scores for patient-rated DYSPHAGIA between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.](image)

The repeated measures ANOVA with correction for baseline dysphagia for 1 to 12 weeks revealed a significant increase of dysphagia over time (p<0.001) with significantly higher scores (p=0.004) during this period for patients treated with primary (CH)RT. This was, however a transient effect and the difference disappeared at 12 weeks.

The repeated analysis ANOVA for late dysphagia from 6 to 24 months after completion of treatment did not show a significant difference anymore between the two treatment groups.

3.3.3. Tube feeding

The results with regard to patient-rated tube feeding in the two treatment groups are summarized in Figure 3.3.

The univariate analysis showed that patients treated with the surgical approach had significantly higher scores for the use of tube feeding at baseline than those treated with primary (CH)RT (p=0.003). Significant differences were also found at week 1 and 2 during treatment and at 12 months after completion of treatment.
The repeated measures ANOVA with correction for baseline tube feeding from 6 to 24 months after completion of treatment revealed a significant increase of tube feeding over time (p<0.001) with significantly higher scores (p<0.05) during this period for patients treated with primary (CH)RT. This was a permanent effect. No such relationship was found for acute feeding tube dependence.

3.3.4. Nutritional supplements
The results with regard to use of nutritional supplements in the two treatment groups are summarized in Figure 3.4.

The univariate analysis showed that patients treated with the surgical approach had significantly higher scores for the use of nutritional supplements at baseline than those treated with non-surgical approach (p=0.003). Significant differences were also found at week 1 and 2 during treatment and at 12 months after completion of treatment.

The repeated measures ANOVA with correction for baseline use of nutritional supplements for week 1-12 revealed a significant increase over time. This was, however, a transient effect and the difference disappeared at 12 weeks.

The repeated measures ANOVA for late nutritional supplement use from 6 to 24 months after completion of treatment did show a significant difference (p=0.027) between the two treatment groups with significantly higher scores during this period for patients treated with the surgical approach. This was, however, a transient effect and the difference disappeared at 18 months.
3.3.5. Social eating
The results with regard to social eating in the two treatment groups are summarized in Figure 3.5.
The univariate analysis showed no significant difference for social eating at baseline between the two treatment groups. However, patients treated with primary (CH)RT developed significantly more problems with social eating from week 5 during treatment up to week 12.

The repeated measures ANOVA corrected for baseline problems with social eating revealed a significant increase of problems with social eating over time but these changes over time did not significantly depend on treatment strategy.
3.3.6. Opening mouth
The results with regard to patient-rated use of opening mouth in the two treatment groups are summarized in Figure 3.6. The univariate analysis showed that patients treated with the surgical approach had significantly higher scores for difficulties with opening their mouth at baseline than those treated with primary (CH)RT (p=0.006). Significant differences were also found at week 2 during treatment.

![Image of Figure 3.6: Mean scores for patient-rated OPENING MOUTH between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.]

The repeated measures ANOVA corrected for baseline showed that opening mouth over time did not depend on the treatment strategy.

3.3.7. Head and neck pain
The results with regard to patient-rated use of head and neck pain in the two treatment groups are summarized in Figure 3.7. The univariate analysis showed that patients treated with the surgical approach had significantly lower scores for head and neck pain than those treated with primary (CH)RT. The repeated measures ANOVA corrected for baseline head and neck pain revealed a significant transient increase of head and neck pain over time but these changes over time did not depend on the treatment strategy.
3.3.8. Pain killer use
The results with regard to the use of pain killers in the two treatment groups are summarized in Figure 3.8.
The univariate analysis showed no significant difference in the score of pain killer use at baseline. However, at week 3 to 12, patients treated with the primary (CH)RT used significantly more pain killers than those treated with the surgical approach.

The repeated measures ANOVA with correction for baseline use of pain killers for 1 to 12 weeks revealed a significant increase of use of pain killers over time (p=0.021) with significantly higher scores during this period for patients treated with primary (CH)RT. This was, however a transient effect and the difference disappeared at 6 months.
3.3.9. Problems with senses
The results with regard to problems with senses in the two treatment groups are summarized in Figure 3.8.
The univariate analysis showed that patients treated with the surgical approach had significantly higher scores for problems with their senses at baseline than those treated with primary (CH)RT (p<0.001). Significant differences were also found during the entire treatment (week 1 to week 12) and at 6, 12, 18 and 24 months after completion of treatment.

![Figure 3.9: Mean scores for patient-rated PROBLEMS WITH SENSES between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.](image)

The repeated measures ANOVA corrected for baseline problems with senses for week 1 to 24 months revealed a significant increase of problems with senses over time but this change over time did not depended on the treatment strategy.

3.3.10. Problems with speech
The results with regard to problems with speech in the two treatment groups are summarized in Figure 3.10.
The univariate analysis showed no significant difference in the score of problems with speech at baseline. However, at week 5 to 7 patients treated with the primary (CH)RT had significantly higher scores for problems with speech than those treated with surgical approach.
The repeated analysis ANOVA for problems with speech for 3 to 7 weeks revealed a significant increase of problems with speech over time (p=0.01) with significantly higher scores during this period for patients treated with primary (CH)RT. No differences were noted anymore after completion of treatment and during longer follow up.
3.3.11. Sticky saliva
The results with regard to sticky saliva in the two treatment groups are summarized in Figure 3.11.

The univariate analysis showed no significant difference in the score of problems with sticky saliva at baseline. However, at week 3 to 12 during the treatment and 6 to 18 months after completion of treatment patients treated with the primary (CH)RT had significantly higher scores for sticky saliva than those treated with surgical approach.

Figure 3.11: Mean scores for patient-rated STICKY SALIVA between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.

The repeated analysis ANOVA for problems with speech for 1 to 12 weeks revealed a significant increase of problems with sticky saliva over time (p=0.003) with significantly
higher scores during this period for patients treated with primary (CH)RT. This was, a permanent effect.

3.3.12. Problems with teeth
The results with regard to problems with teeth in the two treatment groups are summarized in Figure 3.12.
The univariate analysis showed that patients treated with the primary (CH)RT had significantly higher scores for problems with teeth at baseline than those treated with surgical approach (p=0.047). Significant differences were also found at 18 months after completion of treatment.

![Figure 3.12: Mean scores for patient-rated PROBLEMS WITH TEETH between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.](image)

The repeated measures ANOVA with correction for baseline problems with teeth for 1 to 12 weeks revealed a significant increase of problems with teeth over time (p=0.006) with significantly higher scores during this period for patients treated with primary (CH)RT. This was, however a transient effect.
The repeated analysis ANOVA for late problems with teeth from 6 to 24 months after completion of treatment revealed a significant increase of problems with teeth over time (p=0.042) with significantly higher scores during this period for patients treated with primary (CH)RT. This was a small but permanent effect.

3.4 Quality of life
The EORTC QLQ-C30 was used to the more general dimensions of quality of life. The results of the comparison between the two treatment groups are listed below.

3.4.1. Physical functioning
The results with regard to physical functioning in the two treatment groups are summarized in Figure 3.13.
The univariate analysis showed no significant difference in the score of physical functioning at baseline. However, at week 12 patients treated with the surgical approach had significantly (p=0.007) higher scores for physical functioning than those treated with primary (CH)RT.
The repeated measures ANOVA corrected for baseline physical functioning for the late effect revealed that the difference did not depend on the treatment strategy.

3.4.2. Role functioning
The results with regard to role functioning in the two treatment groups are summarized in Figure 3.14.

The univariate analysis showed no significant difference in the score of role functioning at baseline. However, at 24 months patients treated with the surgical approach had significantly (p=0.042) higher scores for role functioning than those treated with primary (CH)RT.

The repeated measures ANOVA corrected for baseline role functioning for the late effect revealed that the difference did not depend on the treatment strategy.
3.4.3. Social functioning
The results with regard to social functioning in the two treatment groups are summarized in Figure 3.15. The univariate analysis showed that patients treated with the primary (CH)RT had significantly higher scores for social functioning at baseline than those treated with surgical approach (p=0.012).

Figure 3.15: Mean scores for SOCIAL FUNCTIONING between the patients treated with (CH)RT versus patients treated with surgery followed by postoperative (CH)RT.

The repeated measures ANOVA corrected for baseline social functioning for the late effect revealed that the difference was not depended on the treatment strategy.

3.4.4. Cognitive functioning
The results with regard to cognitive functioning in the two treatment groups are summarized in Figure 3.15. The univariate analysis showed no significant difference in the score of cognitive functioning at baseline. However, at week 12, 12 months and 24 months patients treated with the surgical approach had significantly (p<0.05) higher scores for cognitive functioning than those treated with primary (CH)RT. The repeated measures ANOVA corrected for baseline cognitive functioning for the late effect revealed that the difference was not depended on the treatment strategy.
3.4.5 Emotional functioning
The results with regard to emotional functioning in the two treatment groups are summarized in Figure 3.17. The univariate analysis showed no significant difference in the score of emotional functioning at baseline. However, at week 12 patients treated with the surgical approach had significantly (p=0.009) higher scores for emotional functioning than those treated with primary (CH)RT.

3.4.6 Global quality of life

The repeated measures ANOVA corrected for baseline emotional functioning revealed that the difference was not depended on the treatment strategy.
The results with regard to global quality of life in the two treatment groups are summarized in Figure 3.18.

The univariate analysis showed no significant difference in the score of global quality of life at baseline. However, at week 12 patients treated with the surgical approach had significantly (p=0.0029) higher scores for global quality of life than those treated with primary (CH)RT.

3.5 Variables

In the appendix the variables which were significant are included in table 38 and 39. We have made a distinction between the treatment group.
4: Discussion

The aim of this research project was to compare patient-rated outcome measures (PROMs) between patients treated with primary surgery followed by adjuvant (CH)RT and patients treated with definitive (CH)RT and to test the hypothesis that patients treated with the non-surgical approach would have a worse QoL. For this purpose, we tested a number of head and neck cancer symptoms as assessed by the EORTC QLQ-H&N35 questionnaire and the more general dimensions of QoL with the EORTC QLQ-C30 questionnaire. These were conducted on several time points during and after completion of the treatment, in order to compare the difference in the outcome measures in the course of time.

The results obtained from the EORTC QLQ-H&N35 questionnaire did show a difference between the two treatment strategies with a tendency towards more local head and neck cancer symptoms over time among those treated with definitive (CH)RT. These differences, however, did not translate in significant differences in time with regard to the more general dimensions of quality of life as assessed with the EORTC QLQ-C30 questionnaire.

In the surgical treatment group, an increased use of nutritional supplement was reported compared to use of patients in the non-surgical therapy group. However, at 18 months after completion of treatment there was no significant difference between the treatment groups. Patients primary treated with (CH)RT reported significantly more problems with their teeth, dysphagia and sticky saliva compared to the patients in the surgical treatment group. The problems with their teeth were present during the treatment and after having completed the treatment. The increase in problems with dysphagia and sticky saliva were only present during the treatment. There was no significant difference between the treatment groups after completing the treatment. Patients treated primarily with (CH)RT used significantly more pain killers during the treatment compared to the patients treated with definitive (CH)RT. They also reported an increased need for tube feeding.

There are a number of reasons why patients treated with definitive (CH)RT experienced more of the abovementioned symptoms. In the primary setting, the total dose administered to the primary tumor site and pathological lymph nodes is 70 Gy and thus significantly higher than used in the postoperative setting where the total dose varies between 56 and 66 Gy depending on the pathological report. Consequently, the total dose administered in the healthy surrounding tissues is much higher in the primary setting. Second, in some cases, the elective nodal areas irradiated can be limited in the postoperative setting based on the pathology findings resulting in markedly lower dose levels in the parotid glands and swallowing structures. These dose differences may well explain the findings of more radiation-induced symptoms as the damage to the normal tissues is mainly depending on dose and volume of irradiated tissues.

A surprising finding was that patients treated with definitive (CH)RT developed more problems with speech during the course of treatment than those treated with TLE while we expected that after TLE more problems with speech would have been reported. There are a number of possible explanations for this finding. First, it could be hypothesized that patients treated with TLE physically and emotionally adapt to the change in their ability to speech after surgical removal of the larynx. Second, the question posed in the EORTC questionnaire (“Do you have problems with speech?”) is sometimes misinterpreted by patients, answering “not at all”, while they cannot speak anymore. By asking individual patients to this apparent discrepancy, patients answer that they could not have problems with speech if they were not able to speak at all. In addition, the compliance of answering this question among the surgically treated patients was lower, meaning that a number of patients did not answer the question at all. Consequently, the outcome of the findings on problems with speech in
probably underestimated in patients who underwent TLA and therefore these results should be interpreted with caution.

4.1 Prospective assessment of QoL
We used of questionnaires consisting of the most important items concerning the effects of treatment for hypopharyngeal and laryngeal carcinoma and thus most relevant for patients dealing with the consequences of their cancer and their treatment. Completing the questionnaires prospectively reduces the possibility of a time bias. Patients don’t have to remember how they were feeling in the past, but can fill the questionnaire based on how they are currently feeling or affected by the treatment. This reduces the change of bias.

When the questionnaires are completed on specific time points, as was done in the current follow up program, it is easier to compare the results between groups. In this way, a mean score representing the results of the entire treatment group at specific time point can be presented and analyzed. Looking at the scores at several time points gives the possibility to evaluate progress or deterioration made by the patients individually and by the treatment groups in general. It also allows us to get a better understand of the effects of the treatment.

4.2 Previous research
These results found in this project are more or less consistent with previous studies. In this regard, Metreau A et al. (2013) neither found significant differences in overall QoL scores between patients treated with primary surgery and those treated with definitive (CH)RT. They also found that in the non-surgical group, more difficulties with having a dry mouth was observed and an increase in weight loss. These results are consistent with our findings. However, in that study more difficulties with smell and taste in the surgical treatment group was found compared to that in the non-surgical group, which is exactly opposite to what was observed in our study. The study did however have a smaller sample size compared to our study. Furthermore, they only had the questionnaires filled in one year after receiving treatment. Therefore, it was not possible to look for changes over time.

A lack of significant differences in the more general QoL scores between surgically and non-surgically patients has been found by other investigators as well (Al-Mamgani A et al. (2012), Al-Mamgani A et al. (2012), Hanna, E., Sherman, A., Cash, D., Adams, D., Vural, E., Fan, C. Y., & Suen, J. Y. (2004), and Müller, R., Paneff, J., Köllner, V., & Koch, R. (2001)). However, other researches did find a difference in the global QoL score between the treatment modalities. Some authors (Williamson JS et al. (2011); Boscolo–Rizzo, P., Maronato, F., Marchiori, C., Gava, A., Mosto, D., & Cristina, M. (2008)) found higher global QoL scores in the non-surgical treatment groups. In the study of Al-Mamgani only hypopharyngeal carcinoma patients were included. Patients were divided into two treatment modality groups, one treated with neck dissection + (C)RT and one treated by (C)RT. The results showed a significantly improved functional outcome in patients treated with (C)RT alone as compared that observed among those treated with neck dissection and (C)RT. There was a decrease of xerostomia reported. In the cross-sectional study of Williamson JS, et al (2011) the questionnaires were completed after therapy only. They found higher global QoL scores in the treatment group which only received RT. The treatment group that received CRT or surgery with CRT had the lowest global QoL scores. In our study, we did not separate the RT and CRT group, which may explain why there is a difference in the results. Boscolo-Rizzo (2008) et al. reported on a study with two groups treated with TLE + RT and CRT. Therefore, the results are difficult to compare with the results of the current study, also because they only assessed QoL after treatment without having any information at baseline.

In contrast to our findings, Burnip E et al. (2013) found better swallowing capacities in the non-surgical treatment group compared to those treated with surgery, but these findings...
were confined to the group of patients treated with RT alone, while no such difference was found for those treated with CRT. In addition, Williamson JS et al. (2011) and Boscolo–Rizzo, P. et al. (2008) found more problems with speech in the surgically treated group. Hamid, OA. et al. (2011) also found more problems with senses, social eating, and social contact and swallowing function in the surgical treatment group. In these studies however, only laryngeal carcinoma patients were included. Hanna E. et al. (2004) found more difficulties in the surgical treatment group concerning the variables use of painkillers, and coughing.

The problem with the literature is that most researches performed cross sectional studies with assessment of QoL after completion of treatment. Therefore, no comparisons can be made between the QoL scores during and after completing treatment or a comparison of the QoL in the course of time. In addition, in most cases, QoL was only assessed at one time point instead of at several time points. This is problematic as we found that for some symptoms, differences between treatment groups were found at certain time points, which were not significant anymore when corrected for baseline symptoms. In addition, the symptom scores and QoL scores showed decreases and increases over time, meaning that comparisons between groups cannot be made reliably if the time intervals relative to the end of treatment are different. In most of the studies reporting on QoL, this information is lacking, which makes the interpretation of these studies very difficult. Other differences between our research and others was the tumor site. Our study included both hypopharyngeal as well as laryngeal carcinoma. Whereas most other study focused only on one location, most frequently laryngeal carcinoma. The treatment modalities also frequently differed compared to our research.

4.3. Effect of differences in pre-treatment variables

One of the problems of this analysis is the retrospective design of this analysis, although the QoL data were prospectively assessed. Due to the non-randomized design of this study, patient groups were not well balanced with regard to a number of pre-treatment variables. We found a significant difference between the two treatment groups in resectability, with more functionally and technically irresectable patients in the non-surgical treatment group.

In addition, patients treated with definitive (CH)RT had significantly less advanced T-stages but significantly more advanced N-stages. These differences may very well explain at least partly the differences found in the mean scores for a number of symptoms. E.g., irresectable patients and patients with more advanced N-stages normally suffer from more symptoms and require larger radiation portals than their counterparts. Therefore, the higher rates of head and neck cancer symptoms found in the group of patients treated with (CH)RT can very well be explained by these factors and not by the treatment itself.

Patients treated with surgery had worse WHO performance scores prior to radiation treatment, which is most probably due to the fact that they were operated upon and were functionally impaired by their recent TLE. In other studies as well as in ours, there is a significant correlation between the general QoL dimensions and WHO performance status. This may very well explain the somewhat lower scores at baseline for some functioning scales (e.g. social functioning).

The removal of the larynx lead to having to breathe through a stoma. Breathing through a stoma can also influences the functioning of the senses. The cells needed for the sensation of smell are located in your nose. If the nose is not used when breathing it can influence the ability to smell. The ability to smell is again needed for the sensation of taste. Losing your ability to smell can decreases the tastes you are able to taste. This can perhaps cause difficulties communicating and it may also because of the change in appearance cause patients to have uncertainties about their appearance. This could be seen in our results, which showed that patients in the surgical treatment group felt more disturbed about their
appearance and a greater decrease in the patients’ ability to open their mouths, the functioning of their senses (in this case the senses smell and taste) and their interaction with their social contacts compared to the patients in the non-surgical therapy group.

Patients treated with definitive (CH)RT reported having more problems with pain, swallowing difficulties, dry mouth, sticky saliva, coughing, speech, and the general feeling of being ill. The problems can be caused by radiation induced tissue damage. This treatment group received higher dose levels of radiation. The pain problems were mainly located in the mouth and throat. It was present during swallowing of liquid, pureed and solid food. This caused an increase in problems with eating and the ability of enjoying their meals. Patients also reported a more difficult time with eating in the company of their family. There was also an increase in the use of pain killers, which can be explained by the increase in pain. The need for tube feeding was also increased. This can be explained by the problems with swallowing, having a dry mouth or sticky saliva. These problems can make it more difficult to eat, which can lead to having the patients choose for using a device to help them with their eating difficulties. They also reported more choking experiences, and having a hoarse voice. All these problems resulted in problems with social contact such as difficulties talking with others, but also having a hard time going outside the house. In contrary to the surgical treatment group reporting an increase in their weight, the non-surgical treatment group there was an increase in reporting weight loss.

The surgical treatment group patients reported more difficulties with performing strenuous activities, whereas non-surgical treatment group patients reported more difficulties with short walks. The problems of performing strenuous activities in the surgical treatment group can be caused by having to breathe through a stoma. The surgical treatment group patients also reported frequently having to stay in a chair or bed during the daytime and being restricted in their work, daily activity, family life, and social abilities. They reported more need for rest, difficulties sleeping, feeling weak, lack of appetite, feeling tired, difficulties concentrating, feeling tense, worrying, and problems with their memory. Even though they had reported significantly more problems, they did report a higher rate of their overall health and a higher QoL score during the past week compared to the patients of the non-surgical treatment group.

4.4 Recommendations and implications

QoL is a subjective method of measurement, which may have several limitations. The questions can be misunderstood as mentioned before, information important for representing the QoL score can be missed, and the time points may not represent the change in QoL well. In addition, some questions were not completed. Reasons why questions or forms were not completed are not provided and not always clear and therefore it remains unclear to what extent this influenced the results. Especially, questions related to sexual functioning were lacking in many patients and were therefore not further analyzed in this report.

The study contains retrospective combined with prospectively elements. The questionnaires were filled in prospectively, but the statistical analysis was conducted retrospectively. Attempts were made to complete missing data retrospectively as much as possible but not all missing data could be recovered.

We did not investigate for predictive factors which might influence the QoL score. Possible predictive factors might be patient factors like age or comorbidity. Other factors might be tumor factors (e.g. stage, primary site) or treatment factors (e.g. the kind of chemotherapy). In our research we did not make a separation between the laryngeal and hypopharyngeal carcinoma patients. Location of the carcinoma might be an influencing factor in the QoL score.
Further investigation is needed wherein QoL questionnaire are filled in after diagnosis and before, and during TLE treatment. Such studies should be fully conducted prospectively. Predictive factors should be investigated and corrected for statically. Missing values should also be statistically corrected for.

The most ideal study design to compare primary surgery followed by postoperative RT of CHRT versus definitive (CH)RT, would be a randomized controlled trial (RCT). However, these RCT’s have been performed in the past and showed that overall survival is similar between the two strategies but with significantly higher rates of a functional larynx. Unfortunately, in these studies QoL was not addressed and it is unlikely that such a study will ever be performed given the results of these RCT’s. The only way to assess QoL is thus by prospective observational studies as done in the current project, which however has a number of methodological problems.
5: Conclusion

Our results showed no differences between the treatment groups regarding functioning and overall global QoL score. Therefore, our hypothesis that patients in the non-surgical treatment group would have worse QoL scores compared to patients in the surgical treatment group could not be confirmed. The changes found in the different QoL items did mostly not depend on the treatment modality that the patients had received.

Some local head and neck cancer symptoms were more frequently observed among patients treated with definitive (CH)RT, in particular during the course of treatment, but in the long term, no significant differences were found for most of these symptoms neither. Based on these results, it cannot be concluded that long term QoL is not depended on the form of treatment.
6: References


Figure 1:

Figure 2.
http://learnhumananatomy.com/larynx/

Table 3.


Figure 3.

Figure 4.
7. Appendix

Repeated Measures ANOVA

<table>
<thead>
<tr>
<th>Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value</th>
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Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

Table 6. Cough

Repeated Measures ANOVA

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Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

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Soort radiotherapie

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| Significance | 0.001 | 0.008 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.003 | 0.001 | 0.001 |
### Table 7. Dry mouth

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### Table 8. Dysphagia

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### Table 9. Tube feeding

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Repeated Measures ANOVA

Table 10. Felt ill

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Repeated Measures ANOVA

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

p-value: 0.014
Effect pattern: Permanent

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

p-value: ns
Effect pattern: Transient

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

p-value: ns
Effect pattern: Permanent

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

p-value: ns
Effect pattern: Transient

Table 11. Nutritional support

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Repeated Measures ANOVA

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

p-value: ns
Effect pattern: Permanent

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

p-value: ns
Effect pattern: Transient

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

p-value: ns
Effect pattern: Permanent

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

p-value: 0.027
Effect pattern: Transient more use of nutritional supplements in postoperative patients

Table 11. Nutritional support
## Repeated Measures ANOVA

<table>
<thead>
<tr>
<th>Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value</th>
<th><strong>p-value</strong></th>
<th><strong>Effect pattern</strong></th>
</tr>
</thead>
<tbody>
<tr>
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<td>Permanent</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th><strong>p-value</strong></th>
<th><strong>Effect pattern</strong></th>
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<th><strong>Effect pattern</strong></th>
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### Table 12. Opening mouth

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<th>W2</th>
<th>W3</th>
<th>W4</th>
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<th>W6</th>
<th>W7</th>
<th>W12</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
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<td>14</td>
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<td>Surgically</td>
<td>Mean</td>
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<td>14</td>
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### Table 13. HN pain

<table>
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<th><strong>p-value</strong></th>
<th><strong>Effect pattern</strong></th>
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</thead>
<tbody>
<tr>
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<table>
<thead>
<tr>
<th>Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value</th>
<th><strong>p-value</strong></th>
<th><strong>Effect pattern</strong></th>
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<tbody>
<tr>
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</tbody>
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<table>
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<th>Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value</th>
<th><strong>p-value</strong></th>
<th><strong>Effect pattern</strong></th>
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<th><strong>p-value</strong></th>
<th><strong>Effect pattern</strong></th>
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Table 14. Pain killer

<table>
<thead>
<tr>
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<th>Surgical Mean</th>
<th>Non-surgical Std. Error of Mean</th>
<th>Surgical Std. Error of Mean</th>
<th>Significance</th>
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<tr>
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<td>7</td>
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<td>43</td>
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</table>

Repeated Measures ANOVA

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

- p-value: ns
- Effect pattern: Permanent

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

- p-value: P=0.021
- Effect pattern: Transient

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

- p-value: ns
- Effect pattern: Permanent

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

- p-value: ns
- Effect pattern: Transient

Table 15. Social contact

<table>
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<th>Non-surgical Mean</th>
<th>Surgical Mean</th>
<th>Non-surgical Std. Error of Mean</th>
<th>Surgical Std. Error of Mean</th>
<th>Significance</th>
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</table>

Repeated Measures ANOVA

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

- p-value: p=0.034
- Effect pattern: Permanent

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

- p-value: ns
- Effect pattern: Transient

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

- p-value: ns
- Effect pattern: Permanent

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

- p-value: ns
- Effect pattern: Transient
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<th>T0</th>
<th>W1</th>
<th>W2</th>
<th>W3</th>
<th>W4</th>
<th>W5</th>
<th>W6</th>
<th>W7</th>
<th>W12</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
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<td>12</td>
<td>24</td>
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<td>1</td>
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</table>

Repeated Measures ANOVA

Table 16. Senses

- Effect of treatment arm on ACUTE symptoms (W1-W7 + W12)
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Permanent

- Effect of treatment arm on ACUTE symptoms (W1-W7 + W12)
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Transient

- Effect of treatment arm on LATE symptoms (M6-M24)
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Permanent

- Effect of treatment arm on LATE symptoms (M6-M24)
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Transient

Table 17. Social eating
### Table 18. Speech

<table>
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<tbody>
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<td>T0</td>
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<td>W2</td>
</tr>
<tr>
<td>Mean</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>N</td>
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Soort radiotherapie

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<th>Surgical</th>
</tr>
</thead>
<tbody>
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<td>W2</td>
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<tr>
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<tr>
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<td>171</td>
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### Repeated Measures ANOVA

<table>
<thead>
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<th>Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value</th>
<th>p-value</th>
<th>Effect pattern</th>
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<tbody>
<tr>
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Table 19. Sticky
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<th>M12</th>
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</table>

**Repeated Measures ANOVA**

Effect of treatment arm on ACUTE symptoms (W1-W7 + W12) CORRECTED for baseline value

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

**Table 20. Teeth**

**Repeated Measures ANOVA**

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

**Table 21. Weight gain**
### Table 22. Weight loss

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#### Repeated Measures ANOVA

- **Effect of treatment arm on ACUTE symptoms (W1-W7 + W12)**
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Permanent

- **Effect of treatment arm on LATE symptoms (M6-M24)**
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Transient

### Table 23. Physical functioning

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- **Effect of treatment arm on ACUTE symptoms (W1-W7 + W12)**
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Permanent

- **Effect of treatment arm on LATE symptoms (M6-M24)**
  - CORRECTED for baseline value
  - p-value: ns
  - Effect pattern: Transient
### Table 24. Role Functioning

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Repeated Measures ANOVA

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### Table 25. Social Functioning

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### Table 27. Emotional Functioning

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Repeated Measures ANOVA

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Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value

Table 27. Emotional Functioning
### Table 28. Global QoL score

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**Repeated Measures ANOVA**

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Table 29. Appetite loss

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**Repeated Measures ANOVA**

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**Significance**

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<th>Effect pattern</th>
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### Table 31. Diarrhoea

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**Significance**

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<th>Effect pattern</th>
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**Repeated Measures ANOVA**

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<th>p-value</th>
<th>Effect pattern</th>
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Table 33. Fatigue

### Table 33. Fatigue

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**Repeated Measures ANOVA**

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| Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value | ns | Transient |

Table 32. Dyspnoea

Table 33. Fatigue
### Table 34. Finance

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<th>M6</th>
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**Repeated Measures ANOVA**

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<th>p-value</th>
<th>Effect pattern</th>
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**Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value**

<table>
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<th>T0</th>
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<th>M12</th>
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**Repeated Measures ANOVA**

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**Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value**

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**Repeated Measures ANOVA**

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<th>Effect pattern</th>
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**Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value**

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**Table 35. Nauseau & Vomiting**
### Table 36. Pain

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**Repeated Measures ANOVA**

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**Effect of treatment arm on LATE symptoms (M6-M24) CORRECTED for baseline value**

Table 37. Insomnia
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<td>Was your mouth sensitive</td>
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<tr>
<td>Did you have pain in your throat</td>
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</tr>
<tr>
<td>Did you have pain swallowing when drinking</td>
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<tr>
<td>Did you have pain swallowing when eating mashed food</td>
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</tr>
<tr>
<td>Did you have pain swallowing when eating solid food</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you choke</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have difficulties opening your mouth</td>
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</tr>
<tr>
<td>Did you have a dry mouth</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Was your saliva sticky</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have problems with your sense of smell</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have problems with you taste</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you cough</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Have you been hoarse</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you feel ill</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Have you been bothered by your looks</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have trouble eating</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you find it difficult to eat in the company of your family</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you find it difficult to eat in front of other people</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have difficulties enjoying your meals</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you find it difficult to talk to other people</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you find it difficult to make a phone call</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have difficulties with having social contacts with your immediate family</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have difficulties with having social contacts with friends</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you have trouble going on the streets</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you use painkillers</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you use dietary supplements</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you use a feeding tube</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you lose weight</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did you gain weight</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Amount of tube feeding</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Table 38. The result of the EORTC QLQ-H&N35 variables

<table>
<thead>
<tr>
<th>Significant scales</th>
<th>Mean higher in non-surgical treatment</th>
<th>Mean higher in surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have any trouble doing strenuous activities</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do you have any trouble taking a short walk</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do you need to stay in bed or a chair during the day</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Where you limited in doing either your work or other daily activities</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Have you had pain</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Did you need to rest</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Do you have trouble sleeping</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Have you felt weak</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Have you lacked appetite</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Were you tired</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did the pain bother you in your daily activities</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do you have trouble concentrating</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do you feel tense</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Are you worried</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do you have trouble with your memory</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did your physical condition or medical treatment stand in the way of your family life</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Did your physical condition or medical treatment stand in the way of your social life</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>How would you judge the past week</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>How would you QoL the</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>past week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 39. The result of the EORTC QLQ-C30 variables