

ORIGINAL ARTICLE

CT-planned internal mammary node radiotherapy in the DBCG-IMN study: Benefit versus potentially harmful effects

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ABSTRACT

Background. The DBCG-IMN is a nationwide population-based cohort study on the effect of internal mammary node radiotherapy (IMN-RT) in patients with node positive early breast cancer. Due to the risk of RT-induced heart disease, only patients with right-sided breast cancer received IMN-RT, whereas patients with left-sided breast cancer did not. At seven-year median follow-up, a 3% gain in overall survival with IMN-RT has been reported. This study estimates IMN doses and doses to organs at risk (OAR) in patients from the DBCG-IMN. Numbers needed to harm (NNH) if patients with left-sided breast cancer had received IMN-RT are compared to the number needed to treat (NNT).

Material and methods. Ten percent of CT-guided treatment plans from the DBCG-IMN patients were selected randomly. IMNs and OAR were contoured in 68 planning CT scans. Dose distributions were re-calculated. IMNs and OAR dose estimates were compared in right-sided versus left-sided breast cancer patients. In six left-sided patients, IMN-RT was simulated, and OAR doses were compared to those in the original plan. The NNH resulting from the change in mean heart dose (MHD) was calculated using a published model for risk of RT-related ischemic heart death.

Results. In original plans, the absolute difference between right- and left-sided $V_{90\%}$ to the IMNs was 38.0% [95% confidence interval (5.5%; 70.5%), $p < 0.05$]. Heart doses were higher in left-sided plans. With IMN-RT simulation without regard to OAR constraints, MHD increased 4.8 Gy (0.9 Gy; 8.7 Gy), $p < 0.05$. Resulting NNHs from ischemic heart death were consistently larger than the NNT with IMN-RT.

Conclusion. Refraining from IMN-RT on the left side may have spared some ischemic heart deaths. Assuming left-sided patients benefit as much from IMN-RT as right-sided patients, the benefits from IMN-RT outweigh the costs in terms of ischemic heart death.

Radiotherapy (RT) to regional lymph nodes in early breast cancer has been a subject of debate ever since adjuvant RT to the mammary region and regional lymph nodes was shown to improve survival in patients with breast cancer [1,2]. One site of nodal disease is the internal mammary lymph nodes (IMNs), and the probability of metastatic involvement of these increases with tumor size, medial tumor localization and axillary metastasis [3]. Neither surgery nor RT to the IMNs has

proved beneficial in patients with early breast cancer [4], thus to date, there is no consensus on whether the IMNs should be part of the RT target. One argument against RT is that due to the anatomic location of the nodes, the ipsilateral lung and especially in patients with left-sided breast cancer, the heart, receives higher doses with IMN-RT. Thus, a small beneficial effect of RT might be counterbalanced by late side effects in these organs at risk (OAR) [5].

The Danish Breast Cancer Cooperative Group (DBCG) has addressed the issue of IMN-RT in a nationwide population-based cohort study. In the years 2003–2007, the DBCG-IMN study allocated patients with early lymph node positive breast cancer to adjuvant IMN-RT based on tumor laterality: Patients with cancer in the right breast received IMN-RT, while patients with left-sided breast cancer did not. This study design was chosen to avoid the potential combined cardio-toxic effect of anthracyclines and RT to the heart in patients with left-sided breast cancer. Preliminary results show that at seven years, overall survival improved by 3% with IMN-RT, corresponding to a hazard rate for death from any cause of 0.86 [95% confidence interval (0.75; 0.99), $p=0.04$]. Equal numbers of deaths due to cardiac disease were observed with ($n=9/1485$) and without IMN-RT ($n=8/1586$) [6].

With the two-dimensional (2D) planning used in the DBCG-IMN, right-sided breast cancer patients received intentionally higher doses to the IMNs than did patients with left-sided breast cancer, while maintaining acceptable dose levels to OAR [7]. The aim of the present study is to investigate whether this was also the case with the 3D CT-based treatment planning that was introduced gradually in the study period. This will enable quantification of the size of the difference in IMN dose coverage and the doses to OAR that brought about the improvement in overall survival in the DBCG-IMN. Furthermore, applying a published dose-response model for risk of RT-related death from ischemic heart disease [8], this study estimates the expected excess number of cardiac deaths in the DBCG-IMN if patients with left-sided breast cancer had received IMN-RT. In other words, would the potential gain in overall survival in patients with left-sided breast cancer have been cancelled out by an increase in cardiovascular deaths caused by the IMN-RT?

Material and methods

Patients

For evaluation of doses to the IMN clinical target volume and OAR, DBCG-IMN patients, all with stage II–III breast cancer were divided into four groups depending on type (mastectomy/lumpectomy) and laterality of operation (left/right). During the DBCG-IMN study period, five of seven DBCG RT-departments introduced CT-based treatment planning with contouring of both target tissues and OAR. In four departments, plans were available for evaluation. Patients were ordered randomly using a list randomizer (www.random.org). In this random order, RT plans were checked for availability, meaning that

the original planning CT scan and treatment plan was present in or could be imported to the treatment planning system of today at the department for recalculation, until a sample of 10% of the plans was reached. The resulting total sample size was 68 CT-based treatment plans (Figure 1). At Rigshospitalet, lumpectomy patients were not included in the DBCG-IMN, as the use of gating in this department allowed IMN-RT for all lumpectomy patients, but not mastectomy patients, as capacities were limited. In another department, Vejle, only lumpectomy patients had received CT-guided treatment planning. Overall, CT-guided treatment planning had been used more frequently in patients with right-sided cancer (sample size 38 right- vs. 30 left-sided).

For the Aarhus patients, a subgroup originally planned to one of the accelerators still in use was selected. This was carried out to enable comparison of the original CT-guided treatment plan calculated with the pencil beam (PB) algorithm with recalculations using the anisotropic analytical algorithm (AAA). A sample size of three patients from each of the four categories: left-/right-sided and mastectomy/lumpectomy was aimed for. However, only two lumpectomy patients with left-sided breast cancer were available, resulting in a total sample size of 11 patients.

Contouring

Original planning CT scans were used for delineation of the IMN target and OAR. Patients had been scanned in treatment position without contrast enhancement from the sixth cervical vertebra to at least 5 cm below the inferior margin of the breast including the lungs. Slice thickness was 2.5–5.0 mm

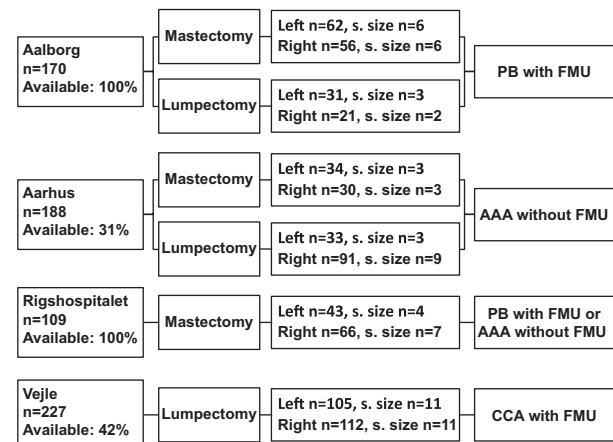


Figure 1. Random sampling of patients stratified on type and laterality of operation was carried out in four departments. Dose distributions were recalculated with various methods as indicated. AAA, anisotropic analytical algorithm; CCA, enhanced collapsed cone algorithm; FMU, fixed monitor units; PB, pencil beam algorithm; S. size, sample size.

depending on the department. In the contouring software available at the respective departments (Eclipse™, Varian Medical Systems, Palo Alto, CA, USA, Aalborg: version 10, Rigshospitalet version 7.5 and 11.0, Aarhus version 11.3 and Oncentra External Beam Nucletron, An Elekta Company, Elekta AB, Stockholm, Sweden in Vejle), the following volumes were delineated by one oncologist (LT) according to national DBCG delineation guidelines [9]: The IMN clinical target volume including ipsilateral IMNs in intercostal spaces 1–4, heart, left anterior descending coronary artery (LADCA) and ipsilateral lung. Original delineated volumes were not used, as delineation guidelines were revised in 2013 [9].

Treatment planning and calculation

Field arrangements in all original treatment plans were tangential photon fields for treatment of residual breast/chest wall combined with an anterior and in some patients a posterior photon field to the periclavicular and axillary lymph nodes. In patients with right-sided breast cancer, the IMNs were included in the tangential fields. Beam energies used were 4–18 MV for tangential fields, 4–8 MV for anterior periclavicular/axillary fields and 10–18 MV for posterior periclavicular/axillary fields. All original plans had been calculated with the PB algorithm. In all cases the standard dose, 48 Gy in 24 fractions, had been prescribed. For evaluation of dose distributions in the original plans, doses to the IMNs and OAR were recalculated. In Aalborg, Aarhus and Rigshospitalet, the preferred algorithm for re-calculation was AAA. However, as data for the beam energy used in the original plan were sometimes only available for calculation with the PB algorithm, this was used in eight of 11 cases at Rigshospitalet and in all 17 cases at the department in Aalborg. Calculation with AAA was in all cases performed without fixed monitor units, as the original beam data were unavailable for some treatment plans. In Vejle, the enhanced collapsed cone algorithm (CCA) with fixed monitor units was used. In all 68 plans, point dose normalization was applied.

In the first three left-sided lumpectomy and three left-sided mastectomy patients sampled in Aarhus, new treatment plans including the IMNs as target were simulated by modifying the fields of the original treatment plan to include the contoured IMN clinical target volume within the 90% isodose line. Dose distributions were calculated using AAA without fixed monitor units for both the original plan and the simulated plan. If the simulated plan violated normal tissue dose constraints as defined in the DBCG-IMN study period (volume of heart receiving more than 20 Gy < 10%, volume of heart receiving more than 40 Gy < 5%, volume of ipsilateral lung receiving

more than 20 Gy < 35%), an alternative plan was created to respect these dose constraints.

To assess the influence of dose calculation algorithm and the use of fixed monitor units on dose estimates, 11 original PB plans were recalculated using AAA with and without fixed monitor units.

Number needed to treat and numbers needed to harm

The number needed to treat (NNT) to avoid one death with IMN-RT was calculated from the reported risk reduction for death with IMN-RT in the DBCG-IMN [6].

Numbers needed to harm (NNH) by inducing one death from ischemic heart disease as a result of increased mean heart dose (MHD) with IMN-RT on the left side were calculated for a patient with an age of 50 years at the time of RT, as the median age reported in the DBCG-IMN was 56 years [6]. Calculations were based on the estimated increase in MHD with simulation of IMN-RT and on Darby et al. [8], who have published estimates of excess cumulative risk of ischemic heart death per whole Gray increase in MHD with every decade passed after treatment. Estimates were on hand for women of 40, 50, 60 or 70 years of age at treatment with no or at least one cardiac risk factor. The number was calculated for the “best case” scenario, in which dose constraints to OAR were respected, and for the “worst case” scenario, in which they were not, for a patient with no cardiac risk factors and for a patient with at least one cardiac risk factor at 10 and 30 years after RT. If, as in the worst case scenario, a 50-year-old patient was treated to a MHD of 3 Gy versus 8 Gy without and with IMN-RT, the cumulative risk of ischemic heart death 10 years after treatment changed from 0.11% to 0.14%. The difference in cumulative risk was used to calculate the NNH as described in “statistics”.

Statistics

Dose-volume histograms (DVH) were calculated for all delineated volumes. The relative volume V irradiated to a minimum dose or proportion of a prescribed dose x, V_x , was determined from the DVH. Mean and maximal doses were obtained from the DVH statistics. For each dose coverage estimate, mean, standard deviation and 95% confidence interval were calculated. As sampling was clustered on RT departments, linear regression with robust standard errors was used to compare average dose estimates from original treatment plans to IMNs and OAR in the 68 patients with left-sided versus right-sided breast cancer. To test if type of operation (mastectomy/lumpectomy) predicted for different sizes of dose estimates for

IMNs and OARs, this was added as a covariate to the regression. No significant influence on dose estimates was detected. Students' paired t-test was used to compare doses to IMNs, heart and ipsilateral lung in six left-sided original plans without IMN treatment versus the corresponding left-sided simulated plans with IMN treatment. Likewise, Students' paired t-test was applied to compare doses from 11 plans that were calculated with the PB algorithm versus AAA with and without fixed monitor units. As the paired t-test assumes a normal distribution of differences, these were plotted in individual (Quantile, Quantile)-plots confirming normality.

An estimate of the NNT with IMN-RT was calculated as (1/absolute risk reduction). Estimates of NNH were calculated as [1/(cumulative risk with IMN-RT-cumulative risk without IMN-RT)] [10].

Results

Recalculated dose estimates

For patients with right-sided breast cancer, in whom IMN-RT was intended, the estimated average $V_{90\%}$ was $73.2\% \pm 26.9\%$ (Table I), whereas in patients with left-sided breast cancer, the average incidental $V_{90\%}$ to the IMNs was $35.2\% \pm 27.7\%$, resulting in an estimated absolute mean difference of 38.0% (5.5%; 70.5%) between the two groups.

Doses to normal tissues varied depending on laterality of the treatment. Although left-sided breast cancer patients did not receive IMN-RT, all heart dose estimates were consistently higher in the delivered RT than in right-sided breast cancer patients with IMN-RT, with for instance a MHD of $4.0 \text{ Gy} \pm 2.0 \text{ Gy}$ being 2.9 Gy (1.7 Gy; 4.0 Gy) higher than that of the patients with right-sided

breast cancer (average MHD $1.1 \text{ Gy} \pm 0.4 \text{ Gy}$). The maximal dose to the LADCA was 38.4 Gy (28.4 Gy; 48.5 Gy) higher in the left-sided patients. In contrast, right-sided breast cancer patients received 20 Gy or more to $31.4\% \pm 4.6\%$ of the ipsilateral lung compared to $25.9\% \pm 6.0\%$ in left-sided breast cancer patients. The absolute estimated difference was 5.4% (1.4%; 9.5%).

Normal tissue doses in simulated treatment plans

The IMN clinical target volume could largely be included within the 90% isodose without violation of dose constraints to heart and ipsilateral lung by widening of the tangential fields in three of six patients with left-sided breast cancer. In the remaining three patients, an additional plan respecting dose constraints was created. Modifications were either cranial displacement of the matchline between the tangential fields and the anterior periclavicular field to lower dose to the ipsilateral lung, or restriction of the lower part of the posterior field borders of the tangential fields to decrease dose to the heart. This meant that dose to the inferior part of the IMN clinical target volume was also decreased. Prioritizing IMN coverage over OAR constraints, $93.3\% \pm 5.1\%$ of the IMN clinical target volume received at least 90% of the prescribed dose (Table II). This led to an increase in MHD of 4.8 Gy (0.9 Gy; 8.7 Gy). Accordingly, heart $V_{20\text{Gy}}$ and $V_{40\text{Gy}}$ also increased with 8.9% (-1.0%; 18.9%) and 6.2% (0.2%; 12.3%). LADCADmax increased with 17.3 Gy (-0.3 Gy; 34.9 Gy) with left-sided IMN-RT. The change was not significant, as the LADCA was in field even in some left-sided treatment plans without IMN-RT. IMN treatment caused an increase in the left lung $V_{20\text{Gy}}$ of 10.2% (2.1%; 18.3%).

Table I. Estimates of doses to internal mammary nodes and organs at risk in 68 original treatment plans.

CTV/OAR	Left (n = 30)	Right (n = 38)	Estimated difference†
IMN $V_{90\%}$ (%)	35.2 ± 27.7	73.2 ± 26.9	38.0 (5.5; 70.5)*
Heart			
MHD (Gy)	4.0 ± 2.0	1.1 ± 0.4	-2.9 (-4.0; -1.7)*
$V_{20\text{Gy}}$ (%)	5.6 ± 4.3	0.1 ± 0.4	-5.4 (-8.5; -2.3)*
$V_{40\text{Gy}}$ (%)	2.4 ± 2.8	$<0.1 \pm <0.1$	-2.3 (-4.1; -0.6)*
LADCADmax (Gy)	39.6 ± 11.9	1.2 ± 0.4	-38.4 (-48.5; -28.4)*
Ipsilateral lung			
$V_{20\text{Gy}}$ (%)	25.9 ± 6.0	31.4 ± 4.6	5.4 (1.4; 9.5)*

CTV, clinical target volume; IMN, internal mammary lymph nodes; LADCADmax, maximal dose to the left anterior descending coronary artery; MHD, mean heart dose; OAR, organ at risk; V_x , relative volume V irradiated to a minimum dose or proportion of a prescribed dose x.

Data are shown as mean values ± 1 SD, 95% confidence interval in parenthesis.

†Estimates calculated using linear regression with robust standard errors, as sampling was clustered on radiotherapy centers.

* $p < 0.05$.

Modification of plans to respect OAR constraints also resulted in significantly increased doses to normal tissues compared to the original plans, but to a less pronounced degree: MHD increased 2.1 Gy (0.5 Gy; 3.7 Gy), heart $V_{20\text{Gy}}$ and $V_{40\text{Gy}}$ 4.8% (1.5%; 8.1%), and 2.5% (0.8%; 4.1%), LADCADmax 16.7 Gy (-1.1 Gy; 34.5 Gy) and lung $V_{20\text{Gy}}$ increased 6.4% (2.6%; 10.1%).

Influence of recalculation algorithm on dose estimates

When PB calculated dose distributions were recalculated with AAA with and without fixed monitor units, the average IMN $V_{90\%}$ increased in both right- and left-sided patients (Table III). This was most pronounced in patients with left-sided breast cancer, where recalculation with AAA with fixed monitor units caused an absolute increase in estimated IMN $V_{90\%}$ of $7.14\% \pm 5.96\%$. Compared to the PB estimate of $16.53\% \pm 26.90\%$, this was also a large relative change. However, due to the uncertainty of the estimates, the difference was insignificant. Regardless of laterality, the difference between the two recalculation methods was only about 1.5%. The average MHD estimate decreased significantly with $0.36 \text{ Gy} \pm 0.14 \text{ Gy}$ and $0.42 \text{ Gy} \pm 0.16 \text{ Gy}$ in left-sided patients and $0.36 \text{ Gy} \pm 0.29 \text{ Gy}$ and $0.38 \text{ Gy} \pm 0.30 \text{ Gy}$ in right-sided patients depending on the method of recalculation. Due to the paired design, a very slight but statistically significant difference of 0.02 Gy (-0.04 Gy ; $< -0.01 \text{ Gy}$) was detected between the two recalculation methods for right-sided patients. Heart $V_{20\text{Gy}}$ and $V_{40\text{Gy}}$ did not show significant difference with recalculation method. For LADCADmax, while recalculation with both methods caused

a slight decrease in magnitude of the estimates ($-0.42 \text{ Gy} \pm 0.35 \text{ Gy}$ and $-0.43 \text{ Gy} \pm 0.35 \text{ Gy}$), there was no detectable difference between recalculation methods. Average ipsilateral lung $V_{20\text{Gy}}$ increased from PB to AAA, but with no significant difference between the two AAA estimates.

Number needed to treat and numbers needed to harm

An improvement in overall survival of 3% translated into a NNT of 33 patients to avoid one death at seven years after IMN-RT. In the "worst case" scenario, the number of patients without cardiac risk factors treated at age 50 needed to cause one death from ischemic heart disease 10 years after treatment was calculated to 3333 using the estimated increase in MHD of 4.8 Gy (0.9 Gy; 8.7 Gy) with IMN-RT in patients with left-sided breast cancer. At 30 years after treatment, the number was 143 patients. In patients of the same age but with at least one cardiac risk factor, 1000 patients had to be treated to cause one heart death 10 years after treatment. At 30 years after treatment, the number was considerably lower: 83 patients. In the best case scenario, using the estimated increase in MHD of 2.1 Gy (0.5 Gy; 3.7 Gy) with IMN-RT in patients with left-sided breast cancer, the corresponding NNH's at 10 and 30 years after treatment were 10,000 and 333 patients without cardiac risk factors, and 1000 and 200 patients with at least one cardiac risk factor.

Discussion

This study evaluates doses to IMNs and OAR in treatments carried out up to a decade ago. Meanwhile,

Table II. Left-side average estimates of dose coverage for internal mammary nodes and organs at risk with and without internal mammary node radiotherapy.

CTV/OAR	Plan 1 (n = 6)	Plan 2 (n = 6)	Difference plan 1 to plan 2	Plan 3 (n = 6)	Difference plan 1 to plan 3
IMN $V_{90\%}$ (%)	29.0 ± 40.4	93.3 ± 5.1	64.3 (26.3; 102.0)*	74.9 ± 25.8	45.9 (18.6; 73.2)*
Heart					
MHD (Gy)	2.6 ± 1.7	7.5 ± 4.7	4.8 (0.9; 8.7)*	4.8 ± 1.8	2.1 (0.5; 3.7)*
$V_{20\text{Gy}}$ (%)	2.3 ± 2.4	11.2 ± 11.6	8.9 (-1.0; 18.9)	7.2 ± 3.7	4.8 (1.5; 8.1)*
$V_{40\text{Gy}}$ (%)	0.6 ± 0.7	6.9 ± 2.4	6.2 (0.2; 12.3)*	3.1 ± 0.7	2.5 (0.8; 4.1)*
LADCADmax (Gy)	27.5 ± 18.9	44.8 ± 1.6	17.3 (-0.3; 34.9)	44.2 ± 3.5	16.7 (-1.1; 34.5)
Ipsilateral lung					
$V_{20\text{Gy}}$ (%)	24.6 ± 4.5	34.8 ± 5.6	10.2 (2.1; 18.3)*	31.0 ± 2.6	6.4 (2.6; 10.1)*

Plan 1 is the original treatment plan with no intent of IMN treatment. Plan 2 is a simulated plan in which the IMN are treated and the coverage of the IMN CTV has first priority. Plan 3 is a simulated plan in which the IMN are treated and the dose constraints for heart and lungs are prioritized over IMN coverage – three of the patients had a plan 3 identical to plan 2.

CTV, clinical target volume; IMN, internal mammary lymph nodes; LADCADmax, maximal dose to the left anterior descending coronary artery; MHD, mean heart dose; OAR, organ at risk; V_x , relative volume V irradiated to a minimum dose or proportion of a prescribed dose x.

Data are shown as mean values ± 1 SD, 95% confidence interval in parentheses.

*Paired t-test, $p < 0.05$.

Table III. Dose estimates resulting from three different calculation methods.

CTV/OAR	Pencil beam		PB to AAA		PB to AAA with FMU		Difference AAA vs. AAA with FMU	
	Left (n=5)	Right (n=6)	Left (n=5)	Right (n=6)	Left (n=5)	Right (n=6)	Left (n=5)	Right (n=6)
IMN V _{90%} (%)	16.53 ± 26.90	85.30 ± 12.78	8.67 ± 6.91*	3.17 ± 1.92*	7.14 ± 5.96	1.70 ± 1.85	-1.53 (-2.76; -0.30)*	-1.47 (-2.14; -0.80)*
Heart								
MHD (Gy)	2.87 ± 1.17	1.12 ± 0.49	-0.36 ± 0.14*	-0.36 ± 0.29*	-0.42 ± 0.16*	-0.38 ± 0.30*	-0.06 (-0.14; 0.01)	-0.02 (-0.04; <-0.01)*
V _{20Gy} (%)	2.14 ± 2.47	0.08 ± 0.19	0.22 ± 0.21	0.01 ± 0.04	0.17 ± 0.19	0.01 ± 0.03	-0.05 (-0.10; -0.01)	-0.01 (-0.02; 0.01)
V _{40Gy} (%)	0.67 ± 1.09	0.01 ± 0.01	0.40 ± 0.45	0.02 ± 0.06	0.28 ± 0.31	0.02 ± 0.04	-0.12 (-0.29; 0.06)	-0.01 (-0.03; 0.01)
LADCADmax (Gy)	34.07 ± 14.23	1.24 ± 0.59	1.26 ± 2.05	-0.42 ± 0.35*	0.30 ± 2.06	-0.43 ± 0.35*	-0.96 (-1.22; -0.70)	-0.01 (-0.02; <0.01)
Ipsilateral lung								
V _{20Gy} (%)	22.73 ± 6.23	31.30 ± 1.98	0.56 ± 0.31*	1.21 ± 0.28*	1.23 ± 1.05	1.08 ± 0.26*	0.67 (-0.92; 2.26)	-0.13 (-0.38; 0.12)

In 11 patients, 6 with right-sided and 5 with left-sided breast cancer, the original PB plan was recalculated using AAA with or without fixed monitor units. The resulting changes in dose estimates and the differences between the two recalculation methods are summarized.

AAA, anisotropic analytical algorithm; CTV, clinical target volume; FMU, fixed monitor units; IMN, internal mammary lymph nodes; LADCADmax, maximal dose to the left anterior descending coronary artery; MHD, mean heart dose; OAR, organ at risk; PB, pencil beam algorithm; V_x, relative volume V irradiated to a minimum dose or proportion of a prescribed dose x.

Data are shown as mean values ± 1 SD, 95% confidence interval in parentheses.

*Paired t-test, p < 0.05.

equipment and algorithms have been updated and improved in a number of ways. Therefore, the methods used in this study are somewhat dictated by circumstance: clinical target volume was chosen over planning target volume as volume of interest, as information on the appropriate margins to add in each department was not available. Two centers, Aarhus and Vejle, focused on right-sided and lumpectomy patients because studies had documented problems with IMN-coverage and high doses to OARs with the simulator-based tangential regimes used in their treatment [5,11]. The imbalance in number of left- and right-sided patients causes a less certain estimate of doses on the left than on the right side, but should not affect the estimated difference between the groups. As for recalculation, in one center, Vejle, original treatment plans could be recalculated with fixed monitor units and a modern algorithm, the enhanced CCA, well suited to the purpose [12]. In Aalborg, only PB calculation was possible, and in the last two centers, recalculation with AAA could be performed in most cases, but without fixed monitor units. As this would not provide the dose actually delivered, a substudy on the accuracy of PB calculation and the effect of recalculating plans with AAA with or without fixed monitor units was undertaken. Results (Table III) indicated that PB calculations consistently underestimated coverage of IMNs and overestimated MHD, although with less than one Gy, regardless of laterality of the breast cancer. The size of the differences in estimates of doses to LADCA, ipsilateral lung and other heart dose parameters were small. Furthermore, differences between the two AAA estimates on OAR doses were negligible, while recalculation with AAA without fixed monitor units caused a slight overestimation of IMN

coverage. This method, however, did produce results closer to the “best estimate” AAA calculation with fixed monitor units than did the PB estimates, and consequently was chosen for simulation of IMN treatment in patients with left-sided breast cancer.

The absolute difference in IMN V_{90%} estimated with the various calculation methods between patients with left- and right-sided breast cancer was 38.0% (5.5%; 70.5%). As PB was used for dose estimation in some cases, IMN doses could be slightly underestimated. In comparison, the 2D tangential techniques used in the DBCG-IMN had an IMN V_{90%} of 16.2% ± 21.3% on the left side, and a V_{90%} of 73.4% ± 23.1% on the right side. With 2D anterior electron fields, the separation between left- and right-sided IMN doses was larger: 8.0% on the left side versus 85.1% (lumpectomy) and 86.9% (mastectomy) on the right side [7]. In other words, the change from 2D to 3D techniques did little to improve the IMN target coverage with tangential techniques, and may even have hampered the detection of an effect of IMN treatment. Still, these are the differences in IMN doses that resulted in a hazard rate for death of 0.86 (0.75; 0.99) in the DBCG-IMN.

Recently, a meta-analysis of preliminary results from the EORTC 22922/10925 [13], the MA.20 [14] and published results from a French study [15], showed significant improvements in overall survival with regional lymph node RT [16]. All studies included in the analysis randomized to adjuvant RT to IMNs alone (French study) or IMN plus medial supra-clavicular nodes (EORTC and MA.20). The combined hazard rate for death was 0.88 (0.80; 0.97). Of these studies, only the EORTC 22922/10925 has published detailed data on IMN doses: In patients

randomized to IMN-RT, doses were similar to the doses observed in the DBCG-IMN, while lower doses were reported in the control arm [13]. Similar IMN doses seem to have resulted in equivalent relative gains in overall survival.

Simulation of IMN-RT in six patients with left-sided breast cancer showed that had these patients received IMN-RT without considering normal tissue dose constraints, i.e. a “worst case” scenario, the resulting NNH by causing one death from ischemic heart disease at 10 years were from 30 to 100 times larger than the NNT to prevent one death at seven years. In the “best case” scenario, NNH’s were even higher. This is in concordance with the very similar numbers of cardiac deaths reported at present. However, “worst case” and “best case” estimates of NNH at 30 years after treatment were much lower for both patients without and with cardiac risk factors, though still larger than the 33 patients needed to treat at seven years. Of course, the estimates are based on a limited sample size, and results should be interpreted with due caution. By widening the tangential fields to include the IMNs, a larger part of the axillary level I was also included. Theoretically, this could contribute to the improved survival with IMN-RT. However, as all patients in the DBCG-IMN received full axillary dissection with a median of 17 nodes removed, and in patients with less than 10 nodes removed, level I was part of the target for RT, this seems unlikely. The model for ischemic heart death after breast cancer RT was developed in a large case control study of Danish and Swedish breast cancer patients treated with RT as early as 1958 up to 2001 [8]. Regimens varied regarding fractionation, dose and field arrangements in the treatment period, and heart dose estimates were calculated using the PB algorithm, which in the present study was shown to deliver estimates of MHD within one Gy of AAA based recalculations [17]. As Darby et al. report increases in cumulative risk in whole Gray increments only, these calculation methods were in effect interchangeable for the purpose of the present study [8]. The range of MHDs in cases and controls was very wide and covered the range of MHDs estimated in the DBCG-IMN patients [17]. Furthermore, the estimates of cumulated risk of death from ischemic heart disease provided by Darby et al., were based on recently WHO-reported rates of death from ischemic heart disease in western European women, supporting the validity of applying the model to the DBCG-IMN study cohort. However, systemic adjuvant treatment with anthracyclines in the DBCG-IMN study may cause these patients to be more vulnerable to RT-induced cardio-toxicity, making the estimates of NNH too large [18]. However, the impact of

RT-induced cardio-toxicity may be mitigated by medical progress made in the treatment of ischemic heart disease during the latest decade. In comparison to our estimates, Brenner et al., also applying the model by Darby et al. estimated 20-year excess risks of any major coronary event including death in US women with low, medium and high baseline cardiac risk as defined by the Reynolds Risk Score. The excess absolute risk for a patient with low baseline risk treated for a left-sided breast cancer to a MHD of 2.17 Gy was 0.22%, while the corresponding excess risk in a patient with high baseline cardiac risk was 3.52%, equivalent to NNH of 455 and 28, indicating that although the risk of radiation-related cardiac death is low, cardiac morbidity could be much more frequent, but also very dependent on the general health of the patient [19].

Estimates of MHD in the 68 patient samples and the former study on the DBCG-IMN 2D-RT show that patients with left-sided breast cancer received higher doses to the heart than did patients with right-sided breast cancer, even if the IMNs were not included in the treatment fields [7]. This underlines that long-term results, meaning more than 10 years of follow-up, both regarding breast cancer mortality and late morbidity should be documented to ensure that a further observed gain in overall survival is not due to patients with left-sided breast cancer dying from ischemic heart disease.

Although the focus of the present study is on RT-induced heart disease, this is not the only late side effect to consider. Simulation of IMN-RT also caused an increase in the amount of ipsilateral lung irradiated with 20 Gy or more. As breast cancer RT is known to be associated with development of second lung cancers, this could be a further disadvantage with IMN-RT [20]. Furthermore, in an earlier series of Swedish patients, supraclavicular and IMN-RT was associated with a slightly increased risk of stroke [21]. Although arm and shoulder morbidity has been found to increase with dose to the shoulder joint in patients receiving IMN-RT, the IMN treatment in itself is unlikely to contribute largely to arm and shoulder morbidity [22].

With newer methods of treatment delivery, e.g. breath hold techniques [23], individualized positioning [24], and more advanced methods for treatment planning [25], IMN-RT can be delivered with even lower doses to OAR than those estimated in the present study.

In summary, IMN-RT has been shown to improve overall survival with 7–10 years of follow-up [6,16]. Estimates on the potential cost of IMN-RT in patients with left-sided breast cancer in terms of RT-induced heart death indicate that even with standard CT-based techniques available

during the DBCG-IMN, IMN-RT in left-sided breast cancer would have been preferable.

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