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LETTER – BREAST ONCOLOGY

Reply to "Multicentric Ipsilateral Invasive Breast Carcinomas Might Have Higher 21-Gene Recurrence Score Compared with Multifocal Ipsilateral Invasive Breast Carcinomas"

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TO THE EDITORS

We appreciate the interesting hypothesis raised by Dr. Altundag regarding possible differences in the 21-gene recurrence score (RS) between multicentric (MC) and multifocal (MF) breast carcinomas (BCs). Traditionally, MC carcinoma is defined as two or more BCs in separate quadrants, and MF as BCs in the same quadrant; however, others have suggested defining MC as multiple tumors in the same breast, and MF as multiple foci of the same tumor.[1,2] These terms are not used uniformly by various authors, which contributes to some confusion on the topic. In comparing MC/MF BCs with unifocal BCs (UBCs), worse prognostic factors (including younger age at diagnosis, larger tumor size, higher grade, presence of lymphovascular invasion, and increased rate of lymph node metastases) have been reported in association with both MC and MF BCs,[3] and, in one study, associated only with MC and not MF BCs.[4] In contrast, Vera-Badillo et al.[5] found relative balance in prognostic factors between MC/MF and UBCs. Conflicting data also exist when examining survival outcomes of patients, with some reporting an association of worse overall survival with MC/MF BCs[5] and others finding no difference in patient outcomes.[2,3]

In our study, we chose to adhere to the American Joint Committee on Cancer (AJCC) staging guidelines for multiple synchronous carcinomas, which do not differentiate between MC and MF given the technical difficulty inherent in precisely distinguishing between the two.[6] Our focus was on the examination of the potential biologic differences, as reflected by the RS, in multiple different foci of BCs in the same individual, rather than a comparison of tumors among different patients. While some studies suggest that multiple synchronous carcinomas have significant biologic differences,[7,8] numerous studies have provided evidence of considerable similarity in the histopathologic and immunohistochemical profiles of multiple foci. Choi et al.[9] and Middleton et al.[10] both found that in those cases of MF/MC BCs having similar histomorphology, it is appropriate to perform ancillary immunohistochemical tests on only one focus, given the nearly identical immunohistochemical patterns in these cases. In contrast, in cases with different morphologies, biomarkers should be evaluated separately.[10] Buggi et al. found considerable heterogeneity in MF breast cancer of the same histologic subtype and recommended independent evaluation of each focus; however, almost 20% of evaluated cases were of different histologic grade and 15% showed variation in mitotic rates between foci.[7] Our findings support the former, showing good concordance (87%) among multiple morphologically similar foci of BCs; however, we did not comment on the clinicopathologic factors between MC and MF in our data set.

To address this inquiry, we re-examined our cohort to differentiate the tumors as either MC or MF, using traditional definitions. Among a total of 53 patients in our study, 29 (55%) had MC BCs and 24 (45%) had MF BCs. Of the

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TABLE 1 Clinicopathologic features of multicentric and multifocal tumors

	Multicentric (n = 65)	Multifocal (n = 51)	p value
Age, years [mean (range)]	52 (32–69)	52 (39–73)	
Tumor size, cm [mean (range)]	1.44 (0.5–4.5)	1.42 (0.5–4.6)	
Recurrence score [mean (range)]	14 (0–42)	14 (4–23)	
Recurrence score categorization [n (%)]			0.573[a]
Low (0–17)	43 (66.1)	38 (74.5)	
Intermediate (18–30)	20 (30.8)	13 (25.5)	
High ($\geq$ 31)	2 (3.1)	0 (0)	
Discordance [n (%)]	4 (6)	3 (6)	1.0000

[a]Calculated by collapsing the high-risk RS group with the intermediate-risk RS group

116 tumors in our study, 65 (56%) were MC and 51 (44%) were MF. Our findings are outlined in Table 1 below. As reported, all included cases showed high concordance and no cases resulted in changes in management based on current treatment guidelines, following the TAILORx trial recommendations. In this study cohort, we found no significant differences in RS between MC and MF BCs.

REFERENCES

1. Carpenter S, Fraser J, Fleming M, Gray R, Halyard M, Pockaj B. Optimal treatment of multiple ipsilateral primary breast cancers. *Am J Surg.* 2008;196(4):530–536.
2. Vlastos G, Rubio IT, Mirza NQ, et al. Impact of multicentricity on clinical outcome in patients with T1-2, N0-1, M0 breast cancer. *Ann Surg Oncol.* 2000;7(8):581–587.
3. Lynch SP, Lei X, Chavez-MacGregor M, et al. Multifocality and multicentricity in breast cancer and survival outcomes. *Ann Oncol.* 2012;23(12):3063–3069.
4. Kanumuri P, Hayse B, Killelea BK, Chagpar AB, Horowitz NR, Lannin DR. Characteristics of multifocal and multicentric breast cancers. *Ann Surg Oncol.* 2015;22(8):2475–2482.
5. Vera-Badillo FE, Napoleone M, Ocana A, et al. Effect of multifocality and multicentricity on outcome in early stage breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2014;146(2):235–244.
6. Amin M, Edge S, Green F, et al. (eds). AJCC cancer staging manual. 8th ed. Chicago, IL: AJCC (2017).
7. Buggi F, Folli S, Curcio A, et al. Multicentric/multifocal breast cancer with a single histotype: is the biological characterization of all individual foci justified? *Ann Oncol.* 2012;23(8):2042–2046.
8. Dawson PJ, Baekey PA, Clark RA. Mechanisms of multifocal breast cancer: an immunocytochemical study. *Hum Pathol.* 1995;26(9):965–969.
9. Choi Y, Kim EJ, Seol H, et al. The hormone receptor, human epidermal growth factor receptor 2, and molecular subtype status of individual tumor foci in multifocal/multicentric invasive ductal carcinoma of breast. *Hum Pathol.* 2012;43(1):48–55.
10. Middleton LP, Vlastos G, Mirza NQ, Eva S, Sahin AA. Multicentric mammary carcinoma: evidence of monoclonal proliferation. *Cancer.* 2002;94(7):1910–1916.