original article

Excess of cardiovascular mortality among node-negative breast cancer patients irradiated for inner-quadrant tumors

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Background: Radiotherapy of the left breast is associated with higher cardiovascular mortality linked to cardiotoxic effect of irradiation. Radiotherapy of inner quadrants can be associated with greater heart irradiation, but no study has evaluated the effect of inner-quadrant irradiation on cardiovascular mortality.

Patients and methods: We identified 1245 women, the majority with breast-conserving surgery, irradiated for primary node-negative breast cancer from 1980 to 2004 registered at the Geneva Cancer Registry. We compared breast cancer-specific and cardiovascular mortality between inner-quadrant (n = 393) versus outer-quadrant tumors (n = 852) by multivariate Cox regression analysis.

Results: After a mean follow-up of 7.7 years, 28 women died of cardiovascular disease and 91 of breast cancer. Patients with inner-quadrant tumors had a more than doubled risk of cardiovascular mortality compared with patients with outer-quadrant tumors (adjusted hazard ratio 2.5; 95% confidence interval 1.1–5.4). Risk was particularly increased in the period with higher boost irradiation. Patients with left-sided breast cancer had no excess of cardiovascular mortality compared with patients with right-sided tumors.

Conclusions: Radiotherapy of inner-quadrant breast cancer is associated with an important increase of cardiovascular mortality, a possible result of higher irradiation of the heart. For patients with inner-quadrant tumors, the heart should be radioprotected.

Key words: breast cancer, breast quadrant, cardiovascular mortality, population based, radiotherapy

introduction

With improving survival rates following breast cancer, patients are increasingly likely to die of other causes [1]. As a result, long-term adverse effects of treatment are of major concern. Cardiovascular disease is particularly important as it represents the main cause of death among women in developed countries. Therapies that might increase the risk of cardiovascular disease can therefore cause more harm than good. To determine which treatment is optimal, clinicians need to be aware of long-term risks and benefits of adjuvant therapies [2].

Several studies have reported that adjuvant radiation therapy for breast cancer is associated with an increased risk of

cardiovascular mortality [3], probably linked to the cardiotoxicity of radiation, especially in patients with left-sided breast cancer where the heart is more exposed to ionizing irradiation. In an overview of randomized trials, long-term irradiated breast cancer survivors with left-sided tumors had a 34% increased risk of death from cardiovascular disease compared with right-sided tumors [4]. Approximately 50% of the patients in these studies underwent radiation treatment before 1975 and had received radiation with techniques today considered obsolete. Today, with more modern radiation techniques and generalization of cardiac protection for left-sided breast cancer, doses to the heart are lower [5]. A reanalysis of randomized trials after 1975 and recent observational studies report an important decrease of the excess cardiovascular mortality linked to radiation of the left breast [5–9].

In addition to tumor side, tumor location within the breast can influence heart exposure. The heart probably being more exposed

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during radiotherapy of inner-quadrant breast tumors, radiation of these tumors may be associated with higher cardiovascular mortality risk as compared with outer-quadrant tumors.

In this study, we aim to evaluate if radiotherapy of inner-quadrant tumors is associated with an increased cardiovascular mortality risk. As we wanted to assess the cardiotoxicity of radiotherapy, we limited the study to lymph node-negative breast cancer patients for whom other putative cardiotoxic adjuvant treatments are usually not indicated.

patients and methods

patients

We used data from the Geneva Cancer Registry, which records all incident cancers occurring in the population of the canton (~435 000 inhabitants in 2004). All hospitals, pathology laboratories, and practitioners are requested to report all cancer cases. Registrars abstract data from medical and laboratory records. Physicians regularly receive questionnaires to secure missing data. Recorded data include sociodemographic variables, tumor characteristics [coded according to the International Classification of Diseases for Oncology (ICD-O)] [10], stage at diagnosis [coded according to the tumor–node–metastasis (TNM) Classification of Malignant Tumors] [11], and treatment received within 6 months after diagnosis.

The registry regularly assesses survival. The index date refers to the date of confirmation of diagnosis or the date of hospitalization if it preceded the diagnosis and was related to the disease. In addition to passive follow-up (routine examination of death certificates and hospital records), active follow-up is carried out yearly by linking the files of the Cantonal Population Office in charge of the registration of the resident population with the Geneva Cancer Registry database, using personal identification numbers.

Exact cause of death is established by systematically consulting clinical records and/or by inquiring of the patient's physician. The cause of death is coded according to the International Statistical Classification of diseases and health-related problems (ICD) established by the World Health Organization [12].

We considered all patients presenting with a primary, invasive lymph node-negative breast cancer diagnosed from 1980 to 2004 and who had received radiation therapy with curative intent. We excluded women with previous or concomitant invasive cancers (except nonmelanoma skin cancer) ($n = 196$), with central ($n = 78$), overlapping ($n = 622$), or unknown ($n = 17$) quadrant locations. The study finally included 1245 women. Patients were followed up until 30 December 2006.

irradiation techniques

All patients underwent radiation therapy at a single university center. The whole breast was treated by a classical two-tangential-field technique with 25 fractions of 2 Gy using 6 mV photons. All patients with breast-conserving surgery received a boost to the tumor bed by an anterior electron field, usually of 6 or 9 MeV, except for the 100 patients randomly allocated to the no-boost arm of the 22881 EORTC boost–no boost trial from 1991 to 1998 [13] and a few patients aged >75 years. Before 1988, the boost dose was 10 Gy, and then it was increased to 16 Gy. The majority of patients also had an ipsilateral internal mammary chain (IMC) anterior field and received 40 Gy in 16 fractions by a mixture of gamma rays and electrons. After 1990, use of internal chain irradiation importantly decreased with <15% of patients receiving such radiation with a mixture of 6 mV photons and 9–12 MeV electrons and 46 Gy in 23 fractions; an oblique anterior field was substituted for the previous anterior one after 2000.

For all breast cancer patients who died of cardiovascular disease, we consulted the clinical files to collect data on cancer recurrence and type and dose of radiotherapy.

variables

Variables of interest included age (in continuous), year of diagnosis (in continuous), tumor differentiation (I, II, III, and unknown), estrogen receptor (ER) status (positive, negative, and unknown), stage coded according to the TNM Classification of Malignant Tumors, surgery (breast-conserving, mastectomy), chemotherapy (yes, no), and hormonal therapy (yes, no). We considered laterality (right, left) and anatomical breast locations (outer quadrants ICD-O code: C50.4, C50.5, and C50.6; inner quadrants: C50.2 and C50.3). Detailed type of surgery was available only from 1989 and ER status only from 1995.

Cause of death was considered in the following three groups: (i) death from breast cancer (ICD C50), (ii) death from cardiovascular disease (ICD I00-I99), and (iii) overall mortality. Additionally, we separately considered death from cardiac disease (ICD I10-I15, I20-I28, I30-I52) and death from other vascular diseases (ICD I00-I09, ICD I60-I99).

statistical analysis

Using chi-square test for heterogeneity (for categorical variables) and Fisher exact t-test (for continuous variables), we compared patient and tumor characteristics and treatment. We compared cardiovascular, breast cancer-specific, and overall mortality between patients with left- versus right-sided breast cancer and with inner-quadrant versus outer-quadrant breast cancer by log-rank tests and by Cox regressions. To evaluate the independent effect of breast cancer laterality, we adjusted mortality risk for variables associated to laterality and cardiovascular disease, breast cancer-specific or overall mortality, respectively. To asses the effect of breast quadrants on mortality risks, we adjusted for factors associated to breast quadrants, cardiovascular disease, breast cancer-specific or overall mortality, respectively. As ER status and tamoxifen use were highly correlated, we adjusted only for ER status.

In order to examine if the effect of irradiation linked to quadrant on cardiovascular mortality differed across age group, type of surgery, use of chemotherapy, use of hormonal therapy, and laterality, we carried out interaction tests. Interaction terms involved quadrant (inner, outer) and age group (<50, ≥50), surgery (breast-conserving surgery, mastectomy), chemotherapy (yes, no), hormonal therapy (yes, no), or laterality (left, right). We also carried out separate analyses to assess the differences in the use of internal mammary lymph node chain irradiation and in the dose of the boost. We considered the following three categories: high level of IMC irradiation and low boost dose (1980–1987), high-level IMC and high boost dose (1988–1990), and low IMC and high boost dose (1991–2004).

All tests were two sided and differences were considered statistically significant at P value <0.05. All analyses were done with SPSS software (Version 14; SPSS Inc., Chicago, IL).

results

Of 1245 patients, 393 (32%) had tumors in the inner quadrants and 852 (68%) in the outer quadrants. The mean follow-up was 7.7 years and 155 women died: 28 of cardiovascular disease including 19 of cardiac disease and nine of other vascular diseases, 91 of breast cancer, and 36 of other causes.

Age, tumor size, T classification, and use of chemotherapy were equally distributed between breast laterality and quadrants (Table 1). The proportion of estrogen-positive tumors was slightly but significantly higher in the right breast than in the left (57.3% versus 52.3%; $P = 0.031$) and hormonal therapy

Table 1. Characteristics of irradiated breast cancer patients according to laterality and quadrant

Characteristics	Laterality		P value	Quadrant		P value
	Right, n (%)	Left, n (%)		Outer, n (%)	Inner, n (%)	
Mean age (years)	57.7	57.2	0.439	57.2	57.9	0.320
Mean tumor size (mm)	17.0	17.5	0.301	17.1	17.7	0.258
Year of diagnosis						
1980–1990	109 (19.3)	135 (19.9)		155 (18.2)	90 (22.9)	
1991–2004	456 (80.7)	544 (80.1)	0.794	697 (81.8)	303 (77.1)	0.052
T classification						
T1	433 (76.6)	518 (76.3)		656 (77.0)	296 (75.3)	
T2	118 (20.9)	143 (21.1)		178 (20.9)	83 (21.1)	
T3–T4	12 (2.1)	15 (2.2)		15 (1.8)	12 (3.1)	
Unknown	2 (0.4)	3 (0.4)	0.994	3 (0.4)	2 (0.4)	0.504
Differentiation						
I	207 (36.6)	206 (30.3)		294 (34.5)	120 (30.5)	
II	204 (36.1)	263 (38.7)		320 (37.6)	147 (37.4)	
III	103 (18.2)	130 (19.1)		166 (19.5)	67 (17.0)	
Unknown	51 (9.0)	80 (11.8)	0.085	72 (8.5)	59 (15.0)	0.004
ER status[a]						
Positive	324 (57.3)	355 (52.3)		467 (54.8)	212 (53.9)	
Negative	43 (7.6)	80 (11.8)		93 (10.9)	30 (7.6)	
Unknown	198 (35.0)	244 (35.9)	0.031	292 (34.3)	151 (38.4)	0.118
Type of surgery[b]						
Breast conserving	483 (85.5)	562 (82.8)		735 (86.3)	311 (79.1)	
Mastectomy	11 (1.9)	25 (3.7)	0.064[c]	19 (2.2)	17 (4.3)	
Unknown	71 (12.6)	92 (13.5)		98 (11.5)	65 (16.6)	0.025[c]
Chemotherapy						
Yes	108 (19.1)	154 (22.7)		185 (21.7)	78 (19.8)	
No	457 (80.9)	525 (77.3)	0.125	667 (78.3)	315 (80.2)	0.453
Hormonal therapy						
Yes	361 (63.9)	373 (54.9)		515 (60.4)	219 (55.7)	
No	204 (36.1)	306 (45.1)	0.001	337 (39.6)	174 (44.3)	0.116
Mean follow-up (years)	7.4	8.0	0.054	7.6	8.0	0.179

[a]Recorded since 1995.
[b]Recorded since 1989.
[c]Calculated chi-square values do not include patients in the category unknown.
ER, estrogen receptor.

was more frequently given for right-sided breast cancer. Also, the proportion of unknown grade was lower for outer than for inner quadrants (8.5% versus 15.0%; $P = 0.004$). The proportion of inner-quadrant cancers was slightly lower in the second than in the first period (30.1% versus 39.2%; $P = 0.012$). Only few patients had mastectomy. Mastectomy was more frequently carried out for left- than for right-sided breast cancer (4.3% versus 2.2%; $P = 0.064$) and for inner-quadrant compared with outer-quadrant tumors (5.2% versus 2.5%; $P = 0.025$).

In univariate Cox analysis, grade, ER status, tumor size, and use of hormonal therapy were significantly linked to breast cancer-specific mortality. For cardiovascular mortality, prognostic factors were age and tumor size (data not shown). Significant prognostic factors for overall mortality were age, period, stage, tumor size, and grade (data not shown).

quadrants

Compared with patients with outer-quadrant tumors, patients with inner-quadrant cancer had worse 10-year overall survival

rates (80.0% versus 87.0%; $P_{log-rank\ test}$ 0.009) and breast cancer-specific survival rates (87.8% versus 90.5%; $P_{log-rank\ test}$ 0.096). Cardiovascular mortality rates were higher among inner quadrants (6.2% versus 1.2%; $P_{log-rank\ test}$ 0.002). Patients with inner-quadrant tumors had a 2.3-fold increased risk of death from cardiovascular disease [Adjusted hazard ratio (HR_{adj}) 2.5, 95% confidence interval (CI) 1.1–5.4, $P = 0.023$] (Table 2; Figure 1). Additional analysis by periods with different radiation protocols showed that the excess of cardiovascular mortality was limited to women diagnosed during 1988–2004. Cardiovascular mortality risk for inner-quadrant tumors was not increased during 1980–1987 when IMC irradiation was high and boost dose was low (HR_{adj} 1.1, 95% CI 0.1–9.2). In contrast, this risk was 11.7 (95% CI 1.1–125) in the period 1988–1990 when IMC irradiation was still in use and the boost dose increased from 10 to 16 Gy. In the period 1991–2004, when IMC radiation declined but boost remained high, the HR_{adj} was 2.6 (95% CI 1.7–7.0) (Table 3).

The risk associated with inner-quadrant tumors was similar for left- and right-sided breast cancer (Tables 4 and 5) Among

Table 2. Number of deaths and crude and adjusted mortality risk (HR) by cause of death according to laterality and quadrant

	Laterality		P value	Quadrant		P value
	Right (N = 565)	Left (N = 679)		Outer (N = 852)	Inner (N = 393)	
Cardiovascular mortality (95% CI)						
No. of deaths	16	12		12	16	
HR_{crude}	1 (reference)	0.55 (0.26–1.16)	0.117	1 (reference)	2.64 (1.25–5.60)	0.011
HR_{adj}	1 (reference)	0.52 (0.24–1.12)[a]	0.095	1 (reference)	2.46 (1.13–5.37)[b]	0.023
10-year mortality cumulative probability	4.5% (2.0–7.0)	1.7% (0.3–3.1)	0.060[c]	1.2% (0.2–2.2)	6.2% (2.9–9.5)	0.002[c]
Breast cancer-specific mortality (95% CI)						
No. of deaths	37	54		52	39	
HR_{crude}	1 (reference)	1.13 (0.74–1.71)	0.580	1 (reference)	1.54 (1.01–2.33)	0.043
HR_{adj}	1 (reference)	1.12 (0.74–1.71)[d]	0.598	1 (reference)	1.40 (0.92–2.15)[e]	0.119
10-year survival	90.1% (86.6–93.6)	89.2% (86.1–92.3)	0.538[c]	90.5% (87.8–93.2)	87.8% (83.5–92.1)	0.096[c]
Overall mortality (95% CI)						
No. of deaths	67	88		89	66	
HR_{crude}	1 (reference)	0.98 (0.71–1.35)	0.890	1 (reference)	1.48 (1.08–2.04)	0.016
HR_{adj}	1 (reference)	0.96 (0.69–1.32)[f]	0.783	1 (reference)	1.37 (0.98–1.89)[g]	0.063
10-year survival	83.2% (78.9–87.5)	85.7% (82.2–89.2)	0.577[c]	87.0% (83.9–90.1)	80.0% (74.7–85.3)	0.009[c]

[a]HRs adjusted for all factors linked to cardiovascular mortality or laterality, i.e. age, tumor size, and ER status.

[b]HRs adjusted for all factors linked to cardiovascular mortality or quadrant, i.e. age, year of diagnosis, tumor size, grade, and type of surgery.

[c]P value for log-rank test.

[d]HRs adjusted for all factors linked to breast cancer mortality or laterality, i.e. tumor size, grade, and ER status.

[e]HRs adjusted for all factors linked to breast cancer mortality or quadrant, i.e. year of diagnosis, tumor size, grade, ER status, and type of surgery.

[f]HRs adjusted for all factors linked to overall mortality or laterality, i.e. age, year of diagnosis, tumor size, grade, ER status, and type of surgery.

[g]HRs adjusted for all factors linked to overall mortality or quadrant, i.e. age, year of diagnosis, tumor size, grade, ER status, and type of surgery.

HR, hazard ratio; HR_{crude}, crude hazard ratio; HR_{adj}, adjusted hazard ratio; CI, confidence interval; ER, estrogen receptor.

patients who died of cardiovascular disease, irradiated patients with breast-conserving surgery for inner-quadrant breast cancer received higher dose to the breast (56.4% versus 48.9% Gy; P = 0.032) than patients with outer-quadrant tumors and received boost to the tumor bed more frequently (38% versus 8%; P = 0.18) (Table 6). However, this last result was not significant. Only few patients received irradiation of the IMC and we observed no difference according to quadrant site (Table 3). Local recurrence occurred in only one patient presenting with right-sided breast cancer of the outer quadrants and who had received additional surgery and radiation to the breast.

Finally, patients irradiated for inner-quadrant versus outer-quadrant breast cancer presented an increased risk of breast cancer-specific mortality significant in nonadjusted analysis [Crude hazard ratio (HR_{crude}) 1.5, 95% CI 1.0–2.3, P = 0.043; HR_{adj} 1.4, 95% CI 0.9–2.2, P = 0.119] and an increased overall mortality risk also significant in nonadjusted analysis (HR_{crude} 1.5, 95% CI 1.1–2.0, P = 0.016; HR_{adj} 1.4, 95% CI 1.0–1.9, P = 0.063).

laterality

Patients with left-sided breast cancer had similar overall, breast cancer-specific, and cardiovascular-specific mortality rates as patients with right-sided breast cancer (Table 2). The HR_{adj} of women with left- versus right-sided breast cancer was 1.0 (95% CI 0.7–1.3) for overall mortality, 1.1 (95% CI 0.7–1.7) for

breast cancer-specific mortality, and 0.5 (95% CI 0.2–1.1) for cardiovascular mortality.

Among patients who died of cardiovascular disease, patients with breast-conserving surgery for left-sided breast cancer received a lower dose tumor boost than patients with right-sided breast cancer (mean dose 11.0 versus 15.7 Gy; P = 0.012) (Table 6).

Additional analysis considering only mortality from cardiac disease (19 deaths) instead of overall cardiovascular mortality confirmed the results presented: the HR_{adj} was 0.7 (95% CI 0.3–1.6) among women with left- versus right-sided breast cancer) and 2.7 (95% CI 1.0–6.8, P = 0.041) among women with inner versus outer quadrant.

None of the interaction tests were significant. With regards to chemotherapy and type of surgery, too few women underwent mastectomy or chemotherapy to provide valuable interaction tests or subgroup analyses. In particular, only 2 of the 30 irradiated women who died of cardiovascular cancer had received chemotherapy. The results remained similar when excluding patients with mastectomy or chemotherapy.

Subgroup analysis showed that the excess of cardiovascular mortality linked to inner quadrant versus outer was similar among patients with hormonal therapy (HR_{adj} 2.4, 95% CI 0.9–6.4) and without (HR_{adj} 2.3, 95% CI 0.6–9.1) and among patients with left- (HR_{adj} 2.17, 95% CI 0.7–7.3) versus right-sided breast cancer (HR_{adj} 2.5, 95% CI 0.9–7.2).
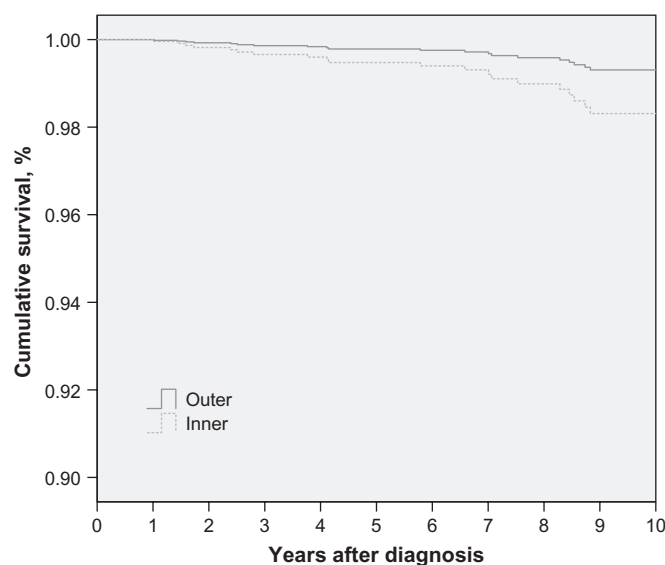
Number of patients at risk at the beginning of each year

Year	1	2	3	4	5	6	7	8	9	10
Outer quadrants	846	795.5	705.5	630.5	559	478.5	408	349	301	259.5
Inner quadrants	390.5	369.5	326.5	288.5	255.5	220.5	196.5	176.5	154.5	130

[a]Survival curves are derived from Cox proportional hazards regression model adjusted for age,

period, tumor size, grade, and type of surgery.

Figure 1. Cardiovascular mortality[a] among irradiated patients according to tumor location.

Table 3. Risk of cardiovascular mortality by quadrant according to levels of boost and IMC[a]

IMC–boost	Quadrant				Risk (95% CI)	P value
	Outer		Inner			
	N	Deaths	N	Deaths		
High IMC–low boost[b] (1980–1987)	72	4	54	2	1.10 (0.13–9.22)	0.928
High IMC–high boost[c] (1988–1990)	83	1	33	3	11.67 (1.09–124.5)	0.042
Low IMC–high boost[b] (1991–2004)	697	7	303	11	2.59 (0.96–6.97)	0.060

[a]Radiation of IMC concerned ∼80% of patients during 1980–1990 and declined to 15% during 1980–1987 and increased to 16 Gy during 1991–2004; boost dose was 10 Gy during 1988–2004.
[b]Adjusted for age, size, grade, and surgery.
[c]Adjusted for age only.
IMC, internal mammary chain; CI, confidence interval.

discussion

To our knowledge, this study is the first to report that patients irradiated for inner-quadrant breast cancer present a more than twofold increased risk of death from cardiovascular disease as compared with patients irradiated for outer-quadrant breast cancer.

Table 4. Risk of cardiovascular mortality linked to quadrant in right- and left-sided breast cancer

Laterality	Quadrant				Risk[a] (95% CI)	P value
	Outer		Inner			
	N	Deaths	N	Deaths		
Right	399	7	166	9	2.51 (0.88–7.18)	0.087
Left	452	5	227	7	2.17 (0.65–7.25)	0.208

[a]Hazard ratios adjusted for age, tumor size, grade type of surgery and period for inner versus outer breast quadrant; only death from cardiovascular disease is considered.
CI, confidence interval.

Radiation therapy is an important component of the local management of breast cancer with significant reductions in the local recurrence, breast cancer mortality risk, and overall mortality [3, 4]. The increase in death from cardiovascular disease among irradiated patients could diminish the benefit of radiation on all survival end points [14]. This could be more important among patients with lymph node-negative breast cancer for whom the benefit of radiotherapy is lower in terms of absolute number of breast cancer deaths [3, 4].

Our results on increased risk of cardiovascular mortality among patients irradiated for inner-quadrant breast cancer should be confirmed by other studies. Although patients were treated in a single institution according to standard protocols,

this study is based on cancer registry data not including information on type and dose of radiotherapy treatment or use of computed tomography simulation for evaluation of doses to critical organs. This is the main limitation of our study.

One can postulate that this excess of mortality linked to inner-quadrant location is related to more frequent radiation of the inner mammary lymph node chain. Irradiation of the IMC has been associated with a more than twofold increased risk of cardiovascular disease whatever the breast cancer laterality [9]. We observed no association between radiotherapy of inner-quadrant breast cancer and cardiovascular mortality for the first period when IMC was irradiated. This association was observed only after 1988, when fewer patients underwent IMC radiation. On the other hand, for the same period, the intensity of the boost importantly increased from 10 to 16 Gy. Also, available data on radiotherapy collected among patients who died of cardiovascular disease show that patients with tumors of the inner quadrants had more often higher boost to the breast and higher dose of breast irradiation than patients with tumors of the outer quadrants. Local recurrence occurred in only one patient with right-sided outer-quadrant breast cancer and who underwent additional surgery and radiation to the breast.

However, these findings could not be extrapolated to the overall population of irradiated patients and we cannot

conclude that boost radiation is at the origin of the excess of cardiovascular risk among patients with inner-quadrant breast cancer.

In our study, the quadrant effect was similar for right- and left-sided breast cancer. Our hypothesis is that boost contributed to the excess of cardiovascular mortality. While this is understandable for left-sided breast cancer, it is not obvious for right-sided tumors, unless the boost fields are extended toward the sternum. Future studies should investigate this further, giving detailed information on radiation treatment.

This study has also inherent limitations due to its observational nature. In theory, no bias exists in the distribution of patient and tumor characteristics according to breast cancer laterality and quadrant. We therefore expected a similar distribution of these variables among patients with left- and right-sided breast cancer or with inner and outer quadrants. We observed that patients with right-sided breast cancer had more often ER-positive tumors, a finding we could not explain. Finally, because of its short follow-up, we cannot definitively rule out a lack of increase in cardiovascular mortality linked to irradiation of the left breast.

This study also reports that tumor location in the inner quadrants is associated with an increased risk of breast cancer-specific mortality. The poorer prognosis of inner-quadrant cancer has been previously reported and largely discussed [15–18]. Patients with tumors of the inner quadrants are probably more prone to have undetected metastases in the IMC. This understaging results in undertreatment with higher breast cancer-specific mortality as a consequence [18].

With regards to laterality, we found no excess risk of cardiovascular mortality among irradiated patients with left-sided breast cancer compared with patients presenting with right-sided tumors.

Adjustments in the beam setup or in field shielding to avoid radiation exposure to the heart during irradiation of left-sided breast cancer has importantly decreased heart irradiation [14] and is probably at the origin of more recent negative reports on the association between laterality and cardiovascular risk [5–9,

Table 5. Risk of cardiovascular mortality linked to laterality in outer- and inner-quadrant breast cancer

Quadrant	Laterality				Risk[a] (95% CI)	P value
	Right		Left			
	N	Deaths	N	Deaths		
Outer	399	7	452	5	0.70 (0.21–2.32)	0.555
Inner	166	9	227	7	0.52 (0.18–1.48)	0.221

[a]Hazard ratios adjusted for age, tumor size, grade type of surgery, and period for inner versus outer breast quadrant; only death from cardiovascular disease is considered.
CI, confidence interval.

Table 6. Type and dose of radiation therapy and cancer recurrence treatment according to laterality and tumor location among irradiated breast cancer patients who died of cardiovascular disease

	Laterality		P value	Quadrant		P value
	Right mean (SE)	Left mean (SE)		Outer mean (SE)	Inner mean (SE)	
No. of patients (N)	16	12		12	16	
Delay between BC and death (days)	2431.7 (353.7)	3258.0 (651.6)	0.245	2645.0 (525.1)	2891.4 (474.0)	0.732
Age (years)	71.5 (2.5)	67.7 (2.3)	0.289	71.0 (1.9)	69.0 (2.7)	0.583
Breast-conserving surgery	12	7	0.60	7	12	0.60
Total dose received (Gy)	52.4 (2.4)	55.7 (2.2)	0.37	48.9 (1.4)	56.4 (2.3)	0.03
Dose to the breast (Gy)	48.5 (0.7)	49.4 (0.7)	0.41	47.5 (1.0)	49.6 (0.4)	0.04
Boost (N)	3	4	0.66	1	6	0.18
Dose of the boost (Gy)	15.7 (0.3)	11.0 (1.0)	0.01	10.0	13.5 (1.2)	0.30
Mastectomy	2	3	0.71	3	2	0.71
Total dose received (Gy)	52.3 (7.3)	56.5 (3.6)	0.59	54.5 (4.8)	55.3 (5.8)	0.93
Dose to the chest wall (Gy)	47.3 (2.3)	47.5 (1.0)	0.91	47.2 (1.3)	47.8 (1.8)	0.80

SE, standard error; BC, Breast cancer diagnosis.

19–22]. However, several recent studies still report higher cardiovascular mortality in patients with left-sided breast cancer [23–26]. Also, the follow-up of our study is relatively short compared with most previous studies, which reported an excess of cardiovascular mortality linked to laterality after 10 years. Our data do not allow us to conclude that irradiation of left-sided breast cancer has no more effect on cardiovascular mortality.

We conclude that women irradiated for tumors of the inner quadrants have an important increased risk of cardiovascular mortality, probably linked to higher radiation exposure to the heart due to the site of the boost. If our results are confirmed, this adverse effect should be taken into account with the expected benefits of such irradiation. Like for left-sided breast cancer, adequate cardiac protection should be provided for radiation therapy for inner-quadrant breast cancer.

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