Ann Surg Oncol (2019) 26:2428–2434
https://doi.org/10.1245/s10434-019-07350-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Multicenter Phase II Study of Intraoperative Radiotherapy of Early Breast Cancer: Ipsilateral Tumor Recurrence

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ABSTRACT

Background. We performed a multicenter phase II study on the efficacy and safety of intraoperative radiotherapy (IORT) as partial breast irradiation using multiple devices.

Methods. The primary endpoint was ipsilateral breast tumor recurrence (IBTR). Key inclusion criteria were $T < 2.5$ cm, age > 50 years, surgical margin > 1 cm, intraoperative pathologically free margins, and sentinel node negative. After resection of the tumor, radiation at 21 Gy was delivered directly to the mammary gland employing an electron linear accelerator in the operating room, otherwise the patient was transported from the surgical suite to the radiation room.

Results. Overall, 142 patients were enrolled in this study and 129 underwent IORT. Stage 0: $n = 4$ (3.1%); stage I: $n = 98$ (76.0%); and stage IIA: $n = 27$ (20.9%). Luminal type: $n = 116$ (89.9%); triple-negative: $n = 9$ (7.0%); and human epidermal growth factor receptor 2: $n = 4$ (3.1%). Median follow-up time was 59.5 months (range 27.5–99.0), and the rate of IBTR was 3.1% (95% confidence interval 0.9–7.8). The toxicities included fibrosis in deep-connective tissue: grade 1, 78.1%; wound infection: grade 3, 1.6% and grade 2, 1.6%; and soft tissue necrosis: grade 3, 0.8% and grade 2, 0.8%. Recurrence in the breast occurred in four cases; the site of recurrence was just under the skin near the primary tumor site, with similar histology and subtype.

Conclusions. In this multicenter phase II study, the rate of IBTR was low and IORT at 21 Gy was feasible in properly selected patients. It is important to use a careful surgical technique to reduce local recurrence because the skin is not included in the radiation field of IORT.

The standard treatment for early breast cancer is breast-conserving therapy (BCT) with whole breast external irradiation therapy (WBI).[1] It has been established that there is no significant difference in the disease-free or overall survival rates between treatment by mastectomy or lumpectomy with WBI for women with early breast cancer.[2,3] WBI actually provides statistically significant local control and survival data out to 15 years in favor of WBI compared with none.[1] On the other hand, local recurrences after BCT with or without WBI arise mostly in the same quadrant as the primary cancer.[4]

The main objective of radiotherapy after BCT is the destruction of residual cancer cells around the main tumor. Partial breast irradiation (PBI) has been tested in clinical trials for selected patients, and these studies have shown adequate local control, minimal toxicity, and good cosmetic appearance.[5–7] Intraoperative radiotherapy (IORT) is one of these PBI methods that has been tested in early-stage breast cancer.[8,9] IORT has been promoted to prospective trials on tolerance to increased IORT doses, which would lead to the use of 21 Gy in the context of breast-conserving surgery as a result of a phase II study.

First Received: 15 September 2018;
Published Online: 16 April 2019

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On the other hand, no data were available on IORT in Asian breast cancer patients. Therefore, as the first step, we performed phase I and II studies to identify the recommended dose and evaluate feasibility in Japanese women in a single institution using a Mobetron® in the operating room.[10,11] A 21 Gy dose was feasible, as it was in European breast cancer patients. As the second step, we performed a feasibility study in an institution that does not have an irradiation device in the operating room because the feasibility of the IORT procedure, including transportation of the patient under general anesthesia, is not well-established, and thus needed to be standardized.[12] Finally, as the third step of standardization in Japan, we performed a multicenter phase II study to evaluate the efficacy and safety of a standard treatment using multiple devices.

PATIENTS AND METHODS

Study Design

This was a single arm, non-randomized, phase II trial evaluating the efficacy and safety of IORT in three institutions. The study was approved by the Research Ethics Review Committee and registered in the international Clinical Trial Board (UMIN000003578). The primary endpoint was the rate of ipsilateral breast tumor recurrence (IBTR), while the secondary endpoints were safety for 5 years and cosmesis. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to commencement of the study.

Eligibility Criteria

Patients with histologically or cytologically proven primary early breast cancer (T1/2, N0, and M0) were eligible for inclusion in this study. Inclusion criteria were $T < 2.5$ cm, desire for breast-conservation surgery, age $>$ 50 years, surgical margin > 1 cm, intraoperative pathologically free margins, and sentinel node-negative. Exclusion criteria were contraindications to radiation therapy, past radiation therapy of the same breast or chest, an extensive intraductal component, and a tumor located in the axillary tail of the breast.

The primary endpoint was the rate of IBTR, and the secondary endpoints were safety and cosmesis. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) V4.0, published in 2009.

After surgery, each patient was scheduled for evaluation at the first, third, and sixth month, and thereafter every 6 months for 5 years, by way of physical examinations. Mammography and ultrasonography examinations were required once per year. Examinations required for a definite diagnosis were performed if recurrence was suspected. Cosmetic evaluation was performed by a physician, based on the standards set forth by the Harvard criteria,[13] at baseline and followed-up at 1 and 3 months after IORT, and every 6 months for 5 years, by way of digital photographs. An excellent score was given when the treated breast was nearly identical to the untreated breast; a good score was assigned when the treated breast was slightly different from the untreated breast; a fair score was assigned when the treated breast was clearly different from the untreated breast, but without being seriously distorted; and a poor score was used for a seriously distorted breast.

Procedures

The operative procedures were performed as follows:

1. Sentinel lymph node biopsy.
2. Partial resection with at least a 1 cm margin around the tumor.
3. Microscopic assessment of margins by frozen sections
4. To protect the thoracic wall, an acrylic resin-Cu disk[14] was placed between the gland and the pectoralis muscle. The disk was larger than the breast target size, and the disks were prepared in diameters of 6–10 cm, with diameter increases at 1 cm intervals. The gland was sutured temporarily over the disk in order to expose the correct portion of the breast to be irradiated, avoiding the skin. The target area for radiation was at least 2 cm from the margins.
5. A proper collimator diameter was selected, and the cone was placed directly in contact with the breast target. The radiation was delivered directly to the mammary gland, exactly on the line of the collimator. The skin margins were gently stretched out of the radiation field in order to avoid skin radiation damage. Radiation was delivered employing a Mobetron® (IntraOp Medical Corporation, CA, USA) in the operating room, otherwise the patient was transported from the surgical suite to the radiation room (Clinac® 21EX, Varian Medical Systems, Inc. CA, USA), and radiation at 21 Gy was delivered. The energy of the electron beam ranged from 6 to 12 MeV, and the optimal energy of the electron beam was selected on the basis of the thickness of irradiated breast tissue measured after temporary reconstruction of the breast.[12] The best dose-distribution of radiotherapy in the gland was achieved if the thickness of the irradiated target remained as homogeneous as possible. An acrylic resin bolus with a 1 cm diameter was used to increase the surface dose distribution on the surgical bed.

The Mobetron® device was used in the operating room, therefore the patient did not have to be transported elsewhere during the surgical procedure.[11] In the institution without the Mobetron® device, a feasibility study was performed before this trial was started,[12] as a result of which it was concluded that patients could be safely transported to the radiation therapy room under general anesthesia.

Statistics

The required number of patients for the phase II study was set at 140, which would allow calculation of at least ± 2% standard error for comparison with a conventional ipsilateral breast recurrence rate of 6% for 5 years.[1] All collected data were analyzed using STATA® version 12.1 (LightStone Corp, Tokyo, Japan).

RESULTS

From April 2010 to April 2015, 142 patients were enrolled, and accrual was completed. The CONSORT diagram is shown in Fig. 1. A total of 129 patients underwent IORT at 21 Gy. Sixty-six patients were treated in the operating room and 63 patients were transported to the radiation room. Patient characteristics are shown in Table 1. Stage 0: $n = 4$ (3.1%); stage I: $n = 98$ (76.0%); and stage IIA: $n = 27$ (20.9%). Luminal type: $n = 116$ (89.9%); triple-negative: $n = 9$ (7.0%); and human epidermal growth factor receptor 2 (HER2): $n = 4$ (3.1%). Patients were mostly of older age, with smaller sized tumors, and of biologically lower risk (hormone receptor-positive and HER2-negative).

One patient was excluded from the efficacy analysis because in the definitive pathology report after the operation, the tumor was present at the inked margin surface for invasive cancer; the patient subsequently wished for, and underwent, mastectomy by reoperation. In total, 128 patients were evaluated for efficacy with regard to IBTR and toxicity.

The median follow-up time was 59.5 months (range 27.5–99.0). IBTR was 3.1% [95% confidence interval (CI) 0.9–7.8] (Fig. 2). Neither regional lymph node recurrence nor metastatic breast cancer were observed. The early toxicities for all patients are shown in Table 2. The toxicities included fibrosis in deep-connective tissue: grade 1, 78.1%; postoperative hemorrhage: grade 1, 4.7%; wound infection: grade 3, 1.6%, grade 2, 1.6%, and grade 1, 1.6%; soft tissue necrosis: grade 3, 0.8%, grade 2, 0.8%, and grade 1, 1.6%; wound dehiscence: grade 1, 1.6%; pain: grade 1, 8.6%.

Cosmetic outcomes are shown in Table 3. Good to excellent cosmetic outcomes were noted in 83.0% of patients at 3 years post IORT, 59.9% at 3 months post IORT, and 78.1% at 1 year post IORT.

We report the details of recurrent cases in Table 4. IBTR occurred in four patients. All patients had biologically lower-risk cancer (hormone receptor-positive and HER2-negative) and underwent hormonal therapy after surgery as an adjuvant therapy. The site of recurrence was just under the skin near the primary tumor site, although the margin of the primary cancer was negative in all cases. The histology and subtype were similar to the primary cancer, thus these tumors were thought to be true

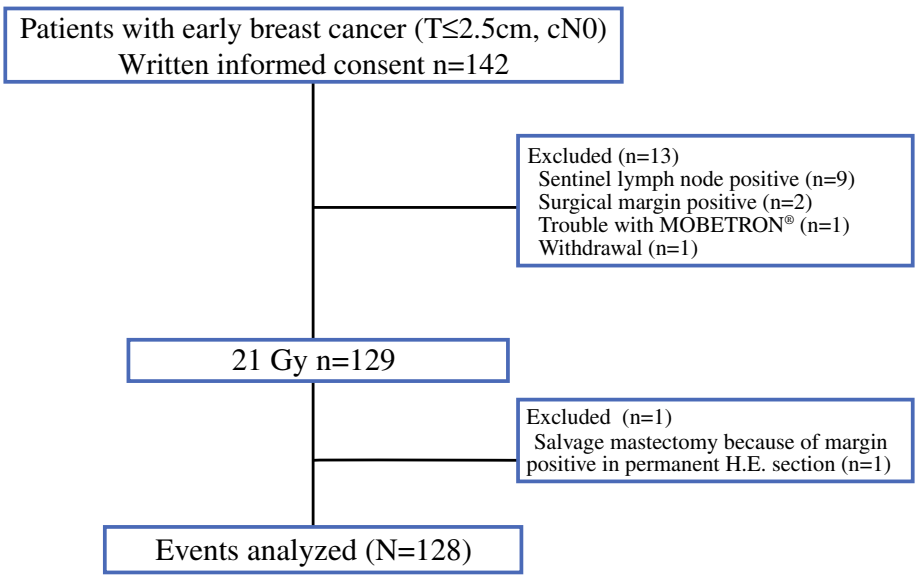

FIG. 1 CONSORT diagram. *CONSORT* CONsolidated standards of reporting trials

TABLE 1 Patient characteristics (n = 129)

Characteristic	No. of patients (%)
Age, years	
50–59	43 (33.3)
60–69	56 (43.3)
≥ 70	30 (23.3)
Mean (range)	63.6 (50–74)
Tumor site	
Upper-inner quadrant	43 (33.3)
Lower-inner quadrant	6 (4.7)
Upper-outer quadrant	64 (49.6)
Lower-outer quadrant	15 (11.6)
Central portion	1 (0.8)
Tumor diameter, mm (pathological tumor size)	
Tis	4 (3.1)
≤ 5	10 (7.8)
> 5, ≤ 10	38 (29.5)
> 10, ≤ 20	54 (41.9)
> 20	23 (17.8)
Histology	
Ductal carcinoma in situ	4 (3.1)
Invasive ductal carcinoma	112 (86.8)
Mucinous carcinoma	5 (3.9)
Invasive lobular carcinoma	4 (3.1)
Adenoid cystic carcinoma	1 (0.8)
Invasive micropapillary carcinoma	1 (0.8)
Secretory carcinoma	2 (1.6)
Histological grade	
1	67 (51.9)
2	46 (35.7)
3	16 (12.4)
Subtype	
Luminal A-like	106 (82.2)
Luminal B-like	10 (7.8)
Luminal-HER2	3 (2.3)
HER2-enriched	1 (0.8)
Triple-negative	9 (7.0)

HER2 human epidermal growth factor receptor 2

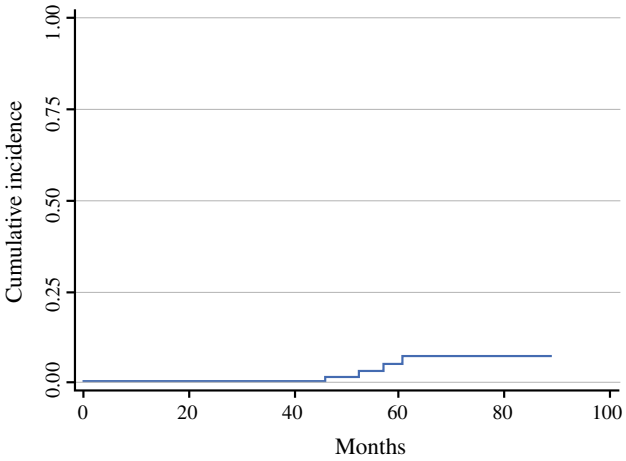

FIG. 2 Ipsilateral breast tumor recurrence. The primary endpoint is the rate of ipsilateral breast tumor recurrence, i.e. 3.1% (95% confidence interval 0.9–7.8), and the median follow-up time was 59.5 months (range 27.5–99.0)

recurrences. After the recurrence site was removed by reoperation, neither regional nor distant recurrence was observed in any of the cases.

DISCUSSION

The standard treatment for early breast cancer is BCT with WBI. In the American Society for Radiation Oncology (ASTRO) statement, the use of IORT as well as accelerated PBI (APBI) is only allowed for specific criteria ('suitable group') outside the setting of a clinical trial.[6,15] Patient selection is then a key critical point in the successful application of APBI.[16–18] Recently, in four major phase III studies of APBI, the rate of IBTR was reported at 0.5% (95% CI 0.2–1.4; median follow-up time was 6.0 years),[19] 1.44% (95% CI 0.51–2.38; median follow-up time was 6.6 years),[20] 3.3% (95% CI 2.1–5.1; median follow-up time was 2.5 years),[21] and 4.4% (95% CI 2.7–6.1; median follow-up time was 5.8 years),[22] respectively. In these trials, there was no significant inferiority with respect to disease-free survival and overall survival compared with WBI.

TABLE 2 Treatment-related toxicities (n = 128)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4–5
Fibrosis deep connective tissue	100 (78.1)	0	0	0
Wound dehiscence	2 (1.6)	0	0	0
Wound infection	2 (1.6)	2 (1.6)	2 (1.6)	0
Postoperative hemorrhage	6 (4.7)	0	0	0
Soft tissue necrosis	2 (1.6)	1 (0.8)	1 (0.8)	0
Pain	11 (8.6)	0	0	0

TABLE 3 Cosmetic outcomes for patients who received intraoperative radiotherapy (n = 128)

Cosmetic outcome	No. of patients (%)
At < 3 months (n = 123)	
Excellent	16 (13.0)
Good	60 (48.8)
Fair	39 (31.7)
Poor	8 (6.5)
Total (excellent + good)	76 (59.9)
At 1 year (n = 119)	
Excellent	33 (27.7)
Good	60 (50.4)
Fair	26 (21.8)
Poor	0 (0)
Total (excellent + good)	93 (78.1)
At 3 years (n = 106)	
Excellent	33 (31.1)
Good	55 (51.9)
Fair	18 (17.0)
Poor	0 (0)
Total (excellent + good)	88 (83.0)

In Japan, a dose-finding phase I study has been performed,[10] and the recommended phase II dose was designed at 21 Gy, at 90% isodose, which had been shown to be feasible in European breast cancer patients and biologically equivalent to a full dose of conventional WBI.[8,23] In this multicenter phase II trial, we were able to confirm safety and applicability as intended in the practice setting. IORT extends the primary operation for an additional approximately 45 min only (the radiotherapy physicist's time to prepare the Mobetron® device), otherwise approximately 60 min for transportation of the patient to the radiation room during the surgical procedure under general anesthesia; however, conventional WBI radiotherapy usually requires 5 weeks of outpatient treatment. Standardization of the operating procedure with a multidevice was mandatory, as in this study.

As for adverse events, fewer skin adverse effects occurred in the IORT group compared with the WBI group.[21,22] A slight fibrosis occurred in 78.1% of patients in this study, but there was no severe fibrosis. This study also indicated that there were few serious adverse events with regard to wound-related complications. In addition, partial breast radiotherapy may achieve improved cosmetic appearance compared with WBI in breasts that are slightly harder or firmer.[19,24] In this trial, the proportion of women with good to excellent cosmetic results was 83.0% at 3 years post IORT, which was comparable with the previous clinical trial data of APBI.[24,25]

TABLE 4 Recurrence cases (n = 4)

Case no.	Age, years	Site of tumor	pT (cm)	pN	Margin	Histological grade	ER	PR	HER2	Ki67 (%)	Histology	Adjuvant therapy	DFI
12	50	Left upper-inner quadrant	1.5	0	Negative	2	Positive	Positive	Negative	< 20	Scirrhous carcinoma	Tamoxifen	46
14	64	Left upper-inner quadrant	0.9	0	Negative	2	Positive	Positive	Negative	< 20	Scirrhous carcinoma	Anastrozole	60.6
21	61	Left lower-outer quadrant	1.5	0	Negative	2	Positive	Positive	Negative	< 20	Scirrhous carcinoma	Anastrozole	57
31	70	Left upper-inner quadrant	1.5	0	Negative	1	Positive	Positive	Negative	< 20	Papillotubular carcinoma	Anastrozole	52.5

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor, *DFI* disease-free interval

In this phase II study, IBTR was 3.1% (95% CI 0.9–7.8; median follow-up time 59.5 months), which is comparable with the IBTR in the IORT arm of a phase III study. In addition, we show the details of the recurrent cases because there are few reports on recurrence in patients who underwent IORT. As above, the biological feature is a key factor in the selection of patients. However, in four cases that recurred in this study, all patients had luminal A-like features. In general, the risk factors for local recurrence after BCT are larger tumor size, higher tumor grade, younger age, lymph node positivity, and close surgical margins.[1,26,27] In particular, in the IORT cases, irradiation of the skin above the cancer nest is not performed.[4,8–10,21,22] No irradiation is preferable with regard to good cosmetic appearance and few adverse events in the skin,[7,23] but we have to learn more from the recurrent cases in this study. The skin is not included in the radiation field in IORT cases, therefore it is important to use a careful surgical technique to dissect the correct superficial layer of the breast or remove the skin up to the tumor to reduce local recurrence. Whether the vertical distance from the skin to the tumor is very close should be evaluated because, if that is the case, the skin should be removed with the tumor.[28] Another reason for the recurrence might be a technical issue related to the position of the tumor; recurrences occurred most frequently in the upper-inner quadrants. Breast tissue in these quadrants is relatively thinner than in other quadrants, thus it was difficult to suture normal breast tissue temporarily over the disk, which consequently resulted in inadequate irradiation doses.

As for margin positivity of the breast tumor, attention should be paid to ensure negative margins on final pathology,[29] although margin positivity does not always influence the rate of local recurrence if effective radiotherapy is delivered.[9,30,31] Intraoperative freezing of sections may be used to reduce positive margins.[32] Aggressive tumor characteristics, such as in HER2-type or basal-type, have been shown to involve higher risk for local recurrence than luminal A or B types.[9,33,34] In such cases, tailored locoregional treatment for early-stage breast cancer has been reported to be mandatory.[35]

CONCLUSION

The rate of IBTR was low in patients treated with IORT at 21 Gy, which was feasible in properly selected breast cancer patients. It is important to use a careful surgical technique to reduce local recurrence because the skin is not included in the radiation field of IORT.

DISCLOSURES Masataka Sawaki, Takeshi Miyamoto, Tomomi Fujisawa, Yoshiyuki Itoh, Takeshi Ebara, Hiroyuki Tachibana, Takeshi Kodaira, Toyone Kikumori, Yasuhiro Yanagita, and Hiroji Iwata have no conflicts of interest to declare.

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