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Breast Cancer

Increased Risk for Ipsilateral Breast Tumor Recurrence in Invasive Lobular Carcinoma after Accelerated Partial Breast Irradiation Brachytherapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer • Accelerated partial breast irradiation • Brachytherapy • Radiation • Breast conserving therapy

Abstract

Background. The suitability criteria for accelerated partial breast irradiation (APBI) from the American Brachytherapy Society (ABS), American Society for Radiation Oncology (ASTRO), and The Groupe Européende Curiethérapie European SocieTy for Radiotherapy & Oncology (GEC-ESTRO) have significant differences.

Materials and Methods. This is a single institution retrospective review of 946 consecutive patients with invasive breast cancer who underwent lumpectomy and APBI intracavitary brachytherapy from 2003 to 2018. Overall survival (OS), breast cancer-specific survival (BCSS), relapse-free survival (RFS), and ipsilateral breast tumor recurrence (IBTR) were estimated with Kaplan-Meier method.

Results. Median follow-up time was 60.2 months. Median age was 68 years (46–94 years). The majority of patients had estrogen receptor (ER)–positive disease (94%). There were 821 (87%) cases of invasive ductal carcinoma and 68 cases (7%) of invasive lobular carcinoma (ILC). The 5-year OS, BCSS, RFS, and IBTR were 93%, 99%, 90%, and 1.5%, respectively. Upon univariate analysis, ILC (hazard ratio [HR], 4.6; $p = .008$) and lack of nodal evaluation (HR, 6.9; $p = .01$) were risk factors for IBTR. The 10-year IBTR was 2.5% for IDC and 14% for ILC. While the ABS and ASTRO criteria could not predict IBTR, the GEC-ESTRO intermediate risk group was associated with inferior IBTR ($p = .04$) when compared to both low risk and high risk groups. None of the suitability criteria was able to predict RFS.

Conclusion. These results show that APBI is an effective treatment for patients with invasive breast cancer. Expansion of the current eligibility criteria should be considered, although prospective validation is needed. Caution is required when considering APBI for patients with ILC. ***The Oncologist*** 2021;26:e1931–e1938

Implications for Practice: In a large retrospective review of 946 patients with early breast cancer treated with partial mastectomy and accelerated partial breast irradiation (APBI) intracavitary brachytherapy, this study demonstrates durable local control. Patients deemed unsuitable or high risk by the American Brachytherapy Society, American Society for Radiation Oncology, and European Society for Radiotherapy and Oncology guidelines were not at increased risk for ipsilateral breast tumor recurrence (IBTR), suggesting that expansion of the current criteria should be considered. Importantly, however, these results demonstrate that caution should be taken when considering APBI for patients with invasive lobular carcinoma, as these patients had relatively high risk for IBTR (10-year IBTR, 14%).

Introduction

Breast conservation therapy with partial mastectomy and whole breast irradiation (WBI) provides many early-stage patients with outcomes similar to radical mastectomy [1, 2]. However, in select cases the entire breast may not require

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Table 1. APBI suitability criteria for patients with invasive breast cancer

		ASTRO			GEC-ESTRO		
Risk Factor	**ABS, Suitable**	**Suitable**	**Cautionary**	**Unsuitable**	**Low risk**	**Intermediate risk**	**High risk**
Age, yr	≥45	≥50	40–49[a]	<40	>50	40–50	≤40
Size, cm	≤3	≤2	2.1–3	>3	≤3	≤3	>3
Margins	≥2 mm	≥2 mm	<2 mm	Positive	≥2 mm	<2 mm	Positive
Histology			ILC			ILC	
Hormone status		ER-positive	ER-negative				
LVSI	Not present	Not present	Limited/Focal		Not present	Not present	Present
EIC		–	≤3 cm	>3 cm	Not present	Not present	Present
Focality		Clinically unifocal, ≤2 cm total	Clinically unifocal, total size 2.1–3 cm	Multifocal, >3 cm	Unifocal	Multifocal, ≤2 cm	Multifocal, >2 cm
Centricity		Unicentric		Multicentric	Unicentric		Multicentric
Nodal status	pN0	pN0		≥ pN1	pN0	pN1mi, pN1a[b]	≥ pN2a, pNx

[a]If all other criteria for suitable are met. Age ≥ 50 years if any of the cautionary factors are present.
[b]Confirmed by axillary lymph node dissection.
Abbreviations: ABS, American Brachytherapy Society; ASTRO, American Society for Radiation Oncology; EIC, extensive intraductal component; ER, estrogen receptor; GEC-ESTRO, The Groupe Européende Curiethérapie - European SocieTy for Radiotherapy & Oncology; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular space invasion.

radiation, but rather only the tumor cavity and surrounding breast tissue at highest risk for recurrence [3]. This has led to the advent of accelerated partial breast irradiation (APBI), a targeted approach that reduces the volume of irradiated breast tissue with the potential to minimize toxicity without increasing the risk of ipsilateral breast tumor recurrence (IBTR). APBI can be delivered via different techniques, including multicatheter interstitial brachytherapy, balloon-based brachytherapy, and external beam radiotherapy (EBRT) [4, 5]. There is a strong body of evidence that supports the use of APBI over WBI in select populations, as it has been demonstrated to have less acute toxicity, better cosmetic outcomes, and similar quality of life [6–9]. The long-term results of RTOG 0413 and the Florence Trial are promising, with favorable toxicity profiles and a low 10-year cumulative incidence of IBTR (3.7%–4.6%) after APBI [10, 11].

Given the targeted approach to therapy, optimal patient selection is crucial for APBI to ensure a low risk of IBTR. Three prominent governing bodies, the American Brachytherapy Society (ABS), the American Society for Radiation Oncology (ASTRO), and Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy Oncology (GEC-ESTRO), have published guidelines delineating the appropriate patient population who will benefit from APBI treatment (Table 1) [12–14]. Although all three guidelines use similar patient and tumor features to identify a subpopulation at low risk for IBTR, there remain important differences. Invasive lobular carcinoma (ILC) subtype, for example, is an intermediate risk factor per GEC-ESTRO guidelines and a cautionary factor per ASTRO guidelines, but is not taken into consideration per ABS guidelines. Similarly, whereas the ABS and GEC-ESTRO guidelines do not include estrogen receptor (ER) status, ASTRO deems ER-negative patients cautionary for APBI.

Given the importance of careful patient selection for APBI and the significant discrepancies within the suitability guidelines, the purpose of this study is to assess these guidelines using a single institutional experience with APBI intracavitary brachytherapy in treating invasive breast cancer.

Materials and Methods

Study Design

This is a retrospective review of 946 patients with invasive breast cancer treated with partial mastectomy followed by APBI intracavitary brachytherapy high dose rate (HDR) from 2003 to 2018. This study was approved by the institutional review board. Women with pathologic confirmation of invasive breast cancer and clinically node-negative, clinically unicentric, and clinically unifocal disease met the inclusion criteria. Of note, the vast majority of cases lacked pathologic details of the extent of extensive intraductal component (EIC) and lymphovascular space invasion (LVSI); the presence of either feature was considered to be a cautionary or high-risk factor by ASTRO and GEC-ESTRO criteria, respectively (Table 1). In addition, cases without surgical lymph node evaluation were considered to be high risk by GEC-ESTRO criteria but were not classified by ASTRO criteria.

Treatment Details

Patients underwent partial mastectomy and placement of a cavity evaluation device (CED). Once final pathology was determined, the partial breast intracavitary applicator was placed. The intracavitary brachytherapy devices used included single-lumen and multi-lumen Mammosite (Hologic Inc., Marlborough, MA), Contura (Hologic Inc., Marlborough, MA), and SAVI (Cianna Medical, Aliso Viejo, CA.). Each patient was treated with Ir-192 HDR unit with a prescription of 340 cGy per fraction to 1 cm from the applicator surface for 10 fractions occurring twice per day, with each fraction separated by at least 6 hours each day.

Table 2. Patient, tumor, and treatment characteristics ($n = 946$)

Characteristic	Entire cohort ($n = 946$), *n* (%)	Cases of IBTR ($n = 18$), *n* (% with IBTR)
Age at treatment, median (range)	68 (46–94)	
≥50 years	932 (98.5)	16 (1.7)
<50 years	14 (1.5)	2 (7.4)
Menopausal status		
Premenopausal	10 (1.1)	0 (0)
Postmenopausal	936 (98.9)	18 (1.9)
Laterality		
Right	450 (47.6)	6 (1.3)
Left	496 (52.4)	12 (2.4)
Histology		
IDC	821 (86.8)	12 (1.5)
ILC	68 (7.2)	4 (5.9)
Other	57 (6.0)	2 (3.5)
Tumor size, median (range) cm	1.1 (0.07–3.5)	
≤3cm	942 (99.7)	18 (1.9)
>3cm	3 (0.3)	0 (0)
Nodal Stage		
pNx	15 (1.6)	2 (13.3)
pN0	927 (97.9)	16 (1.7)
pN1	3 (0.3)	0 (0)
pN2	1 (0.1)	0 (0)
Grade		
1	372 (39.3)	3 (0.8)
2	424 (44.8)	10 (2.4)
3	148 (15.6)	5 (3.4)
Unknown	2 (0.2)	0 (0)
Multifocal	13 (1.4)	0 (0)
LVSI	43 (4.6)	1 (2.3)
EIC	128 (15.9)	0 (0)
Hormone status		
ER+	887 (93.8)	17 (1.9)
ER−	59 (6.2)	1 (1.7)
PR+	783 (82.8)	13 (1.7)
PR−	163 (17.2)	5 (3.1)
Receptor subtype		
HR+/HER2−	797 (84.3)	14 (1.8)
HR+/HER2+	40 (4.2)	3 (7.5)
HR−/HER2+	9 (1.0)	0 (0)
HR−/HER2−	39 (4.1)	1 (2.6)
Unknown	61 (6.5)	0 (0)
Margin status		
≥2 mm	752 (79.5)	12 (1.6)
<2 mm	71 (7.5)	3 (4.2)
Negative, NOS	37 (3.9)	0 (0)
Positive	52 (5.5)	1 (1.9)
Unknown	34 (3.6)	2 (5.9)
APBI device		
SAVI	207 (21.9)	0 (0)
Mammosite	153 (16.2)	8 (5.2)
Mammosite ML	275 (29.1)	1 (3.6)
Contura	210 (22.2)	2 (1.0)
Unknown	6 (0.6)	3 (50.0)
Chemotherapy	110 (11.6)	6 (5.5)
Endocrine therapy		
Patients prescribed endocrine therapy	753 (79.6)	14 (1.9)
Confirmed adherence for 5 years	153 (38.9)	2 (1.3)

Abbreviations: APBI, accelerated partial breast irradiation; EIC, extensive intraductal component; ER, estrogen receptor; HR, hormone receptor; IBTR, ipsilateral breast tumor recurrence; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular space invasion; PR, progesterone receptor; ML, multilumen; NOS, not otherwise specified.

Statistical Analysis

Clinical features were summarized using descriptive statistics. Primary outcomes, including overall survival (OS), breast cancer-specific survival (BCSS), IBTR, and relapse-free survival (RFS), were measured from the time of APBI and estimated with the Kaplan-Meier method, with the log-rank test to test differences in IBTR and RFS by suitability criteria. BCSS accounted only for breast cancer–related deaths, whereas OS accounted for death of any cause. Recurrence in any quadrant of the treated breast was considered an event for IBTR. Failure in the treated breast, contralateral breast, regional lymph nodes, distant regions, or death from any cause were considered events when calculating RFS. The Cox proportional-hazards model was used for univariate analysis of IBTR and RFS. Two-tailed p values <.05 were considered to indicate statistical significance. Statistical analyses were performed using JMP 15 (SAS Institute Inc., Cary, NC).

Results

Patient, Tumor, and Treatment Characteristics

The median age at the time of APBI was 68 years (Table 2). The majority of cases were ER-positive (94%), progesterone receptor (PR)–positive (83%), and HER2-receptor negative (88%). There were 821 patients (87%) with invasive ductal carcinoma and 68 patients (7%) with ILC. A minority of patients (12%) were prescribed adjuvant chemotherapy. The majority (80%) of patients were prescribed endocrine therapy, and of those with adequate follow up ($n = 393$), 153 patients (38.9%) had confirmed adherence to endocrine therapy for 5 years.

There were 852, 862, and 882 patients with adequate clinicopathologic details for suitability determination by the ABS, ASTRO, and GEC-ESTRO guidelines, respectively (Table 3).

Table 3. Outcomes by suitability criteria

Guideline	*n* (%)	5-year IBTR, %	*p* value	5-year RFS, %	*p* value
ABS ($n = 852$)			.185		.155
Suitable	693 (81.3)	1.3		96.8	
Unsuitable	159 (18.7)	2.8		91.0	
ASTRO ($n = 862$)			.693		.591
Suitable	465 (53.9)	1.3		90.8	
Cautionary	339 (39.3)	1.8		88.7	
Unsuitable	58 (6.7)	2.0		91.5	
GEC-ESTRO ($n = 882$)			.038		.537
Low risk	524 (59.4)	0.9		90.4	
Intermediate risk	136 (15.4)	4.6		87.4	
High risk	222 (25.2)	1.1		90.9	

Abbreviations: ABS, American Brachytherapy Society; ASTRO, American Society for Radiation Oncology; GEC-ESTRO, European Society for Radiotherapy & Oncology; IBTR, ipsilateral breast tumor recurrence; RFS, relapse-free survival.

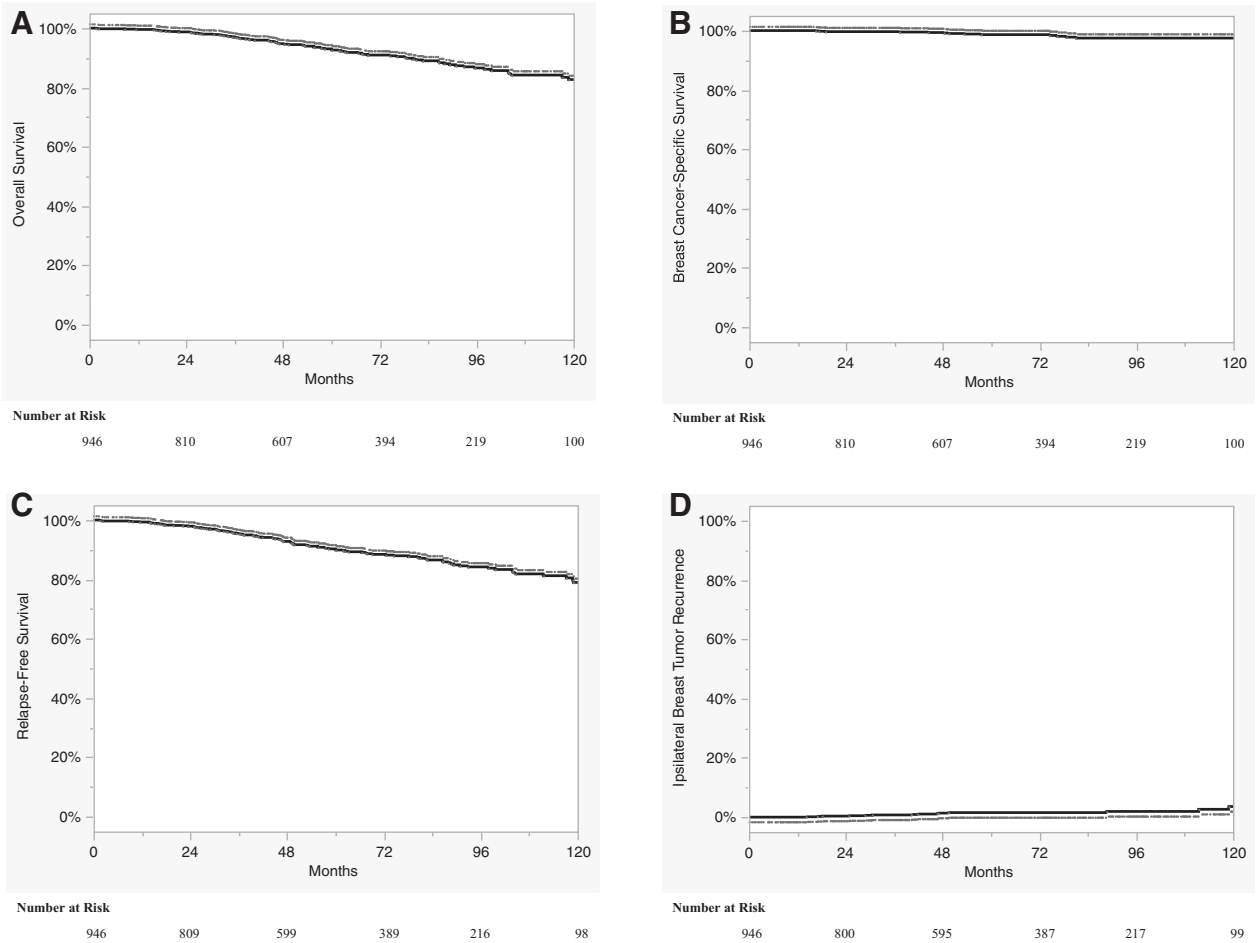


Figure 1. Kaplan-Meier curve depicting the overall survival **(A)**, breast cancer–specific survival **(B)**, relapse-free survival **(C)**, and ipsilateral breast tumor recurrence **(D)** for the entire cohort.

By the ABS criteria, 693 (81%) patients were deemed suitable. By the ASTRO criteria, 465 (54%), 339 (39%), and 58 (7%) were deemed suitable, cautionary, and unsuitable, respectively. By the GEC-ESTRO criteria, 524 (59%), 136 (15%), and 222 (25%) were deemed low risk, intermediate risk, and high risk, respectively.

Clinical Outcomes

The median follow up from the end of APBI was 60.2 months (interquartile range: 36.2–94.2 months). For the entire cohort, the 10-year OS (Fig. 1A), BCSS (Fig. 1B), RFS (Fig. 1C), and IBTR (Fig. 1D) were 82.7%, 97.5%, 79.0%, and 3.6%, respectively. A single patient underwent mastectomy after developing IBTR.

Table 4. Univariate analysis for ipsilateral breast tumor recurrence and relapse-free survival

	IBTR		RFS	
Characteristic	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age				
≥50 years (reference)	1.00		1.00	
<50 years		.999		.999
Size				
≤3 cm (reference)	1.00		1.00	
>3 cm		.999		.999
Margin				
≥2 mm (reference)	1.00		1.00	
<2 mm	2.09 (0.58–7.46)	.258	1.91 (1.10–3.32)	.023
Positive	1.42 (0.18–11.0)	.738	0.81 (0.30–2.22)	.688
Histology				
IDC (reference)	1.00		1.00	
ILC	4.62 (1.49–14.4)	.008	1.51 (0.79–2.91)	.212
Other	2.70 (0.60–12.1)	.194	0.69 (0.25–1.87)	.461
ER status				
Positive (reference)	1.00		1.00	
Negative	0.71 (0.09–5.38)	.743	1.08 (0.55–2.14)	.824
Grade				
1 (reference)	1.00		1.00	
2	2.94 (0.81–10.7)	.101	1.26 (0.83–1.92)	.278
3	3.86 (0.92–16.2)	.065	1.30 (0.76–2.24)	.340
LVSI				
Absent (reference)	1.00		1.00	
Present	0.89 (0.12–6.73)	.907	0.80 (0.33–1.97)	.632
EIC				
Absent (reference)	1.00		1.00	
Present		.999	0.98 (0.49–1.98)	.959
Focality				
Unifocal (reference)	1.00		1.00	
Multifocal		.999		.999
Nodal status				
pN0 (reference)	1.00		1.00	
pN1		.999		.999
pNx	6.85 (1.56–30.0)	.011	1.45 (0.46–4.57)	.525

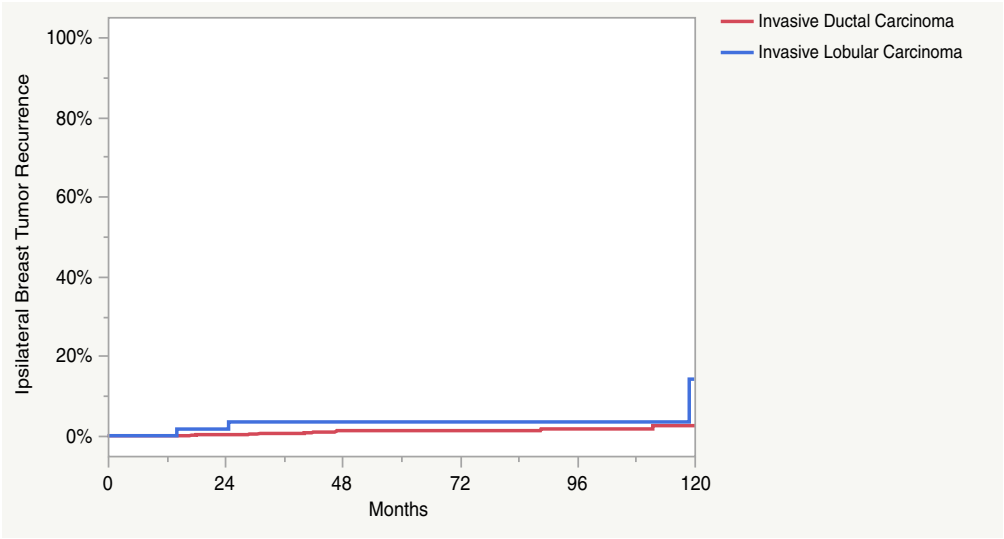
Abbreviations: CI, confidence interval; EIC, extensive intraductal carcinoma; ER, estrogen receptor; HR, hazard ratio; IBTR, ipsilateral breast tumor recurrence; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular space invasion; RFS, relapse-free survival.

The ABS, ASTRO, and GEC-ESTRO suitability criteria failed to significantly predict RFS (Table 3). The ABS and ASTRO criteria were also unable to predict IBTR. Cases deemed intermediate risk by the GEC-ESTRO criteria had a significantly higher risk of IBTR (10-year IBTR 9.2%; $p = .038$).

Upon univariate analysis, invasive lobular carcinoma (hazard ratio [HR], 4.6; $p = .008$) and the absence of nodal evaluation (HR, 6.9; $p = .011$) were associated with higher rates of IBTR (Table 4). The 5- and 10-year IBTR for IDC were 1.3% and 2.5%, respectively (Fig. 2). The 5- and 10-year IBTR for ILC were 3.5% and 14%, respectively. Of the 68 cases of ILC, 54 (78%) had magnetic resonance imaging (MRI) prior to surgery, and all 4 cases of ILC that developed IBTR had MRI prior to surgery. Close margin status (<2 mm) was the only significant risk factor for poor RFS (HR, 1.9; $p = .023$).

Toxicity

There were 211 (22%) cases of postoperative seroma, 25 (3%) cases of postoperative infection, and 128 (14%) cases complicated by fat necrosis. There were higher rates of seroma with multilumen Mammosite (37%) and Contura (28%) devices when compared with other APBI devices ($p < .001$). There were higher rates of fat necrosis with multilumen Mammosite (29%) and single lumen Mammosite (25%) when compared



Number at Risk

Invasive Ductal Carcinoma	821	697	527	344	195	87
Invasive Lobular Carcinoma	68	56	38	23	14	8

Figure 2. Kaplan Meier curve depicting the ipsilateral breast tumor recurrence for patients with invasive ductal carcinoma and for patients with invasive lobular carcinoma.

with other APBI devices ($p = .04$). The rates of infection did not differ by APBI device ($p = .835$).

Discussion

APBI provides a promising alternative for breast conservation therapy, with multiple clinical trials demonstrating decreased toxicity, improved cosmesis, and comparable local control to WBI [6–9]. However, the inclusion criteria for these trials were highly variable, and significant heterogeneity exists in patient selection criteria recommended by ASTRO, GEC-ESTRO, and ABS (Table 1). The present study is an attempt to add to the existing literature in determining the most appropriate guidelines for APBI patient selection.

We demonstrate effective and durable local control after APBI with 10-year IBTR of 3.6% (Fig. 1D), similar to the long-term results of recent clinical trials (10-year IBTR, 3.7%–5.9%) [10, 11, 15]. The Budapest phase III trial, which randomized patients to WBI and multicatheter interstitial brachytherapy APBI, demonstrated no significant difference in 10-year local recurrence (5.9% vs. 5.1%), with APBI associated with more favorable cosmetic results [15]. The Florence trial, a phase III trial comparing WBI with intensity-modulated radiation therapy (IMRT) APBI, also found no significant difference in IBTR between the treatment arms (10-year IBTR, 3.7% vs. 2.5%) [11]. The Rapid trial, a phase III trial comparing WBI with external beam APBI delivered twice per day, found APBI to be noninferior to WBI in preventing IBTR [6]. The RTOG 0413, a similar phase III trial that included both EBRT and brachytherapy APBI, found that APBI did not meet criteria for equivalence with WBI [10]. However, the difference in IBTR at 10 years was less than 1% (4.6% vs. 3.9%). Taken together, these results indicate that APBI via multiple modalities can provide effective local control, but the heterogeneity of inclusion criteria used by each trial underscores the importance of careful patient selection.

Patient selection for APBI is an evolving field, with regular updates made to the consensus guidelines as recently as 2017 [13]. However, prior studies have been unable to demonstrate the ability for these guidelines to significantly predict IBTR [11, 16–21]. Budrukkar et al. investigated the utility of the current guidelines in a retrospective study of 240 women treated with multicatheter interstitial brachytherapy APBI [20]. Although local control did not differ for the risk groups of ABS, ASTRO, or GEC-ESTRO, they did find that these guidelines significantly predicted rates of OS and disease-free survival. Conversely, the present study demonstrates that none of the guidelines were able to predict RFS (Table 3). Although the risk groups of ABS and ASTRO did not differ in IBTR, the GEC-ESTRO intermediate-risk group had a higher risk of IBTR (5-year IBTR, 4.6%) compared with the low-risk (5-year IBTR, 0.9%) and high-risk groups (5-year IBTR, 1.1%; Table 3). A significantly higher proportion of patients less than 50 years of age (14%) and ILC cases (46%) within the GEC-ESTRO intermediate-risk group likely contributed to the higher rates of IBTR in this subgroup. In contrast, the ASTRO cautionary group had significantly fewer cases of younger patients (5%) and ILC (19%).

Prior studies have identified ER-negativity [16, 17, 22–25], tumor size [10, 22], young age [23, 26], positive margins [27], high grade [21, 27], LVSI [21, 25], and EIC [25] as significant risk factors for IBTR after APBI. The present study found that only ILC and the absence of surgical lymph node evaluation were associated with IBTR on univariate analysis (Table 4). However, it should be noted that there were few cases of ER-negativity, positive margins, young age, or high grade in the present study, which likely limited the analysis (Table 2).

The suitability of patients with ILC for APBI is controversial. Historically, patients with ILC were considered high risk for local recurrence after APBI because of higher rates of multifocal disease and positive resection margins [28]. For this reason, MRI prior to surgery for ILC cases can help to exclude high-risk patients. However, it should be noted that all four patients with ILC who developed IBTR underwent preoperative MRI. Whereas some studies have shown a higher risk of IBTR for ILC [25, 29], other studies have failed to identify ILC as a significant predictor of IBTR after APBI [26, 30, 31]. The prospective experience with ILC is limited, as the histology accounts for less than 10% of the study population in select trials [10, 11], whereas others have excluded ILC cases altogether [6, 8, 15]. Although the current ASTRO and GEC-ESTRO guidelines consider ILC to be a cautionary and intermediate risk factor, respectively, the ABS guidelines consider these patients suitable for APBI (Table 1) [12–14]. The present study demonstrates that ILC cases are at an increased risk for IBTR, with a 10-year IBTR of 14% (Table 4; Fig. 2), supporting the notion that these patients should remain intermediate risk for APBI. However, further prospective studies with larger numbers of ILC cases are required to clarify the suitability of these patients for APBI.

This study has significant limitations, including its nonrandomized, retrospective nature, which creates the opportunity for selection bias, as well as a relatively limited follow up. There were a limited number of patients within certain categories of the consensus criteria, such as node-positive disease, that limited the evaluation of the consensus guidelines. Another important limitation was the lack of LVSI and EIC pathologic data that are required for accurate classification of certain cases by the ASTRO and GEC-ESTRO selection criteria. Additionally, our study does not report on cosmetic outcomes, an important potential benefit of APBI over WBI.

Conclusion

Overall, our data demonstrate the efficacy of APBI even in patients deemed unsuitable by ABS, ASTRO, or GEC-ESTRO criteria. This study contributes to the growing body of evidence indicating that expansion of these guidelines may be warranted; however, prospective trials are required to validate these findings. Our data indicate that caution is required when considering APBI for patients with ILC.

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Disclosures

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