AARHUS UNIVERSITY

Project description (5 pages, in English)

Academic title and name: Emma Riis Skarsø, MSc.
Project title: DBCG RT Nation Automation

Background

Challenges in breast cancer radiotherapy

Breast cancer (BC) is the most frequent type of cancer among women in Denmark. Yearly more than 4700 women are diagnosed with BC. Patients operated with breast conserving surgery, a tumour larger than 50 mm and/or having node positive BC are candidates for radiotherapy. All together more than 80% of BC patients are treated with postoperative adjuvant radiotherapy[1-2]. The survival rate has been increasing since 2000, and today around 87% are alive after 5 years. However, in 2016, more than 66.000 people were living in Denmark with the diagnosis and the late-effects of their treatment, including late-effects from radiotherapy. The radiotherapy of BC may lead to irradiating some of the healthy lung and heart (in particular for left sided breast cancer), which can potentially lead to radiation-induced lung cancer or cardiovascular disease later in life[3].

Analysis of unprecedented large cohort shall ensure more effective treatment

During the last four years, the Danish Breast Cancer Group (DBCG) radiotherapy committee has ensured complete reporting of radiotherapy in all Danish BC patients treated since 2008 to the DBCG database (<1% missing information), while also preparing the DBCG RT Nation database. The RT Nation database will contain the largest homogeneous cohort of radiotherapy data, that we know of internationally. The database will include the CT scans, treatment plans, radiation dose distributions and organ delineations for more than 9500 patients, collected and stored in the national infrastructure, the DCMCollab database (https://dcmcollab.rsyd.dk/). The data collection is presently in progress and expected completed within 2021. Having access to such a large number of radiotherapy (RT) plans nationwide will make it possible to conduct retrospective data mining research with a well described large cohort of BC patients, allowing us to conduct studies investigating nationwide trends and ensuring more effective treatment in the future. This PhD project will use the DBCG RT Nation cohort to investigate national trends in delineation practices, the dosimetric effects of these and the possibility of automating and implementing the automatic delineation and treatment planning process in the clinic. The PhD-project presented here has undergone review and received full approval by the DBCG RT committee, securing national participation in the study.

Variations in treatment preparation can influence radiation induced late effects

RT treatment planning (TP) consists of two essential parts: Delineation of target structures and organs at risk (OARs), and optimization of the dose distribution (the treatment plan). Before 2007, the treatment preparation was solely based upon bony landmarks, however in 2007, CT based 3D TP was introduced in Denmark and the treatment plans could now be created with the target area (clinical target volumes CTV) and OAR delineated on an individual basis in the CT scan. This also allowed optimization of the dose distribution to be individualised and calculated with high precision. However, both delineation and dose optimization are manual processes, with substantial subjective assessment and decision making by the involved professionals, it introduces some uncertainty. For organ delineations this means that the identification of target and OARs is prone to uncertainties related to image interpretation. For dose optimization, the manual TP process is 'trial-and-error' based and highly depended on planner expertise. Thus a difference in delineation practice and/or TP can cause a difference in the actual individual radiation dose administered to the target and OARs, such as the heart[4].

Standardisation and automatization of delineation and treatment planning
The first step to homogenizing the TP process, was made in 2013 by the DBCG, when they reached a national consensus guideline for the delineation of CTVs and OARs in BC RT[5-7]. In 2014 ESTRO followed with a consensus guideline between a broad European group [8], providing valuable guidelines for the clinicians to follow when manually delineating the structures. However, while the guidelines improve consistency, they do not remove the subjectivity in the delineations and TP.
As a next step, computer algorithms are being developed for automation processes to mitigate the subjective differences and human errors created during the delineation and TP process. So-called auto-segmentation tools offers the possibility to streamline delineation practices nationwide [9], and novel studies have shown that auto-planning tools, not only can produce high-quality clinically acceptable dose distributions, but also in some cases improve the manually created plans[10-11].

The present project is aimed at analysing differences in delineation practices in BC patients across Denmark, and over a period of time from 2008-2016 and automating the treatment planning process. The aims are (1) to document delineation variations and the effects of introduction of guidelines on delineation practices, (2) to map effects of variations on radiation dose distributions in the treatment plans and (3) to investigate whether auto-delineation and TP can homogenize the plan quality.

Hypotheses:

a) There are systematic differences in delineation practices for both OARs and target across the nation and over time
b) These differences cause dosimetric variations in the BC treatment plans
c) Automation of the treatment planning processes can homogenise the plan quality

Materials and methods:
All data and software necessary for carrying out this project will be available at Aarhus University Hospital (AUH) and DCMCollab.

Data:
The project will include data from approximately 9500 consecutive high-risk BC patients treated in the period 2008-2016 in Denmark. These data are presently being collected in the DBCG RT Nation study, conducted by the PhD student Lasse Refsgaard(CLINFO, AU). In total, the data will consist of CT scans, structure delineations and treatment plans for BC patients with high risk BC.

Software:
Delineations and treatment plans will primarily be visualised in the treatment planning system Eclipse version 13.7 (Varian Medical Systems, Inc), which is available at AUH through an existing research license. Data analysis will be performed in Python.
To auto-generate delineations on the CT scan two different software packages will be used. An commercially available atlas-based auto-segmentation algorithm currently being implemented at the Department of Oncology AUH, and a deep learning convolutional neural network for auto-segmentation currently being developed in Stine Korreman's research group.
To auto-generate treatment plans, two different software packages will be used. A knowledge based planning system, RapidPlan (Varian Medical Systems, Inc) and a machine learning based planning system, RayStation (Raysearch Laboratories, AB). Both are available in dedicated research licenses at AUH.

Q1. Are there systematic differences in delineation practices for OAR and treatment targets across institutions and over time?
Method: Delineation protocols and guidelines used locally at the Danish RT departments during 2008-2013 will be reviewed. A cluster analysis tool will be developed based upon the RT Nation data, to investigate systematic structure delineation differences between radiotherapy departments and characteristics in delineation practices. The usage of a cluster analysis tool is possible due to the large dataset available, and will allow for an unsupervised delineation variability analysis thus avoiding the bias created, when comparing to a *golden standard*. The structure analysis will include delineation of breast target volume chest(CTV) (medial/lateral and cranio/caudal extent), internal mammary node target volume (intercostal spaces included and volume), heart (size, cranio-caudal extension), and left anterior descending coronary artery(LADCA, length and width), and potentially other relevant anatomical structures, see figure 2.
Perspective: This sub-study will illuminate the magnitude of variations in delineations practices nationwide and it will document the effect of introduction of nationwide delineation guidelines. The cluster analysis tool developed will be useful in prospective quality assurance of delineation guidelines.

Q2. How do the differences in delineation practices affect the treatment plans?
Method: The investigation of the dosimetric effects of various delineation practices will be based on the DBCG RT Nation data used in Q1. The radiation dose received by targets and OAR will be scored using the original CT scans, delineations and treatment plans. Figure 3 illustrates a typical dose distribution for a BC patient. A selection of quantitative metrics will be chosen to represent the overall radiation dose for each patient. The scored radiation dose metrics will be related to the various delineation practices, using the cluster analysis tool, to identify any radiation dose differences related with delineation practices. In addition, cluster analysis for similar metrics will be performed based on radiation dose to structures independent of delineation practices. The purpose of this is to distinguish practice differences in trade-offs performed during treatment planning which may not be reflected in

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

delineation practices. The clustering of patients based on radiation dose will be compared with clustering based on delineations, to assess the dosimetric impact of delineation variations.
Perspective: This sub-study will illuminate the dosimetric effects of variations in delineation practices. It will reveal if there are any correlations between different structure delineations and the dosimetric effects, as well as dosimetric variations independently related to dose optimization practices.

Q3. Can automatic delineation of OARs homogenize treatment plan quality?
Method: Automatic delineation of OARs will be investigated by comparing auto-generated delineations with manual delineations. BC patients representing distinct anatomies and delineation practices will be re-delineated with an auto-segmentation tool. The differences between the manual and auto-generated delineations will be quantified for OARs (the whole heart, LADCA and the lung). New treatment plans, according to the DBCG guidelines, will be created on the CT scans with the auto-generated delineation of OARs using the Eclipse treatment planning system. The dosimetric differences between the plans with manual and auto-generated delineations will be identified. Population based dose metrics for the plans based on auto-generated delineations will be compared to metrics for the original plans to analyse whether a more homogeneous plan quality is achieved when using auto-segmentation tools.
Perspective: This sub-study will show the dosimetric differences occurring, when comparing auto-generated and manual delineations. It will provide a basis for introduction of computerized automated delineation, which can improve workflow and reduce uncertainties leading to better overall treatment standard.

Q4. *Investigation and implementation of automatic treatment planning*
Method: The investigation of automatic treatment planning will be based upon the pts used in Q3. Two auto-planning systems will be trained independently and the results will be compared in terms of both dosimetric parameters and user interaction (time spent, and number of interactions necessary). The results will be compared with the clinical TPs for quantification of both plan quality and magnitude of variations.
The best solution will be tested in a prospective quality study with the aim of implementation in routine clinical practice at AUH. This study will be performed in close collaboration with the clinical physicists in the Department of Oncology.
Perspective: This sub-study will finalize the process of improving the treatment plan preparation through automation. The identified optimal solution will be implemented in the clinical routine at AUH.

Research plan:
The research plan is shown in figure 1.
As part of the project, a 6 month visit to The Netherlands Cancer Institute is planned, under the supervision of Professor Uulke van der Heide. The research group is among the leading international research groups within image guided radiotherapy, working particularly with image segmentation and

implications for TP[9]. During the visit, tools developed by the group of Professor van der Heide will be used to perform quality assurance of delineation cluster analysis.

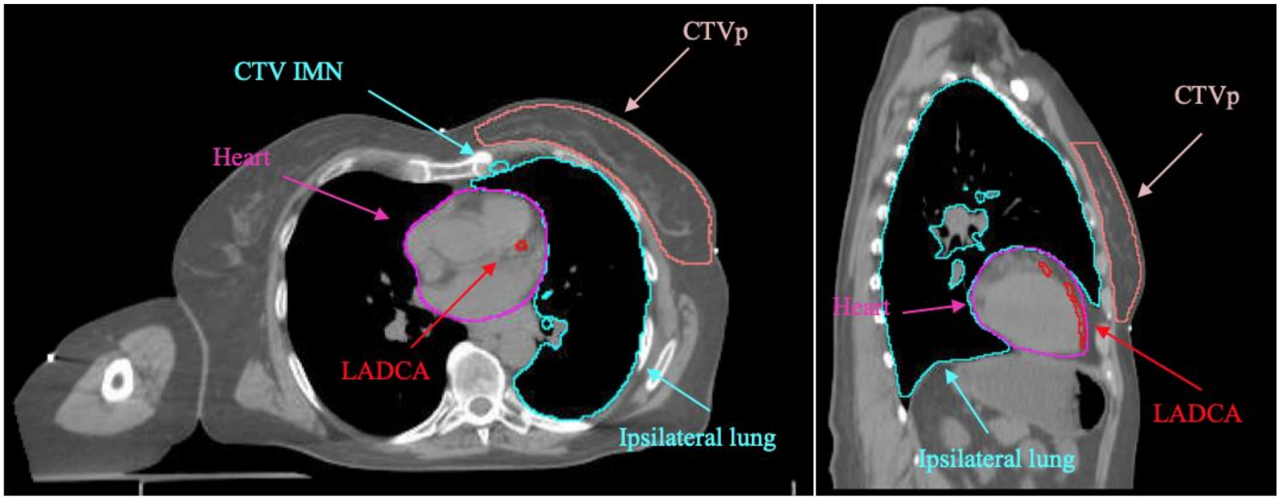
Expected results and impact(Perspectives):
This study will illuminate the magnitude and implications of various treatment preparation practices used in radiotherapy for BC in Denmark, while developing an automated planning strategy. The automated planning strategy is an important tool in providing the basis for nationwide consistent reduction of radiation induced late-effects for BC patients and it will be implemented in the clinical routine at AUH as a part of the project, with a view to expanding to national standards.
Finally, the implications of differences in treatment preparations are not only relevant for BC patients, but for every cancer patient receiving radiotherapy, thus the methods developed and tested in this project are relevant for all patients treated with radiation, no matter the cancer type.
Making treatment preparation more streamlined and automated will provide a higher quality of radiotherapy for the patients. It will release resources to a more individualized treatment which may eventually further improve the survival rate.

Figure 1

	Fall 2021	Spring 2022	Fall 2022	Spring 2023	Fall 2023	Spring 2024
PhD student period						
Q1, review and categorization of delineation protocols						
Q1, development of cluster analysis tools for variations						
Q1, quantification of geometrical differences						
Exchange visit to Netherlands Cancer Institute – quality assurance study						
Q2, selection of quantitative dosemetrics						
Q2, quantification of dose difference in practises						
Q3/Q4, auto-generate delineations and treatment plans						
Q3/Q4, geometric and dosimetric comparison of auto-generated and manual delineations and auto-generated and manual treatment plans						
Q4, implement automated planning in the clinic at AUH						
Write thesis						

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

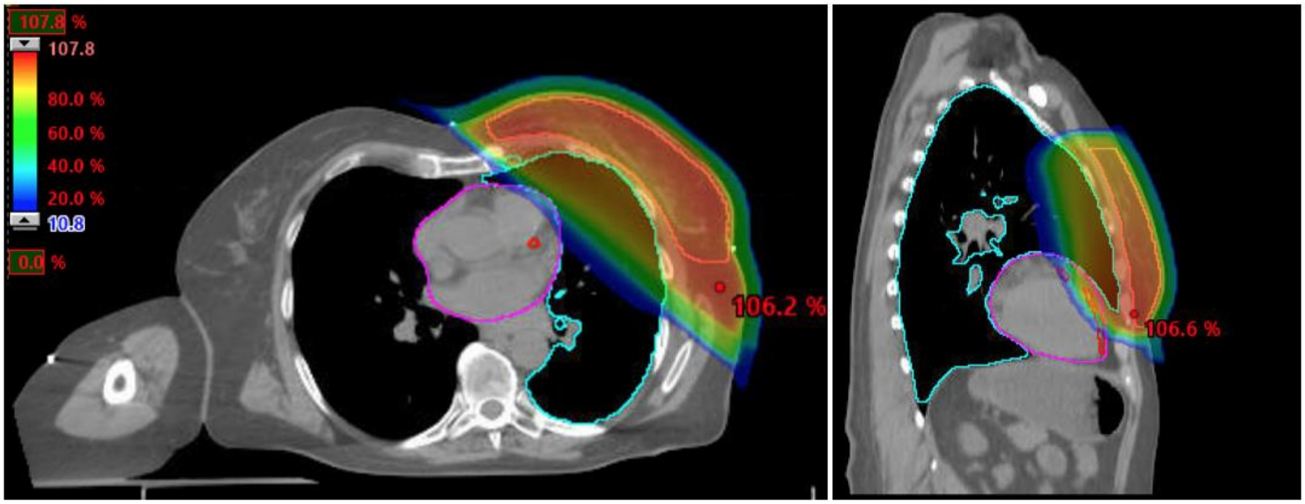
Figure 2



Transversal and sagittal CT slice of a BC patient with a lumpectomy. A selection of important OARs, such as the heart, LADCA and ipsilateral lung are shown. Furthermore a selection of the targets are shown, such as CTVn IMN (internal mammary lymph nodes) and CTVp chest. These delineations form the basis of the treatment plans. This entails, that the quality of the treatment plan directly correlate with the anatomy of the patient and the choice made during the delineation process. If the CTVp chest were drawn more towards the sternum, the consequences will be higher heart and lung dose.

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

Figure 3



The corresponding transversal and sagittal slice of a BC patient with a lumpectomy from figure 2 with dose color wash illustrations(Blue colors indicate low radiation doses and red colors indicates high radiation doses). If the CTVp chest were drawn more towards the sternum, the consequences will be higher heart and lunge dose.

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

References

1. https://www.straaleterapi.dk/kraefttyper/brystkraeft/
2. https://www.cancer.dk/brystkraeft-mammacancer/statistik-brystkraeft/
3. Aznar MC, Korreman SS, Pedersen AN, Persson GF, Josipovic M, Specht L. Evaluation of dose to cardiac structures during breast irradiation. The British Journal of Radiology, 84(2011), 743-746
4. Pitkänen MA, Holli KA, Ojala AT, Laippala P. Quality Assurance in Radiotherapy of Breast Cancer Variability in Planning Target Volume Delineation. Acta Oncologica, 40:1(2001), 55-55
5. Nielsen MH, Berg M, Pedersen AN, Andersen K, Glavicic V, Jakobsen EH, Jensen I, Josipovic M, Lorenzen EL, Nielsen HM, Stenbygaard L, Thomsen MS, Vallentin S, Zimmermann S, Offersen BV. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol. 2013;52:703-710
6. Milo MLH, Offersen BV, Bechmann T, Diederichsen ACP, Hansen CR, Holtved E, Josipovic M, Lörincz T, Maraldo MV, Nielsen MH, Nordsmark M, Nyström PW, Pøhl M, Rose HK, Schytte T, Yates ES, Lorenzen EL. Delineation of whole heart and substructures in thoracic radiation therapy: National guidelines and contouring atlas by the Danish Multidisciplinary Cancer Groups. Radiotherapy and Oncology 150(2020) 121-127
7. Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jagsi R, Lorenzen EL, McArdle O, McGale P, Myerson S, Rahimi K, Vivekanandan S, Warren S, Taylor CW. A cardiac contouring atlas for radiotherapy. Radiotherapy and Oncology 122(2017) 416-422
8. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Verhoeven K, Weltens C, Arenas M, Gabrys D, Kopek N, Krause M, Lundstedt D, Marinko T, Montero A, Yarnold J, Poortmans P. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiotherapy and Oncology 114(2015) 3-10
9. Simões R, Wortel G, Wiersma TG, Janssen TM, van der Heide UA, Remeijer P. Geometrical and dosimetric evaluation of breast target volume auto-contouring. Physics and Imaging in Radiation Oncology 12 (2019) 38-43
10. Cilla S, Laniro A, Romano C, Deodato F, Macchia G, Buwenge M, Dinapoli N, Boldrini L, Morganti AG, Valentini V. Template-based automation of treatment planning in advanced radiotherapy: a comprehensive dosimetric and clinical evaluation. Nature (2020)

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

11. Hansen CR, Bertelsen A, Hazell I, Zukauskaite R, Gyldenkerne N, Johansen J, Eriksen JG, Brink C. Automatic treatment planning improves the clinical quality of head and neck cancer treatment plans. Clinical and Translational Radiation Oncology 1 (2016) 2-8