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Receptor Conversion in Patients with Recurrent Breast Cancer

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Abstract: ***Breast cancer is a highly heterogeneous tumor. Changes in receptor status often are observed at the time of recurrence and metastasis. This phenomenon of receptor transformation has an important impact on the choice of treatment and prognosis of patients. In this paper, we will review the literature related to receptor transformation in recent years, and then discuss the receptor transformation after recurrence of breast cancer patients and the potential mechanisms.***

Keywords: Breast cancer, Receptor conversion, Recurrence, Prognosis**.**

1. Introduction

Breast cancer is currently the malignant tumor with the highest incidence rate among women worldwide, as well as the leading cause of cancer-related deaths [1] [2]. The treatment of breast cancer has formed a comprehensive treatment model based on surgical treatment, endocrine therapy, targeted therapy, and radiation therapy, which has brought about improved prognosis and quality of life for patients. However, tumor recurrence is inevitable when the disease progresses to an advanced stage, which can result in a poor prognosis. The treatment of breast cancer based on surgery, endocrine therapy, targeted therapy and radiation therapy has become well developed. These treatment have brought about improved prognosis and quality of life for patients.

Receptor discordance between primary and metastatic tumors is frequently observed. This receptor conversion alters molecular subtypes, directly affecting treatment efficacy. Emerging evidence suggests that receptor conversion may influence prognosis [3]. Current clinical guidelines recommend reassessing receptor status in metastatic lesions upon first recurrence [3] [4] [5] [6].

This review synthesizes the literature related to receptor conversion in recent years to explore the pattern of receptor conversion in breast cancer patients after recurrence. We also discuss potential mechanisms of receptor conversion and their prognostic implications.

2. Management and Challenges in Recurrent Breast Cancer

Patients can have a worse prognosis due to recurrence events. Therefore, early detection and intervention is beneficial in prolonging the survival time of patients. Follow-up is very important for early identification of recurrence. Imaging tests (e.g. breast ultrasound, mammography, CT and MRI) can effectively identify suspected recurrent lesions. However, biopsy remains the gold standard for confirming malignancy and reassessing pathological and molecular subtypes.

The treatment goal for recurrent breast cancer is to control disease progression, improve quality of life, and prolong survival. Treatment options include chemotherapy, endocrine therapy, targeted therapy and radiation therapy. However, the selection of appropriate treatment options is very complicating. The development of a treatment strategy usually requires a comprehensive assessment of the patient's physical status, the patient's tolerance to treatment, sensitivity to drugs, and previous treatment programs.

There are many challenges in the treatment of patients with recurrent breast cancer. First, tumor cells after recurrence may become resistant to previous treatments, leading to decreased efficacy of first-line treatment regimens. Secondly, receptor status transformation may occur after recurrence, leading to adjustment of treatment strategies and uncertainty of prognosis. Furthermore, treatments (especially chemotherapy) often bring adverse effects, including myelosuppression, cardiotoxicity, and skin rash. These adverse events may affect treatment adherence and in severe cases may even be life-threatening. In addition, relapsed patients may develop psychological problems such as anxiety, depression, and self-loathing, which may affect subsequent treatment.

Precise treatment strategies can reduce the adverse effects associated with treatment and increase the patient's confidence in treatment. Pathology information provided by biopsy can provide clinicians with important drug sensitivity information for the development of subsequent treatment. These data avoid the use of previous regimens even when the sensitivity of the tumor cells to the drug has decreased.

3. Incidence of Receptor Conversion

Receptor conversion after breast cancer recurrence refers to the inconsistency in hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status between primary and metastatic tumors. This phenomenon has important implications for patients' treatment choices and prognosis.

The incidence of receptor conversion is influenced by many factors, including the study population, assay methodology, and definitional criteria. Previous studies reported high variability in the conversion rates of HR and HER2 receptors, with inconsistency rates of 24-38% for estrogen receptor, 33-46% for progesterone receptor, and 12-28% for HER2. The PR conversion rate is higher but more fluctuating, and the

HER2 conversion rate is lower [7] [8] [9] [10] [11]. Woo observed that ER and PR conversion from positive to negative was more common than the reverse, while HER2 conversion rates were balanced [11]. These variations highlight the complexity of receptor conversion and the need for standardized assessment.

4. Factors Influencing Receptor Conversion

It has been reported that receptor conversion may be affected by a variety of factors, including tumor heterogeneity, therapeutic pressure, and limitations of detection technologies.

4.1 Tumor Heterogeneity

Tumor heterogeneity can be divided into the following two types: (1) Intra-tumor heterogeneity refers to the genetic, phenotypic and functional differences of tumor cells in different regions within the same tumor. Variations in receptor expression within a single tumor may lead to sampling bias during biopsy. Multisite sampling is recommended to mitigate this. (2) Inter-tumor heterogeneity refers to the differences in tumor cells between different tumors. Intra-tumor heterogeneity in breast cancer is an important driver of receptor transformation. Ding showed that differences in mutation frequency and gene structure were found between breast cancer metastatic tumors and primary tumors, and that secondary tumors may originate from a small number of cells within the primary tumor [12].

It is hypothesized that tumor cells generate several types of daughter cells with different characteristics during proliferation. These daughter tumor cells differed in terms of proliferation, invasive ability and sensitivity to drugs. A small number of these primary tumor cells metastasized due to their higher dissemination ability.

4.2 Treatment Pressure

Previous therapy can screen tumor subgroups. This screening effect may change in the overall tumor receptor status. Niikura reviewed pathologic information on 182 patients with recurrent HER2 overexpressing breast cancer at MD Anderson Cancer Center. The results of the study found a HER2 conversion rate of 24%, and chemotherapy was associated with loss of positive HER2 receptor expression ($P = 0.022$) [13]. In contrast, Turner noted that HER2-targeted therapies (e.g., trastuzumab) may result in loss of HER2 expression [3]. Most of the relevant studies concluded that hormone receptor deletion is associated with endocrine therapy. It is hypothesized that under the selection of endocrine drug pressure, the tumor cell subgroups that can resist endocrine therapy is more likely to survive as a dominant subgroups. However, there are also findings that ER receptor conversion may be associated with chemotherapy and PR receptor conversion shows a correlation with the use of endocrine therapeutic agents [19]. Treatment Pressure does not perfectly explained the phenomenon of receptor conversion.

4.3 Limitations of Testing Techniques

Different testing methods (e.g., immunohistochemistry, fluorescence in situ hybridization) and sample processing may lead to misclassification of receptor status. Immunohistochemistry is a mature technology with less equipment requirements and can be routinely performed in the pathology departments of most hospitals. It also has the advantage of low cost. So far, it is widely used in the detection of receptor status in clinical practice.

However, the interpretation of immunohistochemistry results depends on the pathologist's experience. IHC results are influenced by sample processing, fixation, antibody selection, and staining protocols. Sighoko reviewed a large amount of previous literature data by Bayesian misclassification correction. This study found that a significant proportion of hormone receptor status inconsistencies could be attributed in misclassifying receptor status [14]. Schettini collected 100 specimens from five pathologists specializing from different institutions. and reproduced the HER 2 IHC scores. The results suggested poor reproducibility of HER 2 IHC scores among pathologists, with 35% of the specimens showing IHC inconsistencies. [15]

The previous studies failed to reach a unified conclusion on the factors influencing the transformation of receptor expression after breast cancer recurrence. This may be related to aspects such as the high heterogeneity of breast cancer tumors and the subjectivity of detection techniques., etc. In addition, Bergeron found that tumors with low HER2 expression status were more likely to express ER after recurrence and possessed lower KI-67 with longer disease-free survival. HER2 status was less stable in patients with lower PR expression in primary tumors [16]. It indicates a possible interaction between receptor statuses.

5. Prognostic Impact of Receptor Conversion

The receptor status of breast cancer lesions is a key factor influencing patient prognosis. HR-positive tumors generally have better outcomes due to endocrine sensitivity, while HER2-positive tumors, though aggressive, benefit from targeted therapies. However, the prognostic significance of receptor conversion remains debated [3] [11] [13] [17] [18] [19] [20] [21] [22].

Some studies suggest that converted HR status does not improve survival compared to persistently negative HR, while persistently positive HR correlates with better outcomes. However, there are also studies found that conversion to negative hormone receptor status after relapse is associated with a poor prognosis. Hormone receptor positive status seems to be regarded as prolonging patient survival in most studies [11] [17] [19]. Can this group of patients whose hormone receptors have converted from negative to positive regain sensitivity to endocrine drugs and improve their prognosis? There is no clear answer to this question.

The survival prognosis of patients after HER2 receptor conversion has also been explored in many literatures, but no agreement has been reached. A meta-analysis indicate HER2 conversion has less prognostic impact than HR conversion [3]. However, emerging therapies like trastuzumab deruxtecan (DS-8201) may benefit HER2-low patients [23].

6. Research Landscapes

Most studies are retrospective, with limited prospective data [24] [25] [26]. The largest retrospective study (N=3,295) reported a 37.7% overall conversion rate, with PR showing the highest (30.1%) and HER2 the lowest (15.4%) [27]. Persistent ER/PR positivity was associated with longer disease-free survival, while HER2 conversion had minimal impact.

Future studies should prioritize prospective designs to prognostic implications of receptor conversion.

7. Conclusions

Receptor conversion in recurrent breast cancer is common and influenced by tumor heterogeneity, treatment selection, and detection methods. Previous literature initially revealed the pattern of receptor conversion, but was unable to confirm the impact of receptor conversion on the survival prognosis of patients. It is expected that the subsequent data will validate the independent effect of receptor conversion on prognosis. This will be helpful in developing individualized therapy for patients with recurrence.

References

[1] Torre LA, Sauer AMG, Chen MS, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: converging incidence in males and females. CA Cancer J Clin. 2016; 66: 182-202

[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66: 115-132.

[3] Turner NH, Di Leo A. HER2 discordance between primary and metastatic breast cancer: assessing the clinical impact. Cancer Treat Rev. 2013 Dec; 39(8): 947-57. doi: 10.1016/j.ctrv.2013.05.003. Epub 2013 Jun 10. PMID: 23764178.

[4] Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4) dagger. Ann Oncol. 2018; 29: 1634-1657.

[5] Carlson RW, Allred DC, Anderson BO, et al. Metastatic breast cancer, version 1.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2012; 10:821-829.

[6] Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2015; 33: 2695-2704.

[7] eung C, Hilton J, Clemons M, et al. Estrogen, progesterone, and HER2/neu receptor discordance between primary and metastatic breast tumours-a review. Cancer Metastasis Rev. 2016; 35: 427-437

[8] Schrijver W, Suijkerbuijk KPM, van Gils CH, van der Wall E, Moelans CB, van Diest PJ. Receptor conversion in distant breast cancer metastases: a systematic review and meta-analysis. J Natl Cancer Inst. 2018; 110: 568-580.

[9] Amir E, Miller N, Geddie W, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol. 2012; 30: 587-592.

[10] Aurilio G, Disalvatore D, Pruneri G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. Eur J Cancer. 2014; 50: 277-289.

[11] Woo JW, Chung YR, Ahn S, Kang E, Kim EK, Kim SH, Kim JH, Kim IA, Park SY. Changes in Biomarker Status in Metastatic Breast Cancer and Their Prognostic Value. J Breast Cancer. 2019 Sep;22(3):439-452. doi: 10.4048/jbc.2019.22.e38. PMID: 31598343; PMCID: PMC6769393.

[12] Ding L, Ellis MJ, Li S, et al: Genome remodelling in a basal-like breast cancer metastasis and xenograft. Nature 464:999-1005, 2010

[13] Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, Tokuda Y, Gonzalez-Angulo AM, Hortobagyi GN, Ueno NT. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol. 2012 Feb 20;30(6):593-9. doi: 10.1200/JCO. 2010.33.8889. Epub 2011 Nov 28. PMID: 22124109; PMCID: PMC3295557.

[14] Sighoko D, Liu J, Hou N, Gustafson P, Huo D. Discordance in hormone receptor status among primary, metastatic, and second primary breast cancers: biological difference or misclassification? Oncologist. 2014 Jun;19(6):592-601. doi: 10.1634/theoncologist. 2013-0427. Epub 2014 May 7. PMID: 24807915; PMCID: PMC4041672.

[15] Schettini F, Chic N, Brasó-Maristany F, Paré L, Pascual T, Conte B, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer. 2021; 7: 1

[16] Bergeron A, Bertaut A, Beltjens F, Charon-Barra C, Amet A, Jankowski C, Desmoulins I, Ladoire S, Arnould L. Anticipating changes in the HER2 status of breast tumours with disease progression-towards better treatment decisions in the new era of HER2-low breast cancers. Br J Cancer. 2023 Jul;129(1):122-134. doi: 10.1038/s41416-023-02287-xIF: 8.8 Q1. Epub 2023 Apr 29. PMID: 37120672; PMCID: PMC10307899.

[17] Hoefnagel LD, Moelans CB, Meijer SL, et al. Prognostic value of estrogen receptor alpha and progesterone receptor conversion in distant breast cancer metastases. Cancer. 2012; 118: 4929-4935.

[18] Li C, Fan H, Xiang Q, et al. Prognostic value of receptor status conversion following neoadjuvant chemotherapy in breast cancer patients: a systematic review and meta-analysis. Breast Cancer Res Treat. 2019; 178: 497-504.

[19] Yang Z, Li N, Li X, Lei L, Wang X. The prognostic impact of hormonal receptor and HER-2 expression discordance in metastatic breast cancer patients. Onco Targets Ther. 2020; 13: 853-863

[20] Matsumoto A, Jinno H, Murata T, et al. Prognostic implications of receptor discordance between primary and recurrent breast cancer. Int J Clin Oncol. 2015; 20(4): 701–8. doi:10.1007/s10147-014-0759-2

[21] Lower EE, Khan S, Kennedy D, et al. Discordance of the estrogen receptor and HER-2/neu in breast cancer from primary lesion to first and second metastatic site. Breast

Cancer (Dove Med Press). 2017; 9: 515–520. doi:10.2147/BCTT.S137709

[22] Yuda S, Shimizu C, Yoshida M, et al. Biomarker discordance between primary breast cancer and bone or bone marrow metastases. Jpn J Clin Oncol. 2019; 49(5): 426–430. doi:10.1093/jjco/hyz018

[23] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N, Cameron DA; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20. doi: 10.1056/NEJMoa2203690. Epub 2022 Jun 5. PMID: 35665782; PMCID: PMC10561652.

[24] Amir E, Miller N, Geddie W, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol. 2012; 30: 587-592.

[25] Amir E, Clemons M, Purdie CA, et al. Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer Treat Rev. 2012;38: 708-714.

[26] Thompson AM, Jordan LB, Quinlan P, et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the breast recurrence in tissues study (BRITS). Breast Cancer Res. 2010; 12(6): R92

[27] Yi ZB, Yu P, Zhang S, Wang WN, Han YQ, Ouyang QC, Yan M, Wang XJ, Hu XC, Jiang ZF, Huang T, Tong ZS, Wang SS, Yin YM, Li H, Yang RX, Yang HW, Teng YE, Sun T, Cai L, Li HY, Chen X, He JJ, Liu XL, Yang SE, Wang JY, Fan JH, Qiao YL, Xu BH. Profile and outcome of receptor conversion in breast cancer metastases: a nation-wide multicenter epidemiological study. Int J Cancer. 2021 Feb 1;148(3):692-701. doi: 10.1002/ijc.33227. Epub 2020 Aug 19. PMID: 32700765.