Mixed invasive ductal lobular carcinomas (mDLC) are clinically more similar to invasive lobular carcinoma (ILC) than to invasive ductal carcinoma (IDC)

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Significance and Background

Mixed invasive ductal lobular carcinomas (mDLC) are an elusive subtype of invasive breast cancer, characterized by their composition of both ductal and lobular components. We have previously shown that similar to ILC, mDLC is less likely than IDC to be ER+ and displays no significant differences with regard to response to neoadjuvant chemotherapy compared to ILC.

➡ Utilizing multiple statistical models including dimension reduction, elastic-net regression and meta-analysis of select studies, we sought to determine whether mDLC clinically align more closely with IDC or ILC subtypes or if they display intermediate or unique features dissimilar to either type.

Methods

Key clinical and histologic parameters were compared between cohorts of patients with mDLC (N = 410), IDC (N = 12,979), and ILC (N = 1,569) identified from cancer registry data of a single large healthcare system. A subset of the aforementioned cohorts who received neoadjuvant chemotherapy, mDLC (N = 17), IDC (N = 180), and ILC (N = 57), were separately compared.

A meta-analysis was performed to compare key clinical parameters between mDLC, IDC, and ILC. Study selection for this analysis is detailed in Figure 1. The meta-analysis was conducted using mixed-effect models.

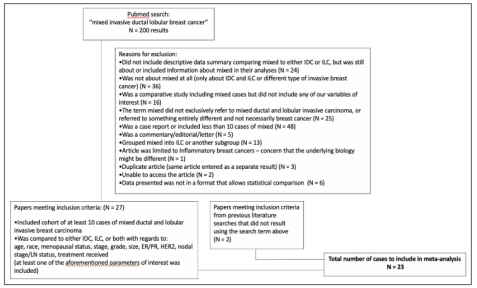

Figure 1. Consort diagram detailing included studies in meta-analysis.

Results

mDLC is less likely to be HER2+ than IDC similar to ILC

	mDLC (N = 410)	ILC (N = 1,569)	p value	IDC (N = 12,979)	p value
Tumor size	19 (12,27.75)	20 (12,35)	**0.036**	16 (10,25)	**<0.001**
Age at Diagnosis	59 (49,68)	61 (51,70)	**0.006**	57 (48,67)	**0.014**
Menopausal Status					
pre/perimenopausal	123 (0.32)	381 (0.26)		3914 (0.33)	
postmenopausal	266 (0.68)	1091 (0.74)	**0.028**	8050 (0.67)	0.69
ER					
Positive	372 (0.92)	1455 (0.96)		9579 (0.78)	
Negative	32 (0.08)	56 (0.04)	**<0.001**	2779 (0.22)	**<0.001**
PR					
Positive	339 (0.84)	1229 (0.82)		8530 (0.7)	
Negative	63 (0.16)	266 (0.18)	0.36	3736 (0.3)	**<0.001**
HER2					
Positive	11 (0.08)	43 (0.06)		814 (0.15)	
Negative	126 (0.89)	711 (0.92)		4316 (0.81)	
Equivocal	4 (0.03)	16 (0.02)	0.49	190 (0.04)	**0.04**

Table 1. mDLC falls between ILC and IDC with regard to age of patient at diagnosis and ER positivity rate. mDLC is less likely found in postmenopausal patients vs ILC, but similar to ILC with regard to HER2+ positivity *(above)*.

mDLC is strongly concordant with ILC as compared to IDC

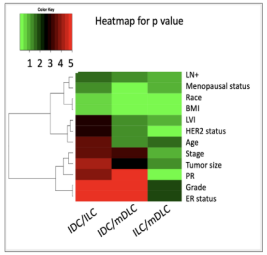

Figure 2. Heatmap visualization of concordance between mDLC, ILC, and IDC cohorts with regard to key clinicopathologic parameters demonstrates strong concordance between mDLC and ILC, with lesser concordance between mDLC and IDC. 1 (green) correlates to a p value of 0.1 signifying concordance, while 5 (red) correlates to p value of 0.00001 or less signifying significant differences *(left)*.

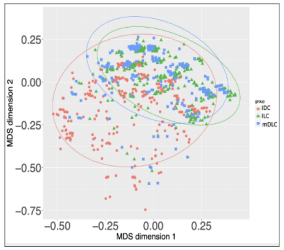

Figure 3. Incorporating data from tumor size, age at diagnosis, ER, PR, HER2, stage, grade, and lymphovascular invasion (LVI) parameters, dimension reduction by multidimentional scaling (MDS) demonstrates significant overlap of the mDLC and ILC cohorts *(above, right)*.

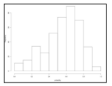

Figure 4. An elastic net regression model based on clinicopathologic parameters displaying moderate separation between IDC and ILC (cross validation AUC of IDC and ILC = 0.75) was devised. mDLC was predicted to align more closely with ILC than IDC, with 272 of cases with probability larger than 0.5 and 198 cases with probability larger than 0.6. *(left)*.

BCS tends to be less successful in mDLC than IDC but more successful than ILC

	Neoadjuvant Chemotherapy				
	mDLC	ILC	p value	IDC	p value
BCS attempted					
Yes	9 (0.53)	19 (0.33)		70 (0.39)	
No	8 (0.47)	38 (0.67)	0.16	110 (0.61)	0.34
Rate of Successful BCS					
Yes	**5 (0.56)**	**6 (0.32)**		**49 (0.7)**	
No	4 (0.44)	13 (0.68)	0.41	21 (0.3)	0.45
pCR					
Yes	**3 (0.18)**	**4 (0.07)**		**24 (0.13)**	
No	14 (0.82)	52 (0.93)	0.34	156 (0.87)	0.71

Table 2. Among patients in whom breast conserving surgery (BCS) was attempted, patients with IDC were more likely to have a successful BCS than those with ILC, with less margin positivity thereby avoiding re-excision and/or completion mastectomy (70% vs 32%, respectively; p = 0.003). Successful BCS was achieved with mDLC 56% of the time, although compared to IDC and ILC statistical significance was not reached. Small study numbers precluded our ability to perform statistical analysis on pathologic complete response rate (pCR) data *(left)*.

Meta-analysis highlights unique differences & similarities between sub-types

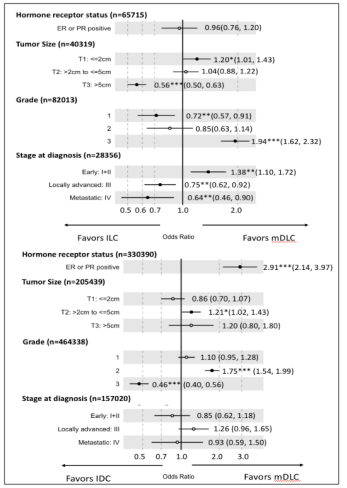

Figure 5. Meta-analysis of key clinical parameters including data from 23 published studies reported as odds ratio between mDLC and ILC *(top)* and mDLC and IDC *(bottom)*. Significant deviation from odds ratio 1.0 denoted by (*). Similar hormone receptor status in mDLC and ILC noted as compared to IDC, differences in grade are seen between the subtypes.

Conclusions

Collectively, the aforementioned findings support a higher concordance between mDLC and ILC as compared to IDC. It is feasible that the lobular component of mDLC tumors is predominant, leading to the observed histopathologic similarities noted between mDC and ILC cohorts. Molecular studies are under way to further understand the underlying complexities of mDLC.