Reduction of organ motion during radiotherapy by non-invasive mechanical ventilation supported breathing control.

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OBJECTIVE: to evaluate the feasibility of quantifying reduced dose to organs at risk by reducing (residual) organ motion and further increasing distances between the radiation target and normal tissues as a result of regularized breathing,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56026

Source
ToetsingOnline

Brief title
Breathing control during radiotherapy. / BreaCoRTH

Condition

- Other condition

Synonym
Organ motion

Health condition

Gezonde proefpersonen zonder aandoeningen. Patiënten die met radiotherapie voor kanker in het thoracale gebied (borst, long, mediastinum) en in het abdomen (levertumoren/metastasen, alvleesklierkanker).

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Koninklijk Wilhemina Fonds (KWF projectnummer 12900)

Intervention

Keyword: Breathing control, Organ motion, Radiotherapy

Outcome measures

Primary outcome

The main outcome is the feasibility to achieve the diverse breathing control strategies in healthy volunteers and cancer patients to quantify reduced organ motion, and in patients to reduce dose to notmal tissues and organs at risk as compared to strategies currently used in clinical practice (i.e. multiple deep inspiration short breath-holds, or free breathing).

Secondary outcome

The secundairy parameters are:

• the practical advantages and limitations of the breathing control strategies for routinely radiotherapy delivery in cancer patients

• cost effectiveness in terms of time investment

• subjects* comfort with the different breathing control strategies assessed by the included subjects

Other study parameters:

• systolic blood pressure

• oxygen saturation

• heart rate

• end tidal partial pressure of carbon dioxide

Study description

Background summary

BACKGROUND: Precise irradiation of tumors in the chest and upper abdomen is complicated by breathing. In order to reduce tumor and organ motion, in current clinical practice patients are instructed several times during one radiation session to hold their breath. However, organ positions have been found to vary with repeated breath-holding, and even during breath-holding, residual motion occurs (results of our pilot study). The regularity and depth of breathing varies per patient and per day, but also during one radiation session. To ensure optimal radiation treatment, the target is expanded by margins. The more irregular and deeper the breathing, the greater the margins around the tumor should be. Inevitably, normal tissues are being exposed to radiation. To overcome these issues, different techniques including non-invasive mechanical ventilation, and non-invasive high frequency ventilation are being investigated with the common goal to reduce respiratory motion. Non-invasive mechanical ventilation supported regularized breathing can reduce respiratory motion compared to free breathing. Furthermore, combining non-invasive mechanical hyperventilation (causing safe hypocapnia) with pre-oxygenation enables single prolonged breath-holding (>5min). Residual organ motion will be abolished when establishing compensated prolonged breath-holding by mechanical re-inflation of oxygen during breath-holding to compensate for gradual lung deflation. High frequency ventilation might be an equally effective and a good alternative to reduce organ motion. Therefore, in this project the strategies of compensated prolonged breath-hold and high frequency ventilation will be compared.

RELEVANCE: If respiratory motion of tumor and organs can be reduced by the application of non-invasive ventilation or percussion ventilation, margins around the tumor or target can be reduced. This reduces the risk of radiation damage and toxicity to normal tissues and organs at risk.

HYPOTHESIS: We hypothesize that thoracic and abdominal organ motion will be maximally reduced using compensated prolonged breath-holding where the normal occurring gradual lung deflation is abolished by mechanical re-inflation of oxygen, and high frequency ventilation might be equally effective, and that regularized breathing is the second-best strategy to reduce organ motion.

Study objective

OBJECTIVE: to evaluate the feasibility of quantifying reduced dose to organs at risk by reducing (residual) organ motion and further increasing distances between the radiation target and normal tissues as a result of regularized breathing, compensated prolonged breath-holding and high frequency ventilation achieved in healthy volunteers and cancer patients, as compared to deep inspiration breath-holding and free breathing.

PRIMARY RESEARCH QUESTION: Which of the breathing-control strategies results in the largest (residual) organ motion reduction?

SECUNDARY QUESTIONS: Which of the strategies is the most appropriate to spare organs-at-risk when irradiating breast and lung cancer, and mediastinal tumors? And when irradiating liver tumors, and pancreatic cancer? With which of the strategies does each individual patient comply easiest?

Study design

BREATHING CONTROL STRATEGIES - HEALTHY VOLUNTEERS
In the pilot study preceding this project, we assessed diaphragm and abdominal organ motion during free breathing short breath-holding, regularized breathing, and prolonged breath-holding using non-invasive mechanical ventilation. We continue the work with healthy volunteers, focusing on regularized breathing, and compensated prolonged breath-holding with reinflation of oxygen to compensate for the gradual lung deflation. This new strategy will be compared with high frequency ventilation. Conform the pilot study, healthy volunteers will be trained in two sessions to be mechanically ventilated inducing regularized breathing, and to prepare for a safe compensated prolonged breath-holding. They will also get used to high frequency ventilation. Only in healthy volunteers we will use ultrasound in the second training session to measure residual motion during the breathing control strategies, and to validate with MRI measurements. During two subsequent sessions, MR images are acquired to quantify residual motion of the diaphragm, chest wall, thoracic organs, lungs and abdominal organs.

BREATHING CONTROL STRATEGIES - CANCER PATIENTS
Patients, in contrary to the healthy volunteers, will receive one training session to practice ventilation, as respiratory control strategies that have not been shown to be optimal during WP1 will not be used for patients. Per patient, the most effective breathing control strategy will be chosen, considering patients comfort with each of the strategies. In addition, not two, but only one MRI is sufficient for patients, because interfraction variations (movement variations) are sufficiently quantified in the healthy volunteers in WP1, and the (residual) movement of the diaphragm and chest wall can be quantified in one MRI session. It is crucial to specifically quantify the (residual) motion of the tumor or the radiation target in the thoracic region, the lungs, liver and pancreas. Previous studies have demonstrated that breast and lung cancer patients tolerate non-invasive ventilation without any problem.

LOWER RADIATION DOSES TO NORMAL TISSUES IN RELATION TO REDUCED ORGAN MOTION
Radiation treatment plans will be generated on patients* CT scans using the reduced margins Furthermore, their MR images will be registered to their CT scans, to generate radiation treatment plans using reduced margins based on reduced organ motion as a consequence of the breathing control strategies under investigation. Dose to normal tissues and organs at risk, will be compared to demonstrate the effect of the breathing control strategies. Clinical implementation will be feasible for compliant patients who can actually and immediately be treated with radiotherapy applying the most appropriate breathing control strategy.

Intervention

• Healthy volunteers and cancer patients are trained in two sessions to undergo non-invasive mechanical (and high-frequenciy) ventilation via a face/nose mask. (Note: Subjects are not under anaesthesia and there is no intubation; they can stop the intervention at any time).
• Patients will be trained in one session to undergo non-invasive ventilation (with varying frequencies) via a mouth/nose mask. (Note: Patients are not under anesthesia and there is no intubation; they can stop the intervention at any time).
• In healthy volunteers, ultrasound imaging will acquired in the second session. Then, in two subsequent sessions, MR images are acquired during the non-invasive ventilation strategies, to measure (reduction) of organ motion.
• No ultrasound images are acquired in patients, and one MRI session is sufficient to measure (redidual) organ movement.
• Finally, subjects will complete a 3-5 item questionnaire to assess their experience with the different breathing control strategies.

Study burden and risks

The burden for subjects is primarily their personal time commitment (normally four sessions totalling approximately 6-8 hours for healthy volunteers, and 2-3 hours for cancer patients). For cancer patients, the training session and the MRI session will be scheduled in parallel to their regular visits for radiation treatment. When dosimetric comparison in treatment planning are favourable, patients could immediately receive treatment using one of these strategies. From our considerable experience, healthy volunteers as well as breast and lung cancer patients generally tolerate well wearing a face mask, being mechanically ventilated and learning and delivering prolonged breath-holds. Our pilot study demonstrated that once trained, our healthy volunteers are also comfortable with doing all this in an MRI. We therefore anticipate no particular difficulties from any of the volunteers and patient groups.
The general health of each subject is screened to exclude relevant medical conditions (i.e., possible risk factors), and subjects will be directly supervised and monitored during the experiments. There are no known risks

associated with hyperventilation in volunteers and cancer patients, nor with breathing 60%O2 for short periods (~1 hour), nor with PBHs of longer than 5 minutes where the sPO2 and blood pressure levels are monitored. Furthermore, all hospital-based precautions will be met by staff and subjects during all experiments. Subjects are always free to remove the face mask, or to withdraw from the study at any time without having to give a reason.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• age >18 years
• adequate communication and understanding skills of Dutch language
• patients referred to or undergoing radiotherapy with DIBH at the department of radiation oncology of the Amsterdam UMC

• condition: KPS >70 or WHO PS max 1 (see 4.3 Exclusion criteria)
• signed informed consent (IC)

Exclusion criteria

• asthma controlled by medication
• moderately to severely impaired lung function (FEV1 <30% of predicted)
• resting PetCO2 >50 mmHg
• manifest cardiac failure
• epilepsy
• hypertension uncontrolled by medication
• brain disease, and/or anomalies of the brain*s vasculature or previous TIA/CVA
• morbid obesity, i.e. BMI >40 kg/m2
• pneumothorax
• renal failure
• claustrophobia
• current pregnancy
• latex allergy
• any 3T MRI contra-indications as stated by the AMC MR safety committee

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-03-2022
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	26-07-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL77351.018.21