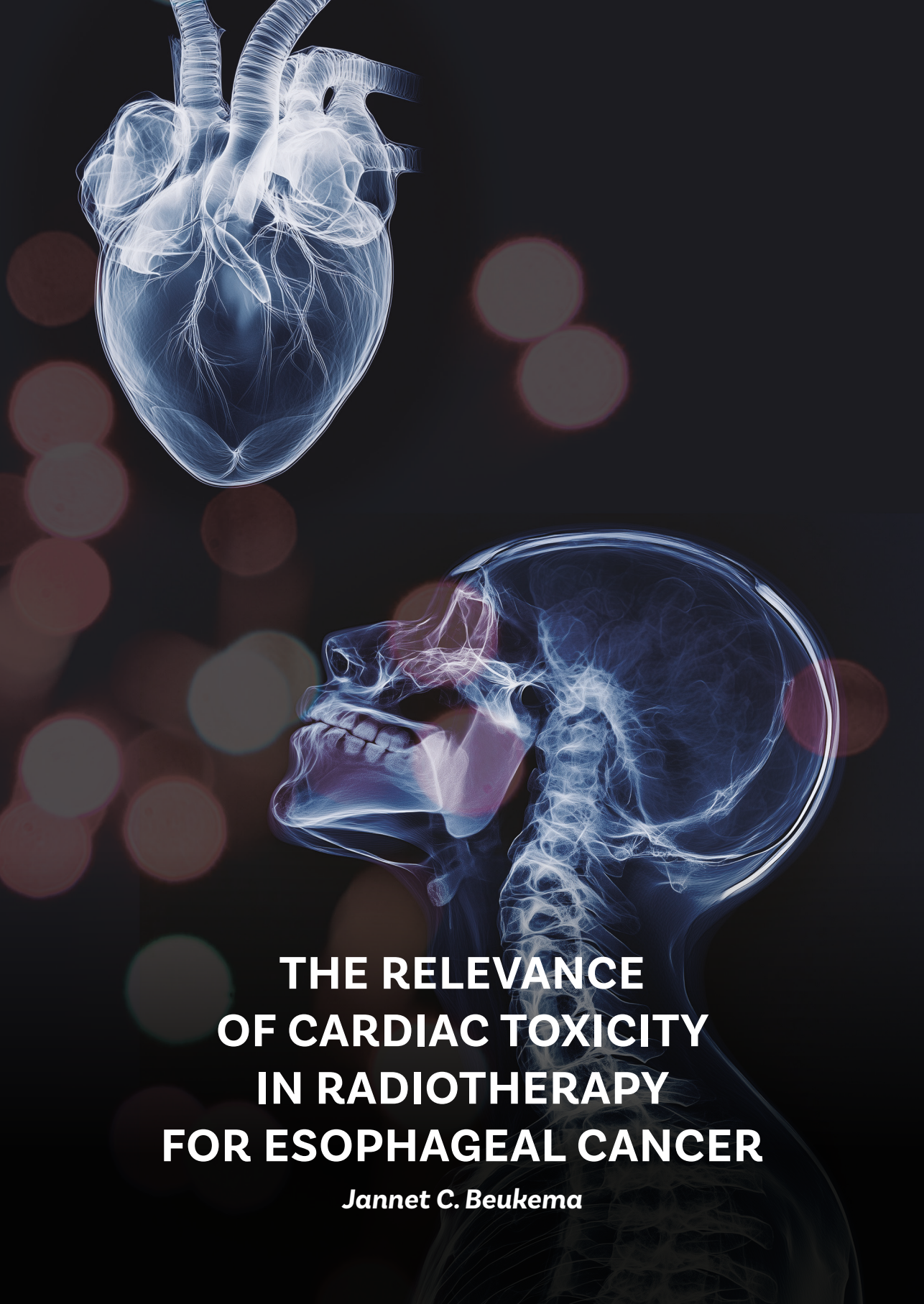

THE RELEVANCE OF CARDIAC TOXICITY IN RADIOTHERAPY FOR ESOPHAGEAL CANCER

Jannet C. Beukema

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Provided by thesis specialist Ridderprint, ridderprint.nl

Printing: Ridderprint

Layout and design:Yasmine Medjadji, persoonlijkproefschrift.nl

rijksuniversiteit groningen

The relevance of cardiac toxicity in radiotherapy for esophageal cancer.

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. ir. J.M.A. Scherpen
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 29 januari 2025 om 16.15 uur

door

Jannette Christine Beukema

geboren op 28 januari 1969

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CHAPTER 1

General introduction

Introduction

In the Netherlands, approximately 3000 new esophageal cancer patients are diagnosed each year and its incidence is still rising, which is especially true for adenocarcinomas located in the distal part of the esophagus. About 60% of patients present with potentially curable disease and the majority undergoes neoadjuvant chemoradiotherapy followed by surgery or definitive (chemo)radiotherapy[1]. Although cure rates improved over the last decade, treatment-induced toxicity is still a matter of concern[2].

For most esophageal cancer patients, radiotherapy target volumes are relatively large and located near critical organs like the heart and the lungs. Therefore, high toxicity rates related to these organs at risk can be expected. However, trade-offs between cardiac and pulmonary toxicities, and thus decisions on how to optimize dose distributions in radiotherapy treatment planning, require more detailed information on toxicities in relation to radiation dose distributions. At the time of the start of this thesis, literature from clinical trials mainly focused on pulmonary toxicity and its relationship with lung dose volume parameters. Whereas literature on radiation induced cardiac toxicity, specifically in esophageal cancer patients, was scarce (Figure 1).

For this reason, we decided to focus this thesis on radiation-induced cardiac toxicity in the treatment of esophageal cancer patients.

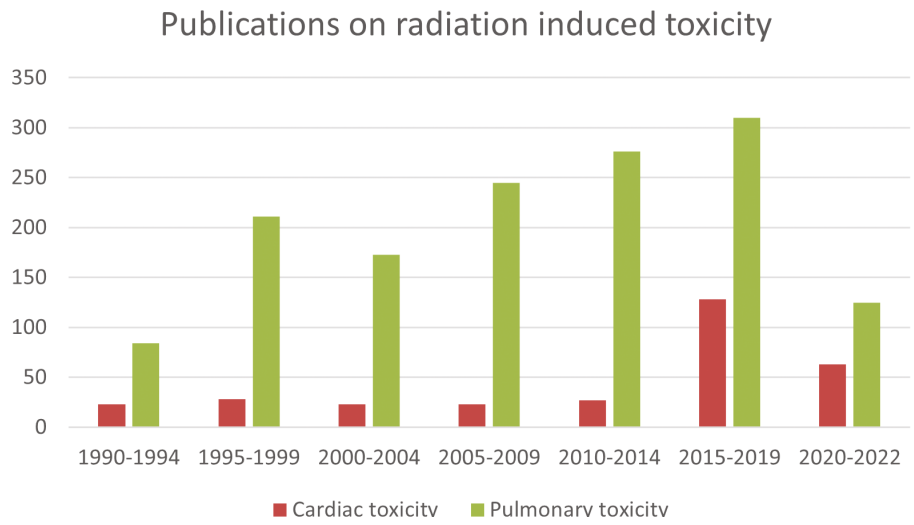
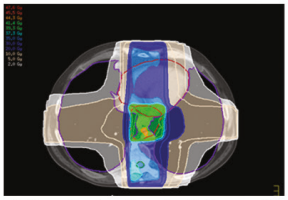


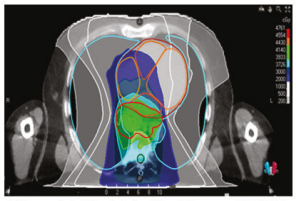
Table 1 timeline of PubMed results when comparing the number of clinical trials on radiation AND “cardiac toxicity” vs “pulmonary toxicity”.

Newer techniques in radiotherapy

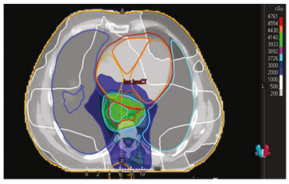
The last decades, radiation technologies have been significantly improved. In the 90's, three-dimensional conformal radiotherapy (3D-CRT) was commonly used. More recently, more advanced technologies like intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) became the new standard. These technologies can deliver highly conformal dose distributions with improved ratios between target coverage and sparing of critical OARs, like the heart and lungs (Figure 1). Moreover, these techniques provide additional flexibility in prioritizing which OARs should be avoided. This prioritizing of dose to critical organs remains a key issue as, especially in photon radiotherapy, as decreasing the dose to one organ, for example the heart, will come at the expense of the radiation dose to other organs, like the lungs. The new kid on the block, proton radiotherapy is an even more advanced technology, which allows a further reduction of the radiation dose to both heart and lungs. However, its availability is limited and therefore it is important to select the patients that benefit most[3].



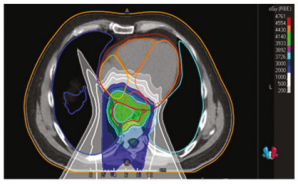
3-dimensional conformal radiotherapy, (3DCRT)
3 beams aiming primarily at lung sparing



Volumetric Modulated Arc Therapy, (VMAT)
Continuously rotating technique aiming primarily at lung sparing



Volumetric Modulated Arc Therapy, (VMAT)
Continuously rotating technique aiming primarily at heart sparing



Proton therapy, 3 beams, sparing heart and lungs

Figure 1, evolution of radiotherapy planning techniques in recent years, techniques do become more conformal

Red=target volume, Green=prescribed dose, Blue=intermediate dose, 40-80% prescribed dose, Grey=low dose, up to 20% prescribed dose.

Dose volume histograms

A dose volume histogram (DVH) in radiotherapy represents the 3 dimensional dose distribution of target volumes or critical organs in a 2D graph. This DVH graph is a cumulative graph, with the radiation dose (in Gray) on the x-axis and the volume (in percentages) on the Y axis. These DVH graphs can be used to compare different treatment plans or techniques. DVH parameters can be extracted from these graphs and are used in scientific literature and radiotherapy guidelines. Values like D98(Gy) are used to describe the plan quality (target coverage) and represents the minimum dose given to 98% of the target volume. V values are used to describe the dose on OARs. E.g., V20 of the heart represents the volume of the heart in percentage that receives 20 Gy or more.

Normal tissue complication probability

Normal Tissue Complication Probability (NTCP) models describe the relation between radiation dose distributions in one or more OARs and the risk of complications. These prediction models are developed by using cohorts of patients who were treated in the past. Next to Dose Volume Histogram (DVH) parameters, other clinical risk factors (like age, smoking, or a cardiac history) can be included in these models to correct for confounding or to improve model performance. These multivariable NTCP-models should preferably be based on large patient cohorts, and validated in independent patient cohorts to assess generalizability in other study populations. These externally validated multivariable prediction models are currently considered the highest level of evidence for the prediction of treatment related complications [4].

Radiation induced pulmonary toxicity.

As mentioned before, most literature in the 90's focused on pulmonary toxicity. Radiation-induced pulmonary toxicity may present with different clinical symptoms, varying from mild dyspnea and non-productive cough to respiratory failure requiring mechanical ventilation which could eventually be fatal. Currently, the most widely used NTCP-models for radiation-induced pulmonary toxicity include the mean lung dose as DVH parameter[5,6], next to clinical factors like age, co-morbidities and the location of the tumor [7].

Radiation induced cardiac toxicity.

Most clinical publications on radiation-induced cardiac toxicity were published after 2015. Historically, cardiac toxicity was considered a (very) late event and increased rates of cardiovascular diseases were observed in long term survivors of breast cancer and Hodgkin lymphoma[8,9]. Incidence rates of myocardial infarction (HR: 1.22(95%CI:1.06-1.42)), pericarditis (HR: 1.61(95%CI: 1.06-2.43)) as well as valve disorders (HR: 1.54(95%CI: 1.11-2.13)) were higher in left-sided breast cancer patients that were treated with radiotherapy as compared to right-sided breast cancer patients. For Hodgkin lymphoma survivors, an increased rate of heart failure (4.9 times) as well as myocardial infarctions (3.6 times) has been observed as compared to normal populations. The combination of radiotherapy and chemotherapy (anthracyclines) resulted in the highest risk of late cardiac toxicity in this population[10].

Literature on cardiac toxicity and radiation dose parameters is limited. The only externally validated NTCP model originates from breast cancer patients. In 2013, Darby et al published this data. The rate of major coronary events increased linearly with the mean radiation dose to the heart by 7.4 % per Gray[11]. These data were validated in another breast cancer population by Boogaard et al [12].

Overall survival as a surrogate for toxicity endpoints?

As causes of death are often unknown, overall survival (OS) and/or death have been used as alternative endpoints in relation to normal tissue dose. This probably originated from trials were better tumor specific survival or local control was observed, while OS rates did not improve or even worsened[13,14]. Analyzing OS as an endpoint instead of toxicity is attractive because it can combine toxicities of, for example lung and heart, while considering tumor prognostic factors, like tumor stage. Moreover, it is a truly relevant endpoint. However, OS does not provide information on causal relationships. In addition, OS is less sensitive and provides less guidance on which specific regions of the thoracic region you should try to spare in radiotherapy treatment planning.

In the treatment of intrathoracic tumors, several prediction models for OS have been developed [5,15,16]. These models include tumor-specific prognostic factors like tumor size or lymph node status next to DVH-parameters of the heart. Only Speirs et included a lung DVH parameter next to a heart DVH parameter in their final multivariable prediction model. The model of Defraene et al. included tumor

size next to smoking (a protective factor for OS) and the mean dose to the heart in their prediction model. This latter model has been validated in another lung cancer cohort as well as in an esophageal cancer cohort[17]. These externally validated prediction models are currently used for optimizing radiotherapy dose distributions and selecting patients for newer techniques like proton therapy in the Netherlands.

Prediction models can be more reliable and reproducible, when you know more about the pathogenesis. This knowledge may help in the preselection of the DVH parameters of (subregions of) critical OARs while developing prediction models [15]. Besides, this may guide choosing the most relevant DVH-parameters in case of multicollinearity, as different anatomically closely related DVH parameters, like the heart, its subregions, and the lungs often have a strong correlation with each other.

Summarizing, although prediction models suggest that irradiation of the heart leads to worse OS, a causal relationship between radiation dose to the heart and toxicity cannot be concluded from these papers. Based on the limited evidence available on radiation induced cardiac toxicity in esophageal cancer, we started this thesis to improve knowledge on the relevance and mechanisms of radiation induced cardiac toxicity as a first step towards NTCP modelling and to guide trade-offs between radiation dose to the heart and the lungs during the treatment planning process.

Outline of this thesis

Chapter 1 is the introduction of this thesis, in which provided background information on the literature at start of the thesis. Furthermore, we explain some of the terminology used and the end we highlight the unmet needs on cardiac toxicity in the treatment of esophageal cancer.

In chapter 2 we performed a review of the available literature on radiation induced cardiac toxicity in the treatment of esophageal cancer.

Chapter 3 consists of an editorial on radiation induced cardiac toxicity to increase awareness under other medical disciplines.

Chapter 4 describes retrospective cohort study based on a population of 216 esophageal cancer patients who underwent curative radio(chemo)therapy to a relatively high radiation dose. We performed multivariable analyses combining clinical data with dose volume parameters to develop multivariable prediction models for heart as well as lung toxicity.

Chapter 5 and 6 describe the results of a cross-sectional prospective study among esophageal cancer survivors treated with neoadjuvant chemoradiotherapy plus surgery versus patients treated with surgery only. We performed several diagnostic tests to objectify clinical as well as subclinical damage that might be caused by the chemoradiation in these so-called survivors. In chapter 5 we focused more specifically on changes seen on MRI, quantified these findings and related them to the spatial dose distribution as given during the neoadjuvant chemoradiotherapy. In

chapter 6 we combined the results of the different imaging techniques, ECG, biomarkers and functional assessments versus clinical events and dose distributions.

Chapter 7 reports on a longitudinal prospective study monitoring cardiac blood biomarkers during and after radiotherapy for esophageal cancer. We hypothesized that these parameters would be useful in future clinical practice and/or trials to predict radiation induced cardiac toxicity. We analyzed relationships with cardiac and pulmonary radiation dose volume parameters and clinical events of both organs at risk.

In chapter 8 we conclude by summarizing the results and discuss future perspectives

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CHAPTER 2

Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer?

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Published in Radiotherapy and Oncology Volume 114(1), 2015, 85-90

Abstract

Purpose: In recent years several papers have been published on radiation-induced cardiac toxicity, especially in breast cancer patients. However, in esophageal cancer patients the radiation dose to the heart is usually markedly higher. To determine whether radiation-induced cardiac toxicity is also a relevant issue for this group, we conducted a review of the current literature.

Methods: A literature search was performed in MEDLINE for papers concerning cardiac toxicity in esophageal cancer patients treated with radiotherapy with or without chemotherapy.

Results: The overall crude incidence of symptomatic cardiac toxicity was as high as 10.8 %. Toxicities corresponded with several dose-volume parameters of the heart. The most frequently reported complications were pericardial effusion, ischemic heart disease and heart failure.

Conclusion: Cardiac toxicity is a relevant issue in the treatment of esophageal cancer. However, valid Normal Tissue Complication Probability models for esophageal cancer are not available at present.

Introduction

Increasing numbers of patients with esophageal cancer are currently being treated with curatively intended combined modality strategies such as chemoradiation, either in the neoadjuvant setting followed by surgery or as definitive treatment. Due to improved outcome, resulting from the addition of chemotherapy to radiotherapy, more patients are surviving treatment of esophageal cancer. Therefore, more patients are at risk for treatment-related toxicity, which is becoming a major concern.

Little data is available on cardiac morbidity and mortality following radiation treatment of esophageal cancer. This may be explained by the fact that cardiac toxicity has traditionally been regarded as a late (or very late) side effect. Given the relatively low incidence of esophageal cancer and previously low cure rates after treatment, data on radiation-induced cardiac toxicity has remained scarce.

Radiation-induced cardiac toxicity in other cancers, such as breast cancer and Hodgkin's lymphoma, has been studied more extensively due to larger numbers of patients and better survival. In these patient groups, higher rates of cardiac death have been found during long-term follow up [1]. However, in esophageal cancer, cardiac doses are generally markedly higher due to the location of the target area close to the heart and/or to the higher total dose.

Currently, no clear guidelines exist on how to distribute the radiation dose between the different organs at risk in radiotherapy treatment planning of esophageal cancer, in particular the relation between the dose to the lungs and to the heart. This question becomes even more relevant with the clinical introduction of new radiation delivery techniques like intensity modulated radiotherapy (IMRT) and proton therapy.

We therefore reviewed the current evidence on types and incidence of radiation induced cardiac toxicity and the possibly association with dose-volume parameters after multimodality treatment for esophageal cancer.

Methods

Medline was searched for “heart”[MESH] AND “radiation therapy [MESH]” AND “ esophageal cancer [MESH]”, to retrieve papers that published on radiation induced cardiac toxicity and/or radiation dose parameters. Papers publishing data on cardiac toxicity and radiation dose parameters between 1970 and the first of July 2013 were included in this review. References of the articles were screened for other papers and included in this review when considered relevant.

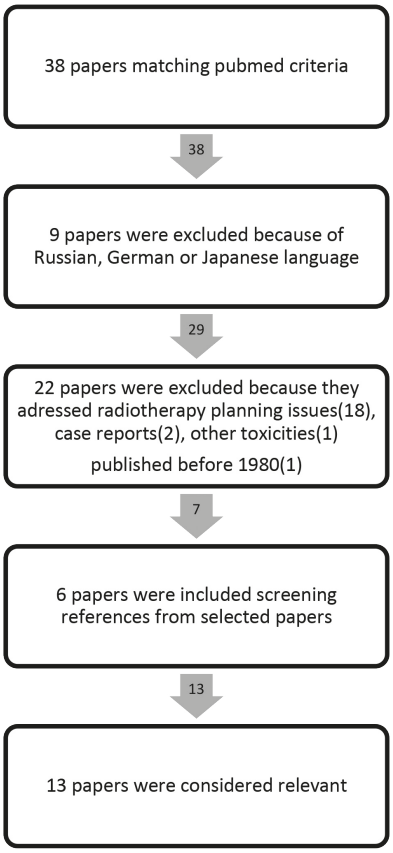

Figure 1

Results

The literature search resulted in a total of 38 papers, of which the abstracts were screened first for their relevance to our review. After initial screening, seven papers were considered relevant. After screening the references from these papers, another 6 papers were retrieved and included. An overview of the selection process is shown in figure 1. All selected papers are listed and briefly summarized in Table 1.

Table 1. Selected papers on cardiotoxicity in chemoradiotherapy for esophageal cancer.[a]

Author	*N*	Total dose RT (dose/fr) (Gy)	FU (months)	Time to event (months)	Toxicities (*N*)	Association with dose distribution parameters
Morota et al. (2009)	69	60 (2)	26.1	10	6% > grade II: pericardial effusion (*n* = 1), valve replacement → heart failure (*n* = 1), cardiac ischemia (*n* = 1), and pleural effusion (*n* = 11)	Not available
Ishikura et al. (2003)	139	60 (2)	53	14	11% > grade II: myocardial infarction → death (*n* = 2) pericardial effusion (*n* = 8) → grade V heart failure (*n* = 2), pleural effusion (*n* = 8)	Not available
Kumekawa et al. (2006)	81	60 (2)	57	Mean within 24	11% > grade II: pericardial effusion (*n* = 3) → grade V heart failure (*n* = 2), cardiac ischemia (*n* = 3) → grade V (*n* = 1), pleural effusion (*n* = 3) → grade V (in combination with pneumonitis) (*n* = 1)	Not available
Martel et al. (1998)	57	37.5–49 (1.5–3.5)	19	8	5% > grade II: pericardial effusion (*n* = 3) → grade V (*n* = 1)	Mean and max heart dose
Wei et al. (2008)	101	45–50.4 (1.8–2)	8.4	5.3	28% any pericardial effusion	Pericardial dose > 26.1 Gy; V5–45 pericard
Shirai et al. (2011)	43	52–70 (1.8–2)	26.9	4	35% any pleural effusion, hypertension (*n* = 11), arrhythmia (*n* = 5), ischemia (*n* = 2), cardiomyopathy (2), mitral regurgitation (1)	Older age and V50 heart
Mukherjee et al. (2003)	15	45–50 (1.8–2)	Not relevant	1	80% any drop in ejection fraction 1 month after CRT	No correlation with heart dose

Table 1. Selected papers on cardiotoxicity in chemoradiotherapy for esophageal cancer.[a] *(Continued)*

Author	*N*	Total dose RT (dose/fr) (Gy)	FU (months)	Time to event (months)	Toxicities (*N*)	Association with dose distribution parameters
Tripp et al (2005)	20	45–54 (1.8–2)	Not relevant	1.5	55% any drop in ejection fraction but in 30% a rise in ejection fraction	No correlation with heart dose
Gayed et al. (2006)	51	50.4–60 (1.8–2)	Not relevant	3	54% perfusion abnormalities and 42% inferior wall ischemia	Irradiated patients; higher dose areas >45 Gy
Gayedet al. (2009)	16	30–50.4 (1.8–2)	14.6	12	43% any cardiac complications: ischemia (*n* = 1), atrial fibrillation (*n* = 2), Pericardial effusion (*n* = 2), heart failure (*n* = 2) → complete heart block grade V (*n* = 1)	Not available
Konski et al. (2012)	102	45–57.6 (1.8)	10.7	4.2	12% > grade 2: pericardial effusion (*n* = 10), myocardial infarction (*n* = 1), sick sinus syndrome (*n* = 1)	Correlation V20, V30 and V40 heart with symptomatic heart toxicity
Jingu et al. (2006)	64	30–70 (2)	Not relevant	9.3	20% increased uptake on FDG PET	Higher SUV values within the radiation fields
Hatakenaka et al. (2012)	31	41–60 (1.8–2)	Not relevant	3 days	Lower left ventricular end diastolic volume and stroke index, an increased heart rate and left ventricular wall motion disorders after treatment	Significant difference in high vs. low left ventricular dose groups

Only the paper published by Jingu et al. had a prospective design, the others were retrospective. All papers combined radiotherapy with chemotherapy, the most frequently used schedule was 5-FU and cisplatinum. Almost all patients were treated with a 3D CRT technique, IMRT was used in a few patients.

Three papers reported specifically on retrospective follow-up data and late cardiopulmonary RTOG rated toxicity in esophageal cancer patients.[2–4] All patients in these studies were treated with concurrent chemoradiation to a total dose of 60 Gy in combination with cisplatin and 5-FU. Target definition and radiotherapy planning were performed with 2-dimensional techniques using simulation films. Therefore, individual cardiac dose distributions were not available and no attempts were made to correlate cardiac dose to toxicity. Patient numbers and details on

grade 3 or higher reported cardiac toxicity in these papers are listed in and marked as the first three papers in table 1.

The most frequently observed side effects were cardiac ischemia, pleural and pericardial effusions and heart failure. These “late toxic events” presented occurred relatively soon after treatment, with a median follow up of 26.1 to 57 months. Grade 3 or higher cardiac toxicity, which is considered clinically relevant, was seen in 5.8%-11.1% of the patients. Given the low cure rates of esophageal cancer in these studies, with 3 years survival rates varying between 22% and 45%, the actuarial rates were not reported, but can be expected to be much higher.

Morota et al. also reported on patient and treatment related risk factors for cardiac events.[3] Older age (>75 years) was the only factor significantly associated with late cardiopulmonary toxicity. They reported a crude incidence of 29% in the older patient group vs. 3% for the younger patients.

In three other studies, the authors aimed to find clinical and dosimetric factors influencing the risk for pericardial(PCE) or pleural effusion(PE).[5–7] Treatment details are summarized as the next three papers in table 1.

Martel et al. was the first to report on pericardial effusion among patients treated with 3D-CRT based on planning-CT and available diagnostic data.[5] Between 1985 and 1991, patients were treated according to 3 different protocols. The only prognostic factor significantly associated with PCE was the dose per fraction (3.5 Gy). After correction, according to the Linear Quadratic model, the mean and maximum heart doses were significant prognostic factors. However, given the relatively small sample size, fitting the data into the Lyman model showed large confidence intervals.

Wei et al. performed a retrospective analysis to identify clinical and dosimetric prognostic factors for PCE in 101 patients with inoperable esophageal cancer.[6] The pericardium was contoured as a shell, by extending the actual heart contour with 0.5 cm. PCE was scored using CT scans routinely made during follow-up visits. The mean time to onset of PCE was 5.3 months, leveling off at 16.7 months after treatment. The crude incidence of PCE was 27.7% and the actuarial incidence at 18 months was 48%. No patient or treatment-related factors could be found that were associated with PCE. However, significant associations were found with several dosimetric factors. Pericardial DVH values correlated better with the incidence of PCE as compared to the cardiac DVH parameters. If the mean pericardium dose was

reduced below 26.1 Gy, the risk for PCE decreased from 73% to 13% at 18 months after treatment. The strongest prognostic factor was a V30 pericardium of >46%.

Shirai et al. retrospectively analyzed 43 esophageal cancer patients.[7] In total, 35% of the patients developed non-malignant PE, including 4 patients (13%) with grade ≥2, which required medical intervention. In the univariate analysis, most cardiac and one lung parameter (V50 lung) were significantly associated with the development of PE. In de multivariate analysis, older age and the cardiac V50 were the only significant prognostic factors for PE.

The left ventricular ejection fraction was studied in two papers [8,9], with relatively low patient numbers. Treatment details are listed in table 1.

A small decline(4-5%) in ejection fraction was found after treatment in both papers. However, no significant association was found between dose distribution and a reduction in ejection fraction.

3D functional cardiac imaging was used to evaluate cardiac toxicity in five papers. [10–14] Treatment details and patient numbers are again listed and marked as the last five papers in table 1. Gayed et al. compared 26 irradiated to 25 non-irradiated esophageal cancer patients from a prospective database[11]. Cardiac risk factors, including demographics were comparable in the two groups. In this cohort, gated myocardial perfusion scans were routinely performed preoperatively and blinded for former treatment. Perfusion abnormalities and wall ischemia were increasingly seen in the irradiated group, but functional parameters (left ventricular ejection fraction, end diastolic and systolic) did not differ significantly. Most perfusion defects were found in the higher dose areas (>45 Gy), 70% vs. 25%. However, the mean heart dose was not statistically higher in the patients with abnormal perfusion scans.

In another study from the same investigators, the clinical implications of these perfusion abnormalities in 24 lung and 16 esophageal cancer patients were investigated [10]. Although new perfusion defects were seen in about 1/3 of the patients, no significant relationship was found with symptomatic cardiac complications after a rather short median follow up of 10.9 months.

Konski et al. evaluated 74 esophageal cancer patients using FDG-PET.[12] The FDG uptake declined, especially in the lateral myocardial wall, shortly after treatment. A significant association was found between the V20, V30 and V40 of the heart and symptomatic cardiac toxicity. The V40 was 69.2% vs. 53.8% among patients with

or without symptomatic cardiac toxicity, respectively. No associations were found between cardiac toxicity and medical history, surgery or decreased FDG uptake of the myocardium.

In contrast, Jingu et al. found increased FDG uptake within the irradiated field after a median time of 9.3 months after treatment for esophageal cancer. In a prospective study, 8 patients underwent additional ultrasound, MRI and myocardial SPECT to investigate the state of metabolism and vascular flow in the myocardium. The SPECT studies suggested microvascular damage and impairment in perfusion and fatty acid metabolism; under these ischemic conditions, glucose metabolism increases. MRI scans with gadolinium showed delayed enhancement in only 2 patients and was thought to be relatively insensitive to myocardial damage.

Hatahenaka et al. reported on the results obtained in 31 patients treated with chemoradiation.[13] Patients were subjected to cardiac MRIs before, during and shortly after therapy. Patients were divided into a low left ventricle dose group (mean LV dose of 0.33 Gy, predominantly upper and middle esophageal tumors), and a high dose group with a mean dose of 18.1 Gy. The LV ejection fraction (LVEF), LV end diastolic volume index and left ventricular stroke index were significantly lower after treatment, which was also the case for wall motion disorders in segments 8, 9 and 10. The heart rate was significantly higher after treatment. In the low dose group, only LVEF was decreased, suggesting a role for cisplatinum.

In conclusion, these five imaging studies showed early wall motion disorders and reduced or increased uptake within the irradiated area on different imaging modalities, which indicates a local effect in the myocardium. Changes in the metabolism of the irradiated areas may explain these effects.

Discussion

This review was undertaken to evaluate the current evidence on the types and incidence of radiation induced cardiac toxicity after multimodality treatment for esophageal cancer, in order to improve radiotherapy treatment decision making.

The incidence of clinically relevant cardiac complications was reported in 6 out of 10 reviewed papers. The overall crude incidence was 10.8 % (range: 5%-44%). Most events occurred within 2 years after treatment. Given the low overall survival rate of 3 years, the actuarial incidence rate for cardiac complications is expected to be much higher.

The high complication rates in these retrospective studies were not confirmed by prospective (randomized) esophageal cancer trials. This could be explained by the relatively simple radiation delivery techniques used in most of the retrospective studies. Moreover, the total dose was relatively high, 60 Gy in 3 out of the 6 papers, versus 50.4 Gy which is currently the standard in many European countries and the USA. On the other hand, it is very likely that cardiac morbidity was poorly reported in the older trials because the relationship with the given treatment was not well acknowledged at that time.

Studies reporting on randomized preoperative CRT do not provide much additional information regarding toxicity. Most of these trials had relatively low patient numbers . In meta-analyses, only postoperative morbidity, mortality and overall survival have been reported.[15–18]. Furthermore, the two largest trials , have a relative short follow up and one of them has not even been fully published. [18,19]

Bosch et al. on the other hand focused more specifically on chemoradiation-induced morbidity. They retrospectively compared 96 patients treated with preoperative CRT (41.4 Gy/carbo/taxol) with matched controls who were treated with surgery only.[20] In this study, rates of pneumonia, cardiac arrhythmia and pleural effusion were observed more frequently in the preoperatively treated group. Despite these events, no differences in hospital stay or short-term mortality were found, which is in line with the meta-analysis data.

On the other hand, in a meta-analysis investigating the role of postoperative radiotherapy for lung cancer, a relative increase in mortality of 21% was found in the irradiated group.[21] Although the authors were unable to analyze causes of death in this meta-analysis, non-cancer-related causes of death were suggested since the local recurrence rates were reduced by postoperative radiotherapy. The latter might be a relevant finding for the treatment of esophageal cancer as target volumes for lung cancer are comparable with those for esophageal cancer.

As mentioned previously, it is not always clear if cardiac events are actually related to radiation treatment. A strong argument for radiation-induced cardiac toxicity in this patient group is the association with dose-volume parameters. Based on the current literature, however, it remains difficult to determine the most relevant dose parameter. An important reason is probably that the toxicities – and thus the endpoints – used in these studies were diverse. It is very unlikely that focal wall motion disorders as seen in the imaging studies correspond to the same DVH parameters as the risk of developing pericarditis.

Not only treatment related factors were significant related to cardiac toxicity, older age and female sex gave a significantly higher risk in two[3,7] and one[12] of the reviewed papers. However, patient numbers are low and these non-treatment related risk factors should be confirmed in larger patient groups. The challenge for the future will be to decide which clinical endpoints are relevant and should be incorporated into an NTCP model for esophageal cancer patients.

Pericardial effusion was the most frequently observed complication, with an actuarial rate of 48%. [6] The biological mechanism behind PE is considered inflammatory. [22] In most cases, pericardial effusion is self-limiting and asymptomatic, but may progress into heart failure and death.[2–4] The observed incidence depends heavily on the use of routine imaging techniques, such as CT scans. Although it is the easiest clinical endpoint to incorporate into a model (high rate and objective), pericarditis is not expected to have a significant impact on the quality of life of the surviving patients.

Secondary ischemic events occur frequently in esophageal cancer patients treated with radiotherapy or CRT, not only as a very late side effect, but also during the first 2 years after completion of treatment. However, radiotherapy may not be the only risk factor for this cardiac event. Esophageal cancer patients generally have a number of risk factors for ischemic heart disease, including older age, histories of tobacco use and/or obesity.[23] All patients were irradiated combined with chemotherapy, most often with cisplatinum and 5-FU, which are both associated with increased risks of thrombus formation. [24–26] Based on the available data, it was impossible to correct for these potential confounding factors.

Heart failure, the third most frequently observed complication after radiotherapy or chemoradiation, may be the result of other cardiac events, including myocardial infarction, pericarditis and valvular disorders. It may very well be possible that these different cardiac events with different underlying mechanisms relate to different dose-volume response relationships and as such may result in secondary cardiac events. These kind of relationships should be adjusted for in multivariable prediction models.

Clinical research on functional imaging and other cardiac function parameters is necessary to better understand the mechanisms of radiation induced-cardiac toxicity and to identify the most critical parts of the heart for each of the aforementioned clinical endpoints.

Most of the presented imaging studies showed wall motion disorders and changes in metabolism of the myocardium in the higher radiation dose areas. These changes are in line with results from autopsy and animal studies showing damage to microvasculature, focal ischemia and fibrosis.[22] Although these changes did not result in decreased LVEF, changes in end diastolic volume, stroke indices and heart rate were observed. The LVEF may underestimate the actual cardiac damage because of the compensatory reserve of the myocardium that enables adequate ventricular outcome even when part of the myocardium dysfunctions. Reduced end diastolic volumes are known to precede a decline of the ejection fraction.[27] As imaging studies were performed shortly after treatment, these later changes were not observed. Animal studies in mice showed progressive malfunctioning of mitochondria and progressive fibrosis in the myocardium at 40 weeks after treatment.[28,29] These changes did not result in changes in cardiac function. However, in the high dose group, a significant proportion of the mice died suddenly during follow up. These sudden deaths may imply that compensatory mechanisms may not maintain cardiac function for a longer period of time.[30] Additional clinical imaging studies at later time points after treatment as well as other cardiac functional assessments are required to get more insight into the pathophysiological mechanisms of cardiac toxicity and thus should be included in future research.

Evidence regarding radiation induced cardiac toxicity is available from studies in other tumor sites with high rates of cardiac death and morbidity in irradiated patients with long term follow up.[1,31,32] Most of these articles reported frequent late or very late side effects. The studies presented in this review suggest earlier toxicity with events in the first two years after treatment. Recently, Darby et al.[1] reported on the relationship between radiation dose and major cardiac events among breast cancer patients and compared them with a population-based matched control group. They found 44% of the events in the first 10 years, with no significant trend in time. In that study, the estimated mean dose to the heart was only 4.9 Gy, which is much lower than that observed among patients treated for esophageal cancer. They observed an increase in the relative risk for ischemic heart disease of 7.4% per 1 Gy mean heart dose. There was no suggestion the increase in risk was less pronounced in the higher dose group (mean dose above 10 Gy). Interestingly, they found the mean heart dose to be more relevant for ischemic events than the dose to the left anterior descending coronary artery, but as dose reconstruction in such a small organ is less reliable as shown by Lorenzen et al, this remains to be confirmed by others.[33]

Esophageal cancer patients are different from breast cancer and lymphoma patients, as their prognosis is poorer and the radiation doses to the heart are much higher. In current routine clinical practice, radiation oncologists consider the spinal cord and lungs as the most important critical organs. Although the results of our review confirm that the heart should also be considered to be a critical organ, the optimal distribution of the dose between the various OARs remains to be determined. In general, a reduction of the dose to the heart, even with advanced radiation delivery techniques such as IMRT or VMAT, will result in a higher lung dose with an increased risk of radiation pneumonitis and fibrosis. Proton therapy may overcome this problem, but is not widely available and relatively expensive. Therefore, selection of the patients who will benefit most from proton therapy will be essential.[34] However, if the precise association between radiation-induced side effects and the dose-volume parameters is not clear, the translation of observed differences in dose distributions between protons and photons into clinical benefits remains difficult.

Accurate multivariable prediction models on radiation-induced toxicity are necessary to estimate the potential added benefits of various techniques.

Although we showed that cardiac toxicity is a relevant problem in the treatment of esophageal cancer, we will obviously need more esophageal cancer patients with strict follow up data and dose distributions on critical organs as current data are insufficient to make prediction models for radiation-induced cardiac toxicity in these patients. As causes of death are often hard to identify, overall survival in addition to disease specific survival is very important to avoid underestimation of cardiac toxicity. Imaging studies and cardiac function parameters during follow up will help us identifying the most relevant clinical endpoints and critical parts of the heart.

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CHAPTER 3

Cardiac toxicity in the radiation treatment of esophageal cancer: an emerging concern.

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Published in Future Cardiology 2015 Volume 11(4), 367-369

Editorial

The number of patients with oesophageal cancer treated with curatively intended combined modality strategies such as chemoradiation, either in the neo-adjuvant setting followed by surgery or as definitive treatment, is increasing. Due to the rising incidence of oesophageal cancer in combination with improved outcome, in particular due to the addition of neo-adjuvant chemoradiation prior to surgery, the prevalence of oesophageal cancer survivors will increase significantly [1,2]. Therefore, the absolute number of patients at risk for developing late treatment-related toxicity is rising as well.

Radiation-induced cardiac toxicity has been studied particularly in patients treated for breast cancer or Hodgkin's disease, as this toxicity has been considered most relevant because of their more favourable long term survival outcome [3,4]. In these patient groups, higher rates of cardiac events and increased cardiac mortality have been observed during long-term follow up. Recently, a significant relationship between cardiac radiation dose and the risk of cardiac events was found for breast cancer patients treated with radiotherapy [5]. These data can be used to estimate the risk for cardiac complications as a function of radiation dose and baseline risk.

In the treatment of oesophageal cancer the radiation dose to the heart is generally much higher than in the aforementioned patient groups. Assuming that the "breast cancer model" for cardiac events can also be used for oesophageal cancer patients, the relative risk on cardiac events will increase more than two-fold compared to the baseline risk. As oesophageal cancer patients often have several cardiovascular risk factors, the absolute access risk for cardiac events is expected to be much higher than in breast cancer.

In a recent literature review on cardiac toxicity in oesophageal cancer patients we found an overall risk of severe cardiac events of more than 10 % [6]. The most frequently observed clinical side effects were cardiac ischemia, pleural and pericardial effusions and heart failure. These grade III or higher late toxicities occurred relatively soon after treatment, with a median follow up of 26 to 57 months, and are thus considered clinically relevant. Given the low cure rates of esophageal cancer in these studies, with 3 years survival rates varying between 22% and 45%, the actuarial rates were not reported, but will be much higher. Moreover, given that survival rates after neo-adjuvant chemoradiation and surgery are close to 50% after 5 years, a further increase of severe cardiac toxicity may be expected.

In imaging studies during follow up, myocardial wall motion disorders and changes in the metabolism of the myocardium were observed. These changes are in line with animal and autopsy studies showing damage to microvasculature, focal ischemia and fibrosis of the myocardium [7].

The problem with cardiac events after radiotherapy is that it is not possible to determine in individual patients whether such an event is actually related to radiation treatment itself. However, there are strong arguments to conclude that at least part of cardiac events after radiotherapy are radiation-induced, such as the significant association between cardiac radiation dose and the incidence of cardiac events [8,9]. Based on the current literature, however, it remains difficult to define a clear cut threshold for the radiation dose that can be given without any risk. In this regard, it is important to mention that Darby et al. did not find a threshold dose and concluded that every Gray on the heart matters. Furthermore, the heart is a complex organ containing numerous different sub volumes leading to a variety of different biological changes when irradiated. E.g., coronary artery events are most probably related to high radiation dose levels on small sub volumes, while the risk of heart failure may be more related to a lower dose on large volumes of the heart. Therefore, it is unlikely that one threshold dose can be defined that covers all late toxicities related to different parts of the heart.

Given that there are many other risk factors for cardiac events, multivariable prediction models are needed that take into account not only dose volume metrics but also patient and other treatment-related factors.

Current modern radiation treatment techniques can be used to modify the radiation dose to the heart. However, attempts to reduce the dose to the heart will generally increase the low to intermediate dose to the lungs[10], resulting in an increased risk of radiation pneumonitis and pulmonary fibrosis. Reducing the total dose or even omitting the radiotherapy treatment will certainly reduce toxicity rates but this will certainly jeopardize local control rated and tumor specific survival rates, as recent studies showed worse results with lower radiation dose [11].

In fact, proton therapy is the only radiation delivery technique that can reduce the dose to the heart without increasing the lung dose [12]. At present, however, the capacity for proton therapy is limited and only few proton therapy facilities are actually treating patients. The benefit in terms of dose reduction that can be obtained with protons varies widely among individual patients, meaning that proton therapy will not result in a clinical benefit in terms of a clinically relevant reduction

of radiation-induced cardiac complications for all patients. Proper selection of patients who benefit most is of the utmost importance. In the Netherlands, the so-called model-based approach will be used to select patients that will benefit most from proton therapy in terms of late toxicity [13]. For this purpose, multivariable prediction models are urgently needed.

At present, with an increasing number of long term survivors, awareness of the risk of radiation-induced cardiac morbidity and mortality, by radiation oncologists and cardiologist is of major importance; radiation oncologists as they make the tradeoffs for treatment decisions regarding the balance between toxicity risks and dose distributions on critical organs and should consider to refer patients for preventive programs and cardiologists who must realize that cure rates for esophageal cancer are rising and that these patients have increased risks for cardiac morbidity.

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CHAPTER 4

Can we safely reduce the radiation dose to the heart while compromising the dose to the lungs in oesophageal cancer patients?

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Published in Radiotherapy and Oncology 2020, Volume 149(222-227)

Abstract

Purpose: The aim of this study was to evaluate which clinical and treatment-related factors are associated with heart and lung toxicity in oesophageal cancer patients treated with chemoradiation (CRT). The secondary objective was to analyse whether these toxicities are associated with overall survival (OS)

Materials and Methods: The study population consisted of a retrospective cohort of 216 oesophageal cancer patients treated with curative CRT. Clinical and treatment related factors were analysed for OS and new pulmonary and cardiac events by multivariable regression analyses. The effect of these toxicities on OS was assessed by Kaplan Meyer analyses.

Results: Multivariable analysis revealed that pulmonary toxicity was best predicted by the mean lung dose. Cardiac complications were diverse; the most frequently occurring complication was pericardial effusion. Several cardiac dose parameters correlated with this endpoint. Patients developing radiation pneumonitis had significantly worse OS than patients without radiation pneumonitis, while no difference was observed in OS between patients with and without pericardial effusion. OS was best predicted by the V45 of the lung and tumour stage. None of the cardiac dose parameters predicted OS in multivariable analyses.

Conclusion: Cardiac dose volume parameters predicted the risk of pericardial effusion and pulmonary dose volume parameters predicted the risk of radiation pneumonitis. However, in this patient cohort, pulmonary DVH parameters (V45) were more important for OS than cardiac DVH parameters. These results suggest that reducing the cardiac dose at the expense of the dose to the lungs might not always be a good strategy in oesophageal cancer patients.

Introduction

Over the last decade, increasing numbers of oesophageal cancer patients have been treated with radiotherapy, either in the neo-adjuvant setting followed by surgery or as definitive treatment. Due to neo-adjuvant CRT, cure rates have improved [1,2]. As a consequence, the number of oesophageal cancer survivors at risk of developing late toxicity is has risen correspondingly.

Traditionally, radiotherapy planning for these patients has aimed at adequate target coverage while focussing on dose limitation for the spinal cord and lungs in order to prevent radiation-induced toxicities. In recent years, there has been an increasing awareness of radiation-induced cardiac toxicity. In breast cancer patients, prediction models for cardiac toxicity [3,4] indicate a linear increase of the risk of major coronary events by 7.4% per Gray.

However, in the radiotherapy treatment of oesophageal cancer the radiation dose to the heart is generally much higher and oesophageal cancer patients generally have less favourable cardiovascular risk profiles. Therefore, prediction models describing the relationship between dose parameters and cardiac events developed in breast cancer patients cannot be automatically extrapolated to oesophageal cancer patients.

Limited data currently exists for radiation-induced cardiac toxicity in oesophageal cancer patients. Grade III cardiac toxicities are observed in about 10 percent of these cases and occur relatively early after treatment. Numerous dose volume parameters of the heart are significantly associated with a variety of cardiac toxicity endpoints. However, multivariable prediction models for cardiac toxicity are not available and it remains unclear which threshold dose levels should be used in routine clinical practice [5–9]. Nevertheless, in some studies, including of patients with lung and oesophageal cancer, significant associations were found between cardiac dose and OS, suggesting that cardiac toxicity is a relevant and possibly underestimated problem in the treatment of these patients [10–16].

Even with modern photon techniques, such as IMRT and VMAT, attempts to reduce cardiac dose is generally accompanied by higher dose levels to the lungs, thus increasing the risk of pulmonary toxicity. The optimal balance between cardiac and pulmonary toxicity and its influence on overall survival remains to be determined.

The main objective of this study was therefore to evaluate which clinical and treatment-related factors are associated with cardiac and/or lung toxicity in oesophageal cancer patients after definitive CRT. The secondary objective was to determine whether these toxicities are associated with OS.

Methods and materials

The study population of this retrospective cohort study consisted of 216 oesophageal cancer patients who had been referred to the department of radiation oncology in Osaka for definitive CRT from January 2007 to December 2013. All patients had histologically confirmed carcinoma of the oesophagus and were staged using CT scans of the neck, chest and abdomen and endoscopic evaluation. When local treatment was considered, endoscopic ultrasound was performed. Based on these findings, patients were restaged according to the 7th edition of the AJCC cancer staging manual [17].

Target volume delineation was performed on a 3D planning CT scan. The clinical target volume (CTV) consisted of the primary tumour and suspicious lymph nodes with a 2-3 cm margin in cranio-caudal direction along the oesophagus and 5-10 mm margin in the transversal plane. An additional margin of 5-10 mm was taken from CTV to PTV in all directions. For T2 and T3 tumours and in the case of positive lymph nodes, an area of elective nodal irradiation was delineated depending on the location of the tumour. For all these patients, the mediastinum was treated to a total dose of 40 Gy. For upper and middle thoracic tumours, the supraclavicular region was included in the elective nodal area as well. For the middle and distal tumours, the truncal region was included in the target volume and in some cases, elective nodal irradiation was omitted based on poor clinical condition or very poor prognostic factors.

For each patient, the whole heart (WH) and its substructures, including the right and left atria (RA and LA, resp.) and right and left ventricles (RV and LV, resp.) were contoured using an automatic delineation tool based on the atlas by Feng et al[18]. Since the pericardium cannot be identified on CT images, we used a surrogate pericardium (PC), by creating a 3D structure with the WH contour as inner border and the WH + 5 mm as outer border. The lungs were delineated and considered as one organ.

Treatment was given on a daily basis, using 10 MV photons in 1.8 to 2.0 Gy daily fractions to a total dose of 50.4 to 66.0 Gy (median dose: 60 Gy). All patients were

treated with 3D-conformal radiotherapy (3D-CRT). In 205 out of 216 patients, radiotherapy was combined with chemotherapy which mostly consisted of 5-FU infusions combined with cisplatin. In case of renal dysfunction or poor performance status a combination of 5-FU with nedaplatin (8) or docetaxel (14) was administered. Only few patients received neo-adjuvant (9) and/or adjuvant (7) chemotherapy as well.

All patients were subjected to a follow up program consisting of follow up visits every 3-6 months for the first 2 years and every 6 months thereafter. Each visit included a physical test, blood test, oesophageal endoscopy and CT scan of the neck, chest and abdomen. Hospital charts of all patients were reviewed for the occurrence of complications and tumour status. Late toxicities were assessed in accordance with the Common Terminology Criteria for Adverse Events version 4.0.

The dose distributions were recovered from the treatment planning system. Dose-volume parameters including doses to whole heart, substructures of the heart and lungs in 5% bins and mean doses were imported in the database.

The clinical endpoints were newly diagnosed cardiac and pulmonary events and overall survival. Dose-volume histogram (DVH) parameters, treatment and patient-related parameters as mentioned in Table 1 and 2 were included as potential risk factors. Cardiac events were analysed as a composed endpoint for all cardiac events as listed in table 3, but also separately as their aetiologies may be different. Tumour-related parameters, like stage, N-status and elective irradiation, were not taken into account in the logistic regression analyses because of their correlation with DVH parameters. However, for OS these known prognostic factors for OS were included in the multivariable Cox regression analysis.

To analyse possible associations of clinical and treatment-related factors with cardiac and lung toxicity, univariable logistic regression analysis was performed, using a cut-off level of p-value <0.2. The selected parameters were tested for multicollinearity using an R-square threshold > 0.8. Clinical factors were excluded in case of a high number of missing data and in case the number of equivalent cases in one group was smaller than 10% (Table 2).

The remaining clinical and dosimetric parameters were included in a multivariable forward stepwise logistic regression analysis based on largest significant log-likelihood differences, which was performed in SPSS. Variables were added to the final model when the model significantly improved ($p<0.05$) based on the likelihood

ratio test. For the OS analyses a forward stepwise multivariable cox regression was used based on the log-likelihood. To test the internal validity, the entire variable selection for both the toxicities and survival was repeated in 1000 bootstrap samples (i.e. with replacement). The selected model optimism was evaluated by calculating the difference between the performance of the models in each bootstrap and in the original sample, according to the TRIPOD statement.[19] Both the area, and the adjusted area under de ROC curves are presented in order to quantify the predictive power of the analyses.

Finally, the effect of the toxicities on OS was analysed using Kaplan Meier analyses.

Table 1 Tumour and treatment characteristics

Tumour and treatment characteristics	
Stage 1	73(34.7%)
Stage 2	57(26.3%)
Stage 3	78(36.2%)
Stage 4	8(3.7%)
N0	102(47.2%)
N1/N2/N3	114(52.8%)
Tumour location	
Cervical	47(21.8%)
Mid	114(52,8%)
Distal/GE junction	55(23.2%)
Pathology	
SCC	212(98%)
Other	4(2%)
Prescribed dose	60 Gy(50.4-66.0)
Elective irradiation	135(62.5%)
Chemotherapy	205(94.9%)

Table 2 Clinical risk factors

Parameter				
Age at start treatment	median	68[40-88]		
Gender	female	36(17%)		
	male	180 (83%)		
WHO 0 vs 1 or higher	0	169(78%)		
	>0	46(21%)		
		Yes	**No**	**Unknown**
Family history(cadiovasc disease)**		12(6%)	83(38%)	121(56%)
Smoking		185 (86%)	29(13%)	2(1%)
Use of alcohol		193 (89%)	21(10%)	2(1%)
Any cardiac history*		26 (12%)	190(88%)	
Diabetes Mellitus		27(12%)	189(88%)	
Hypercholesterolaemia		22(10%)	194(90%)	
Hypertension		81(37%)	135(63%)	
COPD**		2(1%)	214(99%)	
High BMI(>=26)**		15(7%)	201(93%)	

* Any cardiac history, ischaemic event, rythm disorders, heart failure, valve disorders

**not taken into analysis because of too many missing values or low numbers per group

Results

All new cardiopulmonary complications during follow up are summarized in Table 3. Radiological changes in the lungs were only scored as radiation pneumonitis if they remained after the use of antibiotics. In 60 out of 216 patients (27.8%), radiologic features of radiation-induced pneumonitis were observed on follow up CT scans. 3 patients experienced clinical symptoms requiring steroids (grade 2), 6 of them were hospitalized (grade 3), another 4 patients eventually died of this complication (grade 5).

Table 3 Follow up and toxicity

New pulmonary events	
Radiation pneumonitis grade 1	47(22%)
Radiation pneumonitis grade 2	3(1%)
Radiation pneumonitis grade 3	6(3%)
Radiation pneumonitis grade 4	0(0%)
Radiation pneumonitis grade 5	4(2%)
New cardiac events	
Pericardial effusion grade 2	60(28%)
Pericardial effusion grade 3	9(4%)
Angina pectoris any grade	3(1%)
Myocardial infarction any grade	4(2%)
Heart failure any grade	8(4%)
Arythmia any grade	8(4%)
Valvular disease any grade	1(0%)
Survival status at last FU	
Alive, no evidence of disease	105(49%)
Alive with recurrent disease	33(15%)
Dead by index tumor	57(26%)
Dead by toxicity	5(2%)
Dead intercurrent disease	16(7%)

Univariate logistic regression analysis showed that most lung dose parameters and some cardiac substructure dose parameters were significantly associated with pneumonitis. Of the clinical factors, only diabetes mellitus (DM) was associated with this endpoint (suppl. data figure 7). Multivariable logistic regression analysis showed that radiation pneumonitis was best predicted by the mean lung dose (MLD) only, with an odds ratio of 1.18 per Gy MLD (this model had an AUC of 0.67 (adjusted AUC after bootstrapping = 0.63)).

Bootstrap analysis confirmed the robustness of the selection of the MLD into the model. Calibration plots of the observed vs. calculated risk of complications using the Hosmer-Lemeshow test showed a good performance of the model as well (suppl. data figure 1 and 2) .In 69 out of 216 (31.9%) patients, pericardial effusion (PE) was seen on the follow up CT scans. Nine of these patients developed clinical symptoms of heart failure. Two other patients presented with heart failure without signs of pericardial effusion. They both had a cardiac history (1 valvular disease, 1 ischaemic heart disease). Other cardiac events were diverse and are listed in Table 3. The numbers of the separate toxicities were too low for reliable modelling procedures. Combining clinical cardiac events did not result in a predictive model. In univariate analysis, most cardiac, but no lung, dose volume-parameters were related to PE. None of the clinical factors were significantly associated with PE (suppl. data figure 8). In the multivariable analysis, PE was significantly associated with the volume of the RV receiving a dose higher than 35 Gy (V35): OR = 1.03 (95%CI 1.017-1.039). This model had an AUC of 0.73 (95% CI 0.66-0.80)

However, most dose volume parameters, including the mean dose values of the WH, pericardium and RV, performed similarly well in predicting PE (table 4). Most of the heart parameters were highly correlated so we eventually decided to present three models for PE with the mean dose to the RV, the whole heart and to the pericardium as explanatory variables, to facilitate a comparison with results from the literature and use of the models in routine daily practice. All models are presented in table 4 and the model using the mean pericardial dose is depicted in figure 1.

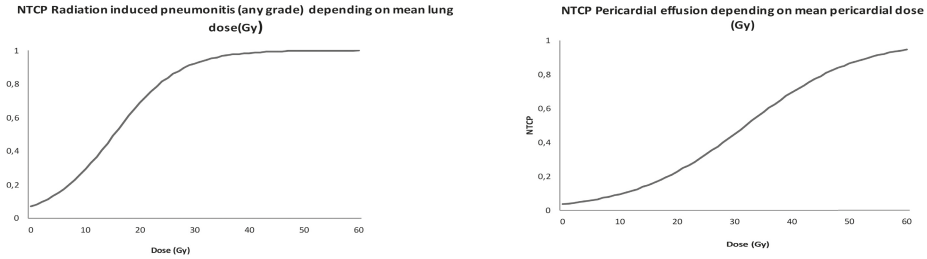

Figure 1 NTCP curves on radiaton induced pulmonary and cardiac toxicities

The bootstrap procedure and calibration curves again confirmed the robust selection of dose volume parameters in the model (suppl. data figure 3, 4); the adjusted AUC's are included in table 4. With a median follow up of 27 months, 97 out of 216 patients developed locoregional failures. The median disease-free survival was 64 months (95% CI 58.7-69.3 months). The median OS was not reached.

Univariable analysis showed that all lung as well as several cardiac dose parameters were associated with OS. However the high dose pulmonary DVH parameters performed significantly better in predicting this endpoint (suppl. data figure 9). Significant clinical factors for worse OS were high tumour stage, high WHO-score, diabetes mellitus (DM), positive lymph nodes and the use of elective radiotherapy. In the Cox-regression analysis, the V45 of the lungs, DM and tumour stage remained significantly associated with OS. The final model is presented in table 4

Table 4 NTCP models on toxicity endpoints using a logistic regression analysis and cox regression models on overall survival

Endpoint (logistic regression)	Explanatory variable	Intercept	Odds ratio	CI (95%)	Significance	performance	Adjusted AUC
Radiation pneumonitis	Mean dose lung	-2,56	1,18	[1,07-1,30]	0,00		
(Nagelkerke R^2=0.08)						AUC 0,67[0,58 -0,75]	0,63
Pericardial effusion	Mean dose pericard	-3,26	1,11	[1,06-1,16]	0,00		
(Nagelkerke R^2=0.17)						AUC 0,73[0,66-0,80]	0,70
Pericardial effusion	Mean dose heart	-3,11	1,09	[1,05-1,12]	0,00		
(Nagelkerke R^2=0,16)						AUC 0,72[0,65-0,79]	0,69
Pericardial effusion	Mean dose RV	-3,24	1,08	[1,05-1,11]	0,00		
(Nagelkerke R^2=0,20)						AUC 0,73 [0,67-0,80]	0,71
Endpoint (cox regression)	**Explanatory variable**		**Hazard Ratio**	**CI (95%)**	**Significance**	**performance**	**Adjusted AUC**
Overall Survival (Cox regression)	V 45 Lung		1.23	[1.09-1.39]	0.00		
	Stage I and II vs Stage III and IV		2.34	[1.38-3.96]	0.00		
	Diabetes		0.33	[0.13-0.83]	0.02		
						AUC 0.73 [0.67-0.80]	AUC 0.70

After the bootstrapping procedure, the same variables were selected and included in the preferred model. The adjusted AUC was 0.69 (suppl. data figure 5).

Kaplan Meier analyses with regard to the effect of these toxicities on OS showed a significantly worse OS for patients presenting with radiation-induced pneumonitis (p=0.013). Patients presenting with pericardial effusion had similar OS as compared to those without pericardial effusion. All analyses are summarized in figure 2.

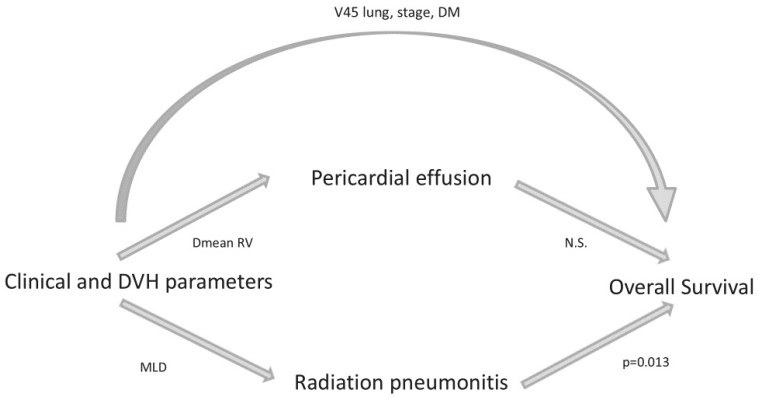

Figure 2 Overview of the performed analyses and its relationships and predictive factors (Vmean RV=mean dose on the right ventricle, MLD=mean lung dose, DM=diabetes Mellitus)

In order to get more insight in causal relationships between toxicity and OS, we reanalysed OS data censoring the patients having a radiation pneumonitis. The same variables remained significant for OS (Stage, DM and V45 lung). Performing the same analyses on patients who developed radiation pneumonitis, the heart dose (V55heart) was the only predictor significantly predicting OS. (Suppl. table 1)

Discussion

In this paper, we aimed to identify clinical and/or dosimetric parameters that are related to cardiac and/or pulmonary toxicity in oesophageal cancer patients and analysed its effect on overall survival. The total prescribed dose in this patient group was relatively high which explains the OS compared favourable to the literature and the relatively high complication rates in this patient group. This allowed us to develop a multivariable prediction model for both heart and lung toxicity and report a comprehensive analysis of these toxicities in oesophageal cancer patients. Cardiac and pulmonary toxicities are clinically relevant side effects and decisions on the preferred dose distribution in an individual patient should be based on the risk of toxicity of both organs at risk.

Regarding pulmonary toxicity, there is only limited data on the risk of radiation pneumonitis in oesophageal cancer patients treated with definitive CRT. The published papers do not provide an odds- or hazard ratio for radiation pneumonitis in this patient group [20,21].

Our model on pericardial effusion is in line with other retrospective publications [7,22,23]. Dose response relationships with different cardiac dose parameters were described in all of these publications. Hayashi, et al. presented the odds ratios of several cardiac DVH parameters related to PE. Our odds ratios seemed to be slightly lower but remained within their 95% confidence intervals[22]. Wei, et al. analysed doses both to the pericardium and whole heart and also found a stronger association for the pericardial dose vs. mean heart dose on PCE, indeed suggesting a local inflammatory effect[23].

To determine which toxicity is most relevant and consequently which organ at risk should be prioritized in our planning strategies, we finally focused on OS as an endpoint. In the multivariable analysis, we found that the dose to the lungs but not the radiation dose to the heart influenced OS significantly in this patient population. Moreover, the subgroup of patients with radiation pneumonitis had a worse OS in Kaplan Meier analysis, as opposed to the patients diagnosed with pericardial effusion, a side effect which did not seem to influence OS. However, when repeating the survival analyses censoring patients with a RP, the same variables remained significant for OS, suggesting the clinical diagnosis of radiation pneumonitis itself might not be the cause for worse OS. In the patient group presenting with radiation pneumonitis, we found the heart dose the most important predictor for OS.

These findings suggest that worse OS can be caused by radiation dose to both organs at risk, but the biological mechanism remains unknown. Given the prognostic significance of a heart dose parameter in the radiation pneumonitis patient group, and not in the whole group, a possible explanation can be found in the physiological interaction of the heart and lungs.

In preclinical studies, this interaction between heart and lung irradiation was objectified. Combining radiation on heart and lungs resulted in a synergistic effect on cardiopulmonary toxicity in rats. On pathologic examinations this interaction seemed to be caused by small vascular damage in lung tissue and perivascular fibrosis in heart tissue, resulting in pulmonary hypertension and reduced diastolic function [24,25].

Clinically, worse OS rates after (higher dose) thoracic radiotherapy despite better local control also suggests underreported toxicity, perhaps even unrecognized toxicity [10,24]. In several (SEER) database studies, higher cardiac death rates were reported in distal tumours and with the use of “older radiotherapy techniques” suggesting radiation induced toxicity of the heart [12,25–27]. More recent publications, like ours, are able to present DVH data on different critical organs and its relation to overall survival. Although several papers have been published on the correlation of cardiac dose with OS, there are reasons to be cautious of increasing the dose to the lungs in an attempt to spare the heart. The correlations found with cardiac dose in the literature might have been a reflection of the absence of cardiac toxicity models while lung toxicity models have been available for a longer period of time, resulting in strict planning criteria for the V20 of the lungs and the mean lung dose. Furthermore, in several of the earlier mentioned trials, not only the dose to the heart but total dose to the lungs was predictive for OS as well [11,16,28–30].

Altogether it is important to consider both heart and lungs as organs at risk in the treatment of thoracic indications. Especially in VMAT or IMRT techniques, cardiac dose reduction will be at the expense of a higher lung dose. Proton therapy on the other hand can reduce both the radiation dose to the heart and lungs. In a recent trial randomizing between photon and proton CRT, a significant reduction of treatment related complications was seen; the total toxicity score was 2.3 times lower after proton radiotherapy, compared to IMRT treated patients[31]. Therefore, it is preferable to combine both heart and lung DVH parameters in these prediction models. These models should originate from prospective data and be validated in independent cohorts to be robust against institutional differences. A further understanding of the mechanisms behind these toxicities can facilitate

the development of these models and make them more robust in different patient groups by not only selecting the best performing variables in that cohort of patients but including the most (clinically) relevant parameters [32]. Besides this, more knowledge in mechanisms will help in early detection and preventive measurements in these patient groups.

We did not find a convincing explanation for the better survival of diabetic patients in this multivariable model. The difference in overall survival in these diabetic patients in univariate analysis became apparent after 20 months, suggesting it was not tumour related but might be patient or therapy related as the highest risk for tumour recurrence is within the first two years (figure 7, suppl. data). Diabetic patients had a significantly higher dose to the lungs and experienced radiation pneumonitis more frequently but, in these patients, it did not seem to influence overall survival as much as it did in the non-diabetic patients. A possible explanation might be a stricter follow up in these patients in which more preventive measurements might have been taken. A stricter patient selection for the curative treatment schedule might be another explanation.

Summarizing, cardiac dose volume parameters predicted the risk of pericardial effusion and pulmonary dose volume parameters predicted the risk of radiation pneumonitis. However, in this patient cohort, pulmonary DVH parameters (V45) were more important for OS than cardiac DVH parameters. These results suggest that reducing the cardiac dose at the expense of the dose to the lungs might not always be a good strategy in oesophageal cancer patients.

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CHAPTER 5

Radiation induced myocardial fibrosis in long-term esophageal cancer survivors.

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Published in Int J Radiation Oncol Biol Phys 2021, Vol. 110(4), 1013-1021

Abstract

Purpose: Radiation-induced cardiac toxicity is a potential lethal complication. The aim of this study was to assess whether there us a dose-dependent relationship between radiation dose and myocardial fibrosis in patients who received neoadjuvant chemoradiation(nCRT) for esophageal cancer(EC).

Materials and methods: Forty patients with EC treated with a transthoracic esophagectomy with (n = 20) or without (n = 20) nCRT (CROSS study regimen) were included. Cardiovascular magnetic resonance imaging (1.5 Tesla) for left ventricular (LV) function, late gadolinium enhancement, and T1 mapping were performed. Extracellular volume (ECV), as a surrogate for collagen burden, was measured for all LV segments separately. The dose-response relationship between ECV and mean radiation dose per LV myocardial segment was evaluated using a mixed-model analysis.

Results: Seventeen nCRT and 16 control group patients were suitable for analysis. The mean time after treatment was 67.6 ± 8.1 (nCRT) and 122 ± 35 (controls) months ($p = 0.02$). In nCRT patients, we found an significantly higher mean global ECV of 28.2% compared with 24.0% in the controls ($p<0.001$). After nCRT, LV myocardial segments with elevated ECV had received significantly higher radiation doses. In addition, a linear dose-effect relation was found with a 0.136% point increase of ECV for each Gray ($p<0.001$) There were no differences in LV function measures and late gadolinium enhancement (LGE) between both groups.

Conclusion: Myocardial ECV was significantly higher in long-term EC survivors after nCRT compared to surgery only. Moreover, this ECV increase was linear with the radiation dose per LV segment, indicating radiation-induced myocardial fibrosis.

Introduction

The clinical introduction of neo-adjuvant chemoradiotherapy (nCRT) prior to surgery provided an important survival benefit for esophageal cancer (EC) patients.[1] However, recent studies have shown that there is a substantial risk of cardiac toxicity and even mortality attributable to nCRT that potentially jeopardizes the benefit of nCRT.[2–5] Wang et al [6] reported grade ≥3 cardiac events in 18% of patients with EC who were treated with chemoradiotherapy. Radiation modality (hazard ratio: 1.7) or mean heart dose (hazard ratio: 1.03) were significantly associated with these complications. Moreover, patients who developed these cardiac complications had worse overall survival (OS: 5 years 38% vs 52%). The exact mechanism of toxicity underlying this increased risk of cardiac complications remains unknown. [7] Knowledge on these mechanisms might help reduce the toxicity risks, aiming to maximize the benefit of nCRT and ultimately improve survival in patients with EC.

Various cardiac pathologies have been described because of thoracic irradiation. Shortly after radiotherapy, acute inflammatory effects could be observed.[8] Months to years after radiotherapy, chronic pericarditis, (major) coronary events, non-ischemic cardiomyopathies, conduction disorders and valve problems can occur.[9–11]

Only limited data exists on the mechanism and extent of direct irradiation damage to the myocardium. Cardiac irradiation has been observed to cause reduced micro-vascularization and myocardial fibrosis in mice.[12] For detection of focal fibrosis, Cardiovascular Magnetic Resonance (CMR) with late Gadolinium Enhancement (LGE) is the gold standard in clinical practice.[13,14] After thoracic radiation therapy, LGE was a result of ischemic fibrosis after myocardial infarction, but also a sign of focal non- ischemic fibrosis in high-dose regions.[15,16] However, eye- balling fibrosis on LGE requires significant myocardial fibrosis to be present, and diffuse fibrosis is even harder to detect in the absence of normal myocardium. In these cases, T1 mapping, including extracellular volume (ECV) calculation, has the potential to make an important contribution to clinical risk stratification, because of its ability to enable detection and quantify myocardial fibrosis at a much earlier stage compared with LGE.[17,18] ECV has already been shown to correlate strongly with histologic collagen burden, and its levels have been found to correlate with increased risks of heart failure or cardiac death.[19] In a recent study by Takagi et al,[20] ECV changes in the myocardium were reported in EC patients after definitive CRT.

In neo-adjuvant setting, in which the prescribed dose to the tumor is lower, the myocardium still receives substantial radiation doses. Therefore, we hypothesize that diffuse myocardial fibrosis occurs after nCRT in a dose dependent way.

The aim of this cross-sectional pilot study was to test the hypothesis that nCRT can cause radiation-induced myocardial fibrosis in EC survivors by comparing the left ventricular myocardial ECV of nCRT patients to those undergoing surgery only and assessing the dose-effect relation per myocardial segment.

Materials & Methods

Patients

This cross-sectional pilot study was approved by the local research ethics committee and registered at clinicaltrials.gov (NCT03396614, METC2017/335). All EC patients treated with a transthoracic esophagostomy between 2000 and 2012 in the University Medical Center Groningen who were alive without evidence of disease were eligible for this study. Survival and disease status were checked with their general practitioners. The exclusion criteria were thoracic radiation therapy or (adjuvant) chemotherapy other than nCRT according to the CROSS regimen[1] and any contraindication for cardiac magnetic resonance imaging (eg, pacemaker, metal not compliable with MRI).

For this study, we included 20 patients with EC treated with nCRT followed by transthoracic esophagectomy and 20 patients with EC treated with surgery alone as a control group. In total, 36 nCRT patients and 40 control patients were contacted, and received written informed consent from 22 and 26 patients, respectively. Inclusion was in the order of response received.

Radiation Therapy and Chemotherapy

The nCRT was given according to the CROSS-regime[1] with a total dose of 41.4 Gy in 23 fractions of 1.8 Gy, five times a week, combined with weekly concurrent chemotherapy. All patients were treated with 3D conformal radiotherapy (3DCRT).

The concurrent chemotherapy consisted of carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m^2 of body-surface area) and was administered intravenously for a maximum of five cycles.

Extraction of dose-volume parameters

For evaluation of radiation dose distributions, the original planning CT scans and corresponding treatment plans and delineated structures of each patient were transferred to the Mirada Medical treatment planning system (version 1.2.0). Additional contouring of the different substructures of the heart; the left ventricle (LV), right ventricle (RV), left atrium (LA) and right atrium (RA), were automatically contoured in Mirada using an atlas-based tool. All structures were checked and adapted according to the cardiac contouring atlas of Feng et al.[21] In addition, the myocardium of the left ventricle was defined and divided in 17 segments corresponding with the standardized myocardial 17-segment model in order to find relations in dose distributions and cardiac MRI measures.[22,23] The workflow to create these segments is shown in *figure 1*.

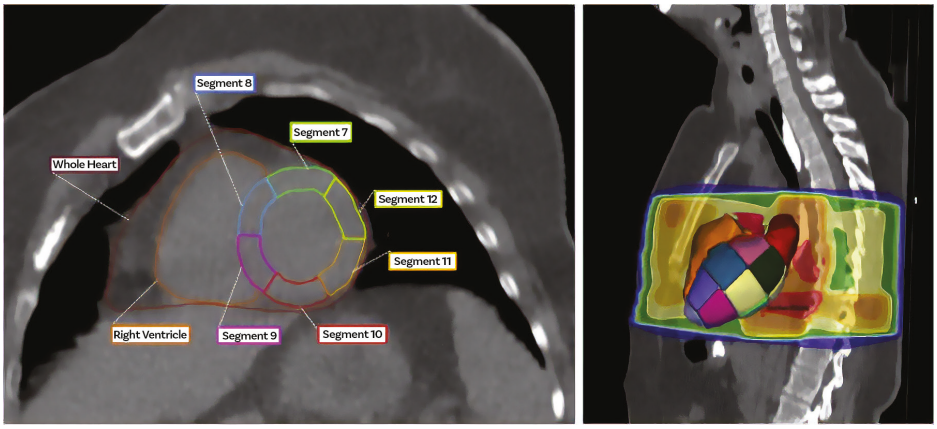

Figure 1. Workflow for segmentation of the 17 myocardial segments of the left ventricle on radiation therapy planning computed tomography (CT; according to the 17-segment model proposed by the American Heart Association) 1. Angulate planning CT perpendicular to the long axis of the left ventricle to create a short axis view; 2. Check and adjust contours of whole heart (WH), left ventricle (LV), right ventricle (RV), left atrium (LA), and right atrium (RA); 3. Create left ventricular wall (1 cm thick); 4. Define basal, mid, and apical slices (devide ventricle where lumen is visible into 3 equal slices) and segment 17 (true apex); 5. Divide the basal and mid part in 6 equal segments (60? angle). Divide the apical part in 4 equal segments (90? angle). Start with the septal segments (2, 3, 8, 9, and 14) for adequate positioning; 6. Angulate CT with new structures back to normal position. 7. Extract dose-volume histogram parameters for WH, LV, RV, LA, RA and segment 1 to 17. On the left side, an example is showed of an angulated planning CT (short axis view) and the method of delineation of the heart substructures and myocardial segments on a midventricular slice. The right picture demonstrates the ability to obtain dose parameters per (sub)structure using this 3-dimensional model of the heart.

Image acquisition

Cardiac Magnetic Resonance image acquisition was performed on a 1.5 Tesla scanner (Magnetom Avanto-fit, Siemens Healthineers, The Hague, Netherlands) equipped with a phased-array five channel coil for cardiac imaging. Long-axes cines were visualized in 4 chamber, 2 chamber left, and left ventricular outflow tract views. The heart was covered from the atria to the ventricular apex using short-axis cine views. Native (long) T1 series were performed covering basal, mid and apex in three corresponding short axis planes, using an optimized motion corrected single breath hold 5(3)3 MOLLI sequence. The gadolinium based contrast agent Dotarem™ was used (0.2 mmol/kg body weight at 2mL/s). Equivalent post contrast (short) T1 series were scanned 12 minutes after injection. Matching long and short axis planes were used for late gadolinium enhancement imaging, starting 15 minutes after injection, using standard clinical sequences with standard parameters. All images were acquired anonymously in accordance with the Good Clinical Practice guidelines of our centre and stored digitally for offline analysis.

Image analysis

The acquired images were post-processed with Circle CVI[42] (Circle Cardiovascular Imaging, Calgary, Canada [version 5.6.7]). T1 values (time in ms) were measured by drawing endocardial and epicardial left ventricular contours manually in the basal, mid, and apical short axis views on the native 8 acquired echo images and subsequently registered and subdivided using the ESC 16 segment model.[22] All delineations were performed by one observer (CG) and checked by a dedicated cardiac radiologist (NP). Extracellular volume fraction (ECV) was calculated using the standard formula with correction for red blood cell density in the blood pool (hematocrit).[24] The hematocrit was obtained on the day of the MRI acquisition.

Statistical analysis

SPSS (version 23) was used for statistical analysis. All data were expressed with mean ± standard deviation(SD). The irradiated group and non-irradiated control groups were compared using a *t* test for continuous data and a χ^2 test for categorical data. All statistical tests were two-sided and group differences were considered statistically significant if at $p < 0.05$.

ECV was considered to be elevated if it deviates >2 SD above the mean global ECV of the control group. To investigate a possible relationship between radiation dose to the segments of the LV myocardium and ECV, we calculated these individual segments. All statistics were performed at the LV myocardial segment level using a mixed-model regression analysis with random intercept to correct for patient-

to- patient variance. Mixed-model analyses were performed using MLwiN (Version 2.22, Centre for Multilevel Modelling, University of Bristol, Bristol, United Kingdom).

Results

Patients

Two EC survivor groups participated: 20 patients that received nCRT prior to surgery and 20 patients that were treated with surgery alone as a control group. After exclusion (figure 2), 16 patients of the control group and 17 patients of the nCRT group were suitable for analysis. In one control patient, the basal slice was scanned to close to the mitral valve, because of this partial volume artefact basal segments were excluded (native and post contrast T1 values and ECV calculation). Due to ECG-triggering artefacts, we excluded some myocardial segments (figure 2) from post-contrast T1 measures and ECV calculations.

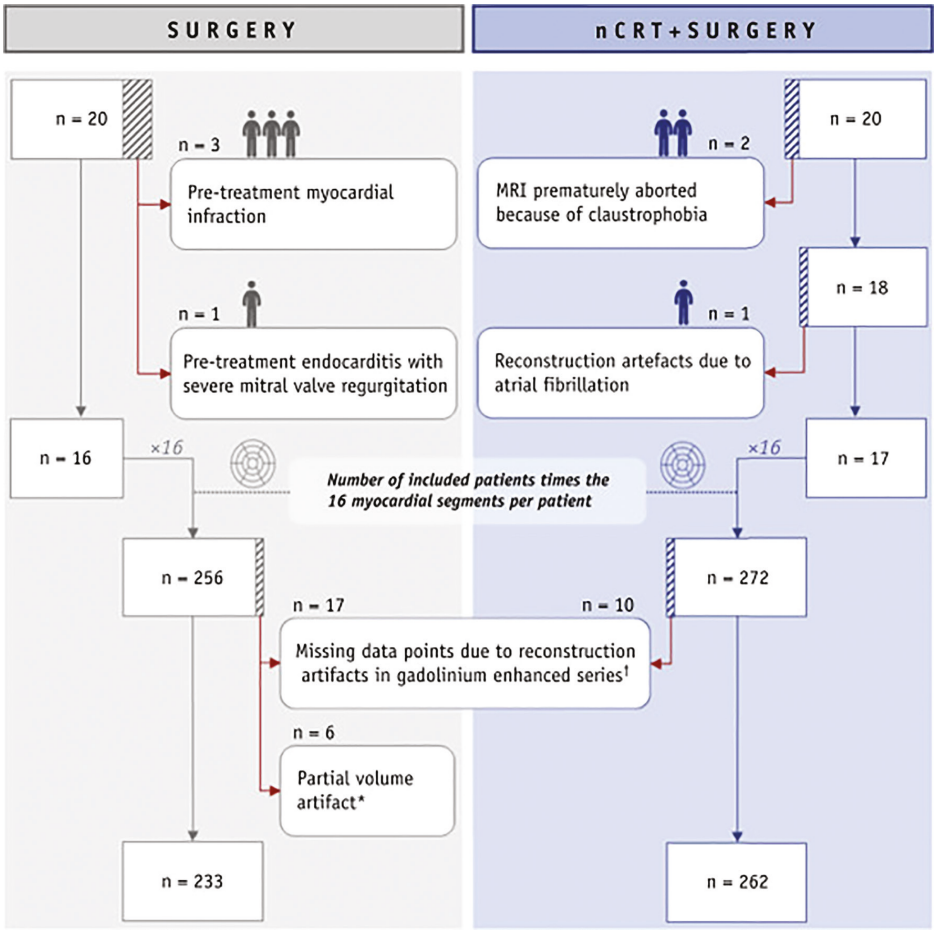

Figure 2. Inclusion flowchart at the patient level (top) and left ventricle myocardial segment level (bottom) for extracellular volume calculation. The red arrows point out the excluded patients (top) or myocardial segments (bottom). *Basal slice was scanned too close to the mitral valve in 1 patient. †CMR reconstruction artifacts were seen in 2 neoadjuvant chemoradiotherapy and 2 surgery only patient.

Patient characteristics, cardiac risk factors and events during follow up are presented in *table 1*. Time after treatment was significantly longer for the control group (122 versus 87 months). There were more former smokers, patients with atrial fibrillation and diabetes mellitus in the nCRT group at time of inclusion.

	Surgery (n = 16)	nCRT + Surgery (n = 17)	
Gender **Male** **Female**	13 3	11 6	P = 0.286
Age (years)	71.8 ± 9.6	67.6 ± 8.1	P = 0.180
Time after treatment (months)	122 ± 35	87 ± 23	P = 0.002
WHO PS 0 vs higher	10 (13)	11 (14)	P = 0.895(0.935)
BMI	25.5 ± 2.8	24.8 ± 5.1	P = 0.625
Smoking status **Current smoker** **Past smoker**	3 7	1 15	P = 0.024
Hypertension	3 (3)	6 (3)	P = 0.289 (0.935)
Diabetes Mellitus	1 (1)	7 (5)	P = 0.019 (0.116)
Hypercholesterolemia	2	6	P = 0.127
Coronary artery disease	2 (2)	1 (0)	P = 0.509 (0.133)
Atrial fibrillation	0 (0)	5 (1)	P = 0.019 (0.325)

Table 1: Patient characteristics and cardiac risk factors. Baseline (prior to treatment) values are shown between brackets.

Radiation therapy and Chemotherapy

All patients of the nCRT group received the full course of radiation and chemotherapy.

On average, the mean heart dose (MHD) was 22.9 ± 4.0 Gy, with a mean dose to the cardiac substructures of 17.8 ± 5.8 Gy to the LV, 25.9 ± 4.9 Gy to the RV, 32.0 ± 8.1 Gy to the LA and 23.3 ± 8.3 Gy to the RA. The mean MLD was 7.5 ± 2.5 Gy and the mean V5 Gy of the lungs was 39.8 ± 15.8%. The left ventricular dose distribution is visualized in figure 3 and 4 using the mean dose per myocardial segment.

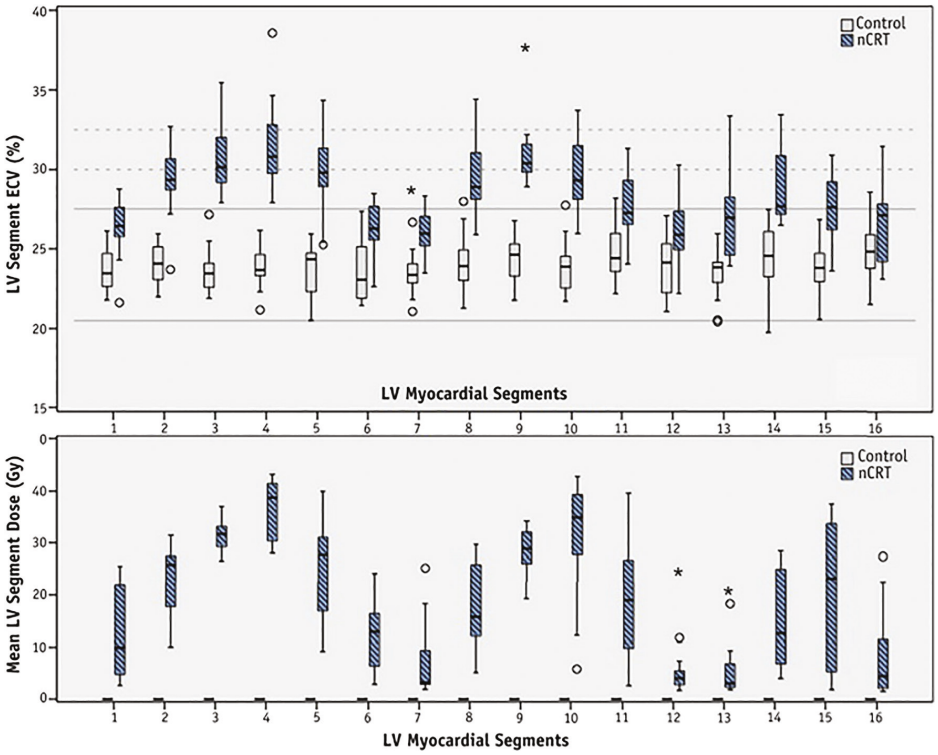

Figure 3. Box plots show extracellular volume (ECV) measurements (top) and mean dose (bottom) per myocardial segment for nCRT and control patients. For ECV, the solid lines represent the lower and upper border of the normal range (mean ± 2 SD) and the dashed lines elevated ECV (+ 3 SD and +4 SD). Box plots show medians, quartiles, ranges and outliers. Outliers are displayed as dots (1,5-3 interquartile ranges) and stars (>3 interquartile ranges).

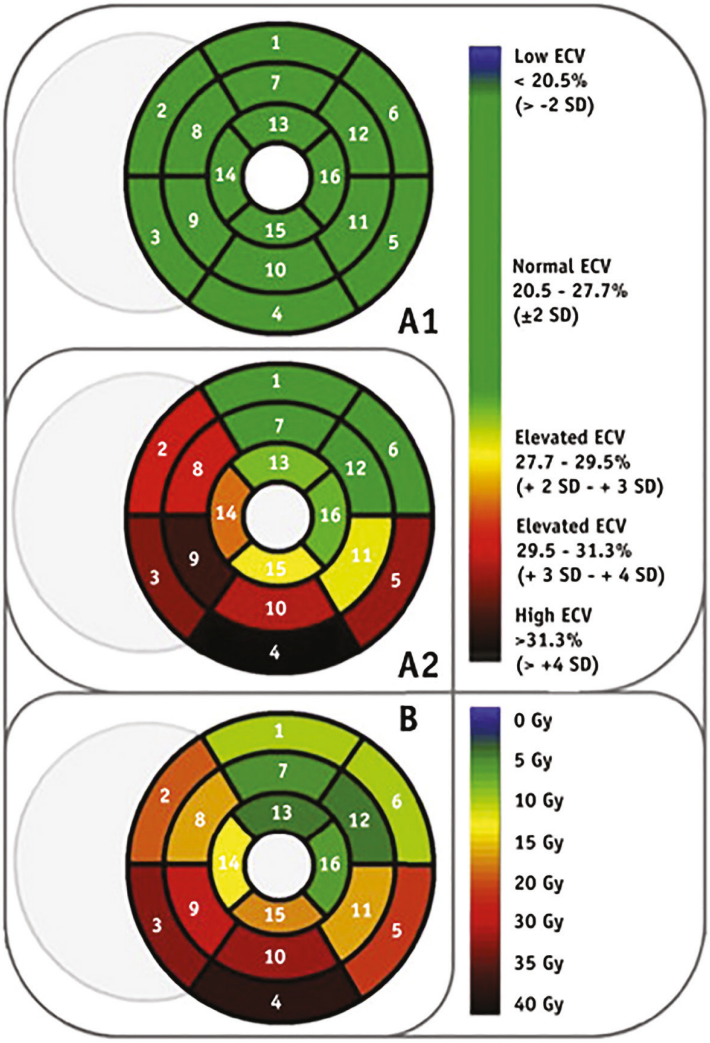

Figure 4. (A1) Mean extracellular volume per left ventricular (LV) myocardial segment control patients. (A2) Mean extracellular volume per LV segment neoadjuvant chemoradiotherapy patients. (B) Average mean dose per LV myocardial segment (neoadjuvant chemoradiotherapy group).

Cardiovascular Magnetic Resonance: Function measurements

Left ventricular ejection fraction was 57.9 ± 13.6% in the nCRT group versus 57.4 ± 7.8% in the control group. End systolic volume index was 35.2 ± 10.0 versus 36.5 ± 8.9 ml/m2 and end diastolic index was 62.1 ± 15.0 versus 64.4 ± 15.9 ml/m2 for nCRT and control patients respectively. These differences were not statistically significant.

Cardiovascular Magnetic Resonance: Myocardial native T1, Postcontrast T1 and ECV

To assess whether radiation dose to the heart could cause myocardial fibrosis, we performed T1 mapping to characterize the myocardial tissue of the LV.

The mean native myocardial T1 relaxation time was 959.2 ± 34.7 ms for patients who received nCRT and 949.9 ± 28.4 ms for control patients (p = 0.40). The radiologist (NP) reported intramural LGE in 4 irradiated patients versus 1 control patients (p = 0.17). In addition, the post-contrast T1 values were 404.9 ± 25.1 ms and 431.6 ± 33.7 ms for nCRT and control patients respectively (p = 0.02), which indicates more diffuse LGE in the nCRT group. ECV measurements, as a surrogate for histologic collagen burden of the myocardium, were higher in nCRT patients compared with control patients (28.4% ± 1.0% vs 24.0% ± 0.9%; P < .001). This increased mean global ECV indicates diffuse myocardial fibrosis in nCRT patients, which may be attributed to the cardiac co-irradiation.

When focusing on the LV myocardial segment level, mean ECV was quite similar in all segments of the control patients (figure 3). Large ECV deviations between segments were seen in the nCRT group, with the highest ECV values measured in the basal and mid septal and inferior segments (e.g. segment 2, 3, 4, 5, 8, 9, 10), which is typically the area of the left ventricular wall that is located near the esophagus and nodal regions (radiotherapy target volume) and therefore receives the highest radiation dose. For the nCRT group, the mean dose in the LV segments with elevated ECV (>27.7 %) was on average 24 Gy versus 11 Gy in segments with normal ECV (p = 0.03). However, even segments that received low radiation doses showed increased ECV compared to control segments. For instance, we found on average 26.3 % ECV in segments with a mean dose ≤ 5 Gy (n = 55), which is significantly higher than the mean ECV of 24.0% in the control group (p=0.03).

Figure 4 indicates the mean LV segmental ECV for nCRT (A2) and control (A1) patients. For the nCRT patients, the dose distribution (B) is shown as an average mean segment dose for the corresponding segments. Mean segment dose and ECV for each individual LV myocardial segment (nCRT patients) are presented in figure 5. Mixed model analyses show a significant effect of myocardial segment mean dose on ECV (0.136, 95%CI 0.114 – 0.158, p<0.001). Variables such as age, hypertension, atrial fibrillation, diabetes mellitus and hypercholesterolemia, time after treatment and lung dose(mean lung dose, V5 an V20 lung) were no confounders. The final random intercept model in the irradiated group, after internal validation using 2500 semiparametric bootstrap samples, was ECV = 25.88 + (0.136*mean myocardial

segment dose (Gy)), which seems to confirm our initial hypothesis that thoracic radiation induces dose-dependent (sub)clinical myocardial fibrosis. Differences in LV function were not found between patients with normal and elevated mean global ECV (supplementary data in Table E3)

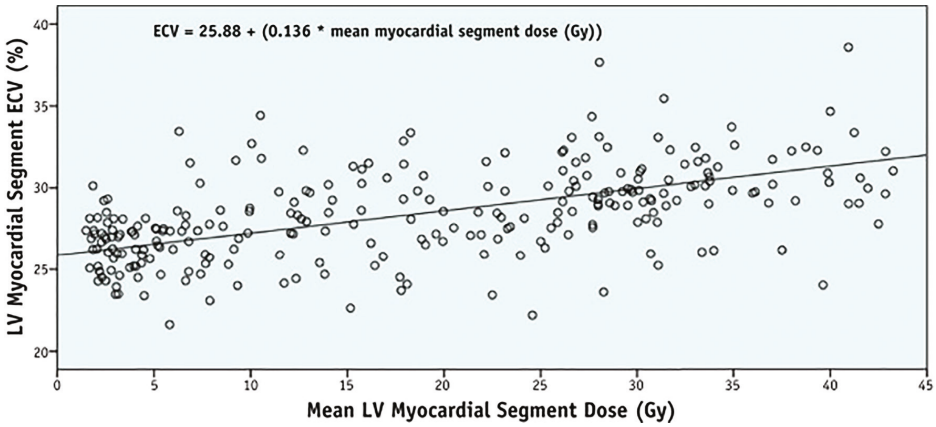

Figure 5. Scatter plot visualizing the effect of mean dose per left ventricular myocardial segment (x-axis) on extracellular volume (y-axis) in neoadjuvant chemoradiotherapy patients. Each dot represents one left ventricular myocardial segment of a patient. The association between radiation dose and increased extracellular volume that was established using mixed-model analysis with a random intercept is represented by the formula.

Discussion

We observed myocardial damage in patients with EC after nCRT with a prescribed dose of only 41.4 Gy. To our knowledge, this study shows for the first time a linear dose-response relationship between mean radiation dose per myocardial segment and ECV. Since ECV is a good surrogate for histological collagen burden, our results demonstrate that co-irradiation of the heart causes direct damage to the myocardium in terms of diffuse fibrosis.[25] It is well established that elevated ECV is associated with increased risk of heart failure and cardiac death.[26–28]

In line with this, myocardial fibrosis might contribute to the evaluated risk of cardiac complications and/or mortality after thoracic radiation therapy. The literature shows that the mean heart dose is an independent predictor of cardiac complications and OS in patients with EC treated with nCRT.[2,29] We demonstrated that radiation to the heart causes an increase in ECV in a dose-dependent way. This myocardial fibrosis might be one of the mechanisms that contributes to worse OS when the heart is exposed to higher radiation doses. However, we found no differences in CMR parameters between the groups and therefore could not demonstrate the clinical impact of elevated ECV in our study, which might be explained by the smaller sample size.

Pre-clinical studies have already shown that direct injury of the myocardium due to irradiation is associated with decreased microvascular density, vessel leakage and perivascular fibrosis.[12,30] In line with this, several studies reported regional hypoperfusion within the radiation field using myocardial scintigraphy for breast cancer patients.[31–33] Similarly, gated Myocardial Perfusion Imaging revealed significantly more myocardial perfusion defects within the first year after concurrent chemoradiation for esophageal cancer compared to control patients.[34] An autopsy study found diffuse pericellular or perivascular fibrosis, especially when the radiation dose to the heart exceeded 30 Gy.[35] In the present study, the radiation dose in these segments was on average 24 Gy if ECV was elevated (> 27.7%) versus 11 Gy in segments with normal ECV ($p = 0.03$). Even in segments that received a relatively low radiation dose (mean dose < 5 Gy), ECV was slightly higher than in control segments, 26.3% versus 24.0% respectively ($p = 0.03$) (figure 3). Concurrent chemotherapy might have contributed to the effect of the radiotherapy on ECV, especially in the low dose segments. However, we demonstrated an independent linear dose effect relation between mean dose per segment and ECV.

Increased rates of (major) coronary events after thoracic radiotherapy are frequently reported, and in breast cancer and Hodgkin lymphoma patients a clear dose-response relationship has been demonstrated.[36,37] However, rather than the coronary artery flow territories, the changes in segmental ECV in the nCRT group follow the dose distribution (figure 4).[38,39] CMR with LGE was used in several other studies to detect fibrosis due to myocardial ischemia. A recent imaging study in 20-years survivors of Hodgkin disease found LGE in 29% of the patients, and the vast majority showed an enhancement pattern matching with myocardial infarction.[15] In our study only one patient (6%) experienced an occult myocardial infarction after nCRT. However, we found intramural LGE in 4 patients (24%), a pattern that can be observed in non-ischemic cardiomyopathies.[13] Umezawa et al. [16] analyzed patients with EC approximately 1 year after definitive chemoradiation (CRT) (60-70 Gy). In 46% of the patients, intramural LGE was detected. The lower rates of LGE in our cohort may be attributed to the lower radiation dose in the neoadjuvant setting. The relation that Umezawa et al.[16] found between the presence of LGE in the LV myocardial segments and radiation dose supports this. The researchers described 15% LGE in segments that received a radiation dose between 40 Gy and 60 Gy and 21% if the segmental dose exceeded 60 Gy. How radiation-induced myocardial damage develops over time is unknown. A prospective Japanese study performed in EC patients treated with definitive CRT demonstrated an increase in native T1 of 7% ($p < 0.05$) and 5% ($p > 0.05$) and in ECV of 24% ($p < 0.05$) and 14% ($p > 0.05$) in the basal septum (irradiated area) at 0.5 and 1.5 years follow up respectively, compared to baseline[20]. In addition, post-contrast T1 values showed a significant decrease at 1.5 year when compared to baseline. The apical lateral wall was measured as control (non-irradiated volume) and did not show differences over time. An explanation for the initial increase of ECV might be the presence of myocardial inflammation shortly after radiotherapy, as also suggested by the authors.[12,40] It is known that in case of myocardial inflammation, ECV can lead to an overestimation of the extent of myocardial fibrosis.[41]

This cross-sectional study has two limitations. Firstly, the cohort size is limited. As a consequence, we could not determine risk factors that might affect ECV changes after radiotherapy, or correlate elevated ECV with cardiac function measures. Secondly, patients who already died prior to the study were not in the cohort. Since cardiac toxicity is known to negatively influence overall survival,[2] our study is indeed likely affected by a selection bias, which might have led to an underestimation of the risk of myocardial toxicity.

The results of the current study emphasize the need to prevent the induction of radiation induced myocardial fibrosis by reducing the heart dose optimizing photon radiotherapy dose distributions or reduction of heart dose using proton radiotherapy.[42] Furthermore, early monitoring of myocardial fibrosis using EVC improves the detection of patients at risk. Future studies need to indicate whether treatment with anti-fibrotic agents such as angiotensin-converting enzyme and aldosterone inhibiters might be beneficial for these patients.[43]

Conclusion

We found a linear dose-effect relationship between myocardial ECV and mean radiation dose per myocardial segment of the left ventricle. Patients treated with nCRT followed by surgery had significantly increased mean global myocardial ECV measures compared to patients that were treated with surgery only. Therefore, this study demonstrates that EC survivors develop myocardial fibrosis as a direct consequence of co-irradiation to the heart.

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CHAPTER 6

Late cardiac toxicity of neo-adjuvant chemoradiation in esophageal cancer survivors: a cross-sectional pilot study.

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Published in Radiotherapy and Oncology 2022, Volume 167, 72-77

Abstract

Purpose: Although cure rates in esophageal cancer (EC) have improved since the introduction of neoadjuvant chemoradiation (nCRT), evidence for treatment-related cardiac toxicity is growing, of which the exact mechanisms remain unknown. The primary objective of this study was to identify (subclinical) cardiac dysfunction in EC patients after nCRT followed by surgical resection as compared to surgery alone.

Materials and Methods: EC survivors followed for 5-15 years after curative resection with (n = 20) or without (n = 20) nCRT were enrolled in this prospective cross-sectional pilot study. All patients underwent several clinical and diagnostic tests in order to objectify (sub)clinical cardiac toxicity including cardiac CT and MRI, echocardiography, ECG, 6-minutes walking test, physical examination and EORTC questionnaires.

Results: We found an increased rate of myocardial fibrosis (Linear late gadolinium enhancement (LGE) 4 vs. 1; p=0.13; mean extracellular volume (ECV) 28.4 vs. 24.0; p<0.01), atrial fibrillation (AF) (6 vs. 2; p=0.07) and conduction changes in ECG among patients treated with nCRT as compared to those treated with surgery alone. The results suggested an impact on quality of life in terms of worse role functioning for this patient group (95.0 vs. 88.8; p=0.03).

Conclusion: Based on our analyses we hypothesize that in EC patients, radiation-induced myocardial fibrosis plays a central role in cardiac toxicity leading to AF, conduction changes and ultimately to decreased role functioning. The results emphasize the need to verify these findings in larger cohorts of patients.

Introduction

Although cure rates of esophageal cancer (EC) patients have been improved since the introduction of neo-adjuvant chemoradiation (nCRT), radiation-induced cardiac toxicity might jeopardize the beneficial effect of this treatment. The CROSS trial showed a significant increase in survival rates for patients treated with nCRT prior to surgery compared to patients treated with surgery alone with acceptable acute and perioperative toxicity [1,2]. Quality of life was similar in both groups at one year after treatment [3]. Therefore, nCRT became the standard treatment for EC in large parts of the world. However, after thoracic radiotherapy for haematological malignancies, lung or breast cancer, radiation-induced cardiac and pulmonary toxicity has increasingly been acknowledged as a clinically relevant problem. [4–6]. SEER database studies including EC patients showed more cardiac deaths among irradiated patients as opposed to those treated with surgery [7,8]. Recent studies comparing, modern organ sparing radiotherapy techniques like IMRT or proton therapy with more conventional techniques found lower rates of all cause or cardiac morbidity and mortality [9–11]. Furthermore, higher (cardiovascular) postoperative complication rates were found in irradiated patients as well as patients treated with less advanced radiotherapy techniques [12–15].

These findings suggest that treatment-related cardiovascular morbidity is a clinically relevant problem in EC patients. In retrospective studies, high rates of atrial fibrillation, pericardial effusion, heart failure and cardiac wall motion disorders have been described [16–19]. However, so far, prospective imaging studies have not been systematically performed in EC patients. Moreover, information of the biological mechanisms resulting in cardiovascular toxicity is lacking. Therefore, assessment of subclinical cardiac toxicity using advanced cardiac imaging techniques may provide a better understanding of these mechanisms and may identify targets to prevent cardiac toxicity in the treatment of EC.

Therefore, the main objective of this prospective hypothesis-generating cross-sectional pilot study was to identify subclinical and clinical cardiopulmonary abnormalities in EC survivors after nCRT followed by resection and compared to patients treated with surgery alone.

Materials & Methods

In this pilot study, we included 40 EC survivors who were treated 5 to 15 years ago. Twenty patients were treated with nCRT followed by surgery. Since the EC population is generally older with several (cardiopulmonary) comorbidities, 20 patients treated with surgery only were included as a control group. During the time frame 2002-2010, our hospital participated in the CROSS trial. At that time, multimodality treatment was not considered standard of care and therefore we expected to include EC survivors with comparable baseline cardiopulmonary risk factors. Because of the limited number of survivors, we included patients that were 2 years before, during and 2 years after the recruitment period of the CROSS trial. Thereafter, nCRT was considered standard of care. nCRT was given according to the CROSS trial with a total dose of 41.4 Gy in 23 fractions combined with weekly concurrent carboplatin and paclitaxel [1]. 3-Dimensional conformal radiotherapy was used during this time frame. Beam directions usually consisted of two opposing beams, adding a third, lateral beam to decrease the dose to the heart. According to the protocol, the volume of lung tissue receiving 20 Gray (V20) did not exceed 30 %, the V40 of the heart did not exceed 30%, and the V30 of the liver did not exceed 60%.

The current study was approved by the local ethics committee and registered in clinicaltrials.gov (NCT03396614). All patients treated for EC with curative surgery plus or minus neoadjuvant CRT were selected from our institutional database. After verification of survival and disease status with their general practitioners, we contacted patients whether they were willing to participate in this study. In total, 36 nCRT patients and 40 control patients were contacted. Written informed consent was given by 22 and 26 patients respectively. Inclusion was done in order of response.

Participants visited our hospital for one day. They were interviewed on issues concerning medical history and physical functioning. In addition, the EORTC Quality of life questionnaires (EORTC-QLQ), measuring cancer patients' physical, psychological and social health (C-30) and OES-18, focusing on EC cancer patients, were completed. After a routine physical examination, a 6-minute walking test (6MWT) was performed as measurement for functional capacity and physical fitness [20,21]. Blood biomarkers were taken to evaluate myocardial damage: NT pro BNP is considered an early biomarker for heart failure and is prognostic for cardiac events and overall survival [22] and HS-TNT is considered as a measurement

for myocardial necrosis and predicts the development of heart failure and overall survival as well [23].

Echocardiography was performed according to the guidelines of the European Association of Cardiovascular Imaging [24]. This protocol included assessments of right and left systolic and diastolic function parameters, strain imaging, valve disorders and signs of pulmonary hypertension.

An ECG triggered CT-scan was performed on a dual source CT-scanner without contrast enhancement in order to quantify the number of coronary calcifications. This was calculated and expressed as the Coronary Artery Calcium (CAC) score based on the Agatston method [25].

A cardiac MRI scan was performed during breath hold and ECG monitoring on a 1.5 Tesla MRI scanner (Magnetom Avanto-fit, Siemens Healthineers, The Hague, Netherlands). T1 images were acquired with and without contrast enhancement in order to assess patterns of myocardial fibrosis and to enable T1 mapping to quantify myocardial abnormalities. Cine and delayed enhancement images (4 chamber, 2 chamber and short axis) were acquired for functional evaluation and measurements[26,27]. Results of the imaging techniques were assessed while being blinded for treatment group and medical history.

In order to identify possible relationships between dose distribution parameters and diagnostic tests, detailed information on cardiac radiation dose distributions was collected. The radiotherapy planning CT scan, 3D treatment plan and delineated structures were transferred to the Mirada Medical treatment planning system (version 1.2.0). Additional contouring of substructures, and the left ventricular myocardial segments of the heart was subsequently performed according to previously published guidelines [28,29]. These retrospective data were exported to our research database.

As this trial was designed as a pilot study, it was not powered for statistically significant ($p<0.05$) differences between the two groups. We consider differences up to a p value below 0.20 relevant for further analyses and worthwhile presenting. Binary endpoints were analysed using a logistic regression analysis, while for continuous endpoints a linear regression analysis was performed. To compensate for potential imbalances between the groups we tested and corrected for confounding variables. Mean values were used in presenting the data.

Results

Forty patients were included in this study, of which 20 received nCRT prior to surgery and 20 were treated with surgery only. An overview of patient characteristics, cardiac risk factors, clinical events at baseline and during follow up is presented in table 1.

Table 1 Patient population including cardiac comorbidities at baseline and during/after treatment*

	Surgery(n=20)	CRT + Surgery(n=20)	p value	age corrected p value
Age (yrs)	74.0 [46-91]	67.8 [50-81]	0.04	
Follow up after treatment (months)	126	88	0.01	
WHO 0 vs higher (%)	60	55	ns	
BMI	25.4	25.0	ns	
Current smoker	3	1	ns	
Hypertension	6(5)	7(4)	ns	
Diabetes Mellitus	3(3)	6(7)	ns	
Hypercholesterolaemia	5(3)	7(7)	ns	
Coronary artery disease	4(2)	2(1)	ns	
Arrythmia**	2(0)	6(1)	0.11	0.07
Heart failure	2(2)	1(0)	ns	
peripheral thrombosis	1(0)	2(0)	ns	
Peripheral arterial disease	0(0)	1(0)	ns	
Valvular replacement	1(1)	0(0)	ns	
COPD	1(0)	2(2)	ns	

*Between brackets numbers before esophagectomy
**Arrythmias (AF) were most often diagnosed within the first half year after treatment
ns=non-significant

In the surgery only group, patients were older (74 vs 67.8 years, p=0.04), and the median follow up after treatment was significantly longer (126 vs 88 months, p=0.01). No statistically significant differences were found in clinical cardiac or pulmonary events except for cardiac arrhythmia. In the nCRT group, 6 patients were diagnosed with atrial fibrillation vs. 2 in the control group (p=0.11, age corrected p=0.07).

At the time of analysis, patients in the nCRT group reported higher fatigue scores (EORTC QLQ-C30) 13.8 vs 9.1 (p=0.13) and lower role functioning scores 88.6 vs 95.0. (p=0.13). These differences could be explained by the differences in the questions ”Were you tired” (p=0.07), “Were you limited in doing your work” (p=0.03) and “were you limited in doing your hobbies” (p=0.01) and not by the effect on social or family life. When correcting for age, the difference in role functioning was statistically

significant between the groups (p=0.03). No differences were found in pulmonary symptoms (EORTC QLQ-LC13).

The results regarding laboratory findings, ECG and 6-minutes walking test are summarized in Table 2. QTc intervals on ECG were significantly shorter in the nCRT patients. No other signs for conduction disorders were found.

Table 2 Questionnaires, blood tests, ECG, 6MWT*

	Surgery(n=20)	CRT + Surgery(n=20)	p value	age corrected p value
Global health (EORTC QLQ-C30)	72.1 (2.9)	70.4 (2.7)	ns	ns
Physical functioning (EORTC QLQ-C30)	89.3 (2.5)	88.0 (2.0)	ns	0.15
Role functioning (EORTC QLQ-C30)	95.0 (3.3)	88.8 (2.4)	0.13	0.03
Emotional functioning (EORTC QLQ-C30)	94.7 (1.7)	91.9 (2.4)	ns	ns
Cognitive functioning (EORTC QLQ-C30)	90.6 (2.5)	96.3 (1.6)	0.07	ns
Fatigue (EORTC QLQ-C30)	9.2 (2.1)	13.8 (2.1)	0.13	0.15
ECG				
PQ time(ms)	182 (6.7)	175 (6.7)	ns	ns
QRS complex(ms)	94 (2.7)	90 (2.3)	0.18	0.11
QT (Bazet corrected)(ms)	432 (4.1)	423 (3.4)	0.10	0.03
6-minute walking test (% predicted)	74.6 (3.4)	70.9 (3.6)	ns	
Blood tests				
HS-TNT(ng/L)	14.0 (1.9)	10.6 (1.0)	0.13	ns
NT-pro BNP(ng/L)	250 (93.2)	362 (108.1)	ns	0.19

*Standard error of the mean(SEM) between brackets

Thoracic CT-scans were performed in all patients. CAC scores were less reliable in 6 patients because of cardiac interventions (CABG and coronary stents). However, scores of these patients did not influence the conclusion: there was no difference between the groups.

Functional and dimensional parameters were measured using echocardiography and cardiac MRI. No significant differences were seen between the two treatment groups regarding signs of pulmonary hypertension, systolic or diastolic dysfunction and valve disorders. A significant difference in myocardial wall thickness of the septum (p=0.04) was observed, but when correcting for age, the effect of radiotherapy on this parameter became non-significant (table 3). A complete overview of these data is added as supplementary data (Sup 1).

Table 3 imaging echo, CT and MRI**

	Surgery(20)	CRT + Surgery(20)	p value	age corr
CAC score (CT scan)	735 (249)	350 (173)	0.20	ns
Left atrium Volume Index(LAVI ml/m^2)	35.1 (3.6)	30.1 (2.5)	ns	ns
Number of patients with MRI	20	18		
Intramural contrast enhancement(LGE)	1	4	0.12	0.13
Mean ECV *	24.0 (0.3)	28.4 (0.3)	<0.01	<0.01
Septum thickness(mm)	9.9 (0.4)	8.7 (0.4)	0.04	0.14

*Only eligible results(n=27), **standard error of the mean between brackets

A linear pattern of cardiac late gadolinium enhancement (LGE) which is considered a sign of local non ischemic fibrosis [30] was observed in 4 out of 18 irradiated patients vs. in 1 out of 20 non-irradiated patients (Figure 1, p=0.13). Within the nCRT group, the mean radiation dose to the heart (MHD) was significantly higher (26.6 vs. 21.8 Gy, p=0.01) in patients showing linear LGE. T1 mapping was performed in these patients[31]. Mean extracellular volume (ECV) value is an objective quantitative measurement of myocardial fibrosis of the left ventricle, and was calculated by using both the T1 native and the T1 post contrast map[27]. In multilevel analysis, myocardial segments showing this linear LGE (10 vs 262) indeed showed higher ECV values (p=0.01), received a higher radiation dose (p=0.03) and these patients had higher hs-TNT (p=0.03) values.

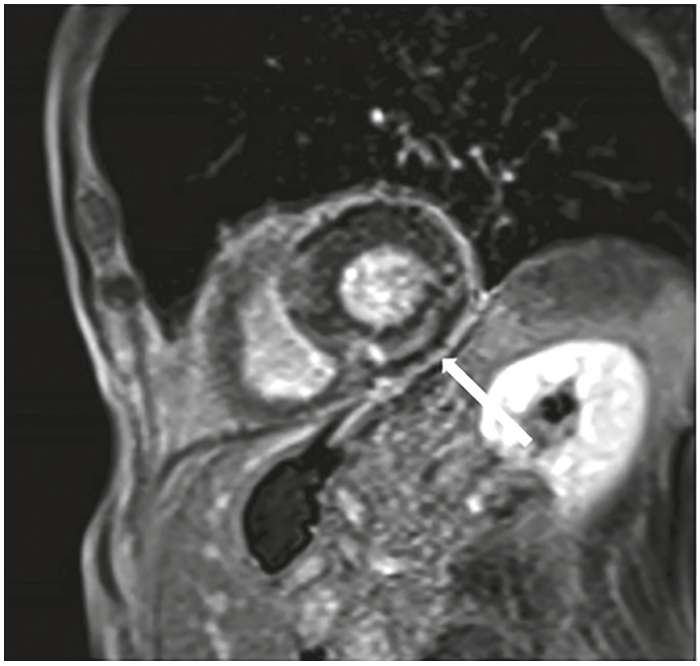

Figure 1 linear late gadolineum enhancement, a sign of non ischaemic fibrosis

As the prevalence of atrial fibrillation (AF) was higher among nCRT patients compared to the surgery alone group (6 vs. 2, p=0.07), we performed additional analyses in order to unravel the possible mechanisms behind this complication and its consequences for physical functioning (Table 4).

Table 4 differentiating factors in patients with or without (a history) of atrial fibrillation**

	AF (n=8)	no AF (n=32)	p value	Age corrected p value
Mean RT dose right atrium(Gy)	18.4 (4.5)	9.7 (2.3)	0.09	0.05
Mean RT dose left atrium(Gy)	26.3 (5.8)	13.0 (2.9)	0.05	0.02
Mean RT dose right ventricle(Gy)	21.1 (4.7)	10.9 (2.3)	0.07	0.03
Mean RT dose left ventricle(Gy)	11.9 (3.0)	7.8 (1.7)	ns	ns
Left ventricular ejection fraction(%)	51.5 (5.8)	59.4 (1.4)	ns	0.04
Right ventricular ejection fraction(%)	46.0 (4.5)	50.7 (1.1)	0.13	0.13
6-minute walking test (%predicted)	64.8 (6.2)	74.7 (2.6)	0.10	
Global health(EORTC QLQ-C30)	62.5 (5.2)	73.4 (2.0)	0.03	0.03
Physical functioning(EORTC QLQ-C30)	84.4 (3.1)	89.7 (1.8)	0.18	ns
Dyspnoea total(QLQ LC-13)	1.8 (0.3)	1.4 (0.1)	0.07	0.08
NT pro BNP(ng/L)	852.9 (260.8)	169 (32.8)	0.01	0.01
HS TNT(ng/L)	15.8 (4.1)	11.4 (1.0)	0.16	0.17
Mean ECV(%)	27.9 (0.8)	26.1 (0.5)	0.13	0.11
Log. regression analyses predicting AF	regression coefficient		p value	AUC
Left atrium volume index(LAVI ml/m2)	0.08		0.1	0.65
Mean left atrium dose(Gy)	0.05		0.06	0.69
LAVI/left atrium dose*	0.11/0.11		0.02/0.02	0.93

*Multivariate analysis with corresponding regression coefficients and p values per predicting item
** standard error of the mean between brackets

Patients with AF received markedly higher radiation doses to the heart, especially to the atria. This was not only seen in the entire group investigated but also when the analysis was restricted to the irradiated patient group. However, in this analysis, it did not become statistically significant in most substructures of the heart (supplement 2).

AF has hemodynamic consequences which resulted in lower ejection fractions and higher NT pro BNP levels. Additionally, AF patients performed worse on the 6-minutes walking test (64.6 vs. 74.7% of predicted, p=0.10). The most common cause of AF in the general population is hypertension and atrial dilatation (LAVI). In this study, a borderline significant association was found between LAVI and AF (p=0.10). However, when combining this factor with a radiation dose parameter in the multivariate regression analyses, both parameters became statistically significant (p=0.02) with a high AUC (0.93).

Discussion

The aim of this hypothesis-generating pilot study was to identify late subclinical cardiac toxicity after nCRT for esophageal cancer. An overview of these results is visualized in Figure 2. The results suggest an effect on myocardial fibrosis and an increased rate of AF. In this small population of patients treated with nCRT followed by surgery, the prevalence of AF was higher than after surgery alone (p=0.07 (corrected for age)). These findings are in line with those from several previous reports, showing an increased incidence of AF after thoracic irradiation [13,32–34].

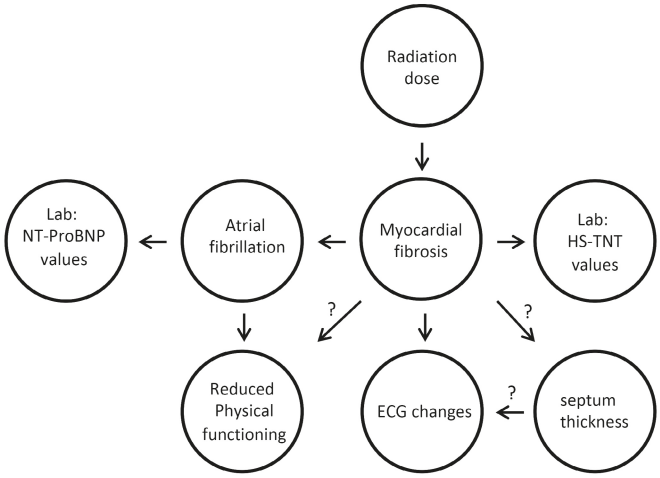

Figure 2 Overview of relevant findings

There might be a causal relationship between myocardial fibrosis and the development of AF. Most patients who develop AF have fibrosis in the atrial wall (e.g. as a consequence of hypertension, valvular disease and atrial dilatation[35]). When looking at the patient group with AF in the current study, a relatively high radiation dose was given to the atria because of its close proximity to the target volume. Given the linear dose response relationship with fibrosis that we found in the left ventricular myocardial wall [31], it is likely that the atrial walls developed fibrosis as well. These findings are supported by preclinical studies, in which fibrosis was associated with decreased end diastolic diameter of the irradiated atria [36]. Unfortunately, ECV cannot be measured in an atrial wall since the walls are too thin. Although both mechanisms (wide atria as measured by LAVI and radiation dose to the atria) were only related to AF with borderline significance in this population, we evaluated these variables both in a multivariate analysis and found that they became statistically significant with high discriminating power (AUC 0.93). These

findings suggest that myocardial fibrosis as induced by radiotherapy is a second mechanism in the development of AF in this irradiated population.

Other investigators suggested that inflammatory reactions may also lead to AF [36].Indeed, if the interval between treatment and onset of the arrhythmia is short, local inflammation due to nCRT eventually leading to fibrosis could be one of the mechanisms. However, in this cross-sectional study with assessments of cardiac abnormalities 5 to 10 years after treatment this question remains unanswered.

Development of AF is a clinically relevant adverse event. Patients with AF are at higher risk of developing a stroke. Moreover, AF may cause or enhance heart failure and patients require hospitalization more frequently. Moreover, AF patients have worse overall survival rates [37,38].

In the current study, we were not able to identify cardiac systolic or diastolic dysfunction secondary to myocardial fibrosis based on ultrasound measurements. This could be explained by the small sample size and the fact that many of the echocardiographic parameters were not assessable because of poor acoustic windows. Therefore, we were not able to analyse sufficient parameters for an adequate diastolic function assessment nor to perform strain imaging. Another reason could be the selection bias as we only included long term survivors.

Surprisingly, we did not find a difference in coronary calcifications as measured by the CAC-score between the two treatment groups. In this study population, known prognostic factors such as hypertension, age and diabetes were associated with higher calcium scores. Nor did we find any relationship between radiation dose and CAC score. This might also be explained by the small sample size and the fact that we analysed long-term survivors, whereas patients with cardiovascular risk factors might have experienced cardiac complications and mortality sooner after treatment[34]. In addition, most coronary arteries are located in lower dose regions as opposed to the radiation dose in e.g., breast cancer patients. Therefore, coronary problems might be less important in this patient group.

In the current study, the relaxation time after ventricle contraction (QTc interval) and the width of the QRS complex were significantly shorter in the irradiated group (table 2). We did not find a good explanation for the changes in QTc time. This can be caused by differences in heart rate, prior infarctions, or the use of cardiac medication. The shorter QRS complex can, however, be caused by myocardial fibrosis (ECV values) as detected on MRI as described earlier in a large, otherwise

healthy, study population[39]. In this paper, both shorter QRS complexes and lower voltages were seen in linear correlation with age and ECV values(supplementary 3). In addition to the shorter QRS complex we indeed found a microvoltage ECG in 2 (vs 0) of the irradiated patients. Our results are therefore in line with these findings. Lower voltages ECG's can be caused by, for example, pericardial effusion, pericardial fibrosis and by an infiltrating cardiomyopathy[40], which are known complications after irradiation of the heart[41,42]. The thinner septum between the ventricles may actually also be in line with these findings as thinner myocardial walls(fibrosis) may result in lower voltage ECG's. These findings could be relevant as prognosis in otherwise healthy adults with low voltage ECG's is worse[43]

We did correct for age difference between the groups in these analyses because age has been well recognized as a prognostic factor for cardiac comorbidities. We realized there was a difference in interval after treatment as well. Theoretically, this may influence the number of cardiac events, but this did not seem to change significance levels and therefore did not have an effect in this population.

It should be stressed that this was a relatively small cross sectional hypothesis-generating pilot study and therefore neither definitive conclusions nor causality based on these results can be drawn. Furthermore, while the patients group of this study were treated using 3-dimensional radiotherapy, current techniques such as IMRT or proton therapy have reduced the dose to critical organs such as the heart, and thus, in future studies, lower toxicity rates would be expected. However, the clinical diagnosis of AF and ECG changes of the heart, as described in the current study, can be related to radiation dose dependent myocardial fibrosis as seen on MRI. These clinically relevant findings can provide further insight into the mechanisms behind radiation induced cardiac complications, which need to be further explored. More information is needed on consequent clinical symptoms and cardiac dysfunction in order to estimate the possible benefit of primary and secondary preventive measures.

In conclusion we hypothesize that in EC patients, radiation-induced myocardial fibrosis plays a central role in cardiac toxicity leading to AF, conduction changes and ultimately to decreased role functioning. The results emphasize the need to verify these findings in larger cohorts of patients.

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CHAPTER 7

Blood biomarkers for cardiac damage during and after radiotherapy for esophageal cancer: a prospective cohort study

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Published in Radiotherapy and Oncology 2024 Volume 200

Abstract

Purpose: The aim of this study was to test the hypothesis that the levels of High Sensitive Troponin T (HS-TNT) and N-terminal Brain Natriuretic Peptide (NT-ProBNP) increase after radiation therapy in a dose dependent way and are predictive for clinical cardiac events.

Materials and Methods: Blood samples during and after radiotherapy of 87 esophageal cancer patients were analyzed regarding the course of HS-TNT and NT-ProBNP levels and their relationship with clinical toxicity endpoints and radiation dose volume parameters.

Results: HS-TNT values at the end of treatment correlated with the mean heart dose ($p=0.02$), whereas the rise of NT-ProBNP correlated with the mean lung dose ($p=0.01$). Furthermore, the course of both HS-TNT ($p<0.001$) and NT-ProBNP ($p<0.01$) levels were significantly different for patients who developed new cardiac events as opposed to those without new cardiac events.

Conclusion: Significant correlations were found for both biomarkers with radiation dose and clinical toxicity endpoints after treatment. Therefore, these markers might be of additional value in NTCP models for cardiac events and might help us unravelling the mechanisms behind these toxicity endpoints.

Introduction

The relevance of radiation-induced cardiopulmonary toxicity has been acknowledged for years. Numerous studies have shown a relationship between either radiation technique or dose and cardiopulmonary toxicity and overall survival [1–4]. However, the exact mechanisms and course of radiation-induced tissue damage remain to be determined [5–7].

Cardiac biomarkers serve as an easy and fast screening method for the diagnosis of heart diseases. Elevated troponins, like High Sensitive Troponin T (HS-TNT) are considered biomarkers for myocardial necrosis and are established prognostic factors for heart failure and overall survival [8,9]. In addition, N-terminal Brain Natriuretic Peptide (NT-ProBNP) is considered an early biomarker for heart failure and is a prognostic factor for cardiac events and overall survival [10–12] . These biomarkers have been studied extensively in oncologic patients receiving chemotherapy. HS-TNT levels are higher after cardiotoxic chemotherapy, like Adriamycin and HER-2 Neu inhibitors[13], while elevated HS-TNT levels are associated with decreased left ventricular (LV) function [14]. Therefore, these biomarkers have been advocated by the European Cardio-Oncology Study Group for its use in risk assessment and diagnosis of cardiovascular disease in cardiotoxic cancer treatments [13]. However, limited data exists on the association between radiation-induced toxicity and these biomarkers. The available literature suggests a role for NT-ProBNP, as it rises after radiotherapy treatment, but a relation with radiation dose was reported in only three out of nine papers [15–23]. A rise in HS-TNT levels after radiotherapy treatment was only reported in two out of these nine papers, while a relation with radiation dose could only be confirmed in one paper [Skytta et al]. However, these 9 studies were relatively small, and in most papers breast cancer patients were included, in which the dose to the heart is relatively low. Furthermore, in some studies, baseline values were missing, or patients were pre-treated with systemic agents. The results of these studies are summarized in Table 1 of the supplementary data.

In esophageal cancer patients, the radiation dose to the heart is relatively high, and patients share common risk factors for cardiovascular diseases. Because of the potential role of cardiac biomarkers in the diagnosis of cardiac injury and its relationship with prognosis in cardiologic literature, we designed this prospective longitudinal study to evaluate whether standard use of these biomarkers could be helpful to evaluate cardiac toxicity during and after intrathoracic radiotherapy.

The aim of this study was therefore, to test the hypothesis that the levels of these biomarkers increase after radiation therapy in a dose dependent way and to test if these biomarkers are predictive for clinical cardiac events .

Materials & Methods

To be eligible for this study, patients had to have histologically proven EC and to be planned for curatively intended neoadjuvant chemoradiotherapy (neoCRT), definitive chemoradiotherapy (dCRT) or radiotherapy (dRT) alone. The study was approved by the local ethical review board (clinicaltrial.gov NCT02481778) and written informed consent was obtained in all patients.

Blood samples were taken before commencing treatment, at the last day of radiotherapy, and during follow up visits at 4 weeks, 6 months, and 1 and 2 years after completion of treatment (Figure 1). HS-TNT and NT-ProBNP concentrations in serum were measured and the results were blinded for the treating physicians to minimize the risk of bias in selecting patients for different treatment options and the scoring of clinical events. Treatment was given according to our institutional standard which are in line with European guidelines [24]. Next to target volumes, the lungs, the heart and its substructures were contoured according to previously published guidelines by Feng et al. [25]. Dosimetric parameters were extracted from the treatment planning system for each patient including maximum, mean and the V-values in 5 Gy bins. All patients were included in our standard follow up program in which details of treatment, (cardiac) comorbidities, use of medication and all cardiopulmonary events are scored according to the common terminology criteria of adverse events (CTCAE) version 5. In addition to clinical visits, patients were contacted by phone by a research nurse to assess the EORTC quality of life questionnaires (LC-13, OES-18, and ACE-27) during follow up. Stable and pre-existing comorbidities were not registered as cardiac events during follow up. Non-tumor related death was analysed as a surrogate for toxicity as the exact cause of death is often not recognized as toxicity.

The primary endpoint was change in NT-ProBNP between baseline and 1 year after treatment, as we want to evaluate whether there is a dose-dependent rise of NT proBNP. Our sample size calculation was therefore based on a 0.9% increase of NT-ProBNP per Gray mean heart dose (MHD). Estimating a 15% standard deviation in NT-ProBNP levels and an expected standard deviation of 7 Gy in MHD, 52 patients were needed at one year (90% power). With a 70% survival at 1 year and a 10% dropout because of poor clinical condition 87 patients were required.

Secondary objectives were to evaluate whether there was an association between HS-TNT and NT-ProBNP levels at different time points (including the course of these biomarkers) and dose to organs at risk (OARs). Furthermore, we evaluated the association of these biomarkers with clinical events, and the association between radiation dose and clinical events (figure 1) .

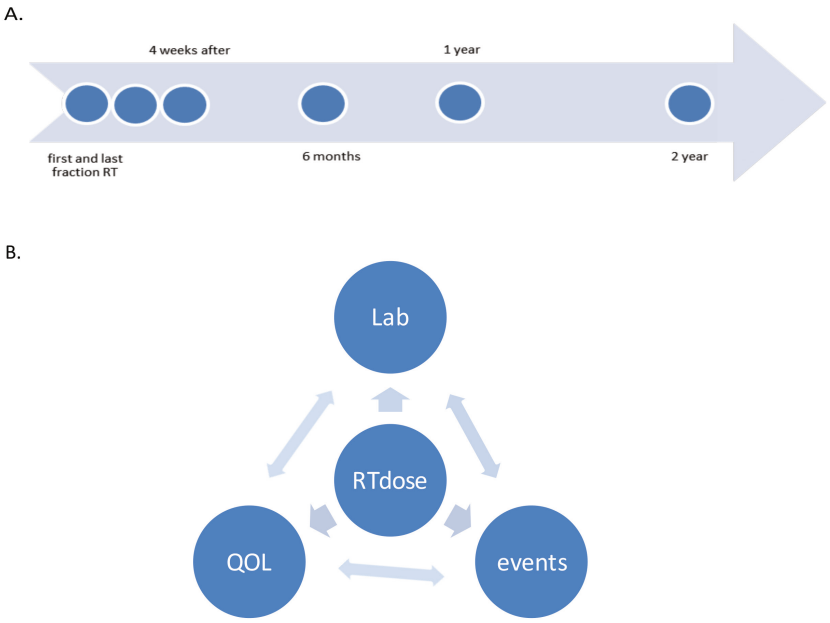


Figure 1: A. Timeline trial and B. Intended analyses.

Analyses at the different time points were performed using logistic or linear regression analyses for binary and continuous endpoints, respectively. Longitudinal analyses analysing associations between subjects within the groups were performed using MANOVA (multivariate analyses of variance) for repeated binary measurements, whereas generalized estimating equation analyses (GEE) were used for the continuous parameters. To compensate for potential confounders, we included other clinical factors reported in literature in the multivariable analysis.

Results

The study population of this prospective cohort study was composed of 87 EC patients, treated with curatively intended nCRT, dCRT or dRT. Nine more patients were included in this study, and replaced, because of missing or incorrect baseline values (n=6), withdrawal informed consent (n=2) or not meeting the eligibility criteria (n=1). Baseline characteristics and treatment details are presented in Table 1.

Table 1 Patient characteristics, treatment characteristics and follow up (n=87)

			Missing
Age(mean)	67.1[87-46]		
Gender	72 males	15 females	
Hypertension(medication indicated)	29 (33%)		
DM	19 (22%)		
COPD	15 (17%)		
Smoking current	30 (34%)		1 (1%)
Past or current smoker	66 (76%)		1 (1%)
Heart attack parents<60 9 (10%)			
Cardiac history			
Cardiac any event history	33 (38%)		
Myocardial infarction (MI)	10 (11%)		
Coronary ischemia (CI)	18 (21%)		
Rhythm disorder	11 (13%)		
Heart failure	1 (1%)		
Valve disorder	3 (3%)		
Treatment			
Chemotherapy	82 (94%)	95% Carbo/Taxol ; 5% 5-FU/Cispl	
Pathology	Adeno 67	SCC 17	Unknown 3
RT dose	44.2	SE 0.57	
Mean lung dose (MLD)	8.28	SE 0.31	
Mean heart dose (MHD)	19.25	SE 0.75	
Surgery performed	51	36	
Events during follow up			
Any new cardiac event*	25 (29%)		
Myocardial infarction	2 (2%)		
Coronary ischemia	5 (6%)		
Rhythm disorder	15 (17%)		
Pleural effusion	14 (16%)		
Pericardial effusion	2 (2%)		

Table 1 Continued.

		Missing
Valvular disease	2 (2%)	
Heart failure	8 (9%)	
Any new pulmonary event	19 (22%)	
Pneumonia	8 (9%)	
Respiratory failure	9 (10%)	
Progressive or new COPD	3 (3%)	
Available lab values at follow up		
Baseline	87 (100%)	
End of treatment	81 (93%)	
4 weeks	79 (91%)	
6 months	65 (75%)	
1 year	49 (56%)	
2 years	33 (38%)	
Reasons for stopping early		
Death, tumor related	26 (30%)	
Death, non-tumor related	14 (16%)	
Stopped because of progressive disease	12 (14%)	
Stopped, other reason	2 (2%)	

* All patients scored with MI were scored having CI as well

Abbreviations: AC: adenocarcinoma, SCC: squamous cell carcinoma, SE: standard error

Mean age was 67.1 years old and 33 out of 87 patients (38%) had a history of cardiac events prior to treatment. The majority, 51 out of 87 patients (59%), underwent surgery after nCRT and only 5 patients were treated with dRT. Patients who underwent surgery were significantly younger (mean 65 vs. 70 years old, $p<0.01$), were less likely to have a cardiac event history (29 vs. 50%, $p=0.05$), but experienced significantly more cardiac complications during follow up (37% vs 17%, $p=0.04$).

At one year, only 49/87 patients were available for analyses. The majority (38/87) of patients stepped out earlier because of tumor progression or tumor related death. Details on follow up data regarding survival, tumor recurrence and on cardiac and pulmonary events are presented in Table 1.

All events occurred during follow up(within 2 years after treatment), but not during treatment. Twenty five patients (29%) developed a new cardiac event, while 19 patients (22%) experienced a new pulmonary event. Significant associations were found between several lung dose parameters and pulmonary events. The lung V5

was the best predictor for pulmonary events. The mean lung V5 in patients with and without a pulmonary event was 55% vs 45%, respectively (p=0.02).

When combining all cardiac events, no significant associations were found between DVH parameters and cardiac events. However, a significant association was found between new rhythm disorders and the mean dose to the left atrium (MLAD). The MLAD was 32.4 Gy among those with new rhythm disorders and 27.5 Gy in those without (p=0.03). Details on associations between radiation dose and events are presented in supplementary data 2.

During treatment and follow up, both serum levels of HS-TNT (p<0.001) and NT-ProBNP (p<0.05) increased as compared to their baseline values. One NT-ProBNP outlier was excluded from the analyses (details in supplementary data 3).

In the longitudinal analyses, the rise of HS-TNT over time was related to several DVH parameters of the heart (e.g., MHD regression coefficient 0.25; p=0.02). When cardiac event history was included as potential confounding factor, even more DVH parameters of the heart became statistically significant and the effect seemed more pronounced, as the regression coefficient increased (e.g., MHD regression coefficient 0.31; p<0.01). Moreover, cardiac history was also significantly associated with the course of HS-TNT in the longitudinal analyses (regression coefficient 8.1, p<0.01)(Table 2A). When looking more specifically at the different timepoints, we found a significant relation for the absolute values of HS-TNT at the end of treatment with several DVH parameter of the heart, including MHD, V25, V30 and V40 heart. Whereas, for relative values compared to baseline, only the V35 heart correlated significantly (regression coefficient 2.49; p=0.03). At later time points, these associations were not statistically significant anymore (Table 2B). The use of substructures of the heart instead of whole heart DVH parameters did not change these results.

The levels NT-ProBNP fluctuated over time in many patients and were not normally distributed. For this reason, we analysed the change of NT-ProBNP compared to baseline at the different time points. In the longitudinal analyses, we did not find any significant associations with cardiac or pulmonary radiation dose parameters. When analysing NT-ProBNP at different timepoints, a significant association was observed with several radiation dose parameters to the lungs (e.g., mean lung dose, p<0.01)) at the end of treatment but not at later time points (Table 2C).

Table 2 Course of lab values(a) and lab values at separate moments (b,c) versus radiation dose

A. HS-TNT course (longitudinal GEE analysis)			
	Univariate analyses HS-TNT	Multivariate analyses HS-TNT	
DVH parameters	Regr.coefficient (β) ; p value	DVH parameters(β; p value)	Cardiac history(β; p value)
V5 heart	0.05; p=0.04	0.07; p<0.01	8.40; p<0.01
V20 heart	NS	0.09; p=0.01	8.57; p<0.01
V25 heart	0.12; p=0.02	0.14; p<0.01	8.37; p<0.01
V30 heart	0.18; p=0.03	0.20; p<0.01	8.31; p<0.01
V35 heart	NS	NS	8.35; p<0.01
V40 heart	NS	NS	8.10; p<0.01
MHD	0.25; p=0.02	0.31; p<0.01	8.49; p<0.01
V5 Lung	NS		
V20 Lung	NS		
MLD	NS		
Cardiac event history	8.1; p<0.01		
Any new cardiac event	NS		

B. HS-TNT at different time moments versus radiation dose parameters								
HS-TNT absolute values	V5 Lung	V20 Lung	MLD	V25 Heart	V30 Heart	V35 heart	V40 Heart	MHD
Baseline	NS	NS	NS	NS	NS	NS	NS	NS
end of treatment	NS	NS	NS	0.17; p=0.01	0.23; p=0.01	NS	0.46; p=0.01	0.34; p=0.02
4 weeks	NS	NS	NS	NS	NS	NS	NS	NS
6 months	NS	NS	NS	NS	NS	NS	NS	NS

1 year	NS	NS	NS	NS	0.48; p=0.02	NS	NS	NS
2 years	NS	NS	NS	NS	0.56; p=0.05	NS	NS	NS
HS-TNT(% to baseline)	V5 Lung	V20 Lung	MLD	V25 Heart	V30 Heart	V35 heart	V40 Heart	MHD
end of treatment	NS	NS	NS	NS	NS	2.49; p=0.03	NS	NS
4 weeks	NS	NS	NS	NS	NS	NS	NS	NS
6 months	NS	NS	NS	NS	NS	NS	NS	NS
1 year	NS	NS	NS	NS	NS	NS	NS	NS
2 years	NS	NS	NS	NS	NS	NS	NS	NS

Correlation coefficients and Significance levels of (the rise) of HS-TNT vs radiation dose parameters

C. NT-ProBNP(% baseline)								
	V5 lung	V20 lung	MLD	V25 Heart	V30 Heart	V35 Heart	V40 Heart	MHD
end of treatment*	4.56; p<0.01	15.06; p<0.01	30.93; p<0.01	NS	3.77; p=0.04	5.45; p=0.04	10.44; p<0.01 *	NS
4 weeks**	NS	NS	NS	NS	NS	NS	NS	-8.20; p=0.05
6 months	NS	NS	NS	NS	NS	NS	NS	NS
1 year	NS	NS	NS	NS	NS	NS	NS	NS
2 years	NS	NS	NS	NS	NS	NS	NS	NS

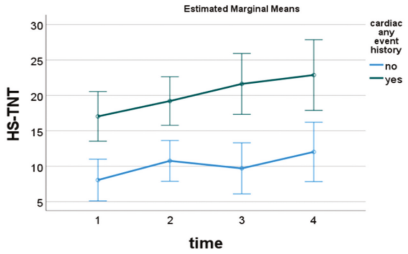
Correlation coeficients and significance levels of the rise of NT proBNP vs radiation dose parameters

* when combining MLD with heart V30, V35 or V40, the heart parameters lose significance

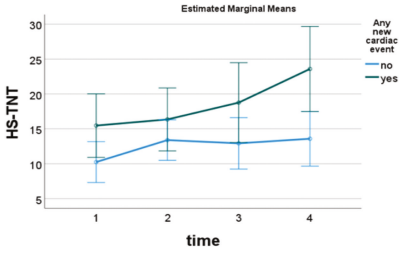
**negative dose response in the mean heart dose (correspondingto the low dose range V values)was not considerd relevant because of low number of patients with these low V values and when correcting for e.g. cervical tumours with low, low dose range heart values it loses significance. results did not change when excluding the outlier of absolute values case number 5

The course of both HS-TNT ($p<0.01$) and NT-ProBNP ($p<0.01$) levels were significantly different for patients with new cardiac events versus for those without (Figures 2B and D). The difference in the course of HS-TNT levels was most pronounced in time frame 3 (between 4 weeks and 6 months after treatment) while a trend was seen in time frame 2 (between end of treatment and 4 weeks). Regarding NT-ProBNP, a significant difference was only found in time frame 3 ($p<0.01$). Patients with a history of cardiac events prior to treatment had significantly higher levels of HS-TNT ($p<0.01$) and NT-ProBNP ($p<0.01$) at baseline, but the overall course of these biomarkers was similar to those observed among patients without a history of cardiac events. Interestingly, patients without a cardiac history showed significantly better recovery of HS-TNT-levels after treatment compared to those with a cardiac event history ($p=0.03$) (Figures 2A and C).

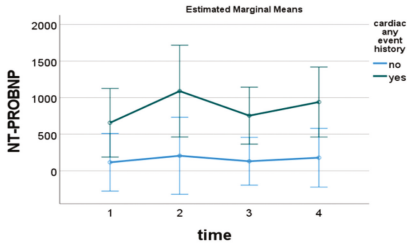
For patients with, or without new pulmonary events, no significant differences in the course of HS-TNT or NT-ProBNP levels were observed. However, there was a trend towards a stronger rise in HS-TNT ($p=0.07$) for patients with new pulmonary events, as compared to those without (Figure 2E and F) .



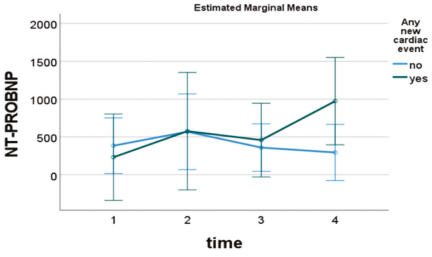
A. HS-TNT course for patients with or without a cardiac event history difference within patients between groups p=0.19, a significant difference is ony seen in time frame 2-3 (p=0.03)



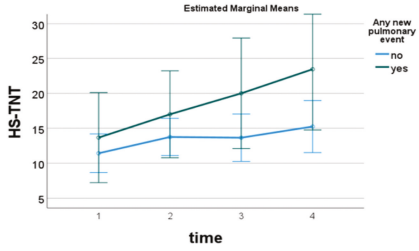
B. HS-TNT course for patients with or without a new cardiac event difference within patients between groups p=0.03



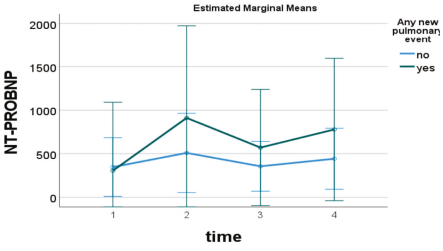
C. NT-PROBNP course for patients with or without a cardiac event history Difference within patients between groups p=NS



D. NT-ProBNP course for patients with or without a new cardiac event Difference within patients between groups p<0.01



E. HS-TNT course for patients wtih or without a new pulmonary event Difference within patients between groups p=0.07



F. Pro BNP course for patients with or without a new pulmonary event Difference within patients between groups p=NS

Time 1=baseline, time 2= end of treatment, time 3= 4 weeks after treatment, time 4= 6 months after treatment. Errorbars of 95 % CI between groups

Figures 2 MANOVA analyses on biomarkers vs toxicty endpoints

In the MANOVA analysis, patients that died from cardiopulmonary or unknown causes (n=11), as a surrogate for grade 5 toxicity, showed a significantly different rise of both HS-TNT (p=0.03) as well as NT-proBNP (p=0.01), as compared to patient who did not die or died of other known causes. Regarding HS-TNT, this difference was predominantly seen in the first 4 weeks after treatment (time frame 2), while for NT-ProBNP this difference was seen in time frame 1 (p<0.01, during treatment) and timeframe 3 (p<0.01, 4 weeks-6 months after treatment). As five of these 11 patients died within 6 months after treatment, the number patients left is too small to draw firm conclusions (more details in supplementary 4).

We did not find any significant associations between the QOL endpoints and changes of lab values, clinical events or DVH parameters.

Discussion

The aim of this study was to test the hypothesis that the levels of NT-proBNP and HS-TNT increase after radiation therapy as a function of radiation dose. To evaluate whether these biomarkers can be helpful to detect cardiopulmonary toxicity, associations between these biomarkers and cardiac events and/or death were evaluated as well.The results suggest that both HS-TNT and NT-ProBNP are associated with the development of cardiopulmonary events, as the rise of both biomarkers after treatment was related to non-tumor related death as well as to new cardiac events. However, whether these markers can be used for early detection of cardiopulmonary toxicity remains to be determined. The rise of these markers during treatment was not significantly associated with these events, nor with non-tumor related death at later time points. Given the limited number of patients available at follow up and the trends seen in the longitudinal analyses, it is worthwhile to perform larger studies to gain more insight in the relationship between different factors and events.

Different mechanism may be responsible for changes over time in the cardiac blood biomarkers. First, the rise of HS-TNT over time was significantly associated with cardiac radiation dose, suggesting direct radiation-induced cardiac damage. Secondly, NT-ProBNP was related to radiation dose to the lungs suggesting indirect mechanisms affecting the heart. Preclinical data showed that radiation exposure to the lungs resulted in higher vascular resistance in the lungs, which increased the pressure in the entire cardiovascular system [26,27]. This is supported by the fact that NT-ProBNP is a known marker for cardiac failure, which may also result from increased vascular resistance in the lungs and pulmonary hypertension. At later time frames, the rise of these biomarkers was associated with clinical cardiac events.

Unfortunately, the overall survival of our study population was worse than expected and thus the number of patients left at 12 months after treatment was too low for proper analyses. Consequently, we focused on the analysis up to 6 months after treatment. Furthermore, this dataset was not sufficiently powered to correct for multiple confounding factors, like whether or not an esophagectomy was performed after neoCRT. As mentioned in the results section, patients who

underwent nCRT followed by an esophagectomy, had better overall survival, and higher (post-operative) complication rates. Although we can't perform these subgroup analyses, this suggest surgery plays an important role in toxicity rates within this patient group. Regarding the effect of chemotherapy, the vast majority, 94% of the patients, was treated with a combination therapy and although we know chemotherapy is potentially cardiotoxic[28], we can't draw any conclusions on the role that chemotherapy played in the toxicity rates. Furthermore, for the same reasons, we were also not able to correct for known risk factors for cardiac events, like hypertension, diabetes, and age. Nonetheless, worse recovery of HS-TNT was seen amongst patients with cardiac event history at baseline. Moreover, cardiac event history was found to be a confounding factor in the multivariable longitudinal analysis of the rise of HS-TNT, which impacted the radiation dose response effect. Both findings are in line with the papers of e.g. Banfill, Wang and Atkins et al [2,5,29]. They found a significant dose effect relationship for cardiac death in patients with a cardiac event history as opposed to patients without a cardiac event history. This may be explained by worse recovery of myocardial tissue damage after thoracic irradiation for patients with a cardiac event history.

In this paper we did not find significant associations between DVH parameters and the combined cardiac toxicities instead of the (too low number of) separate events. Clearly these toxicities originate from different biological mechanisms, which may relate different to the radiation dose distribution to (subregions of) the heart. So for future studies, combining toxicities as an endpoint in NTCP modelling is therefore not a solution for low numbers of the separate events.

There are several reasons for the fact that we found significant correlations between cardiac blood biomarkers with radiotherapy dose parameters as well as with clinical events, while others did not [15–23](Supplementary data, Table1). First, our baseline values were not affected by prior chemotherapy. Second, as compared to breast cancer patients treated with radiotherapy, more cardiac damage can be expected in esophageal cancer patients because of the higher radiation dose to the heart and lungs, as they are in close proximity to the tumor. Furthermore, we were able to perform longitudinal analyses for radiotherapy dose effects linked to clinical events during follow up.

Blood biomarkers can be an important tool, not only for baseline risk assessment and decision-making on preventive measures, but also to select patients for multimodality treatment and/or radiation technique (e.g., proton therapy). Additional studies are warranted to explore the added value of cardiac blood biomarkers on a

routine basis. These kinds of observational studies might improve our knowledge on the mechanisms and development of cardiopulmonary toxicities. The latter is becoming increasingly relevant as several papers suggested worse overall survival with higher radiation dose exposure to the heart, which is not only related to cardiac events but also to haematological toxicities[30,31]

In summary, rises in HS-TNT and NT-ProBNP levels at the end of radiotherapy for esophageal cancer were associated with radiation dose parameters to heart and lungs, and at later time points to clinical cardiac events after treatment. Therefore, these biomarkers may help us to further unravel the mechanisms of cardiac toxicity after thoracic radiotherapy and to identify patients at risk for cardiopulmonary events.

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CHAPTER 8

Summarized discussion and future perspectives.

Summarized discussion and future perspectives

The aim of this thesis was to get more knowledge on the relevance and mechanisms of cardiac toxicity in the treatment of esophageal cancer (EC). Hopefully, this work will contribute improving radiotherapy treatment planning by enabling educated trade-offs between heart and lungs doses.

This thesis includes a review of the available literature and reports on the results of three clinical trials.

Chapter 2 contains an overview of the literature at that time (2015) reporting on incidences and the spectrum of cardiac toxicities seen after (chemo)radiotherapy with or without surgery. These papers reported relatively high incidences of cardiac toxicities. In most papers, a relation with radiation dose volume parameters of the heart was found using different cut of values. However, at that time, no normal tissue complication probability (NTCP) models were published. These results, as well as more recent papers are incorporated in the discussion hereafter [1].

In chapter 4, we report on the results of a retrospective analyses on 216 patients treated with chemoradiotherapy for EC. Cardiac dose volume parameters predicted the risk on pericardial effusion, whereas pulmonary dose volume parameters predicted the risk of radiation pneumonitis. Overall survival was significantly worse for patients presenting with a radiation-induced pneumonitis ($p=0.01$). Patients developing pericardial effusion, had similar overall survival as compared to patients who did not develop pericardial effusion. In the multivariable prediction model for overall survival, lung dose volume parameters remained significant next to tumour stage, in contrast to cardiac dose volume parameters. These results suggest that reducing the cardiac dose at the expense of the lungs might not always be a good idea [2].

In chapter 5 and 6, we focussed on late toxicity in EC survivors after multimodality treatment. In this cross-sectional (CROSS SECT) study, we evaluated clinical and subclinical damage of the heart in twenty patients treated with surgery alone, as compared to twenty patients who were treated with neoadjuvant chemoradiation followed by surgery .

In chapter 5 we investigated the association between radiation dose and myocardial fibrosis as measured by the extracellular volume (ECV) on cardiac MRI. These ECV values are considered a surrogate for histologic collagen burden in the myocardium.

We found a linear dose response relationship between mean radiation dose to the segments of the left ventricle and their ECV values. These results suggest that (co) irradiation of the heart causes direct damage to the myocardium [3].

In chapter 6 we compared the same two groups of patients and evaluated the combined results of CT, MRI, quality of life (QoL) questionnaires, blood biomarkers for cardiac damage and echocardiography. In this pilot study, we hypothesized that myocardial fibrosis plays a central role in cardiac toxicity leading to atrial fibrillation, conduction changes and decreased role functioning. Due to the limited number of patients however, these results need to be verified in a larger preferably prospective cohort study. Results are further explored in the discussion section hereafter [4].

Chapter 7 reports on the results of a prospective longitudinal study monitoring cardiac blood biomarkers during and after (neoadjuvant) (chemo)radiotherapy for EC. In this study, an association was found between the rise of these biomarkers during treatment and radiation dose parameters to the heart and lungs. During follow up, these markers were mainly associated with clinical events and overall survival, but no significant relationships were found with radiation dose distribution parameters. We feel however that these biomarkers can further help unravelling mechanisms behind cardiac toxicity in future clinical trials. In the meanwhile, they have been incorporated in some clinical trials [5].

In this summarizing chapter, a number of subjects will be further explored in more detail.

Incidence of cardiac toxicity

Our literature review on radiation-induced cardiac toxicity in the treatment of oesophageal cancer (EC) revealed crude incidence rates as high as 5-44%[6]. However, the available literature mainly consists of retrospective studies from Asian countries. Prescribed doses were relatively high, and the radiation techniques used were outdated compared to what is considered current standard. For these reasons, toxicity rates may be lower nowadays. Moreover, retrospective studies are often hampered by incomplete follow up data and publication bias, which may cause underreporting of cardiac events.

Randomized controlled trials (RCT's) investigating neoadjuvant chemoradiation followed by surgery versus surgery alone did not report higher cardiac toxicity rates in the neoadjuvant CRT (nCRT) arm as compared to these observed in the surgery alone arm [7]. Although these trials were not powered for detecting differences in cardiac toxicity, the question arises whether cardiac events are really caused by chemoradiation. However, causality with radiotherapy becomes more likely in case of a significant relationship between radiation dose to the heart and cardiac events.

There is general consensus that determining the true incidence of radiation-induced cardiac toxicity remains difficult from retrospective studies as cardiac events occur rather frequently in this older population with cardiac risk factors. One would preferably need larger randomized trials or meta analyses "powered" to evaluate toxicity rates. This requires strict follow up and maybe even routine consultations of the cardiologist before and after treatment. An alternative, because of the selection bias in randomised trials, is probably using standardized follow up data and compare this with a non-irradiated EC patient group.

The different cardiac syndromes

The most common reported cardiac toxicities are pericardial effusion, atrial fibrillation and ischemic events.

Pericardial Effusion(PE):
In the third chapter we developed an NTCP model for pericardial effusion. We found a significant dose response relationship between the mean heart dose (MHD) and pericardial effusion (PE) with an odds ratio of 1.09 per Gray. This is in line with other papers published in the literature on PE in EC patients.

PE is an objective endpoint but often asymptomatic and thus, the reported incidences are highly dependent on the amount of routine CT scans or echocardiography's performed during follow up. In most papers reporting on PE, as well as in our own study, the prescribed target dose was relatively high and patients were treated with relatively outdated techniques. In our population, the MHD was 26.4 [13.3-37.5] Gy resulting in 69 patients (32%) with PE during follow up. Nowadays, the prescribed dose is lower, and constraints on the heart dose are generally more strict [8,9]. This is most likely the reason that lower incidence rates are reported in recent clinical trials [7,10,11].

Haddad et al reported on the clinical consequences of pericardial effusion during follow up and outcome of oncologic patients with pericardial effusion as seen on echocardiography. Thirteen percent of patients with PE (217/1645) were symptomatic and needed drainage. The majority (98%) of the patients were drained percutaneously (212/217) with a 99% success rate and low (2%) (serious) complication rate requiring extra interventions. It should be noted however, that out of the patients who were drained percutaneously, only 33 patients (16%) were treated with mediastinal radiotherapy less than one year before presentation. Overall survival of these patients was not significantly different from patients not treated with prior radiotherapy [12].

In summary, at present, symptomatic PE is a rare complication and when it occurs, the majority of the patients doesn't need treatment. Treatment of pericardial effusion itself is relatively safe and effective.

Atrial fibrillation(AF)
Atrial fibrillation is another well-known complication after multimodality treatment for EC cancer[1,13]. In the paper of Cai et all, AF accounted for 24% (22/91) of all

cardiac complications after CRT for EC[11]. On the other hand, AF is quite common in the elderly population and is frequently seen in the perioperative period after intrathoracic surgery, which is relevant to mention as most patients are treated with CRT in the neo-adjuvant setting [14].

In our retrospective study (chapter 3), the number of patients with newly diagnosed AF (N=8 (4%)) was relatively low and consequently insufficient for reliable modelling procedures.

In our cross-sectional study (Chapter 4), we found a difference in the onset of AF between the irradiated patient group and the non-irradiated surgical group who were on average older and thus we expected a higher AF rate after surgery alone. However, the opposite was found, with six patients diagnosed with AF in the nCRT versus two patients in the surgery alone group. Although the numbers are very small, we tried to look further into the mechanisms behind this toxicity as the study was designed as an hypothesis generating pilot study. Radiation dose to the left atrium was associated with a new onset of AF when corrected for age. In this study, we performed several imaging techniques, which enabled us to correct for other possible confounders, such as a wide atrium (left atrial volume index(LAVI)), another well-known risk factor for the development for AF in the general population. In the univariate analysis, both mean left atrium dose and LAVI showed borderline significant association with AF. However, when LAVI and radiation dose to the left atrium were combined in a multivariable model, both parameters were significantly associated with AF, and the model showed a high discriminative power with a high area under the curve (AUC 0.93). These findings suggest that clinical and baseline risk factors are important confounders that may affect toxicity endpoints and its relationship with radiation dose distributions.

Our results are in line with those found by Song et al, who reported on 677 oesophageal cancer patients who underwent surgery after neoadjuvant CRT and tried to find risk factors for new onset AF [15]. In the multivariate analysis, only higher age ($p<0.00$) and higher prescribed radiation dose ($p=0.03$) remained significant. However, in this study, radiation exposure to the heart itself was not considered.

Regarding the association between radiation dose to (substructures) of the heart and the onset of AF, only two papers have been published so far. The first study was performed in lung cancer patients [16], and reported the maximum dose in the sinoatrial (SA) node located in the right atrium to have the best association with the onset of AF.

In the second, more recent paper including oesophageal cancer patients, Cai et al. performed an analysis on risk factors for the arrhythmic patients (n=29) and found in multivariable analyses, next to the cardiac history, the LA V50 to be the best dosimetric parameter for arrhythmic events (HR 1.02, 95%CI [1.01-1.04])[18]. This means that the increase in volume (in %) of the left atrium receiving a dose of more than 50 Gy increases the risk on AF with 2%).

The SA node is the so-called pacemaker regulating the heart frequency by the sympathetic and parasympathetic nervous system, the AV node seems even more important in the regulation of the heartbeat by delaying the electric impulses to the ventricles. It should be noted that information on the pathophysiology of AF in the general population is still unknown. The most quoted theory is that impulses from the SA node are overwhelmed by electric impulses originating from other parts of the atria. Fibrosis of the atrial walls seems to play a central role in the development of atrial fibrillation. Given the relatively high dose applied to the atria and the linear dose response relationship of the development of fibrosis as described in chapter 5, radiation-induced local fibrosis of the atria could play a role in the development of AF in these patients.

In addition, local inflammatory reactions and ectopic foci are mentioned as possible factors for radiation-induced AF in cardiologic literature as well. For that reason, different parts of the atria might be susceptible for radiation-induced toxicity resulting in increased rates of atrial fibrillation [17–20].

These two papers reporting on the association of dose with substructures of the heart, suggest that the increased rate of AF is probably a local effect of the given radiation dose somewhere in the atria. The difference found in the paper including lung cancer patients [Song] as compared to the paper including oesophageal cancer patients, could be explained by the differences in dose distributions of lung cancer as compared to oesophageal cancer patients, as noted before. The oesophagus is located next to the left atrium (delineated in red, figure 1), whereas lungs are located next to the right atrium (delineated orange, figure 1).

In order to be able to optimize radiation dose distributions, it becomes increasingly important to identify subregions within the heart that are most susceptible for radiation. Especially with more advanced techniques, like proton therapy, dose to specific cardiac regions, like the right atrium in oesophageal cancer patients can be avoided, whereas decreasing the mean dose to the left atrium remains challenging (Figure 1). Reduction of set up margins around the clinical target volume using daily

adaptive treatments as well as a reduction of the clinical target volume itself are probably better options to reduce the radiation dose to the left atrium.

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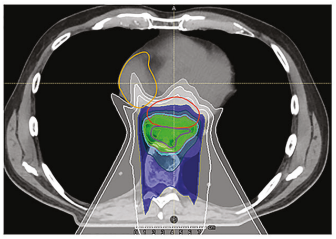

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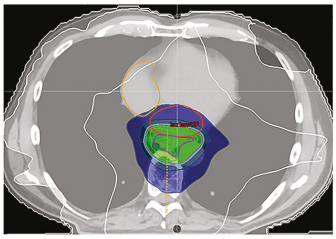

	Photons	Protons
MHD	17.0 Gy	7.5 Gy
Left atrium (mean dose)	29.2 Gy	25.1 Gy
Right atrium (mean dose)	14.5 Gy	4.7 Gy
Left Atrium V40 (%)	17.5%	21.4%
Right atrium V40 (%)	0.4%	0.5%

Plan comparison between a proton(A) and a photon dose(B) distribution. Differences between MHD are much bigger then seen in the mean dose in the left atrium (red), therefore the risk reduction on atrial fibrillation is not expected to be large using this newer technique

Figure 1, dose distribution of an esophageal cancer patient comparing a proton and a photon dose distribution and its relation to the dose of the atria

It is worthwhile to prevent AF, as AF is a clinically relevant adverse event. Patients with AF are at a higher risk of developing stroke and generally need anticoagulants. Moreover, AF may cause or enhance heart failure, and patients require hospitalization more frequently and have worse overall survival rates [21].

In summary, AF is a frequently occurring complication after chemoradiotherapy (and surgical resection) for EC. AF is most likely related to the radiation dose to the atria which causes fibrosis. Due to the close proximity of the oesophagus to the atria of the heart it is unlikely that treatment plan modification by newer radiotherapy techniques will reduce the risk of AF. Therefore, these new technologies should be combined with margin reduction, in order to reduce the risk of AF.

Ischaemic events

Although ischemic events have been reported after (c)RT for EC, it is not a frequently occurring complication in the studies performed in this thesis. However, myocardial infarction might be underreported because of the risk of sudden death and therefore might not have been recognized as a coronary event.

In our retrospective cohort, we only found 4 patients (2%) presenting with a myocardial infarction, whereas, in the CROSS SECT study, we did not find a

difference in coronary calcifications either. The number of coronary calcifications (CAC scores), which is a known predictor for cardiovascular events, was similar in the irradiated patient group as compared to the patients treated with surgery as single treatment modality. Moreover, we did not find a relationship between CAC scores and radiation dose volume parameters of the (subregions) of the heart. A major limitation of this study was its cross-sectional study design. First, we did not have reliable information on baseline CAC scores. Second, as we only analysed EC survivors, patients with cardiovascular risk factors, with consequently higher CAC scores, might have died sooner after treatment. Moreover, irradiated patients were treated with the CROSS regimen, with a relatively low prescribed dose of 41.4 Gy.

However, in a more recent paper by Cai et al, the authors reported that 19% of the cardiac complications after definitive CRT for EC were attributed to ischemic events [11]. In a larger population (n=716 patients), combining their data with another institute, they analysed risk factors for the combined endpoint coronary events and heart failure. In this analysis they found that multivariable prediction models including the dose to coronary arteries instead of the dose to the heart performed significantly better with a higher AUC [22]. This is in line with the results obtained in studies on breast cancer in which the dose to the left ventricle (next to the LAD) and dose to the LAD were better predictors for ischaemic coronary events, than the mean dose to the heart [23].

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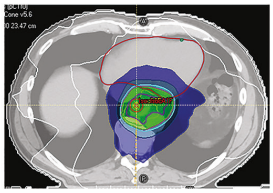
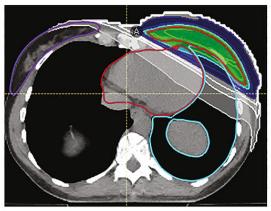


organ	Esophagus	Breast
Mean Heart Dose (MHD)	17.0 Gy	2.5 Gy
Left atrium (mean dose)	29.2 Gy	1.1 Gy
LAD	9.9 Gy	16.5 Gy

B



Plan comparison between an esophageal cancer photon dose distribution(A) and a breast cancer photon dose distribution(B)
Although the mean dose to the heart is relatively low in breast cancer patients, the mean dose to the left coronary artery (in red) is much higher.
In esophageal cancer patients the distance of the LAD (in green) to the target volume is larger. The radiation dose given at the coronaries in these treatment plans is lower as compared to the breast cancer patients.
This might be an explanation for the different cardiac toxicity profiles of these diseases

Figure 2, dose distribution of an esophageal cancer versus a breast cancer patient and its relation to the dose of the coronary arteries (LAD)

Looking at the dose distributions in oesophageal and breast cancer patients (figure 2), the lower numbers of coronary events in oesophageal cancer patients as compared to breast cancer patients might partly (next to the worse overall survival

in oesophageal cancer patients) be explained by the differences in radiation dose distributions. In breast cancer, the LAD and left ventricle are located close to the target volume, whereas in EC, the distance between the target and these OARs is much larger.

Concluding, although ischaemic events seemed a less frequently occurring complication in oesophageal cancer patients as compared to breast cancer patients, radiation dose to coronary arteries is associated with coronary events in EC patients as well. Therefore, radiation dose can and should be reduced in these subregions of the heart in EC cancer patients.

Other and combined cardiac toxicities

In Chapter 3, we showed that it was not possible to find an association with radiotherapy dose if we combined all types of cardiac toxicities. Clearly different toxicities originate from different biological mechanisms which might relate different to the radiation dose distribution to (subregions of) the heart. Combining toxicities as an endpoint in NTCP modelling is not a solution for low numbers of the separate events. Furthermore, many of the toxicities are related. For example, heart failure can be a consequence of an ischemic event, can be a consequence of pericardial effusion, as well as a valve disorder. The number of these "other" events were, and are in most of the oesophageal cancer papers, insufficient to draw firm conclusions on a dose response relationship.

We tried to look further into heart failure and its mechanisms after radiotherapy for EC cancer. We expected myocardial fibrosis as described in the CROSS-SECT study would be a precursor for heart failure.

However, local fibrosis as seen on imaging studies was not associated with cardiac functional parameters in the papers included in our review. Nor did we find associations with functional parameters indicating for example, left or right sided heart failure versus myocardial fibrosis in our CROSS SECT study.

This can be explained by the limited number of patients included in these imaging studies and our CROSSECT study. An additional comment is that the effects seen, might have been too small to detect (sub)clinical consequences even in larger trials.

Furthermore, we have to realize, that there are more (intrathoracic) critical organs at risk for radiation induced toxicity. In the retrospective study in chapter 3, we found that pulmonary toxicity and radiation dose was more important for overall

survival than cardiac dose and toxicity. Interaction of pulmonary and cardiac toxicity has been shown to be another factor to take into account[24,25]. Furthermore, in more recent literature a correlation was found of different radiation techniques or prescribed dose and the development of lymphopenia in EC patients[26,27]. Lymphopenia is on its turn related to local tumour control as well as overall survival in this patient group [28]. The later could also explain the relatively poor response rates in the chemoradiotherapy arm of the ESOPEC study. We are curiously awaiting on the final paper, in which we hope to get more details on the radiotherapy protocol and the given dose to relevant organs at risk, such as the heart.

Use of substructures in NTCP modelling

In contrast to the past, where the mean heart dose was used in the NTCP modelling, nowadays, cardiac substructures are commonly used in finding associations between cardiac toxicities and dose distributions.

Using these substructures has advantages as shown in papers were associations between radiation dose and cardiac substructures were generally stronger compared to associations with the mean heart dose. This can be explained by the fact that dose distributions in the heart are not homogeneous and that certain subregions of the heart can be more susceptible for certain radiation-induced complications. The highest dose is being given to tissues that are located next to the target volume. The mean dose to the heart is often not representative for the dose to this subregion of the heart which receives the highest dose. In our population of oesophageal cancer patients, the highest mean dose is given to the left atrium, closely followed by the dose to the left ventricle and the right atrium, while the right ventricle received a relatively low dose. Cardiac dose distributions in EC patients are quite different from those in breast cancer patients This, and differences in cardiovascular risk profiles, can explain the difference in cardiac toxicities seen after treating these different thoracic indications for radiotherapy.

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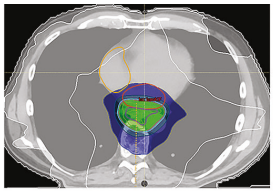

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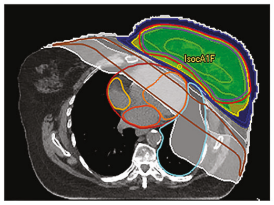

organ	Esophagus	Breast
Mean Heart Dose (MHD)	17.0 Gy	3.1 Gy
Left atrium (mean dose)	29.2 Gy	1.3 Gy
Left ventricle (mean dose)	16.6 Gy	4.4 Gy

Plan comparison between an esophageal photon (A) and a breast cancer photon dose(B) distribution.
Overall radiation dose to the different critical organs of the heart is much higher in esophageal cancer patients.
The MHD does not seem representative for the dose to the left atrium. In esophageal cancer patients it is much higher, in breast cancer patients it is much lower as compared to the MHD
These differences seem bigger using newer techniques like proton therapy.

Figure 3 dose distribution of an esophageal cancer versus a breast cancer patient differences in MHD vs dose in subregions of the heart

Two papers published by Atkins et all and Prunaretti ea. indeed confirmed this. Looking at the mean dose to the heart was not representative for the dose in a specific subregion (figure 3), especially when using more modern techniques [29,30]. This effect is visualized in figure 1 in EC patients, whereas the mean heart dose was about half using a proton therapy plan compared to the photon plan , the dose difference in the left atrium was much smaller

Another advantage of using dose distributions to cardiac substructures instead of the dose distributions to the whole organ is that this will probably give more insight in the possible mechanisms behind these toxicities, which could guide new optimization strategies in preventing these side effects.

However, there are drawbacks in delineating substructures. Some of these substructures are small and more difficult to delineate, leading to an increase in contouring variabilities between centres and physicians and this more uncertainties in interpreting the results of studies on dose-effect relationships. Both may introduce a potential bias in NTCP modelling. Moreover, in smaller organs, it is more likely to have smaller difference in dose distributions within this organ. Especially when located closely to the target volume, it will be difficult to find a dose response relationship but merely an on-off relationship (within or without your target volume) as a toxicity endpoint.

A second drawback is history, as many of the current knowledge and validated models are based on the mean heart dose. Introducing these newer models, using subregions of the heart, will require time, both for generating and validating these new models.

Future perspectives

My thesis focussed on cardiac toxicities. They are relevant as they can influence both overall survival and quality of life in different ways. Moreover, these different toxicities have various relationships with radiation dose distributions. Prioritizing these toxicities, and the associated organs at risk remains a challenging issue.

In EC, the total toxicity burden has been proposed as a composite endpoint of different toxicities and was used in clinical trials[18,19]. This total toxicity burden prioritized different complications and weighted them by their severity. More serious toxicities were assigned higher scores, and eventually were summed up per patient. In the future, this total toxicity burden can be used in clinical trials as an endpoint in evaluating, for example, new technologies.

Another endpoint which is very relevant for individual is quality of life (QOL). QOL could reflect the combined impact of different toxicities in the treatment of EC cancer. Within the CROSS trial, the largest trial randomizing patients between neoadjuvant chemoradiotherapy followed by surgery and surgery only, no significant differences in QOL at different time points during the first year after treatment were found [31]. This was explained by the relatively low prescribed radiation dose in combination with mild chemotherapy, but it should be noted that the authors reported lower compliance rates to the QOL questionnaires in the surgery only group. Poor compliance rates are an important source of bias in QOL studies as both patients having a poor performance as well as patients not suffering any side effects will be less tentative responding on questionnaires. Moreover, QOL scores were not scored during treatment, for example during hospitalization post-surgery or during CRT. In a QOL meta-analysis among patients treated with definitive CRT, baseline values were lower as compared to the standard population. However, these values did not decline during follow up despite a relatively high rate of late toxicities seen after treatment. Taking these findings into consideration, one could question whether QOL scores are a representative method to evaluate radiation-induced complications of EC patients [32].

Finally, the question remains what endpoints should be considered most relevant, both for patients and as endpoint for future clinical trials. Overall survival probably qualifies as it is an objective unbiased endpoint which is most relevant and easy to score. Several recent modelling studies indeed used overall survival as an endpoint and found radiation dose parameters to be a predictor for overall survival in intrathoracic tumours in multivariate analyses [33–36]. Although this suggests

radiation induced cardiac toxicity, it actually does not give any information on the cause of death or whether this is related to cardiac complication.

As all mentioned endpoints have their limitations, another, more sensitive method of detecting differences between treatment groups has been proposed by Song ea. The individual patient wants to live, with a good quality of life and preferably without toxicity. In this method, patients within de different treatment arms are first compared on the most important outcome, when there is no difference, lower priority outcomes are evaluated in these patients [37]. This method will be more sensitive in finding differences between groups as it combines overall survival with QOL and toxicities as a (primary) endpoint.

For further research, I expect both types of research are needed. Studies like used in the current thesis will generate hypotheses on possible mechanisms and dose-effect relationships of toxicities, resulting in which (sub)substructures are most relevant tin radiation-induced toxicity development. This can be used to guide optimizing radiation treatment plans. Whether this eventually results in relevant clinical advantages for patients, needs to be confirmed in either randomised trials or prospective validation cohorts (real life data). Within these “confirming” trials, data on overall survival as well as on QOL and toxicity should be collected. Using multiple endpoints to quantify treatment benefit, like proposed by Song ea. as mentioned before, probably have a higher sensitivity in detecting clinically relevant differences and can be used to evaluate new radiotherapy techniques and treatment plan optimalisation.

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APPENDICES

Inleiding

Jaarlijks worden er in Nederland ongeveer 3000 nieuwe patiënten met slokdarmkanker gediagnosticeerd. Ongeveer 60% van deze patiënten heeft potentieel curabele ziekte en ondergaat veelal neoadjuvante chemoradiotherapie gevolgd door chirurgie of definitieve (chemo)radiotherapie. Hoewel de curatiekansen in het afgelopen decennium zijn verbeterd, blijft de door behandeling veroorzaakte toxiciteit een punt van zorg. De bestralingsvolumes voor slokdarmkankerpatiënten zijn vaak groot en bevinden zich in de buurt van kritieke organen zoals het hart en de longen. Het optimaliseren van dosisverdelingen in de radiotherapiebehandeling vereist goede informatie over de toxiciteit van deze verschillende organen in relatie tot de dosisverdeling van de radiotherapie. Dit is essentieel om hierin een weloverwogen keuze te maken. De relatie tussen de dosis op een kritiek orgaan en het risico op toxiciteit wordt beschreven in een zogenaamd NTCP (Normal Tissue Complication Probability) model. De bestralingsdosis die op een orgaan gegeven wordt is af te lezen in een zogenaamde dosis-volumehistogram (DVH).

Bij de start van dit proefschrift was er weinig gepubliceerd over straling geïnduceerde cardiale toxiciteit bij slokdarmkankerpatiënten. Destijds ging de aandacht voornamelijk uit naar pulmonale toxiciteit en de relatie hiervan met DVH-parameters, maar het sparen van de long gaat vaak ten koste van het hart. Dit leidde bij ons tot de keuze om onze focus te leggen op straling geïnduceerde cardiale toxiciteit.

In Hoofdstuk 2 wordt een overzicht gegeven van de literatuur met betrekking tot de incidentie en het spectrum van cardiale toxiciteit na (chemo)radiotherapie bij slokdarmkankerpatiënten. Deze artikelen meldden een relatief hoge incidentie van (diverse) cardiale problematiek. In de meeste artikelen werd een relatie gevonden met DVH-parameters van het hart, waarbij verschillende drempelwaarden werden gevonden waarboven het risico verhoogd was. Op dat moment waren er echter geen NTCP-modellen beschikbaar die de relatie tussen de dosisverdeling en het risico op cardiale toxiciteit beschreven.

In Hoofdstuk 4 rapporteren we de resultaten van een retrospectieve analyse van 216 patiënten behandeld met chemoradiotherapie voor slokdarmkanker. Het risico op pericardiale effusie werd voorspeld door cardiale DVH-parameters, terwijl pulmonale DVH-parameters het risico op radiatiepneumonitis voorspelden. De algehele overleving was significant slechter voor patiënten met straling geïnduceerde pneumonitis (p=0.01). Patiënten die pericardiale effusie ontwikkelden, hadden dezelfde algehele overleving vergeleken met patiënten zonder pericardiale

effusie. In het multivariabele predictiemodel voor totale overleving waren naast tumorstadium alleen DVH-parameters voor de long significante predictoren. Deze resultaten suggereren dat het verminderen van de dosis op het hart ten koste van de longen niet altijd een goed idee is.

In Hoofdstuk 5 en 6 richtten we ons op late toxiciteit bij overlevenden van slokdarmkanker na multimodale behandeling. In deze cross-sectionele (CROSS SECT) studie vergeleken we klinische en subklinische schade aan het hart bij twintig patiënten behandeld met alleen chirurgie ten opzichte van twintig patiënten behandeld met neoadjuvante chemoradiatie gevolgd door chirurgie.

In Hoofdstuk 5 onderzochten we het verband tussen stralingsdosis en myocardfibrose, aan de hand van het extracellulaire volume (ECV) op een cardiale MRI. Deze ECV-waarden worden beschouwd als een surrogaat voor fibrose in het hartspierweefsel. We vonden een lineaire dosis-responsrelatie tussen de gemiddelde stralingsdosis op de segmenten van de linkerhartkamer en hun ECV-waarden. Deze resultaten suggereren dat bestraling van het hart fibrose van het hartspierweefsel veroorzaakt.

In Hoofdstuk 6 vergeleken we dezelfde twee patiëntengroepen en evalueerden we de gecombineerde resultaten van CT, MRI, kwaliteit van leven (QoL)-vragenlijsten, bloedbiomarkers voor cardiale schade en echocardiografie. In deze pilotstudie concludeerden we dat myocardfibrose mogelijk een centrale rol speelt bij cardiale toxiciteit die kan leiden tot atriumfibrilleren, geleidingsveranderingen en een verminderd functioneren in het dagelijks leven.

Hoofdstuk 7 rapporteert de resultaten van een prospectieve studie waarin cardiale bloedbiomarkers voor, tijdens en na (neoadjuvante) (chemo)radiotherapie voor slokdarmkanker werden gemonitord. In deze studie werd een verband gevonden tussen de stijging van deze biomarkers tijdens de behandeling en DVH-parameters van het hart en de longen. Tijdens de follow-up waren deze markers geassocieerd met het doormaken van hartziekten en met (niet tumor gerelateerde) overleving. Tijdens de follow up werd er geen significant verband gevonden tussen bloedbiomarkers en DVH-parameters.

Hieronder worden een aantal onderwerpen verder uitgewerkt en besproken.

Incidentie

In onze review over door radiotherapie geïnduceerde cardiale toxiciteit bij de behandeling van slokdarmkanker vonden we een cumulatieve incidentie tussen de 5-44%. De beschikbare literatuur bestond echter voornamelijk uit retrospectieve studies uit Aziatische landen. Voorgeschreven doseringen waren hoger dan die wij in Nederland gebruiken en de gebruikte stralingstechnieken waren verouderd in vergelijking met wat momenteel als standaard wordt beschouwd. t Hartziekten komen natuurlijk ook bij niet behandelde mensen regelmatig voor. Om een betere inschatting te kunnen geven van de huidige incidentie van cardiale toxiciteit door behandeling zouden grotere (gerandomiseerde) onderzoeken of meta-analyses “gepowered” moeten zijn om toxiciteitspercentages te evalueren. Een alternatief is het gebruik van gestandaardiseerde follow-upgegevens waarbij de vergelijking wordt gemaakt met een niet-bestraalde patiëntengroep.

Verschillende cardiale syndromen

Pericardiale Effusie (PE):

In hoofdstuk 3 hebben we een NTCP-model ontwikkeld voor pericardiale effusie. We vonden een significante relatie tussen de gemiddelde hartdosis (MHD) en pericardiale effusie met een odds ratio van 1.09 per Gray. De gerapporteerde incidentie van PE is echter sterk afhankelijk van de hoeveelheid routinematige CT-scans en/of echocardiografieën tijdens follow-up. In de recente literatuur is symptomatische PE zeldzaam en, wanneer het zich voordoet, heeft de meerderheid van de patiënten geen behandeling nodig. Behandeling van pericardiale effusie is relatief veilig en effectief en daarmee lijkt het met de huidige bestralingstechnieken een minder relevant probleem te zijn.

Atriumfibrillatie (AF):

AF is een bekende complicatie na multimodale behandeling voor slokdarmkanker. In ons retrospectieve onderzoek (hoofdstuk 3) was het aantal patiënten met nieuw gediagnosticeerde AF relatief laag. In ons cross-sectioneel onderzoek (hoofdstuk 4) vonden we een verschil in het voorkomen van AF tussen de bestraalde groep en de niet-bestraalde chirurgische groep. Het risico op AF nam toe met een toename van de dosis op het linker atrium. Volgens onze hypothese, zoals geformuleerd in dit hoofdstuk, is AF gerelateerd aan de stralingsdosis op het atrium, mogelijk door de ontstane fibrose aldaar. Het bestralingsvolume van slokdarmkankerpatiënten ligt echter vaak vlakbij het atrium van het hart, waardoor het verminderen van de stralingsdosis op het atrium een uitdagend probleem zal blijven.

Ischemische gebeurtenissen(hartinfarct of angina pectoris):
Hoewel ischemische gebeurtenissen zijn gemeld na (chemo)radiotherapie voor slokdarmkanker, is de incidentie in de studies van dit proefschrift laag. Dit zou kunnen komen omdat de kransslagaderen relatief ver verwijderd zijn van de slokdarm en daarmee een wat lagere dosis krijgen dan gedeelten van het hart die dichter bij het doelvolume gelegen zijn. In de literatuur is stralingsdosis op de kransslagaders echter wel geassocieerd met coronaire gebeurtenissen. Daarmee blijft het belangrijk de stralingsdosis op de kransslagaderen van het hart te beperken.

Andere en gecombineerde cardiale toxiciteit:
Het gebruik van een gecombineerd eindpunt in NTCP-modelling, zoals het combineren van alle soorten cardiale toxiciteit, lijkt geen oplossing voor lage aantallen van de afzonderlijke gebeurtenissen. In onze studies konden we geen dosis effect relatie aantonen bij het combineren van de verschillende vormen van toxiciteit. Verschillende syndromen hebben verschillende mechanismen en zijn waarschijnlijk op een andere manier gerelateerd zijn aan de stralingsdosis op (sub regio's van) het hart.

Het kijken naar de sub regio's van het hart
In de laatste jaren wordt, in plaats van de gemiddelde dosis op het hele hart, steeds vaker gebruik gemaakt van dosis op specifieke substructuren van het hart om een verband te vinden met cardiale toxiciteit. Het gebruik van deze substructuren heeft voordelen, zoals blijkt uit artikelen waarin het verband tussen stralingsdosis in cardiale substructuren en cardiale toxiciteit over het algemeen sterker wordt als men kijkt naar de associaties met de gemiddelde hartdosis. Dit kan worden verklaard door het feit dat de dosisverdeling van de radiotherapie in het hart niet homogeen is waarbij de hoogste dosis doorgaans gegeven wordt aan weefsels die zich dichter bij het doelvolume bevinden. Daarmee is de gemiddelde dosis op het hart vaak niet representatief voor de dosis op deze substructuren van het hart. In onze populatie van patiënten met slokdarmkanker was de gemiddelde dosis in het linker atrium het hoogst, gevolgd door de gemiddelde dosis in de linker ventrikel en het rechter atrium, terwijl de dosis in de rechter ventrikel relatief laag bleef. Cardiale dosisverdelingen bij patiënten met slokdarmkanker verschillen aanzienlijk van die bij borstkankerpatiënten . Dit, en de aanwezige verschillen in cardiovasculaire risicoprofielen, kunnen het verschil in cardiale bijwerkingen verklaren die worden gezien na bestralingsbehandeling van de verschillende tumortypen in de thorax

Verwachtingen en doelen voor de toekomst

Dit promotieonderzoek richtte zich op de verschillende vormen van cardiale toxiciteit. Ze zijn allemaal belangrijk omdat ze zowel de overleving als de kwaliteit van leven op verschillende manieren kunnen beïnvloeden. De verschillende toxiciteiten zijn echter op verschillende manieren gerelateerd aan de dosisverdeling in de cardiale substructuren. Het prioriteren van de verschillende toxiciteiten tijdens het proces van treatment planning blijft daarmee een uitdagend probleem.

Recent is voorgesteld om bij patiënten met slokdarmkanker meer te gaan kijken naar de totale toxiciteitslast (total toxicity burden) als een samengesteld eindpunt van verschillende toxiciteit. Dit is ook al toegepast in een gerandomiseerde studie. Deze totale toxiciteitslast geeft prioriteit aan bepaalde complicaties door een wegingsfactor toe te kennen op basis van hun ernst en klinische relevantie. Ernstige toxiciteit kreeg een hogere score en deze scores werden uiteindelijk per patiënt opgeteld. In de toekomst zou deze totale toxiciteitslast gebruikt kunnen worden als eindpunt in klinische studies bij het evalueren van bijvoorbeeld nieuwe technologieën.

Een ander relevant eindpunt voor de patiënt is de kwaliteit van leven (QoL). QoL kan worden gebruikt om de impact van verschillende vormen van toxiciteit bij de behandeling van slokdarmkanker te bepalen. De twee belangrijkste beperkingen van het gebruik van de QoL-vragenlijsten zijn dat het momentopnames zijn en dat het in de praktijk vaak moeilijk is voldoende ingevulde vragenlijsten terug te krijgen. Lage responspercentages zijn een potentiële bron van bias. Ook blijken QoL-scores niet altijd overeen te komen met de mate van toxiciteit die gezien werd in die populatie. Daarmee is het de vraag of QoL voldoende representatief is om straling gerelateerde toxiciteit bij slokdarmkankerpatiënten te evalueren.

Tot slot blijft het de vraag welke eindpunten het meest relevant zijn, zowel voor patiënten als voor toekomstig klinisch onderzoek. De algehele overleving kwalificeert hiervoor waarschijnlijk het meest omdat het een objectief eindpunt is en bijzonder relevant. In verschillende recente modelleringsstudies is algehele overleving als eindpunt gebruikt en in deze studies werden verschillende DVH-parameters als voorspellers voor algehele overleving geïdentificeerd. Hoewel dit suggereert dat straling geïnduceerde cardiale toxiciteit een rol speelt, is er geen informatie over de doodsoorzaak beschikbaar waardoor een oorzakelijk verband onzeker blijft.

Aangezien alle eindpunten hun beperkingen hebben, is een andere relevante, en meer gevoelige methode voorgesteld in de literatuur. Deze methode gaat uit van

het principe dat iedere individuele patiënt wil leven, met een goede kwaliteit van leven en bij voorkeur zonder toxiciteit. In deze methode worden patiënten binnen de verschillende behandelingsgroepen eerst met elkaar vergeleken op het belangrijkste resultaat. Wanneer er dan geen verschil is, worden minder belangrijke resultaten geëvalueerd. Deze methode, de generalised pairwise comparison method, zal gevoeliger zijn in het vinden van verschillen tussen groepen omdat het algehele overleving combineert met QoL en toxiciteit als een (primair) eindpunt.

Voor de toekomst verwacht ik dat verschillende soorten onderzoek nodig zijn. Allereerst zijn er studies nodig zoals gebruikt in dit proefschrift voor het genereren van hypothesen over mogelijke mechanismen en relaties tussen dosis in cardiale (sub)structuren en straling geïnduceerde schade. Deze gegevens kunnen worden gebruikt om bestralingsplannen te optimaliseren. Of dit uiteindelijk resulteert in een relevant klinisch voordeel voor patiënten, moet worden bevestigd in gerandomiseerde studies of prospectieve validatiecohorten (real-life data). In deze studies moeten gegevens over algehele overleving, evenals over QoL en toxiciteit, worden verzameld. Het combineren van meerdere eindpunten geeft meer mogelijkheden om klinisch relevant verschillen te detecteren en kan daarmee worden gebruikt om de optimalisatie van behandelingsplannen en/of nieuwe radiotherapietechnieken te evalueren.

(Access) to supplementary data:

Chapter 4 *Retrospective analyses*
https://www.thegreenjournal.com/cms/10.1016/j.radonc.2020.05.033/attachment/eae3c981-684e-48d1-993f-4cebf7e3146c/mmc1.docx

Chapter 5 *MRI data CROSS SECT*
https://www.redjournal.org/cms/10.1016/j.ijrobp.2021.02.007/attachment/97c87153-f531-40d8-b18e-d4be26151082/mmc1.docx

Chapter 6 *Overview on CROSS SECT data*
https://www.thegreenjournal.com/cms/10.1016/j.radonc.2021.11.029/attachment/63099d47-39b4-4df7-98a9-ab80d35e50c1/mmc1.xlsx

Chapter 7 *Blood biomarkers*
https://www.thegreenjournal.com/article/S0167-8140(24)00749-7/fulltext#supplementaryMaterial

Curriculum vitae

Jannet Beukema werd op 28 januari 1969 geboren in Zetten. In 1987 behaalde ze haar atheneum diploma aan het Heldring College in Zetten, waarna ze startte met de studie geneeskunde aan de Rijks Universiteit Groningen. Gedurende haar coschappen in het Deventer Ziekenhuis en het St Elisabeth Ziekenhuis op Curaçao ontstond haar interesse in de radiotherapie. Na het arts examen in 1995 was ze werkzaam als arts assistent niet in opleiding in de interne geneeskunde (Deventer) en Radiotherapie (Groningen) waarna ze in 1997 startte met de opleiding tot Radiotherapeut in het Radiotherapeutisch Instituut Limburg (R.T.I.L). (opleiders J.M.A de Jong en J.Jager)

Sinds 2002 is ze werkzaam als Radiotherapeut in het Universitair Medisch Centrum Groningen met als aandachtsgebieden de gastro-enterologie, de gynaecologie en de brachytherapie. Sinds 2014 werden deze klinische taken gecombineerd met het doen van wetenschappelijk onderzoek, wat uiteindelijk resulteerde in dit proefschrift.

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Dankwoord

Aan het einde van dit proefschrift, wil ik graag enkele mensen bedanken, die direct of indirect, hebben bijgedragen aan de totstandkoming ervan. Ik realiseer me dat het niet volledig zal zijn, bij voorbaat mijn excuses daarvoor.

Beste Hans, dank voor je begeleiding. Je wist vaak de vinger op de zere plek te leggen. Met de opmerkingen in de tekst kon ik vaak wel weer verder. Die fine-tuning van teksten, nou ja dat heb je waarschijnlijk al wel door, dat is niet echt mijn ding, sorry daarvoor.

Beste Peter, toen we startten woonde je nog bij me op de gang, wat een goede mogelijkheid bood om regelmatig bij je binnen te lopen en te discussiëren over de zin en onzin van de analyses. Je wist de andere, meer biologische kant te belichten. Veel dank voor je input en soms geruststellende woorden.

Kristel, de laatste maar zeker niet de minste in deze promotiecommissie, zonder jou was ik er nooit aan begonnen en had ik het, denk ik, ook niet afgemaakt. Dank voor je goede zorg, het meelezen in teksten, de laatste controle bij het insturen van de artikelen, maar vooral voor je inspirerend enthousiasme en het ontwikkelen van nieuwe onderzoeksideeën.

Leden van de leescommissie en opponenten, dank voor jullie aanwezigheid en de tijd die jullie besteed hebben aan dit proefschrift.

Co-auteurs en reviewers van de tijdschriften, dank voor jullie meedenken in de projecten, het verbeteren van de artikelen en jullie kritische blik. Het heeft zeker bijgedragen en vaak nieuwe ideeën opgeleverd.

Datamanagers, jullie hebben veel werk verzet voor deze studies. Lotte, dank voor het indienen van de studies bij de METC en de opbouw van de databases. Grace, bedankt voor het inplannen en bellen van de patiënten voor de bloedafname-afspraken in de CARD-studie (en het invullen van de CRF's, enzovoort). Ook veel dank aan de anderen voor alle ondersteuning bij de contacten met de METC, het exporteren van de studiedata, en het beheer van studies en CRF's waarbij we "slechts" participeren.

Medewerkers van administratie en planbureau voor het accurate verzamelen van gegevens en het inplannen van afspraken. Fijn dat dit altijd met een glimlach kan...

De patiënten service, alle prikmomentjes binnen de CARD studie onder een studiepatiëntnummer. Nog belangrijker is de zorg en aandacht die jullie bieden aan de patiënten – dat wordt enorm gewaardeerd.

De planning en VSIM, het terughalen en opnieuw doorrekenen van de planningen, het (opnieuw) gebruik van de hartatlas voor deze studie patiënten maar ook hier, boven alles, de goede zorg die jullie leveren op de CT en de mooiste planningen die jullie afleveren met een steeds lagere hart en longdosis.

Laboranten op de linacs en bij de verificatie, dank voor het geven van de behandelingen. Het is een technisch vak, maar ik krijg ook vaak complimenten van patiënten over de persoonlijke benadering die zij ervaren. Dat waarderen zij enorm, en ik ook!

Dank afdeling ICT(RT) voor de hulp bij de SFP data en andere computer gerelateerde problemen die ik tegen kwam in dit traject.

Het secretariaat, bedankt voor het ad hoc inplannen van afspraken met Hans, de gezelligheid en alle andere zaken waarin jullie mij hebben ondersteund.

Onderzoekers van de afdeling met uitgebreide expertise in toxiciteit en modellering, zoals Hans- Paul, Sanne, Arjen, Kees, en Marianne, jullie hebben de afgelopen jaren veel bijgedragen aan de opstart van het onderzoek binnen onze afdeling. Ik heb veel geleerd van jullie wijze woorden en de presentaties op dinsdagen – dank daarvoor

Crystal, jij was essentieel voor de voortgang van het onderzoek, het verzamelen van de data en de waardevolle discussies binnen de CROSS SECT-studie. Jouw nauwkeurigheid was onmisbaar. Dank daarvoor! Ik vind het fijn dat we een gedeeld aandachtsgebied hebben en elkaar daardoor nog regelmatig spreken.

Edwin, misschien had je het niet altijd door, maar ik heb veel gebruik gemaakt van de gegevens die jij ook nodig had voor jouw project. Het verzamelen van de DVH-data kost veel tijd en inspanning, waarvoor ik je graag wil bedanken.

Als radiotherapeut is goede zorg alleen mogelijk in samenwerking met tumorwerkgroepen en collega's uit andere disciplines. Daarom wil ik de gynaecologen, chirurgen, internisten, MDL-artsen, maar ook de pathologen, radiologen, nucleair geneeskundigen, en last but not least de gespecialiseerd verpleegkundigen en casemanagers binnen deze disciplines, bedanken voor hun goede zorg en de prettige samenwerking.

Clustergenoten van het GYN-team: Stefan, Maaike en ja, Betty, soms hoor jij daar ook nog een beetje bij. Het is een fijn dat we moeiteloos en efficiënt zaken van elkaar kunnen overnemen tijdens vakanties of wanneer dat nodig is. Ons wekelijkse intekenoverleg biedt een goed moment om bij te praten, niet alleen over patiëntenzorg en logistiek, maar ook over wat ons privé bezighoudt. Dit maakt het werk zeer aangenaam. Het brachyteam met laboranten, fysici en fysisch medewerkers hoort hier zeker ook bij. De vele (maan)dagen op het ODBC en in het brachy-hok zijn een welkome afwisseling in de week. Dank voor de goede zorg, zowel voor de patiënten als voor elkaar

Clustergenoten van de upper GI: Kristel, Charlotte en Margriet, wat leuk om weer terug te zijn in dit aandachtsgebied en mooi dat we deze promotie samen kunnen volbrengen. Co-promotor en paranimfen, dank jullie wel! Op naar een mooie toekomst met veel nieuwe ontwikkelingen en projecten.

Collega-radiotherapeuten, AIOS, PA-ers, Fysici en andere niet genoemde collegae, jullie vormen een leuke en diverse groep. We zijn inmiddels met velen en onderverdeeld in verschillende aandachtsgebieden, waardoor we elkaar misschien wat minder vaak zien en spreken. Dat hoeft niet erg te zijn; als we elkaar nodig hebben, weten we elkaar altijd te vinden. Bart, onze teamleider (geen "teamlijder"), dank je wel.

Agata, mijn geliefde kamergenoot, en Anne en Hiske, voor jullie komt de eindstreep ook in zicht. Nog even volhouden – het komt goed!

Tot slot

Familie en vrienden zorgen voor de nodige afwisseling en hebben op die manier ook bijgedragen aan een "werkstuk" zoals dit. Mijn ouders hebben me altijd geïnspireerd om nieuwe uitdagingen aan te gaan – en dit proefschrift was er daar zeker één van. Ik heb misschien wat lang gewacht met het uiteindelijke product, waardoor jullie niet allebei de eindstreep hebben meegemaakt. Mama, ik ben dankbaar dat jij er wel bij kunt zijn.

Rob, jij bent misschien wel de belangrijkste, zonder jou had ik dit, denk ik, niet afgemaakt. Dank je voor je liefde, ons samenzijn en de vele dingen die we samen ondernemen. Ik hou van je.