Breast Cancer Res Treat (2014) 143:343–350
DOI 10.1007/s10549-013-2813-6

CLINICAL TRIAL

Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS)

Julia S. Wong · Yu-Hui Chen · Michele A. Gadd · Rebecca Gelman · Susan C. Lester · Stuart J. Schnitt · Dennis C. Sgroi · Barbara J. Silver · Barbara L. Smith · Susan L. Troyan · Jay R. Harris

Received: 4 December 2013 / Accepted: 6 December 2013 / Published online: 18 December 2013

Abstract Whether wide excision with margins ≥1 cm is sufficient treatment for small low- or intermediate-grade ductal carcinoma in situ (DCIS) is unclear. This is an updated analysis of a phase II, single-arm, prospective trial testing this hypothesis. A total of 158 patients with low- or intermediate-grade DCIS who underwent wide excision alone (without radiation or tamoxifen) were entered onto the trial from 1995 to 2002. Entry criteria included mammographic extent ≤2.5 cm, predominantly low or intermediate nuclear grade, and excision with final microscopic margins ≥1 cm. Eight-year minimum potential follow-up was required for inclusion in the analysis; the final population comprised 143 patients. Cumulative incidence curves were generated to assess rates of local recurrence (LR) or other events. Median follow-up time was 11 years. Nineteen patients (13 %) had LR as a first event within 8 years. Thirteen LR (68 %) were DCIS only and six (32 %) were invasive. Fourteen (74 %) occurred in the original quadrant. The 10-year estimated cumulative incidence of LR was 15.6 %. The estimated annual percentage rate of LR was 1.9 % per patient-year. With longer follow-up, there remains a substantial and ongoing risk of LR in patients with favorable DCIS treated with wide excision margins without radiation. This information should be useful as patients and clinicians weigh the options of wide excision with and without radiation.

Keywords Ductal carcinoma in situ · Local recurrence · Wide excision

Introduction

The incidence of ductal carcinoma in situ (DCIS) increased from 5.8/100,000 women in the 1970s to 32.5/100,000

This manuscript contains original work and was presented in part at the 53rd Annual Meeting of the American Society for Radiation Oncology, Miami, FL, USA, October 2011.

J. S. Wong (✉) · B. J. Silver · J. R. Harris
Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School , Boston, MA, USA
e-mail: jwong@lroc.harvard.edu

Y.-H. Chen · R. Gelman
Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA

M. A. Gadd · B. L. Smith
Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

S. C. Lester
Department of Pathology, Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

S. J. Schnitt
Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

D. C. Sgroi
Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

S. L. Troyan
Department of Surgery, Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

women in 2004 when a plateau was reached [1, 2]. Improved mammographic and pathologic evaluation has led to detection of smaller lesions, often managed with breast-conserving surgery and radiation therapy (RT).

Four randomized trials confirm the benefit of RT after breast-conserving surgery, showing a substantial reduction in ipsilateral local recurrence (LR) [3–8]. Retrospective analyses suggest that some DCIS (low- or intermediate-grade lesions with "favorable" features) might be treated effectively with wide excision alone with a low rate of LR [9]. The challenge has been to reproduce these results in a prospective trial. Currently, treatment is variable and the options confusing for women and their doctors. Hence, the Institute of Medicine named DCIS one of the highest priority topics for comparative effectiveness research [10].

The purpose of this study was to prospectively evaluate selected patients with the aim of identifying a subgroup that could be treated with excision alone with a low recurrence rate. We described our initial study results in 2006, after early closure due to an unacceptably high LR rate [11]. In that analysis, with a median follow-up time of 40 months, a 5-year LR rate of 12 % was observed. The current study describes the updated results with a median follow-up time of 11 years, making it considerably more definitive.

Patients and methods

Eligibility and enrollment

The study design and patient eligibility have been described previously [11]. In brief, patients with low- or intermediate-grade DCIS measuring $\leq$2.5 cm and margins $\geq$1 cm were eligible for this IRB-approved trial conducted under informed consent. A total of 158 patients were entered from 1995 to 2002, when the study was closed prematurely because the number of recurrences crossed the predetermined stopping boundary.

Patients underwent mammograms with magnification views and DCIS size was determined either mammographically or clinically. Grade was defined by predominant nuclear grade. Each patient's slides were reviewed by a dedicated breast pathologist. Patients underwent wide excision with final histologic margins $\geq$1 cm or a negative re-excision. Chest wall and skin margins $\leq$1 cm were permitted if oriented clearly as such. A specimen radiograph was required, and if calcification removal was uncertain, a negative post-excision mammogram was required. Tamoxifen was not permitted. Patients were followed with ipsilateral mammograms every 6 months for 5 years, then annually; contralateral mammograms were obtained annually.

Statistical analysis

The study originally had a sequential design using the exact conditional Poisson test with planned analyses at a maximum of three time points and the design was amended in May 1999 to distinguish between a 1 and 2 % annual LR rate. Using the amended design, the overall type I error probability was 5 % and the power was 88 %. An initial report was published in 2006 [11]. The following updated analysis represents data as of February 2013, and is the 8-year analysis. The objectives are to update the distribution of failures and evaluate the effects of patient characteristics and disease factors on the risk of failures.

Statistical methods

Only LR and contralateral breast cancer (CBC) within 8 years were considered as events in this analysis. Follow-up was defined as time from registration to the first event. First events occurring >8 years after registration were not included in the primary analysis (i.e., all data censored at 8 years). Among the 158 patients, 12 without events were followed <8 years and were excluded from the main analysis. In addition, three patients died within 8 years without documented events and were also excluded. The final analysis therefore included 143 patients. Of note, while on study, one patient developed a stage I lung malignancy that was resected without further treatment; she has been followed >8 years without failure and was included in the analysis.

The number of events and estimated annual rate of recurrences were calculated overall and for subgroups defined by patient, disease, and treatment factors. The estimated annual rate of each event type was defined as the number of events divided by the total follow-up patient-years in the relevant subgroup. For patients with events within 8 years of follow-up, follow-up time was from registration to the event date. For patients without events within 8 years after registration, follow-up time was 8 years. Step-up multinomial logistic regression models were done. Relative risk ratios (RRRs) were defined as the risk ratio of either LR or CBC relative to the reference category (no events) for one subgroup of patients compared to the others. A two-sided significance level of 0.05 (for the LR RRR or the CBC RRR or both) was the criterion to include a variable in the model based on the log-likelihood ratio test.

Cumulative incidence rates of LR and CBC and associated 95 % confidence intervals were constructed using the method of Gray [12], which assumes that time to these events is statistically independent. Although estimated annual rates of recurrence and RRRs were calculated using data up to 8 years of follow-up, the analysis of cumulative

incidence used all available data among the 143 patients included in the main analysis. Among the patients free of events, 81 were followed >10 years, and the cumulative incidence rates at 10 years are also reported.

Results

Initial patient, tumor and treatment characteristics

Median age at diagnosis was 51 years (range 35–80). The median mammographic size of the initial DCIS was 0.8 cm. A total of 84 % underwent re-excision of which 93 % were negative. The median number of blocks containing DCIS was 2 (range 1–9). Predominant nuclear grade was low in 55 %. The highest nuclear grade (HNG) was low in 46 %, intermediate in 45 %, and high in 7 % (nine women with predominantly low-intermediate grade DCIS had a small percentage of high-grade nuclei). Necrosis was present in 40 %. Median follow-up time was 11.0 years (range 4.3–14.4).

Distribution of events by patient characteristics and pathologic factors

Among the 143 women included in the final analysis, 32 (23) had first events within 8 (5) years of follow-up, of which 19 (14) were LR and 13 (9) were CBC. Table 1 shows the numbers of each event type by initial clinical and tumor characteristics.

Local recurrences

Among the 19 LRs as the first event, 13 (68 %) were DCIS and 6 (32 %) were invasive. A total of 14 of 19 (74 %) occurred in the same quadrant as the primary tumor. Of the six invasive LRs, one included axillary involvement and three occurred in the same quadrant as the primary tumor. The LR rate was 1.9 % per patient-year. Patients with HNG = 3 had the highest rate of LR. Salvage treatment was as follows: seven women underwent excision, RT and tamoxifen; six chose mastectomy; five had excision and RT; and one had excision, RT, and chemotherapy. To date, no patient with LR has developed distant metastases or died. Of note, in addition to these 19 LRs, 5 other women had breast events that occurred >8 years after protocol registration and were therefore not included in the main analysis; of these, 4 were first-event LRs (3 invasive, 1 DCIS), and 1 (DCIS) occurred after a CBC.

Other events

Of the 13 CBCs, 3 (23 %) were DCIS and 10 (77 %) were invasive. The CBC rate was 1.3 % per patient-year. One additional CBC occurred >8 years after registration and was omitted from the main analysis. No patient experienced distant metastasis as a first event; one developed bone metastasis after CBC. There was one second malignancy (primary lung cancer), and four deaths from other causes.

Associations between patient, disease and treatment characteristics and events

Associations between characteristics and events (LR or CBC) were assessed. Variables evaluated in the model selection process, besides those indicated in Table 1, included time from diagnosis to registration; time from surgery to registration; architectural pattern; presence of calcifications on pathologic review; and presence of lobular carcinoma in situ, atypical lobular hyperplasia, and atypical ductal hyperplasia.

The final model, including mammographic size ≤0.5 cm, mammographic size unknown, HNG = 3, age at registration ≥60, re-excision and number of blocks with DCIS >2, is shown in Table 2. In general, the effects of these covariates on the occurrence of LR and CBC were in the same direction, but the effect size varied. Among these variables, HNG = 3, age >60, no re-excision, and >2 blocks with DCIS were significantly associated with a higher risk of LR, with RRRs of 14.0, 6.3, 7.7, and 3.7, respectively, after adjusting for the effects of other variables in the model. As for CBC, mammographic size ≤0.5 cm and number of blocks with DCIS >2 were significantly associated with a higher risk of CBC, with RRRs of 22.8 and 4.2, respectively, after adjusting for other variables.

Cumulative incidence

The estimated cumulative incidence of LR for all 143 patients was 9.8 % (95 % CI 4.9, 14.7) at 5 years, 13.3 % (95 % CI 7.7, 18.9) at 8 years, and 15.6 % (95 % CI 9.6, 21.6) at 10 years (Fig. 1; breakdown by invasive versus DCIS shown in Fig. 2). For CBC, the estimated cumulative incidence was 6.3 % (95 % CI 2.3, 10.3), 9.1 % (95 % CI 4.4, 13.8), and 9.1 % (95 % CI 4.4, 13.8) at 5, 8, and 10 years, respectively.

Discussion

In 2006, we reported a cumulative 12 % LR rate at 5 years among 158 patients entered on this trial of wide excision alone for DCIS, suggesting that even carefully selected patients had a substantial LR rate when RT was omitted. Now, with a minimum follow-up of 8 years and a median of 11 years, the 10-year cumulative incidence of LR is 15.6 %.

Table 1 Clinical and pathologic characteristics

Characteristics	*N*	Total follow-up time (patient-year)	No. without event (%)	No. with LR first	Estimated annual percentage rate (LR)	No. with CBC first	Estimated annual percentage rate (CBC)
All patients	143	993	111 (78)	19	1.9	13	1.3
Age at registration, years							
35–45	34	242	28 (82)	2	0.8	4	1.7
46–50	37	258	30 (81)	4	1.6	3	1.2
51–59	42	310	34 (81)	5	1.6	3	1.0
60–81	30	182	19 (63)	8	4.4	3	1.6
Menopausal status							
Unknown	3	19	2 (67)	1	5.3	0	0.0
Pre	58	396	45 (78)	5	1.3	8	2.0
Peri	17	135	16 (94)	1	0.7	0	0.0
Post	65	443	48 (74)	12	2.7	5	1.1
Mammographic size (by quartiles)							
Unknown	54	366	41 (76)	7	1.9	6	1.6
Q1 (0.1–0.5 cm)	29	196	20 (69)	3	1.5	6	3.1
Q2 (0.6–0.9 cm)	24	168	20 (83)	3	1.8	1	0.6
Q3 (1.0 cm)	21	145	16 (76)	5	3.4	0	0.0
Q4 (1.1–2.5 cm)	15	119	14 (93)	1	0.8	0	0.0
Total tissue volume excised (by quartiles)							
Unknown	23	164	18 (78)	2	1.2	3	1.8
Q1 (2.6–40.0 cm)	30	215	25 (83)	3	1.4	3	1.4
Q2 (40.1–73.0 cm)	29	207	22 (76)	6	2.9	0	0.0
Q3 (73.1–110.2 cm)	31	218	26 (84)	3	1.4	3	1.4
Q4 (112.4–425 cm)	30	188	20 (67)	5	2.7	4	2.1
Re-excision							
No	23	142	15 (65)	6	4.2	2	1.4
Yes	120	851	96 (80)	13	1.5	11	1.3
Residual cancer in re-excision ($n = 120$)							
No	111	800	83 (75)	10	1.3	10	1.3
Yes	9	51	5 (56)	3	5.9	1	2.0
Prior core biopsy							
No	96	675	76 (79)	10	1.5	10	1.5
Yes	47	319	35 (74)	9	2.8	3	0.9
Predominant nuclear grade							
Unknown	2	16	2 (100)	0	0.0	0	0.0
1	79	553	62 (78)	10	1.8	7	1.3
2 and 3	62	424	47 (76)	9	2.1	6	1.4
Highest nuclear grade							
Unknown	2	16	2 (100)	0	0.0	0	0.0
1	66	460	51 (77)	8	1.7	7	1.5
2	65	466	54 (83)	7	1.5	4	0.9
3	10	52	4 (40)	4	7.7	2	3.8
No. of blocks with DCIS							
Unknown	9	65	8 (89)	1	1.5	0	0.0
1	63	456	51 (81)	6	1.3	6	1.3
2	34	241	28 (82)	4	1.7	2	0.8
3	13	81	9 (69)	2	2.5	2	2.5
4–9	24	151	15 (63)	6	4.0	3	2.0

Table 1 continued

Characteristics	*N*	Total follow-up time (patient-year)	No. without event (%)	No. with LR first	Estimated annual percentage rate (LR)	No. with CBC first	Estimated annual percentage rate (CBC)
Presence of necrosis (some with more than 1)							
Unknown	8	57	7 (88)	1	1.8	0	0.0
Absent	78	553	62 (79)	8	1.4	8	1.4
Central or small foci	57	384	42 (74)	10	2.6	5	1.3

Q Quartile, *DCIS* ductal carcinoma in situ, *NED* no evidence of disease (alive and without cancer at 8 years), *LR* local recurrence, *CBC* contralateral breast cancer

Four large randomized trials confirm the benefit of RT after breast-conserving surgery for DCIS, showing a reduction in LR (invasive or DCIS) of approximately 50–60 % [3–8]. This reduction, seen across all subgroups of patients with DCIS, has been the main factor influencing the use of RT. However, RT consumes time and resources, and carries a risk of toxicity (however low with modern techniques). Furthermore, while the reduction in LR is well-established, no survival benefit with the use of RT has been demonstrated [3–8, 13].

Accordingly, attention has been focused on identifying subgroups of patients in whom RT can be omitted safely. A retrospective analysis described a 3 % LR rate at 8 years for selected patients managed with excision alone and wide margins; however, a 12-year update of a subset of these patients described a 13.9 % LR rate [9, 14]. In the prospective Eastern Cooperative Oncology Group (ECOG) E5194 single-arm trial of excision alone, patients with high-grade DCIS measuring $\leq$1 cm with margins $\geq$3 mm had a 15.3 % LR rate at 5 years [15]. Patients with low/intermediate-grade DCIS measuring $\leq$2.5 cm with margins $\geq$3 mm had a 5-year LR rate of 6.1 %. Some differences in methodology between the ECOG study and ours are notable. The ECOG definition of low/intermediate grade was nuclear grade 1 or 2 with limited or no foci of necrosis whereas ours was predominant nuclear grade 1 or 2 and did not specify necrosis. The ECOG specimens were processed with complete sequential embedding (not routine). In addition, tamoxifen was not allowed in our study, but in the ECOG study, 31.3 % of the equivalent patients intended to use it. The importance of these differences is debatable. In a recent ECOG update, with a median follow-up of 8.8 years, the 10-year LR rate for the low/intermediate-grade group (14.6 %) approached that of the high-grade group (19.0 %) [16]. The updated ECOG results are now very similar to ours.

In the final model in our study, the presence of even a small percentage of high nuclear grade, no re-excision, age $\geq$60 and >2 blocks containing DCIS were all associated with a significantly higher RRR for LR. Size has been described in the literature with variable effects on LR [5, 17, 18]. While grade was defined as *predominant* nuclear grade, women with *any* high-grade nuclei had an elevated risk of LR, which persisted with longer follow-up. Low/intermediate-grade DCIS, unlike high-grade, has a long natural history; it is necessary to follow these patients beyond 5 years for late recurrences [19]. It is harder to interpret the meaning of the "no re-excision" variable's association with increased LR; it may be confounded with size or other unknown variables in this setting. Young age has been shown in other series to be associated with increased LR; why older age is associated with LR in this setting is unclear.

We observed an unusually high rate of CBCs (cumulative incidence of 6.3 % at 5 years), possibly a reflection of the small sample size. In the ECOG experience, the 5-year CBC rate was 3.7 %, and in the Radiation Therapy Oncology Group (RTOG) trial mentioned below, the 5-year rate of CBC was 2–3 %. The reason for the association between smaller mammographic size and CBC in our study is unclear.

There are several endpoints to consider in the treatment of DCIS. The most important is the risk of invasive recurrence and the subsequent likelihood of distant metastasis. This risk can be lowered with adjuvant radiation and/or tamoxifen. The updated ECOG results and ours both show an overall LR risk of about 15 % at 10 years for women treated with excision alone with widely negative margins. Assuming a 50–60 % reduction with the addition of radiation (as seen in the four initial large trials), this risk is reduced to about 7 % at 10 years. If half of the LRs are invasive, the risk of invasive recurrence is reduced to 3–4 %. Adding tamoxifen to radiation for patients with estrogen receptor-positive DCIS achieves a relative risk reduction of about 30 % [5]; the risk of invasive recurrence is then <3 %. (An 85 % reduction with radiation, as seen in the RTOG trial, would lower the rate even further.) In updated results of the National Surgical Adjuvant Breast and Bowel Project DCIS trials [5], invasive LR was associated with increased mortality (HR = 1.75; $p < 0.001$). In another series of 1,236 patients who underwent mastectomy or excision with or without RT, 63 had an invasive

Table 2 Distribution of failures by variables in the final model

Characteristics	*N*	Total follow-up time	No. with NED (%)	No. with LR first	Estimated annual percentage rate (LR)	No. with CBC first	Estimated annual percentage rate (CBC)
All patients	143	993	111 (78)	19	1.9	13	1.3
Mammographic size							
Unknown	54	366	41 (76)	7	1.9	6	1.6
≤ 0.5 cm^3	29	196	20 (69)	3	1.5	6	3.1
>0.5 cm^3	60	432	50 (83)	9	2.1	1	0.2
Highest nuclear grade							
1, 2, and unknown	133	941	107 (80)	15	1.6	11	1.2
3	10	52	4 (40)	4	7.7	2	3.8
Age at registration, years							
<60	113	811	92 (81)	11	1.4	10	1.2
≥60	30	182	19 (63)	8	4.4	3	1.6
Re-excision							
No	23	142	15 (65)	6	4.2	2	1.4
Yes	120	851	96 (80)	13	1.5	11	1.3
Number of blocks with DCIS							
1, 2, and unknown	106	762	87 (82)	11	1.4	8	1.0
>2	37	231	24 (65)	8	3.5	5	2.2

Number without event includes patients who were alive and without LR or CBC at 8 years

LR Local recurrence, *CBC* contralateral breast cancer

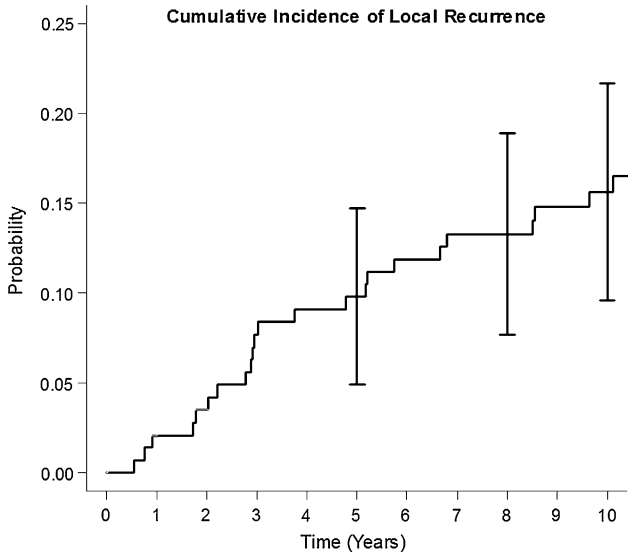

Fig. 1 Estimated cumulative incidence of LR

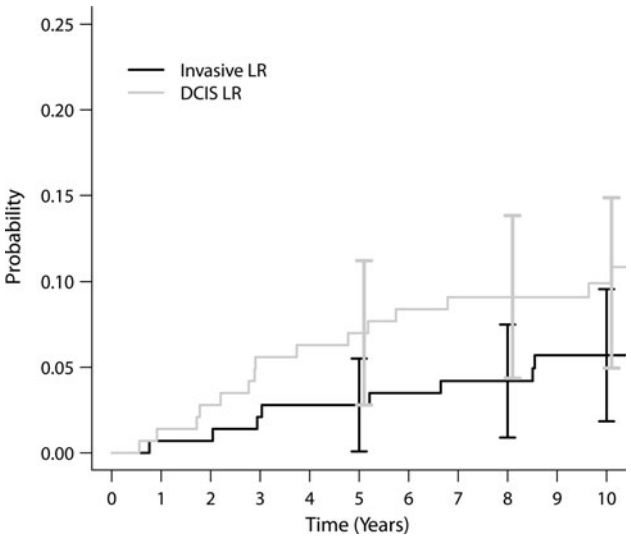

Fig. 2 Estimated cumulative incidence of LR: DCIS versus invasive

recurrence; among those, the distant-disease probability was 15 % and the 12-year breast cancer-specific mortality was 12 % [20]. In a European trial of excision with or without RT, 14/60 patients (23 %) with invasive recurrence developed distant metastases [21]. In another recent series, 16/66 patients (24 %) with invasive LR developed distant metastases [22]. In a multi-institutional study of 422 patients treated with excision and RT, 42 had local-only first failure; their rate of freedom from distant metastases was 89 % at 8 years and their cause-specific survival rate was 92 % [23]. Thus, there are risks of distant metastases and death in women with an invasive recurrence. All LRs

in our study were salvaged; whether these results hold with longer follow-up remains to be seen. It is important to convey these risks when counseling patients whether to pursue RT and to note that such treatment is generally well-tolerated and cost-effective [24]. The RTOG recently presented early results from a randomized trial of RT versus observation in 636 patients with small, low/intermediate-grade DCIS with margins ≥3 mm [25]. A total of 62 % took tamoxifen. With a median follow-up time of 6.46 years, the 5-year LR rate in the RT group was 0.4 versus 3.2 % in the observation group ($p = 0.0023$), an 85 % reduction. Moreover, the effect of RT on local control in DCIS is durable [5–7]. The impact of LR (even if non-invasive) can be distressing to patients; the accompanying work-up and need for additional treatment take a toll psychologically, and on family life, work, and finances.

Local control continues to improve with refinements in clinicopathologic evaluation and treatment. A review of DCIS treated with breast-conserving surgery and RT at our combined institutions from 1976 to 1990 showed a 15 % risk of LR at 10 years [26]. This led to more meticulous mammographic and pathologic evaluation, achievement of clearly negative margins and the routine use of a boost, resulting in a much lower risk of LR (0/246 patients recurred with a median follow-up of 58 months) [27].

Our study and ECOG E5194 suggest that margins, DCIS size, and grade are insufficient for distinguishing a subgroup of patients managed without RT in whom LR rates will remain <10–15 % with long-term follow-up. Anatomic factors (i.e., margins) may have less importance than biological ones; we now characterize invasive cancers by biological subtype, which predicts behavior and response to treatment. Biomarkers in DCIS have shown promise [28] but none thus far has been robust enough to use in clinical practice. The Oncotype DX assay, used to predict the risk of distant relapse and the potential benefit from chemotherapy for invasive cancers, has been modified for use in DCIS [16]. When performed on 327 DCIS cases from ECOG E5194, a recurrence score was calculated using an optimized gene-expression algorithm; score was significantly associated with outcome. These results are promising and worthy of further investigation; the development of a molecular test may help define a subgroup of patients in whom wide excision will suffice.

Our study has limitations, including small numbers and the use of predominant nuclear grade. Our logistic regression analysis to identify variables associated with LR did not yield conclusive findings; some results were consistent with others' findings, while some were not (likely due to a small number of events).

In summary, our results show that with longer follow-up, there remains a substantial and continuing risk of LR in patients with small low/intermediate-grade DCIS treated with wide excision with margins ≥1 cm without RT. Notably, most LRs occurred in the same quadrant as the primary lesion. Invasive LR and DCIS LR have different implications. As patients may value outcomes differently, it is important to convey all the risks and benefits. The information provided here should be useful as patients and their clinicians weigh the options of wide excision with and without radiation. An observational registry such as this one may help provide prognostic information on lesions of "low malignant potential" as some have called for a reevaluation of the nomenclature of such lesions [29]. Strategies to evaluate initial management decisions may be useful [30]. Standard clinical and pathologic variables are inadequate for describing a favorable subpopulation for wide excision alone. Further study of biomarkers and gene-expression patterns is warranted to determine if there are patients with low/intermediate-grade DCIS who are at low risk of LR after wide excision alone.

Conflict of interest The authors declare no conflict of interest.

References

1. Brinton LA, Sherman ME, Carreon JD et al (2008) Recent trends in breast cancer among younger women in the United States. J Natl Cancer Inst 100:1643–1648
2. Virnig BA, Tuttle TM, Shamliyan T et al (2010) Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 102:170–178
3. Fisher ER, Dignam J, Tan-Chiu E et al (1999) Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 86:429–438
4. Fisher B, Land S, Mamounas E et al (2001) Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. Semin Oncol 28:400–418
5. 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. J Natl Cancer Inst 103:478–488
6. 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
7. Bijker N, Meijnen P, Peterse JL 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
8. Holmberg L, Garmo H, Granstrand B et al (2008) Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J Clin Oncol 26:1247–1252
9. Silverstein MJ, Lagios MD, Groshen S et al (1999) The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 340:1455–1461
10. Initial National Priorities for Comparative Effectiveness Research (2009). The National Academies Press, Washington, DC

11. Wong JS, Kaelin CM, Troyan SL et al (2006) Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 24:1031–1036
12. Gray RJ (1988) A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141–1154
13. Correa C, McGale P, Taylor C et al (2010) Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010:162–177
14. Macdonald HR, Silverstein MJ, Lee LA et al (2006) Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. Am J Surg 192:420–422
15. Hughes LL, Wang M, Page DL et al (2009) Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 27:5319–5324
16. 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
17. Alvarado R, Lari SA, Roses RE et al (2012) Biology, treatment, and outcome in very young and older women with DCIS. Ann Surg Oncol 19:3777–3784
18. Pinder SE, Duggan C, Ellis IO et al (2010) A new pathological system for grading DCIS with improved prediction of local recurrence: results from the UKCCCR/ANZ DCIS trial. Br J Cancer 103:94–100
19. Solin LJ, Kurtz J, Fourquet A et al (1996) Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol 14:754–763
20. Lee LA, Silverstein MJ, Chung CT et al (2006) Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in situ of the breast. Am J Surg 192:416–419
21. 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
22. Roses RE, Arun BK, Lari SA et al (2011) Ductal carcinoma-in situ of the breast with subsequent distant metastasis and death. Ann Surg Oncol 18:2873–2878
23. Solin LJ, Fourquet A, Vicini FA et al (2001) Salvage treatment for local recurrence after breast-conserving surgery and radiation as initial treatment for mammographically detected ductal carcinoma in situ of the breast. Cancer 91:1090–1097
24. Suh WW, Hillner BE, Pierce LJ et al (2005) Cost-effectiveness of radiation therapy following conservative surgery for ductal carcinoma in situ of the breast. Int J Radiat Oncol Biol Phys 61:1054–1061
25. McCormick B (2012) RTOG 9804: a prospective randomized trial for "good risk" ductal carcinoma in situ (DCIS), comparing radiation (RT) to observation (OBS). ASCO Meeting Abstracts 30:1004
26. 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
27. Halasz LM, Sreedhara M, Chen YH 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
28. Lari SA, Kuerer HM (2011) Biological markers in DCIS and risk of breast recurrence: a systematic review. J Cancer 2:232–261
29. Esserman LJ, Thompson IM, Reid B (2013) Overdiagnosis and overtreatment in cancer: an opportunity for improvement. JAMA 310:797–798
30. Soeteman DI, Stout NK, Ozanne EM et al (2013) Modeling the effectiveness of initial management strategies for ductal carcinoma in situ. J Natl Cancer Inst 105:774–781