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ORIGINAL ARTICLE

Swallowing therapy and progressive resistance training in head and neck cancer patients undergoing radiotherapy treatment: randomized control trial protocol and preliminary data

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ABSTRACT

Background: Head and neck cancer (HNC) patients are often challenged by treatment induced dysphagia and trismus. Traditionally, rehabilitation is initiated when loss of function has already occurred. There is increasing evidence that it is of benefit to patients to initiate an early rehabilitation process before and during treatment. HNC patients have a unique set of functional challenges such as pre- and post-treatment dysphagia, pain and weight loss. The aim of the trial is to investigate the effects of swallowing and mouth-opening exercises combined with progressive resistance training (PRT) during radiotherapy. This report presents the protocol, interim inclusion and feasibility data.

Material and methods: The trial (clinicaltrials.gov NCT02385929) is a multicenter randomized controlled trial (RCT) with a parallel-group randomization (1:1). The planned sample size of 240 HNC patients is randomly assigned to either (1) twice weekly PRT and three times weekly swallowing exercises by physio- and occupational therapists, respectively, as well as daily home exercises throughout radiotherapy or (2) standard care. Inclusion criteria are patients with cancer in the larynx, pharynx, oral cavity, or unknown primary tumor who are referred to radiotherapy with curative intent. Outcomes are measured at end-of-treatment and two, five, and 12 months post-treatment.

Interim results: In 16 months, 321 HNC patients were screened for eligibility. Of these, 131 (41%) were eligible according to inclusion criteria. One-hundred-and-fifteen patients were invited to participate of which 69 (60%) were enrolled in the trial and randomized for either intervention or control group with 10 drop-outs (14%). The six pilot patients adhered more than 90% to the program.

Conclusion: Preliminary results show that exercise according to protocol is tolerable and feasible.

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Rehabilitation of cancer patients is initiated following active cancer treatment. However, emerging data suggest that cancer patients may benefit from initiating early prehabilitation before and throughout treatment, in order to prevent symptoms and late effects [1]. Prehabilitation thus aims to preserve and enhance pretreatment functional capacity for better tolerance of treatment, facilitate recovery, and prevent development of severe late effects [2].

Head and neck cancer (HNC) patients have challenges clustering around dysphagia, xerostomia, pain, and weight loss [3–5]. Dysphagia is considered the most prominent complication to HNC treatment as it impacts physical function and reduces quality of life (QoL) [6,7]. In addition, between 9 and 31% of HNC patients meet public health guidelines for physical activity [8]. Silver et al. [9] showed that weight loss in HNC patients treated with chemoradiotherapy began after only one week of treatment and that most weight loss was of lean body mass (LBM) rather than fat. Loss of LBM was significantly associated with declining physical performance and increased functional dependence [10].

Research based on pilot studies and small scale trials suggests that the potential benefit from interventions to promote general physical activity and exercise before, during and after treatment may be of value for this patient group [11–13], and that HNC patients may also benefit from exercises before and during treatment to promote strength, mobility, and endurance of base of tongue, pharyngeal constrictors, and suprahyoid strap muscles [14–17].

The primary objective of SYNK (Danish for swallow) is to investigate the effect on swallowing of a bimodal program of swallowing and mouth-opening exercises and progressive resistance training (PRT) during radiotherapy treatment compared to standard care. Secondary aims include effects on symptoms such as fatigue, pain, nausea or xerostomia, health-related QoL, depression and anxiety, nutritional status, tube dependency and intake of different textures, and also

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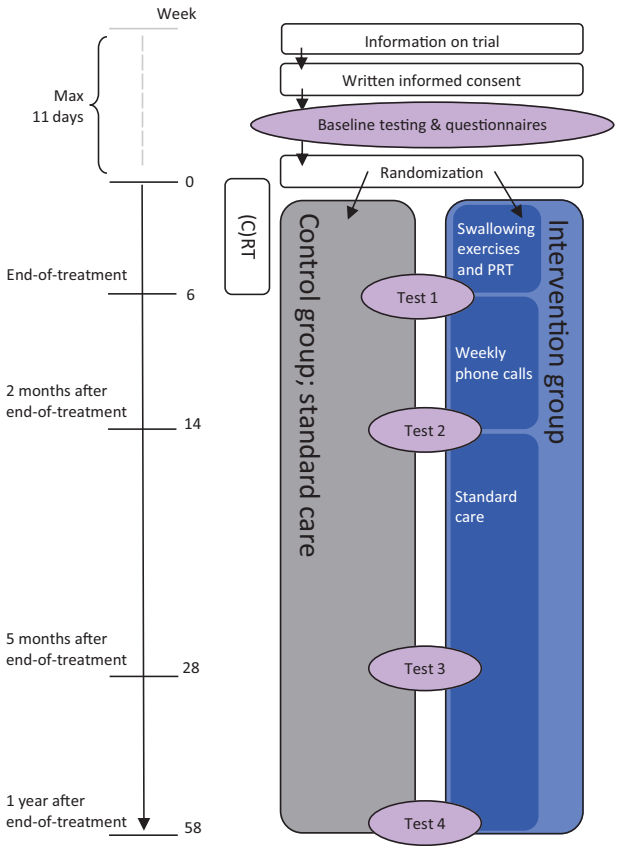

Figure 1. Trial design and timeline for participation.

length of hospital stays. We present here the study protocol, interim data on inclusion and pilot data on adherence to the SYNK program.

Material and methods

Study design

SYNK is a multicenter randomized controlled trial (RCT) with a parallel-group randomization (1:1). A total of 240 patients from the Departments of Oncology, Rigshospitalet and Naestved Hospital, both University of Copenhagen, will be assigned to a bimodal program of swallowing exercises and PRT or standard care (Figure 1).

The following patients are included: aged 18 years or more and diagnosed with incident cancer in larynx, hypopharynx, oral cavity, oropharynx, or unknown primary tumor. Patients should be treated with curative intent and be self-reliant in activities of daily life.

Patients with recurrence or new primary malignancy, patients who do not speak Danish, who cannot cooperate, are pregnant, diagnosed with severe comorbidities that reduce compliance with the intervention, or patients who cannot cooperate with Fiberoptic Endoscopic Evaluation of Swallowing (FEES) are excluded.

When eligibility is established via review of medical records, patients are provided written and oral information about the trial. Upon signed informed consent baseline examinations is conducted followed by randomization. Patients who decline to participate are invited to fill out the baseline questionnaire. The randomization sequence is computer generated and developed by an impartial statistician in a trial management database (synk.cancer.dk). Randomization is stratified by center, concomitant chemotherapy (cisplatin yes/no) and tumor subsite: (1) oropharynx or unknown primary; (2) hypopharynx; (3) larynx or (4) oral cavity with a 1:1 allocation ratio in block sizes of eight. Once baseline tests are conducted stratification parameters are entered in the trial management database by project occupational therapist (OT) who subsequently informs the participant by telephone on group allocation. The allocation sequence is concealed from researchers and outcome assessors. In Denmark, it is normal practice that OTs specialize in swallowing therapy. OTs involved in the trial are trained in facio oral tract therapy (FOTT) and have experience from acute neurology and cancer therapy.

Intervention group

The intervention consists of two parts: (1) swallowing and mouth-opening exercises and (2) PRT. Both swallowing and PRT exercises, supervised by OT and physiotherapists (PT) are continued throughout the radiotherapy.

Swallowing exercises

Three times a week participants perform a swallowing and mouth-opening exercise program under supervision by OT applied as an individual selection of some or all of the following: Mendelsohn maneuver, Masako maneuver, Effortful swallow, Shaker exercise, jaw movement exercises, tongue base resistance training, exercises for tongue coordination and movement, Valsalva, and supraglottic swallowing technique. The individualized program is regularly adjusted to accommodate the increasing and changing difficulties through the course of radiotherapy. Each participant is provided a booklet with written instructions on each exercise. The exercise program is to be performed three times daily and participants are asked to keep a training logbook to evaluate adherence to home exercises. During the first two months after end-of-treatment the OT makes weekly phone calls to the participants to encourage continuous engagement in home-based exercises, and to advise patients on modifications of the exercise program.

Progressive resistance training

Twice weekly participants do PRT supervised by PT. Following a short warm-up the PRT sessions consists of leg press, knee extension, chest press, and lateral pull down with three sets of 5–8 repetitions at 70–85% of one repetition maximum (RM), and three sets of abdominal crunch and back extensions with 10–14 repetitions. A fixed progression model is followed to ensure hypertrophy training. Participants are RM tested at baseline and after three weeks. Orthopedic limitations are taken into consideration to ensure safe intensity increase. If necessary, progression is done differently, for instance by increasing duration and the number of exercises or by adjusting number of sets and/or

repetitions. After each PRT session participants are offered approximately 10 g of protein (protein rich chocolate milk or alike) to boost protein uptake immediately post-workout.

Standard care

The control group receives standard care in accordance to current practice at each of the two hospitals. At one hospital standard care include a two-hour education session run by nurse, dietician, and physician prior to radiotherapy and a two-hour follow-up session on late effects two months after radiotherapy. A video and a pamphlet with neck and jaw movement exercises are provided. No OT or PT guidance are systematically offered prior to or during radiotherapy. In the other hospital standard care include referral to OT assessment prior to radiotherapy with instruction in relevant swallowing exercises. OT follow-up frequency and referral to PT depends on individual assessments and all patients are followed up by OT two weeks after end-of-treatment. In both hospitals patients are regularly provided counseling by dietician.

Assessments

Baseline data is obtained from medical records. Participants complete questionnaires at baseline, at end of radiotherapy and two, five and 12 months after radiotherapy, and meet for clinical observer-rated assessments on same occasions as illustrated in Table 1. An OT, who is blinded to group allocation, performs observer-rated outcome measures (Table 1).

Statistical methods

Sample size estimations

The sample size calculation was based on the detection of relevant clinical change on the fatigue subscale of EORTC QLQ-C30 [18] as fatigue is the primary endpoint for the PRT intervention. According to the EORTC QLQ-C30 scoring manual a change of 10 + points can be considered a moderate to large clinical significant change. Assuming a significance level of 0.05 and power of 80% we need 100 patients in each arm to detect a difference of 10 points [standard deviation (SD) 25]. With an expected dropout of 20% we plan to randomize 240 patients in the SYNK trial.

Statistical analyses

All analyses will be on an 'intention-to-treat' basis. First, dysphagia as a binary variable (normal vs. abnormal swallowing) is assessed. Second, a continuous outcome; penetration aspiration scale (PAS) is used to compare the change in penetration aspiration score [19]. PAS is scored independently by two outcome assessors immediately after FEES examination. For the secondary outcomes the mean changes from baseline will be compared using multiple regression analyses for fatigue, LBM, weight, mouth opening, pain, physical functioning and strength, tube dependency, and QoL. Sensitivity analysis will be conducted to analyze the effect of missing covariates and patients lost to follow-up.

Ethics and data protection

This trial is approved by the Research Ethics' Committee of the Capital Region, Denmark (H-2-2014-074 including amendment 47007 and 51092) and the Danish Data Protection Agency (30-1378). The trial is registered at clinicaltrials.gov: NCT02385929.

Preliminary results

Feasibility of the SYNK program

In a pilot study we enrolled six of nine eligible patients who were all offered the intervention (Tables 2 and 3) and obtained an adherence rate to the intervention of 91% for the PRT and 92% for the swallowing therapy, with completers participating in 25 sessions (range 20–27). During the two months radiotherapy completers performed daily home-training exercises with an average exception of two days (range 0–5).

Table 1. Assessments in the SYNK trial.

		Time point				
	Measure	Baseline	End-of-treatment	2[a]	5[a]	12[a]
Medical history	• Cancer diagnosis, Co-morbidity, Current Disease stage, Treatment modality -and dose, HPV status etc.	X				
	• Tube dependency (days of), PEG and nasogastric respectively		Throughout trial, continuously			
Observer-rated	• Penetration Aspiration Score/FEES	X		X		X
	• 30 seconds sit-to-stand test (STS)	X	X	X	X	X
	• Body weight	X	X	X	X	X
	• Maltron bio-impedance; LBM	X	X	X		
	• Therabite Range of Motion scale	X	X	X	X	X
	• Functional Oral Intake Scale (FOIS)	X	X	X	X	X
	• ECOG performance	X	X	X	X	X
Patient-reported outcomes (questionnaires)	• Quality of Life Questionnaire – Core (EORTC QLQ-C30)	X	X	X	X	X
	• Quality of Life Questionnaire – Head and Neck Cancer (EORTC QLQ H&N35)	X	X	X	X	X
	• Health-Related Quality of Life	X	X	X	X	X
	• MD Anderson Dysphagia Inventory (MDADI)	X	X	X	X	X
	• Swallowing screening (EAT-10)	X		X		X
	• Pain; Numerical rating scale (NRS)	X	X	X	X	X
	• Major Depression Inventory (MDI)	X	X	X	X	X
	• Symptom Check List (SCL-92) anxiety subscale	X	X	X	X	X

[a]Months after end-of-treatment.

Table 2. Demographic, disease and treatment characteristics of 6 pilot participants, 69 RCT participants, and 46 who refused to participate (decliners) in the SYNK trial.

	Pilot $n=6$	RCT $n=69$ (%)	Decliners $n=46$ (%)
Mean age at inclusion in years (range)	57 (42–67)	62 (39–80)	63 (42–76)
Age (years)			
<49	1	3	4
50–59	3	26 (38)	12 (26)
60–69	2	28 (41)	18 (39)
≥70	–	12 (17)	12 (26)
Sex			
Male	3	57 (83)	34 (74)
Female	3	12 (17)	12 (26)
Tumor site			
Oropharynx	3	38 (55)	20 (43)
Larynx	2	21 (30)	11 (24)
Cavum oris	–	4	9
Hypopharynx	1	5	5
Unknown primary	–	1	1
p-16 (HPV)			
Positive	3	33 (48)	15 (33)
Negative	3	31 (45)	29 (63)
Unknown	–	5	2
Disease stage			
I	1	9	7
II	–	7	7
III	2	10 (14)	9
IV	3	43 (62)	23 (50)
Treatment			
Radiotherapy only	1	29 (42)	25 (54)
Concurrent chemo- and radiotherapy	5	33 (48)	16 (35)
Surgery before (chemo)radiotherapy	–	7	5

Participants found it both necessary and useful to participate in the intervention. We concluded that PRT and swallowing therapy are feasible in HNC patients undergoing radiotherapy.

Interim inclusion into SYNK

We screened 321 patients and 115 of 131 eligible (88%) patients were invited to participate and 69 out of these (53%) were randomized with a total of 10 drop-outs (14%). Ten of the 46 patients who declined participation completed the baseline questionnaire (Figure 2). Of the invited patients, 79% were men; oropharyngeal cancers accounted for 50% of the diagnoses, followed by laryngeal cancers (28%), cancers in the oral cavity (11%), hypopharynx (9%) and lymph node metastases from unknown primary tumor (2%). Patients had been referred to radiotherapy only (47%), chemoradiotherapy (43%), or surgery followed by (chemo)radiotherapy (10%). The majority (57%) had stage IVA-B cancer, and 42% were HPV-associated (p16-positive) (Table 2). Logistic regression was performed to assess the differences between participants and patients who refused to participate (*decliners*). The model contained six variables (age, sex, primary tumor site, HPV status, treatment, and disease stage). No significant differences were seen between participants and decliners in any of the variables ($p>0.05$). Table 3 displays self-reported lifestyle and socioeconomic characteristics of 69 participants and 10 decliners who completed baseline questionnaires.

Table 3. Self-reported socioeconomic and lifestyle characteristics of 6 pilot participants, 69 RCT participants and 10 patients who refused to participate ('decliners') but who filled in the baseline questionnaire in the SYNK trial.

	Pilot $n=6$ (%)	RCT $n=69$ (%)	Decliners with baseline questionnaire $n=10$
Civil status			
Single	–	23 (33)	3
In a relationship but living alone	–	8	1
Married/Cohabiting	6	33 (48)	6
Missing	–	5	–
Children			
No children	–	13 (19)	1
Children living at home	2	8	2
Children not living at home	4	43 (62)	7
Missing	–	5	–
Labor market affiliation			
Employed	4	31 (45)	3
Unemployed	1	5	1
Pensioner, regular	1	24 (35)	6
Early retirement	–	4	–
Missing	–	5	–
Highest education			
Low[b]	2	16 (23)	4
Medium[b]	1	26 (38)	5
High[b]	3	22 (32)	1
Missing	–	5	–
Smoking			
Current smoker	2	16 (23)	2
Used to smoke	4	35 (51)	4
Never smoked	–	11 (16)	3
Missing		7	1
Pain			
No pain, NRS = 0	–	21 (30)	4
Mild pain, NRS = 1–3	4	28 (41)	3
Moderate pain, NRS = 4–6	1	6	2
Severe pain, NRS = 7–10	1	7	1
Missing	–	7	–
Alcohol (units per week)			
Never drinks alcohol	–	12 (17)	3
<7/14[a]	4	31 (45)	3
7–14/14–21[a]	–	10 (15)	3
>14/21[a]	2	7	–
Missing	–	9	1

[a]National alcohol recommendations; Low risk: ≤7 units for women and ≤14 units for men. High risk: >14 units for women and >21 units for men; [b]Short education: primary through lower secondary, Medium education: Upper secondary, High education: Tertiary (>13 years) (high short 15 years, high medium 16 years, high long >16 years).

Discussion

To our knowledge SYNK is the first trial with an individually planned and supervised exercise intervention that targets both dysphagia and general physical function among HNC patients during radiotherapy.

HNC patients constitute a relatively small patient group and prior experience has shown that these patients can be hard to include in supportive care trials [13,20]. So far, we have achieved a high invitation rate among eligible patients and further managed to include more than half of invited patients. Inclusion does not seem to be related to any demographic or disease-specific factors in this interim analysis.

The rationale behind SYNK is 'use it or lose it'. Acute toxic effects of radiotherapy with consequent decrease in oral intake and tube insertion may prompt disuse atrophy on top of accumulating radiation tissue damage [15,21]. The SYNK swallowing exercise program cover exercises specifically recommended for preventive and therapeutic swallowing interventions in HNC patients although currently not used in the Danish standard care [22]. PRT is introduced to halt the

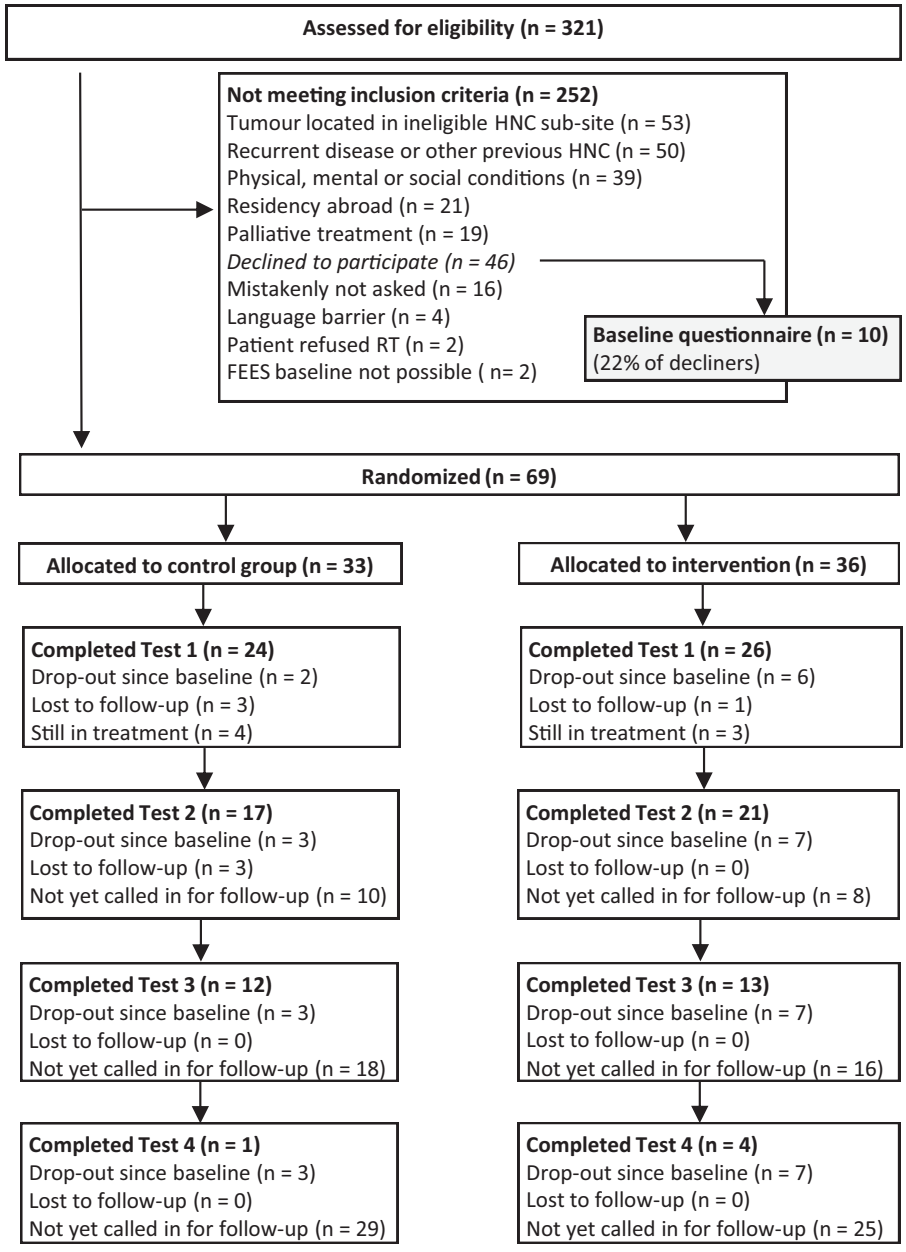

Figure 2. CONSORT flow diagram, patient flow 11 May 2015–5 September 2016.

wasting of muscle mass secondary to reduced intake of food and other acute effects of radiotherapy [23,24] and thus buffer against decline in physical function and other QoL aspects [9]. The PRT module builds on principals and exercises already tested and used in cancer patients undergoing chemotherapy and described by Adamsen et al. [25]. Despite potential benefits of aerobic training on other outcomes we chose to focus on resistance training which is known to build muscle mass in healthy adults [26]. At the time of initiating SYNK in 2015 no published trials had tested the effect or feasibility of PRT *during* treatment on HNC patients specifically. However, Lonbro et al. [13] showed promising results in rebuilding LBM by performing PRT with HNC patients *after* radiotherapy. This taken together with the high adherence to both the supervised and home-based training seemed an appropriate and realistic intervention modality for the target group.

The SYNK program is relatively intensive with both supervised and home-based swallowing exercises and PRT. However, the planning of the SYNK program actively accommodates patients' busy treatment schedules to minimize waiting time between appointments. Hence, all training sessions and outcome assessments are planned to match already scheduled events that are part of standard care, including radiotherapy, chemotherapy, dietary counseling, doctor's appointments, etc. Taken together with the high adherence to both the swallowing and the resistance training, still the SYNK program seemed an appropriate and realistic intervention modality for the target group.

In conclusion, the high rate of invitation as well as inclusion so far may reflect that the SYNK intervention is acceptable to both health staff and patients despite the timing of approaching patients and the busy schedule in the short

time span between diagnosis, treatment planning, and initiation. Further, pilot adherence indicates that SYNK is both feasible and acceptable to patients during radiotherapy.

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Disclosure statement

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