

# Angiogenesis Imaging Study Using [ $^{18}\text{F}$ ] RGD-K5 PET/CT in Patients with Lymphoma Under Chemotherapy.

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## Original research

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# Abstract

**Background :** Our aim was to measure the impact of two cycles of standard chemotherapy on tumoral neoangiogenesis by [<sup>18</sup>F] Fluorine arginine-glycine-aspartic (RGD-K5) Positron Emission Tomography – Computed Tomography (PET) on patients presenting with lymphoma.

Twenty one patients were prospectively included in Rouen’s Henri Becquerel Cancer Center. Fluorodeoxyglucose (FDG) and RGD-K5 PET were performed before (C0) and after (C2) two cycles of chemotherapy. End of treatment FDG PET was performed for final staging. Maximum Standardized Uptake Value (SUVmax), Mean SUV and Metabolic Tumor Volume (MTV) were measured for all lesions. RGD SUVmax and meanSUV were also analysed in 13 normal organs at C0 and C2. Patient’s treatment response was considered using Deauville score (DS) on end of treatment FDG PET. (DS 1 to 3 were considered as responders, DS 4 and 5 non-responders).

**Results :** Nineteen patients had both C0 FDG and C0 RGD PET. Twelve patients had both C2 FDG and C2 RGD, completed treatment protocol and were included for end of treatment analysis. No statistical difference was found on normal organs RGD uptake before and after chemotherapy for SUVmax and SUVmean. On C0 RGD, apart from Classical Hodgkin lymphoma (cHL) and Grey Zone Lymphoma (GZL), other lymphoma sub-types had low RGD uptake ( $p < 0.001$ ). Regarding FDG, there was no significant difference for SUVmax, SUVmean and MTV on C0 and C2 between patients with cHL and non Hodgkin lymphoma (NHL)... On C2 RGD, non-responder patients had higher SUVmax, and SUVmean compared to responder patients ( $p < 0.001$ ). There was no significant difference for RGD MTV between responder and non-responder patients.

**Conclusions :** Our study showed significant higher initial RGD uptake in patients presenting with cHL and GZL compared to NHL. Non responder patients also had higher post chemotherapy RGD uptake compared to responder patients. Issues raised by RGD uptake, particularly in cHL, are yet to be explored and need to be confirmed in a larger population.

## 1- Background

Angiogenesis is a fundamental process involved in a variety of physiological as well as pathological conditions. The growth of solid tumors remains restricted to 2-3 mm in diameter until the onset of angiogenesis (1). The concept of antiangiogenic therapy in clinical oncology aims at stopping cancer progression by suppressing the tumor blood supply and there are more than 20 angiogenic growth factors which have been studied, including their receptors and signal transduction pathways. This increasing use of targeted therapies leads to a growing demand for imaging the tumor’s response to these treatments. Such biomarkers would not only facilitate clinical trials of new drugs but could also be used to aid in the selection of optimal treatment for individual patients (“personalized medicine”).

Positron Emission Tomography (PET) using tracers for assessment of glucose metabolism by [<sup>18</sup>F] Fluorodeoxyglucose (FDG) is well established, and plays a crucial role in initial staging and treatment

response assessment, especially in patients with lymphoma (2). Integrin  $\alpha\text{v}\beta\text{3}$  is a heterodimeric transmembrane glycoproteins consisting of an  $\alpha$ - and  $\beta$ -subunit which plays an important role in angiogenesis (3). They interact in cell-cell- and cell-matrix-interactions, easing endothelial growth and cell migration, and therefore paving the way to angiogenesis (4). In tumors, integrins assist the progress of tumor development and tumor metastasis by facilitating endothelial and tumor cell migration. An important phenomenon that depends on cell-extracellular matrix (ECM) interactions is the growth or sprouting of new blood vessels from a pre-existing vascular bed (4). It has been found that several ECM proteins like vitronectin, fibrinogen and fibronectin interact with integrins via the amino acid sequence arginine-glycine-aspartic acid or RGD in the single letter code (3). Based on these findings, monomeric, multimeric and cyclic peptides including the RGD sequence have been introduced to allow integrin  $\alpha\text{v}\beta\text{3}$  imaging, and to picture pathological angiogenesis. Targeting specific angiogenesis molecular markers by PET imaging, like the integrin  $\alpha\text{v}\beta\text{3}$ , might be used for angiogenesis imaging. Also, L. Li et al., recently showed that high RGD uptake on pre-treatment PET predicted antiangiogenic response in refractory patients presenting with solid cancer (5). Patients presenting with solid tumors which had low RGD uptake did not benefit from antiangiogenic effect. Patients presenting with high RGD uptake benefited from antiangiogenic effect. Therefore, RGD imaging could also be used for response assessment of antiangiogenic therapies.

RGD-K5 PET/CT has been used in clinical studies on patients presenting with head and neck cancer (6), breast cancer (7) and lung cancer (8). To the best of our knowledge, no previous clinical imaging study of angiogenesis in patients presenting with lymphoma has been performed.

The main objective of this study was to measure the impact of two cycles of standard chemotherapy on tumoral neoangiogenesis assessed by RGD-K5 PET/CT on patients presenting with lymphoma.

The secondary objective of this study was to analyze RGD uptake according to patient's lymphoma subtype.

## **2- Methods**

### **a) Population and treatment**

This prospective study included 21 patients between July 2016 and November 2019 in Rouen's Henri Becquerel Cancer Centre presenting with biopsy-proven lymphoma. To avoid partial volume effect on RGD PET, only patients with a target lesion of at least 3 cm on CT were included. All patients were treated according to standard routine practice and national guidelines and to their histological subtype. Patients with indolent lymphomas and no treatment criteria may not receive treatment. All patients were staged using FDG PET/CT (FDG). Additional RGD-K5 PET/CT (RGD) was performed before or after initial and intermediate FDG (median +7 days, range -4; +22 for initial FDG and median -0.5 days, range -5; +1 for intermediate FDG). Intermediate imaging using FDG and RGD was performed after two cycles of chemotherapy for patients receiving treatment. No additional treatment was performed between FDG and

RGD imaging. All patients had final FDG for final Deauville score staging at end of treatment. Patients with final Deauville score of 4 or 5 were considered non-responders and final Deauville score of 1, 2 or 3 as responders (9). All participants were followed at least 12 months after end of treatment. The study was conducted in accordance with the precepts of the Helsinki declaration and received approval by the Ethical Committee. All patients gave written consent for the study. Favourable opinion from the North-west Committee for the protection of persons was given (ref CPP 02/008/2014). EudraCT number was 2015-000757-20 and the study National Clinical Trial identifier was NCT02490891 first posted on the 7<sup>th</sup> of July 2015, <https://www.clinicaltrials.gov/ct2/show/NCT02490891>.

## **b) PET-CT imaging**

Patients had baseline (C0), and intermediate (C2) FDG and RGD PET. Regarding protocol, intermediate RGD was not performed at C2 if RGD was negative at C0. FDG was performed according to EANM procedure guidelines (10). An activity of 3.5 MBq/kg of [<sup>18</sup>F] FDG was injected after 20 minutes of rest. Sixty minutes later ( $\pm 10$  min), the acquisition began with non-injected CT in the cephalocaudal direction on a General Electric 710 PET/CT (Buc, FRANCE). The images were acquired with the patients' arms positioned over the head while breathing freely. The PET data were then acquired in the caudocephalic direction using a whole-body protocol (2 min per bed position). The delay between injection and acquisition was standardized to 60 minutes in order to obtain a normalized counting rate for all patients.

RGD was performed using Siemens® PETnet's RGD-K5. Patients were not at fast. Standard dose of 4 MBq/kg (Maximum of 450 MBq) was administered after 60 minutes at rest. Images were acquired on same PET machine as for FDG, using the same bed protocol, but with 100kV and 80 mAs CT parameters to avoid unnecessary irradiation. Estimated additional estimated dose delivered for RGD was 10 mSv. The tracer uptake was quantified using the standardized uptake value (SUV) calculated as tissue concentration (Bq/g)/[injected dose (Bq)/body weight (g)].

## **c) PET analysis**

All FDG and RGD PET were analysed by one junior and one senior nuclear physicians. On FDG, all lesions (primary tumor and involved lymph nodes) with significant uptake were considered allowing Maximal Standardized Uptake Value (SUVmax), mean SUV (SUVmean), and Metabolic Tumor Volume (MTV) using a 41% of SUVmax threshold.

On RGD, on addition to SUVmax and SUVmean on all lesions, SUVmax and SUVmean were also considered in 13 organs: occipital cortex, thyroid, ascending aorta, inside left ventricular, lung, liver, spleen, gall bladder, kidney cortex, iliopsoas muscle, femoral head, T12 vertebra and inferior vena cava. Organs were excluded of normal uptake analysis if pathological on FDG PET or CT. For RGD's MTV, threshold was determined by adaptive method and if necessary, by expert's visual sampling.

## d) Treatment and follow-up

All patients were treated according to national guidelines according to their histological subtype. Chemotherapy was performed using standard protocols. The patients were followed up by physical examination and FDG imaging. Biopsy was performed for any suspicious residual/recurrent tumors whenever possible.

## e) Histopathological analysis

All patients had a biopsy proven lymphoma. All tumor tissues were routinely fixed in 4% buffered formaldehyde and processed by standard methods into paraffin blocks. Four micrometer slides were prepared and stained with hematoxylin and eosin. A senior pathologist noted the number of vascular sections and the presence of capillary vascularization via ERGmarker by field of view. For the ERG antibody (EP111, 1/100, pH9, Epitomics, Burlingame, USA), the immunochemistry was performed with VECTASTAIN ABC Rabbit IgG Kit (Vector, California). Samples were examined under an Olympus DX51 microscope (Olympus, Paris, France). All pathological samples were reviewed by one senior pathologist.

## f) Statistical analysis

Mean and standard deviation were used for descriptive data. Student test (or Mann-Whiney if population sample beneath five) were performed for patients or PET comparison. All the significance thresholds were set at 0.05 (2-tailed test). Statistics were performed using MedCalc® software. (MedCalc Statistical Software version 13.1.2; MedCalc Software bvba, Ostend, Belgium)

## 3- Results

Patient's clinical data are summarized in Table 1. Nineteen patients (7 women and 12 men) were included. Mean age at diagnostic was  $55 \pm 13$  years. ECOG Performance Status was inferior or equal to 1 in 18 patients (95%). Nine patients had stage IV lymphoma (47%). The median follow-up time was 17.8 months (range 12-28). No patient died during or after treatment. One patient had synchronous lymphoma, and thus both primary lesions were analysed.

Nineteen patients had both C0 FDG and C0 RGD PET. Twelve patients had both C2 FDG and C2 RGD, had completed treatment protocol and were included for end of treatment analysis.

Normal RGD organs SUVmax are shown in Figure 1. No statistical difference was found before (C0) and after (C2) chemotherapy for SUVmax and SUVmean in normal organs. High RGD uptake in the gall bladder (SUVmax  $15,5 \pm 6,7$  [range 6,8-25,8] on C0 and  $18,4 \pm 9.6$  [range 6,3-34,7] on C2 – not shown on Figure 1 for visual comfort) was due to radiotracer's elimination

Ex vivo analysis was performed on 10 patient's initial biopsy. No correlation was found between the endothelial cell marking via the ERGmarker, the number of vascular sections and C0 and C2 RGD uptake (data not shown).

RGD uptakes were analysed according to histological subtype (Figure 2). Apart from classical Hodgkin lymphoma (HL), and grey zone lymphoma (GZL) other lymphoma sub-types had low RGD uptake. RGD uptakes were therefore compared between cHL and non-Hodgkin lymphoma (NHL) - (including grey zone lymphoma).

To illustrate these results is displayed on figure 3 a patient who had synchronous follicular and classical hodgkin lymphoma. Patient had a history of cHL in 2014 which was considered in full remission after 8 ABVD cycles, with early bone relapse in 2015. Bone relapse was successfully treated with 4 ICE cycles. Patient could not undergo autologous bone marrow transplant due to stem cell collection failure. In september 2017, patient seeked her hematologist for cervical swelling. Cervical biopsy revealed grade II follicular lymphoma. Initial FDG revealed lymph node and left sacrum wing involvement. However, RGD uptake was only significant for the left sacrum wing. Dissimilarity between FDG and RGD uptake questioned on patient's histopathological sub-type. Bone biopsy was performed and confirmed concomitant bone cHL relapse.

On table 2 are summarized FDG and RGD uptakes on C0 and C2 according to patients presenting with HL and NHL. On C0 and C2 FDG, there was no significant difference for SUVmax, SUVmean and MTV between patients with HL and NHL. On C0 RGD, patients with HL had higher SUVmax, SUVmean and MTV than NHL. On C2 RGD, there was no significant difference for SUVmax, SUVmean and MTV between HL and NHL. An example is presented on figure 4.

On table 3 are summarized FDG and RGD uptakes on C0 and C2 according to final Deauville score. On C0 and C2 FDG, and on C0 RGD there was no significant difference for SUVmax, SUVmean and MTV between responder and non-responder patients. On C2 RGD, non-responder patients had higher SUVmax, and SUVmean compared to responder patients (Figure 5). There was no significant difference for RGD MTV between responder and non-responder patients.

## **4- Discussion**

To the best of our knowledge, this is the first clinical study using RGD in patients with lymphoma. Patients presenting with cHL had significant higher RGD uptake on baseline RGD than NHL. Our prospective study showed that non responder patients had higher RGD uptake on C2 RGD compared to responder patients.

RGD-K5 is an expensive (around 1000€) and difficult product to synthesize. Due to RGD-K5 production technical problems, two patients were lost of sight, two RGD PET were delayed and ten potentially includable patients were withdrawn. No patients had their treatment delayed because of RGD.

Our study allows to measure RGD uptake in normal organs before and after chemotherapy. Chemotherapy did not affect normal organs uptakes (11).

Preliminary histopathological results performed on initial biopsy showed no correlation between endothelial cell marking via the ERGmarker, the number of vascular sections and C0 and C2 RGD uptake. Endothelial cell marking via the ERGmarker is an indirect expression of neovascularization. The number of vascular sections were counted per 3.15 cm<sup>2</sup> frame. Further histopathological biopsies are necessary to confirm these results.

Patients with cHL had higher RGD uptake. cHL is mainly characterized by the presence of Reed Sternberg cells (RSC) which are multinucleated neoplastic cells. RSC are derived from B germinal centre and produce their own growth factors, Th2 cytokines and chemokines which creates high inflammatory infiltrate (12). The RSC constitute only a minor component of the tumor (usually 1-3%), whereas the majority of the malignancy is composed of a mixed inflammatory infiltrate variably composed of lymphocytes, eosinophils, fibroblasts, macrophages, and plasma cells (13). RSC also expresses high Vascular Endothelial Growth Factor (VEGF) which facilitates tumor progression (14). High RGD uptake in cHL compared to NHL could be due to  $\alpha v\beta 3$  overexpression in neovessels. An alternative explanation could be the presence of  $\alpha v\beta 3$  receptors on tumoral inflammatory cells. Complementary histopathological studies are being considered to verify these hypotheses.

SUVmax FDG was non-significant between responder and non-responder patients because two patients presenting with DLBCL had intermediate Deauville score at 4 and final Deauville score at 2.

One of the major issues which is raised by RGD uptake is its ability to predict antiangiogenic drug response. On the one hand, patients with DLBCL had in our study low RGD uptake. Seymour *et al.*, (16) showed lack of Bevacizumab (anti VEGF) efficacy in DLBCL when added to standard chemotherapy compared to chemotherapy alone. Low RGD uptake in DLBCL could therefore be linked to the lack of anti-angiogenic treatment efficiency. On the other hand, patients with HL had in our study high RGD uptake. Pre-clinical study on xenografts of Hodgkin, showed efficiency of anti-angiogenic treatments (17). No clinical data of antiangiogenic drugs in HL in human is available. However, that with high RGD uptake in HL found in our study, interrogates on testing anti-angiogenic treatments in refractory patients presenting with HL.

Non responder patients had higher RGD uptake than responders on C2 PET (Figure 6). Further studies are necessary to understand if uptake is due to neoangiogenesis or inflammatory process. Integrins are a class of heterodimeric cell surface adhesion receptors that are overexpressed on tumor endothelial cells during tumor angiogenesis, resulting in cancers that are more invasive, more migratory, and better able to survive in different microenvironments. Among integrins,  $\alpha v\beta 3$  is highly expressed in tumors such as osteosarcomas, neuroblastomas, glioblastomas, malignant melanomas, breast, lung and prostate carcinomas but its expression is weak in most healthy organ systems (34).

Limits of our study are the small number of patients but patients did present with heterogeneous histological lymphoma subtypes.

## Conclusion

Our study showed significant higher initial RGD uptake in patients presenting with cHL compared to NHL. Non responder patients also had higher post chemotherapy RGD uptake compared to responder patients. Issues raised by RGD uptake, particularly in cHL, are yet to be explored and need to be confirmed in a larger population.

## List Of Abbreviations

Bq : Becquerel

C0 : exams performed before chemotherapy

C2 : exams performed after 2 cycles of chemotherapy

cHL : Classical Hodgkin Lymphoma

DS : Deauville Score

EANM : European Association of Nuclear Medicine

ECM : Cell-extracellular Matrix

GZL : Grey Zone Lymphoma

MTV : Metabolic Tumor Volume

NHL Non Hodgkin Lymphoma

PET : Positron Emission Tomography

RGD/K5 : [18F] Fluorine arginine-glycine-aspartic

## Declarations

### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This prospective study favourable opinion from the North-west Committee for the protection of persons was given (ref CPP 02/008/2014).

EudraCT number was 2015-000757-20 and the study National Clinical Trial identifier was NCT02490891. All patients signed written consent prior to inclusion

### **Consent for publication**

Not applicable

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

All authors declare that they have no competing interests

### **Funding**

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### **Authors' contributions**

DT was involved in data acquisition, literature research and manuscript writing. PB was involved in study design, pharmaceutical preparation and theoretical support. SB, PD and ST were involved in revise of the manuscript and theoretical support. VC, HT and FJ were involved in study design and review. PV was involved in data acquisition, theoretical support and revise of the manuscript. All the authors agreed on the content of the final manuscript. All authors read and approved the final manuscript.

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## Tables

Table 1 :

## Baseline characteristics of patients included

<b>Clinical Features</b>	<b>Value</b>
Mean age at diagnostic $\pm$ SD (year)	55 $\pm$ 13
Mean height $\pm$ SD (cm)	171.6 $\pm$ 7.55
Mean weight $\pm$ SD (kg)	78 $\pm$ 16
Sex (n)	
Female	7
Male	12
ECOG Performance Status (n)	
0	11
1	7
2	1
3 - 4	0
Histological subtype (n)	
.Classical Hodgkin lymphoma	6
DLBCL	4
Follicular lymphoma	3
Mantle-cell lymphoma	3
T-cell Lymphoma	1
Poppema	1
Grey zone Lymphoma	1
Tumor stage (n)	
IE	1
II A	3
II B	4
III	2
IV	9
Bone marrow biopsy involvement (n)	
. Negative	13

Positive	5
Unknown	1
Nodal site (n)	18
Extra-nodular site (n)	
Spleen	3
Lung	1
Liver	1
Skin	1
Tongue	1
Mean LDH level $\pm$ SD (UI/L)	485 $\pm$ 256
Chemotherapy type (n)	
ABVD	7
R-CHOP	6
None	3
Bendamustine	1
R-CVP	1
ACVBP	1
Prophylactic Intrathecal Methotrexate	
Yes	2
No	17
Number of patients analyzed (n)	19
Total number of patients (n)	21

Table 2:

FDG and RGD uptake in Hodgkin and non-Hodgkin patients before (C0) and after (C2) chemotherapy.

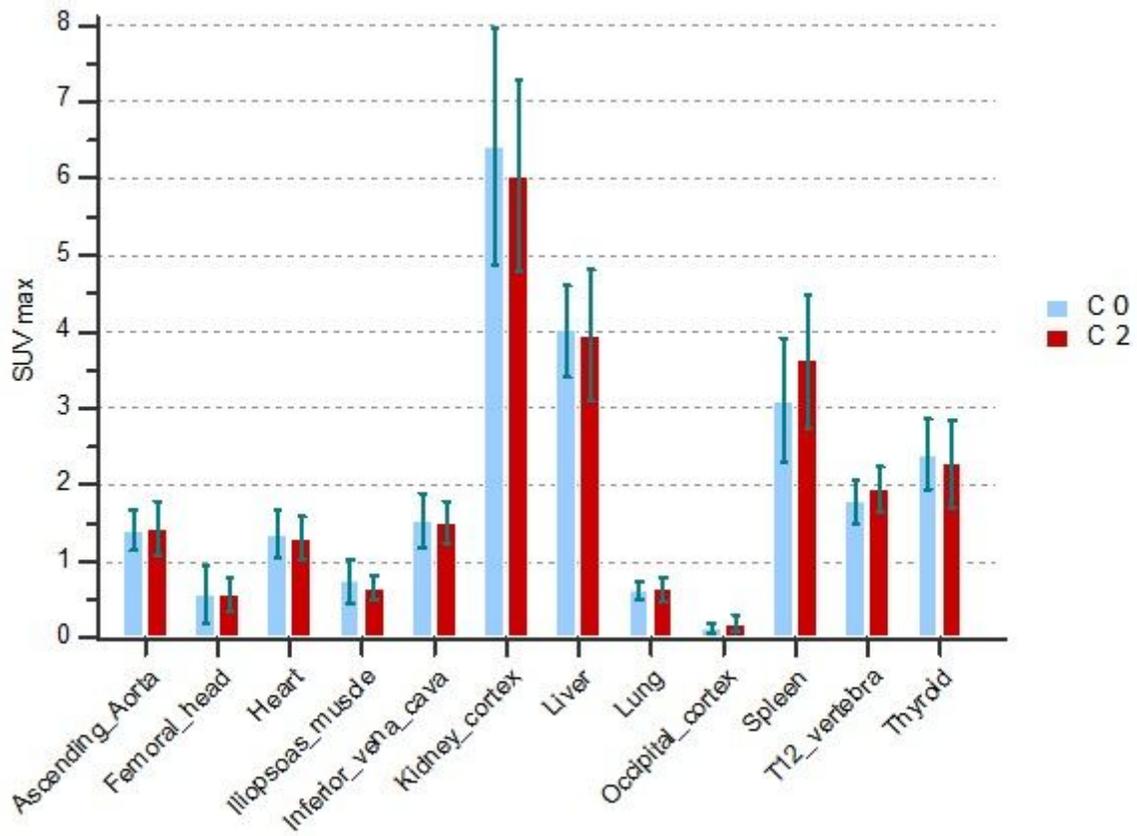
	C0			C2		
	Hodgkin	Non-Hodgkin	<i>p</i> value	Hodgkin	Non-Hodgkin	<i>p</i> value
FDG	n = 6	n = 13		n = 6	n = 10	
SUVmax ± SD	14,8 ± 4,7	17,0 ± 8,6	0,56	2,6 ± 1,3	5,1 ± 2,0	0,02
MTV ± SD	91.8 ± 60	254 ± 306	0,22	33 ± 65	27,6 ± 40.6	0,4
RGD	n = 6	n = 13		n = 5	n = 7	
SUVmax ± SD	3,9 ± 1,4	1,9 ± 1,1	0,002	3,1 ± 1,1	3,6 ± 1,8	0,6
MTV ± SD	145 ± 125	3,2 ± 9	<0,001	46 ± 45	45 ± 99	0,9

Table 3:

FDG and RGD uptake on initial (C0) and intermediate (C2) PET-CT according to final Deauville Score (DS) (Responder = 4 and 5 DS; Non – Responder = 1, 2 and 3 DS).

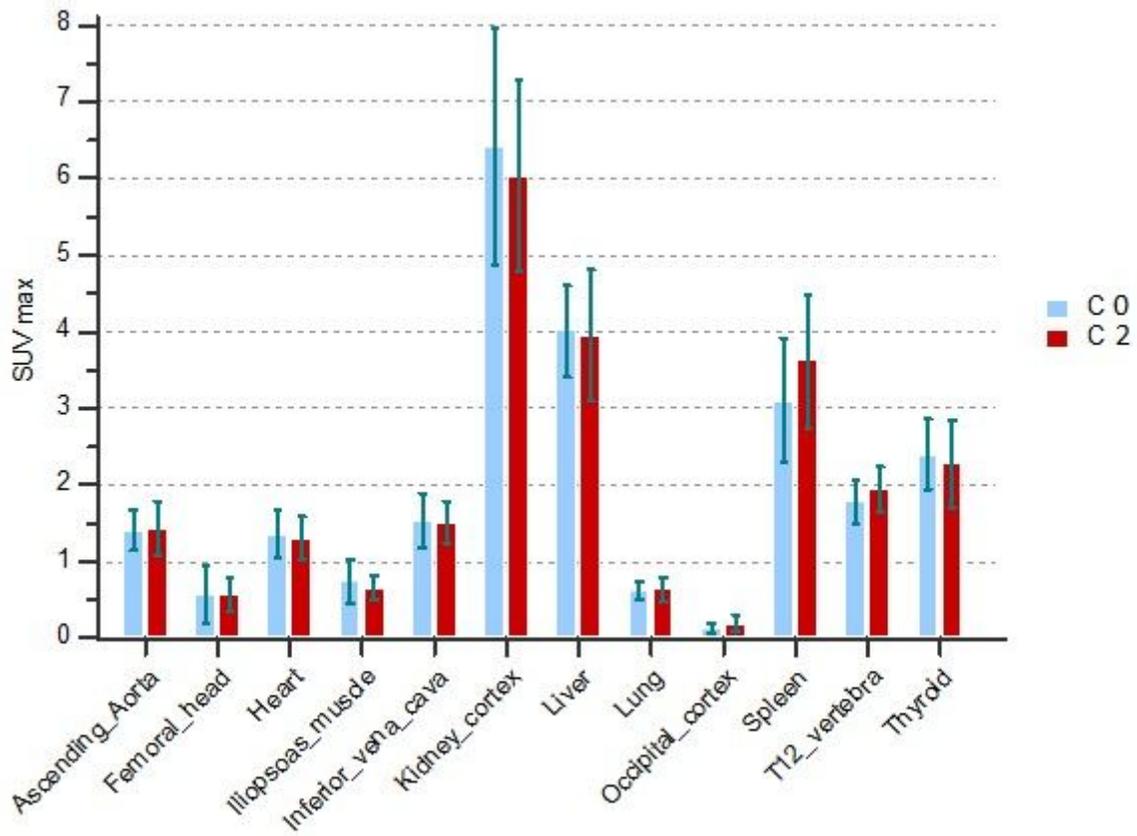
	C0			C2		
	Responder	Non-Responder	<i>p</i> value	Responder	Non-Responder	<i>p</i> value
FDG	n = 6	n = 6		n = 6	n = 6	
SUVmax ± SD	18,3 ± 7,3	14,6 ± 5,7	0,35	3,4 ± 1,9	5,6 ± 2,3	0,09
MTV ± SD	183 ± 189	462 ± 474	0,32	10,4 ± 19,1	53,9 ± 54,6	0,18
RGD	n = 6	n = 6		n = 6	n = 6	
SUVmax ± SD	2,61 ± 1,8	3,21 ± 1,6	0,56	2,41 ± 1,1	4,43 ± 1,1	0,01
MTV ± SD	43,5 ± 67,1	21 ± 40,4	0,59	10,5 ± 8,53	96,0 ± 124	0,22

## Figures



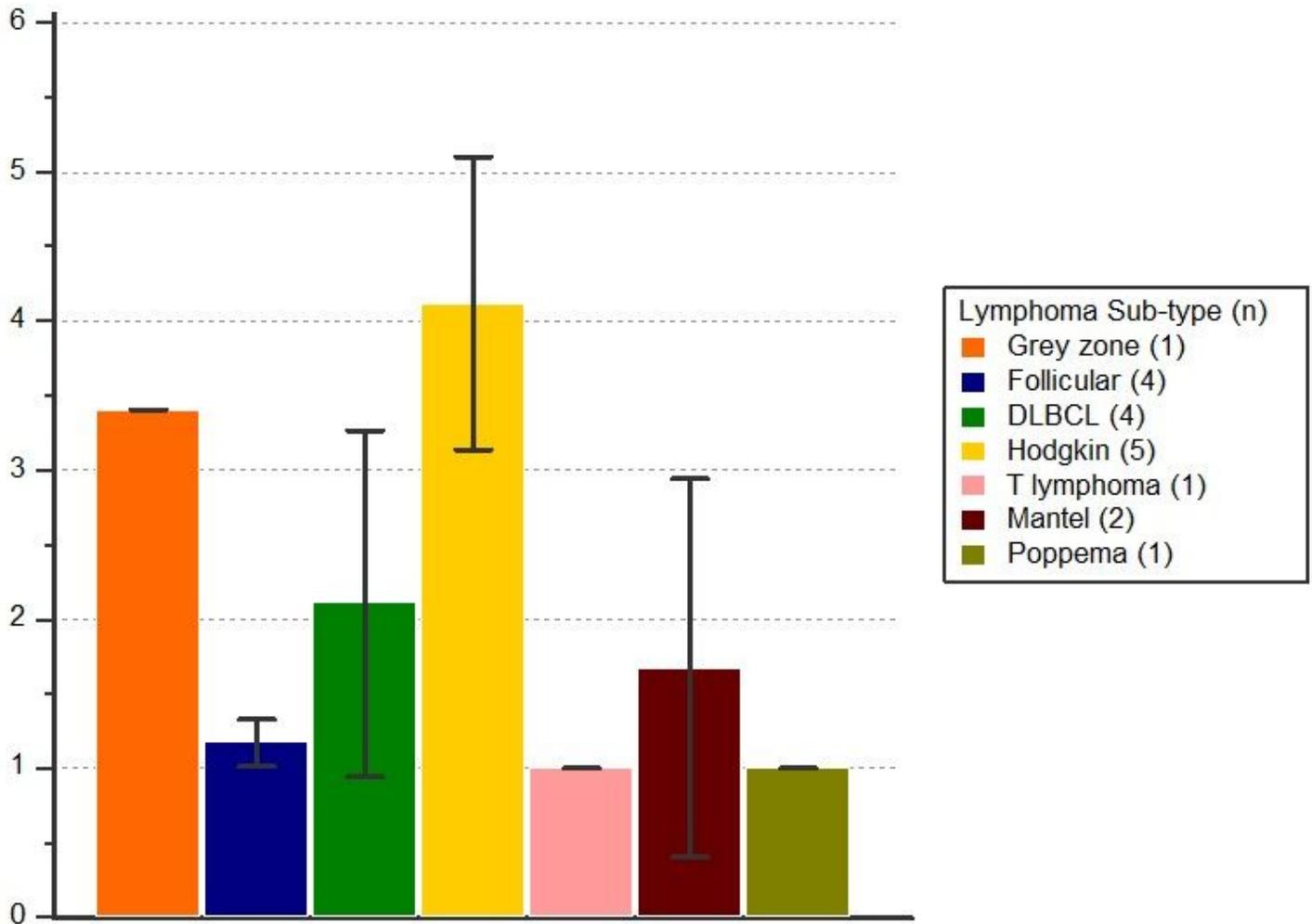
**Figure 1**

SUV max uptake in organs before (C0) and after (C2) chemotherapy.



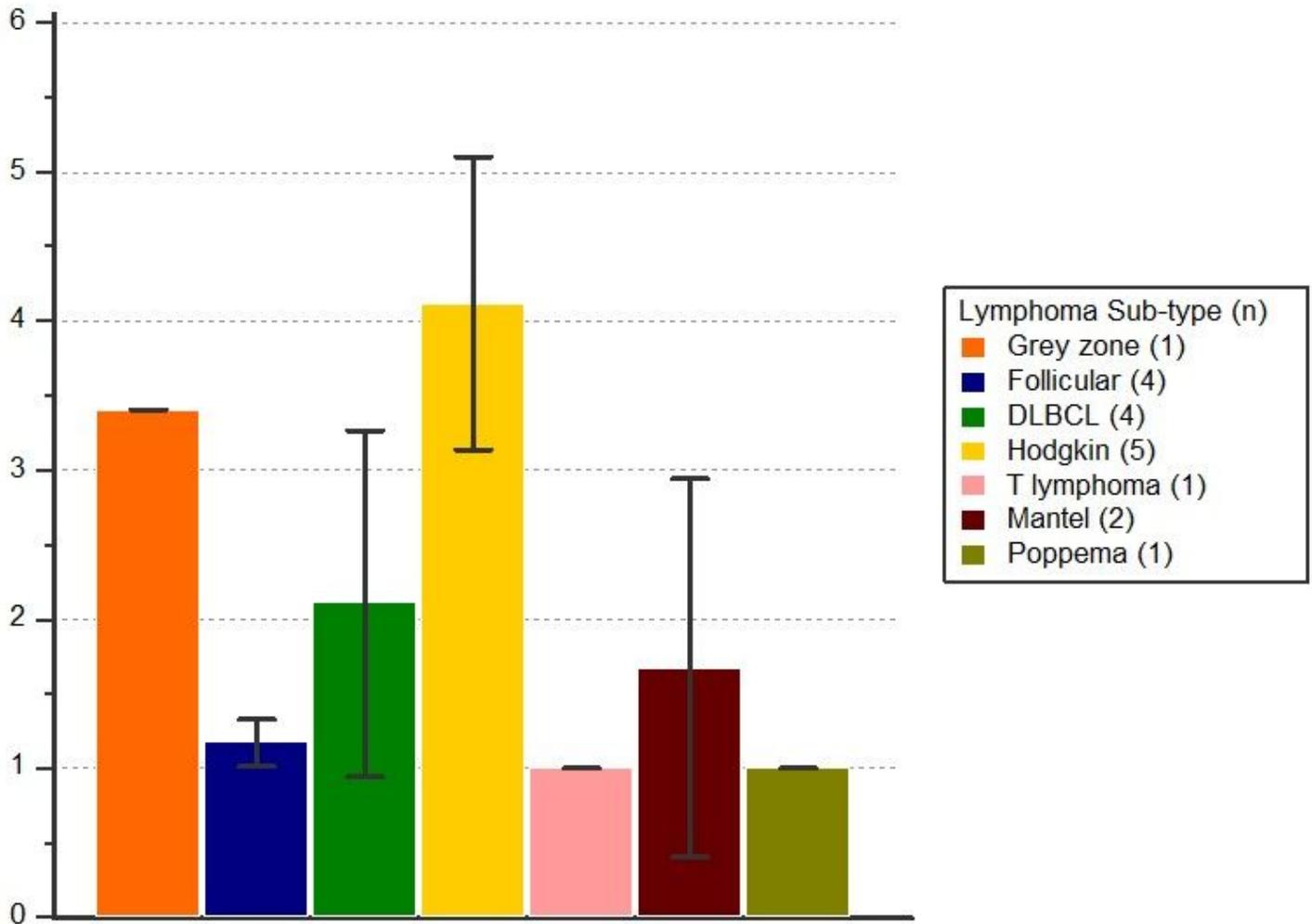
**Figure 1**

SUV max uptake in organs before (C0) and after (C2) chemotherapy.



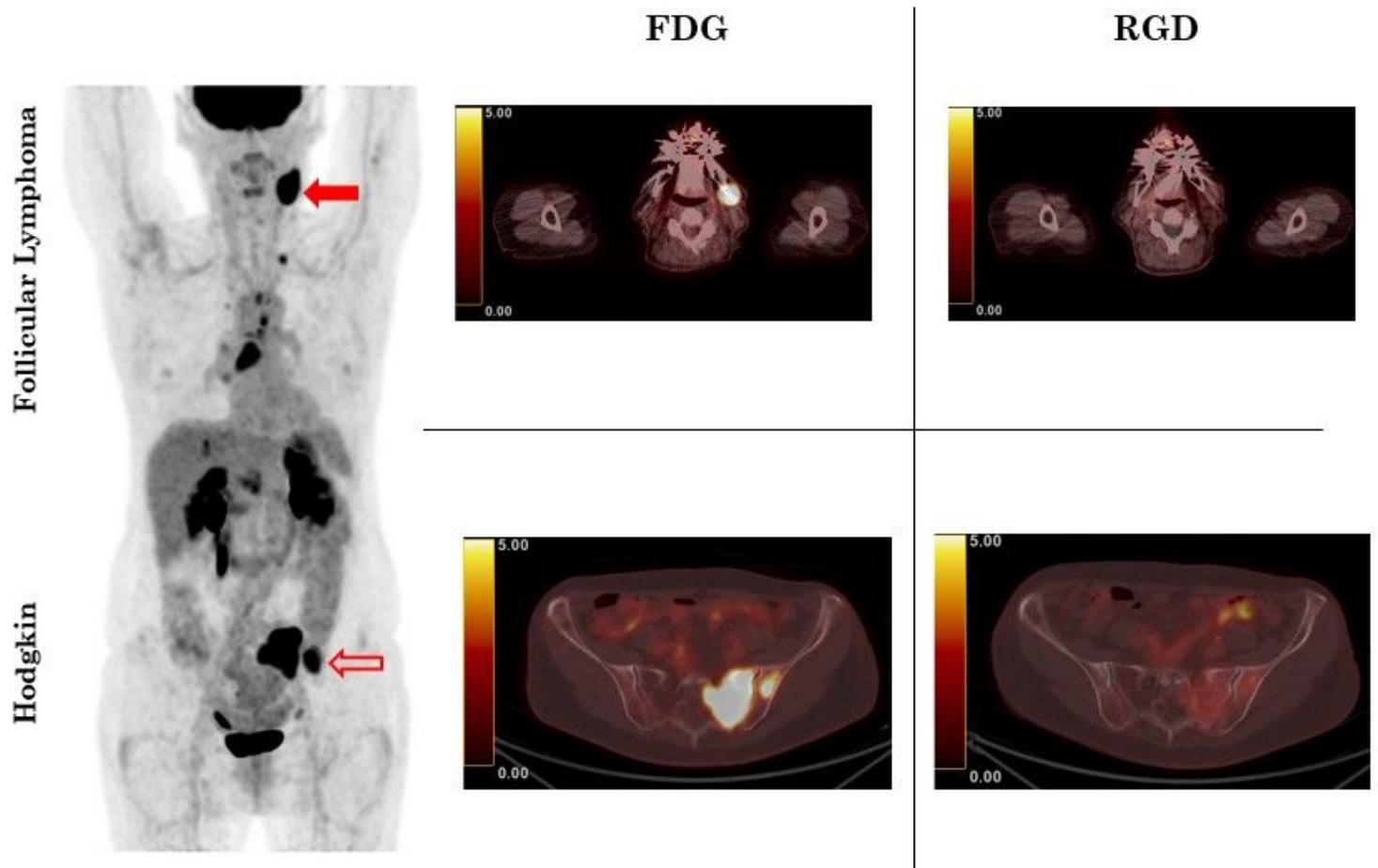
**Figure 2**

C0 RGD uptake according to histological subtype.



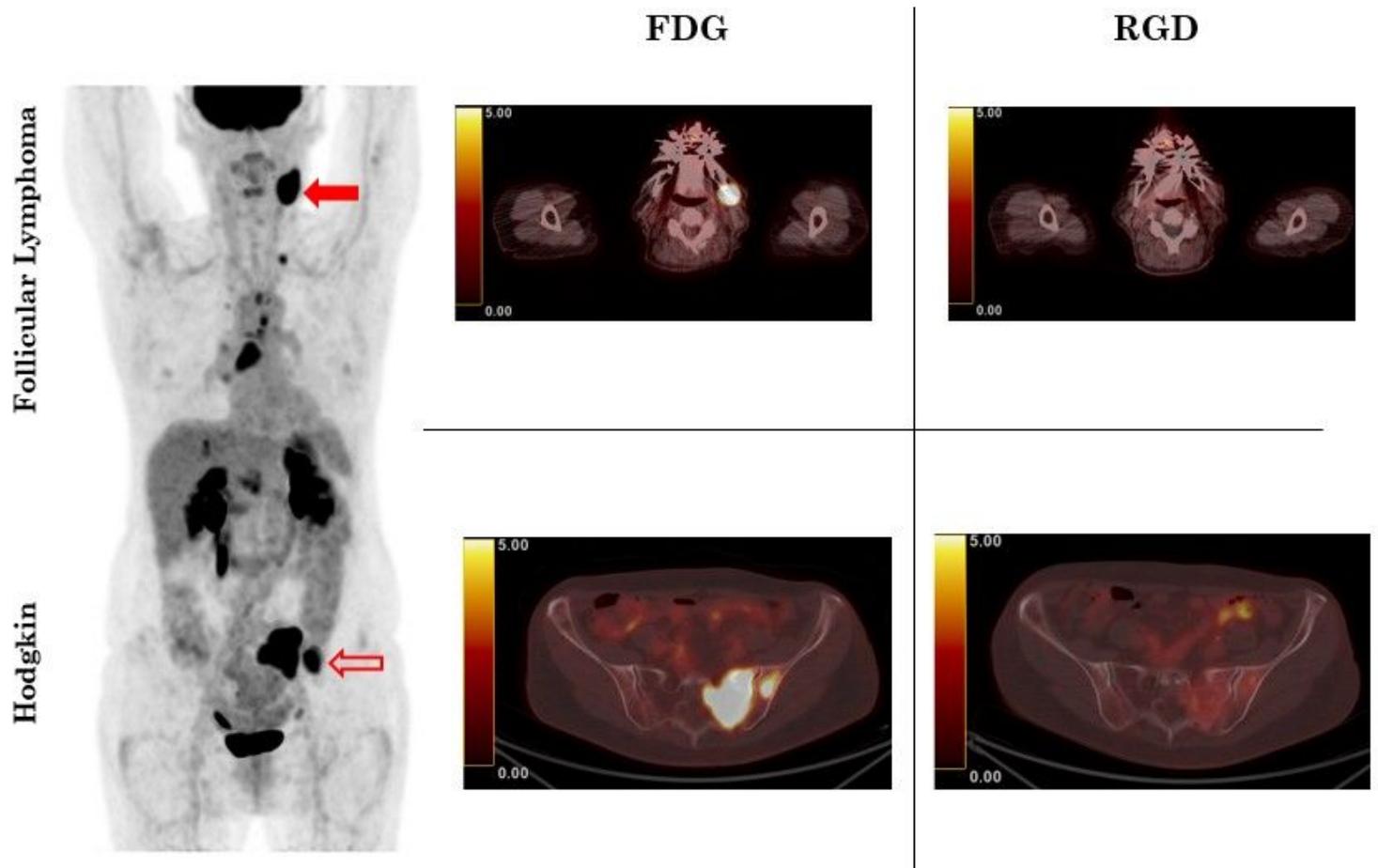
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C0 RGD uptake according to histological subtype.



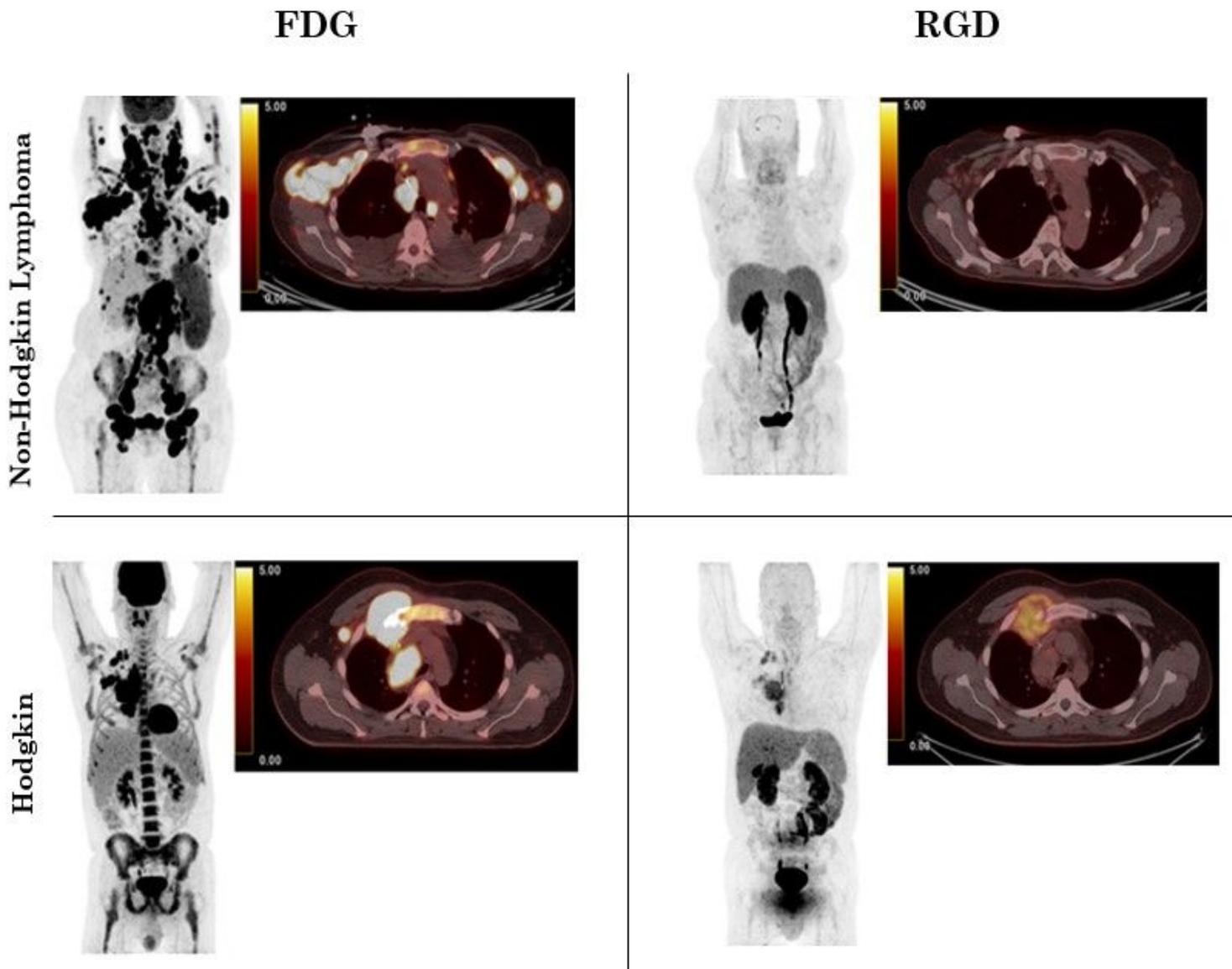
**Figure 3**

FDG Maximum Intensity Projection (left) in patient presenting with synchronous biopsy proven Follicular (full red cross) and Hodgkin (empty red cross) lymphoma. On axial PET/CT (middle and right column) both lesions had significant FDG uptake (middle column). No RGD uptake in follicular lymphoma (right column, upper row). Significant RGD uptake in Hodgkin lymphoma. (Right Column, bottom row).



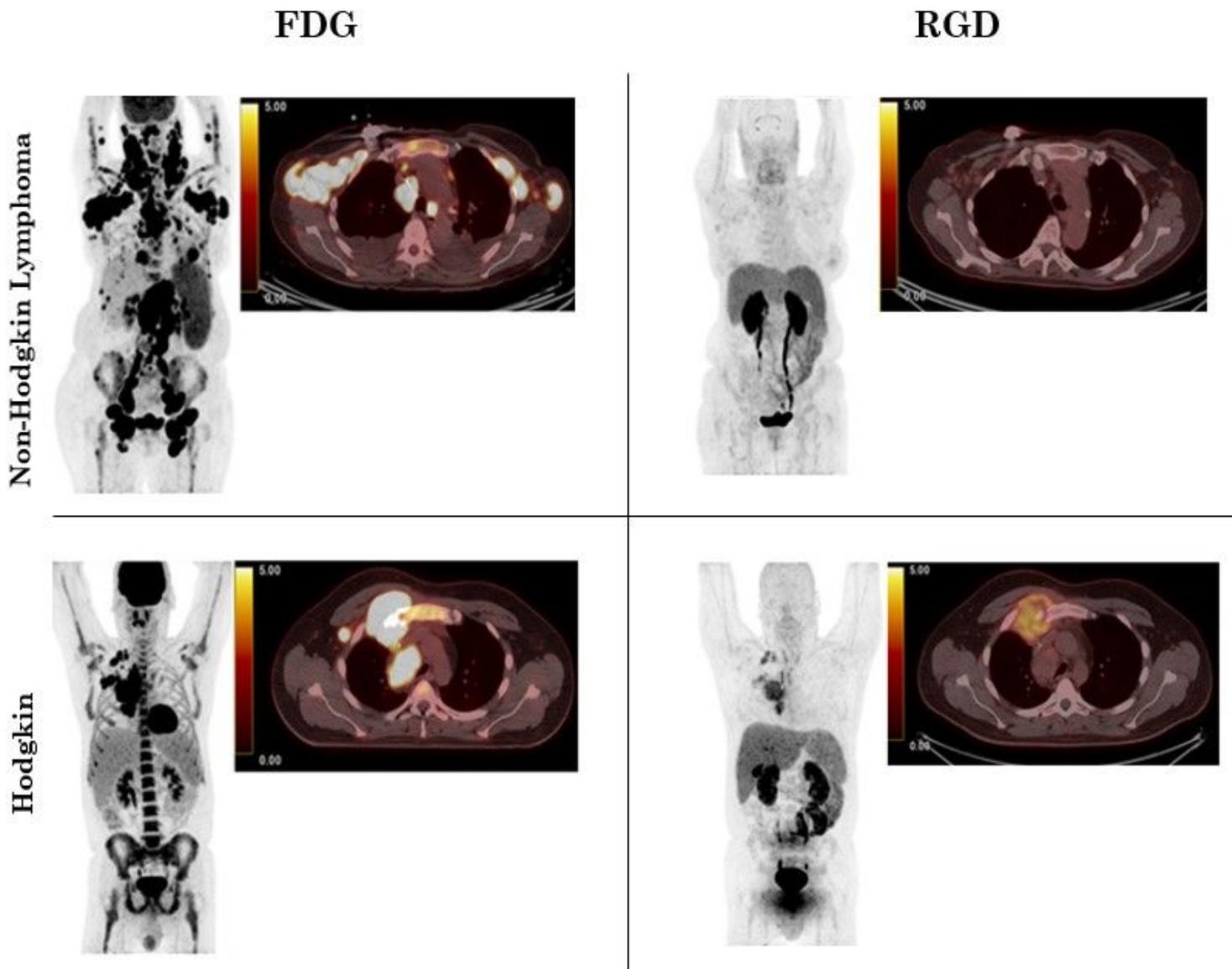
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FDG Maximum Intensity Projection (left) in patient presenting with synchronous biopsy proven Follicular (full red cross) and Hodgkin (empty red cross) lymphoma. On axial PET/CT (middle and right column) both lesions had significant FDG uptake (middle column). No RGD uptake in follicular lymphoma (right column, upper row). Significant RGD uptake in Hodgkin lymphoma. (Right Column, bottom row).



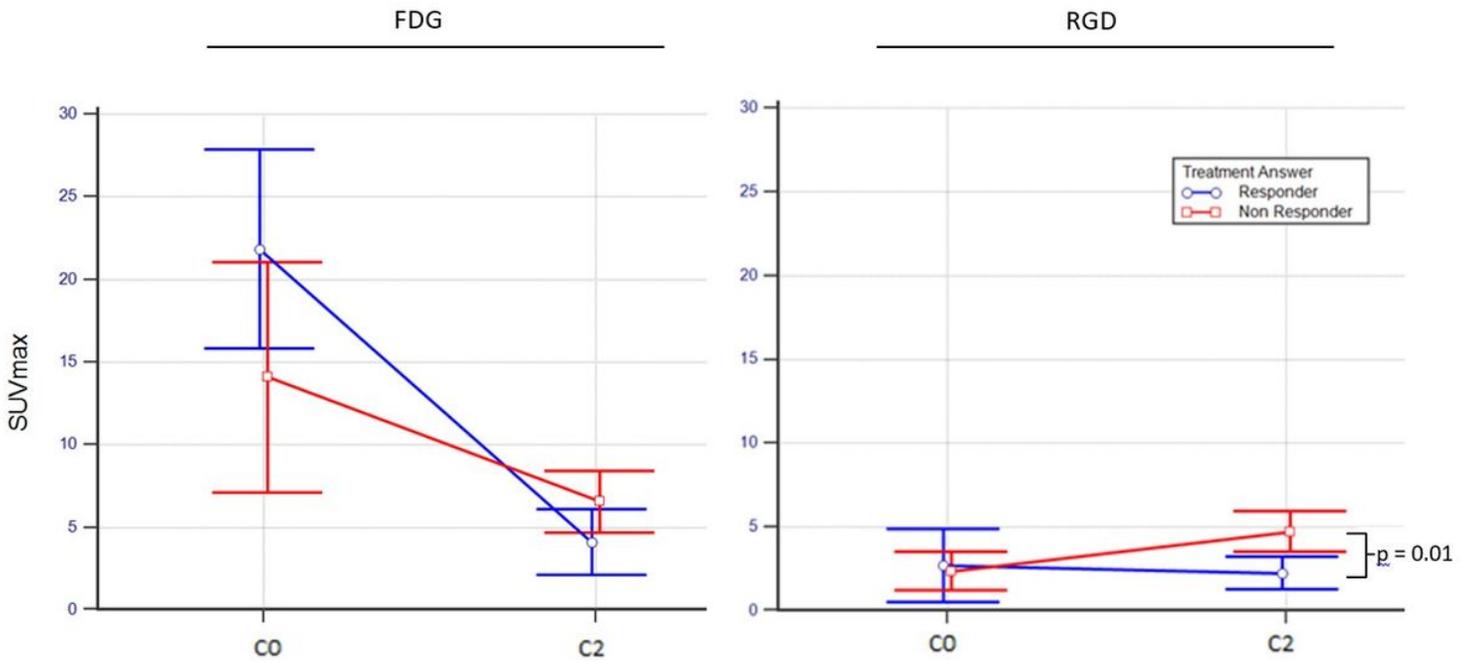
**Figure 4**

FDG (left column) and RGD (right column) uptake in patients with non-Hodgkin lymphoma (upper row) compared to classical Hodgkin lymphoma (bottom row) at baseline (C0).



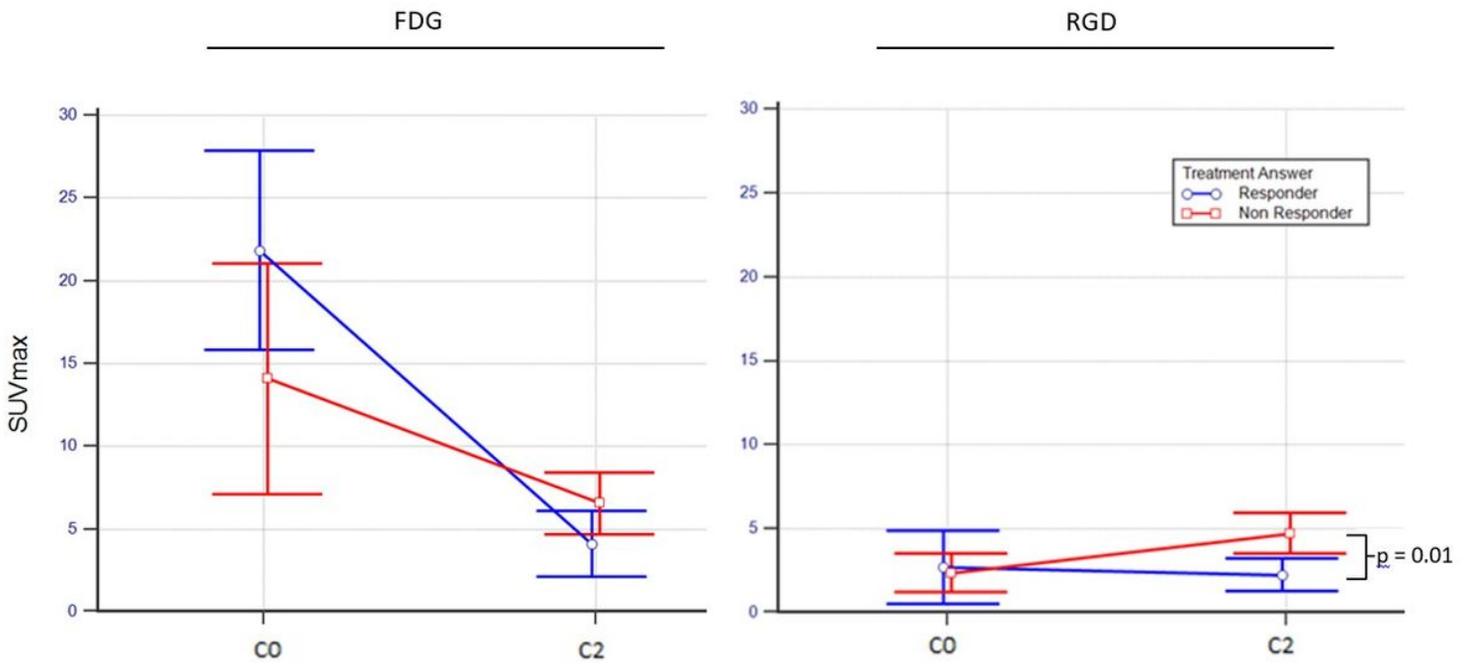
**Figure 4**

FDG (left column) and RGD (right column) uptake in patients with non-Hodgkin lymphoma (upper row) compared to classical Hodgkin lymphoma (bottom row) at baseline (C0).



**Figure 5**

FDG (left) and RGD (right) SUVmax on initial (C0) and intermediate (C2) PET-CT according to final Deauville score (DS). (Non- Responder = 4 and 5 DS, Responder = 1,2 and 3 DS).



**Figure 5**

FDG (left) and RGD (right) SUVmax on initial (C0) and intermediate (C2) PET-CT according to final Deauville score (DS). (Non- Responder = 4 and 5 DS, Responder = 1,2 and 3 DS).