Special commentary

The changing landscape in radiotherapy for breast cancer: Lessons from long term follow-up in some European breast cancer trials

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A R T I C L E   I N F O

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A B S T R A C T

This review describes the developments in the radiation treatment of breast cancer based on some randomized European trials during the past decades. It will focus on the relevance of long term follow-up in breast cancer patients, starting with the surprising and important change in treatment results during follow-up shown in a locally advanced breast cancer trial. Breast conserving therapy (BCT) in stage I and II breast cancer was explored and tested in a randomized trial to prove equivalence between BCT and mastectomy. The positive outcome led to trials in breast conserving therapy with lower doses and partial breast irradiation. Finally the need for finding genetic profiles for predicting treatment response will be addressed. These trials have demonstrated a major improvement in local control.

The role of radiotherapy for breast cancer has changed dramatically during the last decades. Initially mastectomy was the standard care for operable breast cancer and irradiation was used mostly in an attempt to palliate inoperable disease or for postmastectomy irradiation. The development of Co60 apparatus and linear accelerators allowed for delivery of higher tumour doses herewith obtaining tumour control in locally advanced breast cancer. The encouraging results in obtaining local control in advanced breast cancer have led to a trial exploring the value of adjuvant systemic treatment in these patients. The surprising change in the treatment results during follow-up of the locally advanced breast cancer trial will be addressed. These patients were treated with irradiation alone or in combination with systemic treatment. The encouraging results by obtaining tumour control with irradiation in these advanced tumours has led to exploration of breast conserving therapy (BCT) in stage I and II breast cancer. In order to prove equivalence BCT was compared with mastectomy in a randomized trial. The positive outcome of this trial led to subsequent studies in breast conserving therapy aiming to further improve local control. These trials have demonstrated a major improvement in local control rates in recent decades. Therefore, several strategies for de-escalation in low-risk patients are currently under investigation, such as partial breast irradiation instead of whole breast irradiation or omission of radiotherapy. This review will conclude with describing the selection of patients for preoperative accelerated partial breast irradiation, aiming at reducing toxicity and at the same time providing information on the response of radiotherapy. Currently, clinicopathological factors are used for patient selection, but gene expression profiling could be of additive value.

Locally advanced breast cancer: the EORTC trial 10792 trial

The EORTC 10792 trial in locally advanced breast cancer was initiated in 1979 at a time when systemic therapy with hormones or chemotherapy was mostly given for distant metastases in breast cancer patients. It aimed to assess the possible contribution of adjuvant hormonal therapy (HT) or chemotherapy (CT) on both local control and survival. 410 Patients with inoperable breast cancer were randomized between radiotherapy (RT) alone versus RT with HT, and RT with HT and CT [1]. The results demonstrated that permanent tumour control in advanced breast cancer could be achieved without surgery, with radiotherapy alone or in combination with systemic treatment. It was the first randomized trial that showed improved local control by adding chemotherapy or hormonal therapy to radiotherapy in breast cancer (Fig. 1). Interim analysis during the course of the trial showed that there was a major benefit in terms of survival in favour of adjuvant CT. The
accrual rate then slowed down considerably, as some trial participants became aware of this benefit. Consequently, the trial was closed earlier than planned. At the time of the closure of this trial a significant improvement of survival was observed in patients who received CT ($P = .004$); nevertheless, with a longer follow-up this effect disappeared ($P > .05$). Initially, HT did not appear to improve survival ($P = .16$); but in the latest analysis, a significant improvement of survival was seen ($P = .02$) (Fig. 2, Addendum Fig. A1). It is also important to mention that a consistent 25% reduction in the death hazard ratio has been seen at all evaluations since trial closure in patients who received HT. The improvement in survival obtained with HT became therefore apparent only after long-term follow-up evaluation. The best survival results were observed in patients who received RT, HT, and CT ($P = .02$), with a reduction of 35% in the death hazard ratio [1,2]. As the improved survival rates were not influenced by age we concluded that even young inoperable breast cancer patients might benefit from HT, while at the time of publication adjuvant hormonal therapy was only prescribed for the postmenopausal patient. This trial taught us the potential danger of drawing conclusions based on only short term follow-up data. Another lesson was that a trial statistician should not unblind the trial data, and should certainly not inform trial participants on the possible outcome, as that was of major influence on the accrual of patients. As a result, strict rules have since been established for randomized trials for independent data monitoring committees (IDMC) for evaluation of treatment toxicity and efficacy including futility analyses to prevent selection bias or change in accrual during the course of a trial.

**Mastectomy versus BCT: the EORTC trial 10801**

Up to the 1980s a radical mastectomy, usually the Halsted, or modified radical mastectomy (MRM) such as the Patey or Madden procedure, was the standard treatment for most patients regardless of the stage of their disease. The above mentioned findings in preserving the breast in patients with locally advanced breast cancer together with the expertise in French radiotherapy centres led to the exploration of breast-conserving therapy (BCT) [3]. However, an unacceptably high level of local recurrences in patients after BCT was observed in the Guys hospital trial [4]. The preliminary results of 2 clinical trials in the treatment of tumours 2 cm or smaller [5,6] showed much more favourable results than observed in the Guy’s trial. Evidence on the long term results especially in patients with stage II disease (tumours larger than 2 cm and/or positive lymph nodes) was lacking at that time. Therefore we started a randomized, multicentre EORTC trial in 1980: comparing BCT with MRM for patients with tumours up to 5 cm and axillary node negative or positive disease. From the 868 patients most had stage II disease, 80% of them had a tumour sized between 2.1 and 5 cm [7,8]. BCT comprised of lumpectomy with an attempted margin of 1 cm of healthy tissue and complete axillary clearance, followed by radiotherapy to the breast of 50 Gy in 5 weeks and a boost dose to the tumour bed of 25 Gy. The initial results showed that MRM resulted in better local control than BCT, but this did not affect overall survival or time to distant metastases. After evaluating the psychological and cosmetic effects we concluded that body image in the BCT group was significantly more positive than in the MRM group. Patients treated with BCT

![Fig. 1. IMPACT OF ADJUVANT chemotherapy and, or hormonotherapy on locoregional recurrence rate after radiotherapy (xrt) for locally advanced breast cancer. Adapted from Ref. [1].](image1)

![Fig. 2. Reversal of fortune: change in P values during and after finishing the locally advanced breast cancer trial. Adapted from Ref. [1].](image2)
even had less fear of recurrence of the cancer and would, if necessary, choose the same treatment again [9]. After a long term follow-up of 22.1 years there was still an increase of the local recurrence rate in the BCT patients. (Addendum Fig. A2). Nevertheless BCT and mastectomy resulted in similar survival and distant metastases rates in a trial, with mainly stage II breast cancer patients. There was also no difference between the groups in time by age (Fig. 3) [8]. These long-term trial results -with similar survival results after BCT or after mastectomy- are in line with the meta-analysis of the EBCTCG [10]. This led us to conclude that BCT including radiotherapy, offered as standard care to patients with early breast cancer seems to be justified for patients with stage I and II disease with tumours up to 5 cm with equal efficacy in patients younger or older than 50 years of age.

Boost versus no Boost, EORTC trial 22881 and the Young Boost trial

The equal survival after BCT or mastectomy led us to consider whether reduction of the treatment intensity was possible by lowering the radiation boost dose. Especially as there was some concern about the worse outcome of cosmesis in some patients treated within the 10801 trial. A boost dose of 16 Gy was compared with no boost after whole breast irradiation, instead of the 25 Gy boost as used in the 10801 trial. More than 5000 patients with microscopically complete excision for invasive disease followed by whole-breast irradiation of 50 Gy in 5 weeks were randomized to receive a 16 Gy boost or no boost ClinicalTrials.gov, NCT02295033). The main purpose of this study was to analyse which subgroups of patients would benefit from a higher radiation dose, and whether local control would affect survival. At 10 years of follow-up we found that a boost dose of 16 Gy led to improved local control in all age groups, the benefit of the boost was observed in all tumour types and histological grades (Fig. 4, Addendum Fig. A3) [11,12]. Patients younger than 50 years of age at time of diagnosis mostly profited from this higher radiation dose. Remarkably, in the final analysis after 20 years of follow-up local control curves are continuously separated in all age groups. In case of ipsilateral breast tumour recurrence in the majority of patients mastectomies as first salvage treatment were applied, probably explaining why there was no difference in survival despite the improvement of local control by giving a boost dose [13].

We concluded therefore a radiation boost after whole-breast irradiation has no effect on long-term overall survival, but can improve local control, although it increases the risk of moderate to severe fibrosis (cumulative incidence 30.4% vs 15%). The largest absolute benefit was seen in young patients and fortunately the increase in fibrosis was independent of age. The benefit of the extra radiation dose in older patients was limited and a boost dose can therefore be avoided in most patients older than age 60 years. To estimate the benefit of a boost dose on local control in individual patients on beforehand, we developed a nomogram for local control and fibrosis [14,15].

The association of pathological prognostic factors with local control was studied in a separate analysis. It showed again that young age and the presence of DCIS adjacent to the invasive tumour increased the risk of local recurrence. In patients with both prognostic factors the boost reduced the risk with an HR of 0.37, leading to an absolute risk reduction of 16% at 20 years. This analysis showed that even after 5 years of follow-up the local recurrence rate continued to increase in patients with adjacent DCIS, with further separation of the curves (Fig. 5). Surprisingly the impact of high grade malignancy decreased over time. This underlines the importance of long-term follow-up to correctly estimate absolute effects in patients with breast cancer [16]. Similarly Laurberg et al. showed that with longer follow up there is a continuous increase in local recurrence after BCT, which even seems to affect the survival in young patients [17].

In an attempt to further improve the local recurrence rate in young patients a dose escalating trial was initiated: “Young Boost” trial clinicaltrials.gov; NCT00212121. The main objectives were to compare the effect of a high boost dose (26 Gy) with a low boost dose (16 Gy) in breast conserving therapy on the local recurrence rate and cosmesis, and secondly to test the genotypic and phenotypic profiles of breast tumours in young patients with invasive breast cancer and its relation to local recurrence after BCT and their radiosensitivity. The trial has already been completed with an accrual of more than 2400 patients. The trial outcome will be analysed at 10 years follow up in 2020.

Preoperative accelerated partial breast irradiation (PAPBI)

To further reduce the treatment burden accelerated partial breast irradiation (APBI) has been advocated as an alternative to whole breast irradiation (WBI) for early stage breast cancer in elderly women. APBI can be delivered by three-dimensional conformal external-beam radiation, but large inter-observer variability in defining the tumour bed postoperatively has been shown. This is becoming even more complicated because of the increased use of oncoplastic surgery, leading to larger irradiated volumes [18]. This uncertainty can be overcome by giving radiotherapy before surgery which also allows us to measure the tumour
response by imaging and pathological evaluation and find biomarkers. We anticipated that this approach may avoid the development of breast induration/fibrosis and worse cosmetic outcome, as seen in Canadian trial [19], due to the fact that with surgery the irradiated high dose area is removed. We therefore initiated a multi-centre preoperative accelerated partial breast irradiation phase II trial (PAPBI) ClinicalTrials.gov, NCT01024582. Low risk patients of 60 years and older were preoperatively irradiated with IMRT instead of postoperative radiotherapy. The main objective was to investigate the impact of a short fractionated schedule given preoperatively on local control, cosmesis and breast fibrosis. The first results on 70 patients treated in our PAPBI trial show low complication rates, limited fibrosis in a small volume and good–excellent cosmetic results. In contrast to what was seen in the boost trials, in which the cosmetic results diminished during follow-up. In the PABPI trial the cosmetic results improve with longer follow-up. We concluded therefore that preoperative PBI is a feasible and widely available technique with promising results for a selected group of patients [18]. In these patients Sophie Bosma found important differences in the gene profiles before and after irradiation with whole genome analysis. Horton et al. reported a similar approach but with a dose escalating phase I study using one single fraction of radiation in 32 patients [20]. They concluded that their single dose preoperative irradiation is feasible in breast cancer and has the potential to challenge the current treatment paradigm and provide a path forward to identify radiation response biomarkers. Our phase II study is now completed with 137 patients. The feasibility of our phase II trial formed the basis for a randomized phase III trial Clinicaltrials.gov: NCT02913729 comparing pre- versus postoperative partial breast irradiation. The goal is to assess the cosmetic effect in female patients aged 51 years or older with early stage breast cancer. An additional goal in this study is to assess tumour response to radiotherapy and to identify biomarkers in order to design more individualized treatment strategies for breast cancer patients treated with breast conserving therapy.

**Predictive markers for local recurrences after BCT?**

Gene expression profiling has been successfully applied to distinguish molecular subtypes in breast cancer and to predict the risk of metastasis and overall survival [21,22]. More recently, gene expression profiling has also been used in trying to identify signatures predicting response to neoadjuvant chemotherapy and the benefit of chemotherapy in early breast cancer [23,24]. In addition, gene expression profiling of primary breast carcinomas using microarray technology has already been used to discover a signature associated with a higher risk of true local recurrence after BCT. However, results have been contradictory. With Nuyten we suggested that the wound signature could identify subgroups of patients being at increased risk of developing a local recurrence after BCT [25]. He was followed by Kreike; he could not confirm the wound response signature and other classifiers in a series of 165 young (<50 years old) premenopausal Dutch patients. Kreike constructed a local recurrence classifier based on the expression...
of 111 genes and validated this profile on an independent data set of 161 consecutive patients who underwent BCT using a different microarray platform [26]. This classifier was mostly characterized by proliferation but did not yield a significant independent additive value as young age remained the sole predictive factor of local recurrence in multivariate analysis. Servant and colleagues therefore tried to validate the 111-gene classifier proposed by Kreike in a well-characterized data set of 343 patients [27]. They were unable to validate this classifier or to define a strong classifier for local relapse after BCT superior to clinical variables. Tramm et al. identified and validated a DBCG-RT 7 gene profile, identifying patients with very low risk of a local recurrence and no benefit from post-mastectomy radiotherapy [28]. A follow-up study indicated that this prognostic and predictive effect of the DBCG-RT profile was independent of intrinsic subtype, regardless of which method was used for determining the molecular subtypes [29]. Eschrich and colleagues developed a radiosensitivity molecular signature (radiosensitivity index) and validated their radiosensitivity index in 2 independent breast cancer data sets. Although, this radiosensitivity molecular signature did predict distant metastases, an impact on locoregional breast recurrences could not be determined in their breast cancer data sets [30]. Recently, studies of the 21-gene Oncotype DX and 70-gene signature MammaPrint suggested these assays can identify patients with a high risk of locoregional recurrence after mastectomy or BCT, although they cannot distinguish between patients who should benefit from mastectomy or BCT [31,32]. Speers and colleagues developed a molecular signature for radiation response in breast cancer that is enriched for biologic concepts implicated in response to radiation therapy, including DNA damage repair and cell cycle regulation [33]. Their validation suggested that their signature performs previous signatures and may more accurately stratify the likelihood of local recurrence of breast cancer. These uncertainties in predicting the treatment outcome of irradiated patients with breast cancer suggest the need for validating the assays described in major trials such as the “Young Boost” trial clinicaltrials.gov; NCT00212121 which has just been completed. The results of this randomized trial will hopefully lead to a validated gene profile predicting which patients <51 years benefit from a higher dose and which patients are radiation resistant and for whom other treatment options are a better choice. The major advantage of the aforementioned assays is the fact that these data sets are now available online and can be tested in an independent manner on material from trial patients. Based upon the whole genome analysis from the PAPBI phase II and III trial, which provide information about radiosensitivity in vivo, and the RNA sequencing studies of patients with a local recurrence in the Young Boost trial we hope to establish a radiosensitive gene signature.

**Discussion**

The trials described here reflect major changes in the intensity of treating patients with breast cancer that have occurred during the last decades, starting with obtaining tumour control with radiotherapy for locally advanced breast cancer whether or not in combination with systemic therapy. Subsequently the possibility of breast conserving therapy by demonstrating equal survival after mastectomy or breast conserving therapy, despite a few more local failures after BCT. Furthermore the additional benefit of adjuvant systemic treatment by improving local control after radiotherapy which was seen in the locally advanced breast cancer trial and in the boost vs no boost trial. The boost vs no boost trial showed that especially young patients were at high risk for a local recurrence, fortunately a boost dose of 16 Gy appeared beneficial in these young patients. The long term follow-up of the boost vs no boost trial showed the possibility of reducing the treatment intensity by omitting the boost dose in selected groups of patients, without harming the survival. The lack of impact on survival, despite a higher local recurrence rate in the no boost group, may be explained by the efficacy of salvage mastectomy in the majority of patients with a local recurrence, whether or not combined with adjuvant systemic treatment.
Fig. 6. Local Recurrence rate in three BCT trials with early breast cancer from 1980 till 2016. Updated from Refs. [8,12].

Fig. A1. Reversal of fortune: survival curves during follow up after treatment for locally breast cancer with Radiotherapy alone or in combination with hormones and or chemotherapy (adapted from Ref. [1]). A1a Survival for adjuvant chemotherapy at trial closure, and five years after trial closure, A1c Survival for adjuvant hormonotherapy 5b years after trial closure.
The higher local recurrence rate in younger patients was the mean reason for a special trial for with intensified treatment by delivering a higher radiation dose in a randomized set up. Although the trial results are not yet unblinded it is obvious that there is a major improvement in local control in this young patient group as a whole when compared with the previous trials results (Fig. 6). These low local recurrence rates after BCT are also reported by others [34]. This brings us to the limitations of older trials, as the present results are certainly different from the past ones. The better results are probably reflecting a change in treatment policy on different levels, like better surgical and radiotherapy treatment techniques, improved radiological and pathological methods and reporting the increased application of systemic treatment, and more effective systemic treatments including targeted anti-Her-2 neu treatment. Another explanation may be a major shift in patient population as a result of screening and better public awareness, leading to more elderly patients with grade 1 tumours ER + tumours treated with BCT although this is not the case for the patients under 50 years of age. This means that the outcome of older trials cannot directly be translated to the patient seen nowadays, but the changing environment should be taken into account. At the same time the strength of the older trials is the long term follow-up. They demonstrated the impact of hormonal therapy on survival. They demonstrated a better local control can be achieved in early breast cancer by intensifying the treatment, but this came with a price; reduced cosmetic outcome. Of note these long term data demonstrated that risk factors may change in time: high grade tumours have an increased local recurrence risk only during the first 5 years of follow up, while in patients with adjacent DCIS a continuous increase of local recurrences is seen during follow-up [16]. Nevertheless, the impact of a boost dose remains, even a further separation of the curves was observed after 5 year follow-up, especially in patients with DCIS adjacent to the invasive tumour (Fig. 5). It therefore underlines the importance of long term trial follow-up to correctly estimate absolute effects in patients with breast cancer.

This article focus mainly on the impact of lessons derived from a few selected trials. Other improvements aimed at reduction of the treatment burden and toxicity will therefore not be discussed. These include IMRT and image guided breath hold treatment, to spare the skin heart and lungs [35,36], the use of shorter treatment schedules and avoidance of radiation in older women with early breast cancer [37,38]. Partial breast irradiation (PBI) with IORT, implants or external irradiation is more and more used to limit the irradiated breast volume, and sparing heart and lungs [39].

The increased rate of early breast cancer patients as mentioned above related to increased use of mammography screening suggest that an increasing significant proportion of patients will never develop any clinical symptoms of breast cancer and therefore should be considered as overtreated. In addition, local control rates especially in older patients are very high. To address this situation, it is even more important nowadays to develop assays to predict the radiation response to determine which patient will benefit from irradiation in combination with surgery. Some trials in Europe and the USA have already started to investigate withholding radiotherapy in favourable cases, whether or not based upon molecular subtyping. By giving preoperative partial breast irradiation in a research setting tumour samples are compared before and

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**Fig. A2.** Kaplan–Meier curves for: **a** overall survival, **b** distant metastases, **c** local control in patients with a diagnosis of clinical stage I or II invasive carcinoma of the breast after breast-conserving therapy (BCT) and mastectomy. **O** = observed, **N** = number of patients; **BCT** = Breast Conserving Treatment. Adapted from Ref. [8].
after irradiation to identify imaging and genomic markers of radiation response [18,21]. Hopefully this will lead to a more selective and individualized use of radiotherapy and finding targets for combined radiotherapy and novel targeting drugs.

Conflict of interest

None.

Appendix A.

See Figs. A1–A3.

References


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