Breast Cancer Research and Treatment (2019) 178:607–615
https://doi.org/10.1007/s10549-019-05428-0

CLINICAL TRIAL

Long-term outcomes of breast-conserving therapy for women with ductal carcinoma in situ

Laura E. G. Warren[1] · Yu-Hui Chen[2] · Lia M. Halasz[3] · Jane E. Brock[4] · Alexander Capuco[1] · Rinaa S. Punglia[1] · Julia S. Wong[1] · Mehra Golshan[5] · Jennifer R. Bellon[1]

Received: 28 June 2019 / Accepted: 27 August 2019 / Published online: 6 September 2019

Abstract

Purpose Improved imaging, surgical techniques, and pathologic evaluation likely have decreased local recurrence rates for patients with ductal carcinoma in situ (DCIS). We present long-term outcomes of a large single-institution series after breast-conserving surgery (BCS) and adjuvant radiation therapy (RT).

Methods We retrospectively reviewed the records of 245 women treated for DCIS with BCS and RT between 2001 and 2007. Competing risk analysis was used to calculate local recurrence (LR) as a first event with the development of a second non-breast malignancy, contralateral breast cancer, and death as competing first events.

Results At a median follow-up of 10.6 years, 4 patients had a LR (2 DCIS, 2 invasive) as a first event with a cumulative LR incidence of 0.0% and 1.5% at 5 and 10 years, respectively. Most patients had > 2 mm margins (90%), specimen radiographs (93%), and received a tumor bed boost (99%). The majority (60%) of patients with hormone receptor-positive disease received adjuvant endocrine therapy. Ten-year cumulative incidence of contralateral breast cancer (CBC) was 7.9%, second non-breast malignancy was 4.5%, and death unrelated to breast cancer was 3.5%. Family history, age at diagnosis, and receipt of endocrine therapy were not significantly associated with the development of CBC (all $P > 0.05$).

Conclusions With mature follow-up, our rates of local recurrence following breast-conserving therapy for DCIS remain very low (1.5% at 10 years). The incidence of CBC was higher than the LR incidence. Predisposing factors for the development of CBC are worthy of investigation.

Keywords Breast cancer · Ductal carcinoma in situ · Outcomes · Breast-conserving therapy · Radiation therapy

Introduction

Early studies examining adjuvant radiation therapy (RT) following breast-conserving surgery (BCS) for patients with ductal carcinoma in situ (DCIS) showed that RT reduced the risk of local recurrence by approximately 50% [1, 2]. However, a more recent randomized study suggested as much as a 90% relative reduction in local recurrence (LR) with the addition of RT after BCS [3]. A report from our institution of 76 patients with DCIS treated with BCS and RT between 1976 and 1990 had an actuarial 10-year LR rate of 15% [4]. However, given improvements in mammographic and pathologic evaluation, in addition to improved surgical and radiation techniques over the past several decades, we hypothesized that the incidence of LR at our institution had likely decreased. We reported on the results of 246 consecutive patients treated with BCS and adjuvant RT for DCIS at our institution between 2001 and 2007 and found no LR at

This manuscript contains original work that was presented in part at the San Antonio Breast Cancer Symposium, San Antonio, TX, December 2016.

✉ Laura E. G. Warren
laura_warren@dfci.harvard.edu

[1] Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA

[2] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA

[3] Department of Radiation Oncology, University of Washington, Seattle, WA, USA

[4] Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

[5] Department of Surgery, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA

five years [5]. Given the possibility of recurrences after five years in this patient population, we performed this long-term analysis. Additionally, we sought to better understand the utilization of specimen radiograph and post-operative mammography in this patient population.

Methods and materials

The methods of this study have been previously described [5]. Briefly, we retrospectively reviewed the records of 245 women consecutively treated for ductal carcinoma in situ with breast-conserving surgery (BCS) and adjuvant radiation therapy at a single institution between 2001 and 2007. Patients with prior malignancy (except non-melanoma skin cancers), synchronous bilateral breast cancer, microinvasive disease, or an incomplete course of radiation therapy were excluded. One woman included in the prior analysis was excluded from this analysis as she subsequently underwent a prophylactic bilateral mastectomy following her initial diagnosis of DCIS. Patient data were collected in a prospectively maintained database. The institutional review board approved this study.

Diagnosis and treatment

All patients underwent physical examination and diagnostic mammography as part of their initial work-up. Other imaging, including magnetic resonance imaging and ultrasound, was optional. During the time period of this study, the institutional surgical margin goal was 3 millimeters (mm). For this study, all surgical margins, including the anterior and posterior margins, were assessed. Surgical margins greater than 2 mm were considered negative and ink on DCIS was considered positive. Margins greater than 0 mm but 2 mm or less were considered close. Routine estrogen receptor (ER), progesterone receptor (PR), and HER-2 immunohistochemistry (IHC) staining began in 2003 and was read by specialized breast pathologists. ER/PR positive was defined as any staining for ER and/or PR. HER-2 positive was defined as 3 + on IHC. Fluorescence in situ hybridization was not routinely done. There are no standard institutional guidelines regarding the indications for post-operative mammogram in this patient population. Post-operative mammograms are obtained at the discretion of the treating provider(s).

Follow-up evaluation and end points

The patients were routinely seen in follow-up within six months of completion of radiation therapy and every six months thereafter. Mammography was generally performed annually. The primary end point of the study was time to ipsilateral breast cancer recurrence as a first event. Secondary end points included development of regional (ipsilateral supraclavicular, infraclavicular, axillary or internal mammary lymph nodes) or distant metastases, contralateral breast cancer (CBC), development of other malignancies, and death.

Statistical analysis

Descriptive statistics were used to characterize patient, tumor, and treatment characteristics. Cumulative incidence of local recurrence (LR) was calculated both as a crude local recurrence rate and with a second non-breast malignancy, CBC, and death as competing events. Kaplan–Meier method was used to estimate the LR rate and log–log transformation was used to calculate the confidence intervals. Competing risk regression was used to evaluate the association between contralateral breast cancer and clinical as well as pathologic features. Kaplan–Meier estimates were used for overall survival at ten years. All P values were two-sided, and P values lower than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) except the competing risk analysis, which was performed using R 2.15.0.

Results

Two hundred and forty-five patients were included in this analysis. Patient, tumor, and treatment characteristics can be seen in Table 1. The median age at diagnosis was 54 (range: 32–84). The majority of patients were postmenopausal (58.2%) without a family history of breast cancer (81.7%). Most patients had ER- or PR-positive DCIS (71.0%) that were grade 2 (44.9%) or grade 3 (38.8%). Of those patients known to be hormone receptor positive ($n = 174$), 105 (60.3%) received adjuvant endocrine therapy.

Approximately one-quarter (25.3%, 62 of 245) of the patients required at least one re-excision for negative (> 2 mm) margins. The final surgical margin was negative in 221 patients (90.2%), close in 23 (9.4%), and positive in 1 (0.4%). The one positive margin was at the deep margin and the surgeon reported the deep margin to be at the pectoralis fascia. In the 23 patients with close margins, 13 (56.5%) had focally close margins at 2 mm and the decision was made not to pursue additional surgery. The surgeon felt there was no additional breast tissue to be removed in the area of the close margin for six patients, including four patients with close anterior or deep margins. For the remaining four patients (17%), one patient refused re-excision and three patients did not undergo additional surgery as a result of multidisciplinary consensus (documented in the medical record in all cases) that the benefit of additional surgery for 1 mm focal margins was limited and re-excision was not recommended.

Table 1 Patient, tumor, and treatment characteristics

	N	%
Age at diagnosis, years		
Median	54.3 years	
Range	32.3–84.3 years	
Age at diagnosis, quartile		
Quartile 1	32.3–47.7 years	
Quartile 2	47.8–54.3 years	
Quartile 3	54.4–61.1 years	
Quartile 4	61.1–84.3 years	
Menopausal status		
Premenopausal	85	34.8
Perimenopausal	17	7.0
Postmenopausal	142	58.2
Unknown	1	–
Family history		
No first-degree relatives	197	81.7
One or more first-degree relatives	44	18.3
Unknown	4	–
Number of re-excisions		
0	184	75.1
1	46	18.8
2	12	4.9
3	3	1.2
Specimen radiograph at initial excision		
No	18	7.3
Yes	227	92.7
Specimen Radiograph at Initial Excision (Only patients with any calcifications; $n = 197$)		
No	0	0
Yes	197	100
Post-operative mammogram after initial excision		
No	143	58.4
Yes	102	41.6
Post-operative mammogram after initial excision (only patients with any calcifications; $n = 197$)		
No	95	48.2
Yes	102	51.8
Abnormal [positive] mammogram after initial excisions		
No	76	74.5
Yes	26	25.5
N/A	143	–
Tumor location		
Deep to nipple	3	1.2
Central portion	16	6.5
Upper inner	35	14.3
Lower inner	10	4.1
Upper outer	113	46.3
Lower outer	19	7.8
Overlapping lesions	48	19.7
Unknown	1	–
Extent of DCIS		
Median proportion of involved blocks	0.21	
Median no. of involved blocks	3	

Table 1 (continued)

	N	%
Calcifications present		
No	48	19.6
Yes	197	80.4
Highest grade		
1	40	16.3
2	110	44.9
3	95	38.8
Hormone receptor status		
ER and PR negative	13	7.0
ER and/or PR positive	174	93.0
ER/PR unknown	58	–
HER2 status		
Negative	129	79.1
Positive	34	20.9
Unknown	82	–
ADH present		
No	113	46.1
Yes	132	53.9
ALH present		
No	183	74.7
Yes	62	25.3
LCIS present		
No	207	85.5
Yes	38	15.5
Final margin		
Negative (> 2 mm)	221	90.2
Close (≤ 2 mm)	23	9.4
Positive	1	0.4
Radiation therapy		
Median total dose, cGy (range)	6000 (4240–6420)	
Median whole breast dose, cGy (range)	4400 (4000–5220)	
Median boost dose, cGy (range)	1600 (0–1800)	
Radiation therapy boost		
No	2	0.8
Yes	243	99.2
Endocrine therapy		
No	119	48.6
Yes	126	51.4
Endocrine therapy if ER + or PR + ($n = 174$)		
No	69	39.7
Yes	105	60.3

DCIS ductal carcinoma in situ, *IQR* interquartile range, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *ADH* atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ

The vast majority (92.7%) of patients had a radiograph of the surgical specimen at the time of the initial BCS. All patients with calcifications on initial diagnostic mammogram had a specimen radiograph (100%; $n = 197$). Of the 18 patients who did not have a specimen radiograph, six underwent surgery at an outside institution and may have had a specimen radiograph; however, these records were not available for review for this analysis. Therefore, there were 12 patients operated on at Brigham and Women's/Dana-Farber Cancer Institute where specimen radiograph was not documented or not obtained. Patients who did and did not undergo re-excision for margins after the first excision did

not have different rates of specimen radiograph (91.8% vs. 92.9%, respectively; $P = 0.77$).

One hundred and two patients underwent a post-operative mammogram after their initial surgery (102/245, 41.6%). There was not a significant relationship between margin status at the time of initial resection and utilization of post-operative mammogram, with 41.8% (77/184) of patients with negative margins undergoing post-operative mammogram and 41.0% (25/61) of patients who had at least one re-excision undergoing post-operative mammograms ($P = 0.91$). Of the 102 patients who underwent post-operative mammogram, 26 (25.5%) had an abnormal mammogram. Among these 26 patients, two patients did not undergo an additional re-excision but both had core needle biopsies in the mammographic areas of concern that were negative; 21 had one re-excision; and three had two re-excisions. In the 24 patients who underwent re-excision, residual DCIS was identified in 16 patients (66.7%). The median whole breast radiation therapy dose was 4400 cGy (range: 4000–5520 cGy). Nearly all patients ($n = 243$; 99.2%) received a boost to the surgical cavity. The median boost dose was 1600 cGy (range: 0–1800 cGy). Only two patients in the cohort received hypofractionated breast radiation therapy.

At a median follow-up of 10.6 years, the crude incidence of local recurrence was 1.6% (95% CI:[0.5%, 4.9%]) at 10 years. The cumulative incidence of local recurrence at 10 years using the competing risk analysis was 1.5% (95% CI:[0%, 3.2%]. The median time to local recurrence from initial diagnosis of DCIS was 8.1 years (range: 6.9–13.1 years). The median age at initial diagnosis of DCIS for these four patients was 57. 8 years (range: 45.9–68.2 years). Three of the 4 patients with local recurrence (75%) had high-grade DCIS at presentation; one (25%) had intermediate-grade DCIS. All had negative final margins at the time of their initial surgery and all had specimen radiograph to confirm the biopsy clips were present in the surgical specimen. None of these patients had post-operative mammogram after their definitive surgery. All four of the patients had tumors that were estrogen receptor (ER) positive; one of the four received adjuvant endocrine therapy (25%). All received adjuvant radiation therapy to a median total dose to the surgical cavity of 6000 cGy (range: 5700–6100 cGy). Two patients had an in situ recurrence while two patients had an invasive recurrence. All four patients were treated with mastectomy at the time of recurrence and had no evidence of disease at the time of this analysis (median follow-up after diagnosis of recurrence: 2.2 years; range: 1.1–4.0 years). Of 105 patients who had tumors that were ER or PR positive and received endocrine therapy, one patient had a subsequent local recurrence (1.0%). Of the 69 patients who were ER or PR positive but did not receive adjuvant endocrine therapy, there were three local recurrences (4.3%) ($P = 0.30$). No patients developed regional nodal or distant metastasis as a first or any recurrence.

The ten-year cumulative incidence of CBC was 7.9% with 20 patients developing CBC as a first event. The median time from initial DCIS diagnosis to CBC was 7.3 years (range: 0.6–12.8 years). The median age at initial diagnosis of DCIS was 50.8 years (range, 39.6–84.3 years) among the patients who ultimately developed a CBC. Of the 20 CBC diagnoses, eight were DCIS (40.0%) and 12 (60.0%) were invasive. The initial breast cancer was ER positive in 13 patients (65.0%); the ER status was unknown in the remaining 7 (35.0%). Eleven of 20 (55.0%) had taken endocrine therapy, including seven of 13 patients with known ER-positive tumors (53.8%). Three (15.0%) of these twenty patients had LCIS present at the time of initial DCIS surgery. Univariable analysis did not find family history, receipt of endocrine therapy, or age at diagnosis of the initial DCIS were significantly associated with CBC (all P values > 0.05, results not shown). Although no variables were found to be statistically significant on univariable analysis, multivariable analysis was performed, with age at diagnosis categorized using quartiles in one model and dichotomized by median in another. Again no variables were found to be significantly associated with the development of CBC (all P values > 0.05, results not shown).

Thirteen patients (5.3%) developed a second malignancy, which included endometrial (3), fallopian tube (2), gallbladder (1), leukemia and thyroid (1), lung (4), ovarian (1), and uterine (1) cancers. The five- and ten-year cumulative incidence rates of local recurrence, contralateral breast cancer (CBC), second malignancy, and death can be seen in Table 2.

Table 2 Cumulative incidence rates of local recurrence (LR), contralateral breast cancer (CBC), second malignancy, and death as first events in competing risk analysis

Event type	Number of events as first event	5-yr cumulative incidence rate (95% CI)	10-yr cumulative incidence rate (95% CI)
LR	4	0%	1.5% (0%, 3.2%)
CBC	20	2.5% (0.5%, 4.5%)	7.9% (4.1%, 11.8%)
Second non-breast malignancy	13	2.6% (0.5%, 4.6%)	4.5% (1.8%, 7.3%)
Death	7	1.2% (0%, 2.7%)	3.5% (0.9%, 6.1%)

Discussion

At a median follow-up of 10.6 years, the ten-year cumulative incidence of local recurrence following BCS and adjuvant RT for DCIS is less than 2%. These data demonstrate that the low rates of local recurrence seen at five years persist with longer-term follow-up [5]. All patients with DCIS treated with BCS and adjuvant RT were included in this study, regardless of patient or tumor characteristics, and were treated at a single institution in a multidisciplinary homogeneous fashion. Intraoperative specimen radiograph was obtained in greater than 90% of patients. Greater than 90% of patients had final surgical margins equal to or greater than 2 mm. Approximately 52% of patients who initially presented with calcifications on diagnostic mammograms underwent a post-operative mammogram. All patients with abnormal post-operative mammograms subsequently either underwent surgical re-excision or core needle biopsy to address the region of concern.

Nearly all patients in this study underwent resection to final margins equal to or greater than two millimeters. This approach is consistent with published consensus guidelines from the Society of Surgical Oncology, American Society for Radiation Oncology, and American Society of Clinical Oncology on surgical margins for BCS for patients with DCIS who will be receiving adjuvant RT [6]. Their recommendations are based on a meta-analysis [7] and other studies [8, 9] that demonstrated a reduced risk of LR with negative (≥ 2 mm) as compared to close or positive margins. Specimen radiograph, which is routine practice at our institution, has been shown to identify patients who may need additional margin excision at the time of initial surgery, thereby reducing the need for re-excision [10, 11].

Other modern studies have seen similarly low rates of local recurrence following BCS and RT for DCIS. RTOG 9804 prospectively randomized 636 patients with good-risk DCIS to adjuvant RT versus observation [3]. Tamoxifen was optional; 62% of patients received it in the adjuvant setting. For those patients in RTOG 9804 who received adjuvant RT, the cumulative rate of LR at seven years was 0.9%. These results are comparable to those in the current study. However, this is noteworthy given that RTOG 9804 only included patients with low- or intermediate-grade disease while 40% of patients in the current study had high-grade disease. Similarly, ECOG-ACRIN E5194 enrolled patients with DCIS onto two study cohorts; the first included patients with low- or intermediate-grade DCIS with tumors 2.5 cm or smaller. The second included patients with high-grade DCIS measuring 1 cm or smaller [12]. None of the patients received radiation; Tamoxifen was given to 30%. The 12-year rate of developing an ipsilateral local recurrence, either DCIS or invasive carcinoma, was 14.4% and 24.6% at twelve years, in cohort one and two, respectively. The rates of recurrence in E5194 increased through the 12 years of follow-up and demonstrated that despite investigator efforts to select favorable patients for omission of RT, there was still a relatively high rate of ipsilateral breast recurrence after surgery alone. Patients and their physicians need to weigh the estimated risks of recurrence with the potential toxicities of radiation therapy.

The factors influencing the very low recurrence rates in this study, despite being a consecutive series of patients, are difficult to precisely define. Our study does include a number of patients with less favorable features including higher grade and younger age (35% of patients were premenopausal). A SEER analysis examining the utilization of adjuvant endocrine therapy for DCIS found that in their study population, only 21% and 4% of women took adjuvant Tamoxifen or aromatase inhibitors, respectively, after surgery for DCIS [13]. As shown in NSABP B24 [14], the UK/ANZ DCIS trial [15], and NSABP B35 [16], adjuvant endocrine therapy is known to reduce the risk of local recurrence for patients with DCIS so potentially the local recurrence rates in this series are lower than other published series as a result of increased utilization of uptake of adjuvant endocrine therapy in this study population (51% in our cohort in all patients; 60% in those known to be ER +). It is also possible that the nearly universal utilization of a boost may have contributed to the low recurrence rates in this study. A surgical bed boost has been shown to result in a small but significant decrease in local recurrence for patients with DCIS across age groups [17]. In comparison to this study, RTOG 9804 [3] specifically prohibited a boost while in the UK/ANZ DCIS [15] and EORTC 10853 [18] trials it was not recommended. The upcoming results of the Trans-Tasman Radiation Oncology Group (TROG) 07.01 trial (Clinicaltrials.gov NCT00470236) will hopefully further clarify the importance of the boost in patients with DCIS.

Another possible hypothesis is that recurrence rates are low secondary to modern multidisciplinary treatment approaches to DCIS as this study only examined patients treated 2001 and later. This hypothesis is supported by a study by Subhedar and colleagues that demonstrated improved local recurrence rates in the more modern era based on nearly 3000 cases of DCIS at their institution (13.6% vs. 6.6% 5-year recurrence rate for patients treated 1978–1998 vs. 1999–2010; hazard ratio 0.62, $P < 0.0001$). [19] Interestingly, even when controlling for a variety of other risk factors for local recurrence, treatment in the more modern era remained significantly associated with decreased recurrence rates. The RTOG 9804 results and the results of this series compare favorably to older series examining the rates of local recurrence in patients treated with BCS and

RT for DCIS that found ten-year LR rates as high as 10–13% [20, 21]. Collectively these data do suggest that the low rates of recurrence seen in patients treated since 1999–2000 are perhaps attributable to evolving and improving management of DCIS in more recent years.

Another possible explanation is that although there were some higher risk features, including grade and age, the overall volume of in situ disease was relatively small. While precise measurement of extent of DCIS is challenging, using the technique of multiplication of number of blocks involved by 4 mm to estimate DCIS size [22] would result in a median DCIS size of 1.2 cm in this series, which would be considered favorable by RTOG 9804 or ECOG 5194 criteria [3, 12]. It is possible that the breast cancer specialization of all of the multidisciplinary teams at our tertiary care institution, including pathology, radiology, and surgery, may lead to earlier detection of DCIS, therefore resulting in lower overall volume of disease, more complete pathologic evaluation of the surgical margins, and therefore low 10-year recurrence rates.

Our study identified a higher rate of CBC (7.9%) than LR. This incidence of CBC results is consistent with prior studies examining the rates of CBC in patients treated with adjuvant RT following BCS for DCIS (Table 3). We did not identify any risk factors for the development of CBC in our analysis. Significant risk factors for the development of CBC following an initial diagnosis of in situ or invasive breast cancer that have been identified in other studies include black race, lobular histology, family history, estrogen receptor status, and age at diagnosis [23–27]. Other studies have also demonstrated a reduction in risk of CBC for patients taking adjuvant endocrine therapy for DCIS [1, 15, 28].

This study is inherently limited by its retrospective design, which likely introduces selection bias regarding which patients were included in this study population. However, as consecutive patients were included in the initial prospective database with the only eligibility criteria being a diagnosis of pure DCIS treated with BCS and adjuvant RT, this cohort represents patients with heterogeneous patient and tumor features. The very small numbers of events limit the statistical power to determine risk factors for local or contralateral recurrences. Another limitation is that as post-operative mammograms were at the discretion of the treating provider and only 52% of patients with mammographic calcifications had post-operative mammogram performed, it is difficult to draw conclusions regarding the necessity of post-operative imaging in this patient population or the impact of this imaging on local recurrence. Another limitation of any retrospective chart review is the potential that data of interest may not have been documented and/or able to be located. For example, whether there was a specimen radiograph was of interest in this study but for patients who underwent surgery at an outside institution, records were unavailable as to whether this was actually performed. Similarly, it is possible it was performed but not documented at our institution.

The strengths of this study include the homogenous treatment approach, specifically that all patients underwent BCS followed by adjuvant RT with the goal surgical margin consistent with recently published guidelines, and pathologic review by one group of pathologists. Additionally, given the size of our institution, patients were treated by over thirty different surgeons and radiation oncologists, limiting the likelihood that our results are unique to a small number of providers.

In conclusion, our results should be reassuring to patients undergoing BCS and adjuvant RT for DCIS that their risk of local recurrence is very low at institutions that utilize modern surgical, radiographic, and pathologic techniques and are attentive to achieving negative surgical margins. These data along with the excellent long-term survival for patients with DCIS also support the need for research, such as the currently enrolling Comparison of Operative to Monitoring and Endocrine Therapy (COMET) trial (Clinicaltrials.gov NCT02926911), to identify patients in whom the omission of surgery and/or radiation therapy does not result in an unacceptably high rate of local recurrence. It is also likely that genomic tests, such as Oncotype DCIS [29, 30] and PreludeDx [31], will increasingly be utilized to help risk stratify patients and better estimate the benefits of adjuvant RT. Overall, the excellent outcomes with surgery and adjuvant radiation therapy compel a multidisciplinary

Table 3 Incidence of local recurrence and contralateral breast cancer in studies of patients with ductal carcinoma in situ treated with breast-conserving surgery and radiation therapy

Study	Design	No. patients	Dates treated	10-year incidence of LR (%)	10-year incidence of CBC
Current Study	Retrospective, single institution	245	2001–2007	1.5	7.9%
McCormick et al. [3]	Prospective, randomized	287	1998–2006	0.9	7 year: 3.9% (1.5–6.4%)
Kong et al. [20]	Population-based registry, Ontario	1607	1994–2003	13	5%
EBCTCG [2]	Meta-analysis	1878	1985–1998	12.9	7.2%
Solin et al. [12]	Retrospective, 10 institutions	1003	1973–1995	10	9% (7–11%)

discussion about opportunities to de-escalate therapy in this patient population. The decision to receive or to omit adjuvant radiation therapy remains incumbent upon a conversation between medical providers and patients regarding the goals of care, potential impact on oncologic outcomes, and side effects of radiation therapy.

Funding There was no specific funding supporting this research.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The DF/HCC institutional review board approved this study and waived the requirement for informed consent.

References

1. Wapnir IL, Dignam JJ, Fisher B et al (2011) Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. JNCI J Natl Cancer Inst 103:478–488. https://doi.org/10.1093/jnci/djr027
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, Correa C et al (2010) Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst. https://doi.org/10.1093/jncimonographs/lgq039
3. McCormick B, Winter K, Hudis C et al (2015) RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 33:709–715. https://doi.org/10.1200/JCO.2014.57.9029
4. Hiramatsu H, Bornstein BA, Recht A et al (1995) Local recurrence after conservative surgery and radiation therapy for ductal carcinoma in situ: possible importance of family history. Cancer J Sci Am 1:55–61
5. Halasz LM, Sreedhara M, Chen Y-H et al (2012) Improved outcomes of breast-conserving therapy for patients with ductal carcinoma in situ. Int J Radiat Oncol Biol Phys 82:e581–e586. https://doi.org/10.1016/j.ijrobp.2011.08.015
6. Morrow M, Van Zee KJ, Solin LJ et al (2016) Society of surgical oncology-American Society for radiation oncology-American Society of clinical oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol. https://doi.org/10.1200/JCO.2016.68.3573
7. Marinovich ML, Azizi L, Macaskill P et al (2016) The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 23:3811–3821. https://doi.org/10.1245/s10434-016-5446-2
8. Bijker N, Peterse JL, Duchateau L et al (2001) Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in situ: analysis of European organization for research and treatment of cancer trial 10853. J Clin Oncol 19:2263–2271. https://doi.org/10.1200/jco.2001.19.8.2263
9. Fisher ER, Costantino J, Fisher B et al (1995) Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. Cancer 75:1310–1319
10. McCormick JT, Keleher AJ, Tikhomirov VB et al (2004) Analysis of the use of specimen mammography in breast conservation therapy. Am J Surg 188:433–436. https://doi.org/10.1016/j.amjsurg.2004.06.030
11. Cabioglu N, Hunt KK, Sahin AA et al (2007) Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. Ann Surg Oncol 14:1458–1471. https://doi.org/10.1245/s10434-006-9236-0
12. Solin LJ, Gray R, Hughes LL et al (2015) Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol 33:3938–3944. https://doi.org/10.1200/JCO.2015.60.8588
13. Zujewski JA, Harlan LC, Morrell DM, Stevens JL (2011) Ductal carcinoma in situ: trends in treatment over time in the US. Breast Cancer Res Treat 127:251–257. https://doi.org/10.1007/s10549-010-1198-z
14. Allred DC, Anderson SJ, Paik S et al (2012) Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol 30:1268–1273. https://doi.org/10.1200/JCO.2010.34.0141
15. Cuzick J, Sestak I, Pinder SE et al (2011) Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 12:21–29. https://doi.org/10.1016/S1470-2045(10)70266-7
16. Margolese R, Cecchini RS, Julian TB et al (2016) Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. Lancet 387:849–856. https://doi.org/10.1016/S0140-6736(15)01168-X.Primary
17. Moran MS, Zhao Y, Ma S et al (2017) Association of radiotherapy boost for ductal carcinoma in situ with local control after whole-breast radiotherapy. JAMA Oncol 20:292–298. https://doi.org/10.1001/jamaoncol.2016.6948
18. Donker M, Litière S, Werutsky G et al (2013) Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol 31:4054–4059. https://doi.org/10.1200/JCO.2013.49.5077
19. Subhedar P, Olcese C, Patil S et al (2015) Decreasing recurrence rates for ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery over 30 years. Ann Surg Oncol 22:3273–3281. https://doi.org/10.1245/s10434-015-4740-8
20. Kong I, Narod SA, Taylor C et al (2014) Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ: a population-based outcomes analysis. Curr Oncol 21:e96–e104. https://doi.org/10.3747/co.21.1604
21. Solin LJ, Fourquet A, Vicini FA et al (2005) Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. Cancer 103:1137–1146. https://doi.org/10.1002/cncr.20886
22. Lester SC, Bose S, Chen Y et al (2009) Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. Arch Pathol Lab Med 133:15–25
23. Gao X, Fisher SG, Emami B (2003) Risk of second primary cancer in the contralateral breast in women treated for early-stage

breast cancer: a population-based study. Int J Radiat Oncol Biol Phys 56:1038–1045
24. Broët P, de la Rochefordière A, Scholl SM et al (1995) Contralateral breast cancer: annual incidence and risk parameters. J Clin Oncol 13:1578–1583. https://doi.org/10.1200/jco.1995.13.7.1578
25. Vaittinen P, Hemminki K (2000) Risk factors and age-incidence relationships for contralateral breast cancer. Int J Cancer 88:998–1002
26. Liu Y, Colditz GA, Gehlert S, Goodman M (2014) Racial disparities in risk of second breast tumors after ductal carcinoma in situ. Breast Cancer Res Treat 148:163–173. https://doi.org/10.1007/s10549-014-3151-z
27. Chowdhury M, Euhus D, Onega T et al (2017) A model for individualized risk prediction of contralateral breast cancer. Breast Cancer Res Treat 161:153–160. https://doi.org/10.1007/s10549-016-4039-x
28. Forbes JF, Sestak I, Howell A et al (2016) Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 387:866–873. https://doi.org/10.1016/S0140-6736(15)01129-0
29. Solin LJ, Gray R, Baehner FL et al (2013) A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 105:701–710. https://doi.org/10.1093/jnci/djt067
30. Rakovitch E, Nofech-Mozes S, Hanna W et al (2017) Multigene expression assay and benefit of radiotherapy after breast conservation in ductal carcinoma in situ. J Natl Cancer Inst 109:1–8. https://doi.org/10.1093/jnci/djw256
31. Bremer T, Whitworth PW, Patel R et al (2018) A biological signature for breast ductal carcinoma in situ to predict radiotherapy benefit and assess recurrence risk. Clin Cancer Res 24:5895–5901. https://doi.org/10.1158/1078-0432.CCR-18-0842