OncoTargets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Patient-Derived Organoids for Guiding Neoadjuvant Chemotherapy in Bilateral Primary Breast Cancer: A Case Report

Meng Cao[1,*], Rong Wang[2,*], Xiaohan Cheng[1], Huiping Yu[3], Qi Tong[4], Yongzhong Yao[1]

[1]Division of Breast Surgery, Department of General Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, 210008, People's Republic of China; [2]Department of Medical Oncology, Jiangsu Province Hospital, The First Affiliated Hospital With Nanjing Medical University, Nanjing, 210029, People's Republic of China; [3]Department of Pathology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, 210008, People's Republic of China; [4]Department of Radiology, Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, Nanjing, 210008, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yongzhong Yao, Division of Breast Surgery, Department of General Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing, 210008, People's Republic of China, Email njglyyz0124@126.com

Abstract: Neoadjuvant chemotherapy (NAC) is the standard of care for locally advanced breast cancer, but the response to chemotherapy is unpredictable due to unknown information on the tumor drug sensitivity. Patient-derived organoids (PDOs) have recently been revealed to be a promising platform for assessing drug sensitivity in many cancers. A 46-year-old woman presented to the hospital due to an accidentally discovered mass in the left breast. Based on core-needle biopsies, pathologic examination showed invasive breast cancer in both breasts. In combination with immunohistochemistry, the patient was diagnosed with left breast cancer IIB with axillary lymphatic metastasis and right breast cancer IIA. The NAC with albumin-bound paclitaxel, epirubicin and cyclophosphamide was used. Although partial response was assessed overall, the left tumor did not lessen significantly; thus, organoids from bilateral breasts were cultured. After treatment with PDO-sensitive vinorelbine and carboplatin, partial response was achieved in the left compared with the initial tumor. Meanwhile, bilateral mastectomy was performed successfully, with pathological complete response achieved in the right. This typical case suggests that the PDOs from bilateral primary breast cancers can serve as a powerful tool to identify the sensitivity to NAC, thus providing novel treatment options at the patient-specific level.

Keywords: bilateral breast cancer, neoadjuvant chemotherapy, organoids, drug sensitivity testing, clinical response

Introduction

Breast cancer is the most common malignancy in women worldwide and has surpassed lung cancer as the most frequently diagnosed cancer. According to GLOBOCAN estimates, there were approximately 2.31 million new cases of female breast cancer and 0.67 million new deaths in 2022.[1] Although over 90% of breast cancer patients are diagnosed at an early stage, there are still a subset of them eventually experiencing recurrence due to the heterogeneous features of breast cancer.[2] Currently, the major treatment modalities for breast cancer include surgery, chemotherapy, radiotherapy, and hormonal therapy. Since the 1980s, neoadjuvant chemotherapy (NAC) has been the standard of care for locally advanced breast cancer, which not only makes breast-conserving surgery more feasible but also tends to eliminate micrometastatic lesions.[3,4] Nevertheless, it is unpredictable for the response to chemotherapy due to unknown information on the tumor drug sensitivity following treatment initiation.[5] Although a lot of patients are treated, only a few of them derive benefits.

Recently, patient-derived organoids (PDOs), three-dimensional in-vitro cellular structures from human tissue-specific stem cells, have been demonstrated to be a promising model system for drug discovery in many cancers, with the

Received: 25 June 2024
Accepted: 20 December 2024
Published: 6 March 2025

advantages of accurately recapitulating the histopathological architecture, genetic and molecular features of parental tumors.[6,7] A previous study indicated that the successfully established breast cancer PDOs could serve as an effective platform for assessing patient-specific drug sensitivity.[8] Thus far, however, there has been a lack of studies about the PDO model for predicting NAC sensitivity in breast cancer. Here, we established the tumor organoids from a patient with bilateral primary breast cancer and demonstrated that the PDOs could effectively identify the sensitivity to NAC to optimize the treatment.

Case Presentation

A 46-year-old woman presented to the hospital due to an accidentally discovered mass in the left breast. Color-Doppler ultrasound showed a solid low-echo mass with calcification (BI-RADS 4b) in the left breast and cystic nodules in both breasts, but with a larger nodule (BI-RADS 2) in the right breast. She previously had no history of malignancies and family history. For further examination and treatment, she came to our hospital on March 1, 2022. Magnetic resonance imaging (MRI) showed diffused, non-phymatoid enhancement in the left breast and mildly enlarged lymph nodes in the left axilla and two blood-supplying enhanced nodules in the right upper lateral breast (Figure 1). On March 9, 2022, the pathological results of the left tumor from a core-needle biopsy with 16-gauge needle revealed invasive breast cancer with the propensity of non-specific type, WHO III, but without obvious components of carcinoma in situ, and meanwhile, a small number of heterocysts were observed through lymph node biopsy in the left axilla, suggesting the possibility of metastatic adenocarcinoma. The pathological results of the right tumor from a core-needle biopsy with 16-gauge needle showed invasive breast cancer with the propensity of non-specific type, WHO II, accompanied by components of carcinoma in situ. Immunohistochemistry (IHC) indicated HER2 (0), ER (-), PR (15%+), Ki-67 (approximate 80%+ in dense regions) and AR (-) for the left tumor, as well as HER2 (1+), ER (-), PR (-), Ki-67 (approximate 40%+) and AR (-) for the right tumor (Figure 2). The patient was finally diagnosed with left breast cancer IIB with axillary lymphatic metastasis and right breast cancer IIA.

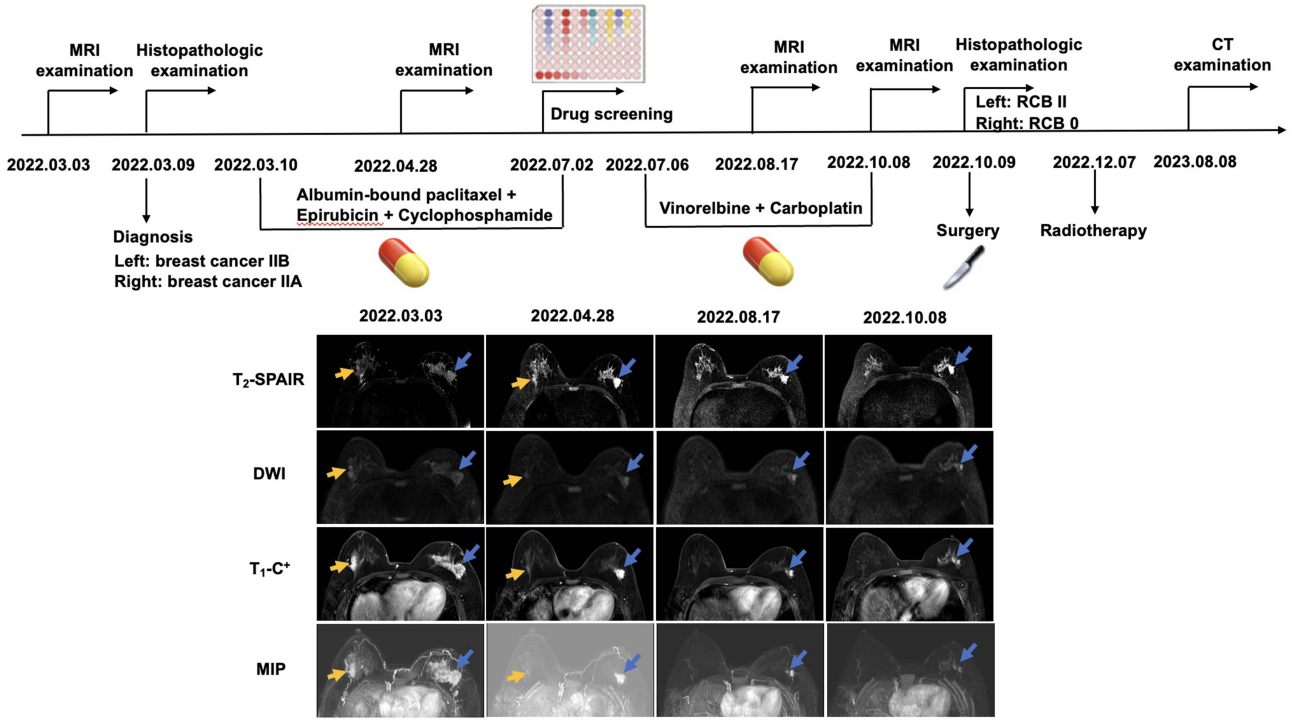

Figure 1 Diagnostic and treatment timeline of the patient and the breast magnetic resonance imaging images at different time points. The yellow arrows point to the right tumor, and the blue arrows point to the left tumor.

 https://doi.org/10.2147/OTT.S484293

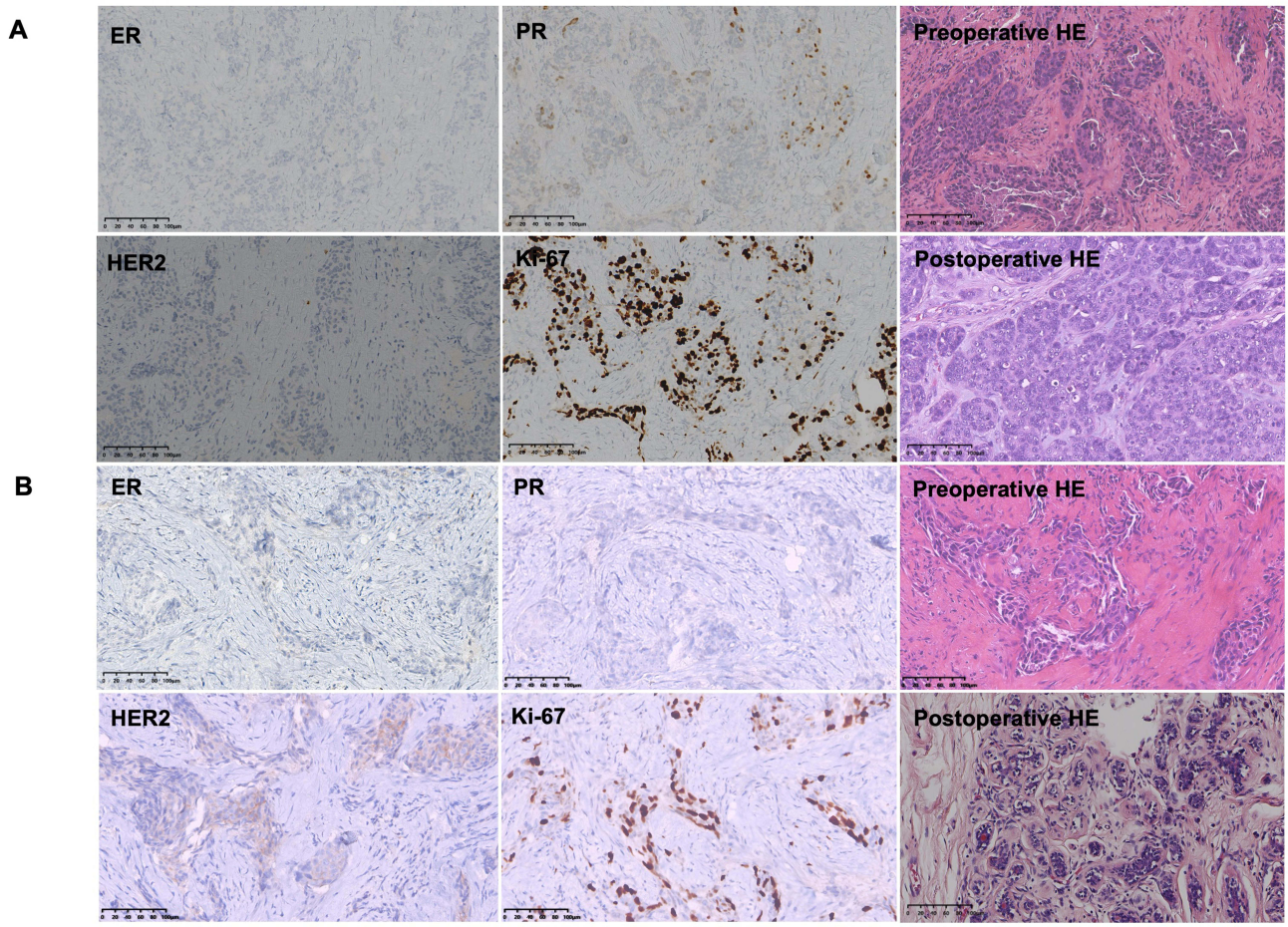

Figure 2 Representative hematoxylin-eosin (HE) staining and immunohistochemical images of the left (**A**, 20×) and right breasts (**B**, 20×).

To be treated with surgery successfully, the patient began to receive NAC with albumin-bound paclitaxel (400 mg), epirubicin (148 mg) and cyclophosphamide (900 mg), with 21 days as a cycle. After use of two cycles, MRI showed a lessened mass in the left breast and partially alleviated lymphadenectasis in the left axilla, as well as a weakened enhancement of two enhanced nodules in the right upper lateral breast (Figure 1). According to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), partial response was assessed based on the overall changes of bilateral tumors, but for the left tumor the decrease was not significant. Therefore, the core-needle biopsy tissues from the left and right breasts were both collected and transported to the laboratory on ice within 24 h for the organoid culture. As described previously,[9] tissues were washed, minced and digested after rinsing with precooled PBS. Cell pellets were collected using centrifugation. When Matrigel was added, Matrigel suspension and cells were seeded onto 6-well plates and placed in a 37°C incubator for 15 min. Once the droplets were solidified, Jiabili® culture medium (Kingbio Medical [Chongqing] Co., Ltd., China) was added and cultured at an incubator (37°C, 5% CO_2). The medium was changed every 2–3 days. When organoids grew well and tended to stabilize, the culture was terminated. Subsequently, organoids were seeded onto 96-well plates, and corresponding drugs were added. Additionally, at least three compound pores and negative controls were set. Adenosine triphosphate bioluminescence assays were used to quantitatively detect the number of viable cells in organoids. Through drug sensitivity testing, it was observed that the left tumor was most sensitive to fulvestrant, followed by vinorelbine and 5-fluorouracil (Figure 3A and B), while the right tumor was most sensitive to vinorelbine, followed by carboplatin and 5-fluorouracil (Figure 3C and D). Accordingly, the NAC with vinorelbine (40 mg) and carboplatin (350 mg) were used on July 6, 2022. After two courses of treatment, MRI showed a reduced nodular shadow in the left breast and two shrunken enhanced nodules in the right breast (Figure 1). Although the nodular

https://doi.org/10.2147/OTT.S484293

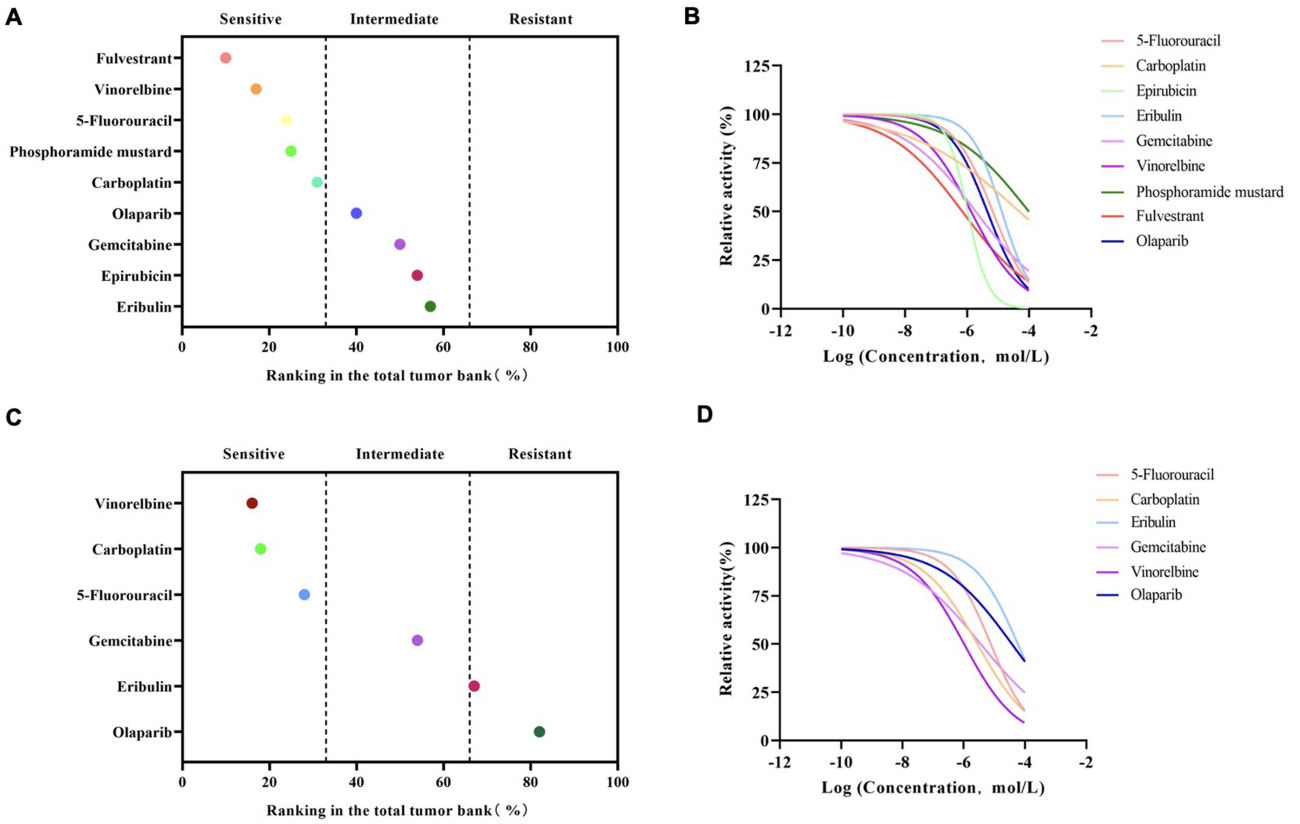

Figure 3 Drug sensitivity results of the left breast tumor (**A** and **B**) and the right breast tumor (**C** and **D**).

shadow in the left breast is slightly enlarged than the last examination, two enhanced nodules in the right breast almost disappeared following four courses of treatment (Figure 1).

On October 9, 2022, a modified radical mastectomy for the left tumor and a radical mastectomy combined with an ipsilateral sentinel lymph node biopsy for the right tumor were performed. Postoperative pathology of the left sample indicated that there were tumor beds with the invasive lesion of 0.7 cm in the outer nipple and 1.0 cm in the inner nipple. It could be observed intravascular cancer thrombi, but not cancerous tissues invading the nerve, which was assessed as grade 3 based on Miller-Payne (MP) classification. Meanwhile, cancerometastasis occurred in 3 ipsilateral axillary lymph nodes. According to the 8th version of the American Joint Committee on Cancer, IIB (ypT1bn, ypN1a, cM0) was diagnosed. Postoperative pathology of the right sample showed that the tumor beds in the outer breast changed after chemotherapy, without residual tumor tissues and lymphatic metastasis. Grade 5 was assessed based on MP classification, and ypT0, ypN0, and cM0 were diagnosed (Figure 2). Thus, the left tumor was pathologically assessed as residual cancer burden (RCB) II, while the right tumor was evaluated as RCB 0 (complete response). On December 7, 2022, the left sub- and supra-clavicular, chest wall and internal mammary radiotherapy was conducted, with the planning target volume of 50 Gy/25f. Until now, the patient recovered well, and Color-Doppler ultrasound of breasts showed no space-occupying lesions in bilateral chest walls and no swollen lymph nodes in bilateral axillae.

Discussion

Overcoming drug resistance is one of the great challenges for improving the therapeutic effect of malignancies. Although several potential mechanisms of drug resistance, such as activation of multiple signaling pathways, genetic alterations, and variations in tumor microenvironment, have been unveiled,[10–12] there is still a lack of effective models that can accurately recapitulate the tumor biological and molecular characteristics and predict the treatment responses. In recent years, the PDO, an in-vitro culture model, has been established successfully in multiple cancers, including breast

cancer.[13] However, it remains unknown whether the PDO model can be generated successfully in drug-treated breast tumors to guide the individualized treatment. In this study, we first described a case of drug-treated bilateral primary breast cancer who pathologically achieved CR for the right tumor after use of the PDO-based drug sensitivity testing to guide the NAC. Importantly, the partial response in the left tumor was also achieved following the treatment with the PDO-sensitive vinorelbine and carboplatin compared with the initial tumor. These findings all highlight the importance of PDOs in identifying the sensitivity to NAC at an individual level.

Bilateral breast cancers are classified into synchronous and asynchronous/metachronous based on the time when the cancers develop in both breasts. A young age at first diagnosis is found to be associated with a relatively high risk of contralateral breast cancer, and the annual risk of contralateral breast cancer is 0.5% on average after diagnosis of breast cancer.[14] In our case, asynchronous bilateral breast cancers (left: IIB, right: IIA) were diagnosed due to tumorigenesis in both breasts at different times. Currently, neoadjuvant therapy remains to be preferable for stage II/III, triple-negative, and HER-2 positive breast cancers, as well as for many higher-stage ER-positive breast cancers.[15] Meanwhile, the case in our study suffered from left axillary lymph node metastasis, conforming to the indications of neoadjuvant therapy. Thus, the NAC with albumin-bound paclitaxel, epirubicin and cyclophosphamide was used according to the Chinese Society of Clinical Oncology Breast Cancer Guidelines in 2022.[16] Although partial response was assessed overall, the decrease in the left tumor was not significantly following four cycles of NAC. Under the guidance of the PDO-based drug screening, the NAC with vinorelbine and carboplatin was used, and radical mastectomy for both breasts was performed successfully.

Conventional two-dimensional cell cultures generally fail to preserve the structural, physiological, and functional features of in-vivo cells, although they are simple in operation and cost-efficient. Patient-derived xenograft (PDX) models can either help to understand the tumor biological features or to identify the best sensitive drugs for individuals, but with low success rates and time consumption, especially the establishment of breast cancer PDX models.[17] Organoids are multicellular in-vitro miniscule models originated from adult or embryonic stem cells with the capability of self-organization and self-renewal, which retain the key cellular and molecular characteristics of the parental tumors while maintaining intratumor heterogeneity and tumor microenvironment, thus useful for high-throughput drug screening.[18] Accumulating evidence has suggested the feasibility of tumor-derived organoids as an effective platform to assess drug efficacy at the patient-specific level, offering personalized treatment recommendations for patients with various cancers.[7,8] In this study, the PDOs from bilateral breast cancers were established to guide the neoadjuvant therapy, and pathological complete response was obtained in the right tumor after mastectomy. Although the left postoperative pathology showed RCB II, the partial response in the left tumor was achieved following the treatment with the PDO-sensitive vinorelbine and carboplatin for four cycles compared with the initial tumor, suggesting that the PDOs are amenable to in-vitro drug screening testing to identify the sensitivity to NAC.

Conclusion

This is the first case of establishing the PDOs in bilateral primary breast cancers. Our results demonstrate that the PDOs from breast cancer can serve as a powerful tool to identify the sensitivity to NAC, thus providing novel treatment options at the patient-specific level.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for publication of the health information in anonymised form. Institutional review board approval was not required, given the patient provided written consent.

Consent for Publication

All authors approved the publication of the manuscript.

Funding

This study was supported by Nanjing Drum Tower Hospital Special Funding Projects for Clinical Research – General Programs from Medical Center (No.: 2022-YXZX-ZL-03).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–263. doi:10.3322/caac.21834
2. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. 2020;38:3987–3998. doi:10.1200/JCO.20.02514
3. Mieog JS, van der Hage JA, van de Velde CJ, van der Hage JA. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg*. 2007;94:1189–1200. doi:10.1002/bjs.5894
4. Asselain B, Barlow W, Bartlett J; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19:27–39. doi:10.1016/S1470-2045(17)30777-5
5. Yang D, Chen MB, Wang LQ, et al. Bcl-2 expression predicts sensitivity to chemotherapy in breast cancer: a systematic review and meta-analysis. *J Exp Clin Cancer Res*. 2013;32:105. doi:10.1186/1756-9966-32-105
6. Nagle PW, Plukker JTM, Muijs CT, et al. Patient-derived tumor organoids for prediction of cancer treatment response. *Semin Cancer Biol*. 2018;53:258–264. doi:10.1016/j.semcancer.2018.06.005
7. Broutier L, Mastrogiovanni G, Verstegen MM, et al. Human primary liver cancer-derived organoid cultures for disease modeling and drug screening. *Nat Med*. 2017;23:1424–1435. doi:10.1038/nm.4438
8. Chen P, Zhang X, Ding R, et al. Patient-Derived Organoids Can Guide Personalized-Therapies for Patients with Advanced Breast Cancer. *Adv Sci*. 2021;8:e2101176. doi:10.1002/advs.202101176
9. Liu X, Han X, Wei S, et al. Case report: patient-derived organoids promoting personalized treatment in invasive urothelial carcinoma. *Front Oncol*. 2024;14:1424677. doi:10.3389/fonc.2024.1424677
10. Kim C, Gao R, Sei E, et al. Chemoresistance Evolution in Triple-Negative Breast Cancer Delineated by Single-Cell Sequencing. *Cell*. 2018;173:879–93.e13. doi:10.1016/j.cell.2018.03.041
11. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised Phase 2 trial. *Lancet Oncol*. 2014;15:747–756. doi:10.1016/S1470-2045(14)70160-3
12. Nedeljković M, Damjanović A. Mechanisms of Chemotherapy Resistance in Triple-Negative Breast Cancer-How We Can Rise to the Challenge. *Cells*. 2019;8:957. doi:10.3390/cells8090957
13. Sachs N, de Ligt J, Kopper O, et al. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. *Cell*. 2018;172:373–386.e10. doi:10.1016/j.cell.2017.11.010
14. Narod SA. Bilateral breast cancers. *Nat Rev Clin Oncol*. 2014;11:157–166. doi:10.1038/nrclinonc.2014.3
15. Burstein HJ, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol*. 2021;32:1216–1235. doi:10.1016/j.annonc.2021.06.023
16. Li J, Jiang Z. Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guidelines in 2022: stratification and classification. *Cancer Biol Med*. 2022;19:769–773. doi:10.20892/j.issn.2095-3941.2022.0277
17. Murayama T, Gotoh N. Patient-Derived Xenograft Models of Breast Cancer and Their Application. *Cells*. 2019;8:621. doi:10.3390/cells8060621
18. Praharaj PP, Bhutia SK, Nagrath S, et al. Circulating tumor cell-derived organoids: current challenges and promises in medical research and precision medicine. *Biochim Biophys Acta Rev Canc*. 2018;1869:117–127. doi:10.1016/j.bbcan.2017.12.005