Phase III randomised trial

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

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Abstract

Background and aim: Numerous consensus reports recommend that postmastectomy radiotherapy (RT) in addition to systemic therapy is indicated in high-risk patients with 4+ positive nodes, but not in patients with 1–3 positive nodes. A subgroup analysis of the DBCG 82 b&c trials was performed to evaluate the loco-regional recurrence rate and survival in relation to number of positive nodes.

Materials and methods: In the DBCG 82 b&c trials 3083 pre- and postmenopausal high-risk women were randomized to postoperative RT in addition to adjuvant systemic therapy. Since many patients had relatively few lymph nodes removed (median 7), the present analysis was limited to 1152 node positive patients with 8 or more nodes removed.

Results: The overall 15-year survival rate in the subgroup was 39% and 29% (p = 0.015) after RT and no RT, respectively. RT reduced the 15-year loco-regional failure rate from 51% to 10% (p < 0.001) in 4+ positive node patients and from 27% to 4% (p < 0.001) in patients with 1–3 positive nodes. Similarly, the 15-year survival benefit after RT was significantly improved in both patients with 1–3 positive nodes (57% vs 48%, p = 0.03) and in patients with 4+ positive nodes (21% vs 12%, p = 0.03).

Conclusion: The survival benefit after postmastectomy RT was substantial and similar in patients with 1–3 and 4+ positive lymph nodes. Furthermore, it was not strictly associated with the risk of loco-regional recurrence, which was most pronounced in patients with 4+ positive nodes. The indication for RT seems therefore to be at least equally beneficial in patients with 1–3 positive nodes, and future consensus should be modified accordingly.

Keywords: Postmastectomy radiotherapy; Breast cancer; Positive lymph nodes; Randomized clinical trial

One of the most controversial questions regarding indication for postmastectomy irradiation is whether or not radiotherapy is indicated in patients with small tumors with 1–3 positive nodes. In numerous recent consensus reports and guidelines concerning postoperative radiotherapy in breast cancer, the recommendation is no radiotherapy to patients with 1–3 nodes positive as the only criterion [1–7]. The background for this conclusion is the general assumption that only patients with very high risk of loco-regional recurrence will benefit from postoperative radiotherapy in terms of survival. This is also supported by the most recent EBCTCG overview analysis published in 2005, in which the survival gain from radiotherapy is interpreted to be directly proportional to the reduction of loco-regional recurrences [8].

A typical explanation is expressed in the following citation from the NIH Consensus Report 2000 [3]: “There is evidence that women with high risk of loco-regional tumor recurrence after mastectomy benefit from postoperative radiotherapy. This high-risk group includes women with four or more positive nodes or an advanced primary tumor… At this time, the role of postmastectomy radiotherapy for women with one to three positive lymph nodes remains uncertain and is being examined in a randomized clinical trial”.

So far no trial dedicated to solve this issue has been conducted. However, there have been some attempts. The National Cancer Institute of Canada Clinical Trials Group (www.ctg.queensu.ca) MA25 study was designed to randomly assign patients with 1–3 positive nodes to receive either loco-regional radiotherapy or no radiotherapy after mastectomy, but the study was closed because of lack of accrual. However, another study from the same group
(MA20) has been activated. It includes patients who have undergone breast-conserving surgery, high risk node positive and node negative, who are randomly allocated to receive standard breast radiotherapy versus loco-regional radiotherapy. The patients are stratified according to number of involved nodes. Pending proper inclusion of patients in ten years or more time, this trial may provide additional evidence on the role of loco-regional radiotherapy in the subgroup of women with 1–3 positive nodes. In addition, the European SUPREMO study (www.supremo-trial.com) has recently been activated. In this study patients with an expected intermediate risk (i.e., 1–3 nodes positive or ductal carcinoma grade III) of loco-regional recurrence after mastectomy are randomized to chest wall irradiation versus no radiotherapy. Again, it will take quite some years before any conclusive results become available.

On this basis, it would be interesting to investigate if a subgroup analysis of the two largest and most recent postmastectomy trials [9–15] can provide valuable information. In the following a subgroup analysis of the DBCG 82 b&c protocols is presented with an attempt to evaluate whether the separation between 1–3 and 4 or more positive lymph nodes is a relevant descriptor of the indication for postmastectomy radiotherapy in high risk patients also receiving systemic therapy.

Materials and methods

Summary of DBCG 82 b&c protocol

In the DBCG 82 b&c trials [9–15] a total of 3083 pre- and postmenopausal high-risk women were randomly assigned to postoperative RT in addition to adjuvant systemic therapy. Overall, the results showed a significant reduction in loco-regional recurrences and mortality in all irradiated patients. The two studies were conducted from November 1982 to March 1990. Among the 3083 patients included, 1708 were pre- and menopausal (DBCG 82b), and 1375 patients were postmenopausal and below 70 years of age (DBCG 82c). Only high-risk patients were included, defined as patients who were node positive and/or a T3 or T4 tumor and/or skin or deep fascia invasion.

Selection of subgroup

Due to the fact that only a median of 7 lymph nodes have been removed it was not possible to do a detailed analysis of the importance of nodal status (including the role of number of positive nodes) in the whole patient material. Therefore, for the current study we have selected a subgroup of 1152 patients who met the criteria of having 8 or more nodes removed (above the median value) and who were node positive.

Treatment

The treatment included macro-radical surgery. Only patients assessed operable could be included. 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 for adjuvant systemic therapy and randomization to postoperative radiotherapy. The systemic therapy in pre- and menopausal patients consisted of 8–9 cycles of CMF (600, 40, and 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 radiotherapy 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). 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- to 2-week interval the CMF was continued every 4 weeks for a total of 8 cycles in irradiated patients. A detailed description of the radiotherapy technique and compliance has recently been published [12]. Of special notice is the fact that the applied radiotherapy has avoided irradiation of the heart, and thus no excess cardiac morbidity and death has been recorded [13].

Follow-up, endpoints, and statistical analysis

Long-term follow-up information was obtained for all patients as previously described [14,15]. The endpoints were overall survival and loco-regional recurrence after mastectomy without simultaneous distant metastases (LRR). An LRR was defined as any reappearance of cancer in the ipsilateral chest wall and/or axillary and/or supra/infraclavicular nodes without any prior or simultaneous distant failure. If distant metastases occurred within one month of the LRR the patient was not included in this analysis.

The probability of LRR and overall survival was calculated by the Kaplan–Meier method. Using this method for estimating other events than survival may result in an overestimate due to the non-independence between competing different events [15,16]. For this reason, we also present the absolute frequencies of the endpoint. This principle is also applied in the EBCTCG overview [8]. When calculating the probability of LRR, censuring was done in the case of distant metastasis, contralateral breast cancer, death or the date of last contact, whatever occurred first. Comparison between the subgroups was performed by the log rank test using a level of significance of 5% and with a two-sided test.

The bottom line estimation of "number of patients needed treat" was calculated as suggested by Greenhalgh [17]. 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. The evaluation date for recurrences and survival was November 15, 2004, which resulted in a median potential follow-up time after mastectomy of 18 years (range 15–22). Calculations were done using the BMDP 1L and 2L programme.

Results

The relationship between the groups of patients according to number of positive nodes and postoperative treatment is shown in Table 1. It appears that the four groups were evenly distributed regarding classical tumor
and patient characteristics. The 1152 patients with eight or more nodes removed included in the present study did not differ from the overall cohort of 3083 patients [9,10,14].

Within 15 years after treatment a total of 179 (16%) patients suffered from an LRR and 762 (66%) patients had died. The LRR was distributed between 23/563 (4%) in the RT group and 156/589 (26%) in the no RT group, resulting in a 15-year actuarial value of 6% and 37%, respectively, \( p < 0.001 \) and a relative risk (RR) of 0.12 (0.07–0.19, 95% cf.l.). A similar effect was seen when evaluating the outcome using survival where 343 (61%) patients had died in the RT group and 419 (71%) patients in the no RT group. The 15-year survival values were 39% and 29%, respectively \( (p = 0.015) \), and with an RR of 0.63 (0.49–0.81, 95% cf.l.).

Fig. 1 shows a similar analysis, but evaluated separately as a function of 1–3 or 4 and more positive lymph nodes. RT resulted in a substantial reduction in the 15 year loco-regional failure rate from 51% to 10% \( (p < 0.001) \) in 4+ positive node patients and from 27% to 4% \( (p < 0.001) \) in patients with 1–3 positive nodes, respectively. In contrast, the reduction in the 15-year loco-regional failure rate was most pronounced in patients with large tumors (7% vs 43% for RT and no RT, respectively) compared to small tumors (4% vs 29% for RT and no RT, respectively). This influence of tumor size was observed in both nodal subgroups and did consequently not offset the overall conclusion regarding outcome and number of positive nodes.

A different way to assess the potential benefit of postmastectomy radiotherapy can be performed by a “bottom line” calculation which estimates the absolute and relative risk reduction and, most illustratively also the number of patients needed to treat to achieve the wanted benefit. As seen in Table 2, these values are almost identical irrespective of number of positive nodes, and furthermore of such a magnitude that for every ten patients irradiated approximately two LRR and one death can be avoided. Overall, this indicates that postmastectomy radiotherapy is beneficial in the described cohort of high-risk patients and, importantly, unrelated to the number of positive lymph nodes.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and tumor characteristics by nodal status and treatment</th>
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<tbody>
<tr>
<td></td>
<td>1–3 positive nodes</td>
</tr>
<tr>
<td></td>
<td>No RT</td>
</tr>
<tr>
<td>All pts</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>276 (100)</td>
<td>276 (100)</td>
</tr>
<tr>
<td>Menopausal status and systemic therapy</td>
<td></td>
</tr>
<tr>
<td>Premenopausal (CMF)</td>
<td>159 (58)</td>
</tr>
<tr>
<td>Postmenopausal (TAM)</td>
<td>117 (42)</td>
</tr>
<tr>
<td>Age &lt;41</td>
<td>34 (12)</td>
</tr>
<tr>
<td>&lt;41–50</td>
<td>93 (34)</td>
</tr>
<tr>
<td>51–60</td>
<td>68 (25)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>81 (29)</td>
</tr>
<tr>
<td>Tumor size &lt;21 mm</td>
<td>131 (47)</td>
</tr>
<tr>
<td>21–50</td>
<td>133 (48)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Tumor type (WHO)</td>
<td>Ductal, NOS</td>
</tr>
<tr>
<td>Lobular</td>
<td>26 (9)</td>
</tr>
<tr>
<td>Medullary</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Unknown/others</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Malignancy grade (Ductal carcinoma, NOS)</td>
<td>Grade I</td>
</tr>
<tr>
<td>Grade II</td>
<td>114 (49)</td>
</tr>
<tr>
<td>Grade III</td>
<td>46 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>
The results from the present subgroup analysis strongly indicate that the benefit of postoperative radiotherapy is equally pronounced in patients with 1–3 nodes positive and in patients with 4+ nodes. Thus, the present results may compensate for the lack of more evidence in order to recommend radiotherapy in patients with 1–3 nodes positive along with patients with 4+ nodes, where it is a standard treatment. This has also been pointed out before, but apparently not with sufficient strength to influence the consensus reports [7,18,19].

In addition to the data presented here, there is accumulating information from other subgroup analyses that supports our results. Thus, the 20-year results of the British Columbia study have shown that the impact of radiation therapy for all survival outcomes in the subgroup with 1–3 nodes involved was similar to the subgroup with 4+ nodes involved and had a magnitude of risk reduction, which for both groups were of the same order as in the present subgroup analysis [20]. Further, in the 2005 EBCTCG overview [8] additional data are presented (Annex-figures 2d and 2e) which indicate the same benefit of radiotherapy to patients with 1–3 nodes positive and patients with 4+ nodes.

Table 2
The Bottom line estimate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1–3 pos. nodes</th>
<th>4+ pos. nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoint: loco-regional recurrence</strong></td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Number of patients needed to treat to avoid an LRR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endpoint: death</strong></td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Number of patients needed to treat to avoid a death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative and absolute risk reduction and number of patients needed to treat to achieve benefit of postmastectomy radiotherapy as a function of number of positive lymph nodes. Estimates are calculated for the benefit of avoiding an isolated first loco-regional recurrence or death.
patients with 1–3 and 4+ positive nodes, respectively. This may however be a circular argument since most of the patients in this EBCTCG subgroup in fact are from the DBCG 82 protocols.

Only patients with 8 or more nodes removed have been included in our current analysis, whereas this was not corrected for in the EBCTCG subgroups. A selection of a proper group of patients relevant for the study might assure a more precise answer. However, the overall LRR and survival rates observed in the present subgroup were similar to those observed in the entire DBCG 82 b&c study. This implies that the current subgroup, despite being selected to secure the best evaluable patients regarding surgical/axillary procedure, in fact did not differ from the overall study population. The results from the subgroup analysis are therefore most likely representative for the entire study.

The background for the continuing debate about the indication for radiotherapy, especially in the two subgroups of node positive patients, can be seen as part of the history of the paradigmatic shift in the management of breast cancer towards more aggressive loco-regional treatments. This is due to the fact that loco-regional radiation therapy improves survival by reducing local recurrences not prevented by adjuvant systemic therapy [1,2,21]. The multiple randomized radiotherapy trials conducted in the past have included both node negative and node positive patients, but have not been stratified according to the degree of nodal involvement. From overview analyses of these studies it has clearly been demonstrated that radiotherapy reduces the local recurrence rate irrespective of nodal status, whereas a reduction in breast cancer mortality and overall mortality could only be found in node positive patients [8]. But despite the fact that a survival benefit thus was seen in all node positive patients, this has only led to a consensus about treating patients at high risk of loco-regional recurrence (i.e., patients with primary tumor >5 cm, or more than 4 positive nodes) [1–7]. The explanation for that is firstly a concern about the potential for increased risk of late cardiac morbidity which could outweigh a modest reduction in breast cancer death [2,4]. Secondly, it is generally assumed, and especially described by the EBCTCG Group, that a threshold for the absolute gain in the local recurrence rate (>10% within the first 5 years) is needed before a survival benefit can be expected [8].

This explanation might not be quite true from a theoretical point of view. The aim of radiotherapy is to secure loco-regional control and to improve survival. Radiotherapy can eradicate residual loco-regional tumor deposits after surgery with adjuvant systemic therapy, and thereby improve local control and reduce the risk of secondary dissemination from these deposits. But only patients who have not yet developed distant metastases or patients who will have their limited occult distant metastases controlled by adjuvant systemic therapy can obtain additional survival benefit from irradiation. Other patients may only benefit in terms of loco-regional tumor control.

It is well documented that the risk of both local recurrence and distant recurrence increases with the number of nodes involved as well as increasing tumor size and other prognostic factors [19,22]. This implies that in patients who have many nodes involved the likelihood of developing distant metastases is very large, and therefore only a limited proportion of these patients can obtain survival benefit, despite their possibly obtaining a large reduction in loco-regional failures. On the contrary, in patients with fewer nodes involved and a consequential lower risk of distant metastases, a larger proportion can obtain survival benefit although they have a smaller risk of local failures. Thus, the improvement in survival may not directly be linked and proportionate to the improvement in loco-regional control.

In the DBCG protocols the target was the chest wall and peri-clavicular, axillary, and parasternal lymph nodes [9,10,12]. Major effort was made to optimize the treatment with regard to dose, fractionation, timing and treatment technique, so no radiation related excess non-breast cancer death or unacceptable toxicity was found at later follow up [13,23]. Avoiding such negative effect of radiotherapy in the Danish trials is probably one of the reasons for the positive outcome, but it is difficult to clarify how much the coverage of each of the target areas has contributed to the tumor control. Neither can it be generalized from these studies how much of the target should be included in patients nowadays, taken into account the changes in the standard adjuvant systemic therapy to more cardiotoxic drugs (antracyclines, taxanes, trastuzumab) and the modification of the surgical procedures. It is a matter of choosing a balance between risks and benefits in the current situation. Some information about the target may come from the SUPREMO study, which only includes the chest wall in the target irrespective of tumor location and presence of positive nodes, and from the EORTC 22922/10925 study which on the contrary only includes the supraclavicular and internal mammary nodes, in an almost similar patient group [24].

It is obvious that the number of positive lymph nodes solely is an extremely crude way of defining a potential indication for adjuvant therapy. More information may come from adding other clinico-pathological parameters (e.g., capsule and vascular invasion, malignancy grading, etc.). In addition, recent years have given increasing knowledge about the prognostic value of new molecular and genetic markers in order to select patients for adjuvant therapy [25–27]. This gives an obvious potential to further define and individualize the indications for postmastectomy radiotherapy, and is currently being tested in available tissue from patients in the DBCG trial.

The present study is characterized by a high frequency of loco-regional failures in patients treated with a radiotherapy technique which on the other hand apparently has avoided excess non-breast cancer death [13]. The overall conclusion may be modified if a small risk of non-breast cancer death exists, and/or if the absolute number of local failures is substantially less than the current level. The latter may be the situation in patients treated with a more sufficient surgery, especially if the tumors are small and of low grade [22], and such considerations must therefore be part of the overall decision making.

If there, as mentioned before, exist a lower absolute level of loco-regional failures which are requested to secure a survival benefit is not known. Although reasonable, such considerations are not part of the published consensus rapport, which in general only crudely classifies patients
based on 1–3 or 4 or more positive nodes [1–7]. Our analysis is therefore addressing this crude separation, but hopefully will further research make this more graduated, and consequently we may end up with an individualized approach towards the indication for postmastectomy irradiation. Whether new clinical trials are needed to gain such knowledge, or if the data can be generated from additional analysis from existing trials remains a question. Under all circumstances are there still substantial information to be gained from the past studies, and that should be fully explored in order to secure us the best possible knowledge and guidance for potential new trials in this area.

Conclusion

Postmastectomy radiotherapy significantly and substantially improved loco-regional control and overall survival in all node-positive patients. This improvement was as pronounced in patients with 1–3 positive nodes as in patients with 4 or more positive nodes, and nearly the same number of patients is needed to treat to avoid a loco-regional recurrence and/or death in both groups. This does add to the need for reconsideration and modification of the current guidelines for the indication for postmastectomy irradiation.

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