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A retrospective cohort study on late, treatment-induced morbidity after primary and adjuvant treatment in breast cancer patients

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Abstract

Background: Improvements in the treatment of breast-cancer has the positive effect on survivorship, this results in a group of patients where breast cancer has evolved from an acute life-threatening illness into a more chronic health state [1] and side- and adverse effects persist over longer periods of time. Knowledge is as of yet limited within the Dutch population as long-term and late effects [2]. This studies compares available medical records of Ziekenhuis Groep Twente (ZGT) and Medisch Spectrum Twente (MST) and the Comprehensive Cancer Organization (IKNL) to research the incidence of these long-term and late effects after different breast cancer therapies.
Method: A cohort study is performed existing of three cohorts. The data is retrospectively collected, ordered and compared for occurrence of late effects 10-15 years after different breast cancer therapies. These breast cancer therapies are represented by the control group cohort 1, which received mastectomy, cohort 2 that received breast conserving therapy and radiotherapy of the breast, and cohort 3 that received breast conserving therapy, radiotherapy of the breast, and chemotherapy with or without immunotherapy (Trastuzumab) with or without hormone therapy (Tamoxifen/Aromatase inhibitor) or hormone therapy alone. Data analysis is performed to investigate the influence of treatment on the occurrence of late adverse effects. Analysis is done by creating confounder adjusted Cox-regression hazard ratios, and Kaplan-Meier analysis.
Results: Ten years post-surgery, cohort 2 and 3 show increased occurrence of fatigue and lymphedema of the arm compared to the control group. Cohort 1 had significantly more occurrences of bowel/anal diseases than cohort 2 and 3, while the latter cohorts have an added risk for the development of these adverse effects due to more extensive adjuvant therapy. Neurological, pulmonal and cardiological adverse effects did not show any correlation between their respective prevalence of adverse effects and treatments.
Conclusion: This study did find evidence for significant differences in outcomes, some are expected while other were remarkable. To increase the quality of informed decisions by patient and healthcare alike, further research is required by increasing population sample and the addition of Patient reported outcome measures (PROMs).

Keywords: Mastectomy, breast-conserving therapy, radiotherapy, chemotherapy, hormone therapy, adjuvant systemic therapy, treatment-induced complications, adverse effects

Contents

Introduction

Cancer is becoming more commonplace; in 1989 56,000 patients were newly diagnosed with cancer in the Netherlands compared to 116,000 patients in 2018 an increase of 107.14 %. In 2018 a variety of cancers occur, with breast cancer accounting for 26.6 % of the total cancer occurrences [3].

Since 1989 the incidence of breast cancer has risen with approximately 50% while the population has grown with approximately 16.1 % [4] [5]. There has also been an increase in prevalence of breast cancer within the Dutch population due to improved treatment and the implementation of population screening [6]. Part of the increased prevalence is due to increased treatment options and efficacy, which can be seen as a positive development. This increased survivorship does create more breast cancer survivors, where breast cancer is evolving from an acute life-threatening illness into a rather more chronic condition health state [1]. This might also imply that the presence of adverse effects due to treatment persists over longer periods of time.

Many of these adverse effects are due to the treatment of breast cancer. Part of these adverse effects can be attributed to primary treatment such as mastectomy or breast conserving surgery, these treatments are comparable in survival outcomes but breast conserving therapy results in less mental disorders such as depression [7] [8] [9]. In addition to these primary treatments a staging procedure can be carried out such as sentinel lymph node dissection (SLND) with or without an axillary lymph node dissection (ALND), which are known to cause adverse effects such as lymphedema of the arm and shoulder function [10] [11] [12].Studies have shown that adjuvant treatments such as chemotherapy and hormone therapy are effective and increase survival but also increase cardiac toxicity [13], risk of cardiovascular diseases [14], exert detrimental effects on skeletal health and increase fracture risk [15]. Radiotherapy has proven its efficacy but also increases the risk of moderate to severe fibrosis [16] and the exposure of ironizing radiation to the heart increases the subsequent rate of ischemic heart disease [17].

Globally these adverse effects of treatment are known to manifest many years after primary treatment. Knowledge is as of yet limited within the Dutch population about these late adverse effects [2]. The aim of this study is to identify the risk factors that breast-cancer treatments pose on late effects. To answer this question as accurately as possible, cohorts have been created. These Cohorts are comprised of common treatment combinations. These combinations comprise of the type of surgery, adjuvant radiation therapy and adjuvant systemic therapy (see *figure 1*). A total of 168 patients are included, of which data is collected at the hospitals Ziekenhuis Groep Twente (ZGT) and Medisch Spectrum Twente (MST) and the Comprehensive Cancer Organization (IKNL) to create an unique database within the Netherlands. This database will contain information on medical history, current medical management and outcomes of patients who received treatment for breast cancer. This database provides unique opportunities due to the time these patients have received follow-up over a minimum period of 10 years.

Methods

This study will take into account a wide spectrum of possible late treatment associated morbidity, divided under the categories of general effects, neurological effects, pulmonal effects and cardiological effects. The data is subsequently collected, ordered and compared for incidences of late effects till 10-15 years after different breast cancer therapies. These breast cancer therapies are represented by 3 cohorts (see figure 1) which all underwent surgery with an axillary staging procedure sentinel lymph node dissection (SLND) or an axillary lymph node dissection (ALND). Statistical analysis consists of the comparison of occurrence of adverse effects, creation of Kaplan-Meier event free survival and hazard ratios created through Cox-regression.

Cohorts ***Figure 1***

Cohort 1 is included as control-group, patients associated with this cohort have undergone a mastectomy and axillary staging procedure (SLND or ALND) without further therapy

Cohort 2 contains breast cancer patients that received breast-conserving surgery, axillary staging procedure (SLND or ALND) and radiation therapy. Radiation therapy consists of whole breast radiation therapy which can be augmented with a boost.

Cohort 3 received the most comprehensive treatment consisting of breast-conserving surgery, axillary staging procedure (SLND or ALND), radiation therapy, adjuvant systemic treatment. Radiation therapy consists of whole breast radiation therapy which can be augmented with a boost. Systemic treatment consists of chemo therapy with or without immunotherapy (=Trastuzumab, in case of her-2 positive breast cancer) and/or hormone therapy. Chemo therapy can include AC (Adriamycin and cyclophosphamide) or FEC (fluorouracil, epirubicin and cyclophosphamide) regimen. Hormone therapy include treatment with Tamoxifen and/or aromatase inhibitors (arimidex, letrozole).

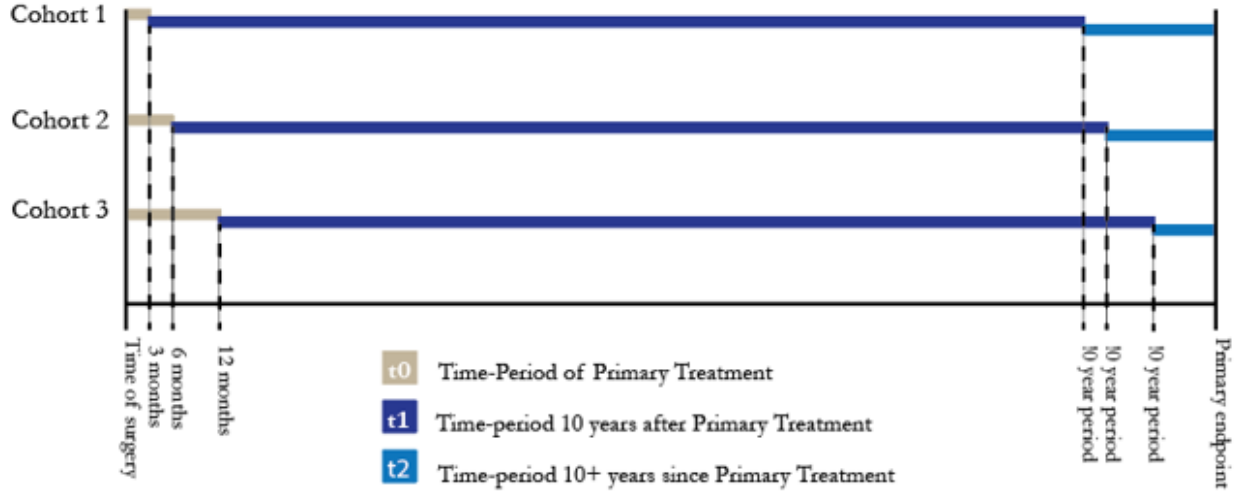
Patient data collection

Patients are identified at 2 hospitals, ZGT and MST having been treated for breast cancer between 2003-2009. Demographic, Medical history, health risks and health status data of patients are obtained by reviewing patient's medical records within the databases of ZGT and MST. Patients from all cohorts are checked for eligibility based on the following criteria:

- a minimum 10 years survival or follow-up
- did not receive radiotherapy of adjuvant systemic therapy for other primary malignancies during the period between primary treatment for breast cancer and 10 years after with the exception of basal cell carcinoma and squamous cell carcinoma of the skin treated with local radiation therapy
- did not receive radiotherapy and / or adjuvant systemic before primary breast cancer treatment with the exception of basal cell carcinoma and squamous cell carcinoma of the skin treated with local radiation therapy
- no local of regional recurrence or occurrence of metastases or contralateral breast cancer during the period between primary treatment for breast cancer and 10 years after

After the eligibility check data was collected with outcome measures ranging from binary, continuous to time to event. Time to event is calculated by subtracting the primary treatment time from the event time. Data on the effects was collected in three time periods: t0 is the time during primary treatment which contains different length of time due to the type of treatments. This is done to differentiate the acute adverse effects by the treatment from the late effects, the more comprehensive the treatment the longer t0. Cohort 3 is an exception as it contains two t0, as patient can additionally receive chemo therapy which lengthens t0 to 12 months opposed to 6 months. For t1 time is the 10 years after t0, and t2, which is follow-up at 10+ years which registers the presence and degree of severity of the effects 10 years or more after t0. The primary endpoint is defined as the time of surgery to last follow-up or death.

Figure 2. Subdivision of time periods in this study



The Hospital databases were used to obtain baseline characteristics of patients at time t0 on age, Body mass index (calculated from height and weight), smoking history, number of used medications, the presence of hypertension, hypercholesterolemia, diabetes mellitus. In time-period t1 and t2 outcome variables are collected which contains incidence of health effects and health status of the patients. The number of variables collected is larger than the number of variables included within the study. Covariates are included in the study on the basis of association with the outcome, changing the cause-specific hazard of the outcomes.

The data was obtained from multiple data sources within the hospital databases such as: laboratory tests (Blood tests, Urine tests), medical imaging reports (X-ray, CT-scan, MRI-scan, Dexa-scan), reports by healthcare professionals and hospital correspondence. All included variables are presented within the results and all collected variables can be viewed within appendix A. The data was collected between 06-2020 and 09-2020.

Statistical analysis

Descriptive analysis is performed to observe the patient's demographic characteristics and pre-existent risk factors at the time of primary treatment t0 as seen in table 1.

These included variables were then evaluated on their distribution differences, a one-way three-level ANOVA is used to evaluate differences in continuous variables, Kruskal Wallis test was used for non-normal distributed continuous variables and chi-square test to evaluate differences of categorical variables. The data is inspected for homogeneity of the variables between cohorts, heterogenic variables which is sufficiently significant at a cut-off point of 0.05 p-value are included to adjust Cox-regression hazard ratios for potential confounding.

Incidence of all adverse effects are compared between cohorts, and between sub cohorts on receiving the treatment Axillary lymph node dissection (ALND) or Sentinel lymph node dissection (SLND). The extra sub cohorts are included as the treatments ALND and SLND are known risk factors for lymphedema of the arm and impaired shoulder movement [18]. Appendix A shows all descriptive data, it contains all gathered variables and it also contains variables which are not taken into account in the analysis. These variables are excluded due to their low prevalence and the high amount of variability of the values, this would require a larger number of patients to improve statistical power and generate statistically significant results.

Using the Kaplan-Meier method, event-free survival (EFS) of the cohorts was assessed separately in t1 and 10+ years (t2), and shown in a landmark analysis. EFS is created using time between adverse effects and surgery time of each patient. Several acute adverse effects can contain multiple points in time where an effect occurs, such as Pneumonias. The time of the first event is used to calculated the time between adverse effect and surgery time. OS

is created using endpoint death and the censoring of patients at date of last follow-up. To compare the survival distributions between cohorts of DFS and OS, a Mantel-Cox test is performed.

Adjusted and unadjusted hazard ratios are created with a cox-regression analysis to determine the influence of each cohort on all adverse effects in t1 and t2 as the cohorts represent different treatment combinations. These hazard ratios are created by using time till adverse effects as underlying time scale. Multivariate hazard ratios are created for adverse effects that are affected by confounding variables by including additional relevant patient's demographics and pre-existent risk factors. For the variable to qualify to be a relevant risk factor, it first has to be statistically significantly (P-value < 0.10) different between the three cohorts. Then the influence will be checked to be significantly influential (P-value < 0.10) via a univariate cox regression model. When the significance is reached a second multivariate model will be made including the adverse effect and relevant variable.

Results

Baseline characteristics of Study Cohorts

Baseline characteristics of patients are shown in table 1. A total number of 168 patients are included of which 57 (33.9%) in cohort 1, 55 (32.7%) in cohort 2 and 56 (33.3%) in cohort 3. Four characteristics are shown to be statistically significantly (P-value < 0.10) different between the 3 cohorts. Cohort 3 shows a significantly lower average age at the time of surgery compared to cohort 2 and 3, and a wider spread of ages. Cohort 3 also has a significantly lower number of patients with hypercholesterolemia at t0 compared to cohort 2 and 3. Usage of medication at the time of surgery is also significantly different, as the average number is equivalent but the spread is wider for cohort 2. The mean follow-up years show little difference but the difference (p-value of 0.053) is created due to the spread of the range, as cohort 1 shows a wider range than cohort 2 and 3.

Table 1. *Baseline characteristics of the cohort populations at t0*

Characteristics	**Cohort 1 (Mastectomy) (n=57)**	**Cohort 2 (BCS + RT) (n=55)**	**Cohort 3 (BCS + RT + Adj) (n=56)**	**P-value**
Age (Mean ± SD)	**59.47 ± 9.06**	**60.13 ± 8.49**	**55.82 ± 12.54**	**0.058**
BMI (Mean ± SD)	26.99 ± 5.56	27.87 ± 6.19	27.54 ± 4.86	0.737
Smoking				0.316
- non-smoker	44 (77.2%)	38 (69.1%)	36 (64.3%)	
- smoker	13 (22.8%)	17 (30.9%)	20 (35.7%)	
Pack years (Median ± Q_1 – Q_3)	26 (19-38)	35 (17-45)	25 (13-32)	0.335
Hypertension	21 (36.8%)	26 (47.3%)	23 (41.1%)	0.531
Hypercholesterolemia	**15 (26.3%)**	**12 (21.8%)**	**6 (10.7%)**	**0.100**
Diabetes mellitus	9 (15.8%)	7 (12.7%)	8 (14.3%)	0.898
Number of used medications (Median ± Q1 – Q3)	**1 (0-2)**	**2 (1-4)**	**1 (0-2)**	**0.008**
Follow-up years (Q_1 – Q_3)	**12.95 (11-15)**	**12.65 (12-14)**	**12.25 (11-13)**	**0.053**
Surgical treatment				
Lumpectomy + SLND	0 (0%)	8 (14.5%)	27 (48.2%)	
Lumpectomy + ALND	0 (0%)	47 (82.5%)	29 (51.8%)	
Mastectomy	1 (1.8%)	0 (0%)	0 (0%)	
Mastectomy + SLND	26 (45.6%)	0 (0%)	0 (0%)	
Mastectomy + ALND	30 (52.6%)	0 (0%)	0 (0%)	
Adjuvant treatment				
Hormone therapy	0 (0%)	0 (0%)	24 (42.9%)	
Chemotherapy	0 (0%)	0 (0%)	9 (16.1%)	
Hormone therapy + Chemotherapy	0 (0%)	0 (0%)	23 (41.1%)	

Incidence of adverse effects

Incidence of general adverse effects during t1 and t2 can be observed in table 2. Incidence of lymphedema of the arm is significantly different (p=0.002) ten-year post-surgery (during t2), as cohort 1 has 0 occurrences compared to cohort 2 with 2 (3.6%) and cohort 3 with 5 (8.9%). Fatigue is also significantly different (p<0.001) ten-year post-surgery, as cohort 2 has 9 (16.4%) occurrences and cohort 3 has 8 (28.6%) compared to the 2 (3.5%) of cohort 1. Osteopenia is most occurring for cohort 3 at 14 (25%), then for cohort 1 at 7 (12.3%), and 3 (5.5%) for cohort 2 at a significant difference (p=0.011). Incidence of Bowel diseases is significantly different during both t1 (p=0.003) and t2 (p=0.016), and the incidence of Gastric diseases is significantly different during t1 (p=0.023).

Table 2. *Occurrence of general adverse effects in t1 and t2 (ten-year post-surgery)*

Adverse effects	Cohort 1 (Mastectomy) (n=57)	Cohort 2 (BCS + RT) (n=55)	Cohort 3 (BCS + RT + Adj) (n=56)	P-value
Fatigue	15 (26.3%)	18 (32.7%)	16 (28.6%)	0.752
Ten years post-surgery	**2 (3.5%)**	**9 (16.4%)**	**8 (14.3%)**	**<0.001**
Ulceration	2 (3.5%)	2 (3.6%)	3 (5.4%)	0.861
Ten years post-surgery	0 (0%)	1 (1.8%)	2 (3.6%)	0.358
Lymphedema of the arm	4 (7%)	5 (9.1%)	10 (17.9%)	0.156
Ten years post-surgery	**0 (0%)**	**2 (3.6%)**	**5 (8.9%)**	**0.002**
Breast/Thoracic pain	24 (42.1%)	31(56.4%)	26 (46.4%)	0.303
Ten years post-surgery	16 (28.1%)	18 (32.7%)	10 (17.9%)	0.121
Psychosocial problems	10 (17.5%)	9 (16.4%)	7 (12.5%)	0.741
Ten years post-surgery	2(3.5%)	4 (7.3%)	2 (3.6%)	0.674
Impaired shoulder mobility	8 (14.0%)	9 (16.4%)	7 (12.5%)	0.856
Ten years post-surgery	1 (1.8%)	6 (10.9%)	5 (8.9%)	0.221
Tissue necrosis	0 (0%)	3 (5.5%)	2 (3.6%)	0.225
Ten years post-surgery	0(0%)	3 (5.5%)	2 (3.6%)	0.225
Osteopenia	**7 (12.3%)**	**3 (5.5%)**	**14 (25%)**	**0.011**
Osteoporosis	6 (10.5%)	9 (16.4%)	5 (8.9%)	0.445
Osteopenia/Osteoporosis Ten years post-surgery	13 (22.8%)	11 (20%)	7 (12.5%)	0.346
Bowel/anal diseases	**17 (29.8%)**	**21 (38.2%)**	**6 (10.7%)**	**0.003**
Ten years post-surgery	**11 (19.3%)**	**4 (7.3%)**	**2 (3.6%)**	**0.016**
Gastric diseases	**6 (10.5%)**	**11 (20%)**	**2 (3.6%)**	**0.023**
Ten years post-surgery	2 (3.5%)	2 (3.6%)	1 (1.8%)	0.646
Rib fracture	3 (5.3%)	2 (3.6%)	0 (0%)	0.243

Incidence of neurological adverse effects can be observed in table b1. The adverse effect concentration disorder is significantly different (p=0.043) during t1 as only cohort 2 has any occurrences (3, 5.5%). Incidence of Transient ischemic attack is also significantly different during t1 (p=0.028), as cohort 1 has 6 (10.5%) occurrences, cohort 2 has 2 (3.65%) and cohort 3 has no occurrences. Table b2 presents the incidence of all pulmonal adverse effects during t1, and for t2 all adverse effects are clustered as one category. No significant differences between cohorts were observed for the pulmonal adverse effects. In table b3 the incidence of cardiological adverse effects can be observed. When specifically looking at the incidence of Angina pectoris during t1 it shows that it is significantly different (p=0.032), cohort 1 has 2 (3.5%) occurrences vs 7 (12.8%) for cohort 2 and 1 (1.8%) for cohort 3.

Event-free survival

Event-free Survival (EFS) has been evaluated by the Kaplan-Meier method. EFS is defined as the end time of t0 till an event has taken place in t1 and/or t2. The analysis is shown in a landmark analysis which contains the EFS during t1 (0-10 years) and t2 (10+years). Appendix C contains all landmark analyses that were included due to possessing a cohort difference with a P-value < 0.10.

General adverse effects

In figure 3 a significant event-free survival difference for osteopenia can be observed during t1 between cohort 3 and cohort 1 (p=0.047), and cohort 3 and cohort 2 (p=0.014). Cohort 1 and 2 have less occurrences for osteopenia than cohort 3. Figure c1 contains the EFS of Lymphedema of the arm, only t1 is shown due to the fact that there are no dates registered for the new occurrences for lymphedema of the arm during t2. During t1, Cohort 1 (p= 0.095) and cohort 2 (p= 0.183) have less occurrences than cohort 3.

Figure 3. *Occurrence of osteopenia per cohort in t1 and t2*

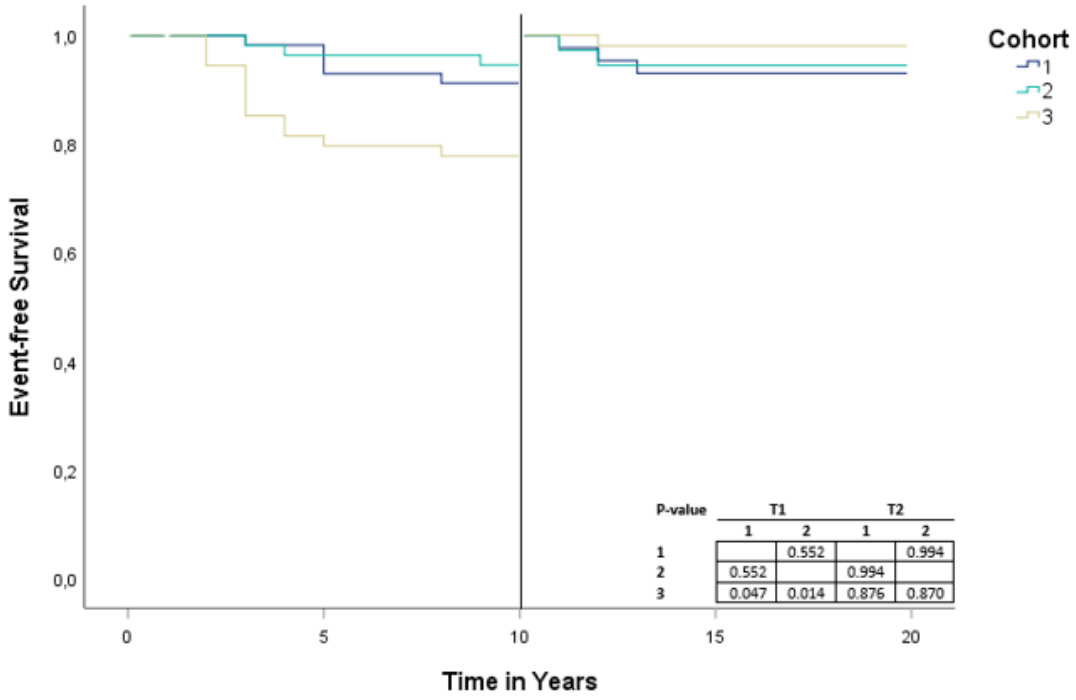
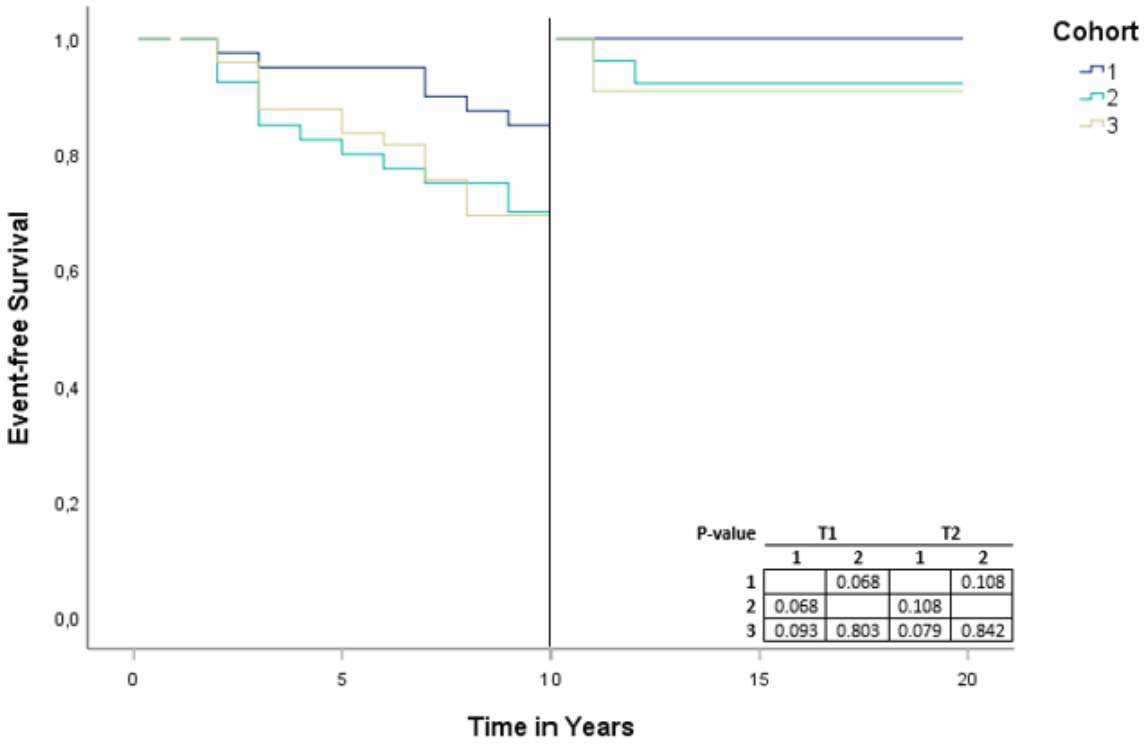


Figure 4 shows the occurrence of breast/thoracic pain. Cohort 1 shows less occurrences during t1 and t2 than cohort 2 and 3. The differences remain the same but the strength of the difference weakens from t1 to t2. Figure c2 shows the EFS of gastric diseases; during t1 significant differences occurred between cohort 3 and cohort 1 (p=0.094) and cohort 2 (p=0.044). During t2 this trend continued but did not achieve a p-value < 0.10. Figure c3 displays the EFS of Bowel/Anal diseases; a significant difference occurs during t1 as cohort 3 shows less occurrences of adverse effects compared to cohort 1 (p=0.075) and cohort 2 (p=0.001). This trend continues during t2 but does not achieve a p-value <0.10.

Figure 4. *Occurrence of breast/thoracic pain per cohort in t1 and t2*



Neurological, Pulmonal and Cardiological adverse effects

Neurological, pulmonal (see figure c4) and cardiological (see figure c5) adverse effects are analyzed in t1 per adverse effect and in t2 in clusters of each respective category, where neurological contains all neurological morbidities, pulmonal all pulmonal etc. Cardiological adverse effects was the only category that contained a statistically significant difference in EFS ($p<0.10$), as cohort 3 experienced a lower number of adverse effects during t2 than Cohort 1 ($p=0.091$) and cohort 2 ($p=0.048$).

Hazard ratios

Hazard ratios are created using cox proportional hazards modelling. Events that occurred in either t1 or t2 were used to calculate the hazard ratios. The created models contain all cohorts, where cohort 1 acts as a control group and is noted as *Referent*. Some adverse effects may also have an adjusted score, which are included when a better fit of the model is achieved. Appendix D contains all complete Cox-regression tables.

In table 3 the hazard ratios of general adverse effects can be observed. Osteopenia expresses a significantly increased hazard ratio (95%) in cohort 3 compared to cohort 1, the hazard ratio is unadjusted 2.69 (1.11 – 6.54) and while adjusted 2.61 (1.07 – 6.35). Bowel/anal diseases likewise shows a decreased hazard ratio in cohort 3 compared to cohort 1 both unadjusted 0.32 (0.13 – 6.54) and adjusted 0.38 (0.15 – 0.97).

Table 3. *The association of cohorts with adverse effects in t1 and t2*

Adverse effects	Cohort 1 HR (95% CI)	Cohort 2 HR (95% CI)	Cohort 3 HR (95% CI)
General adverse effects			
Osteopenia	*Referent*	0.72 (0.23 – 2.27)	**2.69 (1.11 – 6.54)**
Osteopenia [d]	*Referent*	0.79 (0.25 – 2.53)	**2.61 (1.07 – 6.35)**
Osteoporosis	*Referent*	1.60 (0.57 – 4.49)	0.85 (0.26 – 2.78)
Breast/thoracic pain	*Referent*	1.40 (0.82 – 2.39)	1.00 (0.58 – 1.75)
Breast/thoracic pain [b]	*Referent*	1.40 (0.82 – 2.38)	0.91 (0.52 – 1.60)
Gastric diseases	*Referent*	1.92 (0.71 – 5.19)	0.32 (0.07 – 1.60)
Bowel/anal diseases	*Referent*	1.35 (0.71 – 2.57)	**0.32 (0.13 – 0.81)**
Bowel/anal diseases [c]	*Referent*	1.52 (0.79 – 2.93)	**0.38 (0.15– 0.97)**
Neurological adverse effects			
Cognitive disorder	*Referent*	0.65 (0.23 – 1.82)	0.68 (0.24 – 1.92)
Cognitive disorder [a b c]	*Referent*	0.68 (0.24 – 1.94)	1.11 (0.37 – 3.32)
Carpal tunnel syndrome	*Referent*	0.72 (0.23 – 2.28)	**0.28 (0.06 – 1.34)**
Carpal tunnel syndrome [d]	*Referent*	0.65 (0.21 – 2.10)	**0.33 (0.07 – 1.61)**
Pulmonal adverse effects			
Pneumonia	*Referent*	1.58 (0.68 – 3.69)	0.59 (0.20 – 1.77)
Pneumonia [b d]	*Referent*	1.43 (0.60 – 3.40)	0.70 (0.23 – 2.10)
Pleural fluid	*Referent*	**0.67 (0.26 – 1.77)**	**0.39 (0.26 – 1.77)**
Pleural fluid [b d]	*Referent*	**0.60 (0.23 – 1.61)**	**0.49 (0.15 – 1.59)**
Pulmonary fibrosis	*Referent*	0.26 (0.03 – 2.31)	0.76 (0.17 – 3.40)
Pulmonary fibrosis [b c d]	*Referent*	0.16 (0.02 – 1.46)	0.78 (0.16 – 3.80)
Pulmonary fibrosis [b d]	*Referent*	0.20 (0.02 – 1.77)	1.09 (0.23 – 5.19)
Cardiological adverse effects			
Valvular heart disease	*Referent*	**0.46 (0.17 – 1.21)**	**0.47 (0.18 – 1.23)**
Valvular heart disease [a d]	*Referent*	**0.44 (0.16 – 1.17)**	**0.53 (0.20 – 1.43)**
Arrhythmia	*Referent*	2.01 (0.69 – 5.89)	1.04 (0.30 – 3.60)
Arrhythmia [a d]	*Referent*	2.00 (0.68 – 5.93)	1.31 (0.37 – 4.65)

[a] Adjusted for Hypercholesterolemia
[b] Adjusted for age of time of diagnosis
[c] Adjusted for follow-up time
[d] Adjusted for number of medications used at time of diagnosis

The categories of neurological, pulmonal and cardiological adverse effects did not contain significant hazard ratios, there are however several hazard ratios that approach these bounds as seen in table 3 which might predict future significance. For neurological adverse effects, cohort 3 exhibits a decreased hazard ratio (95%CI) of 0.28 (0.06 – 1.34) for Carpal tunnel syndrome when unadjusted, and adjusted a hazard ratio of 0.33 (0.07 – 1.61). For pulmonal adverse effects, both cohort 2 and 3 exhibit decreased hazard ratios for pleural fluid both unadjusted and adjusted. For cardiological adverse effects, valvular heart disease shows that cohort 2 displays an unadjusted decreased hazard ratio (95%CI) of 0.46 (0.17 – 1.21) and adjusted 0.44 (0.16 – 1.17), and cohort 3 an unadjusted decreased hazard ratio of 0.47 (0.18 – 1.23) and adjusted 0.53 (0.20 – 1.43).

Discussion

A modest study population with a median follow up of 13 years, a comprehensive list of adverse effects and baseline characteristics were used to evaluate the correlation between the treatments of the cohorts and adverse effects. Cohort 1 was used as control group and only underwent mastectomy as treatment, cohort 2 underwent breast conserving surgery with SLND or ALND staging and radiotherapy, cohort 3 underwent the most extensive treatment including breast conserving surgery with SLND or ALND staging, radiotherapy, systemic therapy and/or hormonal treatment (see figure 1). 10 years post-surgery, cohort 2 and 3 show increased occurrences of fatigue and lymphedema of the arm compared to the control group. For cohort 3 this outcome is in accordance with earlier studies [19] [20]. The outcome is however unexpected for cohort 2, as it did not undergo systemic adjuvant therapy which is a risk factor for late fatigue.

Bowel diseases showed an unexpected outcome, during t2 cohort 1 had more occurrences of bowel/anal diseases than cohort 2 and cohort 3, while the latter cohort has a possible added risk for the development of these adverse effects due to more extensive adjuvant therapy. Partial adjustment was made to counteract known confounders, but our study could not account for all possible risk factors for bowel/anal diseases. Neurological, pulmonal and cardiological adverse effects did not show any correlation between their respective adverse effects and treatments.

General adverse effects

Fatigue

Fatigue showed a significant difference in occurrence, more than ten years post-surgery; both cohort 2 and cohort 3 have an increased occurrence of fatigue in t2. This could be attributed to their more extensive treatment compared to cohort 1, as adjuvant systemic treatment is known to contribute to increased fatigue after treatment [21] [20] [22] [23]. However, the outcome is unusual for cohort 2 as this group did not undergo systemic adjuvant therapy. Concrete evidence linking fatigue as a late effect to adjuvant treatment is difficult [21]. In the long follow-up period, a large pool of confounders can be encountered [22] [19] [24]. Cox-regression analysis of Fatigue did not yield a significant hazard ratio, with or without adjustment for available relevant confounders.

Osteopenia/osteoporosis

A higher risk of osteopenia can be observed for cohort 3 compared to cohort 1 and 2. This implies an increased risk for patients that underwent additional chemotherapy and hormone therapy, which is in line with earlier research [25] [26]. One would also expect osteoporosis to occur more in cohort 3, which is not the case. A possible explanation could be the presence of unaccounted confounders in this study, as there are numerous confounders identified in earlier studies [27] [28]. Influential characteristics not included are the use of synthetic glucocorticoids, the amount of dietary calcium intake and the amount of physical activity. Another explanation for the divergent outcome could be a false statistical significance due to the categorizing of the continuous variable, bone density into osteopenia and osteoporosis. Another explanation could be that patients which receive treatment with hormone therapy are more likely to receive screening for osteopenia and osteoporosis due to hormone therapy being a known risk factor, and receiving treatment sooner. While patients of cohort 1 and 2 have a lower chance of diagnosis, because diagnosis might happen only after symptoms become apparent.

The unadjusted and adjusted hazard ratio for osteopenia is increased for cohort 3, which supports earlier found increased occurrence for cohort 3. The hazard ratio for osteoporosis does not yield any significant results.

Lymphedema of the arm

Lymphedema of the arm shows increased occurrences for both cohort 2 and 3 compared to cohort 1, of which only the differences during t2 are significant. The landmark-analysis shows that cohort 3 has significantly worse event-free survival compared to cohort 1 and 2, which suggests that the treatment of cohort 3 influences the outcome during t1. This concurs with several earlier studies where both radio- and chemotherapy are a risk factor for the occurrence of lymphedema of the arm [10] [29]. Cox-regression analysis of lymphedema of the arm also showed a near significant unadjusted hazard ratio for cohort 3 showing at an increased chance of occurring. The hazard ratio was significant when adjusted for the number of medications patients took at the time of treatment at t1.

According to an extensive systematic review and meta-analysis in 2013 [29], four possible confounders were found that revealed strong evidence suggesting their influence on the occurrence of lymphedema of the arm. Axillary lymph node dissection, the number of lymph nodes dissected, mastectomy and having a higher body mass index influence the occurrence of lymphedema of the arm. However, the number of lymph nodes dissected was not collected in our population sample. The risk factor ALND was collected and if we would follow earlier research one would expect that cohort 2 would have the highest occurrence of Lymphedema of the arm as roughly 80% of the studied population underwent ALND versus 50 % for cohort 3 and 1. So the outcome of cohort 2 and 3 having an increased occurrence could be linked to the high number of ALND treatments for cohort 2 and for cohort 3 due to the combination of undergoing ALND and/or chemo therapy.

Bowel/anal and gastric diseases

Bowel- and anal diseases exhibit a significant lower prevalence in t1 for cohort 3, which is counter intuitive and would suggest that adjuvant chemotherapy would lower occurrence. Previous studies suggest that chemotherapy negatively affect the gastrointestinal system of women with breast cancer [21] [30].This unexpected outcome might be attributed to several unaccounted-for risk factors, and partly to that 42.9% of cohort 3 did not receive chemo therapy and the average age is lowest in cohort 3. In t2 outcome results diverge from t1 as there are no significant differences within the current study population. The results overall are subject to the wide range of scored results, as bowel- and anal diseases encompasses a wide range of diseases such as diverticulitis, gastroenteritis or chronic obstipation.

Neurological adverse effects

A number of studies indicate that treatments for breast cancer cause adverse neurological effects, both short term [31] [32] and long term [33]. This outcome was partially observed in this study, as all cohorts show an occurrence of adverse effects however a correlation would be expected between the severity of the treatment and the number of occurrences of adverse effects but this was not shown.

Cohort 2 displayed more occurrences of concentration disorder during t1 than cohort 1 and 3. Transient ischemic attacks in t1 were more prevalent in cohort 1, compared to cohort 2 and cohort 3. Which is remarkable, as an increased occurrence is expected for cohort 3 as number of patients underwent chemotherapy which is known to induce neurotoxicity affecting functioning of the brain [34], and also increases the risk of stroke [35]. This divergent outcome could in part be explained due to the fact that no adjustment for confounders such as age was possible due to missing data on the time of occurrence of the adverse effects.

Pulmonal adverse effects

In this study no significant difference in pulmonal adverse effects between the cohorts were present. Several known risk factors for pulmonal adverse effects were accounted for, but the list of risk factors for pulmonary diseases is vast. For example, factors such as the presence of air pollution, allergens or occupational risks can influence the development of asthma [36] [37]. So potentially, missing these risk factors could influence our outcomes by unknowingly limiting the number of occurrences. A more likely cause for the absence of significant differences is the natural low prevalence of adverse pulmonary effects. Other studies on the occurrence of pneumonitis and pulmonary fibrosis after systemic therapy indicate very low occurrences [38] [39].

Consensus is not reached on the influence of combined treatments by both chemotherapy and radiotherapy on the development of pulmonary diseases, as a study by Vogelius et al. (2012) claims these treatments as risk factor [40]. However, other studies do not observe an extra risk for pneumonitis when combining radiotherapy and chemotherapy [39] [41].

Cardiological adverse effects

Angina pectoris and conduction disorders occurred at a higher rate for cohort 2 during t1, but this trend did not carry over to t2 nor did it occur with the Cox-regression or Kaplan-Meier analysis. Earlier research indicates that radiotherapy provokes thoracic complications [41] and cardiac toxicity [42] but not necessarily conduction disorders. However, Cohort 3 has the most extensive treatment, which is comparable to cohort 2 plus the addition of chemotherapy with or without trastuzumab and with or without hormone therapy. Both these treatments are known to increase cardiac toxicity [42] so a higher occurrence as cohort 2 of angina Pectoris and conduction disorders would be expected. This difference could be explained due to no adjustment being made to confounders as Cox-regression which is adjusted does not show any significant differences.

Analysis for t2 was performed on a clustered cardiological adverse effect. Cohort 1 was most susceptible to develop cardiological adverse effects, and cohort 3 the least, the Kaplan-Meier analyses showed statistically significant differences. However, these results from the Kaplan-Meier are non-adjusted for age as the lower mean age of cohort 3 is an influential factor on this result.

Strengths and Limitations

A key strength of the study is the wide spectrum of collected baseline data, which is employed to inspect differences between cohorts to adjust for possible confounders. This wide spectrum of data extends also to the adverse effects being collected.

The above strength cuts both ways, as the broad spectrum of adverse effects also demands for a wide array of collected baseline data to correct for confounding. This baseline data is provided for but can always be improved upon by collecting more adverse effect relevant data. It also asks for a larger study population, as some of these adverse effects are more uncommon in occurrence. In this study this has been countered by clustering some adverse effects during t2 under one common denominator such as pulmonal, neurological and cardiological adverse effects, this has created an indication of outcome but it is still unclear if this is a true significant outcome.

This clustering does also apply to single adverse effects as bowel/anal and gastric diseases are an amalgamation of several diseases. The clustering of these diseases does however not take into account individual disease characteristics such as severity, or health state such as it being acute or chronic in nature, which affects outcome reliability.

As resources go into collecting a large amount of data on a wide variety of data per patient, this limits the number of patients that can be collected. This smaller sample size results in a weakened power and precision of results and makes it harder to detect weak correlation between treatment and outcome. Detecting correlation between treatment and outcome is already an inherent weakness of researching late effects. Another challenge is the selection bias that occurs due to selecting patients with sufficient survival time. As all factors influence the survival are also potential confounders.

Conclusions

This study did find evidence for significant differences in outcomes, some are in accordance of current knowledge such as the occurrence of Lymphedema of the arm and provide the impression of legitimacy of found results. However, the results provided by some adverse effects are remarkable and require further research to increase the quality of informed decisions by patient and healthcare provider alike. This could be attained by increasing population sample and the addition of patient reported outcome measures (PROMs).

References

[1] B. Balasz and P. Tuso, “Breast Cancer Survivorship: A Comprehensive Review,” *The Permanente Journal,* vol. 19, no. 2, pp. 48-79, 2015.

[2] S. Agrawal, “Late effects of cancer treatment in breast cancer survivors,” *South Asian Journal of Cancer,* vol. 2, no. 3, pp. 112-115, 2014.

[3] INKL, “persberichten,” IKNL, 3 February 2019. [Online]. Available: https://www.iknl.nl/over-iknl/pers/persberichten/aantal-gevallen-van-kanker-in-dertig-jaar-verdubbe. [Accessed 6 June 2020].

[4] IKNL, “Incidentie borstkanker,” Integraal kankercentrum Nederland, [Online]. Available: https://www.iknl.nl/kankersoorten/borstkanker/registratie/incidentie. [Accessed 10 21 2020].

[5] CBS, “CBS Statline,” 24 March 2020. [Online]. Available: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37556/table?fromstatweb. [Accessed 6 June 2020].

[6] IKNL, “Monitor bevolkingsonderzoek borstkanker,” [Online]. Available: https://www.iknl.nl/kankersoorten/borstkanker/onderzoek/monitor-bevolkingsonderzoek. [Accessed 21 October 2020].

[7] M. C. Van Maaren, L. de Munck, G. H. De Bock, J. J. Jobsen, T. van Dalen, S. C. Linn, P. Poortmans, L. J. A. Strobbe and S. Siesling, “10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study,” *The Lancet Oncology,* vol. 17, no. 8, pp. 1158-1170, 2016.

[8] M. Salibasic and S. Delibegovic, “The Quality of Life and Degree of Depression of Patients Suffering from Breast Cancer,” *Medical Archives,* vol. 72, no. 3, pp. 202-205, 2018.

[9] L. Saskia, G. Werutsky, I. S. Fentiman, E. Rutgers, M.-R. Christiaens, E. V. Limbergen, M. H. A. Baaijens, J. Bogaerts and H. Bartelink, “Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial,” *Lancet Oncology,* vol. 13, no. 4, pp. 412-419, 2012.

[10] A. C. P. R. Pereira, R. J. Koifman and A. Bergmann, “Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up,” *The Breast,* vol. 36, pp. 67-73, 2017.

[11] A. Lucci, L. Mackie McCall, P. D. Beitsch, P. W. Whitworth, D. S. Reintgen, P. W. Blumencranz, A. M. Leitch, S. Saha, K. K. Hunt and A. E. Giuliano, “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,* vol. 25, no. 24, pp. 3657-3663, 2007.

[12] R. Belmonte, M. Messaggi-Sartor, M. Ferrer, A. Pont and F. Escalada, “Prospective study of shoulder strength, shoulder range of motion, and lymphedema in breast cancer patients from pre-surgery to 5 years after ALND or SLNB,” *Supportive Care in Cancer,* no. 26, pp. 3277-3287, 2018.

[13] H. A. Azim Jr, E. d. Azambuja, M. Colozza, J. Bines and M. J. Piccart, “Long-term toxic effects of adjuvant chemotherapy in,” *Annals of Oncology,* vol. 22, no. 9, pp. 1939-1947, 2011.

[14] A. Matthews, S. Stanway, R. E. Farmer, H. Strongman, S. Thomas, A. R. Lyon, L. Smeeth and K. Bhaskaran, “Long term adjuvant endocrine therapy and risk of cardiovascular,” The BMJ, 2018.

[15] S. K. Ramchad, Y.-M. Cheung, B. Yeo and M. Grossmann, “The effects of adjuvant endocrine therapy on bone health in women with breast cancer,” *Journal of Endocrinology,* vol. 241, no. 3, pp. 111-124, 2019.

[16] H. Bartelink, P. Maingon, P. Poortmans, C. Weltens, A. Fourquet, J. Jager, D. Schinagl, B. Oei, C. Rodenhuis, J.-C. Horiot, H. Struikmans, E. Van Limbergen, Y. Kirova, P. Elkhuizen, R. Bongartz, R. Miralbell, D. Morgan, J.-B. Dubois, V. Remouchamps, R.-O. Mirimanoff and L. Collette, “Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial,” *The Lancet oncology,* vol. 16, no. 1, pp. 47-56, 2015.

[17] S. C. Darby, M. Ewertz, P. McGale, A. M. Bennet, U. Blom-Goldman, D. Brønnum, C. Correa, D. Cutter, G. Cagliardi, B. Gigante, M.-B. Jensen, A. Nisbet, R. Peto, K. Rahimi, C. Taylor, D. Phil and P. Hall, “Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer,” *The New England Journal of Medicine,* vol. 368, no. 11, pp. 987-998, 2013.

[18] G. H. Sakorafas, G. Peros, L. Cataliotti and G. Vlastons, “Lymphedema following axillary lymph node dissection for breast cancer,” *Surgical oncology,* vol. 15, no. 2, pp. 153-165, 2006.

[19] J. E. Bower, J. Wiley, L. Petersen, M. R. Irwin, S. W. Cole and P. A. Ganz, “Fatigue after breast cancer treatment: Biobehavioral predictors of fatigue trajectories,” *Health Psychology,* vol. 37, no. 11, pp. 1025-1034, 2018.

[20] D. L. Lovelace, L. R. McDaniel and D. Golden, “Long-Term Effects of Breast Cancer Surgery, Treatment, and Survivor Care,” *Journal of Midwifery & Women's Health,* vol. 64, no. 6, 2019.

[21] B. Smoot, M. Wampler and K. S. Topp, “Breast Cancer Treatments and Complications: Implecations for Rehabilitaion,” *Rehabilitation Oncology,* vol. 27, no. 3, pp. 16-26, 2009.

[22] J. E. Bower, “Cancer-related fatigue: Mechanisms, risk factors, and treatments,” *Nature Reviews Clinical Oncology,* vol. 11, no. 10, pp. 597-609, 2014.

[23] M. A. Andykowski, K. A. Donovan, C. Laronga and P. B. Jacobsen, “Prevalence, PredicPrevalence, Predictors, and Characteristics of Off-Treatment Fatigue in Breast Cancer Survivors,” *Cancer,* vol. 116, no. 24, pp. 5740-5748, 2010.

[24] R. Puigpinós-Riera, G. Serral, M. Sala, X. Bargallo, M. J. Quintana, M. Espinoza, R. Manzanera, M. Domenech, F. Macia, J. Grau and E. Vidal, "Cancer-related fatigue and its determinants in a cohort of women with breast cancer: the DAMA Cohort," *Supportive care in cancer,* vol. 28, no. 11, pp. 5213-5221, 2020.

[25] S. D'Oronzo, S. Stucci, M. Tucci and F. Silvestris, "Cancer treatment-induced bone loss (CTIBL): pathogenesis and clinical implications," *Cancer treatment reviews,* vol. 41, no. 9, pp. 798-808, 2015.

[26] C. Orts Christensen, D. Cronin-Fenton, T. Froslev, A. P. Hermann and M. Ewertz, "Change in bone mineral density during adjuvant chemotherapy for early-stage breast cancer," *Supportive care in cancer,* vol. 24, no. 10, pp. 4229-4236, 2016.

[27] P. F. Schnatz, K. A. Marakovits and D. M. O'sullivan, "Assessment of Postmenopausal Women and Significant Risk Factors for Osteoporosis," *Obstetrical & Gynecological Survey,* vol. 65, no. 9, pp. 591-596, 2010.

[28] E. Curtis, C. Litwic, C. Cooper and E. Dennison, "Determinants of muscle and bone aging," *Journal of Cellular Physiology,* vol. 230, no. 11, pp. 2618-1625, 2015.

[29] T. Disipio, S. Rye, B. Newman and S. Hayes, "Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis," *The Lancet. Oncology,* vol. 14, no. 6, pp. 500-515, 2013.

[30] Z. Livshits, R. B. Rao and S. W. Smith, "An Approach to Chemotherapy-Associated Toxicity," *Emergency Medicine Clinics of North America,* vol. 32, no. 1, pp. 167-203, 2014.

[31] F. Filipa, S. Pereira, J. M. Castro-Lopes and N. Lunet, "A prospective study on the neurological complications of breast cancer and its treatment: Updated analysis three years after cancer diagnosis," *The Breast,* vol. 29, pp. 31-38, 2016.

[32] D. R. Rivera, P. A. Ganz, M. S. Weyrich, H. Bandos and J. Melnikow, "Chemotherapy-Associated Peripheral Neuropathy in Patients With Early-Stage Breast Cancer: A Systematic Review," *Journal of the National Cancer Institue,* vol. 110, no. 2, 2018.

[33] H. Bandos, J. Melnikow, D. R. Rivera, S. M. Swain, K. Sturtz, L. Fehrenbacher, J. L. Wade, A. M. Brufsky, T. B. Julian, R. G. Margolese, E. C. McCarron and P. A. Ganz, "Long-term Peripheral Neuropathy in Breast Cancer Patients Treated With Adjuvant Chemotherapy: NRG Oncology/NSABP B-30," *Journal of the National Cancer Institute,* vol. 110, no. 2, 2018.

[34] K. Hermelink, "Chemotherapy and cognitive function in breast cancer patients: The so-called chemo brain," *Journal of the National cancer Institute,* vol. 2015, no. 51, pp. 67-69, 2015.

[35] H.-S. Jang, J. Choi, J. Shin, J.-W. Chung, O. Young Bang, G.-M. Kim, W.-K. Seo and J. Lee, "The Long-Term Effect of Cancer on Incident Stroke: A Nationwide Population-Based Cohort Study in Korea," *Frontiers in Neurology,* vol. 10, no. 52, 2019.

[36] R. Beasley, A. Sempirini and E. A. Mitchell, “Risk factors for asthma: is prevention possible?,” *The Lancet,* vol. 386, no. 9998, pp. 1075-1085, 2015.

[37] M. Kuruvilla, K. Vanijcharoenkarn, J. A. Shih and F. Eun-Hyung Lee, “Epidemiology and risk factors for asthma,” *Respiratory Medicine,* vol. 149, pp. 16-22, 2019.

[38] C. Omarini, E. Thanopoulou and S. R. D. Johnston, “Pneumonitis and pulmonary fibrosis associated with breast cancer treatments,” *Breast Cancer Research and Treatment,* vol. 146, pp. 245-258, 2014.

[39] A. Kubo, K. Osaki, T. Kawanaka, S. Furutani, H. Ikushima and H. Nishitani, “Risk factors for radiation pneumonitis caused by whole breast irradiation following breast-conserving surgery,” *The Journal of Medical investigation,* vol. 56, no. 3-4, pp. 99-110, 2009.

[40] I. R. Vogelius and S. M. Bentzen, “A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis,” *Acta Oncologica,* vol. 51, no. 8, pp. 975-983, 2012.

[41] C. Chargari, F. Riet, M. Mazevet, E. Morel, C. Lepechoux and E. Deutsch, “Complications of thoracic radiotherapy,” *Quarterly Medical Review,* vol. 42, no. 9, pp. 342-351, 2013.

[42] J. Caron and A. Nohria, “Cardiac Toxicity from Breast Cancer Treatment: Can We Avoid This?,” *Current Oncology Reports,* vol. 20, no. 61, 2018.

[43] M. Camilleri, H. Malhi and A. Acosta, “Gastrointestinal Complications of Obesity,” *Gastroenterology,* vol. 152, no. 7, pp. 1656-1670, 2017.

[44] M. J. Hassett, J. O'Malley, J. R. Pake, J. P. Newhouse and C. C. Earle, “Frequency and Cost of Chemotherapy-Related Serious,” vol. 98, no. 16, pp. 1108-1117, 2006.

[45] N. G. Zaorsky, Y. Zhang, L. T. Tchelebi, H. B. Mackley, V. M. Chinchilli and B. E. Zacharia, “Stroke among cancer patients,” *Nature communications,* vol. 10, 2019.

[46] H. Nakada, M. Inoue, K. Furuya, H. Watanabe, K. Ikegame, Y. Nakayama, M. Ohmori and H. Nakagomi, “Fat necrosis after breast-conserving oncoplastic surgery,” *Breast Cancer,* vol. 26, no. 1, pp. 125-130, 2018.

[47] B. Ozcina, S. A. Guler, N. Kocaman, M. Ozkan, B. M. Gulluoglu and V. Ozmen, “Breast cancer related lymphedema in patients with different loco-regional treatments,” *Breast,* vol. 3, no. 21, pp. 361-365, 2012.

Appendix A

Collected variables

1. **Patient Characteristics at time of primary treatment**(**t0**): Hospital, date of birth, length, weight, Breast Cancer laterization, Surgical treatment type, surgery date, Re-excision, pT, pN, Age (calculated as difference between surgery date and date of birth), Radiation therapy(Yes/No, Location, Date), Radiation boost (Yes/No, dose), Type of Adjuvant therapy, Adjuvant therapy date, Metastasis (Yes/No, Date), Locoregional recurrence(Yes/No, Date), Recurrence Axillary or Peri clavicular or Parasternal (Yes/No, Date), Contralateral breast cancer (yes/No, Date), Second primary tumor (Yes/No, Location, Date), Death (Yes/No, Date, Cause of death , End of follow-up date
   Pre-existent Risk Factors at time of primary treatment (**t0**): age, BMI, Diabetes mellitus (Insulin dependent yes/no), Hypertension, Hypercholesterolemia, Smoking, Pack-years, number of used medications
2. **General adverse effects** (**at three points in time; t0, t1 and t2**):
   t0: Fatigue (Yes/no), Psychosocial (Yes/no), impaired shoulder mobility (yes/no), Osteopenia (Yes/no), Osteoporosis (Yes/no), Rib Fracture (Yes/No, Location), Lymphedema (Yes/No, Location), Gastric (Yes/no), Bowel, Work (Yes/no)
   t1: Fatigue (Yes/No, Date), Psychosocial (Yes/No, Date), Impaired shoulder mobility (Yes/No, Date), Skin Ulceration (Yes/No, location, Date), Tissue necrosis breast/ thoracic wall (Yes/No, location, Date), Osteopenia (Yes/No, Date), Osteoporosis(Yes/No, Date),Bone fracture (Yes/No, location), Rib Fracture (Yes/No, Location), Lymphedema (Yes/No, Location, severity CTCAE v5.0), Pain breast/thoracic wall homolateral(Yes/No, Date, CTCAE v5.0 and use of analgesics), Gastric(Yes/No, Date, severity CTCAE v5.0), Bowel (Yes/No, Date, severity CTCAE v5.0), Work (Yes/no/partial/retired/not applicable)
   t2: General adverse effects (yes/no/severity CTCAE v5.0/total recovery with treatment/ total recovery without treatment): Fatigue, Psychosocial, Impaired shoulder mobility, Skin ulceration, Tissue Necrosis, Osteopenia/osteoporosis, Lymphedema, Thorax pain, Gastric, Bowel
3. **Neurological adverse effects** (**at three points in time; t0, t1 and t2**):
   t0: Brachial plexus Neuropathy (Yes/No, Location), Poly Neuropathy (Yes/no, Location, date),Cognitive impairment (Yes/No, Diagnosis by relevant medical professional, severity CTCAE v5.0), Concentration disorder (Yes/No), Cerebral infarction (Yes/No, Number),Transient ischemic attack (Yes/No, number), Carpal tunnel syndrome (Yes/No, Left/right), Meningioma (Yes/No)
   t1: Brachial plexus Neuropathy (Yes/No, Date, strength, pain, sensory, function, location), Poly Neuropathy (Yes/No, Date, strength, pain, sensory, treatment policy), Cognitive impairment (Yes/No, Diagnosis by relevant medical professional, date, severity CTCAE v5.0), Concentration disorder (Yes/No, Date, severity CTCAE v5.0), Cerebral Infarction (Date, Number, localization, strength, sensory, communication problems), Transient ischemic attack (Date, Number, localization, strength, sensory, communication problems), Carpal tunnel syndrome (Yes/No, date, localization, strength, pain, sensory, surgery, injection, brace), Meningioma (Yes/No, date)
   t2: Neurological adverse effect (Status, no adverse neurological effects after treatment, full recovery without additional treatment, complete recovery with additional treatment, Incomplete recovery with function loss, disabled, death)
4. **Pulmonary adverse effects** (**at three points in time; t0, t1 and t2**):
   t0: Chronic Obstructive Pulmonary Disease (COPD) (Yes/no, GOLD classification), Asthma (Yes/no), Obstructive lung disease (Yes/no), Other lung diseases (Yes/no), Lung function test (Yes/no, numerical results)
   t1: Chronic Obstructive Pulmonary Disease (COPD) (Yes/no, developed after treatment yes/no, date, Gold classification), Asthma (Yes/no, developed after treatment yes/no, date), Pneumonia (Yes/no, number, date first pneumonia, location of pneumonia), Radiation pneumonitis (Yes/no, date, level of severity CTCAE v5.0, location right/left/both sides), Radiation fibrosis (Yes/no, date, location right/left/both sides, localization lobe, level of severity CTCAE v5.0), Bronchiectasis (Yes/no, date, Location right/left/both sides), Secondary lung cancer (Yes/no, date, location left/right, location lobe), Nonspecific obstructive

lung disease (Yes/no, date), Pleural fluid (Yes/no, date, location right/left/both sides), lung function test (yes/no, numerical results of last known lung function.
t2: Pulmonary adverse effect (Status, no adverse pulmonary effects after treatment, full recovery without additional treatment, complete recovery with additional treatment, Incomplete recovery with function loss, disabled, death)

5. **Cardiological adverse effects and interventions** (**at three points in time; t0, t1 and t2**):
   t0: Cardiomyopathy (Yes/no), left ventricular ejection fraction (severity CTCAE v5.0), Congestive heart failure (severity CTCAE v5.0), Ventricular assist device (Yes/no), Heart transplant (Yes/no), Coronary artery disease (Yes/no), Angina Pectoris (Yes/no), Myocardial Infarction (Yes/no), Coronary Artery Bypass Graft (CABG) (Yes/no), Percutaneous Coronary Intervention (PCI) (Yes/no),
   Valvular Heart Disease (location aortic, mitral, tricuspidal/pulmonary, severity CTCAE v5.0), Arrhythmia (Yes/no), Conduction abnormalities (Yes/no), Pericarditis (Yes/no), Pacemaker (Yes/no), Implantable Cardioverter Defibrillator (ICD) (Yes/no)
   t1: Cardiomyopathy (Yes/no, date, type dilated/restrictive/ hypertrophic cardiomyopathy), left ventricular ejection fraction (severity CTCAE v5.0), Congestive heart failure (Yes/no, date, type systolic/diastolic/combination, severity (NYHA classification), Ventricular assist device (Yes/no, date), Heart transplant (Yes/no, date), Coronary artery disease (Yes/no, location LCA, LCA→LAD, LCA→LCX, RCA), Angina Pectoris (Yes/no, date, type stable/unstable, Canadian Cardiovascular Society score I t/m IV), Myocardial Infarction (Yes/no, date), Percutaneous Coronary Intervention (PCI) (Yes/no, date), Coronary Artery Bypass Graft (CABG) (Yes/no, date), Valvular Heart Disease (severity CTCAE v5.0, location aortic/mitral/tricuspid/pulmonary valve), Arrhythmia (Yes/no, date, type), Conduction abnormalities (Yes/no), Pericarditis (Yes/no), Pacemaker (Yes/no), Implantable Cardioverter Defibrillator (ICD) (Yes/no, date, type), pacemaker (Yes/no, date), Pericarditis (Yes/no, date, type constrictive/exudative)
   t2: Cardiological adverse effect (Status, no adverse cardiological effects after treatment, full recovery without additional treatment, complete recovery with additional treatment, Incomplete recovery with function loss, disabled, death)

Appendix B

Incidence of adverse effects

Table B1. *Occurrence of neurological adverse effects in t1 and aggregated in t2*

Adverse effects	Cohort 1 (Mastectomy) (n=57)	Cohort 2 (BCS + RT) (n=55)	Cohort 3 (BCS + RT + Adj) (n=56)	P-value
Brachial plexus neuropathy	1 (1.8%)	2 (3.6%)	1 (1.8%)	0.758
Polyneuropathy	3 (5.3%)	6 (10.9%)	5 (8.9%)	0.547
Cognitive disorder	9 (14.8%)	6 (10.9%)	5 (8.9%)	0.652
Concentration disorder	0 (0%)	3 (5.5%)	0 (0%)	0.043
Stroke	2 (3.5%)	6 (10.9%)	2 (3.6%)	0.166
Transient ischemic attack	6 (10.5%)	2 (3.6%)	0 (0%)	0.028
Carpal tunnel syndrome	7 (12.3%)	5 (9.1%)	2 (3.6%)	0.239
Meningioma	0 (0%)	2 (3.6%)	0 (0%)	0.125
Neurological adverse effects ten years post-surgery	13 (22.8%)	13 (23.6%)	8	0.448

Table B2. *Occurrence of pulmonal adverse effects in t1 and aggregated in t2*

Adverse effects	Cohort 1 (Mastectomy) (n=57)	Cohort 2 (BCS + RT) (n=55)	Cohort 3 (BCS + RT + Adj) (n=56)	P-value
Radiation Pneumonitis	0 (0%)	2 (3.6%)	0 (0%)	0.125
Pneumonia	9 (14.8%)	13 (23.6%)	5 (8.9%)	0.108
Pulmonary fluid	10 (17.5%)	7 (12.8%)	4 (7.1%)	0.247
Pulmonary fibrosis	6 (10.5%)	2 (3.6%)	3 (5.4%)	0.306
Bronchiectasis	3 (5.3%)	3 (5.5%)	0 (0%)	0.211
Secondary Lung Carcinoma	1 (1.8%)	1 (1.8%)	1 (1.8%)	1.000
COPD	4 (7%)	4 (7.3%)	2 (3.6%)	0.652
Asthma	1 (1.8%)	0 (0%)	3 (5.4%)	0.168
Obstructive nonspecific lung disease	2 (3.5%)	2 (3.6%)	0 (0%)	0.359
Other	11 (19.3%)	3 (5.5%)	9 (16.1%)	0.359
Pulmonal adverse effects ten years post-surgery	6 (10.5%)	9 (16.4%)	11 (19.6%)	0.415

Table B3. *Occurrence of cardiological adverse effects in t1 and aggregated in t2*

Adverse effects	Cohort 1 (Mastectomy) (n=57)	Cohort 2 (BCS + RT) (n=55)	Cohort 3 (BCS + RT + Adj) (n=56)	P-value
Cardiomyopathy	5 (8.8%)	6 (10.9%)	1 (1.8%)	0.148
Congestive heart failure	7 (12.3%)	8 (14.5%)	3 (5.4%)	0.263
Angina pectoris	2 (3.5%)	7 (12.8%)	1 (1.8%)	0.032
Myocardial infarction	2 (3.5%)	1 (1.8%)	1 (1.8%)	0.790
Valvular heart disease	13 (22.8%)	6 (10.9%)	6 (10.75)	0.118
Arrhythmia	5 (8.8%)	10 (18.2%)	5 (8.9%)	0.215
Conduction disorders	4 (7%)	5 (9.1%)	0 (0%)	0.082
Pericarditis	0 (0%)	1 (1.8%)	0 (0%)	0.356
Cardiological adverse effects ten years post-surgery	11 (19.3%)	8 (14.5%)	4 (7.1%)	0.167

Appendix C

Landmark analyses Kaplan-Meier

Figure C1. *Occurrence of lymphedema of the arm per cohort in t1*

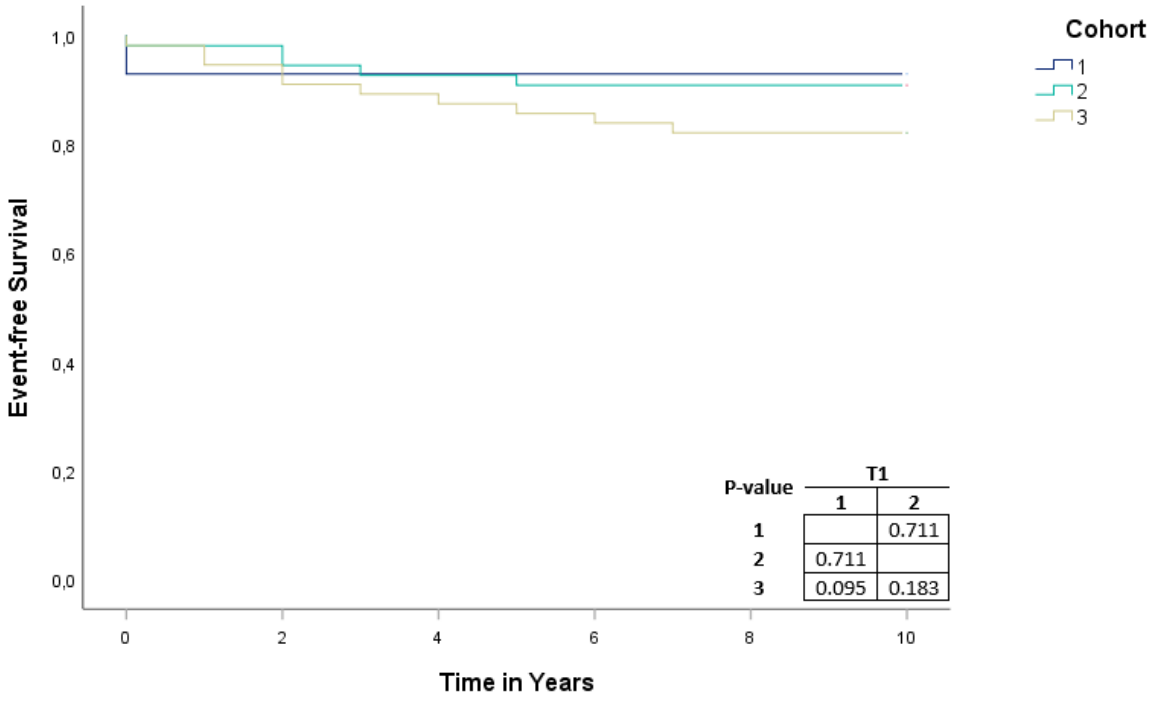


Figure C2. *Occurrence of gastric diseases per cohort in t1 and t2*

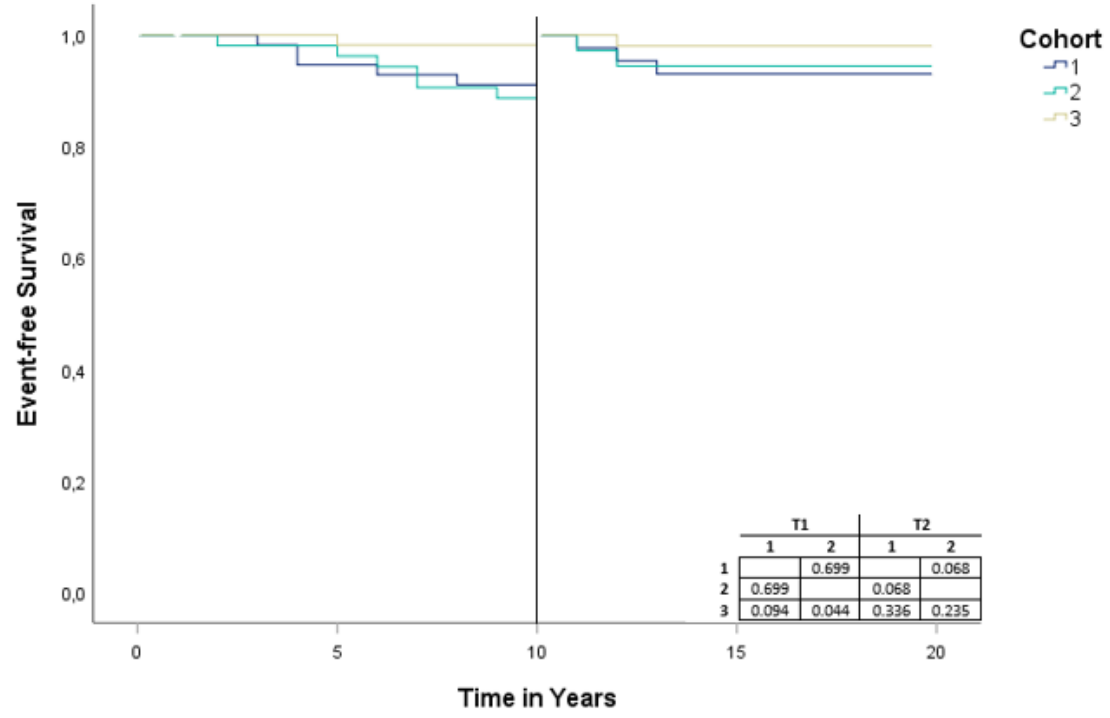


Figure C3. *Occurrence of bowel/anal diseases per cohort in t1 and t2*

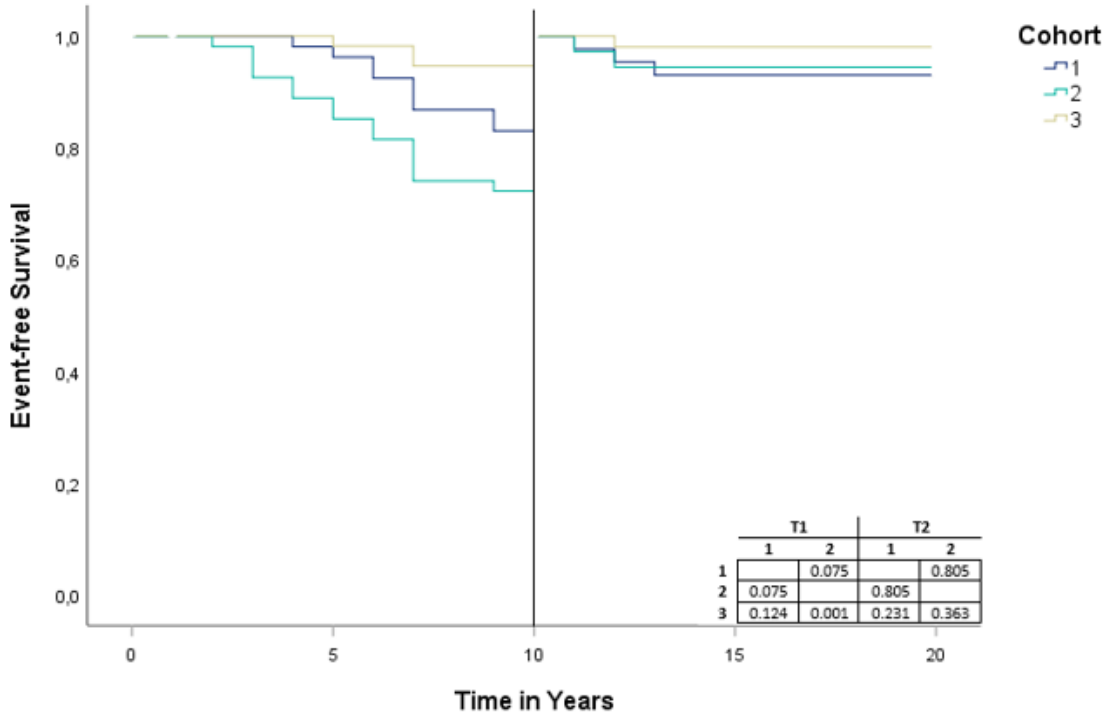


Figure C4. *Occurrence of pulmonal adverse effects per cohort in t1 and t2*

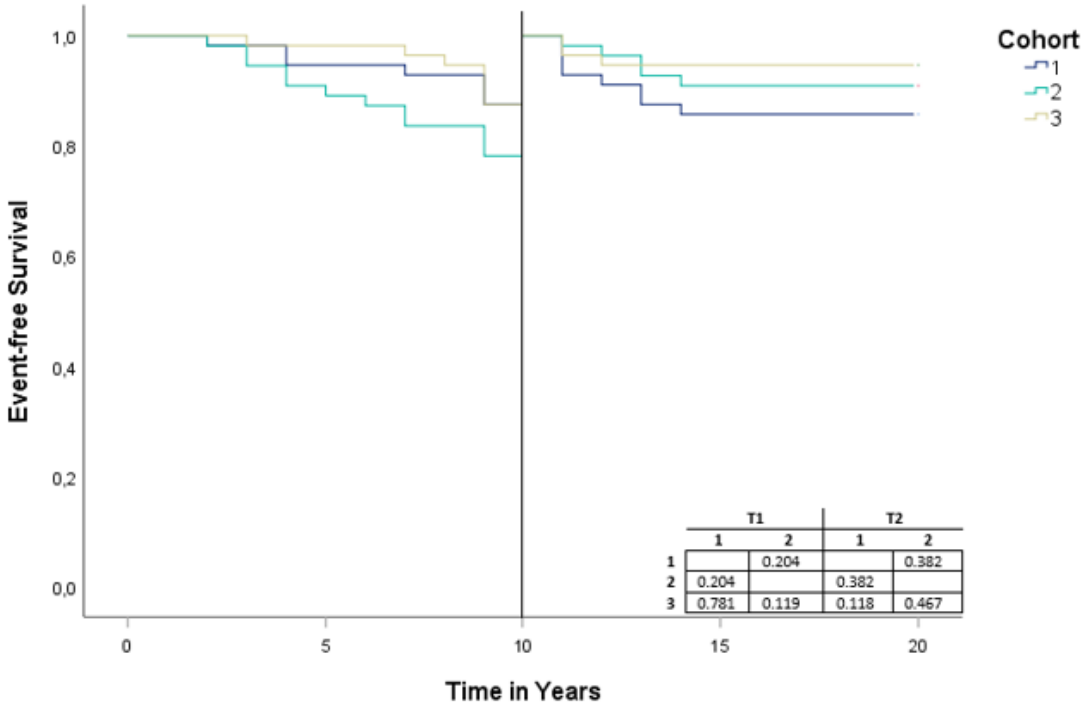
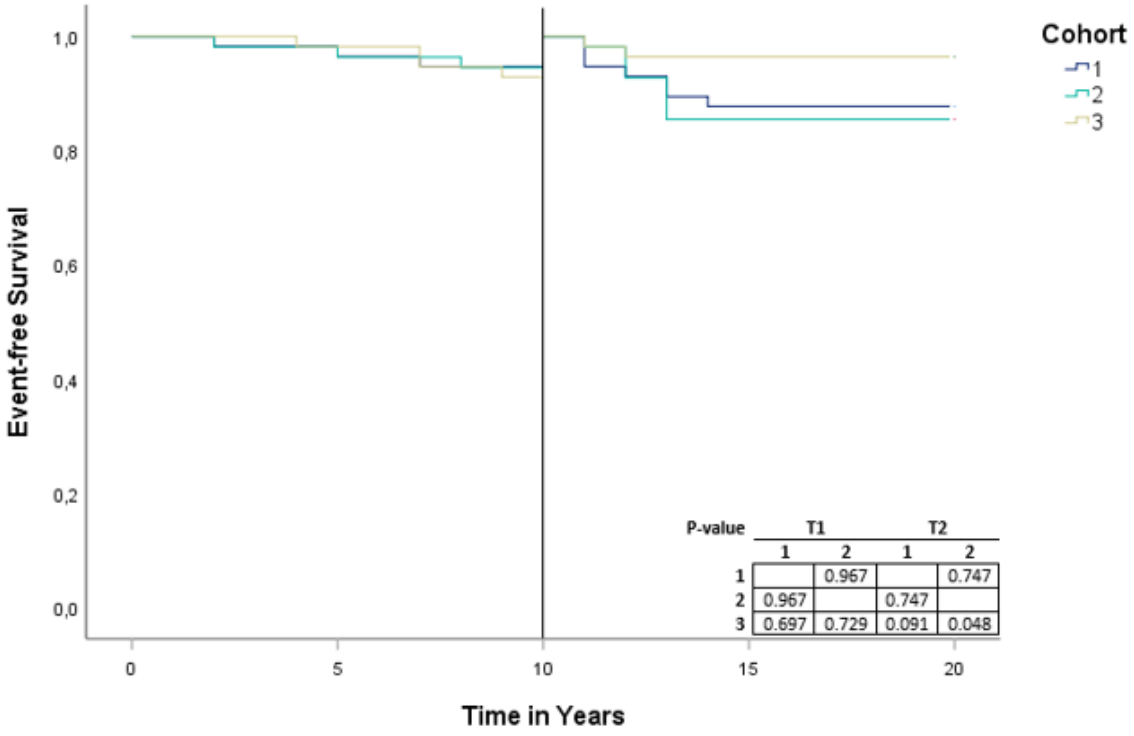


Figure C5. *Occurrence of cardiological adverse effects per cohort in t1 and t2*



Appendix D

Cox-regression tables

Table D1. *The association of cohorts with general adverse effects in t1 and t2*

Adverse effects	Cohort 1 HR (95% CI)	Cohort 2 HR (95% CI)	Cohort 3 HR (95% CI)
Fatigue	*Referent*	1.29 (0.65 – 2.56)	1.10 (0.55 – 2.23)
Fatigue [a]	*Referent*	1.31 (0.66 – 2.59)	1.27 (0.62 – 2.62)
Psychosocial problems	*Referent*	0.90 (0.37 – 2.21)	0.69 (0.26 – 1.81)
Psychosocial problems [b]	*Referent*	0.92 (0.37 – 2.27)	0.54 (0.20 – 1.48)
Impaired shoulder movement	*Referent*	1.17 (0.45 – 3.02)	1.29 (0.51 – 3.27)
Ulceration	*Referent*	1.05 (0.15 – 7.44)	1.55 (0.51 – 9.28)
Ulceration [c]	*Referent*	1.12 (0.16 – 8.07)	1.31 (0.22 – 7.84)
Necrosis of Tissue/Fat	*Referent*	-	-
Osteopenia	*Referent*	0.72 (0.23 – 2.27)	2.69 (1.11 – 6.54)
Osteopenia [d]	*Referent*	0.79 (0.25 – 2.53)	2.61 (1.07 – 6.35)
Osteoporosis	*Referent*	1.60 (0.57 – 4.49)	0.85 (0.26 – 2.78)
Osteoporosis [d]	*Referent*	1.42 (0.50 – 4.06)	0.91 (0.28 – 3.01)
Osteopenia/osteoporosis	*Referent*	0.97 (0.44 – 2.11)	1.67 (0.82 – 3.38)
Rib Fracture	*Referent*	-	-
Lymphedema of the arm	*Referent*	1.28 (0.34 – 4.75)	2.57 (0.81 – 8.21)
Lymphedema of the arm [d]	*Referent*	1.60 (0.41 – 6.27)	**3.60 (1.03 – 12.54)**
Breast/thoracic pain	*Referent*	1.40 (0.82 – 2.39)	1.00 (0.58 – 1.75)
Breast/thoracic pain [b]	*Referent*	1.40 (0.82 – 2.38)	0.91 (0.52 – 1.60)
Gastric diseases	*Referent*	1.92 (0.71 – 5.19)	0.32 (0.07 – 1.60)
Bowel/anal diseases	*Referent*	1.35 (0.71 – 2.57)	0.32 (0.13 – 0.81)
Bowel/anal diseases [c]	*Referent*	1.52 (0.79 – 2.93)	0.38 (0.15– 0.97)

[a] Adjusted for Hypercholesterolemia
[b] Adjusted for age of time of diagnosis
[c] Adjusted for follow-up time
[d] Adjusted for number of medications used at time of diagnosis

Table D2. *The association of cohorts with neurological adverse effects in t1 and t2*

Adverse effects (Adjusted for)	Cohort 1 HR (95% CI)	Cohort 2 HR (95% CI)	Cohort 3 HR (95% CI)
Brachial plexus neuropathy	*Referent*	2.06 (0.19 – 22.77)	1.00 (0.06 – 16.06)
Polyneuropathy	*Referent*	2.05 (0.51 – 8.18)	1.72 (0.41 – 7.22)
Cognitive disorder	*Referent*	0.65 (0.23 – 1.82)	0.68 (0.24 – 1.92)
Cognitive disorder [a b c]	*Referent*	0.68 (0.24 – 1.94)	1.11 (0.37 – 3.32)
Concentration disorder	*Referent*	-	-
Stroke	*Referent*	3.13 (0.63 – 15.50)	1.02 (0.14 – 7.27)
Stroke [c]	*Referent*	2.49 (0.50 – 12.51)	1.23 (0.17 - 8.99)
Transient ischemic attack	*Referent*	-	-
Carpal tunnel syndrome	*Referent*	0.72 (0.23 – 2.28)	0.28 (0.06 – 1.34)
Carpal tunnel syndrome [c]	*Referent*	0.65 (0.21 – 2.10)	0.33 (0.07 – 1.61)
Meningioma	*Referent*	-	-

[a] Adjusted for age of time of diagnosis
[b] Adjusted for Hypercholesterolemia
[c] Adjusted for number of medications used at time of diagnosis
[d] Adjusted for follow-up time

Table D3. *The association of cohorts with pulmonal adverse effects in t1 and t2*

Adverse effects	Cohort 1 HR (95% CI)	Cohort 2 HR (95% CI)	Cohort 3 HR (95% CI)
Radiation pneumonitis	*Referent*	-	-
Pneumonia	*Referent*	1.58 (0.68 – 3.69)	0.59 (0.20 – 1.77)
Pneumonia [a c]	*Referent*	1.43 (0.60 – 3.40)	0.70 (0.23 – 2.10)
Pleural fluid	*Referent*	0.67 (0.26 – 1.77)	0.39 (0.26 – 1.77)
Pleural fluid [a c]	*Referent*	0.60 (0.23 – 1.61)	0.49 (0.15 – 1.59)
Pulmonary fibrosis	*Referent*	0.26 (0.03 – 2.31)	0.76 (0.17 – 3.40)
Pulmonary fibrosis [a c d]	*Referent*	0.16 (0.02 – 1.46)	0.78 (0.16 – 3.80)
Pulmonary fibrosis [a c]	*Referent*	0.20 (0.02 – 1.77)	1.09 (0.23 – 5.19)
Bronchiectasis	*Referent*	-	-
Secondary lung cancer	*Referent*	1.02 (0.06 – 16.37)	1.01 (0.06 – 16.18)
Secondary lung cancer [b]	*Referent*	1.20 (0.08 – 19.25)	1.66 (0.10 – 28.15)
COPD	*Referent*	1.03 (0.26 – 4.13)	0.50 (0.09 – 2.74)
Asthma	*Referent*	-	-
Obstructive nonspecific lung disease	*Referent*	-	-

[a] Adjusted for age of time of diagnosis
[b] Adjusted for Hypercholesterolemia
[c] Adjusted for number of medications used at time of diagnosis
[d] Adjusted for follow-up time

Table D4. *The association of cohorts with cardiological adverse effects in t1 and t2*

Adverse effects	Cohort 1 HR (95% CI)	Cohort 2 HR (95% CI)	Cohort 3 HR (95% CI)
Cardiomyopathy	*Referent*	1.24 (0.38 – 4.05)	0.20 (0.02 – 1.68)
Cardiomyopathy [a b c]	*Referent*	1.09 (0.31 – 8.31)	0.31 (0.03 – 2.80)
Cardiomyopathy [a b c d]	*Referent*	2.01 (0.49 – 8.55)	0.62 (0.06 – 6.29)
Congestive heart failure	*Referent*	0.88 (0.27 – 2.88)	0.55 (0.14 – 2.21)
Congestive heart failure [a c]	*Referent*	0.72 (0.22 – 2.38)	0.84 (0.20 – 3.54)
Angina pectoris	*Referent*	3.78 (0.79 – 18.19)	0.50 (0.05 – 5.56)
Myocardial infarction	*Referent*	0.51 (0.05 – 5.67)	0.50 (0.05 – 5.51)
Valvular heart disease	*Referent*	0.46 (0.17 – 1.21)	0.47 (0.18 – 1.23)
Valvular heart disease [b c]	*Referent*	0.44 (0.16 – 1.17)	0.53 (0.20 – 1.43)
Arrhythmia	*Referent*	2.01 (0.69 – 5.89)	1.04 (0.30 – 3.60)
Arrhythmia [b c]	*Referent*	2.00 (0.68 – 5.93)	1.31 (0.37 – 4.65)
Conduction disorders	*Referent*	-	-
Pericarditis	*Referent*	-	-

[a] Adjusted for age of time of diagnosis
[b] Adjusted for Hypercholesterolemia
[c] Adjusted for number of medications used at time of diagnosis
[d] Adjusted for follow-up time