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Editorial

Is FAP the key to unlocking treatment for rare soft-tissue sarcomas?

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Abstract: Fibroblast activation protein (FAP) is highly expressed in various sarcomas, including solitary fibrous tumors (SFTs). In recent years, radiolabeled FAPI tracers have emerged as potential therapeutic targets. In SFTs with high FAP expression, ^{90}Y-FAPI-46 demonstrated promising therapeutic efficacy. These findings highlight the potential of FAPα expression as a clinically relevant biomarker for patient selection and establish ^{90}Y-FAPI-46-based radiopharmaceutical therapy as a promising and meaningful therapeutic option for patients with malignant SFT.

Keywords: Fibroblast activation protein (FAP), solitary fibrous tumors (SFTs), radiopharmaceutical therapy, radiolabeled FAPI tracers

Introduction

Solitary fibrous tumor (SFT) is a rare mesenchymal tumor characterized by a spindle-cell shape. Typically, most SFTs have a benign progression, but they may sometimes display aggressive characteristics associated with local, distant recurrences and poor outcomes, with a reported 5-year survival rate of approximately 60% [1]. The recommended treatments for patients with developed metastatic disease are limited, and the median overall survival is typically low, ranging from only 12 to 18 months [2, 3]. This evidence demonstrates the critical importance of novel molecular-targeted therapies to enable precision medicine approaches for SFT. Fibroblast activation protein-α (FAPα) is a type II transmembrane serine protease with dipeptidyl peptidase. It shows overexpression in several sarcoma subtypes. Notably, FAPα was identified as highly expressed in both tumor cells and surrounding stromal fibroblasts in SFT. This provides an opportunity for making FAPα an attractive imaging and therapeutic target.

One research group in Germany has evaluated ^{90}Y-FAPI-46, a FAP-targeted radiopharmaceutical, in patients with advanced sarcomas, including SFT. They demonstrated the feasibility of ^{90}Y-FAPI-46 therapy for sarcoma [4]. A retrospective study published in 2024 included 11 patients treated with ^{90}Y-FAPI-46. The results indicate that four of these patients discontinued treatment due to the progression of the disease, while the remaining five completed the full treatment cycles [5]. Recently, case reports of three patients showed that ^{90}Y-FAPI-46 demonstrated remarkable efficacy in the treatment of malignant SFT [6]. Before receiving radioligand therapy, all three patients had received multiple lines of standard therapy, including surgery, radiotherapy, and chemotherapy, but the disease all recurred. Biopsy analysis showed that the FAPα mRNA levels were generally elevated (**Figure 1A**), and all cases showed that 100% FAPα-positive tumor cells. These molecular findings were confirmed by in vivo imaging: ^{68}Ga-FAPI-46 PET/CT showed enhanced tracer uptake in most patients' lesions, with more than half of the lesions having a maximum SUV value exceeding 10. Given the biological heterogeneity observed in SFT, these data provide strong evidence that FAPα mRNA profiling and ^{68}Ga-FAPI-46 PET/CT imaging may serve as effective tools for identifying optimal candidates for ^{90}Y-FAPI-46 therapy. Aside from a brief episode of thrombocytopenia observed in one patient, ^{90}Y-FAPI-46 therapy was well tolerated across all four treatment cycles in the three reported cases. Following four cycles, all three patients demonstrated clear therapeutic benefit, as assessed by both RECIST and PERCIST criteria, including measurable reductions in lesion size and/or metabolic activity (**Figure 1B-D**). It is also worth noting that, although most SFTs originate in the thorax, particularly from the pleura [7], the three cases presented in this report were all primary retroperitoneal or pelvic SFTs, and all occurred in female patients. Whether high FAP mRNA expression observed in these cases is related to the anatomical site of the primary tumor remains unknown and warrants further investigation. Previous studies have also shown that SFTs typically exhibit moderate to high uptake of FAPI tracers on PET imaging, likely reflecting the fibrogenic and stroma-rich tumor microenvironment characteristic of these tumors [8, 9].

The report also highlights important considerations for clinical application. As shown in prior studies, ^{90}Y-FAPI-46 is not universally effective across all SFT patients; careful patient selection remains essential. The three cases presented here represent only a subset of SFT patients with biologically favorable profiles, those exhibiting strong FAPα expression at both the transcriptomic and imaging

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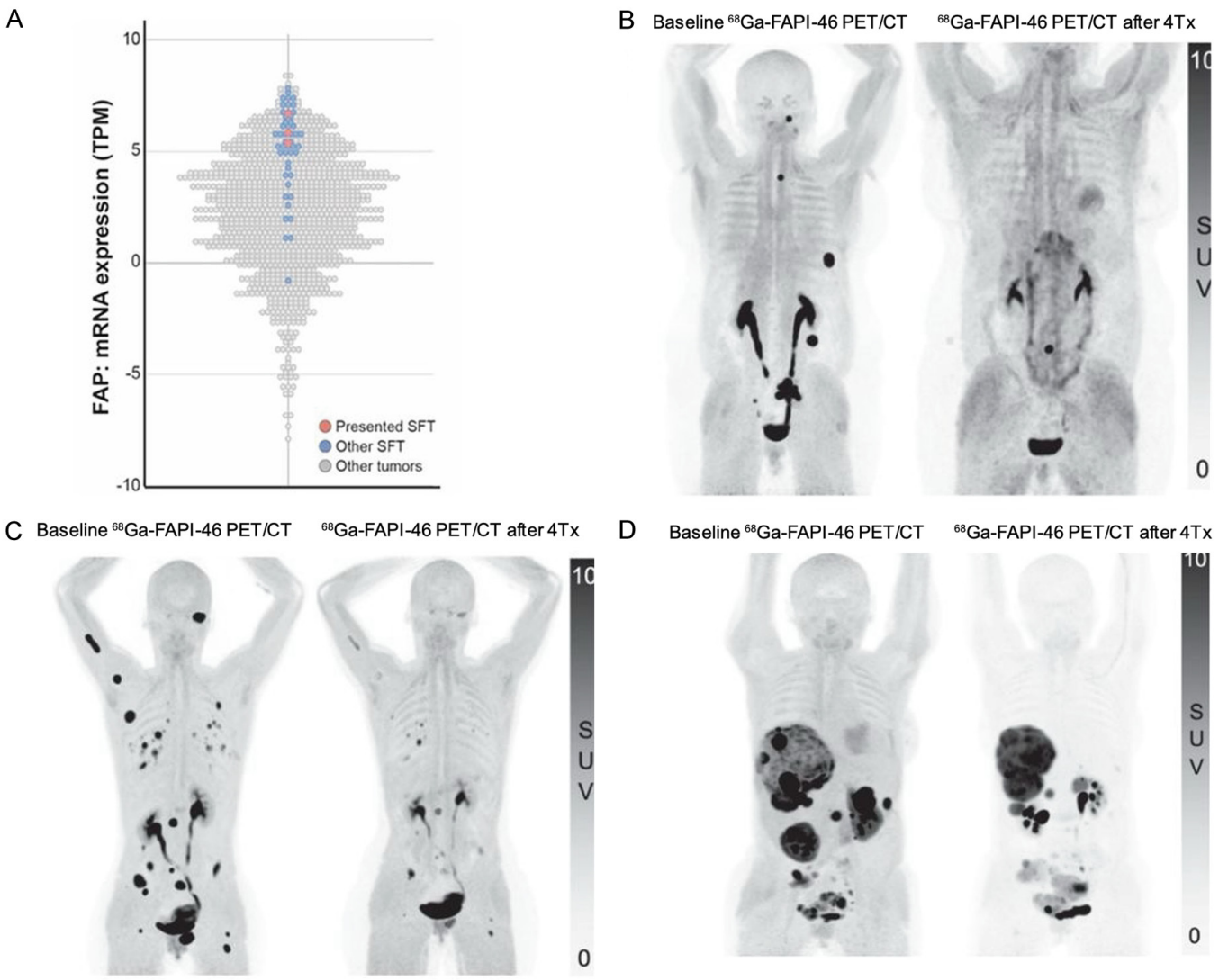

Figure 1. FAP mRNA expression of SFT from 3 patients (red dots) compared with previously analyzed SFTs (blue dots, n = 45) and other tumor entities (gray dots, n = 995) from pancancer MASTER cohort (A). Maximum-intensity-projection images at baseline and follow-up ^{68}Ga-FAPI-46 PET/CT after four cycles (4Tx) of ^{90}Y-FAPI-46 for patients A (B), B (C), C (D). Reprinted from [6]. © SNMMI.

levels. Overall, these patients demonstrated favorable short-term outcomes following ^{90}Y-FAPI-46 therapy; however, continued long-term follow-up remains essential, as overall survival and progression-free survival will ultimately determine the therapeutic value of this approach.

Conclusion

For a rare disease such as SFT, where diagnosis, recruitment, and therapeutic progress remain challenging, the ability to assemble a cohort that underwent coordinated ^{68}Ga-FAPI-46 PET and subsequent ^{90}Y-FAPI-46 therapy, and to observe clinical improvement in several of them, is a notable achievement. It reinforces the value of FAPα expression as a practical biomarker for identifying patients who are most likely to benefit from FAPI-based radiopharmaceutical therapy and provides further support for ^{90}Y-FAPI-46 as a viable therapeutic strategy for malignant SFT.

Disclosure of conflict of interest

None.

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