SUPPLEMENTAL MATERIAL

Table S1. Variables used to study predictors of adverse events.

Variables
Age, years
Tumor characteristics
Left versus right-sided breast cancer
Tumor size (1-4, unknown)
Nodal status (0-3, unknown)
Tumor Stage (I-IV, unknown)
Tumor Grade (1-3, unknown)
Estrogen receptor positive
Progesterone receptor positive
HER2 receptor positive
Treatment characteristics
Treatment Setting (neoadjuvant vs. adjuvant)
Irradiation mediastinal and subclavian nodes
Mean heart dose
Treatment with hormonal therapy
Treatment with chemotherapy
Treatment with HER2 inhibitors
Cardiovascular risk factors
History of cardiovascular disease
Mayo Clinic Risk Score

HER2: human epidermal growth factor receptor 2.

Table S2. proportional hazard assumption Cox multivariable models.

	Overall mortality		MACE		AF		HF	
Tumor characteristics	**Chisq**	**p**	**Chisq**	**p**	**Chisq**	**p**	**Chisq**	**p**
Left versus right-sided breast cancer	0.768	0.381	0.006	0.938	-	-	-	-
Tumor size	<0.001	0.987	0.026	0.871	-	-	1.202	0.27
Nodal status	0.031	0.861	0.129	0.719	0.003	0.96	0.163	0.69
Tumor Stage	0.227	0.633	0.004	0.949	0.006	0.94	0.005	0.94
Tumor Grade	2.848	0.091	0.123	0.725	-	-	2.508	0.11
Estrogen receptor positive	4.650	0.031	0.230	0.512	-	-	-	-
Progesterone receptor positive	1.906	0.167	1.867	0.172	-	-	-	-
HER2 receptor positive	0.709	0.400	1.790	0.181	-	-	-	-
Treatment characteristics								
Treatment Setting (neoadjuvant vs. adjuvant)	0.367	0.545	1.371	0.242	0.036	0.85	-	-
Irradiation mediastinal and subclavian nodes	0.118	0.732	3.040	0.081	-	-	-	-
Mean heart dose	1.503	0.220	2.177	0.140	0.008	0.93	0.881	0.35

Treatment with hormonal therapy	-	-	-	-	-	-	-	-
Treatment with chemotherapy	0.416	0.519	0.136	0.713	-	-	-	-
Treatment with HER2 inhibitors	0.300	0.584	1.935	0.164	-	-	-	-
Cardiovascular risk factors								
History of cardiovascular disease	0.258	0.612	0.001	0.969	0.322	0.57	0.287	0.59
Mayo Clinic Risk Score	0.045	0.832	0.422	0.516	-	-	0.100	0.75

HER2: human epidermal growth factor receptor 2; MACE: Major Adverse Cardiac Event, AF: Atrial Fibrillation/Flutter; HF: Heart Failure; Chisq: chi-squared test.

Table S3. Univariable and multivariable Cox regression for overall survival of 1095 patients with unilateral breast cancer treated with radiation therapy in 2007 or 2008.

	Univariable		Multivariable	
Tumor characteristics	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
Left or right-sided breast cancer	1.055 (0.809 – 1.376)	0.694	0.881 (0.561 – 1.385)	0.584
Tumor size	1.574 (1.365 – 1.814)	<0.001	0.722 (0.455 – 1.171)	0.187
Nodal status	1.567 (1.367 – 1.797)	<0.001	1.237 (0.866 – 1.767)	0.242
Tumor Stage	1.796 (1.494 – 2.159)	<0.001	1.370 (0.715 – 2.627)	0.343
Tumor Grade	1.508 (1.235 – 1.841)	<0.001	1.739 (1.166 - 2.591)	0.007
Estrogen receptor positive	0.557 (0.407 – 0.762)	<0.001	0.854 (0.410 – 1.780)	0.674
Progesterone receptor positive	0.603 (0.455 – 0.799)	<0.001	0.591 (0.322 – 1.084)	0.89
HER2 receptor positive	0.695 (0.434 – 1.114)	0.130	0.921 (0.219 – 3.862)	0.910
Treatment characteristics				
Treatment Setting (neoadjuvant vs. adjuvant)	2.611 (1.856 – 3.672)	<0.001	2.782 (1.304 – 5.936)	0.008
Irradiation mediastinal and subclavian nodes	0.916 (0.686 – 1.223)	0.553	0.764 (0.224 - 2.616)	0.669

Mean heart dose	1.049 (1.003 – 1.098)	0.037	1.048 (0.996 – 1.103)	0.072
Treatment with hormonal therapy	0.518 (0.382 – 0.702)	<0.001	-	-
Treatment with chemotherapy	1.134 (0.863 – 1.489)	0.366	0.702 (0.151 – 3.264)	0.651
Treatment with HER2 inhibitors	0.512 (0.292 – 0.897)	0.019	0.404 (0.082 – 1.981)	0.264
Cardiovascular risk factors				
History of cardiovascular disease	2.666 (1.792 – 3.965)	<0.001	1.182 (0.547 – 2.554)	0.670
Mayo Clinic Risk Score	1.101 (1.027 – 1.180)	0.006	1.116 (0.772 - 1.614)	0.559

CI: confidence interval; HER2: human epidermal growth factor receptor 2.

Table S4. Univariable and multivariable Cox regression for major adverse cardiac events in 1095 patients with unilateral breast cancer treated with radiation therapy in 2007 or 2008.

	Univariable		Multivariable	
Tumor characteristics	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
Left or right-sided breast cancer	1.036 (0.723 – 1.485)	0.847	0.775 (0.428 – 1.404)	0.401
Tumor Size	1.304 (1.064 – 1.598)	0.010	0.847 (0.432 – 1.661)	0.629
Nodal Status	1.281 (1.051 – 1.561)	0.014	1.594 (0.937 – 2.710)	0.085
Tumor Stage	1.325 (1.034 – 1.697)	0.026	0.788 (0.322 – 1.931)	0.603
Tumor Grade	1.111 (0.861 – 1.433)	0.419	1.306 (0.811 – 2.103)	0.273
Estrogen receptor positive	1.461 (0.834 – 2.559)	0.185	2.053 (0.533 – 7.904)	0.296
Progesterone receptor positive	1.072 (0.703 – 1.633)	0.747	1.891 (0.741 – 4.829)	0.183
HER2 receptor positive	0.567 (0.287 – 1.120)	0.103	0.098 (0.002 – 6.248	0.273
Treatment characteristics				
Treatment Setting (neoadjuvant vs. adjuvant)	1.283 (0.721 – 2.284)	0.397	2.754 (0.815 – 9.306)	0.103

Irradiation mediastinal and subclavian nodes	1.261 (0.830 – 1.917)	0.277	0.379 (0.082 – 1.747)	0.214
Mean heart dose	1.087 (1.029 – 1.148)	0.003	1.093 (1.024 – 1.167)	0.007
Treatment with hormonal therapy	1.521 (0.868 – 2.664)	0.142	-	-
Treatment with chemotherapy	0.797 (0.548 – 1.159)	0.236	0.062 (0.008 – 0.484)	0.007
Treatment with HER2 inhibitors	0.404 (0.178 – 0.919)	0.031	0.880 (0.013 – 58.724)	0.952
Cardiovascular risk factors				
History of cardiovascular disease	6.928 (4.494 – 10.681)	<0.001	2.386 (1.096 – 5.197)	0.029
Mayo Clinic Risk Score	1.035 (0.942 – 1.138)	0.471	2.664 (1.625 – 4.367)	0.001

CI: confidence interval; HER2: human epidermal growth factor receptor 2.

Table S5. Mortality and cardiovascular event rates in 1095 patients treated for left-sided versus right-sided breast cancer.

| Endpoint | Left (n=551) | | Right (n=544) | | Rate ratio |
	Number of events	Rate (95% CI)	Number of events	Rate (95% CI)	(95% CI)
All-cause mortality	107	20.4 (16.6-24.2)	111	21.5 (17.5-25.4)	0.95 (0.73-1.24)
CV mortality	10	1.9 (0.7-3.1)	12	2.3 (1.0-3.6)	0.82 (0.36-1.90)
Non-CV mortality	97	18.5 (14.8-22.1)	99	19.1 (15.4-22.9)	0.97 (0.73-1.27)
Cancer mortality	53	10.1 (7.4-12.8)	54	10.4 (7.7-13.2)	0.97 (0.66-1.41)
Fatal + non-fatal coronary endpoints	18	3.5 (1.9-5.0)	12	2.3 (1.0-3.7)	1.47 (0.71-3.05)
Fatal heart failure	4	0.8 (0.0-1.5)	4	0.8 (0.0-1.5)	0.99 (0.25-3.94)
Non-fatal heart failure	23	4.5 (2.6-6.3)	28	5.6 (3.5-7.6)	0.80 (0.46-1.40)
Fatal + non-fatal heart failure	26	5.0 (3.1-7.0)	30	5.9 (3.8-8.0)	0.85 (0.51-1.44)
Atrial fibrillation	22	6.2 (3.6-8.7)	19	5.6 (3.1-8.0)	1.11 (0.60-2.05)

About half of the patients (n=551, 50.3%) had left-sided breast cancer. Mean age and the prevalences of smoking, diabetes and hypertension were similar (P>0.27) among patients with left-sided and right-sided breast cancer (age: 57.6 ± 12.0 vs 56.8 ± 12.6 years, ever smoking: 31.9% vs 29.6%, hypertension: 28.7% vs 29.4%, diabetes: 6.2% vs 6.2%). Incidence of endpoints according to the localization of the cancer:

Rates are expressed as number of events per 1000 subject years.

CI: confidence interval; CV: cardiovascular.

Table S6. Mortality and cardiovascular event rates in 1088 breast cancer patients by anthracycline chemotherapy treatment.

Endpoint	Anthracycline CTX (n=514)		No anthracycline CTX (n=574)			
	Number of events	Rate (95% CI)	Number of events	Rate (95% CI)		Rate ratio (95% CI)
All-cause mortality	99	20.6 (16.6-24.6)	118	21.3 (17.5-25.1)		0.96 (0.74-1.26)
CV mortality	5	1.0 (0.1-1.9)	17	3.1 (1.6-4.5)		0.34 (0.12-0.92)
Non-CV mortality	94	19.5 (15.6-23.4)	101	18.3 (14.7-21.8)		1.07 (0.81-1.41)
Cancer mortality	68	14.1 (10.8-17.5)	39	7.0 (4.8-9.3)		2.00 (1.35-2.97)
Fatal + non-fatal coronary endpoints	9	1.9 (0.7-3.1)	21	3.8 (2.2-5.5)		0.49 (0.23-1.07)
Fatal heart failure	4	0.8 (0.0-1.6)	4	0.7 (0.0-1.4)		1.15 (0.29-4.60)
Non-fatal heart failure	25	5.3 (3.2-7.4)	26	4.8 (3.0-6.6)		1.11 (0.64-1.92)
Fatal + non-fatal heart failure	28	5.9 (3.7-8.1)	28	5.1 (3.2-7.0)		1.16 (0.69-1.96)
All fatal + non-fatal cardiovascular endpoints	37	7.9 (5.4-10.5)	59	11.0 (8.2-13.8)		0.72 (0.48-1.09)

	Anthracycline CTX (n=514)			No anthracycline CTX (n=574)			
Endpoint	Number of events	Rate (95% CI)		Number of events	Rate (95% CI)		Rate ratio (95% CI)
Atrial fibrillation	10	3.5 (1.3-5.7)		31	7.6 (4.9-10.2)		0.46 (0.23-0.94)

For this analysis 7 patients were excluded because of missing information on anthracycline chemotherapy treatment. Of the remaining 1088 patients, 514 (47.2%) received anthracycline chemotherapy (CTX). Event rates in patients receiving/not receiving anthracycline CTX are as follows:

Rates are expressed as number of events per 1000 subject years.

CI: confidence interval; CV: cardiovascular; CTX: chemotherapy.

Table S7. Univariable and multivariable Cox regression for atrial fibrillation or flutter in 1095 patients with unilateral breast cancer treated with radiation therapy in 2007 or 2008.

	Univariable		Multivariable	
Tumor characteristics	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
Left or right-sided breast cancer	0.821 (0.448 – 1.501)	0.521	-	-
Tumor size	1.383 (0.993 – 1.928)	0.055	-	-
Nodal status	1.794 (1.341 – 2.402)	<0.001	1.765 (0.717 – 4.344)	0.216
Tumor Stage	1.937 (1.274 – 2.944)	0.002	0.973 (0.258 – 3.671)	0.968
Tumor Grade	0.819 (0.544 – 1.226)	0.329	-	-
Estrogen receptor positive	2.220 (0.685 – 7.192)	0.183	-	-
Progesterone receptor positive	1.198 (0.573 – 2.507)	0.631	-	-
HER2 receptor positive	0.338 (0.082 – 1.400)	0.135	-	-
Treatment characteristics				
Treatment Setting (neoadjuvant vs. adjuvant)	2.397 (1.063 – 5.408)	0.035	3.032 (0.510 – 18.020)	0.223

Irradiation mediastinal and subclavian nodes	0.932 (0.478 – 1.827)	0.836	-	-
Mean heart dose	1.163 (1.057 – 1.281)	0.002	1.113 (0.999 – 1.240)	0.053
Treatment with hormonal therapy	2.368 (0.731 – 7.669)	0.150	-	-
Treatment with chemotherapy	0.737 (0.385 – 1.412)	0.291	-	-
Treatment with HER2 inhibitors	0.189 (0.026 – 1.378)	0.100	-	-
Cardiovascular risk factors				
History of cardiovascular disease	3.366 (1.528 – 7.417)	0.003	1.783 (0.351 – 9.064)	0.486
Mayo Clinic Risk Score	1.007 (0.862 – 1.177)	0.928	-	-

CI: confidence interval; HER2: human epidermal growth factor receptor 2.

Table S8. Univariable and multivariable Cox regression for heart failure in 1095 patients with unilateral breast cancer treated with radiation therapy in 2007 or 2008.

	Univariable		Multivariable	
Tumor characteristics	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
Left or right-sided breast cancer	1.037 (0.621 – 1.730)	0.890	-	-
Tumor size	1.607 (1.221 – 2.116)	0.001	0.611 (0.239 – 1.564)	0.304
Nodal status	1.466 (1.133 – 1.896)	0.004	1.460 (0.736 – 2.895)	0.279
Tumor Stage	1.777 (1.248 – 2.531)	0.001	1.134 (0.388 – 4.445)	0.661
Tumor Grade	1.531 (1.046 – 2.240)	0.028	1.936 (0.955 – 3.924)	0.067
Estrogen receptor positive	0.781 (0.401 – 1.524)	0.469	-	-
Progesterone receptor positive	0.929 (0.516 – 1.673)	0.807	-	-
HER2 receptor positive	0.659 (0.263 – 1.652)	0.373	-	-
Treatment characteristics				
Treatment Setting (neoadjuvant vs. adjuvant)	1.435 (0.648 – 3.177)	0.373	-	-

Irradiation mediastinal and subclavian nodes	1.013 (0.537 – 1.910)	0.968	-	-
Mean heart dose	1.134 (1.030 – 1.248)	0.010	1. 100 (0.978 – 1.237)	0. 113
Treatment with hormonal therapy	0.854 (0.438 – 1.664)	0.642	-	-
Treatment with chemotherapy	1.267 (0.749 – 2.144)	0.377	-	-
Treatment with HER2 inhibitors	0.611 (0.220 – 1.692)	0.343	-	-
Cardiovascular risk factors				
History of cardiovascular disease	5.511 (3.090 – 9.831)	<0.001	3.205 (1. 006 – 10.208)	0.049
Mayo Clinic Risk Score	1.166 (1.020 – 1.334)	0.025	1.305 (0.980 – 1.738)	0.069

CI: confidence interval; HER2: human epidermal growth factor receptor 2.

Figure S1. Mayo Clinic Risk Score.

1. Risk assessment
Tests: TTE with strain, EKG, cTn

Medication-related risk	Patient-related risk factors
High (risk score 4): Anthracyclines, Cyclophosphamide, Ifosfamide, Clofarabine, Herceptin *Intermediate (risk score 2):* Docetaxel, Pertuzumab, Sunitinib, Sorafinib *Low (risk score 1):* Bevacizumab, Dasatinib, Imatinib, Lapatinib *Rare (risk score 0):* For example, Etoposide, Rituximab, Thalidomide	• Cardiomyopathy or heart failure • CAD or equivalent (incl. PAD) • HTN • Diabetes mellitus • Prior or concurrent anthracycline • Prior or concurrent chest radiation • Age <15 or >65 years • Female gender

Overall risk by Cardiotoxicity Risk Score (CRS)
(risk categories by drug-related risk score *plus* number of patient-related risk factors:
CRS >6: very high, 5-6: high, 3-4: intermediate, 1-2: low, 0: very low)

2. Monitoring recommendations

Very high cardiotoxicity risk: TTE with strain before every (other) cycle, end, 3-6 months and 1 year, optional ECG, cTn with TTE during chemotherapy

High cardiotoxicity risk: TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional ECG, cTn with TTE during chemotherapy

Intermediate cardiotoxicity risk: TTE with strain, mid-term, end and 3-6 months after chemotherapy, optional ECG, cTn mid-term of chemotherapy

Low cardiotoxicity risk: Optional TTE with strain and/or ECG, cTn at the end of chemotherapy

Very low cardiotoxicity risk: None

3. Management recommendations
Applies as preventive measures before and with abnormalities during/after chemotherapy

Very high cardiotoxicity risk: Initiate ACE-I/ARB, Carvedilol, and statins, starting at lowest dose and start chemotherapy in 1 week from initiation to allow steady state, up-titrate as tolerated

High cardiotoxicity risk: Initiate ACE-I/ARB, Carvedilol, and/or statins

Intermediate cardiotoxicity risk: Discuss risk and benefit of medications

Low cardiotoxicity risk: None, monitoring only

Very low cardiotoxicity risk: None, monitoring only
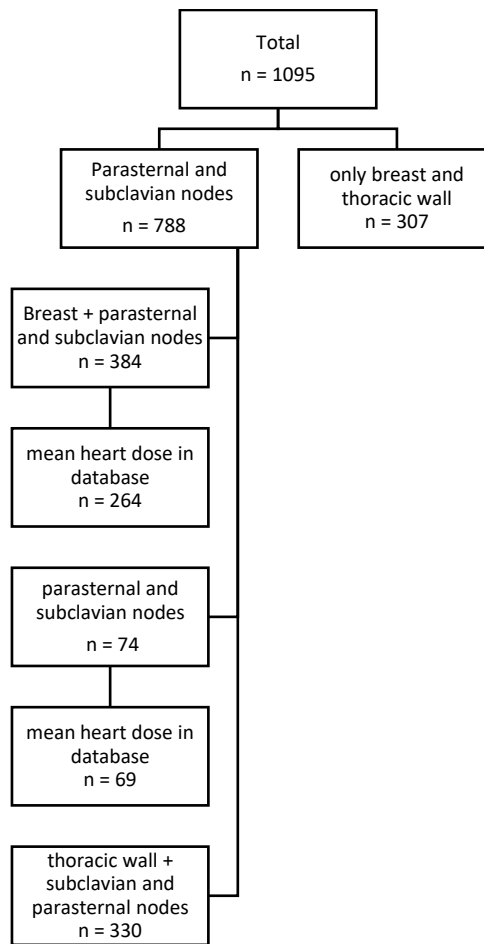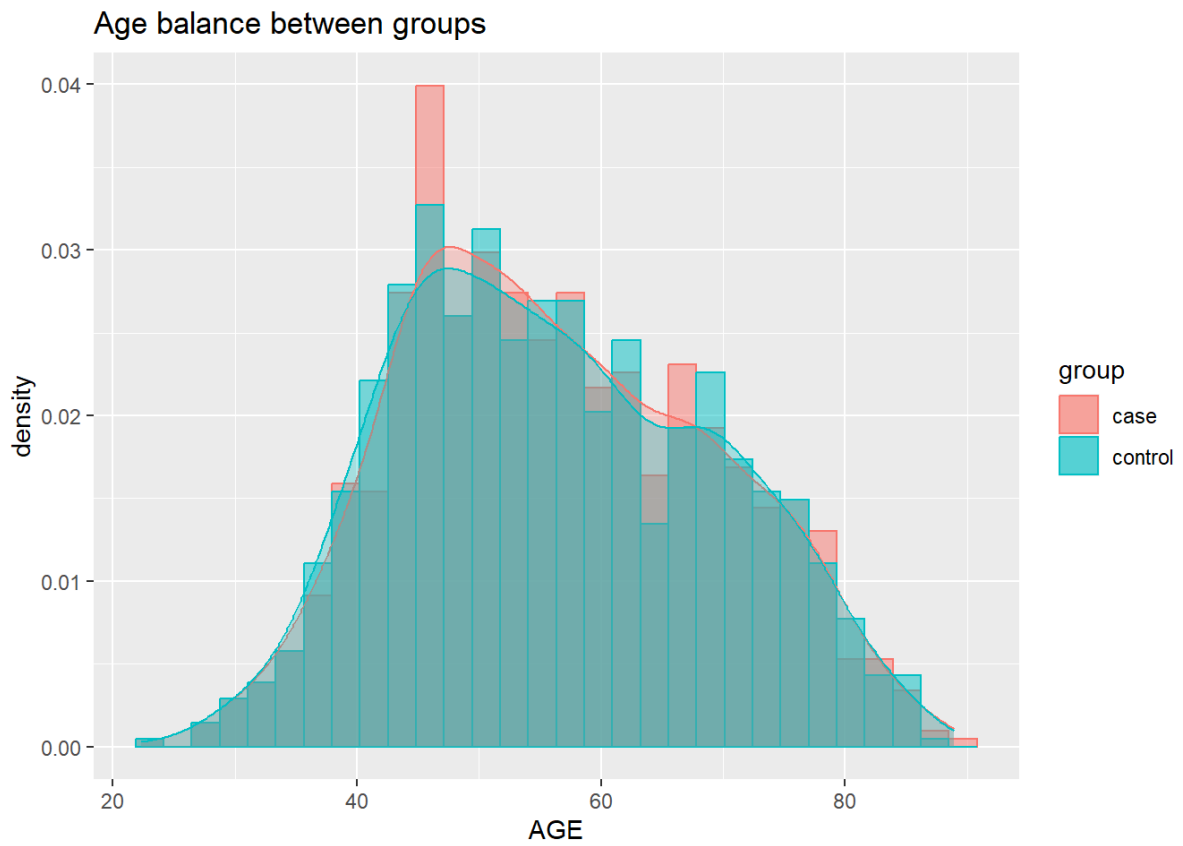
Figure S2. Subgroups radiation therapy.

Figure S3. Matching.

Age balance between groups

Variables	Cases	Controls
Smoking		
No	586	586
Yes	318	318
Hypertension		
No	588	588
Yes	316	316
Diabetes		
No	843	843
Yes	61	61

Figure S4. coefficient (natural log of the hazard ratio) over time of Estrogen Receptor Positivity in Cox multivariable model of mortality.