



B-mode and Doppler ultrasound of bitches' kidneys with mammary neoplasia submitted to adjuvant chemotherapy¹

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ABSTRACT- Pinto da Silva L.O., Santos M.C.S., Pina B.F., Souza G.N. & Ferreira M.L.G. 2023. **Mode-B and Doppler ultrasound of bitches' kidneys with mammary neoplasia submitted to adjuvant chemotherapy.** *Pesquisa Veterinária Brasileira* 43:e07212, 2023. Postgraduate Program in Animal Clinic and Reproduction, Faculdade de Veterinária, Universidade Federal Fluminense, Av. Almirante Ary Parreiras 507, Icaraí, Niterói, RJ 24220-000, Brazil. E-mail: ligiaoliveira@id.uff.br

Mammary neoplasia represents the most frequently diagnosed type of neoplasia in bitches. Although surgical removal is the procedure of choice for therapeutic management, chemotherapy protocols appear as important allies and adjuvants. Despite the great advances that have occurred in the field of cancer therapy, the systemic repercussions of these drugs still impose important limitations on their use. In this sense, the development of increasingly targeted therapeutic protocols and preventive monitoring of patients represent important strategies to avoid possible complications – among them, Acute Kidney Injury (AKI). Routinely, ultrasound evaluation is used to identify morphological or metastatic variations in abdominal cavity organs. Acting complementary to the B-mode evaluation, Doppler mapping proves to be efficient in recognizing alterations in vascular hemodynamics. Therefore, the objective of the present study was to evaluate the use of B-mode and Doppler ultrasound to identify renal morphological and hemodynamic alterations in bitches with mammary neoplasia submitted to adjuvant chemotherapy protocols that associate gemcitabine with carboplatin. Thirteen bitches were included, without distinction of breed and between seven and 13 years of age. The animals were evaluated ultrasonographically at two different times during three consecutive chemotherapy cycles: before (T0) and one and a half hours after each cycle (T1), for 42 days. No morphological changes were observed in B-mode throughout the chemotherapy protocol. However, the Doppler velocimetry indices demonstrated statistical differences before (T0) and after (T1) the administration of the drugs. It was concluded that Doppler ultrasound could be used as a complementary method for monitoring the renal response of patients exposed to nephrotoxic drugs and potentially causing renal injury.

INDEX TERMS: Ultrasonography, B-mode, Doppler, kidney, dogs, mammary neoplasia, adjuvant chemotherapy, gemcitabine, carboplatin, nephrotoxicity.

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RESUMO.- [Ultrassonografia modo-B e Doppler dos rins de cadelas com neoplasias mamárias submetidas à quimioterapia adjuvante.] As neoplasias mamárias representam o tipo de neoplasma mais frequentemente diagnosticado em fêmeas da espécie canina. Embora a remoção cirúrgica seja o procedimento de eleição para a conduta terapêutica, os protocolos quimioterápicos aparecem como importantes aliados e adjuvantes. Apesar dos grandes avanços ocorridos na área da terapia oncológica, as repercussões sistêmicas destes fármacos ainda impõem importantes limitações ao seu uso. Neste sentido, o desenvolvimento de protocolos

terapêuticos cada vez mais direcionados e o monitoramento preventivo dos pacientes representam estratégias importantes para evitar possíveis complicações - dentre elas, a injúria renal aguda (IRA). Rotineiramente, a avaliação ultrassonográfica é utilizada para identificação de variações morfológicas ou metastáticas em órgãos da cavidade abdominal. Atuando de forma complementar à avaliação em modo-B, o mapeamento Doppler mostra-se eficiente no reconhecimento de alterações na hemodinâmica vascular. Portanto, o objetivo do presente estudo foi avaliar a utilização da ultrassonografia modo-B e Doppler como método para identificação de alterações morfológicas e hemodinâmicas renais em cadelas com neoplasias mamárias submetidas a protocolos quimioterápicos adjuvantes que associam a gencitabina à carboplatina. Foram incluídas 13 fêmeas caninas, sem distinção quanto a raça e com idades entre sete e 13 anos. Os animais foram avaliados ultrassonograficamente em dois momentos distintos durante três ciclos quimioterápicos consecutivos: antes (T0) e uma hora e meia após a realização de cada ciclo (T1), totalizando 42 dias. Não foram observadas alterações morfológicas em modo-B ao longo do protocolo quimioterápico. Entretanto, os índices dopplervelocimétricos demonstraram diferenças estatísticas antes (T0) e após (T1) a administração dos fármacos. Concluiu-se que a ultrassonografia Doppler pode ser utilizada como método complementar para o monitoramento da resposta renal de pacientes expostos a fármacos nefrotóxicos e potencialmente causadores de injúrias renais.

TERMOS DE INDEXAÇÃO: Ultrassonografia, modo-B, Doppler, rins, cão, caninos, neoplasia mamária, quimioterapia adjuvante, gencitabina, carboplatina, nefrotoxicidade.

INTRODUCTION

The significant prevalence of mammary tumors in veterinary medicine demands increasing diagnostic and therapeutic advances. In this regard, both the veterinary medicine consensus (Cassali et al. 2014, 2018, 2020) as well as those from Human Medicine (Goetz et al. 2019, Pashayan et al. 2020) for the diagnosis and treatment of mammary neoplasia agree that the surgical approach is the method of choice in cases of primary mammary lesions. However, considering relevant criteria and indicators of malignancy, adjuvant chemotherapy protocols can be indicated postoperatively to improve prognosis and increase patient survival (Cassali et al. 2014, 2018, Goetz et al. 2019, Vail et al. 2019).

Despite extensive knowledge about the pharmacokinetics of chemotherapeutic drugs, systemic repercussions still impose important limitations on their use (Chu & DeVita Jr. 2019). In this sense, preventive monitoring of patients represents an important strategy to avoid possible complications, among them, acute kidney injury (AKI) – given the extensive involvement of the kidneys in the excretion process of numerous antineoplastic drugs and their metabolites (De Nardi et al. 2016, Chu & DeVita Jr. 2019), including gemcitabine and carboplatin.

According to the classification published in 2016 by the International Renal Interest Society (IRIS), the diagnosis of AKI in small animals is based primarily on variations in serum creatinine and urine output. However, recent studies show that these two markers have low sensitivity in identifying early-stage renal dysfunction (Delanaye et al. 2017, Ronco et al. 2017, 2019).

Doppler ultrasound detects hemodynamic changes that may represent the first signs of disorders in renal functionality. In this sense, intrarenal artery flow analysis has been used in a complementary way to B-mode ultrasound as a predictive method for the early diagnosis of AKI in several clinical conditions causing nephropathies (Barbero et al. 2018, Quaiá et al. 2018, Gasser et al. 2020).

Therefore, the objective of the present study was to evaluate, through B-mode and Doppler ultrasonography, the morphological and hemodynamic alterations caused in the kidneys of bitches with mammary neoplasia submitted to adjuvant chemotherapy protocols that associate gemcitabine with carboplatin.

MATERIALS AND METHODS

Ethical statement. The study was conducted at “Universidade Federal Fluminense” (UFF), Niterói/RJ, Brazil, following the ethical principles of animal experimentation, according to the Ethics Committee on Animal Use (CEUA/UFF) under protocol number 7829290419.

Selection of animals. We selected 13 bitches previously diagnosed with malignant mammary neoplasia without systemic metastases and with an indication for adjuvant chemotherapy by the association protocol of gemcitabine and carboplatin. Before the beginning of the protocol, all animals were submitted to brachial vein puncture and collection of approximately 8 mL of whole blood – making it possible to perform a complete blood count and liver and kidney profile, and only animals clinically able to undergo the chemotherapy protocol were included. The blood count values were obtained using a BC 2800 Vet Mindray electronic counter, and the biochemical dosages were measured by spectrophotometry on a CM250 Wiener Lab.

Adjuvant chemotherapy. Animals with an indication for adjuvant chemotherapy were given three cycles of gemcitabine (200mg/m²/IV) associated with carboplatin (10mg/kg/IV) at regular intervals of 21 days, following the consensus for diagnosis, prognosis and treatment of mammary tumors of dogs (Cassali et al. 2014).

Ultrasonographic evaluation. The ultrasound equipment used for the exams was a General Electric (GE) Logiq V2, with B-mode, color and pulsed Doppler resources, besides two broadband multifrequency electronic transducers – one micro convex and one linear, with frequencies ranging from 3.0MHz to 13MHz. The ultrasound evaluations were performed by a single operator, thus ensuring greater uniformity during data collection.

Before the ultrasound examination, the guardian was instructed to perform an 8-hour food fast for the animal to minimize the formation of ultrasound imaging artifacts from the gastrointestinal tract. Initially, the animal was positioned in dorsal decubitus and manually restrained to have trichotomy of the entire abdominal region and flanks performed, allowing greater amplitude of movement of the transducer and reducing the presence of air in the ultrasound interface. Then the ultrasound transmission gel (Carbogel) used for ultrasound examinations was applied. The animals were positioned in dorsal and lateral decubitus, and the abdominal and paralumbar ultrasound windows were used.

The kidneys were evaluated in B-mode according to the following parameters: dimensions (usual, increased or decreased) according to the normal ultrasonographic parameters established by Barr et al. (1990), contours (regular or irregular), corticomedullary definition (preserved or unpreserved), corticomedullary ratio (preserved or unpreserved), shape (preserved or unpreserved), echogenicity (normoechoic, hyperechoic or hypoechoic) comparing the echogenicity of renal cortex with the splenic and hepatic parenchyma without

echogenicity changes, as described by D'Anjou & Penninck (2015), echotexture (usual or altered, when focal lesions were present), renal pelvis (preserved or altered) and perirenal region (preserved or altered). The color Doppler mode allowed the evaluation of renal perfusion (normal or decreased). The spectral mode allowed the measurement of the resistivity index of the interlobar renal arteries (normal or increased) being indicative of abnormalities values exceeding 0.72, as described by Novellas et al. (2007) and the pulsatility index of the interlobar renal arteries (normal or increased) values above 1.52 are considered abnormal, as described by Novellas et al. (2007).

Classification of renal perfusion into preserved or decreased was performed using color Doppler mapping, according to the dynamic assessment of the filling of the intrarenal arteries and veins throughout the parenchyma. In a manner adapted to that proposed by Barozzi et al. (2007), the mappings that demonstrated hilar and interlobar vessels in most of the parenchyma were considered preserved and could even include the arcuate and interlobular arteries – which are more difficult to visualize. Decreased perfusion was considered in cases where only a few vessels were identifiable, mainly in the renal hilum region.

The color box was positioned over the kidneys to obtain these data, and the lowest pulse repetition frequency (PRF) was adjusted without the occurrence of the artifact called *aliasing*. After setting the PRF, the image gain was raised to the maximum possible level to better fill the vessels – however, without the resulting image noise (Fig.1).

Quantitatively, we aimed to measure the resistivity indexes (RI) and pulsatility indexes (PI) of the interlobar renal arteries in the cranial, middle and caudal regions of both kidneys - considering the average of these measurements as the intrarenal RI and PI (Fig.2). To locate the segments, flow mapping was performed from color Doppler. The directional line was positioned according to the chosen vessel and its trajectory. At this time, the calibration of the sample volume, which varied from 2 to 3mm, occurred. Although the calculation of the hemodynamic indices is independent of the angle, it was agreed that the insonation angle obtained by the sound beam's directional line and the vessel's axis evaluated would be kept at values below 60°. For best spectrum quality, the smallest velocity scale that displayed the spectral trace was selected.

Routine testing per chemotherapy cycle. The animals included in the study underwent blood sampling for serum urea and creatinine 24 hours before each of the three chemotherapy cycles. However, they were ultrasonographically evaluated at two different times: time 0 (one hour before each of the three chemotherapy cycles) and time 1 (one and a half hours after each of the three chemotherapy cycles) for 42 days of follow-up.

Statistical analysis. The parameters in B-mode and Doppler referring to corticomedullary definition, corticomedullary ratio, shape, echogenicity, echotexture, perirenal region, and renal perfusion remained unchanged throughout the chemotherapy protocol, and no statistical tests were required. Meanwhile, statistical analyses were conducted in the Statistical Package for the Social Science program (SPSS, version 8.0) to evaluate the variables of IR, PI, urea and creatinine levels, and renal measurement concerning the three chemotherapy cycles and times (0 and 1). Analysis of variance (ANOVA) with a 5% confidence interval was used to test the relationship between the variables. Subsequently, the normality pattern was confirmed by the Shapiro-Wilk test. Variables that presented a normal distribution were subjected to the parametric Student's t-test. In contrast, variables with a non-normal distribution were subjected to the non-parametric Mann-Whitney or median test.

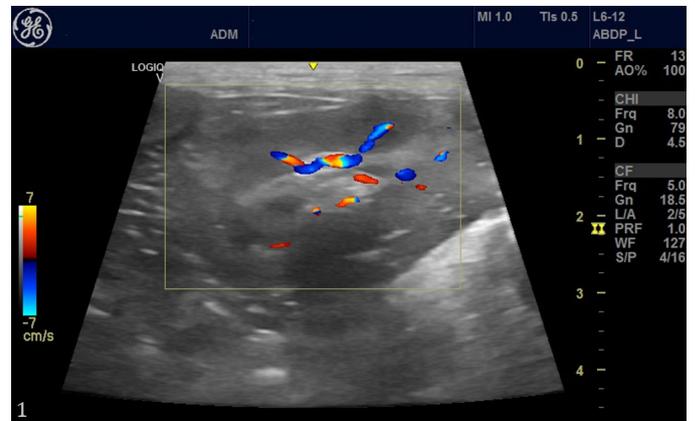


Fig.1. Ultrasonographic evaluation of the left kidney, demonstrating vascular filling of the interlobar arteries by color Doppler.

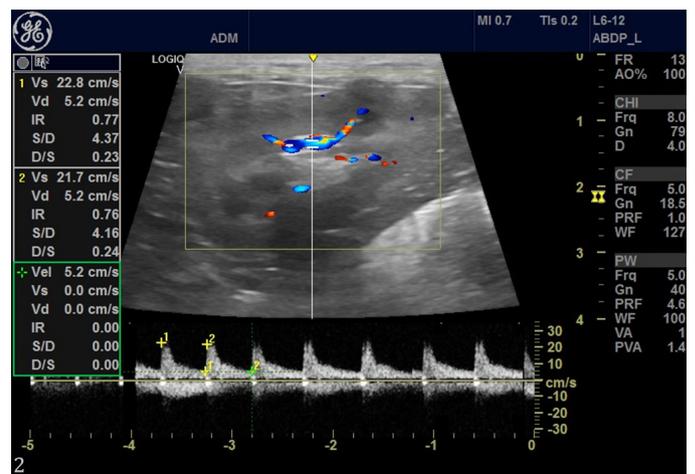


Fig.2. Triplex Doppler image of the interlobar arteries with spectral tracing, in which at least three similar and consecutive spectral waves are observed, making it possible to calculate the hemodynamic indices.

RESULTS

Thirteen bitches were included, of which seven were breed type defined (Poodle, Shih-tzu and Dachshund) and six were not. Their ages ranged from seven to 13 years (mean = 9.69 years and standard deviation = 1.70), and their weight ranged from 5 to 20kg (mean = 12.07kg and standard deviation = 5.63kg).

B-mode ultrasound evaluation

The ultrasound evaluation at time 0 of the first cycle made it possible to establish the individual sonographic patterns of each patient. In this sense, no changes in the morphological parameters referring to the corticomedullary definition, corticomedullary ratio, shape, echogenicity, echotexture, and perirenal region of the kidneys evaluated over the three chemotherapy cycles were evidenced. Regarding renal measurements, the analysis of variance showed no significant difference when comparing the measurements obtained between times 0 and 1 throughout the protocol (Table 1).

Doppler ultrasound evaluation

Color Doppler mapping showed no changes in renal perfusion at times 0 and 1 evaluated over the three chemotherapy cycles. However, the analysis of variance showed a significant difference ($P < 0.001$) between the left kidney pulsatility index (LKPI), right kidney pulsatility index (RKPI), left kidney resistivity index (LKRI), and right kidney resistivity index (RKRI) when measured at time 0 and 1 (Fig.3 and 4), characterized by an increase in the Doppler velocity indexes at time 1 of the three chemotherapy cycles evaluated.

Laboratory evaluation

Additionally, serum urea and creatinine measurements taken 24 hours before the three chemotherapy cycles did not show significant statistical variations (Table 2).

DISCUSSION

Within systemic therapies, adjuvant chemotherapy represents a frequently recommended modality. It is performed after surgical removal of the primary tumor to eliminate residual tumor cells and possible metastatic foci (Vail et al. 2019).

However, due to the important role played by the kidneys in the excretion of chemotherapeutic drugs, these agents have been associated with the development of AKI arising from tubulointerstitial, glomerular damage, electrolyte and hemodynamic changes, development of hypertension and proteinuria (Glezerman & Jaimes 2016, Malyszko et al. 2017, Rosner & Perazella 2017).

The B-mode ultrasound allows the evaluation of renal morphology by an accessible, innocuous and painless method, enabling the correlation of different studies that use this tool. In the animals followed in the study, the sonographic data referring to renal morphology showed no significant changes. However, this finding does not rule out the occurrence of kidney damage. Also, Rivers et al. (1997) histologically confirmed the occurrence of different degrees of tubular necrosis in dogs with no sonographically detectable morphological changes in the kidneys.

Regarding renal length, no statistically significant changes were observed before (T0) and after (T1) the administration of the chemotherapeutic drugs in any of the three cycles evaluated. These results differ from what Martín et al. (2017)

Table 1. Renal measurement according to the chemotherapy cycles and significance level (P) for comparison between times 0 and 1 throughout the protocol

Renal measurement (cm)	Cycles	Time	N	Mean	SD	Median	P-value
Left kidney*	1	0	13	4.69	0.65	4.68	0.88
	1	1	13	4.76	0.74	4.92	
	2	0	13	4.64	0.65	4.59	0.90
	2	1	13	4.67	0.62	4.57	
	3	0	13	4.65	0.65	4.69	0.48
	3	1	13	4.75	0.62	4.68	
Right kidney*	1	0	13	4.68	0.91	4.92	0.99
	1	1	13	4.68	0.94	4.80	
	2	0	13	4.73	0.92	4.92	0.88
	2	1	13	4.79	0.92	4.92	
	3	0	13	4.63	0.81	4.93	0.99
	3	1	13	4.63	0.86	4.82	

N = number of animals, SD = standard deviation; * Non-parametric (the median test).

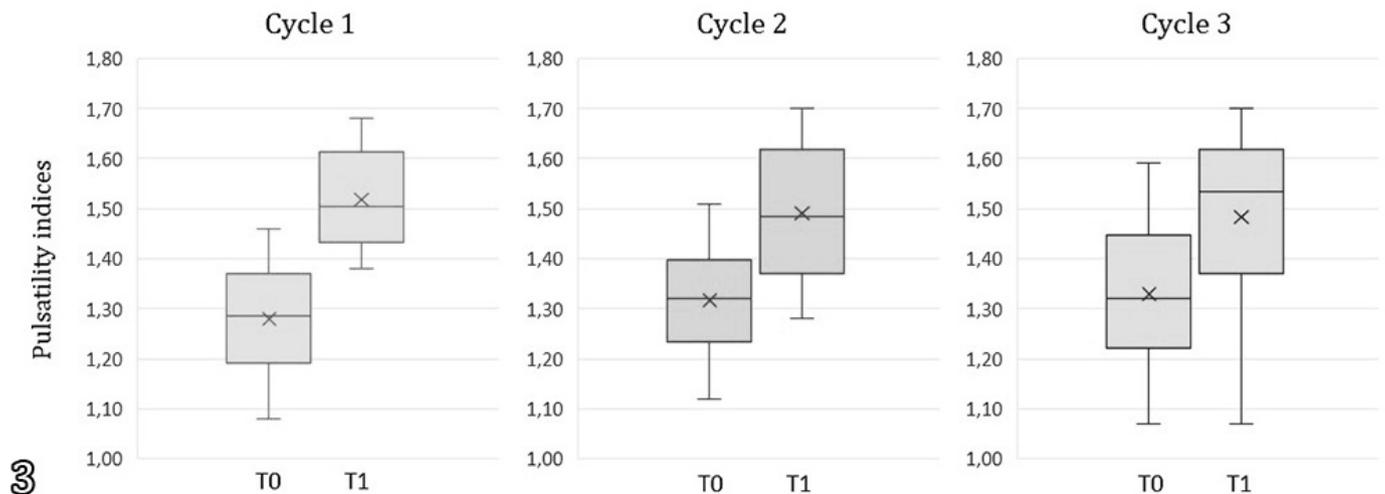


Fig.3. Boxplot graphs representing the variation in pulsatility indices at T0 and T1, in each of the three chemotherapy cycles.

observed, who showed increased renal dimensions one and a half hours after iodinated contrast media administration in dogs undergoing CT scanning. Complementarily, Gasser et al. (2020) reported the increased ratio of renal length to aortic artery diameter in bitches with pyometra, subsequently diagnosed with AKI by histopathological examination.

Mareschal et al. (2007) demonstrated a positive linear relationship between renal length and aortic artery diameter, and this is the method of choice by many authors for evaluating renal measurement. However, the effect of hydration on aortic luminal diameter was not evaluated and highlighted as a possible significant variable. In the present study, we chose to use the dimensions proposed by Barr et al. (1990), who correlated animal weight to kidney length to minimize the influence of intravenous fluid therapy performed after chemotherapy cycles. This method does not consider the body score of the animals evaluated. It has ranges with large amplitude of normality, which may indicate a lower sensitivity in detecting small variations in renal measurements.

Since the hemodynamic variations resulting from AKI can anticipate significant changes in urea and creatinine rates (Ronco et al. 2019, Kelahan et al. 2019), the value of Doppler ultrasound for the early diagnosis of this condition becomes evident. For this study, we performed a hemodynamic evaluation by measuring the RI and PI of the interlobar arteries. While the RI considers the peak systolic velocity and the end-diastolic velocity, the PI correlates these two variables to the average velocity during the cardiac cycle, making it possible to detect changes in the spectral waves.

Based on the hemodynamic evaluation, Lee et al. (2014) detected that the action of compensatory mechanisms in the kidneys of Beagles began to be evidenced one to two hours after intravenous administration of saline solution in the superhydration range and was characterized by Doppler velocimetry changes. In another study, Martín et al. (2017) observed, through B-mode and Doppler ultrasonography, the morphological and hemodynamic variations in the kidneys after intravenous administration of iodinated contrast media to perform CT scans in dogs, and Gasser et al. (2020) analyzed the application of B-mode and Doppler ultrasound in the detection of AKI in bitches with septicemic conditions resulting from pyometra. Based on the literature consulted, we opted for the ultrasound evaluation at two times (T0 and T1) throughout the three chemotherapy cycles.

As reported by Martín et al. (2017), who showed greater variations in Doppler velocimetry indices one and a half hours after intravenous administration of iodinated contrast media, we observed a significant increase in IR and PI one and a half hours after (T1) each of the three chemotherapy cycles.

However, there were no statistical differences between the values obtained at T0 of each cycle, indicating the return to the initial hemodynamic parameters up to 21 days after the administration of chemotherapeutic drugs. These data corroborate with Ma et al. (2019) and Ronco et al. (2019), who pointed out that the kidneys have intrinsic regulatory systems that act to minimize renal hemodynamic changes.

In this study, we did not perform the histopathological evaluation of the kidneys in a complementary manner to

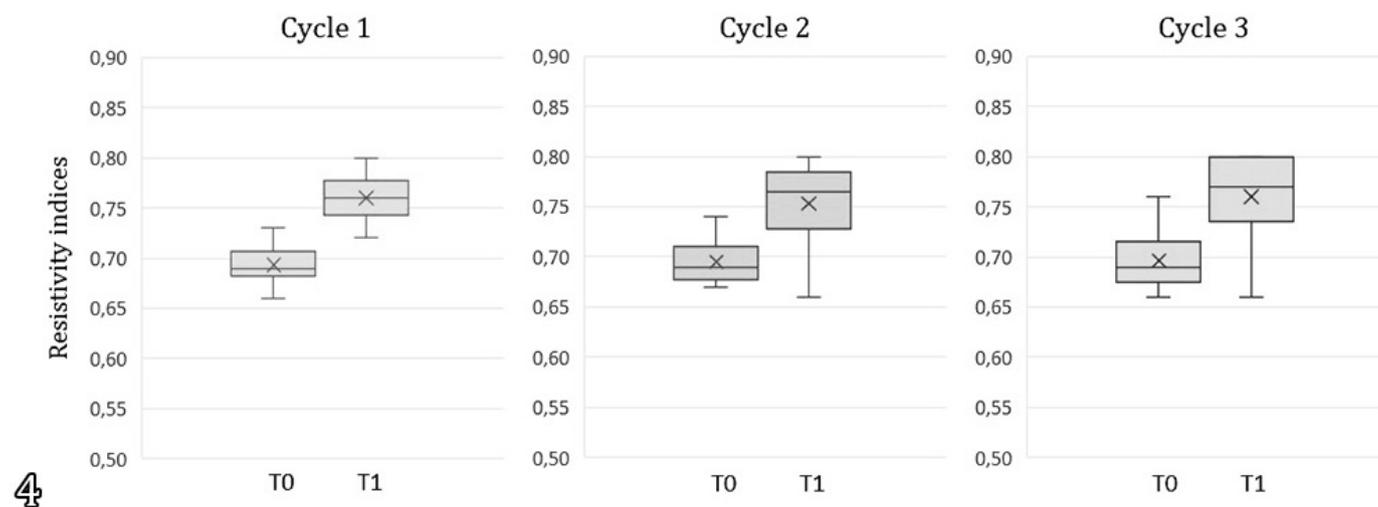


Fig.4. Boxplot graphs representing the variation of resistivity indices at T0 and T1, in each of the three cycles evaluated.

Table 2. Descriptive statistics of the urea and creatinine variables, according to each of the three evaluated cycles

Variables	Cycles	N	Mean	SD	Median	P-value
Urea*	1	13	48.77	27.25	46	0.73
	2	13	48.92	16.85	47	
	3	13	47.54	13.05	51	
Creatinine**	1	13	1.02	0.30	1	0.90
	2	13	0.99	0.23	1	
	3	13	1.05	0.22	1.1	

N = number of animals, SD = standard deviation; * Non-parametric (the median test), ** parametric Student's t-test

B-mode and Doppler ultrasound evaluation. However, these parameters have often been related in the literature to glomerulosclerosis and tubulointerstitial lesions (Spatola & Andrulli 2016).

One of the limitations of the present study was that some complementary tests were not performed. Laboratory tests could have been performed for evaluating renal function – such as urine density – and detecting possible kidney damage in the animals followed in the study – such as urinary gamma-glutamyltransferase (GGT) and urinary protein/creatinine ratio.

Another limitation was that creatinine was not measured at T1. However, although variations in creatinine rates are considered predictive factors for the diagnosis of AKI by IRIS, several authors state that this marker has low sensitivity for the detection of early renal dysfunction (Hall 2016, Dahlem et al. 2017, Meersch et al. 2017, McKenna et al. 2020). In this regard, symmetric dimethylarginine (SDMA) is an important alternative (Dahlem et al. 2017, Harjen et al. 2021).

The laboratory analyses that quantified the urea and creatinine values before each of the three chemotherapy cycles (T0) showed no statistically significant changes throughout the protocol. Therefore, despite the variations in hemodynamic indices evidenced at T1, no changes in renal functionality could be detected by creatinine measurements and consequently characterized as renal injury over the cycles. This result seems to indicate that the chemotherapy protocol used did not result in permanent damage to kidney function in the period studied.

CONCLUSIONS

B-mode ultrasound showed no morphological changes in the kidneys of bitches with mammary neoplasia submitted to adjuvant chemotherapy of the association of gemcitabine and carboplatin over the 42 days of follow-up. In turn, the spectral Doppler mode identified variations in resistivity and pulsatility indices one and a half hours after the protocol but not between the three cycles studied.

It was concluded that Doppler ultrasound proved to be an efficient technique for monitoring renal intravascular dynamics. It can be used as a complementary method for monitoring the renal response of patients exposed to nephrotoxic drugs and potentially causing acute renal injury.

Conflict of interest statement.- The authors have no conflict of interest.

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