BreastCare

Review Article

Breast Care 2015;10:247–252
DOI: 10.1159/000437194

Published online: July 15, 2015

Accelerated Partial Breast Irradiation in Clinical Practice

Frederik Wenz[a] Felix Sedlmayer[b] Carsten Herskind[a] Grit Welzel[a] Elena Sperk[a] Christian Neumaier[a] Benjamin Gauter-Fleckenstein[a] Jayant S. Vaidya[c] Marc Sütterlin[d]

[a]Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany;
[b]Department of Radiotherapy and Radiation Oncology, LHK Salzburg, Paracelsus Medical University, Salzburg, Austria;
[c]Division of Surgery and Interventional Science, University College London, United Kingdom;
[d]Department of Gynecology and Obstetrics, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Keywords

Breast cancer · Radiotherapy · Partial breast irradiation · Intraoperative radiotherapy

Summary

Accelerated partial breast irradiation (APBI) has been under clinical investigation for more than 15 years. There are several technical approaches that are clinically established, e.g. brachytherapy, intraoperative radiotherapy (IORT), or external-beam radiotherapy. The understanding of the underlying biology, optimal technical procedures, patient selection criteria, and imaging changes during follow-up has increased enormously. After completion of several phase III trials using brachytherapy or IORT, APBI is currently increasingly used either in phase IV studies, registries, or in selected patients outside of clinical studies. Consensus statements about suitable patients are available from several international and national societies like ASTRO, ESTRO, and DEGRO. One may expect that 15–25% of patients undergoing breast-conserving surgery may qualify for APBI, i.e. patients with small invasive ductal breast cancer without clinical lymph node involvement.

Introduction

Radiotherapy plays a substantial role after breast-conserving surgery (BCS) in order to reduce local recurrences in the conserved breast and thereby to improve cancer-specific and overall survival [1]. After establishing the clinical value of fractionated whole-breast radiotherapy (WBRT) to a total dose of 50 Gy about 30 years ago, recent efforts have concentrated on tailoring radiotherapy to the individual risk of the patient. Several studies have tried to identify patients who need no radiotherapy at all [2]. However, none of the prospective randomized trials was successful in identifying a low-risk cohort of patients in whom the local recurrence rates were identical to those in patients undergoing radiotherapy. Trials designed on the analysis of local relapse patterns [3] according to the initial histology have focused on reducing the dose and the volume in appropriately selected patients. Irradiation of a smaller volume, in this case the tumor bed with only a safety margin, allows an increase of the daily dose without excessively increasing the rate of late toxicity. This development was supported by novel insights into breast cancer tumor biology. The concept of accelerated partial breast irradiation (APBI) was rigorously tested in several large-scale clinical studies [4–7], and has now entered clinical guidelines (for a summary, see [8, 9]). The current article reviews some of the underlying biological concepts, summarizes the results of the practice-changing clinical trials and tries to give an overview on the current status of ongoing additional clinical studies.

Biological Rationale [10–13]

Fractionation, i.e. the prescription of total doses and daily single doses in radiation oncology, has been dominated for decades by knowledge gained from in vitro studies, animal experiments with fast growing squamous cell carcinoma, and clinical data mainly from head-and-neck tumors. It is well established that a reduction in the daily fraction size must be compensated by an increase of the total dose to achieve the same biological effect. The way different tumor and normal tissues react to changes in the daily fraction size is usually characterized by a parameter known as the α/β ratio. Classical radiobiological thinking suggests that tumor cells and acutely reacting tissues like skin, mucous membranes, and the bone marrow have a high α/β ratio in the range of 10 Gy, whereas

KARGER

Fax +49 761 4 52 07 14
Information@Karger.com
www.karger.com

1661–3791/15/0104–0247$39.50/0

Accessible online at:
www.karger.com/brc

Professor Frederik Wenz, MD
Department of Radiation Oncology
University Medical Center Mannheim, University of Heidelberg
Theodor-Kutzer Ufer 1–3, 68167 Mannheim, Germany
frederik.wenz@umm.de

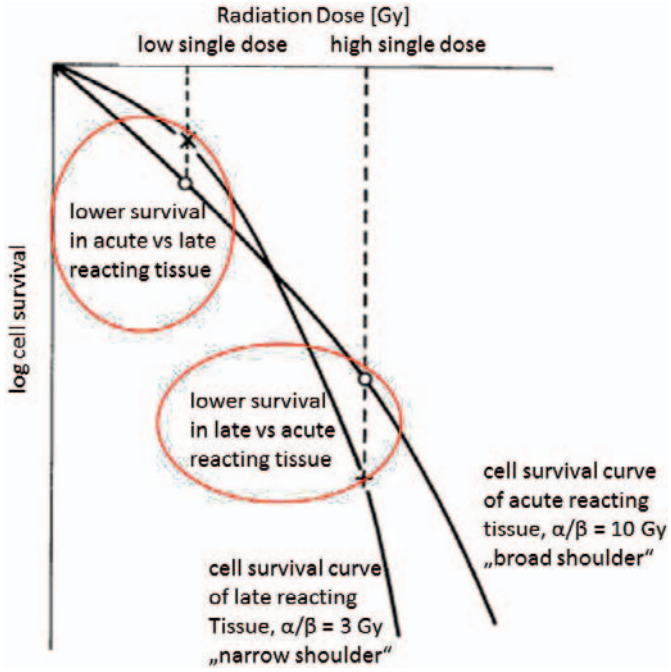

Fig. 1. Cell survival curves in vitro. An increasing radiation dose leads to lower cell survival. Depending on the cell type, the survival curve may have a different shape, which is mathematically characterized by the parameter α/β given in gray. A low value of α/β implies a larger curvature (narrow shoulder), while a higher α/β value is associated with less curvature (broad shoulder, more linear slope at low doses). It is well established that a reduction in the daily fraction size must be compensated by an increase of the total dose to achieve the same biological effect. The way different tumor and normal tissues react to changes in the daily fraction size is usually characterized by the α/β ratio. The difference in α/β values implies that late reacting tissue is spared relative to tumor cells when the daily fraction size is reduced and the total dose is increased by the amount that will give the same rate of local tumor control. Conversely, increasing the size of the daily dose fraction would increase damage to the late reacting normal tissue if the total dose were adjusted to keep the tumor control rate constant.

late reacting tissues, e.g. breast, brain and lung, have low α/β values in the range of 2–5 Gy, with different shapes of the cell survival curves in vitro (fig. 1). Fractionated radiotherapy with single doses of 2–3 Gy yields a differential effect in the sense of normal-tissue sparing in late reacting tissue compared to tumor cells, whereas higher single doses would reverse this, leading to higher rates of clinical late damage. Based on this dogma, higher single doses were strictly avoided in curative radiation oncology for decades.

New clinical data, especially those derived from clinical studies in patients with adenocarcinoma of the prostate [14] and the breast [15, 16], have led to a re-thinking of the classical concepts. Several analyses suggest that the α/β ratio for breast cancer is in the range of 3–4 Gy. Whenever there is no difference in the α/β values between the tumor and the surrounding normal tissue, there will be no clinical gain regarding normal-tissue sparing in giving radiotherapy in small fractions, as has been demonstrated by several clinical trials.

However, as has been known from stereotactic radiosurgery (SRS) series applying very high single doses to brain metastases, there is a strong relationship between the size of the high-dose volume and the risk of radiation-induced late damage [17]. Thus, higher doses can be given to a tumor if the volume of normal tissue in the high-dose field is kept small. The successful concept of radiosurgery was recently modified and refined and can now be applied in the form of stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) to primary or secondary tumors in the body, e.g. lung, liver, adrenals, and bones, with impressive clinical results regarding local control (for reviews, see [18, 19]).

In the past decade, new interest in the biological effects of high single doses was stimulated by the technical development and clinical establishment of SRS and SBRT. Certain biological effects on tumor cells (seed) and from the surrounding microenvironment (soil) can only be observed when single doses above certain thresholds around 3–5 Gy and around 8–10 Gy are given. Local tumor cell killing may be potentiated by a saturation of the repair machinery and by additional effects on the vasculature [13]. In addition, non-target effects may lead to increased cell killing in the vicinity of the macroscopic tumor [20], and abscopal effects mediated by the immune system may lead to distant tumor cell killing [21].

Results from Clinical Studies

Three prospective randomized clinical studies establishing the role of APBI in clinical practice have been published up to now.

The Hungarian Partial Breast Irradiation Trial

Ten-year data have been reported from a Hungarian single-center trial comparing WBRT (n = 130, 50 Gy) with partial breast radiotherapy (n = 88, multi-catheter brachytherapy 7 × 5.2 Gy, n = 40, electrons 50 Gy) in small (pT1 pN0–1mi) non-lobular (G1–2, no extensive intraductal component (EIC)) breast cancers. The 10-year actuarial rate of local recurrence was between 5 and 6% in both arms, with higher excellent to good cosmetic outcome (81% vs. 63%) after partial breast irradiation (PBI) [4].

TARGeted Intraoperative radioTherapy (TARGIT)-A(lone) Trial

The TARGIT-A trial was a prospective, randomized multicentric trial. It included patients with unifocal small breast cancer with non-lobular histology and tested the concept of single-dose intraoperative radiotherapy (IORT; fig. 2) during BCS, which was followed by external-beam WBRT only in patients with additional risk factors. 5-year data on local control and overall survival were recently published, demonstrating the non-inferiority of the experimental arm regarding the primary endpoint of ipsilateral in-breast tumor recurrence in the range of 1–3%. There was a trend for better overall survival and significantly less breast and arm symptoms after IORT-only treatment with 20 Gy using a miniature X-ray generator (Intrabeam®, Carl Zeiss Meditec, Oberkochen, Germany) [5, 6, 22].

ELectron IntraOperative radioTherapy (ELIOT)

A randomized single-center study was performed at the European Institute for Oncology (EIO) in Milan, Italy. Patients were ei-

ther randomized to a single dose of 21 Gy of intraoperative electron radiotherapy (ELIOT or IOERT) or to standard WBRT. The inclusion criteria were broader than in the TARGIT-A trial, and no additional WBRT was given for patients with risk factors. The local recurrence rate was slightly higher in the experimental arm (about 4% vs. 1%); however, in patients without risk factors like the European Society of Therapeutic Radiology and Oncology (ESTRO) consensus or American Society for Radiation Oncology (ASTRO) consensus 'APBI suitable' criteria, there were identical local recurrence rates in both arms [7].

Ongoing Clinical Studies with APBI as Single Modality

TARGIT-E(lderly)

Elderly patients with small, invasive ductal breast cancer were included into the prospective TARGIT-E trial (NCT01299987). The rationale of this non-randomized single-arm study was to compare, in a sequential manner, at predefined time points, the local recurrence rates after risk-adapted IORT with recurrence rates derived from randomized clinical studies with and without WBRT after BCS [23]. More than 500 patients were recruited from 29 national and international centers in less than 4 years. The first preplanned safety analysis (n = 80, median follow-up of 20.5 months) demonstrated the low complication rate of this approach [23]. Data on local recurrence rates and quality of life will be available in the near future.

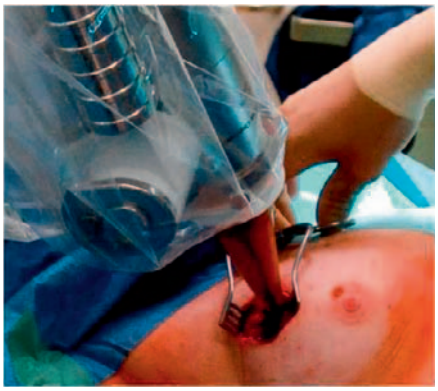

Fig. 2. IORT during BCS using the Intrabeam® system (Carl Zeiss Meditec, Oberkochen, Germany).

TARGIT-C(onsolidation)

In order to further consolidate the results from single-dose APBI, a prospective phase IV study (NCT02290782) [24] was initiated, including patients starting at the age of 50 years (fig. 3). It is a non-randomized single-arm study using the experimental arm of the TARGIT-A study and prospectively compares the local control rates with the best published results from clinical trials using external-beam WBRT. 351 evaluable patients are planned. The expected local relapse rates are 0.825% and 1.375% after 3 and 5 years, respectively. Discontinuation of the trial is scheduled if the local relapse rates rise to 1.55%, 2.4%, or 4% after 1, 3, or 5 years. Power calculations result in 387 patients with a calculated dropout and loss-to-follow-up rate of 10%, an alpha of 0.05 and a beta of 0.10.

NSABP B-39/RTOG 0413

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 study is a randomized phase III trial comparing conventional whole-breast irradiation (WBI) with PBI for women with stage 0, I, or II breast cancer [25]. Several APBI techniques are allowed, i.e. external beam, mammosite brachytherapy, or multi-catheter

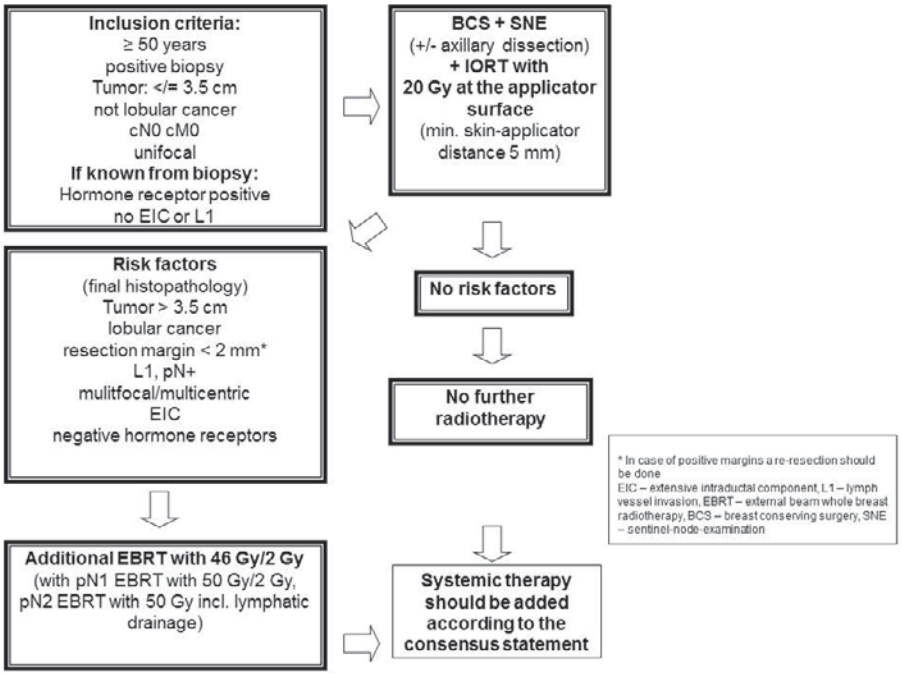

Fig. 3. Flow chart of the ongoing TARGIT-C trial corresponding to the experimental arm of the TARGIT-A study. The TARGIT-E trial used basically the same approach but different entry criteria (70 years and older).

brachytherapy. The primary goal is to determine whether irradiation limited to the region of the tumor bed following lumpectomy provides equivalent local tumor control in the breast compared to conventional WBI. No results on outcome have been reported up to now.

Groupe Européen de Curietherapie-ESTRO

The Breast Cancer Working Group of the Groupe Européen de Curietherapie (GEC)-ESTRO deals with clinical and technical issues of breast brachytherapy. In the last decade, several groups have implemented multi-catheter brachytherapy technique and 3-dimensional (3-D) computed tomography (CT)-based brachytherapy treatment planning for the management of breast cancer. One of the most important projects was the development and conduction of the first European multicentric breast brachytherapy trial comparing the efficacy of multi-catheter APBI to conventional WBI. The study included 1,233 patients up to the year 2009 in 16 centers from 7 European countries. No clinical results on outcome of the phase III trial have been reported up to now, although the results from the phase II trial appear promising [26, 27].

Ongoing Clinical Studies on APBI Combined with External-Beam WBRT

TARGIT-B(oost)

Temporal and geographic miss are potential disadvantages of applying the external-beam boost following oncoplastic surgery, months of chemotherapy, and weeks of external-beam WBRT. For theoretical reasons, i.e. lack of geographic and temporal miss [2], applying the boost already during surgery using IORT, i.e. optimal location and optimal timing, may be superior to the standard of care usually applied as an external-beam boost [28–31]. In order to test the superiority of a TARGIT IORT boost compared to an external-beam boost, the multicentric, prospective, randomized TARGIT-B study was initiated. More than 20 centers have already started recruiting, and 1,800 young or high-risk patients will be included.

Hypofractionated WBI preceded by IntraOperative electron Boost (HIOB)

In an attempt to further reduce overall treatment duration without compromising local control rates, the multicenter HIOB trial was started in January 2011 as an International Society of Intraoperative Radiation Therapy (ISIORT) investigator-initiated study. In this trial, the intraoperative boost with electrons (IOERT) of 10 Gy is combined with hypofractionated WBRT (15 × 2.7 Gy) for stage I/II breast cancer. A similar concept of IOERT plus short-term WBRT was tested in a phase II design by the Milan group [32]. The HIOB trial design follows a sequential probability ratio test (SPRT), defining annual in-breast recurrence rates as benchmarks for successful treatment. Superiority of the intervention is defined by falling below the best published evidence in non-IORT cohorts. Beside tumor-related endpoints, major emphasis is made on treatment tolerance and cosmetic outcome [33].

As of August 2014, within 10 active institutions, 645 patients have been recruited, 481 of them already in follow-up and analyzed by March 2015. Perioperatively, no major complications were observed. 4 weeks after the end of WBI and with 479 evaluated patients, 177 patients (37%) showed no reactions at all (Common Toxicity Criteria (CTC) 0), 277 (58%) presented with faint (CTC 1) and 24 (5%) with moderate-to-brisk erythema (CTC 2), respectively. G0–I late reactions (late-effects normal-tissue subjective, objective, management and analytic (LENT-SOMA) scales) occurred at a mean frequency of 97%, 96%, 98%, and 96% after 4–5 months, 1, 2, and 3 years of follow-up, respectively. Cosmesis was repeatedly assessed and referenced against the baseline appearance prior to WBI, which was scored as sufficient (excellent and good) in 69%/74% of 614 subjective/447 objective evaluations. The respective results at 4–5 months, 1, 2, and 3 years post radiotherapy were 87%/75% of 418/378, 89%/77% of 306/164, 83%/75% of 132/107, and 84%/87.5% of 31/24 ratings. At a median follow-up period of 12.6 months (range 0.5–37 months), 3 patients had metastasized, 2 had died, and no in-breast recurrence was noted.

In sum, tolerance of a combined IOERT/hypofractionated WBI regimen was excellent; acute reactions were moderate and late reactions insignificant in short-term assessments. With regard to postoperative appearance, early cosmetic results are not impaired by this regimen. Both tumor control and cosmetic outcome have to be evaluated on long-term follow-up.

Imaging Changes after APBI

Since the establishment of BCS, structural changes like parenchymal scarring, local edema, fat necrosis, and dystrophic calcification have been described to occur at the original tumor site. Mammography is recommended as the leading method for radiological follow-up after BCS, with ultrasound as an additional option in selected cases. In case of uncertain or suspect findings, further diagnostic procedures like magnification mammography, magnetic resonance imaging (MRI), and needle biopsy have to be considered.

Increased structural changes in the tumor bed after IORT have been reported [34], although these are typically not associated with symptoms or cosmetic changes (fig. 4). Distinct postoperative changes can be found in more than 50% of patients. IORT is associated with a high incidence of fluid wound cavities, fat necrosis, and oil cysts. However, distinct postoperative changes on mammography after IORT are not necessarily associated with a relevant diagnostic uncertainty [35]. Additional procedures due to unclear findings in the tumor bed became necessary in a study by Wasser et al. [35] in 7% (IORT) vs. 8% (control group) of the patients.

The same is true for magnetic resonance mammography during follow-up [36]. Persistent wound cavities, which were associated with a persisting rim of contrast enhancement, have been reported in up to 80% of the patients. Knowing these imaging changes and the respective time course does not cause problems in the interpretation of the images or in the differential diagnosis.

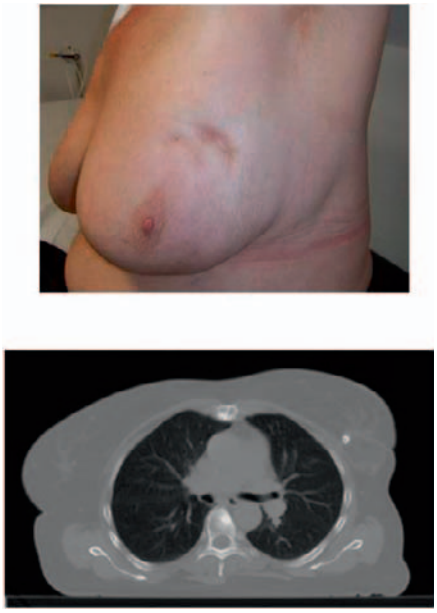

Fig. 4. Outcome 3 years after BCS and IORT. Imaging changes like calcifications are typically more pronounced after APBI as compared to standard WBRT without compromising cosmesis.

APBI in Special Clinical Situations (Patients with Pacemakers or Cardioverter/Defibrillators)

In parallel to the demographic changes of the total population, we also encounter an aging cohort of patients with breast cancer displaying more and more comorbidities which may pose novel problems for the treating radiation oncologist. Modern cardiac implanted electronic devices (CIED; cardiac pacemakers (PM) and cardioverter/defibrillators (ICD)) are increasingly used and may pose a specific challenge to the treating physicians when radiotherapy for breast cancer is planned. Ionizing radiation at doses of 2–10 Gy has been reported to interfere with modern devices which are equipped with complementary metal oxide semiconductor circuitries (CMOS) and random access memories (RAM). Possible effects on the implanted devices include, for example, altered sensitivity, amplitude changes, telemetry and programming defects, or even loss of function. Guidelines, e.g. from the German National Society of Cardiologists and the German Society for Radiation Oncology, have been published recently, highlighting this problem and suggesting adequate measures to avoid damage to implanted cardiac devices [37]. However, using external-beam radiotherapy for breast cancer avoidance of relevant doses to the CIED cannot always be achieved. Reasons for CIED failures in radiotherapy are under investigation. Evidence points out that direct placement in the linear accelerator (LINAC) beam or scatter radiation with an uncertain threshold dose (somewhere > 2 Gy) will eventually harm the electronic parts. Reported CIED failures point towards photon energies > 10 MV causing the generation of photoneutrons and leading to failures in CIEDs that were located even distant to the isocenter. APBI may be a valuable alternative in these cases because of low beam energy and steep dose gradients, and there have already been clinical reports on the successful application of IORT in the vicinity of pacemakers [38].

Conclusion and Future Directions

APBI has been under clinical investigation for more than 15 years. The understanding of the underlying biology, optimal technical procedures, patient selection criteria, and imaging changes during follow-up has increased enormously. After the completion of several phase III trials with long-term follow-up [39], APBI is currently increasingly used either in phase IV studies, in registries, or in selected patients in routine clinical practice outside of clinical studies [40, 41]. One may expect that 15–25% of the patients undergoing BCS may qualify for APBI alone, and up to 60% for APBI as a boost followed by WBRT [9].

Disclosure Statement

FW received research grants, travel grants and honoraria from Elekta, Nucletron and Carl Zeiss Meditec. FS declares no conflict of interest. CH, ES, CN, MS received travel grants from Carl Zeiss Meditec. JSV received research grants, travel grants and honoraria from Carl Zeiss Meditec.

References

1 Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y, Peto R: 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;378:1707–1716.

2 Wenz F, Blank E, Welzel G, Hofmann F, Astor D, Neumaier C, Herskind C, Gerhardt A, Sütterlin M, Kraus-Tiefenbacher U: Intraoperative radiotherapy during breast-conserving surgery using a miniature X-ray generator (Intrabeam®): theoretical and experimental background and clinical experience. Women's Health (Lond Engl) 2012;8:39–47.

3 Vaidya JS, Tobias JS, Baum M, Keshgar M, Joseph D, Wenz F, Houghton J, Saunders C, Corica T, D'Souza D, Sainsbury R, Massarut S, Taylor I, Hilaris B: Intraoperative radiotherapy for breast cancer. Lancet Oncol 2004;5:165–173.

4 Polgár C, 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;108:197–202.

5 Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HMR, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M: TARGeted Intraoperative radioTherapy Alone versus whole breast radiotherapy for breast cancer (TARGIT-A trial) – results of an international prospective randomised phase III trial. Lancet 2010;376:91–102.

6 Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, Eiermann W, Metaxas M, Sperk E, Sütterlin M, Brown D, Esserman L, Roncadin M, Thompson A, Dewar JA, Holtveg HM, Pigorsch S, Falzon M, Harris E, Matthews A, Brew-Graves C, Potyka I, Corica T, Williams NR, Baum M; on behalf of the 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;383:603–613.

7 Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14:1269–1277.

8 Sedlmayer F, Sautter-Bihl ML, Budach W, Dunst J, Fastner G, Feyer P, Fietkau R, Haase W, Harms W, Souchon R, Wenz F, Sauer R: DEGRO practice guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825–833.

9 Sperk E, Astor D, Keller A, Welzel G, Gerhardt A, Tuschy B, Sütterlin M, Wenz F: A cohort analysis to identify eligible patients for intraoperative radiotherapy (IORT) of early breast cancer. Radiat Oncol 2014; 9:154.

10 Herskind C, Steil V, Tiefenbacher U, Wenz F: Radiobiologic aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X-rays for early-stage breast cancer. Radiat Res 2005;163:208–215.

11 Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F: Sphere of equivalence – a novel target volume concept for intraoperative radiotherapy using low-energy X-rays. Int J Radiat Oncol Biol Phys 2008;72:1575–1581.

12 Herskind C, Wenz F: Radiobiological comparison of hypofractionated accelerated partial breast irradiation (APBI) and single-dose intraoperative radiotherapy (IORT) with 50-kV X-rays. Strahlenther Onkol 2010; 186:444–451.

13 Herskind C, Wenz F: Radiobiological aspects of intraoperative tumor-bed irradiation with low energy X-rays (LEX-IORT). Transl Cancer Res 2014;3:3–17.

14 Fowler J, Chappell R, Ritter M: Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50:1021–1031.

15 Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C: Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–520.

16 Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR; 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;14:1086–1094.

17 Flickinger JC: An integrated logistic formula for prediction of complications from radiosurgery. Int J Radiat Oncol Biol Phys 1989;17:879–885.

18 Boda-Heggemann J, Lohr F, Wenz F, Flentje M, Guckenberger M: kV cone-beam CT based IGRT: a clinical review. Strahlenther Onkol 2011;187:284–291.

19 Tree AC, Khoo V, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, Huddart RA, Nutting CM, Ostler PJ, van As NJ: Stereotactic body radiotherapy for oligometastases. Lancet Oncol 2013;14:e28–e37.

20 Veldwijk M, Zhang B, Wenz F, Herskind C: The biological effect of high single doses: a possible role for non-target effects in cell inactivation. PLoS One 2014; 9:e84991.

21 Demaria S, Formenti SC: Role of T lymphocytes in tumor response to radiotherapy. Front Oncol 2012;2:95.

22 Welzel G, Boch A, Sperk E, Hofmann F, Kraus-Tiefenbacher U, Gerhardt A, Sütterlin M, Wenz F: Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. Radiat Oncol 2013;8:9.

23 Neumaier C, Sperk E, Welzel G, Abo-Madyan Y, Kraus-Tiefenbacher U, Keller A, Gerhardt A, Suetterlin M, Wenz F: TARGIT-E(lderly) – prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer. BMC Cancer 2012;12:171.

24 TARGIT-C: *https://clinicaltrials.gov/ct2/show/NCT02290782*.

25 NSABP B-39/RTOG 0413: *https://clinicaltrials.gov/ct2/show/NCT00103181*.

26 Ott OJ, Hildebrandt G, Pötter R, Hammer J, Hindemith M, Resch A, Spiegl K, Lotter M, Uter W, Kortmann RD, Schrauder M, Beckmann MW, Fietkau R, Strnad V: Accelerated partial breast irradiation with interstitial implants: risk factors associated with increased local recurrence. Int J Radiat Oncol Biol Phys 2011;80:1458–1463.

27 Strnad V, Hildebrandt G, Pötter R, Hammer J, Hindemith M, Resch A, Spiegl K, Lotter M, Uter W, Bani M, Kortmann RD, Beckmann MW, Fietkau R, Ott OJ: Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. Int J Radiat Oncol Biol Phys 2011;80:17–24.

28 Vaidya J, Baum M, Tobias JS, Massarut S, Wenz F, Murphy O, Hilaris B, Houghton J, Saunders C, Corica T, Roncandin M, Kraus-Tiefenbacher U, Melchert F, Keshtgar M, Sainsbury R, Douek M, Harrison E, Thompson A, Joseph D: Targeted intraoperative radiotherapy (TARGIT) yields very low recurrence rates when given as a boost. Int J Radiat Oncol Biol Phys 2006;66:1335–1338.

29 Wenz F, Welzel G, Blank E, Hermann B, Steil V, Suetterlin M, Kraus-Tiefenbacher U: Intraoperative radiotherapy (IORT) as a boost during breast conserving surgery (BCS) using low kV X-rays – the first five years of experience with a novel approach. Int J Radiat Oncol Biol Phys 2010;77:1309–1314.

30 Blank E, Kraus-Tiefenbacher U, Keller A, Welzel G, Bohrer M, Sütterlin M, Wenz F: Single center long term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays. Ann Surg Oncol 2010;17(suppl 3):352–358.

31 Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sütterlin M, Wenz F: Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. Breast Cancer Res Treat 2012;135:253–260.

32 Ivaldi GB, Leonardi MC, Orecchia R, Zerini D, Morra A, Galimberti V, Gatti G, Luini A, Veronesi P, Ciocca M, Sangalli C, Fodor C, Veronesi U: Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. Int J Radiat Oncol Biol Phys 2008;72:485–493.

33 Fastner G, Reitsamer R, Murawa D, Milecki P, Hager E, Ciabattoni A, Brimmer R, Reiland J, Budach W, Sedlmayer F: Hypofractionated WBI plus IOERT-boost in early stage breast cancer (HIOB): updated results of a prospective trial. Radiother Oncol 2015; 115(suppl 1):abstr S234.

34 Engel D, Schnitzer A, Brade J, Blank E, Wenz F, Sütterlin M, Schönberg S, Wasser K: Are mammographic changes in the tumor bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT-A). Breast J 2013;19:92–95.

35 Wasser K, Ruch M, Brade J, Schoeber C, Kraus-Tiefenbacher U, Schnitzer A, Engel D, Wenz F, Sütterlin M, Schönberg SO, Büsing KA: Do structural changes in the tumor bed after intraoperative radiotherapy (IORT) of breast cancer complicate the evaluation of mammograms in a long-term follow-up? Eur J Radiol 2012;81:255–259.

36 Wasser K, Schnitzer A, Engel D, Krammer J, Wenz F, Kraus-Tiefenbacher U, Sütterlin M, Schönberg SO, Weisser G: First description of MR mammographic findings in the tumor bed after intraoperative radiotherapy (IORT) of breast cancer. Clin Imaging 2012; 36:176–184.

37 Gauter-Fleckenstein B, Israel CW, Dorenkamp M, Dunst J, Roser M, Schimpf R, Steil V, Schäfer J, Höller U, Wenz F: DEGRO/DGK guideline for radiotherapy in patients with cardiac implantable electronic devices. Strahlenther Onkol 2015;191:393–404.

38 Keshtgar MR, Eaton DJ, Reynolds C, Pigott K, Davidson T, Gauter-Fleckenstein B, Wenz F: Pacemaker and radiotherapy in breast cancer: is targeted intraoperative radiotherapy the answer in this setting? Radiat Oncol 2012;7:128.

39 Vaidya JS, Bulsara M, Wenz F, Joseph D, Saunders C, Massarut S, Flyger H, Eiermann W, Alvarado M, Esserman L, Falzon M, Brew-Graves C, Potyka I, Tobias J, Baum M: Pride, prejudice, or science – attitudes towards the results of the TARGIT A trial of targeted intraoperative radiotherapy for breast cancer. Int J Radiat Oncol Biol Phys 2015;92:491–497.

40 Sole CV, Calvo FA, Ferrer C, Pascau J, Marsiglia H: Bibliometrics of intraoperative radiotherapy. Analysis of technology, practice and publication tendencies. Strahlenther Onkol 2014;190:1111–1116.

41 Piroth MD: Risk adapted targeted intraoperative radiotherapy versus whole breast radiotherapy in breast cancer patients. Strahlenther Onkol 2014;190:767–769.