Preventive rehabilitation in patients treated with chemoradiation for advanced head and neck cancer
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Chapter 1

General introduction and outline of thesis
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GENERAL INTRODUCTION

Head and neck cancer
Head and neck cancer, mostly of squamous cell origin, concerns all malignancies between the base of skull and the clavicles. The majority of the lesions arise in the mucosa of the various sites of the upper respiratory and alimentary tract, i.e. oral cavity, naso-, oro- and hypopharynx, larynx, and the sino-nasal complex. These sites of origin of head and neck cancer are shown in Fig. 1, together with various sub-sites.

Epidemiology
The most important risk factors of head and neck cancer (still) are tobacco and alcohol abuse [1;2]. Another risk factor, discovered more recently, is human papillomavirus infection [3]. Incidence rates of head and neck cancer show geographic and socio-economic variations, and in general it occurs more frequently in men than in women [4;5]. The mean survival for head and neck cancer in Europe between 1995-1999 was 36.5%. Northern Europe had the highest 5-year relative survival for tongue, oral cavity and oropharynx sites, whereas Southern and Central Europe had the highest survival rates for hypopharynx and laryngeal cancers [6]. The age-adjusted 5-year survival in the Netherlands was well above average in Europe, both in men and women (Fig. 2a and 2b) [7].

In the Netherlands, the annual standardized age-adjusted incidence of head and neck cancer over the last ten years (1998-2008) is about 15 new patients per 100,000 inhabitants (Table 1) [8].

Staging
For uniform reporting on tumor size, worldwide two staging systems are used, in the USA the American Joint Committee on Cancer (AJCC) classification and in Europe the International Union against Cancer Committee (UICC) classification. These staging systems classify the size of the primary tumor (T0-4), the nodal status (N0-3), and the occurrence of distant metastasis (M0-1). A higher T stage (e.g. T3 or T4) indicates a larger primary tumor in the head and neck area, and a higher N stage (N1, N2 or N3) indicates a larger lymph node involvement. Various combinations of T, N, and M are grouped in stages I-IV, as shown in Fig. 3, and the stage III-IV tumors are also referred to as advanced head and neck cancer.
Figure 1 | a. Anatomic sites of the head and neck; b. sub-sites larynx: supraglottis, glottis and subglottis; sub-sites hypopharynx: piriform sinus, postcricoid area, and posterior wall; c. sub-sites oral cavity: lips, mobile tongue, floor of mouth, alveolar ridge, hard palate, and buccal mucosa; d. sub-sites oropharynx: base of tongue, soft palate, tonsillar fossa, and posterior wall.
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Table 1 | European Standardized Rate (ESR) for age-adjusted incidence per 100,000 of head and neck cancer in The Netherlands between 1998-2008 (The Netherlands Cancer Registry) [8].

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Figure 2 | a. and b. Comparison of age-adjusted five-year survival for Head and Neck cancer for men and women in the Netherlands and in European countries (diagnosed in 1995-1999, and followed to December 2003). The countries are “colored” by region by a range of grey (from light grey for Nordic countries to dark grey for Eastern countries, and middle grey for Europe) [7].

Figure 3 | Stage grouping for Head and Neck cancer using the TNM-staging system; T = primary tumor, N = Nodal status.
Management of head and neck cancer

Since the head and neck region embodies complex anatomical structures essential for breathing, swallowing, voicing and speech, cancer in this region may affect these anatomical structures and, consequently, have a negative impact on related functions. Unfortunately, management of the disease may also cause extensive (aesthetic and) functional problems. Furthermore, alterations in appearance and deterioration of swallowing, voice, and speech function often result in social withdrawal and emotional distress [9-12].

In general, primary, curative treatment of head and neck cancer depends on the site and size of the tumor, and can consist of radical surgery, radiotherapy, or a combination of both treatment modalities. These treatment options have functional side effects such as dysphagia, voice, or speech problems [10]. In an attempt to minimize these treatment-related functional problems, or in cases of anatomical or functional inoperability, adjuvant chemotherapy as part of concurrent chemotheraphy and radiotherapy (CCRT) protocols has gained popularity [13-15]. These so-called organ preservation protocols improve loco-regional control and long-term survival in all advanced head and neck cancers except laryngeal cancer [16-19]. Unfortunately, organ preservation does not necessarily imply preservation of function [11;20-23], and also CCRT appears to have significant adverse effects on functions such as swallowing, voice, speech, as well as on reducing the overall quality of life [20;24-29]. These CCRT-related functional issues are the focus of this dissertation, and therefore, other treatment modalities will not be discussed in depth from this point onwards.

Negative functional side effects of CCRT

The addition of chemotherapy to radiotherapy is associated with a substantial increase of early and late toxicities [30]. The most well-known and frequently reported negative side-effects of CCRT are dysphagia, trismus, voice and speech problems, and quality of life limitations.

Dysphagia

One of the most disabling adverse effects that CCRT may bring about is the disruption of normal swallowing function (dysphagia). The normal swallowing act consists of 4 phases: the oral preparatory phase, the oral phase, the oropharyngeal phase, and the esophageal phase (Fig. 4). During the oral preparatory phase, the bolus (liquid or food) is manipulated in the mouth, and masticated if necessary. During the oral phase, the tongue pushes the bolus backwards. When the bolus subsequently passes the anterior faucial arches, the oral stage of the swallow is ended and the swallowing reflex is triggered. This initiates the pharyngeal phase: the velopharyngeal port is closed to prevent food or liquid from entering the nasal cavity; peristatic movement of pharyngeal constrictors forcefully carries the bolus down through the pharynx to the level of the upper esophageal sphincter, thus preventing residue which might be aspirated;
the larynx is closed (at the level of the aryepiglottic folds, false folds and true vocal folds) to prevent the passing bolus from entering the airway; moreover, there is a retroflection of the epiglottis and the hyoid bone and the larynx move upward and forward, which, combined with the relaxation of the cricopharyngeal sphincter, allows the bolus to pass into the esophagus. In the esophageal phase the bolus is carried through the cervical and thoracic esophagus into the stomach by esophageal peristalsis [31]. During these swallowing phases various muscles in the tongue, floor of mouth and pharynx are activated, such as the intrinsic tongue musculature, the larynx elevators and the upper, middle and inferior constrictor pharyngeal musculature, as well as the mastication musculature such as the masseter muscle and the medial and lateral pterygoid muscles.

Dysphagia may already be present at initial diagnosis due to the size and the site of the tumor, necessitating tube feeding even before onset of treatment [32]. Severe dysphagia, requiring tube feeding, may also develop during treatment because of the acute side effects of radiotherapy, often enhanced by the chemotherapy [22;29;33]. When tube feeding replaces oral intake, swallow - and mastication musculature is no longer actively used and might therefore atrophy (so-called non-use atrophy) [34].

Aside from tumor-related and/or acute treatment-related causes of dysphagia, there are also long-term dysphagia issues. Several studies which examined the long-term effects of CCRT found a continued negative effect on swallowing function and nutritional status even up to one year after treatment. The most common abnormalities described in the literature are: reduced retraction of the base of tongue, delay in the swallowing reflex, decreased inversion of the epiglottis, reduced elevation of the larynx, and bolus residue in the valleculae or on the posterior pharyngeal wall after completion of the swallow [20;28;34-37]. In addition, CCRT seems to increase aspiration rate [25;35;37], and an additional neck dissection seems to reduce laryngeal elevation further [35].
Trismus
Reduced mouth opening is a common side effect of CCRT, sometimes reaching pathological proportions (when it is termed “trismus”) [38-42]. Mouth opening in healthy populations shows extensive variation. For instance, in a sample of the Irish adult population, a range of 24.6 to 62.0 mm maximum interincisor mouth opening (MIO) was measured in males (mean 43.3 mm) and 24.0 to 57.7 mm in females (mean 41.1 mm) [43]. The cut-off point for trismus, and thus the value where MIO becomes pathological, is ill-defined and uniform criteria are lacking in the literature. In the Netherlands, based on a study in 89 head and neck cancer patients, Dijkstra et al. [44] defined trismus as a MIO equal to or below 35 mm, a criterion we have adopted.

Trismus may be caused by tumor invasion in the mastication musculature and thus already be present at first presentation. Furthermore, (chemo) radiotherapy might induce trismus because it may directly affect the muscles involved in jaw opening, eventually causing fibrosis [45]. Moreover, in patients confined to tube feeding, non-use atrophy of the musculature might also play a role in the development of trismus. This condition of pathologically restricted mouth opening may cause poor oral hygiene, limit dental intervention and impair oral intake, swallowing and speech [38].

Voice and speech impairment
Since many head and neck tumors are located in the larynx and/or the vocal tract, negative effects on voice and speech are likely to occur. Moreover, CCRT treatment may cause considerable tissue - and subsequent functional changes, potentially also negatively affecting quality of voice and speech. Regrettably, voice and speech changes are not commonly reported outcome measures in studies on advanced head and neck cancer, despite their influence on daily communication, which contributes significantly to a person’s identity and personality [46], well-being and overall quality of life [47;48].

Normal phonation (voice production) requires sufficient airflow, healthy (smooth and flexible) vocal folds, and a cyclic, symmetric closing and opening of the vocal folds. Although the cavities of the vocal tract contribute to the voice’s characteristic timbre, pathological voice quality mainly is related to irregular vocal fold vibration and/or insufficient vocal fold closure. Phonation forms the carrier wave for voiced speech. During speech, voicing is molded dynamically as articulatory gestures change the dimensions of vocal tract cavities over time, creating different vowels, etcetera. Speech therefore requires volitional, coordinated movement of the articulators and can be affected severely by changes in muscle or tissue properties of for example the tongue or the soft palate [49].

Tumor growth and invasion, as well as the treatment have different effects on voice and speech outcomes. To distinguish the effects on these two outcomes, it is generally accepted and helpful to differentiate between tumors above the hyoid bone (non-laryngeal/vocal tract tumors i.e. tumors in the oral cavity, oropharynx, and/or nasopharynx), and below that anatomical structure
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(laryngeal and hypopharyngeal/sound source tumors). In non-laryngeal sites, the tumor itself will not primarily affect voice quality, yet, depending on its location, it will affect speech. In patients with laryngeal tumors, the tumor often only has a direct negative effect on voicing. The negative side effects of CCRT depend on the location of the tumor and on which areas are within the radiation field. In laryngeal cancers treatment can affect both voice and speech, when radiotherapy also comprises (part of) the vocal tract, and in non-laryngeal tumors the same is possible, but since the larynx mostly can be spared, effects on voice quality are often limited. Also, radiation to lymph nodes in the neck can affect voice quality, because this can increase edema in the larynx. Unfortunately, however, outcomes are often summarized across tumor sites and many studies are not consistent in separating voice and speech terminology/problems.

Vocal fold paralysis, edema, mucositis, scarring (resulting in rigid tissues), changes in mucosal hydration, xerostomia, and reduced range of articulatory motion have been observed as a result of radiotherapy. Patient reported adverse effects of radiotherapy with respect to voice are, for instance, voice fatigue, reduced voice volume and dynamics. The addition of chemotherapy (causing extra side effects, such as nausea, vomiting and/or altered taste) considerably worsens the radiotherapy effects [48;50-55].

Quality of life impairment

The diagnosis and treatment of cancer lead to a significant deterioration of quality of life (QOL), and diminished social, emotional (mental), behavioral and physical functioning. Besides the obvious reporting of loco-regional, disease-specific and/or overall survival results, QOL measurements are now considered indispensable when assessing treatment outcomes in head and neck cancer [12]. Worldwide, many different structured and validated questionnaires have been developed to analyze the patient’s perspective regarding survival, and physical/psychosocial functioning [56]. Numerous studies have shown the relevance of health-related QOL measurements in head and neck and other cancers.

In Europe, the most widely used structured QOL questionnaire for cancer in general has been developed by the EORTC (EORTC C30) [57]. Complaints assessed with this instrument can be divided broadly into emotional functioning (especially anxiety, uncertainty and powerlessness), physical functioning (especially fatigue and pain), social functioning (because of loss of contacts and lack of understanding from the environment), cognitive functioning, and finally, role functioning [58]. As an adjunct to this general questionnaire, a questionnaire has been developed that addresses specific head and neck issues, such as (oral) pain, speech, swallowing, oral dysfunction, and social interaction (HN35) [59]. Apart from the EORTC C30 and HN35 questionnaires, there are many other structured and validated QOL instruments [59-64]. Although these questionnaires have resulted in a better understanding of the impact of treatment on head and neck cancer patients, specific detailed information related to swallowing function
or voice problems is often too general and too limited to detect subtle changes. Therefore, structured study-specific questionnaires, which include more detailed and symptom-specific questions relevant to this specific cancer group, are necessary [65,66] and several studies have indeed shown the added value of these questionnaires [65-67].

Rehabilitation

In view of the abovementioned functional sequels of (CC)RT a question that comes to mind is: Which rehabilitation programs or techniques or exercises are available that are known to alleviate these negative effects in this population?

Many exercises have been developed to combat specific problems related to swallowing. Different exercises train specific (groups of) muscles or activate or stretch certain structures necessary during swallowing. The most well-known are the Mendelsohn maneuver, the supraglottic swallow, the effortful swallow, gargling tasks, the tongue-hold maneuver (also called Masako maneuver), the head-lift exercise according to Shaker and range of (jaw) motion exercises [68-74]. Most of these exercises were developed for, and evaluated in patients suffering from neurological diseases, such as stroke or Parkinson’s, but some studies also included head and neck cancer patients. Veis et al. [74] analyzed several stretch exercises and concluded that the gargle task elicited the greatest tongue base retraction in a group of subjects with suspected dysphagia (e.g. head/neck cancer, progressive and sudden onset neurologic damage, Parkinson’s disease, stroke, muscular dystrophy). Lazarus et al. [72] evaluated the effects of several voluntary maneuvers in head and neck cancer patients and concluded that tongue base-pharyngeal wall pressure increased most during an effortful swallow and the tongue-holding maneuvers (Masako). Interestingly, the effectiveness of the effortful swallow maneuver also improved oral (tongue-palate) pressures in healthy middle-aged and older adults, when compared to non-effortful swallows [71]. Similarly, Fujii et al. [70] found a significant increase in the posterior pharyngeal wall bulging using the Masako maneuver in young healthy adults. Logemann et al. [72] reported that the super-supraglottic swallow maneuver resulted in changes in airway entrance closure and hyo-laryngeal movement, and that fewer swallowing disorders were observed in irradiated head and neck cancer patients who used this maneuver.

With respect to trismus there is not much evidence to support the various proposed therapeutic/preventive options - mainly reported in case studies, reviews and guidelines [40]. Traditionally, trismus is treated with physical therapy and jaw stretching exercises using, for example, tongue blades. More recently, jaw stretching devices, such as the TheraBite Jaw Motion Rehabilitation System (Atos Medical AB, Hörby, Sweden) and the Dynasplint Trismus System (DTS; Dynasplint Systems, Inc, Severna Park, MD, USA) were introduced to manage trismus. These devices have demonstrated some efficacy in improving trismus related to head and neck cancer, but large randomized prospective trials comparing these new devices with more traditional approaches are lacking [68,75-77]. Only one randomized trial, analyzing patients who had undergone
irradiation for cancer of the head and neck, compared standard stretching exercises, standard exercises supported with the use of tongue depressors, and exercises with the TheraBite device. This study showed that, measured over a period of 10-weeks, the TheraBite-supported exercises did improve mouth opening significantly [68]. The study sample was unfortunately rather small with only 21 patients in total, so that the results need to be interpreted with caution.

In another study, the TheraBite device reduced pain more effectively than tongue depressors [78]. Dijkstra et al. [69] found significantly increased mouth opening after physical therapy (including the therapeutic tools of rubber plugs, tongue blades, dynamic bite opener and the TheraBite). Incidentally, in the latter study the increase in mouth opening was significantly better for patients with trismus unrelated to cancer. With only one small Randomized Controlled Trial (RCT) and a few non-randomized studies, further research is needed to corroborate these results and investigate long-term effects of jaw exercises with or without the use of medical devices [79].

In view of the fact that voice and speech changes are not commonly reported outcome measures in advanced head and neck cancer, it is not surprising that even less has been reported about prevention and/or rehabilitation of communication problems post CCRT [9].

**Prevention**

Mostly, rehabilitation starts when there is something to rehabilitate, e.g. posttraumatic. However when there is a predictable treatment-induced ‘trauma’, one could also initiate rehabilitation before treatment, potentially preventing or at least limiting the side effects of the treatment. The question is: are there techniques that have been shown to prevent the adverse side-effects caused by (CC)RT?

In terms of prevention, literature primarily focuses on limiting the radiotherapy dose to the musculature involved in swallowing and mastication using Intensity-Modulated Radiation Therapy (IMRT) [80]. Significant technological advancement in the form of IMRT indeed has helped to reduce the overall adverse effects of CCRT and thus improve quality of life after CCRT [80-85]. Evolved from 3-dimensional (3D) conformal radiotherapy, IMRT targets the tumor volume with high dose radiation while minimizing the effect on surrounding healthy tissues. Several studies showed that the severity of the effects of radiotherapy appears to be dependent on the total radiation dose, radiation field, fraction size and treatment duration [80-85]. In many institutes IMRT therefore has become the standard of care for radiotherapy in head and neck cancer [25;83;85;86]. However, sparing musculature in this way, without addressing the risk of muscle atrophy due to immobilization/non-use during tube feeding, might not be sufficient to reduce functional problems after CCRT [80]. Keeping the involved musculature active during CCRT despite cessation of swallowing (by regularly applying stretching and strengthening exercises as mentioned previously) might be a relevant adjunct to lowering the dose to these muscles.
Literature on prevention of CCRT-related swallowing impairment with specific exercises is even scarcer than that on posttreatment rehabilitation. Given et al. [87] suggest that speech and swallowing pathologists should address functional outcomes like swallowing before and during CCRT to enhance the functional outcomes posttreatment. There are only three non-randomized studies, which have addressed pretreatment swallowing exercises of head and neck cancer patients [88-90]. Kulbersh et al. [90] reported that the dysphagia-specific QOL-scores of 25 head and neck cancer patients treated with CCRT, who received pretreatment swallowing education and exercises, were significantly better than those of 12 control patients, who received swallowing exercises at the first visit after completion of treatment. The case-control study by Caroll et al. [88], which seems to be a sub-analysis of the data of Kulbersh et al. [90], also suggested that pretreatment swallowing exercises do improve posttreatment swallowing function in head and neck cancer patients (N=18) receiving CCRT. A large-scale non-randomized prospective study in Sweden, comparing 190 patients receiving an early verbal and written preventive rehabilitation program (swallowing and mouth opening exercises) based on self-care, and 184 control patients not being offered a systematic rehabilitation program, did not find a beneficial effect in the first group [89]. Randomized controlled studies investigating whether rehabilitation exercises can prevent or at least diminish long-term swallowing or mouth opening problems because of CCRT so far have not been published, but are obviously in great demand. Even less is known about the possibilities of trismus or voice and speech prevention. In this respect, it is noteworthy that the Dutch “Oral- and Oropharyngeal Carcinoma Guideline” states that patients with head and neck cancer, who are treated with curative (chemo)radiation, should routinely receive appropriate logopaedic rehabilitation during and after treatment [79]. Therefore, it has become ‘ethically challenging’ to design a randomized controlled trial with a non-rehabilitation control group. Moreover, even if a program consisting of some or all logopaedic rehabilitation methods, mentioned above, could be considered the gold standard, it is still uncertain if this is the most effective approach.

Alternative, innovative approaches
Other innovative exercises have been developed recently and have proven to be effective, and therefore might be used as alternative to traditional logopaedic exercises [91]. One of these ‘new’ exercise regimes concerns a medical device-based rehabilitation protocol. This device is the TheraBite Jaw Motion Rehabilitation System, a handheld portable instrument, which has been designed to mechanically assist anatomically correct mandible motion in patients experiencing mandible hypomobility and/or limited mouth opening/ trismus [68;78]. It is applied to the anterior teeth or arches of the upper and lower jaw, after which the patient can passively move the lower jaw by manually pressing the device [68;78]. The rationale for such a device-based rehabilitation program is that tolerance for the TheraBite is good, it is easy to use and compliance tends to be high [78]. Furthermore, Burkhead et al. [91], who designed an exercise
program in which patients were encouraged to swallow with the TheraBite opened at increasing percentages of the maximum interincisor opening of the mouth (MIO), found that the largest muscle activity could be registered with the TheraBite opened at 50% of the MIO (Fig. 5), and that the same muscles were activated that are activated in standard logopaedic exercises and swallowing maneuvers mentioned above.

Moreover, the swallowing exercises with the use of the TheraBite seem to be less complex and easier to learn than standard logopaedic exercises (schematically shown in Fig. 6), the latter being strongly dependent on the ability to follow instructions carefully and accurately [92;93], and consequently having a potential negative influence on compliance. For a complete overview of the exercises and their instructions see Appendix A and B.

Figure 5 | Demonstration of the Experimental exercises with the use of the TheraBite device, i.e. place the mouthpieces between the teeth, slowly squeeze the Lever to the 50% border, and swallow with the mouthpieces open and your tongue as far as possible up and forwards, and close the mouth gently and slowly (see also Appendix B).

Figure 6 | Schematic illustration of the three Standard logopaedic exercises, i.e. the effortful swallow, the Masako maneuver, and the super-supraglottic swallow (see also Appendix A).
Compliance

Apart from the discussion about which of the various rehabilitation exercises would be optimal, one also has to keep in mind that it is still uncertain whether these relatively ill patients are able or willing to spend extra time and energy on such rehabilitation programs, while undergoing burdensome CCRT. Given the physical discomforts such as nausea, vomiting, fatigue, mucositis, and pain associated with CCRT, it is imperative for preventive exercises to be as uncomplicated as possible in order not to compromise compliance.

SCOPE AND OUTLINE OF THIS THESIS

In view of the widespread awareness of the functional sequels of CCRT, it is disappointing that so little effort has been directed toward developing and implementing preventive exercise programs – not only posttreatment, after the functional/anatomical harm has occurred, but also pretreatment to possibly prevent or minimalize the functional side-effects of CCRT. However, prospective randomized studies, which investigate whether rehabilitation or precautionary exercises prevent long-term swallowing or mouth opening problems of CCRT, are still lacking. Therefore, a prospective Randomized Controlled Trial (RCT) was designed to assess the preventive effects of two rehabilitation programs for patients with advanced head and neck cancer treated with CCRT. In this RCT one group received standard logopaedic exercises, and because of ethical reasons as mentioned before no non-treatment control group could be included. Instead, an experimental group that practiced with an alternative, innovative approach (the TheraBite device) was included in the rehabilitation program.

The aims of this thesis are to present the current knowledge about the functional sequels of CCRT in advanced head and neck cancer, and to report the results of this RCT. The hypothesis of this RCT was that preventive stretching and strengthening exercises in the experimental group have a better preventive and long-term effect on jaw motion, swallowing function, and speech than those in the standard group. In addition, we expected that the well-known radiation dose relationships between dysphagia and trismus, and the mean dose received on important swallowing and mastication structures might be less damaging because of the preventive exercise programs.

Chapter 2 consists of a systematic literature review, which was carried out to appraise existing knowledge of swallowing-related functional outcomes and rehabilitation strategies after CCRT. Chapter 3 provides an overview of the pretreatment organ function in a cohort of 55 patients with advanced head and neck cancer, enrolled in the above mentioned RCT, based on a comprehensive multidimensional protocol, investigating various clinical outcome measures and
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patients' views.

Chapter 4 describes the preventive short-term effects (10-weeks posttreatment) of the 2 rehabilitation programs applied in the RCT, and focuses on the feasibility of the programs and patients' compliance, based on the various objective and subjective parameters from the multidimensional assessment protocol.

Chapter 5 describes the preventive long-term effects (1-year posttreatment) of the 2 rehabilitation programs applied in the RCT, using various objective and subjective parameters from the multidimensional assessment protocol.

Chapter 6 describes the relationship between the mean radiation dose to structures important for swallowing, mastication and salivation, and the functional outcomes dysphagia, trismus, and xerostomia as measured through the various objective and subjective parameters from the multidimensional assessment protocol in this RCT.

Chapter 7 contains the systematic review on voice and speech outcomes of chemoradiation for advanced head and neck cancer.

Chapter 8 reports on perceptual judgments and patients' perception of voice and speech after CCRT in this patient population.

Chapter 9 comprises the summary, final discussion and perspectives.
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