A prospective study on the need of gated (GAT) radiotherapy in left sided breast cancer patients treated at the Technical University Munich (TUM) The GATTUM Trial: Study Protocol

Marciana Nona Duma, Markus Oechsner, Christina Ertl, Petra Mozes, Silvia Reitz, Kai Joachim Borm, Stephanie Elisabeth Combs

Submitted to: JMIR Research Protocols on: August 13, 2018

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Abstract

Background: Deep inspiration breathhold (DIBH) it is the most widely used technique for heart sparing. Nonetheless, treatment preparation, patient coaching and treatment planning/delivery can be more time consuming than conventional techniques.

Objective: The aim of our study is to find predictive measurements that will allow an estimation of the heart dose reduction by DIBH and thus allow a precise selection of these patients.

Methods: The GATTUM trial is a single institution, prospective pilot study. 150 breast cancer patients who will undergo radiotherapy at the university hospital “Klinikum rechts der Isar” will be included in the study. All patients will undergo breathing triggered radiation planning with a CT during free breathing (FB) and a CT during deep inspiration breath hold (DIBH). Patients without cardiac risk factors with heart Dmean ≤ 3 Gy and for patients with cardiac risk factors with heart Dmean ≤ 2Gy are recommended to undergo radiation therapy in DIBH. The primary endpoint of the study is to identify measurements that will predict the heart dose reduction in DIBH. Secondary endpoints include quality of life and cosmesis.

Results: The measurements that we aim to find by this study are to be performed on a planning CT or a diagnostic CT performed beforehand; easy to perform by each staff member; correlated with clinical data (such as breast size; heart and lung morphometry; heart and lung comorbidities) and correlated with the a 3D CRT tangential field “standard” dose distribution.

Conclusions: This study could help to improve the knowledge about the necessity of respiratory-gated radiotherapy. We expect that evidence-based indications regarding optimization-criteria for radiation planning of breast cancer patients can be determined for the first time. Clinical Trial: The study was retrospectively registered on the 23rd of May 2018 on clinicaltrials.gov with the following ID: NCT03534570. https://clinicaltrials.gov/ct2/show/NCT03534570 The study is currently recruiting patients. The first patient was recruited on 15th October 2015.

(JMIR Preprints 13/08/2018:11894)
DOI: https://doi.org/10.2196/preprints.11894

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A prospective study on the need of gated (GAT) radiotherapy in left sided breast cancer patients treated at the Technical University Munich (TUM)

The GATTUM Trial: Study Protocol

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Abstract:

Background: Deep inspiration breathhold (DIBH) is the most widely used technique for heart sparing. Nonetheless, treatment preparation, patient coaching and treatment planning/delivery can be more time consuming than conventional techniques.

Objectives: The aim of our study is to find predictive measurements that will allow an estimation of the heart dose reduction by DIBH and thus allow a precise selection of these patients.

Methods: The GATTUM trial is a single institution, prospective pilot study. 150 breast cancer patients who will undergo radiotherapy at the university hospital ‘Klinikum rechts der Isar’ will be included in the study. All patients will undergo breathing triggered radiation planning with a CT during free breathing (FB) and a CT during deep inspiration breath hold (DIBH). Patients without cardiac risk factors with heart $D_{\text{mean}} \geq 3$ Gy and for patients with cardiac risk factors with heart $D_{\text{mean}} \geq 2$ Gy are recommended to undergo radiation therapy in DIBH. The primary endpoint of the study is to identify measurements that will predict the heart dose reduction in DIBH. Secondary endpoints include quality of life and cosmesis.

Conclusion: The measurements that we aim to find by this study are to be performed on a planning CT or a diagnostic CT performed beforehand; easy to perform by each staff member; correlated with clinical data (such as breast size; heart and lung morphometry; heart and lung comorbidities) and correlated with the a 3D CRT tangential field “standard” dose distribution. This study could help to improve the knowledge about the necessity of respiratory-gated radiotherapy. We expect that evidence-based indications regarding optimization-criteria for radiation planning of breast cancer patients can be determined for the first time.

Trial registration: The study was retrospectively registered on the 23rd of May 2018 on clinicaltrials.gov with the following ID: NCT03534570. [https://clinicaltrials.gov/ct2/show/NCT03534570] The study is currently recruiting patients. The first patient was recruited on 15th October 2015. Current status: recruiting.

Keywords: DIBH; breast cancer; heart toxicity; radiotherapy; GATTUM trial
Introduction

There are five radiation-induced late cardiac sequelae described: myocardial infarction/ischaemic heart disease, congestive heart failure, valvular diseases, arrhythmias/conduction defects and pericarditis [1-3]. In breast cancer radiotherapy, external beam radiotherapy is delivered mainly by tangential fields that encompass the mammary gland. Due to the field arrangement and depending on the anatomical circumstances (i.e. distance of the heart to the thoracic wall), some parts of the heart might lie in the radiation field [4]. Thus, three of the five late toxicities were also described in breast cancer patients: ischemic heart diseases, congestive heart failure and valvular diseases [1].

Radiation dose reduction to the heart will probably translate in a long term reduction of radiation induced toxicities [5]. Several approaches are available to reduce the heart dose during radiotherapy of breast cancer. Roughly, they can be divided in three categories: displacing the heart out of the treatment field; irradiating a smaller planning target volume (PTV) and using modern, highly conformal radiotherapy techniques [6]. The displacement of the heart out of the treatment field can be achieved either by a modified patient setup – i.e. prone position [7, 8] or by specific breathing techniques – i.e. deep inspiration breath hold (DIBH) / gating / tracking [9-13]. Another idea is to solely irradiate a small volume around the lumpectomy cavity [14, 15]. A third approach that can be pursued if heart-sparing is intended, is to reduce the heart dose by modern radiation techniques like intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) [16-18].

The soundest data are available on DIBH. Thus, it is the most widely used technique for heart sparing [19, 20]. Nonetheless, treatment preparation, patient coaching and treatment planning/delivery can be more time consuming than with conventional techniques. Further, some patients, profit greatly from DIBH, others barely. To date there are no clear criteria which patients do benefit a priori from DIBH, and therefore often highly advanced treatment planning is performed without any clinical benefit.

Very few studies dealt with the topic of cardiac movement during breathing/in deep inspiration and predictive values for cardiac doses. They were mostly performed on 4D computed tomographies (4D-CTs) and can not be extrapolated to DIBH [21, 22].

The aim of our study is to find predictive measurements, values or markers that will allow an estimation of the heart dose reduction by DIBH.
Methods

The GATTUM trial is a single institution, prospective pilot study. 150 left sided breast cancer patients who will undergo radiotherapy at the university hospital ‘Klinikum rechts der Isar’ will be included in the study (Figure 1).

All patients will undergo radiation planning with a kilo-voltage computed tomography (kVCT) scan (Siemens medical solutions, Erlangen, Germany) during free breathing (FB) and deep inspiration breath hold (DIBH) with an axial slice thickness of 3 mm. The patients will be placed in a supine position on a wing board with both arms over the head. The real-time Position Management system (RPM, Varian Medical Systems, Palo Alto, CA, USA) will be used for breathing management and during treatment.

Planning volume and the risk organs will be defined for each patient in both CTs. The definition of the organs at risk and the PTV is conducted in accordance with national and international guidelines [23, 24]. The OARs will be: right mammary gland, left lung, right lung, whole heart, left anterior descending artery (LAD), left ventricle.

3D treatment planning will be performed on the FB-CT and on the DIBH-CT for every patient with 3D conformal radiotherapy (3D-CRT). All plans will consist of 2 opposing tangential beams with additional beam segments to achieve optimal target dose coverage and homogeneity. Dose calculation will be performed using the anisotropic analytical algorithm (AAA) with a calculation grid size of 2.5 x 2.5 mm.

The PTV prescribed dose will be either 50 Gy with 2 Gy per fraction or 50.4 (1.8Gy per fraction) for the whole breast. The dose will normalized to the median dose of the PTV (according to ICRU 83 [25]). If clinically indicated, a boost of 10-16 Gy will be applied to the tumor bed [26]. In our department intraoperative radiotherapy (IORT), 3D-CRT, VMAT or 3D electrons are used for boost irradiation depending on tumor site, dosimetry etc. As the employed techniques are very different and the boost target volume location varies widely between patients, we will not be including the boost dose in the analysis of the primary endpoint.

Patients without cardiac risk factors with mean heart dose ($D_{\text{mean}}$) ≥ 3 Gy and for patients with cardiac risk factors with $D_{\text{mean}}$ ≥ 2Gy will undergo radiation therapy in DIBH. The heart doses were defined in accordance to the available literature [27]. The goal of the treatment planning is to be below a 5% risk of any acute coronary events.

For example, it is assumed, that the risk for a 50-year-old woman without existing cardiac risk factors to die from an ischemic related heart disease by the age of 80 is increased from 1.9% (the risk of a “normal”, not irradiated 80 years old women) to 2.4% following a radiation therapy with an average heart dose of 3 Gy. The absolute risk of suffering from an acute coronary event would increase from 4.5% to 5.4% for the very same patient (i.e. an absolute increase of about 0.9
percent). The goal would be to undercut the 5.4% risk by DIBH, thus gating patients with a heart $D_{\text{mean}} \geq 3\text{Gy}$ in FB.

However, a 50-year old woman with known cardiac factors has an increased risk of suffering from an acute cardiac event as well as of dying from ischemic heart diseases. The same average heart dose of 3 Gy imposes a risk of 4.1% to die from a cardiac event and a risk of 9.7% for an acute coronary event according to Darby et al. In order to achieve a risk reduction which would be comparable to a patient who is not cardiac handicapped the average heart dose would need to be 2 Gy [27].

## Results

### Primary and secondary study endpoints

The primary endpoint of the study is to identify measurements that will predict the heart dose reduction in DIBH.

The measurements that we aim to find by this study are:

- correlated with the a 3D CRT tangential field “standard” dose distribution
- predictive for the heart dose reduction by DIBH
- easy to perform by each staff member
- to be performed on a planning CT or a diagnostic CT performed beforehand
- correlated with clinical data such as: breast size; heart and lung morphometry; heart and lung comorbidities.

Secondary endpoints include quality of life and cosmesis.

### Statistics

#### 1. Power analysis

The aim of this pilot study is to predict factors that help to identify patients, who benefit the most from the use of DIBH techniques. Since new methods and measurements will be developed and evaluated in our study, it is difficult to estimate the expected values and differences. Therefore, conventional power analyses are not feasible for this project.

The inclusion of 150 patients allows the comprehensive analysis of the different evaluated measurements.
2. Analysis plan

Descriptive analysis

Means, standard deviations, percentages, ranges and confidence intervals of $95\%$ will be used to summarize:

- The questionnaire medical data including Quality of Life and CTCAE scores
- CT measurements density analyses
- The changes of the target volumes and the organs at risk during DIBH
- The geometric data derived from manual and computer based measurements during DIBH and FB
- Dose distribution to the target volume and the organs at risk

Univariate analysis

Based on the measured parameters we identify patients that benefit from DIBH the most. Decision criterion is a reduced dose distribution in the heart and the other organs at risk. Using especially developed measurements and algorithms, we will test which parameters predict the dose distribution in the organs at risk. For statistical testing paired non-parametric tests (Wilcoxon signed rank test to compare medians, $\chi^2$-Test to compare categorical parameters) will be used. The correlation between the different covariates will be investigated using the Spearman's rank correlation coefficient.

Multivariate analysis

Predicting factors with significant influence in the univariate analyses will be included in multivariate analyses models. Here for multivariate regression models will be used.

Current status

Recruiting. First results expected early 2020.
Discussion

The aim of the GATTUM study is to find predictive measurements, values or markers that will allow an estimation of the heart dose reduction by DIBH. Thus decisions about which radiation therapy techniques should be employed for breast cancer might be standardized.

Modern concepts of radiation therapy, especially for breast cancer lead to extreme differences in local doses of different partial volumes and anatomic structures of the heart whereas the differences can embrace up to two orders depending on the radiotherapy technique. The most commonly used heart-sparing technique in the German speaking countries is DIBH [19, 20], but there is no consistent approach for heart sparing in patients with breast cancer. The main impediment in offering all breast cancer patients heart-sparing techniques is for most radiation oncologist the time / resource consumption [19]. Further, some patients, profit greatly from DIBH, others barely. Moreover, we know that for specific endpoints, the heart $D_{mean}$ in FB is not always sufficient [4]. For e.g., the $D_{mean}$ heart is not always a good surrogate parameter for the dose to the LAD, as it might underestimate clinically significant doses in one-third of the patients.

Very few studies dealt with the topic of predictive measurements for cardiac movement during breathing. Qi et al. used 4D-CTs to measure the maximum heart depth (maximum heart depth, MHD) and the depth of the LAD (DLAD). These measurements were able to predict the average heart dose during specific phases of free breathing [21].

Nevertheless, the MHD and the DLAD as predictors of heart dose, measured in the 4D-CT during free breathing, are not relevant for patients who receive radiation therapy during deep inspiration breath hold. Nemoto and his coworkers conducted distance measurements in the CT scanner with different gating-techniques. The greatest distance of the heart and the inner thoracic wall was measured during deep inspiration breath hold (1.7 cm). Craniocaudally the heart moved around 2 cm during deep inspiration compared to end inspiration (1.5 cm) [22].

No studies are available on the morphometric changes in the heart and heart substructures (such as the LAD) during DIBH. In this study the dose distribution at different partial heart volumes will be prospectively tested and evaluated for a large patient population for the first time.

This study could help to improve the knowledge about the necessity of respiratory-gated radiotherapy. We expect that evidence-based indications regarding optimization-criteria for radiation planning of breast cancer patients can be determined for the first time.
Declarations

Acknowledgment
We are thankful to Renate Schunke, our study nurse for this study.

Ethics approval and consent to participate:
The ethics committee of Klinikum rechts der Isar, TU München has approved this study (304/15s). Participants enrolled in the study provide their written informed consent.

Availability of data and material
The data supporting this study are included within the article.

Consent for publication
Not applicable.

Competing interests:
The authors declare that they have no competing interests.

Funding
The initiation and completion of the study protocol was funded by the Bavarian Ministry of Environment and Health ("Bayerisches Staatsministerium für Umwelt und Gesundheit"). Award Number: 83f-U8816.04-2010/2-41

Authors' contributions:
MND and MO initiated the project. MND, KJB, MO and SEC completed the study protocol and wrote the manuscript. SR, PM and CE provide patient care. MND and SEC – finalized the manuscript and perform active study coordination.
List of abbreviations

GATTUM trial – “A prospective study on the need of gated (GAT) radiotherapy in left sided breast cancer patients treated at the Technical University Munich (TUM)” trial

PTV - planning target volume

DIBH - deep inspiration breath hold

IMRT- intensity-modulated radiation therapy

VMAT - volumetric modulated arc therapy

4D-CT - 4D computed tomography

kVCT - kilo-voltage computed tomography

FB - free breathing

RPM - real-time Position Management system

LAD - left anterior descending artery.

3D-CRT - 3D conformal radiotherapy

AAA - anisotropic analytical algorithm

IORT – intraoperative radiotherapy

$D_{\text{mean}}$ - mean heart dose

CTCAE v.04- Common Terminology Criteria for Adverse Events Version 4.0

EORTC QLQ-C30 - EORTC Quality of Life Questionnaire: Core Questionnaire

EORTC QLQ-BR23 - EORTC Quality of Life Questionnaire: Breast module
Figure 1. Flowchart of the GATTUM study

$D_{mean}$ – mean heart dose; FB - free breathing; DIBH – deep inspiration breath hold; CTCAE v.04- Common Terminology Criteria for Adverse Events Version 4.0; EORTC QLQ-C30 - EORTC Quality of Life Questionnaire: Core Questionnaire; EORTC QLQ-BR23 - EORTC Quality of Life Questionnaire: Breast module
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