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Scientific Article

# A Single-Institution Experience in the Preoperative Selection of DCIS Patients for IORT using the ASTRO Consensus Guidelines

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**Abstract**

**Purpose:** Intraoperative radiation therapy (IORT) as a form of accelerated partial breast irradiation (APBI) is controversial given the limited evidence to support its efficacy. However, it remains an attractive option for low-risk patients with ductal carcinoma in situ (DCIS), who derive a small absolute benefit in local control with standard whole breast irradiation (WBI). We examine how the American Society for Therapeutic Radiation Oncology (ASTRO) APBI consensus guidelines (CG) may be applied to the preoperative selection of patients with DCIS for IORT and determine treatment outcomes by CG group.

**Methods and Materials:** We identified patients with biopsy-proven pure DCIS enrolled in an institutional prospective registry IORT database using the Zeiss Intrabeam® device between September 2013 and February 2017. Based on available preoperative clinicopathologic information, patients were deemed suitable, cautionary, or unsuitable for IORT according to the ASTRO CG. Change in CG group based on final pathologic diagnosis was determined, and additional therapy was recommended for unsuitable patients. Outcome in terms of ipsilateral breast tumor recurrence was determined.

**Results:** A total of 61 DCIS lesions in 60 patients were treated with IORT. Preoperatively, 21 patients (35%) were suitable and 36 (59%) were cautionary. Four (6%) were unsuitable because of lesion size but declined WBI. Final pathologic diagnosis changed the CG grouping of 10 patients (16%) because of either occult high-grade disease in 2 (3%) or close/positive margins in 8 (13%). Ultimately 12 patients total were considered unsuitable, of whom 8 (66%) accepted additional WBI after IORT. At a median follow-up of 2.2 years, ipsilateral breast tumor recurrence was identified among 2 suitable, 1 cautionary, and no unsuitable patients.

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**Conclusion:** Further investigation is necessary to refine selection of patients with DCIS who may be optimally treated with IORT alone. High acceptance of additional therapy among unsuitable patients resulted in excellent outcomes. The use of biomarkers in addition to traditional clinical and pathologic factors may help to better select patients for IORT.


## Introduction

In the era of screening mammography there are growing concerns about the overdiagnosis and overtreatment of ductal carcinoma in situ (DCIS). Many patients undergo treatment for DCIS that may never progress to invasive cancer or affect overall survival. Current ongoing studies are focused on the de-escalation or complete omission of treatment for a subset of patients with DCIS.[1–3] However, to date, breast-conserving surgery followed by 3 to 5 weeks of whole breast irradiation (WBI) remains the standard of care for all-comers with DCIS.

DCIS is a significantly heterogeneous disease entity. Certain clinical and pathologic features of DCIS (high grade, larger lesion size, smaller margin width) and patients (young age) have been found to be important in predicting local recurrence.[4] In the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network E5194 study, 2 patient cohorts (cohort 1: low-intermediate–grade disease measuring $\leq$2.5 cm; cohort 2: high-grade disease measuring $\leq$1 cm) were prospectively observed after surgical excision alone. The presence of cautionary high-grade disease resulted in a significantly higher rate of ipsilateral breast events, which at 12 years was 14.4% for cohort 1 versus 24.6% for cohort 2 ($P = .003$).[5] The Radiation Therapy Oncology Group (RTOG) 9804 study was a prospective, randomized trial that compared standard WBI with observation alone after surgical excision of "good-risk" DCIS (screen-detected, low-intermediate–grade DCIS measuring $\leq$2.5 cm with margins $\geq$3 mm). At 7 years the local recurrence rate was 0.9% versus 6.7% in the observation arm ($P < .001$).[6] These studies indicate the wide range in baseline risk for local recurrence after excision of DCIS. The absolute benefit in local control with standard WBI can be quite small; therefore there is significant interest in treatment options that may better balance the risks and benefits of treatment.

Intraoperative radiation therapy (IORT) as a form of accelerated partial breast irradiation (APBI) is an attractive alternative to standard WBI in the treatment of early-stage breast cancers. IORT is a potentially more cost-effective treatment option compared with WBI, offering patients a therapy that is delivered in a single fraction at the time of surgery with fewer treatment-related side effects in the short and long term.[7,8] The Targeted Intraoperative Radiotherapy (TARGIT-A) and Intraoperative Radiotherapy with Electrons (ELIOT) trials have helped to define a subset of patients with invasive breast cancers for whom IORT is noninferior to standard WBI.[9,10] There is significant interest in using IORT in the management of DCIS, but doing so remains controversial given the available evidence to indicate its efficacy and to guide patient selection.

Limited data exist regarding the use of IORT for DCIS patients. Rivera et al[11] reported on their experience with 35 patients with DCIS treated with the Carl Zeiss Intrabeam® device. They included patients with lesions measuring up to 4 cm of all histologic grades excised with at least 2 mm margins. At a median follow-up of 3 years, they reported a local recurrence rate of 5.7%. Silverstein et al[12] conducted a prospective IORT trial of 204 patients with early-stage breast cancer using the Xoft electronic brachytherapy (eBx®) system. They included a subset of 42 patients with DCIS with lesions measuring up to 3 cm of all histologic grades. With more than 4 years of follow-up, they reported a local recurrence rate of 6.7% among patients with DCIS. Lastly, researchers who conducted a multi-institutional study including 41 patients with DCIS among a cohort of more than 250 patients with breast cancer treated with the Xoft eBx® system reported 2 recurrences among their patients with DCIS (4.9%) at a short follow-up of 16 months.[13] Interestingly, the patients in this study were significantly younger compared with TARGIT-A and ELIOT patients, with 16.5% of the patient cohort <45 years old. It is unclear what percentage of patients in these studies would be deemed suitable for APBI according to American Society for Radiation Oncology (ASTRO) guidelines. The results suggest that IORT for DCIS may result in recurrence rates comparable to those of the TARGIT-A and ELIOT trials; however, appropriate patient selection is key.

In 2016 ASTRO updated its APBI consensus guidelines (CG) to include low-risk DCIS as suitable for APBI, defined by the RTOG 9804 trial entry criteria.[14] The guidelines are written primarily for other forms of APBI delivered in the adjuvant setting after surgery using external beam radiation or multicatheter brachytherapy. Here we present our single-institution experience with

DCIS IORT focusing on the preoperative selection of patients for IORT guided by the updated ASTRO APBI guidelines. We describe the impact of final pathologic diagnosis on patient CG group suitability, subsequent treatment recommendations, and outcomes.

## Materials and Methods

### Patient eligibility

Patients treated with breast IORT were prospectively enrolled in our institutional registry database between September 1, 2013, and February 15, 2017. We performed a retrospective review to identify a cohort of patients with a pathologic diagnosis of pure DCIS on initial diagnostic biopsy. Patients were excluded from our present analysis if they were found to have microinvasive or invasive disease on diagnostic biopsy, or if they had received prior ipsilateral WBI or thoracic irradiation for another primary malignancy.

### Preoperative imaging and pathologic evaluation

Preoperative size assessment and eligibility for IORT was based on conventional imaging alone, including mammogram and/or ultrasound. Magnetic resonance imaging of the breasts was not routinely performed and was only available for a subset of patients, ordered at the surgeon's discretion.

Pathologic characteristics of tumors from the time of initial diagnostic biopsy and lumpectomy were obtained from the original pathology reports. Immunohistochemistry staining was routinely performed for both the estrogen receptor and progesterone receptor and interpreted according to the American Society of Clinical Oncology and College of American Pathologists Guidelines. Tumors were considered hormone receptor (HR) positive if the estrogen receptor and/or progesterone receptor had $\geq$1% positive staining.[15]

### Intraoperative treatment

A dose of 20 Gy was prescribed and delivered to the lumpectomy cavity surface at the time of breast-conserving surgery using 50kV x-rays by the Intrabeam device (Carl Zeiss, Oberkochen, Germany). A spherical applicator (range, 1.5-5.0 cm) was chosen at the discretion of the radiation oncologist and operating surgeon to most appropriately fit the lumpectomy cavity. Ultrasound was performed to confirm a minimum skin to applicator distance of 10 mm. Sentinel lymph node dissection at the discretion of the surgeon was not routinely performed. Patients were seen in follow-up at 2 weeks after IORT to review final surgical pathologic report of the lumpectomy specimen.

**Table 1** Patient clinical and pathologic characteristics (n = 61)

| Characteristics | n (%) |
|---|---|
| Age (y) | |
| 40-49 | 4 (6) |
| 50-59 | 16 (26) |
| ≥60 | 41 (68) |
| Clinical size | |
| ≤2.5 cm | 55 (91) |
| 2.6-3 cm | 2 (3) |
| >3 to 4 cm | 2 (3) |
| >4 cm | 2 (3) |
| Grade | |
| Low-intermediate | 30 (49) |
| High | 31 (51) |
| Subtype | |
| ER/PR+ | 56 (92) |
| ER/PR− | 4 (6) |
| Unknown | 1 (2) |
| Margins | |
| Positive | 5 (8) |
| <2 mm | 3 (5) |
| 2-2.9 mm | 3 (5) |
| ≥3 mm | 50 (82) |

*Abbreviations:* ER = estrogen receptor; PR = progesterone receptor.

### Recommendations for additional therapy

Re-excision followed by adjuvant WBI was recommended for positive surgical margins and routinely discussed for close surgical margins of <2 mm according to the 2016 Society of Surgical Oncology (SSO)/ASTRO/American Society of Clinical Oncology (ASCO) CG.[16] Additional WBI alone was routinely discussed and strongly recommended in the presence of high-risk pathologic features such as large lesion size (>3 cm), close surgical margins, extensive multifocal disease, and occult nodal positivity. WBI was also discussed for occult microinvasive or invasive disease and recommended if the invasive component was determined to be HR negative because subset analysis of HR negative patients in both the TARGIT-A and ELIOT trials had higher rates of ipsilateral breast events.[9,10]

### Endpoint analysis and follow-up

Patient charts were reviewed to determine the incidence of biopsy-proven local and/or regional recurrences, as well as compliance with recommended hormonal therapy at last follow-up. Details regarding any salvage therapy at the time of recurrence were recorded.

**Table 2** Interpretation of ASTRO APBI Consensus Guidelines for DCIS and intraoperative radiation therapy

| Patient group | Criteria | Treatment recommendation |
|---|---|---|
| Suitable | *Preoperative*<br>• Age ≥50 y<br>• Screen detected<br>• Unifocal<br>• Size ≤2.5 cm<br>• Low to intermediate grade<br>*Postoperative*<br>• Resected with margins ≥2 mm* | • No further treatment after BCS/IORT |
| Cautionary | *Preoperative*<br>• Age 40-49 y if all other criteria for "suitable" are met<br>• ≥50 y if patient has at least 1 "cautionary" factor and does not have any "unsuitable" factors:<br>• Clinically detected<br>• High-grade<br>• HR negative<br>• Size 2.6-3.0 cm<br>*Postoperative*<br>• Resected with margins ≥2 mm<br>• Occult HR-positive T1mi/T1 disease | • No further treatment after BCS/IORT |
| Unsuitable | *Preoperative*<br>• Age <40 y<br>• Age ≥40 y but has "unsuitable" factors:<br>• Size >3 cm<br>*Postoperative*<br>• Resected with close (<2 mm) or positive margins<br>• Occult HR-negative T1mi/T1 disease† | • Re-excision lumpectomy and WBI for positive margins<br>• Re-excision lumpectomy discussed for close margins<br>• WBI for HR-negative T1mi/T1 disease |

*Abbreviations:* APBI = accelerated partial breast irradiation; ASTRO = American Society for Radiation Oncology; BCS = breast-conserving surgery; DCIS = ductal carcinoma in situ; HR = hormone receptor; IORT = intraoperative radiation therapy; T1mi/T1 = microinvasive/invasive; WBI = whole breast irradiation.

Based on the 2016 ASTRO APBI Updated Consensus Guidelines.[14]

Patient should meet both preoperative and postoperative criteria to remain in a suitability group.

* ASTRO guidelines define wide local excision with margin ≥3 mm as suitable.

† HR-negative T1mi/T1 disease considered unsuitable for IORT alone given higher rate of IBTR observed in the TARGIT-A and ELIOT trials among this patient subset.

## Results

### Patient characteristics and preoperative APBI suitability

Sixty patients with 61 biopsy-proven DCIS lesions received breast IORT at the time of surgery. One patient in our cohort presented with synchronous DCIS primaries of the bilateral breasts that were treated with bilateral IORT. The median age of our patient cohort was 63 years (range, 44-84 years). A total of 55 patients (92%) were postmenopausal, and 59 (98.3%) presented with screen-detected disease. Based on preoperative conventional imaging, the median extent of disease was 0.8 cm (range, 0.2-4.2 cm). Disease grade based on diagnostic biopsy specimen tissue was low-intermediate in 32 (52%) and high in 29 (48%). A summary of our patients' clinical and pathologic characteristics is presented in Table 1.

Based on available preoperative clinical and pathologic characteristics (age, mode of detection, lesion size, and grade) we applied the ASTRO APBI guidelines to our cohort of IORT patients. An outline of the guidelines interpreted specifically for DCIS and intraoperative therapy is shown in Table 2. Twenty-one patients (35%) were suitable for APBI according ASTRO guidelines. Thirty-six patients (59%) were considered cautionary because of the presence of at least 1 high-risk feature, including high-grade disease in 28 (45.9%), size > 2.5 cm but ≤ 3 cm in 2 (3.3%), HR negative in 8 (1.3%), and age < 50 years in 4 (6.7%). Four patients (6%) were unsuitable because of lesion size >3 cm; however, they declined standard whole breast therapy.

### Final pathologic findings and changes in patient APBI suitability

Review of final pathologic findings from the time of lumpectomy revealed a median lesion size of 0.6 cm (range, 0-3 cm). Three patients (5%) were found to have close margins (<2 mm), and 5 (8.2%) had positive

**Table 3** Summary of patient preoperative and postoperative suitability factors

| Preoperative suitability group | Reason | | | | | |
|---|---|---|---|---|---|---|
| | n | Grade | Size | HR negative* | Age | Palpable |
| Suitable | 21 | | | | | |
| Cautionary | 36 | 28 | 2 | 4 | 4 | 1 |
| Unsuitable | 4 | | 4 | | | |
| **Postoperative group change** | **n** | **Grade** | **Size** | **Close margins** | **Positive margins** | **T1mi/T1** |
| Suitable to cautionary | 2 | 2 | | | | |
| Cautionary to unsuitable | 8 | | | 3 | 5 | |

*Abbreviations:* DCIS = ductal carcinoma in situ; HR = hormone receptor; T1mi/T1 = microinvasive/invasive.
* HR negative DCIS component.

margins. Occult HR-positive microinvasive disease was revealed in 2 patients (3.3%), and HR-positive invasive disease was revealed in 3 patients (4.9%). Sentinel lymph node dissection was performed in 2 unsuitable patients because their preoperative imaging revealed disease spanning more than 3 cm. Neither dissection revealed occult nodal involvement.

Incorporation of final pathologic findings from the time of lumpectomy (ie, pathologic size and grade, margin status, occult invasive disease) to our cohort changed CG group suitability in 10 patients (16%). Among our initial cohort of 21 patients who met all suitable criteria preoperatively, 2 (9.5%) became cautionary based on the presence of occult high-grade disease. No additional high-risk pathologic findings were present to shift suitability in these patients (margins, HR-negative invasive disease); however, 3 patients were found to have HR-positive invasive disease on final pathologic examination. For our cohort of 36 patients who initially met cautionary criteria preoperatively, 8 (22%) were found to have additional unsuitable factors for APBI, including final close margins in 3 (8.3%) and positive margins 5 (13.9%). A summary of preoperative CG group suitability and group changes based on final pathologic diagnosis is presented in Table 3 and illustrated in Figure 1.

## Additional therapy after IORT

All 5 patients with positive margins underwent re-excision lumpectomy with clear margins, followed by WBI. One of 3 patients with initial close margins (<2 mm) underwent re-excision, with 2 of these patients also receiving adjuvant WBI. A median dose of 4005 cGy in 15 daily fractions was prescribed for WBI. Patients with occult invasive disease were not routinely recommended additional therapy unless their invasive component was HR negative. In total 12 patients in our cohort were considered unsuitable, including 4 patients who declined WBI in the upfront setting and 8 patients who were found to have unsuitable disease based on final pathologic examination. Among these 12 patients, 8 (66%) accepted additional recommended therapy (re-excision and/or WBI). A summary is presented in Figure 2. Hormonal therapy was recommended to all women with HR-positive disease. Of the 56 patients with HR-positive disease, 40 (71%) initiated hormonal therapy, and only 35 (62%) remained compliant at last follow-up.

## Local recurrences and salvage therapy

At a median follow-up of 2.2 years (range, 2.1-51.3 months), 3 (4.9%) local recurrences of DCIS occurred in the ipsilateral breast. Two of these recurrences were found within the original involved breast quadrant and the third was found in an adjacent quadrant among 2 suitable patients and 1 cautionary patient. A summary is presented in Table 4.

## Discussion

In our single-institution experience of DCIS IORT, we found a 2-year ipsilateral breast tumor recurrence (IBTR) of 4.9%. This is comparable to other reports of DCIS

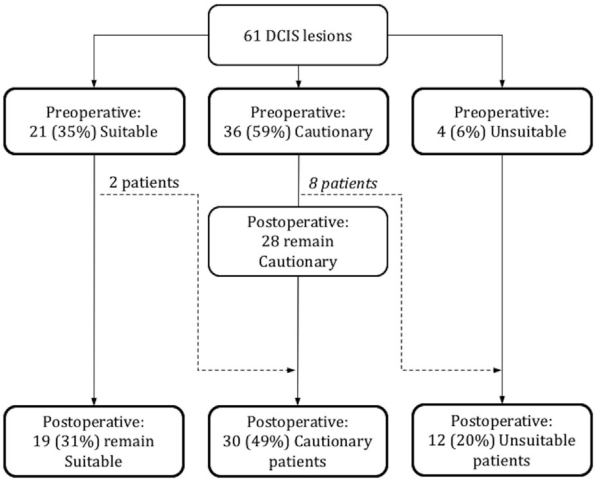


**Fig. 1** Patient preoperative and postoperative ASTRO consensus guideline group suitability.

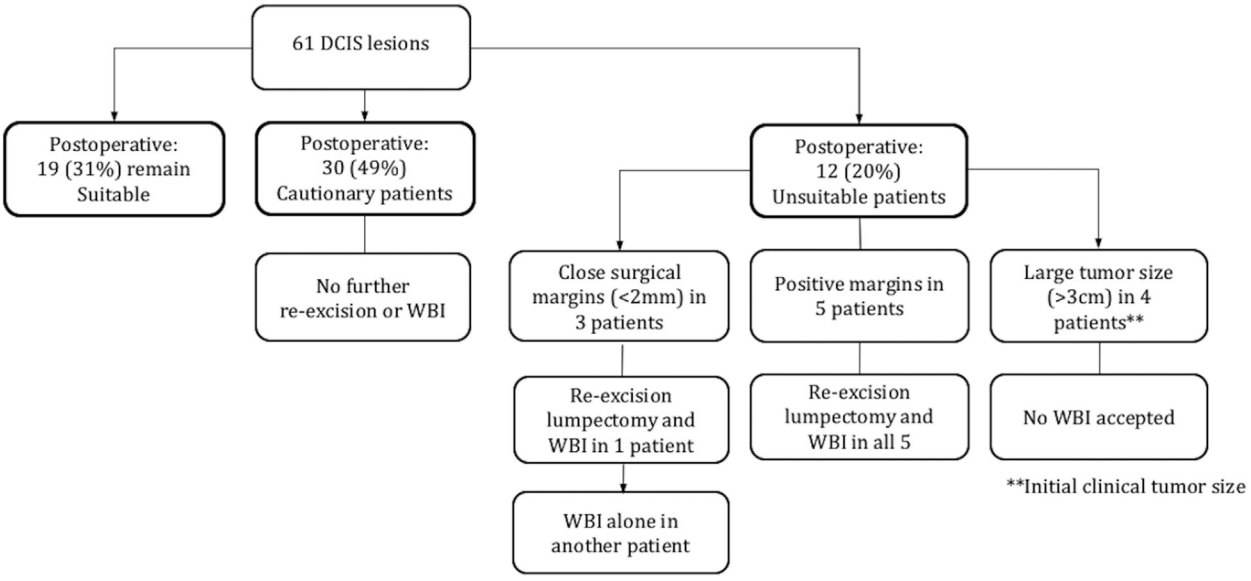


**Fig. 2** Patient postoperative ASTRO consensus guideline group suitability and acceptance of additional therapy.

managed with intraoperative therapy.[11,13] The majority of our patients were considered cautionary for APBI according to ASTRO guidelines because of the presence of high-grade DCIS. Deconstructing the proposed guidelines into preoperative and postoperative criteria specifically for application to patient selection for IORT, we found a shift in approximately 15% of our patients to a less suitable CG group based on final lumpectomy pathologic examination (9.5% among suitable patients, 22% among cautionary patients). Ultimately, recommendations for additional therapy were based on final CG group suitability. Additional therapy was recommended to all unsuitable patients and discussed in a subset of cautionary patients. The high acceptance of additional therapy among unsuitable patients likely explains the lack of recurrences among these patients. Two of 3 of our recurrences were found in suitable patients. Neither patient had initiated adjuvant hormonal therapy.

The ability of the ASTRO CG to adequately stratify patients treated with APBI by risk for recurrence has not been strongly supported when applied to large patient cohorts with invasive breast cancers.[17–19] A pooled analysis from William Beaumont Hospital and the American Society of Breast Surgeons MammoSite Registry Trial of more than 2000 patients with early-stage invasive breast cancers treated with either brachytherapy or 3-dimensional conformal APBI found that the 2009 ASTRO APBI guidelines did not stratify their patient cohort by statistically different risks of IBTR.[20] At 5 years, the rate of IBTR was 2.5% among suitable patients, 3.3% for cautionary patients, and 4.6% for unsuitable patients ($P = .2$). On the contrary, Leonardi et al[21] applied the ASTRO guidelines to a cohort of 1822 patients treated with IORT with electrons (ELIOT) as a sole modality and found the patients to be well stratified by 5-year IBTR (suitable 1.5%, cautionary 4.4%, and unsuitable 8.8%; $P = .0003$). In addition, the rate of distant metastases was significantly different among unsuitable versus suitable or cautionary patients in this study. Two separate

**Table 4** Summary of patients with ipsilateral breast recurrence

| Preoperative suitability | Postoperative suitability | High-risk features | Hormonal therapy? | Location of IBTR | Time to IBTR | Salvage therapy | Findings |
|---|---|---|---|---|---|---|---|
| 1 Suitable | Suitable | | No | Adjucent to lumpectomy site | 4 mo | Repeat BCS and WBI | G2 DCIS |
| 2 Suitable | Suitable | | No | Adjacent quadrant | 26 mo | Repeat BCS | G3 DCIS |
| 3 Cautionary | Cautionary | G3 | Yes | Lumpectomy bed | 6 mo | Mastectomy | Multifocal G3 DCIS |

*Abbreviations:* BCS = breast-conserving surgery; DCIS = ductal carcinoma in situ; G = grade; IBTR = ipsilateral breast tumor recurrence; WBI = whole breast irradiation.

institutions retrospectively evaluated the use of APBI specifically among ASTRO cautionary and unsuitable patients, respectively.[22,23] In both studies, ASTRO guidelines did not differentiate a subset of patients with significantly worse rates of IBTR. In fact, in both studies, estrogen receptor negativity was the single variable associated with a higher IBTR among patients, highlighting the importance of inherent aggressive tumor biology that may lead to inferior outcomes.

The selection of patients who may be suitably treated with APBI with low subsequent risk of recurrence requires refinement. The use of clinical and pathologic factors alone does not accurately risk stratify patients. The Oncotype DX® DCIS Score is a 12-gene expression assay that provides patients with an individualized prediction of 10-year risk of any local recurrence (DCIS or invasive cancer) after treatment with breast-conserving surgery alone. It was validated in 2 studies, the Eastern Cooperative Oncology Group study E5194 and Ontario DCIS Cohort, in more than 1500 patients total.[24,25] Studies have found that use of the DCIS score can alter adjuvant therapy recommendations in up to 30% of patients, demonstrating the utility of genomic testing in providing additional information beyond clinical and pathologic factors alone.[26] Current assays have not yet been examined in the setting of IORT, and the validity and utility of doing so remains unclear. The results of our experience, however, highlight the need to further optimize patient selection for IORT.

Lastly, the issue of adequate margin for DCIS in the setting of APBI remains an area of contention. The updated ASTRO guidelines recommend wide local excision with margins $\geq$3 mm.[14] This is based on the historic RTOG 9804 trial, which randomized patients with low-risk DCIS to either WBI or observation alone. The conservative margin recommendation was justified given that patients would be observed with no further treatment on this trial. Other professional societies such as the American Brachytherapy Society recommend margins $\geq$2 mm, extrapolated from the recent SSO/ASTRO/ASCO margin guidelines for DCIS in the setting of WBI.[27] Shah et al[28] evaluated the impact of margin status among more than 1000 patients enrolled in the American Society of Breast Surgeons MammoSite® Registry Trial, including a subset of about 190 patients with DCIS. Among patients with DCIS, there was a statistically higher IBTR at 6 years among patients with close ($<$2 mm) margins compared with patients with negative margins (17.6% vs 4.2%, $P = .004$). Therefore, in our interpretation of the ASTRO guidelines (Table 2), we define a margin of $\geq$2 mm as appropriate for both suitable and cautionary patients. This is more consistent with clinical practice at our institution because we do not routinely recommend additional therapy after IORT for margins $\geq$2 mm.

## Conclusions

We present our single-institution experience in the selection and treatment of DCIS patients with IORT. Although our study is small with limited follow-up, we highlight the preoperative selection of patients for IORT guided by the ASTRO APBI CG guidelines and describe a significant shift of CG group suitability based on final pathologic findings. Future prospective trials are needed to further refine appropriate selection of patients with DCIS for IORT, likely with the incorporation of additional biomarkers.

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