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REVIEW ARTICLE

A Review of Intraoperative Radiotherapy After Neoadjuvant Chemotherapy in Patients with Locally Advanced Breast Cancer: From Bench to Bedside

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Abstract

Purpose Adjuvant whole-breast irradiation with a boost to the tumor bed is the standard of treatment after breast-conserving surgery. Boost dose can be delivered either intraoperatively or externally. The purpose of this study is to review the literature regarding intraoperative radiation therapy (IORT) after neoadjuvant chemotherapy (NACT) in patients with locally advanced breast cancer (LABC).

Methods The present study is a review of English-language articles regarding IORT after NACT in patients with LABC published between 1998 and 2020. For this, the databases of PubMed, Medline, Web of Science, EBSCO, IEEE, Scopus, and Springer were searched. The results of the studies were combined using the random-effects model in the meta-analysis.

Results In patients with LABC who have received NACT, our review demonstrated encouraging results for boost IORT in terms of toxicity (0% in Spaich et al.'s single-arm study) and local control (96% in Homaei Shandiz et al.'s single-arm study). In comparison to the external beam irradiation boost (EBIB), IORT was noninferior in local control (98.5 vs 88.1%, p-value 0.2 in Fastner et al.'s study) and superior in overall survival (HR = 0.19, $p = 0.016$ in Kolberg et al.'s study).

Conclusions IORT (electron or photon) after NACT in patients with LABC is a safe procedure with comparable efficacy to EBIB. Highly accurate dose prescription, evasion of the proliferative cytokine cascade, and elimination of the effects of geometric and temporal miss all lead to this conclusion that boost IORT may be superior to EBIB.

Keywords Intraoperative radiotherapy · Locally advanced breast cancer · Local recurrence · Neoadjuvant chemotherapy

Abbreviations

BCM	Breast cancer mortality
BCS	Breast-conserving surgery
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
EBIB	External beam irradiation boost
EBRT	External beam radiotherapy
HR	Hazard ratio

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IMRT	Intensity-modulated radiation therapy
IOERT	Intraoperative radiation therapy with electrons
IORT	Intraoperative radiation therapy
kV	Kilovoltage
LABC	Locally advanced breast cancer
LCR	Local control rate
LINAC	Linear accelerators
LRCR	Locoregional control rate
LRFS	Local recurrence-free survival
NACT	Neoadjuvant chemotherapy
OS	Overall survival
pCR	Pathologic complete response
QA	Quality assurance
SIB	Simultaneous integrated boost
TARGIT	Targeted intraoperative radiotherapy
TN	Triple-negative
WBI	Whole-breast irradiation

Introduction

The treatment of breast cancer has evolved along with changing its presentation over time [1]. For decades, mastectomy was considered the standard of care for all malignant breast lesions; however, currently, the goal is preserving the breast [2]. Breast-conserving surgery (BCS) is currently the treatment of choice for its equivalent clinical outcomes when combined with adjuvant whole-breast irradiation (WBI); however, BCS has less psychosocial impact [3–5]. Of note, this type of surgery is not possible in all circumstances, for instance, when the ratio of breast size to the tumoral mass is not enough to preserve breast cosmetic appearance. In this condition, neoadjuvant chemotherapy (NACT) or hormonal therapy may be effective choices for tumor shrinkage and increase the possibility of breast preservation [6–10]. Neoadjuvant therapy is the preferred initial approach in the setting of locally advanced breast cancer (LABC), especially for patients with triple-negative (TN) or HER2 + tumors [11]. However, its role in the management of early-stage breast cancer with the purpose of downstaging, increasing the chance of BCS, and improving cosmetic results is currently under investigation [12]. After BCS, regardless of neoadjuvant treatment, adjuvant WBI with a boost to the tumor bed is recommended [13]. The boost dose could be administered through intraoperative radiation therapy (IORT) during surgery or external beam radiotherapy (EBRT) during or after external WBI [14, 15]. The latter can be delivered sequentially after conventional EBRT or with the simultaneous integrated boost (SIB) technique using intensity-modulated radiation therapy (IMRT). The SIB technique has several benefits over the sequential boost. For example, shorter overall treatment time, fewer toxicities, more homogeneous dose distribution, and obviating the need for the application of electron therapy [16].

In this review article, we aimed to highlight the role of IORT in patients with LABC after NACT. In the following sections, first, we introduce the databases and keywords of the research. Then, we present the summary of studies evaluating the role of boost radiotherapy in patients with LABC who have received NACT followed by a short practical description of IORT modalities in the "Results" section. Thereafter, we discuss the studies specifically addressing the role of IORT in this group of patients.

Methods

Research Design and Search Strategy

This review article was carried out by searching studies in major available databases, including PubMed, Medline, Web of Science, EBSCO, IEEE, Scopus, and Springer, from 1998 to 2020. In addition, references of the selected articles and grey literature were evaluated. To ensure that no relevant papers have been lost, the lists of review articles were also fully investigated. The keywords used for the search were "intraoperative radiotherapy" AND/OR "locally advanced breast cancer" AND/OR "neoadjuvant chemotherapy" AND/OR "Intraoperative radiotherapy with electrons" AND/OR "Intraoperative radiotherapy with photon". The search strategy was modified and customized for each database.

Inclusion and Exclusion Criteria

The inclusion criteria were full-text available descriptive and clinical trials (in the English language) concerning the aforementioned keywords, which have been published from 1998 to 2020. Exclusion criteria were when only the abstract was available and not in the timeline of the study.

Quality Assessment

The present study employed the STROBE (strengthening the reporting of observational studies in epidemiology) for the quality assessment of the included articles.

Results

Thirteen studies were evaluated. Based on the results of the present review, IORT is beneficial in patients with LABC, and substitution of external beam irradiation boost (EBIB)

by IORT does not compromise the outcome in terms of local recurrence.

Breast-Conserving Surgery After Neoadjuvant Chemotherapy

Table 1 demonstrates an overview of clinical trials dealing with breast-conserving therapy after NACT in patients with LABC. Primary studies on NACT in breast cancer, including phase III randomized trials, have revealed a minimal survival benefit but an increased likelihood of breast preservation. Moreover, response to NACT may guide chemotherapy in the adjuvant phase. Eight out of 13 studies evaluating NACT in LABC (mostly phase II–III trials) have reported the pathologic complete response (pCR) to NACT (median: 36%, range: 3–87%). Of note, the low rate of pCR did not translate to long-term local–regional and ipsilateral breast tumor recurrence.

Intraoperative Radiotherapy

The American Society for Radiation Oncology (ASTRO) has issued the inclusion criteria for accelerated partial breast irradiation (including IORT) of early-stage breast cancer, including negative surgical margins by ≥ 2 mm (*suitable*) or < 2 mm (*cautionary*), age ≥ 50 years old (*suitable*) or patients age 40–49 who meet other pathologic suitability criteria (*cautionary*), and patients with low-risk ductal carcinoma in situ (DCIS) disease. The original guideline has a few differences: (1) did not include DCIS, (2) named age ≥ 60 years old as suitable and 50–59 years old with the aforementioned condition as the *cautionary* group for IORT [17]. The main limitation of IORT is the lack of final pathologic information on tumor size, histology, margins, and nodal status. When unexpected findings (e.g., positive surgical margin or positive sentinel node) are encountered, additional WBI may be indicated, thereby reducing some of the convenience and low-toxicity

Table 1 Overview of clinical trials dealing with breast-conserving therapy after neoadjuvant chemotherapy in cases of LABC

Authors	Method	F/U	No	Phase	Hor +	Her 2 +	pCR/ NACT	WBI	Boost	IBTR	LRR
Beriwal et al. [41]	RC	Med: 60 m	153	II, III	NR	NR	24%	45/50 Gy	16/20 Gy via Ext. electrons	4%	7%
Chen et al. [42]	RC	5 years	340	I–III	NR	NR	NR	Med: 50 Gy	10 Gy via Ext. electrons	5%	9%
Min et al. [43]	RC	Med: 55 m	251	II, III	NR	NR	NR	50.4 Gy	10 Gy via Ext. electrons	7.6%	10%
Fisher et al. [44]	RCT	5 years	504	I–III	NR	NR	NR	NR	NR	7.9%	13.6%
Mauriac et al. [45]	RCT	Med. 124 m	40	II, III	NR	NR	NR	NR	NR	15%	22.5%
Calais et al. [46]	PC	Med. 38 m	45	II, III	NR	NR	20.2%	45 Gy in 2.25 Gy PF/day for 4 days per week	15 Gy via Ext. Electrons/Brachy (Ir192)	9%	9%
Schwartz et al. [47]	RC	Med. 29 m	55	II, III	NR	NR	NR	45 Gy	20 Gy via Ext. electrons	1.8%	1.8%
Cance et al. [48]	RC	Med. 70 m	21	III	45%	NR	15%	NR	NR	9.5%	14.2%
Parmar et al. [49]	RC	Med. 32 months	188	II, III	33.5%	NR	49%	50 Gy	15–20 Gy (technique NR)	8%	13.3%
Bonadonna et al. [50]	PC	Med. 65 m	455	II, III	NR	NR	3%	NR	NR	6.8%	NR
Tanioka et al. [51]	RC	Med. 46 m	48	II, III	35.3%	89.5%	54.5%	50 Gy/25	NR	NR	10.4%
Sweeting et al. [52]	RC	Med. 77 m	54	II, III	42%	27%	87%	NR	NR	3.8%	13%
Mittendorf et al. [53]	RC	Med. 86 m	652	II, III	NR	NR	48%	50 Gy	10 Gy via Ext. electrons	6%	8%

Ext external beam, *F/U* follow-up, *Hor* hormone, *IBTR* ipsilateral breast tumor recurrence, *LRR* locoregional recurrence, *m* months, *med* median, *M/S* molecular subtype, *No* number of patients, *NR* not reported, *pCR/NACT* pathologic complete response to neoadjuvant chemotherapy, *PC* prospective cohort, *RCT* randomized clinical trial, *RC* retrospective cohort, *WBI* whole-breast irradiation

advantages of sole IORT. However, IORT as a tumor bed boost has also been studied and appears to be a safe procedure [18]. One of the controversies in the application of IORT is the existence of several consensus guidelines for selection criteria (including ASTRO, Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology [GEC-ESTRO], and the TARGIT group) that may result in varied indications of WBI after IORT that may influence the final results. Another controversy is that the results of previous IORT trials are difficult to apply to patients who have positive sentinel lymph node biopsy but no axillary dissection [19].

Patients with LABC require WBI after BCS, and to achieve optimum local control and possibly overall survival (OS), patients should also receive radiation boost to the tumor bed [20, 21]. The boost radiation can be delivered during surgery (i.e., IORT) or as a part of adjuvant EBRT. In the following section, the two common IORT approaches used during BCS are described [22].

Intraoperative Radiation Therapy with Electrons (IOERT)

There are three mobile electron-beam linear accelerators (LINAC) designed to deliver IORT, including Mobetron, LIAC, and Novac7.

The Mobetron® is an X-band LINAC. The X-band waveguide accelerates electrons to energies of 4, 6, 9, and 12 meV. Mobetron delivers 20 Gy at 2 min. LIAC accelerators can produce electron beams with four nominal energies of 4, 6, 9, and 12 meV [23]. Beam energies typically increase in steps of 2 meV or 3 meV [24]. If the NOVAC or LIAC machine is located in an operating room above ground level, using a combination of lead and borated polyethylene (5%) is good for shielding. The role of borated polyethylene is to stop the neutrons, and the lead is to eliminate the secondary photons [25].

Intraoperative Radiation Therapy with Photons

This method consists of two systems, INTRABEAM and Axxent. The INTRABEAM® system (Carl Zeiss Meditec AG, Oberkochen, Germany) consists of a graphic interface between the user and control console (named the user terminal), X-ray source (a.k.a., XRS 4 Miniaturized Linear Accelerator), the control console (controls the X-ray source), quality assurance (QA) equipment, a support stand, and different applicators. XRS 4 consists of an electron gun which emits electrons, the accelerating unit which accelerates the electrons to a maximum of 50 kilovoltages (kV), and two pairs of bending coils which guide the electron beam through a 10 cm hollow tube (i.e. the probe) that drifts electrons to the gold target and generates X-rays through the Bremsstrahlung effect. This design provides a spherical dose distribution [26]. The INTRABEAM system has the capability of using four types of applicators: (1) spherical applicators, (2) surface applicators, (3) flat applicators, and (4) needle applicators [27–29]. Treatment time depends on the prescribed dose and applicator size. The treatment time to deliver 20 Gy is between 7 and 49 min. Table 2 summarizes the treatment time for different applicators to deliver 20 Gy.

The Xoft S700 Axxent™ system operates at energies between 20 and 50 kV, but the more practical energy is 50 kV. This system has a microminiature X-ray tube that is located inside a flexible and disposable sheath. Inside this sheath is filled with water, and the device cools down. The nominal dose rate of the machine is 0.6 Gy/min at 3 cm of water, which is higher than that for the INTRABEAM system because of the cooling effect of water on the X-ray target.

The radiation protection of an intraoperative 50 kV X-ray unit has largely been investigated. Shielding the treatment field with a tungsten sheet combined with a movable shield for anesthesiologist and physicist—that monitor the treatment—is sufficient to reduce doses to an acceptable level [30].

Discussion

In the study by Fastner et al. (2015), tumor bed boost by IOERT during BCS was compared with EBIB (by electrons or photons) in patients with LABC who have received NAC and adjuvant WBI in terms of local control rate (LCR) and locoregional control rate (LRCR). The 6-year LCR and LRCR were nonsignificantly higher in the IOERT group than in the EBIB group (98.5 vs 88.1%, p-value 0.2 and 97.2 vs 88.1%, p-value = 0.3, respectively) [31]. This may be due to a highly accurate dose prescription in IORT with the elimination of effects of geometric and temporal miss. Moreover, in situ delivery of radiation during IORT

Table 2 Treatment time for different applicators to deliver 20 Gy [25]

Applicator diameter (mm)	Treatment time (min)
15	7.07
20	11.53
25	17.43
30	24.98
35	18.57
40	26.8
45	36.58
50	48.82

Table 3 Demographic data of patients enrolled in the studies on IORT after neoadjuvant chemotherapy in patients with locally advanced breast cancer

Authors	Method	Groups (n)	Age (y)	Stage	Her2 + (n)	Hor + (n)	pCR/NACT
Fastner et al. [31]	CS	IOERT (81)	Median:48	I/IIA: 25 IIB ≤ 56	8	55	14
		EBIB (26)	Median:53.5	I/IIA: 10 IIB ≤ 16	3	19	1
Fastner et al. [54]	RC	IOERT (14/71)	Median:55	N/R	N/R	N/R	3
Kolberg et al. [32]	RC	IORT (61)	Mean:54.9 ± 1.45	Mean: 2.16 ± 1.12 cm Node positive (n): 33	37	39	19
		EBIB (55)	Mean:57.8 ± 1.46	Mean: 2.59 ± 1.34 cm Node positive (n):30	37	38	13
Kolberg et al. [35]	RC	IORT (40)	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]
		EBIB (30)	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]
Spaich et al. [36]	RC	IORT (13)	Mean = 50	Mean:1.2–5 cm I/IIA: 9 IIB = 4	1	9	4
Manikhas et al. [37]	RCT	IORT (49)	N/R[a]	T2N0M0	N/R[a]	N/R[a]	N/R[a]
		Mastectomy (51)	N/R[a]	T2N0M0	N/R[a]	N/R[a]	N/R[a]
Cotrina et al. [38]	RC	IORT (42)	Mean = 47.9	Stage II: 61.9% Stage III: 38.1%	24	19	16
Moini et al. [39]	RC	IORT (255)	Mean = 26.7	Stage I: 11.5% Stage II: 60.0% Stage III: 28.5%	56	151	N/R
		EBIB (321)	Mean = 49.0	Stage I: 21.9% Stage II: 49.8% Stage III: 28.3%	55	231	N/R
Homaei Shandiz et al. [40]	CT	IORT (24)	Mean = 43.5	T1N2: 1 T2N0: 7 T2N1: 9 T3N0: 2 T3N1: 2 T3N2: 3	7	15	6

CS case series, *CT* clinical trial, *EBIB* external beam irradiation boost, Hor hormone, *IOERT* intraoperative radiotherapy with electrons, *IORT* intraoperative radiotherapy, *N/R* not reported, *pCR/NACT* pathologic complete response to neoadjuvant chemotherapy, *RC* retrospective cohort, y: years old

[a]Not reported in the abstract. The main text was not available

Table 4 Treatment details of studies on IORT after neoadjuvant chemotherapy in patients with locally advanced breast cancer

Authors	Groups (n)	Boost dose (TD/dpf)	Boost technique	PTV boost	EBRT dose	EBRT technique	RNI (n)
Fastner et al. (2015) [31]	IOERT (81)	10 Gy	Tube sizes of 4–8 cm and electron energies between 4 and 18 meV	A rim of tissue of at least 2 cm in all directions	51–57 Gy/ 1.7–1.8 Gy	Tangential three-dimensional conformal radiotherapy (photons, 6 MV) in supine position	32
	EBIB (26)	12 Gy (range, 6–16 Gy)/ 2 Gy	Electrons (88%) or photons (8%)	Tumor bed	51–57 Gy/ 1.7–1.8 Gy	Tangential three-dimensional conformal radiotherapy (photons, 6 MV) in supine position	10
Fastner et al. (2016) [54]	IOERT (14/ 71)	9.6 Gy (range 7–12 Gy)	Median tube sizes of 6 cm (range 4–8 cm) and median electron energies of 6 meV (range 4–18 meV)	A rim of tissue of at least 2 cm in all directions	54 Gy/ 1.6–1.85 Gy	Tangential three-dimensional conformal radiotherapy technique (6 MV photons)	8
Kolberg et al. (2016) [32]	IORT (61)	20 Gy to the surface of the applicator	50 kV X-ray source	N/R	50 Gy/2 Gy	N/R	–
	EBIB (55)	10 Gy/2 Gy or 16 Gy/ 2 Gy	Photons	N/R	50 Gy/2 Gy	N/R	–
Kolberg et al. (2017) [35]	IORT (40)	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]
	EBIB (30)	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]
Spaich et al. (2017) [36]	IORT (13)	20 Gy to the surface of the applicator	50 kV X-ray source	N/R	46.0 Gy/ 1.8–2.0 Gy	N/R	–
Manikhas et al. (2018) [37]	IORT (49)	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]
	Mastectomy (51)	–	–	–	–	–	–
Cotrina et al. (2019) [38]	IORT (42)	N/R[a]	INTRABEAM® (an X-ray source)	N/R[a]	N/R[a]	N/R[a]	N/R[a]
Moini et al. (2020) [39]	IORT (255)	20 Gy to the surface of the applicator	50 kV X-ray source	A rim of tissue of 2–5-5 cm in all directions	50 Gy/2 Gy	Tangential three-dimensional conformal radiotherapy (photons, 6 MV) in supine position	N/R
	EBIB (321)	10 Gy/2 Gy	Photons	N/R	50 Gy/2 Gy	Tangential three-dimensional conformal radiotherapy (photons, 6 MV) in supine position	N/R
Homaei Shandiz et al. (2020) [40]	IORT (24)	20 Gy	INTRABEAM® (an X-ray source)	Tumor bed	46-50 Gy/ 2 Gy	N/R	N/R

EBIB external beam irradiation boost, *dpf* dose per fraction, *EBRT* external beam radiotherapy, *IOERT* intraoperative radiotherapy with electrons, *N/R* not reported, *PTV* planning target volume, *RNI* regional node irradiation, *TD* total dose

[a]Not reported in the abstract. The main text was not available

Table 5 Outcome of IORT after neoadjuvant chemotherapy in patients with locally advanced breast cancer

Authors	Groups (n)	Median follow-up (months)	IBTR (n)	RR (n)	DM-CLBR (n)	Outcome
Fastner et al. (2015) [31]	IOERT (81)	59	2[a]	1	13–3	6-y LCR: 98.5%
						6-y LRCR: 97.2%
	EBIB (26)	67.5	2[a]	1	6–0	6-y LCR: 88.1%
						6-y LRCR: 88.1%
Fastner et al. (2016) [54]	IOERT (14/71)	97	5	0	0	8-y LCR: 89%
						8-y DFS: 80%
						8-y OS: 69%
Kolberg et al. (2016) [32]	IORT (61)	49	6	N/R	3	5-y LCR: 88.5%
						5-y DFS: 88.5%
						5-y OS: 96.7%
	EBIB (55)	49	4	N/R	7	5-y LCR: 79.9%
						5-y DFS: 71%
						5-y OS: 81.7%
Kolberg et al. (2017) [35]	IORT (40)	49	N/R[c]	N/R[c]	N/R[c]	5-y DFS in HER2 + : 83.3%
						5-y DFS in TN: 87.5%
						5-y OS in HER2 + : 100%
						5-y OS in TN: 87.5%
	EBIB (30)	49	N/R[c]	N/R[c]	N/R[c]	5-y DFS in HER2 + : 71.7%
						5-y DFS in TN: 60.0%
						5-y OS in HER2 + : 91.7%
						5-y OS in TN: 74.1%
Spaich et al. (2017) [36]	IORT (13)	40	1	0	0	–
Manikhas et al. (2018) [37]	IORT (49)	N/R[c]	N/R[c]	N/R[c]	N/R[c]	–
	Mastectomy (51)	N/R[c]	N/R[c]	N/R[c]	N/R[c]	–
Cotrina et al. (2019) [38]	IORT (42)	N/R[c]	3	0	1[b]	1-y DFS: 97.2%
						2-y DFS: 90.5%
						3-y DFS: 90.5%
						1-y OS: 100%
						2-y OS: 100%
						3-y OS: 92.3%
Moini et al. (2020) [39]	IORT (255)	14 (mean)	3	N/R	12	1-y DFS: 99.9%
						2-y DFS: 93.3%
						5-y DFS: 85.1%
	EBIB (321)	14 (mean)	8	N/R	20	1-y DFS: 96.9%
						2-y DFS: 94.3%
						5-y DFS: 86.0%
Homaei Shandiz et al. (2020) [40]	IORT (24)	29.5	1	2[d]	3	2-y DFS: 87.1%
						2-y OS: 95.5%

CLBR contralateral breast recurrence, *DFS* disease-free survival, *DM* distant metastasis, *IBTR* ipsilateral breast tumor recurrence, *LCR* local control rate; *LRCR* locoregional control rate, *RR* regional recurrence, *N/R* note reported, *OS* overall survival, *TN* triple-negative

[a]All in the former index quadrant

[b]One patient developed local and distant recurrence

[c]Not reported in the abstract. The main text was not available

[d]One patient developed regional and distant recurrence

permits higher doses that may positively affect the results. In the retrospective study by Kolberg et al. (2016), the clinical outcomes of IORT with the targeted intraoperative radiotherapy (TARGIT) technique using an intraoperative dose of 20 Gy (with a 50 kV X-ray source) were compared with EBIB in patients with LABC who have received NAC. While the differences in local recurrence-free survival (LRFS), disease-free survival (DFS), and breast cancer mortality (BCM) were not statistically significant, the 5-year OS was significantly in favor of the TARGIT-IORT group (hazard ratio [HR] = 0.19 (0.04–0.87), $p = 0.016$) [32]. The toxicity of IORT as a boost after was comparable with the average postoperative morbidity after BCS [33]. The higher OS in the IORT group may be due to the rapid effect of IORT on the local tumor microenvironment and wound fluid that could be absorbed and cause systemic beneficial effects [34]. Subsequently, Kolberg et al. (2017) compared the results of the TARGIT-IORT technique with EBIB as the tumor bed boost during BCS after NACT in patients with TN or HER2 + LABC. By demonstrating the nonsignificant trend for better 5-year OS (HER2 + : 100% vs. 91.7%, $p = 0.22$ and TN: 87.5% vs. 74.1%, $p = 0.488$) and 5-year DFS (HER2 + : 83.3% vs. 77.0%, $p = 0.38$ and TN: 87.5% vs. 60%, $p = 0.22$) for TARGIT-IORT, the authors concluded noninferiority of TARGIT-IORT as an intraoperative boost in these high-risk patients [35].

Spaich et al. (2017) reported the acute and late complications of IORT following NACT in patients with LABC. By reporting no severe toxicity, they concluded that IORT during BCS after NACT is a safe procedure that may enhance the treatment strategies in this group of patients. In this retrospective study, 13 patients received IORT with low-energy X-rays (50 kV). After a median follow-up of 37 months, local recurrence occurred in one patient who had several risk factors for recurrence, including young age, advanced tumor size with poor response to chemotherapy (ypT2), high-grade biology (G3), and lymphovascular invasion [36]. In a prospective cohort by Manikhas et al. (2018), 51 patients with cT2N0M0 breast cancer who received NACT (62.7%) or exemestane (37.3%) followed by BCS with IORT (using the INTRABEAM system) and WBI were evaluated for clinical outcomes. Following a median follow-up of 24 months, the authors found no local recurrence and considered IORT as an effective modality in local control. The authors reported nonsignificant results for delayed toxicity of IORT and WBI [37]. In a retrospective study, Cotrina et al. (2019) reported their experience on IORT (using INTRABEAM) in patients with LABC who have received NACT. After a minimum 6-month follow-up, the rate of local recurrence was 7.1% [38].

To compare the efficacy of IORT (50 kV X-ray) and EBRT as a boost dose in patients with breast cancer, Moini et al. (2020) conducted a retrospective analysis. In this study, 576 patients with stage 1–3 breast cancer were enrolled. With a median follow-up of 54 months, the investigators found nonsignificant superiority for the IORT group in terms of local control (1.2 vs 2.5%, $p = 0.36$) and concluded that IORT may provide better local control. Although 15% of the IORT group and 13% of the EBRT group received neoadjuvant chemotherapy, a subanalysis was not separately provided [39]. In a single-arm phase II clinical trial, Homaei Shandiz et al. (2020) evaluated the clinical efficacy and toxicities of IORT in patients with LABC who have received NAC. In this study, 20 Gy IORT was delivered during BCS using the INTRABEAM system. By reporting a local recurrence of 4% and grade 3–4 toxicity of 12.5%, the authors concluded that IORT following NAC is an effective and safe procedure [40]. Table 3–5 summarize the patients' demographics, treatment details, and clinical outcomes of the abovementioned studies.

Conclusions

In this review, we presented a basis for the use of IORT after NACT in patients with LABC and discussed the current evidence regarding its clinical outcome. Highly accurate dose prescription, evasion of the proliferative cytokine cascade, and elimination of the effects of geometric and temporal miss all lead to this conclusion that boost IORT may be superior to EBIB. In this context, most of the data have reported comparable results with an external boost in terms of local control. A retrospective study addressed the survival benefit of IORT as a boost. Until well-designed randomized trials become available, these findings must be interpreted with caution.

Compliance with Ethical Standards

Conflict of interest The author declares that there is no conflict of interest.

References

1. Salek R, Shahidsales S, Mozafari V. Changing pattern in the clinical presentation of breast cancer in the absence of a screening program over a period of thirty-three years in Iran. Breast. 2016;28:95–9. https://doi.org/10.1016/j.breast.2016.05.003.
2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong J-H, Wolmark N. 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. 2002;347(16):1233–41.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. The Lancet. 2011;378(9804):1707–16. https://doi.org/10.1016/S0140-6736(11)61629-2.
4. Manganiello A, Hoga LAK, Reberte LM, Miranda CM, Rocha CAM. Sexuality and quality of life of breast cancer patients post mastectomy. Eur J Oncol Nurs. 2011;15(2):167–72.
5. Sun M-Q, Meng A-F, Huang X-E, Wang M-X. Comparison of psychological influence on breast cancer patients between breast-conserving surgery and modified radical mastectomy. Asian Pac J Cancer Prev. 2013;14(1):149–52.
6. Asselain B, Barlow W, Bartlett J, Bergh J, Bergsten-Nordström E, Bliss J, Boccardo F, Boddington C, Bogaerts J, Bonadonna G, Bradley R, Brain E, Braybrooke J, Broet P, Bryant J, Burrett J, Cameron D, Clarke M, Coates A, Coleman R, Coombes RC, Correa C, Costantino J, Cuzick J, Danforth D, Davidson N, Davies C, Davies L, Di Leo A, Dodwell D, Dowsett M, Duane F, Evans V, Ewertz M, Fisher B, Forbes J, Ford L, Gazet J-C, Gelber R, Gettins L, Gianni L, Gnant M, Godwin J, Goldhirsch A, Goodwin P, Gray R, Hayes D, Hill C, Ingle J, Jagsi R, Jakesz R, James S, Janni W, Liu H, Liu Z, Lohrisch C, Loibl S, MacKinnon L, Makris A, Mamounas E, Mannu G, Martín M, Mathoulin S, Mauriac L, McGale P, McHugh T, Morris P, Mukai H, Norton L, Ohashi Y, Olivotto I, Paik S, Pan H, Peto R, Piccart M, Pierce L, Poortmans P, Powles T, Pritchard K, Ragaz J, Raina V, Ravdin P, Read S, Regan M, Robertson J, Rutgers E, Scholl S, Slamon D, Sölkner L, Sparano J, Steinberg S, Sutcliffe R, Swain S, Taylor C, Tutt A, Valagussa P, van de Velde C, van der Hage J, Viale G, von Minckwitz G, Wang Y, Wang Z, Wang X, Whelan T, Wilcken N, Winer E, Wolmark N, Wood W, Zambetti M, Zujewski JA. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27–39. https://doi.org/10.1016/S1470-2045(17)30777-5.
7. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ, Albain KS, André F, Bergh J, Bonnefoi H, Bretel-Morales D, Burstein H, Cardoso F, Castiglione-Gertsch M, Coates AS, Colleoni M, Costa A, Curigliano G, Davidson NE, Di Leo A, Ejlertsen B, Forbes JF, Gelber RD, Gnant M, Goldhirsch A, Goodwin P, Goss PE, Harris JR, Hayes DF, Hudis CA, Ingle JN, Jassem J, Jiang Z, Karlsson P, Loibl S, Morrow M, Namer M, Kent Osborne C, Partridge AH, Penault-Llorca F, Perou CM, Piccart-Gebhart MJ, Pritchard KI, Rutgers EJT, Sedlmayer F, Semiglazov V, Shao Z-M, Smith I, Thürlimann B, Toi M, Tutt A, Untch M, Viale G, Watanabe T, Wilcken N, Winer EP, Wood WC. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2013. Ann Oncol. 2013;24(9):2206–23. https://doi.org/10.1093/annonc/mdt303.
8. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015. https://doi.org/10.1093/annonc/mdv298.
9. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thürlimann B, Senn HJ, André F, Baselga J, Bergh J, Bonnefoi H, Burstein H, Cardoso F, Castiglione-Gertsch M, Coates AS, Colleoni M, Curigliano G, Davidson NE, Di Leo A, Ejlertsen B, Forbes JF, Galimberti V, Gelber RD, Gnant M, Goldhirsch A, Goodwin P, Harbeck N, Hayes DF, Huober J, Hudis CA, Ingle JN, Jassem J, Jiang Z, Karlsson P, Morrow M, Orecchia R, Kent Osborne C, Partridge AH, de la Peña L, Piccart-Gebhart MJ, Pritchard KI, Rutgers EJT, Sedlmayer F, Semiglazov V, Shao Z-M, Smith I, Thürlimann B, Toi M, Tutt A, Viale G, von Minckwitz G, Watanabe T, Whelan T, Winer EP, Xu B. Tailoring therapies—improving the management of early breast cancer: St Gallen international expert consensus on the primary therapy of early breast cancer 2015. Ann Oncol. 2015;26(8):1533–46. https://doi.org/10.1093/annonc/mdv221.
10. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, Margolese RG, Hoehn JL, Vogel VG, Dakhil SR, Tamkus D, King KM, Pajon ER, Wright MJ, Robert J, Paik S, Mamounas EP, Wolmark N. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778–85. https://doi.org/10.1200/jco.2007.15.0235.
11. Curigliano G, Burstein HJ, E PW, Gnant M, Dubsky P, Loibl S, Colleoni M, Regan MM, Piccart-Gebhart M, Senn HJ, Thurlimann B, Andre F, Baselga J, Bergh J, Bonnefoi H, S YB, Cardoso F, Carey L, Ciruelos E, Cuzick J, Denkert C, Di Leo A, Ejlertsen B, Francis P, Galimberti V, Garber J, Gulluoglu B, Goodwin P, Harbeck N, Hayes DF, Huang CS, Huober J, Hussein K, Jassem J, Jiang Z, Karlsson P, Morrow M, Orecchia R, Osborne KC, Pagani O, Partridge AH, Pritchard K, Ro J, Rutgers EJT, Sedlmayer F, Semiglazov V, Shao Z, Smith I, Toi M, Tutt A, Viale G, Watanabe T, Whelan TJ, Xu B (2017) De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen international expert consensus conference on the primary therapy of early breast cancer 2017. Ann Oncol 28 (8):1700-1712. doi: 10.1093/annonc/mdx308.
12. Cain H, Macpherson IR, Beresford M, Pinder SE, Pong J, Dixon JM. Neoadjuvant therapy in early breast cancer: treatment considerations and common debates in practice. Clin Oncol (R Coll Radiol). 2017;29(10):642–52. https://doi.org/10.1016/j.clon.2017.06.003.
13. Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev. 2017. https://doi.org/10.1002/14651858.CD011987.pub2.
14. Kolberg H-C, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M, Bulsara M, Vaidya JS, Liedtke C. Targeted intraoperative radiotherapy tumor bed boost during breast conserving surgery after neoadjuvant chemotherapy in hormone receptor positive HER2 negative breast cancer. J Clin Oncol. 2017a. https://doi.org/10.1200/JCO.2017.35.15_suppl.e12090.
15. Jalali R, Singh S, Budrukkar A. Techniques of tumour bed boost irradiation in breast conserving therapy: current evidence and suggested guidelines. Acta Oncol. 2007;46(7):879–92.
16. Chen K-W, Hsu H-T, Lin J-F, Yeh H-L, Yeh D-C, Lin C-Y, Chan S, Hsieh H-Y. Adjuvant whole breast radiotherapy with simultaneous integrated boost to tumor bed with intensity modulated radiotherapy technique in elderly breast cancer patients. Transl Cancer Res. 2020;9:S12–22.
17. American Society for Radiation Oncology (2016) Updated ASTRO guideline expands pool of suitable candidates for accelerated partial breast irradiation. https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2016/Updated-ASTRO-guideline-expands-pool-of-suitable-c. Accessed September 5, 2020
18. Harris EE, Small W Jr. Intraoperative radiotherapy for breast cancer. Front Oncol. 2017;7:317.
19. Dutta SW, Showalter SL, Showalter TN, Libby B, Trifiletti DM. Intraoperative radiation therapy for breast cancer patients: current perspectives. Breast Cancer Targets Ther. 2017;9:257.
20. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L,

Whelan T, Wang Y, Peto R. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707–16. https://doi.org/10.1016/s0140-6736(11)61629-2.
21. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst. 2004;96(2):115–21.
22. Williams NR, Pigott KH, Brew-Graves C, Keshtgar MRS. Intraoperative radiotherapy for breast cancer. Gland Surg. 2014;3(2):109–19. https://doi.org/10.3978/j.issn.2227-684X.2014.03.03.
23. Natanasabapathi G (2012) Modern Practices in Radiation Therapy. InTech publishing Croatia. https://www.intechopen.com/books/modern-practices-in-radiation-therapy.
24. Hensley FW. Present state and issues in IORT physics. Radiat Oncol. 2017;12(1):37.
25. Gunderson LL, Willett CG, Calvo FA, Harrison LB. Intraoperative Irradiation. USA: Springer publishing New York; 2011.
26. Schneider F, Clausen S, Thölking J, Wenz F, Abo-Madyan Y. A novel approach for superficial intraoperative radiotherapy (IORT) using a 50 kV X-ray source: a technical and case report. J Appl Clin Med Phys. 2014;15(1):167–76.
27. Bodner WR, Hilaris BS, Alagheband M, Safai B, Mastoras CA, Saraf S. Use of low-energy X-rays in the treatment of superficial nonmelanomatous skin cancers. Cancer Invest. 2003;21(3):355–62.
28. Schneider F, Fuchs H, Lorenz F, Steil V, Ziglio F, Kraus-Tiefenbacher U, Lohr F, Wenz F. A novel device for intravaginal electronic brachytherapy. Int J Radiat Oncol Biol Phys. 2009;74(4):1298–305.
29. Wenz F, Schneider F, Neumaier C, Kraus-Tiefenbacher U, Reis T, Schmidt R, Obertacke U. Kypho-IORT-a novel approach of intraoperative radiotherapy during kyphoplasty for vertebral metastases. Radiat oncol. 2010;5(1):11.
30. Eaton D, Gonzalez R, Duck S, Keshtgar M. Radiation protection for an intra-operative X-ray device. Br J Radio. 2011;84(1007):1034–9.
31. Fastner G, Reitsamer R, Ziegler I, Zehentmayr F, Fussl C, Kopp P, Peintinger F, Greil R, Fischer T, Deutschmann H, Sedlmayer F. IOERT as anticipated tumor bed boost during breast-conserving surgery after neoadjuvant chemotherapy in locally advanced breast cancer–results of a case series after 5-year follow-up. Int J Cancer. 2015;136(5):1193–201. https://doi.org/10.1002/ijc.29064.
32. Kolberg HC, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M, Liedtke C, Bulsara M, Vaidya JS. Targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy. Strahlenther Onkol. 2017;193(1):62–9. https://doi.org/10.1007/s00066-016-1072-y.
33. Kolberg H-C, Loevey G, Akpolat-Basci L, Stephanou M, Untch M (2015) Intraoperative radiotherapy as a boost after neoadjuvant chemotherapy: DFS after a median follow-up of 4 years. American Society of Clinical Oncology. https://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.e12050.
34. Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, Berton S, Perin T, Candiani E, Reccanello S. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. Clin Cancer Res. 2008;14(5):1325–32.
35. Kolberg HC, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M, Bulsara M, Vaidya JS, Liedtke C. 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. 2017b;12(2):93–100. https://doi.org/10.2174/1574887112666170201142458.
36. Spaich S, Tuschy B, Sperk E, Wenz F, Sütterlin M. Initial experience of intraoperative radiotherapy as tumour bed boost after neoadjuvant chemotherapy in breast cancer patients. Transl Cancer Res. 2017;6(2):416–23.
37. Manikhas A, Grinev I, Oganesyn A, Chikrizov S, Manikhas GM (2018) The experience of the usage of intraoperative radiation therapy after neoadjuvant systemic therapy for breast cancer. American Society of Clinical Oncology. https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e12621.
38. Cotrina J, Galarreta J, Pinillos M, Vilchez S. Abstract P3–12–17: intraoperative radiotherapy (IORT) after neoadjuvant chemotherapy in patients with breast cancer–experience in the cancer institute of lima-peru. Cancer Res. 2019. https://doi.org/10.1158/1538-7445.sabcs18-p3-12-17.
39. Moini N, Akbari ME, Mirzaei H, Hosseini Daghigh SM, Zayeri F, Hajizadeh N, Hajian P, Malekzadeh M. Intraoperative boost radiotherapy with 50 kV X-Rays versus external radiotherapy in breast cancer: single-center experiences. Int J Cancer Manag. 2020;13(3):e98561. https://doi.org/10.5812/ijcm.98561.
40. Homaei Shandiz F, Fanipakdel A, Forghani MN, Javadinia SA, Mousapour Shahi E, Keramati A, Fazilat-Panah D, Babaei MM. Clinical efficacy and side effects of IORT as tumor bed boost during breast-conserving surgery in breast cancer patients following neoadjuvant chemotherapy. Indian J Gynecol Oncol. 2020;18(2):46. https://doi.org/10.1007/s40944-020-00389-5.
41. Beriwal S, Schwartz GF, Komarnicky L, Garcia-Young JA. Breast-conserving therapy after neoadjuvant chemotherapy: long-term results. Breast J. 2006;12(2):159–64. https://doi.org/10.1111/j.1075-122X.2006.00225.x.
42. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, Strom EA, McNeese MD, Kuerer HM, Ross MI, Singletary SE, Ames FC, Feig BW, Sahin AA, Perkins GH, Schechter NR, Hortobagyi GN, Buchholz TA. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. J Clin Oncol. 2004;22(12):2303–12. https://doi.org/10.1200/jco.2004.09.062.
43. Min SY, Lee SJ, Shin KH, Park IH, Jung SY, Lee KS, Ro J, Lee S, Kim SW, Kim TH, Kang HS, Cho KH. Locoregional recurrence of breast cancer in patients treated with breast conservation surgery and radiotherapy following neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys. 2011;81(5):e697-705. https://doi.org/10.1016/j.ijrobp.2010.10.014.
44. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB Jr, Hoehn JL, Lees AW, Dimitrov NV, Bear HD. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16(8):2672–85. https://doi.org/10.1200/jco.1998.16.8.2672.
45. Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, Dilhuydy JM, Bonichon F. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Institut bergonie bordeaux groupe sein (IBBGS). Ann Oncol. 1999;10(1):47–52.
46. Calais G, Berger C, Descamps P, Chapet S, Reynaud-Bougnoux A, Body G, Bougnoux P, Lansac J, Floch OL. Conservative treatment feasibility with induction chemotherapy, surgery, and radiotherapy for patients with breast carcinoma larger than 3 cm. Cancer. 1994;74(4):1283–8.
47. Schwartz GF, Birchansky CA, Komarnicky LT, Mansfield CM, Cantor RI, Biermann WA, Fellin FM, McFarlane J. Induction

chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. Cancer. 1994;73(2):362–9.
48. Cance WG, Carey LA, Calvo BF, Sartor C, Sawyer L, Moore DT, Rosenman J, Ollila DW, Graham M. Long-term outcome of neoadjuvant therapy for locally advanced breast carcinoma: effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. Ann Surg. 2002;236(3):295–302. https://doi.org/10.1097/01.sla.0000027526.67560.64.
49. Parmar V, Krishnamurthy A, Hawaldar R, Nadkarni MS, Sarin R, Chinoy R, Nair R, Dinshaw KA, Badwe RA. Breast conservation treatment in women with locally advanced breast cancer–experience from a single centre. Int J Surg. 2006;4(2):106–14. https://doi.org/10.1016/j.ijsu.2006.01.004.
50. Bonadonna G, Valagussa P, Brambilla C, Ferrari L, Moliterni A, Terenziani M, Zambetti M. Primary chemotherapy in operable breast cancer: eight-year experience at the milan cancer institute. J Clin Oncol. 1998;16(1):93–100. https://doi.org/10.1200/jco.1998.16.1.93.
51. Tanioka M, Shimizu C, Yonemori K, Yoshimura K, Tamura K, Kouno T, Ando M, Katsumata N, Tsuda H, Kinoshita T, Fujiwara Y. Predictors of recurrence in breast cancer patients with a pathologic complete response after neoadjuvant chemotherapy. Br J Cancer. 2010;103(3):297–302. https://doi.org/10.1038/sj.bjc.6605769.
52. Sweeting RS, Klauber-Demore N, Meyers MO, Deal AM, Burrows EM, Drobish AA, Anders CK, Carey LA. Young women with locally advanced breast cancer who achieve breast conservation after neoadjuvant chemotherapy have a low local recurrence rate. Am Surg. 2011;77(7):850–5.
53. Mittendorf EA, Buchholz TA, Tucker SL, Meric-Bernstam F, Kuerer HM, Gonzalez-Angulo AM, Bedrosian I, Babiera GV, Hoffman K, Yi M, Ross MI, Hortobagyi GN, Hunt KK. Impact of chemotherapy sequencing on local-regional failure risk in breast cancer patients undergoing breast-conserving therapy. Ann Surg. 2013;257(2):173–9. https://doi.org/10.1097/SLA.0b013e3182805c4a.
54. Fastner G, Hauser-Kronberger C, Moder A, Reitsamer R, Zehentmayr F, Kopp P, Fussl C, Fischer T, Deutschmann H, Sedlmayer F. Survival and local control rates of triple-negative breast cancer patients treated with boost-IOERT during breast-conserving surgery. Strahlenther Onkol. 2016;192(1):1–7. https://doi.org/10.1007/s00066-015-0895-2.