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Predictive factors of upstaging DCIS to invasive carcinoma in BCT vs mastectomy

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ABSTRACT

Background: Upstaging from DCIS to invasive ductal carcinoma varies widely from 0 to 59%. We aim to identify risk factors associated with upstaging in all DCIS patients and based on specific surgical intervention.

Methods: Patients with a pre-operative diagnosis of DCIS undergoing BCT or mastectomy were reviewed. Multivariable analysis was performed to identify risk factors for upstaging.

Results: In total, 623 patients had a preoperative diagnosis of DCIS. Upstaging occurred in 74 patients (12%) overall. There was no difference in upstaging rates between mastectomy and BCT (11% v 14% $p = 0.27$). Sentinel lymph node biopsy was positive in 4/212 patients (1%). Multivariable analysis revealed suspicion of microinvasion (OR 5.7 95%CI2.2–14.9), surgeon suspicion of invasive disease (OR 2.7, 95% CI 1.2–6.4) and larger size/multicentric/extensive tumor (OR 1.9 95% CI 1.1–3.4) increase risk of upstaging.

Conclusions: Suspicion of microinvasion, surgeon suspicion, and tumor size can be used to help guide the use of sentinel lymph node biopsy. For patients without these high risk characteristics, it is hard to justify the use of concurrent SLN biopsy for patients who undergo BCT.

Introduction

Ductal carcinoma in situ (DCIS) is a malignant proliferation confined to the ductal system that is a non-obligate precursor to invasive breast cancer. Ductal carcinoma in situ accounts for nearly 20% of all newly diagnosed malignant breast lesions and as mammography and MRI have improved in the recent past, the rates of detection have increased.[1–3] The surgical treatment of DCIS and invasive ductal carcinoma follow similar guidelines for excision options for the breast lesion.[4] Staging of the axilla is not needed for DCIS unless there is suspicion of an invasive component.[4,5] Due to the fact that most patients with a preoperative diagnosis of DCIS do not harbor an invasive component, performing a lymph node biopsy (SLN) for all DCIS patients is both expensive and potentially morbid.[6] The management challenge is that patients diagnosed by core needle biopsy have an inherent risk of upstaging to invasive cancer at the time of surgery.[7] Multiple previous reports have shown upstaging rates widely ranging from 0 to 59% with a mean of approximately 26%.[8] Due to the fact that SLN biopsy is unreliable to perform after a mastectomy, the recommendation has been to perform a SLN biopsy in patients treated for DCIS with mastectomy.

Identifying DCIS patients at high risk of harboring invasive disease has been the target of many studies to date.[9–15] These studies have varied greatly in their variables measured as well as final predictors of invasion. Multiple studies have shown a palpable mass, larger size of lesion, and higher grade to be associated with an increased risk of upstaging with additional studies showing no relationship amongst these variables.[8,12,16–20] On evaluation of the literature, we identified limited studies which include suspicion of microinvasion on pathology or surgeon suspicion of invasive disease.[13,14] In our study we aim to further evaluate risk factors associated with upstaging from initial biopsy for all patients and

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further determine if differences exist between breast conservation and mastectomy patients regarding these risk factors.

Methods

A prospectively collected database was used to draw patients from the years 1996–2017. Inclusion criteria were any patient undergoing either breast conservation therapy or mastectomy with a preoperative diagnosis of ductal carcinoma in situ on their initial biopsy. Patients with a past history of invasive carcinoma were excluded from the study. While patients with pathologically confirmed microinvasion were excluded, patients with only suspicion of microinvasion were included in the study.

A retrospective review of prospectively collected data was performed. Patient demographics (age, race, BMI, menopausal status), clinical variables (type of biopsy performed, palpability of the lesion, surgeon suspicion of invasive disease), imaging findings (lesion size, centricity of lesions, nature of mammographic findings, whether MR imaging was performed) and histopathologic characteristics (grade, suspicion of microinvasion, presence of comedo necrosis, ER/PR status) were collected and reviewed. Operative and post-operative data collected included final surgery performed, whether sentinel lymph node biopsy was performed, SLN positivity, and final T-stage.

Sixty percent of biopsies were performed at outside institutions vs 40% performed at Mayo Clinic in Arizona. Biopsies performed at Mayo Clinic included US guided, stereotactic and rarely MRI guided biopsies. The guidelines at our institution are that US guided biopsies typically consist of 3 cores with a 13–14 gauge needle. Stereotactic and MRI guided biopsies typically were performed with a 9 gauge needle and 6–12 cores were taken. All pathology specimens, both from outside institutions and Mayo Clinic, were reviewed by only specialty trained breast pathologists at our institution. Consultation with a second specialty trained breast pathologist and performance of myoepithelial markers was performed at the pathologist's discretion. All surgeons included in the study are fellowship trained in either breast or surgical oncology and all in academic practice. Years of experience varied given the long time frame of the study.

Patient demographics, clinical and pathology characteristics were compared between patients undergoing breast conservation therapy vs. mastectomy and for those who were upstaged vs. not upstaged. Categorical variables were compared by chi-square test for frequency data and continuous variables were compared by use of ANOVA F-test. Clinically significant variables on univariate analysis were considered in a multiple logistic regression model using forward selection to further identify independent risk factors for upstaging. Odds ratios and 95% confidence intervals were estimated. Separate models were constructed for patients undergoing BCT vs. mastectomy as well as a combined model including surgery type. SAS version 9.4 (Cary, NC) was used for analysis. P values < 0.05 were considered significant.

Results

A total of 623 patients were identified as having a pre-operative diagnosis of ductal carcinoma in situ. Of these patients, 552 (89%) had undergone image guided core needle biopsy while 68 (11%) had undergone open biopsy. A total of 396 (64%) patients underwent breast conservation therapy vs 227 patients (36%) had undergone mastectomy.

Patients who underwent breast conservation therapy tended to be older, were more frequently post-menopausal, less frequently had genetic testing performed, had smaller mean tumor size, less frequently had surgeon suspicion of invasive disease, less frequently had a palpable lesion and less frequently had MRI performed (Table 1).

A total of 74 patients (12%) were upstaged from a preoperative diagnosis of DCIS to invasive disease (Table 3). Of these patients, There was no significant difference in the rate of upstaging to invasive disease between those treated with BCT (43/396, 11%) and those treated with mastectomy (31/227, 14%, $p = 0.27$). Among those upstaged, 93% had T1 lesions with the majority $\leq$ T1b. No tumors were upstaged to T3 or T4 lesions. T-stage patterns were similar for both BCT and mastectomy patients.

As expected, mastectomy patients more frequently underwent sentinel lymph node biopsy (71 v 13%, $p < 0.001$). A total of 212 patients ultimately underwent sentinel lymph node biopsy (BCT 50 vs mastectomy 162). All patients who underwent mastectomy had their SLN biopsy at the time of their mastectomy. No patients who did not undergo a SLN biopsy and mastectomy upstaged to invasive disease. Of the patients who underwent BCT, 52% had their SLN biopsy at the time of their lumpectomy whereas the other half underwent SLN biopsy as a second procedure. Among the 26 patients who had concurrent lumpectomy and SLN biopsy, 8 (31%) were upstaged to invasive cancer. Four patients (1%) were found to have a positive SLN, three in the BCT group (two with concurrent SLN biopsy vs one with delayed SLN biopsy) and one in the mastectomy group. The SLN was the only positive lymph node in all four cases.

On univariate analysis, upstaged patients more frequently had suspicion of microinvasion on initial biopsy, were PR negative, had surgeon suspicion of invasive disease, had mass on mammogram, and had larger lesion size (Table 2). There was no difference in age,

Table 1
Patient demographics BCT v Mastectomy.

Variable	BCT (n = 396)	Mastectomy (n = 227)	p-value
Age (years), mean (SD)	64.5 (11.0)	58.5 (12.3)	<0.001
Post-menopausal	330 (83%)	161 (71%)	<0.001
BMI, mean (SD)	26.9 (5.8)	26.2 (5.8)	0.18
Mammogram Findings[a]			
Missing	146	1	0.18
Calcifications only	191 (76%)	173 (77%)	
Calcifications and mass	24 (10%)	20 (9%)	
Mass or distortion only	31 (12%)	22 (10%)	
Other	4 (2%)	11 (5%)	
Tumor Size, mean (SD) cm	1.4 (1.4)	3.1 (2.4)	<0.001
Surgeon suspicion of invasion	36 (9%)	42 (19%)	<0.001
Pathology with suspicion of microinvasion	25 (6%)	24 (12%)	0.02
Palpable by surgeon	27 (7%)	37 (16%)	<0.001
MRI performed	83 (21%)	92 (41%)	0.001

[a] Percentages listed are of the patients with mammogram findings recorded.

Table 2
Upstaged patient demographics.

	n	Upstaged (n = 74)	Not upstaged (n = 549)	p-value
Procedure				
BCT	396	43 (11%)	353 (89%)	0.30
Mastectomy	227	31 (14%)	196 (86%)	
Grade				
Low or intermediate	312	46 (14%)	266 (86%)	0.02
High	284	24 (8%)	260 (91%)	
Hormone status				
ER positive	450	56 (12%)	394 (88%)	0.29
PR positive	392	43 (11%)	349 (89%)	0.01
ER/PR negative	96	16	80	0.27
Palpable	64	11 (17%)	53 (83%)	0.17
Mean Lesion Size		2.6 (0.6–10.8)	2.0 (0–12.0)	0.001
Median Lesion Size		3.3	1.2	0.001
Lesion size or character				
Size < 2.0 cm or unifocal	437	43 (10%)	394 (90%)	0.01
Size > 2.0 cm, multifocal, or extensive	182	31 (17%)	151 (83%)	
Surgeon Suspicion of Invasive Disease	78	31 (40%)	47 (60%)	<0.001
Pathology with suspicion of invasion	52	26 (50%)	26 (50%)	<0.001
Mammogram Findings				
Calcifications only	364	42 (12%)	322 (88%)	<0.001
Calcifications and mass/distortion	44	13 (30%)	31 (70%)	
Mass/distortion only	53	14 (26%)	39 (74%)	

Table 3
T-stage breakdown for upstaged patients in the BCT group, mastectomy group, and total.

T-stage	Breast Conservation Therapy			Mastectomy			Total		
	n	Upstaged (n = 43)	Total (n = 396)	n	Upstaged (n = 31)	Total (n = 227)	n	Upstaged (n = 74)	Total (n = 623)
T1mic	6[a]	14%	2%	7	23%	3%	13	18%	2%
T1a	15	35%	4%	12	39%	5%	27	36%	4%
T1b	12	28%	3%	5	16%	2%	17	23%	4%
T1c	8	19%	2%	4[a]	13%	2%	12	16%	2%
T2	2**	5%	1%	3	10%	1%	5	7%	1%
T3	0	0%	0%	0	0%	0%	0	0%	0%

Note.
[a] Denotes patients with positive sentinel lymph node biopsy.

estrogen receptor positive status, or presence of a palpable lesion for upstaged patients (Table 2). While there were multiple patients that did not have lesion size included in imaging reports, upstaged patients had a greater mean and median tumor size compared to non-upstaged patients when tumor size was included. When grouped by lesion size and centricity, upstaged patients more frequently had either lesion >2 cm, multifocal, or multicentric disease. Additionally, upstaged patients more frequently had either a mass/distortion with calcifications or mass/distortion alone compared to non-upstaged patients. Calcifications alone were seen more frequently in non-upstaged patients (Table 2). Fifty-two patients were found to have suspicion of microinvasion on initial biopsy and of these only 50% were found to have invasive ductal carcinoma on final pathology. Seventy-eight patients were identified as having surgeon suspicion of invasive disease and 40% of these patients ultimately were upstaged (Table 2). Of the 64 patients with palpable lesions only 18% were upstaged to invasive cancer.

In multivariable analysis, when evaluating the entire population only suspicion of microinvasion, surgeon suspicion of invasive disease, and larger size/multicentricity were found to be associated with upstaging (Table 4). When evaluating the two types of surgical treatment separately, multivariable analysis of the breast conservation group revealed surgeon suspicion of invasive disease and lesion size/grouping to be associated with increased risk of upstaging. In patients having undergone mastectomy, multivariable analysis revealed suspicion of microinvasion on biopsy and surgeon suspicion of invasive disease to be associated with increased risk of upstaging. Higher grade was not associated with increased risk of upstaging in any of our analyses. Patients without surgeon suspicion of invasive disease, with a lesion size <2.0 cm or unifocal disease and with high grade pathology had a <5% risk for being upstaged. In comparison, patients with surgeon suspicion of invasive disease, lesion size >2.0 cm or extensive disease and with low grade pathology had a 75% chance of being upstaged.

Table 4
Multivariable logistic regression analysis.

	Adjusted Odds Ratio	95% CI
Breast Conservation Therapy		
Surgeon Suspicion	7.9	3.5–17.9
Tumor Size >2.0 cm, multifocal, or extensive	2.6	1.1–5.8
Grade (High vs Low/Int)	0.3	0.1–0.6
Mastectomy		
Surgeon suspicion	3.1	1.0–9.5
Suspicion on biopsy	6.0	1.8–19.4
All Patients		
Surgeon Suspicion	2.7	1.2–6.4
Suspicion on biopsy	5.7	2.2–14.9
Tumor Size > 2.0 cm, multifocal, or extensive	1.9	1.1–3.4
Grade (High vs Low/Int)	0.4	0.2–0.7

Discussion

The current study demonstrates that suspicion of microinvasion on percutaneous biopsy is a powerful predictor of upstaging and that surgeons are able to synthesize the available data to form a judgement of the risk of upstaging that is also powerfully predictive. There were limited prior studies which included suspicion of microinvasion in their analyses. Suspicion of microinvasion was the only major risk factor which classified patients as high risk in a predictive model by Coufet et al.[14] Four independent risk factors were identified: size >30 mm, palpability, mass on ultrasound, and suspicion of microinvasion on histopathology. Additional studies by Lee et al. and Arazi-Kleinman evaluated patients with suspicion of microinvasion and reported upstaging rates of 81% and 44% respectively.[21,22] These were fairly consistent with our upstaging rate of 50% of patients with suspicion of microinvasion.

Surgeon suspicion of invasive disease was used in this study and defined as whether the surgeon specifically stated their suspicion in the medical record. This was ultimately the only variable which remained significant in multivariable analysis in all three multivariable analyses. Amongst patients with surgeon suspicion, 40% were upstaged. Admittedly, this variable is quite difficult to normalize and may in fact vary from surgeon to surgeon. Each surgeon likely uses their own criteria to define who he/she defines as high risk, but in this study surgeons synthesized factors such as suspicion of microinvasion on core biopsy, size of lesion, palpable lesions, mass on imaging, and grade in their considerations. Our institution has available a nomogram calculator to calculate upstage risk that incorporates grade, presence of a mass, number of foci, and size based on an analysis of patients at a separate site but this tool was not available for the vast majority of the time-period of the current cohort.[11] Despite the uncertainty in what contributes to each surgeon's suspicion in each case, it is clear that the judgement of a surgeon should not be ignored in this situation. From review of the literature, we were not able to find other studies which used a similar variable in their analyses.

Lesion size has been identified on numerous previous studies as a risk factor for increased upstaging rates.[12,19,20] Specifically, most studies used 2.0 cm as a cutoff which is what was used in the current study. Given the fact that a large percentage of our images did not have specific lesion size stated, we combined patients with lesion size <2.0 cm and patients with unifocal disease and compared them to those with lesion size >2.0 cm and patients with multifocal/multicentric disease. Not surprisingly patients with larger lesion or multifocal/multicentric disease were more frequently upstaged to invasive disease at 17%. This data further supports current literature regarding size as a predictive factor.

Surprisingly, higher grade was actually associated with a lower rate of upstaging in our study. This is in contrast to multiple studies including a well done analysis by Jakub et al. which showed high grade to be associated with increased upstaging (OR2.85, 95% CI 1.38–5.84)[8,12]. We struggle to offer explanation to this discrepancy but our studies did vary in inclusion criteria – patients with suspicion of microinvasion and patients with open biopsy were excluded in Jakub' s study. Also surprising was that palpable lesions were not more frequently upstaged. Patients with a palpable lesion had a 17% chance of upstaging which was not statistically different than those without palpable lesions. In multiple previous studies, including Jakub et al.'s recent analysis, palpability was frequently a strong predictor and occasionally the only predictor of upstaging.[8,12,17,18] These two may be related to the type of patients we see at our institution and related to selection bias. Most of our patients participate in breast cancer screening which may skew our results compared to other institutions who have lower penetration of regular screening among their patient populations.

Prediction nomograms have been published using common risk factors to determine whether the patient is at high for upstaging. Most recently, Jakub et al. developed a nomogram that was validated on a training set.[12] This nomogram demonstrated that mass lesion, multicentric disease, high grade, and larger tumor size was associated with upstaging to invasive breast cancer. As previously mentioned they did not include suspicion of microinvasion. A previous nomogram by Lee et al. demonstrated that larger size, smaller core needle size, lack of hormone receptor expression, intermediate or high grade, and non-cribiform subtype were associated with upstaging.[11] An earlier study used an algorithm and assigned points to the most significant upgrade factors for upgrade in non-palpable DCIS and found that mass on mammogram, size greater than 2 cm, and screening interval greater than three years was the most important.[19]The prediction models except for the most recent nomogram(Jakub) have not been validated on external datasets.

Limitations of this study included its retrospective nature as well as occasional missing data. Over 100 patients were missing the characteristics of mammogram findings which precluded inclusion in the multivariable analysis. Presence of mass was identified on univariate analysis as a risk factor and has been identified on multiple previous studies as a risk factor.[12,19,20] It is unclear whether this would have altered our final results. Additionally, more specific data in regards to biopsy type, imaging findings, and histopathologic findings could have allowed a more precise predictive model. Specifically, with the more frequent use of advanced imaging techniques including MRI and CEDM, inclusion of specific findings on these modalities will further contribute to our understanding of high and low risk DCIS patients.[1–3]

Conclusions

For patients with a pre-operative diagnosis of DCIS, suspicion of microinvasion on biopsy, surgeon suspicion of invasive disease, and size of tumor can be used to help guide the use of sentinel lymph node biopsy at the time of index surgery. For patients who undergo lumpectomy, outside of high risk characteristics, it is hard to justify the use of concurrent SLN biopsy for the low risk of upstaging and even lower risk of lymph node metastases. If a patient has the above risk factors and reason to avoid a second operation, sentinel lymph node biopsy can be justified at the index operation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.12.069.

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