CASE REPORT

Re-Evaluation of Ipsilateral Multiple-Focal Breast Cancer: Case Report and Literature Review

Lei Hou, MM; Ziyi Fan, MM; Luming Zheng, MD

ABSTRACT

Objective • Ipsilateral multiple breast cancer is a unique situation in which multiple breast cancer lesions are present in the same or different quadrant of the breast. While current research on ipsilateral multiple breast cancer primarily focuses on its existence or heterogeneity, it is important to evaluatethe risk level stratification of heterogenous lesion and determine the intensity of anti-tumor treatments for every lesion, achieving a rational and personalized anti-cancer strategy.

Case Description • We present a 55-year-old woman with a lump in the lateral quadrant of her left breast, who was diagnosed invasive breast cancer with a background of ductal carcinoma in situ in two lesions of the left breast. The immunohistochemistry examination revealed that the lateral cancer lesion was Luminal B subtype while the lower cancer lesion HER2 positive subtype. Aditionally, the axillary lymph node dissection and immunohistochemistry showed 7 positive lymph nodes originating from ER-positive lesion. After systemic imaging screening, the clinical TNM stage for ER positive subtype was III A and HER2 positive subtype IA. The discovery shifted the conventional understanding that HER2 positive subtype usually had a higher TNM stage than ER positive subtype under the premise of consistent tumor volume and treatment strategy should be readjusted to reduce over-treatment and the risk of recurrence for high-risk tumor. However, little is mentioned about the risk level stratification of foci in ipsilateral multiple breast cancer and its weight in treatment strategy in clinical guidelines for breast cancer.

Conclusion • This case highlights the need for more evidence-based data to support risk-level stratification of heterogenous foci and treatment decisions for ipsilateral multiple breast cancer and challenges current clinical practice. (*Altern Ther Health Med.* 2024;30(12):381-387).

Lei Hou, MM, Attending Doctor; Department of Thyroid and Breast Surgery, The 960th Hospital of the PLA Joint Logistics Support Force, Jinan, China; Department of HPB Surgery, Shandong University Cancer Center, Jinan, China. **Ziyi Fan,** MM, Associate Chief Physician; **Luming Zheng,** MD, Associate Chief Physician; Department of Thyroid and Breast Surgery, The 960th Hospital of the PLA Joint Logistics Support Force, Jinan, China.

Corresponding author: Lei Hou, MM
E-mail: houlei2003@163.com

INTRODUCTION

Breast cancer is a significant health issue for women. Ipsilateral multifocal breast cancer (IMBC) refers to synchronous isolated multiple (located in one quadrant) or multicentric (located in different quadrants) invasive breast cancer lesions in the ipsilateral breast. IMBC foci and their additionally detected biological characteristics directly influence the anatomic tumor-node-metastasis (TNM) stage, prognostic TNM stage, treatment management, and prognosis of the patients. The huge difference in detection rate is attributed to the specificity and sensitivity of imaging modalities, biopsy performance, and the final pathology report. In an extensive investigation focused on the preoperative MRI assessment of occult breast cancer lesions, pathology biopsies revealed that 8.1% of the cases were diagnosed with ipsilateral multifocal breast cancer, whereas 3.1% were identified with contralateral breast cancer.[1] In an IMBC pathology research, the immunohistochemistry analysis for multifocal breast cancer revealed that the expression of ER, HER2, and Ki-67 holds significant clinical relevance ($P < .001$).[2]

Breast cancer, a complex and heterogeneous disease, can be categorized into five molecular subtypes based on the expression status of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2), and proliferative fraction (Ki-67%). These subtypes include: hormone receptor positive/HER2 negative with low

Ki 67 level (Luminal A subtype), hormone receptor positive/HER2 negative with high KI67 level (Luminal B subtype), hormone receptor negative/HER2 positive (HER2 positive subtype), triple-negative type (TN subtype), and hormone receptor positive/HER2 positive subtypes. Each subtype necessitates distinct adjuvant therapies. Advancements in endocrine therapy, anti-HER2 therapy and other targeted treatments have significantly improved systemic approaches for high-risk level breast cancer patients, leading to better disease-free survival and overall survival. A comprehensive understanding of IMBC encompasses not only the identification of all potential therapeutic targets but also the development of enhanced adjuvant strategies founded on precise risk-level stratification.

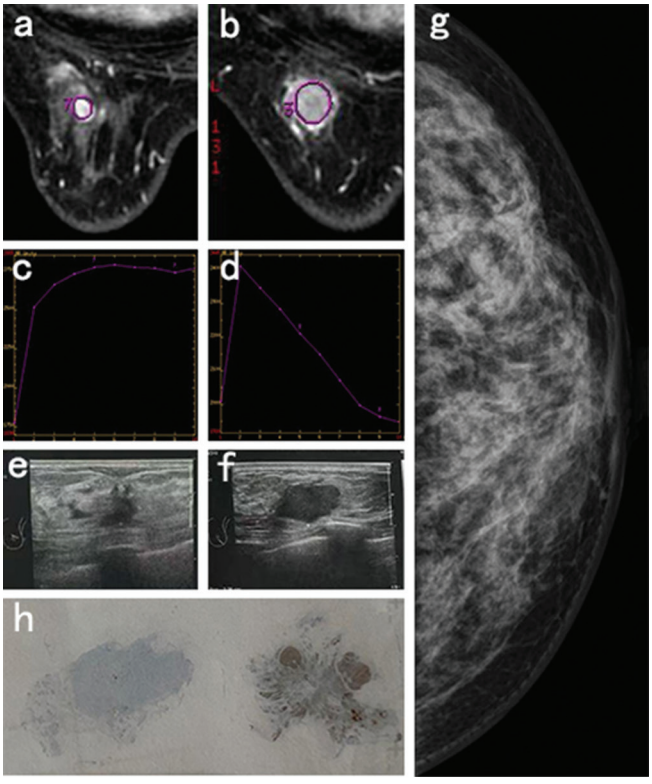
Till now, there is no clear guidance to direct the clinical practice of IMBC with heterogeneity. In circumstances of IMBC with heterogeneous differences, foci and its corresponding risk level stratification, compared to IMBC with information of foci alone, is worth further investigation. This case provided details of clinical practice from physical examination, imaging evaluation, surgery, and pathologic analysis of IMBC and finally resulted in reasonable adjuvant chemotherapy, radiation therapy, anti-HER2 target therapy, and endocrine therapy based on present clinical practice guidelines.

CASE DESCRIPTION

A 55-year-old woman presented with a lump in her left breast. She had no history of abortion, surgery, chronic disease, or family history of malignancy. Physical examination of bilateral breasts, axillary lymph nodes, and supraclavicular lymph nodes only revealed a hard and irregular mass about 2 cm located in the lower quadrant of the left breast. Mammography revealed multiple calcifications in the lateral quadrant of the left breast, which measures approximately 3.5 cm in diameter. The mammography findings were categorized as Breast Imaging-Reporting and Data System (BI-RADS) BI-RADS IV a, indicating a suspicious abnormality. Figure 1. Breast ultrasound (US) showed 2 irregular lesions, each measuring about 2 cm in size, BI-RADS IV b. Figure 1. Magnetic Resonance Imaging (MRI) further confirmed the presence of two distinct masses in different quadrant of the left breast. These masses exhibited different diameters and enhanced curves, raising suspicion of malignancy, BI-RADS IV b. Figure 1. Additionally, an additional mass with type I enhance-curve was discovered in the right breast, BI-RADS III. It is important to note that no enlarged axillary lymph nodes were observed during the clinical examination or imaging evaluations. Considering the clinical and imaging findings, a bilateral breast mass biopsy was performed before modified radical mastectomy.

The tumor in the right breast and the two tumors in the left breast were all marked under guidance of ultrasound prior to surgery and completely excised during the operation. During surgery, the lesion in lower region of left breast appeared harder, denser and paler than the lesion in lateral region. Rapid frozen section analysis was performed, and it

Figure 1. a. Mass in Lateral quadrant. b. Mass in lower quadrant. c. T1 weighted imaging for lateral mass: High Signal. Time-signal intensive curve (TIC): type II. d. T1 weighted imaging for lower mass: High Signal, heterogeneous internal enhancement. TIC curve: type III. e. Ultrasound image of lateral mass. f. Ultrasound image of lower mass. g. Cranial-Caudal (CC) position of left breast mammography showed the lateral quadrant irregular lesion with calcification. h. Macroscope contrast of ER expression for lateral and lower quadrant lesions. The picture showed totally different ER expression, growth or invasive pattern between the lesions.



was found that there was an intraductal papilloma in the right breast and invasive breast cancer with ductal carcinoma in situ (DCIS) in the lateral and lower quadrant of the left breast. Following this, axillary lymph node dissection was carried out, which revealed 7 positive lymph nodes in all 21 dissected lymph nodes.

The lesion in the left breast's lateral quadrant had a diameter of 2 cm. It was identified as invasive carcinoma, non-special type, and WHO Grade II. The expression status for ER was positive (>90%, 3+)， PR was also positive (3-5%, 3+), HER2 was negative (-), and Ki-67 was 15%. Figure 2. The lesion in the left breast's inferior quadrant also had a diameter of 2 cm. The pathology report identified it as invasive carcinoma, non-special type, WHO Grade II. However, the expression status for ER and PR were negative, HER2 was positive (3+), and Ki-67 was 40 %. Figure 3. The two lesions located in different quadrants of the left breast behaved as completely different molecular subtypes, be classified as Luminal A subtype and HER2 positive subtype. Further IHC examination was conducted on all the metastatic

Figure 2. a. Hematoxylin-eosin (HE) staining of lateral quadrant lesion showed invasive cancer, non-special type, WHO grade II. b. IHC of ER: strong positive, ＞90%. c. IHC of PR: positive, 3-5%. e. IHC of HER2: negative. Ki-67: 15%.

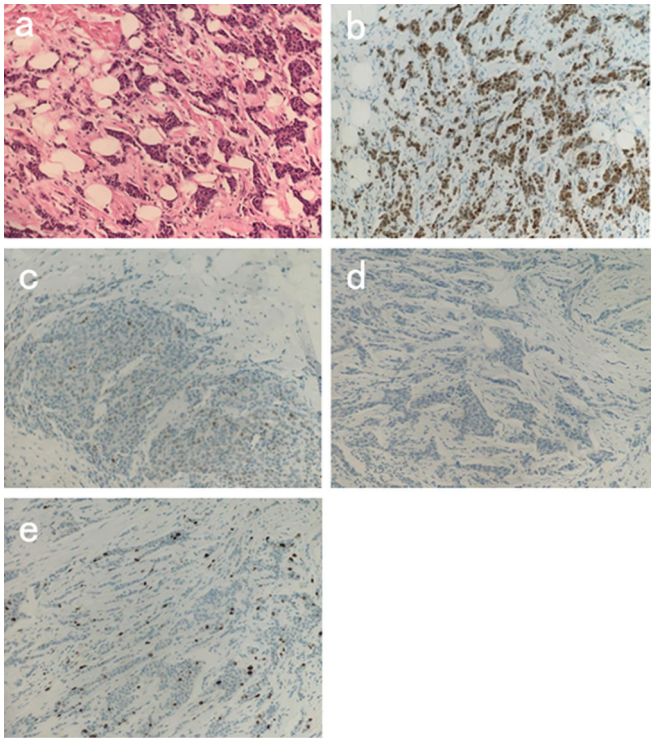
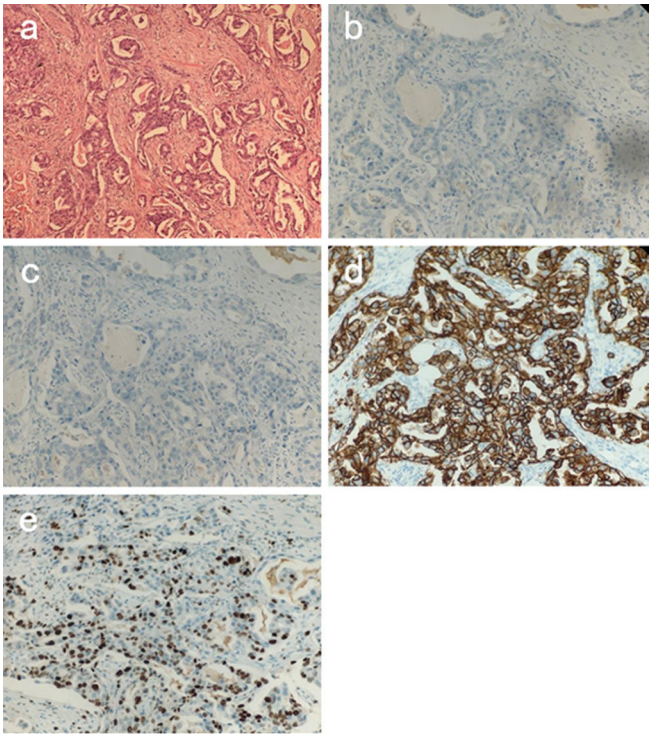


Figure 3. a. HE staining of lower quadrant lesion showed invasive cancer, non-special type, WHO grade II. b. IHC of ER: negative. c. IHC of PR: negative. d. IHC of HER2: strong positive. e. Ki-67: 40%.

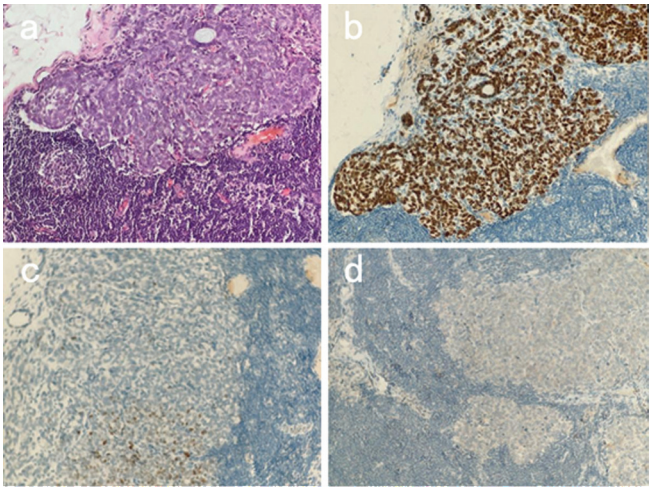


lymph nodes. The results showed that all lymph nodes originated from lateral quadrant lesions based on the IHC expression. The expression status of positive lymph nodes for ER was positive(>90%, 3+), PR was also positive (3-5%, 3+), while HER2 was negative (-). Figure 4.

Preoperatively, the hormone levels were tested, and the results indicated that the patient was still in a premenopausal status. The hormone levels were as follows: Estradiol 46.60 pmol/L, Prolactin 147.3 mIU/L, luteinizing hormone 17.9 IU/L, follicle-stimulating hormone 25.58 IU/L. Systemic imaging screening did not reveal any distant metastasis.

After a multi-disciplinary tumor board discussion, treatment strategies were determined empirically. Invasive breast cancer with high risk-level factors, like positive lymph nodes, high-level Ki-67 percentage and positive HER2 expression need chemotherapy and target therapy. The patient was prescribed AC-THP chemotherapy and target therapy regimen. The first 4 cycles include epirubicin(A) 90 mg/m^2 and Cyclophosphamide (C) 600 mg/m^2, which were administered every 3 weeks for 4 cycles. The following 4 cycles include Paclitaxel (T) administered at a dose of 80 mg/m2 weekly for 12 weeks. Additionally, Trastuzumab (H) at a loading dose of 8 mg/Kg followed by 6 mg/Kg every 3 weeks and Pertuzumab (P) with a loading dose of 840 mg followed by 420 mg every 3 weeks were resumed at the 5th cycle for 1 year. The patient was recommended to undergo radiotherapy as a component of the treatment plan following chemotherapy, owing to the presence of more than three positive lymph nodes. Given that the patient was in a premenopausal status, she was prescribed ovarian function suppression (OFS) along with an aromatase inhibitor (AI) for 5 years. Furthermore, a CDK4/6 inhibitor was prescribed for the initial two-year period of treatment due to the high-risk level stratification of luminal A subtype.

Figure 4. a. HE staining of positive lymph node (represent all positive lymph nodes). b. IHC of ER: strong positive, >90%. c. IHC of PR: PR: positive, 3-5%. d. IHC of HER2: negative.



DISCUSSION

In the past, the definition of invasive multifocal and multicentric breast cancer was based on the geographic

location of invasive lesions, whether they were located in one quadrant (multifocal) or a different quadrant (multicentric). However, this theory was denied by recent anatomy or embryonic research.[3] Currently, IMBC is defined as the presence of multiple well-demarcated invasive breast cancers with the same or different biological origin in the same breast.[4] IMBC can be identified through physical examination, imaging discoveries, surgical biopsy, and pathological examination. These methods help determine the consistency or heterogeneity of breast cancers. The heterogeneity of tumor histology, WHO grade, intrinsic molecular subtype, gene profile, and positive lymph nodes originating from the same cancer foci suggests different risk profiles and prognoses.[2,5] The clinical significance of IMBC lies in the detection of additional therapeutic targets, risk stratification, and potential shifts in treatment strategies.

Detection of IMBC

The detection of IMBC can vary widely, ranging from 3.7-75%, depending on factors such as physicians' knowledge of IMBC, imaging sensitivity and detection, biopsy, and pathology findings.[6] The initial steps in detecting IMBC involve the patient's chief complaint, physical examination, and imaging screening, which provide basic information. Unpalpable breast masses incidentally discovered during imaging screening or palpable breast mass with no findings in imaging screen suspicious of malignancy require further evaluation. Physicians must know IMBC to ensure a comprehensive biopsy. During the biopsy process, samples or the entire breast are delivered to the pathologist for analysis. The pathologist identifies all invasive foci and provides a detailed pathology report. Each step in the diagnostic process needs to be completed thoroughly to ensure accurate detection and reporting. Failure to complete any part of the process may fail to recognize and report suspicious malignancies.

The decision to conduct imaging screening or detect additional breast cancer foci is dependent on several factors, including imaging indication, availability, medical cost and candidate patients.[1,7,8] Mammography is the classic examination in breast cancer screening for women over 40 years old, with a detection rate varying 40% to 85%.[9] However, its limitations have been observed in studies such as the American College of Radiology Imaging Network 6666 research, which found that mammography only detected 69.5% of invasive cancer compared to ultrasound's detection rate of 91.4%.[10] In this case, mammography only showed a lateral calcification area with blurred tumor contour under dense breast background, despite the patient being 55 years old. Ultrasound (US) is less expensive, more available than mammography, and more sensitive to invasive cancer, making it a good supplement to mammography. However, the US can be more easily interfered with due to the diverse information obtained by different physicians or equipment.[11] Magnetic resonance imaging (MRI) has been found to detect more than 10% of invasive lesions that were occult in mammography, allowing for a thorough biopsy of all the invasive lesions.[1] MRI is often considered a complementary tool for mammography and ultrasound,[12,13] although it does come with a higher false positive rate. In this case, MRI was able to identify all invasive lesions surrounding DCIS and intraductal papilloma in the contralateral breast, providing more comprehensive clinical information for surgical navigation and biopsy. However, MRI's clinical application rate is much lower than ultrasound and mammography due to higher cost, longer operation time, and more technical requirements. A complete imaging examination can compensate for the shortcomings of physical examination, display all lesions, clarify the existence of IMBC, and allow clinicians to further determine its heterogeneity in subsequent biopsy and pathology.

Intraoperative frozen section analysis confirmed the presence of invasive breast cancer with the same diameter and DCIS component in both foci. Till now, through physical examination, imaging screening, surgical biopsy, and intraoperative pathology findings, we have made a final diagnosis of IMBC according to its definition. Furthermore, it is important to note that there can be differences between clinical tumor size and pathologic tumor size for various reasons.[14] The Clinical manifestation of tumor size may be affected by the presence of DCIS component. Tumor size for different molecular subtypes might also be overestimated or underestimated in MRI due to various enhancement patterns. Pathologic tumor staging is typically considered more accurate than clinical tumor size, as it directly measures invasive foci's diameter. Pathologist should not be solely reliant on clinical or imaging reports when performing biopsies and should instead biopsy the largest tumor while considering the presence of other cancer foci. Pathologic measurement of every invasive cancer should be considered to obtain the most comprehensive and accurate assessment.

Heterogeneity Analysis of IMBC

The clinical findings of the 2 invasive breast cancer foci in this case indicate significant differences. Firstly, the invasive cancer in the lateral quadrant of the left breast was not palpable by the patient. Secondly, mammography did not detect invasive cancer in the lower quadrant. Additionally, the 2 invasive foci exhibited different enhancement curves in MRI, suggesting heterogeneity between them.[13,14] Figure 1. All the above suggest the existence of heterogeneity between the foci.

According to the CAP/ASCO guidelines, invasive multicentric and multifocal breast cancer can be divided into 6 groups based on the biologic origin of all the invasive lesions, with only one group is considered to have different biological origins, while the remaining groups have homologous biological origin. CAP/ASCO recommends performing IHC examination on the largest tumor in cases of multifocal breast cancer.[15,16] However, the rationality of this recommendation has been questioned by some oncologists.[17,18] In scenarios where two invasive foci share identical tumor dimensions and histological characteristics, opinions may diverge regarding the necessity of conducting additional immunohistochemical evaluations for both lesions.

Moreover, a preliminary examination of ER expression of the 2 invasive foci revealed different staining patterns that should be observed with the naked eye. Figure 1. It has been reported that IMBC with a background of DCIS and different ER expression is associated with an increased detection of HER2 positivity.[19,20] Further IHC of HER2 staining verified this theory. The Ki-67% value between the two invasive lesions also showed heterogeneous differences, indicating variations in the proliferative abilities. In summary, the two lesions in this case exhibit completely different dissimilarity from each other, which is a rare occurrence and has never been reported till now.[21]

Heterogeneity is indeed a prominent characteristic of cancer cells. Genetic profiling tests can help overcome the limitations of tissue biopsy and aid in developing a more comprehensive treatment strategy.[22] Liquid biopsy, analyzing circulating gene information of breast cancer in the bloodstream, has been showing to provide a more comprehensive assessment of cancer characteristics compared to tissue biopsy.[6,23] However, some limits currently restrict the clinical application of liquid biopsy.[22] For instance, IHC remains the gold standard for determining the mainstream treatment strategy for breast cancer. The positive results obtained from circulating DNA testing need to be interpreted in the context of IHC or well-studied cancer pathways that post-marketing drugs may target.[24] The presence of circulating tumor cells is influenced by various factors, including the TNM stage, characteristics of cancer cells, and technical platforms used, which can introduce a certain level of uncertainty. Nevertheless, large-scale clinical trials have demonstrated that liquid biopsy exhibits advantages over tissue biopsy in identifying disease heterogeneity, disease progression, and resistance pathways, thus holding promise for improving therapy efficiency.

Risk Level Stratification

Comparing with unifocal breast cancer, IMBC is known to be more aggressive, often with higher lymph node stage grade and increased incidence of metastatic events.[25] The American Joint Committee on Cancer (AJCC) defines the T stage as the largest invasive breast cancer without taking into account histology, molecular characteristics, or metastatic disease. The total number of positive lymph nodes is also attributed to the largest invasive lesion without tracing their origin.[16] The TNM staging system is an independent factor for risk stratification in breast cancer. To provide a comprehensive assessment, modified TNM (mTNM) staging should consider tumor size, isolated breast cancer lesions with unique histology or molecular subtypes, the origin of positive lymph nodes, and metastatic information when available. Limited clinical trials have investigated the origin of all positive lymph nodes through immunohistochemical analysis to determine the invasiveness or prognosis of each IMBC foci due to biological complexity.[26] Empirically, when considering factors such as age, histology, WHO grade, pathologic tumor diameter, molecular subtype grouping, and Ki-67% value, the risk level stratification of HER2 positive lesion is typically higher compared to ER-positive lesion. However, the absence of TNM stage information makes it difficult to fully determine the risk level stratification or clinical prognosis for different molecular subtypes.

The feasibility of tracing the origin of positive lymph nodes has confirmed that the metastatic disease originates from the ER-positive lesion. This case highlights the importance of conducting an IHC examination of metastatic lymph nodes and provides new insight into IMBC cases with discordance in molecular expression.

According to AJCC 8th edition and NCCN 3.2022 edition, the anatomical stage of ER-positive lesion is classified as III A (T1N2M0), and the prognostic pathology stage is IB; On the other hand, the anatomic stage of HER2-positive case is IA (T1N0M0) and the prognostic stage is IA. By considering both the anatomical and prognostic pathologic TNM stage of the 2 foci, a more comprehensive risk level stratification of multifocal tumors can be achieved. This allows for a treatment strategy that is better supported by evidence.

Treatment management

The treatment strategy for IMBC may not be extensively mentioned in guidelines for clinical practice. However, temporal strategies can be formulated based on available literature and clinical trials, considering the risk level of each invasive focus. The systemic treatment strategy for IMBC should include chemotherapy, endocrine therapy, and anti-HER2 therapy, tailored according to each cancer focus's molecular expression and risk level stratification, as well as relevant practice guidelines. Based on the anatomic TNM stage and pathologic prognostic stage, the ER-positive lesion is typically staged at higher risk level than the HER2-positive lesion. Therefore, all treatments should aim to benefit both lesions while prioritizing the ER-positive lesion. Chemotherapy strategy often involves sequential administration of anthracycline-cyclophosphamide (AC) followed by taxane (T), as this has been widely accepted. Considering her premenopausal status, endocrine therapy strategy may include ovarian function suppression (OFS) plus aromatase inhibitor (AI) for a duration of 5 years, with the addition of CDK4/6 inhibitors of Arbacilli for 2 years, as recommended in the CSCO 2022 edition. Regarding anti-HER2 therapy, the approach has shifted from dual-target therapy with enhanced adjuvant neratinib therapy to dual-target therapy or single agent trastuzumab therapy without enhanced adjuvant Neratinib therapy for lower risk level of HER2 positive cancer.

Guidelines and clinical practices for breast cancer have indeed evolved significantly in recent years due to advancements in medicine. Enhanced adjuvant therapy or prolonged adjuvant thereapy has the potential to improve disease-free survival and overall survival of patients with higher risk level as recommended by clinical gudielines. In locally advanced breast cancer without distant metastasis, higher risk stratification of the ER-positive and HER2-negative molecular subtype may warrant the use of CDK4/6

inhibitors along with endocrine therapy for a duration of 2 years. Similarly, for higher-risk stratification of the ER-positive or ER-negative, HER2-positive molecular subtype, enhanced anti-HER2 therapy may be necessary for 1 year after standard adjuvant anti-HER2 therapy.

Coincidence of high risk stratification of both Luminal A subtype and HER2 positive subtype is seldomly seen in clinical practice. In such cases, the continuation of adjuvant endocrine therapy and enhanced anti-HER2 therapy is recommended. However, clinical trials for the initial treatment of breast cancer without metastasis do not specifically mention whether CDK4/6 inhibitors should be resumed or not. Recognizing higher-risk stratification in triple-negative breast cancer that coincides with other molecular subtypes can be challenging. If such a situation arises, combining capecitabine with endocrine therapy or anti-HER2 therapy would depend on the oncologist's experience and knowledge.

In recent years, there have been significant advances in the field of breast cancer treatment. Various new chemotherapeutic drugs, targeted therapies, immune checkpoint inhibitors, and cancer biotherapies have been introduced to clinical practice. These treatments have partially been accepted by medical insurance and have greatly improved overall survival and prognosis for breast cancer patients.[27,28] The introduction of these anti-cancer therapies has added complexity to evaluating indications, contraindications, benefits, and side effects. Studies have shown that a combination of anti-HER2 therapy, endocrine therapy, and CDK4/6 therapy in metastatic breast cancer with both ER and HER2 positivity has achieved positive anti-tumor effect, long-term disease-free survival, and overall survival.[29] It is important to note that there are differences in mechanisms and pathways involved in tumor growth, proliferation, metastasis, and drug resistance between breast cancer with dual targets subtype and breast cancer with two different subtypes with a single target.[30] The ER and HER2 double-positive molecular subtype, for example, exhibits cross-talk between the ER and HER2 pathway, making it more responsive to Neratinib therapy.[31] Conversely, the Luminal subtype with higher risk levels benefits from CDK4/6 inhibitor therapy. Clinical practice guidelines have evolved to address the progression made in various aspects of breast cancer treatment. However, challenges still remain in the treatment of IMBC. Further research is needed to determine the optimal therapeutic combinations, treatment sequence, and duration to achieve optimal efficacy while reducing relative toxicity.

CONCLUSION

In brief, IMBC is a more complex condition compared to unifocal breast cancer. It differs in terms of definition, detection, heterogeneity analysis, risk level stratification, and management strategy formulation.[21] IMBC requires more comprehensive approaches in terms of adjuvant therapy, target therapy, and enhanced therapy, which are derived from evidence-based clinical trials. However, IMBC has received relatively less attention in the literature. Therefore, there is a need for more clinical studies and guidelines to reassess IMBC and provide precise and concrete evidence-based treatment strategies that consider its heterogeneity. Upon discovering IMBC, it is crucial to individually identify each target and subtype within IMBC. Treatment should not only cater to the characteristics of each target but should also involve a more precise risk stratification of each target to reduce overtreatment. Furthermore, subtypes associated with higher risks should undergo intensified and prolonged treatment, thereby benefiting patients with high-risk IMBC.

Limitations are obvious in this study. This is the first case about risk level stratification of heterogeneity in IMBC. We lacked data of 5-year disease-free time and overall survival time. We need more data to reveal the true incidence of IMBC to expose its various targets, risk stratification, and the prognosis after more precise treatment.

AUTHORS CONTRIBUTIONS

Lei Hou: Conceptualization, methodology, writing original draft preparation, and supervision. Ziyi Fan, Luming Zheng: Investigation, software, statistical analysis.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICAL STATEMENT

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). This report has been approved by the Ethics Committee of the 960th Hospital of the PLA Joint Logistics Support Force (Approval No. 2023-025) with the patient's informed consent. A copy of the written consent is available for review by the editorial office of this journal.

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