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Project description

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Project title: Dose response relationships and risk factors in breast cancer radiotherapy

Background

In Denmark >4.700 women are yearly diagnosed with breast cancer (BC) and a total of 65.000 are living with the diagnosis and the consequences of therapy (www.cancer.dk). The prognosis has improved over the last decades, and 82% are now alive at 5 years. Since 2008, screening mammography has been routine in DK, and >70% of the patients diagnosed with breast cancer now are treated with breast conserving surgery. All patients operated with breast conserving surgery for BC, or having node-positive BC, or a tumor >50mm are candidates for radiotherapy, thus 3.500 BC patients have radiotherapy annually. Due to demographic changes with more elderly people it is expected that the numbers of all cancer incidences including BC will further increase in the near future, thus more patients will need radiotherapy including radiotherapy for BC. Based on clinically controlled randomized trials, the DBCG Radiotherapy Committee has updated and modernized radiotherapy of early BC in DK in an evidence-based way and obtained valuable data in around 5.000 modern treated patients to be used for further research purposes since 2009 (1-6). Radiotherapy plans from all Danish radiotherapy trial patients have been centralized in the DCMCollab database, and they constitute a valuable collection of plans from a well described cohort of BC patients. The DBCG therefore has a unique opportunity to explore the radiotherapy plans, and has now decided to establish a nationwide unique bank of radiotherapy plans by collecting all consecutive radiotherapy plans from high risk BC patients in the period 2008-2017. At Aarhus University Hospital, 2612 BC patients received loco-regional radiotherapy 2008-2017, and by extrapolation the number totals 12.000 patients in all of DK. During the last 3 years the DBCG radiotherapy committee has prepared the so-called DBCG RT Nation study framework by ensuring complete reporting of radiotherapy in all Danish BC patients to the DBCG database (<1% missing information). Having access to such a large number of radiotherapy plans nationwide allows performing studies investigating nationwide trends and effects. The present project commences the first two studies in this framework, aimed at mapping specific radiation dose-response relationships to sensitive organs at risk near the breast – heart and lung. With the start of the Danish Particle Therapy Center in 2019, it is important to develop protocols for referral of patients to proton therapy. The studies presented here can both identify high risk patients who would particularly benefit from receiving radiotherapy with protons.

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Collection, preparation and QA of data

Collection of the 12.000 radiotherapy plans from all the Danish centers is the first task in the project. This will be done primarily by the participating centers exporting the radiotherapy plans to the DCMCollab database, but requires prior instruction on procedure for standardization and nomenclature. This will in practice be done by visiting the centers for development of specific procedures for each center. Subsequently, a quality assurance process will be performed for the data in the DCMCollab database. This is to ensure that standardization and nomenclature is followed. Furthermore, it will be validated that the DBCG criteria for patient selection are followed correctly, and that the radiotherapy techniques used follow the DBCG radiotherapy guidelines. For the studies to be performed here, radiotherapy doses to target and organs at risk will be collected through computer assisted methods from the DCMCollab database. Data on patient, tumor and treatment characteristics are available in the DBCG database.

This collection and preparation of data in itself comprises a large workload, and in addition to serving as data validation for the studies described below, it will be utilized to feed data to a separate phase IV study aimed at surveying the changes implemented in the DBCG RT guideline of March 2014, where the first results from the DBCG IMN study (Internal Mammary Nodes) documented an overall survival gain from IMN radiotherapy (7).

STUDY 1 – pre-treatment calcium score risk factor for radiation induced heart disease

In a recent Dutch publication, pre-treatment coronary artery calcium scores were detected in planning CT scans from a smaller cohort of BC patients and showed correlation with risk of acute coronary event (8). Calcium was detected in 10% of the plans, and after correcting for confounding factors, a dose-response relationship between level of calcium score and risk of heart disease was seen. In the present study, this correlation will be investigated in our large cohort, including detailed mapping of dose-response relationships for substructures in the irradiated heart.

Hypotheses:

1. It is possible to measure calcium scores using machine learning methods for automated processing in 12.000 radiotherapy plans used for BC radiotherapy.
2. There is a dose-response relationship between level of calcium score and risk of heart disease (i.e. calcium scores are prognostic).
3. At a given radiation dose to the heart, the risk of heart disease is increased, if calcium is present (i.e. calcium scores are predictive).

Materials and methods:

- 12.000 radiotherapy plans in the DCMCollab database.
- Information on heart disease from the West and East Danish Heart Disease Banks and the national registry of diagnoses (Landspatientregisteret).

A machine learning method to detect calcification of cardiac vasculature in CT scans will be developed (in line with that described in (8)), and validated for use in planning CT scans for BC patients. For a subset of the 12.000 radiotherapy plans, calcium scoring will be performed using the automated machine learning method as well as manually by physician inspection. The automatically detected calcium scores will be compared with physician scores, and potential adjustments to the algorithm will be performed. The method will then be used to perform automated calcium scoring for all BC patients in the DCMCollab database.

Second, patients will be grouped according to discrete intervals of calcium score, and the prevalence of heart disease in each group will be found through lookup in the national registry of diagnoses.

Third, in each calcium score group the dose response relationship for heart disease will be calculated. Different metrics for radiotherapy dose to the heart will be tested, including mean heart dose and different dose levels. The dose response relationships will be compared for the different calcium score groups to identify potential increased risk.

Perspectives:

In daily clinic the calcium scores can be detected in the radiotherapy plans at no extra cost and if they show prognostic / predictive significance, it has the potential to change treatment of BC patients.

Proton therapy may be a better treatment for future BC patients with calcium in the heart - as illustrated in figure 1, proton therapy gives considerably lower radiation dose to the heart compared with standard radiotherapy.

Second, BC patients at high risk of developing heart disease can be identified in the almost 5.000 radiotherapy plans from trial BC patients. Thus, there will be potential to start relevant treatment preventing heart disease in these patients.

STUDY 2 – low dose bath dose-response for lung toxicity in complex radiotherapy

Radiotherapy planning is in constant development and new technical improvements further optimize therapy. The majority of BC patients are treated with tangential radiotherapy field with a relatively low radiation dose to the lungs. Up to around 5% of BC patients treated with loco-regional radiotherapy have anatomical issues making standard planning difficult. These issues may be e.g. pectus excavatum,

and patients operated with immediate reconstruction. These complex patients are often treated with inverse intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) resulting in a large dose-bath to heart and lungs. Easily more than 5 Gy is delivered to >70% of the lung, as illustrated in figure 2. There is no data on the long-term consequences of this for the patient. During 2019 the randomized DBCG RT Recon trial will open for accrual, and a large number of patients operated with immediate breast reconstruction is expected for radiotherapy as a consequence of that trial. Thus the use of inverse IMRT will likely increase.

Hypotheses:

1. It is possible to quantify the amount of radiotherapy dose to the lungs in BC patients treated with different radiotherapy techniques. Radiotherapy plans with a large low dose bath to the lungs can be identified.
2. BC patients who had a large low dose bath to their lungs do not have more lung symptoms/disease compared with patients treated with conventional radiotherapy.
3. It is possible to invite BC patients treated with standard and inverse IMRT techniques to report lung morbidity through Patient Reported Outcome Measures (PROM).

Materials and methods:

- 12.000 radiotherapy plans in the national DCMCollab database.
- Information on lung disease from the national registry of diseases (Landspatientregisteret) and PROMs. The PROM questionnaire will be developed as part of the PROM work package (WP7) in the Danish Cancer Society National Research Center for Radiotherapy.

First step of this study is to divide the 12.000 radiotherapy plans in the database into two subsets containing those treated with IMRT/VMAT techniques and those with standard techniques, respectively. This is not a trivial task, since there is no unique identifier for the radiotherapy technique in the radiotherapy plan information, and in some cases there may not be any explicit information to denote radiotherapy technique. A data retrieval method combining several identifiers (such as plan name, field intensity maps, number of fields) will be developed, and manually validated and adjusted for a subset of the 12.000 plans, before the entire database is processed for division into the two groups. For both groups, the population distributions of lung doses are found and compared, for various dose levels including the volume receiving 5, 10, 15 and 20 Gy, and mean lung dose. The low lung dose level which is the most distinctive separator of the two groups, i.e. between the radiotherapy techniques, is then identified. This separator dose level is subsequently used to divide the 12.000 radiotherapy plans into two groups based on lung dose bath rather than on radiotherapy technique,

one group with a large low dose bath to the lungs, and one group without the low dose bath. The group with large low dose bath is expected to comprise around 250 patients, and their radiotherapy plans will be verified individually as inverse IMRT type.
For the second part of the study, the potential adverse effects of a low dose bath to the lungs will be investigated. The estimated 250 patients in the low dose bath group are cases, and for every case 2 control patients will be matched (treatment year, age, adjuvant systemic therapy) from the group without low dose bath, and all cases and controls will be asked for PROM incl smoking history and previous lung disease. Based on the PROMs, a dose response relationship is calculated for various lung dose parameters.
Perspectives:
1) There are no guidelines now to inform on safety of low dose bath to the lungs in the adjuvant BC radiotherapy setting, thus the results from this nationwide study will provide new knowledge on a clinical problem, for the group of patients being treated with advanced radiotherapy techniques.
2) If a dose-response relationship between lung dose and morbidity is established, this may serve as a guidance to refer BC patients for proton therapy.
3) It will be possible to identify patients in the BC radiotherapy trials who may be at high risk of developing a radiation induced lung disease, for potential preventive treatment.

Time plan and collaboration

This nationwide trial is conducted on behalf of DBCG and the DBCG Radiotherapy Committee, and has received partial funding from the Danish Cancer Society. It will include BC patients treated in all Danish radiotherapy departments (6 out of 8 centers providing radiotherapy were co-applicants on the grant). The applicant will carry out the major part of data analysis in studies 1 and 2, whereas data collection and validation (including PROM for study 2) will be done in collaboration with physicists and oncologists in the DBCG Radiotherapy Committee. In figure 3, a time plan is shown for the project – the time plan spans 4 years, pending application for reduced working hours throughout the project.

Chair of the DBCG Radiotherapy Committee Professor Birgitte Offersen will co-supervise the project, with Professor of Medical Physics Stine Korreman as primary supervisor. Stine Korreman has extensive prior experience in research related to reduction of toxicity in breast cancer radiotherapy, and to proton therapy. The project will include a research stay at University Medical Center Groningen for exchange of methodology for calcium scoring and modelling of dose-response relationship.

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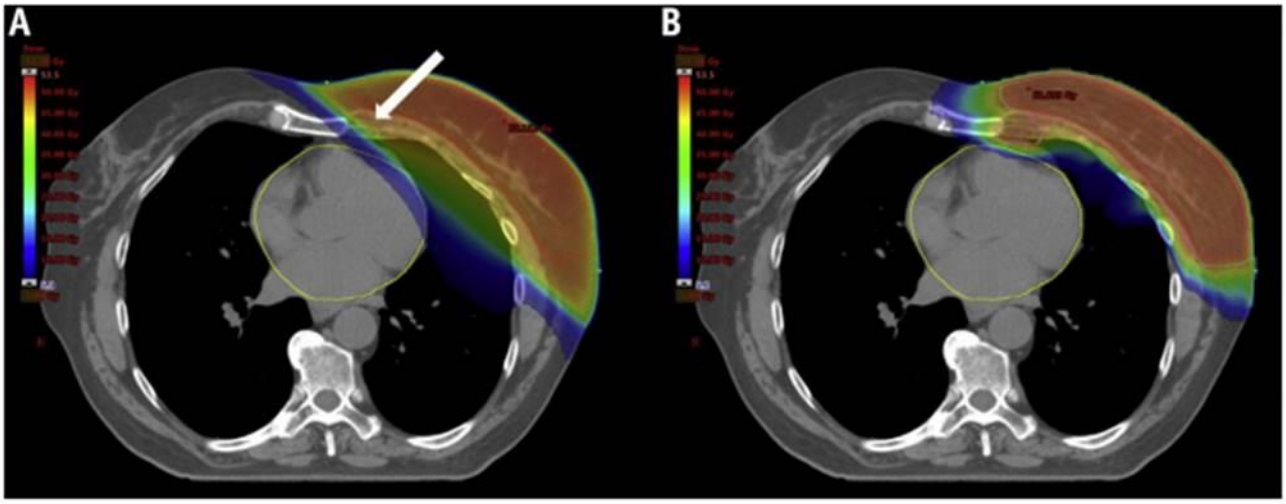
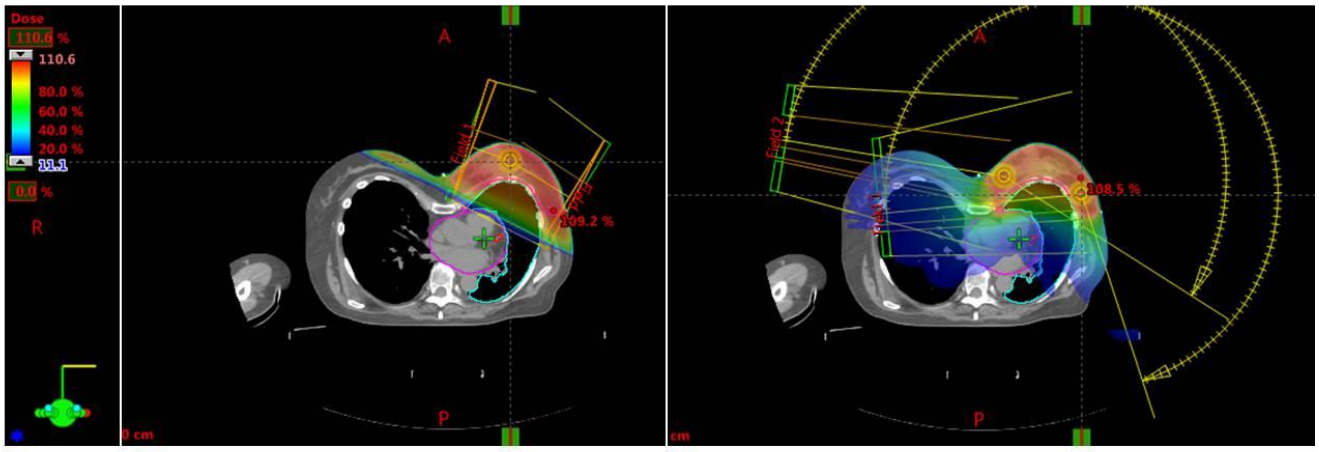
Figure 1:



Dose wash illustrations (blue colours indicate low radiation doses, and red colours indicate high radiation doses) for a breast cancer patient for (A) an standard photon therapy plan with two tangential fields, and (B) a 2-field proton therapy plan. The white arrow indicates the internal mammary node target. Figure from (9).

Figure 2:



Dose wash illustrations (blue colours indicate low radiation doses, and red colours indicate high radiation doses) for a breast cancer patient with complex pectus excavatum anatomy for (A) an standard photon therapy plan with two tangential fields, and (B) a VMAT photon therapy plan with two isocenters (from 10).

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Figure 3:

	Spring 2020	Fall 2020	Spring 2021	Fall 2021	Spring 2022	Fall 2022	Spring 2023	Fall 2023
Data collection, preparation and QA								
Study 1, develop machine learning method for calcium scoring								
Study 1, co-registration of calcium score with heart disease								
Study 1, model heart dose response relationship (+visit to UMC Groningen)								
Study 2, retrieval of IMRT and VMAT plans, incl mapping of lung doses								
Study 2, model lung dose response relationship (incl PROM)								
Write thesis								

Time plan for project. The time plan stretches over four years, pending application for reduced workload throughout the duration of the PhD project.

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