

Optimal approach in early breast cancer: Radiation therapy

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Radiation therapy significantly reduces by at least 70% the relative risk of local and regional recurrences for breast cancer after surgery. A positive influence on overall survival has been clearly demonstrated, especially for patients with a high absolute risk for locoregional recurrences. However, this is partially counterbalanced by late toxicity (dependent upon the radiation dose) especially to cardiac structures. Apart from this toxicity, a clear influence of radiation-therapy-related factors on functional and cosmetic outcome has also been demonstrated. Over time, technical improvements have led to a marked reduction in dose to the neighbouring organs, with a consequent drop in acute and late toxicity. This has also allowed the introduction of shorter radiation schedules, lowering the burden of treatment to the patient and the hospital. Several tools, techniques and guidelines have been developed to optimise the balance between the desired reduction in recurrence rates and side effects.

The multidisciplinary team should discuss all available treatment options for every individual breast cancer patient. Individualisation of the selection of the optimal combination of treatments, depending on patient and tumour-related factors, is of utmost importance. Apart from direct tumour-related outcomes, cosmesis and potential side effects have to be taken into account. Counselling should include known risk factors for survival and complications, including comorbidity.

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1. Introduction

Radiation therapy (RT) forms an integral component of the management of early-stage breast cancer. Over the years, significant progress – accelerating over time – has resulted from our growing knowledge of the biology and the natural behaviour of breast cancer as well as from technical improvements in RT. While initially research focused on optimising locoregional disease control by combining surgery with RT, the introduction of breast-conserving therapy (BCT) initiated a period of research aimed at lowering the burden of treatment [1,2]. At the same time, adjuvant systemic treatment became widely used, resulting in a reduced risk of metastases and thereby improving overall survival. The interaction between the benefits from both locoregional and systemic treatments opened the way to further

improving the clinical outcome for breast cancer patients in terms of survival as well as quality of life.

The 21st century started with a number of developments, including fine-tuning of the indications for RT for each individual target volume (intact breast, post-mastectomy chest wall, axillary, internal mammary and supraclavicular lymph nodes) depending on the clinicopathological features of an individual patient's disease, as well as hypofractionation and accelerated partial breast irradiation.

2. Prognostic factors influencing locoregional treatment

Several prognostic factors determine the risk of recurrence at local, regional and distant sites. On the basis of this, recom-

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recommendations for both local and systemic treatments for patients with breast cancer are defined.

Factors influencing the risk of recurrence include tumour size, tumour grade, margin status, lymph-node involvement, oestrogen and progesterone receptor status, HER-2/neu status and patient age. Whereas the relative benefit of locoregional and systemic therapy remains largely independent of these factors, they greatly determine the absolute benefit that can be expected. For systemic therapy they also determine the selection of its type (endocrine therapy, chemotherapy, trastuzumab, or a combination of these).

Age may also influence treatment recommendations as it helps to predict the relative risk for death related to cancer compared to death from other causes. In general, treatment tolerability, especially for chemotherapy, tends to decrease with increasing age.

Patients who are BRCA1 or BRCA2 mutation carriers should receive extensive counselling to discuss the possible approaches, including BCT and mastectomy, and even including prophylactic contralateral mastectomy given their increased risk of developing a second primary breast cancer in either breast in the future [3,4].

3. Breast conserving therapy

3.1. Lumpectomy with or without radiation therapy

It is well recognised that up to 80% of patients with invasive breast cancer may benefit from BCT, which offers rates of disease control and survival similar to those of mastectomy. This was confirmed by the meta-analyses of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [5]. Candidates for BCT include patients with unicentric disease that can be removed with negative margins and with acceptable cosmetic results.

The size of an invasive breast cancer, in relation to overall breast size, in a patient considering BCT will determine whether neoadjuvant chemotherapy or endocrine therapy is required to reduce the size of the primary tumour prior to definitive surgery. Patients with multicentric tumours and inflammatory breast cancer are not considered candidates for BCT. Patients with multifocal tumours within a single quadrant of the breast – which can be removed in a single segmental resection with clear margins and a cosmetically acceptable result – may be considered candidates for segmental resection followed by whole-breast RT. Oncoplastic surgical techniques that are becoming more widely used clearly extend the range of possibilities for BCT with acceptable cosmetic outcomes in patients that were offered mastectomy in the past.

Excision alone without RT may occasionally be considered for patients at low risk of recurrence. In these cases, it is recommended that the negative margins be wide (≥ 10 mm). For instance, patients older than 70 years with oestrogen-receptor-positive T1 primary tumours may choose to forgo whole breast RT, if they accept receiving 5 years of endocrine therapy, because of their lower risk of local recurrence in the breast. However, whole breast irradiation in this setting does reduce the risk of local recurrence by at least two thirds [6]. Moreover, adjuvant hormonal treatment – which also carries side effects – can be avoided if RT is given.

3.2. Boost

The purpose of the boost is to deliver additional radiation to the area at the highest risk of harbouring microscopic residual disease: namely, the primary tumour bed and immediately surrounding breast parenchyma. Multiple studies have shown that this area has the highest risk of recurrence in the breast [7,8].

While the EORTC trial 10801 comparing mastectomy and BCT demonstrated equivalent overall survival rates for up to 20 years after treatment, a significant difference in local control was seen between the participating centres, and the high boost dose of 25 Gy that was used resulted in a significant proportion of the patients with severe fibrosis and a poor cosmetic outcome [9]. The next EORTC “boost” trial 22881/10882 paid special attention to quality assurance, fibrosis and cosmetic scoring. The boost dose was lowered from 25 Gy to 16 Gy, which was randomised against no boost at all. This trial and two other prospective randomised trials showed that delivering a boost dose to the tumour bed after whole breast irradiation significantly reduces the local recurrence rate [7,10,11]. Young age appears to be the most significant independent patient factor related to local recurrence. The absolute effect of the boost – reducing the local recurrence rate relatively by 41% overall – was much more marked for younger patients (Fig. 1) [7,12]. The cosmetic results were scored as excellent to good in 86% of patients receiving no boost and in 71% of patients receiving a boost. Apart from the boost dose, other predictors for cosmetic outcome included whole breast dose and megavolt energy, type of boost, energy of electrons, and use of adjuvant chemotherapy or hormonal therapy [13]. An inhomogeneous dose distribution of whole breast RT negatively influenced the risk for developing fibrosis, similar to the findings of Donovan and colleagues [14]. Based on this trial, nomograms have been developed to predict in individual patients the impact of a boost dose of 16 Gy on the rate of ipsilateral breast relapse (<http://research.nki.nl/ibr>) and fibrosis [13,15].

To evaluate the need for a further increase in the boost dose from 16 Gy to 26 Gy for patients up to 50 years of age, the “Young Boost Trial” (NCT00212121) was run in The Netherlands, Germany and France between 2004 and 2011. Early analysis of the results, without splitting up for the randomisation arm, shows that the estimated local recurrence rate remains far below the results obtained in trials, despite the much younger age in the population investigated.

3.3. Accelerated partial breast irradiation

As previously mentioned, after lumpectomy with surgical axillary staging, the standard of care is whole breast irradiation with or without a boost dose. However, accelerated partial breast irradiation (APBI) is rapidly emerging as a treatment option for early-stage invasive breast cancer in certain clinical scenarios. It may be considered in women who are ≥ 50 years of age, with tumours that are pathologically 3 cm or smaller, and node-negative. Ideally, these patients should be treated in the framework of clinical trials because of the more limited long-term data for APBI compared with those for whole breast

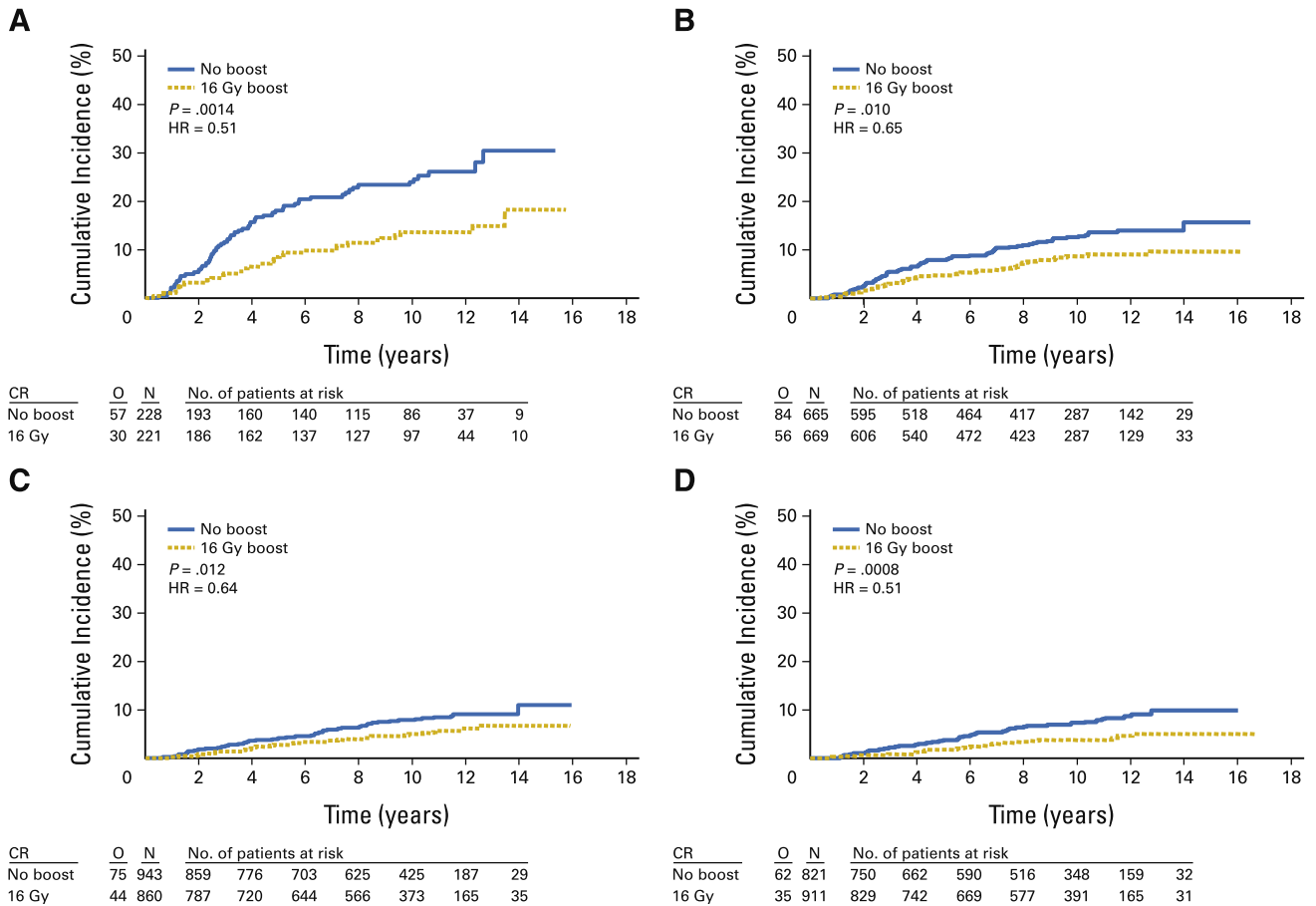


Fig. 1 – Cumulative incidence of breast cancer recurrence according to age group. Reproduced with permission from [7].

irradiation [16–18]. It is expected that in the near future, after completion of the prospective randomised clinical trials comparing APBI with standard whole breast irradiation, a precise definition of the place of APBI will become available.

3.4. Young patients

It is important to see the clear decrease in local recurrence rates over time in the EORTC 10801, EORTC 22881–10882 and Young Boost trials (Fig. 2) [19]. The explanation of this continuous improvement is multifactorial and includes technical and diagnostic factors and the increasing use of adjuvant systemic treatment. It is well established that chemotherapy and hormonal treatment reduce local recurrence rates by about 35–50%. Indeed, according to the consensus at the time, virtually no patient who participated in the EORTC 10801 trial, and only 31% of the patients participating in the EORTC 22881–10882 trial, received adjuvant systemic treatment, while in the Young Boost trial nearly all patients received systemic treatment, often combined chemotherapy and hormonal treatment [12]. Therefore, results from the past after BCT in young patients should not be considered as a contraindication for offering this treatment today to patients <50 years of age. Some caution might remain for very young patients (≤35 years of age) in view of the relative scarcity of data and the possibly different aetiological factors in these patients. Indeed, in two large Dutch population-based cohort studies of

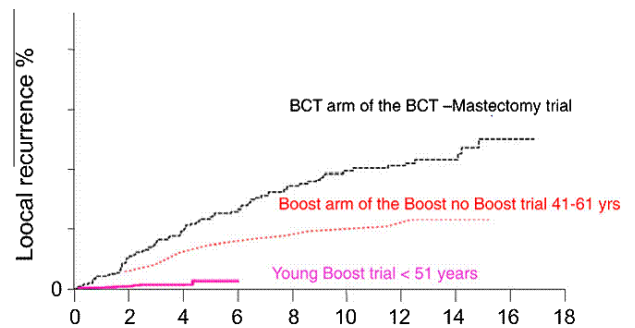


Fig. 2 – Local breast recurrence rate in three consecutive trials. Reproduced with permission from [19].

young breast cancer patients, conflicting results were found on comparing BCT with mastectomy [20,21].

3.5. Ductal carcinoma in situ

For non-invasive disease (ductal carcinoma in situ, DCIS), treatment options depend on the extent of the disease. For mammographically detected unifocal lesions, which can be removed in a single lumpectomy specimen with good cosmetic results, BCT is an excellent option. Clear surgical margins of at least 2 mm are recommended [22]. Postoperative radiation therapy is indicated to eliminate potential residual

microscopic disease. Whole breast irradiation is considered the standard of care after lumpectomy, as it reduces the risk of recurrence in the breast by approximately 50–60% at 10 years of follow-up [23]. Half of the recurrences are invasive cancer and half are DCIS, with a similar risk reduction for both after radiation therapy. A boost dose to the primary tumour bed might further reduce the local recurrence rate [24]. Axillary surgical lymph node evaluation is not required for patients with pure DCIS because it is associated with an extremely low risk of nodal involvement. Sentinel-node biopsy may be considered in the presence of extensive or high-grade DCIS, especially if a mastectomy is performed. For patients with more extensive DCIS, or for those wishing to avoid radiation therapy, total mastectomy with or without breast reconstruction is the preferred option.

4. Mastectomy

4.1. Chest wall irradiation

If mastectomy with surgical axillary staging is selected as the primary surgical treatment option, recommendations for post-mastectomy radiation therapy (PMRT) are based on the risk of locoregional failure in the chest wall or in the undissected regional lymphatics (upper part of the axilla including the infraclavicular region, supraclavicular region, and internal mammary region). Available data are essentially based on comprehensive locoregional treatment, making it currently impossible to define clear recommendations for chest wall irradiation only.

If the primary tumour is <5 cm in diameter and if there is no axillary nodal involvement, the risk of locoregional failure is <10% without PMRT, so RT is not recommended in this clinical scenario [25]. Clinicopathological factors associated with a high risk ($\geq 20\%$) of locoregional recurrence without PMRT include four or more involved lymph nodes, $\geq 20\%$ involvement of the number of axillary lymph nodes, T4 tumours, and T3 tumours combined with axillary nodal involvement [25,26]. One to three positive lymph nodes after primary chemotherapy are also associated with a higher risk of locoregional recurrence. Therefore, PMRT is recommended in all these clinical settings [27]. If mastectomy with surgical axillary staging is performed prior to chemotherapy, the current National Cancer Comprehensive Network guidelines strongly suggest that post-chemotherapy radiation be considered to the chest wall and undissected regional lymphatics, also in the setting of one to three positive lymph nodes. Other tumour- and patient-related factors that are associated with a higher risk of locoregional recurrence without PMRT include: T3, tumour size of ≥ 4 cm with involved lymph nodes, age <40 with involved lymph nodes, grade 3, lobular histology, lymphovascular invasion and involved lymph nodes, largest axillary node ≥ 2 cm, gross extranodal extension of ≥ 2 mm, involved lymph nodes with fewer than ten axillary lymph nodes dissected, and premenopausal status with lymphovascular space invasion [28,29]. As the debate on the use of PMRT in intermediate-risk patient groups continues, most guidelines refer to a combination of risk factors [30,31].

Nowadays, most patients presenting with risk factors will receive adjuvant systemic treatment. Especially in locore-

gionally advanced disease (the typical indication for mastectomy), primary systemic treatment is becoming progressively more popular. In general, the indications for PMRT remain the same, although the pathological stage is not reliably known and the response to systemic treatment might be used for adjusting the recurrence risks. In general, patients presenting with clinical stage III disease (4 or more suspicious or confirmed positive lymph nodes on pretreatment ultrasound, cT3N1 disease, or cT4 disease) prior to chemotherapy should undergo PMRT. Patients presenting with clinical stage IV disease who experience a complete response to systemic therapy or those being treated with curative intent should be considered for PMRT as well. In patients with close or positive margins and clinical T3, N0 disease, PMRT to at least the chest wall should be considered. PMRT should also be considered in patients presenting with T1–2, N1 disease and one or more of the following clinicopathological features: residual tumour size >2 cm, residual lymph-node-positive disease after chemotherapy, age <40 years and lymphovascular invasion.

4.2. Radiation therapy and breast reconstruction

The number of women requesting breast reconstruction after mastectomy is increasing. In particular, immediate breast reconstruction (IBR) is becoming more popular for breast cancer patients who are not good candidates for breast-conserving therapy. Uncertainty exists about the preferred type (using implanted material, autologous tissue, or a combination) of IBR in patients requiring PMRT to minimise the complication and reoperation rates and to optimise cosmetic outcome. Other concerns are the safety and efficacy of IBR, the possible risk of a delay in starting adjuvant systemic treatment and the influence on the quality of RT delivery in terms of dose homogeneity and target volume coverage [32,33].

In general, PMRT is associated with a higher rate of capsular contracture following IBR using an implant. However, good results can be obtained in the majority of these patients [34]. Fewer data exist on PMRT following IBR using autologous tissue, although most authors report that the outcome in terms of complication rates and cosmetic results is better when compared with implant reconstruction only [32,35,36]. Surgical intervention, including free fat grafting, can be used to improve – if needed – long-term results after IBR and PMRT. Most data confirm that IBR is not associated with a significant delay in starting adjuvant therapy. A homogeneous dose of radiation to the chest wall with/without the regional lymph nodes can be delivered with acceptable heart and lung doses if optimised modern RT techniques – including procedures for adjustment of respiratory movement, highly conformal 3D and IMRT – are appropriately used (Fig. 3) [37,38].

Few data are available on the influence of pre-reconstruction PMRT on tissue expander breast reconstruction. In general, a higher frequency of capsular contracture and a slightly higher reoperation rate for procedures using implants are seen, leading to worse patients' and surgeons' subjective evaluations. On the other hand, a history of PMRT alone should not dictate the type of reconstruction [39]. Patients who develop neither severe skin changes nor subcutaneous fibrosis may still be considered for implant-based breast

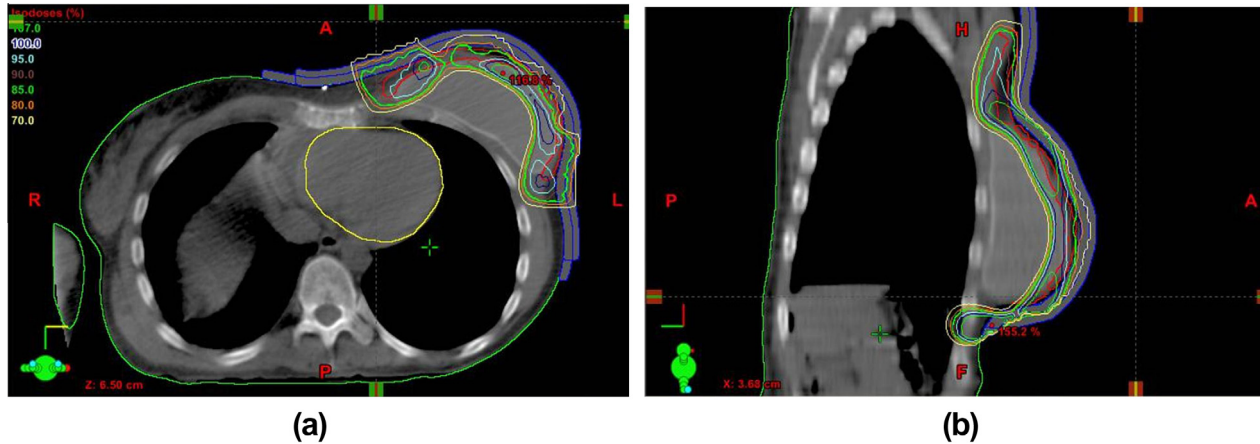


Fig. 3 – Individualised treatment plan using multiple electron beams for chest wall irradiation in a patient with an immediate breast reconstruction with an implant (a) axial slice; (b) sagittal slice).

reconstruction [35,40–42]. Pre-reconstruction RT seems not to influence the overall success rate of reconstruction using autologous tissue, nor to contribute to postoperative complications. However, it increases the rate of vascular complications in free flap breast reconstructions, seen mostly during surgery itself. In general, the cosmetic outcome and satisfaction in women reconstructed with autologous tissue is higher than in those with implant-based reconstruction. The optimal timing for breast reconstruction after PMRT is unclear. Often, an interval of 12 months between PMRT and reconstruction is advised, but some state that breast reconstruction with autologous tissue can potentially be performed earlier [43,44].

5. Regional radiation therapy

The indications for regional RT are independent of the type of surgery to the breast (BCT or mastectomy). Therefore, most of what was stated in the subsection “chest wall irradiation” is also applicable to this chapter.

The EBCTCG overview confirmed that PMRT and RT in the framework of BCT improves specific and overall survival in all breast cancer patient subgroups with involved axillary lymph nodes as well as in node-negative patients treated with BCT [45]. In most older trials, comprehensive locoregional RT was used. Based on this, a division into three risk categories for locoregional relapse is made with a proposal for selecting the target volumes for RT (Tables 1 and 2) [46].

The clinically most relevant drainage of the breast tissue is to the ipsilateral lower axilla. Therefore, staging most often includes at least a sentinel-node biopsy to estimate the degree of axillary lymphatic involvement by the tumour; this provides the most important single prognostic factor for patients with breast carcinoma. In general, nodal involvement occurs in an orderly fashion [47]. The other major route of lymphatic spread is via the ipsilateral internal mammary chain (IMC). They are primarily found in the first three intercostal spaces. Internal mammary chain drainage is correlated with tumour location in the breast [48]. The identification rate for IMC disease with sentinel node procedures depends on the technique of the procedure itself, being high-

Table 1 – Risk categories for locoregional relapses after mastectomy and axillary clearance. Ax LN +, involved axillary lymph nodes. Reproduced with permission from [47].

Risk category	Low	Intermediate	High
Tumor stage	T1-2	T1-2	T3-4
Number of Ax LN +	0	1-3	> 3
Grade	1-2	3	
Vascular invasion	-	+	
Histology	ductal	lobular	
Risk	< 10%	10-20%	> 20%

Table 2 – Indication for irradiation of the different target volumes after mastectomy and axillary clearance as well as for regional radiation therapy (RT) in the framework of breast-conserving therapy (BCT). Yes, evidence and generally accepted; Yes?, evidence but not generally accepted; No?, limited evidence, however advocated by some authors; No, no evidence. Reproduced with permission from [47].

Risk category	Low	Intermediate	High
Thoracic wall	No?	Yes?	Yes
Supraclavicular	No?	Yes?	Yes
Internal mammary	No	Yes?	Yes?
Axilla	No	No	No

est with an intra-tumoural injection of tracer followed by a peri-tumoural injection, and lowest with a subdermal or peri-areolar injection [49].

Supraclavicular nodal involvement generally represents stages of advanced regional disease and carries a poorer prognosis. The major route of cancer spread to the supraclavicular lymph nodes is via the axillary lymph nodes [50].

Since the publication of the ACOSOG Z0011 trial – showing that axillary surgery is probably not required for patients with a positive sentinel-node biopsy and treated with BCT, including tangential field irradiation to the whole breast – uncertainty exists about RT to a positive axilla without further axillary clearance [51]. A proposal based on the combination

of several treatment- and tumour-related factors is being developed in the Netherlands.

6. Radiation related toxicity

There is ample evidence to suggest that cardiac irradiation is detrimental, although cardiac consequences of RT of the breast have long latencies estimated to become detectable only ≥ 15 years after treatment. The EBCTCG overview of randomised trials demonstrated that the gain in locoregional control was not fully translated into an improvement in overall survival, suggesting that survival benefit with RT becomes at least partially offset by increased cardiovascular deaths [5]. In particular, radiation techniques that have incorporated large volumes of the heart have been shown to negatively impact on overall survival [52].

Therefore, minimising cardiac irradiation is a critical aspect of treatment planning. Depending on the individual case, changing the gantry angle, the collimator angle, or shaping – with small cardiac blocks or MLC leaves – the borders of the medial and/or lateral tangential fields can result in adequate coverage of the primary tumour site and most of the breast while excluding the heart from the high-dose region. These treatment field modifications should be customised to the normal tissue anatomy of the individual patient, the location of the primary tumour bed and the contour of the breast. In addition, in cases where the tumour bed is very close to the heart, treatment at deep inspiration can be advantageous [53–55].

Further research is warranted to understand the dose–response relationship leading to radiation-induced cardiovascular disease. Current research focuses on the one hand on optimising the radiation therapy techniques to limit the exposure of cardiac structures and lung tissue to radiation, and on the other hand on examining which cardiac substructures are most related to the induction of late toxicity and mortality [52,56–58]. Of importance is also the requirement to conduct proper follow-up, which is indispensable for evaluation of long-term treatment effects after radiation therapy and to advise patients on how to adapt their life style in the case of an elevated risk of cardiovascular toxicity [59].

7. Technical developments

Donovan and colleagues were among the first to confirm on a clinical level the advantages of optimisation of RT dose distribution. In a randomised prospective trial they investigated the influence of dose homogeneity on late adverse effects after BCT to evaluate whether the additional costs in infrastructure and staffing are justified [14]. With forward-planned IMRT, they minimised dose inhomogeneity in the breast significantly. Of great importance is that they were able to associate this with the change in breast appearance during follow-up as scored by photographic as well as by clinical assessment. These results confirm the sensitivity of late normal tissue effects to fraction size [60]. Therefore, 3D dose planning should be routinely implemented, even more with hypofractionated RT schedules.

A broad spectrum of RT techniques are described in the literature, ranging from low complexity (conventional, wedge-

based approaches using limited beam angles) to highly modulated, multiple-angle photon techniques [61–63]. As some of the highly complex techniques might lead to a higher dose to the organs at risk (heart, lungs, contralateral breast), their implementation should be carefully considered and coupled with other technological improvements [64].

A rapidly increasing number of RT departments are using hypofractionated RT schedules, especially after the publication of the long-term results of large prospective trials [65–67]. With this, whole breast RT duration can be reduced from the conventional 5 weeks to 3 weeks. Adding to this obvious advantage to the patients, a boost dose for BCT is becoming more selectively applied to only those patients with a high risk of local recurrence, reducing the treatment by 1–1.5 weeks and decreasing the risk of fibrosis.

The use of electrons and brachytherapy as boost modalities is gradually being replaced by 3D-CRT photon beam techniques. Interest in this technique has recently been stimulated with the introduction of the simultaneous integrated boost (SIB) technique, in which the dose to the whole breast is combined with a simultaneous boost to the primary tumour bed [68]. Apart from logistical advantages for the RT department, it significantly reduces the boost field sizes thanks to both improved conformality and electronic equilibrium [69].

Patients with large pendulous breasts may be treated in the prone position to minimise skin folds in the breast, such as the infra-mammary fold. Placing the patient in the prone position also allows the surgical bed to fall farther away from the rib cage, increasing the distance between the cardiac structures and the lumpectomy site.

Breathing-adapted treatment reduces the impact of respiratory motion on the motion of the target volume. Treatment delivery under deep inspiration also increases the distance between the breast and the heart for left-sided breast cancer patients, reducing the RT dose to the heart [53–55,70].

8. Challenges

8.1. Target volume delineation

The primary objective of radiation therapy is to eradicate microscopic residual disease after surgery. The areas at highest risk of recurrence after mastectomy are the chest wall and the undissected lymph-node regions. In the case of BCT, the entire breast can contain residual or potential multicentric disease as well. On the basis of the work by Holland et al., the highest residual tumour cell density is expected to be adjacent to the original tumour site [71]. This explains why at least 80% of the early failures after BCT occur in the same quadrant as the original primary tumour.

The regions to be treated constitute the clinical target volumes, to which an additional margin needs to be included to account for internal motion, patient motion, and setup uncertainty, resulting in the planning target volume that will be used for RT planning. The transition from clinically set-up 1D treatments to fully virtually prepared 4D RT plans is highly dependant on proper target volume delineation, which is considered by most radiation oncologists as currently being the weakest link in the quality chain of breast cancer RT, with a

high inter-observer variation [72]. These variations appear to be clinically significant both in terms of dosimetric target coverage as well as exposure of the organs at risk [73]. To improve consistency in target volume delineation, a number of initiatives have been undertaken, after which it has been demonstrated that training as well as the availability of clearly written guidelines decreases inter- and intra-observer variability [72]. ESTRO has given a high priority to increasing its online educational and professional services. Within this resource, a multifunctional platform for volume delineation has been created. This will also be used to facilitate the organisation of teaching courses and the writing of internationally accepted guidelines.

8.2. Individualisation

To properly individualise, we should take into account several factors, including prognosis, risk-to-benefit ratios, patient expectations and specific anatomy. Therefore we should consider every single patient as a unique combination of personal, disease and anatomical factors. Based on this we can discuss proper decision-making in a multidisciplinary setting and with the patient.

As for RT, treatment planning – based on a complete 3D dataset – can now be fully individualised to the patients' anatomy and the delineated target volumes, taking into account the dose to normal structures. In general, a standard set-up RT technique will fit most patients, and every department should accrue experience with a standard approach that best fits their own way of working. However, individualisation of techniques should be done on the basis of the anatomy of each single patient. As an example, the entire chest wall may sometimes be treated with electron-beam fields [57]. With a five-field technique a homogeneous dose to the thoracic wall (and the IMC if indicated) can be delivered with a much lower dose to the underlying lungs and heart compared with tangential photon fields, especially in patients with a markedly curved thoracic wall [74]. Also, a partially wide tangential approach, including the IMC lymph-node region together with the chest wall or breast in a single pair of fields, can be used when a separate IMC field cannot be employed due to the patients' anatomy.

8. Future perspectives

The future lies in a multidisciplinary approach and a coming together of the indications for all types of treatment, including surgery, RT and systemic treatment. At present, few treatments are clinically linked (such as lumpectomy combined with whole breast RT). However, we can no longer neglect the interactions within the therapeutic spectrum. Therefore, we should focus more on treatment packages instead of simply adding one treatment to another.

As an example, the management of the axilla is expected to change markedly in the coming years. Even the standard use of the sentinel node procedure is challenged in some patient categories where the need (or lack of need) for systemic treatment can be estimated on the basis of other prognostic information. Use of axillary clearance as a routine procedure is rapidly decreasing and might even become extinct when re-

sults from trials such as the EORTC AMAROS trial become known [75].

Another example is the issue of the patient at very low risk who might be offered years of hormonal treatment or a short course of whole or partial breast RT, with the challenge of demonstrating the added value of combining both approaches together. This fits well into the drive to optimise the cost/benefit ratio of cancer treatment, especially in times of limited financial resources [76].

The response to systemic treatment can be used in high-risk patients as a predictor for improved survival. It is likely that these high-risk patients might benefit most in terms of overall survival from optimal locoregional treatment [77]. Perhaps a proportion of these patients might even be treated without surgery.

Another issue that will only be solved after the presentation of data from recent prospective trials is the selection of the areas to be treated. While irradiation of the IMC lymph-node area is the most strongly debated, an early analysis did not show an increased level of toxicity [78].

New biological targeted agents should be tested in combination with RT. Similar to chemotherapy, several studies testing the prognostic and predictive value of genomic and proteomic tests are being conducted.

The duration of RT for breast cancer has reduced from 6–7 weeks to 3–4 weeks over the last few years. Further reduction to even fewer fractions in a shorter time period is the subject of recent and ongoing trials [79]. This should help to end the discussion about the sequence of RT and systemic treatments by decreasing the possible postponement of the latter with a shorter RT course.

Conflict of interest statement

None declared.

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