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

Vahid Zangouri
Shiraz University of Medical Sciences
Hamid Nasrollahi
Shiraz University of Medical Sciences
Ali Taheri
Shiraz University of Medical Sciences
Majid Akrami
Shiraz University of Medical Sciences
Peyman Arasteh
Shiraz University of Medical Sciences
Seyed Hassan Hamedi
Shiraz University of Medical Sciences
Masoumeh Ghoddusi Johari
Shiraz University of Medical Sciences
Nazanin Karimaghaee
Shiraz University of Medical Sciences
Aliye Ranjbar
Shiraz University of Medical Sciences
Sedigheh Tahmasebi (Sedigheh.tahmasebi@yahoo.com)
Shiraz University of Medical Sciences
Ahmad Mosalaei
Shiraz University of Medical Sciences
Abdolrasoul Talei
Shiraz University of Medical Sciences

Research article

Keywords: Intraoperative radiation therapy; Breast cancer; Middle East; Recurrence

Posted Date: August 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-57682/v1

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 patient 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 patients (0.4%) had metastasis.

Median (IQR) time to recurrence was 23 (13, 36) among the six patient 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 experience 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 ± 7.79 years old. In total, 32.9% of patients had a family history of BC. Mean age of pregnancy was 21.70 ± 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 ± 7.79
	Median (IQR)	56 (50, 62)
Sex - no. (%)	Female	252 (100)
	Male	0
Weight - Kg		70.40 ± 11.31
Height - Cm		158.69 ± 6.81
BMI - Kg/m^2		27.96 ± 4.29
Age of menstruation - yrs		13.36 ± 1.41
Age at first pregnancy -yrs		21.70 ± 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 ± 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
Hypercholestrolemia - 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).

Table 3
Comparison of inclusion criteria for IORT between our study and the ELIOT and TARGIT-A studies.

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 intermiediat 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			

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

center.

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

(PR); human epidermal growth factor 2 (HER2); contraceptive medication (OCP); standard deviations (SD); interquartile range (IQR)

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.

Funding

The study was funded by Shiraz University of Medical Sciences (fund number 14085-01-01-1396).

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.

Acknowledgement

Authors would like to thank the patient for their kind participation and cooperation in our study.

References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. New England Journal of Medicine. 2002;347(16):1233-41.

2. Shah C, Vicini F, Shaitelman SF, Hepel J, Keisch M, Arthur D, et al. The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation. Brachytherapy. 2018;17(1):154-70.
3. Harris EER, Small W, Jr. Intraoperative Radiotherapy for Breast Cancer. Front Oncol. 2017;7:317-.
4. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. The Lancet. 2014;383(9917):603-13.
5. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. The lancet oncology. 2013;14(13):1269-77.
6. Talei A, Tahmasebi S, Akrami M, Zangouri V, Rezaianzadeh A, Arasteh P, et al. The Shiraz Breast Cancer Registry (SBCR): study design and primary reports. Personalized medicine. 2018;15(6):471-9.
7. Merdad AA, Bahadur YA, Fawzy EE, Hassouna AH, Eltaher MM, Alghaithy ZK, et al. Phase II study on the use of intraoperative radiotherapy in early breast cancer. Saudi Med J. 2013;34(11):1133-8.
8. Therapy ISoir. [Available from: http://www.isiort.org/memberssupporters/.
9. The American Society of Breast Surgeons, Consensus Guideline on Accelerated Partial Breast Irradiation [Available from: https://www.breastsurgeons.org/docs/statements/Consensus-Statement-for-Accelerated-Partial-Breast-Irradiation.pdf.
10. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Practical radiation oncology. 2017;7(2):73-9.
11. Vaidya JS, Bulsara M, Saunders C, Flyger H, Tobias JS, Corica T, et al. Effect of Delayed Targeted Intraoperative Radiotherapy vs Whole-Breast Radiotherapy on Local Recurrence and Survival: Long-term Results From the TARGIT-A Randomized Clinical Trial in Early Breast Cancer. JAMA oncology. 2020:e200249-e.
12. Yu W, Lin Z, Ju Z-J, Li X-R, Zhang Y-J, Kong Q-L, et al. Intraoperative radiation therapy delivered prior to lumpectomy for early-stage breast cancer: a single institution study. Am J Cancer Res. 2015;5(7):2249-57.
13. Wareńczak-Florczak Z, Roszak A, Bratos K, Milecki P, Karczewska-Dzionk A, Włodarczyk H. Intraoperative radiation therapy as part of breast conserving therapy of early breast cancer-Results of one-year follow-up. Rep Pract Oncol Radiother. 2013;18(2):107-11.
14. Morlino A, La Torre G, Lapadula L, Cammarota A. IORT in breast cancer. Our experience of the first patients treated. Ann Ital Chir. 2017;88:253-7.
15. Chowdhry VK, Bushey JA, Kwait RM, Goldberg S, Ritchie J, Ji Y-L, et al. Intraoperative radiation therapy as part of planned monotherapy for early-stage breast cancer. J Radiat Oncol. 2018;7(2):167-73.

16. Akrami M, Arasteh P, Mokhtari M, Tahmasebi S, Zangouri V, Hosseini S, et al. Does metaplastic breast carcinoma demonstrate a different clinicopathological behavior in our region: The Shiraz Breast Cancer Registry. The Breast Journal. 2018;25.
17. Akrami M, Sepahdar A, Arasteh P, Tahmasebi S, Zangouri V, Askari A, et al. Do site and type of metastasis in breast cancer show a changing pattern with increased age? A cross comparison of clinicopathological characteristics between age groups. World Journal of Surgical Oncology. 2018;16.
18. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. Semin Oncol. 2009;36(3):237-49.
19. Merlo DF, Ceppi M, Filiberti R, Bocchini V, Znaor A, Gamulin M, et al. Breast cancer incidence trends in European women aged 20–39 years at diagnosis. Breast cancer research and treatment. 2012;134(1):363-70.
20. Bodmer A, Feller A, Bordoni A, Bouchardy C, Dehler S, Ess S, et al. Breast cancer in younger women in Switzerland 1996–2009: a longitudinal population-based study. The Breast. 2015;24(2):112-7.

Figures

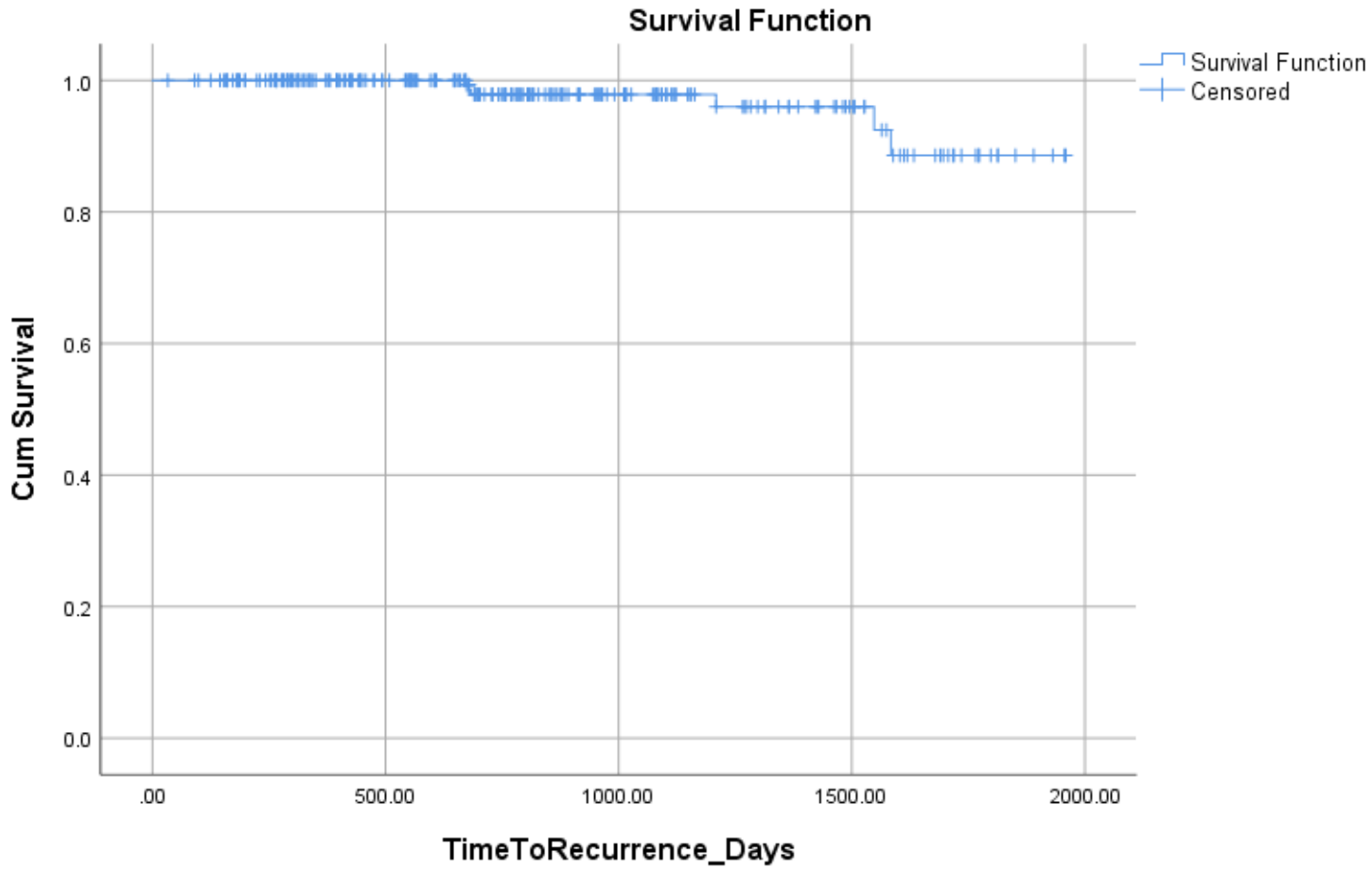

Figure 1

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