

Discordance in Biomarker Expression in Breast Cancer After Metastasis: Single Center Experience in India

Ajay Gogia, MD, DM¹; S. V. Suryanarayana Deo, MS¹; Dayanand Sharma, MD¹; Rakesh K. Phulia, MD, PhD¹; Sanjay Thulkar, MD¹; Prabhat S. Malik, MD, DM¹; and Sandeep Mathur, MD¹

PURPOSE Biomarker—estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/*neu*)—discordance plays an essential role in the management and prognosis of patients with metastatic breast cancer. Rates of discordance have been previously reported around 12% to 35%, 30% to 50%, and 5% to 15%, respectively, in Western literature. Data are sparse regarding the same from developing countries, such as India.

METHODS We performed an ambispective review of paired biomarker status in patients with breast cancer—stage I, II, and III as per American Joint Committee on Cancer, 7th edition—who developed metastasis at recurrence (N = 103 patients). Biomarker status and clinical and radiologic parameters were documented at baseline and subsequent follow-up.

RESULTS Discordance was present in 21.3% for ER, 29.1% for PR, and 15.5% for HER2/*neu* receptor. In our cohort, 7.8% had positive to negative ER and 13.6% negative to positive. Whereas 21.4% had positive to negative PR, 7.8% had negative to positive PR. Approximately 6.8% had positive to negative HER2/*neu* receptor and 8.7% negative to positive. In our cohort, 41 patients (40%) had single-site metastasis—bone, 15.5%; lung, 11.7%; nonregional lymph node, 7.8%; liver, 3.9%; and brain, 0.97%. More than one site of metastasis was present in 62 patients (60%). The most common sites of metastasis were visceral—lung and liver—followed by bone, nonregional lymph node, skin, and brain.

CONCLUSION The current study demonstrated that metastatic disease evolution in breast cancer is characterized by change in the tumor biology, which leads to discordance in receptor status. Repeat biomarker studies at metastatic recurrence is warranted, especially if treatment plans include hormone and targeted therapy.

J Global Oncol. © 2019 by American Society of Clinical Oncology

Licensed under the Creative Commons Attribution 4.0 License 

INTRODUCTION

Breast cancer represents the most common cancer in Indian women, with an age-adjusted rate of 25.8 cases per 100,000 women and a mortality rate of 12.7 per 100,000 women.¹ Incidence of metastatic breast cancer (MBC) has been reported to be approximately 5% to 25% from various centers in India.² In a previous study from our center, we found that 26.5% of patients were diagnosed with MBC on initial presentation and 22% developed metastasis at recurrence.³ In India, most patients with MBC receive treatment at tertiary care centers because of a lack of services at primary and secondary centers. MBC treatment depends on patients' hormone and human epidermal growth factor receptor 2 (HER2/*neu*) status. Receptor discordance between primary and recurrent breast cancer in estrogen receptor (ER), progesterone receptor (PR), and HER2/*neu* has been documented to be approximately 12% to 35%, 30% to 50%, and 5% to 15%,

respectively, in Western literature, but data from developing countries is limited.⁴⁻⁹ The 4th European School of Oncology–European Society of Medical Oncology (ESO–ESMO) international consensus guidelines for advanced breast cancer recommend repeat biopsy and documentation of any discordance in receptor status at metastasis, but this is yet to find a place in the national Indian Council of Medical Research guidelines.^{10,11}

Change in receptor status as an aid to decide additional management and prognosis in MBC must be tested in a randomized controlled trial. From the Indian perspective—where the impact of the disease is high and patients present with advanced stage disease with increasing incidence—an epidemic of breast cancer in the near future may result.¹² In such a situation, the best use of health care resources—with newer therapies and a multidisciplinary treatment approach—serves as an indispensable tool for the

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 12, 2019 and published at ascopubs.org/journal/jgo on April 5, 2019; DOI <https://doi.org/10.1200/JGO.18.00184>

evidence-based management of MBC. Outside the context of public health care, Indian medical oncologists also need to address individual patient priorities and their rights for current standard management. With the background of the above facts and the lack of recommendations in Indian management guidelines, we designed an ambispective cohort study to compare hormone receptors—ER and PR—and HER2/*neu* receptor at baseline and first metastasis. To our knowledge, this is the first work to document receptor status change in patients from India.

METHODS

We designed an ambispective study with the aim of documenting discordance in biomarker (ER, PR, and HER2/*neu*) status in patients with breast cancer (stage I, II, and III per American Joint Committee on Cancer, 7th edition) who develop metastasis on follow-up and the resultant change in therapy. When patients develop metastasis, there may be only distant metastasis or distant metastasis with locoregional recurrence. In the current study, we documented biomarker status at baseline from primary breast lesion and at first metastasis from the locoregional or metastatic site (Table 1). This study was conducted at All India Institute of Medical Science (New Delhi, India). We reviewed the records of our patients who developed metastasis between January 2013 and August 2018, recruiting them in a prospective (n = 65 patients) and retrospective manner (n = 38 patients). Ethical clearance was provided by the institute ethics committee (reference No. IECPG-539/26.10.2016), and informed consent was obtained from patients who were recruited prospectively. During the study period, 205 patients with breast cancer developed metastasis at recurrence. Of these patients, 103 were considered for analysis. Approximately 102 patients were excluded as a result of various reasons as given in Figure 1. Patients who had bone-only metastasis without any locoregional recurrence, impending organ failure (visceral crisis), and poor performance status were not subjected to rebiopsy. Patients who were diagnosed with recurrence using fine-needle aspiration cytology, fluid cytology, and incomplete clinical and pathologic details were not included in this study (Fig 1). However, patients with bone-only metastasis and locoregional recurrence were included in our study. A

tissue for biomarker analysis was obtained using Tru-cut biopsy or surgical resection at recurrence from various sites as given in Table 1.

Pathology: Immunohistochemistry and Fluorescence In Situ Hybridization

Hormone and HER2/*neu* were documented using the standard immunohistochemistry method and results were interpreted by two pathologists. Allred scoring was used for reporting ER/PR receptor status, and we recorded the percentage of cells showing ER positivity and intensity. A score of 3+ was considered positive.¹³ HER2/*neu* receptor was documented per the ASCO/College of American Pathologists guidelines.¹⁴ A score of 3+ was considered positive and 2+ was considered equivocal. All 2+ results of HER2/*neu* were confirmed using the fluorescence in situ hybridization method per standard ASCO/College of American Pathologists guidelines.¹⁴ Histologic type was assessed according to the WHO standard.

Treatment Protocol

Our institute protocol of combination chemotherapy for primary tumor management is anthracycline–taxane or taxane–platinum-based chemotherapy—four-cycle fluorouracil 600 mg/m² plus epirubicin 75 mg/m² plus cyclophosphamide 600 mg/m² followed by four-cycle docetaxel 85 mg/m² (or docetaxel 75 mg/m² + carboplatin area under the curve 6). Those patients who underwent modified radical mastectomy received adjuvant radiotherapy 50 Gy/25 fractions over 5 weeks when indicated. Those who underwent breast-conserving surgery received adjuvant radiotherapy 50 Gy/25 fractions with 16-in-8 fraction boost over 2 weeks. Endocrine therapy (ET), 10 years tamoxifen, or 5 years aromatase inhibitor was administered to hormone receptor (HR) –positive patients and 1 year of trastuzumab for HER2/*neu*-positive patients. Institute protocol for MBC management is a single agent or combination chemotherapy, ET, cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, and targeted therapy based on receptor status.

Statistical Analysis

Data documented from hospital records included age, sex, menopausal status, side, histology, biomarker status (ER, PR, and HER2/*neu*), stage, and site of metastasis. Nominal data presented as number and percentage and continuous data presented as medians and range. Data were analyzed using STATA software (version 13; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

RESULTS

Patient Characteristics

Clinical and pathologic characteristics at baseline are listed in Table 2. Median age of presentation was 47 years (range, 26 to 72 years). The most common histology was infiltrating ductal carcinoma. The majority of patients presented with locally advanced disease (stage I, 6.8%; stage II, 32%; and

TABLE 1. Various Sites of Repeat Biopsy at Recurrence

Site of Repeat Biopsy	No. (%)
Breast lump and chest wall lesion	43 (41.8)
Lung	9 (8.7)
Liver	25 (24.3)
Lymph node	16 (15.5)
Ovary	1 (0.97)
Brain	1 (0.97)
Others	5 (4.8)
Missing data	3 (2.9)

TABLE 2. Baseline Characteristics and Therapy Received for Primary Tumor (N = 103)

Characteristic and Therapy	Value
Median age, years (range)	47 (26-72)
Sex	
Male	2 (1.9)
Female	101 (98.1)
Menopausal status	
Premenopausal female	42 (41.6)
Postmenopausal female	59 (58.4)
Side	
Right	48 (46.6)
Left	55 (53.4)
Histology	
IDC	98 (95.1)
ILC	5 (4.9)
Stage at baseline (per AJCC 7th edition)	
I	7 (6.8)
II	33 (32)
III	63 (61.2)
Receptor status	
HR positive	31 (30.1)
HR and HER2/ <i>neu</i> positive	19 (18.4)
HER2/ <i>neu</i> positive	24 (23.3)
TNBC	29 (28.2)
Site of metastasis	
Bone only (with locoregional recurrence)	16 (17.4)
Lung/pleura only	12 (12.6)
Nonregional lymph node only	8 (7.8)
Liver only	4 (3.9)
Brain only	1 (0.97)
Mixed	62 (60)
Surgery	
MRM	85 (82.5)
BCS	18 (17.5)
Chemotherapy	
Taxane–anthracycline	81 (78.64)
Taxane–carboplatin	5 (4.85)
Others	7 (6.8)
No adjuvant chemotherapy	10 (9.7)
Other therapy	
Radiotherapy at locoregional site	65 (63.1)
Endocrine therapy (n = 50 HR-positive patients)	47 (94)

(Continued in next column)

TABLE 2. Baseline Characteristics and Therapy Received for Primary Tumor (N = 103) (Continued)

Characteristic and Therapy	Value
Trastuzumab (n = 43 HER2/ <i>neu</i> -positive patients)	16 (37.2)

NOTE. Data are given as No. (%), unless otherwise noted.

Abbreviations: AJCC American Joint Committee on Cancer; BCS, breast-conserving surgery; ER, estrogen receptor; HER2/*neu*, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MRM, modified radical mastectomy; PR, progesterone receptor; TNBC, triple-negative breast cancer.

stage III, 61.2%; on the basis of American Joint Committee on Cancer, 7th edition).

In our cohort, 41 patients (40%) had single-site metastasis, including bone (16 patients; 15.5%), lung (12 patients; 11.7%), nonregional lymph node (eight patients; 7.8%), liver (four patients; 3.9%), and brain (one patient; 0.97%). More than one site of metastasis was present in 62 patients (60%; Table 2). The most common sites of metastasis were visceral (lung and liver) followed by bone, nonregional lymph node, skin, and brain. Baseline biomarker status demonstrated that 31 patients (30.1%) were HR positive, 19 (18.4%) were both HR and HER2/*neu* receptor positive, 24 (23.3%) were HER2/*neu* receptor only positive, and 29 (28.2%) were triple-negative breast cancer as listed in Table 2. For primary tumor management, approximately 85 patients (82.5%) underwent modified radical mastectomy, 18 patients (17.5%) underwent breast-conserving surgery, 81 patients (78.64%) received taxane–anthracycline-based chemotherapy, 47 patients (94% HR positive and 45.6% of the whole cohort) received ET, and 16 patients (37.2% HER2/*neu* positive and 15.5% of the whole cohort) received trastuzumab. Approximately 65 patients (63.1%) received radiotherapy (Table 2).

Discordance in Biomarkers at the Time of Metastasis

In our cohort of 103 patients, discordance was present in 22 (21.3%) for ER, 30 (29.1%) for PR, and 16 (15.5%) for HER2/*neu* receptor status. Approximately eight patients (7.8%) had positive to negative ER status transition and 14 (13.6%) negative to positive. Whereas 22 patients (21.4%) had positive to negative PR status, eight patients (7.8%) had negative to positive PR status. Overall, nine patients (9.2%) had positive to negative HR (ER or PR or both) and 12 negative to positive. Approximately seven patients (6.8%) had positive to negative HER2/*neu* receptor status and nine (8.7%) negative to positive (Table 3).

Therapeutic Impact of Discordance in Receptor Status

Per the 4th ESO–ESMO international consensus guidelines for advanced breast cancer, all patients who were receptor positive at least once at baseline or at metastasis should be administered ET or targeted therapy according to receptor status.¹⁰ Considering the above guidelines, 62 patients

TABLE 3. Discordance in Biomarkers Between Primary Tumor and at Metastasis (N = 103)

Type of Receptor	Change in Receptor Status at Metastasis			
	Positive to Negative	Negative to Positive	No Change: Status Remained Positive	No Change: Status Remained Negative
ER	8 (7.8)	14 (13.6)	39 (37.9)	42 (40.8)
PR	22 (21.4)	8 (7.8)	12 (37.5)	52 (50.5)
HR	9 (8.7)	12 (11.7)	41 (39.8)	41 (39.8)
HER2/ <i>neu</i>	7(6.8)	9 (8.7)	36 (34.9)	51 (49.5)

NOTE. Data are given as No. (%).

Abbreviations: ER, estrogen receptor, HER2/*neu*, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor.

were eligible for ET and 51 patients were eligible for targeted therapy. Among eligible patients, 41 patients (66.1%) received ET and 24 (47%) received targeted therapy (Table 4). Of 12 patients who were negative to positive for HR, nine received ET, and of nine patients who were positive to negative for HR, three received ET. Of nine patients who were negative to positive for HER2/*neu*, three received targeted therapy, and of seven patients who were positive to negative for HER2/*neu*, three received targeted agent. In conclusion, of 21 patients who had receptor gain (HR, n = 12; HER2/*neu*, n = 9), we could modify treatment

in 12 patients (ET, n = 9; targeted therapy, n = 3), per new receptor status.

DISCUSSION

MBC is a heterogeneous disease and most patients present with advanced stage disease in India. There are multiple mechanisms proposed for the discordance in biomarkers: a switch in the biology of the disease; sampling error in focally receptor-positive cancers; limited reproducibility of receptor assays; heterogeneous tumors with different clinical characteristics, disease course, and responses to specific treatment; and previous treatment that may change in receptor status.¹⁵⁻¹⁹ A systematic approach for the management of MBC is essential to improve patient outcomes and prognoses. Data from previous Western studies suggest that the discordance of ER, PR, and HER2/*neu* between primary and metastatic disease may be clinically relevant. There is no such study published from India. We designed an ambispective study with the intent of documenting change in biomarker status from baseline to first metastasis and to observe subsequent change in therapy. A summary of our study and various previous studies from Western countries is documented in Table 5. Precise comparison of our present study with previous studies is difficult because all parameters were not reported in other studies. In this study, an effort was made to evaluate trends in HR change at metastasis for patients who present with breast cancer in India.

We found that the discordance was most common in PR, followed by ER and HER2/*neu* receptor. Results showed a similar trend, but in relatively different proportions from that documented in previous studies. We observed that the median age of presentation was 47 years, which is 5 to 10 years less when compared with other studies, with the exception of the study by Sari et al. Most of our patients presented in advanced stage: 61.2% of patients presented in stage III, whereas only 32% were stage II, and 6.8% were stage I. Of patients, 40% had single organ involvement, whereas the remaining 60% had multiorgan involvement. This indicates that disease burden is substantially higher in patients at the time of metastasis. Compared with other studies, the proportion of HR-positive breast cancer

TABLE 4. Details of Therapy Received After Metastasis

Therapy Received at Metastasis	No. (%)
Chemotherapy (N = 103)	
Single-agent taxane	35 (34)
Gemcitabine–carboplatin	18 (17.5)
Vinorelbine–capecitabine	6 (5.8)
Single-agent capecitabine	6 (5.8)
Taxane–carboplatin	2 (1.9)
Other	9 (8.7)
No chemotherapy	27 (26.2)
Endocrine therapy (n = 62 patients were eligible for endocrine therapy)	
Aromatase inhibitor	23 (37.1)
Fulvestrant	9 (14.5)
Tamoxifen	6 (9.7)
Palbociclib–fulvestrant	3 (4.8)
No endocrine therapy	21 (33.9)
Targeted therapy received (n = 51 patients were eligible for targeted therapy)	
Trastuzumab	14 (27.5)
Trastuzumab + pertuzumab	6 (11.7)
Lapatinib	2 (3.9)
TDM1	2 (3.9)
No targeted therapy	27 (53)

Abbreviation: TDM1, trastuzumab emtansine.

TABLE 5. Comparison With Other Studies

Variable	Present Study	Dieci et al ⁴	De Dueñas et al ⁵	Sari et al ⁶	Lindström et al ⁷	Hoeftnagel et al ⁸	Amir et al ⁹
No. of patients	103	119	196	75	439	233	119
Median age, years (range)	47 (26-72)	51 (26-87)	57 (30-92)	44.5 (21-76)	NR	53.9 (25-93)	61 (28-87)
Premenopausal	41.6	57.7	31	57.7	NR	NR	NR
Postmenopausal	58.4	37.2	69	47.2			
Baseline stage					NR	NR	NR
I	6.8	19.3	16	7.7			
II	32	34.5	50	28.2			
III	61.2	18.5	22	41.1			
IV	—	—	12	7.7			
Others	—	27.5	—	15.4			
Histology			NR	NR	NR		NR
IDC	95.1	77.3				82.4	
ILC	4.9	16				8.6	
Other	—	6.7				9	
Site of recurrence		NR		NR	NR		NR
Bone	17.4		18			18.5	
Liver	3.9		23			27	
Lung	12.6		9			18.5	
Brain	0.9		—			18.9	
Nonregional LN	7.8		—			—	
Skin/soft tissue	—		22			32.6	
Locoregional	—		19			—	
Other	60 (> 1 site metastasis)		10			3	
Receptor status							
ER positive	45.7	79	—	62.8	71.6	74.7	—
PR positive	58.9	61	—	62.8	58.4	74.2	—
HR positive	48.5	—	53	—	—	—	71
HER2/neu positive	41.7	17.7	27	25.6	27.9	20.2	11.7
Primary therapy	90.3	73	81	NR	NR	NR	NR

(Continued on following page)

TABLE 5. Comparison With Other Studies (Continued)

Variable	Present Study	Dieci et al ⁴	De Dueñas et al ⁵	Sari et al ⁶	Lindström et al ⁷	Hoefmager et al ⁸	Amir et al ⁹
Receptor change							
ER	21.3	13.4	21	36	32.4	15.1	12.6
PR	29.1	39	35	54.2	40.7	32.6	31.2
HER2	15.5	11	16	14.7	14.5	5.2	5.5

NOTE. Data are given as No. (%), unless otherwise noted.

Abbreviations: ER, estrogen receptor; HER2/*neu*, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LN, lymph node; NR, not reported; PR, progesterone receptor.

(48.5%) is lower, whereas the proportion of HER2/*neu*-positive breast cancer is higher in this study (41.7%). This helps to explain why the discordance in HR status (at metastasis) is relatively less and discordance in HER2/*neu* receptor status is relatively greater in our cohort. In a study by De Dueñas et al,⁵ different results were reported in central and local laboratories. Receptor changes recorded were higher at the local level compared with the central laboratory (change in HER2/*neu*, 16% v3%; change in ER, 21% v13%; and change in PR, 35% v28%, respectively). This highlights the importance of a standardized technique for assay and reporting of receptor status. In another study by Lindström et al,⁷ receptor change was reported at multiple relapses. This indicates that breast cancer is a heterogeneous disease, and metastatic disease evolution is associated with a change in receptor level after each progression. Receptor loss is associated with decreased survival as documented by Dieci et al, whereas Amir et al documented no difference in survival.^{4,9} The impact of receptor discordance on survival still is not conclusive and prospective studies are required to answer this question. Hoefnagel et al⁸ reported that the most common discordance is associated with PR, as documented in other studies. We found that all published studies had noted the importance of receptor status documentation at metastasis, despite varying results.

Documentation of change in receptor status at disease progression may help to improve disease management and patient care. In the current study, many of our patients did not receive targeted therapy and CDK4/6 inhibitor as a result of financial constraints. In patients with HER2/*neu*-positive disease, only 37.2% received trastuzumab for primary therapy, whereas 47% patients received targeted therapy for metastasis. Approximately 14.5% and 4.8% of HR-positive patients received fulvestrant and CDK4/6 inhibitor, respectively. This indicates that many of our patients were not able to afford costly newer therapies for the treatment MBC; however, there are many upcoming patient assistance programs from the government of India and many nongovernment organizations. For instance, the prime minister relief fund for patients with cancer, Ayushman Bharat scheme, free-of-charge medication for patients below the poverty line, and free-of-charge necessary chemotherapy medicine and hormonal agents (tamoxifen and anastrozole) for patients visiting government hospitals of India, such as All India Institute of Medical Science.^{20,21} With the help of these assistance programs and a decrease in the cost of trastuzumab compared with the price 5 years ago, we expect that these proportions will improve in the near future. The current international guideline for the treatment of advanced breast cancer recommends rebiopsy in advanced breast cancer at first

metastasis, but existing Indian Council of Medical Research guidelines 2016 do not mention the importance of repeat biopsy.^{10,11} The present study may serve to inform and fill the lack of an existing national guideline. We do not suggest reallocating health care resources for costly newer therapy in patients with MBC, but to rationalize the use of the best available therapeutic options.

The strength of our study is its ambispective design coupled with the receptor status documentation on the initial visit and with metastasis. We have linked HER2/*neu* 2+ status with fluorescence in situ hybridization analysis. A relative weakness of our study is the collection of data for few of the cohort patients in a retrospective manner. This study is not powered for survival analysis, and a large prospective multicenter study is required to answer this question. The current study may serve to challenge many centers in India, where routine rebiopsy is not performed at patient presentation with metastatic recurrence.

To our knowledge, this is the first study from a developing country to report receptor status change in MBC; however, this study does not address whether to withdraw ET or targeted therapy after the loss of receptor status. As a result of tumor heterogeneity, the biopsy sample may not show receptor positivity at one site, but other sites may be positive. Therapy withdrawal may deprive the patient of the benefit of targeted agents. Fluoroestradiol positron emission tomography/computed tomography may address this question of assessing receptor status in all metastatic sites in the near future. Therapy withdrawal may deprive the patient of the benefit of ET and targeted therapy. From the 4th ESO–ESMO international consensus guidelines for advanced breast cancer, “If the results of tumor biology in the metastatic lesion differ from the primary tumor, it is currently unknown which result should be used for treatment decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (endocrine therapy and/or anti HER2 therapy) when receptors are positive in at least one biopsy, regardless of timing.”^{10(p4)} We followed the same principle and offered appropriate therapy for eligible patients; however, as stated, only approximately one half of patients received targeted agents, and 4.8% patients received CDK4/8 inhibitor.

In light of the above findings, we recommend that patients with newly diagnosed metastatic disease undergo repeat biopsy, which will not only help to confirm the diagnosis of recurrence but also will also allow for a re-examination of receptor status. However, we acknowledge that there is an unmet need for prospective studies from developing countries verifying receptor status in new metastases and the resultant changes in survival.

AFFILIATION

¹All India Institute of Medical Science, New Delhi, India

Institute ethical committee provided clearance (reference No. IECPG-539/26.10.2016) and study consent was obtained from patients recruited prospectively.

CORRESPONDING AUTHOR

Ajay Gogia, MD, DM, All India Institute of Medical Science, Ansari Nagar, New Delhi, 110029; e-mail: ajaygogia@gmail.com.

PRIOR PRESENTATION

Presented at the 2018 American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 4, 2018.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Administrative support: Prabhat S. Malik

Provision of study materials or patients: S. V. Suryanarayana Deo

Collection and assembly of data: Ajay Gogia, Dayanand Sharma, Sandeep Mathur

Data analysis and interpretation: Ajay Gogia, Dayanand Sharma

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated.

Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Prabhat S. Malik

Research Funding: Bristol-Myers Squibb

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors thank the patients who participated in the study as well as the departments of medical oncology, pathology, radio-diagnosis, and nuclear medicine for their support. This work was submitted as part of a dissertation by Manish Sharma, MD, now deceased.

REFERENCES

- Malvia S, Bagadi SA, Dubey US, et al: Epidemiology of breast cancer in Indian women. *Asia Pac J Clin Oncol* 13:289-295, 2017
- Gogia A, Raina V, Deo SVS, et al: Triple-negative breast cancer: An institutional analysis. *Indian J Cancer* 51:163-166, 2014
- Sharma M, Gogia A, Deo SVS, et al: Profile of metastatic breast carcinoma: Single center experience from a developing country. *J Clin Oncol* 36:15s, 2018 (suppl; abstr e13102)
- Dieci MV, Barbieri E, Piacentini F, et al: Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: A single-institution analysis. *Ann Oncol* 24:101-108, 2013
- de Dueñas EM, Hernández AL, Zotano AG, et al: Prospective evaluation of the conversion rate in the receptor status between primary breast cancer and metastasis: Results from the GEICAM 2009-03 ConVerHER study. *Breast Cancer Res Treat* 143:507-515, 2014
- Sari E, Guler G, Hayran M, et al: Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. *Med Oncol* 28:57-63, 2011
- Lindström LS, Karlsson E, Wilking UM, et al: Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. *J Clin Oncol* 30:2601-2608, 2012
- Hoefnagel LD, van de Vijver MJ, van Slooten H-J, et al: Receptor conversion in distant breast cancer metastases. *Br Canc Res* 12:R75, 2010 <http://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr2645>
- 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* 38:708-714, 2012
- Cardoso F, Senkus E, Costa A, et al: 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol* 29:1634-1657, 2018
- India Against Cancer: ICMR consensus documents for cancer management. <http://cancerindia.org/in/icmr-consensus-documents-for-cancer-management/>
- Shetty P: India faces growing breast cancer epidemic. *Lancet* 379:992-993, 2012
- Harvey JM, Clark GM, Osborne CK, et al: Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 17:1474-1481, 1999
- Wolff AC, Hammond MEH, Allison KH, et al: Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update. *J Clin Oncol* 36:2105-2122, 2018
- Pusztai L, Viale G, Kelly CM, et al: Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. *Oncologist* 15:1164-1168, 2010
- Bertos NR, Park M: Breast cancer: One term, many entities? *J Clin Invest* 121:3789-3796, 2011
- Wu JM, Fackler MJ, Halushka MK, et al: Heterogeneity of breast cancer metastases: Comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. *Clin Cancer Res* 14:1938-1946, 2008
- Pectasides D, Gaglia A, Arapantoni-Dadioti P, et al: HER-2/neu status of primary breast cancer and corresponding metastatic sites in patients with advanced breast cancer treated with trastuzumab-based therapy. *Anticancer Res* 26:647-653, 2006
- Mittendorf EA, Wu Y, Scaltriti M, et al: Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. *Clin Cancer Res* 15:7381-7388, 2009
- India Against Cancer: Financial aid and resources. <http://cancerindia.org/in/financial-aid-and-resources/>
- National Portal of India: Ayushman Bharat—National Health Protection Mission. <https://www.india.gov.in/spotlight/ayushman-bharat-national-health-protection-mission>

