Physiological Biodistribution of 68Ga-DOTA-NOC in Normal Pediatric and Adult Population

By:

Hira Tahir, Ubaira Shaukat, M. Numair Younis and Abu Baker Shahid

Institute of Nuclear Medicine and Oncology Lahore (INMOL)

Objectives

To establish the physiological biodistribution pattern of 68Ga-DOTA-NOC in various organs in pediatric and adult subjects in our local clinical setup and identify a range of SUVmax and SUVmean and to contribute to international data.

Materials and Methods

Sample Selection

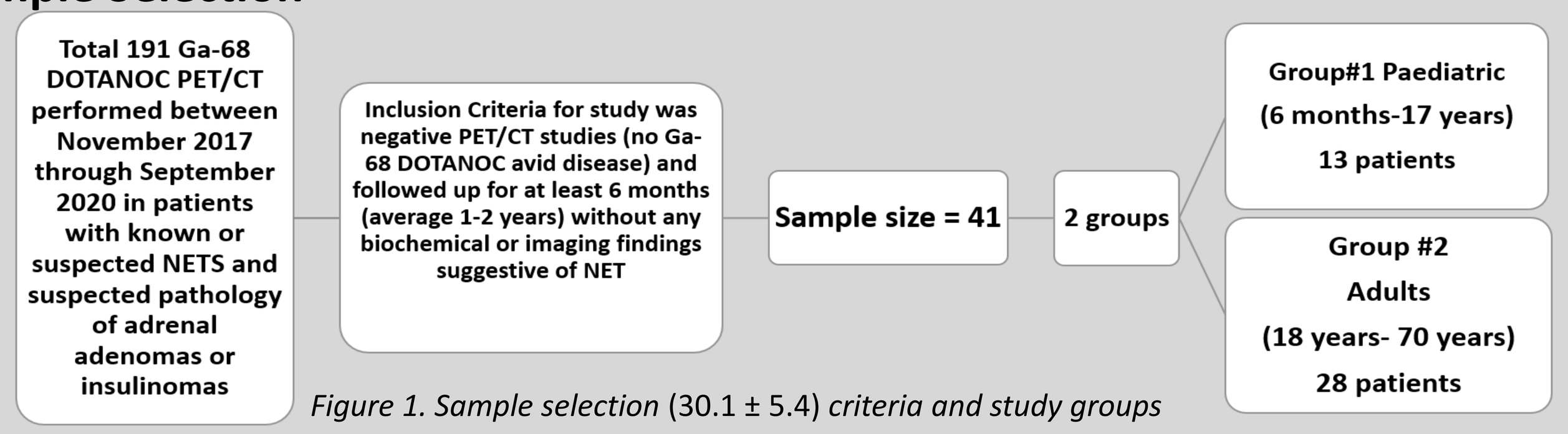


Figure 1. Sample selection (30.1 ± 5.4) criteria and study groups

Ga 68 DOTA-NOC PET/CT Kit Preparation

Ga 68 DOTANOC is prepared from Ge68/Ga68 generator of 50 mCi from iTG Germany. All reagents/kits are procured from iTG and peptide (DOTA-NOC) are got from ABX Germany. In IQS-TS chemistry synthesis module, as per prescribed SOPs, after the generator is eluted, production of Ga 68 DOTANOC completes in 15 minutes. Product is collected in sterile vial after passing from 0.22um filter.

QC of the product is performed for identity (using dose calibrator , TLC, HPLC-y), purity (radiochemical purity 97.5%), injectability (ph=6.2) and biological purity(using LAL test: 17.5 EU/ml). Ge-68 breakthrough test was also performed and level of 68Ge in the final preparation was lower than 0.001% of the 68Ga radioactivity.

Ga 68 DOTA-NOC PET/CT Patients Preparation and Procedure

Informed consent was taken and thorough explanation of the test was given to the patient. Blood pressure, pulse, height, weight, blood sugar levels were noted. I/V line was maintained. Inj. Ga 68 DOTANOC (2 MBq/kg) was given I/V. The activity administered ranged from 100 to 200 MBq. Patients voided before scanning to reduce the background noise as well as the radiation dose to the kidneys and bladder.

Ga 68 DOTANOC PET/CT Image Acquisition

Data was acquired using Discovery ST PET/CT system (GE, healthcare, USA). The timing of image acquisition ranges between 45-90 min after injection. Subjects were allowed to breathe normally during PET and CT acquisitions. During acquisitions, patient were remained in supine position with their arms raised above their head. CT images were acquired prior to PET acquisition (3.8mm slice thickness, 100 kV, 50 mA) and time of acquisition was 5 seconds per bed position for seven to eight bed positions. PET emission data were acquired at 3 minutes/bed position from the base of the skull to feet/midthigh in three dimensional mode Bismuth Germanium scanner (BGO). PET images were reconstructed using CT data by iterative reconstruction. Attenuation corrected PET/CT images were reviewed on Mac System.

Ga 68 DOTANOC PET/CT Image Analysis

68Ga-DOTA-TATE PET/CT images were analyzed by two nuclear medicine physicians and one third year resident. Maximum and mean standardized uptake values (SUVmax and SUVmean) values were calculated from a 2 cm volume of interest (ROI) applied in the transaxial attenuation-corrected PET slice in various organs and structures in both adult group and pediatric group. SUVmax was defined as the SUVmax in the ROI. SUVmean was taken as the average SUV concentration in ROI. structures for each patient using at least 2cm circular ROIs, avoiding inclusion of any activity from adjacent organs. Lung measurements were performed in the lower lobes away from the hilar vasculature, and kidney measurements were performed by avoiding the inclusion of pelvicalyceal urinary activity.

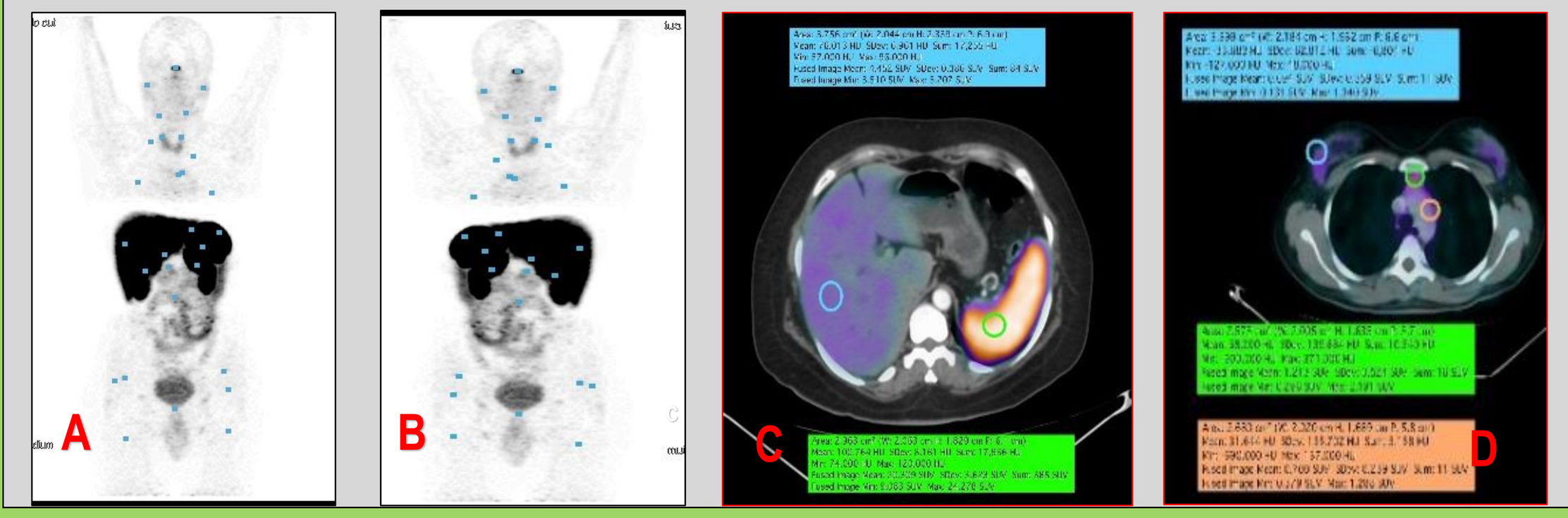


Figure 2. (A,B) ROIs drawn on various organs shown in anterior and posterior projection MIP images (C,D) Transaxial images showing ROIs of 2 cm on liver, spleen, breast, thymus and arch of aorta (mediastinum)

Ga 68 DOTANOC PET/CT Image Analysis (Continued…)

SUVmax and SUVmean were evaluated on axial images in 24 normal anatomical structures including pituitary gland, parotid glands, submandibular glands, thymus, thyroid gland, mediastinum, lungs, breast, stomach, small intestine, liver, spleen, pancreas head, pancreas body, right adrenal gland, left adrenal gland, right kidney, left kidney, prostate, uterus, trapezius muscle, gluteal muscles, iliac crest, and femora were obtained.

*2 cm ROIs could not be drawn on few organs like pituitary, thyroid gland and adrenal gland in pediatric group due to smaller organ size and anatomical location of adrenals (overlap with kidneys in case of larger ROIs)

Ga 68 DOTANOC PET/CT Images Statistical Analysis

Demographics of study sample were analyzed.

Univariate descriptive statistics [frequency, maximum and minimum value, mean, median, standard deviation (SD) and range] were calculated on SPSS 20.

The SUVmax values were categorized as **high** (more than 50th percentile of liver), **moderate** (less than liver), **mild** (between moderate and minimal), and **minimal** (organ having least SUVs) as suggested by studies of Ozguven et. al [1] and Moradi et. al [2].

Graphical and tabular representation was done using Microsoft Excel.

Results

Demographics of Study Population

Study Population= 41 subjects	Group 1 Pediatric Group	Group 2 Adult Group
No of subjects (N)	13	28
Age (Range)	6 months – 17 years	18 years - 70 years
Age(Mean)	8.5 years	38 years
Males(N)	6	15
Females(N)	7	13

Table 1. Range, mean age and no (N) of males and females in Group 1 and 2

SUVmax and SUVmean of various oragns in Pediatric Group (Group 1)

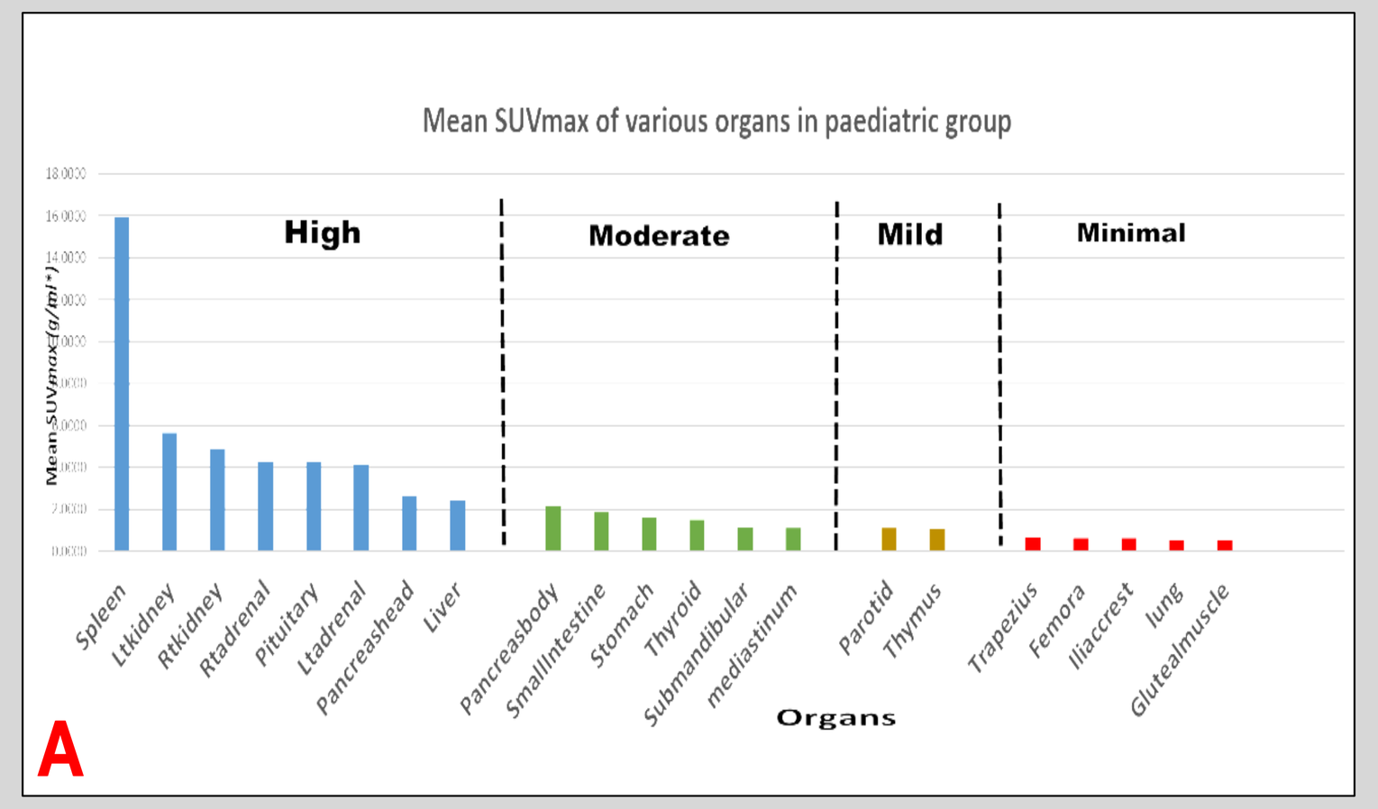
Organ	N	Range SUVmax (g/ml*)	Minimum SUVmax (g/ml*)	Maximum SUVmax (g/ml*)	Mean SUVmax (g/ml*)	Std. Deviation SUVmax (g/ml*)
Spleen	13	24.20	3.80	28.00	15.9385	9.08162
Ltkidney	13	2.40	4.50	6.90	5.6692	.88070
Rtkidney	13	2.30	3.80	6.10	4.8462	1.01293
Rtadrenal	13	12.4	1.6	14	4.3	4.55
Pituitary	13	15.10	1.30	16.40	4.2769	5.40188
Ltadrenal	13	12.40	1.60	14.00	4.1538	4.41769
Pancreashead	13	3.60	1.20	4.80	2.6308	1.33815
Liver	13	3.50	1.00	4.50	2.4462	1.34822
Pancreasbody	13	1.80	1.20	3.00	2.1923	.63438
SmallIntestine	13	1.50	1.20	2.70	1.8615	.56353
Stomach	13	1.60	.80	2.40	1.5846	.67063
Thyroid	13	1.70	1.00	2.70	1.5308	.58364
Submandibular	13	1.00	.80	1.80	1.1538	.44463
mediastinum	13	1.00	.80	1.80	1.1154	.36251
Parotid	13	1.40	.60	2.00	1.0923	.58233
Thymus	13	.80	.80	1.60	1.0769	.31925
Trapezius	13	1.10	.30	1.40	.6846	.33378
Femora	13	.70	.40	1.10	.6231	.26190
Iliaccrest	13	.40	.40	.80	.6154	.16756
lung	13	0.4	0.4	0.8	0.56	0.16
Glutealmuscle	13	.50	.40	.90	.5231	.18777

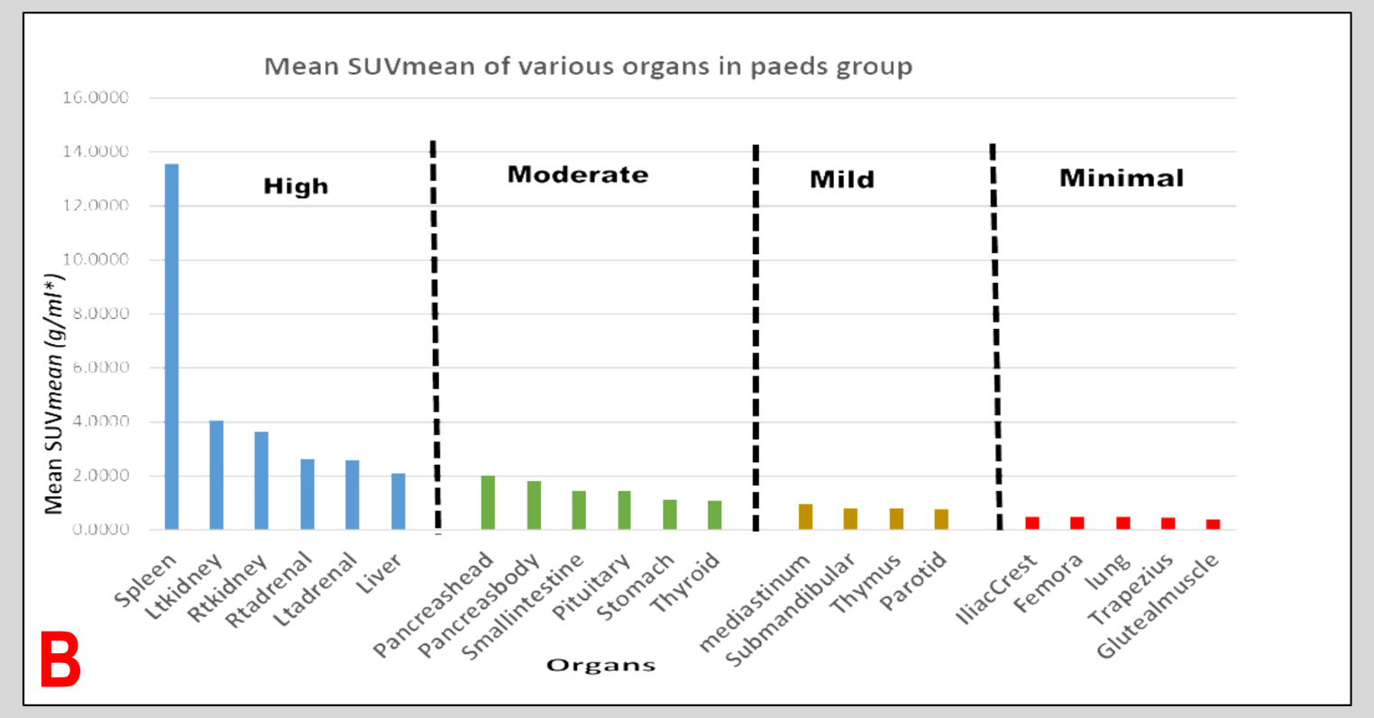
Table 2. Range, minimum, maximum, mean and standard deviation of maximum standardized uptake value (SUVmax) in various organs in pediatric group (number of subjects N=13). Color coding: Blue-high uptake, Green-moderate, Yellow- mild, Pink-minimal

Organs	N	Range SUVmean (g/ml*)	Minimum SUVmean (g/ml*)	Maximum SUVmean (g/ml*)	MEAN SUVmean (g/ml*)	Std. Deviation SUVmean (g/ml*)
Spleen	13	21.40	3.60	25.00	13.5692	8.46871
Ltkidney	13	2.00	3.00	5.00	4.0615	.64877
Rtkidney	13	2.00	2.50	4.50	3.6231	.74067
Rtadrenal	13	4.50	1.40	5.90	2.6231	1.48220
Ltadrenal	13	5.90	1.00	6.90	2.5769	2.05676
Liver	13	2.70	.90	3.60	2.1000	1.09545
Pancreashead	13	2.30	1.10	3.40	2.0077	.86839
Pancreasbody	13	1.60	1.10	2.70	1.8154	.58998
Smallintestine	13	1.10	.80	1.90	1.4462	.45756
Pituitary	13	3.00	.80	3.80	1.4462	1.05957
Stomach	13	1.30	.60	1.90	1.1154	.40383
Thyroid	13	.80	.80	1.60	1.1077	.33031
mediastinum	13	1.00	.60	1.60	.9385	.34044
Submandibular	13	.40	.70	1.10	.8231	.17394
Thymus	13	.30	.70	1.00	.8231	.12352
Parotid	13	.80	.50	1.30	.7692	.33263
IliacCrest	13	.40	.30	.70	.5000	.16833
Femora	13	.70	.30	1.00	.4800	.24781
lung	13	0.4	0.3	0.7	0.47	0.21
Trapezius	13	.80	.20	1.00	.4600	.30655
Glutealmuscle	13	.50	.20	.70	.3900	.15525

Table 3. Range, minimum, maximum, mean and standard deviation of mean standardized uptake value (SUVmean) in various organs in pediatric group (number of subjects N=13).Color coding: Blue-high uptake, Green-moderate, Yellow- mild, Pink-minimal

Results





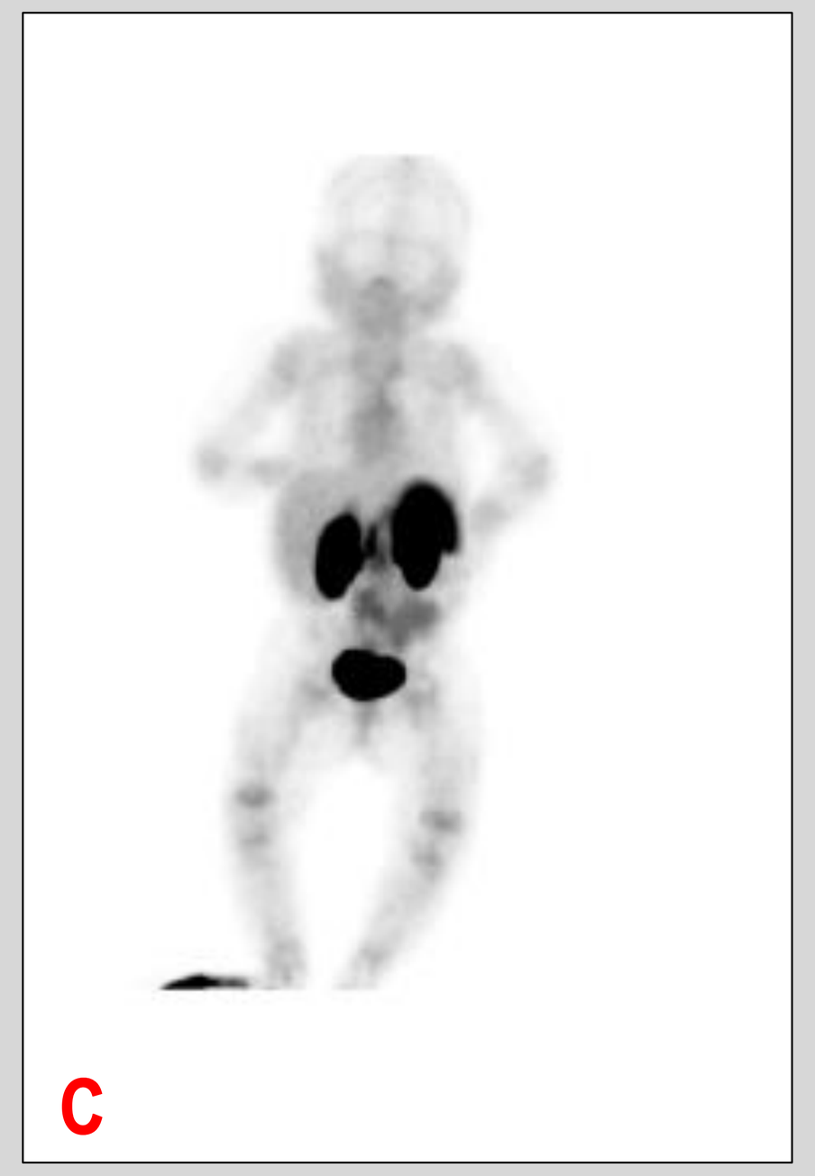


Figure 3. (A,B) Graphical representation of mean SUVmax and mean SUVmean in various organs in pediatric group and categories into high, moderate, mild and minimal based on uptake of Ga 68 DOTA-NOC.
C. Physiological bio distribution of Ga 68 DOTANOC in a child as seen in MIP image

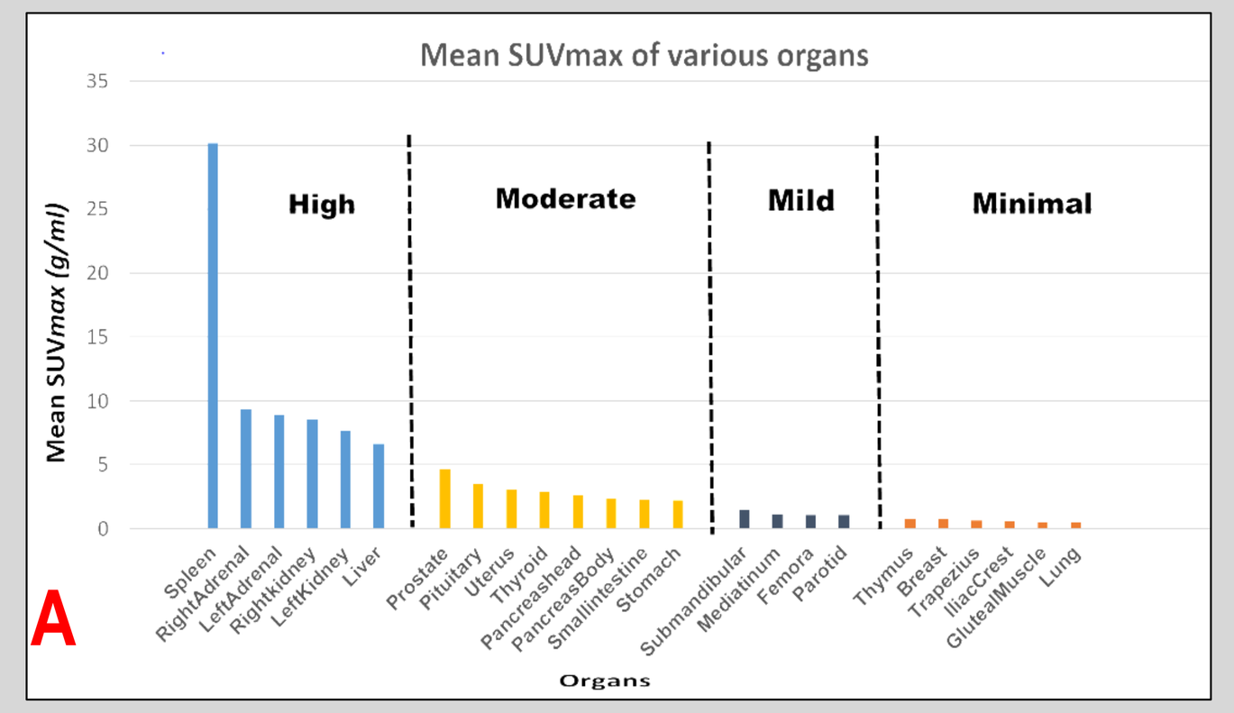
SUVmax and SUVmean of various oragns in Adult Group (Group 2)

Organ	N	Range SUVmax (g/ml*)	Minimum SUVmax (g/ml*)	Maximum SUVmax (g/ml*)	Mean SUVmax (g/ml*)	Std. Deviation SUVmax (g/ml*)
Spleen	28	19.40	19.60	39.00	30.1643	5.41057
RightAdrenal	28	20.0	2.0	22.0	9.339	5.3724
LeftAdrenal	28	18.0	3.0	21.0	8.925	4.7582
Rightkidney	28	14.8	3.9	18.7	8.575	3.8030
LeftKidney	28	10.0	4.0	14.0	7.671	2.8963
Liver	28	7.00	3.60	10.60	6.6357	1.86830
Prostate	15	7.8	1.7	9.5	4.700	3.0115
Pituitary	28	13.9	2.1	16.0	3.500	2.7046
Uterus	12	1.5	2.3	3.8	3.100	1.5593
Thyroid	28	4.2	1.2	5.4	2.914	1.1569
Pancreashead	28	4.80	1.00	5.80	2.6321	1.39684
PancreasBody	28	4.00	1.10	5.10	2.3250	1.00981
Smallintestine	28	3.20	.50	3.70	2.2964	1.00939
Stomach	28	5.20	.30	5.50	2.2357	1.47377
Submandibular	28	1.9	.7	2.6	1.493	.4729
Mediatinum	28	1.2	.7	1.9	1.143	.4220
Femora	28	1.0	.2	2.2	1.100	.2999
Parotid	28	2.2	.3	2.5	1.096	.4918
Breast	13	0.9	0.4	1.3	.740	.3400
Trapezius	28	1.0	.3	1.3	.661	.3281
IliacCrest	28	.8	.4	1.2	.600	.2160
GlutealMuscle	28	.50	.30	.80	.5179	.15167
Lung	28	1.0	.1	1.1	.518	.2583

Table 4. Range, minimum, maximum, mean and standard deviation of maximum standardized uptake value (SUVmax) in various organs in ADULT group (number of subjects N=28). Color coding: Blue-high uptake, Green-moderate, Yellow- mild, Pink-minimal

Organs	N	Range SUVmean (g/ml*)	Minimum SUVmean (g/ml*)	Maximum SUVmean (g/ml*)	Mean SUVmean (g/ml*)	Std. Deviation SUVmean (g/ml*)
Spleen	28	14.0	16.0	30.0	24.536	4.0413
Liver	28	5.70	3.00	8.70	5.2821	1.57810
RightAdrenal	28	10.2	.8	11.0	5.007	2.7790
LeftAdrenal	28	9.6	1.4	11.0	4.696	2.7362
RightKidney	28	9.7	1.0	10.7	3.714	2.7595
LeftKidney	28	4.5	1.3	5.8	3.618	1.2449
Pituitary	28	5.7	.7	6.4	2.700	1.5000
Prostate	15	4.2	1.3	5.5	2.670	1.7520
Thyroid	28	1.7	.8	2.5	1.675	.5176
PancreasBody	28	3.90	.50	4.40	1.6429	.93192
Pancreashead	28	2.2	.7	2.9	1.496	.6692
Smallintestine	28	2.3	.4	2.7	1.443	.7249
Stomach	28	3.6	.1	3.7	1.289	.8950
Uterus	12	1.5	2.3	3.8	1.043	0.3800
Submandibular	28	1.5	.4	1.9	.957	.2987
Thymus	4	1.1	0.4	1.5	.900	.4500
Femora	28	5.9	.1	6.0	.761	1.4873
Breast	13	.9	0.4	1.3	.760	.3500
Parotid	28	1.2	.4	1.6	.700	.2494
Mediatinum	28	.9	.4	1.3	.679	.2713
Trapezius	28	.5	.2	.7	.375	.1669
IliacCrest	28	.7	.2	.9	.371	.1675
Lung	28	.7	.1	.8	.336	.2041
GlutealMuscle	28	.50	.10	.60	.3300	.13089

Table 5 . Range, minimum, maximum, mean and standard deviation of mean standardized uptake value (SUVmean) in various organs in ADULT group (number of subjects N=28). Color coding: Blue-high uptake, Green-moderate, Yellow- mild, Pink-minimal



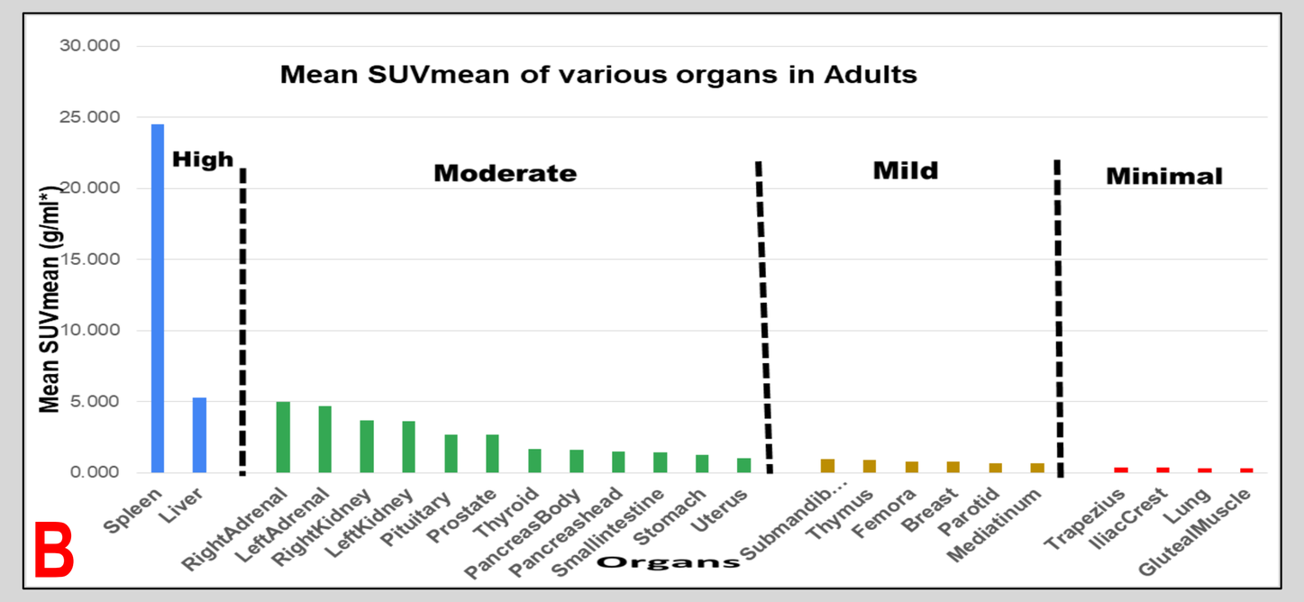


Figure 4. (A,B) Graphical representation of mean SUVmax and mean SUVmean in various organs in adult group and categories into high, moderate, mild and minimal based on uptake of Ga 68 DOTA-NOC.
C. Physiological bio distribution of Ga 68 DOTANOC in An adult as seen in anterior projection MIP image

- Highest uptake of Ga 68 DOTA NOC was observed in spleen followed by adrenals, kidneys and liver in both groups.
- In **pediatric** group highest uptake (SUVmax) was noted in spleen (15.9 ± 9.1) followed by kidneys, adrenals, pituitary, pancreatic head and liver in descending order. Moderate uptake was noted in pancreatic body, small intestine, stomach, thyroid, mediastinum. Mild to minimal uptake was noted in thymus, parotid, lungs, muscle and bones. Pituitary gland showed a wide range of uptake values (SUVmax 1.3-16.4). Pancreatic head showed relatively increased uptake as compared to body. Submandibular gland showed variable pattern.
- Difference in SUVmax and SUVmean categorization was observed for pituitary, pancreatic head which were in high uptake group on the basis of SUVmax but in moderate category according to SUVmean. SUVmax being a better representative of uptake of radiopharmaceutical could be used more reliably for categorizing organ uptake into high, moderate, mild or minimal.

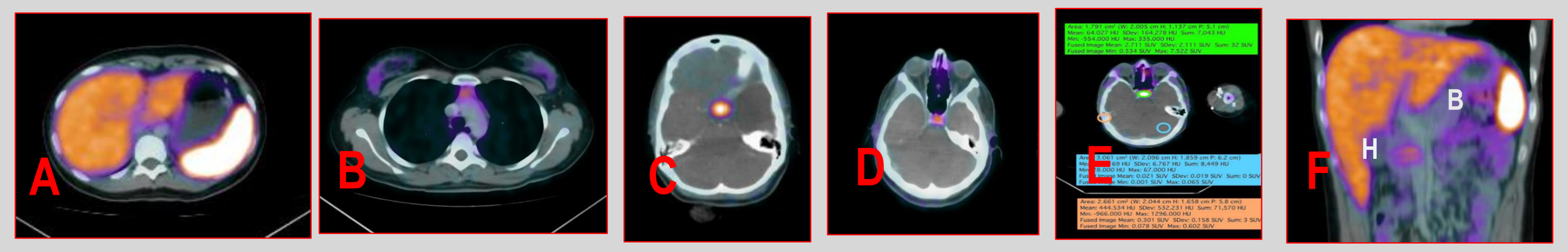


*Figure 5. A- Highest uptake noted in spleen on trans axial PET/CT image. B-Mild to minimal uptake noted in mediastinum and thymic tissue. C- High uptake (SUVmax 12.1) in pituitary gland D- low uptake in pituitary gland (SUVmax 1.3), showing variation in uptake pattern of pituitary gland . E- only area of high uptake in brain is pituitary gland while uptake in cerebellum and cranial vault is minimal. F- coronal PET/CT fused image showing more Ga 68 DOTANOC uptake in pancreatic head **H** (SUVmax 3.0) as compared to pancreatic body **B** (SUVmax 1.2) .*

- In **adult** group, highest uptake was noted in spleen (30.1 ± 5.4) followed by adrenals, kidneys and liver. Moderate uptake was noted in pancreas head and body, small intestines, stomach, thyroid, prostate and uterus. Mild to minimal in breast, salivary glands, mediastinum, lung, muscles and bones.
- Difference in SUVmax and SUVmean categorization was observed for adrenal glands and kidneys which were in high uptake group on the basis of SUVmax but in moderate category according to SUVmean. SUVmax being a better representative of uptake of radiopharmaceutical could be used more reliably for categorizing organ uptake into high, moderate, mild or minimal.
- **Inter group** analysis showed that submandibular gland and mediastinum showed moderate uptake in pediatric group and mild uptake in adult group.

Conclusions

- Ranges of the SUVmax and SUVmean of 68Ga-DOTA-NOC obtained in the different organs in both pediatric and adult groups were determined and mild differences in the uptake pattern among the two groups were also noted.
- The range observed in different organs in our study groups provides a benchmark which may be used by other researchers in identifying abnormal /malignant pathologies.
- Our data is expected to contribute towards global efforts in reliably identifying semi-quantitative techniques for evaluation of NETs in patients undergoing 68Ga-DOTA-NOC PET/CT studies.

References:
[1] Özgüven S, Filizoğlu N., KesimS. Physiological Biodistribution of 68Ga-DOTA-TATE in Normal Subjects. Mol Imaging Radionucl Ther 2021;30:39-46
[2] Moradi F, Jamali M, Barkhodari A, Schneider B, Chin F, Quon A, Mittra ES, Iagaru A. Spectrum of 68Ga-DOTA TATE Uptake in Patients With Neuroendocrine Tumors. Clin Nucl Med 2016;41:281-287.