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REVIEW

The evolution of targeted intra operative radiotherapy in early breast cancer

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Abstract
Targeted intraoperative radiotherapy (IORT) delivers a single dose of radiation to a fresh tumour bed immediately after lumpectomy, commonly used to treat early breast cancer (EBC). It is delivered during the same sitting, with improved patient compliance and better sparing of adjacent healthy tissue, compared to conventional adjuvant radiotherapy to the whole breast. The recently published 12-year results (median follow up of 8.6 years) of the TARGIT-A trial offers reliable conclusions, of comparable oncological outcomes with a reduced toxicity profile supporting IORT as a replacement for whole breast external beam radiotherapy (EBRT) for suitable patients with EBC. Reduced need of multiple hospital visits is an added logistic advantage which makes IORT a cost-effective, less painful and cosmetically favourable alternative to standard EBRT, now included in several international guidelines with growing popularity among clinicians worldwide.

Keywords Radiotherapy · Breast cancer · Intraoperative · External beam · Whole breast irradiation · Accelerated partial breast irradiation · Breast conserving surgery · TARGIT

Introduction

Intraoperative radiotherapy (IORT) delivers ionising radiation during surgery, using electron beams, high-dose brachytherapy with radioisotopes (Iridium-192) or kilovoltage (kV) X-rays (Vicini et al. 2019 Dec 14; Tobias et al. 2004; Vaidya et al. 2004, 2005; Nag et al. 2011) (Fig. 1), in a single sitting, directly irradiating the freshly operated tumour bed up to predetermined margin. With the principles of precision with direct visualisation, it aims to improve local control and reduce damage to adjacent vital structures such as the heart and the lungs. While its first use was in the 1960s, the advent of lower kV devices and mobile linear accelerators have enabled its use in standard operating theatres (Coombs et al. 2016).

With rising incidence, over 2.3 million people are diagnosed with breast cancer (BC) globally, with a current lifetime risk of 1 in 8 Western women (Calvo et al. 2013). This review article focuses on the shift from the established practice of whole breast radiotherapy to partial breast irradiation following breast conserving treatment (BCT) in EBC and explores the current standing and applicability of IORT as a modality in EBC that may be preferred in suitable patients.

Radiotherapy for early breast cancer

BCT is the mainstay for early breast cancer with a small tumour: breast ratio. Long term results from randomized controlled trials (RCTs) found it to be as good as mastectomy in terms of overall survival. Small differences in local disease control have been considered acceptable in view of greatly improved quality of life (QoL) (Drew et al. 1997; Vaidya et al. 2010; Njeh et al. 2010; Ghose et al. 2024). In these trials, lumpectomy was accompanied by adjuvant whole breast irradiation (WBI), delivered as 50 Gray (Gy)

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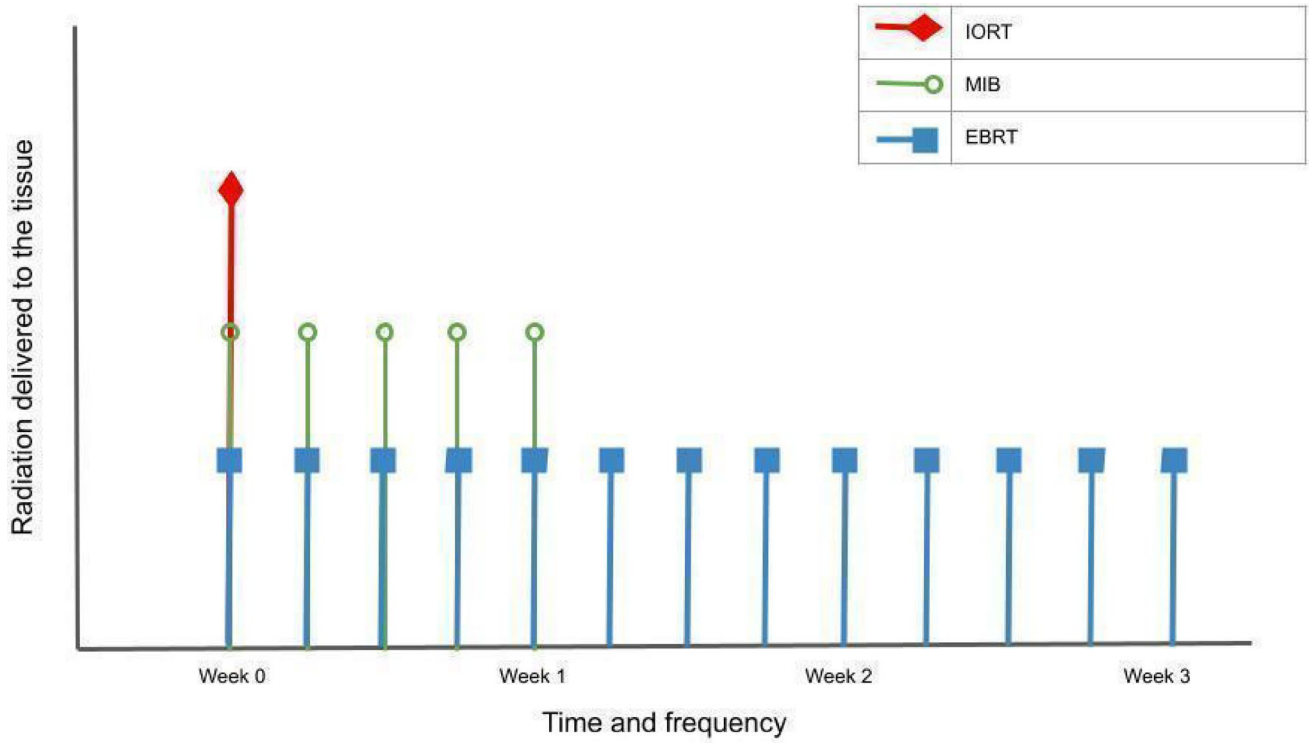


Fig. 1 Representation of the radiation dose delivered overall treatment time and frequency in various types of radiotherapy

in 25 fractions over 5 to 6 weeks (Drew et al. 1997; Vaidya et al. 2010). More recent RCTs confirmed that hypofractionated WBI i.e., 40 to 42.5 Gy in 15–16 fractions over 3 weeks showed similar disease control and toxicity (Program and Institute). However, 1-week ultra-hypofractionated EBRT regimens with higher doses per fraction (5 fractions over 1 week) yielded non-inferior local disease control but more late toxicities (23% risk of fibrosis of the breast) when compared to moderate hypofractionation (15 fractions over 3 weeks). This was further confirmed by the latest 10-year findings of the FAST-Forward trial. It reported a higher incidence of late toxicities in normal tissue (12.6%) in the 1-week regimen group (5 fractions over 1 week) compared to the moderate hypofractionation group at 5 years. Notably, recurrence rates remained low, and local control and late effects on normal tissues, such as breast induration, posed no significant difference at 10 years compared to 5 years (Fastner et al. 2020; Brunt et al. 2024).

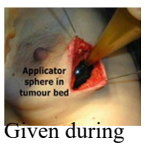
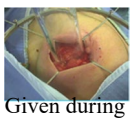
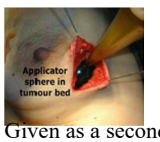
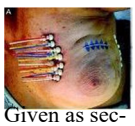
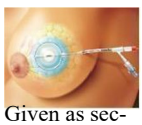
Since the mid-1980s, breast cancer mortality has reduced from 59 per 100,000 in 1984 to about 33 per 100,000 adult women in 2019 (Cancer Research UK 2018) with overall survival of 90–95%. Therefore, it is prudent to minimise long term toxicities of treatments—including local, systemic, financial and social toxicity. One of the approaches to address these issues is accelerated partial breast irradiation (APBI) as an alternative to whole breast EBRT (Veronesi et al. 1981).

The rationale for partial breast irradiation comes from a clinico-pathological paradox. Two-thirds of mastectomy specimens reveal multicentric foci and a large proportion of these are in other quadrants. However, in over 90% cases, local recurrence (LR) occurs near the initial tumour, regardless of margin status or whether radiotherapy is given or not. Therefore, it was hypothesised that targeting radiation to only the tissue around the tumour should yield similar local control rates as whole breast EBRT (Vaidya et al. 1996; Baum et al. 1997; Fisher et al. 2002 Oct 17). Most partial breast RT trials (apart from IMPORT Low) use hypofractionation strategies allowing delivery of treatment over a shorter period (i.e., during surgery which adds 0 days to patient journey) as compared to the conventional 3–6 weeks for EBRT, potentially reducing cost for both patients and treating centres.

Three major approaches of delivering APBI have been developed—IORT, brachytherapy and EBRT (Table 1).

Though multicatheter interstitial brachytherapy (MIB) has emerged to be an attractive technique of APBI, optimal placement, maintenance of brachytherapy catheters and administration of the radioactive isotope requires a special shielded operating theatre, expertise, patient compliance, prolonged hospital stay and can leave multiple scars at the sites of catheter insertion. In case of IORT, the duration of treatment is limited to 20–30 min immediately after the surgical excision and is all completed during the primary

Table 1 Modern trials comparing partial breast irradiation with whole breast radiotherapy (Vaidya et al. 2021a)

	Intraoperative		Post-operative 2nd procedure interstitial			Post-operative external beam	
	TARGIT-A Risk-adapted TARGIT-IORT during lumpectomy	Electron IORT during lumpectomy ELIOT	TARGIT-A delayed second procedure TARGIT-IORT	Interstitial wires × 5 days GEC-ESTRO	NSAPB-B039 Balloon (6% of exp. arm)	NSAPB-B39/ RAPID/Florence 3DCRT /IMRT	IMRT IMPORT-low
Patients							
Total	2298	1305	1153	1184	811	2193/ 1754/ 520	1343
At 6-yr FU	1967	676	1068	784	708	1915/ 1548/ 503	661
KM curves to	12 years	9 years	12 years	6.5 years	10 years	10/9/10.5 yrs	7 years
Tumours	Medium risk	Medium risk	Low risk	Low risk	Low risk	Low risk	Low risk
Grade 3 (%)	20%	20%	6%	9%	1%	1%/15%/11%	9%
Pos. nodes (%)	22%	26%	6.5%	0%	10%	10%/1%/ 10%	3%
5-year local recurrence	2.11% vs. 0.95%	4.4% vs. 0.4%	3.96% vs. 1.05%	1.44% vs.0.92%	2.8% vs. 2.1%	2.8/2.3/2.5% vs 2.1/1.7/1.3%	0.5% vs. 1.1%
Non-inferiority Margin and whether achieved?	2.5% (bkgr 6%) Non-inferior	Equivalence margin 4.5% (bkgr 3%) (4.4% v 0.4%)	2.5% (bkgr 6%) No Non-inferior in HR + HER-, ET	3% (bkgr 4%) Non-inferior	NA Not equivalent	NA/ 2.75% (bkgr 4%)/ 2% (bkgr 3%) Not equivalent/ non-inferior	2.5% (bkgr 2.5%) Non-inferior
Breast cancer control similar to WBRT?	Yes	No	Yes	Yes	No	No/Yes/Yes	Yes
Toxicity/QOL less or more than WBRT?	Less toxicity, better QOL	Not reported	Less toxicity, better QOL	Less toxicity, but wire-entry scarring not reported	More toxicity, QOL not reported	Generally, more toxicity, QOL not reported	No major difference
Deaths from other causes different?	Sig. reduced (HR0.59); by 4.4% at 12y	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
Significant scatter radiation to vital organs?	No	Possibly, if lead shield is not properly used	No	Yes	Yes	Yes	Yes
Additional hospital visits and time?	No additional visits for 80% 20% had supplemental WBRT (~16 half days)	No additional visits	Additional surgical procedure for 1 dose single dose 1 full day	Additional procedure 10# over 5 days, 2# /day as inpatient 5 full days	Additional procedure 10 # over 8 days 2#/ day 5 full days	10# twice per day over 5–8 days or 5# over 2 weeks 5.5 full days or 6 half days over 2wks	16 hospital visits 16 half-days
Where is it done?	Standard OR like c-arm fluoroscopy	Lead-lined walls	Standard OR like c-arm fluoroscopy	Lead-lined walls	Lead-lined walls	Lead lined bunker	Lead lined bunker
How it is done?	 Given during lumpectomy surgery	 Given during lumpectomy surgery. Needs extensive dissection + deep lead shield	 Given as a second procedure by re-opening the lumpectomy wound	 Given as second-procedure and radioactive wires remain in place for 4 days (in-patient)	 Given as second procedure and the balloon remains in place for 8 days (in-patient)	 Given as twice daily treatments over 8 days or 5 non-consecutive days over 2 weeks	 Given as daily doses for 15 days over 3 weeks

surgery, under the same anaesthesia, eliminating the requirement for repeated hospital visits and catheter-maintenance. This improves the quality of life for patients (Corica et al. 2016; Welzel et al. 2013) and is preferred by patients (Corica et al. 2014; Alvarado et al. 2014; Tang et al. 2021) even to the shortened 5-days hypofractionated regimen (Bagga et al. 2023; Small et al. 2019).

Multiple landmark trials have studied different methods of delivering EBRT in the most effective way. One of these was RAPID, which delivered radiation at 38.5 Gy/10

fractions twice daily at least 6 h apart. It was found that over 8 years, ipsilateral breast tumour recurrence (IBTR) was 3% in ABPI and 2.8% in WBI (Haviland et al. 2013). NSABP B-39 compared radiation at 38.5 Gy/10 fractions twice daily to brachytherapy. 10-year total incidence of IBTR was 4.6% after APBI and 3.9% after WBI. However, there was no reduction in non-breast cancer mortality and OS did not differ between both treatments. Rates of acute and late toxicities were similar in both treatment modalities, but cosmetic appearance was worse for APBI compared to WBI after 36 months (Krug et al. 2021) IMPORT LOW had three groups of patients: 40 Gy WBI (control group), 36 Gy WBI and 40 Gy to the partial breast, and those with 50 Gy to the partial breast only. The trial found that the 5-year estimated total incidence of local relapse was 1.1%, 0.2% and 0.5% respectively in the groups; unfortunately, patients reported outcomes differed in only 2 of the 72 outcomes studied WBI (Publications Postoperative Radiotherapy For Breast Cancer and Consensus Statements November 2016; Vaidya et al. 2018) The randomised phase III APBI-IMRT Florence trial is another study comparing APBI to WBI with promising outcomes. While the overall survival was comparable in the APBI and WBI arm, the APBI arm showed a marginally better breast cancer specific survival rate and significantly less acute and late toxicity as well as cosmetic outcomes. The sample size as reported by the authors was found to be insufficient to establish non inferiority (Meattini et al. 2020; Marrazzo et al. 2023) (Fig. 2).

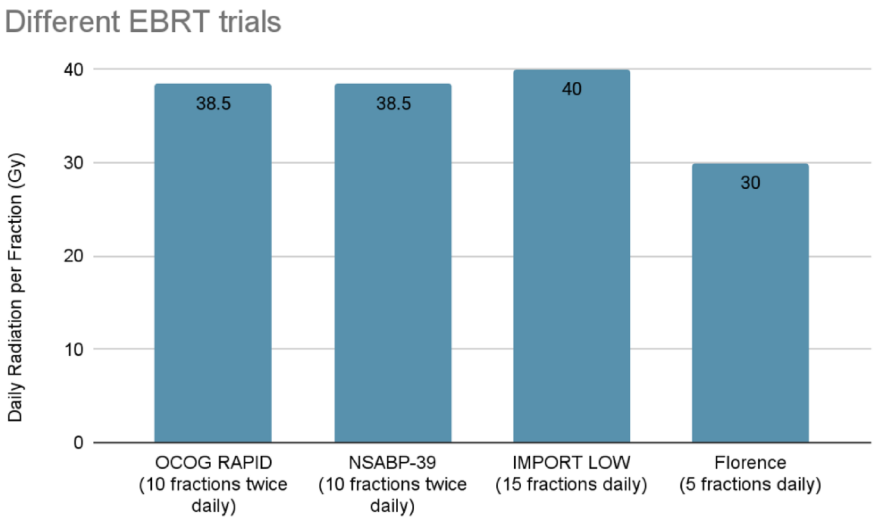
Besides the above mentioned trials, several studies have compared WBI and APBI in early breast cancer, considering several aspects such as quality of life, toxicity and recurrence. A meta-analysis of 10 RCTs showed that the APBI groups reported significantly higher local recurrence rates while there was no significant difference in regional recurrence rates, distant metastasis or overall survival. No significant difference was noted in disease free survival or breast cancer mortality (Xiang et al. 2021). A similar study found that APBI had higher rates of ipsilateral breast recurrence that was found to be statistically significant and poorer overall survival (Ooi et al. 2021). These findings were contradicted by another recent study involving 14 RCTs which found the difference in ipsilateral breast recurrence to not be statistically significant between APBI and WBI. Additionally, fewer acute adverse events were reported (Shumway et al. 2023). Similar outcomes were reported in favour of APBI by another study by Wujanto et al. that included 34 RCTs (Wujanto et al. 2023) (Table 2).

Intraoperative radiotherapy

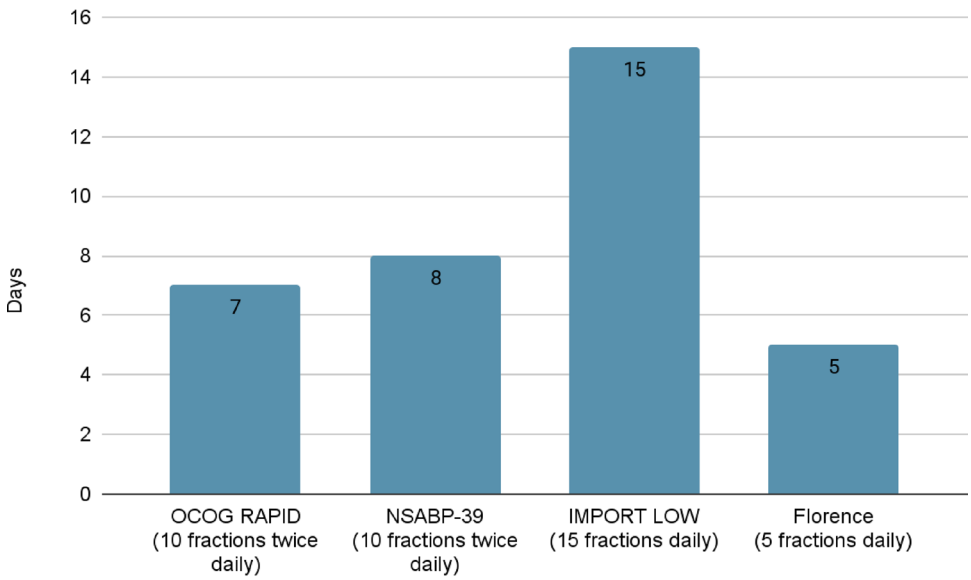
Intraoperative radiotherapy in the early 1960s used single high dose gamma rays from a cobalt unit and electrons from a betatron. Within a decade, in-room linear accelerators were installed in dedicated IORT facilities (Vicini et al. 2004) However, the need for specially built operation theatres and very heavy equipment did not allow its widespread use. In early 1990s, miniaturised low energy X-ray machines alongside mobile self-shielding linear accelerators actively became part of clinical practice. Various societies have been formed to develop and popularise the technique further, including International Society of Intraoperative Radiation Therapy (ISIORT) and Targit Collaborative group (TCG) (Pérez et al. 2017).

Radiobiologic rationale of IORT

The radiobiological implication of IORT boils down to extreme hypofractionation (high dose in a single dose) and its relative biological effectiveness (RBE), the parameter that compares the extent of tissue damage of different types and energies of ionising radiation. Fractionation and dose-rate are among other factors impacting RBE (Whelan et al. 2019). Historically, the linear quadratic model was used to determine biologically equivalent dose (BED) while using various fractionation schemes for radiation (de Souza et al. 2023). In the context of BC, which is a slow growing tumour, this led to the discovery of considerable therapeutic gain while using hypofractionation. The efficacy of lower energy X-rays was explained by the decreased energy of secondary electrons and increased linear energy transfer which improved the RBE of photons with decreasing energy. The RBE of 40 kV photons was found to be 1.4 in comparison to 4 mV photons and that of 50 kV electronic brachytherapy is 40–50% higher than Ir192/Co60 (Marthinsen et al. 2010). Moreover, radiation delivered during surgery significantly mitigates positive margins and improves tumour control in breast tissue nearer to the surgical bed that is better oxygenated, enhancing radiation-induced cell kill. Investigators developed the ‘sphere of equivalence’ theory using the linear quadratic formula to use 50 kV X-rays used in TARGIT-IORT as a function of depth, which explained better tumour control in closer proximity to the applicator as opposed to poorer control with increasing distance (Harris and Small 2017).



3(a)



3(b)

Fig. 2 Representation of different EBRT Trials with **a** Radiation dose and **b** Duration of treatment

Techniques of IORT

Electron IORT

Dedicated intraoperative electron radiotherapy (IOERT) facilities made the use of depth dose distribution of variable electron energies easier. However, it was the introduction of smaller, self-shielded mobile accelerators, that made the use of IOERT cost effective and popular. In this technique, the target area is closely packed by drawing the lateral walls of the excised cavity together so it may be covered by the applicator, generally 2 cm larger than the target. Following the ELIOT trial, a shield is generally inserted between the target area and the pectoralis muscle, to shield tissue at risk behind the target (Hensley 2017; Intra et al. 2006).

The delivery of accelerated electrons at doses of 20–21 Gy, to the lumpectomy cavity, is done by mobile electron accelerators using 3–12 MeV (Watson 2019). This

Table 2 Table summarising the EBRT trials- OCOG-RAPID (2019), NSABP B-39, IMPORT-LOW and Florence trial

	OCOG-RAPID (2019)	NSABP B-39	Import low	Florence trial
Advantages with APBI	Non-inferiority established	Non-inferiority established	Non-inferiority established	Acute and late toxicities are significantly less with better cosmetic outcomes
Disadvantages with APBI	More late toxicity Worse cosmetic outcome Multiple visits	Worse cosmetic outcome Multiple visits	Higher rate of contralateral breast primary cancers Multiple visits – not different from WBI	Absolute difference in ipsilateral breast tumour recurrence was 1.2% higher in APBI
Daily radiation per fraction	38.5 Gy in 10 fractions, twice daily	38.5 Gy in 10 fractions, twice daily	40 Gy in 15 fractions, once daily	30 Gy in 5 fractions, once daily
Duration of treatment	7 days	8 days	15 days	7 days
Rate of ipsilateral breast tumour recurrence in APBI versus WBI	3% versus 2.8%	4.6% versus 3.9%	0.5% versus 1.1%	3.7% versus 2.5%

requires the posterior part of the cavity to be shielded as well. Electron energies of 4 to 18 MeV may be used in linear accelerator based IOERT (Fastner et al. 2013). The initial prototype accelerators were developed in-house and have been replaced entirely today by light-weight mobile accelerators. These may easily be installed in the operating room without having to shift the patient and their specialised designs minimise interactions of defocused electrons. Commercially available ones include the Mobetron, the Liac and the Novac 7. (Hensley 2017). Dedicated mobile linear accelerators used for IORT today are advantageous compared to conventional non-dedicated linear accelerators. The conventional accelerators are typically non-mobile requiring patient transport and lower dose rates increase the overall treatment time. Additionally, standard applicators do not strictly cater to the size and shape of the target tumour bed (Baghani et al. 2015).

The delivery of IOERT (used in the ELIOT randomised trial) requires surgical dissection of the breast off the pectoral muscle posteriorly (where the shield is inserted) and from the skin anteriorly. The dissected gland is then brought together, and a cylindrical applicator is inserted in the wound (which may need to be enlarged to accommodate it) (see Fig. 1). Such extensive tissue dissection can de-vascularise the edges of the gland, specifically the very tissue that needs irradiation. This in the context of reduced oxygenation making radiation less effective. Temporarily, sutures are used to hold adjacent tissues in place, within reach of the electron beam. Ultrasonography is used to gauge tissue depth and based on that dose, electron tube diameters and electron energies are determined. There is increased flexibility in terms of target volume shapes, uniform dose delivery and increased depth of penetration. Applicators are available in a variety of shapes and sizes and undergo constant shape conformation to be able to irradiate wider areas within minutes (Biggs et al. 2011).

IORT

Mobile self-shielding devices such as Intrabeam® (Carl Zeiss AG, Germany) and Axxent® Electronic Brachytherapy System (Xoft Inc., Fremont, California) deliver low kV radiation (20–50 kV) with steep dose gradients (Mourtada 2016). Intrabeam® is a miniaturised accelerator with a 50 kV photon beam produced by accelerating an electron beam to the tip of a 3.2 mm drift tube to form an isotropic point source. The system uses multi-use spherical applicators ranging from 1.5–5 cm diameter with a 20–45 min treatment time that varies with the size of the applicator. It is then inserted and apposed to the tumour bed by surgical sutures (Hensley 2017 Dec). This is the device that has been tested in the TARGIT-A randomised trial. Axxent® is a more recently developed electronic brachytherapy machine where the source of radiation is a miniature, X-ray tube with high dose, low energy delivery, as a part of a flexible catheter with many lumens, producing 40–50 kV X-rays at the tip. Even though originally intended for fractionated PBI using variable currents and voltages, it is being used for single fractions as well. It delivers the radiation using spherical/ellipsoidal balloons of 3–6 or 5–7 cm for a treatment duration of 10–20 min. However, the Axxent device has not been used in a randomised trial. The greatest advantage of using low energy kV X-rays for IORT is that there is no requirement of special shielding or additional radiation safety measures in a standard operation theatre. However, this modality generally employs spherical cavities requiring similar tumour beds, which is not always the case. This requires manoeuvring the tumour bed and surrounding tissue by the surgeon. Comparatively, it provides limited penetration making dose adjustment at different depths difficult especially in the presence of blood or air (Herskind and Wenz 2014).

HDR IORT

High dose rate (HDR) IORT has a steep dose fall off and can deliver high targeted doses using Iridium-192 HDR afterloader. Even though the cost for a dedicated system can be reduced, a shielded operating room is necessary. It is delivered using surface applicators such as superflab or Harrison-Anderson-Mick (HAM) applicators. This method carries the disadvantage of reduced depth of penetration, increasing the time required to deliver treatment. However, the applicators are flexible and come in larger sizes depending on size of tumour (Nag et al. 2011). Another newly introduced device, the Papillon+™ system for breast IORT is being used to deliver 20 Gy within a minute. It is in phase II trials but with reassuring results so far (Chand-Fouché et al. 2023 Jan).

IORT versus EBRT as APBI

EBRT has traditionally been the modality used for most solid tumours post resection to reduce LR rates. However, as it is delivered in multiple fractions over a long period of time, there may be a repopulation of the tumour stem cells within the irradiated tissue between delivery of fractions**.** Moreover, it also risks injury to the surrounding normal tissue. Despite better tumour response at higher doses, EBRT can only be delivered up to doses within normal tissue tolerance, affecting its ability to achieve optimum local control (Small et al. 2022; Chen et al. 2022).

IORT, on the contrary, is more focussed. TARGIT-IORT is delivered from within the breast rather than from outside. It has shown to have much lesser normal tissue toxicities, allowing more dose escalation compared to EBRT. In context of its precise nature and immediacy, it removes any harm from delay after surgery that invariably accompanies post-operative EBRT. This also makes re-irradiation easier with IORT in recurrent cancers. Theoretically, IORT can be used as the only radiation treatment and in higher risk cases, can be used in conjunction with fractionated EBRT. Prompted by the improved local control with TARGIT-Boost (Vaidya et al. 2006) the randomised TARGIT-B trial is testing whether TARGIT-IORT as a tumour bed boost improves local control and survival (Tom et al. 2019).

IORT as boost

Boost IORT was put to practice by an American Institute in Ohio and a French Institute in Montpellier, based on 72 patients treated with IOERT (Sedlmayer et al. 2017). Multiple studies have focused on the use of IORT in this manner with promising results (Harris and Small 2017; Sedlmayer et al. 2017, 2014). Boost doses are typically delivered as external beam electrons of 10–16 Gy (5–8 × 2 Gy) or using HDR brachytherapy via interstitial implants (Kametriser et al. xxxx; Harris et al. 2014). Sedlmayer et al. found that LR rates were < 1% at median follow-up of 6 years after a single dose of 10 Gy IOERT. This was slightly higher in patients with triple negative BC and Grade 3 tumours. Even so, BC was found to be more sensitive to higher single doses of IORT. Boost IORT reduces the time needed for RT while only marginally increasing intraoperative time. It prevents repopulation of tumour cells in the postoperative period by acting on them directly or blocking wound fluid formation and collection which may encourage cell proliferation (Sedlmayer et al. 2017).

Use of IORT as a tumour bed boost has shown promising results. Boost IORT also extends to peripheries of the tumour which are eventually irradiated as part of WBI; as opposed to PBI which carries the risk of under dosage in distant quadrants with tumour burden. Hence, this is applicable in a wider range of situations involving different risk strata (Small et al. 2019) such as lobular cancer which are known to have a higher possibility of multiquadrant involvement. Two ongoing, multicentric boost IORT trials in combination with EBRT are TARGIT-B and HIOB, both of which test the efficacy of IORT boost before the patient receives hypofractionated WBI over 3 weeks (Hochhertz et al. 2023; Stoian et al. 2023).

Clinical trials implementing IORT

Safety and efficacy of IORT in the EBC setting is backed by better cosmetic outcomes, improved survival, and tumour control (Lemanski et al. 2010; Neumaier et al. 2012; Meneveau et al. 2020). The major phase III trials include TARGIT-A (targeted intraoperative radiotherapy) and ELIOT (intraoperative radiotherapy with electrons) where a comparison has been drawn between conventionally used fractionated WBI and IORT as single-dose PBI. However, a few other trials relevant to this modality of treatment (including boost) are also discussed.

The TARGIT group of trials

TARGIT-A randomised trial

TARGIT-A compared standard fractionated whole breast EBRT to risk-adapted RT including single dose low kV IORT ± WBI. Spanning across 11 countries, it involved 33 centres and 3,451 patients from 2000 to 2012. Its non-inferiority statistical design anticipated a 15% chance of adverse pathologic features such as positive excision margins, lobular carcinoma or extensive intraductal component on final pathology resulting in additional WBI after initial

IORT delivered during the definitive surgery. The primary endpoint of the study was in-breast recurrence (IBR) and at the end of five years, TARGIT-IORT was found to be non-inferior to EBRT (0.95% in the standard EBRT arm and 2.11% in the risk adapted RT (TARGIT) arm). This difference of 1.16% was within the predetermined non-inferiority margin of 2.5% (Vaidya et al. 2017, 2020). The chance of a patient remaining alive without a LR or preserving the breast or remaining distant relapse-free or of dying from BC was no different between TARGIT-IORT and EBRT. The Kaplan–Meier curves for the two arms of the trial overlapped for these outcomes. OS was superior by about 4.4% at 12 years with TARGIT-IORT in the patients with grade 1 or 2 cancers (overlapping curves for grade 3 cancers). Prognosis after the rare LR was much worse for patients in the EBRT arm but remained excellent (and unchanged) in the TARGIT-IORT arm of the trial (Vaidya et al. 2021b). Compared to WBI, there were fewer skin related side effects. The TARGIT-IORT also found lower RT related non-breast cancer (cardiovascular, lung problems and other cancers) mortality (Vaidya et al. 2020, 2023). Clinically significant complications such as hematoma, infection, and other grade 3 toxicities were comparable between the two groups and were noted in fewer than 3.3% participants. 2013 follow up results reported nil wound related differences and fewer dermatological toxicities in the IORT group. Cosmetically, IORT outcomes were twice as good as WBI (Corica et al. 2018) However, more scar calcifications and radiography induced fat necrosis (56%) was seen in the IORT arm in a subgroup analysis (Engel et al. 2013). Subsequent studies found no differences between the two groups, in incidences of breast oedema, lymphoedema, hyperpigmentation, or pain. The risk of fibrosis is higher when a boost dose is given; however, overall, there is no difference between the two arms of the trial (Sperk et al. 2012). In another subgroup analysis it was found that persistent pain post RT was less in the IORT group than WBI (Andersen and Flyger 2013).

Cohort (non-randomised) studies of TARGIT-IORT

Numerous centres around the world have published patient series about IORT highlighting its efficacy and safety in treating BC. In 2020, a prospective observational study by Lemanski et al. in France evaluated one-day IORT as the sole radiation treatment for selected BC patients. Among the first 200 patients treated (median age: 68), the LR rate was 2.5%, with 1 and 5-year recurrence-free survival rates of 100% and 95.2%, respectively. At 12 months post-surgery, 86.9% of patients reported excellent satisfaction with IORT, as well as cosmetic results being rated at least good by 89.4% of patients and 97.3% of physicians (Lemanski et al. 2020). A large single centre study in Italy by Vinante et al. explored TARGIT-IORT as a partial breast irradiation (PBI) modality for EBC, demonstrating a 5-years in-breast tumour recurrence rate of 2.4% overall and 3% in the exclusive IORT group. High-grade toxicity events were rare (0.6%), which included cases of skin necrosis, severe fibrosis, and radiation-induced angiosarcoma. This study, therefore, confirmed both the safety and efficacy of TARGIT-IORT, aligning with TARGIT-A trial results and supporting its use as a PBI modality (Vinante et al. 2022). Additionally, a 2021 study from France by Guillerm et al. analysed 191 patients (mean age: 76) wherein IORT led to a 5-year local relapse rate of 1.7% in elderly women with ER + BC. 91% of patients achieved excellent or good cosmetic outcomes (Guillerm et al. 2022). Barbancho et al. also investigated this when studying 42 patients in Spain; 17 of which had used EPBI treatment, and 25 IORT. IORT had a nearly sevenfold lower risk of acute toxicity (OR 6.92, 95% CI 1.30–36.8, $p<0.05$) and an eight-fold lower risk of chronic toxicity (OR 8.25, 95% CI 1.77–38.4, $p<0.01$) compared to EPBI. Alongside this, IORT resulted in fewer symptoms, better quality of life scores, and superior aesthetic outcomes (Isabel et al. 2024). The reviewed studies collectively support the use of IORT as an effective and safe treatment option for EBC.

TARGIT-R was a retrospective registry study in North America involving 19 institutions from 2007 to 2013. 50 kV IORT was applied to 822 participants. They were recruited as per ASTRO 2009 guidelines with median age (67 years) ER positive (91%), HER-2 non amplified (89%), less than 2 cm (90%), grade 1–2 (83%) without lymph-vascular invasion (91%) and sentinel node negative (89%). More than 50% participants had a preoperative breast MRI.110 had prior WBI, 537 had no previous WBI, 115 had boost IORT and 60 had IORT post lumpectomy. The study had a median follow up of 2 years. However, there are major concerns that do not make these results reliable representation of outcome from TARGIT-IORT and these results are the only results that diverge from rest of the worldwide experience. The concerns are that the report only includes follow up of 477 of 935 patients (only 51% follow up is reported). 33% (157/477) patients would have been ineligible for TARGIT-A (lobular/DCIS). 59% did not receive EBRT after positive margins. 30% did not receive proper endocrine therapy (Valente et al. 2016, 2021). Their preliminary results were similar to TARGIT-A when the follow up was much more complete. Majority of the recurrences occurred more than 1 cm from the site of lumpectomy. IORT alone showed 2.4% LR whereas secondary IORT showed 6.6% of them. Patients with IORT boost had LR in 1.8% and 1.7% among those treated in conjunction with WBRT (Valente et al. 2021; Smith and Kuerer 2021).

Other applications of TARGIT-IORT have been in patients who cannot have EBRT because of previous EBRT or other co-morbidities. It has also been used in patients with delayed recurrence in the breast after BCT who prefer to preserve their breasts (Kolberg et al. 2023). The localised nature of RT makes it ideal for women with cosmetic breast implants for whom EBRT can lead to hard and painful capsular contracture (Kolberg et al. 2019).

TARGIT-US nonrandomised prospective cohort study

TARGIT-US is an ongoing single-arm, phase IV registry study following TARGIT-A, recruiting women who would be treated with breast IORT post operatively for EBC. 25 centres in the US are recruiting participants for the trial if they are of age 45 and above with tumours smaller than 3.5 cm that were ER + HER2- and were planning to undergo BCT; with 1500 estimated participants. All recruited patients will receive a single fraction of IORT at 20 Gy dose over 15–40 min from the Intrabeam®, intra-operatively after removal of the tumour. Patients will be treated with additional EBRT without boost if high risk features such as invasive lobular histology or positive nodes are discovered on final pathology (Alvarado et al. 2015). The estimated date for the completion of the trial is 31st December 2026. The follow up period is a minimum of 5 years. The first follow up is at 6 weeks, then 6 monthly for 3 years, followed by annually for two years. The primary endpoint is IBR rates and secondary endpoints include OS, relapse-free survival, toxicity, and morbidity. In case of recurrence, patients will be physically examined followed by biopsy or cytology. Local tumour control will be assessed, and site of relapse will be documented to better understand if it is due to MCF or outside the treated field. Late skin related and other adverse events will be recorded and graded according to NCI-CTCAE v4.0 criteria. All local toxicity and adverse events such as wound infection, delayed wound healing, serum and haematoma will be assessed according to Radiation Therapy Oncology Group (RTOG) (Refaat et al. 2022).

TARGIT-B randomised trial

This ongoing interventional randomised trial focuses on the comparison of outcomes between TARGIT IORT boost and EBRT in EBC. It is a randomised, prospective trial involving 35 centres from 12 countries across the UK, Europe, USA, Asia, Middle East, and S Africa. Many of these centres had actively recruited patients for TARGIT -A trial. The alternate hypothesis is that the targeted IORT boost delivered to the tumour bed as a single dose has better outcomes than the conventional EBRT boost therapy, particularly in cases with higher possibilities of LR post operatively. Centres with access to Intrabeam® and those in line with the local inclusion/exclusion criteria are participating, involving patients with higher chances of IBRs after breast conserving surgery. According to protocol, all patients are to receive WBI (EBRT) and other required adjuvant therapy. The follow up routine is determined to be every 6 months for the first 3 years and then once every year. The primary endpoint is ipsilateral breast recurrence rate while secondary endpoints are site of recurrence, progression free-survival, OS, QoL and patient satisfaction and health economics.

The study that first used TARGIT-IORT in women involved 25 patients (Vaidya et al. 2001, 2002), all of whom subsequently received EBRT at full dose. The phase II study involving 300 patients was updated soon after (Vaidya et al. 2006). The randomised trial aims to recruit 1796 participants (1707 plus 5% more for potential attrition) who were within the parameters of the inclusion criteria: younger than 46 years of age, or older women with either gross nodal involvement, lymphovascular involvement or more than one tumour at the primary site but resectable as a single specimen through BCT. Older women also had to meet one of the following criteria: (i) ER and/or PR-, (ii) lobular histology (iii) Grade III tumour (iv) involved nodes (v) post-neoadjuvant chemotherapy, (vi) any other factor that the team considers makes them unsuitable for TARGIT-IORT as the sole RT; HER2 status may be positive or negative. Other patients who were considered had large tumours that had shrunk in size in response to neoadjuvant chemotherapy (NACT) and were therefore eligible for BCT or those with multiple high-risk factors pointing to a higher chance of recurrence. However, patients diagnosed with bilateral BC or with comorbidities that severely hamper their life expectancy, were not included. Patients with a previous history of malignant disease were included if the relapse free interval at 10 years was expected to be 90% or more. Patients with last BC surgery (not axillary) done in 30 days or less were excluded. The published results of the study are awaited and will combine clinical examination and mammography with or without ultrasound at follow up. The primary and secondary endpoints will be evaluated along with the expenses borne by the patients, the NHS, and social services (Comparison and of Intra-operative Radiotherapy Boost with External Beam Radiotherapy Boost in Early Breast Cancer 2024). An important outcome from the TARGIT-A trial suggested that the high single dose of TARGIT-IORT during lumpectomy may have an abscopal effect, of reducing non-breast cancer deaths and improving OS (Vaidya et al. 2021b; Kolberg et al. 2017a, b, c) and this will be tested in a randomised fashion in the TARGIT-B trial.

The ELIOT randomised trial

The ELIOT trial setting is similar to TARGIT-A except in its use of IOERT, not excluding lobular cancers, and not allowing addition of EBRT post-operatively. It was conducted as a single institution study in the Institute of Oncology, Milan between 2000 and 2007 to compare fractionated EBRT and single dose IOERT. EBRT was delivered as 50 Gy with 10 Gy as boost and IOERT as 21 Gy without WBRT. 1,305 women, between 48 and 75 years of age, were recruited for the study with stage I-II invasive BC up to 2.5 cm size. The study had a predetermined margin of 7.5% for LR. Statistical design was an equivalence endpoint. Most participants had low risk tumours, ER + (90%), HER2-(97%) and negative nodes (74%) (Orecchia et al. 2003). OS between the EBRT group and the IOERT group showed a marginal difference (96.8% and 96.9% respectively, $p = 0.59$). IBR was found to be low in both groups (0.4% and 4.4% respectively), within the pre-specified margin ($p < 0.0001$). Side effects such as pain, breast fibrosis and retraction were comparable between the two groups with slightly higher incidences of fat necrosis in patients who underwent IOERT. However, skin toxicity, dryness, pruritus, and erythema occurred less in those receiving IOERT compared to WBRT ($p < 0.04$). A subgroup analysis involving 119 patients from the IOERT arm, at 6 years follow up showed very good cosmetic outcome and 32% had grade 2 fibrosis. Grade 3 fibrosis was noted in 6% (Orecchia et al. 2021). Similar outcomes were noted in a subgroup analysis study comprising of 71 patients. Fewer cosmetic changes were noted in the irradiated breast as compared to the untreated breast including, breast contour, breast overlap and relative breast area (Struikmans et al. 2016). The study reflected higher chances of LR in patients with tumour grade III or IV and size > 2 cm, positive nodes and triple negative histology. While the outcomes were similar to TARGIT-A, higher recurrences were documented compared to WBI with ELIOT and authors and others discuss the potential reasons for this in the discussion section and correspondence (Orecchia et al. 2003; Vaidya et al. 2021c) (Fig. 3).

The BIO-boost ISIORT europe pooled analysis

This was a retrospective analysis put together to understand the evidence available in trials involving boost IORT with electrons. This study was put together by seven institutions from various nations to evaluate long term outcomes. 10 Gy IOERT dose prior to WBI with 50–54 Gy was implemented. Most patients had prognostic factors for LR. In the 6-year follow up, only 16 in-breast recurrences were noted, and the tumour control rate was placed at 99.2%. Grade 3 tumour was found to be predictive of recurrence ($p = 0.031$) in a multivariate analysis. A similar univariate trend was observed in younger patients and those with negative hormonal status. WBI was administered at different times with a delay following IOERT and it was not found to be influencing LR. Retrospective matched-pair pooled analysis for the first 190 patients from Salzburg IOERT who received 10 Gy were compared to those that received 6 × 2 Gy as external e-boost and the 10-year follow up found LR to be 1.6% and 7.2% respectively. This was clearly indicative of the impact of IOERT on LR. The conclusion overall, was in favour of boost IOERT (Harris and Small 2017; Sedlmayer et al. 2007).

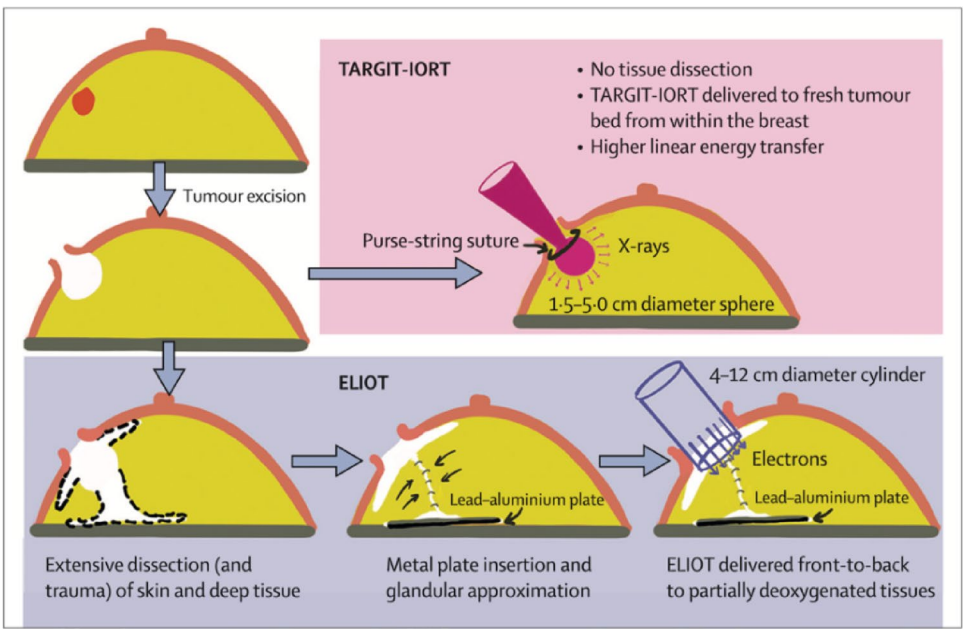


Fig. 3 Comparison of radiation delivery to tumour site in TARGIT-IORT and ELIOT (Vaidya et al. 2021d)

The HIOB trial

This ongoing prospective, multicentre, single arm non-randomised trial, started in 2011, was designed to deliver boost IOERT prior to hypo-fractionated WBI of 15 × 2.7 Gy per fraction, with 5 fractions per week (total dose 40 Gy) in EBC. It was set up primarily in an attempt to reduce the overall treatment duration without hampering local control rates. This was similar to a phase II design tested by the Milano group using short-term WBRT following IOERT. The primary endpoint of this trial is the proof of a superior new treatment regimen, i.e., outcomes that go below the lower limit of the estimated 5-year LR rate within respective age groups.

1464 women, above 35 years of age, consented to participate. They had histologically diagnosed invasive BC, with a T1-2, N0-1 stage, and G1-3 grade. Women with multifocal disease within the same quadrant at a distance of 5 cm or less, with a certain degree of freedom of surgical margins (R0) were also included, irrespective of their HER2 and hormonal receptor status. The timeline for therapy was determined to be day 36 to 56 post operatively and a gap of up to 9 months is allowed between IOERT and WBRT. Tumour related endpoints mainly involved annual in-breast recurrence surveillance and disease-free survival, but also emphasised on toxicity and cosmetic outcomes. The effectiveness of a combined regimen as opposed to the conventional RT is the hypothesis being tested. The results are to be compared to the best published results in gold standard RT, usually implying fractionated WBRT with 50 Gy (25 × 2) and an external tumour bed boost with 10–16 Gy electrons (5–8 × 2). No complications were noted perioperatively. At 4 weeks post WBI, mild to moderate erythema was noted in about 300 patients. Acute toxicity was assessed using the CTC toxicity scoring system. Using the LENT-SOMA scoring, late reactions were seen to occur in a mean frequency of 97% at 4–5 month follow up, 96% at 1 year, 98% at 2 years and 96% at 3 years. Cosmetic outcomes were evaluated by both doctors and patients. Subjective and objective outcomes were sufficient (good/excellent) at 69% (subjective) and 74% (objective). The assessment was done using the van Limbergen Scoring System. At the 12.6-month median follow-up, no in-breast recurrences were observed, metastasis occurred in 3 patients and two patients died. The overall findings point towards excellent results with minimal acute reactions and insignificant late reactions so far. In the short-term evaluation, cosmetic outcomes are satisfactory as well. The primary end point, LR at 5 years, is being assessed using the Sequential Probability Ratio test (Fastner et al. 2020, 2022; Boost et al. 2024).

Real world evidence using IORT

Besides the large multicentre trials leading up to international guidelines on recommendations for IORT (covered in next section), multiple simultaneous studies allowed retrospective evaluation. A list of worldwide publications related to TARGIT-IORT is available at https://targit.org.uk/publications. Ciabattoni et al.'s single centre experience of 245 patients over five years proved that IOERT was more beneficial than EBRT in local control of BC (Ciabattoni et al. 2021). Seol et al. compared outcomes of patients receiving IORT versus EBRT, between various hospitals within a singular health system. They showed a decrease in LR rates for BC in patients receiving IORT, as compared to those in the observation group. However, in this instance, IORT was not as effective as EBRT (Chen et al. 2022). Tang et al. studied preference of IORT in early endocrine responsive BC in patients ≥ 65 years. Out of their 63 patients, 74.6% chose IORT over other options such as WBRT, despite inadequate survival benefit data. This was indicative of the convenience of radiation delivery being a patient priority (Tang et al. 2021). Another study by the same group concluded that in a clinical setting, patients who were offered IORT had higher IBTR rate than in TARGIT-A. This led to changes in institutional protocol and recommendation of additional adjuvant RT or endocrine therapy as per the TARGIT-A criteria (Tang et al. 2023). Notably, in TARGIT-A, patients with TARGIT-IORT as the sole RT, had the same level of local control as those who received TARGIT-IORT as tumour bed boost or those who had whole breast EBRT.

Abo-Madyan et al. reported from a single centre long term follow up that the use of IORT was found to have lower LRs (Abo-Madyan et al. 2019). This was supported by Mosiun et al. who drew similar conclusions in both low-risk and high-risk EBC (Mosiun et al. 2023). Martinez et al. found lower rates of RT related toxicities and post-operative complications. 34.4% were given further fractions of EBRT due to close margins, with no significant difference in LR or OS (Martinez et al. 2023). Another study by Stefanelli et al. confirmed the benefits of IOERT in a select group of patients concluding that a thorough screening process is essential to maximise beneficial outcomes (Stefanelli et al. 2023). An added advantage of IORT is the improved quality of life, as reported by Omosule et al. (Omosule et al. 2023) (Table 3).

IORT in international guidelines

It is important to note that according to the 2025 ASTRO clinical practice guidelines, IORT is no longer recommended outside of clinical trials or multiinstitutional registry. stating increased concerns about higher rates of IBR

Table 3 International Guidelines regarding eligibility criteria for IORT treatment modality in Early Breast Cancer (Correa et al. 2017; Wenz 2017; Shah et al. 2018; Schäfer et al. 2018; Budrukkar et al. 2020; Liedtke et al. 2018; Eraso et al. 2023)

Criteria	Nice 2018 (TARGIT-IORT)	ABS (2018)	ASBrS (2018)	ASTRO (2017, 2023)	AGO (2017)	GEC-ESTRO (2020)	ESMO/ESO	EUSOMA-SIOG (2021)	MSAC—Australia	SPAIN 2023
AGE	As per multidisciplinary team decision	≥45 years	≥45 years for all tumour types	≥50 years 40–49 years if all other criteria met	>50 years	≥50 years	≥50 years	≥50 years	≥45 years	>60 years >50 years if post-menopausal with other criteria
HISTOLOGY	As per multidisciplinary team decision	All invasive subtypes and DCIS	All invasive subtypes DCIS	All invasive subtypes and Pure DCIS	non-lobular, non-extensive DCIS	DCIS	Non-lobular subtypes Low grade DCIS	Invasive subtypes	Primary invasive ductal carcinoma	Invasive ductal carcinoma or favourable histological subtypes
TUMOUR SIZE	As per multidisciplinary team decision	≤3 cm	≤3 cm	≤3 cm		≤2 cm		≤3 cm	≤3 cm	≤2.5 cm
STAGE	As per multidisciplinary team decision	Tis, T1, T2	Tis, T1, T2 (≤3 cm)	Tis, T1, T2	pT1 pN0 R0	T1, T2 (≤2 cm)	T1, T2	T1, T2 (≤3 cm)	T1, T2	T1, T2 (≤2.5 cm)
MARGIN	As per multidisciplinary team decision	NA	NA	NA	NA	NA	Negative	≥1 mm radial margin	NA	Clear margins
NODAL STAGE	As per multidisciplinary team decision	Negative	Negative	Negative	Negative	≤4 nodes	Negative	Negative	Negative	Negative
Hormonal status	As per multidisciplinary team decision	NA	NA	ER positive, HER2 non-amplified	HR positive	Non triple negative status	NA	HR positive, HER2neu negative	ER positive	Positive hormone receptor
LVI	As per multidisciplinary team decision	NA	NA	Positive	NA	Positive	Negative	NA	Nil	Negative
Histologic Grade	As per multidisciplinary team decision	NA	NA	1–2	NA	1–3	NA	1–2	1–2	NA

compared to other APBI or WBI, survival after local recurrence, as well as late toxicities and urges a conservative approach to alternatives to WBI. Further prospective studies in their patient population have been recommended to support IORT (American Society for Radiation Oncology, American Society of Clinical Oncology, Society of Surgical Oncology 2025) In contrast to their American counterpart, ESTRO 2025 has published favourable data, analysing the current clinical practice schemes over the last 10 years as part of the GEC-ESTRO guidelines. The low rates of late toxicities, excellent local-control and survival outcomes indicate a turning point for IORT as a treatment modality. A comparison between the two was drawn by the ISIORT working group which called for a nuanced and balanced perspective to preserve a convenient and beneficial treatment option for the selected patient populations (Fastner et al. 2025).

Comparison of outcomes (IORT vs. WBI)

WBI and APBI in the form of EBRT and MIB, have minimal differences with regard to OS, disease free survival and local control (Veronesi et al. 2002; Strnad et al. 2016). Trials concerning IORT suggest favourable outcomes, in terms of LRs, OS, QoL, complications due to therapy and logistical aspects.

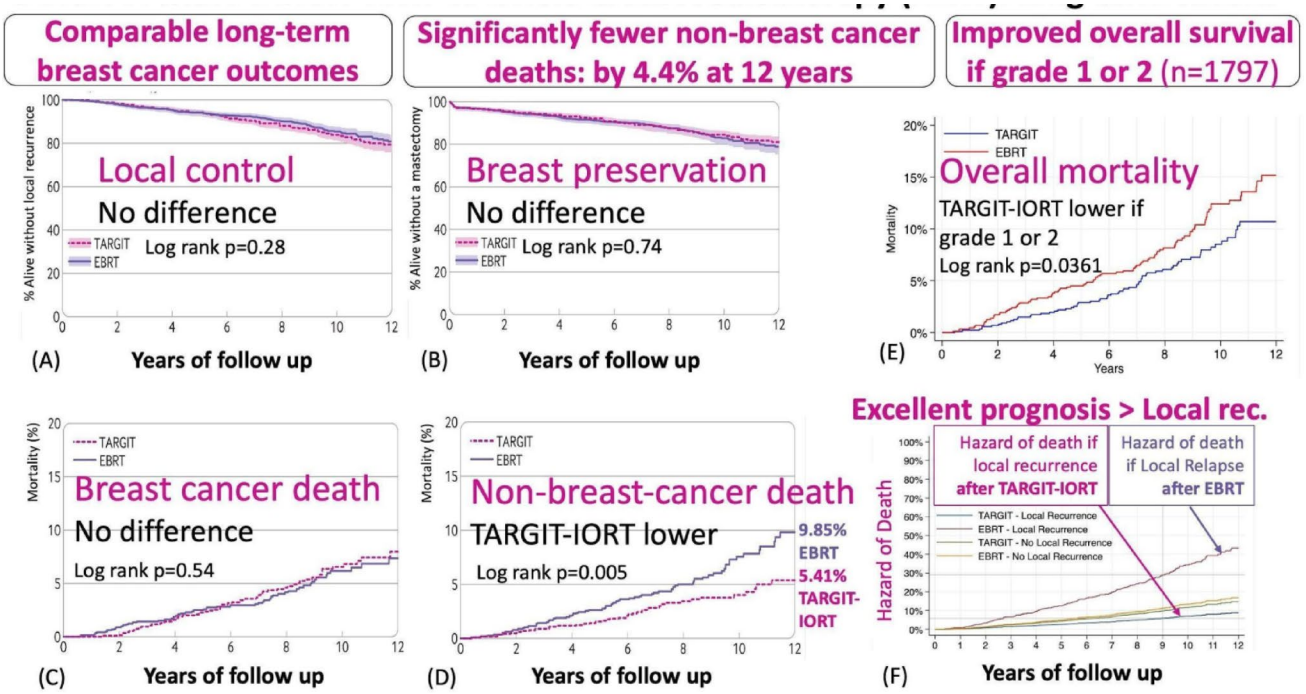


Fig. 4 Representation of the long-term results of the TARGIT-A Trial: TARGIT-IORT vs EBRT (**a**–**f**) (Vaidya 2023).

Complications

Owing to the lower amount of total dose received by the whole breast, cosmetic outcomes were favourable in > 90% of the patients undergoing IORT (Kraus-Tiefenbacher et al. 2006). Better cosmetic outcomes and lower rate of wound-related complications were observed at follow-up periods of 1 month, 6 months and 12 months (Ciabattoni et al. 2021). Grade 3 and 4 RT-related complications were also found to be lower in cohorts receiving IORT, as compared to whole breast radiation (Vaidya et al. 2014). Notable among these was RT associated angiosarcoma (RAAS) seen as a late complication in the radiation field, whose incidence was naturally much lower with IORT as compared to EBRT.

Survival outcomes

The long-term outcomes of the randomised TARGIT-A trial provided evidence that the local control rate was comparable between IORT and EBRT (Calvo et al. 2013). Compared with EBRT, TARGIT-IORT demonstrated overall fewer deaths from cardiovascular causes, lung problems and other cancers leading to improved OS in the large subgroup patients with grade 1 and 2 cancers with no detriment in grade 3 cancers. Adapting the trial to include the risk of recurrence, the original cohort of patients were assessed for LR, and difference in TARGIT-IORT and EBRT was minimal (Rate of risk was 2.11% and 0.95% respectively) (Vaidya et al. 2014). A retrospective observational study conducted by Lei et al., using data from 18 population-based registries, compared EBRT with IORT. The study demonstrated no significant difference in the OS of both cohorts. It also reported no significant difference in cancer-specific survival between the patients who received EBRT and those who received IORT (Small et al. 2022). He et al. in a recent meta-analysis revealed that there was no significant difference in the average 5-year OS in patients receiving EBRT (94.9%) and IORT (94.1%) (He et al. 2021).

With the advent of radical surgical techniques and RT to manage BC, there's been a decrease in overall mortality due to BC. Vaidya et al.'s meta-analysis concluded that the overall mortality rate in patients receiving partial breast radiation was 25% lower than those receiving WBI (Vaidya et al. 2016). A non-randomised study of SEER data of over 3200 patients suggested that patient who received IORT had higher survival compared with those who had no RT ($p = 0.028$) (Mi et al. 2022). Specific studies in IORT revealed that the OS rate at 5 years was similar in patients receiving EBRT and IORT (Small et al. 2022; Vaidya et al. 2014). There were significantly lesser non-breast cancer related deaths among patients receiving IORT. This was attributed to the lower risk of cardiovascular toxicity and toxicity from radiation induced cancers of nearby oesophagus and lung, due to RT, due to restriction of the site of radiation delivery to the tumour bed (Vaidya et al. 2014) (Fig. 4).

Local recurrence

Satisfactory local control of BC, and prevention of LR is of utmost importance in all the surgical and RT technique. The principle behind partial breast irradiation, is to achieve non-inferiority, to ensure that survival is not jeopardised, and potentially reduce toxicity and improve quality of life. At 5-year follow-up, the risk of LR with TARGIT was non-inferior to EBRT when all patients were analysed together. However, analysis of two subsets of patients according to timing of delivery of TARGIT demonstrated that TARGIT being delivered at the time of lumpectomy was comparable to EBRT as against delayed-TARGIT given afterward by reopening the surgical wound. The local-recurrence free survival, mastectomy-free survival, distant-disease free survival and OS were not different between the two randomised arms (Vaidya et al. 2020).

Quality of life

The quality of life of patients is increasingly gaining in importance as one of the endpoints of trials and studies in IORT, given the role it plays in decisions made regarding treatment. This is an important consideration for both patients and healthcare professionals. In a survey among health professionals in Australia by Corica et al., they found that in a hypothetical setting, most were willing to replace EBRT with IORT. The survey had consistent outcomes at two different points in time, spanning 7 years and for varying degrees of risk (Corica et al. 2018).

In a patient survey spanning ten years conducted by Alvarado et al., it was found that when faced with WBRT or IORT as therapeutic options, patients preferred IORT with a median increase in risk of 2.3% of LR. Over 90% patients would accept IORT over WBRT with similar or slightly higher risks (Alvarado et al. 2014). Welzel et al. conducted a subgroup study among German participants of the TARGIT-A trial using BR23 and EORTC QLQ-C30 and found that the IORT group had improved overall functioning and significantly less breast or arm symptoms and generalised pain (Welzel et al. 2013).

Cosmetic outcomes

Clinical and patient testimonials exhibit that IORT can provide better cosmetic outcomes than EBRT without compromising the recurrence rate at 5 years (Corica et al. 2016). Reports done on patient accounts of cosmesis and breast related QoL were looked into by Corica et al. Participants who received TARGIT-IORT showed that Excellent-Good cosmetic results were more frequent than Fair-Poor results in both groups, and patients who received TARGIT-IORT reported better breast-related QOL than EBRT patients. Moreover, significant differences in QOL were observed at 6 months and 1 year, with EBRT patients experiencing moderately worse breast symptoms (Corica et al. 2016). A clinical trial by Keshtgar et al. used an objective tool to evaluate cosmetic outcomes; this was done through the use of digital photographs taken at baseline and annually for up to 5 years. These photos were then analysed with BCCT core software for symmetry, colour, and scarring. There were 342 patients included in this trial, with the photos being classified as either Excellent/Good (EG) or Fair/Poor (FP). TARGIT patients had significantly higher odds of EG outcomes than EBRT patients at year 1 (OR 2.07) and year 2 (OR 2.11), demonstrating TARGIT's superior cosmetic results (Keshtgar et al. 2013). This demonstrates TARGIT's superior cosmetic results, supporting its use over conventional EBRT for better aesthetic outcomes.

Cost effectiveness of IORT

Recent studies have examined the cost-effectiveness of BC RT techniques, highlighting the potential benefits and savings associated with TARGIT-IORT. Using the Markov model for cost-utility analysis, Vaidya et al. showed that TARGIT-IORT was less costly (£12,455 vs. £13,280) and produced higher quality-adjusted life-years (QALYs) (8.15 vs. 7.97) over a 10-year period than EBRT (Vaidya et al. 2017). Alvarado et al. observed that single-dose IORT yielded lower costs and higher QALYs versus a 6-week course of WB-EBRT, with average cost savings of $5,191 (Alvarado et al. 2013). Eisavi et al.'s systematic review compared cost-effectiveness of IORT vs EBRT in EBC. The cost-effectiveness variables included: treatment costs, health state utilities, local and distant recurrence rates, probabilities of metastasis, recurrent cancer, and death for both IORT and EBRT. Of the 1155 identified studies, only eight met the inclusion criteria, with 4 studies favouring IORT and 3 favouring EBRT as cost-effective (Eisavi et al. 2020). Moloney et al.'s UK-based cost-effectiveness analysis found that using the INTRABEAM device for IORT in BC surgery resulted in significant cost reductions (£4,821 vs. £9,404) and QALY gains (14.61 vs. 14.08) when compared to WB-EBRT. Additionally, the INTRABEAM device dominated WB-EBRT over a lifetime—showing a cost reduction of £4,583 and a QALY increase of 0.53 (Moloney et al. 2023). TARGIT-IORT shows significant promise as a cost-effective alternative to traditional EBRT for EBC treatment. These findings support its wider implementation, providing an especially compelling case for its inclusion into real world clinical practice and health policy.

Future of IORT in early breast cancer

IORT changes the composition of cytokines within the wound fluid, which exerts an anti-tumorigenic effect including anti chemotactic, reduced invasiveness, motility and proliferation activity (Wuhrer et al. 2021; Belletti et al. 2008) These effects are over and above the conventionally known direct tumoricidal effect of RT.

Besides the impact of IORT on EBC, this modality has several additional benefits. Bargallo-Rocha et al.'s Mexican experience concluded that on optimisation of IORT, up to 12% cost reduction could be achieved for patients, making breast conserving options more accessible to patients in resource-limited countries. Similar studies establish the preference of IORT over other modes of RT by patients for multiple reasons. Besides cost effectiveness, it also reduces the number of trips to the hospital, in turn reducing time spent there post operatively. TARGIT-IORT has long term follow up data (8.6 median and 19 years maximum follow up) and has the largest patient-years follow up and promising results seen in the initial publications (12, 111) have been confirmed in terms of logistic benefit, therapeutic gain, comparable breast survival and reduced non-breast cancer mortality, in a selected EBC landscape. It is already a standard modality for treating EBC in over 250 centres globally and is estimated that its use would cause 2000 fewer non-breast cancer related deaths. It has been incorporated in multiple international guidelines and proved useful in light of the rec1ent pandemic by minimising hospital exposure (Vaidya et al. 2022). A UK study estimated that if TARGIT IORT were to become the standard treatment for EBC in eligible patients, it could save 1200 tonnes of CO2 emissions, and nearly 5 million miles of travelling (Coombs et al. 2016).

The current NICE guidelines followed by the NHS in the UK continue to advocate for EBRT (40 Gray in 15 fractions) as the standard modality for adjuvant RT to chest wall with or without nodal regions with or without tumour bed boost by electrons or brachytherapy (Institute and for Health and Care Excellence 2024) and recommends use of TARGIT-IORT in centres that have the equipment and expertise (Guideline TA501, 31 Jan 2018). They are currently in the process of updating the 2018 guidelines in view of the robust long-term results of the TARGIT-A trial. IORT is being increasingly recognised by international guidelines along with its growing popularity among clinicians worldwide. To conclude, health policy makers and related stakeholders may be advised to consider ensuring adequate funds and resources for setting up IORT operating theatres in cancer centres, in view of its substantial benefit to patients in terms of length and quality of life in a cost-effective manner.

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Declarations

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References

Vicini FA, Cecchini RS, White JR, Arthur DW, Julian TB, Rabinovitch RA, Kuske RR, Ganz PA, Parda DS, Scheier MF, Winter KA (2019) Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 394(10215):2155–2164

Tobias JS, Vaidya JS, Keshtgar M, D'Souza DP, Baum M (2004) Reducing radiotherapy dose in early breast cancer: the concept of conformal intraoperative brachytherapy. Br J Radiol 77:279–284

Vaidya J, Tobias J, Baum M, Keshtgar M, Joseph D, Wenz F et al (2004) Intraoperative radiotherapy for breast cancer. Lancet Oncol 5:165–173

Vaidya J, Tobias J, Baum M, Wenz F, Kraus-Tiefenbacher U, D'Souza D et al (2005) TARGeted intraoperative radioTherapy (TARGIT): an innovative approach to partial-breast irradiation. Semin Radiat Oncol 15:84–91

Nag S, Willett CG, Gunderson LL, Harrison LB, Calvo FA, Biggs P (2011) IORT with electron-beam, high-dose-rate brachytherapy or low-kV/electronic brachytherapy: methodological comparisons. Intraoperative irradiation: techniques and results. Humana Press, Totowa, NJ, pp 99–115

Coombs NJ, Coombs JM, Vaidya UJ, Singer J, Bulsara M, Tobias JS et al (2016) Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. BMJ Open 6:e010703

Calvo FA, Sole CV, Herranz R, Lopez-Bote M, Pascau J, Santos A, Muñoz-Calero A, Ferrer C, Garcia-Sabrido JL (2013) Intraoperative radiotherapy with electrons: fundamentals, results, and innovation. Ecancermedicalscience 7:339

Drew PJ, Turnbull LW, Kerin MJ, Carleton PJ, Fox JN (1997) Multicentricity and recurrence of breast cancer. Lancet 349(9046):208–209

Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M (2010) Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 376(9735):91–102

Njeh CF, Saunders MW, Langton CM (2010) Accelerated partial breast irradiation (APBI): a review of available techniques. Radiat Oncol 5:1–28

Ghose A, Stanway S, Sirohi B, Mutebi M, Adomah S (2024) Advanced breast cancer care: the current situation and global disparities. Semin Oncol Nurs 40(1):151551

SEER Program, National Cancer Institute, 2004–2019

Fastner G, Reitsamer R, Urbański B, Kopp P, Murawa D, Adamczyk B, Karzcewska A, Milecki P, Hager E, Reiland J, Ciabattoni A (2020) Toxicity and cosmetic outcome after hypofractionated whole breast irradiation and boost-IOERT in early stage breast cancer (HIOB): first results of a prospective multicenter trial (NCT01343459). Radiother Oncol 1(146):136–142

Brunt AM, Cafferty F, Wheatley DA, Patel J, Sydenham MA, Kirby AM, Coles CE, Poole K, Fleming H, Alhasso A, Bloomfield DJ, Chan C, Churn M, Cleator S, Goodman A, Griffin C, Haviland JS, Kirwan CC, Nabi Z, Sawyer E, Somaiah N, Syndikus I, Yarnold JR, Bliss JM (2024) Hypofractionated breast radiotherapy for 1 week vs 3 weeks: 10-year efficacy and late normal tissue effects in the FAST-Forward randomised trial. Radiother Oncol

Cancer Research UK. Breast cancer mortality statistics [Internet]. Cancer research UK. CRUK; 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality#heading-Two

Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, Gallus G, Greco M, Luini A, Marubini E, Muscolino G (1981) Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 305(1):6–11

Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I (1996) Multicentricity of breast cancer: whole-organ analysis and clinical implications. Br J Cancer 74:820–824

Baum M, Vaidya JS, Mittra I (1997) Multicentricity and recurrence of breast cancer. Lancet 349:208

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347(16):1233–1241

Vaidya JS, Bulsara M, Baum M, Alvarado M, Bernstein M, Massarut S et al (2021a) Intraoperative radiotherapy for breast cancer: powerful evidence to change practice. Nat Rev Clin Oncol 18(3):187–188

Corica T, Nowak AK, Saunders CM, Bulsara M, Taylor M, Vaidya JS et al (2016) Cosmesis and breast-related quality of life outcomes after intraoperative radiation therapy for early breast cancer: a substudy of the TARGIT-A trial. Int J Radiat Oncol Biol Phys 96:55–64

Welzel G, Boch A, Sperk E, Hofmann F, Kraus-Tiefenbacher U, Gerhardt A et al (2013) 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 8:9

Corica T, Joseph D, Saunders C, Bulsara M, Nowak AK (2014) Intraoperative radiotherapy for early breast cancer: Do health professionals choose convenience or risk? Radiat Oncol 9:33

Alvarado MD, Conolly J, Park C, Sakata T, Mohan AJ, Harrison BL et al (2014) Patient preferences regardingintraoperative versus external beam radiotherapy following breast-conserving surgery. Breast Cancer Res Treat 143:135–140

Tang A, Cohan CM, Beattie G, Cureton EL, Svahn JD, Lyon LL et al (2021) Patients older 65 years withearly breast cancer prefer intraoperative radiation as a locoregional treatment choice. Ann Surg Oncol 28:5158–5163

Bagga S, Swiderska N, Hooker C, Royle J, Oconnor ME, Freeney S et al (2023) Qualitative exploration of patients' experiences with Intrabeam TARGeted intraoperative radiotherapy (TARGIT-IORT) and external-beam radiotherapy treatment (EBRT) for breast cancer. BMJ Open. https://doi.org/10.1101/2023.09.14.23295478

Small W Jr, Thomas TO (eds) (2019) Intraoperative radiotherapy (IORT)–a new frontier for personalized medicine as adjuvant treatment and treatment of locally recurrent advanced malignancy. Frontiers Media SA, Lausanne

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 (2013) 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 14(11):1086–1094

Krug D, Baumann R, Combs SE, Duma MN, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD (2021) Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: considerations regarding FAST and FAST-Forward. Strahlenther Onkol 197:269–280

RCR Publications Postoperative Radiotherapy for Breast Cancer UK Consensus Statements November 2016

Vaidya JS, Bulsara M, Wenz F, Tobias JS, Joseph D, Baum M (2018) Targeted radiotherapy for early breast cancer. Lancet 391:26–27

Meattini I, Marrazzo L, Saieva C, Desideri I, Scotti V, Simontacchi G, Bonomo P, Greto D, Mangoni M, Scoccianti S, Lucidi S (2020) Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. J Clin Oncol 38(35):4175–4183

Marrazzo L, Meattini I, Simontacchi G, Livi L, Pallotta S (2023Jan 1) Updates on the APBI-IMRT-Florence Trial (NCT02104895) technique: from the intensity modulated radiation therapy trial to the volumetric modulated arc therapy clinical practice. Pract Radiat Oncol 13(1):e28-34

Xiang X, Ding Z, Feng L, Li N (2021) A meta-analysis of the efficacy and safety of accelerated partial breast irradiation versus whole-breast irradiation for early-stage breast cancer. Radiat Oncol 16:1–2

Ooi KH, Koh WY, Ho F, Tseng MS, Tan TH, Koh V, Leong YH, Chia D, Tey J, Soon YY (2021) Efficacy and safety of adjuvant breast radiation therapy for patients with early-stage breast cancer: a systematic review and network meta-analysis. Int J Radiat Oncol Biol Phys 111(3):e208

Shumway DA, Corbin KS, Farah MH, Viola KE, Nayfeh T, Saadi S, Shah V, Hasan B, Shah S, Mohammed K, Riaz IB (2023) Partial breast irradiation compared with whole breast irradiation: a systematic review and meta-analysis. JNCI J Natl Cancer Inst 115(9):1011–1019

Wujanto C, Lee CC, Meng T, Ooi KH, Tan TH, Koh WY, Tseng MS, Koh V, Yeoh T, Leong YH, Chia D (2023) Adjuvant breast radiation therapy for early-stage breast cancer or ductal carcinoma

in-situ in the breast: a systematic review and network meta-analysis of randomized trials. Int J Radiat Oncol Biol Phys 117(2):e214
Vicini FA, Kestin LL, Goldstein NS (2004) Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: a pathologic analysis. Int J Radiat Oncol Biol Phys 60(3):722–730
Pérez M, Schootman M, Hall LE, Jeffe DB (2017) Accelerated partial breast irradiation compared with whole breast radiation therapy: a breast cancer cohort study measuring change in radiation side-effects severity and quality of life. Breast Cancer Res Treat 162:329–342
Whelan TJ, Julian JA, Berrang TS, Kim DH, Germain I, Nichol AM, Akra M, Lavertu S, Germain F, Fyles A, Trotter T (2019) External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 394(10215):2165–2172
de Souzae Silva AR, Yoshimoto FH, da Silva JL, de Brito LH, Hanna SA (2023) Principles of radiation oncology. inoncodermatology: an evidence-based, multidisciplinary approach to best practices. Springer, Cham, pp 203–223
Marthinsen AB, Gisetstad R, Danielsen S, Frengen J, Strickert T, Lundgren S (2010) Relative biological effectiveness of photon energies used in brachytherapy and intraoperative radiotherapy techniques for two breast cancer cell lines. Acta Oncol 49(8):1261–1268
Harris EE, Small W Jr (2017) Intraoperative radiotherapy for breast cancer. Front Oncol 22(7):317
Hensley FW (2017) Present state and issues in IORT physics. Radiat Oncol 12(1):1–30
Intra M, Luini A, Gatti G, Ciocca M, Gentilini OD, Viana AA, Chagas EM, Berrettini A, Schuh F, Scarpa D, Orecchia R (2006) Surgical technique of intraoperative radiation therapy with electrons (ELIOT) in breast cancer: a lesson learned by over 1000 procedures. Surgery 140(3):467–471
Watson PG (2019) Dosimetry of a miniature x-ray source used in intraoperative radiation therapy. McGill University, Montreal
Fastner G, Sedlmayer F, Merz F, Deutschmann H, Reitsamer R, Menzel C, Stierle C, Farmini A, Fischer T, Ciabattoni A, Mirri A (2013) IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: long term results of an ISIORT pooled analysis. Radiother Oncol 108(2):279–286
Baghani HR, Aghamiri SM, Mahdavi SR, Akbari ME, Mirzaei HR (2015) Comparing the dosimetric characteristics of the electron beam from dedicated intraoperative and conventional radiotherapy accelerators. J Appl Clin Med Phys 16(2):62–72
Biggs P, Willett CG, Rutten H, Ciocca M, Gunderson LL, Calvo FA (2011) Intraoperative electron beam irradiation: physics and techniques. Intraoperative irradiation techniques and results. Humana Press, Totowa, NJ, pp 51–72
Mourtada F (2016) Physics of intraoperative radiotherapy for the breast. Short course breast radiotherapy: a comprehensive review of hypofractionation, partial breast, and intra-operative irradiation. Springer, Cham, pp 317–325
Herskind C, Wenz F (2014) Radiobiological aspects of intraoperative tumour-bed irradiation with low-energy x-rays (LEX-IORT). Transl Cancer Res 3(1)
Chand-Fouché ME, Colnard C, Gal J, Kee DL, Dejean C, Gautier M, Feuillade J, Mana A, Fouché Y, Delpech Y, Dejode M (2023) Feasibility and early toxicity of intraoperative radiotherapy for breast cancer using the papillon+ system: first results. Clin Transl Radiat Oncol 1(38):47–52
Small W Jr, Refaat T, Feldman SM, Holmes D (2022) Risk-stratified intraoperative radiation therapy as a definitive adjuvant radiation therapy modality for women with early breast cancer. Pract Radiat Oncol 12(4):320–323
Chen Q, Qu L, He Y, Xu J, Deng Y, Zhou Q, Yi W (2022) Prognosis comparison between intraoperative radiotherapy and whole-breast external beam radiotherapy for T1–2 stage breast cancer without lymph node metastasis treated with breast-conserving surgery: a case–control study after propensity score matching. Front Med 3(9):919406
Vaidya JS, Baum M, Tobias JS, Massarut S, Wenz F, Murphy O et al (2006) Targeted intraoperative radiotherapy (TARGIT) yields very low recurrence rates when given as a boost. Int J Radiat Oncol Biol Phys 66:1335–1338
Tom MC, Joshi N, Vicini F, Chang AJ, Hong TS, Showalter TN, Chao ST, Wolden S, Wu AJ, Martin D, Husain Z (2019) The American brachytherapy society consensus statement on intraoperative radiation therapy. Brachytherapy 18(3):242–257
Sedlmayer F, Reitsamer R, Wenz F, Sperk E, Fussl C, Kaiser J, Ziegler I, Zehentmayr F, Deutschmann H, Kopp P, Fastner G (2017) Intraoperative radiotherapy (IORT) as boost in breast cancer. Radiat Oncol 12(1):1–7
Sedlmayer F, Reitsamer R, Fussl C, Ziegler I, Zehentmayr F, Deutschmann H, Kopp P, Fastner G (2014) Boost IORT in breast cancer: body of evidence. Int J Breast Cancer 1:2014
Kametriser G, Kopp M, Vaszi A, Anderhuber K, Dagn K, Gynegology S, Reitsamer R, Glück S, Wilhelm C. HIOB
Harris EJ, Mukesh M, Jena R, Baker A, Bartelink H, Brooks C, Dean J, Donovan EM, Collette S, Eagle S, Fenwick JD (2014) Efficacy and mechanism evaluation. NIHR Journals Library, Southampton
Hochhertz F, Hass P, Röllich B, Ochel HJ, Gawish A (2023Aug) A single-institution retrospective analysis of intraoperative radiation boost during breast-conservation treatment for breast cancer. J Cancer Res Clin Oncol 149(9):5743–5749
Stoian R, Exner JP, Gainey M, Erbes T, Gkika E, Popp I, Spohn SK, Krug D, Juhasz-Böss I, Grosu AL, Sprave T (2023) Comparison of intraoperative radiotherapy as a boost vs simultaneously integrated boosts after breast-conserving therapy for breast cancer. Front Oncol 13:1210879
Lemanski C, Azria D, Gourgon-Bourgade S, Gutowski M, Rouanet P, Saint-Aubert B, Ailleres N, Fenoglietto P, Dubois JB (2010) Intraoperative radiotherapy in early-stage breast cancer: results of the montpellier phase II trial. Int J Radiat Oncol Biol Phys 76(3):698–703
Neumaier C, Elena S, Grit W, Yasser AM, Uta KT, Anke K, Axel G, Marc S, Frederik W (2012Dec) TARGIT-E (lderly)—prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer. BMC Cancer 12(1):1–7
Meneveau MO, Petroni GR, Varhegyi NE, Hulse JC, Schroen AT, Brenin DR, Janowski EM, Berger AC, Lazar MA, Simone NL, Showalter TN (2020Sep 1) Toxicity and cosmetic outcomes after treatment with a novel form of breast IORT. Brachytherapy 19(5):679–684
Vaidya A, Vaidya P, Both B, Brew-Graves C, Bulsara M, Vaidya JS (2017Aug 1) Health economics of targeted intraoperative radiotherapy (TARGIT-IORT) for early breast cancer: a cost-effectiveness analysis in the United Kingdom. BMJ Open 7(8):e014944
Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, Alvarado M, Douek M, Saunders C, Flyger HL, Eiermann W (2020 Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ 19:370
Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S et al (2021b) New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer. Br J Cancer 125:380–389
Vaidya JS, Bulsara M, Wenz F, Sperk E, Massarut S, Alvarado M, Williams NR, Brew-Graves C, Bernstein M, Holmes D, Vinante L

(2023) The TARGIT-A randomized trial: TARGIT-IORT versus whole breast radiation therapy: long-term local control and survival. Int J Radiat Oncol Biol Phys 115(1):77–82
Corica T, Nowak AK, Saunders CM, Bulsara MK, Taylor M, Williams NR, Keshtgar M, Joseph DJ, Vaidya JS (2018) Cosmetic outcome as rated by patients, doctors, nurses and BCCT core software assessed over 5 years in a subset of patients in the TARGIT-A trial. Radiat Oncol 13(1):1
Engel D, Schnitzer A, Brade J, Blank E, Wenz F, Suetterlin M, Schoenberg S, Wasser K (2013) 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 19(1):92–95
Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sutterlin M et al (2012) Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. Breast Cancer Res Treat 135:253–260
Andersen KG, Flyger H (2013) Targeted intraoperative radiotherapy and persistent pain after treatment. Targeted intraoperative radiotherapy in oncology. Springer, Berlin, Heidelberg, pp 85–91
Lemanski C, Bourgier C, Draghici R, Thézénas S, Morel A, Philippe R et al (2020) Intraoperative partial irradiation for highly selected patients with breast cancer: results of the INTRAOBS prospective study. Cancer Radiother 24(2):114–119
Vinante L, Vaidya J, Angela C, Mileto M, Piccoli E, Avanzo M et al (2022) Results from a large single institute experience of targeted intraoperative radiotherapy (TARGIT-IORT) as partial breast irradiation modality. Eur J Cancer 175:S49
Guillerm S, Bourstyn E, Itti R, Cahen-Doidy L, Quéro L, Labidi M et al (2022) Intraoperative radiotherapy for breast cancer in elderly women. Clin Breast Cancer 22(1):e109–e113
Isabel A, Martínez A, Jimenez M, Sanz J, Maria NP et al (2024) Comparison of partial irradiation techniques in breast cancer: Intraoperative radiotherapy vs external partial irradiation Study of long-term effectiveness, complications, and quality of life. Eur J Surg Oncol 50(2):107550
Valente SA, Tendulkar RD, Cherian S, O'Rourke C, Greif JM, Bailey L, Uhl V, Bethke KP, Donnelly ED, Rudolph R, Pederson A (2016) TARGIT-R (Retrospective): North American experience with intraoperative radiation using low-kilovoltage X-rays for breast cancer. Ann Surg Oncol 23:2809–2815
Valente SA, Tendulkar RD, Cherian S, Shah C, Ross DL, Lottich SC, Laronga C, Broman KK, Donnelly ED, Bethke KP, Shaw C (2021) TARGIT-R (retrospective): 5-year follow-up evaluation of intraoperative radiation therapy (IORT) for breast cancer performed in North America. Ann Surg Oncol 28:2512–2521
Smith BD, Kuerer HM (2021) Same-day breast cancer surgery and TARGIT-IORT: Better than selective omission of radiotherapy? Ann Surg Oncol 28:2419–2420
Kolberg HC, Niesing H, Vaidya JS, Akpolat-Basci L, Maguz A, Hoffmann O et al (2023) Breast conserving surgery in combination with targeted intraoperative radiotherapy compared to mastectomy for in-breast-tumor-recurrence. Anticancer Res 43:733–739
Kolberg HC, Uhl V, Massarut S, Holmes D, Kolberg-Liedtke C, Kelly EW et al (2019) Targeted intraoperative radiotherapy during breast-conserving surgery for breast cancer in patients after implant augmentation. Anticancer Res 39:4215–4218
Alvarado M, Gallant E, Rice JS, Grobmyer SR, Harris EE, Holmes D, Pavord D, Small W. TARGIT-US: a registry trial of targeted intraoperative radiation therapy following breast-conserving surgery
Refaat T, Gros SE, Small W Jr (2022) The case for risk-stratified IORT for early breast cancer. Brachytherapy 21(6):719–722
Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S et al (2001) Targeted intra-operative radiotherapy (TARGIT): an innovative method of treatment for early breast cancer. Ann Oncol off J Eur Soc Med Oncol ESMO 12:1075–1080
Vaidya J, Baum M, Tobias J, Morgan S, D'Souza D (2002) The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. Eur J Surg Oncol 28:447–454
A Comparison of Intra-operative Radiotherapy Boost with External Beam Radiotherapy Boost in Early Breast Cancer. (TARGIT-B) ClinicalTrials.gov [Internet]. clinicaltrials.gov. [cited 2024 Jul 8]. Available from: https://clinicaltrials.gov/ct2/show/NCT01792726
Kolberg HC, Lovey G, Akpolat-Basci L, Stephanou M, Fasching P, Untch M et al (2017a) targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy - a subgroup analysis of hormone receptor-positive HER2-negative breast cancer. Breast Care (Basel) 12:318–323
Kolberg, H. C., Loevey, G., Akpolat-Basci, L., Stephanou, M., Fasching, P. A., Untch, M. et al. Targeted intraoperative radiotherapy tumour bed boost during breast conserving surgery after neoadjuvant chemotherapy in HER2 positive and triple negative breast cancer. Rev Recent Clin Trials (2017).
Kolberg HC, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M et al (201c) Targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy. Strahlenther Onkol Organ Dtsch Rontgenges 193:62–69
Orecchia R, Ciocca M, Lazzari R, Garibaldi C, Leonardi MC, Luini A, Intra M, Gatti G, Veronesi P, Petit JI, Veronesi U (2003Dec 1) Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. Breast 12(6):483–490
Orecchia R, Veronesi U, Maisonneuve P, Galimberti VE, Lazzari R, Veronesi P, Jereczek-Fossa BA, Cattani F, Sangalli C, Luini A, Caldarella P (2021) Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. Lancet Oncol 22(5):597–608
Struikmans H, Snijders M, Mast ME, Fisscher U, Franssen JH, Immink MJ, Marinelli A, Merkus J, Petoukhova A, Speijer G, Koper P (2016) Single dose IOERT versus whole breast irradiation. Strahlenther Onkol 192(10):705
Vaidya JS, Bulsara M, Massarut S, Sperk E, Wenz F, Tobias JS et al (2021c) Partial breast irradiation with intraoperative radiotherapy in the ELIOT trial. Lancet Oncol 22:e295–e296
Vaidya J, Bulsara M, Samuele M, Sperk E, Wenz F, Tobias J (2021) Partial breast irradiation with intraoperative radiotherapy in the ELIOT trial. Lancet Oncology; 22(7):e295.
Sedlmayer F, Fastner G, Merz F, Deutschmann H, Reitsamer R, Menzel C, Ciabattoni A, Petrucci A, Hager E, Willich N, Orecchia R (2007) IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: results of an ISIORT pooled analysis. Strahlenther Onkol 183(2):32–34
Fastner G, Reitsamer R, Gaisberger C, Hitzl W, Urbański B, Murawa D, Matuschek C, Budach W, Ciabattoni A, Reiland J, Molnar M (2022) Hypofractionated whole breast irradiation and boost-IOERT in early stage breast cancer (HIOB): first clinical results of a prospective multicenter trial (NCT01343459). Cancers 14(6):1396
Intra-operative electron boost and hypofractionated whole-breast irradiation during breast-conserving treatment (BCT) (HIOB) ClinicalTrials.gov [Internet]. www.clinicaltrials.gov. [cited 2024 Jul 8]. Available from: http://www.clinicaltrials.gov
Ciabattoni A, Gregucci F, Fastner G, Cavuto S, Spera A, Drago S, Ziegler I, Mirri MA, Consorti R, Sedlmayer F (2021) IOERT versus external beam electrons for boost radiotherapy in stage I/II breast cancer: 10-year results of a phase III randomized study. Breast Cancer Res 23(1):46

Tang A, Cohan CM, Beattie G, Cureton EL, Svahn JD, Lyon LL, Kelly JF, Shim VC (2021) Patients older 65 years with early breast cancer prefer intraoperative radiation as a locoregional treatment choice. Ann Surg Oncol 28:5158–5163

Tang A, Dzubnar JM, Kelly JF, Banks KC, Phillips JL, Cureton EA, Svahn JD, Mai V, Lyon LL, Thomas ES, Shim VC (2023) Intraoperative radiation therapy: a large integrated health care system's approach and outcomes. Perm J 27(1):45

Abo-Madyan Y, Welzel G, Sperk E, Neumaier C, Keller A, Clausen S, Schneider F, Ehmann M, Sütterlin M, Wenz F (2019) Single-center long-term results from the randomized phase-3 TARGIT-A trial comparing intraoperative and whole-breast radiation therapy for early breast cancer. Strahlenther Onkol 195(7):640–647

Mosiun JA, See MH, Teoh LY, Danaee M, Lai LL, Ng CH, Yip CH, Teh MS, Taib NA, Bustam A, Malik RA (2023) Comparison of clinical outcomes between low-and high-risk groups of early breast cancer patients treated with intraoperative radiotherapy in addition to external beam radiation: a multi-centre prospective study. World J Surg 47(1):201–208

Martinez C, Meterissian S, Saidi A, Tremblay F, Meguerditchian AN, Fleiszer D, Lambert C, David M, Panet-Raymond V, Abdulkarim B, Hijal T (2023) Targeted intraoperative radiation therapy during breast-conserving surgery for patients with early stage breast cancer: a phase II single center prospective trial. Adv Radiat Oncol 8(5):101236

Stefanelli A, Farina E, Mastella E, Fabbri S, Turra A, Bonazza S, De Troia A, Radica MK, Carcoforo P (2023) Full-dose intraoperative electron radiotherapy for early breast cancer: evidence from a single center's experience. Cancers 15(12):3239

Omosule M, Silva-Minor D, Coombs N (2023) Case Report: Intraoperative radiotherapy as the new standard of care for breast cancer patients with disabling health conditions or impairments. Front Oncol 18(13):1156619

Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, White J, Harris JR (2017) Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Pract Radiat Oncol 7(2):73–79

Wenz F (2017) Keynote address at the American Society of Breast Surgeons 18th annual meeting: current and future application of intraoperative radiotherapy (IORT) in the curative and palliative treatment of breast cancer. Ann Surg Oncol 24:2811–2817

Shah C, Vicini F, Shaitelman SF, Hepel J, Keisch M, Arthur D, Khan AJ, Kuske R, Patel R, Wazer DE (2018) The American brachytherapy society consensus statement for accelerated partial-breast irradiation. Brachytherapy 17(1):154–170

Schäfer R, Strnad V, Polgár C, Uter W, Hildebrandt G, Ott OJ, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL (2018) Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. Lancet Oncol 19(6):834–844

Budrukkar A, Telkhade T, Wadasadawala T, Shet T, Upreti RR, Jalali R, Badwe R, Gupta S, Sarin R (2020) A comparison of long-term clinical outcomes of accelerated partial breast irradiation using interstitial brachytherapy as per GEC-ESTRO, ASTRO, updated ASTRO, and ABS guidelines. Brachytherapy 19(3):337–347

Liedtke C, Jackisch C, Thill M, Thomssen C, Müller V, Janni W, AGO Breast Committee (2018) GO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2018. Breast Care 13(3):196–208

Eraso A, Sanz J, Ibáñez R, Alonso LM, Calín A, Casamayor MC, et al. (2023) Primer consenso español sobre el uso de la radioterapia intraoperatoria en el cáncer de mama. Conclusiones del panel de expertos. Revista de Senología y Patología Mamaria - J Senol Breast Dis 36(3). Available from: https://www.elsevier.es/es-revista-revista-senologia-patologia-mamaria--131-articulo-primer-consenso-espanol-sobre-el-S0214158223000324

American Society for Radiation Oncology, American Society of Clinical Oncology, Society of Surgical Oncology (2025) ASTRO, ASCO, and SSO Evidence-Based guideline update: partial breast irradiation for early-stage breast cancer and DCIS. Pract Radiat Oncol 15(1):48–49. https://doi.org/10.1016/j.prro.2024.02.010

Fastner G, Larsen S, Roeder F, Leonardi MC, Desmet A, Grecula J, Philippson C (2025) ASTRO guidelines for partial breast irradiation for patients with early-stage invasive breast cancer: a disturbing change of paradigm for intraoperative radiation therapy. Pract Radiat Oncol 15(1):48–49. https://doi.org/10.1016/j.prro.2024.02.010

Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347(16):1227–1232

Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T et al (2016) 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 387(10015):229–238

Kraus-Tiefenbacher U, Bauer L, Scheda A, Fleckenstein K, Keller A, Herskind C et al (2006) Long-term toxicity of an intraoperative radiotherapy boost using low energy X-rays during breast-conserving surgery. Int J Radiat Oncol Biol Phys 66(2):377–381

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M et al (2014) 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 383(9917):603–613

He L, Zhou J, Qi Y, He D, Yuan C, Chang H et al (2021) Comparison of the oncological efficacy between intraoperative radiotherapy with whole-breast irradiation for early breast cancer: a meta-analysis. Front Oncol 17(11):759903

Vaidya JS, Bulsara M, Wenz F, Coombs N, Singer J, Ebbs S et al (2016) Reduced mortality with partial-breast irradiation for early breast cancer: a meta-analysis of randomized trials. Int J Radiat Oncol Biol Phys 96(2):259–265

Mi Y, Zuo X, Cao Q, He J, Sui X, Li J et al (2022) Intraoperative radiotherapy versus no radiotherapy for early stage low-risk breast cancer patients undergoing breast-conserving surgery: a propensity score matching study based on the SEER database. Clin Transl Oncol 24:2409–2419

Vaidya JS, Bulsara M, Saunders C, Flyger H, Tobias JS, Corica T et al (2020) Effect of delayed targeted intraoperative radiotherapy vs whole-breast radiotherapy on local recurrence and survival: long-term results from the TARGIT-a randomized clinical trial in early breast cancer. JAMA Oncol 6:e200249

Alvarado MD, Conolly J, Park C, Sakata T, Mohan AJ, Harrison BL, Hayes M, Esserman LJ, Ozanne EM (2014) Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery. Breast Cancer Res Treat 143:135–140

Welzel G, Boch A, Sperk E, Hofmann F, Kraus-Tiefenbacher U, Gerhardt A, Suetterlin M, Wenz F (2013) 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 8(1):1–8

Keshtgar MRS, Williams NR, Bulsara M, Saunders C, Flyger H, Cardoso JS et al (2013Jul 23) Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer:

results from a randomised controlled trial. Breast Cancer Res Treat 140(3):519–525
Alvarado MD, Mohan AJ, Esserman LJ, Park CC, Harrison BL, Howe RJ et al (2013) Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. Ann Surg Oncol 20(9):2873–2880
Eisavi M, Rezapour A, Alipour V, Mirzaei HR, Arabloo J (2020) Cost-effectiveness analysis of intraoperative radiation therapy versus external beam radiation therapy for the adjuvant treatment of early breast cancer: a systematic review. Med J Islamic Republic Iran
Moloney E, Mashayekhi A, Javanbakht M (2023) EE506 targeted intraoperative radiation therapy as an adjuvant to surgery for the treatment of breast cancer in England: a UK-based cost-effectiveness analysis of intrabeam. Value Health 26(6):S151–S152
Wuhrer A, Uhlig S, Tuschy B, Berlit S, Sperk E, Bieback K, Sütterlin M (2021) Wound fluid from breast cancer patients undergoing intraoperative radiotherapy exhibits an altered cytokine profile and impairs mesenchymal stromal cell function. Cancers (Basel) 13(9):2140
Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F et al (2008) Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. Clin Cancer Res off J Am Assoc Cancer Res 14:1325–1332
Vaidya JS, Vaidya UJ, Baum M, Bulsara M, Joseph D, Tobias JS et al (2022) Global adoption of single-shot targeted intraoperative radiotherapy (TARGIT-IORT) to improve breast cancer treatment – better for patients, better for health care systems. Front Oncol 12:786515
National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management. Available from: https://www.nice.org.uk/guidance/ng101. Accessed April 21st 2024

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