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Systematic review

Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: A systematic review

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ABSTRACT

New strategies for adjuvant radiotherapy of early breast cancer are being investigated in several phase III randomised trials at the present time. Accelerated partial breast irradiation (APBI) is a way to offer an early breast cancer patient, who has had breast conservative surgery, an adjuvant radiotherapy of short duration aimed at the tumour bed with a certain margin. The rationale of this strategy is that most local recurrences appear close to the tumorectomy cavity and a wish to spare the patient late radiation morbidity. This review discusses the background for APBI, the different techniques, and we highlight possible pitfalls using these techniques. A systematic overview of all phase I and II studies is provided. Patient selection for this therapy is pivotal and based on evidence from previous studies on patient/tumour characteristics and pattern of local recurrences we propose inclusion criteria for patients in APBI protocols.

The standard of care for adjuvant therapy of early breast carcinoma includes whole breast irradiation in case a breast conserving strategy is applicable. The purpose of the irradiation is to minimise the risk of local failure and thus ultimately improve disease-specific survival without causing side effects to the heart or lungs or impede cosmesis. This strategy includes irradiating the mammary gland and in node-positive patients also loco-regional lymph nodes with doses around 50 Gray in 25 fractions delivered as daily treatment 5 days per week for 5–6 weeks. Several large trials have demonstrated this as a safe procedure with local failure rates of 0.5–1% per year of follow-up and acceptable side effects and cosmesis [1–3]. The latest Early Breast Cancer Trialists Collaborative Group (EBCTCG) systematic review confirmed a 75% reduction in local recurrence risk after radiotherapy, and showed that the prevention of 4 local recurrences prevents 1 cancer-related death at 10 years, corresponding to 1–5 fewer deaths per 100 node-negative patients and 5–10 fewer deaths per 100 node-positive patients treated [2]. A dose–response relationship has also been demonstrated in the "EORTC 22881–10882 boost versus no boost trial" where significantly fewer local failures were seen among young patients (<50 years) who received an additional boost of 16 Gray in 8 fractions to the tumor bed [4]. Lately this significant effect has also been demonstrated in patients > 50 years with longer follow-up, the overall hazard ratio being 0.59 (95% CI, 0.46–0.76) in favour of boost, however, the absolute risk reduction is most pronounced among women <50 years [5]. The cosmetic result from whole breast irradiation using 50 Gy/25 fractions has been reported acceptable with a relatively low frequence of fibrosis. For example in the "boost versus no boost trial" cosmesis was systematically investigated and after 10 years the cumulative incidence of severe fibrosis was 4.4% (99% CI, 3.5–5.7%) in patients treated with 50 Gy/25 fractions combined with a boost of 16 Gy/8 fractions versus 1.6% (99% CI, 1–2.3%) in patients treated without boost. For moderate fibrosis the corresponding figures were 28.1% (99% CI, 27.6–28.6) with boost versus 13.2% (99% CI, 11–15.0%) without boost [5].

During the last decade an alternative to the well-documented whole breast irradiation has been investigated, the so-called accelerated partial breast irradiation (APBI) where only a limited volume of the mammary gland is irradiated with a high dose in 1 to 10 fractions delivered in up to 5 days.

Objectives

This report contains a systematic search for articles describing studies on partial breast irradiation with the aim to collect all reports where early (i.e., operable) breast cancer patients have been treated with this approach, i.e., phase I and II studies. Furthermore, we review the background and rationale for APBI, treatment techniques used, and radiobiological aspects.

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Search methods for identification of studies

The systematic search for literature was done in Scopus, Pubmed, and Embase, and the search words were "accelerated partial breast irradiation", "apbi", "apbi OR partial breast irradiation", the latter also combined with "AND morbidity" and "AND prognosis". Further search was done by "related articles", and the reference lists of articles describing clinical trials were also systematically searched. Studies only reported in abstracts were not included in this review. Websites of American and European clinical trial registers were also searched. Studies where partial breast irradiation was used as a boost in conjunction with whole breast irradiation and case reports were not included in the analysis. The last search was done on April 1st, 2008. Using this strategy 177 documents were retrieved of which 116 were original articles (omitting reviews ($n = 40$), editorials ($n = 7$), letters ($n = 8$), and conference papers ($n = 6$)). Among the 116 original articles, 69 original articles were isolated describing 33 studies (omitting physics/technical articles ($n = 35$), non-english articles ($n = 7$), papers on metastatic breast cancer ($n = 4$), re-irradiation ($n = 1$)).

Rationale for APBI

The relative reduction of local failure by post-lumpectomy whole breast irradiation is the same among young and older women, however, the absolute local failure risk reduction in older women diagnosed with low risk cancer is modest [1], and it has therefore been questioned if a group of patients could be identified that did not benefit from standard 5–6 weeks of daily irradiation. On the other hand, a study by Schnitt et al. [6], has demonstrated that omission of radiation therapy in a group of highly selected low risk breast cancer patients was not favourable. They conducted a prospective study of conservative surgery alone in 87 women radically operated with wide excision and minimum 1 cm pathologically documented negative margin for unicentric T1 ductal, mucinous or tubular carcinoma without an extensive intraductal component or lymphatic vessel invasion and pN0. Median age was 67 years, and no adjuvant RT or systemic therapy was offered. The study was closed prematurely due to an unacceptable high incidence of local recurrence, the annual local recurrence rate being 3.6% with a median follow up 56 months.

Furthermore, at least in the USA it has been documented that socio-economic factors influence the patient's choice of breast conserving strategy, thus women with limited financial means and/or with long travel distances to the radiation department tend to choose mastectomy even though a lumpectomy was feasible [7]. Also, in some areas up to 25% of older patients treated with lumpectomy do not receive irradiation for these reasons [8]. Lately, a study was presented based on more than 175,000 patients diagnosed with early breast cancer who were registered in the SEER database [9]. In the period 1992–2003 the rate of breast conserving surgery (BCS) was increased from 41% to 60%, whilst the rate of RT after BCS decreased from 79% to 71%, thus the authors conclude that the "declining rate of adequate local treatment may ultimately forecast an increased local recurrence rate after BCS".

However, another aspect is whether it is necessary to irradiate the whole mammary gland. The principle of whole breast irradiation is based on irradiating microscopic foci of mammary carcinoma in the mammary gland, whereas the principle of APBI is to irradiate only a limited volume of the breast, mainly the tumour bed. A few studies have systematically addressed the extent of foci of premalignant and malignant disease in the breast at lumpectomy [10–14]. In the study by Holland et al. mastectomy specimens from more than 300 women diagnosed with invasive breast carcinoma who fulfilled the criteria for breast conserving therapy were systematically investigated [10]. Irrespective of tumor size, around 40% of the cases had no other foci in the breast of pre-malignancy/malignancy, thus 60% of the cases had residual foci. At a distance from the primary carcinoma >2 cm, 14–16% had invasive tumor foci in the breast. In a study of 30 mastectomy specimens, Vaidya et al. found multicentric foci (MCF) in 19 cases (63%), and in 15 of these (79%) MCF was present beyond the primary tumoŕs quadrant [11]. These data are supported by Faverly et al., who in 135 mastectomy specimens simulated surgical breast-conserving procedures and studied multifocality and multicentricity [12]. In 53% of the cases breast carcinoma of limited extent was identified, and this was not significantly related to patient age, T or N status, type or grade of the tumor or to mode of detection or mammographic aspect of the index tumor. Another study investigated the presence of residual tumor in 87 patients who had a mastectomy or re-excision due to pathologic margins after a segmental resection [13]. Residual tumor was found in 35 of the 87 cases. Rosen et al simulated partial mastectomy in 203 mastectomy specimens and found invasive carcinoma left behind in the mastectomy specimen in 26% of the cases with tumor <2 cm and in 38% of cases with tumor size >2 cm, and this was irrespective of patient age, axillary status and mammogram report [14].

LR without radiotherapy (RT)

It has been uniformly demonstrated previously that the local recurrence rate is significantly lowered due to adjuvant radiotherapy to the mammary gland [15–22]. The Milan group randomized women <70 years operated with quadrantectomy for invasive carcinoma <2.5 cm irrespective of lymph node status to either quadrantectomy alone ($n = 273$) or quadrantectomy + RT ($n = 294$) [15]. The RT consisted of opposing tangential fields to the mammary gland only of 50 Gy/25 fractions, 5 fractions weekly, and some patients had a boost of 10 Gy/5 fractions. Chemotherapy and endocrine therapy was given when indicated. At a median follow up of 9 years, the ipsilateral local recurrence was significantly higher for women who had had a quadrantectomy alone (59 cases out of 273) compared to those who had received operation and RT (16 cases out of 294 patients). This finding was seen irrespective of age, primary tumor size, lymph node status and histology. The local recurrences were located close to the area of the quadrantectomy in 85% of the cases no matter if RT was given. The rate of recurrence elsewhere in the breast was similar to the rate of recurrence in the contralateral breast [15]. Fisher et al [16] demonstrated a similar benefit from adjuvant RT in 1137 patients diagnosed with early breast cancer and followed median 12 years where the cumulative incidence of local recurrence among patients who had lumpectomy alone was 35% whereas it was 10% among patients who were also offered adjuvant RT ($P = 0.001$). This finding was seen both in node-negative and node-positive patients. Unfortunately the localisation of the recurrence in the ipsilateral breast was not indicated. Liljegren et al. [17] randomized 381 patients with pT1, pN0 invasive carcinoma treated with sector resection to either resection alone ($n = 197$) or resection + RT (54 Gy/27 fractions, 5 fractions weekly) ($n = 184$). After 10 years follow-up the local recurrence rate was 8.5% in irradiated patients compared to 24% in non-irradiated patients ($P = 0.0001$). There were 57 local recurrences in all, 10 of which occurred in patients previously irradiated, and 38 (67%) of the recurrences were located in the surgical field. Some large trials have tried to select women with an anticipated particularly low risk of relapse based on tumor and biological aspects and randomized these women to ± radiotherapy combined with Tamoxifen (excluding young patients, including pT1–2, pN0, low-moderate malignancy grade, oestrogen receptor positive, negative surgical margins) [18,19], but data on local relapses unequivocally point to the significant benefit of radiother-

apy in all patients. In neither of the above mentioned studies the localization of the local recurrences has been reported separately in irradiated and non-irradiated patients.

LR with RT

Only few studies have reported the localization of the local recurrences after radiotherapy in detail [5,20,23,24]. Touboul et al. [23] followed 528 patients with invasive carcinoma $\leqslant$3 cm, 75% were pN0 and median age was 52 years. The type of surgery was wide excision (83%) or quadrantectomy (17%). The RT consisted of 45–50 Gy in 16–35 fractions, and node-positive patients had the periclavicular and axillary lymph node area irradiated also in almost every case. A boost dose of 5–25 Gy was delivered in 423 of the patients, and systemic therapy was given when indicated. Median follow up was 87.5 months. Local recurrence was seen in 54 patients, and of 39 pathologically evaluable recurrences, 33 were classified as true local recurrences and 6 as new ipsilateral primary carcinomas. In 26 cases (48%) the recurrence was in the same quadrant as the primary tumor, in 22 cases (41%) in another quadrant, and in 6 cases (11%) in both the same and another quadrant. In the most recent report on local recurrences in the "boost versus no boost" trial with a follow up of median 10.8 years, local recurrence was seen in 278 patients of 2657 patients treated without boost, and in 165 patients of 2661 patients treated with boost [5]. The local recurrences (pooled from both RT arms) were distributed as 47% in the area of the primary tumor, 10% in the scar, 29% outside the area of the primary tumor, and in 13% of the cases diffusely in the whole mammary gland.

In the Swedish study on 1187 patients operated with sector resection (pT1–2, pN0) and randomized to ± RT the 5 year cumulative local recurrence rate was 14% (95% CI, 11–19%) vs 4% (95% CI, 3–7%) in favour of RT. They found 78 ipsilateral breast recurrences in the surgery only group and 26 in the surgery + RT group, and 90% of the recurrences were located in the same quadrant as the primary tumor [20].

The venue of partial breast irradiation prompted Freedman and coworkers to investigate the pattern and long-term risk of local recurrence after breast conserving operation followed by whole breast irradiation of 50 Gy in 25 fractions [24]. They investigated 1990 women (237 DCIS, 1273 T1, and 480 T2, stage 0–II) followed for median 80 months and found 120 local recurrences, 71 (59%) were classified as true local, i.e., confined to the original quadrant, and 49 (41%) as elsewhere, i.e., involving outside the quadrant. The classification of the nature of the recurrence was done prospectively by the judgement of the physician based on clinical examination, imaging studies and the pathology report. The rate of "true" local recurrence was 2%, 5%, and 7% (95% CI, 5–9%) at 5, 10, and 15 years, whereas for "elsewhere" recurrences the corresponding local recurrence rates were 1%, 2%, and 6% (95% CI, 3–9%). The rate of contralateral breast cancer at 15 years was 13% (95% CI, 10–16%). Interestingly, this study shows a difference in the time to recurrence, the "true" recurrences appearing first but resulting in no difference at 15 years in "true" and "elsewhere" recurrences, and it is also demonstrated that the "elsewhere" recurrence rate at 15 years of follow up was half the rate of new contralateral breast cancer, indicating a benefit from whole breast irradiation.

Risk of contralateral breast cancer

For comparison, the 15 year actuarial risk of contralateral breast cancer ranges from 9.1% to 14%, and the highest risk is seen in women with a family history of breast cancer [25–27]. A woman with a primary breast cancer has a two to sixfold increased risk of developing a contralateral breast cancer compared to the risk of general population women to develop a first primary breast cancer, and 2–11% of breast cancer women will develop a contralateral breast cancer in their lifetime [28].

Is there a subgroup of patients who can be spared radiotherapy?

In the studies from Milan and Sweden, where the patients were operated by quadrantectomy or sector resection, subgroups of patients could be identified that had an acceptable low long-term risk of breast recurrence despite the lack of adjuvant radiotherapy [15,17], however, these subgroups were non-stratified and there were only very few patients at risk of long-term recurrence, thus the data is not solid enough to support a strategy of conservative surgery with wider margins. Using a cosmetically more acceptable strategy of less extensive surgery with a lumpectomy of excising 0.5–1 cm margin of normal breast (histologically tumor free), no low-risk group could be identified in the Ontario trial where adjuvant radiotherapy could be omitted [29]. In the subgroup of patients >50 years, $T < 1$ cm, N0, and grade 1/2, the ipsilateral recurrence rate at median follow up 7.6 years was 19% without radiotherapy.

Recently a detailed review has analysed if a subgroup of patients could be identified that might be spared radiotherapy. Based on optimal techniques for breast surgery, newest systemic therapies (chemotherapy and endocrine therapy) and different comorbidity factors it was not possible to propose guidelines to select women who could be spared adjuvant radiotherapy [30].

Aspects of the extent of surgery

One has to consider that the localization of a local recurrence in these studies both with and without irradiation is not easily comparable, since the extension of the surgery varies considerably from a quadrantectomy to a sector resection to a lumpectomy. This could mean that a local recurrence close to the operation cavity after a quadrantectomy corresponds to a recurrence "elsewhere" in the breast if a lumpectomy had been performed. Furthermore, the reports only consider "first events", and in the far majority of the above mentioned cases of local recurrence a salvage mastectomy was performed. This may explain the tendency towards a higher proportion of local recurrences located close to the area of the primary tumor in non-irradiated patients, whereas data shows that only half of the local recurrences in patients treated with whole breast irradiation occur close to the area of the primary tumor. Furthermore, due to the slow nature of local recurrences in breast cancer, very long follow up is needed.

The local recurrence rate after breast conserving strategy has decreased steadily over the last decade due to a combination of different factors: improved surgery techniques focusing on achieving negative surgical margins, more effective chemotherapy and hormonal therapy where Tamoxifen is followed by an aromatase inhibitor in post-menopausal women, CT-based radiotherapy assuring that the right target is hit, and also the criteria for offering the patients adjuvant therapy have decreased so that fewer patients are now classified low risk. It seems the incidence of early breast cancer has peaked in the USA, and since 2002 also in Europe, and adjuvant breast radiotherapy is a heavy burden in the radiotherapy facilities. Taken together the question emerges if it is possible to select patients to be offered radiotherapy to only a limited volume around the tumor bed and to increase the dose per fraction (since the treated volume is smaller) and provide the therapy in fewer fractions than standard. Many centres have now investigated partial breast irradiation in phase I and II trials. The spokesmen for this therapy anticipate that the local recurrence rates will remain unchanged since most of the local recurrences are said to occur in/close to the tumour bed, and they furthermore expect that the

cosmesis will be acceptable, since the smaller treated volume will compensate for the larger dose per fraction. The shorter treatment time (1–5 days) is preferred by the patients and beneficial for waiting time to radiotherapy, and it may also be an advantage biologically, since tumour repopulation may be minimized/avoided.

To explore this further, large randomized phase III trials on accelerated partial breast irradiation are running at the present time in North America (NSABP/RTOG), Canada (OCOG/RAPID), Europe (GEC-ESTRO, IMPORT-LOW), Milan and UK (Targit). These studies are based on different techniques, which will be presented in the following.

Techniques of APBI

Interstitial brachytherapy

One of the first techniques developed for APBI was multicatheter interstitial brachytherapy (Table 1). With this approach the treatment time is reduced from the traditionally 5 weeks to 5–8 days or even less. The technique was initially used to deliver a tumor bed boost after whole breast irradiation, and it has been one of the most used methods for APBI in North America. Catheters are placed through the breast tissue surrounding of the lumpectomy cavity typically at 1–1.5 cm intervals, the number of catheters being determined by the size and shape of the target, and the configuration of the catheters is guided by the understanding of brachytherapy dosimetry. Table 1 highlights the studies based on this approach. Either high dose rate (HDR) or low dose rate (LDR) brachytherapy is used, and since the approach is rather new, no consensus exists regarding total dose or dose per fraction nor regarding patient selection criteria. The selection of 34 Gy in 10 fractions BID HDR was based on equivalence of the BED of this schema to 45 Gy in 4.5 days LDR regimen used in early trials of APBI [31].

The inclusion criteria for the North American phase III trial are $T \leqslant 3$ cm, 0–3 positive lymph nodes, estrogen receptor ±, chemo- and/or endocrine therapy accepted and no age limits. The patients are randomized between conventional whole breast irradiation of 50–50.4 Gy, 1.8–2.0 Gy/fraction *versus* APBI. If the patient is randomized to APBI, this can be performed using interstitial brachytherapy with 34 Gy/10 fractions, with 2 fractions daily, 5 days, using HDR interstitial brachytherapy or a MammoSite device (see below), or the radiotherapy is delivered as 3D external conformal RT using 38.5 Gy/10 fractions, 2 fractions daily, 5 days. The study was initiated March 2005, but due to a disproportionate rate of accrual of low-risk patients, accrual to specific low-risk patient populations was closed as of March 2007, and the goal is now to include 4300 patients over 4.6 years.

Brachytherapy using MammoSite

The MammoSite balloon brachytherapy device received approval from the American Food and Drug Administration (FDA) May 2002 based on a study by Keisch et al. [32] (Table 2). Initially the approach was approved as an adjunct to whole-breast radiotherapy, and the use of it as monotherapy can only occur under trial. It consists of a double-lumen catheter with an inflatable balloon at the distal tip. The balloon is placed in the lumpectomy cavity (either during the primary operation or guided by ultrasound up to 10 weeks post-operatively), and is then filled by saline and contrast material such that the surrounding tissue is stretched tightly around it. A high-dose rate source is then inserted through the inner lumen into the center of the balloon, and the radiation is delivered to the shell of tissue immediately surrounding the lumpectomy cavity. The most widely used regimen is 34 Gy in 10 fractions, twice daily, 5 days, and the dose is prescribed 1 cm from the surface of the balloon. The rationale for this dose is based on linear–quadratic model calculations of the equal expected radiobiologic effects by 34 Gy in 10 fractions and 45 Gy (0.5 Gy/h) LDR [31].

3D conform external radiotherapy (3D CRT)

The only non-invasive technique for APBI is 3D CRT, which is a technique developed at the William Beaumont Hospital in 2003 [33] (Table 3). The aim was to develop a method to provide adjuvant partial breast irradiation without the need of an additional surgical procedure, furthermore to improve dose homogeneity in the target volume, since this was anticipated to improve cosmesis and lower the risk of symptomatic fat necroses. Also, most radiotherapy departments already have the technological tools available making the method more user-friendly. The technique is founded on the patient lying in supine position with the ipsilateral arm elevated, and the patient is then CT scanned. As discussed in the original paper "the appropriate CTV for partial-breast RT is subject to considerable debate", and Baglan and coworkers suggest the CTV be the lumpectomy cavity +1.5 cm uniformly expanded around the lumpectomy cavity but limited to 5 mm from the skin surface and 5 mm from the lung–chest wall interface. Based on studies of respiratory mobility the PTV is defined as CTV +0.5 cm to account for breathing motion and +0.5 cm to accommodate for expected variation in patient setup. The dose and fractionation in the original study was 34 Gy in 10 fractions, 5 days, but after treating 5 patients the acute toxicity was considered minimal, and the dose was elevated to 38.5 Gy in 10 fractions. This study has formed the basis to the NSABP B-39/RTOG 0413 study [34].

Intraoperative radiotherapy (IORT)

Intraoperative electron radiotherapy is a method for adjuvant radiotherapy developed in Milan based on irradiating the surgical field immediately after tumor is removed [35] (Table 4). The first patient was treated in 1999, and now a phase III trial is accruing. A dose-escalating phase I/II study established the preferred dose to 21 Gy given in one fraction by electrons 3–12 MeV with a dedicated linear accelerator in the operating room [36]. Patients are operated by quadrantectomy after which the remaining breast parenchyma is separated from the fascia pectoralis and an aluminum–lead shielding disc to protect the thoracic wall, heart, and lung during radiation is placed below the gland. Then the tumor bed is reconstructed by sutures and an applicator connected to an accelerator is placed over the area, so that a margin of 1.5–3 cm is irradiated with electrons to a dose of 21 Gy. The decision on margin size and angle of the applicator is made by the radiation oncologist together with the surgeon. Afterwards all the materials are removed and the breast is reconstructed cosmetically. Technically, this treatment can also be given by a Mobetron or a Novac 7 [37].

Intraoperative targeted radiotherapy (TARGIT) is another alternative based on "soft" X-rays of 50 kV provided by an Intrabeam device. The dose used by this method is 20 Gy in one fraction prescribed 1 mm from the applicator's surface, and the typical physical dose at 1 cm from the applicator is thus 5–7 Gy. The patient is operated with a lumpectomy, and based on the size of the lumpectomy cavity; various sizes of applicator spheres are available. The one with best fit to the cavity is chosen, and with a purse-string suture the mammary gland tissue is skillfully apposed to the applicator sphere so that the skin is minimum 1 cm from the applicator. The irradiation is given over 20–25 min.

With both intraoperative methods the final pathology report arrives days *post-festum*, which has been one of the major criticisms of the technique. This has in some institutions been handled by providing the "intraoperative" radiotherapy within a few weeks

Table 1
Clinical outcome of APBI with Interstitial brachytherapy

Institution APBI technique	Number of patients (median follow-up)	Inclusion criteria and Definition of target	Comments on selection or technique	Ipsilateral breast recurrence	Cosmesis and complications
The William Beaumont Hospital, USA *HDR*: 32-34 Gy/8-10 fr/ 4-5 days *LDR*: 50 Gy, 96 hours [55–58]	199 patients 5.7 years (LR), *LDR* (1993-1999) 6.8 years *HDR* (1995-2001) 3.8 years (LR) 6.4 years (cosmesis)	⩾40 years, ductal only, T ⩽ 3 cm, margins ⩾ 2 mm, no EIC, pN0 (prior to 1997 also pN1) Lumpectomy cavity + 1–2 cm	40% *HDR* (71 pts treated with 32 Gy, and since 1999 8 pts with 34 Gy) 60% *LDR* Before 1997 pts with pN1 were included 41/199 pts had minor protocol violations	5 year actuarial local failure rate 1.2% *LDR*: 5 year local failure rate 0.9% *HDR*: 5 year local failure rate 2.1%	7% acute infection, 4% late infection 11% fat necrosis at ⩾ 5 years[a] Good/excellent cosmesis[b] in > 90%
Ochsner Clinic, USA [59] *HDR*: 32-34 Gy/8-10 fr/4-5 days *LDR*: 45 Gy, 4 days	50 patients, 6.3 years	T<4 cm, pN0 and pN1, neg margins Segmental mastectomy + 2 cm Lumpectomy cavity + 2 cm peripherally and 1 cm superficially and deeply	Extensive surgery, Short follow-up for cosmesis score	8% locoregional recurrence	Cosmesis scored at median 20 months: 22% grade I/II compl, 8% grade III compl, 75% had an excellent/ good cosmesis.[a] All based on[a]
Ochsner Clinic, USA [60] 34 Gy/10 fr /5 days *LDR*: 45 Gy, 4 days	99 patients, 2.7 years	Non-lobular, T ⩽ 3 cm, neg margins, pN0 and pN1 Lumpectomy cavity +2 cm peripherally and 1 cm superficially and deeply		NA	Late grade III tox 18% (LDR) and 4% (HDR), no late grade IV tox. All based on[a]
London Regional Cancer Center, Ontario [61] *HDR* 37.2 Gy/10 fr/5 days	39 patients 7.6 years	T1, T2, N0, neg margins, nonlobular. Lumpectomy cavity with no margins	31% had margins ⩽2 mm, 19% had lobular carcinoma, median implant volume only 30 cc. 28% single plane implant, 8% had EIC, only 79% were N0	16.2% at 5 years 10% elsewhere failure rate	Median overall cosmetic score 89% 13% had fat necrosis.[a] All based on[a]
Tufts New England [31,62–64] *HDR* 34 Gy/10 fr/5 days	75 patients 6.1 years	T1, T2, pN0, pN1 Neg margins, nonlobular Lumpectomy cavity + 2 cm		41 of the patients were treated in Virginia and had 0 locoregional recurrences at median 3.5 years follow-up [31] Another 33 of the patients were reported in [63] and had an actuarial 4 year LR 3%	Cosmesis[a] Excellent / good / fair-poor 67% / 24% / 9% at last follow-up. Late skin tox[c] grad 1 / 2 / 3 77%, 19%, 4%. Late subcutaneous tox gr 1 / 2 / 3 / 4 55%, 15%, 12%, 18%
Tufts New England [65] *LDssR* 50, 55, and 60 Gy	48 patients 1.9 years	T1, N0 Lumpectomy cavity + 3 cm		NA	Very good –excellent cosmesis 91.8% 12.5% perioperative complications 25% had fibrosis, 8% moderate to severe fibrosis. Based on[a]
Tufts New England [66] *HDR* 34 Gy/10 fr/5 days	32 patients 7 years	T1, T2, pN0, pN1, nonlobular, neg margins Lumpectomy cavity + 2 cm		5 year actuarial LR 6.1%	18% had fat necorsis >5 years 35.7% moderate to severe subcutaneous fibrosis >5 years 89% excellent cosmesis at 5 years Toxicity based on [c] and cosmesis on[a]
University of Kansas [67] *LDR* 20-25 Gy	24 patients 3.9 years	⩾60 years, T ⩽ 2 cm, grade 1 or 2, pN0-1 Lumpectomy cavity + 1 cm	Inadequate dose	0	Cosmesis good to excellent in 100%, no late complications, based on[a]
Guys Hospital, London [68,69]*LDR* 55 Gy, 5 days	27 patients 6 years	<70 years, T < 4 cm, pN0-1 Lumpectomy cavity + 2 cm	Positive margins in 55%, EIC in 41%, T > 4 cm in 11%	37%	Cosmesis good to excellent in 83%, no fibrosis, based on[a]
Guys Hospital, London [70] *LDR* 45 Gy, 4 days	49 patients 6.3 years	<70 years, T ⩽ 4 cm, Lumpectomy cavity + 2 cm	43% positive margins	18%	Abnormal breast in 58%, based on[a]
National Institue of Oncology, Hungary [71,72] *HDR* 30.3-36.4 Gy/7 fr, 4 days	45 patients 6.8 years	pT1, pN0-N1mi, ductal only, grade 1 or 2, neg margins Lumpectomy cavity + 2 cm	Surgical marins < 2 mm in 31% Single implant in 7%	6.7% breast rec 7-year actuarial elsewhere breast failure rarte 9.0%	Cosmesis excellent / good in 84.4%, fat necrosis 20%, ⩾grade 2 late radiation reaction 26.7%, based on[b]

(*continued on next page*)

Table 1 (*continued*)

Institution APBI technique	Number of patients (median follow-up)	Inclusion criteria and Definition of target	Comments on selection or technique	Ipsilateral breast recurrence	Cosmesis and complications
National Institute of Oncology, Hungary [73,74] *HDR* 36.4 Gy/7 fr/4 days (n = 88) or *External electron beam irradiation* 50 Gy/25 fr (n = 40)	128 patients 5.5 years	pT1, pN0-Nimi, grade 1 or 2, nonlobular, no EIC, > 40 years Lumpectomy cavity + 2 cm	At least 1 cm macroscopic free margin. Preterm closure of phase III study to join GEC-ESTRO phase III trial	5-year actuarial local recurrence rate 4.7%, elsewhere breast recurrence rate 3.1%	Excellent to good in 81.2% (HDR) and 70% (electrons), based on[b] 4-year actuarial fat necrosis 36.5% (HDR) and 17.7% (elec), based on institutional scheme
Erlangen, Germany [75–78] *HDR* (36%) 32 Gy/8 fr/5 days *PDR* (64%)49.8 Gy in 83 consecutive fractions of 0.6 Gy each hour/5 days	274 patients 2.7 years	T⩽3 cm, pN0-N1mi, >2 mm clear margins, ER+, no EIC, ⩾35 years Lumpectomy cavity + 2 cm (distance to skin < 1 cm)	16% lobular 7% margins< 2 mm or unknown 7% minor protocol violations	3-year local control rate 99.6%	Cosmesis excellent to good in 94% Acute toxicity in 6.6% Fat necrosis 4.7% Breast tissue fibrosis in 19.3% and telangiectasia in 12.8% Scoring based on[b], [c], [d]

Number of patients refers to patients diagnosed with invasive cancer.
[a] Cosmesis scored according to institutional guidelines.
[b] Cosmesis scored according to Harvard criteria[79].
[c] Skin and subcutaneous toxicity scored according to Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group system[80].
[d] Acute and late side effects based on LENT SOMA[81].

after the primary operation, where the woman is taken back to the operation theatre and the sutures cut, and then the RT is given.

Dosimetric comparison of the different techniques and technical notes

The above mentioned methods for APBI have different characteristics in dose rate and dose distribution. In a study by Bovi et al. treatment plans from 15 patients treated by either multicatheter brachytherapy (n = 5), MammoSite brachytherapy (n = 5), and 3D CRT (n = 5) were compared [38]. The dose volume histograms (DVHs) for PTV, breast and lung showed that the most homogenous coverage of PTV was achieved by 3D CRT, and both methods of brachytherapy resulted in volumes of the PTV receiving more than 200% of the prescribed dose (hot spots). This finding is in harmony with the analysis by Weed et al. [39]. However, the integral dose to the non-target part of the breast is higher with 3D-CRT compared to interstitial and MammoSite brachytherapy [38,39]. One study has compared dosimetrically four different techniques for PBI in the same patients [40]. Thirteen post-lumpectomy interstitial brachytherapy patients underwent pre-implant CT scans in prone and supine positions and a CT scan with implants. Delineations of CTVs and PTVs were done in all three scans, and DVH analyses and mean doses to normal tissues (NTD_{mean}) were compared. The authors concluded that the coverage of PTV for all techniques was excellent, and the dose to the heart was low in every case, however, the interstitial brachytherapy and treatment of the patient in prone position resulted in greater normal tissue sparing (especially ipsilateral breast and lung) as compared to supine position for 3D CRT [40]. In a study from the National Institute of Oncology, Budapest, dosimetric comparisons were made among the plans from 24 patients treated with a MammoSite device (MS) and in 17 patients receiving interstitial brachytherapy (IB) where the patients were CT scanned after implantation [41]. The average volume of PTV for MS and IB was 109.6 and 63.4 cm^3, respectively. The average V90 (the percentage of PTV receiving ⩾90% of prescribed dose), V100, V150 and V200 were 96%, 88%, 27%, and 3% for MS, and 76%, 70%, 26%, and 9% for IB, respectively, and the reported dose homogeneity indices (DHI) were 0.70 (MS) and 0.63 (IB). D_{max} for skin, lung and heart were 97%, 66%, and 27% for MS and 45%, 54%, and 31% for IB, respectively. The dose for MammoSite was 34 Gy/10 fractions/5 days and for interstitial brachytherapy 36.4 Gy/7 fractions/4 days (5.2 Gy/fraction). For both techniques these figures raises concerns about *double trouble*, especially for the IB technique using 5.2 Gy/fraction. For the MS technique V150 (=5.1 Gy per fraction, total dose 51 Gy) is given to average 29.6 cm^3, and the corresponding figures for the IB technique show that 7.8 Gy per fraction (=54.6 Gy total) is given to average 16.5 cm^3. Based on the LQ-model these figures can be recalculated to 2 Gy equivalence, thus for α/β ratios of 3 and 10 respectively, the $D_{2\ Gy}$ in the V150 of MS the doses are 82.6 Gy (α/β = 3) and 64.2 Gy (α/β = 10), and for the IB technique the doses are 118 Gy (α/β = 3) and 81 Gy (α/β = 10). Fortunately, the treated volumes were relatively small; however, small inaccuracies quickly translate into serious overdose.

Definition of CTV

Definition of the CTV is influenced by the clinical features in the breast, e.g., tissue stranding from the surgical cavity, proximity to the pectoral muscle, dense breast parenchyma and benign calcifications in the breast are associated with low interobserver concordance [42]. To aid the contouring, surgically placed clips after lumpectomy have been demonstrated strong radiographic surrogates of the cavity [43]. If clips are not used, substantial differences in delineation of the lumpectomy cavity even by dedicated breast radiation oncologists can be seen [44]. Also, written guidelines for contouring CTV has been demonstrated to significantly lower the interobserver variability and minimize the volumes for radiation [45]. The treatment may be further optimized a few millimeters by the use of cone-beam CT to adjust the position of the target optimally [46,47].

Radiobiological implications and concerns

Hypofractionation is not a new idea, and therefore much data exist, also in adjuvant radiotherapy for breast cancer, showing the problems that can happen following just 3 Gy per fraction summarising to 36 Gy for adjuvant breast irradiation [48]. Only "the tip of the ice berg" of the problems following the hypofractionated RT for most of these unfortunate patients have been studied and published, but we still see them in the clinic. The far majority of these

Table 2
Clinical outcome of APBI with MammoSite (all studies used an Iridium Ir 192 source)

Institution APBI technique	Number of patients (median follow-up)	Inclusion criteria and Definition of target	Comments on selection or technique	Ipsilateral breast recurrence	Cosmesis and complications
American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial, 97 Institutions [32,82–86] 34 Gy / 10 f / 5 days	1255 patients 2.5 years	>45 years, T ⩽ 2 cm, N0, neg margins, ductal only, applicator placement < 10 weeks postoperative, cavity ⩾ 3 cm in one dimension, no EIC, Inclusion accepted pre- and postoperatively	45% had balloon placed during lumpectomy, 55% post-lumpectomy (median 3 weeks, range 1 day-21 weeks). 9% had balloon explanted (low skin distance, poor conformity, poor margins on histology, balloon deflation, N+ disease, large T, adverse events). In tables patients are included with T > 2 cm, N+, pos margins, RT 731 days after lumpectomy, 35 years.	2-year actuarial LR 1.11% 3-year actuarial LR 1.79% Axillary failure 0.4%	Good-excellent cosmesis in ⩾93%[b] Seroma[a] 23.9%, symptomatic in 10.6%. Fat necrosis 1.5%[a]
Texas Cancer Clinic, San Antonio [87] 34 Gy / 10 f / 5–7 days	67 patients 1.1 year	⩾45 years, T < 3 cm, N0, neg margins, lumpectomy cavity 3–6 cm	Skin reaction closely associated with skin dose. Suggests skin dose should be limited to 120% of prescribed dose (40.8 Gy).	NA	56% no skin reaction, 35% had erythema, 6% / 3% dry / moist desquamation. Cosmesis[a] excellent-good in 96%
Kaiser Permanente Los Angeles Medical Center [88,89] 34 Gy / 10 f / 5–7 days	51 patients 1.3 years	⩾45 years, T ⩽ 2 cm, N0, ductal only, neg margins,		0	Excellent-good cosmesis[b] in 95%. There were no grade 3 or 4 toxicities. [c]
Rush University Medical Center, Chicago [90,91] 34 Gy / 10 f / 5–7 days	78 patients 2.2 years	⩾45 years, T < 3 cm, N0, neg margins	70 pts had follow-up > 6 months: 18/70 pts had DCIS, 8/70 pts had mixed ductal / lobular, 2/70 had lobular carcinoma.	Crude local failure rate 7.1%, crude in-breast failure rate 5.7%. In 2 of the 5 local failures lobular carcinoma / LCIS was present at primary lumpectomy. One failure in a patient 43 years old and N+.	At median 1.1 year follow-up excellent-good cosmesis[b] in 93% Infection in 13.3%
Medical University of South Carolina [92] 34 Gy / 10 f / 5–7 days	37 patients (7 with DCIS only) 0.6 years	Any age, pTis-pT2N1, neg margins	Mean skin dose 31.3 Gy (range, 13–55.8 Gy) Mean balloon volume 62 cm^3 (range, 35–70 cm^3)	NA	Operative wound complications 8%, RTOG grade[c] 2 and 3 in 5.4% and 2.7%. Wound infection 16.2%, Seroma 32.4%. Catheter failure due to leak / rupture 5.4% / 8%
Tufts New England [93,94] 34 Gy / 10 f / 5-7 days	38 patients 1.4 years	Any age, T<3 cm, ductal and DCIS, N0 (solitary nodal micrometastasis accepted), neg margins>1 mm	Significant association between presence of seroma and suboptimal cosmesis	NA	Persistent seroma > 6 months 68.4%, transient seroma 8%, Cosmesis[a] excellent-good in >95%
European MammoSite trial [95,96] 34 Gy / 10 f / 5-7 days Multiinstitutional phase II	28 patients 1.2 years	⩾60 years, T ⩽ 2 cm, ductal only, grade 1/ 2, margins ⩾ 5 mm, ER +, balloon-skin distance ⩾ 7 mm, lumpectomy cavity > 3 cm, no EIC	Study reports on 28 patients treated solely with MammoSite and 16 patients in whom the MammoSite therapy was a boost.	0	Cosmesis[b] not listed for patients treated solely with MammoSite

Number of patients refers to patients diagnosed with invasive cancer.
[a] Cosmesis scored according to institutional guidelines.
[b] Cosmesis scored according to Harvard criteria[79].
[c] Skin and subcutaneous toxicity scored according to Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group system[80].

Table 3
Clinical outcome of APBI with 3D-CRT

Institution APBI technique	Number of patients (median follow-up)	Inclusion criteria and Definition of target	Comments on selection or technique	Ipsilateral breast recurrence	Cosmesis and complications
William Beaumont Hospital [97] 34-38.5 Gy / 10 f / 5-7 days	91 patients 2 years	⩾50 years, T ⩽ 3 cm, ductal only, neg margins (⩾2 mm), N0, no EIC, no skin involvement, no Pagets disease CTV: Lumpectomy cavity + 10–15 mm PTV= CTV + 1 cm (⩾5 mm to skin surface and 5 mm to lung-chest wall interface) Patient supine	After treating 6 patients acute toxicity allowed increasing dose to 38.5 Gy	0	Cosmesis[b]ood/excellent in 100% (at 6 months), 93% (at 1 year), 91% (at 2 years), 90% (at ⩾3 years) 3 year grade I/II telangiectasia, fibrosis, and fat necrosis in 9%, 18%, and 9%. Based on. [c]
RTOG study 0319 [34] 38.5 Gy / 10 f / 5–7 days	51 patients, study based on 42 of these patients accrued from 17 different institutions Follow-up time not specified	T1-2, N0-1, neg margins, ductal including NOS (not lobular), no EIC CTV: Lumpectomy cavity + 10–15 mm PTV= CTV + 1 cm (⩾5 mm to skin surface and 5 mm to lung-chest wall interface) Patient supine		NA	Grade I, II and III skin toxicity in 42%, 15% and 2%[a]
New York University [98] 25 Gy / 5 f / 10 days 27.5 Gy / 5 f / 10 days 30 Gy / 5 f / 10 days	10 patients Minimum 3 years (range 3-4.4 years)	Nonpalpable, postmenopausal, pT1, N0, segmental mastectomy, neg margins ⩾ 2 mm, ER/PgR +, no EIC, All ptns declined standard RT Prone position CTV= surgical cavity PTV= CTV + 10–20 mm		0	Cosmesis[a] good –excellent in 100% No late radiation changes seen
New York University [99] 30 Gy / 5 f / 10 days	47 patients 1.5 years	Nonpalpable, postmenopausal, pT1, pN0 or cN0 combined with T < 1 cm, segmental mastectomy, neg margins ⩾5 mm, ER/PgR +, no EIC, All ptns declined standard RT Prone position CTV= surgical cavity PTV= CTV + 15–20 mm		0	Grade 1–2 erythema in 60% Grade 1 late toxicity in 30%, no grade 2-3 Based on[c]
Massachusetts General Hospital[100] Protons 32 Cobalt Gray Equivalent in 4 CGE fractions, twice daily, 4 days. For patients treated with 2-3 fields, one field was treated per fraction	20 patients 1 year	T1, pN0, neg margins ⩾ 2 mm, No EIC, nonlobulary and nonpapillary carcinoma, no lymphovascular invasion Supine position PTV= lumpectomy cavity + 15–20 mm, ⩾5 mm to skin surface and lung-chest wall interface	Significant acute skin toxicity Median interval between surgery and RT: 55 days (range, 32–91 days) for 19 ptns not having chemotherapy, one patient had chemotherapy (174 days after surgery).	0	Global good-excellent cosmesis[b] at 6 and 12 months 89% and 100% Acute skin toxicity moderate / severe in 79% at 3–4 weeks, Moderate / severe moist desquamation in 22% at 6-8 weeks. Telangiectasia in 15%.. 1 documented rib fracture
Florence University Hospital [101] 30 Gy / 5 f / 10 days	5 patients ⩽0.5 year	Postmenopausal, T ⩽ 2.5 cm, wide excision or quadrantectomy, neg margins ⩾5 mm, non-lobular, no EIC		0	At 3 months mild skin changes in index quadrant[c]
Rocky Mountain Cancer Center [102] 34 Gy / 10 f / 5 days 38.5 Gy / 10 f / 5 days	55 patients 0.8 years	⩾45 years, pT1, pN0, neg margins (⩾2 mm) Supine position CTV=tumor bed + 1 cm PTV= CTV + 1, ⩾5 mm to skin surface and lung-chest wall interface	Type of surgery not stated. All ptns started RT on Mondays. IMRT reduces ipsilateral normal breast volume within 100%, 75% and 50% isodose lines compared to non-IMRT	0	Cosmesis[a] good-excellent in 98%. Breast pain mild / moderate in 35% / 4%. Telangiectasia in 2%.
Christie Hospital, Manchester [103,104] Electrons 8-14 MeV, 40-42.5 Gy / 8 fr / 10 days, average field size 8x6 cm	353 patients 8 years	⩽70 years, cN0, cT ⩽ 4 cm,	Incomplete resection in 10%, unknown resection status in 10%. No axillary operation Pathological T unknown in 42%, Lobular in 10%	8-year actuarial breast recurrence rate 25% (ductal) and 34% (lobular)	Fibrosis minimal in 51%, marked in 14%. Telangiectasia none/minimal in 36%, marked in 33%. Fat necrosis in 5%, oedema in 2%, rib fracture in 2%, All based on[c]

Number of patients refers to patients diagnosed with invasive cancer.
[a] Cosmesis scored according to institutional guidelines.
[b] Cosmesis scored according to Harvard criteria[79].
[c] Skin and subcutaneous toxicity scored according to Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group system[80].

Table 4
Clinical outcome of APBI with IORT

Institution APBI technique	Number of patients (median follow-up)	Inclusion criteria and Definition of target	Comments on selection or technique	Ipsilateral breast recurrence	Cosmesis and complications
European Institute of Oncology, Milan[d] [36,105,106] 21 Gy electrons[d]	590 patients 1.7 years[106] Mean 3.5 years (n = 101) [36,105]	T ⩽ 2.5 cm, unifocal Quadrantectomy with intended ⩾1 cm margin around tumor, Target: minimum 4–5 cm around tumor bed, sometimes up to 10 cm in diameter [107]	Focally positive margins at final pathology report are accepted, whilst "extensive" positive margins result in reoperation[c] lobular carcinoma in 8.1%. 5% cN0, and SN or axillary dissection not performed in these 5% [36,105]	Local recurrence in 0.5%, ipsilateral second breast carcinoma 0.5%, axillary lymph node metastases 0.2% [106]	Mild/severe fibrosis in 3.0%/ 0.2%, lyponecrosis in 2.5%, hematoma in 0.3%, skin retraction in 0.3% Based on[a]
Santa Chiara Hospital, Trento, Italy [108] 20 Gy, 7 pts 22 Gy, 20 pts 24 Gy, 20 pts	47 patients 4 years	>45 years, cT1, cN0, ER/PgR +, no intraductal carc. Quadrantectomy + margin ⩾1 cm around tumor Target: tumor bed + 2–3 cm. In 40 pts dose was prescribed to the 90% isodose curve, in 7 pts to Dmax	Lobular carcinoma in 13%, Fibrosis primarily found in 22/24 Gy group In 8% mammography and sonography suggested malignancy during follow up and rebiopsy of benign lesions was required.	0 LR	Fibrosis[a] grade 2 in 30%, Grade 3 in 2% Grade 3 skin change 4% Asympt fat necrosis in 25.5%, symptomatic in 2% Cosmesis excellent/good 92%, fair in 6%, poor in 2% Cosmesis according to[b]
University of North Carolina [109] Preoperative RT with electrons 9–12 MeV, aiming at 15 Gy to tumor center and 90% isodose at 1 cm deep to tumor	10 patients 0.5 year	⩾55 years, pT ⩽ 3 cm,pN0, ductal carcinoma, PTV based on ultrasound, covers tumor + 1.5–2 cm. Following RT, partial mastectomy was performed.	Originally included n = 23, but due to technical problems and surprises at final pathology report only 10 pts received "classical" IORT.	NA	Evaluation of cosmesis started at > 6 months, so very limited. Based on[a]
State University of Buffalo [110] 15–20 Gy 120 kV low energy X-rays	7 patients Mean 10.3 years	Stage I-IIB		29%	Acceptable, based on[b]
TARGIT					
University College, London [111] 20 Gy with 50kV low energy X-rays prescribed 1 mm from surface of applicator	25 patients 2 years	T1-2, N0-1. Operation was wide excision	12% lobular carcinoma. Margin status not reported. 50 Kv, 5 Gy 1 cm from applicator	0	Acceptable[b]

Number of patients refers to patients diagnosed with invasive cancer.
[a] Skin and subcutaneous toxicity scored according to Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group system[80].
[b] Cosmesis scored according to institutional guidelines.
[c] In the Milan trial positive margins after quadrantectomy was seen in 4% [112].
[d] In the phase I trial [36] 101 patients were included in a dose escalation study of 10, 15, 17, 19, and 21 Gy, where 10 and 15 Gy was given as a boost to whole breast irradiation, whilst 17–21 Gy was radical irradiation (n = 84 patients). In the first 55 patients, dose was prescribed to D_{max}, i.e., the 100% isodose curve. However, at reanalyzing the methodology this was found to result in underdosing the deepest part of the target in breasts with a residual thickness of 25 mm. Thus, the study was modified so the following patients received the prescribed dose at the 90% isodose curve, resulting in a D_{max} of 23.3 Gy. The preferred energy is 3–9 MeV.

misfortunes happened during the days of the NSD formula, and since the formula was able to "predict" acute side effects the clinicians only became aware of the severe troubles many years later when some institutions started to evaluate their patients for morbidity. During the three decades passing since the NSD formula, the trend in RT in most of Europe and the United States has been to increase the number of fractions more and more to exploit the difference in shape of the curves for acute and late reacting tissues. All the techniques of partial breast irradiation move in the opposite direction, and the total dose, dose per fraction, volume, and overall treatment time varies significantly, and thus the radiobiological implications vary considerable.

Given the α/β ratios for breast carcinoma and late reacting normal tissue, the therapeutic ratio will always decrease when hypofractionation is used. Lately, the sensitivity of breast carcinoma to dose per fraction has been estimated to 4.0 Gy with a broad 95% CI 1.0–7.8 Gy [49], which is low compared to previously published data [50], but even taking this in consideration the α/β ratios for late reacting normal tissue are lower, e.g., the α/β ratios for subcutis using the endpoints fibrosis and telangiectasia have been estimated to 1.7 Gy (95% CI 0.6–2.6) and 2.6 Gy (95% CI 2.2–3.3), respectively [51]. A decreasing therapeutic ratio is seen when either tumor control decreases and/or normal-tissue toxicity increases. Based on the LQ-model, recalculation of a dose to $D_{2\ Gy}$ using, e.g., a schedule of 38.5 Gy/10 fractions shows for an α/β 5.5 Gy that the "tumor dose" is 48 Gy, but the dose for late reacting normal tissue is increased even more to 52.8 Gy. If the α/β ratio were 10 for breast carcinoma, as assumed just a few years ago, the "tumor dose" would decrease to 44.4 Gy, putting the patient in a situation with probable lower tumor control combined with increased risk of late effects. The LQ-model does not take volume and overall treatment time into account.

The ultimate hypofractionation occurs in IORT, where 20–21 Gy is given in one fraction with either 3–9 MeV electrons or 50 kV X-rays. There are no radiobiological models that can describe what is happening during such high doses. For the IORT method of 21 Gy, the electrons with 3–9 MeV is prescribed at the 90% isodose curve and delivered perpendicular to the tissues. The 80% isodose curves range from 13 mm (3 MeV) to 24 mm (9 MeV) [52]. For the 50 kV X-rays the dose is only 5–7 Gy 1 cm from the surface of the applicator indicating that only a thin shell around the lumpectomy cav-

Table 5
Comparison of PBI techniques

	3D CRT	Interstitial brachytherapy HDR, LDR, PDR	MammoSite	Targit, 50 kV X-rays	IORT, electrons
Coverage of target Thickness of cavity wall irradiated	Best PTV = tumor bed + 20–25 mm. Often 5 mm to field edge from PTV	Variable 1–2 cm	Good Dose prescribed to 1 cm from surface of applicator	Good Dose prescribed to 1 mm from surface of applicator. 5–7 Gy 10 mm from applicator	Good Dose prescribed to 90% isodose line. 80% isodose at 13 mm (3 MeV)–24 mm (9 MeV)
Dose homogeneity	Best	Fair	Fair	Fair	Fair
Sparing of normal breast / other organs	Least	Good	Good	Best	Varies with location
Skin dose	Least	Least	Variable	Least (can shield)	Least
Technical feasibility for various size, shape or location of cavity	Suitable for virtually all cases	Not suitable if inadequate tissue or near axilla	Not suitable for large/irregular cavities, or at the periphery of the breast	Not suitable for large/ irregular cavities, or at the periphery of the breast	Not suitable for tumors near brachial plexus/axilla or skin
Expertise required	Average	High	Average	High	Very high
Potential for wide spread use	Very good	Fair	Very good	Fair	Limited
Main drawback	Relatively higher dose to normal tissue and breathing motion	Adequacy of target coverage in some cases and wider applicability	Cavity shape and size. Although easy to use, stringent QA is required. Skin dose may be high	Very limited depth irradiated; cavity shape and size. Histology not available	Wider applicability. Histology not available. Based on quadrantectomy

Modified from Sarin [113].

Table 6
Prospective randomized phase III trials of accelerated partial breast irradiation

Institution/trial	Trial design	*N*	Control arm	Experimental arm	Status
NSABP B-39/RTOG 0413 [114]	Equivalence	4300 patients Lumpectomy Stage 0, I or II $T \leqslant 3.0$ cm pN1 neg margins any age	WBI 50–50.4 Gy, 1.8–2.0 Gy per fraction to whole breast followed by optional boost to 60–66 Gy	34 Gy in 3.4 Gy fractions using multi-cathether brachytherapy or MammoSite balloon catheter or 38.5 Gy in 3.85 Gy fractions using 3D CRT #	Start March 2005, since March 2007 closed to low-risk patients
RAPID/Ontario Clinical Oncology Group[b]	Equivalence	2128 patients Lumpectomy $\geqslant 40$ years, DCIS, pT < 3 cm, pN0, non-lobular, No BRCA 1 or 2	WBI 42.5 Gy/16 f/22 days (small breasts), 50 Gy/25 f/35 days (large breasts). Optional boost of 10 Gy/ 4–5 f	3D CRT 38.5 Gy/10 f/5–8 days Minimum daily fraction separation 6–8 h	Start January 2006
GEC-ESTRO [115]	Non-inferiority, non-irrelevant, 3% difference	1170 patients, Lumpectomy $\geqslant 40$ years, $T \leqslant 3$ cm, $\leqslant 1$ micrometastasis in axilla, neg margins $\geqslant 2$ mm ($\geqslant 5$ mm for lobular or pure DCIS)	WBI, 50–50.4 Gy, 1.8–2.0 Gy per fraction to whole breast followed by optional boost to 60 Gy	Interstitial brachytherapy # 32 Gy/8 fractions HDR, 30.3 Gy/7 fractions HDR, 50 Gy PDR	Start May 2004
IMPORT-LOW, UK	Non-inferiority	1935 patients Lumpectomy $\geqslant 50$ years, pT $\leqslant 2$ cm, pN0 (isolated tumor cells <0.2 mm allowed) non-lobular, grade I or II, neg margins $\geqslant 2$ mm	WBI 40 Gy/15 f/3 weeks	ARM 1: 36 Gy/15 f (2.4 Gy/f) to low risk areas and 40 Gy/15 f (2.67 Gy/f) to region of primary tumor ARM 2: 40 Gy/15 f to region of primary tumor Based on IMRT and supine position	Start September 2006
ELIOT, Milan [116]	Equivalence	824 patients Quadrantectomy Age >48 years, any invasive cancer $\leqslant 2.5$ cm, pN0	WBI 50 Gy/ 25 fractions followed by optional boost 10 Gy	Intraoperative 21 Gy single fraction, electrons up to 9 MeV	Start December 2000
TARGIT [111] multicentric trial	Equivalence	1600 patients "Pragmatic trial" where the treating institution judges the patient to be suitable. Non-lobular and no EIC (if EIC or ILC on final pathological report, WBI is added)	WBI according to institutional guidelines at the participating center	20 Gy low-energy X-rays 50 kV intraoperative single fraction	Start March 2000

WBI, whole breast irradiation.
All treatments given BID with a fraction separation of $\geqslant 6$ h, for a total of 7–10 treatments given on 4–5 days over a period of 4–10 days.
http://www.clinicaltrials.gov/ct/show/NCT00282035.

ity receives relevant radiation dose. It is known from the EORTC boost *versus* no boost trial that an additional 16 Gy to the tumor bed is needed to cause a reduction of the local recurrences by a factor 2 [5], therefore the 50 kV can only, at the best, provide a therapeutic dose in a short distance. One could argue that the treated volume by this method corresponds to a quadrantectomy, and Veronesís group has demonstrated that the local recurrence rate for patients treated with quadrantectomy alone is significantly higher than for patients who received post-operative adjuvant radiotherapy also [15].

Economy

Cost comparison analyses have been performed considering both societal and patient cost. An American study comparing whole breast irradiation (50 Gy/25 fractions; 60 Gy/30 fractions (IMRT-based); 42.5 Gy/16 fractions) with accelerated partial breast irradiation (3D CRT (± IMRT), MammoSite and Interstitial brachytherapy HDR) identified whole breast irradiation with 42.5 Gy/16 fractions as the optimal strategy in terms of societal cost, whilst 3D CRT (± IMRT) was advantageous if the costs of both the society and patient were considered [53].

Future

In the debate of partial breast irradiation, the greatest and most valid concern is its oncological safety [54]. The risk of progression of occult microscopic foci in the breast, premalignant or malignant, has to be considered, but the pattern of ipsilateral recurrence after surgery without radiotherapy suggests that most multicentric foci may be of uncertain clinical significance [11]. However, the reason why these multicentric foci do not reach clinical significance may be that the patient has a salvage mastectomy at the time of the *first* local recurrence, which presumably most often occurs close to the original tumor where the concentration of tumor cells is most pronounced. Ultimately, this could be an argument in favour of whole breast irradiation + boost. Already for other epithelial cancers partial-organ treatment is routine, e.g., lung lobectomy, partial cystectomy, and hemithyroidectomy, and the key word in these cases is proper patient selection. No doubt the key to long-term success for partial breast irradiation is proper patient selection. Different patient selection criteria have been applied in the phase I, II, and III studies performed to date, and due to short follow up no consensus have been reached yet. The American Society of Breast Surgeons has proposed a consensus recommendation for PBI where the patient is selected based on >50 years, $T \leqslant 2$ cm, pN0, infiltrating ductal carcinoma or ductal carcinoma *in situ*, and microscopically negative margins (>2 mm) (http://www.breastsurgeons.org/officialstmts/officialstmt3.shtml). No consensus exists on the preferred technique for PBI, and they all have different characteristics (Table 5). Table 6 highlights the running phase III trials, and it is seen that the comparability among the studies is low; the inclusion criteria, the total doses and dose per fraction are different, so based on Tables 5 and 6 more questions emerge than answers. Many parameters are varied by performing PBI, therefore the interpretation of patient outcome will be influenced by the following: patient inclusion criteria, total dose, dose per fraction, acceleration, volume, and timing related to chemotherapy/endocrine therapy.

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