Thieme

Correlations Between Ultrasonographic Findings of Invasive Lobular Carcinoma of the Breast and Intrinsic Subtypes

Korrelation der sonografischen Befunde des invasiven lobulären Mammakarzinoms und der intrinsischen Subtypen

Authors

Xin Wen[1, 2], Yingjiao Yu[3], Xiwen Yu[4], Wen Cheng[2], Zhuozhong Wang[5], Lin Liu[6], Lei Zhang[1], Ling Qin[7], Jiawei Tian[1]

Affiliations

1 Ultrasound, the Second Affiliated Hospital of Harbin Medical University, Harbin, China
2 Ultrasound, Harbin Medical University Cancer Hospital, Harbin, China
3 Ultrasound, General Hospital of Daqing Oil Field, Harbin, China
4 Office, Heilongjiang Academy of Medical Sciences, Harbin, China
5 Epidemiology and Biostatistics, School of Public Health, Harbin Medical University, Harbin, China
6 Breast Disease Surgery, the Second Affiliated Hospital of Harbin Medical University, Harbin, China
7 Pathology, Harbin Medical University Cancer Hospital, Harbin, China

Key words

invasive lobular carcinoma, ultrasound, BI-RADS, correlations, intrinsic subtype

received 19.02.2018
accepted 14.08.2018

Bibliography

DOI https://doi.org/10.1055/a-0715-1668
Published online: September 25, 2018
Ultraschall in Med 2019; 40: 764–770

ISSN 0172-4614

Correspondence

Prof. Jiawei Tian
ultrasound, the Second Affiliated Hospital of Harbin Medical University, Baojian Rd. 148, 150086 Harbin, China
Tel.: ++ 86/4 51/86 67 58 46
jwtian2004@163.com

ABSTRACT

Purpose To analyze the ultrasonographic findings of invasive lobular carcinoma (ILC) of the breast in 360 women and the correlations between the characteristics and the intrinsic subtypes.

Materials and Methods We evaluated the imaging findings according to the lexicon of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). The included ultrasonographic features were shape, orientation, margin, echo pattern, posterior features, calcifications, the vascularity of the masses and the presence of architectural distortions. The associations between those features and the intrinsic ILC subtypes were investigated.

Results The most common manifestations of ILC on ultrasound (US) were hypoechoic masses with irregular shape, parallel orientation, spiculated margin, posterior acoustic shadowing, no calcification and blood vessels in the rim. The patients in the luminal A subtype were the youngest, and the patients in the HER2 overexpression subtype were the oldest ($p = 0.01$). On US, the HER2 overexpression subtype was characterized by microlobulated margins ($p = 0.002$), while the luminal A subtype and the luminal B subtype mostly had spiculated margins. The basal-like subtype was distinctive in that it had no posterior features ($p = 0.041$), rather than acoustic shadowing, and the masses in the HER2 and basal-like subtypes were larger than in the other two groups ($p = 0.03$).

Conclusion There were significant differences and several trends in the ultrasonographic characteristics of different intrinsic subtypes, which may supply accurate imaging diagnostic criteria to assist in the management of individuals with ILC.

ZUSAMMENFASSUNG

Ziel Untersuchung der Ultraschallbefunde des invasiven lobulären Karzinoms (ILC) der Brust bei 360 Frauen, sowie die Zuordnung der Charakteristika zu den intrinsischen Subtypen.

Materialien und Methoden Wir haben die Ergebnisse der Bildgebung nach dem Atlas der BI-RADS („American College of Radiology Breast Imaging Reporting and Data System“) ausgewertet. Die eingeschlossenen Ultraschallmerkmale waren Form, Ausrichtung, Rand, Echomuster, posteriore Merkmale, Verkalkungen, die Vaskularität der Herdläsionen und das Auftreten von Architekturstörungen. Der Zusammenhang dieser Merkmale mit den intrinsischen ILC-Subtypen wurde untersucht.

Ergebnisse Die häufigsten Manifestationen des ILC im Ultraschall (US) waren Echo-arme Herdläsionen mit irregulärer Form, paralleler Ausrichtung, spikuliertem Rand und posteriorem Schallschatten, keine Verkalkung und Blutgefäße im Randbereich. Patienten mit luminalem Subtyp-A waren die

jüngsten und diejenigen Patienten mit HER2-Überexpression-Subtyp waren die ältesten (p = 0,01). Im US war der HER2-Überexpression-Subtyp durch mikrolobulierte Ränder gekennzeichnet (p = 0,002), während die luminalen Subtypen A und B meist spikulierte Ränder aufwiesen. Der „basal-like" Subtyp war hingegen dadurch charakterisiert, dass er außer einem Schallschatten keine posterioren Merkmale (p = 0,041) aufwies. Außerdem waren die Herdbefunde bei den Subtypen HER2 und „basal-like" größer als bei den beiden anderen Gruppen (p = 0,03).

Schlussfolgerung Die verschiedenen intrinsischen Subtypen zeigten bezüglich der US-Charakteristika signifikante Unterschiede sowie einige Tendenzen. Diese könnten somit genaue diagnostische Bildgebungskriterien liefern, um das Patientenmanagement bei ILC zu unterstützen.

Introduction

Due to its special histopathologic features and growth pattern, invasive lobular carcinoma (ILC) of the breast has long been known to be challenging to diagnose with mammograms, making it difficult to provide individualized therapy. Magnetic resonance imaging (MRI) has advantages with respect to measuring tumor size and staging ILC lesions [1–4], although there is no evidence supporting the routine use of MRI to obtain a lower secondary surgery rate [5–7]. Although higher sensitivities of ILC diagnosis on ultrasound (US) have been reported [8, 9], US has always been considered as an adjunct to a suspicious mammography or physical examination in published studies [8, 10]. In view of the differences in clinical behavior between ILC and invasive ductal carcinoma (IDC), many doctors adhere to special treatment guidelines for ILC, based on molecular biologic features such as the estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) statuses instead of lobular histology [11, 12]. However, the reported ultrasonographic appearances of ILC vary and have been limited by a small sample size [13–15], which creates a diagnostic barrier to further targeted therapy of ILC.

The study objective was to analyze the ultrasonographic findings of ILC according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon [16] and to correlate those characteristics with the intrinsic ILC subtypes.

Methods

Patients with ILC

The study was focused on breast patients who were diagnosed as having ILC by postoperative pathology between January 2011 to June 2017 from three medical institutes, where US is performed as a routine imaging tool in addition to mammography for all resident breast tumor patients before any clinical management. Ultrasonographic and histopathologic characteristics were recorded, and the associations were analyzed only when the two datasets were both available.

US devices and characteristics

US examinations were performed using high-frequency transducers (7–18 MHz) in several units (GE Healthcare, Chalfont St Giles, UK; Philips Healthcare, Bothell, WA, USA; Siemens, Erlangen, Germany; Supersonic imaging, Aix en Provence, France; Esaote, Genova, Italy; and Mindray Digital Ultrasound Imaging System, Shenzhen, China). It should be noted that the ultrasound department is an independent department in almost all Chinese hospitals, and the breast USs in these three hospitals were performed by specialist breast ultrasonographers.

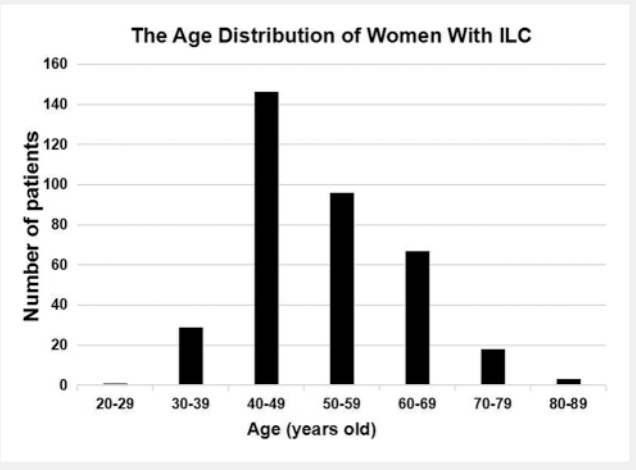
The ultrasonographic features were independently rescreened according to the 5th BI-RADS lexicon (the BI-RADS used clinically between 2003 and 2014 was the 4th edition, so we re-evaluated each imaging report of all the included patients between 2011 and 2014 using the 5th edition of BI-RADS) by two experienced doctors (who have worked on breast ultrasonic diagnosis for more than six years). Discrepancies were resolved with two additional experienced ultrasonic doctors by joint consensus. The ultrasonographic characteristics were recorded as follows: (1) the presentation of a mass or architectural distortion; (2) the shape, orientation, margin and echo pattern of a mass; (3) the posterior features, calcifications, and vascularity of a mass or architectural distortion; (4) the tumor size measured on US.

Histopathologic features and tissue specimens

A dedicated pathologist reviewed 252 pathology records at the Harbin Medical University Cancer Hospital, 67 ILC cases from the Second Affiliated Hospital of Harbin Medical University Hospital and 41 cases from the General Hospital of Daqing Oil Field Hospital.

The histopathologic features in this study included the ER, PgR, HER2, and Ki-67 labeling indexes. The intrinsic subtypes were defined according to the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 [17] as follows: (1) the luminal A subtype was "ER and PgR positive, HER2 negative, and Ki-67 low (< 14 %)"; (2) the luminal B subtype was "ER positive, HER2 negative, and at least one of: Ki-67 high (≥ 14 %), PgR negative or low (< 14 %), and recurrence risk high based on multigene-expression assay (if available); ER positive, HER2 overexpressed or amplified, any Ki-67, and any PgR"; (3) the HER2 overexpression subtype was "HER2 overexpressed or amplified, and ER and PgR absent"; and (4) the basal-like subtype was "ER and PgR absent, and HER2 negative".

Buffered formalin was used for the preservation of tissue specimens. The samples were stained by hematoxylin and eosin (H&E). ER, PgR and HER2 were analyzed immunohistochemically. The Allred score (which defined scores ≥ 3 as positive) was used for ER and PgR evaluation [18]. HER2 positive was defined as grade 3 +, and fluorescence in situ hybridization (FISH) was performed at grade 2 + for a positive diagnosis [19]. The percentage of Ki-67



▶ **Fig. 1** Age distribution of women with ILC. The age was when the patient was diagnosed with ILC.

stained cells out of the total counted tumor cells was considered the Ki-67 status.

Statistical analysis

The correlations of age and tumor size with the intrinsic subtypes were evaluated by one-way ANOVA and SNK tests. The associations between US features and intrinsic subtypes were assessed by χ^2 tests and Bonferroni corrections. All analyses in this study were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), with $P < 0.05$ as the threshold for statistical significance.

Results

Patients and US characteristics

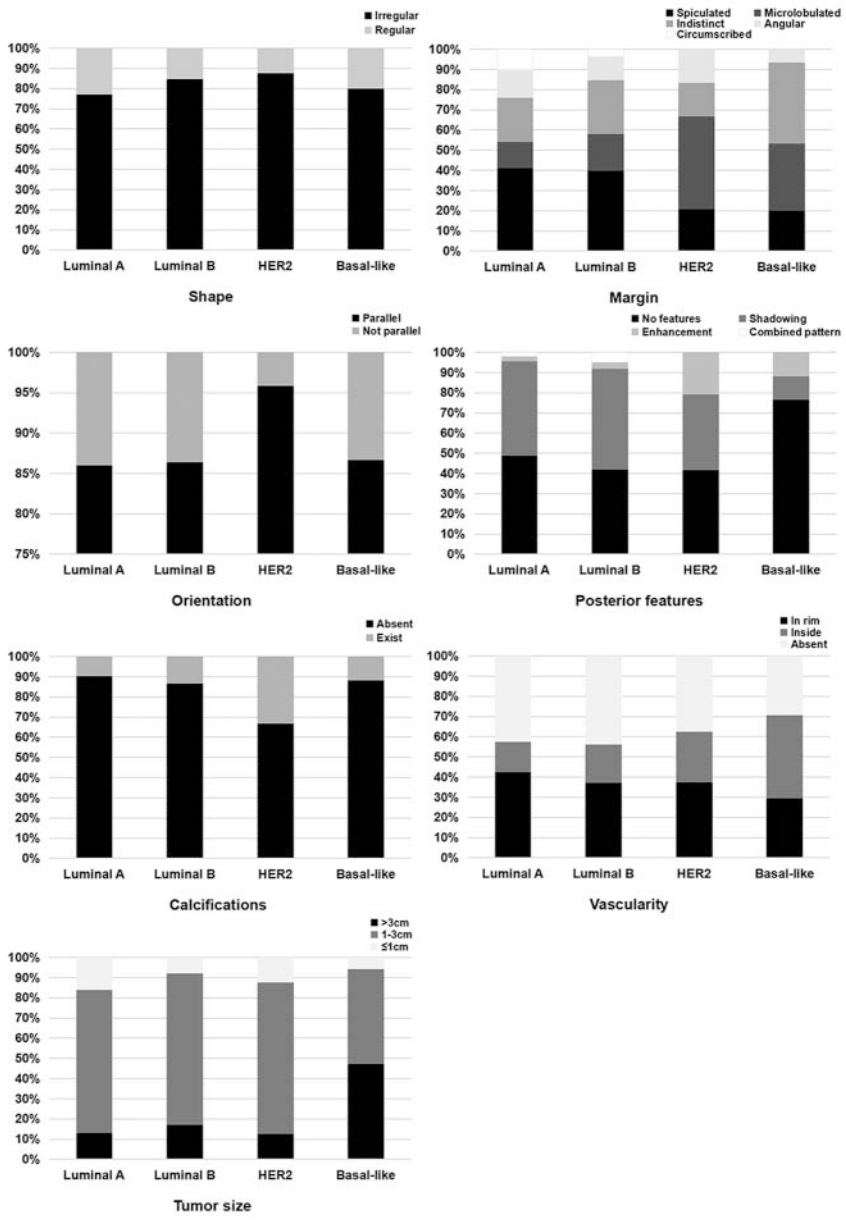
360 women ranging in age from 24 to 85 years old (median age: 51 years) with 385 masses were diagnosed pathologically as having ILC in three hospitals from January 2011 to June 2017. The age distribution of the 360 patients is shown in ▶ **Fig. 1** with a high incidence in perimenopausal women, especially those aged 40 to 49 years. There were 148 patients (38.9 %) with axillary lymphatic metastasis. Of all cases, 228 (63.3 %) were treated with modified radical mastectomy, 109 (30.3 %) were treated by mastectomy with sentinel lymph node dissection, and only 23 (6.4 %) underwent breast conserving surgery (BCS). Among the 378 masses with usable immunohistochemical features, 32.3 % (122) were luminal A subtype, 56.4 % (213) were luminal B subtype, 6.9 % (26) were HER2 subtype, and 4.5 % (17) were basal-like subtype. 344 patients with 369 pathological masses were examined by both US and mammography. Of all cases, 11 (3.0 %) were missed on US, 34 (9.2 %) were missed on mammography, and 7 (1.9 %) were missed on both devices, which indicated that 27 of the 34 (79.4 %) mammographically missed carcinomas could be visualized by US. Additionally, among the 369 masses, 337 (91.3 %) were categorized as BI-RADS 4 or 5 by US, 301 (81.6 %) were categorized as BI-RADS 4 or 5 by mammography, and 286 (77.5 %) were categorized as BI-RADS 4 or 5 by both US and mammography,

▶ **Table 1** Ultrasonographic characteristics of 353 ILCs according to the BI-RADS lexicon

findings		Number	Ratio (%)
masses		319	90.4
architectural distortion		34	9.6
shape (n = 319)	irregular	263	82.5
	regular	56	17.6
	▪ oval	53	94.6
	▪ round	3	5.4
orientation (n = 319)	parallel	278	87.2
	not parallel	41	12.9
margin (n = 319)	circumscribed	16	5.0
	not circumscribed	303	95.0
	▪ indistinct	80	26.4
	▪ angular	40	13.2
	▪ microlobulated	62	20.5
	▪ spiculated	121	39.9
echo pattern (n = 319)	hypoechoic	303	95.0
	hyperechoic	7	2.2
	complex cystic and solid	7	2.2
	heterogeneous	2	0.6
posterior features (n = 353)	no posterior features	159	42.2
	enhancement	17	4.8
	shadowing	165	49.6
	combined pattern	12	3.4
calcifications (n = 353)	no calcifications	304	86.1
	calcifications	49	13.9
vascularity (n = 353)	absent	142	40.2
	internal vascularity	65	18.4
	vessels in rim	146	41.4

which means that 95.0 % (286/301) of the mammographically dedicated carcinomas could be diagnosed correctly by US, whereas 84.9 % (286/337) of the sonographically dedicated carcinomas were also correctly diagnosed by mammography.

A total of 353 masses were included in the evaluation of US features. 1 of the 360 patients was excluded because of a lack of US information. 11 masses (2.9 %) were missed on US, and 20 patients (5.6 %) were misdiagnosed as having multifocal or multicentric distribution, which resulted in their exclusion. The tumor size was 0.5–9.5 cm on US, with a mean size of 2.2 ± 1.2 cm. The ultrasonographic findings of the 353 ILCs are summarized in ▶ **Table 1**, according to the BI-RADS lexicon. Among the 353 ILCs, 319 (90.4 %) were "masses" and 34 (9.6 %) were "architectural distortions" on US grayscale. Of the 319 masses, 263 (82.5 %) were irregular in shape, and 56 (17.5 %) had regular shapes. Most masses had a parallel orientation (n = 278, 87.2 %) on US section, and a few had a ratio of anteroposterior to trans-



▶ **Fig. 2** Comparisons of ultrasonographic features in intrinsic subtypes. **a** shape; **b** margin; **c** orientation; **d** posterior features; **e** calcifications; **f** vascularity; **g** tumor size.

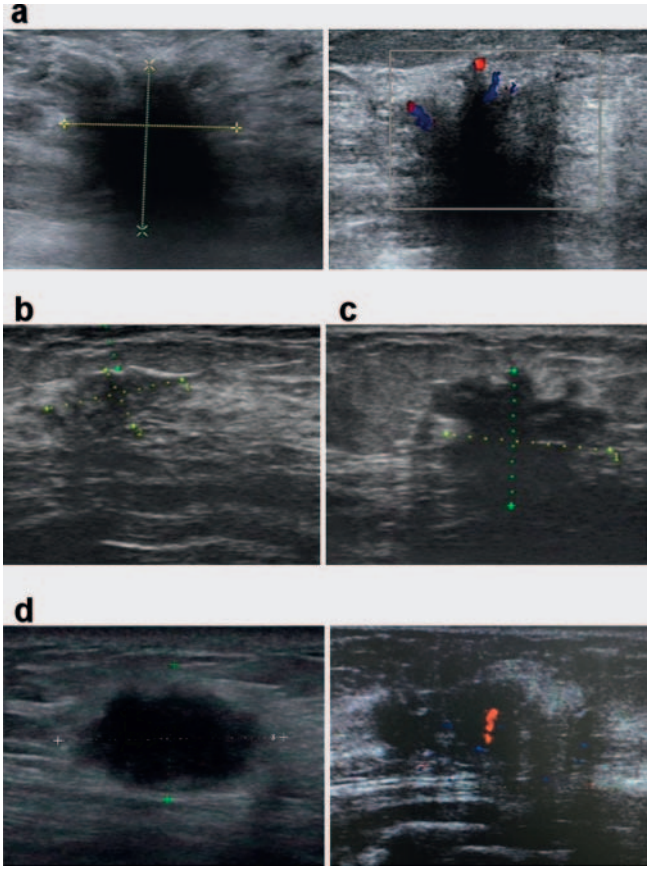
verse diameter (A/T) > 1 (n = 41, 12.9 %). Only 16 (5.0 %) masses had circumscribed margins, while 95.0 % of the masses did not have circumscribed margins. Furthermore, among those without circumscribed margins, the most common type was spiculated margins (n = 121, 39.9 %) followed by indistinct (n = 80, 26.4 %) and microlobulated (n = 62, 20.5 %) margins. Angular margins (n = 40, 13.2 %) were the rarest. Like other breast tumors, ILC on US was mostly hypoechoic (95.0 %). Acoustic shadowing (49.6 %) behind a mass or architectural distortion was the most common posterior feature on US imaging. Any kind of suspicious calcifications (86.1 %) were not commonly found in (or around) a mass or architectural distortion. Regarding the vascularity presented on US, masses or architectural distortion was characterized by blood signals in the rim (41.4 %) rather than in internal vessels (18.4 %).

Correlation of each US feature with intrinsic subtype

A total of 348 masses met the eligibility criteria (with ultrasound and relevant histopathological features both available) and were included in the correlation analysis. The patients in the luminal A group were the youngest (mean age: 49.9 ± 9.2 years), and the patients in the HER2 overexpression group (mean age: 57.2 ± 12.7 years) were the oldest (p = 0.01).

The ratios of the subtypes were compared for every ultrasonographic finding, and the results are shown in ▶ **Fig. 2**. Significant

differences in mass margin were identified between the HER2 group and the luminal A and luminal B groups ($p = 0.006$, $p = 0.024$). The HER2 subtype was characterized by microlobulated margins ($p = 0.002$), whereas the luminal A and luminal B subtypes were mostly characterized by spiculated margins. Although no significant difference was found between the basal-like subtype and the other three subtypes in terms of margin, there was a tendency towards a positive relationship between the basal-like subtype and indistinct margins. Most of the basal-like subtype presented no posterior features ($p = 0.041$), and of those demonstrated, the least common was posterior shadowing ($p = 0.019$). Despite not reaching statistical significance, shadowing was an important posterior manifestation in the luminal A, luminal B and HER2 subtypes. Regarding the tumor sizes measured on US, significant differences were identified between the HER2, the basal-like subtypes and the luminal A, luminal B subtypes ($p = 0.03$). Masses in the basal-like group were the largest (mean size, 3.0 ± 1.3 cm), followed by the HER2 subtype with a mean size of 2.3 ± 1.0 cm, and the masses in the luminal A subtype were the smallest, with a mean size of 2.0 ± 1.1 cm. As shown in ▶ **Fig. 2**, the vascularity of the luminal A, luminal B and HER2 subtypes usually presented as blood signals in the rim, while the basal-like subtype commonly had vessels inside the mass. However, the difference was not significant. In addition, no significant differences in aspects such as mass shape, orientation, echo pattern and calcification were found among the intrinsic subtypes. All subtypes were hypoechoic and were characterized by irregular shapes, parallel orientation, and no calcifications. The typical ultrasonographic appearance of each subtype is presented in ▶ **Fig. 3**.



▶ **Fig. 3** The typical appearance of ILC on US. **a** luminal B (similar to luminal A): a hypoechoic mass with irregular shape, parallel orientation, spiculated margin, posterior shadowing, no calcification, and blood signals in the rim; **b** architectural distortion; **c** HER2: a hypoechoic mass with irregular shape, parallel orientation, microlobulated margin, posterior shadowing, and no calcification; **d** basal-like: a hypoechoic mass with irregular shape, parallel orientation, indistinct margin, no posterior features, no calcifications, and internal blood signals.

Discussion

As the second most common subtype of invasive breast carcinoma, ILC accounts for 5–15 % of all breast cancers [20] and has unique biologic and clinical behaviors. Many scholars have been investigating the clinicopathological characteristics of ILC from the molecular standpoint to develop individualized therapies. At the same time, more accurate imaging diagnostic criteria should be established according to the differences among intrinsic subtypes and varying histopathological features. In addition, with improved imaging technology and resolution, US is not only used to distinguish between cysts and solid masses but also for the differential diagnosis of benign and malignant masses and health screening. Especially for Chinese women, whose breast fibroglandular tissue is mostly dense, US is an essential imaging modality for breast examination, whether palpation is abnormal or not. Consequently, the ultrasonographic findings of ILC collected from the patients included in the current study are comprehensive. Moreover, the US features were standardized according to the BI-RADS lexicon.

The age distribution of the women with ILC included in this study is different from that reported by Grazia et al. [12], with younger patients in China from 2011 to 2017 suffering from ILC (median age: 51 vs. 64.6 years). This may be due to variations in race, menopausal diversity and differences regarding published time. In our cohort, only a few women received BCS, which was consistent with the investigation of Truin et al. [21]. They reported ILC with neoadjuvant chemotherapy was less likely to receive BCS than IDC. Of the total 369 ILCs screened by both US and mammography, 11 masses presented normally on US grayscale, which means a false-negative rate of 3.0 % (contrasted by mammography with 9.2 %), in agreement with the rates reported by Porter AJ and Kombar et al. [9, 22]. Although multifocal or even bilateral presentations are clinical characteristics of ILC, it is interesting that 5.6 % of patients with a pathologically confirmed single large mass were misdiagnosed as having multiple small masses by US grayscale in the current study. The diffuse growth pattern with single-cell invasion and a lack of desmoplastic stromal reaction [23] may account for this misdiagnosis of ILC on US. This progressive feature could even lead to missed diagnosis of ILC on mammography. The loss of E-cadherin in most ILCs results in fewer cancer cells and more low-density fat per unit volume of tumor [9], which may have less of an effect on ultrasonic diagnosis.

Consequently, the sensitivity of US is higher than that of mammography.

Published studies have compared ultrasonographic and mammographic features of ILC with those of IDC [9, 21]. However, US was performed after a suspected or invisible mammography in those studies, which may lead to bias in their conclusions. It has been reported that the tumor characteristics and patient outcomes were similar between pure ILCs and mixed ductal and lobular breast cancers [24]. Therefore, we did not analyze the patient cohort based on "pure" and "mixed" classifications. The most common ultrasonographic appearances of ILC found in this study were an irregular parallel hypoechoic mass with spiculated margins, posterior shadowing and blood signals in the rim, without calcifications or an architectural distortion with posterior shadowing. Among these features, irregular shape, spiculated margin, no calcifications, and acoustic shadowing behind a mass or architectural distortion were in accordance with previous reports [9–11, 13, 15]. Taking mass orientation into account, the more common appearance of ILC shown in this study was a mass parallel to the skin (87.2 %), in contrast to the higher perpendicular orientation rate of 74.3 % reported by Kombar et al. [22]. This huge difference may have partly resulted from the different samples, while we agree with Cawson et al., who reported, "ILCs were 77 % less likely to be taller than wide" compared to IDCs [25]. As an important aspect of BI-RADS 2013, the vascularity of ILC on US was analyzed in our study. On color Doppler ultrasound, most ILCs were shown as masses or architectural distortions with blood signals in the rim instead of inside. The most common infiltrating pattern of ILC is single cells spreading through the stroma [26], so the angiogenesis of ILC may develop without disturbing the normal ductal system inside.

In our study, the luminal B subtype, accounting for 56.4 % of the total, was the most common subtype in Chinese women with ILC. This result was similar to what has been reported by Huang et al. [27], who found that the prevalence of the luminal A subtype was lower than that of the luminal B subtype in the Chinese series. Although a different prevalence of the intrinsic subtypes was shown between Chinese and Caucasian women, the similar gene transcription patterns across ethnic groups indicated common clinical management worldwide [27]. Therefore, the ultrasonographic findings based on intrinsic subtypes in the current study may be valuable as a multiracial reference for imaging diagnosis before individual cancer management. Significant differences in age were found among the intrinsic subtypes, with the youngest patients being in the luminal A subtype and the oldest patients in the HER2 subtype. This result affirms the important role of age in the accurate diagnosis and individual treatment of ILC according to intrinsic subtype.

To our knowledge, there have been no published studies correlating the ultrasound characteristics of ILC with the intrinsic subtypes, although several authors have shown the imaging findings of different histologic subtypes such as classic and pleomorphic ILC [13, 14]. In our study, the luminal A subtype and the luminal B subtype more often had spiculated margins, while the HER2 subtype was characterized by microlobulated margins, and the basal-like subtype appeared to tend towards having indistinct margins. It is generally recognized that mass margins are related partly to the infiltrating pattern of the tumors. However, it is not clear whether the invasive pattern or other related factors are different among the intrinsic subtypes. The current evaluation of the margin aspects may offer some cues. Furthermore, spiculated margins, considered a good prognostic factor for invasive breast cancer [28], were correspondingly shown more frequently in the luminal subtypes in our study. Unlike the luminal subtypes and the HER2 subtype, the basal-like subtype was less likely to show posterior shadowing. Previous studies have reported that necrosis in tumors is a feature of basal-like breast cancer [29], which may reduce the acoustic impedance of tumors on the US image, resulting in "no posterior feature" or even "posterior enhancement". Masses in the HER2 and basal-like subtypes were obviously larger than in the luminal A and luminal B subtypes in the current study, which may indicate the rapid aggressive progression of HER2 overexpression and basal-like breast cancer from the tumor size point of view. Furthermore, unlike the luminal subtypes and the HER2 subtype, which frequently appeared as having vessels in the rim, the vascularity of the basal-like subtype was mostly detected as internal blood signals on US. This kind of blood supply pattern may be another factor promoting the growth of basal-like tumors.

Conclusion

The chief limitation of this study was that it was a retrospective investigation. The analysis was limited to preserved imaging and pathological data. Therefore, prospective studies with predetermined inclusion and exclusion criteria should be conducted in the future.

In conclusion, we systemically described the representative ultrasonographic features of ILC in this study. To some extent, despite the overlap of several points of US manifestation, significant differences or some tendency of distinction were presented among the different intrinsic subtypes. The results may help to perfect the accurate imaging criteria for diagnosis of ILC before any targeted or individual management is attempted.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Munot K, Dall B, Achuthan R et al. Role of magnetic resonance imaging in the diagnosis and single-stage surgical resection of invasive lobular carcinoma of the breast. Brit J Surg 2002; 89: 1296–1301

[2] Mann RM, Hoogeveen YL, Blickman JG et al. MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat 2008; 107: 1–14

[3] Heil J, Buehler A, Golatta M et al. Do patients with invasive lobular breast cancer benefit in terms of adequate change in surgical therapy from a supplementary preoperative breast MRI? Ann Oncol 2012; 23: 98–104

[4] Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat 2017; 165: 273–283

[5] Morrow M, Keeney K, Scholtens D et al. Selecting patients for breast-conserving therapy: the importance of lobular histology. Cancer 2006; 106: 2563–2568

[6] Alice K, Stephanie B, Katherine E et al. Preoperative breast MRI and surgical outcomes in elderly women with invasive ductal and lobular carcinoma: a population-based study. Breast Cancer Res Treat 2014; 143: 203–212

[7] Heil J, Bühler A, Golatta M et al. Does a supplementary preoperative breast MRI in patients with invasive lobular breast cancer change primary and secondary surgical interventions? Ann Surg Oncol 2011; 18: 2143–2149

[8] Lopez JK, Bassett LW. Invasive lobular carcinoma of the breast: spectrum of mammographic, US, and MR imaging findings. RadioGraphics 2009; 29: 165–176

[9] Porter AJ, Evans EB, Foxcroft FM et al. Mammographic and ultrasound features of invasive lobular carcinoma of the breast. J Med Imag Radiat On 2014; 58: 1–10

[10] Johnson K, Sarma D, Hwang ES. Lobular breast cancer series: imaging. Breast Cancer Res 2015; 17: 94–102

[11] Jacobs C, Ibrahim Mohamed FK, Clemons M et al. Treatment choices for invasive lobular breast cancer: a doctor survey. J Eval Clin Pract 2015; 21: 740–748

[12] Grazia A, Valerie JB, Gary MC et al. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 2004; 6: R149–R156

[13] Butler RS, Venta LA, Wiley EL et al. Sonographic evaluating of infiltrating lobular carcinoma. Am J Roentgenol 1999; 172: 325–330

[14] Jung HN, Shin JH, Han BK et al. Are the imaging features of the pleomorphic variant of invasive lobular carcinoma different from classic ILC of the breast? The Breast 2013; 22: 324–329

[15] Jones KN, Magut M, Henrichsen TL et al. Pure lobular carcinoma of the breast presenting as a hyperechoic mass: incidence and imaging characteristics. Am J Roentgenol 2013; 201: W765–W769

[16] D'Orsi CJ, Sickles EA, Mendelson EB et al. ACR-BIRADS® Atlas. Breast Imaging Reporting and Data System. 5th ed Reston, VA: American College of Radiology; 2013

[17] Goldhirsch A, Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013; 24: 2206–2223

[18] Allred DC, Harvey JM, Berardo M et al. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 1998; 11: 155–168

[19] Wolff AC, Hammond MH, Schwartz JN et al. American Society of Clinical Oncology/College of American pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25: 118–145

[20] Li CI, Anderson BO, Daling JR et al. Trends in incidence rates of invasive lobular and ductal breast carcinoma. JAMA 2003; 289: 1421–1424

[21] Truin W, Vugts G, Roumen RMH et al. Differences in response and surgical management with neoadjuvant chemotherapy in invasive lobular versus ductal breast cancer. Ann Surg Oncol 2016; 23: 51–57

[22] Kombar OR, Fahmy DM, Brown MV et al. Sonomammographic characteristics of invasive lobular carcinoma. Breast Cancer: Targets and Therapy 2012; 4: 115–124

[23] Ulrich L. Lobular breast cancer – the most common special subtype or a most special common subtype? Breast Cancer Res 2015; 17: 99–100

[24] Bharat A, Gao F, Margenthaler JA. Tumor characteristics and patient outcomes are similar between invasive lobular and mixed invasive ductal/lobular breast cancers but differ from pure invasive ductal breast cancers. Am J Surg 2009; 198: 516–519

[25] Cawson JN, Law EM, Kavanagh AM. Invasive lobular carcinoma: sonographic features of cancers detected in a BreastScreen Program. Australas Radiol 2001; 45: 25–30

[26] McCart Reed AE, Kutasovic JR, Lakhani SR et al. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. Breast Cancer Res 2015; 17: 12–23

[27] Huang XY, Dugo M, Callari M et al. Molecular portrait of breast cancer in China reveals comprehensive transcriptomic likeness to Caucasian breast cancer and low prevalence of luminal A subtype. Cancer Med-US 2015; 7: 1016–1030

[28] Evans AJ, Pinder SE, James JJ et al. Is mammographic spiculation an independent, good prognostic factor in screening-detected invasive breast cancer? Am J Roentgenol 2006; 187: 1377–1380

[29] Lerma E, Peiro G, Ramón T et al. Immunohistochemical heterogeneity of breast carcinomas negative for estrogen receptors, progesterone receptors and Her2/neu (basal-like breast carcinomas). Mod Pathol 2007; 20: 1200–1207