Multi-center study on patient selection for and the oncologic safety of intraoperative radiotherapy (IORT) with the Xoft Axxent® eBx® System for the management of early stage breast cancer in Taiwan

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Abstract

Background

In this multi-center study, we report the patient selection criteria for and preliminary oncologic outcomes associated with intraoperative radiotherapy (IORT) delivered by the Xoft Axxent® eBx® system for early-stage breast cancer in Taiwan.

Methods

Patients with early breast cancer in Taiwan received breast conserving surgery and received IORT with Xoft Axxent® eBx® System during 2013–2015 was search from database of Taiwan IORT study cooperative group (T-IORTSCG). Patients' clinicopathologic characteristics and early post-operative results were collected and reported.

Results

During the study period, 26 hospitals in Taiwan performed a total of 261 Xoft IORT procedures for breast cancer. The mean age of them was 52.9 ± 9.8 years (37–72), and tumor size was 1.5 ± 0.8 cm (0.1–4.2 cm) for invasive cancer and 1.2 ± 0.8 cm (range, 0.2–3.0 cm)
for ductal carcinoma in situ (DCIS) lesions. Lymph node metastasis was found in 6 (2.3%) patients. The patients received IORT in Taiwan differed markedly from those used in the ELIOT and TARGIT-A studies. Specifically, patients selected for IORT in Taiwan tended to be younger, their tumors tended to be larger and the prevalence of lymph node metastasis tended to be lower. Among these 261 patients, 8 (3.1%) patients required whole breast radiotherapy. During a mean follow up of 15.6 months, locoregional recurrence was observed in 2 (0.8%) patients.

Conclusion
In real world experience, patients received IORT differed quite significantly with criteria formulated by trials. The preliminary results of IORT in Taiwan showed it is well acceptable by patients and clinicians.

Introduction
Breast conserving surgery (BCS) followed by whole-breast external beam radiotherapy (WBRT) has become the mainstay of surgical treatment for early-stage breast cancer [1, 2]. WBRT reduces the likelihood of local recurrence in the conserved breast and lowers the risk of death due to breast cancer [3]. However, conventional WBRT, which is administered daily over a 6- to 7-week period, precludes a significant proportion of women from receiving the full course of radiation treatment [4–6]. Intraoperative radiotherapy (IORT), in which postoperative whole-breast irradiation is substituted for one session of radiotherapy with the same equivalent dose during surgery, solves this problem by allowing for treatment to be completed on the same day. Recent trials such as electron intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT trial) [7] and targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial) [8, 9] have demonstrated that IORT in some selected groups of low-risk early breast cancer patients results in acceptable outcomes and could, therefore, serve as an alternative to conventional WBRT.

IORT using the Axxent electronic brachytherapy (eBX) system (Xoft, Inc., San Jose, CA) for the treatment of breast cancer is a relative new method of delivering accelerated partial breast irradiation (APBI) that aims to replace WBRT in selected women suitable for BCS. The one-year results of a trial utilizing eBX to deliver 5-day APBI treatment have shown it to be an effective alternative method with minimal acute side-effects [10]. Another single-institution trial also found that delivery of IORT via the eBX system was efficacious and safe for women with early-stage breast cancer [11].

The Xoft IORT using the Axxent electronic brachytherapy (eBX) system was introduced for the treatment of breast cancer in Taiwan in May of 2012. The Taiwan IORT study cooperative group (T-IORTSCG) was established to monitor the effectiveness of and clinical outcomes associated with the Xoft Axxent® eBX® IORT delivery system for the management of early-stage breast cancer in Taiwan. In this multi-center study, we report the patient selection criteria for and preliminary oncologic outcomes associated with this new type of radiotherapy.

Materials and methods
Patients
In this study, we collected clinicopathologic data from the T-IORTSCG database on patients who underwent IORT for breast cancer during the period January 2013 to December 2015 at
T-IORTSCG-affiliated institutions. The clinicopathologic data collected from the database included patient characteristics, type of surgery, type and dose of IORT, recurrence, and survival status at the most recent follow-up. The data gathered from the database covered more than 95% of the IORT procedures performed in Taiwan during the study period and therefore can be interpreted as representing the status of IORT in Taiwan. All data were collected by chart review by a specially trained nurse and confirmed by the principle investigator (HWL). The study was approved by the Institutional Review Board of the Changhua Christian Hospital (CCH IRB No.: 151004). Due to the retrospective and chart review nature of this study, the ethics committees (IRB) in our hospital decided no written or verbal informed consent was needed by the participants. Patient records/information was anonymized and de-identified prior to analysis.

Patient selection for IORT

A preoperative tissue diagnosis of cancer of the breast was required prior to the operation. Pre-operative mammography and sonography were used in all patients to determine their eligibility for IORT. Magnetic resonance imaging (MRI) was used optionally for selection of patients’ suitability for IORT. Liver sonography, chest X ray, and whole body bone scan were used in all patients to exclude the possibility of distant metastasis.

The inclusion and exclusion criteria were based on those reported previously [7–9, 11–14]. The inclusion criteria for patients suitable for IORT were unifocal tumors of less than 3 cm, no evidence of lymph node involvement, the presence of invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS), and a minimum age of 45 years. Contraindications for IORT included inflammatory breast cancer, breast cancer with chest wall or skin invasion, locally advanced breast cancer, breast cancer with extensive axillary lymph node metastasis (stage IIIA or later), and severe co-morbid conditions such as heart disease, renal failure, liver dysfunction, or poor performance status as assessed by primary care physicians. All patients underwent extensive preoperative counseling by the surgeon and the radiation oncologist. Radiation treatment options were explained to the patients, including standard WBRT as well as IORT.

Surgical treatment and eBX IORT procedures

The protocol for carrying out IORT via the Xoft Axxent® eBx® delivery system is described in detail by Ivanov et al. [11], and illustrated in Fig 1. In brief, sentinel lymph node biopsy (SLNB) [15] was usually done first. Then BCS was performed, and intra-operative frozen section for margin status analysis was not mandatory. After excision of the tumor and a margin of healthy tissue, breast tissue dissection was carried down to the level of the pectoralis fascia in preparation for IORT. The tumor bed was mobilized to ensure that there was a distance of at least 10 mm between the surface of the applicator and the skin in order to reduce the risk of radionecrosis (Fig 1). The radiation source was inserted into the balloon and radiation therapy was initiated. A planned dose of 20 Gy to the balloon surface was delivered over an average of 8–15 mins. After radiation treatment, the retention sutures, the eBX balloon and the lead shield were removed. The lumpectomy cavity was irrigated and closed in a standard manner or an oncoplastic technique was performed to prevent parenchyma defects [16, 17].

Post-operative systemic therapy and follow-up

Postoperative adjuvant hormone therapy, chemotherapy and radiotherapy were given to patients according to current breast cancer treatment guidelines [18, 19]. The rate of positive surgical margin involvement, locoregional recurrence, distant metastasis, and mortality were...
recorded and analyzed. In current study, the definition of negative margin was no tumor on ink. Total incidence of recurrence or death due to breast cancer was ascertained at the most recent follow-up, which ended on July 2016.

### Statistical analyses

Data are expressed as mean ± standard deviation (SD) for continuous variables. Categorical variables were tested by the chi-square test when appropriate. Differences in means of continuous variables were tested by the Student’s t test. All p values are two-tailed; a p value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the statistical package SPSS for Windows (Version 19.0, SPSS, Chicago).

### Results

During the study period, a total of 261 patients with breast cancer received IORT procedures with the Xoft Axxent® eBx® system in Taiwan. The mean age of the patients was 52.9 ± 9.8 years. The mean tumor size was 1.5 ± 0.8 cm (0.1–4.2 cm) for invasive cancer and 1.2 ± 0.8 cm for in situ cancer.
(0.15–3.0 cm) for DCIS lesions. Most (95.8%) of them were node negative breast cancer patients (Table 1).

Of those 261 patients who received IORT, 8 (3.1%) patients received WBRT (Fig 2). During a median follow up of 15.6±6.5 months, locoregional recurrence was observed in 2 (0.8%) patients (Table 2). The development and application of Xoft IORT system in Taiwan was as shown in Fig 3.

The criteria used by the participating hospitals to select patients for IORT were compared with those used in the ELIOT [7] and TARGIT-A [8] studies, and summarized in Table 3. The clinical and pathologic manifestations of patients received IORT in current study differed markedly from those used in the ELIOT and TARGIT-A studies. Specifically, patients selected for IORT in Taiwan tended to be younger (16.5% <45 y/o in T-IORTSCG, 7% 48–49 y/o in ELIOT, and 2% <45 y/o in TARGIT-A, P<0.01), their tumors tended to be larger (T2 tumor 21.4% in T-IORTSCG compared to 13% in ELIOT, and 14% in TARGIT-A, P<0.01), the prevalence of lymph node metastasis tended to be lower (92.7% node negative in T-IORTSCG compared to 74% in ELIOT, and 82% in TARGIT-A, P<0.01).

**Discussion**

Targeted radiation can be delivered to the tumor bed intraoperatively by a number of energy sources. ELIOT involves administering electrons in one session during surgery with a total dose of 21 Gy [7, 12]. The Intrabeam device, which was used in the TARGIT-A trial [8, 9], is a miniature electron beam-driven X-ray source that provides a point source of low-energy X-rays (50 kV maximum) at the tip of a 3.2-mm diameter tube. The Axxent eBX system, which was used in the current study, is an alternative to radioactive-isotope based therapy [11]. eBX utilizes a miniature X-ray source to deliver high-dose radiation to the target area at low energy, thus obviating the need for a highly shielded environment [11]. The system, which received Food and Drug Administration (FDA) approval for the treatment of breast cancer in January 2006 [11], is a relatively new method of delivering APBI and aims to replace WBRT in women suitable for BCS. As shown in Fig 3, the rapid increase in the number of hospitals in Taiwan that have adopted the Xoft Axxent® eBX® system for IORT is an evidence for its wide acceptance among surgeons and radiation oncologists as a treatment modality for women who are eligible for BCS.

A number of clinical trials have provided evidence that IORT is an efficacious treatment modality [7–9, 11, 12]. However, the indications for IORT are not well defined and varied among trials. As young age is viewed as a poor prognostic factor for disease recurrence [12], the criteria for suggestion of age for patients to receive IORT was not clear defined. According to the recent ASTRO guidelines [13] and the GEC-ESTRO working group recommends [14], partial-breast irradiation should be attempted in women greater than 50 years. The age criteria was a minimum of 45 year-old or older in TARGIT-A and other study [9, 11], or aged 48–75 years in ELIOT [7]. Although the mean age in our study was 52.9 ± 9.8, 16.5% of the patients were younger than 45 years. This may be reflected that young female has higher motivation to decrease the frequency of visit to hospital, and economy more independent to afford the fee of IORT (cost about $8000 US dollars in Taiwan), which was not reimbursed by our national insurance. In ELIOT [7] and GEC-ESTRO [20] trials, age was not a poor prognostic factor for disease local recurrence. However, the safety of younger (age less than 45) patients to receive IORT should be caution.

Most trials agreed that IORT is most appropriate for women with unifocal disease detected on conventional breast images [9, 11], and MRI was not mandatory. However, the upper limitation of tumor size has not been determined. In the ELIOT trial it was found that IORT was...
Table 1. Clinicopathologic characteristics of patients selected for Xoft IORT in Taiwan.

| Characteristic                              | N = 261 |          |          |
|--------------------------------------------|---------|----------|----------|
| Age                                        | 52.9 ± 9.8 (37–72) |          |          |
| Age <45                                    | 43      | (16.5%)  |          |
| Age 45–60                                   | 147     | (56.3%)  |          |
| Age >60                                    | 56      | (21.5%)  |          |
| Age NA                                     | 15      | (5.7%)   |          |
| Tumor Size (in situ, cm) n = 41             | 1.2 ± 0.8 (0.15–3.0) |          |          |
| Tumor Size (invasive, cm) n = 220           | 1.5 ± 0.8 (0.1–4.2) |          |          |
| T1a                                        | 18      | (8.2%)   |          |
| T1b                                        | 40      | (18.2%)  |          |
| T1c                                        | 108     | (49.1%)  |          |
| T2                                         | 47      | (21.4%)  |          |
| T2 NA                                      | 7       | (3.1%)   |          |
| Lymph node                                 |         |          |          |
| N0                                         | 250     | (95.8%)  |          |
| N1                                         | 5       | (1.9%)   |          |
| N2                                         | 1       | (0.4%)   |          |
| NA                                         | 5       | (1.9%)   |          |
| Stage                                       |         |          |          |
| Tis                                        | 42      | (16.1%)  |          |
| I                                          | 152     | (58.2%)  |          |
| IIA                                        | 54      | (20.7%)  |          |
| IIB                                        | 3       | (1.1%)   |          |
| IIIA                                       | 1       | (0.4%)   |          |
| NA                                         | 9       | (3.4%)   |          |
| Pathology                                  |         |          |          |
| IDC+DCIS                                    | 194     | (74.3%)  |          |
| ILC+LCIS                                    | 5       | (1.9%)   |          |
| DCIS                                       | 42      | (16.1%)  |          |
| Mucinous carcinoma                          | 6       | (2.3%)   |          |
| Papillary carcinoma                         | 3       | (1.1%)   |          |
| NA                                         | 11      | (4.2%)   |          |
| ER                                         |         |          |          |
| Positive                                   | 219     | (83.9%)  |          |
| Negative                                   | 34      | (13.0%)  |          |
| NA                                         | 8       | (3.1%)   |          |
| PR                                         |         |          |          |
| Positive                                   | 195     | (74.7%)  |          |
| Negative                                   | 58      | (22.2%)  |          |
| NA                                         | 8       | (3.1%)   |          |
| HER-2                                       |         |          |          |
| Positive                                   | 34      | (13.0%)  |          |
| Negative                                   | 204     | (78.2%)  |          |
| NA                                         | 23      | (8.8%)   |          |
| Ki-67                                       |         |          |          |
| <14%                                       | 106     | (40.6%)  |          |
| >14%                                       | 90      | (34.5%)  |          |
| NA                                         | 65      | (24.9%)  |          |

(Continued)
effective for small tumors with a maximum tumor diameter of 2.5 cm suitable for BCS [7]. In the study by Ivanov et al, IORT was determined to be appropriate for tumors measuring less than 3 cm [11], and in the TARGIT-A trial, the therapy was shown to be effective for any tumor suitable for wide local excision [9]. Currently, patients selected to receive IORT were suggestive to have smaller tumor (≤2 cm) to prevent local recurrence [7].

Table 1. (Continued)

| Margin                  | N = 261     |
|-------------------------|-------------|
| Positive                | 6 (2.3%)    |
| Negative                | 255 (97.7%) |
| Lymph node surgery      |             |
| SLNB                    | 254 (97.3%) |
| SLNB+ALND               | 2 (0.8%)    |
| NA                      | 5 (1.9%)    |
| Mean follow-up (months) | 15.6±6.5 (6.9–40.4) |

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, DCIS: ductal carcinoma in situ, ER: estrogen receptor, PR: progesteron Receptor, HER-2: human Epidermal Growth Factor Receptor 2, SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection, NA: not available.

https://doi.org/10.1371/journal.pone.0185876.t001

Fig 2. Flow chart of patients received intraoperative radiotherapy with the Xoft Axxent® eBx® delivery system. *case summary for recurrence after IORT. Case 1: 51 y/o female with right breast cancer, which was located at upper outer quadrant of breast. She received breast conserving surgery, sentinel lymph node biopsy (SLNB), and IORT. SLNB: negative for lymph node metastasis (0/2). Pathology showed DCIS, tumor size: 3 cm, ER(+, 90%), PR(+, 40%), and HER-2(+). She received adjuvant endocrine therapy with tamoxifen. Local recurrence was found at the same quadrant (right upper outer) of operated breast (tumor size: 0.6 cm, CNB: infiltrating ductal carcinoma) 1 year post surgery. Salvage simple mastectomy and SLNB were performed. Adjuvant endocrine therapy was shifted to letrozole due to hormone positive breast cancer. Case 2: 65 y/o female diagnosed with right breast cancer (CNB: DCIS (tumor size: 2.3 cm), high grade, ER(-), PR(-), HER-2(+)) over upper outer quadrant. She received BCS + SLNB + IORT. Pathology showed: DCIS with microinvasion (0.1 cm), lymph node negative. She received adjuvant therapy with letrozole. Locoregional recurrence was found over right axilla (lymph node size 1 cm, CNB: IDC) 1 year post surgery. Axillary lymph node dissection was performed, and she received adjuvant chemotherapy with 4 cycles of 5-FU, lipodoxorubicin, and cyclophosphamide. Then another 4 cycles of docetaxel were given. She also received whole-breast external beam radiotherapy (WBRT) and letrozole treatment.

https://doi.org/10.1371/journal.pone.0185876.g002
Lymph node status was not strictly regulated in either the ELIOT or TARGIT-A trial, but node negative status was a criterion in some study [11]. Lymph node metastasis is regarded as the most important poor prognostic factor [21]. It remains unclear, however, whether lymph node metastasis is a contraindication for IORT. In the ELIOT trial, four or more positive nodes were associated with poorer prognosis [7]. In that trial, 21% of patients who received IORT had 1–3 positive lymph nodes and in the TARGIT-A trial [8] 15% of patients had 1–3 positive lymph nodes (Table 3). Based on those findings, low burden axillary disease (<3 positive nodes) is not a contraindication for IORT [7, 12]. In meta-analysis [22], adjuvant radiation of regional nodes for node positive breast cancer have shown an improvement in overall survival. Patients who received IORT with positive lymph nodes, either diagnosed before IORT

| Timing and types of intra-operative radiotherapy (IORT) performed. | N = 261 |
|---------------------------------------------------------------|---------|
| **IORT dose**                                                 | 20 Gy irradiation |
| **Duration of procedure**                                     | 28 ± 10 minutes (19–53) |
| **Duration of radiotherapy**                                  | 11 minutes, (8–15) |
| Xoft balloon                                                 | N = 261 |
| 3–4 cm spherical balloon                                      | 30cc | 178 | (68.2%) |
| balloon applicator                                           | 35cc | 18  | (6.9%)  |
| 30–45 cc                                                     | 40cc | 26  | (10.0%) |
| n = 227 (87.0%)                                               | 45cc | 4   | (1.5%)  |
|                                                             | 50cc | 1   | (0.4%)  |
| 4–5 cm spherical balloon                                      | 45cc | 5   | (1.9%)  |
| balloon applicator                                           | 50cc | 15  | (5.7%)  |
| 45–75 cc                                                     | 55cc | 2   | (0.8%)  |
| n = 29 (11.1%)                                               | 60cc | 3   | (1.1%)  |
|                                                             | 70cc | 3   | (1.1%)  |
|                                                             | 75cc | 1   | (0.4%)  |
| NA = 5 (1.9%)                                                |      | 5   | (1.9%)  |
| **IORT**                                                     |        |     |        |
| **Timing**                                                   |        |     |        |
| Immediate intra-operation                                     | 253   | (97.0%)|
| Post pathology                                               | 8     | (3.0%) |
| **Indication**                                               |        |     |        |
| IORT only                                                    | 253   | (97.0%)|
| IORT follow by WBRT                                          | 8     | (3.0%) |
| **WBRT**                                                     |        |     |        |
| **Lymph node**                                               |        |     |        |
| Negative                                                     | 250   | (95.8%)|
| Positive                                                     | 6     | (2.3%) |
| NA                                                           | 5     | (1.9%) |
| **Margin**                                                   |        |     |        |
| Negative                                                     | 255   | (97.7%)|
| Positive                                                     | 6     | (2.3%) |
| **Locoregional recurrence**                                  |        |     |        |
| No                                                           | 259   | (99.2%)|
| Yes                                                          | 2     | (0.8%) |
| **Mortality**                                                |        |     |        |
| No                                                           | 261   | (100%)|
| Yes                                                          | 0     | (0%)  |

IORT: intra-operative radiotherapy, WBRT: whole-breast external beam radiotherapy, NA: not available.

https://doi.org/10.1371/journal.pone.0185876.t002

Lymph node status was not strictly regulated in either the ELIOT or TARGIT-A trial, but node negative status was a criterion in some study [11]. Lymph node metastasis is regarded as the most important poor prognostic factor [21]. It remains unclear, however, whether lymph node metastasis is a contraindication for IORT. In the ELIOT trial, four or more positive nodes were associated with poorer prognosis [7]. In that trial, 21% of patients who received IORT had 1–3 positive lymph nodes and in the TARGIT-A trial [8] 15% of patients had 1–3 positive lymph nodes (Table 3). Based on those findings, low burden axillary disease (<3 positive nodes) is not a contraindication for IORT [7, 12]. In meta-analysis [22], adjuvant radiation of regional nodes for node positive breast cancer have shown an improvement in overall survival. Patients who received IORT with positive lymph nodes, either diagnosed before IORT
or found after final pathologic check-up, should be discussed whether further radiotherapy would be needed.

In the TARGIT-A trial [8, 9], only patients with histological diagnosis of IDC were selected to receive IORT whereas in other study [11], patients with either IDC or DCIS were recruited. Preoperative histologic diagnosis of lobular carcinoma was a criterion for exclusion in the TARGIT-A trial [9] and other study [11] as lobular tumors are associated with a higher propensity for being multifocal [23, 24]. However, in the ELIOT trial, lobular histology was neither a poor prognostic factor nor a contraindication for IORT [7]. Most trials [7, 8, 11] and guidelines [13, 14] do not include neoadjuvant chemotherapy as an indication for IORT or partial breast irradiation. Whether IORT is appropriate for patients with DCIS is unclear? In ASTRO and GEC-ESTRO guideline, APBI is not recommended as treatment for pure DCIS [13, 14]. However, in recent published GEC-ESTRO trial, 6% of APBI patients were pure DCIS [20]. In our study, 16.8% of patients who received IORT had pure DCIS lesions.

Whether patients with pure DCIS lesions should receive IORT as adjuvant radiotherapy to prevent local recurrence remains unclear and requires further study.

In our current study, 2 (0.8%) patients were found to have locoregional recurrences (one patient found to have local recurrence in the same quadrant of operated breast, and the other with regional recurrence at the axilla) in the mean 15.6 months follow-up period (Fig 2). The 5-year local recurrence rate was 4.4% in ELIOT, and 3.3% in TARGIT-A trials. According to the results of the ELIOT trial, patients with disease characteristics associated with local recurrence such as tumor size greater than 2 cm, tumor of grade 3, four of more positive nodes, and triple-negative tumors should not be treated with IORT alone [7]. The 2 patients, who diagnosed to have locoregional recurrence in the conserved breast (or axilla) in our study, were found within 1.5 year post operation. The new diagnosed breast cancer lesion could not to be sure to be a “recurrence” after BCS followed by Xoft IORT or a “pre-existing multifocal or...
Table 3. Comparison of patients selection criteria of Xoft IORT in Taiwan with ELIOT and TARGIT-A trials.

| Indication for IORT | ELIOT trial | TARGIT-A trial | T-IORTSCG | P value |
|---------------------|-------------|----------------|-----------|---------|
| Age (years)         | 48–49       | 44 (7%)        | <45       | 17/1113 (2%) | Mean 52.9 ± 9.8 | <0.01 |
|                     | 50–59       | 286 (44%)      | 45–54     | 212/1113 (19%) | <45 | 43 (16.5%) |
|                     | 60–69       | 259 (40%)      | 55–64     | 443/1113 (40%) | 45–60 | 147 (56.3%) |
| ≥70                 | 62 (10%)    | 65–74          | 355/1113 (32%) | >60 | 56 (21.5%) |
|                     | ≥74         | 86/1113 (8%)   | NA        | 15 (5.7%) |
| Tumor size          | ≤1 cm       | 199 (31%)      | <1 cm     | 381/1056 (36%) | <0.01 |
|                     | 1–1.5 cm    | 243 (38%)      | 1–2 cm    | 531/1056 (50%) | 1.2 ± 0.75 (0.15–3.0) |
|                     | 1.5–2 cm    | 120 (19%)      | >2 cm     | 144/1056 (14%) | Tumor Size (invasive, cm) |
|                     | >2 cm       | 83 (13%)       | Unknown   | 57/1113 (5%) | 1.49 ± 0.77 (0.1–4.2) |
|                     |             |                | T1a       | 18 (8.2%) |
|                     |             |                | T1b       | 40 (18.2%) |
|                     |             |                | T1c       | 108 (49.1%) |
| Poor prognosis if tumor >2cm |       |                | T2        | 47 (21.4%) |
|                     |             |                | NA        | 7 (3.1%) |
| Lymph node status  | None        | 478 (74%)      | 0         | 866/1059 (82%) | N0 | 242 (92.7%) | <0.01 |
|                     | 1–3         | 138 (21%)      | 1–3       | 155/1059 (15%) | N1 | 12 (4.6%) |
|                     | ≥4          | 51 (5%)        | >3        | 38/1059 (4%) | N2 | 1 (0.4%) |
| Poor prognosis if >4 nodes metastasis | Unknown | 54/1113 (5%) | NA | 6 (2.3%) |
| Histology           | Ductal      | 524 (81%)      | Invasive ductal carcinoma | IDC+DCIS 194 (74.3%) | <0.01 |
|                     | Lobular     | 53 (8%)        | 102/1070 (95%) | ILC+LCIS 5 (1.9%) |
|                     | Ductal and lobular | Invasive lobular carcinoma | DCIS 42 (16.1%) | |
|                     | Other       | 53 (8%)        | Mixed     | 32/1070 (3%) | Papillary cancer 3 (1.1%) |
|                     |             |                | Unknown   | 43/1113 (4%) | NA | 11 (4.2%) |
| Grade               | G1          | 196 (31%)      | 1         | 341/1040 (33%) | 0.02 |
|                     | G2          | 305 (48%)      | 2         | 540/1040 (52%) |
|                     | G3          | 129 (20%)      | 3         | 159/1040 (15%) |
|                     |             |                | Unknow    | 73/1113 (7%) |
| Poor prognosis if >G3 | ER negative | 63 (10%)       | Oestrogen-receptor positive | ER 0.16 |
|                     | Positive    | 583 (90%)      | 962/1063 (90%) | Positive 219 (83.9%) |
|                     | Oestrogen-receptor negative | 101/1063 (10%) | NA | 8 (3.1%) |
|                     | Oestrogen-receptor status unknown | 50/1113 (4%) |
| PR                  | Negative    | 158 (24%)      | PR        | 0.62 |
|                     | Positive    | 487 (76%)      | Positive | 195 (74.7%) |
|                     |              |                | Negative  | 58 (22.2%) |
|                     |              |                | NA        | 8 (3.1%) |
| HER-2               | HER-2 (ERBB2 receptor status | Positive | 132/991 (13%) | Positive 34 (13.0%) |
|                     |             | Negative       | 859/991 (87%) | Negative 204 (78.2%) |
|                     | Not done    | 31/1113 (3%)   | NA        | 23 (8.8%) |
|                     | Unknow      | 91/1113 (8%)   | ≤14%      | 106 (40.6%) | <0.01 |
| Ki-67               | <14%        | 263 (41%)      | >14%      | 90 (34.5%) |
|                     | 14–20%      | 138 (21%)      |          | (Continued) |
multicentric breast cancer lesion” found shortly after treatment. It might be reasonable that incorporating MRI into pre-operative screening could reduce the possibility of enrolling “occult multi-focal or multicentric breast cancer patients” [25], and therefore decrease the early “recurrence”.

In our study, 8 (3.1%) patients who received IORT via the Xoft Axxent® eBx® system required WBRT. Three of them due to positive lymph node metastasis, one due to local recurrence, and the other four due to positive surgical margin (Fig 2). In the TARGIT-A trial, 15.2% of patients required supplemental WBRT after TARGIT [8]. As the concept of risk adapted IORT, it is recommended that supplemental WBRT be administered to patients who present with tumor-free margins smaller than 1 mm, extensive in-situ components, or unexpected invasive lobular carcinoma [8].

In the current study we investigated the indications for and clinical outcomes associated with the delivery of IORT via the Xoft Axxent® eBx® IORT system in patients with primary operable breast cancer at medical centers in Taiwan during the period of 2013–2015. Our analysis revealed that the selection criteria used by the participating hospitals in this study differed markedly from those used in the ELIOT and TARGIT-A studies. Specifically, patients selected for IORT in Taiwan tended to be younger, their tumors tended to be larger and the prevalence of lymph node metastasis tended to be lower. Limitations in this study include its retrospective nature and possible selection bias. The lack of long-term follow-up results in the current study precluded us from determining whether the Xoft Axxent® eBx® system results in adequate local disease control. However, current study did provide important information for patients receiving IORT with Xoft Axxent® eBx® system in a real world experience, which was derived from a national population based database.

In conclusion, the Xoft Axxent® eBx® system is well-accepted by physicians and patients in Taiwan. The characteristics of patients selection in our study might reflect the need of patients desired for IORT. Our findings together with those from previous studies should help delineate the role and value of this new adjuvant radiotherapy technique in the field of breast cancer.

Supporting information

Table 3. (Continued)

| Indication for IORT | ELIOT trial | TARGIT-A trial | T-IORTSCG | P value |
|---------------------|-------------|---------------|-----------|---------|
| >20%                | 244         | (38%)         | NA        | 65      | (24.9%) |

T-IORTSCG: Taiwan IORT study cooperative group, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, DCIS: ductal carcinoma in situ, ER: estrogen receptor, PR: progesteron Receptor, HER-2: human Epidermal Growth Factor Receptor 2, NA: not available.

Supporting information

S1 Table. Detailed patient information of our study.

(XLS)

Acknowledgments

The authors would like to thank Ya-Ling Lin, Shu-Ling Chen, and Yu-Fen Wang for their assistance of this study.

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