FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

DIOGO JOÃO DUARTE DA SILVA

Safety and kinetic variation profile of 177Lu-DOTA-TATE uptake in Neuroendocrine Tumors

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE MEDICINA NUCLEAR

Trabalho realizado sob a orientação de:

GRACINDA COSTA

PAULO GIL

CÉLIA GOMES

ANTERO ABRUNHOSA

FEVEREIRO 2017

Safety and kinetic variation profile of ^{177}Lu-DOTA-TATE uptake in Neuroendocrine Tumors

Silva D[a], Gil P[b], Costa G[b], Gomes C[c], Abrunhosa A[d]

[a]Faculty of Medicine of the University of Coimbra, Portugal

[b]Centro Hospitalar e Universitário de Coimbra, Portugal

[c]Institute for Biomedical Imaging and Life Sciences, University of Coimbra, Portugal

[d]Institute of Nuclear Sciences Applied to Health, University of Coimbra, Portugal

Abstract

Introduction: Neuroendocrine tumors (NETs) constitute a particularly rare type of tumors characterized by their endocrine metabolism, unique histological pattern and biological heterogeneity. Despite their indolent course, many patients develop multiple unresectable metastatic disease affecting mainly the liver, bones and lymph nodes. In those cases, current therapeutic options have a limited efficacy. Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-[DOTA0,Tyr3]-octreotate(DOTA-TATE) constitutes a promising new treatment modality for inoperable metastatic NETs. Notwithstanding being proved effective and safe, PRRT still struggles with the lack of established protocols and guidelines.

Aim: The main goal of this study was to contribute to improve PRRT planning by providing insight about the safety and pharmacokinetic profile of ^{177}Lu-DOTA-TATE when used on current therapeutic protocols for NET.

Materials and Methods: Sixteen patients with progressive multi-metastatic disease were consecutively enrolled from July 2013 to May 2016. Ten men and six women (67.6 ± 13.4 years) received three cycles of PRRT with ^{177}Lu-DOTA-TATE (17.9 ± 6.5 GBq) to treat 57 metastatic lesions (33 in the liver and 22 in the bones). Individual lesion ^{177}Lu-DOTA-TATE uptake was evaluated trough treatment. Toxicity parameters assessed included full blood count, liver and renal function before, during and after treatment. Data analysis comprised a Wilcoxon test for variable comparison and linear regression using Spearman's coefficient.

Results: A similar uptake profile for liver and bone metastases was found with an overall reduction on ^{177}Lu-DOTA-TATE uptake from the first to the third cycle. Regarding safety, acute myelotoxicity (Grade I and II) was found five weeks after each cycle without significant bone marrow, hepatic or nephrotoxicity after treatment.

Conclusion: Our results demonstrate that PRRT with ^{177}Lu-DOTA-TATE has a tolerable safety profile, with minimum acute myelotoxicity after each cycle and minimum nephrotoxicity after the entire treatment. Our correlation studies revealed that pre-treatment laboratorial evaluation constitutes a reliable starting point for patients' selection and extrapolation of toxicity outcomes. Moreover, we proposed a feasible approach to dosimetry that established an intra and inter-cycle variation profile for ^{177}Lu-DOTA-TATE uptake.

Keywords: Neuroendocrine tumours, Peptide Receptor Radionuclide Therapy, Lutetium, Safety, Dosimetry

Resumo

Introdução: Os tumores neuroendócrinos constituem um tipo raro de neoplasias caracterizadas pelo seu metabolismo endócrino, padrão histológico único e heterogeneidade biológica. Apesar da progressão insidiosa, uma grande percentagem de doentes desenvolve doença metastática irressecável principalmente a nível hepático, ósseo e ganglionar. Nestes casos, a Terapêutica Radiometabólica com ^{177}Lu-[DOTA0,Tyr3]-octreotate(DOTA-TATE) constitui uma opção terapêutica promissora devido à eficácia limitada das atuais opções terapêuticas disponíveis. Apesar da eficácia e segurança da Terapêutica Radiometabólica terem sido demonstradas, a inexistência de protocolos ou orientações clínicas transversais a todas as instituições constitui uma limitação à sua implementação.

Objetivo: Com o intuito de melhorar o planeamento, pretendemos avaliar a toxicidade e perfil farmacocinético da captação de ^{177}Lu-DOTA-TATE quando usado em esquemas de Terapêutica Radiometabólica para tratamento de tumores neuroendócrinos.

Materiais e Métodos: Dezasseis doentes multimetastizados foram progressivamente selecionados, entre julho de 2013 e maio de 2016. Dez homens e 6 mulheres (67,6±13,4 anos) foram submetidos a 3 ciclos de Terapêutica Radiometabólica com ^{177}Lu-DOTA-TATE (17,9±6,5 GBq) para tratamento de 57 metástases (33 hepáticas e 22 ósseas). A variação da intensidade de captação do ^{177}Lu-DOTA-TATE nas lesões foi avaliada ao longo de todo o tratamento. Os parâmetros de toxicidade incluíram hemograma com fórmula leucocitária, função hepática e renal antes, durante e após tratamento. A análise estatística incluiu a comparação de variáveis pelo teste de *Wilcoxon* e a determinação do coeficiente de *Spearman* para avaliar a existência de correlação entre variáveis.

Resultados: As metástases hepáticas e ósseas apresentaram um perfil de captação semelhante, com redução da captação de ^{177}Lu-DOTA-TATE do primeiro para o terceiro ciclo. Mielotoxicidade aguda (Grau I e II) foi observada 5 semanas após cada ciclo sem toxicidade medular, hepática ou renal significativa após o tratamento.

Conclusão: Os nossos resultados demonstraram um perfil de toxicidade adequado com mielotoxicidade mínima após cada ciclo e sem nefrotoxicidade significativa após 3 ciclos. Os estudos de correlação mostraram que as avaliações laboratoriais pré-tratamento podem servir como ponto de partida para a seleção de doentes. Por fim, propusemos um esquema de dosimetria clinicamente exequível e capaz de determinar o perfil de captação de ^{177}Lu-DOTA-TATE intra e inter-ciclos.

Palavras-chave: Tumores neuroendócrinos, Terapêutica Radiometabólica, Lutécio, Toxicidade, Dosimetria.

Introduction

Neuroendocrine tumours (NETs) constitute a rare heterogeneous group of tumours arising from neuroendocrine cells and comprise carcinoids, non-carcinoid gastroenteropancreatic tumours, medullary carcinoma of the thyroid, chromophobe pituitary tumours, small cell lung cancer and Merkel cell tumours[1].

Despite the considerable variety of NETs, collectively they only account for 0.5% of all gastrointestinal and bronchopulmonary diagnosed cancers[2,3]. With a prevalence of 35 cases per 100 000 people and an incidence constantly growing (reaching an European age-adjusted rate between 13.3 – 21.3 per 100 000 people/year), NETs resemble a gap between low incidence and prevalence tumours [4]. Age at diagnosis is generally lower than for carcinomas and estimated to be around the 5th decade of life.

Due to the heterogenic behaviour associated to these tumours choosing the best treatment remains a challenging aspect. A multidisciplinary approach is required and an integration between different treatment modalities is needed[5]. The main curative option for NETs is surgical resection, either for localized and advanced disease[6]. Nonetheless, the indolent course associated to NETs is responsible for a great percentage of patients presenting multi-metastatic disease at time of diagnosis. Consequently, surgery in those cases is not feasible and patients need medical management to relief symptoms and limit tumour's growth and metastization[6,7].

Medical therapy for NETs can be divided into chemotherapy, biotherapy and molecular targeted agents. Biotherapy and molecular targeted therapies rely on the overexpression of somatostatin receptors (SSTR) by neuroendocrine cells, being the SSTR2 the dominant type[8].

Biotherapy with cold, long-acting somatostatin analogs (SSA) such as Octreotide or Lanreotide is based on peptide effects on tumour mediated by peptide receptors[9]. Targeted therapy with SSA labelled with radioisotopes relies on the selective binding to overexpressed somatostatin receptors and accumulation of radioactivity in the tumour area[10]. This selective accumulation establishes the basis of the *Theranostics* concept since accumulated activity can be used both for imaging or radiation therapy – Peptide Receptor Radionuclide Therapy (PRRT)[11].

PRRT with radiolabelled SSAs is a promising new treatment modality that meets the need for an effective treatment option for the large group of patients to whom surgery with curative intent is not an option[12]. It involves systemic administration of a radiopharmaceutical composed of a beta-emitting radionuclide chelated to a SSA and allows the targeted delivery of cytotoxic radiation to tumour cells[13].

Radiolabelled SSAs comprise a cyclic octapeptide (Tyr^3-octreotide or Tyr^3-Octreotate), a chelator and a radioactive element. The most used isotopes for treatment are the beta-emitters 90-Ytrium (^{90}Y) and 177-Lutetium (^{177}Lu) [11]. Furthermore, ^{177}Lu is a gama-emittor within two ranges – 113 keV and 208 keV- of gamma emission that enables its use for post-treatment imaging and dosimetry assessments[13].

Despite being proved effective on the treatment of metastatic NETs, PRRT still struggles with the lack of established protocols and guidelines[13]. Several studies have proved the efficacy and safety of PRRT using ^{90}Y and/or ^{177}Lu, with patients achieving objective response and clinical benefits without significant associated toxicity[14]. Bone marrow and kidneys constitute the limiting organs with myelo and nephrotoxicity being described in various studies[13,14,15]. Moreover, the lack of a widely accepted dosimetry scheme makes bespoke planning of PRRT a needed goal hard to achieve[15].

Aim

The main goal of this study was to contribute to improve PRRT planning by providing insight about the safety and pharmacokinetic profile of ^{177}Lu-DOTA-TATE when used on current therapeutic protocols for NET.

Materials and Methods

Study Design

The present dissertation aims to provide a complete vision of the use of Peptide Receptor Radionuclide Therapy on the treatment of Neuroendocrine Tumours. Designed as a retrospective study with the intent of analyse the pathway of sixteen patients diagnosed with NETs from the moment they were referred to undergo Peptide Receptor Radionuclide Therapy until three cycles of treatment were completed. This study focused only on routinely acquired clinical data analysis and, therefore, the Ethics Committee of the Faculty of Medicine of the University of Coimbra waived the need for additional consent.

Only patients that fully met the inclusion criteria defined, did not present any exclusion criteria and gave written informed consent to receive standard-of-care PRRT were accepted. Patients were enrolled at different times during the three years' duration of the study.

Inclusion and Exclusion Criteria

The inclusion (Table 1) and exclusion (Table 2) criteria used for enrolling patients into treatment with PRRT were based on the joint practical guidance elaborated by the International Atomic Energy Agency (IAEA), European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI)[13].

Table 1: Summary of inclusion criteria.

Stage		**Histology and Immunohistochemistry**		**SSTR Expression**	
IV	Progressive inoperable or multi-metastatic NET.	**Mitotic Index Proliferation Index (Ki-67)**	G1 and G2	**^{68}Ga-DOTA-NOC PET/CT**	Lesion uptake superior to normal liver parenchyma uptake
		Biological Markers	CgA+	**Whole-body Scintigraphy (WBS) with Somatostatin Analogs**	

Table 2: Summary of exclusion criteria.

Clinical Assessment		Laboratory Tests		Renal Scintigraphy	
Life Expectancy	< 3 months	**Blood Counts**	Haemoglobin < 8 gr/dL Leucocytes < 2 G/L Platelets < 75 G/L	**Glomerular Filtration Rate (GFR)**	< 40 mL/min
Karnofsky Index	≤ 50%	**Liver Function**	Total Bilirubin > 3x the upper reference limit Albumin > 30 g/L		
ECOG Performance Status	≥ 4	**Renal Function**	Creatinine > 1.7 mg/dL	**Elimination Pattern**	Obstructive

Patients

Sixteen patients with progressive inoperable or multi-metastatic disease were consecutively enrolled from July 2013 to May 2016. Table 3 resumes the main characteristics of the cohort. Ten males and six females with a mean age of 67.6 ± 13.4 years (28 – 81 years). All patients met the inclusion and exclusion criteria defined.

Table 3: Patient characteristics

Cohort	
Number of patients	16
Mean age (years)	67.6 ± 13.4
Sex	10 males, 6 females
Primary Tumour	
Lung NET	5 (31%)
Pancreatic NET	4 (25%)
Ileum NET	3 (19%)
NET of unknown origin	2 (12.5%)
Thyroid NET (medullary thyroid carcinoma)	1 (6.3%)
Jejunum NET	1 (6.3%)
Metastasis	
Liver	15 (93.8) (33 lesions)
Bone	10 (62.5%) (22 lesions)
Mean Activity (GBq)	17.9 ± 6.5
Mean Activity (mCi)	558.6 ± 84.4

^{177}Lu-DOTA-TATE

Lutetium-177 is a betta and gamma-emitter with a physical half-life of 6.7 days. It has a mean β-particle energy of 0.133 MeV and a maximum of 0.498 MeV. Converting these energies into tissue penetration, Lutetium-177 has a mean soft-tissue range of 0.23 mm and a maximum range of 1.7 mm. The γ-emission is characterized by a double emission peak of 113 keV (6%) and 208 keV (11%)[13].

DOTA-TATE is a short form for [DOTA0.Tyr3,Thr8]-octreotide or [DOTA0,Tyr3]-octreotate. It is a somatostatin analogue peptide where DOTA constitutes the bifunctional chelating molecule[13].

PRRT with ^{177}Lu-DOTA-TATE – Therapeutic Scheme

The therapeutic scheme used was three cycles of treatment with three months interval between each cycle. Before the first cycle patients must have undergone a pre-treatment evaluation composed of a ^{68}Ga-DOTA-NOC PET/CT scan, Computed Tomography (CT) scan (if needed), Renal Scintigraphy and a full blood work-up including renal and liver function. Also, patients must have stopped any treatment with long-acting somatostatin analogue (like octreotide LAR) at least 6 weeks before PRRT (for short-acting analogue 3 days is enough). During the 3 months interval between cycles, patients performed a full clinical assessment at the 5th and 10th week after each cycle[13]. This assessment was composed of a full clinical examination and a blood work-up including renal and liver function. At the end of treatment, a post-treatment evaluation was performed and patients underwent a full clinical examination, a ^{68}Ga-DOTA-NOC PET/CT scan and, if needed, Computed Tomography (CT) scan.

^{177}Lu-DOTA-TATE administration protocol

Before the administration of ^{177}Lu-DOTA-TATE an antiemetic (Aprepitant-oral plus Ondansetron-intravenous) was given to each patient. Thirty minutes before the beginning of treatment an intravenous infusion on Aminoplasmal Hepa® was started, using a perfusion rate of 400 ml/h during 6 hours to achieve a total volume of 2.5 L. After 30 minutes, slow intravenous administration of ^{177}Lu-DOTA-TATE was performed during 30 to 60 minutes.

Aminoplasmal Hepa®

Aminoplasmal Hepa® was used for renal protection during treatment with ^{177}Lu-DOTA-TATE. It is an Infarmed's approved drug for parenteric nutrition since 21/04/2011. The quantitative and qualitative composition is described in table 4.

Table 4: Quantitative and qualitative composition

Aminoplasmal Hepa® - 100 ml of solution contains	
L- Leucine	1.360 g
L- Isoleucine	0.880 g
Lysine Acetate	1.060 g
L- Methionine	0.120 g
L- Phenylalanine	0.160 g
L-Threonine	0.460 g
L-Tryptophan	0.150 g
L- Valine	1.060 g
L- Arginine	0.880 g
L- Histidine	0.470 g
L-Glycine	0.630 g
L- Alanine	0.830 g
L- Proline	0.710 g
L- Serine	0.370 g
L- Asparagine H_2O	0.055 g
L- Aspartic Acid	0.250 g
L- Glutamic Acid	0.570 g
L- Ornithine hydrochloride	0.166 g
N-acetyl-L-tyrosine	0.086 g
Acetylcysteine	0.080 g

Toxicity Evaluation

Toxicity assessment was performed by comparing the analytic values (Table 5) obtained before the first cycle of treatment with the values obtained at the 5th and 10th week after each treatment. Also, a comparison between the values obtain before and after the 3 cycles of treatment was performed. Afterwards, the 1st 12 months of post-treatment follow-up were analysed.

Table 5: Laboratorial Parameters

	Renal Function	Liver Function	Medullar Function
Parameters Assessed	Serum Creatinine	Alanine Transaminase Aspartate Transaminase Alkaline Phosphatase Gama-Glutamyl Transferase Total Bilirubin	Haematocrit Haemoglobin Red Blood Cells White Blood Cells Platelets

2-D dosimetry studies

Three ^{177}Lu-DOTA-TATE post-therapeutic whole-body scintigraphy (ptWBS) were obtained at 4 hours, 24 hours and 7 days after each treatment cycle. An external radioactivity source, with known activity, was placed near the patient in the acquisition field. A General Electric™ *Millennium Discovery VG* and a Phillips™ *BrightView XCT* dual detector gamma camera were used, applying fabricants' specifications. Using planar (2-D) scintigraphic anterior and posterior images, ^{177}Lu-DOTA-TATE uptake and quantification were evaluated in a General Electric's *Xeleris 4.0 Functional Imaging Workstation* (v2.0 and v3.0). For each patient, metastatic target lesions and respective background (Bkg) were selected in the ptWBS, based on the lesion definition and on the size and/or uptake intensity. Anterior and posterior scans were analysed separately and measurements performed using circular regions of interest (ROI) around each selected target lesion (Figure 1). Radioactivity counts (Cts) obtained for each lesion were corrected for background (Bkg) and geometric mean (GM) was calculated. A ROI was also drawn for the external radioactivity source and the Cts were recorded and used for the target lesions ^{177}Lu-DOTA-TATE activity calculus (equation 3). A total of 57 metastases (33 liver metastases and 22 bone metastases) were evaluated over time, using the above described methodology, allowing intra and inter-therapeutic evaluation of lesions activity. All imaging analysis and data collection were performed by the same operator.

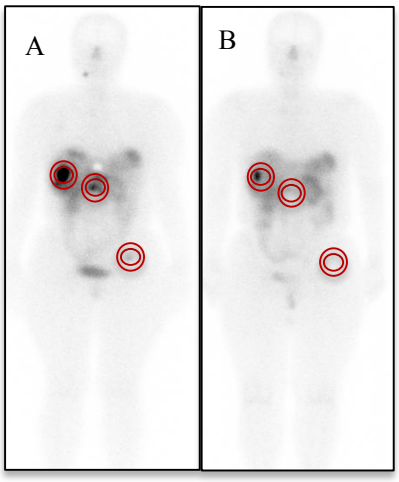


Figure 1: Assessment of metastases ^{177}Lu-DotaTate uptake. Example of a 52 years-old patient with pancreatic NET. A) ptWBS after 1st cycle showing hepatic, lymph-node and bone metastases. ROIs were placed in target lesion; B) ptWBS after the 3rd cycle showing decreased uptake.

The total counts of each metastatic lesion were assessed for both anterior and posterior scans using equation 1, geometric mean of both scans calculated using equation 2 and ^{177}Lu-DOTA-TATE activity extrapolated with equation 3.

Equation 1:

$$Metastasis'\ ROI\ Cts = Lesion'\ ROI\ Cts - \left(Background'\ ROI\ Cts * Metastasis'\ ROI\ Area * \frac{(Background'\ ROI\ Cts - Metastasis'\ ROI\ Cts)}{Background'\ ROI\ Area - Metastasis'\ ROI\ Area}\right)$$

Equation 2:

$$GM\ (A/P) = (Anterior\ \ Metastasis'\ ROI\ \ Cts * \ Posterior\ Metastasis'ROI\ \ Cts)^{0,5}$$

Equation 3:

$$177Lu\ Activity = \frac{GM\ (Metastasis)}{GM\ (Source)} * Source\ activity\ (uCi)$$

Statistical Analysis

All variables were assessed for normality using the Shapiro-Wilk or Kolmogorov-Sminorv tests pending on the total *n* and variables with p values<0,05 were considered as following a normal distribution (Table 6).

A Wilcoxon test was used for variable comparison, both for toxicity and dosimetry studies, during and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE.

The existence of correlation between the *pre-treatment, inter-cycle* and *post-treatment laboratorial work-up* was assessed by computing the corresponding Spearman coefficient. Correlation strength was established using the criteria defined on table 6.

Statistical analysis was performed using SPSS V.22.

Table 6: Correlation coefficient and relationship strength

Correlation coefficient	Correlation strength
]0 – 0.2[	Very weak
[0.2 – 0.4[	Weak
[0.4 – 0.6[	Moderate
[0.6 – 0.8[	Strong
[0.8 – 1[	Very strong
1	Excellent

Table 7: Normality Tests

Normality Tests					
Kolmogorov-Sminorv (n>25)		**Shapiro-Wilk (10≤n<25)**			
Liver Metastasis		Bone Metastasis		Alanine Transaminase	p=0.031
1^{s} Cycle 4 H (Counts)	p=0.000	1^{s} Cycle 4 H (Counts)	p=0.000	Aspartate Transaminase	p=0.000
1^{s} Cycle 24 H (Counts)	p=0.000	1^{s} Cycle 24 H (Counts)	p=0.000	Alkaline Phosphatase	p=0.001
1^{s} Cycle 7th Day (Counts)	p=0.000	1^{s} Cycle 7th Day (Counts)	p=0.000	Gama-Glutamyl Transferase	p=0.041
2nd Cycle 4 H (Counts)	p=0.000	2nd Cycle 4 H (Counts)	p=0.000	Total Bilirubin	p=0.001
2nd Cycle 24 H (Counts)	p=0.000	2nd Cycle 24 H (Counts)	p=0.000	Haematocrit	p=0.041
2nd Cycle 7th Day (Counts)	p=0.000	2nd Cycle 7th Day (Counts)	p=0.000	Haemoglobin	p=0.030
3rd Cycle 4 H (Counts)	p=0.000	3rd Cycle 4 H (Counts)	p=0.000	Red Blood Cells	p=0.006
3rd Cycle 24 H (Counts)	p=0.000	3rd Cycle 24 H (Counts)	p=0.000	White Blood Cells	p=0.036
3rd Cycle 7th Day (Counts)	p=0.000	3rd Cycle 7th Day (Counts)	p=0.012	Platelets	p=0.020
1^{s} Cycle 4 H (Activity)	p=0.000	1^{s} Cycle 4 H (Activity)	p=0.000	Serum Creatinine	p=0.001
1^{s} Cycle 24 H (Activity)	p=0.000	1^{s} Cycle 24 H (Activity)	p=0.000		
1^{s} Cycle 7th Day (Activity)	p=0.000	1^{s} Cycle 7th Day (Activity)	p=0.057		
2nd Cycle 4 H (Activity)	p=0.000	2nd Cycle 4 H (Activity)	p=0.023		
2nd Cycle 24 H (Activity)	p=0.000	2nd Cycle 24 H (Activity)	p=0.000		
2nd Cycle 7th Day (Activity)	p=0.000	2nd Cycle 7th Day (Activity)	p=0.000		
3rd Cycle 4 H (Activity)	p=0.000	3rd Cycle 4 H (Activity)	p=0.062		
3rd Cycle 24 H (Activity)	p=0.000	3rd Cycle 24 H (Activity)	p=0.000		
3rd Cycle 7th Day (Activity)	p=0.000	3rd Cycle 7th Day (Activity)	p=0.000		

Results

Toxicity

Bone Marrow Toxicity

Lack of significant toxicity was verified for the values of haematocrit (p>0.05; Figure 2), haemoglobin (p>0.05; Figure 3) and white blood cells total count (p>0.05; Figure 5). However, when comparing red blood cells total count before and after 3 cycles of PRRT a significantly difference was found (*p=0.023;* Figure 4). Platelets values were significantly different when comparing pre-treatment assessment with assessments at the 5th week after 1st cycle (*p=0.001*), at the 10th week after 1st cycle (*p=0.01*), at the 5th week after 2nd cycle (*p=0.019*) and at the 5th week after 3rd cycle (*p=0.015*).

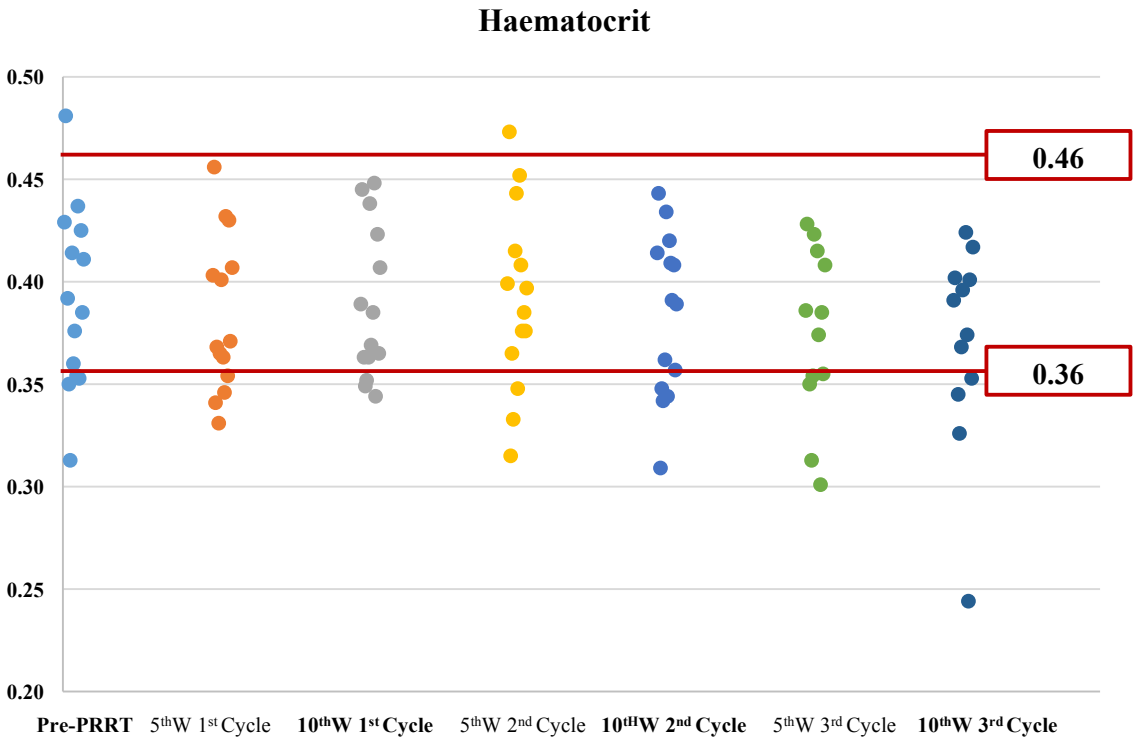


Figure 2: Evolution pattern of haematocrit values

No statistically significant difference was found between the values of haematocrit before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE (p>0.05). Also, no statistically significant difference was found between the values of haematocrit obtained before PRRT and 5 or 10 weeks after the first, second and third cycle of PRRT. From the comparison between the values obtained five weeks after each cycle, no significant statistically difference was found for the values of haematocrit obtained at the 5th week after the first cycle and values of the 5th week after second and third cycle (p>0.05). Statistically difference was found after comparing the values of haematocrit obtained at the 5th week after the second cycle with values obtained at the 5th week after third cycle *(p=0.04)*. When comparing assessments performed 10 weeks after each cycle no statistically significant difference was found.

Abbreviations: 5thW - 5th week; 10thW - 10th week

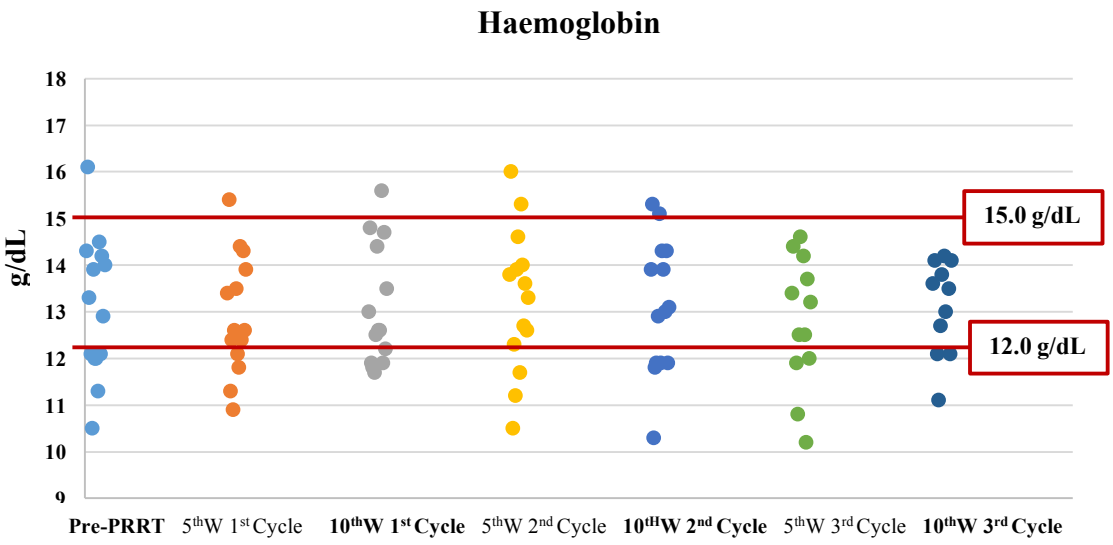


Figure 3: Evolution pattern of haemoglobin values

No statistically significant difference was found between the values of haemoglobin before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p>0.05$). No statistically significant difference was found between the values of haemoglobin obtained before PRRT and 5 or 10 weeks after the first, second and third cycles. When comparing assessments performed 5 weeks after each cycle, no significant statistically difference was found for the values of haemoglobin obtained at the 5th week after the first cycle and the values of the 5th week after second and third cycle ($p>0.05$). No statistically difference was found when comparing the values of haemoglobin obtained at the 5th week after the second cycle with values obtained at the 5th week after third cycle *($p=0.05$)*. From the comparison between values obtained ten weeks after each cycle, no statistically significant difference was found.

Abbreviations: 5thW - 5th week; 10thW - 10th week

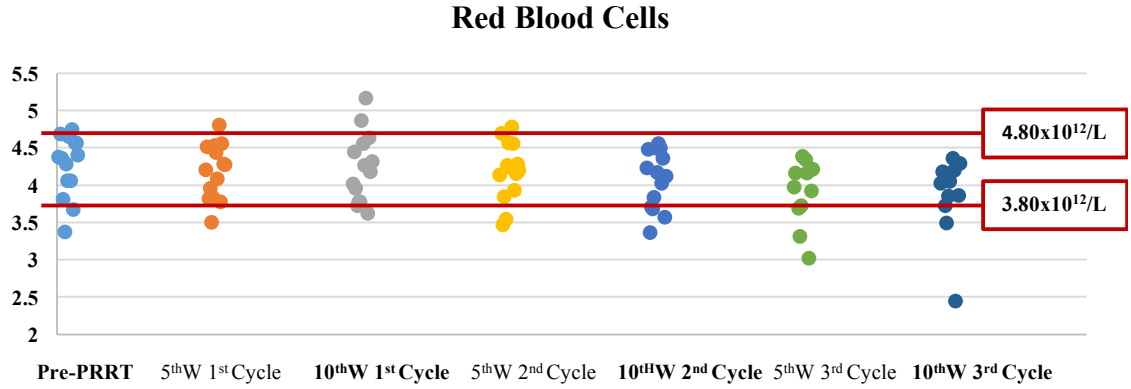


Figure 4: Evolution pattern of red blood cells total count

Statistically significant difference was found between the values of red blood cells total count before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p=0.023$). Moreover, statistically significant difference was found between the values of red blood cells total count between the 5th week after the first and the 5th week after the third cycle ($p=0.011$). No statistically significant difference was found when comparing the assessment performed 5 weeks after the second and third cycle *($p=0.05$)*.

No statistically significant difference was found between the assessments performed before PRRT and 5 weeks after the first and second cycle. Statistically significant difference was found when comparing the evaluation done before PRRT and 5 weeks after the third cycle (*$p=0.019$*). No statistically significant difference was found between the values of red blood cells obtained before PRRT and 10 weeks after the first, second and third cycles.

From the comparison between the values obtained five weeks after each cycle, no statistically significant difference was found after comparing the values of red blood cells total count obtained at the 5th week after the first cycle with the values of the 5th week after the second cycle (p>0.05). Statistically significant difference was found after comparing the values of red blood cells total count obtained at the 5th week after the first and third cycle *(p=0.011)*. Furthermore, no statistically significant difference was found when comparing the values of red blood cells total count obtained at the 5th week after the second and third cycles *(p=0.05)*.

When comparing the assessments performed 10 weeks after each cycle, no statistically significant difference was found for the comparison between values obtained at the 10th week after the first and after the second cycle. Also, no statistically significant difference was found for the comparison between the 10th week after the second with the 10th week after the third cycle. However, significant statistically difference was found for the evolution of the total count of red blood cells from the 10th week after first cycle to the 10th week after the third cycle (*p=0.026*).

Abbreviations: 5thW - 5th week; 10thW - 10th week

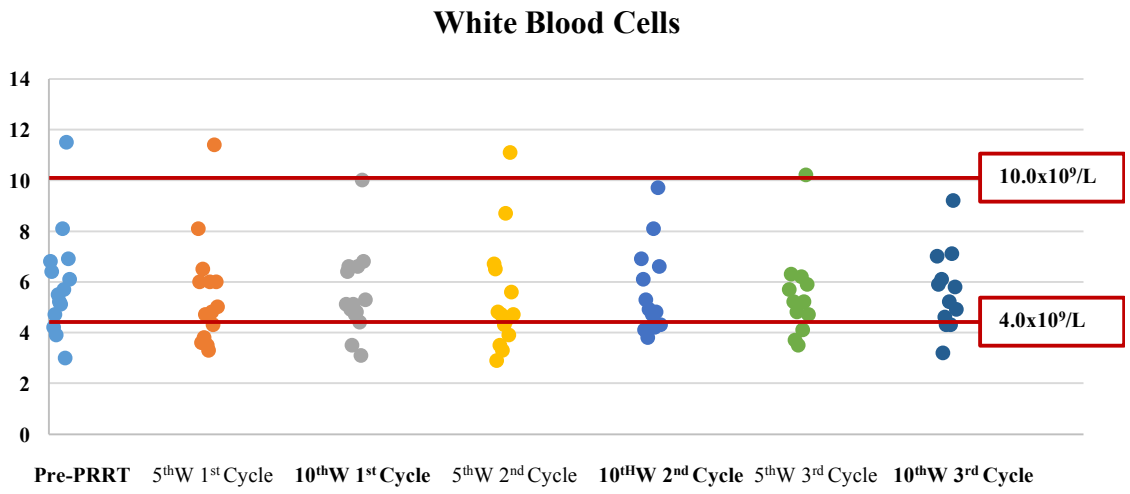


Figure 5: Evolution pattern of white blood cells

No statistically significant difference was found between the values of white blood cells total count before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE (p>0.05). Analysing the evolution of white blood cells total count, no statistical significant difference was found before PRRT and 5 weeks after the first and third cycle (p>0.05). However, statistically significant difference was found when comparing the measurement before PRRT and 5 weeks after the second cycle (*p=0.035)*. No statistically significant difference was found between the values of white blood cells total count obtained before PRRT and 10 weeks after the first, second and third cycles.

When comparing the assessments performed five weeks after each cycle, no statistically significant difference was found. Also, no statistically significant difference was found from the comparison between the assessments performed ten weeks after each cycle.

Abbreviations: 5thW - 5th week; 10thW - 10th week

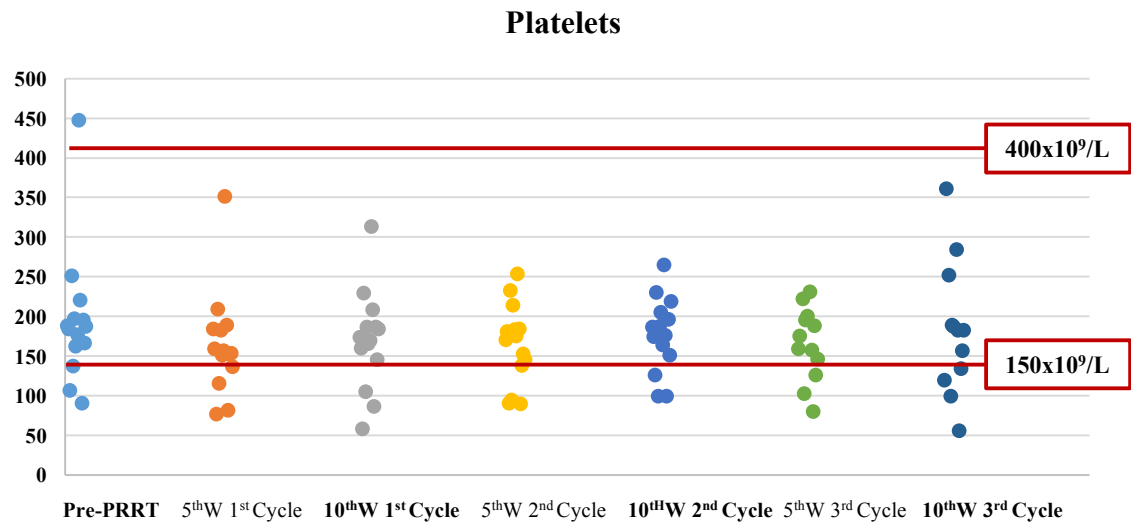


Figure 6: Evolution pattern of platelets total count

No statistically significant difference was found between the values of platelets total count before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE (p>0.05).

Assessment of platelets total count before PRRT and five weeks after each cycle found statistically significant difference for every cycle ($p^{1st\ cycle} = 0.001$; $p^{2nd\ cycle} = 0.019$; $p^{3rd\ cycle} = 0.015$).

When comparing the assessment performed before PRRT and ten weeks after the first cycle of treatment statistically significant difference was found ($p=0.01$). However, no statistically significant difference was found between the values of white blood cells total count obtained before PRRT and ten weeks after the second and third cycles.

When comparing the assessments performed five weeks after each cycle, no statistically significant difference was found. Also, no statistically significant difference was found from the comparison between the assessments performed ten weeks after each cycle.

Abbreviations: 5thW - 5th week; 10thW - 10th week

Hepatotoxicity

Lack of significant toxicity was verified for the values of alanine transaminase ($p>0.05$; Figure 7), aspartate transaminase ($p>0.05$; Figure 8), alkaline phosphatase ($p>0.05$; Figure 9), gama-glutamyl transpeptidase ($p>0.05$; Figure 10) and total bilirubin ($p>0.05$; Figure 11) when comparing assessments performed before and after 3 cycles of PRRT.

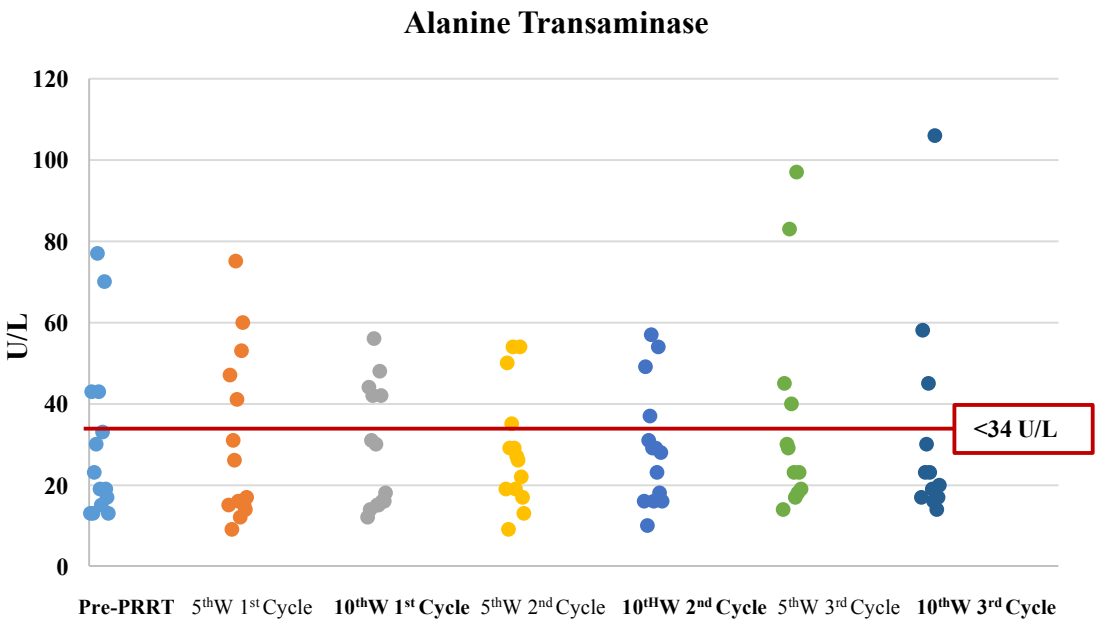


Figure 7: Evolution pattern of alanine transaminase

No statistically significant difference was found between the values of alanine transaminase before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p>0.05$). Significant statistically difference was only found when comparing the values of Alanine Transaminase obtained at the 10th week after first cycle with the values obtained at the 10th week after second cycle *($p=0.028$)*.

Abbreviations: 5thW - 5th week; 10thW - 10th week

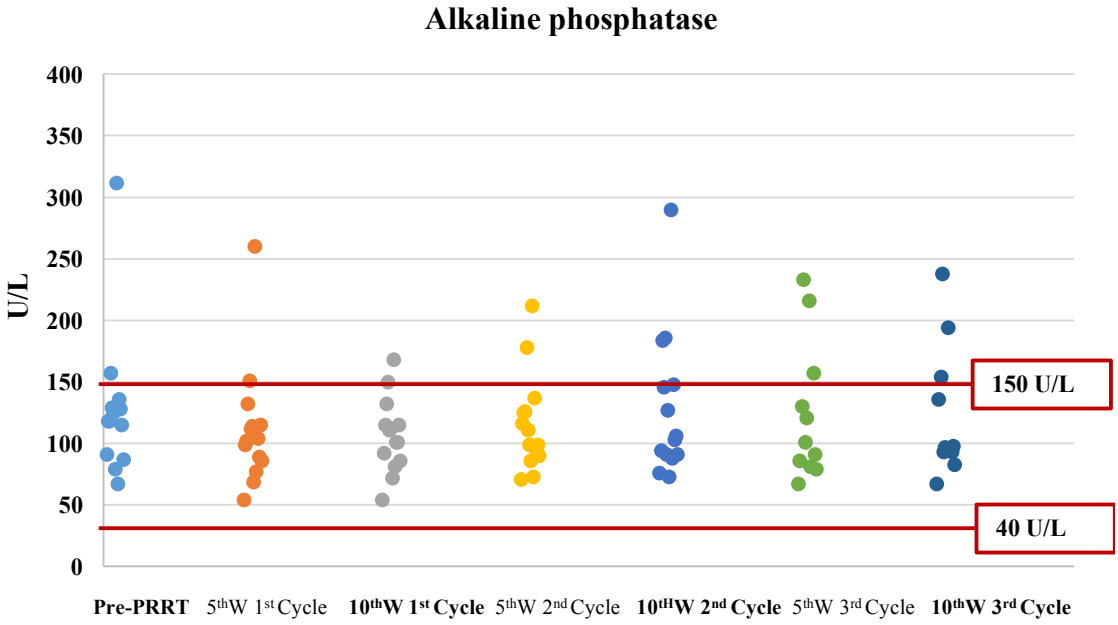


Figure 8: Evolution pattern of alkaline phosphatase

No statistically significant difference was found between the values of alkaline phosphatase before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p>0.05$). Similarly, no statistically significant difference was found when comparing any other assessment ($p>0.05$).

Abbreviations: 5thW - 5th week; 10thW - 10th week

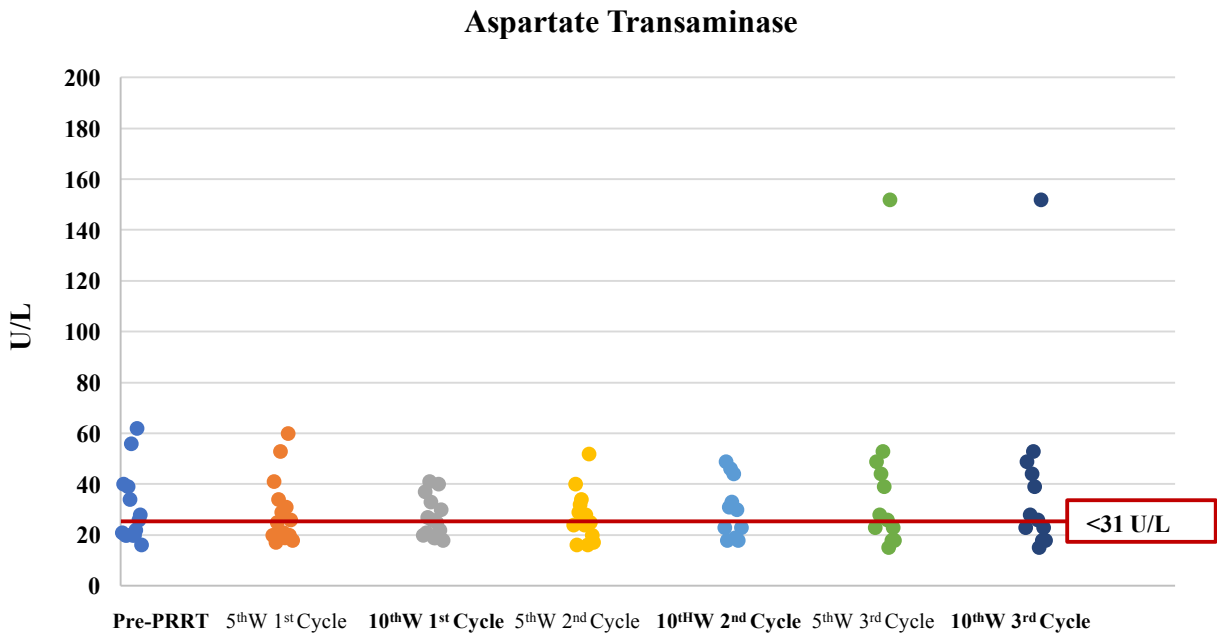


Figure 9: Evolution pattern of aspartate transaminase

No statistically significant difference was found between the values of aspartate transaminase before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p>0.05$). Significant statistically difference was only found when comparing the values of Aspartate Transaminase obtained at the 10th week after first cycle with the value obtained at the 10th week after second cycle *($p=0.019$).*

Abbreviations: 5thW - 5th week; 10thW - 10th week

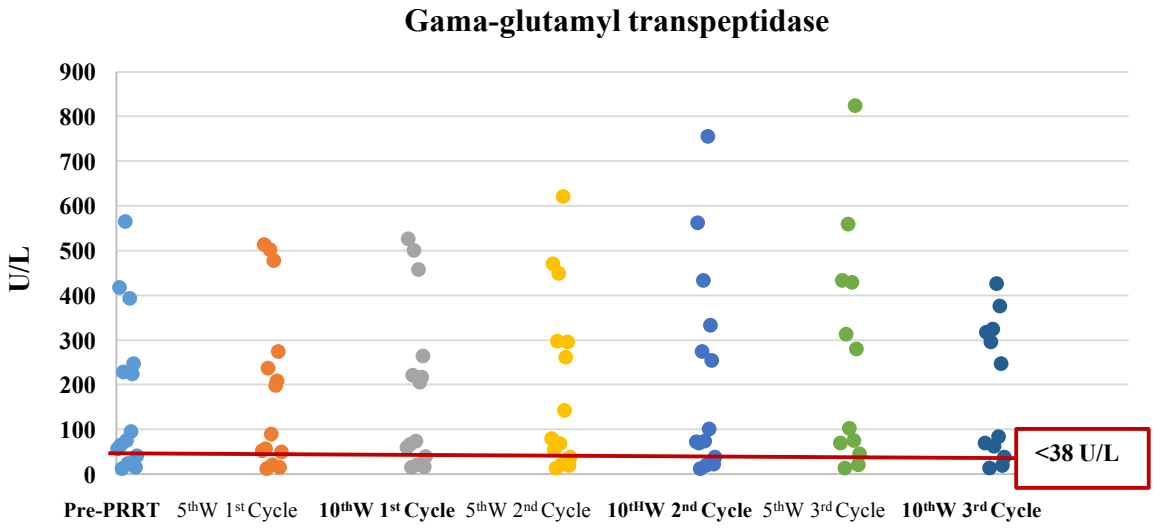


Figure 10: Evolution pattern of gama-glutamyl transpeptidase

No statistically significant difference was found between the values of gama-glutamyl transpeptidase before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE (*$p>0.05$*). Statistically significant difference was found when comparing the values of gama-glutamyl transpeptidase before PRRT and 5 weeks after the third cycle *($p=0.025$).*

Abbreviations: 5thW - 5th week; 10thW - 10th week

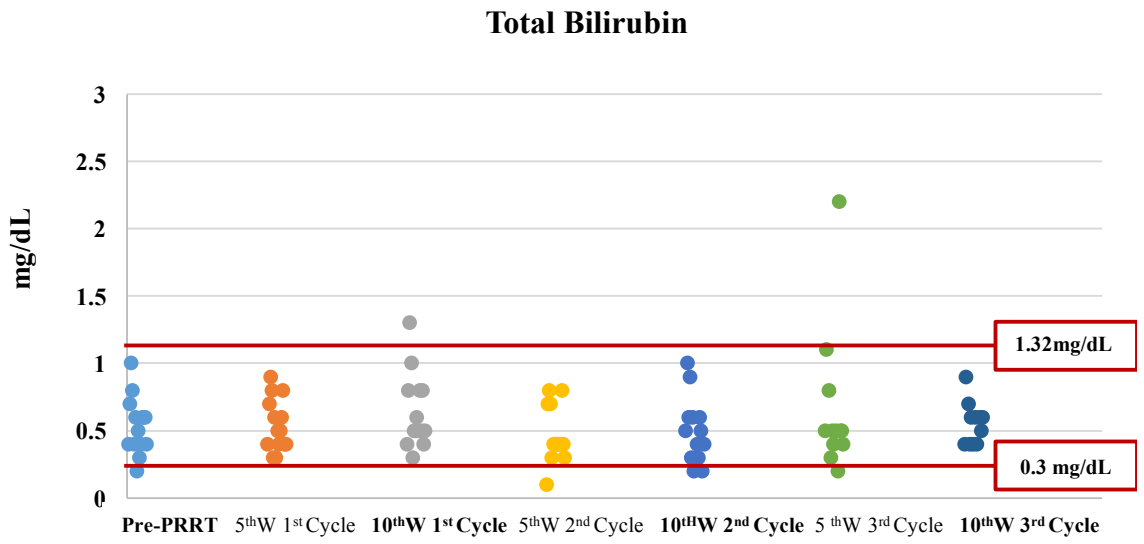


Figure 11: Evolution of total bilirubin

No statistically significant difference was found between the values of total bilirubin values before and after 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p>0.05$). Statistically significant difference was found when comparing the total bilirubin values assessed at the 5th week after the first cycle with the values assessed at the 5th week after the second cycle ($p=0.025$).

Abbreviations: 5thW - 5th week; 10thW - 10th week

Nephrotoxicity

Lack of significant toxicity was found when comparing serum creatinine values before, during and after PRRT ($p>0.05$; Figure 12).

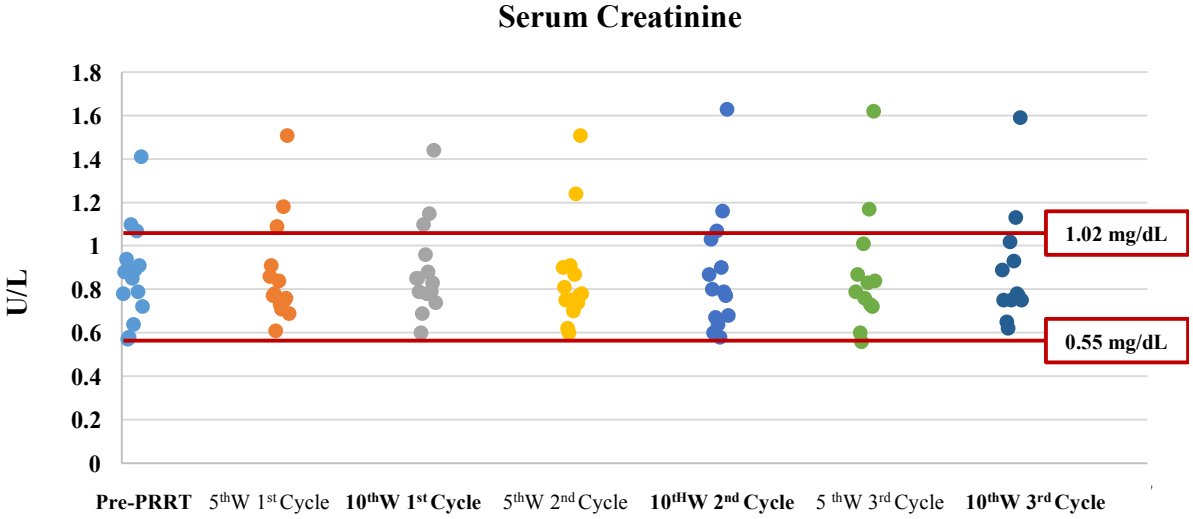


Figure 12: Evolution of serum creatinine

No statistically significant difference was found in any comparison of serum creatinine assessments before, during and after the 3 cycles of PRRT with ^{177}Lu-DOTA-TATE ($p>0.05$).

Abbreviations: 5thW - 5th week; 10thW - 10th week

Table 7.1: Summary of intra-cycles assessments – Median Values

		Liver Function						Medular Function				Renal Function
		ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TB (mg/dL)	Plt	Hb	RBC	WBC	Htc	Cr (mg/dL)
	Pre-PRRT	26.50	28.00	125.00	158.50	0.50	185.50	13.10	4.37	5.60	0.39	0.87
1st Cycle	**5thW**	28.50	29.00	112.00	203.00	0.45	154.50	12.60	4.24	4.90	0.37	0.81
	10thW	27.00	26.00	111.00	210.50	0.50	171.00	12.60	4.22	5.10	0.38	0.85
2nd Cycle	**5thW**	28.00	27.00	111.00	201.50	0.40	172.50	13.45	4.22	4.70	0.39	0.84
	10thW	29.00	33.00	106.00	177.00	0.45	181.00	13.05	4.15	4.85	0.39	0.83
3rd Cycle	**5thW**	26.00	26.00	121.00	190.50	0.50	167.00	12.85	4.07	5.20	0.38	0.81
	10thW	21.50	32.00	98.00	165.00	0.60	182.00	13.25	4.04	5.50	0.38	0.86

Summary of intra-cycle laboratorial work-ups during the full length of treatment. Highlighted values correlate with inter-cycles comparison on table 7.2.

Table 7.2: Summary of inter-cycles assessments – *p* values

		1st Cycle			2nd Cycle		3rd Cycle	
		Pre-PRRT	**5thW**	**10thW**	**5thW**	**10thW**	**5thW**	**10thW**
1st Cycle	**5thW**	Platelets (*p=0.001*)						
	10thW	Platelets (*p=0.010*)						
2nd Cycle	**5thW**	WBC (*p=0.035*) Platelets (*p=0.019*)	TB (*p=0.025*)					
	10thW			ALT (*p=0.028*) AST (*p=0.019*)				
3rd Cycle	**5thW**	RBC (*p=0.023*) Platelets (*p=0.015*) GGT (*p=0.025*)	RBC (*p=0.011*)		Haematocrit (*p=0.04*) Haemoglobin (*p=0.05*) RBC (*p=0.05*)			
	10thW	RBC (*p=0.023*)		RBC (*p=0.026*)				

Summary of inter-cycle laboratorial work-ups comparison during the full length of treatment. Highlighted values correlate with intra-cycle values on table 7.1.

Correlation Studies

A very strong to strong positive correlation was found for every hepatic parameter assessed (Figures 1-5; $0.6< \rho <1$) with exception to correlation between alkaline phosphatase pre-^{177}Lu-DOTA-TATE and the value obtained post-treatment ($\rho=0.55;\ p=0.005$). Analysing the same correlation for serum creatinine values, we found that the initial value pre-PRRT presents a very strong to strong positive correlation with every other assessment ($0.6< \rho <1$) with exception to the evaluation performed at the 5th week after 2nd cycle ($\rho=0.376,\ p=0.185$).

Nonetheless, parameters used to access myelotoxicity showed a different correlational behaviour during the length of treatment. On one hand, haematocrit, haemoglobin and red blood cells total count showed a strong positive correlation ($0.6< \rho <0.8$) between pre-PRRT values and values acquired five and ten weeks after the 1st cycle. Also, a moderate positive correlation was found between the values of red blood cells total count pre-PRRT and the post-therapeutic values. On the other hand, white blood cells presented a very strong to strong positive correlation for every analysis ($0.6< \rho <1$) with exception for the correlation between pre-PRRT values and values assessed ten weeks after 3rd cycle ($\rho=0.329,\ p=0.29$).

Correlation Studies ALT

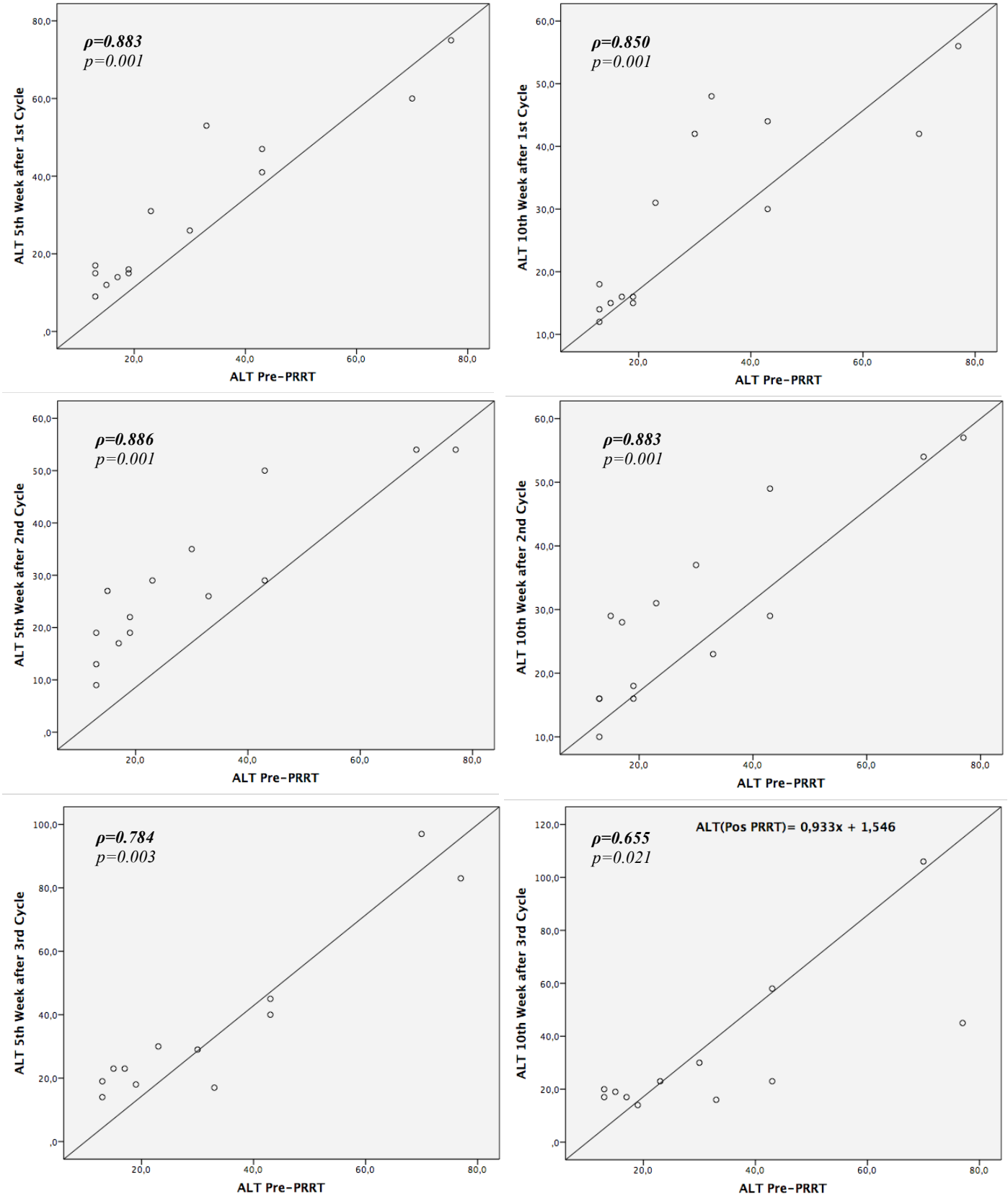


Figure 13: Correlation between ALT values – A very strong positive correlation was found between the variable *ALT Pre-PRRT* and the variables *ALT 5th Week after 1st Cycle* (ρ=0.883, p=0.001), *ALT 10th Week after 1st Cycle* (ρ=0.850, p=0.001), *ALT 5th Week after 2nd Cycle* (ρ=0.886, p=0.001), *ALT 10th Week after 2nd Cycle* (ρ=0.833, p=0.001). A strong positive correlation was found between the variable *ALT Pre-PRRT* and the variables *ALT 5th Week after 3rd Cycle* (ρ=0.784, p=0.003) and *ALT 10th Week after 3rd Cycle* (ρ=0.655, p=0.021)

Correlation Studies AST

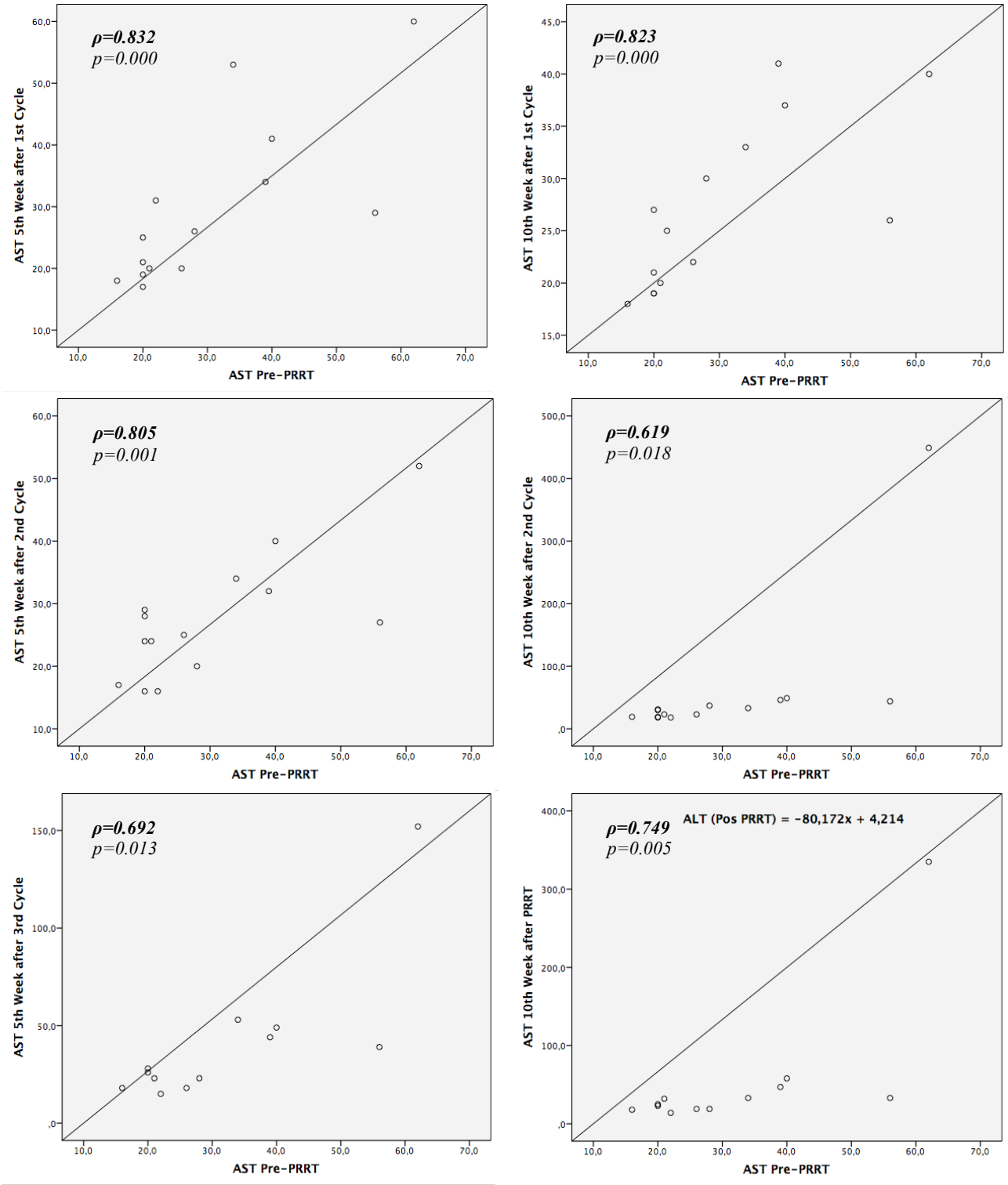


Figure 14: Correlation between AST values - A positive very strong correlation was found between the variable *AST Pre-PRRT* and the variables *AST 5th Week after 1st Cycle* (ρ=0.832, p=0.000), *AST 10th Week after 1st Cycle* (ρ=0.823, p=0.000), *AST 5th Week after 2nd Cycle* (ρ=0.805, p=0.001). A positive strong correlation was found between the variable *AST Pre-PRRT* and the variables *AST 10th Week after 2nd Cycle* (ρ=0.619, p=0.018), *ALT 5th Week after 3rd Cycle* (ρ=0692, p=0.013) and *ALT 10th Week after 3rd Cycle* (ρ=0.749 p=0.005).

Correlation Studies ALP

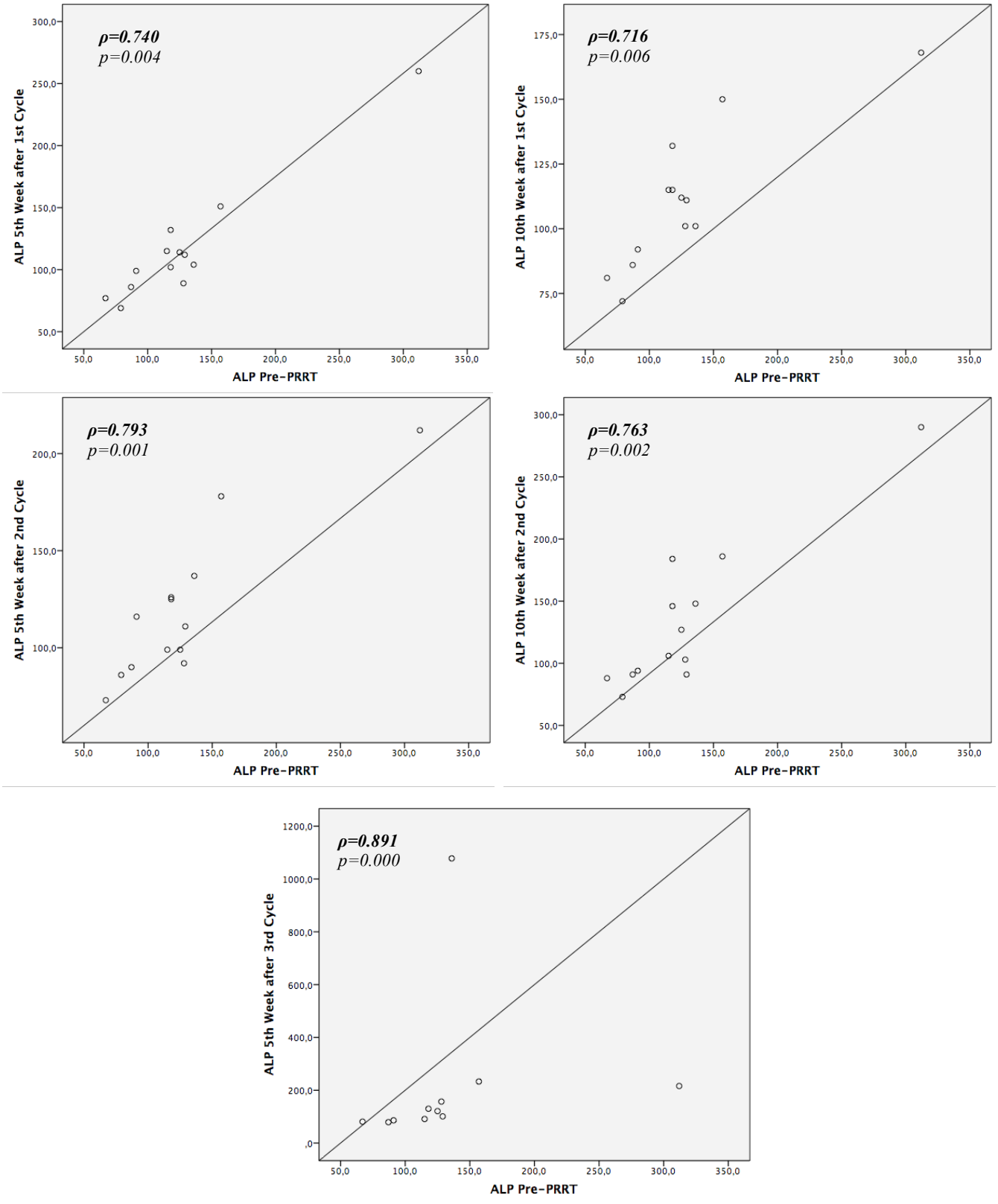


Figure 15: Correlation between ALP values - A positive very strong correlation was found between the variable *ALP Pre-PRRT* and the variable *ALP 5th Week after 3rd Cycle* (ρ=0.891, p=0.000). A positive strong correlation was found between the variable *ALP Pre-PRRT* and the variables *ALP 5th Week after 1st Cycle* (ρ=0.740, p=0.004), *ALP 10th Week after 1st Cycle* (ρ=0.716, p=0.006), *ALP 5th Week after 2nd Cycle* (ρ=0.793, p=0.001) and *ALP 10th Week after 2nd Cycle* (ρ=0.763, p=0.002). No statistically meaningful correlation was found between the variable *ALP Pre-PRRT* and the variable *ALT 10th Week after 3rd Cycle* (p=0.005).

Correlation Studies GGT

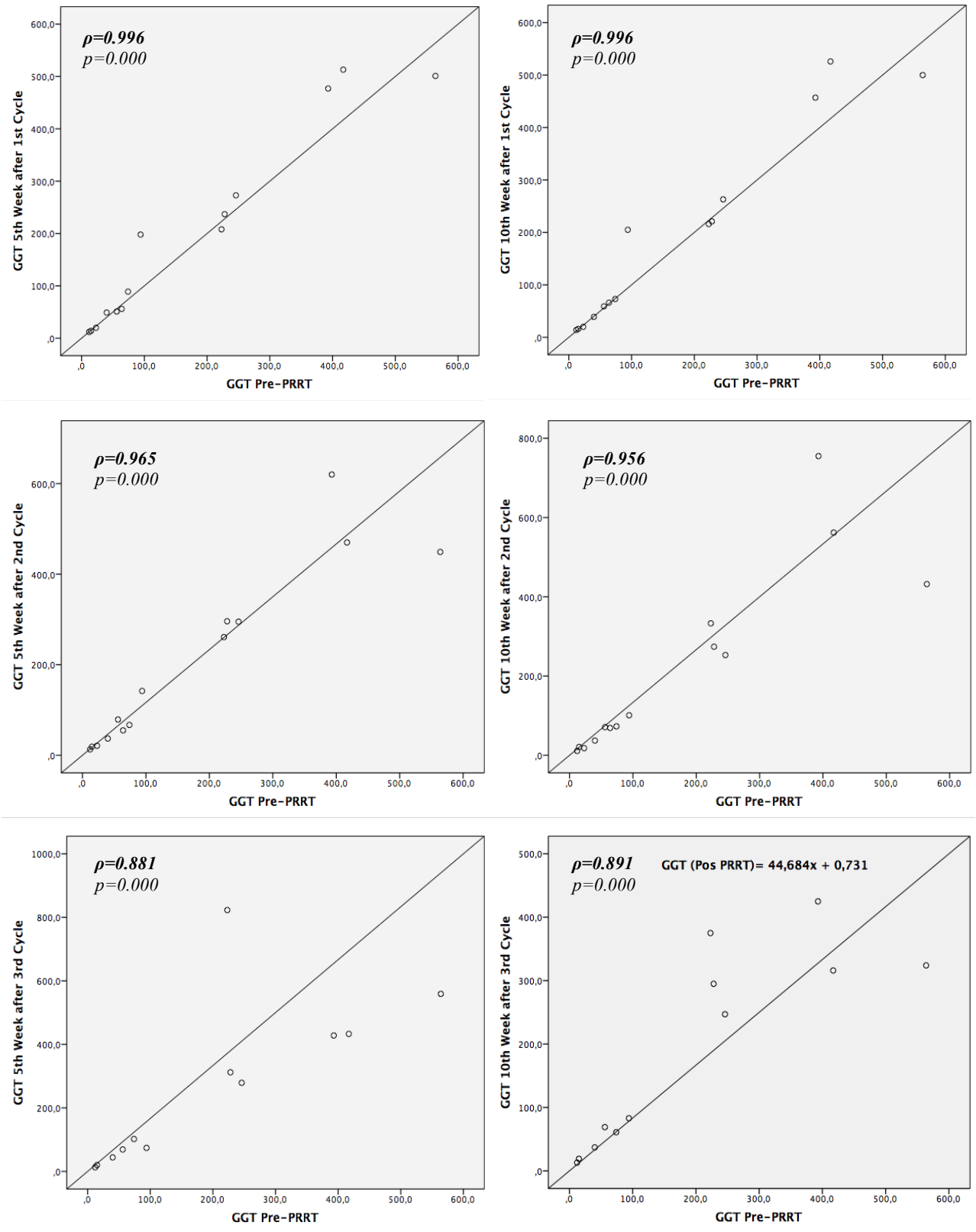


Figure 16: Correlation between GGT values - A positive very strong correlation was found between the variable *GGT Pre-PRRT* and the variables *GGT 5th Week after 1st Cycle* (ρ=0.996, p=0.000), *GGT 10th Week after 1st Cycle* (ρ=0.996, p=0.000), *GGT 5th Week after 2nd Cycle* (ρ=0.965, p=0.000), *GGT 10th Week after 2nd Cycle* (ρ=0.956, p=0.000), *GGT 5th Week after 3rd Cycle* (ρ=0.881, p=0.000) and *GGT 10th Week after 3rd Cycle* (ρ=0,891, p=0.000)

Correlation Studies Total Bilirubin

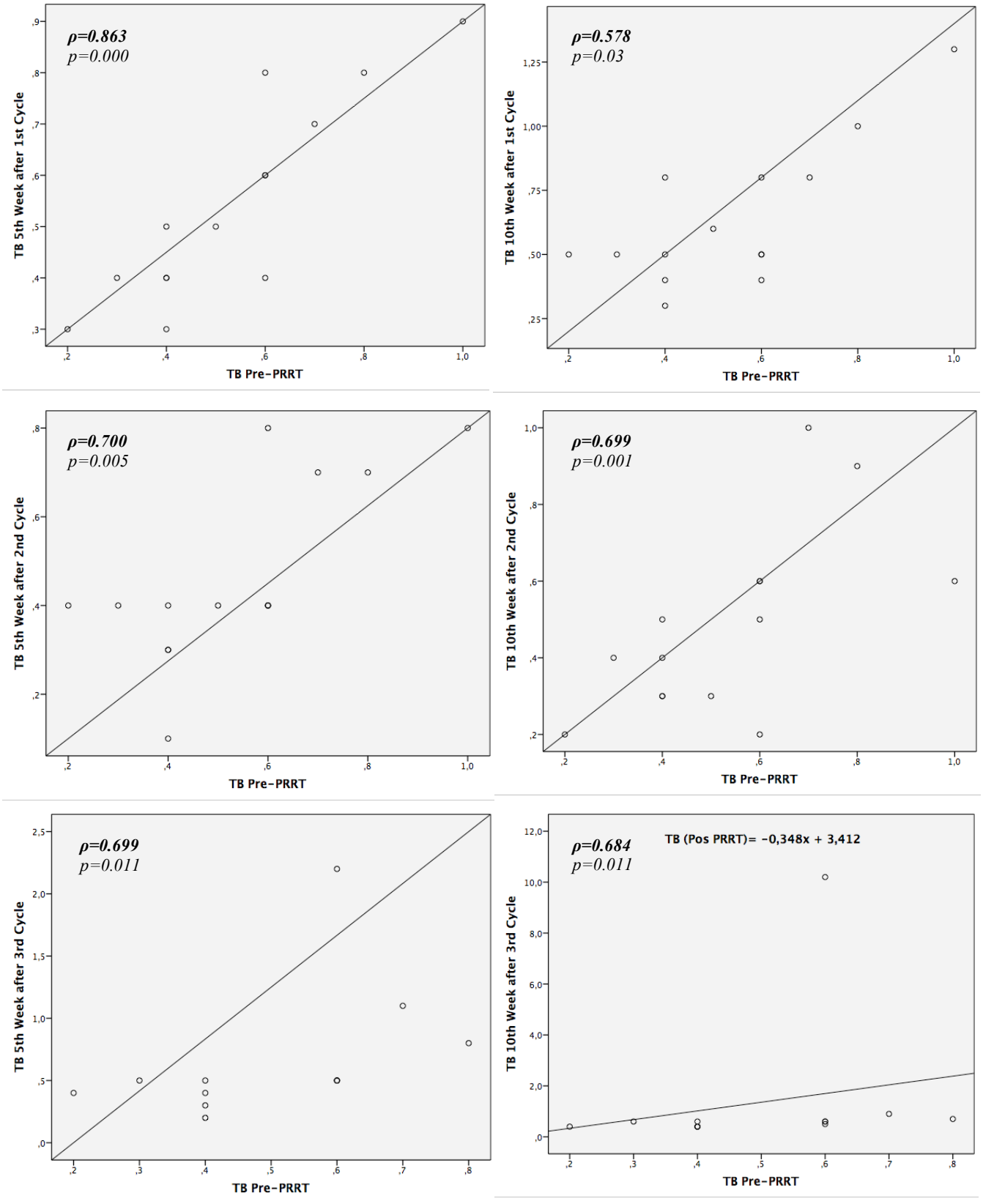


Figure 17: Correlation between TB values - A positive very strong correlation was found between the variable *TB Pre-PRRT* and the variable *BT 5th Week after 1st Cycle* (ρ=0.863, p=0.000). A positive strong correlation was found between the variable *TB Pre-PRRT* and the variables *TB 5th Week after 2nd Cycle* (ρ=0.700, p=0.005), *TB 10th Week after 2nd Cycle* (ρ=0.699, p=0.001), *TB 5th Week after 3rd Cycle* (ρ=0.699, p=0.011) and *TB 10th Week after 3rd Cycle* (ρ=0.684, p=0.014). A positive moderate correlation was found between the variable *TB Pre-PRRT* and the variable *TB 10th Week after 1st Cycle* (ρ=0.578, p=0.03).

Correlation Studies Creatinine

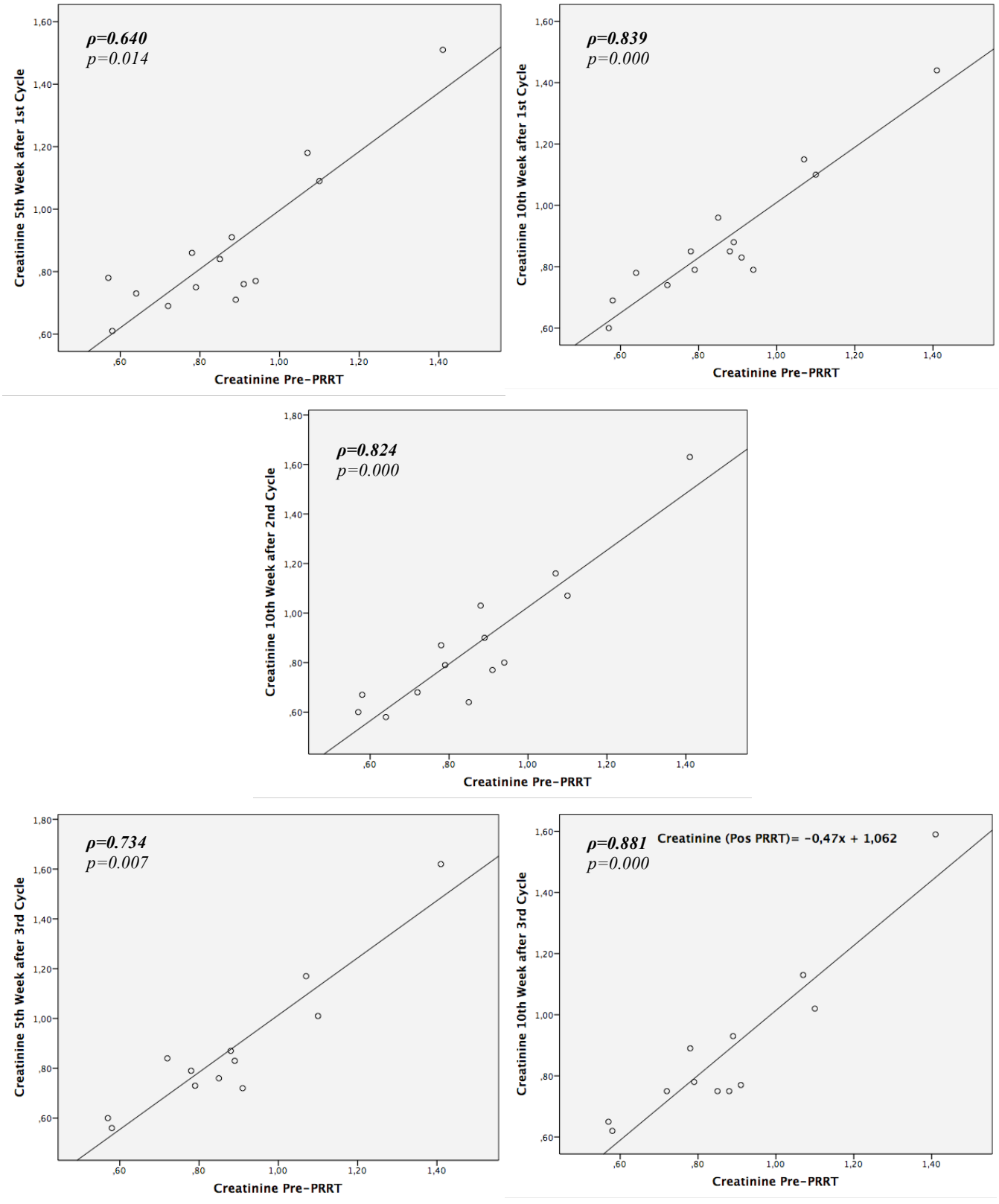


Figure 18: Correlation between Creatinine values - A positive very strong correlation was found between the variable *Creatinine Pre-PRRT* and the variables *Creatinine 10th Week after 1st Cycle* (ρ=0.839, p=0.000), *Creatinine 10th Week after 2nd Cycle* (ρ=0.824, p=0.000) and *Creatinine 10th Week after 3rd Cycle* (ρ=0,881, p=0.000). A positive strong correlation was found between the variable *Creatinine Pre-PRRT* and the variables *Creatinine 5th Week after 1st Cycle* (ρ=0.640, p=0.014) and *Creatinine 5th Week after 3rd Cycle* (ρ=0.734, p=0.007). No statistically meaningful correlation was found between the variable *Creatinine Pre-PRRT* and the variable *Creatinine 5th Week after 2nd Cycle* (ρ=0.376, p=0.185).

Correlation Studies Haematocrit

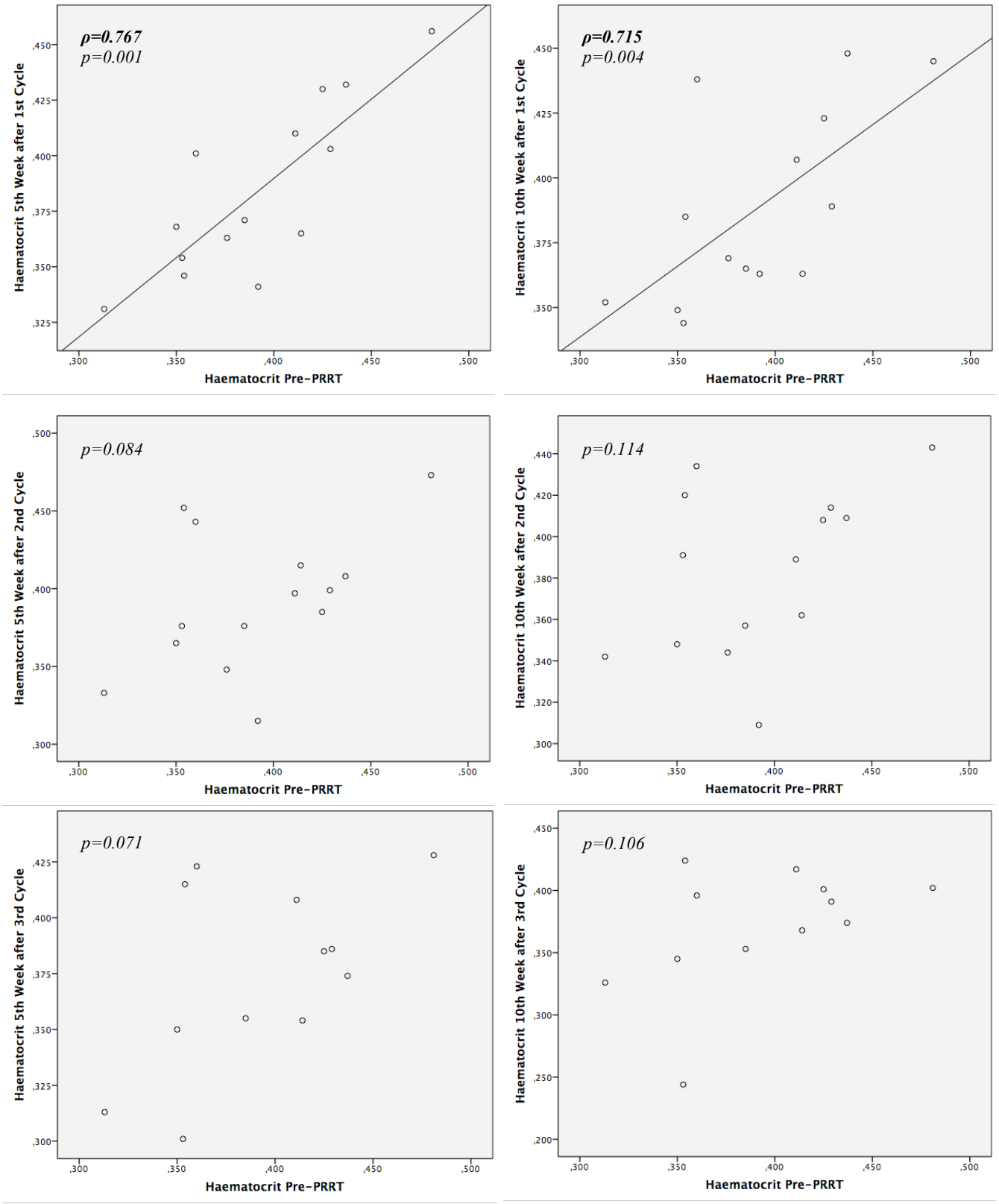


Figure 19: Correlation between Haematocrit values- A positive strong correlation was found between the variable *Haematocrit Pre-PRRT* and the variables *Haematocrit 5th Week after 1st Cycle* (ρ=0.767, p=0.001) and *Haematocrit 10th Week after 1st Cycle* (ρ=0.715, p=0.004). No statistically meaningful correlation was found between the variable *Haematocrit Pre-PRRT* and the variable *Haematocrit 5th Week after 2nd Cycle* (ρ=0.477, p=0.084), *Haematocrit 10th Week after 2nd Cycle* (ρ=0.477, p=0.114), *Haematocrit 5th Week after 3rd Cycle* (ρ=0.538, p=0.071) and *Haematocrit 10th Week after 3rd Cycle* (ρ=0.490, p=0.106).

Correlation Studies Haemoglobin

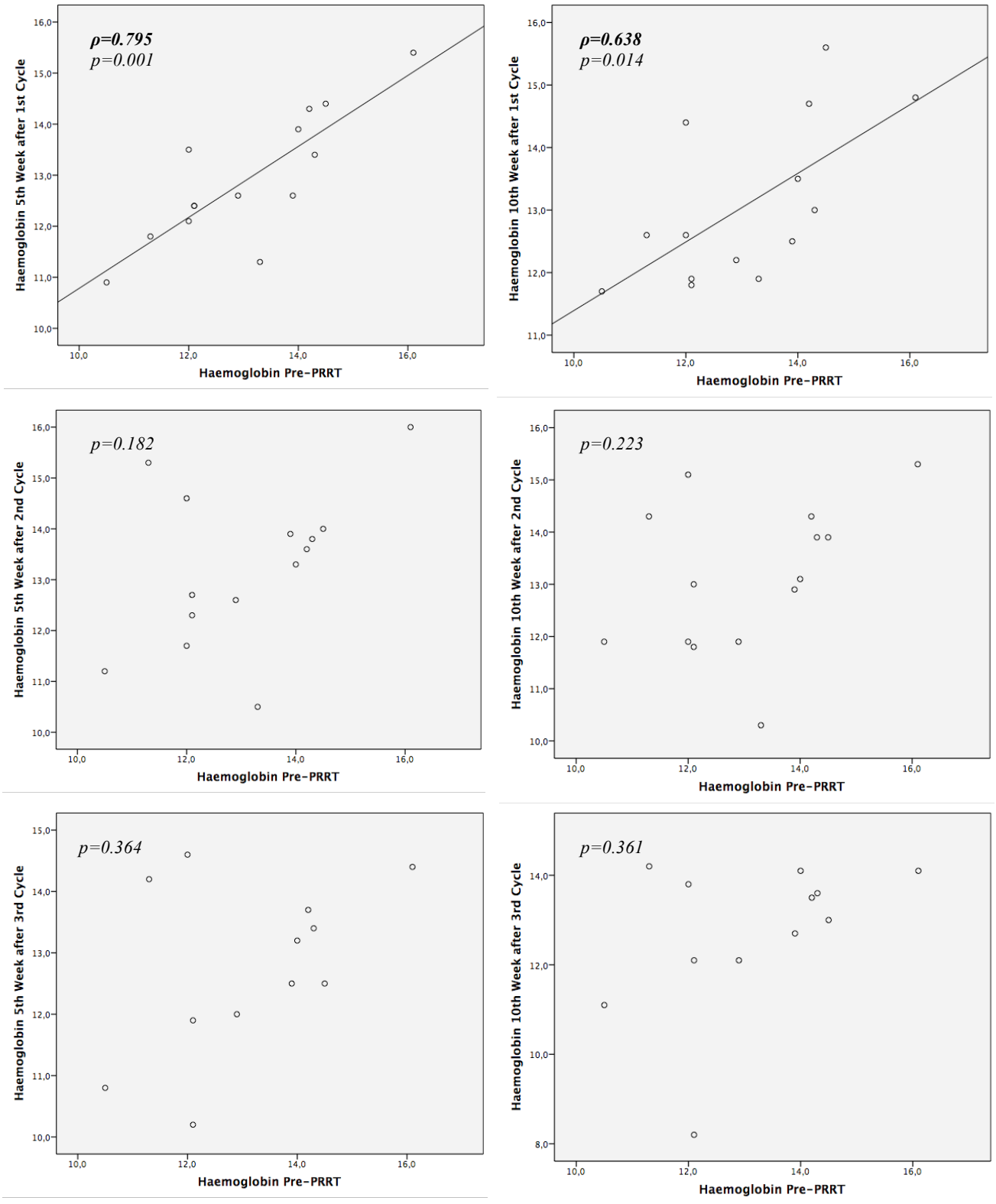


Figure 20: Correlation between Haemoglobin values- A positive strong correlation was found between the variable *Haemoglobin Pre-PRRT* and the variables *Haemoglobin 5th Week after 1st Cycle* (ρ=0.795, p=0.001) and *Haemoglobin 10th Week after 1st Cycle* (ρ=0.638, p=0.014). No statistically meaningful correlation was found between the variable *Haemoglobin Pre-PRRT* and the variable *Haemoglobin 5th Week after 2nd Cycle* (ρ=0.379, p=0.182), *Haemoglobin 10th Week after 2nd Cycle* (ρ=0.348, p=0.223), *Haemoglobin 5th Week after 3rd Cycle* (ρ=0.288, p=0.364) and *Haemoglobin 10th Week after 3rd Cycle* (ρ=0.290, p=0.361).

Correlation Studies Red Blood Cells

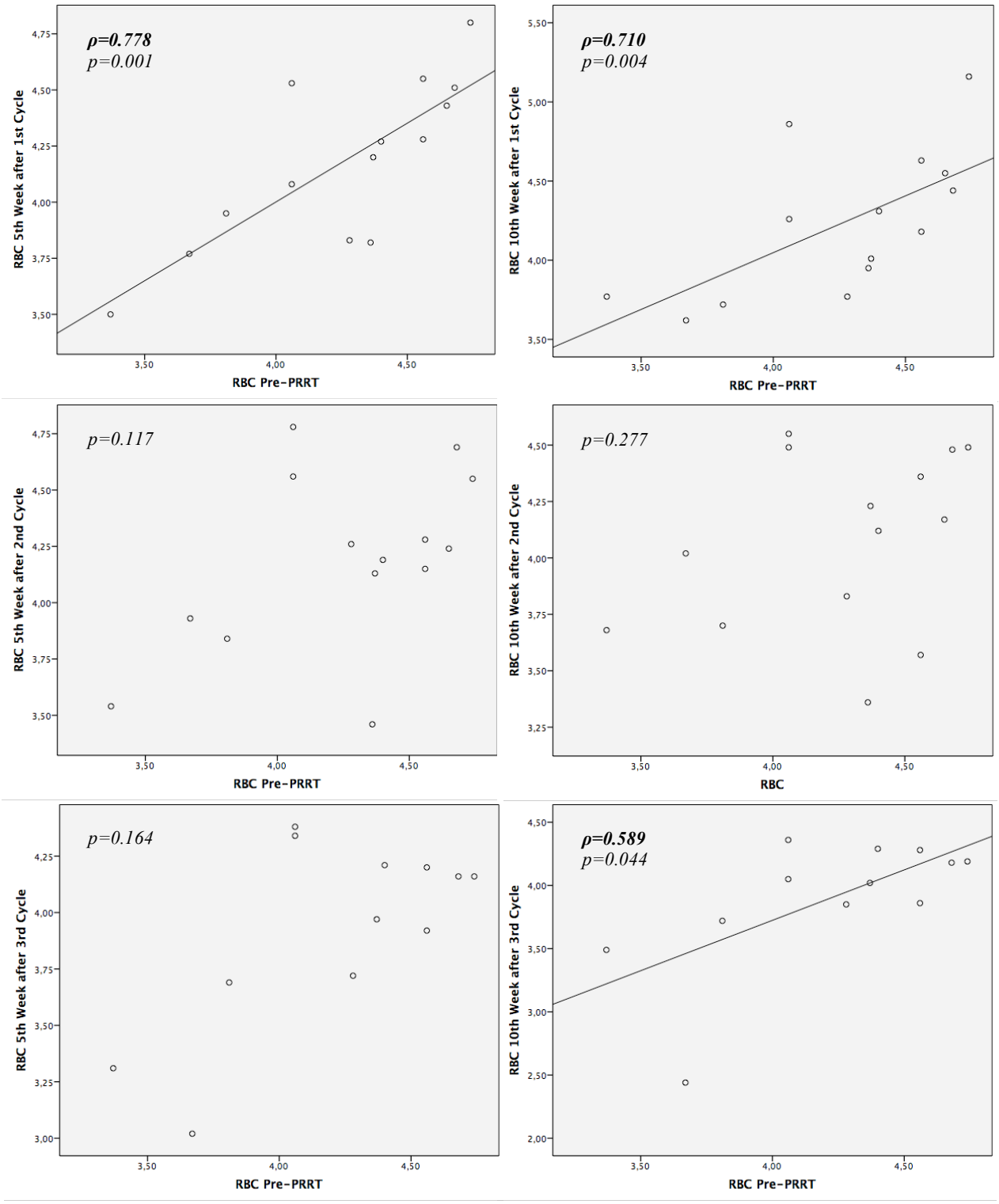


Figure 21: Correlation between Red Blood Cells Total Count- - A positive strong correlation was found between the variable *RBC Pre-PRRT* and the variables *RBC 5th Week after 1st Cycle* (ρ=0.778, p=0.001) and *RBC 10th Week after 1st Cycle* (ρ=0.710, p=0.004). A positive moderate correlation was found between the variable *RBC Pre-PRRT* and the variable *RBC 10th Week after 3rd Cycle* (ρ=0.589, p=0.044). No statistically meaningful correlation was found between the variable *RBC Pre-PRRT* and the variable *RBC 5th Week after 2nd Cycle* (ρ=0.438, p=0.117), *RBC 10th Week after 2nd Cycle* (ρ=0.312, p=0.277) and *RBC 5th Week after 3rd Cycle* (ρ=0.429, p=0.164).

Correlation Studies White Blood Cells

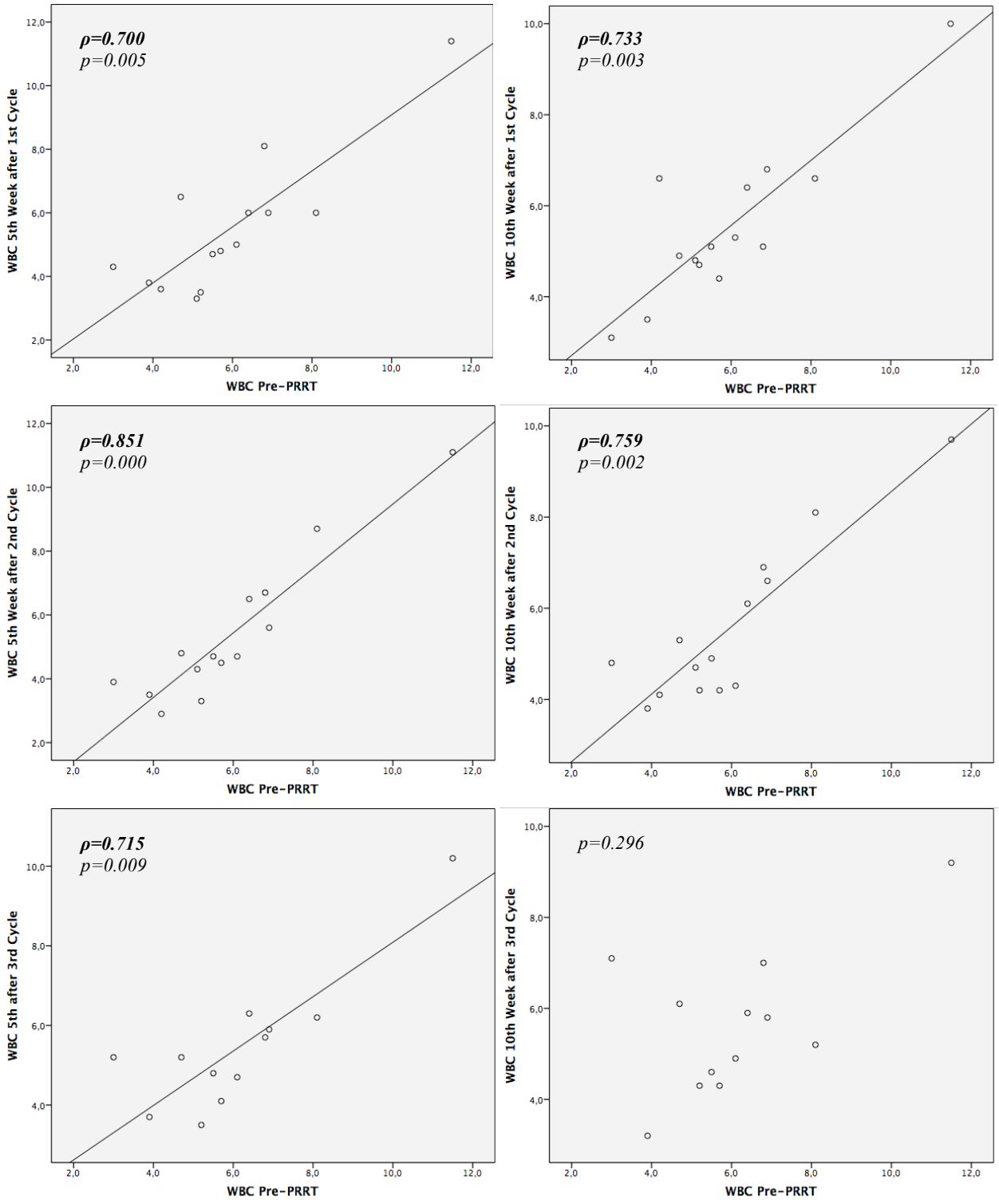


Figure 22: Correlation between White Blood Cells Total Count- A positive very strong correlation was found between the variable *WBC Pre-PRRT* and the variable *WBC 5th Week after 2nd Cycle* (ρ=0.851, p=0.000). A positive strong correlation was found between the variable *WBC Pre-PRRT* and the variables *WBC 5th Week after 1st Cycle* (ρ=0.700, p=0.005), W*BC 10th Week after 1st Cycle* (ρ=0.733, p=0.003), W*BC 10th Week after 2nd Cycle* (ρ=0.759, p=0.002), W*BC 5th Week after 3rd Cycle* (ρ=0.715, p=0.009). No statistically meaningful correlation was found between the variable *WBC Pre-PRRT* and the variable W*BC 10th Week after 3rd Cycle* (ρ=0.329, p=0.296).

Correlation Studies Platelets

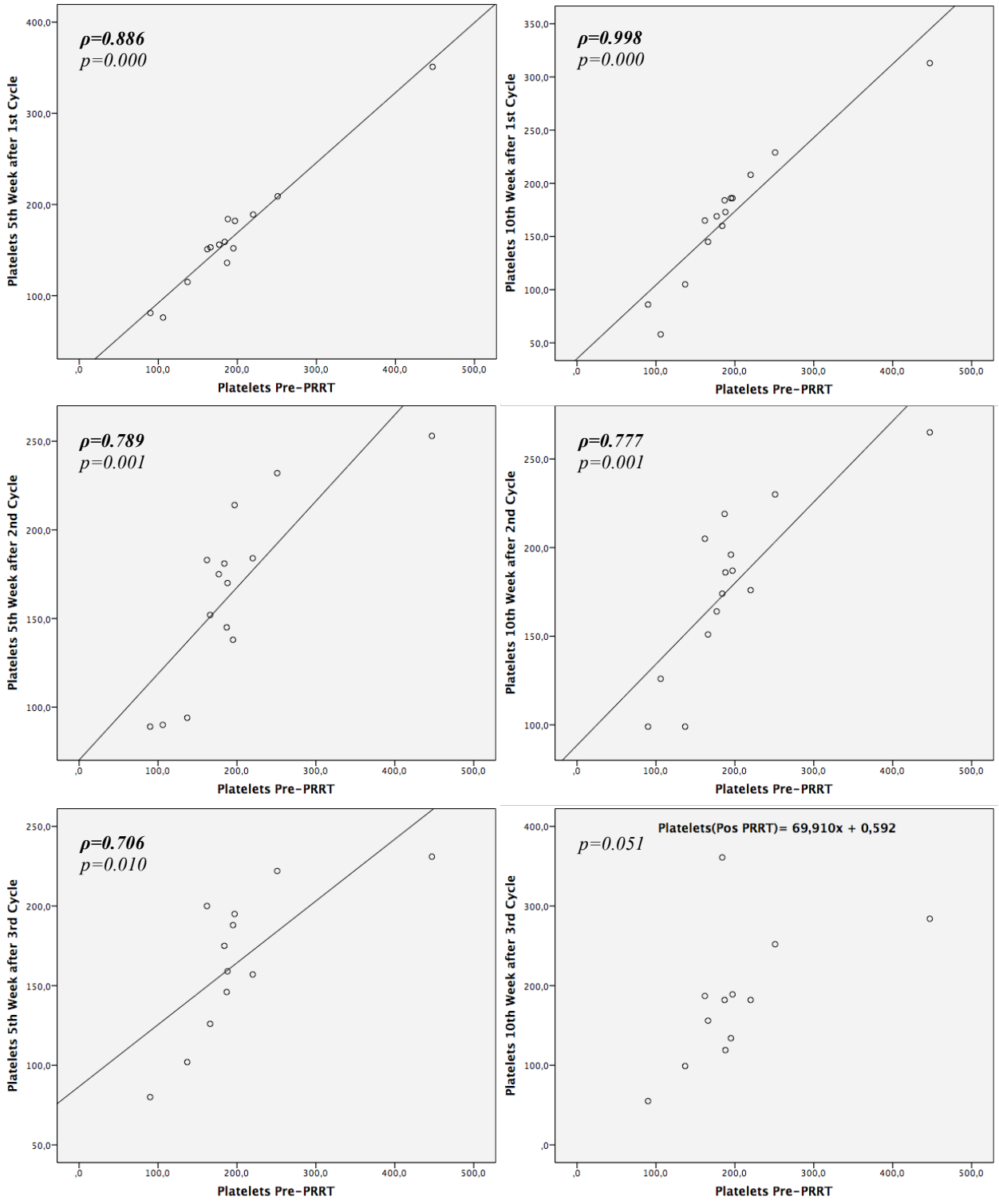


Figure 23: Correlation between Platelets values- - A positive very strong correlation was found between the variable *Platelets Pre-PRRT* and the variables *Platelets 5th Week after 1st Cycle* (ρ=0.886, p=0.000), *Platelets 10th Week after 1st Cycle* (ρ=0.998, p=0.000). A positive strong correlation was found between the variable *Platelets Pre-PRRT* and the variables *Platelets 5th Week after 2nd Cycle* (ρ=0.789, p=0.001), *Platelets 10th Week after 2nd Cycle* (ρ=0.777, p=0.001) and *Platelets 5th Week after 3rd Cycle* (ρ=0.706, p=0.010). No statistically meaningful correlation was found between the variable *Platelets Pre-PRRT* and the variable *Platelets 10th Week after 3rd Cycle* (ρ=0.574, p=0.051).

Follow-up profile

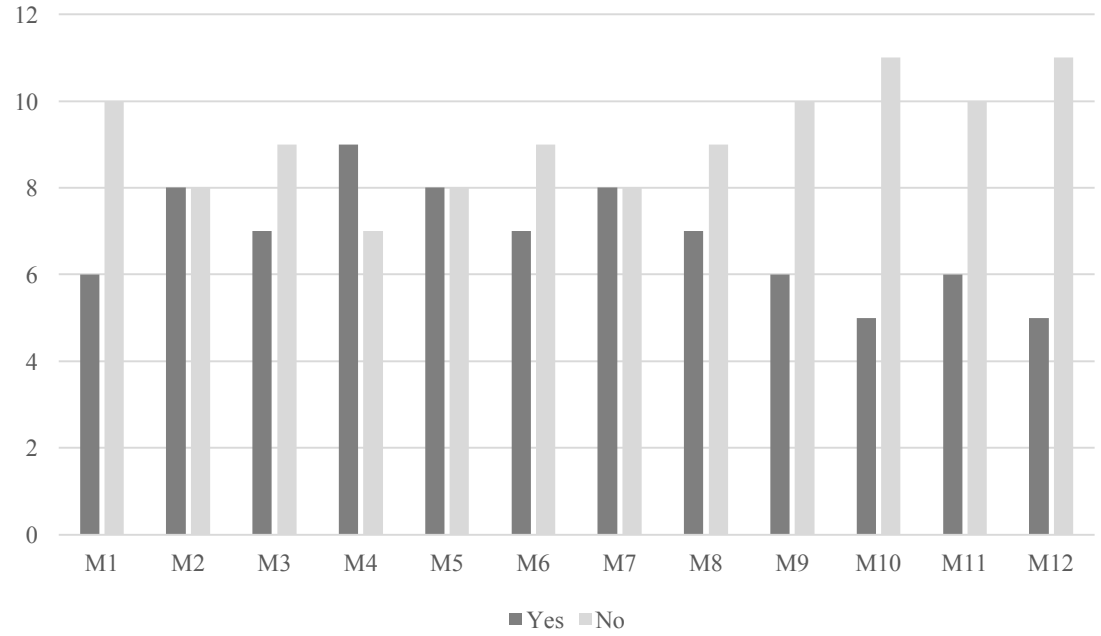


Figure 24: Follow-up effectiveness – Analysis of the existence of a laboratory work-up during the months following the last cycle of PRRT.

2D Dosimetry

For each one of the three cycles, radioactivity counts (Cts) and inferred ^{177}Lu-DOTA-TATE uptake activity were assessed for all 57 selected target lesions (33 liver and 22 bone metastases) over time (4 hours, 24 hours and 7th day) by applying the proposed methodology to both anterior and posterior ptWBS (Figure 1). A decrease was found for the total number of counts and inferred ^{177}Lu-DOTA-TATE activity measured between the first and the last ptWBS for liver and bone metastases (Table 9.1 – 9.3). Comparison between the various time points was also performed (Table 10).

Table 9.1: Median counts (Cts) and inferred median ^{177}Lu-DOTA-TATE uptake comparison between first and third cycle 4H ptWBS.

		Metastatic Site	Lesion Counts (Median)	^{177}Lu-DOTA-TATE (μCi) (Median)		
4 Hours	1st Cycle ptWBS	Liver	15534.3	169.6		
		Bone	5400.2	15.3		
	3rd Cycle ptWBS	Liver	9845.9	69.0		
		Bone	3361.9	24.0	*p* value	
	1st /3rd (%)	Liver	**-36.6%**	**-59.3%**	***p=0.037***	***p=0.055***
		Bone	**-38.4%**	**+57.6%**	***p=0.046***	***p=0.665***

Table 9.2: Median counts (Cts) and inferred median ^{177}Lu-DOTA-TATE uptake comparison between first and third cycle 24H ptWBS.

		Metastatic Site	Lesion Counts (Median)	^{177}Lu-DOTA-TATE (μCi) (Median)		
24 Hours	1st Cycle ptWBS	Liver	13034.0	192.2		
		Bone	1868.1	79.0		
	3rd Cycle ptWBS	Liver	9231.8	40.0		
		Bone	1346.3	10.5	*p* value	
	1st /3rd (% of decrease)	Liver	**29.2%**	**79.2%**	***p=0.007***	***p=0.000***
		Bone	**27.9%**	**86.7%**	***p=0.575***	***p=0.004***

Table 9.3: Median counts (Cts) and inferred median ^{177}Lu-DOTA-TATE uptake comparison between first and third cycle 7th Day ptWBS.

		Metastatic Site	Lesion Counts (Median)	^{177}Lu-DOTA-TATE (μCi) (Median)		
7th Day	1st Cycle ptWBS	Liver	5461.1	64.2		
		Bone	828.0	6.4		
	3rd Cycle ptWBS	Liver	1476.6	35.0		
		Bone	557.3	4.1	*p* value	
	1st /3rd (% of decrease)	Liver	**73.0%**	**45.4%**	***p=0.001***	***p=0.000***
		Bone	**32.7%**	**35.7%**	***p=0,082***	***p=0.301***

Using median values, the variation of counts and ^{177}Lu-DOTA-TATE uptake was assessed during the entire treatment (Figures 25 - 26). A constant decrease on the number of counts and uptake was observed with a similar variation profile both for liver and bone metastases. Conversely, variation along treatment for the ratio $\frac{\text{Counts or } 177\text{Lu-DOTA-TATE uptake}}{\text{Area of metastasis}}$ was performed and presented a similar behaviour to the absolute parameters referred previously (Figures 25 - 26).

Table 10: Median values for Radioactivity counts and ^{177}Lu-DOTA-TATE uptake.

			Counts	^{177}Lu-DOTATATE Activity (μCi)	^{177}Lu-DOTATATE Activity /Area (μCi)	Counts/Area
1st Cycle	4 Hours	**Liver**	15534.3	169.6	1.2	65.8
		Bone	2574.3	15.2	0.2	27.8
	24 Hours	**Liver**	13034.0	192.2	0.7	82.8
		Bone	1868.0	79.0	0.7	22.6
	7th Day	**Liver**	5461.1	64.2	0.3	32.2
		Bone	387.1	6.4	0.1	7.0
2nd Cycle	4 Hours	**Liver**	14851.5	66.6	0.3	61.0
		Bone	2717.3	8.91	0.1	31.2
	24 Hours	**Liver**	9740.3	87.8	0.3	42.2
		Bone	1708.1	5.8	0.1	17.7
	7th Day	**Liver**	4041.7	36.3	0.2	15.4
		Bone	321.6	3.2	0.1	4.5
3rd Cycle	4 Hours	**Liver**	9846.0	69.0	0.3	44.2
		Bone	1585.9	24.0	0.2	15.1
	24 Hours	**Liver**	9231.8	40.0	0.2	34.2
		Bone	1346.3	10.5	0.1	13.3
	7th Day	**Liver**	1476.6	35.0	0.1	9.3
		Bone	428.5	4.1	0.1	3.6

Table 11: Intra and inter-cycle variation of radioactivity cycles and ^{177}Lu-DOTA-TATE uptake.

			1st Cycle				2nd Cycle						3rd Cycle					
			24H		7D		4H		24H		7D		4H		24H		7D	
1st Cycle			**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**
4 Hours	**Liver**	**Cts**	*p*=0.068 **-16%**		*p*=0.000 **-64%**		*p*=0.082 **-4%**						*p*=0.037 **-36%**					
		µCi	*p*=0.367 **+13%**		*p*=0.000 **-62%**		*p*=0.001 **-60%**						*p*=0,055 **-59%**					
	Bone	**Cts**		*p*=0.025 **-27%**		*p*=0.000 **-85%**		*p*=0.100 **+5%**						*p=0.0460* **-36%**				
		µCi		*p*=0.011 **+418%**		*p*=0.001 **-58%**		*p*=0.079 **-41%**						*p=0.665* **+57%**				
24 Hours	**Liver**	**Cts**			*p*=0.000 **-58%**				*p*=0.040 **-24%**						*p*=0.007 **-29%**			
		µCi			*p*=0.000 **-66%**				*p*=0.000 **-54%**						*p*=0.000 **-79%**			
	Bone	**Cts**				*p*=0.000 **-79%**				*p*=0.305 **-9%**						*p*=0.575 **-27%**		
		µCi				*p*=0.001 **-91%**				*p*=0.004 **-93%**						*p*=0.004 **-86%**		
7th Day	**Liver**	**Cts**					*p*=0.000 **+171%**				*p*=0.201 **-25%**						*p*=0.001 **-72%**	
		µCi					*p*=0.130 **+3%**				*p*=0.304 **-43%**						*p*=0.000 **-45%**	
	Bone	**Cts**						*p*=0.000 **+601%**				*p*=0.927 **-16%**						*p*=0.082 **-32%**
		µCi						*p*=0.003 **+39%**				*p*=0.352 **-49%**						*p*=0.301 **-35%**

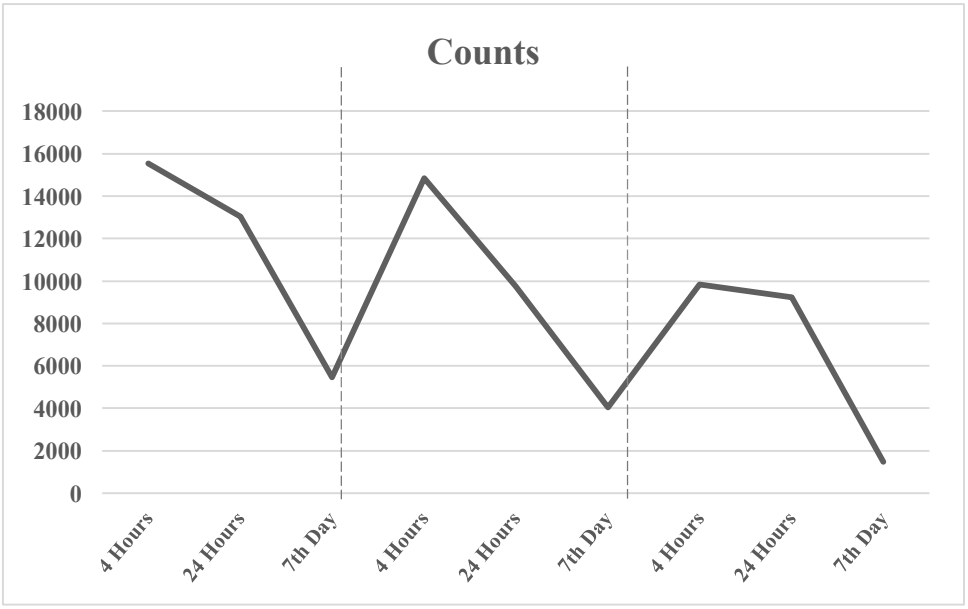
Table 11: Intra and inter-cycle variation of radioactivity cycles and ^{177}Lu-DOTA-TATE uptake.

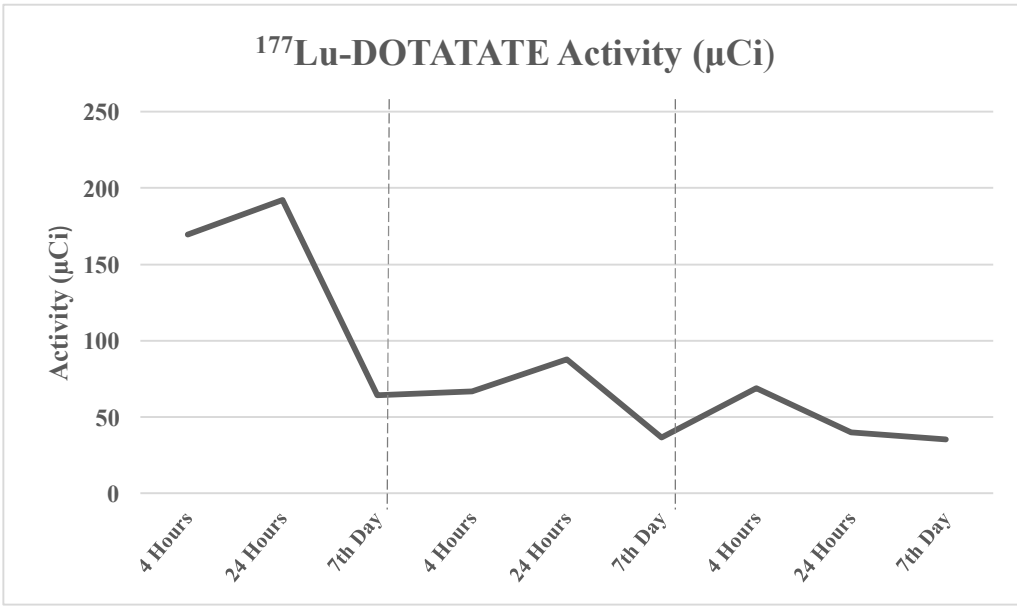
										2nd Cycle						**3rd Cycle**		
						4H		**24H**		**7D**				**4H**		**24H**		**7D**
				Liver	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**	**Liver**	**Bone**
2nd Cycle	4 Hours	**Liver**	**Cts**			*p*=0.174 **-34%**		*p*=0.000 **-72%**		*p*=0.137 **-33%**							
			µCi			*p*=0.970 **+31%**		*p*=0.568 **-45%**		*p*=0.209 **+3%**							
		Bone	**Cts**				*p*=0.033 **-37%**		*p*=0.000 **-88%**		*p*=0.001 **-41%**						
			µCi				*p*=0.520 **-35%**		*p*=0.023 **-63%**		*p*=0.017 **+169%**						
	24 Hours	**Liver**	**Cts**					*p*=0.000 **-58%**				*p*=0.019 **-5%**					
			µCi					*p*=0.048 **-58%**				*p*=0.133 **+54%**					
		Bone	**Cts**						*p*=0.000 **-81%**				*p*=0.006 **-21%**				
			µCi						*p*=0.002 **-43%**				*p*=0.687 **+82%**				
	7th Day	**Liver**	**Cts**							*p*=0.000 **+143%**				*p*=0.000 **-63%**			
			µCi							*p*=0.159 **+89%**				*p*=0.000 **-3%**			
		Bone	**Cts**								*p*=0.000 **+393%**						*p*=0.095 **-33%**
			µCi								*p*=0.008 **+639%**						*p*=0.159 **-26%**

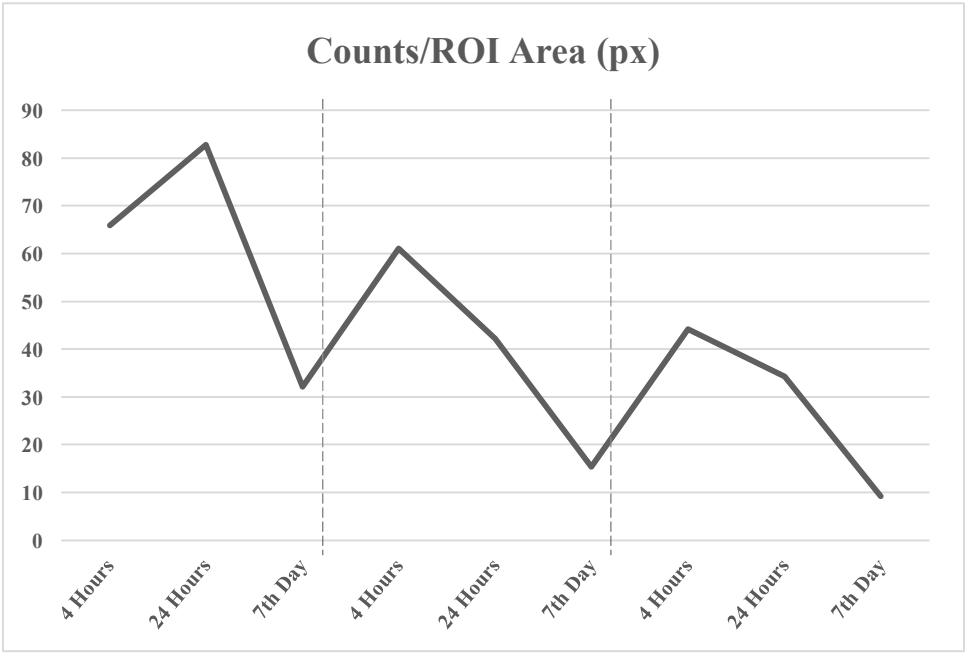
Table 11: Intra and inter-cycle variation of radioactivity cycles and ^{177}Lu-DOTA-TATE uptake.

				3rd Cycle					
				4H		24H		7D	
				Liver	Bone	Liver	Bone	Liver	Bone
3rd Cycle	4 Hours	Liver	Cts			*p=0.554* **-6%**		*p=0.000* **-85%**	
			µCi			*p=0.038* **-41%**		*p=0.000* **-49%**	
		Bone	Cts				*p=0.072* **-15%**		*p=0.000* **-72%**
			µCi				*p=0.003* **-56%**		*p=0.000* **+45%**
	24 Hours	Liver	Cts					*p=0.000* **-84%**	
			µCi					*p=0.000* **-12%**	
		Bone	Cts						*p=0.001* **-68%**
			µCi						*p=0.001* **-69%**
	7th Day	Liver	Cts						
			µCi						
		Bone	Cts						
			µCi						

Figure 25: Liver metastases – Radioactivity counts and ^{177}Lu-DOTA-TATE uptake profile.







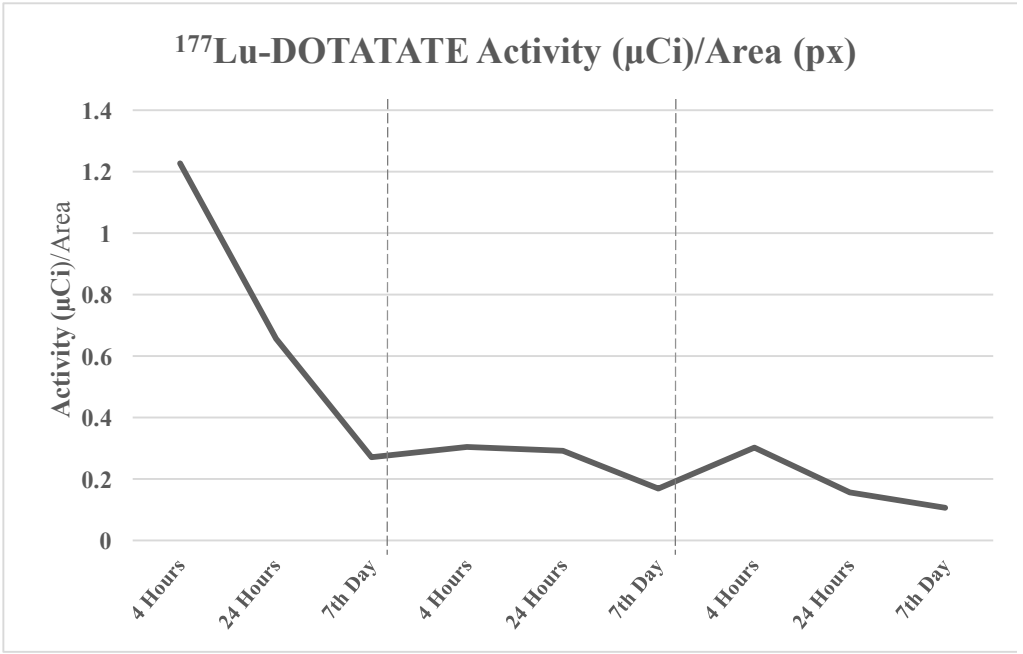
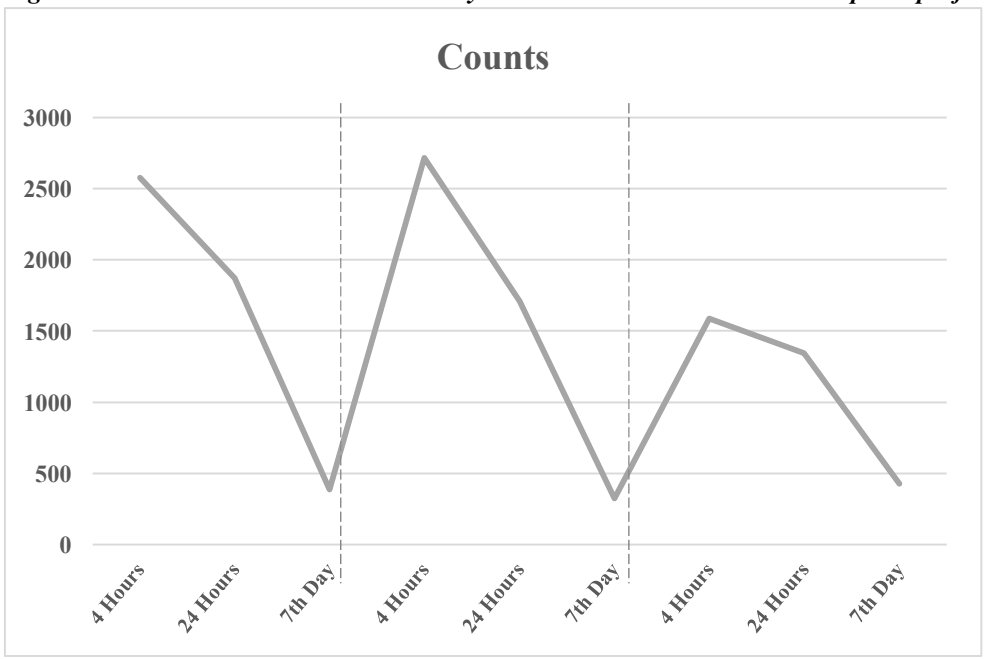
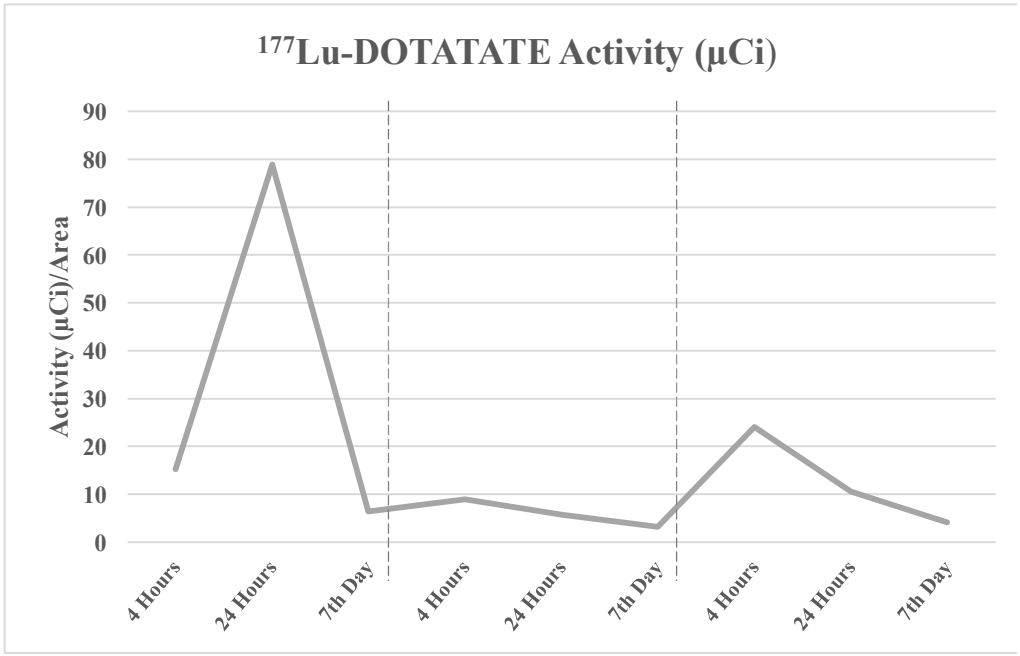
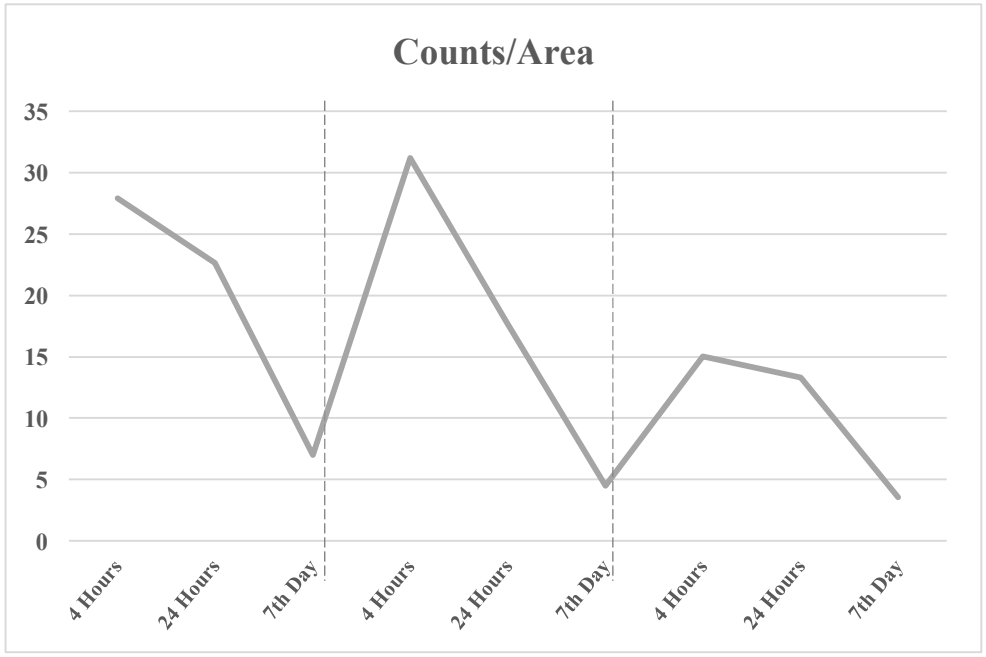
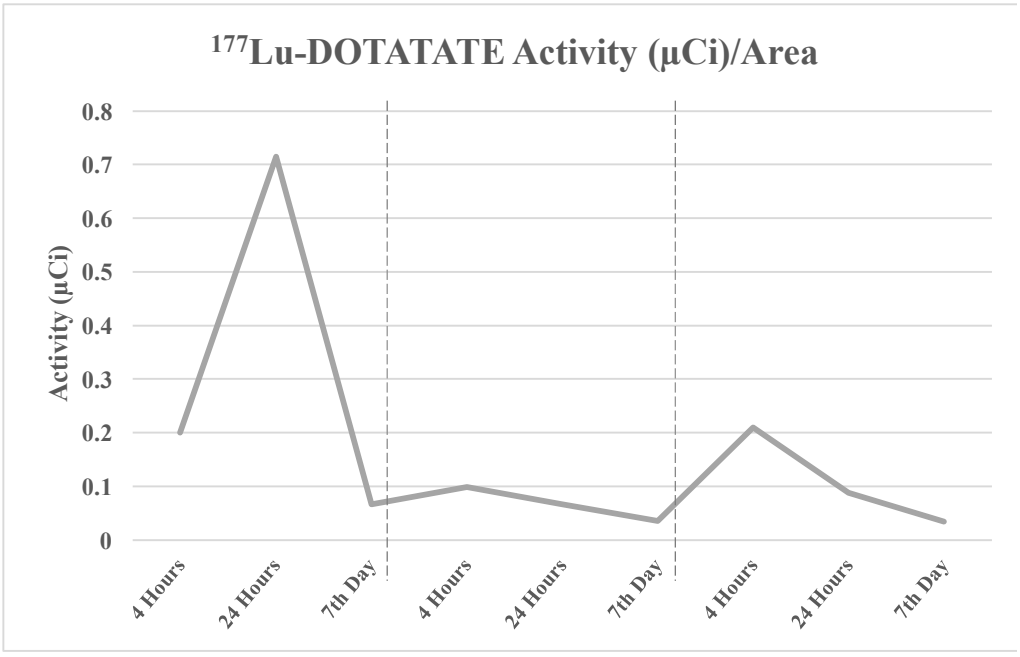


Figure 26: Bone metastases – Radioactivity counts and ^{177}Lu-DOTA-TATE uptake profile.









Treatment outcomes

After 3 cycles of PRRT with ^{177}Lu-DOTA-TATE, 9 (56.25%) patients achieved partial response (PR), 1 (6.25%) showed stable disease (SD), 4 (25%) remained with progressive disease (PD) and 2 (12.5%) patients died from complications not related to treatment.

Discussion

Personalized medicine relies on bespoken therapeutic schemes and targeted therapies to achieve the best ratio between therapeutic effectiveness and toxicity[16]. During the last twenty years, PRRT has been used with both efficacy and minimal toxicity[16,17].

However, since the introduction of ^{90}Y-octreotide in 1996 and the emerging of ^{177}Lu-octreotate in 2000, PRRT clinical protocols are locally defined and based on clinical biases of each institution. Therefore, standard-of-care PRRT remains as a "promising" treatment modality using orphan drugs and a wide range of protocols that vary in selection criteria for treatment[18]. Despite 2012 ESMO clinical practice guidelines for bronchial/thymic[19] and GEP-NETs[20] try to establish a standardized approach for NETs, PRRT was only vaguely referred and its position on therapeutic schemes was not clearly defined due to the lack of robust validating data.

NETTER-1 trial recently published the results from phase III studies suggesting a potential survival benefit after treatment with ^{177}Lu-DOTA-TATE and a favourable safety profile. Analysis of the safety profile associated to ^{177}Lu-DOTA-TATE treatment imply the assessment of dose-limiting organs such as kidneys and bone marrow but also liver function before, during and after treatment[17,21].

The results of our study found no statistically significant difference between the assessments performed before PRRT and after 3 cycles of therapy which stays in line with all the major results published.

Bone Marrow toxicity

Knowing that there is no major toxicity described at the end of 3 cycles of treatment, inter–cycle assessments were performed to evaluate the behavioural pattern of the same parameters through the course of treatment. Looking to values dispersion at five and ten weeks after each cycle (Figures 2 - 5) we found that variation was similar during the

length of treatment. Major differences were stated for values of red blood cells and white blood cells. Statistical significant difference was found when comparing the values of white blood cells before PRRT and 5 weeks after the second cycle (*p=0.035*) and for red blood cells total count between the values of red blood cells total count before and after 3 cycles (*p=0.023*).

Applying the Common Terminology Criteria for Adverse Events (CTCAE v4.0, 2010), no signs or symptoms of severe anemia were referred after 3 cycles of ^{177}Lu-DOTA-TATE. Three patients (18.5%) presented Grade I anemia - values of haemoglobin between the lower limit of normal (LLN) and 10.0 g/dL - ten weeks after treatment. Inter-cycle evaluation revealed that 4 patients (25%) presented Grade I anemia five weeks after each cycle with values ranging from 12.0 g/dL to 10.0 g/dL. However, the same number of patients presented values lower than the LLN in the evaluation performed pre-PRRT. These findings are in line with literature that describes minimal acute myelotoxicity as the most common side effect occurring after administration (4 – 6 weeks) of ^{177}Lu-DOTA-TATE [16,17,22,23]. During this study follow-up period (12 months) no myelodysplastic syndrome (MSD) and acute leukaemia cases– therapy related myeloid neoplasms - were reported [24].

Hepatotoxicity

Despite the liver being a frequent site of metastatic spread from NETs, hepatotoxicity is commonly underestimated during toxicity studies and rarely has been reported. Applying the Common Terminology Criteria for Adverse Events (CTCAE v4.0, 2010) to our cohort, 2 (12.5%) patients showed an increase in alanine transaminase (ALT) values ten weeks after treatment (grade I, ALT= 40 – 103 U/L) with 1 (6.25%) patient showing grade 2 toxicity (ALT= 106 U/L). Nevertheless, considering the evolution of ALT values along the length of treatment we found pre-PRRT grade I toxicity (40 < ALT < 80) in 4 (25%) patients and at the 5th and 10th week after first cycle 5 (31.25%) patients revealed grade I toxicity. Until the end of treatment, 4 (25%) patients consistently presented with grade I toxicity and increasing values of ALT with 1 (6.25%) patient normalising ten weeks after the third cycle. Analysing the values of aspartate transaminase (AST), 6 (37.5%) patients presented grade I toxicity at the pre-PRRT (34 – 62 U/L) and at the 5th week after first cycle (AST =34 – 60 U/L) evaluations. Throughout the rest of treatment, 5 (31.25%) patients consistently presented grade I toxicity with AST values increasing

until the evaluations performed after third cycle. At the 5th and 10th weeks after third cycle, 5 (31.25%) patients showed grade I toxicity (AST =39 – 53 U/L) and 1 (6.25%) patient grade II toxicity (AST= 152 U/L). Regarding alkaline phosphatase (ALP) values, 2 (12.5%) patients showed grade I toxicity at the assessment performed pre-PRRT (ALP =157 – 312 U/L) which was maintained until the evaluations performed after the third cycle. At the two assessments performed after the third cycle, 3 (18.75%) patients presented with grade I toxicity (ALP =157 – 238 U/L) and 1 (6.25%) patient with grade 3 toxicity ($ALP^{5th\ week}$= 1078; $ALP^{10th\ week}$=1213). Values of gamma-glutamyltransferase (GGT) were also assessed with 5 (31.25%) patients presenting grade I toxicity (40 – 94 U/L) and 6 (37.5%) patients grade 3 toxicity (223 – 564 U/L) at the pre-PRRT assessment. After the first cycle, 4 (25%) patients revealed grade I toxicity (GGT =49 – 89 U/L) and 7 (43.75%) patients grade 3 toxicity (GGT =198 – 526 U/L) at both 5th and 10th weeks controls. At assessments done 5 and 10 weeks after second cycle, 3 (18.75%) patients showed grade I toxicity (GGT =55 – 79 U/L), 1 (6.25%) patient presented grade II toxicity ($GGT^{5th\ week}$= 142; $GGT^{10th\ week}$= 101) and 7 (43.75%) patients grade 3 toxicity (GGT =253 – 755 U/L). Analysing the evolution after the third cycle, 3 (18.75%) patients had grade I toxicity (GGT =44 – 74 U/L), 1 (6.25%) patient grade II toxicity ($GGT^{5th\ week}$= 102) and 1 (6.25%) patient had grade IV toxicity ($GGT^{5th\ week}$= 823 U/L) at the 5th week assessment. During the control performed 10 weeks after, 3 (18.75%) patients showed grade I toxicity (GGT =61 – 83 U/L) and 6 (37.5%) patients grade III toxicity (247 – 425 U/L).

Despite hepatotoxicity not being a preeminent evidence on our study, the transient elevations of ALT, AST, ALP values reflect the common laboratory abnormalities described in literature such as hepatocellular injury and mixed liver injury[25].

Nephrotoxicity

Serum creatinine was assessed to determine the extent of nephrotoxicity associated to PRRT with ^{177}Lu-DOTA-TATE and the efficacy of Aminoplasmal Hepa® for renal protection.

Before PRRT was started, only 3 (18.75%) patients had serum creatinine values that could be fitted into grade I toxicity. During the subsequent assessments, this distribution remained stable with only 2 (12.5%) patients presenting grade I toxicity from the assessment performed at the 5th week after second cycle until the end of treatment.

These findings suggest that PRRT with ^{177}Lu-DOTA-TATE has minimal nephrotoxicity when correct administration of amino acids is performed before treatment[26].

Pre-treatment laboratorial profile as a toxicity predictor

Despite not being associated to significant toxicity, the enrolment of patients into a successful PRRT treatment protocol is mainly reliant on the capacity of going through treatment without limitative toxicity. The criteria used to select patients constitutes a major factor influencing the outcomes and number of cycles of treatment. Studies have been done trying to understand the connection between common risk factors and final toxicity associated to ^{177}Lu-DOTA-TATE[26].

To evaluate if pre-treatment assessment could be used as a predictor of post-treatment toxicity we correlated the initial values with values obtained during inter-cycle evaluations and after 3 cycles of therapy. A very strong to strong positive correlation was found for every hepatic parameter assessed (Figures 13 - 17; $0,6< \rho <1$) with exception to the correlation between alkaline phosphatase pre ^{177}Lu-DOTA-TATE and the value obtained post-treatment ($\rho=0.55;\ p=0.005$). Analysing the same correlation for serum creatinine values, we found that the initial value pre-PRRT presents a very strong to strong positive correlation with every other assessment ($0.6< \rho <1$) with exception to the evaluation performed at the 5th week after 2nd cycle ($\rho=0.376,\ p=0.185$).

Nonetheless, parameters used to access myelotoxicity showed a different correlational behaviour during the length of treatment. On one hand, haematocrit, haemoglobin and red blood cells total count showed a strong positive correlation ($0.6< \rho <0.8$) between pre-PRRT values and values acquired five and ten weeks after the 1st cycle. Also, a moderate positive correlation was found between the values of red blood cells total count pre-PRRT and post-therapeutic values. On the other hand, white blood cells presented a very strong to strong positive correlation for every analysis ($0.6< \rho <1$) with exception for the correlation between pre-PRRT values and values assessed ten weeks after 3rd cycle ($\rho=0.329,\ p=0.29$).

Although our results seem to provide some support for the use of pre-laboratorial assessment as a predictor of toxicity - strong positive correlations found for parameters such as AST, ALT, GGT, serum creatinine, red blood cells – there is a lack of homogeneous evolutional behaviour through treatment and of strong randomized studies to support this evidence[26,17].

Follow-up after treatment

Evaluating the follow-up performed during 1 year after the last cycle of PRRT we noticed that in the first 6 months almost half of the patients did not have a monthly evaluation with this percentage increasing over time (Figure 24). For intermediate and long-term follow-up, the joint practical guidance elaborated by the IAEA, EANM and SNMMI states that a complete blood cell count (with mean corpuscular volume), liver and renal function tests should be performed every 8-12 weeks[13].

2D Dosimetry

Most standard-of-care PRRT protocols rely on a "one-size-fits-all" approach with fixed doses of radiopharmaceutical administered irrespectively of the type of NET or patient specificities. This is mainly related to the lack of an adequate, validated and easy to apply method of performing intra and inter cycle dosimetry assessments and to the complex models available[27].

The Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine proposed a schema for assessment of absorbed dose which should establish the basis for dosimetry quantification[28]. The complexity associated to the model made it hard for it to be widely accepted on routine clinical practice but lead to the establishment of more realistic models by the Radiation Dose Assessment Resource (RADAR) Task Group. Anatomic phantom models using non-uniform rational b-spline modelling were used to create reference pregnant women (3 stages of gestation), new-borns, 1 year old, 5 years old, 10 years, 15 years and both genders adults for the purposes of internal radiation dosimetry[29]. These models, using complex Monte Carlo simulations, were integrated on the development of commercial available software for internal dosimetry such as OLINDA/EXM[30].

However, the difficulty to accurately replicate some key parameters related to radionuclides such as variable individual organ volumes, biodistribution, uptake, homogeneous radioactivity distribution and specific organ modelling (e.g bone marrow) brings some controversy to dosimetry[31]. Adding to this the fact of being an imprecise time consuming process with little supporting evidence for better clinical outcomes using dosimetry evaluations, some claims have been raised that probably it should not play a central role on PRRT planning.[18] Nonetheless, some studies have demonstrated a relation between absorbed dose and response.[32]

Bearing in mind that clinical feasible precise dosimetry is a hard goal to achieve, we applied a clinical practical model to estimate the metastatic uptake profile of ^{177}Lu-DOTA-TATE throughout treatment and estimate the uptake difference between the first and last administration. A similar uptake profile for liver and bone metastases was found with a progressive decrease from the first to third cycle (Figures 25-26). An overall reduction on ^{177}Lu-DOTA-TATE uptake for liver and bone metastasis was estimated and corroborated by a corresponding overall reduction on the total number of counts (Tables 9.1 – 9.3). This reduction was supported by the treatment outcomes assessed with 9 (56.25%) patients achieving partial response (PR) and 1 (6.25%) showing stable disease (SD) after 3 cycles of PRRT.

If PRRT outcomes are mostly related to absorbed dose/biological effective dose and its variation during treatment, the heterogenic outcomes associated to NETs may need further explanation. Specific characteristics of tumor and individual patient's features may play an important role[18].

Conclusion

We demonstrate that Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTA-TATE has a tolerable safety profile, with minimum acute myelotoxicity after each cycle and minimum nephrotoxicity after the entire treatment. Our correlation studies reveal that pre-treatment laboratorial evaluation constitutes a reliable starting point for patients' selection and extrapolation of toxicity outcomes. Moreover, we propose a feasible approach to dosimetry that established an intra and inter-cycle variation profile for ^{177}Lu-DOTA-TATE uptake and showed that a significant decrease from the first to the last cycle of treatment occurs. This constitutes a simple proposal aiming to help clinicians plan PRRT treatment based on pre-treatment laboratory work-up and ^{177}Lu-DOTA-TATE uptake profile.

Hence, a paradigm change from "one-fits-all" to a personalized approach is needed. From the biological point of view, this could be achieved by a deep study of NETs genetic profile and cell death pathways triggered. From the clinical perspective, a European integrated strategy with establishment of specialized centres for PRRT, the elaboration of a platform to gather multicentric data and the establishment of specific guidelines should help improve the *state of the art* on Neuroendocrine Tumours and Peptide Receptor Radionuclide Therapy.

Bibliography

1. Barakat MT, Meeran K, Bloom SR. Neuroendocrine tumours. *Endocr Relat Cancer*. 2004;11:1–18.

2. Meeker A, Heaphy C. Gastroenteropancreatic endocrine tumors. *Molecular and Cellular Endocrinology*. 2014;386(1–2):101–120.

3. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: A population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121(4):589–597.

4. Elettra M, Maria R, Noemi C, Gabriele C, Francesco P, Gianfranco DF. Digestive Neuroendocrine Neoplasms: a 2016 overview. *Digestive and Liver Disease*. 2016;48(8):829–835.

5. Ilett E, Langer S, Olsen I, Federspiel B, Kjær A, Knigge U. Neuroendocrine Carcinomas of the Gastroenteropancreatic System: A Comprehensive Review. *Diagnostics*. 2015;5(2):119–176.

6. Tamburrino D, Spoletini G, Partelli S, Muffatti F, Adamenko O, Crippa S, Falconi M. Surgical management of neuroendocrine tumors. *Best practice & research. Clinical endocrinology & metabolism*. 2016;30(1):93–102.

7. Oberg KE. The Management of Neuroendocrine Tumours : Current and Future Medical Therapy Options Statement of Search Strategies Used and Sources of Information Classi fi cation. 2012;24:282–293.

8. Kulaksiz H, Eissele R, Schulz S, Cetin Y, Arnold R. Identification of somatostatin receptor subtypes 1, 2A, 3, and 5 in neuroendocrine tumours with subtype specific antibodies. 2002:52–61.

9. Rinke A, Krug S. Neuroendocrine tumours - Medical therapy: Biological. *Best Practice and Research: Clinical Endocrinology and Metabolism*. 2016;30(1):79–91.

10. Körner M. Specific biology of neuroendocrine tumors: Peptide receptors as molecular targets. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2016;30(1):19–31.

11. Öberg K. Molecular Imaging Radiotherapy: Theranostics for Personalized Patient Management of Neuroendocrine Tumors (NETs). *Theranostics*. 2012;2(5):448–458.

12. Brabander T, Teunissen JJM, Van Eijck CHJ, Franssen GJH, Feelders RA, de Herder WW, Kwekkeboom DJ. Peptide receptor radionuclide therapy of neuroendocrine tumours. *Best practice & research. Clinical endocrinology & metabolism*. 2016;30(1):103–14.

13. Zaknun JJ, Bodei L, Mueller-Brand J, Pavel ME, Baum RP, Hörsch D, O'Dorisio MS, O'Dorisiol TM, Howe JR, Cremonesi M, Kwekkeboom DJ. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *European Journal of Nuclear Medicine and Molecular Imaging*. 2013;40(5):800–816.

14. Paganelli G, Sansovini M, Ambrosetti A, Severi S, Monti M, Scarpi E, Donati C, Ianniello A, Matteucci F, Amadori D. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. *European Journal of Nuclear Medicine and Molecular Imaging*. 2014:1–7.

15. Hardiansyah D, Maass C, Attarwala AA, Müller B, Kletting P, Mottaghy FM, Glatting G. The role of patient-based treatment planning in peptide receptor radionuclide therapy. *European Journal of Nuclear Medicine and Molecular Imaging*. 2016;43(5):871–880.

16. Horsch D, Ezziddin S, Haug A, Gratz KF, Dunkelmann S, Miederer M, Schreckenberger M, Krause BJ, Bengel FM, Bartenstein P, Biersack HJ, Pepperl G, Baum RP. Effectiveness and side-effects of peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow-up. *European Journal of Cancer*. 2016;58:41–51.

17. Bergsma H, Konijnenberg MW, Kam BLR, Teunissen JJM, Kooij PP, de Herder WW, Franssen GJH, van Eijck CHJ, Krenning EP, Kwekkeboom DJ. Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course. *European Journal of Nuclear Medicine and Molecular Imaging*. 2016;43(3):453–463.

18. Bodei L, Kidd M, Baum RP, Modlin IM. PRRT: Defining the Paradigm Shift to Achieve Standardization and Individualization. *J Nucl Med*. 2014;55:1753–1756.

19. Hellman P, Ferolla P, Papotti M. clinical practice guidelines Neuroendocrine bronchial and thymic tumors : ESMO Clinical Practice Guidelines for diagnosis , treatment clinical practice guidelines. 2012;23(Supplement 7).

20. Öberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2012;23(SUPPL. 7).

21. Kwekkeboom DJ. GEPNETs update: Radionuclide therapy in neuroendocrine tumors. *European journal of endocrinology / European Federation of Endocrine Societies*. 2015;172(1):R1–R8.

22. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, Baum RP, Mittra E, Hobday T, Hendifar A. Significantly Improves Progression-Free Results of the Phase III NETTER-1 Trial. 2015;(September):1–28.

23. Sabet A, Ezziddin K, Pape U-F, Ahmadzadehfar H, Mayer K, Pöppel T, Guhlke S, Biersack H-J, Ezziddin S. Long-Term Hematotoxicity After Peptide Receptor Radionuclide Therapy with 177Lu-Octreotate. *Journal of Nuclear Medicine*. 2013;54(216 mCi):1857–1861.

24. Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. *Best Practice and Research: Clinical Haematology*. 2013;26(4):309–317.

25. Yang Y, Soulen MC, Pryma DA, Bennett B, Wild D, Nicolas G, Teitelbaum UR, Metz DC. Peptide Receptor Radionuclide Therapy – Induced Hepatotoxicity in Patients With Metastatic Neuroendocrine Tumors. 2015;40(11):845–850.

26. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, Lepensky C, Kwekkeboom DJ, Baum RP, Krenning EP, Modlin IM. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *European journal of nuclear medicine and molecular imaging*. 2015;42(1):5–19.

27. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjogreen Gleisner K. MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative 177Lu SPECT applied for Dosimetry of Radiopharmaceutical Therapy. *Journal of Nuclear Medicine*. 2015;9881(26):151–162.

28. Bolch WE, Eckerman KF, Sgouros G, Thomas SR, Mird SNM, Wesley C, Brill AB, Fisher DR, Roger W, Meredith R, Sgouros G, Thomas SR, Wessels BW. MIRD Pamphlet No . 21 : A Generalized Schema for Radiopharmaceutical Dosimetry — Standardization of Nomenclature. 1976;(21):477–485.

29. Stabin MG, Xu XG, Emmons MA, Segars WP, Shi C, Fernald MJ. RADAR Reference Adult, Pediatric, and Pregnant Female Phantom Series for Internal and External Dosimetry. *J Nucl Med*. 2012;53(3):1807–1813.

30. Stabin MG, Sparks RB, Crowe E. OLINDA / EXM : The Second-Generation Personal Computer Software for Internal Dose Assessment in Nuclear Medicine. 2005:1023–1028.

31. Cremonesi M, Ferrari M, Di Dia A, Botta F, De Cicco C, Bodei L, Paganelli G. Recent issues on dosimetry and radiobiology for peptide receptor radionuclide therapy. *Quarterly Journal of Nuclear Medicine and Molecular Imaging*. 2011;55(2):155–167.

32. Lu-dotatate TU, Ilan E, Sandstr M, Wassberg C, Sundin A, Garske U, Eriksson B, Granberg D, Lubberink M. Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide. :177–183.