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Spontaneous tumors in dogs and cats: Models for the study of cancer biology and treatment

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Abstract

Spontaneous tumors in dogs and cats are appropriate and valid model tumor systems available for testing cancer therapeutic agents or studying cancer biology. The pet population is a vastly underutilized resource of animals available for study. Dogs and cats develop spontaneous tumors with histopathologic and biologic behavior similar to tumors that occur in humans. The tumors with potential relevance for human cancer biology include osteosarcoma, mammary carcinoma, oral melanoma, oral squamous cell carcinoma, nasal tumors, lung carcinoma, soft tissue sarcomas, and malignant non-Hodgkin's lymphoma.

Canine osteosarcoma is a malignant aggressive bone tumor with a 90% matastasis rate after surgical amputation. Its predictable metastatic rate and pattern and its relative resistance to chemotherapy make this tumor particularly attractive for studying anti-metastasis approaches. Canine and feline malignant mammary tumors are fairly common in middle-aged animals and have a metastatic pattern similar to that in women; that is, primarily to regional lymph nodes and lungs. Chemotherapy has been minimally effective, and these tumors may be better models for testing biological response modifiers.

Oral tumors, especially melanomas, are the most common canine malignant tumor in the oral cavity. Metastasis is frequent, and the response to chemotherapy and radiation has been disappointing. This tumor can be treated with anti-metastatic approaches or biological response modifiers. Squamous cell carcinomas, especially in the gum, are excellent models for radiation therapy studies.

Nasal carcinomas are commonly treated with radiation therapy. They tend to metastasize slowly, but have a high local recurrence rate. This tumor is suitable for studying radiation therapy approaches.

Primary lung tumors and soft tissue sarcomas are excellent models for studying combined modality therapy such as surgery with chemotherapy or biological response modifiers.

Finally, non-Hodgkin's lymphoma is a common neoplastic process seen in the dog. These tumors respond to combination chemotherapy and have great potential as a model for newer chemotherapeutic agents and biological response modifiers.

This paper will further elaborate on the relative merits of each tumor type as a model for human cancer therapy and biology.

Introduction

There is long-standing controversy concerning the role of animal models in human clinical cancer therapeutic research [1–4]. Most investigators would agree that animal models play a very important role; however, the most appropriate models for testing clinically relevant hypotheses are not

clearly defined. It has been stated that 'only a small proportion of the animal tumor systems used in current therapy research can be claimed to be free from manifest or latent artifacts of a kind that can be highly influential on the data obtained by their use' [1].

Animal tumor models, as defined by Herberman [4], should serve as a pattern for analogous situations with human tumors. Chemically induced rodent tumors and virally induced tumors have serious limitations. Spontaneous tumors may provide unique opportunities to study disease without the potential for imposed artifacts [1]. This paper will provide the reader with an overview of some of the common malignancies diagnosed in dogs and cats, which are spontanous in nature and may serve as suitable models for human cancer therapy and cancer biology.

The United States pet population has been a vastly underutilized resource for cancer therapy studies. Approximately 55% of all households in the United States own a total of 64.5 million pet dogs and cats, and 70% of all dog and cat owners utilize veterinary services. Veterinary health care in the United States is sophisticated and similar to human health care systems in terms of surgical procedures, diagnostic techniques, and pharmaceutical use. Cancer is a major cause of pet animal deaths. In one study, in which the cause of death was determined in a series of 2,000 autopsies, 45% of the dogs that lived to 10 years or older died of cancer. Regardless of age, 23% of the dogs presented for autopsy died of cancer [5]. Dogs develop tumors twice as frequently as humans, but cats only half as frequently. The location and incidence of various tumors depend on a number of variables, predominantly age, breed, sex, and geographic location. In general, dogs and cats develop similar cancers at sites very analogous to those in humans. The malignancies that are of practical use for therapeutic study are osteosarcoma, mammary neoplasia, oral melanoma, oral squamous cell carcinoma, nasal tumor, lung cancer, soft tissue sarcomas, and malignant non-Hodgkin's lymphoma.

Canine osteosarcoma

Osteosarcoma in dogs closely resembles osteosarcoma in humans. Osteosarcoma is estimated to occur in more than 6,000 dogs in the United States per year, and that figure may be increasing with the growing popularity of large and giant breeds [6]. It is primarily a disease of middle-aged to older animals, with a median age of 7 years. However, osteosarcoma has been reported in dogs as young as 6 months. Osteosarcoma is most likely to occur in large and giant breeds. Fewer than 5% of cases reported have occurred in dogs weighing less than 25 pounds, and the tumor appears to be more size- than breed-related. As in humans, males are affected 2:1 over females. Osteosarcoma in humans is generally a disease of adolescence, and is a rare tumor affecting only 2000 to 2200 people per year in the United States.

More than 75% of osteosarcomas in dogs occur in long bones, and the remainder occur in the axial skeleton, which is also true in humans [7]. The metaphyseal region is most frequently affected. The tumor is twice as likely to occur in the front limb (major weight bearing limbs) as in the rear limbs. The distal radius and proximal humerus are the two most common locations. In the rear limbs, tumors are evenly distributed between the distal femur, distal tibia, and proximal tibia, with the proximal femur being a slightly less common site. Osteosarcoma is a highly metastatic tumor, and 90% of affected animals that do not receive some form of systemic therapy will develop metastasis, generally to the lungs, within 1 year of amputation or control of the primary tumor [8]. In humans, metastasis occurs within 2 years after amputation without chemotherapy in 80% of those treated. In dogs, the median survival time for surgery alone has been reported to be between 3 to 4 months [9]. Currently therapy consists of either amputation or limb salvage combined with adjuvant chemo- or immunotherapy. Amputation alone provides good primary tumor control; however, long-term survival is poor due to metastatic spread.

Various chemotherapic and immunologic agents have been used in the adjuvant setting with amputation in attempts to improve long-term survival

[10–18]. Chemotherapy agents tested include high dose methotrexate with leucovorin rescue, doxorubicin, cisplatin, and other combinations of drugs. (These are summarized in Table 1). To date, the only chemotherapeutic protocols that have had a significant effect on delaying the development of metastasis are cisplatin alone and cisplatin with doxorubicin. In one study, 19 dogs received adjuvant chemotherapy 2 weeks after amputation. Doxorubicin (30 mg/m^2 IV) was administered on day one and cisplatin (60 mg/m^2 IV) was administered on day 21. The treatment cycle was repeated twice. Survival was compared with 19 dogs who underwent amputation only. The median survival of the 19 dogs treated with amputation and chemotherapy was 10 months, which was significantly longer than the median survival of those dogs treated by surgery alone [13]. In a more recent study of 36 dogs receiving cisplatin chemotherapy combined with amputation, the median survival time was 9 months for dogs receiving chemotherapy versus 4 months for dogs receiving amputation alone [15].

Immunotherapy has been shown to be effective in dogs with osteosarcoma. In a recently published study dogs with primary, previously untreated osteosarcoma were randomized to either amputation alone or amputation plus liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (MTP-PE) [18]. Lipsome-encapsulated MTP-PE has been shown to prevent the development of metastasis and result in its regression in rodent tumor models. Immediately following surgery dogs were randomized to receive either empty liposomes (placebo) or liposome-encapsulated MTP-PE (2 mg/m^2 i.v. twice weekly × 8 weeks). Twenty-seven dogs were entered into this study. Of these, 14 received a placebo (empty liposome). The median survival time for those dogs receiving placebo was 77 days (range: 31–438 days). Dogs receiving the liposome-encapsulated MTP-PE had a three-fold increase in survival time, with a median of 222 days (range 81–974 + days) (Fig. 1). Currently, studies are in progress comparing chemotherapy (cisplatin) to chemotherapy plus liposome-encapsulated MTP-PE. Although preliminary, the results indicate that dogs on the liposome-encapsulated MTP-PE have longer survival times than dogs receiving chemotherapy alone [19].

Histologically, osteosarcoma in dogs and humans is virtually indistinguishable, and osteosarcomas in both humans and dogs are likely to be a high histologic grade. The tumor rapidly metastasizes in both species. The striking similarities, combined with the abundance of canine cases each year, make osteosarcoma in dogs an excellent model for study of osteosarcoma in humans.

Canine mammary neoplasms

Breast cancer is the most common malignant neoplasm in women. In the United States 1 out of every 14 women is likely to develop breast cancer. Similarly, mammary neoplasms are the most common tumor in the female dog, representing 52% of all neoplasms.

As in women, canine mammary tumors are clearly hormonal-dependent tumors. The risks for dogs ovariectomized prior to the first estrus if 0.05%; for dogs after the forth estrus the risk increases to 26% [20]. In women early pregnancy and

Table 1. Summary of published results: Osteosarcoma chemotherapy trials

Study date	Treatment groups	Number of dogs	Median survival (Mos)
Henness, 1977	Amputation, cyclophosphamide, doxorubicin, methotrexate-leucovorin	11	6.0
Cotter, 1978	Amputation, methotrexate-leucovorin	5	4.0
Madewell, 1978	Amputation, doxorubicin	14	3.5
Shapiro, 1986	Amputation, cisplatin	5	10.0
Mauldin, 1988	Amputation, doxorubicin, cisplatin	19	10.0
Straw, 1990	Amputation, cisplatin	36	9.0

early oophorectomy lower the incidence. Additional evidence for hormonal component to this disease is based on the fact that both estrogen and progesterone receptors have been identified in canine mammary gland tumors]21, 22]. Most studies indicate that between 50% and 60% of all malignant mammary tumors contain either estrogen or progesterone receptors, and these receptors are present in about 70% of benign mammary tumors. In humans, estrogen receptors are present in over 60% of the tumors. Between 41% and 53% of the mammary tumors that occur in the bitch are considered malignant [23]. Most malignant mammary tumors classified as epithelial tumors are carcinomas. Depending upon the classification system used, the carcinomas may be further subdivided into simple carcinomas, complex carcinomas, adenocarcinoma, and solid carcinoma. Mammary tumors can also be evaluated on the basis of the degree of nuclear differentiation: poorly differentiated, moderately differentiated, and well differentiated. The degree of differentiation is usually inversely related to the tumor's aggressiveness. As in women, as tumors become less differentiated they tend to lose their hormone receptors [21].

Sarcomas account for less than 5% of all mammary tumors and are much less common than carcinomas. Most dogs with sarcomas die of recurrence or metastasis within 9–12 months.

In canine mammary tumors the significant prognostic factors have been histologic type, degree of invasion, degree of nuclear differentiation, evidence of lymphoid cellular reactivity in the tumor vicinity, tumor size, lymph node involvement, hormone receptor activity, ulceration, and fixation [22–26]. The factors that do not seem to be associated with prognosis are tumor location, type of surgery, ovariohysterectomy at surgery, age of patient, and number of tumors present.

In one recently published study, histologic stage was correlated with disease-free interval after mastectomy in 233 dogs with mammary cancer (Table 2) [23]. In this study only 19% of dogs with Stage 0 disease (malignant proliferation limited to the anatomic borders of the mammary duct system) had 20% recurrence or metastasis rate within 2 years after initial mastectomy, compared to 60% recurrence or metastasis rate in dogs with Stage 1 disease (malignant proliferation extending beyond the anatomical borders of the mammary duct system into the surrounding stroma) and 95% recurrence or metastasis rate in dogs with Stage 2 disease (invasion into vascular or lymphatic vessels). Thus, prognosis is very good for dogs with preinvasive carcinoma.

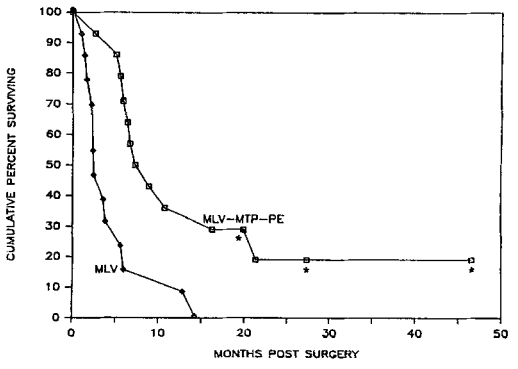

Fig. 1. Survival of dogs with osteosarcoma treated by amputation and either MLV-MTP-PE or MLV. Dogs receiving MLV-MTP-PE (n = 14) had significantly longer survival times ($p < 0.01$) than those receiving MLV (n = 13). * = still alive.

The degree of differentiation is usually inversely related to tumor aggressiveness. Dogs with poorly differentiated tumors have a greater than four-fold increased risk of developing recurrence or metastasis in less than 2 years after mastectomy, with an overall 90% rate compared to 63% for moderately differentiated tumors. Dogs with well differentiated tumors have a 20% recurrence or metastasis rate within 2 years of their mastectomy. Another factor that has been shown to correlate with prognosis is lymphoid cell infiltrate (termed lymphoid reactivity) observed in the tumor vicinity. Dogs with mammary cancer that do not have evidence of lymphoid reactivity at the time of initial mastectomy have a three-fold increased risk developing recurrence or metastasis within 2 years compared to dogs that show lymphoid reactivity. Dogs with lymphoid reactivity had a 45% recurrence or metastasis within 2 years, and dogs without lymphoid reactivity had an 83% recurrence or metastasis rate within 2 years. The presence of the lymphoid reactivity is a very significant observation in the dog, indicating an immunologic response directed to-

ward the tumor. Dogs with tumors showing immunologic reactivity may be appropriate for studies involving immunotherapy.

Tumor size is also a very important prognostic factor [23–25]. Dogs with invasive cancer that have less than 3 cm in diameter have a significantly better prognosis than dogs with malignant tumors, that are 3 cm or more in diameter. In a recent study of dogs with invasion of tumor into lymphatic vessels or lymph nodes, no significant differences were found regardless of tumor size [24]. Lymph node metastasis has also been shown to correlate with survival time: 80% of dogs with lymph node involvement have recurrence or metastasis within 6 months, while dogs with negative lymph nodes usually have a 30% recurrence or metastasis rate within 2 years of surgery.

The treatment of choice for canine mammary tumors remains surgical excision. Studies comparing simple versus radical mastectomy have failed to show that one surgical procedure is superior to another [26]. It would thus seem that histologic features such as degree of invasion, degree of differentiation, tumor size, and lymphatic involvement are the most important features related to the prognosis. Studies using combination chemotherapy such as cyclophosphamide, vincristine, and methotrexate and combinations of doxorubicin and cyclophosphamide have failed to demonstrate any significant antitumor activity in the dog. There are few beneficial effects noted with radiation therapy in canine malignant mammary tumors.

Table 2. Prognosis related to clinical and histologic features

	% recurrence at	
	12 mos.	24mos.
Tumor size		
< 3 cm	30	40
⩾ 3–5 cm	70	80
> 5 cm	70	80
Histological grade		
Stage 0	10	20
Stage 1	40	60
Well differentiated		40
Moderately differentiated		63
Poorly differentiated		77
Stage II	85	95
Lymph node status		
Negative	20	30
Positive	90	100
Lymphoid cellular reactivity (Stage I)		
Positive		45
Negative		83

Studies with nonspecific immunomodulation using levamisole [26] and *Corynebacterium parvum* with BCG have little advantage over surgery alone [27]. However, one study reported that combining intratumoral injection of BCG cell walls with surgery increased survival time over surgery alone [28]. Another study reported that canine mammary tumor cells treated with neuraminidase and used as a vaccine had antitumor activity in dogs [29].

There are no published reports regarding the effectiveness of the antiestrogen tamoxifen in canine mammary tumors. The issue of ovariohysterectomy as a treatment for canine mammary tumor remains unsolved. In one study of 154 dogs treated with mastectomy and ovariohysterectomy the mean survival time was reported to be 8.4 months [30]; this compares to mean survival times of 8 and 10 months in other studies of mastectomy alone. There have been no well-designed prospective studies that clearly address the issue of ovariohysterectomy as an adjunct treatment for dogs with malignant mammary tumors. Canine mammary neoplasms seem to be appropriate models for study. Certain features of this tumor are similar to human breast cancer, including predominance of carcinoma, metastatic pattern, hormonal dependency on tumor development, and certain prognostic factors. Features that are unlike human breast cancer include lack of response to chemotherapy and hormonal ablation. Canine mammary neoplasms may be better models for the study of biologic response modifiers because of the influence of lymphoid cellular reactivity on prognosis.

Feline mammary tumors

Feline mammary tumors are the third most common tumors, and are primarily observed in middle-aged cats of about 10 to 12 years of age. Early ovariohysterectomy may have some protective ef-

fect on the development of feline mammary tumors, although the effect is not as great as that seen in dogs. Exogenous administration of progestins such as megestrol acetate have been associated with mammary tumor development. Progesterone receptors have been identified on feline mammary tissue, although the levels have been very low [31]. Estrogen receptors are rarely detected.

Among feline mammary tumors, 80% to 90% are considered malignant. Adenocarcinoma predominates among malignant tumors; carcinoma and sarcoma are second and third in prevalence. Feline mammary tumors tend to grow rapidly and to metastasize to local lymph nodes and lungs.

Surgery remains the treatment of choice for feline malignant mammary tumors. Studies have shown that radical mastectomy – that is, removal of all glands on the involved side – significantly reduces local recurrence [32]. Because tumor size appears to be the most significant prognostic factor, early detection and diagnosis are vitally important to controlling this disease]33].

Combination chemotherapy using doxorubicin and cyclophosphamide has been shown to induce short-term partial and complete response in 50% of cats with metastatic or nonsectable local disease [34].

Studies using nonspecific biological response modifiers such as levamisole and bacterial vaccines combined with surgery have shown minimal results in reducing recurrence or prolonging survival time in cats [35]. In a very recent study of an autogenous tumor cell vaccine combined with BCG, there was no effect on recurrence and survival time in cats [36].

The most significant prognostic factors affecting recurrence and survival for feline mammary tumors are tumor size, extent of surgery, and histologic grade. Tumor size is the single most important prognostic factor. Cats with tumors greater than 3 cm in diameter have a median survival of 6 months after surgery. Cats with tumors 2 to 3 cm in diameter have a significantly better prognosis; the median is about 2 years. Cats with tumors less than 2 cm in diameter have a median survival time of 3 years [32].

Very few studies have been performed to evaluate the effectiveness of local therapy in malignant feline mammary tumors. One study showed that radical mastectomy reduces local recurrence but does not increase overall survival time [32]. The degree of nuclear differentiation will also influence biological behavior: cats with well-differentiated tumors and few mitotic figures have been shown to have increased survival times. Cats seem to be a good model for the study of breast cancer. These tumors tend to be highly malignant and have a predictable metastatic pattern. As in women, feline mammary adenocarcinoma responds to chemotherapy, particularly doxorubicin. There is no evidence that hormonal therapy is effective.

Oral melanoma

The oral cavity of the dog is a very common site for a wide variety of malignant and benign cancers. The most common malignancies diagnosed in the oral cavity are malignant melanoma, squamous cell carcinoma, and fibrosarcoma. Malignant melanoma is the most common oral tumor diagnosed. Oral melanoma in the dog is an important natural model for the study of experimental therapeutic studies because of the similarities to human melanoma. Both are aggressive, rapidly growing tumors that invade surrounding tissues and metastasize to regional lymph nodes and lungs. Both malignant melanoma and squamous cell carcinoma have a potentially high metastatic rate. For malignant melanoma, the treatment of choice is radical surgery. Approximately 25% of the dogs with oral malignant melanomas survive 1 year or more. The only known variables that have prognostic significance are size and the ability of the first treatment to afford local control [37, 38]. Dogs with tumors of less than 2 cm in diameter have a median survival of 17 months, as compared to dogs with lymph node involvement or tumors greater than 2 cm in diameter, whose median survival time is 6 months.

Recurrent oral melanoma is worse than disease that is locally controlled with the first attempt [38]. Factors such as age, breed, sex, degree of pigmentation, microscopic appearance, and anatomic site are not prognostic factors. Oral melanomas

tend to be relatively resistant to treatment. Attempts at using chemotherapy such as DTIC with and without cyclophosphamide have yielded only partial responses. Studies using radiation therapy have shown that approximately 25% of the oral melanomas will respond to treatment, but because of the potential for metastasis the long-term control with radiation has been somewhat disappointing. Biological response modification has shown some promise with this particular tumor. In one study 42 dogs were treated with surgery combined with *Corynebacterium parvum* and compared to a group of 47 dogs treated by surgery alone [37]. Dogs with enlarged regional (submandibular) lymph nodes underwent a lymphadenectomy. All dogs were made tumor-free with surgery. The median survival time for dogs treated by surgery alone was 7.5 months; for dogs treated by surgery and *C. parvum* the median survival was 12 months. When the dogs with small tumors (less than 2 cm in diameter) were excluded from the analysis, the median survival time for dogs treated only with surgery was 4 months, as compared to 8 months for dogs treated with the combined therapy ($p < 0.05$). This study indicates that *C. parvum* retards disease in dogs with malignant melanoma, and further indicates that *C. parvum* may be more effective in the treatment of dogs with advanced oral melanoma. Canine oral melanomas are excellent tumors to use in studying the influence of biological response modifiers. The major drawbacks are that many of these tumors have metastasized by the time they are diagnosed, and depending on location, complete surgical removal can be very difficult.

Oral squamous cell carcinoma

Squamous cell carcimonas are the second most common malignancy in the oral cavity. In humans, the vast majority of oral cancer is squamous cell carcinoma; treatment includes surgery with or without the addition of radiation therapy. In the dogs, the prognosis for squamous cell carcinoma varies widely according to the site in the mouth. Cancers in the rostral mouth are curable with surgery or radiation, while those in the tonsil or base of the tongue are highly metastatic and are likely to recur locally or regionally.

Canine oral squamous cell carcinomas appear to be reasonable models for experimental radiation therapy. When adjusted for number of fractions and the time interval for the therapy, tumor control doses and normal tissue complications are reported to be similar to those for radiation therapy for T2 and T3 oral squamous cell carcinomas in humans [39].

Nasal tumors

Nasal cancer accounts for approximately 1% of all canine neoplasms. It is speculated, but unproven, that long-nosed dogs or dogs living in urban environments with resultant nasofiltering of pollutants may be at a higher risk. The average age of affected dogs is 10 years, and medium to large breed dogs may be more commonly affected. A slight male predilection has been reported. Cancer of the nasal cavity and paranasal sinuses is rare in humans. It generally affects persons over 40 years of age, and is twice as common in men as in women.

In dogs, carcinomas (mainly adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma) comprise nearly two-thirds of intranasal or paranasal sinus cancer. Sarcomas (fibrosarcoma, chondrosarcoma, osteosarcoma, and undifferentiated sarcoma) make up the bulk of the remaining cancers. In humans, squamous cell carcinoma is the most common tumor. In dogs, all of these malignancies are characterized by progressive local invasion, and the metastatic rate at the time of diagnosis is usually between 15%–20%. Regional lymph nodes remain the most common site of metastasis; however, these tumors can metastasize to the lung [40–42].

The treatment of choice for this particular tumor is radiation therapy alone or combined with surgical debulking [40]. Debulking surgery is usually necessary when using orthovoltage radiation, but it has not been necessary when using high energy radiation, such as cobalt or megavoltage. The 1-year survival range for dogs treated with radiation

therapy is 38% to 57%; the 2-year survival range is 30% to 48% [41, 42]. The prognosis for carcinomas is better than that for sarcomas, and adenocarcinomas respond better than squamous cell carcinoma or undifferentiated carcinoma. The rate of metastasis in dogs undergoing radiation therapy and relapsing is greater than 50%. Canine nasal tumors seem to have a biological behavior similar to human nasal and paranasal sinus tumors. They are excellent models for studying radiation therapy approaches.

Primary lung cancer

Compared to humans, dogs rarely develop primary lung cancer, which accounts for only 1% of all canine cancers diagnosed.

Attempts to correlate urban living and passive cigarette smoking with lung cancer have not yet shown an association. However, dogs exposed to cigarette smoke (with or without concomitant asbestos instillation) through a tracheostomy develop lung cancer at a dramatically increased rate. In the general population the average age at diagnosis is 10 years, and there is no apparent sex or breed predilection. Metastatic disease from nonlung cancer primaries is much more common than primary lung cancer in the dog and the cat.

Almost all lung cancers are adenocarcinomas. Adenocarcinomas are further classified by location as bronchial, bronchoalveolar, or alveolar carcinomas. They can be further graded as differentiated or undifferentiated, and undifferentiated tumors have a higher incidence of metastasis. Squamous cell carcinoma is less commonly reported [43].

Metastasis can occur through lymphatics, through the airways, hematogenously, or transpleurally. Over 50% of undifferentiated adenocarcinomas and over 90% of squamous cell carcinomas metastasize [43]. Surgical excision remains the primary treatment for lung cancer in the dog. The best prognosis is seen in animals with solitary lesions that are small in diameter (less than 2 cm), negative lymph nodes, and no malignant effusion. In this group of animals, over 50% can be expected to live at least 1 year postoperatively. Of the malignant cancers, adenocarcinomas have a better prognosis than squamous cell carcinoma. Larger tumors or those with evidence of lymph node involvement will have median survival times of approximately 8 months [44]. Animals with smaller tumors have an expected survival time of 18 to 20 months. A very limited series of cases testing combinations of cisplatin with vindesine or vinblastine have shown some partial responses [40]. Primary lung cancer in dogs has some similarities to human lung cancer, and may serve as a model for selected therapeutic approaches. Late diagnosis and insufficient numbers make it very difficult to obtain enough cases to do a clinical trial.

Soft tissue sarcomas

In general, soft tissue sarcomas in dogs and cats have a pathologic appearance, clinical presentation, and behavior that is similar to those in humans. Soft tissue sarcomas are relatively rare, and constitute about 1% of the malignant tumors seen in the dog and cat. Fibrosarcoma, hemangiosarcoma, and hemangiopericytoma are major types of soft tissue sarcomas in the dog. In the cat, solitary, nonvirally induced fibrosarcomas are common. Sarcomas reported less frequently in the dog include neurofibrosarcoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma, leiomyosarcoma, and malignant fibrous histiocytoma. Except for hemangiosarcoma, most soft tissue sarcomas are predominantly locally invasive tumors with variable to low metastatic potential. Most sarcomas identified in humans are recognized in animals. As in humans, the most common sites appear to be the limbs followed by the trunk and the head and neck. Radical surgical excision remains the treatment of choice; however, sarcomas have been reported to respond to chemotherapeutic agents, particularly combinations of doxorubicin, cyclophosphamide, and vincristine.

Soft tissue sarcomas are generally thought to be resistant to conventional doses of irradiation. Although higher doses have higher control rates, the chance of normal tissue complication also increases. Combinations of chemotherapy or hyperther-

mia with radiation are showing promise for improved control over radiation alone.

The prognosis for canine soft tissue sarcoma depends on the histologic type, degree of cellular differentiation, number of mitotic figures, location, and success of complete surgical excision.

Hemangiosarcoma, also known as malignant hemangioendothelioma or angiosarcoma, occurs more frequently in the dog than other species. Most reports find that the German Shepherd dog is the most commonly affected [45].

In the dog the site of primary involvement for hemangiosarcoma is usually the spleen, although the tumor has been reported in many locations. Hemangiosarcomas tend to metastasize rapidly, and they may have widespread metastasis at the time of diagnosis. They tend to metastasize predominantly through the hematogenous routes, and the most frequently reported sites are the liver and lungs. Surgery remains the treatment of choice for animals with hemangiosarcoma. In the case of the hemangiosarcoma of the spleen, a complete splenectomy is necessary. Overall, median survival times for dogs undergoing splenectomy range from 2 to 3 months [46]. Attempts at using nonspecific immunotherapy, such as a mixed bacterial vaccine *(Serratia marcescens* and *Streptococcus pyogenes),* with or without combination chemotherapy such as vincristine, cyclophosphamide, and methotrexate have had minimal effects on extending survival time [46]. However, studies are underway which indicate that combination chemotherapy using doxorubicin, cyclophosphamide, and vincristine may be beneficial in preventing recurrence or metastasis when combined with surgical excision.

Sarcomas in the dog and cat can serve as good models for therapeutic approaches. These tumors tend to respond to radiation and/or chemotherapy in a way that is similar to that of human soft tissue sarcomas.

Malignant non-Hodgkin's lymphoma

Malignant lymphoma is the third most common neoplasm seen in the dog. Middle-aged and old dogs of all breeds are usually affected, but lymphoma has been diagnosed in dogs less than 1 year of age. The incidence is 30/100,000 dogs at risk, and is higher than that in humans. Unlike that of most other species (e.g., non-human primates, cats, cattle, poultry, and mice), lymphoma in dogs has not been associated with retroviral infection, and thus appears to be similar to human non-Hodgkin's lymphoma. Most dogs with lymphoma present with nonpainful generalized peripheral lymphadenopathy. However, involvement can be seen in the cranial mediastinal, gastrointestinal tract, and skin. Primary extranodal forms such as the ocular and central nervous system are less commonly observed.

Canine lymphomas are morphologically heterogeneous, almost always diffuse, and usually high grade. Most canine lymphomas fit into two or three groups; diffuse large cell lymphoma, immunoblastic lymphoma, and small lymphocytic lymphoma. Dogs almost always have widespread disease. Most canine lymphomas are surface immunoglobulin positive, and many of these will express pan T-cell antigens. There are pan T-cell positive and serum immunoglobulin tumors that are usually associated with clinical hypercalcemia, and show cleaved cell morphology [47].

Canine lymphoma can be a rapidly fulminating disease. Without chemotherapy most dogs will survive less than a month after the diagnosis is established. The vast majority of canine malignant lymphomas can be managed by combination chemotherapy. Most chemotherapy protocols will include combinations of drugs such as prednisone, vincristine, cyclophosphamide, L-asparaginase, and doxorubicin. Lymphoma is one of the most chemoresponsive neoplasm in dogs; complete remission rates as high as 80% and median survival times of 10 to 14 months have been reported.

The clinical stage (based on extent of disease) has been shown to be of prognostic importance. Dogs with localized disease, regional involvement, or multicentric involvement (without liver, spleen, or bone marrow involvement) seem to have a better prognosis. The anatomical site is also important. Primary cutaneous lymphoma (multiple sites), diffuse gastrointestinal lymphoma, and pri-

mary central nervous involvement are associated with a poor response to therapy.

Hypercalcemia is a relatively common paraneoplastic condition in dogs with lymphoma, and has been shown to influence survival adversely in dogs undergoing chemotherapy.

One study has shown that females have a better prognosis than males [48]. In a study of 147 dogs with lymphoma treated with one chemotherapy protocol, females had a median survival time of 11 months versus 7 months for males. Of the 12 dogs that survived 2 years or longer, 9 were females and 3 were males. The underlying reason for this difference is unknown. Similarly, females have been shown to have a better prognosis in humans with non-Hodgkin's lymphoma [49].

Histologic classification has also been shown to be of prognostic importance. As in human patients, dogs with high grade tumors tend to respond better to chemotherapy, showing complete responses and longer remission times than dogs with low grade lymphomas. Dogs with 'T-cell' lymphomas tend to have lower response rates to chemotherapy as well as shortened remission and survival times [47].

Studies using biological response modifiers have yielded mixed results. Studies using the chemical immunomodulator levamisole in combination with chemotherapy have proved to be unrewarding [50], while those using a mixed bacterial vaccine *(Serratia marcescens* and *Streptococcus pyogenes)* have improved remission time but not survival time. Intralymphatic (IL) administration of a tumor cell vaccine has been used in dogs placed in remission with combination chemotherapy. Median survival time for the dogs given chemotherapy alone was 6 months, as compared with 11 months for dogs given IL vaccine plus chemotherapy. Unfortunately, survival times for the groups were not significantly different [51].

Another approach to prolonging survival and remission in dogs with malignant lymphoma is the addition of autologous bone marrow transplantation (ABMT). ABMT has been used in conjunction with total body irradiation (TBI) in the treatment of dogs with malignant lymphoma. The dog appears to be a good model for ABMT, and the approaches used in dogs have helped to determine optimal use of ABMT in humans [52].

The canine lymphoma model has also been used to study L-asparaginase covalently modified with polyethylene glycol (PEG). PEG L-asparaginase is less immunogenic, and is therefore less toxic, than native L-asparaginase [53, 54]. Studies in the dog have shown that PEG L-asparaginase is as effective as native L-asparaginase, yet is less toxic than the native enzyme.

Conclusions

There are several other distinguishing features that make pet animals attractive comparative models:

- Dogs and cats are outbred animals (like humans). They share the same environment as their owners, and may serve as sentinels for changes in the patterns of cancer development seen in humans.
- Most animal cancers progress at a more rapid rate than cancer in humans. They can, therefore, be studied more rapidly, and the results can be extrapolated to humans.
- There are few established treatments for animals in veterinary medicine. It is easier and morally acceptable to attempt new forms of therapy rather than wait until all other treatments have failed.
- The growing confrontation between animal rights groups and research workers who utilize animals will inevitably become an increasingly public issue. Many of the animal rights/welfare organizations desire an absolute ban on animal experimentation. However, privately owned animals can be entered into experimental studies with informed consent from the owner.
- The biological behavior and response to treatment of many of the spontaneous malignancies seen in the dog and cat are similar to those seen in humans; they are therefore very appropriate and essential models for studying human cancer.

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