Prognostic Value and Influence of Receptor Conversion on Treatment Regimen in Metastatic Breast Cancer at the First Time of Recurrence

Jiming Shen^{a, b} Lu Xu^{a, b} Jing Shi^{a, b} Lei Zhao^{a, b} Sha Shi^{a, b} Jing Feng^{a, b}
Xu Han^{a, b} Yu Shi^{a, b} Qiaochu Wei^{a, b} Dongni Wang^{a, b} Mingfang Sun^c
Xiaoyi Mi^c Yue'e Teng^{a, b}

^aDepartment of Medical Oncology, First Hospital of China Medical University, Shenyang, China; ^bKey Laboratory of Anticancer Drugs and Biotherapy of Liaoning Province, First Hospital of China Medical University, Shenyang, China; ^cDepartment of Pathology, First Hospital and College of Basic Medical Sciences of China Medical University, Shenyang, China

Keywords

Estrogen receptor · Human epidermal growth factor receptor 2 · Progesterone receptor · Receptor conversion · Metastatic breast cancer

Abstract

Purpose: At the first time of metastatic breast cancer recurrence, conversion of the receptors status may occur between primary lesions and metastatic lesions, including the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Whether the decision of the treatment regimen is based on the primary receptor status or that of metastatic lesions is still unclear. **Methods:** This study enrolled 411 female patients with a diagnosis of metastatic breast cancer at the first time of recurrence to explore the influence of receptor conversion on prognosis prediction and treatment regimen of patients with metastatic breast cancer. **Results:** ER and PR changes from negative to positive are both prognostic factors for patients with breast cancer. Patients receiving endocrine therapy showed a better survival after recurrence than those using chemotherapy alone in the ER or PR Prim– Met+ subgroup. Patients in the HER2 Prim– Met+ subgroup using HER2-targeted therapy in multilines showed a post-recurrence survival advantage. In the bone re-biopsy subgroup, the PR change from positive to negative appeared to be more frequent than at other re-biopsy sites. **Conclusions:** Pa-

tients with metastatic breast cancer should perform re-biopsy to clarify the receptor status of the first metastatic lesions, which may provide clinicians valuable evidence to conduct treatments with higher precision.

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Introduction

Breast cancer has the highest incidence in women, and although survival has gradually improved over the years, one third of the patients diagnosed with early breast cancer will still progress to metastatic disease with a poor prognosis [1, 2]. Therapy for breast cancer has been developed into precision treatments in which the status of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) is important [3–6]. Actually, a large part of treatment regimens for patients with metastatic breast cancer rely on hormone receptor status and the molecular subtype of the primary lesion. However, the correlation between the receptor conversion in metastatic lesions and the prognostic decision-making remains unclear.

Accumulating evidence has shown that the status of ER, PR, and HER2 is inconsistent to a certain extent between the primary and metastatic lesions, and the proportion of receptor conversion at different sites is not comparable [7–16]. In a previous clinical practice guideline, the

Table 1. Patients' basic clinicopathological characteristics of their primary sites

Variable	All patients	%	ER				PR			
			positive	%	negative	%	positive	%	negative	%
Patients, <i>n</i>	411		242	58.88	169	41.12	228	55.47	183	44.53
Biopsy of relapse										
Puncture	301	73.24								
Surgery	110	26.76								
Age, years										
Average	48 (26–79)		47 (26–79)		47 (26–76)		46 (26–79)		50 (28–76)	
Median	48 (26–79)		47 (26–79)		48 (26–76)		46 (26–79)		49 (28–76)	
<35 years	41	9.98	33	13.64	8	4.73	29	12.72	12	6.56
35–60 years	331	80.54	185	76.45	146	86.39	181	79.39	150	81.97
>60 years	39	9.49	24	9.92	15	8.88	18	7.89	21	11.48
Menopausal status										
Menopause	272	66.18	154	63.64	118	69.82	141	61.84	131	71.58
Premenopausal	134	32.60	84	34.71	50	29.59	84	36.84	50	27.32
NA	5	1.22	4	1.65	1	0.59	3	1.32	2	1.09
BMI, <i>n</i>										
≤18.4	13	3.16	11	4.55	2	1.18	8	3.51	5	2.73
18.5–23.9	160	38.93	97	40.08	63	37.28	90	39.47	70	38.25
24.0–27.9	172	41.85	95	39.26	77	45.56	94	41.23	78	42.62
≥28	66	16.06	41	16.94	25	14.79	36	15.79	30	16.39
T stage, <i>n</i>										
Tis	8	1.95	3	1.24	5	2.96	3	1.32	5	2.73
T1	116	28.22	72	29.75	44	26.04	71	31.14	45	24.59
T2	227	55.23	133	54.96	94	55.62	123	53.95	104	56.83
T3	30	7.30	14	5.79	16	9.47	11	4.82	19	10.38
T4	12	2.92	6	2.48	6	3.55	6	2.63	6	3.28
NA	18	4.38	14	5.79	4	2.37	14	6.14	4	2.19
N stage, <i>n</i>										
N0	161	39.17	96	39.67	65	38.46	93	40.79	68	37.16
N1	110	26.76	63	26.03	47	27.81	57	25.00	53	28.96
N2	65	15.82	40	16.53	25	14.79	36	15.79	29	15.85
N3	54	13.14	27	11.16	27	15.98	25	10.96	29	15.85
NA	21	5.11	16	6.61	5	2.96	17	7.46	4	2.19
Stage, <i>n</i>										
0	7	1.70	2	0.83	5	2.96	2	0.88	5	2.73
I	65	15.82	41	16.94	24	14.20	37	16.23	28	15.30
II	194	47.20	117	48.35	77	45.56	111	48.68	83	45.36
III	120	29.20	64	26.45	56	33.14	59	25.88	61	33.33
NA	25	6.08	18	7.44	7	4.14	19	8.33	6	3.28
HER2 status, <i>n</i>										
HER2+	96	23.36	40	16.53	56	33.14	40	17.54	56	30.60
IHC only ¹	30	7.30	18	7.44	12	7.10	18	7.89	12	6.56
HER2–	270	65.69	175	72.31	95	56.21	162	71.05	108	59.02
NA	15	3.65	9	3.72	6	3.55	8	3.51	7	3.83

Median follow-up of the patients after relapse was 57.2 months. *n*, number of patients; NA, not available. ¹ HER2(++), FISH was not performed.

importance of reevaluating the receptor status in metastatic breast cancer lesions has been emphasized as the receptor conversion can provide important guidance for treatment and, consequently, improved prognosis [17]. Therefore, determination of the ER, PR, and HER2 status in metastatic lesions is key to treatment since hormone receptor status can affect treatment decisions to pave the way towards a better prognosis in metastatic breast cancer. Therapeutic regimens for patients with conversion of the receptor status from primary to metastatic lesions have always been of concern for clinicians, particularly since the guidelines have not been clearly defined [18, 19].

In this study, we aimed to evaluate the frequency and prognostic value of receptor conversion between primary and first metastatic lesions in 411 patients at the first time of metastatic breast cancer recurrence. We also clarified the impact of receptor conversion on the choice of treatment and adapted treatment based on the reevaluation of metastatic lesions. This has shown significant improvements in the prognosis of patients with metastatic breast cancer. Our study has provided evidence for precision treatment according to the receptor status during the reevaluation of metastatic lesions of breast cancer.

Table 2. Conversion of ER, PR, and HER2 (*n* = 411)

Primary site	<i>n</i>	%	Metastasis site	<i>n</i>	%
ER+	242	58.88	ER+	194	80.17
			ER–	48	19.83
ER–	169	41.12	ER+	49	28.99
			ER–	120	71.01
PR+	228	55.47	PR+	153	67.11
			PR–	75	32.89
PR–	183	44.53	PR+	45	24.59
			PR–	138	75.41
HER2+	96	23.36	HER2+	45	47.37
			IHC without FISH	35	36.84
			HER2–	13	13.68
			NA	3	3.16
HER2–	270	65.69	HER2+	18	6.82
			IHC without FISH	63	23.86
			HER2–	172	65.15
			NA	17	6.44

NA, not available.

Materials and Methods

Patients

We collected the data of 635 patients with advanced breast cancer from the Department of Oncology, the First Affiliated Hospital of China Medical University, between January 2001 and September 2019. All the patients had previously undergone radical resection of the primary lesion and repeat pathological biopsy of the first metastatic lesion. The exclusion criteria were as follows: (1) patients with missing immunohistochemical results of ER and PR status in both primary and metastatic lesions and (2) patients who were lost to follow-up; 411 patients were finally included. This study was approved by the Ethics Committee of the First Hospital of China Medical University. We obtained informed consent from every patient.

Repeat biopsy of metastatic lesions includes pathological examination after puncture and pathological examination after surgical resection. The immunohistochemical results of ER, PR, and HER2 status were from 2 independent pathology experts. Expression of ER and PR $\geq 10\%$ was considered to be positive for primary and metastatic lesions, respectively. HER2 status was defined as negative when the immunohistochemical result of HER2 was – or 1+ and as positive when the immunohistochemistry result was 3+. When the immunohistochemistry result of HER2 is 2+, it is recommended that patients should be tested for HER2 fluorescence in situ hybridization (FISH) to make a final determination of HER2 status.

The last follow-up date of all patients was October 2019. Six patients (1.44%) were lost to follow-up.

Statistical Analysis

Post-recurrence survival is defined as the time a patient was first pathologically diagnosed with metastatic breast cancer to the patient's death or her last follow-up visit (October 2019). Kaplan-Meier analysis was used to obtain survival curves. The log-rank test was applied to calculate statistical significance (*p* value). Differ-

ences in the conversion among different metastatic sites were calculated using the χ^2 test. *p* < 0.05 is considered to be statistically significant. All statistical tests were performed on SPSS 24.0 software.

Results

Clinical Characteristics of the Patients with Primary Breast Cancer

This study included 411 female patients diagnosed with metastatic breast cancer at the first time of recurrence. Their basic clinicopathological characteristics are summarized in Table 1. The median follow-up time after recurrence was 57.2 months. In 26.76% of the patients, metastases were confirmed pathologically by surgical resection while 73.24% were identified by puncture. According to the ER and PR status of the 411 patients with primary tumors, 242 (58.88%) were ER+ and 228 (55.47%) were PR+. At the time of the initial diagnosis of breast cancer, 80% of patients were between 35 and 60 years of age, a ratio that was relatively equivalent between the ER+ or ER– and PR+ or PR– subgroups; 66% of women were menopausal. More than 50% of patients were in T2 stage, and the proportion of patients in N0 stage was relatively high. Nearly 50% of patients were of grade II; 8% of patients had a HER2 immunohistochemical result of 2+, but no further HER2-FISH testing was performed due to patient reasons.

Fig. 1. Kaplan-Meier survival curves in patients with various ER status subtypes (A), patients with various PR status subtypes (B), and patients with various HER2 status subtypes (C).

Table 3. Sites of re-biopsy and proportion of receptor conversion at each site

Site	Total		ER: Prim- Met+		ER: Prim+ Met (-)		PR: Prim- Met+			PR: Prim+ Met-		
	n	%	n	%	n	%	n	%	p value	n	%	p value
Total	411	100.00	49	11.92 ^a	48	11.68 ^b	213	51.82	0.087	75	18.25	0.067
Brain	7	1.70	1	14.29	1	14.29	0	0.00	1.000	3	42.86	0.228
Liver and lung	78	18.98	9	11.54	9	11.54	5	6.41	0.154	17	21.79	0.368
Other internal organs	44	10.71	5	11.36	9	20.45	3	6.82	0.501	8	18.18	0.990
Lymph nodes and soft tissue	232	56.45	25	10.78	22	9.48	200	86.21	0.036	33	14.22	0.016
Bone	27	6.57	6	22.22	4	14.81	5	18.52	0.325	9	33.33	0.066
Opposite breast	23	5.60	3	13.04	3	13.04	0	0.00	0.165	5	21.74	0.866

^a p = 0.683, ^b p = 0.451.

Receptor Conversion between Primary Tumor and Metastatic Diseases

The frequency of receptor conversion is shown in Table 2. Among the 242 patients with ER+ primary lesions, 48 (19.38%) patients with ER+ primary lesions changed to ER- metastatic lesions, and among 169 patients with ER- primary lesions, 49 (28.99%) patients were ER+ in metastatic lesions. Similarly, the PR status of 75 (32.89%) of 228 patients changed from positive to negative, while 45 (24.59%) of the 183 patients converted from negative to positive. With the exception of patients without clarified HER2 status, 13.68% changed from primary HER2+ to metastatic HER2-, and 6.44% from primary HER2- to metastatic HER2+.

According to the status conversion of ER, PR, and HER2 between primary and first metastatic lesions, patients were divided into 4 subgroups: Prim- Met+, Prim+ Met-, Prim+ Met+, and Prim- Met-. There were significant differences in post-recurrence survival (ER: $p = 0.000$, PR: $p = 0.013$) in the ER and PR groups (Fig. 1a, b), but there was no statistical difference in the HER2 group (Fig. 1c, $p = 0.358$).

Site of Re-Biopsy and Proportion of Receptor Conversion at Each Site

The recurrence and metastasis re-biopsy site varied from patient to patient (Table 3); in 56.45% of patients, the re-biopsy sites were lymph nodes, soft tissue, or skin.

Fig. 2. Immunohistochemistry results of 3 patients with ER+/PR+ primary and metastatic lesions and PR- metastatic lesions. Adjuvant therapy regimens, first-line therapy regimens, recurrence-free survival (RFS) and time-to progression (TTP) were listed. OFS, ovarian function suppression.

Other internal organs include distant lymph nodes, chest, and abdominal organs except for the liver and lung. In all patients, both the proportions of ER from positive to negative and negative to positive were about 12%, whereas the proportion of PR from negative to positive was 10.95%, and the proportion of PR from negative to positive was 18.25%.

For the PR Prim+ Met- and Prim- Met+ groups, no statistical differences were observed ($p = 0.087$, $p = 0.067$) in receptor conversion at metastatic sites. Therefore, in these 2 groups, the conversion of the receptors at the target site were compared with the conversion of the receptors at all remaining re-biopsy sites. The χ^2 test was used to confirm that there were significant differences in the PR status conversion in lymph nodes, soft tissue, or skin compared with the other sites in the PR Prim+ Met- subgroup ($p = 0.016$) and the PR Prim- Met+ subgroup ($p = 0.036$). For the PR Prim+ Met- subgroup, the PR status

conversion of bone metastasis sites tended to be different from other sites ($p = 0.066$).

There are 9 patients in the PR Prim+ Met- subgroup with bone re-biopsied, and 3 of them caught our attention. The ER status of primary and metastatic lesions of these 3 patients was positive (2+ or 3+), and thus they accepted endocrine therapy as first-line regimens (Fig. 2). All of them obtained benefits from adjuvant endocrine therapy as their recurrence-free survival was 18.2, 90.1, and 143.3 months, respectively. However, all of the 3 patients were resistant to the endocrine therapy because time to progression from first-line treatment was <1 year.

Influence of Receptor Conversion after Re-Biopsy on First-Line Treatment

Endocrine therapy and HER2-targeted therapy are very important treatments currently in use. We have

Table 4. Treatment after re-biopsy

Variable	n (%)
First-line regimens of ER and/or PR Prim– Met+	77
Chemotherapy	29 (37.66)
Endocrine therapy and/or chemotherapy	36 (46.75)
HER2-tageted therapy	11 (14.29)
No treatment	1 (1.30)
Multiline regimens of HER2 Prim– Met+	18
Chemotherapy	2 (11.76)
Endocrine therapy and/or chemotherapy	4 (23.53)
HER2-tageted therapy	12 (70.59)

Fig. 3. Kaplan-Meier survival curves in patients in ER or PR Prim– Met+ subgroups received different first-line regimens (A) and patients in HER2 Prim– Met+ subgroup with or without HER2 targeted therapy in multiline treatment (B).

observed the first-line treatment options in the ER or PR Prim– Met+ subgroups and multiline treatment options in the HER2 Prim– Met+ subgroup (Table 4). Of the 77 patients in the ER or PR Prim– Met+ subgroup, 36 (46.75%) were subjected to endocrine therapy with or without chemotherapy as first-line treatment regimen, and 29 (37.66%) had chemotherapy alone. In order to rule out the effects of HER2-targeted therapy, we excluded 11 patients on HER2-targeted therapy containing herceptin. Patients on endocrine therapy had a significantly better prognosis than patients on chemotherapy alone (Fig. 3a; $p = 0.029$). Also, we analyzed the impact of targeted therapy on prognosis in the HER2 Prim– Met+ subgroup and concluded that the prognosis of 12 patients on HER2-targeted therapy in multiline treatment tended to be better than that of 6 patients on chemotherapy or endocrine therapy only (Fig. 3b; $p = 0.436$).

Discussion

In this study, comparing the status of ER, PR, and HER2 between primary and first metastatic lesions in 411 patients with metastatic breast cancer treated in a single center, it was found that the receptor status did undergo a conversion, to a certain extent, between primary and metastatic sites. Patients had a significantly better prognosis when ER or PR status changed from negative to positive in univariant analysis. However, the post-recurrence survival of patients treated with endocrine therapy as first-line regimen was significantly better than that of patients treated with chemotherapy alone when ER or PR changed from negative to positive. All the results indicate that re-biopsy of the metastatic site to detect the receptor status is important to be able to tailor treatment to the individual patient with metastatic breast cancer.

An increasing number of guidelines recommends a re-biopsy of metastatic breast cancer to determine the receptor status and molecular subtype [17–19]. Several previous studies have found that the rates of receptor status conversion were different, but due to small sample sizes, the ratios of negative to positive and positive to negative have not been separately calculated. In a systematic review and meta-analysis, Schrijver et al. [16] found that the rates of receptor conversion differed among different metastatic sites. In our study, the rates of ER and PR receptor status conversion were calculated in detail using a large number of patients accrued in a single center. The rate of PR status conversion in lymph nodes, soft tissue, or skin is significantly different from other sites suggesting that, in future clinical work, these patients should be subjected to a re-biopsy to determine outcome and future therapy based on the receptor status. Interestingly, the proportion of receptor conversion after re-biopsy of bone metastases was different compared with other sites in the PR Prim+ Met– subgroup, which has great implications for future clinical work to establish the applications of endocrine therapy. Thus, patients with bone metastases should undergo a distinctive therapeutic approach as they should perform re-biopsy of metastases actively.

Usually, endocrine therapy is the first choice for hormone receptor-positive metastatic breast cancer without visceral crisis, although previous studies have shown that when endocrine resistance develops, nearly half of the patients have PR loss, and PR– status can guide the prediction of resistance [20–23]. When PR changes from positive to negative, perhaps resistance to endocrine therapy should be considered. In this study, there were 3 special patients with ER+/PR+ primary lesions who benefited from the adjuvant endocrine therapy, but the PR status changed to negative after re-biopsy at the first time of bone recurrence. They were primarily resistant to first-line endocrine therapy because of relatively short interval from first-line therapy to progression. We could not draw the conclusion that metastatic breast cancer patients with a PR change from positive to negative at the bone recurrence site are resistant to first-line endocrine therapy due to the limited number of patients, but the therapy regimens of metastatic breast cancer patients with bone recurrence and PR conversion are worthy further investigation. Whether the PR conversion from positive to negative at bone metastatic site can be a biomarker of endocrine therapy resistance needs to be addressed in future clinical work.

Previous studies and this article have shown that receptor conversion is an important factor in predicting the prognosis of patients with metastases [8, 9, 11, 24]. In fact, the clinicians' priority is to know if the receptor conversion can influence their clinical decisions and therefore patient outcome. At present, conclusive data on receptor conversion in metastatic lesions still lack, and there are no clear

guidelines providing information about treatment regimens and receptor status in metastatic lesions. Therefore, to the best of our knowledge, for the first time, we retrospectively explored the effect of receptor conversion on the decision of first- or multiline regimens and on the prognosis of patients with metastatic breast cancer. Nearly half of the patients were on regimens containing endocrine therapy as the first-line treatment according to the receptor status of metastatic sites, when ER or PR change from negative to positive. The post-recurrence survival was significantly better than that based on the primary receptor status applying chemotherapy only. However, there was no statistically significant better prognosis in patients in the HER2 Prim– Met+ subgroup who received HER2-targeted therapy in multiline treatment, which may be due to the small sample size. Consequently, in clinical practice, clinicians should provide patients with an individualized treatment plan based on the patient's own situation combined with receptor conversion information at metastatic sites.

Our study also has some limitations. First, as a retrospective study, patients included in this study are admitted to a single center, and there will be some bias. The sample size in some subgroups is small and multicentric. Thus, a prospective study in a large patient cohort is needed to confirm the results. Second, due to some patient-related factors, the proportion of ambiguous HER2 status is high. This also requires larger sample data to further clarify the impact of HER2 conversion on patient prognosis. Finally, due to limitations of the re-biopsy methods, patients with multiple metastases generally choose only 1 metastasis for re-biopsy, which may also have some impact on the results.

Conclusion

In the 411 patients with pathologically diagnosed metastatic breast cancer at the first time of recurrence studied in a single center, ER and PR conversions were found to affect the prognosis of patients and decisions regarding the treatment regimen. Patients may benefit from therapy regimens based on the receptor status of metastatic lesions. It is clear that the receptor status at metastatic sites and receptor conversion between the primary and metastatic lesions have important effects on tailored treatment of metastatic breast cancer, which may significantly improve the prognosis of patients with metastatic breast cancer.

Statement of Ethics

This study was approved by the Ethics Committee of the First Hospital of China Medical University. We obtained informed consent from every patient.

Conflict of Interest Statement

All authors declare that there are no potential conflicts of interest including any financial, personal, or other relationships with other people or organizations that could inappropriately influence this work.

Funding Sources

This work was supported by the National Natural Science Foundation of China (NSFC, No. 81672605), National Key R&D Program of China (No. 2018YFC1311600), and the Science and Technology Plan Project of Liaoning Province (No. 2016007010).

Author Contributions

All authors contributed to the study. The study was designed by Yue'e Teng. Material preparation and data collection were performed by Jiming Shen, Lu Xu, Jing Shi, Lei Zhao, Sha Shi, Jing Feng, Xu Han, Yu Shi, Qiaochu Wei, Dongni Wang, Mingfang Sun, and Xiaoyi Mi. Analyses were performed by Jiming Shen and Lu Xu. The first draft of the manuscript was written by Jiming Shen, and reviewed and edited by Yue'e Teng and Lu Xu. All authors read and approved the final manuscript.

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