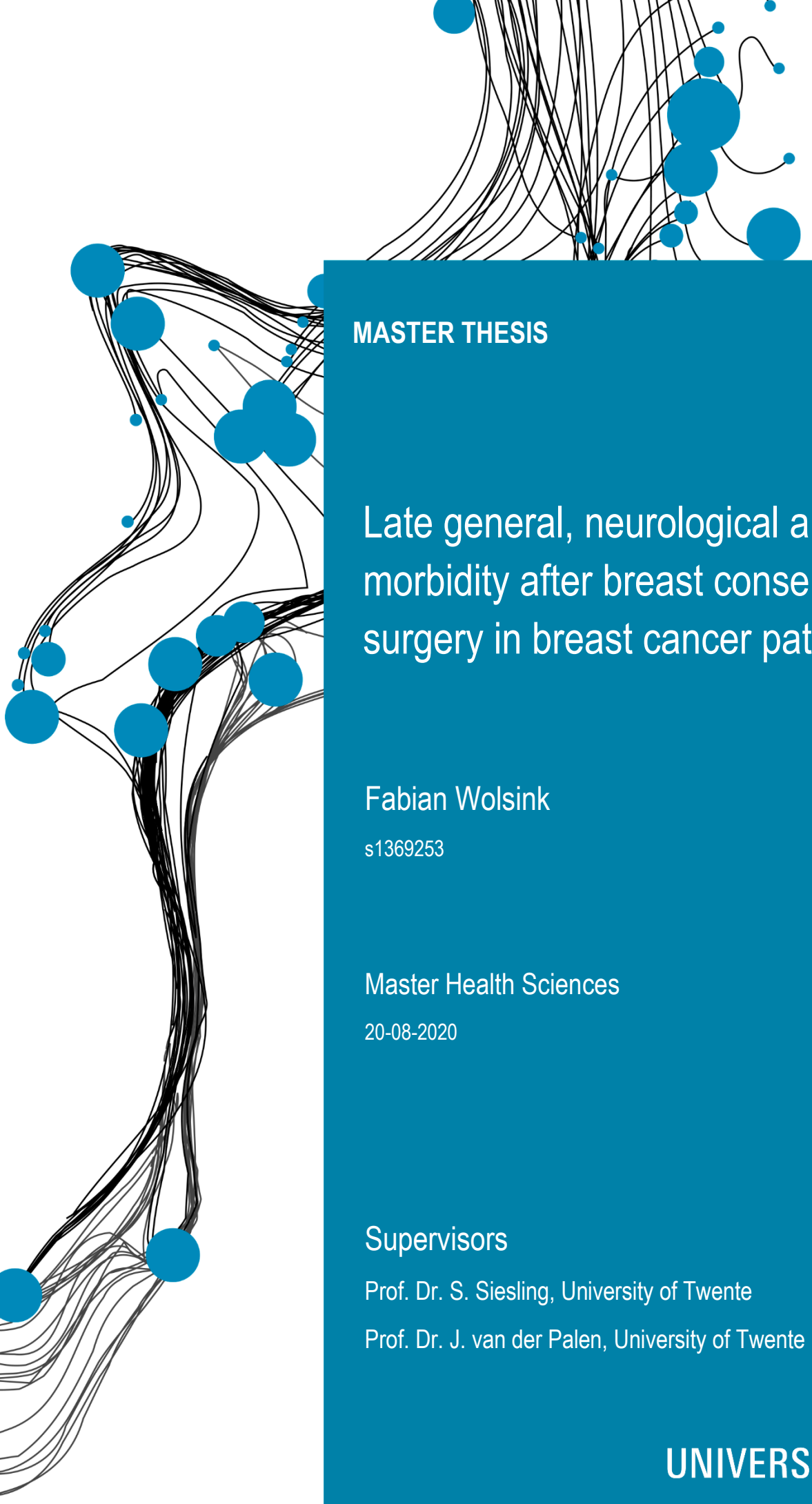

MASTER THESIS

Late general, neurological and cardiac morbidity after breast conserving surgery in breast cancer patients

Fabian Wolsink

s1369253

Master Health Sciences

20-08-2020

Supervisors

Prof. Dr. S. Siesling, University of Twente

Prof. Dr. J. van der Palen, University of Twente

UNIVERSITY OF TWENTE.

ABSTRACT

Background

Breast cancer (BC) is the most common known cancer among women worldwide. Current treatments consist of radiotherapy, adjuvant systemic therapy and locoregional therapy. While the survival rate continues to improve because of more advanced treatments and earlier detection, it becomes increasingly important to have a better understanding of possible long-term adverse effects of BC treatment.

Methods

This retrospective cohort study focusses on patients treated with breast conserving surgery (BCS) and radiotherapy (n=95), BCS, radiotherapy (RT) and adjuvant systemic therapy (n=107) and patients treated with BCS, RT, adjuvant systemic therapy and loco-regional therapy (n=62). All patients were treated in Medical Spectrum Twente (MST) and Ziekenhuisgroep Twente (ZGT) between 1989 and 2007. Patient-specific data and late general, cardiovascular and neurological effects were retrieved from the electronic patient data systems (EPD) from MST and ZGT. Baseline characteristics and late adverse effects were compared between the three treatment groups and left- and right sided BC by chi-square. Possible confounders in relation to adverse effects, oncological treatment and treated breast side were evaluated by Cox regression analyses. Kaplan-Meier analyses were used to evaluate survival distributions of disease free survival (DFS) and overall survival (OS).

Results

The combination of all general late effects were significantly different between the cohorts. Next to this long-term exhaustion problems, and lymphedema were significantly different between the treatment groups. Furthermore the combination of all cardiovascular effects were comparable, based on received treatment, however a significant difference was found for Percutaneous Coronary Intervention(PCI) and Angina Pectoris (AP). Based on laterality a difference was found in all cardiovascular adverse events. Finally, no neurological differences were found between the treatment groups.

Conclusion

In this study, a higher risk of cardiac morbidity was found for BC patients treated for right-sided BC vs. left-sided BC. This could indicate a more accurate irradiation in current techniques to prevent overdoses to the heart. Furthermore a significantly increased risk was found for lymphedema and exhaustion. There was no difference observed in the development of neurological adverse events. Furthermore no significant differences were found for Cardiovascular – and neurological disease free survival. When looking at general disease free survival (GDFS), the patients who received RT+ST+LT had a significantly lower survival than patients treated with RT only and RT+ST.

Keywords

Breast conserving surgery, radiotherapy, adjuvant therapy, loco-regional therapy, cardiac morbidity, neurological morbidity, laterality, disease-free survival

TABLE OF CONTENTS

INTRODUCTION

Worldwide, breast cancer is the second most common cancer among men and women. When we look at women only, the most frequent one and the leading cause of cancer death [1]. Female breast cancer accounts for 2.1 million newly diagnosed cases in 2018 worldwide. Compared to other cancer cases among women, breast cancer represents almost 25% of all cases [2]. In the Netherlands 2018 counted 14,882 new cases of breast cancer [3].

Over the past years, the incidence of breast cancer in the Netherlands stabilised, while the mortality decreased. The 5-years survival rate was 87% and the 10- years survival rate in the Netherlands grew to 77%. This survival depends on the grade of breast cancer. Ductal carcinoma in situ (DCIS) has the highest survival rate with approximately 98% after 10 years, while the 5- and 10-year survival rate of people with metastatic breast cancer was only 17% and 8%, respectively [5].

The number of long-term survivors of breast cancer is rapidly growing, because treatments are more advanced and early detection of the breast cancer through screening programs [10,11]. This results in a high prevalence of patients who live long and might encounter late side effects of breast cancer treatment. Although early detection of breast cancer, due to mammographic screening, contributes to the higher survival rate of patients, it can also lead to overdiagnosis [6,7,8,9]. In countries that make use of screening programs, breast cancer is often detected before one can clinically diagnose the disease. Overdiagnosis is a diagnosed condition that would otherwise not go on to cause symptoms or death [9]. In other words, it is possible a patient will be treated for breast cancer, while it is unnecessary to do so. This overdiagnosis leads to an unintended increase of late effects in breast cancer patients due to cancer therapies. Both overdiagnosis and the increase of long-term breast cancer survivors result in more long-term side effects, which is why it is important to explore these adverse effects for a better understanding.

Current interventions of breast cancer consist of mastectomy and breast conserving treatments, radiotherapy, chemotherapy and hormonal therapy. Which treatment a patient receives is dependent on a combination of the tumour and patient characteristics; i.e. the breast cancer stage (tumour size, nodal status and distant metastasis [19], receptor status (Oestrogen, Progesterone and Herceptin) and the overall health status of the patient. Treatment decisions are made in a shared decision process between patient and physician.

To be able to properly consider which treatment should be given to a patient, it is important to carefully consider the outcomes of the treatment, possible side-effects and potential treatment-induced late effects. The primary objectives of radiotherapy and adjuvant therapies are primarily focussed on breast cancer outcomes and short-term safety of the patient, however little attention has been given to the long-term treatment-induced side effects [16,17]. These effects may differ per given treatment and significantly compromise patients' quality of life (QoL) and mortality.

A better understanding of both long – and short-term effects of breast cancer treatment will contribute to a more measured use of these treatments in terms of individual patient risks, so adverse effects can be reduced [17]. These effects can have a negative impact on for example cardiovascular health [14]. Cardiovascular disease (CVD) is the leading cause of death among women who survived breast cancer. The longer a patient survives, the greater the chance of mortality due to

other causes than cancer itself [15]. For example, research showed the chance of developing heart failure increases as a patient receives a greater cumulative dose of chemotherapy due to chemo-related toxic effects [14]. Furthermore, neurological complications of breast cancer treatment are taken into account in this study. Other studies, that were mainly focussed on short-term complications, showed for instance that half of the mentioned population presented at least one neurological complication in three years of follow-up [18]. However, little is known about the long-term treatment-induced neurological effects.

To understand how adverse effects of breast cancer treatment develop over time, this retrospective study focuses on patients that have survived for at least ten years after their first treatment of breast cancer. These effects can differ per treatment and should be carefully considered by the patient and physician. The aim of this study therefore is to determine the long-term general, neurological and cardiac morbidity of breast cancer treatments in women that were treated with radiotherapy with or without adjuvant therapy and women that were treated with radiotherapy, adjuvant therapy and locoregional therapy. These data can contribute to earlier detection and treatment of possible side effects, which can result in a better quality of care for future patients.

PATIENTS & METHODS

This retrospective study focusses on patients with breast cancer who were treated with breast conserving surgery (BCS) in Medical Spectrum Twente (MST) or Ziekenhuisgroep Twente (ZGT). The data of this cohort was obtained from a database of the radiation department of MST. The database consists of all patients diagnosed with breast cancer treated with radiation therapy after BCS from 1987 to 2018 in MST and surrounding hospitals. Three different treatment groups were distinguished, patients with BCS followed by Radiotherapy (RT) only, BCS followed by RT and adjuvant systemic therapy (ST) and BCS followed by RT, adjuvant systemic therapy and locoregional therapy (LT). All patients included in this study were treated with breast conserving surgery (BCS) between 1989 and 2007. Patients were excluded from this study if breast cancer was not their first-know cancer and if they survived less than 10 years.

Breast conserving surgery consisted of lumpectomy possibly combined with axillary lymph node dissection (ALND) or sentinel lymph node dissection (SLND) followed by irradiation of the whole breast. The irradiation consisted of a dose of 50 Gray possibly followed by a booster of 14 Gray targeting the regional breast area. The radiation therapy was given five times a week in doses of 2 Gray. Adjuvant systemic therapy consisted of chemotherapy, hormonal therapy or a combination of chemotherapy and hormonal therapy. A further description of the treatment can be found in Appendix I.

All patients were randomly selected from the database that was obtained from the Radiology department of the MST. In total 95 patients, treated with radiotherapy only, were selected, 107 patients treated with radiotherapy and adjuvant systemic therapy and 62 patients treated with radiotherapy, adjuvant systemic therapy and locoregional therapy. All patients received radiotherapy in MST and were surgically treated in MST or ZGT.

The dataset of the radiology department used for this study already contained variables such as date of birth, laterality, surgical type of treatment, date of surgery, TNM-stage, radiation dose and type and date of adjuvant systemic therapy. This data was supplemented with patient-specific data retrieved from the electronic patient data systems (EPD) from MST and ZGT. The data consisted of general information and comorbidities known at the moment of diagnosis such as height, weight, diabetes mellitus (I or II), insulin dependency, hypertension, hypercholesterolaemia, smoking behaviour and how much and which medication the patient was using. Furthermore late general, cardiovascular and Neurological effects were collected from the EPD. Smoking behaviour of the patient was divided into three groups, non-smokers, ex-smokers and current smokers. Pack-years, if known, was also noted to quantify the tobacco consumption [20]. In most of the cases, the date patients stopped smoking, was not known, therefore ex-smokers and smokers were combined in further analyses. This data was collected to determine possible confounders.

Statistical methods

BMI and age of the patients at the time of surgery were calculated for further analyses. Next to this, the latest known follow-up was noted, as well as the dates of eventual recurrences and metastases. The latest known follow-up was defined as the last known medical appointment or the patient's death. Additionally, general, neurological and cardiovascular late effects were collected from the patient files and scored. Dates of diagnosis were noted if this was applicable. Demographics of the population were presented by descriptive statistics.

To analyse equality in the demographics, one-way ANOVA was used in case of continuous variables (Follow-up period, Age, Height, Weight and BMI) and Chi-square tests in case of categorical variables (smoking behaviour, comorbidities, surgical treatment and oncological treatment). The continuous variables were examined whether they were normally distributed. No variables were found that were not normally distributed, therefore ANOVA was used for these variables.

Frequency of general, neurological and cardiovascular late effects were analysed separately on differences between the three cohorts by using Chi-Square tests. The Fisher's Exact Test was performed if the expected count was less than 5. Next to this, the incidence of total general, neurological and cardiovascular late effects was compared between the treatment groups by using ANOVA. The risk of cardiac toxicity from breast cancer radiotherapy is higher for left-sided breast cancer patients due to human anatomy than right-sided breast cancer [21,22,23]. Therefore, cardiovascular late effects and patient characteristics were also separately analysed on differences in laterality of the breast cancer by using Chi-square and in total by one-way ANOVA.

General, neurological and cardiological disease free survival was calculated for the three cohorts. Disease free survival was defined as the period from surgery until the first major adverse effect occurred. The survival distributions were compared by making use of log-rank distributed Kaplan-Meier analyses.

Cox regression analysis was used to evaluate survival distributions and demographic variables for possible confounding. Variables that differed between the treatment groups and variables that were univariately related ($p<0.10$) to the time to event were analysed in a multivariate Cox regression.

All statistical analyses were performed in IBM SPSS Statistics 25.

RESULTS

In this study 264 patients were included. These patients were treated with BCS and radiotherapy only (95), BCS, radiotherapy and adjuvant systemic therapy (107) and BCS, radiotherapy, adjuvant systemic therapy and loco-regional therapy (62). All patients were treated with breast conserving surgery between 02-05-1986 and 08-09-2007. The 169 patients who received adjuvant systemic therapy were treated with hormonal therapy in 80 cases (47%), 50 were treated with chemotherapy (30%), and 39 received a combination of hormonal – and chemotherapy (23%). The age of the patients when BCS was executed varied between 32 and 77 years with a mean age of 55 years. The mean follow up time was 17.7 years, ranging from 10 to 32 years. Patient and treatment characteristics can be found in table 1.

Table 1. Patient and treatment characteristics for women treated with breast-conserving surgery followed by radiotherapy only (RT), radiotherapy and adjuvant systemic therapy (RT + ST) and radiotherapy , adjuvant systemic therapy and locoregional therapy (RT + ST + LT) between 1986-2007 in MST and ZGT

	RT (n=95)	RT + ST (n=107)	RT + ST+ LT (n=62)	P-value
Characteristics				
Follow-up years (Mean ± SD)	17.6 (± 4.4)	17.6 (± 4.5)	17.9 (± 5.5)	0.875
Age (Mean ± SD)	57.1 (± 9.3)	53.7 (± 10.5)	52.7 (± 7.7)	0.006
*Height, cm (Mean ± SD)**	167.1 (± 5.4)	165.4 (± 6.3)	165.0 (± 6.1)	0.202
*Weight, kg (Mean ± SD)***	77.4 (± 17.6)	77.6 (± 15.0)	73.4 (± 15.2)	0.201
*BMI, kg/m^2 (Mean ± SD)****	27.3 (± 6.6)	28.7 (± 6.8)	27.0 (± 4.5)	0.298
Smoking habits				0.461****
Smoker + Ex-smoker	32 (35.6%)	33 (36.7%)	25 (27.8%)	
Smoker	16 (16.8%)	17 (69.2%)	17 (27.4%)	
Ex-smoker	16 (40.0%)	16 (40.0%)	8 (20.0%)	
Never-smoker	63 (36.2%)	74 (42.5%)	37 (21.3%)	
Comorbidities				
Diabetes	11 (11.6%)	12 (11.2%)	18 (29%)	0.004
Hypertension	29 (30.5%)	36 (33.6%)	33 (53.2%)	0.010
Hypercholesterolaemia	13 (13.7%)	16 (15.0%)	20 (32.3%)	0.007
Number of medications	0.7 (± 1.2)	0.9 (± 1.4)	0.9 (± 1.6)	0.432
Surgical treatment				0.014
Lumpectomy	0 (0.0%)	1 (0.9%)	4 (6.5%)	
Lumpectomy + ALND	92 (96.8%)	105 (98.1%)	58 (93.5%)	
Lumpectomy + SLND	3 (3.2%)	1 (0.9%)	0 (0.0%)	
Oncological treatment				
Hormonal therapy	0 (0.0%)	59 (73.8%)	21 (26.2%)	
Chemotherapy	0 (0.0%)	29 (58.0%)	21 (42.0%)	
Hormonal -and chemotherapy	0 (0.0%)	19 (48.7%)	20 (51.3%)	

**known for 157 women **know for 228 women ***known for 157 women ****Smokers and ex-smokers combined vs never-smokers, at time of treatment*

As can be seen from table 1, the age of the patients when they received BCS varied significantly between the cohorts. Diabetes was seen more often in patients treated with RT, followed by adjuvant systemic and locoregional therapy. Next to this hypertension and hypercholesterolaemia were also most commonly present in patients that were treated with both adjuvant and locoregional therapy. Furthermore, the surgical treatment differed significantly between the cohorts. Most patients were treated with lumpectomy in combination with axillary node dissection, but lumpectomy only was mostly applied to the cohort treated with radiotherapy, systemic therapy and locoregional therapy, while lumpectomy + sentinel node dissection was mostly applied to the RT only cohort. Age, diabetes, hypertension, hypercholesterolaemia and the surgical treatment varied significantly between the three groups. These characteristics were therefore taken into account in the cox regression to analyse if they were confounders.

Analysis of general late effects between the cohorts

Table 2 shows the frequency of the general late effects that occurred during follow-up in the three cohorts. There was no observed difference in the combination of all general late effects. However, several particular late effects were found to be significantly different between the cohorts. Patients of the third cohort suffered the most from exhaustion, while patients that received only radiotherapy where the least exhausted. Furthermore, lymphedema was most commonly observed in patients treated with RT + ST + RT. Next to these effects, osteopenia + osteoporosis approached significance between the studied cohorts and finally, a difference was observed in chest/thorax pain between the three patient groups. Therefore, these effects were taken into account in further multivariate analyses.

Table 2. General late effects for women treated with breast-conserving surgery followed by radiotherapy only (RT), radiotherapy and adjuvant systemic therapy (RT + ST) and radiotherapy , adjuvant systemic therapy and locoregional therapy (RT + ST + LT) between 1986-2007 in MST and ZGT

	RT (n=95)	RT + ST (n=107)	RT + ST+ LT (n=62)	P-value
General late effect				
Exhaustion	50 (52.6%)	60 (56.1%)	46 (74.2%)	0.019
Psychosocial complaints	24 (25.3%)	25 (23.4%)	23 (37.1%)	0.133
Reduced shoulder mobility	39 (41.1%)	34 (31.8%)	26 (41.9%)	0.283
Ulceration irradiated skin	7 (7.4%)	13 (12.1%)	0 (0.0%)	0.016
Tissue necrosis	4 (4.2%)	8 (7.5%)	2 (3.2%)	0.414
Osteopenia + Osteoporosis	19 (20.0%)	25 (23.4%)	22 (35.5%)	0.080
Spontaneous rib fracture	0 (0.0%)	2 (1.9%)	1 (1.6%)	0.421
Lymphedema	36 (37.9%)	48 (44.9%)	49 (79.0%)	0.001
Chest/Thorax pain	13 (13.7%)	10 (9.3%)	15 (24.2%)	0.029
Intestinal problems	9 (9.5%)	18 (16.8%)	10 (16,1%)	0.279
Second primary tumour	37 (38.9%)	34 (31.8%)	17 (27,4%)	0.295
*All general late effects**	84 (88.4%)	96 (89.7%)	60 (96,8%)	0.176
Total general events	240	280	217	

**patients who developed at least one general late effect*

To determine the effect of received treatment on the development of general late effects, all effects were univariately analysed by Cox regression (table 3).

Table 3. Hazard ratios, confidence intervals and p-values from univariate regression analysis for all general late effects in women treated with BCS, followed by RT only, RT + ST and RT + ST + LT

	Univariate HR of Treatment*	95% CI	P-value
General late effect			
Exhaustion	1.026 1.637	(0.705 – 1.494) (1.093 – 2.451)	0.033
Psychosocial complaints	0.880 1.582	(0.503 – 1.541) (0.893 – 2.804)	0.121
Reduced shoulder mobility	0.699 1.002	(0.441 – 1.107) (0.610 – 1.646)	0.227
Tissue necrosis	1.781 0.762	(0.536 – 5.914) (0.140 – 4.160)	0.430
Osteopenia + Osteoporosis	1.207 1.948	(0.664 – 2.192) (1.054 – 3.600)	0.094
Lymphedema	1.189 2.960	(0.772 – 1.833) (1.919 – 4.565)	<0.001
Chest/Thorax pain	1.802 1.650	(0.809 – 4.014) (0.669 – 4.071)	0.029
Intestinal problems	1.802 1.650	(0.809 – 4.014) (0.669 – 4.071)	0.310
Second primary tumour	0.758 0.589	(0.476 – 1.209) (0.331 – 1.048)	0.169
All general late effects	0.967 1.556	(0.721 – 1.297) (1.114 – 2.172)	0.013

**cohort RT+ST vs RT only / cohort RT+ST+LT vs RT only*

Based on the results in table 2 and table 3: exhaustion, lymphedema, osteopenia + osteoporosis, chest/thorax pain and all general late effects were taken into account in multivariate analyses.

The surgical treatment had a significant influence on exhaustion problems of the patient and hypertension was confirmed as a confounder on the development of lymphedema. All general late effects together were significantly influenced by the age of the patient. Furthermore, no significant risk factors were found for osteopenia + osteoporosis and chest/thorax pain. These confounders were taken into account in the multivariate Cox regression analyses for general late effects. The adjusted hazard ratios for exhaustion, lymphedema and all general late effects are presented in table 4.

Table 4. General late effects via Cox regression, confounders, unadjusted and adjusted HR. Cohort 1 (RT only) and surgical treatment (lumpectomy only) act as reference group

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Exhaustion		
Cohort (RT + ST)	1.026 (0.705 – 1.494)	1.062 (0.728 – 1.550)
Cohort (RT + ST + LT)	1.637 (1.093 – 2.451)	1.681 (1.108 – 2.549)
Surgical treatment (Lump + ALND)		0.671 (0.242 – 1.863)
Surgical treatment (Lump + SLND)		3.989 (0.944 – 16.852)
Lymphedema		
Cohort (RT + ST)	1.189 (0.772 – 1833)	1.143 (0.741 – 1.763)
Cohort (RT + ST + LT)	2.960 (1.919 – 4.565)	2.625 (1.682 – 4.098)
Hypertension		1.513 (1.064 – 2.151)
All general late effects		
Cohort (RT + ST)	0.967 (0.721 – 1.297)	0.990 (0.738 – 1.328)
Cohort (RT + ST + LT)	1.556 (1.114 – 2.172)	1.671 (1.188 – 2.352)
Age		1.014 (1.000 – 1.028)

Cohort RT+ST+LT shows a significant difference for exhaustion before and after adjusting for the confounder surgical treatment, more patients suffer from exhaustion problems after receiving the combination of systemic therapy and locoregional therapy.

Furthermore, cohort RT+ST+LT also shows a correlation with suffering from lymphedema. After adjusting for the confounder hypertension this correlation is still significant. Finally, the combination of all general late effects is significant correlated, after adjusting for age, to the treatment of patients in cohort RT+ST+LT. Patients of this cohort suffer more from general late effects than patients treated with RT only or RT + ST.

Table 5 shows the frequency of cardiovascular late effects and interventions observed during the follow-up period. There was no late effect that was significantly different between the three cohorts. For the cardiovascular interventions, the need of an Implantable Cardioverter Defibrillator (ICD) was significantly different between the cohorts, three patients of the third cohort received an ICD, while only one patient of the first and second cohort received an ICD. Furthermore, Percutaneous Coronary Intervention (PCI) approached significance and was therefore taken into account in further multivariate analysis. However, ICD was not taken into account because of too little known cases. Finally, there was no significant difference observed in the total of cardiovascular events.

Table 5. Cardiovascular late effects for women treated with breast-conserving surgery followed by radiotherapy only (RT), radiotherapy and adjuvant systemic therapy (RT + ST) and radiotherapy , adjuvant systemic therapy and locoregional therapy (RT + ST + LT) between 1986-2007 in MST and ZGT

	RT (n=95)	RT + ST (n=107)	RT + ST+ LT (n=62)	P-value
Cardiovascular late effect				
Cardiomyopathy	6 (6.3%)	9 (8.4%)	8 (12.9%)	0.356
Congestive heart failure	11 (11.6%)	7 (6.5%)	4 (6.5%)	0.359
Angina pectoris	9 (9.5%)	9 (8.4%)	1 (1.6%)	0.145
Myocardial infarction	4 (4.2%)	6 (5.6%)	2 (3.2%)	0.759
Valvular heart disease	19 (20.0%)	15 (14.0%)	6 (9.7%)	0.193
Arrhythmia	19 (20.0%)	21 (19.6%)	7 (11.3%)	0.308
Conduction disorders	4 (4.2%)	7 (6.5%)	5 (8.1%)	0.591
Pericarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cardiovascular intervention				
Percutaneous Coronary Intervention	6 (6.3%)	6 (5.6%)	9 (14.5%)	0.091
Coronary Artery Bypass Graft	4 (4.2%)	3 (2.8%)	1 (1.6%)	0.640
Pacemaker	3 (3.2%)	3 (2.8%)	2 (3.2%)	0.984
Implantable Cardioverter Defibrillator	1 (1.1%)	0 (0.0%)	3 (4.8%)	0.041
*All cardiovascular late effects**	36 (37.9%)	35 (32.7%)	23 (37.1%)	0.802
Total cardiovascular events	86	86	48	

**patients who developed at least one cardiovascular late effect*

Analysis of cardiovascular late effects between the cohorts

To determine the effect of treatment on cardiovascular late effects, all effects were univariately analysed (table 6).

Table 6. P-values , hazard ratios and confidence intervals (95% CI) from univariate Cox regression for cardiovascular late effects in patients treated with RT only (reference group) vs treatment with RT +ST vs treatment with RT + ST + LT

	HR of treatment*	95% CI	P-value
Cardiovascular late effect			
Cardiomyopathy	1.388	(0.494 – 3.900)	0.407
	2.055	(0.712 – 5.931)	
Congestive heart failure	0.566	(0.220 – 1.461)	0.392
	0.539	(0.171 – 1.693)	
Angina pectoris	0.888	(0.352 – 2.237)	0.073
	0.159	(0.020 – 1.257)	
Myocardial infarction	1.321	(0.373 – 4.684)	0.757
	0.749	(0.137 – 4.092)	
PCI	0.914	(0.295 – 2.835)	0.108
	2.458	(0.874 – 6.910)	
CABG	0.671	(0.150 – 2.998)	0.641
	0.385	(0.043 – 3.449)	
Valvular heart disease	0.650	(0.328 – 1.288)	0.143
	0.427	(0.169 – 1.076)	
Arrhythmia	0.976	(0.524 – 1.818)	0.218
	0.508	(0.213 – 1.211)	
Conduction disorders	1.480	(0.432 – 5.069)	0.729
	0.461	(0.438 – 6.192)	
Pacemaker	0.801	(0.160 – 4.011)	0.946
	0.755	(0.123 – 4.642	
All cardiovascular events	0.875	(0.549 – 1.393)	0.839
	0.977	(0.579 – 1.649)	

**cohort RT+ST vs RT only / cohort RT+ST+LT vs RT only*

Based on the results in table 5 and 6, a multivariate analysis with the possible confounders age, diabetes, hypercholesterolemia, hypertension and surgical treatment was done for angina pectoris and Percutaneous Coronary Intervention(PCI).
According these analyses, age, hypertension, diabetes and the surgical treatment did not have a significant influence on the need of a PCI, however, hypercholesterolemia did have an influence (p=0.009).

For angina pectoris, hypertension and surgical treatment showed no direct correlation, however, hypercholesterolemia (p=0.108) and diabetes (p=0.106) approached significance and age did have a significant influence (p=0.051). These confounders were taken into account in the multivariate Cox regression analyses for cardiovascular late effects. The adjusted hazard ratios for angina pectoris and PCI are presented in table 7.

Table 7. Cardiovascular late effects via Cox regression, confounders, unadjusted and adjusted HR. Cohort 1 (RT only) acts as reference group

	Unadjusted HR (95% CI)	**Adjusted HR (95% CI)**
Angina pectoris		
Cohort (RT + ST)	0.888 (0.353 – 2.237)	1.032 (0.407 – 2.617)
Cohort (RT + ST + LT)	0.159 (0.020 – 1.257)	0.139 (0.017 – 1.146)
Hypercholesterolemia		2.764 (1.030 – 7.418)
Diabetes		2.562 (0.922 – 7.116)
Age		1.052 (1.001 – 1.107)
PCI		
Cohort (RT + ST)	0.914 (0.295 – 2.835)	0.923 (0.297 – 2.862)
Cohort (RT + ST + LT)	2.458 (0.874 – 6.910)	1.935 (0.672 – 5.574)
Hypercholesterolemia		3.038 (1.242 – 7.429)

Angina pectoris shows a significant difference, namely, in cohort RT+ST+LT less cases of AP were found than in cohort RT only and RT+ST. After adjusting for the confounders hypercholesterolemia, diabetes and age, the impact of cohort RT+ST+LT still approaches significance (p=0.067).
PCI showed a significant difference for cohort RT+ST+LT, breast cancer patients in this cohort were more in need of this intervention than patients in cohort RT only and RT+ST, however, after adjusting for hypercholesterolemia, this correlation is not significant anymore.

To explore the impact of radiotherapy on the heart, right – and left-sided breast cancer patients were compared and analysed. No significant differences were found in patient and treatment characteristics between patients that were treated for right – and left-sided breast cancer. Therefore no characteristics were included in the Cox regression to evaluate their confounding influence. Details of these calculations can be found in Appendix II

To determine the effect of treated breast side on cardiovascular late events, all cardiac effects were univariately analysed. Table 8 presents the cardiovascular late effects in relation to right – and left - sided breast cancer, Among women with right-sided breast cancer 40.3% developed one or more cardiovascular events (n= 52), while women with left-sided breast cancer developed at least one effect in 31,1% of the cases (n= 42).
There were 127 cardiac events among women with right – sided breast cancer and 93 among women with left – sided breast cancer. There was no difference observed in the total of cardiovascular events between left – or right sided breast cancer, however, the need of an Implantable Cardioverter Defibrillator (ICD) differed significantly. Other cardiovascular late effects were comparable.

Table 8. Comparison of cardiovascular morbidity for right - and left sided breast cancer patients treated with breast conserving surgery follow by radiotherapy only, radiotherapy and adjuvant systemic therapy, and radiotherapy, adjuvant systemic therapy and locoregional therapy

	Right – sided (n=127)	**Left – sided (n=93)**	**P-value**
Cardiovascular late effect			
Cardiomyopathy	15 (11.6%)	8 (5.9%)	0.101
Congestive heart failure	12 (9.3%)	10 (7.4%)	0.369
Angina pectoris	12 (9.3%)	7 (5.2%)	0.196
Myocardial infarction	6 (4.7%)	6 (4.4%)	0.936
Valvular heart disease	22 (17.1%)	18 (13.3%)	0.399
Arrhythmia	25 (19.4%)	22 (16.3%)	0.513
Conduction disorders	8 (6.2%)	8 (5.9%)	0.925
Cardiovascular intervention			
Percutaneous Coronary Intervention	12 (9.3%)	9 (6.7%)	0.429
Coronary Artery Bypass Graft	6 (4.7%)	2 (1.5%)	0.133
Pacemaker	5 (3.9%)	3 (2.2%)	0.433
Implantable Cardioverter Defibrillator	4 (3.1%)	0 (0.0%)	0.039
*All cardiovascular late effects**	52 (40.3%)	42 (31.1%)	0.119
Total cardiovascular events	127**	93***	

**patients who developed at least one cardiovascular late effect ** for 52 women ***for 42 women*

Analysis of cardiovascular late effects between left – and right sided BC patients

To determine the effect of treated breast-side on cardiovascular late effects, all effects were univariately analysed (table 9). Pericarditis, Ventricular Assist Device, Heart transplant and Implantable Cardioverter Defibrillator were not included because of insufficient cases for any further analysis.

Table 9. Hazard ratios, confidence intervals (95% CI) and p-values from univariate Cox regression for cardiovascular late effects in left - and right sided breast cancer

	Univariate HR of Treated Breast side*	95% CI	P-value
Cardiovascular late effect			
Cardiomyopathy	2.190	(0.927 – 5.175)	0.074
Congestive heart failure	1.391	(0.600 – 3.225)	0.442
Angina pectoris	1.962	(0.772 – 4.989)	0.157
Myocardial infarction	1.100	(0.355 – 3.413)	0.869
PCI	1.507	(0.634 – 3.580)	0.353
CABG	3.301	(0.666 – 16.363)	0.144
Valvular heart disease	1.411	(0.755 – 2.636)	0.280
Arrhythmia	1.356	(0.761 – 2.416)	0.302
Conduction disorders	1.254	(0.467 – 3.365)	0.654
Pacemaker	2.221	(0.524 – 9.424)	0.279
All cardiovascular events	1.514	(1.005 – 2.279)	0.047

**right-sided breast cancer patients vs. left-sided breast cancer patients **patients who developed at least one cardiological late effect*

Most late effects were comparable for right vs. left-sided breast cancer patients. The only variable that approached significance was Cardiomyopathy. Next to that, all cardiovascular effects together showed a significant difference, right-sided breast cancer patients suffered more from cardiovascular late events than left-sided breast cancer patients.

No possible confounders were found in earlier analysis in relation to lateralization, therefore no multivariate regression was performed.

Analysis of neurological late effects the cohorts

Table 10 contains all neurological late effects. Among women that received RT only, 20% developed at least one neurological late effect, women who received RT and ST developed in 23,4% of the cases at least one neurological late effect and 30,6% of the women who received RT, ST and LT developed a late effect. In total 81 neurological late effects were diagnosed during follow-up. No significant difference was found in the distribution of these cases among the three cohorts. Furthermore, there were no individual neurological late effects that significantly differed.

Table 10. Neurological late effects for women treated with breast-conserving surgery followed by radiotherapy only (RT), radiotherapy and adjuvant systemic therapy (RT + ST) and radiotherapy , adjuvant systemic therapy and locoregional therapy (RT + ST + LT) between 1986-2007 in MST and ZGT

	RT (n=95)	RT + ST (n=107)	RT + ST+ LT (n=62)	P-value
Neurological late effect				
Brachial plexus neuropathy	0 (0.0%)	1 (0.9%)	1 (1.6%)	0.503
Polyneuropathy	4 (4.2%)	7 (6.5%)	3 (4.8%)	0.748
Ischemic stroke	7 (7.4%)	10 (9.3%)	7 (11.3%)	0.700
Transient ischemic attack	8 (8.4%)	4 (3.7%)	3 (4.8%)	0.338
Carpal tunnel syndrome	5 (5.3%)	9 (8.4%)	9 (15.4%)	0.131
Meningioma	1 (1.1%)	1 (0.9%)	1 (1.6%)	0.918
All neurological late effects)*	19 (20.0%)	25 (23.4%)	19 (30.6%)	0.307
Total neurological events	25	32	24	

**patients who developed at least one neurological late effect*

To determine the effect of received treatment on neurological late effects, all neurological effects were separately analysed through univariate cox regression (table 11). All three cohorts were taken into account, with cohort 1 (RT only) acting as reference group. No significant relation was found between the different treatments and neurological morbidity. However, patients in the third cohort generally were more at risk of neurological late events (HR =1.566). Furthermore, no significant differences were found for a specific neurological late effect.

Table 11. P-values , hazard ratios and confidence intervals (95% CI) from univariate Cox regression for neurological late effects in patients treated with RT (reference group) vs treatment with RT +ST vs treatment with RT + ST + LT

	HR of treatment*	95% CI*	P-value
Neurological late effect			
Polyneuropathy	1.548	(0.453 – 5.292)	0.753
	1.095	(0.244 – 4.914)	
Ischemic stroke	1.282	(0.488 – 3.370)	0.777
	1.442	(0.505 – 4.120)	
Transient ischemic attack	0.403	(0.120 – 1.350)	0.266
	0.462	(0.120 – 1.778)	
Carpal tunnel syndrome	1.600	(0.535 – 4.782)	0.180
	2.735	(0.913 – 8.190)	
All neurological events	1.193	(0.656 – 2.169)	0.389
	1.566	(0.827 – 2.965)	

**cohort RT+ST vs RT only / cohort RT+ST+LT vs RT only*

Disease free and overall survival

Both disease free survival and overall survival were evaluated by performing Kaplan-Meier analysis. Disease free survival was defined as the time between surgery and a main adverse event (general, cardiovascular or neurological).

Kaplan Meier analyses were performed to explore if there was a difference in time until a major adverse event was diagnosed. The first survival analysis (figure 1) was performed to have a look at the general late effects (general disease-free survival (GDFS (in years))) versus the different types of treatment in the treatment groups. A significant difference was found in the time between treatment and the first general late side effect for the three cohorts (p=0.008).

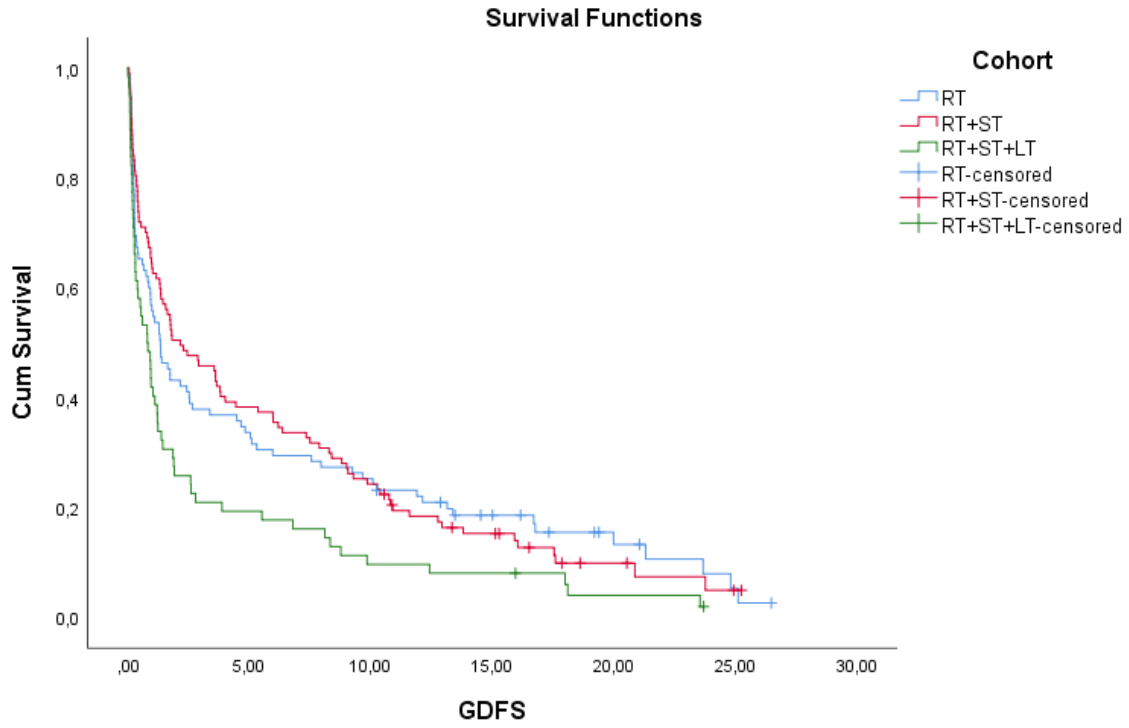

Figure 1. General disease-free survival (GDFS) in years by Kaplan-Meier analysis for patients treated with breast-conserving surgery followed by radiotherapy only, radiotherapy and adjuvant systemic therapy, and radiotherapy, adjuvant systemic therapy and locoregional therapy.

The second survival analysis (figure 2) represents the cardiovascular disease-free survival (CDFS (in years)) in relation to the different treatments. There was no significant difference found in the time between treatment and the first cardiovascular event for the several cohorts (p= 0.840)

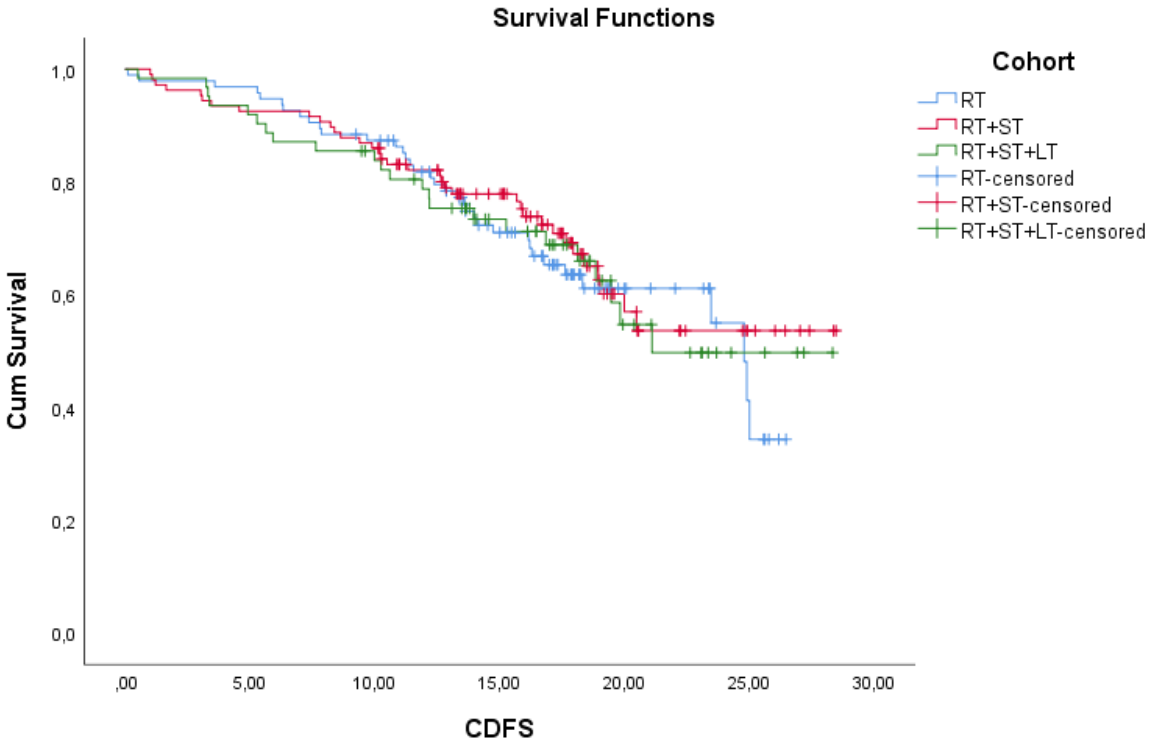

Figure 2. Cardiovascular disease-free survival (CDFS) in years by Kaplan-Meier analysis for patients treated with breast-conserving surgery followed by radiotherapy only, radiotherapy and adjuvant systemic therapy, and radiotherapy, adjuvant systemic therapy and locoregional therapy

The third survival analysis (figure 3) shows the distribution of neurological disease-free survival (NDFS (in years)) for the different treatment groups. No significant difference was found for the three cohorts (p= 0.377)

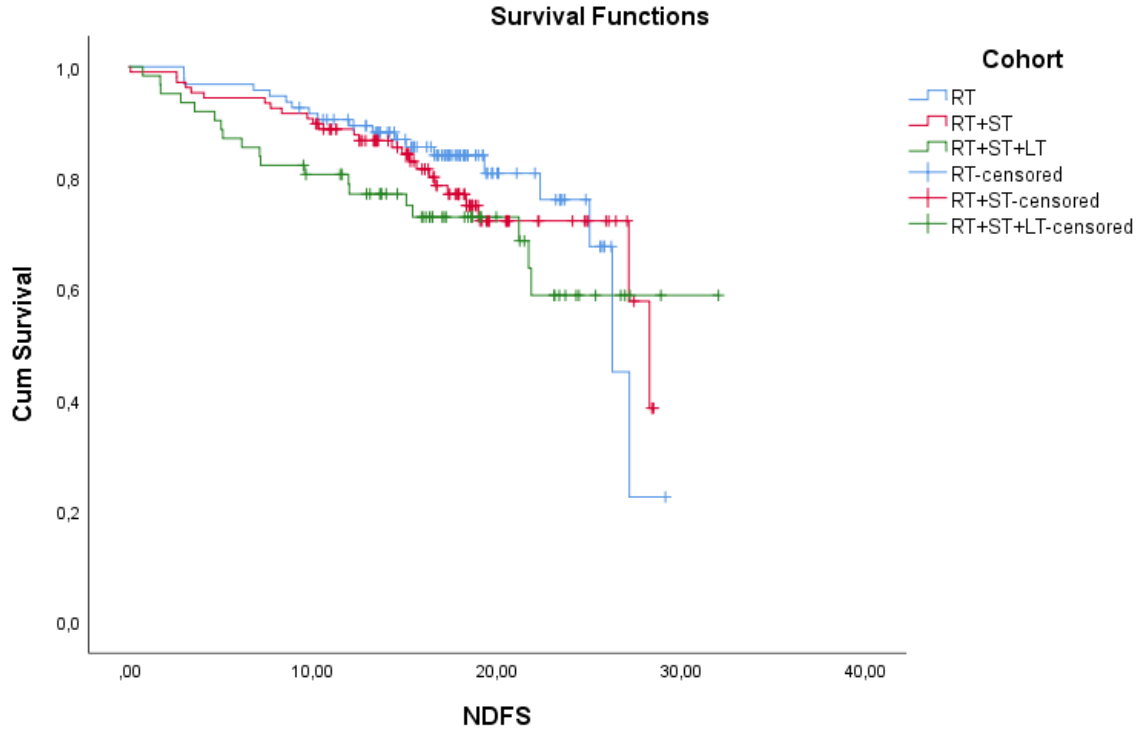

Figure 3. Neurological disease-free survival (NDFS) in years by Kaplan-Meier analysis for patients treated with breast-conserving surgery followed by radiotherapy only, radiotherapy and adjuvant systemic therapy, and radiotherapy, adjuvant systemic therapy and locoregional therapy

Finally, the fourth survival (figure 4) analysis represents the overall survival of the included patients (OS (in years)) in relation to the treatment groups. There was no significant difference found in mortality (p=0.804) up to 32 years after surgery.

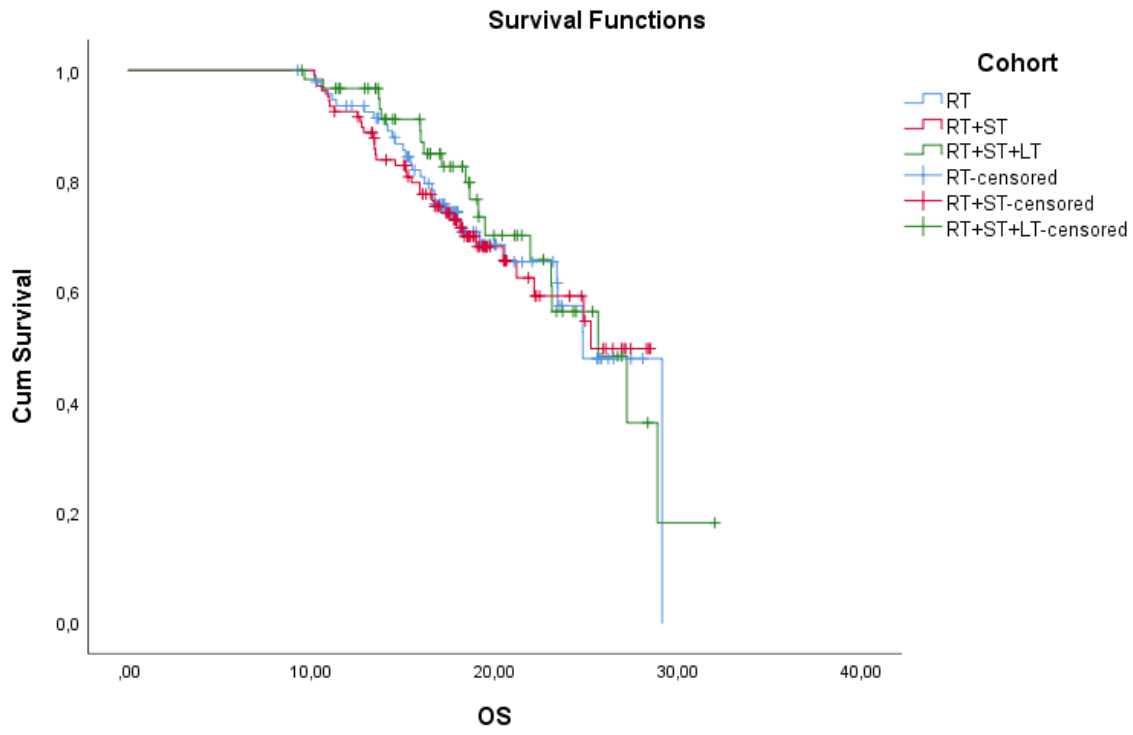

Figure 4. Overall survival (OS) in years by Kaplan-Meier analysis for patients treated with breast-conserving surgery followed by radiotherapy only, radiotherapy and adjuvant systemic therapy, and radiotherapy, adjuvant systemic therapy and locoregional therapy

DISCUSSION

This study was conducted to determine long-term general, cardiologic and neurological effects in breast cancer patients that were treated with BCS followed by radiotherapy with or without adjuvant systemic and locoregional therapy. Differences between these treatment groups were analysed to find possible correlations between treatment and diagnosed late effects. In total 264 patients were included in this study. The study results indicate that the follow-up period was comparable between the three cohorts, therefore the period of occurrence and diagnosis of adverse effects after BC treatment was similar for the different treatments. No significant differences were found in the survival distributions of neurological and cardiovascular disease free survival, however a significant difference in general disease free survival was found. Furthermore, the distribution of overall survival showed no significant difference.

General late effects

At a median follow-up time of 17.7 years, 88.4% of the patients treated with RT only suffered from general late effects, while 89.7% of the patients treated with RT + ST were diagnosed with at least one late effect and 96.8% of the patients that were treated with RT + ST +LT.

Patients in the third cohort suffered significantly more from exhaustion problems than patients in the first cohort (p=0.023). This is in line with Jacobsen et al. (1999) who concluded that exhaustion is indeed a long-term side effect of certain forms of breast cancer treatment [24]. A study from 2012, that recruited breast cancer patients diagnosed with breast cancer in 2001-2005, concluded, after a median follow-up of 5.8 years, that chemotherapy appears to have a stronger impact on long-term exhaustion problems than radiotherapy [25]. Fatigue levels substantially increased during both chemo – and radiotherapy, but patients who received both therapies reported higher fatigue levels than patients who received radiotherapy only. Exhaustion problems were widely known in this study, but the more extensive the received treatment, the more common it was diagnosed. Extensive treatments could therefore be possible markers for more aggressive disease, and result in more long-term exhaustion problems. Another significant increased risk was found for lymphedema. Patients in the third cohort were significantly more often diagnosed with lymphedema than patients in the first cohort, while overall, more than half of the included patients suffered from lymphedema. Most patients included in this study received lumpectomy + ALND (96.5%), compared to lumpectomy + SLND (1.5%) and lumpectomy only (2%) . Other studies show that ALND is associated with a higher risk of lymphedema than SLND and lumpectomy, which supports our findings [26-28]. Earlier studies also show that radiotherapy is an important risk factor for lymphedema, particularly radiation involving the axilla [28,29]. This could indicate that patients who receive more radiation through treatment, are more at risk of developing lymphedema. This is in line with our findings, since patients in the third cohort were the only treatment group that received locoregional radiotherapy next to the regular radiation.

Moreover, no significant difference was observed in OS between the three different cohorts, however, this study did observe a significant difference in disease free survival (figure 1), while the first and second cohort were comparable, the survival curve of the third cohort shows a lower disease free survival concerning general late effects. This may also be explained by the possibility of more aggressive disease in patients treated with RT + ST +LT, which was not taken into account in the survival analyses. It is highly plausible that patients, who suffered from more aggressive BC, received a more extensive treatment and therefore suffered from more late adverse effects.

Furthermore, exhaustion and lymphedema both had a considerable influence on the DFS, therefore the already mentioned risk factors can contribute to the significant difference in survival.

Cardiovascular late effects

In this study 35.6% of the patients were diagnosed with CVD or were in need of cardiovascular interventions during follow-up. No statistically significantly differences were found in DFS between patients treated with RT only, RT + ST and RT+ST+LT up to 32 years after BCS.
No cardiovascular interventions differed significantly, and most cardiac morbidities were comparable. A significant difference was found for ulceration of the irradiated skin, however, this effect was not taken into account because of unclear disease progression, since the ulceration will heal over time normally and therefore will not be a late adverse effect of BC treatment. Furthermore, a significant difference was found between the treatment groups for patients who suffered from angina pectoris (p=0.077). A study from James et al. estimated that for a 50-year-old woman without a cardiac risk history and a mean heart dose of 3 Gray, the risk of death because of ischaemic heart disease, would be increased from 1.9 to 2.4% with radiation treatment. When a woman was known with at least one cardiac risk factor, this risk would increase from 3.4 to 4.1% [30]. Another study from Darby et al. concluded that radiation exposure of the heart during radiotherapy increased the risk of developing ischaemic heart disease, proportionally to the mean dose to the heart. The increase in this study started within the first 5 years after RT and continued for at least 20 years [31]. This is in line with our findings, since the included patients were diagnosed with AP until 21 years after BCS followed by RT. In our study, most cases were found in the first and second cohort, while additional locoregional therapy in the third cohort resulted in fewer cases. This may be explained by the fact that patients in the third cohort were significantly younger than the patients in cohort 1 and 2. Age was determined to be of significant influence on the development of AP in this study, according our analyses (table 6+7). This could explain fewer cases of AP in patients treated with RT+ST+LT. Next to that, diabetes had a significant correlation with AP. This is highly plausible according Almdal et al. who revealed that Diabetes type 2 is an independent risk factor of ischemic heart disease, which often causes AP [32].

Moreover, this study shows a significant difference in right-sided breast cancer patients vs. left-sided breast cancer patients. Right- sided BC patients suffered more from cardiac morbidity and were more in need of a cardiac intervention, than left – sided breast cancer patients. Several studies have stated that left-sided breast cancer patients are more at risk of cardiac toxicity because of anatomy, than right-sided. However, modern irradiation techniques, such as three-dimensional conformal radiotherapy (3DCRT) and CT based irradiation, should reduce the heart doses and therefore the risk of cardiovascular adverse effects, significantly [22,33-35]. A study from Taylor et al. that compared Danish and Swedish BC radiotherapy during 1977-2001 concluded that the mean heart dose for women treated in Sweden decreased from 12.0 to 7.3 Gray for left-sided and from 3.6 to 3.2 Gray for right-sided radiotherapy [36]. Although a direct explanation for the higher probability of cardiac toxicity in right-sided BC patients in this study could not be found, the results could indicate that modern radiotherapy techniques do prevent the heart from being irradiated unnecessarily and therefore protect the patient from cardiac toxicity. Furthermore a difference was found for cardiomyopathy. According a study from Chen et al. which identified 45537 women with a mean age of 76.2 years between 2000 and 2007 cardiomyopathy is a common complication for older women after adjuvant systemic and chemotherapy. In this study the women were equally divided between the treatment groups, no direct explanation was found for the difference in laterality [37].

Finally, a significant difference was found for the need of an ICD in right-sided BC patients, however, there were few cases known, no further analysis was possible and no reliable assumptions could be made.

Neurological late effects

At a medium follow-up time of 17.7 years, 23.8% of the studied BC patients suffered from at least one neurological late effect. No significant difference was found in DFS between patients that were treated with radiotherapy only and radiotherapy + adjuvant chemo/hormonal therapy with or without locoregional therapy. Furthermore, no statistically significantly risk factors were found for neurologic toxicity between the cohorts.

Overall survival

The overall survival analyses in figure 4 showed comparable results for all three patient groups. This could indicate that the studied therapies were comparably effective in the treatment of BC. Assuming that patients who suffered from more aggressive BC, received more extensive treatment than patients who suffered from less severe BC.

Strengths and weaknesses

A strength of this study is the long follow-up period from 10 to 32 years, with a median of 17.7 years. The extensive follow-up period resulted in a clear reflection of the disease progression and possible adverse general, cardiovascular and neurological late events. Furthermore, the different cohorts can be compared well on the basis of the mean follow-up period (table 1).

In this study, a relatively small research population was included, which resulted in limited power. Some calculations were not possible and others were less reliable because few cases with long term adverse effects were observed. Furthermore, little was known about the lifestyle and genetic background of patients, therefore it was hard to determine whether a diagnosed adverse effect could be the result of BC treatment, or because of genetic influence or lifestyle factors. E.g. smoking habits were mainly noted, however, in most patient files it was not known how much the patient was smoking and if the patient was still smoking after BC treatment. Furthermore e.g. arrhythmia was regularly diagnosed in this research group, however, in most cases any genetic predisposition was not known.

Not all information was available in the electronic patient file, because of the long follow-up period, a big part of the data was not collected electronically by the medical specialists, which probably resulted in less usable documentation and missing values for this study.

Finally, it is desirable to include a control group who did not receive radio – and/or adjuvant systemic therapy, but only mastectomy. This control group, would better enable the examination of radiotherapy influences on BC patients.

CONCLUSION

In this study, a lower risk of angina pectoris was found for the RT+ST+LT cohort than for patients treated with RT only and RT+ST. Next to this a higher risk of cardiac morbidity was found for BC patients treated for right-sided BC vs. left-sided BC. This could indicate a more accurate irradiation in current techniques to prevent overdoses to the heart. Furthermore a significantly increased risk was found for lymphedema and exhaustion after BC treatment, these adverse effects should be carefully considered during treatment, because of their possible influence on quality of life of the patient. Finally, no significantly increased risk of neurological toxicity was found in patients treated with BCS followed by RT vs. patients that were treated with BCS followed by RT and adjuvant systemic therapy vs. patients treated with RT, adjuvant systemic therapy and locoregional therapy.
When looking at survival distributions, no significant differences were found for Cardiovascular – and neurological disease free survival, however, the general disease free survival was significantly lower for patients treated with RT+ST+LT than patients treated with RT only and RT+ST.
Further research with a larger study group and the inclusion of mastectomy as a control group is needed to give a better insight into possible late adverse effects and the differences between the several BC treatments and treated breast side. Next to this, the inclusion of mastectomy as a treatment is desirable to have a better understanding of the influence of RT.

REFERENCES

[1] Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., ... & Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer*, *136*(5), E359-E386.

[2] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *68*(6), 394-424.

[3] https://www.volksgezondheidenzorg.info/onderwerp/borstkanker/cijfers-context/trends#node-trend-nieuwe-gevallen-borstkanker

[4] https://www.rivm.nl/en/breast-cancer-screening-programme/breast-cancer-in-netherlands

[5] https://iknl.nl/oncologische-zorg/nieuws/nieuws-detail/2017/10/10/borstkanker-in-nederland-meer-aandacht-voor-behandeling-uitgezaaide-ziekte

[6] Harding, C., Pompei, F., Burmistrov, D., & Wilson, R. (2019). Long-term relationships between screening rates, breast cancer characteristics, and overdiagnosis in US counties, 1975–2009. *International journal of cancer*, *144*(3), 476-488.

[7] Paci, E., Miccinesi, G., Puliti, D., Baldazzi, P., De Lisi, V., Falcini, F., ... & Rosso, S. (2006). Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. *Breast Cancer Research*, *8*(6), R68.

[8] Bleyer, A., & Welch, H. G. (2012). Effect of three decades of screening mammography on breast-cancer incidence. *New England Journal of Medicine*, *367*(21), 1998-2005.

[9] Welch, H. G., & Black, W. C. (2010). Overdiagnosis in cancer. *Journal of the National Cancer Institute*, *102*(9), 605-613.

[10] Miller, K. D., Siegel, R. L., Lin, C. C., Mariotto, A. B., Kramer, J. L., Rowland, J. H., ... & Jemal, A. (2016). Cancer treatment and survivorship statistics, 2016. *CA: a cancer journal for clinicians*, *66*(4), 271-289.

[11] Mols, F., Vingerhoets, A. J., Coebergh, J. W., & van de Poll-Franse, L. V. (2005). Quality of life among long-term breast cancer survivors: a systematic review. *European journal of cancer*, *41*(17), 2613-2619.

[12] Fanous, I., & Dillon, P. (2015). Paraneoplastic neurological complications of breast cancer. *Experimental hematology & oncology*, *5*(1), 29.

[13] Bodai, B. I., & Tuso, P. (2015). Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. *The Permanente Journal*, *19*(2), 48.

[14] Mehta, L. S., Watson, K. E., Barac, A., Beckie, T. M., Bittner, V., Cruz-Flores, S., ... & Pina, I. L. (2018). Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation, 137(8), e30-e66.

[15] Patnaik, J. L., Byers, T., DiGuiseppi, C., Dabelea, D., & Denberg, T. D. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Research, 13(3), R64.

[16] Ewertz, M., & Jensen, A. B. (2011). Late effects of breast cancer treatment and potentials for rehabilitation. Acta Oncologica, 50(2), 187-193.

[17] Azim Jr, H. A., De Azambuja, E., Colozza, M., Bines, J., & Piccart, M. J. (2011). Long-term toxic effects of adjuvant chemotherapy in breast cancer. Annals of oncology, 22(9), 1939-1947.

[18] Pereira, S., Fontes, F., Sonin, T., Dias, T., Fragoso, M., Castro-Lopes, J., & Lunet, N. (2014). Neurological complications of breast cancer: study protocol of a prospective cohort study. BMJ open, 4(10), e006301.

[19] TNM classification version 7 (Sobin LH, Gospodarowicz MK, Wittekind Ch. *TNM classification of malignant tumours.* UICC, seventh edition, 2009)
https://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&id=40075&richtlijn_id=1014.

[20] Khan, J. C., Thurlby, D. A., Shahid, H., Clayton, D. G., Yates, J. R. W., Bradley, M., ... & Bird, A. C. (2006). Smoking and age-related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. *British Journal of Ophthalmology*, *90*(1), 75-80.

[21] Piroth, M. D., Baumann, R., Budach, W., Dunst, J., Feyer, P., Fietkau, R., ... & Röser, A. (2019). Heart toxicity from breast cancer radiotherapy. *Strahlentherapie und Onkologie*, *195*(1), 1-12.

[22] Sardaro, A., Petruzzelli, M. F., D'Errico, M. P., Grimaldi, L., Pili, G., & Portaluri, M. (2012). Radiation-induced cardiac damage in early left breast cancer patients: risk factors, biological mechanisms, radiobiology, and dosimetric constraints. *Radiotherapy and Oncology*, *103*(2), 133-142.

[23] Hooning, M. J., Botma, A., Aleman, B. M., Baaijens, M. H., Bartelink, H., Klijn, J. G., ... & Van Leeuwen, F. E. (2007). Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *Journal of the National Cancer Institute*, *99*(5), 365-375."

[24] Jacobsen, P. B., & Stein, K. (1999). Is Fatigue a Long-term Side Effect of Breast Cancer Treatment? Breast cancer patients are more likely to experience fatigue following adjuvant chemotherapy or autologous bone marrow transplantation than following regional therapy. *Cancer Control*, *6*(3), 256-263.

[25] Schmidt, M. E., Chang-Claude, J., Vrieling, A., Heinz, J., Flesch-Janys, D., & Steindorf, K. (2012). Fatigue and quality of life in breast cancer survivors: temporal courses and long-term pattern. *Journal of Cancer Survivorship*, *6*(1), 11-19.

[26] Armer, J. M., Fu, M. R., Wainstock, J. M., Zagar, E., & Jacobs, L. K. (2004). Lymphedema following breast cancer treatment, including sentinel lymph node biopsy. *Lymphology*, *37*(2), 73-91.
[27] Lucci, A., McCall, L. M., Beitsch, P. D., Whitworth, P. W., Reintgen, D. S., Blumencranz, P. W., ... & Giuliano, A. E. (2007). Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *Journal of Clinical Oncology*, *25*(24), 3657-3663.

[28] Norman, S. A., Localio, A. R., Kallan, M. J., Weber, A. L., Torpey, H. A. S., Potashnik, S. L., ... & Solin, L. J. (2010). Risk factors for lymphedema after breast cancer treatment. *Cancer Epidemiology and Prevention Biomarkers*, *19*(11), 2734-2746.

[29] Wanchai, A., Armer, J. M., Stewart, B. R., & Lasinski, B. B. (2016). Breast cancer-related lymphedema: A literature review for clinical practice. *International Journal of Nursing Sciences*, *3*(2), 202-207.

[30] James, M., Swadi, S., Yi, M., Johansson, L., Robinson, B., & Dixit, A. (2018). Ischaemic heart disease following conventional and hypofractionated radiation treatment in a contemporary breast cancer series. *Journal of medical imaging and radiation oncology*, *62*(3), 425-431.

[31] Darby, S. C., Ewertz, M., McGale, P., Bennet, A. M., Blom-Goldman, U., Brønnum, D., ... & Jensen, M. B. (2013). Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine*, *368*(11), 987-998.

[32] Almdal, T., Scharling, H., Jensen, J. S., & Vestergaard, H. (2004). The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13 000 men and women with 20 years of follow-up. Archives of internal medicine, 164(13), 1422-1426.

[33] Menezes, K. M., Wang, H., Hada, M., & Saganti, P. B. (2018). Radiation matters of the heart: a mini review. *Frontiers in cardiovascular medicine*, *5*, 83.

[34] Erven, K., Jurcut, R., Weltens, C., Giusca, S., Ector, J., Wildiers, H., ... & Voigt, J. U. (2011). Acute radiation effects on cardiac function detected by strain rate imaging in breast cancer patients. *International Journal of Radiation Oncology* Biology* Physics*, *79*(5), 1444-1451.

[35] Baglan, K. L., Sharpe, M. B., Jaffray, D., Frazier, R. C., Fayad, J., Kestin, L. L., ... & Vicini, F. A. (2003). Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). *International Journal of Radiation Oncology* Biology* Physics*, *55*(2), 302-311.

[36] Taylor, C. W., Brønnum, D., Darby, S. C., Gagliardi, G., Hall, P., Jensen, M. B., ... & Ewertz, M. (2011). Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977–2001. Radiotherapy and Oncology, 100(2), 176-183.

[37] Chen, Jersey, et al. "Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer." Journal of the American College of Cardiology 60.24 (2012): 2504-2512.

[38] Behandeling van borstkanker. Chemotherapie bij borstkanker. kanker.nl. Dec 2018. Available from: https://www.kanker.nl/kankersoorten/borstkanker/behandeling-van-borstkanker/chemotherapie-bij-borstkanker

[39] Chemotherapy for Breast Cancer. American Cancer Society. Oct 2017. Available from: https://www.cancer.org/cancer/breast-cancer/treatment/chemotherapy-for-breast-cancer.html

[40] https://www.cancer.org/cancer/breast-cancer/living-as-a-breast-cancer-survivor/follow-up-cfter-breast-cancer-treatment.html

[41] Collins, R. F., Bekker, H. L., & Dodwell, D. J. (2004). Follow-up care of patients treated for breast cancer: a structured review. *Cancer treatment reviews*, *30*(1), 19-35.

[42] Landelijke richtlijn borstkanker. Nazorg en controle. Oncoline.nl. Feb 2013. Available from: https://www.oncoline.nl/borstkanker

APPENDIX I – DESCRIPTION OF TREATMENT

Chemotherapy is a treatment with cytostatic drugs that can be given intravenously or oral. These drugs kill the cancer cells or slow down the cell division. The drugs spread through most parts of the body within the blood vessels to reach cancer cells. Chemotherapy is given for a period of three to six months in several cycles alternated by periods of rest [38,39]. Hormonal therapy is a treatment with medicines that reduce the production of hormones or reduce their influence. This treatment can only be successful if the breast cancer is hormone receptor-positive. Hormonal therapy mostly consists of tamoxifen in combination with aromatase inhibitors [38,39]. Postmenopausal women are treated five to ten years, a few years of tamoxifen, followed by aromatase inhibitors for a few years, or in reversed order. Premenopausal women are mostly treated with tamoxifen for five years. In metastatic breast cancer the duration of the treatment can be extended to ten years. In this case the goal is not to cure but to inhibit the cancer [38,39]. After treatment patients will receive follow-up care for at least five years. At first every few months, but the frequency of these appointments will decrease during time [40]. This follow-up first aims to be able to early detect recurrence of the breast cancer or new primary tumours by annually taking a mammography. Next to that, one can evaluate the provided therapy, screen for possible associated side effects, give psychosocial support and determine the quality of life of the patient [41,42]. After five years a patient is usually referred back to the family doctor, mammography will then take place every two years at the hospital [41].

APPENDIX II – PATIENT CHARACTERISTICS RIGHT – AND LEFT-SIDED BREAST CANCER

Table 12. Patient and treatment characteristics comparison in women treated for right or left-sided breast cancer

	Rigth - sided	Left - sided	P-value
Characteristics			
Follow-up years (Mean ± SD)	17.67 (± 4.5)	18.66 (± 4.7)	
Age(Mean ± SD)	55.45 (± 9.5)	53.98 (± 9.6)	0.213
*Height, cm (Mean ± SD)**	165.3 (± 6.2)	166.4 (± 5.7)	0.240
*Weight, kg (Mean ± SD)***	76.2 (± 14.3)	76.6 (± 16.1)	0.861
*BMI, kg/m^2 (Mean ± SD)****	27.9 (± 5.2)	27.6 (± 6.9)	0.761
Smoking habits			0.451*****
Smoker + Ex-smoker	43 (33.3%)	47 (34.8%)	
Smoker	22 (17.1%)	28 (20.7%)	
Ex-smoker	21 (16.3%)	19 (14.1%)	
Never-smoker	86 (66.7%)	88 (65.2%)	
Comorbidities			
Diabetes	18 (14.0%)	23 (17.0%)	0.502
Hypertension	50 (38.8%)	48 (35.6%)	0.612
Hypercholesterolaemia	22 (17.1%)	27 (20.0%)	0.635
Number of medications	0.8 (± 1.3)	0.9 (± 1.4)	0.786
Surgical treatment			0.878
Lumpectomy	3 (2.3%)	2 (1.5%)	
Lumpectomy + ALND	124 (96.1%)	131 (97%)	
Lumpectomy + SLND	2 (1.6%)	2 (1.5%)	
Oncological treatment			0.154
Hormonal therapy	38 (29.5%)	42 (31.1%)	
Chemotherapy	20 (15.5%)	30 (22.2%)	
Hormonal -and chemotherapy	25 (19.4%)	14 (10.4%)	
No oncological treatment	46 (35.7%)	49 (36.3%)	

**known for 157 women **know for 228 women ***known for 157 women ****Smokers and ex-smokers combined vs never-smokers*