Title:

Risk of cardiovascular disease after cancers of the lung and esophagus treated with definitive radiotherapy

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Problem and research question

Curatively intended radiotherapy (RT) is a treatment option for patients with good performance status and loco-regionally advanced non-small cell lung cancer (NSCLC) and esophageal cancer (EC) resulting in 5 year cure rates of 15-30% depending on the stage of the cancer and patient related conditions. During the last 10 years the survival is luckily increasing, this creates a need to focus on potential toxicities on a longer term than a few years. Due to the location of the heart in the thorax, irradiation of the lungs and the esophagus invariably involves some RT dose to the heart. Increased cardiac mortality rates have been demonstrated subsequent to RT for Hodgkin´s lymphoma [1] and breast cancer [2], but little is known about cardiac mortality in survivors from NSCLC and EC. Detection and quantification of the presence of coronary artery calcium (CAC) with computerised tomography (CT) has proven to be a reliable biomarker for cardiovascular events in non cancer patients [3]. In current studies CAC is an independent factor that adds superior to the traditional risk factors. In the Danish Lung Cancer Screening Trial, CAC was a robust prognostic measure of fatal or non-fatal cardiovascular events [4]. Accumulating evidence suggests that administration of statins to high risk patients may reduce not only the risk of cardiovascular disease, but also reduce the risk of dying from cancer [5].

In this project, the following questions will be adressed:

1. Does a high CACs prior to RT have a prognostic survival effect among patients irradiated for NSCLC and EC?
2. Does treatment with statins have a favorable influence on survival in NSCLC- and EC patients with high CACs treated with definitive RT?
3. Is an increase in CACs after RT associated with higher mortality in patients irradiated for NSCLC and EC?
4. Is early and late toxicity to the heart detectable by cardiac imaging using echocardiography of the heart, cardiac magnetic resonance and electrocardiogram?

Background

Lung and Esophageal Cancer

Lung cancer is a frequent type of malignant disease. In Denmark 4800 patients are diagnosed with the disease every year. Approximately 25% have loco-regional advanced disease and are offered curatively intended RT, often in combination with chemotherapy, if they are in good performance status[6]. Recently published studies indicate a small, but definite improvement in survival [7]. To improve local control, escalations in RT dose is tested in clinical trials [8]. However, dose escalation may increase toxicity.

The incidence of EC in Denmark is 500 patients per year. The disease has, as lung cancer a poor prognosis with a 5-year overall survival of 15 % [9]. Similar to lung cancer definitive RT is also a treatment option for EC. In addition, the two groups of patients are alike regarding age, smoking history, treatment modality with RT. Due to the location of the heart in the mediastinum, irradiation of NSCLC and EC often involves some RT dose to the heart.

The acute side effects to RT in thorax are well known [10]. However, RT induced cardiac toxicity is not as well described in NSCLC and EC as it is in other cancer groups, such as early stage breast cancer [11] and Hodgkin's lymphoma [12]. For breast cancer patients RT dose to the heart increases the risk of 5-, 10-, and 15-year cardiac mortality for patients with left sided breast cancer, compared to patients with right sided breast cancer [13]. The rates of major coronary events increased linearly with the mean dose to the heart by 7.4 % per Gy, starting at one Gy [14].

A recent published study (RTOG 0617) where standard RT dose compared to dose escalation had a negative result. Additional analyses on data from this study indicated that increasing RT dose to the heart had a negative impact on survival [15]. Data on late toxicity such as cardiac morbidity and mortality are scarce for patients with NSCLC and EC treated with definitive RT, with only a few retrospective studies published [16, 17].

Coronary artery calcium score (CACS)

CACs is highly useful for cardiovascular risk stratification for patients with already known cardiovascular disease and for patients with intermediate risk for cardiovascular disease. The presence of coronary artery calcium is associated with a 10-fold higher risk of adverse cardiovascular events in non-cancer patients. We perform CACs evaluation in a CT-scan. The CT definition of coronary atherosclerosis is the establishment of pixels with a CT-number of > 130 Hounsfield Units. The higher Hounsfield Units the higher CACs, and the higher risk of cardiac disease [18]. In breast cancer, three studies has been performed on CACs and risk of cardiovascular disease, one reporting a positive association [19] and two others, no association [20, 21]. To our knowledge, there are no published studies on CACs, survival and radiotherapy on patients with diagnosed lung or esophageal cancer. However, there are studies stating that the evaluation of CACs is conductible on non-gated CT scans [4].

Cardiac Magnetic Resonance (CMR)

The advantages of CMR are the visualization the heart chambers, endocardial and epicardial borders. These advantages make CMR the most optimal tool to detect small changes in the left ventricular (LV) ejection fraction and LV mass. Furthermore, examination with gadolinium-based contrast agents offers the potential advantage of visualizing fibrosis of the myocardium in an early stage.

Even though RT is associated with increased risk of cardiac related morbidity and mortality in early stage breast cancer, the structural changes in heart has not been mapped [2], and neither has the ideal image modality to record this potential structural change.

Cholesterol lowering medications and atherosclerosis

High serum cholesterol is a main cause of coronary atherosclerosis, which can lead to coronary artery disease. RT is possibly a factor in acceleration of atherosclerosis. Statins reduce LDL cholesterol and atherosclerosis and thus the risk of a major coronary event. Treatment with statin is recommended if CACs is higher than zero and with presence of other risk factors [22, 23]. Apart from their role in preventing heart diseases in patients with high cholesterol, recent evidence suggests that statins have anti-tumor properties [24]. Inconsistent results have been reported on the association between statin use and mortality from lung cancer. A recent meta-analysis included 17 studies of which 10 related to NSCLC and did not have an effect in overall survival in randomised controlled trials, but decreased all-cause motality in cohort studies [25]. For EC, 5 retrospective cohort studies have been analysed, including a total of 24,576 patients, overall statin use was associated with imroved overall and disease-free survival [26]. None of the studies of NSCLC and EC were conducted in Denmark. Overall the results in statins and how these affect the mortality are inconsistent in cancer patients treated with RT. In Denmark we have a possibility in doing registry based studies with valid data, thereby providing important data with impact on clinical parctice.

Aim

Aims and hypothesis for the four planned studies as described in the following.

Study 1

Aim: To investigate if baseline CACs has survival importance for patients with NSCLC and patients with EC undergoing RT as seen in patients without cancer

Hypothesis: NSCLC and EC patients with high CACs treated with definitive RT have a worse prognosis compared to patients with low CACs.

Study 2

Aim: To investigate if treatment with statin has an impact on survival in NSCLC patients and EC patients with high CACs treated with definitive RT.

Hypothesis: NSCLC and EC patients with high CACs treated with definitive RT and statin has better OS compared to the patients with high CACs undergoing RT, but without statin.

Study 3

Aim: To investigate if increase in CACs post RT results in higher mortality for patients with NSCLC and EC treated with definitive RT.

Hypothesis: Patients with an increase in CACs after definitive RT has poorer survival compared to patients with stable CACs after RT.

Study 4

Aim: To investigate baseline cardiac function in NSCLC patients prior to RT. In addition investigate if RT induced cardiac damage can be mapped by CMR.

Hypothesis: We can map RT induced cardiac damage on CMR and a dose response relation for normal tissue complication probability is possible to establish.

Study design

Study 1

A register based cohort study

We will investigate all NSCLC patients and EC treated with definitive RT in Denmark in the period 2014-2015. We plan to exam CT-scan made for planning RT in order to perform the CACs. The patients are identified from the databases of the Danish Lung Cancer Group (DLCG) and Danish EsophagoGastric Cancer Group (DEGC).

We will perform the project in collaboration with Department of Cardiology, Odense University Hospital.

All radiotherapy centers in Denmark as well as the Danish Oncological Lung cancer Group (DOLG) and the Danish EsophagoGastric Cancer Group (DEGC) have accepted to support this project.

The Danish Patient Safety Authority approved the project.

Study 2

A register based cohort study

Same study population as in study 1.

We collect information on usage of statins from The Danish National Prescription Registry (Lægemiddelstatistikregisteret (LSR)).

Study 3

A register based cohort study

Same population as in Study 1 and 2.

During follow up all patients with NSCLC and EC treated with RT are evaluated with CT scans and medical history every three months for the first two years and every six months thereafter for another 3 years. These CT-scans enable us to follow the development in CACS over time.

For study 1-3 baseline data on patient and tumor charachteristics are gathered. Standard statistical methods, as proportions, multivariable Cox regression and Kaplan-Meier analyses will be used.

Study 4

A prospective study for NSCLC patients treated with definitive RT at Department of Oncology (2014-2021). **COLA COr Loco-regional Advanced lung cancer "***The effect of radiotherapy on the heart in loco-regional advanced NSCLC patients treated with definitive radiotherapy measured by different image modalities".* Approved by the Committee on Health Research Ethics (S-20160086). We offer examination of the heart with CMR, ECHO and ECG.

Part A: The patients will be included in the study prior to RT. We plan to perform examination with CMR, ECHO and ECG scheduled at 1.5, 6, 12 and 24 months.

Part B: A prospective study, the patients receive information about the study at the scheduled follow-up visit 12-24 months after definitive RT for NSCLC and we offer examination of the heart with ECG, ECHO and CMR as in part A of Study 4.
Aim: To investigate baseline cardiac function in NSCLC patients prior to RT. In addition investigate if RT induced cardiac damage can be mapped by CMR.

For all four studies two databases are established in OPEN (Open Patient data Exploratory Network – OP_1144)) in order to store the data from all four studies. The Danish Data Protection Agency has licensed data storage.

Sample size and statistics

Study 1, 2 and 3

Study 1 and 2 are descriptive study of the cohort treated with the given modality in 2014-2015 in Denmark.

For all parts of the project, data is obtained from patient registries. Data on demographics (gender, age at diagnosis), tumor characteristics (histology, location, stage), treatment (surgery, chemotherapy, RT) is obtained from DLCR and DEGC. Exposure to statins (type of statin, time periods of use (pre and post diagnosis)) is collected from LSR.

Information on cardiac disease and other relevant comorbidities are obtained from The Danish National Patient registry. Standard statistical methods will be used to describe the study populations. Overall and disease free survival will be assessed by Kaplan-Meier analyses. Multivariable Cox regression models are used to estimate the hazard ratios and 95% conficence intervals. We have refrained from a formal calculation of statistical power, because the distribution of exposure variables, such as CACs and treatment with statins, is unknown in the study population.

Study 4

This is an explorative study, which means that it is not possible to make a power calculation of the sample size. However, based on studies on cardiac toxicity in early stage breast cancer after RT, cardiac event may possibly occur in around 20% of the patients [27, 28]. In order to ensure valid results, and not just random noise from a single scan, it is important to have around 10 events in each sub-study. Assuming similar numbers of cardiac events in this group of NSCLC patients as in breast cancer patients this study will require 50 patients in each sub-study.

Ethics

The project has four parts. The first three parts are working on data from already treated patients and the results will not influence the outcome of the patients. Future patients will benefit on increased knowledge in the topic.

The fourth study meets the Helsinki Declaration and the national requirement for studies of patients with cancer. All patients receive oral and written information about the study and provide a written informed consent before enrolment. There are potential side effects for patients participating in CMR as there is need for intravenous contrast. There is inconvenience for the patients in case of claustrophobia and the need of additional testing in a

hospital. In case of abnormal findings in CMR, ECG and ECHO, an experienced cardiologist will treat the patients according to best practice.

Limitations

The studies are epidemiological cohort studies, the limitations can be misclassification bias and it can be hard to control for confounders. Danish registries are reliable; however, there are general problems such as incomplete data. Furthermore, diagnosis established at primary care are not a part of The Danish National Patient Registry leading to a lower prevalence of certain less serious conditions as for example atrial fibrillation.

Feasibility

DCCC DOC (Danish Comprehensive Cancer Center Onco-Cardiology group) initiated the project. DOC representatives include oncologists and cardiologists from all over Denmark. DOLG (Danish Oncology Lung Cancer group) and DEGC (Danish EsophagoGastric Cancer Group) support the project. The project is carried out under strong supervision from two experienced oncologists, a cardiologist and a medical phycist. All oncology centers in Denmark contribute with patients, and experienced oncologists are a part of the study group. The infrastructure of the project is already accomplished; with initiated project databases and analysis of CACs. SDU has granted approval of the PhD project and the PhD student.

Publications

The results of the studies will be published in international journals, whatever the result will be. Four publications are planned (one from each study). Supervisors and collaborators are offered co-authorships according to regulations.

Clinical relevance

This study will generate new knowledge on a possible relationship between CACs and survival, and a potential effect from statins on NSCLC and EC patients. Besides investigating a possible cardiac damage post RT, the prospective study will investigate if patients have an unknown cardiac disease before RT. In addition, it may be possible to identify a dose – response relationship between dose to the heart and structures.

With the results of these studies, we hope to improve the treatment. If results from this project indicate that statin use can prevent the development of cardiac toxicity, we plan to perform a national randomized study of treating patients at risk with statins.

Finally, we hope that study four can contribute in optimizing the heart function for patients at risk. Additionally, to develop normal tissue constraints for different substructures in the heart.

This is a national project strongly supported by the radiotherapy committees of DOLG and DEGC, this will facilitate implementation of the results in daily clinical practice in order to benefit future patients.

Time lines

First year (2020)

- Applying the Danish Data Protection Agency for approval of data storing.
- Establish database in OPEN
- Gather RT plan and planning CT scan in order to measure CACS for study one from the radiotherapy centers in Denmark.

Second year (2021)

- Prepare manuscript for study one
- Gather data for study two and three
- Prepare manuscripts for study two and three

Third year (2022)

- Prepare manuscripts for study 4
- Write thesis and submission of PhD-thesis.

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