# Long-term follow-up outcomes of intraoperative radiotherapy for breast-conserving treatment in early breast cancer: A retrospective cohort study

XIAOFAN XU[1,2*], LU WANG[3*], YUANYUAN CAO[4], JINGYI WANG[5], JIE YAO[1,2], LIQUN HUO[1,2], YUQING SONG[2], WEI DING[6], JUN GU[2] and QIURONG LI[1,2]

[1]Research Institute of General Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu 210002, P.R. China; [2]Research Institute of General Surgery, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu 210002, P.R. China; [3]Research Institute of General Surgery, Jinling Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210002, P.R. China; [4]Medical Service Training Center, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu 210002, P.R. China; [5]Department of Biostatistics, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 211166, P.R. China; [6]Department of Radiation Oncology, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu 210002, P.R. China

Received November 1, 2024; Accepted April 17, 2025

DOI: 10.3892/ol.2025.15092

**Abstract.** Intraoperative radiotherapy (IORT) has been used as a novel therapeutic alternative for breast-conserving surgery (BCS) in patients with breast cancer. However, the long-term outcomes and safety of IORT in patients with breast cancer remain incompletely understood. Therefore, the present study aimed to explore the long-term outcomes of IORT following BCS, focusing on the oncological outcomes and cosmetic consequences compared with postoperative RT (PORT) in patients with breast cancer. Patients with early-stage breast cancer who underwent BCS followed by IORT or PORT between January 2016 and October 2020 at the Research Institute of General Surgery, Jinling Hospital, Nanjing Medical University (Nanjing, China), were retrospectively reviewed. After screening, a total of 59 patients were included in the present study and divided into two groups according RT records as follows: The IORT group (n=21) and the PORT group (n=38). The clinical data of all patients, including surgical and RT complications, cosmetic grading and scoring, and other events, were collected and retrospectively analyzed. No significant difference was observed in terms of the mean follow-up time in the IORT (5.89±1.57 years) and PORT (6.09±1.60 years) groups (P>0.05). Compared with PORT, IORT showed non-inferior therapeutic efficacy, with no significant differences in postoperative complications (surgical site infection and chronic pain; P>0.05). Notably, the IORT group achieved superior cosmetic outcomes, with 95.2% (20/21) of patients achieving a rating of excellent/good vs. 44.7% (17/38 patients) in the PORT group (P<0.001), alongside higher median cosmetic scores at all postoperative intervals (P<0.01). IORT also reduced healthcare utilization, shortening hospitalization by 23.8 days (12.1±5.1 vs. 35.9±3.5 days; P<0.001) and lowering costs significantly (33,117.98±6,281.17 vs. 77,789.55±7,000.90 CNY; P<0.001). These findings suggest that IORT offers comparable safety, improved cosmesis and greater cost-effectiveness than PORT, supporting its integration into clinical practice for eligible patients.

*Correspondence to:* Dr Qiurong Li or Dr Jun Gu, Research Institute of General Surgery, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, 305 East Zhongshan Road, Nanjing, Jiangsu 210002, P.R. China
E-mail: liqiurongjue@126.com
E-mail: gujunnj@163.com

*Contributed equally

*Key words:* early breast cancer, breast conserving therapy, intraoperative radiotherapy, postoperative radiotherapy, external whole breast radiation

## Introduction

Breast cancer is among the most commonly diagnosed types of cancer worldwide, and its burden has been growing over the course of the last few decades. In 2020, >2.3 million new cases and 685,000 associated deaths were reported globally (1). It is estimated that, owing to population growth and aging, the numbers of annual new cases and deaths from breast cancer will reach >3 million and >1 million, respectively, by the year 2040 (2). Clinical treatment of breast cancer has remained challenging for clinicians.

Breast-conserving surgery (BCS) refers to a combined treatment consisting of surgical tumor resection and post-operative radiotherapy (PORT). A number of clinical trials have shown that overall survival and local recurrence rates

for BCS are comparable with those associated with total mastectomy (3,4). As such, BCS has been implemented as the first choice alternative to radical mastectomy in patients, especially those with early breast cancer (EBC). As an essential component of BCS, PORT is performed using external whole-breast radiation and additional exposure to the tumor bed for reducing local recurrence and mortality (5). PORT is typically initiated following the surgical treatment and completed during a period of 5-7 weeks (five irradiations per week, 1.8-2 Gy/time). The total dose of the irradiation is generally 50-60 Gy for patients with a negative tumor margin, although this may be increased to 66 Gy for those with a positive margin (6). One drawback of this therapy is that the high-dose irradiation received may cause significant co-morbidities, including nausea, vomiting, diarrhea and damage to adjacent tissues (7). Other aspects of PORT are a long treatment time and high costs, which present a large burden for patients. To obviate the need to attend long-term and daily RT, a great number of patients are obliged to opt for a total mastectomy instead, thereby precluding a significant proportion of patients from receiving PORT. Moreover, in the case of patients receiving chemotherapy, the initiation of PORT may be delayed, which is likely to result in an increased risk of local relapse. Therefore, there is an urgent need to develop novel irradiation strategies for the purposes of eliminating such problems and improving clinical outcomes in patients with EBC.

A previous study indicated that up to 90% of local recurrences in patients with breast cancer occur near the primary tumor site, which inspired the development of accelerated partial breast irradiation (APBI), a targeted treatment approach (8). As a technique of APBI, intraoperative RT (IORT) began to be utilized 20 years ago, and has since been applied as an effective therapeutic strategy for irradiation therapy in cases of breast cancer (9,10). Unlike traditional PORT, IORT delivers a concentrated dose of radiation directly to the tumor bed during surgery, thereby minimizing radiation exposure to surrounding healthy tissue. This technique aims to reduce the treatment time and to enhance patient convenience, while maintaining efficacy (9,10). Several retrospective and prospective clinical trials, and two randomized clinical trials, have been conducted comparing IORT with PORT (11-15). The data revealed that IORT had equal local control and patient survival rate, and slightly improved cosmetic outcomes compared with PORT. However, the role of IORT combined with BCS remains controversial, largely because outcomes could be influenced by multiple factors, such as patient selection bias, surgical margin status, adjuvant systemic therapies or surgeon expertise, making it challenging to isolate IORT's specific impact. Based on the previous observations, we hypothesized that IORT might be effective for the treatment of EBC and may produce superior cosmetic results compared with PORT. The current retrospective cohort study explores the role of IORT following BCS, with focus on the oncological outcomes and cosmetic consequences compared with PORT. The efficacy, safety, cosmetic outcome and cost-effectiveness are compared between IORT and PORT, and the data should contribute towards an improved understanding of the benefits of IORT, which would aid clinical decision-making.

## Patients and methods

*Patient selection and data collection*. In the present retrospective cohort study, the data of patients with early-stage breast cancer who underwent BCS followed by IORT or PORT between January 2016 and October 2020 at the Research Institute of General Surgery, Jinling Hospital, Nanjing Medical University (Nanjing, China) were retrospectively reviewed. All diagnoses were based on the 2012 World Health Organization classification of breast tumors (16), with pathological type and histological grade independently evaluated by two experienced pathologists. Tumor staging followed the 7th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis guidelines (17). Clinical data were extracted from the hospital's electronic medical records and analyzed retrospectively. Inclusion criteria were as follows: i) Female patients, aged 18-75 years, with confirmed breast cancer; ii) tumors located >3 cm from the nipple and being <2.5 cm in size (verified by ultrasonography and magnetic resonance imaging); iii) receipt of BCS with IORT or PORT; and iv) confirmed negative tumor margins. Exclusion criteria included recurrent/metastatic breast cancer, a history of upper limb surgery or trauma, systemic diseases predisposing to swelling (e.g., myocardial infarction and renal dysfunction), pregnancy/lactation and prior treatment for arm lymphedema. After screening, 59 patients met the criteria and were categorized into the IORT (n=21) or PORT (n=38) groups based on RT records. Clinicopathological characteristics are summarized in Table I. The study protocol received ethical approval from the Ethics Committee of Jinling Hospital, Nanjing Medical University (approval no. 2024DZKY-148) and adhered to the Declaration of Helsinki (2013 revision).

*BCS assessment*. All patients underwent an extended resection of a breast tumor and a sentinel lymph node biopsy. Carbon nanoparticles were used as the tracer in sentinel lymph node biopsy, and the nodes underwent immediate pathological examination. If no lymph node metastasis was identified, the extended resection of the tumor was allowed to continue. In cases where sentinel lymph node metastasis was identified, an axillary lymph node dissection was also performed, in which a fusiform incision was made on the surface of the tumor to remove the tumor. The distance from the margin to the tumor was >1 cm. The resected specimens were anatomically labeled as cephalic (up), caudal (down), lateral (left/right), cutaneous (front), nipple (central) and deep/basal (back) margins. Intraoperative pathological evaluation was performed on all margins. Breast-conserving surgery (BCS) proceeded only when clear margins were confirmed. In cases with positive margins, additional tissue adjacent to the involved margin was excised and re-evaluated by the pathologist until margin clearance was achieved. For patients receiving IORT, RT was administered by radiologists prior to the wound closure. All participants provided written informed consent prior to undergoing surgical treatment and subsequent adjuvant RT (either IORT or PORT), after being comprehensively informed about the nature, risks, benefits and alternatives of both therapeutic approaches, including detailed explanations of the procedural differences, potential side effects and expected outcomes associated with each modality.

Table I. Characteristics of all patients (n=59) in the retrospective cohort, including the IORT (n=21) and PORT (n=38) groups.

| Parameters | All patients, % (n) | IORT, % (n) | PORT, % (n) | P-value |
|---|---|---|---|---|
| Age, years | | | | 0.028 |
| <50 | 54.2 (32) | 33.3 (7) | 65.8 (25) | |
| ≥50 | 45.8 (27) | 66.7 (14) | 34.2 (13) | |
| Side | | | | 0.786 |
| Left | 44.1 (26) | 47.6 (10) | 42.1 (16) | |
| Right | 55.9 (33) | 52.4 (11) | 57.9 (22) | |
| Tumor size, cm | | | | 0.739 |
| ≤2 | 79.7 (47) | 76.2 (16) | 81.6 (31) | |
| >2 | 20.3 (12) | 23.8 (5) | 18.4 (7) | |
| Number of positive nodes | | | | 0.699 |
| 0 | 88.1 (52) | 95.2 (20) | 84.2 (32) | |
| 1-3 | 6.8 (4) | 4.8 (1) | 7.9 (3) | |
| ≥4 | 5.1 (3) | 0.0 (0) | 7.9 (3) | |
| Histology | | | | 0.571 |
| IDC | 64.4 (38) | 71.4 (15) | 60.5 (23) | |
| Mixed[a] | 20.3 (12) | 9.5 (2) | 26.3 (10) | |
| Other | 15.3 (9) | 19.0 (4) | 13.2 (5) | |
| Grade | | | | 0.766 |
| 1 | 72.9 (43) | 76.2 (16) | 71.1 (27) | |
| 2 | 20.0 (13) | 23.8 (5) | 21.1 (8) | |
| 3 | 5.1 (3) | 0.0 (0) | 7.9 (3) | |
| Molecular subtype | | | | 0.337 |
| Luminal A | 30.5 (18) | 42.9 (9) | 23.7 (9) | |
| Luminal B | 49.2 (29) | 47.6 (10) | 50.0 (19) | |
| HER2-positive (non-luminal) | 8.5 (5) | 4.8 (1) | 10.5 (4) | |
| Triple-negative | 11.9 (7) | 4.8 (1) | 15.8 (6) | |
| ER | | | | 0.109 |
| Positive | 78.0 (46) | 90.5 (19) | 71.1 (27) | |
| Negative | 22.0 (13) | 9.5 (2) | 28.9 (11) | |
| PR | | | | 0.370 |
| Positive | 72.9 (43) | 81.0 (17) | 68.4 (26) | |
| Negative | 27.1 (16) | 19.0 (4) | 31.6 (12) | |
| HER2 | | | | 0.214 |
| Positive | 74.6 (44) | 85.7 (18) | 68.4 (26) | |
| Negative | 25.4 (15) | 14.3 (3) | 31.6 (12) | |
| Proliferative index (Ki-67) | | | | 0.034 |
| ≤20% | 47.5 (28) | 66.7 (14) | 36.8 (14) | |
| >20% | 52.5 (31) | 33.3 (7) | 63.2 (24) | |
| Neoadjuvant treatment | | | | 0.286 |
| Yes | 6.8 (4) | 0.0 (0) | 10.5 (4) | |
| No | 93.2 (55) | 100.0 (21) | 89.5 (34) | |
| Adjuvant treatment | | | | |
| Endocrine therapy | 81.4 (48) | 95.2 (20) | 73.7 (28) | 0.077 |
| Chemotherapy | 86.4 (51) | 81.0 (17) | 89.5 (34) | 0.438 |
| Anti-HER2 therapy | 20.3 (12) | 9.5 (2) | 26.3 (10) | 0.181 |
| Median follow-up time, years [median (range)] | 6.1 (3.8-8.5) | 6.1 (3.8-8.0) | 6.0 (3.8-8.5) | |

[a]IDC with infiltrating lobular carcinoma or other carcinoma mixed. IDC, invasive ductal carcinoma; IORT, intraoperative radiation therapy; PORT, postoperative radiation therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.


Figure 1. Intraoperative irradiation in progress.

*IORT and PORT.* IORT was performed by the radiologists using a mobile electron beam MOBETRON® system (cat. no. Mobetron2000; Intraop Medical Corp.) placed in the operating room (Fig. 1). The irradiation area included the tumor bed and the tissues both surrounding it (~2 cm) and below it (~1 cm). The patients received a radiation dose of 18-20 Gy, determined by tumor characteristics (size, pathological type, molecular subtype and margin status) along with patient-specific factors such as age and clinical condition. This dosage was adjusted from a protocol described in a previous report (18). Depending on the size of the tumor bed, treatment cones and energy levels were adjusted to ensure 90% coverage of the target irradiation area. The radiation was delivered at a dose rate of 10 Gy/min, and the entire radiation procedure, including pre-treatment alignment of the linear accelerator with the collimator, was completed within 3-5 min. Following IORT, the treatment cone was removed and the surgical site was inspected. The surrounding glands near the tumor bed were carefully sutured, with efforts made to close any residual lacunae. Subcutaneous tissue and skin were then closed in layers. Postoperatively, chemotherapy and endocrine therapy were initiated based on the final pathological findings.

In the PORT group, patients were treated using Elekta Precise RT equipment (cat. no. precise1070; Elekta Instrument AB). Postoperative RT was performed by irradiation of the entire breast and lymphatic area with a total dose of 50 Gy, administered at doses of 1.8-2.0 Gy each time (5 times/week). The patients with a negative margin were able to receive a total dosage of up to 60 Gy, whereas those with a positive margin required escalated dosing up to 70 Gy. Following postoperative RT, chemotherapy and endocrine therapy were subsequently performed according to the pathological results.

*Follow-ups and outcome evaluation.* The patients were followed up by visits to the clinic or telephone calls to evaluate the outcomes of surgery and RT, including cosmetic complications, recurrence, metastasis events and survival. The acute and late radiation injuries were evaluated according to the criteria of radiation injury constituted by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (19,20). Cosmetic outcomes were assessed according to the cosmetic scale of the Radiation Therapy Oncology Group (21,22). The scale included four different categories, designated as follows: i) 'Excellent', signifying that the shape of the affected breast was not different from that of the healthy breast, and there was no visible distortion or skin change; ii) 'good', meaning that a slight difference in the shape of the affected breast, such as slight skin distortion, retraction or mild hyperpigmentation, was identified; iii) 'fair', which meant that <25% of the affected breast exhibited distortion of breast symmetry or moderate hyperpigmentation; and iv) 'poor', which signified that >25% of the affected breast exhibited a severe distortion of breast symmetry or moderate hyperpigmentation. Cosmetic outcomes were also assessed

Table II. Evaluation criteria for cosmetic outcomes of standardized breast-conserving treatment in early breast cancer.

| Evaluation Dimension | Specific description | Score |
|---|---|---|
| Breast shape | Bilateral breasts are largely symmetrical, with minor differences visible only upon close inspection. Contour is near-normal, with minimal impact on overall appearance. | 2 points |
| | Moderate asymmetry or contour irregularity in bilateralbreasts, visibly affecting overall appearance. | 1 point |
| | Severe asymmetry or deformity, with loss of normal breast shape and significant aesthetic detriment. | 0 point |
| Skin condition | Mild skin irregularity, faint scarring or minimal pigmentation/ wrinkling; not readily noticeable. | 2 points |
| | Moderate skin irregularity, visible scarring or noticeable pigmentation/wrinkling, but without severe aesthetic impact. | 1 point |
| | Severe skin irregularity, thick/obvious scarring or significant pigmentation/wrinkling, markedly affecting appearance. | 0 point |
| Nipple and areola | Vertical discrepancy between bilateral nipple-areola complexes ≤2 cm. Minor variations in size, shape or color (subtle or absent compared with contralateral side). | 2 points |
| | Vertical discrepancy >2 and ≤3 cm. Significant differences in size, shape or color, causing noticeable aesthetic impact. | 1 point |
| | Vertical discrepancy >3 cm or severe abnormalities (e.g., discoloration), substantially compromising breast appearance. | 0 point |
| Texture of the breast | Soft texture, consistent with contralateral breast; no indurations, lumps or abnormal sensations. | 2 points |
| | Slight firmness or mild induration present, without affecting overall tactile quality. | 1 point |
| | Marked firmness, obvious indurations or palpable lumps, significantly impairing tactile quality. | 0 point |
| Patient satisfaction | Patient expresses high satisfaction, reporting results meet or exceed expectations; fully accepts post-operative breast appearance and function. | 2 points |
| | Patient reports general satisfaction, with minor unresolved concerns about outcomes. | 1 point |
| | Patient dissatisfied; results fail to meet expectations, with significant concerns about breast appearance or function. | 0 point |

using a modified evaluation framework across five dimensions: Breast shape, skin condition, nipple and areola, texture of the breast and patient satisfaction (23,24). Detailed criteria for this scoring framework are provided in Table II.

*Statistical analysis*. Continuous variables are expressed as the mean ± standard deviation for normally distributed data or the median with interquartile range (IQR) for non-normally distributed data. Categorical variables are reported as counts and percentages. Normality of continuous variables was assessed using the Shapiro-Wilk test. Unpaired Student's t-test was applied for normally distributed continuous variables, and the Wilcoxon rank-sum test was used for non-normal or ordinal data (e.g., cosmetic scores). Categorical variables were analyzed using the Fisher's exact test. All tests were two-sided, with $P<0.05$ considered to indicate a statistically significant difference. Analyses and graph generation were performed using GraphPad Prism 9.0 (Dotmatics).

## Results

*Clinical characteristics of the patients*. A total of 59 patients diagnosed with breast cancer were included in the present study and categorized into the IORT (n=21 patients) and PORT (n=38 patients) groups. The clinical data of the patients were collected retrospectively and analyzed. When comparing the two groups, no significant differences were identified in terms of the tumor side, tumor size, number of positive nodes, histology, grade, molecular subtype, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), neoadjuvant treatment or adjuvant treatment (Table I). The IORT cohort demonstrated a significantly younger mean age compared with the PORT group ($P<0.05$),

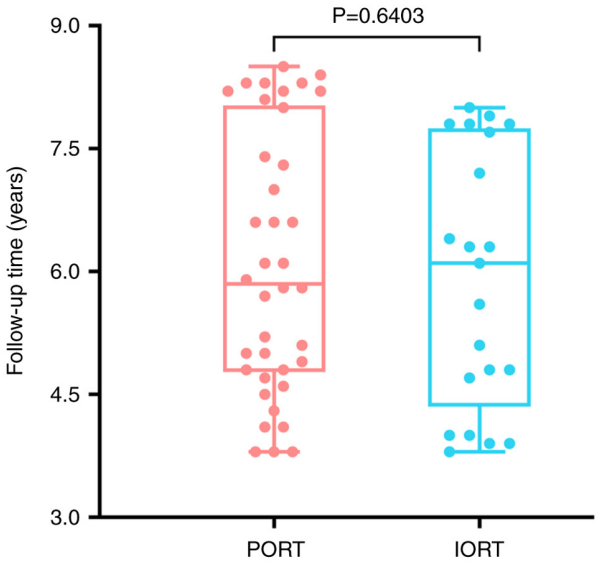


Figure 2. Comparison of follow-up time between the IORT and PORT groups. IORT, intraoperative radiation therapy; PORT, postoperative radiation therapy.

while exhibiting a significantly decreased prevalence of high tumor proliferative activity (Ki-67>20%) than the PORT cohort (P<0.05).

*Follow-up and prognosis*. Long-term follow-ups of the patients were conducted to assess the efficiency and safety of IORT in patients with EBC who were receiving BCS. No significant difference in the follow-up time was observed in the IORT (5.89±1.57 years) and PORT (6.09±1.60 years) groups (P>0.05) (Fig. 2). The median follow-up time in the IORT group was 6.1 years, ranging from 3.8-8.0 years (Table I). For the patients receiving PORT, the median follow-up time was 6.0 years (range: 3.8-8.5 years).

*Local control and recurrence rates*. In the IORT group, none of the patients developed local relapse or distant metastasis in the period of follow-up. Similarly, none of the patients developed local relapse in the PORT group, although one patient did develop lung metastasis and was treated with thoracopic surgery. The overall survival rate for both groups was 100% in the follow-up period. These data indicated that IORT provided effective local control of the tumor, and the local recurrence rates were comparable with those achieved using PORT. Furthermore, the use of IORT did not result in any compromise of the overall survival rates when compared with PORT.

*Comparative analysis of treatment-related morbidity*. The analysis of treatment-related complications revealed distinct patterns between the IORT and PORT groups. In the IORT cohort, no radiation-associated complications were documented (Table III). Surgical complications occurred in 2 IORT patients (9.5%, 2/21), manifesting as fat liquefaction that resolved within ~10 days through dressing changes. One of these cases developed abscesses requiring drainage and antibiotics, achieving full wound healing within 2 weeks. Fat liquefaction presented in 3 cases (7.9%) of 38 patients in the PORT group, with no significant intergroup difference compared with the IORT group (P>0.05). Conversely, the PORT group demonstrated substantial radiation-induced morbidity: 24 patients (63.2%, 24/38) developed grade 1-4 acute skin toxicity per RTOG criteria (19), including 5 grade 3-4 cases (13.2%, 5/38). Hematological toxicity affected 28 patients in the PORT group (28.6% grade 3-4), accompanied by 2 cases of grade 1-2 pneumonitis. Additionally, PORT exhibited significantly higher rates of hyperpigmentation (P<0.001), radiodermatitis (P<0.001), radiation-related pain (P<0.05) and acute hematological toxicity (P<0.01) compared with IORT. Notably, neither acute nor late radiation injuries were observed in the IORT group (Table III).

*Late radiation injury*. According to the definition of RTOG late radiation injury (18), late skin toxicity (grades 1-3) was observed in 3 patients of the PORT group. A total of 9 patients had late radiation injury of the leukocytes. Of these patients, 5 (55.6%) still had different levels of leukopenia at 1 year after RT. Patients with RT-induced lung injury did recover 1 year after RT, as confirmed by CT. None of the patients in the IORT group experienced late radiation injury (Table III).

*Dosimetric profile of organs at risk (OARs)*. The dosimetric profile of OARs represents a crucial parameter for assessing treatment safety and efficacy of irradiation therapy. The V5 and V20 dose-volume parameters, defined as the percentage of organ volume exposed to ≥5 Gy and ≥20 Gy radiation respectively, were employed to quantify post-treatment radiation burden on OARs. In the PORT group, the dosimetric analysis revealed the following: The V5 and V20 values for the ipsilateral lung were 46.62±16.11 and 21.65±8.29%, respectively (Table IV). For the total lung, the V5 and V20 values were 24.46±8.84 and 11.05±4.39%, respectively, with a mean lung dose (MLD) of 8.06±2.98 Gy. For the heart, the V5 and V20 values were 13.74±11.56 and 1.86±2.40, respectively, with a mean heart dose of 3.32±2.00 Gy. For IORT, electron beams exhibited a rapid dose fall-off, which significantly limits radiation exposure to surrounding normal tissues. Combined with the precise energy control and the use of shielding, IORT could ensure effective sparing of the OARs, and as a result, no significant injuries in adjacent organs and tissues were seen in the IORT group. Although the PORT technique could achieve an optimal dose distribution to reduce the risk of irradiation-associated complications, including pneumonitis and cardiotoxicity, it was evident that IORT might be a much safer treatment alternative for selected patients with breast cancer.

*Breast cosmetic outcomes*. Postoperative cosmetic outcomes were assessed using standardized grading and scoring criteria as aforementioned. High-quality outcomes (excellent/good grades) were achieved in 95.2% (20/21) of the IORT group, including 16 patients (76.2%) with excellent ratings and 4 with good ratings (Table V). By contrast, only 42.1% (16/38) of the PORT group achieved these grades, with 4 excellent ratings and 12 good ratings. The IORT cohort demonstrated a significantly higher rate of excellent cosmetic outcomes compared with the PORT group (P<0.001; Table V). Longitudinal cosmetic scores further demonstrated the advantage of IORT, with a stable median score of 10 (IQR, 10-10; ranges, 7-10 at 1 week, 8-10 at 1 month, and 9-10 at 6 months and 1 year).

Table III. Complications of surgery and radiotherapy.

A, Wound-associated complication

| Complication/injury | IORT (n=21) | PORT (n=38) | P-value |
|---|---|---|---|
| Fat liquefaction | 2/21 | 3/38 | 0.999 |
| Wound infection | 2/21 | 1/38 | 0.999 |
| Pain | 0/21 | 0/38 | >0.999 |
| Breast oedema | 0/21 | 0/38 | >0.999 |
| Seroma | 0/21 | 0/38 | >0.999 |

B, RTOG acute radiation injury

| Complication/injury | IORT (n=21) | PORT (n=38) | P-value |
|---|---|---|---|
| Leukocyte | | | |
| Grade 1-2 | 0/21 | 22/38 | <0.001 |
| Grade 3-4 | 0/21 | 6/38 | 0.207 |
| Skin | | | |
| Grade 1-2 | 0/21 | 19/38 | <0.001 |
| Grade 3-4 | 0/21 | 5/38 | 0.293 |
| Lung | | | |
| Grade 1-2 | 0/21 | 2/38 | 0.344 |
| Grade 3-4 | 0/21 | 0/38 | - |
| Heart | | | |
| Grade 1-4 | 0/21 | 0/38 | - |

C, RTOG/EORTC late radiation injury

| Complication/injury | IORT (n=21) | PORT (n=38) | P-value |
|---|---|---|---|
| Leukocyte | | | |
| Grade 1-3 | 0/21 | 9/38 | 0.071 |
| Grade 4-5 | 0/21 | 0/38 | - |
| Skin | | | |
| Grade 1-3 | 0/21 | 3/38 | 0.241 |
| Grade 4-5 | 0/21 | 0/38 | - |
| Lung | | | |
| Grade 1-5 | 0/21 | 0/38 | - |
| Heart | | | |
| Grade 1-5 | 0/21 | 0/38 | - |

RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research on Treatment of Cancer; IORT, intraoperative radiotherapy; PORT, postoperative radiotherapy.

In the PORT group, the cosmetic score was significantly lower, as revealed by a median score of 8 (IQR, 6-9; range, 4-10), 7 (IQR, 6-8; range, 3-10), 8 (IQR, 7-9; range, 5-10) and 9 (IQR, 8-10; range, 6-10) at 1 week, 1 month, 6 months and 1 year, respectively (all P<0.01; Fig. 3).

*Length of stay*. In the IORT group, the total duration of hospitalization was 12.1±5.1 days. By contrast, in the PORT group, the total length of stay (including RT) was 35.9±3.5 days (Fig. 4), representing a significant difference in the treatment time between the two groups (P<0.001). In addition, the patients treated with PORT also spent more time on trips to the hospital (data not shown).

*Health care costs*. A comparative cost analysis was conducted between the two groups, quantifying healthcare expenditures specific to radiation therapy, including treatment delivery, hospitalization, nursing care and associated

Table IV. Dosimetric profile of OARs.

| | PORT | | | |
|---|---|---|---|---|
| OAR | V5 value, % | V20 value, % | Mean dose, Gy | IORT |
| Total lung | 24.46±8.84 | 11.05±4.39 | 8.06±2.98 | No significant injury |
| Ipsilateral lung | 46.62±16.11 | 21.65±8.29 | | |
| Heart | 13.74±11.56 | 1.86±2.40 | 3.32±2.00 | No significant injury |

V5 and V20 values represent the percentage volume of an organ receiving ≥5 or ≥20 Gy radiation dose, respectively; OAR, organ at risk; IORT, intraoperative radiotherapy; PORT, postoperative radiotherapy.

Table V. Percentages of breast cosmetic grading in the patients treated with PORT (n=38) and IORT (n=21).

| Treatment | Excellent | Good | Fair | Poor |
|---|---|---|---|---|
| PORT, % (n) | 10.53 (4) | 31.58 (12) | 39.47 (15) | 18.42 (7) |
| IORT, % (n) | 76.19 (16) | 19.04 (4) | 4.76 (1) | 0.00 (0) |
| P-value | <0.001 | 0.300 | 0.004 | 0.094 |

IORT, intraoperative radiotherapy; PORT, postoperative radiotherapy.

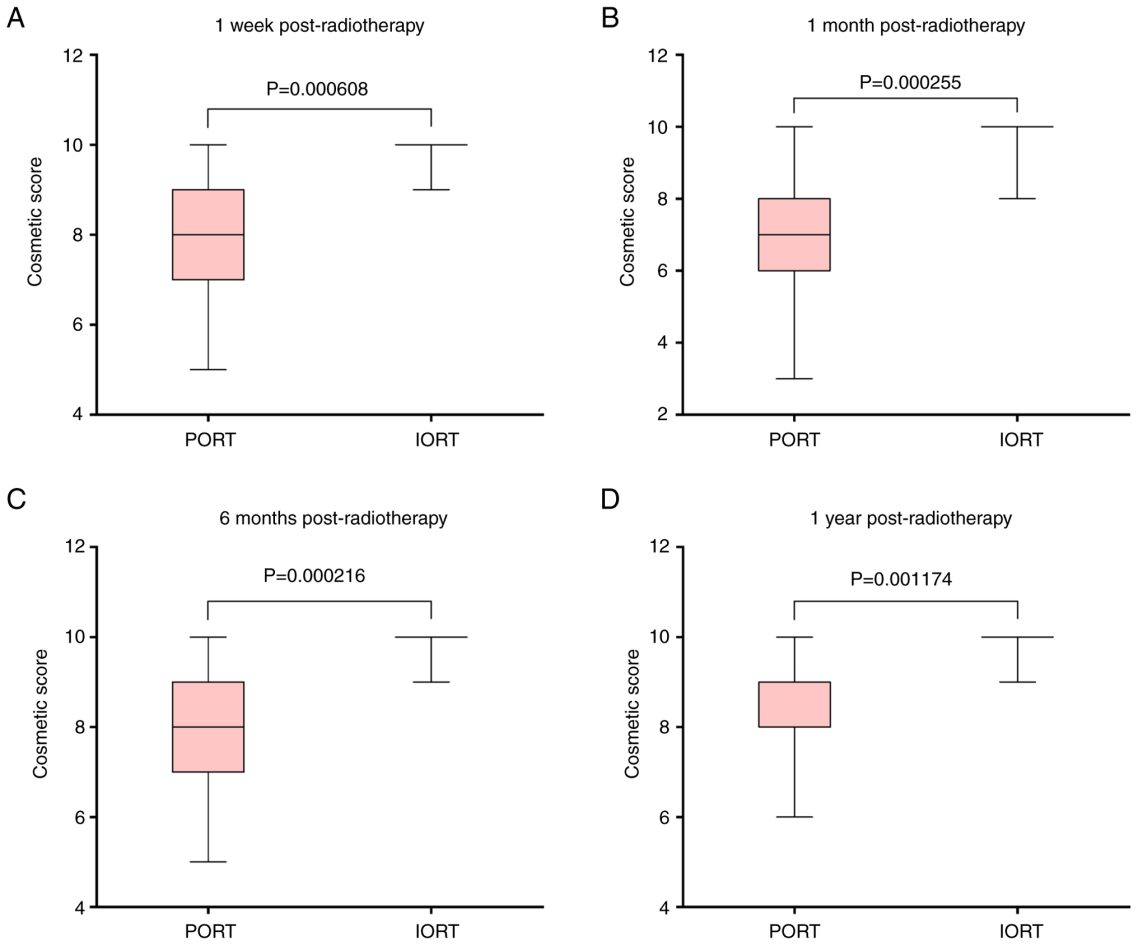


Figure 3. Breast cosmetic score comparisons between the IORT and PORT groups at four postoperative time points. (A) At 1 week: PORT=median, 8 (IQR, 6-9; range 4-10) vs. IORT=median, 10 (IQR, 10-10; range, 7-10), P=0.000608. (B) At 1 month: PORT=median, 7 (IQR, 6-8; range, 3-10) vs. IORT=median, 10 (IQR, 10-10; range, 8-10), P=0.000265. (C) At 6 months: PORT=median, 8 (IQR, 7-9; range, 5-10) vs. IORT=median, 10 (IQR, 10-10; range, 9-10), P=0.000216. (D) At 1 year: PORT=median, 9 (IQR, 8-10; range, 6-10) vs. IORT=median, 10 (IQR, 10-10; range, 9-10), P=0.001174. IORT group boxes are absent due to identical Q1, median and Q3 values (all scores=10). IORT, intraoperative radiation therapy; PORT, postoperative radiation therapy; IQR, interquartile range.

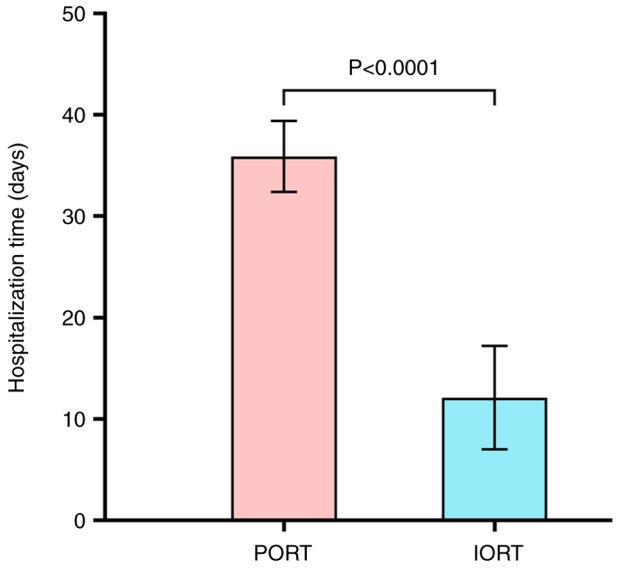


Figure 4. Comparison of total hospitalization time between the IORT and PORT groups. IORT, intraoperative radiation therapy; PORT, postoperative radiation therapy.

pharmaceuticals/medical supplies. In the IORT group, the mean health care costs were 33,117.98±6,281.17 Chinese Yuan (CNY), which was significantly lower compared with that of the PORT group (77,789.55±7,000.90 CNY) (P<0.001) (Fig. 5A). Also, the mean cost of IORT was significantly lower than that of PORT (P<0.001) (Fig. 5B). The patients receiving PORT also tended to spend more on clinical visits and transportation, although these costs were not included in the overall health care costs. These data suggested that the use of IORT could alleviate some of the economic burden for patients with EBC who receive BCS.

## Discussion

BCS combined with RT is a standard treatment for EBC. Traditionally, PORT has been the norm; however, IORT has emerged as an innovative alternative (9). The current study was a retrospective cohort study exploring the efficacy, safety and cosmetics of IORT in patients with early-stage breast cancer undergoing BCS. The data demonstrated that IORT offered similar effectiveness to PORT while at the same time causing fewer common complications and less financial burdens than PORT. More importantly, IORT exhibited better cosmetic outcomes for such patients, suggesting it as a new treatment option for patients with breast cancer undergoing BCS.

RT is the critical component of breast-conserving therapy received by patients with EBC. The traditional routine of PORT is to irradiate the entire breast and lymphatic area 5 days a week, with the administration of 1.8-2.0 Gy/fraction up to a total dose of 50 Gy (9). Certain patients, such as those with breast cancer presenting with positive margins, multifocal disease, young age (<40 years) and high-grade tumors, have to receive an additional irradiation dose of 10-15 Gy to the tumor bed, leading to an extended RT duration (5-6 weeks, or even much longer). Although PORT has been demonstrated to reduce local recurrence by 70% and to improve survival by 5-7% (25), certain patients may reject BCS due to the lengthy period of PORT. In addition, PORT needs to be performed after chemotherapy and wound healing. This delay may cause a higher risk of local relapse (26). The goal of BCS is to remove the tumor and to minimize the effects of changes in breast appearance and function, thereby improving the quality of life for patients after the operation (27). Moreover, the cosmetic side effects of PORT, including skin fibrosis and hyperpigmentation, may lead to a considerable number of patients giving up BCS. A previous study showed that 21% of women did not receive RT following BCS on account of the aforementioned reasons (28).

Given the fact that local recurrence mainly occurs near to the tumor bed following BCS, APBI has gradually gained in popularity. Current technologies of APBI include brachytherapy, three-dimensional conformal RT (3D-CRT), intensity-modulated radiation therapy (IMRT) and IORT. Brachytherapy is mainly performed according to the MammoSite® RT system (29). The major advantage of this technology is that the device can be placed in the operation room and guided by ultrasound following the operation. 3D-CRT and IMRT are non-invasive techniques, although they have the disadvantages of being susceptible to the breathing and positioning of the patients (30). IORT is the latest APBI technique to have been developed. Compared with the other APBI techniques, IORT can be performed at the same time as surgery, and is not affected by the patient's breathing and posture, which ensures the accuracy of irradiation of the tumor bed (31). The radiation dosage of IORT on the tumor bed is usually 20 Gy, which is less than that of fractionated irradiation, but is equivalent to the dose of fractionated irradiation (70 Gy) (32). At present, several studies have shown the non-inferiority of IORT for EBC in terms of overall survival rates when comparing between patients receiving IORT and those receiving whole-breast PORT (33,34). Representative prospective clinical trials include the TARGIT-A trial reported by Vaidya *et al* (13) and the ELIOT trial reported by Veronesi *et al* (14). Both trials showed that IORT and PORT achieve similar overall survival rates for EBC, supporting the effectiveness of IORT in its clinical application (35). However, the TARGIT-A trial showed that the 5-year overall recurrence rate in the IORT group was higher compared with that of the whole-breast irradiation group (hazard ratio, 1.44; P=0.053), whereas the 5-year ipsilateral breast tumor recurrence rate was higher than the IORT target value (3.3% vs. 1.3%; P=0.042). This may have been due to the fact that some of the patients in the TARGIT-A trial did not meet the criteria recommended by the American Society of Radiological Oncology for APBI treatment (36). In terms of skin side-effects, the incidence of grade 3-4 skin toxicity in the TARGIT-A group was found to be lower compared with that in the whole-breast irradiation group (0.2% vs. 0.8%; P=0.029), which contributed to the difference in cosmetic outcomes of BCS.

Cosmetic outcome is an important determinant in treatment choice following BCS. Previous studies have shown that the cosmetic effects of IORT are neither inferior nor better compared with those achieved by external irradiation (37-39). In the present study, the cosmetic outcomes in the IORT group were found to be satisfactory. Only 1 patient was graded as fair due to the presence of an abscess, whereas the remaining 20 patients (95.2%) were graded as excellent (76.2%) or good

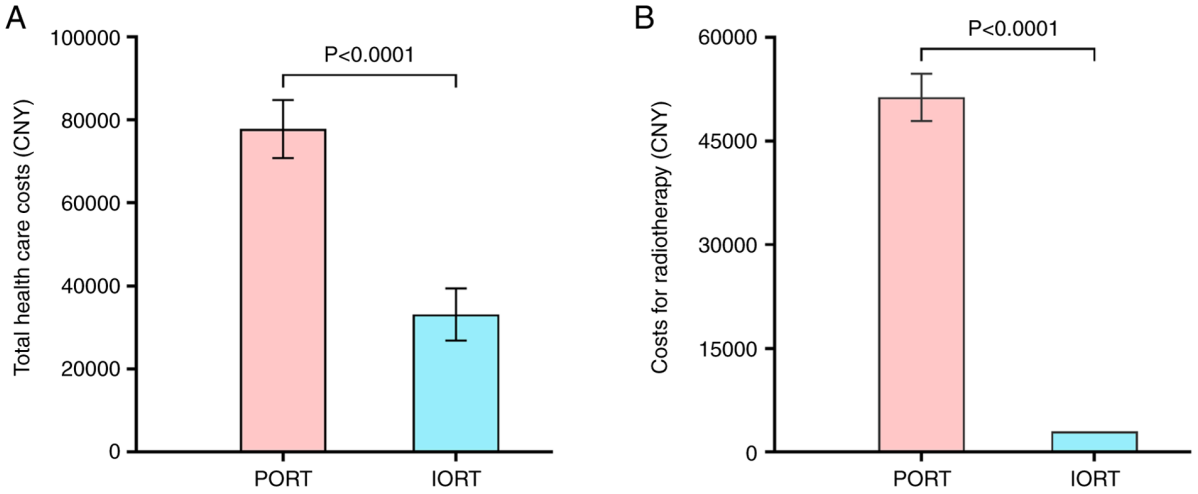


Figure 5. Costs for total health care and RT. (A) Total health care costs for breast-conserving treatment in both groups are shown. (B) Costs for RT (IORT or PORT) are shown. RT, radiotherapy; IORT, intraoperative radiation therapy; PORT, postoperative radiation therapy; CNY, Chinese Yuan.

(19.0%) (Table V). By contrast, only 42.1% (16/38) of the PORT group achieved excellent or good grades, with 4 excellent ratings (10.5%) and 12 good ratings (31.6%). This result demonstrated that IORT could achieve improved cosmetic outcomes in patients, which was in agreement with the recent findings reported by Shandiz *et al* (12). Furthermore, additional complications of RT occurred in the PORT group in the present study, including hyperpigmentation, radiodermatitis, radiation-induced pain and radiation-induced acute hematological toxicity. Fat liquefaction was more frequent in the IORT group compared with the PORT group, although this difference was not found to be significant. Age appears to be an important factor associated with fat liquefaction and infection of the incision following IORT, since the patients with fat liquefaction or local infection were all >60 years old. This may be due to the fact that the ratio of the breast gland to adipose tissue is higher in older patients, and older patients were more common in the IORT group.

Recent studies have established the long-term oncological efficacy of IORT (40-42). Chi *et al* (40) conducted a retrospective analysis of 164 patients with breast cancer and 83 ductal carcinoma *in situ* (DCIS) cases treated with IORT (20 Gy single fraction) at a single institution in Taiwan. With a mean follow-up time of 64.3 months, a higher locoregional recurrence rate was observed using IORT (9.8%) compared with using whole-breast irradiation (3.0%), although metastasis and mortality rates were comparable between groups. Hanna *et al* (41) prospectively validated the feasibility of non-dedicated linear accelerators for IORT (21 Gy single fraction), reporting a 7.2% local recurrence rate over a median follow-up time of 145 months (range, 12.8-187.1 months). These findings underscored the importance of an extended follow-up, as late recurrences may occur beyond 10 years. Sarria *et al* (42) further supported the utility of IORT as an upfront boost in an international cohort of 653 patients from Peru, Spain and Germany, demonstrating local control outcomes comparable to external beam RT. Short-term outcomes were explored by Fadavi *et al* (11) and Shandiz *et al* (12). Fadavi *et al* (11) compared intraoperative electron RT followed by hypofractionated whole breast irradiation to conventional whole-breast irradiation, finding comparable acute and late toxicity profiles over a median follow-up time of 12 months. Shandiz *et al* (12) reported an 8.3% recurrence rate and manageable toxicity (e.g., grade III fibrosis in 8.3% of cases) with IORT as a tumor bed boost post-neoadjuvant chemotherapy (NAC) over a median follow-up time of 29.5 months. Both studies concluded that IORT achieved acceptable short-term outcomes in local control, toxicity and cosmesis, aligning with the findings of Keramati *et al* (9) in their 2020 review of post-NAC settings. This consistency further supports the applicability of IORT beyond NAC-specific cohorts. Collectively, these findings affirm the viability of IORT as a simplified, effective alternative to whole-breast irradiation in appropriately selected patients, which is consistent with the present findings on long-term oncological safety. In contrast to prior works, the present study advances the clinical understanding of IORT by addressing underexplored dimensions. First, while earlier research prioritized oncological outcomes, the present study highlights cosmetic results as a critical metric, demonstrating significantly higher rates of 'excellent/good' outcomes with IORT (95.2%) vs. PORT (44.7%). This distinction emphasizes the potential of IORT to enhance quality of life, a priority for patient-centered care. Second, the present study uniquely quantified socioeconomic benefits, revealing that IORT could markedly reduce healthcare costs and shorten hospitalization compared with PORT, offering actionable insights for cost-sensitive healthcare systems. Third, whilst Chi *et al* (40) demonstrated the long-term efficacy of IORT in a retrospective single-institution cohort, the present study built on these findings by confirming its safety in another Chinese population and offering new insights into cost-effectiveness. Finally, by focusing on a distinct cohort of Chinese patients, the present work addressed regional disparities in treatment response and healthcare-resource allocation, factors often overlooked in global IORT research. Collectively, the present study bridged a critical gap in the literature and provided a comprehensive framework to optimize IORT implementation across diverse clinical and socioeconomic settings.

The primary advantage of IORT lies in its ability to deliver adjuvant radiation concurrently with surgery,

significantly shortening treatment duration compared with PORT. Additionally, IORT minimizes radiation exposure to healthy tissues, reducing toxicity risks. However, this approach has inherent limitations. For instance, final pathological details, such as surgical margin status and lymph node involvement, remain unavailable during IORT delivery, creating potential discrepancies between intraoperative frozen-section and final histopathological results. Thus, rigorous patient selection is critical in clinical practice. While the present findings offer therapeutic insights for EBC, several limitations warrant acknowledgment. First, this preliminary retrospective study included a small, heterogeneous cohort, encompassing node-positive patients and those receiving neoadjuvant therapies, reflecting real-world practice but introducing variability. Treatment allocation (IORT vs. PORT) was influenced by clinician judgment and patient preference, risking selection bias and baseline imbalances in tumor biology or comorbidities. Reliance on retrospective data restricted access to detailed information, such as HER2 status and adjuvant therapy adherence, limiting robust confounder adjustment. The modest sample size further precluded subgroup analyses or propensity score matching.

While the heterogeneity of the cohort enhances real-world generalizability, several confounding factors may influence the analysis of IORT and PORT outcomes in the present study. Patient selection bias could arise from imbalances in tumor characteristics (e.g., size and HER2 status), age or comorbidities between groups (43,44). For instance, younger patients or those with aggressive tumor biology in the IORT group might skew recurrence rates, independent of treatment efficacy. Surgical variability, such as differences in margin status or surgeon proficiency with IORT techniques, could disproportionately affect local control outcomes if one group had suboptimal tumor excision or inconsistent radiation delivery (45). Adjuvant therapies further complicate comparisons: Disparities in chemotherapy, endocrine therapy or PORT protocols (e.g., whole-breast vs. partial irradiation) might mask or amplify treatment-related effects on survival or toxicity (46). Baseline cosmetic differences, including breast size or tumor location, could confound aesthetic outcomes, as smaller breasts or peripherally located tumors may inherently favor better cosmesis regardless of RT type (47). Socioeconomic and geographic factors might introduce systemic bias, as patients opting for IORT (often requiring specialized resources) may have better healthcare access or higher health literacy, improving compliance and artificially enhancing outcomes (46). Follow-up heterogeneity, such as variations in surveillance intensity (e.g., imaging frequency), could lead to underdetection of recurrence in less-monitored groups (48,49). Finally, psychosocial factors, such as patient preferences for shorter treatment duration, might select for populations prioritizing convenience over risk, influencing perceived satisfaction or compliance (50,51). Collectively, these confounders risk distorting comparisons by attributing outcomes to treatment modality rather than underlying imbalances. For example, if IORT cohorts included more low-risk tumors or received more adjuvant therapies, its apparent superiority in local control could reflect selection bias rather than inherent efficacy. Conversely, socioeconomic disparities might exaggerate the cost burden of PORT if marginalized populations disproportionately received it. To mitigate these issues, multivariable adjustments, propensity score matching or randomized trials are critical to isolate the true effects of IORT vs. PORT. These factors collectively weaken causal inferences regarding the non-inferior safety and superior cosmetic efficacy of IORT, underscoring the need for prospective trials with standardized data collection to validate these findings. Future studies with prospective and randomized design, which will feature larger patient cohorts with selected patients, are warranted to validate the current findings.

In conclusion, in patients with EBC undergoing BCS, IORT demonstrates non-inferior oncological safety and tumor control compared with PORT, while excelling in cosmetic outcomes, cost-effectiveness and treatment efficiency. For low-to-intermediate-risk patients prioritizing quality of life and convenience, IORT offers a patient-centric alternative without compromising oncological rigor. PORT remains critical for high-risk cases with the need for comprehensive radiation. This paradigm aligns with personalized oncology, balancing clinical efficacy with practical benefits to enhance therapeutic value. Further studies, including large-scale trials and investigations into multimodal strategies, are warranted to refine patient selection and validate long-term outcomes, ensuring broader applicability of IORT in modern EBC management.

**Acknowledgements**

Not applicable.

**Funding**

This study was funded by the Project of Social Development Foundation of Jiangsu Province, China (grant no. BE2017726) and the Medical Research Project of Jinling Hospital, Nanjing Medical University (grant no. 22LCZLXJS33).

**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

QL, JG and XX conceptualized the study and designed the experimental methods. XX, LW, YC, JY and WD collected and analyzed the data. LH and YS performed the follow-up of the patients. JW and XX analyzed data. QL, XX and LW were responsible for interpretation of the data. XX was responsible for writing the original draft and editing the figures. QL, JG and XX reviewed and edited the manuscript. QL supervised the study and contributed to the revision of the manuscript. All authors read and approved the final version of the manuscript. XX, LW, YC, JW, JY, LH, YS, WD, JG and QL confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Jinling Hospital, Nanjing Medical University (Nanjing, China; approval

no. 2024DZKY-148) and was conducted in accordance with The Declaration of Helsinki. The participants provided written informed consent prior to taking part in the study.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### References


1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70: 7-30, 2020.
2. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, Vignat J, Gralow JR, Cardoso F, Siesling S and Soerjomataram I: Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast 66: 15-23, 2022.
3. Rajan KK, Fairhurst K, Birkbeck B, Novintan S, Wilson R, Savović J, Holcombe C and Potter S: Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy for early-stage breast cancer: Meta-analysis. BJS Open 8: zrae040, 2024.
4. Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A and Jensen MB: Breast conserving surgery versus mastectomy: Overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). Acta Oncol 57: 19-25, 2018.
5. Recht A: Whole-breast irradiation is the preferred standard of care for the majority of patients with early-stage breast cancer. J Clin Oncol 38: 2263-2267, 2020.
6. Polgár C, Kahán Z, Ivanov O, Chorváth M, Ligačová A, Csejtei A, Gábor G, Landherr L, Mangel L, Mayer Á and Fodor J: Radiotherapy of breast cancer-professional guideline 1st central-eastern european professional consensus statement on breast cancer. Pathol Oncol Res 28: 1610378, 2022.
7. Wang K and Tepper JE: Radiation therapy-associated toxicity: Etiology, management, and prevention. CA Cancer J Clin 71: 437-454, 2021.
8. Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, Metaxas M, Harte KJ, Sliski AP and Thomson E: Targeted intra-operative radiotherapy (Targit): An innovative method of treatment for early breast cancer. Ann Oncol 12: 1075-1080, 2001.
9. Keramati A, Javadinia SA, Gholamhosseinian H, Fanipakdel A, Shandiz FH and Taghizadeh-Hesary F: A review of intraoperative radiotherapy after neoadjuvant chemotherapy in patients with locally advanced breast cancer: From bench to bedside. Indian J Gynecol Oncolog 8: 110, 2020.
10. Hepel JT and Wazer DE: Partial breast irradiation is the preferred standard of care for a majority of women with early-stage breast cancer. J Clin Oncol 38: 2268-2272, 2020.
11. Fadavi P, Nafissi N, Mahdavi SR, Jafarnejadi B and Javadinia SA: Outcome of hypofractionated breast irradiation and intraoperative electron boost in early breast cancer: A randomized non-inferiority clinical trial. Cancer Rep (Hoboken) 4: e1376, 2021.
12. Shandiz FH, Fanipakdel A, Forghani MN, Javadinia SA, Shahi EM, Keramati A, Fazilat-Panah D and Moein Babaei M: Clinical efficacy and side effects of IORT as tumor bed boost during breast-conserving surgery in breast cancer patients following neoadjuvant chemotherapy. Indian J Gynecol Oncolog 18: 46, 2020.
13. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, Brew-Graves C, Potyka I, Morris S, Vaidya HJ, *et al*: An international randomised controlled trial to compare TARGeted intraoperative radiotherapy (TARGIT) with conventional postoperative radiotherapy after breast conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). Health Technol Assess 20: 1-188, 2016.
14. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, *et al*: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol 14: 1269-1277, 2013.
15. Zhang L, Zhou Z, Mei X, Yang Z, Ma J, Chen X, Wang J, Liu G, Yu X and Guo X: Intraoperative radiotherapy versus whole-breast external beam radiotherapy in early-stage breast cancer: A systematic review and meta-analysis. Medicine (Baltimore) 94: e1143, 2015.
16. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH and van de Vijver MJ: WHO classification of tumours of the breast, 4th edition, Vol 4. Lyon, IARC Press, 2012.
17. Singletary SE, Connolly JL and Hortobagyi GN: Breast. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A: AJCC Cancer Staging Manual. 7th edition, Springer, NY, USA, pp 347-376, 2010.
18. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, *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. Lancet 383: 603-613, 2014.
19. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31: 1341-1346, 1995.
20. Sawaki M, Sato S, Noda S, Idota A, Uchida H, Tsunoda N, Kikumori T, Aoyama Y, Ishihara S, Itoh Y and Imai T: Phase I/II study of intraoperative radiotherapy for early breast cancer in Japan. Breast Cancer 19: 353-359, 2012.
21. Kimple RJ, Klauber-DeMore N, Kuzmiak CM, Pavic D, Lian J, Livasy CA, Esler L, Moore DT, Sartor CI and Ollila DW: Cosmetic outcomes for accelerated partial breast irradiation before surgical excision of early-stage breast cancer using single-dose intraoperative radiotherapy. Int J Radiat Oncol Biol Phys 79: 400-407, 2011.
22. Liu L, Li XR, Ma L, Zhang YJ, Wang JD, Kong QL, Zheng YQ, Yu W and Li R: Observation on short-term effect of breast-conserving operation plus intraoperative radiotherapy in 64 breast cancer patients. Chin J Breast Dis (Electronic Ed) 4: 683-691, 2010 (In Chinese).
23. Harris JR, Levene MB, Svensson G and Hellman S: Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 5: 257-261, 1979.
24. Zhang BN, Shao ZM, Qiao XM, Li B, Jiang J, Yang MT, Wang S, Song ST, Zhang B and Yang HJ: A prospective multicenter clinical trial of breast conserving therapy for early breast cancer in China. Zhonghua Zhong Liu Za Zhi 27: 680-684, 2005 (In Chinese).
25. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S, *et al*: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 366: 2087-2106, 2005.
26. Punglia RS, Saito AM, Neville BA, Earle CC and Weeks JC: Impact of interval from breast conserving surgery to radiotherapy on local recurrence in older women with breast cancer: Retrospective cohort analysis. BMJ 340: c845, 2010.
27. Chai F, Zhao QL, Zhang JF and Huang YQ: Short-term effect of breast conserving surgery combined with intraoperative radiotherapy in 60 patients with breast cancer. Chin J Breast Dis (Electronic Ed) 11: 13-18, 2017 (In Chinese).
28. Tuttle TM, Jarosek S, Habermann EB, Yee D, Yuan J and Virnig BA: Omission of radiation therapy after breast-conserving surgery in the United States: A population-based analysis of clinicopathologic factors. Cancer 118: 2004-2013, 2012.
29. Niehoff P, Ballardini B, Polgár C, Major T, Hammer J, Richetti A and Kovács G: Early European experience with the MammoSite radiation therapy system for partial breast brachytherapy following breast conservation operation in low-risk breast cancer. Breast 15: 319-325, 2006.
30. Banglan KL, Sharpe MB, Jaffray D, Frazier RC, Fayad J, Kestin LL, Remouchamps V, Martinez AA, Wong J and Vicini FA: Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). Int J Radiat Oncol Biol Phys 55: 302-311, 2003.
31. Liu L and Li XR: Research progress of breast conserving surgery combined with intraoperative radiotherapy for breast cancer. Chin J Health Care Med 13: 166-169, 2011.
32. Herskind C, Griebel J, Kraus-Tiefenbacher U and Wenz F: Sphere of equivalence-a novel target volume concept for intraoperative radiotherapy using low energy X rays. Int J Radiat Oncol Biol Phys 72: 1575-1581, 2008.
33. Melnik I, Yerushalmi R, Sobol Y, Magen A, Givon-Madhala O, Birinbaum Y, Fenig E and Sharon E: Intraoperative radiation therapy for breast cancer-Immediate and 30-month oncological outcomes. Breast J 26: 946-951, 2020.

34. Gondim GRM, Makdissi FBA, Fogaroli RC, Collins JBD, Iyeyasu H, de Castro DG, Silva MLG, Chen MJ, Coelho TM, Ramos H and Pellizzon ACA: Intraoperative breast radiotherapy: Survival, local control and risk factors for recurrence. Rep Pract Oncol Radiother 24: 551-555, 2019.
35. Meng YQ, Xu XF, Gu J, Wu B, Zhu XX and Guan XX: Application of intraoperative radiotherapy in breast conserving surgery for early breast cancer. J Med Postgra 30: 534-536, 2017 (In Chinese).
36. Shaitelman SF, Lin HY, Smith BD, Shen Y, Bedrosian I, Marsh GD, Bloom ES, Vicini FA, Buchholz TA and Babiera GV: Practical implications of the publication of consensus guidelines by the American society for radiation oncology: Accelerated partial breast irradiation and the national cancer data base. Int J Radiat Oncol Biol Phys 94: 338-348, 2016.
37. Keshtgar MR, Williams NR, Bulsara M, Saunders C, Flyger H, Cardoso JS, Corica T, Bentzon N, Michalopoulos NV and Joseph DJ: Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: Results from a randomized controlled trial. Breast Cancer Res Treat 140: 519-525, 2013.
38. Cracco S, Semprini G, Cattin F, Gregoraci G, Zeppieri M, Isola M, Ceschia T, Cedolini C and Parodi PC: Impact of intraoperative radiotherapy on cosmetic outcome and complications after oncoplastic breast surgery. Breast J 21: 285-290, 2015.
39. Corica T, Nowak AK, Saunders CM, Bulsara MK, Taylor M, Williams NR, Keshtgar M, Joseph DJ and Vaidya JS: Cosmetic outcome as rated by patients, doctors, nurses and BCCT.core software assessed over 5 years in a subset of patients in the TARGIT-A Trial. Radiat Oncol 13: 68, 2018.
40. Chi MS, Ko HL, Yang TL, Liu YF, Chi KH and Cheng FT: Comparative long-term oncological outcomes of intraoperative radiotherapy vs. whole-breast irradiation in early breast cancer: A single institute study. Front Oncol 14: 1411598, 2024.
41. Hanna SA, Bevilacqua JLB, de Barros ACSD, de Andrade FEM, Piato JRM, Pelosi EL, Martella E, da Silva JLF, Carvalho HA and Jacomo AL: Long-term results of intraoperative radiation therapy for early breast cancer using a nondedicated linear accelerator. Adv Radiat Oncol 8: 101233, 2023.
42. Sarria GR, Ramos ML, Palacios A, Del Castillo R, Castro F, Calvo A, Cotrina JM, Heredia A, Galarreta JA, Fuentes-Rivera P, *et al*: Long-term outcomes of an international cooperative study of intraoperative radiotherapy upfront boost with low energy x-rays in breast cancer. Front Oncol 12: 850351, 2022.
43. Lv Y, He L, Wang C, Zhang L, Zhang B and Song Y: A systematic review of clinical outcomes and radiotherapy-associated toxicity in multicatheter accelerated partial breast irradiation. Medicine (Baltimore) 98: e14407, 2019.
44. Zhao XR, Tang Y, Wu HF, Guo QS, Zhang YJ, Shi M, Cheng J, Wang HM, Liu M, Ma CY, *et al*: Influence of age as a continuous variable on the prognosis of patients with pT1-2N1 breast cancer. Breast 66: 136-144, 2022.
45. Bundred JR, Michael S, Stuart B, Cutress RI, Beckmann K, Holleczek B, Dahlstrom JE, Gath J, Dodwell D and Bundred NJ: Margin status and survival outcomes after breast cancer conservation surgery: Prospectively registered systematic review and meta-analysis. BMJ 378: e070346, 2022.
46. Curigliano G, Burstein HJ, Gnant M, Loibl S, Cameron D, Regan MM, Denkert C, Poortmans P, Weber WP and Thürlimann B; St Gallen Consensus Conference Panelists 2023: Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. Ann Oncol 34: 970-986, 2023.
47. Jansen LA, Backstein RM and Brown MH: Breast size and breast cancer: A systematic review. J Plast Reconstr Aesthet Surg 67: 1615-1623, 2014.
48. Lafranconi A, Pylkkänen L, Deandrea S, Bramesfeld A, Lerda D, Neamțiu L, Saz-Parkinson Z, Posso M, Rigau D, Sola I, *et al*: Intensive follow-up for women with breast cancer: Review of clinical, economic and patient's preference domains through evidence to decision framework. Health Qual Life Outcomes 15: 206, 2017.
49. Browall M, Forsberg C and Wengström Y: Assessing patient outcomes and cost-effectiveness of nurse-led follow-up for women with breast cancer-have relevant and sensitive evaluation measures been used? J Clin Nurs 26: 1770-1786, 2017.
50. Jensen AB: Psychosocial factors in breast cancer and their possible impact upon prognosis. Cancer Treat Rev 18: 191-210, 1991.
51. Saita E, Acquati C, Molgora S, Vagnini D, Piccolo EM, Valenti F, Stratta G and Grassi MM: Locally advanced breast cancer (LABC) and delayed care: A qualitative analysis of psychosocial factors. Psychol Health Med 28: 408-418, 2023.