

The Prognostic Impact of Determining Treatment Plans Based on Discordant Metastatic Tumor Receptors on Relapse

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Abstract

Background: For over 2 decades, breast cancer researchers have studied the clinical importance of testing the receptor status of metastatic tumors. Little evidence suggests that treatment plans based on metastatic tumor receptor status test results improve the clinical outcomes of patients. In fact, evidence exists that changes to treatment plans based on this retesting, when discordant, are harmful to patient outcomes.

Methods: A literature review evaluated the current state of evidence regarding treatment plans based on the retest results of metastatic tumors when different from the primary tumor. A retrospective observational study was designed to validate the literature findings. Data from the University of Tennessee Cancer Institute was queried for patients with recurrent metastatic breast cancer (MBC) from 2000 to 2014, yielding 124 complete and relevant recurrent MBC records. Of the 124 patients, 92 cases had the receptor status of their metastatic tumor evaluated. Fourteen patients' receptor status were discordant with their primary tumors. Eight of these patients' first-line treatment plans were based on the primary tumor receptor status, and 6 patients' first-line treatment plans were based on the receptor status of their metastatic tumors.

Results: The sample revealed that MBC patients with discordant receptor results, whose first-line treatment plan was based on their primary tumors, had additional median survival of 40 months, with a P value of .049 utilizing the log-rank test. No other published research has explicitly made such a comparison.

Conclusions: This study indicates that first-line treatment plans for patients with MBC based on the receptor status of the primary tumor instead of the metastatic tumor extends life expectancy of patients. This research could impact the lives of 6000 women with MBC per year in the United States.

Key Words: Breast cancer, metastatic, recurrence, discordance, receptor status, survival

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Introduction

In the recurrent metastatic breast cancer (MBC) setting, a growing consensus encourages retesting the receptor status of metastatic tumors. However, there is scant evidence to suggest that changing first-line treatment plans based on the status improves clinical outcomes. In fact, evidence exists that changes to first-line treatment plans can harm patient outcomes.¹⁻³ Decades of research surrounding this topic exists, yet the most important question has not yet been addressed:

When receptors are discordant, should first-line treatment plans rely on the receptor status of the primary tumor or on the receptor status of the metastatic tumor?

Approximately 6000 US women a year are diagnosed with discordant receptor results. These patients and their physicians must choose between disparate treatment plans indicated by the discordance.³ Currently, insufficient research-based evidence exists to inform guidelines for national and international standards when discordance occurs.

The purpose of this research was to determine the impact on patient outcomes in recurrent MBC diagnoses with discordant receptors when the first-line treatment plan was based on the receptor status of metastatic tumors instead of the receptor status of the primary tumors.

Methods

Overview

A thorough review of research published prior to November 2014 on MBC tumor retesting was performed. From that analysis, a hypothesis was formed: *In discordant cases, if the first-line treatment plan is based on the receptor status of the primary tumor, the median life expectancy of patients with MBC will be longer than those whose first-line treatment plan is based on the receptor status of the metastatic tumor.* We designed a retrospective observational study testing this hypothesis. This study queried the Tumor Registry at the University of Tennessee Cancer Center. All patients in the registry with recurrent MBC from January 1, 2000, to September 30, 2014, were considered. Proven endocrine and targeted therapies were available by 2000 for all patients in the

FIGURE 1. Study Decision Flow

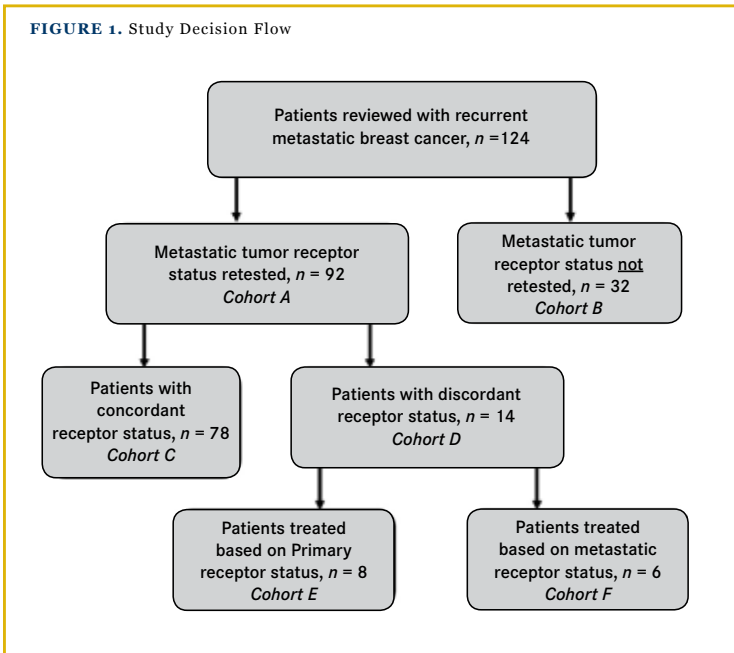
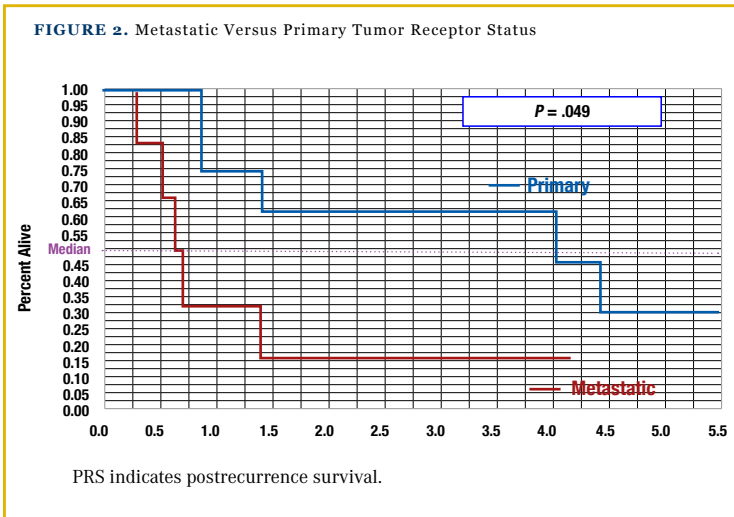


FIGURE 2. Metastatic Versus Primary Tumor Receptor Status



the primary or the metastatic tumor receptor status. These 2 groups are represented as cohorts E and F in **Figure 1**.

The study’s main objective was to compare the treatment plan impact of cohorts E and F. The literature review revealed multiple studies that compared cohorts C and D,^{1,2,5-14} and 1 study comparing groups A and B,⁶ as depicted in **Figure 1**. No research explicitly had a protocol to compare the survival rates of cohorts E and F.

The literature that evaluated the clinical impact of discordance did so by comparing the survival of patients with concordant versus discordant tumors (cohorts C and D). These studies revealed that cohort D patients are always, to some degree, confounded with cohort F. Our analysis is unique because this confounding effect is removed by specifically comparing the survival curves of groups E and F.

Patient Outcomes

In this study, patient outcomes were measured by: (1) 5-year postrecurrence survival (PRS) time curves, calculated as the time from metastatic recurrence to death or censoring, and (2) the first-line follow-up scan results using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) standard.¹⁵

Phenotypes and Discordance

The term “discordance” was strictly defined as a difference in the primary tumor receptor status (phenotype) and the metastatic tumor phenotype that warranted a change in treatment plan based on current National Comprehensive Cancer Network standards.¹⁶ The 4 phenotypes in this study were triple-negative breast cancer (TNBC), hormone receptor positive (HR+ and HER2-negative), HER2-positive (HER2/neu+ and HR-negative), and positive breast cancer (PBC) (**Table 1**). Dieci et al⁸ also used these 4 phenotypes in their research.

Data Parameters

Based on our protocol, we identified the variables necessary to conduct the research. Variable information was extracted from The University of Tennessee Cancer Center Tumor Registry and the electronic medical records and paper charts of the study’s patients. Patients having MBC with recurrences between January 1, 2000, and November 1, 2014, were reviewed. HER2 testing was not common until 2000.

study.⁴ Institutional Review Board permission was granted by the Graduate School of Medicine and the University of Tennessee.

Study Decision Flow

Figure 1 outlines the study protocol. This study screened patients with a recurrence of MBC and determined whether they needed receptor status retesting (cohorts A and B in **Figure 1**).

Retested patients were grouped by whether their primary and metastatic tumor receptor statuses were concordant or not (C and D). Discordant patients were further parsed by whether their first-line medical treatment plan was based on

Statistical Methods

Statistical methods were determined a priori. To compare the survival data of cohorts E and F, the log-rank test for Kaplan-Meier survival curves was used. Cox regression analysis was utilized for multivariate analyses. Chi-square analyses were completed on the RECIST v1.1 data. Univariate tests were reported on available covariates using t-tests and chi-square analysis. SAS JMP Pro version 10.0 was used for all analyses.

Results

Patient Characteristics

Of 317 patient records evaluated, 124 met the study protocols established and provided complete information. Many records included in the search were not recurrences of MBC and/or had extensive missing data.³ Out of 124 patients, 92 had tumor retesting, with 14 receptor status results discordant with their primary tumors. Eight patients had their first-line treatment plan based on their primary tumor receptor status and, 6 had the plan based on the tumor receptor status of their metastatic tumors. The sampling breakdown is shown in **Figure 1**.

Treatment Strategy Survival and First-Scan Results

Our study compared clinical outcomes of patients with MBC with discordant results on whether their first-line treatment plans were based on the primary or metastatic tumor receptor status. The results of this comparison showed that survival rates for patients whose first-line treatment plans were based on the receptor status of their primary tumors (n = 8) were better than patients whose plans were based on the metastatic tumor receptor status (n = 6; 48 vs 8.4 months, respectively; P = .049; **Figure 2**).

Our findings demonstrated that patients with recurrent MBC with treatment plans using the receptor status of their primary tumors had a median survival of 48 months versus 8 months for patients whose plans were based on the metastatic receptor status. This sample difference of a 40-month life expectancy was consistent with the results of Liedtke et al,¹ who evaluated the impact of discordance only.

Chi-square analysis based on the RECIST v1.1 standard was not statistically significant (P = .164). However, the results are consistent with our hypothesis, given that: (1) of the 5 patients who had progressive disease at the first re-scan, 4 were treated based on their metastatic tumor receptors; (2) 5 of the 7 patients with stable disease were treated based on their primary tumors; and (3) the only patient with a partial response was treated based on primary tumor receptor status.

TABLE 1. Receptor Phenotypes

Receptor Combination	Description	Phenotype
ER-, PR-, HER2-	TNBC	TNBC
ER+, PR+, HER2-	HR+	HR+
ER+, PR-, HER2-	ER+, PR-	HR+
ER-, PR+, HER2-	ER-, PR+	HR+
ER-, PR-, HER2+	HER2+, HR-	HER2+
ER+, PR+, HER2+	PBC	PBC
ER-, PR+, HER2+	HR+, HER2+	PBC
ER+, PR-, HER2+	HR+, HER2+	PBC

ER- indicates estrogen receptor–negative; ER+, estrogen receptor–positive; HER2+, HER2-positive; HR-, hormone receptor–negative; HR+, hormone receptor–positive; PBC, positive breast cancer; PR-, progesterone receptor–negative; PR+, progesterone receptor–positive; TNBC, triple-negative breast cancer.

Univariate Analysis

A 2-sample univariate analysis was performed on each available covariate for the 14 discordant patients. This tested whether statistically significant differences existed between patients with treatment plans based on their primary tumor receptor status and those with treatment plans based on the metastatic tumor (**Table 2**). Multivariate analyses of 124 patients yielded 6 statistically significant covariates.³ (see asterisks in **Table 2**). The fact that no univariate results were statistically significant was not unexpected, given the combined sample size of 14.

The visceral nature (location) of the metastatic disease did present some concerns in the univariate analysis. All patients with treatment plans based on their metastatic tumor receptor status had metastatic tumors rated as visceral, while only 4 of 8 patients with first-line treatment plans based on their primary tumor were rated visceral. Thus, visceral and metastatic treatment plans were statistically confounded. None of the 14 patients were deemed to be in visceral crisis at the time of metastatic diagnosis. Two evaluations were performed to assess the confounding impact: (1) Cox regression analysis on the 14 discordant patients and (2) Kaplan-Meier survival analysis on visceral patients only. Both tests compared the impact of first-line treatment plans on survival outcomes. Each analysis yielded results consistent with the overall findings of our study.³ The univariate and multivariate analyses provided evidence that the covariate confounding did not impact our study conclusions.

TABLE 2. Univariate Analysis

Variable	First-Line Treatment Based on Metastatic Tumor Receptors (n = 6)	First-Line Treatment Based on Primary Tumor Receptors (n = 8)	Statistical Significance (P value)
Age at time of recurrence, years	56.1	55.3	.890
Time to recurrence in days	1596.5	1390.9	.729
Primary tumor size*	35.8	27.0	.463
Number of positive lymph nodes at primary diagnosis*	7.0	8.0	.832
Age at initial diagnosis, years	51.7	51.5	.975
Primary tumor phenotype*	HER2+ (1), HR+ (2), PBC (3), TNBC (0)	HER2+ (1), HR+ (6), PBC (1), TNBC (0)	.450
Metastatic tumor phenotype	HER2+ (1), HR+ (1), PBC (0), TNBC (4)	HER2+ (0), HR+ (1), PBC (2), TNBC (5)	.723
AJCC Sample 17	S1 (0), S2 (3), S3 (3)	S1 (2), S2 (3), S3 (3)	.600
Location of recurrence*	Distant (6), Regional (0)	Distant (6), Regional (2)	.473
Visceral nature of recurrence	Nonvisceral (0), Visceral (6)	Nonvisceral (4), Visceral (4)	.085
Adjuvant hormone therapy	Yes (3), No (3)	Yes (4), No (3) Missing (1)	.999
Adjuvant chemotherapy*	Yes (5), No (1)	Yes (5), No (3)	.580
Adjuvant radiation	Yes (5), No (1)	Yes (5), No (3)	.580
Adjuvant trastuzumab*	Yes (4), No (2)	Yes (2), No (6)	.242

Statistically significant variable in one of various multivariate analyses.

AJCC indicates American Joint Committee on Cancer; HER2+, HER2-positive; HR+, hormone receptor positive; PBC, positive breast cancer; S1, Stage 1; S2, Stage 2; S3, Stage 3; TNBC, triple-negative breast cancer.

Discussion

Clinical practice guideline recommendations are provided by 3 standards organizations regarding treatment of metastatic patients with discordant tumor receptor status.^{16,18,19} Although each standard contains slight variations in verbiage and caveats, all suggest considering the metastatic tumor receptor status to assist in determining first-line treatment plans for recurrent MBC. No references to published research are provided to support the guidelines. Two standards clearly indicate that no data are available to support their recommendations. Both our analysis and literature review contradict these guidelines, instead advocating that MBC treatment decisions be based on the receptor status of the primary tumor.

Retesting Metastatic Tumors

The literature review consistently supported the importance

of retesting metastatic tumors for confirmation of diagnosis of MBC²⁰⁻²³ and to assess discordance between the receptor status of the primary and metastatic tumors.^{2,8,24-26} A recent meta-analysis by Aurilio et al²⁵ summarized 48 articles that involved 3000 to 4000 tumors. They found discordance rates of 20%, 33%, and 8% for estrogen receptor, progesterone receptor, and HER2, respectively.

Several authors, directly or indirectly, explored the impact that retesting tumor receptors had on first-line treatment plan determination, estimating the percentage of treatment plan decisions based upon the metastatic tumor status when it was discordant with the primary tumor. Five articles^{8,24,27-29} found that first-line treatment plan decisions were influenced 50% to 70% of the time by the existence of discordance, with the more recent studies trending to a higher percentage.

Clinical Outcomes of Discordance

Researchers investigated the clinical outcomes of patients with discordant receptors focusing on life expectancy without directly testing the effect of changing treatment plans based on discordance.^{7,9,10,12-14} Our careful analysis of several Discussion sections yielded evidence that changing treatment plans based on the metastatic tumor receptor status was more harmful than helpful.³ A strong illustration of this evidence is found in Liedtke et al,¹ where the inappropriate use of targeted therapies due to discordance was discussed as a potential cause of poor survival. The authors implied that patients with discordant receptor status were often treated contrary to what the primary tumor status would indicate and that this change likely contributed to poor life expectancy. The authors reported that the median PRS rate for patients with TNBC with concordant receptors was 43 months. Patients with TNBC (primary tumor) whose metastatic tumor receptors were discordant experienced a 15.6-month median PRS.¹ The complete evidence in the literature and a discussion of potentially contradictory data can be found in Pannell.³

The challenge of evaluating research on discordance, its impact on treatment decisions, and the subsequent effect on survival outcomes was that discordance and treatment plan determinations were confounded. This was highlighted in Turner and Di Leo's²³ literature review of the prognostic impact of discordance. Our study is the first designed to address this confounding and to estimate the impact that first-line treatment plan decisions have on the clinical outcomes.

Research Limitations

Our sample size is statistically small. Although several publications investigating discordance had small sample sizes,^{1,2,7,14} our study's requirement to further divide discordant cases impacts the statistical precision of our analysis. In retrospective observational studies, evaluating the potential effect of covariates is important. While our covariate analysis found no evidence for potential bias, it remains possible that unknown confounding effects exist.

Future Research

Future research should increase the sample size and breadth of this study, engaging additional researchers and cancer centers. Additionally, the exact causes of discordance have been speculated about but not definitively determined.²¹ The ultimate question of interest is: *Why would determining first-line treatment plans based on the primary tumor receptor status, as opposed to the metastatic tumor, result in better patient outcomes?* The only answer proposed in our literature review was by Liedtke et al,¹ who provided a discussion of the po-

tential impact of measurement error in testing metastatic tumor receptor status in patients with MBC. Foukakis et al²¹ further discussed measurement error; Sighoko et al³⁰ attempted to measure the impact of measurement error on discordance; and Heofnagel et al³¹ discussed the variation of receptor measurements between different metastases in the same patient.

Conclusions and Recommendations

The evidence in this research is consistent with our hypothesis. Ultimately, the study showed that patients with MBC who had discordant results and first-line treatment plans based on their primary tumors rather than their metastatic tumors had a longer median life expectancy of 40 months. This evidence is supported by: a thorough literature review of historical data, a log-rank test with a *P* value of .049, a covariate analysis, and a sensitivity analysis.³

Since 1989, the clinical impact of testing metastatic tumors for receptor status to inform first-line treatment plans has been studied.³² Prior to our research, no definitive conclusions regarding the impact of retesting receptor status on the clinical outcomes of patients with MBC had been drawn. Our research goal is to influence changes in international and national standards regarding determination of first-line treatment plans in discordant cases of MBC and to provide a higher level of evidence for those standards. Based on our research, we propose the following:

Where discordance between the primary and metastatic tumor receptor status would indicate different treatments, the status of the primary tumor should take precedence when developing the first-line treatment plan for a patient with newly diagnosed, recurrent metastatic breast cancer. Strong clinical evidence to the contrary must be present to warrant basing the treatment plan on the metastatic tumor receptor status.

Our recommendation is made with a suggested level of evidence of 2B.

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BRCA Mutations and Outcome in Epithelial Ovarian Cancer: Experience in Ethnically Diverse Groups

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Abstract

Variation in the worldwide prevalence of *BRCA1* and *BRCA2* mutations is well recognized. We analyzed *BRCA* mutation type variability in 585 *BRCA*-tested epithelial ovarian cancer patients from different ethnic populations. Of these patients, 98 (16.8%) were carriers of the *BRCA1* mutation, and 34 (5.8%) were carriers of *BRCA2*. Among the *BRCA1/2* carriers, there were 29 mutation types. The widest variation in mutation types was in non-Jewish Caucasians. Our analysis showed statistically improved overall survival and a tendency towards improved first progression-free survival across all *BRCA* mutation subtypes, compared to non-carriers.

Key words: *BRCA1* mutation, *BRCA2* mutation, epithelial ovarian cancer, mutation subtype, 185delAG, 5382insC, 6174del

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Variation in the worldwide prevalence of *BRCA1* and *BRCA2* mutations is well recognized.^{7,9} In the Ashkenazi Jewish (AJ) population, the *BRCA1/2* mutation spectrum is represented mainly by 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*.¹⁰ Other populations display a large variety of *BRCA* mutations, so that ethnicity-specific prevalences of *BRCA1/2* mutations are less clearly defined.

We previously described *BRCA* mutation type variability in a retrospective cohort comprising 190 stage IV *BRCA*-tested patients with EOC from New York City, Israel, and Italy diagnosed between 1995 and 2009.¹¹ The present paper is an update of that study; the analysis was extended to include 585 *BRCA*-tested patients with EOC from the same medical centers diagnosed between 1995 and 2014. The study objectives were to describe *BRCA* mutation type variability in different ethnic populations, and to compare progression-free survival (PFS) and overall survival (OS) among patients with nonhereditary EOC, *BRCA* mutation carriers, and subtypes of *BRCA* mutations.

Materials and Methods

We reviewed medical records of 1200 patients diagnosed with EOC between 1995 and 2014 at New York University (NYU) Cancer Institute, Tel Aviv Sourasky Medical Center (Israel), and Padova Clinical Cancer Centers (Italy). Patients with EOC or histologically confirmed extra-uterine Müllerian carcinoma (ovarian, tubal, and primary peritoneal) who were tested for *BRCA* mutation status were included in the analysis. Clinical data retrieved included institution, patient age at diagnosis, ethnicity, comorbidities, stage of disease, tumor histology, tumor grade, patient and family cancer history, *BRCA* mutation status, *BRCA* mutation type, prior surgical management, first-line chemotherapy, chemotherapy for recurrent disease, date of first relapse, platinum sensitivity, PFS, OS, and status at the most recent follow-up.

Statistical Methods

The characteristics of *BRCA* carriers were compared with those of the noncarriers (NCs). Progression-free survival

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological malignancies in the Western world.^{1,3} The strongest known risk factors are mutations in either the *BRCA1* or *BRCA2* gene, which account for approximately 10% of EOC cases.^{3,5}

BRCA1 and *BRCA2* are tumor suppressor genes involved in the regulation of cellular proliferation, chromosomal stability, and DNA repair by homologous recombination (HR).⁵ Cells that cannot repair DNA double-strand breaks due to deficiencies in the HR pathway are more susceptible to malignant transformation.⁵ Homologous recombination-deficient cells also cannot repair DNA damage induced by platinum adducts; therefore, they are particularly platinum-sensitive.⁶

BRCA mutation carriers represent a unique group of patients who are commonly diagnosed at a younger age, have improved sensitivity to platinum-based chemotherapy, and have an overall improved prognosis.^{4,6}