



New classification for advanced breast cancer patients experiencing disease progression during salvage treatment: a single-center retrospective cohort study

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Background: Attributed to inter-tumor heterogeneity, the therapeutic effect of salvage treatment is diverse and different malignant lesions might manifest various therapeutic responses among advanced breast cancer (ABC) patients. The present study aimed to explore the influence of the mode of lesion response on the subsequent treatment and to subclassify ABC patients for precise prognosis prediction.

Methods: Based on the inclusion and exclusion criteria, ABC patients were retrospectively collected and followed up in the Guangdong Provincial Hospital of Chinese Medicine between 2018 and 2021. The treatment responses of all malignant lesions were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Testing subclassified models were constructed based on different assembly mode of progressed malignant lesions for further classification of ABC patients experiencing disease progression following first-line treatment. Multivariate survival analyses were performed to assess the second-line progression-free survival (PFS) of various subgroups and screen the suitable classification model. The most suitable model was utilized to classify enrolled ABC patients as a heterogeneous progression-disease (Heter-PD) group or homogeneous progression-disease (Hom-PD) group. Univariate analysis and multivariate Cox regression survival analyses were performed to assess the prognostic value of each variable.

Results: A total of 70 ABC patients experiencing disease progression after first-line treatment were enrolled into the analyses and underwent median follow-up of 10.36 months. We constructed 3 testing models and Model C (Hom-PD was defined when all the target and non-target lesions were evaluated as progression, with or without new lesions) could further distinguish ABC patients with worse survival. The second-line progression-free survival (PFS) times were significantly different between two groups (11.04 *vs.* 6.07 months, $P=0.034$). For ABC patients retaining partial medication after disease progression of first-line treatment, the Heter-PD group showed a tendency of better second-line PFS than the Hom-PD group (13.18 *vs.* 3.61 months, $P=0.430$).

Conclusions: Based on the disease progression mode after first-line treatment, the classification model could classify ABC patients as Hom-PD and Heter-PD subgroups, which manifest distinct prognoses during the sequential treatment. For Heter-PD patients, retainment of partial medication might be a rational choice for second-line therapy.

Keywords: Advanced breast cancer (ABC); tumor heterogeneity; heterogeneous disease progression

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Introduction

Breast cancer (BC) is the most common cancer in women worldwide (1). In 2021, more than 280,000 new cases and 43,000 deaths of BC were recorded in the United States (2). Despite dramatic progress of BC adjuvant treatment, recurrence and distant metastasis still occurs in about 30% of patients (3,4).

Tumor heterogeneity is an important feature of malignant tumor, manifesting as differences of genotype and phenotype between patients or malignant lesions of different organs in the same patient (inter-tumor heterogeneity) (5). Due to the different subtypes of tumor cells, which show various phenotypic characteristics, growth rates and invasion ability, the therapeutic sensitivity to anti-tumor treatment is diverse among various tumor lesions (6,7).

Assessment of therapeutic effect is based on the determination of response or progression. The most frequently used response evaluation criterion in clinical trial is the Response Evaluation Criteria in Solid Tumors (RECIST), firstly published in 2000 (8). The updated RECIST 1.1 further updated the assessment of tumor burden and lymph nodes.

Based on RECIST 1.1 criteria, the determination of overall response evaluation is dependent on the sum of the longest diameters for all target lesions and the evaluation of non-target lesions. The response assessment is classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The PD status includes 3 conditions: target lesions progression, non-target lesions progression and new lesions. For patients with new lesions and no progression of target/non-target lesions, only the new lesions are deemed insensitive to systemic treatment, while the original target/non-target lesions remain under acceptably control. However, no prognostic predictive model of ABC patients considered the therapeutic responses of different lesions.

In the present study, we enrolled advanced breast cancer (ABC) patients with PD after first-line treatment and proposed 3 classification models based on the evaluation of the response status of all malignant lesions. The 3 classification models were proposed and verified to facilitate

more precise identification of patients with different prognoses. We aimed to evaluate and verify the most accurate model that could further subclassify the PD status and identify patients with different prognoses. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1618/rc>).

Methods

Study population

The present study was retrospective cohort study, and electronic medical records of ABC patients from January 2018 to December 2021 at Guangdong Provincial Hospital of Chinese Medicine were retrospectively reviewed. The inclusion criteria were as follows: (I) pathologically and/or radiographically confirmed advanced metastasis; (II) age: 18–75 years old; (III) female; (IV) Eastern Cooperative Oncology Group (ECOG) score: 0–2 grade. The exclusion criteria were as follows: (I) previous immunotherapy for metastatic BC; (II) another non-measurable disease present at the time of ABC diagnosis (osteoblastic bone metastasis, meningeal lesions, ascites, pleural effusion, pericardial effusion, pulmonary cancerous lymphangitis); (III) brain metastasis; (IV) had previously received local treatment (surgery or radiotherapy) for breast tumor lesion or metastatic lesions after ABC diagnosis; (V) did not undergo regular follow-up and therapeutic evaluation; (VI) insufficient clinicopathological data.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2020-349-01) and informed consent was taken from all the patients before inclusion.

Data collection

Age, malignancy family history data and diagnosis timing were collected for each participant. Data of pathologic characteristics were recorded, including pathologic stage,

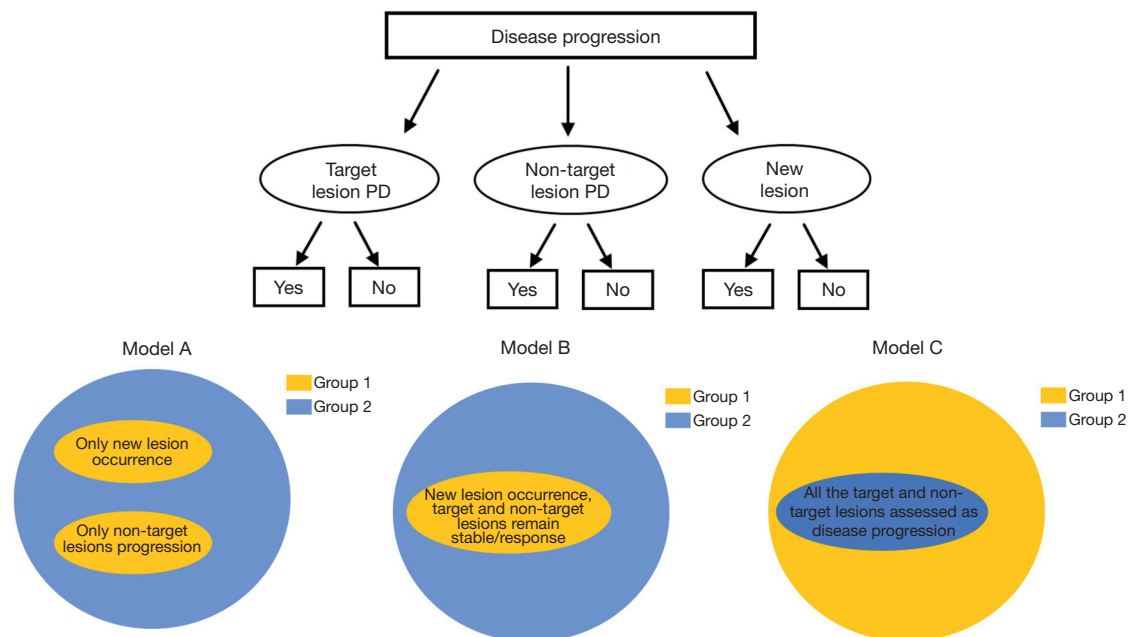


Figure 1 Construction of testing classification models.

histologic type, grade, hormonal receptor status, human epidermal growth factor receptor-2 (HER2) expression and Ki-67. For treatment of ABC, the first- and second-line therapeutic information were recorded (drug regimens, duration). Furthermore, the changes of radial line of target and non-target lesions were recorded to perform therapeutic evaluation. The overall therapeutic evaluation was assessed according to the RECIST 1.1 criteria respectively.

Model construction and follow-up

In the RECIST 1.1 criteria, the following conditions are defined as PD: (I) progression of target lesions; (II) progression of non-target lesions; (III) occurrence of new lesions. Based on the permutation and combination of various conditions with potential clinical implication, several testing models were constructed for subclassification of ABC patients (Figure 1). After the therapeutic evaluation as disease progression and the initiation of second-line treatment, enrolled participants received regular symptom assessment and computerized tomography (every 2–4 cycles for chemotherapy patients and every 2–6 months for endocrine therapy patients) based on the National Comprehensive Cancer Network (NCCN) guideline. The primary end point was disease progression after the second-line treatment according to RECIST 1.1 criteria.

Statistical analyses

Mann-Whitney U test or Student's were utilized for comparison of continuous variables, and the comparison of categorical variables was via χ^2 or the Fisher's exact test. Any locoregional recurrence, distant recurrence or contralateral primary BC was considered as disease-free survival (DFS) event among non-de novo BC patients after adjuvant treatment. The first-line progression free survival (PFS) was defined as the interval from the first diagnosis of metastasis to disease progression, and the second-line PFS was defined as the interval between the initiation of second-line treatment and the disease progression/subsequent disease progression). Patients without event at the date of last follow-up or lost to follow-up were censored. The primary outcome was second-line PFS. Kaplan-Meier survival analyses were performed to preliminarily evaluate the classification models and subgroups were compared by the log-rank test, and the most suitable model was chosen for further analyses. Multivariate analyses were performed using the Cox proportional hazards model to identify potential factors associated with second-line PFS, estimating hazard ratios (HRs) and 95% confidence intervals (95% CIs). Stratified analyses were performed to assess the difference between 2 groups of ABC patients. The software SPSS 19.0 and GraphPad Prism 9.3 were used for all analyses, and

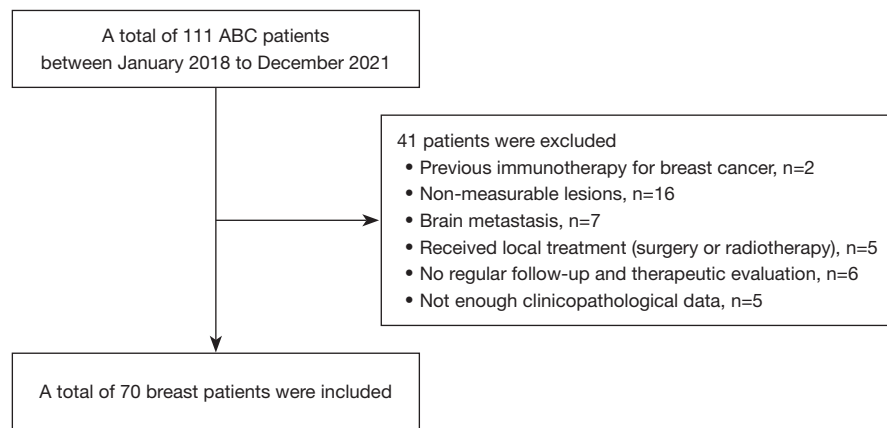


Figure 2 Patient enrollment flow diagram. ABC, advanced breast cancer.

2-tailed $P \leq 0.05$ was considered statistically significant.

Results

Clinicopathologic characteristics of participants

A total of 70 ABC patients were identified and finally enrolled in the study analyses (Figure 2). Table 1 showed the baseline clinicopathologic characteristics. There were 25 *de novo* metastatic BC patients, with 45 participants experiencing disease recurrence during the postoperative follow-up. There were 62.9% and 38.6% of overall participants were estrogen receptor-positive/progesterone receptor-positive and HER2-positive respectively. Seventy percent of patients received chemotherapy as first-line salvage treatment, and all HER2-positive ABC participants received anti-HER2 therapies (trastuzumab, pertuzumab or lapatinib).

Models analyses and patient subgroup definition

The mean follow-up time was 10.36 months and 94.3% of participants experienced PD during second-line therapy at the end of the follow-up. The second-line treatment was based on the respective clinician decision, and the median second-line PFS for the overall cohort was 7.10 (95% CI: 4.21–10.01) months. Ultimately, 3 testing models were proposed (details in Table 2). The survival curves of the 3 testing models were shown in the Figure 3, and the results indicated that Model C could further distinctly classify ABC patients with different PFS during second-line treatment. Therefore, based on Model C, we defined group 2 as the homogeneous progression-disease (Hom-PD) group (all the

target and non-target lesions were evaluated as PD based on RECIST 1.1, with or without new lesions), and group 1 as heterogeneous progression-disease (Heter-PD) group.

Among all participants, 54.3% ($n=38$) of ABC patients experienced Heter-PD after first-line treatment, while Hom-PD was observed among 32 participants (45.7%). Clinicopathologic characteristics between the Heter-PD and Hom-PD groups were compared and no significant difference was proven (Table 1). The median first-line PFS was similar between these 2 groups (7.96 *vs.* 7.50 months, $P=0.658$). The second-line PFS was significantly different between Heter-PD and Hom-PD groups (11.04 *vs.* 6.07 months, HR =0.604, 95% CI: 0.366–0.998, $P=0.49$, Figure 3C).

Identification of independent prognostic parameters

In the univariate and multivariate survival analyses evaluating the prognostic factors of second-line PFS (Table 3), the results indicated that the mode of disease progression was significantly associated with second-line PFS (HR =0.570, 95% CI: 0.338–0.960, $P=0.034$). Whereas, age, initial stage, hormone receptor status, and HER2 status did not significantly influence survival of ABC patients during the second-line treatment (Table 3, all $P>0.05$).

Among visceral metastases subgroup, ABC patients with Heter-PD experienced longer second-line PFS compared with Hom-PD ABC patients (9.50 *vs.* 4.28 months, $P=0.045$, Figure 4), and a similar tendency was observed in the bone/soft tissue metastases subgroup but no statistical significance was revealed (HR =0.508, 95% CI: 0.171–1.509, $P=0.223$) in the subgroup survival analyses. For ABC

Table 1 Characteristics of advanced breast cancer patients

| Characteristics | Overall (N=70) | Heterogeneous PD (N=38) | Homogeneous PD (N=32) | P value |
|---|----------------|-------------------------|-----------------------|---------|
| Age, years | 49.71±10.28 | 49.87±10.06 | 49.53±10.68 | 0.981 |
| Initial stage, n (%) | | | | 0.775 |
| Stage I-III | 45 (64.3) | 25 (65.8) | 20 (62.5) | |
| Stage IV | 25 (35.7) | 13 (34.2) | 12 (37.5) | |
| HR status, n (%) | | | | 0.580 |
| Negative | 26 (37.1) | 13 (34.2) | 13 (40.6) | |
| Positive | 44 (62.9) | 25 (65.8) | 19 (59.4) | |
| HER2 status, n (%) | | | | 0.866 |
| Negative | 43 (61.4) | 23 (60.5) | 20 (62.5) | |
| Positive | 27 (38.6) | 15 (39.5) | 12 (37.5) | |
| Metastatic sites, n (%) | | | | 0.834 |
| Visceral | 49 (70.0) | 27 (71.1) | 22 (68.8) | |
| Bone & soft tissue | 21 (30.0) | 11 (28.9) | 10 (31.2) | |
| First-line chemotherapy [#] , n (%) | | | | 0.567 |
| Taxane-containing regimens | 27 (54.0) | 17 (58.6) | 10 (47.6) | |
| Non taxane-containing regimens | 23 (46.0) | 12 (41.4) | 11 (52.4) | |
| First-line endocrine therapy [#] , n (%) | | | | 0.218 |
| AI | 17 (85.0) | 9 (100) | 8 (72.7) | |
| FUL | 3 (15.0) | 0 (0) | 3 (27.3) | |
| Partial drug retainment, n (%) | | | | 0.147 |
| Yes | 19 (27.1) | 13 (34.2) | 6 (18.7) | |
| No | 51 (72.9) | 25 (65.8) | 26 (81.3) | |
| DFS, months* | 48.73±36.96 | 49.96±37.89 | 47.18±36.68 | 0.247 |
| First-line PFS, months | 7.96±1.23 | 7.96±1.81 | 7.50±1.18 | 0.658 |

* , for the *de novo* advanced breast cancer patients, the DFS information were not collected; [#] , 50 patients received chemotherapy as first-line treatment and the remaining 20 patients received endocrine therapy. HR, hormone receptor; HER2, human epidermal growth factor receptor-2; AI, aromatase inhibitor; Ful, fulvestrant; DFS, disease-free survival; PFS, progression-free survival.

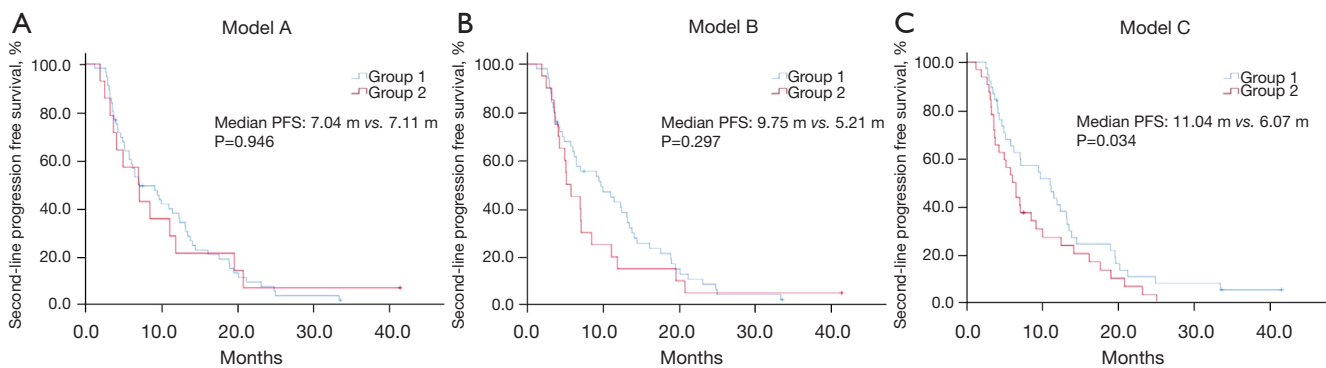
patients with negative hormone receptor, heterogeneous mode of disease progression was also associated with better second-line PFS (13.85 *vs.* 6.07 months, $P=0.001$, *Figure 4*). Furthermore, the length of first-line PFS could influence the survival outcome of the 2 groups. Among ABC patients who experienced shorter first-line PFS (<6 months), the Heter-PD group had superior second-line PFS compared with the Hom-PD group (11.14 *vs.* 3.78 months, $P=0.001$). In subgroup analyses based on the treatment regimens, the result showed that the second-line PFS of Heter-PD group was significantly longer than that of Hom-PD group in

chemotherapy subgroup (11.04 *vs.* 5.79 months, $P=0.043$). No statistical difference of second-line PFS between groups was found in the endocrine treatment groups (9.75 *vs.* 8.54 months, $P=0.764$).

Among the 70 enrolled ABC patients, 19 retained partial medication (all were trastuzumab among HER2-positive patients). Based on the therapeutic response during the first-line treatment, 13 participants were classified as the Heter-PD group and the other 6 participants were Hom-PD group. The survival analysis indicated that the Heter-PD group experienced better second-line PFS than the

Table 2 The subclassification models for advanced breast cancer patients experiencing disease progression after first-line treatment

| Models | Group 1 | Group 2 |
|---------|---|--|
| Model A | Only new lesion occurrence or non-target lesions progression | The other patients assessed as disease progression |
| Model B | Only new lesion occurrence, target and non-target lesions remain stable or response | The other patients assessed as disease progression |
| Model C | The other patients assessed as disease progression | All the target and non-target lesions assessed as disease progression, with or without new lesions |

**Figure 3** The Kaplan-Meier plot of second-line PFS in three subclassification models among ABC patients. The relevant subclassification criteria of Model A, B, and C are shown in *Table 2*. PFS, progression-free survival; ABC, advanced breast cancer.**Table 3** Hazard ratios of clinicopathologic variables on univariate and multivariate analyses for second-line PFS in enrolled advanced breast cancer patients

| Variables | Univariate analysis | | Multivariate analysis | |
|--|---------------------|---------|-----------------------|---------|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age at BC diagnosis (<45 vs. ≥45 years) | 1.022 (0.611–1.708) | 0.935 | 0.812 (0.446–1.479) | 0.497 |
| Initial stage (stage I–III vs. stage IV) | 1.133 (0.954–1.346) | 0.154 | 1.146 (0.956–1.373) | 0.141 |
| Hormone receptor status | 1.362 (0.819–2.267) | 0.234 | 1.239 (0.726–2.113) | 0.432 |
| HER2 status | 0.847 (0.516–1.390) | 0.511 | 0.732 (0.436–1.230) | 0.239 |
| First-line PFS | 0.980 (0.960–1.002) | 0.037 | 0.972 (0.949–0.996) | 0.020 |
| Heter-PD vs. Hom-PD | 0.604 (0.366–0.998) | 0.049 | 0.570 (0.338–0.960) | 0.034 |

HR, hazard ratio; CI, confidence interval; BC, breast cancer; HER2, human epidermal growth factor receptor-2; PFS, progression-free survival; Heter-PD, heterogeneous progression disease; Hom-PD, homogeneous progression disease.

Hom-PD group (13.18 vs. 3.61 months). Nevertheless, due to the limited number of participants, no statistical significance was verified ($P=0.430$).

Discussion

The RECIST 1.1 criteria is the common tool to monitor the treatment response in solid tumor. Oncologists maintain,

adjust or discontinue current treatment depending on the therapeutic assessment by RECIST criteria. At baseline, the total tumor burden is categorized as measurable or non-measurable lesions, and the former is further categorized as target lesions and non-target lesions. All target lesions are measured according to the long-axis diameter (LAD) of solid lesions and short-axis diameter (SAD) of lymph nodes. The status of PD is defined as unequivocal progression

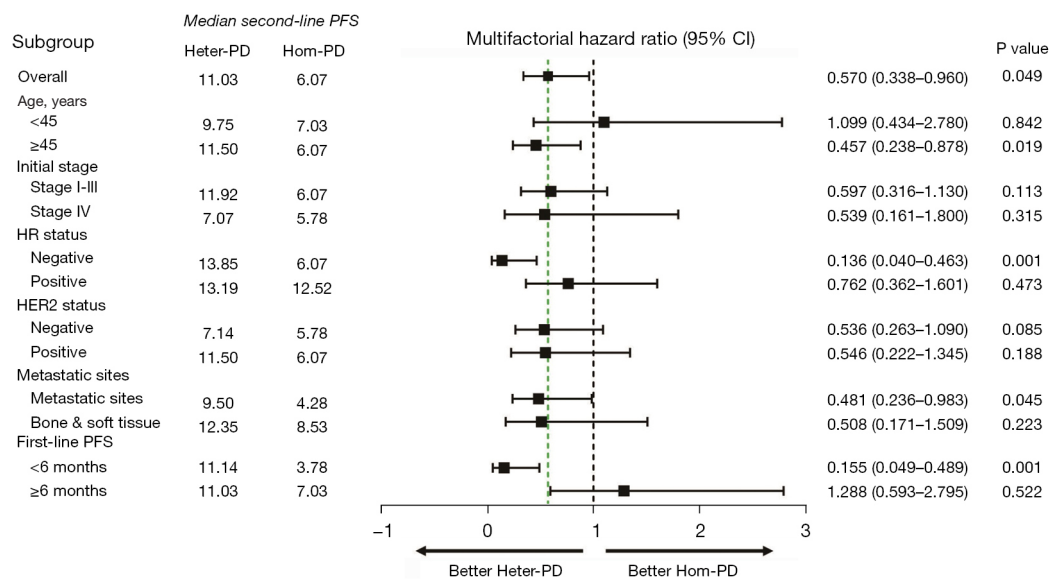


Figure 4 Univariate and multivariate analyses of second-line PFS with Cox proportional hazards in enrolled ABC patients. PFS, progression-free survival; ABC, advanced breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor-2.

of target lesions and/or existing non-target lesions and/or occurrence of new lesions. However, distinct treatment response might occur in various metastatic lesions due to the tumor heterogeneity.

Genetic instability is displayed by BC cells (deletion, amplification, point-mutations, and so on), leading to the high variability of cancer genomes and promoting genetic heterogeneity and different treatment response. Tumor heterogeneity is perhaps the primary cause of drug resistance and plays a significant role in treatment failure (9), which can be further classified as inter- and intra-tumor heterogeneity. The former represents the interindividual heterogeneity of tumors or differences between distinct lesions within the same patient, while the latter means cellular differences among individual lesions (10). Previous studies have indicated that tumor heterogeneity is produced by the interplay between the genome and epigenome/transcriptome (11,12).

The stochastic model proposed by Peter Nowell proposes that tumors arise from a single mutated cell and acquire mutations eternally (13). Genomic alterations are obtained via multiple mutational processes, producing spatial and temporal genetic diversity (14). Each mutation might produce specific subpopulation of tumor cells, possessing different capacities for proliferation, invasion, and migration. According to basic principles of Darwinian evolution, cellular clones with advantages would survive and

expand, while those with less favorable adaptations become extinct (10). Under ecosystem-selective pressure, cellular mutation could lead to convergent evolution or spatial segregation of clones in primary and metastatic sites (15). Based on this speculation, the therapeutic responses of different malignant lesions are probably diverse due to the tumor heterogeneity.

It is considered that selective therapeutic pressure could facilitate the emergence of new resistance mutations and change of tumor phenotype finally (16). In the present study, we retrospectively analyzed the treatment response of ABC patients after first-line treatment. Based on the clinical implication and the diameter alternation of each malignant lesion, we proposed 3 classification models to further classify ABC patients with different prognoses during second-line treatment. The results indicated that ABC patients experiencing PD of target and non-target lesions regardless of new lesions occurrence (Hom-PD group) had shorter second-line PFS than the Heter-PD group (11.04 vs. 6.07 months).

The heterogeneous nature of BC increases drug resistance of the tumor (17). Therapeutic regimens can target cancer cells, and the genetic alterations of cancer cells influence the therapeutic response of antineoplastic drugs (18). Furthermore, the tumor microenvironment is different among various metastatic lesions, and the interaction between different subclones of cancer cells and

stromal cells complicate the diversity of drug resistance (19). Inter-tumor heterogeneity means the differences between various tumor lesions of the same origin. Due to the existence of spatial heterogeneity, it is essential to monitor the evolution of malignant burden and modify antineoplastic treatment. These heterogeneous tumors manifest unique biological behaviors and molecular markers, causing variable drug resistance and clinical outcomes (20). Previous studies have indicated that genetic mutations, epigenetic modifications, and/or tumor microenvironment are the primary causes of intratumor heterogeneity (21-23).

For patients with heterogeneous PD, even the overall evaluation of the therapeutic response is disease progression, some tumor lesions are still under acceptable control with existing treatment, while other lesions manifest drug resistance. Conversely, homogeneous PD indicates the total resistance of medication among all lesions. The possible mechanism may be due to the potential tumor mutation burden or key genetic locus mutation, causing the improvement of tumor cell proliferation and drug resistant capacity. These 2 distinct disease progression modes may indicate a variety of mutation burden and genetic modification ability of cancer cells, being equal to the difficulty degree of anti-tumor treatment. However, further analyses, such next generation sequencing, are required to verify these hypotheses.

Clinically, visceral metastases are always correlated with higher tumor burden, reduced therapeutic response, and shorter survival (24). Tumor burden is a vital factor associated with the curability (25). In tumors that are highly sensitive to treatment, combining multiple drugs could permit sequential decreases in tumor burden until complete eradication (26). The Goldie–Coldman hypothesis incorporates tumor size and emergence of resistance (27). In our study, even the occurrence of heterogeneous disease progression was not associated with metastatic sites; Heter-PD patients experienced better second-line PFS than the Hom-PD patients (9.50 *vs.* 4.28 months, $P=0.045$) among visceral metastatic BC patients in the subgroup survival analysis. However, in the bone and soft tissue metastases subgroup, no difference in PFS was observed between Heter-PD group and Hom-PD group ($P=0.223$).

Despite the breakthrough of antineoplastic medication, no effective and specific treatment for heterogeneous tumors has yet been applied (7). The rapid development of inter-tumor heterogeneity causes difficulty in clinical tumor treatment (28,29). It is vital to measure the tumor

heterogeneity in clinical practice. The comparison of multiple, spatially separated breast tumor lesions, integrating genetic, epigenetic, transcriptomic, and proteomic analyses, could provide more information of tumor heterogeneity and refine patient treatment (30,31). Currently, next-generation sequencing (NGS) of tumor samples at diagnosis or at recurrence is frequently-used tool for evaluation of tumor heterogeneity. However, it cannot accurately evaluate tumor heterogeneity. Several strategies may be feasible to solve the problem of tumor heterogeneity. The first strategy is to target common pathway among different cancer cell clones (28). The second strategy is to inhibit the transition of cellular heterogeneity by interfering the cell shifting, such as inhibiting c-Met, the TGF-beta gene (32,33).

Our study has some limitations. Firstly, due to the single-institution retrospective characteristic, the overall sample size was relatively small, which may have influenced the accuracy and reliability of the statistical analyses. Secondly, inherent selection bias existed due to the retrospective design of the present study. Thirdly, salvage treatment regimens were not unified, which may influence the accuracy of relevant statistical analyses.

Conclusions

For ABC patients, the mode of disease progression after first-line treatment is an independent factor influencing the therapeutic response of sequential treatment. Patients with Heter-PD experienced better PFS than the Hom-PD subgroup, which might help clinicians to further classify specific patients and make more informed treatment decisions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1618/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1618/dss>

Conflicts of Interest: All authors have completed the

ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1618/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2020-349-01) and informed consent was taken from all the patients before inclusion.

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