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Original Article

Assessment of Eligibility and Utilization of Accelerated Partial Breast Irradiation in Korean Breast Cancer Patients (KROG 22-15)

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Purpose We investigated the proportions of patients eligible for accelerated partial breast irradiation (APBI) among those with pT1-2N0 breast cancer, based on the criteria set by the American Society for Radiation Oncology (ASTRO), the Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO), the American Brachytherapy Society (ABS), and the American Society of Breast Surgeons (ASBS). Additionally, we analyzed the rate of APBI utilization among eligible patients.

Materials and Methods Patients diagnosed with pT1-2N0 breast cancer in 2019 were accrued in four tertiary medical centers in Korea. All patients had undergone breast conserving surgery followed by radiotherapy, either whole breast irradiation or APBI. To determine which guideline best predicts the use of APBI in Korea, the F1 score and Matthews correlation coefficient (MCC) were determined for each guideline.

Results A total of 1,251 patients were analyzed, of whom 196 (15.7%) underwent APBI. The percentages of eligible patients identified by the ASTRO, GEC-ESTRO, ABS, and ASBS criteria were 13.7%, 21.0%, 50.5%, and 63.5%, respectively. APBI was used to treat 54.4%, 37.2%, 27.1%, and 23.7% of patients eligible by the ASTRO, GEC-ESTRO, ABS, and ASBS criteria, respectively. The ASTRO guideline exhibited the highest F1 score (0.76) and MCC (0.67), thus showing the best prediction of APBI utilization in Korea.

Conclusion The proportion of Korean breast cancer patients who are candidates for APBI is substantial. The actual rate of APBI utilization among eligible patients may suggest there is a room for risk-stratified optimization in offering radiation therapy.

Key words Early breast cancer, Radiotherapy, Accelerated partial breast irradiation, APBI guidelines

Introduction

The current standard treatment for early breast cancer is breast-conserving surgery (BCS) followed by breast radiotherapy [1,2]. Traditionally, whole breast irradiation (WBI) was administered over 25-28 fractions, taking 5-6 treatment weeks. Moderate hypofractionated regimen reduced the treatment duration to 3-4 weeks. In addition, accelerated partial breast irradiation (APBI) has been a subject of numerous trials to reduce overall treatment time further and the treatment volume as well. Many randomized phase 3 trials have demonstrated the non-inferiority of APBI to WBI in selected low-risk early breast cancer [3-6]. These findings support the adoption of APBI as an alternative treatment option, offering comparable local control and survival [1,2].

Several guidelines seek to determine patient eligibility for APBI [7-10], including those of the American Society for Radiation Oncology (ASTRO), the Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO), the American Brachytherapy Society (ABS), and the American Society of Breast Surgeons (ASBS). The guidelines vary in their specific criteria, but commonly considered factors include age (typically over 45-50 years), negative lymph nodes, negative resection margin, tumor size less than 2 or 3 cm, and no lymphovascular space invasion (LVSI).

The percentages of 'suitable' patients for APBI by the ASTRO guideline were 41.2% and 39.0% of early breast cancer in the studies using Surveillance Epidemiology and End Results (SEER) and National Cancer Database (NCDB),

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respectively [11,12]. However, Korean breast cancer patients are younger at diagnosis than are other breast cancer populations [13]. Furthermore, the small breast size of Korean patients can render APBI challenging and potentially unfeasible [14]. Given the clinical differences between Korean and Western patients, we investigated the proportion of patients eligible for APBI among Korean women with pT1-2N0 invasive breast cancer who underwent BCS, based on the ASTRO, GEC-ESTRO, ABS, and ASBS criteria. Additionally, we derived the rate of APBI utilization among eligible patients.

Materials and Methods

1. Patients

Patients diagnosed with pT1-2N0 breast cancers in 2019 were accrued from four institutions, three of which routinely administer APBI. All patients underwent BCS followed by radiotherapy, either WBI or APBI. Patients with a history of prior breast cancer, thoracic radiotherapy, neoadjuvant chemotherapy, bilateral breast cancer, or distant metastasis at diagnosis were excluded.

2. Guidelines

The ASTRO, GEC-ESTRO, ABS, and ASBS guidelines are summarized in Table 1. These guidelines consider clinicopathologic factors including age, histology, tumor size, resection margin status, LVSI, estrogen receptor status, human epidermal growth factor receptor 2 (HER2) expression, extensive intraductal component (EIC), focality and centricity of the tumor. We classified patients using the criteria shown in Table 1. Notably, EIC is considered only in 'cautionary' factors as an EIC ≤ 3 cm in ASTRO guideline. We considered a total tumor size ≤ 3 cm to be both 'suitable' and 'cautionary'; an EIC was excluded from the 'suitable' group. Additionally, the ABS and ASBS guidelines allowed that patients with focal LVSI are eligible for APBI. However, given certain limitations in the pathological reports, LVSI classifications (focal or extensive) were not available. To ensure consistency and accuracy, we implemented strict criteria; no LVSI was permitted by the ABS and ASBS guidelines.

3. F1 score and Mathews correlation coefficient

To investigate which guideline best predicted APBI use, we derived F1 scores and Matthews correlation coefficients (MCCs) for all guidelines [15]. These metrics predict correlations between binary datasets. We defined the following terms for our analysis. True positive (TP): APBI was performed for patients recommended by the guidelines; True negative (TN): WBI was performed for patients not recommended for APBI; False positive (FP): WBI was performed for patients recommended for APBI; False negative (FN): APBI was performed for patients not recommended for APBI.

The formulae for the F1 score and MCC are as follows:

Table 1. Summary of clinical guidelines for accelerated partial breast irradiation

	ABS	ASBS	ASTRO ('suitable')	ASTRO ('cautionary')	GEC-ESTRO ('low-risk')	GEC-ESTRO ('intermediate-risk')
Age (yr)	≥ 45	≥ 45	≥ 50	≥ 40	> 50	> 40, ≤ 50
Histology	All invasive	All invasive	All invasive, but not ILC	All invasive, including ILC[a]	IDC, mucinous, tubular, medullary, colloid	IDC, ILC, mucinous, tubular, medullary, colloid
Tumor size (cm)	≤ 3 (total)	≤ 3 (total)	≤ 2 (tumor) ≤ 3 (total)	2-3 (tumor)[a] ≤ 3 (total)	≤ 3 (tumor size)	≤ 3 (tumor size)
Lymph node	pN0	pN0	pN0	pN0	pN0	pN0
Margin	Negative	Negative	≥ 2 mm	Close (< 2 mm)[a]	≥ 2 mm	Close (< 2 mm)
LVSI	No	No	No	Yes[a]	No	No
ER	Any	Any	Positive	Negative[a]	Any	Any
HER2	Negative	Any	Any	Any	Any	Any
EIC	Any	Any	No	≤ 3 cm[a]	No	No
Focality	Unifocal	Any	Unifocal	Unifocal[b]	Unifocal	Any

ABS, American Brachytherapy Society; ASBS, American Society of Breast Surgeons; ASTRO, American Society for Radiation Oncology; EIC, extensive intraductal component; ER, estrogen receptor; GEC-ESTRO, Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular invasion. [a]At least one of these factors is required for the ASTRO 'cautionary' classification, [b]Clinically unifocal with a total size of 2.1-3.0 cm.

Table 2. Patient characteristics

Variable	Total patients (n=1,251)	WBI (n=1,055)	APBI (n=196)	p-value
Age (yr)				
< 45	218 (17.4)	216 (20.5)	2 (1.0)	< 0.001
45-50	277 (22.1)	248 (23.5)	29 (14.8)	
> 50	756 (60.4)	591 (56.0)	165 (84.2)	
Laterality				
Left	621 (49.6)	525 (49.8)	96 (49.0)	0.902
Right	630 (50.4)	530 (50.2)	100 (51.0)	
Axillary surgery				
SLNBx	1,222 (97.7)	1,029 (97.5)	193 (98.5)	0.499
ALND	25 (2.0)	23 (2.2)	2 (1.0)	
Not done	4 (0.3)	3 (0.3)	1 (0.5)	
Histology				
IDC	1,155 (92.3)	982 (93.1)	173 (88.3)	< 0.001
ILC	44 (3.5)	40 (3.8)	4 (2.0)	
Others	52 (4.2)	33 (3.1)	19 (9.7)	
Size (invasive tumor only) (cm)				
≤ 2	973 (77.8)	794 (75.3)	179 (91.3)	< 0.001
> 2 and ≤ 3	234 (18.7)	218 (20.7)	16 (8.2)	
> 3	44 (3.5)	43 (4.1)	1 (0.5)	
Size (including DCIS) (cm)				
≤ 2	788 (63.0)	620 (58.8)	168 (85.7)	< 0.001
> 2 and ≤ 3	307 (24.5)	282 (26.7)	25 (12.8)	
> 3	156 (12.5)	153 (14.5)	3 (1.5)	
EIC				
Positive	322 (25.7)	294 (27.9)	28 (14.3)	< 0.001
Negative	883 (70.6)	727 (68.9)	156 (79.6)	
N/A	46 (3.7)	34 (3.2)	12 (6.1)	
Focality				
Unifocal	1,082 (86.5)	902 (85.5)	180 (91.8)	0.023
Multifocal	169 (13.5)	153 (14.5)	16 (8.2)	
Centricity				
Unicentric	1,245 (99.5)	1,049 (99.4)	196 (100)	0.620
Multicentric	6 (0.5)	6 (0.6)	0	
Resection margin				
Positive	74 (5.9)	73 (6.9)	1 (0.5)	< 0.001
Close (< 2 mm)	436 (34.9)	404 (38.3)	32 (16.3)	
Negative (≥ 2 mm)	615 (49.2)	495 (46.9)	120 (61.2)	
N/A[a)]	126 (10.1)	83 (7.9)	43 (21.9)	
LVSI				
Positive	129 (10.3)	127 (12.0)	2 (1.0)	< 0.001
Negative	1,122 (89.7)	928 (88.0)	194 (99.0)	
ER status				
Positive	1,000 (79.9)	806 (76.4)	194 (99.0)	< 0.001
Negative	251 (20.1)	249 (23.6)	2 (1.0)	
HER2 status				
Positive	153 (12.2)	151 (14.3)	2 (1.0)	< 0.001
Negative	1,097 (87.7)	903 (85.6)	194 (99.0)	
N/A	1 (0.1)	1 (0.1)	0	

(Continued to the next page)

Table 2. Continued

Variable	Total patients (n=1,251)	WBI (n=1,055)	APBI (n=196)	p-value
Ki-67 (%)				
< 20	803 (64.2)	622 (59.0)	181 (92.3)	< 0.001
≥ 20	445 (35.6)	430 (40.8)	15 (7.7)	
N/A	3 (0.2)	3 (0.3)	0	
Adjuvant chemotherapy				
Yes	426 (34.1)	409 (38.8)	17 (8.7)	< 0.001
No	825 (65.9)	646 (61.2)	179 (91.3)	
Adjuvant endocrine therapy				
Yes (TMX)	535 (42.8)	481 (45.6)	54 (27.6)	< 0.001
Yes (AI)	421 (33.7)	311 (29.5)	110 (56.1)	
No	295 (23.6)	263 (24.9)	32 (16.3)	

Values are presented as number (%). AI, aromatase inhibitor; ALND, axillary lymph node dissection; APBI, accelerated partial breast irradiation; DCIS, ductal carcinoma *in situ*; EIC, extensive intraductal component; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular space invasion; N/A, not available; SLNBx, sentinel lymph node biopsy; TMX, tamoxifen; WBI, whole breast irradiation. [a]Resection margin status was negative, but safety margin width unknown.

$$\text{F1 score}=\frac{2*TP}{2*TP+FP+FN}$$

$$\text{MCC}=\frac{TP*TN-FP*FN}{\sqrt{(TP+FP)*(TP+FN)*(TN+FP)*(TN+FN)}}$$

The F1 score ranges from 0 to 1. A score of 0 indicates that the TP rate is 0, reflecting misclassification of all positive samples. Conversely, a score of 1 indicates FP and FN rates of 0, i.e., perfect classification. The MCC ranges from −1 to 1, where −1 indicates TP and TN rates of 0, i.e., perfect misclassification, and 1 indicates FP and FN values of 0, i.e., perfect classification. A value of 0 suggests randomness, akin to coin tossing. Higher values of both metrics indicate strong correlations between predictions and reality.

In this analysis, we excluded the ASTRO 'cautionary' group and the GEC-ESTRO 'intermediate-risk' group because F1 score and MCC are used to evaluate 2×2 datasets, and the ASTRO 'cautionary' and GEC-ESTRO 'intermediate-risk' groups lack explicit recommendations regarding the use of APBI. As one institution did not routinely offer APBI, this analysis employed only data from the other three institutions that routinely offer APBI.

Results

A total of 1,251 patients were accrued, of whom 196 (15.7%) received APBI. The dose-fractionation schedules of the three institutions that routinely offer APBI differed: 30 Gy/5fx, 38.5 Gy/10fx, and 40 Gy/10fx. All three institutions employed external beam APBI: magnetic resonance-guided radiotherapy in one, intensity-modulated radiotherapy (IMRT) in another, and the CyberKnife system in the third. The median patient age was 53 years; 60.4% of patients were older than 50 years. The proportion of pT1 tumors was 77.8%; 3.5% of patients had invasive tumors of diameter > 3 cm. Age and tumor size were the principal factors used to choose between WBI and APBI. In addition, the resection margin, LVSI, estrogen receptor, HER2, adjuvant chemotherapy, and endocrine therapy statuses differed between the WBI and APBI patients. The patient characteristics are summarized in Table 2.

In terms of APBI eligibility, 13.7%, 21.0%, 50.5%, and 63.5% of patients were eligible according to the ASTRO, GEC-ESTRO, ABS, and ASBS guidelines, respectively. Of these patients, the proportions who underwent APBI were 54.4%, 37.2%, 27.1%, and 23.7%, respectively. Table 3 summarizes the percentages of eligible patients according to each guideline. APBI was delivered to 10.2% of patients in the ASTRO 'cautionary' group and to 2.1% in the 'unsuitable' group. For the GEC-ESTRO guideline, 8.6% of patients underwent APBI in the intermediate-risk group and 5.9% in the high-risk group. The risk factors for 'unsuitable' patients by the ASTRO guideline who received APBI were a total tumor size > 3 cm (n=3), a positive resection margin (n=1), and tumor multifocality (n=4).

Korean radiation oncologists prefer the ASTRO guideline to the others. The F1 score and MCC were higher for the ASTRO guideline (0.76 and 0.67, respectively) than for the GEC-ESTRO (0.56 and 0.38), ABS (0.54 and 0.37), and ASBS (0.50 and 0.34) guidelines (Fig. 1).

Table 3. Proportions of patients eligible for accelerated partial breast irradiation according to each guideline

Criteria	Total patients (n=1,251)	WBI (n=1,055)	APBI (n=196)	Actual APBI rates
ASTRO[a]				
Suitable	158 (13.7)	72 (7.2)	86 (55.1)	86/158 (54.4)
Cautionary	610 (52.9)	548 (54.9)	62 (39.7)	62/610 (10.2)
Unsuitable	386 (33.4)	378 (37.9)	8 (5.1)	8/386 (2.1)
GEC-ESTRO[a]				
Low-risk	242 (21.0)	152 (15.2)	90 (58.4)	90/242 (37.2)
Intermediate-risk	385 (33.3)	352 (35.2)	33 (21.4)	33/385 (8.6)
High-risk	527 (45.7)	496 (49.6)	31 (20.1)	31/527 (5.9)
ABS				
Acceptable	632 (50.5)	461 (43.7)	171 (87.2)	171/632 (27.1)
Unacceptable	619 (49.5)	594 (56.3)	25 (12.8)	25/619 (4.0)
ASBS				
Recommended	794 (63.5)	606 (57.4)	188 (95.9)	188/794 (23.7)
Not recommended	457 (36.5)	449 (42.6)	8 (4.1)	8/457 (1.8)

Values are presented as number (%). ABS, American Brachytherapy Society; APBI, accelerated partial breast irradiation; ASBS, American Society of Breast Surgeons; ASTRO, American Society for Radiation Oncology; GEC-ESTRO, Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology; WBI, whole breast irradiation. [a]Using only the available data.

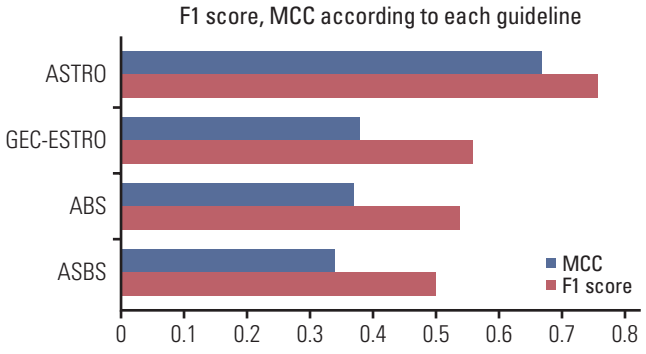

Fig. 1. The F1 score and Matthew Correlation Coefficient to each guideline. ABS, American Brachytherapy Society; ASBS, American Society of Breast Surgeons; ASTRO, American Society for Radiation Oncology; GEC-ESTRO, Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology; MCC, Matthew correlation coefficient.

Discussion

In this study, we evaluated the eligibility for APBI per international guidelines in Korean patients with early breast cancer. Although we have shown that substantial proportions are eligible for APBI, the actual utilization rate of APBI remains low, which implies the potential room for additional APBI.

Multiple phase 3 randomized trials have demonstrated the non-inferiority of APBI in terms of oncological outcomes [3-6]. In the RAPID trial, external beam APBI was delivered at 38.5 Gy/10fx twice daily [3]. Although the 8-year ipsilateral breast tumor recurrence (IBTR) rates of APBI and WBI were similar (3.0% and 2.8% respectively), adverse late events and poor cosmesis were observed more frequently in the APBI group, potentially attributable to the twice-daily treatment regimen. The largest randomized trial was the NSABP B-39/RTOG 0413 trial of 4,216 patients [4]; the absolute difference in the 10-year IBTR rates between APBI and WBI was 0.7%. Although that study failed to meet the non-inferiority criteria, the absolute difference was very small, and the adverse event rates were similar between the two groups. The GEC-ESTRO trial, which utilized multi-catheter brachytherapy for APBI, reported the difference in the 10-year local recurrence rates between APBI and WBI was 1.93%, which was statistically insignificant [5]. APBI patients reported significantly better subjective cosmetic outcomes. The Florence trial enrolled 520 patients treated at a single institution with external beam APBI at 30 Gy/5fx [6]. The difference in the 10-year IBTR rate was insignificant (1.2%), and less toxicity and better cosmesis were reported in the APBI arm. Together, the data show that APBI affords oncological outcomes that are not inferior to those of WBI in select patients with low-risk early breast cancer. The adverse events and cosmetic outcomes are similar, although the former vary by the treatment technique and the dose-fractionation regimen employed.

The proportions of patients eligible for APBI were reported using both population- and hospital-based databases from the United States [11,12]; the SEER and NCDB studies indicated that 74.6% and 72.5% of patients, respectively, were eligible using the ABS guideline. The proportion in our study

(50.5%) was lower, reflecting the updated ABS risk factors such as unifocality and HER2 status. However, the proportions of patients eligible according to the ASTRO and GEC-ESTRO guidelines differed significantly. The proportions of 'suitable' patients according to the ASTRO guideline were 41.2% and 39.0% in the SEER and NCDB studies, respectively. The SEER and NCDB studies found that the proportions of low-risk patients according to the GEC-ESTRO guideline were 74.6% and 45.7%, respectively. These substantial differences between the SEER and NCDB studies can be attributed to variations in age criteria, resection margin status, and the prevalence of LVSI. Additionally, the corresponding figures were even lower, 13.7% for ASTRO 'suitable' and 21.0% for GEC-ESTRO 'low-risk' group in this study, reflecting both population differences (pT1-2N0 patients in the SEER study, pN0 patients > 40 years of age in the NCDB study, and pT1-2N0 patients in this study) and pathological features that were not evaluated in the SEER and NCDB studies. Additionally, the ASTRO and ABS guidelines were revised in 2016 and 2022, respectively. The updates in these guidelines involve changes in age criteria and LVSI, which could potentially account for differences in the proportion of eligible patients. In fact, adverse pathological findings such as EIC, LVSI, and close resection margins were evident in upto 40% of patients, resulting in a lower than expected proportion of 'suitable' patients according to the ASTRO criteria. As adverse features were substantial according to this study, comprehensive evaluation of pathological features should be done for determining eligibility of APBI.

The resection margin status critically affects the locoregional recurrence of breast cancer patients [16,17]. All APBI guidelines emphasize the importance of a negative resection margin; two guidelines recommend a safety margin ≥ 2 mm [7-10]. However, several studies reported that positive superficial or deep resection margins did not significantly impact the local recurrence rate [18-20]. The policies of our participating institutions in terms of surgical resection depth varied. Thus, the proportions of positive or close superficial/deep resection margins differed across the institutions (S1 Table). As the current APBI guidelines do not distinguish superficial/deep margins from parenchymal resection margins, the APBI eligibility rates also varied across the institutions. However, when assuming the superficial and deep resection margins were negligible, the institutional eligibility rates were comparable (S2 Table). As cosmetic outcomes become of more concern, it is likely that more patients will exhibit positive or close superficial/deep margins. Thus, future guidelines should address marginal status when defining eligibility.

As evidence on long-term treatment outcomes accumulates, APBI use is increasing. A recent survey of Korean radiation oncologists reported that 17% offered APBI to treat early breast cancer in 2022, higher than the 2017 figure of only 5% [21]. Additionally, they have reported that more than half of respondents (7 out of 12) followed ASTRO guideline. We found that F1 score and MCC were the highest in ASTRO guideline, implying that the actual practice of APBI has a strong correlation with ASTRO guideline, consistent with the survey data. Several Korean APBI studies have been published [22,23]. Lee et al. [22] compared APBI with hypofractionated WBI for patients who were 'suitable' according to the ASTRO guideline. Although no significant difference in the oncological outcome was apparent between the two arms, APBI reduced acute and late toxicities. In a prospective cohort study, Byun et al. [23] compared APBI and WBI for patients with early breast cancer; APBI was associated with significantly lower fibrosis of the uninvolved breast quadrant at both 6 and 12 months compared with WBI.

Although APBI utilization has increased, it remains low [24]. The possible explanations include the small breast size of Korean women and reimbursement issues. One prospective Korean study found that during APBI planning using a three-dimensional conformal technique, 57.1% of patients exhibited variations from the dose constraints of the RTOG 0319 protocol, primarily attributable to higher doses to the ipsilateral breast or organs at risk [14]. Additionally, half of ipsilateral breast had dose more than 50% of prescribed dose (V50) in 9.5% of patients and the median V50 for the ipsilateral breast was 41.9%. Another Korean study reported similar findings; the mean V50 for the ipsilateral breast was 50.3% after IMRT planning [25]. Another important factor contributing to the low utilization of APBI comes from the reimbursement issue. Korean facilities are typically reimbursed by the number of treatment fractions. Conventional radiotherapy is delivered in 25-28 fractions, moderate hypofractionated radiotherapy in 15-20 fractions, and APBI in 5-10 fractions. Consequently, facilities receive lower reimbursement for APBI due to the reduced number of treatment fractions. Thus, appropriate compensation for APBI treatment should be considered to reduce gap between the guidelines and the actual use of APBI.

One of the weaknesses of this study lies in the limited institutions which do not represent whole breast cancer patients in Korea. Additionally, some pathologic features such as LVSI and resection margin status were unavailable in some patients due to the retrospective nature of our study. Despite these limitations, we comprehensively investigated the clinicopathologic factors of all guidelines when categorizing our patients and reported APBI utilization according to each set of guidelines.

In conclusion, we report a substantial proportion of early breast cancer is eligible for APBI in Korea. However, current

actual utilization of APBI is relatively low, suggesting a room for risk-stratified optimization in offering radiation therapy for breast cancer.

Electronic Supplementary Material

Supplementary materials are available at the Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2301-164-1403), and the need for informed consent was waived.

Author Contributions

Conceived and designed the analysis: Kim K, Shin KH.
Collected the data: Chun SJ, Jo JH, Kim YB, Park S, Ahn SJ, Kim SS, Shin KH.
Contributed data or analysis tools: Chun SJ, Kim K, Shin KH.
Performed the analysis: Chun SJ, Kim K.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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