Supplementary Materials

Methodology for patient studies

Radiolabeling of [^{68}Ga]Ga-DOTAGA.(SA.FAPi)$_2$

All the procedures were performed in sterile conditions in a laminar flow to maintain sterility. For the [^{68}Ga]Ga-DOTAGA.(SA.FAPi)$_2$ radiolabeling, the required amount of the buffers such as 1 mL 0.4 M sodium acetate, pH 4 or 0.6-1 mL of 1 M HEPES buffer, pH 5.5 were used. Different ligand-to-radionuclide ratios were investigated across nine batches of radiolabelling to evaluate the most suitable ligand: radionuclide ratio (L:R).

The $^{68}GaCl_3$ solution (~925 MBq) was eluted from the ^{68}Ge/^{68}Ga-generator (ITG Garching, Germany) using 0.05 M HCl and added to the vial containing the buffer-peptide mixture and incubated at 95°C for 10 minutes. The light C18 cartridge (Sep-Pak Plus Light C18) required for purification was preconditioned by 5 mL of ethanol followed by air and then rinsed with 10 mL of Ultrapure water. After heating, the radiolabelled product was passed through the pre-conditioned cartridge and purged with air followed by water and air to dryness and the effluent was collected in a waste vail for free $^{68}GaCl_3$.

The radiolabeled DOTA.SA.FAPi retained in the C18 cartridge was eluted with 1 mL of 50% ethanol. The cartridge was purged with 10 mL of 0.9% saline solution and air to dryness. The preparation was subjected to Millipore filtration prior to the administration to the patient and was delivered as 10 mL solution with the saline. The product was visually checked and pH was determined using the pH paper.

Radiochemical purity

Radiochemical purity (RCP) of [^{68}Ga]Ga-DOTAGA.(SA.FAPi)$_2$ was determined by ITLC after the radiopharmaceutical purification. Sodium citrate buffer (0.1 M), pH 4 was used as mobile phase and Silica gel impregnated aluminium strips (ITLC-SG strips) were used as stationary phase. The developed TLC strip was read in the TLC scanner (Bioscan) to determine the radiochemical purity using proportional counter.

Radiolabeling of [^{68}Ga]Ga-DOTANOC

^{68}Ga (1,110-1,850 MBq [30-50 mCi]) was eluted from a ^{68}Ge/^{68}Ga generator (ITG) using 0.1 M HCl. The eluent was loaded on a miniaturized column of organic cation-exchanger STRATA X C column to preconcentrate (using 80% acetone/0.15 M HCl). The processed ^{68}Ga was directly eluted with 97.7% acetone/0.05 M HCl into the reaction vial containing 30-50 mg of DOTANOC. Synthesis was performed at approximately 95°C for 10-15 min, followed by transferring of product from the reaction vessel on to the C-18 cartridge. The labelled product from the C-18 cartridge is eluted finally by 70% ethanol and further rinsed with 10 ml normal saline.

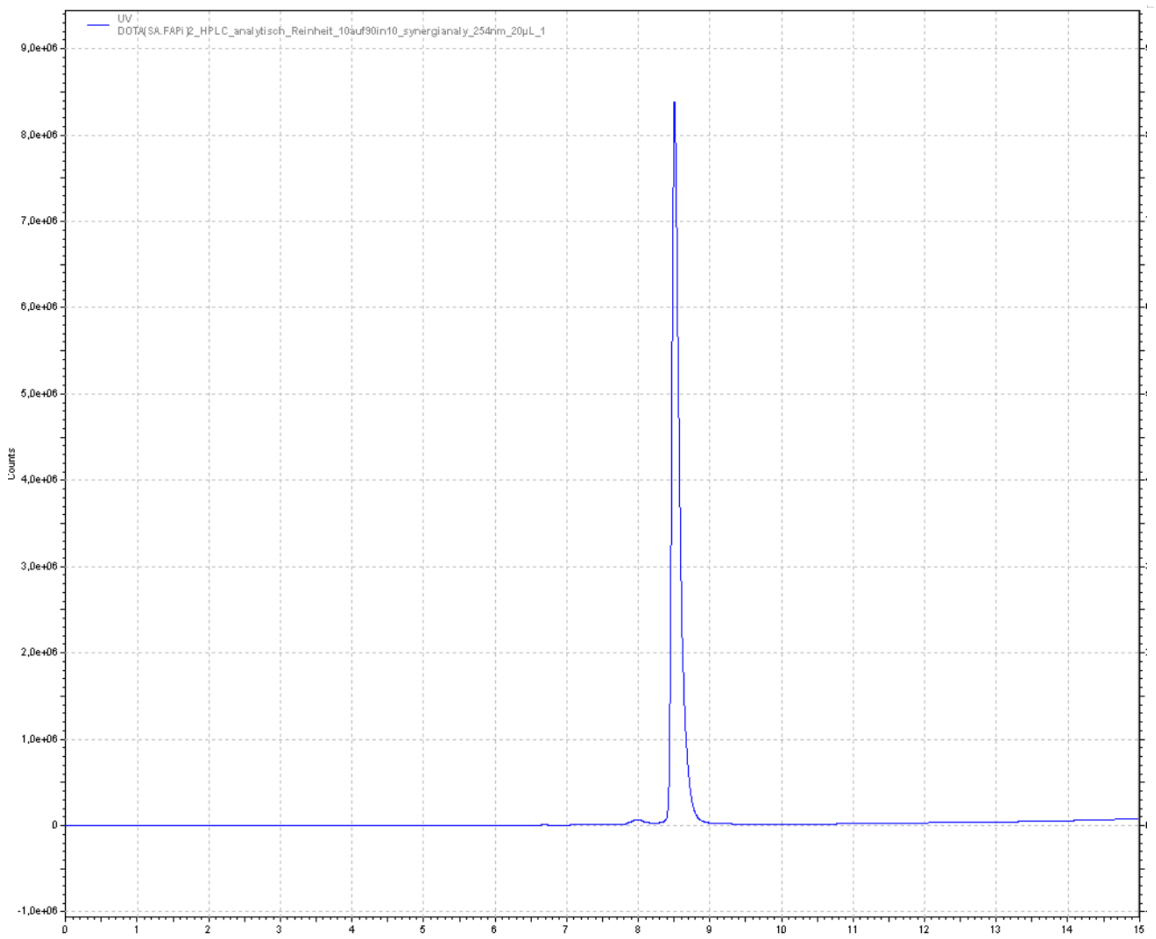

Figure S1. Analytical HPLC profile of DOTA.(SA.FAPi)$_2$ [Compound 5], linear gradient condition of 10-90% MeCN (+0.1% TFA)/90-10% Water (+0.1% TFA) in 10 min, 1 mL/min.

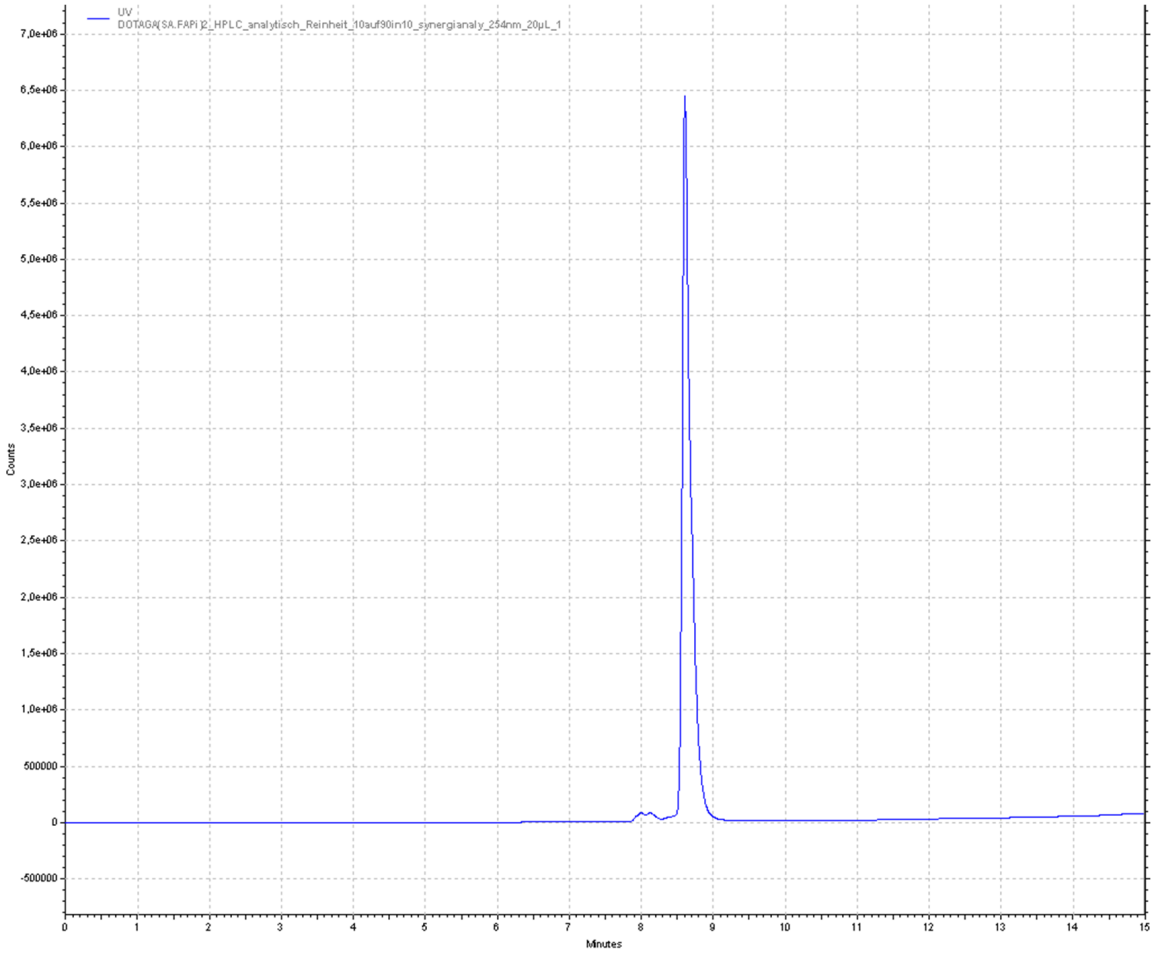

Figure S2. Analytical HPLC profile of DOTAGA.$(SA.FAPi)_2$ [Compound 12], linear gradient condition of 10-90% MeCN (+0.1% TFA)/90-10% Water (+0.1% TFA) in 10 min, 1 mL/min.

Table S1. Comparison of SUL values among various radiotracers in six patients (The values are given as median and interquartile range (IQR))

Organs	SUL_{peak} [^{68}Ga]Ga-DOTAGA.$(SA.FAPi)_2$	SUL_{avg} [^{68}Ga]Ga-DOTAGA.$(SA.FAPi)_2$	SUL_{peak} [^{68}Ga]Ga-DOTA.SA. FAPi	SUL_{avg} [^{68}Ga]Ga-DOTA.SA. FAPi	SUL_{peak} [^{18}F]F-FDG	SUL_{avg} [^{18}F]F-FDG
Lacrimal glands	1.28	0.80	2.78	1.51	5.39	2.66
	0.94-2.24	0.46-1.30	1.22-4.34	0.58-2.43	1.93-8.84	1.15-4.16
Oral mucosa	1.84	1.42	2.19	1.60	2.34	1.60
	1.71-2.01	1.36-1.49	1.59-2.78	1.36-1.83	1.85-2.83	1.24-1.96
Salivary glands	1.75	1.24	4.88	4.02	1.75	1.26
	1.15-2.34	0.78-1.69	4.72-5.41	3.08-4.70	1.29-2.20	0.96-1.55
Thyroid	0.81	0.40	4.37	2.21	1.09	0.63
	0.47-1.15	0.21-0.58	3.51-5.32	1.89-3.38	0.89-1.29	0.51-0.76
Heart contents/blood pool	7.80	6.10	1.19	0.86	1.43	1.15
	6.68-9.03	5.71-7.31	0.84-1.54	0.64-1.08	1.34-1.51	1.06-1.23
Liver	4.54	3.02	0.61	0.30	2.13	1.72
	4.03-4.66	2.62-3.12	0.38-0.83	0.25-0.35	2.06-2.19	1.60-1.83
Spleen	5.83	4.88	0.89	0.64	1.61	1.28
	5.81-7.35	4.72-5.41	0.79-0.98	0.59-0.69	1.42-1.79	1.15-1.40
Pan-creas	8.38	5.99	2.59	1.85	1.48	1.03
	6.27-9.74	3.80-6.98	2.57-2.60	1.77-1.93	1.43-1.53	0.96-1.10
Duo-denum	1.94	1.29	1.24	0.58	1.15	0.81
	1.21-2.66	0.73-1.89	1.10-1.37	0.51-0.64	0.77-1.53	0.46-1.16
Kidneys	4.48	3.82	3.92	2.39	7.45	4.53
	4.34-5.93	3.63-5.12	2.00-5.84	1.33-3.45	2.24-12.7	1.74-7.31
Psoas Muscle	0.93	0.91	1.74	1.12	0.66	0.44
	0.62-1.24	0.88-0.93	0.96-3.24	0.75-1.93	0.56-0.76	0.30-0.57
Bone (L4 verte-brae)	0.53	0.43	2.35	2.00	1.22	0.94
	0.52-0.53	0.41-0.44	1.60-2.74	1.47-2.06	1.18-1.25	0.87-1.01
Femur	0.60	0.46	1.11	0.72	0.64	0.50
	0.59-0.61	0.43-0.49	1.06-1.36	0.62-0.99	0.60-0.68	0.44-0.55
Brain normal paren-chyma	0.27	0.21	0.04	0.02	6.22	4.75
	0.12-0.34	0.16-0.23	0.02-0.05	0.01-0.02	4.29-8.15	3.22-6.27

Table S2. Comparison of SUL values of the regions of interest for [^{68}Ga]Ga-DOTA.SA.FAPi and [^{68}Ga]Ga-DOTAGA.$(SA.FAPi)_2$ related to the 63-year old female patient (related to **Figure 9**)

Regions of Interest	[^{68}Ga]Ga-DOTA.SA.FAPi 1 h p.i.		[^{68}Ga]Ga-DOTAGA.$(SA.FAPi)_2$ 1 h p.i.		[^{68}Ga]Ga-DOTAGA.$(SA.FAPi)_2$ 3 h p.i.	
	SUL	SUL_{avg}	SUL	SUL_{avg}	SUL	SUL_{avg}
Heart contents (blood pool)	1.2	0.9	6.1	4.8	7.1	4.8
Pancreas	2.7	2.4	10.2	6.6	9.9	7.7
L2 vertebra tumor	2.7	1.8	12.8	10.4	12.1	9.4
Right ischium	5.9	4.2	10.0	8.7	11.7	8.9
Left femur	1.8	1.4	9.1	8.9	9.4	8.5

Table S3. Comparison of SULpeak of metastases and lesions (related to **Table 4**) for the different radiotracers

S. No	Site of metastases	[^{68}Ga]Ga-DOTA.SA.FAPi SULpeak	[^{68}Ga]Ga-DOTAGA.(SA.FAPi)$_2$ SULpeak	[^{18}F]FDG SULpeak	[^{68}Ga]Ga-DOTANOC SULpeak
1	Pelvic bone	6.9	8.6	4.8	NA
2	Iliac bone	5.9	11.6	4.8	NA
3	Neck node	7.6	8.9	5.4	NA
4	Lung mass	3.7	7.7	2.8	NA
5	Neck node	8.6	12.8	1.2	1.6
6	Lumbar vertebra	8.6	12	1.9	3.6

NA: not assessed.