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EFFECTIVENESS OF CONVENTIONAL CHEMOTHERAPY IN THE TREATMENT OF MAMMARY CARCINOMA IN FEMALE DOGS – A SYSTEMATIC REVIEW

EFETIVIDADE DA QUIMIOTERAPIA CONVENCIONAL NO TRATAMENTO DO CARCINOMA MAMÁRIO EM CADELAS – UMA REVISÃO SISTEMÁTICA

EFICACIA DE LA QUIMIOTERAPIA CONVENCIONAL EN EL TRATAMIENTO DEL CARCINOMA MAMARIO EN PERRAS – UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Conventional chemotherapy is the most commonly used treatment option for female dogs with mammary carcinoma. It is based on the maximum tolerated dose for the patient, which may cause significant adverse effects and requires treatment interruption periods to allow recovery of normal cells. These intervals may permit tumor growth and the development of drug resistance. This research was registered and approved by PROSPERO. The objective of this systematic review was to determine whether conventional chemotherapy is effective in the treatment of mammary carcinomas in female dogs. The results were evaluated based on clinical response indicators according to RECIST criteria. A total of 1,158 articles were identified, of which 1,002 were excluded after title screening and 144 after abstract screening. Fourteen articles were selected for full-text analysis; two were excluded at this stage and one article was no longer available in full. Therefore, 11 studies were included in the final evaluation. The analyzed studies demonstrated higher complete response rates, longer disease-free intervals, and improved survival rates in animals treated with conventional chemotherapy.

Keywords: Breast Cancer. Canine. Clinical Indicators. Oncology. Survival.

RESUMO

A quimioterapia convencional é a opção de tratamento mais comum para cadelas com carcinoma mamário. É baseada na dose máxima tolerada pelo paciente, podendo causar efeitos adversos importantes, e necessita de tempo de interrupção do tratamento para recuperação das células do paciente, o que pode permitir crescimento tumoral e resistência aos fármacos. A pesquisa foi aprovada pela PROSPERO. O objetivo desta revisão

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sistemática foi responder se a quimioterapia convencional é eficaz no tratamento de carcinomas mamários em cadelas. Os resultados foram baseados nos indicadores de resposta clínica de acordo com os critérios RECIST. Foram encontrados 1158 artigos, dos quais foram excluídos 1002 na leitura dos títulos e 144 na leitura dos resumos, passando 14 artigos para a leitura na íntegra, quando foram excluídos mais dois artigos e um dos artigos não se encontra mais disponível, tendo sido avaliados 11 artigos, que demonstraram melhor taxa de resposta completa, maior tempo livre de doença e taxa de sobrevivência.

Palavras-chave: Canino. Câncer de Mama. Indicadores Clínicos. Oncologia. Sobrevida.

RESUMEN

La quimioterapia convencional es la opción de tratamiento más común para perras con carcinoma mamario. Se basa en la dosis máxima tolerada por el paciente, lo que puede provocar efectos adversos significativos y requiere periodos de interrupción del tratamiento para permitir la recuperación de las células normales. Estos intervalos pueden favorecer el crecimiento tumoral y el desarrollo de resistencia a los fármacos. Esta investigación fue registrada y aprobada por PROSPERO. El objetivo de esta revisión sistemática fue determinar si la quimioterapia convencional es eficaz en el tratamiento de carcinomas mamarios en perras. Los resultados se evaluaron con base en indicadores de respuesta clínica según los criterios RECIST. Se identificaron un total de 1.158 artículos, de los cuales 1.002 fueron excluidos tras la lectura de los títulos y 144 después de la lectura de los resúmenes. Catorce artículos fueron seleccionados para la lectura completa; dos fueron excluidos en esta etapa y uno ya no estaba disponible en su totalidad. Por lo tanto, se incluyeron 11 estudios en la evaluación final. Los estudios analizados demostraron mayores tasas de respuesta completa, mayor tiempo libre de enfermedad y mayores tasas de supervivencia en los animales tratados con quimioterapia convencional.

Palabras clave: Cáncer de Mama. Canino. Indicadores Clínicos. Oncología. Supervivencia.

1 INTRODUCTION

Mammary tumors in female dogs occur with increasing frequency in routine veterinary practice (Cassali et al., 2014; De Nardi, 2016), due to the increased longevity of animals (Estralioto; Conti, 2019). The use of cytostatic drugs is one of the most important tools in the management of neoplastic diseases, and their use enables not only prolonged survival time but also an improvement in the quality of life of many animals with cancer (Goldschmidt et al., 2016; Sorenmo et al., 2013).

Conventional chemotherapy uses the maximum tolerated dose for the patient (Goldschmidt et al., 2016), which may cause adverse effects and therefore requires an interval between administrations sufficient to allow normal tissues susceptible to the drugs to recover before the next administration (Sorenmo et al., 2013).

In this context, the aim of this systematic review was to investigate the available information regarding the use and effect of chemotherapy in canine mammary tumors, to identify the efficacy of different treatments based on robust scientific evidence, and to identify areas in which existing research is limited, in order to guide future research and treatment development efforts, thereby helping veterinarians make more assertive decisions and improve the quality of care for oncology patients.

2 THEORETICAL FRAMEWORK

Canine mammary carcinoma is a complex and heterogeneous disease that encompasses a wide spectrum of histological types and biological behaviors. According to Goldschmidt, Peña and Zappulli (2016), mammary tumors in dogs present considerable morphological variability, which may influence tumor progression, metastatic potential, and response to treatment. The development of mammary neoplasms is associated with multiple factors, including hormonal influence, genetic predisposition, and environmental conditions, contributing to the complexity of the disease and its clinical management.

The biological behavior of mammary tumors in female dogs is strongly associated with prognostic factors such as tumor size, histological grade, lymphatic invasion, and clinical staging. Studies have demonstrated that animals with larger tumors or higher histological grades tend to present lower survival rates and greater metastatic potential (Dias et al., 2016; Gundim et al., 2016). Furthermore, tumor classification systems and staging protocols have been developed to guide therapeutic decisions and improve prognostic evaluation, as highlighted in the consensus guidelines proposed for canine mammary tumors (Cassali et al.,

2014; Cassali et al., 2020).

Surgical removal remains the main therapeutic approach for canine mammary tumors, particularly in localized disease. Mastectomy aims to remove the primary tumor mass and reduce the risk of local recurrence and metastatic spread. However, in cases involving aggressive tumors or advanced clinical stages, surgery alone may not be sufficient to control disease progression (Lavalle et al., 2012). In these situations, complementary therapeutic strategies are often considered in order to improve patient outcomes.

Among these strategies, chemotherapy has been investigated as a potential adjuvant treatment for dogs with malignant mammary tumors. Chemotherapeutic protocols may involve different classes of antineoplastic agents, including alkylating agents, anthracyclines, and platinum-based compounds. These drugs act through mechanisms that interfere with DNA replication and cellular proliferation, aiming to control residual tumor cells following surgical treatment (Frimberger & Moore, 2022). The selection of a chemotherapy protocol may vary depending on tumor characteristics, clinical stage, and the general health status of the patient.

Several clinical investigations have evaluated the potential benefits of chemotherapy in dogs with mammary carcinoma. Studies using agents such as doxorubicin, carboplatin, and gemcitabine have explored their effects on survival time, disease-free interval, and recurrence rates (Simon et al., 2006; Marconato et al., 2008; Nunes et al., 2019). In addition, other pharmacological approaches have been studied in veterinary oncology, including the use of perioperative desmopressin due to its possible antimetastatic effects and influence on tumor progression (Hermo et al., 2008; Sorenmo et al., 2020).

Despite advances in the understanding of canine mammary carcinoma and the development of various treatment protocols, the role of conventional chemotherapy in improving clinical outcomes remains a subject of ongoing investigation. Differences in study design, chemotherapy protocols, and patient populations have contributed to variability in reported results (Tran et al., 2014; Frimberger & Moore, 2022). Therefore, a comprehensive evaluation of available scientific evidence is essential to clarify the effectiveness of chemotherapy in the management of mammary carcinoma in female dogs and to support evidence-based decision-making in veterinary oncology.

3 METHODS

3.1 SEARCH STRATEGY AND SELECTION CRITERIA

A systematic literature review was carried out, implying the synthesis of studies using a clear and reproducible methodology, based on the recommendations of the Cochrane Collaboration (Higgins and Green, 2011). To define the research question, the PICO methodology was considered, defining the study population, the intervention, the comparison for each intervention, and the outcomes to be measured. The entire study was previously submitted to and approved by the International Prospective Register of Systematic Reviews (PROSPERO), under registration code CRD42022321858. The PICO acronym was applied as described below: Participants: female dogs with mammary carcinoma; Intervention: conventional chemotherapy treatment; Comparison: treated groups and untreated groups or groups treated with other possible therapies, excluding chemotherapy; Outcome: clinical indicators of treatment efficacy, namely overall response rate (complete or partial), duration of response, and survival rate and time. The question described for this investigation was: Is conventional chemotherapy effective in the treatment of canine mammary tumors?

The database search strategy used the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) terms, in addition to proximity operators, in the databases MEDLINE (PubMed), ELSEVIER (Science Direct and Scopus), WOS (Web of Science), and SCIELO (SciELO). The primarily defined combinations of terms and keywords were: (bitches OR dogs) AND (breast cancer) AND (chemotherapy OR “antineoplastic agents”), in order to answer the question regarding the efficacy of conventional chemotherapy; the searches were carried out on August 19, 2022.

The search and article selection stages were carried out independently by two reviewers, one assistant reviewer (M.P.R.) and one principal reviewer (M.P.R.D.), who was responsible for conducting the other stages of the systematic review. The inclusion and selection criteria for the articles were randomized observational and experimental clinical studies, in vivo, in English or Portuguese, with female canine participants of any age diagnosed with mammary tumors. Studies were included in which animals were treated with conventional chemotherapy protocols, in comparison with group(s) not exposed to chemotherapy, which had not received any treatment or had been treated with other types of available antitumor therapies.

Studies were excluded when the main intervention was not chemotherapy, such as studies based on the use of other therapeutic protocols such as immunotherapy,

radiotherapy, electrochemotherapy, and/or photodynamic therapy or mastectomy alone, as well as articles whose main objective was other types of evaluation rather than chemotherapy efficacy through the outcome data sought. Articles that did not compare the treated group with the untreated group were excluded. The excluded articles were grouped according to the reason for exclusion for justification purposes, based on titles or abstracts. In the next stage, all eligible studies were read in full and relevant data were extracted from the text and graphs of the included studies. In the case of missing data, the authors of the corresponding articles were contacted once in an attempt to obtain the missing information. A narrative synthesis of the included data was determined, structured around the type of intervention studies, target, population characteristics, type of outcome, and content of the intervention.

3.2 DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

Relevant data were extracted from all included studies by two independent reviewers (Initials). To assess risk of bias, we used the SYRCLE Risk of Bias (RoB) tool (Hooijmans et al., 2014). This stage was carried out independently by two reviewers (Initials). Possible disagreements between reviewers were resolved with the assistance of a third reviewer (PIRF).

4 RESULTS

4.1 STUDY SELECTION

The initial database search for studies on conventional chemotherapy resulted in a total of 1,384 articles, of which 226 duplicates were identified using the Zotero® platform. After removing duplicates, 1,158 articles remained for the systematic review screening process. Title screening led to the exclusion of 1,002 articles that were not selected for abstract reading, leaving 156 articles for the next stage.

During the abstract screening phase, 142 articles were excluded, leaving 14 articles for full-text evaluation. At this stage, two studies were excluded because their primary focus was not the efficacy of conventional chemotherapy, but rather the toxicity and pharmacokinetics of chemotherapeutic drugs. Additionally, the study by Ravikumar et al. (2002) could not be included because the full text was no longer available. Consequently, 11 articles met the predefined inclusion criteria and were included for full-text analysis and data extraction.

4.2 CHARACTERISTICS OF THE INCLUDED STUDIES

All studies selected for this systematic review were conducted with female dogs diagnosed with mammary tumors, considered to be in good general health condition and previously submitted to mastectomy, except for the study by Kuruoglu et al. (2020), in which mastectomy was performed four weeks after the last session of conventional chemotherapy. The control group consisted of animals treated exclusively with surgery, while the remaining groups subsequently received chemotherapy.

Regarding mammary tumors, as previously defined, only studies involving mammary carcinomas were selected. However, these tumors varied in terms of size, number of nodules, histological grade, and tumor stage, and not all authors provided this information (Table 1).

Table 1

Data of interest extracted prior to treatment according to the population and experimental design for the systematic review on the effectiveness of conventional chemotherapy for mammary carcinoma in female dogs.

Authors	Number of nodules (no. of animals)		Histological grade of nodules (I–III) (no. of animals)		Neoplasm stage (I–V) (no. of animals)		Total number of animals
Kuruoglu et al, 2020	Single nodule	4	I	9	I	*	16
			II	6	II	*	
	Multiple nodules	12	III	1	III	*	
					IV	*	
					V	*	
Sorenmo et al, 2020	*		I	12	I	4	24
			II	7	II	9	
			III	6	III	5	
					IV	6	
					V	0	
Nunes et al, 2019	*		I	59	I	318	682
			II	26	II	132	
			III	3	III	90	
					IV	42	
					V	2	
Machado et al, 2018	*		I	0	I	0	60
			II	**	II	***	
			III	**	III	***	
					IV	0	
					V		
Panjak et al, 2014	Single nodule	5	I	*	I	*	35
			II	*	II	*	
	Multiple nodules	30	III	*	III	*	
					IV	*	
					V	*	
Tran et al, 2014	Single nodule	43,6	I	*	I	31	94
			II	*	II	5	
		56,4	III	*	III	13	

	Multiple nodules				IV	37	
					V	8	
Lavalle et al, 2012	*		I	*	I	*	37
			II	*	II	*	
			III	*	III	*	
					IV	*	
					V	*	
Marconato et al., 2008	Single nodule	5	I	0	I	*	20
			II	13	II	*	
	Multiple nodules	15	III	6	III	*	
					IV	*	
					V	*	
Hermo et al., 2008	*		I	7	I	0	21
			II	7	II	****	
			III	7	III	****	
					IV	0	
					V	0	
Simon et al., 2006	*		I	0	I	2	31
			II	26	II	8	
			III	5	III	16	
					IV	5	
					V	0	
Karayannopoulou et al., 2001	*		I	9	I	6	16
			II	7	II	5	
			III	0	III	5	
					IV	0	
					V	0	

Information not available.
*** The author reports that animals with histological tumor grades II and III were included but does not specify how many animals belonged to each grade.*
**** The author reports that animals with tumor stages II or III were included but does not specify how many animals belonged to each stage.*
***** The author reports that animals with tumor stages III or IV were included but does not specify how many animals belonged to each stage.*

The studies involving conventional chemotherapy used different drugs or drug combinations, administered at varying doses, routes, and frequencies of administration (Table 2).

Table 2

Data of interest extracted from the selected studies according to the intervention for the systematic review on the effectiveness of conventional chemotherapy for mammary carcinoma in female dogs.

Authors	Chemotherapeutic drug	Dose (mcg/kg ou mg/m²)	Route of administration	Treatment regimen	Follow-up period (months)
Kuruoglu et al, 2020	Doxorubicin + Cyclophosphamide	30mg/m² + 100mg/m²	IV	4 cycles every 21 days	48 months

Sonremo et al., 2020	Desmopressin	3mcg/kg	SC	1 administration before and another 30 minutes after mastectomy	48 months
Nunes et al., 2019	Carboplatin	300 mg/m²	IV	4 cycles every 21 days	60 months
	Carboplatin + Doxorubicin	30 mg/m²		4 cycles every 21 days, administered alternately	
Machado et al, 2018	Carboplatin	300 mg/m²	IV	6 cycles every 21 days	48 months
Sorenmo et al, 2020	Vincristine + Methotrexate + Cyclophosphamide	0,5mg/m² + 15mg/m² + 50mg/m²	IV	Vincristine + Methotrexate on day 1 and Cyclophosphamide from days 2 to 5, for 3 cycles every 21 days	48 months
Tran et al, 2014	Doxorubicin + Carboplatin	*	IV	*	24 months
	Mitoxantrone + Carboplatin	*	IV	*	
	Doxorubicin/Carboplatin	*	IV	*	
Lavalle et al, 2012	Carboplatin	300 mg/m²	IV	3 cycles every 21 days	24 months
Marconato et al, 2008	Gemcitabine	800 mg/m²	IV	Minimum of 4 and maximum of 10 sessions	24 months
Hermo et al, 2008	Desmopressin	1mcg/kg	SC	1 administration before and another 30 minutes after mastectomy	48 months
Simon et al, 2006	Doxorubicin	30mg/m²	IV	5 cycles every 21 days	48 months
	Docetaxel	30mg/m²			
Karayannopoulou et al., 2001	5-Fluorouracil + Cyclophosphamide	150mg/m² + 100mg/m²	IV	4 cycles every 21 days, administered simultaneously	24 months

* Information not available.

Among the numerous factors evaluated in relation to the results, information on clinical indicators of treatment efficacy was selected (Table 3). Partial response was excluded because, in the selected studies, mastectomy was performed before or shortly after conventional chemotherapy, making it impossible to observe tumor volume reduction in the evaluated patients, which is the defining criterion for this type of response. In the study by Kuruoglu et al. (2020), which was the only one in which mastectomy was not performed prior

to chemotherapy, a partial response was observed in 12.5% and a complete response in 56.5% of the patients in the treated group. None of these animals showed disease progression, and 31.5% presented stable disease.

Table 3

Data of interest extracted from the selected articles according to the outcomes for the systematic review on the effectiveness of conventional chemotherapy for mammary carcinoma in female dogs.

Authors	Complete response rate[1] (% of animals)		Response duration[2] (days)		Survival rate[3] (%)		Survival time[4] (days)	
Kuruoglu et al, 2020	GC	*	GC	*	GC	100	GC	*
	QC	12,5	QC	*	QC	100	QC	*
Sonremo et al, 2020	GC	*	GC	140	GC	*	GC	635
	QC	*	QC	348	QC	*	QC	688
Nunes et al, 2019	GC	*	GC	*	GC	*	GC	330
	QC	*	QC	*	QC	*	QC	964
Machado et al, 2018	GC	*	GC	*	GC	*	GC	150
	QC	*	QC	*	QC	*	QC	180
Pankaj et al, 2014	GC	*	GC	*	GC	50	GC	169
	QC	*	QC	*	QC	50	QC	162
Tran et al, 2014	GC	*	GC	*	GC	*	GC	194
	QC	*	QC	*	QC	*	QC1	228
							QC2	128
							QC3	347
Lavalle et al, 2012	GC	*	GC	*	GC	*	GC	63
	QC	*	QC	*	QC	*	QC	390
Marconato et al, 2008	GC	27	GC	175	GC	40	GC	178
	QC	76	QC	124	QC	100	QC	203
Hermo et al, 2008	GC	20	GC	*	GC	*	GC	351
	QC	63	QC	*	QC	*	QC	600
Simon et al, 2006	GC	11	GC	294	GC	*	GC	370
	QC	63	QC	434	QC	*	QC	390
Karayannopoulou et al., 2001	GC	25	GC	30 -60	GC	28,6	GC	*
	QC	75	QC	30	QC	75	QC	*

[1] Complete response: total disappearance of tumors and clinical signs. [2] Duration of response: mean number of days until relapse after complete response (CR) or disease progression after partial response (PR). Disease progression is defined as an increase of more than 25% in tumor size or the appearance of new lesions. [3] Survival rate: percentage of animals alive after the treatment period. [4] Survival time: period from the beginning of treatment until death (from any cause) (Withrow et al., 2003). GC: Control group. QC: Group treated with conventional chemotherapy (QC1 and QC2 were used when more than one chemotherapeutic drug protocol was tested with different results). * Information not presented. Green: Positive result. Red: Negative result.

The complete response rate was positive in the studies that reported this outcome. Marconato et al. (2008) demonstrated remission in 76% of treated patients and in 27% of animals in the control group, a result very similar to that reported by Karayannopoulou et al. (2001), who observed 75% in the treated group and 25% in the control group. Hermo et al. (2008) and Simon et al. (2006) observed complete response in 63% of the treated group, while Hermo et al. (2008) reported 20% in the control group and Simon et al. (2006) reported 11% in the control group.

The same authors also reported survival rates. Kuruoglu et al. (2020) did not record any deaths in either group. Marconato et al. (2008) also reported no deaths in the treated group but observed a survival rate of 40% in the control group. Karayannopoulou et al. (2001), however, reported a survival rate of 75% in the treated group and 28.6% in the control group (CG), while Pankaj et al. (2014) reported a mortality rate of 50% in both groups.

The most prominent differences in mean survival time were observed in the treated group in the studies by Nunes et al. (2019), with 964 days, and Hermo et al. (2008), with 600 days, compared with 330 and 351 days in the control groups, respectively, which is considered a positive outcome. Furthermore, Lavalle et al. (2012) reported similarly positive results, with a mean survival time of 390 days in the treated group and 63 days in the control group.

In contrast, other authors who reported this outcome did not observe significant differences between groups. Machado et al. (2018) reported 180 days of survival in the treated group and 150 days in the control group. Pankaj et al. (2014) reported a mean survival of 162 days in the treated group and 169 days in the control group. Simon et al. (2006) reported mean survival times of 390 days in the treated group and 370 days in the control group. Additionally, Tran et al. (2014) found that one of the conventional chemotherapy protocols tested resulted in a worse outcome (128 days) compared with the control group (194 days), although a similar survival time was observed in another treated group within the same study (228 days).

Sorenmo et al. (2020) stratified survival time according to prognostic factors. For tumors smaller than 3 cm, the mean survival time was 245 days in the control group and 348 days in the treated group, whereas for tumors larger than 3 cm it was 908 days in the control group and 818 days in the treated group. For clinical stages III and IV, survival time was 382 days in the control group and 483 days in the treated group, while for stages I and II it was 818 days in the control group and 1050 days in the treated group. Regarding histological

grade, grade III tumors presented a mean survival of 245 days in the control group and 348 days in the treated group. For grade II tumors, the control group showed a mean survival of 754 days, while the treated group presented 1394 days, which was the best response observed. Although most of the other comparisons also showed more favorable results in the treated group, in tumors with histological grade I the survival time was lower in the treated group (322 days) than in the control group (908 days).

The duration of response until the appearance of new lesions, either local or metastatic, was reported by Marconato et al. (2008), who observed a shorter duration in the treated group (124 days) compared with the control group (175 days). In contrast, Sorenmo et al. (2020) did not report new lesions in the treated group, whereas new lesions occurred after 153 days in the control group in grade III tumors. Karayannopoulou et al. (2001) did not observe differences in this parameter. Only Simon et al. (2006) reported a longer disease-free interval in the treated group (434 days) compared with the control group (294 days).

Regarding the occurrence of new lesions, the study by Hermo et al. (2008) reported a higher number of metastatic cases in the control group (27%) and a higher rate of local recurrence (70%) compared with the treated group (9% and 30%, respectively). Similarly, Simon et al. (2006) reported 42% of local recurrences in the control group and 25% in the treated group.

4.3 RISK OF BIAS AND QUALITY OF THE INCLUDED STUDIES

The analysis of the risk of bias and the quality of the studies included in the review was performed after the data extraction stage using the Risk of Bias (RoB) tool from the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) for animal intervention studies (Hooijmans et al., 2014). Two researchers independently performed the risk of bias assessment, and since there was no disagreement between them, it was not necessary to consult a third reviewer. The results were presented in a summary table (Table 4).

Table 4

Results of the bias analysis and methodological quality of the studies selected for the systematic review on the effectiveness of conventional chemotherapy for mammary carcinoma in female dogs using the SYRCLE Risk of Bias tool (Hooijmans et al., 2014).

Authors	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other biases
	1	2	3	4	5	6	7	8	9	10
Kuruoglu et al., 2020[12]	?	+	?	?	?	+	-	+	+	+
Sorenmo et al., 2020[13]	+	+	?	?	+	+	+	+	+	+
Nunes et al., 2019[14]	?	?	?	?	+	+	+	+	+	+
Machado et al., 2018[15]	+	+	+	?	+	+	+	+	+	+
Pankaj et al., 2014[16]	?	-	-	?	?	+	+	+	?	+
Tran et al., 2014[17]	+	+	+	?	+	+	+	?	?	+
Lavalle et al., 2012[18]	?	+	?	?	?	?	?	+	?	+
Marconato et al, 2008[19]	?	+	?	?	?	?	+	+	?	+
Hermo et al., 2008[20]	+	+	?	?	?	+	+	+	?	+
Simon et al., 2006[21]	+	+	?	?	+	+	+	+	+	+
Karayannopoulou et al., 2001[22]	+	+	?	?	?	+	?	+	?	+

YES + NO - UNCLEAR ?

YES indicates low risk of bias; NO indicates high risk of bias; UNCLEAR indicates that the risk of bias could not be determined.

The ten items evaluated included:

Was the allocation sequence adequately generated and applied?

Were the groups similar at the beginning of the study, or were they adjusted for confounding factors in the analysis?

Was the allocation to different groups adequately concealed?

Were the animals randomly housed during the experiment?

Were the caregivers and/or investigators blinded to the intervention received by each animal during the experiment?

Were the animals randomly selected for outcome assessment?

Was the outcome assessor blinded?

Were incomplete outcome data adequately addressed?

Are the study reports free from selective outcome reporting?

Was the study apparently free from other problems that could result in a high risk of bias?

The control and treatment groups did not present similar baseline characteristics, considering that the animals differed in age, clinical stage of the disease, histological tumor grade, environment, nutrition, nursing care, breed, and number of affected mammary glands. These factors were not evenly distributed between groups, which may increase the probability of bias. The selected articles conducted prospective studies involving animals with naturally occurring disease undergoing clinical treatment. Therefore, the allocation of animals was determined by patient admission and the availability of the intervention. Since the extracted data were measured through mortality rate, overall survival time, disease-free interval, and treatment response, the probability of measurement error was considered minimal. Consequently, the moderate risk of bias was not considered to have significantly influenced

the results obtained.

5 DISCUSSION

Adjuvant conventional chemotherapy is the most routine form of applying this treatment regimen in veterinary medicine (Goldschmidt et al., 2017), as verified here in all selected studies, except for Kuruoglu et al. (2020), who used neoadjuvant chemotherapy. From a research standpoint, this fact is quite interesting because it allows the analysis of tissue changes induced by chemotherapeutic agents in vivo and their comparison with clinical and imaging characteristics before surgery.

Tumor size is considered an important prognostic characteristic. According to Ferreira et al. (2017) and Cassali et al. (2020), dogs with mammary tumors larger than 5 cm have shorter survival than those with smaller tumors. Campos and Lavalle (2017) also pointed out that mammary tumors smaller than 3 cm have a better prognosis compared with larger masses. The articles selected for this systematic review did not present a correlation between tumor size and the outcomes achieved, which limited the analysis of treatment efficacy, given that other researchers have found that conventional chemotherapy works better in smaller neoplasms (Frimberger; Moore, 2022).

Four studies in this systematic review presented information on the number of nodules. In two of them, 25% of the evaluated female dogs had single nodules and 75% had multiple nodules (Kuruoglu et al., 2020; Marconato et al., 2008). In the other two studies, 15% and 85% (Pankaj et al., 2014) and 43.6% and 56.4% (Tran et al., 2014) of the female dogs had single and multiple nodules, respectively. Likewise, Sorenmo et al. (2011) stated that dogs with mammary tumors generally present more than one tumor, with the prevalence of multiple nodules reaching 70% of female dogs with mammary neoplasms (Campos; Lavalle, 2017).

Tran et al. (2014) observed mean survival in female dogs of 1,226 days with stage I neoplasms, 924 days in stage II, 287 days in stage III, 165 days in stage IV, and 224 days in stage V. Karayannopoulou et al. (2001), however, reported that all stage II patients, 100%, developed pulmonary metastases and died within two years after surgery. Other studies reported a higher occurrence of metastases in grade III mammary tumors compared with grades I and II (Dias et al., 2016; Dolka et al., 2016; Gundim et al., 2016). When tumor stage and histological grade of the neoplasms were related to the efficacy of conventional chemotherapy, it was possible to observe that, in most of the included studies, there was an unequal distribution of cases (Kuruoglu et al., 2020; Nunes et al., 2019; Machado et al., 2018;

Marconato et al., 2008), which may have interfered with the obtained results.

Among those that performed separate analyses in order to study a homogeneous population with regard to tumor behavior, Sorenmo et al. (2020) and Simon et al. (2006) found no differences in survival time and metastasis, respectively. Sorenmo et al. (2020) reported a median overall survival of 818 days in the treated group and 754 days in the control group. Simon et al. (2006), when evaluating stage II neoplasms, found that the median time to metastasis was 490 days in the control group and, in the group of patients that received conventional chemotherapy, the time to metastasis ranged from 99 to 2,585 days.

In another study, it was found that female dogs in the treated group had significantly better survival than those in the control group. Karayannopoulou et al. (2001) reported that 60% of the female dogs with stage I neoplasia and all female dogs with stage II disease developed metastases and died within two years after surgery, whereas in the treated group all female dogs lived more than two years after surgery. Cassali et al. (2020), when reporting a mean survival of 331 days in animals with stage IV disease, mentioned that conventional chemotherapy is advisable in tumors with grade III or clinical stage IV and V.

Regarding stratification by treatment type, comparison was difficult due to the heterogeneity in the choice of chemotherapeutic drugs and treatment regimens among researchers. The selection of protocols in the studies was in accordance with Cirillo (2008), who stated that, in chemotherapeutic treatment, the main protocols combine two or three drugs and that the choice should be based on clinical and/or histological criteria. The protocol used by Kuruoglu et al. (2020), doxorubicin and cyclophosphamide, showed strongly positive chemotherapy results. This finding corroborates the protocol used by Daleck et al. (1998), who observed, over a one-year period, 8.7% mortality and 65.21% of animals without metastases or local recurrences.

Several authors demonstrated no significant difference in time to metastasis or survival (Hermo et al., 2011a) or in cell growth (Benavente et al., 2016) with the use of desmopressin at different doses and routes of administration. Furthermore, in the study by Sorenmo et al. (2020), the result was slightly more promising only with regard to duration of response, with 140 days in the control group and 348 days in the treated group. On the other hand, Hermo et al. (2008) found better results in the treated group regarding the number of animals with complete response, 63% in the treated group and 20% in the control group, and mean survival time, 600 days in the treated group and 351 days in the control group. In a later study, Hermo et al. (2011b) also demonstrated a significant survival benefit in the group treated with

desmopressin in female dogs with grade 2 and 3 mammary tumors.

Carboplatin was used by Nunes et al. (2019) and Lavalle et al. (2012), with better survival results for the treated group, 964 and 390 days, than for the control group, 330 and 63 days, respectively. In a study of carcinomas at other sites, 18% partial response, 55% stable disease, and 27% disease progression during the clinical trial were observed, with a clinical benefit rate of 73% (Shepard-Olivares et al., 2017), reinforcing recommendations for its use, alone or in combination with other chemotherapeutic agents, due to the demonstration of clinical benefit by several authors (Menard et al., 2018; De Vos et al., 2005; De Vos et al., 2012).

Machado et al. (2018) and Tran et al. (2014), in contrast, found no differences in comparative outcomes between groups. Tran et al. (2014) did not observe improved survival rates when comparing the three treated groups with the control groups, but pointed out that the use of mitoxantrone in combination with carboplatin as first-line adjuvant chemotherapy was associated with better long-term survival, reinforcing the findings of Charney et al. (2005) in a retrospective study on malignant effusions.

In addition to what was previously mentioned regarding the use of doxorubicin in chemotherapy combination protocols, Simon et al. (2006) used it alone and found no clinical benefits, despite demonstrating a longer disease-free interval in patients in the treated group. In the same study, the effects of docetaxel were also evaluated, likewise without evidence of beneficial results, but with a shorter disease-free interval until the appearance of metastases compared with doxorubicin, 167 and 231 days, respectively.

Regarding the protocol used by Pankaj et al. (2014), who combined vincristine, methotrexate, and cyclophosphamide without obtaining differences between the control and treated groups, no other articles using the same medications were found in the present search. Among them, the most commonly used is cyclophosphamide, which was also used in another study included in the present systematic review, in combination with 5-fluorouracil (Karayannopoulou et al., 2001), showing positive results regarding the percentage of animals that achieved complete response, 75% in the treated group and 25% in the control group, and survival rate, 75% in the treated group and 28.6% in the control group. Moreover, although no articles using the combination of cyclophosphamide and 5-fluorouracil were found in the present search, both drugs are supported for use in the treatment of carcinomas in several organs in the canine species (Machado et al., 2019; Marcheti et al., 2011; Menard et al., 2018; Sorenmo, 2003).

Favorable results were found by Marconato et al. (2008), who used gemcitabine and recorded no deaths in the treated group 203 days after the beginning of treatment, compared with 60% mortality in the control group, and found a complete response rate of 76% in the treated group versus 27% in the control group. These findings contrast with the study by Anjos et al. (2016), who used the combination of gemcitabine and carboplatin and observed pulmonary metastasis and 100% mortality, with a mean survival of only 88 days.

In another study using this same drug combination, more promising results were found, with a complete response rate of 13% in dogs with neoplasms in different locations, such as prostatic carcinoma, bronchoalveolar carcinoma, and nasal adenocarcinoma. In this study, 67% of owners reported that the clinical signs attributed to the tumor were no worse than before treatment was instituted, and 33% reported improvement in clinical signs when compared with those observed before treatment initiation (Dominguez et al., 2009). Regarding the chemotherapy protocol, gemcitabine as a single agent is widely studied and used in the treatment of neoplasms in humans. However, in veterinary medicine, studies are scarce and satisfactory effects have not been observed (Rodaski et al., 2008).

There was considerable inhomogeneity among the included studies, resulting from the different drugs, dosages, and intervention times, as well as the type of mastectomy, unilateral or bilateral, tumor stage and histological grade, age, weight, among other individual factors and types of statistical analysis. Therefore, statistical comparison among the presented data was not possible. This study highlights a gap in the literature and, consequently, encourages further investigation of these drugs and treatment regimens, preferably with standardized groups according to specific tumor and clinical configurations.

6 CONCLUSIONS

The synthesis of the studies included in this review indicates that the proposed objective was achieved, since the available evidence points to a clinical benefit associated with the use of conventional chemotherapy in female dogs with mammary tumors.

Most of the evaluated studies reported favorable results, including higher rates of complete or partial remission, improvement in associated clinical signs, and prolonged survival when compared with animals not subjected to adjuvant treatment. Although there is methodological heterogeneity among the studies, particularly regarding the protocols used, histological types, clinical stages, and response assessment criteria, the body of evidence points to a consistent clinical benefit of conventional chemotherapy.

However, the observed limitations reinforce the need for new controlled and standardized studies with a robust methodological design, in order to define more precise protocols according to histological type, tumor staging, combination and number of drugs, dose, administration interval, and clinical setting, whether adjuvant, neoadjuvant, or palliative. These investigations are essential to optimize therapeutic decision-making in canine mammary oncology.

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