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Abstract:
Immuno-PET imaging of the tumor antigen HER2/neu allows for the noninvasive detection and monitoring of oncogene expression; such detection and monitoring are of prognostic value in patients with breast cancer. Compared with the full-size antibody trastuzumab, smaller protein tracers with more rapid blood clearance permit higher imaging contrast at earlier time points. Antigen-binding fragments (Fabs) of antibodies with moderately prolonged circulation achieved through the genetic fusion with a long, conformationally disordered chain of the natural amino acids Pro, Ala, and Ser (PASylation)-a biologic alternative to chemical conjugation with polyethylene glycol, PEG-offer a promising tracer format with improved pharmacokinetics for in vivo imaging. Recently, the transition metal radionuclide (89)Zr has attracted increasing interest for immuno-PET studies, complementing the conventional halogen radionuclide (124)I. To allow direct comparison of these 2 radioactive labels for the same protein tracer, the recombinant ?HER2 Fab fused with 200 Pro, Ala, and Ser (PAS200) residues was either conjugated with (124)I via an iodination reagent or coupled with deferoxamine (Df) and complexed with (89)Zr. After confirmation of the stability of both radioconjugates and quality control in vitro, immuno-PET and biodistribution studies were
performed with CD1-Foxn1(nu) mice bearing HER2-positive human tumor xenografts. (89)Zr-Df-Fab-PAS200 and (124)I-Fab-PAS200 showed specific tumor uptake of 11 and 2.3 percentage injected dose per gram 24 h after injection, respectively; both led to high tumor-to-blood (3.6 and 4.4, respectively) and tumor-to-muscle (20 and 43, respectively) ratios. With regard to off-target accumulation, overt (124)I activity was seen in the thyroid, as expected, whereas high kidney uptake was evident for (89)Zr; the latter was probably due to glomerular filtration and reabsorption of the protein tracer in proximal tubular cells. Both (89)Zr- and (124)I-labeled versions of HER2 Fab-PAS200 allowed PET tumor imaging with high contrast. With its residualizing radiometal, the tracer (89)Zr-Df-Fab-PAS200 showed better in vivo stability and higher tumor uptake.

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