Developing a Novel High-precision Radiotherapy for Low Risk Early-stage Breast Cancer in Korean Women - Stereotactic Partial Breast Irradiation with CyberKnife M6

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Directed by Professor Yong Bae Kim

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Won Hee Lee

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Purpose: Accelerated partial breast irradiation (A-PBI) in Korean women has been considered impracticable, owing to small breast volume and lack of high-precision radiotherapy experience. We present the first experience of stereotactic-PBI (S-PBI) with CyberKnife M6 to investigate feasibility and early toxicities in Korean women.

Materials and Methods: A total of 132 breasts receiving S-PBI at our institution between November 2015 and October 2018 were reviewed. Patients were selected based on American Society for Radiation Oncology (ASTRO), American Brachytherapy Society (ABS), American Society of Breast Surgeons (ASBrS), and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) guidelines. At the beginning, dose of 34 Gy in 10 fractions daily was used following the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 protocol. A dose of 30 Gy in 5 fractions every other day (NCT01162200) was used from March 2017; gold fiducials were routinely inserted for tracking from September 2017. Constraints regarding organs-at-risk followed the NSABP-B39/RTOG 0413 protocol.

Results: Median follow-up was 14 months. Patients were categorized as “suitable” (70.5%) or “cautionary” (29.5%) according to 2017 ASTRO guidelines. No tracking failure occurred after gold fiducial insertion.

Median planning target volume (PTV) and PTV-to-whole breast volume ratio was 80.4 mL (interquartile range, 60.5–108.2 mL) and 17.0% (13.6–19.0%), respectively. Median PTV $V_{95\%}$, PTV D_{max}, and ipsilateral breast $V_{50\%}$ were 97.5% (95.6–98.6%), 105.3% (104.2–106.4%), and 35.2% (28.5–39.8%), respectively. No immediate post-S-PBI grade $\geq$2 toxicity was reported except grade 2 induration in 3 breasts. All patients remain disease-free to date.

Conclusion: The first use of S-PBI in Korean women was feasible and safe for selected early breast cancer. Based on these results, we have initiated a prospective study (NCT03568981) to test S-PBI in whole breast irradiation for selected early breast cancer.

Key words : stereotactic partial breast irradiation, accelerated partial breast irradiation, breast cancer, Korean, feasibility studies, dosimetric outcomes, early toxicity

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I. INTRODUCTION

Breast conserving therapy consisted of breast conserving surgery and whole-breast irradiation had been established as the standard treatment in early breast cancer. However, accelerated partial breast irradiation (A-PBI) has emerged as an alternative to whole breast irradiation (WBI). Previous studies in patients with low-risk early-stage breast cancer show that rates of local recurrence after A-PBI are extremely low, and most cases are limited to the vicinity of the original tumor bed (1-3). Several prospective randomized trials demonstrated that A-PBI is associated with a non-inferior ipsilateral breast tumor recurrence (IBTR) rate, excellent cosmesis, and low treatment-related toxicity compared to WBI, although there are some variabilities in outcomes owing to use of different radiation techniques and patient selection criteria (4-8). However, while A-PBI has been widely adopted worldwide for selected patients with early breast cancer, A-PBI adoption remains limited in South Korea. The “Patterns of practice” study revealed that the use of A-PBI is far from widespread in South Korea (9).

As stereotactic body radiation therapy (SBRT) has become a new paradigm in field of radiation oncology due to its special radio-biologic nature and development of high-precision techniques, it is now widely used in various types of cancer. Recently, SBRT has widened its use in early breast cancer, in the form

of stereotactic accelerated partial breast irradiation (S-PBI). With advancements in high-precision radiotherapy techniques, SBRT has become an emerging option for early breast cancer, in the form of stereotactic A-PBI (S-PBI). Several Western institutions have shown that S-PBI is a safe and feasible treatment in patients with early breast cancer who meet strict criteria (10-12). Nonetheless, experience of S-PBI in Korea is also extremely limited.

In these backgrounds, we have implemented the novel technique of A-PBI in Korean women, and we report here our first experience in South Korea of using S-PBI for highly selected early breast cancer. Our aim was to investigate the feasibility and early treatment toxicity profile of S-PBI in Korean women.

II. MATERIALS AND METHODS

1. Patient selection

We reviewed patients treated with S-PBI using CyberKnife M6 (Accuray Incorporated, Seoul, South Korea) at our institution between November 2015 and October 2018. Patients referred for radiotherapy after breast-conserving surgery for breast cancer were screened by radiation oncologists for suitability for S-PBI, based on consensus guidelines of the American Society for Radiation Oncology (ASTRO), American Brachytherapy Society (ABS), American Society of Breast Surgeons (ASBrS), and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) (13-16). Low risk breast cancer patients in this study were defined as patients satisfying the criteria of all of the above guidelines. These low risk patients were preferentially selected for S-PBI. Updates to guidelines during the course of the study were applied immediately (17, 18). Ultimately, patients categorized as “suitable” as well as “cautionary” according to the ASTRO guidelines were included in the study. When patients’ age was between 45 and 49, they were considered for S-PBI only if all of their pathologic characteristics fell into “suitable” group by ASTRO

guidelines. However, the criterion of extensive intraductal carcinoma in the guidelines was not strictly considered due to our institution's generous surgical margin in partial mastectomy.

Patients who experienced surgical complications (i.e., scar dehiscence, wound infection), had positive resection margins, were younger than 45 years, or had multicentric tumors were ineligible for S-PBI. Only patients who had a follow-up period of longer than 6 months were included in this study. All patients diagnosed with breast cancer were evaluated preoperatively using breast magnetic resonance imaging (MRI), ultrasonography, and mammography. During breast conserving surgery, patients with infiltrating carcinoma were required to have sentinel lymph node biopsy. For ductal carcinoma in situ (DCIS) tumors with calcifications seen on pre-operative mammograms, negative post-operative mammograms were required before radiotherapy.

2. Fiducial utilization and simulation

S-PBI performed with CyberKnife M6 tracked either surgical clips or gold fiducials as fiducial markers. At commencement of the study in November 2015, S-PBI used tracking surgical clips inserted into the tumor bed. Patients were screened by X-ray fluoroscopy to check that the surgical clips were visible as fiducial markers; those whose surgical clips were invisible or untrackable on radiography underwent A-PBI using volumetric arc therapy. Since September 2017, the gold fiducials have been routinely inserted, with three gold fiducials inserted into patients' breasts at a 1 cm margin from the postoperative tumor cavity under ultrasonographic guidance. Upon insertion, the fiducials were placed in a non-coplanar position with respect to the radiographic orthogonal images of the CyberKnife M6, and the greatest possible extent of angular separation was aimed for. Mammography was performed immediately after insertion to confirm the presence of the gold fiducials, and simulation computed tomography (CT) was carried out at least 1 week later to minimize the effect of fiducial migration (19). Before gold fiducial insertion, they were placed on the breast skin surface near the incisional scars (2 on both ends of the scar and another 2 perpendicular to it) for

tracking when it was first introduced to our department in July 2017. For CT-simulation, non-contrast 1 mm cut CT scan was obtained, and then non-contrast 3 mm cut CT scan was obtained with scar marking done by radiopaque angio-catheter on surgical scar. Vac-Lok (CIVCO Radiotherapy, Coralville, IA, USA) devices were used to immobilize patients in the supine position with arms placed overhead.

3. Treatment planning

CT images were imported into MIM software (MIM Software Inc., Cleveland, OH, USA) for target delineation. The target was delineated on the non-contrast 1 mm cut CT scan. The surgical tumor cavity was identified based on pre- and postoperative images, surgical clips, and the incisional scar. The incisional scar was delineated through fusion of non-contrast 3 mm cut CT scan with the 1 mm cut CT scan. The clinical target volume (CTV) was defined as a uniform 1 cm margin expansion from the tumor cavity, excluding the skin and chest wall. A margin of at least 5 mm from the breast skin surface was required. Chest wall structures such as the pectoralis muscle or ribs were excluded from the CTV. Routinely, the planning target volume (PTV) requires additional margin accounting uncertain setup errors. But, we defined the PTV as equal to the CTV, using a robotic stereotactic tracking system capable of real-time respiratory tracking. The ipsilateral breast, contralateral breast, skin, chest wall, both lungs, heart, left anterior descending coronary artery, esophagus, thyroid, and spinal cord were delineated as organs-at-risk. The contoured PTV and ipsilateral whole breast volume were measured using MIM software. The PTV-to-whole breast ratio (PTV/WB) was calculated for each breast. An example of target delineation for S-PBI is shown in Fig. 1.

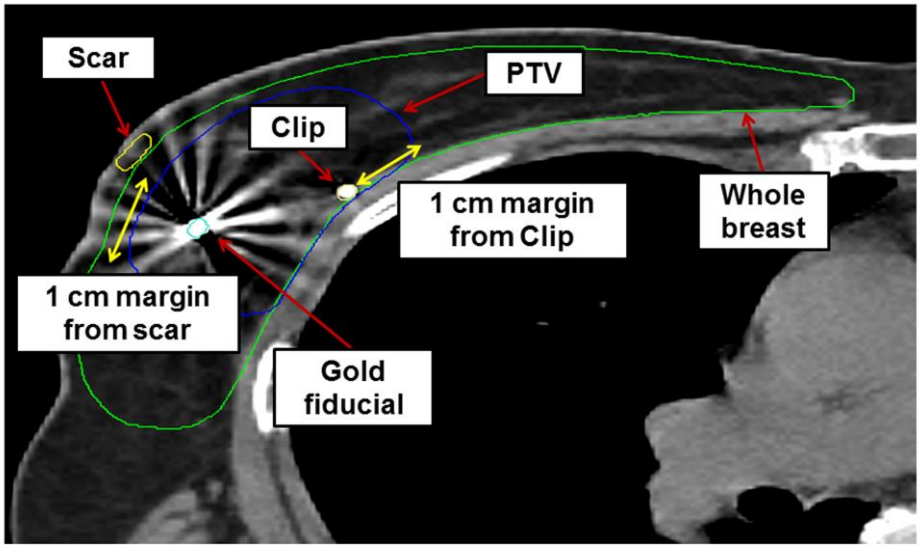

Fig 1. Example of axial cut image of target delineation for stereotactic accelerated partial breast irradiation.

The prescribed dose was initially 34 Gy in 10 fractions, identical to that of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 protocol. Radiotherapy was delivered daily following this fractionation scheme, because of strict reimbursement rules under the Korean National Health Insurance (KNHI) system. From March 2017 the dose prescription followed that of the University of Texas Southwestern (UTSW), which proved safe and feasible in their phase I study (NCT01162200) (12). In this regimen, radiotherapy was delivered every other day. The S-PBI was planned such that the PTV receiving 95% of the prescribed dose ($V_{95\%}$) would be over 95% of the total PTV, and the maximum point dose (D_{max}) allowed for the PTV was less than 107%. Constraints to organs-at-risk mostly followed those of the NSABP B-39/RTOG 0413 protocol: less than 60% of ipsilateral breast was to receive more than 50% of prescribed dose ($V_{50\%} < 60\%$), maximum point dose allowed for contralateral breast was to be less than 1 Gy ($D_{max} < 1$ Gy), less than 15% of ipsilateral lung was to receive more than 30% of prescribed dose ($V_{30\%} < 15\%$), less than 15% of contralateral lung was to receive

more than 5% of prescribed dose ($V_{5\%}$ < 15%), less than 5% of heart (right-sided lesions) was to receive more than 5% of prescribed dose ($V_{5\%}$ < 5%), less than 40% of heart (left-sided lesions) was to receive more than 5% of prescribed dose ($V_{5\%}$ < 40%), maximum point dose allowed for chest wall was to be less than 1 Gy (D_{max} < 40.8 Gy), and maximum point dose allowed for skin was to be less than 1 Gy (D_{max} < 49.3 Gy).

4. Treatment and follow-up

Robotic stereotactic radiotherapy using the CyberKnife M6 with fiducial tracking was used in all patients. Before every treatment, orthogonal X-ray images (from 45° and 135° angles with respect to the surface) were acquired after patient setup to visualize and align the fiducials with those in the original orthogonal X-ray images. If only 2 fiducials were detectable during treatment, treatment required authorization from a radiation oncologist. Whenever the fiducials were untrackable or out of expected patient motion during S-PBI, the machine automatically ceased radiation.

Patients were interviewed and examined by the treating physician during the course of therapy, followed by routine visits every 6–12 months after S-PBI. Routine surveillance consisted of medical interviews, breast examinations, and mammography, in addition to optional breast ultrasonography and MRI. Toxicity assessment was performed using the Harvard scale, and mainly included breast skin color change and induration assessments. In addition, skin thickness was measured by assessing ultrasound images obtained before surgery and 6–12 months after radiotherapy (if available). Both the skin above the tumor bed and the skin of the opposite quadrant of the ipsilateral breast (at least 5 cm away from the tumor bed) were measured at each time point.

We selected a cohort of 237 breasts that received WBI during the same period that the S-PBI was undertaken, for comparison of skin thickness. Similar to the S-PBI patients, skin thickness of these breasts was measured before surgery and 6-12 months after radiotherapy. At each time point, the same location of the skin as the S-PBI breasts was measured. All these breasts exhibited pathologically

T1, node-negative breast cancers that received WBI of 40.05 Gy in 15 fractions, combined with a simultaneously integrated boost of 48 Gy in 15 fractions to the tumor bed by intensity-modulated radiation therapy (IMRT).

III. RESULTS

1. Patient characteristics

Between November 2015 and October 2018, 2077 patients (2124 breasts) were referred for radiotherapy after undergoing breast-conserving surgery. After screening, 131 patients (132 breasts; 6.2% of total referred breasts) received S-PBI. The median follow-up was 14 months (range, 6–40 months). The patient characteristics are summarized in Table 1. Among the total of 131 patients, the median age was 60 years (range, 46–85 years), and 95 breasts (72.0%) had invasive ductal carcinoma with a median tumor size of 1.1 cm (range, 0.1–2.5 cm). Five patients had metastatic lymph nodes (1–2 sentinel lymph node metastases with no perinodal extension). The tumor grade was 1 or 2 in 121 breasts (91.7%). Only one tumor had lymphovascular invasion, and all had clear resection margins. All tumors except 1 were estrogen receptor-positive. The breasts were categorized as “suitable” (70.5%) or “cautionary” (29.5%) according to the updated 2017 ASTRO guidelines. The most common reason for being classified as “cautionary” was extensive intraductal carcinoma of less than 3 cm (24 breasts).

Table 1. Patient characteristics (per breast)

Characteristic	N	%
Age (median year, range)	60 (46–85)	
Pathologic type		
DCIS	19	14.4
IDC	95	72.0
Others	18	13.6
Tumor size (median cm, range)	1.1 (0.1–2.5)	

N stage		
N0	127	96.2
N1	5	3.8
RM		
Negative	132	100.0
Close or Positive	0	0.0
Grade		
Grade 1	59	44.7
Grade 2	62	47.0
Grade 3	11	8.3
LVI		
No	131	99.2
Yes	1	0.8
EIC		
No	108	81.8
Yes	24	18.2
ER		
No	1	0.8
Yes	131	99.2
ASTRO guideline category		
Suitable	93	70.5
Cautionary	39	29.5
Unsuitable	0	0.0

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; N stage, nodal stage; RM, resection margin; LVI, lymphovascular invasion; EIC, extensive intraductal carcinoma; ER, estrogen receptor; ASTRO, American Society for Radiation Oncology.

2. Technical feasibility of S-PBI

One hundred-four breasts (78.8%) were tracked by inserted gold fiducials,

while in 22 (16.7%) and 6 (4.5%) it was by surgical clips, and gold fiducials placed on the skin surface, respectively. Before routine insertion of gold fiducials, 101 breasts were considered for S-PBI but tracking failure occurred in 73 of them; these patients received A-PBI via volumetric arc therapy. After September 2017 gold fiducials were routinely inserted for A-PBI candidates (104 breasts), among whom no tracking failure occurred. Of this latter group, all 3 inserted fiducials were trackable in 83 breasts (75.5% of all with inserted fiducials), and 2 of the 3 were trackable in 27 breasts (24.5%). The median treatment time was 35 minutes (range, 25–52 minutes) (Table 2).

Table 2. Treatment characteristics

Characteristic	N	%
Dose prescription		
34 Gy/10 fractions	15	11.4
30 Gy/5 fractions	117	88.6
Tracked marker		
Inserted gold fiducials	104	78.8
Fiducials on skin surface	6	4.5
Surgical clip	22	16.7
Number of tracked gold fiducials (among inserted)		
3 fiducials	83	75.5
2 fiducials	27	24.5
Treatment time (median min, range)	35 (25–52)	

3. Dosimetric outcomes

The median whole breast volume was 513.5 mL (interquartile range [IQR], 399.6–667.4 mL), while the median PTV was 80.4 mL (IQR, 60.5–108.2 mL). The median PTV/WB was 17.0% (IQR, 13.6–19.0%). The dosimetric parameters for S-PBI in this study are shown in Table 3, while the PTV and PTV/WB in this

study are compared to those found in other similar S-PBI studies in Table 4. The median PTV $V_{95\%}$ was 97.5% (IQR, 95.6–98.6%), and PTV D_{max} was 105.3% (IQR, 104.2–106.4%). The median ipsilateral breast $V_{50\%}$, ipsilateral lung $V_{10\ Gy}$, and contralateral lung $V_{1.5\ Gy}$ were 35.2% (IQR, 28.5–39.8%), 2.3% (IQR, 1.5–3.3%), and 0.0% (IQR, 0.0–0.0%), respectively. The median skin and chest wall D_{max} were 26.7 Gy (IQR, 25.5–28.3 Gy) and 30.0 Gy (IQR, 29.4–31.3 Gy), respectively. The mean dose for the heart was median 0.8 Gy (IQR, 0.5–1.3 Gy) and 0.4 Gy (IQR, 0.3–0.5 Gy), for left- and right-sided lesions, respectively. Fig. 2. shows an example of an isodose line and dose-volume histogram of an S-PBI plan that successfully satisfied all dosimetric goals.

Table 3. Dosimetric outcomes of stereotactic partial breast irradiation

Dosimetric parameters	Median (interquartile range)
PTV $V_{95\%}$	97.5% (95.6–98.6%)
PTV D_{max}	105.3% (104.2–106.4%)
Ipsilateral breast $V_{50\%}$	35.2% (28.5–39.8%)
Contralateral breast D_{max}	0.8 Gy (0.5–1.1 Gy)
Ipsilateral lung $V_{20\ Gy}$	0.1% (0.0–0.3%)
Ipsilateral lung $V_{10\ Gy}$	2.3% (1.5–3.3%)
Contralateral lung $V_{1.5\ Gy}$	0.0% (0.0–0.0%)
Heart mean dose (left-sided lesions)	0.8 Gy (0.5–1.3 Gy)
Heart mean dose (right-sided lesions)	0.4 Gy (0.3–0.5 Gy)
Skin D_{max}	26.7 Gy (25.5–28.3 Gy)
Chest wall D_{max}	30.0 Gy (29.4–31.3 Gy)

$V_{x\%}$, percentage of volume receiving X% of the prescribed dose; $V_{x\ Gy}$, percentage of volume receiving X Gy; D_{max}, maximum point dose

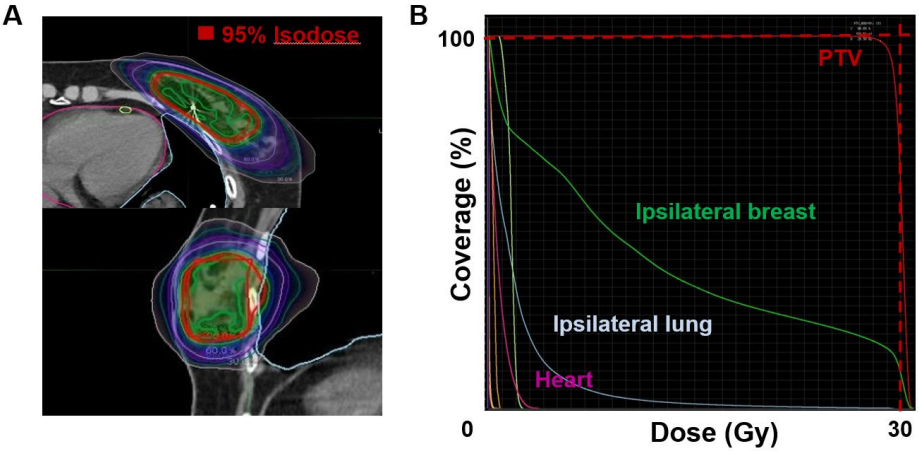

Fig 2. Example of (A) isodose line (upper: axial; lower: sagittal) and (B) dose volume histogram of S-PBI plan that satisfied all dosimetric goals.

4. Physician-rated early toxicity and change in breast skin thickness

After a median follow-up of 14 months, no IBTR, regional recurrence, or distant metastasis was detected in any of the patients. Fig. 3. shows the toxicity data at the end of each follow-up period. Immediately after S-PBI, 111 breasts (84.1%) had no breast skin color change, and 82 (62.1%) had no palpable induration. No grade 2 or higher breast color change was reported, and grade 2 induration was observed in 3 breasts, which had persisted since immediately after the completion of surgery. After 6 months of follow-up, grade 1 color change and grade 1 palpable induration were noted in 2 and 7 breasts, respectively. Among the 97 breasts where follow-up of 1 year was reached, none showed color change and only 8 showed grade 1 induration. Finally, among the 15 breasts where follow-up of 2 years was reached, none showed any color change or induration. In terms of other treatment-related toxicities, 1 breast had grade 1 breast edema, and 1 had grade 2 breast cellulitis which was successfully managed with oral antibiotics.

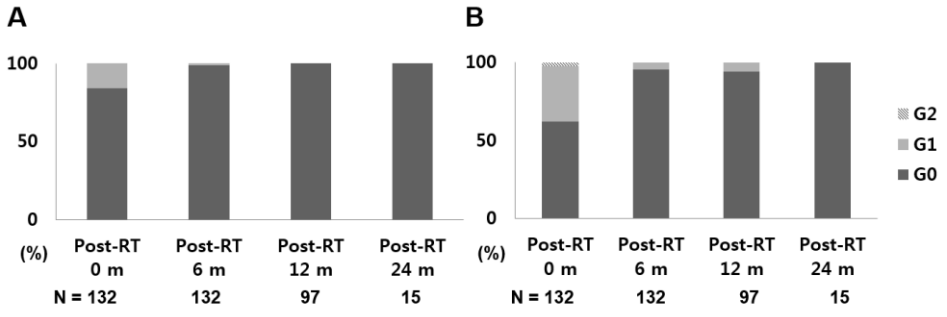

Fig 3. Outcomes of early toxicity; (A) skin color change, (B) breast induration.

In S-PBI breasts, the median increase in skin thickness above the tumor bed was 800 μm (range, -600–+3200 μm), while skin of the opposite quadrant of the tumor bed in the ipsilateral breast increased by a median of 100 μm (range, -600–+1100 μm) (Fig 4.). In WBI breasts, the median increase in skin thickness above the tumor bed was 1000 μm (range, -200–+5200 μm), while in the opposite quadrant of the tumor bed in the ipsilateral breast it increased by a median of 400 μm (range, -300–+3300 μm). Changes in skin thickness of the opposite quadrant were significantly smaller in the S-PBI group compared to the WBI group ($p<0.01$).

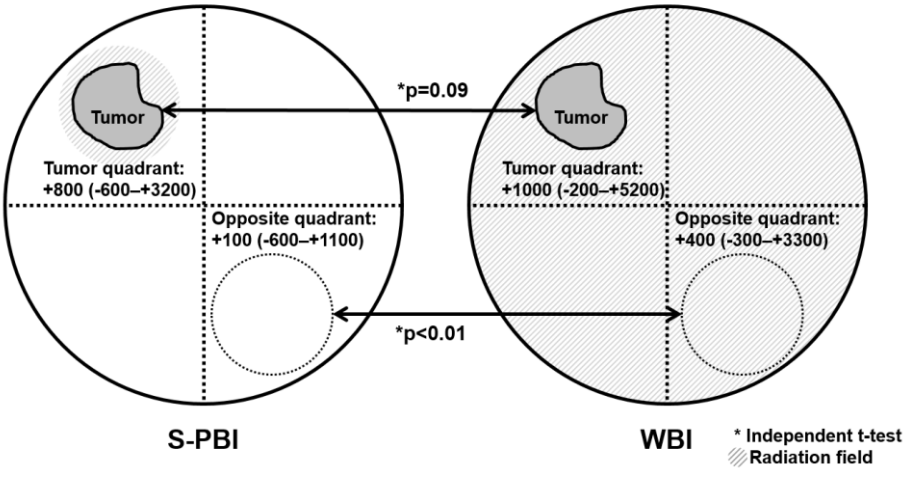

Fig 4. Changes in skin thickness after surgery followed by stereotactic partial breast irradiation (S-PBI) or whole breast irradiation (WBI). Changes in skin thickness are defined as breast skin thickness before surgery subtracted from breast skin thickness at 1 year after radiation. Values are presented in micrometers (range).

IV. DISCUSSION

Our first experience of S-PBI in South Korea revealed that it is a feasible and safe treatment in highly selected early breast cancer patients in Korean women. The high-precision radiotherapy technique showed excellent fiducial tracking abilities, with excellent dosimetric outcomes and minimal early toxicity, despite the relatively small breast volumes. To our knowledge, this is the first experience of S-PBI use in Korean women.

Over the last 3 decades, prospective trials using various techniques have demonstrated that A-PBI is non-inferior to WBI (4-7). However, only 4.7% of total radiation oncology facilities in South Korea use A-PBI (9). This could be due to several reasons. First, patient selection is limited, owing to the younger age distribution of breast cancer in South Korea compared to the Western hemisphere (20). In addition, even though many radiation oncologists have sufficient clinical experience in high-precision radiotherapy, they usually feel that it is unnecessary to apply such techniques because of the relatively small breast volumes and favorable clinical outcomes with conventional techniques. The A-PBI trial conducted in Korea, phase I/II KROG (Korean Radiation Oncology Group) 0804 trial has tried to evaluate the technical feasibility of A-PBI with 3D-CRT. As a result, considerably large portion (23.8%) of total patients in this study had major dosimetric goal violations regarding organs at risk largely due to high ratio of PTV to ipsilateral breast volume. The study concluded that A-PBI with 3D-CRT could not be reproduced in Korean breast cancer patients, especially in breasts with small volume, mainly due to major violation in surrounding ipsilateral normal

breast (21). Lastly, but most practically, the KNHI system's reimbursement system, based on fraction number, has been a major obstacle to use of A-PBI.

A-PBI using various techniques have proven to be non-inferior to WBI, but pros and cons regarding each technique have been brought up. Recently, radical advances in IMRT and image guidance have provided a potential breakthrough for A-PBI, as shown in an Italian prospective trial (22). The phase III trial in Italy that compared A-PBI using IMRT to WBI showed non-inferior IBTR, overall survival, and less toxicity in the A-PBI arm. S-PBI, a further developed form of high-precision IMRT, has the potential to circumvent the limitations in Korean women. While A-PBI using conventional IMRT may carry risks owing to respiratory motion uncertainty, the novel high-precision technique of S-PBI addresses this with real-time motion tracking via fiducial markers, allowing minimal PTV margin expansion. This unique technique offers opportunity to offset respiratory uncertainty while maintaining the strength of IMRT. Minimized PTV volume with minimal margin expansion has led to clinical trials on decreased total fractions or increased radiation dose per fraction in early breast cancer. We believe that S-PBI could provide a breakthrough for A-PBI in South Korea.

Our S-PBI was performed after careful patient selection. We considered all available A-PBI guidelines for patient selection. Only 6.2% of total breasts referred for radiotherapy were selected for S-PBI, and none were categorized as "unsuitable" according to the ASTRO guidelines. We were especially cautious when selecting patients aged 45-50 years, the gray zone among different guidelines (13-18). In this age group, only those without any relative contraindications were selected. As a result, despite the young age at which breast cancer frequently occurs in South Korea, as mentioned previously (20), we successfully managed to select the optimal group for S-PBI among Korean women.

We have also shown the technical feasibility of S-PBI in highly selected patients with early breast cancer. S-PBI was highly successful in terms of fiducial utilization, with no tracking failure after the adoption of routine gold fiducial

insertion. All patients deemed eligible for A-PBI successfully underwent the procedure after fiducial insertion. The safety and efficacy of gold fiducial insertion for A-PBI has been well established by the UTSW, whose methods we followed (19). Usage of fiducial markers is also known to increase set-up accuracy compared to set-up based on bony landmarks (23). The treatment time per fraction remained reasonable compared to the UTSW S-PBI study even after meeting strict dosimetric goals (12). Each S-PBI treatment may be relatively longer than that for WBI, but the substantially shortened treatment total fraction ultimately saves both time and costs. Out first attempt at S-PBI in South Korea successfully proved that it is technically feasible in Korean women.

The dosimetric analyses in this study showed that S-PBI with minimal PTV expansion resulted in excellent dosimetric parameters in Korean women. During our initial S-PBI setup, we intended to set dose-volume constraints and define PTV based on the NSABP B-39/RTOG 0413 protocol, which establishes PTV as a uniform 1 cm expansion of CTV. However, we believed that modification of the definition of PTV was necessary, considering poor dosimetric outcomes in the ipsilateral breast in the Korean Radiation Therapy Oncology Group (KROG) 0804 study (21). The KROG 0804 study suggested the PTV/WB to be less than 0.16 in order to avoid major dosimetric deviations. Based on the high precision of S-PBI with successful fiducial tracking, we figured that modification to the PTV definition was in need. In addition, the preference of our surgeons for cavity shave margins over inked margins was considered. The two different policies for adequate margin evaluation are shaved margin from the lumpectomy cavity and inked margin on specimen. In our institution, surgeons prefer the cavity shaved margin to inked margin from the specimen, although the latter is recommended by the Society of Surgical Oncology – ASTRO guidelines (24). Although shaved margin could readily achieve negative margin (25), it inevitably increases the volume of excised breast tissue compared to the inked margin method. Thus, we chose a much smaller PTV definition than that of the NSABP B-39/RTOG 0413 protocol.

As a result, not only were the ipsilateral breast dosimetric goals

successfully satisfied in all breasts in our study, but the median ipsilateral breast $V_{50\%}$ in our study was 35.8%, much lower than that of the KROG study (21). Compared to the Western A-PBI reports (Table 4), the ipsilateral breast $V_{50\%}$ in our patients was as low as those in Western S-PBI studies despite the disadvantage in PTV/WB in our patients due to different ethnic composition (11, 26, 27). On the other hand, the ipsilateral breast $V_{50\%}$ was dramatically lower than those in A-PBI studies using three-dimensional conformal radiation therapy (3D-CRT), ranging from 42% to 49% (28-31). This could be explained by the substantial PTV margin expansion mandated by respiratory and setup uncertainties in 3D-CRT. Likewise, our delicate S-PBI planning achieved consistent dosimetric profiles compared to those observed in Western S-PBI studies in other organs-at-risk, without compromising PTV coverage or creating PTV hot spots (11, 26, 27). These results demonstrated that S-PBI could overcome the disadvantage of relatively small breast volumes in Korean women.

Table 4. Comparison of PTV, PTV-to-whole breast ratio, and irradiated ipsilateral breast volume among published studies of external beam accelerated partial breast irradiation

	PTV volume (mL)	PTV to whole breast ratio (%)	Ipsilateral breast $V_{50\%}$ (%)
Korean studies		Median (range)	
Present study	80.4 (21.4–211.2)	17.0 (5.5–26.0)	35.2 (12.3–52.6)
KROG 0804	108.9	14.8	-
Western studies			
Winthrop/Swedish[b)]	114[a)] (39–241)	-	29/26 (16–39)
Georgetown[b)]	70[a)] (35–142)	-	31 (8–58)
UTSW[b)]	87.4 (36.1–268.9)	9.4	-
Milan[b)]	88.1 (32.3–238.8)	-	29[a)] (20–33)

University of Michigan[c)]	185.8[a)] (59.8–382.0)	-	47.9 (22.7–79.1)
William Beaumont[d)]	268.1[a)] (61.8–623.0)	17[a)]	49 (39–61)
Tufts[d)]	296[a)] (67–950)	18 / 24[a) e)]	42
NYU[d)]	228[a)] (57–1118)	22[a)]	47 (23–75)

PTV, planning target volume; $V_{x\%}$, percentage of volume receiving X% of the prescribed dose; KROG, Korean Radiation Oncology Group; UTSW, University of Texas Southwestern; NYU, New York University; [a)]shown in mean value; [b)]stereotactic partial breast irradiation; [c)]intensity modulated radiation therapy; [d)]3-dimensional conformal radiotherapy; [e)]excellent, good / fair, poor cosmesis, respectively.

Early toxicities after S-PBI were minimal in our study. Although a few grade 1 or 2 palpable indurations due to surgery were observed, most patients did not experience any breast color change or palpable induration immediately after S-PBI. Any minimal color change or palpable induration had mostly recovered by the first follow-up visit. Breast skin thickness is well known for its relationship with palpable induration, and radiotherapy is a well-known cause of thickening (32). In our study, the change in skin thickness after S-PBI appears to be limited to the tumor bed, in contrast to the diffuse skin thickening observed after WBI. These favorable toxicity profiles are comparable to those of the UTSW's identical dose cohort (12). They are also remarkably more favorable than those observed in prospective 3D-CRT A-PBI trials (7, 33, 34). The RTOG 0319 trial, a phase I/II trial of 3D-CRT based A-PBI, reported 7.7% of total patients had grade 3 toxicities. The NSABP-B39/RTOG 0413 trial, a phase III trial of 3D-CRT based A-PBI, reported less than 12% had grade 2 fibrosis-cosmesis and fibrosis-deep connective tissue toxicity rates in early toxicity results. The interim cosmetic and toxicity results of RAPID demonstrated that 3D-CRT based A-PBI increases rates of adverse cosmesis and late grade 1 and 2 toxicity (grade 1 or 2 induration or fibrosis; 50% at 3 years) compared to whole breast irradiation. Although total dose

and fractionation schedules in each study were different, our S-PBI resulted in lower early toxicity rates compared to these studies, despite the disadvantage in breast volume in our patient group. Long term follow-up results from brachytherapy A-PBI trials resulted in lower skin related toxicity rates, but brachytherapy has its inevitable weakness in the potential of hematoma, infection, and experience entry barriers (4-6, 8). In contrast to widespread concerns about hypofractionated radiotherapy in South Korea, S-PBI proved to be safe in terms of early toxicities in Korean women, despite small breast volumes.

Despite these positive findings, the KNHI reimbursement system still acts as a major barrier to S-PBI. The unreasonably low total income from S-PBI compared to WBI would ultimately prevent adoption of any form of A-PBI in Korean hospitals, even with sufficient proof of the technical feasibility and safety of S-PBI. Given the rapid developments in high-precision radiotherapy, the reimbursement system based on fraction size as a new parameter is a solution that should be actively considered (35). This could motivate hospitals to reduce loadings for patients, and ultimately provoke widespread use of A-PBI in Korean women.

Limitations of our study are its retrospective, single-institution nature, the limited number of patients, and the relatively short follow-up period. Longer follow-up may reveal whether these promising dosimetric outcomes and minimal early toxicity would translate into rare late toxicities and excellent cosmesis. However, we firmly believe that our first experience of S-PBI in Korean women will act as a cornerstone for widespread use of A-PBI in this population.

V. CONCLUSION

In conclusion, the first experience of novel S-PBI in Korean women demonstrated that it is a feasible and safe treatment for carefully selected patients with early breast cancer. Despite smaller breast volumes, outstanding dosimetric outcomes and successful fiducial tracking were achieved, with rare early toxicities. Based on this first experience in South Korea, we have initiated a prospective study (NCT03568981) to test S-PBI in terms of cosmesis and quality of life

compared to WBI in early breast cancer.

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APPENDICES

None

ABSTRACT(IN KOREAN)

사이버나이프 M6를 이용한 첨단 방사선치료기술 – 정위적 부분 유방 방사선치료의 저위험 한국 조기 유방암 환자에의 적용과 그 발전

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이 원 희

목적: 대다수의 한국 방사선종양학 의사들은 한국 여성에서의 부분 유방 방사선치료를 실행 불가능한 것으로 여겨왔다. 이는 타인종에 비해 상대적으로 유방 부피가 작고, 첨단 정밀 방사선치료기술에 대한 경험이 부족하기 때문이다. 이를 극복하기 위해 본 기관에서 사이버나이프 M6를 이용한 첨단 방사선치료기술인 정위적 부분 유방 방사선치료를 한국 여성에서 최초로 사용하였고, 본 연구에서 이 치료법의 실행 가능성과 초기 독성을 분석하고자 하였다.

대상 및 방법: 2015년 11월부터 2018년 10월까지 본 기관에서 정위적 부분 유방 방사선치료를 받은 총 132 건을 분석했다. 환자선택은 American Society for Radiation Oncology (ASTRO), American Brachytherapy Society (ABS), American Society of Breast Surgeons (ASBrS), and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) 에서 권고하는 가이드라인을 따랐다. 초기에는 National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413을 따라 34 Gy/10 fx의 선량을 처방하여 매일 치료하였으나, 2017년 3월부터는 NCT01162200에서 사용한

30 Gy/5 fx의 선량을 격일로 처방하였다. 2017년 9월부터는 fiducial로 사용하기 위해 금침 삽입을 매 치료 전에 하였다. 정상 장기에 대한 선량 제한 목표는 NSABP-B39/RTOG 0413의 제한을 따랐다.

결과: 추적관찰의 중위값은 14개월이었다. 환자들의 70.5%는 2017 ASTRO 가이드라인에 따르면 70.5%가 “suitable”로, 29.5%가 “cautionary”로 분류되었다. Fiducial로 금침을 삽입한 이후부터는 기계의 치료시 추적 실패는 없었다. Planning target volume (PTV)의 중위값은 80.4 mL (사분위수, 60.5–108.2 mL) 였으며, PTV와 전체유방의 비의 중위값은 17.0% (13.6–19.0%) 였다. 처방선량의 95% 이상을 받는 PTV 부피, PTV의 최대 점선량, 처방선량의 50% 이상을 받는 동측유방 부피의 중위값은 각각 97.5% (95.6–98.6%), 105.3% (104.2–106.4%), 35.2% (28.5–39.8%) 이었다. 정위적 부분 유방 방사선치료 직후에 2등급 이상의 독성은 3건의 2등급 유방 뭉침 외에는 없었다. 모든 환자들은 현재까지 재발은 없다.

결론: 한국 여성 중 저위험 조기 유방암 환자에서의 최초의 정위적 부분 유방 방사선치료는 실행가능하고 안전한 것으로 나타났다. 이 결과를 바탕으로 본 기관에서는 저위험 조기 유방암 환자에서 전체 유방 방사선치료와 정위적 부분 유방 방사선치료를 비교하는 전향적 연구를 시작하였다.

핵심되는 말 : 정위적 부분 유방 방사선치료, 부분 유방 방사선치료, 유방암, 한국인, 실행가능성, 선량 분포, 초기 독성

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