

Mammographic calcification can predict outcome in women with breast cancer treated with breast-conserving surgery

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Abstract. The impact of calcification in patients with breast carcinoma treated with breast-conserving surgery (BCS) is unclear. The present study aimed to determine the outcome of breast cancer patients with calcification treated with BCS. The records of 409 patients with breast carcinoma treated with BCS from January 2005 to December 2008 were reviewed. Patients were categorized as those with calcification (on mammography or ultrasonography), or those without calcification (neither on mammography nor ultrasonography). The local relapse free survival time (LRFS), disease free survival time (DFS) and overall survival time (OS) were compared, and subgroup analysis was performed based on morphological types and distribution patterns of mammographic calcification. Survival analysis demonstrated that patients with calcification had a significantly increased risk of local recurrence, distant metastasis and mortality compared with those without calcification [relative risk (RR) and 95% confidence interval (CI): local recurrence, 2.46 and 1.11-5.44; distant metastasis, 2.24 and 1.19-4.24; mortality, 2.50 and 1.06-5.86]. Subgroup analysis revealed that the distribution patterns (rather than morphological types of calcification) accounted for the increased risk of recurrence following BCS. Patients with mammographic calcification of liner/segmental distribution had significantly decreased LRFS (RR=6.20; 95% CI, 2.26-16.98), DFS (RR=6.81; 95% CI, 2.86-16.20) and OS (RR=9.14; 95% CI, 2.53-33.00), while patients with mammographic calcification of clustered distribution did not have significantly decreased LRFS, DFS and OS ($P>0.05$), compared with those without

calcification. In addition, the mammographic calcification spreading along the ducts was more likely to be accompanied by an extensive intraductal component ($P<0.001$). Finally, the outcome of patients with calcification on breast ultrasound was as good as those without calcification. Patients with mammographic calcification, particularly those with calcification spreading along the ducts, have a higher risk of recurrence following BCS, which has a negative impact on long-term survival. Calcification identified on breast ultrasonography does not affect the survival of patients treated with BCS.

Introduction

Breast-conserving therapy (BCT), which consists of breast-conserving surgery (BCS) and radiation therapy, has become the standard treatment for women with early-stage breast cancer (1-4). However, compared with those treated by mastectomy, patients receiving BCS have increased rates of local in-breast recurrence (3,5). Previous studies revealed that local recurrence following BCT may independently predict distant metastasis and poor disease-specific survival (6,7). Identifying the potential risk factors of local recurrence following BCS is helpful for the selection of appropriate candidates for BCS and clinical decision-making.

Previous studies have revealed that the radiological appearance of breast tumors may reflect pathological changes and the aggressiveness of the cancer (8-12). Calcification is an important radiological feature of breast cancer, and a number of studies have suggested that calcification on mammography is associated with an increased risk of local and distant recurrence following mastectomy (13-16). However, there remains little evidence on the association between the radiological appearance of breast cancer and the risk of local recurrence in patients who undergo BCS. It remains controversial whether patients with calcification on mammography have increased rates of local recurrence compared with those without calcification following BCS. Calcification is also often encountered in breast ultrasonography (BUS) examinations. It remains unclear whether calcification on BUS has prognostic values in patients with breast carcinoma.

In the present study, the association between pre-surgery radiological appearance, (particularly the morphology and distribution patterns of calcification) and post-surgery

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pathological characteristics was firstly examined. Additionally, the survival outcomes of patients receiving breast-conserving surgery with or without calcification were compared, including local in-breast recurrence, distant metastasis and overall survival time (OS). The prognosis of patients with calcification on breast ultrasonography examination was analyzed. It was then determined whether the distribution and morphology affect local in-breast recurrence, distant metastasis and OS of patients treated with BCS. The associations between calcification features, including morphology and distribution patterns, surgical margin status and extensive intraductal component were also examined.

Patients and methods

Patients. The present study was approved by the Institutional Review Board of the Tianjin Medical University Cancer Institute and Hospital (Tianjin, China). In total, the records of 409 patients with a diagnosis of breast carcinoma who were treated with BCS were retrospectively reviewed between January 2005 and December 2008. To be included in the present study, patients were required to have received pre-surgery mammography and BUS at the Cancer Institute and Hospital of Tianjin Medical University (Tianjin, China) and have available results for review. The exclusion criteria were as follows: Younger than 20 or older than 70 years old; previous history of other malignant neoplasms including breast cancer; distant metastasis at the time of diagnosis; and local relapse within six months of the surgery.

Data. Demographic, diagnostic, clinical, pathological, treatment and follow-up data were reviewed from the medical records of the patients and the follow-up system at the center. Patients were divided into three groups: No calcification; mammographic calcification; and BUS calcification (calcification only in BUS). The mammographic patterns were classified as mass, architectural distortion, calcification or a combination of calcification with mass or architectural distortion. The morphology of calcification in mammograms of the patients was categorized as one of four types: Micro-calcification; pleomorphic calcification; casting calcification; and large/coarse/spherical calcification (benign calcification). Patients with micro-calcification, pleomorphic calcification and casting calcification were merged as one group in the final analysis. The distribution patterns of calcification in mammograms of the BCS patients were divided into clustered, liner/segmental (ductal spreading), or scattered type.

Statistical analysis. The χ^2 or Fisher's exact tests were used for categorical parameters, while a t-test was used for the analysis of continuous data. The association between calcification types and lymph node status, with or without adjustment for tumor size and histological grade, was analyzed using a binary logistic regression model. The Kaplan-Meier method was applied as in the survival analysis to calculate the local relapse free survival (LRFS), disease free survival (DFS), and OS times. The log-rank test was used to compare differences among survival curves. The Cox proportional hazards model was used to estimate the effect of mammographic calcification types on long-term prognosis, adjusting for potential factors

including margin status, tumor size, histological grade, lymph node status, receptor status and treatment modality.

Results

Patient characteristics. A total of 589 patients who had a histological diagnosis of breast carcinoma and received BCS were identified. Mammograms and BUS reports were available for review in 433 patients. A total of 24 patients were excluded by exclusion criteria. Overall, 409 patients were included in the final analysis. Among them, 238 patients did not have calcification on either mammogram or BUS and were defined as the BCS group without calcification. Of the remaining 171 patients who were defined as the BCS group with calcification, 135 patients had calcification on mammogram and 36 did not have calcification on mammogram, but had calcification signs in BUS tests.

The majority (96.6%) of the patients included in the present study were Han Chinese women. The demographic, surgical and pathological characteristics of the patients are summarized in Table I. The median age of the patients was 50 years (24-70 years) and 51 years (20-70 years) in the BCS groups with and without calcification, respectively. In the calcification and non-calcification groups, 52.38 and 52.36% of the women were premenopausal, respectively. A total of 6 (3.5%) and 2 (0.8%) of the patients received neoadjuvant chemotherapy in the BCS groups with and without calcification, respectively. The majority of patients had received quadrantectomy rather than lumpectomy. Negative margin status was achieved in 93.6 and 92.9% of the patients with and without calcification, respectively. A margin ≤ 5 mm was defined as close.

Tumor attributes. The main histological type of the tumor was invasive ductal carcinoma. The majority of tumors were grade 2 or 3. The mean tumor sizes were 1.84 and 1.79 cm for patients with and without calcification, respectively. Axillary lymph node status was available for 398 patients; 23.4 and 17.7% of the patients had involved lymph nodes in the groups with and without calcification, respectively. Hormonal receptor (HR; estrogen receptors and/or progesterone receptors) and human epidermal growth factor (Her-2) status was available for 403 patients; 77.7 and 73.4% of the patients were HR-positive, while 86.7 and 90.1% of the patients were Her-2-negative in the groups with and without calcification, respectively.

Post-surgery therapy. Of the 409 patients included in the present study, 391 received post-surgery radiation therapy (PSRT); the rate of having PSRT was 89.7 and 90.7% in the groups with and without calcification, respectively. Post-surgery adjuvant chemotherapy, based mainly on anthracycline and taxane, was administered to 151 and 209 patients of the groups with and without calcification, respectively. In HR positive patients, tamoxifen and aromatase inhibitors were used for premenopausal and postmenopausal patients, respectively. Anti-Her-2 therapy (Trastuzumab) was not routinely used in our center prior to 2008.

Calcification and long-term outcome of breast conserving surgery. To investigate whether calcification on pre-surgery mammogram and/or BUS impacted the long-term outcome of

Table I. Characteristics of patients with or without calcification.

Characteristic	BCS with calcification, n	BCS without calcification, n	P-value
Total	171	238	
Age, median (range)	50 (24-70)	51 (20-70)	
Menopausal status			0.99
Premenopausal	88	122	
Postmenopausal	80	111	
Surgery			0.59
Quadrantectomy	163	224	
Lumpectomy	8	14	
Margin status			0.78
Negative	160	221	
Positive/close ^a	11	17	
Neoadjuvant chemotherapy			0.07
No	165	236	
Yes	6	2	
Histological type			0.71
Invasive ductal carcinoma	135	193	
Invasive lobular carcinoma	4	8	
Ductal carcinoma <i>in situ</i>	4	3	
Others	28	34	
Histological grade			0.70
1	14	21	
2	95	158	
3	14	17	
Tumor size			0.47
Mean ± standard deviation, cm	1.84±0.86	1.79±0.79	
T1	132	195	
T2	35	38	
T3	2	2	
Axillary lymph node status			0.17
Negative	128	190	
Positive	39	41	
ER/PR status			0.33
Positive	129	174	
Negative	37	63	
Her-2 status			0.29
Positive	22	23	
Negative	144	210	
Radiation therapy			0.74
Yes	148	205	
No	17	21	
Chemotherapy			0.86
Unknown (n=7)	3	4	
Yes	151	209	
No	17	25	
Hormonal therapy			0.92
Yes	119	161	
No	10	13	

^aA margin ≤5 mm was defined as close. BCS, breast conserving surgery; ER, estrogen receptor; PR, progesterone receptor; Her-2, human epithelial growth receptor-2.

Table II. Outcome of patients with or without calcification.

Outcome	BCS with calcification, n (%)	BCS without calcification, n (%)	P-value
Local/regional relapse			0.02
Yes	16 (9.4)	9 (3.78)	
No	155 (90.6)	229 (96.22)	
Distant metastasis			0.01
Yes	18 (10.53)	10 (4.20)	
No	153 (89.47)	228 (95.80)	
Breast carcinoma mortality			0.01
Yes	15 (8.8)	7 (2.9)	
No	156 (91.2)	231 (97.1)	

BCS, breast-conserving surgery.

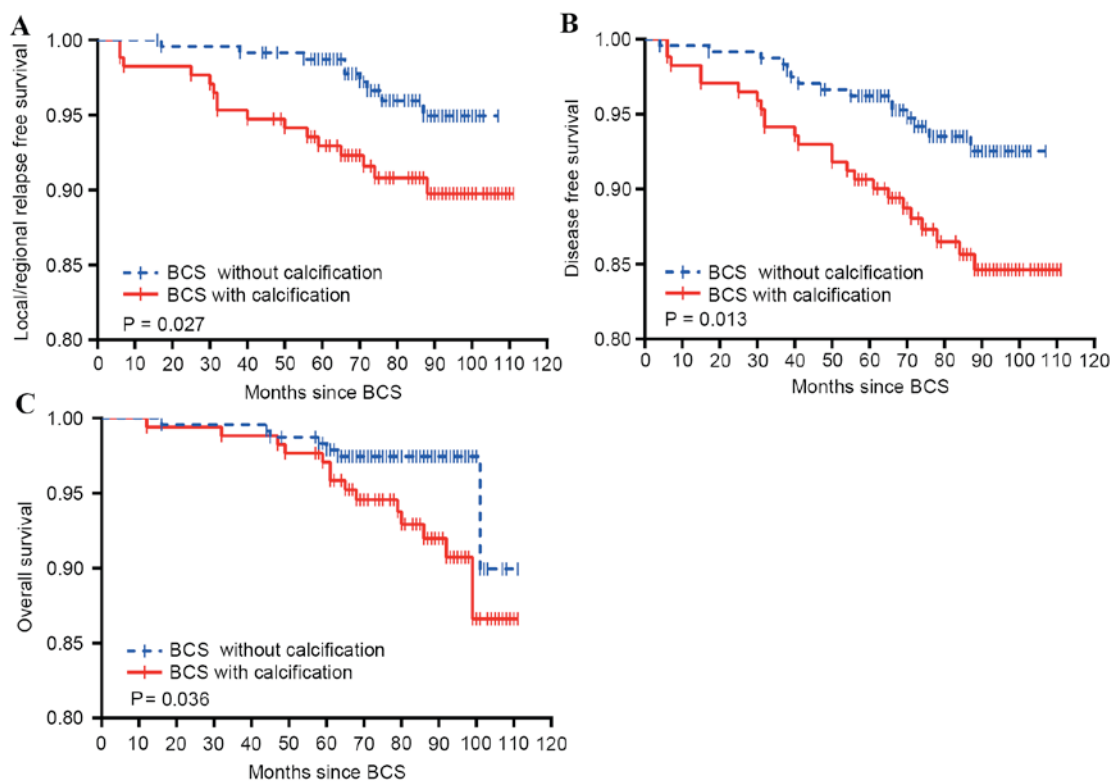


Figure 1. Impact of calcification on long-term outcome in patients with breast cancer treated with BCS. Patients who had calcification on pre-surgery examination (mammography and/or breast ultrasound) had (A) poorer cumulative local/regional relapse free survival, (B) disease free survival, and (C) overall survival, compared with those who did not have calcification on either mammography or BUS. BCS, breast-conserving surgery; BUS, breast ultrasonography.

BCS, the rates of local/regional recurrence, distant metastasis and mortality were studied in BCS patients with and without calcification.

The median follow-up time of all the patients was 85 months. In total, 16 (9.4%) and 9 (3.78%) local/regional relapses occurred in patients who received BCS with and without calcification, respectively ($P=0.02$; Table II). Similarly, more distant metastasis occurred in patients who had calcification [18 (10.53%) vs. 10 (4.20%), respectively; $P=0.01$]. In patients with calcification, 5 local/regional relapses occurred concurrently and 4 occurred at a different time with distant metastasis. In those without calcification on mammography

and who underwent BUS, 1 local/regional relapse occurred concurrently, and 3 occurred at a different time with distant metastasis. All patients who had local/regional recurrence without distant metastasis received salvage mastectomies and additional lymph node dissection, if necessary. In patients who had distant metastatic diseases, the treatments were combinations of radiation therapy, chemotherapy, hormonal therapy and supportive care.

Survival analysis comparing the LRFS, DFS, and OS was also performed in patients treated by BCS with or without calcification. As shown in Fig. 1, patients who had calcification on pre-surgery examination (mammography and/or BUS)

Table III. Number of patients with calcification by morphological types and distribution patterns.

Calcification	Number of patients, n	Percentage, %
Morphology	171	100.0
BUS calcification	36	21.1
Benign calcification	16	9.4
Casting calcification	2	1.2
Micro-calcification	23	13.5
Pleomorphic calcification	94	55.0
Distribution	171	100.0
BUS calcification	36	21.1
Diffuse/scattered	7	4.1
Liner/segmental	35	20.5
Clustered	93	54.4

BUS, breast ultrasonography.

had poorer cumulative LRFS, DFS and OS, compared with those who did not have calcification on either mammography or BUS. Following the adjustment of potential confounding factors, compared with patients without calcification, those with calcification had a 2.46-fold [relative risk (RR), 2.46; 95% confidence interval (CI), 1.11-5.44], 2.24-fold (RR, 2.24; 95% CI, 1.19-4.24), and 2.50-fold (RR, 2.50; 95% CI, 1.06-5.86) increased risk of local/regional recurrence, distant metastasis and mortality, respectively, subsequent to receiving BCS.

The data from Fig. 1 indicated that patients with calcification on mammograms or BUS may have an increased risk of relapse, metastasis and mortality. However, the causes for this phenomenon remain unclear. As previously mentioned, calcification was divided into different types according to the morphology and distribution; it was unclear whether the morphology or the distribution pattern of calcification in each group was responsible for the increased risk of BCS failure. To clarify, subgroup analyses concerning the associations between different calcification types or distribution patterns, and the pathological and clinical outcomes of the cancer, were performed.

Calcification and tumor characteristics. The number of patients with different types and distribution patterns of calcification are presented in Table III. Patients with calcification only in BUS examination (n=36) were defined as BUS calcification. In the following analyses, patients with benign calcification (large/coarse/spherical calcification (n=16), were merged with those with BUS calcification, while patients with casting calcification (n=2), micro-calcification (n=23) and pleomorphic calcification (n=94) were merged as one group, defined as micro/pleomorphic calcification. All the calcifications with diffuse/scattered distribution patterns (n=7) were benign calcifications and were therefore merged with the BUS calcification group. Patients who did not exhibit calcification on either mammography or BUS (n=238) were used as the reference group. The potential confounding factors, consisting

of age, menopausal status, tumor size, histological grade, HR status and Her-2 status, were adjusted by inclusion of the factors in the logistic regression analysis.

Positive/close margin status is an established risk of local recurrence following BCS (1). Table IV shows the post-surgery margin status of patients with calcification of different types and distribution patterns. No evidence showed that calcification increased the chance of positive/close margin status on pathological examination. The histological grades of tumors of patients with different types and distribution patterns of calcification were also analyzed. No association was identified between calcification and increased histological grades (grade 2 and 3; Table V). Patients with calcification exhibited high rates of lymph node metastasis, particularly in those with micro/pleomorphic calcification and those with ductal spreading calcification (liner/segmental distribution, calcification distributed along the ducts); however, the differences were not statistically significant (P>0.05; Table VI).

Outcome of patients with calcification of different types and distribution patterns. These data indicated that mammographic calcification may be an independent risk factor of local/regional relapse. The cumulative rates of local/regional relapse, distant metastasis and mortality in patients with calcification of different types and distribution patterns were then analyzed.

Firstly, associations between calcification types and the cumulative rates of local/regional relapse, distant metastasis and mortality were investigated. Fig. 2 shows the outcomes of the LRFS, DFS and OS of patients with BCS, based on the calcification types. Patients with micro-calcification, pleomorphic calcification and casting calcification had significantly increased rates of local (P=0.008) and distant relapse (P<0.001) as well as decreased OS (P=0.003). To study whether calcification or the distribution patterns impacted the long-term prognosis of patients with BCS, survival analyses by distribution patterns, which were adjusted for age, menopausal status, histological grade, tumor size, lymph node status, HR status and Her-2 status, were performed with Cox regression analysis. As shown in Fig. 3, patients with calcification distributing along the ducts, or calcification with liner and segmental distribution were at a significantly increased risk of local recurrence, distant metastasis and mortality. The relative risk was 6.20 (95% CI, 2.26-16.98), 6.81 (95% CI, 2.86-16.20) and 9.14 (95% CI, 2.53-33.00) for LRFS, DFS and OS, respectively. Although patients with calcification of clustered distribution also demonstrated increased risk of disease relapse and mortality, the trends were not statistically significant. Furthermore, the outcome of patients with BUS calcification was as good as those without calcification.

Calcification distribution patterns and extensive intraductal component. As demonstrated in Fig. 2, the incidence of recurrence, metastasis and mortality were higher in patients with micro/pleomorphic calcification compared with those without calcification. The following subgroup analysis of the distribution of calcification revealed that patients with micro/pleomorphic calcification with a clustered distribution did not possess a significantly increased risk of relapse, metastasis and mortality. However, patients with micro/pleomorphic

Table IV. Margin status of patients with calcification by different morphological types and distribution patterns.

Characteristic	Margin status, n (%)		OR (95% CI)	
	Negative	Positive/close	Crude	Adjusted ^a
Morphology				
No calcification	217 (92.7)	17 (7.3)	1.00	1.00
BUS calcification+benign calcification	49 (94.2)	3 (5.8)	0.80 (0.22-2.82)	0.74 (0.20-2.69)
Micro/pleomorphic-calcification	111 (93.3)	8 (6.7)	0.94 (0.39-2.24)	0.99 (0.40-2.43)
Distribution				
No calcification	217 (92.7)	17 (7.3)	1.00	1.00
BUS calcification+benign calcification	49 (94.2)	3 (5.8)	0.78 (0.22-2.78)	0.73 (0.20-2.66)
Clustered	78 (92.9)	6 (7.1)	0.98 (0.37-2.59)	1.02 (0.38-2.76)
Ductal spreading	33 (94.3)	2 (5.7)	0.77 (0.17-3.50)	0.86 (0.18-4.06)

^aAdjusted for age, menopausal status, tumor size, hormonal receptor status and human epidermal growth receptor-2 status. BUS, breast ultrasonography; OR, odds ratio; CI, confidence interval.

Table V. Histological grade of tumors of patients with calcification by different morphological types and distribution patterns.

Characteristic	Histological grade, n (%)		OR (95% CI)	
	1	2+3	Crude	Adjusted ^a
Morphology				
No calcification	19 (10.4)	163 (89.6)	1	1
BUS calcification+benign calcification	4 (9.3)	39 (90.7)	1.14 (0.37-3.53)	1.30 (0.41-4.15)
Micro/pleomorphic-calcification	10 (12.5)	70 (87.5)	0.82 (0.36-1.84)	0.72 (0.31-1.68)
Distribution				
No calcification	19 (10.4)	163 (89.6)	1	1
BUS calcification+benign calcification	4 (9.3)	39 (90.7)	1.14 (0.37-3.53)	1.30 (0.41-4.14)
Clustered	9 (15.3)	50 (84.7)	0.65 (0.28-1.52)	0.57 (0.23-1.39)
Ductal spreading	1 (4.8)	20 (95.2)	2.33 (0.30-18.36)	2.09 (0.17-3.50)

^aAdjusted for age, menopausal status, tumor size, hormonal receptor status, and human epithelial growth receptor-2 status; OR, odds ratio; CI, confidence interval; BUS, breast ultrasonography.

calcification with a liner/ segmental distribution were at a significantly increased risk of local recurrence, distant metastasis and mortality compared with patients with no calcification. These data suggest that the distribution patterns rather than the morphological types account for the increased risk of recurrence following BCS. An extensive intraductal component (EIC) is defined as >25% of the mass of an invasive tumor in intraductal carcinoma. Intraductal carcinoma was observed within and outside of the tumors with an EIC. Previous studies revealed that mammographic calcification of liner, segmental or diffuse distribution pattern were correlated with EIC (17). Therefore, the presence of EIC in tumors of patients with different calcification distribution patterns was analyzed. As shown in Table VII, >20% of patients with calcification of ductal spreading pattern had tumors with EIC; the rate was significantly increased (P<0.001). No association was observed between EIC and positive/close margin status.

Among patients with calcification of ductal spreading pattern, those with EIC had a significantly increased incidence of local/regional recurrence (P=0.03), while the rates of distant metastasis and mortality were not statistically different (Table VIII).

Discussion

BCS, followed by radiation therapy, is now the standard treatment for early breast cancer; it may achieve an OS equivalent to mastectomy (1-4). Patients who can tolerate radiation therapy and have lesions that can be removed with adequate margins and acceptable cosmetic results are appropriate candidates for BCS (1,18). Calcification is an important radiological feature of breast cancer (19). Calcification is not an absolute contraindication of BCS; however, patients with diffuse malignant-appearing micro-calcifications are

Table VI. Regional lymph node status of patients with calcification by different morphological types and distribution patterns.

Characteristic	Lymph node status, n (%)		OR (95% CI)	
	Negative	Positive	Crude	Adjusted ^a
Morphology				
No calcification	174 (81.7)	39 (18.3)	1	1
BUS calcification+benign calcification	40 (76.9)	12 (23.1)	1.34 (0.64-2.79)	1.35 (0.59-3.11)
Micro/pleomorphic-calcification	88 (76.5)	27 (23.5)	1.37 (0.79-2.38)	1.55 (0.80-3.01)
Distribution				
No calcification	174 (81.7)	39 (18.3)	1	1
BUS calcification+benign calcification	40 (76.9)	12 (23.1)	1.34 (0.64-2.79)	1.35 (0.59-3.11)
Clustered	63 (76.8)	19 (23.2)	1.35 (0.72-2.50)	1.62 (0.78-3.36)
Ductal spreading	25 (75.8)	8 (24.2)	1.43 (0.60-3.40)	1.36 (0.43-4.31)

^aAdjusted for age, menopausal status, histological grade, tumor size, hormonal receptor status, and human epithelial growth receptor-2 status. OR, odds ratio; 95% CI, 95% confidence interval; BUS, breast ultrasonography.

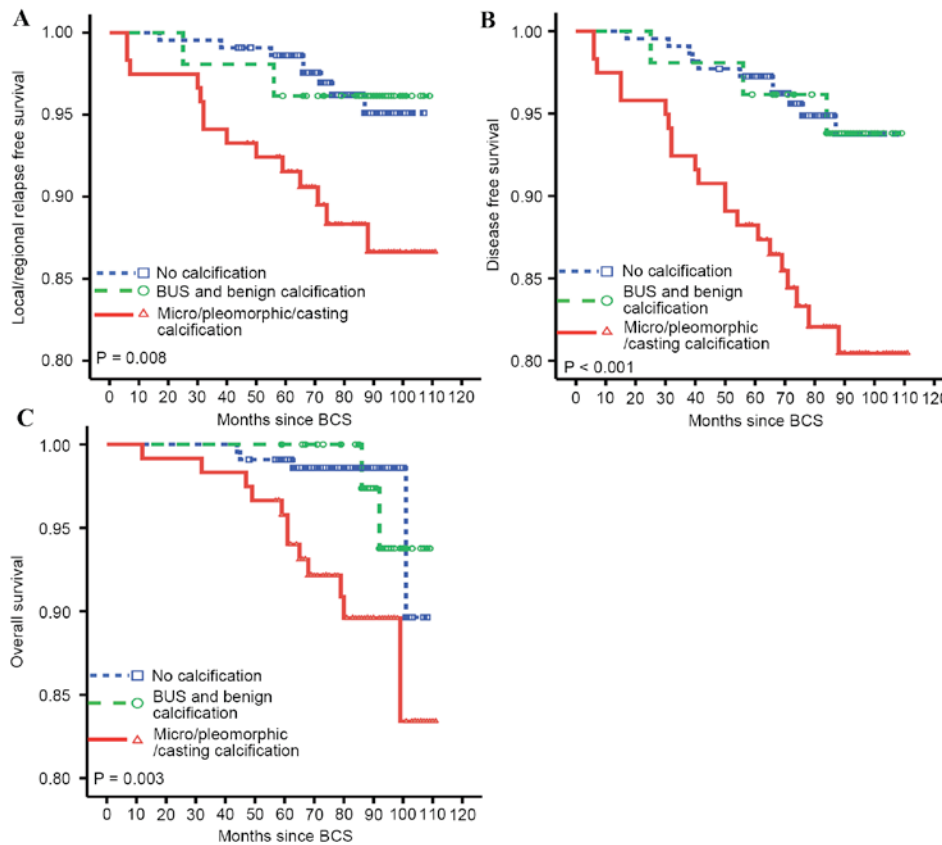


Figure 2. Effect of morphological type of calcification on long-term outcome. The outcomes of cumulative (A) local/regional relapse free survival, (B) disease free survival, and (C) overall survival of patients with BCS, based on morphological type of calcification. BCS, breast-conserving surgery; BUS, breast ultrasonography.

not recommended to undergo BCS (10,20). Previous studies have evaluated the role of mammographic features of breast carcinoma as prognostic factors for women with breast carcinoma (8-11,13-16); however, to the best of our knowledge, there is little previous study regarding the predictive value of calcifications found on pre-surgery radiological tests, particularly mammography, for breast cancer patients who

received BCS. In addition, calcification can also be identified in BUS examinations, and it remains unclear whether calcification on BUS has prognostic values in patients with breast carcinoma.

Several studies have investigated the predictive value of mammographic tumor features on women with small invasive breast cancer (14-16). Thurfjell *et al* (16) revealed

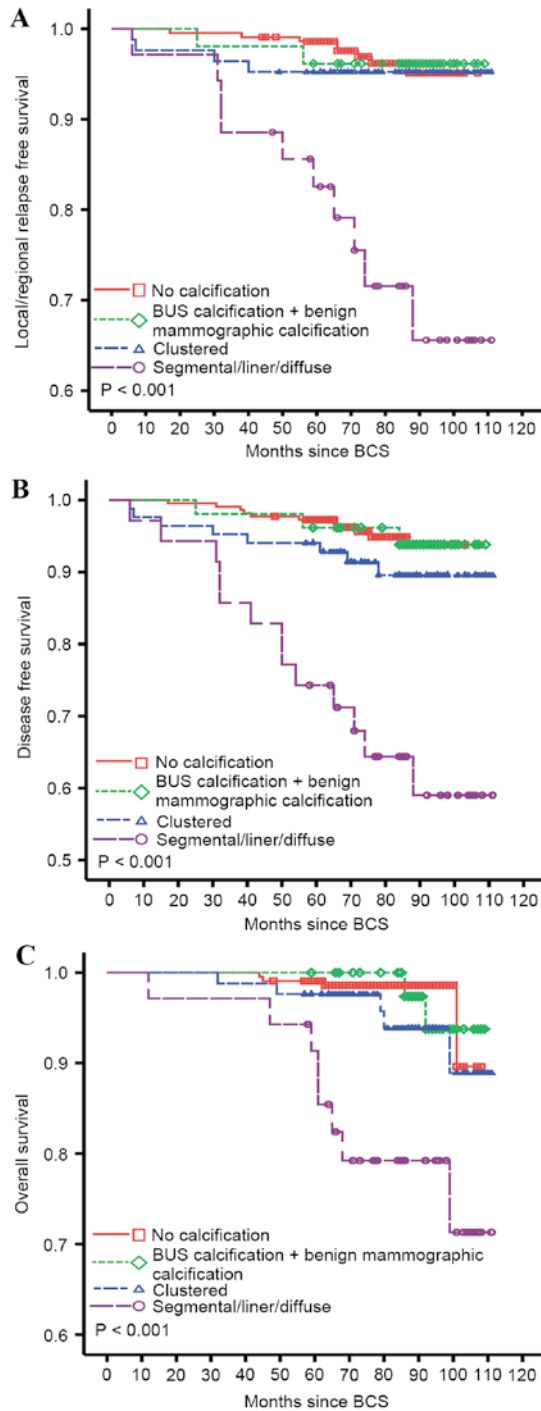


Figure 3. Effect of the distribution pattern of calcification on long-term outcome. The outcomes of cumulative (A) local/regional relapse free survival, (B) disease free survival, and (C) overall survival of patients with BCS, based on distribution pattern of calcification. BCS, breast-conserving surgery; BUS, breast ultrasonography.

that mammographic appearance presenting as casting or pleomorphic calcifications alone had a significantly worse prognosis than other types of mammographic appearance in small invasive breast cancer, which was confirmed by the later series studies (14,15). Conversely, there are certain studies doubting the ability of mammographic calcification to predict the survival outcomes of patients (21-23). In the present study, the outcome of 409 breast cancer patients with or without calcification, who had received BCS and

Table VII. Incidence of extensive intraductal components in tumors of patients with different calcification distribution patterns.

Distribution of calcification	Extensive intraductal component, n (%)		P-value
	No	Yes	
No calcification	237 (99.6)	1 (0.4)	<0.001
BUS calcification +benign calcification	50 (96.2)	2 (3.8)	
Clustered	79 (94.0)	5 (6.0)	
Ductal spreading	27 (77.1)	8 (22.9)	

BUS, breast ultrasonography.

Table VIII. Outcomes of patients with calcification of ductal spreading distribution pattern by extensive intraductal component.

Outcome	Extensive intraductal component, n (%)		P-value
	No	Yes	
Local/regional relapse			0.03
Yes	5 (18.5)	5 (62.5)	
No	22 (81.5)	3 (37.5)	
Distant metastasis			0.12
Yes	8 (29.6)	5 (62.5)	
No	19 (70.4)	3 (37.5)	
Breast cancer mortality			0.35
Yes	5 (18.5)	3 (37.5)	
No	22 (81.5)	5 (62.5)	

post-surgery adjuvant treatment, were retrospectively studied. Initial analyses demonstrated that patients with calcification had an increased risk of local and distant relapse following BCS compared with those who had BCS without calcification, which was consistent with the majority of current studies (13-16). In addition, subgroup analysis of the present study suggested that the distribution patterns rather than morphological types of calcification correlated with the increased risk of local and distant failure in patients with calcification following BCS. Patients with calcification distributed along the ducts, or calcification with liner and segmental distribution, had a significantly increased risk of local recurrence, distant metastasis and mortality, which suggested that BCS was not suitable for those patients with calcification spreading along the ducts. Similar trends were identified in those with calcification of clustered distribution, but the trends were not statistically significant. Namely, clustered micro-calcification and pleomorphic calcification are not absolute contraindications of BCS, but patients should be

informed that they have a potentially increased risk of local failure following BCS and should be followed up closely. For patients with BUS calcification, the outcome was as good as the outcome for patients without calcification, and thus should be treated similarly.

Previous studies revealed that certain types of calcification, particularly casting calcification, were associated with more aggressive characteristics of invasive ductal carcinoma, as well as ductal carcinoma *in situ* (DCIS), such as increased histological grades, negative HR status, positive Her-2 status, positive lymph node status and comedo necrosis in DCIS (8-12). Casting calcification is considered a relative contraindication of BCS in the Tianjin Medical University Cancer Institute and Hospital, and there were only two cases of casting calcification in the present study. No association was identified between calcification, either by morphological types or by distribution patterns, and more invasive tumor characteristics, including larger tumor size, increased histological grade and a triple-negative phenotype. However, it was identified that patients with calcification spreading along the ducts on mammograms were more likely to have tumors with EIC. It was reported that EIC associated with an increased risk of residual disease and patients with EIC had an increased risk of in-breast recurrence (17,24-28). Numerous other studies showed that negative margins were adequately safe for patients with EIC-positive tumors (29,30). However, as reported by Holland *et al* (31), the majority of tumors with EIC involved up to a whole quadrant. Furthermore, since these lesions are frequently non-palpable, it is challenging to obtain adequate negative margins during the surgery. In the present study, it was identified that patients with calcification spreading along the ducts on mammograms possessed an increased rate of EIC, and patients with EIC had an increased risk of local/regional relapse. However, no association was identified between EIC and positive/close margin status. The present results indicated that EIC may reflect a diffuse and multifocality growth pattern of the tumor, which may increase the false negative rate of surgical margins, and thus lead to increased local recurrence.

Previous studies demonstrated that although patients treated with BCS had increased rates of local recurrence compared with those treated with mastectomy, the overall survival rates were similar (1-5). However, in the present study, patients with calcification were identified to have increased rates of distant metastasis and mortality, mainly caused by calcification spreading along the ducts. Previous studies identified that patients with calcification, particularly with casting type calcification, had a poorer outcome, regardless of the local treatments (13-16). It remains unclear whether mastectomy could improve the outcome of patients with calcification spreading along the ducts. Additional studies are required to compare the outcome of patients with calcification spreading along the ducts treated by BCS and mastectomy.

In conclusion, the present study demonstrated that patients with calcification have an increased risk of developing local/regional and distant relapse subsequent to BCS, compared with patients without calcification. The distribution pattern, rather than the morphological type of calcification, was correlated with a poor outcome in patients with calcification. In addition, the tumors with calcification spreading along the ducts on mammograms were more likely to have an

EIC, and the existence of an EIC was a predictive factor of local failure in patients with calcification treated with BCS. Therefore, from a clinical point of view, it was hypothesized that patients with calcification spreading along the ducts should not be recommended to undergo BCS; at least not prior to additional prospective studies showing that patients with this type of calcification have a similar outcome whether they receive BCS or mastectomy. Alternative surgery approaches, including those involving oncoplastic technologies, are preferable choices. Clustered micro-calcification and pleomorphic calcification are not absolute contraindications of BCS, but patients should be informed that they have a potentially increased risk of local failure subsequent to BCS and should be followed up closely. Patients who do not have calcification on mammograms, but do have calcification on BUS, have a similar outcome subsequent to BCS as those without calcification, and therefore should be treated similarly.

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