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Short title: **Detection of (sub) clinical toxicity in irradiated vs. non-irradiated surgically treated esophageal cancer patients: a pilot study**

Acronym: **CROSS SECT**

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Coordinating investigator: **Prof. J.A. Langendijk**

Principal investigator: **J.C. Beukema, MD**

Sponsor: **UMCG**

Independent expert: **dr. W. Noordzij, MD PhD, Nuclear physician**

Laboratory sites: **routine assessments**

Writing committee:
J.C. Beukema, MD, Radiation oncologist
C.T. Muijs, MD, PhD, Radiation oncologist
A. Crijns, MD PhD, Radiation oncologist
C. de Groot, MD, Radiation oncologist in training
Prof. J. Plukker, MD, PhD, Oncologic surgeon
Prof. R. Vliegenthart, MD, PhD, Radiologist
J.P. van Melle, MD, PhD, Cardiologist
D.J.A. de Groot, MD, PhD, Medical oncologist
P. v. Luijk, PhD Senior Researcher
L. Kors, MSc, Datamanager.
Prof. J.A. Langendijk, MD, PhD, Radiation oncologist

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
For non-commercial research: **Head of Department:** **Prof. J.A. Langendijk, MD, PhD** Dept. of Radiation Oncology UMCG Groningen The Netherlands j.a.langendijk@umcg.nl phone +31 50 361 5532		
Coordinating Investigator/Project leader/Principal Investigator: **J.C. Beukema, MD** **Radiation Oncologist** Dept. of Radiation Oncology UMCG Groningen The Netherlands j.c.beukema@umcg.nl phone +31 50 361 9382		

Table of contents

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
CTCAE	**Common Terminology Criteria for Adverse Events**
CRT	**ChemoRadiotherapy**
NeoCRT	**Neoadjuvant chemoradiotherapy**
DVH	**Dose Volume Histogram**
EC	**Esophageal cancer**
GCP	**Good Clinical Practice**
hs-CRP	**High sensitivity C-reactive protein**
hs-TNT	**High sensitivity troponin T**
METC	**Medical research ethics committee (MREC); in Dutch: Medisch ethisch toetsing commissie (METC)**
NSCLC	**Non small cell lung cancer**
NTCP-model	**Normal Tissue Complication Probability model**
NT pro BNP	**N-terminal pro-B-type natriuretic peptide**
PDRP	**Prospective Data Registration Program**
OS	**Overall survival**
RT	**Radiotherapy**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

Inhoud

1. INTRODUCTION AND RATIONALE 8
2. OBJECTIVES 10
3. ENDPOINTS 11
4. OTHER STUDY PARAMETERS 11
5. STUDY DESIGN 12
6. STUDY POPULATION 12
6.1. Population (base) 12
6.2. Inclusion criteria 12
6.3. Exclusion criteria 12
7. SAMPLE SIZE CALCULATION 13
8. METHODS 13
8.1. Randomisation, blinding and treatment allocation 13
8.2. Study procedures 13
8.3. Withdrawal of individual subjects 16
8.4. Replacement of individual subjects after withdrawal 16
8.5. Follow-up of subjects withdrawn from treatment 17
9. *SAFETY REPORTING* 17
9.1. Section 10 WMO event 17
9.2. AEs, SAEs and SUSARs 17
10. STATISTICAL ANALYSIS 18
10.1. Primary study parameter(s) 18
10.3. Other study parameters 18
11. ETHICAL CONSIDERATIONS 18
11.1. Regulation statement 18
11.2. Recruitment and consent 18
11.3. Objection by minors or incapacitated subjects 19
11.4. Benefits and risks assessment, group relatedness 19
11.5. Compensation for injury 20
11.6. Incentives (if applicable) 20
12. DATA COLLECTION, DATA MANAGEMENT, MONITORING AND PUBLICATION 20
12.1. Electronic case report forms 20
12.2. Use of computerized systems 20
12.3. Retention of records 20
12.4. Data Management Plan 21
12.5. Monitoring and Quality Assurance 21
12.6. Anonymization of data 21
12.7. Amendments 21
12.8. Annual progress report 21

12.9. Temporary halt and (prematurely) end of study report 22
12.10. Public disclosure and publication policy 22
13. REFERENCES 23

SUMMARY

Rationale: Radiation-induced cardiac and pulmonary toxicity after treatment for intra-thoracic tumors is a clinically relevant problem, which may jeopardize the benefit of (neo-adjuvant) (chemo) radiotherapy. Although cure rates are rising since the introduction of neo-adjuvant chemoradiation (neo-CRT) as current standard treatment for esophageal cancer (EC), recent studies showed that there is a substantial risk of non-cancer treatment-related death in these patients [1–6]. Furthermore, this risk is underestimated as the cause of death of many patients remains unknown, since the distinction between tumor related and non-cancer related death can be difficult.

Cardiac and pulmonary toxicity and its interaction as seen in pre-clinical studies might explain for these unknown deaths as suggested in several clinical studies [6–9]. Clinical imaging studies performed shortly after treatment showed changes in different cardiac function parameters, all related to radiation dose parameters [10–13]. Systematic imaging studies analysing subclinical toxicities at longer follow up have never been performed, most probably because of poor survival rates. However, identification of the magnitude of (subclinical) cardiopulmonary toxicity, by performing several cardiopulmonary function tests, is essential in this patient group as this toxicity is most likely the cause of the increased mortality after thoracic radiotherapy. For future perspectives, these results can be used to select the best diagnostic methods for a prospective cohort study to develop prediction tools for cardiopulmonary toxicity. Finally, this might lead to optimization of radiotherapy dose-distributions (including patient selection for proton therapy) and hopefully reduce radiation induced cardiopulmonary toxicity and improve overall survival.

Objective:

The main objective of this study is to determine the most suitable diagnostic test to identify cardiopulmonary (dys)function in EC survivors treated with neo-CRT followed by surgical resection. Furthermore, we want to estimate the difference in cardiopulmonary (dys)function in EC survivors treated with neo-CRT followed by surgical resection compared to EC survivors who were treated with surgical resection alone.

Study design: Cross-sectional pilot study

Study population: 40 EC patients who were treated with curative intent by esophageal resection with or without neo-CRT

Intervention (if applicable): Not applicable.

Main study parameters/endpoints:

As this is an exploratory pilot study to determine the most suitable diagnostic tests for future studies, there will be several endpoints related to (sub)clinical cardiopulmonary dysfunction. Signs of myocardial ischemia, systolic or diastolic dysfunction, rhythm and valve disorders, pericardial effusion and fibrosis, myocardial fibrosis, focal wall motion disorders and coronary calcifications will be analyzed. The cardiopulmonary (dys)function in EC survivors treated with neo-CRT followed by surgical resection will be compared to cardiopulmonary (dys)function in EC survivors treated with surgical resection alone.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Several tests will be performed at one time point, 5-10 years after given treatment. If the findings of the test indicate cardiovascular complications, the patient will be referred to the cardiologist for further analysis and/or preventive measures. As one of the tests, cardiac MRI, including gadolinium (Dotarem 0.2 mmol/kg) enhancement will be performed. Potential side effects of gadolinium include brief headache, nausea (feeling sick) and dizziness for a brief time following the injection. Allergic reactions are rare. Furthermore, a cardiac CT scan will be performed with a total radiation exposure of 0.6 mSv (less than a third of the annual background radiation dose), the risks will be minimal.

1. INTRODUCTION AND RATIONALE

Background

Increasing numbers of patients with intra-thoracic tumours are currently treated with curatively intended combined modality strategies such as chemoradiation (CRT) either in the neo-adjuvant setting followed by surgery or as definitive treatment. Due to improved outcome resulting from the addition of chemotherapy to radiotherapy (RT) and due to the clinical introduction of neo-CRT prior to surgery, the prevalence of EC survivors is rising [5,14,15]. Therefore, the absolute number of patients at risk for treatment-related toxicity is rising as well.

There is increasing evidence that radiotherapy induces cardiac and pulmonary damage. In esophageal cancer patients, pericarditis during and shortly after radiotherapy is the most frequently observed side effect, which should be regarded as an acute inflammatory effect [16] . In the first year after treatment, wall motion disorders with changes in end diastolic volume have been observed [13,17]. These wall motion disorders are most probably caused by changes in the microvasculature. In addition, increased rates of coronary artery disease, myocardial infarctions, heart failure, as well as pericarditis, arrhythmia and valvular disorders have been observed, and may appear after longer latency times [18–20]. Systematic imaging studies analysing subclinical toxicities at longer follow up have never been performed, most probably because of poor survival rates. Preclinical studies indicate cardiopulmonary changes not only relate to the radiation dose given to the heart but also to the dose given to the lung [8,21]. The mechanism behind this phenomenon seems to be an increased pressure in the pulmonary arteries due to vascular fibrosis which leads to diastolic dysfunctioning of the heart due to a volume overload.

Furthermore, the results of several clinical studies suggested that some severe treatment-related morbidity and mortality remains unrecognized but is associated with radiation exposure to the heart and lungs. For example, the meta-analysis on the added value of postoperative radiotherapy after surgical resection for non-small cell lung cancer (NSCLC) revealed significantly worse overall survival (OS) in patients receiving post-operative radiotherapy [2], suggesting that thoracic radiation causes lethal toxicities of the lungs and/or mediastinal structures. In a dose escalation trial in NSCLC a significantly worse OS was seen in the high dose group. Overall survival turned out to be associated with the radiation dose to the heart [1]. In EC the introduction of newer techniques, like IMRT, significantly reduced the risk on cardiac death [9,22]. Furthermore, in a randomised trial comparing neo-adjuvant chemotherapy to neo-

CRT, neo-CRT had a significantly better response rate, however this did not result in a survival benefit. An explanation was found in a higher rate of non-cancer related death already during the first year of follow up [3].

In summary these data demonstrate that thoracic radiotherapy induces not only clinical but also subclinical toxicity, which might explain the unrecognized grade 5 toxicity, as a result of high dose thoracic radiotherapy. Identification of the magnitude of (subclinical) cardiopulmonary toxicity, by performing several cardiopulmonary function tests, is essential in this patient group as this toxicity is most likely the cause of the increased mortality after thoracic radiotherapy. For future perspectives, these results can be used to select the best diagnostic methods for a prospective cohort study to develop prediction tools for cardiopulmonary toxicity.

Patient population

As many of our EC patients are older and have cardiopulmonary problems as a result of their age, co-morbidities or lifestyle habits, we would like to compare a cohort of patients treated for EC who did or did not undergo (chemo)radiotherapy.

A cohort of these patients is available, as neo-CRT has become standard treatment since 2012 after the publication of the so-called CROSS trial, demonstrating an important survival benefit in the group that received neo-CRT followed by surgery compared to patients treated with surgery alone. During this time period and the time period shortly before and after, patients were treated either with or without neo-CRT. In this time period we did not select patients on cardiopulmonary co-morbidities or age, so we expect comparable groups. Part of these patients were already retrospectively analyzed and compared on short term (within 90 days) morbidity and mortality after resection [23]. These data were published in 2013. We demonstrated an increased incidence of pneumonia and rhythm disorders in patients treated with neo-CRT, but no difference was noted in neither hospital and intensive care unit stay nor in mortality or overall morbidity between these two groups. As these patients were treated in the time period 2000-2012 and thus will have a 5-15 years follow up there is a sufficiently large patient cohort available to prospectively analyze clinical and subclinical cardiac changes and/or toxicities.

Which tests would be interesting at longer follow up or study parameters

As mentioned in the introduction, the main focus of this study is (subclinical) cardiopulmonary (dys)functioning. The most important late (subclinical) toxicities we expect to find at longer follow up are: diastolic dysfunction, coronary artery disease, cardiac wall motion disorders, heart failure, pulmonary hypertension, pericardial effusion and/or constriction, cardiac arrhythmia and valve disorders. A number of these endpoints will eventually result in heart failure.

- Anamnesis and physical examinations will be performed in these patients
- In case a pulmonologist or cardiologist has been consulted, additional information will be collected from hospital records of these specialists.
- Radiotherapy treatment parameters will be collected from our database in case the patient was treated with radiotherapy.
- 6 minute walking test
- Echocardiogram
- CTTC scan
- Cardiac MRI scan
- ECG

Laboratory tests: NT-pro BNP, cholesterol, CRP and hs-TNT, eGFR, HbA1c, hematocrit.

2. OBJECTIVES

Primary Objectives:

The main objective of this study is to determine the most suitable diagnostic test to identify cardiopulmonary (dys)function in EC survivors treated with neo-CRT followed by surgical resection. Furthermore, we want to estimate the difference in cardiopulmonary (dys)function in EC survivors treated with neo-CRT followed by surgical resection compared to EC survivors who were treated with surgical resection alone.

1. To determine the differences in clinical cardiac and pulmonary events, (cardiac ischaemia, heart failure, arrhythmia, valve disorders, pulmonary hypertension, COPD) as clinically diagnosed since treatment between patients treated with neo-CRT and surgery alone.
2. To determine the difference in other (subclinical) parameters as tested by echo cardiogram, 6 minute walking test, CT scan, MRI scan and biomarkers.
3. To analyse the current CAC scores in both patient groups.
4. To determine the difference between the baseline and current CAC scores.

5. To determine the difference between ECG findings currently and on baseline.
6. To correlate the different subclinical imaging parameters to the radiation dose given to the heart and lungs
7. To correlate CAC scores with the given dose distribution on plannings CT scan

3. ENDPOINTS

As this is an exploratory pilot study to determine the most suitable diagnostic tests for future studies, there will be several endpoints related to (sub)clinical cardiopulmonary dysfunction. Signs of myocardial ischemia, systolic or diastolic dysfunction, rhythm and valve disorders, pericardial effusion and fibrosis, myocardial fibrosis, focal wall motion disorders and coronary calcifications will be analyzed.

The cardiopulmonary (dys)function in EC survivors treated with neo-CRT followed by surgical resection will be compared to cardiopulmonary (dys)function in EC survivors treated with surgical resection alone.

4. OTHER STUDY PARAMETERS

For the purpose of this study, the following parameters will be assessed in all patients:

- Cardiac risk factors
    - Smoking status
    - Age
    - Detailed cardiac history including medical letters from cardiologists when available
    - Detailed pulmonary history including medical letters from pulmonologists when available
    - Alcohol consumption
    - Family history on cardiac events
    - Hypertension
    - D.M.
    - Use of medication
- Combination with chemotherapy
- Postoperative complications and interventions
- Sex
- Daily activities and/or sport

- Original clinical tumor stage (TNM)
- Original tumour length at endoscopy
- Original pathologic tumor stage (TNM)
- Volume (cc) of the irradiated planning target volume
- For irradiated patients; radiotherapy treatment parameters and dose distributions
    - Dose Volume Histogram of the heart
    - Dose Volume Histogram of different cardiac subvolumes
    - Dose Volume Histogram of the lungs

5. STUDY DESIGN

This is a cross sectional pilot study with patients who were or were not treated with neo-CRT.

6. STUDY POPULATION

6.1. Population (base)

Patients with EC treated with or without neo-CRT, alive without evidence of disease, treated between 2000 and 2012 at the University Medical Centre Groningen will be eligible. Twenty patients will be included in both treatment groups. Length of follow up after treatment does not seem to be an important confounding factor as surgery is not considered to be an important risk factor for late toxicity.

6.2. Inclusion criteria

- Treated for EC with a curative resection between 2000 and 2012
- Age >= 18 years
- Written informed consent
- No signs of tumor recurrence or new other malignancies.

6.3. Exclusion criteria

- Thoracic radiotherapy for indications other than EC.
- Contra indication for cardiac MRI, pacemaker, cochlear implants, metal not compliable with MRI.

7. SAMPLE SIZE CALCULATION

As this is a pilot study to determine (sub-clinical) cardiopulmonary toxicity, a total of 40 patients, 20 in each group, will be included in this study.

8. METHODS

8.1. Randomisation, blinding and treatment allocation

Not applicable

8.2. Study procedures

Candidates will be selected from the surgical and radiotherapy database. General practitioners will be checked for their survival status. An introduction letter, including patient information for this study, will be sent to the surviving patients to explain the study and ask them to consider participation in this research project. Patients are given the opportunity to call the researcher for further information and questions about the study. Patients can give their informed consent by sending the written informed consent. After receiving the informed consent, appointments will be made whenever possible on one day in consultation with the patient.

- Interview and physical examination 45 minutes
- 6 minute walking test plus explanation 30 minutes
- ECG 15 minutes
- Laboratory tests 5 minutes
- Echocardiogram 30 minutes
- Cardiac CT scan 10 minutes
- Cardiac MRI scan 40 minutes

Anamnesis and physical examination:

The patients will be interviewed on matters concerning their medical history, cardiopulmonary complaints and patients will be asked to fill in the following questionaires: EORTC ACE27, EORTC LC13, EuroQOL 5D and the EORTC C30. A general physical examination will be performed, including length and weight.

6 minute walking test:

Gives an estimate of the general functioning status of the patients during follow up. It is known to correlate with maximum oxygen uptake and physical fitness without laboratory test [24].

Laboratory tests:

NT pro BNP and hs TNT are known markers in cardiology for myocardial damage and "volume overload" like in diastolic dysfunction. Blood markers like cholesterol, CRP, HbA1 will help determining the baseline risk on cardiac events. eGFR will be checked before gadolinium is infused in order to minimize risks on its possible side effects. It is necessary to determine hematocrit for calculation of the extracellular volume (ECV).

ECG

Simple screening instrument to indicate hypoxia, pericarditis, past infarctions, bundle branch blocks and rhythm disorders

Echocardiogram:

An echocardiogram is performed as a safe non-invasive screening technique, which is able to measure hypertrophy of the myocardium, pericarditis, wall motion disorders, blood flows and pressures, which are functional parameters who could indicate pulmonary hypertension and diastolic- or systolic dysfunction and valve disorders[25].

The echocardiographic assessment will be performed by the Echocardiography Core lab (www.G-ICL.com) facility, of the UMCG. The echocardiographic protocol includes assessments of systolic and diastolic function of both ventricles according to the guidelines of the European Association of Cardiovascular Imaging (EACVI). Specifically we will assess:

1. Tricuspid annular plane systolic excursion (Tapse)
2. Velocity of the tricuspid annular systolic motion (RV s')
3. Right ventricle fractional area change
4. Doppler notching of right ventricular outflow tract signal
5. Tricuspid valve Doppler velocity
6. Pulmonary valve Doppler velocity
7. Myocardial performance index (Tei index)
8. Pulmonary artery acceleration time
9. Pulmonary valve end diastolic velocity
10. Cardiac Output
11. Left ventricle systolic function

12.Left ventricle diastolic dysfunction
13.Valvar abnormalities
14.Left ventricle eccentricity index
15.Right ventricle strain
16.Right atrium volume
17.Inferior Caval Vein collapsibility
Also 2D strain echocardiography will be performed to establish subtle changes in myocardial function.

Cardiac CT imaging :
CT imaging will be performed on a latest generation dual-source CT scanner (Siemens Medical Solutions, Forchheim, Germany). A non-enhanced CT high pitch spiral acquisition in diastole with prospective electrocardiography (ECG) triggering will be performed with a standard protocol (120 kV tube potential; ref mAs 75) with an associated radiation dose of 0.6 mSv (less than a thrird of the annual background radiation dose). On the CT acquisition, the amount of coronary calcification will be calculated and expressed as a Coronary Artery Calcium (CAC) score based on the Agatston method.
The CAC score can be used to compare the current and baseline status (using the diagnostic CT scans performed before treatment) and is a reliable instrument for coronary disease [26]. Furthermore, dose distributions can be correlated with the coronary artery calcifications by fusing diagnostic CT scans with the planning CT scans in irradiated patients.
The CAC score at baseline will be used to estimate the baseline risk on cardiac events

Cardiac MRI:
Cardiac MRI will be performed with a 1.5- or 3.0-Tesla MRI scanner (Siemens Medical Solutions, Forchheim, Germany). Imaging is performed during breath-hold at end-expiration. During the procedure, ECG is continuously monitored. After acquisition of scout views for the determination of the standard orientations of the heart, cine images will be acquired for functional evaluation and measurements (4 chamber, 2 chamber, short axis). T1 acquisitions are performed before and after injection of 0.2 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Villepinte, France). T1 mapping is a parametric quantitative sequence, which provides tissue-specific T1 values. For T1 mapping, a 5(3)3 sampling scheme of the heart is performed,

using a modified Look Locker sequence. Pixel-wise T1 maps of the myocardium are acquired in 3 short-axis views with inline motion correction. The major advantage of T1 mapping sequences is their potential for quantitative objective assessment of myocardial abnormalities. Myocardial pathologies leading to T1 changes include diffuse myocardial fibrosis, edema, inflammation, and infiltrative diseases such as amyloidosis, Fabry disease, and hemosiderosis. The comparison of T1 values before and after Gadolinium enable the quantitative estimation of myocardial interstitial remodeling and extracellular space expansion, to evaluate myocardial extracellular volume. Ten minutes after the Gadolinium injection, a late Gadolinium enhancement (LGE) series is performed to assess possible myocardial infarction and gross fibrosis. Image post-processing includes the measuring of cardiac dimensions, ventricular volumes, LV and RV function, LV mass, and T1 tissue values.

Radiotherapy treatment plan

The radiotherapy details, CT scan and delineated structures will be transferred to our current planning system in order to extract dose distributions and dose to the critical organs as, dose volume histograms will be exported. The cardiac CT scan will be co registered to our planning CT scan in order to correlate high dose regions to present coronary artery disease .

Participants will be in the hospital for 6-8 hours, including waiting time in between the tests.

In case, a clinically relevant, (subclinical) abnormality is diagnosed we will contact the patient and its general practitioner. The possible clinical consequences will be discussed with the cardiologist involved, and, if indicated, the patients will be referred to the cardiologist for further analyses or preventive measures.

8.3. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4. Replacement of individual subjects after withdrawal

Patients will be asked to participate in this project when treated in this time period up to a maximum of 40 patients .

8.5. Follow-up of subjects withdrawn from treatment

No further follow up is required.

9. *SAFETY REPORTING*

9.1. Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2. AEs, SAEs and SUSARs

Adverse events, serious adverse events and suspected unexpected serious adverse reactions will not be assessed in this study as no clinical relevant adverse events, serious events and suspected unexpected serious adverse reactions are expected.

10. STATISTICAL ANALYSIS

10.1. Primary study parameter(s)

Different cardiopulmonary parameters will be presented by means and standard deviations and will be compared between the groups using and independent t-test, with Bonferroni correction if applicable.

10.2. Other study parameters

Risk factors for cardiac and pulmonary complaints will be presented in frequency tables and tested for statistical significant differences between both groups using an independent t-test

Location of focal wall abnormalities and arteriosclerosis and its relation to high dose regions will be presented in a table.

11. ETHICAL CONSIDERATIONS

11.1. Regulation statement

This study will be conducted in accordance with the Declaration of Helsinki 2013 (Fortaleza, Brazil) and in accordance with the principles of 'Good Clinical Practice' and the Medical Research Involving Human Subjects Act (WMO).

11.2. Recruitment and consent

Candidates will be selected from the surgical and radiotherapy database. General practitioners will be checked for their survival and disease status. An introduction letter and patient information sheet explaining the purpose and procedure of this study will be sent to the patients. Patients are given the opportunity to call or email the researcher for further information and questions about the study. Patients can give their informed consent by sending the written informed consent. If a patient has not given an answer within two weeks after receiving the letter, we will sent a second letter as a reminder. After we receive the consent the appointments will be made on whenever possible on one day in consultation with the patient.

Patients consent will be noted on an informed consent form compliant with the local and ethical regulations.

If during the study the patient for whatever reason no longer wishes to participate, he/she can withdraw his/her consent at any time.

Prior to the start of the study, the protocol has to be approved by the medical ethics review committee of the participating institution. Approval will be indicated in writing with reference to the final protocol number and date.

11.3. Objection by minors or incapacitated subjects

Not applicable.

11.4. Benefits and risks assessment, group relatedness

The risk of participation in this study is very low. Patients have to visit the hospital once. The patient will have to stay in the hospital for approximately 6-8 hours. Within this time period anamnesis, questionnaires, physical examination and additional tests will be performed.
Blood withdrawal may result in local tenderness or hematoma, which are self-limiting.
Cardiac MRI scan requires IV contrast infusion with gadolinium, with the use of gadolinium there is a very low risk of anaphylactic reactions, nausea and headache, besides, the small bore used in MRI scanning may trigger claustrophobic feelings
Echo, ECG and the walking test do not cause any harm to the patients.
CT scan will give radiation exposure but as the total dose of this cardiac CT scan is relatively low total radiation dose of 0.6 mSv (less than a third of the annual background radiation dose), the risks will be minimal.
Patients participating will be evaluated for subclinical cardiopulmonary (dys)funtioning. Patients will be referred to a cardiologist or pulmonologist for early intervention if considered necessary, this might improve quality of life or even life expectancy.

The results of this pilot study will form the basis for a subsequent prospective observational cohort study in which the most promising tests and clinical endpoints will be used to assess correlations with radiotherapy dose metrics with the ultimate aim to develop prediction models. These models can be used for model-based radiotherapy treatment plan optimization and to select patients for the best radiation technique, e.g. proton therapy.
Furthermore, the result of such a prospective cohort study might indicate the necessity of preventive measures for cardiopulmonary toxicity in the future.

11.5. Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The Insurance company Onderlinge Waarborgmaatschappij Centramed, Postbus 191, 2270 AD Voorburg, takes out the insurance policy. The assurer and the insurance policy comply with the requirements laid down by order of “Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen” (Staatsblad, 1 september 2003).

11.6. Incentives (if applicable)

Additional costs like traveling expenses and meals during the hospital visit will be reimbursed.

12. DATA COLLECTION, DATA MANAGEMENT, MONITORING AND PUBLICATION

12.1. Electronic case report forms

Wherever possible, all data will be entered directly into the eCRF. Where needed, paper source documents can be used. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each subject enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. If a subject withdraws from the study, the reason must be noted on the end of study form of the eCRF. The investigator should ensure the accuracy, completeness and timeliness of the data recorded in the eCRF and in all required reports.

12.2. Use of computerized systems

When clinical observations are entered directly into an investigational site’s computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

12.3. Retention of records

The principal investigators, involved specialist researchers and the data management will have access to the source data. All data will be stored during a period of twenty years.

12.4. Data Management Plan

If data will be entered directly in the eCRF the DMP will also include a Source Identification List. The Source Identification List will identify any data to be recorded directly in the eCRF (i.e., no prior written or electronic record of data), and which data should be considered source data.

12.5. Monitoring and Quality Assurance

The department will be monitored by a trained and qualified monitor. Monitoring frequency is dependent on the risk classification for the study.

12.6. Anonymization of data

All files used for analysis will be anonymized to ensure patient privacy.
Anonymisation will be performed as follows: RT-CROSS-SECT-nr, where, nr denotes consecutive inclusion number. Central data management will give out a study number for each participating patient at the end of the registration process and will safeguard the code and number. The Principal investigator and the data management will have access to the source data.

12.7. Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC.

Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

12.8. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject,

numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.9. Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of eight weeks. The end of the study is defined as the last patient's last visit.

The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the investigator will notify the accredited METC within fifteen days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.10. Public disclosure and publication policy

The trial will be registered at clinicaltrials.gov and published in a major scientific journal regardless of its results. The principal investigator and the study statistician will review the data and perform the statistical analyses. The results will be published by the principal investigators, the study statistician, the study radiologist, the study cardiologist, plus additional persons contributing substantially to the analysis and interpretation of study results.

13. REFERENCES

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