

Study of the Discordance of the HR / HER2 Status between Primary Tumor and Metastases of Breast Cancer Conducted at the Aerospace Medical Center of Rabat and Comparison with Literature Data

Fahd Bennani Smires*, Houda Echchachoui, Zakaria Iloughman, Mouna Elghazi, Meryem Zerrik, Mohamed Chemsia
Aeromedical center of the Military Hospital Mohamed 5, Rabat, Morocco

*Corresponding author: Fahd Bennani Smires | Received: 24.11.2018 | Accepted: 05.12.2018 | Published: 10.01.2019

DOI: [10.21276/sijog.2019.2.1.1](https://doi.org/10.21276/sijog.2019.2.1.1)

Abstract

Therapeutic modalities for metastatic breast cancer have not stopped progressing in recent years, in particular hormone therapy targeting hormonal receptors (HR), and targeted therapies targeting Human Epidermal Growth Factor Receptor-2 (HER2), which allowed to improve the overall survival of patients over expressing these receptors, however, the high risk of metastatic relapse makes the prognosis remain impaired. Among the causes of these relapses, the phenotypic instability, which would be at the origin of expression change of the HR and HER 2 on the surface of tumor cells. This discordance of phenotypic expression between the primary tumor and the metastatic relapse leads to an assessment of therapeutic modalities initially undertaken? Through this work, we will compare our study about 17 female flight crew with metastatic breast cancer, conducted at the aerospace medical center of the military hospital Mohamed 5 of Rabat, with literature data.

Keywords: Breast cancer, Metastatic relapse, Discordance, Human Epidermal Growth Factor Receptor-2 (HER2), Hormonal receptors (HR).

Copyright @ 2019: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Despite the contributions related to various adjuvant treatments in the initial management of localized breast cancer, approximately 20% of patients will have a metastatic relapse [1]. Markers such as Hormonal Receptors: HR (estrogen receptors (ERs), progesterone receptors (RPs)) and Human Epidermal Growth Factor Receptor-2: HER2, known on the initial tumor, are then used during therapeutic decisions in the metastatic phase. HR and HER2 status are important predictive markers in the therapeutic management of breast cancer. Literature data suggest that there is discordance of status of these receptors between primitive tumor and metastatic relapse. This tumor heterogeneity implies the question of resistance to treatment in metastatic phase [2].

METHODS

A formal approval of this study was obtained from the Ethical and Protocol Committee of the Faculty of medicine of the University Mohamed 5 of Rabat. This study was conducted in accordance with the

Helsinki Declaration. We conducted a retrospective study at the Aerospace medical center of the Military Hospital Mohamed 5 in Rabat, from 15th February 2016 to 15th December 2018, with the aim of studying the discordance of RH and HER2 status between the primary tumor of breast cancer and contralateral or local metastatic recurrence, and comparison of these data with literature data.

RESULTS

A total of 17 cabin crew with metastatic breast cancer was identified; this consisted of 17 female patients and no male patients. The average age of patients was between 30 and 50 years. We studied the HR and HER2 status on the primary tumor of breast cancer, and on metastasis at the time of relapse in 17 patients. The sites of biopsies at the time of the metastatic relapse were different, namely: superficial adenopathies in 1 case, the skin in 1 case, the liver in 8 cases, the bone in 4 cases, the lung in 1 case, and the pleura in 2 cases (Figure 1).

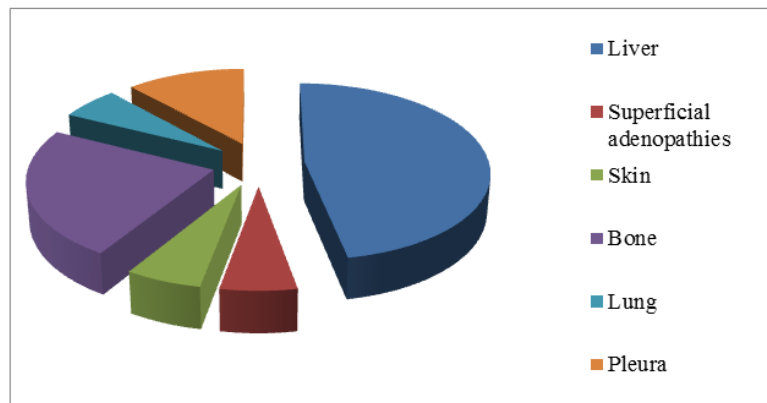


Fig-1: Different biopsy sites of the metastatic relapses

The time between the onset of the primary illness and the metastatic relapse varied between eighteen months and six years.

A change in the phenotypic status HR and / or HER2: Discordance was observed in 58% of the cases. With regard to hormonal receptors, the change in HR status from positive to negative was objectified in 17%

of cases, and the change in HR status from negative to positive was objectified in 12% of cases. Regarding human epidermal growth factor receptor 2, the change of the HER2 status from positive to negative (positivity) is objectified in 6% of cases. There was in no way a change in HER2 status from positive to negative. In one case, there was a combined change in both RH and HER2 status (Table 1).

Table-1: Rates of discordance between the primitive tumor and the metastatic relapse

	Way of change	Percentage
	HR+ → HR-	17%
Hormone Receptors (HR)	HR- → HR+	12%
Human Epidermal Growth Factor Receptor-2 (HER2)	HER2- → HER2+	6%
	HER2+ → HER2-	0%

DISCUSSION

The variation of expression of HR and HER2 between the primary tumor and the metastases can modify the therapeutic decision, and thus, can in some cases improve the prognosis of the patients, that's why, a series of retrospective studies have been conducted on the variability of expression of HR and HER2 for both locoregional recurrences and metastatic relapses.

Regarding the expression of HR, few studies have addressed the issue. They were performed on a small number of patients and / or from very heterogeneous tissue materials. HR was measured by biochemical methods. Discordance rates reported varied from 10% to 40% for estrogen receptors (ER) and progesterone receptors (PR) [3], as in the case of our series: 29%. Recently, an interesting Swedish study conducted in the Karolinska Cancer Center, had interested more than 1000 patients, and had essentially focused on expression's modification of hormonal receptors (HR). The discordance rates observed for this cohort were 32.4%, 40.7% for ER, PR respectively [4].

Concerning HER2, its overexpression and/or the amplification of the corresponding gene seem to be an early event of mammary carcinogenesis, and is

maintained over time, which explains the low rate of discordance found in the literature and which is close to 5% [5], near to the percentage of discordance of our series: 6%. Literature analysis reports concordance rates between primary tumor and metastases ranging from more than 80 to 100% depending on the studies and techniques used (often > 90%). A summary of published data is summarized in (Table 2).

A study of Regitnig *et al.* about 31 patients reported 15 cases of HER2 status modifications, 3 of which impacted the therapeutic decision [14]. The series of Santinelli *et al.* reported a discordance's rate of 13,3% for locoregional recurrences, and a rate of 27,6% for metachronous metastatic relapses [30]. Among the 48 patients reported by Zidan *et al.* 14% had a change in their HER2 status between primary and metastatic tumor [16].

Current data literature allows showing the phenotypic variability of tumor cells during their evolution. All these results make the case of the practice of a biopsy at the time of relapse, whether metastatic or locoregional, because it will allow an adaptation of the therapeutic decision in about 15% of cases [37].

Table-2: Results of retrospective HER2 status discordance studies

Authors	Secondary location biopsied	Number of patients (n)	Discordance rates HER 2	Rate of therapeutic modification
Masood et al. (6)	M ^a	50	8 %	-
Shimizu et al. (7)	LR ^b /M	21	0 %	-
Simon et al. (8)	N ^c	125	9,6 %	-
Tanner et al. (9)	M	46	0 %	-
Vincent-Salomon et al. (10)	M	44	4,5 %	-
Lindström et al. (4)	M	104	14,5 %	-
Gancberg et al. (11)	M	107	6 %	-
Taucher et al. (12)	LR	85	10 %	-
Burstein et al. (13)	LR	23	26 %	-
Regitnig et al. (14)	M	31	22 %	-
Carlsson et al. (15)	N	47	0 %	-
Zidan et al. (16)	M	58	14 %	7 %
Gong et al. (17)	LR/M	60	3 %	-
Pectasides et al. (18)	M	16	38 %	-
Hurley et al. (19)	RL	23	43 %	-
D'Andrea et al. (20)	N	90	3,9 %	-
Harris et al. (21)	LR	18	11 %	-
Mittendorf et al. (22)	LR	25	32 %	-
Simmons et al. (23)	M	13	0 %	-
Lower et al. (24)	M	382	34 %	-
Wilking et al. (25)	LR/N/M	151	10 %	-
Thompson et al. (26)	M	137	9 %	-
Cardoso et al. (27)	N	370	2 %	-
Lear-Kaul et al. (28)	M	12	41 % IHC-0 % FISH	-
Lorincz et al. (29)	M	23	8,7 %	-
Santinelli et al. (30)	LR/N/M	119/M (35)	28,6 % M	-
Tapia et al. (31)	M	105	7,6 %	-
Niikura et al. (32)	M	182	24 %	-
Aitken et al. (33)	N	194	8,9 %	-
Amir et al. (34)	LR/M	271	10 %	14 %
Broom et al. (35)	M	100	5,5 %	-
Xiao et al. (36)	M	66	15,1 %	-

M: Metastatic relapse, LR: Locoregional relapse, N: Ganglionic relapse

Two main reviews can be made to all of these studies, first, the low number of patients included in the studies, like our study (17), secondly, the limitations of pathology techniques used to assess the status of target receptors, for example: Immunohistochemistry (IHC) techniques are operator-dependent and have relatively limited reproducibility, the HER status assessment by FISH (fluorescence in situ hybridization) is commonly accepted as more reliable, but only a portion of these studies had used it [23,31].

CONCLUSION

The frank demonstration by the different studies that there is a phenotypic variation of the RH and HER2 status make the case for the need of a reevaluation of the tumor phenotype by performing biopsies on the metastatic sites, which would have an impact on the therapeutic decision and could improve patient survival.

Competing interests

The authors declare that they have no competing interests.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *The Lancet*, 365(9472), 1687-1717.
2. Brennan, M. J., Donegan, W. L., & Appleby, D. E. (1979). The variability of estrogen receptors in metastatic breast cancer. *The American Journal of Surgery*, 137(2), 260-262.
3. Jacot, W., Pouderoux, S., Bibeau, F., Leaha, C., Chateau, M. C., Chapelle, A., & Romieu, G. (2011). Variation d'expression des récepteurs hormonaux et d'HER-2 dans l'évolution du cancer du sein: quelles implications en pratique clinique?. *Bulletin du Cancer*, 98(9), 1059-1070.
4. Lindstrom, L. S., Karlsson, E., Wilking, U. M., Johansson, U., Hartman, J., Lidbrink, E. K., ... & Bergh, J. (2012). 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(21), 2601-2608.
5. Houssami N, Macaskill P, Balleine RL, Bilous M, Pegram MD. HER2 discordance between primary

- breast cancer and its paired metastasis: tumor biology or test artefact? Insights through meta-analysis. *Breast cancer research and treatment*. 2011 Oct 1;129(3):659.
6. Masood, S., & Bui, M. M. (2000). Assessment of Her-2/neu overexpression in primary breast cancers and their metastatic lesions: an immunohistochemical study. *Annals of Clinical & Laboratory Science*, 30(3), 259-265.
 7. Shimizu, C., Fukutomi, T., Tsuda, H., Akashi-Tanaka, S., Watanabe, T., Nanasawa, T., & Sugihara, K. (2000). c-erbB-2 protein overexpression and p53 immunoreaction in primary and recurrent breast cancer tissues. *Journal of surgical oncology*, 73(1), 17-20.
 8. Simon, R., Nocito, A., Hübscher, T., Bucher, C., Thorhorst, J., Schraml, P., ... & Schötzu, A. (2001). Patterns of her-2/neu amplification and overexpression in primary and metastatic breast cancer. *Journal of the National Cancer Institute*, 93(15), 1141-1146.
 9. Tanner, M., Järvinen, P., & Isola, J. (2001). Amplification of HER-2/neu and topoisomerase II α in primary and metastatic breast cancer. *Cancer research*, 61(14), 5345-5348.
 10. Vincent-Salomon, A., Jouve, M., Genin, P., Fréneaux, P., Sigal-Zafrani, B., Caly, M., ... & Sastre-Garau, X. (2002). HER2 status in patients with breast carcinoma is not modified selectively by preoperative chemotherapy and is stable during the metastatic process. *Cancer*, 94(8), 2169-2173.
 11. Gancberg, D., Di Leo, A., Cardoso, F., Rouas, G., Pedrocchi, M., Paesmans, M., ... & Larsimont, D. (2002). Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites. *Annals of Oncology*, 13(7), 1036-1043.
 12. Taucher, S., Rudas, M., Mader, R. M., Gnant, M., Sporn, E., Dubsky, P., ... & Wenzel, C. (2003). Influence of neoadjuvant therapy with epirubicin and docetaxel on the expression of HER2/neu in patients with breast cancer. *Breast cancer research and treatment*, 82(3), 207-213.
 13. Burstein, H. J., Harris, L. N., Gelman, R., Lester, S. C., Nunes, R. A., Kaelin, C. M., ... & Christian, R. L. (2003). Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. *Journal of Clinical Oncology*, 21(1), 46-53.
 14. Regitnig, P., Schippinger, W., Lindbauer, M., Samonigg, H., & Lax, S. F. (2004). Change of HER-2/neu status in a subset of distant metastases from breast carcinomas. *The Journal of pathology*, 203(4), 918-926.
 15. Carlsson, J., Nordgren, H., Sjöström, J., Wester, K., Villman, K., Bengtsson, N. O., ... & Blomqvist, C. (2004). HER2 expression in breast cancer primary tumours and corresponding metastases. Original data and literature review. *British journal of cancer*, 90(12), 2344.
 16. Zidan, J., Dashkovsky, I., Stayerman, C., Basher, W., Cozacov, C., & Hadary, A. (2005). Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. *British journal of cancer*, 93(5), 552.
 17. Gong, Y., Booser, D. J., & Sneige, N. (2005). Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. *Cancer*, 103(9), 1763-1769.
 18. Pectasides, D., Gaglia, A., Arapantoni-Dadioti, P., Bobota, A., Valavanis, C., Kostopoulou, V., ... & Economopoulos, T. (2006). HER-2/neu status of primary breast cancer and corresponding metastatic sites in patients with advanced breast cancer treated with trastuzumab-based therapy. *Anticancer research*, 26(1B), 647-653.
 19. Hurley, J., Doliny, P., Reis, I., Silva, O., Gomez-Fernandez, C., Velez, P., ... & Slamon, D. J. (2006). Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *Journal of clinical oncology*, 24(12), 1831-1838.
 20. D'Andrea, M. R., Limiti, M. R., Bari, M., Zambenedetti, P., Montagutti, A., Ricci, F., ... & Mingazzini, P. L. (2007). Correlation between genetic and biological aspects in primary non-metastatic breast cancers and corresponding synchronous axillary lymph node metastasis. *Breast cancer research and treatment*, 101(3), 279-284.
 21. Harris, L. N., You, F., Schnitt, S. J., Witkiewicz, A., Lu, X., Sgroi, D., ... & Kamma, M. (2007). Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. *Clinical Cancer Research*, 13(4), 1198-1207.
 22. Mittendorf, E. A., Wu, Y., Scaltriti, M., Meric-Bernstam, F., Hunt, K. K., Dawood, S., ... & Hortobagyi, G. N. (2009). Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. *Clinical Cancer Research*, 1078-0432.
 23. Simmons, C., Miller, N., Geddie, W., Gianfelice, D., Oldfield, M., Dranitsaris, G., & Clemons, M. J. (2009). Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases?. *Annals of oncology*, 20(9), 1499-1504.
 24. Lower, E. E., Glass, E., Blau, R., & Harman, S. (2009). HER-2/neu expression in primary and metastatic breast cancer. *Breast cancer research and treatment*, 113(2), 301-306.
 25. Wilking, U., Karlsson, E., Skoog, L., Hatschek, T., Lidbrink, E., Elmberger, G., ... & Bergh, J. (2011). HER2 status in a population-derived breast cancer cohort: discordances during tumor

- progression. *Breast cancer research and treatment*, 125(2), 553-561.
26. Thompson, A. M., Jordan, L. B., Quinlan, P., Anderson, E., Skene, A., Dewar, J. A., & Purdie, C. A. (2010). Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). *Breast cancer research*, 12(6), R92.
27. Cardoso, F., Leo, A. D., Larsimont, D., Gancberg, D., Rouas, G., Dolci, S., ... & Piccart, M. (2001). Evaluation of HER2, p 53, bcl-2, topoisomerase II- α , heat shock proteins 27 and 70 in primary breast cancer and metastatic ipsilateral axillary lymph nodes. *Annals of oncology*, 12(5), 615-620.
28. Lear-Kaul, K. C., Yoon, H. R., Kleinschmidt-DeMasters, B. K., McGavran, L., & Singh, M. (2003). Her-2/neu status in breast cancer metastases to the central nervous system. *Archives of pathology & laboratory medicine*, 127(11), 1451-1457.
29. Lőrincz, T., Tóth, J., Badalian, G., Tímár, J., & Szendrői, M. (2006). HER-2/neu genotype of breast cancer may change in bone metastasis. *Pathology & Oncology Research*, 12(3), 149-152.
30. Santinelli, A., Pisa, E., Stramazzotti, D., & Fabris, G. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. *International journal of cancer*, 122(5), 999-1004.
31. Tapia, C., Savic, S., Wagner, U., Schöneegg, R., Novotny, H., Grilli, B., ... & Terracciano, L. (2007). HER2 gene status in primary breast cancers and matched distant metastases. *Breast Cancer Research*, 9(3), R31.
32. Niikura, N., Liu, J., Hayashi, N., Mittendorf, E. A., Gong, Y., Palla, S. L., ... & Ueno, N. T. (2012). Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. *Journal of Clinical Oncology*, 30(6), 593.
33. Aitken, S. J., Thomas, J. S., Langdon, S. P., Harrison, D. J., & Faratian, D. (2009). Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases. *Annals of Oncology*, 21(6), 1254-1261.
34. Amir, E., Miller, N., Geddie, W., Freedman, O., Kassam, F., Simmons, C., ... & Tannock, I. F. (2012). Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. *Journal of clinical oncology*, 30(6), 587.
35. Broom, R. J., Tang, P. A., Simmons, C., Bordeleau, L., Mulligan, A. M., O'MALLEY, F. P., ... & Clemons, M. J. (2009). Changes in estrogen receptor, progesterone receptor and Her-2/neu status with time: discordance rates between primary and metastatic breast cancer. *Anticancer research*, 29(5), 1557-1562.
36. Xiao, C., Gong, Y., Han, E. Y., Gonzalez-Angulo, A. M., & Sneige, N. (2011). Stability of HER2-positive status in breast carcinoma: a comparison between primary and paired metastatic tumors with regard to the possible impact of intervening trastuzumab treatment. *Annals of Oncology*, 22(7), 1547-1553.
37. Curigliano, G., Bagnardi, V., Viale, G., Fumagalli, L., Rotmensz, N., Aurilio, G., ... & Della Vigna, P. (2011). Should liver metastases of breast cancer be biopsied to improve treatment choice?. *Annals of oncology*, 22(10), 2227-2233.