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Correspondence

Prognosis of patients with multifocal breast cancer

Dear Editor,

In their report, Kim et al [1] provide further evidence that different foci of multifocal breast cancer occasionally arise from different progenitor cells. They conclude that the current College of American Pathologists' guideline that suggests using "only the largest tumor for tumor staging and determination of treatment methods" is "insufficient."

I agree with the authors' conclusion for 2 reasons. First, for most invasive breast cancers (hormone receptor positive/HER2 negative and lymph node negative), the National Comprehensive Cancer Network already endorses molecular profiling (quantitative messenger RNA assessment) to predict prognosis with adjuvant hormonal therapy or chemotherapy or both, rather than the size of the largest tumor [2]. Their endorsement is based on multiple reports of these assays being of greater value than metrics such as tumor size and grade. Also, the American Joint Commission on Cancer similarly has now included pathologic prognostic staging with quantitative messenger RNA (mRNA) profiling as part of staging for this same group of invasive breast cancers [2].

However, the National Comprehensive Cancer Network has not addressed how this change applies to multifocal or synchronous invasive breast cancers. Based on the results reported by Kim et al and the other studies, they cite in their report that, because different tumors in a patient with multifocal or synchronous invasive cancers can demonstrate molecular differences, these same different tumors would be expected to harbor different quantitative mRNA profiles as well, as has been shown by Karsten et al [3]. If recurrence risks from each of multiple tumors are considered independent events, then it follows that for a single tumor, a lower risk of recurrence and therefore lower absolute systemic adjuvant therapy benefit would be expected when compared with the higher recurrence risk expected from one or the other or both from each of 2 tumors. For example, if a patient has 2 tumors, each with a 20% recurrence risk based on quantitative mRNA profiling (and therefore an 80% likelihood of no recurrence from each), then the risk of recurrence from one or the other or both would be $1.00 - (0.8 \times 0.8) = 0.36$. In other words, the risk of recurrence from one or the other or both would be estimated to be 36%.

The incorporation of quantitative mRNA profiling into standard guidelines enhances our ability to predict prognosis and benefit from adjuvant systemic therapies. In part because of the occasional somatic molecular differences noted by Kim et al in different tumors of patients with multifocal disease, quantitative mRNA profiles of each tumor in a patient with multifocal or synchronous invasive breast cancers should help impart more precise prognostic and benefit estimates for patients with multifocal or synchronous tumors.

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Prognosis of patients with multifocal breast cancer—reply

Dear Editor:

We thank Dr Sorscher for his interest in our article on clonality analysis of multifocal breast cancers. Disappointingly, multiple breast cancer has not been included in the eighth American Joint Committee on Cancer staging system as an independent risk factor. The current TNM staging system adopts the size of the largest invasive tumor for T

staging. The incidence of multicentric/focal breast cancer (*multiple breast cancer*, henceforth) has ranged from 3.7% to 75% [1]. It has been reported that multiple breast cancer is one of the significant factors concerning overall survival, local recurrence, and distant metastasis [2]. As pathologists, evaluation of breast cancer specimens with multicentric/focal breast cancer is labor intensive and a time-consuming process. A report has mentioned that the reason for "the largest diameter only" guideline is due to practicality and convenience [3]. Thus, we believe that incidence of multiple breast cancer has been underestimated until now. The prognostic significance of multiple breast cancer remains unclear in some reports [4]. It is no wonder that the leading authority in American Joint Committee on Cancer for breast cancer might have thought that evidence for significance of multiplicity was insufficient to add as a prognostic factor. However, it is well known that the chance for the cancer cell to metastasize is proportional to the tumor burden.

In regard to survival, a large meta-analysis using 22 studies comprising 67 557 breast cancer patients concluded a correlation of multifocal breast cancer with worse overall survival, disease-free survival, and disease-specific survival [5]. A retrospective study was conducted on survival-related events with 5691 breast cancer patients, which has revealed a significant increase in local relapse and distant metastasis among patients of the multiple-tumor group in comparison to those of the unifocal group [2]. Concerning the choice of surgery or treatment options, the preoperative diagnosis is crucial for breast cancer management to avoid positive resection margins. However, current imaging modalities, such as magnetic resonance imaging, still have limitations in the imaging diagnosis [4]. Furthermore, there is no consensus on terminology between pathologists and radiologists. For more helpful radiologic conclusions, pathologic-radiologic correlation studies are necessary and should be actively pursued.

In addition to practical aspects in the clinical management of multiple breast cancer, we are interested in multiple breast cancer for the following reasons: (1) if multiple breast cancers originate from single primary cancer through intramammary metastasis (monoclonal) or synchronous genetically separate tumor foci (multiclonal), or (2) if there is any familial propensity of genetic field effect in the patients with multiple breast cancer, or (3) if there is any intervention of immune mechanism in development of multiple breast cancer. We have shown that multifocal tumors can be of different origins despite having similar histopathologic characteristics or being located close to each other [1]. These suggested that patients with multiple breast tumor can have different treatment options.

Because the prognostic value and pathogenesis of multiple breast cancer remain unclear, further attention and studies, such as RNA profiling, are needed for better understanding and disclosing the impact of multiple breast cancer.

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Telocytes as possible precursors of *PDGFRA*-mutant gastrointestinal mesenchymal tumors—rejoinder

To the Editor:

We read with interest the reply by Manley et al to our letter supporting telocytes (TCs) as possible precursors of gastrointestinal mesenchymal tumors [1,2]. We would like to clarify that the tumors we think derive from TCs along with inflammatory fibroid polyps (IFPs) are actually *PDGFRA*-mutant gastrointestinal stromal tumors (GISTs), that is, "genuine" GISTs (concurring to form this tumor group together with the other GIST subtypes, distinguished by diverse pathogenetic mechanisms, which likewise feature distinctive morphology and clinical features). Therefore, in this regard, the definition "*PDGFRA*-mutant polyps arising sporadically and syndromically within the stomach and diagnosed as