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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References

[1] Kim H, Kim CY, Park KH, Kim A. Clonality analysis of multifocal ipsilateral breast carcinomas using X-chromosome inactivation patterns. Hum Pathol 2018;78:106-14.
[2] Weissenbacher TM, Zschage M, Janni W, et al. Multicentric and multifocal versus unifocal breast cancer: is the tumor-node-metastasis classification justified? Breast Cancer Res Treat 2010;122:27-34.
[3] Moon HG, Han W, Kim JY, et al. Effect of multiple invasive foci on breast cancer outcomes according to the molecular subtypes: a report from the Korean Breast Cancer Society. Ann Oncol 2013;24:2298-304.
[4] Bendifallah S, Werkoff G, Borie-Moutafoff C, et al. Multiple synchronous (multifocal and multicentric) breast cancer: clinical implications. Surg Oncol 2010;19:e115-23.
[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;146:235-44.

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

GISTs," ascribed to us by Manley and colleagues, is inaccurate. Actually, *PDGFRA*-mutant GISTs are in most cases not polypoid, rather constituting intramural masses, with clear-cut histologic and immunophenotypical features [3]. We have recently produced morphogenetic evidence of the origin of these tumors, along with typical IFPs, from TCs, exploiting the opportunity offered by the concurrent presence of a prominent TC hyperplasia [4]. In the same article, we proposed to define IFP as "telocytoma" because this term conveys both the neoplastic and histotypic natures of these tumors.

Conversely, tumors typical of *PDGFRA*-mutant syndrome whose nosology is less straightforward are the fibrous tumors defined as GISTs by De Raedt and colleagues [5] and described also by Carney and Stratakis [6] and by ourselves [7]. These tumors not only do not exhibit morphologic features typical of GISTs but also do not express CD117 and DOG1; in addition, they have been found mostly in the small intestine, unlike *PDGFRA*-mutant GISTs, which show a strong predilection for the stomach. We have previously discussed in depth this issue, supporting these "fibrous tumors" as a possible variant of IFP [7].

In conclusion, in our opinion, *PDGFRA* mutations can determine 3 types of lesions in the gastrointestinal tract: (1) typical *PDGFRA*-mutant GIST, (2) typical IFP (telocytoma) and its variant formerly defined as "fibrous tumors", and (3) TC hyperplasia. Of note, the latter and the "fibrous tumors" variant of IFP (telocytoma) hitherto have been described exclusively in germline *PDGFRA* mutant settings, that is, in *PDGFRA*-mutant syndrome.

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References

[1] Giustiniani MC, Lanza P, Ricci R. Telocytes as possible precursors of *PDGFRA*-mutant gastrointestinal mesenchymal tumors. Hum Pathol 2018;82:298-9.
[2] Manley P, Walia JS, Kirsch R, Riddell R. Telocytes as possible precursors of *PDGFRA*-mutant gastrointestinal mesenchymal tumors—reply. Hum Pathol 2018;82:299-300.
[3] Ricci R, Dei Tos AP, Rindi G. GISTogram: a graphic presentation of the growing GIST complexity. Virchows Arch 2013;463:481-7.
[4] Ricci R, Giustiniani MC, Gessi M, et al. Telocytes are the physiological counterpart of inflammatory fibroid polyps and PDGFRA-mutant GISTs. J Cell Mol Med 2018;22:4856-62.
[5] de Raedt T, Cools J, Debiec-Rychter M, et al. Intestinal neurofibromatosis is a subtype of familial GIST and results from a dominant activating mutation in PDGFRA. Gastroenterology 2006;131:1907-12.
[6] Carney JA, Stratakis CA. Stromal, fibrous, and fatty gastrointestinal tumors in a patient with a PDGFRA gene mutation. Am J Surg Pathol 2008;32:1412-20.
[7] Ricci R, Martini M, Cenci T, et al. PDGFRA-mutant syndrome. Mod Pathol 2015;28:954-64.

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

To the Editor,

We are flattered that Giustiniani et al have chosen to use the term "telocytoma," first mentioned in the literature by us in our reply to their letter [1], to describe inflammatory fibroid polyps (IFPs). This may prove a confusing term if *PDGFRA*-mutant gastrointestinal stromal tumors (GIST) also arise from the telocyte as they suggest.

If the cell of origin of gastric *PDGFRA*-mutant GISTs is the telocyte, the molecular pathogenesis is clearly more complex than that of the IFP. There are as yet no described gastric CD117- or DOG1-positive progenitor telocyte cells associated with these GISTs, suggesting that the cell of origin is not the mature telocyte, or that there are additional unknown sporadic mutations within the telocyte. We await the upcoming publication of Ricci et al [2]. We would also encourage others to study the skin in familial *PDGFRA* mutation patients with coarse facies and/or broad hands and evaluate the role of the telocyte in producing this particular phenotype.

In patients with a familial *PDGFRA* mutation, there is widespread PDGFRA overexpression resulting in variable hyperplasia of CD34, PDGFRA-positive telocyte cells in the stomach and intestine. The hyperplasia may take the form of firm flat masses in the intestine, called fibrous tumors by some, but these areas are often contiguous with elevated plateaus and/or polyps [3]. Because these shapes all directly reflect the PDGFRA-driven hyperplasia of telocytes, it is unnecessary to distinguish IFPs from fibrous tumors as Giustiniani and colleagues repeatedly do, although in their article, none of their IFPs have discrete borders [4].

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