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Biology, Treatment, and Outcome in Very Young and Older Women with DCIS

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Abstract

Background—This study examines a modern cohort of women with ductal carcinoma-in-situ (DCIS) in order to identify potential differences in clinical presentation, treatments, and outcome based on age.

Methods—From 1996 to 2009, a total of 2037 patients with pure DCIS were treated. Clinical presentation, pathologic factors, type of surgery and adjuvant therapy, and local recurrence rates among age groups were compared and analyzed. Median follow-up was 5.2 years.

Results—There were 132 patients (6.5 %) aged <40, 1,690 (83 %) aged 40–70, and 215 (10.5 %) aged >70. Younger patients (<40) were significantly more likely to have a family history of breast cancer, present with clinical symptoms, undergo mastectomy with immediate reconstruction, and have a contralateral prophylactic mastectomy ($P < 0.05$). Older patients (>70) were significantly less likely to use adjuvant radiotherapy and tamoxifen ($P < 0.05$). No significant differences were found in DCIS size, estrogen receptor status, necrosis, or contralateral breast cancer based on age. Among women <40, 29.3 % had evidence of multicentric disease versus 17.7 and 13.3 % in the women aged 40–70 and those >70, respectively ($P = 0.004$). On multivariate analysis, younger age (<40), larger-size DCIS (≥1.5 cm), and no use of radiotherapy were significant independent predictors of locoregional recurrence. The 5 year rates of local recurrence were 10.1 % in women <40 compared with 3.2 % in older women ($P = 0.005$).

Conclusions—Younger patients with DCIS more often have multicentric disease, present with clinical findings, and opt for or require mastectomy with immediate reconstruction. Conservative surgery is only appropriate for younger patients if adjuvant radiotherapy is delivered.

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Since the implementation of breast screening via mammography, ductal carcinoma-in-situ (DCIS) accounts for 20–30 % of all diagnosed breast cancers in the United States.[1] The primary aim in treatment of DCIS is prevention of invasive breast cancer. The ways in which this is accomplished should be dictated by the biology of the DCIS. As illustrated in the Van Nuys prognostic index for DCIS, all patients with DCIS warrant an individualized multidisciplinary approach according to their clinical and pathologic characteristics.[2] This treatment can vary from a segmental mastectomy with or without adjuvant radio-therapy to a mastectomy, and can even include a contralateral prophylactic mastectomy (CPM). The clinical features and pathology that guide management are examined in this study focusing on women younger than 40 years compared with older patients. This group is of great interest because they do not undergo routine screening mammography and the incidence of DCIS in this group appears to be rising.[3,4]

Recent studies have shown that younger women with DCIS are not only unique in their presentation, but also in their treatment and outcomes. Bijker et al. and Tunon-de-Lara et al.[5,6] found that women under 40 were more likely to present clinically with a mass, nipple discharge, and/or pain. This is clearly a result of lack of screening in these younger women. It has also been found that younger women are more likely to undergo mastectomy on their index side as well as CPM with immediate reconstruction.[6,7] With regard to locoregional recurrence (LRR), there are a number of conflicting studies as to whether young age is a risk factor. However, most have concluded that younger patients tend to develop LRR more often.[6,8–13]

The objective of this study was to identify differences in clinical presentation, treatment, and outcome based on age through examination of a modern cohort of women with pure DCIS treated at a single institution. The goal was to identify features that will aide in individualizing the care of women with DCIS and determine what merits aggressive surgical resection and adjuvant therapies.

METHODS

After receiving approval from the institutional review board of the University of Texas MD Anderson Cancer Center, the MD Anderson Breast Cancer Management System database was utilized to identify 2,037 patients with a diagnosis of pure DCIS who were treated with surgery with or without radiotherapy between January 1996 and July 2009 and who had a minimum follow-up time of 1 year. Demographic, diagnostic, clinical, pathologic, treatment, and follow-up variables were analyzed with respect to the patient's age at initial diagnosis of DCIS. Patient age at diagnosis were categorized into three groups: <40, 40–70, and >70 years.

Initial presenting signs were characterized as either a clinical symptom or radiologic finding. Surgical specimens were evaluated per routine MD Anderson standards. Whole specimens were radiographed to identify the targeted mammographic lesion and then inked in different colors to identify each face of the specimen, then sectioned into 3- to 5-mm slices. The pathologist examined the slices grossly to identify suspicious areas and noted their proximity to margins. The slices were also then radiographed, and the radiologist reviewed the films to determine the extent of any radiographic abnormalities and their proximity to margins. Final margin width was determined by examination of permanent paraffin-embedded sections. The number of permanent sections evaluated by the pathologist was based on the gross evaluation and the radiologic extent of the abnormality as well as the size of the specimen. Nuclear grade was categorized as either well differentiated lesions (I) or intermediate and poorly differentiated lesions (II and III). Multifocality was defined as the histologic presence of two foci of tumor in the same quadrant of the diseased breast.

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Multicentricity was defined as the histologic presence of tumor in multiple quadrants of the diseased breast, and if there was >5 cm spacing between disease foci. Beginning in 2003, estrogen receptor (ER) status was routinely evaluated for cases of DCIS. Surgical margins were categorized as negative or close/positive. Close/positive margins were defined as the presence of duct or ducts involved by DCIS <2 mm from the inked surface of the specimen. During the study interval, radiation typically consisted of 50 Gy in 25 fractions to the whole breast, followed by a 10–14 Gy tumor bed boost.

The chi-square test was used to compare age groups with respect to categorical variables. The Kruskal–Wallis test was used to compare age groups with respect to continuous variables. Kaplan–Meier product limit methods were utilized to calculate time to LRR, and differences in these outcomes were compared between the different variables with the log-rank test. LRR was defined as ipsilateral local or regional recurrence of either DCIS or invasive breast cancer. Cases were censored at the time of recurrence, last follow-up, or death from any cause. Time to local or regional recurrence or development of contra-lateral breast cancer was defined from the date of surgery. Significant covariates associated with LRR identified by univariate unadjusted analyses were utilized in an adjusted multivariate Cox proportional hazards model to identify independent predictors of LRR. Hazard ratios and 95 % confidence intervals were generated for demographic and clinical characteristics and treatment variables. All reported *P* values are 2-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed by Stata/ IC (release 11.1; StataCorp, College Station, TX) and Statistica (release 9.0; StatSoft, Tulsa, OK).

RESULTS

Between 1996 and 2009, a total of 2037 patients with pure DCIS were evaluated and treated at our institution. Of these, 132 patients (6.5 %) were under age 40, 1690 (83 %) were aged 40–70, and 215 (10.5 %) were aged >70 (Table 1). For all patients, the median duration of follow-up from the time of surgery was 5.2 years (range 1–14.3 years).

Relationship of Age at Diagnosis and Clinical, Pathologic, and Treatment Characteristics of DCIS

Clinical, pathologic, and treatment characteristics for all patients are summarized in Table 1. In the age group >70 years, patients of Hispanic and Asian/Pacific Islander were less represented than white and African American patients. Of the 132 patients younger than 40 years, 85 (64.4 %) had a family history of breast and/or ovarian cancer. However, this was the case in only 878 (46 %) of the 1905 women 40 years and older ($P < 0.001$). Bilateral breast cancer at diagnosis was not significantly different among the age groups, ranging from 6.8 to 7.9 % among the three age groups. Seventy-four (56.1 %) of those under 40 presented with clinical, rather than radiologic, signs of breast cancer, compared with 265 patients (14 %) over 40 ($P < 0.001$). Clinical symptoms included a palpable mass (59.5 %), nipple discharge (10.7 %), and/or breast pain (17.6 %). Mammographic and pathologic lesion size were not significantly different among the age groups. Women younger than 40 more frequently had higher nuclear grade DCIS ($P = 0.049$). Presence of necrosis and ER status was not significantly different among age groups, although there was a trend toward a higher rate of ER-positive DCIS among women younger than 40 compared with older patients ($P = 0.070$). Younger patients with DCIS were significantly more likely to have multicentric and multifocal DCIS. Among the women under 40 years, 29.3 % had evidence of multicentric disease versus 17.7 and 13.3 % in the women aged 40–70 years and those over 70 years, respectively ($P = 0.004$). In addition, women under 40 years were also more likely to have evidence of multifocal disease than the older women, 30.1 versus 17.3 % and 13 %, respectively ($P = 0.002$).

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Women younger than 40 were significantly more likely than patients older than 40 to undergo mastectomy with immediate reconstruction (P <0.001) and to have a CPM (P <0.001). Women older than 70 years were more likely to undergo lumpectomy (P = 0.014) compared with women younger than 70 years and were less likely to receive adjuvant radiotherapy (P = 0.003) or use adjuvant tamoxifen (P = 0.008) than younger patients

LRR and Development of Contralateral Breast Cancer among Different Age Groups with DCIS

Forty-three patients developed LRR (Table 2). Six local recurrences occurred in patients who received mastectomy, and 37 occurred in women who received breast-conserving surgery (BCS). Overall, patients younger than 40 were significantly more likely to have a LRR than older patients (P = 0.005). The LRR was DCIS in 27 patients (62.8 %) and invasive breast cancer in 16 patients (37.2 %). Among patients younger than 40, all recurrences were DCIS. Table 3 lists the 5 year LRR rates of patients stratified by surgery type and use of adjuvant radiotherapy and tamoxifen. Overall, there was no significant difference in LRR rates in younger versus older among women who received mastectomy or BCS when followed by radiotherapy. However, there were significant differences among patients who did not receive adjuvant radiotherapy after BCS. The 5 year LRR was 22.9 % in those under 40 years, as opposed to 8 and 4.1 % in the other two age groups, when radiotherapy was omitted (P = 0.014).

To address other factors that may influence the risk of LRR, Table 3 presents univariate and multivariate analyses of factors associated with risk of local relapse for the 1,216 patients undergoing BCS. On univariate analysis of patients treated with BCS, women under 40 years had a higher 5 year LRR rate of 10.1 versus 3.2 % in women 40 years or older (P = 0.005). Larger size DCIS (≥1.5 cm) was associated with higher 5 year LRR rate of 5.6 %; whereas the 5 year LRR rate in smaller lesions was 2.2 % (P = 0.018). Patients who received adjuvant radio-therapy were significantly less likely to experience a local relapse (2.3 vs. 7.9 %, P = 0.018). Margin status (included only four patients with a positive margin), ER status, and nuclear grade were not found to be associated with an increased risk of LRR on univariate analyses in this patient cohort. On multivariate analysis, women younger than 40 years, larger size DCIS (≥1.5 cm), and lack of radio-therapy were found to be significant independent predictors of LRR.

A total of 67 patients developed a contralateral breast cancer during the study period (Table 2). Overall, 47.8 % of cases were DCIS, and 52.2 % were invasive. In terms of overall development of contralateral breast cancer, 1,679 women were at risk, and no statistically significant difference was observed among the three age groups. However, in comparison to older patients, patients younger than 40 were significantly more likely to develop a contralateral breast cancer that was DCIS (85.7 %) as opposed to invasive breast cancer (14.3 %) (P = 0.031).

DISCUSSION

This is one of the largest series evaluating the outcome of young women with DCIS based on clinical and biologic features. With the exception of a study by Tunon-de-Lara et al.[14], which evaluated 207 women younger than 40 years, most previous series included women aged 40, and often as old as 45. Like many of these studies, we found that younger age is associated with higher LRR.[5,6,8,10–13] Overall, our results show that young patients (<40) were significantly more likely than patients older than 40 to have a family history of breast and ovarian cancer, to present with clinical symptoms, to have higher nuclear grade (II or III) DCIS, to undergo mastectomy with immediate reconstruction, and to have a CPM. Young women were also more likely to present with multicentric or multifocal DCIS. Older

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patients (>70) were significantly less likely to use adjuvant radio-therapy and tamoxifen and significantly more likely to undergo lumpectomy compared to mastectomy. Younger age (<40), larger size DCIS (≥1.5 cm), and lack of radio-therapy after BCS were significant independent predictors of LRR. Among women who underwent BCS and who did not receive radiotherapy, the 5 year rate of LRR was significantly higher among younger patients.

The presenting features and outcome of women younger than 40 is of particular interest to study in a modern cohort of patients because these women do not generally undergo screening mammography unless considered to be at high risk for breast cancer development. As would be expected in women not undergoing screening mammography, our results confirm that younger women are more likely to present with clinical symptoms rather than radiologic findings.[5,6,15] Of the women younger than 40 years old, 56.1 % presented clinically, compared with 13.9–15 % in the older groups. It is interesting to note that, in contrast to earlier studies, in our series, younger women did not present with larger-size DCIS.[6,11] These earlier studies also found that younger women were also more likely to develop LRR associated with larger DCIS.

Our study indicates that young women with DCIS are significantly more likely to have multicentric and multifocal disease. This is a novel finding and may contribute to the reasons why some younger women actually receive or require a mastectomy for treatment, and why elimination of adjuvant radiotherapy among younger patients with BCS is associated with unacceptably high rates of local recurrence. Rakovitch et al.[16] showed that multifocality in DCIS is associated with higher LRR in women treated with BCS. However, they also found that the LRR could be lowered with the addition of radiotherapy, similar to our findings. Lagios and colleagues looked at the incidence of multicentricity in DCIS and found it to be 32 % but did not find an association with age.[17,18] Simpson et al. found that all high-grade lesions (n = 12) in their series had multicentric DCIS.[19] Although no correlation was made with age, it could be in line with our finding that younger women present with higher-grade DCIS.

Our results confirm previous findings that LRR is significantly higher among women who did not receive radiotherapy after BCS. This was especially true in younger women. Numerous studies have shown that young age is significantly associated with LRR.[5, 6,11,20–22] A study by Turaka et al.[23] did not find an association with age, but it is important to note that their study only included 24 patients who were 40 years old or younger. Radiotherapy is clearly important in reducing LRR after BCS, as observed in the current study. Many others have reported this finding as well.[2,5,20,24–27] Smith et al.[28] found that it contributed to a significant reduction in LRR in women over 65 years old. A more recent study by Ho et al.[29] showed no difference in LRR in women over 60 whether or not radiotherapy was used, suggesting that it may be safely eliminated in some older women. This coincides with our findings that young women benefit to a higher degree than older women from radiotherapy after BCS.

Our study noted an increase in CPM in younger women with DCIS. Our study reports a rate of 21.2 % of CPM in women under 40, whereas Tuttle et al. reports a rate of 12.6 %. Tuttle et al.[7] observed that the rate of CPM increased over the years of their study, which looked at patients through 2005. Our increased rate of CPM may be partially because we included patients through 2009, which would logically show a higher rate than in 2005. Of the 100 young women who did not undergo a CPM, four developed a contralateral breast carcinoma. Our reported 5 year rate of contralateral breast cancer ranged between 2.2 and 4 % among our three studied age groups, with no statistically significant difference between them. This is in line with a previous study by Gao et al. that reported a 5 year rate of contralateral breast

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cancer of 3.3 %.[30] The NSABP-B17 study showed that 4.3 % of women who underwent BCS for DCIS developed contralateral breast cancer.[31] These data should be useful in appropriately counseling patients on their absolute small risk of developing contralateral breast cancer.

The present study has several strengths, including a large data set of patients evaluated and treated in the modern era at a single institution using standardized diagnostic imaging, pathology, and multidisciplinary clinical practice protocols. In addition, unlike other reports in the literature, in specifically looking at younger women, we do not include women at age 40 who would have undergone routine screening mammography.

A limitation of this study is the nonrandomization of the treatment administered. Although the choice of mastectomy may have been driven by multicentricity, for example, in those who were eligible for BCS, the choice was not randomized. In addition, the decision to undergo adjuvant radiotherapy was also not randomized, but rather driven by physician recommendations and patient preference, which may introduce unmeasured selection bias. Although prospective, randomized trials are ideal, the low incidence of DCIS in these young women makes such a trial unrealistic.

Variation in the biology and outcome of DCIS in younger versus older patients is likely multifactorial and may partially be due to nonuse of screening mammography in younger women but perhaps due to other hormonal or yet-to-be-identified molecular alterations. Young-onset DCIS is more often higher grade, is multicentric or multifocal, is diagnosed on the basis of clinical findings, and is associated with higher LRR. Younger patients are more likely to opt for or require mastectomy with immediate reconstruction, although conservative surgery with radiotherapy is appropriate in select women. In the absence of radiotherapy, conservative surgery is associated with an unacceptably high rate of locoregional recurrence in young women.

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TABLE 1

Patient and DCIS characteristics by age at diagnosis (n = 2037, univariate analyses)[a]

Characteristic	Patient age			*P*		
	<40 Years	40–70 Years	>70 Years	All groups	<40 versus ≥40 Years	≤70 versus >70 Years
No. of patients	132 (6.5)	1690 (83.0)	215 (10.5)			
Race						
White	91 (68.9)	1222 (72.3)	170 (79.1)			
African American	20 (15.2)	179 (10.6)	33 (15.3)			
Hispanic	12 (9.1)	166 (9.8)	7 (3.3)			
Asian/Pacific Islander	8 (6.1)	100 (5.9)	5 (2.3)			
Other	1 (0.7)	23 (1.4)	0 (0)	0.002	0.641	0.004
Age						
Median (range)	37 (18–39)	54 (40–70)	74 (71–89)	<0.001	<0.001	<0.001[b]
<21 years	2 (0.1)					
21–30 years	10 (0.5)					
31–39 years	120 (5.9)					
Exactly 40 years		37 (1.8)				
41–50 years		573 (28.1)				
51–60 years		658 (32.3)				
61–70 years		422 (20.7)				
>70 years			215 (10.6)			
Any family history of breast and/or ovarian cancer	85 (64.4)	794 (47.0)	84 (39.1)	<0.001	<0.001	0.011
First-degree family history of breast and/or ovarian cancer	26 (19.7)	346 (20.5)	62 (28.8)	0.017	0.641	0.004
Presence of bilateral breast cancer at diagnosis	9 (6.8)	121 (7.2)	17 (7.9)	0.908	0.855	0.679
Initial presenting signs[c]						
Clinical	74 (56.1)	233 (13.9)	32 (15.0)			
Radiologic	58 (43.9)	1446 (86.1)	181 (85.0)	0.001	0.001	0.476
Dimension						
Largest recorded mammographic dimension, median (range)[d]	2.4 (0.2–15)	2.0 (0.01–20)	2.2 (0.3–11.3)	0.737	0.537	0.670[b]
Largest recorded pathologic dimension, median (range)[e]	1.2 (0.1–19)	1.3 (0.01–18)	1.2 (0.09–16)	0.642	0.469	0.593[b]
Disease						

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Characteristic	Patient age			*P*		
	<40 Years	40–70 Years	>70 Years	All groups	<40 versus ≥40 Years	≤70 versus >70 Years
Multicentric[f]	29 (29.3)	215 (17.7)	21 (13.3)	0.004	0.003	0.100
Multifocal[g]	28 (30.1)	204 (17.5)	20 (13.0)	0.002	0.001	0.098
Nuclear grade[h]						
I	6 (4.7)	162 (9.8)	26 (12.2)			
II or III	121 (95.3)	1491 (90.2)	188 (87.9)	0.080	0.049	0.206
Necrosis present	59 (44.7)	630 (37.3)	79 (36.7)	0.227	0.086	0.759
ER status[i]						
Positive	64 (88.9)	820 (80.7)	100 (76.3)			
Negative	8 (11.1)	196 (19.3)	31 (23.7)	0.095	0.070	0.178
Surgery						
BCS	56 (42.4)	1015 (60.1)	145 (67.4)			
Mastectomy	76 (57.6)	675 (39.9)	70 (32.6)	0.001	0.001	0.014
Immediate breast reconstruction (in patients who underwent mastectomy)	64 (82.1)	449 (66.4)	11 (15.7)	<0.001	<0.001	<0.001
Contralateral prophylactic mastectomy	28 (21.2)	118 (7.0)	4 (1.9)	<0.001	<0.001	0.001
Chemotherapy						
Adjuvant tamoxifen (in all patients)	38 (28.8)	630 (37.3)	59 (27.4)	0.004	0.087	0.008
Adjuvant tamoxifen (in patients who underwent BCS)	20 (35.7)	462 (45.5)	39 (26.9)	<0.001	0.270	<0.001
Adjuvant tamoxifen (in patients who underwent mastectomy)	18 (23.7)	168 (24.9)	20 (28.6)	0.761	0.766	0.483
Adjuvant radiotherapy (in patients who underwent BCS)	46 (82.1)	828 (81.6)	103 (71.0)	0.011	0.729	0.003
Adjuvant tamoxifen and radiotherapy (in patients who underwent BCS)	19 (67.9)	408 (75.4)	29 (47.5)	<0.001	0.584	<0.001

DCIS ductal carcinoma-in-situ, *ER* estrogen receptor, *BCS* breast-conserving surgery

[a] *P* values are from the chi-square test unless otherwise indicated

[b] Calculated by the Kruskal-Wallis test

[c] Initial presentations were not available for 13 patients

[d] Largest mammographic dimensions recorded in 890 patients

[e] Largest pathological sizes recorded in 1534 patients

[f] Multicentric disease status recorded in 1469 patients

[g]Multifocal diseased status recorded in 1416 patients

[h]Nuclear grades were not available for 43 patients

[i]ER status was determined in 1219 patients

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TABLE 2

Local regional recurrence and development of contralateral breast cancer according to age and treatment stratification[a]

Characteristic	Patient age			*P*		
	<40 Years	40–70 Years	>70 Years	All groups	<40 versus ≥40 Years	≤70 versus >70 Years
LRR, *n* (%)						
Total	6 (10.7)	34 (3.4)	3 (2.1)	0.016	0.005	0.390[b]
DCIS	6 (100.0)	20 (58.8)	1 (33.3)			
Invasive	0 (0)	14 (41.2)	2 (66.7)	0.086	0.005	0.390
5 years LRR rate						
Mastectomy (*n* = 821)	0 %	1.3 %	0 %	0.504	0.427	0.434[b]
BCS with radiotherapy, all patients (*n* = 977)	6.4 %	2.1 %	2.6 %	0.324	0.143	0.701[b]
BCS with radiotherapy, margins ≥2 mm (*n* = 877)	7.0 %	2.0 %	3.2 %	0.185	0.067	0.986[b]
BCS without radiotherapy (*n* = 239)	22.9 %	8.0 %	3.1 %	0.014	0.006	0.235[b]
BCS without radiotherapy or tamoxifen (*n* = 174)	25.9 %	9.2 %	0 %	0.005	0.003	0.095[b]
BCS with radiotherapy without tamoxifen (*n* = 521)	5.0 %	3.1 %	4.0 %	0.639	0.882	0.359[b]
BCS with radiotherapy with tamoxifen (*n* = 456)	8.3 %	1.0 %	0 %	0.002	<0.001	0.479[b]
Development of contralateral breast cancer, *n* (%)[c]						
Total	4 (4.4)	56 (4.0)	7 (3.8)	0.995	0.926	0.988[b]
DCIS	4 (100.0)	24 (42.9)	4 (57.1)			
Invasive	0 (0)	32 (57.1)	3 (42.9)	0.076	0.031	0.600
5 years rate of development of contralateral breast cancer[c]						
Overall	2.2 %	3.5 %	4.0 %	0.995	0.926	0.988[b]
In patients receiving tamoxifen (*n* = 611)	4.6 %	2.9 %	2.3 %	0.540	0.808	0.273[b]
In patients not receiving tamoxifen (*n* = 1068)	1.4 %	3.9 %	5.7 %	0.931	0.788	0.772[b]

LRR locoregional recurrence, *DCIS* ductal carcinoma-in-situ, *BCS* breast-conserving surgery

[a] *P* values are from the chi-square test unless otherwise indicated

[b] Calculated by the Kaplan–Meier method and differences compared by the log-rank test

[c] Excludes patients who had contralateral prophylactic mastectomy, bilateral breast cancer at diagnosis, and history of contralateral breast cancer

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TABLE 3

Univariate and multivariate Cox proportional hazard analysis of clinicopathologic and treatment factors associated with local relapse after BCS for DCIS (n = 1216)

Variable	5 year LRR rate (%)	Univariate *P*	Hazard ratio	95 % Confidence interval	Multivariate *P*
Age					
≥40 years	3.2	0.005	1.00 (reference)		
<40 years	10.1		2.70	1.06–6.93	0.038
Initial presentation[a]					
Clinical	5.6	0.026	1.00 (reference)		
Radiological	3.2		0.58	0.28–1.24	0.160
Pathological size[b]					
<1.5 cm	2.2	0.018	1.00 (reference)		
≥1.5 cm	5.6		2.72	1.23–6.01	0.013
Margin status[c]					
Negative	3.7	0.270	1.00 (reference)		
Close/positive[d]	2.2		0.51	0.21–1.23	0.134
ER status[e]					
Positive	2.6	0.078	1.00 (reference)		
Negative	5.3		2.23	0.71–7.04	0.171
Grade[f]					
I	2.2	0.340	1.00 (reference)		
II/III	3.7		1.80	0.54–6.03	0.340
Radiotherapy			1.00 (reference)		
Yes	2.3	0.018			
No	7.9		2.68	1.36–5.26	0.004
Endocrine use					
Yes	2.0	0.087	1.00 (reference)		
No	4.6		1.29	0.62–2.68	0.490

BCS breast-conserving surgery, *DCIS* ductal carcinoma-in-situ, *LRR* locoregional recurrence, *ER* estrogen receptor

[a] Initial presentation signs were not available for 7 patients

[b]Largest pathological sizes were recorded in 900 patients

[c]Margins were not available for 12 patients

[d]Positive in 4 patients; close (<2 mm) in 99 patients

[e]ER status was determined in 743 patients

[f]Grade was not recorded in 29 patients

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