Ann Surg Oncol (2017) 24:1221–1226
DOI 10.1245/s10434-016-5711-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast-Conserving Surgery Alone for Ductal Carcinoma In Situ: Factors Associated with Increased Risk of Local Recurrence

Alessandra Mele, MD[1], Pritesh Mehta, MD[2], Priscilla J. Slanetz, MD, MPH[2], Alexander Brook, PhD[2], Abram Recht, MD[3], and Ranjna Sharma, MD[4]

[1]Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [2]Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [3]Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [4]Division of Surgical Oncology, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

ABSTRACT

Purpose. This retrospective study was aimed at identifying clinicopathologic characteristics associated with an increased risk for ipsilateral local recurrence (LR) in patients with ductal carcinoma in situ (DCIS) treated with wide local excision (WLE) alone without radiotherapy (RT).

Methods. All patients with DCIS treated with WLE alone at the Beth Israel Deaconess Medical Center, Boston, MA, USA, between the years 2000 and 2010 were identified. We collected data on demographics, parity, personal or family history of breast cancer, exogenous hormone use, tobacco use, comorbidities, genetic mutation carrier status, imaging interval, and tumor-specific characteristics.

Results. Overall, 222 patients were included in the study. Median follow-up time was 8 years. LR occurred in 9% of patients, with a recurrence rate of 11.3 per 1000 person-years. The risk of recurrence was lower for patients with nuclear grade (NG) I tumors than for patients with NG II or NG III tumors (3, 8.5, and 19%, respectively; $p = 0.01$). The median margin width was 1 mm in patients experiencing LR versus 1.8 mm in patients without LR ($p = 0.3$). Patients who had used exogenous hormones, or patients with a history of tobacco use, had higher rates of LR than those who did not, although the difference did not reach statistical significance.

Conclusions. Our data indicate that higher NG, narrower margin width, use of exogenous hormones, and smoking history may be associated with an increased risk of LR. The evaluation of these factors may be helpful when considering whether or not to use adjuvant RT for patients with DCIS.

First Received: 2 August 2016;
Published Online: 29 November 2016

R. Sharma, MD
e-mail: rsharma1@bidmc.harvard.edu

Following the introduction of screening mammography, ductal carcinoma in situ (DCIS) of the breast has been increasingly diagnosed and now represents 20–25% of all breast cancers in the US.[1] Breast-conserving therapy (BCT), wide local excision (WLE) of the tumor followed by radiotherapy (RT), is accepted as a valid treatment modality for DCIS, with survival rates similar to those achieved with mastectomy.[2–4] Randomized trials have shown a reduction in local recurrence (LR) rates in patients treated with RT after surgical resection,[5–8] but have not demonstrated a survival advantage compared with resection alone.[5,9,10] Whether adjuvant RT is an appropriate treatment for all patients remains controversial, with many physicians feeling that this practice may be overtreatment in selected patients in whom the risk of recurrence is very low.

Although radiation treatment is generally well tolerated, it is associated with side effects such as fatigue, skin irritation, cardiac and pulmonary toxicity, and brachial plexopathy. Importantly, there is an increased risk of developing secondary cancers, including gastrointestinal, urogenital, hematological, lung, and skin and soft tissue malignancies.[11–13] Furthermore, in case of an LR, previous radiation treatment renders BCT not feasible in most patients.

In this study, we aimed to retrospectively identify clinicopathological characteristics associated with an increased risk for ipsilateral LR in patients who did not receive RT,

thereby allowing us to define a select patient population who may benefit from a WLE-alone protocol, omitting adjuvant RT.

METHODS

After obtaining approval from the Institutional Review Board, we searched the tumor registry of the Beth Israel Deaconess Medical Center, Boston, MA, USA, for all patients with DCIS treated with WLE between the years 2000 and 2010. Patients who underwent adjuvant radiation therapy after WLE were excluded from the study, along with patients who received follow-up care at a different institution. Of the 296 patients who were initially identified, 74 were excluded. The remaining 222 patients defined the cohort for this study.

We performed a retrospective review of the electronic medical records for all patients who met the inclusion criteria, and extracted information on demographics, parity, personal or family history of breast cancer, exogenous hormone use, tobacco use, comorbidities, genetic mutation carrier status, imaging interval, and tumor-specific characteristics (size, margins, grade, architectural subtype, presence of necrosis, estrogen receptor status), as well as the use of tamoxifen or aromatase inhibitors as adjuvant therapy.

The primary endpoint for this study was to determine the risk of LR in this patient population who only had WLE of their DCIS. We performed statistical analyses to determine the risk of LR. We used the Cochran–Armitage test for trend to compare time to recurrence across tumor grades, the Kruskal–Wallis test and t test to compare continuous variables between groups, and Fisher's exact test to compare categorical variables between groups. Kaplan–Meier estimates and the log-rank test were used for analysis of recurrence. The log-rank test for trend was used to compare recurrence across tumor grades, while linear regression was used to evaluate the trend in time to recurrence across tumor grades. Statistical significance was set at $\alpha = 0.05$, and calculations were performed using Matlab (Mathworks, Natick, MA, USA).

RESULTS

Overall, 296 eligible patients with a mean age at diagnosis of 59 years (range 33–90) were initially identified. Seventy-four patients were excluded from the analysis because they were not followed in our institution after undergoing WLE, resulting in the inclusion of 222 patients in our study cohort. The median follow-up time was 8 years (range 0.11–16.6). The characteristics of the study population, as well as the patients who were lost to follow-up are summarized in Table 1.

Nineteen patients (9%) in our study experienced an LR, with a recurrence rate of 11.3 per 1000 person-years (Fig. 1). The median time from excision to LR was 4.2 years (range 0.8–11.7), and the mean age at diagnosis of the initial breast cancer in patients who developed a recurrence was 54.9 years, which was not significantly different from patients who did not develop an LR (59.5 years; $p = 0.1$).

Sixty-four patients (29%) had a nuclear grade (NG) I tumor, 118 (53%) had an NG II tumor, 26 (12%) had an NG III tumor, and in 14 patients (6%) the NG was not recorded. The recurrence-free survival decreased significantly with increasing grade ($p = 0.0062$) (Fig. 2), with a median time to recurrence of 9.9 years for patients with NG I, 3.9 years for patients with NG II, and 3.4 years for those with NG III ($p = 0.023$).

The clinical variables examined for risk of LR are shown in Table 2. The risk of recurrence was significantly lower for patients with NG I tumors compared with patients with NG II or NG III tumors (3.1, 8.5, and 19.2%, respectively; $p = 0.01$). Patients experiencing LR had a median margin width of 1.0 mm, compared with a margin of 1.8 mm in patients without LR; however, the difference was not statistically significant ($p = 0.3$).

Patients who had used oral contraceptives or hormone replacement therapy, as well as patients with a history of tobacco use, had higher rates of LR than those who did not (Table 2), although these differences did not reach statistical significance (14.8 vs. 6.2%, $p = 0.14$; and 17.1 vs. 7.4%, $p = 0.08$, respectively).

Although the risk of LR in patients who used fertility treatments in our study population was statistically significant ($p = 0.05$), this is not a reliable conclusion since it is based on a very small subset of patients in our study cohort (Table 2).

No significant association was observed between the use of tamoxifen or aromatase inhibitors and the risk of LR (Table 2). In addition, a personal history of breast cancer, as well as a family history of breast cancer, did not contribute to the risk of LR.

DISCUSSION

Several randomized trials and meta-analyses have confirmed the benefit of RT after BCT for the treatment of DCIS.[14–16] In all studies, RT reduced the incidence of invasive and non-invasive recurrences irrespective of age at diagnosis, tumor size, grade, architecture, and margin status; however, RT did not alter the risk of distant

TABLE 1 Characteristics of the study population

	Study population [$n = 222$]		Patients lost to follow-up [$n = 74$]	
Mean age at diagnosis (range)	59	(33–90)	61	(37–91)
Tumor grade [n (%)]				
I	64	(28.8)	15	(20.3)
II	118	(53.2)	27	(36.5)
III	26	(11.7)	27	(36.5)
NA	14	(6.3)	5	(6.8)
Median follow-up time, years (range)	8.0	(0.1–16.6)		
Local recurrences [n (%)]	19	(8.6)		
Mean age at recurrence (range)	60	(39–92)		
Median time to recurrence, years (range)	4.2	(0.8–11.7)		

NA not available

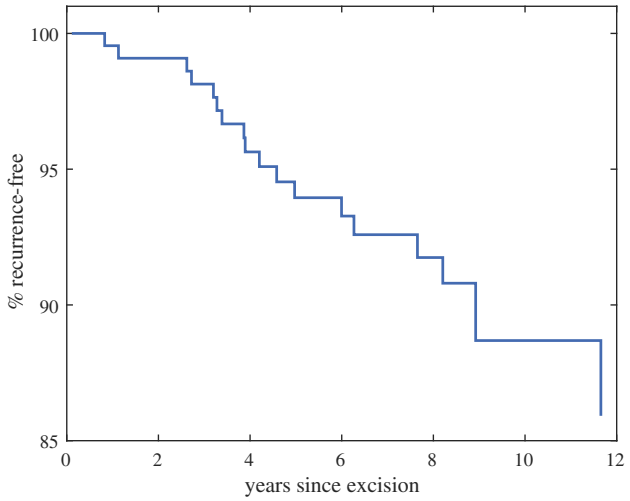

FIG. 1 Kaplan-Meier curve for recurrence-free survival after wide local excision alone

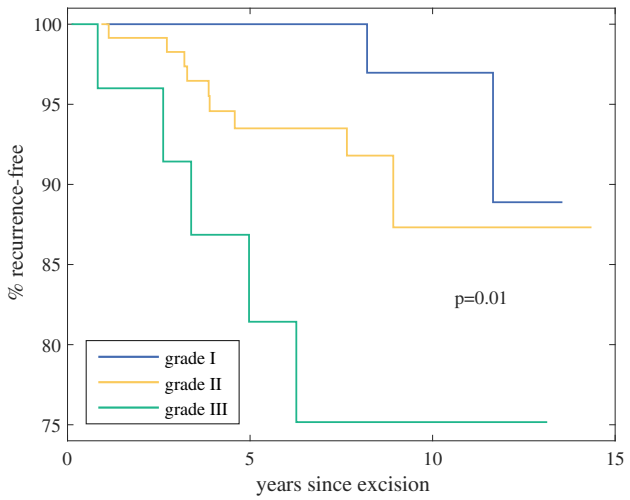

FIG. 2 Kaplan-Meier curve for recurrence-free survival after wide local excision alone by nuclear grade

recurrence and did not decrease mortality among patients with DCIS.[16,17]

Studies have thus focused on identifying subsets of patients at low risk of recurrence in whom RT could be safely omitted. The Radiation Therapy Oncology Group (RTOG) 9804 trial examined the outcomes of RT in patients with low-risk DCIS (low- or intermediate-grade DCIS measuring <2.5 cm with resection to negative margins of ≥3 mm).[18] After a median follow-up of 7 years, RT after BCT was associated with a reduced risk of LR, compared with observation (LR rates of 0.9 and 6.7%, respectively), but no difference in either disease-free survival or overall survival. Data from a 2016 large longitudinal study including over 30,000 patients with DCIS treated with BCT show that adjuvant RT only improves survival in patients with higher NG, age younger than 60 years, and tumor size >1.6 cm.[19]

In our study cohort, 9% of patients experienced an LR. This rate might have been slightly underestimated due to the relatively higher proportion of patients with high NG among patients lost to follow-up, compared with those included in the analysis. The risk of recurrence was highest for patients with NG III tumors, and the time to recurrence shorter for these high-grade patients. Furthermore, a narrower resection margin seemed to be associated with increased risk of recurrence, although the difference was not statistically significant.

In multiple studies, high NG and margin positivity have been shown to be associated with LR in women treated with BCT.[20–22] As an example, a population-based study from Ontario with a median follow-up of 10 years found the actuarial 10-year local failure rates were 14% for 109 unirradiated patients with low NG DCIS, 18% for 484 patients with intermediate NG, and 26% for 322 patients with high NG.[21] However, the effect of grade has been

TABLE 2 Distribution of clinical variables and crude recurrence rates in patients with and without local recurrence

Prognostic factors	Patients without LR	Patients with LR	Crude recurrence rate (%)	*p*-Value (difference in crude rates)	5-year Kaplan–Meier LR rates (%)	*p*-Values (difference in Kaplan–Meier LR)
Family history of breast cancer						
Yes	48	6	11.1	0.58	7.6	0.89
No	139	13	8.6		6.1	
Personal history of breast cancer						
Yes	9	1	10.0	1.0	0.0	0.98
No	179	18	9.1		6.8	
Nulliparous						
Yes	51	7	12.1	0.29	5.6	0.30
No	136	11	7.5		6.1	
Oral contraceptives or HRT						
Yes	52	9	14.8	0.06	8.7	0.14
No	122	8	6.2		5.2	
Fertility treatments						
Yes	3	1	25.0	0.31	50.0	0.05
No	171	16	8.6		5.9	
Tamoxifen use						
Yes	76	8	9.5	0.81	5.0	0.81
No	120	11	8.4		7.1	
Aromatase inhibitor use						
Yes	15	1	6.3	1.0	6.7	0.60
No	182	18	9.0		6.2	
Ever use of tobacco						
Yes	34	7	17.1	0.07	13.2	0.08
No	150	12	7.4		4.9	
Tumor grade						
I	62	2	3.1		0.0	
II	108	10	8.5	0.01	6.5	0.01
III	21	5	19.2		18.6	
Margins						
Positive	47	6	11.3	0.39	8.3	0.34
Negative	150	12	7.4		4.8	

The table shows the number of patients with and without LR, crude recurrence rates for the study period, *p*-values for the difference in crude recurrence rates for each prognostic factor, 5-year Kaplan–Meier local recurrence rate estimates, and log-rank *p*-values for the difference in survival for each prognostic factor

LR local recurrence; *HRT* hormone replacement therapy

difficult to determine as nearly all randomized trials and retrospective studies did not require a specific minimum tumor-free margin width. In those studies, the effect of grade may have been confounded by the effect of margin width. Even in studies in which data on both grade and margin width have been available, investigators often did not report LR rates related to grade by margin width category.

The effect of grade in unirradiated patients can be seen best in patients with wide margins. The Harvard cooperative study of excision alone for DCIS, which required a margin width of 10 mm or no tumor on re-excision, showed crude LR rates of 14% (8/59) for patients with highest NG 1, 11% (7/61) for highest NG 2, and 50% (4/8) for those with highest NG 3 at a median follow-up of 11 years, excluding patients who developed a prior contralateral breast cancer.[22] A recent update of the Eastern Cooperative Oncology Group (ECOG) 5194 trial, in which all patients had a minimum tumor-free margin width of at least 3 mm, found that patients with low- or intermediate-grade lesions had a lower 12-year local failure rate (14.4%) than those with high-grade DCIS (24.6%), with a median follow-up of 12.3 years.[20]

The association of margin width with the risk of recurrence has been demonstrated in a meta-analysis of 22 trials

including 4660 patients with DCIS treated with BCT and RT.[23] In this study, a margin ≥2 mm was associated with a nearly 50% reduction in the risk of LR compared with a margin <2 mm. In our cohort, patients with LR had a narrower median resection margin compared with patients without LR (1.0 vs. 1.8 mm), although the difference was not statistically significant.

The evaluation of tumor-specific factors and margin status can be helpful in deciding whether the use of adjuvant RT optimizes treatment plans in patients with DCIS. Moreover, patient-specific factors, such as smoking history and exogenous hormone use, should also be taken into consideration. In our cohort, we found that patients with a history of tobacco use and oral contraceptive pill or hormone replacement therapy use had an increased risk of LR, although it did not reach statistical significance.

The use of postoperative RT in patients with a history of tobacco use, especially in those who are current smokers, may pose a concern regarding the risk of a second primary lung cancer. Lung cancers following radiation therapy administered for breast cancer treatment are almost entirely limited to current or former smokers.[24–26] However, the absolute excess risk appears to be small, even when large lung volumes are irradiated. No increase in risk has been found among women receiving RT after lumpectomy, in whom small lung volumes were generally irradiated.[27–29] For instance, in patients undergoing mastectomy, postmastectomy radiation therapy was only associated with an estimated excess of approximately nine lung cancer cases per 10,000 women who survived more than 10 years from diagnosis in one study.[29] Thus, smokers with DCIS are likely to have very little excess risk for developing lung cancer,

We did not find a significant reduction in recurrence rates among women treated postoperatively with tamoxifen, although multiple randomized trials and one meta-analysis demonstrated that in women treated with BCT, adjuvant tamoxifen with or without adjuvant RT reduces the risk of ipsilateral and contralateral DCIS.[10,30,31] The small sample size and lack of detailed information on duration and adherence to the prescribed treatment likely did not allow us to detect an effect of endocrine therapy on the risk of tumor recurrence in our cohort.

Although patient age has been shown to be associated with the risk of LR, with risk decreasing with increasing age, we did not observe an effect of age on the risk of LR in our dataset. Our study, which included only eight patients aged 40 years or younger, was clearly underpowered to detect an effect of age on the risk of LR. However, in a study of 2996 women (141 patients younger than 40 years of age) treated with BCS over 30 years, the risk of recurrence was approximately 20 and 50% lower for women aged 40–49 years and 50–79 years, respectively, compared with women younger than 40 years of age.[32] In another study including 418 women (30 patients younger than 40 years of age) treated with BCS followed by breast irradiation, the 10-year rate of local failure was 31% for patients younger than 40 years of age, 13% for age 40–49 years, 8% for age 50–59 years, and 6% for patients aged >60 years.[33]

We acknowledge the limitations of our study, which include its retrospective nature, single institution sample, and small sample size; however, we feel this is a valuable contribution to this debated topic in contemporary practice.

CONCLUSIONS

The results of our study suggest that adjuvant RT may be an appropriate choice in patients who have unfavorable clinicopathologic characteristics and less extensive surgery. Personal risk factors and lifestyle habits may also contribute to a poor clinical outcome. Further studies are necessary to better understand the biology of the carcinoma and its impact on clinical outcome.

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