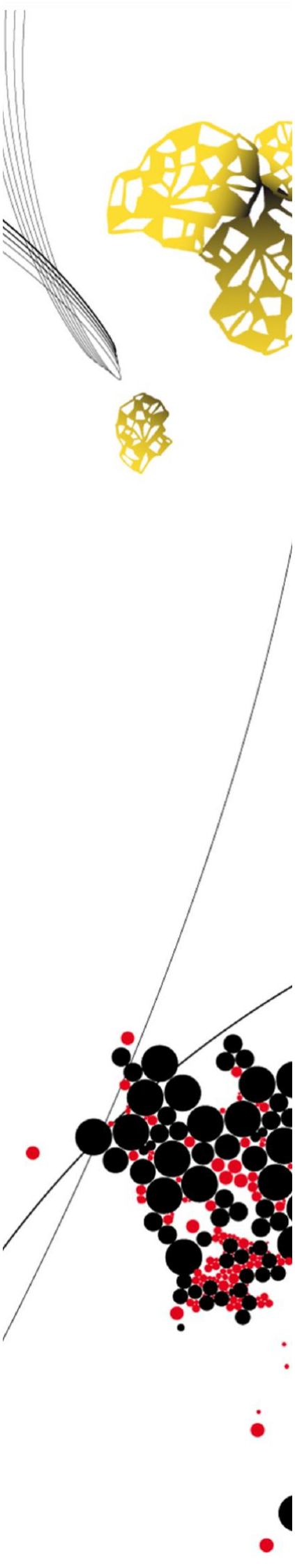

UNIVERSITY OF TWENTE.

Faculty of Science and Technology

Late, treatment associated morbidity after breast-conserving therapy in breast cancer patients.

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M.Sc. Thesis

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Abstract

Background: Breast cancer is 1 of the most common types of cancer in the Netherlands. There are several treatment options that depend on different factors. There are two types of surgery: mastectomy and breast conserving surgery. Breast conserving surgery is generally combined with radiotherapy. Mastectomy is combined with radiotherapy if necessary. Both forms of surgical treatments are combined with systemic therapy if indicated. Systemic treatment may include chemotherapy with or without immunotherapy and/or hormonal therapy. Several studies have been conducted on short-term side effects. However, little to no data is known about long-term side effects of these different treatment methods. The aim of this study is to investigate effects more than ten years after treatment of different breast cancer treatments.

Method: A retrospective cohort study was conducted with 4 cohorts. These cohorts consist of 1) women who underwent mastectomy without any adjuvant treatment, 2) breast conserving surgery with whole breast radiotherapy, 3) breast conserving surgery with whole breast radiotherapy and adjuvant systemic treatment and 4) breast conserving surgery with whole breast radiotherapy and regional radiotherapy and adjuvant systemic treatment. The data were collected from the databases (EPD's) of Ziekenhuisgroep Twente (ZGT), Medisch Spectrum Twente (MST) and Nederlandse Kanker Registratie (IKNL) and consists of women treated between 2000 and 2009. The data are divided into t0 (the moment of surgery), t1 (up to 10 years after surgery) and t2 (≥ 10 years after surgery).

Results: Cohort 4 is 1.5 times more likely to develop general adverse effects compared with cohort 1 and 2.5 times more likely to develop pulmonary adverse effects. Lymphedema of the arm (p=<.001) and pulmonary fibrosis were also most common among women in cohort 4. Breast/thoracic wall pain (p=.002) was most common among women in cohort 2. Myocardial infarction and conduction disorders were most common among women in cohort 3. Survival data show for pulmonary effects much lower for cohort 4 compared to the other cohorts. This is also true for osteopenia. Regarding myocardial infarction, cohort 3 shows lower values compared to the other cohorts.

Conclusion: This study shows evidence of significant differences in late adverse events. The most significant differences belong to the category of general adverse effects and these are most common in women who have had breast-conserving therapy followed by whole breast irradiation and regional irradiation, adjuvant chemotherapy with or without immunotherapy and/or hormonal treatment. Through the results, women can make considerations regarding the shared decision-making process.

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Introduction

Breast cancer is 1 of the most common types of cancer. In the Netherlands, 1 in 7 women will develop breast cancer. In 2019, 14,808 women were diagnosed with breast cancer. Breast cancer occurs mainly in women between the ages of 50 and 70, but it can occur at any age. Of all patients, 20% are younger than 50 years. Partly because of research, the 5-year breast cancer survival rate has increased from 52% to 89% over the past 60 years [1]. The majority of breast cancer-related fatalities in women occur as a result of the disease's metastatic spread rather than the development of the main tumor [2].

There are different types and grades of breast cancer that develop in the breast. This is divided into invasive and non-invasive breast cancer. Non-invasive breast cancer, or also called carcinoma in situ, does not spread into surrounding tissue and thus cannot metastasize. This type is often found through a screening mammogram and will rarely present as a lump in the breast. The most common type of breast cancer is invasive ductal carcinoma. This type of cancer originates in the milk ducts and spreads to surrounding tissue. Moreover, this type can metastasize through the lymph nodes or bloodstream. Tumor on which breast cancer is classified are HER2-positive breast cancer, ER and PR-receptor positive breast cancer and inflammatory breast cancer [3].

Local treatment

There are several treatment options for breast cancer. Multiple factors influence the treatment choice: the patient's age, the subtype of the tumor including the stage of the tumor, hormone receptor status, HER2 status, genomic testing, general health, menopausal status, the presence of mutations in inherited breast cancer genes and patient preferences [2].

Early stages (M0) of invasive breast cancer will generally be treated first by surgery. The aim of this surgery is to remove the tumor with a margin and the assessment and removal of the axillary gland for any metastases. The tumor is pathologically examined and if tumor cells are present in the margin, sometimes a second operation will have to take place to remove the remaining cells when indicated. Occasionally it is necessary to remove the entire breast (mastectomy) or a combination of breast-conserving therapy and radiotherapy. The most common side effects of mastectomy surgery are impaired arm and shoulder mobility, impaired aesthetics, breast asymmetry, pain and lymphedema.

For higher stages of invasive breast cancer, it is often advised to do a combination of (neo)adjuvant systemic therapy, surgery and radiotherapy. Moreover, the sentinel node procedure is always used in these forms. This involves searching for and removing the sentinel node. When metastases are found, axillary gland dissection usually follows. The main side effects of the axillary procedure are lymphedema of the arm, axillary pain and shoulder function limitation.

As mentioned before, radiotherapy is another form of therapy that can be used. Radiotherapy involves the use of X-rays, a radioactive source or both. The aim of this therapy is to kill cancer cells locally.

Radiotherapy can also cause several side effects. The side effects of radiotherapy are mainly determined by the area being irradiated. In addition, fatigue may occur. A study conducted in 2016 among breast cancer patients concluded that the most common side effects were skin erythema, fatigue, telangiectasia, pain, breast swelling, and loss of hair in the armpit and chest area. Less common side effects are breast shrinkage, lymphedema, cardiac complications, lung problems, sore throat, brachial plexopathy, and damage to the bones [4].

Systemic treatment

Moreover, there are also forms of systemic treatments. These treatments may include hormonal therapy, immunotherapy, chemotherapy. The choice of the best systemic treatment depends on several factors, such as tumor characteristics, tumor burden, risk of toxicity, age, patient preferences, history of treatments, co-morbidities, severity of tumor-related symptoms and metastasis sites [5].
Combination of two or more regimens of local therapy and systemic treatment can improve the quality of life, mainly for patients with metastatic breast cancer [2]. Moreover, the MammaPrint has been developed. This test can predict which women need additional chemotherapy and who do not. This reduces the chances that there are women who will receive chemotherapy unnecessarily.

Hormonal therapy, applied to hormone sensitive tumors, often known as endocrinal therapy, is a successful and well-tolerated anti-cancer medication. The toxicity associated with the other treatments is also reduced with the use of hormonal therapy. Additionally, it may be administered prior to surgery, after surgery, or in palliative treatment [2].
However, individuals may experience sensitivity to hormone therapy or resistance. Hormonal therapy has several side effects. A study conducted between 2012 and 2013 concluded that hot flushes, sweats, joint pain, weight gain, reduction in libido and reduction in energy were the most common. Overall, more than half of the women reported being somewhat to highly affected by the side effects [6].

Another form of therapy is chemotherapy. These cytotoxic drugs can be administered orally or intravenously to kill cancer cells throughout the body [5]. However, this form of therapy also has multiple side effects. It varies per individual how much it affects a person and which side effects they will experience. The most common potentially life-threatening side effects are high fever and bleeding or bruising. In addition, flu-like symptoms, sore mouth or soreness in the vein are risky if they get worse [7]. Other side effects that are common include diarrhea, fatigue, nausea and vomiting, hair loss, constipation, problems with mouth, throat and gums and poorer condition [8]. Chemotherapy is combined with immunotherapy in Her2Neu-receptor positive breast cancer. The most common side effects of immunotherapy are fever, chills and fatigue. Side effects that are less common are diarrhea, nausea, skin rashes, dizziness and abdominal pain.

Most of the side effects mentioned so far are short-term side effects. However, little is known about long-term side effects in relation to the different treatments. The aim of this study is therefore to determine long-term side effects related to the different treatments in women who have achieved at least 10 years of follow-up. This results in the following research question:

What are the long-term adverse effects (up to 10 years and beyond) after mastectomy surgery compared with breast-conserving therapy combined with radiotherapy, chemotherapy (with or without immunotherapy) and/or hormonal therapy in terms of neurological, pulmonary, cardiac and general adverse effects?

Method

Study design

The design of this study is a retrospective cohort study, investigating long-term effects related to the treatment of breast cancer.

Study population

Table 1 shows the 4 cohorts of this study. The data was collected from the databases (EPD's) of Ziekenhuisgroep Twente (ZGT) and Medisch Spectrum Twente (MST), in the Netherlands. Data were also obtained from the Dutch Cancer Registry (IKNL) for the women with mastectomy surgery only. All patients have been treated for breast cancer between 2000 and 2009.

Table 1: The treatments of the four different cohorts of patients

Cohort 1	Control group: only mastectomy
Cohort 2	Breast conserving surgery (BCS) followed by whole breast irradiation (WBI)
Cohort 3	BCS followed by WBI, adjuvant chemotherapy with or without immunotherapy and/or hormonal treatment
Cohort 4	BCS followed by WBI and regional irradiation, adjuvant chemotherapy with or without immunotherapy and/or hormonal treatment

Patients were selected who received treatment for breast cancer between the years 2003 and 2009. There were 6 exclusion criteria:

1. Follow-up data from surgery is less than 10 years.
2. No axillary-stage surgery.
3. Distant metastasis has occurred within 10 years of treatment.
4. Ipsilateral loco and/or regional recurrence of mammary carcinoma within 10 years of treatment.
5. Contralateral mammary carcinoma before treatment, at the time of treatment or within 10 years of treatment. Patients who underwent secondary ablation (for no malignancy) because of gene carrier or other reason or ablation because of DCIS (without radiotherapy) were not excluded.
6. Other malignancy before treatment, at the time of treatment or within 10 years of treatment for which radiotherapy or systemic therapy was given, excluding basal cell carcinoma or squamous cell carcinoma of the skin that has been irradiated.

Data collection

The data were divided about 3 time periods. The time of surgery is identified as t0. In cohort 1, t0 is identified as the time of mastectomy. In cohorts 2, 3 and 4, t0 is the time of the first lumpectomy. A time of 10 years after the primary treatment is named as t1 and t2 means the time longer than 10 years after treatment. First, data is collected at the time of t0. Here, the patient's Body Mass Index (BMI) is calculated and information on diabetes and insulin dependence, hypertension, hypercholesterolemia, smoking and medication. Furthermore, treatment related information was collected: the surgery performed, the pT and pN stage of the tumor, left or right localisation of the tumor, whether radiotherapy was received and if so, what type of radiotherapy, whether systemic treatment has been given and if so, which form of systemic treatment, and whether there were any recurrence of breast disease or other tumors or second breast cancer contralateral. Finally, the variables were categorized into general effects present before or during treatment (t0), general late effects (t1 and t2), neurological effects present before or during treatment (t0), neurological late effects (t1 and t2), pulmonary effects present before or during treatment (t0), pulmonary late effects (t1 and t2), cardiac effects present before or during treatment (t0) and cardiac late effects (t1 and t2). Adverse effects are considered late effects at t1. However, when certain complications were already present at t0, these complications are not considered late effects unless they are cases that are expected to be transient. An overview of all variables and the variables associated with the categories is given in Appendix A. Some variables, such as COPD, are divided into t0, late effect and new. COPD new is identified when the patient acquired COPD after treatment or when the patient already had this condition at t0 but experienced exacerbation due to medication, for example. The variables osteopenia and osteoporosis were differentiated separately. However, when a patient has osteoporosis, that patient also has osteopenia. For the women with mastectomy treatment, the late adverse effects of treatment were recorded from 3 months after t0. For women with breast-conserving surgery, radiotherapy and/or antihormonal therapy, it is 6 months after t0 and for women with breast-conserving therapy, radiotherapy and adjuvant chemotherapy with/ without immunotherapy (and/or antihormonal therapy), 12 months after t0. From here, the follow up time starts.

The data collected comes from various sources, such as pathology reports, blood tests, various records, DEXA scans, MRI scans etc. and letters and other notes from the specialists or GPs.

CTCAE score

The status of undesirable late effects was scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The score refers to the severity of the effect. There are 5 grades:

Grade 1: mild symptoms, asymptomatic, clinical or diagnostic observations only, intervention not indicated.

Grade 2: moderate, minimal, local or non-invasive intervention indicated, limitation of age-appropriate instrumental ADL.

Grade 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, limitation of self-care ADL.
Grade 4: life-threatening consequences, urgent intervention indicated.
Grade 5: death. Patients may have died from metastases of the primary breast cancer, from other tumours or from other causes such as cardiac problems. However, these patients were included in the study.

Statistical analysis

The statistical software IBM SPSS version 25 was used for the analyses. First, data has been prepared. Missing values were detected through frequency tables and adjusted or filled in as necessary. Histograms were made for all significant variables to check whether the data were normally distributed. General data are presented by patient group. This includes demographic data and underlying conditions. A series of tests were used to examine whether there were significant differences between the distributions of the 4 groups. For continuous normally distributed variables, the one-way ANOVA was used. For non-normally distributed variables the Kruskal Wallis test was used and for categorical variables the Chi-squared test. When a variable has a value <0.10, it is included for confounding.
Then, 4 new variables were created with the time from surgery until someone suffered a first adverse effect. These effects were categorized into the 4 groups: general, neurological, pulmonary and cardiac. A Cox regression was used to look for statistically significant differences in survival of the different cohorts with associated hazard ratios and confidence intervals. To make it more visual, Kaplan Meier curves have been created for the 4 categories with the corresponding Log Rank Mantel Cox values. Then the categories were specified into the different adverse effects with corresponding frequencies and p-values by means of cross tables. Variables where statistically significant differences were found (p=<0.10) were included for further analysis.
Hazard ratios and confidence intervals were also created for these specific variables using Cox regression. Potential confounders for each variable were added to the Cox regression model. Confounders per variable were determined using a one-way ANOVA and a Chi-square test. When a statistically significant difference was demonstrated between the 4 groups (p=<0.10) in the univariate model, this variable was included as a confounder and a second multivariate model was run with the adverse effect and potential confounder. When the multivariate model showed that the confounder was not significant, this variable was removed from the model. All variables included in the analysis are visually represented by means of a Kaplan Meier curve. Moreover, a Landmark Analysis was done from 10 years after surgery. The x-axis of all landmark analysis figures start from 10 years after treatment.

Results

A total of 403 women were included in the study. Of these, 119 were in cohort 1, 94 in cohort 2, 134 in cohort 3 and 56 in cohort 4. The mean age of all cohorts combined is 59.2 ± 10.2 years. The mean follow-up duration of all cohorts is 12.8 ± 1.8 years. Table 2 shows the patient characteristics for each cohort. The patient characteristics differed between the cohorts for insulin dependent Diabetes Mellitus, hypercholesterolemia, smoking, pT (tumour size), pN (nodal status), type of axillary surgery and metastases. 36.1% of women in cohort 1 had axillary node dissection compared with 63.9% who had sentinel node biopsy. In cohort 2, this was 13.8% versus 86.2%; in cohort 3 41.8% versus 58.2%, and in cohort 4 92.9% versus 7.1% women (p=<.001). Finally, 1.7% of the women in cohort 1 developed metastases, versus none in cohort 2, 1.5% in cohort 3, and 14.3% in cohort 4 (p=<.001).

Table 2: Baseline patient characteristics per cohort

	Cohort 1 (n=119)	Cohort 2 (n=94)	Cohort 3 (n=134)	Cohort 4 (n=56)	p-value
Age at diagnosis (years)	60.66 ± 9.9	59.86 ± 9.4	58.2 ± 11.0	57.1 ± 9.6	**.089**
BMI	27.4 ± 5.2	26.7 ± 7.2	27.5 ± 5.1	26.5 ± 5.0	.592
Duration of the follow-up (years)	13.0 ± 1.9	13.0 ± 1.3	12.0 ± 5.1	13.7 ± 2.4	**<.001**
Presence of disease during t0					
Diabetes Mellitus	15 (12.6%)	9 (9.6%)	14 (10.4%)	3 (5.4%)	.642
Insulin dependent Diabetes Mellitus	7 (5.9%)	4 (4.3%)	1 (0.7%)	0	<.001
Hypertension	43 (36.1%)	38 (40.4%)	56 (41.8%)	15 (26.8%)	.383
Hypercholesterolemia	32 (26.9%)	14 (14.9%)	21 (15.7%)	4 (7.1%)	**.007**
Smoking Never smoker Past smoker Present smoker	 71 (59.7%) 18 (15.1%) 19 (16.0%)	 48 (51.1%) 17 (18.1%) 29 (30.9%)	 82 (61.2%) 16 (11.9%) 36 (26.9%)	 39 (69.7%) 6 (10.7%) 11 (19.6%)	**<.001**
Pack years of smoking	11.73 ± 17.3	15.6 ± 20.9	12.0 ± 15.9	27.5 ± 17.2	.141
Number of medications	1.9 ± 2.3	2.7 ± 2.2	1.7 ± 2.0	1.2 ± 1.8	**.031**
Tumour specifications					

Laterality Right Left	 69 (58.0%) 95 (79.8%)	 42 (44.7%) 52 (55.3%)	 63 (47.0%) 71 (53.0)	 28 (50.0%) 28 (50.0%)	.206
pT (tumour size) T1a: 0.1cm - 0.5cm T1b: >0.5cm - 1.0cm T1c: >1.0cm - 2.0cm T1: ≤ 2cm T2: > 2cm - <5.1cm T1: multifocal T2: multifocal	 29 (24.4%) 27 (22.7%) 42 (35.3%) 1 (0.8%) 12 (10.1% 7 (5.9%)	 7 (7.4%) 38 (40.4%) 43 (45.7%) 2 (2.1%) 4 (4.3%)	 5 (3.7%) 73 (54.5%) 1 (0.7%) 49 (36.6%) 5 (3.7%) 1 (0.7%)	 3 (5.4%) 23 (41.1%) 28 (50.0%) 1 (1.8%) 1 (1.8%)	**<.001**
pN (nodal status) N0 N0 ITC (isolated tumor cells) N1: 1-3 N2: 4-9 N3: >9 N1 micro	 109 (91.6%) 1 (0.8%) 4 (3.4%) 5 (4.2%)	 82 (87.2%) 9 (9.6%) 3 (3.2%)	 81 (60.4%) 4 (3.0%) 40 (29.9%) 9 (6.7%)	 13 (23.2%) 36 (64.3%) 6 (10.7%) 1 (1.8%)	**<.001**
Type of axillary staging: Axillary dissection Sentinel node biopsy	 43 (36.1%) 76 (63.9%)	 13 (13.8%) 81 (86.2%)	 56 (41.8%) 78 (58.2%)	 52 (92.9%) 4 (7.1%)	**<.001**
Adjuvant treatment Chemotherapy Hormone therapy Chemotherapy + hormone therapy Chemotherapy + immunotherapy Chemotherapy + immunotherapy + hormone therapy			 23 (17.2%) 63 (47.0%) 39 (29.1%) 2 (1.5%) 6 (4.5%)	 9 (16.1%) 14 (25.0%) 29 (51.8%) 2 (3.6%) 1 (1.8%)	**<.001**
Local recurrence	2 (1.7%)	3 (3.2%)	4 (3.0%)	3 (5.4%)	.614
Regional recurrence	0	0	1 (0.7%)	1 (1.8%)	.374
Second contralateral primary breast tumor	11 (9.2%)	3 (3.2%)	6 (4.5%)	1 (1.8%)	.104
Second primary tumor elsewhere	24 (20.2)	20 (21.3%)	24 (17.9%)	14 (25.0%)	.731

Cohort 1: BMI 10 missing, medications number 2 missing, pT 1 missing

Cohort 2: BMI 12 missing, locoregional recurrence 1 missing

Cohort 3: BMI 9 missing, adjuvant treatment 1 missing

Cohort 4: BMI 9 missing, medication number 1 missing, adjuvant treatment 1 missing

Table 3 shows the uncorrected Hazard Ratio's for the different cohorts compared to Cohort 1 (referent). The general adverse effects category shows a statistically significant (p=<0.10) difference between

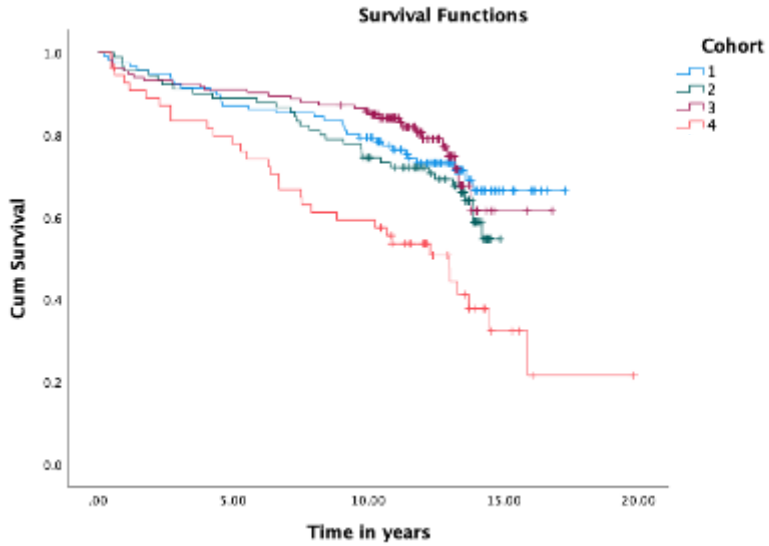
cohorts. Women in cohort 4 are 1,5 times more likely to develop general adverse effects compared to cohort 1 (p=.027). The pulmonary category shows a significant hazard ratio for women in cohort 4 compared with women in cohort 1. Women in cohort 4 are 2.47 times more likely to experience a pulmonary adverse effect compared with women in cohort 1.

Table 3: Cox regression of the adverse effects per cohort

Adverse effects	Cohort 1	Cohort 2 HR (95.0% CI)	Cohort 3 HR (95.0% CI)	Cohort 4 HR (95.0%)
General	Referent	1.08 (0.80 - 1.47)	1.20 (0.91 - 1.58)	**1.50 (1.05 - 2.13)**
Neurological	Referent	0.95 (0.58 - 1.57)	1.01 (0.63 - 1.60)	0.82 (0.45 - 1.51)
Pulmonary	Referent	1.26 (0.78 - 2.04)	0.89 (0.54 - 1.46)	**2.47 (1.52 - 4.02)**
Cardiac	Referent	1.38 (0.87 - 2.18)	1.22 (0.78 - 1.92)	0.64 (0.36 - 1.15)

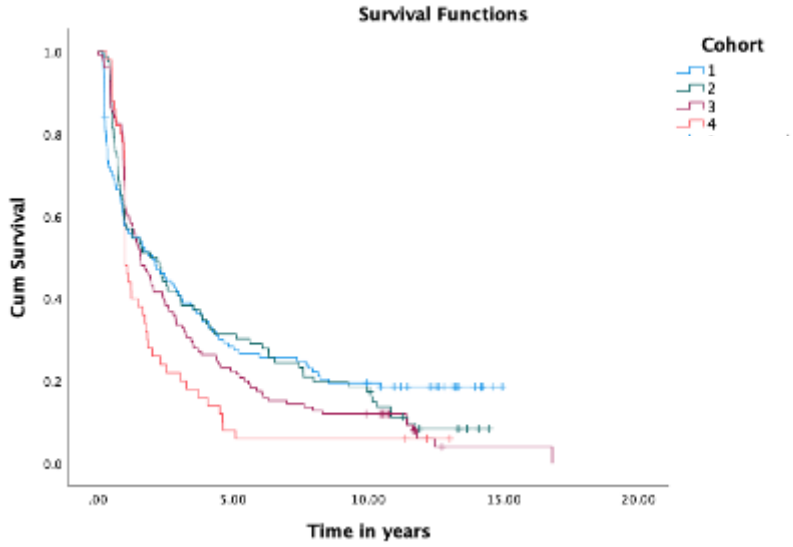
Figure 1 shows the graphical representation for event-free survival related to pulmonary events. Cohort 4 has more pulmonary events than cohorts 1, 2 and 3. Figure 2 presents the curve of general adverse effects. The survival curves of the other categories are in Appendix B.

Figure 1: Survival curve regarding pulmonal adverse events.



Log Rank Mantel Cox = <.001

Figure 2: Survival curve regarding general events



Log Rank Mantel Cox = .146

Table 4 shows the Cox regression for the different cohorts corrected for any confounders, with cohort 1 as the referent cohort. Cohort 4 shows a corrected hazard ratio of 1.76 (1.21 - 2.56) for the time to develop a general adverse event compared to cohort 1. This also applies to cohort 3 with a HR of 1.32 (1.00 - 1.76). The time to occurrence of a pulmonary event for cohort 4, adjusted for confounders, is 2.72 (1.65 - 4.47) compared with cohort 1. The time to a cardiac event has a significantly increased hazard ratio for cohort 2 of 1.51 (0.95 - 2.42) compared to cohort 1.

Table 4: Cox regression adjusted for confounders

Adverse effects	Cohort 1	Cohort 2 HR (95.0% CI)	Cohort 3 HR (95.0% CI)	Cohort 4 HR (95.0%)
General Adjusted: number of medications, pT	Referent	1.05 (0.78 - 1.43)	**1.32 (1.00 - 1.76)**	**1.76 (1.21 - 2.56)**
Neurological Adjusted: number of medications, hypercholesterolemia, pT	Referent	0.99 (0.59 - 1.66)	1.27 (0.79 - 2.04)	1.32 (0.69 - 2.52)
Pulmonary Adjusted: smoking, number	Referent	0.98 (0.60 - 1.60)	0.81 (0.49 - 1.34)	**2.72 (1.65 - 4.47)**

of medications				
Cardiac Adjusted: follow up, number of medications, age	Referent	**1.51 (0.95 - 2.42)**	1.32 (0.81 - 2.15)	1.01 (0.56 - 1.85)

Table 5 shows the numbers for overall effects at the time of T0, as a late effect and presence ≥ 10 years after treatment. ≥ 10 years after treatment, 9 (7.6%) women in cohort 1, 13 (13.8%) women in cohort 2, 16 (11.9%) women in cohort 3 and 5 (8.9%) women in cohort 4 still experienced fatigue. Tissue necrosis of the breast or chest wall shows a significant difference as late effect (p=<.001) and ≥ 10 years after treatment (p=.009) between the 4 cohorts. This also applies for osteopenia (p=.033) and osteopenia/osteoporosis ≥ 10 years after treatment (p=.003). 12 (10.1%) women from cohort 1, 7 (7.4%) women from cohort 2, 20 (14.9%) women from cohort 3 and 36 (64.3%) women from cohort 4 experienced lymphoedema of the arm as a late effect (p=<.001). The same was true for the difference in late effect ≥10 years after treatment (p=<.001). The presence of breast or thoracic wall pain also shows a significant difference as a late effect (p=.002) and as presence ≥ 10 years after treatment (p=<.001). Finally, the presence of bowel diseases 10 years after treatment shows a significant difference (p=.009).

Table 5: General adverse effects per cohort

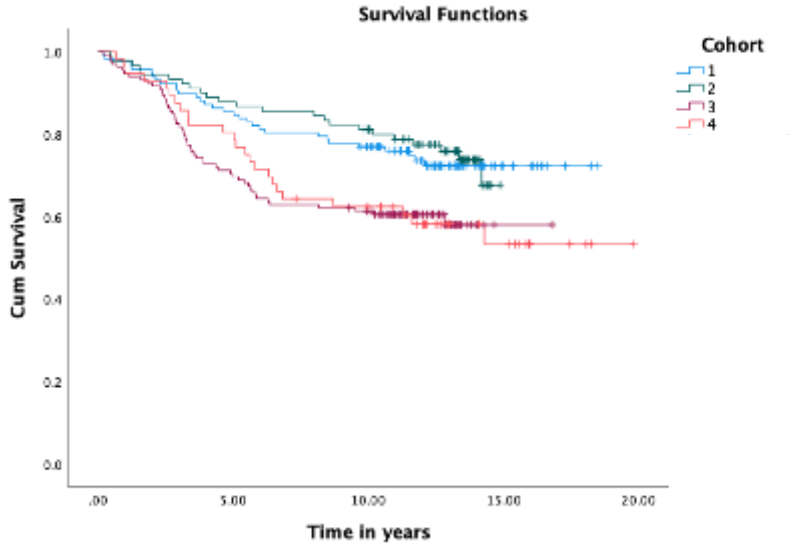
	Cohort 1 (n=119)	Cohort 2 (n=94)	Cohort 3 (n=134)	Cohort 4 (n=56)	p-value
Fatigue					
T0	7 (5.9%)	7 (7.4%)	16 (11.9%)	3 (5.4%)	.411
Late effect	42 (35.3%)	36 (38.3%)	66 (49.3%)	22 (39.3%)	.143
Present ≥ 10 years after treatment	9 (7.6%)	13 (13.8%)	16 (11.9%)	5 (8.9%)	.458
Psychosocial complaints					
T0	12 (10.1%)	14 (14.9%)	13 (9.7%)	5 (8.9%)	.563
Late effect	28 (23.5%)	23 (24.5%)	31 (23.1%)	12 (21.4%)	.742
Present ≥ 10 years after treatment	13 (10.9%)	7 (7.4%)	14 (10.4%)	4 (7.2%)	.194
Reduced mobility of the shoulder joint					
T0	2 (1.7%)	3 (3.2%)	3 (2.2%)	2 (3.6%)	.845
Late effect	25 (21.0%)	21 (22.3%)	27 (20.1%)	14 (25.0%)	.896
Present ≥ 10 years after treatment	5 (4.2%)	9 (9.5%)	6 (4.4%)	7 (12.5%)	.114
Ulceration of the skin					
Late effect	2 (1.7%)	4 (4.3%)	4 (3.0%)	1 (1.8%)	.673
Present ≥10 years after treatment	0	1 (1.1%)	2 (1.4%)	1 (1.8%)	.852
Tissue necrosis of the chest wall of the breast					

Late effect *Present ≥ 10 years after treatment*	0 0	7 (7.4%) 6 (6.4%)	17 (12.7%) 12 (8.9%)	8 (14.3%) 9 (16.1%)	**<.001** **.009**
Osteopenia T0 Late effect **Osteoporosis** T0 Late effect *Osteopenia/osteoporosis present ≥ 10 years after treatment*	 7 (5.9%) 32 (26.9%) 5 (4.2%) 15 (12.6%) 26 (21.8%)	 8 (8.5%) 27 (28.7%) 7 (7.4%) 18 (19.1%) 17 (18.1%)	 14 (10.4%) 55 (41.0%) 4 (3.0%) 17 (12.7%) 30 (22.4%)	 2 (3.6%) 24 (42.9%) 0 10 (17.9%) 17 (30.4%)	 .333 **.033** .130 .434 **.003**
Rib fracture T0 Late effect	 0 5 (4.2%)	 0 3 (3.2%)	 1 (0.7%) 1 (0.7%)	 0 3 (5.4%)	 .570 .257
Lymphedema of the ipsilateral arm T0 Late effect *Present ≥10 years after treatment* CTCAE 1 CTCAE 2 CTCAE 3	 0 12 (10.1%) 2 (1.7%) 11 (9.2%) 1 (0.8%) 0	 1 (1.1%) 7 (7.4%) 3 (3.2%) 5 (5.3%) 1 (1.1%) 0	 4 (3.0%) 20 (14.9%) 7 (5.2%) 9 (6.7%) 6 (4.5%) 1 (0.7%)	 0 36 (64.3%) 16 (28.6%) 19 (33.9%) 16 (28.6%) 1 (1.8%)	 .136 **<.001** **<.001**
Breast/thoracic wall pain Late effect *Present ≥10 years after treatment*	 43 (36.1%) 6 (5.0%)	 55 (58.5%) 12 (12.8%)	 68 (50.7%) 25 (18.6%)	 19 (33.9%) 9 (16.1%)	 **.002** **<.001**
Gastric diseases T0 Late effect *Present ≥10 years after treatment* CTCAE 1 CTCAE 2 CTCAE 3	 15 (12.6%) 28 (23.5%) 14 (11.7%) 13 (10.9%) 14 (11.8%) 1 (0.8%)	 8 (8.5%) 21 (22.3%) 6 (6.4%) 10 (10.6%) 10 (10.6%) 0	 9 (6.7%) 20 (14.9%) 9 (6.7%) 1 (0.7%) 17 (12.7%) 2 (1.5%)	 6 (10.7%) 15 (26.8%) 7 (12.6%) 9 (16.1%) 5 (8.9%) 0	 .430 .191 .305
Bowel diseases T0 Late effect *Present ≥10 years after treatment* CTCAE 1 CTCAE 2 CTCAE 3 CTCAE 4	 12 (10.1%) 39 (32.8%) 21 (17.6%) 22 (18.5%) 12 (10.1%) 2 (1.7%) 2 (1.7%)	 6 (6.4%) 39 (41.5%) 9 (9.7%) 10 (10.6%) 23 (24.5%) 6 (6.4%) 0	 11 (8.2%) 34 (25.4%) 10 (7.4%) 12 (9.0%) 14 (10.4%) 8 (6.0%) 1 (0.7%)	 7 (12.5%) 20 (35.7%) 8 (14.4%) 7 (12.5%) 4 (7.1%) 4 (7.1%) 4 (7.1%)	 .592 **.079** **.009**

Cohort 1: psychosocial complaints 10 years 1 missing, gastric diseases 1 missing

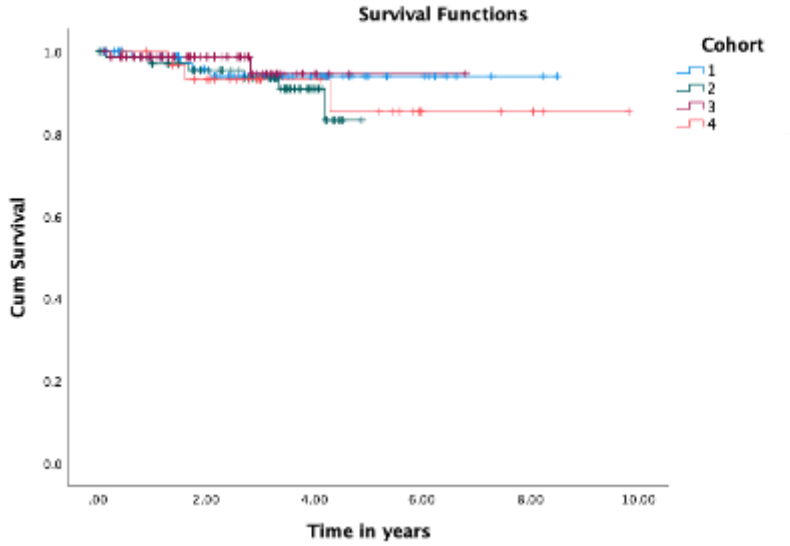
Figure 3 shows that more events of osteopenia occur in cohorts 3 and 4. However, this difference between the cohorts weakens after 10 years as seen in the landmark analysis in figure 4. The x-axis in figure 4 starts from 10 years after surgery.

Figure 3: Survival curve regarding osteopenia events



Log Rank Mantel Cox = .006

Figure 4: Landmark analysis regarding osteopenia events



Log Rank Mantel Cox = .709

The neurological adverse effects are specified in table 6. Significant differences were found regarding brachial plexus neuropathy (p=.041) and carpal tunnel syndrome (p=.012).

Table 6: Neurological adverse effects per cohort

	Cohort 1 (n=119)	Cohort 2 (n=94)	Cohort 3 (n=134)	Cohort 4 (n=56)	p-value
Brachial plexus					

neuropathy T0 Late effect	 0 0	 0 2 (2.1%)	 0 1 (0.7%)	 0 3 (5.4%)	 **.041**
Polyneuropathy T0 Late effect	 1 (0.8%) 5 (4.2%)	 1 (1.1%) 7 (7.4%)	 1 (0.7%) 6 (4.5%)	 1 (1.8%) 7 (12.5%)	 .925 .134
Cognitive disorder T0 Late effect CTCAE 1 CTCAE 2 CTCAE 3	 1 (0.8%) 15 (12.6%) 5 (4.2%) 10 (8.4%) 0	 1 (1.1%) 10 (10.6%) 4 (4.3%) 3 (3.2%) 3 (3.2%)	 1 (0.7%) 17 (12.7%) 11 (8.2%) 3 (2.2%) 3 (2.2%)	 0 2 (3.6%) 1 (1.8%) 0 1 (1.8%)	 .904 .273
Concentration disorder T0 Late effect CTCAE 1 CTCAE 2 CTCAE 3	 0 2 (1.7%) 0 2 (1.7%) 0	 0 5 (5.3%) 4 (4.3%) 0 1 (1.1%)	 0 4 (3.0%) 3 (2.2%) 1 (0.7%) 0	 0 0 0 0 0	 .371
Stroke T0 Late effect	 6 (5.0%) 3 (2.5%)	 4 (4.3%) 8 (8.5%)	 2 (1.5%) 5 (3.7%)	 0 4 (7.1%)	 .170 .171
Transient ischemic attack T0 Late effect	 1 (0.8%) 9 (7.6%)	 1 (1.1%) 5 (5.3%)	 4 (3.0%) 7 (5.2%)	 0 2 (3.6%)	 .341 .724
Carpal tunnel syndrome T0 Late effect	 2 (1.7%) 18 (15.1%)	 1 (1.1%) 7 (7.4%)	 1 (0.7%) 5 (3.7%)	 3 (5.4%) 7 (12.5%)	 .150 **.012**
Meningioma T0 Late effect	 0 1 (0.8%)	 1 (1.1%) 3 (3.2%)	 0 1 (0.7%)	 0 1 (1.8%)	 .348 .434
Neurological adverse effects ≥ 10 years after treatment	23 (19.3%)	14 (14.9%)	13 (9.6%)	10 (17.9%)	.165

Cohort 2 neurological adverse effects 10 years after treatment 1 missing

The pulmonary adverse effects are described in table 7. The variables radiation pneumonitis (p=<.001), pneumonia (p=.069), pulmonary fluid (p=.022), pulmonary fibrosis (p=<.001), bronchiectasis (p=.013), COPD new (p=.034) show a statistically significant difference between the 4 cohorts.

Table 7: Pulmonary adverse effects per cohort

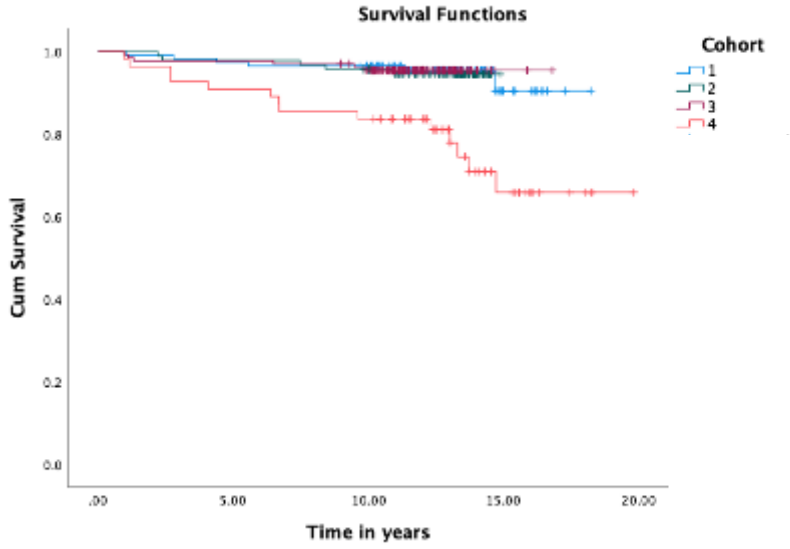
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	p-value

	(n=119)	(n=94)	(n=134)	(n=56)	
Radiation Pneumonitis Late effect	0	2 (2.1%)	2 (1.5%)	1 (1.8%)	.512
Pneumonia Late effect	14 (11.8%)	15 (16.0%)	9 (6.7%)	12 (21.4%)	**.025**
Pleural effusion Late effect	16 (13.4%)	7 (7.4%)	5 (3.7%)	8 (14.3%)	**.022**
Pulmonary Fibrosis Late effect	9 (7.6%)	6 (6.4%)	6 (4.5%)	15 (26.8%)	**<.001**
Bronchiectasis Late effect	6 (5.0%)	3 (3.2%)	1 (0.7%)	6 (10.7%)	**.013**
Secondary lung cancer Late effect	2 (1.7%)	2 (2.1%)	1 (0.7%)	3 (5.4%)	.222
COPD T0 Late effect COPD new (arise after treatment)	 2 (1.7%) 9 (7.6%) 8 (6.7%)	 3 (3.2%) 10 (10.6%) 7 (7.4%)	 7 (5.2%) 10 (7.5%) 1 (0.7%)	 2 (3.6%) 9 (16.1%) 7 (12.5%)	 .623 .246 .034
Asthma T0 Late effect Asthma new (arise after treatment)	 9 (7.6%) 9 (7.6%) 6 (5.0%)	 7 (7.4%) 10 (10.6%) 3 (3.2%)	 4 (3.0%) 8 (6.0%) 4 (3.0%)	 1 (1.8%) 3 (5.4%) 2 (3.6%)	 .171 .538 .827
Obstructive nonspecific lung disease T0 Late effect	 3 (2.5%) 5 (4.2%)	 1 (1.1%) 3 (3.2%)	 3 (2.2%) 6 (4.5%)	 1 (1.8%) 2 (3.6%)	 .884 .964
Pulmonary adverse effects ≥ 10 years after treatment	19 (16.0%)	16 (17.0%)	17 (12.7%)	11 (19.6%)	.634

Cohort 1: COPD t0 1 missing, Asthma t0 1 missing, obstructive nonspecific lung disease t0 1 missing

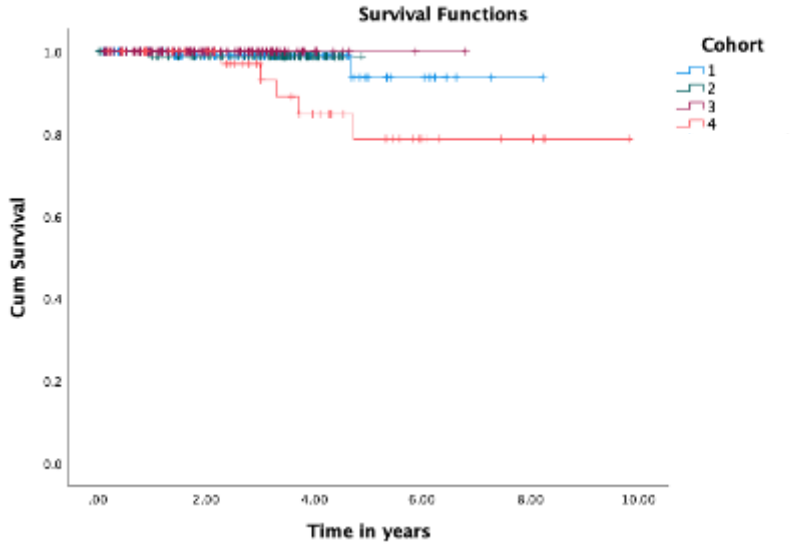
Figure 5 shows that cohort 4 has more events regarding pulmonary fibrosis than cohorts 1, 2 and 3. The difference between cohort 4 and the other cohorts widens slightly after 10 years as can be seen from the landmark analysis in figure 6. The x-axis in figure 6 starts from 10 years after surgery.

Figure 5: Survival curve regarding pulmonary fibrosis events



Log Rank Mantel Cox = <.001

Figure 6: Landmark analysis regarding pulmonary fibrosis events



Log Rank Mantel Cox = .025

In table 8, cardiac adverse effects data can be seen. Coronary artery disease is not significant, but the various individual variables about the location of the anomalies are significantly different. Angina pectoris also shows a significant difference (p=.002) with 5 (4.2%) women in cohort 1, 6 (6.4%) in cohort 2, 9 (6.7%) in cohort 3 and 2 (3.6%) in cohort 4. This also applies to myocardial infarction (p=.011), valvular heart diseases for various valves, and conduction disorders (p=.005).

Table 8: Cardiac adverse effects per cohort

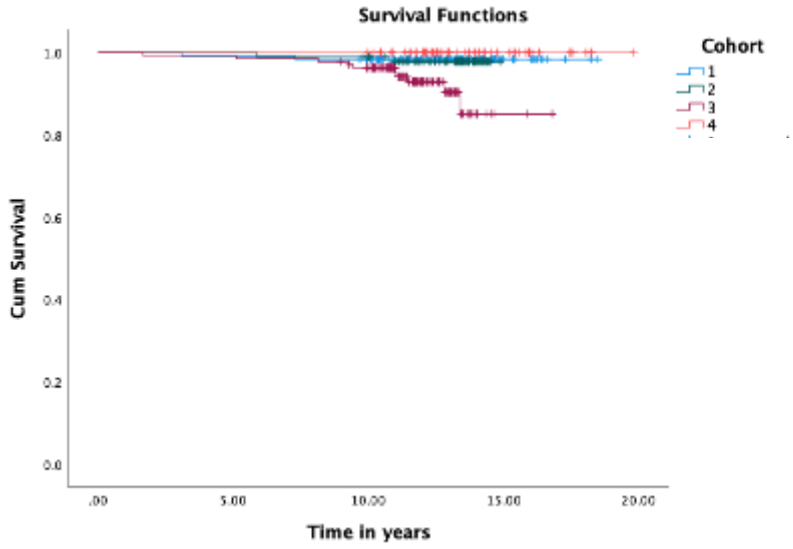
	Cohort 1 (n=119)	Cohort 2 (n=94)	Cohort 3 (n=134)	Cohort 4 (n=56)	p-value
Cardiomyopathy					
T0	4 (3.4%)	4 (4.3%)	0	1 (1.8%)	.135
Late effect	10 (8.4%)	13 (13.8%)	11 (8.2%)	5 (8.9%)	.486
Congestive heart failure					
T0	0	1 (1.1%)	1 (0.7%)	0	.647
Late effect	13 (10.9%)	12 (12.8%)	11 (8.2%)	3 (5.4%)	.577
Coronary artery disease					
T0	4 (3.4%)	3 (3.2%)	5 (3.7%)	1 (1.8%)	.921
Late effect	5 (4.2%)	5 (5.3%)	14 (10.4%)	2 (3.6%)	.138
Left coronary					
T0	1 (0.8%)	0	0	0	**.004**
Late effect	1 (0.8%)	3 (3.2%)	0	0	**.087**
Left anterior descending					
T0	3 (2.5%)	1 (1.1%)	3 (2.2%)	1 (1.8%)	**.007**
Late effect	4 (3.4%)	1 (1.1%)	11 (8.2%)	0	**<.001**
Left circumflex					
T0	2 (1.7%)	2 (2.1%)	2 (1.5%)	0	**.006**
Late effect	2 (1.7%)	2 (2.1%)	3 (2.2%)	2 (3.6%)	**.001**
Right coronary					
T0	3 (2.5%)	1 (1.1%)	2 (1.5%)	1 (1.8%)	**.007**
Late effect	4 (3.4%)	3 (3.2%)	8 (6.0%)	0	**<.001**
Angina pectoris					
T0	5 (4.2%)	3 (3.2%)	6 (4.5%)	0	.453
Late effect	5 (4.2%)	6 (6.4%)	9 (6.7%)	2 (3.6%)	.752
Myocardial infarction					
T0	2 (1.7%)	4 (4.3%)	3 (2.2%)	1 (1.8%)	.641
Late effect	2 (1.7%)	4 (4.3%)	10 (7.5%)	0	**.011**
Valvular heart disease					
Aortic					
T0	4 (3.4%)	4 (4.3%)	1 (0.7%)	1 (1.8%)	.174
Late effect	22 (18.5%)	7 (7.5%)	12 (9.0%)	1 (1.8%)	**.005**
Mitral					
T0	7 (5.9%)	10 (10.6%)	8 (6.0%)	2 (3.6%)	.219
Late effect	28 (23.5%)	17 (18.1%)	28 (20.8%)	7 (12.6%)	.283
Tricuspid					
T0	3 (2.5%)	6 (6.4%)	2 (1.5%)	1 (1.8%)	.200
Late effect	15 (12.6%)	20 (21.3%)	12 (8.9%)	13 (23.2%)	**.014**
Pulmonary					

T0 Late effect	0 2 (1.7%)	1 (1.1%) 12 (12.8%)	1 (0.7%) 4 (2.9%)	0 10 (17.9%)	.647 **.002**
Arrhythmia T0 Late effect	 7 (5.9%) 19 (16.0%)	 10 (10.6%) 18 (19.1%)	 11 (8.2%) 34 (25.4%)	 1 (1.8%) 12 (21.4%)	 .200 .311
Conduction disorders T0 Late effect	 5 (4.2%) 12 (10.1%)	 1 (1.1%) 8 (8.5%)	 2 (1.5%) 21 (15.7%)	 1 (1.8%) 3 (5.4%)	 .378 **.005**
Pericarditis T0 Late effect	 0 0	 0 0	 0 1 (0.7%)	 1 (1.8%) 0	 .102 .570
Cardiac adverse effects ≥ 10 years after treatment	23 (19.4%)	11 (11.8%)	29 (21.7%)	9 (16.1%)	.289

Cohort 2: cardiac adverse effects 10 years after treatment 4 missing

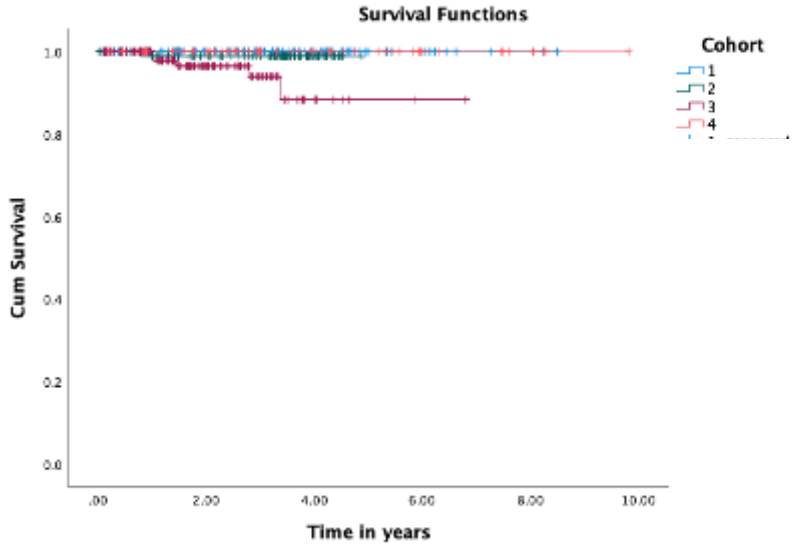
Figure 7 shows that more myocardial infarctions occur in the women in cohort 3. This difference remains present from 10 years of follow-up duration visible in figure 8. The x-axis in figure 8 starts from 10 years after surgery.

Figure 7: Survival curve regarding myocardial infarction events



Log Rank Mantel Cox = .005

Figure 8: Landmark analysis regarding myocardial infarction events



Log Rank Mantel Cox = .007

Table 9 shows the various adverse effects with associated (corrected) hazard ratios. The first line is the unadjusted variable and below is the adjusted one. When there is no second line, it means there are no confounders for the variable in question. Women in cohort 3 were 1.81 times more likely to develop osteopenia compared with cohort 1. Moreover, women in cohort 4 were 6.45 times more likely to develop lymphedema and 4.89 times more likely to develop pulmonary fibrosis compared with cohort 1. Women in cohort 3 were 5.63 times more likely to develop conduction disorders corrected for hypercholesterolemia, number of medications and age compared with women in cohort 1.

Table 9: Adverse effects unadjusted and adjusted for confounders.

Adverse effects	Cohort 1	Cohort 2 HR (95.0% CI)	Cohort 3 HR (95.0% CI)	Cohort 4 HR (95.0%)
Fatigue ≥ 10 years	Referent	1.79 (0.48 - 6.73)	0.98 (0.18 - 5.49)	0.53 (0.06 - 4.75) .
Osteopenia Adjusted (age)	Referent	0.92 (0.54 - 1.58) 0.95 (0.55 - 1.62)	**1.81 (1.16 - 2.83)** **1.97 (1.26 - 3.08)**	**1.73 (1.02 - 2.95)** **1.88 (1.10 - 3.20)**
Osteoporosis Adjusted (hypercholesterolemia, age)	Referent	1.40 (0.68 - 2.91) 1.60 (0.76 - 3.34)	1.13 (0.56 - 2.30) 1.30 (0.63 - 2.65)	1.54 (0.69 - 3.47) 1.92 (0.84 - 4.40)

Lymphedema Adjusted (follow up, pN)	Referent	0.70 (0.28 - 1.78) 0.63 (0.25 - 1.62)	1.47 (0.72 - 3.02) 1.49 (0.71 – 3.11)	**9.03 (4.68 - 17.43)** **6.45 (3.16 - 13.17)**
Breast/thoracic wall pain	Referent	**1.85 (1.24 - 2.76)**	**1.47 (1.00 - 2.15)**	0.83 (0.48 - 1.42)
Bowel diseases Adjusted (smoking, number of medications)	Referent	1.34 (0.86 - 2.10) 1.28 (0.81 - 2.04)	0.74 (0.46 - 1.19) 0.78 (0.48 - 1.26)	0.80 (0.45 - 1.42) 0.96 (0.53 - 1.74)
Pneumonia Adjusted (number of medications, smoking)	Referent	1.56 (0.74 - 3.26) 1.29 (0.61 - 2.75)	0.71 (0.30 - 1.65) 0.68 (0.29 - 1.61)	1.73 (0.80 - 3.75) 2.14 (0.98 - 4.70) .
Pulmonary fibrosis	Referent	1.05 (0.32 - 3.46)	1.01 (0.32 - 3.14)	**4.89 (1.87 - 12.74)**
Myocardial infarction Adjusted (number of medications)	Referent	1.15 (0.16 - 8.16) 1.11 (0.16 - 7.87)	**5.39 (1.17 - 24.69)** **6.08 (1.31 - 28.36)**	- -
Conduction disorders Adjusted (hypercholesterolemia, number of medications, age)	Referent	1.11 (0.40 - 3.08) 1.64 (0.56 - 4.78)	**2.95 (1.28 - 6.82)** **5.63 (2.24 - 14.14)**	0.66 (0.17 - 2.50) 1.42 (0.36 - 5.60)

Discussion

This study investigated the possible late adverse effects after 10-year disease free survival of women treated for breast cancer in different ways. Cohort 1 underwent mastectomy and served as a control group. Cohort 2 underwent breast conserving surgery followed by whole breast irradiation. Cohort 3 underwent breast conserving surgery followed by whole breast irradiation, followed by adjuvant chemotherapy with or without immunotherapy and/or hormonal therapy and cohort 4 underwent breast conserving surgery followed by whole breast irradiation with a regional nodal irradiation followed by adjuvant chemotherapy with or without immunotherapy and/or hormonal therapy. The general adverse effects category shows that women in cohort 4 are more likely to develop general adverse effects compared to women who underwent mastectomy alone. Women in cohort 3 were also more likely to develop overall adverse events compared to women in cohort 1. In addition, women in cohort 4 are also more likely to have pulmonary adverse effects compared to those in cohort 1.

Fatigue

Cohorts 2 and 3 both had an increased incidence of fatigue. However, the presence of fatigue in cohort 4 is lower than the other cohorts. This is a remarkable result as women with more extensive treatment would be expected to report fatigue more often. Another reason for this could be that cohort 4 contains the least number of women. However, there were no significant confounders.

Osteopenia/osteoporosis

Women who underwent breast-conserving therapy followed by whole breast irradiation, adjuvant chemotherapy with or without immunotherapy and/or hormonal treatment had an increased risk of osteopenia compared to the other cohorts. This also applies for osteoporosis. One explanation could be that this cohort contained the most women and they received more extensive treatment with adjuvant chemotherapy and/or hormonal treatment. This is in line with previous studies [9][10][11]. Another extra explanation could be that women in this cohort had on average the shortest follow-up duration and a previous study showed that recent breast cancer survivors have a higher risk of developing osteopenia [10].

Lymphedema of the arm

Women in cohort 4 were significantly more likely to have lymphoedema of the ipsilateral arm than those in the other cohorts. The numbers are still highest ≥ 10 years after surgery for women in cohort 4. This can be explained by the extensive treatment of the women in cohort 4 combined with regional nodal irradiation. Previous studies have shown that lymphoedema of the arm is the most significant adverse effect in locoregional treatment of breast cancer [12][13]. When treated with systemic treatment such as chemotherapy and/or axillary/periclavicular radiotherapy, this risk will be increased.

Moreover, there is an increased risk of lymphoedema after axillary node dissection compared to a sentinel node procedure. In cohort 4, almost 93% of women underwent axillary node dissection.

Breast/thoracic wall pain

The results show that women in cohort 2 suffered most from chest or thoracic wall pain. This number is still highest ≥ 10 years after surgery in cohort 2. Side effects of breast radiotherapy include chest or thoracic wall pain, however, it would be expected that women in cohort 3 and 4 would suffer more from this due to the systemic treatment of which breast/thoracic wall pain is also a side effect. This is not an expected outcome. One explanation could be that women in cohort 2 received a higher dose. Another explanation that could apply is that the women in cohorts 3 and 4 experienced other symptoms, so the focus was not on having breast/thoracic wall pain.

Bowel diseases

Numbers related to bowel diseases are lower for women in cohort 3 compared with the other cohorts. This is a remarkable finding since previous research has shown that chemo and hormonal therapy increase the risk of inflammatory bowel diseases [14]. One explanation could be that only 17.2% women in cohort 3 received chemotherapy. In addition, all types of bowel diseases were included in this study so results could turn out differently than expected.

Pneumonia/pulmonary fibrosis

Pneumonia was most common in cohort 4. This could be explained by the fact that women in cohort 4 received additional regional irradiation. A 2006 article describes pneumonia as a long-term effect of radiotherapy and especially when the lungs are additionally affected [12]. Moreover, the risk of pneumonia with chemotherapy is higher due to increased risk of infections from leukopenia. The Cox regression shows a higher risk for developing pneumonia for women in cohort 4 compared to women in cohort 1 with confounders included. This also applies to pulmonary fibrosis. Women in cohort 4 reported most cases of pulmonary fibrosis. A study by Poortmans et al. concluded that pulmonary fibrosis is a side effect of lymph node irradiation [15]. However, this article did use a different study group in which parasternal irradiation took place.

Myocardial infarction

The highest incidence of myocardial infarction occurred in cohort 3. Previous research concludes that women treated with chemotherapy have a higher risk of myocardial infarction [13]. However, this result was not found to be significant. Remarkably, no myocardial infarctions occurred among the women in cohort 4. Indeed, it would be expected that more myocardial infarctions would occur here due to treatment with additional radiotherapy since previous research has shown that radiotherapy increases the risk of myocardial infarction [16]. One explanation could be that regional irradiation

generally did not involve parasternal irradiation. More cardiac symptoms may also be expected when the lateralization of the tumor is on the left side. However, this was not analyzed in this study. The study by Paszat et al. also showed that smoking history is a risk factor for myocardial infarction [16]. This could influence the results as cohort 3 contains more women who smoke or have smoked. However, this study found that smoking is not a significant confounder for myocardial infarction.

Conduction disorders

Women in cohort 3 were most affected by conduction disorders. The Cox regression shows significant results for women in cohort 3 compared to cohort 1. A 2011 article named that chemotherapy could cause conduction disorders [17]. However, it would then be expected that cohort 4 would also have more conduction disorders. A previous study concluded that patients receiving radiotherapy have a higher risk of conduction disorders and other cardiac problems such as arrhythmias [18]. One explanation could be that cohort 3 included more women with hypercholesterolemia. This study has shown that this is a confounder for conduction disorders. Moreover, women in cohort 3 are on average slightly older than women in cohort 4, which could also lead to unexpected results as age appears to be a risk factor for conduction disorders.

Strengths and limitations

A strength of this study is the wide range of adverse events that have been registered. Many adverse events were collected at time before or during surgery (t0), up to 10 years after surgery (t1) and ≥ 10 years after surgery (t2). This gives a better overview of which events are present before/at the time of surgery, which are present after and which are still present 10 years after surgery. Another strength of this study was its long follow-up duration, with the longest follow-up duration of 19.8 years after surgery. So far, there is little data with this follow up duration. Finally, the sample size of this study is large enough to make valid statements.

Besides its strengths, this study has some limitations that need to be considered. This study did not include a measure of severity of adverse effects for all the adverse events. Also, this study did not focus on any treatment of these adverse effects and whether women recovered from them. Another weakness of this study is that it only accessed data from the hospitals. The databases contained (referral) letters from, for example, the GP or psychologist. However, this study concerns a retrospective study and a drawback is that not everything was noted by specialists. Moreover, women may have complaints known only to the GP or may not have reported certain complaints because they did not suffer much. As a result, information may have been missed.

Recommendations for further research

To increase the quality of this study, future research could be done with a larger sample size. Especially in cohort 4, fewer women were included compared to the other cohorts. If more women will be included in this cohort, the results can be argued with more strength. In addition, future research is needed to include the degree of severity of an adverse event and whether it was treated for. This may provide more information and possibly make considerations of a particular treatment easier. Moreover, the study could be complemented by questionnaires sent to patients. In this way, the study can be supplemented with information from the patient herself. This allows to reduce some information bias.

Conclusion

This study compared the long-term effects up to at least 10 years after surgery with different treatment modalities for women with breast cancer. Significant differences were found for developing general, pulmonary and cardiac adverse effects. Like previous research, this study also shows that women who have had chemotherapy and/or hormonal therapy are more likely to develop osteopenia. Moreover, lymphedema and pulmonary fibrosis were more common in women from cohort 4. Finally, women from cohort 2 reported the most breast/thoracic wall pain and were most likely to still have it. Myocardial infarction and conduction disorders are most common in women in cohort 3 and they are most likely to have these compared to women in cohort 1. The results of this study can be taken into account in deciding the best treatment for the patient and what the associated potential side effects might be.

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Appendix A

Overview variables

1. Baseline variables with tumor treatment data

Nr.	Code variabele	Beschrijving variabele	Scoring	Bron
Algemene patiënten gegevens (t0)				
1.	Zkh_nr	MST ziekenhuis nummer van de patiënt	Numeriek	
2.	Patient_ID	Geboortedatum + voor letter + eerste 3 letters van achternaam	Tekst	
3.	Cohort	Behandelingsgroep	1 = ablatio + SN of OKD 2 = BCS + RT mamma 3 = BCS + RT mamma + adj. Syst. therapie 4 = BCS + RT mamma en regionaal + adj. Syst. therapie	
4.	Ziekenhuis	Ziekenhuis waar patiënt primair is behandeld	1 = MST 2 = ZGT	
5.	Geboortedatum	Geboortedatum	dd-mm-jj	
6.	Lengte	Lengte van patiënt in meter	Numeriek	
7.	Gewicht	Gewicht van patiënt in kilogram	Numeriek	
8.	BMI		Numeriek	
9.	Diabetes Mellitus	Diabetes Mellitus	1 = ja 2 = nee	
10.	Insuline afhankelijk	Insulineafhankelijke diabetes mellitus	1 = ja 2 = nee	
11.	Hypertensie	Hypertensie (bepalend: met medicatie)	1 = ja 2 = nee	
12.	Hypercholesterolemie	Hypercholesterolemie (medicatie hiervoor: ... statine)	1 = ja 2 = nee	
13.	Roken	Roken (op datum van diagnose)	1 = ja	

			2 = nee 3 = > 1 jaar gestopt 4 = < 1 jaar gestopt	
14.	Packed years	Packed years	Numeriek	
15.	Medicatie aantal	Aantal medicijnen (op datum van diagnose)	Numeriek	
16.	Lateralisatie mammacarcinoom	Lateralisatie mammacarcinoom (Let op: IKNL is andersom)	1 = rechts 2 = links	
17.	Chirurgische ingreep	Chirurgische ingreep	1 = lumpectomie 2 = lumpectomie + okselklierdissectie (OKD) 3 = quadrantectomie + okselklierdissectie 4 = quadrantectomie 5 = lumpectomie + sentinel node (SN) 6a = ablatio + SN 6b = ablatio + OKD (6c = ablatio alleen)	
18.	Chir datum	Datum van chirurgische ingreep	dd-mm-jj	
19.	Reexcisie	Reexcisie na oorspronkelijke chirurgische ingreep	1 = ja 2 = nee	
20.	pT	Primaire tumor op basis van pathologische bevindingen	1 = T1 ≤ 2cm 2 = T2 > 2cm - <5.1cm 3 = T3 > 5cm 4 = T4 5 = T2 mult 6 = T1 mult 7 = T1a: 0.1 – 0.5cm 8 = T1b: > 0.5cm – 1.0cm 9 = T1c: >1,0cm – 2.0 cm	

21.	pN	Regionale klieren op basis van pathologische bevindingen	1 = N0 2 = N1: 1 – 3 positieve klieren 3 = N2: 4 – 9 positieve klieren 4 = N3: > 9 positieve klieren 5 = N1micro: micrometastasen > 0.2mm t/m 2.0mm 6 = N0 ITC (isolated tumor cells) / N0(i+), ≤0.2mm	
22.	Radiotherapie	Radiotherapie	1 = ja 2 = nee	
23.	Rad locatie	Doelgebieden radiotherapie Regionaal is axillair en supraclaviculair gebied Parasternaal is achter het borstbeen	1 = mamma 2 = mamma + regionaal 3 = mamma + parasternaal 4 = IRMA 5 = mamma + axilla (per 01-01-03) 8 = nvt 9 = onbekend	
24.	Rad datum	Datum start radiotherapie	dd-mm-jj	
25.	Boost	Boost-bestraling	1 = ja 2 = nee	
26.	Boosttd	Boost-bestraling (extra dosis bestraling op de plek waar de tumor heeft gezeten)	1 = 14 Gy 2 = 15 Gy 3 = geen 4 = overige 5 = 20 Gy 6 = 16 Gy 7 = 26 Gy 8 = 13,3 Gy	

			9 = 38,5 Gy	
27.	Type adj syst therapie	Type adjuvante therapie	1 = hormonaal 2 = chemotherapie 3 = hormonaal + chemotherapie 4 = geen 5 = trial 6 = ovari/zola 7 = 1+6 8 = 1+2+6 9 = onbekend 10= 2 +Herceptin 11= 10 + 1 12 = 1+6+10 13 = Herceptin + 1	
28.	Adj datum	Datum start adjuvante systemische therapie	dd-mm-jj	
29.	Metastase	Metastase	1 = ja 2 = nee	
30.	Meta_datum	Datum diagnose metastasering op afstand (bij voorkeur pa-datum, anders datum beeldvorming waarop metastasering is vastgesteld)	mm-jj	
31.	Locrec	Recidief mamma of thoraxwand (ipsilateraal, inclusief DCIS)	1 = ja 2 = nee	
32.	Locrec_datum	Datum (pa-datum) diagnose recidief mamma of thoraxwand	mm-jj	
33.	Regrec	Recidief axillair of periclaviculair of parasternaal ipsilateraal	1 = ja 2 = nee	
34.	Regrec_datum	Datum diagnose regionaal recidief (ipsilateraal) (pa-datum, indien niet bekend dan datum beeldvorming waarop regionaal recidief zichtbaar is)	mm-jj	
35.	Tumormamma cl	2e primaire tumor contralaterale mamma (inclusief DCIS)	1 = ja 2 = nee	
36.	Tumormamma cl_datum	Datum diagnose (pa-datum) mammacarcinoom contralateraal (inclusief DCIS)	mm-jj	
37.	2e prim tumor elders	2e primaire tumor elders (niet mammacarcinoom) na T0, zie invulinstructie	1 = ja 2 = nee	

38.	2e prim tumor elders_datum	Datum diagnose (pa-datum) 2e primaire tumor elders (niet mammacarcinoom) na T0, zie invulinstructie	mm-jj	
39.	2e prim tumor elders_locatie	Locatie 2e primaire tumor elders. Ook links en/of rechts vermelden na T0, zie invulinstructie	Tekst	
40.	OL	Overleden	1 = ja 2 = nee	
41.	Einde FU_datum	Datum laatste gegevens HIX 6.3(MST), HIX 6.3(ZGT) met de volgende uitzonderingen (na 10 jaar): a. bij recidief/meta mammacarcinoom/contralateraal mammaca òf bij 2e primaire (waarvoor radiotherapie en/of chemotherapie), dan datum aanhouden van diagnose van bovenstaande b. bij overlijden de datum van overlijden als a. niet heeft plaatsgevonden	dd-mm-jj	
42.	OL_datum	Datum overlijden. Is meestal zelfde als 41, als pt is overleden. In geval van 41a zijn deze data verschillend.	dd-mm-jj	
43.	OL_oorzaak	Oorzaak overlijden (secundaire maligniteit kan ook 2e primaire van contralaterale mamma zijn, dit dan wel noteren bij item 44 en 47.)	1 = tgv primaire mammaca 2 = tgv secundaire maligniteit 3 = cardiale oorzaak 4 = pulmonale oorzaak 5 = neurologische oorzaak 6 = overig	
44.	OL_specifiek	Notitie bij de reden van het overlijden	Tekst	
45.	Exclusie		1 = ja 2 = nee	
46.	Reden exclusie	Ad 2: SN of OKD of SN + OKD. NB Bij SN minimaal 1 klier gevonden met pa. Ad 5: patiënten die secundair een ablatio (bij pa geen maligniteit) hebben ondergaan vanwege gen	1 = FU < 10 jr of laatste FU gegevens < 10 jr na T0	

		dragerschap of andere reden of een ablatio vanwege DCIS (zonder radiotherapie) niet excluderen Ad 6: basaalcelcarcinoom of plaveiselcelcarcinoom van de huid dat bestraald is niet excluderen	2 = geen okselstadiërende ingreep verricht 3 = hematogene metastasering < 10 jr na T0 4 = ipsilateraal loco en/of regionaal recidief mammacarcinoom <10 jaar na T0 5 = contralateraal mammacarcinoom vòòr of ten tijde van T0 of < 10 jaar na T0 6 = andere maligniteit vòòr of ten tijde van T0 of < 10 jaar na T0, waarvoor RT en/of systemische therapie 7 = anders	
47.	Opmerkingen		Tekst	
48.	Behandeling recidieven/metastasen/2e primaire tumoren	Beschrijving behandeling van recidieven, metastasen, 2e primaire tumoren	Tekst	
49.	Reconstructie	Beschrijving eventuele reconstructie na ablatio mammae/borstsparende behandeling	Tekst	

2 Variables for toxicity analysis

Algemene effecten aanwezig voor of tijdens behandeling (t0)				
1.	VH_t0	Vermoeidheid voor/tijdens t0	1 = ja 2 = nee	
2.	PSK_t0	Psychosociale klachten (bv. angststoornis, doorverwezen naar psycholoog of revalidatieprogramma, concentratiestoornis door bv. burn-out, depressiviteit, relatieproblemen of elders) voor/tijdens t0	1 = ja 2 = nee	
3.	VMS_t0	Verminderde mobiliteit arm/schoudergewricht voor/tijdens t0	1 = ja 2 = nee	
4.	OPI_t0	Osteopenie voor/tijdens t0	1 = ja 2 = nee	
5.	OSP_t0	Osteoporose voor/tijdens t0	1 = ja 2 = nee	
6.	RF_t0	Ribfractuur voor/tijdens t0	1 = ja 2 = nee	
7.	RF_loc_t0	Locatie van de ribfractuur voor/tijdens t0	1 = rechts 2 = links 3 = rechts en links	
8.	LO_t0	Lymfoedeem voor/tijdens t0	1 = ja 2 = nee	
9.	LO_loc_t0	Locatie van lymfoedeem voor/tijdens t0 (alleen bij klachten)	1 = rechts 2 = links 3 = rechts en links	
10.	Maag_t0	Maagaandoening voor/tijdens behandeling	1 = ja 2 = nee	Zie CTCAE 5.0 pg 32,33
11.	Darm_t0	Darmaandoening voor/tijdens behandeling	1 = ja 2 = nee	Zie CTCAE 5.0 pg 26 t/m 29, 34 t/m 43
12.	Werk	Betaald werk voor/tijdens behandeling ja/nee; niet van toepassing in dit geval bij patiënten van 65 jaar en ouder	1 = ja 2 = nee 8 = niet van toepassing 9 = onbekend	

Algemene late effecten			
Nr.	**Code variabele**	**Beschrijving variabele**	**Scoring**
1.	VH	Vermoeidheid: ja/nee	1 = ja 2 = nee
2.	VH_datum	Diagnose datum vermoeidheid	mm-jj
3.	VH_10 jaar	Vermoeidheid aanwezig ≥ 10 jaar na lump/ablatio	1 = ja 2 = nee
4.	PSK	Psychosociale klachten (angststoornis, depressiviteit, concentratiestoornis (psychologische oorzaak), relatieproblemen of problemen elders, doorverwezen naar psycholoog of revalidatie programma): ja/nee	1 = ja 2 = nee
5.	PSK_datum	Diagnose datum PSK	mm-jj
6.	PSK_10 jaar	Psychosociale klachten aanwezig ≥ 10 jaar na lump/ablatio	0 = niet gekregen na borstkankerbehandeling 1 t/m 4 volgens CTCAE 5.0 pg 115 t/m 118 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling 7 = geen achteruitgang bekende psychosociale klachten
7.	VMS hl	Verminderde mobiliteit schoudergewricht homolateraal: ja/nee	1 = ja 2 = nee
8.	VMS_datum hl	Diagnose datum verminderde mobiliteit arm/schoudergewricht homolateraal	mm-jj
9.	VMS_gevolg hl	Fysiotherapie nodig door VMS: ja/nee	1 = ja 2 = nee
10.	VMS_10 jaar hl	Verminderde mobiliteit schoudergewricht homolateraal aanwezig ≥ 10 jaar na lump/ablatio	0 = niet gekregen na borstkankerbehandeling 1 t/m 3 volgens CTCAE 5.0 pg 97 5 = volledig herstel zonder behandeling

			6 = volledig herstel met behandeling 7 = geen achteruitgang bekende mobilteitsstoornis schoudergewricht homolateraal
11.	ULC	Ulceratie van de huid (zweervorming): ja/nee (kunnen ook diabetische ulcera zijn, bijv. tpv de voeten)	1 = ja 2 = nee
12.	ULC_datum	Diagnose datum ulceratie van de huid	mm-jj
13.	ULC_loc	Locatie ulceratie (exacte beschrijving, ook links of rechts	Tekst
14.	ULC_10 jaar	Ulceratie aanwezig ≥ 10 jaar na lump/ablatio	0 = niet gekregen na borstkankerbehandeling 1 t/m 4 CTCAE 5.0 pg 147 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling
15.	WN borstwand/borst hl	Weefselnecrose borstwand/borst (celdood) homolateraal: ja/nee	1 = ja 2 = nee
16.	WN_datum	Diagnose datum weefselnecrose	dd-mm-jj
17.	WN_loc	Locatie weefselnecrose	1: rechts 2: links 3: rechts en links
18.	WN_10 jaar	Weefselnecrose aanwezig ≥ 10 jaar	0 = niet gekregen na borstkankerbehandeling 1 t/m 4 CTCAE 5.0 pg 96, 149 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling
19.	OPI	Osteopenie	1 = ja 2 = nee
20.	OPI_datum	Diagnose datum osteopenie	dd-mm-jj

21.	OSP	Osteoporose	1 = ja 2 = nee
22.	OSP_datum	Diagnose datum osteoporose	dd-mm-jj
23.	OSP_botfractuur	Botfractuur door osteoporose	1 = ja 2 = nee
24.	OSP_botfractuur_loc	Locatie botfractuur	Tekst
25.	OPI/OSP_10 jaar	Osteopenie/Osteoporose aanwezig ≥ 10 jaar na lump/ablatio	0 = niet gekregen na borstkankerbehandeling 1 t/m 3 CTCAE 5.0 pg 100 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling 7 = geen achteruitgang bekende osteopenie/osteoporose
26.	RF	(Plotselinge) ribfractuur (door bestraling): ja/nee	1 = ja 2 = nee
27.	RF_datum	Datum van diagnose ribfractuur	mm-jj
28.	RF_loc	Locatie ribfractuur met vermelding van zijde links, rechts	Tekst
29.	LO	Lymfoedeem	1 = ja 2 = nee
30.	LO_datum	Diagnose datum lymfe oedeem	mm-jj
31.	LO_CTC	Lymfoedeem: CTCAE 5.0 1 t/m 3 pg 154 + tekst hiernaast (bij OKD hogere kans op lymfoedeem dan bij SN; bij ook radiotherapie regionaal weer hogere kans)	1 = 5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection 2 = >10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin

			folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL 3 = >30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL
32.	LO_loc	Locatie van lymfe-oedeem	1: rechts 2: links 3: beide
33.	LO_10 jaar	Lymfoedeem aanwezig ≥ 10 jaar na lump/ablatio	0 = niet gekregen na borstkankerbehandeling 1 t/m 3 CTCAE 5.0 pg 154 + tekst zie boven 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling (7 = geen achteruitgang bekend lymfoedeem, zelden)
34.	BorTho_pijn hl	Pijnklachten borst/thoraxwand homolateraal	1 = ja 2 = nee
35.	BorTho_pijn hl_datum	Datum van borst/thoraxwand hl pijnklachten	mm-jj
36.	BorTho_pijn hl_10 jaar	Pijnklachten borst/thoraxwand aanwezig ≥ 10 jaar na lump/ablatio	0 = geen pijnklachten borst/thoraxwand na borstkankerbehandeling gekregen 1 t/m 3 CTCAE 5.0 pg 96 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling
37.	BorTho_pijn hl_10 jaar_analgeticum	Gebruik analgeticum/analgetica	0 = geen pijn 1a = geen pijn met analgetica (Paracetamol/NSAID's, zonder opiaten)

			1b = pijn zonder analgetica 2 = pijn met analgetica (inclusief NSAID's, zonder opiaten) 3 = geen pijn/pijn met gebruik van opiaten
38.	Maag	Maagaandoening: ja/nee	1 = ja 2 = nee
39.	Maag_datum	Datum maagaandoening	mm-jj
40.	Maag_spec	Beschrijving aandoening	Tekst
41.	Maag_CTC	Ernst maagaandoening volgens CTCAE	CTCAE 5.0 1 t/m 4 pg 32,33
42.	Maag_10 jaar	Maagaandoening aanwezig ≥ 10 jaar na lump/ablatio	0 = geen maagaandoening na borstkankerbehandeling gekregen/aangetoond 1 t/m 4 CTC 5.0 pg 32,33 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling 7 = geen achteruitgang bekende maagaandoening
43.	Darm	Darmaandoening ja/nee	1 = ja 2 = nee
44.	Darm_datum	Datum darmaandoening	mm-jj
45.	Darm_spec	Beschrijving aandoening	Tekst
46.	Darm_CTC	Ernst darmaandoening volgens CTCAE	CTCAE 5.0 1 t/m 4 pg 26 t/m 29, 34 t/m 43, 103
47.	Darm_10 jaar	Darmaandoening aanwezig ≥ 10 jaar na lump/ablatio	0 = geen darmaandoening na borstkankerbehandeling gekregen/aangetoond 1 t/m 4 CTC 5.0 pg 26 t/m 29, 34 t/m 43, 103 5 = volledig herstel zonder behandeling 6 = volledig herstel met behandeling

			7 = geen achteruitgang bekende darmaandoening
48.	Werkhervatting	1 = betaald werk na behandeling volledig hervat, dwz met zelfde of meer aantal uren dan voor/tijdens behandeling 2 = geen hervatting van betaald werk 3 = betaald werk na behandeling deels hervat, d.w.z. minder uren tov voor/tijdens behandeling 4 = pensioengerechtigde leeftijd (65 jaar)	1 = ja 2 = nee 3 = deels 4 = pensioen 8 = niet van toepassing 9 = onbekend
49.	Werkhervatting_ datum	Datum hervatting betaald werk	mm-jj
50.	Werk_10 jaar	1 = betaald werk na behandeling volledig hervat, dwz met zelfde of meer aantal uren dan voor/tijdens behandeling 2 = geen betaald werk meer 3 = betaald werk na behandeling deels hervat, d.w.z. minder uren tov voor/tijdens behandeling 4 = pensioengerechtigde leeftijd (≥ 65 jaar)	1 = ja 2 = nee 3 = deels 4 = pensioen 9 = onbekend

Neurologische effecten aanwezig voor of tijdens behandeling (t0)				
1.	BPN_t0	Brachiale plexus neuropathie aanwezig voor/tijdens t0	1 = ja 2 = nee	Literatuur
2.	BPN_loc_t0	Locatie van brachiale plexus neuropathie voor/tijdens t0	1 = rechts 2 = links 3 = rechts en links	Literatuur
3.	PNP_t0	Polyneuropathie voor/tijdens t0	1 = ja 2 = nee	Literatuur
4.	PNP_datum_t0	Datum van polyneuropathie voor/tijdens t0	mm-jj	Literatuur
5.	PNP_loc_t0	Locatie van polyneuropathie voor/tijdens t0	1 = rechts 2 = links 3 = rechts en links	Literatuur
6.	Cogn. stoornis_t0	Cognitieve stoornis voor/tijdens behandeling	1 = ja 2 = nee	
7.	Cogn. stoornis_t0 obj.	Cognitieve stoornis geobjectiveerd door geriater of neuroloog	1 = ja 2 = nee	
8.	Cogn. stoornis_t0 CTCAE	Mate van cognitieve stoornis	1 = mild 2 = matig 3 = ernstig	CTCAE 5.0 pg 105

9.	Concentratie-stoornis_t0	Concentratiestoornis aanwezig voor/tijdens behandeling	1 = ja 2 = nee	
10.	HI_t0	Herseninfarct voor/tijdens t0	1 = ja 2 = nee	Proefschrift Lucille Dorresteijn
11.	HI_aantal_t0	Hoe vaak heeft de patiënt een herseninfarct gehad voor de borstkanker behandeling	Numeriek	Proefschrift Lucille Dorresteijn
12.	TIA_t0	TIA voor/tijdens t0	1 = ja 2 = nee	Proefschrift Lucille Dorresteijn
13.	TIA_aantal_t0	Hoe vaak heeft de patiënt een TIA gehad voor de borstkanker behandeling	Numeriek	Proefschrift Lucille Dorresteijn
14.	CTS_t0	Carpaal tunnel syndroom voor/tijdens t0	1 = ja 2 = nee	Neuroloog
15.	CTS_loc_t0	Locatie van carpaal tunnel syndroom voor/tijdens t0	1 = rechts 2 = links 3 = rechts en links	Neuroloog
16.	MNG_t0	Meningeoom voor/tijdens t0	1 = ja 2 = nee	Neuroloog

Neurologische late effecten				
Nr.	**Code variabele**	**Beschrijving variabele**	**Scoring**	
1.	BPN	Brachiale plexus neuropathie: ja/nee	1 = ja 2 = nee	
2.	BPN_datum	Diagnose datum brachiale plexus neuropathie	mm-jj	
3.	BPN_kracht	Verminderde kracht door BPN: ja/nee	1 = ja 2 = nee	
4.	BPN_pijn	Pijn door BPN: ja/nee	1 = ja 2 = nee	
5.	BPN_gevoel	Verminderd tast/gevoel door BPN: ja/nee	1 = ja 2 = nee	
6.	BPN_functie	Functieverlies door BPN: ja/nee	1 = ja 2 = nee	
7.	BPN_loc	Locatie BPN	1: rechts 2: links 3: rechts en links	
8.	PNP	Polyneuropathie: ja/nee	1 = ja 2 = nee	
9.	PNP_datum	Diagnose datum perifere neuropathie	mm-jj	
10.	PNP_kracht	Verminderde kracht door PNP: ja/nee	1 = ja 2 = nee	
11.	PNP_pijn	Pijn door PNP: ja/nee	1 = ja 2 = nee	
12.	PNP_gevoel	Verminderd tast/gevoel door PNP: ja/nee	1 = ja 2 = nee	

13.	PNP_beleid	Beleid aangepast door PNP (chemokuur uitgesteld of dosis vermindering of andere chemo): ja/nee	1 = ja 2 = nee	
14.	Cogn. stoorn.	Cognitieve stoornis ja/nee	1 = ja 2 = nee	
15.	Cogn. stoorn._obj.	Cognitieve stoornis geobjectiveerd door geriater of neuroloog	1 = ja 2 = nee	
16.	Cogn.stoorn._datum	Datum cognitieve stoornis	mm-jj	
17.	Cogn. stoorn._ CTC	Ernst cognitieve stoornis CTCAE 5.0 pg 105	1 = mild 2 = matig 3 = ernstig	
18.	Concentr.stoorn.	Concentratiestoornis ja/nee	1 = ja 2 = nee	
19.	Concentr.stoorn._da-tum	Datum concentratiestoornis	mm-jj	
20.	Concentr.stoorn._CTC	Ernst concentratiestoornis CTCAE 5.0 pg 105	1 = mild 2 = matig 3 = ernstig	
21.	HI	Herseninfarct ja/nee	1 = ja 2 = nee	
22.	HI_datum	Datum diagnose eerste herseninfarct na borstkanker behandeling	mm-jj	
23.	HI_aantal	Hoe vaak heeft patiënt een HI gehad na borstkanker behandeling?	Numeriek	
24.	HI_sg	Stroomgebied waarin eerste HI na borstkanker behandeling heeft plaatsgevonden	1: A cerebri anterior (aca) (grote hersenen) 2: A cerebri media (acm) (grote hersenen) 3: A cerebri posterior (ACP) (grote hersenen) 4: A basillaris (kleine hersenen) 5: A vertebralis (kleine hersenen)	
25.	HI_kracht	Verminderde kracht door HI	1 = ja 2 = nee	
26.	HI_gevoel	Verminderd gevoel door HI	1 = ja 2 = nee	
27.	HI_wvp	Woordvindproblematiek/afasie na HI	1 = ja 2 = nee	
28.	TIA	Transient ischemic attack: ja/nee	1 = ja 2 = nee	
29.	TIA_datum	Diagnose datum eerste TIA na borstkankerbehandeling	mm-jj	
30.	TIA_aantal	Hoe vaak heeft patiënt een TIA gehad na borstkanker behandeling?	Numeriek	
31.	TIA_kracht	Verminderde kracht door TIA	1 = ja 2 = nee	
32.	TIA_gevoel	Verminderd gevoel door TIA	1 = ja 2 = nee	
33.	TIA_wvp	Woordvindproblematiek/afasie door TIA	1 = ja 2 = nee	

34.	TIA_sg	Stroomgebied waarin eerste TIA na borstkanker behandeling heeft plaatsgevonden	1: A cerebri anterior (Aca) (grote hersenen) 2: A cerebri media (acm) (grote hersenen) 3: A cerebri posteriori (ACP) (grote hersenen) 4: A basillaris (kleine hersenen) 5: A vertebralis (kleine hersenen)	
35.	CTS	Carpaal tunnel syndroom, bepaald door EMG: ja/nee	1 = ja 2 = nee	
36.	CTS_datum	Diagnose datum CTS	mm-jjjj	
37.	CTS_loc	Locatie CTS	1: rechts 2: links 3: beide	
38.	CTS_kracht	Verminderde kracht door CTS	1 = ja 2 = nee	
39.	CTS_pijn	Pijn door CTS	1 = ja 2 = nee	
40.	CTS_gevoel	Verminderd gevoel door CTS	1 = ja 2 = nee	
41.	CTS_operatie	Was er een operatie nodig om CTS te verhelpen?	1 = ja 2 = nee	
42.	CTS_injectie	Was er een injectie nodig om CTS te verhelpen?	1 = ja 2 = nee	
43.	CTS_brace	Was er een brace nodig om CTS te verhelpen?	1 = ja 2 = nee	
44.	MNG	Meningeoom (hersenvlies tumor) goedaardig: ja/nee	1 = ja 2 = nee	
45.	MNG_datum	Diagnose datum MNG	mm-jj	
46.	Neuro_10 jaar	Status neurologische aandoening(en) ≥ 10 jaar na lump/ablatio	0 = geen neurologische aandoening na borstkankerbehandeling gekregen/aangetoond 1 = volledig herstel zonder behandeling 2 = volledig herstel met behandeling 3 = incompleet herstel met functieverlies 4 = geïnvalideerd 5 = overleden 7 = geen achteruitgang bekende neurologische aandoening	
47.	Neuro_10 jaar_specifiek	Beschrijving neurologische aandoening(en) ≥ 10 jaar (tot einde FU met ernst van de aandoening (CTCAE of score)	Tekst	

Pulmonale effecten aanwezig voor of tijdens behandeling (t0)				
1.	Rad_afwijk_t0	Aanwezigheid interstitiële longaandoening(en)?	1 = ja 2 = nee	
2.	Rad_afwijk_class_t0	Oorzaak interstitiële longaandoening.	1 = Interstitiële longziektes;	

			2 Frequente infecties; 3; Bronchiectasieën; 4=overig	
3.	COPD_t0	Aanwezigheid COPD	1 = ja 2 = nee	
4.	COPD_klasse_t0	GOLD klasse COPD in tweeën verdeeld, klasse l en ll (mild en gemiddeld) samen en klasse lll en lV (hevig en erg hevig) samen	1 = mild-gemiddeld (GOLD I/II) 2 = hevig – erg hevig (GOLD III/IV)	
5.	Astma_t0	Aanwezigheid astma	1= ja 2 = nee	
6.	Obstructief aspecifiek longlijden	Bij gebruik van inhalatiemedicatie via HA of andere arts, consult longarts niet persé noodzakelijk	1 = ja 2 = nee	
7.	Overig_t0	Aanwezigheid van overige longaandoeningen	1 = ja 2 = nee	
8.	Overig_bes_t0	Beschrijving van overige longaandoening op t0	Tekst	
Longfunctie onderzoek (laatste voor t0) (voor = waarde voor luchtwegverwijdende medicatie, na = waarde na luchtwegverwijdende medicatie indien gegeven)				
9.	LF_t0	Longfunctieonderzoek gedaan? (laatste bekend voor t0, ‘’voor’’’ is voor medicatie, ‘’na’’ is na medicatie	1 = ja 2 = nee	Samara bestand
10.	LF_datum_t0	Datum van longfunctie onderzoek	dd-mm-jjjj	
11.	TLC_voor_t0	Totale long-capaciteit in l (voor)	Numeriek	
12.	FEV1_voor_t0	Forced expiratory volume in l (voor)	Numeriek	
13.	VC_voor_t0	Vital Capacity in cc (voor)	Numeriek	
14.	TLCO_voor_t0	Diffusie capacity (DLCO) in % (voor)	Numeriek	
15.	KCO_voor_t0	Moxide transfer Coeefficient in % (voor)	Numeriek	
16.	TLC_na_t0	Totale long-capaciteit in l (na)	Numeriek	
17.	FEV1_na_t0	Forced expiratory volume in l (na)	Numeriek	
18.	VC_na_t0	Vital Capacity in cc (na)	Numeriek	
19.	TLCO_na_t0	Diffusie capacity (DLCO) in % (na)	Numeriek	
20.	KCO_na_t0	Moxide transfer Coeefficient in % (na)	Numeriek	

Pulmonale late effecten				
Nr.	**Code variable**	**Beschrijving variabele**	**Scoring**	**Bron**
1.	Acute_Rad_Pneu-monitis	Aanwezigheid radiatie Pneumonitis	1 = ja 2 = nee	
2.	Acute_Rad_Pneu-monitis_datum	Datum van diagnose	mm-jj	
3.	Acute_Rad_Pneu-monitis_grade	Gradatie acute Pneumonitis	1 = asymptomatisch, maar wel aanwezig. Geen interventie noodzakelijk 2 = symptomatisch. Medische interventie	CTCAE 5.0

			geïndiceerd; Hoesten en/of benauwdheid. 3 = erge symptomen, beperkt in ADL; zuurstof geïndiceerd; mogelijke behandeling met corticosteroiden. 4 = levensbedreigende situatie, urgente interventie geindiceerd (tracheotomy en/of intubatie)	
4.	Acute_Rad_pneumonitis_loc	Locatie links rechts	1 = rechts 2 = links 3 = rechts + links	
5.	Pneumonie		1 = ja 2 = nee	
6.	Aantal pneumonieën	Tot ≥ 10 jaar na ablatio/lump	Numeriek	
7.	Pneumonie_1ste_ datum	Datum optreden eerste pneumonie na behandeling	mm-jj	
8.	Pneumonieën_loc	Locatie(s) pneumonieën	1 = rechts 2 = links 3 = rechts + links	
9.	PV	Aanwezigheid pleuraal vocht	1 = ja 2 = nee	Literatur (1)
10.	PV _datum	Datum diagnose pleuraal vocht	mm-jj	
11.	PV_loc	Locatie links rechts	1 = rechts 2 = links 3 = rechts + links 8 = nvt 9 = onbekend	
12.	PF	Pulmonary Fibrosis	1 = ja 2 = nee	CTCAE 5.0
13.	PF_datum	Datum diagnose PF	mm-jj	
14.	PF_loc	Locatie van fibrose	1 = rechts 2 = links 3 = rechts + links	
15.	PF_loc_kwab	Beschrijving van localisatie van lob	Tekst	
16.	PF_grade	Pulmonary Fibrosis gradatie CTCAE 5.0 pg 138 1 t/m 5 Daar tgv RT regelmatig enige fibrose gezien wordt zonder direct merkbare en aangetoonde gevolgen extra item toegevoegd: 7 = geringe fibrose, geen hypoxie	1 = sprake van fibrose in <25% van de long (CT), sprake van hypoxie 2 = sprake van fibrose in 25 – 50 % van de long, sprake van hypoxie 3 = sprake van meer dan 50% fibrose in long, erge hypoxie, sprake van rechtszijdig hartfalen 4 = levensbedreigende situatie (intubatie en ademondersteuning noodzakelijk, meer dan	CTCAE 5.0 pg 138 1 t/m 5

			75% van de long heeft fibrose. 5 = dood 7 = geringe fibrose, geen hypoxie	
17.	PF_overig	Overige notities bij PF	Tekst	
18.	Bronchiectasiën	Bronchiectasiën gediagnosticeerd na behandeling	1 = ja 2 = nee	radioloog
19.	Bronchiectasieën_datum	Datum diagnose Bronchiectasiën	mm-jj	
20.	Bronchiectasieën_loc	Locatie links rechts	1 = rechts 2 = links 3 = rechts + links	
21.	LK_sec	Secundaire longkanker	1 = ja 2 = nee	
22.	LK_sec_datum	Datum diagnose longkanker	mm-jj	
23.	LK_sec_loc	Localisatie van secundaire longkanker	1 = rechts 2 = links	
24.	LK_sec_loc2	Verdere notities (kwab)	Tekst	
25.	COPD	Aanwezigheid COPD	1 = ja 2 = nee	
26.	COPD_Nieuw	COPD ontstaan na borstkankerbehandeling ja/nee	1 = ja 2 = nee	
27.	COPD_Nieuw_datum	Datum diagnose COPD na borstkankerbehandeling	mm-jj	
28.	COPD_klasse	Gold klasse COPD -bij diagnose COPD_nieuw of -bij bestaand COPD bij eerste controle longarts na registratietermijn borstkankerbehandeling	1 = Mild/gemiddeld (GOLD I/II) 2 = Hevig/ erg hevig (GOLD III/IV)	
29.	Astma	Aanwezigheid astma	1 = ja 2 = nee	
30.	Astma_Nieuw	Astma ontstaan na borstkankerbehandeling ja/nee	1 = ja 2 = nee	
31.	Astma_Nieuw datum	Datum diagnose Astma na borstkankerbehandeling	mm-jj	
32	Obstructief aspecifiek longlijden	Bij gebruik van inhalatiemedicatie via HA of andere arts, consult longarts niet persé noodzakelijk	1 = ja 2 = nee	
33.	Obstructief aspecifiek longlijden_datum	Datum aanwezigheid Obstructief aspecifiek longlijden, zie voor uitleg item 6 bij T0	mm-jj	
34.	Long_overig	Beschrijving van overige longaandoeningen.	Tekst	
35.	Long_10 jaar	Status longaandoening(en) ≥ 10 jaar na lump/ablatio	0 = geen longaandoening na borstkankerbehandeling gekregen/aangetoond òf alleen radiologisch zonder (merkbaar) funktieverlies 1 = volledig herstel zonder behandeling 2 = volledig herstel met behandeling 3 = incompleet herstel met functieverlies	

			4 = geïnvalideerd 5 = overleden 7 = geen achteruitgang bekende longaandoening	
36.	Long_10 jaar_specifiek	Beschrijving longaandoening(en) ≥ 10 jaar (tot einde FU met ernst van de aandoening (CTCAE of score)	Tekst	
Longfunctie onderzoek late pulmonale effecten, laatste bekende (≠t0) (voor = waarde voor luchtwegverwijdende medicatie, na = waarde na luchtwegverwijdende medicatie indien gegeven)				
37.	LF	Longfunctie-onderzoek gedaan?	1 = ja 2 = nee	Samara bestand
38.	LF_datum	Datum van longfunctie onderzoek	mm-jj	
39.	TLC_voor	Totale long-capaciteit in l (voor)	Waarde	
40.	FEV1_voor	Forced expiratory volume in l (voor)	waarde	
41.	VC_voor	Vital Capacity in cc (voor)	waarde	
42.	TLCO_voor	Diffusie capacity (DLCO) in % (voor)	waarde	
43.	KCO_voor	Moxide transfer Coeefficient in % (voor)	waarde	
44.	TLC_na	Totale long-capaciteit in l (na)	Waarde	
45.	FEV1_na	Forced expiratory volume in l (na)	waarde	
46.	VC_na	Vital Capacity in cc (na)	waarde	
47.	TLCO_na	Diffusie capacity (DLCO) in % (na)	waarde	
48.	KCO_na	Moxide transfer Coeefficient in % (na)	waarde	

d) Cardiologische effecten

Cardiologische effecten aanwezig voor of tijdens behandeling (t0)				
1.	CMP_t0	Hartspierziekte voor/tijdens t0	1 = ja 2 = nee	CTCAE/ literatuur
2.	LVEF_t0	Ejectiefractie linkerventrikel	0= EF%: >50 1= EF%: 50 - 40% 2= EF%: 39 - 20% 3= EF%: <20%	CTCAE5.0
3.	CHF_t0	Hartfalen voor/tijdens t0 Klasse hartfalen New York Heart Association (NYHA) classification: - NYHA-klasse I: geen klachten bij normale lichamelijke inspanning. - NYHA-klasse II: enige klachten en beperkingen bij normale lichamelijke inspanning. - NYHA-klasse III: belangrijke beperkingen en klachten bij lichte inspanning (bijvoorbeeld honderd meter lopen). - NYHA-klasse IV: klachten in rust en ernstige beperkingen.	0 = nee 1 = NYHA-klasse I 2 = NYHA-klasse II 3 = NYHA-klasse III 4 = NYHA-klasse IV	literatuur
4.	VAD_t0	Ventricular Assist Device voor/tijdens t0	1 = ja 2 = nee	
5.	Hart_transpl_t0	Hart transplantatie voor/tijdens t0	1 = ja 2 = nee	
6.	CAD_t0	Kransslagaderaandoening (angina pectoris/hartinfarct) voor/tijdens t0	1 = ja 2 = nee	literatuur

7.	CAD_LCA_t0	Afwijking van left coronary artery (LCA) voor/tijdens t0	1 = ja 2 = nee	literatuur
8.	CAD_LAD_t0	Afwijking van left anterior descending (LCA → LAD) voor/tijdens t0	1 = ja 2 = nee	literatuur
9.	CAD_LCX_t0	Afwijking van left circumflex artery (LCA → LCX) voor/tijdens t0	1 = ja 2 = nee	literatuur
10.	CAD_RCA_t0	Afwijking van right coronary artery (RCA) voor/tijdens t0	1 = ja 2 = nee	literatuur
11.	AP_t0	Angina pectoris voor/tijdens t0	1 = ja 2 = nee	literatuur
12.	MI_t0	Hartinfarct voor/tijdens t0	1 = ja 2 = nee	CTCAE 5.0
13.	PCI_t0 = PTCA_t0	Percutane Coronaire Interventie voor/tijdens t0	1 = ja 2 = nee	
14.	CABG_t0	Coronary Artery Bypass Graft voor/tijdens t0	1 = ja 2 = nee	
15.	VHD_AV_t0	Afwijking van aortic valve voor/tijdens t0, zie voor grade nummer 28.	0 = geen afwijking 1 = grade 1 2 = grade 2 3 = grade 3 4 = grade 4	CTCAE 5.0, pg 6
16.	VHD_MV_t0	Afwijking van mitral valve voor/tijdens t0, zie voor grade nummer 28.	0 = geen afwijking 1 = grade 1 2 = grade 2 3 = grade 3 4 = grade 4	CTCAE 5.0, pg 6
17.	VHD_TV_t0	Afwijking van tricuspid valve voor/tijdens t0, zie voor grade nummer 28.	0 = geen afwijking 1 = grade 1 2 = grade 2 3 = grade 3 4 = grade 4	CTCAE 5.0 Pg 6
18.	VHD_PV_t0	Afwijking van pulmonary valve voor/tijdens t0, zie voor grade nummer 28.	0 = geen afwijking 1 = grade 1 2 = grade 2 3 = grade 3 4 = grade 4	CTCAE 5.0 Pg 6
19.	HRS_t0	Hartritmestoornis voor/tijdens t0	1 = ja 2 = nee	literatuur
20.	GS_t0	Geleidingsstoornis voor/tijdens t0	1 = ja 2 = nee	literatuur
21.	Pericarditis_t0	Pericarditis voor/tijdens t0	1 = ja 2 = nee	CTCAE 5.0
22.	PM_t0	Pacemaker voor/tijdens t0	1 = ja 2 = nee	

23.	ICD_t0	Implantable Cardioverter Defibrillator (ICD) voor/tijdens t0	1 = ja 2 = nee	

Cardiologische late effecten - variabelen			
Nr.	**Code variable**	**Beschrijving variabele**	**Scoring**
1.	CMP	Hartspierziekte	1 = ja 2 = nee
2.	CMP_datum	Hartspierziekte diagnose datum	mm-jj
3.	CMP_type	Type hartspierziekte	1=Dilated Cardiomyopathy (DCMP) 2=Restrictive Cardiomyopathy (RCMP) 3=Hypertrophic Cardiomyopathy (HCMP)
4.	CMP_LVEF	Ejectiefractie linkerventrikel gradatie (CTCAE 5.0): - EF%: >50% (normal) - EF%: 40% to 50% (mild dysfunction) - EF%: 39 - 20% (moderate dysfunction) - EF%: < 20% (severe dysfunction) → BRON: Common Terminology Criteria for Adverse Events (CTCAE) →Laagst gemeten LVEF noteren	0= EF%: >50 1= EF%: 50 - 40% 2= EF%: 39 - 20% 3= EF%: <20%
5.	CHF	Hartfalen	1 = ja 2 = nee
6.	CHF_datum	Hartfalen diagnose datum	mm-jj
7.	CHF_type	Type hartfalen	1=Systolisch hartfalen 2=Diastolisch hartfalen 3= Combinatie van beide
8.	CHF_klasse	Klasse hartfalen New York Heart Association (NYHA) classification: - NYHA-klasse I: geen klachten bij normale lichamelijke inspanning. - NYHA-klasse II: enige klachten en beperkingen bij normale lichamelijke inspanning.	1=NYHA-klasse I 2=NYHA-klasse II 3=NYHA-klasse III 4=NYHA-klasse IV

		- NYHA-klasse III: belangrijke beperkingen en klachten bij lichte inspanning (bijvoorbeeld honderd meter lopen). - NYHA-klasse IV: klachten in rust en ernstige beperkingen.	
9.	VAD	Ventricular Assist Device	1 = ja 2 = nee
10.	VAD_datum	Ventricular Assist Device implantatie datum	mm-jj
11.	Hart_transpl	Harttransplantatie	1 = ja 2 = nee
12.	Hart_transpl_datum	Harttransplantatie datum	mm-jj
13.	CAD	Kransslagaderaandoening (angina pectoris/ hartinfarct)	1 = ja 2 = nee
14.	CAD_LCA	Afwijking van left coronary artery (LCA)	1 = ja 2 = nee
15	CAD_LAD	Afwijking van left anterior descending (LCA →LAD)	1 = ja 2 = nee
16.	CAD_LCX	Afwijking van left circumflex artery (LCA → LCX)	1 = ja 2 = nee
17.	CAD_RCA	Afwijking van right coronary artery (RCA)	1 = ja 2 = nee
18.	AP	Angina pectoris	1 = ja 2 = nee
19.	AP_datum	Angina pectoris diagnose datum	mm-jj
20.	AP_type	Type angina pectoris: - Stabiele angina pectoris: drukkend gevoel bij inspanning, emotie, overgang van warmte naar koude of na zware maaltijden - Instabiele angina pectoris: klachten niet (meer) voorspelbaar en ook in rust	1=Stabiele angina pectoris 2=Instabiele angina pectoris
21.	AP_klasse	Klasse angina pectoris a.d.h.v. Canadian Cardiovascular Society (CCS) grading of angina pectoris	1=Grade I 2=Grade II 3=Grade III

		I= Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion. II=Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold or in wind or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. III= Marked limitation of ordinary physical activity. Waling one or two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace. IV= inability to carry on any physical activity without discomfort, angina syndrome may be present at rest.	4=Grade IV
22.	MI	Hartinfarct	1 = ja 2 = nee
23.	MI_datum	Hartinfarct datum	mm-jj
24.	PCI = PTCA	Percutane Coronaire Interventie	1 = ja 2 = nee
25.	PCI_datum	Percutane Coronaire Interventie datum	mm-jj
26.	CABG	Coronary Artery Bypass Graft	1 = ja 2 = nee
27.	CABG_datum	Coronary Artery Bypass Grafting datum	mm-jj
28.	VHD_AV	Afwijking van aortic valve (CTCAE 5.0, pg 6) Grade 1: Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging Grade 2: Asymptomatic; moderate regurgitation or stenosis by imaging	0=geen afwijking 1=grade 1 2=grade 2 3=grade 3 4= grade 4

		Grade 3: Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	
29.	VHD_MV	Afwijking van mitral valve Gradatie zie nr. 28	0=geen afwijking 1=grade 1 2=grade 2 3=grade 3 4= grade 4
30.	VHD_TV	Afwijking van tricuspid valve Gradatie zie nr. 28	0=geen afwijking 1=grade 1 2=grade 2 3=grade 3 4= grade 4
31.	VHD_PV	Afwijking van pulmonary valve Gradatie zie nr. 28	0=geen afwijking 1=grade 1 2=grade 2 3=grade 3 4= grade 4
32.	VHD_datum	Hartklepafwijking diagnose datum	mm-jj
33.	HRS	Hartritmestoornis	1 = ja 2 = nee
34.	HRS_datum	Hartritmestoornis diagnose datum	mm-jj
35.	HRS_type	Type hartritmestoornis	1=Boezemfibrilleren/atriumfibrilleren 2=Boezemflutter/atriumflutter 3=Boezemtachycardie/atriumtachycardie 4=Bradycardie 5=Ventrikelfibrilleren 6=Ventrikeltachycardie 7=Overig

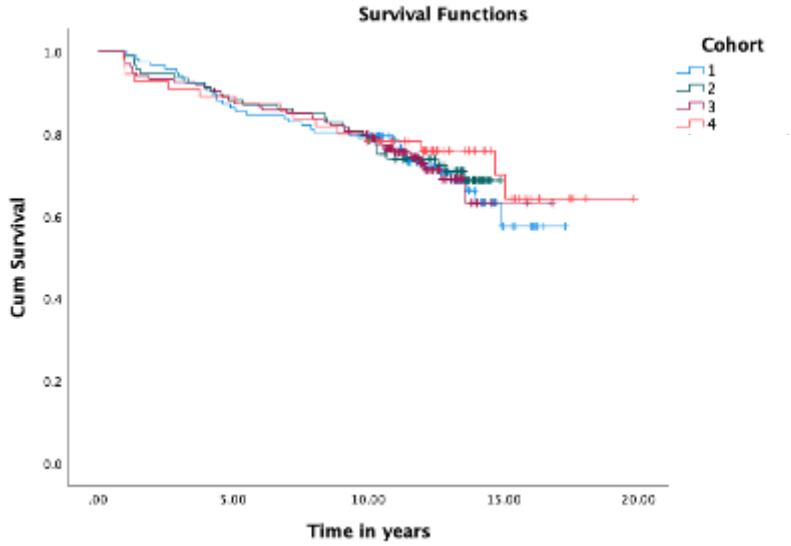
36.	GS	Geleidingsstoornis	1 = ja 2 = nee
37.	GS_datum	Geleidingsstoornis diagnose datum	mm-jj
38.	GS_type	Type geleidingsstoornis	1=Atrioventricular (AV)-blok 2=Linker bundel tak blok (LBTB) 3=Rechter bundel tak blok (RBTB) 4=Sinusknoopdisfunctie 5=Bifasciculair bundeltakblok 6=Overig
39.	PM	Pacemaker	1 = ja 2 = nee
40.	PM_datum	Pacemaker implantatie datum	mm-jj
41.	ICD	Implantable Cardioverter Defibrillator (ICD)	1 = ja 2 = nee
42.	ICD_datum	Implantable Cardioverter Defibrillator (ICD) implantatie datum	mm-jj
43.	Pericarditis	Hartvliesontsteking	1 = ja 2 = nee
44.	Pericarditis_datum	Hartvliesontsteking diagnose datum	mm-jj
45.	Pericarditis_type	Type hartvliesontsteking	1=Pericarditis constrictiva 2=Pericarditis exsudativa
46.	Overig	Overige cardiale klachten en/of bevindingen	Tekst
47.	Cardio_10 jaar	Status cardiologische aandoening(en) ≥ 10 jaar na lump/ablatio	0 = geen cardiologische aandoening na borstkankerbehandeling gekregen/aangetoond 1 = volledig herstel zonder behandeling 2 = volledig herstel met behandeling 3 = incompleet herstel met functieverlies 4 = geïnvalideerd 5 = overleden

			7 = geen achteruitgang bekende cardiologische aandoening
48.	Cardio_10 jaar_specifiek	Beschrijving cardiologische aandoening(en) ≥ 10 jaar (tot einde FU met ernst van de aandoening (CTCAE of score)	Tekst
49.	Opmerkingen hele itemlijst	Opmerkingen over aangetroffen bijzonderheden hele itemlijst	Tekst

Appendix B

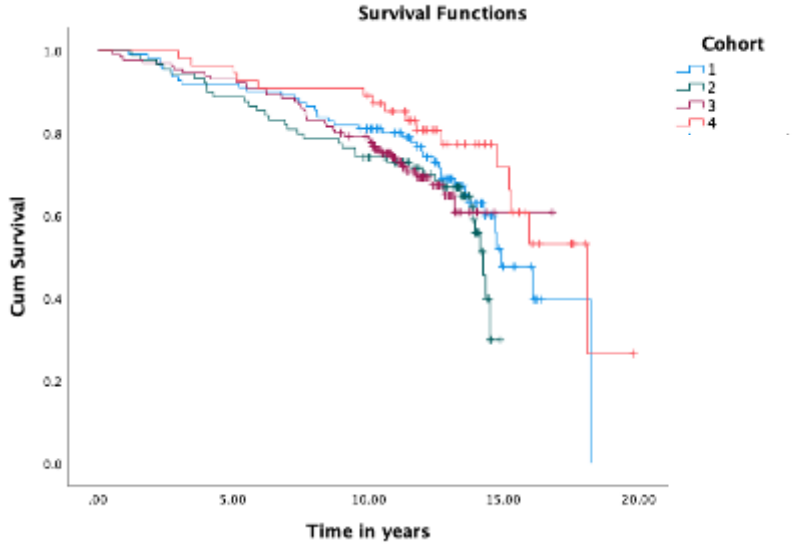
Kaplan Meier curves and Landmark analyses

Figure B2: Survival curve regarding neurological events



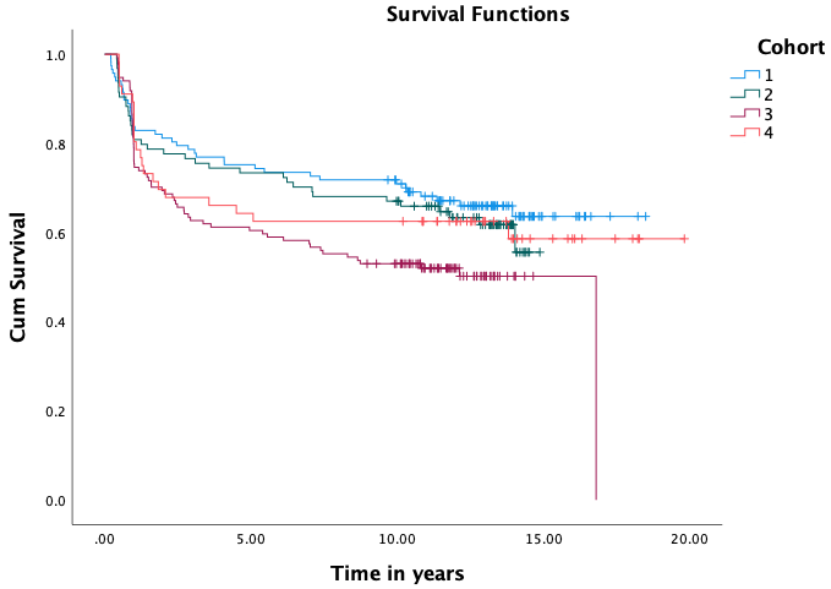
Log Rank Mantel Cox = .916

Figure B3: Survival curve regarding cardiac events



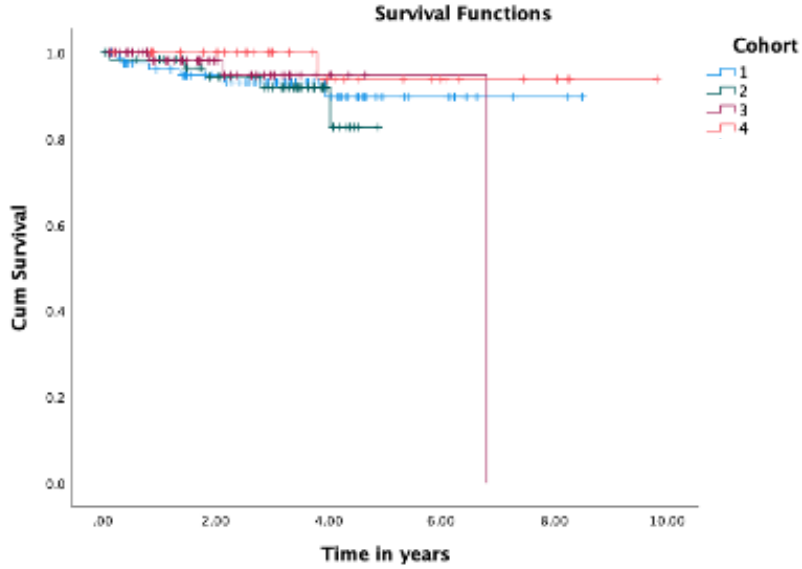
Log Rank Mantel Cox = .082

Figure B4: Survival curve regarding fatigue events



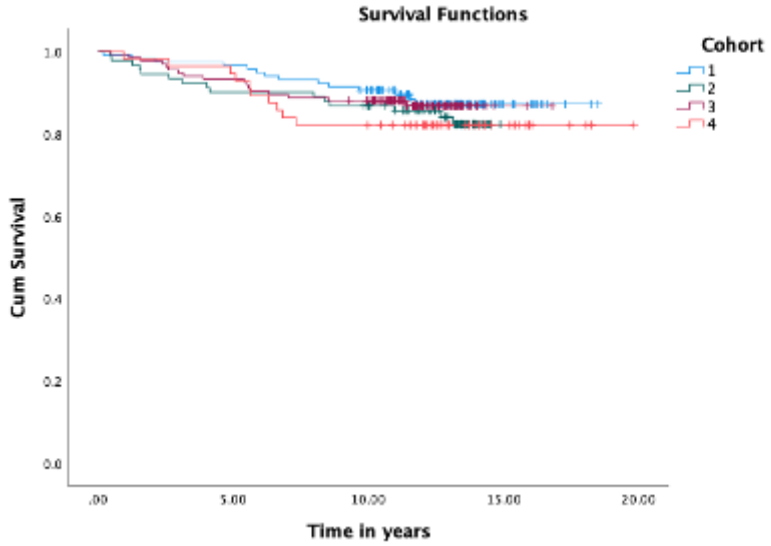
Log Rank Mantel Cox = .059

Figure B5: Landmark analysis regarding fatigue events



Log Rank Mantel Cox = .560

Figure B6: Survival curve regarding osteoporosis events



Log Rank Mantel Cox = .682

Figure B7: Landmark analysis regarding osteoporosis events

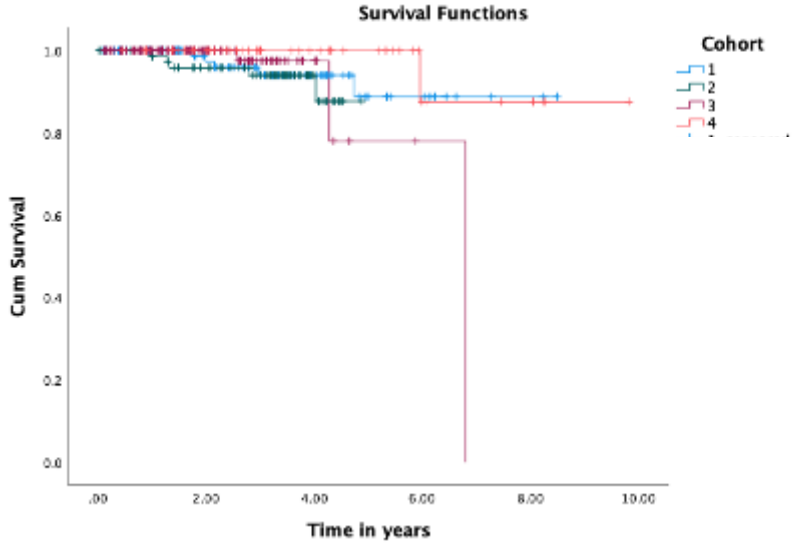
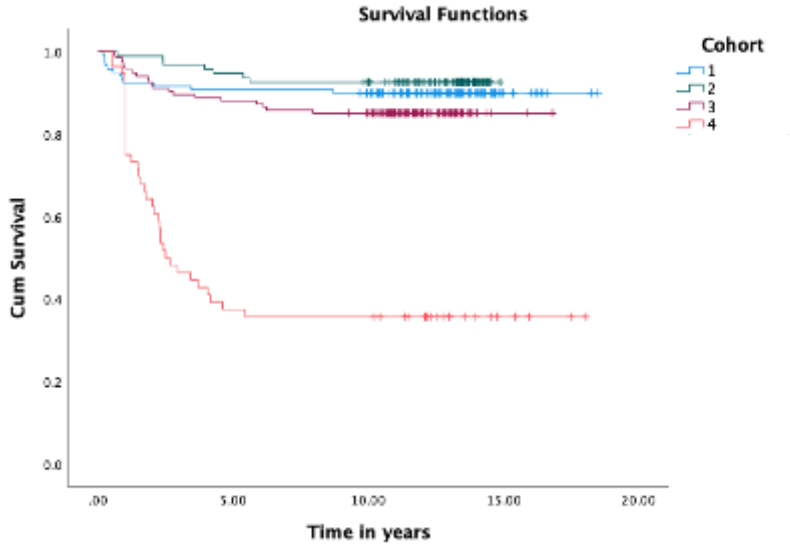
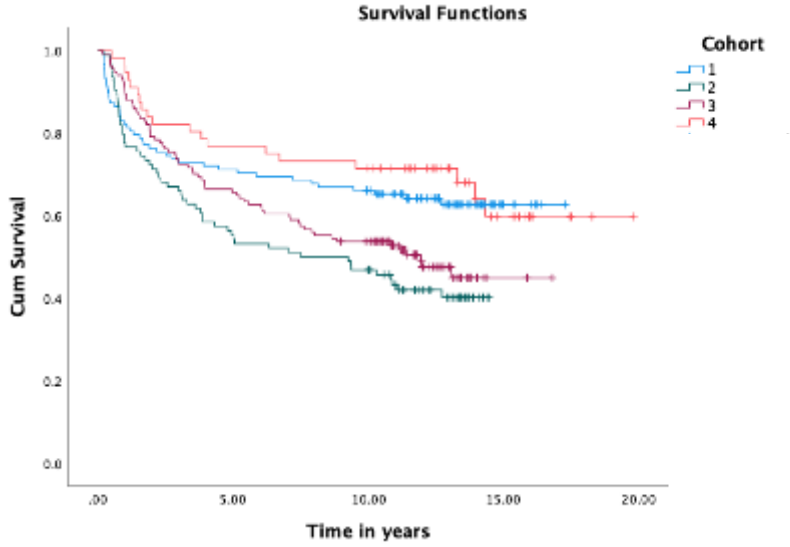


Figure B8: Survival curve regarding lymphedema events



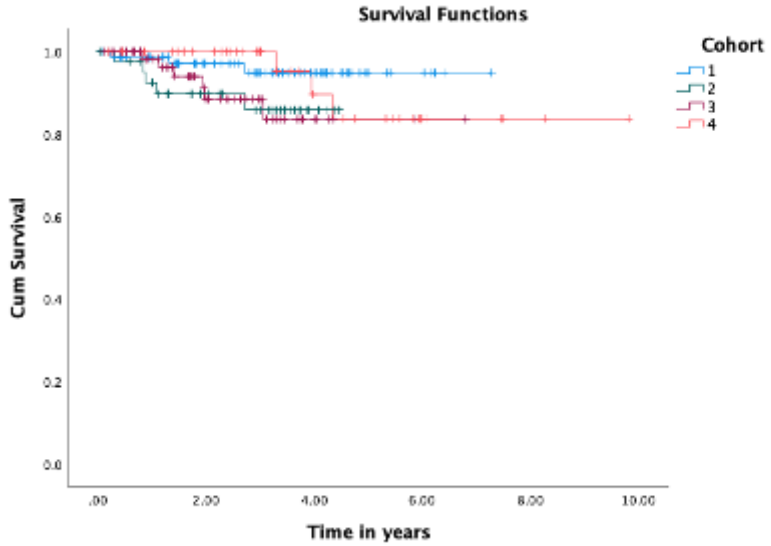
Log Rank Mantel Cox = <.001

Figure B9: Survival curve regarding breast/thoracic wall pain events



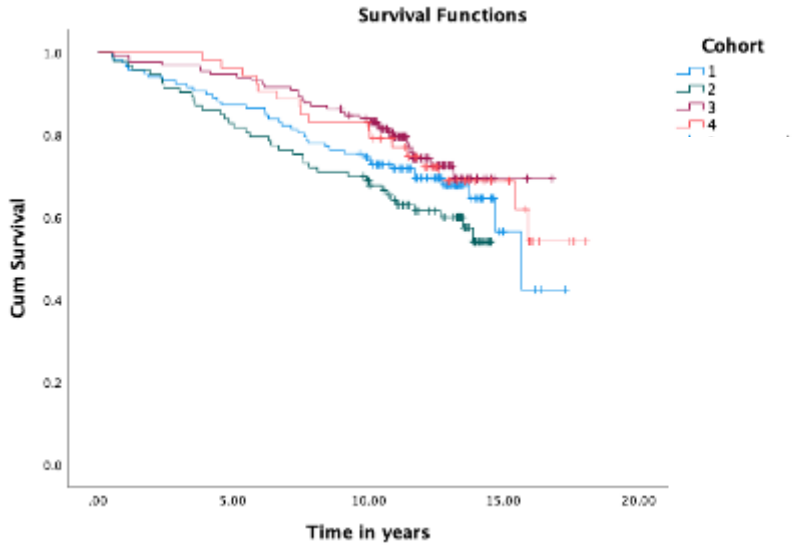
Log Rank Mantel Cox = .002

Figure B10: Landmark analysis regarding breast/thoracic wall pain



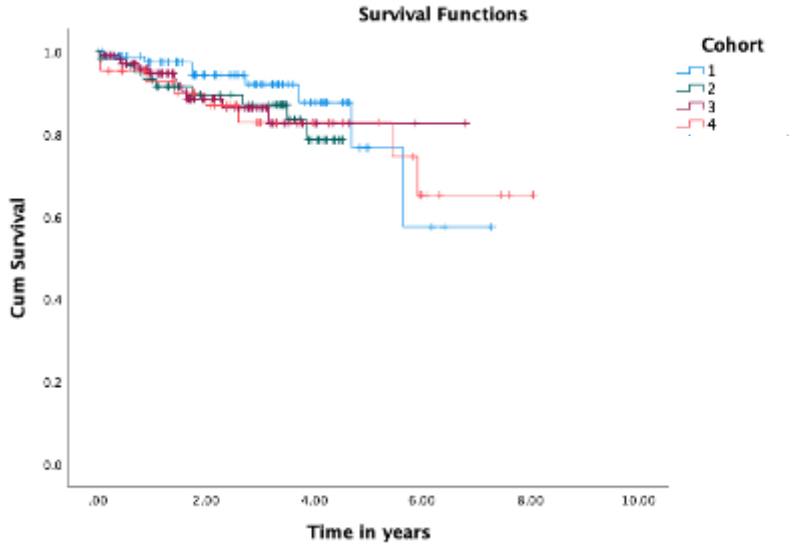
Log Rank Mantel Cox = .213

Figure B11: Survival curve regarding bowel diseases



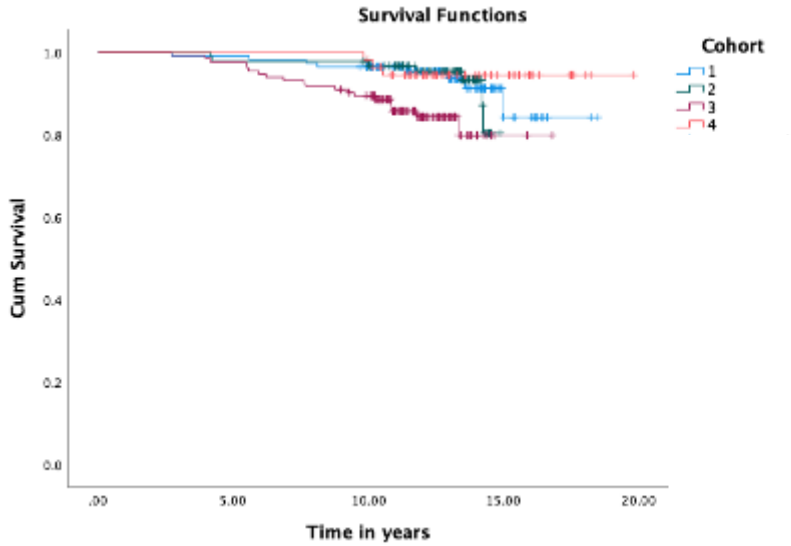
Log Rank Mantel Cox = .072

Figure B12: Landmark analysis regarding bowel diseases



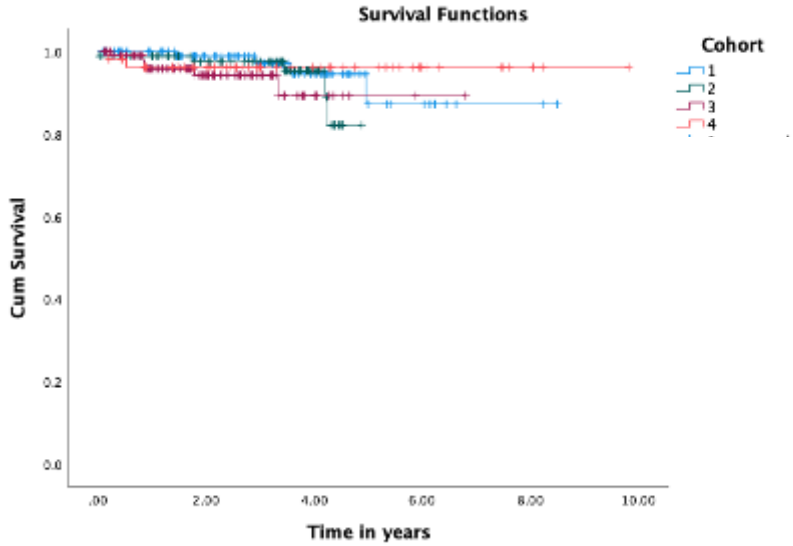
Log Rank Mantel Cox = .767

Figure B13: Survival curve regarding conduction disorders



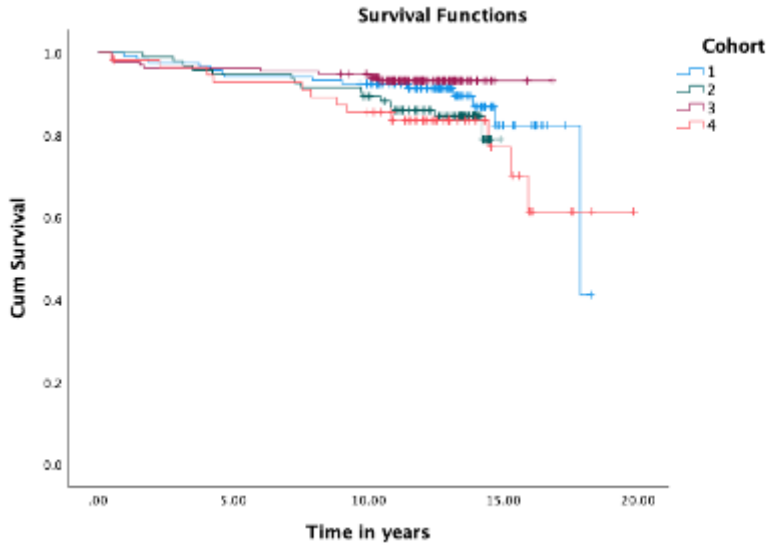
Log Rank Mantel Cox = .005

Figure B14: Landmark analysis regarding conduction disorders



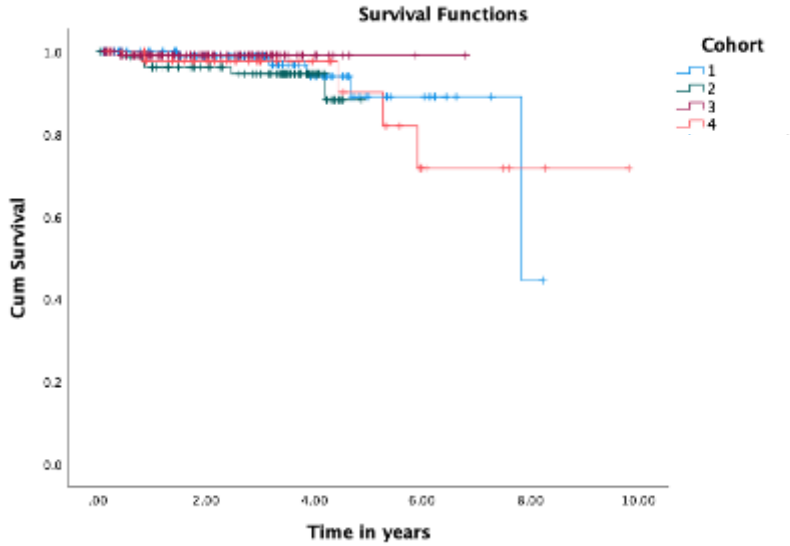
Log Rank Mantel Cox = .426

Figure B15: Survival curve regarding pneumonia events



Log Rank Mantel Cox = .128

Figure B16: Landmark analysis regarding pneumonia events



Log Rank Mantel Cox = .397