Effects of Prophylactic Swallowing Exercises on Dysphagia and Quality of Life in Patients with Head and Neck Cancer Receiving (Chemo) Radiotherapy

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Abstract

Background: Squamous carcinoma of the head and neck (HNC) has a high incidence in our context. Although therapeutic radiotherapy protocols try to preserve swallowing function and essential speech organs, dysphagia is a frequent symptom in the acute and long-term phases, due to the toxic effects of therapies needed to confront the illness. Some studies have shown prophylactic oropharyngeal exercises to be quite useful in improving swallowing function after completion of chemo-radiation therapy (CRT) protocols; others have focused on their use to prevent or minimize post-CRT swallowing dysfunction. Patients' quality of life deteriorates greatly during CRT, with a peak of maximum intensity during the days immediately after finishing CRT treatment. Afterwards, function gradually improves, although scope or timeframe remains undetermined. Available evidence suggests that exercise therapy prior to oncological treatment could potentially improve deglutition and quality of life; however, a randomized study is needed to confirm this observation. Design/Methods: The Redyor singe-blind randomized clinical trial is designed to compare the effect of prophylactic oropharyngeal exercises on quality of life, dysphagia, and sustainability to the length of rehabilitative treatment. At enrollment, participants will be randomly assigned to one of two treatment groups. Both groups follow the protocol described here, although one group begins the training 2 weeks before initiating CRT and the other group just after finishing the therapy. Both groups will complete standard swallow therapy for training submental muscles involved and 3 sets of 5 inspiratory and expiratory repetitions using the Orygen Dual® valve, with a progressive weekly increase in workload. Discussion: This ongoing clinical trial, registered in 2016, is based on the hypothesis that undergoing a pre-radiotherapy rehabilitation (pre-habilitation) program will have greater benefits (less decrease in quality of life, less delay in swallowing parameters, and less severe dysphagia) compared to post-CRT rehabilitation. The primary objective is to assess dysphagia severity and evaluate quality of life due to swallowing dysfunction in HNC patients. Secondary objectives are to assess the correlation between a clinical variable and instrumental parameters in this period

Background

Squamous head and neck cancer (HNC) has high incidence in developed countries. HNC is categorized according to the area of the head or neck in which it occurs, with greater incidence in the larynx, followed by the oropharynx, oral cavity, and hypopharynx. At the time of diagnosis, 1% of all patients have a distant metastasis, with the highest rate (4%) observed in the nasopharynx and earlier-stage tumors located in the larynx and the oral cavity. Tobacco and alcohol use and human papilloma virus (HPV) infection are the most important risk factors.(1)

Although chemo-radiation therapy (CRT) protocols have been designed to preserve swallowing function and essential speech organs, dysphagia is a frequent symptom in these patients and the primary adverse effects are usually associated with acute or late swallowing disturbances.(2–6) Preservation of underlying anatomical structures does not guarantee normal function. CRT affects target areas and may result in lack of coordination of swallowing phases, lack of swallow coordination with respiratory function, reduced elevation of larynx, delayed laryngeal closure, loss of tongue strength, and prolonged

oral and pharyngeal time in swallowing.(6–9) Radiation-induced dysphagia pathogenesis includes an initial process of acute inflammation with the appearance of edema, which may be followed by fibrosis of the soft tissues resulting in neurological alteration and muscle damage. Xerostomia, pain, and pharynx obliteration are the key elements of acute-phase dysphagia. At 3 months, many patients have regained swallowing function. In later stages, with the appearance of diffuse fibrosis of the connective tissue and skin in the irradiated area, changes are observed in the efficacy and safety of swallowing. It is believed that hypoxia and chronic oxidative stress could perpetuate tissue damage even long after the end of treatment, which would explain the appearance of dysphagia in the chronic phase.(10) These side-effects contribute to higher rates of malnourishment, weight loss, and bronchoaspiration,(6),(11) resulting in a need for alternative or supplementary methods for feeding and hydration, both early and long-term.(8)

For years, delays have been reported in referring HNC patients undergoing CRT to Rehabilitation Departments. Patients were only referred when they presented with obvious swallow deficits or the consequent malnourishment, weight loss, changes in voice characteristics, etc., often months or years post-CRT.(12) The greater the delay, the worse is the patient's detrimental muscle disuse and swallow dysfunction.(13,14)

In recent years, there has been a growing interest in swallowing interventions. Potential benefits of prophylactic exercises conducted during(15–17), soon after(18), or before the CRT intervention(19) have been described, and an improvement in functional swallow outcomes and quality of life parameters after respiratory therapy (RT) intervention has been reported.(14) Nevertheless, supportive care for earlier dysphagia management in rehabilitation departments continues to play a secondary role in HNC diagnosis in most health systems.(9,12)

New ways to treat HNC dysphagia in an early intervention are now being explored, using Inspiratory and Expiratory Muscle Training (IEMT) –an *"old"* technique developed for patients with chronic obstructive pulmonary disease (COPD)(20) that has shown its usefulness in patients with dysphagia(21–25). Designed to improve respiratory muscle strength, IEMT also trains muscles involved in coughing, speech, and swallowing.(26) The hypothesis of the ongoing ReDyOr (**Re**habilitation **Dy**sphagia **Or**opharyngeal Cancer) study is that improvement of the swallowing function is due to the strengthening of the suprahyoid muscle (anterior portion of the digastric, mylohyoid, and geniohyoid). The suprahyoid/submental muscles participate in the pharyngeal phase of swallowing. Their weakness or lack of coordination can decrease the amplitude of the hyoid, causing an inadequate opening of the upper esophageal sphincter that exposes the airway to the passage of the bolus. Some authors have evaluated the effect of IEMT on the swallow muscles by videofluoroscopy swallow studies (VFSS), noting that the amplitude of the hyoid movements increase during training, both in the oral (jaw and tongue) and pharyngeal phases.(27) The usefulness of IEMT to train respiratory, cough, speech, and swallowing muscles is well established in pathologies other than COPD, such as stroke-related dysphagia,(28) but the most recent neurophysiological findings suggest the capacity for improving motor recruitment of the suprahyoid musculature, the activity of pharyngeal musculature, and the palate, as well as an increase in

the amplitude of the movements of the hyoid,(29),(30) could be considered and included as a new therapeutic tool for the treatment of HNC swallowing disturbances in the acute stage after diagnosis.

Available data suggest that pre-habilitation exercises could further improve these results.(18,19) The ReDyOr study is based on the hypothesis that an early intervention could promote a sustainable improvement in preservation of swallow function and quality of life. The main objective of this study is to explore the benefits of an early 8-week rehabilitation program (IEMT added to standard swallowing exercises), compared with participation in the same program after CRT completion. Secondly, this study aims to compare the effectiveness of the VFSS and Volume-Viscosity Swallow Test (V-VST) for screening dysphagia and to evaluate the effect of an IEMT and standard swallow exercises in a home-based dysphagia rehabilitation program in patients with HNC undergoing CRT.

Trial Design

The ReDyor study is a prospective randomized single-blind clinical trial aimed to determine the benefits of early rehabilitation to preserve swallow function and quality of life in patients with HNC receiving radiotherapy. The study is carried out in the Physical Medicine and Rehabilitation Department (Hospital de l'Esperança, Parc de Salut Mar, Barcelona), following the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).(31) Throughout the recruitment period, patients who provide their informed consent (Additional file 1) to participate will be randomized to one of two groups: early intervention or post-CRT intervention. No major changes to methods after the start of the study are planned. This trial has been approved by the local Clinical Ethics Committee (Additional File 2).

Methods

Subjects

Patients with advanced HNC receiving radiotherapy will be eligible to participate in this clinical trial. Potential participants will be excluded if they have previous history of HNC and/or head or neck radiation therapy or surgical treatment, or of dysphagia due to causes other than cancer. Inclusion and exclusion criteria are listed in **Table 1**.

Settings and locations

Recruitment will be carried out in the Radiotherapy Department at the Parc de Salut Mar (Hospital del Mar and Hospital de l'Esperança), Barcelona, Catalonia, Spain. Baseline dysphagia assessments will be performed in the Swallowing Disorders Unit of the Physical Medicine and Rehabilitation Department at Hospital de l'Esperança and all VFSS assessments will be conducted in collaboration with a radiologist. Statistical analysis will be done at the Hospital del Mar, in the Medical Research Institute (IMIM). Study sites and phases are summarized in the flow diagram (**Figure 1).**

During the study period, the patient will be excluded from the study if any of the following occurs: emergence of any of the exclusion criteria, onset of any disease or medical condition that will make it

difficult for the patient to continue participation, decision to withdraw from the study for any reason, transfer out of the service area, or death, impossibility to practice exercises due to medical condition.

Intervention

The training protocol consists of IEMT and standard swallowing exercises. Patients are instructed to maintain a rate of 15-20 breaths/min using the Orygen-Dual® valve (described elsewhere in detail) (21,22), a respiratory device that allows patients to train inspiratory and expiratory muscles simultaneously. Training loads will be set at a pressure equivalent to 10 maximal repetitions (if tolerated). These external pressures will be regulated weekly at 30% of maximal inspiration/expiration respiratory measures obtained. Patients will be instructed to perform 3 sets of 5 repetitions and standard swallowing exercises (mobility and tonicity exercises of the tongue, palate, larynx, and constrictor muscles), 3 times/day, 5 days/week, for 21 weeks. An experienced swallowing therapist will supervise IEMT weekly. The protocol will be the same for both groups, but one group will start 2 weeks before CRT and the other one will begin immediately after completing CRT **(Figure 1).**

Outcome measures

Main outcome variables:

· Change in dysphagia severity observed by VFSS and assessed with the Penetration-Aspiration Scale: scores 1-2 indicate normal swallowing, 3-5 penetration, and ≥6 aspiration.

· Change in quality of life, assessed with the European Organization of Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) and its Head and Neck Cancer Module (QLQ-H&N35).

Secondary outcome variables:

· Mouth opening or the maximal interincisor opening (MIO) of the mouth, using the Therabite® range of motion scale

· Maximum isometric tongue pressure (MIP) in an anterior position

· Maximum inspiratory and expiratory pressures (PImax and PEmax, respectively)

· Volume-Viscosity Swallow Test, a screening test to detect swallowing disturbances. The V-VST evaluates impaired security (tone of voice, coughing during or after eating, or desaturation >3% compared to baseline pulse oximetry) and efficacy in oral and pharyngeal phases.

· Subjective difficulty of swallowing will be assessed by a Visual Analogic Scale (VAS). This scale ranges from 0 to 10; a low score indicates no difficulties in eating and a high score, no oral intake.

· Peak Cough flow (PCF) will be used to evaluate the effect on respiratory muscle training on voluntary cough. It is measured with spirometer in liters/minute. Patients will be instructed to perform 3 repetitions

of voluntary cough, the best one will be chosen.

Study protocols

Patients eligible for inclusion who do not meet any exclusion criteria will be referred for baseline function assessment to the Rehabilitation Department. The study outcomes will be assessed at baseline (pre-RT, tx), at the beginning of RT (t1), at the end of RT (t3), and thereafter at 3 months (t4), 6 months (t5), and 12 months (t6). The Redyor schedule of enrollment is shown in **Figure 2**.

Randomization and blinding

Participant randomization to study groups will be performed independently of the hospital's physical therapists. When a new patient meets the eligibility criteria, a researcher (PF) in the Radiotherapy department will inform the licensed physical therapist (OPC), who will assign the anonymized patient record to one of the study groups using a random number generator program. The interdisciplinary researchers (EM, AGS, PF) will be blinded to study group assignments over the entire study period. After data analysis has been completed, results will be released to all patients and to participating clinicians and researchers.

Sample size calculation

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, and assuming a 20% loss to follow-up, a total sample size of 52 patients (26 in each group) will be required to detect a difference ≥10 units in the test of quality of life and 2 units in the PAS.

Statistical analysis

Numerical variables will be expressed descriptively as mean and standard deviation (*SD*). The evaluation of the correlations between variables will be based on the quantitative variables obtained from the various studies and bivariate (ordered Spearman correlation) and multivariate (multiple regression) analysis. Student t-test for paired data will be used for comparison of the quantitative variables before and after the intervention. The level of alpha risk accepted for all tests will be 0.05.

Ethics and dissemination

National and international research ethics guidelines will be followed, including the Deontological Code of Ethics, Declaration of Helsinki, and current confidentiality laws concerning personal data in Spain *(Ley Orgánica 15/1999, 13 December)* and the European Union *(European Parliament and Council Regulation EU 2016/619)*. Detailed, understandable oral and written information will be provided to patients and family members, and informed consent to participate will be signed by all participants. In patients with dementia, written informed consent will be obtained from the main caregiver (Additional file 1). The Redyor study protocol and the informed consent process have been reviewed and approved by the Clinical Ethics Committee of the *Institut Hospital del Mar d´Investigacions Mèdiques*, Barcelona, Spain

(*Comité Ètic d'Investigació Clínica Parc de Salut Mar*: reference number 2015/6288/I) (Additional file 2). Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines will be followed throughout (32) (Additional file 3). This trial is supported by the *Asociación Española contra el Cáncer* (AECC) and was registered at www.clinicaltrials.gov with code NCT02900911 on February 9, 2016.

Discussion

Rehabilitation intervention in acute HNC patients is currently limited in Spain. Swallow disturbances are considered a side-effect during CRT, and early swallowing and speech intervention is not systematically considered. Acute side-effects are considered "*normal*" in the development of the illness and during treatment, and the Rehabilitation Department becomes involved only when a patient demands a referral or a clinician requests an evaluation; decision protocols have not yet been developed. On the other hand, there is increased interest in facing this problem, first by developing a good screening method to determine which patients require evaluation, and then evaluating new treatment techniques, including in-home training.

A challenge when dealing with dysphagia related to HNC is determining the clinical profile of patients who might benefit from rehabilitation interventions (e.g. IEMT). Research is urgently needed to identify the usefulness of various dysphagia screening methods and therapeutic interventions such as IEMT.

Limitations of the study (Pros and cons)

The study has several potential limitations that must be considered. First, losses to follow-up are common in cancer studies; to address this concern, sample size estimation assumed a loss of about 20% of patients (higher than the usual 10-15% used in previous studies). Second, the study lacks a control group; however, this design is justified by the available evidence of the benefits of swallow and speech therapy in patients with HNC-related dysphagia.

Repercussions of the Redyor Study

Interventions to help patients confront, manage, and treat dysphagia are urgently needed. The lack of randomized controlled trials in the early diagnosis of HNC and the high number of patients lost to follow-up due to CRT side-effects highlight the potential scientific contributions of this study.

Trial Status

Protocol version number: Redyor_2

Begin recruitment: 03/25/2015

End- recruitment: 08/21/2018

End Data collection: 04/29/2019

Trial status: Enrollment is in progress; final data collection will end May 2019

List Of Abbreviations

CRT: Chemo-Radiotherapy treatment; VFSS: videofluoroscopy swallowing study.

Declaration Section

Ethical approval and consent to participate

National and international research ethics guidelines will be followed, including the Deontological Code of Ethics, Declaration of Helsinki, and current confidentiality laws concerning personal data in Spain *(Ley Orgánica 15/1999, 13 December)* and the European Union *(European Parliament and Council Regulation EU 2016/619)*. The Redyor study protocol and the informed consent process have been reviewed and approved by the Clinical Ethics Committee of the *Institut Hospital del Mar d´Investigacions Mèdiques*, Barcelona, Spain (*Comité Ètic d'Investigació Clínica Parc de Salut Mar*. reference number 2015/6288/I) (Additional file 2). Standard Protocol followed SPIRIT guidelines will be followed throughout (Additional file 3) and was registered at www.clinicaltrials.gov with code NCT0209009911 on February 9, 2016. *Informed Consent* (Additional file 1) was obtained from all individual participants included in the study.

Data availability statements

The datasets generated and/or analyzed during the current study are not publicly available due to the amount of data generated but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PF and AGS are the principal investigators for this trial. They designed the protocol and are responsible for oversight of all aspects of the study. NBS is the physiatrist co-investigator for this study, and this study is included as a part of her doctoral thesis and research profile. She is responsible for oversight of the primary data collection site and has contributed to study design and manuscript preparation and review. OPC is a research associate working on this study. He has designed the database used for data

collection and will randomize the patients. EMN is a research associate. She has contributed to protocol design and manuscript preparation and review. All authors read and approved the final manuscript.

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References

REFERENCES

1. Quer M, León X, Orús C, Recher K, Gras JR. Analysis of 2,500 squamous cell carcinoma of the head and neck. Acta Otorrinolaringol Esp. 2001 Apr;52(3):201–5.

2. Stenson KM, MacCracken E, List M, Haraf DJ, Brockstein B, Weichselbaum R, et al. Swallowing function in patients with head and neck cancer prior to treatment. Arch Otolaryngol Head Neck Surg. 2000 Mar;126(3):371–7.

3. Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009 Jun;17(3):172–8.

4. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys. 2009 Oct 1;75(2):385–92.

5. Murphy BA, Gilbert J. Dysphagia in head and neck cancer patients treated with radiation: assessment, sequelae, and rehabilitation. Semin Radiat Oncol. 2009 Jan;19(1):35–42.

6. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MWS, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. NIH Public Access; 2012 Dec 1;118(23):5793–9.

7. Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. J Clin Oncol. 2006 Jun 10;24(17):2636–43.

8. Kraaijenga SAC, Oskam IM, van der Molen L, Hamming-Vrieze O, Hilgers FJM, van den Brekel MWM. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. Oral Oncol. 2015 Aug;51(8):787–94.

9. Pauloski BR, Rademaker AW, Logemann JA, Lazarus CL, Newman L, Hamner A, et al. Swallow function and perception of dysphagia in patients with head and neck cancer. Head Neck. 2002 Jun;24(6):555–65.

10. Tedla M, Valach M, Carrau RL, Varga I, Profant M, Mráz P, et al. Impact of radiotherapy on laryngeal intrinsic muscles. Eur Arch Otorhinolaryngol. 2012 Mar 8;269(3):953–8.

11. Barnhart MK, Ward EC, Cartmill B, Robinson RA, Simms VA, Chandler SJ, et al. Pretreatment factors associated with functional oral intake and feeding tube use at 1 and 6 months post-radiotherapy (+/-chemotherapy) for head and neck cancer. Eur Arch Otorhinolaryngol. 2017 Jan;274(1):507–16.

12. Schindler A, Denaro N, Russi EG, Pizzorni N, Bossi P, Merlotti A, et al. Dysphagia in head and neck cancer patients treated with radiotherapy and systemic therapies: Literature review and consensus. Crit Rev Oncol Hematol. 2015 Nov;96(2):372–84.

13. Pauloski BR, Logemann JA. Impact of tongue base and posterior pharyngeal wall biomechanics on pharyngeal clearance in irradiated postsurgical oral and orophayngeal cancer patients. Head Neck. 2000;22:120–31.

14. Wall LR, Ward EC, Cartmill B, Hill AJ, Porceddu S V. Adherence to a Prophylactic Swallowing Therapy Program During (Chemo) Radiotherapy: Impact of Service-Delivery Model and Patient Factors. Dysphagia. Springer US; 2016 Nov 14;32(2):1–14.

15. Tang Y, Shen Q, Wang Y, Lu K, Wang Y, Peng Y. A Randomized Prospective Study of Rehabilitation Therapy in the Treatment of Radiation-induced Dysphagia and Trismus. Strahlentherapie und Onkol. 2011 Jan 10;187(1):39–44.

16. Cnossen IC, van Uden-Kraan CF, Witte BI, Aalders YJ, de Goede CJTT, de Bree R, et al. Prophylactic exercises among head and neck cancer patients during and after swallowing sparing intensity modulated radiation: adherence and exercise performance levels of a 12-week guided home-based program. Eur Arch Otorhinolaryngol. 2017 Feb;274(2):1129–38.

17. Duarte VM, Chhetri DK, Liu YF, Erman AA, Wang MB. Swallow preservation exercises during chemoradiation therapy maintains swallow function. Otolaryngol - Head Neck Surg (United States). 2013;149(6):878–84.

18. Roe JW, Ashforth KM. Prophylactic swallowing exercises for patients receiving radiotherapy for head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. 2011 Jun;19(3):144–9.

19. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012 Apr 1;138(4):376–82.

20. Gea J, Agustí A, Roca J. Pathophysiology of muscle dysfunction in COPD. J Appl Physiol. 2013 May;114(9):1222–34.

21. Marco E, Ramírez-Sarmiento AL, Coloma A, Sartor M, Comin-Colet J, Vila J, et al. High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. Eur J Heart Fail. 2013 Aug;15(8):892–901.

22. Guillén-Solà A, Messagi Sartor M, Bofill Soler N, Duarte E, Barrera MCMC, Marco E. Respiratory muscle strength training and neuromuscular electrical stimulation in subacute dysphagic stroke patients: A randomized controlled trial. Clin Rehabil. 2016;31(6):026921551665244.

23. Messaggi-Sartor M, Guillen-Solà A, Depolo M, Duarte E, Rodríguez DA, Barrera M-C, et al. Inspiratory and expiratory muscle training in subacute stroke: A randomized clinical trial. Neurology. 2015;85:564–72.

24. Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2012;13(1):33–43.

25. De Menezes KKP, Nascimento LR, Polese JC, Ada L, Teixeira-Salmela LF. Effect of high-intensity home-based respiratory muscle training on strength of respiratory muscles following a stroke: a protocol for a randomized controlled trial. Brazilian J Phys Ther. 2017;21(5):372–7.

26. Park JS, Oh DH, Chang MY, Kim KM. Effects of expiratory muscle strength training on oropharyngeal dysphagia in subacute stroke patients: A randomised controlled trial. J Oral Rehabil. 2016;43(5):364–72.

27. Sapienza CM. Respiratory muscle strength training applications. Curr Opin Otolaryngol Head Neck Surg. 2008;16:216–20.

28. Menezes KK, Nascimento LR, Avelino PR, Alvarenga MTM, Teixeira-Salmela LF. Efficacy of Interventions to Improve Respiratory Function After Stroke. Respir Care. 2018 May 29;respcare.06000.

29. Wheeler KM, Chiara T, Sapienza CM. Surface electromyographic activity of the submental muscles during swallow and expiratory pressure threshold training tasks. Dysphagia. 2007 Apr 9;22(2):108–16.

30. Hutcheson KA, Hammer MJ, Rosen SP, Jones CA, McCulloch TM. Expiratory muscle strength training evaluated with simultaneous high-resolution manometry and electromyography. Laryngoscope. 2017;127(4):797–804.

31. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010 Jun 1;152(11):726–32.

32. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013 Jan;346:e7586.

Tables

Table 1. Inclusion and exclusion criteria of ReDyOr study

Inclusion Criteria	Exclusion criteria
Advanced HNC	Previous history of HNC
Receiving Radiotherapy	Previous head or neck radiation therapy
	Surgical treatment on HNC area
	dysphagia due to causes other than cancer

HNC: Head and neck cancer

Figures

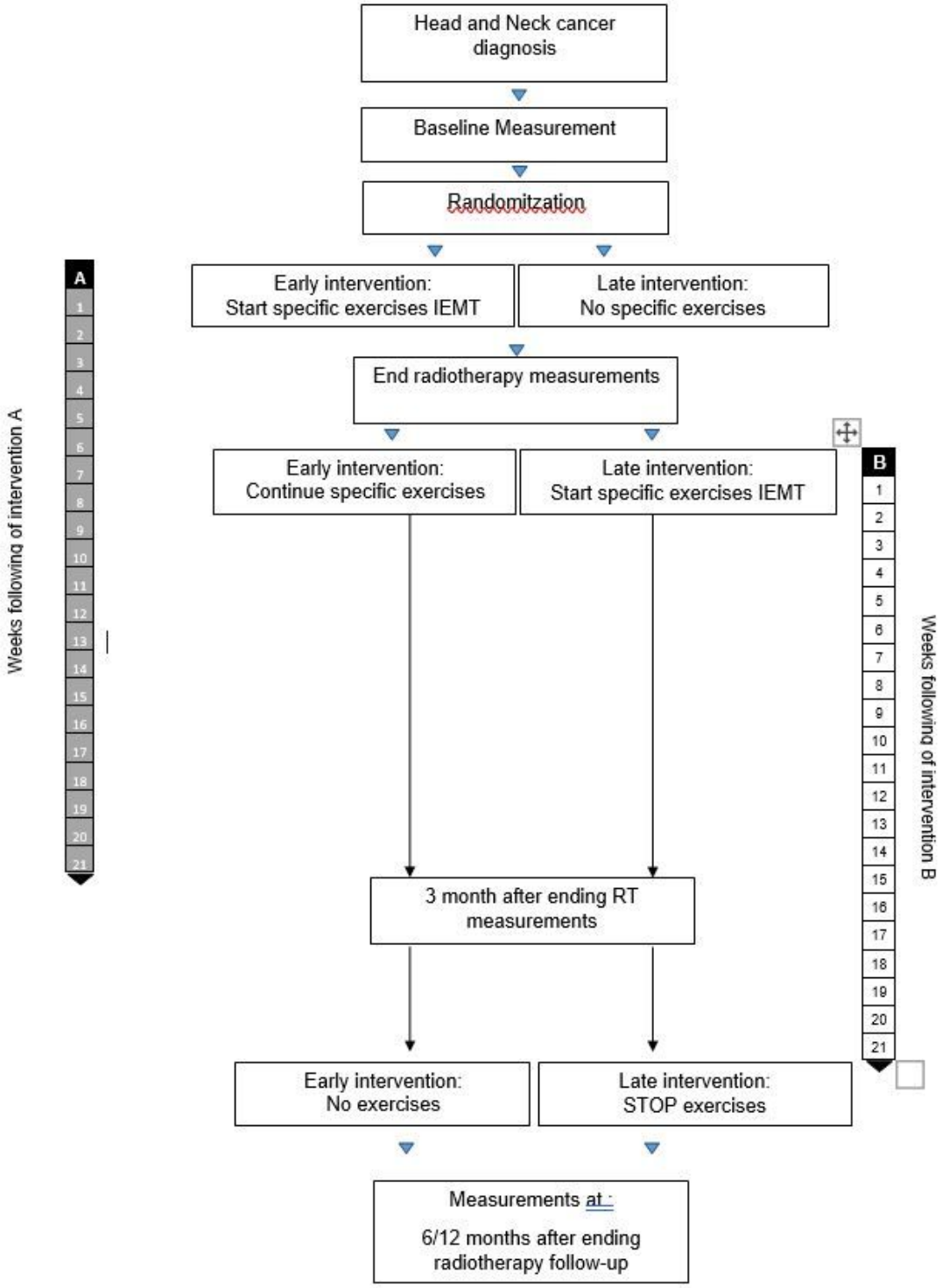
Head and Neck cancer diagnosis
Baseline Measurement
Randomitzation
Early intervention: Start specific exercises IEMT
Late intervention: No specific exercises
End radiotherapy measurements
Early intervention: Continue specific exercises
Late intervention: Start specific exercises IEMT
3 month after ending RT measurements
Early intervention: No exercises
Late intervention: STOP exercises
Measurements at :
6/12 months after ending radiotherapy follow-up
Weeks following of intervention A
Weeks following of intervention B
A
B

Figure 1

		STUDY PERIOD								
	Enrolment	Allocation		Post-allocation						Close-out
TIMEPOINT**	$-t_1$	0	T_x	t_1	t_2	t_3	t_4	t_5	t_6	t_x
			Base line	Pre-RT	RT	End-RT	3mo post RT	6mo post RT	12mo post RT	
ENROLMENT:										
Eligibility screen										
Informed consent										
Anamnesis										
Allocation										
INTERVENTIONS:										
Starting Intervention A				X						
Starting Intervention B						X				
Finishing Intervention A							X			
Finishing Intervention B								X		
ASSESSMENTS:										
List outcomes variables										

**TIMEPOINT: t_1 *Before starting RT;* t_2 *During the RT;* t_3 *After finishing RT;* t_4 *Three months after finishing RT;* t_5 *Six months after finishing RT:* t_6 *Twelve months after finishing RT.*

Figure 2

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc
- supplement2.pdf