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Clinical Investigation

Long-term Cardiac Mortality After Hypofractionated Radiation Therapy in Breast Cancer

Kristin Holm Tjessem, MD,* Safora Johansen, PhD,† Eirik Malinen, PhD,‡ Kristin V. Reinertsen, MD, PhD,* Turi Danielsen, PhD,‡ Sophie D. Fosså, MD, PhD,* and Alexander Fosså, MD, PhD*

**Department of Oncology, Oslo University Hospital, National Resource Centre for Late Effects after Cancer Treatment; †Department of Oncology, Oslo University Hospital-Radium Hospital, and Division of Radiotherapy/Radiography, College of Oslo and Akershus, Faculty of Health; and ‡Department of Medical Physics, Oslo University Hospital, Oslo, Norway*

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Summary

This was a retrospective case−control study of mortality from ischemic heart disease in 1566 breast cancer patients followed up for >20 years after locoregional radiation therapy. Hypofractionation with 4.3 Gy × 10 and parasternal irradiation with photon beams were significantly associated with increased risk of mortality. Differences in mortality emerged after more than 10 years. This emphasizes the need of long follow-up before conclusions can be made regarding the safety of hypofractionated radiation therapy.

Purpose: To explore very-long-term mortality from ischemic heart disease (IHD) after locoregional radiation therapy of breast cancer (BC) in relation to degree of hypofractionation and other treatment variables.

Methods and Materials: Two hypofractionated regimens used for locoregional radiation therapy for BC from 1975 to 1991 were considered. Patients received 4.3 Gy × 2/week (10 fractions; target dose 43 Gy; n=1107) or 2.5 Gy × 5/week (20 fractions; target dose 50 Gy; n=459). To estimate cardiac doses, radiation fields were reconstructed in a planning system. Time to death from IHD was the endpoint, comparing the groups with each other and with age-matched, cancer-free control individuals, modeled with the Cox proportional hazards model.

Results: Patients given 4.3 Gy × 10 had an increased risk of dying of IHD compared with both the 2.5 Gy group (hazard ratio [HR] = 2.37; 95% confidence interval [CI]: 1.06-5.32; $P=.036$) and the control group (HR = 1.59; 95% CI: 1.13-2.23; $P=.008$). Photon beams for parasternal fields gave an increased risk of dying of IHD compared with electron beams (HR = 2.56; 95% CI: 1.12-5.84; $P=.025$). Multivariate analysis gave an increased risk for the 4.3-Gy versus 2.5-Gy regimen with borderline significance (HR = 2.90; 95% CI: 0.97-8.79; $P=.057$) but not for parasternal irradiation.

Conclusions: The degree of hypofractionation and parasternal photon beams contributed to increased cardiac mortality in this patient cohort. Differences emerged after 12 to 15 years, indicating the need of more studies with observation time of 2 decades.

Reprint requests to: Kristin Holm Tjessem, MD, Department of Oncology, Oslo University Hospital, National Resource Centre for Late Effects after Cancer Treatment, Postboks 4953, Nydalen, 0424 Oslo, Norway. Tel: (+47) 99-70-92-49; E-mail: krtjes@ous-hf.no

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Introduction

During the past 5 decades, locoregional megavoltage radiation therapy has been used successfully together with surgery and chemotherapy in the treatment of breast cancer (BC), reducing the risk of local recurrence and prolonging the patients' lives.

In the middle of the 1960s, hypofractionated radiation therapy was introduced based on the recognition of moderate radiosensitivity of BC cells. Lack of radiation therapy capacity also promoted the initiation of hypofractionation, allowing resource-saving treatment schedules. Radiobiologic models of that time were used to equalize different fractionation regimens with respect to normal tissue toxicity (1, 2). However, around 1980, it became evident that late adverse effects in normal tissue were unexpectedly high after hypofractionated radiation therapy (2, 3).

During the past decade, hypofractionated radiation therapy has been reintroduced. Current regimens are often less hypofractionated than in earlier decades, and computer tomography (CT)-based conformal treatment planning is mainly used, aiming also to reduce the dose to critical organs such as the heart. Reports on approximately 10-year follow-up of patients receiving such radiation therapy are promising regarding efficacy and toxicity (4, 5). However, it is known from long-term survivors of different cancer types, including BC, that cardiovascular side effects may become clinically manifest several decades after radiation therapy (6).

We analyzed the 20-year risk of death of ischemic heart disease (IHD) in BC patients who received hypofractionated locoregional radiation therapy at Norwegian Radium Hospital from 1975 to 1991. At that time, 2 hypofractionated radiation regimens were used: 4.3 Gy $\times$ 10 and 2.5 Gy $\times$ 20. In 1998, a systematic survey among survivors treated with these schedules revealed a higher level of side effects after the 4.3-Gy schedule compared with published findings after traditional radiation therapy, and compared with the 2.5-Gy schedule. The results of this survey are available as an internal report (Eriksetin B and Kvinnsland S, personal communication). An additional 15 years have now elapsed, enabling comparison of cause-specific mortality in the 2 patient cohorts. We aimed to explore long-term IHD mortality in relation to the degree of hypofractionation and other treatment variables.

Methods and Materials

Patients

Eligible patients, identified from the Norwegian Radium Hospital (NRH) radiation therapy registry, were women with no malignancy before their first-time diagnosis of BC (nonmelanoma skin cancer allowed), who received local or locoregional radiation therapy with treatment beginning in 1975 to 1991. Patients receiving reirradiation of the same region were excluded. Data were retrieved from 3 registries: (*1*) NRH radiation therapy registry: date of treatment start, target volume and dose, fractionation pattern, type of radiation and energy (Co^{60}, linear accelerator, photons, electrons); (*2*) Cancer Registry of Norway (CRN): date of diagnosis, stage, laterality, date and cause of death. To assess the quality of register data, 100 patient charts were reviewed. The most likely cause of death in nearly all patients was determined, and this coincided with the cause reported by CRN. (*3*) Statistics Norway supplied 10 randomly selected cancer-free control individuals per patient matched on age, education, and county of residence.

We used ICD-9 and ICD-10 to classify causes of death as BC (ICD-9174, ICD-10 C.50.9), IHD (ICD-9410-414, ICD-10 I20-I25), cardiovascular disease (CVD, ICD9 390-459, ICD 10 I00-I99) and other causes. Since it was the most prevalent cause of cardiac death, only death resulting from IHD was considered in the present analysis.

Treatment strategies

In the 1970s and early 1980s, the majority of BC patients in Norway underwent modified or radical mastectomy with or without axillary lymph node dissection. Toward the end of the 1980s, breast-conserving treatment became available. Adjuvant chemotherapy or hormone treatment was frequently given to patients with stage II and III disease, but none of the registries used provided reliable data. Two fractionation patterns of radiation therapy were analyzed: 4.3 Gy $\times$ 10 given as 2 weekly fractions or 2.5 Gy $\times$ 20 applied as 4 weekly fractions, both for 5 weeks. The regimens were in use contemporarily between 1975 and 1991, but the 4.3 Gy $\times$ 10 was gradually superseded during that time by the 2.5 Gy $\times$ 20 regimen. The choice of regimen for each individual patient was based on practical considerations and to some extent on the stage of the disease.

The arrangement of tangential (TF), parasternal (PF), axillary, and/or supraclavicular fields was dependent on the clinical situation of the individual and based on national treatment guidelines at the time. TFs did not cover the parasternal lymph nodes and were used postoperatively in patients after breast-conserving treatment, in those with tumor-positive margins after mastectomy, preoperatively to downstage larger tumors, or applied as definite therapy in inoperable stage III patients. A PF was applied to most patients with stage II and III disease. In stage II patients with central/medial tumors without known axillary metastases, the PF was used before 1985 but mostly omitted thereafter. The PF was drawn 5 cm wide, with the medial border in the sternal midline, proximal and distal margins just below the sternal head of the clavicle, and at the level of the xiphoid process, respectively. A supraclavicular field including the axillary apex was applied together with a PF in axillary lymph node-positive patients with centrally or medially located tumors, with measures taken to omit overdosage in the border area between the PF and supraclavicular field. An axillary field was added when axillary lymph node dissection was deemed nonradical. In patients with locoregional recurrence, combinations of the fields above were used according to the individual situation. Radiation therapy was given mainly by ^{60}Co units or linear accelerators with 5-MV photons, but electron beams (10-16 MeV) were used with increasing frequency over time in PFs.

To obtain approximate values for cardiac doses, the outlined field arrangements were simulated for left-sided and right-sided BC in CT planning images of a patient of normal build using Oncentra, version 4.1 (Nucletron BV, Veenendaal, The Netherlands). For tangential, supraclavicular, and axillary fields, 4-MV photons were used; also, 4-MV photons were chosen as the corresponding depth dose characteristics in between ^{60}Co and 5-MV beams. For PFs, either 4-MV photons or 12-MeV electrons were used. Dose-volume histograms for the heart were extracted, and the dose was converted to equivalent dose in fractions of 2 Gy using the linear quadratic cell survival formalism and a/b = 3 Gy

(7). The equivalent dose delivered to 5% of the volume ($D_{5\%}$) was used as the representative dose to the heart.

Statistics

Continuous variables were described using medians and ranges and categoric variables as proportions. Groups were compared using the Mann-Whitney *U* test and χ^2 test as appropriate. Time to death of IHD was right truncated at 20 years. The effects of selected covariates were modeled using Cox proportional hazards models adjusted for age (when comparing patient groups) and stratified by matched set (for comparison between patients and control individuals). Results were expressed with hazard ratios (HR) and 95% confidence intervals (CI). *P* values <.05 were considered statistically significant. Analyses were performed using SPSS, version 18.0.

Results

Dosimetric data

Preliminary analyses showed that only the PF and TFs contributed significantly to cardiac dose, and only these fields were considered further. In Table 1, $D_{5\%}$ resulting from different field arrangements is listed. The PF gave higher doses to the heart compared with other fields, and left-sided disease and photons for PF were associated with higher doses than were right-sided disease or electron beams. For a given arrangement, the equivalent $D_{5\%}$ doses in the 4.3-Gy and 2.5-Gy regimens were rather similar, as were the corresponding dose-volume histograms (data not shown). However, the 4.3-Gy regimen always gave slightly higher doses for the field arrangements resulting, in significant exposure to the heart.

Patients' characteristics

We identified 1321 patients treated with 4.3 Gy × 10 and 595 patients treated with 2.5 Gy × 20. Of these, 214 in the 4.3-Gy group and 136 in the 2.5-Gy group were excluded owing to violations of the eligibility criteria, mostly because they had received treatment to metastatic, not local or locoregional disease, resulting in 1107 and 459 eligible patients in the 2 groups (Table 2).

The median age at irradiation was similar in both groups, and there was no difference in BC laterality. Most of the patients had stage II or III disease. There was a higher proportion of patients with stage III disease in the 2.5-Gy group (30.5% vs 17.9%, *P*<.001) and a larger proportion with stage IV disease in the 4.3-Gy group (11.7% vs 8.5, *P*<.001). The median follow-up time of the 226 surviving patients was 20 years in both groups, but 16 patients in the 2.5-Gy group had a shorter follow-up time than 20 years (range, 18.2-20 years) (*P*<.001).

In the 4.3-Gy group, 90.9% of patients received radiation therapy including a PF, compared with 35.3% in the 2.5-Gy group (*P*<.001). The proportions of patients with left-sided or right-sided BC who received a PF were not significantly different: 74.2% and 76.4%, respectively.

Treatment groups and causes of death

In the 4.3-Gy group, 954 patients (86%) died, compared with 386 (84%) in the 2.5-Gy group. Death due to BC was registered for 806 patients (72%) in the 4.3-Gy group and 335 (73%) in the 2.5-Gy group. There was no difference in either overall mortality or BC mortality between the groups (Table 3).

In the 4.3-Gy group, 40 patients (4%) died of IHD, compared with 7 patients (2%) in the 2.5-Gy group. In Cox regression analysis, patients in the 4.3-Gy group had an increased risk of death due to IHD compared with patients treated with 2.5 Gy (HR = 2.37, CI: 1.06-5.32, *P* = .036), with the difference emerging first after 10 to 15 years (Fig. 1).

Parasternal irradiation as such was not associated with increased mortality from IHD when patients from both fractionation schedules were compared. However, within the group of patients who received a PF, photon beams were associated with an increased risk of dying of IHD compared with electron beams (HR: 2.56, 95% CI: 1.12-5.84, *P* = .025).

Treatment before 1984 was associated with an increased risk of dying of IHD (HR: 2.87, CI: 1.34-6.17 *P* = .006) compared with treatment from 1984 onward. Patients treated for left-sided cancer did not have increased risk of dying of IHD compared with right-sided BC.

Treatment groups versus control group

Patients in the 4.3-Gy group had increased risk of dying of IHD compared with their control individuals (HR: 1.59, CI: 1.13-2.23, *P* = .008). No elevated risk of death resulting from IHD was found in the 2.5-Gy group compared with control individuals (Table 3).

Compared with control individuals, patients treated with parasternal photon fields had an increased risk of dying of IHD (HR: 1.79, CI: 1.21-2.67, *P* = .004). Treatment with parasternal electron beams was not associated with an increased risk of dying of IHD when patients and control individuals were compared.

Patients receiving radiation therapy before 1984 had an increased risk of dying of IHD (HR: 1.67, CI: 1.18-2.36, *P* = .004) when compared with control individuals, whereas patients treated from 1984 to 1991 did not.

Multivariate and subgroup analyses

Fractionation regimen and the use of different beam qualities for PFs, both treatment factors associated univariately with IHD mortality, were entered into a multivariate Cox model (Table 4). The 4.3-Gy group retained its association with an increased risk of IHD, but with borderline significance only (HR = 2.90; 95% CI: 0.97-8.76; *P* = .057). The use of PFs with either photons or electrons was not associated with increased risk. Strong association with the other 2 parameters prohibited entry of treatment period as a variable in the model. A subgroup analysis of all patients having received a PF (n = 1168) gave an increased risk for the 4.3 Gy × 10 fractionation regimen compared with the 2.5 Gy × 20, again with borderline significance (HR = 6.3; 95% CI: 0.96-45.97; *P* = .069). Analyses of the impact on fractionation in subgroups with different beam qualities for PF were not informative.

Discussion

This retrospective study analyzed BC patients treated until 1991 with local or locoregional radiation therapy, most of them also with a PF. The study results indicate that highly hypofractionated

Table 1 Dose to 5% of heart volume ($D_{5\%}$) converted to equivalent dose in fractions of 2 Gy

	Right-sided disease		Left-sided disease	
Type of radiation	4.3 Gy × 10-2 Gy eq*	2.5 Gy × 20-2 Gy eq	4.3 Gy × 10-2 Gy eq	2.5 Gy × 20-2 Gy eq
TF	0.6	0.7	1.0	1.1
Electrons in PF	0.3	0.3	21.3	20.5
Photons in PF	24.0	22.9	53.1	47.2
TF + electrons in PF	0.8	1.0	30.3	28.3
TF + photons in PF	26.5	25.0	52.5	46.7

Abbreviations: TF = tangential field; PF = parasternal field.
* Dose converted to equivalent of 2 Gy per fraction.

radiation therapy and parasternal photon beam irradiation may both be associated with increased risk of death resulting from IHD. Differences were found for patients treated with 4.3-Gy fractions compared with 2.5-Gy fractions and for patients treated with parasternal photon beams compared with electron beams. For both treatment parameters, differences also emerged in comparison with matched healthy women. Multivariate analysis suggested that the degree of hypofractionation is the most important contributor to IHD mortality. The findings underscore the need for longer follow-up of recent trials before conclusions can be made about the safety of contemporary hypofractionated radiation therapy (4, 5, 8, 9).

Recently, several studies have evaluated hypofractionated radiation therapy in BC, most notably the randomized controlled trials START A and B. The endpoints of these trials are locoregional tumor relapse, late normal tissue effects, and

Table 2 Patient demographics, treatment variables, and causes of death

Characteristic	4.3 Gy × 10	%	2.5 Gy × 20	%	*P* Value
Total number of patients	1107	-	459	-	-
Median age, years (range)	58.8 (23.6-85.3)	-	58.4 (25.6-94.1)	-	.810
Laterality					
Right	500	45.2	225	49.0	.165
Left	607	54.8	234	51.0	-
Median observation time/years (range)					
All patients	4.5 (0.1-20.0)	-	3.9 (0.1-20.0)	-	.043
Surviving patients	20 (20-20)	-	20 (18.2-20)	-	<.001
Stage					
1	212	19.2	75	16.3	-
2	553	50.0	201	43.8	-
3	198	17.9	140	30.5	<.001
4	129	11.7	394	8.5	-
Unknown	15	1.4	4	0.9	-
Field arrangement					
Including parasternal field					
Parasternal and tangential fields	706	63.8	99	21.6	-
Parasternal and fields other than tangential	300	27.1	63	13.7	-
Without parasternal field	-	-	-	-	<.001
Including tangential field	74	6.7	274	59.7	-
Including fields other than tangential	12	1.1	8	1.7	-
Unknown	15	1.3	15	3.3	-
Beam quality (in parasternal field)					
Electrons	246	24.5	114	70.4	<.001
Photons	760	75.5	48	29.6	-
Treatment period					
1977-1983	945	85.4	36	7.8	<.001
1984-1991	162	14.6	423	92.2	-
Total number of deaths	954	86.2	386	84.1	.469
Cause of death					
Breast cancer	806	72.8	335	73.0	.243
Cardiovascular disease	73	6.6	21	4.6	.091
Ischemic heart disease	40	3.6	7	1.5	.036
Other causes	75	6.8	30	6.5	.933

Table 3 Univariate Cox regression analysis of treatment parameters and risk of death resulting from ischemic heart disease

Treatment variable	Ischemic heart disease		
	HR	95% CI	*P* value
4.3 Gy vs 2.5 Gy	2.37	1.06-5.32	.036
4.3 Gy vs controls	1.59	1.13-2.23	.008
2.5 Gy vs controls	0.78	0.36-1.68	.530
Parasternal field radiation vs no parasternal field radiation	0.915	0.43-1.97	.820
Photon beams vs electron beams	2.56	1.12-5.84	.025
Photon beams vs no parasternal radiation	1.41	0.65-3.08	.383
Electron beams vs no parasternal radiation	0.76	0.54-1.27	.300
Photon beams vs controls	1.79	1.21-2.67	.004
Electron beams vs controls	0.76	0.35-1.64	.480
No parasternal radiation vs controls	0.99	0.48-2.07	.985
Early treatment (1977-1983) vs late treatment (1984-1991)	2.87	1.34-6.17	.006
Early treatment vs controls	1.67	1.18-2.36	.004
Late treatment vs controls	0.74	0.36-1.53	.416
Laterality (left vs right)	0.93	0.52-1.66	.812

Abbreviations: CI = confidence interval; HR = hazard ratio.

quality of life. START A compared 3 patterns of fractionation: 3.2 × 13 (41.6 Gy), 3.0 Gy × 13 (39 Gy), and the conventional 2.0 Gy × 25 (4). With a median observation time of 5.1 years, 3.2 Gy × 13 was found to be similar to the conventional regimen (2.0 Gy × 25) in terms of local tumor control and late normal tissue effects. The 39-Gy regimen had a lower rate of late effects but was associated with an increase in locoregional relapse. In START B, women with early BC received either 2.0 Gy × 25 (50 Gy) over 5 weeks or 2.67 Gy × 15 (40 Gy) over 3 weeks. After a median follow-up time of 6 years, the findings indicated lower rates of late effects by photographic and patient-reported assessments in the hypofractionated regimen compared with the conventional regimen (8). In the UK FAST trial, women were randomly assigned to 50 Gy in 25 fractions or to a total dose of 28.5 or 30 Gy, given as once-weekly fractions of 5.7 or 6.0 Gy, respectively (10). After a median follow-up time of 3 years, the 28.5-Gy schedule was comparable with the 50-Gy regimen, whereas the patients given the 30 Gy regimen had a significantly higher risk of late adverse effects. Notably, the late effects studied in START trials A and B and UK FAST trials involve cosmetic outcome only, and no long-term cardiac morbidity or mortality has been reported yet.

Marhin et al (11) studied the impact of fraction size on cardiac mortality in a retrospective population-based study including 7447 women irradiated with TFs only. The median follow-up time was 7.9 years. There was no difference in cardiac mortality in women treated with hypofractionated regimens (most frequently 2.5-2.75 Gy per fraction) compared with those treated with fractions of 1.8 to 2 Gy. There was a nonsignificant trend toward increased cardiac mortality for patients with left-sided BC treated with fractions >2 Gy. Because patients with PFs were excluded, cardiac doses were probably lower than in our cohort, reflected in a lower rate of cardiac deaths: 1.3% of patients dying of cardiac events compared with 3% dying of IHD alone in our series. We did not find any

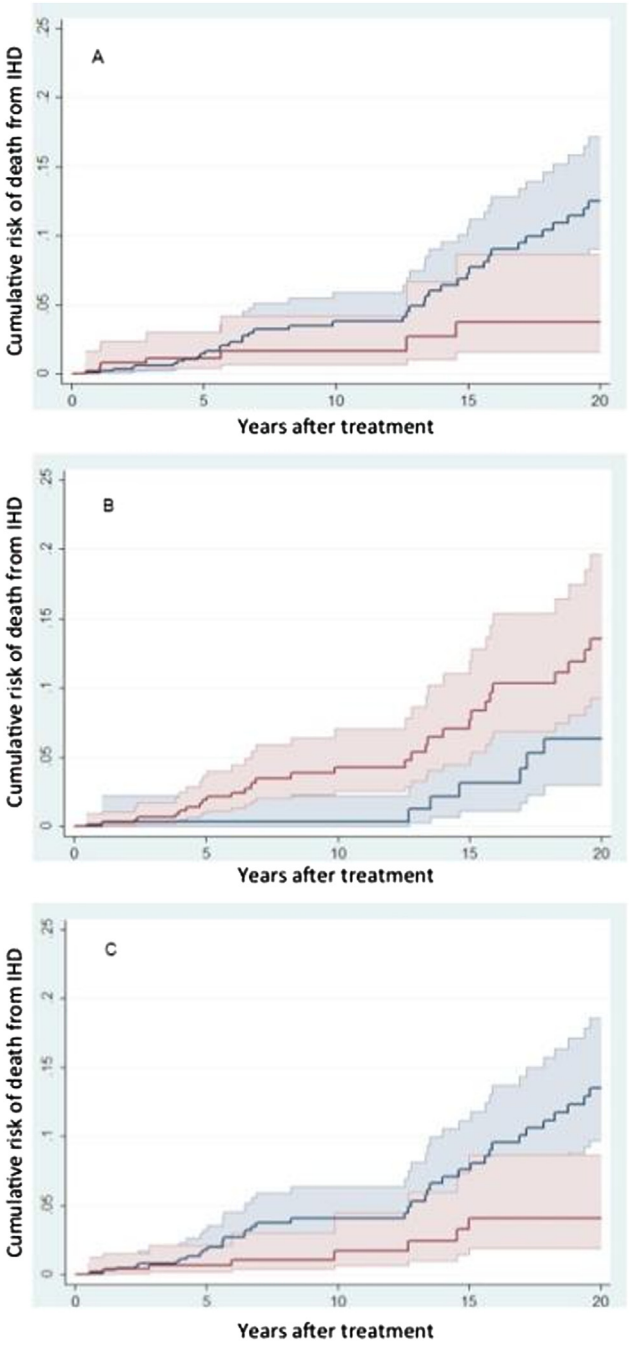

Fig. 1. Cumulative risk of death from ischemic heart disease (IHD) (A) 4.3-Gy group (blue line) versus 2.5-Gy group (red line). (B) Parasternal electron radiation (blue line) versus parasternal photon radiation (red line). (C) Treatment years 1975-1983 (blue line) versus treatment years 1984-1991 (red line).

excess mortality in our 2.5-Gy group, the group that less frequently received PFs, supporting the notion that moderately hypofractionated regimens without parasternal irradiation seem to be associated with little excess cardiac mortality.

The fractionation regimens compared in the present study were used contemporarily for similar groups of patients, and also in part in competition with the more regular 2.0 Gy × 25 regimen. Because there was no randomization or otherwise specified patient

Table 4 Multivariate Cox regression analysis of treatment parameters and risk of death resulting from ischemic heart disease

	Ischemic heart disease		
Treatment variable	HR	95% CI	*P* Value
4.3 Gy vs 2.5 Gy	2.90	0.97-8.76	.057
Photon beams vs no parasternal radiation	0.70	0.26-1.88	.695
Electron beams vs no parasternal radiation	0.34	0.11-1.04	.336

Abbreviations: CI = confidence interval; HR = hazard ratio.

selection for the different regimens, the groups were not fully balanced for important patient and treatment parameters, all of which may have influenced the outcome. Some of these differences in patient selection we may have detected, whereas others may have passed unrecognized and thus represent unknown confounders in our analysis. We do not, however, believe that differences in stage of BC between the groups is important, because the risk of death resulting from IHD, once a patient has become a long-term survivor, is probably not influenced by stage or other BC-related parameters. However, patients with the 4.3 Gy $\times$ 10 regimen more often received parasternal irradiation shown in our simplified and retrospective dose planning with modern CT to contribute most to cardiac doses. We found no difference in IHD mortality when comparing patients who did or did not receive a PF. However, there was an increase in death resulting from IHD in patients receiving parasternal photon fields compared with electrons. The role of PF irradiation in BC is debatable. Nilsson et al (12) found an increased risk of coronary artery stenosis after radiation therapy, including parasternal photon beams to both the left and the right internal mammary chain, and several studies have found increased risk of cardiac disease in patients irradiated with such fields (13, 14). On the other hand, Højris et al (15) found no increase in morbidity or mortality from IHD in a randomized trial comparing adjuvant radiation therapy, including a parasternal electron field, with no radiation therapy.

The present study showed no differences in IHD mortality comparing left-sided with right-sided disease. This is in contrast to other studies demonstrating an increased risk of cardiac death after treatment for left-sided BC (16). Not all studies confirm this, however (17, 18). Frequent irradiation toward the right internal mammary chain in the present study may be an explanation for this discrepancy. A right-sided PF is associated with a lower total cardiac dose, but important structures such as the right proximal coronary artery will receive similar doses as do structures on the left side in left-sided fields, probably putting the patient at risk of IHD and death (12). Furthermore, most studies showing a difference in cardiac morbidity or mortality between left-sided and right-sided BC have studied cohorts considerably larger than those reported herein or with TFs only, and thus may have a higher power to detect such differences (16, 19, 20).

The patient cohort and the treatment studied in this report are no longer in use, especially relating to the simple 2-dimensional treatment planning and the use of PFs, even with photons, in most patients. Furthermore, we have no individual cardiac dose parameters to relate to outcome. This limits the applicability of the results to contemporary treatment of BC. However, modern patients receive more complex treatments, including other cardiotoxic components (anthracyclines, trastuzumab) and have a better prognosis concerning their BC. This may aggravate the problems of cardiac late sequelae of radiation therapy, possibly also relating to excess risk brought about by hypofractionation.

In conclusion, the degree of fractionation and photon beams in the PF contributed to increased IHD mortality in this patient cohort. The differences in IHD mortality emerged 12 to 15 years after treatment, and the increased risk among BC patients treated with hypofractionated radiation therapy thus indicates that a follow-up time of at least 2 decades is needed to evaluate safety of such irradiation.

References

1. Winston BM, Ellis F, Hall, et al. The Oxford NSD calculator for clinical use. *Clin Radiol* 1969;20:8−11.
2. Fletcher GH. Hypofractionation: Lessons from complications. *Radiother Oncol* 1991;20:10-15.
3. Bates TD. The 10-year results of a prospective trial of post-operative radiotherapy delivered in 3 fractions per week versus 2 fractions per week in breast carcinoma. *Br J Radiol* 1988;61:625-630.
4. The UK. Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet Oncol* 2008;9:331-341.
5. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;81:59-68.
6. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-565.
7. Dörr W. Pathogenesis of normal tissue side effects. In: Joiner M, van der Kogel A, editors. Basic Clinical Radiobiology. 4th ed. London: Hodder Arnold; 2009. p. 178-181.
8. The UK. Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet* 2008;371:1098-1107.
9. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; 362:513-520.
10. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiother Oncol* 2011;100:93-100.
11. Marhin W, Wai E, Tyldesley S. Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localized breast cancer. *Int J Radiat Oncol Biol Phys* 2007;69:483-489.
12. Nilsson G, Holmberg L, Garmo H, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012;30:380-386.
13. Hooning MJ, Botma A, Aleman BMP, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;99:365-375.
14. Paszat LF, Vallis KA, Benk VMA, et al. A population-based case-cohort study of the risk of myocardial infarction following radiation therapy for breast cancer. *Radiother Oncol* 2007;82:294-300.
15. Højris I, Overgaard M, Christensen JJ, et al. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: Analysis of DBCG 82b and 82c randomised trials. *Lancet* 1999;354:1425-1430.
16. Darby S, Mc Gale P, Peto R, et al. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: Nationwide cohort study of 90 000 Swedish women. *BMJ* 2003;326: 256-257.

17. Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst* 2005;97: 419-424.
18. Doyle JJ, Neugut AI, Jacobson JS, et al. Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients. *Int J Radiat Oncol Biol Phys* 2007;68:82-93.
19. McGale P, Darby SC, Hall P, et al. Incidence of heart disease of 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol* 2011;100:167-175.
20. Borger JH, Hooning MJ, Boersma LJ. Cardiotoxic effect of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. *Int J Radiat Oncol Biol Phys* 2007;69:1131-1138.