UNIVERSITI PUTRA MALAYSIA

CANCER CHEMOTHERAPY PRACTICE IN DOGS AND CATS IN UNIVERSITY VETERINARY HOSPITAL, UPM: A RETROSPECTIVE STUDY FROM 2013 TO 2017

EVELYN TIE YII YII

Ip
FPV 2018 22

CANCER CHEMOTHERAPY PRACTICE IN DOGS AND CATS IN UNIVERSITY VETERINARY HOSPITAL, UPM: A RETROSPECTIVE STUDY FROM 2013 TO 2017

EVELYN TIE YII YII

A project paper submitted to the

Faculty of Veterinary Medicine, Universiti Putra Malaysia

In partial fulfilment of the requirement for the

DEGREE OF DOCTOR OF VETERINARY MEDICINE

Universiti Putra Malaysia

Serdang, Selangor Darul Ehsan.

MARCH 2018

It is hereby certified that we have read this project paper entitled "**CANCER CHEMOTHERAPY PRACTICE IN DOGS AND CATS IN UNIVERSITY VETERINARY HOSPITAL, UPM: A RETROSPECTIVE STUDY FROM 2013 TO 2017**" by Evelyn Tie Yii Yii and in our opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfilment of the requirement for the course VPD 4999 – Final Year Project.

ASSOC. PROF. DR. GAYATHRI THEVI SELVARAJAH
D.V.M (UPM), PhD (Netherlands)
Senior Lecturer
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Supervisor)

DR. THONG HOE FOONG
D.V.M. (UPM)
Veterinary Officer
University Veterinary Hospital
Universiti Putra Malaysia
(Co-Supervisor)

This project is special dedicated to:

All veterinarians

My family and friends who always beside me

Dogs and cats we so value.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my project supervisor, Assoc. Prof. Dr. Gayathri Thevi Selvarajah for the time, wisdom, expertise, and guidance that she had granted me throughout the duration of this project, and my studies at the faculty.

I also would like to thank my project co-supervisor, Dr. Thong Hoe Foong for his assistance, unwavering support and encouragement to improve this project.

Besides, I would like to thank assistant veterinary officer, Ms. Aisas and staff of University Veterinary Hospital (UVH), UPM: Mr. Didi and Ms. Mageswari for always lending me a helping hand when retrieving case files and collecting data.

A special thank you to my final year project gang including Xhirryne Yong, Lee Jie Min, Set Thing, Joy Xine, Samuel and Ikhwan who collecting data together with me throughout the duration of final year project. I also would like to thank all my classmates of DVM 2018 who assisted my directly or indirectly.

Last but not least, my most heartfelt gratitude to my family, especially my parents for their support throughout my studies.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

ABSTRAK

Abstrak daripada kertas projek yang dikemukkakn kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripda keperluan kursus VPD 4999 – Projek Ilmiah Tahun Akhir.

EVELYN TIE YII YII

Penyelia: Prof. Madya Dr. Gayathri Thevi Selvarajah

Penyelia bersama: Dr. Thong Hoe Foong

AMALAN KEMOTERAPI KANSER PADA ANJING DAN KUCING DI HOSPITAL VETERINAR UNIVERSITI (UVH), UPM: SATU KAJIAN RETROSPEKTIF DARI TAHUN 2013–2017

Kebanyakan amalan veterinar haiwan kecil yang menyediakan amalan kemoterapi berada di kawasan Selangor, dan Hospital Veterinar Universiti (UVH) adalah salah satu daripadanya (Loh *et al.,* 2014). Maklumat mengenai amalan kemoterapi di UVH, UPM belum dinilai secara retrospektif. Objektif kajian ini adalah (1) menentukan bilangan dan jenis kanser pada anjing dan kucing yang dirawat dengan kemoterapi sitotoksik, (2) menentukan jenis ubat, kekerapan penghantaran dan kesan sampingan yang dilaporkan berdasarkan pelbagai ubat sitotoksik yang dihantar dan (3) untuk menentukan kos yang dikenakan dalam protokol kemoterapi pelbagai kanser dalam anjing dan kucing yang dirawat di UVH antara tahun 2013 dan 2017. Kajian ini dijalankan secara retrospektif

dengan mengkaji buku log kes yang terdapat dalam Bilik Kemoterapi dan rekod dalam UVH. Data yang dikumpulkan tertakluk kepada analisis deskriptif menggunakan SPSS versi 20.0. Ujian sebenar Fisher dan analisis Kaplan-Meier telah dilakukan di mana perlu. Nilai $P<0.05$ dianggapkan tererti statistik pada selang keyakinan 95%. Sebanyak 113 haiwan menerima kemoterapi sitotoksik untuk kanser dalam UVH (83 anjing dan 30 kucing). Sebanyak 429 dos (78%) ubat sitotoksik suntikan diberikan kepada anjing dan 123 dos (22%) kepada kucing. Kanser yang paling biasa dirawat pada anjing adalah tumor venereal boleh pindah manakala limfoma pada kucing. Vinkristin adalah ubat kemoterapi anti-kanser sitotoksik suntikan yang paling kerap digunakan dengan jumlah 474 dos selama lima tahun. Kesan sampingan kemoterapi dalam kedua-dua anjing dan kucing adalah anemia dan thrombocytopenia, dengan satu tindak balas tisu ubat extravasation. Kos purata untuk setiap rawatan kemoterapi tanpa mengira spesies adalah RM 247. Kajian ini menunjukkan bilangan ubat sitotoksik yang diberikan kepada anjing adalah paling tinggi berbanding dengan kucing dan bagaimanapun langkah keselamatan diperlukan oleh semua pengendalian kakitangan yang bekerja dengan kemoterapi sitotoksik.

Kata Kunci: Kemoterapi kanser, UVH, tumor venereal boleh pindah, limfoma, vinkristin, anaemia, thrombocytopenia

ABSTRACT

An abstract of the project paper presented to Faculty of Veterinary Medicine in partial fulfilment of the course VPD 4999 – Final Year Project.

EVELYN TIE YII YII

Supervisor: Assoc. Prof. Dr. Gayathri Thevi Selvarajah

Co-Supervisor: Dr. Thong Hoe Foong

CANCER CHEMOTHERAPY PRACTICE IN DOGS AND CATS IN UNIVERSITY VETERINARY HOSPITAL, UPM: A RETROSPECTIVE STUDY FROM 2013 TO 2017

Most of small animal veterinary practices which provide chemotherapy are in Selangor area, and University Veterinary Hospital (UVH) is one of them. Information on chemotherapy practice in UVH, UPM has not been evaluated retrospectively. The objectives of this study were (1) to determine the number and types of cancer in dogs and cats treated with cytotoxic chemotherapy, (2) to determine the drug types, frequency of delivery and reported side effects based on the various cytotoxic drugs delivered and (3) to determine the costs incurred in chemotherapy protocols of various cancers in dogs and cats presented to UVH between 2013 and 2017. The study was conducted retrospectively by reviewing case log books available in the Chemotherapy Room and records in UVH. The data collected was subjected to descriptive analysis using SPSS version 20.0. Fisher's

exact test and Kaplan-Meier analysis were performed where necessary. P-value <0.05 was considered statistically significant at 95% confidence interval. A total of 113 animals received cytotoxic chemotherapy for cancer in UVH (83 dogs and 30 cats). A total of 429 doses (78%) of injectable cytotoxic drugs were delivered to dogs and 123 doses (22%) to cats. The most common cancer treated in dogs was transmissible venereal tumour while lymphoma in cats. Vincristine is the most frequently used injectable cytotoxic anti-cancer chemotherapy drug with a total of 474 doses delivered over the five years. Common side effects of chemotherapy in both dogs and cats were anaemia and thrombocytopenia, with a single case of drug extravasation tissue reaction. The average cost for chemotherapy delivery per visit regardless of species was RM 247. This study revealed that high number of cytotoxic drugs are delivered to dogs compared to cats and nevertheless the safety precautions are necessary for all staff handling and working with cytotoxic chemotherapy.

Keywords: Cancer chemotherapy, UVH, transmissible venereal tumour, lymphoma, vincristine, anaemia, thrombocytopenia

1.0 INTRODUCTION

Cancer chemotherapy is defined as the use of anti-neoplastic agents in the treatment of malignant growth (Studdert *et al.*, 2012). Cancer chemotherapy is indicated for being most effective single therapy for lymphoproliferative and myeloproliferative disorders such as lymphoma, myeloma and leukaemia; as adjuvant treatment after surgical resection for highly metastatic neoplasia such as osteosarcoma; shrinking large tumour prior to surgery and relieve pain; improving cell kill with combination of radiotherapy (Morris & Dobson, 2001; North & Banks, 2009).

Mechanism of action of cancer chemotherapy to cure and treat tumours is through killing rapid dividing cells generally via targeting DNA in the cell nucleus or affect a cell's ability to synthesize protein (Shields, 2016). Cancer chemotherapeutic agents are classified into several groups based on their mode of action, anti-neoplastic activity and toxicity (Dobson, 1998). The drug classes include alkylating agents, antimetabolites, anti-tumour antibiotics, vinca alkaloids, hormones, anthracycline analogues and miscellaneous agents (Chun *et al.,* 2007; Dobson, 1998; Lana & Dobson, 2010). Examples of alkylating agents are cyclophosphamide, chlorambucil, melphalan, thiotepa, lomustine and busulphan (Chun *et al*., 2007; Dobson, 1998). Antimetabolite agents include cytarabine, gemcitabine, methotrexate, and 5-Fluorouracil (Barber & Burgess, 2016; Chun *et al*., 2007; Dobson, 1998). Anti-tumour antibiotics consist of doxorubicin, mitoxantrone, and actinomycin D (Biller *et al*., 2016) whereas hormone includes prednisolone. Examples of vinca alkaloids include vincristine and vinblastine while miscellaneous agents contain cisplatin, carboplatin, paclitaxel, piroxicam, hydroxycarbamide and L-Asparaginase (Lana & Dobson, 2010).

Chemotherapeutic agents can be used as a single agent or multi-agent therapy in dogs and cats. Combination drug protocol reported more advantaged than single drug protocol, which is maximizing cell kill and maintaining acceptable toxicities, having greater efficacy against a heterogeneous tumour population, and slower development of drug resistance (Lana & Dobson, 2010; Chun *et al.,* 2007). For example, combination chemotherapy protocol (vincristine, L-asparaginase, cyclophosphamide, doxorubicin, prednisolone) had increased remission rate for dogs with stage I-III lymphoma, particularly in young and small animal (Zemann *et al*., 1998).

The most common route of administration of chemotherapeutic agent in small animals is intravenous. The route of administration depends on chemotherapy drugs used, type of tumour being treated and patient receiving medication (Steffy-Morgan, 2009).

Chemotherapeutic agent cannot differentiate normal and tumour cells because both normal and tumour cells are active dividing cells (Chun *et al.*, 2007). Toxicity is the major concern of side effect caused by cytotoxic chemotherapy drugs. The most common toxicity of cancer chemotherapy is hematopoietic toxicities (MacDonald, 2009). Other common toxicities include gastrointestinal toxicities and cutaneous reaction such as alopecia, hypersensitivity and extravasation. Several toxicities including hepatotoxicity, pancreatitis, cardiotoxicity, uroepithelial toxicity, pulmonary toxicity, neurotoxicity, and nephrotoxicity are caused by selected cytotoxic chemotherapy agents (Dhaliwal, 2009).

Cancer chemotherapy is one of the expensive aspects of health care in human medicine (Vanderpuye & Yarney, 2014). Veterinary cancer therapy is more likely similar to human cancer chemotherapy. Cost of chemotherapy of each patient varies depending, chemotherapy protocol for specific types of tumour, treatment duration, hospitalization if

necessary, and diagnostic tests such as blood test, radiography and ultrasonography (Chauhan *et al.*, 2018).

Most of the small animal veterinary practices which provide chemotherapy are in Selangor area and University Veterinary Hospital (UVH) is one of them (Loh *et al.*, 2014). However, the information of chemotherapy practice in University Veterinary Hospital (UVH) has not been evaluated retrospectively. Therefore, the objectives of this study are (1) to determine the number and types of cancer in dogs and cats treated with cytotoxic chemotherapy, (2) to determine the drug types, frequency of delivery and reported side effects based on the various cytotoxic drugs delivered and (3) to determine the costs incurred in chemotherapy protocols of various cancers in dogs and cats presented to UVH between 2013 and 2017.

2.0 LITERATURE REVIEW

2.1 Demographics of tumour in dogs and cats

Cancer (malignant neoplasia) becomes a major cause of death in companion animals (Adams *et al.*, 2010). Species, breed, age, sex and neuter status are predisposing factors to get neoplastic disease. Canine has higher incidence rate to get neoplasia compared to feline (Vascellari *et al.*, 2009). Purebred dogs and cats have a higher risk than cross-bred (Grüntzig *et al.* 2015; Vascellari *et al.,* 2009). This is due to pure breed has less genetic variation than cross-breed and hereditary predisposed to several types of neoplasia (Dobson, 2013). For canine, there are few examples: Golden Retriever is predisposed to mast cell tumour, lymphoma and hemangiosarcoma while Boxer is susceptible to develop mast cell tumour and brain tumour (Dobson, 2013). For feline, Siamese has a predilection for lymphoma (Dobson, 2010). Moreover, the risk of developing malignant neoplasia is increased with age in both canine and feline (Vascellari *et al.*, 2009). This is due to the risk of developing aberrantly dividing cells is increased, and immune system becomes less effective to detect and eradicate those aberrant cells (Kitchell & Dervisis, 2010). Besides that, based on a study done by Merlo *et al.* (2008), female dogs have higher incidence rate to develop male dogs due to mammary gland tumour is the most frequent type of tumour. However, another study stated that female and male dogs have same incidence rate (Vascellari *et al.*, 2009). For feline, female cats have a higher risk of developing malignant tumour than male cats (Graf *et al.*, 2015). Furthermore, sex hormones such as estrogen, progesterone, androgen and testosterone will influence the risk of developing some tumours such as mammary tumour (Smith, 2014). Intact female dogs and cats have a higher risk to develop mammary tumours than neutered animals due

to influence of sex hormones in mammary carcinogenesis (Henry, 2010). A research showed that dogs spayed prior to their first estrus have only 0.5% risk of developing mammary tumours (Schneider *et al.*, 1969) whereas cats spayed prior to 6 months old have 91% reduction in risk of developing mammary tumour (Overley *et al.*, 2005). Presence of testosterone causes intact male dogs to be more predisposed to perinal adenoma than castrated male dogs but not prostate cancer (Henry, 2010). However, there are some studies suggest that neutered dogs and cats have higher risk of developing neoplasia in other locations besides genital organs as compared to intact dogs and cats (Graf *et al.*, 2015; Grüntzig *et al.*, 2016).

2.2 Common types of tumour in dogs

Based on a study in Italy, the annual incidence rate for tumour development in dogs is 282.2 per 100,000 dogs and 50% is malignant (Vascellari *et al.*, 2009). There are few common types of neoplasia in dogs, including mammary gland tumour, skin tumour, osteosarcoma, and lymphoma (Todorova, 2006). In United Kingdom, the most common site of tumour in insured dog is skin and soft tissue, and followed by mammary gland, urogenital, lymphoid, endocrine and alimentary. The most common type of tumour is cutaneous histiocytoma, followed by lipoma, adenoma, soft tissue sarcoma, mast cell tumour and lymphoma (Dobson *et al.*, 2002). A study done at Switzerland showed that the most common tumour is epithelial, and followed by mesenchymal, lymphoid, melanoma, skeletal and gonadal tumours (Grüntzig *et al.*, 2015), while in northern Italy, the most common site of tumour is mammary gland, and followed by skin and soft tissue, testicle, spleen, ovary and gingiva (Baioni *et al.*, 2017). In Malaysia, there is no study

done on prevalence of canine neoplasia, but there is one study done on prevalence of canine mammary tumour (Sahabi *et al.*, 2015) and a study of prevalence of canine neoplasia treated with chemotherapy done by Loh *et al.* (2014). The study showed that the most common type of tumour is transmissible venereal tumour, and followed by lymphoma, mast cell tumour, mammary gland tumour, squamous cell carcinoma, osteosarcoma, and leukemia (Loh *et al.,*2014). In conclusion, the types of canine neoplasia vary depending on geographic location where the study was done.

2.3 Common types of tumour in cats

According to a study done by Vascellari *et al.*, (2009), the incidence rate of cats to develop neoplasia in northern Italy is 77 per 100,000 cats which is lower than dogs. The risk of developing malignant tumour is higher than benign tumour (Vascellari, *et al.*, 2009). In Switzerland, the most common location of developing tumour in cat is skin, and followed by connective tissue, sexual organs, gastrointestinal tract, respiratory system and others. Epithelial tumour is the most common type of tumour in this study, followed by mesenchymal, lymphoid, melanoma, skeletal and neural neoplasia (Graf *et al.*, 2015). In Southeast Brazil, the most frequent tumour in cats is squamous cell carcinoma, and followed by mammary carcinoma, fibrosarcoma, lymphoma, haired skin adnexal tumour and mammary adenoma (Kimura *et al.*, 2012). The most common type of tumour in Italy is skin and soft tissue tumours, and followed by mammary, lymphoid and intestine (Vascellari *et al.*, 2009). Prevalence of feline neoplasia has not done in Malaysia. However, the most common type of neoplasia treated by chemotherapy in cat is

lymphoma, followed by mammary gland tumour, squamous cell carcinoma, leukemia, mast cell tumour and hemangiosarcoma (Loh *et al.*, 2014).

2.4 Current treatments for tumours in dogs and cats

Three main treatments for cancer in animals as in human are surgery, radiotherapy and chemotherapy (Morris & Dobson, 2001). Surgery is the most effective treatment for the majority of solid neoplasm. Surgery is indicated for diagnosis, as definitive treatment for solid and low grade tumours, cytoreduction of tumour mass prior to radiotherapy, as pain management, and as prophylaxis treatment (Morris & Dobson, 2001). The extension of surgical margin depends on type of tumour, location of tumour, and part of tissues that are adjacent to the tumour (Biller *et al.*, 2016). Surgical excision techniques can be classified into intrascapular, marginal, wide and radical (Baba & Câtoi, 2007; Pope, 2009; Farese & Withrow, 2013). Intrascapular excision is rarely indicated in veterinary surgery (Pope, 2009). Marginal excision involves removal of tumour outside or on pseudocapsule (macroscopic) and leaves microscopic disease (Farese & Withrow, 2013). Marginal excision is enough for many benign tumours such as lipoma (Pope, 2009). Extensive or wide excision is used on locally invasive tumours such as basal cell carcinoma, squamous cell carcinoma and mast cell tumour. This is done by en bloc removal of the tumour with sufficient surrounding tissue (Morris & Dobson, 2001; Pope, 2009). Radical excision is used for poorly localized or highly malignant neoplasia such as ungual carcinoma and bone sarcoma (Baba & Câtoi, 2007). This can be done by removing entire compartment such as amputation (Farese & Withrow, 2013).

Radiotherapy is a type of cancer treatment using radiation to be absorbed by cells, causing apoptotic cell death through excitation and ionisation (Morris & Dobson, 2001). Radiotherapy is indicated for voluminous or extensive type of tumours, tumours that are inaccessible to surgical excision and metastasized tumours (Baba & Câtoi, 2007). Types of radiation used include X-rays, gamma rays and electron (Morris & Dobson, 2001). Radiation can be delivered by an external source (teletherapy), application of radioactive sources interstitially (brachytherapy), or systematically by radioactive isotopes (North & Banks, 2009). Tumours that commonly treated by radiotherapy are oral tumours, nasal tumours, brain tumours and pituitary tumours, superficial tumours of trunk and extremities, and bone tumours (Larue & Gordon, 2013).

Chemotherapy is primarily used in treatment of cancer disease with metastasis and dissemination, prolongation of survival time, and eradication of some diseases (Baba & Câtoi, 2007). Chemotherapy involves use of different classes of cytotoxic drugs which have anti-tumour properties, and can be given as single agent or combination with other drugs (Morris & Dobson, 2001). Mechanism of action of these anti-neoplastic drugs is targeting dividing cells and interfering with process involved in progression through cell cycle (Gustafson & Page, 2013). Chemotherapy drugs are dosed on basis of body surface area in square metres, and can be administrated via intravenous, oral, intraperitoneal, intramuscular, subcutaneous, or intralesional routes (Lana & Dobson, 2010).

In addition to surgery, radiotherapy and chemotherapy, there are other treatment modalities with limited application, including immunotherapy, electrochemothrapy, cryosurgery, photodynamic therapy, hyperthermia and laser therapy (North & Banks, 2009).

2.5 Basic cancer chemotherapy principle

2.5.1 Use of chemotherapy

Chemotherapy is a common treatment used in veterinary cancer patient in addition to surgery and radiation therapy (MacDonald, 2009). Most of chemotherapy is given systemically in small animals. Indications of chemotherapy to be used include being most effective single therapy for lymphoproliferative and myeloproliferative disorders such as lymphoma, myeloma and leukaemia; as adjuvant treatment for highly metastasis tumour after surgery such as osteosarcoma; shrinking large tumour prior to surgery and relieve pain; improve cell kill together with radiation (Morris & Dobson, 2001; North & Banks, 2009). There are three stages of chemotherapy which are induction therapy, maintenance therapy and rescue therapy (Morris & Dobson, 2001). Induction therapy involves the use of short dosing interval but more aggressive drug combination in order to reduce the number of tumour cells and induce a complete remission if ideally (Chun *et al*., 2007). Maintenance therapy involves the use of less intensive treatment regime than induction therapy to maintain remission (Morris & Dobson, 2001). Rescue therapy is indicated for relapsed tumours by using more aggressive agents which the tumours have not been exposed to (Morris & Dobson, 2001). Chemotherapy can be used as adjuvant therapy, neoadjuvant therapy and palliative therapy (Gustafson & Page, 2013). Adjuvant therapy is used after surgery or radiation to delay recurrence or metastasis (Lana & Dobson, 2010). Neoadjuvant therapy is applied before primary treatment of the disease (Rodriguez, 2009). Palliative therapy is delivered to improve quality of life of the animal by reducing clinical signs of unresectable or disseminated disease that is associated with functional disturbance or pain (Gustafson and Page, 2013).

2.5.2 Mechanism of action

Chemotherapeutic or anti-neoplastic agent is a chemical agent used for curing or treating cancer by killing rapid dividing cells generally through targeting DNA in the cell nucleus, or affect a cell's ability to synthesize protein (Shields, 2016). Chemotherapeutic agent cannot differentiate normal and tumour cells because both normal and neoplastic cells are active dividing cells (Chun *et al.*, 2007). However, normal cells have more capable of response, repair and repopulate on chemotherapy-induced damage than neoplastic cells (Hong & Khanna, 2003). The sensitivity of chemotherapeutic agent towards normal cells in decreasing order: peduncle cells of bone marrow and lymphocytes, mucous cells of gastrointestinal tract, liver and kidney cells, cells of basal epithelial layer, and nervous system cells (Baba & Câtoi, 2007). The usual chemotherapy toxicity signs include bone marrow suppression, gastrointestinal signs, alopecia and cardiotoxicity (Baba & Câtoi, 2007).

Chemotherapeutic agents can be classified into phase-specific drug which kills cells in one phase of cell cycle, phase-independent drug which kills cells at any point in the cycle, and cell cycle-independent drug which kills both dividing and non-dividing cells (Norris & Withrow, 1984; Freres, Jerusalem & Moonen, 2017).

2.6 Use of cancer chemotherapeutic agents

2.6.1 Common classes of chemotherapeutic agents

Cancer chemotherapeutic agents are classified into several groups based on their mode of action, anti-tumour activity and toxicity (Dobson, 1998). The drug classes

include alkylating agents, antimetabolites, anti-tumour antibiotics, vinca alkaloids, hormones, anthracycline analogues and miscellaneous agents (Dobson, 1998; Chun *et al.*, 2007; Lana & Dobson, 2010).

Alkylating agents are further divided into nitrogen mustard derivatives, ethyleneimine derivatives, alkyl sulphonates, triazine derivatives and nitrosoureas (Dobson, 1998). Their mode of action to against tumour cells is inserting an alkyl group, and changing the structure of DNA to interfere with transcription, replication and repair machinery, thus inhibit DNA, RNA and protein synthesis (Chun *et al.*, 2007). Nitrogen mustard derivatives include cyclophosphamide, chlorambucil and melphalan (Dobson, 1998). Cyclophosphamide has been most widely used in veterinary medicine among these alkylating agents (Norris & Withrow, 1984). Cyclophosphamide is used in combination with other chemotherapeutic drugs to treat lymphoma and various carcinomas and sarcomas (Chun *et al.*, 2007). It interferes with DNA replication, RNA transcription and replication, and disrupts nuclei acid function (Biller *et al.*, 2016). Cyclophosphamide is activated by liver microsomal enzymes, thus its use should be avoided in animal with hepatic insufficiency (Norris & Withrow, 1984). Chlorambucil cross-linking with cellular DNA to treat lymphoma, chronic lymphocytic leukemia, mast cell tumour and IgM myeloma (Biller *et al.*, 2016). Melphalan is used with prednisolone to treat multiple myeloma and lymphoma (Dobson, 1998; Chun *et al.*, 2007). Ethyleneimine derivatives such as thiotepa are indicated for malignant effusion by instillation into body cavities, and carcinoma of bladder by bladder instillation (Dobson, 1998). Under nitrosoureas derivatives, lomustine has been used to treat brain tumours, canine mast cell tumours and as a rescue agent for resistant lymphoma (Chun *et al.*, 2007). Alkyl sulphonates such as busulphan are used for chronic granulocytic leukaemia while triazine derivatives such as

dacarbazine are used in combination with doxorubicin or dactinomycin for relapsed lymphoma (Dobson, 1998; Chun *et al.*, 2007).

Antimetabolites include cytarabine, gemcitabine, methotrexate, and 5-Fluorouracil which act as structural analogues of metabolites required for purine and pyrimidine synthesis (Chun *et al.*, 2007; Barber & Burgess, 2016; Dobson, 1998). These antimetabolites can be differentiated into antifolates and pyrimidine analogue (Freres *et al.*, 2017). Cytarabine is a pyrimidine analog and kills cells undergoing DNA synthesis and blocks the progression of cells from G_1 phase to S phase (Chun *et al.*, 2007). It is indicated to treat lymphoma that affects central nervous system and leukemia (Barber & Burgess, 2016). Gemcitabine is similar to cytarabine as a pyrimidine analogue and is limited used in lymphoma and various carcinomas (Barber & Burgess, 2016). Methotrexate inhibits folic acid reductase which is needed for reduction of dihydrofolate to tetrahydrofolate, thus inhibits DNA synthesis (Biller *et al.,* 2016). This drug is indicated as part of combination of chemotherapy protocol to treat lymphoma (Chun *et al.*, 2007). 5-Fluorouracil acts as pyrimidine analog by metabolizing into a nucleotide to bind into RNA and inhibiting DNA synthesis. It is used in combination with chemotherapy protocol to treat carcinoma and sarcoma, nasal adenocarcinoma, and GI and mammary carcinoma (Chun *et al.*, 2007). Other antimetabolites include 6-Mercaptopurine, 6-Thioguanine and azathioprine (Dobson, 1998).

Anti-neoplastic antibiotics which are not cell cycle-specific consist of doxorubicin, mitoxantrone, and actinomycin D (Biller *et al*., 2016). These agents are derived from soil fungi and form stable complexes with DNA, thus results in inhibition of DNA synthesis and transcription (Dobson, 1998). In this class of chemotherapeutic agent, doxorubicin is

derived from the Streptomyces yeast species and able to inhibit DNA synthesis, DNA-dependent RNA synthesis and protein synthesis (Chun *et al.*, 2007; Biller *et al*., 2016). Doxorubicin is the most active against canine lymphoma, and has efficacy against sarcomas and carcinomas (Moore, 2010). Mitoxantrone is a synthetic anti-tumour antibiotic which inhibits topoisomerase II enzyme (Lana & Dobson, 2010). This drug is indicated for canine lymphoma and some carcinomas such as urinary bladder carcinoma. It has a lower risk of cardiotoxicity than doxorubicin and can be used when doxorubicin is contraindicated (Moore, 2010). Actinomycin D is derived from Streptomyces yeast species, and it works by intercalation of DNA and inhibition of RNA and protein synthesis (Chun *et al.*, 2007; Lana & Dobson, 2010). It is used as non-cardiotoxic substitute for doxorubicin in multiple drug protocols for lymphoma, as a rescue agent for lymphoma, and carcinomas such as anal sac and perianal adenocarcinoma (Chun *et al.*, 2007; Lana & Dobson, 2010).

Vinca alkaloids are derived from periwinkle plant and are cell cycle specific which targets M phase (Lana & Dobson, 2010). They bind to the microtubular protein and inhibit the formation of mitotic spindle, thus inhibiting mitosis (Dobson, 1998). Examples of vinca alkaloids include vincristine and vinblastine (Lana & Dobson, 2010). Both vincristine and vinblastine can be used to treat lymphoma and mast cell tumour. Other than that, vincristine can be indicated for leukaemia, sarcomas and transmissible venereal tumour (TVT) (Lana & Dobson, 2010). Based on one study done by Hantrakul *et al.* (2014), TVT able to be regressed completely by three to eight administrations of vincristine.

Hormone such as prednisolone is used in combination protocols as it has anti-tumour activity against lymphoma, mast cell tumours, leukaemia and plasma cell tumours (Chun *et al.*, 2007; Lana & Dobson, 2010). Prednisolone works by binding cytoplasmic receptor sites which then interact with DNA and inhibit cell division (Lana & Dobson, 2010). It also inhibits mitosis in lymphocytes (Barber & Burgess, 2016). Besides that, anthracycline analogues which include idarubicin and epirubicin are analogs of doxorubicin that are less cardiotoxic (Chun *et al.*, 2007). These drugs are commonly used in human medicine as an alternative of doxorubicin, but limited information in veterinary medicine (Chun *et al.*, 2007).

Miscellaneous agents contain cisplatin, carboplatin, paclitaxel, piroxicam, hydroxycarbamide and L-Asparaginase (Lana & Dobson, 2010). Heavy metal compound of cisplatin and platinum containing compound of carboplatin have the same mechanism of action by binding within and between DNA strands, thus inhibiting protein synthesis (Chun *et al.*, 2007). Both are used to treat canine osteosarcoma and various carcinomas (Barber & Burgess, 2016). Paclitaxel is used to treat mammary carcinoma and some sarcomas by binding to the microtubular protein and preventing formation of mitotic spindle, thus inhibiting mitosis (Lana & Dobson, 2010). For piroxicam, it is an NSAID of oxicam class which has anti-tumour effect and is used as adjunct for treating tumour. It has been used to suppress some tumours expressing COX receptors such as transitional and squamous cell carcinoma, and mammary adenocarcinoma (Papich, 2016). Hydroxycarbamide is used to treat polycythaemia vera and myelogenous or basophilic leukaemia by inhibiting conversion of RNA to DNA through destruction of ribonucleoside diphosphate reductase (Lana & Dobson, 2010). L-Asparaginase is an enzyme derived from bacteria that able to hydrolyse asparagine which is needed for

protein synthesis (Dobson, 1998). This drug is effective for lymphoma in dogs but less effective in cats (Moore, 2010).

2.6.2 Combination of chemotherapeutic agents

Chemotherapeutic agents can be used alone or as multi-agent therapy Goldie *et al.* (1982) theorized that single chemotherapeutic agent has the potential of resulting drug-resistant clone in tumour cells (Lana & Dobson, 2010). Therefore, induction regime should be dose-intensive and involve multiple drugs because single agent is not curative (Chun *et al.*, 2007). Combination of chemotherapeutic drugs is able to act on heterogeneous cell population by different mechanism of action (Morrison, 2002). Advantages of choosing combination of drugs protocol are able to maximize cell kill and maintain acceptable toxicities, have greater efficacy against a heterogeneous tumour population, and slower development of drug resistance (Lana & Dobson, 2010; Chun *et al.,* 2007). Principles of combining chemotherapeutic drugs include choosing only drugs proven to have efficacy when used alone; selecting a drug that does not overlap the toxicities or mechanism of action of other drugs used; using drugs at their optimal dose and schedule; giving drugs at consistent time intervals (Morrison, 2002). Combination of chemotherapeutic drugs has shown benefit in case of canine lymphoma. Several studies have done and proved that combination of doxorubicin with COP protocol has increased both median remission and median survival time over either doxorubicin alone or COP protocol without doxorubicin (Gustafson & Page, 2013). There is also another study done by Zemann *et al.* (1998) showed that combination chemotherapy protocol (vincristine, L-asparaginase, cyclophosphamide, doxorubicin, prednisolone) had increased remission

rate for dog with stage I-III lymphoma, particularly in young and small animal (Zemann *et al*., 1998).

2.6.3 Routes of administration of chemotherapeutic agents

The most common route of administration of chemotherapeutic agent in dog and cat is intravenous and followed by others such as oral, intramuscular, subcutaneous, intralesional and intraperitoneal. The route of administration depends on chemotherapy drugs used, type of tumour being treated and patient receiving medication (Steffy-Morgan, 2009).

For intravenous route of administration, it is important to ensure that the catheter placed at vein is clean and secured because some of chemotherapy drugs are vesicant which will cause necrosis upon extravasation. Peripheral veins are preferred due to ease of monitoring for extravasation (Lana & Dobson, 2010). There are two types of catheters that can be used for intravenous route of injection which are butterfly catheter and indwelling catheter. Indwelling catheter is used to deliver intravenous drugs especially those vesicant chemotherapeutic drugs (Steffy-Morgan, 2009). Chemotherapy drugs that can be given intravenously include carboplatin, cyclophosphamide, doxorubicin, mitoxantrone, vincristine, vinblastine, 5-fluorouracil, cisplatin, and actinomycin D (Steffy-Morgan, 2009; Moore, 2010).

Oral route of administration of cytotoxic anti-neoplastic drugs is similar to any other pilling procedure (Steffy-Morgan, 2009). During oral administration, personal protective equipment should be worn. Tablets or capsules should be never crushed or opened to

prevent aerosol contamination (Allen & Crump, 2011). It should be ensure that tablet is completely consumed by patient and followed by a syringe of water (Lana & Dobson, 2010). Oral chemotherapy drugs include chlorambucil, cyclophosphamide, lomustine and piroxicam (Moore, 2010).

Moreover, intramuscular and subcutaneous administration of chemotherapy drugs are given at caudal thigh region or lumbar region and intrascapular region respectively (Steffy-Morgan, 2009). After inserting a needle, the syringe must be aspirated for any blood to prevent giving intravenously (Lana & Dobson, 2010). Drug that can be given intramuscularly or subcutaneously is L-asparaginase (Moore, 2010). Furthermore, intralesional route of chemotherapy drug is given in the surface of masses located in the skin or subcutaneous such as skin tumour, osteosarcoma and oral melanoma (Kitchell *et al.*, 1994; Kitchell *et al*., 1995; Withrow *et al*., 2004; Kirby & Miller, 2010). Intralesional chemotherapy drugs should not be vesicant. Examples of intralesional drugs are cisplatin, 5-fluorouracil and bleomycin (Steffy-Morgan, 2009).

Other than that, intraperitoneal route of chemotherapy is given to expose tumour present within peritoneal cavity to higher concentration of drug for more prolonged time periods (Markman, 1999). Intraperitoneal chemotherapy drug is used to treat carcinomatosis, sarcomatosis and mesothelioma which spread through serosal seeding instead of lymphatic or blood vessels (Charney *et al.*, 2005). Intraperitoneal drugs include cisplatin, 5-fluorouracil, carboplatin and mitoxantrone (Steffy-Morgan, 2009).

2.7 Side effects of chemotherapeutic agents

2.7.1 Hematologic toxicity

Hematologic effects are the most frequently observed as bone marrow is sensitive to effect of chemotherapy due to its high mitotic rate and growth fraction (Chu & Rubin, 2018; Lana & Dobson, 2010). Neutrophils are primarily affected and followed by thrombocytes. Anaemia may resulted, but is usually mild and rarely significant (North & Banks, 2009). Neutropenia is the most serious and dose-limiting toxicity. The nadir (time of the lowest neutrophil count) varies with individual drugs (MacDonald, 2009). Neutropenia is likely to be developed 7 to 10 days after the administration of most of chemotherapy drugs except vinblastine, paclitaxel and carboplatin, and rebound within 4-5 days (Vail, 2009; North & Banks, 2009). Vinblastine and paclitaxel cause neutropenia as early as 4 to 5 days while carboplatin causes neutropenia as late as 2 to 3 weeks (Vail, 2009). Animals with <1000 neutrophils/μL have a risk of fever and sepsis (MacDonald, 2009). Therefore, close monitoring is required and white blood cells count should be checked prior to chemotherapy delivery. A delay in treatment is necessary if animal is neutropenic and a blood test is required before continuing treatment. Broad spectrum antibiotic is required if animal has neutropenia, fever and sepsis (North & Banks, 2009). Thrombocytopenia associated with chemotherapy is rarely severe and does not require treatment. However, chemotherapy should be delayed if counts are $<50 \times 10^9$L (Lana & Dobson, 2010). Anaemia is a common finding with cancer animal and is rarely significant for the side effect of chemotherapy because it is often indistinguishable from anaemia associated with tumour itself (Dobson, 1998; Dhaliwal, 2009).

2.7.2 Gastrointestinal toxicity

Vomiting, nausea and diarrhoea are most common signs of gastrointestinal toxicity (Dhaliwal, 2009). Vomiting is caused by the effect of drug on the central nervous system (CNS) vomiting centre or chemotherapy trigger zone (MacDonald, 2009). Vomiting can be acute, within 6-12 hours of post-administration or delayed which within 24-48 hours of post-administration (Lana & Dobson, 2010). Acute vomiting usually is self-limiting, but anti-emetics and supportive treatment may be required for those with persistent vomiting (North & Banks, 2009). Chemotherapy drugs that often cause vomiting are cisplatin and high-dose cyclophosphamide (Chu & Rubin, 2018). Chemotherapy also has an indirect effect secondary to drug-induced gastrointestinal inflammation and damage, leading to diarrhoea (MacDonald, 2009). Diarrhoea is induced when chemotherapy drugs damage the rapidly dividing epithelial mucosa of gastrointestinal tract. Chemotherapy-induced neutropenia allows injured mucosa to become infected and serve as an entry for bacteria and fungi (Chu & Rubin, 2018). Diarrhoea can be ranged from mild with hyporexia and soft stool to severe vomiting and bloody diarrhoea (MacDonald, 2009). This sign is generally self-liming, but antibiotic, intestinal protectant and supportive treatment should be given if severe (Dhaliwal, 2009; Vail, 2009b). Drugs that can occasionally cause severe diarrhoea are doxorubicin, methotrexate, 5-fluorourancil and actinomycin D (Couto, 2014).

2.7.3 Skin reaction

Alopecia is more severe in dogs than cats. Alopecia in dogs is breed-dependent especially those breeds with continually growing hair (North & Banks, 2009). A study done by Falk *et al.*, (2016) stated that wire or curly coat-type of dog breeds are more likely to have alopecia effect than straight coat-type due to predominant anagen hair follicles to be targeted by chemotherapy drug such as doxorubicin. However, hair will grow back after chemotherapy is stopped. Cats rarely develop alopecia but will lose their whiskers (Lana & Dobson, 2010).

Extravasation is caused by vesicant or irritant drug leaking into surrounding tissue, resulting in severe local tissue necrosis and sloughing, typically near the injection site of peripheral catheter (Biller *et al*., 2016). Tissue necrosis can be resulted from extravasation of vincristine, vinblastine, doxorubicin and actinomycin D (Couto, 2014). Clinical signs associated with extravasation are pain, erythema, moist dermatitis and necrosis. These signs may occur 1-7 days after vincristine or vinblastine injection and up to 7-10 days after doxorubicin (Lana & Dobson, 2010). Extravasation can be prevented by a systemic and evidence-based approach to administration techniques, and trained and experienced staff (Biller *et al*., 2016). If extravasation occurs, drug should be aspirated out as much as possible, local infiltration of the area with corticosteroids, ice pack therapy 4-5 times/ day for 3 days and long-term monitoring (Biller *et al.,* 2016; Chu & Rubin, 2018).

2.7.4 Specific drugs associated toxicities

Cardiotoxicity is seen primarily with doxorubicin in dogs, rarely in cats. There are two forms of cardiotoxicities in dogs which are acute and chronic. Acute reaction is characterized by cardiac arrhythmia that develops during or soon after administration. Chronic reaction results dilated cardiomyopathy or congestive heart failure (Couto, 2014; Lana & Dobson, 2010). Besides that, haemorrhagic cystitis is the side effect of the use of cyclophosphamide and ifosfamide due to irritation of bladder mucosa caused by acrolein metabolite (North & Banks, 2009). Nephrotoxicity can be caused by cisplatin and methotrexate in dogs, and doxorubicin in cats. These drugs should be caution in patients with renal disease. Therefore, renal function should be screened prior to administration, and saline diuresis should be given before and after administration (Lana & Dobson, 2010). Moreover, neurotoxicity is the side effect of vinca alkaloids, cisplatin and 5-fluorouracil (Lana & Dobson, 2010). 5-fluorouracil will cause fatal in cats, thus it is contraindicated in cats (Dhaliwal, 2009). Lomustine causes hepatotoxicity if long-term administration, thus liver function should be checked frequently (North & Banks, 2009). Furthermore, pulmonary toxicity can be caused by bleomycin and cisplatin. Cisplatin is contraindicated in cats due to it causes severe pulmonary edema and pulmonary effusion which able lead to death (Lana & Dobson, 2010).

2.8 Cost of chemotherapy

In human medicine, cancer therapy is one of expensive aspects of health care as it involves screening, diagnosis, treatment, surveillance and palliative measures. Screening is done to detect early cancer, then proceed with diagnosis which involves radiological, nuclear and molecular testing. Treatment comprises surgeries, chemotherapy and other therapies. Surveillance involves doctor's consultation, blood test, radiological and nuclear imaging. Palliative care comprises of pain management and others to improve quality of life (Vanderpuye & Yarney, 2014). Veterinary cancer therapy is more likely as human medicine. Cost of chemotherapy of each patient varies depending, chemotherapy protocol for specific types of tumour, treatment duration, hospitalization if necessary, and diagnostic tests such as blood test, radiography and ultrasonography (Chauhan *et al.*, 2018).

3.0 MATERIALS AND METHODS

3.1 Study population

All recorded cases in the Chemotherapy Log Book where included in this study. Case records of specific dogs and cats that received chemotherapy in University Veterinary Hospital from 2013 to 2017 were gathered. The data obtained include case number, ID of patient, species, sex, age, neuter status, breed, type of tumour diagnosed based on cytology or histopathology, frequency of drug delivered, type of drug delivered, site of injection, survival days, cost involved in every visit of cancer chemotherapy and entire protocol, and side effects after cancer chemotherapy which based on blood parameters, history and physical examination.

3.2 Retrospective data acquisition

The case log book available at the chemotherapy room of University Veterinary Hospital (UVH) was used as primary source of data. Data which was recorded in the chemotherapy case log book include date, signalment of patient, type of tumour, owner's name, type of drug delivered, frequency, and site of injection. Blood result, history, physical examination and cost including consultation fee, blood test, cytotoxic drug used and administration fee were obtained by retrieving case records from UVH archives and reviewed retrospectively. Survival time for each patient was calculated from post first chemotherapy until death. All data were tabulated into Microsoft Excel software. Data of canine and feline were separated. The age of dogs and cats was categorised into either $\leqslant$ 2 years old or >2 years old. Dog breeds were categorised based on pedigree and non-pedigree whereas cat breeds were categorised into Domestic Short Hair (DSH) and

pedigree. Types of tumours were categorised based on types of cells which were epithelial, mesenchymal and round cells. Tumours were also grouped into blood localisation and others localisation. Side effects of chemotherapy (anaemia, leukopenia, thrombocytopenia, lymphopenia, extravasation, vomiting, diarrhoea and petechial haemorrhage) were recorded as yes or no. The cost of chemotherapy for each patient, each species and every year were calculated manually.

3.3 Data analysis

Statistical analysis was performed using SPSS®, version 20 (IBM Corporation, U.S. 1989, 2011). Descriptive data analysis was used for all categorical variables in this study. Breeds, types of tumours, tumour classification, types of pedigree and side effects of chemotherapy were analysed into percentage and frequency with canine and feline separated. Age of dogs and cats receiving chemotherapy was analysed in order to know mode and median of age. Frequency of cytotoxic chemotherapy drugs delivered was identified over the years, frequency of types of chemotherapy delivered over the years, different sites of administration, and total income generated by UVH through cancer chemotherapy over the years were identified into bar chart with canine and feline separated.

Kaplan-Meier survival method was used to compare survival times between pedigree and non-pedigree in dogs, between TVT and lymphoma in dogs, and between DSH and pedigree in cats. Comparison is considered significant if $p<0.05$ within a 95% confidence interval.

Fisher's exact test was used to determine the association between species with sex, neuter status, age group and tumour localisation, and association between pedigree type

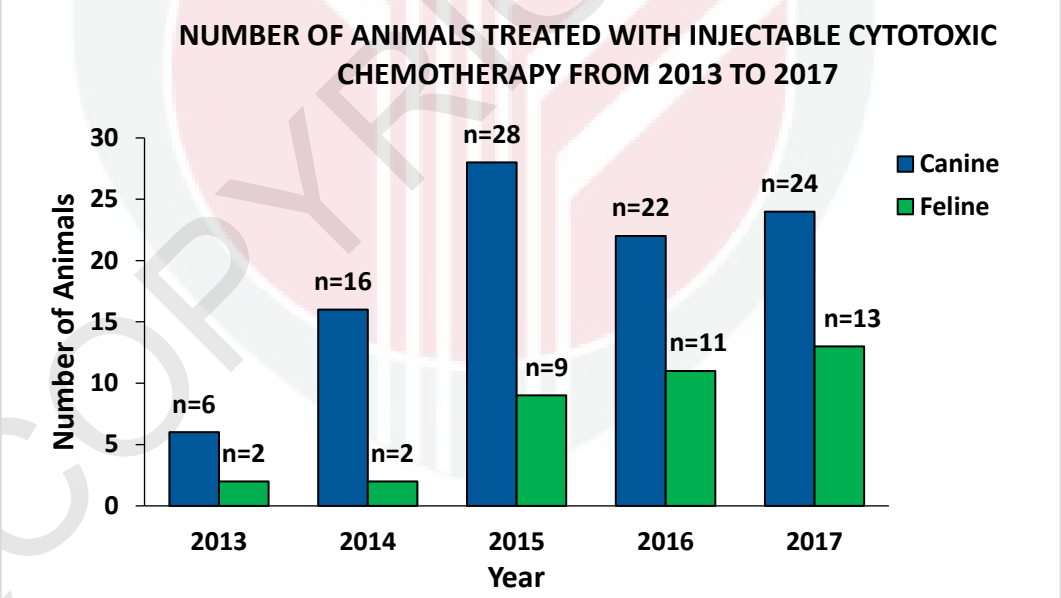
with sex, neuter status, age group and tumour localisation with dogs and cats separated. Odds ratio was computed to determine the distribution of odds between those categories. Association is considered significant if $p<0.05$ within a 95% confidence interval.

4.0 RESULTS

4.1 Number of animals treated with injectable cytotoxic chemotherapy

A total of 113 animals receiving injectable cytotoxic chemotherapy in University Veterinary Hospital (UVH), University Putra Malaysia (UPM) from 2013 to 2017, 83 cases of them were dogs and 30 were cats. The number of dogs increased from 2013 to 2015. From 2013 to 2017, the number of cats receiving chemotherapy was increased gradually from 2 to 13 *(Figure 1)*.

Figure 1: Number of animals treated with cytotoxic cancer chemotherapy in UVH, UPM from 2013 to 2017



4.2 Breed distribution

Among 83 dogs that received cancer chemotherapy, 54% (n=45) were pedigree breeds and 46% (n=38) were non-pedigree breeds. There were 19 different dog breeds. The most frequent breed was local (43.4%), followed by Golden Retriever (14.5%) and Shih Tzu (8.4%) *(Table 1)*. In cats, Domestic Short Hair was most common with 83.3% (n=25) and the remaining 17% (n=5) were of pedigree breeds which include Persian (6.7%, n=2), Siamese (6.7%, n=2) and Maine Coon (3.3%, n=1).

Table 1: Types of breed in dogs receiving cancer chemotherapy in UVH, UPM.

Breeds	**Frequency (n)**	**Percent (%)**
Local	36	43.4
Golden Retriever	12	14.5
Shih Tzu	7	8.4
GSD	3	3.6
Rottweiler	3	3.6
Terrier	3	3.6
Beagle	2	2.4
Cocker Spaniel	2	2.4
Labrador	2	2.4
Miniature Pinscher	2	2.4
Mixed breed	2	2.4
Siberian Husky	2	2.4
Basset Hound	1	1.2
Boxer	1	1.2
Bulldog	1	1.2
Dobermann	1	1.2
Pomeranian	1	1.2
Schnauzer	1	1.2
Spitz	1	1.2
Total	83	100.0

4.3 Sex distribution

The gender of dogs that received chemotherapy was 57.8% (n=48) male and 42.2% (35) female. 63.9% (n=53) were intact and 36.1% (n=30) were neutered. In cats, 56.7% (n=17) were male and 43.3% (n=13). Among these cats, 63.3% (n=19) were neutered and 36.7% (n=11) were intact.

4.4 Age distribution

The median age of dogs receiving chemotherapy was 7 to 8 years old with numbers from 10 to 17 over the years *(Figure 2)*. The median age of cats receiving cancer chemotherapy was 5-6 years. The highest number of cats receiving cancer chemotherapy was at 1 to 2 years (n=10) and followed by 7 to 8 years (n=9) *(Figure 3)*.

Figure 2: Age distribution of dogs receiving cancer chemotherapy in UVH, UPM.

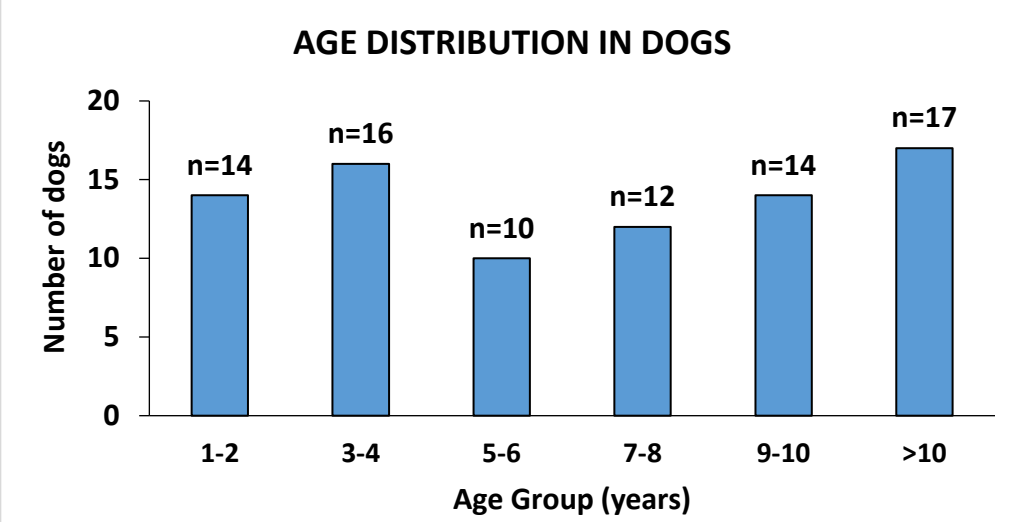
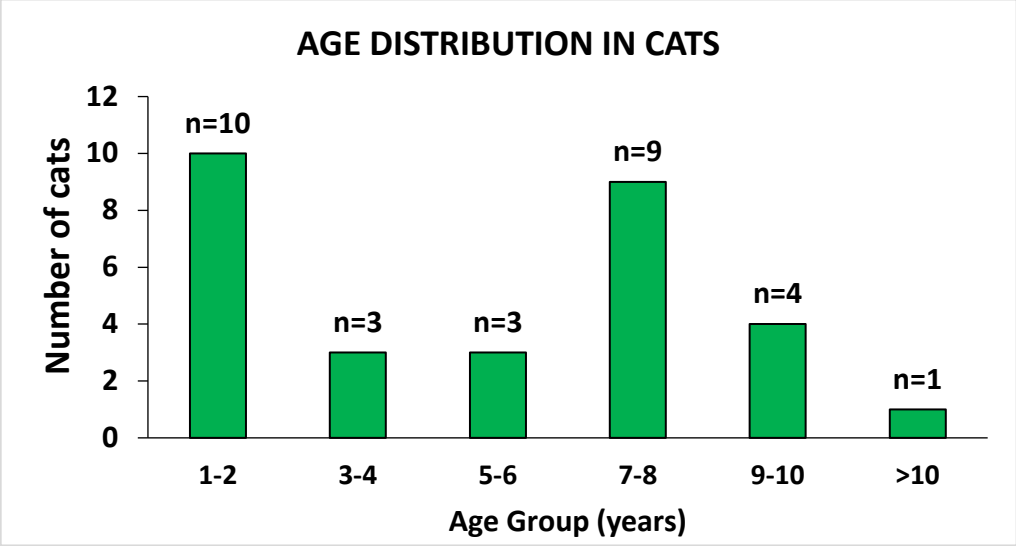


Figure 3: Age distribution of cats receiving cancer chemotherapy in UVH, UPM



.

4.5 Most common tumour cell type and location

Overall, the most frequent tumour cell type treated with cytotoxic chemotherapy was round cells (77.9%, n=88), followed by epithelial cells (15%, n=17) and mesenchymal cells (7.1%, n=8). The most frequent type in dogs was round cells (80.7%, n=67), followed by epithelial cells (9.6%, n=8) and mesenchymal cells (9.6%, n=8). There were two types of tumour cells in cats which were round cells (70%, n=21) and epithelial cells (30%, n=9). Thus far none for mesenchymal type of tumours in cats.

The most frequent tumour location in dogs receiving cytotoxic chemotherapy was cutaneous (n=37), followed by hematopoietic (n=25), soft tissue (n=10), oral (n=9), and bone (n=2) *(Figure 4)*. While, hematopoietic (n=19) was the most common location of tumour in cats receiving cancer chemotherapy, followed by soft tissue (n=10) and cutaneous (n=1) *(Figure 5)*.

Figure 4: Different tumour locations in dogs receiving chemotherapy.

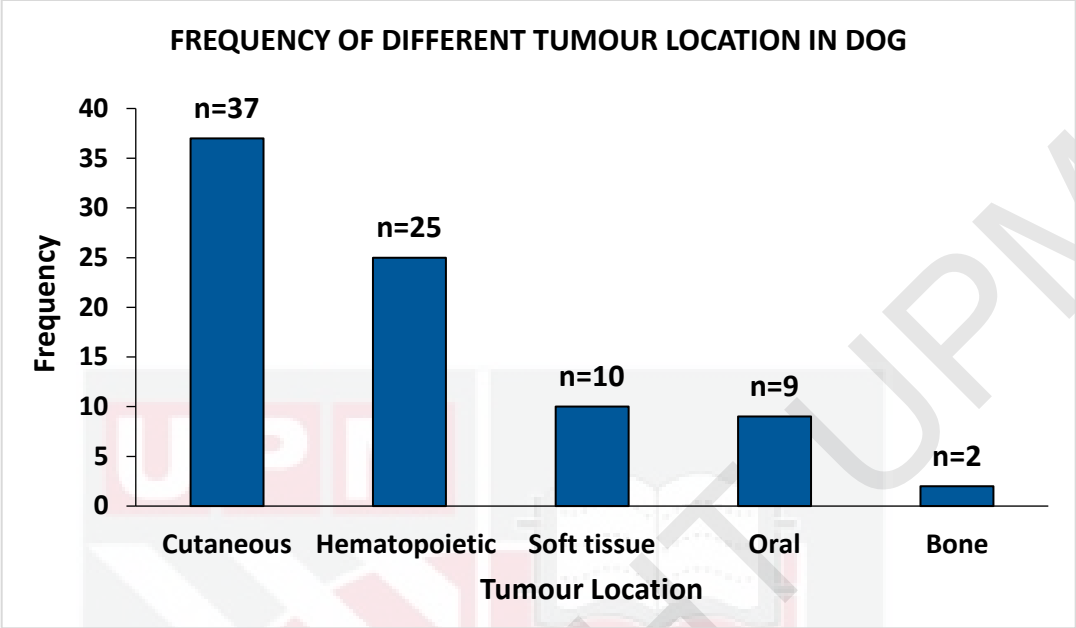
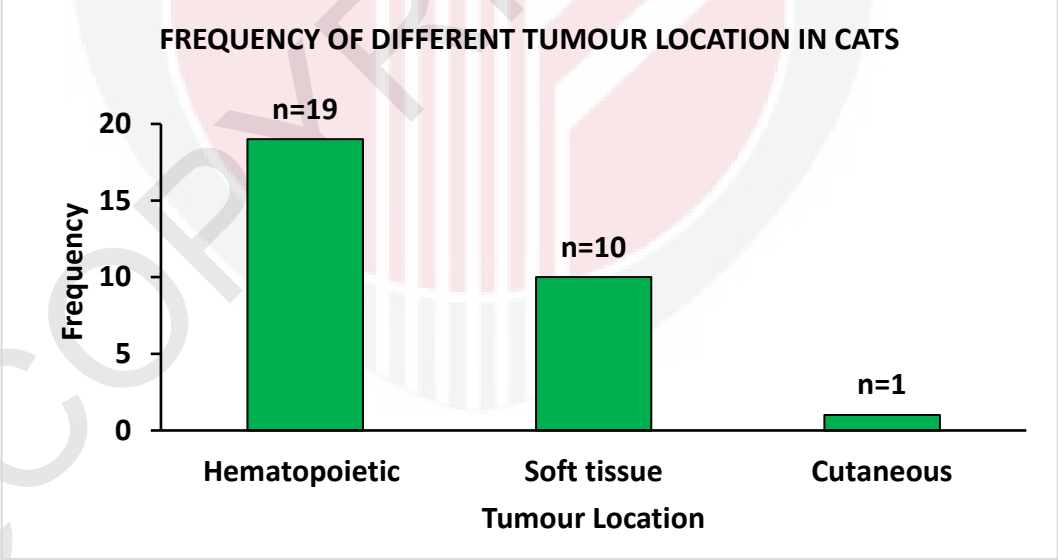


Figure 5: Different tumour locations in cats receiving cancer chemotherapy.



4.6 Distribution of the most common type of tumour

The type of tumour that was commonly treated by cytotoxic chemotherapy in dogs was transmissible venereal tumour (34.9%), followed by lymphoma (27.7%) *(Table 2)*. For cats, the most frequent type of tumour treated by cytotoxic chemotherapy was lymphoma (60%), followed by adenocarcinoma (23.3%) *(Table 3)*.

Table 2: Types of tumour in dogs receiving cancer chemotherapy.

Types of Tumour	Frequency (n)	Percent (%)
TVT	29	34.9
Lymphoma	23	27.7
Mast cell tumour	7	8.4
Oral Melanoma	5	6.0
Lymphocytic Leukemia	3	3.6
Adenocarcinoma	4	4.8
Squamous cell carcinoma	3	3.6
Fibrosarcoma	2	2.4
Osteochondrosarcoma	2	2.4
Cutaneous hemangiosarcoma	1	1.2
Esophageal sarcoma	1	1.2
Liposarcoma	1	1.2
Mesothelioma	1	1.2
Rhadomyosarcoma	1	1.2
Total	83	100.0

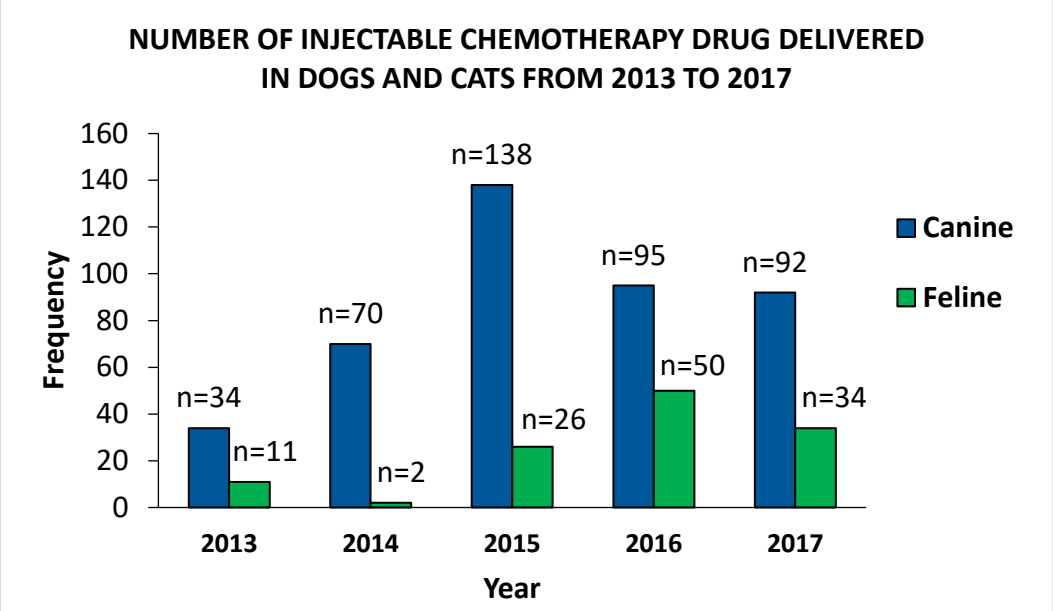
Table 3: Types of tumour in cats receiving cancer chemotherapy.

Types of Tumour in Cats	Frequency (n)	Percent (%)
Lymphoma	18	60.0
Adenocarcinoma	7	23.3
Lymphoid leukemia	1	3.3
Mast cell tumour	1	3.3
Melanoma	1	3.3
Nasal carcinoma	1	3.3
Squamous cell carcinoma	1	3.3
Total	30	100.0

4.7 Injectable cytotoxic chemotherapy drugs delivered

A total of 552 doses of injectable cytotoxic chemotherapy drugs were delivered to dogs and cats from 2013 to 2017. Dogs received 77.7% (n=429) of the doses while cats received 22.3% (n=123) of the doses. Mean of cytotoxic chemotherapy drugs delivered to each patient was 5 doses with a minimum dose of 1 and maximum doses of 25. The number of doses in 2015 was the highest. There was a fluctuation pattern in the number of injectable chemotherapy drugs delivered in cats from 2013 to 2017 *(Figure 6)*.

Figure 6: Number of injectable cytotoxic chemotherapy drug doses delivered in dogs and cats.



The injectable cytotoxic chemotherapy drug commonly used in UVH, UPM was vincristine (n=475), followed by carboplatin (n=37), cyclophosphamide (n=30), and doxorubicin (n=10) *(Figure 7)*. A total of 83% (n=358) of injectable cytotoxic chemotherapy drugs delivered in dogs were vincristine, 8% (n=35) were carboplatin, 6% (n=25) were cyclophosphamide and 3% (n=11) were doxorubicin *(Figure 8)*. Doxorubicin was not used in cats. The injectable cytotoxic chemotherapy drugs used in cats were vincristine (94%, n=116), cyclophosphamide (4%, n=5) and carboplatin (2%, n=2) *(Figure 9)*.

Figure 7: Types of injectable cytotoxic drugs used in UVH, UPM.

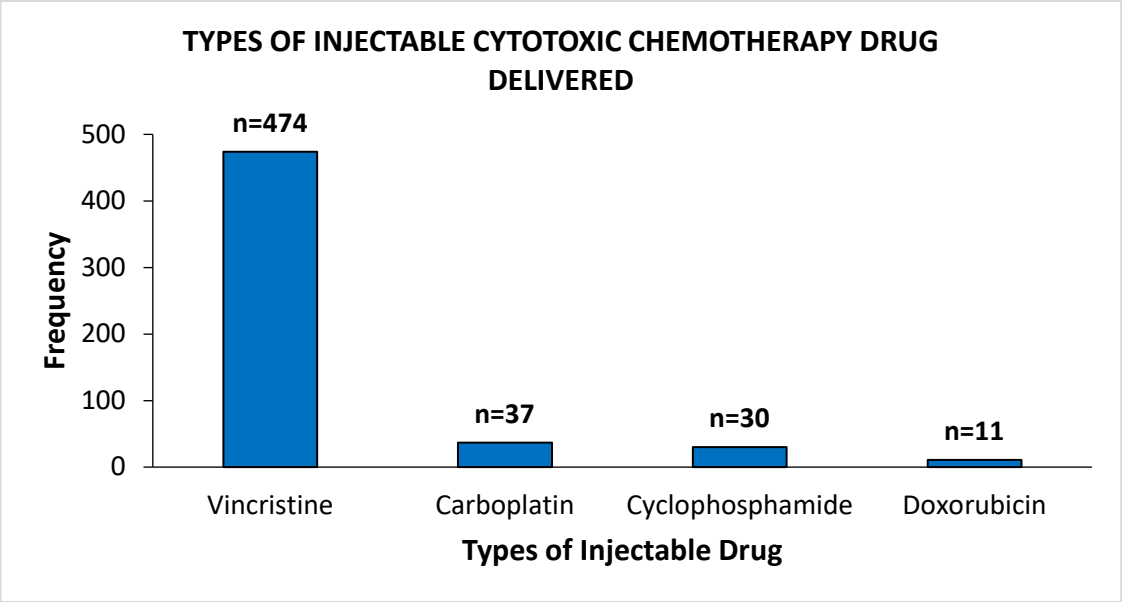


Figure 8: Types of injectable cytotoxic chemotherapy drugs used in dogs.

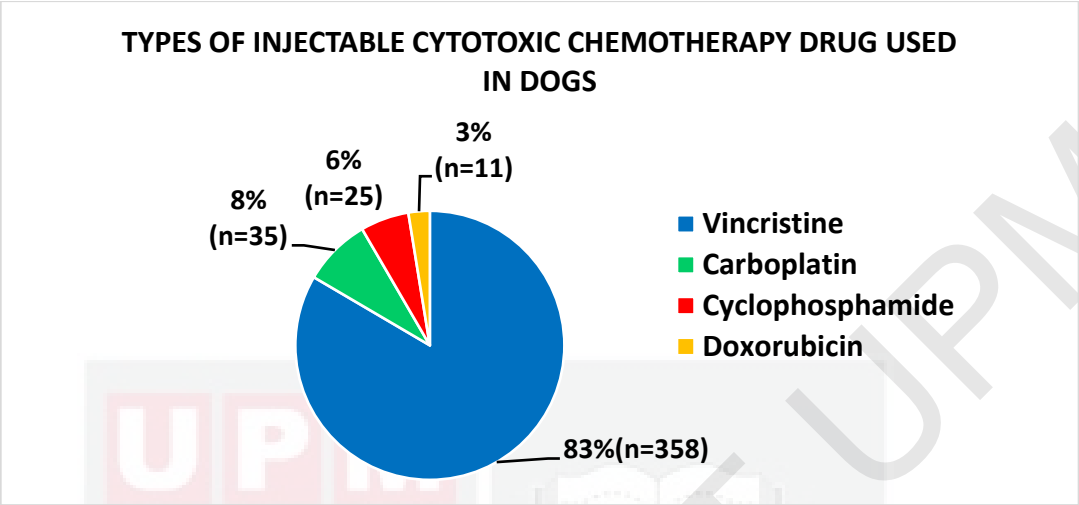
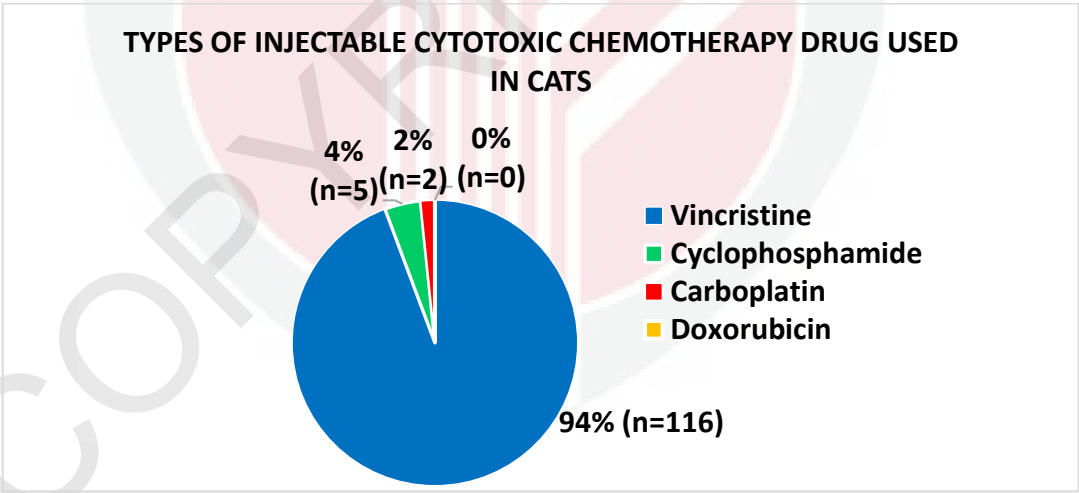
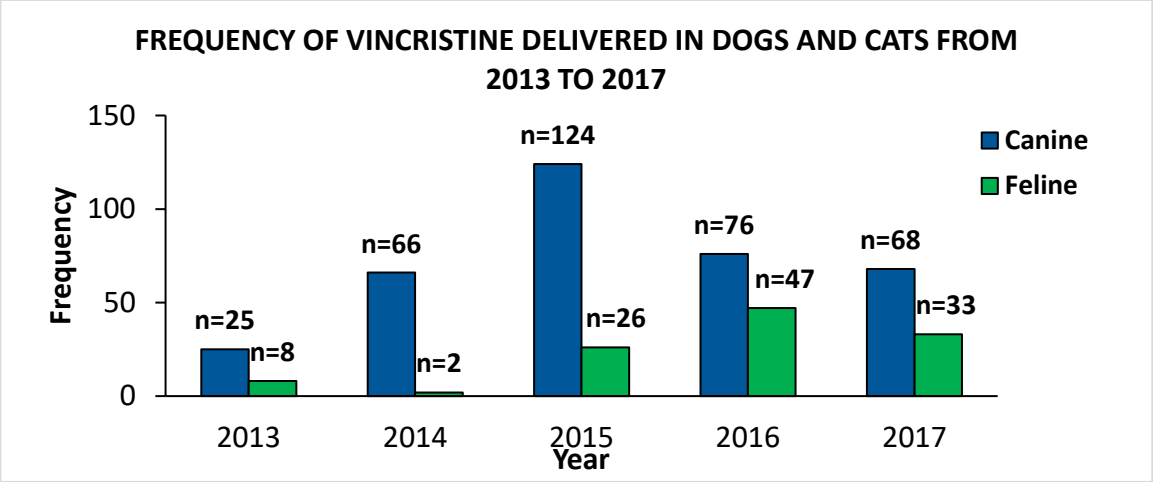


Figure 9: Types of injectable cytotoxic chemotherapy drugs used in cats.



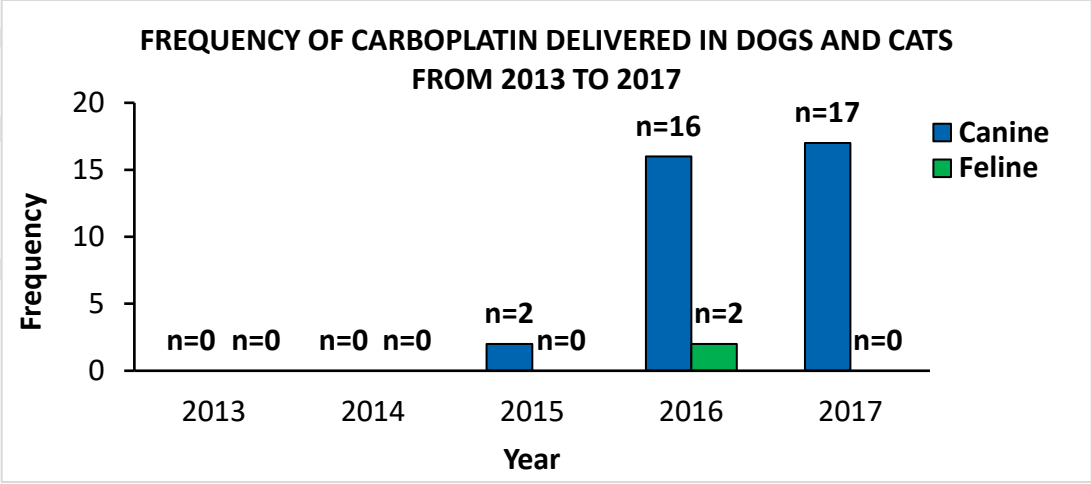
The number of vincristine delivered in dogs increased from 2013 to 2015 and decreased in 2016 and 2017. There was a fluctuation pattern in frequency of vincristine used in cats from 2013 to 2017 *(Figure 10)*.

Figure 10: Vincristine used in dogs and cats.



The number of carboplatin doses delivered was recorded highest in two years which was 2016 and 2017, whereas only 2 doses of carboplatin delivered in cats in 2016 and none for the other years *(Figure 11)*.

Figure 8: Carboplatin delivered in dogs and cats.



For dogs the frequency of cyclophosphamide in 2015 was the highest, but reduced in 2016 and 2017. For cats, cyclophosphamide was only used in 2013, 2016 and 2017 *(Figure 12)*. Doxorubicin was only used in dogs but not in cats over 5 years. The frequency of doxorubicin in 2013 was 1 and no doxorubicin used in 2014. There were 2 doses of doxorubicin given in 2015, 1 dose in 2016, and 6 doses in 2017 *(Figure 13)*.

Figure 9: Cyclophosphamide used in dogs and cats.

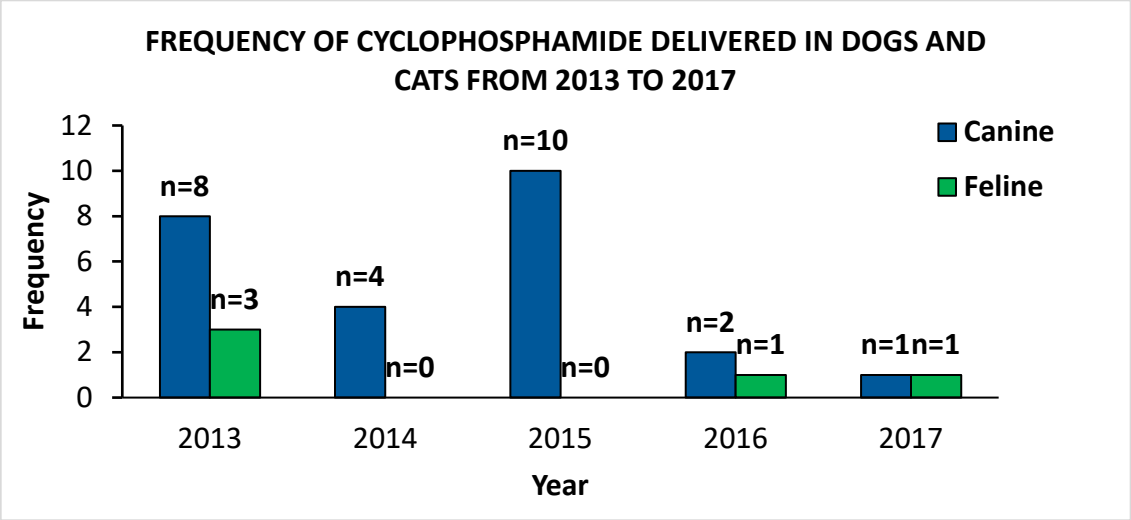
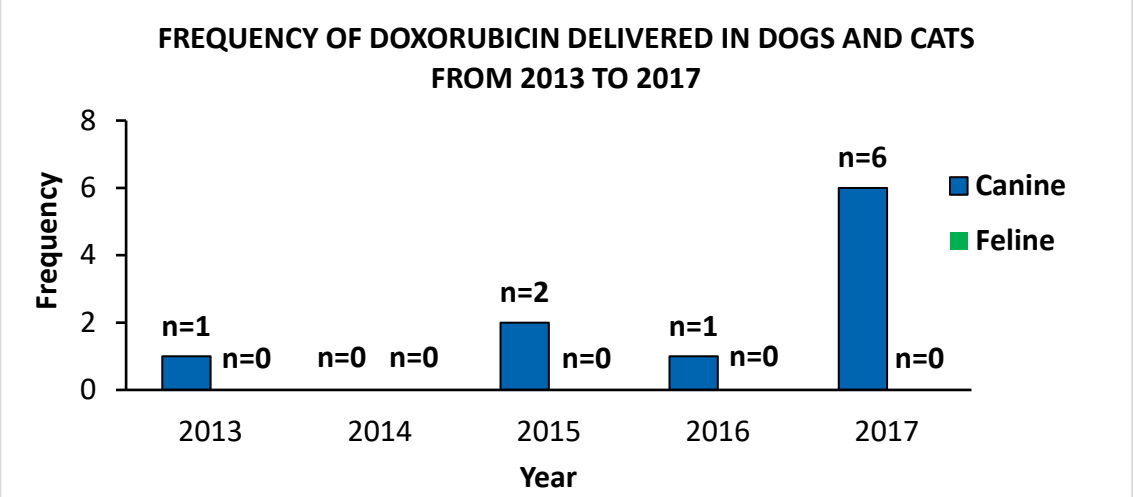


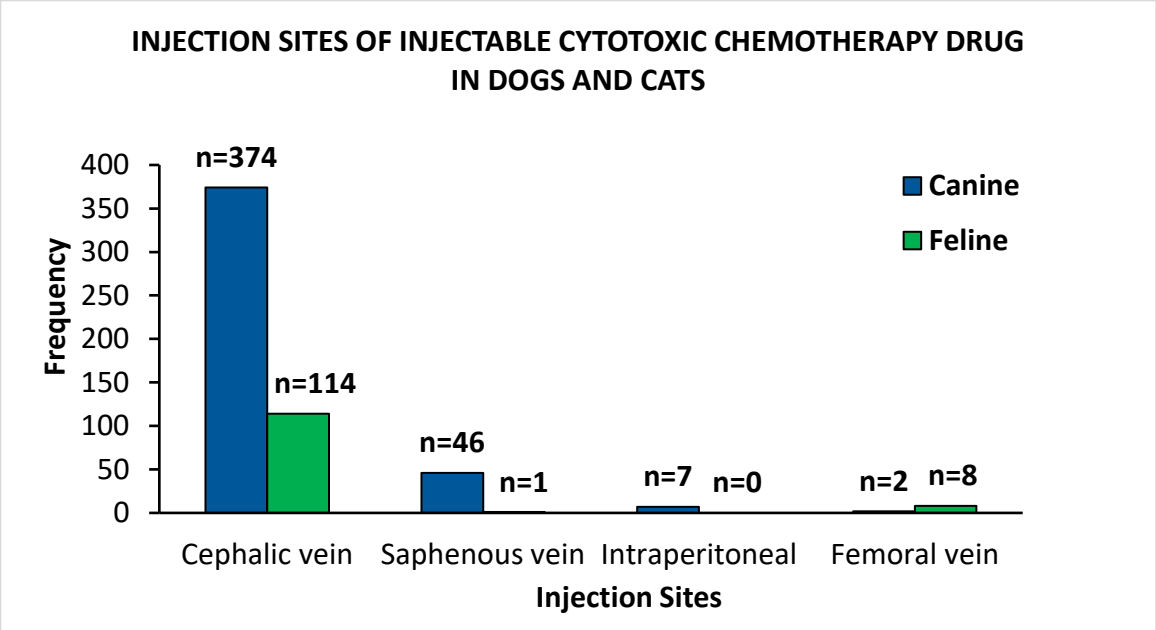
Figure 10: Doxorubicin delivered in dogs and cats.



4.8 Administration sites of cytotoxic chemotherapy drugs in dogs and cats

There were four injection sites commonly used for cytotoxic chemotherapy in UVH, UPM. The most common site of administration in dogs was cephalic vein (n=374), followed by saphenous vein (n=48), intra-peritoneal (n=7) and femoral vein (n=2). The most common injection site of chemotherapy drug was cephalic vein (n=114), followed by femoral vein (n=8) and saphenous vein (n=1). Intraperitoneal route was not used in any of the cats in this facility *(Figure 14)*.

Figure 11: Injection sites of injectable cytotoxic chemotherapy drugs in dogs and cats.



4.9 Side effects of cytotoxic chemotherapy in dogs and cats

Among dogs receiving cytotoxic chemotherapy, 22.9% (n=19) were with missing data for hematopoietic toxicities. A total of 50.6% (n=42) developed anaemia, 20.5% (n=17) developed leukopenia, 43.4% (n=36) of dogs were thrombocytopenic. There were 30.1% (n=25) develop lymphopenia. All dogs (100%, n=83) received chemotherapy did not have extravasation sign after administration. Only 16.9% (n=14) of dogs developed vomiting, diarrhoea in only 6% (n=5) and petechial haemorrhage was observed in 3.6% (n=3) of dogs in this cohort of study *(Table 4)*.

Table 4: Side effects of cancer chemotherapy in dogs.

Side Effects		**Yes**	**No**	**Missing Data**	**Total**
Anaemia	n	42	22	19	83
	%	50.6%	26.5%	22.9%	100%
Leukopenia	n	17	47	19	83
	%	20.5%	56.6%	22.9%	100%
Thrombocytopenia	n	36	28	19	83
	%	43.4%	33.7%	22.9%	100%
Lymphopenia	n	25	39	19	83
	%	30.1%	47%	22.9%	100%
Extravasation	n	0	83	0	83
	%	0%	100%	0%	100%
Vomiting	n	14	66	3	83
	%	16.9%	79.5%	3.6%	100%
Diarrhoea	n	5	75	3	83
	%	6.0%	90.4%	3.6%	100%
Petechial Haemorrhage	n	3	77	3	83
	%	3.6%	92.8%	3.6%	100%

Among cats that received chemotherapy, 60% (n=18) had anaemia, 10% (n=3) developed leukopenia, 68% (n=18) had thrombocytopenia and 36.7% (n=11) with lymphopenia. There were 3.3% (n=1) of cats developed drug extravasation reaction. Compared to dogs, 3.3% (n=1) of vomiting, diarrhoea and petechial haemorrhage signs were missing data. 23.3% (n=7) developed vomiting, 3.3% (n=1) had diarrhoea and none developed petechial haemorrhage *(Table 5)*.

Table 5: Side effects of cancer chemotherapy in cats.

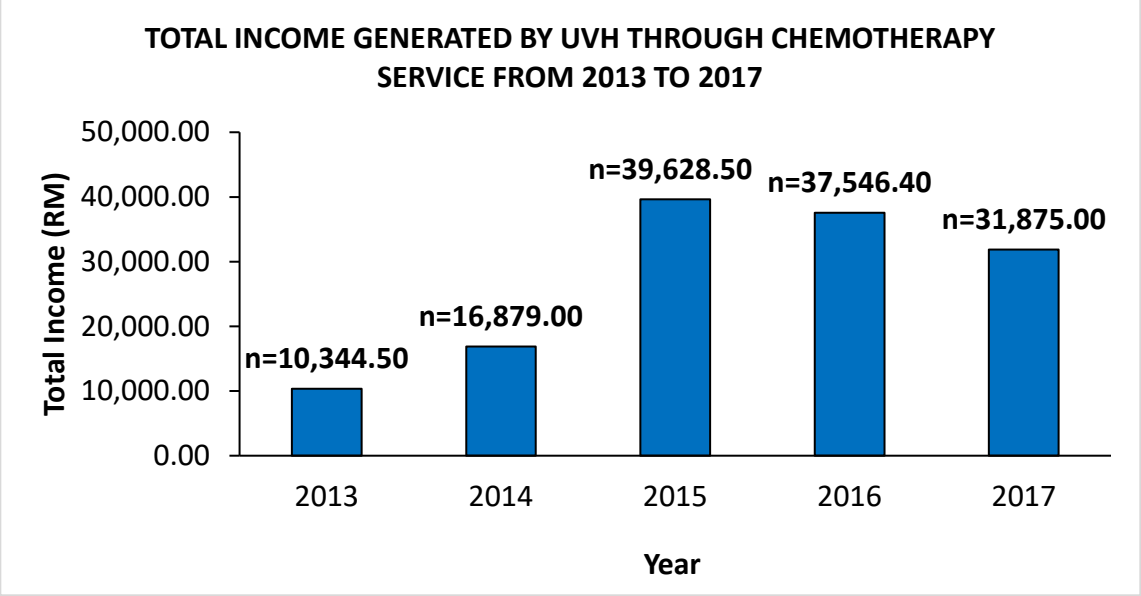
Side Effects		**Yes**	**No**	**Missing Data**	**Total**
Anaemia	n	18	5	7	30
	%	60%	16.7%	23.3%	100%
Leukopenia	n	3	20	7	30
	%	10%	66.7%	23.3%	100%
Thrombocytopenia	n	18	5	7	30
	%	60%	16.7%	23.3%	100%
Lymphopenia	n	11	12	7	30
	%	36.7%	40%	23.3%	100%
Extravasation	n	1	29	0	30
	%	3.3%	96.7%	0	100%
Vomiting	n	7	22	1	30
	%	23.3%	73.3%	3.3	100%
Diarrhoea	n	1	28	1	30
	%	3.3%	93.3%	3.3	100%
Petechial Haemorrhage	n	0	29	1	30
	%	0%	96.7%	3.3%	100%

4.10 Costs involved for cytotoxic chemotherapy and total income generated by injectable cytotoxic chemotherapy service

From 2013 to 2017, a total of RM 136,273.40 income was generated by UVH, UPM through cytotoxic chemotherapy service. 78.9% (n=RM 107,478.40) of total income was generated by cytotoxic chemotherapy in dogs and 21.1% (n=RM 28,745) was from chemotherapy in cats. With a total 552 doses of cytotoxic chemotherapy drugs over 5 years, the average cost involved in one visit of cancer chemotherapy was RM247. The average cost of cancer chemotherapy for each patient was RM 1,206 with minimum cost of RM 170 and maximum cost of RM 5943.

There highest income generated overall is in 2015 with RM 39,628.50, however the income dropped to RM 37,546.40 in 2016 and RM 31,875 in 2017 *(Figure 15).*

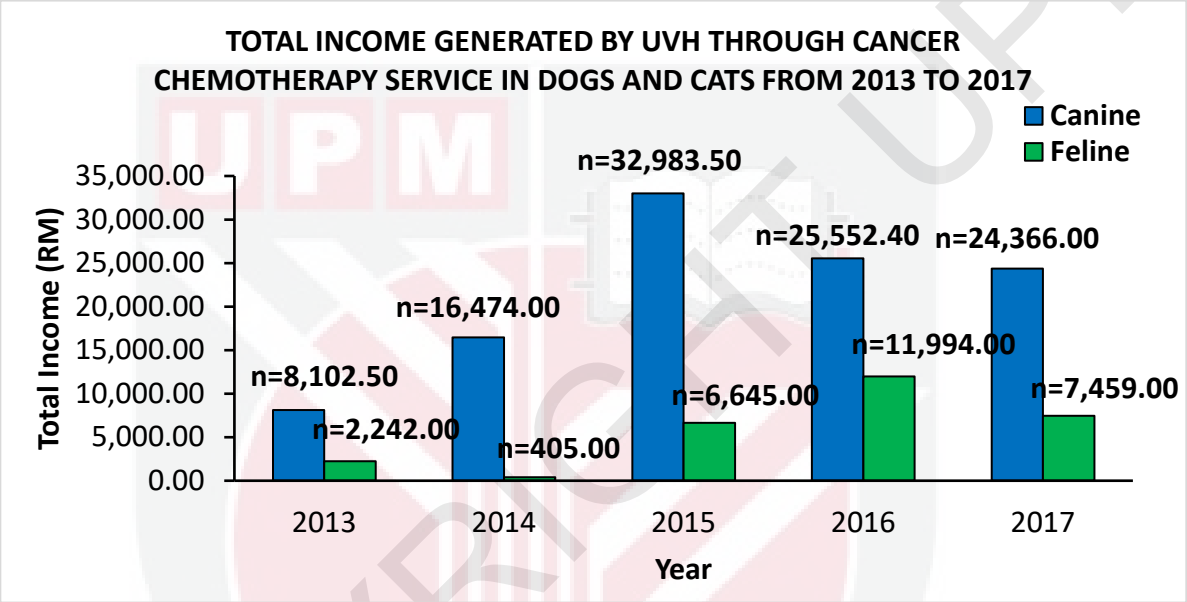
Figure 12: Total income generated by UVH through cancer chemotherapy service from 2013 to 2017



.

From 2013 to 2017, total income generated through cancer chemotherapy service is higher among dogs compared to cats *(Figure 16)*.

Figure 13: Total income generated through cancer chemotherapy in dogs and cats from 2013 to 2017.



4.11 Survival analysis in dogs and cats with different factors

The survival probabilities for non-pedigree dog receiving cytotoxic chemotherapy drugs were higher than survival probabilities for pedigree dog receiving cytotoxic chemotherapy drugs. Pedigree dogs had 14.62 times of risk to die than non-pedigree dogs (Log Rank *p*-value <0.001) *(Figure 17)*. For comparison between TVT and lymphoma, dogs with TVT was 29.359 times more likely to survive than dogs with lymphoma (Log Rank *p*-value <0.001) *(Figure 18)*. However, there was no differences in survival probabilities among different breeds of cats as compared to the common breed DSH cats (Log Rank *p*-value=0.754) *(Figure 19)*.

Figure 14: Kaplan-Meier curve showing survival of dogs receiving cancer chemotherapy according to types of pedigree. There was significant difference in survival time between types of pedigree (P<0.001, CI 95%, X^2=14.620).

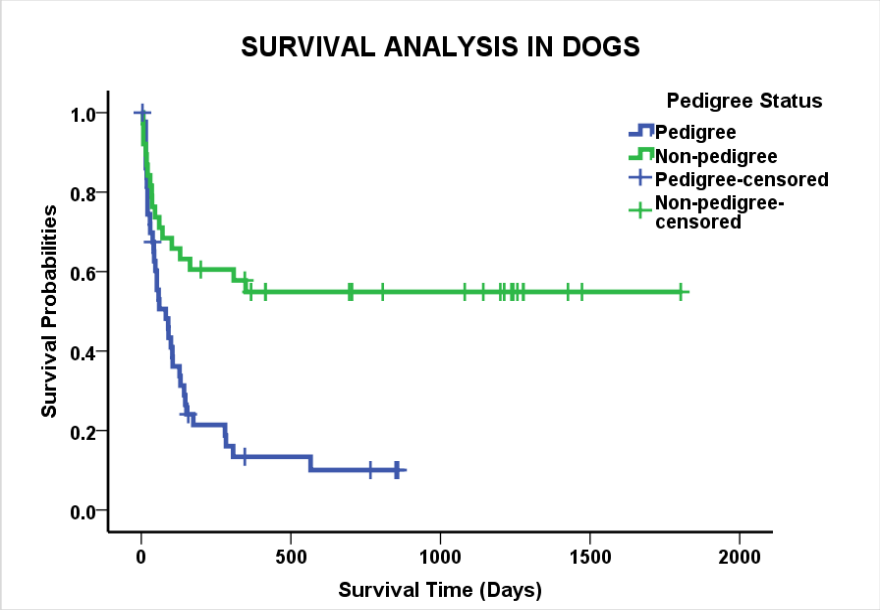


Figure 15: Kaplan-Meier curve showing survival of dogs receiving cancer chemotherapy according to types of tumour. There was significant difference in survival time between types of tumour (P<0.001, CI 95%, X^2=29.359).

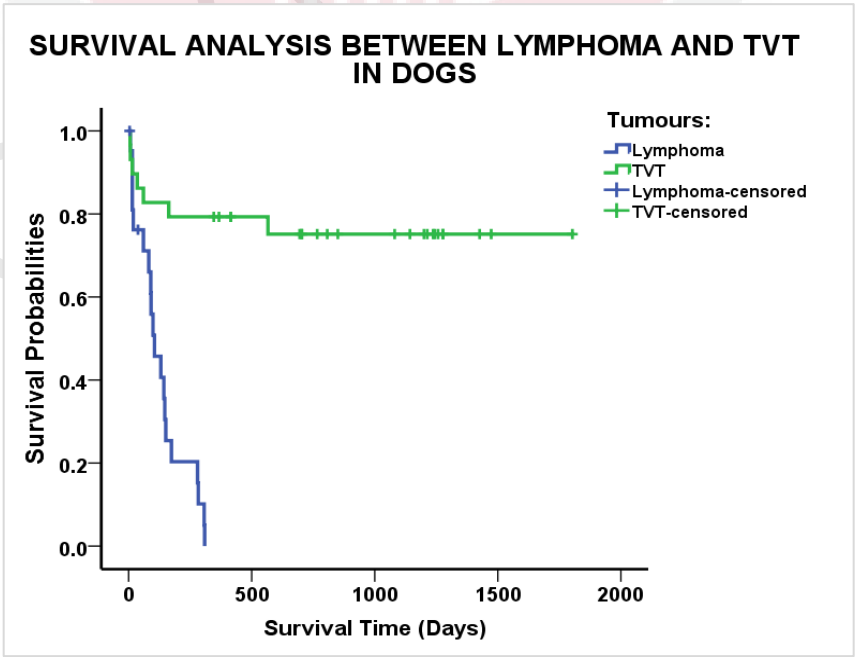
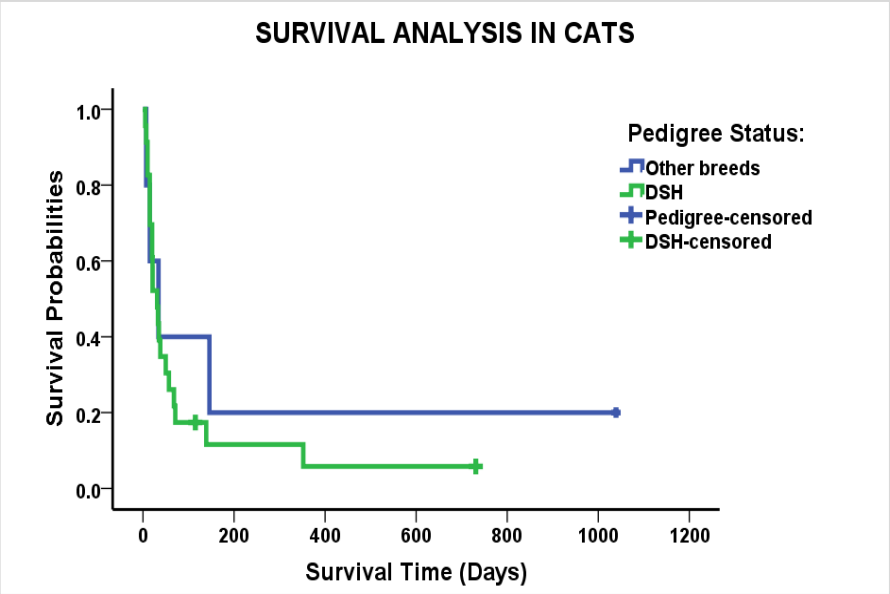


Figure 16: Kaplan-Meier curve showing survival of cats receiving cancer chemotherapy according to types of pedigree. There was no significant difference in survival time between types of pedigree (P=0.754, CI 95%, X^2=0.098).



4.12 Influence of host factors on breed receiving cancer chemotherapy

When compared among canine species, there was no significant association (Fisher's exact test) observed between sex and neuter status with breed pedigree due to both *p*-values (0.118 and 0.649) were more than α=0.05. There was significant association observed between age and tumour localization with breed pedigree due to both p-values (0.009 and <0.001) were less than α =0.05. ≤2 years old of age was less likely to be pedigree dog receiving cancer chemotherapy compared to >2 years old. Odds of 0.175 (CI 95%, 0.045 – 0.687) for pedigree dog in ≤2 years old of age when compared among canine species. Haematopoietic neoplasia is more commonly treated with injectable

cytotoxic drugs which is more common in pedigree dogs compared to other types of solid tumours with odds of 11.159 (CI 95%, 2.993 – 41.608) *(Table 6).*

When cases were compared with feline species, there was no significant association (Fisher's exact test) observed among sex, age and tumour localization with breed pedigree due to p-values for these factors (0.628, 0.640 and 1.000) were more than α=0.05. There was statistically significant association observed between neuter statuses with breed pedigree in cats as *p*-value (0.047). Intact cats of DSH breed were less likely to receive chemotherapy than neutered cats because intact cats had odds of 0.097 (CI 95%, 0.009 – 1.028) than neutered cats. *(Table 6)*

Table 6: Risks of receiving cancer chemotherapy, comparing pedigree and non-pedigree in dogs, DSH and other breeds in cats.

	Comparison with Canine species				**Comparison with Feline species**			
Host factor	**Pedigree**	**Non-pedigree**	***p*-value**	**OR (95% CI)**	**DSH**	**Others**	***p*-value**	**OR (95% CI)**
Sex								
Female	15	30	0.118	--	10	3	0.628	--
Male	20	18			15	2		
Neuter Status				--	7	4	**0.047**	**0.097 (0.009, 1.028)**
Intact	30	15	0.649		18	1		
Neutered	23	15						
Age								
⩽2 years	3	42	**0.009**	**0.175 (0.045, 0.687)**	9	1	0.640	--
>2 years	11	27			16	4		
Tumour Localization				**11.159**				--
Blood	22	3	**<0.001**	**(2.993,**	16	3	1.000	
Others	23	35		**41.608)**	9	2		

5.0 DISCUSSION

In this study, 113 medical records of dogs and cats who received cytotoxic chemotherapy in University Veterinary Hospital (UVH), UPM were reviewed for 5 years from 2013 to 2017. Those that diagnosed with cancer and without receiving cancer chemotherapy in UVH was not included in this study. Cancer chemotherapy practice information including the number of animals treated, types of tumour treated, types of cytotoxic drugs and side effects of cancer chemotherapy used were determined based on case records with cancer chemotherapy in UVH. Cancer chemotherapy is commonly used to treat malignant cancer in dogs and cats to reduce the growth of tumours and spread of malignant neoplastic cells (Williams *et al.*, 2017). A survey was conducted in Malaysia in 2014, where forty-two clinics in Malaysia have chemotherapy services for dogs and cats.

In this study which was focussed on data from animals subjected to chemotherapy at UVH, the number of animals presented for cytotoxic chemotherapy was 113. A total of 78% of them were dogs and 22% were cats. This suggests that dogs are more commonly presented with neoplasia and dog owners are inclined towards chemotherapy as treatment option for their pet dogs as compared to cats which is observed in other studies where more dogs were found with tumours at their practices (Brønden *et al.*, 2009; Vascellari *et al.*, 2009). The number of dogs increased from 2013 to 2017 due to UVH is a referral hospital and is equipped with cancer chemotherapy facilities. Thus, more tumour cases are referred to UVH for second opinion and treatment. However, the number of cases decreased slightly after 2015 and there was an increased trend in cat cases from 2013 to 2017 due to more cases were referred to UVH.

This study discovered that local dogs were the most frequent breed received cytotoxic chemotherapy in UVH. This result was different from other studies done by Bhaiyat *et al.* (2013) and Baioni *et al.* (2017) in other countries which stated that German Shepherd had the highest number of developing tumours. This is due to local dog is a popular pet in Malaysia which is managed as semi-roamer or free roamer. Besides that, the Domestic Short Hair cats had the highest number of receiving cytotoxic chemotherapy in UVH and this was similarly noted in the study done by Zambelli (2015) in South Africa. The Domestic Short Hair cat is a popular pet found in Malaysia thus overrepresented in this study.

There were 30 dogs (36%) received cytotoxic chemotherapy in UVH with age of less than 4 years old. This was contradicted by other studies where old age was prone to develop tumour and the mean age was 10 years old (Komazawa *et al.*, 2016). Among the 30 dogs in this study, 22 of them were diagnosed with transmissible venereal tumour (TVT). TVT commonly occurs at 3 years of age which is when the dogs are sexually active (Santiago-flores *et al.*, 2012). Chemotherapy is the most effective treatment for TVT (Calvet *et al.*, 1982; Nak *et al.*, 2005). Surgical treatment has shown less effective and has possible of relapse due to tumour cell transplantation into the surgical wound (Theilen & Madewell, 1979). Thus, more young age dogs with TVT was presented to UVH for treatment. After 4 years of age, the number of cases in dogs increased with age due to the risk of developing aberrantly dividing cells is increased, and immune system becomes less effective to detect and eradicate those aberrant cells (Kitchell & Dervisis, 2010). Besides that, cats with age of 1 to 2 years old had the highest number of receiving cytotoxic chemotherapy due to all of them were diagnosed with mediastinal lymphoma which is in agreement with other studies (Teske *et al.*, 2002). Mediastinal lymphoma often

found in cats with FeLV positive (Macy & Reeds, 2010) and most of FeLV-positive cats were young age (Arjona *et al.*, 2000).

Most common tumour cell type in dogs (80.7%) and cats (70%) in this study were round cell tumour. Transmissible venereal tumour, lymphoma and mast cell tumour were common tumours in dogs in this study while lymphoma was common in cats. These tumours were classified as round cell tumour and they are often treated with injectable cytotoxic chemotherapy (Morris, 2001; Taylor, 2010; Amorim *et al.*, 2018). This result was similar to a study done by Loh *et al*. (2014) in Malaysia. A study done in India also showed that TVT was the most frequent tumour (Gandotra, *et al*., 1993). TVT is commonly found in dogs that are in close contact with one another and exhibit unrestrained sexual activity (Purohit, 2008). In Malaysia, local dogs are managed as semi-roamer or free-roamer that are sexually intact. TVT spreads widely in tropical or subtropical urban areas with limited control of free-roaming dog population (Ganguly, *et al*., 2013). Therefore, they have a high chance to develop TVT and spread to each other. Feline lymphoma was common in this study as FIV and FeLV are common in domestic cat in peninsular Malaysia (Bande *et al.*, 2012). FIV increases 6 folds of risk to develop lymphoma, FeLV increases 62 folds of risk, concurrent FIV and FeLV increase 77 folds of risk (Shelton, *et al*., 1990). This causes cats have a higher risk of developing lymphoma, thus more cats with lymphoma presented to UVH for cytotoxic chemotherapy.

The common cytotoxic chemotherapy drug used in dogs and cats was vincristine. This result was consistent with studies done by Loh *et al*. (2014) in Malaysia and Cave *et al.* (2007) in United Kingdom. Vincristine is indicated to treat lymphoma in dogs and cats, TVT in dogs and some soft tissue sarcoma in combination of other drugs (Moore,

2010). The mode of mechanism of vincristine acting on TVT and lymphoma is binding to microtubular protein and inhibit the formation of mitotic spindle, thus inhibiting mitosis of neoplastic cells (Dobson, 1998). TVT in dogs and lymphoma in cats had the higher frequency of receiving cytotoxic chemotherapy in UVH, thus vincristine was used frequently to treat these tumours. Doxorubicin was the least common cytotoxic drug to be used in dogs and cats even though this drug is more effective than vincristine. This is due to side effects of doxorubicin causing irreversable cumulative cardiotoxicity in dogs and cats, and renal toxicity in cats (Moore, 2010).

Cephalic vein was the most common route for cytotoxic chemotherapy drug delivery in dogs and cats because it is easier to monitor for extravasation (Lana & Dobson, 2010) and to stabilize an indwelling catheter. Saphenous veins either lateral or medial were used when cephalic veins were used for previous intravenous injections or develop severe hematoma due to failure at attempts to insert indwelling catheter. Lateral saphenous vein was an alternative site for cytotoxic chemotherapy drugs in dogs instead of medial saphenous vein. This is due to medial saphenous vein is smaller than lateral sphenous vein in dogs (Davis, 2009). On the other hand, medial saphenous veins was an alternative site in cats because lateral sphenous vein is smaller than medial saphenous vein (Davis, 2009). Intraperitoneal site was less commonly used because this site is specific for tumours including metastatic lesions located within the peritoneal cavity (Markman, 1999). This site was used in dogs in this study as there was a case of mesothelioma in peritoneal cavity.

Based on history, physical examination and blood parameters after cytotoxic chemotherapy, hematopoietic toxicity was the most common side effect in dogs and cats

receiving cytotoxic chemotherapy. Among the hematopoietic toxicities, more dogs and cats showed anaemia and thrombocytopenia instead of leukopenia. Anaemia and thrombocytopenia could be due to paraneoplastic syndromes specific to seleted tumour type. Anaemia can be resulted from low red blood cells production caused by bone marrow infiltration and myelophthisis from tumours such as lymphoma, leukemia, myeloma and histiocytic sarcoma. Neoplastic cells also release cytokines that suppress myelopoiesis (Elliott, 2014). Thrombocytopenia can be caused by lymphoma, hemangiosarcoma and melanoma through increased platelet utilization, platelet destruction and decreased platelet production (Elliott, 2014). Thrombocytopenia in cats could be false thrombocytopenia commonly observed in cats which can be caused by platelet aggregation and platelets too large to be detected by haematology instrument (Tvedten, 2012). Blood smear can be used to distinguish true thrombocytopenia and pseudothrombocytopenia in cats.

The average cost of cytotoxic chemotherapy per visit was RM 247 which include consultation fee, blood test, cytotoxic drug and administration fee. Additional tests such as radiography for metastasis check, oral medications, hospitalization and fluid therapy were not included. However, the cost of cancer chemotherapy varies with types of drugs used because every drug has a different price. In this study, the total income generated by UVH through cancer chemotherapy was based on the number of cases presented and the number of cytotoxic chemotherapy drugs delivered in dogs and cats. From 2013 to 2015, there was increased of total income due to more cases were referred to UVH which is a referral hospital and is equipped with chemotherapy facilities. However, there was a decrease in total income from 2016 to 2017 because other private clinics started to practice cancer chemotherapy especially using vincristine (personal communiations). More

owners prefer to do cancer chemotherapy at private clinics which are closer to their home after their pets were diagnosed with tumour in UVH. They only come to UVH for certain types of cytotoxic drug which are available in UVH such as cyclophosphamide. Besides than the aforementioned reason, towards 2016 and 2017, more highly malignant solid tumour cases were presented which warranted drugs such as carboplatin and doxorubicin which does not require weekly administrations, hence it would be recorded as less doses delivered and less number of visits for these patients requiring such protocols as compared to using vincristine in some cases on weekly basis and require frequent doses.

Non-pedigree dog that received cancer chemotherapy had 14.62 times of higher survival rate than pedigree dog in this study. This is due to most of non-pedigree dogs developed TVT which is curable by cytotoxic chemotherapy if TVT is in initial stage of progression (Boscos and Ververidis, 2004). Complete remission can be achieved after 2 to 8 injections of vincristine with once a week (Calvet, *et al*., 1982). Some of TVT cases died due to were diagnosed lately and the tumour was metastasized to other distant sites. Moreover, dogs with TVT had 29.36 times of higher survival probability than dogs with lymphoma in this study. Compared to TVT, lymphoma is not a curable tumour by cancer chemotherapy. Cancer chemotherapy is used for prolongation of survival time of lymphoma. The median survival time of lymphoma with complete remission by using multi-agent therapy was 12 months (Vail, 2009a). Furthermore, there was no significant difference in survival rate between Domestic Short Hair cats and pedigree cats after receiving cytotoxic chemotherapy in this study. This is due to all cat breeds have same opportunities to develop tumour especially lymphoma which does not have breed predilection.

Pedigree dogs with age less than 2 years old had less chance to receive cancer chemotherapy than those with more than 2 years old when compared with non-pedigree dog. This is because less pedigree dog developed TVT which commonly affected young age due to the management of pedigree dogs as indoor. Most of pedigree dogs developed tumours that are common in old age such as lymphoma, mast cell tumour, squamous cell carcinoma, and so on. There is a study showed similar results that only 23.64% of dogs developed tumours were less than 5 years old (Grüntzig *et al.*, 2015). Tumour development is common in old age due to the risk of developing aberrantly dividing cells is increased, and immune system becomes less effective to detect and eradicate those aberrant cells (Kitchell & Dervisis, 2010). Besides that, pedigree dogs that received cytotoxic chemotherapy had 11.159 times of higher risk to develop haematopoietic neoplasia compared to other types of tumours when compared with non-pedigree dogs. This result was similar to other studies that showed pedigree dogs had 2.3 times higher risk than non-pedigree dogs for developing malignant tumour of lymphoid tissues (Vascellari *et al.*, 2009). There was no significant association between sex and neuter status with pedigree dogs receiving cancer chemotherapy. These results were contradicted to other studies that showed neutered dogs have higher risk of developing tumours (Grüntzig *et al.*, 2016). Mammary gland tumour cases are common in intact female dogs but mostly were not subjected for chemotherapy. Neutered DSH cats had a higher risk than intact cats to receive cytotoxic chemotherapy when compared with other breeds. This result was consistent with other studies showing neutered males and females had the highest number developing tumour than intact males and females (Graf *et al.*, 2015).

Limitations of this study were the retrieved data were incomplete due to loss to follow up as some cases went to private clinics which were convenient for owners to

continue cancer chemotherapy at UVH. Some cases stopped the cancer chemotherapy after administration of few doses due to owner did not have compliance or had financial constraint. Besides that, retrieving data from the manual or paper recording system was time-consuming as every single file has to be searched from the archive room, and read through pages by pages to obtain data needed. Moreover, some cases that were diagnosed with tumours have the potential of doing cancer chemotherapy, however, the option of doing cancer chemotherapy was rejected by owners. Thus, the data on the number of animals received injectable cytotoxic cancer chemotherapy in this study could be more than the data collected.

For recommendation, a study on the prevalence of neoplasia in canine and feline presented to University Veterinary Hospital, UPM can be carried out because this study is yet to be established in Malaysia. This study able to let us know the percentage of cases that was diagnosed with tumour are treated by cancer chemotherapy, thus evaluating the acceptance of owner towards cancer chemotherapy.

6.0 CONCLUSION

In conclusion, the number of dogs received cytotoxic chemotherapy was higher than cats in UVH, UPM from 2013 to 2017. However, this data can't be used as the prevalence of neoplasia in dogs and cats because this study only included those receiving cancer chemotherapy in UVH. The most common type of neoplasia treated in dogs was TVT whereas lymphoma was in cats. More dogs with malignant neoplasia received chemotherapy compared to cats. The most common injectable cytotoxic chemotherapy drug used in dogs and cats was vincristine. The common side effects of chemotherapy in dog and cat are anaemia and thrombocytopenia. The average cost of cancer chemotherapy per visit was less than RM300, thus alternative hypothesis was rejected.

REFERENCES

Adams, V. J., Evans, K. M., Sampson, J., & Wood, J. L. N. (2010). Methods and mortality results of a health survey of purebred dogs in the UK. *Journal of Small Animal Practice*, 51(10), 512–524.

Allen R, Crump K. (2011). Chemotherapy handling, safety, and disposal. In Crump, K., & Thamm, D., *Cancer chemotherapy for the veterinary health team*. West-Sussex, UK: Wiley-Blackwell, 57-69.

Amorim, R. L., Grandi, F., & Ferreira, M. (2018). Brazilian Consensus For The Diagnosis, Treatment and Prognosis of Cutaneous Mast Cell Tumours in Dogs. *Ivestigação*, *17*(1), 01–15.

Arjona, A., Escolar, E., Soto, I., Barquero, N., Martin, D., & Gomez-Lucia, E. (2000). Seroepidemiological survey of infection by feline leukemia virus and immunodeficiency virus in Madrid and correlation with some clinical aspects. *Journal of Clinical Microbiology*, *38*(9), 3448–3449.

Baba, A. I., & Câtoi, C. (2007). Chapter 19: Principles of anticancer therapy. In Baba, A.I., & Câtoi, C., *Comparative Oncology* (pp. 671-787). Bucharest: The Publishing House of the Romanian Academy.

Baioni, E., Scanziani, E., Vincenti, M. C., Leschiera, M., Bozzetta, E., Pezzolato, M., Desiato, R., Bertolini, S., Maurella, C., Ru, G. (2017). Estimating canine cancer incidence: Findings from a population-based tumour registry in northwestern Italy. *BMC Veterinary Research*, *13*(1), 1–9.

Bande, F., Arshad, S. S., Hassan, L., Zakaria, Z., Sapian, N. A., Rahman, N. A., & Alazawy, A. (2012). Prevalence and risk factors of feline leukaemia virus and feline immunodeficiency virus in peninsular Malaysia. *BMC Veterinary Research*, *8*(1), 33.

Barber, L., & Burgess, K. (2016). Overview of Antineoplastic Agents. In *The Merck Veterinary Manual 11th Edition: 1603-1615.*

Bhaiyat, M. I., Chikweto, A., Tiwari, K. P., Deallie, C., Pawaiya, R. S., Inga, A., Younger, C. H., Sharma, R. N. (2013). Research Article: A retrospective Study of Canine Tumours in Grenada , West Indies. *Advances in Animal and Veterinary Sciences*, *1*(5), 134–139.

Biller, B., Berg, J., Garrett, L., Ruslander, D., Wearing, R., Abbott, B., Patel, M., Smith, D., Bryan, C. (2016). 2016 AAHA Oncology Guidelines for Dogs and Cats. *Journal of the American Animal Hospital Association*, *52*(4), 181–204.

Boscos, C. M., & Ververidis, H. N. (2004). Canine TVT--Clinical Findings, Diagnosis and Treatment. *Sci. Proc WSVA-FECAVA-HVMS World Congress*, *2*, 758–761.

Brønden, L. B., Lindstrand, S., Nielsen, S. S., Toft, N., & Kristensen, A. T. (2009). Validation of data collected in the Danish Veterinary Cancer Registry. *Veterinary and Comparative Oncology*, *7*(3), 207–211.

Calvet, C. A., Leifer, C. E., & McEwen, E. G. (1982). Vincristine for the treatment of Transmissible Venereal Tumour in the dog. *Journal of America Veterinary Medicine Association*, *181*(2), 163–164.

Cave, T. A., Norman, P., & Mellor, D. (2007). Cytotoxic drug use in treatment of dogs and cats with cancer by UK veterinary practices (2003 to 2004). *Journal of Small Animal Practice*, *48*, 371–377.

Charney, S. C., Bergman, P. J., McKnight, J. A., Farrelly, J., Novosad, C. A., Leibman, N. F., & Camps-Palau, M. A. (2005). Evaluation of intracavitary mitoxantrone and carboplatin for treatment of carcinomatosis, sarcomatosis and mesothelioma, with or without malignant effusions: A retrospective analysis of 12 cases (1997-2002). *Veterinary and Comparative Oncology*, *3*(4), 171–181.

Chauhan, A. S., Prinja, S., Ghoshal, S., Verma, R., & Oinam, A. S. (2018). Cost of treatment for head and neck cancer in India. *PLoS ONE*, 13(1), 1–13.

Chu, C., & Rubin, S. (2018). Basic Principles of Chemotherapy. In P. DiSaia, W. Creasman, R. Mannell, S. McMeekin, & D. Mutch, *Clinical Gynecologic Oncology* (9th Edt, pp. 449–469). Canada: Elsevier.

Chun, R., Garrett, L., & Vail, D. M. (2007). Cancer Chemotherapy. In S. J. Withrow & D. M. Vail (Eds.), *Withrow and MacEwen's Small Animal Clinical Oncology* (4th Edt, pp. 163–188). United States: Saunders Elsevier.

Couto, C. G. (2014). Complications of Cancer Chemotherapy . In R. Nelson, & C. G. Couto, *Small Animal Internal Medicine* (5th Edt, pp. 1144-1153). Mosby.

Davis, H. (2009). Chapter 61 – Peripheral Venous Catheterization. In D. C. Silverstein & K. Hopper (Eds.), *Small Animal Critical Care Medicine* (pp. 260–263). Canada: Saunders Elsevier.

Dhaliwal, R. S. (2009). Tumour-and Treatment-Related Complications. In C. Henry & M. L. Higginbotham (Eds.), *Cancer Management in Small Animal Practice* (pp. 122–128). Canada: Saunders Elsevier.

Dobson, J. (1998). Options for the use of chemotherapy in small animals Part 1. Anticancer drugs. *In Practice*, *20*, 403–413.

Dobson, J. M. (2010). Introduction: Cancer in Cats and Dogs. In J. Dobson & B. Lascelles (Eds.), *BSAVA Manual of Canine and Feline Oncology* (3rd ed., pp. 1–5). BSAVA.

Dobson, J. M. (2013). Breed-Predispositions to Cancer in Pedigree Dogs. *ISRN Veterinary*

Science, 1–23.

Dobson, J. M., Samuel, S., Milstein, H., Rogers, K., & Wood, J. L. N. (2002). Canine neoplasia in the UK: Estimates of incidence rates from a population of insured dogs. *Journal of Small Animal Practice*, *43*(6), 240–246.

Elliott, J. (2014). Paraneoplastic syndromes in dogs and cats. *In Practice*, *36*(9), 443–452.

Falk, E. F., Lam, A. T. H., Barber, L. G., & Ferrer, L. (2016). Clinical characteristics of doxorubicin-associated alopecia in 28 dogs. *Veterinary Dermatology*, *26*, 142–150.

Farese, J. P., & Withrow, S. J. (2013). Surgical Oncology. In S. J. Withrow, D. M. Vail, & R. L. Page (Eds.), *Withrow and MacEwen's Small Animal Clinical Oncology* (5th ed., pp. 149–156). Elsevier Inc.

Freres, P., Jerusalem, G., & Moonen, M. (2017). *Categories of Anticancer Treatments*. In P. Lancellotti, J. Zamorano, & M. Galderisi (Eds.), *Anticancer Treatments and Cardiotoxicity: Mechanisms, Diagnostic and Therapeutic Interventions* (pp. 7-11). Elsevier Inc.

Gandotra, V., Chauhan, F., & Sharma, R. (1993). Occurrence of Canine Trasmissible Venereal Tumour and Evaluation of Two Treatments. *Indian Vet. J.*, 70:854-857.

Ganguly, B., Das, U., & Das, A. (2013). Canine Transmissible Venereal Tumour: A Review. *Vet Comp Oncol*, *14(1),* 1-12.

Graf, R., Grüntzig, K., Hässig, M., Axhausen, K. W., Fabrikant, S., Welle, M., Meier, D., Guscetti, F., Folkers, G., Otto, V., Pospischil, A. (2015). Swiss Feline Cancer Registry: A Retrospective Study of the Occurrence of Tumours in Cats in Switzerland from 1965 to 2008. *Journal of Comparative Pathology*, *153*(4), 266–277.

Grüntzig, K., Graf, R., Boo, G., Guscetti, F., Hässig, M., Axhausen, K. W., Fabrikant, S., Welle, M., Meier, D., Folkers, G.Pospischil, A. (2016). Swiss Canine Cancer Registry 1955-2008: Occurrence of the Most Common Tumour Diagnoses and Influence of Age, Breed, Body Size, Sex and Neutering Status on Tumour Development. *Journal of Comparative Pathology*, *155*(2–3), 156–170.

Grüntzig, K., Graf, R., Hässig, M., Welle, M., Meier, D., Lott, G., Erni, D., Schenker, N. S., Guscetti, F., Boo, G., Axhausen, K., Fabrikant, S., Folkers, G. Pospischil, A. (2015). The Swiss canine cancer registry: A retrospective study on the occurrence of tumours in dogs in Switzerland from 1955 to 2008. *Journal of Comparative Pathology*, *152*(2–3), 161–171.

Gustafson, D. L., & Page, R. L. (2013). Cancer Chemotherapy. In S. J. Withrow, D. M. Vail, & R. L. Page (Eds.), *Withrow and MacEwen's Small Animal Clinical Oncology* (5th Edt, pp. 157–179). Saunders Elsevier.

Hantrakul, S., Klangkaew, N., Kunakornsawat, S., Tansatit, T., Poapolathep, A., Kumagai, S., & Poapolathep, S. (2014). Clinical Pharmocokinetics and Effects of Vincristine Sulfate in Dogs with Transmissible Venereal Tumour (TVT). *J Vet Met Sci*, 76(2): 1549-1553.

Henry, C. (2010). Hormonal Impact on Carcinogenesis. In C. Henry & M. L. Higginbotham (Eds.), *Cancer Management in Small Animal Practice* (pp. 25–27). Canada: Saunders Elsevier.

Hong, S.-H. & Khanna, C. (2003). Chapter 165 Chemotherapy of neoplasia. In Slatter, D. (ed.) Textbook of Small Animal Surgery (Third Edition). United States: Saunders, pp. 2345–2355.

Kimura, K. C., Gárate, A. P., & Dagli, M. L. Z. (2012). Retrospective study of neoplasms in domestic animals: A survey between 1993 and 2002 of the Service of Animal Pathology, Department of Pathology, School of Veterinary Medicine and Animal Science, University of Sao Paulo, Southeast Brazil. *Brazilian Journal of Veterinary Pathology*, *5*(2), 60–69

Kirby, J. S., & Miller, C. J. (2010). Intralesional chemotherapy for nonmelanoma skin cancer: a practical review. *J Am Acad Dermatol*, 63:689-702.

Kitchell, B., & Dervisis, N. (2010). Pathophysiology and Tumour Cell Growth. In C. Henry, & M. Higginbotham, *Cancer Management in Small Animal Practice* (pp. 1-9). Canada: Saunders Elsevier.

Kitchell, B. E., Brown, D. M., Luck, E. E., Woods, L. L., Orenberg, E. K. & Bloch, D. A. (1994). Intralesional implant for treatment of primary oral malignant melanoma in dogs. *J Am Vet Med Assoc*, 204:229-236.

Kitchell, B. K., Orenberg, E. K., Brown, D.M., Hutson, C., Ray, K., Woods, L., & Luck, E. (1995). Intralesional sustained-release chemotherapy with therapeutic implants for treatment of canine sun-induced squamous cell carcinoma. *Eur J Cancer*,31(12):2093-2098.

Komazawa, S., Sakai, H., Itoh, Y., Kawabe, M., Murakami, M., Mori, T., & Maruo, K. (2016). Canine tumour development and crude incidence of tumours by breed based on domestic dogs in Gifu prefecture. *Journal of Veterinary Medical Science*, *78*(8), 1269–1275.

Lana, S., & Dobson, J. (2010). Principles of Chemotherapy. In J. Dobson, & B. Lascelles, *BSAVA Manual of Canine and Feline Oncology 3rd Edition* (pp. 60-79). BSAVA.

Larue, S. M., & Gordon, I. K. (2013). Radiation Therapy. In S. J. Withrow, D. M. Vail, & R. L. Page (Eds.), *Withrow and MacEwen's Small Animal Clinical Oncology* (5th Edt, pp. 180–197). Saunders Elsevier.

Loh, C. Y., Abdullah, R., & Selvarajah, G. T. (2014). Cancer Chemotherapy In Dogs and Cats In Malaysian Small Animal Veterinary Practices. *Final Year Project Presented to University Putra Malaysia, pp. 1-56.*

MacDonald, V. (2009). Chemotherapy: Managing side effects and safe handling. *Canadian Veterinary Journal*, *50*(6), 665–668.

Macy, D., & Reeds, K. (2010). Viral Carcinogenesis. In C. Henry, & M. L. Higginbotham, *Cancer Management in Small Animal Practice* (pp. 20-25). Canada: Saunders Elsevier.

Markman, M. (1999). Intraperitoneal Chemotherapy. *Critical Reviews in Oncology/Hematology 31*, 239–246.

Merlo, D. F., Rossi, L., Pellegrino, C., Ceppi, M., Cardellino, U., Capurro, C., Ratto, A., Sambucco, P. L., Sestito, V., Tanara, G., Bocchini, V. (2008). Cancer Incidence in Pet Dogs: Finding of the Animal Tumour Registry of Genoa, Italy. *J Vet Intern Med*, *22*, 976–984

Moore, A. (2010). Commonly Used Chemotherapy Drugs. *NAVC Clinician's Brief*, 61-66; 101-106.

Morris, J. (2001). Haematopoietic System. In J. Morris & J. Dobson (Eds.), *Small Animal Oncology* (pp. 228–251). Blackwell Science.

Morrison, W. (2002). Cancer In Dogs and Cats: Medical and Surgical Management (2nd Edition, pp. 332-358). Lippincott, Williams & Wilkins

Nak, D., Nak, Y., Cangul, I. T., & Tuna, B. (2005). A clinico-pathological study on the effect of vincristine on Transmissible Venereal Tumour in the dog. *J. Vet. Med. A. Physiol. Pathol. Clin. Med.*, *52*(7), 366–370.

Norris, A. M., & Withrow, S. J. (1984). A Review of Cancer Chemotherapy for Pet Animals. *The Canadian Veterinary Journal*, 25(4), 153–157.

North, S., & Banks, T. (2009). Small Animal Oncology: An Introduction. Saunders Elsevier, pp. 31–60.

Overley, B., Shofer, F. S., Goldschmidt, M. H., Sherer, D., & Sorenmo, K. U. (2005). Association between ovarihysterectomy and feline mammary carcinoma. *Journal of Veterinary Internal Medicine*, 19(4), 560–563.

Papich, M. (2016). Saunders Handbook of Veterinary Drugs (Fourth Edition). United State: Elsevier, pp. 643–645.

Pope, E. R. (2009). Surgical Interventions in Cancer. In C. Henry & M. L. Higginbotham (Eds.), Cancer Management in Small Animal Practice (pp. 136–145). Canada:

Saunders Elsevier.

Purohit, G. (2008). Canine transmissible venereal tumor (TVT): a review. *The Internet Journal of Veterinary Medicine*, *6*(1), 1–7.

Rodriguez, C. O. (2009). Basic Chemotherapy Principles. In C. Henry & M. L. Higginbotham (Eds.), Cancer Management in Small Animal Practice (pp. 101–104). Canada: Saunders Elsevier.

Sahabi, K., Selvarajah, G. T., Noordin, M. M., & Dhaliwal, G. K. (2015). Retrospective histopathological study of canine mammary gland tumours diagnosed from 2006 - 2012 in University Putra Malaysia. *J. Vet. Malaysia, 27(1),* 1–6.

Santiago-flores, M. L., Jaro, M. C., Recuenco, F. C., Reyes, M. F., & Amparo, M. R. G. (2012). Clinical Profile of Canine Transmissible Venereal Tumour Cases. *Philipp. J. Vet. Anim. Sci.*, *38*(1), 63–72.

Schneider, R., Dorn, C., & Taylor, D. (1969). Factors Influencing Canine Mammary Cancer Development and Postsurgical Survival. *J Natl Cancer Inst*, *43*, 1249–1261.

Shelton, G., Grant, C., Cotter, S., Gardner, M., Hardy, W., & DiGiacomo, R. (1990). Feline immunodeficiency virus and feline leukemia virus infections and their relationships to lymphoid malignancies in cats: a retrospective study (1968-1988). *J Acquir Immune Defic Syndr, 3*(6), 632-630.

Shields, M. (2017). Chapter 14: Chemotherapeutics. In S. McCreath, & R. Delgoda, *Pharmacognosy* (pp. 295-307). Mica Haley.

Smith, A. (2014). The Role of Neutering in Cancer Development. *Vet Clin Small Anim*, 965-975.

Steffy-Morgan, J. D. (2009). Chemotherapy Administration. In C. Henry & M. L. Higginbotham (Eds.), Cancer Management in Small Animal Practice (pp. 114–118). Canada: Saunders Elsevier.

Studdert, V. P., Gay, C. C., & Blood, D. C. (2012). *Saunders Comprehensive Veterinary Dictionary* (Fourth Edt, pp. 211). United States: Saunders Elsevier

Taylor, K. (2010). Female Reproductive Tumours. In C. Henry, & M. L. Higginbotham, *Cancer Management in Small Animal Practice* (pp. 268-274). Canada: Saunders Elsevier.

Teske, E., Van Straten, G., Van Noort, R., & Rutteman, G. R. (2002). Chemotherapy with cyclophosphamide, vincristine, and prednisolone (COP) in cats with malignant lymphoma: New results with an old protocol. *Journal of Veterinary Internal Medicine*, *16*(2), 179–186.

Theilen, G., & Madewell, B. (1979). Tumours of the Skin and Subcutaneous Tissues. In

G. Theilen, & B. Madewell (Eds.), *Veterinary Cancer Medicine* (pp. 123-191). Philadelphia: Lea and Febiger.

Todorova, I. (2006). Prevalence and Etiology of the Most Common Malignant Tumours in Dogs and Cats. *Bulgarian Journal of Veterinary Medicine*, 9(2), 85–98.

Tvedten, H. (2012). Hemostatic Abnormalities. In M. Willard, & H. Tvedten (Eds.), *Small Animal Clinical Diagnosis by Laboratory Methods (Fifth edition)* (pp. 102-105). United State: Saunders Elsevier.

Vail, D. M. (2009). Lymphoma in Dogs : Diagnosis & Treatment. *NAVC Clinicain's Brief*, 15–19.

Vail, D. M. (2009). Supporting the Veterinary Cancer Patient on Chemotherapy: Neutropenia and Gastrointestinal Toxicity. *Topics in Companion Animal Medicine*, 24(3), 122–129.

Vanderpuye, V. D., & Yarney, J. (2014). Cost Effectiveness of Cancer Therapies in Africa. *J Med Diagn Meth*, Vol 3:1-3.

Vascellari, M., Baioni, E., Ru, G., Carminato, A., & Mutinelli, F. (2009). Animal tumour registry of two provinces in northern Italy: incidence of spontaneous tumours in dogs and cats. *BMC Veterinary Research*, *5*:39.

Williams, J., Phillips, C., & Byrd, H. M. (2017). Factors which influence owners when deciding to use chemotherapy in terminally Ill pets. *Animals*, *7*(3), 1–12.

Zambelli, A. B. (2015). Feline Cancer Prevalence in South Africa (1998 – 2005): Contrasts with the Rest of the World. *Journal of Basic and Applied Sciences*, *11*(31), 370–380.

Zemann, B. I., Moore, A. S., Rand, W. M., Mason, G., Ruslander, D. M., Frimberger, A. E., Wood, C. A., L'Heureux, D. A., Gliatto, J., & Cotter, S. M. (1998). A Combination Chemotherapy Protocol (VELCAP-L) for Dogs with Lymphoma. *J Vet Intern Med*, 12:465-470.

Withrow, S. J., Liptak, J. M., Straw, R.C., Dernell, W. S., Jameson, V. J., Powers, B. E., Johnson, J. L., Brekke, J. H. & Douple, E. B. (2004). Biodegradable cisplatin polymer in limb-sparing surgery for canine osteosarcoma. *Ann Surg Oncol*, 11(7):705-713.

APPENDIX 1: Case records of dogs and cats receiving cancer chemotherapy in UVH, UPM.

CASE NO	ID	SP.	SEX	NEUTER (N/I)	AGE	BREED	TYPE OF TUMOUR	FREQ OF DRUG	ALIVE/ DEAD	DAYS OF SURVIVAL	COST (RM)	ANEMIA	LEOKO-PENIA	THROMBO-CYTOPENIA	LYMPHO-PENIA	EXTRA-VASATION	VOMIT	DIARRHEA	PETE. HRR
28485	Peaches	C	F	Neutered	7	Local	MCT	12	D	130	2966.5	No	Yes	No	No	No	No	No	No
29834	Mickey	C	M	Intact	12	ShihTzu	Lymphoid leukemia	15	A	157	3826	Yes	No	No	No	No	Yes	No	No
32666	Sammi	C	F	Neutered	12	Schnauzer	MCT	5	D	58	1142	Yes	No	Yes	No	No	No	Yes	No
33524	Tasha	C	F	Neutered	10	ShihTzu	Lymphoma	10	D	131	2364	Yes	No	Yes	No	No	No	No	No
45395	Abby	C	F	Neutered	4	Rottweiler	Lymphoma	8	D	143	1907.5	Yes	No	Yes	No	No	Yes	No	No
49171	Lucky	C	M	Intact	4	Local	TVT	7	A	1803	1619	No	Yes	Yes	No	No	No	No	No
52429	Tiger	C	M	Intact	12	Local	Lymphocytic leukemia	2	D	18	581	Yes	No	Yes	No	No	No	No	Yes
52802	Darkie	C	F	Neutered	13	Local	MCT	4	D	46	838.5	No	Yes	Yes	Yes	No	Yes	Yes	No
54335	Hitam	C	F	Intact	3	Local	TVT	1	A	1473	190	No data	No data	No data	No data	No	No	No	No
55076	Darkie	C	M	Intact	5	Local	TVT	5	A	1426	1263	No	Yes	Yes	No	No	No	No	No
55126	Popo	C	M	Neutered	9	ShihTzu	MCT	2	D	43	589.5	No	Yes	Yes	Yes	No	No	No	No
55890	Boboy	C	M	Intact	1	Local	TVT	2	A	1237	445	No	No	Yes	Yes	No	No	No	No
55899	Coco	C	F	Intact	12	ShihTzu	Lymphoma	1	D	15	170	No data	No data	No data	No data	No	No	No	No
56320	FaFa	C	F	Neutered	2	Local	TVT	3	A	1213	602.5	No	No	No	No	No	No	No	No
57220	Rockey	C	M	Intact	6	Golden Retriever	Lymphoma	6	D	174	1578.5	Yes	No	Yes	No	No	No	No	No
57246	Girl Girl	C	F	Neutered	4	Local	TVT	4	A	1277	857.5	Yes	No	Yes	No	No	No	No	No
57290	Siaw Bai	C	F	Neutered	3	Local	TVT	6	A	1277	1449	No	No	Yes	No	No	No	No	No
57808	Jin Jin	C	F	Neutered	3	Local	TVT	3	A	1257	739.5	No	No	Yes	No	No	No	No	No
57826	Boy Boy	C	M	Intact	3	Local	TVT	10	A	1243	2275	No	No	No	No	No	No	No	No
58326	Macy	C	F	Intact	8	Basset Hound	Lymphoma	14	D	307	3761	Yes	No	Yes	Yes	No	No	No	Yes
58338	Le Le	C	F	Intact	1	Local	TVT	6	A	1200	1280.5	No	No	Yes	Yes	No	No	No	No
59693	Rushio	C	M	Intact	9	Cocker Spaniel	MCT	5	D	38	664.5	Yes	No	No	No	No	No	No	No
59749	Bobby	C	M	Neutered	5	Terrier Mix	TVT	8	A	1143	1903	No	Yes	No	Yes	No	No	No	No

60925	Tin Tin	C	M	Neutered	11	Golden Retriever	Lymphoma	10	D	147	2475	Yes	Yes	Yes	Yes	No	No	No	No
60996	Poppy	C	F	Neutered	5	Local	TVT	25	A	1081	5943	Yes	Yes	Yes	Yes	No	No	No	No
61065	Lui Lui	C	F	Neutered	8	Local	Lymphoma	13	D	309	2544.5	Yes	No	No	Yes	No	No	No	No
61069	Weiler	C	M	Intact	4	Golden Retriever	Lymphoma	7	D	99	1762	Yes	Yes	No	Yes	No	No	No	No
61075	Kofi	C	M	Intact	7	Golden Retriever	Lymphoma	6	D	60	1513	Yes	No	Yes	No	No	No	No	No
61077	Angel	C	F	Neutered	10	Golden Retriever	Lymphoma	11	D	283	2907.5	Yes	No	Yes	Yes	No	Yes	No	No
61124	Chubby	C	M	Neutered	10	GSD	Oral SCC	2	D	47	645	Yes	No	No	No	No	No	No	No
61151	Anti	C	F	Intact	2	Local	TVT	1	D	6	294.5	No data	No data	No data	No data	No	No	No	No
61790	Cody	C	M	Neutered	11	Rottweiler	Oral melanoma	3	D	42	971.5	Yes	No	No	No	No	No	No	No
61923	Cookie	C	F	Neutered	12	Cocker Spaniel	Lymphoma	10	D	105	1910.5	Yes	No	No	No	No	No	No	No
61929	Rambo	C	M	Intact	8	Rottweiler	Lymphoma	1	D	15	302.5	No data	No data	No data	No data	No	No	No	No
61957	Kiddy	C	F	Intact	1	Local	TVT	6	D	60	1444	Yes	Yes	Yes	Yes	No	No	No	No
65098	Diamond	C	M	Intact	7	Spitz	TVT	5	A	850	1283	No	Yes	No	No	No	Yes	No	No
63816	Bruce	C	M	Intact	5	Bull Dog	Osteochondro-sarcoma	2	A	858	340	No data	No data	No data	No data	No	No data	No data	No data
63839	Taro	C	M	Intact	10	Bull Terrier	Invasive SCC	1	D	15	194.5	No data	No data	No data	No data	No	No	No	No
65009	Rooney	C	M	Intact	6	Beagle	Lymphoma	9	D	91	1732	Yes	No	No	Yes	No	Yes	No	No
65013	Chester	C	M	Intact	11	Miniature Pinscher	Tonsillar SCC	1	D	15	445	No data	No data	No data	No data	No	No	No	No
65036	Brownie	C	F	Intact	3	Local	TVT	4	A	695	903.9	Yes	No	Yes	No	No	No	No	No
65069	Peggy	C	F	Neutered	11	Golden Retriever	Lymphoma	6	D	82	1495	Yes	No	No	Yes	No	No	No	No
65147	Rocky	C	M	Intact	7	Golden Retriever	Lymphocytic leukemia	1	D	7	340	Yes	No	Yes	No	No	No	No	No
66503	Jason	C	M	Intact	3	Local	TVT	10	A	807	2339	Yes	No	Yes	No	No	Yes	Yes	No
66582	Kickey	C	F	Neutered	8	Papillon X	Oral melanoma	3	D	36	666	Yes	No	No	No	No	No	No	No
67744	Ricky	C	M	Intact	1	Pomeranian	TVT	2	A	766	530	No	No	No	No	No	No	No	No
67760	Nopy	C	M	Intact	4	S. Husky	TVT	17	D	566	4151	No	Yes	Yes	Yes	No	No	Yes	No
67817	Sweetie	C	F	Intact	7	Boxer	MCT	4	D	29	1073	No	No	No	No	No	No	No	No

67906	Jiva	C	M	Intact	7	Golden Retriever	Rhadomyo-sarcoma	3	D	104	1945.5	Yes	Yes	Yes	No	No	Yes	No	No
67938	Skippy	C	M	Intact	7	Local	Mesothelioma	7	D	349	2666	Yes	Yes	No	Yes	No	Yes	No	No
68594	Wei Wei	C	F	Neutered	2	Local	TVT	1	A	704	345	No	Yes	No	No	No	No	No	No
68604	Doggy	C	M	Intact	3	Local	TVT	8	A	703	1974	Yes	No	Yes	Yes	No	No	No	No
68657	Brador	C	M	Neutered	5	Labrador	Lymphoma	2	D	19	444	Yes	No	Yes	No	No	Yes	No	No
69959	Sera 2	C	F	Intact	3	Local	TVT	3	D	35	752	Yes	No	No	No	No	No	No	No
70154	Prince	C	M	Intact	9	Local	TVT	11	D	163	2540	Yes	No	Yes	Yes	No	No	No	No
70162	Kero	C	M	Intact	10	Golden Retriever	Oral melanoma	1	D	30	436	No	No	No	No	No	No	No	No
71276	Sara	C	F	Neutered	14	Local	Oral melanoma	3	D	71	900	No data	No data	No data	No data	No	No data	No data	No data
71365	Lassie	C	M	Intact	4	ShihTzu	Lymphoma	1	D		170	No data	No data	No data	No data	No	No	No	No
71419	Lara	C	F	Neutered	9	GSD	MGT	2	D	18	1004	Yes	No	No	No	No	No	No	No
71452	Matt	C	F	Neutered	7	Local	Lymphoma	1	D	7	190	No data	No data	No data	No data	No	No	No	No
72772	Milo	C	F	Intact	2	S. Husky	Osteochondro-sarcoma	4	A	346	1128	No	No	No	No	No	No	No	No
72789	Leo	C	M	Intact	2	Dobermann	Lymphoma	15	D	280	3391	Yes	No	Yes	Yes	No	Yes	Yes	Yes
74060	Fate	C	M	Neutered	1	Local	TVT	8	A	415	1765	Yes	No	Yes	Yes	No	No	No	No
74073	Boy Boy	C	M	Neutered	5	Local	TVT	8	A	415	1826	Yes	No	Yes	No	No	No	No	No
74196	Sujie	C	F	Intact	4	Miniature Pinscher	Lymphoma	6	D	90	1474	Yes	No	Yes	Yes	No	Yes	Yes	No
74909	Jax	C	M	Intact	1	Local	TVT	2	A	367	445	Yes	No	Yes	Yes	No	No	No	No
74931	Troy	C	M	Intact	2	Local	TVT	1	D	15	194.5	No data	No data	No data	No data	No	No	No	No
74972	Don	C	M	Intact	1	Local	TVT	8	A	346	1772	No	No	Yes	Yes	No	No	No	No
74994	Eddie	C	M	Intact	1	Local	TVT	1	D	7	317	No data	No data	No data	No data	No	No	No	No
76235	Shan Yuan	C	M	Intact	12	Local	MCT	1	D	30	222	No data	No data	No data	No data	No	No	No	No
76271	Happy	C	F	Intact	6	Local	MGT	1	D	21	282	No data	No data	No data	No data	No	No	No	No
76340	Leo	C	M	Intact	5	Beagle	Lymphoma	10	D	151	2265.5	Yes	Yes	Yes	Yes	No	Yes	No	No
76461	Bibi	C	M	Intact	12	Local	Liposarcoma	4	D	102	1933	Yes	No	No	No	No	No	No	No
77747	Zai Zai	C	M	Intact	12	Terrier	Fibrosarcoma	1	D	21	194.5	No data	No data	No data	No data	No	No	No	No

77843	Mercedes	C	F	Intact	11	Local	Cutaneous hemangiosarcoma	3	A	199	1082	No	Yes	No	No	No	No	No	No
77862	Sazey	C	F	Intact	9	Golden Retriever	MGT	1	D	128	782	No data	No data	No data	No data	No	No	No	No
78497	Joyce	C	F	Neutered	13	Golden Retriever	Esophageal sarcoma	1	D	21	432	No data	No data	No data	No data	No	No data	No data	No data
80004	Tom	C	M	Intact	9	Silky Terrier	Oral melanoma	2	D	52	569	No data	No data	No data	No data	No	No	No	No
80102	Jasper	C	M	Neutered	10	Golden Retriever	FSA	2	D	52	686	No	No	Yes	No	No	No	No	No
80126	Akira	C	M	Intact	13	ShihTzu	Adenocarcinoma	1	D	21	314	Yes	No	No	No	No	No	No	No
80138	Debu	C	M	Intact	10	Labrador	Lymphoma	5	A	38	1270	Yes	No	No	Yes	No	No	No	No
81526	Maxine	C	F	Intact	2.5	GSD	Lymphoma	1	A	4	222	No data	No data	No data	No data	No	No	No	No
69944	Ken Ken	C	M	Neutered	10	ShihTzu	Lymphoma	1	D	15	327	Yes	No	No	No	No	Yes	No	No
48169	Kiki	F	M	Intact	5	Siamese	Lymphoma	17	A	1039	4329	Yes	No	Yes	No	No	No	No	No
51438	Nala	F	F	Neutered	7	DSH	Clear cell carcinoma	4	D	33	967	No	Yes	Yes	No	No	Yes	No	No
51698	White-White	F	F	Neutered	5	DSH	Lymphoma	7	D	50	1275	Yes	No	Yes	Yes	Yes	No	No	No
52855	Marcos	F	M	Neutered	8	DSH	Lymphoid leukemia	1	D	7	272	No data	No data	No data	No data	No	No	No	No
56030	Roger Jr	F	M	Neutered	2	DSH	Lymphoma	1	D	15	215	No	No	Yes	Yes	No	No	No	No
56776	Nash	F	M	Intact	0.8	DSH	Lymphoma	1	D	15	190	No data	No data	No data	No data	No	No	No	No
66107	Max	F	M	Intact	4	DSH	Lymphoma	1	D	15	345	Yes	No	Yes	No	No	No	No	No
67260	Aroyo	F	F	Intact	7	Persian	Ceruminous gland adenocarcinoma	7	D	146	1606	Yes	No	Yes	No	No	Yes	No	No
67334	Tommy	F	M	Neutered	9	DSH	MCT	4	D	31	1069	Yes	No	No	No	No	Yes	No	No
67527	Milo	F	M	Neutered	9	DSH	SCC	1	D	5	222	No data	No data	No data	No data	No	No	No	No
68066	Mamos	F	M	Neutered	10	DSH	Nasal adenocarcinoma	10	A	731	2354	Yes	Yes	Yes	Yes	No	No	No	No
68295	Cici	F	F	Neutered	1	DSH	Lymphoma	9	D	139	1979	Yes	No	Yes	Yes	No	No	No	No
71031	Manja	F	M	Neutered	2	DSH	Lymphoma	15	D	352	3620	Yes	Yes	Yes	Yes	No	No	No	No
71520	Kia	F	M	Neutered	0.7	DSH	Lymphoma	1	D	15	264	Yes	No	Yes	Yes	No	No	No	No
72357	Boyo	F	M	Intact	2	DSH	Lymphoma	3	D	35	809	Yes	No	Yes	No	No	Yes	Yes	No

72372	Bin Bin	F	M	Neutered	8	DSH	Lymphoma	3	D	21	681	Yes	No	Yes	Yes	No	No	No	No
73542	Sassy	F	F	Intact	2	DSH	Lymphoma	1	D	20	299	No data	No data	No data	No data	No	No	No	No
73584	Kiki	F	F	Neutered	8	DSH	Lymphoma	1	D	10	381	Yes	No	Yes	Yes	No	No	No	No
75269	Lucy	F	F	Neutered	3	Siamese	Lymphoma	4	D	34	884	Yes	No	No	No	No	No	No	No
75942	Besar	F	M	Intact	5	DSH	Nasal adenocarcinoma	2	D	38	444	Yes	No	Yes	Yes	No	Yes	No	No
76512	Peperni	F	M	Intact	9	Maine Coon	Adenocarcinoma	1	D	7	222	No data	No data	No data	No data	No	No	No	No
76568	Uteh	F	F	Intact	8	DSH	Adenocarcinoma	3	D	20	748	Yes	No	No	Yes	No	No	No	No
76649	Wofy	F	F	Neutered	1.5	DSH	Lymphoma	4	D	57	1020	No	No	Yes	No	No	Yes	No	No
79835	TJ	F	F	Neutered	1	DSH	Lymphoma	8	A	115	1172	No	No	No	No	No	No	No	No
80476	Honey	F	F	Intact	1	Persian	Lymphoma	1	D	15	222	No data	No data	No data	No data	No	No data	No data	No data
80858	Chiki	F	F	Neutered	8	DSH	MGT	1	D	15	372	No	No	No	No	No	No	No	No
80868	Tompok	F	M	Neutered	13	DSH	Lymphoma	1	D	10	222	No data	No data	No data	No data	No	No	No	No
63361	Chomel	F	F	Neutered	8	DSH	Melanoma	4	D	68	957	Yes	No	Yes	No	No	No	No	No
63366	Arjuna	F	M	Intact	7	DSH	Adenocarcinoma	5	D	71	1206	Yes	No	Yes	Yes	No	Yes	No	No
64290	Toyu	F	M	Neutered	3	DSH	Lymphoma	2	D	21	449	Yes	No	Yes	No	No	No	No	No