Intraoperative radiation therapy for early stage breast cancer: experiences from Iran

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Abstract

Background and objective Currently no definite guideline exists on the use of intraoperative radiation therapy (IORT) among patients with early stage BC. We report our experiences with IORT among breast cancer (BC) patients in our region.

Methods All patients who received radical IORT from April 2014 on to March 2020 were included in the study. Patient selection criteria were as followed: age equal or older than 45 years old; all cases of invasive carcinomas, moreover in lobular carcinomas only after MRI and confirmation, and in cases with ductal carcinoma in-situ (DCIS) only those with low, intermediate grade, tumor size of equal or less than 2.5cm and a margin of 2-3mm; those between 45 and 50 years old with a tumor size of 0-2cm, those between 50 and 55 years old with a tumor size of 2-2.5cm, and those ≥55 years old with a tumor size of 2.5-3cm; those with invasive tumors a negative margin and in cases of DCIS a margin of 3mm; a negative nodal status (exception in patients with micrometastasis); and a positive estrogen receptor status.

Results Overall, 252 patients entered the study. Mean (SD) age of patients was 56.43±7.79 years. In total, 32.9% of patients had a family history of BC. Mean tumor size was 1.56±0.55 cm. Median (IQR) follow-up of patients was 24 (13, 36) months. Overall, 6 patients (2.4%) experienced recurrence in follow-up visits, among which three (1.2%) were local recurrence, two (0.8%) were regional recurrence and one patient (0.4%) had metastasis.

Median (IQR) time to recurrence was 23 (13, 36) among the six patients who had recurrence.

Overall, 11 patients (4.3%) with DCIS in our study received IORT. All these patients had free margins in histopathology examination. None of these patients experienced recurrence.

Conclusion For the first time, we categorized patients according to age and tumor size and older patients with larger tumor sizes were considered appropriate candidates for IORT. Our series showed a successful experience with the use of IORT in a region where facilities for IORT are limited using our modified criteria for patient selection.

Introduction

Accelerated partial breast irradiation (APBI) has been recently been considered as an appropriate substitute for whole breast irradiation (WBI) among patient with early stage, low risk breast cancer (BC) that have undergone breast conserving surgery (BCS) (1, 2). Intraoperative radiation therapy (IORT) is a type of APBI which includes delivering a single dose of radiation after BCS (3).

Currently no definite guideline exists on the use of IORT among patients with early stage BC. Moreover, aside to the TARGIT (4) and ELIOT clinical trials (5) that have mainly compared IORT to WBI and have evaluated the efficacy of IORT among patients with early stage BC, different study designs and more importantly different criteria for IORT has made reports from different institutions and regions of the
world variable. Furthermore, following these reports a large debate has been ongoing on the efficacy of IORT in the settings of early BC.

BCs may have different genetics, clinicopathology and behavior in different geographic regions (6) and to date limited reports have been published on IORT in BC in the Middle East (7). In this study we aimed to report our experiences and lessons with IORT among patients with BC using data from the largest BC registry in Iran.

**Methods**

**Study settings**

This study was conducted as part of the Shiraz Breast Cancer Registry which is a surgical registry affiliated to Shiraz University of Medical Sciences, Motahhari Clinic, Shiraz, Iran. This is the main referral center for patient with BC in Southern and Central Iran. The registry includes data on baseline characteristics, histopathology, imaging and clinical information related to each patient. Protocol of the center has been described elsewhere (6).

**Patients**

This report includes all patient who received radical IORT in our center from April 2014 on to March 2020.

IORT was first performed in April 2014 in our center in Faghihi Hospital, Iran. This was the second center in Iran and is among the few centers in the world that has been approved by the International Society of intraoperative radiation therapy for IORT in 2018 (8).

Based on our institutional guidelines which was prepared with a joint committee of experts in surgical oncology, radiation oncology and considering the guidelines of the American Society for Radiation Oncology, and the American Society of Breast Surgery, ELIOT and TARGIT trials (5, 9–11), patients with the following criteria received IORT as part of their treatment regimen: 1) Age equal or older than 45 years old; 2) Regarding histology all cases of invasive carcinomas were considered candidates, moreover in lobular carcinomas caution was taken and these patients were considered candidates only after MRI and confirmation of the radio-oncologist, and in cases with ductal carcinoma in-situ (DCIS) only those with low, intermediate grade, tumor size of equal or less than 2.5 cm and a margin of 2–3 mm were considered candidates; 3) Regarding tumor size those between 45 and 50 years old with a tumor size of 0–2 cm, those between 50 and 55 years old with a tumor size of 2-2.5 cm, and those equal and more than 55 years old with a tumor size of 2.5-3 cm were considered candidates; 4) Regarding marginal status those with invasive tumors a negative margin is considered sufficient and in cases of DCIS a margin of 3 mm was considered a candidate; 5) Regarding nodal status patient should have a negative nodal status and the exception is considered in patients with micrometastasis; 6) Regarding hormone receptor status, patients should have a positive estrogen receptor status.

For the current report those with boost IORT, were excluded.
IORT

IORT was carried out in our center using the Liac Sordina mobile linear accelerator. Electrons with 6, 8, 10 and 12 MeV were used according to the depth of the tumor which was measured using a marked needle. A dose of 21 Gy was administered to 95% isodose. Electron energy was chosen according to the thickness of the tissue that was prepared for radiation. Diameter of collimators was 4–6 cm and was chosen according to the diameter of the tumor and the tissue that is prepared by the surgeon for IORT.

Variables

Data on baseline characteristics (age, sex and BMI), obstetric and gynecological indices, use of oral contraceptive medication (OCP) or hormone replacement therapies, underlying diseases, social history including cigarette and alcohol use, clinical and surgery related information including type of axillary management, tumor size and grade, invasion, estrogen (ER) and progesterone (PR) receptors and human epidermal growth factor 2 (HER2) receptor status, chemotherapy before and after surgery, histopathology information and prognosis of patients were gathered.

Statistical analysis

Data were analyzed using the statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA), for windows, version 20. Plots were created using the Kaplan-Meier analysis. Data are reported as frequency and percentage for qualitative data and as means and standard deviations (SD) for quantitative data with normal distribution and as median and interquartile range (IQR) for quantitative data without a normal distribution.

Results

In total 252 patients had radical IORT during the study period in our centers and entered the study. All our patients were females. Mean (SD) age of patients was $56.43 \pm 7.79$ years old. In total, 32.9% of patients had a family history of BC. Mean age of pregnancy was $21.70 \pm 5.47$ years old. Majority of patients had a menopause (76.1%).

Other baseline characteristics of patients are shown in Table 1.
Table 1
Baseline characteristics of patient who received IORT.*

| Variables                        | Statistics                      |
|----------------------------------|---------------------------------|
| Age - yrs                        | Mean $56.43 \pm 7.79$           |
|                                  | Median (IQR) $56 \ (50, 62)$     |
| Sex - no. (%)                    | Female $252 \ (100)$            |
|                                  | Male $0$                        |
| Weight - Kg                      | $70.40 \pm 11.31$               |
| Height - Cm                      | $158.69 \pm 6.81$               |
| BMI - Kg/m$^2$                   | $27.96 \pm 4.29$                |
| Age of menstruation - yrs       | $13.36 \pm 1.41$                |
| Age at first pregnancy - yrs     | $21.70 \pm 5.47$                |
| Number of pregnancy - no. (%)    | 1 $18 \ (7.6)$                  |
|                                  | 2 $56 \ (23.6)$                 |
|                                  | 3 $62 \ (26.2)$                 |
|                                  | 4 $42 \ (17.7)$                 |
|                                  | 5 or more $74 \ (24.9)$         |
| Menopause - no. (%)              | Yes $191 \ (76.1)$              |
|                                  | No $50 \ (19.9)$                |
|                                  | Not sure $10 \ (4)$             |
| Age at menopause - yrs           | $48.90 \pm 4.59$                |
| Oral contraceptive use - no. (%)| Yes $154 \ (61.1)$              |
|                                  | No $98 \ (38.9)$                |
| Hormone replacement therapy use- no. (%) | Yes $5 \ (2.1)$        |
|                                  | No $235 \ (97.9)$               |
| Diabetes - no. (%)               | Yes $46 \ (18.3)$               |
|                                  | No $206 \ (81.7)$               |
| Hypertension - no. (%)           | Yes $71 \ (28.2)$               |
|                                  | No $181 \ (71.8)$               |
| Variables                                      | Statistics |
|-----------------------------------------------|------------|
| Hypercholesterolemia - no. (%)                | Yes        |
|                                               | 73 (29)    |
|                                               | No         |
|                                               | 179 (71)   |
| Hypothyroidism - no. (%)                      | Yes        |
|                                               | 39 (15.5)  |
|                                               | No         |
|                                               | 213 (84.5) |
| Hyperthyroidism - no. (%)                     | Yes        |
|                                               | 6 (2.4)    |
|                                               | No         |
|                                               | 246 (97.6) |
| Family history of breast cancer - no. (%)     | Yes        |
|                                               | 83 (32.9)  |
|                                               | No         |
|                                               | 169 (67.1) |
| Cigarette use - no. (%)                       | Yes        |
|                                               | 1 (0.4)    |
|                                               | No         |
|                                               | 251 (99.6) |
| Waterpipe use - no. (%)                       | Yes        |
|                                               | 24 (9.5)   |
|                                               | No         |
|                                               | 228 (90.5) |
| Alcohol use - no. (%)                         | Yes        |
|                                               | 1 (0.4)    |
|                                               | No         |
|                                               | 251 (99.6) |
| Breast side involvement - no. (%)             | Right      |
|                                               | 121 (48)   |
|                                               | Left       |
|                                               | 131 (52)   |

IORT: intraoperative radiation therapy; BMI: body mass index

*All plus-minus values are means and standard deviations unless stated otherwise.

The mean tumor size among our patients was 1.56 ± 0.55 cm. In histopathology, majority of patients had grade 1 (44.6%) and 2 (41.4%) BC. Moreover, with regard to grade of nucleus most patients had grade 1 (43.9%) and 2 nucleus grade (34.5%). In total, 71.7% of patients had in-situ components. The most common type of invasion was lymphovascular invasion which was seen among 14.5% of patients. Three patients in our report required additional surgery which included mastectomy. Moreover, two patients underwent re-excision of margins.

All of our patients were ER positive and majority of patients were PR positive (93.4%). In total, 14.6% of patients who underwent IORT had overexpression of HER2.

Regarding treatment specifics, 83.7% of patients received chemotherapy after breast conserving surgery. Most patients received hormone therapy (98.3%), from which patients mostly received letrozole alone.
(65.3%) followed by tamoxifen alone (24.2%) and the rest received either a combination of tamoxifen and laterazole (9.3%) or aromasins (1.3%).

In total 11 patients (4.3%) with DCIS in our study received IORT. All these patients had free margins in histopathology examination. None of these patients experience recurrence.

Median (IQR) follow-up of patients was 24 (13, 36) months. Overall, 6 patients (2.4%) experienced recurrence in follow-up visits, among which three (1.2%) were local recurrence, two (0.8%) were regional recurrence and one patients (0.4%) had metastasis.

Median (IQR) time to recurrence was 23 (13, 36) among the six patient who had recurrence. Figure 1 shows Kaplan-Meier plot for disease free survival (recurrence).
Table 2
Clinical characteristics of patients who received IORT.*

| Variables                        | Statistics       |
|----------------------------------|------------------|
| Type of breast surgery - no. (%) | Quadrantectomy   |
|                                  | 249 (98.8)       |
|                                  | Quadrantectomy + mastectomy |
|                                  | 3 (1.2)          |
| Type of axillary management - no. (%) | SLNB            |
|                                  | 252 (100)        |
| Pathology subtype - no. (%)      | Invasive ductal carcinoma |
|                                  | 227 (95)         |
|                                  | Invasive lobular carcinoma |
|                                  | 6 (2.4)          |
|                                  | Invasive tubular carcinoma |
|                                  | 5 (2)            |
|                                  | Mucinous         |
|                                  | 3 (1.2)          |
|                                  | Papillary        |
|                                  | 3 (1.2)          |
|                                  | Other            |
|                                  | 8 (3.2)          |
| Tumor size - cm                  | 1.56 ± 0.55      |
| Tumor grade - no. (%)            | 1                |
|                                  | 99 (44.6)        |
|                                  | 2                |
|                                  | 92 (41.4)        |
|                                  | 3                |
|                                  | 31 (14)          |
| Grade of nucleus - no. (%)       | 1                |
|                                  | 65 (43.9)        |
|                                  | 2                |
|                                  | 51 (34.5)        |
|                                  | 3                |
|                                  | 32 (21.7)        |
| In-situ component - no. (%)      | Yes              |
|                                  | 157 (71.7)       |
|                                  | No               |
|                                  | 60 (27.4)        |
|                                  | Unknown          |
|                                  | 2 (0.9)          |
| Tumor necrosis - no. (%)         | Yes              |
|                                  | 76 (38.6)        |
|                                  | No               |
|                                  | 120 (60.9)       |
|                                  | Unknown          |
|                                  | 1 (0.5)          |
| Invasion - no. (%)               | Perineural       |
|                                  | 19 (8.6)         |
|                                  | Lymphatic-vascular |
|                                  | 32 (14.5)        |
|                                  | All              |
|                                  | 10 (5)           |
|                                  | None             |
|                                  | 159 (71.9)       |
| Variables                                      | Statistics           |
|------------------------------------------------|----------------------|
| Esterogon receptor - no. (%)                   | Positive 240 (100)   |
|                                                | Negative 0           |
| Progesterone receptor - no. (%)                | Positive 225 (93.4)  |
|                                                | Negative 16 (6.6)    |
| HER2 overexpression - no. (%)                  | Positive 31 (14.6)   |
|                                                | Negative 182 (85.4)  |
| Chemotherapy before surgery - no. (%)          | Yes 0               |
|                                                | No 252 (100)         |
| Chemotherapy after surgery - no. (%)           | Yes 205 (83.7)       |
|                                                | No 40 (16.3)         |
| IORT type - no. (%)                            | Radical 252 (100)    |
| Hormone therapy - no. (%)                      | Yes 236 (98.3)       |
|                                                | No 4 (1.7)           |
| Type of hormone therapy - no. (%)              | Tamoxifen 57 (24.2)  |
|                                                | Laterazole 154 (65.3)|
|                                                | Tamoxifen + laterazole 22 (9.3) |
|                                                | Aromasins 3 (1.3)    |
| Recurrence - no. (%)                           | Yes 6 (2.4)          |
|                                                | Local 3 (1.2)        |
|                                                | Regional 2 (0.8)     |
|                                                | Metastatic 1 (0.4)   |
|                                                | No 246 (97.6)        |
| Follow-up duration - months                    | Mean 26.39 ± 16.00   |
|                                                | Median (IQR) 24 (13, 36) |

SLNB: sentinel lymph node biopsy

*All plus-minus values are means and standard deviations unless stated otherwise.

Discussion
We presented our experience with the use of IORT among patients with BC in our region using our own specific institutional criteria. We found that during a median follow-up of 2 years 2.4% of our patients developed recurrence, furthermore no mortality was documented among patients.

The ELIOT clinical trial study (5) compared standard EBRT and IORT. They used the following criteria of: age 48–75 years, tumor size ≤ 2.5 cm for selection of patients for IORT. In their study they did not consider hormone receptor status and pathology sub-type as criteria for patient selection. Authors reported a five year loco-regional recurrence of 5.4% vs. 0.8% (p < 0.0001) and a 5.1% vs. 4.8% (p = 0.94) rate of distant metastasis for patients who received IORT compared to those who received external radiotherapy. Moreover, they recorded a death rate of 3.2% among patients in the IORT arm. Majority of their patients in the IORT arm were between 50–70 years old (84%), had a tumor size of less than 1.5 cm (69%), had zero positive lymph nodes (74%), had grade 2 tumors (48%), were oestrogen (90%) and progesterone (76%) receptor positive. Most of their patients also received endocrine therapy alone (75%) compared to chemotherapy and combined endocrine and chemotherapy.

One of the largest studies on the comparison of WBR and IORT is the TARGIT-A study which was conducted in 11 countries (4). In this large study they only included women older than 45 years old with unifocal ductal carcinomas and low energy photon was used. They recorded a 3.3% rate of local recurrence and a 3.9% mortality rate among patients who received IORT. In their study most of their cancers were grade 1 and 2 (85%), smaller than 2 cm (87%), ER positive (93%) and PR positive (82%). The overall, median follow-up of their patients was 2 years and five months.

Following the two large clinical trial studies on IORT other centers have further reported their institutional experiences with IORT in early stage BC (12–14). Among which chowdhry et al. (15) from the Massachusetts General Hospital reported on 109 patient who received IORT. They had a median follow-up of 29.9 months, during which 2 of their patients (1.8%) experienced local recurrence and one patient (0.9%) had regional recurrence. In this study they included only patients with T1N0 with smaller than 3 cm tumors that were estrogen positive. All their patients also had a negative margin. Their median tumor size was 9.3 mm and majority of their patients had invasive ductal carcinoma (69.7%) followed by ductal carcinoma in-situ (27.5%). Their three year diseases free survival and overall survival was 97.2% (95%CI 88.9–99.3) and 96.0% (95%CI 84.9–99.0), respectively.

Patient selection for IORT is of vital importance and requires a multidisciplinary approach. Accordingly we set-up our criteria based on a consensus of a joint committee of surgical oncologists, pathologists and radiation oncologists. We have further compared our criteria with that of the two largest clinical trial studies on IORT (the ELIOT and the TARGIT-A) in Table 3. We selected patients for IORT who were older than 45 years old for IORT, which was younger than the criteria of the American Society for radiation oncology (10). This was mainly due to the fact that Iranians tend to show BC at a lower age compared to norms of other regions in the world (16, 17). When comparing our outcomes with that of other centers in the world, we had similar, if not better, outcomes. This shows that our modified criteria for patient selection rendered good clinical outcomes. During our median follow-up of 24 months we had no
mortality among our patients who received IORT. Our 97.7% 5-year disease free survival is similar to reports from other regions and centers of the world (12).

None of our 11 patients with DCIS experienced any recurrence during a medial follow-up of 22 months in our study. This shows that with careful patient selection those with DCIS will safely benefit from IORT.

Another interesting point was that almost one third of our patients had a family history of BC, this may be the result of the screening program of family members of individuals with BC, which is applied in our

| Criteria                          | Our study                                      | ELIOT                           | TARGIT-A                      |
|-----------------------------------|------------------------------------------------|---------------------------------|--------------------------------|
| Age - yrs                         | ≥ 45                                           | 48 ≤ age < 75                   | ≥ 45                           |
| Histology sub-type                | Invasive ductal carcinoma                      | Invasive carcinoma (unifocal)   | Invasive carcinoma            |
| Lobular carcinoma (with MRI and radio-concologist confirmation) | Lobular carcinoma (with MRI confirmation)     | No lobular                      |
| DCIS (low and intermediat grade, tumor size ≤ 2.5sm and margin of 2–3 mm) | -                                              | -                               |
| Tumor size                        | 45-50yrs old then 0-2cm                       | ≤ 2.5 cm                       | < 2 cm or < 3.5 (with N0-1 and M0 with cytology or histology confirmation) |
| 50-55yrs old then 2-2.5 cm        | -                                              | -                               |
| > 55yrs old then 2.5-3cm          | -                                              | -                               |
| Marginal status                   | Invasive tumor = negative margin               | -                              | -                              |
| DCIS = > 3 mm                     | -                                              | -                               |
| Nodal status                      | Negative                                       | -                              | -                              |
| Or micro-metastasis               | -                                              | -                               |
| Hormone receptor status           | ER+                                            | -                              | -                              |
| Others                            | -                                              | -                              | Previously diagnosed and treated contralateral breast cancer |

IORT: intraoperative radiation therapy; DCIS: ductal carcinoma in-situ; ER: estrogen receptor
We had a low local recurrence rate (1.2%) during a median (IQR) follow-up of 24 months, which may be attributed to multiple factors. First was the follow-up duration as longer follow-ups may result in higher rates of recurrence. Second relates to our criteria for patient selection which resulted in appropriate selection of candidates for IORT.

For the first time, we categorized patients according to age and tumor size and those older with larger tumor sizes were considered appropriate candidates for IORT. This specific classification was done as younger individuals usually demonstrate more aggressive tumor behavior (18–20). Our experience showed that based on our classification this form of patients selection resulted in good clinical outcomes. This approach could further be implemented in the selection criteria for IORT in other centers in the world.

This study was not without limitation and warrant further discussion. Although this was one of the largest single-center reports in literature and the largest in the Middle East, due to the low number of patients who had recurrence conducting a separate analysis to determine the predictors of recurrence in this population was not feasible. As this is among main referral centers in Iran and among few centers that have facilities for IORT, patients referred from different regions of Iran to receive IORT, accordingly this study can be representative of the Iranian population. As IORT is relatively new in the Middle East and guidelines on the use IORT are constantly being modified, certain modification to selection criteria of patients to receive IORT are expected according to characteristics of BC within each specific population. Facilities for IORT are still not widely available in Iran and in other centers in the Middle East, and our results may not be applicable in most centers due to lack of infrastructure. Although our experience showed good outcomes at 24 months (median) follow-up, long term follow-ups are still lacking due to the novelty of the procedure in our region and institution. In this study we merely reported on clinical outcomes and epidemiology of patients who received IORT in our institution, it would be interesting to cross compare these patients with those who had similar BC conditions and received WBR to evaluate percentage of local recurrence as some studies have shown that these individuals will experience higher rates of local recurrence (11).

**Conclusion**

Our series showed a successful experience with the use of IORT in a region where facilities for IORT are limited using our own modified criteria for patient selection.

**List Of Abbreviations**

Accelerated partial breast irradiation (APBI); whole breast irradiation (WBI); breast cancer (BC); breast conserving surgery (BCS); ductal carcinoma in-situ (DCIS); estrogen receptor (ER); progesterone receptors
Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Shiraz University of Medical Sciences (ethics code#IR.sums.med.1396.s179). Written and informed consent was obtained from the patient's for participation in this study.

Consent for publication

Patients gave their written and informed consent for the publication of data.

Availability of data and material

Authors and institution may request the data from the study by directly contacting the corresponding author.

Competing interests

Authors have no competing interest to declare regarding the manuscript.

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Authors' contributions

VZ, HN, MA, SHH, ST, AM and AT aided in conceptualization and study design. AT, MGJ, AR aided in data gathering. PA and MGJ aided in data analysis. VZ, HN, MA, and PA aided in interpretation of results. VZ, PA, HN aided in preparation of manuscript. AT, MA, SHH, MGG, NK, AR, ST, AM and AT aided in critical revision of final manuscript. All authors have approved the final form of the manuscript.

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Figures

![Survival Function](image)

**Figure 1**
The figure shows the Kaplan–Meier plot for disease-free survival among patients who underwent IORT.