BRÖSTCANCER FÖRBUNDET

Forskningsrapport

Huvudsökande:
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Frågeställning:
Är dagens strålbehandling efter bröstbevarande kirurgi säker?

Tre frågor till Fredrika:

Hur kan resultatet av er forskning hjälpa patienterna, rent konkret?
Strålbehandling efter bröstbevarande kirurgi är en väsentlig del av behandlingen för en stor del av kvinnor med tidig bröstcancer. Med gammal teknik, och stora strålfält kunde strålbehandlingen förr ge biverkningar i form av ökad risk för död i hjärtsjukdom.

Vi har nu redovisat på individnivå hur det gick för de patienter som behandlades inom ramen för studien SweBCG 91A med start 1991, och har kunnat fastslå att de som fick strålbehandling inte hade någon ökad risk för hjärtsjukdom jämfört med dem som inte fick strålbehandling med 20 års uppföljning.

”Rent konkret betyder det här, i allmänhet, att de patienter som rekommenderas postoperativ strålbehandling inte behöver vara oroliga för någon betydande ökad risk för hjärtsjukdom som biverkan.”

Hur viktigt har stödet från Bröstcancerförbundet varit för er forskning?
Helt avgörande för att jag och mina kollegor har kunnat lägga ner all tid det tar för att sammanställa ett så här stort projekt.

Vad vill du hälsa alla Bröstcancerförbundets givare?
Tack för att ni hjälper till att möjliggöra klinisk bröstcancerforskning!

Hela den vetenskapliga rapporten, samt artikel publicerad i International Journal of Radiation Oncology finns att läsa på efterföljande sidor.

Är dagens strålbehandling efter bröstbevarande kirurgi säker? Långtidsuppföljning av SweBCG91RT studien

Populärvetenskaplig redovisning

Strålbehandling efter bröstcancerkirurgi har använts sedan 40-talet. Under 1970-talet startade studier som visade att strålbehandling efter bröstbevarande kirurgi gav samma låga återfallsrisk som den operationsmetod där hela bröstet togs bort. Nästa steg i utvecklingen var att studera om man kunde hitta patientgrupper med så låg risk för återfall att man kunde undvara strålbehandlingen. Flera sådana studier har genomförts utan att någon sådan tydlig riskgrupp har kunnat definieras. Inom Svenska Bröstcancergruppen startade 1991 en studie i Uppsala-Örebro, Västra och Södra regionerna där patienterna randomiserades till strålbehandling eller inte efter bröstbevarande kirurgi. Vi har utvärderat effekten på lång sikt och funnit att strålbehandlingen har minskat återfallen i det behandlade bröstet, lokala återfall, men inte påverkat patienternas överlevnad.
Många strålbehandlingsstudier har kunnat visa en ökad risk för död i hjärt-kärlsjukdom hos kvinnor som fått strålbehandling. Detta har varit mest tydligt hos patienter som fick behandling fram till cirka 90-talet med äldre teknik, och det krävs långa uppföljningar för att åskådliggöra detta.

Vi sökte medel från Bröstcancerförbundet för projektet ”Ökad kardiovaskulär dödlighet hos kvinnor som erhållit tangentiell strålbehandling efter bröstbevarande kirurgi? Långtidsuppföljning av SweBCG91RT studien.”, och fick anslag för 2014, 2015 och 2016.

Vi ville undersöka hur det har gått för patienterna i den svenska studien för att se om det fanns någon ökad dödlighet framför allt i hjärtsjukdom hos dem. Vi bedömde att det var betydelsefullt för dagens patienter eftersom den behandling som gavs 1991 och framåt är lik den vi ger idag. Vi ville studera alla patienters överlevnad och hos dem som avlidit ville vi ta reda på dödsorsaken. Vi ville även studera vilket behov av slutenvård de patienter som ingick i studien hade haft efter sin behandling. Resultaten ville vi sedan koppla till huruvida de fått strålbehandling eller ej. Vi redovisar data från befolkningsregistret, dödsorsaksregistret, patientregistret (som innehåller data om slutenvård), cancerregistret samt Swedeheart som är ett register som samlar data om hjärtsjukvård i Sverige.

Studien inkluderade nästan 1200 patienter, som alla var opererade med bröstbevarande kirurgi pga bröstcancer. Patienterna hade sjukdom lokaliserad till bröstet, och inga metastaser i lymfkörtlarna i armhålan. Patienterna randomiserades till strålbehandling eller ingen ytterligare behandling. I början av 90-talet var det ovanligt att patienter med så lokaliserad sjukdom fick någon annan, adjuvant behandling, och så var det också bland dessa patienter. Vi har följt patienterna i 20 år. Resultaten visar att strålbehandling inte innebar någon ökad risk hjärtsjukdom, eller död i hjärtsjukdom. I gruppen som fått strålbehandling var det vanligare med hjärtkirurgi senare i livet, men det gällde patienter som fått strålbehandling på höger sida, så det är svårt att koppla till strålbiverkan. I strålgruppen var stroke något vanligare som dödsorsak, vilket vi inte helt kan förklara, eftersom blodkärl som leder till hjärnan inte påverkas av denna sorts behandling. Vi diskuterade de fynden med en neurolog som är specialiserad på stroke, och fann då att bland de aktuella patienterna var det vanligast att en blödning orsakade skadan, och inte en blodpropp som annars är vanligare. Vi spekulerar därför i om den ökade frekvensen av stroke kan vara orsakad av blodförtunnande läkemedel, snarare än av strålbehandlingen i sig, eller att det orsakas av slumpen.

Det fanns ingen skillnad i sekundära maligniteter, eller lungcancer, bland de som fått och inte fått strålbehandling.

Angående strålbehandlingen kunde vi återskapa exakt vilka doser 157 patienter hade fått, vilket är unikt, eftersom studier om äldre tiders strålbehandling ofta grundar sig på estimerade doser. Vi kunde jämföra med dagens doser, i de fall behandlingen givits utan så kallad gatingteknik, och konstatera att de ligger rätt så lika, vilket antyder att även dagens behandling är säker.

Sammanfattningsvis kan man säga att projektets titel ”Ökad kardiovaskulär dödlighet hos kvinnor som erhållit tangentiell strålbehandling efter bröstbevarande kirurgi?” kan besvaras med att strålbehandling efter bröstbevarande kirurgi är säker, vilket är mycket betydelsefullt att kunna meddela dagens patienter som ibland har uppfattningen att behandlingen är behäftad med stor risk för allvarliga biverkningar.

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Clinical Investigation

No Increased Cardiac Mortality or Morbidity of Radiation Therapy in Breast Cancer Patients After Breast-Conserving Surgery: 20-Year Follow-up of the Randomized SweBCGRT Trial

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Purpose: Radiation therapy (RT) after breast-conserving surgery reduces locoregional recurrences and improves survival but may cause late side effects. The main purpose of this paper was to investigate long-term side effects after whole breast RT in a randomized clinical trial initiated in 1991 and to report dose-volume data based on individual 3-dimensional treatment plans for organs at risk.

Methods and Materials: The trial included 1187 patients with T1-2 N0 breast cancer randomized to postoperative tangential whole breast RT or no further treatment. The prescription dose to the clinical target volume was 48 to 54 Gy. We present 20-year follow-up on survival, cause of death, morbidity, and later malignancies. For a cohort of patients (n = 157) with accessible computed tomography–based 3-dimensional treatment plans in Dicom-RT format, dose-volume descriptors for organs at risk were derived. In addition, these were compared with dose-volume data for a cohort of patients treated with contemporary RT techniques.

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Research data are not available at this time.

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Results: The cumulative incidence of cardiac mortality was 12.4% in the control group and 13.0% in the RT group ($P = .8$). There was an increase in stroke mortality: 3.4% in the control group versus 6.7% in the RT group ($P = .018$). Incidences of contralateral breast cancer and lung cancer were similar between groups. The median D_{mean} (range) heart dose for left-sided treatments was 3.0 Gy (1.1-8.1), and the corresponding value for patients treated in 2017 was 1.5 Gy (0.4-6.0).

Conclusions: In this trial, serious late side effects of whole breast RT were limited and less than previously reported in large meta-analyses. We observed no increase in cardiac mortality in irradiated patients. Doses to the heart were a median D_{mean} of 3.0 Gy for left-sided RT. The observed increase in stroke mortality may partly be secondary to cardiac side effects, complications to anticoagulant treatment, or to chance, rather than a direct side effect of tangential whole breast irradiation.

Introduction

Radiation therapy (RT) for early-stage breast cancer reduces the rates of recurrence and death from breast cancer.[1,2] In previous studies with long-term follow-up, unavoidable irradiation to the heart and great vessels during RT after breast cancer surgery increased the subsequent risk of cardiac and cerebrovascular disease.[3-15] However, the risk seems to be lower in patients treated in more recent eras.[7,16-19] A limitation of cardiac-related dose-response studies with long-term follow-up is that the dose distributions often are extracted from reconstructions on a limited number of "typical computed tomography (CT) scans."[6,20-22]

Increasing use of systemic treatment, including anthracyclines and/or trastuzumab and other Her2 blocking agents, with cardiac side effects reinforces the importance of minimizing radiation exposure to the heart and other organs at risk (OARs).[23] With improving survival rates after breast cancer, patients are increasingly likely to die of other causes. As a result, long-term adverse effects of treatment are of major concern.

We previously published data on late side effects of locoregional RT after mastectomy in a trial initiated in 1978, with increased cardio- and cerebrovascular mortality in irradiated patients with breast cancer, most evident in the postmenopausal population.[9] We now present long-term follow-up data from a randomized trial initiated in 1991 regarding the clinical endpoints of total mortality, cause-specific mortality and morbidity, and cardiovascular interventions after tangential whole breast RT after breast-conserving surgery. To correlate these findings with RT dose-volume data to OARs from individual CT-based dose distributions are presented for a cohort of trial patients with accessible Dicom-RT data. We also present corresponding dose-volume data on today's treatment techniques for comparison.

Methods and Materials

Trial design

The original trial explored whether whole breast RT after breast-conserving surgery could be omitted in groups of patients with breast cancer with low estimated risk of local recurrences. The trial procedure, inclusion criteria, and effect of RT have been described earlier.[24-28] In short, from 1991 to 1997, 1187 women aged <76 years with pTI-IIA N0 invasive breast cancer were randomized to no further treatment (control group) or postoperative whole breast RT (RT-group) after a standardized partial mastectomy and axillary clearance of levels I and II.[29] Patients were followed annually for 10 years with bilateral mammography and thereafter referred to the Swedish nation-wide breast screening program for women 50 to 75 years of age. With 15-year follow-up, we found that RT reduced ipsilateral breast recurrences in all subgroups, but survival was not improved.[24]

RT technique

RT was administered as tangential opposing beams with 4 to 6 MV photons. Treatment was given 4 to 5 days a week in 24 to 27 fractions to a total target dose of 48 to 54 Gy. Dose was specified at the intersection point of the opposing tangential beams or at the center of the clinical target volume, defined as remaining breast parenchyma according to the International Commission on Radiation Units and Measurements (ICRU).[30] For all patients, individual computerized dose planning with wedge compensators was used. Three-dimensional dose planning on multiple CT slices 10 mm apart was used for 69% of the patients; for the remainder, 2-dimensional planning based on 3 CT slices was used. The trial protocol did not specify restrictions on heart and lung doses.

Dose-volume metrics

The dose-volume analysis includes trial patients with accessible Dicom-RT data from one of the trial centers (hereafter termed "Dicom-RT patients"). Patients were excluded if they had received RT to the thoracic region more than once and if CT slice thickness was larger than 20 mm. For comparison with the current state of the art, dose-volume data for all patients treated with left-sided tangential breast RT in free breathing at the RT department in x during 2017 (n = 157) were collected.

Guidelines for target definition 2017 were similar to those in the trial.

Original treatment plans were recalculated with the collapsed cone algorithm in Oncentra MasterPlan v.4.0 (Elekta AB, Stockholm, Sweden) and heart, left anterior descending coronary artery (LADCA), and ipsilateral lung were resegmented. The prescribed dose was 50 Gy in 25 fractions (54 Gy in 27 fractions for 2 patients). Treatment planning in 2017 was done in Eclipse version 13.6 with the Anisotropic Analytical Algorithm (Varian Medical Systems, Palo Alto, CA). For details, see Appendix.

Volumes, near maximum doses ($D_{2\%}$), mean doses (D_{mean}), volume receiving 20 Gy or more (V_{20Gy}) (lung), and cumulative dose-volume histograms for OARs were extracted with the MICE toolkit ver. 0.5.1.3 (NONPI Medical AB, Sweden).

Medical therapy

Adjuvant systemic therapy was not regulated by the study protocol but was prescribed for some stage II patients according to regional treatment guidelines. Eight percent received either tamoxifen or chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil, or in a few cases a combination of tamoxifen and chemotherapy (Table 1).

Follow-up and ascertainment of data from patient records and national registries

All patients' hospital records and treatment charts from the RT departments were monitored at visits at participating hospitals. Updates on mortality, cause of death, and morbidity were made using the unique national personal identification numbers and the following Swedish national registers: the National Population Register, including residency and vital status for all inhabitants in Sweden[31]; the National Cause of Death Register, with coverage of >99% of all deaths among Swedish residents[32]; the National Patient Register, which is a compilation of each individuals hospital discharge records, initiated in 1964 and with 99% coverage of admissions to public hospitals since 1988, held by the National Board of Health and Welfare[33]; and SWEDEHEART (The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies).

Table 1 Patient characteristics in the per-protocol population (n = 1144) and Dicom-RT cohort (n = 124)

	Control (n = 580)	RT (n = 564)	Dicom-RT (n = 124)
Age (y)			
Median (range)	60 (32-78)	59 (31-78)	60 (39-74)
<50 y, n (%)	122 (21)	98 (17)	19 (15)
50-59 y, n (%)	168 (29)	187 (33)	43 (35)
60-69 y, n (%)	221 (38)	212 (38)	44 (35)
≥70 y, n (%)	69 (12)	67 (12)	18 (15)
Tumor size (mm)			
Median (range)	12 (1-40)	12 (2-50)	12 (2-30)
Receptor status, n (%)			
ER+ and/or PgR+	345 (84)	337 (85)	60 (80)
ER− and PgR−	64 (16)	60 (15)	15 (20)
Not analyzed	171	167	49
Patients with cardiac diagnosis before randomization, n (%)	33 (5.7)	24 (4.3)	4 (3.2)
Radiation therapy dose (Gy)			
Median (range)	0	50 (42-58)	50 (50-54)
ITT population, N = 1178	n = 587	n = 591	
No adjuvant treatment, n (%)	532 (90.6)	548 (92.7)	
Endocrine treatment only	42 (7.2)	34 (5.8)	
Chemotherapy only	7 (1.2)	5 (0.85)	
Endocrine treatment and chemotherapy	6 (1.0)	4 (0.65)	
Cumulative overall mortality at 20 y (95% CI)*	42.9% (38.8%-46.9%)	42.5% (38.4%-46.0%)	
Cumulative breast cancer mortality at 20 y (95% CI)†	18.0% (15.0%-21.0%)	15.8% (12.9%-18.0%)	

Abbreviations: CI = confidence interval; ITT = intention to treat; RT = radiation therapy.
Cumulative mortality in the ITT is presented as background data (n = 1178).
* Follow-up for survival until March 3, 2015.
† Follow-up for causes of death until December 31, 2013.

This is the Swedish national quality registry concerning heart disease and has several subregisters. Those used for this project were the Swedish Coronary Angiography and Angioplasty Registry, the cardiothoracic surgery registry, and the Swedish Transcatheter Cardiac Intervention Registry. The Swedish Coronary Angiography and Angioplasty Registry holds data on consecutive patients from all 26 centers that perform coronary angiography and percutaneous coronary intervention (PCI) in Sweden. The cardiothoracic surgery registry and Swedish Transcatheter Cardiac Intervention Registry record preprocedural, procedural, and postprocedural characteristics of all open-heart surgeries and transcatheter procedures.[34-36] We also present data from the National Cancer Registry[37] regarding new and possibly secondary malignancies in irradiated volume and contralateral breast cancer.

All diagnoses were classified according to International Classification of Disease, Injuries and Cause of Death 8 (1969-1986), 9 (1987-1996), and 10 (from 1997 onward). We present follow-up for overall mortality until March 31, 2015, cause of death until December 31 2013, and morbidity measured as admissions to hospital until December 31, 2013. Data are from Cancer Registry through December 31, 2015, and from SWEDEHEART until December 31, 2016.

Selection of diagnoses

When analyzing causes of death and morbidity, we grouped the diagnoses as follows: (1) breast cancer, (2) cardiac disease, (3) stroke, (4) lung cancer, and (5) benign pulmonary disease. Table E1 shows the codes for the diagnoses present in the different registries according to International Classification of Disease 8, 9, and 10. From SWEDEHEART we show data on PCI and open-heart surgery.

We also analyzed prerandomization care for cardiac disease to determine whether a history of cardiac disease influences the risk of late side effects of RT.

Statistical methods

Overall mortality was illustrated by cumulative mortality curves, and cumulative cause-specific mortality was illustrated using cumulative incidence functions with other causes of death as competing events.[34,38] Morbidity for a defined group of diseases was defined as time to first admission for that diagnosis. The cumulative incidence of first admission to hospital for the disease was determined with death as a competing event. Logrank tests were used to assess quantitative estimates and statistical significance in comparisons of overall mortality, cause-specific mortality, and first admission to hospital for different diseases. Cardiac mortality was also studied by comparing RT for left- and right-sided breast cancer. In the analyses, we studied 2 populations: (1) patients according to intention to treat (ITT) and (2) patients treated per protocol (PPP). We excluded patients who were noncompliant with RT randomization (ie, randomized to RT but not receiving it or randomized to no RT but were irradiated). Overall mortality and breast cancer mortality are important efficacy endpoints, and hence the ITT results are presented. The other endpoints are regarded as side effects, and for them we used the PPP.

For dose-volume data analysis, comparisons between groups were done with the Wilcoxon rank sum test. To assess influence on cardiac morbidity and mortality, time-to-event analyses were performed separately for each dose measure by means of the Cox proportional hazards model. Time to event was calculated from start of RT, and dose was included as a linear covariate.

Endpoints

A death was allocated to a certain group when either the underlying or a contributing cause belonged to the group (ie, 1 patient could have more than 1 cause of death). This approach was chosen so as not to overlook, for example, cardiac disease as a contributing cause of death in a woman with another underlying death cause, such as recurrent breast cancer. Causes of hospital admissions were classified likewise (eg, an admission was classified as being for cardiac disease when either the principal diagnosis or one of the secondary diagnoses was cardiac disease).

Results

During 1991 to 1997, 1187 women were included in the trial, of whom 594 were allocated to no RT (control) and 593 to RT. Nine patients were excluded because of major violations of inclusion criteria. A flow chart of the trial according to Consolidated Standards of Reporting Trials guidelines[39] is shown in Figure 1. Seven women in the control group received RT, and 27 women in the RT group were not irradiated and are thus excluded from the PPP. In the dose-volume analysis, 194 patients had accessible Dicom-data; 132 were included (left sided n = 59 [48%] and right sided n = 65 [52%]) (Fig. E1 and Table E2).

Patient characteristics of the PPP and Dicom-RT patients are shown in Table 1. The PPP-RT and Dicom-RT groups were well balanced, indicating that the subgroup used for analyzing individual 3-dimensional (3D)-dose distributions is representative of the patient cohort receiving RT.

At the end of follow-up on March 31 2015, 636 patients in the ITT were alive, with a median follow-up for survival of 21.3 years. Among the deceased, we lack information about cause of death on 36 patients owing to time-lag in the Causes of Death Registry (19 in the control group and 17 in the RT group). One patient in the RT group is accounted for as deceased but is missing in the Causes of Death Registry. Fifty-nine patients in the ITT population (5%) received hospital care for cardiac disease before randomization (34

in the control group [5.8%] and 25 [4.2%] in the RT group), and corresponding numbers in the PPP were 33 and 24.

Overall mortality

In the ITT population, there was no statistically significant difference in overall mortality between the groups at 20 years: 42.9% in the control group versus 42.5% in the RT group. Breast cancer mortality was also similar: 18.0% (confidence interval, 15.0%-21.0%) in the control group versus 15.8% (confidence interval, 12.9%-18.0%) in the RT group (Table 1). In the control group of the ITT population, 269 patients were deceased at the end of follow-up in March 2015, with similar overall mortality between patients treated for left- or right-sided cancers (data not shown).

Cardiac mortality

One hundred thirty-seven patients had cardiac disease as an underlying or contributing cause of death (Table 2). The cumulative incidence of cardiac mortality at 20 years was 12.4% in the control group and 13.0 % in the RT group, with similar results if the left or right side was irradiated (Fig. 2a). The most common subtypes of cardiac disease as cause of death were ischemic cardiac disease and congestive heart failure (data not shown).

Stroke mortality

Fifty-six patients had stroke as an underlying or contributing cause of death (Table 2). The cumulative incidence at 20 years was 3.4% in the control group and 6.7% in the RT group ($P = .018$; Fig. 2b), with similar results if the RT was delivered to the left or right breast. When further analyzing the circumstances concerning 34 patients with stroke as the exclusive underlying cause of death (eg, not contributing)—15 in the control group and 19 in the RT group—we found that there were fewer cases of intracerebral bleeding in the control group than in the RT group, at 1 versus 5.

Cardiac and stroke comortality

Cardiac mortality as underlying cause of death exclusively was reported in 10.4% in the control group and 9.8% in the RT group ($P = .8$). Stroke as underlying cause of death exclusively was 1.4% and 3.6%, respectively, ($P = .028$) as described above. However, 2.0% in the control group and

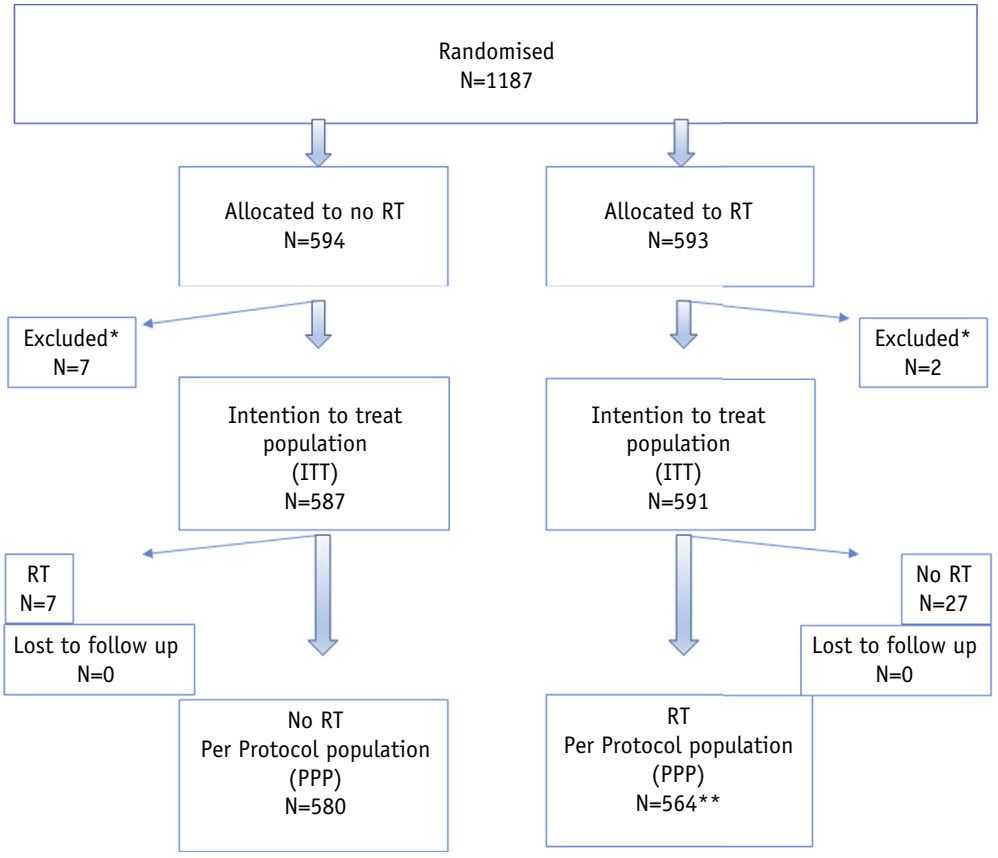

Fig. 1. Flow chart, according to Consolidated Standards of Reporting Trials (CONSORT) guidelines, of all randomized patients in the xx trial. *Due to major violation of inclusion criteria. **One patient was lost to follow-up concerning cause of death and only contributes to survival data.

Table 2 Cause-specific mortality at 20 years in the per-protocol population

Mortality	Control (n = 580)	Radiation therapy (n = 563*)	*P* value
Cardiac mortality	67 12.4% (9.8%-15.4%)	70 13.0% (10.3%-16.0%)	.8
Stroke mortality	19 3.4% (2.1%-5.1%)	37 6.7% (4.8%-9.0%)	.018
Death from lung cancer	10 1.7% (0.9%-3.1%)	10 1.9% (1.0%-3.4%)	1.0
Death from benign pulmonary disease	40 7.1% (5.2%-9.5%)	34 6.4% (4.5%-8.7%)	.5
Deceased, but cause of death not yet registered	19	18	

Number of cases, cumulative incidence (95% confidence interval), and log-rank *P* value. For each group, death as either underlying or contributing cause is accounted for; thus, a patient can belong to more than 1 of these groups. Follow-up until December 31, 2013.

* One woman lost to follow-up for cause of death (died in 2004 without a registration of cause of death).

3.2% in the RT group had both stroke and cardiac mortality as cause of death (underlying and contributing) ($P = .26$).

Mortality from lung cancer

The mortality from lung cancer was similar in the 2 groups: 1.7% and 1.9% in the control and RT group, respectively, ($P = 1.0$) (Table 2).

Mortality from benign pulmonary disease

Mortality from benign pulmonary disease was also similar in the 2 groups: 7.1% in the control group and 6.4% in the RT group ($P = .5$) (Table 2).

Secondary malignancies

The cumulative incidence of invasive contralateral breast cancer was 8.7% in the control group and 8.6% in the RT group ($P = .9$). The cumulative incidence of lung cancer was 1.6% in the control group and 2.6% in the RT group ($P = .28$), with no data on laterality. One patient in the RT group had a malignant tumor in the soft tissue of the thoracic wall, not further specified (Table 3).

Morbidity

At 20 years, the cumulative incidence of admission to hospital with a cardiac diagnosis was 29.7% in the control group and 31.0% in the RT group (32.0% in patients irradiated on the right side and 30.0% in those treated on the left side). In SWEDEHEART, the cumulative incidence of PCI at 20 years was 1.9% in the control group (11 women) and 2.7% in the RT group (15 women) ($P = .433$). The cumulative incidence of open-heart surgery was 2.1% in the control group, 5.2% in patients irradiated on the right side, and 3.4% in patients treated on the left side (12, 15, and 9 patients, respectively) (Table 3). The most common surgical procedures were bypass surgery and aortic valve surgery. One patient had both bypass and valvular surgery. Among patients who underwent open heart surgery, 10% subsequently died of stroke, compared with 5% among the 1104 in the PPP who did not undergo open-heart surgery. The cumulative incidence of admission to hospital with stroke at 20 years was 11.6% in the control group and 13.2% in the RT group ($P = .469$). The cumulative

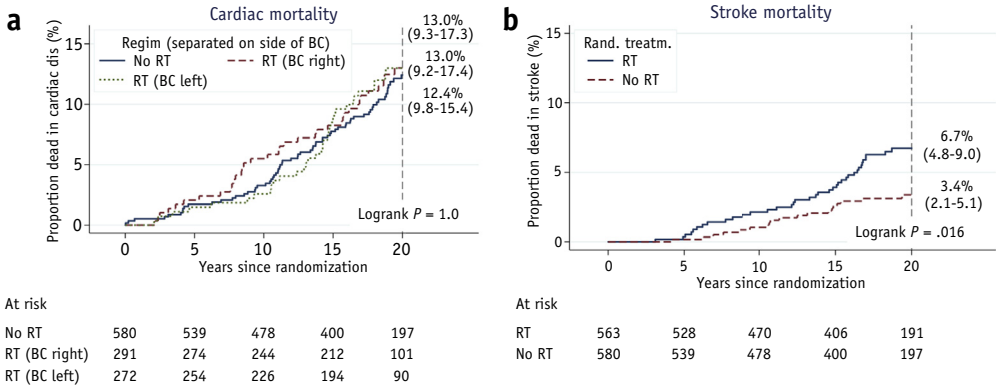

Fig. 2. (a) Cumulative incidence of cardiac mortality at 20 years in the per-protocol population. (b) Cumulative incidence of stroke mortality at 20 years in the per-protocol population.

Table 3 Cumulative incidence (95% confidence interval) and log-rank *P* value in the per-protocol population at 20 years for first admission to hospital because of cardiac disease or stroke, invasive contralateral breast cancer, lung cancer, and interventions for cardiac disease

	Control	Radiation therapy		*P* value
Cardiac disease	29.7% (25.9%-33.6%)	31.0% (27.2%-35.0%)		.7
Stroke	11.6% (9.0%-14.4%)	13.7% (11.0%-16.8%)		.33
Contralateral breast cancer	8.7% (6.6%-11.2%)	8.6% (6.5%-11.1%)		.9
Lung cancer	1.6% (0.8%-2.8%)	2.6% (1.5%-4.2%)		.28
Malignant tumor in the thoracic wall (1 case only)	0	1		
Percutaneous coronary intervention		Right side	Left side	
	2.1% (1.2%-3.6%)	3.8% (2.0%-6.5%)	2.2% (0.9%-4.6%)	.33*
Open heart surgery		Right side	Left side	
	2.1% (1.1%-3.5%)	5.2% (3.1%-8.2%)	3.4% (1.7%-6.1%)	.06*

* Right- versus left-sided treatment.

incidence of first admission to hospital with a benign pulmonary disease was 24.1% in the control group and 25.9% in the RT group ($P = .66$) (Table 3).

Dose-volume metrics

Dosimetric data for heart and LADCA are shown in Table E2 and Figures E2 and E3. The large range in dose data was primarily due to the variation in the patient-to-patient anatomy.

There were no statistically significant associations between cardiac morbidity or mortality and heart or LADCA dose metrics (Table E4a-b). The dose distributions were similar for patients with or without cardiac events. For volume metrics, on the other hand, there was strong evidence ($P = .0016$) of an association between heart volume and cardiac morbidity and moderate evidence ($P = .027$) of an association between the segmented LADCA volume and cardiac mortality.

OAR dose metrics for left-sided treatments for Dicom-RT patients and contemporary treatments from 2017 for heart, LADCA, and ipsilateral lung are presented in Table E5 (dose-volume histograms in Fig. E2). All dose metrics were significantly lower for patients treated in 2017 compared with Dicom-RT patients.

Discussion

With more than 20 years of follow-up with individual clinical and registry data on every patient, we saw no increased cardiac mortality in irradiated patients irrespective of whether the patient was treated on the left or the right side. Laterality did not carry prognostic information because mortality in control patients did not differ between patients with left- and right-sided disease. There were more cases of open-heart surgery in the RT group, which did not reach statistical significance, and this was reflected in neither a higher incidence of admission to hospital for the RT group nor more invasive procedures such as PCI.

History of admission to hospital with a cardiac diagnose did not differ between the ITT and PPP groups, indicating that prerandomization cardiac disease not was a reason for patients, or doctors, to cancel planned RT. However, we did see increased mortality from stroke when both underlying and contributing causes of death were counted. This increase included scattered diagnoses such as intracerebral bleedings, infarctions, and cerebrovascular disease not otherwise specified, including late effects of cerebrovascular disease. Among the 19 cases with stroke as underlying cause of death in the RT group, 5 died of intracerebral bleeding (26%), compared with 1 patient in the control group. One may speculate whether these bleedings were caused by anticoagulants due to a heart condition (ie, arrhythmia or valvular surgery), rather than vascular damage in the target volume causing an embolus to the cerebral circulation,[12] considering less than 20% of strokes are hemorrhagic in the general Swedish population.[40]

Another consideration is the fact that more patients in the RT group had gone through open-heart surgery, with the possibility of cerebrovascular complications.[41] Earlier trials with locoregional RT after mastectomy and RT in patients with head and neck cancers have shown increased incidence of ischemic cerebrovascular disease, which has been interpreted as side effects of RT to the great vessels such as the aorta and proximal carotid artery with subsequent stenosis and/or embolization.[9,12,42,43] These anatomic structures were not included in the RT fields with tangential beams, so this is not considered a probable explanation.

In patients with rectal cancers, more cardiovascular side effects were seen in patients given preoperative RT than in those who did not receive that treatment.[44] In our trial, increased stroke mortality did not correspond to any increased morbidity in the aspect of admission to hospital under these diagnoses, which would have been expected if the RT itself indeed led to cerebrovascular complications.

There was no increase in benign or malignant lung disease in irradiated patients, unlike the findings by Taylor et al.[21]

The dose levels in the trial based on individual CT-based dose distributions were an average D_{mean} of 3.1 Gy and 1.0 Gy to the heart for left- and right-sided treatments, respectively. The corresponding figures for patients treated in 1958 to 2001 estimated by Darby et al[6] were 6.6 Gy and 2.9 Gy, respectively. For trials started during the 1990s, 4.9 Gy and 1.5 Gy were reported by Taylor et al.[21] These doses are considerably higher than in this trial. Data for the Dicom-RT patients indicate that there are large patient-to-patient anatomy variations; therefore, access to original CT-based treatment-planning data is crucial for accurate estimations of dose to normal tissues. With a median follow-up of 7.6 years, van den Bogaard et al[45] validated the model by Darby et al[6] using dosimetry data for individual treatment plans. Median D_{mean} (range) to the heart for left-sided patients was 4.44 Gy (0.99-15.25). For the Dicom-RT patients the corresponding figures are slightly lower at 3.0 Gy (1.1-8.1).

Based on female death rates in the 15 European Union member states in Western Europe, Darby et al[6] reported that a mean absorbed dose to the heart of 3 Gy (as in the present trial) in a 50-year-old woman with 1 or more cardiac risk factors would increase her risk of death from ischemic heart disease before the age of 80 years from 3.4% to 4.1% (an absolute increase of 0.7 percentage points). This figure would be even smaller based on data from Taylor et al.[21] It should be stressed that our trial is not powered to validate or reject these risk figures.

When dose descriptors for heart and LADCA for Dicom-RT patients were compared with free breathing patients treated in 2017 at our department in Lund, the doses to these OARs were even lower. Hence, the risk for radiation-induced cardiac events in women irradiated today is likely to be even lower than in this trial.

The association between heart volume and cardiac morbidity is in line with the knowledge that an enlarged heart can be an indication of heart disease.[46]

The strengths of this trial are that it is randomized and population based with 31% of eligible patients included, and dose-volume data for OARs are based on individual CT-based dose distributions. We have individual follow-up data with access to national registries with practically full coverage on mortality, cause of death, and admission to hospital. The RT was 3D CT-based dose planning, although restrictions for OARs were not used at that time (ie, dose-volume constraints, maximum heart distance, and maximum lung distance).[47]

The limitations are that we have no data on risk factors for cardiac disease or stroke, such as smoking habits, obesity, diabetes mellitus, or hypertension, but these factors are likely to be evenly distributed by the randomization. Because outpatient data on vascular morbidity are lacking, less serious morbidity could not be taken into account, which may cause a bias.

Conclusions

In this trial with tangential 3D planned RT, serious late side effects were limited and clearly less than previously reported in large meta-analyses. We saw no increased cardiac mortality in irradiated patients, nor did we observe any increase in morbidity or secondary malignancies. The median D_{mean} (interquartile range) for the heart was 3.0 Gy (1.7-3.9) for left-sided treatment and the OAR doses were even lower for patients treated today in free breathing. The observed increase in stroke mortality may partly be secondary to cardiac side effects, complications to anticoagulant treatment, or to chance, rather than a direct side effect of tangential breast irradiation.

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