The Breast xxx (2016) 1–10

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer

Maria Cristina Leonardi [a, *], Rosalinda Ricotti [a], Samantha Dicuonzo [a, b], Federica Cattani [c], Anna Morra [a], Veronica Dell'Acqua [a], Roberto Orecchia [b, d], Barbara Alicja Jereczek-Fossa [a, b]

[a] Radiotherapy Division, European Institute of Oncology, Milan, Italy
[b] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[c] Medical Physics Unit, European Institute of Oncology, Milan, Italy
[d] Scientific Directorate, European Institute of Oncology, Milan, Italy

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form
27 June 2016
Accepted 8 July 2016
Available online xxx

Keywords:
Breast cancer
Adaptive radiotherapy
High-precision radiotherapy
Technological advances
Tumor biology

ABSTRACT

Radiotherapy improves local control in breast cancer (BC) patients which increases overall survival in the long term. Improvements in treatment planning and delivery and a greater understanding of BC behaviour have laid the groundwork for high-precision radiotherapy, which is bound to further improve the therapeutic index. Precise identification of target volumes, better coverage and dose homogeneity have had a positive impact on toxicity and local control. The conformity of treatment dose due to three-dimensional radiotherapy and new techniques such as intensity modulated radiotherapy makes it possible to spare surrounding normal tissue. The widespread use of dose-volume constraints and histograms have increased awareness of toxicity. Real time image guidance has improved geometric precision and accuracy, together with the implementation of quality assurance programs. Advances in the precision of radiotherapy is also based on the choice of the appropriate fractionation and approach. Adaptive radiotherapy is not only a technical concept, but is also a biological concept based on the knowledge that different types of BC have distinctive patterns of locoregional spread. A greater understanding of cancer biology helps in choosing the treatment best suited to a particular situation. Biomarkers predictive of response play a crucial role. The combination of radiotherapy with molecular targeted therapies may enhance radiosensitivity, thus increasing the cytotoxic effects and improving treatment response. The appropriateness of an alternative fractionation, partial breast irradiation, dose escalating/de-escalating approaches, the extent of nodal irradiation have been examined for all the BC subtypes. The broadened concept of adaptive radiotherapy is vital to high-precision treatments.

Introduction

Radiotherapy is an essential component of early breast cancer (BC) management, which significantly improves overall survival in patients treated both with conservative surgery (CS) and with radical mastectomy [1]. Decision making in radiation oncology has always been based mainly on histopathological and clinical features. The introduction of gene expression profiles has pioneered an era of increasingly effective therapies for targeting tumours on a molecular basis, dividing BC into subtypes with different tumour behaviour and treatment response [2]. The time is ripe to make radiotherapy fully adaptive by embracing the biological behaviour of tumours, considering their different potential and pathways for recurrence [3]. More personalized radiotherapy must replace the approach of "one size only" [4]. This broader concept of adaptive radiotherapy, which goes beyond the technical definition, has already gained ground among radiation oncologists (ROs). However, current knowledge, derived from studies based mainly on pathology rather than on biology, makes it difficult to adapt treatment to the individual patient. In spite of the huge technological advances and the wealth of choice of treatment modalities and techniques, there is a general tendency to treat all BC with the same regime, irrespective of tumour response or how much benefit

* Corresponding author. Divisione di Radioterapia, Istituto Europeo di Oncologia, Via Ripamonti 435, 20141 Milano, Italy. Fax: +39 02 94379227.
E-mail address: cristina.leonardi@ieo.it (M.C. Leonardi).

http://dx.doi.org/10.1016/j.breast.2016.07.010
0960-9776/

is gained [5–7]. Radiotherapy has achieved great precision in planning and delivering treatment and innovations are being made continuously. The meta-analyses show that as radiation techniques have been refined, local control has increased, toxicity-related mortality has decreased and the benefit to survival stands out clearly [1,8,9]. Modern radiotherapy is expected to improve survival even more because treatment has become more effective and safer. The challenge nowadays is targeting not the tumour volume [10], but the population, who would most benefit from a specific treatment, balancing the costs and the benefits (clinical outcome and quality of life).

This paper addresses the current and the potentially available tools for high-precision radiotherapy to tailor treatments, not only to individual anatomy for the greatest degree of conformity, but also to tumour profile for more accurate risk stratification.

The biological tools of high-precision radiotherapy

In radiation oncology, very few biomarkers are used in a clinical setting. Decision-making is still based upon TNM staging and clinicopathological features such as age, positive margins, high tumour grade, presence of lymphovascular invasion, tumour size, etc. Differences in response and benefit according to the subgroup emerge clearly throughout the literature [11]. The European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups trial "boost versus no boost" has clearly demonstrated that a higher dose increases local control in selected, age-correlated, subgroups, suggesting an underlying radioresistance [12]. The Oxford meta-analysis shows that the therapeutic impact of radiotherapy was greater in estrogen receptor (ER)-positive tumours, suggesting an underlying radiosensitivity [13]. In spite of increasing awareness of the differences, the current recommendations tend to fall into general risk categorizations that rarely consider tumour biology profile [14]. One example is the issue related to nodal radiotherapy in the case of 1–3 positive axillary nodes, since the Early Breast Cancer Trialists' Collaborative Group review highlighted the benefit to all patients with low nodal involvement, without providing any risk stratification to assess its magnitude [15]. At the 14th St. Gallen Consensus, most panellists agreed that adverse pathology or young age should be considered when identifying patients requiring radiotherapy [16]. Predictive biomarkers are steadily growing in importance with a view to tailoring treatments. They are bound to be even more valuable if the TNM staging is incomplete, as in the case of patients with one or two positive sentinel node but no axillary dissection. If the number of involved nodes is not known, the extent of the radiation fields must be based on tumour features, possibly using validated nomograms, to estimate residual nodal burden [17,18]. There are several ongoing trials (OPTIMAL, POSNOC, SENOMAC, SINODAR, INSEMA, SOUND trials) [19], some of them including biological stratification, to guide ROs in tailoring radiation fields when the actual nodal involvement is unknown.

As well as the widely available immunohistochemistry techniques, molecular signatures such as MammaPrint and OncotypeDX are also being investigated in the field of locoregional treatment [20]. Using the 21-genes OncotypeDX recurrence score, Mamounas et al. [21] showed that, among patients from National Surgical Adjuvant Breast and Bowel Project trials, there is a significant association between local recurrence (LR) and high recurrence score, which outweighs other traditional factors, including tumour grade and size at multivariable analysis. A multi-joint task force developed a highly radiotherapy-specific multigene expression model, the radiation sensitivity index (RSI), to predict radiation responsiveness. In the BC setting, when combined with intrinsic subtypes and age, RSI was able to identify patients who would least benefit from radiotherapy (ER negative/RSI resistant) or who are in need of a dose escalation approach (Luminal/RSI resistant) [22]. In addition, inside the triple-negative (TN) subtype, the authors described subpopulations with a different risk of LR (RSI sensitive and RSI resistant), for whom personalized radiotherapy may be considered. It has become evident that the diversity of BCs makes specific local strategies necessary [22]. A retrospective analysis of the combined Danish Breast Cancer Cooperative Group (DBCG) 82b/c postmastectomy radiation (PMRT) trials, in which patients underwent mastectomy and were thereafter randomized to ± PMRT following systemic therapy, found that luminal A tumours benefitted the most from radiotherapy, while the HER-2 positive and TN subtypes were less likely to exhibit a reduction in LR due to radiotherapy and experienced no significant overall survival improvement [23]. In this trial population, a subsequent gene expression analysis on the frozen tumour samples available identified a 7-gene predictive model for LR, dubbed the "DBCG-radiotherapy" profile, which was able to predict the benefit of PMRT more accurately than molecular subtypes by themselves [24]. In fact, although there was a general correlation between the "DBCG-radiotherapy" profile and the subtypes, as was expected, the existence of "low LR risk" and "high LR risk" groups were to be found in all of the subtypes, including a small number of Luminal A patients who did not experience any additional reduction in LR with PMRT when compared to the no-PMRT randomized group, which is in contrast with the original analysis.

Novel approaches to locoregional treatment, including dose escalation should be tried out on these subgroups, when identified. High expectations are placed on the ability to predict good or bad responders in order to offer less or more intensified treatments, by varying the fractionation, dose, volume or by combining radiosensitizing targeted therapies. Currently, the less expensive immunohistochemistry (IHC) surrogates for the main intrinsic biological subtypes are readily available to ROs and several studies have shown that they are able to independently predict LR after radiotherapy. Almost all of them ascribe a lower rate to the Luminal A subtype and a higher rate to basal −like/TN and HER-2 positive tumours [25–32]. The overall 5-year incidence of LR in patients treated with CS and radiotherapy at the Dana Farber Institute was 2.1%, dropping to 0.8% in the Luminal A subtype [33]. In addition, in this study, increasing age was associated with a decreased risk of LR at multivariate analysis. In the Electron Intraoperative Radiotherapy (ELIOT) randomized trial molecular classification, showed that luminal A had the lowest risk of LR [1.4%) [34]. The value of looking at tumour and patient features as an entirety in the attempt to identify a favourable subgroup, was explored by Liu et al. [35], by using six-immunohistochemistry -marker panels, in the context of the Toronto-British Columbia trial, dedicated to older node-negative patients randomized to receive tamoxifen with or without radiotherapy. By combining Luminal A and low-risk features (>60 years, T1, grade 1/2], the 10-year LR rate was 3.1% compared to 11.8% for the high-risk subtypes (HER-2 positive and basal type). Besides, the addition of radiotherapy to tamoxifen did not yield higher local control. The small benefit from radiotherapy for older women with favourable tumour features receiving endocrine therapy has long been emphasized. The criterion of age, along with other risk factors, is also taken into account for accelerated partial breast irradiation (APBI) according to the American Society for Radiation Oncology (ASTRO) and European Society for Therapeutic Radiology and Oncology (ESTRO) recommendations [36,37]. APBI represents a challenge for high-precision radiotherapy, considering the important implications of patient selection and proper target volume identification [38]. The advantages of APBI techniques are that it reduces the volume treated, with a potential decrease in normal tissue toxicity, and it shortens the treatment

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

time, which reduces RT waiting lists, treatment costs and is more convenient for the patient. Over and above these positive aspects, the main concern is the effectiveness of the treatment. The key to successful outcome lies in identifying patients with a low risk of harbouring occult neoplastic foci outside the index breast quadrant. The integration of clinical data, histopathological features, biomolecular factors and, possibly, genetic profiles, might help to provide a framework for deciding when APBI can be safely prescribed. As well as ongoing trials [39,40] or those which have been closed but are not yet mature [41,42], the results from Hungarian [43], GEC-ESTRO [44], Spanish [45] IMPORT LOW [46] and Florence University [47], randomized trials have confirmed the efficacy of APBI in selected patients. These modern trials did not show any statistically significant difference in local control between the APBI and the whole breast radiotherapy (WBRT) arms, unlike those dating back to the eighties [48,49], in which patient selection was less strict and the techniques used were less conformal. The intraoperative techniques [34,50] might be penalised by the lack of full tumour view at the time of radiation delivery, although preoperative/intraoperative pathological assessment is recommended. However, the TARGIT trial [50] allowed for WBRT if the final histological report revealed high-risk features, formally fulfilling the criterion for adaptive radiotherapy. An overview of phase III trials on APBI is shown in Table 1.

Although recent updated trials support the omission of radiotherapy in selected patients, several confirmatory trials are on the way. They are dedicated to women aged 50 and over, presenting T1N0, low-intermediate grade, hormone-sensitive and HER-2 negative, who plan to receive endocrine therapy. Favourable tumour profiles are identified either by immunohistochemical (LUMINA trial from the Ontario Clinical Oncology Group), or Oncotype DX RS (IDEA trial from the University of Michigan), or Prosigna PAM50 assay (PRECISION trial from the Dana-Farber Cancer Institute) [19,51].

By contrast, luminal B and higher-risk subtypes, characterized by more aberrant genomes, showed a higher risk of LR and greater benefit from radiotherapy. Regarding the role of Ki-67, high expression was found to be associated with an increased risk of LR, even in small node negative tumours [52,53]. However, the addition of radiotherapy did not always result in better outcome, highlighting the need to investigate alternative regimens. Interestingly, high Ki-67 turned out to be the only factor to interact significantly with the effect of axillary radiotherapy on the risk of recurrence. For patients not receiving axillary dissection in the GRISO 053 trial, high Ki-67 acted as a successful indication for axillary radiotherapy, which benefitted disease free survival [54].

TN and HER-2 positive are known to have an increased risk of developing LR, irrespective of the type of surgery [11]. The perceived outcome for HER-2 positive is influenced negatively by the pre-trastuzumab era and recent trials are likely to give a different perspective. In preclinical studies, the association of trastuzumab with ionizing radiation enhances the radiosensitivity of breast cancer cell lines, through DNA repair inhibition and increased tumour cell death [55]. Clinically, while no increased toxicity is reported, improved outcome has been seen in several studies [55]. In HER2-positive patients receiving trastuzumab, the LR was far lower than TN patients [56] and whole breast radiotherapy resulted in optimal local control [57]. Conversely, APBI or even mastectomy without radiotherapy worsened outcome, which shows the value of extensive radiotherapy for this subtype [57].

Basal-like/TN are characterized by early relapse, poor disease free and overall survival. Currently, there is no indication that basal-like/TN patients should receive different radiotherapy regimens [58,59], except in the case of APBI, which is recommended only in clinical trials [60]. Basal-like/TN belongs to the subgroup that is unsuitable for APBI according to ASTRO/ESTRO [36,37], and, in the ELIOT randomized study, it indicated an increased risk of LR [34]. However, in the presence of this relatively aggressive phenotype, ROs tend to deliver more aggressive treatments, including larger radiation fields or dose escalation [29]. For instance, a basal-like/TN phenotype might make it advisable to add a supraclavicular field if the axilla has not been dissected and there are one or two positive sentinel nodes, or to prescribe PMRT in early stage BC [18,61]. Novel radiosensitizers, such the PARP inhibitors, may increase the efficacy of radiotherapy [25]. Table 2 summarizes radiosensitivity and pattern of recurrence in accordance with molecular classification.

That it is safe to omit radiotherapy has long been doubted in the case of ductal carcinoma in situ (DCIS) [5]. Biomarkers can be used in addition to traditional clinicopathology to select adjuvant treatment. High Ki-67 tumours seem to benefit the most from radiotherapy, irrespective of nuclear grade and necrosis [62], whereas radiotherapy is seen to have no effect on Luminal A DCIS with Ki-67 < 14%. All HER-2 positive DCIS are responsive to radiotherapy, showing a significant decrease in all local relapse-related events except for invasive recurrences [63]. Based on the results of the Eastern Cooperative Oncology Group E5194 trial, which enrolled low/intermediate grade DCIS or small high-grade DCIS, the 12-gene panel, known as the OncotypeDX DCIS Score, was able to discriminate between a low or high risk of LR, either invasive or in situ [64].

Considering the recent redefinition of the alfa/beta ratio for BC, there is a growing body of evidence advocating the use of hypofractionation [65], characterized by short overall duration with increased dose/fraction. The effectiveness of altering the fractionation has been examined for all the subsets [66]. A first analysis in the randomized Canadian study conducted by Whelan, evaluating whole-breast radiotherapy; a 3-week hypofractionated schedule versus a 5-week schedule in nodal negative women after CS, high-grade tumours had a higher incidence of LR when treated with hypofractionation than with standard radiotherapy [15.6% vs. 4.7%, respectively) [67]. The lesser sensitivity to accelerated radiation schedules was not confirmed in a subsequent analysis with a different grading score system [68], in keeping with the UK START A and B trials [69]. In addition, further investigations on the Canadian study population, using a six biomarker panel, found that the molecular subtype was an independent predictor of LR, outperforming other clinical–pathological parameters, but did not predict response to hypofractionation, suggesting that tumours of all grades and molecular subtypes may be effectively treated with alternative schedules [68].

The technological tools of high-precision radiotherapy

In the radiotherapy setting, technological innovation has led to remarkable improvements in every phase related to treatment, from simulation to planning to delivery, with the aim of minimizing normal organ toxicity and improving local control. The fundamental step towards high-precision radiotherapy was the introduction of the computed tomography (CT) scan, which emphasized the passage from a two-dimensional to a three-dimensional (3D) perspective [70]. The high conformability of 3D radiotherapy, supported by the implementation of new treatment planning systems equipped with multileaf collimators (MLC) and beam-eye-views, has led to a remarkably improved dosimetric accuracy and to a precise reconstruction of patient anatomy, including the complex relationships of adjacent organs or structures. The optimization of dose distribution limits the hot spots, areas receiving a higher dose than that prescribed, which could give rise to severe late effects [71]. This phenomenon known as “double trouble” in conventional fractionation turns into “triple trouble” in the case of

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

Table 1
Overview of phase III trials on APBI. For each trial, the inclusion criteria, the number of patients (N pts), the median follow-up period (F-up) and the techniques and schedules are shown. The main findings of the trials are reported: local recurrence (LR), overall survival (OS) and cosmetic outcome. True recurrence refers to the reappearance of the breast cancer in the index quadrant while marginal miss recurrence refers to reappearance close to the margin of the tumour bed. DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, HDR-BRT = high dose rate brachytherapy, PDR-BRT = pulsed dose rate brachytherapy, 3D-CRT = three-dimensional conformal external beam radiation therapy N.A. = data not available.

Trial (Enrolment period)	Inclusion criteria	N pts	F-up [years]	APBI		WBRT		LR rate APBI vs WBRT (p-value)	OS rate APBI vs WBRT (p-value)	Cosmetic
				Technique	Dose fractionation	Technique	Dose fractionation			
Christie Hospital (1982–1987) Single institution [48]	age < 70 T < 4 cm cN0	708	8	Electrons (8–14 MeV)	40–42.5 Gy in 8 fr	Tangential fields (4 MV)	40 Gy in 15 fr	25% vs 13% (***p < 0.0001***)	73% vs 72% (No significant differences)	N.A.
Cookridge Hospital (1986–1990 closed) Single institution [49]	pT1/pT2 pN0/pN1 Free margins	174	8	Cs^{137} or Co^{60} or Electrons (6–8 MeV) or Tangential fields	50 Gy in 20 fr	Tangential fields + Boost (Cs^{137} or Co^{60} or electrons)	40 Gy in 15 fr + max 15 Gy in 5 fr	12% vs 4% **(p = 0.07)** *True recurrences: 7/10*	70% vs 73% (*p = 0.7474*)	N.A.
BUDAPEST (1998–2004) Single institution [43]	age >40 (≤40 initially included) pT1 pN0/pN1mi Grade ≤ 2 Free margins Unifocal *Excluded: DCIS, LCIS, invasive lobular carcinoma, extensive intraductal component*	258	10.2	HDR-BRT *If unsuitable implantation* Electrons (6–15 MeV)	36.4 Gy in 7 fr 42-50 Gy in 25 fr	Tangential fields (6–9 MV) or telecobalt	50 Gy in 25 fr	5.9% vs 5.1% (*p = 0.77*) *True/marginal miss recurrences: 2.4 vs 3.4%* (*p = 0.72*)	79.7% vs 82.1% (*p = 0.73*)	Excellent and good APBI vs WBRT 81% vs 63% (***p < 0.01***)
GEC-ESTRO (2004–2009) Multi-centre [44]	age ≥ 40 invasive or DCIS pTis/pT1/pT2 (T < 3 cm) pN0/pNmi Free margins (>2 mm, ≥5 mm lobular invasive/DCIS) No lympho-vascular invasion	1184	6.6	HDR-BRT PDR-BRT	32 Gy in 8 fr or 30.3 Gy in 7 fr (twice daily) 50 Gy (0.60–0.80 Gy pulse)	Tangential fields (4–10 MV) + boost (electrons)	50–50.4 Gy in 25–28 fr + 10 Gy in 5 fr	1.44% vs 0.92% (*p = 0.42*) *True/marginal miss recurrence: 10/14*	97.3% vs 95.6% (*p = 0.11*)	Severe fibrosis (grade 3) APBI vs WBRT 0% vs 0.2% (*p = 0.46*)
Hospital de la Esperanza (–) single institution [45]	age ≥ 60 invasive or ductal carcinoma pT2 (T ≤ 3 cm) pN0 Grade ≤ 2 NO extensive intraductal component Free margins (>3 mm)	102	5	3D-CRT	37.5 Gy in 10 fr twice daily (6 h apart)	Tangential field + optional boost	48 Gy in 24 fr + 10 Gy	0% vs 0%	similar	Excellent and good APBI vs WBRT >75% vs >84% (similar)
IMPORT LOW (2006–2010) Multi-centre [46]	age ≥ 50 invasive carcinoma no lobular histology pT1/pT2 (T ≤ 3 cm) pN0/pN1 Free margins (≥2 mm)	2018	5.7	IMRT	Test 2: 40 Gy in 15 fr (partial breast)	Tangential fields	Control: 40 Gy in 15 fr Test 1: 36 Gy in 15 fr (whole breast) + 40 Gy in 15 fr (boost)	Test 2: 0.5% vs 1.1% (Control) and 0.2% (Test1)	N.A.	Moderate/marked changes *(reported by patients)* APBI (Test 2) vs WBI (Control): 15% vs 27% (***p = 0.005***)

Florence University (2005–2013) Single institution [47]	age ≥ 40 T < 2.5 cm pN0/pN1 Unifocal Free margins (≥5 mm)	520	5	Step and shoot IMRT (6 MV)	30 Gy in 5 non-consecutive fr (over 2 weeks)	Tangential fields + Boost (electrons)	50 Gy in 25 fr + 10 Gy in 5 fr	1.5% vs 1.4% (p = 0.86) *True recurrences: 0% vs 1.4%* *(p = 0.11)*	99.4% vs 96.6% (***p = 0.057***)	Skin fibrosis ABPI vs WBRT 4.5% vs 11.2% Excellent and good APBI vs WBRT 100% vs 99.2% (***p = 0.045***)
ELIOT (2000–2007) single institution [34]	age:48-75 T ≤ 2.5 cm cN0 Unifocal	1305	5.8	Intraoperative electrons	21 Gy in 1 fr	Tangential fields + Boost (electron)	50 Gy in 25 fr + 10 Gy in 5 fr	4.4% vs 0.4 (***p = 0.0001***) *True recurrences: 2.5% vs 0.4%* (***p = 0.0003***)	96.8% vs 96.6% (p = 0.59)	Skin side-effects: APBI < WBI (***p = 0.0002***)
TARGIT (2000–2012) Multi-centre [50]	age ≥ 45 invasive ductal carcinoma unifocal	3451	2.5	Intraoperative photons (50 kV) Intraoperative photons + EBRT	20Gy in 1 fr *(at 1 cm depth 5 −7 Gy)* 20Gy in 1 fr + EBRT (*dose site specific*)	Tangential fields + Boost permitted	40-56 Gy + 10-16 Gy	3.3% vs 1.3% (***p = 0.042***)	96.1% vs 94.7% (***p = 0.099***)	Wound related complications: similar Skin complication grade3-4: APBI < WBRT
RAPID (2006–2011) Multi-centre [41]	age > 40 invasive or DCIS T ≤ 3 cm pN0 M0 Free margins	2135	3	3D-CRT (6–18 MV)	38 Gy in 10 fr twice daily (6 h apart)	Tangential fields (4–18 MV) + optional boost *wedges, and forward planned or IMRT permitted*	42.5 Gy in 16 fr or 50 Gy in 25 fr + 10 Gy in 4/5 fr	pending	N.A.	Excellent and good APBI vs WBI (reported by *physicians)* 35% vs 17% (***p < 0.001***)
NASBP-B.39/RTOG-0413 (2005–2013) Multi-centre [42]	age ≥ 18 invasive and/or DCIS T ≤ 3 cm unifocal/ microscopic multifocality pN0/pN1 Free margins	4300	N.A.	multi-catheter brachytherapy MammoSite® balloon catheter 3D-CRT	34 Gy in 10fr twice daily (6 h apart) 38.5 Gy in 10 fr twice daily (6 h apart)	Tangential field + optional boost (photons or electrons)	50 Gy in 25 fr or 50.4 Gy in 28 fr + 10–16.2 Gy in 5 –9 fr	pending	pending	pending
IRMA (2008-ongoing) Multi-centre [39]	age ≥ 49 invasive pT1/pT2 (T < 3 cm) pN0/pN1 unifocal Free margins (≥2 mm)	To enrol 3302	N.A.	3D-CRT	38.5 Gy in 10 fr twice daily (6 h apart)	Tangential fields (4–6 MV) boost permitted (electron photons)	45 Gy in 18fr or 50 Gy in 25 fr or 50.4 Gy in 28 fr + 10-16 Gy in 5–8 fr	N.A.	N.A.	N.A.
SHARE (2010-ongoing) Multi-centre [40]	age ≥ 50 postmenopausal status ≥ 12 months all types of invasive T≤2 cm) pN0/pN0 (i+) unifocal Free margins (≥2 mm)	To enrol 2800	N.A.	3D-CRT (≥4 MV) photons or mixed (photons and electrons)	40Gy in 10 fr twice daily (6 h apart)	Tangential fields + boost (electrons or photons or mixed)	50 Gy in 25 fr + 10-16 Gy in 5–8 fr 42.5 Gy in 16 fr or 40 Gy in 15 fr	N.A.	N.A.	N.A.

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

Table 2
Summary of radiosensitivity and pattern of recurrence. Molecular classifications of breast cancers are based on immunohistochemistry. Suggestion for therapeutic approaches is indicative. Decision –making for radiation techniques and volumes must integrate biological, clinical and pathological factors. True: any reappearance in the same quadrant as the primary tumour; Elsewhere: any reappearance of carcinoma in other quadrants; RT: radiotherapy; APBI: accelerated partial breast irradiation.

Molecular subtypes	Radiosensitivity	Locoregional recurrence rate	Pattern of recurrence	Possible therapeutic approach
Luminal A	High [3,4,11,25]	Low [3,4,11,25]	True [11,26–28,30,31,33,34]	Whole breast RT To discuss: - no RT [19] - dose descalation [12] - APBI [26,34]
Luminal B	Intermediate [3,4,11,25]	Intermediate [3,4,11,25]	True and elsewhere [26–28,34,57] Regional [31,53,54]	Whole breast RT To discuss: - dose escalation [22] - regional nodal RT [16,54]
HER2/neu positive	Low [3,4,11,25]	intermediate/high (post- and pre -trastuzumab) [3,4,11,25]	True [26,34,28] Regional [11,23,31,32]	Whole breast RT To discuss: - dose escalation [23,33] - regional nodal RT [16,18,31]
Basal-like/triple negative	Very low [3,4,11,25,58]	High [3,4,11,56,58]	True [28] and elsewhere [26,27,34,58] Regional [11,23,30,31,56,58]	Whole breast RT To discuss: - regional nodal RT [16,18,29,31] - dose escalation [22,23] - radiosensitizers [25]

hypofractionation, where dose/fraction size is increased [66]. Reducing exposure to the organs at risk (OARs) by means of precise 3D reconstruction [72], decreases toxicity and paves the way to safe dose escalation. The combination of dosimetric data and data regarding clinical toxicity makes it possible to chart complex dose–response relationships and to define specific tolerance doses for OARs. A comprehensive review of clinical tolerance and dose–effect correlations of the most commonly irradiated organs was organized in the Quantitative Analysis of Normal Tissue Effect in the Clinic (QUANTEC) project, published in 2010 [73]. Models linking dose with toxicity and tumour control, based on radiobiological and mathematical principles, were used to predict the normal tissue complication probability (NTCP) and tumour control probability (TCP), enabling ROs to evaluate the potential treatment outcome [74].

Positive findings that reflect how technological advances translate into medical benefit are represented by the rise in local control, with its effect on survival, and by the ever lower cardiac toxicity [1,8,9]. The expected local failure at 5 years after CS has shifted from a rough 5% incidence in studies over twenty-years-old [75] to 1% or less in the modern era [76], made possible by advances in surgery, radiotherapy and medical oncology. There are less

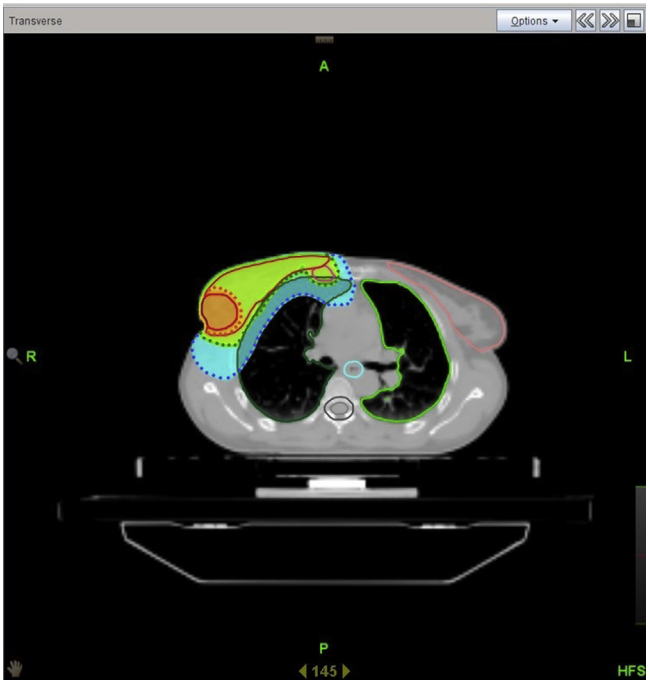

Fig. 1. Transversal view of a treatment plan for whole breast with simultaneous integrated boost and internal mammary chain irradiation. From the inside to outside, the dotted lines correspond to 95% of the boost dose (orange), 95% of the prescribed dose to the breast and the internal mammary nodes (green) and 50% of the boost dose (blue); Tomotherapy® Treatment Planning System. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

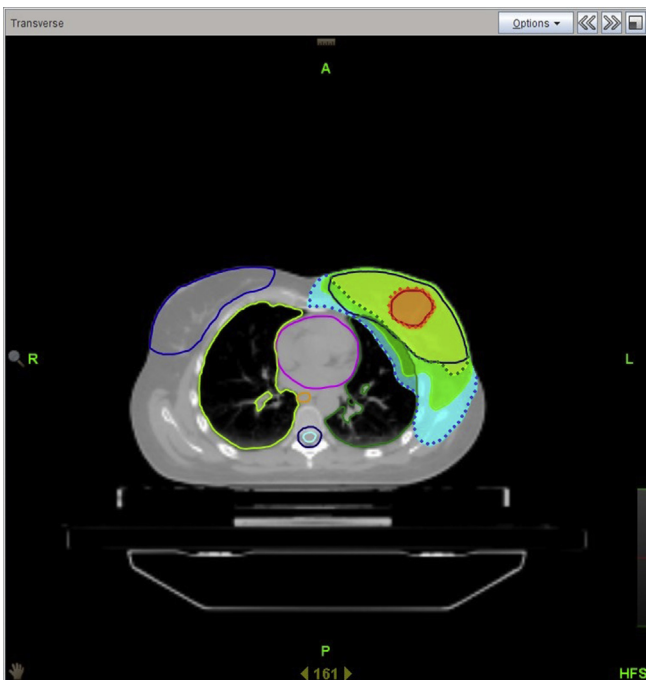

Fig. 2. Transversal view of a treatment plan for whole breast irradiation with simultaneous integrated boost. From the inside to outside, the dotted lines correspond to 95% of the boost dose (orange), 95% of the prescribed dose to the breast and the internal mammary nodes (green) and 50% of the boost dose (blue); Tomotherapy® Treatment Planning System. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

cardiac events because of a reduced dose to the myocardium and coronary arteries even when the locoregional field includes the internal mammary nodes, as demonstrated by recent trials [77,78]. Moreover, modern radiotherapy offers the breath hold technique, which displaces the heart away from the chest wall, and respiratory gating techniques, where radiotherapy delivery is triggered by thoracic expansion, leading to a corresponding decrease in the estimated NTCP for excess cardiac mortality [79].

Nowadays the technological evolution has taken a step forward as intensity-modulated radiotherapy (IMRT) based on different types of delivery (step & shoot, sliding windows, Tomotherapy®, volumetric arc therapy) and stereotactic ablative radiotherapy (SART) has entered into routine practice [80,81]. The dose distribution can be painted around the target volume with a steep dose gradient. For IMRT, the dose distribution is characterized by a concavity at the edge of the higher doses that fits well with breast conformation and spares OARs (Fig. 1) [82].

In WBRT randomized trials, IMRT BC patients reported lower acute side effects, late changes in breast appearance and impaired cosmesis than those in the control arm [80,83,84]. Low incidence of side effects was also observed in APBI trials [46,47]. In the Florence University trial [47], acute and chronic toxicity and cosmesis were significantly better in the APBI arm using IMRT compared to the WBRT arm treated with a 3D technique. Conversely, adverse cosmesis and late toxicity occurred in the APBI arm of RAPID trial [41], using 3D conformal technique, although with a different fractionation.

The IMRT technique allows the simultaneous delivery of different dose levels to different target volumes within a single treatment fraction: this approach is defined as the “simultaneous integrated boost technique” (SIB). The SIB technique is of particular interest because it can be used to yield higher doses to the critical area (boost volume) (Figs. 1 and 2) without increasing the overall treatment time [85].

The IMPORT LOW [46] and HIGH trials were designed to deliver 3-level radiation dose distribution to the breast, including dose escalation in high-risk and dose/volume descalation in low risk patients. They are able to investigate the dose modulation effect across the breast in order to reflect individual recurrence risk [86].

SART in BC provides excellent results mainly in the treatment of metastases; it delivers a high dose/fraction for good local control, it exploits the steep dose gradient to improve tolerance and it delivers the treatment in few fractions for an optimal quality of life [87].

Within the radiation landscape, proton therapy for BC is still in its infancy, but preliminary reports seem promising in terms of OARs sparing, especially in the case of extensive radiation fields [88].

High-precision radiotherapy demands accurate identification of target and OARs. Adequate contouring is the fundamental prerequisite for an effective and safe treatment plan. However, contouring is a process prone to errors and inter- and intra-operator variability [89]. In particular, the tumour bed is subject to topographical uncertainties; consequently, many authors recommend the use of surgical clips to mark the lumpectomy site [90]. The integration of radiological/metabolic imaging such as Magnetic Resonance (MR) and Positron Emission Tomography with CT simulation can provide useful information for high-precision contouring of areas needing to be boosted or spared [91,92]. To improve the consistency of contouring among ROs, several working groups have provided consensus instructions and atlases [93,94]. Recently, software for the auto-segmentation of volumes of interest has been developed to support radiotherapy planning [95]. Besides, the possibility of microscopic extension of the tumour beyond the anatomic borders defined by the atlases should be carefully considered by ROs, especially when high-precision techniques are used [96].

An essential aspect of the advances in physics and technology is expressed in the quality of treatment execution. High conformability means high sensitivity to any changes occurring in the patient during the course of radiotherapy. Displacement of the target due to organ motion, anatomical changes in the patient's body or inaccurate setup affects dose distribution, leading to inadequate target coverage or excessive irradiation of the OARs. This is of particular concern when dose escalation or hypofractionation are used. Immobilization devices, as simple as the forearm support or prone and lateral decubitus, help to maintain patients in a fixed and reproducible position that decreases heart and lung irradiation [97]. Strategies to verify target shape, volume and position, and to correct the topographical inconsistencies with the original plan, are part of image-guided radiotherapy (IGRT), which uses various devices, such as electronic portal imaging, cone beam CT, megavoltage CT, ultrasound, optical imaging and fiducial markers [98]. In the case of substantial deviations from the original treatment plan that cannot be adjusted by means of couch, machine or MLC shifts, it becomes necessary to re-plan and re-optimize the dose distribution [99]. This kind of adaptive radiotherapy can be done offline, with a time lapse, or even online, with a fast re-planning system to elaborate a new plan for the current treatment session. Besides interfraction motion, also intra-fraction motion has become relevant because delivery time is longer with modern radiotherapy machines, extensive locoregional treatment and hypofractionation schedules [100]. Displacements are related to uncontrolled physiological behaviour; coughing, body relaxation, suggesting that non-invasive continuous monitoring should be envisaged [101,102]. Treatment rooms should be equipped with a movement tracking system to monitor and compensate for target motion during irradiation. The MR linear accelerator (MR-linac) represents a further step towards a fully adaptive intra-fraction planning system [103]. More precise tracking of target and organs at risk, thanks to advanced soft-tissue visualization, should lead to narrower safety margins around the target and to smaller treated volumes, making it possible to escalate the dose safely.

Predicting toxicity is an important step for cost effectiveness and quality of life, but it is subject to great individual variability and has a multifactorial genesis. Moreover, innovative therapies, such as alternative radiation schedules or target agents, pose new challenges and increase the complexity. Predictive markers of radiation-induced toxicity could be used to identify patients who are bound to suffer from severe normal tissue reactions to radiation, in order to offer personalized schedules. Severe late radiation-induced toxicities were correlated to a low rate of radiation-induced CD8 T-lymphocyte apoptosis [104]. Severe late effects were seen in patients with four or more Single Nucleotide Polymorphisms in candidate genes (ATM, TGFB1, XRCC1, XRCC3, SOD2, and RAD21] [105]. Currently, the evidence is insufficient and inconsistent because of the complex mechanisms behind radiation-induced toxicity and the inter-patient variations in radiosensitivity but the ability to identify a genetic signature which would help to determine which patients are likely to develop severe early or late normal tissue injury is appealing.

Closing remarks

Modern radiotherapy is devoted to more selective treatments, with the aim of optimizing the coverage of tumours and areas at risk and minimizing the involvement of healthy tissue. A plethora of technological tools is available to target the tumour and/or the areas at risk and is now part of daily practice. Further implementations, such as the routine use of fast re-planning and the potential of MRI-linac, will soon be entering the radiation oncology scenario. Adaptive radiotherapy, as a general concept, has already

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

developed to take account of the patient's anatomy and the geometric conformation of the tumour. However, technological advances seem likely to reach a plateau in the near future and, if there is to be a continuation towards ever more cost-effective treatments, they must be accompanied by a better understanding of tumour biology. Radiotherapy needs to be adaptive to tumour profile. In the context of a multidisciplinary approach, radiation oncology decision-making must combine the clinical-pathological and the biological features involved in radiation response, without overlooking the contribution made by systemic therapies and patient-related factors, such as age or comorbidities [106]. The best approach for the individual patient can cover a wide range of choices, from no treatment at all, to partial breast irradiation to loco-regional irradiation, even including the internal mammary chain. Recent research and clinical evidence have generated few certainties but some new hypotheses that make tumour biology the most important challenge for ROs in the proper selection of patients and treatments.

Acknowledgment

This work was partially supported by research grant from Accuray Inc. titled “Data collection and analysis of Tomotherapy and CyberKnife breast clinical studies, breast physics studies and prostate study”.

The authors wish to thank Mrs. Verlie Anne Jones who assisted in the proof-reading of the manuscript.

Abbreviations

BC	breast cancer
CS	conservative surgery
ROs	radiation oncologists
ER	estrogen receptor
LR	local recurrence
RSI	radiation sensitivity index
TN	triple-negative
DBCG	Danish Breast Cancer Cooperative Group
PMRT	postmastectomy radiation
APBI	accelerated partial breast irradiation
WBRT	whole breast radiotherapy
IHC	immunohistochemistry
ASTRO	American Society for Radiation Oncology
ESTRO	European Society for Therapeutic Radiology and Oncology
ELIOT	Electron Intraoperative Radiotherapy
DCIS	ductal carcinoma in situ
CT	computed tomography
3D	three-dimensional
MLC	multileaf collimators
OARs	organs at risk
QUANTEC	Quantitative Analysis of Normal Tissue Effect in the Clinic
NTCP	normal tissue complication probability
TCP	tumour control probability
IMRT	intensity-modulated radiotherapy
SART	stereotactic ablative radiotherapy
SIB	simultaneous integrated boost technique
MR	Magnetic Resonance
IGRT	image-guided radiotherapy
MR-linac	MR linear accelerator

Conflict of interest statement

The authors indicated no potential conflict of interest.

References

[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378(9804):1707–16.
[2] Bibault J-E, Fumagalli I, Ferté C, Chargari C, Soria J-C, Deutsch E. Personalized radiation therapy and biomarker-driven treatment strategies: a systematic review. Cancer Metastasis Rev 2013;32:479–92.
[3] Sioshansi S, Huber KE, Wazer DE. The implications of breast cancer molecular phenotype for radiation oncology. Front Oncol 2011 Jun 28;1:12.
[4] Harbeck N, Salem M, Nitz U, Gluz O, Liedtke C. Personalized treatment of early-stage breast cancer: present concepts and future directions. Cancer Treat Rev 2010;36:584–94.
[5] Morrow M, Katz SJ. Addressing overtreatment in DCIS: what should physicians do now? J Natl Cancer Inst 2015;107(12):djv290.
[6] Marta GN, de Moraes FY. Postoperative nodal irradiation in breast cancer patients with 1 to 3 axillary lymph nodes involved: the debate continues. Expert Rev Anticancer Ther 2015;15(11):1257–9.
[7] Calvo FA, Sole CV, Rivera SR, Lizarraga S, Infante MA, et al. The use of radiotherapy for early breast cancer in woman at different ages. Clin Transl Oncol 2014;16(8):680–5.
[8] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al., Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366(9503):2087–106.
[9] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000;355(9217):1757–70.
[10] Orecchia R, Leonardi MC. Partial breast irradiation: targeting volume or breast molecular subtypes? Breast 2013;22:S137–40.
[11] Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat 2012;133(3):831–41.
[12] Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, , et alEuropean Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015;16(1):47–56.
[13] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378(9793):771–84.
[14] Yang TJ, Ho AY. Radiation therapy in the management of breast Cancer. Surg Clin N. Am 2013;93(2):455–71.
[15] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383(9935):2127–35.
[16] Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al., Panel Members. Tailoring therapies-improving the management of early breast cancer: St gallen International Expert consensus on the primary therapy of early breast Cancer 2015. Ann Oncol 2015;26(8):1533–46.
[17] Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;32(32):3600–6.
[18] Haffty BG, Wood R. Positive sentinel nodes without axillary dissection: implications for the radiation oncologist. J Clin Oncol 2011;29(34):4479–81.
[19] Protocols available at: www.clinicaltrials.gov.
[20] Britten A, Rossier C, Taright N, Ezra P, Bourgier C. Genomic classifications and radiotherapy for breast cancer. Eur J Pharmacol 2013;717:67–70.
[21] Mamounas EP, Tang G, Fisher B, Paik S, Shak S, Costantino JP, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010;28(10):1677–83.
[22] Torres-Roca JF, Fulp WJ, Caudell JJ, Servant N, Bollet MA, van de Vijver M, et al. Integration of a radiosensitivity molecular signature into the assessment of local recurrence risk in breast Cancer. Int J Radiat Oncol Biol Phys 2015;93(3):631–8.
[23] Kyndi M, Sorensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J, Danish Breast Cancer Cooperative Group. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. J Clin Oncol 2008;26:1419–26.
[24] Tramm T, Kyndi M, Myhre S, Nord S, Alsner J, Sørensen FB, et al. Relationship between the prognostic and predictive value of the intrinsic subtypes and a validated gene profile predictive of loco-regional control and benefit from post-mastectomy radiotherapy in patients with high-risk breast cancer. Acta Oncol 2014;53:1337–46.

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

[25] Langlands FE, Horgan K, Dodwell DD, Smith L. Breast cancer subtypes: response to radiotherapy and potential radiosensitisation. Br J Radiol 2013;86(1023):20120601.
[26] Veronesi U, Orecchia R, Luini A, Galimberti V, Zurrida S, Intra M, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. Breast Cancer Res Treat 2010;124(1):141–51.
[27] Albert JM, Gonzalez-Angulo AM, Guray M, Sahin A, Strom EA, Tereffe W, et al. Estrogen/progesterone receptor negativity and HER2 positivity predict locoregional recurrence in patients with T1a,bN0 breast cancer. Int J Radiat Oncol Biol Phys 2010;77(5):1296–302.
[28] Hattangadi-Gluth JA, Wo JY, Nguyen PL, Abi Raad RF, Sreedhara M, Niemierko A, et al. Basal subtype of invasive breast cancer is associated with a higher risk of true recurrence after conventional breast-conserving therapy. Int J Radiat Oncol Biol Phys 2012;82(3):1185–91.
[29] Khan AJ, Milgrom SA, Barnard N, Higgins SA, Moran M, Shahzad H, et al. Basal subtype, as approximated by triple-negative phenotype, is associated with locoregional recurrence in a case-control study of women with 0–3 positive lymph nodes after mastectomy. Ann Surg Oncol 2014;21(6):1963–8.
[30] Nguyen PL, Taghian AG, Katz MS, Niemierko A, Abi Raad RF, Boon WL, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 2008;26(14):2373–8.
[31] Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 2010;28(10):1684–91.
[32] Millar EK, Graham PH, O'Toole SA, McNeil CM, Browne L, Morey AL, et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. J Clin Oncol 2009;27(28):4701–8.
[33] Arvold ND, Taghian AG, Niemierko A, Abi Raad RF, Sreedhara M, Nguyen PL, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol 2011;29(29):3885–91.
[34] Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14(13):1269–77.
[35] Liu F-F, Shi W, Done SJ, Miller N, Pintilie M, Voduc D, et al. Identification of a low-risk luminal a breast Cancer cohort that may not benefit from breast radiotherapy. J Clin Oncol 2015;33:2035–40.
[36] Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74(4):987–1001.
[37] Polgár C, Van Limbergen E, Pötter R, Kovács G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence. Radiother Oncol 2010;94(3):264–73.
[38] Kirby Anna M, Coles Charlotte E, Yarnold John R. Target volume definition for external beam partial breast radiotherapy: clinical, pathological and technical studies informing current approaches. Radiotherapy Oncol 2010;94.3:255–63.
[39] Frezza G, Bertoni F, IRMA. Breast Cancer with Low Risk of Local Recurrence: Partial and accelerated Radiation with Three-Dimensional Conformal Radiotherapy (3DCRT) vs. Standard Radiotherapy After Conserving Surgery (Phase III Study). Available at: https://clinicaltrials.gov/ct2/show/NCT01803958.
[40] Belkacemi Y, Bourgier C, Kramar A, Auzac G, Dumas I, Lacornerie T, et al. SHARE: a French multicenter phase III trial comparing accelerated partial irradiation versus standard or hypofractionated whole breast irradiation in breast cancer patients at low risk of local recurrence. Clin Adv Hematol Oncol 2013;11:76–83.
[41] Olivotto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, Germain I. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol 2013;31(32):4038–45.
[42] NSABP B-39/RTOG 0413. A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) for women with stage 0, I, or II breast Cancer. 2011. Available at: https://clinicaltrials.gov/ct2/show/NCT00103181.
[43] C1 Polgár, Fodor J, Major T, Sulyok Z, Kásler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol 2013 Aug;108(2):197–202. http://dx.doi.org/10.1016/j.radonc.2013.05.008. Epub 2013 Jun 3.
[44] Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al., Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 2016 Jan 16;387(10015):229–38. http://dx.doi.org/10.1016/S0140-6736(15)00471-7. Epub 2015 Oct 19.
[45] Rodríguez N, Sanz X, Dengra J, Foro P, Membrive I, Reig A, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2013;87(5):1051–7.
[46] Coles C, Agrawal R, Ah-See ML, Algurafi H, Alhasso A, Brunt AM, et al. Partial breast radiotherapy for women with early breast cancer: first results of local recurrence data for IMPORT LOW (CRUK/06/003). Eur J cancer 2016, April;57. S4–S4.
[47] Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, Orzalesi L. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 2015;51(4):451–63.
[48] Magee B, Swindell R, Harris M, Banerjee SS. Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: results from a randomised trial. Radiother Oncol 1996 Jun;39(3):223–7.
[49] Dodwell DJ, Dyker K, Brown J, Hawkins K, Cohen D, Stead M, et al. A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer. Clin Oncol R Coll Radiol 2005 Dec;17(8):618–22.
[50] Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014 Feb 15;383(9917):603–13.
[51] Bellon JR. Personalized radiation oncology for breast cancer: the new frontier. J Clin Oncol 2015;33(18):1998–2000.
[52] Selz J, Stevens D, Jouanneau L, Labib A, Le Scodan R. Prognostic value of molecular subtypes, ki67 expression and impact of postmastectomy radiation therapy in breast cancer patients with negative lymph nodes after mastectomy. Int J Radiat Oncol Biol Phys 2012;84(5):1123–32.
[53] Colleoni M, Rotmensz N, Peruzzotti G, Maisonneuve P, Viale G, Renne G, et al. Minimal and small size invasive breast cancer with no axillary lymph node involvement: the need for tailored adjuvant therapies. Ann Oncol 2004;15(11):1633–9.
[54] Zurrida S, Bagnardi V, Curigliano G, Mastropasqua MG, Orecchia R, Disalvatore D, et al. High Ki67 predicts unfavourable outcomes in early breast cancer patients with a clinically clear axilla who do not receive axillary dissection or axillary radiotherapy. Eur J Cancer 2013;49(15):3083–92.
[55] Adamowicz K, Marczewska M, Jassem J. Combining systemic therapies with radiation in breast cancer. Cancer Treat Rev 2009 Aug;35(5):409–16.
[56] Zhang C, Wang S, Israel HP, Yan SX, Horowitz DP, Crockford S, et al. Higher locoregional recurrence rate for triple-negative breast cancer following neoadjuvant chemotherapy, surgery and radiotherapy. SpringerPlus 2015;4:386.
[57] Brollo J, Kneubil MC, Botteri E, Rotmensz N, Duso BA, Fumagalli L, et al. Locoregional recurrence in patients with HER2 positive breast cancer. Breast 2013;22(5):856–62.
[58] Moran MS. Radiation therapy in the locoregional treatment of triple-negative breast cancer. Lancet Oncol 2015;16(3):e113–22.
[59] Eiermanna W, Bergh J, Cardoso F, Conte P, Crown J, Curtin NJ, et al. Triple negative breast cancer: proposals for a pragmatic definition and implications for patient management and trial design. Breast 2012;21:20–6.
[60] Moser EC, Vrieling C. Accelerated partial breast irradiation: the need for well-defined patient selection criteria, improved volume definitions, close follow-up and discussion of salvage treatment. Breast 2012;21:707–15.
[61] Kunkler IH, Canney P, van Tienhoven G, Russell NS. MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol R Coll Radiol 2008;20(1):31–4.
[62] Lazzeroni M, Guerrieri-Gonzaga A, Botteri E, Leonardi MC, Rotmensz N, Serrano D, et al. Tailoring treatment for ductal intraepithelial neoplasia of the breast according to Ki-67 and molecular phenotype. Br J Cancer 2013 Apr 30;108(8):1593–601.
[63] Curigliano G, Disalvatore D, Esposito A, Pruneri G, Lazzeroni M, Guerrieri-Gonzaga A, et al. Risk of subsequent in situ and invasive breast cancer in human epidermal growth factor receptor 2-positive ductal carcinoma in situ. Ann Oncol 2015;26(4):682–7.
[64] Solin LJ, Gray R, Baehner FL, Butler SM, Hughes LL, Yoshizawa C, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 2013;105(10):701–10.
[65] Holloway CL, Panet-Raymond V, Olivotto I. Hypofractionation should be the new 'standard' for radiation therapy after breast conserving surgery. Breast 2010;19:163–7.
[66] Yarnold J, Navita Somaiah N, Bliss JM. Hypofractionated radiotherapy in early breast cancer: clinical, dosimetric and radio-genomic issues. Breast 2015;24:S108–13.
[67] Whelan TJ, Pignol J-P, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20.
[68] Bane AL, Whelan TJ, Pond GR, Parpia S, Gohla G, Fyles AW, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. Ann Oncol 2014;25:992–8.
[69] Haviland JS, Yarnold JR, Bentzen SM. Hypofractionated radiotherapy for breast cancer. N Engl J Med 2010;362:1843. Letter to the editor.

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010

[70] Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gérard JP. Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 2013;10(1):52–60.
[71] MacLeod N, McIntyre A, Canney PA. What are the minimal standards of radiotherapy planning and dosimetry for "hypofractionated" radiotherapy in breast cancer? Breast 2010;19:172–5.
[72] Graham PH. Cardiac dosimetry for adjuvant left-sided breast radiotherapy: patterns with 2D- versus 3D-era planning and correlates of coronary dose with maximum depth of myocardial exposure. J Med Imaging Radiat Oncol 2014;58:517–22.
[73] Jackson A, Marks LB, Bentzen SM, Eisbruch A, Yorke ED, Ten Haken RK, et al. The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S155–60.
[74] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S10–9.
[75] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347(16):1227–32.
[76] Botteri E, Bagnardi V, Rotmensz N, Gentilini O, Disalvatore D, Bazolli B, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol 2010;21(4):723–8.
[77] Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Eortc radiation oncology and breast Cancer groups., internal mammary and medial supraclavicular irradiation in breast Cancer. N Engl J Med 2015;373(4):317–27.
[78] Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. MA.20 study investigators. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373(4):307–16.
[79] Shah C, Badiyan S, Berry S, Khan AJ, Goyal S, Schulte K, et al. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. Radiother Oncol 2014;112(1):9–16.
[80] Dayes I, Rumble RB, Bowen J, Dixon P, Warde P. Members of the IMRT indications expert panel. Intensity-modulated radiotherapy in the treatment of breast cancer. Clin Oncol R Coll Radiol 2012;24(7):488–98.
[81] Allison RR, Patel RM, McLawhorn RA. Radiation oncology: physics advances that minimize morbidity. Future Oncol 2014;10(15):2329–44.
[82] Mouwa KW, Harris JR. Hypofractionation in the era of modulated radiotherapy (RT). Breast 2013;22:S129–36.
[83] Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, et al. Breast technology group. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007;82(3):254–64.
[84] Barnett GC, Wilkinson J, Moody AM, Wilson CB, Sharma R, Klager S, et al. A randomised controlled trial of forward-planned radiotherapy (IMRT) for early breast cancer: baseline characteristics and dosimetry results. Radiother Oncol 2009;92(1):34–41.
[85] Lee H-H, Hou M-F, Chuang H-Y, Huang M-Y, Tsuei L-P, Chen F-M, et al. Intensity modulated radiotherapy with simultaneous integrated boost vs. conventional radiotherapy with sequential boost for breast Cancer – A preliminary result. Breast 2015;24:656–60.
[86] Donovan EM, Ciurlionis L, Fairfoul J, James H, Mayles H, Manktelow S, et al. Planning with intensity-modulated radiotherapy and tomotherapy to modulate dose across breast to reflect recurrence risk (IMPORT High trial). Int J Radiat Oncol Biol Phys 2011 Mar 15;79(4):1064–72. http://dx.doi.org/10.1016/j.ijrobp.2009.12.052. Epub 2010 Jun 3.
[87] Scorsetti M, Franceschini D, De Rose F, Tiziana Comito T, Villa E, Iftode C, et al. Stereotactic body radiation therapy: a promising chance for oligometastatic breast cancer. Breast 2016;26:11–7.
[88] Orecchia R, Fossati P, Zurrida S, Krengli M. New frontiers in proton therapy: applications in breast cancer. Curr Opin Oncol 2015;27(6):427–32.
[89] Van Mourik AM, Elkhuizen PH, Minkema D, Duppen JC, Dutch Young Boost Study Group, van Vliet-Vroegindeweij C. Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. Radiother Oncol 2010;94:286–91.
[90] Coles CE, Yarnold J. Localising the tumour bed in breast radiotherapy. Clin Oncol R Coll Radiol 2010;22:36–8.
[91] Giezen M, Kouwenhoven E, Scholten A, Coerkamp EG, Heijenbrok M, Jansen WP, et al. Magnetic resonance imaging– versus computed tomography–based - target volume delineation of the glandular breast tissue (clinical target volume breast) in breast-conserving therapy: an exploratory study. Int J Radiat Oncol Biol Phys 2011;81:804–11.
[92] Cho O, Chun M, Oh YT, Kim MH, Park HJ, Heo JS, et al. Can initial diagnostic PET-CT aid to localize tumor bed in breast cancer radiotherapy: feasibility study using deformable image registration. Radiat Oncol 2013;8:163.
[93] White J, Tai A, Arthur D, Buchholz T, MacDonald S, Marks L, et al. Breast cancer atlas for radiation therapy planning: Consensus definitions. Available at: www.rtog.org/.
[94] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Sola AB, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114(1):3–10.
[95] Iglesias JE, Sabuncu MR. Multi-atlas segmentation of biomedical images: a survey. Med Image Anal 2015;24(1):205–19.
[96] Gentile MS, Usman AA, Neuschler EI, Sathiaseelan V, Hayes JP, Small W. Contouring guidelines for the axillary lymph nodes for the delivery of radiation therapy in breast cancer: evaluation of the RTOG breast cancer atlas. Int J Radiat Oncol Biol Phys 2015;93(2):257–65.
[97] Probst H, Bragg C, Dodwell D, Green D, Hart J. A systematic review of methods to immobilise breast tissue during adjuvant breast irradiation. Radiography 2014;20(1):70–81.
[98] Goyal S, Kataria T. Image guidance in radiation therapy: techniques and applications. Radiol Res Pract 2014;2014:705604.
[99] Chen X, Qiao Q, DeVries A, Li W, Currey A, Tracy Kelly T, et al. Adaptive Replanning to account for lumpectomy cavity change in sequential boost after whole-breast irradiation. Int J Radiat Oncol Biol Phys 2014;90(5):1208–15.
[100] Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys 2006;33(10):3874–900.
[101] Wiant DB, Wentworth S, Maurer JM, Vanderstraeten CL, Terrell JA, Sintay BJ. Surface imaging-based analysis of intrafraction motion for breast radiotherapy patients. J Appl Clin Med Phys 2014;15(6):4957.
[102] van Heijst TC, Philippens ME, Charaghvandi RK, den Hartogh MD, Lagendijk JJ, Desirée van den Bongard HJ, et al. Quantification of intrafraction motion in breast radiotherapy using supine magnetic resonance imaging. Phys Med Biol 2016 Jan 21;61(3):1352–70.
[103] Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. Radiother Oncol 2008;86(1):25–9.
[104] Azria D, Riou O, Castan F, Nguyen TD, Peignaux K, Lemanski C, et al. Radiation-induced CD8 T-lymphocyte apoptosis as a predictor of breast Fibrosis after radiotherapy: results of the prospective multicenter French trial. EBioMedicine 2015;2(12):1965–73.
[105] Reuther S, Szymczak S, Raabe A, Borgmann K, Ziegler A, Petersen C, et al. Association between SNPs in defined functional pathways and risk of early or late toxicity as well as individual radiosensitivity. Strahlenther Onkol 2015;191(1):59–66.
[106] Kunkler IH, Ward C, Langdon SP. Technical innovation in adjuvant radiotherapy: evolution and evaluation of new treatments for today and tomorrow. Breast 2015;24:S114–9.

Please cite this article in press as: Leonardi MC, et al., From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer, The Breast (2016), http://dx.doi.org/10.1016/j.breast.2016.07.010