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ORIGINAL ARTICLE

Breast conservation therapy for ductal carcinoma in situ (DCIS): does presentation of disease affect long-term outcomes?

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Abstract
Background For DCIS patients eligible for breast conservation treatment (BCT), it remains unclear whether presenting with physical signs/symptoms (Phys) confers a worse long-term prognosis compared to mammographically detected DCIS (Mam).
Methods We collected data on 669 DCIS patients treated with BCT from 1974 to 2007 of whom 80 were identified as category "Phys" and 589 were in category "Mam."
Results Treatment parameters (i.e., the RT dose delivered, boost, rates of stereotactic biopsy, re-excision, node dissection) did not differ significantly between the two cohorts (p = NS). At a 60-month median follow-up, significant associations included younger age at presentation ($p < 0.001$), non-white race ($p = 0.041$), larger tumor size ($p = 0.002$), more 1°/2° papillary histology (1°, $p = 0.001$; 2°, $p = 0.005$) for the Phys cohort. As expected, mammograms were more likely to show mass/nodules/asymmetrical densities and less likely to show microcalcifications for the Phys versus Mam group ($p < 0.0001$). There were no differences in family history, multifocality, grade, necrosis, or residual disease at re-excision, nodal involvement, status of margins, or ER/PR/HER-2 between the cohorts. The local relapse-free survival was similar at 5 years (100 vs. 96.9 %, $p = 0.116$) and 10 years (96.2 vs. 96.2 %, $p = 0.906$), with no significant overall survival difference at 10 years (97.5 vs. 95.9 %, $p = 0.364$) between the Phys and Mam patients, respectively. On multivariate analysis, presentation was not an independent predictor of local relapse-free survival or overall survival when accounting for age, race, tumor size, mammogram appearance, and adjuvant hormone treatment.
Conclusions Our findings suggest that although some clinicopathological differences exist between DCIS patients presenting with physical signs/symptoms compared with those presenting with mammographically detected disease, long-term outcomes are similar for patients appropriately selected for BCT.

Keywords Radiation therapy · Breast-conserving surgery · Ductal carcinoma in situ (DCIS) · Mammographically detected · Breast cancer

Introduction

Before the widespread use of mammography, ductal carcinoma in situ (DCIS), a noninvasive precursor to invasive ductal carcinoma, was often detected by physical signs or symptoms such as palpable mass, nipple discharge, or skin changes, and accounted for only 0.8–5.0 % of all breast cancers [1]. Now, with the pervasive use of routine mammographic screening, DCIS accounts for approximately 20 % of mammographically detected breast cancers [2]. With earlier detection leading to the increased overall incidence of DCIS, the proportion of mammographically detected DCIS cases that would progress to invasive

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malignancy if left treated remains unknown, given the standard of care to treat all eligible DCIS with a breast-conserving approach. Consequently, some argue that mammographically detected DCIS is overdiagnosed and overtreated, and the debate on the appropriate age for starting screening mammography has been ongoing for more than a decade [3]. Supporting this argument, a recent study showed that for mammographically detected cancers, review of prior mammograms for minimal changes at the site of cancer did not predict staging and grade and thus concluded that there was little possible gain by earlier diagnosis [4].

Specifically for DCIS, it remains unclear whether patients presenting with physical signs or symptoms that lead to the diagnosis represent a cohort with more aggressive disease with worse outcomes compared with asymptomatic patients detected by screening mammography alone. The purpose of our current study was to evaluate a large cohort of DCIS patients treated uniformly with breast-conserving surgery followed by radiation therapy to determine if patients presenting with physical signs or symptoms (Phys) predict for more aggressive clinical pathological features or outcomes compared with mammographically detected DCIS (Mam).

Patients and methods

Patient selection

Our study cohort consists of 669 patients diagnosed with DCIS from 1974 to 2007 who were treated with breast-conserving surgery and adjuvant radiotherapy to the intact breast at our institution. Patients were appropriately selected for breast-conserving therapy (BCT) based on whether they had an area of involvement that was amenable to local excision with negative margins without compromising cosmesis. All patients received adjuvant radiation therapy for their DCIS. After Human Investigations Committee (HIC)/Internal Review Board (IRB) approval, a chart review was conducted for methods of presentation, relevant clinicopathological factors (age at diagnosis, family history, race, estrogen-receptor status, grade, size, mammographic appearance, histology, margin status, use of adjuvant hormone), and outcome parameters. Patients received whole breast radiation therapy followed by a boost as per our institutional standard, to a total median dose of 64 Gy.

Statistical analysis

All clinical and pathological features of the two cohorts were entered into a database and analyzed using SPSS V.18 (SPSS, Chicago, IL, USA). All tests of statistical significance were two sided, and $p < 0.05$ was considered statistically significant. Bivariate analyses for the association between co-variables and Phys/Mam were performed using χ^2 analysis and Fisher's exact test. Outcome parameters analyzed included ipsilateral breast recurrence-free survival (defined as time from the date of diagnosis to the date of recurrence in the treated breast), contralateral breast recurrence-free survival (defined as time from the date of diagnosis to the date of recurrence in the contralateral breast), and overall survival (interval between the date of diagnosis and death from any cause). All events were calculated using the Kaplan–Meier product-limit method, and the differences were assessed by the log-rank test. Univariate and multivariate outcome analyses were conducted.

Results

Patient and tumor characteristics

Among the 669 patients, 80 patients presented with physical findings such as palpable mass, nipple discharge, and/or skin changes and comprised our cohort of DCIS patients presenting with physical findings (Phys). The remainder ($n = 589$) presented with clinically occult disease that was detected only by mammography, and were allocated as the mammographically detected cohort (Mam). The median follow-up was 5 years. Although the data go back to 1974, the majority of the patients were from the late 1990s and 2000s and some of these patients were lost to follow-up. The incidence of Phys over the study period in 4-year increments from 1974 to 2009 is shown in Fig. 1. As expected, there was a steady decline in patients presenting with physical findings from the 1970s to 2009. The proportion of patients in Phys compared to Mam has therefore drastically reduced from 1:3 in 1982–1985 to 1:10 in 2006–2009.

In terms of clinicopathological features, no statistically significant differences were found in the final margin

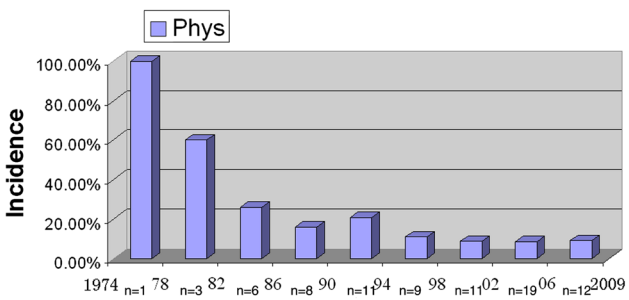

Fig. 1 Incidence of *Phys* (patients presenting with physical findings) over the study period in 4-year increments from 1974 to 2009

status, nodal status, ER/PR or HER-2 status, family history, multifocality, DCIS grade, and necrosis or presence of residual disease at re-excision between the two cohorts (all, $p > 0.05$). The age at diagnosis differed significantly between the two cohorts; specifically, more patients in the Phys group presented at a younger age (<40 years) than in the Mam group (16 vs. 5 %, respectively, $p < 0.001$). Patients in the Phys group were more likely to be non-white (i.e., African–Americans, Hispanics, or Asian) than those in the Mam group (27 vs. 17 %, $p = 0.041$). The pathological mean tumor size was larger in the Phys group than in the Mam group (1.433 vs. 1.071 cm, $p = 0.002$). Furthermore, papillary histology was more often associated with the Phys cohort than the Mam cohort (papillary, 35 vs. 14 %, $p = 0.001$); this difference was also significant for the secondary histology for both cohorts (papillary: 31 vs. 12 %, $p = 0.005$). As expected, the mammographic appearance of the Phys cohort (when available for review) was more likely to show mass nodules, mass calcification, and asymmetrical density and was less often associated with microcalcifications than the Mam group ($p < 0.0001$). In terms of the treatment delivered, there were no significant differences in the RT dose delivered, boost, rates of stereotactic biopsies, re-excisions after lumpectomy, axillary dissections, or sentinel node biopsies performed between the two cohorts. Table 1 summarizes these clinical and pathological tumor characteristics.

Clinical outcomes

Figure 2 shows survival curves by outcomes. Clinical outcomes of the Phys and Mam cohorts at 10 years are detailed in Table 2. Despite some significant differences in clinical and pathological features between the two groups, there were no significant differences in ipsilateral breast recurrence-free survival at 5 years (100 vs. 96.9 %, $p = 0.116$) and 10 years (96.2 vs. 96.2 %, $p = 0.906$), with no significant overall survival difference at 10 years (97.5 vs. 95.9 %, $p = 0.364$) between the two cohorts of patients. In those patients treated with hormonal therapy, the ipsilateral breast recurrence-free survival at 5 and 10 years was 100 and 100 %, respectively, in the Phys patients and 99.1 and 98.7 %, respectively, in the Mam patients (p = NS). The contralateral breast recurrence-free survival was 96.2 vs. 97.3 % at 5 years ($p = 0.943$) and 94.2 vs. 94.4 % at 10 years ($p = 0.997$) for the Phys versus Mam patients, respectively. On multivariate analysis, presentation was not an independent predictor of local relapse-free survival or overall survival when accounting for age, race, tumor size, mammogram appearance, and adjuvant hormone treatment (Table 3).

Table 1 Patient characteristics and treatments for the Phys and Mam cohorts

Parameter	Phys	Mam	p value
Clinicopathological characteristics			
Age at diagnosis (years)			
≤40	13 (16)	30 (5)	0.0001
>40	67 (84)	559 (95)	
Family history			
No	58 (77)	383 (67)	0.064
Yes	17 (23)	191 (33)	
ER			
Negative	11 (31)	84 (28)	0.694
Positive	25 (70)	222 (73)	
PR			
Negative	12 (35)	101 (36)	0.929
Positive	22 (65)	179 (64)	
HER-2			
Negative	9 (90)	58 (74)	0.44
Positive	1 (10)	21 (27)	
Race			
White	58 (73)	484 (83)	0.041
Non-white	21 (27)	100 (17)	
Mammogram appearance			
Microcalcs	23 (50)	428 (82)	<0.001
Mass calc	2 (4.3)	29 (5.5)	
Mass nodule	18 (38)	49 (9)	
Asymmetrical density	4 (9)	18 (3)	
Multifocal tumor			
No	19 (76)	158 (80)	0.658
Yes	6 (24)	40 (20)	
Size of tumor (cm)	1.433	1.071	0.002
DCIS grade			
GI	14 (33)	133 (28)	0.669
GII	18 (42)	199 (41)	
GIII	11 (26)	152 (31)	
Primary histology			
Papillary	20 (35)	67 (14)	0.001
Cribriform	15 (26)	157 (32)	
Solid	12 (21)	145 (30)	
Comedo	11 (19)	120 (25)	
Secondary histology[a]			
Papillary	8 (31)	28 (12)	0.005
Cribriform	13 (50)	86 (36)	
Solid	2 (7.7)	66 (28)	
Comedo	3 (12)	59 (25)	
DCIS necrosis			
No	30 (60)	215 (47)	0.075
Yes	20 (40)	245 (53)	
Margin status			
Negative	50 (81)	400 (77)	0.463

Table 1 continued

Parameter	Phys	Mam	*p* value
<3 mm	9 (15)	105 (20)	
Positive	3 (5)	16 (3)	
Residual tumor			
No	28 (74)	243 (77)	0.633
Yes	10 (26)	72 (23)	
Median WBRT dose (cGy)	5,000	5,000	–
Tumor bed RT boost			
No	18 (23)	109 (19)	0.393
Yes	62 (78)	480 (82)	
Median RT boost dose (cGy)	1,400	1,600	0.469
Adjuvant treatments			
Axillary dissection			
No	66 (87)	522 (93)	0.087
Yes	10 (13)	42 (7)	
Sentinel node biopsy			
No	70 (91)	521 (92)	0.731
Yes	7 (9)	45 (8)	
Re-excision			
No	36 (50)	328 (57)	0.315
Yes	36 (50)	251 (44)	
Adjuvant hormone			
No	52 (71)	315 (58)	0.031
Yes	21 (29)	230 (42)	

Phys patients presenting with physical findings, *Mam* patients presenting with clinically occult mammographically detected disease, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor 2, *G* grade, *calc* calcifications, *microcalcs* microcalcifications, *RT* radiation therapy, *WBRT* whole breast radiation therapy

[a] Secondary histology refers to the second most commonly seen pattern on histology

Discussion

In this study, we evaluated a large cohort of DCIS patients uniformly treated with BCT to determine if presentation with clinical signs/symptoms (Phys) versus mammographically detected disease (Mam) correlated to clinicopathological features or outcomes. Although several smaller studies have attempted to characterize pathological differences between Phys and Mam DCIS patients, to our knowledge, this is the largest study to date to compare clinicopathological features in these two cohorts with distinct presentation and the only study to correlate presentations to outcomes. We demonstrated that the Phys cohort presented at a significantly younger age, was more often associated with non-white race, larger tumor size, and papillary 1° and 2° histology compared with the Mam group. As expected, the Phy cohort were more likely to show mass nodules, mass calcification, and asymmetrical densities and less likely to show pleomorphic

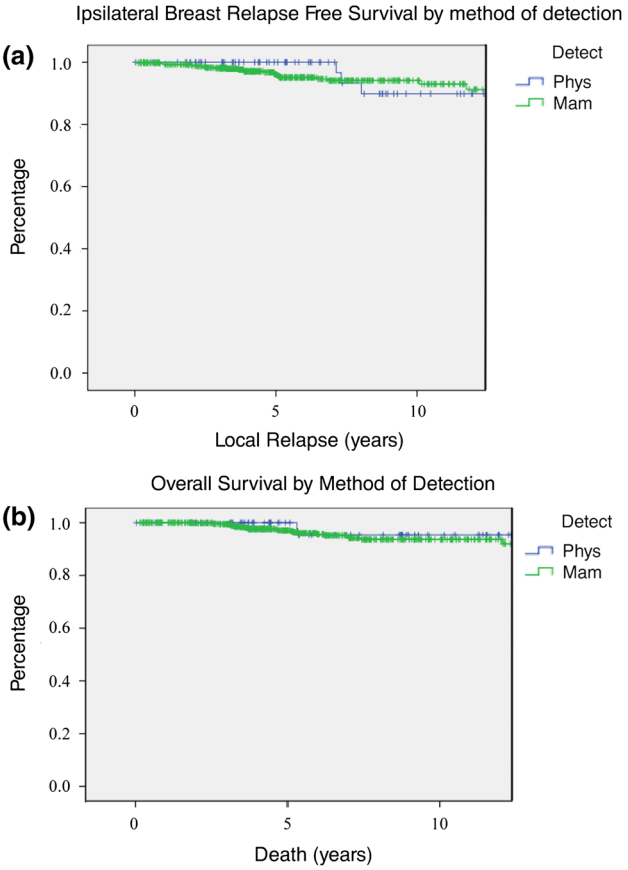

Fig. 2 Outcomes by presentation at 5 and 10 years, with findings not statistically significant for a ipsilateral breast tumor recurrence (**a**) and overall survival (**b**). *Mam* patients presenting with clinically occult mammographically detected disease

Table 2 Univariate analysis of ipsilateral breast recurrence-free, contralateral breast recurrence-free, and overall survival for Phys and Mam patients at 5 and 10 years

Variable (years)	Phys	Mam	*p* value
IBRFS	$n = 79$	$n = 581$	
5	100	96.9	0.116
10	96.2	96.2	0.906
IBRFS with hormonal therapy	$n = 21$	$n = 227$	
5	100	99.1	0.671
10	100	98.7	0.593
CBRFS	$n = 52$	$n = 372$	
5	96.2	97.3	0.943
10	94.2	94.4	0.997
Overall survival	$n = 79$	$n = 579$	
10	97.5	95.9	0.364

Phys patients presenting with physical findings, *Mam* patients presenting with clinically occult mammographically detected disease, *IBRFS* ipsilateral breast recurrence-free survival, *CBRFS* contralateral breast recurrence-free survival

Table 3 Multivariate analysis of local relapse and overall survival

Parameter	Local recurrence		Overall survival	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*
Presentation		0.673		0.943
Mam	1.0 (referent)		1.0 (referent)	
Phys	1.588 (0.185–13.636)		1.080 (0.128–9.092)	
Age		0.993		0.015
≤50	1.0 (referent)		1.0 (referent)	
>50	1.005 (0.367–2.748)		18.461 (1.779–191.630)	
Race		0.765		0.638
White	1.0 (referent)		1.0 (referent)	
Non-white	0.731 (0.094–5.713)		0.604 (0.074–4.933)	
Tumor size		0.051		0.137
≤1 cm	1.0 (referent)		1.0 (referent)	
>1 cm	2.498 (0.994–6.273)		2.325 (0.765–7.066)	
Mammogram appearance		0.324		0.787
Microcalcs	1.0 (referent)		1.0 (referent)	
Other	0.514 (0.137–1.930)		0.832 (0.220–3.152)	
Adjuvant hormone		0.297		0.903
No	1.0 (referent)		1.0 (referent)	
Yes	0.442 (0.095–2.053)		0.931 (0.296–2.932)	

Phys patients presenting with physical findings, *Mam* patients presenting with clinically occult mammographically detected disease, *microcalcs* microcalcifications

microcalcifications than the Mam group, but there were no differences in margin status, nodal status, estrogen receptor/progesterone receptor (ER/PR) or HER-2 status, family history, multifocality, grade, necrosis, or presence of residual disease at re-excision between the two cohorts. Outcomes (ipsilateral and contralateral breast relapse and overall survival) did not differ significantly between the two groups.

Similar to our findings, several smaller series have suggested differences in histology subtypes for Mam versus Phy patients, with micropapillary disease most frequently associated with the Phys cohort [5–8]. As expected and also reported by others, our Phys cohort was also more likely to show mass nodules, mass calcifications, and asymmetrical densities and less likely to show microcalcifications than the Mam group [5, 9]. Our data were also consistent with previous studies in that Phys patients presented at a younger age (<40 years) compared with the Mam group [9]. Although we found that patients in the Phys group were more likely to be non-white (i.e., African–Americans, Hispanics, or Asian) than those in the Mam group, to our knowledge no published reports have compared the racial distribution between Phys and Mam DCIS patients. The existing data on the presence of necrosis within the two cohorts are conflicting. Some suggest no difference in the proportion of comedo necrosis between the symptomatic and the screening-detected groups [9], whereas other studies suggest that Mam DCIS is more often associated with necrosis [3]. Our findings trended toward increased necrosis in Mam patients (53 vs. 40 %, $p = 0.075$). One possible explanation is that DCIS with necrosis has more malignant-appearing characteristics on imaging and, consequently, is more likely to be recalled at mammographic screening. Lastly, our findings of larger mean tumor size in the Phys group are also documented in the existing literature [6, 9, 10].

It is relevant to recognize that HER2 status was only examined in 10 (13 %) of the 80 Phys cases, given the era in which most of these cases were treated pre-dated routine testing of the HER2 receptor, particularly for in-situ disease. Of these 10 cases, only 1 patient (10 %) had HER2neu-positive DCIS. In contrast, 27 % (21/79) of the Mam patients had positive expression of HER2neu. Previous studies have shown that HER2neu status is strongly associated with the prognosis of patients with DCIS [11, 12]. It is possible that our results are confounded by a selection bias whereby patients within the Phys cohort present with physical findings and were eligible for BCT and were also HER2 negative. This selection bias results in the ultimate equivalent outcomes of the two cohorts. However, the limited HER2neu status information available in our dataset (particularly for the Phys group) does not allow us to draw any conclusions regarding HER2 and our two cohorts.

Our outcome analysis suggests there is no difference in ipsilateral breast tumor recurrence rates, contralateral breast tumor recurrence rates, or overall survival between the two groups of patients. One may argue, therefore, that early detection of DCIS by mammography may not portend better outcomes and therefore it may not be cost effective to screen patients for earlier detection because patients

presenting with physical symptoms will have comparable outcomes to those mammographically detected. However, this argument is based on an important assumption: that patients in the Phys cohort (i.e., clinically symptomatic DCIS) are presenting in a more advanced phase of the natural disease progression for DCIS compared with those detected by mammography (i.e., hypothesizing that mammographically detected DCIS progresses to DCIS with symptoms before developing into invasive cancer). Another possible scenario is that mammographically detected DCIS may pathologically progress without signs or symptoms, directly invading the basement membrane such that it directly develops into invasive cancer without symptoms (i.e., mammographically detected, clinically occult invasive cancer). Clearly, in this argument the patient would be upstaged, and it is well documented that Stage I disease has a worse overall prognosis than DCIS [13]. It is wholly possible, based on the randomized trials [14, 15], that adjuvant radiation eliminates any difference in outcome between the Phys and Mam groups, despite the poorer prognostic features of the Phys group (i.e., younger age at presentation, larger tumor size, etc.).

Another possible explanation for the equivalent outcomes may be that the careful selection of patients for BCT and optimized treatment delivery (lumpectomy and radiation in all patients) eliminated any advantage gained through earlier detection. Additional considerations should include the possibility of our findings representing a type II statistical error (falsely negative) caused by the small numbers of events in our cohorts and lack of statistical power to detect significant differences. Ultimately, larger studies with longer follow-up in DCIS cohorts uniformly treated with radiotherapy after lumpectomy are needed.

The limitations of our study include those inherent to its retrospective nature. Some clinicopathological factors were unknown in more than half of the cases (e.g., ER, PR, and HER2 status), limiting the validity of multivariate analysis. In addition, the study outcomes may be underpowered by the small number of events. Furthermore, selection bias (i.e., exclusion of patients undergoing mastectomy for DCIS) may confound the results. Despite these limitations, it is important to note that our policy of treating DCIS at our institution has not significantly differed, with most patients routinely receiving conventionally fractionated whole breast radiation to 46–50 Gy followed by a conedown/boost. Nevertheless, our data add to the limited literature on outcomes in DCIS patients presenting with physical signs or symptoms and suggest that DCIS patients presenting with symptoms, despite some significant clinical/pathological differences, have outcomes similar to their counterparts detected by screening alone when they are appropriately selected for BCT and uniformly receive radiation.

Conclusion

Our current study demonstrates more aggressive clinicopathological features in the Phys versus Mam cohort, with ultimate outcomes being equivalent after breast-conserving surgery and uniform adjuvant radiation therapy for both DCIS patient groups. These findings suggest that BCT should remain a reasonable treatment option for all DCIS patients, irrespective of method of presentation, and that DCIS patients should be carefully selected for a breast conservation approach based on the feasibility of complete surgical resectability and maintaining an acceptable cosmetic outcome. DCIS presenting with clinical symptoms should not preclude a breast conservation approach.

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Conflict of interest The authors of this manuscript have no conflicts of interest.

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