Modern radiotherapy for breast cancer: Update and new developments

Moderne Strahlentherapie beim Mammakarzinom: Update und neue Entwicklungen

Authors

Eva Meixner[1, 2, 3, 4], **Jürgen Debus**[1, 2, 3, 4, 5]

Affiliations

1 Abteilung für RadioOnkologie und Strahlentherapie, Universitätsklinikum Heidelberg, Heidelberg, Deutschland
2 Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Deutschland
3 National Center for Tumor diseases (NCT), Heidelberg, Deutschland
4 Heidelberger Ionenstrahl-Therapiezentrum (HIT), Heidelberg, Deutschland
5 Clinical Cooperation Unit Radiation Oncology, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Deutschland

Keywords

deep inspiration breath hold, proton beam radiotherapy, cardiotoxicity, partial breast irradiation, RT omission

Schlüsselwörter

tiefe Atemanhaltetechnik, Protonentherapie, Kardiotoxizität, Teilbrustbestrahlung, RT-Verzicht

Bibliography

Senologie 2024; 21: 273–281

DOI 10.1055/a-2289-0436

ISSN 1611-6453

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Correspondence

PD Dr. med. Eva Meixner
Universitätsklinikum Heidelberg, Abteilung für RadioOnkologie und Strahlentherapie,
Im Neuenheimer Feld 400, 69120 Heidelberg, Deutschland
Eva.Meixner@med.uni-heidelberg.de

Deutsche Version unter: https://doi.org/10.1055/a-2289-0436.

ABSTRACT

The delivery of radiotherapy for breast cancer has evolved significantly over the years. The aim of this review is to highlight important developments and current concepts. Postoperative hypofractionated three-dimensional conformal or intensity-modulated photon radiotherapy continues to be the standard application after breast-conserving surgery to improve local control. New therapy techniques in deep inspiration breath hold or physical-biological advantages of proton beam therapy offer innovative therapy methods with regard to the protection of normal tissue and reduced cardiotoxicity. Ultra-hypofractionated therapy concepts and the integration of a simultaneous integrated boost in hypofractionated therapy concepts also enable the duration of treatment to be reduced to a few days or weeks. In low-risk constellations, the radiation volume may also be de-escalated to partial breast irradiation, and if life expectancy is severely restricted at the same time, the omission of postoperative radiotherapy might be critically discussed. The oncological benefit of an irradiation of the regional lymph node regions continues to be confirmed in locally advanced, node-positive carcinomas and further enables the omission of surgical axillary lymph node dissection with low morbidity in individualized therapy approaches.

ZUSAMMENFASSUNG

Die Durchführung der Strahlentherapie beim Mammakarzinom hat sich im Laufe der Jahre deutlich weiterentwickelt. Ziel dieser Übersichtsarbeit ist es, einige wichtige Entwicklungen und aktuelle Konzepte aufzuzeigen. Die postoperative perkutane, hypofraktionierte 3 D-konformale oder intensitätsmodulierte Photonen-Bestrahlung stellt weiterhin die Standardapplikation nach brusterhaltender Operation zur Verbesserung der Lokalkontrolle dar. Neue Therapietechniken in tiefer Inspiration oder physikalisch-biologische Vorteile einer Protonentherapie bieten in Hinblick auf die Schonung des Normalgewebes und reduzierter Kardiotoxizität innovative Therapieverfahren. Ultra-hypofraktionierte Therapiekonzepte sowie die Integration eines simultan integrierten Boosts auch in hypofraktionierte Therapiekonzepte ermöglichen, die Behandlungsdauer auf wenige Tage bis Wochen zu reduzieren. Bei Niedrigrisiko-Konstellationen kann zudem das Bestrah-

lungsvolumen auf eine Teilbrustbestrahlung deeskaliert, bei gleichzeitig stark eingeschränkter Lebenserwartung potenziell auch der vollständige Verzicht auf eine adjuvante Radiotherapie kritisch diskutiert werden. Der onkologische Benefit durch die Bestrahlung der regionären Lymphabflusswege bestätigt sich weiterhin bei lokal fortgeschrittenen, nodal-positiven Karzinomen und ermöglicht mit geringer Morbidität in individualisierte Therapieansätze den Verzicht auf eine operative axilläre Lymphknotendissektion.

In the interdisciplinary management of breast cancer, irradiation is a key component for achieving effective oncological control. Driven by technological advances as well as the optimization and individualisation of therapeutic approaches, radiotherapy has significantly evolved over the last decades. The aim of this review article is to provide insight into modern developments in adjuvant radiotherapy for breast cancer and to discuss the pertinent evidence from current studies.

Breast-conserving surgery (BCS) with adjuvant radiotherapy (RT) is currently the standard of care in the oncological management of breast cancer, offering an equally effective alternative to mastectomy. The primary goal of adjuvant radiotherapy is to improve local control and, with it, achieve improvements in overall survival and breast cancer-specific mortality [1].

Post-operative, percutaneous photon radiotherapy continues to be the standard application. After computed tomography (CT)-based planning and contouring of the target volume and adjacent organs at risk, it is delivered using a conventional linear accelerator.

Cardiotoxicity

Especially patients with left-sided tumours are at an increased risk of cardiotoxicity following adjuvant radiotherapy due to the close anatomical vicinity to the heart.

In a ground-breaking study on cardiovascular events after postoperative irradiation of the breast, evaluating 2168 women over the period 1958–2001, Darby et al. found an increase in the relative risk of major coronary events, rising linearly by 7.4 % per Gy mean heart dose [2]. In their study, the mean heart dose was 4.9 Gy (range: 0.03–27.72 Gy); the comparison of left-sided to right-sided irradiation found significantly higher mean heart doses for the left side (6.6 Gy and 2.9 Gy, respectively). The risk of cardiovascular events began to increase within the first 5 years after radiotherapy and persisted for at least 20 years. For example, in a 50-year-old woman without pre-existing cardiac risk factors, who received a mean heart dose of 3 Gy during adjuvant radiotherapy, her risk of death from ischemic heart disease before age 80 years increased from 1.9 % to 2.4 %, corresponding to an absolute risk increase of 0.5 %. In the case of a woman of the same age with at least one cardiac risk factor, this would even correspond to a risk increase from 3.4 % to 4.1 %, i. e. an absolute risk increase of 0.7 %. A further cardiotoxicity analysis, based on the dataset from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, evaluated almost 27 000 patients who received postoperative RT between 1973 and 1989 [3]. It showed that in 1979 the relative risk increase for mortality of ischemic heart disease in women with left-sided breast tumours was 1.5 times compared to right-sided tumours. Thanks to technical optimizations of radiotherapy techniques, the relative risk of death from ischemic heart disease decreased by 6 % with each year after 1979 in women with left-sided disease [3]. Over time, various additional developments have helped to further reduce the cardiac radiation dose and thus contributed to the fact that long-term follow-up studies covering periods of up to 15 years have found no significant differences in cardiac morbidity after irradiation of left-sided compared to right-sided breast cancer [4]. Especially the use of breathing-controlled radiotherapy in deep inspiration breath hold (DIBH) results in an increase in the distance between heart and breast and thus leads to a further reduction in the dose to cardiac substructures.

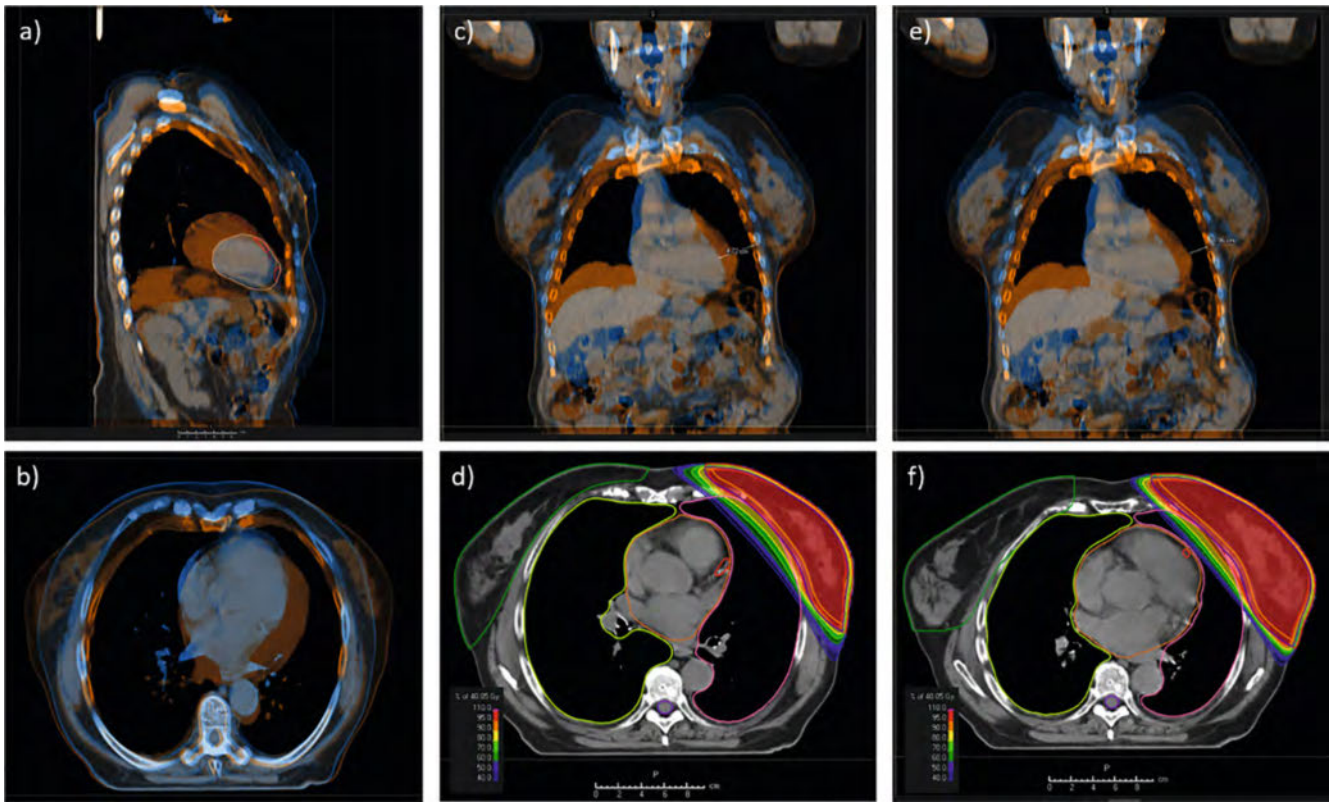
▶ **Fig. 1** shows as an example the fusion of two radiotherapy planning CT scans of a patient, one in deep inspiration breath hold (DIBH, blue) and the other in free breathing (FB, orange), in sagittal (a) and axial (b) slices as well as the resulting increased distance between chest wall and heart in the coronal slices of approx. 4.7 cm (DIBH, c) and 1.9 cm (FB, e). In the resulting comparative plans for left-sided hypofractionated whole-breast irradiation, a dose reduction at the left anterior descending artery (LAD) from 5.0 Gy to 2.9 Gy compared to FB was achieved.

This technique is particularly attractive when radiation treatment of the internal mammary lymph nodes is required and when patients concomitantly receive cardiotoxic systemic therapy. Given the possibility that the mean whole-heart dose is not the best predictor for various forms of radiation-induced heart disease, modern radiotherapy planning comprises individualized contouring and definition of dose limits for specific cardiac substructures, taking exemplarily the coronary arteries and the left ventricle separately into account [5].

Partial-breast radiotherapy

Hypofractionated whole breast irradiation (WBI) over a treatment period of about 3 weeks in 15–16 fractions continues to be the current standard of care in adjuvant radiotherapy. However, partial breast irradiation (PBI) of the tumour bed may represent a potential alternative in selected, node-negative breast cancer patients.

PBI can be delivered using various techniques, such as multicatheter brachytherapy [6, 7] and intensity-modulated percutaneous radiotherapy [8, 9] (APBI-IMRT Florence Trial). The long-term 10-year follow-up data of these randomized trials confirm that partial breast irradiation is an alternative to WBI, offering comparable results for local control with low toxicity, especially with regard to cosmetic and fibrotic changes in the breast



▶ **Fig. 1** Fusion of two radiotherapy planning CT scans in deep inspiration breath hold (DIBH, blue) and free breathing (FB, orange) in sagittal (**a**), axial (**b**) and coronal slices (**c** and **e**), as well as the resulting radiotherapy plans for left-sided, hypofractionated whole-breast irradiation (**d** and **f**).

(IMPORT-LOW) [10]. A list of selected studies on partial breast irradiation is provided in ▶ **Table 1**.

Intraoperative radiotherapy (IORT) of the tumour bed is another technique of partial breast RT; IORT is once delivered to the tumour bed at the operating table during BCS after tumour resection as a high single dose on a small volume. It ensures reliable identification of the tumour bed without any geographical mismatch due to oncoplastic tissue rearrangements and is a substitute for several weeks of treatment sessions on working days.

There are various techniques available for delivering IORT: During kV IORT, typically spherical applicators are placed into the resection cavity to deliver a high radiation dose to the tumour bed with usually 50 kV x-rays. This radiation treatment can be administered as a stand-alone therapy or as a boost with subsequent percutaneous irradiation. Greater penetration depths can be achieved with intraoperative electron radiotherapy (IOERT). After installation of a rigid tube, the tumour bed can be treated with usually 3–12 MeV electrons in a matter of minutes. If necessary, the radiation field can be shaped to meet the specific needs of the individual patient by placing radiation-absorbing metal shields or tamponades to mobilize organs at risk.

However, the available data on the oncological control achieved using IORT for partial breast irradiation is inconsistent. The long-term data of the randomized TARGIT IORT trial [11] on women aged 45 years or older with invasive ductal carcinoma up to 3.5 cm in size and cN0-N1 showed no significant difference between intraoperative kV IORT PBI with 1 × 20 Gy compared to WBI.

However, the randomized prospective ELIOT trial [12] found increased local recurrence rates after partial breast radiotherapy by means of IOERT of the tumour bed in the long-term follow-up. The 5-, 10- and 15-year in-breast recurrence rates were 4.2, 8.1 and 12.6 %, respectively, after stand-alone IOERT partial breast irradiation, while they were only 0.5, 1.1 and 2.4 %, respectively, in the whole breast RT group [13]. Although this difference had no effect on overall survival, these results highlight the need for critical patient selection; however, criteria related to age and eligible tumour size are discussed very differently in the recommendations of the various specialist societies (DEGRO [14], GEC-ESTRO [15], ASTRO [16]). The recommendation with regard to which method should be given priority is primarily dependent on the local technical availability, the expertise of the user and the anatomical situation.

Fractionation regimes

Today's standard of care for adjuvante WBI is moderate hypofractionation in 15 to 16 working day fractionation sessions [17, 18]. In patients with biological risk factors and in premenopausal patients, supplementary boost radiotherapy should be used to help prevent recurrences especially in the tumour bed area [19]. For this, it is crucial to ensure that the postoperative localization of the tumour bed is clearly identified in the radiotherapy planning CT scan, considering initial tumour location, analysis of preoperative imaging studies, postoperative scaring, identification of tumour bed clips, and anatomical rearrangements related to onco-

▶ **Table 1** Table of selected studies on partial breast irradiation for breast cancer.

Study	Technique	Details	Follow-up period	Whole breast (WBI)	Partial breast (PBI)	p-value/statistics	Toxicity
GEC-ESTRO [6, 7]	Interstitial brachytherapy	n = 1184 2004–2009 50 Gy WBI + 10 Gy boost vs. brachytherapy (HDR: 8 × 4 Gy in 4 days, 7 × 4.3 Gy in 4 days; PDR: 50 Gy in 3–4 days)	5-yr LC 5-yr OS 10-yr LC 10-yr OS	0.9 % 95.6 % 1.58 % 89.5 %	1.4 % 97.3 % 3.51 % 90.5 %	p = 0.42 p = 0.11 (non-significant) p = 0.074 p = 0.5 (non-significant)	Lower grade 2–3 Skin toxicity: 5.7 % WBI vs. 3.2 % APBI Lower grade 3 Late toxicity (suspected fibrosis): 4 % WBI vs. 1 % PBI
TARGIT-A [11]	Intraoperative radiotherapy (kV IORT)	n = 3451 2000–2012 ≥ 45 yrs, T1–2 (< 3.5 cm), cN0–1 WBI vs. 50 kV IORT 20 Gy	5 yrs (update)	0.95 %	2.11 %	Non-inferiority	Significant reduction Grade 3–4 skin toxicity with IORT
ELIOT [12, 13]	Intraoperative radiotherapy (IOERT)	n = 1305 2000–2007 48–75 yrs, T1–2 (< 2.5 cm) IOERT PBI 21 Gy vs. WBI 50 Gy + 10 Gy boost	5-yr LC 10-yr LC 15-yr LC 5-yr OS 10-yr OS 15-yr OS	0.5 % 1.1 % 2.4 % 96.8 % 92.7 % 82.4 %	4.2 % 8.1 % 12.6 % 96.8 % 90.7 % 83.4 %	Significantly higher risk of local recurrence non-significant	PBI lower skin toxicity
IMPORT-LOW [10]	Percutaneous RT	n = 2018 2007–2010 ≥ 50yrs, T1–2 (≤ 3 cm), pN0–1 (max. 3 nodes) 40 Gy WBI vs. 40 Gy PBI	5-yr LC	1.1 %	0.5 %	non-significant	PBI better cosmetic outcome and less breast indurations
Florence-IMRT [8, 9]	Percutaneous RT	n = 520 2005–2013 WBI 50 Gy + 10 Gy boost vs. APBI: TD 30 Gy in 5 days	5-yr LC 5 yrs OS 10-yr LC 10-yr OS	1.5 % 96.6 % 2.5 % 96.7 %	1.5 % 99.4 % 3.7 % 97.8 %	non-significant non-significant	APBI better acute and long-term toxicity and better cosmetic outcome

APBI: accelerated partial breast irradiation, HDR: high-dose-rate, IO(E)RT: intraoperative (electron)radiotherapy, yr(s): years, LC: local control, n = sample size, OS: overall survival, PBI: partial breast irradiation, PDR: pulsed dose rate, RT: radiotherapy, WBI: whole breast irradiation.

plastic advancement flaps within the breast as described in the operative reports. While dose escalation in patients with a residual tumour postoperatively is still not regarded as equivalent to re-excision, it can be a treatment option if the tumour is deemed unresectable [20].

A boost can be delivered either sequentially after completion of the basic WBI plan or simultaneously integrated in the plan; the latter is the current standard of care for conventionally fractionated radiotherapy. With the publication of the results of the randomized phase 3 IMPORT HIGH trial [21] (n = 2617), initial data on the safety of simultaneous integrated boost radiotherapy are now available for hypofractionated concepts too. The authors concluded that the application of a hypofractionated SIB concept in 15 fractions is equally safe compared to sequential boost application and, with 5-year in-breast recurrence rates below 5 %, oncologically non-inferior with regard to local control. The 5-year incidence of moderate or marked breast induration was 11.5 % in the sequential boost cohort and 10.6 % with integration of a simultaneous boost up to a total dose of 48 Gy in 15 fractions. A further dose escalation to the tumour bed up to a total dose of 53 Gy provided no additional oncological benefit, but significantly increased breast induration rates (15.5 %). Data from non-inferiority studies on the integration of a simultaneously integrated boost in hypofractionated concepts from a blinded interim analysis of the HYPOSIB and NRG/RTOG 1005 trials also demonstrate safe application and oncological equivalence in preliminary results presented at the DEGRO-2024 Congress and the ASTRO-2022 Annual Meeting. It appears to be safe to integrate these concepts into everyday clinical practice with a significant reduction in treatment time, even though the final full publications of the HYPOSIB and NRG/RTOG1005 trials are still not available.

While conventional fractionation in 25 to 30 sessions remains the current standard of care for the irradiation of lymph node regions on the national level [17], the alternative of hypofractionation of nodal volumes has already become the standard of care in the recommendations of the European Society for Radiotherapy and Oncology (ESTRO) [22]. However, data supporting these recommendations remain limited to date.

Wang et al. found that hypofractionation was non-inferior to conventional fractionation with regard to acute and late toxicity in the postoperative irradiation of lymph node regions [23]. As per protocol, however, none of the patients received radiotherapy to the axillary lymph nodes; in about 98 % of patients, radiotherapy was delivered using two-dimensional irradiation, while tangential three-dimensional irradiation and IMRT was used in only about 3 % and 2 % of cases, respectively.

The retrospective evaluation of the prospective START trials [24] found a statistically significant increase in the rate of shoulder stiffness for the 42.9 Gy hypofractionated START-pilot group compared to the 50 Gy group. However, this effect was not confirmed for the START-A and START-B groups where no evidence of a difference in patient-reported limitations in arm and shoulder mobility between the hypofractionated regimen and the conventionally fractionated control group was found. The START protocols excluded irradiation of the internal mammary region.

At the ESTRO 2022 and 2023 Congresses, respectively, Offersen et al. [25] presented an analysis of the Danish Breast Cancer Group (DBCG) (NCT02384733) including 2879 nodal-positive patients and Rivera et al. [26] presented results of the HypoG01: UNICANCER trial (NCT03127995), both of which showed non-inferiority of hypofractionation with regard to arm lymphedema with moderate hypofractionation (40 Gy) of the lymph node region compared to conventional fractionation (50 Gy) over a 3-year period. Also as an abstract presentation at the ESTRO 2022 Congress, Wheatley et al. [27] announced results from a 3-year interim analysis of the nodal subgroup of the FAST-FORWARD trial and showed non-inferiority of greater hypofractionation of lymph node regions with 26 Gy in 5 fractions compared to moderate hypofractionation of 40 Gy in 15 fractions with regard to side effects affecting the arm and shoulder region. However, the full publications of the latter 3 randomized trials are still pending and long-term effects (> 5 years) from randomized prospective studies on radiation-induced plexopathy or cardiac toxicity are also still missing.

Aside from partial breast radiotherapy, modern fractionation concepts include ultra-hypofractionated radiotherapy that can reduce treatment duration to a few days or weeks.

Given that changing the total dose and the single dose can potentially have biological effects on tissue radiosensitivity and repair capacity which are different for normal tissue and tumour cells, modern dose fractionation effects must first be evaluated for oncological equivalence and safety. The randomized, multicentre phase 3 FAST trial [28] showed the equivalence of adjuvant WBI in only 5 weekly repeating sessions over a period of 10 years. Similarly, the concept of the randomized phase 3 FAST-Forward trial [29], in which the 26 Gy total dose was delivered in 5 fractions within one week, showed oncological non-inferiority compared to moderate hypofractionation in 15 fractions without evidence of increased acute toxicity.

Omission of RT

Recently, the option of omitting postoperative radiotherapy after breast-conserving surgery has once again become the subject of increasing discussion for selected patient populations. The primary endpoint of the prospective single-arm IDEA trial [30] was the 5-year local recurrence rate in postmenopausal women aged 50 years or older in whom adjuvant radiotherapy was omitted after BCS. These patients not only had biological/clinical low-risk factors with pT1 pN0, hormone receptor-positive, Her2neu-negative tumours, but also a low genomic risk with an Oncotype DX 21-gene Recurrence Score of ≤ 18. The ipsilateral in-breast recurrence rates were 3.3 % and 3.6 % (50–59 years and 60–69 years, respectively). Despite the low recurrence rates achieved, the authors themselves consider the short follow-up period of 5 years to be problematic for the evaluation of radiotherapy omission.

In the PRIME II trial, Kunkler et al. [31] also evaluated the omission of postoperative irradiation in R0-resected, nodal-negative, hormone receptor-positive women aged 65 years or older with a tumour size of up to 3 cm. After BCS, they received adjuvant endocrine hormone therapy. The patients were randomly allocated to receive either postoperative RT with 40–50 Gy (n = 658) in 15 to 25 fractions or no radiotherapy (n = 668). The primary 5-year

in-breast recurrence rates of the initial publication showed a marked increase in risk (hazard ratio 5.19) associated with the omission of radiotherapy; with 4.1 %, these rates were significantly higher in the group without further radiotherapy compared to 1.3 % after WBI. The 10-year update of the data [31] showed a further significant increase in the risk of local recurrence for the overall cohort to 9.5 % after RT omission compared to only 0.9 % after RT. Strikingly, in a subgroup analysis of tumours with only low expression of oestrogen receptors, the local recurrence rate after 10 years was as high as 19.1 % when RT was omitted compared to 0 % after postoperative RT. However, no effect on overall survival was found (93.9 % after 5 years as well as 80.8 % (without RT) and 80.7 % (with RT) after 10 years. The distant control was also comparable in both groups. Further randomized trials, comparing adjuvant RT vs. no further irradiation, conducted by Hughes et al. (CALGB 9343) [32], Fyles et al. [33] and Pötter et al. [34], also clearly describe an effect of adjuvant RT with significant reduction of the local and regional axillary recurrence risks. In addition, a retrospective SEER dataset analysis of almost 12 000 patients [35] showed for women with early stage breast cancer (70–79 years, T1mic-T1c, N0, ER+) in the case of biological evidence of a dedifferentiated grading (G3) a significant advantage of adjuvant RT also in 10-year overall survival compared to RT omission (92 % with RT vs. 87 % without RT; p = 0.02).

While the resulting local and regional recurrence rates in these studies appear to be low overall, even if radiotherapy is omitted, a significant oncological improvement in outcome associated with adjuvant RT is found in these low-risk patient populations too, but with no improvement in disease-free and overall survival. Thus, a complete omission of RT should only be considered after critical discussion in the interdisciplinary tumour conference and, in particular, with due consideration of possible radiotherapy de-escalation strategies, including partial breast radiotherapy and ultra-hypofractionation. In addition to a merely statistical, percentage-based description of the local recurrence risk, it is important not to disregard the emotional impact of a recurrence, the potential need to utilize the healthcare system and possible losses in quality of life. In routine clinical practice, the patient should be actively involved in a participatory decision-making process that assesses the individual risks and benefits to enable the patient to transparently weigh up the treatment options after discussion of oncological recommendations and potential side-effects.

Another area of research is the benefit of multigene signatures for personalized treatment decisions and risk assessment with regard to a possible omission of radiotherapy. At this stage, these genomic test results have not yet been incorporated into individualized clinical recommendations for radiotherapy treatment. However, analyses of locoregional recurrence risk based on 16-gene signatures (POLAR, Profile for the Omission of Local Adjuvant Radiation) [36] in training and validation cohorts provide indications as to which patients are likely to derive greater benefit from postoperative radiotherapy. However, the overlap of the studied gene expression profiles in only one gene with established multi-gene signatures in clinical use, such as Prosigna, Onctoype DX and Mammaprint, is still making interpretation of the results and transferability to clinical practice a challenge.

Regional lymph nodes—surgical de-escalation

Axillary lymph node staging plays a major role in prognostication and determining the extent of regional tumour spread, both clinically and surgically, and helps to determine the best therapy. Sentinel lymph node biopsy (SLNB) remains the standard of care in nodal staging; however, more recent studies have called the necessity and oncological benefit of performing SLNB in patients with breast cancer in very early stages into question.

The multicentre phase 3 SOUND trial (Sentinel Node vs. Observation After Axillary Ultrasound) by Gentilini et al [37] randomized 1405 clinically nodal-negative women with tumours up to 2 cm in size to a sentinel lymph node biopsy group and a group with no axillary intervention. Disease-free 5-year survival in the no axillary surgery group was with 98.0 % not inferior to that in the SLNB group (97.7 %). With regard to the adjuvant radiotherapy, the authors list only a few details on the irradiation technique used and the dose applied to the regional lymph node basin. Almost 98 % of patients in both groups received adjuvant RT (98.0 % and 97.6 % in the SLNB group and no axillary surgery group, respectively); 10.7 and 10.8 %, respectively, received IOERT partial breast irradiation analogous to ELIOT with 21 Gy, while in 83.8 and 81.1 %, respectively, conventional WBI was delivered over a period of 3 to 5 weeks.

Especially, information on the number of three-dimensional tangential irradiations with potentially high therapeutic doses in the axilla is not provided. According to radiotherapy quality assurance data from the INSEMA trial [38], which also evaluated the surgical omission of an SLNB intervention in clinically nodal-negative patients with early breast cancer, three-dimensional conformal irradiation was used in the majority (76.1 %) of patients with usually conventional fractionation (83.8 %). As the result of this tangential irradiation, level I and II axillary lymph nodes were unintentionally treated with a relative mean dose of 85.4 % and 14.9 % of the prescribed breast radiation dose, respectively. It is still not clear whether such a low radiotherapeutic dose contributes to an oncological effect in patients with subclinical nodal involvement or whether an escalation in the form of an expansion of the irradiation volume of the lymph node region should be considered as a consequence for radiotherapy.

While it is possible to omit further surgical treatment in patients without prior neoadjuvant chemotherapy in the case of a negative sentinel lymph node or micrometastasis, the detection of axillary nodal macrometastasis in such patients means that further active treatment with surgery or radiotherapy is indicated. Since the publication of the AMAROS and ACOSOG-Z0011 trials, surgical de-escalation can be considered equivalent in patients with positive sentinel lymph nodes and sentinel lymphonodectomy alone, omitting axillary lymph node dissection, if it is followed by postoperative radiotherapy of the regional lymph node basin [39, 40]. This concept has already been part of standard guideline-based therapy for several years now [17]. Along with this approach, increased toxicity reduction has been reported. In the 10-year update of the AMAROS trial, arm morbidity rates were even revised upwards [41]. With radiotherapy, it was possible to significantly reduce the incidence of lymphedema compared to axillary dissection (5-year lymphedema risk after RT 11.9 % vs. 24.5 % after surgery).

This approach has also been confirmed by the recently published results of the multicentre, prospective SENOMAC trial with 1 to 2 positive sentinel lymph nodes [42]. In the study, 1335 patients were treated with sentinel lymphonodectomy (SLN) alone, while 1205 women were randomized to undergo complete axillary lymphadenectomy (ALNE). This was followed by local radiotherapy, including the reginal lymph nodes, in 89.9 % of the sentinel group and 88.4 % of the ALNE group. The 5-year recurrence-free survival in the two groups was comparable at 89.7 % and 88.7 % (SLN and ALNE, respectively) and thus confirmed the oncological non-inferiority of surgical de-escalation.

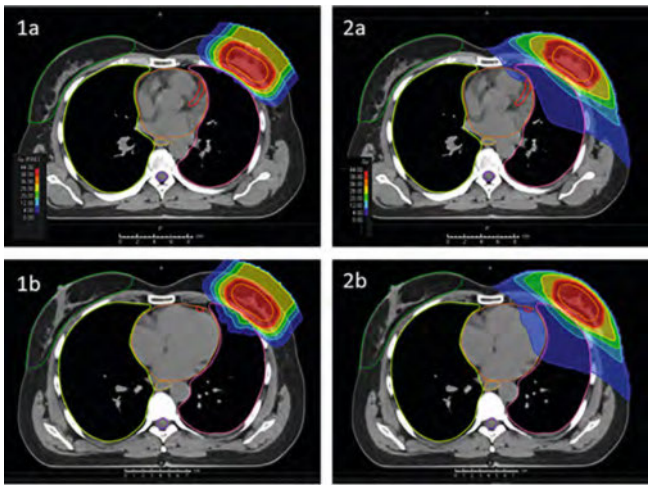
Thus, by the use of modern radiotherapy techniques and the inclusion of lymph node regions, toxicity can significantly be reduced and quality of life better maintained in individualized treatment concepts.

The important role of radiotherapy to regional lymph nodes in multimodal therapy concepts has most recently been confirmed in the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [43]. It showed that postoperative radiotherapy to regional lymph nodes was associated with significantly lower mortality. However, this effect was demonstrated only for patients from 8 modern trials conducted in the period 1989–2008, in which radiotherapy was delivered especially to the internal mammary region (n = 4 studies; 5420women), the internal mammary and supraclavicular regions (n = 1; 4004 women), the internal mammary and supraclavicular and axillary regions (n = 1; 1832women), the supraclavicular region alone (n = 1; 476 women), and the axilla alone (n = 1; 435 women). The estimated absolute 15-year reduction in breast cancer recurrence increased with the number of positive lymph node metastases detected: In node-negative patients, radiotherapy to regional lymph nodes was shown to result in a reduction of 2.3 %, in women with 1 to 3 positive lymph nodes of 2.9 % and in women with ≥ 4 positive lymph node metastases in a reduction of 4.3 %. The corresponding absolute 15-year rates of reduction in breast cancer mortality were 1.6 %, 2.7 % and 4.5 %, respectively, depending on the number of positive lymph nodes, as stated above.

Proton beam therapy

Another innovative radiotherapy technique, in addition to the photon-based technical optimization of conventional radiation techniques, is the use of particle therapy with protons. Physically, the dosimetric profile of proton beam therapy (PBT) has been shown to be superior to photon-based three-dimensional conformal and intensity-modulated techniques, both in terms of dose reduction to adjacent organs at risk and target volume coverage [44, 45, 46, 47, 48].

PBT offers advantageous physical properties due to the modulation of the Bragg peak, which is characteristic for protons, with maximum dose deposition in the target volume and a steep dose drop off beyond the target. Additionally, the use of this technology enables treatments with lower integral doses to the whole body of the patient (▶ **Fig. 2**) as well as potentially greater radiobiological effects and tumour responses [48].



▶ **Fig. 2** Radiotherapy planning CT scan of a patient with comparison plans in 2 representative axial slices each for a left-sided, hypofractionated partial breast irradiation with protons (**1a** and **1b**) as well as photons (**2a** and **2b**). Contours: Target structures: planning target volume (PTV) (rot); clinical target volume (CTV) (orange). Organs at risk: ipsilateral lung (pink), contralateral lunge (green), left anterior descending artery (red), cardiac muscle (orange), contralateral breast (green), spinal cord (purple), oesophagus (yellow).

PBT has advanced significantly in the treatment of breast cancer patients, although its full potential and translation into greater clinical benefit compared to conventional photon therapy remains to be validated [49].

Galland-Girodet et al. presented 7-year long-term cosmetic outcomes of a phase 1 feasibility study with 19 patients treated with partial-breast PBT or three-dimensional conformal photon RT [44]. The patient-reported cosmetic outcome after PBT was with 92 % comparable to that of photon patients (96 %), while the physician rating of overall cosmesis was poorer for PBT (protons 62 % vs. photons 94 %). No significant differences were found with regard to breast pain, oedema, fibrosis, fat necrosis, epitheliolysis, and rib pain or fracture; however, a higher rate of long-term skin toxicities and telangiectasia was reported. The 7-year local recurrence rates of PBT and three-dimensional photon partial-breast irradiation were oncologically comparable with 6 % after PBT and 4 % after photons.

Bush et al. published 5-year results of 100 patients treated with PBT with 40 GyRBE in 10 daily fractions, using a skin-sparing approach [46].The cosmetic outcome of this treatment was for all breast sizes only mild to moderate radiation dermatitis (62 % grade 1 or 2) without higher-grade (≥ 3) skin toxicity. Long-term skin toxicities included grade 1 telangiectasia in 7 % and fat necrosis in 1 % of patients.

PBT has the potential to significantly reduce the dose in healthy tissues while maximizing the coverage of the target volume; achieving this goal remains a challenge for intensity-modulated RT with photons, particularly in the internal mammary region. However, there is still a lack of grade 1 and grade 2 evidence for the treatment of patients with breast cancer using PBT [49]. Given the limited availability of proton beam therapy centres in Germany as well as the more complex procedures with high demands on

robust irradiation, technically complex planning and the challenges of imaging position verification, this technique with its higher maintenance and delivery costs is still not a standard service covered by German health insurance funds for the postoperative treatment of breast cancer.

Conclusions

The modernization of radiotherapy techniques has enabled the use of irradiation with few side effects and an effective improvement of oncological control. Current studies continue to provide solid evidence in support of radiotherapy as an important pillar of disease management and allow the realization of individualized multimodal therapy concepts.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Darby S, McGale P, Correa C 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): 1707–1716. doi:10.1016/S0140-6736(11)61629-2.

[2] Darby SC, Ewertz M, McGale P et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368 (11): 987–998. doi:10.1056/NEJMoa1209825.

[3] Giordano SH, Kuo YF, Freeman JL et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 2005; 97 (6): 419–424. doi:10.1093/jnci/dji067.

[4] Patt DA, Goodwin JS, Kuo YF et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. J Clin Oncol 2005; 23 (30): 7475–7482. doi:10.1200/JCO.2005.13.755.

[5] Duane F, Aznar MC, Bartlett F et al. A cardiac contouring atlas for radiotherapy. Radiother Oncol 2017; 122 (3): 416–422. doi:10.1016/j.radonc.2017.01.008

[6] Strnad V, Polgár C, Ott OJ et al. Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology. Accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy compared with whole-breast irradiation with boost for early breast cancer: 10-year results of a GEC-ESTRO randomised, phase 3, non-inferiority trial. Lancet Oncol 2023; 24 (3): 262–272. doi:10.1016/S1470-2045(23)00018-9.

[7] Strnad V, Ott OJ, Hildebrandt G 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; 387: 229–238. doi:10.1016/S0140-6736(15)00471-7.

[8] Meattini I, Marrazzo L, Saieva C et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020; 38 (35): 4175–4183. doi:10.1200/JCO.20.00650

[9] Livi L, Meattini I, Marrazzo L et al. 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): 451–463. doi:10.1016/j.ejca.2014.12.013.

[10] Coles CE, Griffin CL, Kirby AM et al. IMPORT Trialists. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017; 390: 1048–1060. doi:10.1016/S0140-6736(17)31145-5.

[11] Vaidya JS, Bulsara M, Baum M et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ 2020; 370: m2836. doi:10.1136/bmj.m2836.

[12] Veronesi U, Orecchia R, Maisonneuve P et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013; 14 (13): 1269–1277. doi:10.1016/S1470-2045(13)70497-2.

[13] Orecchia R, Veronesi U, Maisonneuve P et al. Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. Lancet Oncol 2021; 22 (5): 597–608. doi:10.1016/S1470-2045(21)00080-2.

[14] Strnad V, Krug D, Sedlmayer F et al. Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guideline for partial-breast irradiation. Strahlenther Onkol 2020; 196 (9): 749–763. doi:10.1007/s00066-020-01613-z.

[15] Polgár C, Van Limbergen E, Pötter R et al. GEC-ESTRO breast cancer working group. 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 (2009). Radiother Oncol 2010; 94 (3): 264–273. doi:10.1016/j.radonc.2010.01.014.

[16] Shaitelman SF, Anderson BM, Arthur DW et al. Partial Breast Irradiation for Patients With Early-Stage Invasive Breast Cancer or Ductal Carcinoma In Situ: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2024; 14 (2): 112–132. doi:10.1016/j.prro.2023.11.001.

[17] Ditsch N, Wöcke A, Untch M et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2022. Breast Care (Basel) 2022; 17 (4): 403–420. doi:10.1159/000524879.

[18] Haviland JS, Owen JR, Dewar JA et al. START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013; 14 (11): 1086–1094. doi:10.1016/S1470-2045(13)70386-3.

[19] Kindts I, Laenen A, Depuydt T et al. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev 2017; 11 (11): CD011987. doi:10.1002/14651858.CD011987.pub2.

[20] Lupe K, Truong PT, Alexander C et al. Subsets of women with close or positive margins after breast-conserving surgery with high local recurrence risk despite breast plus boost radiotherapy. Int J Radiat Oncol Biol Phys 2011; 81 (4): e561–e568. doi:10.1016/j.ijrobp.2011.02.021.

[21] Coles CE, Haviland JS, Kirby AM et al. IMPORT Trial Management Group. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. Lancet 2023; 401: 2124–2137. doi:10.1016/S0140-6736(23)00619-0.

[22] Meattini I, Becherini C, Boersma L et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol 2022; 23 (1): e21–e31. doi:10.1016/S1470-2045(21)00539-8

[23] Wang SL, Fang H, Song YW et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019; 20 (3): 352–360

[24] Haviland JS, Mannino M, Griffin C et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol 2018; 126 (1): 155–162

[25] Offersen B, Alsner J, Nielsen HM et al. OC-0102 DBCG phase III randomized trial of hypo- vs standard fractionated RT in 2879 pN+ breast cancer pts. Radiother Oncol 2022; 170: S76–S77

[26] Rivera S, Karamouza E, Kirova Y et al. HypoG01:UNICANCER phase 3 trial of locoregional hypo vs normo fractionated RT in early breast cancer. Presented at ESTRO Annual Meeting 2023. doi:10.1016/S0167-8140(23)08699-1

[27] Wheatley D, Haviland J, Patel J et al. OC-0101 First results of FAST-Forward phase 3 RCT nodal substudy: 3-year normal tissue effects. Radiother Oncol 2022; 170: S75–S76

[28] Brunt AM, Haviland JS, Sydenham M et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol 2020; 38 (28): 3261–3272. doi:10.1200/JCO.19.02750.

[29] Murray Brunt A, Haviland JS, Wheatley DA et al. FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020; 395: 1613–1626. doi:10.1016/S0140-6736(20)30932-6.

[30] Jagsi R, Griffith KA, Harris EE et al. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol 2024; 42 (4): 390–398. doi:10.1200/JCO.23.02270.

[31] Kunkler IH, Williams LJ, Jack WJ et al. PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 2015; 16 (3): 266–273. doi:10.1016/S1470-2045(14)71221-5.

[32] Hughes KS, Schnaper LA, Bellon JR et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013; 31 (19): 2382–2387. doi:10.1200/JCO.2012.45.2615.

[33] Fyles AW, McCready DR, Manchul LA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004; 351 (10): 963–970. doi:10.1056/NEJMoa040595

[34] Pötter R, Gnant M, Kwasny W et al. Austrian Breast and Colorectal Cancer Study Group. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. Int J Radiat Oncol Biol Phys 2007; 68 (2): 334–340. doi:10.1016/j.ijrobp.2006.12.045.

[35] Escott CE, Zaenger D, Switchencko JM et al. The Influence of Histologic Grade on Outcomes of Elderly Women With Early Stage Breast Cancer Treated With Breast Conserving Surgery With or Without Radiotherapy. Clin Breast Cancer 2020; 20 (6): e701–e710. doi:10.1016/j.clbc.2020.05.007.

[36] Sjöström M, Fyles A, Liu FF et al. Development and Validation of a Genomic Profile for the Omission of Local Adjuvant Radiation in Breast Cancer. J Clin Oncol 2023; 41 (8): 1533–1540. doi:10.1200/JCO.22.00655

[37] Gentilini OD, Botteri E, Sangalli C et al. SOUND Trial Group. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol 2023; 9 (11): 1557–1564. doi:10.1001/jamaoncol.2023.3759.

[38] Hildebrandt G, Stachs A, Gerber B et al. Central Review of Radiation Therapy Planning Among Patients with Breast-Conserving Surgery: Results from a Quality Assurance Process Integrated into the INSEMA Trial. Int J Radiat Oncol Biol Phys 2020; 107 (4): 683–693. doi:10.1016/j.ijrobp.2020.04.042

[39] Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15 (12): 1303–1310. doi:10.1016/S1470-2045(14)70460-7

[40] Giuliano AE, Ballman KV, McCall L et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017; 318 (10): 918–926. doi:10.1001/jama.2017.11470.

[41] Bartels SAL, Donker M, Poncet C et al. Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981–22023 AMAROS Trial. J Clin Oncol 2023; 41 (12): 2159–2165. doi:10.1200/JCO.22.01565.

[42] de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med 2024; 390 (13): 1163–1175. doi:10.1056/NEJMoa2313487.

[43] Early Breast Cancer Trialists' Collaborative Group(EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet 2023; 402: 1991–2003. doi:10.1016/S0140-6736(23)01082-6

[44] Galland-Girodet S, Pashtan I, MacDonald SM et al. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase 1 trial. Int J Radiat Oncol Biol Phys 2014; 90 (3): 493–500. doi:10.1016/j.ijrobp.2014.04.008.

[45] Bush DA, Slater JD, Garberoglio C et al. A technique of partial breast irradiation utilizing proton beam radiotherapy: comparison with conformal x-ray therapy. Cancer J 2007; 13 (2): 114–118. doi:10.1097/PPO.0b013e318046354b

[46] Bush DA, Do S, Lum S et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. Int J Radiat Oncol Biol Phys 2014; 90 (3): 501–505. doi:10.1016/j.ijrobp.2014.05.1308

[47] Wang X, Zhang X, Li X et al. Accelerated partial-breast irradiation using intensity-modulated proton radiotherapy: do uncertainties outweigh potential benefits? Br J Radiol 2013; 86 (1029): 20130176. doi:10.1259/bjr.20130176.

[48] Vitti ET, Parsons JL. The Radiobiological Effects of Proton Beam Therapy: Impact on DNA Damage and Repair. Cancers (Basel) 2019; 11 (7): 946. doi:10.3390/cancers11070946

[49] Mutter RW, Choi JI, Jimenez RB et al. Proton Therapy for Breast Cancer: A Consensus Statement From the Particle Therapy Cooperative Group Breast Cancer Subcommittee. Int J Radiat Oncol Biol Phys 2021; 111 (2): 337–359. doi:10.1016/j.ijrobp.2021.05.110.