Progress in radiotherapy for early breast cancer

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Introduction

The technical developments in radiotherapy and the developments in genomics have led to a considerable change in the treatment and research for early breast cancer patients. Results of meta-analysis demonstrated the impact of radiotherapy on local control and survival, boosting therefore new possibilities of sophisticated radiotherapy approaches to allow further minimizing the late toxicity of radiotherapy.

Impact of radiotherapy on local control

Several clinical trials have confirmed that breast conserving therapy (BCT) leads to a survival rate similar to that of mastectomy for patients with early breast cancer. Since then trials have continuously demonstrated that the local recurrence rate was significantly reduced by adding radiotherapy after a wide local excision or quadrantectomy. These trial results were combined within the EBCTCG meta-analysis, which showed that the local recurrence rate will significantly be reduced from 32% to 10% at 10 years after local excision by irradiation of the whole breast [1]. The same meta-analysis also demonstrated that at 15 years a significant reduction of breast cancer mortality was obtained; these results were similar as seen by post-mastectomy radiotherapy. One can conclude from this meta-analysis, that by adding radiotherapy one can prevent a significant number of patients the distress of discovering a local recurrence, and the avoidance of salvage mastectomy. The meta-analysis also showed that avoiding four local recurrences results in the avoidance of one breast cancer death at 15 years follow-up, both for post-mastectomy radiotherapy as well as for whole breast irradiation after wide local excision (Figure 1) [1].

Impact of age and radiation dose on local control

In an interesting population-based study of nearly 10 000 patients treated for breast cancer evaluating patient-, pathology- and treatment-related parameters for recurrence risk and survival, Kroman et al. [2] looked at the mortality effects of BCT with breast irradiation compared with mastectomy in patients ≤50 years of age in Denmark between 1982 and 1998. There was no difference in survival between patients receiving BCT and mastectomy. However, patients <35 years treated with BCT had a significantly increased risk of local recurrence compared with patients aged between 45 and 49 years. This negative effect of younger age and margins on local control has also been reported by a number of retrospective studies [3–6], including Arriagada et al. [3]: an important report due to the long follow-up of 22 years, illustrating the need for continued alertness in the follow-up of patients treated at a young age; and Jobsen et al. [4]: a large retrospective study emphasizing the importance of age and surgical margins as risk factors for local recurrence.

In a detailed analysis of the results of the EORTC ‘boost versus no boost’ trial, which included 5569 patients with early stage breast cancer, only young age (<40 years) and the boost dose were independent factors related to local control [7]. For patients aged ≤35 years, the local control rate was 82%, whereas for patients >60 years the figure was 97%. The trial randomized patients following a complete local excision and 50 Gy irradiation to the whole breast to either no further irradiation or a boost of 16 Gy to the tumor bed. For patients ≤40 years the boost decreased the local recurrence rate from 20% to 10% at 5 years. Recent information on long-term follow-up has shown that giving a boost dose after whole breast irradiation further reduces the local recurrence rate with a factor 2 not only for young patients but also for older patients [8].

Impact of adjuvant systemic treatment on local control

A randomized clinical trial of the EORTC already showed that adding adjuvant chemotherapy or hormonal therapy for locally
advanced breast cancer led to a significant reduction of the local recurrence rate (Figure 2) [8]. A similar phenomenon was observed also by Livi et al. [9] in a large retrospective study with >3000 patients treated with BCT and in our EORTC boost–no boost trial [10]. One may therefore conclude that systemic chemotherapy or hormonal therapy reduces the local recurrence rate another 30–50% after radiotherapy for breast cancer.

can systemic adjuvant treatment replace radiotherapy in selected cases?

A few trials have attempted to avoid radiotherapy by randomizing between local excision plus tamoxifen versus local excision and tamoxifen plus radiotherapy [11–14]. In these trials different inclusion criteria were used. The trend of the trial results was very similar: addition of radiotherapy to patients who had already received local excision plus tamoxifen led to a 67–76% reduction of the local recurrence rate (Table 1). This relative reduction rate was similar as shown in the meta-analysis by adding radiotherapy after wide local excision alone [1].

In an older patient with a very small well-differentiated invasive tumor, one expect that the local recurrence rate is very low. After local excision with sufficient margins treatment with hormone therapy might therefore be sufficient in selected patients. However, at present we do not have the diagnostic tools to identify patients who need radiotherapy and patients who do not. In the future micro-arrays or proteomics may guide this decision [15].

sequencing radiotherapy and systemic treatment

A major debate for a long time has been whether or not radiotherapy should be given first. In a small scale trial, which compared the radiotherapy/chemotherapy sequence with the opposite, disease-free survival appeared to improve if chemotherapy was given first [16]; this finding was not significant. The study also showed a higher number of local recurrences in patients who had at first received chemotherapy (Figure 3a). A recent update did not, however, show a difference in local recurrence rate between treatment arms (Figure 3b) [17]. In a meta-analysis by Huang et al. [18] the local recurrence rate was, however, 16% for patients who had initially received chemotherapy and 6% for patients who had initially received radiotherapy. Furthermore, the local recurrence rate appeared to double if radiotherapy was postponed for >8 weeks after operation. In a meta-analysis by Mauri et al. [19] a 22% higher local recurrence rate was observed when chemotherapy was given before radiotherapy. One of the reasons for this high recurrence rate might be caused by the fact that the full treatment with radiotherapy and surgery would not have been completed for patients who responded well in these trials (Figure 4). Considering the outcome of this meta-analysis one can conclude that giving chemotherapy before or after local treatment has no impact on survival. One can conclude therefore that the sequence of radiotherapy and chemotherapy has no impact on survival; however, it is associated with an increase local recurrence rate if chemotherapy is given first.

![Figure 2. Locally advanced breast cancer impact of adjuvant treatment on local control [2].](image)

Table 1. Wide local excision and tamoxifen versus wide local excision, tamoxifen and radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor size</th>
<th>n</th>
<th>Treatment</th>
<th>Follow-up (years)</th>
<th>Breast recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest (1996)</td>
<td>&lt;40 mm</td>
<td>294</td>
<td>TAM or CMF</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>291</td>
<td>+ RT</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Fisher (2002)</td>
<td>≤10 mm</td>
<td>334</td>
<td>TAM</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>334</td>
<td>RT</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Hughes (2007)</td>
<td>≥70 years</td>
<td>319</td>
<td>TAM + RT</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>≤20 mm</td>
<td>317</td>
<td>+ RT</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Fyles (2006)</td>
<td>≥50 years</td>
<td>383</td>
<td>TAM</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>≤20 mm</td>
<td>386</td>
<td>+ RT</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

CMF, cyclophosphamide + methotrexate + 5-fluouracil; F/U, follow-up; RT, radiotherapy; TAM, tamoxifen.
trastuzumab and radiotherapy

Trastuzumab has been shown to decrease the regenerative capacity of the myocardium after treatment with anthracyclines [20]. At present, only limited data are available on the possible increase of late cardiotoxicity after radiotherapy given in combination with trastuzumab. Haylard has recently presented the results of the NCCTG N9831 trial, where patients were randomized between doxorubicin and cyclophosphamide versus doxorubicin, cyclophosphamide and paclitaxel followed by trastuzumab or in the third arm doxorubicin, cyclophosphamide and paclitaxel, while trastuzumab and radiotherapy is given during paclitaxel treatment [21]. No increased heart toxicity was observed in patients who underwent radiotherapy during trastuzumab treatment. Nevertheless, one has to be careful, as the late toxic effects of radiotherapy may occur several years after treatment. It is therefore advised to minimize the volume of heart and lung tissue exposed to irradiation, which is possible with modern radiotherapy equipment.

reduction of toxicity by modern radiation techniques

Long-term results of clinical trials have shown late cardiotoxicity, including deaths, due to radiotherapy. Data from Hurkmans [22] and Gagliardi [23] suggested that the excess of cardiac mortality is related to the volume of cardiac tissue exposed to irradiation. In a recent publication by Hooning et al. [24] it was shown that radiotherapy and especially treatment of the internal mammary lymph nodes led to more congestive heart failure. Even more important was the observation that adding only six cycles of CMF led to a significant increase in late congestive heart failure, an effect that occurred only ≥15 years after treatment (Figure 5). As doxorubicin, in combination with cyclophosphamide, has nowadays replaced CMF this problem may occur even more in the future in patients who received BCT, as doxorubicin is cardiotoxic as well. There is already knowledge from children who have been treated several years ago that this will lead to increased cardiotoxicity.

Modern treatment techniques with intensity-modulated radiotherapy and image-guided radiotherapy, have now the possibility of avoiding radiation of the heart for example with the cone beam CT linear accelerators. Therefore this modern approach should be widely applied in patients who receive BCT and adjuvant systemic treatment (Figure 6).

partial breast irradiation

Recent interest has focused on accelerated partial breast irradiation (APBI). APBI is the delivery of radiation to a limited target volume—the surgical cavity plus a 1–2 cm margin—generally in a single treatment or over 1 week. This contrasts with conventional whole breast radiotherapy which generally takes 5–7 weeks. APBI has been designed for patient convenience; it is not expected to improve local control or survival.

A number of theoretical arguments have been advanced for and against APBI. Since its introduction in the 1990s, APBI has been used in multiple phase I–II clinical trials with short-term (5-year) local failure rates that are similar to those for whole breast irradiation. Support for APBI has been based upon observations of in-breast failures after traditional radiation therapy. These failures are seen most frequently (70–80%) at or near the site of the original tumor.

The optimal APBI technique has not been determined. At least four methods of APBI have been described: (i) brachytherapy implant; (ii) balloon brachytherapy (MammoSite); (iii) external beam radiation treatment with or without IMRT; (iv) intraoperative radiation treatment (IORT) using electrons [ELIOT (electron intra-operative treatment)] or an ortho–voltage source [TARGIT (targeted intra-operative radiotherapy)]. Each of these APBI methods has potential advantages and disadvantages, and none has been proved superior to another.

Several phase III randomized trials comparing APBI with conventional whole breast radiation are accruing patients. Each trial is evaluating a different APBI technique, but each trial uses whole breast photon radiotherapy as the control arm. Several randomized European trials are being run by the European Institute of Oncology (Milan, Italy), University College of London (UK), the EORTC and the National Institute of Oncology (Budapest, Hungary). Five-year results of the latter trial have already been published [24]. In North America, one
trial is being run jointly by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) and another in Canada. The total planned accrual for these five randomized trials is >8000 patients.

Until presentation of the results of these trials one may consider APBI still as experimental, especially as the radiation schemes used are given in a short overall time with a high dose per fraction.

**micro-arrays and radiotherapy**

Gene expression profiling has been successfully applied to distinguish molecular subtypes in breast cancer and to predict metastases and overall survival. More recently, gene expression profiling has also been used in trying to identify signatures predicting response to neo-adjuvant chemotherapy treatment and prognosis after treatment with tamoxifen. A recently published pooled analysis shows that local recurrence is associated with an increased risk of developing distant metastases and subsequent death from breast cancer. Moreover, local recurrence requires treatment (usually salvage mastectomy) and is associated with anxiety for affected patients.

It is therefore important to tailor BCT in such a way that the risk of local recurrence is kept as low as possible, while optimizing the quality of life, including the cosmetic appearance of the breast. To select patients who are likely to benefit from BCT, clinico-pathological parameters are currently used to stratify patients by risk of local recurrence. These existing prognostic factors are far from perfect, and additional or better predictors of local recurrence would be of great potential benefit. Aggressive treatment including a larger excision volume and/or a higher local radiotherapy dose ('boost') significantly decreases the risk of local recurrence but results in impaired cosmetic outcome. In patients considered to be at low risk of local recurrence, the boost dose could be forgone and in patients with a high risk a boost should be administered or even escalated. Furthermore, for patients at very high risk of local recurrence a primary mastectomy can be offered. Nuyten et al. [25] have presented a method of integrating biologically derived gene expression profiles and

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**Figure 4.** Neo-adjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis [13].

**Figure 5.** Risk of congestive heart failure by radiotherapy and chemotherapy [18].
clinical data to build a classifier for local recurrence after BCT. Although numbers of events are small and the resulting confidence intervals are wide, it is the first classifier based on microarray analysis to specifically predict local recurrence after BCT.

disclosures
No significant relationships.

references