Part One

Chapter 1
Molecular Biology of Cancer and Aging

The roots of the problems of cancer and aging involve the molecular changes of aging priming aging (cellular senescence). These changes prime aging cells to be more susceptible to the effects of environmental carcinogens. These changes are only partly understood and may or may not be reversible.

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What Is Cancer? How Does It Start?

Hippocrates coined the name for malignant cancer from the Greek word for crab (*karkinos*), because tumors resembled the claws of a crab. Cancer is an insidious, nefarious, complex, obstinate, and disruptive disease. Cancer is an intricate set of biological aberrations that originate in the nucleus of cells that transform and progress with diverse heterogeneity, which is not completely understood. Cancer results in the uncontrolled and reckless growth of destructive cells that overwhelm the body as they accumulate. Cancer's immortal cells replicate relentlessly. They can use existing vessels or recruit cells to form new blood vessels via angiogenesis for nourishment. Cancer cells slip into the lymphatic and vascular systems and invade vital structures via metastasis to ultimately kill its host with its fatal agenda.

This chapter will attempt to describe the intricacies of cancer's malignant processes. Terms are defined and readers will be subjected to only a small taste of the alphabet soup milieu that drives the intracellular and extracellular microenvironment. As you read, keep in mind that this is an attempt to illustrate the essentials of a complex disruptive process and forgive or congratulate me if the text has oversimplified or exemplified cancer!

Normal cellular division creates a constant flow of injured genes. These defective genes are regularly corrected by innate repair mechanisms present in normal cellular function. Certain genetic point mutations become multifarious if they are not repaired. Genetic damage occurs in cells that lack coordinating signals necessary for self-repair. If genetically damaged cells escape innate detection and destruction and are allowed to live and replicate, cancer gets a foothold and then proceeds with its mechanistic drivers to grow and metastasize and disrupt vital functions.

Each of the trillions of cells that compose a body contains over one hundred thousand genes, arranged in chromosomes. The DNA that composes normal genes is called a "proto-oncogene." A proto-oncogene encodes all genetic information and regulates cell replication so that cells can replenish themselves normally in the bone marrow, intestine, skin, connective tissue, and organs when needed. Genes also regulate normal wound healing, hair growth, puberty, and gestation (Abeloff et al. 2004).

Canine and Feline Geriatric Oncology: Honoring the Human–Animal Bond, Second Edition. Alice Villalobos with Laurie Kaplan.

About one in every million cell divisions undergoes a point mutation resulting in defective, aberrant, or altered genes that clone and initiate tumorigenesis. These genetic mutations can be seen by the immune system as copy errors and they are normally corrected by immunosurveillance. If the mutations are involved in the mechanism that controls repair, replication, proliferation, tumor suppression, or telomere (the terminal portion of genes, encoding programmed cell death) control, the defective genes are converted into oncogenes and their descendant cells take on a renegade behavior.

Cancer evolves on a cellular and sub-cellular level through three basic stages: initiation, promotion, and progression. *Initiation* involves exposure to carcinogens such as sun, tobacco smoke, alcohol, herbicides (2,4-D weed killer), insecticides, asbestos, free radicals, viruses, infections and so forth. This initial exposure may result in permanent damage "hits" to DNA. Initially this damage may not be a direct cause of cancer; however, continued exposure causes more gene "hits" and increases the risk of tumorigenesis. Tumor initiation and promotion is also seen in chemically induced tumors in experimental animals.

Promotion events are poorly understood. The *promoter* (an abnormal DNA base sequence in genes) stimulates cell division and results in the accumulation of cells that cause the formation of tumors. Aging, poor diet, obesity, toxins, smoke, and chemicals injure the stability of genes and are also considered potential promoters.

Progression to malignancy occurs when the tight controls that normally govern cell cycle progression are suppressed or break down. This results in the uncontrolled growth of abnormal immortal cells (cells that do not respond to normal cell death signals). Progression also involves the ability of cancer cells to initiate the formation of new capillaries (angiogenesis) to nurture growth. The most malignant cancer cells invade surrounding tissue, work their way into vessels and lymphatics and metastasize to distant parts of the body.

These events involve proteins that function by giving and receiving signals on the surface of the cell and along complex and intricate intracellular pathways in the process of cell-to-cell communication. Understanding the complexity and specifics of cell signaling and the alphabet soup that names the proteins and receptors can be overwhelming to the busy practitioner. There are basic families and systems of signaling that share certain pathways that aid and abet neoplastic changes. These basic mechanisms are fascinating and some have clinical relevance. Targeting aspects of these basic signaling mechanisms holds the key to promising therapeutics that will interfere with clonal evolution, progression, and relapse in cancer patients. Scientists attempt to manipulate the proteins that govern the intricate cell signals in ways to prevent, protect, and reverse cancer, especially in the senescent (Ihle 2004).

Tumor Suppressor Genes, Apoptosis, and Genomics

Tumor suppressor genes (*p53*) are responsible for repair of the hordes of copy errors and genetic damage that occurs during normal cell replication. When tumor suppressor genes malfunction, the risk of cancer rises. Tumorigenesis may also arise due to the loss of programmed cell death (apoptosis) signaling pathways. All normal cells have a certain life span dictated by telomere shortening after every division and suicide signaling. Suicide mechanisms to self-terminate can malfunction due to mutations of the signaling systems for apoptosis, causing cells to persist and become immortal. Scientists have identified the programmed death ligand 1 (PD-L1) gene, which promotes cancer by protecting cancer cells from T-cell mediated destruction. A ligand is a molecule on the cell surface that binds to another (usually larger) molecule. Researchers are very enthusiastic about using PD-L1

as a treatment target. Targeting PD-L1 and other tumor specific ligands is expected to provide great benefit in controlling aggressive and advanced cancer in patients in the future, with fewer adverse events.

Cell immortality is dangerous to the host. Armed with immortality and lack of suppression by tumor suppressor (*p53*) genes, these aberrant cells become malignant. They replicate and accumulate into clones of neoplastic cells. The clones undergo successive genetic changes that select for growth factors and chaotic replication. Malignant clones acquire the ability to create their own capillary blood supply (angiogenesis). These new capillaries provide nourishment and oxygen for new cell growth, thus allowing more abnormal cells to accumulate and create larger tumors. Tumors send their most vigorous, athletic scout cells into lymphatic vessels and capillaries. These resilient scout cells are able to slip under the radar of the immune system using checkpoint inhibitors that protect them from being detected and recognized for destruction by the immune system. The cells travel and metastasize into immortal tumor clonogens (cell clones or tumor stem cells that are more resistant to treatment). Clonogens may appear anywhere in the body (Khanna 2004; Morrison 2002).

Because renegade cancer cells have minimal cell death, do not curb their telomeres, and bypass senescence, they continue to divide and replicate tumultuously without repairing. Cancer cells grow wildly without control since they lack the ability to terminate themselves through apoptosis. In frenzy, they push, crowd, and dissolve their way into the society of normal tissue cells causing mayhem. *The battle against cancer is often won or lost at this microscopic preclinical stage.*

Most scientists realize that the real and decisive battle against cancer is truly fought at this molecular and immune system level, long before the tumor has expanded and accumulated enough cells to be detected. At this early, preclinical stage, a healthy, militant immune surveillance system could identify and eliminate every renegade cancer cell. Unfortunately, aging is associated with a weakened immunosurveillance system, leaving our geriatric patients at greater risk for cancer. New technology may enhance the immune system to detect and destroy malignant cancer cells.

Cancer genomics helps researchers identify the biological drivers of particular cancers. By blocking the effects of these drivers, targeted therapy may be able to inhibit cancer progression. Many human cancers have a correlation between the presence of certain genomic aberrations and the clinical outcome of the tumor and/or the tumor's response to therapy. Therefore, many chromosome aberrations are of prognostic value and the information generated via machine data collaboration may be used by clinicians to determine the most appropriate therapy. It is inevitable that veterinary oncology will benefit enormously from data derived from genomics and that this era will see a huge shift in the ways in which companion animal cancer patients are evaluated and subsequently treated (Breen 2009).

Cancer and Aging

Cancer is a disease, but aging is not. Aging is the phenotype of the normal phenomenon of cellular senescence. Carcinogenesis is a nefarious multistep process that takes time. Aging animals provide that time as their life span increases. Cancer's multistep process, enhanced by a longer exposure to carcinogens, emerges as a major syndrome associated with aging. Basic molecular and genomic research proposes many reasons for the increased incidence of cancer in older animals. Aging is associated with a decline in antitumor defenses. Older animals have less resistance, less immune competence, less DNA repair, more damaged tumor suppressor genes (*p53*), reduced numbers and function of mitochondria, and defects in biological responses. Aging is associated with diminished functional reserve of multiple organ systems, sarcopenia (muscle loss) and an increase prevalence of

chronic diseases, which may cause frailty and stress, causing the geriatric body to be more susceptible to cancer.

Certain proteins or cytokines such as interleukin-6 (IL-6), D-dimer, and C-reactive protein (CRP) are found to be elevated in the aging process. D-dimer is a product of fibrin lysis and CRP is an acute phase protein produced in the liver. These cytokines increase with inflammation and age-related conditions such as osteoarthritis. Cancer creates an immune challenge, which drives the activation and release of a cascade of cytokines including tumor necrosis factor (TNF-α, cachexin), which is responsible for creating the hypermetabolic state of cachexia. TNF-α, IL-6, D-dimer, and CRP also increase with cytokine signaling induced by inflammation, infection, cancer, thromboembolism, and acute illness.

These factors are likely to be responsible for the higher incidence and mortality rate from cancer in older and geriatric companion animals. Cancer cells proliferate with anarchy and defiance of the normal constraints that keep cell growth and division in check. Cancer instigates cytokine dysregulation and a domino effect as it disrupts the aging body.

Research hopes to provide new molecular and genomic detection and prevention methods to target and tackle the intricate cytokines and signaling steps of cancer as it evolves. The goal would be to "target" cancer out of existence at the precancerous stage, before it embarks on its fatal course. One day, we may be able to provide dogs and cats with immunoprophylaxis using preventative cancer vaccines, and chemoprophylaxis using tumor specific agents (Modiano 2016).

One Medicine and Cancer Awareness

Human and animal cancers and diseases often share a similar pathogenetic process. Companion animals are often good comparative models for human cancer. This concept fueled the "One Medicine" philosophy, which was strong in the late 1960s to 1970s. The One Medicine concept has reemerged in the last decade with universal vigor and it is universally supported by the CancerMoonShot2020 campaign. Client education regarding prevention and awareness of risk factors can help companion animals live longer and avoid some cancers. Educating pet owners about carcinogenesis, and the preliminary stages and early warning signs of cancer may help save millions of beloved pets. A well-informed clinician, using improved diagnostics in a timely fashion, can help clients with geriatric pets identify and treat cancer in its earliest stages, which may offset its devastation.

The most obvious tumors in elderly dogs and cats appear on the body surface, in the skin, in the subcutis layer below the skin, or fixed to the body wall. Cutaneous cancers may appear as tumors, ulcers, non-healing sores or petechiae (pinpoint blood blisters). They may appear as plaques or crusts on the ears, eyelids, and nose and in the non-pigmented skin of sun-exposed senior cats and dogs. The contemporary veterinarian will not suggest, "Let's wait and see if it grows." It is justifiable to examine every mass on a geriatric pet (other than obvious warts) with fine needle aspiration (FNA) cytology to determine whether the mass is truly a lipoma, inflammation, a mast cell tumor, or a malignant tumor. Read the section on cytology.

Epigenetics, Environmental Influences, Toxins, and Risk Factors

Epigenetics is the study of how genes are switched on and off. The multistep process of cancer development over time explains why we see more cancer in aging animals. One Medicine researchers view animals as sentinels that parallel human diseases and cancers that result from environmental

exposure. Certain environmental factors have been found to cause inflammation and epigenetic changes that initiate and promote cancer. It may take many years for environmentally induced cancer to develop in people whereas the same exposure may take less time to cause cancer in companion animals. Overall, cancer risk increases with exposure, time and age. The most well-known environmental risk factors for cancer in people are smoking, snuff and betel nut chewing, obesity, lack of exercise, unhealthy eating habits, occupation, viruses, family history, alcohol, toxins, asbestos, ultraviolet light (tanning beds), sun, radiation exposure, prescription drugs, reproductive factors, pollution, and unknown causes (medicinenet.com/cancer/article.htm). Infection with human papilloma virus (HPV), human immunodeficiency virus (HIV), hepatitis B and C infections, and *Helicobactor pylori* are associated with cancer worldwide. Certain food additives such as preservatives, nitrates, chemicals, and aflatoxins are known to be carcinogenic. These carcinogens are associated with epigenetic changes causing gastrointestinal (GI), hepatic, and bladder cancer in humans and are presumed to create similar risk for exposed companion animals as they age.

Certain dogs and cats also have additional breed predispositions to environmental toxins. For instance, Scottish Terriers are 20 times more susceptible to bladder cancer than other breeds of dogs and are at greatest risk if exposed to 2,4-D lawn herbicides (Raghavan et al. 2004). Cancer is promoted in the skin by solar radiation in white cats and dogs. They develop squamous cell carcinoma (SCC) because the non-pigmented skin of the feline face and canine ventrum is highly susceptible to "hits" that result in mutations from solar exposure. Cancer is promoted in the lymph nodes by toxins and retroviruses, and iatrogenically by local inflammation and neoplastic transformation resulting from adjuvanted feline leukemia virus (FeLV), rabies virus vaccines, and other injections (Ford 2004; Macy 2004).

Cats ingesting particulate residue from cigarette smoke contaminating their fur are at greater risk for developing oral and GI cancer (Snyder, Bertone, and Moore 2001). Cats exposed to smokers lick carcinogens deposited on their coats and thus are at increased risk for oral squamous cell carcinoma. Cats exposed to smokers are also at greater risk for lymphoma of the GI tract. Lymphoid tissue, reproductive organ tissue, and growth plates may be more susceptible to epigenetic changes and mutagenesis by their inherent nature. Lymphoid cells may undergo genetic damage through mechanisms triggered by environmental radiation and toxins. Exposure to 2,4-D weed killer is associated with greater risk of lymphoma in dogs. Obviously, there are many more environmental factors in modern living that may influence epigenetic changes and the multistep genetic mutations that transition into cancer's development that threatens the lives of dogs and cats as they age.

Risk factors related to size, breed, and age play a role in development of bone cancer (osteosarcoma), which most frequently appears in the growth plates of the long bones of late middle-age to senior large breed and geriatric giant breed dogs, while being rare in small dogs and cats. Reproductive tissue is at risk of developing cancer over time. Mammary tissue is sensitive to hormonal influence in female dogs of most but not all breeds as most are protected from breast cancer if their ovaries were removed by 2 years of age. Some publications speculate that sex hormones may have a protective role due to an increased incidence of cancer in dogs neutered at young ages versus intact dogs (Hart et al. 2014).

Immuno-Oncology or Onco-Immunology

There is tremendous research interest in immune checkpoint pathways in the growing arena of "Immuno-Oncology" or "Onco-Immunology." Research has revealed how the T-cell immune response receptors, given the name programed death-1 (PD-1) receptors, that normally should detect

and destroy tumors cells, are suppressed by dual ligands called PD-L1 and PD-L2, which are on the surface of cancer cells. Scientists found that cancer cells also suppress and downregulate the T-cell's cytotoxic mediators that should destroy them and that cancer cells create an immunosuppressive microenvironment (www.discoverthepd1pathway.com). This One Medicine immuno-oncology information has prompted the development of targeted therapy agents to stop the PD-L1 and PD-L2 ligands from connecting with PD-1 checkpoints and allow T-cells to continue immunosurveillance. The ability to use checkpoint inhibitors to gain information on efficacy and adverse events in clinical trials in veterinary medicine will bring benefit to humans and companion animals in the battle against cancer (Nass and Gorby 2015).

Retroviral and Infectious Disease in Cancer

Retrovirus infections, such as FeLV and feline immunodeficiency virus (FIV), cause diseases related to immune suppression and lymphoma in cats and rank as the main cause of infectious morbidity in cats. Papilloma virus causes self-limiting transmissible oral papillomas in young dogs. As yet, no virus has been found to cause other cancers in dogs.

Cancer is augmented by retroviruses that are found in many animal species, from mice to birds to cats to cattle to primates to humans. Retroviruses enter the body and cause mutations in susceptible cells. Cats have the feline sarcoma virus (FSV). FeLV and FIV both cause mutations in lymphocytes, immunosuppression, anemia, pancytopenia, leukemias, and lymphoid tumors. Thymic tumors and lymphadenopathy were seen in young to middle aged cats before the late 1980s and currently most lymphomas primarily affect the gut in older cats. FeLV also causes chronic wasting, abortions, and fading kitten syndrome (Theilen, Madewell, and Gardner 1987; Pedersen et al. 1987).

A large survey found the prevalence of FeLV and FIV each at 3% in the cat population (Little 2005). Some cats survive into their geriatric years while remaining retrovirus infected. Both FeLV and FIV attack the immune system, causing a drop in the number and activity of T-cells. This results in opportunistic infections, anemia, and weight loss similar to acquired immune deficiency syndrome (AIDS) in humans with HIV. Testing and vaccines are available for cats at risk. The FIV vaccine currently available obfuscates detection of truly infected cats due to false positive results following vaccination. Kittens of vaccinated queens test positive up to 3 months of age due to passive transfer of antibodies (MacDonald et al. 2004).

Canine lymphoma occurs in 83% of all canine hematopoietic (blood-related) malignancies and makes up 7–24% of all canine cancers (Vail, Pinkerton, and Young 2013). It is not associated with a virus or an acquired immune deficiency syndrome. Boxers are more likely to have T-cell lymphoma, whereas Rottweilers are more prone to B-cell lymphoma than other breeds (Lurie, Lucroy, and Griffey 2004). Infection with *Helicobacter* may stimulate immune responses that may promote GI lymphoma in humans. The increased incidence of lymphoma found in Golden Retrievers may hypothetically be related to infection with *Bartonella* and stimulation of specific immune responses. However, more research relating infectious disease to cancer in companion animals requires extensive epidemiologic studies and sophisticated testing.

All animals have a specific gut microbiota that operates in balance. Dysbiosis is a state of altered microbial community that disrupts the symbiotic relationship and causes or contributes to disease or dysfunction. Polymerase chain reaction (PCR) gene amplification and research technology may verify the hypothesis that certain infectious diseases and variations in the gut microbiome content may contribute to tumorigenesis. Although evidence is emerging in this area, more research is necessary to

elucidate the role of the gut microbiota in pancreatic, laryngeal, and gallbladder cancers in addition to colorectal cancer in humans (Kelly et al. 2016). No doubt that companion animal cancer patients will benefit from this very interesting research in dysbiosis, which may also shed light on the microbiota's relationship to cancer malnutrition and cancer cachexia.

Endocrine Influences in Tumorigenesis

Endocrine, autocrine, and sex hormones also play a role in tumorigenesis when stimulatory signals occupy the normal cell membrane receptors of target tissues. Altered tissue growth factor genes can also promote cells toward transformation. Dysregulation of normal growth regulatory pathways, ligand binding, and constitutive activation of transmembrane tyrosine kinase receptor activity all promote carcinogenesis.

A practical example of this altered microenvironment is the carcinogenic effect of progesterone on the mammary tissue of intact female dogs and cats. Many but not all breeds of intact dogs are at risk for developing mammary tumors as they age. The risk is minimal with early ovariohysterectomy (OVH) and reduced if OVH is by $2^1/_2$ years in dogs. Carcinomas can be iatrogenically initiated in mammary tissue with progesterone therapy in cats. Testosterone plays a similar causative role for perianal tumors in intact male dogs. However, sex hormones may confer a protective effect against hemangiosarcoma and OSA, as speculated by publications that find a decreased rate of these tumors in intact dogs (Hart et al. 2014).

Feline Injection Site Sarcoma (FISS)

Adjuvanted vaccines containing killed FeLV and rabies virus with aluminum hydroxide were implicated to act as carcinogenic promoters of normal inflammatory oncogenes in some genetically predisposed cats in the early 1990s. Localized postvaccinal panniculitis that progressed to persistent inflammatory reactions caused malignant transformation at vaccine sites, initiating promitogenic (pro cell division) signaling and genetic mutations and translocations. This genetic damage occurs in the C-myc oncogenes and C-kit oncogenes. They become activated and replace normal oncogenes, resulting in the unregulated stimulation of fibroblasts. If tumor suppressor genes (antioncogenes, antisense) such as the ubiquitous p53 genes are damaged, there is too little self-inhibition and autonomous cell death. Consequently, in a variable time period from 4 months to 15 years, vaccine-associated inflammation may ultimately direct mutation and mutagenesis of reactive fibroblasts that undergo the intricate phenomenon of transition into malignant high grade fibrosarcomas or other types of sarcomas. The location was most commonly in the interscapular region and the incidence is somewhere within 1/1,000 and 1/10,000 of vaccinated pet cats (Ford 2004; Macy 2004). FISS is deceptively invasive with a very high recurrence rate postsurgically. Cats that were treated with surgery, radiation, and chemotherapy and gained long term survival endured metastasis at a rate of 22%. The Vaccine-Associated Feline Sarcoma Task Force was formed in 1996 and worked with The American Association of Feline Practitioners to change vaccination practices and to address issues and disseminate information. It was disbanded in 2005. However, a survey in Canada did not find a decrease in FISS prevalence from 1992 to 2010 despite recommended changes in feline vaccination protocols. This raises the ethical debate for veterinarians to explain options to clients so that they may decide which product safety profile they would prefer to use for their cat (Wilcock, Wilcock, and Bottoms 2012).

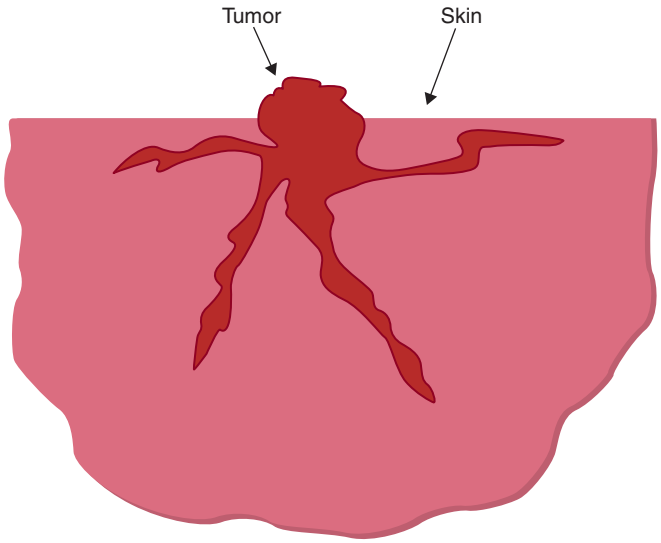

Figure 1.1. This cartoon displays the octopus-like shape of a cancerous mass with its head and streaming tentacles that extend into the normal tissues.

How Cancer Kills

Cancer kills because of its freedom from regulatory constraints, which allows for its persistent unrestrained growth that develops resistance to treatment. Cancer overtakes its victims with its exponential cell kinetics. After only seven to eight doublings, the cells of a tumor will reach a critical volume that becomes incompatible with host survival. Cancer patients die due to the rapid exponential growth and metastasis of their tumors.

A tumor one cubic centimeter in diameter (about the size of a grape) contains one billion cells, of which 10% are blood vessel cells undergoing angiogenesis to feed and oxygenate the tumor cells that enables them to metastasize. Many tumors, especially soft tissue sarcomas, develop tentacles that use enzymes such as metalloproteinase to dissolve cell walls and invade adjacent normal tissues. They invade tissue along the fascial planes or by direct extension applying pressure to surrounding structures such as nerves, vessels, and organs. It is easy to visualize a cancerous mass as an octopus, with its palpable head and its streaming cells acting as the tentacles that insidiously reach into and invade normal tissues (Figure 1.1).

Cancer also kills by altering and stealing sugar and carbohydrate nutrition from its victims to feed its own troops of invading renegade cells. Cancer-induced weight loss is an involuntary cancer–host interaction resulting in cancer cachexia. Pets with thick fur coats and older geriatric dogs and cats with age-related sarcopenia and mild to moderate geriatric cachexia may camouflage the debilitating condition of cancer cachexia in its early stages.

Mechanisms of Metastasis

Metastases is the spread of cancer cells to new areas of the body. Metastatic lesions arise either by direct spread and invasion into areas immediate to the primary tumor and/or by cellular travel to

distant locations, primarily to the lungs, liver, and spleen in animals and humans and including the bones in humans. The prognosis for metastatic cancer (generally called Stage IV cancer) is generally poor. The cancer cells that venture out into the circulatory system from primary or secondary tumors to metastasize can be thought of as the most outgoing and vigorously athletic cancer cells from a malignant tumor. Metastatic cells creep and slip into adjacent lymphatic and vascular channels. This creeping process is called diapedesis. These resilient cancer cells defy host immunosurveillance and travel via the lymphatics and circulatory system to distant locations in the body. Microscopically, scientists can see small clumps of cancer cells sending out "scout" cells that undergo diapedesis as they creep out of the primary tumor.

Cancer cells can destroy their surrounding stroma by dissolving the walls of their neighbor cells with a signaling system that regulates lysis by metalloproteinase enzymes. The cells squeeze through or between endothelial cells and pass into and creep along the walls of capillaries or vessels of the lymphatic system. These scout cells are the immortal "marathon runners" of the clone and are the most resistant to destruction. These "marathon" malignant cells must detach from the primary tumor and its extracellular matrix and defy normal death by *anoikis* (apoptosis due to loss of cellular contact). The initiation and execution of *anoikis* is mediated by different pathways, all of which terminally converge into the activation of caspases and downstream molecular pathways, culminating in the activation of endonucleases, DNA fragmentation, and cell death. The induction of the *anoikis* program occurs through the interplay of two apoptotic pathways, the intrinsic pathway, which is the perturbation of mitochondria, or the extrinsic pathway, which involves triggering cell surface death receptors (Paoli, Giannoni, and Chiarugi 2013). However, cancer cells defy the normal programed cell death pathway of *anoikis* as they take on immortal properties and become cancer stem cells, which are resistant to most conventional cancer therapies due their "stemness."

The marathon cancer cells escape their matrix and slip into the circulation system under the radar of the immune system and go on to lodge and create micrometastases in a new site with tougher, more resistant progeny cells. These cells react to the microenvironment signals that allow them to divide and survive with acquired immortal properties. Cancer cell signaling recruits endothelial cells for neoangiogenesis and they grow and accumulate into a detectable metastatic mass (Khanna 2004).

In part, the ability of a neoplasm to grow exponentially is due to the fact that metastases can further metastasize. This biological phenomenon can be used to explain to pet owners why metastatic lesions found in the lungs, liver, bone marrow, or brain are more resistant to the previously used first line chemotherapy and radiation therapy treatments.

The "liquid biopsy" is a new test that can detect metastatic cancer cells in the blood using a chip device that captures cancer cells with antibodies attached to carbon nanotubes. In the future, "liquid biopsy" tests may be able to diagnose cancers at earlier stages and yield their genomic information to customize treatment based on the specific markers of the patient's cancer (Khorsravi et al. 2016). New advances in precision based immunotherapy may be able to halt the neoplastic process during the development of metastasis (www.CancerMoonShot2020.com).

Angiogenesis

Angiogenesis is a normal regulated process that takes place during wound healing, gestation, and growth. We would all look like Frankenstein if we did not heal properly. The microenvironment of cancer cells allows signals for pathological neoangiogenesis. Cancer cells create new blood vessels and capillaries to feed and bring oxygen to their progeny of growing renegade cells. One mechanism

may involve recruiting angioblasts and circulating endothelial precursor cells (EPCs) as with hemangiosarcoma and other solid tumors (Lamerato-Koziki et al. 2005). However, "inducing angiogenesis" is not an essential hallmark of all cancers. Some non-angiogenic tumors use or co-opt and exploit pre-existing vessels and newly formed ones to feed themselves as they grow and metastasize. This finding adds more complexity and raises the question of the relative importance of angiogenesis versus pre-existing vessels in the high proportion of cancers containing both. It is hard to pinpoint how much angiogenesis and how much pre-existing vessels are contributing to tumor growth. These findings are therefore seriously questioning the idea that all tumors will respond to antiangiogenesis therapy (Pezzella et al. 2015).

Without angiogenesis, most tumors cannot enlarge beyond a few millimeters or become large enough to be detected on radiographs and imaging scans. This is why antiangiogenesis agents are intriguing to use. This approach is especially kinder and gentler for geriatric cancer patients because there is a low adverse event profile when prescribed as metronomic chemotherapy. However, since not all tumors depend on angiogenesis, it would be great to have a diagnostic test that can differentiate as to which patients will benefit from metronomic therapy aimed at inhibiting angiogenesis.

Why Are There So Many Kinds of Cancer?

Researchers recognize at least 200 types of cancer – that is approximately as many cancers as there are types of tissue in the body. Each individual's cancer is different in terms of its prognosis and treatment. Its properties depend on the type of tissue from which it arose and on which tissues it subsequently invades. The names and terminology for various cancers are generally based on the cell of origin. Each type of cancer has its own name with specific unique variations, characterizations, and behavior. This information forms the premise for most practicing oncologists in that if we can name a cancer, we can diagnose it and stage it and understand and predict its biologic behavior in a specific patient. Geriatric patients have one more layer of complexity due to the aging process and associated comorbidities. Cancer can be classified into five basic groups: carcinomas, sarcomas, blood cancer, central nervous system (CNS) cancer, and cancers of miscellaneous or unknown origin (Table 1.1).

Tissue biopsy and/or fine needle aspiration (FNA) cytology provide the cell morphology or structural characteristics that enable us to determine the cell type of a specific tumor for diagnosis. Intricate tests that examine the DNA array of tumors and that stain cells for certain protein markers are needed to identify the genetic phenotype of cells that are microscopically and morphologically indistinguishable from one another, such as T-cell and B-cell lymphomas.

The nomenclature that is used in oncology and pathology has its origins in Latin and Greek. Pathologists will change terminology and classifications from time to time. The words and acronyms describing the molecular biology of tumors and the mechanisms of targeted drug action used in the field of oncology and tumor immunology represent by far the largest alphabet soup and the most confusing terminology in medicine.

An understanding of oncology requires familiarity with tumor tissue origins and with the names and various biological behaviors of each cancer, based on its general tissue type. The biopsy report specifies the type of cancer and this is synonymous with its diagnosis. Staging the cancer tells us something about the size of the primary tumor, whether it is localized or has infiltrated local lymph nodes or regional nodes, and if it is metastatic to distant locations in the body.

Table 1.1. Common Terminologies and Abbreviations for Basic Types of Cancer Based on Tissue of Origin

General Tissue of Origin	Specific Tissue of Origin	Basic Cancer Type (Terminology/Abbreviations)
	CARCINOMA (CA)	
Skin/epidermis (ectoderm)	Squamous cell: skin, tonsil, respiratory	Squamous cell carcinoma (SCC)
	Basal cell	Basal cell carcinoma (BCC)
	Wax glands	Adenocarcinoma (AC)
	Sweat glands	Sebaceous gland AC; ceruminous gland AC
		Apocrine gland AC
	Anal sac	Anal sac AC
	Reproductive tissue	
	Breast	Breast cancer (MGAC)
	Prostate	Prostatic AC
	Uterus	Uterine AC
Glandular tissue with ducts or tubes (endoderm)	Testes (may produce sex hormones)	Sertoli or interstitial (Leydig) cell carcinoma
	Ovaries (may produce sex hormones)	Ovarian granulosa cell tumor
	Respiratory tract	Respiratory AC
	Gastrointestinal tract	Intestinal AC
	Hepatobiliary: liver, bile duct	Hepatocellular (HC), cholangiocellular carcinoma (CC)
	Kidney	Renal cell AC (RCC)
	Bladder	Transitional cell carcinoma (TCC)
		Endocrine tumors
Hormone-producing ductless glands (may produce paraneoplastic syndromes)	Thyroid gland	Thyroid AC
	Adrenal gland	Pheochromocytoma, adrenal AC
	Pituitary gland	Pituitary AC
	Pancreas	Pancreatic AC
	Heart	Heart base tumor (HBT)
	SARCOMA (SA)	
	Fibrous connective tissue	Fibrosarcoma (FSA)
	Vascular: endothelial cells, angioblasts	Hemangiosarcoma (HSA)
Connective tissue (mesenchymal)	Vascular: pericytes	Hemangiopericytoma (HPCT)
	Skeletal muscle	Rhabdomyosarcoma (RMS)
	Smooth muscle	Leiomyosarcoma (LMS)
	Peripheral nerve	Schwannoma (neurofibrosarcoma) (nerve sheath tumor) (NTS)
	Bone and joint	Osteosarcoma (OSA); synovial cell sarcoma
	Plasma cells	Multiple myeloma; IgM macroglobulinemia
Combination of epidermal and neuroendocrine tissue	Melanocytes containing melanin granules	Malignant melanoma, melanosarcoma (MM)
Allergy cells in skin; gut	Mast cells containing vasoactive chemicals	Mast cell tumor (MCT) Mastocytoma, mastosarcoma

(*continued*)

Table 1.1. (***Continued***)

General Tissue of Origin	Specific Tissue of Origin	Basic Cancer Type (Terminology/Abbreviations)
	BLOOD CANCERS	
Blood-forming cells	Hematopoietic cells	Leukemias
	Lymphoid cells (in cats +/– retrovirus)	Lymphomas (T-cell, B-cell) (lymphosarcoma) (LSA)
	Lymphoid cells	Cutaneous lymphoma (T-cell, B-cell) (epi- or non-epitheliotrophic) (CL)
	Hemangioblasts/angioblasts (Pluripotent stem cells of bone marrow)	Hemangiosarcoma
	CENTRAL NERVOUS SYSTEM (CNS)	
Central nervous system (Neuroendoderm)	Brain	Brain tumors Meningioma Glial, ependymal, neuronal, and embryonal tumors
	Pineal gland	Pituitary tumor
	Choroid plexus	Choroid plexus carcinoma
	Spinal cord	Spinal tumors
	MISCELLANEOUS OR UNKNOWN CELL OF ORIGIN	
	Dendritic cells (Histiocytes)	Histiocytosis
	Macrophages	Malignant (MH); systemic (SH); cutaneous (CH)
	Pleomorphic, bizarre fibroblast-like and/or histiocyte-like cells with spindle and round cell characteristics	Malignant fibrous histiosarcoma (MFH) (solitary or multicentric)
Unknown cell types of the immune system	Histiocytic round cells	Transmissible venereal tumor (TVT)
	Pleomorphic atypical lymphoid cells	Pulmonary lymphomatoid granulomatosis (PLG)
	Monocytes	Unknown
	Langerhans cells	Unknown
	Plasma cells that produce IgG or lambda light chains in the cytoplasm	Plasmacytoma, reticulum cell sarcoma, Merkel cell tumor of neuroendocrine origin, atypical histiocytoma, cutaneous plasma cell tumor
Mesoderm (mixed epithelial/ mesenchymal)	Epithelial lining cells of coelomic cavities	Mesothelioma
Thymic epithelium	Thymus	Thymoma (infiltrated with mature lymphocytes)

Imaging helps us to acquire more diagnostic details for staging purposes and surgical or radiation treatment planning. The biopsy report also allows the histologic grading of tumors (I, II, III), and states if it is well, moderate, or poorly differentiated, in the hope that this will help the clinician predict their biological behavior. Naming, staging, and grading are considered essential in order to

make decisions and plan cancer treatment. However, in veterinary medicine, some patients' carers do want advice, even if they cannot afford staging.

Diagnostic Molecular Technology

Genomics tools have developed rapidly since the publication of the complete canine genome sequence in 2005 by researchers at the Broad Institute of MIT and Harvard (www.broad.mit.edu/mammals/dog). In combination with resources allowing wider access to tumor tissue and the ability to conduct clinical trials, the stage is set for rapid advancement of knowledge about canine diversity, disease genes and pathways, aging, cancer susceptibility, and importantly lymphoma. One Medicine researchers know that dogs are a great lymphoma model because they share many significant similarities with human non-Hodgkin lymphoma and learning more will benefit dogs and humans (Richards and Suter 2015).

Some malignancies grow so rapidly that they are difficult to classify by cell type. They are called "un" or "de" differentiated. In such cases, immunohistochemical stains can help to classify cells for diagnostic and subsequent therapeutic purposes. All cancers have a gene signature and new technology assays will reveal their identity. The pathologist will offer these stains when necessary. It is a good idea to pursue the newer sophisticated genomics diagnostic testing such as that offered by Innogenics™, which will advance the accuracy of diagnostics and help determine if a tumor has a high or low metastatic potential and provide information to improve treatment planning and prognosis. The Innogenics Enlight™ assay technology offers personalized biomarker and genomic information with treatment options for dogs (www.innogenics.org).

When applicable, tumor markers can be used to identify certain types of neoplastic cells. Tumor markers, which are generally specific antigens, may be found in tissue samples and in serology samples from the patient. Pathologists can now identify certain growth factors and receptors in tumor tissue that can be used for the development of therapeutic strategy as well as to determine disease prognosis. Markers found in blood are commonly used in human cancer patients following treatment to monitor for recurrence. Markers may be positive when a tumor is clinically undetectable but they may also rise due to other factors. This situation places clinicians in a quandary. If the clinician cannot locate the tumor, should he or she interpret rising positive markers as recurrence or as background cross-reactivity? This conundrum frustrates decision making for attending doctors and all concerned. Ruling out other causes and good clinical judgment should prevail.

Our profession has the availability of exciting new tests such as the mast cell tumor (MCT) panel and genetic profile testing. The MCT panel runs all the special stains for MCT markers. Early indications suggest that a panel of markers like the MCT panel may be helpful in predicting the biological behavior of a patient's initial tumor. Following tumor markers sequentially may enable early detection of microscopic recurrence. With this information, however, comes the responsibility of ethical and practical decision making. The clinician must deal with the inherent lack of specificity of some tumor markers and still make the call to treat or not to treat the patient for suspected recurrence (see Chapter 8). This quandary places a huge responsibility on clinicians. Should we treat to be safe rather than sorry? Should the considerations be modified for aging pets?

New technology using gene arrays (maps) will enhance our ability to know the molecular details of specific tumors. Soon oncologists will be able to characterize cancers further by genetic markers and mechanisms that may express one growth factor over another or a certain enzyme or cytokine. This information will benefit cancer patients with improved modes for targeted therapy. Detailed testing

with gene arrays may be affordable and routinely available for veterinary patients in coming years. Practitioners will need to comprehend the gross terminology in the field of oncology and stay abreast of the ever-increasing ability and advantages of delving into the molecular structures and functions involved in neoplasia with emerging technology and therapy.

We may change our approach to cancer and treatment philosophy in the future. With new diagnostics and treatment options such as: antiangiogenesis agents, nanoparticles, gene therapy, targeted therapy, stealth antibody therapy, and checkpoint inhibitors, we may soon be able to address cancer on general terms and ambush its basic molecular mechanisms. In the future, we may be able to prevent common cancers such as lymphoma, hemangiosarcoma, and osteosarcoma in dogs with prophylactic vaccine cocktails. We may one day abandon the conventional standard approach to crisis oncology that dictates us to ask, "What is it? Where is it? Now let's cut it out, irradiate it, or poison it."

Aberrations in oncogenic pathways are the fundamental underpinnings of cancer phenotypes. These are shared between human and canine lymphomas in many cases. As more targeted therapies become available, understanding which genes are dysregulated and which are "Achilles heels" for a particular type of cancer becomes increasingly important.

What Are Sarcomas, Carcinomas, and Adenocarcinomas?

Sarcomas are malignancies that originate in connective tissue. Soft tissue sarcomas (STSs) arise from connective tissue other than bone. STSs are tumors that originate in the connective tissue found in skin, muscle, vasculature, and fibrous tissue. These tumors belong to a large group of tumors and are often treated similarly (Table 1.2). Because people can see and feel the entire body surface of their pet animals, family members or the groomer initially discover many STSs.

Sarcomas of bone are osteosarcoma, chondrosarcoma, synovial cell sarcoma, and tumors arising from any other bone constituent. In addition, any other tumor type including metastatic adenocarcinomas may infiltrate bone. Pet owners often misunderstand the basic concept of metastasis to the bone. They may say, "My father died of bone cancer, now my dog has it," when in fact, the father had metastatic prostate cancer that invaded the pelvic bone. The same is true for metastatic breast cancer in women. Clients tell us that their mother or sister died of lung or bone cancer, but it was actually metastatic breast cancer. Animals do not have as high an incidence of bone invasion from metastatic cancer as humans do. Most likely, either animal cancer patients do not survive long enough for the metastasis to occur or their bones are endowed with some unknown sanctuary mechanism. Bone cancer in dogs is an identical model for bone cancer in humans. The study of molecular mechanisms of mutation and sarcomagenesis in multiple species may result in prevention therapies (C3O, 2016, http://bit.ly/2cur1M2).

Table 1.2. Soft Tissue Sarcomas of Clinical Significance in Dogs

Mast cell tumor	Malignant melanoma
Nerve sheath tumor (Schwannoma)	Hemangiopericytoma
Fibrosarcoma	Hemangiosarcoma
Neurofibrosarcoma	Plasmacytoma
Myxofibrosarcoma	Rhabdo(myo)sarcoma
Myxosarcoma	Malignant fibrous histiocytoma
Fibroma (invasive)	Liposarcoma
Synovial cell sarcoma	Reticulum cell sarcoma

Blood Cancer

Blood is a connective tissue and sarcomas of hematopoietic cells are commonly referred to as blood cancer or leukemias and lymphomas. They are further classified as to the type of leukemia by the cell of origin: lymphoblastic, chronic lymphocytic, myelogenous, acute myelogenous, granulocytic, multiple myeloma, plasma cell, erythrocytic, and so forth. There are numerous types of non-Hodgkins lymphomas (NHL) in dogs and cats and they sadly cause high mortality. The World Health Organization (WHO) system of classification for canine NHL is currently used with an 83% accuracy amongst 17 pathologists (Valli et al. 2011).

As clinicians, we are familiar with large cell, blastic, cleaved cell, small cell, T-cell, B-cell lymphoma in dogs. It is helpful to differentiate lymphomas by immunophenotyping during the workup phase in dogs. This would provide a more accurate expectation of response and overall prognosis, since T-cell lymphomas, which are more common in Boxers, are more resistant to standard treatment. Feline lymphomas are classified according to the National Cancer Institute working formulation (Valli et al. 2000). The *Veterinary and Comparative Oncology Journal* published Volume 14 as a supplement devoted exclusively to canine and feline lymphoma in August 2016, with an editorial by D.J. Argyle and F. Pecceu. This special supplement issue brought together key publications on lymphoma and serves as an excellent reference.

Carcinomas and Adenocarcinomas in Dogs and Cats

The terms "carcinoma" (CA) and "adenocarcinoma" (AC) generally apply to cancer that arises in the epithelial tissues of skin and body organs. People often use "carcinoma" synonymously with "cancer" because 80–90% of human cancer cases are carcinomas. ACs originate in abnormal gland cells that are in the lining or inner surface of a cavity or organ. Adenomas are benign tumors of gland cells that, over time, may transition into malignant tumors. ACs and adenomas may originate in any part of the body. The skin and delicate mucous membranes are commonly affected in senior pets. Dogs are prone to develop sebaceous, apocrine (anal sac), perianal, ceruminous, salivary, and sweat gland tumors, while cats are prone to basal cell tumors.

Breast cancer, which is sex hormone related, is commonly encountered in intact female dogs or in dogs spayed after $2^1/_2$ years of age. It is less common in cats. Squamous cell carcinoma (SCC) that appears in lightly pigmented facial skin of cats and in the glabrous skin of lightly pigmented dogs is solar induced. However, SCC also appears in the oral cavity, tongue, tonsils, esophagus, nasal and paranasal sinuses, respiratory tract, and nail beds. Some reports have associated tonsillar SCC in dogs with environmental pollution and oral SCC and GI lymphoma in cats with exposure to coat-associated carcinogens from cigarette smoke.

ACs in the abdomen may originate from glands such as the liver, colon, intestine, stomach (gastrinoma), kidney, bladder, pancreas, prostate, and adrenal. Widespread dissemination of cancer in the abdomen and throughout the rest of the body is often termed as "carcinomatosis." The term may also include other tissue types. AC may also originate from any gland in the neuroendocrine or reproductive system such as the thyroid glands, pancreas, adrenal glands, pituitary gland, ovaries, uterus, testicles, and prostate. These tumors often cause paraneoplastic syndromes related to their cell products. Anal sac AC is well known for causing malignant hypercalcemia. However, other malignancies, especially lymphoma, may also cause this potentially life-threatening paraneoplastic syndrome.

Nasal AC in pets may extend past the ethmoid plate into the brain. Primary CNS brain tumors are very pleomorphic. Only choroid plexus tumors of the brainstem, which are poorly responsive to treatment, are classified as carcinomas. AC may appear in the ciliary body in the eye and occasionally in the glands of the eyelids.

Aortic body (heart base tumors, chemodectoma) and bronchogenic AC originate in the chest cavity. Bronchogenic AC is often found as a round solitary mass in the caudal chest. If it is located in the distal lung lobe without nodal metastases, affected dogs may have good survival times following lobectomy. Cats rarely have primary lung cancer, but when they do, it is generally found to be SCC, which may metastasize to the digits and resist treatment.

Mesotheliomas originate from the epithelial lining of the pleura, pericardium, and peritoneum. They originate in the chest and abdominal cavity, causing malignant effusions. In humans, mesotheliomas are associated with asbestos inhalation. They are rare in dogs and cats – most mesotheliomas diagnosed in pets are actually ACs.

Pulmonary lymphomatoid granuloma (PLG) is a rare condition categorized as a precancer that may confuse the clinician. It occurs in middle-aged dogs, appears as massive pulmonary involvement with very large nodules, and infiltrates similarly to an end stage AC or sarcoma. It is important to distinguish this disease from AC as most cases of PLG respond nicely to treatment and have a favorable prognosis despite the enormity of the lesions.

Some malignant tumors have cells that are so undifferentiated or "dedifferentiated" that the pathologist can only report them as anaplastic carcinomas with no indication of the cell type of origin. This was the case with Alfie, the author's $11^1/_2$-year-old Australian Shepherd. Ultrasound-guided FNA cytology of Alfie's mass revealed two populations of bizarre cells appearing to be both carcinoma and sarcoma. The histopathologic diagnosis was undifferentiated carcinoma with no definite gland of origin. Direct visualization at exploratory laparotomy disclosed that Alfie's carcinoma was hepatic in origin.

The biological behavior of most ACs is aggressive with a persistent tendency for metastasis. Most ACs expand to a detectable size by outward growth (like an onion) and by direct extension into local tissue. The cells use matrix metalloproteinase enzymes to dissolve neighboring cell walls for local invasion. Through diapedesis, AC cells gain entry into lymphatic and capillary vessels and then disseminate throughout the body.

Locoregional recurrence and lymph node invasion are common, followed by widespread metastasis (Figure 1.2). Metastatic AC generally appears as nodular cell clones in the lungs, liver and other abdominal structures, brain, and eyes. AC may further metastasize to bone and dermis (Figure 1.3). On rare occasions, AC may metastasize to the digits in cats. German Shepherd dogs may develop a rare form of renal AC, classified as cystadenocarcinoma, which causes the bizarre formation of multiple benign fibrous nodules in the skin.

ACs are commonly visualized as fluffy, or milliary, infiltrates or nodules in chest X-rays of pets in advanced stage disease. Some pets develop pulmonary effusion and hemoptysis (coughing up blood). Nasal cancer patients exhibit chronic unilateral nasal discharge and/or frank hemorrhage (epistaxis). Some dogs and cats develop occult disease with warning signs of coughing, gagging, exercise intolerance, or dyspnea due to pulmonary compromise from the metastatic disease process.

What Can Be Done to Halt Cancer in Pets?

Until recently, the overall goals of research and therapy in veterinary cancer medicine have been twofold: firstly, to cure or palliate existing cancer while leaving the patient with a good quality of

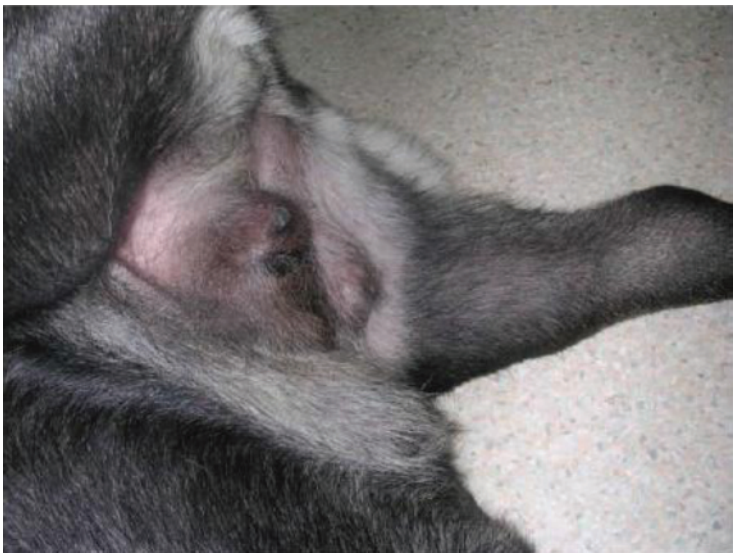

Figure 1.2. This large primary mammary gland adenocarcinoma caused edema and swelling of Bear Brown's perineum and legs.

life and, secondly, to prevent cancer cells from colonizing in the body. However, with the Cancer-MoonShot2020 tremendous optimism has been revived in the potential benefits of immunotherapy. Scientists are finding ways to awaken or to relieve suppression of the immune system's job to detect and destroy cancer cells. They also have developed technology to "train" the immune surveillance system of the body to kill cancer cells at any stage of disease, including advanced stage patients that are considered terminal.

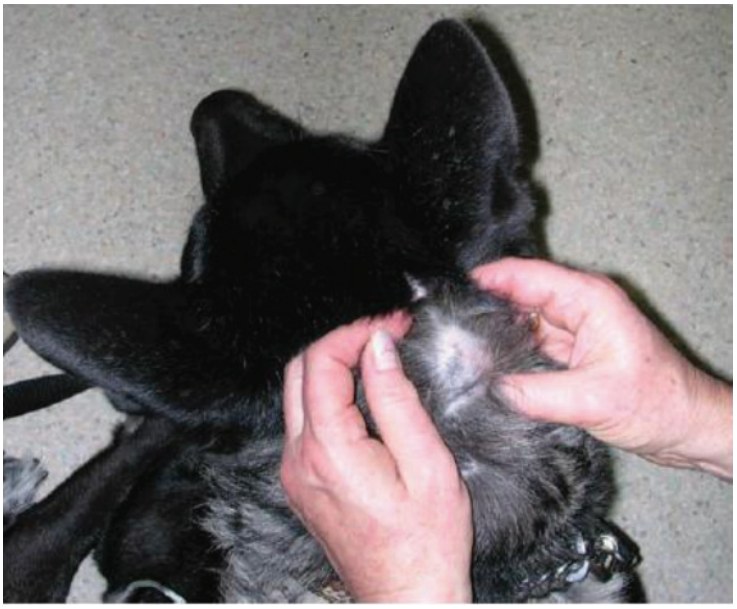

Figure 1.3. 12-year-old F/S Akita, Bear Brown, with a metastatic mammary gland adenocarcinoma lesion in the skin of her dorsal neck.

Proposed ways to win the battle against cancer also include chemoprevention and nutritional concepts such as "starving the cancer cells while feeding the patient." Another approach is to use supplements that support the immune system and microenvironment on a preventative basis. Some supplements may have antineoplastic or protective effects in helping the liver to function and detoxify. Some act as antioxidants that scavenge free radicals. The terms immunonutrition and chemoprevention are used when discussing this approach by this author.

Future therapies for cancer may control it through medications that will cripple its aberrant angiogenesis capabilities or cripple its ability to create lytic enzymes and cytokines. For example, "targeted" gene therapy, such as the small molecule protein kinase inhibitors, may become the norm. Inhibitors of angiogenesis such as Avastin® block vascular endothelial growth factor (VEGF) by injection. Oral metronomic chemotherapy and multitargeted tyrosine kinase inhibitors such as masitinib, toceranib, dasatinib, AngioStop®, etc., that have antiangiogenic activity will be included in combinatorial protocols. Drugs that inhibit metalloproteinase enzymes prevent cancer cells from dissolving neighbor cell walls to slow invasive behavior. Some of these agents may be given for permanent maintenance therapy or used in chemoprevention protocols.

Innovative treatments such as precision or personalized therapy, with vaccines or specific gene therapy, may be used to control cancer by correcting replication defects. In gene therapy, special genes are transfected into bacterial, viral or cellular vectors and injected into the patient. These therapeutic genes then signal the cells of cancer patients to produce specific proteins that will, it is hoped, suppress or destroy the tumor. In antiangiogenesis gene therapy, proteins such as endostatin and angiostatin may be used to arrest the angiogenesis process. Gene therapy may offer several ways to fight back at the microscopic level where cell-to-cell signaling in the neoplastic battlefield is most crucial. Researchers are also studying the use of stem cells in cancer therapy to help replace bone marrow and organs that may have been destroyed by treatment or by the neoplastic invasion.

It is quite possible that, in the near future, the use of surgery to "cut and slash" at tumors, chemotherapy to "poison" cancer cells (along with trillions of healthy cells innocently undergoing cell division), or radiation therapy to "burn" cancer cells (along with millions of innocent normal bystander cells) will become methods of the past.

One approach that uses natural or synthetic substances to prevent cancer by interrupting mutation, oncogenesis, angiogenesis, and metastasis is called "chemoprevention" or "chemoprophylaxis" by mainstream conventional medicine (Bergman 1999). An example of chemoprevention for women at high risk for recurrent breast cancer would be the use of antiestrogen medications such as tamoxifen and raloxifene (Love 2000). Another example of chemoprevention is the use of calcium supplements to decrease the risk of colorectal cancer in humans (Popchain 2004). Research will identify more helpful compounds that may protect or offer support for geriatric pets against cancer. The use of metformin to enhance the efficacy of chemotherapy by suppressing the multiple drug resistance gene (MDR1) is an example of repositioning existing drugs and placing them in combinatorial protocols. (MacDonald et al. 2015)

There are millions of microscopic skirmishes between immune cells and cancer cells in a body on a daily basis. Macrophages, NK (Natural Killer) cells, and cytotoxic T-cells operate by signal cell transduction. Much of this action takes place on cell membranes while the intracellular signaling systems are affected. The body's surveillance cells and tumor suppressor genes (especially *p53*) work for the immune system and can eliminate renegade cancer cells if they are activated, trained, or empowered and if they can avoid being suppressed by tumor cell ligands. It is at this cellular microenvironment level, the microscopic proteomic, metabolomic field, where the true battle against cancer is won or lost. It is here that the battle should be fought, not when a tumor is already established.

Nutritional and holistic treatment promotes prevention and balance with the use of a healthy diet and supplementation with natural substances such as fatty acids, antioxidants, supplements, and nutraceuticals. The agents used are known or believed to operate at the cell surface signaling level to work on the immune system and/or to protect or detoxify various organs and systems to prevent or lower the risk of cancer. Data regarding the efficacy of large-scale trials is available online from ClinicalTrials.com.

A significant segment of the pet-owning community is drawn toward nutrition and holistic medicine for the prevention and/or ancillary treatment of cancer in aging pets. These methods are popular with the people who believe in them; however, Western medicine remains skeptical as few controlled clinical studies can verify claims. Holistic, alternative, and complementary medicine and its many branches of nurturing therapies may have a positive contribution to make in the overall care and well-being of the cancer patient. The holistic approach attempts to care for the entire patient and enhance the quality of life by decreasing uncomfortable symptoms and feelings, seeking to balance the body's systems including emotions, and supporting the immune system. Holistic medicine also actively addresses the nutrition of patients on a preventative and therapeutic basis. There are various types of alternative and holistic medicine including acupuncture, chiropractic, massage therapy, homeopathy, and herbal medicine. Some approaches are under justifiable scrutiny by the watchful and the skeptical, but clinicians should be aware that when faced with advanced and aggressive cancer, the pet carer is often compelled to seek information beyond his or her local veterinarian's scope or comfort zone. It is estimated that 8–10% of human cancer patients whose diagnosis has been confirmed by tissue biopsy decline mainstream therapy (Love 2000). This may be true for pet owners as well. This is viewed as potentially harmful to the patient if the pet owner foregoes the opportunity for curative conventional therapy.

The quest to self-educate with information from the Internet may confuse worried caregivers initially. However, eventually their quest and your consultation and recommendations will empower them with the information needed for comprehensive, personal decision making for their pets. Ultimately, practitioners may use the best from both worlds by combining and interdigitating the most successful conventional treatments with the most supportive complementary treatments to palliatively extend a dear pet's life. This blending and delivery of many different types of medical knowledge is called "integrative medicine." Taking an integrative approach to help their geriatric pet with cancer will most likely be welcomed by your clients.

Much Is Left Unsaid and Unaddressed

Cancer is the grim reaper of geriatric pets. Cancer colonizes from genetic error and environmental insult through the steps of initiation, promotion, and progression. When cancer becomes clinically obvious in a geriatric oncology pet, the battle to save that pet's life will require skill (both interpersonal and medical) and luck. The decisions made at the onset of clinical detection often dictate the ultimate fate of that pet. Those decisions include not only clinicopathological considerations of the patient but also considerations of emotional and psychosocial sensitivities of the family. These issues may exist with any geriatric oncology case presenting at early, middle, and advanced stages of disease.

This book illuminates emotional and decision-making issues in geriatric oncology that are often left unaddressed in textbooks. It will also clearly outline the information that each pet owner should acquire from a consultation with the primary veterinarian and then, on a more specialized level, from their referral veterinarian. There is a cry for help to the veterinary profession from deeply bonded pet

owners because many of their needs, including clear clinician-to-client communication, emotional support, pet pain control, and end of life care issues, such as when to enter a hospice, are not handled properly.

Too often, vital interactive information is lost or forgotten in the hurry through exam rooms. Attending doctors, staff, and carers leave much unsaid that needs to be said. Veterinarians who learn to mindfully listen to their clients, and understand attachment, and how the human–animal bond factors into the geriatric pet–cancer equation, will gain a tremendous potential for enriching their practice. Veterinarians, who devote time to compassionately transfer vital "soft" information to their care-giving clients, truly serve the needs and expectations of the companion animal community in our society.

Ageism

Ageism, or bias against old people and old animals that limits medical options to extend life, is not uncommon in our modern society. Shelters are always getting old animals that people do not want any longer or cannot afford. You may not know that your client might be afraid that you will not help their geriatric pet because of its old age. Of course, ageism undermines our ethical duty to always act in the best interests of the patient, geriatric or not! Finessing complex cases with fastidious care will avoid many complications, especially in patients with comorbidities and advanced disease.

As doctors and healers, we need to have the discussion that offers the option of Pawspice, akin to human palliative medicine, which treats the primary cancer in kinder gentler ways and addresses symptoms. The use of metronomic chemotherapy is a kinder, gentler, and effective approach that may benefit cancer patients without the adverse events related to standard chemotherapy (Mutsaers 2014). We must also recognize when further treatment is futile and offer clients the option of true hospice, which is palliative comfort care that does not treat the cancer. When our patients show signs that they are actively starting to die, we need to emphasize the value and the purpose of the hospice vigil and assist the family in decision making for euthanasia. These principles will help ease the bumpy road that is end of life.

Physiologic and Chronologic Aging Variability

There is no straightforward method for defining the age at which dogs and cats become "senior" or "geriatric." Of the two species, dog aging is more difficult to pin down due to genetic variability, breed longevity, environmental influences, body weight, and whether or not the dog is obese. Overfeeding and obesity have been shown to reduce the longevity of dogs by 2 years. This may be true for obese cats as well. One study found that almost 30% of our nation's senior dogs were overweight. By 12 years of age, only 5% of dogs were overweight, and 16% were underweight (Donoghue 1991). The ravages of age interacting with the molecular events and genetic mutations that generate cancer may be potentially reversible with treatment.

Clients often ask, "How can I estimate my pet's age in comparison with human aging?" A 1-year-old medium-sized dog has accelerated maturation and is comparable to a 15-year-old teenager. During the middle years, the aging process slows down, adding only 4 years per 1 human year. During the last 25% of a pet's life, aging accelerates.

"Senior" is a term that softens the concept of aging and flows well into "geriatric." "Senior" prepares pet owners to witness the comparatively accelerated aging of their beloved companion animals. The

term "senior" is commonly used to describe dogs over the age of 7 years and cats over the age of 9 years.

I propose that large dogs be considered senior after 5 years of age and giant breed dogs be considered senior after $4^1/_2$ years of age. Using the term "senior" to describe dogs and cats that have reached 60% of their life expectancy seems reasonable.

"Geriatric" is defined as the state of being in the last 25% of one's life expectancy (Abeloff et al. 2004). The term "geriatric" is commonly and arbitrarily used to describe dogs and cats over 8 years of age, even though cats and small breed dogs live longer than large and giant breed dogs. The life expectancy for cats and small dogs (less than 20 pounds) is 9 to 13 years. The life expectancy for medium-sized dogs weighing 21–50 pounds is $9–11^1/_2$ years. Large dogs weighing 51–90 pounds have a life expectancy of $7^1/_2–10^1/_2$ years. Giant breed dogs weighing over 90 pounds have the shortest life expectancy, only 6–9 years.

For this text, all cats, and dogs weighing under 90 pounds, that are over 8 years of age, and all giant breed dogs over 5 years of age, are considered geriatric. Clients are enlightened when they see comparable aging tables showing the variations between animals and humans by species and weight. A combination of several comparable aging charts for pet cats and dogs stratified by weight was prepared for this text to illustrate the ranges of opinion (Table 1.3).

We often encounter exceptions to the rule when we see chronologically old pets that are physiologically youthful. Some geriatric animals are not afflicted with the usual arthritis, spondylosis, nuclear sclerosis, visual and hearing deficits, muscle loss, and cognitive dysfunction of their counterparts. This vitality may be the best reason, next to financial limitations, that explains why geriatric medicine is applied on a somewhat arbitrary basis from one clinician to the next.

The clinician who fails to recommend health screening for a senior or geriatric pet because the pet is physiologically youthful deprives that patient of the potential benefits of an early diagnosis of cancer. The synergism of cancer with aging involves the molecular changes of aging that prime senescent cells to the effects of environmental carcinogens (Balducci 1994). We must individualize our management approach to suggest preventative screening for early detection of cancer in our geriatric patients. A protocol composed of personalized therapy utilizing guidance from cancer genomics testing and combinatorial modalities may best control cancer while maintaining a good quality of life for each geriatric patient.

Incidence

There are currently more than 170 million pets in the United States and each year more than one million dogs are treated for cancer (www.nap.edu21830). Cancer kills 50% of all dogs over the age of 10 and one in four dogs under the age of 10. Cancer kills one-third of the feline population.

A 1998 Gallup Poll found that 39% of the 58 million dogs that were in the general population were "senior" and that 47% of the senior group was considered "geriatric." The US dog population increased from 65 million to 80 million between the first and second editions of this text. Now we can estimate that the senior dog population increased from 25.35 million to 32 million and that the geriatric dog population increased from 12 million to 15 million. Since half of dogs over the age of 10 develop cancer, this translates into 6–7.5 million canine cancer patients that our relatively small profession may potentially encounter in the US. Osteosarcoma was diagnosed in 8,000 dogs in the US each year before 2005 (Eldredge and Bonham 2005). However, current estimates note an increase to 10,000–12,000 dogs diagnosed with bone cancer per year in the US. Bladder cancer accounts for

Table 1.3. Comparative Aging Chart for Cats and Dogs

Chronologic Age	Human Age Equivalent for Feline	Canine by Weight				
		0–20# 0–9kg	21–50# 10–23kg	51–90# 24–41kg	91–120# 42–54kg	>120# >54kg
		Human Age Equivalent for Canine in Years				
3 months	5	5	5	5	5	>5
6 months	8–10	10	10	10	10	>10
9 months	12	11	11	13	15	>15
1 YEAR	15–24	12–15	14	16	20	>20
2	21–24	19	21–24	23	26	>26
3	25–42	25–28	25–29	24–34	28–39	>39*–40
4	29–32	32	32–34	35–42	43–49	>49*
5	33–48	32–36	36–39	43–49	40–58	>59*
6	37–40	40	40–44	44–49	49–69	>69*
7	41–44	44	47–49	50–55	62–79	>79*
8	45–57	48	50–54	56–63	64–89	>89*
9	49–52	52–53	56–59	61–68	71–99	>99*
10	52–56	56–57	60–64	68–73	79–87	
11	56–60	60–63	65–69	72–76	88–95	
12	61–66	64–67	69–74	77–83	96–102	
13	66–70	68–70	74–79	84–88	103–108	
14	71–74	72–73	78–84	88–94	109–114	
15	75–80	76	83–89	94–99	115–122	
16	80–84	80	87–94	99–104	123+	
17	85–89	84	92	104–108		
18	90–94	88	96	109–114		
19	95–98	92	101	115–120		
20	99–102	96	105	120–123		
21	102–105	99	109			
22	105–108	102	113			
23	?	104	117		**GERIATRIC**	
24	?	107				
25	?	109				
26	?	112				
27	–					

Source: This table is a compilation of several comparative aging charts by William Fortney, DVM, Director of Community Care at Kansas State University School of Medicine; Ron Kurtus, School for Champions, 2005; Fred Metzger, DVM, ABVP, State College, PA, for Senior Care Vet. Ec. Supplement, 1998; Alice Mills, DVM; and Feline Medicine, DVM, Best Practices, 2002. The table was adapted by Villalobos to reflect patient population 12-17-16.

Note: Physiological differences exist between cats and dogs when using their chronologic age. In dogs, the breed, size, and weight create further differences between chronologic and physiologic aging. This table is a compilation of aging tables showing comparable aging for cats as well as for small, medium, large, and giant dogs per standard weight. Overweight and obese dogs have a greater comparable age and shorter life span than normal-weight dogs.

*Information from William Fortney.

2% of all canine tumors and can affect up to 20,000 pets each year, with Scottish Terriers being at 19 times greater risk (www.nap.edu21830). It can be estimated that as many as 2.5 million dogs may die from hemangiosarcoma overall (Lamerato-Koziki et al. 2005). Pet cats in the US increased from 77.6 million to 90 million. The estimated prevalence of cancer-related death in the geriatric cat population is approximately 32%. It is plain to see that there is an increasing demand for expertise in canine

and feline geriatric oncology and compassionate end of life care is upon our profession. This trend is worldwide.

Preventable Tumors in Geriatric Pets

As companion animals age, they develop many of the same types of tumors that are found in humans. Since pets do not smoke cigarettes, they do not often get lung cancer. There is epidemiologic research from Tufts University and Amherst College, however, showing that cats exposed to carcinogenic cigarette smoke are at greater risk of developing certain cancers. Their surveys found that smoking for 3–5 years in the presence of cats increases their risk for oral and lingual SCC and for GI lymphoma by three to five times. Cats consume coat-associated carcinogens in the form of smoke particles that settle on their fur. It has been shown that smoking stimulates COX-2 in mucus membranes as a mechanism of carcinogenesis. A few reports claim that dogs living in cities where air pollution is heavy may be at a higher risk for tonsillar SCC.

The most preventable cancers in dogs are mammary, ovarian and uterine, testicular, and perianal. Female dogs spayed before the first heat period are protected from reproductive organ cancer for life. Male dogs neutered under 4 years of age are spared testicular and perianal tumors (some of which are malignant).

Another preventable cancer that afflicts the skin of dogs and cats is solar-induced skin cancer. Any unpigmented skin that is exposed to an excess of sun undergoes "field cancerization." The entire field of exposed skin is more prone to develop actinic SCC or cutaneous hemangiosarcoma. Application of daily sunscreen, keeping pets in the shade, or keeping them indoors during the heat of the day will deter skin cancer. Lesions appear as pets age due to the cumulative genetic damage from solar exposure and field cancerization.

The future may bring us tumor prevention vaccines for common malignancies in companion dogs and cats. If these vaccines can reduce the incidence of hemangiosarcoma from one in five Golden Retrievers down to one in sixty or reduce the incidence of lymphoma from one in eight to one in eighty Golden Retrievers, that would demonstrate excellent prevention efficacy (Modiano, World Veterinary Cancer Congress, Brazil, 2016).

Summary

Understanding theoretical cancer biology, genomics, immuno–oncology, and senescence is essential for the contemporary veterinarian who treats geriatric cancer patients. The increasing association of cancer with senescence places our aging pet population at greater risk for the many manifestations of neoplasia. How cancer, and its treatment, impacts and affects the geriatric oncology patient is paramount when offering options. Managing cancer in the oldest portion of our diverse pet population is only anecdotal at this time. Because pets are living longer and the human–animal bond, as a celebrated relationship, has created extremely devoted pet caregivers, there is an increasing demand and need for more information and expertise in veterinary geriatric oncology. Caring for geriatric oncology patients is an arena where academic know-how must be blended with good clinical judgment, compassion, and honor for the human–animal bond.

Soon new applications against cancer will involve improved diagnostics, combinatorial therapeutics along with the early and routine use of immunoprophylaxis, chemoprophylaxis, and gene therapy.

The genetic codes for dogs and cats are available for imaginative and hypothetical research. It may soon be possible to correct breed-related predispositions to certain cancers. Perhaps some day we will be able to perform genetic adjustments for pets at risk for cancer. Perhaps, through gene therapy, we will be able to prevent mast cell cancer for Boxers, Bulldogs, and related breeds and reduce the cancer risk for lymphoma and sarcomas in cats and Golden Retrievers. Perhaps we can reprogram large and giant dog breeds to sidestep osteosarcoma and hemangiosarcoma. Frankly, I look forward to the day when the eradication of animal cancer will put my Animal Oncology Consultation Service and Pawspice practices out of business!

> Medical genetics is rapidly developing. I suspect someone looking at the new edition of Ettinger and Feldman a hundred years from now will laugh at what we all had to say. We must remain alert to growth and changing paradigms in medicine.
>
> *Stephen Ettinger, DVM, ACVIM*

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https://www.mycancergenome.org/ This is an excellent information source for cancer molecular genomics.
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