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Assessment of the effect of paclitaxel-prednisolone -maropitant neo-adjuvant chemotherapy on metastatic pulmonary lesions associated with canine mammary tumours using thoracic radiography#

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Abstract

Canine mammary tumours associated with pulmonary metastasis assume significant treatment challenges in dogs due to limited protocols and reduced surgical suitability. This study evaluated the therapeutic effects of a neoadjuvant chemotherapy protocol using a dose-dense protocol involving paclitaxel, prednisolone and maropitant in eight dogs. Treatment response was evaluated by monitoring changes in tumour volume and by assessing changes in metastatic lesions through thoracic radiography. Assessment of the protocol based on tumour volume revealed only partial response. Various pulmonary metastatic lesions including fine miliary nodules, pulmonary micronodules, nodules and masses were identified. These lesions showed diverse radiographic outcomes following therapy, such as complete disappearance of select nodules, reduction in size or stabilisation without further progression. Findings in this study suggest potential benefit in selected cases and support longer-duration protocols for improved outcomes.

Keywords: *Canine mammary tumour, pulmonary metastasis, neoadjuvant chemotherapy, thoracic radiography*

Mammary tumours are among the most frequently diagnosed neoplasms in female dogs, accounting for nearly 50 per cent of all canine tumours and occurring more often in females than in males (Mohammed et al., 2011; Nair et al., 2021b). Their development is multifactorial, with age, hormonal status, breed, diet, and obesity identified as major risk factors, particularly in dogs over eight years of age and pure-bred dogs have a high prevalence in developing mammary neoplasms (Nair et al., 2021b; da Silva et al., 2023). Malignancy is more common in old, intact females, especially those that have whelped, while spaying at an ideal age reduces the risk significantly (Sorenmo et al., 2009; Ramesh et al., 2019).

Mammary gland carcinomas are frequently diagnosed in adult female dogs, with around 50 per cent of tumours being malignant, and many exhibiting invasive behaviour and metastasis to lymph nodes and lungs (Marconato et al., 2019). The risk of metastasis increases significantly without surgical intervention (Moulton et al., 1970), with the

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lungs being the most common metastatic site (Brodey et al., 1983). Although computed tomography (CT) is more sensitive for detecting pulmonary metastases, thoracic radiography still offers a high positive predictive value where a CT facility is not available (Lekshmi et al., 2021) and three-view radiographs especially left lateral views are essential for accurate detection (Ober and Barber, 2006).

Neoadjuvant chemotherapy (NAC) is widely used in human breast cancer to downstage tumours, target micro metastases, reduce recurrence and to assess treatment response (Korde et al., 2021). It also improves surgical outcomes by shrinking tumour size, reducing oedema and better defining margins, enhancing resectability in large or invasive neoplasms (Farese et al., 2019; Gustafson and Bailey, 2019). Canine mammary tumours with pulmonary metastasis present a significant challenge in veterinary surgical oncology due to the lack of standardised treatment protocols and the compromised status of affected animals. Therefore, this study was aimed at assessing the effect of neoadjuvant chemotherapy using paclitaxel–prednisolone–maropitant combination on malignant/metastatic mammary tumours in dogs. This article highlights the pulmonary metastatic patterns of different types of malignant/metastatic mammary tumours in dogs and effect of the above said protocol on pulmonary metastatic lesions (Poirier et al., 2004; Cartagena-Albertus et al., 2019; Nair et al., 2021a; Gong et al., 2023; Kuruoglu et al., 2024).

Materials and methods

The study was carried out on clinical cases of canine mammary neoplasms presented to the University Veterinary Hospitals of Kerala Veterinary and Animal Sciences University at Kokkalai and Mannuthy over a ten-month period, from 11/11/2024 to 12/09/2025. Eight dogs having mammary neoplasms with confirmed metastasis were selected based on tumour node metastasis (TNM) staging for the study irrespective of age, breed and sex. Dogs were included in the study if malignancy was confirmed by pulmonary metastasis on thoracic radiographs and fine-needle aspiration cytology of the sentinel lymph node, tumour having poorly defined surgical margin with no prior paclitaxel treatment. Exclusion criteria comprised of absence of distant metastasis, tumour ulceration, markedly abnormal blood parameters or body condition and concurrent treatment for other health conditions. Owners provided informed consent, confirming eligibility and willingness to follow the study protocol. The study adhered to established animal welfare ethical guidelines. Dogs underwent thorough clinical examination and were subjected to neoadjuvant chemotherapy with a dose dense regimen of weekly paclitaxel at the dose rate of 60 mg/m^2 IV (Gong et al., 2023; Kuruoglu et al., 2024) and prednisolone at the dose rate of 1 mg/kg IM (Poirier et al., 2004; Nair et al., 2021a). Maropitant was administered at the dose rate of 1 mg/kg, SC on the day of chemotherapy followed by oral supplementation of maropitant (2mg/kg) for four days (Cartagena-Albertus et al., 2019). This protocol was continued for three weeks or until a significant reduction in tumour size was observed with clearly appreciable surgical margins. The efficacy of neoadjuvant chemotherapy in reducing tumour size and improving surgical margin demarcation was evaluated through weekly inspection, palpation and biometry. Changes during and after treatment were recorded. Patient health status, including physical activity and food intake, was monitored after each chemotherapy session. The effect on metastatic spread was assessed using thoracic radiography in the first and third weeks. Changes in haemato-biochemical parameters were also assessed on the day of presentation and third week of chemotherapy. Statistical analysis of the data on changes in haemato-biochemical parameters and tumour biometry were conducted using SPSS version 24.0. by applying repeated measures of ANOVA.

Thoracic radiography

Thoracic radiography was performed using a 200 mA X-ray machine with a computed radiography system to detect pulmonary metastases using lateral thoracic view, with dorsoventral views added when necessary. The lesions of pulmonary metastases on radiographs were interpreted based on the experimentations made by Weerakody and Niknejad (2019) and Lekshmi et al. (2021) given in Table 1. The distribution was classified as single or multiple, located in regions such as the perihilar, cranioventral, caudodorsal or caudoventral lung fields (Mai et al., 2008). Effect of chemotherapy on pulmonary metastatic lesions were evaluated by first- and third-week thoracic radiography. Lesions observed on the thoracic radiograph were categorised as target lesions if their longest diameter was 20 mm or greater, while those with a smaller diameter were classified as non-target lesions. A maximum of five lesions in a view could be selected as target lesions and the response was evaluated based on the increase or decrease in the sum of the diameters along with disappearance or spread of non-target lesions and

Table 1. Classification of pulmonary metastasis lesions

Early Pulmonary Metastasis (EPM)	Advanced Progressive Pulmonary Metastasis (APPM)
• Initial stage • Fine miliary nodules (<2 mm) • Pulmonary micronodules (2–7 mm) • ≤ 25% of lung parenchyma	• Extensive and progressive • Numerous diffuse micronodules • Pulmonary nodules (7–30 mm) • Large masses (>30 mm) • > 25% of lung parenchyma

the presence or absence of new lesions (Eisenhauer et al.,2009).

Results and discussion

Classification of pulmonary lesions in all the dogs are depicted in Table 2.

The present study evaluated the response of pulmonary metastatic lesions to chemotherapy protocol in dogs, revealing individual variability in treatment outcomes. These findings were consistent with previous studies suggesting that the response of metastatic lung lesions could vary depending on lesion type, disease stage and anatomical location (Baumann et al., 2004; Dennis, 2008; Borgeresi et al., 2023).

In early-stage metastasis, dogs A2 and A4 initially exhibited fine miliary nodules on thoracic radiographs, which partially regressed following chemotherapy (Fig. 2&4). Dog A3, presented with a solitary pulmonary mass measuring 65.98 mm, showed a modest reduction in size to 62.12 mm after treatment (Fig. 3). This aligns with observations by Huth et al. (1980), who reported that preoperative chemotherapy may lead to a range of responses, from significant tumour shrinkage to slower tumour progression and increased doubling time. The mild size reduction in A3, accompanied by increased radiodensity in the dorsoventral view, may reflect post-treatment changes such as central necrosis or fibrotic transformation.

Dog A1 demonstrated extensive pulmonary nodules prior to treatment, which, following chemotherapy, reduced considerably, with disappearance of target lesions and diminished radiographic clarity of residual nodules (Fig. 1). This pattern, also reported by Perez et al. (2000), was indicative of a favourable therapeutic effect. The absence of new metastatic lesions further supported the positive impact of chemotherapy. Such radiographic changes suggested cytoreduction and fibrotic transformation, consistent with descriptions by Spasov et al. (2018) and Lekshmi et al. (2021).

In dog A5, multiple large nodules and masses were identified on both lateral and dorsoventral views (Fig. 5). Following chemotherapy, several non-target lesions were resolved, while target lesions exhibited increased radiodensity and reduced definition, particularly in the caudal lung lobes where some of them got completely resolved. This mixed response characterised by regression of some lesions and stabilisation in others highlighted the complex nature of the chemotherapeutic effects. Notably, radiologic changes such as cavitation and calcification might occur as a result of tumour necrosis or airway obstruction from tumour infiltration, as described by Jung et al. (2004).

Thoracic radiographic findings of Dogs A6, A7 and A8 are depicted in Fig. 6,7 and 8 respectively. These dogs could not complete the treatment and died due to advanced metastasis complicated by other comorbidities.

In the present study, neoadjuvant chemotherapy was utilised to reduce tumour size, alleviate paraneoplastic oedema, improve surgical margin definition and facilitate surgical decision-making, while simultaneously addressing pulmonary metastasis, as supported by earlier reports from Chun et al. (2007), Gustafson and Bailey (2019) and Nair (2021). Dose-dense chemotherapy, which involves administering standard drug doses at shorter intervals, has been shown to enhance therapeutic efficacy without

Table 2. Classification of pulmonary metastatic lesions and histopathology findings

Sl. No	Animal No.	Distant metastasis-pulmonary	Thoracic radiograph findings	TNM Stage of tumour	Histopathology
1	A_1 (two masses)	Extensive micronodules and pulmonary nodules with reticulonodular pattern	APPM	V	Carcinosarcoma, Tubular carcinoma
2	A_2	Presence of miliary nodules with reticulonodular pattern	EPM	V	Fibrosarcoma
3	A_3	Single pulmonary mass at caudo-dorsal area of lung parenchyma	APPM	V	Solid carcinoma
4	A_4	Presence of miliary nodules with interstitial pattern at caudo-dorsal area of lung parenchyma	EPM	V	Carcinoma mixed type
5	A_5	Extensive pulmonary masses	APPM	V	Papillary carcinoma
6	A_6	Diffused pulmonary mass at perihilar region	APPM	V	Death
7	A_7	Presence of miliary nodules with interstitial pattern at caudodorsal lung parenchyma	EPM	V	Death
8	A_8	Pulmonary micro nodules with interstitial pattern at perihilar and caudal areas of lung parenchyma	APPM	V	Cystic papillary carcinoma (Post mortem sample)

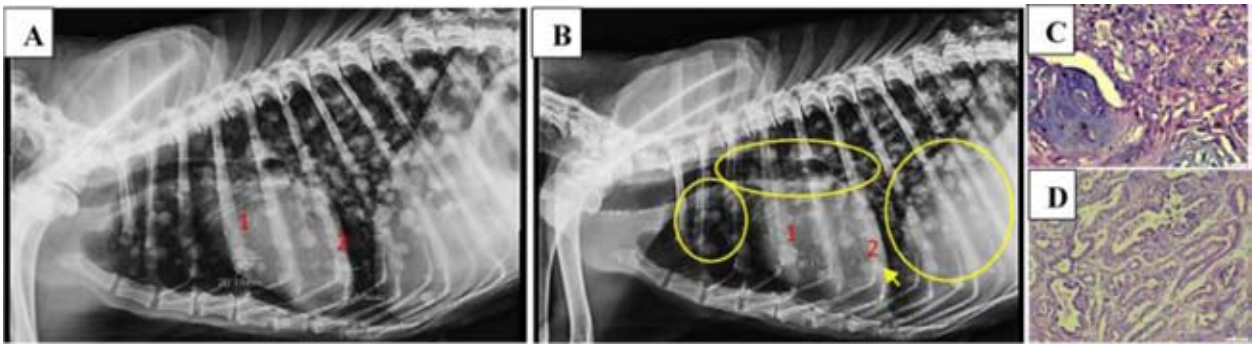

Fig. 1. (Dog A_1, lateral view): A) On presentation- extensive pulmonary nodules and micronodules with reticulonodular pattern. Two target lesions (1) at the 4th rib costochondral junction measuring 20.49 mm and (2) located caudally at costochondral junction of 6th rib 22.68 mm. B) On third week – target lesion (1) showing slight reduction in size as 18.06 mm and (2) disappearance of lesion (marked by arrow). There was resolution and size reduction in non-target lesions along with loss of radiographic definition. No new lesions could be observed (more evident in rounded regions). C) Carcinosarcoma (H&E, 400x) - Malignant basophilic chondroid matrix and an uneven arrangement of neoplastic epithelial cells. D) Tubular carcinoma (H&E, 400x) - Irregular tubules lined by atypical cuboidal to columnar epithelial cells with vesicular nuclei.

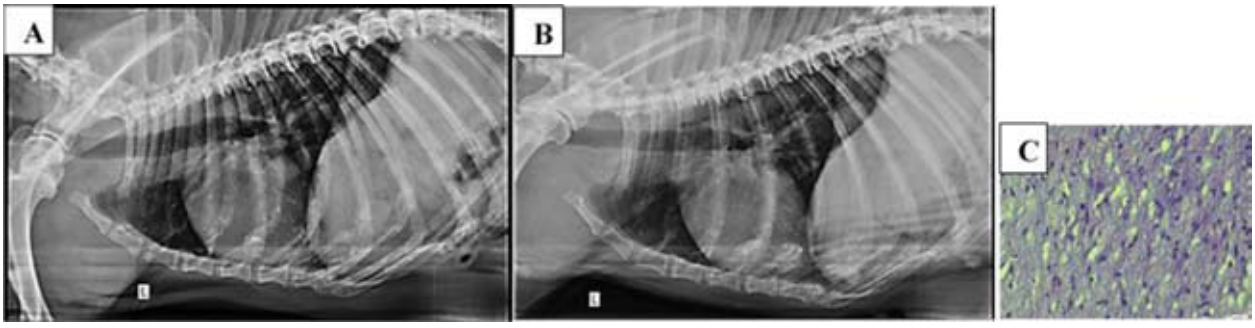

Fig. 2. (Dog A_2, Lateral view): A) On presentation- presence of prominent miliary nodules with reticulonodular pattern B) Third week – Disappearance of some lesions along with reduced radiographic clarity of remaining could be observed. Reduced bulkiness of nodules at perihilar region. C) Fibrosarcoma (H&E, 400x) - Malignant proliferation of fibrous connective tissue in interwoven pattern

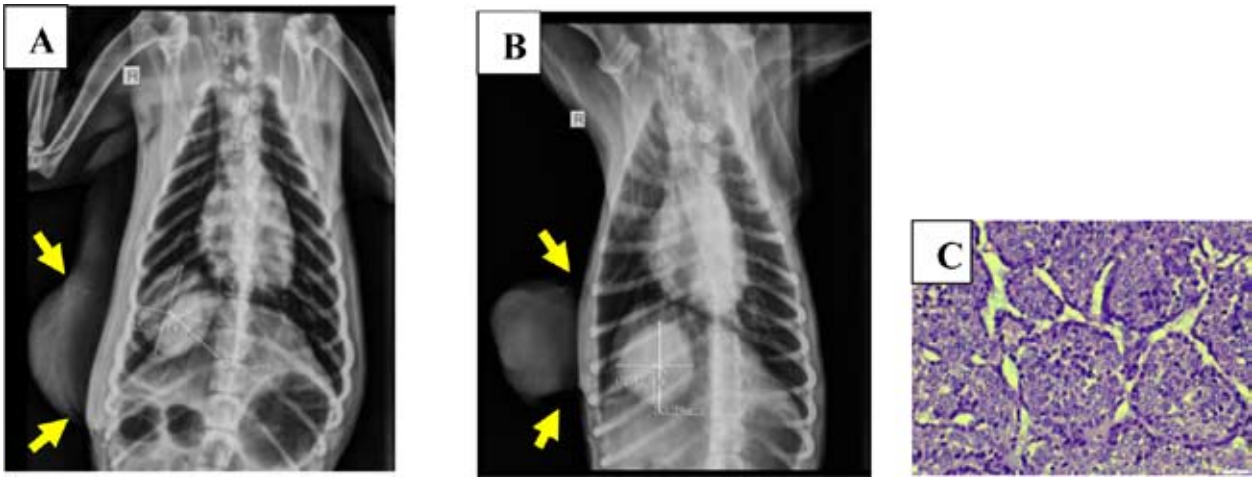

Fig. 3. (Dog A_3, dorso-ventral view): A) A solitary pulmonary mass measuring diameter 65.98 mm at the caudo dorsal area. Mammary tumour with a wide base firmly adhered to the body is also visible (arrow) B) Slight reduction in diameter to 62.12 mm with increased radiodensity indicating calcification. Mammary tumour is seen with good surgical margin and loosely attached to the body(arrow). C) Solid carcinoma (H&E, 400x) - Pleomorphic epithelial sheets of cells arranged in a solid pattern without lumen.

increasing toxicity (Citron, 2008), with low-dose paclitaxel-based regimens improving antitumour immunity, survival and tolerability in both human and canine malignancies (Chang et al., 2012; Burotto et al., 2019; Poirier et al., 2004; Kuruoglu et al., 2024). Paclitaxel was found to inhibit the growth and spread of breast cancer cells by suppressing cofilin-1 activity regulated by Aurora kinase, indicating that it could serve as an effective therapeutic agent for treating human breast cancer (Zhang et al., 2018). The neoadjuvant use of corticosteroids such as prednisolone has demonstrated significant clinical benefits in canine tumours, including tumour size reduction, resolution of

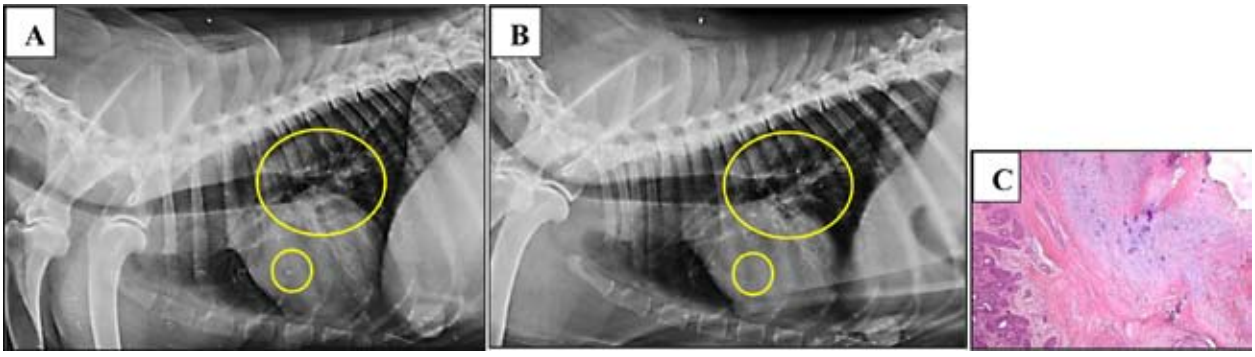

Fig. 4. (Dog A_4, Lateral view): A) Presence of prominent miliary nodules at the perihilar and middle portion of lung parenchyma. B) Reduced radiographic quality of nodules along with disappearance of some nodules. C) Carcinoma arising in benign mixed tumour (H&E, 100x)- Malignant epithelial component and benign mesenchymal component.

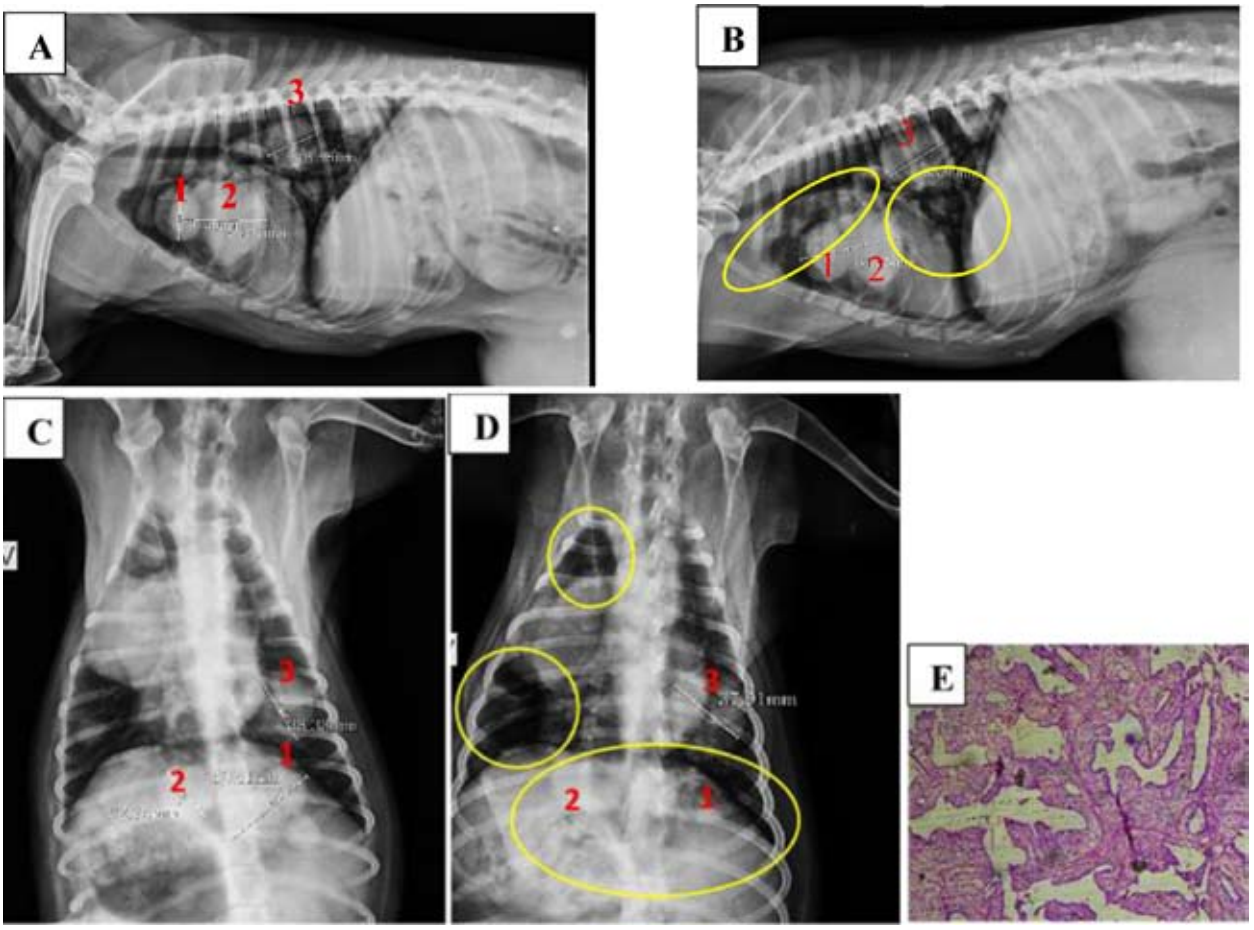

Fig. 5. (Dog A_5, Lateral view and dorso-ventral view): A) On presentation – lateral view revealed diffuse pulmonary masses and pulmonary nodules especially more concentrated at cranioventral and caudodorsal lung parenchyma. Target lesions (1), (2), (3) measuring diameter 36.50 mm, 56.37mm and 34.98mm respectively. B) Third week – lateral view- coalescence of target lesion (1) and (2) with a total diameter 61.65mm, lesion (3) showed increase in diameter to 38.99mm with loss of radiographic definition, Disappearance and reduction in size of nodules are visible at cranioventral and caudoventral lung parenchyma (rounded). C) On presentation- dorsoventral – Target lesions (1), (2), and (3) measuring 50.41mm, 32.75mm and 38.33mm respectively. D) Third week- dorsoventral- complete remission of target lesion (1) and (2) along with some non-target lesions in the caudal lobes of lung parenchyma. Lesion (3) showed reduction in diameter to 37.91mm with loss of radiographic definition. Lesions at the cranial and middle lobe area disappeared(rounded). E) Papillary carcinoma (H&E, 100x) Frond like papillary projections with fibrovascular cores lined by neoplastic epithelium.

paraneoplastic oedema and improved surgical margins (Stanclift and Gilson, 2008; Linde et al., 2021; Nair, 2021). Additionally, NK-1 receptor antagonists such as maropitant exhibit direct antitumour activity and enhance chemotherapy tolerability by suppression of release of substance P, with evidence of antiproliferative effects and mitigation of chemotherapy-induced gastrointestinal toxicity when combined with paclitaxel (Munoz et al., 2015; Borrego et al., 2016; Cartagena-Albertus et al., 2019). Collectively, these findings provided a strong rationale for

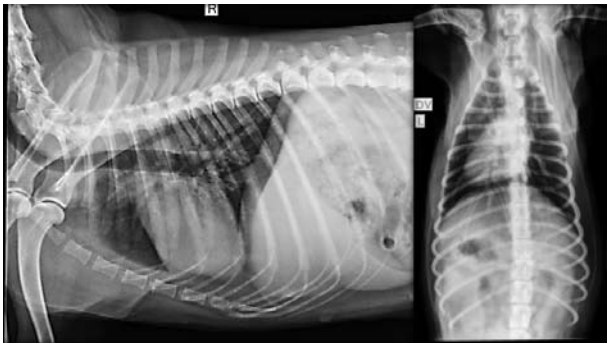

Fig. 6. (Dog A_6, Lateral and dorsoventral view): Diffused pulmonary mass at perihilar region

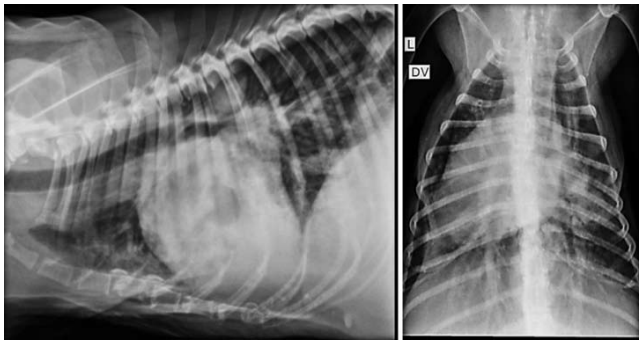

Fig. 7. (Dog A_8, Lateral and dorsoventral view): Presence of miliary nodules with interstitial pattern at caudodorsal lung parenchyma

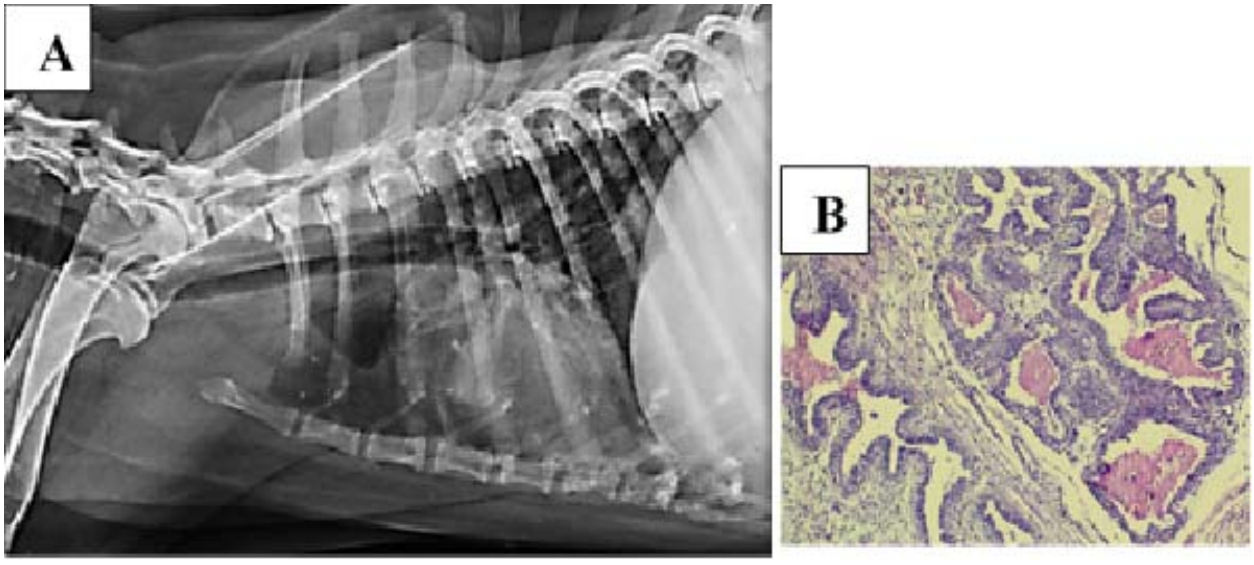

Fig. 8. (Dog A_7, Lateral view): A) Pulmonary micro nodules with interstitial pattern at perihilar and caudal areas of lung parenchyma. B) Cystic papillary carcinoma (H&E, 400x) - Papillary proliferations within cystic dilated ducts and cuboidal to columnar tumour cells

the selected neoadjuvant chemotherapy protocol in the management of metastatic canine mammary neoplasms.

Gong et al. (2023) reported that weekly administration of Paclitaxel at 60 mg/m^2 for 12 weeks in humans improved survival, reduced toxicity, and enhanced quality of life, while Kuruoglu et al. (2024) found the same regimen to be effective, safe, and well-tolerated in dogs with stage II–IV malignant mammary tumours when combined with appropriate premedication. Collectively, these findings support that a prolonged weekly paclitaxel protocol offers sustained therapeutic benefits with minimal adverse effects, underscoring its value as a long-term treatment strategy.

Conclusion

The study demonstrated that neoadjuvant chemotherapy using a combination of paclitaxel, prednisolone and maropitant was generally well tolerated in dogs with mammary tumours complicated by pulmonary metastasis. Radiographic evaluation of pulmonary metastases also revealed diverse treatment responses, ranging from partial regression of lesion and stabilisation to complete resolution in some areas, particularly in early-stage or solitary lesions. These findings underscore the need for longer treatment durations and individualised assessment based on histopathological and radiological characteristics to optimise the therapeutic impact of neoadjuvant chemotherapy in canine mammary tumours with pulmonary involvement.

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