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Loco-regional outcomes of adjusted breast radiotherapy with conventional fractionation after breast conserving surgery

De-escalation of whole breast irradiation dose

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Abstract

We compared the cumulative incidence of ipsilateral breast tumor recurrence (IBTR) between 2 whole breast irradiation (WBI) dose range with conventional fractionation.

We retrospectively reviewed 1122 patients who received WBI at 2 institutions between 2004 and 2012. One institution delivered WBI 41.4 to 45 Gy followed by boost 14 to 18 Gy (adjusted group), while the other delivered WBI 50 to 50.4 Gy followed by boost 10 Gy (standard group).

The median follow-up period was 85 months. The 10-year cumulative incidence in all patients was 6.1% (95% confidence interval [CI]: 4.3%–8.4%) for IBTR and 3.0% (95% CI: 1.7%–4.8%) for regional recurrence. The 10-year cumulative incidence of IBTR was not significantly influenced by WBI dose (6.3% in the adjusted group vs 5.2% in the standard group, $P = .136$). Comparable IBTR rates between the 2 groups were observed regardless of clinical and pathological factors. The WBI dose was not significantly associated with the 10-year cumulative incidence of regional recurrence in these groups (3.5% in the adjusted group vs 0.5% in the standard group, $P = .214$).

De-escalated WBI doses while intensifying tumor bed boost did not compromise local and regional outcomes compared to standard group.

Abbreviations: BCS = breast-conserving surgery, CF = conventional fractionated, CI = confidence interval, EQD2 = equivalent dose in 2-Gy fractions, IBTR = ipsilateral breast tumor recurrence, PBI = partial breast irradiation, RT = radiation therapy, WBI = whole breast irradiation.

Keywords: breast cancer, conventional fractionation, ipsilateral breast tumor recurrence, regional recurrence, whole breast irradiation

1. Introduction

Breast-conserving surgery (BCS) followed by radiation therapy (RT) has been established as a mainstay of treatment for early breast cancer, as it produces survival rates equivalent to those following mastectomy while preserving cosmetic outcomes of breast.[1–3]

Traditionally, the whole breast is included in the clinical target volume because of the notion that microscopically residual tumor cells may remain after BCS; moreover, whole breast treatment techniques are easily applicable. However, whole breast irradiation (WBI) is often associated with serious side effects during and after treatment. In particular, toxicities such as cardiac and pulmonary sequelae can take years or decades to develop,[4,5] and they adversely affect the patients' quality of life. Therefore, relevant clinicians should concern avoiding RT-induced toxicities.

Treatment outcomes for breast cancer, including ipsilateral breast tumor recurrence (IBTR) rates, have improved owing to more precise preoperative imaging work-ups, standardized surgical management of primary tumors, administration of effective systemic treatments, and advances in RT.[6] In addition, the majority of IBTRs tend to occur around the initial tumor bed regardless of the presence of the risk factors and the IBTR rate at the initially uninvolved quadrant is rare.[7,8] The decreased incidence rate of IBTR has enabled the advent of alternatives to

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standard conventional fractionated WBI (CF-WBI); these have fewer RT-induced toxicities without compromising treatment outcomes.

Because the total dose and treatment volume have been major determinants of RT-induced toxicities, alternatives to CF-WBI have been explored via reducing the total dose or treatment volume; such techniques include various hypofractionation schemes and partial breast irradiation (PBI).[9–13] Although the use of these techniques is increasing owing to better compliance, equivalent local control, and fewer toxicities, they are contraindicated in many patients.[14,15] Therefore, CF-WBI with a total dose of 50 to 50.4 Gy in 25 to 28 fractions is still used at many institutions.[16,17]

Before actively adopting hypofractionated WBI or PBI, our institution developed a new strategy of CF-WBI that reduces the dose of the CF-WBI while escalating that of the tumor bed boost. In this study, we compared local and regional outcomes of patients receiving the adjusted breast RT dose and those receiving the standard prescribed dose.

2. Methods

2.1. Patients

This study was approved by the Institutional Review Board of each participating institution. We reviewed medical records of 1122 consecutive patients with early-stage breast cancer who underwent RT after BCS between 2004 and 2012 at 2 institutions. Patients were excluded if they

1) had a previous malignancy or synchronous double primary cancer (except thyroid cancer),
2) received neoadjuvant treatments,
3) received WBI with a total dose of less than 40 Gy,
4) presented with distant metastasis at initial diagnosis,
5) had bilateral invasive breast cancer, or
6) were lost to follow-up with no work-up.

2.2. Treatment

All patients underwent BCS at 2 participating institutions. Axillary evaluation was performed via sentinel lymph node biopsy only (n = 708) or axillary lymph node dissection (n = 402). The remaining 12 patients with microinvasive primary tumor did not undergo any axillary evaluation. After surgery, adjuvant chemotherapy was administered to 916 patients (72.7%) in accordance with standard clinical practice during this time interval. Adjuvant hormone therapy was administered to all patients with positive hormone receptor status. In total, 1088 patients (97.0%) received adjuvant systemic treatments.

Adjuvant RT was initiated in the middle of the chemotherapy course or sequentially after the completion of all scheduled chemotherapy. All patients were treated in the supine position. In almost all cases, WBI was performed with a standard tangential field; wedges or the field-in-field technique were used to ensure homogeneous dose distributions. The intensity modulated technique was implemented in 13 patients who received internal mammary nodal irradiation. The total dose of WBI and tumor bed boost at the 2 institutions differed; 1 prescribed WBI doses of 41.4 to 45 Gy with tumor bed boost doses of 14 to 18 Gy (adjusted group), while the other prescribed WBI doses of 50 to 50.4 Gy with tumor bed boost dose of 10 Gy (standard group).

One hundred forty-nine patients received regional nodal irradiation with a median total dose of 45 Gy (range, 45–50.4 Gy). The target volume of the regional nodal irradiation in the majority of patients was the supraclavicular or axillary area; only 34 patients received internal mammary nodal irradiation.

2.3. Statistical analysis

The clinicopathological parameters between the 2 groups were compared using the Chi-Squared or Fisher exact test for categorical variables and the Kruskal–Wallis test for continuous variables. IBTR was defined as the first ipsilateral in-breast recurrence (invasive or non-invasive). Regional recurrence was defined as the first recurrence at the ipsilateral axillary,

Table 1

Patient characteristics.

	Adjusted group (n = 924)	Standard group (n = 198)	*P* value
Age (median)	47	50	<.001
Menstruation			<.001
Premenopause	598 (64.7%)	96 (48.5%)	
Postmenopause	326 (35.3%)	102 (51.5%)	
Laterality			>.99
Left	474 (51.3%)	101 (51.0%)	
Right	450 (48.7%)	97 (49.0%)	
Resection margin			>.99
Close or positive	161 (17.4%)	34 (17.2%)	
Negative	763 (82.6%)	164 (82.8%)	
Histologic grade			.747
1 or 2	483 (53.6%)	100 (55.2%)	
3	418 (46.4%)	81 (44.8%)	
LVI			.263
Negative	569 (71.4%)	75 (65.8%)	
Positive	228 (28.6%)	39 (34.2%)	
Biological subtype			.002
Luminal A-like	649 (70.2%)	116 (58.6%)	
Luminal B-like	74 (8.0%)	24 (12.1%)	
HER2 overexpression	61 (6.6%)	12 (6.1%)	
Basal-like	136 (14.7%)	42 (21.2%)	
unknown	4 (0.4%)	4 (2.0%)	
Pathologic T stage			.053
1	633 (68.5%)	150 (75.8%)	
2	291 (31.5%)	48 (24.2%)	
Axillary evaluation			<.001
None	9 (1.0%)	3 (1.5%)	
SLNB	645 (69.8%)	63 (31.8%)	
ALND	270 (29.2%)	132 (66.7%)	
Pathologic N stage			.883
0	698 (75.5%)	151 (76.3%)	
1	172 (18.6%)	34 (17.2%)	
2	42 (4.5%)	11 (5.6%)	
3	12 (1.3%)	2 (1.0%)	
AJCC stage			.298
1	517 (56.0%)	121 (61.1%)	
2	353 (38.2%)	64 (32.3%)	
3	54 (5.8%)	13 (6.6%)	
Adjuvant CTx			>.99
No	252 (27.3%)	54 (27.3%)	
Yes.	672 (72.7%)	144 (72.7%)	
RNI			<.001
No	825 (89.3%)	148 (70.7%)	
Yes	99 (10.7%)	50 (25.3%)	
OTT (median)	45 days	46 days	<.001

AJCC = American Joint Committee on Cancer, ALND = axillary lymph node biopsy, CTx = chemotherapy, HER2 = human epidermal growth factor receptor 2, LVI = lymphovascular invasion, OTT = overall treatment time, RNI = regional nodal irradiation, SLNB = sentinel lymph node biopsy.

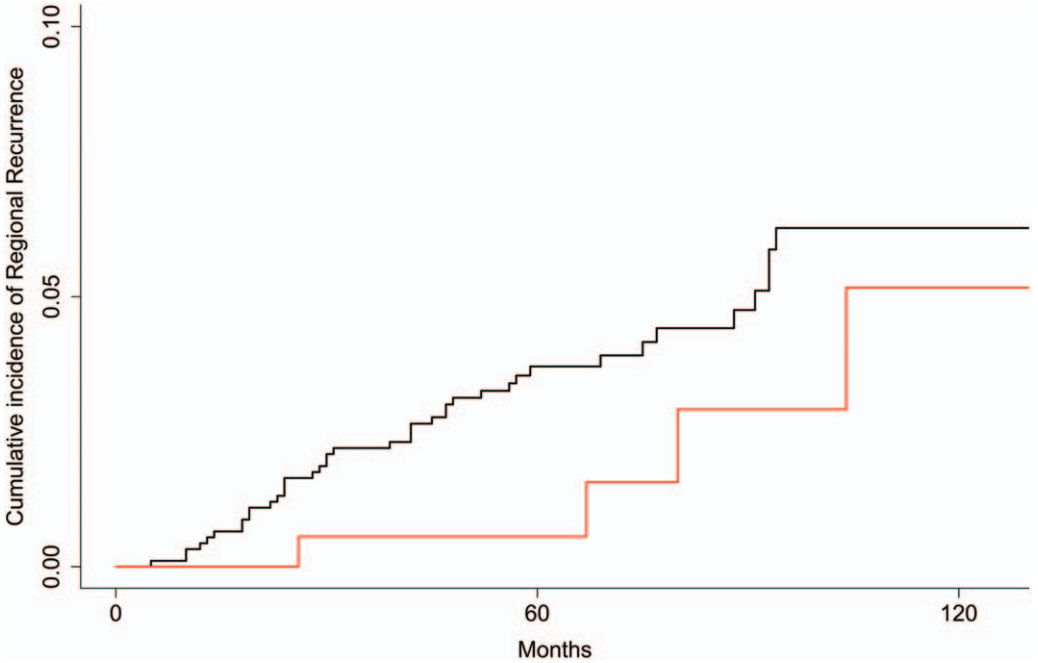

Figure 1. Cumulative incidence of ipsilateral breast tumor recurrence in all patients (black line, adjusted group; red line, standard group).

supraclavicular, and/or internal mammary lymph node area. Isolated IBTR and/or regional recurrence was confirmed by biopsy. The 10-year cumulative incidence rate of IBTR and regional recurrence was calculated from the date of surgery to the date of pathological confirmation using Gray test. The competing risks included regional recurrence, distant metastasis, contralateral breast tumor, or intercurrent death. For regional recurrence, the competing risks included IBTR, distant metastasis, contralateral breast tumor, or intercurrent death. Multivariate analysis was performed using the competing risk proportional hazards method (Fine and Gray test). A 2-sided *P*-value $<.05$ was considered significant. All statistical analyses were performed using the R software, version 3.3.3 (www.r-project.org).

3. Results

3.1. Patient characteristics

All patient characteristics are summarized in Table 1. The median age was significantly younger in the modified dose group than in the standard dose group. Hormone receptor-positive disease was not significantly different between the 2 groups (78.5% for the adjusted group vs 72.6% for the standard group, $P=.085$). The human epidermal growth factor receptor status was not significantly different ($P=.21$). Overall, patients in the standard group underwent more aggressive axillary management, including surgical dissection and regional nodal irradiation.

3.2. IBTR

During the median follow-up period of 85 months, 45 patients experienced IBTR with a 10-year cumulative incidence of 6.1% (95% confidence interval [CI], 4.3%–8.4%) (Fig. 1). There was no significant difference in IBTR rates between the 2 groups (Table 2). An age <40 years (hazard ratio [HR], 2.79; $P<.001$), incomplete resection margin status (HR, 3.23; $P<.001$), high histologic grade (HR, 1.62; $P=.003$), and non-luminal A-like subtypes (HR, 1.59; $P<.001$) were significantly associated with IBTR. The competing risk regression model revealed that an age <40 years, incomplete resection margin, and non-luminal A-like types were significantly associated with an increased risk of IBTR (Table 3).

3.3. Regional recurrence

Twenty-five patients experienced regional recurrence. The axillary area was the most common (n = 14) followed by the supraclavicular (n = 12) and internal mammary nodal area (n = 3). The 10-year cumulative incidence of regional recurrence was 3.0% (95% CI, 1.7%–4.8%) (Fig. 2). The adjusted group was not significantly associated with an increased the risk of regional recurrence (Table 2). Competing risk regression analysis revealed that histologic grade 3 and lymphovascular space invasion were independent factors associated with an increased risk of regional recurrence (Table 3).

Table 2

10-year cumulative incidence of local and regional events (Gray test).

	Adjusted group	Standard group	HR	*P* value
IBTR	6.3% (4.3–8.7)	5.2% (1.4–12.7)	.469	.136
Regional recurrence	3.5% (2.0–5.7)	0.5% (0.05–2.8)	.415	.215

HR = hazard ratio, IBTR = ipsilateral breast tumor recurrence.

Table 3

Competing risk regression analysis.

	IBTR			Regional recurrence		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥40 yr	.368	.192–0.708	.003			
Suboptimal RM	3.781	1.999–7.153	<.001			
HG 3	1.109	.753–1.634	.60	2.237	1.285–3.90	.004
LVSI				3.996	1.662–9.61	.002
Subtype	1.548	1.223–1.96	<.001			
LA-like	1					
LB-like	3.284	1.252–8.610	.016			
HER2	6.533	2.751–15.512	<.001			
Basal-like	3.587	1.512–8.5.8	.004			
Standard group	.370	.121–1.127	.08	.653	.149–2.87	.57

CI = confidence interval, HER2 = human epidermal growth factor receptor 2, HG = histologic grade, HR = hazard ratio, IBTR = ipsilateral breast tumor recurrence, LA = luminal A, LB = luminal B, LVSI = lymphovascular space invasion, RM = resection margin.

3.4. IBTR according to age, grade, stage, and hormone receptor status

The 10-year cumulative incidence of IBTR was not significantly different between the 2 groups in young patients (Table 4). For patients with histologic grade 3, there was no significant difference in the 10-year cumulative incidence of IBTR between the 2 groups ($P = .376$). In patients with hormone receptor-negative status, the adjusted group did not show significantly increased 10-year cumulative incidence of IBTR ($P = .367$). The 10-year cumulative incidence of IBTR was not significantly different between the 2 groups among patients with both luminal A-like subtype ($P = .323$) and non-luminal A-like subtype ($P = .117$) tumors.

3.5. Toxicities

None of patients complained severe acute toxicities including wet desquamation, breast edema, and pneumonitis. At the end of follow-up, there were no late cardiac or pulmonary toxicities between the 2 groups.

4. Discussion

In this study, de-escalation of WBI doses while increasing the tumor bed boost dose did not result in increased rates of IBTR or regional recurrence. Equivalent incidences of IBTR and regional recurrence between the 2 groups were observed regardless of the presence of high-risk factors for IBTR. As this adjusted breast RT had advantages of being free from the limitations of hypofractionated WBI or PBI, patients ineligible for hypofractionated WBI or PBI may benefit from this strategy.

The standard CF-WBI doses of 50 to 50.4 Gy originated from early prospective randomized trials in which the majority of patients did not receive systemic treatments, and in which the systemic treatment regimens were not optimal.[1,2] Although the

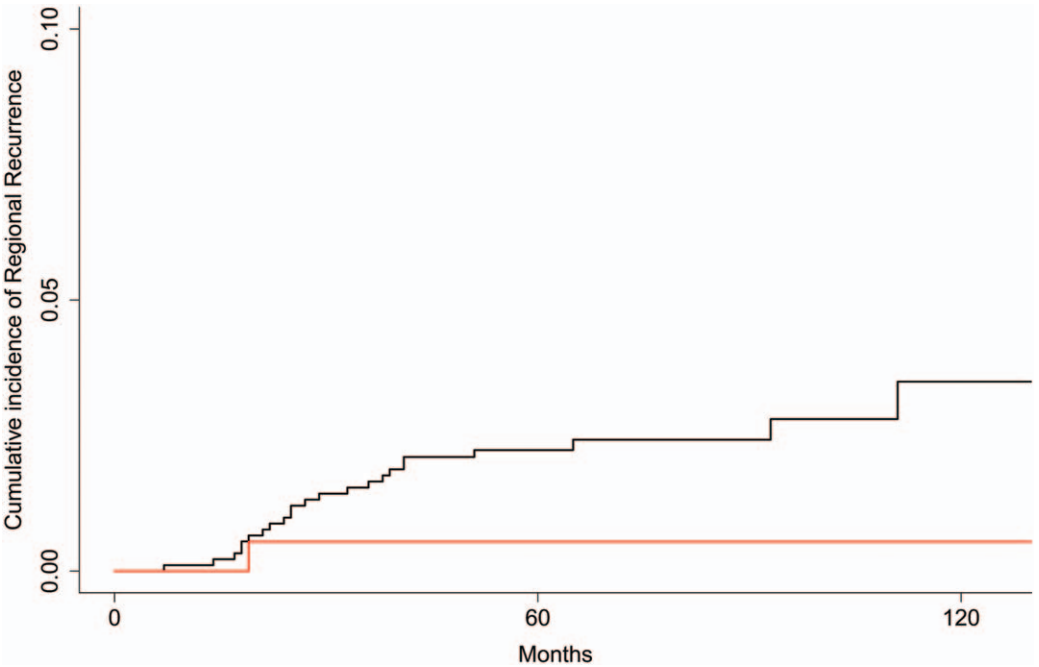

Figure 2. Cumulative incidence of regional recurrence in all patients (black line, adjusted group; red line, standard group).

Table 4

The effect of WBI doses on IBTR and regional recurrence according to the age, grade, hormone receptor status, and stage.

	Adjusted group	Standard group	*P* value
Age			
<40 yr	14.5%	10.0%	.249
≥40 yr	4.3%	3.5%	.338
HG			
1–2	3.5%	4.5%	.324
3	9.7%	8.1%	.376
Hormone receptor			
Negative	12.0%	11.2%	.367
Positive	4.8%	3.0%	.121
Biological subtypes			
Luminal A-like	4.4%	3.9%	.324
Non-luminal A-like	11.1%	7.3%	.117
T stage			
pT1	6.7%	5.9%	.179
pT2	5.2%	2.3%	.503

HG = histologic grade, IBTR = ipsilateral breast tumor recurrence, WBI = whole breast irradiation.

primary goal of systemic treatments is to reduce distant metastasis, it is evident that such treatments can contribute to the improvement of local and regional control. Therefore, the intensity of adjuvant local treatment can be reduced for patients receiving systemic treatments. In this study, the majority of patients (97.0%) received some type of systemic treatment with chemotherapy, hormone therapy, or both based on contemporary guidelines. Therefore, the adjusted group may experience equivalent IBTR rates as the standard group despite decreased WBI doses, partly owing to the use of contemporary systemic treatments.

The different shapes of the dose-response curves between control of the subclinical breast tumor foci and the risk of normal tissue damage can be plausible explanation for comparable local control rates observed in the adjusted group. In general, the dose-response curve for the subclinical tumor foci control is shallower than that for normal tissue; therefore, a reduction in the total WBI dose is expected to decrease local tumor control to a lesser extent while greatly sparing normal tissue.[18,19] This rationale formed a basis for several prospective randomized trials that showed that hypofractionated WBI can achieve local control rates similar to those of standard CF-WBI.[9–12] Notably, the total doses of various hypofractionated schemes calculated as equivalent dose in 2-Gy fractions (EQD2) were relatively lower than that of CF-WBI (50 Gy in 25–28 fractions).[19,20] For example, the total EQD2 of hypofractionated WBI at 40 Gy in 15 fractions is 44.8 Gy. This suggests that the total EQD2 of CF-WBI can be reduced without decreasing local and regional outcomes. However, the prognostic impact of reducing the CF-WBI dose has not been investigated. Our study showed that the adjusted group with an EQD2 of 39.9 to 43.4 Gy exhibited local control that was equivalent to that of the standard group.

Most patients received WBI using tangential fields, which can deliver incidental radiation doses to regional lymphatic areas, albeit not at clinically therapeutic levels.[21–23] However, the influence of the incidental doses on treatment outcomes cannot be neglected. Indeed, PBI is associated with a significantly higher risk of ipsilateral axillary recurrence than CF-WBI, even in patients with low tumor burdens.[24] Patients in the standard group received more aggressive axillary management even though there was no significant difference in the regional recurrence rates between the 2 groups. This finding implies that a total dose of 41.4 to 45 Gy would presumably be sufficient for regional control. Further studies are required to confirm that coverage of regional lymphatic areas with lower radiation doses does not increase the risk of regional recurrence.

This study had several limitations that ought to be considered when interpreting the results. First, selection bias existed owing to the study's retrospective design. In particular, patients in the standard group were carefully selected for BCS, as they were of relatively older age and had smaller tumor sizes. Second, the numbers of patients were not evenly distributed because of different hospital volumes. Third, we could not compare IBTR rates between different WBI dose ranges in a specific subset of patients with negative hormone receptors who did not receive adjuvant chemotherapy. Finally, we could not assess cosmesis and late toxicities because of the lack of available data. As one of the most important reasons for lowering the total dose is to reduce late toxicities, thorough evaluations of such toxicities will strengthen the rationale for lowering the total WBI dose. Fewer side effects in the adjusted group can be predicted based on a prospective randomized trial performed in Australia that found that the delivery of reduced CF-WBI of 45 Gy in 25 fractions followed by a tumor bed boost of 16 Gy in 8 fractions showed better cosmetic outcomes than the control group (50 Gy in 25 fractions of WBI without a tumor bed boost).[25]

5. Conclusion

In conclusion, de-escalating WBI doses while increasing the tumor bed boost did not increase the risk of IBTR and regional recurrence over the standard treatment group. This finding was also observed in patients with high-risk factors for IBTR, including age < 40 years, high-grade tumor, primary tumor size >2 cm, negative hormone receptor status, and non-luminal A-like subtypes. In patients who receive optimal adjuvant systemic treatments based on their clinical and pathological features, this adjusted breast RT appears to be a feasible strategy for achieving acceptable treatment outcomes compared to traditionally conventional fractionation schemes.

Author contributions

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Validation: Mison Chun, Young-Taek Oh, O Kyu Noh.
Writing – original draft: Sang-Won Kim.
Writing – review & editing: Sang-Won Kim.

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