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RADIOLOGY APPROACH TO INVASIVE BREAST LOBULAR CARCINOMA – INITIAL EXPERIENCE

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ABSTRACT

It is well known that invasive lobular carcinoma (ILC) accounts for approximately 5-15 % of invasive breast cancers that remain one of the most common malignancies among women globally. ILC is distinguished from the more common invasive ductal carcinoma (IDC) by characteristics histopathology features. The aim of the study was to emphasize the need of more specified diagnostic imaging approach in order to detect breast ILC, based on our institution experience. We describe a number of 17 female cases (58±7 years) who presented: breast fullness/asymmetry – 11 patients (64.7 %), pain – 2 patients (11.7 %), and the rest 4 patients (23.5 %) were asymptomatic. Diagnostic modalities used in this study were: 2D Mammography, Ultrasound, Digital Breast Tomosynthesis (DBT), and core biopsy in guidance by Ultrasound. On 2D Mammography, visible mass was found in 8 patients (47 %), and architectural distortion was found in 4 patients (23.5 %). On DBT additional 5 patients were examined from the total number of patients, and additional lesions were found such as occult lesions and additional architectural distortion. Using DBT, occult lesion was found in 3 patients (17.6 %) and architectural distortion was found in 2 patients (11.7%). Due to these inconclusive findings, DBT was carried out to improve visualization especially in those with more glandular tissue. The occult lesions were seen in 3 patients, which showed as false negative on 2D, as well as an architectural distortion in 2 patients, additionally seen on DBT. This multimodality approach, including DBT, holds promise for more reliable detection of occult lesions and distortions especially in denser breast, and for better clinical outcomes in patients with ILC, respectively.

Keywords: invasive lobular carcinoma; imaging methods; digital breast tomosynthesis

INTRODUCTION

Breast cancer remains one of the most common malignancies among women worldwide, with diverse histological subtypes that differ in their biology, clinical presentation, response to therapy, and prognosis. Among these, invasive lobular carcinoma (ILC) accounts for approximately 5-15% of invasive breast cancers [1, 2, 3]. Thus, ILC is distinguished from the more common invasive ductile carcinoma (IDC) by characteristics histopathology features. Classically, ILC cells are small, uniform, and un-cohesive, often invading the stroma in single-file or linear arrangements, with minimal desmoplastic response. This pattern is largely due to loss of cell-cell adhesion,

most notably mediated by E-cadherin, a protein encoded by the CDH1 gene. Loss or dysfunction of E-cadherin (through mutations, truncations, or other mechanisms) is a hallmark of ILC [4, 5, 6]. By clinical and radiological aspect, ILC presents diagnostic challenges. Because of its low cohesion and diffuse infiltration, it may have less cohesion and diffuse infiltration, and it may be less conspicuous on mammography and ultrasound, more difficult to palpate, and often presents at a larger size or at more advanced stage, compared to IDC. Detection sensitivity is lower, while mammography may miss lesions or show only subtle findings such as architectural distortion or asymmetry rather than well-defined mass [1, 7, 8]. Molecularly, ILC is typically estrogen receptor (ER) – positive and human epidermal growth factor receptor 2 (HER 2) - negative, with lower proliferative indices (e.g. Ki-67) than many IDC but may occur more frequently in certain variants (e.g. pleomorphic or histiocytoid) with distinct behavior [6, 8, 9, 10]. Despite its distinctiveness, many treatment guidelines and clinical decision-making frameworks have historically been derived largely from studies dominated by IDC. There is increasing awareness that ILC may require tailored approaches in diagnosis (imaging, pathology), surgical management (margins, extent of surgery), systematic therapy (endocrine treatments, chemotherapy, potential new targets), and long-term follow up [2, 12, 15]. The aim of the study was to emphasize the need of specified diagnostic imaging approach in order to discover breast ILC, based on our experience.

MATERIALS AND METHODS

We describe 17 female cases at age of 58±7 years, where 76.5% out of all cases presented symptoms, such as: breast fullness/asymmetry 11 (64.7%) and pain 2 (11.7%). Diagnostic modalities that were used in this study were: 2D Mammography, Ultrasound, DBT, and core biopsy with guidance by the ultrasound. Mammography and DBT imaging were performed using the equipment of Healthineers Revelation, Siemens, Germany, following standard clinical protocols, where the radiation dose for one breast with 2D Mammography was 2-3 mGy for 2 projections, Cranio-Caudal (CC) and Medio Lateral Obliquus (MLO), and DBT (3D Mammography) was slightly higher, 3-4 mGy in all projections. The study was conducted as cross sectional, collecting the patients with breast symptoms and the asymptomatic ones which were submitted to diagnostic modalities. Out of 17 patients, 5 were submitted to DBT additionally due to visualization of architectural distortion only on one 2D mammographic projection and also due breast density. Inclusive criteria were: female patients, above age of 40 years old, patients underwent at least 2 imaging modalities, patients underwent breast biopsies and with material given to histopathology analysis. Exclusive criteria were male patients, patients younger than 40 years old, pregnant and breast-feeding women, and patients with breast implants.

RESULTS

Using 2D Mammography, out of 17 patients, a visible mass was found in 8 patients (47%) and architectural distortion was found in 4 patients (23.5%), but using DBT, lesions were found in 3 more patients (17.6%) and architectural distortion was found in 2 more patients (11.7%). Thus, DBT was carried out to improve the visualization in our study for the additional 5 patients out of 17 that were detected by using DBT (29.4%). Therefore, DBT adds value by detecting cases that are occult and were not seen on standard mammography (a number of 3 out of 17 patients - 17.6%) and distortions that are overlapped by the parenchyma especially in the breast density of ACR 3 and ACR 4 (a number of 2 out of 17 patients - 11.7%). Core biopsy was done in all patients enrolled in the study that confirmed the diagnosis of breast ILC with differentiation within histopathology analysis (Table 1).

Table 1. *The presentation of the different lesion number of the cases (n=17) seen by 2D Mammography and by DBT*

Lesion	2D	DBT
Mass	8	3
Architectural distortion	4	2

The higher number of 10 cases had the following pathological results: with estrogen receptor positive (ER+), progesterone receptor positive (PR+) and HER2 negative (HER-) breast ILC. Other 6 cases were estrogen receptor

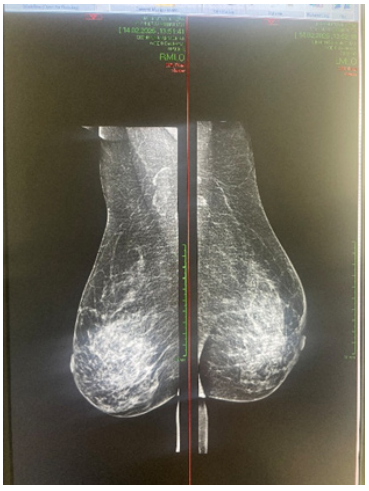
positive (ER+), progesterone receptor positive (PR+) and HER2 positive (HER+) breast ILC and 1 case was Triple negative (ER-, PR-, HER-) breast ILC (Table 2).

Table 2. *Pathological results of histochemistry analysis and differentiation of the lesion of the cases (n=17), concerning ILC features*

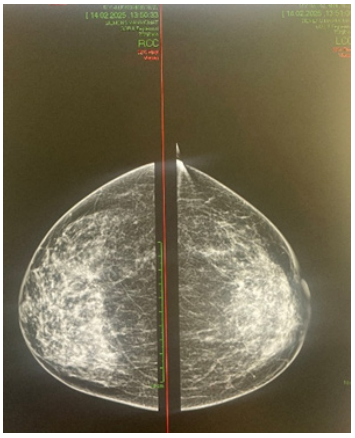
	Hormone dependence	N (number of cases)
I group	ER +, PR+, HER-	N=10 2D Mammography - 6 patients; DBT - 4 patients
II group	ER +, PR+, HER+	N= 6 2D Mammography - 5 patients; DBT - 1 patients
III group	ER -, PR-, HER-	N=1 2D Mammography - 1 patient

ER - estrogen receptor; PR – progesterone receptor; HER – human epidermal growth factor receptor

On the following images the presentations of the lesions and architectural distortions, using 2D, DBT and ultrasound are shown. DBT was crucial for detection of the lesions and architectural distortions in 5 patients (29.3%) (Picture 1a, Picture 1b, Picture 2).



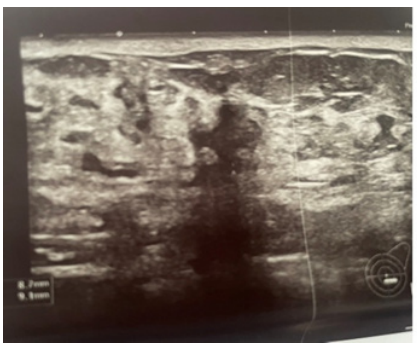
Picture 1a. *Architectural distortion, retromammary located, seen in the left breast using 2D Mammography in MLO (Medio Lateral Obliquus) projection*



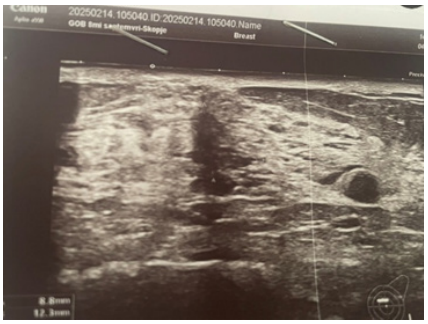
Picture1b. *Architectural distortion, retromammary located, seen in the left breast using 2D Mammography in CC (Cranio Caudal) projection*

Picture 2. *Architectural distortion and the border, seen more clearly, using Digital Breast Tomosynthesis (DBT) in MLO (Medio Lateral Obliquus) projection.*

In one of the patients, there were two changes in the left breast, seen on DBT and proved by ultrasound, one had pathological findings of ILC, and the other had pathological finding of hyperplasia and fat atypical changes (Picture 3a, Picture 3 b).

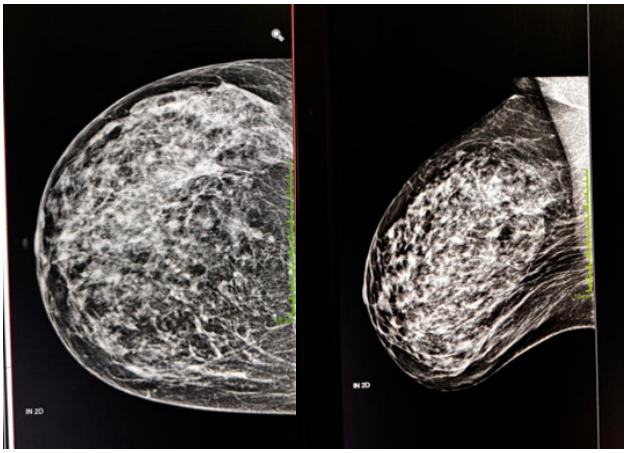


Picture 3a.
Ultrasound pathological findings of ILC in left breast at 16 o'clock

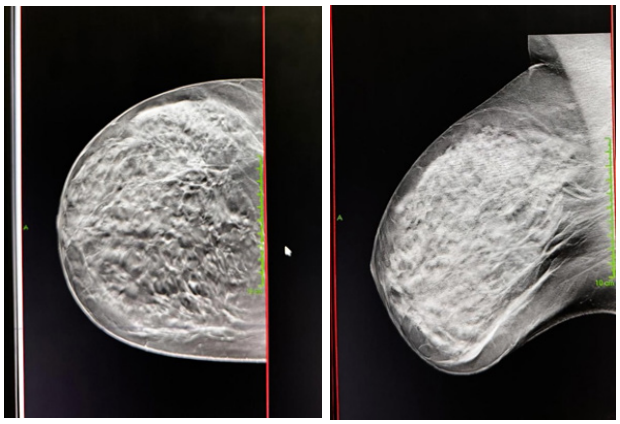


Picture 3b. *Ultrasound pathological findings of hyperplasia and fat atypical changes in left breast at 10 o'clock*

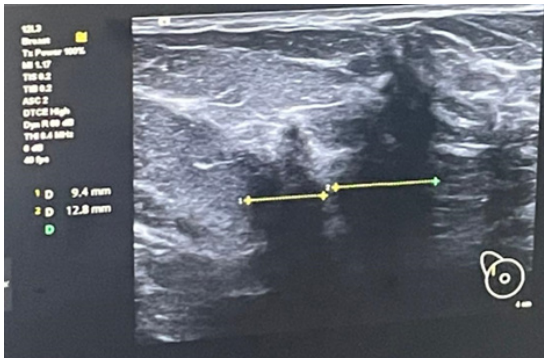
Previously, it was shown the benefit of using DBT in patient with architectural distortion, but DBT also contributed for detecting occult lesions especially in patients with dense breast, as shown in the following images (Picture 4a, Picture 4b, Picture 5a, Picture 5b, Picture 6).



Picture 4a and 4b. *Right breast seen on 2D Mammography in CC (Cranio Caudal) and MLO (Medio Lateral Obliquus) views - heterogenous parenchymal density with architectural distortion in the superior-lateral quadrant.*



Picture 5a and 5b. *Right breast seen on DBT in CC (Cranio Caudal) and MLO (Medio Lateral Obliquus) views - two occult lesions in superior-lateral quadrant of right breast are seen on DBT.*



Picture 6. *Ultrasound of the supero-lateral quadrant of the right breast - two hypoechoic lesions with histopathology analysis of ILC*

DISCUSSION

AIt is evident that ILC remains a persistent diagnostic challenge in breast imaging due to its distinctive histopathology growth pattern. Unlike IDC, ILC often lacks a defined mass, produces minimal desmoplastic reaction, and infiltrates breast parenchyma in a linear or diffuse manner. As a result, it frequently appears on 2D Mammography as a subtle architectural distortion, focal asymmetry, or as radiographic occult, particularly in women with dense breast tissue [15]. These limitations contribute directly to delayed detection and underestimation of disease extent. We found that breast ultrasound, while valuable in dense breasts and in clarifying equivocal mammographic findings, also struggles with ILC. Its sonographic presentation is often nonspecific hypoechoic shadow without a mass making interpretation operator depen-

dent and sometimes inconclusive [16]. Thus, we also found that the combined use of 2D Mammography and ultrasound, although superior to either alone, remains insufficient for reliable detection of ILC while DBT provides a crucial solution to these shortcomings. By eliminating tissue overlap, DBT enhances the conspicuity of architectural distortions and visualization of the occult lesions. In a large cohort from the Breast Cancer Surveillance Consortium, the cancer detection rate for ILC increased from 0.33 per 1000 women with 2D Mammography to 0.45 per 1000 with DBT overall, and among women with dense breasts it rose to 0.54 per 1000 (relative risk 1.53, 95% CI-confidence interval of 1.09–2.14) [17]. Similarly, in a multi-reader study, DBT recovered 18–27% of ILC cases that were occult on synthesized 2D Mammography, substantially improving lesion conspicuity and diagnostic confidence [18]. Moreover, DBT has also been shown to better delineate tumor margins and lesion extent, which is essential in surgical planning given ILC's high frequency of multifocality and multi-centricity [19, 20]. The clinical evidence supporting DBT integration is now sufficiently robust to warrant a paradigm shift. Due to these facts, DBT should not be regarded as an optional adjunct but as an indispensable modality in the diagnostic pathway for ILC. In our study, besides the 12 patients, detected by 2D Mammography and Ultrasound, we found additional 5 cases with ILC, 3 with occult lesions and 2 with architectural distortion. These patients were mostly with the overlapping of the glandular tissue within the lesion. Its superiority in detecting and characterizing ILC is further reflected in international guideline recommendations. From a prognostic standpoint, the behavior of ILC diverges from IDC. Some studies have shown that patients with ILC have better short-term outcomes, especially in the first five years after diagnosis, but tend to have higher risks of late recurrence and worse outcomes in long term follow up, particularly beyond five or ten years [8, 2, 11, 12]. In a large SEER-based study (Surveillance, Epidemiology, and End Results), ILC had superior breast cancer-specific survival (BCSS) compared to IDC in the first five years, but worse BCSS in subsequent years [6, 10, 11, 15, 16, 20]. Another study comparing luminal ILC vs. luminal IDC found that although luminal ILC patients had favorable prognostic features, their disease-free survival (DFS) and overall survival (OS) were significantly worse compared to luminal IDC, particularly for larger tumors or node-positive disease [11]. Metastatic patterns also differ, so ILC frequently metastasis to unusual sites (such as the peritoneum, gastrointestinal tract, gynecologic organs, and even leptomeninges), more so than IDC. Bone metastases are common, and in cases with bone-only metastases, ILC has been associated with worse outcomes compared with IDC [8, 13, 14]. Concerning ILC consequences, The European Commission Initiative on Breast Cancer (ECIBC) advises the use of DBT (as first diagnostic modality) or 2D Mammography (conditional recommendation, very low certainty of evidence) in organized screening programs, particularly in women with dense breasts (ECIBC, 2021) [22]. Likewise, the Italian College of Breast Radiologists (ICBR), together with Italian scientific and professional bodies involved in developing and implementing guidelines and quality assurance programs for breast cancer screening and follow-up such as SIRM and GISMa (advocates synthetic Mammography plus DBT (sDM/DBT) as the preferred modality whenever feasible [23]. In this context, reliance on 2D Mammography and Ultrasound alone for diagnosing ILC is no longer defensible in modern breast imaging practice. Therefore, the failure to integrate DBT, risks perpetuating delayed or missed diagnoses, underestimation of tumor burden, and less favorable surgical outcomes. Given the diffuse, subtle, and infiltrative behavior of ILC, a multimodality approach incorporating DBT alongside Ultrasound and 2D Mammography provides the most reliable pathway for timely detection, accurate staging, and improved patient prognosis. Regarding to our experience, breast Ultrasound complements 2D Mammography by improving lesion detection in dense breast tissue and in cases where mammographic findings are inconclusive. However, Ultrasound also faces challenges with ILC as the infiltrative growth pattern may manifest as vague shadowing without a discrete mass, resulting in equivocal interpretation and increased operator dependence. Thus, while the combination of 2D Mammography and Ultrasound improves detection rates, it may still miss or underestimate the extent of ILC. Therefore, DBT offers significant advantages in this setting by acquiring quasi-3D images through multiple low dose projections. It reduces tissue overlap, a major limitation of conventional Mammography. This capability enhances the visualization of subtle architectural distortions, spiculations,

and asymmetries, which are hallmarks often associated with ILC, but poorly depicted on 2D Mammograms. Recent studies have reported that DBT increases cancer detection rates and improves characterization of invasive lobular tumors compared with Mammography alone, particularly in women with dense breast parenchyma [17, 24]. Moreover, DBT has been shown to refine lesion localization and margin assessment, both of which are crucial in surgical planning for ILC given its tendency for multicentricity and diffuse infiltration [25, 26]. The integration of DBT with Ultrasound not only improves diagnostic confidence but also reduces recall rates and unnecessary biopsies by providing a clearer morphological assessment.

This study illustrates the diagnostic difficulties associated with ILC and underscores the critical role of additional imaging, besides Mammography and Ultrasound, in accurately characterizing the tumor, because of its potential for multifocal, multicentric, and contralateral spread, through imaging and staging, very essential for appropriate treatment planning. Thus, ILC frequently presents subtle signs on standard imaging modalities, necessitating a comprehensive, multimodal imaging strategy to ensure early diagnosis and accurate assessment. Therefore, we followed images shown on 2D Mammography in two projections – Cranio Caudal (CC) and Medio Lateral Obliquus (MLO) vs. DBT obtained in 12 projections. By 2D Mammography we succeeded to detect a visible mass in 8 cases (47%), and architectural distortion in 4 cases (23.5%) out of 17 patients, but by DBT we detected additional 3 cases (17.6%) with occult lesion and 2 cases (11.7%) with architectural distortion.

Our findings support the growing consensus that DBT should not merely be considered an adjunct, but an essential component of the diagnostic workflow for ILC. While Ultrasound remains valuable for further lesion characterization and biopsy guidance, and 2D Mammography continues as the population-wide screening backbone, the addition of DBT markedly improves the sensitivity and accuracy of imaging-based diagnosis. Future prospective studies with larger ILC cohorts are warranted to further quantify the incremental benefit of DBT, especially regarding early detection and surgical outcome optimization [17, 27].

CONCLUSION

In conclusion, the unique imaging challenges of ILC underscore the need for incorporating DBT alongside 2D Mammography and Ultrasound. This multimodality approach holds promise for more reliable detection, accurate staging, and ultimately, better clinical outcomes in patients with ILC. Therefore, DBT is not merely advantageous but essential. Its systematic integration into diagnostic protocols for ILC represents a critical advance toward overcoming long-standing imaging limitations and improving outcomes, especially in women with dense breast.

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Резиме

РАДИОЛОШКИ ПРИСТАП ЗА ИНВАЗИВНИОТ ЛОБУЛАРЕН КАРЦИНОМ НА ДОЈКА – ПОЧЕТНО ИСКУСТВО

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Од сите карциноми на дојка, кои се едни од најчестите малигнитети кај жените во светот, на инвазивниот лобуларен карцином (ИЛК) mu припаѓаат околу 5-15 %. Овој карцином се разликува од почестиот инвазивен дуктален карцином (ИДК) по карактеристичните хистопатолошки карактеристики. Целта на студијата беше да се нагласи потребата од индивидуален пристап на дијагностичкото испитување, со цел да се открие ИЛК на дојката врз основа на нашето искуство. Испитани се 17 случаи од женски пол (58 ± 7 години), од кои 11 пациентки (64,7 %) чувствувале тежина и имале асиметрија, 2 (11,7 %) пациентки чувствувале болка, а другите 4 пациентки (23,5 %) биле асимптоматски. Дијагностичките модалитети користени во оваа студија беа: 2D-мамографија, ултразвук, дигитална томосинтеза на дојка (ДТД) и биопсија под водство на ултразвук. Со 2D-мамографијата, од 17 пациентки кај 8 пациентки (47 %) беше најдена лезија, а кај 4 пациентки (23,5 %) беше најдена архитектурна дисторзија. Со ДТД дополнително беа прегледени 5 пациентки од вкупниот број од 17 пациентки, од кои кај 3 пациентки (17,6 %) беше најдена окултна лезија, додека кај 2 пациентки (11,7 %) беше најдена архитектурна дисторзија. Поради некомплетните наоди со претходните методи, а со цел подобра визуализација, беше спроведена ДТД, особено кај оние пациентки со густа жлездена структура на дојките. Со користењето на ДТД окултните промени беа појасно видливи кај 3 пациенти, кои на 2Д-мамографијата се прикажаа како лажно негативни, како и архитектурната дисторзија, која кај 2 пациентки дополнително беше видена. Овој мултимодален пристап, вклучувајќи ја ДТД, овозможува откривање окултни лезии, дисторзии, особено кај погусти дојки, со цел навремено откривање и подобар исход кај пациентките со ИЛК.

Клучни зборови: инвазивен лобуларен карцином, методи за снимање, дигитална томосинтеза на дојка