Original Article

Intra-operative partial breast irradiation versus external whole breast irradiation for early breast cancer

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ABSTRACT

Aims: Intra-operative radiotherapy (IORT) is a new alternative way to give radiation therapy. During surgery to remove breast cancer, radiation is given as a single dose directly to the area where the tumor used to be. The aim of the study was to compare the results of IORT as partial breast irradiation and external whole breast irradiation (EBRT) for early breast cancer in elderly patients after breast-conserving surgery. The results were retrospectively analyzed from a single institution. We report 7-year results for local control.

Settings and Design: Cross-sectional study.

Methods and Material: Between November 2012 and December 2019, 21 Gy partial breast irradiation was applied intra-operatively to 40 selected patients. Two of these patients were excluded from the study, and 38 patients were evaluated. Also, 38 patients who had EBRT and had similar properties to that of IORT patients were selected to compare the treatment results in terms of local control.

Statistical Analysis Used: SPSS version 21 was used for statistical analysis. Patient groups undergoing IORT and EBRT were analyzed with the Kolmogorov–Smirnov test. The groups were examined in terms of demographic features using t-test, and $P < 0.05$ was considered as statistically significant. Local recurrence rates were calculated by Kaplan–Meier analysis.

Results: The median follow-up time was 58 months (range 20–95 months). The local control was 100% in both groups, and no local recurrences were observed.

Conclusion: IORT seems to be a safe and effective alternative to EBRT for early breast cancer in elderly patients.

KEY WORDS: Breast cancer, breast-conserving surgery, breast irradiation, partial breast irradiation, whole-breast irradiation

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INTRODUCTION

Adjuvant radiotherapy after breast-conserving surgery has equivalent results to mastectomy in terms of survival and local recurrence. Adjuvant external whole breast irradiation (EBRT) is the standard of care for patients with early breast cancer.[1-3] The local recurrence rates following EBRT are less than 10% at 10 years compared with 25–30% following conservative surgery without radiotherapy.[4] Considering the studies, even in low-risk patients' omission of radiotherapy increases the risk of local relapse.[5]

Standard radiotherapy delivers 45–50 Gy to the whole breast, followed by a 10–16 Gy boost to the tumor; therefore, it requires 5–7 weeks treatment time. This is a long time, especially for women who live distant from a radiotherapy center. Recent studies on women who receive breast-conserving surgery show that 80% of recurrences occur close to the tumor bed. Therefore, researchers thought that it may not be necessary to irradiate the whole breast or irradiate the part at the greatest risk with a higher dose, and a shorter treatment time could be enough for selected early cancer patients. Based on this result, accelerated partial breast irradiation (APBI) has been developed as an alternative to EBRT. Intra-operative radiotherapy (IORT) is a modality of APBI.[6,7]

TARGIT-A, a prospective non-inferiority trial, compared intra-operative APBI with EBRT in terms of local recurrence (LR) and overall survival (OS).

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Cite this article as: Güzle Adaş Y, Uyar S, Yazıcı Ö. Intra-operative partial breast irradiation versus external whole breast irradiation for early breast cancer. J Can Res Ther 2023;19:165-8.

Submitted: 23-Dec-2020
Accepted in Revised Form: 29-Jul-2022
Published: 16-Mar-2023

Access this article online
Website: www.cancerjournal.net
DOI: 10.4103/jcrt.JCRT_1843_20
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The study concluded that IORT was non-inferior; the 5-year LRs for intra-operative RT and EBRT were 3.3% and 1.3%, respectively, $P = 0.04$ (non-inferior); the overall mortalities for intra-operative RT and EBRT were 3.9% and 5.3%, respectively ($p = 0.09$).[8]

IORT has a shorter course of treatment than EBRT and less toxicity by limiting the volume of normal tissues exposed to radiation. The potential disadvantages are the final pathological status of surgical margins and that lymph nodes are not available at the time of treatment delivery, so patients should be carefully selected. The American Society for Radiation Oncology (ASTRO) reported the consensus on the characteristics of patients on the use of IORT for APBI in early-stage breast cancer.[9,10]

In the present retrospective study, we compared the results of intra-operative APBI versus EBRT for breast cancer in terms of local control.

MATERIALS AND METHODS

Between November 2012 and December 2019, 40 early breast cancer patients were treated with intra-operative electron radiation therapy (IOERT) as a part of treatment after breast-conserving surgery. Patients who received IORT were evaluated by a multi-disciplinary team which consists of experienced radiation oncologists and surgeons before the surgery the approval from the ethics committee was obtained 10.09.2019.

Our patient selection criteria for IORT as partial breast irradiation as reported in ASTRO guidelines were as follows: patient age ≥60 years, unifocal and unicentric tumors with no lymph-vascular space invasion, invasive ductal or other favorable sub-types (mucinous, tubular, and colloid), positive estrogen receptor, tumor maximum diameter ≤2 cm, any grade, clear surgical margins, and a negative sentinel lymph node in the frozen section. Pure ductal carcinoma *in situ* was not allowed; also, neoadjuvant treatments were not allowed before surgery.[10]

Patients who were evaluated by the multi-disciplinary team and selected for IORT were informed by the radiation oncologists before treatment and consent received from patients.

In our clinic, a mobile linear accelerator (Mobetron Intraop Medical Incorporated, Santa Clara, US) which has four electron energy levels, 4, 6, 9, and 12 Mev, is being used for IORT. Different sized circular applicators are available for different field sizes between 3 and 10 cm, and all these applicators have different angles of 0°, 15°, and 30°. The appropriate energy and applicators are chosen according to tumor size, tumor location, and depth of the gland. The volume should include the entire surgical bed with a safety margin of 1–2 cm.

If surgical margins are clear and the sentinel lymph node is negative, 21 Gy of IORT as APBI is applied to the patient. The APBI applicator is placed in the tumor bed with an applicator, and a single dose of 21 Gy is given. The treatment time was 45–70 seconds because of different dose rates.

Two of 40 patients in the IORT group were excluded from this study because one of the patients had positive margins after final pathology and underwent mastectomy; one patient received whole breast and lymphatic irradiation because of micro-metastases in the lymph node. To compare the IORT group with the whole breast irradiation group, we evaluated all early breast cancer patients who received EBRT and boost for the tumor bed between November 2012 and December 2019. We included 38 patients to this group, who have similar ages and pathological properties to the IORT group. The external breast irradiation dose was 50 Gy in 25 fractions to the whole breast and a boost dose of 10–16 Gy to the tumor bed in 5–8 fractions.

SPSS version 21 was used for statistical analysis. Patient groups undergoing IORT and EBRT were analyzed with the Kolmogorov–Smirnov test. The groups were examined in terms of demographic features using t-test, and $P < 0.05$ was considered as statistically significant. Local recurrence rates were calculated by Kaplan–Meier analysis.

RESULTS

From November 2002 to December 2019, 38 patients with early-stage breast cancer, who received 21 Gy partial breast irradiation in our department, and the clinical results of these patients were retrospectively compared to 38 other early breast cancer patients who received EBRT. Patient and tumor characteristics are summarized in Table 1.

The median follow-up time was 58 months (range 20–95 months). The median age was 70 years (range 60–88 years) for the IORT group and 67 years (55–89 years) for the EBRT group in Figure 1. The tumor sizes were ≤1 cm for 15 patients (40%); 1–2 cm for 23 patients (60%) for the IORT group; and ≤1 cm for ten patients (26%), 1–2 cm for 24 patients (66%), and 2 cm for four patients (8%) for the EBRT group in [Figure 2]. The tumor grades were grade 1 in 25 patients and grade 2 in 13 patients in the IORT group. In the EBRT group, 22 patients had grade 1, and 16 patients had grade 2 tumors. ER was positive in all patients, whereas the progesterone receptor was positive in 32 patients in the IORT group and 29 patients in the EBRT group. Sentinel lymph node biopsy was negative for all patients. There was no lymph-vascular space invasion and extensive ductal carcinoma *in situ* component as well. There was no statistically important difference between the patient or tumor characteristics of the two groups except the ki-67 status. Ki-67 was statistically higher in the EBRT group.

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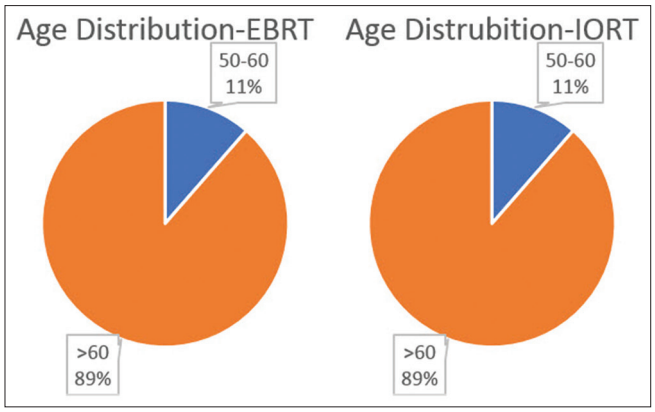

Figure 1: Age distribution for EBRT and IORT

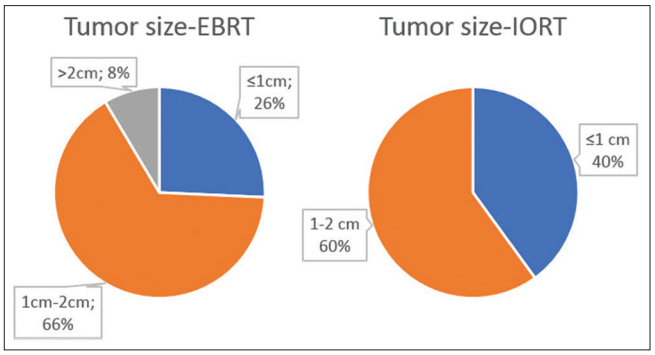

Figure 2: Tumor size for EBRT and IORT

Table 1: Patient characteristics

	EBRT	IORT	*P*
Age			
Mean	67 (55-89)	70 (60-88)	0.25
50-60	10 (%23)	6 (%11)	
>60	28 (%77)	32 (%89)	
Tumor diameter			
Mean	1,53 cm±0.52	1,25 cm±0.43	0.36
≤1 cm	10 (%26)	15 (%40)	
1-2 cm	24 (%66)	23 (%60)	
>2 cm	4 (%8)	0	
Grade			
Gr1	22 (%67)	25 (%66)	
Gr2	16 (%33)	13 (%34)	
SLNB			
Negative	38 (%94)	38 (%100)	
Positive	0	0	
ER			
Negative	0	0	
Positive	38	38	
PR			
Negative	9 (%20)	6 (%14)	
Positive	29 (%80)	32 (%86)	
Ki67			
Mean	27,6±23.8	15,7±13.4	0.03
≤%20	20 (%51)	28 (%74)	
>20%	18 (%49)	10 (%26)	

Local recurrence was defined as the recurrence in the same breast, and no local recurrences were observed in both groups.

DISCUSSION

IORT is one of the accelerated partial breast irradiation modalities. The lumpectomy site is irradiated with a single dose in IORT.

Two large randomized trials, TARGIT-A and ELIOT, highlighted the efficacy of IORT. TARGIT-A was a non-inferiority study in which 3451 patients from 11 countries were enrolled. The study compared intra-operative APBI with EBRT in terms of LR and OS. The study concluded that IORT was non-inferior; the 5-year LRs for IORT and EBRT were 3.3% and 1.3%, respectively, $P = 0.04$ (non-inferior); the overall mortalities for IORT and EBRT were 3.9% and 5.3%, respectively ($p = 0.09$).[6]

ELIOT was an equivalence trial. In ELIOT, IOERT was used like in this study. The ELIOT trial concluded that IOERT was equivalent to EBRT in terms of local recurrence (4,4% IOERT vs 0,4% with EBRT).[4]

In the ELIOT study, they observed 1822 patients between January 2000 to December 2008; in the TARGIT-A trial, 3451 patients were enrolled; we observed 38 patients for both groups. We observed that any LR rate in the IORT group was not significantly different from that in the EBRT group. This may be because of our limited number of patients.

In the study of Williams *et al*.,[11] single-fraction 21 Gy IORT was performed to 215 early-stage invasive or *in situ* breast cancer cases. In this study, 13 patients received whole breast irradiation after IOERT for adverse pathological features. Of 202 cases with only IORT, 89 patients experienced ipsilateral breast tumor recurrence. When the ASTRO APBI suitability criteria were applied, the local recurrence rate was significantly lower for suitable patients versus unsuitable patients (1,6% vs 21.0% $P = 0.0002$). This result shows that patient selection criteria are so important for APBI.

In our clinic, we perform IORT according to ASTRO criteria, and all the properties of the patients who receive IORT must be suitable to ASTRO criteria. This may be one of the reasons for not observing any local recurrences in our IORT group.

The most important advantage of IORT is completing adjuvant radiation therapy at the same time as surgery. However, this advantage may also be a disadvantage. Because there may be differences between the frozen pathology and final pathology results. In two of our patients, we observed this difference. One surgical margin was reported as positive, whereas it was negative in the frozen report and this patient had gone to mastectomy; one sentinel lymph node was reported to be micro-metastatic, whereas it was reported to be negative in the frozen report. We excluded these two patients from this study, but this may be evaluated as a disadvantage of IORT.

This study has some limitations. İt is a retrospective study limited to a single institution. The number of patients is limited when compared to the other large prospective studies. Despite a nearly 5 years follow-up time, this time interval is short to evaluate the local control in early-stage breast cancer.

CONCLUSION

IORT is a safe and effective treatment modality for selected early-stage breast cancer patients. IORT in general reduces the duration of the conventional radiotherapy course. In the meantime, EBRT remains the standard irradiation modality for breast cancer: those given IORT should be carefully selected. More studies with more patients are needed to evaluate both clinical outcomes and cosmetic results of IORT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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