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LETTER TO THE EDITOR

# Long-term outcomes of intraoperative radiotherapy for early-stage breast cancer in China: a multicenter real-world study

Dear Editor,

Intraoperative radiotherapy (IORT) is an accelerated partial breast irradiation (APBI) treatment that is accomplished intraoperatively. Numerous clinical trials indicate that IORT is safe and effective, non-inferior to standard whole-breast external beam radiotherapy (EBRT) for low-risk patients who receive breast-conserving surgery [1–3]. Nevertheless, these studies mainly included non-Asians and thus lack adequate evidence to support the value of IORT in Asian patients with breast cancer. Many Asian females cannot complete the long-term EBRT because of the per capita medical resource-limited settings. APBI can greatly shorten total treatment time, and IORT may be a suitable APBI technique for those patients considering the dense and small-size breasts of Asian females.

Herein, we performed a "real-world" multicenter retrospective analysis of 451 patients from 4 Chinese clinical institutions, with the intent to evaluate IORT treatment outcomes, complications, and cosmetic outcomes for patients with breast cancer in China. Patients were divided according to the IORT type: targeted intraoperative radiotherapy (TARGIT) and electron intraoperative radiotherapy (ELIOT). The detailed materials and methods can be found in the Supplementary file.

The median follow-up time was 5.4 (range, 1.0-11.9) years. The clinical data of the 451 patients are displayed in Supplementary Table S1. A total of 101 (22.4%) had positive lymph nodes and received IORT as a boost followed by 5 weeks of EBRT, while the other patients (78%) had IORT as their sole irradiation treatment. All patients underwent sentinel lymph node (SLN) biopsy for axillary management, and an immediate axillary lymph node dissection was then performed for patients with positive SLNs. No positive margin was found in all patients. Patients received postoperative chemotherapy and endocrine therapy based on the pathological results.

There were 13 (2.9%) recurrences, 6 (1.3%) cases of distant metastases, and 4 (0.8%) deaths. Among the 13 recurrences, 7 were ipsilateral breast recurrence, 4 were ipsilateral axillary lymph node recurrence, and 2 were ipsilateral chest wall recurrence. The ipsilateral breast tumor recurrence (IBTR) rate was 1.5%, while the locoregional recurrence (LRR) rate was 2.8%. The clinical data of patients with recurrence are displayed in Supplementary Table S2. The median time to recurrence was 4.1 (range, 1.0-5.7) years.

Among the 6 cases of distant metastasis, 3 (0.6%) were bone metastases, 1 (0.2%) was contralateral breast metastases. The clinical data of metastatic patients are displayed in Supplementary Table S3. The median time to metastases were 4.4 (range, 2.3-5.0) years.

There was only one (0.2%) breast cancer-related death, and 3 patients died of other diseases. For the entire cohort, the 5-year disease-free survival (DFS) and overall survival (OS) rates were 98.2% and 99.1%, respectively (Figure 1A-B). The DFS and OS between the TARGIT and ELIOT groups showed no significant differences (Figure 1C-D). The LRRs of the TRAGIT and ELIOT groups were 2.5% and 3.2% ($P = 0.782$).

Next, the irradiation-related adverse events occurred after surgery were assessed (Supplementary Table S4). Within 3 years after surgery, irradiation-related adverse events decreasedwith time, and no severe (grade 3 or 4) adverse events were observed. The overall rate of late adverse events was relatively low, and patient tolerance was good.

Cosmetic outcomes were evaluated (Supplementary Table S5). Breast cosmesis of all patients before radiotherapy were normal. The rates of excellent/good breast cosmesis were 63.0%, 82.7%, and 90.1% at 3 months, 1 year, and 3 years after surgery. The ameliorating trend of cosmetic outcomes may be due to the rapid radioactive decay and

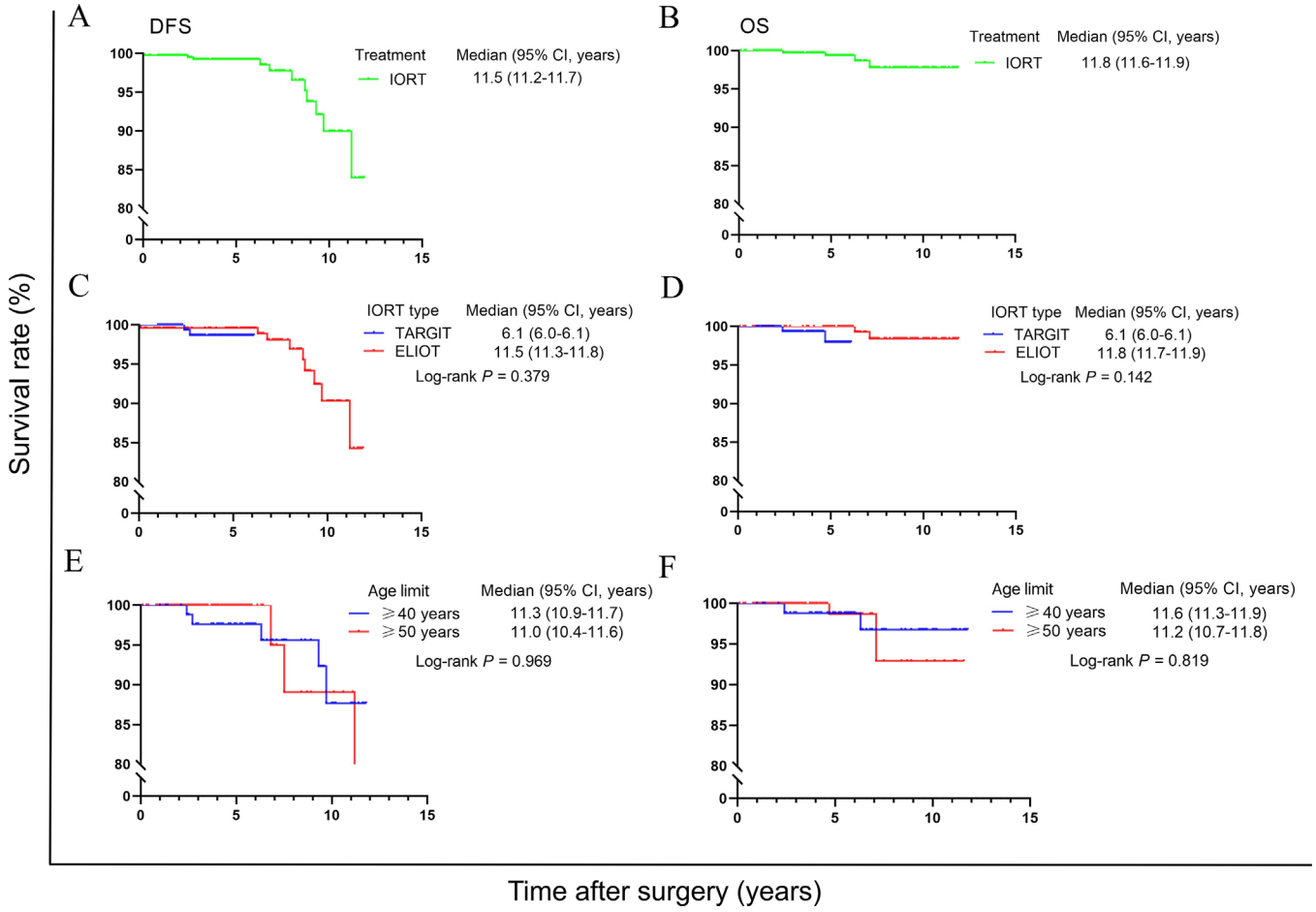


**FIGURE 1** Kaplan–Meier survival curves of the 451 patients with early-stage breast cancer who underwent IORT. (A-B) Kaplan-Meier DFS (A) and OS (B) curves of the entire cohort**.** (C-D) Kaplan-Meier DFS (C) and OS (D) curves of patients in the TARGIT and ELIOT groups. (E-F) Kaplan-Meier DFS (E) and OS (F) curves of the entire IORT group (≥40 years old) and the patients who met the ASTRO consensus criteria (≥50 years old).

Abbreviations: IORT, intraoperative radiotherapy; DFS, disease-free survival; OS, overall survival; ASTRO, American Society for Radiation Oncology; CI, confidence interval

improvement of patients' tolerance to irradiation along time.

Several prospective studies evaluated the safety and efficacy of IORT. The TARGIT-A (TARGeted Intraoperative radioTherapy Alone) short-term follow-up publication [1] showed that patients who received IORT had a IBRT rate similar to those who received EBRT (2.1% vs 1.1%, $P = 0.310$). With long-term follow-up (median, 8.6 years), the LRR rate was 3.1% in the TARGIT-IORT group and 1.2% in the EBRT group [2]. In the TARGIT-R study [4], a large-cohort retrospective study in North America, the 5-year IBTR rate was 8% in the IORT group and 6.6% for all patients. Heidelberg University published the 8.5-year results for their 184 randomized patients enrolled in TARGIT-A, showing that IORT provided a local control rate similar to EBRT (IORT 0.0% vs. EBRT1.2%). The difference of LRR between the prospective randomized controlled trials [1,5] and the retrospective study [4] support the application of IORT in the "real world."

In the ELIOT study [6], after a median follow-up time of 5.8 years, the LRR rate was significantly higher in the IORT group than in the EBRT (4.4% vs. 0.4%, $P < 0.001$). There were no significant differences in the 5-year OS rates between the two groups (96.8% vs. 96.9%). The IORT group showed significantly fewer skin-related side effects than the EBRT group ($P < 0.001$). Ciabattoni et al. [3] confirmed the oncologic iso-efficacy of the ELIOT boost versus the EBRT boost while obtaining better cosmetic results by ELIOT boost. The 5- and 10-year IBTR rates were 0.8% and 4.3% after ELIOT, compared to 4.2% and 5.3% after EBRT boost ($P = 0.709$). The 5- and 10-year LRR rates were 4.7% and 7.9% after ELIOT versus 5.2% and 10.3% after EBRT ($P = 0.762$).

In the present study, the IBTR, LRR, OS, and DFS rates were comparable with those reported by the aforementioned trials [1,4,6]. These findings confirmed that the efficacy of IORT was non-inferior to that of EBRT. We also confirmed that there were no significant differences in OS after TARGIT-IORT and ELIOT-IORT. The 3-year rate of good to excellent cosmetic outcomes was 90.1%, and no severe radiation-related adverse events occurred.

There is no unified standard for IORT yet, and we compared the suitability of enrollment criteria of the American Society for Radiation Oncology (ASTRO) consensus statement [7] and TARGIT [1] and ELIOT trials [6] (Supplementary Table S6). When the ASTRO consensus guidelines was applied to selecting patients in the present study, only 208 (46.1%) of the 451 patients would be eligible. Among them, 5 had local recurrence in the ipsilateral breast and 2 in ipsilateral axillary lymph nodes, 4 had distant metastases, and 1 died of cancer-related metastases. The LRR rate was 3.3%, and the 5-year DFS and OS rates were 100.0% and 99.5%, respectively. In the present real-world study, the patients were all at least 40 years old. Evaluation of the DFS and OS between the entire IORT group and the patients who met the ASTRO criteria showed no significant differences ($P = 0.969$; $P = 0.819$) (Figure 1E-F). We propose that the age limit for IORT could be lowered to 40 years and older in Asian, especially Chinese females. As such, more patients can benefit from this affordable treatment even in regions with limited medical resources.

In summary, patients treated by IORT achieved satisfactory prognosis with minor complications and excellent cosmetic outcomes. Our proposal needs to be verified in future prospective studies.

## DECLARATIONS

### FUNDING

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### COMPETING INTERESTS

The authors declare that there is no conflict of interest.

### AUTHORS' 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.

### AVAILABILITY OF DATA AND MATERIALS

Data and materials can be provided upon reasonable request to the corresponding author.

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## SUPPORTING INFORMATION

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