Postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy. A 30-year long-term report from the Danish breast cancer cooperative group DBCG 82bc trial

Marie Overgaard a, Hanne Melgaard Nielsen b, Trine Tramm c, Inger Højris b, Trine Lønbo Grantzau a, Jan Alsner a, Birgitte Vrou Offersen a,b, Jens Overgaard a,* on behalf of the DBCG Radiotherapy Group 1

a Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark; b Department of Oncology, Aarhus University Hospital; and c Department of Pathology, Aarhus University Hospital, Denmark

Abstract

Background: Between 1982 and 1990 the Danish Breast Cancer Cooperative Group (DBCG) conducted a randomized trial in high-risk pre- and postmenopausal (<70 years) breast cancer patients comparing mastectomy plus adjuvant systemic therapy alone versus the same treatment plus postoperative irradiation.

Aim: To present a comprehensive analysis of the complete DBCG 82bc study with a 30-year long-term follow-up of the cancer therapeutic effect and survival, together with an additional focus on the potential long-term life-threatening morbidity related to cardiac irradiation and/or the risk of secondary cancer induction.

Methods: A total of 3083 patients with pathological stage II and stage III breast cancer were after mastectomy randomly assigned to receive adjuvant systemic therapy and postoperative irradiation to the chest-wall and regional lymph nodes (1538 pts), or adjuvant systemic therapy alone (1545 pts). Pre- and postmenopausal patients (DBCG 82b) received 8–9 cycles of CMF with an interval of 4 weeks, whereas postmenopausal patients (DBCG 82c) received tamoxifen 30 mg daily for one year. The median follow-up time was 34 years. The primary endpoints were loco-regional recurrence (LRR) and overall mortality, and the secondary endpoints were distant metastasis, breast cancer mortality, and irradiation related late morbidity.

Results: Overall the 30-year cumulative incidence of loco-regional recurrence was 9% in irradiated patients versus 37% in non-irradiated patients who received adjuvant systemic therapy alone (HR: 0.21 [95% cfi 0.18–0.26]). Distant metastasis probability at 30 years was 49% in irradiated patients compared to 60% in non-irradiated (HR: 0.77 [0.70–0.84]). Consequently, these figures resulted in a reduced breast cancer mortality: 56% vs 67% (HR: 0.75 [0.69–0.82], and overall mortality (81% vs 86% at 30 years (p < 0.0001), HR: 0.83 [0.77–0.90] in favor of irradiation. Radiotherapy did not result in any significant excess death of other courses, such as ischemic heart disease, HR: 0.82 [0.58–1.18]; nor secondary lung cancer HR: 1.44 [0.92–2.24], or other non-cancer related death HR: 1.15 [0.92–1.45].

Conclusion: The study definitely demonstrate that optimal long-term treatment benefit of high-risk breast cancer can only be achieved if both loco-regional and systemic tumor control are aimed for. Therefore, radiotherapy has an important role in the multidisciplinary treatment of breast cancer. The PMRT treatment did not result in excess ischemic heart damage, nor in other non-breast cancer related death.

© 2022 The Authors. Published by Elsevier B.V. Radiotherapy and Oncology 170 (2022) 4–13 This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

The DBCG 82bc randomized trial recruited between 1982 and 1990 3083 patients in a clinical trial to address the importance of postmastectomy radiotherapy (PMRT) to high-risk breast cancer patients who also received adjuvant systemic treatment [1,2]. The trial was initiated at a time where the role of local tumor control was heavily debated in the light of the potential importance of controlling a nidus for subsequent disseminated disease. The study...
therefore challenged the Alternative Hypothesis formulated by the late Bernard Fisher as an alternative to the original Halstedian Hypothesis, which states that tumors spread in an orderly defined manner, and that the extent and nuances of the loco-regional treatment are the dominant factors influencing patient outcome [3]. Fisher’s systemic paradigm claimed that the dissemination of breast cancer had taken place at the time of the diagnosis, although there was only clinical evidence of loco-regional disease. This paradigm was later modified by Hellman into the Spectrum Hypothesis [4], saying that breast cancer is a heterogeneous disease – a spectrum ranging from a disease that remains local throughout the course, to a disease which is systemic when first detectable. Thus, there could be situations where metastases would develop as a consequence of residual inadequately treated loco-regional disease, which therefore needed to be controlled. In retrospect, the DBCG 82bc trial did challenge this hypothesis. The study was first published in two pivotal papers [1,2] with an outcome which was in favor of the Hellman Spectrum paradigm. In the following years the data were more detailed elaborated [5–16], both regarding the heterogeneity of the outcome as well as regarding the potential morbidity. The results gained wide interest and has subsequently been supported by several large meta-analyses [17,18], and consequently made the basis for major international guidelines regarding the indication for PMRT. However, a complete report of the full DBCG 82bc study has never previously been published. Since the natural history of radiotherapy in breast cancer demand long-term follow-up, both regarding recurrence of the disease and the potential risk of late treatment related morbidity, we hereby present 30 years’ follow-up data of the world’s largest randomized trial of postmastectomy radiotherapy. This allows an evaluation of the final outcome of such intervention as well as a focus on potential late (radiation) morbidity, not least the risk of secondary cancer induction [19] and ischemic heart disease [5]. The latter has recently drawn significant attention and has become a major factor in the discussion of the indication for, and the applied technique in breast cancer radiotherapy [20,21]. Furthermore, our treatment technique did include the internal mammary lymph nodes and our study has therefore addressed the two most pertinent issues in breast radiotherapy, namely the importance of including relevant regional lymph nodes in the radiation field and the avoidance of excess cardiac irradiation [22,23].

The aim of the present analysis was to present a comprehensive analysis of the complete DBCG 82bc study and evaluate the long-term effect of radiotherapy after modified radical mastectomy in high-risk pre- and postmenopausal patients also receiving adjuvant systemic therapy. The analysis will especially focus on the importance of loco-regional and distant tumor control, breast cancer mortality, overall survival, and life-threatening treatment related morbidity.

Material and methods

A detailed description of the protocol design and treatment has previously been given [1,2,6,7,24]. After mastectomy, pre- and menopausal women (protocol DBCG 82b) were equally randomized to PMRT + CMF (cyclophosphamide, methotrexate, 5-fluorouracil) versus CMF alone versus CMF + TAM (tamoxifen). Similarly, post-menopausal women (protocol DBCG 82c) were randomized to PMRT + TAM versus TAM alone or CMF + TAM. Since the present report will address the role of radiotherapy, the patients randomized to combined PMRT and systemic treatment (CMF or TAM, respectively) will be compared to the treatment groups receiving the same systemic treatment only. The patients randomized to combined systemic therapy with CMF + TAM are not included in the present analysis, but the outcome has been reported elsewhere [25,26].

Study participants

Women with high-risk early breast cancer were randomly assigned to receive postoperative radiotherapy in addition to adjuvant systemic therapy.

Between September 1982 and March 1990, we included 3083 patients, 1708 were pre- and menopausal, and 1375 patients were postmenopausal and below 70 years of age. High-risk status was defined as node positive and/or T > 5 cm and/or invasion of the skin or pectoral fascia. Pre- and menopausal patients were randomized to PMRT + CMF (cyclophosphamide, methotrexate, and fluorouracil) (852 patients) versus CMF alone (856 patients) in protocol DBCG 82b and postmenopausal patients were randomized to PMRT + TAM (tamoxifen) (686 patients) versus TAM alone (689 patients) in protocol DBCG 82c.

The demographic, clinical and pathologic characteristics of patients in relation to protocol and treatment are given in Table 1 and Supplementary Table 1, and shows that they are equally distributed among randomized groups: 44% of the women were 50 years of age or below; 60% had tumors above 2 cm in diameter. Most women (86%) had a ductal carcinoma, which were grade 1 in 26%, grade 2 in 52% and grade 3 in 22% of the cases. A median of 7 axillary nodes were removed at surgery, and positive axillary lymph-nodes were present in 91% of the patients, with 31% having 4 or more positive nodes identified.

Treatment

The treatment included macro-radical surgery. All patients were treated with total mastectomy with partial axillary dissection with the intention to remove level 1 and partly level 2 axillary nodes and all macroscopically enlarged lymph nodes. After surgery patients were referred to adjuvant systemic therapy and randomization to PMRT or not. The systemic therapy in pre- and menopausal patients consisted of 8–9 cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil in a dose of 600, 40, 600 mg/m²) i.v. every 4 weeks for 9 months. Postmenopausal patients received tamoxifen 30 mg daily for 48 weeks.

Patients who were randomized to receive PMRT were treated with a dose of 48–50 Gy in 22–25 fractions in 5 weeks to the chest wall and regional lymph nodes (internal mammary nodes, peri-clavicular nodes, and the axilla). A detailed description of the radiotherapy technique and compliance has previously been published [6,24], and it should be noted that the technique secured avoidance of irradiation to the heart [5]. All but 132 patients were treated on a linear accelerator, the remaining patients were treated with 250 KV X-rays using the McWhirther technique [6]. The timing of radiotherapy in patients receiving CMF was the following: One cycle of CMF, then after 1 week start of radiotherapy for 5 weeks and after another 1–2-week interval the CMF was continued every 4 weeks for a total of 8 cycles in irradiated patients. The compliance to PMRT was high and only 77 of 1538 (5%) of the patients randomized to PMRT, did not complete the specified radiat treatment [6].

Follow-up, endpoints, and statistical analysis

Long-term follow-up information was obtained for all patients as previously described [7,10,12]. Denmark has a public national health care system, with a detailed registration of all patients, therefore we have been able to secure a full follow-up with...
recording of all relevant events until at least 1st of April 2021. With the exception of 7 patients who emigrated, all patients were followed until death or at least for 30 years, with a median observation time of 34 years estimated using reverse Kaplan-Meier. Patient and treatment characteristics were compared using chi-squared test.

The primary endpoints were loco-regional recurrence (LRR) and overall mortality. LRR was defined as any reappearance of cancer in the ipsilateral chest wall and/or axillary and/or supra/infraclavicular nodes. Secondary endpoints included distant metastasis, any recurrence (LRR or distant metastasis), contralateral breast cancer, breast cancer death, second malignant disease (lung or other cancer, incidence and death), ischemic heart disease (incidence and death), and other causes of death.

The probability of overall survival, and risk differences between treatment arms, were calculated using the Kaplan-Meier estimator and the log-rank test for comparison [27]. The probabilities of all other endpoints were calculated using the Aalen-Johansen estimator and Gray's test for comparison [27], and risk differences were calculated using the pseudo value approach. Cox proportional hazards models were used to obtain cause-specific hazard ratios (HR) [27]. Multivariate models were stratified by menopausal status and adjusted for age, tumour size, histology/grade, and deep fascia and skin invasion. Incidence data and HRs are presented with 95% confidence intervals.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>All (N = 3083)</th>
<th>No PMRT (N = 1545)</th>
<th>PMRT (N = 1538)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal (CMF)</td>
<td>1708</td>
<td>856</td>
<td>852</td>
<td>1.00</td>
</tr>
<tr>
<td>Postmenopausal (TAM)</td>
<td>1375</td>
<td>689</td>
<td>686</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>53 (22–70)</td>
<td>53 (22–70)</td>
<td>53 (25–70)</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>385</td>
<td>196</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>41–50 years</td>
<td>976</td>
<td>495</td>
<td>481</td>
<td></td>
</tr>
<tr>
<td>51–60 years</td>
<td>899</td>
<td>436</td>
<td>463</td>
<td></td>
</tr>
<tr>
<td>≥61 years</td>
<td>823</td>
<td>418</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 mm</td>
<td>1194</td>
<td>593</td>
<td>601</td>
<td>0.42</td>
</tr>
<tr>
<td>21–50 mm</td>
<td>1462</td>
<td>722</td>
<td>740</td>
<td></td>
</tr>
<tr>
<td>&gt;51 mm</td>
<td>396</td>
<td>213</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>31</td>
<td>17</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Nodes removed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>1842</td>
<td>908</td>
<td>934</td>
<td>0.27</td>
</tr>
<tr>
<td>≥8</td>
<td>1241</td>
<td>637</td>
<td>604</td>
<td></td>
</tr>
<tr>
<td>Positive nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>267</td>
<td>141</td>
<td>126</td>
<td>0.38</td>
</tr>
<tr>
<td>1–3</td>
<td>1856</td>
<td>920</td>
<td>936</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>958</td>
<td>484</td>
<td>474</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Histology/Malignancy grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma*</td>
<td>2663</td>
<td>1320</td>
<td>1343</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>696</td>
<td>347</td>
<td>349</td>
<td>0.46</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1382</td>
<td>695</td>
<td>687</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>585</td>
<td>278</td>
<td>307</td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>289</td>
<td>155</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Unknown/other</td>
<td>131</td>
<td>70</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Deep fascia invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2488</td>
<td>1246</td>
<td>1242</td>
<td>0.81</td>
</tr>
<tr>
<td>Yes</td>
<td>512</td>
<td>260</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>83</td>
<td>39</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Skin invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2739</td>
<td>1371</td>
<td>1368</td>
<td>0.85</td>
</tr>
<tr>
<td>Yes</td>
<td>326</td>
<td>166</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>18</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*The group 'Ductal carcinoma' is the sum of the groups 'Grade 1-3' and is not included as a distinct group in any analysis.

**In the multivariate analysis, the patients who were unknown regarding deep fascia invasion and skin invasion were set to ‘No’.

Definitions of events, competing events, and censoring are described in details in Supplementary Document. Patients were censored at emigration or 1st of April 2021, whatever occurred first and prior to any other event. All time estimates were done using the date of mastectomy as initial value. The treatment effect was evaluated in accordance with the intention to treat principle. The patients were included in their randomization group, irrespective of whether they completed the planned treatment or not. Results were judged significant if the p value was less than 0.05. No attempts were made to correct for multiple comparisons. Calculations were done using Stata 17.0 (StataCorp LLC, Texas, USA).

Results

After 30 years of follow-up 1853 (60%) patients had developed a recurrence including 731 (24%) with loco-regional failure, and 2699 (88%) had died, 1916 (62%) from or with breast cancer and 783 (25%) from other causes (Supplementary Table 2). The patterns of failure and frequency of events in relation to tumor characteristics and treatment are shown in Supplementary Tables 3A-3E. The frequency of loco-regional recurrences increased with tumor size, invasion of pectoral fascia or skin, number of positive nodes, and grade of anaplasia in ductal carcinomas, irrespective of treatment.
Postmastectomy radiotherapy resulted in a fourfold reduction of the 30-year loco-regional failure rate from 37% to 9% with a univariate hazard ratio (HR) for loco-regional failure of 0.21 [95% CI 0.18–0.26], p < 0.0001. This in turn resulted in a reduced overall mortality with a 5% difference after 30 years (81% vs 86% for irradiated and non-irradiated patients, respectively, HR 0.83 [0.77–0.90], p < 0.0001 (Fig. 1). Similarly, PMRT significantly reduced the risk for developing distant metastasis: HR 0.77 [0.70–0.84]; the failure due to any recurrence: HR 0.65 [0.59–0.71]; and death from breast cancer: HR 0.75 [0.69–0.82]; whereas there was no significant difference in death from other cancer: HR 1.12 [0.90–1.40]. Neither did PMRT increase the risk for development of a contralateral breast cancer: HR 0.78 [0.61–0.98]. (Fig. 2). Other causes of death not related to the breast cancer or its treatment were not significantly different among the two treatment groups HR 1.15 [0.92–1.45].

Fig. 3A shows that the statistically significant reduction in the cumulative incidence of loco-regional tumor failure that was observed among the irradiated patients was present in all subgroups, and the addition of irradiation to systemic treatment generally reduced the frequency of loco-regional recurrence to between one third to one fourth of the comparable non-irradiated groups (Supplementary Table 3A). Although less pronounced, the overall mortality figures revealed a similar significant benefit, which again was seen in all subgroups (Fig. 3B, Supplementary Table 3E). A multivariate analysis confirmed this outcome for both endpoints (Fig. 3C and D). Similar did uni- and multivariate analyses using different endpoints (Supplementary Fig. 1), demonstrating the same pattern in outcome, irrespectively of endpoints.

The results confirmed the major prognostic factors in high-risk breast cancer to be large tumor size, high grade of anaplasia and more than 4 positive nodes as the most prominent indicators of poor prognosis, both regarding risk of loco-regional failure (Fig. 4A), distant metastasis (Supplementary Fig. 4B), and the consequently risk of dying (Fig. 4B).

A multivariate Cox regression analysis stratified for menopausal status/protocol and using loco-regional recurrence as endpoint found radiotherapy together with large tumor size, and ≥4 pathological lymph nodes to be most crucial for the outcome (Fig. 4C). Using death from any cause as an endpoint, the same parameters together with age between 41 and 50 years were found to be most important (Fig. 4D). The outcome for the different endpoints followed the same pattern (Supplementary Fig. 4).

Subgroup analysis

When analyzed as a function of protocol (i.e. menopausal status and type of systemic therapy) the pattern of response (Supplementary Table 2) and effect of PMRT (Supplementary Fig. 2) were in principle the same in the two protocols, and similar to what was seen in the overall analysis. The only difference was slightly more non-breast cancer related deaths among the older postmenopausal patients.

PMRT reduced the 30-year loco-regional failure rate from 46% to 13% in 4+ positive nodes patients, and from 34% to 8% in patients with 1–3 positive nodes. Similarly, the 30-year breast cancer related mortality after PMRT was significantly reduced in both patients with 1–3 positive nodes (48% vs 60%) and in patients with 4+ positive nodes (74% vs 88%). A detailed analysis for all endpoints can be seen in Supplementary Fig. 3.

The trial was performed before the introduction of hormone receptor analysis and other biomarkers, but also tumor histopathology and grade of anaplasia was found to influence the outcome (Fig. 4 and Supplementary Figs. 4 and 5). Ductal carcinomas were the most frequent (86%) and among these were tumors with low malignancy grade the most sensitive to PMRT (Fig. 3 and Supplementary Fig. 1). A similar beneficial pattern was also found for tumors of small size (<20 mm).

Late effects

We have previously described the late sequelae of radiation with focus on shoulder movement and lymphedema [9]. In the present analysis, attention is given to long-term life-threatening morbidity related to cardiac irradiation and/or the risk of secondary cancer induction. After 30 years of observation, we found no radiation related difference in the incidence of ischemic heart disease (IHD) [HR 0.86 [0.67–1.10], nor in the mortality HR 0.82 [0.58–1.18]. (Fig. 5A, B). IHD occurred most frequently in the postmenopausal patients, but to the same extent in both treatment arms (Supplementary Table 2). Also, the risk of developing contralateral breast cancer was unrelated to the use of radiotherapy, with a 30-years incidence of 9% and 10%, for irradiated or non-irradiated patients, respectively (Fig. 2C). There were slightly more cases with secondary lung cancer among the irradiated patients (HR 1.51 [0.98–2.33], and HR 1.44 [0.92–2.26] for incidence and mortality, respectively). (Fig. 5C, D) but not to a statistically significant degree, and similarly did secondary non-lung cancer occur with same frequency in both treatment arms (Fig. 5E, F).

M. Overgaard, Hanne Melgaard Nielsen, T. Tramm et al. Radiotherapy and Oncology 170 (2022) 4–13
Death from other causes, which with increasing observation time become relatively more frequent, did not differ as a function of postmastectomy irradiation (HR 1.15 [0.92–1.45]).

An overall summary of the outcome is given in Fig. 6. Fig. 6A summarizes the cause-related mortality, and demonstrate that the only significant difference was related to more frequent breast cancer deaths in the non-irradiated group of patients. Fig. 6 B gives an overview of the primary and secondary endpoints and shows that PMRT given to patients with high-risk early breast cancer results in markedly reduced loco-regional recurrences, fewer distant metastases and consequently a significant reduction of any recurrences. In turn this results in a significant reduction in overall death, due to less breast cancer death, whereas death from ischemic heart disease, secondary lung or other cancer, and death from other causes did not differ significantly between patients receiving PMRT or not.

Discussion

This long-term evaluation of PMRT in high-risk breast cancer patients given systemic therapy confirmed our conclusions that radiotherapy results in a substantial reduction of local regional recurrences, which in turn also results in fewer distant metastases, less breast cancer deaths, and after 30 years a significantly better overall survival of the irradiated patient group. Our results strongly support the initial concept by Tubiana and co-workers [28], which points to the regional lymph nodes as the nidus for later distant dissemination and the consequential ‘Spectrum Hypothesis’ formulated by Samuel Hellman in 1994. This previously mentioned hypothesis “considers breast cancer to be a heterogeneous disease that can be thought of as a spectrum of proclivities extending from a disease that remains local throughout its course to one that is systemic when first detectable”. Thus, there could be situations where metastases would develop as a consequence of residual inadequately treated loco-regional disease [4]. Such disease may be occult at the time of treatment and may very likely have spread to the regional lymph nodes in the axilla, periclavicular or internal mammary lymph nodes. Our long-term analysis consequently confirms this hypothesis, which is also substantiated by contemporary trials [29,30] and several EBCTCG meta-analyses [17,18]. Clarke et al. [17] further estimated that every four local failures, which can be avoided, will result in one less death from breast cancer. In our study, this finding is even more pronounced with a five-year risk reduction in loco-regional recurrence of 23%, resulting in a 10% reduction in breast cancer mortality after 15 years (ratio 2.3:1) and a similar reduction in overall mortality of 9% (ratio 2.6:1). The reduction in breast cancer mortality was even more pronounced after 30 years (12%) although the difference in overall mortality, due to increasing number of deaths from other causes, were reduced to 5%.

In a more recent study, we explored and confirmed the importance of regional lymph node (especially internal mammary nodes), irradiation as an important factor in reducing overall mortality, not least in node positive patients [23]. An observation which now is confirmed in several randomized trials [22].

Both the surgical technique, especially when it comes to handling of the axilla and the systemic treatment were not comparable
to current therapy, and the numbers of loco-regional recurrences found in our study is much higher than what is currently observed [31,32]. Although this may have quantitative implications for the indication for treatment, it does not seem to alter the natural history of breast cancer.

The long-term evaluation confirmed our previous subgroup studies in patients with 8 lymph nodes removed [10,13], namely that the outcome is heterogeneous both regarding the biological properties of the tumors and the variation in loco-regional versus survival benefits. The loco-regional recurrence rate and the reduction by radiotherapy is most prominent in the biological advanced and aggressive tumors with 4+ positive nodes, but it is the less aggressive tumors with 1–3 positive lymph nodes, which have both the absolute and relatively largest improvement in overall survival after PMRT. Thus, there does not exist a general relationship between the reduction in local regional failure and subsequent improvement in the overall survival.

Whereas indications for breast cancer radiotherapy to a large extent are based on patients age, tumor size and nodal status, the histopathological characteristics and biomarkers related to tumor subtypes have played a limited role. Our previous subgroup analysis of 1068 patients, where such characteristics have been analyzed [12–14] showed marked heterogeneity in response as a function of tumor subtypes. Most characteristic was the fact that the systemic benefit of PMRT was found to be most pronounced in patients with less aggressive tumors, such as hormone receptor positive, HER2 negative and Luminal A type. More aggressive tumors mainly have benefit in terms of reduced loco-regional recurrences, but with limited long-term survival benefit, probably because such tumors may have disseminated prior to the loco-regional treatment and is not controllable, especially with the less aggressive systemic treatment applied in this trial [12,13].

In the preparatory process of the protocols, major efforts were used to define a comprehensive target volume which could be covered by a simple 2D treatment plan based on individual measurements from the patient, in an attempt to spare critical structures such as spinal cord, lung and heart [24]. Obviously PMRT is associated with a certain risk of morbidity [9] but with the applied technique life threatening late morbidities in the form of cardiovascular problems and secondary cancer induction were largely avoided. The heart shielding treatment of the chest wall [5,6], was introduced by serendipity, because the study was initiated prior to the focus of long-term cardiac related late mortality in breast cancer patients [20,32]. With a shorter observation time, we have previously showed that the use of an electron field to the chest wall did not yield any detectable enhanced incidence

---

**Fig. 3.** Subgroup analysis on the effect of radiotherapy on locoregional recurrence (A: univariate, C: multivariate) and overall mortality (B: univariate, D: multivariate).
or morbidity of ischemic heart disease [5]. Since this phenomenon is associated with a substantial latency time, beyond 10 years [33], our current study with more than 30 years follow-up is the first randomized trial to confirm the benefit of such avoidance, as the hazard ratio for death of ischemic heart disease is 0.81 [0.58–1.13]. Although our 2D treatment technique can be further improved [34] this avoidance of excess cardiac morbidity was a major factor in the long-term beneficial outcome of this treatment [35].

Although not statistically significant we observe a slight, but late increase in lung cancer risk with a hazard ratio of the same magnitude as that observed in larger studies [19,21,36], suggesting that radiation induced lung cancer may occur as a consequence of breast irradiation. No other long-term excess courses of death were associated with PMRT, especially no differences in the risk of developing a contralateral breast cancer, or any other cancer associated with postmastectomy irradiation. Other late problems associated with arm mobility, lymphedema, (pulmonary)fibrosis and other troublesome late effects are often associated with the combined multimodality, and overall, one should be aware of the combination of irradiation, surgery and systemic therapy, which in these delicate anatomical areas may cause long-term morbidity for some patients [37,38].

This has also been the basis for the development of loco-regional treatment of breast cancer, in the many years since the DBCG 82 trial, where the more effective and aggressive systemic therapy is likely to lessen the need for intensive radiotherapy to all patients [39]. Current clinical trials are attempting to adjust these parameters, which furthermore should be seen in the light of an overall change in the breast cancer disease, which increasingly is showing more favorable prognostic features, and also have become more frequent in elderly patients, so the therapeutic burden must be adjusted accordingly [40].

As previously mentioned, the DBCG 82bc study did also include a third arm evaluating the role of combined CMF + TAM (without PMRT). The use of such combined CMF + TAM did not yield any survival benefit when compared to CMF alone (DBCG 82b) [25], or TAM alone (DBCG 82c) [26], suggesting that more intense systemic therapy would likely not change the conclusion of the present study.

In conclusion, the 30-year long-term evaluation of the DBCG 82bc study demonstrates that postmastectomy radiotherapy strongly improved the loco-regional tumor control and subsequent survival. This gives evidence to the hypothesis that residual inadequately treated loco-regional disease can be the nidus for a subsequent dissemination. Adjuvant radiotherapy must therefore be considered an important part of the multidisciplinary treatment of early breast cancer, and all relevant local and regional tumor sites must be included in the radiotherapy target in balance with the extent of surgery. This can be achieved without serious or even lethal late effects. Our study also underlines that breast cancer is a disease with a natural history, which require long-term observation in order to provide the proper conclusions of therapeutic intervention.

### Fig. 4.
Factors associated with locoregional recurrences (A: univariate, C: final multivariate model) and overall mortality (B: univariate, D: final multivariate model).
Fig. 5. Effect of radiotherapy on ischemic heart disease (A: incidence, B: mortality), second primary cancer, lung (C: incidence, D: mortality), and second primary cancer, non-lung (E: incidence, F: mortality).
Conflict of interest
The authors declare that none of them have any conflicts on interest in relation to the present publication.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.03.008.

References
[10] Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007;82:247–53.
Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery.


