Preventive rehabilitation in patients treated with chemoradiation for advanced head and neck cancer
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Summary, general discussion and perspectives
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SUMMARY

Chapter 1 gives a brief overview of the epidemiology, staging and management of head and neck cancer, and of organ preserving concomitant chemoradiotherapy (CCRT), presently the treatment of choice for many cases of advanced anatomical and/or functional inoperable head and neck cancer. Organ preservation, however, is not always synonymous with function preservation, and the many functional side-effects resulting from CCRT, i.e. dysphagia, trismus, voice and speech impairment and an overall decrease in quality of life are outlined, as are the basic aspects of the swallowing physiology and the possibilities to rehabilitate the various structures and muscle groups involved.

In Chapter 2 a systematic review is presented, which focuses on the effects of tumor and CCRT on functions such as swallowing, mouth opening, nutrition, pain and quality of life in patients with advanced head and neck cancer. Additionally, the systematic search (time-period January 1997 to August 2007) concerned (evidence-based) techniques or strategies known to alleviate or rehabilitate the loss of function(s) associated with CCRT. In total 15 relevant articles met the inclusion criteria and the majority of the studies appeared to focus on the outcomes swallowing, quality of life, and nutrition. Two studies only reported on the outcome pain, but none of the reviewed papers reported on the outcome trismus. And only two papers mentioned rehabilitation options, but specific information was lacking.

To increase our insight in the function impairment caused by both tumor and CCRT, and to assess effects of known and newly developed rehabilitation measures, therefore, the Randomized Controlled Trial (RCT) “Prevention of trismus, swallowing and speech problems in patients treated with chemo-radiotherapy for advanced head and neck cancer” was set up. The results of this RCT are the main focus of this thesis, and are described in the following Chapters (Chapters 3-8). In this prospective clinical study, 55 patients with primary advanced (stage III and IV) head and neck tumors in the oral cavity, oropharynx, hypopharynx, larynx or nasopharynx were enrolled (accrual period September 2006 - April 2008). Written informed consent was obtained from all patients before they entered the study. Patients were evaluated before treatment, 10-weeks after CCRT (short-term results), and 1-year posttreatment. The patients were randomized in one of the two preventive rehabilitation groups: the standard and the experimental exercise group. Both groups received comparable stretch and strengthening (swallowing) exercises, the only difference being that the experimental arm utilizes a special jaw-mobilizing device (TheraBite) for the exercises. The idea behind these stretch and strength exercises is to prevent none-use atrophy of the musculature involved in swallowing and mouth-opening, which is almost inevitable when
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patients become confined to tube-feeding, which is often needed to maintain an optimal alimentary status during and after treatment.

In Chapter 3 the baseline evaluation of the 55 included patients is provided through various clinical outcome measures and patients’ views. A comprehensive, multidimensional assessment protocol was used that included quality of life, swallowing, mouth opening, and weight changes. This protocol revealed that already before the onset of CCRT quite a number of problems existed. The most frequent problems concerned swallowing, pain, and weight loss. Interestingly, there also appears to be a discrepancy between the clinical outcome measures and patients’ perception, especially with respect to laryngeal penetration and/or aspiration, which was not always experienced by the patients. So, the baseline results of this RCT show that a structured, multidimensional assessment protocol of clinical measures and patients’ views appear to be necessary to gain insight in all (perceived) pre-existing functional and quality of life problems in advanced head and neck cancer patients.

In Chapter 4 the short-term results are presented. The main findings for the 49 patients available for analyses were that the feasibility of the rehabilitation programs was good (all patients were able to execute the exercises independently within a week) and that compliance was satisfactory (mean days practiced per week was 4). However, despite these positive facts, the preventive exercises did not prevent, in the short-term, a decrease in mouth opening, oral intake, and weight. On the other hand, comparing the results of this RCT with a previous, equivalent CCRT study at our institute, fewer patients were still tube-dependent in the present study. The comparable in-house CCRT study only differed with respect to the absence of a preventive exercise program. Thus, the short-term results indicate that preventive rehabilitation (regardless of the approach, i.e., experimental or standard) in advanced stage head and neck cancer patients is feasible and shows reasonable compliance despite burdensome CCRT, and that compared with historical controls, the exercises at least reduce the severity of various functional short-term effects to some extent.

In Chapter 5 the 1-year results of 37 disease free and evaluable patients are presented. Also at the one-year assessment point there was no difference between the preventive rehabilitation arms. However, the pooled results, which we again compared to the results from the preceding CCRT trial at our institute, suggest that preventive swallowing exercise programs limit functional problems. Additionally, the significant association found between the occurrence of trismus 1-year posttreatment and the (mean) maximum mouth opening pretreatment, implies that baseline mouth opening in patients receiving CCRT should be a part of routine evaluation, to allow timely identification of patients at risk for developing trismus.

In Chapter 6 the side effects (dysphagia, trismus and xerostomia) of (chemo-)IMRT at 10-weeks
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and 1-year posttreatment in relation to dose parameters of structures involved in swallowing, mastication, and salivation is assessed. Several statistically significant dose-effect relationships between objective as well as subjective dysphagia and trismus measures and the mean doses or dose volumes >40 Gy to the critical swallowing-, and mastication structures were found. In part, the results confirm earlier findings reported in the literature. Since dose relationships seem to vary at different measurement points, a strict multidimensional assessment protocol, including objective and subjective assessments, is mandatory. Finally, although no thresholds were found, delineating organs at risk for treatment planning is essential to reduce potentially damaging radiation doses to these structures.

The following two chapters (7 and 8) discuss the possible effects of tumor and CCRT on voice and speech (thus on communication). Chapter 7 concerns a systematic review of the literature on voice and speech effects of CCRT (search period 1991-2009). The main conclusions of the 20 articles that met the inclusion criteria (14 on voice, and 10 on speech) are similar to those for the swallowing part of the study. There appears to be large variation and not much consistency and structure in the reported posttreatment outcomes data, baseline assessments often are lacking, and generally no clear distinction is made between the effects of tumor sites and radiation. The latter seems relevant because one can expect that tumors in or adjacent to the sound source (larynx/hypopharynx) will affect voice more than speech, whereas tumors in or adjacent to the vocal tract (oral cavity, naso/oropharynx) will affect speech more than voice. Overall, the literature indicates that voice and speech deteriorate during CCRT, improve again in the first few months after treatment, and often exceed pre-treatment levels after one year or longer, although normal values are seldom reached again. Based on our systematic review we concluded that there is an urgent need for structured standardized multi-dimensional speech and voice assessment protocols for patients with advanced head and neck cancer treated with CCRT. Such an assessment protocol, therefore, was also included in this RCT and part of the results is given in chapter 8.

Chapter 8 describes perceptual judgments and patients’ perception of voice and speech in this study population. Based on a standard Dutch text and a diadochokinetic task, expert listeners rated voice and speech quality (GBRAS-based; Grade, Breathiness, Roughness, Asthenia, Strain) and articulation (overall, and more specifically for [p], [t], [k]). The voice and speech rated at baseline (N=55), at 10-weeks (N=49) and 1-year posttreatment (N=37) were compared using the Comparative Mean Opinion Scores (CMOS). We found that voice and speech deteriorated at 10-weeks and improved thereafter, although some aspects had not resolved at one-year. The majority of patients (70%) considered their voice and speech ‘not as it used to be’ (measured by a structured, study-specific questionnaire). In addition, the perceptual experiment indeed revealed some differences between vocal tract and sound source tumors, i.e. at the 1-year
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versus 10-weeks posttreatment comparison the larynx-hypopharynx tumor group was judged to have a more strained voice than the non-laryngeal tumor group. Overall, (perceptual) CCRT effects on voice and speech seem to peak at 10-weeks posttreatment, and level off at 1-year, but at that assessment point the majority of patients still perceive their voice as different from baseline. Since all the patients received strength and stretch exercises and these were geared to train swallowing musculature, we could not assess the effects of these exercises on speech or voice. However, as in chapter 4, we compared the results with the previous equivalent in-house trial (which differed only in that no preventive exercise were given), and the present results seem more positive. This may be explained by the phenomenon of neuroplasticity: i.e. training of swallowing function may have some effect on voice and speech (and vice versa).

FINAL DISCUSSION

At the present time, organ preserving concomitant chemoradiotherapy (CCRT) is considered the method of choice for the treatment of locally advanced, (functional) unresectable head and neck cancer, because results, with loco-regional control rates of 50% to 70%, exceed those for radiation alone [1;2]. However, it has also become clear that sparing the anatomy in this way does not necessarily preserve the function of the organ involved. Several studies have shown that CCRT is predictably associated with disabling acute and chronic dysphagia, which cause nutritional limitations and have a negative impact on overall quality of life [3-7]. In an effort to limit these side effects the main focus until now has been on the application of IMRT, which is increasingly used to limit the radiation doses to the musculature involved in swallowing and mastication [8]. Although this is a sensible and reasonably effective approach, there are limitations to what can be achieved, because the proximity of the tumor to the musculature and structures at risk often prohibits sparing them from radiation damage. Moreover, the issue of ‘non-use atrophy’ of the swallowing musculature, provoked by the often-avoidable cessation of oral intake due to local tumor growth and/or radiation-induced mucosa toxicity, is not addressed by IMRT. Therefore, it is quite surprising that, despite the widespread awareness of these predictable functional sequels of CCRT, few attempts have been made to try to alleviate these function impairments (chapter 2). Prospective randomized controlled trials (RCT), which investigate whether rehabilitation or precautionary exercises prevent long-term swallowing or mouth-opening problems after CCRT, are still lacking. This thesis therefore aimed to present the current knowledge about the functional negative side effects of CCRT in advanced head and neck cancer patients, and to report on the effectiveness of preventive exercises in the short- and long-term. Since such exercises are recommended as the standard of care in the Netherlands,
(although no strong evidence exists that these exercises are effective in this patient group [9]), it was deemed unethical to include a control group that did not receive preventive exercises. Therefore, randomization was done between a standard group receiving traditional logopaedic swallowing exercises and an experimental group receiving comparable stretch and strength exercises, but with an innovative approach using a jaw-mobilizing medical device, TheraBite. The TheraBite specifically addresses several structures at risk, such as the mandibular joint and the mastication musculature, and in addition, swallowing with the TheraBite device - held at 50% of the maximum mouth opening - also exercised the musculature relevant for swallowing. It was hypothesized that the experimental group would have some advantage over the standard group because the device has a good track record in terms of patient-compliance. Therefore, somewhat better preventive and long-term functional effects were envisaged in the experimental group.

Regrettably in terms of RCT outcome, no significant differences were found between the 2 preventive exercises arms on the short or long-term. Thus the findings of this RCT cannot advise us as to the best preventive approach that will minimize the negative side effects of CCRT. The effectiveness of the standard exercises as well as the exercises performed with the jaw-mobilizing device seems to be comparable. Nevertheless, it must be noted that after 1-year only 37 patients (20 in the standard and 17 in the experimental group) were available for analyses and only limited overall functional problems were found, which could be the reason we did not find statistically significant differences between the 2 exercise groups. The finding that all three trismus patients in this study were in the standard arm is however one salient fact. On the positive side, having 2 exercise arms with comparable functional outcomes, allowed us to pool the results so that analysis and comparison with other studies became more meaningful. Since the drawback of this study is that a non-exercise control group was not included, and we were interested in the possible effectiveness and benefits of preventive exercises, a comparison with a preceding in-house CCRT trial and comparable studies in the literature was made. As discussed in chapter 4 and 5, in the present RCT 76% of patients were still tube-dependent at completion of CCRT and 37% at 10-weeks posttreatment. In the preceding in-house RCT, (equivalent except that no preventive exercises were given), these figures were less favorable with 86% (157/183) of the patients still tube dependent at the end of the treatment and 62% (112/180) at 12 weeks posttreatment [10]. Nevertheless, it must be noted that all patients included in the present RCT received IMRT whereas the majority, but not all patients had IMRT in the in-house study of Ackerstaff et al. [10]. Thus, IMRT could have influenced these sizeable differences to some extent, especially the 25% lower tube-dependency at 10-12 weeks. However, no thresholds were found, but delineating organs at risk for treatment planning is essential to reduce potentially damaging radiation doses to these structures.

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We further compared the results of the present RCT with the literature [11-13]. To our knowledge there are only two non-randomized studies with small patient samples [12-13], as discussed in chapters 4 and 5, and only one more recent non-randomized study with large patient samples that could be used for comparison [11]. These 3 studies also assessed pretreatment swallowing exercises of head and neck cancer patients [11-13]. Kulbersh et al. reported that the dysphagia-specific Quality of Life 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 controls, who received swallowing exercises at the first visit after the completion of their treatment [13]. The case-control study by Caroll et al., which seems to be a sub-analysis of the data of Kulbersh et al., also suggested that pretreatment swallowing exercises do improve posttreatment swallowing function in head and neck cancer patients (N=18) receiving CCRT [12].

These positive findings are in contrast to those of Ahlberg et al., who compared 84 head and neck cancer patients receiving a preventive training program to a control group of 121 patients who did not in a prospective nonrandomized study [11]. These authors did not find significant differences between the groups, but it must be noted that these preventive exercises were given to patients receiving a range of treatment modalities (surgery, and/or radiotherapy, with or without chemotherapy), that swallowing function was only assessed with a questionnaire, and that the functional outcome comprised of weight loss. Besides, the preventive training program was based on early self-care rehabilitation, for which compliance data should have been collected, before anything can be said about the (lack of) effectiveness of the program applied. Melchers et al. e.g. investigated factors influencing usage of the TheraBite and found that internal motivation, perceived effect, self-discipline, and having a clear exercises goal had a positive influence on adherence/compliance [14]. With regard to logopaedic strengthening exercises, these are known to be quite complex and require the ability to follow instructions carefully and accurately [15;16]. It seems that frequent monitoring by the speech therapist is essential to safeguard compliance and achieve better results. In the present RCT, patients were monitored regularly (on average bi-monthly), which could have induced compliance in spite of advanced disease and the burden of the intensive concomitant chemoradiotherapy.

As there were no randomized studies to compare our results with (apart from the studies mentioned in chapters 4 and 5 and mentioned in the previous paragraph), we also compared our results with studies that did not include preventive exercises, but purely investigated functional outcomes after CCRT. Because assessment protocols vary substantially among studies, we focused on the outcome measure that was most reliably/consistently reported among these studies, i.e. the tube dependency rate. Fig. 1 gives an overview of relevant studies reporting percentages of tube dependency at 1-year posttreatment. Most of these studies also show an increase in tube dependency during treatment and a decrease after completion of the CCRT.
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At 1-year posttreatment, the percentages of patients who are still tube dependent vary from 2 to 60% (mean 31%). Except for the study from Koiwai et al. [17], who only provided the 1-year number, none of the studies reached a level close to 0% at that observation point (Fig. 1). In the case-control study by Carroll et al. (N=18), in which half of the patients received pretreatment exercises, 3 patients of the exercise group (33%) were still tube dependent at 1-year [18]. In two studies all the patients received prophylactic tube feeding before the onset of treatment [18;19], and in another study the vast majority of patients started pretreatment with gastrostomy tube feeding [20]. Up to 1-year posttreatment the 10 patients in this latter study were still tube-dependent. Four studies also reported the percentage of patients still needing a feeding tube at 18-months (13%) or 24-months (10-75%) posttreatment [21-24]. The comparison of the results of the abovementioned ‘literature-control’ studies with the present RCT seem to suggest that exercises activating the swallowing and masticatory musculature effectively reduce functional sequelae associated with CCRT, particularly in the long run. This is especially true when looking at the occurrence of tube dependency in the different ‘control’ studies, which indicates that the number of patients still needing a feeding tube at 1-year was considerably lower in our prospective study. There was only 1 ‘literature-control’ study with similar results, but this was a non-randomized retrospective study [17].

Weight loss in relation to tube feeding was another parameter of interest for comparison. Studies in which patients treated with CCRT (prophylactically) received a feeding tube, showed more tube-dependency, or delayed feeding tube removal. Chen et al. [25] concluded that prophylactic feeding tube placement in patients treated with CCRT for advanced head and neck carcinoma (AHNC) effectively prevented acute weight loss and the need for intravenous hydration. However, in our study the percentages of acute weight loss after treatment (approximately 10-weeks) in patients not needing a feeding tube (mean -6 kg, or -7%; N=10), were in the same range as the patients receiving prophylactic feeding tube in Chen et al. [25] (mean -5% after 3 months; no exact weight figures given), and Rutter et al. [26] (mean -9.1 kg after 3 months; no percentage given). At 1-year posttreatment the mean weight loss was less in our study (mean -3 kg or -4%) compared to the study of Rutter et al. [26] (mean -8.2 kg, again no percentage given). This suggests that even without prophylactic tube feeding patients are able to maintain oral intake and keep their weight loss acceptable; the role of preventive swallowing exercises might well have been decisive for this.

Furthermore, in the study by Chen et al. [25], the proportion of tube-dependent patients, 6- and 12-months posttreatment was significantly higher (41% and 21%), compared to those without a prophylactic tube feeding (8% and 0%) [25]. The authors’ explanation was that tube feeding made the patients ‘lazy’. Carroll et al. also discussed this aspect in their case-control study, suggesting that long-term use of feeding tubes could be related to ‘learned non-use’, even
when pretreatment swallowing training was provided [18]. Patients apparently are so used to their feeding tube, that they are reluctant to have it removed even though they are functionally able to swallow. Or patients might simply lack confidence after such a long time of non-use. Finally, as mentioned before ‘non-use atrophy’ might occur, because the structures involved in swallowing or chewing are not in use, and that is exactly what should be avoided.

Figure 1 | Percentage of feeding tubes at different points of time in patients treated with concomitant chemoradiotherapy (CCRT) as reported in the literature and compared to the results of this study.

PERSPECTIVES

In view of the findings of this RCT and the above reviewed literature, we formulated a number of clinical suggestions to minimize the sequels of CCRT, optimize care in advanced head and neck cancer patients, and hence improve quality of life after treatment:

- Baseline videofluoroscopy assessment of swallowing function before the onset of
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... patients’ reported swallowing difficulties, pretreatment videofluoroscopy should be an integral part of the baseline assessment of patients with advanced head and neck cancer.

- Baseline mouth opening measurement: patients who already have a limited mouth opening at initial diagnosis are at higher risk of developing trismus, and should furthermore be monitored and treated more cautiously.

- Preventive rehabilitation by a speech pathologist familiar with the specifics of the available exercises and medical devices should optimally start before or within the first week of the onset of CCRT. This in view of the good feasibility and acceptable compliance when these patients receive early counseling and regular follow-up, and the prospect of minimizing functional problems of CCRT.

- Oral feeding should be encouraged and stimulated for as long as possible. A strong involvement of the dietician is mandatory to limit weight loss before, during and after treatment.

- Unless strictly necessary (e.g. to prevent acute excessive weight loss, dehydration, and/or aspiration), prophylactic placement (‘according to protocol’) of a feeding tube should be avoided. Not only to prevent ‘non-use atrophy’, but also in view of the fact that tube placement is not without complications, e.g. aspiration, bleeding, infection, gastric perforation [27-29]. If clinically unavoidable, or when a protocol has to be followed, it is even more crucial that the speech pathologist monitors and trains the patients’ swallowing and mouth opening function in order to keep all involved musculature and structures active.

- Even when tube feeding is supplied, e.g. for hydration, or optimal dietary intake, oral intake – if not precluded because of aspiration – should be stimulated to keep all swallowing muscles optimally active (even if exercises are prescribed as well).

- Posttreatment patients should be monitored regularly, to remove the feeding tube as soon as possible and limit the negative effects of continued (perceived) swallowing problems on quality of life.

- Sparing the parotid gland(s) to avoid xerostomia is more or less standard already, but, if at all feasible, the swallowing and mastication structures should also be delineated and spared during IMRT-planning provided it is oncologically safe.

- Apart from the potential positive effect that swallowing therapy might have on voice and speech through the phenomenon of neuroplasticity, a further reduction of the negative effects of CCRT on voice and speech might be achieved by additional (preventive) speech therapy. This should obviously be tailored to individual patients’ needs and wishes, keeping in mind that at one-year the majority of patients still consider their voice and speech “not
On the whole it is important to stress that the treatment of advanced head and neck cancer frequently results in impaired shoulder function, lymph edema in the face and neck, general fatigue, poorer overall physical functioning, and psychosocial problems [30;31]. Recent research has shown that targeted rehabilitation and optimal restoration of function can improve participation in society and quality of life significantly [32-38]. Thus, to improve the overall quality of life in patients, and to stimulate patients to regain their place in society, using their own abilities, an even broader multidisciplinary approach than addressed in this thesis is needed.

Because no such multidisciplinary rehabilitation program was available for this patient group, the Netherlands Cancer Institute recently developed and implemented such a specialized head and neck rehabilitation program (www.nki.nl/hoofdhalsrevalidatie), based on the International Classification of Functioning, Disability and Health (ICF) model (http://class.who-fic.nl/browser.aspx?scheme=ICF-nl.cia). To address all the issues involved, a multi-disciplinary rehabilitation team is needed which also includes other disciplines than the specialties directly involved in the curative cancer treatment, such as surgical, radiation, and medical oncologists, nurse-specialist, dentist, speech therapist, a medical rehabilitation specialist, dietician, physical therapist, occupational therapist, and a psycho-social worker/nurse. This program, a total package that includes all relevant rehabilitation components, is tailored to the individual needs and circumstances of the patient, guaranteeing optimal care through so-called SMART-goals (goals that are Specific, Measurable, Acceptable, Realistic, and Timed).

This elaborate focus on all relevant functional sequels of head and neck cancer treatment endorses individual care that goes beyond cure, incorporating extensive rehabilitation so that the patient regains an acceptable quality of life and optimal participation in the society.
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Reference List


