Single institute experience of intraoperative radiation therapy in early-stage breast cancer

Mau-Shin Chi, MD,a Hui-Ling Ko, MD,a Chang-Cheng Chen, MSa, Chung-Hsien Hsu, MSb, Liang-Kuang Chen, MDb, Fiona Tsui-Fen Cheng, MDC∗

Abstract
Intraoperative radiation therapy (IORT) is an alternative to whole breast irradiation in selected early-stage breast cancer patients. In this single institute analysis, we report the preliminary results of IORT given by Axxent Electronic Brachytherapy (eBT) system.

Patients treated with lumpectomy and eBT within a minimum follow-up period of 12 months were analyzed. Eligible criteria include being over the age of 45, having unifocal invasive ductal carcinoma (IDC) or ductal carcinoma in situ <3 cm in diameter, not exhibiting lymph node involvement on preoperative images, and negative sentinel lymph node biopsy. The eBT was given by preloaded radiation plans to deliver a single fraction of 20 Gray (Gy) right after lumpectomy.

From January 2016 to April 2019, a total of 103 patients were collected. There were 78 patients with IDC and 25 with ductal carcinoma in situ. At a mean follow-up time of 31.1 months (range, 14.5–54.0 months), the local control rate was 98.1%. Two IDC patients had tumor recurrences (1 local and 1 regional failure). Post-IORT radiotherapy was given to 4 patients. There were no cancer related deaths, no distant metastases, and treatment side effects greater than grade 3 documented.

We report the largest single institute analysis using the eBT system in Taiwan. The low recurrence and complication rates at a 31.1 month follow-up time support the use of the eBT system in selected early-stage breast cancer patients.

Abbreviations: APBI = accelerated partial breast irradiation, BC = breast cancer, BCT = breast conservation therapy, DCIS = ductal carcinoma in situ, fx = fraction, Gy = Gray, IDC = invasive ductal carcinoma, IORT = intraoperative radiation therapy, RT = radiotherapy, SLNB = sentinel lymph node biopsy, WBI = whole breast irradiation.

Keywords: breast cancer, ductal carcinoma in situ, intraoperative radiation therapy, radiotherapy

1. Introduction
Breast cancer (BC) is the most frequently diagnosed and the most prevalent cause of cancer-related deaths in the female population. Incidences of BC correlate with genetics, preferred diet, lifestyles, nutrients, decreased physical activity, and smoking.[1–3] Fortunately, 60% to 70% of BC patients are diagnosed during early stages.[3] Treatment of early-stage BC consists of either breast conservation therapy followed by adjuvant radiotherapy (RT) or modified radical mastectomy, both with or without systemic therapies based on pathological characteristics.[4,5] Adjuvant RT reduced microscopic disease burden, halved the 10-year local recurrence rate, and for every 4 patients treated, 1 death is avoided.[6] Consequently, a higher recurrence rate was inevitably found in those who forgo adjuvant RT.[7] However, a 4- to 6-week adjuvant RT course may be a burden to those who are frail or live in rural areas.[8,9] Therefore the trend of global practice and patients’ preference are shifting toward a hypofractionated schedule.[10–12]

Accelerated partial breast irradiation (APBI), define as delivering high dose radiation to smaller breast volume at a shorter time, is emerging as an alternative to conventional whole breast irradiation (WBI) in selected early-stage BC patients.[13] The American Society for Radiation Oncology (ASTRO) in conjunction with the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) IORT task force issued rigorous criteria for APBI.[14,15] Intraoperative radiation therapy (IORT) is a form of APBI that delivers a single fraction of high dose radiation right after lumpectomy to mitigate the possible side effects of WBRT. Additional advantages include avoiding geographic and temporal target misses, reduced irradiated volumes, and the availability to complete treatment right after surgery.[16] Two randomized trials, ELIOT (electron IORT) and TARGIT-A (X-ray IORT), reported comparable local control and cosmetic outcomes with WBI in highly selected early-stage BC.[17,18] are the backbone of considering IORT as an alternative to WBRT.

The Axxent electronic brachytherapy (eBT) system (Xoft/iCad, Inc., San Jose, CA) uses a miniature X-ray source (50 kVp) to a single IORT delivery 20 Gy by a balloon applicator.[19,20] The electronic X-ray source has the same steep depth dose behavior as...
brachytherapy isotopes such as I-125 or Pd-103, but at a higher dose rate and adjustable beam penetration capability.\textsuperscript{[21-23]} However, there were only limited single site analysis of eBT published.\textsuperscript{[24-26]} Since the introduction of eBT to Taiwan in May 2012, the Taiwan IORT study cooperative group (T-IORTSCG) has conducted a multicenter retrospective analysis, which reported a 0.8% locoregional recurrence risk at 15.6 months follow-up.\textsuperscript{[27]} The eBT system went online at our institute in January 2016, and we quickly became one of the most experienced centers in Taiwan. The goal of this analysis is to provide the largest single institute preliminary oncological outcomes of early-stage BC treated by eBT with the longest follow-up time in Taiwan.

2. Materials and methods

2.1. Patient selection

From January 2016 to April 2019, patients treated with the eBT system were retrospectively collected. Analyzed data included the disease status, surgical findings, and control rate of IORT with a minimum follow-up period of 12 months. This study was approved by the Institutional Review Board of Shin Kong Wu Ho-Su memorial hospital. The inclusion criteria for eBT included patients older than the age of 45, with unifocal invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS) <3cm in diameter, without lymph node involvement on preoperative images, and a negative sentinel lymph node biopsy (SLNB) during lumpectomy. Each patient is required to undergo preoperative mammography and breast sonography. RT options including WBI and IORT were explained to the patients by the surgeon and radiation oncologist.

2.2. Treatment device

The eBT system uses a 50kV X-ray tube as treatment source. A spherical applicator with a diameter of 30 to 40 mm containing 3 ports, 1 of which to a robotic arm, 2 for inflation and drainage of treatment balloon. During treatment, the robotic arm pushes the X-ray source into the balloon. Prior to beam-on, the balloon will be checked for its reproducibility.

2.3. Surgical treatment and IORT procedures

SLNB with frozen-section diagnoses were done for all IDCs. Only patients with negative SLNB (pN0 i+ allowed) would proceed to IORT. Lumpectomy was carried down to the level of the pectoralis fascia, and intraoperative frozen section for margin status was recommended. Once the lumpectomy cavity was created, an appropriately sized balloon would be inserted. A balloon-to-tissue apposition was done by retention sutures to maintain balloon-to-skin distance of least 10 mm. A flexible lead shield was then placed above the operation field before IORT to decrease radiation leakage. Then the treatment dose of 20 Gy will be delivered to balloon surface.

Once the IORT is completed, the lead shield, eBT balloon, and retention sutures were removed. The lumpectomy cavity was irrigated and closed with standard or oncoplastic techniques. Surgical margin and final lymph node status were assessed on the final pathology report. Negative microscopic margins were recommended by institute protocol. Patients with positive surgical margins upon final pathology are strongly suggested for re-excision or adjuvant WBI.

2.4. Adjuvant treatment and follow-up

Postoperatively, patients were seen by both the surgeon and radiation oncologist. Patients with estrogen-receptor and/or progesterone-receptor positive tumors were prescribed either tamoxifen or aromatase inhibitors. For tumors >1 cm in diameter or positive lymph nodes on final pathology report, adjuvant chemotherapy was prescribed according to guidelines, unless refused by the patient or not suitable due to comorbidities. For patients with >2 lymph nodes, adjuvant WBI are highly recommended beside chemotherapy. A 6-month surveillance postoperative mammography was performed and every 6 months thereafter.

3. Results

3.1. Patient characteristics and treatment

A total of 103 patients were collected, 78 patients with IDC and 25 with DCIS. The mean age was 59.7 years old (range, 46–81 years old). The mean tumor size was 1.3 cm (range, 0.5–3 cm) for IDC and 1.3 cm (range, 0.1–2.6 cm) for DCIS. The prescribed dose for IORT was 20 Gy in a single fraction (fx), and the mean beam-on time was 515 seconds. Sixteen patients had positive lymph nodes on final pathology, 3 with micrometastases (N1mi) and 13 with single axillary lymph node (N1a). Seven patients (4 with IDC and 3 with DCIS) had positive surgical margins and were all involved with DCIS component. 92% (n = 94) had positive estrogen or progesterone receptors, and 3% (n = 4) had positive Her-2. The patient and treatment demographics were shown in Table 1.

3.2. Oncologic outcomes and adverse events

The mean follow-up period was 31.1 months (range, 14.5–54.0 months). The local control rate was 98.1% for all subjects (2/103 recurred); was 97.4% (2/78 recurred) for IDC; and 100% for DCIS. No patients were lost at the follow-up. For 7 patients with positive surgical margins, 5 underwent re-excision for negative margin, 2 received adjuvant RT due to refusal of re-excision. All patients with positive hormone receptors (n = 94) received adjuvant hormone therapy. Twenty four patients had adjuvant chemotherapy, including 10 out of 16 patients with positive lymph node metastases (62.5%). None of the patients had distant metastases, and none deceased.

Four patients had adjuvant RT after IORT, 1 with local recurrence, 1 with axillary lymph node metastases, and 2 with positive surgical margins. The patient with local recurrence received WBI with a focal boost to 60 Gy; patient with axillary nodal metastases was irradiated with 54 Gy in 27fx to breast and regional nodal regions; the 2 patients who had positive surgical margins but refused re-excision received partial breast RT with 15 Gy in 6 fx over the lumpectomy area.

Postoperatively, there were no side effects higher than grade 3 were documented. During the follow-up period, no rib fractures, wound infections, nor fat necrosis were noted. The 2 patients with local-regional recurrence salvaged with RT dose >50 Gy had grade 1 dermatitis and esophagitis during treatment and
soon recovered within 1 month. Two patients with partial breast RT showed no treatment related toxicities.

3.3. Two cases with salvage surgery followed by WBI

3.3.1. Case 1. A 46-years-old woman with right breast IDC received lumpectomy and IORT in August 2016. Post-surgical pathology reported a 2.2 cm tumor, positive estrogen-receptor/progesterone-receptor status, Her-2 was negative, and surgical margin was negative, pT2N0M0. Adjuvant chemotherapy and hormone therapy were given. In January 2018, she was presented with palpable right axillary nodules. Biopsy proved metastatic lymph node and she received salvage axillary lymph node dissection. The final pathology reported 4 positive lymphadenopathies. She received adjuvant WBI after a second chemotherapy course. The irradiated field consisted of the right breast and regional nodes. Thirty Gray was prescribed to right breast and regional nodes with an additional 24 Gy boost to postoperative surgical bed (Fig. 1). The mean exposed right lung dose was 12.75 and 2.13 Gy to left lung. Patient completed the RT course smoothly with only grade 1 esophagitis and dermatitis, which quickly recovered within 1 month.

3.3.2. Case 2. A 62-years-old woman with left IDC was treated with lumpectomy and IORT in February 2018. Pathology reported a 2.4 cm tumor, triple negative and negative surgical margins, pT2N0. Adjuvant chemotherapy was given according to the guideline. In November 2018, she had local recurrence near the surgical scar. A salvage tumor excision with flap reconstruction was performed. After a second course of chemotherapy, she received adjuvant WBI (50 Gy in 25fx) with a boost to 60 Gy at the surgical scar site (Fig. 2). The mean left lung dose was 14.23 Gy, and right lung was 1.58 Gy. She had only grade 1 dermatitis over the previous lumpectomy region during WBI, and she remained disease-free at the time of writing.

4. Discussion

We reported the largest single institute IORT analysis in Taiwan, with local control rate of 1.9% during a 31.1-month follow-up. The largest phase III ELIOT and TARGIT-A trials demonstrated a 5-year local recurrence rate of 4.4% and 3.3% by IORT, compared with 0.4% and 1.3% by WBI[17,18]. In comparison with other eBT treatment analyses (Table 2), our patients demonstrated similar local control rate, had smaller tumor size and less positive surgical margins, yet the incidence of positive lymph nodes at final pathology seems to be higher. The T-IORTSG study also pointed out Taiwanese women chose IORT to decrease hospital visits due to work issues and being more economically independent (IORT was not reimbursed by national health care system),[27] which was similar to our patients.

While most early-stage BC recurred at same quadrant as original,[28,29] IORT aims to complete adjuvant treatment “fast and accurately.” From the view of patient safety, IORT ensures

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**Table 1**

| Patient characteristics utilizing the eBT system. (n = 103) |
|---|---|
| **Age, yrs** | |
| 45–50 | 15 |
| 50–60 | 35 |
| >60 | 53 |
| **Tumor size (DCIS, cm)** | 1.3 (range, 0.1–2.6) |
| **Tumor size (IDC, cm)** | 1.5 (range, 0.5–3) |
| **Tumor stage (n)** | |
| Tis | 25 |
| T1a | 5 |
| T1b | 18 |
| T1c | 40 |
| T2 | 15 |
| **Lymph node status (n)** | |
| N0 | 62 |
| N1 micro | 3 |
| N1a | 13 |
| **ER** | |
| Positive | 94 |
| Negative | 9 |
| **PR** | |
| Positive | 89 |
| Negative | 14 |
| **Her-2** | |
| Positive | 4 |
| Negative | 99 |
| **Surgical margin** | |
| Positive | 7 |
| Negative | 96 |
| **Balloon size, cm³** | |
| 30 | 89 |
| 35 | 12 |
| 40 | 1 |
| 70 | 1 |

ER = estrogen-receptor, PR = progesterone-receptor.

* Only patients with IDC received sentinel lymph node biopsy (n = 78).
adjuvant RT is given on-time and minimizes viral exposure for patient and medical staff, especially during the COVID pandemic.\[30,31\] From the view of radioprotection, the electronic X-ray source allows the IORT process to be conducted safely in a 3-mm-lead “light-shielded” operative room, as an 120kVp fluoroscope. During treatment, the source applicator was covered by a tungsten-silicone shield, the “FLEXISHIELD,” to minimize radiation leakage within 1 m from source to background level.\[32\] Compared with WBI, the radiation exposure to ipsilateral and contralateral breast, spinal cord, and heart was also lower with IORT.\[33\] The IORT treatments were mostly done by the eBT system in Taiwan,\[27\] and the number of patients opting for IORT is increasing. As shown in Table 3, 39 out of all 84 patients (46.4%) amenable for breast conservation therapy at our institute chose IORT in 2018. Four patients (0.38%) from our analysis received adjuvant RT (1 local; 1 regional; and 2 with positive surgical margins). The 2 true recurrences were diagnosed within 15 months after IORT.\[15\]

Table 2
Comparison of reported analysis utilizing the eBT system.

| Patient number (n) | Tumor component | Local control rate (follow-up months) | Tumor size >3 cm | Positive lymph nodes rate | Positive margin rate |
|-------------------|-----------------|--------------------------------------|-----------------|---------------------------|---------------------|
| Institute data    | 103             | IDC DCIS                              | 1.9% (31.1)     | 0%                        | 15.5%               | 6.8%                |
| Mehta et al\[23\] | 44              | IDC DCIS                              | Not reported (12) | 0%                        | 0%                  | 0%                  |
| Ivanov et al\[24\] | 11              | IDC DCIS                              | 0% (12)         | 0%                        | 0%                  | 0%                  |
| Silverstein et al\[25\] | 201            | IDC ILC DCIS                          | 3% (50)         | 17%                       | 6.8%                | 17.4%               |
| Epstein et al\[26\] | 702             | IDC ILC DCIS                          | 1.8% (20)       | 14%                       | 12.4%               | 16.5%               |
| Silverstein et al\[27\] | 984            | IDC DCIS                              | 2.8% (36)       | 14.7%                     | 3.5%                | 17.4%               |
| Lai et al\[28\]  | 261             | IDC DCIS                              | 3.1% (15.6)     | 3.1%                      | 2.3%                | 2.3%                |

DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma.
free at the time of writing. For patients with adverse pathology, the International Society of Intraoperative Radiation Therapy incorporated IORT as a “tumor bed boost technique” done before WBI. Kaiser et al. reported a 10-year local control rate of 97.2% in 770 BC patients treated by 10Gy IORT followed with median 54Gy WBI. For DCIS patients with positive margins after IORT, either mastectomy or adjuvant WBI followed with median 54Gy WBI. For DCIS patients with positive margins after IORT, either mastectomy or adjuvant WBI followed with median 54Gy WBI. For DCIS patients with positive margins after IORT, either mastectomy or adjuvant WBI followed with median 54Gy WBI.

Table 3

| Total patients (n) | WBI (n) | IORT (n) |
|-------------------|--------|----------|
| 2016              | 62     | 38 (61.3%) | 24 (38.7%) |
| 2017              | 74     | 44 (59.5%) | 30 (40.5%) |
| 2018              | 84     | 45 (53.6%) | 39 (46.4%) |
| 2019 (Jan–Apr)   | 20     | 15 (75%)   | 5 (25%)    |

IORT = intraoperative radiation therapy.

5. Conclusion

We reported the largest single institute eBT data with the longest follow-up time in Taiwan. The local control rate was 98.1% at a mean follow-up time of 31.1 month. Our data was comparable to the published analysis and provide a reference for utilization the eBT system in selected early-stage BC patients. Our results gave a hint that salvage partial breast radiation can be considered in patients with positive margins. A long-term follow-up will continue, and we await the results of the ongoing trials.

Author contributions

Conceptualization: Mau-Shin Chi, Fiona Tsui-Fen Cheng.

Data curation: Mau-Shin Chi, Hui-Ling Ko, Chang-Cheng Chen, Chung-Hsien Hsu, Liang-Kuang Chen.

Writing – original draft: Mau-Shin Chi.

Writing – review & editing: Hui-Ling Ko, Chang-Cheng Chen, Liang-Kuang Chen, Fiona Tsui-Fen Cheng.

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