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EARLY STAGE INVASIVE LOBULAR BREAST CANCER IS UNDERESTIMATED ON CONVENTIONAL IMAGING INCLUDING MRI

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BACKGROUND and AIMS

- In the western world, invasive lobular carcinoma (ILC) represents 15% of all invasive breast cancers (BC).[1,2]
- ILC is characterized by loss or dysfunction of adhesion molecule E-cadherin, leading to a unique infiltrative growth pattern that is unlikely to disrupt the normal architecture of the breast tissue.[3,4]
- This unique growth pattern, combined with the characteristic that ILC typically does not form a palpable mass, makes it challenging to detect on standard breast imaging techniques and to establish an accurate diagnosis.[1,4]
- Mammography is believed to underestimate ILC, while Magnetic Resonance Imaging (MRI) tends to overestimate the extent of ILC.[5]

The aim of this study is to investigate the correlation between clinical and pathology findings regarding **diameter**, **number of foci** and **number of adenopathies** together with factors affecting this correlation.

PATIENTS and METHODS

We performed a single center retrospective study in University Hospitals Leuven, Belgium. Patients that met the following criteria were included:

- Female
- Diagnosed between January 2000 and December 2020 with non-metastatic pure ILC (i.e. not mixed with other histological BC types)
- Received no neoadjuvant therapy

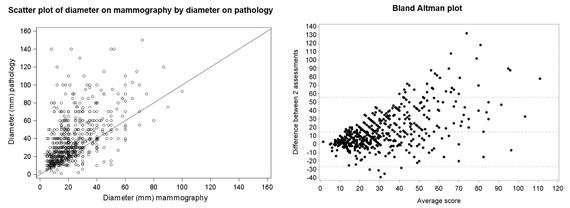
Data on patient and tumor characteristics, pre-operative imaging and pathology were collected for 1029 patients.

	Total	Tumor diameter	Number of foci	Number of adenopathies
Mammography	933	668	921	/
Ultrasound	998	843	/	984
MRI	709	619	703	690
Pathology	1029	1029	1029	1024

Statistical analysis: Imaging and pathology measurements were compared by use of Pearson correlation coefficient, Whitney U test or Chi-square test. Weighted kappa statistics were used to assess agreement.
The number of foci and the number of adenopathies were analysed as ordinal outcomes with categories 0, 1, 2, 3, ≥4. Since the techniques of mammography and ultrasound have evolved in the past 20 years, different time periods were considered in sub-analyses (2000-2004, 2005-2009, 2010-2014, 2015-2020).

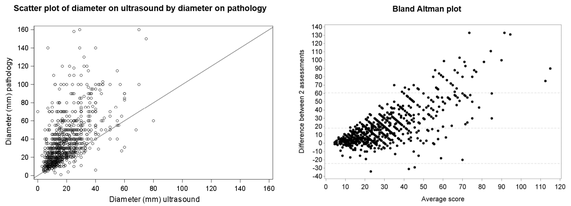
RESULTS DIAMETER

Correlation between mammography and pathology



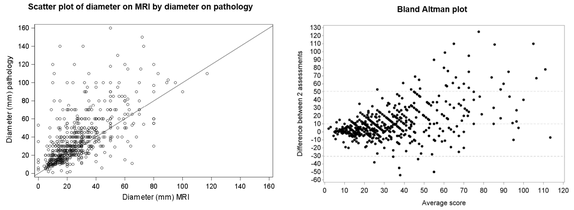
The mean diameter of mammography was 22.50 ± 14.26 mm while that of pathological measurement was 37.14 ± 25.53 mm. Mammography underestimated the tumor size, with an average difference of 14.64 ± 21.15 mm compared to pathology, as shown in the scatter plot and the Bland Altman plot.

Correlation between ultrasound and pathology



The mean diameter estimated by ultrasound (19.08 ± 11.61 mm) was lower than that by pathology (37.26 ± 26.28 mm). The scatter plot and Bland-Altman plot showed that ultrasound significantly underestimated pathology with a mean difference of 18.19 ± 21.66 mm.

Correlation between MRI and pathology



The mean diameter of MRI (27.73 ± 17.85 mm) was lower compared to pathology (37.66 ± 26.65 mm). Similar to mammography and ultrasound, MRI significantly underestimated pathology with a mean difference of 9.93 ± 20.63 mm, which is visualized in both the scatter plot and Bland Altman plot.

RESULTS NUMBER OF FOCI

Correlation between mammography and pathology

Variable	Statistic	1	2	3	>=4
N foci mammography					
1	n/N (%)	666/741 (89.88%)	60/104 (57.69%)	20/40 (50.00%)	18/36 (50.00%)
2	n/N (%)	52/741 (7.02%)	34/104 (32.69%)	10/40 (25.00%)	10/36 (27.78%)
3	n/N (%)	4/741 (0.54%)	3/104 (2.88%)	7/40 (17.50%)	2/36 (5.56%)
>=4	n/N (%)	19/741 (2.56%)	7/104 (6.73%)	3/40 (7.50%)	6/36 (16.67%)

There was an **agreement** on unifocality versus multifocality between pathology and mammography for **81.2% of the patients**.

Correlation between MRI and pathology

Variable	Statistic	1	2	3	>=4
N foci MRI					
0	n/N (%)	7/535 (1.31%)	0/88 (0.00%)	0/42 (0.00%)	0/38 (0.00%)
1	n/N (%)	405/535 (75.70%)	38/88 (43.18%)	9/42 (21.43%)	8/38 (21.05%)
2	n/N (%)	60/535 (11.21%)	32/88 (36.36%)	7/42 (16.67%)	9/38 (23.68%)
3	n/N (%)	12/535 (2.24%)	7/88 (7.95%)	9/42 (21.43%)	9/38 (23.68%)
>=4	n/N (%)	51/535 (9.53%)	11/88 (12.50%)	17/42 (40.48%)	12/38 (31.58%)

In **52.1% of the multifocal cases** reported on MRI, only **1 lesion** was reported by the pathologist.
Result: potential increase in **secondary ultrasounds** and possibly **unnecessary biopsies.**

RESULTS NUMBER OF ADENOPATHIES

Correlation between ultrasound and pathology

Variable	Statistic	0	1	2	3	>=4
N adenopathies ultrasound						
0	n/N (%)	582/600 (97.00%)	123/155 (79.35%)	49/66 (74.24%)	29/35 (82.86%)	58/123 (47.15%)
1	n/N (%)	15/600 (2.50%)	28/155 (18.06%)	10/66 (15.15%)	6/35 (17.14%)	38/123 (30.89%)
2	n/N (%)	1/600 (0.17%)	3/155 (1.94%)	2/66 (3.03%)	0/35 (0.00%)	12/123 (9.76%)
3	n/N (%)	0/600 (0.00%)	0/155 (0.00%)	1/66 (1.52%)	0/35 (0.00%)	4/123 (3.25%)
>=4	n/N (%)	2/600 (0.33%)	1/155 (0.65%)	4/66 (6.06%)	0/35 (0.00%)	11/123 (8.94%)

Considering adenopathies, the **false positive rate** of ultrasound was **3.0%**.
The false negative rate was 68.3%.

RESULTS BREAST DENSITY & YEAR OF DIAGNOSIS

Impact breast density

Variable	Statistic	Type A	Type B	Type C	Type D	P-value
Diameter difference (mm) Pathology - mammography	N	40	188	171	84	0.126
	Mean	12.88	12.09	16.53	14.77	
	Std	22.705	19.217	22.257	17.208	
	Median	6.00	7.00	10.00	10.00	
	IQR	(-0.50; 20.50)	(0.00; 18.50)	(2.00; 25.00)	(2.50; 25.00)	
	Range	(-17.00; 90.00)	(-30.00; 118.00)	(-31.00; 88.00)	(-19.00; 82.00)	

Results showed that a higher breast density level is associated with a larger difference between diameter on pathology versus mammography.

Impact year of diagnosis

Association of Diameter (mm) pathology with	Correlation Statistics	ρ	95% Confidence Interval	P-value	N. obs.
Diameter (mm) mammography [2000-2004]	Spearman	0.540	(0.381; 0.666)	<.0001	98
Diameter (mm) mammography [2005-2009]	Spearman	0.588	(0.468; 0.685)	<.0001	144
Diameter (mm) mammography [2010-2014]	Spearman	0.649	(0.558; 0.723)	<.0001	194
Diameter (mm) mammography [2015-2020]	Spearman	0.565	(0.470; 0.646)	<.0001	232

Results revealed that the correlation between mammography and pathology differs significantly between periods, showing a significantly higher correlation in diameter in [2010-2014] compared to the other three periods.

CONCLUSIONS

- The local extent of pathology in ILC is underestimated by conventional imaging techniques. Unlike previous reports, our results suggest that tumor size of ILC is also underestimated by MRI.
- Ultrasound was inferior to mammography and MRI in estimating tumor size in our series.
- It was confirmed that mammography and MRI tends to overestimate the number of foci which might lead to unnecessary secondary ultrasounds and biopsies.
- The presurgical underestimation of lymph node involvement might increase the need of secondary surgeries.

It is crucial to address these limitations in imaging of ILC and to prioritize the development of enhanced imaging techniques to improve diagnostic accuracy for these patients.

ABBREVIATIONS

- BC: Breast cancer
- ILC: Invasive lobular carcinoma
- MRI: Magnetic Resonance Imaging

REFERENCES

1. Van Baelen K. et al.; Ann Oncol 2022; 33, 769-785
2. Malhotra GK. et al.; Cancer Biology and Therapy 2010; 10, 955-960
3. Thomas M. et al.; Semin Oncol 2019; 46, 121-132
4. Pramod N. et al.; Oncologist 2021; 26, 943-953
5. Gruber I V. et al.; BMC Cancer 2013; 13, 328

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