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Original Article

Prognosis of acute coronary syndromes after radiotherapy for breast cancer

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ABSTRACT

Background and purpose: Breast cancer patients treated with radiotherapy are at increased risk of subsequent acute coronary syndromes (ACS). We aimed to study if radiotherapy also influences the prognosis of these ACS.

Materials and methods: We included all 398 patients diagnosed with ACS following radiotherapy from our hospital-based cohort of early breast cancer patients aged <71 years, treated 1970–2009. Cardiovascular disease incidence and cause of death were acquired through questionnaires to general practitioners and cardiologists.

Internal mammary chain (IMC) irradiation delivers the highest heart doses in breast cancer radiotherapy. Hence, we compared ACS prognosis between patients treated with/without IMC-irradiation. ACS prognosis was assessed through cardiac death, death due to ACS and cardiovascular disease incidence, using multivariable Cox proportional hazard models and by estimating cumulative incidence.

Results: In total, 62% of patients with ACS had received IMC-irradiation and 38% did not (median age at ACS diagnosis, 67 years). Median time between breast cancer and ACS was 15 years.

After ACS, ten-year cumulative risk of cardiac death was 35% for patients who had IMC-irradiation (95% confidence interval [95%CI] 29–41) compared to 24% (95%CI 17–31) for patients without IMC-irradiation (p = 0.04). After correction for confounders, IMC-irradiation remained associated with a less favourable prognosis of ACS compared to no IMC-irradiation (hazard ratio cardiac death = 1.7, 95%CI 1.1–2.5).

Conclusion: Our results suggest that radiotherapy, in case of substantial heart doses, may worsen ACS prognosis. This is an important, novel finding that may impact upon the risk-based care for breast cancer survivors with ACS.

Radiotherapy for breast cancer may expose the heart to radiation [1,2] and is known to be associated with an increased rate of acute coronary syndromes (ACS) [3–8]. This risk appears to increase linearly with increasing mean heart dose [9,10]. In breast cancer radiotherapy, the heart is exposed to the highest doses during irradiation of the internal mammary chain (IMC) [11], and accordingly, highest ACS risk is observed after IMC-irradiation [4,5,12].

Cardiac radiation exposure can induce damage to the micro- and macrovasculature, initiating the process of atherosclerosis and (vascular) fibrosis, which may lead to myocardial ischemia, and subsequent ACS [13]. Mouse studies have shown that general strategies to inhibit age-related atherosclerosis do not seem to inhibit radiation-induced atherosclerosis [14,15], and that radiation-induced vascular pathology differs from age-related atherosclerosis [16]. Hence, it is hypothesized that the prognosis of ACS subsequent to radiotherapy is also different. History of

Abbreviations: ACS, acute coronary syndromes; IMC, internal mammary chain-irradiation; NKI, Netherlands Cancer Institute; Erasmus MC, Erasmus MC Cancer Center; ICD-10, International Classification of Diseases 10th revision; SES, socioeconomic status; HR, hazard ratio; CI, confidence interval; RCA, right coronary artery; LAD, left descending artery; PCI, percutaneous coronary intervention.

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radiation exposure to the heart is currently not included in cardiovascular risk assessment at time of ACS occurrence [17,18], as the outcome of ACS after cardiac radiation exposure for cancer has not been studied. Therefore, we aimed to study if radiotherapy also influences the prognosis of ACS by assessing the effect of previous radiotherapy with or without IMC-irradiation on several prognostic outcomes after ACS in breast cancer survivors.

Methods

Design and study population

We conducted a retrospective cohort study on ACS prognosis of female patients treated with radiotherapy for breast cancer. From our Late Effects Breast Cancer Cohort [12,19], we selected all patients treated with radiotherapy for breast cancer and subsequently diagnosed with an ACS with infarction or a registered cause of death of International Classification of Diseases 10th revision (ICD-10) I21 (acute myocardial infarction), I23 (certain current complications following acute myocardial infarction) or I46 (cardiac arrest). The Late Effects Breast Cancer Cohort comprises 15,624 patients, aged ≤70 years at diagnosis, treated for stage I-IIIA breast cancer or ductal carcinoma in situ from 1970 to 2009 at the Netherlands Cancer Institute (NKI), Amsterdam or the Erasmus MC Cancer Institute (Erasmus MC), Rotterdam, the Netherlands. From this cohort we identified 398 women with an ACS after radiotherapy.

Mean cardiac dose during irradiation of different target fields was previously estimated [12]. We observed highest mean heart doses after IMC-irradiation, with a median mean heart doses ranging from 8.9 to 16.1 Gy depending on e.g. field borders and breast cancer treatment period, compared to 0.6/4.7 Gy for right/left-sided breast only and 2.8/5.3 Gy for right/left-sided chest wall only. Mean heart doses were high for both left- and right-sided IMC-irradiation; range 14.7–16.6 Gy for left-sided and 8.9–13.4 Gy for right-sided. Because strongest ACS risk increases in breast cancer patients are observed after IMC-irradiation [4,5,12], we compared the ACS prognosis between patient groups treated with and without IMC-irradiation.

Information on cardiovascular risk factors was taken into account up until date of ACS, and, with the exception of smoking, were considered to be chronic. Hypercholesterolemia, hypertension, and diabetes mellitus were combined and categorized as: none, one or more risk factors, and unknown. Smoking at time of ACS was taken into account as a separate variable. Categories for SES were based on area-level SES as defined by Statistics Netherlands: below average, average, above average. Assessed outcomes consisted of fatal ACS (defined as death on the day of ACS diagnosis), cardiac death (ICD-10 I00-I52), mortality due to ACS (ICD-10 I21, I23, and I46), and cardiovascular disease incidence following ACS (heart failure and valvular heart disease; including both mor-

Table 1
Breast cancer characteristics and therapy features of 398 patients diagnosed with acute coronary syndrome following radiotherapy for breast cancer.

	ACS following radiotherapy including IMC irradiation		ACS following other type of irradiation (no IMC)		*P*[†]
Characteristic	No.	%	No.	%	
Total no. of patients	245	61.6	153	38.4	
Age at BC diagnosis (years)					
Median (IQR)	51 (46–56)		51 (47–55)		*0.60*
Year of first BC treatment					
1970–1979	114	46.5	41	26.8	
1980–1989	109	44.5	46	30.1	
1990–1999	17[‡]	6.9	41	26.8	
2000–2009	5[‡]	2.0	25	16.3	*<0.001*
Type of surgery[§]					
Wide local excision	56	22.9	100	65.4	
Mastectomy	187	76.3	52	34.0	
Unknown	2	0.8	1	0.7	*<0.001*
Radiation field[§]					
Breast	40	16.3	95	62.1	
Right-sided	18	7.4	41	26.8	
Left-sided	22	9.0	54	35.3	
Chest wall	86	35.1	52	34.0	
Right-sided	41	16.7	24	15.7	
Left-sided	45	18.4	28	18.3	
IMC	119	48.6	n.a.		
Right-sided	63	25.7	n.a.		
Left-sided	56	22.9	n.a.		
Unknown	0	0.0	6	3.9	*<0.001*
Chemotherapy[§]					
No	194	79.2	130	85.0	
Yes	51	20.8	23	15.0	
CMF-like regimens	43	17.6	11	7.2	
Anthracycline-containing regimens[‖]	8	3.3	12	7.8	*0.01*
Endocrine therapy					
No	233	95.1	140	91.5	
Yes	12	4.9	13	8.5	*0.15*

Abbreviations: ACS, acute coronary syndrome; IMC, internal mammary chain; BC, breast cancer; *P*, *p*-value; No., number; IQR, interquartile range; n.a., not applicable; CMF, cyclophosphamide methotrexate fluorouracil.

[†] *P*-value comparing radiation groups. Chi-square test for categorical variables, unpaired *t*-test for continuous data.

[‡] Irradiation to the internal mammary chain field was less frequently used in more recent treatment years in the total Late Effects Breast Cancer cohort; percentage of IMC irradiated patients dropped from 57.9% in the period 1970–1986, to 15.3% in the period 2000–2009.

[§] Primary treatment for breast cancer only.

[‖] Including either epirubicin or doxorubicin.

bidity and mortality), see eTable 1. For patients with ACS as cause of death without prior evidence of cardiac disease, the date of death was used as date of ACS diagnosis. After a worst-case sensitivity analysis, this approach was also used in eight patients without complete cardiovascular morbidity information until date of death. Fatal ACS as an outcome, however, was only scored positive if the date of ACS was the same as the date of death and cardiovascular disease information was complete until death.

Data collection

Detailed description of patient selection and data collection procedures of the Late Effects Breast Cancer Cohort has been published previously [19] and is provided in 'Supplemental methods'. In summary, all patients were identified through the hospital-based cancer registries of the NKI and Erasmus MC. Information on patient-, tumour-, and treatment characteristics, before and after breast cancer, date and cause of death, and cardiovascular dis-

Table 2
Characteristics at time of acute coronary syndrome of 398 patients treated with radiotherapy for breast cancer.

	ACS following radiotherapy including IMC irradiation		ACS following other type of irradiation (no IMC)		*P* [†]
Characteristic	No.	%	No.	%	
Total no. of patients	245	61.6	153	38.4	
Age at ACS diagnosis (years)					
Median (IQR)	69 (63–76)		65 (59–71)		*<0.001*
Year of first ACS diagnosis					
1980–1995	87	35.5	41	26.8	
1996–2005	107	43.7	60	39.2	
2006–2015	51	20.8	52	34.0	*0.01*
Years between BC treatment and first ACS (years)					
Median (IQR)	17 (13–22)		13 (8–19)		*<0.001*
Follow up time after ACS diagnosis					
Median, years (IQR)	5 (1 m-10)		5 (8 m-10)		
No follow up since ACS[§]	55	22.5	19	12.4	
0–1 year	22	9.0	25	16.3	
1–5 years	44	18.0	35	22.9	
5–10 years	62	25.3	35	22.9	
>10 years	62	25.3	39	25.5	*0.03*
BC status at ACS diagnosis					
(Complete) Remission	241	98.4	146	95.4	
(Loco)regional recurrence[‖]	3	1.2	2	1.3	
Metastatic breast cancer	1	0.4	5	3.3	*0.07*
Established cardiovascular risk factors at ACS[#]					
None	130	53.1	54	35.3	
One or more	94	38.4	59	38.6	
Unknown	21	8.6	40	26.1	*<0.001*
Smoking at ACS diagnosis					
No	128	52.2	63	41.2	
Yes	90	36.7	51	33.3	
Unknown	27	11.0	39	25.5	*0.001*
History of cardiovascular disease before ACS					
No[¥]	151	61.6	106	69.3	
Yes	94	38.4	47	30.7	
ACS before BC	1	0.4	3	2.0	
Coronary disease without infarction	38	15.5	18	11.8	
Other[*]	55	22.5	26	17.0	*0.28*
Socio-economic status[¶]					
Below average	51	20.8	28	18.3	
Average	161	65.7	95	62.1	
Above average	23	9.4	24	15.7	
Unknown	10	4.1	6	3.9	*0.30*
Vital status at end of follow-up					
Alive	69	28.2	64	41.8	
Dead	176	71.8	89	58.2	
Fatal ACS[$]	49	20.0	17	11.1	*0.01*

Abbreviations: ACS, acute coronary syndrome; IMC, internal mammary chain; BC, breast cancer; *P*, *p*-value; No., number; IQR, interquartile range; m, months.
[†] *P*-value comparing radiation groups. Chi-square test for categorical variables, unpaired *t*-test for continuous data.
[§] When no follow-up is attained since acute coronary syndrome, the patient has died on the day of acute coronary syndrome diagnosis or died due to an acute coronary syndrome with an unknown date of acute coronary syndrome ($n = 8$).
[‖] Status of (loco)regional recurrence at time of acute coronary syndrome diagnosis was scored as positive if a recurrence was diagnosed $\leq$1 year before acute coronary syndrome diagnosis
[#] Cardiovascular risk factors included are hypercholesterolemia, hypertension and diabetes mellitus.
[¥] If history of CVD before breast cancer was unknown, and no CVD was diagnosed between breast cancer and ACS diagnosis, this was labeled as 'no' ($n = 64$).
[*] Cardiovascular diseases included are valvular heart disease, pericarditis, cardiomyopathy, heart failure, cardiac arrhythmia, stroke, transient ischemic accident and peripheral vascular disease.
[¶] Through linkage with Statistics Netherlands using postal zip code, area-level socioeconomic status was acquired of each patient.
[$] Acute coronary syndrome is considered fatal if the date of (first) acute coronary syndrome was equal to the date of death and cardiovascular disease information was complete until death.

ease information were collected from the registries and medical charts. Breast cancer treatment information was collected for primary breast cancer, regional recurrences and subsequent breast cancers until diagnosis of distant metastases, and concerned all types of therapy (surgery, radiotherapy, and systemic therapy). An overview of breast cancer treatment during the study period is provided as 'Supplemental text'. Linkage with the population-based municipal personal records database was performed to acquire missing dates of death. Questionnaires were sent to general practitioners and cardiologists to obtain detailed information on incidence of cardiovascular diseases (e.g. ACS, stable angina, valvular heart disease, heart failure; both before and after breast cancer), date and cause of death, and information on the cardiovascular risk factors smoking, hypertension, diabetes mellitus, hypercholesterolemia (see also 'Supplemental methods' for further details). Complete follow-up through at least January 1, 2014 was obtained for 83% of the current study population (n = 398). Additionally, two linkages were performed. First, linkage with Statistics Netherlands was performed using postal zip code, to acquire the area-level socioeconomic status (SES) of each patient [20]. Secondly, using linkage methods described previously [21], data from Dutch Hospital Data and the nation-wide cause-of-death registry were used to obtain information on ACS location for the patients diagnosed with ACS during the period 1995–2014.

Statistical analysis

In the analyses of survival after ACS, time at risk started one day before ACS diagnosis and ended at date of diagnosis of the event of interest, death, emigration, distant metastasis, or most recent medical information, whichever came first. When evaluating the rates of heart failure and valvular heart disease following ACS, patients with a history of heart failure or valvular heart disease before ACS were not taken into account. SES, chemotherapy regimen, smoking history, other cardiovascular risk factors, history of cardiovascular disease before ACS, age at ACS diagnosis, and year of ACS diagnosis were considered as possible confounders and tested for interaction. The multivariable regression models included all of these variables except for SES, and used age as time scale.

Differences in characteristics between groups were tested using the two-sample t-test and chi-square test when appropriate. Cumulative incidences were estimated while treating death due to other causes than the outcome of interest as a competing risk [22]. P-values comparing cumulative incidence between groups were calculated using the Pepe and Mori test [23]. Outcome rates were evaluated with multivariable Cox proportional hazards regression models. Model assumptions were verified using residual-based methods [24]. All statistical tests were two-sided, p-values <0.05 were considered statistically significant. Analyses were performed using Stata/SE 13.0 (StataCorp LP, College Station, TX).

Results

We identified 398 patients with ACS following radiotherapy for breast cancer, of whom 38% were irradiated to the breast or chest wall without IMC-irradiation and 62% were treated with IMC-irradiation (Table 1). Median age at breast cancer diagnosis was 51 years in both treatment groups. The majority of patients did not receive chemotherapy (79% of patients with and 85% of patients without IMC-irradiation). Since IMC-irradiation was more frequently used in earlier years, median year of breast cancer diagnosis was earlier in IMC-irradiated patients (1980 vs. 1987), resulting in usage of different types of chemotherapy regimens. Also, because of the longer follow-up duration of the IMC-irradiated group, median time between breast cancer diagnosis and ACS was longer: 17 years vs. 13 years, $p < 0.01$), leading to a somewhat older median age at ACS (69 years vs. 65 years in patients without IMC-irradiation; Table 2). Overall, however, age at ACS largely overlapped between patients treated with and without IMC-irradiation, as did, importantly, the year of ACS diagnosis (eFig. 1). The percentages of patients smoking at ACS diagnosis, with a history of cardiovascular disease, and with one or more of the cardiovascular risk factors hypertension, hypercholesterolemia, or diabetes at ACS were comparable between the treatment groups. At the end of follow-up 71.8% of IMC-irradiated patients had died compared to 58.2% in patients without IMC-irradiation.

Data on the location of ACS were retrieved for 161 (58%) of 277 patients diagnosed between 1995 and 2014. The distribution of ACS location did not significantly differ between the two treatment groups and was unspecified for many patients (40% and 49%, respectively); however, the ACS seemed to be located in the inferior wall more often in patients with IMC-irradiation compared to patients without IMC-irradiation (25.6 vs. 20.9%, p = *0.62*). (Table 3)

Adjusted for potential confounders, IMC-irradiation was associated with an increased cardiac death rate following ACS (hazard ratio [HR] = 1.7, 95%CI 1.1–2.5, p = *0.02*; Table 4). Furthermore, the rate of death on the day of ACS diagnosis was twice as high after IMC-irradiation compared to patients without IMC-irradiation (HR = 2.2, 95%CI 1.2–3.8). The rate of death due to ACS at any moment during follow-up (HR = 1.4, 95%CI 0.90–2.2), and of developing valvular heart disease following ACS (HR = 1.7, 95%CI 0.89–3.2) were both non-significantly elevated after IMC-irradiation. No association was found between IMC-irradiation and heart failure rate following ACS. Of all potential confounders considered (including age and year of ACS diagnosis), only cardiovascular risk factors materially affected the HRs for IMC-irradiation.

Table 3
Location of acute coronary syndrome for 161 patients for whom linkage with the Dutch Hospital Data or cause of death registry was possible.

	ACS following radiotherapy including IMC irradiation		ACS following other type of irradiation (no IMC)		$P^{\dagger}$
Location of acute coronary syndrome	No.	%	No.	%	
Total no. of patients	94	100.0	67	100.0	
ICD-10					
Anterior wall	17	18.1	10	15.0	
Inferior wall	24	25.6	14	20.9	
Other sites	8	8.6	3	4.5	
Unspecified sites	38	40.4	33	49.3	
Subendocardial infarction	7	7.5	7	10.5	*0.62*

Abbreviations: ACS, acute coronary syndrome; IMC, internal mammary chain; BC, breast cancer; P, p-value; No., number; ICD-10, International Classification of Diseases, 10th revision.

† P-value comparing radiation groups. Chi-square test for categorical variables.

Table 4
Risk of cardiovascular morbidity and/or mortality after acute coronary syndrome in patients previously treated with radiotherapy for breast cancer.

	Fatal ACS[#]			Death due to ACS[§]			Cardiac death			Incidence of VHD			Incidence of heart failure		
Multivariable model[†]	*n*/*N*	HR	(95%CI)	*n*/*N*	HR	(95%CI)	*n*/*N*	HR	(95%CI)	*n*/*N*	HR	(95%CI)	*n*/*N*	HR	(95%CI)
Radiation field															
No IMC	17/153	1.00	Ref.	32/153	1.00	Ref.	35/153	1.00	Ref.	17/145	1.00	Ref.	27/150	1.00	Ref.
IMC	49/245	2.15	1.20–3.85	64/245	1.39	0.90–2.16	90/245	1.68	1.11–2.54	41/221	1.68	0.89–3.19	54/231	1.06	0.64–1.75
Chemotherapy															
No chemotherapy	56/324	1.00	Ref.	79/324	1.00	Ref.	106/324	1.00	Ref.	48/299	1.00	Ref.	71/309	1.00	Ref.
CMF-like regimen	8/54	1.19	0.54–2.62	15/54	1.59	0.88–2.87	17/54	1.46	0.85–2.52	7/49	0.81	0.35–1.88	7/53	0.79	0.35–1.77
Anthracycline-containing regimen	2/20	0.72	0.16–3.33	2/20	0.59	0.13–2.59	2/20	0.57	0.13–2.49	3/19	1.69	0.36–7.99	3/19	1.31	0.37–4.60
CVD risk factors at ACS diagnosis[¶]															
None present	18/184	1.00	Ref.	41/184	1.00	Ref.	53/184	1.00	Ref.	33/175	1.00	Ref.	41/174	1.00	Ref.
At least one	39/153	5.05	2.73–9.32	42/153	2.08	1.30–3.32	45/153	2.25	1.49–3.39	16/132	0.68	0.36–1.29	29/146	1.15	0.69–1.94
Unknown	9/61	3.38	1.30–8.80	13/61	1.60	0.74–3.43	16/61	2.07	1.06–4.03	9/60	1.10	0.40–3.03	11/61	1.38	0.63–3.04
Smoking at ACS diagnosis															
No	35/191	1.00	Ref.	50/191	1.00	Ref.	65/191	1.00	Ref.	28/173	1.00	Ref.	39/182	1.00	Ref.
Yes	21/141	0.56	0.31–1.02	30/141	0.69	0.42–1.13	42/141	0.77	0.51–1.18	20/131	0.91	0.48–1.70	34/135	1.16	0.70–1.92
Unknown	10/66	0.91	0.39–2.13	16/66	1.16	0.58–2.29	18/66	1.06	0.57–1.97	10/63	1.20	0.47–3.06	8/64	0.61	0.26–1.46
History of CVD before ACS															
None	31/257	1.00	Ref.	51/257	1.00	Ref.	68/257	1.00	Ref.	24/257	1.00	Ref.	55/257	1.00	Ref.
Yes, coronary	12/60	1.57	0.79–3.13	16/60	1.47	0.82–2.63	22/60	1.55	0.94–2.55	13/52	2.64	1.33–5.21	10/53	1.06	0.52–2.15
Yes, other	23/81	4.98	2.77–8.94	29/81	3.17	1.95–5.15	35/81	2.89	1.88–4.45	11/58	2.02	0.97–4.20	16/71	1.74	0.98–3.10
Year of ACS diagnosis															
1980–1995	30/128	1.00	Ref.	39/128	1.00	Ref.	61/128	1.00	Ref.	17/124	1.00	Ref.	38/124	1.00	Ref.
1996–2005	24/167	0.49	0.28–0.87	41/167	0.71	0.44–1.12	46/167	0.52	0.35–0.78	28/152	1.50	0.80–2.82	28/160	0.64	0.38–1.07
2005–2014	12/103	0.41	0.19–0.87	16/103	0.58	0.31–1.11	18/103	0.44	0.25–0.78	13/91	1.80	0.79–4.07	29/97	0.79	0.41–1.54

Abbreviations: ACS, acute coronary syndrome; VHD, valvular heart disease; *n*/*N*, number of events/number at risk; HR, hazard ratio; CI, confidence interval; IMC, internal mammary chain field; Ref., reference group; CMF, cyclophosphamide methotrexate fluorouracil; CVD, cardiovascular disease.

[†] Age is used as a time scale. Included covariates: chemotherapy (no/cyclophosphamide methotrexate fluorouracil-like/antrhacycline-containing regimen), cardiovascular risk factor at acute coronary syndrome diagnosis (none/at least one/unknown), smoking (yes, no, or unknown), history of cardiovascular disease before acute coronary syndrome (none/yes, coronary/yes, other) and year of acute coronary syndrome diagnosis (1980–1995/1996–2005/2005–2014).

[#] Acute coronary syndrome is considered fatal if the date of (first) acute coronary syndrome was equal to the date of death and cardiovascular disease information was complete until death.

[§] Includes all deaths due to acute coronary syndrome throughout follow up.

[¶] Cardiovascular risk factors included are hypercholesterolemia, hypertension and diabetes mellitus.

Accounting for non-cardiac death by using competing risk analysis, the 10-year cumulative incidence of cardiac death was 34.5% among IMC-irradiated patients (95%CI 28.5–40.6) compared to 23.6% (95%CI 16.8–31.0) among patients without IMC-irradiation (p = 0.04) (Fig. 1B, eTable 3). Interestingly, the largest difference in cumulative incidence of cardiac death seemed to occur at time of ACS. Cumulative incidences of ACS as cause of death and incidence of valvular heart disease following ACS were (non-significantly) higher among patients irradiated to the IMC (eTable 3).

Discussion

To the best of our knowledge, this is the first study on the association between radiotherapy for early breast cancer and the prognosis of subsequent ACS. We showed that IMC-irradiation, which exposes the heart to substantial radiation doses, is associated with a less favourable prognosis of ACS compared to no IMC-irradiation; cardiac death rates following ACS were increased for breast cancer patients previously treated with IMC-irradiation compared to patients diagnosed with ACS following breast cancer treated with radiotherapy without IMC-irradiation. Interestingly, IMC-irradiation was particularly associated with an increased fatal ACS rate. These results could not be explained by age at or year of ACS diagnosis.

Comparing patients treated with and without IMC-irradiation, we were able to examine the effect of a substantial difference in cardiac radiation dose on the prognosis of ACS. Yet, because the comparison group was also exposed to radiation to the heart, we might have underestimated the true radiation effect. Irradiation of to the IMC particularly leads to exposure of the proximal segments of the right coronary artery (RCA) and the mid- and distal segments of the left descending artery (LAD) and diagonal branch (D1) [25–27]. As the RCA importantly supplies the inferior wall, our finding that there seems to be a relative predominance of inferior ACS in IMC-irradiated patients fits with this. This observation needs confirmation, however, as the location of ACS was only available for 23% of the cohort, and the distribution of location did not significantly differ between the two treatment groups. Also, we were not able to validate the data used to assess the location. More proximally located ACS was, however, also observed in a study in Hodgkin lymphoma survivors [28], and might be associated with higher mortality rates [29].

The outcomes assessed in this study included several causes of death (see also eTable 1). Cause of death coded as 'cardiac arrest' (ICD-10 I46) was perceived as death due to ACS as it can entail undiagnosed ACS. This particular cause of death was, however, relatively infrequent, with only seven patients.

Although no comparable studies have been published on ACS outcome after radiotherapy in (breast) cancer survivors, a few studies investigated related topics in heterogeneous groups. Yusuf et al. [30] studied overall survival of ACS in a population previously diagnosed with different types of malignancies and found that chest irradiation (n = 84) was associated with lower overall survival. In adjusted analysis, however, chest irradiation was associated with better overall survival; no cause-specific analyses were presented. The high frequency of advanced stage cancers (88.4% of the cohort was stage >T2 and/or >N1 and/or M1) and the fact that the majority of patients received chemotherapy (66.1% of all patients) may have influenced overall mortality. Rohrmann et al. [31] recently reported that in patients with a history of cancer, guideline-recommended treatment for their ACS was less likely received and that mortality was significantly higher (odds ratio

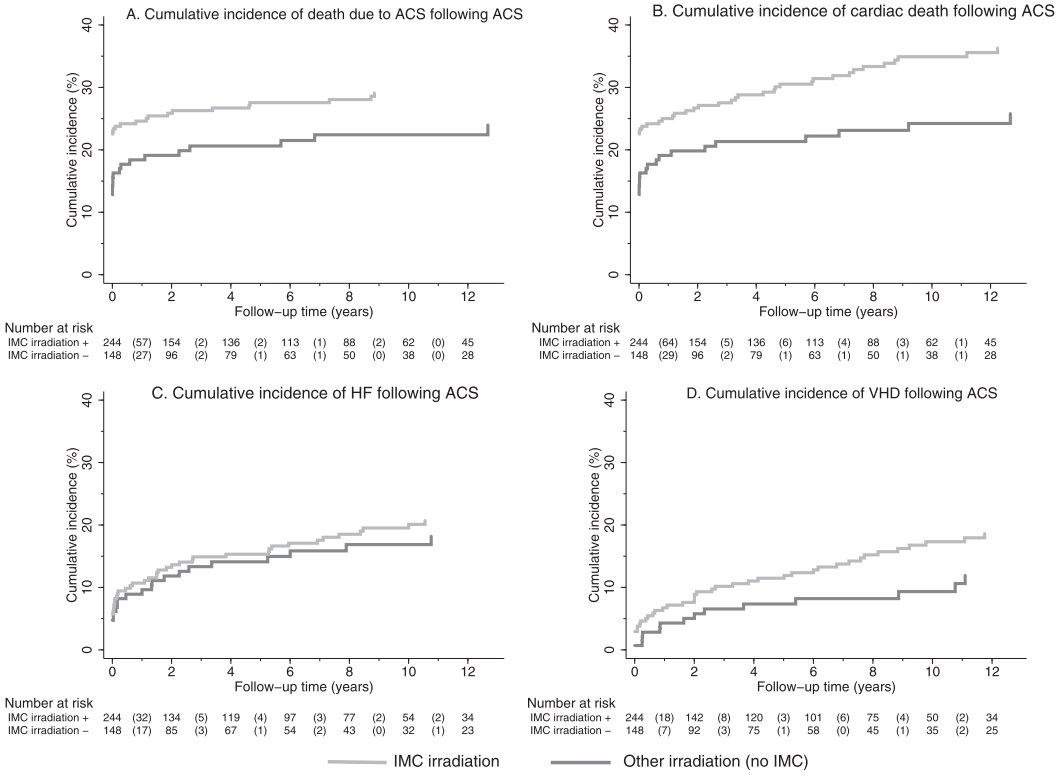

Fig. 1. Cumulative incidence of (A) death due to acute coronary syndrome, (B) cardiac death, (C) heart failure and (D) valvular heart disease following acute coronary syndrome in patients previously treated with radiotherapy for breast cancer, by treatment with internal mammary chain irradiation. Abbreviations: ACS, acute coronary syndrome; IMC, internal mammary chain; HF, heart failure; ACS, acute coronary syndrome; VHD, valvular heart disease. Follow-up time started on the date of acute coronary syndrome. Lines do not start at zero if the event of interest occurred on the day of acute coronary syndrome. Number at risk tables display the number of patients at risk at the given time marks, with the number of events in between the time marks in parentheses. Six patients were diagnosed with distant metastases before acute coronary syndrome and were not included in the analyses.

1.45 95%CI 1.17–1.81) for patients with vs. without a cancer history. This study, however, included any type of cancer patients (including metastatic disease), and data on cancer type, stage, and treatment were not available.

Three studies have investigated the rate of restenosis and (cardiac) death after percutaneous coronary intervention (PCI) comparing patients previously treated with radiotherapy to matched control patients without a history of radiotherapy. However, numbers of patients treated with radiotherapy before PCI were low (15 [32], 41 [33] and 45 [34] patients), and results were inconsistent. Although these studies are not directly comparable and have limitations, they nevertheless suggest that radiotherapy may affect the healing process after microinjury of the coronary arteries, which plays a role in the recovery of all ACS patients. Concordantly, mouse models indicate that the mechanistic pathways behind radiation-induced atherosclerosis might differ from age-related atherosclerosis [14–16].

Regarding cardiovascular morbidity following ACS, we found an increased risk of developing valvular heart disease following ACS in IMC-irradiated patients; possibly this is related to a higher vulnerability of the valves when ischemia occurs [35]. This increase, however, did not reach statistical significance.

When interpreting our results, the strengths and limitations of our study should be considered. Important strengths include the availability of detailed radiotherapy data and extensive data collection from medical charts and from questionnaires sent out to general practitioners and cardiologists, yielding a near to complete follow-up on the occurrence of ACS and its outcome. Unfortunately, however, we had no data on the character and treatment of ACS. Prevalence of ST-elevation ACS and non ST-elevation ACS, the release of cardiac troponins, and specific angiographic data, was not available, whereas these data importantly affect cardiac outcomes. Inherent to studies requiring long-term follow-up since breast cancer diagnosis, current treatments might have been modified. Changes in breast cancer radiotherapy techniques (oblique fields for IMC radiotherapy, intensity modulated radiotherapy and deep inspirational breath hold) have led to significant decrease in cardiac exposure [11]. Because of this, our results cannot be extrapolated to patients receiving IMC-irradiation today; they are, however, very relevant for breast cancer survivors and for other cancer patients who received similar mean heart doses as in our study. Furthermore, albeit with a lower mean heart dose, the heart still is exposed to radiation in patients treated with radiotherapy for (left-sided) breast cancer [11,36]. Darby et al. [9] have shown that even low heart doses increase the incidence of ACS.

In conclusion, radiotherapy is important in treating breast cancer as it improves survival rates and lowers the risk of recurrence [37–40]. However, our results suggest that radiotherapy, in case of substantial heart doses, may worsen the prognosis of subsequent ACS. More research is required to confirm our results and to investigate the pathophysiology underlying our findings. If confirmed, this is important, novel finding may impact upon the risk-based care for breast cancer survivors with coronary syndromes.

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This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.02.007.

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