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Tumour Node Metastasis Staging as Prognostic Indicator for Surgical Decision-making Tool in Canine Mammary and Superficial Neoplasms: A Survival Analysis Study

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ABSTRACT

Background: Streamlining surgical approaches for various neoplasms in dogs utilising tumour node metastasis (TNM) staging and assessment of quality of life (QOL) of a cancer patient has always been a challenge in veterinary surgical oncology. The study was intended to assess TNM staging as a prognostic indicator and basis of surgical decision in canine mammary and superficial neoplasms.

Methods: Thirty six cases of canine neoplasms were studied in three groups based on TNM staging of neoplasms. The histopathology of the excisional biopsy samples were correlated with TNM stages and the response to treatment was assessed using Modified Karnofsky performance scales in dogs and response evaluation criteria in solid tumours (RECIST). The survival status of the animals was compared by Kaplan Meier analysis and results were interpreted using the log rank test.

Result: The TNM staging formed the basis for surgical decision making and direct correlation was detected between TNM staging and histopathological grading of neoplasms. The mean survival time was found more in alone surgical group with TNM stages T_A N_{0-1} M_0, compared to neoadjuvant therapy (T_A N_1 M_{0-1}) and adjuvant therapy groups (T_A N_1 M_1).

Key words: Canine mammary neoplasms, Superficial neoplasms, Surgical decision making, Survival analysis, Tumour node metastasis staging.

INTRODUCTION

In the past few decades, upraise in the canine cancer incidence were recorded with more than 50 per cent older dog population developing cancer and one-fourth of the reported populations eventually dying from it (Lewis *et al.*, 2018). The mainstay treatment option of surgery for cancer got fortified by adopting multimodal approaches like neoadjuvant and adjuvant chemotherapy to combat the deadly disease effectively at an earlier stage. Streamlining surgical approaches to various neoplasms in dogs utilising TNM staging and assessment of quality of life (QOL) of a cancer patient had always been a challenge in veterinary surgical oncology (Kudnig and Seguin, 2012). The present study was aimed to explore the Tumour Node Metastasis (TNM) staging as a prognostic indicator and basis of surgical decision making. The study also envisaged correlation of the TNM staging with the histopathological findings and the survival status of the tumours. Our hypothesis was that there existed significant difference in the overall survival distribution between the different severity of neoplasms treated with surgery alone, neoadjuvant chemotherapy followed by surgery and then surgery followed by adjuvant chemotherapy protocols.

MATERIALS AND METHODS

Thirty six cases of neoplasms in dogs presented to University Veterinary Hospitals of Kerala Veterinary and Animal Sciences University, including 18 mammary and 18 superficial neoplasms during a period of three years from 2018-2020 were selected based on the TNM staging of mammary neoplasms (Sorenmo *et al.*, 2019) and TNM staging of skin and subcutaneous neoplasms (Hauck, 2013). The selected animals were studied in three groups of twelve animals, with each group consisting of six cases of mammary neoplasms and six cases of superficial neoplasms.

Group I-(Surgery alone). These animals serially numbered as I_1, I_2, I_3, I_4, I_5, I_6, I_7, I_8, I_9, I_{10}, I_{11} and I_{12} had localized tumour with well-defined surgical margin and TNM stages-T_A N_{0-1} M_0, which were subjected to curative-intent surgery alone with minimum two cm wide margin radical resections including deep fascial planes.

Group II-(Neo- adjuvant chemotherapy followed by surgery) consisted of twelve animals serially numbered as

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II_1, II_2, II_3, II_4, II_5, II_6, II_7, II_8, II_9, II_{10}, II_{11} and II_{12} with tumours having ill-defined surgical margins with inflammatory changes and TNM stages-$T_A N_1 M_{0-1}$.

Group III-(Surgery followed by adjuvant chemotherapy) consisted of twelve animals serially numbered as III_1, III_2, III_3, III_4, III_5, III_6, III_7, III_8, III_9, III_{10}, III_{11} and III_{12} with presence of malignant features as evident in TNM stages-$T_A N_1 M_1$ (*viz.*, neoplasms of any size with poorly differentiated margins, metastatic changes in lymph node and confirmed pulmonary metastasis).

The neoadjuvant and adjuvant chemotherapies in group II and III were carried out using vinblastine-prednisolone (VBL-P) protocol (vinblastine at 2 mg/ m intravenously and prednisolone at 1 mg/kg body weight intramuscularly) and doxorubicin prednisolone (DOX-P) protocol (doxorubicin at 18 mg/m^2 and prednisolone at 1 mg/kg bodyweight intramuscularly) in biweekly intervals for two cycles.

Suitable surgical options of lumpectomy, a single mastectomy, radical mastectomy, regional mastectomy, unilateral or bilateral mastectomy, radical en-bloc curative-intent surgery, wide margin excision along with the normal tissue, marginal excision just outside pseudocapsule and intralesional debulking excision were performed on case to case basis as per Thomson and Britt (2012) and Withrow (2007). Histopathological analysis and grading of all neoplasms were done as per Goldschmidt and Goldschmidt (2017) and Dennis *et al.* (2011).

Response evaluation was assessed by modified karnofsky performance scales (MKP) adapted for dogs (Morrison, 2002) and response evaluation criteria in solid tumours (RECIST) guidelines (Eisenhauer *et al.*, 2009) on third month and sixth month observations. The observations in all three groups were compared and results were statistically analysed using SPSS version 24. The survival status of the animals after treatment was compared by plotting survival curve using Kaplan Meier analysis and results were interpreted using the log rank test.

RESULTS AND DISCUSSION

TNM staging

The details of the mammary and superficial neoplasms studied in three groups and the TNM staging are depicted in Fig 1, Fig 2 and Table 1. Animals of group I had normal sentinel lymph nodes with very less reactive changes and group II and III animals had reactive to metastatic changes in the lymph node. The physical examination findings of lymph nodes were in accordance with Tuohy *et al.* (2009) who reported the importance of routine sentinel lymph node evaluation as the most important step in TNM staging and clinical assessment aiding in surgical decision making in

Fig 1: Showing details of the mammary neoplasms studied in three groups.

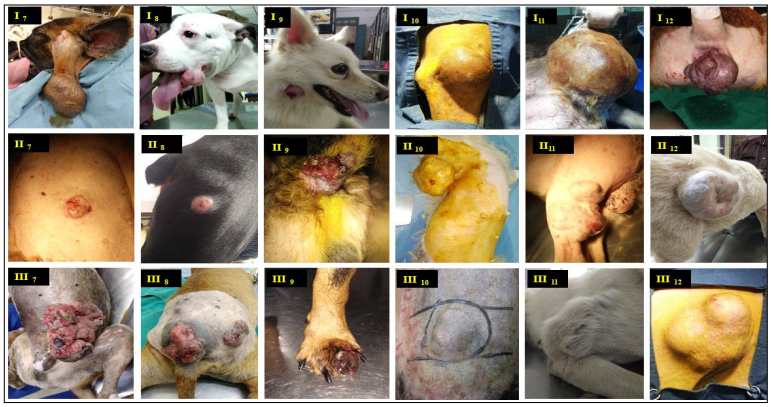

Fig 2: Showing details of superficial neoplasms studied in three groups.

Table 1: TNM staging and Surgical decision making along with correlation by histopathological analysis and response evaluation.

	Animal	TNM Staging	Histopathology of neoplasms	Surgical procedure	RECIST (months)		MKP (months)		DO	Status
					3	6	3	6		
Group-I (Surgery alone)	I 1	$T_2 N_0 M_0$	Simple adenoma	Lumpectomy	CR	CR	0	0	18	Alive
	I 2	$T_3 N_0 M_0$	Intraductal Papillary Adenoma	Lumpectomy	CR	CR	0	0	17	Alive
	I 3	$T_3 N_0 M_0$	Lipoma	Lumpectomy	CR	CR	0	0	8	Alive
	I 4	$T_3 N_0 M_0$	Fibroadenoma	Single mastectomy	CR	CR	0	0	10	Alive
	I 5	$T_3 N_0 M_0$	Fibroadenoma	Regional mastectomy	CR	IR	0	0	5	Alive
	I 6	$T_3 N_0 M_0$	Benign Mixed Tumour	Regional mastectomy	CR	CR	0	0	18	Alive
	I 7	$T_3 N_0 M_0$	Apocrine adenoma	Radical curative intent surgery	CR	CR	0	0	8	Alive
	I 8	$T_2 N_0 M_0$	Fibrolipoma	Radical curative intent surgery	CR	CR	0	0	13	Alive
	I 9	$T_2 N_0 M_0$	Tricho blastoma	Marginal excision	CR	CR	0	0	12	Alive
	I 10	$T_3 N_0 M_0$	Fibroma	Marginal excision	CR	CR	0	0	13	Alive
	I 11	$T_3 N_{1a} M_0$	Lipoma	Intralesional debulking	CR	CR	0	0	11	Dead
	I 12	$T_3 N_0 M_0$	Perianal hepatoid adenoma	Radical curative intent surgery	CR	CR	0	0	11	Alive
Group-II (Neoadjuvant chemotherapy followed by Surgery)	II 1	$T_3 N_1 M_1$	Inflammatory carcinoma	Regional mastectomy	IR	IR	1	2	7	Dead
	II 2	$T_3 N_1 M_1$	Carcinoma-Intraductal Papillary	Lumpectomy	CR	CR	0	0	9	Alive
	II 3	$T_4 N_1 M_1$	Comedocarcinoma	Regional mastectomy	CR	IR	0	0	11	Dead
	II 4	$T_3 N_1 M_1$	Ductal carcinoma	Single mastectomy	CR	CR	0	0	13	Dead
	II 5	$T_3 N_1 M_1$	Malignant mixed tumour	Single mastectomy	CR	CR	0	0	11	Alive
	II 6	$T_3 N_1 M_1$	Adeno carcinoma grade -III	Bilateral thoracic mastectomy	CR	CR	0	0	8	Alive
	II 7	$T_2 N_{1a} M_0$	Tricho lemmoma desmoplastic	Wide margin excision	CR	CR	0	0	9	Alive
	II 8	$T_2 N_{1a} M_0$	Mast Cell tumour	Wide margin excision	CR	CR	0	0	11	Alive
	II 9	$T_3 N_{1b} M_1$	Perianal adenocarcinoma	Marginal excision	CR	CR	0	0	11	Alive
	II 10	$T_3 N_{1b} M_1$	Liposarcoma	Radical resection	CR	CR	0	0	10	Alive
	II 11	$T_3 N_{1b} M_1$	Myxosarcoma	Intralesional debulking	IR	IR	0	0	9	Dead
	II 12	$T_3 N_{1b} M_1$	Sebaceous gland adenocarcinoma	Wide margin excision	CR	CR	0	0	11	Alive
Group-III (Surgery followed by adjuvant chemotherapy)	III 1	$T_3 N_1 M_1$	Adenocarcinoma complex	Regional mastectomy	CR	CR	0	0	10	Alive
	III 2	$T_3 N_1 M_1$	Adenocarcinoma-Papillary Cystic	Single mastectomy	CR	CR	0	0	7	Alive
	III 3	$T_4 N_1 M_1$	Complex carcinoma	Single mastectomy	CR	CR	0	0	12	Alive
	III 4	$T_3 N_1 M_1$	Carcinoma-Intraductal Papillary	Regional mastectomy	CR	CR	0	0	8	Alive
	III 5	$T_4 N_1 M_1$	Invasive carcinoma mammary gland	Regional mastectomy	PD	IR	3	4	4	Dead
	III 6	$T_4 N_1 M_1$	Anaplastic Carcinoma	Regional mastectomy	PD	IR	3	4	4	Dead
	III 7	$T_3 N_{1b} M_1$	Transmissible Venereal Tumour	Radical curative intent surgery	CR	CR	0	0	12	Alive
	III 8	$T_3 N_2 M_1$	Trichoblastic carcinoma	Wide margin excision	CR	PD	0	0	6	Alive
	III 9	$T_3 N_2 M_1$	Osteogenic Melanoma	Radical curative intent surgery	CR	IR	1	2	8	Dead
	III 10	$T_4 N_3 M_1$	Carcinosarcoma	Wide margin excision	CR	IR	0	2	10	Dead
	III 11	$T_4 N_3 M_1$	Synoviosarcoma	Intralesional debulking	IR	IR	1	3	9	Dead
	III 12	$T_4 N_3 M_1$	Fibrosarcoma	Wide margin excision	CR	IR	0	0	3	Alive

Response Evaluation Criteria In Solid Tumours (RECIST)

1. Complete response (CR): Disappearance of all target lesions. 100% resolution of neoplasm. 2. Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions or volume taking as reference the baseline sum diameters or initial volume. 3. Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. 4. Progressive Disease (PD): At least a 20% increase in the sum of diameters or volume of target lesions, taking as reference the smallest sum on study. 5. Invaluable for a response (IR): specific reasons (for example early death, malignant disease; early death, toxicity; tumour assessments not repeated/ incomplete; other).

Modified Karnofsky performance status (MKP)

Grade 0: Fully active without evidence of dyspnea, tiredness or emaciation, able to perform at the pre-disease level. Grade 1: Decreased activity from pre-disease level, but able to function as an acceptable pet /or slight emaciation. Grade 2: Ambulatory only in eating sleeping and consistently defecating and urinating in acceptable areas. Grade 3: Must be force-fed. Unable to confine urination and defecation to acceptable areas. Grade 4: Dead.

DO- Days observed in the study / Status of the animal: 0= Alive, 1= Dead

veterinary oncology. In the present study, early pulmonary metastasis signs were characterized based on the size in ascending order form by fine dots of miliary nodules, pulmonary micronodules, pulmonary nodule, pulmonary mass, multiple solid nodules, single solid mass, cavitary nodules and single cavity mass. Similar classifications were followed by Spasov *et al.* (2018) and Weerakkody (2019). The animals of group II had early metastatic changes and were subjected to neoadjuvant chemotherapy. This was in accordance with Gustafson and Bailey (2019) who recommended neoadjuvant chemotherapy for down staging cancer. The neoadjuvant chemotherapy was also intended for preventing the tumour spread and defining the surgical margin for resection. Similar recommendations were given by Chun *et al.* (2007). The animals selected in the group III had advanced pulmonary metastasis and warranted adjuvant chemotherapy after marginal excision of the neoplasms. Similar recommendations were given by Farese *et al.* (2019).

Histopathological findings

The details of histopathological analysis and grading of neoplasm are depicted in Table 1. In group I animals, TNM staging ($T_A N_{0-1} M_0$) were correlated with benign neoplasms like adenoma, lipoma and benign mixed tumour. Group II ($T_A N_{0-1} M_{0-1}$) and group III animals ($T_A N_{0-1} M_1$) were identified as having neoplasms with aggressive histopathological features of inflammatory carcinoma, intraductal papillary carcinoma, comedocarcinoma, ductal carcinoma, malignant mixed tumour neoplasms, anaplastic carcinoma, osteogenic melanoma, carcinosarcoma, synoviosarcoma and fibrosarcoma.

Response evaluation

Response Evaluation Criteria In Solid Tumours (RECIST) and Modified Karnofsky performance status used to study response evaluation assessment in third and sixth month are enlisted in Table 1. All the cases of group I showed RECIST parameter of CR (complete response) characterized by the disappearance of all target lesions and 100 per cent resolution of neoplasm as observed in the third and sixth-month review with Modified Karnofsky performance status scale 0. Recurrence with advanced pulmonary metastasis despite multimodal therapy of adjuvant chemotherapy was noticed in high grade malignant neoplasms. In Group II and III malignant neoplasms showed invaluable response (IR) to treatment and animals with advanced pulmonary metastasis died on eighth and tenth month respectively. Progressive disease with increase in pulmonary metastasis were reported in invasive carcinoma mammary gland, Anaplastic carcinoma and Trichoblastic carcinoma among Group III animals. These observations were found in accordance with Parachini *et al.*, 2019 who reported that pulmonary metastasis of cutaneous and subcutaneous malignant neoplasms could be considered as a terminal event in dogs. The Kaplan Meier survival curve and log-rank test were used to interpret the results and assess the QOL of the patients after the treatment. The details are depicted in Fig 3. The log-rank test tested the null hypothesis that there existed non significant difference in the overall survival distribution between the groups. In the present study χ^2 value was 9.061, $p<0.05$, therefore, the null hypothesis was rejected indicating that there existed a significant difference between survival distributions for the three groups. The severity of the cases on presentation and the malignancy were more in group III and was correlated with a lower mean survival time of 9.38±0.92 months in group III ($T_A N_1 M_1$), compared to 12.194±0.65 months in group II ($T_A N_1 M_{0-1}$) and 17.12±0.82 months in Group-I. Previous studies by Karayannopoulou *et al.* (2001) and Yamagami *et al.* (1996) also reported lower survival rates in dogs with regional lymph node metastasis than those without lymph node involvement and worst prognosis with distant metastasis. Neoadjuvant chemotherapy or primary chemotherapy selected based on the TNM staging served to downstage a chemo sensitive neoplasm (cytoreduction) before performing a definitive surgical therapy. Similar findings were reported by (Chun *et al.,* 2007), Gustafson and Bailey (2019). The adjuvant chemotherapy acted as an adjunct treatment modality in case of extensive neoplasms with stages $T_A N_1 M_{0-1}$ delaying the recurrence after incomplete surgical excision and also to slow down the distant metastasis. Brunnberg *et al.* (2016) also reported similar findings. Recurrence with advanced pulmonary metastasis despite multimodal therapy of adjuvant chemotherapy was noticed in animals with invasive ductal carcinoma, soft tissue sarcoma (STS) and other malignant superficial neoplasms like osteogenic melanoma, carcinosarcoma, synoviosarcoma and fibro sarcoma. These findings were in accordance with Tran *et al.* (2016) and Bray, (2016).

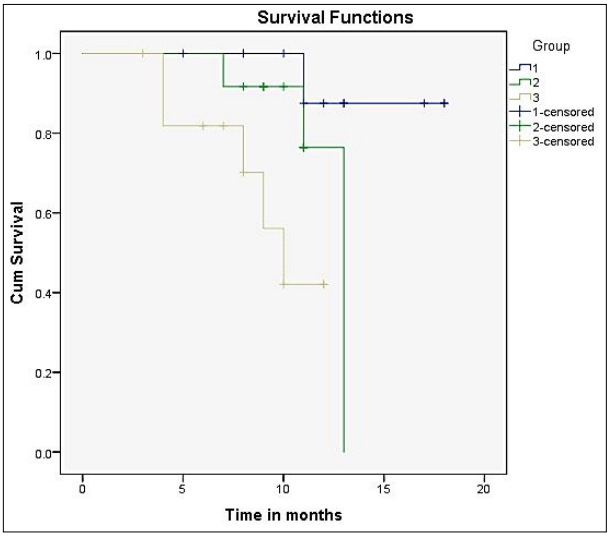

Fig 3: Showing survival function plot comparing three groups.

CONCLUSION

From the present study, it can be concluded that TNM staging of neoplasm can form the basis of surgical planning and act as valid prognostic indicator in canine mammary and

superficial neoplasms. Also the survival status of animals directly depended on the TNM staging and severity detected by histopathological findings.

Ethics approval

Present study followed standard therapeutic and surgical procedures on clinical cases of neoplasms in dogs in accordance with relevant guidelines and regulations. Ethics approval was taken from the university institutional animal ethics committee and as per academic and technical sanction vide Kerala Veterinary and Animal Sciences University order No. KVASU/DAR/Acad/ A2/14528 /2017 dated 06-02-2019.

Competing interests

The authors declare that they have no conflicts of interest.

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