

The paper's results are thought-provoking, particularly considering the crucial role of the tumor microenvironment in lymphoma survival and growth (3). Notably, there has already been significant uptake of FAPI-based agents targeting the tumor microenvironment in lymphoma (4). In the study by Chen et al. (1), immunohistochemistry analysis revealed significantly lower fibroblast activation protein expression cell densities than hexokinase 2 and glucose transporter 1 in most lymphoma subtypes ($P < 0.001$).

Although [^{18}F]FDG PET/CT plays a pivotal role in lymphoma management, a gray zone exists in which its diagnostic performance declines, notably in cases of indolent lymphomas or those with low [^{18}F]FDG avidity. It is intriguing to explore whether a FAPI-based radiotracer could complement or serve as an alternative to [^{18}F]FDG for these specific lymphoma subtypes. However, Chen et al. (1) did not thoroughly address this aspect, mainly because of the limited number of patients with indolent or low-avidity lymphomas. Additionally, their patient population is highly heterogeneous, encompassing various histopathologic patterns and clinical settings for the examinations. To address this limitation, a prospective study with a homogeneous group of patients and a well-defined study design would be desirable.

Another crucial consideration is the evolving landscape of lymphoma treatment. The current standard of care is chemioimmunotherapy, with salvage high-dose chemotherapy and autologous stem cell transplantation serving as the second-line treatments for patients with relapsed or refractory lymphomas (5). However, only a few patients achieve a cure with this intensive approach, and its applicability is restricted by comorbidities and advanced age (6). Recent advancements in immunotherapy involve CD19 chimeric antigen receptor T cells, which are autologous T cells genetically reengineered and approved for the treatment of relapsed or refractory aggressive B-cell lymphomas (7). Nonetheless, despite the high efficacy of chimeric antigen receptor T-cell therapy, a significant number of patients do not respond or experience relapses (8). In this context, FAPI-based radiotracers could be explored in a theranostic context, addressing the molecular target with appropriately radiolabeled agents, similar to current practices in the treatment of neuroendocrine tumors and prostate cancer. However, the role of the FAPI agent in refractory lymphoma patients still remains unexplored.

In conclusion, there is still much to discover regarding the role of FAPI-based radiotracers in hematology. We eagerly await the availability of commercially accessible radiopharmaceuticals to explore the advantages and potential limitations of this class of agents in various clinical settings, laying the foundation for innovative cancer monitoring strategies.

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REPLY: We thank Dr. Guglielmo and Dr. Evangelista for the great summary and thoughtful comments regarding our paper (1). We agree that there is still much to discover regarding the role of fibroblast activation protein (FAP) inhibitor (FAPI)-based radiotracers in hematology—for example, the relationship between FAPI avidity and prognosis and the correlation of heterogeneous and relapsed or refractory lymphomas.

Several recent studies have revealed the distribution of fibrosis in nodular sclerosis Hodgkin lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma (2–4). We accidentally found that primary gastric lymphoma could accumulate ^{68}Ga -labeled FAPI, which highlighted that ^{68}Ga -FAPI is not cancer-specific (5). Most aggressive lymphomas were FAPI-avid, whereas indolent non-Hodgkin lymphoma lesions showed weak FAP staining and mild to moderate ^{68}Ga -FAPI uptake (6). These results are partially consistent with the result of Tataroglu et al., which provided quantitative information about the amount of fibrosis in lymphoma lesions (2). The focus is now to determine which is the superior method, ^{68}Ga -FAPI PET/CT or ^{18}F -labeled FDG PET/CT in indolent lymphoma. Compared with FAP expression in stromal cells, glycolytic markers with high cell density were overexpressed in tumors and the tumor microenvironment, resulting in higher rates of detecting lymphoma lesions. However, our result was not very convincing because of the limited number and heterogeneity of patient population, especially the indolent type.

The ability to detect fibrosis before and after treatment with ^{68}Ga -FAPI PET/CT could be the basis for planning prospective studies compared with treatment with ^{18}F -FDG PET/CT. A prospective study showed that the presence of tumor sclerosis was significantly associated with poor overall survival of patients with advanced-stage nodal follicular lymphoma (7). As Dr. Guglielmo and Dr. Evangelista suggested, a large-scale, well-defined, prospective study should be designed in a homogeneous group to explore the potential role of ^{68}Ga -FAPI PET/CT and the relationship between PET performance, heterogeneity, and prognostic value before and after treatment.

Malignancy theranostics is a novel approach that combines diagnostic imaging and radionuclide therapy. Only a few proof-of-concept studies have been published for FAP-targeted radioligand therapies, radiolabeled with ^{131}I , ^{90}Y , and ^{177}Lu , which showed mixed responses (8–10). It is valuable to explore the role of FAP-targeted radionuclide therapy in refractory lymphoma patients, especially in aggressive lymphomas. Also, combination therapies of FAP-targeted radionuclide therapy and immunotherapy could be explored in relapsed or refractory aggressive non-Hodgkin lymphoma.

Overall, FAPI-based imaging and theranostics have been a highly vibrant research field over the past few years and have been the vanguard of personalized medicine. Beforehand, future larger-scale studies should be conducted to explore the diagnostic and therapeutic value of FAPI-targeted imaging and theranostics in hematology. We hope that our study arouses some interest in this research field.

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