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Predictive factors of major deviation (>20 mm) between lesion sizes measured by magnetic resonance imaging and histology for invasive lobular breast cancer

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1. Introduction

Breast cancer is the most common cancer among women [1]. There are two main histological types of invasive breast cancer: ductal and lobular. Lobular carcinoma represents 10–15% of all invasive breast cancers. These tumours show high expression of hormone receptors (HRs) but poor chemosensitivity. Lobular carcinoma is characterized by a proliferation of non-cohesive small cells growing from lobular epithelium due to intraductal permeative spread within the breast [2]. This histological characteristic explains why the infiltration of breast structures does not distort them, and why it is difficult to palpate the tumour clinically. Indeed, as it spreads, it is difficult to obtain a real radiologic diagnosis. Therefore, the size of the tumour can be under- or overestimated, as can multifocality. Often, lobular carcinoma is associated with lobular carcinoma *in situ* in large areas, which renders the tumours multifocal and/or bilateral. When comparing invasive lobular (ILC) and ductal carcinomas (IDC), Arpino et al. showed that bilateral incidence was higher for ILC than IDC (20.9% vs 11.2%, respectively) [3]. Marpeau et al. reported an incidence rate of synchronous bilateral breast cancer of 2.6%, and 17.7% of cases were ILC [4].

Currently, breast cancer screening (organized or individual) includes at least two standard mammography screenings and an ultrasound, depending on breast density [5]. These two tests have high sensitivity and specificity for ductal carcinoma, but mammography has been shown to underestimate the histological size of ILC [6]. Escolano et al. reported difficulty in diagnosis due to false-negative results, which affected 15% of mammography screenings and 12% of ultrasounds [7]. Parvaiz et al. demonstrated major deviation in 72 classified cases. For an average histological size of 23 mm, the measurements were: 17 mm for mammography, 14.5 mm for ultrasound and 25 mm for magnetic resonance imaging (MRI) [8]. MRI, which is used increasingly in the diagnosis of breast cancer, shows much higher sensitivity in the detection of lobular carcinomas, whether they are *in situ* or invasive. Indeed, due to its high sensitivity for the detection of breast cancer and its high contrast resolution by detection of neo-angiogenesis after

injection of gadolinium, MRI enables better estimation of the real size of the lesion compared with mammography, and also searches for potential multifocal lesions [9]. This would enable better-adapted surgical treatment (mastectomy vs conservative surgery). MRI remains the preferred test to determine the size of a tumour with accuracy, to search for satellite lesions and to search for potential bilaterality. However, it requires creation of a codified report to harmonize measurement criteria and written reports. Deviation between the histological size of a tumour and imaging is reduced for MRI compared with mammography and ultrasound, but the difference is still significant.

The aim of this study was to assess the presence of predictive factors for high discordance (>20 mm) between lesion sizes measured by MRI and histology in women with ILC.

2. Methods

2.1. Study population

A retrospective review was undertaken of data from all consecutive women who had breast surgery for ILC at the study institution from January 2007 to December 2016.

2.1.1. Patient characteristics

Age, parity and body mass index (BMI) were collected for each patient. The World Health Organization classification for BMI was used: underweight, BMI <18.5 kg/m²; normal weight, 18.5 ≤ BMI <25 kg/m²; overweight, 25 ≤ BMI <30 kg/m²; and obese, BMI ≥30 kg/m².

Diabetes, hypercholesterolaemia (total cholesterol >2 g/l), hypertriglyceridaemia (triglycerides >2 g/l), high blood pressure, menopausal status and use of hormone replacement therapy were also recorded.

2.1.2. Therapeutic management

Surgical management [type of breast surgery (conservative or mastectomy), number of

operations (in case of revision surgery for positive margins) and type of associated axillary surgery (sentinel node or axillary node dissection)], neoadjuvant or adjuvant chemotherapy, and adjuvant radiotherapy were recorded.

2.1.3. Imaging procedures

Information was collected regarding whether or not MRI was undertaken. MRI was performed 2–3 weeks before surgery. If the patient had neoadjuvant chemotherapy, the MRI data used were from the pre-operative MRI performed in the 15 days preceding surgery.

Pre-operative MRI was mainly performed at the study hospital on a 1.5 Tesla MAGNETOM Aera (Siemens, Munich, Germany) or HDx (General Electric, Boston, MA, USA) machine and 3 Tesla MAGNETOM Verio (Siemens). Data from MRI performed in other centres were imported into the computer network.

Patients were placed in a prone position with a dual surface antenna. T1- and T2-weighted 2-mm turbo spin-echo axial sections were performed followed by dynamic sequences before and during gadolinium injection in T1-weighted three-dimensional gradient echoes (at 1, 2, 3, 4 and 5 min) with subtractions.

The contrast agent used at the study centre was gadobenic acid (Multihance), injected intravenously at a dose of 0.2 ml/kg.

Interpretation was performed on a console using a picture archiving and communication system (Horizon Medical Imaging, McKesson, Paris, France), and post-treatment (dynamic analysis of lesion enhancement) using Syngo@via software (Siemens).

Contrast uptake by lesions was mainly sought on sequences subtracted at 2 min (time point where it is usually maximal). Lesion analysis was performed using the Breast Imaging Reporting Data System lexicon in accordance with the morphological and enhancement criteria, with dynamic curves used if necessary. However, the later sequences were always studied carefully; this enabled better visualization of certain ILCs, as their weak neo-angiogenesis

delayed contrast acquisition.

Lesions were measured on the subtracted sequences 2 or 3 min after gadolinium injection, in their longest axis, using multiplane reformatting allowed by the three-dimensional isotropic volume sequences.

The size (largest measurement) of the lesion and uni- or multifocal feature (sum of the largest measurements) on MRI were recorded in millimetres.

2.1.4. Histological results

The histological type and size of the lesions (largest measurement; in case of multifocality, sum of the largest measurements) was recorded, together with the presence of another type of invasive cancer. In addition, the status of oestrogen and/or progesterone receptors (absence of expression of HRs was defined as a percentage <10%) and the presence of overexpression of the Her2 protein [interpretation of Her2 was evaluated with a three-level score for the immunohistochemical method (1+ = negative; 3+= positive), and in-situ hybridization when the result was not certain (2+)] were recorded. The uni- or multifocal character of the lesion (multifocal defined as at least two centres of tumour infiltration separated by clear breast tissue), the presence of an in-situ component (with size and grade, if appropriate), the presence of lymphatic tumour emboli, the number of collected and invaded axillary nodes, and the size of clear margins (in millimetres) were also recorded.

Finally, to assess prognosis and survival, the occurrence of potential relapse (locoregional recurrence or distant metastasis), known at the time of data collection (August 2017), was noted. Type of metastasis (bone, visceral, brain or skin), date of diagnosis, date of latest information on the patient, and date of death (if it occurred) were recorded.

2.2. Statistics

Statistical analysis was undertaken using R 3.1.2 (<http://www.cran.r-project.org/>). Categorical

variables were compared using Chi-squared test or Fisher's exact test, and continuous variables were compared using Student's *t*-test. $p \leq 0.05$ was considered to indicate statistical significance.

Time-to-event analyses were calculated using the date of primary surgery as the start point. Women who were alive and without recurrence were censored at the date of last follow-up. Data for survival curves were calculated using the Kaplan–Meier method with log-rank test. Recurrence-free survival and overall survival were analysed.

Multiple logistic regression analysis was used to examine the association between study covariates and discordance between MRI and histological measurements. Missing values were not imputed.

3. Results

Over the study period, 384 women were treated for ILC. Of these, 41 (10.7%) women had an associated in-situ component of ductal carcinoma.

The median age was 65 years (range 35–95 years) and the median BMI was 26 kg/m² (range 16–46 kg/m²). Table 1 shows the demographic characteristics of the study cohort.

<insert Table 1 near here>

In total, 194 (50.5%) women underwent breast-conserving surgery and 190 (49.5%) women underwent mastectomy. Sixty-three (16.4%) women had two surgical procedures to obtain free margins, and two (0.5%) women underwent three surgical procedures. Forty-four percent of re-operated women had residual tumour.

Of the 384 women treated for ILC, 295 had breast MRI. This was performed after surgery in 19 women. MRI data were available for analysis for 246 women (Table 2).

<insert Table 2 near here>

Table 3 shows the histological characteristics of the tumours.

<insert Table 3 near here>

The correlation coefficient between lesion sizes measured by MRI and histology was 0.63 ($p < 0.0001$). MRI underestimated the size of the lesion compared with histological measurements in 107 of 246 (43.5%) cases. For 12 patients, there was a perfect match between MRI and histological measurements. MRI overestimated the size of the lesion compared with histological measurements in 127 of 246 (51.6%) cases. The numbers of cases of under- and overestimation are presented in Table 4.

<insert Table 4 near here>

In the overall population, the mean difference between lesion sizes measured by MRI and histology was +1.7 mm and the median difference was +1 mm [interquartile range (IQR) -5 to +8 mm].

In the case of underestimation, the mean difference between lesion sizes measured by MRI and histology was -16.7 mm and the median difference was -12 mm (IQR -20 to -8 mm).

In the case of overestimation, the mean difference between lesion sizes measured by MRI and histology was +18.9 mm and the median difference was +13 mm (IQR +8.5 to +22.5 mm).

When a 5-mm difference was used to establish deviation in the size of the lesions measured by MRI from those measured by histology, 110 measurements matched, 61 lesions were underestimated by MRI and 75 lesions were overestimated by MRI.

When a 10-mm difference was used to establish deviation in the size of the lesions measured by MRI from those measured by histology, 161 measurements matched, 39 lesions were

underestimated by MRI and 46 lesions were overestimated by MRI.

A difference >20 mm was considered to represent a major deviation, and this was found in 36 patients.

Table 5 shows the results of the univariable analysis that searched for predictive factors for overestimation (>20 mm). Menopausal status ($p=0.01$), HR status, ($p=0.09$) and neoadjuvant chemotherapy ($p<0.001$) were eligible for multivariable analysis, and menopausal status and treatment with neoadjuvant chemotherapy were found to be independent predictive factors of overestimation between lesion sizes measured by MRI and histology using a threshold of 20 mm.

<insert Table 5 near here>

In the univariable analysis that searched for predictive factors for underestimation (>20 mm), histological size ($p<0.001$) and the presence of an in-situ component ($p=0.02$) were eligible for multivariable analysis, and were found to be independent predictive factors of underestimation between lesion sizes measured by MRI and histology using a threshold of 20 mm.

4. Discussion

Mammography, ultrasound and MRI are all used to assess the extent of ILC. Mammography has primarily served as a screening test, and has limited potential for patients with ILC. Contrast-enhanced MRI of the breast is considered to be the most accurate imaging modality, capable of detecting multifocal and contralateral cancers, and enabling changes to be made to therapeutic plans. The results of this study showed that MRI remains a reliable imaging tool in the context of ILC. When a 5-mm difference in absolute value between lesion sizes measured by MRI and histology was used, as in the study by McGhan et al. [10], 110 MRI measurements (45%) matched the histological measurements, 24.8% of MRI measurements were underestimates and

30.5% of MRI measurements were overestimates. In the study conducted by McGhan et al. on 70 patients, 56% had MRI measurements matching the histological sizes and 31% had overestimated MRI measurements. Despite 100% sensitivity for MRI diagnosis in some studies, the specificity is lower (89%) according to a study from Nice [11]. In 2011, Muttalib et al. compared imaging and histopathological sizes of invasive lobular tumours in order to determine outcomes in terms of survival [12]. They found that MRI can search for satellite lesions, but it underestimates lesion size by 59.1%. They considered a deviation <16 mm to be low and a deviation >22 mm to be high. In the present study, major deviation was defined as a difference >20 mm between the two measurements; this affected 14.6% of patients. It should be noted that the present study included all types of ILC, irrespective of size, hormonal status or size of the in-situ component.

In this study, the mastectomy rate was 49.5%; this is in accordance with Katipamula et al., who reported a higher mastectomy rate in patients undergoing MRI before surgery [13]. The present study tried to assess the presence of factors that could predict major deviation (>20 mm) between lesion sizes measured by MRI and histology. For overestimation with this threshold, significant factors on univariate analysis were: menopausal status (OR 0.27, 95% CI 0.10–0.71; $p=0.01$), HR status (HR negative, OR 1.64, 95% CI 0.27–9.89; HR positive, OR 0.64, 95% CI 0.21–1.88; $p=0.09$) and neoadjuvant chemotherapy (OR 10.33, 95% CI 3.58–29.8; $p<0.001$). On multivariate analysis, menopausal status and neoadjuvant chemotherapy were found to be independent predictive factors of overestimation. Menopausal status independently reduced the risk of overestimation, suggesting that the activity of the tumour-surrounding breast tissue influences measurement. One element of response may be the absence of background matrix enhancement in postmenopausal women on MRI. Detection of lesion enhancement and measurements are therefore easier and more reliable.

Underestimation of real tumour size can lead to incomplete surgical excision, and requires re-excision with possible conversion to mastectomy after breast-conserving surgery. In the

present study, almost one-half of re-operated women had residual tumour. MRI reduced the re-operation rate in this study (16.9%) compared with rates published in the literature (29–67%). [14]. The COMICE trial included 1623 women with breast cancer who underwent pre-operative breast MRI, and found no difference in the re-operation rate (19%) [15].

Mann et al. reported a reduced re-excision rate without an increase in the rate of mastectomy in women with ILC. This study was criticized because it included patients over a long time period, so scans were performed using various MRI protocols and field strengths [16].

In Houssami et al.'s meta-analysis of studies with a control group (total of 766 patients with ILC), there were increased mastectomies with routine pre-operative MRI, and weak evidence in favour of a reduced re-excision rate in the ILC subgroup [17].

In the present study, for underestimation, significant factors on univariate analysis were: histological size (OR 1.05, 95% CI 1.02–1.08; $p<0.0001$) and the presence of an in-situ component (OR 4.66, 95% CI 1.01–21.5; $p=0.02$). These two factors were independent predictive factors of underestimation. In a study concerning all types of breast tumours, Khazai et al. showed that tumour type (especially in-situ and invasive lobular tumours) and hormonal status could interfere with the determination of size by imaging and lead to a deviation [18]. Rominger et al. reported an 86% deviation between sizes measured histologically and sizes measured by MRI, with overestimation of 9% and underestimation of 5%; the only predictive factor of deviation in their study was histological type ($p<0.001$) [19].

Concerning treatment by neoadjuvant chemotherapy, evaluation of the tumour response by imaging is essential and is currently performed by breast MRI. However, this evaluation can also be performed by clinical examination, ultrasound or mammography. Yeh et al. showed that MRI had the best correlation with histological size: 71% ($p<0.002$) for MRI, 19% for clinical examination, 26% for mammography and 35% for ultrasound. However, the overestimation rate was 6% and the underestimation rate was 23%, with a residual tumour rate of 29% (95% CI 14–48%) [20]. Balu-Maestro et al. reported 63% residual tumour after treatment by neoadjuvant

chemotherapy for MRI, 43% for ultrasound and 38% for mammography [21]. According to Abraham et al., in 30 of 31 (97%) cases, MRI and histological results were properly correlated, and false-negative results were rare with MRI. The only aetiologies were in-situ carcinoma and small tumours measuring <5 mm [22]. Gilles et al. reported good correlation between MRI and histological measurements after neoadjuvant treatment among 18 patients. Only one patient had a 'mock' MRI linked to the presence of in-situ lobular carcinoma [23].

According to the recommendations of the Collège National des Gynécologues Obstétriciens de France, MRI can be used in situations where mammography and ultrasound are not suitable, such as very dense breasts, high family risk, if there is a radio clinical deviation in appreciation of tumour size, high-grade ductal carcinoma and ILC [24]. The present study found that MRI is an essential imaging tool in the diagnostic and extension analysis of ILC due to more accurate measurement of the tumour centre, detection of satellite centres and the search for bilateral status. Ollivier et al. confirmed this in a meta-analysis by enumerating the different examinations that can be used in the evaluation by neoadjuvant treatment imaging [25]. Tardivon et al. suggested the use of MRI for patients with a high risk of relapse and high-grade invasive tumours >2 cm [26].

This study has limitations due to its retrospective nature and inherent bias. It also has certain strengths. Firstly, this is one of few studies selecting a subgroup of patients with ILC. Secondly, all images, histological data and surgical techniques were maintained by in-house radiologists, pathologists and surgeons, who were specialists in breast cancer at a university hospital.

In conclusion, a minimum 5-mm threshold was used to match results, with a 20-mm-threshold defined as a major deviation. For overestimation, the independent predictive factors for major deviation were menopausal status and neoadjuvant chemotherapy. For underestimation, the independent predictive factors for major deviation were histological size and the presence of an in-situ component. These findings suggest that more attention should be paid to lesion sizes

measured before surgery, and this will help in the appropriate surgical management of patients.

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Conflict of interest

None declared.

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Author queries

This article has been edited extensively – please check the proofs carefully to ensure that your meaning has not been altered

Section 2.1.3: ‘The size (largest measurement) of the lesion and uni- or multifocal feature (sum of the largest measurements) on MRI were recorded in millimetres.’ Is this OK as edited?

Section 4: ‘The COMICE trial included 1623 women with breast cancer who underwent pre-operative breast MRI, and found no difference in the re-operation rate (19%) [15].’ Is this OK as edited?

Section 4: ‘if there is a radio clinical deviation in appreciation of tumour size’ – please clarify

Ref 5 – need author, publisher, city and year. When did you last access this website?

Table 2: NA? Please spell out in full in footnotes

Table 1
Population characteristics

	<i>n</i> =384
Age (years), mean \pm SD (range)	63.4 \pm 12 (35–95)
BMI (kg/m ²), mean \pm SD (range)	25.7 \pm 5.2 (16–46)
Parity, mean \pm SD (range)	2 \pm 1.4 (0–14)
Menopause	285 (74.2%)
HRT	96 (25%)
HBP	119 (31%)
Diabetes	28 7.3%)

BMI, body mass index; HRT, hormonal replacement therapy; HBP, high blood pressure; SD, standard deviation.

Table 2

Size and number of lesions on magnetic resonance imaging (MRI) and histology

<i>n</i> =246	<i>n</i> (%)
Mean size on MRI before surgery, mm (range)	28.4 (0–126)
Mean size on histology, mm (range)	27.3 (0–175)
MRI data	
Number of tumours	
0	6 (2.4)
1	167 (67.9)
2	54 (22)
3	17 (6.9)
4	1 (0.4)
≥5	1 (0.4)
Multifocality	73 (29.7)
Histological data	
Number of tumours	
No residual lesions	1(0.4)
1	150 (61)
2	46 (18.7)
3	41(16.7)
4	5 (2)
≥5	1(0.4)
NA	3 (1.2)
Multifocality	99 (40.3)

Table 3
Histological characteristics

	<i>n (%)</i>
Inflammation	13 (3.4)
Bilateral	29 (7.5)
Multifocal	153 (39.8)
Grade	
1	11 (2.9)
2	318 (82.8)
3	40 (10.4)
Unknown	15 (3.9)
Molecular subtype	
Luminal A	240 (62.5)
Luminal B	126 (32.8)
HER2	6 (1.6)
Triple negative	12 (3.1)
Hormonal receptors	
ER positive/PR positive	288 (75)
ER positive/PR negative	72 (18.7)
ER negative/PR positive	1 (0.3)
ER negative/PR negative	18 (4.7)
Unknown	5 (1.3)
Lymphovascular invasion	34 (8.8)

ER, oestrogen receptor; PR, progesterone receptor.

Table 4

Under- and overestimation of tumour size measured by magnetic resonance imaging compared with histology

Discrepancy between size measured by MRI and histology (mm)	Underestimation (<i>n</i> =107) <i>n</i> (%)	Overestimation (<i>n</i> =127) <i>n</i> (%)
0.5–5	47 (43.9)	51 (40.1)
5–10	22 (20.6)	29 (22.8)
10–15	18 (16.8)	14 (11)
15–20	6 (5.6)	11 (8.7)
20–25	2 (1.9)	6 (4.7)
25–30	7 (6.5)	2 (1.6)
30–50	3 (2.8)	10 (7.9)
>50	2 (1.9)	4 (3.1)

Table 5

Predictive factors for concordance (threshold 20 mm) of tumour size measured by magnetic resonance imaging and histology

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Overestimation				
Age	0.97 (0.93–1.01)	0.11	-	
Parity	0.95 (0.66–1.36)	0.77	-	
BMI	0.94 (0.84–1.04)	0.20	-	
Menopause	0.27 (0.10–0.71)	0.01	0.38 (0.13–1.11)	0.08
Histological size	0.98 (0.95–1.02)	0.34		
ILC vs IDC+ILC	2.21 (0.28–17.3)	0.40	-	
Multifocality	1.08 (0.44–2.64)	0.86	-	
Inflammation	1.20 (0.14–10.08)	0.87	-	
SBR grade	1.96 (0.61–6.29)	0.27	-	
Presence of in-situ component	0.77 (0.31–1.89)	0.57	-	
Hormone receptors		0.09		0.42
ER+/PR-	Reference			
ER-/PR-	1.64 (0.27–9.98)		1.91 (0.26–14.1)	
ER+/PR+	0.64 (0.21–1.88)		0.68 (0.19–2.46)	
NAC	10.3 (3.58–29.8)	<0.001	6.32 (1.89–21.1)	0.004
Underestimation				
Age	0.99 (0.94–1.04)	0.61		
Parity	0.97 (0.66–1.44)	0.91		
BMI	1.06 (0.95–1.18)	0.27		
Menopause	0.89 (0.24–3.35)	0.86		
Histological size	1.05 (1.02–1.08)	<0.001	1.06 (1.03–1.09)	<0.001
ILC vs IDC+ILC	0.39 (0.10–1.50)	0.20		
Multifocality	2.08 (0.69–6.21)	0.18		
Inflammation	1.94 (0.23–16.7)	0.57		
SBR grade	0.65 (0.14–3.05)	0.58		
Presence of in-situ component	4.66 (1.01–21.5)	0.02	6.13 (1.11–33.8)	0.01
Hormone receptors		0.32		
ER+/PR-	Reference			
ER-/PR-	2.74 (0.40–18.9)			
ER+/PR+	0.68 (0.18–2.65)			
NAC	3.01 (0.60–15.1)	0.22		

BMI, body mass index; ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; ER, oestrogen receptor; PR, progesterone receptor; NAC, neoadjuvant chemotherapy; OR, odds ratio; CI, confidence interval.