Redacted protocol information

The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Early preventive physiotherapy versus usual care does not seem to reduce trismus in patients treated with radiotherapy for cancer in the oral cavity or cancer oropharynx: a randomised clinical trial

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Eligibility Criteria

Patients were eligible for the randomised clinical trial if they

- a) had been diagnosed with cancer in the oral cavity or cancer oropharynx and were referred to curative radiotherapy,
- b) were ≥ 18 years old, and
- c) have signed informed consent according to local guidelines.

Patients were ineligible if they

- a) had received operative reconstruction of bone or skin transplant,
- b) during surgery had damaged motor nervous system that affected the neck and shoulder function,
- c) were suffering from diseases which can affect/disturb the symptoms of adverse events in the temporo-mandibular joint, cervical spine or shoulders (e.g. rheumatism, fibromyalgia, arthritis, neurological diseases, work injury),
- d) were diagnosed with severe psychiatric co-morbidity (including dementia),
- e) were in poor general condition, which would significantly impair their participation in the program,

f) were unable to read or understand Danish, which would compromise their ability to understand written and oral information, or

g) were referred to palliative radiotherapy.

The study coordinators obtained approval of the study design from their local ethical board prior to study activation [journal no. (KF) 01 2006-6097]. Patients who gave oral and written consent were referred to the study from the oncology out-patient clinic at the University Hospital of Copenhagen, Rigshospitalet.

Figure 1. Flowchart of the trial design

Treatment plan

Intervention group

The experimental intervention group got the intervention below plus usual care (see below).

The intervention was carried out by the two study coordinators who were both physiotherapists and had 12 and 20 years respectively of working experience with cancer patients. Prior to the onset of the study, exercises were discussed with other physiotherapists and a dentist with special knowledge on trismus in connection with head and neck cancer. The aim of the exercises was to maintain blood circulation and movement of the muscles, joints, and skin and lymph system in the radiated area.

Physical exercise and instruction in self-drainage were delivered as an individually tailored regime. A list of exercises and photographs with specific details concerning the number of times an exercise should be repeated, duration and frequency throughout the day were given as a booklet .

Once a week the participants performed every exercise in the booklet, supervised by the physiotherapist. The weekly intervention had duration of 45 minutes. If the physiotherapist noticed a participant having difficulty in performing e.g. cervical range of motion or tongue movement, the participant would be given advice on performing additional exercises from the booklet for the specific movement problem at home.

For home training all participants performed the same standard program consisting of 3 exercises concerning movement of the temporo-mandibular joint and an additional stretching exercise using the fingers as an aid for opening the mouth wide. The participants were instructed to practice the exercises standing in front of a mirror and were told to perform the exercises at a slow pace. The exercises were not to provoke instant pain. In case of instant pain related to the exercise, the participant was instructed to decrease the range of motion or if that did not help, avoid the specific exercise. Each exercise was

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carried out with 5 repetitions and should be performed 5 times daily. Participants were instructed in an exercise for the greater rhomboid muscle and in using this exercise while sitting, standing or walking. Two stretching exercises with duration of 20 seconds for the tongue muscles and platysma muscle were included in the standard program. The participants in the intervention group were also instructed in using sugar free chewing gum 5 times a day for up to 10 minutes plus if necessary, complementary exercises from the booklet. Chewing gum was delivered from the physiotherapist. If participants had trismus (mouth opening ≤ 35 mm) at the follow up visit 2 months after having completed radiotherapy, the participants were instructed in using wood sticks or TheraBite mouth opening device.

Usual care group

The usual care group received the usual, normal routine care offered by the oncologist and other healthcare providers including instructions in mouth opening exercises by a nurse for approximately 10 minutes prior to the onset of radiotherapy treatment.

Objectives and entire statistical section (including outcomes)

Study objectives

Primary objective

The primary objective was to assess the effect of an early preventive physiotherapy intervention on head and neck cancer patients on mouth opening.

Secondary objective

The secondary objective was to assess the effect of an early preventive physiotherapy intervention on head and neck cancer patients on:

- Active cervical flexion/extension
- Active cervical lateral flexion
- Active cervical rotation

- Tissue tightness in the radiated region during activity
- Health related quality of life and specific symptoms related to head and neck cancer
- To assess the feasibility and compliance of self-care combined with once a week supervised physiotherapy sessions during and 2 months after completing radiotherapy.

Statistical analysis

The primary outcome, change in MID, was compared using a mixed-model analysis of repeated measures. An unadjusted analysis and an analysis adjusted for the stratification variable; operation, were conducted. The impact of disease spread, tumor-size, diagnosis, co-morbidity, and chemotherapy and radiation dose on change in mean MID, were investigated through a mixed-model analysis of repeated measures adjusted for each variable mentioned above, and operation. Missing values for survivors at 5 and 12 months after completing radiotherapy were imputed using best-worst case imputation (highest value imputed in the physiotherapy group, and lowest value in the usual care group) and worst-best case imputation (lowest value imputed in the physiotherapy group, and highest value in the usual care group), and a similar analysis was conducted. Values for dead patients were not imputed. The same approach was used to analyze the scores on the EORTC subscales. A P-value below 0.05 was chosen as statistical significant. All analyses were made using SPSS software, version 19.

Sample size

In the literature a standard deviation of approximately 7 mm on mean maximal interincisor distance was found (1). The minimal important difference was set to 5 mm. With 80% power and a level of significance of 0.05, it was estimated that each study arm should have an amount of at least 49 participants.

Reasons for early cessation of trial therapy

Consent withdrawn

Methods of measurement

Primary outcome

The primary outcome for this trial was the active maximal vertical interincisor distance (MID).

Secondary outcomes

The secondary outcomes were as follows:

- Active flexion/extension of cervical range of motion
- Active lateral flexion of cervical range of motion
- Active rotation of cervical range of motion
- Reported tissue tightness in the radiated region during activity
- Health related quality of life
- Specific symptoms related to head and neck cancer
- Self-reported daily amount of exercises and repetitions
- Number of physiotherapy sessions attended

Primary outcome

The primary outcome was the change in maximal vertical interincisor distance (MID) from entry to 12 months follow-up using the TheraBite Range of Motion Scale, ATOS medical. The measurement was taken between the middle of the front left upper and lower tooth. If there were no teeth, the measurement was taken between the upper and lower gum at level with frenulum labii superioris and inferioris. The TheraBite Range of Motion Scale has been used in other trials (1,2)

and was prior to the onset of this trial examined for inter tester reliability on 15 colleges at the age 26-65 at the University Hospital of Copenhagen. Inter tester reliability: ICC (2.1) = 0.99; standard error of the mean (SEM) -2.02 mm. According to Kropmanns et al. studies have shown, that there is no difference in intra- and inter tester reliability between measurements of head and neck cancer patients and a norm population (3).

In this study trismus was defined as a MID $\leq$ 35 mm, as proposed by Dijkstra et al. (4). Normal mouth opening is considered to be within the range of 40 mm to 70 mm.

Secondary outcomes

The secondary outcomes were active cervical range of motion, measured by the EDI-320 inclinometer attached to a helmet. The inter-tester reliability was examined on 25 head and neck cancer patients in a parallel study. Inter tester reliability: Flexion/extension: ICC (2.3) = 0.91, SEM -12.39°; Lateral flexion: ICC (2.3) = 0.92, SEM -10.31°; Rotation: ICC (2.3) = 0.87, SEM -20.1°. Subjective tissue tightness related to the mouth opening were reported by means of a Likert scale, HRQOL was measured by the European Organization for Research and Treatment of Cancer, generic cancer questionnaire (EORTC QLQ-C30) and specific symptoms related to head and neck cancer by the Head & Neck cancer symptom specific questionnaire (EORTC H&N35). The EORTC QLQ-C30 questionnaire comprises 5 functional scales: physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. There are three symptom scales: fatigue, nausea and vomiting and pain and 6 single items relating to dyspnea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties. It also includes a global health status/QL scale. A one-week time frame is employed. The HRQOL scores were calculated according to the EORTC QLQ-C30 scoring manual (5). All scales and single-item scores are

transformed into a score from 0 to 100. A high score for a functional scale and for the global health status scale represents a high level of functioning, while a high score for a symptom scale or single item represents a high level of symptoms. The EORTC QLQ-H&N35 questionnaire comprises seven subscales: pain, swallowing, senses, speech, social eating, social contact and sexuality. There are 10 single items relating to problems with teeth, dry mouth, cough, opening mouth wide, sticky saliva, weight loss, weight gain, use of nutritional supplements, feeding tubes and painkillers. The module was scored according to the same scoring system as the EORTC QLQ-C30. A clinically important difference is considered to be 10 units difference (6, 7).

Information about age, diagnose, type and date of surgery, type of radiotherapy, chemotherapy and comorbidity was attained from the hospital journal. Patients were asked about smoking habits, alcohol intake, marital status, working status and education.

Adherence was considered high when patients reported, that they performed the prescribed daily exercises and amount of repetitions and attended the weekly physiotherapy sessions. One day per week without exercises during the study was accepted. Medium adherence was when daily exercises with less than the prescribed amount of repetitions were performed, when the patients had up to 2-3 days per week without exercises or did not attend all physiotherapy sessions. Adherence was considered low, when the prescribed exercises were performed in the beginning of the study, but ceased after a short period or were not performed 5 or more days per week and/or only a few physiotherapy sessions were attended.

The physiotherapists undertaking the weekly physiotherapy sessions kept record of attendance and of adverse effects to the physiotherapy intervention.

The training of raters

The 5 raters were physiotherapists working at the University Hospital (2 were recently qualified; the other three had 7, 9 and 19 years of work experience). They were responsible for assessments at day 1 or 2 of the onset of radiotherapy, and at 5 and 12 months after completed radiotherapy. Some of the raters participated in developing the assessment tools and the manual for the rating procedure. All raters were trained under supervision and the manual was followed. Every new rater was trained by an experienced rater until he or she was able to use the precise instructions and commands according to the manual. At all times there were 3 raters available.

References

1. Kent LM, Brennan MT, Noll JL et al. Radiation-induced trismus in head and neck cancer patients. *Support Care Cancer* 16:305-9, 2008.
2. Cohen EG, Deschler DG, Walsh K et al. Early use of a Mechanical Stretching Device to Improve Mandibular Mobility After Composite Resection: A Pilot Study. *Arch Phys Med Rehabil* 86: 1416-1419, 2005.
3. Kropmans THJB, Dijkstra PU, Stegenga B et al. Smallest Detectable Difference in Outcome Variables Related to Painful Restriction of the Temporomandibular Joint. *J Dent Res* 78:784-789, 1999.
4. Dijkstra PU, Huisman PM, Roodenburg JLN. Criteria for Trismus in Head and Neck Oncology. *International Journal of Oral and Maxillofacial Surgery* 35: 337-342, 2006.
5. Fayers PM, Aaronson NK, Bjordal K et al: The EORTC QLQ-C30 Scoring Manual (3rd Edition). European Organisation for Research and Treatment of Cancer, Brussels 2001.

6. Bjordal K, Hammerlid E, Ahlner-Elmqvist M et al. Quality of Life in Head and Neck Cancer Patients: Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol* 17:1008-1019, 1999.
7. Aaronson NK, Ahmedzai S, Bergman B et al: The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 85: 365-376, 1993.