Supplementary Table S1. Amino acid transporter overexpression in epidemiologically relevant cancers (based on global cancer burden data from GLOBOCAN 2022)

Incidence rank (%)	**Mortality rank** (%)	**Cancer site**	**LAT1**	**ASCT2**	**xCT**	**CAT (1/2/3)**	**SNAT2**
1 (12.4)	**1** (18.7)	Lung	✓	✓	✓		
2 (11.6)	**4** (6.9)	Female breast	✓	✓	✓	✓	✓
3 (9.6)	**2** (9.3)	Colorectum	✓	✓	✓	✓[1,2]	
4 (7.3)	**8** (4.1)	Prostate	✓	✓	✓		
5 (4.9)	**5** (6.8)	Stomach	✓	✓		✓[1]	
6 (4.3)	**3** (7.8)	Liver	✓	✓	✓	✓[1]	
7 (4.1)	**24** (0.5)	Thyroid	✓		✓	✓[3]	
8 (3.3)	**9** (3.6)	Cervix uteri	✓	✓			✓
9 (3.1)	**13** (2.3)	Bladder	✓				
10 (2.8)	**11** (2.6)	Non-Hodgkin lymphoma	✓	✓	✓		
11 (2.6)	**7** (4.6)	Esophagus	✓	✓	✓		
12 (2.6)	**6** (4.8)	Pancreas	✓		✓		✓
13 (2.4)	**10** (3.1)	Leukemia	✓			✓[1,2]	
14 (2.2)	**16** (1.6)	Kidney	✓	✓			
15 (2.1)	**19** (1.0)	Corpus uteri*	✓	✓			
16 (2.0)	**15** (1.9)	Lip, Oral cavity	✓	✓	✓		
		Tongue cancer	✓		✓		
17 (1.7)	**22** (0.6)	Melanoma	✓		✓	✓[1]	
18 (1.6)	**14** (2.1)	Ovarium	✓	✓		✓[3]	✓
19 (1.6)	**12** (2.6)	Brain, CNS	✓				
		Neuroblastoma	✓	✓			
		Glioma, glioblastoma	✓		✓		
20 (0.9)	**18** (1.1)	Larynx	✓		✓		
21 (0.6)	**17** (1.2)	Multiple myeloma	✓	✓			

Note: *including endometrial cancer; **1** CAT1, **2** CAT2, **3** CAT3.
Summarized from Scalise (2020)[1], Hafliger (2019)[2], Zhang (2020)[3], and Bray (2024)[4].

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Supplementary Table S2. LAT1-specific PET radiopharmaceuticals in clinical studies (in comparison with [^{18}F]FDG)

Radiopharmaceutical, Study (year)	*N*	Tumor & other pathology examined (*n* of patient)	Number of malignant and/or benign lesions	Study Design	Advantageous feature(s) in comparison with [^{18}F]FDG in the study
[^{18}F]FAMT					
Inoue (1999) [1]	20	Brain tumors	23 mlgn	Pro	Provide high-contrast images of brain tumors
Watanabe (2000) [2]	74	Musculoskeletal tumors: 24 bone, 48 soft tissue	22 mlgn, 53 bngn	Pro	Superior for differentiation between benign and malignant tumors. SUV correlates with tumor grade
Inoue (2001) [3]	19	Lung canc (10), mlgn myeloma (2), chondrosarcoma (1), prostate canc (1), mlgn lymphoma (1), mlgn of unknown origin (1), Schwannoma (1), sarcoidosis (2)	57 mlgn	Pro	Clinically useful in the diagnosis of malignancy. Effective depiction of primary and metastasis lesions in cardiac region or the brain
Ahmed (2001) [4]	22	Schwannoma	25 bngn	Pro	The most reliable for differentiation of schwannoma from malignancy (compared with CT, MRI & ^{18}F-FDG)
Hatayama (2003) [5]	16	Hemangioma	16 bngn	Pro	SUV correlates well with lesion size while that of ^{18}F-FDG was not
Sato (2003) [6]	14	Gliomatosis cerebri (8): Anaplastic (1), grade II astrocytoma (4) grade III astrocytoma (3). Non-neoplastic disease (6)	8 mlgn, 6 bngn	Pro	Increased uptake strongly suggests malignancy. Only one false-negative result due to high intracranial pressure (diffuse tumor infiltrating the whole brain). All true negative results are in the non-neoplasm group.
Suzuki (2004) [7]	52	Tumors on shoulder girdle	14 mlgn, 38 bngn	Pro	Similarly limited for malignancy detection
Suzuki (2005) [8]	57	Fatty tissue tumor (57): liposarcoma (25), lipoma (32)	25 mlgn, 32 bngn	Pro	Equally accurate to differentiate lipoma from liposarcoma (except well-differentiated type)
Higuchi (2006) [9]	3	Pancreatic lesions (3): SQC (1), pancreatitis (2)	1 mlgn, 2 bngn	Pro	Demonstrated true positive for ca and true negative for pancreatitis
Kaira (2007) [10]	41	Lung canc (17): AC (9), SQC (6), NSCLC (2). Sarcoidosis (24)	17 primary mlgn, 16 LNM mlgn, 24 bngn	Pro	More efficient to distinguish sarcoidosis from malignancy
Kaira (2007) [11]	50	NSCLC: AC (28), SQC (18), non-AC (22)	68 mlgn	Pro	More specific for lymph node staging, similarly sensitive for primary tumor
Miyakubo (2007) [12]	43	Maxillofacial tumors: SQC (34), rhabdomyosarcoma (1), mucoepidermoid ca (1), LNM (14). Benign lesions (7)	36 primary mlgn, 14 LNM mlgn, 7 bngn	Pro	Similar accuracy but higher contrast (by visual assessment)
Kaira (2009) [13]	43	Thoracic tumors (35): SQC (9), AC (19), bronchoalveolar ca (3), atypical SQC (2), LCC (1), carcinoid (1)	35 mlgn, 6 bngn	Pro	Higher specificity and slightly lower sensitivity. Closely correlated with angiogenesis (VEGF, CD31, CD34) and cell proliferation (Ki-67)
Kaira (2009) [14]	37	NSCLC (37): AC (18), SQC (15), LCC (2), others (2)	37 mlgn	Ret	More correlated with angiogenesis (VEGF) and proliferative activity (Ki-67)
Kaira (2009) [15]	98	NSCLC (98): AC (57), SQC (31), LCC (5), others (5)	98 mlgn	Ret	Independent and stronger predictor of OS for AC. More accurate for DFS rate prediction
Nakano (2009) [16]	14	Pancreatic lesions (13): pancreatic ca (7), pancreatitis (6)	7 mlgn, 6 bngn	Pro	Less uptake in benign pancreatic lesions
Kaira (2010) [17]	18	Lung canc (18): AC (10), SQC (4), LCC (1), SCLC (3)	18 mlgn	Pro	Uptake after treatment can predict prognosis
Kaira (2010) [18]	59	NSCLC (59): AC (31), SQC (20), LCC (2), others (6)	59 mlgn	Pro	Primary tumor uptake compared with LAT1 expression: Prognostic factor (univariate analysis). Less powerful prognostic factor for OS (multivariate analysis)
Miyashita (2010) [19]	25	Oral SQC	21 mlgn	Pro	Lower sensitivity but better correlation with cell proliferation (Ki-67)
Oriuchi (2010) [20]	88	NSCLC (88): AC (57), SQC (31)	88 mlgn	Pro	Potential prognostic marker for pulmonary AC.
Sohda (2010) [21]	21	Esophageal SQC	21 primary mlgn, 33 LNM mlgn	Pro	Higher specificity but lower sensitivity than ^{18}F-FDG and CT
Tian (2011) [22]	36	Musculoskeletal tumors	13 mlgn, 23 bngn	Pro	Compared with ^{11}C-Choline and ^{18}F-FDG: Lowest sensitivity but highest specificity
Isoda (2012) [23]	11	Multiple myeloma	34 mlgn bone lesions	Pro	Lower lesion-to-background ratio, similar lesion-to-mediastinum ratio
Morita (2012) [24]	21	Bone mets: lung ori (9), esophagus ori (6), stomach ori (1), bile duct ori (1), pancreas ori (1), thymoma ori (1), prostate ori (2)	72 mlgn	Pro	Detect bone metastasis lesions regardless the bone lesion type
Kim (2013) [25]	27	Oral SQC	27 mlgn (20 bone marrow invasion)	Pro	Accurate tumor delineation/tumor volume prediction
Nobusawa (2013) [26]	68	Oral SQC	68 primary mlgn, 279 LNM mlgn	Ret	Higher specificity for LNM, similar specificity for primary tumors
Sohda (2014) [27]	30	LNM of esophageal SQC	30 LNM mlgn	Ret	LNM uptake is a good predictor of complete response to chemoradiotherapy
Sohda (2014) [28]	40	Esophageal SQC	40 mlgn	Ret	Primary tumor uptake is a good predictor of complete response after chemoradiotherapy
Sohda (2014) [29]	42	Esophageal SQC	42 mlgn	Ret	Primary tumor uptake is a good predictor of DFS in operable tumors
Suzuki (2014) [30]	42	Esophageal SQC	42 mlgn	Ret	Uptake correlated wih cell proliferation (Ki-67) and angiogenesis (CD34)

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Radiopharmaceutical, Study (year)	*N*	Tumor & other pathology examined (*n* of patient)	Number of malignant and/or benign lesions	Study Design	Advantageous feature(s) in comparison with [^{18}F]FDG in the study
Kim (2015) [31]	25	Oral SQC	25 mlgn	Ret	More accurate tumor volume prediction. Not overestimated by inflammations
Kodaira (2016) [32]	24	Liver mets (59): AC (21), SQC (23), NE tumor ori (9), carcinoid (6)	59 mlgn	Ret	Could detect metastatic liver lesions from various types of primary tumors (pancreas, lung, rectum, esophagus, and oral canc), except NE tumor
Kaira (2016) [33]	95	Advanced lung canc, stage IIIA (18), stage IIIB (23), stage IV (54): AC (15), SQC (21), LCC (5), SCLC (8), other (6)	55 mlgn	Pro	Metabolic response was an independent factor to predict the OS after first-line chemotherapy
Horiguchi (2017) [34]	38	Glioma: WHO stage II (12), stage III (12), stage IV (14)	12 low grade glioma, 26 high grade	Ret	Higher T/N ratio, able to differentiate low- and high-grade gliomas
Honjo (2017) [35]	142	Esophageal SQC	142 mlgn	Ret	Uptake (and LAT1 expression) correlates with metastasis-associated gene 1 (MTA-1)
Sohda (2018) [36]	82	Esophageal SQC	82 mlgn	Pro	Lower rate of nonspecific uptake
Sohda (2018) [37]	6	Locally advanced esophageal SQC (without distant mets)	6 mlgn	Pro	More accurate modality for complete response judgment at 1 month after chemoradiotherapy
Kumasaka (2018) [38]	112	NSCLC (112): AC (72), SQC (28), other (12)	112 mlgn	Pro	Pretreatment MTV was highly prognostic of OS (median follow up: 1.58 years)
Kim (2019) [39]	160	Oral SQC	160 mlgn	Ret	MTV predict OS (mean follow up: 4.5 years)
Kuriyama (2020) [40]	41	Esophageal SQC	41 mlgn	Ret	High SUV_{max} was a predictor of hot tumor immune status (high PD-L1, high $CD8^+$ lymphocytes within tumors)
Shimizu (2020) [41]	75	NSCLC (75): AC (51), non-AC (24)	75 mlgn	Ret	High uptake was associated with staging, initial treatment, and tumor immune marker (PD-L1) expression. No significant correlations between tumor-infiltrating lymphocytes and SUV_{max}
Suzuki (2021) [42]	31	Intraosseus ca of oral canc (18), maxillo-mandibular actinomycosis/ actinomycotic osteomyelitis (13)	18 mlgn, 13 bngn	Ret	Negative uptake in progressive actinomycotic osteomyelitis lesions (bone resorption with irregular margins, very similar to intraosseus carcinoma) clearly differentiate these lesions from malignancies
[^{18}F]FBPA					
Yoshino (1997) [43]	5	Brain mets (5): breast origin (2), lung origin (3)	8 mlgn	Pro	Along with [^{18}F]FDG, useful to differentiate between tumor progression and radiation necrosis
Mishima (1997) [44]	4	Melanoma (3), brain mets (rhabdomyosarcoma) (1)	6 mlgn	Pro	(※) T/N ratio ranged from 2.3 to 3.38
Kabalka (1997) [45]	2	Glioblastoma multiforme (2)	2 mlgn	Pro	(※) Can be used to determine the distribution of brain tumor tissue and estimate radiodosimetry before BNCT
Imahori (1998) [46]	33	Primary glioma (33): glioblastoma multiforme (13), astrocytoma WHO grade II (8), and anaplastic astrocytoma WHO grade III (12)	25 high grade glioma, 8 low grade glioma	Pro	(※) T/N ratio ranged for high grade glioma were 1.55 – 5.15, while for low grade glioma were 0.8 – 1.95; hence suggested cut off T/N ratio for malignancy was >2
Takahashi (2003) [47]	22	Glioblastoma (9), anaplastic astrocytoma (7), diffuse astrocytoma (6)	16 high grade glioma, 6 low grade glioma	Pro	(※) The mean survival time was significantly shorter in patients with high uptakes
Havu-Aurén (2007) [48]	10	Sporadic & neurofibromatosis (NF2)-related intracranial tumors (10): meningioma (4), Schwannoma (6)	10 bngn	Pro	(※) SUV_{max} (2.4 – 7.6) was two- to fourfold higher in tumor as compared with normal brain and independent of NF2 status
Miyatake (2007) [49]	6	Malignant meningioma (6): papillary (2), atypical (1), anaplastic (1), sarcoma transformed from a meningioma (1)	10 mlgn	Pro	(※) T/N ratio ranged from 2 to 5
Ariyoshi (2007) [50]	4	Recurrent oral canc & cervical LMN (4): SQC (2), AC (1), mucoepidermoid ca (1)	4 mlgn	Pro	(※) T/N ratios ranged from 2.2 to 4.0
Kankaanranta (2007) [51]	12	Head & neck canc (12): SQC (10), adenocystic carcinoma (1), transitional cell ca (1)	12 mlgn	Pro	(※) T/N ratios ranged from 2.5 to 6.3 (median, 3.6)
Fuwa (2008) [52]	5	Head & neck canc (5): SQC (4), adenoid cystic canc (1)	5 mlgn	Pro	(※) T/N ratios ranged from 4.0 to 12.5
Nairai (2009) [53]	12	Glioblastoma multiforme (11), anaplastic astrocytoma (1)	12 mlgn	Pro	(※) High linear correlation between T/N ratio and boron concentration (r^2=0.89), similar to [^{11}C]MET
Kimura (2009) [54]	6	Recurrent oral canc & cervical LMN (6): SQC (2), AC (2), melanoma (1), mucoepidermoid ca (1)	6 mlgn	Pro	(※) T/N ratios ranged from 1.9 to 4.0
Kankaanranta (2012) [55]	15	Head & neck canc (15), mostly SQC (Note: only 15 of 30 pts underwent [^{18}F]FBPA PET studies)	15 mlgn	Pro	(※)T/N ratios ranged from 2.5 to 9.0 (median, 4.1)
Kawabata (2013) [56]	19	High grade meningioma (19): papillary (2), atypical (4), anaplastic (11), sarcoma (1), rhabdoid (1)	19 mlgn	Pro	(※)T/N ratios ranged from 2.0 to 5.0 (18 pts have T/N ratio ≥ 2.7)

Supplementary Table S2. LAT1-specific PET radiopharmaceuticals in clinical studies (in comparison with [^{18}F]FDG)

Radiopharmaceutical, Study (year)	*N*	Tumor & other pathology examined (*n* of patient)	Number of malignant and/or benign lesions	Study Design	Advantageous feature(s) in comparison with [^{18}F]FDG in the study
Tani (2014) [57]	20	Head & neck canc (20): SQC (9), adenoid cystic ca (5), AC (1), basal cell ca (1), NE cell ca (1), salivary duct ca (1), pleomorphic adenoma (1), esthesioneuroblastoma (1)	20 mlgn	Pro	T/N ratios ranged from 1.35 to 5.98. Uptake was correlated with [^{18}F]FDG uptake (r^2=0.72). [^{18}F]FDG SUV_{max} of ≥ 5 can predict [18F]FBPA SUV_{max} of ≥ 2.5.
Kobayashi (2016) [58]	10	Head & neck canc (10): tongue ca (2), oropharynx ca (1), adenoid cystic ca (1), paranasal ca (1), chondrosarcoma (1), buccal mucosa ca (1), soft palate ca (1), melanoma (1), nasopharyngeal ca (1)	10 mlgn	Pro	T/N ratios ranged from 1.73 to 5.21. In 9/10 patients, the spatial distribution of SUVs in the tumor volume positively correlates with that of [^{18}F]FDG. A tumor sub-volume with a high [^{18}F]FDG uptake may predict high accumulation of [^{18}F]FBPA
Watanabe (2017) [59]	7	Head & neck canc (7): SQC (2), adenoid cystic ca (2), rhabdomyosarcoma (2), melanoma (1)	7 mlgn	Pro	(※) T/N ratios ranged from 1.3 to 3.9. SUV_{max} was correlated with that of [^{11}C]MET (r^2=0.72), but not significant
Morita (2018) [60]	28	Head & neck canc SQC (20), malignant melanoma (8)	28 mlgn	Pro	(※) The dynamics of mean T/N ratio in 30, 60, and 12 min of SQC (n = 20) were 3.21, 3.28, and 2.79; while mean T/N ratio of malignant melanoma (n = 8) were 7.89, 7.69, and 6.68.
Beshr (2018) [61]	12	Brain lesions (12): tumor recurrence [6: astrocytoma grade 2 (1), glioblastoma multiforme (1), oligo-astrocytoma grade 2 (1), oligo-astrocytoma grade 3 (1), anaplastic oligo-astrocytoma grade 3 (1), and hemangiopericytoma (1)] and necrosis [6: glioblastoma multiforme (4), meningioma (1), and mets of lung (1)].	12 mlgn	Pro	(※) PET parameters (SUV_{mean}, SUV_{max}, MTV, and total lesion uptake) of tumor recurrence (n=6) were significantly larger (2.9 vs 1.2; 4.6 vs 1.9; 44.9 vs 10.6; and 121 vs 12.3) than that in radiation necrosis (n=6)
Igaki (2020) [62]	120	Analysis 1 & 2: Head & neck SQC (11 & 27), AC (7 & 23), adult type sarcoma (5 & 13), juvenile type sarcoma (3 & 9), malignant melanoma (2 & 7), glioma (2 & 2), unknown histopathology (0 & 1)	120 mlgn	Pro	Analysis 1 (n = 30): SUV_{max} and T/N ratio correlated with that of [^{18}F]FDG (r^2=0.74 and r^2=0.65) Analysis 2 (n = 82): SUV_{max} correlated with that of [^{18}F]FDG (r^2=0.48). No convincible conclusions of clear correlations of SUVmax between [^{18}F]FDG and [^{18}F]FBPA
Lo (2020) [63]	25	Glioblastoma multiforme (12), anaplastic astrocytoma (4), diffuse intrinsic pontine glioma (1), meningioma (1), gingival canc (1), maxillary sinus canc (1), liposarcoma (1), tongue canc (1), buccal canc (1), thyroid canc (1), nasopharyngeal canc (1)	25 mlgn	Pro	(※) T/N ratios of glioblastoma multiforme ranged from 2.44 to 5.56, while other tumors ranged from 2.15 (nasopharyngeal ca) to 5 (buccal canc)
Isohashi (2022) [64]	82	Oral canc (13), soft tissue sarcoma (12), pharyngeal canc (10), salivary gland canc (6), external auditory canal canc (4), diffuse large B-cell lymphoma (3), laryngeal canc (3), skin canc (3), endometrial canc (3), cervical canc (3), mantle cell lymphoma (2), lung AC (2), breast canc (1), esophageal canc (2), ovarian canc (1), olfactory neuroblastoma (1), chronic lymphocytic leukemia (1), gallbladder canc (1), pancreatic canc (1), maxillary canc (1), bile duct canc (1), acute myeloid leukemia (1), canc of unknown primary (1), cervical LNM (1), Paget's disease (1). Benign lesions [11**:** inflammatory granulation (2), abscess (2), radiation osteomyelitis (2), inflammatory lymphadenopathy (1), chemoradiotherapy post-treatment change (1), tonsillitis (1), cholecystitis (1), graft versus host disease (1)]	77 mlgn (22 primary/recurrent and 55 mets), 11 bngn	Pro	The SUV_{max} of [^{18}F]FDG PET/CT did not significantly differentiate malignant tumors from benign lesions, whereas SUV_{max} of [^{18}F]FBPA PET/CT was significantly higher for malignant tumors
Minoji (2023) [65]	3	Colorectal canc (3, all with T2N0M0)	3 mlgn	Pro	The SUV_{max} (compared to that of [^{18}F]FDG) for each tumor were 3.7 vs 17.44; 3.6 vs 8.48; and 3.98 vs 14.35. All tumor lesions were scored 2 (of 4-point scales) in immunohistochemical analysis.
Watabe (2023) [66]	55	Primary lung canc [21: AC (13), SQC (5), NE ca (2), LCC (1)]; Lung mets [6: bladder NE ca (1), rectal ori (2), pharyngeal ori (1), breast ori (1)]; Thymoma [10: type AB (2), B1 (2), B2 (3), B3 (2), and atypical A (1)]; thymic canc (2), carcinoid (2), mesothelioma (1); and benign lesions (13)	42 mlgn, 13 bngn	Pro	SUV_{max} was positively correlated with LAT1 expression (r=0.61). Benign lesions showed significantly lower SUV_{max} than those in maligancies. SUV_{max} weakly correlates with that of [^{18}F]FDG (0.438, P=0.012) Significantly lower uptake in the benign lesions, even when [^{18}F]FDG PET showed high uptake. Thymomas, thymic canc, and mesotheliomas showed moderate uptake, while carcinoid showed low uptake.
[^{18}F]FBY					
Li (2021) [67]	18	Suspect of glioma (13) and normal volunteer (6)	14 glioma		(※) Elevated uptake is consistent with tumor grade and correlated with LAT1 expression (r^2 = 0.80, P < 0.001) T/N ratio was 24.5 in high grade glioma and 2.3 in low grade glioma.

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Radiopharmaceutical, Study (year)	*N*	Tumor & other pathology examined (*n* of patient)	Number of malignant and/or benign lesions	Study Design	Advantageous feature(s) in comparison with [^{18}F]FDG in the study
Kong (2022) [68]	35	Primary diffuse glioma (12): WHO grade II (7), III (2), IV (3); Recurrent diffuse glioma (14): WHO grade II (2), III (6), IV (6); Brain mets (5): breast ori (2), lung ori (2), colorectal ori (1); Others (5): anaplastic pleomorphic xanthoastrocytoma (1), atypical meningioma (1), ganglioglioma (1), gliosis (1), and stable disease	9 low grade glioma, 17 high grade glioma, 7 other mlgn, and 2 bngn (gliosis & stable disease)	Pro	(※) Elevated uptake in most malignant brain tumors (SUV_{max} up to 3.0), while SUV_{max} of normal brain was 0.12. Significant T/N ratio was observed in primary GBM (22.6 ± 6.6), recurrent glioma (23.7 ± 8.3), and metastatic brain tumor (20.2 ± 3.8); while primary lower grade glioma displayed moderate T/N ratio (2.2 ± 1.3).
Kong (2022) [69]	23	Diffuse brain tumors (16): primary WHO grade IV (3), recurrent WHO grade II (1), grade III (6), and grade IV (6); Circumscibed brain tumor (7): mets of breast (2), mets of lung (2), mets of colorectal (1), anaplastic pleomorphic xanthoastrocytoma (1), and atypical meningioma (1)	23 mlgn	Pro	(※) MTVs obtained were larger than tumor volume obtained from contrast-enhanced area in MRI images especially in diffuse tumor; suggesting as a better delineation tool.

Abbreviations: AC adenocarcinoma, **bngn** benign, **ca** carcinoma, **canc** cancer, **DFS** Disease-free survival, **LCC** large cell carcinoma, **LNM** lymph node metastases, **mets** metastasis, **mlgn** malignant, **MTV** metabolic tumor volume, ***N*** number of patients, **NE** neuroendocrine, **NSCLC** non-small cell lung cancer, **ori** origin, **OS** overall survival, **Pro** prospective, **Ret** retrospective, **SCLC** small cell lung cancer, **SQC** squamous cell carcinoma, **SUV** standardized uptake value, **T/N** tumor-to-normal.
(※) [^{18}F]FDG was not used for comparison.

Supplementary Table S2. LAT1-specific PET radiopharmaceuticals in clinical studies (in comparison with [^{18}F]FDG)

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