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Intraoperative radiotherapy versus whole breast radiotherapy in early-stage breast cancer: a retrospective outcome analysis based on ASTRO guidelines on PBI

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Abstract

Background Intraoperative radiotherapy (IORT) is a convenient treatment techniques for patients with early-stage breast cancer. We aimed to compare the outcome of IORT to that of whole-breast external beam radiotherapy (EBRT) in highly selected breast cancer patients based on the 2023 American Society for Radiation Oncology (ASTRO) Clinical Practice Guideline for Partial Breast Irradiation (PBI).

Patients and methods We reviewed patients who underwent breast-conserving surgery (BCS) and received either IORT or EBRT for early-stage breast cancer between 2014 and 2019. The outcomes of these patients were analyzed and compared across different risk stratifications according to the 2023 ASTRO Clinical Practice Guideline for PBI, which categorized the patients into "recommended", "conditionally recommended", or "conditionally not recommended" groups.

Results A total of 732 patients were enrolled with a mean follow-up time of 5.1 years. Among patients in the recommended group, the locoregional recurrence rates were 2.0% for IORT and 2.3% for EBRT ($p=0.978$). Conversely, in the conditionally recommended or conditionally not recommended groups, IORT exhibited significantly higher locoregional recurrence rates compared to EBRT: in the conditionally recommended group, IORT had a recurrence rate of 11.1% versus 3.0% for EBRT ($p=0.044$), and in the conditionally not recommended group, IORT had a rate of 13.8% versus 2.5% for EBRT ($p=0.010$).

Conclusions The locoregional recurrence rate in the IORT group was comparable to that of the EBRT group for patients recommended for PBI. However, for patients categorized as conditionally recommended or conditionally not recommended for PBI, the IORT group showed a higher locoregional recurrence rate, highlighting the need for careful patient selection.

Keywords IORT, EBRT, BCS, IBTR, Lymph node recurrence, APBI, PBI

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Background

Adjuvant radiotherapy reduces the 10-year risk of any recurrence (locoregional or distant) and reduces the 15-year risk of breast cancer death in patients receiving breast-conserving surgery (BCS) for breast cancer [1]. While whole breast irradiation is considered standard of care, it is associated with an increased risk of ischemic

heart disease and second lung cancer due to radiation dose exposure to the heart and lungs [2, 3]. Partial breast irradiation (PBI), which targets a limited volume of tissue surrounding the tumor bed, reduces doses to organs at risk, thereby lowering the risk of secondary tumors and cardiac events compared to whole breast irradiation [4].

Intraoperative radiotherapy (IORT), a type of PBI, serves as an alternative to whole breast external beam radiotherapy (EBRT) for selected patients following BCS for early-stage breast cancer. IORT offers advantages such as improved breast-related quality of life, favorable cosmetic outcomes, and reduced frequency of hospital visits [5–7]. However, the higher rate of ipsilateral breast tumor recurrence (IBTR) in patients treated with IORT compared to those treated with EBRT remains a concern. Findings from trials such as the Electron Intraoperative Radiotherapy Trial (ELIOT trial) and the Targeted Intraoperative Radiotherapy versus Whole Breast Radiotherapy for Breast Cancer (TARGIT-A) trial have proposed offering IORT to carefully selected patients deemed at low risk of IBTR [8, 9].

The American Society for Radiation Oncology (ASTRO) Consensus on Accelerated Partial Breast Irradiation (APBI), published in 2017, defines suitable and cautionary groups for IORT according to previous studies [10]. In 2023, the updated ASTRO Clinical Practice Guideline for PBI provides recommendations for defining eligible patients for PBI [11]. We conducted a retrospective study of patients who underwent BCS and received either IORT or whole breast EBRT for early-stage breast cancer between 2014 and 2019. These patients were categorized into different risk groups according to the 2023 ASTRO guideline for PBI for outcome analysis.

Methods

In this study, 1696 patients with early-stage invasive breast cancer who underwent BCS and completed either IORT or EBRT at China Medical University Hospital between January 2014 and December 2019 were reviewed. We identified 732 patients with invasive breast cancer who were aged over 40 years, had a pathological tumor size ≤ 3 cm, were pathologically margin negative, lacked pathological lymph node metastasis, and met treatment strategies (IORT or EBRT) for outcome analysis (Fig. 1). According to the 2023 ASTRO Clinical Practice Guideline for PBI [11], patients were divided into subgroups based on their treatment modality (IORT or EBRT) for outcome analysis.

The patients were categorized according to the 2023 ASTRO Clinical Practice Guidelines for PBI into "recommended", "conditionally recommended", or "conditionally not recommended" groups [11]. Patients were classified into the recommended group if they met all of the following criteria: grade 1–2 disease, ER-positive histology, age over 40 years, tumor size ≤ 2 cm, and absence of unfavorable factors including human epidermal growth factor receptor 2 (HER2)-positive tumor without anti-HER2 therapy, LVI, invasive lobular histology, positive lymph nodes, and positive surgical margins. Patients without these unfavorable factors but with grade 3 disease, ER-negative histology, or tumor size > 2 cm but ≤ 3 cm were categorized into the conditionally recommended group. Patients with any of the following unfavorable factors were categorized into the conditionally not recommended group: HER2-positive tumors without anti-HER2 therapy, LVI, or invasive lobular histology. The presence of a known germline BRCA1/2 mutation was considered an unfavorable factor; however, BRCA1/2 testing was not conducted in our study cohort, resulting in a lack of relevant data.

Clinicopathologic and clinical characteristics, including patient basic characteristics, surgical pathological results, type of adjuvant radiotherapy, and medication treatment, were collected. The clinical oncological outcomes included IBTR, lymph node recurrence, distant metastasis, overall survival, and breast cancer-related survival.

IORT was conducted using an Elekta Xoft Axxent electronic brachytherapy system. Following intraoperative frozen sectioning of the sentinel lymph node and margin, a planned dose of 20 Gy was applied to the balloon surface in cases without metastatic lymph node involvement or positive resection margins. EBRT was administered either as 42.56 Gy in 16 fractions or 50 Gy in 25 fractions to the whole breast, with a sequential boost of 10–15 Gy to the tumor bed. Alternatively, it was delivered as 50.4 Gy in 28 fractions to the whole breast with a simultaneous integrated boost to the tumor bed, totaling 58.8 Gy. Regional lymph node irradiation was not performed. In cases where metastatic lymph nodes or positive resection margins were present, IORT was not administered. Instead, patients with positive resection margins were offered further resection followed by adjuvant whole breast EBRT. Patients with metastatic lymph nodes were offered whole breast EBRT along with regional lymph node irradiation.

Subsequent follow-ups included history and physical examination at each outpatient visit, breast ultrasound every 6 months, mammography evey year, abdominal ultrasound every 6 months, chest X-ray every 6 months, and bone scan every year or when clinically indicated. Additional imaging was arranged for patients exhibiting symptoms or abnormal findings during routine examinations, suggestive of locoregional or distant relapse.

The endpoints of this study were IBTR, lymph node recurrence, distant metastasis, overall survival, and breast cancer-related survival. IBTR was defined as

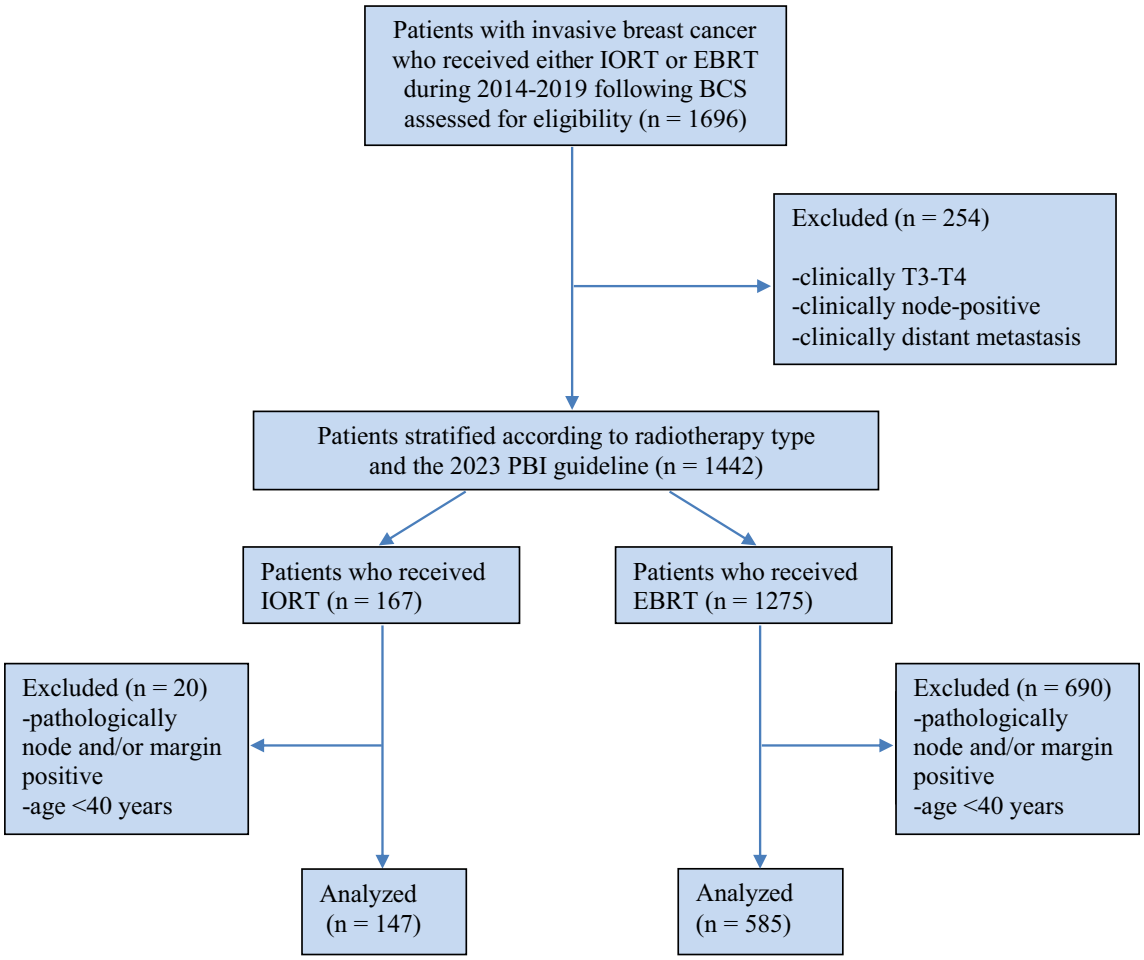

Fig. 1 CONSORT diagram

tumor recurrence in the skin or parenchyma of the ipsilateral breast after BCS plus radiotherapy (either IORT or EBRT) in the absence of regional or distant relapse. Lymph node recurrence was defined as recurrences in ipsilateral axillary, internal mammary, supraclavicular, inflaclavicular nodes. Patients were followed until locoregional and/or distant relapse, death, loss to follow-up, or the end date of study data collection: December 31, 2022.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and were compared using a t test. Categorical variables are expressed as numbers with percentages and were compared using the chi-square test. Clinical outcomes, including IBTR, regional lymph node recurrence, distant metastasis, overall survival, and breast cancer-related survival, were compared between the IORT and EBRT groups using the chi-square test. Kaplan–Meier analysis was performed to depict the cumulative risks of locoregional recurrence of IORT compared to that of EBRT. Log-rank test was used to compare the survival distributions between IORT and EBRT, stratified by different risk groups. Univariate and multivariate Cox regression analyses were used for subgroup analysis of hazard ratios. All the statistical analyses were conducted with IBM SPSS version 19.0. A two-tailed p value < 0.05 was considered to indicate statistical significance.

Results

A total of 732 patients were enrolled in the final data analysis. The mean follow-up time was 5.1 years. The basic characteristics of the selected patients are shown in Table 1.

Overall, of the 732 patients analyzed, 147 patients received IORT, and 585 patients received EBRT. Significant differences were observed in estrogen receptor (ER)/progesterone receptor (PR) status, HER2 status, histologic grade, PBI risk groups, and systemic therapy (chemotherapy, hormone therapy, targeted therapy) between the IORT and EBRT groups. In the IORT cohort, 142 out

Table 1 Patient basic characteristis

	IORT (n = 147)	EBRT (n = 585)	*P* value
Age	54.7 ± 9.7	54.0 ± 8.9	0.405
40–49	53 (36.1)	214 (36.6)	
≥ 50	94 (64.0)	371 (63.4)	
BMI	23.8 ± 4.1	24.0 ± 3.9	0.576
BMI < 18.5	9 (6.1)	23 (3.9)	
18.5 ≤ BMI < 24	83 (56.5)	295 (50.4)	
BMI ≥ 24	55 (37.4)	260 (44.4)	
Lacking data	0 (0.0)	7 (1.2)	
Pathological stage			0.252
T1N0	120 (81.6)	452 (77.3)	
T2N0	27 (18.4)	133 (22.7)	
ER status			< 0.001
ER or PR positive	142 (96.6)	480 (82.1)	
ER and PR negative	5 (3.4)	105 (18.0)	
HER2 status			0.014
HER2 positive	8 (5.4)	84 (14.4)	
HER2 negative	139 (94.6)	494 (84.5)	
HER2 equivocal	0 (0.0)	4 (0.7)	
HER2 untested	0 (0.0)	3 (0.5)	
Histologic type			0.255
Invasive ductal	117 (79.6)	495 (84.6)	
Invasive lobular	8 (5.4)	15 (2.6)	
Mucinous	12 (8.2)	37 (6.3)	
Other	10 (6.8)	38 (6.5)	
Histologic grade			< 0.001
1	44 (29.9)	117 (20.0)	
2	96 (65.3)	345 (59.0)	
3	7 (4.8)	117 (20.0)	
Lacking data	0 (0.0)	6 (1.0)	
Risk Group by 2023 guideline			< 0.001
Recommended	91 (61.9)	267 (45.6)	
Conditionally recommended	27 (18.4)	199 (34.0)	
Conditionally not recommended	29 (19.7)	119 (20.3)	
Resection Margin			0.777
< 2 mm	68 (46.3)	263 (45.0)	
≥ 2 mm	79 (53.7)	322 (55.0)	
Tumor size (mm)	14.5 ± 6.6	15.3 ± 7.1	0.242
≤ 2 cm	117 (79.6)	433 (74.0)	
2 cm < size ≤ 3 cm	30 (20.4)	152 (26.0)	
LVI			0.537
Present	17 (11.6)	68 (11.6)	
Absent	128 (87.1)	514 (87.9)	
Lacking data	2 (1.4)	3 (0.5)	
Chemotherapy			< 0.001
Yes	10 (6.8)	165 (28.2)	
No	137 (93.2)	420 (71.8)	
Hormone therapy			< 0.001
Yes	140 (95.2)	460 (78.6)	
No	7 (4.8)	125 (21.4)	

Table 1 (continued)

	IORT (n = 147)	EBRT (n = 585)	*P* value
Target therapy			0.006
Yes	3 (2.0)	51 (8.7)	
No	144 (98.0)	534 (91.3)	

of 147 patients (96.6%) were ER/PR positive, compared to 480 out of 585 patients (82.1%) in the EBRT group ($p < 0.001$). Additionally, 8 out of 147 patients (5.4%) in the IORT group were HER2 positive, while 84 out of 585 patients (14.4%) in the EBRT group were HER2 positive ($p = 0.014$). There was also a significant difference in the distribution of histologic grades, with a higher percentage of grade 3 tumors observed in the EBRT group (4.8% in the IORT group vs. 20.0% in the EBRT group).

Furthermore, significant differences were noted in the proportions of patients receiving systemic therapy, including chemotherapy (6.8% vs. 28.2%, $p < 0.001$), hormone therapy (95.2% vs. 78.6%, $p < 0.001$), and target therapy (2.0% vs. 8.7%, $p = 0.006$). However, no significant differences were observed in other basic characteristics, including age, body mass index (BMI), pathological stage, cancer histological type, tumor resection margin, and pathological tumor size, between the two groups.

The clinical outcomes of IORT and EBRT were compared. The incidence of IBTR and regional lymph node recurrence in the IORT group was greater than that in the EBRT group. The locoregional recurrence rate was significantly higher in the IORT group (6.1% in the IORT group vs. 2.6% in the EBRT group; $p = 0.030$). The regional lymph node recurrence rate reached statistical significance (3.4% in the IORT group vs. 0.3% in the EBRT group; $p = 0.001$), while IBTR did not (2.7% in the IORT group vs. 2.2% in the EBRT group, $p = 0.720$). There were no significant differences in terms of distant metastasis, total deaths, or breast cancer-related deaths between the two groups (Table 2).

The outcomes of IORT and EBRT were compared according to the 2023 ASTRO Clinical Practice Guideline for PBI. The patients were classified into recommended group, conditionally recommended group, or conditionally not recommended group. Among the 358 patients in the recommended group, no significant differences were observed in terms of IBTR, locoregional recurrence, distant metastasis, total death, or breast cancer-related death, regardless of whether they received IORT or EBRT. Additionally, no occurrences of regional lymph node recurrence were reported in either treatment group (Table 3).

Among the 226 patients in the conditionally recommended group, locoregional recurrence of the patients in the IORT group was significantly higher than that of the EBRT group (11.1% in the IORT group vs. 3.0% in the EBRT group, $p = 0.044$). There were no significant differences observed in terms of distant metastasis, total deaths, or breast cancer-related deaths (Table 4).

Table 2 Comparison between clinical outcomes of IORT and EBRT

	IORT(n = 147)	EBRT(n = 585)	*p* value
IBTR			0.72
No	143 (97.3)	572 (97.8)	
Yes	4 (2.7)	13 (2.2)	
Lymph node recurrence			0.001
No	142 (96.6)	583 (99.7)	
Yes	5 (3.4)	2 (0.3)	
Locoregional recurrence			0.03
No	138 (93.9)	570 (97.4)	
Yes	9 (6.1)	15 (2.6)	
Distant metastasis			0.8
No	144 (98.0)	571 (97.6)	
Yes	3 (2.0)	14 (2.4)	
Total death			0.665
No	142 (96.6)	569 (97.3)	
Yes	5 (3.4)	16 (2.7)	
Breast cancer-related death			0.416
No	145 (98.6)	581 (99.3)	
Yes	2 (1.4)	4 (0.7)	
Follow-up years	4.7 ± 1.6	5.1 ± 1.7	0.013

Among the 148 patients in the conditionally not recommended group, the locoregional recurrence rate was significantly higher in the IORT group compared to the EBRT group (13.8% vs. 2.5%, $p = 0.010$). There were no significant differences in distant metastasis or total deaths between the groups, and no breast cancer-related deaths occurred in either group (Table 5).

The Kaplan–Meier curve for the cumulative probability of locoregional recurrence showed that, for the recommended group, the risk of locoregional recurrence was similar between IORT and EBRT (log-rank test, $p = 0.933$). However, both the conditionally recommended and conditionally not recommended groups exhibited a higher risk of locoregional recurrence within 5 years with IORT compared to EBRT (log-rank test,

Table 3 Comparison between clinical outcomes of IORT and EBRT (recommended group)

	IORT(n = 91)	EBRT(n = 267)	*p* value
IBTR			0.978
No	89 (97.8)	261 (97.8)	
Yes	2 (2.2)	6 (2.3)	
Lymph node recurrence			
No	91 (100.0)	267 (100.0)	
Yes	0 (0.0)	0 (0.0)	
Locoregional recurrence			0.978
No	89 (97.8)	261 (97.8)	
Yes	2 (2.2)	6 (2.3)	
Distant metastasis			0.779
No	90 (98.9)	263 (98.5)	
Yes	1 (1.1)	4 (1.5)	
Total death			0.397
No	87 (95.6)	260 (97.4)	
Yes	4 (4.4)	7 (2.6)	
Breast cancer-related death			0.086
No	90 (98.9)	267 (100.0)	
Yes	1 (1.1)	0 (0.0)	
Follow-up years	5.0 ± 1.5	5.4 ± 1.7	0.169

Table 4 Comparison between clinical outcomes of IORT and EBRT (conditionally recommended group)

	IORT(n = 27)	EBRT(n = 199)	*p* value
IBTR			0.102
No	25 (92.6)	195 (98.0)	
Yes	2 (7.4)	4 (2.0)	
Lymph node recurrence			0.25
No	26 (96.3)	197 (99.0)	
Yes	1 (3.7)	2 (1.0)	
Locoregional recurrence			0.044
No	24 (88.9)	193 (97.0)	
Yes	3 (11.1)	6 (3.0)	
Distant metastasis			0.937
No	26 (96.3)	191 (96.0)	
Yes	1 (3.7)	8 (4.0)	
Total death			0.846
No	26 (96.3)	193 (97.0)	
Yes	1 (3.7)	6 (3.0)	
Breast cancer-related death			0.574
No	26 (96.3)	195 (98.0)	
Yes	1 (3.7)	4 (2.0)	
Follow-up years	4.8 ± 1.4	5.3 ± 1.6	0.784

$p = 0.026$ for the conditionally recommended group and $p = 0.007$ for the conditionally not recommended group) (Fig. 2).

Table 5 Comparison between clinical outcomes of IORT and EBRT (conditionally not recommended group)

	IORT(n = 29)	EBRT(n = 119)	*p* value
IBTR			0.388
No	29 (100.0)	116 (97.5)	
Yes	0 (0.0)	3 (2.5)	
Lymph node recurrence			< 0.001
No	25 (86.2)	119 (100.0)	
Yes	4 (13.8)	0 (0.0)	
Locoregional recurrence			0.01
No	25 (86.2)	116 (97.5)	
Yes	4 (13.8)	3 (2.5)	
Distant metastasis			0.545
No	28 (96.6)	117 (98.3)	
Yes	1 (3.5)	2 (1.7)	
Total death			0.388
No	29 (100.0)	116 (97.5)	
Yes	0 (0.0)	3 (2.5)	
Breast cancer-related death			
No	29 (100.0)	119 (100.0)	
Yes	0 (0.0)	0 (0.0)	
Follow-up years	5.3 ± 1.7	5.4 ± 1.7	0.741

Univariate and multivariate analyses were performed to evaluate risk factors associated with IBTR and regional lymph node recurrence. As depicted in Table 6, a resection margin of less than 2 mm was associated with a greater risk of IBTR, while adjuvant radiotherapy type, BMI, age, ER/PR status, HER2 status, tumor size, histologic grade, and cancer histological type did not reach statistical significance in proving an association with IBTR risk. LVI was not included in the multivariate analysis for IBTR, as all instances of IBTR occurred exclusively in patients lacking LVI.

As depicted in Table 7, risk factors, including receiving IORT as adjuvant therapy, the presence of LVI, and a tumor size > 2 cm, were associated with a greater risk of LN recurrence, while BMI, age, ER/PR status, HER2 status, resection margin, histologic grade, and cancer histological type did not reach statistical significance.

Discussion

The results of our studies showed a significantly greater locoregional recurrence rate in the IORT group than in the EBRT group (Table 2), which is consistent with the findings of previous landmark studies. The results of the TARGIT-A trial showed that the five-year risk of local recurrence in the ipsilateral breast was 3.3% for IORT versus 1.3% for EBRT ($p = 0.042$). The five-year risk of regional lymph node recurrence was 1.1% for IORT and 0.9% for EBRT but was not significantly different

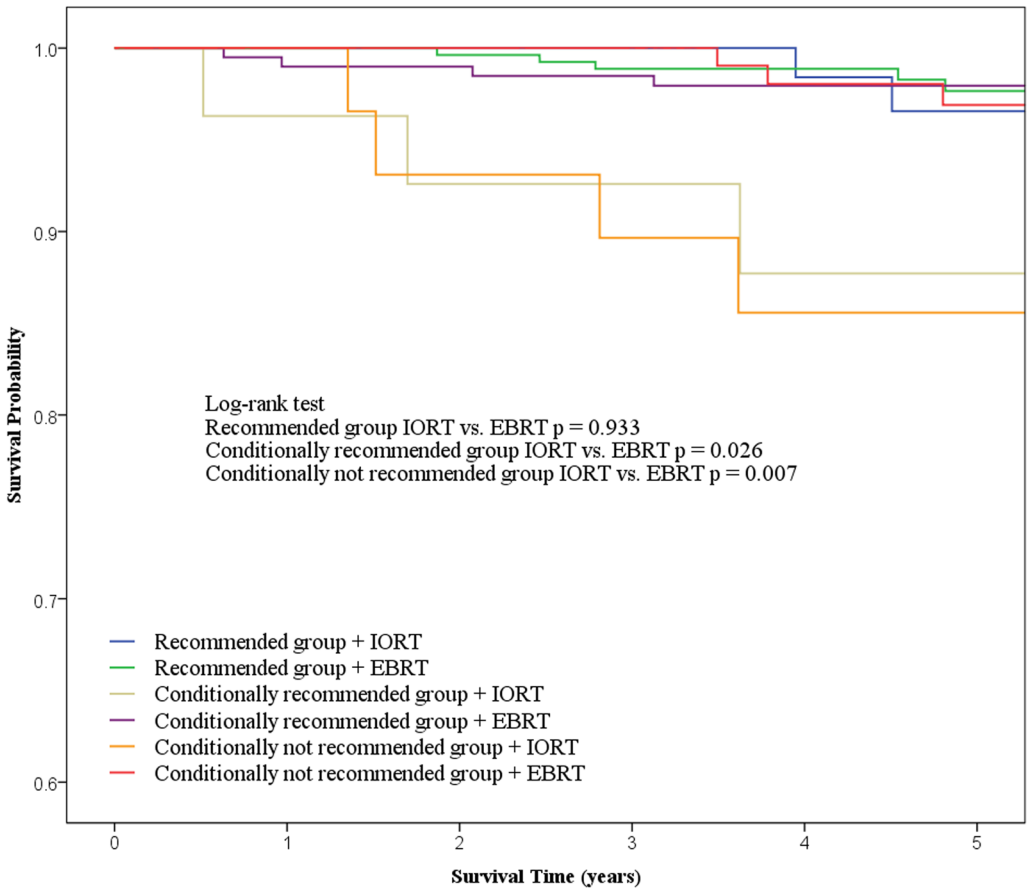

Fig. 2 Kaplan–Meier curves for locoregional recurrence analysis

($p=0.609$) [8]. In contrast, our study showed a significantly greater regional lymph node recurrence rate in the IORT group (3.4% vs. 0.3% in the EBRT group; $p=0.001$). The IBTR was not significantly different (2.7% for IORT vs. 2.2% for EBRT, $p=0.720$). The ELIOT study showed a significantly greater five-year event rate for IBTR (4.2% for IORT vs. 0.5% for EBRT, $p<0.0001$), regional lymph node metastasis (0.9% for IORT vs. 0.3% for EBRT, $p=0.012$), and locoregional tumor recurrence (5.1% for IORT vs. 0.8% for EBRT, $p<0.0001$) [9]. In comparison to the TARGIT-A trial and ELIOT study, our study excluded patients who had risk factors including lymph node metastasis or positive margin and could therefore cause a smaller difference in IBTR between the IORT and EBRT groups.

The results of Leonardi et al. study revealed that the IBTR rate was 4.4% in the cautionary group and 1.5% in the suitable group, as defined by the 2009 ASTRO APBI consensus [12], while the regional lymph node failure rate was 1.9% in the cautionary group and 1.5% in the suitable group. Our study found a higher IBTR rate of 2.2% but a lower regional lymph node recurrence rate of 0.0% in the recommended group. Conversely, regional lymph node recurrence rates were higher in the conditionally recommended group (3.7%) and the conditionally not recommended group (13.8%). Since our study adopted the 2023 ASTRO guideline for PBI and included younger patients, the greater incidence of locoregional recurrence could potentially be attributed to this younger age group and a higher proportion of patients exhibiting high-risk characteristics such as tumor size > 2 cm, resection margin < 2 mm, and presence of LVI. Both the Leonardi et al. study and our study support the idea that IORT is more effective for patients who meet strict criteria and exhibit fewer unfavorable risk factors.

In 2017, the Taiwan Intraoperative Radiotherapy Study Cooperative Group (T-IORTSCG) study analyzed 261 patients with a tumor less than 3 cm in length, no lymph node involvement, invasive ductal carcinoma or ductal carcinoma in situ, and a minimum age of 45 years. Among these patients, 6 patients (2.3%) had positive lymph nodes, and 6 patients (2.3%) had positive margins. Seven out of the 261 patients (3.1%) received supplemental EBRT (3 due to lymph node positivity, 4 due

Table 6 Univariate and Multivariate analysis of risk factors for IBTR

Risk factor	Hazard ratio (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Group				
EBRT	Reference		Reference	
IORT	1.33 (0.43–4.08)	0.619	1.50 (0.47–4.76)	0.49
BMI				
BMI < 24	Reference		Reference	
BMI ≥ 24	0.90 (0.34–2.36)	0.825	0.90 (0.33–2.44)	0.835
Age				
40–49	1.50 (0.46–4.88)	0.5	1.20 (0.36–4.05)	0.768
50–59	0.69 (0.17–2.76)	0.599	0.63 (0.15–2.59)	0.522
≥ 60	Reference		Reference	
ER/PR				
Positive	Reference		Reference	
Negative	1.23 (0.35–4.27)	0.747	1.21 (0.29–5.00)	0.795
HER2				
Negative	Reference		Reference	
Positive	2.61 (0.92–7.40)	0.072	2.51 (0.81–7.75)	0.111
Margin				
≥ 2 mm	Reference		Reference	
< 2 mm	3.77 (1.23–11.55)	0.02	3.54 (1.15–10.93)	0.028
Size				
≤ 2 cm	Reference		Reference	
> 2 cm	1.24 (0.44–3.53)	0.684	1.23 (0.42–3.64)	0.706
Grade				
1–2	Reference		Reference	
3	1.39 (0.45–4.27)	0.562	1.06 (0.29–3.89)	0.928
Cancer type				
IDC	Reference		Reference	
Mucinous	1.77 (0.41–7.75)	0.448	1.62 (0.35–7.51)	0.538

to margin positivity) [13]. The locoregional recurrence rate was extremely low (0.8%, 2 out of 261 patients), with a mean follow-up time of 15.6 months. In our study, 8 out of 167 patients (4.8%) had positive lymph nodes, and 8 out of 167 patients (4.8%) had positive margins. However, we had a lower percentage of patients who received supplemental EBRT (2.4%, 2 due to metastatic lymph node, 1 due to margin positivity, and 1 due to a tumor size > 3 cm, Supplement Table 1) and higher locoregional recurrence rate (6.6%, 11 out of 167 patients, Supplement Table 2). The patients who received supplemental EBRT in both studies did not experience locoregional recurrences, suggesting potential benefits of adding supplemental EBRT.

In 2021, Hsin-Yi Yang et al. revealed significantly greater locoregional recurrence in the IORT group than in the EBRT group, with 10.6% locoregional recurrence in the IORT group and 2.4% in the EBRT group ($p = 0.024$) [14]. Locoregional recurrences tended to occur in patients in the unsuitable and cautionary groups. This finding is consistent with our observation that the locoregional recurrence rates were higher in the conditionally recommended and conditionally not recommended groups. However, the overall locoregional recurrence rate for patients receiving IORT in our study was lower (6.6%). A lower percentage of LVI (12.0% compared with 23.4% in the Hsin-Yi Yang et al. study) and a higher percentage of positive hormone receptors (97.0% compared with 76.6% in the Hsin-Yi Yang et al. study) may have contributed to a lower locoregional recurrence rate (Table 1 and Supplement Table 1).

The study by De Rose et al. compared the IBTR rates of patients undergoing IORT to a matched cohort receiving whole breast irradiation. Patients were stratified according to the 2009 and 2017 ASTRO criteria for APBI. The five-year IBTR rate did not show a significant difference between IORT and EBRT for the suitable group. However, patients in the cautionary group experienced a significantly higher five-year IBTR rate if they underwent IORT [15]. Our findings were consistent with these results, showing that in patients who met the

Table 7 Univariate and Multivariate analysis of risk factors for lymph node recurrences

Risk factor	Hazard ratio (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Group				
EBRT	Reference		Reference	
IORT	10.41 (2.02–53.69)	0.005	100.59 (3.29–3073.30)	0.008
BMI				
BMI < 24	Reference		Reference	
BMI ≥ 24	1.73 (0.39–7.72)	0.475	2.64 (0.53–13.12)	0.235
Age				
40–49	0.70 (0.10–4.98)	0.722	0.37 (0.04–3.13)	0.362
50–59	1.07 (0.18–6.42)	0.94	0.23 (0.02–2.41)	0.218
≥ 60	Reference		Reference	
ER/PR				
Positive	Reference		Reference	
Negative	2.23 (0.43–11.48)	0.339	4.53 (0.28–73.49)	0.288
HER2				
Negative	Reference		Reference	
Positive	1.09 (0.13–9.06)	0.936	1.23 (0.09–16.76)	0.876
Margin				
≥ 2 mm	Reference		Reference	
< 2 mm	3.01 (0.58–15.49)	0.189	2.11 (0.38–11.87)	0.397
Size				
≤ 2 cm	Reference		Reference	
> 2 cm	17.95 (2.16–149.11)	0.008	27.13 (2.79–263.72)	0.004
LVI				
Negative	Reference		Reference	
Positive	5.32 (1.19–23.84)	0.029	6.96 (1.04–46.68)	0.046
Grade				
1–2	Reference		Reference	
3	1.89 (0.37–9.74)	0.447	4.65 (0.17–124.76)	0.36
Cancer type				
IDC	Reference		Reference	
ILC	4.68 (0.56–38.92)	0.153	7.74 (0.47–127.25)	0.152

strict criteria for the recommended PBI group, the IBTR rates for IORT and EBRT were similar. Additionally, the De Rose et al. study reported ten-year and fifteen-year IBTR rates, indicating that differences in outcomes may become more pronounced with longer follow-up periods.

The outcome analysis of our study was conducted in accordance with the 2023 ASTRO Clinical Practice Guideline for PBI [11]. Despite the guideline's hesitation to recommend IORT due to concerns about IBTR, our study showed that patients in the recommended group had a similar IBTR rate between IORT and EBRT. Longer follow-up is needed to confirm these findings.

According to the univariate and multivariate analyses of risk factors, resection margin status was a significant risk factor for IBTR [adjusted HR 3.54 (1.15–10.93), $p = 0.028$], whereas a tumor size > 2 cm [adjusted HR 27.13 (2.79–263.72), $p = 0.004$], LVI [adjusted HR 6.96 (1.04–46.68), $p = 0.046$], and radiotherapy type [adjusted HR 100.59 (3.29–3073.30), $p = 0.008$] were significant risk factors for regional lymph node recurrence.

A retrospective study performed by Michal Falco et al. reviewed 823 patients aged ≥ 60 years with ER-positive, HER2-negative, and cN0 breast cancer who received BCS, with 24.2% of patients (n = 199) receiving IORT. Supplemental EBRT was applied for patients with lymph node metastasis, invasive lobular type, LVI, extensive in situ components, or resection margins < 2 mm. The in-breast relapse-free survival rate was greater in the IORT with supplemental EBRT group than in the IORT only group (100.0% vs. 98.0%), although the difference was not statistically significant [16]. Supplemental EBRT could be considered for those who displayed risk factors, including a close margin < 2 mm.

A study conducted by Gary Freedman et al. analyzed 1262 patients and reported significantly different 10-year cumulative incidences of IBTR among patients with different margin statuses (negative margin, 7%; positive margin, 12%; close margin < 2 mm, 14%; $p = 0.004$). In addition, patients with a close margin < 2 mm had an equal or even greater risk of IBTR than did those with a positive margin. For those with initially positive or close margins, the same risk of 10-year IBTR (7%) could be achieved by re-excision for a final negative margin [17]. Since margin status significantly influences the IBTR rate, it is important to achieve a negative margin > 2 mm by initial excision or re-excision. Several techniques for intraoperative margin assessment are being developed, but additional clinical trials are needed to evaluate the efficacy of these methods [18].

In the ELIOT study, univariate analysis revealed a significantly increased risk of IBTR in patients with risk factors, including a tumor size greater than 2 cm, four or more metastatic axillary lymph nodes, grade 3, Ki-67 > 20%, luminal B or triple-negative breast cancer. Our study revealed that a tumor size greater than 2 cm was associated with a significantly greater risk of lymph node recurrence. Lymphovascular invasion was also associated with a higher risk of lymph node recurrence in our study, but this association was not detected in the ELIOT study [9].

Our study has several limitations, including its retrospective, single-center design and median follow-up time of 5.1 years. According to some studies, the 10-year cumulative incidence of IBTR could differ greatly from the 5-year cumulative incidence [15], which means that a longer follow-up time is needed to detect recurrences occurring more than five years after treatment. In addition, treatment toxicities were not recorded or analyzed in our study.

Conclusions

The locoregional recurrence rate in the IORT group was comparable to that of the EBRT group for patients recommended for PBI, as outlined in the 2023 ASTRO Clinical Practice Guideline. However, for patients categorized as conditionally recommended or conditionally not recommended for PBI, the IORT group experienced a higher locoregional recurrence rate. This suggests that while IORT can be an effective treatment option, its success depends significantly on careful patient selection to achieve optimal outcomes.

Abbreviations

APBI	Accelerated partial breast irradiation
ASTRO	American Society for Radiation Oncology
BCS	Breast-conserving surgery
BMI	Body mass index
EBRT	External beam radiotherapy
ER	Estrogen receptor
HR	Hazard ratio
IBTR	Ipsilateral breast tumor recurrence
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
IORT	Intraoperative radiotherapy
LVI	Lymphovascular invasion
PBI	Partial breast irradiation
PR	Progesterone receptor
TARGIT-A	Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer
TIORTSCG	Taiwan Intraoperative Radiotherapy Study Cooperative Group

Supplementary Information

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Additional file 1.

Additional file 2.

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Author contributions

All authors contributed to study design. WLC contributed to collating of data and statistical analysis. SYG analyzed and interpreted the data, and was a major contributor in writing the manuscript. TCL and JAL reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of China Medical University Hospital, Taiwan [CMUH106-REC3-119(CR-4)].

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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