

Long-term Outcomes of Intraoperative Radiotherapy For Early-stage Breast Cancer in China: A Multicenter Real-World Study

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Abstract

Background: To assess the efficacy, safety, and cosmetic effects of breast-conserving surgery (BCS) combined with intraoperative radiotherapy (IORT) in Chinese people.

Methods: A retrospective analysis was performed on 451 patients who received IORT at four hospitals in China. IORT was delivered directly to the mammary gland before and after surgery. The primary endpoint was ipsilateral breast tumor recurrence (IBTR). The secondary endpoints were locoregional recurrence (LRR), overall survival (OS), disease-free survival (DFS), IORT-related toxicities, and cosmetic outcomes.

Results: The median follow-up was 5.4 years (with a range of 1.0 to 11.9 years). The overall IBTR was 1.5%, LRR was 2.8%, and the OS rate and DFS rate were 96.2% and 99.1%, respectively. Only one (0.2%) breast cancer-related death was recorded. The cancer-related distant metastasis rate was 0.6%. There was no intraoperative or postoperative radiation-related acute hematological toxicity or other complications. Overall, 74.3% of patients graded the cosmetic effect as excellent or good. The LRR for pre-excision IORT was 3.0%, whereas that of post-excision IORT was 2.8% (pre-IORT vs. post-IORT, $p=0.772$). Distant metastases rate was 2.3% for pre-IORT and 1.8% for post-IORT (pre-IORT vs. post-IORT, $p=0.692$). The cancer-related death rate was 0.7% for pre-IORT and 0.0% for post-IORT (pre-IORT vs. post-IORT, $p=0.899$). The DFS rate was 94.7% in the pre-IORT group and 95.3% in the post-IORT group. ($p=0.672$). The LRR was 2.4%, whereas the OS rate was 99.5% after adjusting for the age of patients according to the recommended criteria by the American Society of Therapeutic Radiation Oncology (ASTRO), and the DFS rate was 98.1%.

Conclusions: IORT significantly reduced the treatment time while preserving a high degree of locoregional control and cosmetic effects.

Novelty And Impact

These current studies mainly included non-Asians and thus lack adequate evidence to support the value of IORT in Asian patients with breast cancer. This study is the first multicentered, "real-world" retrospective study with the largest number of patients and the longest follow-up time in Chinese patients with breast cancer.

Introduction

By 2020, female breast cancer surpassed lung cancer as the most diagnosed cancer globally. Early-stage breast cancer exceeds 50% of all breast cancer cases. The age-at-onset of breast cancer is also low. Whole-breast external beam radiotherapy (EBRT) following breast-conserving surgery (BCS) is regarded as the standard care rather than total mastectomy for early-stage breast cancer. Postoperative radiotherapy can significantly reduce local recurrence rates and breast cancer mortality. However, postoperative radiotherapy is inconvenient and costly because of its long-term duration, mostly 5–7 weeks, though it is reduced to 3 weeks by postmastectomy hypofractionated radiotherapy [1]. In low- and middle-income countries, patients may interrupt the long-term EBRT because of duration and cost. Moreover, the large radiation area and the high EBRT dose may reduce the cosmetic effect and cause adverse reactions of radiotherapy such as

radiation pneumonia and heart injury to organs and tissues adjacent to the radiation site. These demerits affect the quality of life of patients, thus limiting utilization of EBRT in BCS.

The rate of breast conservation in China is much lower than that of the western and developed countries. Up to 90% of local recurrences are near the original operation site [2, 3]. Asian women generally have smaller and denser breasts than their Western peers [4, 5], and thus IORT may be more suitable for Asian women with breast cancer. In China, many women do not complete the long-term postoperative radiotherapy because of the per capita medical resource-limited settings, thus significantly hindering EBRT application. Cognizant of this, using IORT as a treatment option may increase the number of women who receive radiotherapy.

IORT is an accelerated partial breast irradiation treatment (APBI) that is accomplished during surgery. According to the 2017 St. Gallen International Expert Consensus Conference, APBI has been generally accepted as non-inferior to standard whole breast irradiation for low-risk patients diagnosed with early breast cancer who receive breast-conserving surgery [6].

IORT is delivered in a single fraction using a large single dose of radiation, with the surgeon directly visualizing the target site during surgery. Compared with whole breast radiotherapy, IORT has several advantages. It is precise and thus ensures the accuracy of the radiation dose received by the tumor bed. It protects healthy peripheral tissues and reduces postoperative radiotherapy complications such as pulmonary fibrosis, skin contracture, and acute or late toxicity. It also has better cosmetic outcomes and prevents delays, thus reducing residual tumor cell repair and proliferation. Jacobs et al. [7] reported that IORT had better outcomes than external beam APBI (EB-APBI) when he compared the health-related quality (HRQL) of life during the first year after treatment.

Numerous clinical trials indicate that IORT is safe and effective. The two common studies are TARGIT intraoperative radiotherapy- Alone (TARGIT-A) [8] and intraoperative electron beam radiation therapy (ELIOT) [9]. TARGIT uses the intra-beam system to generate low-energy X-rays, while ELIOT employs electron beam radiation. Both studies reported that IORT is safe and effective for early-breast cancer patients.

Nevertheless, these current studies mainly included non-Asians and thus lack adequate evidence to support the value of IORT in Asian patients with breast cancer. The application of IORT in China is still in the exploratory stage with only a few long-term follow-up data. Currently, the safety and feasibility of IORT in the Chinese Han population with a median follow-up of 51.8 months have been elucidated [10]. However, a longer follow-up and a larger scale of patients are still needed to verify these findings. Herein, a multicentered retrospective analysis was performed to assess the efficacy, safety, and cosmetic effects of BCS combined with IORT amongst the Chinese people. It was a non-randomized, retrospective review of patients who received TARGIT-IORT and ELIOT-IORT between 2008 and 2018 as a form of treatment of early-stage breast cancer, but not on any clinical trial. The data were collected from patients treated at 4 Chinese clinical institutions with the intent to evaluate IORT treatment outcomes, complications, and cosmetic outcomes for patients treated with IORT in routine clinical practice. It was a "real-world" retrospective study to report results for patients treated with IORT in China's usual clinical practice. The study also compared the efficacy of TARGIT-IORT and ELIOT-IORT, and pre-excision IORT and post-excision IORT. The suitable age for

patients to receive IORT was also explored. This study provides a theoretical foundation for the application of IORT in Asian women with breast cancer.

Materials And Methods

Patients

This study enrolled 477 breast cancer patients who received IORT between June 2008 and August 2018 in four hospitals in China. Among them, 106 were treated in the Cancer Hospital of the Chinese Academy of Medical Sciences, 132 in the Chinese PLA General Hospital (301 hospital), 131 in the First Affiliated Hospital of Zhengzhou University, and 108 in the Peking University Cancer Hospital. The first two hospitals used a mobile electron accelerator (Mobetron®, Intraop Medical, Sunnyvale, CA, USA), while the last two used the Intrabeam system (Carl Zeiss Meditec, Oberkochen, Germany). Twenty-six patients did not complete the follow-up and were excluded. The clinical data of the remaining 451 breast cancer patients who received IORT and completed the follow-up to October 2019 was thus retrospectively analyzed.

Patients with a maximum tumor diameter < 3 cm and who gave consent to BCS were included in the study. The patients were aged ≥ 40 years with no metastasis in the sentinel lymph node biopsy. Preoperative mammography, ultrasound, and MRI were also conducted to exclude multifocal cancer. Preoperative imaging and clinical examination were further done to exclude any significant axillary lymph node involvement. Patients with more than three axillary lymph node metastases were eliminated from the study and treated with modified radical mastectomy and postoperative radiotherapy.

This study followed the declaration of Helsinki. It was approved by the Ethics Committee of the Cancer Hospital Chinese Academy of Medical Sciences, the First Affiliated Hospital of Zhengzhou University, the Peking University Cancer Hospital, and 301 hospital. All participants also provided written informed consent prior to the study.

Surgical process

The surgery comprised several significant steps. First, the sentinel lymph node biopsy with fluorescence examination combined with staining was done to remove the sentinel lymph node completely. The samples were then sent for rapid pathological examination to check for lymph node metastasis. If there was lymph node metastasis, the axillary lymph node dissection (ALND) was done, including clearing at least ten level I and II lymph nodes in the Berg muscle-based categorization. The skin and subcutaneous tissue with the tumor at the center were then removed using a curved or radial incision. The tumor and approximately 2 cm of the adjacent normal breast tissue were then resected. The upper, lower, inner, outer, anterior, and posterior surgical margins of the wound cavity were sent for rapid frozen-section pathological examination. The presence of at least one positive surgical margin necessitated further outward expansion of the excision. However, the incision-surrounding region was prepared for intraoperative radiotherapy (IORT) if all margins were negative.

IORT Treatment

Patients treated with IORT were managed following the guidelines established by the individual treating institutions at the time. As such, the decision for the radiation dose was at the discretion of the physicians.

Except in the Chinese PLA General Hospital, the other hospitals performed radiotherapy prior to lumpectomy, using the mobile electron accelerator (Mobetron®, Intraop, USA) system or Intrabeam system (Carl Zeiss Surgical, Oberkochen, Germany). A purse-string suture was applied to the gland around the tumor bed and tightly wrapped when the electron beam applicator was centered on the sutured gland to ensure homogeneity of the irradiated TARGIT. A 2 mm-thick lead disk positioned under the breast gland was used to protect the chest-wall and underlying ribs, lung, and heart. The original tumor was used as the irradiation center. The Mobetron® equipment or Intrabeam system was placed in the operating room, and their accessories were thoroughly disinfected before the operation. Different sizes of energy and light limiting canisters were selected to ensure that 90% of the prescription dose covered the required irradiated breast tissue, including 1.5 cm outside the cutting edge and 1 cm of the chest wall. After radiotherapy, the light limiting tube was removed from the incision, followed by suturing of the subcutaneous tissue and skin.

The X-ray source of the Intrabeam system has a probe with a length of 10 cm and a diameter of 3.3 mm. Therefore, it generates accelerated electrons at the end of the probe to release low-energy X-rays (50 kV) with an even dose distribution. The tumor bed's surface was irradiated with a prescribed dose of 20 Gy. However, the radiation dose reaching 1 cm deep in tissue outside the tumor bed was only 5–7 Gy.

The energy of the electron beam of the Mobetron® system ranged between 6 and 12 MeV. The prescription dose to the target area was 9 Gy using single irradiation of 3–5 min duration.

In the Chinese PLA General Hospital, ELIOT was delivered before lumpectomy using

a Mobetron (Intraop Medical, Sunnyvale, CA). The machine produces electron beam energies ranging between 4 and 12 MeV. The radiation is delivered from the Mobetron to the tumor bed through an applicator attached to the surgical table. The applicator sizes available for the Mobetron range between 3–10 cm in diameter, with ½ cm increments. Suitable energy and applicator sizes were chosen to ensure coverage of the tumor with anterior and posterior margins of 1 cm and lateral margins of 2 cm. After delivering ELIOT, all patients underwent extensive resection of the tumor to achieve a free margin of at least 1.5-2 cm while maintaining an excellent cosmetic outcome. The specimen was processed and assessed following standard pathologic procedures.

Postoperative therapy

Patients should receive postoperative adjuvant chemotherapy and endocrine therapy based on the clinical data and postoperative pathological results. The use of chemotherapy, hormonal therapy, or both were at the discretion of the treating medical oncologist.

Follow-up and assessment

The primary endpoint was ipsilateral breast tumor recurrence (IBTR), defined as any recurrence in the treated breast. The secondary endpoints were locoregional recurrence (LRR), overall survival (OS), disease-free survival (DFS), IORT-related toxicities, and cosmetic outcomes. LRR was defined as disease recurrence in the

ipsilateral breast and regional lymph nodes, including the ipsilateral chest wall's recurrence. OS events included death from any cause. DFS events included LR, LRR, distant metastasis, or death because of any reason, whichever occurred first. The follow-up period started from the day of IORT, with the first follow-up visit occurring three months after IORT, followed by one follow-up visit at least every six months until December 2019. The follow-up visits included telephone calls and outpatient visits. The aspects evaluated at the follow-up examinations included recurrence, distant metastasis, survival, late complications, and cosmetic effects. Recurrence and distant metastasis were determined by physical examination, imaging, and pathological examination. Late radiotoxicity was assessed based on the criteria issued by the radiation therapy oncology group (RTOG). The criteria mainly grade late-stage responses of the skin, heart, and lungs according to the most severe radiological reactions occurring at any time during the follow-up period. Treatment-related complications were mainly assessed through patient complaints, physical examination, and ultrasound evaluation. Cosmetic effects were evaluated by the same doctor at the end of the follow-up period following the criteria established by Harris et al. The criteria classifies the cosmetic effects into four: excellent (treated breast nearly identical to the untreated breast), good (treated breast slightly different from the untreated breast), fair (treated breast clearly different from the untreated breast but not seriously distorted), and poor (treated breast seriously distorted).

Data analysis

All statistical analyses were done using SPSS version 24 (IBM, Armonk, NY, USA). The survival data were calculated using the Kaplan-Meier method.

The IBTR rates between institutions were compared to check for variabilities amongst institutions and surgeons regarding the IORT surgical placement technique, which would impact recurrence rates. Uni- and multivariate Cox proportional hazards regression models were applied to assess the

association between time to IBTR and patient, tumor, and treatment variables.

The log-rank test was subsequently run to analyze differences between groups. P values less than 0.05 ($P < 0.05$) indicated significant differences between groups.

Results

General characteristics

Between June 2008 and August 2018, 476 female patients with breast cancer were treated with BCS combined with IORT in 4 different hospitals, including the Cancer Hospital of the Chinese Academy of Medical Sciences, the First Affiliated Hospital of Zhengzhou University, Chinese PLA General Hospital, and the Peking University Cancer Hospital. Among them, 25 patients who did not complete the follow-up visits were excluded from the study. The clinical data of the remaining 451 patients are displayed in Table 1. Among the 451 patients, 249 (55.2%) patients had premenopausal breast cancer, while 202 (44.8%) had postmenopausal breast cancer.

Follow-up

The overall median follow-up time was 5.4 years (ranging between 1.0 and 11.9 years). The median follow-up time was 3.8 years (ranging between 1.0 and 6.1 years) for patients who received TARGIT-IORT and 6.6 years (ranging between 1.0 and 11.9 years) for patients who received ELIOT-IORT.

Recurrence outcomes

There were 13 (2.8%) recurrences, 6 (1.3%) cases of metastases, and 4 (0.8%) deaths. Among the 13 recurrences, 7 recurrence cases were ipsilateral breast recurrence, 4 were ipsilateral axillary lymph node recurrence, and 2 were ipsilateral chest wall recurrence. In the same line, 8 patients were treated with ELIOT-IORT. Their recurrence occurred at 9.3 years, 9.7 years, 1.1 years, 8.0 years, 8.7 years, 9.1 years, 6.3 years, 6.8 years after surgery. The remaining 5 were treated with TARGIT-IORT. Their recurrence occurred at 2.7 years, 4.6 years, 6.4 years, 3.1 years, and 4.3 years after surgery. IBTR was 1.5%, while LRR was 2.8%. The clinical data of patients with recurrence is displayed in Table 2.

Distant metastasis developed in 6 (1.3%) patients after 5.7 years, 4.0 years, 5.4 years, 2.3 years, 6.1 years, and 5.7 years. Development of contralateral breast cancer was recorded in 1 patient (0.2%) after 5.4 years post-surgery. It was treated through a modified radical mastectomy. Bone metastases occurred in 3 patients (0.6%). The first patient had right frontal lobe metastasis after 2.3 years post-surgery. The patient was treated using a gamma knife for six months but died. The second patient had thoracic vertebral metastasis 4.0 years after surgery and then lung metastasis 1.0 years later. The patient received chemotherapy. The third patient had lumbar vertebral metastasis with a follow-up time of 6.1 years. The clinical data of metastatic patients are displayed in Table 3.

Survival outcomes

Two patients died of cardiovascular disease, while one died of esophageal cancer without a direct relationship with breast cancer. The overall survival rates (OS) and disease-free survival (DFS) rates were 96.2% and 99.1%, respectively. There was only one breast cancer-related death. The cancer-related death rate was 0.2%. The survival outcomes of the IORT were calculated using the Kaplan-Meier method (Fig. 1). Similarly, the survival outcomes of the two IORT methods were calculated using the Kaplan-Meier method (Fig. 2).

Table 4 summarizes the factors associated with IBTR. Patients' age and lymph node metastasis were independent prognostic factors in univariate analysis ($p \leq 0.05$) but not in multivariate analysis ($p \leq 0.05$).

Complications

Complications amongst the patients were assessed in December 2019. Among the 451 patients, 125 (27.7%) showed mild skin pigmentation and fibrosis, 8 (1.7%) had breast edema, 5 (1.1%) had lymphedema, 5 (1.1%) had a hematoma, 21 (4.6%) had pulmonary fibrosis, 32 (6.4%) suffered from local pain, while 6 (1.3%) experienced wound infections. There were 4 fat deliquescence cases. The average wound healing time was 20 days. Notably, there were no intraoperative or postoperative radiation-related acute hematological toxicity or other complications. The side effects of the enrolled patients are summarized in Table 5.

Cosmetic outcomes

There were no significant differences in the baseline breast cosmesis before radiotherapy. However, the incidence of excellent/good breast cosmesis amongst the patients was 65.0%, 82.7%, and 90.1% at three months, one year, and three years after surgery, respectively. The cosmetic outcomes of the enrolled patients are summarized in Table 6.

Comparison of pre-IORT and post-IORT outcomes

In the Chinese PLA General Hospital, ELIOT was delivered before lumpectomy, while in the Cancer Hospital of the Chinese Academy of Medical Sciences, ELIOT was delivered after lumpectomy. As such, the patients' clinical data from these two hospitals (106 patients from the Cancer Hospital of the Chinese Academy of Medical Sciences receiving post-excision IORT (pre-IORT) and 132 from the Chinese PLA General Hospital receiving pre-excision IORT (post-IORT)) were analyzed to compare their local recurrence and overall survival.

The median follow-up time of post-IORT and pre-IORT was 7.7 years and 7.0 years, respectively. There were three patients with recurrence after pre-IORT treatment and three patients with recurrence after post-IORT treatment. There were 3 and 2 metastases cases after pre-IORT and post-IORT, respectively. One patient in the pre-IORT died of breast cancer-related distant metastasis. No cancer-related death was reported in the post-IORT group. The local recurrence rate was 3% vs. 2.8% (pre-IORT vs. post-IORT, $p = 0.772$). The distant metastases rate was 2.3% vs. 1.8% (pre-IORT vs. post-IORT, $p = 0.692$). The cancer-related death rate was 0.7% vs. 0.0% (pre-IORT vs. post-IORT, $p = 0.899$). The DFS rate was 94.7% in the pre-IORT group and 95.3% in the post-IORT group ($p = 0.672$). However, these differences were not significant (Table 6). The survival outcome of the pre-IORT and post-IORT methods were calculated using the Kaplan-Meier method (Fig. 3).

Comparison of survival outcomes of patients with different inclusion criteria

Herein, the included patients were 40 years and above. This limit was broader than that of the ASTRO (older than 50). Cognizant of this, the outcome of IORT was analyzed in patients categorized as ASTRO to determine the better age limit of IORT amongst the Chinese patients. There were 208 patients aged over 50 years. Among them, five had local recurrence, three had distant metastases, and one died of cancer-related metastases. Their LRR was 2.4%, OS rate was 99.5%, and the DFS rate was 98.1%. The survival outcome of patients with different inclusion criteria was calculated using the Kaplan-Meier method (Fig. 4; 95% confidence interval 10.9–11.6, $p = 0.938$).

Table 1
Patients characteristics (n = 451)

IORT system	Intrabeam	Mobetron	Total number	Total N(%)
Age(years)				
40–45	18	78	96	21.3%
46–49	31	116	147	32.6%
≥ 50	149	59	208	46.2%
Tumor size(cm)				
≤ 2cm	129	191	320	71.1%
>2cm	69	62	131	29.0%
Tumor position				
Outer upper quadrant	46	59	105	23.2%
Outer lower quadrant	26	37	63	14.0%
Inner upper quadrant	23	40	63	14.0%
Inner lower quadrant				
Histology				
IDC	175	222	397	88.0%
DCIS	12	13	25	5.5%
Intraductal papillary carcinoma	6	5	11	2.4%
Mucinous carcinoma	7	8	15	3.3%
Apocrine adenocarcinoma	0	1	1	0.2%
ICC	0	3	3	0.6%
Neuroendocrine carcinoma	0	1	1	0.2%
Lymph node metastasis (pathology)				
N0	135	215	350	78%
N1	63	38	101	22%
Immunohistochemistry				
ER+/ and/or/PR+	183	213	396	87.8%

IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ. ICC, invasive cribriform carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2

IORT system	Intrabeam	Mobetron	Total number	Total N(%)
ER- and PR-	15	40	55	12.2%
Her-2+	97	53	150	33.3%
Her-2-	101	200	301	66.7%
Ki-67(%)				
< 50%	168	208	376	83.4%
≥ 50%	34	42	76	16.9%
IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ. ICC, invasive cribriform carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2				

Table 2
Recurrence cases (n = 13)

Patients	Age (years)	IORT	ER	PR	HER2	Ki-67	Histology	Site of metastases	Follow-up
1	45	TARGIT	+	+	-	10%	IDC	Ipsilateral breast	2.7 years
2	59	TARGIT	+	+	-	50%	IDC	Ipsilateral breast	4.6 years
3	56	TARGIT	+	+	+	15%	IDC	Ipsilateral axillary lymph node	6.4 years
4	51	TARGIT	+	-	-	13%	Mucinous carcinoma	Ipsilateral chest wall	3.1 years
5	50	TARGIT	+	-	+	15%	IDC + DCIS	Ipsilateral breast	4.3 years
6	47	ELIOT	+	+	-	2%	Mucinous carcinoma	Ipsilateral breast	9.3 years
7	46	ELIOT	+	+	+	20%	IDC	Ipsilateral axillary lymph node	9.7 years
8	76	ELIOT	+	+	-	25%	IDC	Ipsilateral axillary lymph node	1.1 years
9	43	ELIOT	+	+	-	15%	IDC	Ipsilateral axillary lymph node	8.0 years
10	52	ELIOT	+	+	-	15%	IDC	Ipsilateral breast	8.7 years
11	47	ELIOT	+	-	-	40%	IDC	Ipsilateral chest wall	6.3 years
12	46	ELIOT	+	+	-	15%	IDC	Ipsilateral breast	6.8 years

IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ

Patients	Age (years)	IORT	ER	PR	HER2	Ki-67	Histology	Site of metastases	Follow-up
13	54	ELIOT	+	-	+	5%	IDC	Ipsilateral breast	9.1 years
IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ									

Table 3
Distant Metastases (n = 6)

Patients	Age(years)	IORT	Site of metastases	death	Follow-up
1	52	ELIOT	Liver metastasis	NO	5.7 years
2	39	ELIOT	Thoracic vertebral metastasis Lung metastasis	NO	4.0 years
3	48	ELIOT	Contralateral breast metastasis	NO	5.4 years
4	76	ELIOT	Right frontal lobe metastasis	YES	2.3 years
5	52	TARGIT	Lumbar vertebral metastases	NO	6.1 years
6	63	TARGIT	Lung metastasis	NO	4.9 years

Table 4
Factors associated with the time to IBTR in patients with early breast cancer undergoing IORT

Variable	Univariate analysis			Multivariate analysis		
	p	HR	95% CI	p	HR	95% CI
Age(years) (40–45;46–49; ≥50)	0.000	1.000	0.000, 6.146	0.167	1.067	0.345, 5.413
Tumor size(cm) (≤ 2cm; >2cm)	0.803	0.874	0.257, 2.976	0.214	0.314	0.051, 2.101
Tumor position	0.704	0.756	0.273, 2.145	0.166	0.313	0.061, 1.616
Histology	0.492	0.253	0.005, 2.798	0.917	1.678	0.003, 4.178
Lymph node metastasis (pathology) (N0; N1)	0.05	3.012	0.063, 13.151	0.671	3.815	2.167, 18.017
ER (+; -)	0.750	1.285	0.276, 5.978	0.108	0.168	0.019, 1.482
PR (+;-)	0.311	2.879	0.373, 2.231	0.168	1.006	0.289, 2.135
Her-2 (+; -)	0.807	1.083	0.572, 2.049	0.639	0.824	0.367, 1.851
Ki-67(%) (< 50%; ≥50)	0.840	0.997	0.968, 1.026	0.914	1.002	0.967, 1.038
Device (TARGIT; ELIOT)	0.398	0.355	(0.032,3.921)	0.843	0.876	0.238, 3.226

Table 5
IORT-related side effects

No. of patients (%)	Breast Fibrosis	Pigmentation	Breast edema	Lymphedema	Hematoma	Pulmonary fibrosis	Pain
At 3 months (n = 451)							
Grade 1	86 (19.1%)	0	8 (1.7%)	15 (3.3%)	5 (1.1%)	21 (4.6%)	32 (6.4%)
Grade 2	4 (1.0%)	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
At 1 year (n = 435)							
Grade 1	106 (24.4%)	76 (18.6%)	12 (2.7%)	11 (2.5%)	0	15 (3.4%)	0
Grade 2	2 (0.4%)	5 (1.1%)	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
At 3 year (n = 395)							
Grade 1	73 (18.4%)	96 (24.3%)	0	4 (1.0%)	0	0	0
Grade 2	2 (0.5%)	5 (1.2%)	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0

Table 6
Cosmetic outcomes of patients who received IORT (n = 430)

No. of patients (%)	Excellent	Good	Fair	Poor	Excellent + Good (%)
At < 3 months (n = 451)	56 (13.0%)	215 (50.0%)	115 (26.7%)	44 (10.2%)	65.0%
At 1 year (n = 435)	112 (25.7%)	248 (57.0%)	60 (13.7%)	15 (3.4%)	82.7%
At 3 year (n = 395)	89 (22.5%)	267 (67.6%)	35 (8.8%)	4 (1.0%)	90.1%

Table 6
Analysis of pre-excision IORT (n = 132) and post-excision IORT (n = 106)

	Pre-IORT	Post-IORT	P-value
Local recurrence	4 (3.0%)	3 (2.8%)	0.772
Distant metastases	3 (2.3%)	2 (1.8%)	0.692
Cancer-related death	1 (0.7%)	0 (0.0%)	0.899
DFS	94.7%	95.3%	0.672

Table 7
Analysis of Eligibility Criteria of Patients

Criterion	ASTRO	TARGIT	ELIOT
Age	≥ 50 years; 40–49 years if all other criteria met	≥ 45 years	48–75 years
Histology	All invasive subtypes pure DCIS	IDC	-
Tumor Size	≤ 3cm	-	≤ 2.5cm
T Stage	Tis, T1, T2	-	-
Margins	Negative	Negative	Negative
Nodal status	Negative	-	-
Other factors	Limited LVI ER + or ER- EIC ≤ 3 cm	-	-

LVI, lymphatic vessel invasion; DCIS, Ductal carcinoma in situ; IDC, invasive ductal carcinoma

Discussion

Patients are increasingly turning their attention to treatment-related adverse reactions, convenience, cost, and cosmetic effects following the continuous improvement in the efficacy of BCS and radiotherapy. Some researchers have tried to reduce the number of radiotherapy sessions. Wang et al. [1] proposed a hypofractionated 3-week schedule of postmastectomy radiotherapy to reduce the time of postoperative radiotherapy. However, the 3-week EBRT is still limited by the large radiotherapy area, damage to peripheral organs, and poor cosmetic results. The proportion of premenopausal breast cancer cases among Asian patients is significantly higher than in European and American patients. Patients may refuse to undergo supplementary EBRT because of the long EBRT time, high cost, and poor cosmetic outcomes, especially in less developed countries with limited and imbalanced medical resources. The breasts of Asian women are smaller and denser and are thus more suitable for IORT because they are radiated more thoroughly during surgery.

Studies postulate that IORT is superior to EBRT regarding side and cosmetic effects [10]. The local relapse and survival rates of IORT are non-inferior to those of EBRT. TARGIT and ELIOT are the two main types of IORT. They use single-dose radiation to the tumor bed during operation with low-energy X-rays and electron beam, respectively.

TARGIT-A trial was the largest international, multicentered, large-cohort, randomized controlled study that enrolled 3451 patients with breast cancer across 11 countries. The 5-year risk of local recurrence was 3.3%

for TARGIT-treated patients versus 1.3% for EBRT-treated patients. However, the latter had more high-grade toxic reactions. There were no significant differences in the overall mortality between the TARGIT group and the EBRT group (3.9% vs. 5.3%), with a median follow-up period of only 2.4 years [3]. IORT was only suitable for a specific low-risk population because of the limited follow-up time of the TARGIT-A trial. Vaidya et al.[11] completed the long-term follow-up of the TARGIT-A trial with a median follow-up time of 8.5 years, covering 2298 patients. After five years of complete follow-up, the local recurrence risk was 2.11% for TARGIT-IORT compared to 0.95% for the EBRT group. There were no significant differences in local recurrence-free survival, mastectomy-free survival, distant disease-free survival, overall survival, and breast cancer mortality [11]. In the TARGIT-R study, a large-cohort retrospective study in North America, ipsilateral breast tumor recurrence (IBTR) was 6.6% for all the patients after five years. The difference between the prospective randomized controlled TARGIT-A and TARGIT-R trials provides the necessary data for the application of IORT in the "real world." It also outlines the necessity of the "real world" study of IORT.

In the ELIOT study, 1305 patients from 28 medical centers across nine countries were enrolled and received IORT using the Mobetron® system. The study had a median follow-up time of 5.8 years. The local recurrence rate (LRR) for the IORT and EBRT groups was 4.4% and 0.4%, respectively. Besides, there were no significant differences in the five-year survival rates between the two groups (96.8%, IORT group vs. 96.9%, EBRT group). However, the IORT group showed significantly fewer skin-related side effects ($p = 0.0002$) than the EBRT group. Nonetheless, the researchers stated that the LRR could decrease to 1.5% with more careful inclusion criteria based on ASTRO [9].

Vicini et al.[12] conducted a randomized, 3-phased study (NSABPB-39/RT0B0413) that compared EBRT with APBI in 4216 patients who underwent mastectomy for ductal carcinoma in situ or invasive breast cancer (pN0 or pN1 with no more than three lymph nodes involved). The primary endpoint was IBTR. At ten years, IBTR was 4.6% for APBI-treated patients and 3.9% for EBRT-treated patients.

However, there are only a few that incorporate Asian populations, particularly Chinese populations. As such, studies including both Asian Chinese and other Asian populations are needed. Wang et al.[13] conducted a multicentered, randomized controlled trial to compare the hypo-fractionated radiotherapy (HFRT) with conventional EBRT after breast-conserving surgery amongst the Asian population with 734 patients from 4 Chinese institutions. The study had a median follow-up time of 73.5 months. The 5-year cumulative incidence of LR was 1.2% for HFRT versus 2.0% for EBRT. In the same line, the 5-year DFS and OS were 93.0% and 97.5% for HFRT, compared with 94.1% and 98.0% for EBRT, respectively.

The recommended criteria by the American Society of Therapeutic Radiation Oncology (ASTRO) [14], European Society of Therapeutic Radiation Oncology (ESTRO) [15], American Brachytherapy Society (ABS) [16], and American Society of Breast Surgeons (ASBrS) have been previously compared [15]. There is no generally accepted guideline for the treatment of the IORT of breast cancer patients. Different countries and organizations have various recommendations for IORT. Herein, low-risk patients with breast cancer were selected for IORT based on recommendations from the combination of the ASTRO consensus statement and TARGIT and ELIOT trials. Table 7 compares the three suitability criteria. Herein, we choose patients aged 40 years or older with unifocal tumor maximum diameter < 3 cm because Asian women have a higher

incidence of premenopausal breast cancer. There was no metastasis in the sentinel lymph node biopsy. However, patients whose postoperative pathological examination revealed more than three axillary lymph node metastases were eliminated.

Previously, IORT has been found to be safe and feasible amongst the Chinese Han population, with a median follow-up of 51.8 months [17]. Herein, 451 patients were enrolled from 4 hospitals in China. The longest follow-up time was 11.9 years. It is the largest multicenter IORT study in China with the longest follow-up time. There are many previous EBRT trials with numerous patients and long follow-up time because it has been the standard treatment after BCS. Cognizant of this, we choose some of the earlier trials for comparison purposes. Herein, the IBTR was 1.5%, LRR was 2.8%, and the OS was 99.1%. These findings were comparable with those of EBRT clinical trials. These findings confirmed that the efficacy of TARGIT and ELIOT is non-inferior to that of EBRT. There were no significant differences in overall survival after TARGIT-IORT and ELIOT-IORT (Fig. 1). However, there are fewer skin adverse effects after IORT than EBRT [8, 9]. In this study, 27.7% of the patients showed mild skin pigmentation and fibrosis, but few severe fibrosis. Another 4.6% of patients had pulmonary fibrosis but no severe radiation-related toxicity. Good to excellent cosmetic outcomes were 63.0% of patients in the first three months after surgery, 83.7% at 1-year post-surgery, and 82.8% at 5-year post-surgery. These findings were comparable with those of the previous IORT studies.

Notably, this study compared the pre-excision IORT and post-excision IORT. In 301 hospital, ELIOT was delivered before lumpectomy. Pre-excisional IORT delivery to the entire tumor reduces TARGIT coverage problems and localization and improves the radiation dose distribution. The cosmesis, toxicity results, and local control have previously been reported [18, 19]. The University of North Carolina is the first registered center to deliver ELIOT to the tumor before surgical excision. However, the 53 patients who received IOERT alone showed 3-year, 5-year, and 6-year local recurrence rates of 8%, 13%, and 15%, respectively [18]. The study attributed the high local recurrence rates to under-estimating intraoperative tumor margins because of delivering ELIOT before excision and at a lower prescription dose. Herein, we compared the outcomes of pre-excision IORT and post-excision IORT. There were no significant differences in local recurrence, metastases, and cancer-related death rates. Based on previous studies, pre-excision IORT is associated with high local recurrence. As such, continued enrollment of patients in well-designed clinical studies is suggested.

Notably, we compared the survival results if patients in this study were selected based on the ASTRO criterion. In the ASTRO criterion, IORT should be delivered to patients belonging to the "Suitability" category of APBI. The "Suitability" category of patients is comprised of patients who are 50 years or older. The patients should have a tumor in the Tis or T1 stage. DCIS could be included when the size ≤ 2.5 cm and resected with margins negative at ≥ 3 m. In the ELIOT study, patients with invasive cancer fitting the "suitability" criteria had a low rate of LRR at approximately 1.5%, pointing out the importance of patient selection. Herein, the 208 patients who met the criteria of "suitability" had an LRR of 2.4%, OS rate of 99.5%, and DFS rate of 98.1%. However, there were no significant differences in LRR, DFS, and OS between patients aged 40 and 50 years older ($p=0.1$). Cognizant of this, we concluded that the age range suitable for IORT should be extended to 40 years and older in Asian women, especially Chinese women. As such, many

patients can benefit from this affordable treatment even in less developed countries with limited medical resources.

Considering the social and economic benefits, IORT is more economical and environmentally friendly than EBRT. Coombs et al.[20] assessed the environmental and social benefits of IORT with patients in the TARGIT-A trial. Introducing TARGIT helped patients in the UK to significantly save time, cost, and fuel and reduce CO2 emissions. Vaidya et al.[21] also reported that TARGIT-IORT gained 0.18 incremental quality-adjusted life-years (QALY) compared to EBRT, thus affirming the TARGIT-IORT is a dominant approach over EBRT.

Nevertheless, this study was limited by several factors. Differences in devices and follow-up time in the four hospitals limited the comparisons. However, a series of factors contribute to our study's validity, including potentially more uniform disease diagnosis, a higher degree of control in treatment implementation, and precise quality assurance, data collection, and follow-up. This limitation was addressed using the same criteria for the patients' follow-ups regardless of the hospital the surgery was done. Second, since the first IORT was used in 2008, some patients were lost in this process. And the criteria of "low-risk" patients have been extended since then.

Notably, this study was not randomized but rather a "real-world" retrospective study reporting outcomes of Chinese patients treated with IORT in China's routine clinical practice. As such, it provides a theoretical basis for future prospective studies.

Conclusion

This study is the first multicentered, "real-world" retrospective study with the largest number of patients and the longest follow-up time in Chinese patients with breast cancer. IORT, both TARGIT and ELIOT are productive and safe alternatives to EBRT in some patients with early breast cancer. The techniques significantly reduce the treatment time while preserving a high degree of locoregional control and cosmetic effects. In the same line, pre-excision IORT is non-inferior to post-IORT. The patients' suitability criterion to receive IORT should be extended to 40 years or older to make it more convenient for more patients to receive adequate treatment in China. This study provides the largest real-world, long-term analysis of the clinical use of IORT for the treatment of early-stage breast cancer in Chinese patients. It also provides the necessary information required to incorporate more patients in further IORT perspective programs.

Declarations

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Author's Contributions

WX and WX designed the study and directed the entire study. FKX wrote original draft and collected and analyzed data. WWY, MXZ and LJQ did validation of data analysis, and reviewed the original draft. YY, ZYT, LJR, WSK, LMH, MP, FQF, ZHM, GYT, LXR, FZQ all contributed to data collection.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Figures

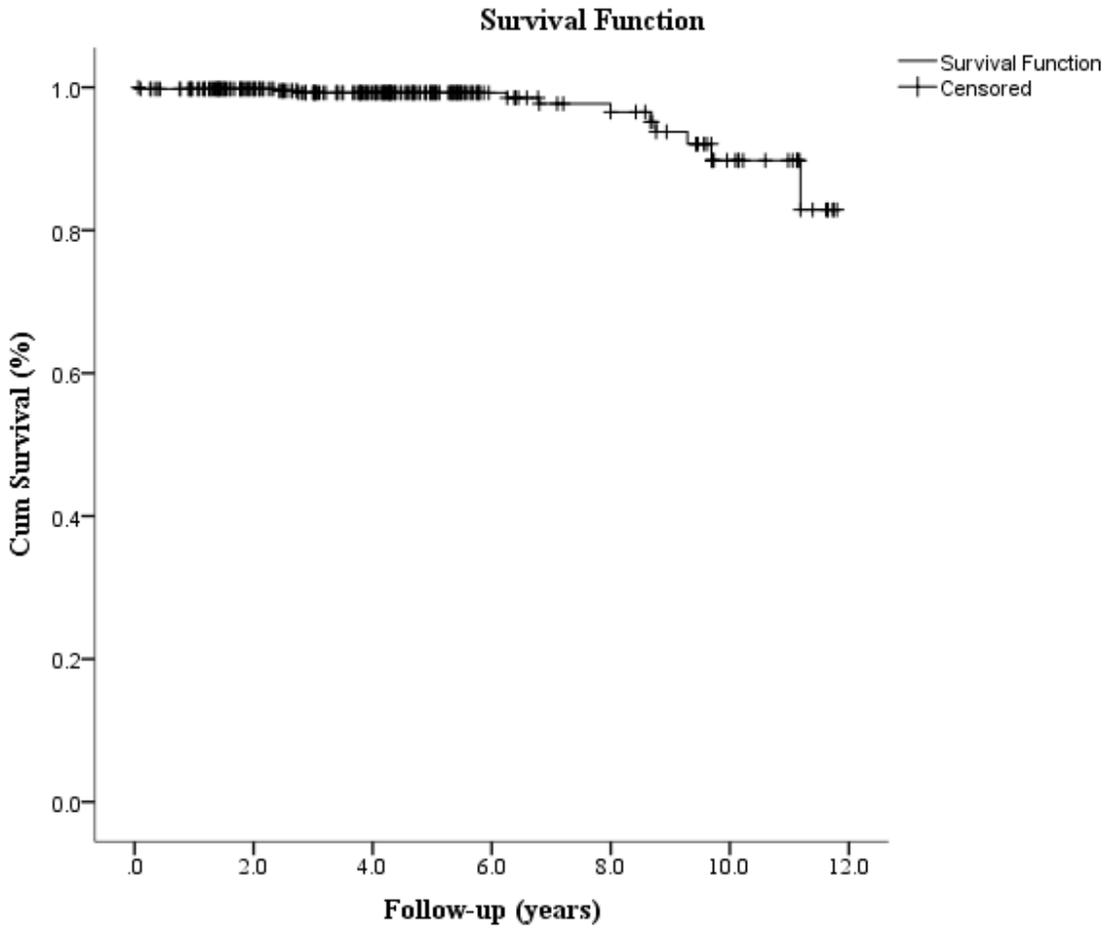


Figure 1

Kaplan-Meier curves showing the DFS after IORT of 451 patients with breast cancer. (95% confidence interval 11.1-11.7)

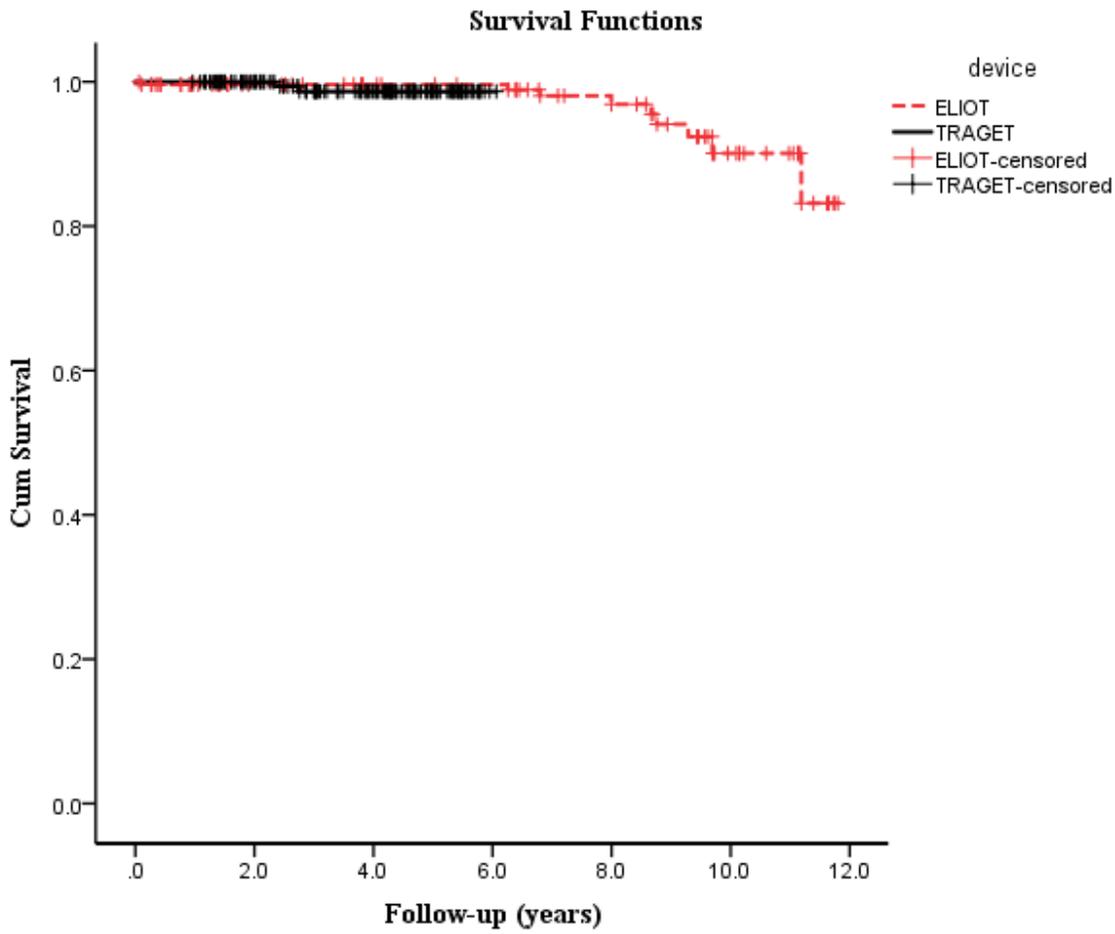


Figure 2

Kaplan-Meier curves showing the DFS after TARGIT-IORT and ELIOT-IORT of 451 patients with breast cancer. (95% confidence interval 11.2-11.7, $p=0.773$)

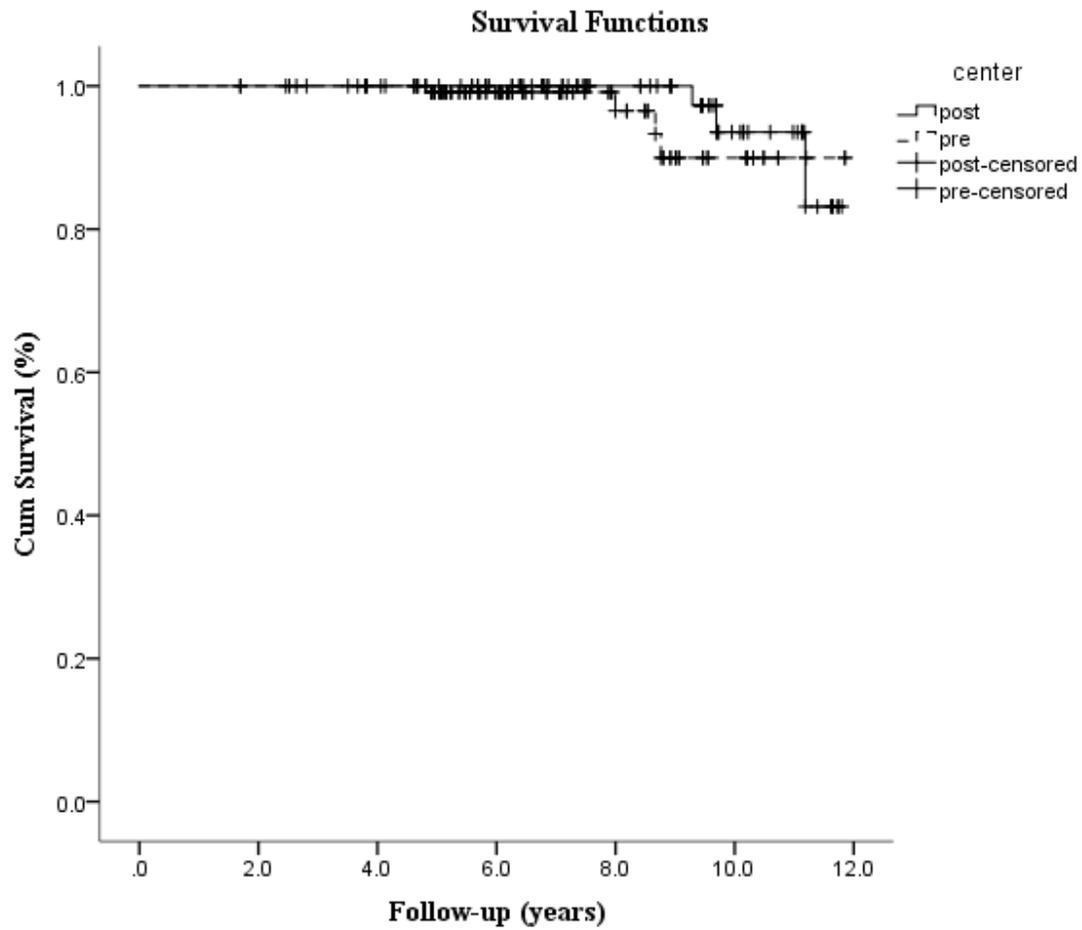


Figure 3

Kaplan-Meier curves showing the DFS after pre-IORT and post-IORT of patients with breast cancer. (95% confidence interval 11.3-11.7, $p=0.797$)

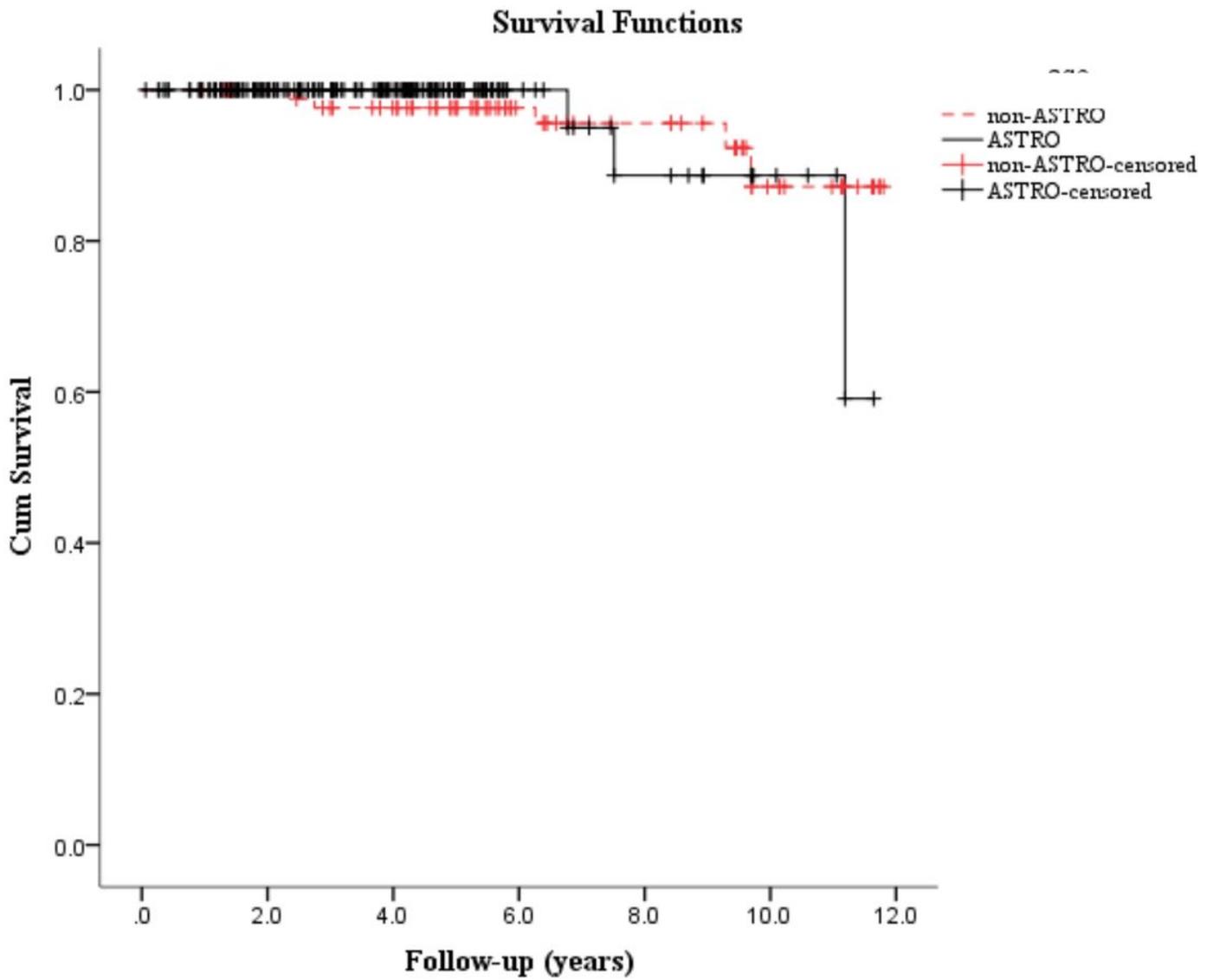


Figure 4

Kaplan-Meier curves for DFS of patients received IORT according to criteria in this study and ASTRO.(95% confidence interval 10.9-11.6, p=0.938)