

Nutrition and Cancer: Frontiers for Cure!

Gregory K. Ogilvie, DVM

Diplomate ACVIM (Specialties of Internal Medicine and Oncology), Professor of Oncology and Internal Medicine
Animal Cancer Center, Medical Oncology Research Laboratory, College of Veterinary Medicine and Biomedical
Sciences, Colorado State University

See your veterinarian for specific recommendations about the nutritional care of your pet with cancer or any other disease. If you have any questions about this material, contact your veterinarian.

Cancer is one of the most common diseases in dogs and cats in the United States, Western Europe and Japan. Cancer cachexia is the most common paraneoplastic syndrome in veterinary medicine. This paraneoplastic syndrome of dogs and cats with a wide variety of malignancies results in profound alterations in carbohydrate, protein and lipid metabolism that subsequently results in anorexia, fatigue, impaired immune function, poor performance and weight loss in the face of adequate nutritional intake.¹ These profound alterations in carbohydrate, protein and lipid metabolism have been documented in dogs and probably in cats with cancer, even before evidence of cancer cachexia was clinically apparent.¹⁻¹¹

The importance of cancer cachexia is underscored by the knowledge that animals and people with cancer cachexia have a decreased quality of life, poor response to treatment, and a shortened survival time when compared to those with neoplastic diseases but do not exhibit clinical or biochemical signs associated with this condition.¹⁻⁸ Therefore, it is obvious that cancer and cancer cachexia are of tremendous importance to the practicing veterinarian.

Nutritional therapy is a key component for the treatment of cancer cachexia and for actually helping control malignant disease in some situations. Specific nutrients can be used as powerful tools to reduce toxicity associated with chemotherapy, radiation therapy, and is important to enhance healing subsequent to surgery. There is little question that nutritional intervention must begin early and must be followed through aggressively to gain maximum benefit....long before the patient exhibits evidence of weight loss, debilitation, or anorexia begin which can in turn enhance response to therapy and improve quality of life.

The purpose of this article is to answer the following questions:

1. What clinically significant alterations in metabolism occur in animals with cancer cachexia?
2. How can knowledge about the metabolic alterations in metabolism change the way you use nutrition to treat your cancer. In other words: what nutrients should you feed your cancer patient?
3. Does surgery, chemotherapy or cancer increase or decrease the energy needs and the amount you should feed your patient?
4. Are there any data on the efficacy of the nutrients my clients constantly ask me about: vitamins, minerals, proteases, garlic, tea and shark cartilage?
5. What are the indications for intervening aggressively with appetite stimulants, tube feeding or total parenteral feeding for your cancer patients?
6. When and how do I place these feeding tubes in my practice?

Metabolic Changes Associated with Cancer Cachexia

Clinically, in many patients there are three phases associated with cancer cachexia.⁵ The first phase is the preclinical "silent" phase is where the patient is not exhibiting any clinical signs of disease, yet there is evidence of biochemical changes such as hyperlactatemia, hyperinsulinemia and alterations in amino acid and lipid profiles. All of these alterations are of impending clinical importance, but the alterations in carbohydrate metabolism appear to be quite profound resulting in the production of tremendous amounts of lactate through energy inefficient anaerobic metabolism. The second phase is the clinical phase where the patient begins to exhibit weight loss, anorexia, lethargy and early evidence of weight loss. These patients are more likely to exhibit side effects associated with chemotherapy, radiation therapy, immune modulation, and surgery. The third and final phase of cancer cachexia is an accentuated form of the second phase; it is associated with marked debilitation, weakness and biochemical evidence of negative nitrogen balance that is also associated with clinical pathologic changes such as hypoalbuminemia. Cancer patients begin to lose carbohydrate and protein stores within the body. Loss of fat depots is noted in this third and final stage of the disease. These patients literally waste away due to the physical effects of the malignancy and the resulting cancer-induced alterations in metabolism.

Carbohydrates, Proteins and Fats and Feeding the Cancer Patient

Carbohydrate Metabolism

Perhaps the most dramatic alterations in metabolism of animals with a wide variety of cancers occur in carbohydrate metabolism. For example, when dogs with a wide variety of malignancies without clinical evidence of cachexia were evaluated with an intravenous glucose tolerance test, lactate and insulin concentrations were significantly higher when compared to controls.¹⁹ The hyperlactatemia and hyperinsulinemia did not improve when these dogs were rendered free of all clinical evidence of cancer with either chemotherapy or surgery.¹⁵ Metabolic alterations result in part because tumors preferentially metabolize glucose for energy by anaerobic glycolysis forming lactate as an end product.^{2,16} The animal must then expend necessary energy via "futile cycling" to convert lactate to glucose by the Cori cycle resulting in a net energy gain by the tumor and a net energy loss by the host.^{14,16-19}

The inability of some tumor bearing animals to tolerate glucose parenterally may have some bearing on the dietary management of the cancer patient. Logically, it can be concluded that diets high in simple carbohydrates may increase the total amount of lactate produced and the need for the host to utilize energy unwisely for conversion of lactate. This may have long-term detrimental effects on animals with cancer.

To test this hypothesis in the dog, a group of dogs with lymphoma were evaluated to determine if a diet high in simple carbohydrates is detrimental compared to a diet low in simple carbohydrates.²⁰ In this study, dogs were randomized and fed isocaloric amounts of either a high fat diet, or a high carbohydrate diet before and after remission was attained with up to 5 dosages of doxorubicin chemotherapy. As hypothesized, the mean lactate and insulin levels from the dogs fed the high carbohydrate diet was significantly higher than the level from the dogs fed the fat diet after the dogs were fed the diets and put into remission with chemotherapy. Interestingly, dogs fed the high fat diet were more likely to go into remission. This study showed, therefore, that diet was effective for influencing response to therapy and select aspects of carbohydrate metabolism.

The bottom line is that simple carbohydrates may not be ideal for the cancer patient. Therefore, when considering a diet for a pet with cancer, a diet that has minimal amounts of simple carbohydrates may be ideal.

Protein Metabolism

Cancer has been shown to result in decreased body muscle mass, skeletal protein synthesis, and alter nitrogen balance while concurrently increasing skeletal protein breakdown, liver protein synthesis, and whole body protein synthesis. 16-18 Tumors preferentially use protein for energy at the expense of the host. 16-18,21-25 Tumors preferentially utilize certain amino acids for gluconeogenesis, which results in abnormal amino acid profiles. These abnormal profiles have been documented in pet animals with a wide variety of cancers. The use of amino acids by the tumor for energy becomes clinically significant for the host when protein degradation and loss exceed synthesis. This can result in alterations in many important bodily functions such as immune response, gastrointestinal function and surgical healing.^{22,23}

Knowledge that cancer preferentially utilizes amino acids and that some amino acids may be therapeutic may be of value when designing a diet for the cancer patient. Providing high quality amino acids or protein in the diet may be of critical importance for the veterinary cancer patient. A quality protein diet that is highly bioavailable may be ideal. Arginine, glycine, cystine and glutamine may be of specific value for therapeutic purposes.²⁶⁻²⁹ Arginine may stimulate lymphocyte blastogenesis. The addition of arginine to total parenteral nutrition solutions has been shown to decrease tumor growth and metastatic rate in some rodent systems.^{26,27} Some amino acids may decrease toxicity associated with chemotherapy. For example, glycine has been shown to reduce cisplatin-induced nephrotoxicity.. Cystine has been shown to be effective for reducing Heinz body anemia in cats. Glutamine has been shown to be effective for reducing histologic and clinical evidence of methotrexate-induced gastrointestinal toxicity in cats.

The bottom line is that a diet that has moderate amounts of highly bioavailable protein may be of value to the cancer patient. Certain amino acids such as glutamine, cystine, and arginine may also be beneficial for some cancer patients.^{32,33}

Lipid Metabolism

Fat loss accounts for the majority of weight loss occurring in cancer cachexia. Therefore, it is not surprising that human beings and animals with cancer have dramatic abnormalities in lipid metabolism.³³⁻³⁷ The decreased lipogenesis and increased lipolysis observed in humans and rodents with cancer cachexia result in increased levels of free fatty acids, very low density lipoproteins, triglycerides, plasma lipoproteins, and hormone dependent lipoprotein lipase activity, while levels of endothelial derived lipoprotein lipase decrease.³⁴ Recently lipid profiles in dogs with a lymphoma were studied.³⁵ It was determined that many of the alterations seen in other species with cancer were also present in dogs. These abnormalities did not normalize when clinical remission is obtained. The clinical significance of these abnormal lipid profiles in dogs with lymphoma is not known, however, abnormalities in lipid metabolism have been linked to a number of clinical problems including immunosuppression which correlates with decreased survival in affected humans.^{16,32,34}

The clinical impact of the abnormalities in lipid metabolism may be lessened with dietary therapy. In contrast to carbohydrates and proteins, some tumor cells have difficulty utilizing lipid as a fuel source while host tissues continue to oxidize lipids for energy.³⁶ This has led to the hypothesis that diets relatively high in fat may be of benefit to the

animal with cancer when compared to a diet high in simple carbohydrates. Further research may reveal that the type of fat, rather than the amount, may be of greater importance. In one study, mean nitrogen intake, nitrogen balance, in vitro lymphocyte mitogenesis, time for wound healing, the prevalence of wound complications, and the duration of hospitalization was significantly better in 85 surgical patients fed an omega-3 fatty acid supplement when compared to controls.^{37,38} Studies of polyunsaturated fatty acids (PUFA's) of the n-3 series, especially eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), indicate that these fatty acids may prevent the development of carcinogen-induced tumors, the growth of solid tumors, as well as the occurrence of cachexia and metastatic disease in experimental tumor models. Fatty acids of the n-3 series have been shown to normalize elevated blood lactic acid and insulin levels in non-malignant conditions. In contrast, PUFA's of the n-6 series appear to enhance tumor development and metastases. These data, along with the epidemiological findings of an inverse relationship between dietary n-3 fatty acid intake and incidence of some cancer, is the basis of research to evaluate the potential benefit of n-3 fatty acids in the prevention of cancer cachexia and therapy of malignancy in cancer patients.

One such study was recently completed in dogs with lymphoma.³⁷ A double blind, randomized study was recently reported to evaluate the hypothesis that polyunsaturated n-3 fatty acids and arginine can improve metabolic parameters, decrease chemical indices of inflammation, enhance quality of life, and extend disease-free interval and survival time in dogs treated for lymphoma. In that study, dogs fed the experimental diet had significantly higher serum levels of polyunsaturated n-3 fatty acids docosahexaenoic acid (C22:6) and eicosapentaenoic acid (C20:5) as well as arginine when compared to controls. Both diets were formulated to be relatively low in simple carbohydrates, with moderate amounts of highly bioavailable proteins. This formulation is designed to enhance the effect of n-3 fatty acids. Higher serum levels of these n-3 fatty acids were associated with lesser plasma lactic acid responses to intravenous glucose and diet tolerance testing. Increasing C22:6 levels was significantly associated with longer disease free interval and survival time for dogs with stage III lymphoma fed the experimental diet.

Another study was recently completed that was designed to determine the effect of a diet supplemented with n-3 fatty acids and arginine on irradiated skin and oral mucosa, carbohydrate metabolism and quality of life in a group of dogs with nasal tumors.⁴⁰ This study showed that fatty acids of the n-3 series normalize elevated blood lactic acid. In a dose dependent manner, n-3 fatty acids result in decreased histologic evidence of radiation damage to skin and mucosa and improve performance scores in dogs with malignant nasal tumors. This would obviously be of great benefit to the cancer patient receiving radiation therapy. These two studies confirm that diets supplemented with polyunsaturated n-3 fatty acids are of benefit for the cancer patient.

The bottom line is that n-3 fatty acids in moderate amounts appear to benefit the cancer patient. More specifically, a diet relatively high in n-3 fatty acids and relatively low in simple carbohydrates has been shown not only to improve alterations in metabolism associated with cancer, but also improve response to chemotherapy and decrease the adverse effects associated with radiation therapy.

Fiber

Soluble and insoluble fiber are both important to prevent cancer and to enhance bowel function. This can be especially important for the cancer patient that may undergo chemotherapy, radiation therapy and surgery. Fiber is important not only to treat disorders of the gastrointestinal tract, but also to prevent concurrent diseases such as clostridial colitis. Therefore, a diet with adequate amounts of soluble and insoluble fiber may be indicated for many

dogs and cats with cancer.

Carbohydrate, Protein, Fat and Fiber, What Do I Feed My Dog with Cancer?

The data noted above suggest that a diet relatively low in simple carbohydrates, with moderate amounts of highly bioavailable proteins as well as soluble and insoluble fiber, and moderate amounts of polyunsaturated fatty acids of the n-3 series may be of value to the cancer patient. Research is needed to address the issue of optimum quantities of carbohydrates, proteins and fats, especially n-3 fatty acids. In addition, the ideal ratio of n-3 fatty acids to n-6 fatty acids also remains an unknown. The ideal diet is made of much more than carbohydrates, proteins and fats. A brief discussion about some of what is known about vitamins, minerals and other ingredients is listed below.

Vitamins, Minerals, Garlic, Tea, Shark Cartilage and the Cancer Patient

Nutrients such as vitamins, minerals, garlic, diet-generated protease inhibitors, tea and shark cartilage have been suspected as being important for the prevention, control and treatment of malignancies for decades, and in some cases, generations. 41-47 This field of study is poorly documented with controlled studies, but is rapidly evolving into mature science that may improve the quality and quantity of life for human and animal patients with cancer. The news media and lay publications often distort or misinterpret the efficacy of vitamin therapy. While it is naive to believe that a single nutrient or set of nutrients will be effective for the treatment of cancer there is optimism to believe that one or more nutrients can be effective for preventing certain types of malignancies in people and in animals. Most veterinarians are asked by their clients if vitamins, minerals, garlic and other nutrients can be beneficial for their pet with cancer. Because there are very few studies in veterinary medicine, studies involving rodents or human cancer patients will be used as models for veterinary disease. While it is not possible to make solid recommendations from these data, it may be adequate to allow the veterinarian to provide some guidance to their clients about these nutrients.

Vitamins

Retinoids, beta carotene and vitamins C, D and E may influence the growth and metastasis of cancer cells via a variety of mechanisms.⁴¹ These vitamins fall into and out of popularity based on the results of select studies and the lay press. The weight of the literature would suggest, however, that many of these vitamins may be of value for some cancer patients. A few of many select examples of the impact of a few vitamins is included below for the interested reader.

Retinoids

Retinoids are not used as a mainstay of cancer therapy, however there is a growing body of knowledge about the anticancer effect of this vitamin in man and animals. In people, 13-cis retinoic acid prevents secondary tumors in patients treated for squamous cell carcinoma of the head and neck^{41,43,46,49,58} and can reverse the effects of cervical human papillomavirus infection.⁵⁴ Retinoic acid when used in the adjuvant treatment of retinoblastoma (a childhood cancer), resulted in translocation of bound receptor vitamin complexes to the nucleus, which results in the regulation of the neuroblastoma gene.^{54,55} Melanoma in mice has been successfully treated with retinoids.⁵⁶

The efficacy of retinoids is not confined to rodents and people. A study was recently completed to evaluate the

synthetic retinoid isotretinoin and etretinate to treat dogs with intracutaneous cornifying epithelioma (ICE), other benign skin neoplasia, and cutaneous lymphoma.⁵⁷ All tumors were diagnosed by histologic examination. Successful treatment with isotretinoin was achieved in dogs with ICE, inverted papillomas, and with epidermal cysts. Successful treatment was achieved with etretinate in dogs with ICE. In addition, remission was achieved in 6 of 14 dogs with cutaneous lymphoma. Adverse effects developed in about 25% of the dogs.

Vitamin C

Vitamin C has been studied continuously over the last several decades as an antioxidant and an agent that can effectively treat conditions such as colds, cardiovascular disease and cancer. There have been some data that vitamin C may be of value for the prevention and treatment of certain types of cancers.^{41,43,46} Water-soluble vitamin C has been widely reported to inhibit nitrosation reactions and prevent chemical induction of cancers of the esophagus and stomach.^{41,42} Processed foods high in nitrates and nitrites, such as bacon and sausage, are often supplemented with vitamin C to reduce the carcinogenic capability of the resultant nitrosamines.

A human tissue culture subline resistant to vincristine that was established from a small cell lung cancer cell line was pretreated with ascorbic acid, resulted in potentiation of the vincristine effects on resistant but not the sensitive cell lines.⁴³ Therefore, ascorbic acid may be one therapeutic alternative for overcoming a drug resistance in some cancer cells.

Vitamin E

Lipid-soluble vitamin E, or alpha tocopherol, can also inhibit nitrosation reactions, but in addition, vitamin E has a broad capacity to inhibit mammary tumor carcinogenesis and colon carcinogenesis in rodents.^{11,58} In addition to its chemopreventative properties, vitamin E may convey potential therapeutic efficacy against certain malignancies.⁵⁹⁻⁶¹ This vitamin does so due to its antiproliferative activity.⁷³⁻⁷⁵ In the study conducted in cooperation between the Comparative Oncology Unit at Colorado State University and the Harvard School of Public Health, Department of Dental Medicine, was done to evaluate the effect of injecting d,l-alpha tocopherol and beta carotene directly into dogs with a variety of oral malignancies. A total of 12 dogs were entered into the study where they received weekly injections of this combination to result in mediation of tumor cell growth. This study resulted in two dogs achieving a complete remission (50% reduction in the original size of the tumor--both soft tissue sarcomas) and minor reduction in tumor size in two other cases. There was no direct evidence of tumor cytolysis in this study. Additional studies have been initiated in humans at Harvard School of Public Health. Additional studies are essential to allow further clarification of the value of these vitamins.

Minerals

Minerals that have been suggested as having chemopreventative or anti-cancer effects and that are of value as nutrients include selenium, copper, zinc, magnesium, calcium, lead, iron, potassium, sodium, arsenic, iodine and germanium. Selenium has been one of the most heavily studied minerals associated with the development of cancer.⁶²⁻⁶⁶ Low serum selenium levels have been seen in human patients with prostate and gastrointestinal cancer.⁷⁶ In rodents, dietary supplementation of selenium has been shown to inhibit colon, mammary gland and stomach carcinogenesis.^{63,64} An additional study is essential to determine whether alteration of selenium levels would be of value for the treatment of veterinary or human cancer patients.

Iron transferrin and ferritin have been linked to cancer risk and cancer cell growth.⁶⁷ Lung cancer, colon, bladder and esophageal cancer in people has been highly correlated with increased serum iron and increased transferrin saturation.⁶⁷ This may be because many tumor cells require iron for growth.

Therapeutic enzymes

Enzymes have therapeutic potential although limited approval in the United States. L-asparaginase is probably the most valuable therapeutic modality for the treatment of lymphoma and leukemia in animals and people.⁸³ Oral enzyme preparations are used for the treatment of chronic pancreatic insufficiency and disaccharidase deficiency. Several enzyme preparations are available in Europe for oral adjuvant treatment of cancer and other diseases. Of those, Wobenzyme and Musal, contain a similar mixture of enzymes. Recent studies report efficacy for the treatment of cancer patients, the mechanism of which is not precisely known. One hypothesis is that these enzymes eliminate pathogenic immune complexes. Therefore, enzymes may indeed be of value for the adjuvant treatment of cancer.

Protease Inhibitors

Garlic in Cancer Prevention and Treatment

There is a great deal of information that suggests that soybean-derived Bowman-Birk inhibitor (BBI) can inhibit or suppress carcinogenesis both in vivo and in vitro.⁶⁸⁻⁷³ Extracts of the Bowman-Birk inhibitor have been shown to inhibit carcinogenesis in several animal model systems, including colon- and liver-induced carcinogenesis in mice, anthracene-induced cheek pouch carcinogenesis in hamsters, and lung tumorigenesis in mice and esophageal carcinogenesis in rats.⁶⁸⁻⁷⁰ Bowman-Birk inhibitor concentration has been shown to inhibit metastasis and weight loss associated with radiation-induced thymic lymphoma in mice.⁷³ Irradiated rodents treated with dietary Bowman-Birk inhibitor concentration have fewer deaths, lower average grade of lymphoma, and larger fat stores than controls. Therefore, this protease inhibitor from soybeans may be an important adjunct to cancer chemotherapy protocols and to prevent secondary cancers.

Epidemiological studies have suggested a correlation between high garlic consumption and reduced risk of cancer development.^{41,43,46,74} Each garlic extract and several garlics and thioalkyl compounds have been shown to inhibit the activation of carcinogens and the bonding of polyarene thiol epoxide to a DNA bases, which caused DNA lesions and initiates chemically-induced carcinogenic process. Garlic and the thioalkyl compounds inhibit carcinogen-induced aberrations in the cell nucleus. In addition, garlic extracts have an anti-promotion effect in animals exposed to carcinogens. Also, garlic exerts direct cytolytic effects against cancer cultured human breast cancer cells and human melanoma cells. Concentrations of garlic used in these studies to arrest cancer cell growth, there is no effect on normal cells. Pretreatment of animals with garlic protects rodents against subsequent induction of tumors by a variety of carcinogens. There are no studies demonstrating the safety and efficacy of garlic for the prevention or treatment of cancer in people or in veterinary medicine.

Tea

While it may be awhile before dogs and cats acquire the taste for tea, there is compelling data that suggests that green and black teas may have anti-cancer properties.⁷⁴⁻⁷⁷ Many clients ask about the potential efficacy of teas or tea extracts for their pet. Green tea extracts contain catechin, and black tea contains fermentation products, theoflavine and theorubigins. These active agents inhibit cancer-promoting agents, protect against oxidative damage, and enhance

antioxidant enzymes. Black tea seems to have soothing properties to reduce the discomfort associated with radiation-induced oral mucositis. The tannic acid and other ingredients act as an astringent and a local anesthetic agent when the oral cavity of affected dogs is lavaged 2 to 3 times a day.

Shark Cartilage

Cartilage has been shown to be antiangiogenic which may be of value for the cancer patient. Some time ago, two studies that were never published in a refereed journal were expounded upon by the lay press. The two studies conducted in Mexico and Cuba were soundly criticized by the medical establishment for lack of histologic confirmation of malignancies and poor quality control. Regardless, at least one well designed study was initiated in the United States to evaluate the efficacy of shark cartilage for the treatment of human malignancies. This study was recently suspended due to the lack of efficacy. This author is not aware of any data published in reviewed or refereed medical literature showing that shark cartilage is effective for treating spontaneously occurring malignancies in an outbred species. Despite this fact, shark cartilage manufacturers have created a multi-million dollar industry and have placed shark numbers at a dangerously low level due to over fishing.

Energy Needs of the Cancer Patient

The standard dogma in most human and veterinary texts is that cancer, trauma, and the process of recovering from surgery induces an increase in the amount of energy substrates burned by the animal.^{1,7,16,17,18} While this is definitely true in some patients, recent research using indirect calorimetry to document the rate fuel is burned in the body has placed these statements in doubt.

In the studies below, data was acquired by indirect calorimetry, a non-invasive method of estimating the amount of food required by the cancer patient. Indirect calorimetry determines the energy expenditure (EE), or the amount of fuel consumed by the cancer patient. This equates to the amount of nutrients needed by that animal.

Does Surgery Increase Energy Expenditure?

Energy expenditure and caloric requirements have been reported to increase in animals with and without cancer that are recovering from surgery. A study was performed to determine if this occurs in dogs.^{78,79} Energy expenditure was in a group of apparently resting, client-owned dogs that had been given general anesthesia for the following surgical procedures: ovariectomy, orchietomy, localized malignant tumor resection, and repair of a major orthopedic problem. Each dog was evaluated before and after surgery and compared to apparently resting normal, client-owned dogs. These data in this study suggest that unlike what has been reported elsewhere, the energy expenditure of dogs that undergo anesthesia and surgery for malignant and non-malignant conditions does not increase from baseline values or when compared to normal client-owned pet dogs. These data may be of value when planning nutritional therapy for dogs recovering from anesthesia and surgery.

Do Dogs with Cancer have Increased Energy Expenditure?

Studies were initiated to determine if animals with cancer have altered energy expenditure and to determine if elimination of cancer with chemotherapy or surgery alters energy expenditure.^{80,81} In the first study⁸⁰, indirect calorimetry was performed on dogs with lymphoma that were randomized into a blind study and fed isocaloric

amounts of either a high fat diet, or a high carbohydrate diet before and after chemotherapy.⁸⁹ Surprisingly, during the initial evaluation period, resting energy expenditure was significantly lower than tumor-free controls. Six weeks after the start of the study, EE was significantly lower in both groups of dogs with lymphoma when compared to the controls and the pretreatment values from the dogs with lymphoma. Dogs fed the diet that is relatively high in fat maintained a more normal energy expenditure than dogs fed a diet relatively high in carbohydrates.

Another study was undertaken to determine energy expenditure of client-owned dogs with nonhematopoietic malignancies in an apparently resting state before and after each tumor was surgically excised.⁸¹ Surgical removal of the tumor did not significantly alter any parameter when all dogs were assessed as a single group, or when these animals were subdivided into the following groups: carcinomas and sarcomas, osteosarcomas and mammary. The values obtained prior to any treatment from the dogs in any group were not significantly different from controls. These data suggest that energy expenditure, and presumably caloric requirements of dogs with non-hematopoietic malignancies, are not different from those obtained from healthy client-owned dogs. Furthermore, these parameters do not change significantly when the tumor is removed surgically and the patient is re-assessed after 4-6 weeks.

Do Critically Ill Dogs have Increased Energy Expenditure?

Determination of energy expenditure of critically ill human patients by indirect calorimetry has become a standard procedure in many hospitals. The energy expenditure of apparently resting dogs critically ill dogs were determined in one hundred and four postoperative and severely traumatized dogs⁸² and compared to a group of 20 clinically normal, apparently resting client owned dogs (controls) and to published normals for normal dogs. The EE of critically ill dogs was not different from the measured values for the controls. The measured EE of the critically ill dogs was significantly lower than the calculated value using the illness/injury/infection energy requirement.

Nutritional Support for the Veterinary Cancer Patient

The ideal method of addressing cancer cachexia is to eliminate the underlying neoplastic condition, however, this is often not possible and efforts to provide nutritional support become important. Specific recommendations for nutritional support of patients with neoplastic disease should be based on estimates of caloric requirements, the patient's current and past nutritional status, and a knowledge of the underlying disease. Enteral feeding should always be considered first: if the gut works, use it! While there are many physiologic and medical reasons why nutritional therapy should begin early, there are also psychological reasons. Clients bring their pets to you because they love them. Most are eager to become part of the health care team to be part of the process of bringing their beloved friend to health while extending love and affection to their pet. This interaction can enhance quality of life for both the patient and the client. Below is a brief review of applied interventional nutrition therapy.

Enteral Nutrition

Enteral dietary therapy has been shown to be a practical, cost-effective, physiologic, and safe modality that may abate or eliminate cancer cachexia, decrease complications from therapy and actually improve response to therapy. Several studies have failed to document the possibility of increasing tumor growth by enhancing the nutritional status of the host.⁸³⁻⁸⁸ The dogma is that mature dogs and cats with a functional gastrointestinal tract that have a history of inadequate nutritional intake for 3-7 days or have lost at least 10% of their body weight over a 1-2 week period of

time are candidates for enteral nutritional therapy. There is no question that this philosophy is short sighted. Nutritional intervention must begin earlier than these guidelines suggest. The key is to prevent problems before they occur.

As a general rule, mature dogs and cats with cancer with functional GI tracts that require nutritional support should have some form of enteral feeding: If the gut works, use it!!! The first step is to enhance appetite. The owner should be given a short term and long range plan for the nutritional support of their pet. This plan allows the veterinary health care team and the owner to have a sequential plan for maintaining nutritional support by first enhancing appetite, second, using tube support in appropriate cases, and third, considering more advanced measures such as total parenteral nutrition for serious problems. The first step, enhancing appetite, begins with the basics: warming the food to just below body temperature; providing a selection of palatable, aromatic foods; and providing comfortable, stress-free surroundings. When these simple procedures fail, such chemical stimulants as benzodiazepine derivatives (e.g., diazepam and oxazepam) and antiserotonin agents (cyproheptadine and pizotifen) can be used. Cyproheptadine (2-4 mg daily or twice daily PO) generally is effective in stimulating appetite in cats, as are megestrol acetate (2.5 mg daily for 4 days, then every 2-3 days thereafter). These drugs can be used concurrently for maximal stimulation of the appetite. Diazepam (0.05-0.5 mg/kg IV) is great for short term therapy in the hospital, but is often not adequate for home therapy. Dogs and cats may have improved appetite when metoclopramide is given orally to decrease nausea associated with chemotherapy or surgery. When all the aforementioned fails, enteral nutritional support via nasogastric, esophagostomy, gastrostomy or jejunostomy tube feeding, designed to deliver nutrients to the GI tract should be considered because it is practical, cost-effective, physiologic, and safe. I-4

Routes of Enteral Feeding

Nasogastric Tubes:

Nasogastric tube feeding is the most common short term feeding method used in private practice today. I-3,5,83,87,88 Nasogastric tube feeding should be considered for short term (< 2 days) use. This form of nutritional therapy is especially valuable for the anorectic postoperative patient. Adequate nutritional support has been shown to decrease the duration of hospitalization, reduce postoperative complications and enhance the healing process. Studies in hospitalized human patients being supplemented with a diet high in n-3 fatty acids, nucleotides and arginine have decreased duration of hospitalization and decreased acquired infections, and an improved immune competence. It is often ideal to place these tubes when the animal is under anesthesia for surgery. The use of small-bore, silastic or polyurethane catheters has minimized complications associated with this delivery system. The procedure is simple to perform.

Nasogastric Tubes Placement: I-3,5,83,87,88

I. Tranquilization is sometimes required during placement of the tube, especially in cats. To decrease any discomfort associated with the initial placement of the catheter, a small amount (0.5-1 ml dog, 0.25 mls for the cat) 2% lidocaine is instilled into the nasal cavity with the nose pointed up. The objective is to reduce any discomfort associated with the administration of the nasal tube. It may be helpful to place a finger on the septum and push the animal's nose back parallel to the long axis of the head, thereby straightening the nasal passageway. This straightening process allows the tube to be passed with ease.

2. The tube is lubricated and passed to the level of the thirteenth rib in dogs and the ninth rib in cats.
3. After the tube has been properly placed, it should be secured. In cats, the tube should be bent dorsally over the bridge of the nose and secured to the frontal region of the head with a permanent adhesive (Superglue®, Loctite Corp, Cleveland, OH). A suture may be used to further secure the tube in place. In dogs, the permanent adhesive should be used to secure the tube to the side of the face that is ipsilateral to the intubated nostril. Care should be taken to prevent any contact with whiskers.
4. An Elizabethan collar should always be used to prevent the patient from removing the tube.

Esophagostomy vs Gastrostomy Tubes.

Recently, esophagostomy tube feeding has gained great popularity because these tubes can be placed easily without special equipment, can be removed at any time, and require no waiting time before feeding begins. 1-3,5,83,87,88 Twenty six to thirty french (Fr) tubes are used in dogs and cats. Esophagostomy tubes can be placed percutaneously with the use of a large curved Carmalt or hemostat, or with an L Device. The L device is a commercially available instrument with a sharp trochar that extends out the end of metal tubing. The sharp trochar is used to bluntly dissect the instrument through surrounding tissues. Complications are rare, but include local cellulitis and occasionally, a dissecting abscess of the cervical tissues. These complications are rare and heal up shortly after the tube is removed and the local reaction treated appropriately.

Gastrostomy tubes are used frequently in veterinary practice for animals that need nutritional support for more than 7 days.1-3,5,83,87,88 Gastrostomy tubes can be placed surgically or with endoscopic guidance or with an L Device. A 5-ml balloon-tipped urethral catheter (e.g., Foley Catheter, Bardex, Murray Hill, NJ) can be placed surgically, as can a mushroom-tipped Pezzer proportionate head urologic catheter (Bard Urological Catheter, Bard Urological Division, Covington, GA). For smaller dogs and cats, an 18- to 24-Fr catheter is used; larger dogs require a 26- to 30-Fr tube. Complications include local or or diffuse peritonitis, bleeding and vomiting.

The majority of medical and surgical faculty at Colorado State University place esophagostomy tubes rather than gastrostomy tubes in all patients that have a functional upper gastrointestinal tract except those that have esophageal motility disorders such as megaesophagus. The esophagostomy tubes are easier to place, maintain and remove than gastrostomy tubes. Most clients are more likely to accept esophagostomy tubes than gastrostomy tubes.

The procedures are as follows:

Esophagostomy Tube Placement:1-3,5

1. The patient is placed under anesthesia and the left lateral cervical skin is clipped and prepared for surgery. The esophagostomy tube is placed in the mid cervical region between the lateral spinous processes dorsally and the jugular vein and carotid artery ventrally.
2. For small to medium sized dogs and all cats, a curved Carmalt or hemostat instrument is placed down the mouth, into the esophagus with the curved portion of the instrument pointing laterally half way between the angle of the jaw and the thoracic inlet. An L device is ideal for larger dogs, however some veterinarians will still use a long curved Carmalt.

3. The Carmalt or L device is then directed laterally so that it "tents" the skin by pushing the tip laterally against the left lateral esophageal wall. A small incision (0.25-0.5 cm) is made over the tip of the Carmalt or L device. The instrument is pushed through the surgically placed hole in the tissue. If a Carmalt is used, the jaws of the Carmalt are opened and the tip of the red rubber feeding tube is grasped with the instrument and pulled partially through the skin out the mouth. The tube is then pushed aborally down the esophagus with the Carmalt to the level of the thirteenth rib in dogs and the ninth rib in cats.

4. If an L device is used, thick (number 2 or 3) suture is passed through the hole in the stylette and the side holes of the feeding tube. The suture is tied tight enough to allow the tip of the tube to abut the end of the device as the stylette is retracted inside the tube. The device and feeding tube are pulled through the skin and partially out the mouth. The tube is then for retroflexion and placement down the esophagus with a 10 gage wire placed into one of the side ports and into the distal tip of the feeding tube. The tube is passed to the level of the thirteenth rib in dogs and the ninth rib in cats and the wire is removed.

5. The esophagostomy tube is then sutured into place and a light wrap is placed over the tube. Note that blenderized commercial diet can begin as soon as the patient can tolerate enteral feeding. The amount of kcals provided is generally 25-50% of daily need and split and administered q 4-8 hours and then increased daily as fast as the patient can tolerate full feeding. Metaclopramide is often added to enhance normal gastrointestinal motility.

Gastrostomy Tube Placement via Surgery: 1-3,5,83,87,88

1. Prior to placement of the tube, the patient is anesthetized and the left paracostal area just below the paravertebral epaxial musculature is clipped and prepared for surgery. A 2- to 3-cm incision is made just caudal to the last rib through the skin and subcutaneous tissue to allow blunt dissection through the musculature into the abdominal cavity.

2. The stomach is inflated through a tube that is placed down the esophagus to allow the surgeon to easily locate the stomach through the opening in the abdominal wall. Stay sutures are placed to allow a temporary fixation of the stomach against the abdominal wall; these stay sutures are used later to help close the muscular wall.

3. Two concentric pursestring sutures of 2-0 nonabsorbable nylon suture are then placed deep in the stomach wall; the first pursestring is deep to the second to allow a two-layered closure.

4. The feeding tube is placed into the lumen of the stomach through a stab incision in the middle of the pursestring sutures. The tip of the catheter generally is clipped off to allow easy introduction of food through the tube and into the stomach.

5. Once the tube is in place, the balloon is inflated with water if the balloon-tipped catheter is used; the Pezzer-tipped catheter has an expanded head that flattens and then returns to its normal shape when a stylet is extended and then removed in the catheter lumen during placement through the stab incision into the stomach.

6. With the tube in place, the pursestrings are tied to cause the stomach to invert in the region adjacent to the tube.

The free ends of the pursestrings are then used to close the lateral abdominal musculature and subcutaneous tissue.

7. The skin is closed before the tube is secured to the abdominal skin by sutures. To prevent the animal from removing the tube, an abdominal wrap and an Elizabethan collar are recommended.

Feeding can begin soon after the animal has recovered from anesthesia. The tube should be checked daily to ensure proper placement. In addition, the tube should be flushed with warm water after each feeding to maintain patency. After 7 to 10 days, an adhesion will form, allowing the tube to be removed or replaced as needed. The fistula generally heals within a week after the tube is removed permanently.

Gastrostomy Tube Placement via Endoscopy: 1-3,5,83,87,88

The percutaneous placement of a gastrostomy tube by endoscopic guidance is quick, safe, and effective.¹⁻⁴ In this procedure, a specialized 20-Fr tube (e.g., Dubhoff PEG, Biosearch, Summerville, NJ; Bard Urological Catheter, Bard Urological Division, Covington, GA) is used in both dogs and cats.

1. The first step is to clip and surgically prepare the area of skin outlined previously, and then distend the stomach with air from an endoscope that is placed into the stomach.

2. Once the stomach is distended to the point that it is in apposition with the body wall, a finger is used to depress an area just caudal to the last left rib below the transverse processes of the lumbar vertebrae. This area of depression is then located by the person viewing the stomach lining by endoscopy.

3. A polyvinylchloride (PVC) over-the-needle IV catheter is placed through the skin and into the stomach in the area previously located by the endoscopist. The stylet is removed to allow the introduction of the first portion of a 5-foot-long piece of 8-lb test weight nylon filament or suture.

4. The piece of nylon is grabbed by a biopsy snare passed through the endoscope. The endoscope and the attached nylon are pulled up the esophagus and out the oral cavity so that the piece of nylon extends through the body wall and out of the mouth of the animal.

5. The end of the gastrostomy tube opposite the mushroom tip is trimmed so that it has a pointed end that will fit inside another PVC catheter, after the stylet is removed and discarded. This second PVC IV catheter is then placed over the nylon suture so that the narrow end points toward the stomach. The free end of the nylon that has just been pulled out of the animal's mouth is sutured to the end of the tube and is tied securely.

6. The catheter-tube combination is pulled firmly but slowly from the end of the suture located outside the abdominal wall until the pointed end of the IV catheter comes down the esophagus and out the abdominal wall.

7. The tube is grasped and pulled until the mushroom tip is adjacent to the stomach wall, as viewed by endoscopy.

8. To prevent slippage, the middle of a 3- to 4-inch piece of tubing is pierced completely through both sides and passed over the feeding tube so that it is adjacent to the body wall. This bumper or retainer is then glued or sutured

securely in place. The tube is capped and bandaged in place.

An Elizabethan collar is almost always required to prevent the animal from removing the tube. To remove the tube once it has been in place for 7 to 10 days, the tube just below the bumper is severed to allow the "mushroom" tip to fall into the stomach. This piece may need to be removed by endoscopy in all but very large dogs.

Needle Catheter Jejunostomy Tube Placement via Surgery: 1-3,5,83,87,88

Needle catheter jejunostomy tubes should be considered for dogs and cats with functional lower intestinal tracts that will not tolerate nasogastric or gastrostomy tube feeding.¹⁻⁴ This method is especially valuable in cancer patients that have had surgery to the upper GI tract. Each and every time a cancer patient is scheduled for an abdominal surgery, a jejunostomy catheter should be considered. It is easier to remove a catheter than it is to place it later when the patient is debilitated. The procedure is as follows :

1. The distal duodenum or proximal jejunum is located and isolated by surgery. A pursestring suture of 3-0 nonabsorbable suture is placed in the antimesenteric boarder of the isolated piece of bowel.
2. A 12-ga needle is placed from the serosa located at the center of the area encircled by the pursestring suture, subserosally 2 to 3 cm through the wall of the intestine, into the lumen of the loop of bowel. Alternatively, a stab incision can be made into the same location of the bowel using a number 11 surgical blade.
3. A 5-Fr nasogastric infant feeding tube is passed through the hypodermic needle or the stab incision to an area down the bowel, 20 to 30 cm from the enterostomy site.
4. If a needle was used, it is then removed.
5. The pursestring is tightened and secured around the tube.
6. The free end of the feeding tube is passed from the serosal surface of the abdominal wall out of the skin through a second hypodermic needle.
7. The loop of bowel with the enterostomy site is secured to the abdominal wall with four sutures that are later cut after the tube is removed in 7 to 10 days, when feeding is complete.
8. As with gastrostomy tubes, complications with this method include peritonitis, diarrhea, and cramping.

Tube Jejunostomy

Weighted jejunostomy tubes are of value because they do not require surgical placement and do not require any special equipment other than the catheter itself. The tubes are ideal for larger cats and medium sized dogs. The concept is quite simple: pass the weighted tube down the nose, into the esophagus and into the stomach. Gravity and normal gastrointestinal function will allow the tube to pass down into the jejunum.

1. Tranquilization is sometimes required during placement of the weighted tubes. To decrease any discomfort

associated with the initial placement of the catheter, a small amount (0.5-1 ml dog, 0.25 mls for the cat) 2% lidocaine is instilled into the nasal cavity with the nose pointed up. The objective is to reduce any discomfort associated with the administration of the weighted tube. It may be helpful to place a finger on the septum and push the animal's nose back parallel to the long axis of the head, thereby straightening the nasal passageway. This straightening process allows the tube to be completely passed with ease into the stomach with enough catheter length to gravity feed to the jejunum..

2. After the tube has been properly placed, it should be secured. In cats, the tube should be bent dorsally over the bridge of the nose and secured to the frontal region of the head with a permanent adhesive (Superglue®, Loctite Corp, Cleveland, OH). A suture may be used to further secure the tube in place. In dogs, the permanent adhesive should be used to secure the tube to the side of the face that is ipsilateral to the intubated nostril. Care should be taken to prevent any contact with whiskers.

3. An Elizabethan collar should always be used to prevent the patient from removing the tube.

Enteral Feeding Methods

The type of nutrients to be used depends largely on the enteral tube that is used and on the status of the patient. 1-3,5,83,87,88 The big question is: what should you feed the cancer patient? The easy answer is, whatever the pet will eat, however, specific therapy is preferred. Blended canned pet foods may be adequate for feeding by esophagostomy and gastrostomy tubes. Whenever possible, consider diets that are relatively low in simple carbohydrates, easily digestible, and that have appropriate soluble and insoluble sources of fiber. The later can be accomplished by adding psyllium to a canned maintenance pet food diet or by using a weight maintaining diet such as Hills Prescription Diet W/D. Because the later has restricted calories, an increased volume of feeding may be needed. Human enteral feeding products are easily administered through nasogastric and jejunostomy tubes (eg: Impact, Osmolite HN, Jevity), however, veterinary enteral products are now available that are specifically tailored for the nutritional needs of animals, especially cats (eg: Clinicare). In any case, feeding usually is not started until 24 hours after the tube is placed except for pets with an esophagostomy tube. Once feeding is started, the amount of nutrients is gradually increased over several days and is administered frequently in small amounts, which allows the animal to adapt to this method of feeding. Continuous feeding may reduce the risk of vomiting caused by overloading the GI tract. Regardless, the tube should be aspirated 3 to 4 times a day to ensure there is not excessive residual volume in the GI tract. The tube should be flushed periodically with warm water to prevent clogging.

Calculating Contents and Volumes

Calculation of the nutritional requirements for enteral feeding is essentially the same as for parenteral feeding noted earlier.1-4. It should be kept in mind that some patients have a very high energy expenditure that may exceed those seen in animals that have infections, sepsis, or burns. Other research suggest that the energy needs of most cancer patients do not exceed that of a healthy animal. Work done by indirect calorimetry suggests that the formula: daily kcals required= $1.1 [30(\text{wt in kg}) + 70]$ may be a reasonable place to start as a target for most cancer patients. Dogs and cats with renal or hepatic insufficiency should not be given high protein loads (< 3 g/100 Kcal in dogs; <4 g/100 Kcal in cats). Because most high-quality pet foods can be put through a blender to form a gruel that can be passed through a large feeding tube, the kcal needs of the animal is divided by the caloric density of the canned pet food to determine the amount of food to feed. The same calculation can be done with human enteral feeding products; the

volume fed may need to be increased if the enteral feeding product is diluted to ensure it is approximately iso-osmolar before administration.

Total Parenteral Nutrition (TPN)

Indications for TPN include those previously discussed for enteral nutrition in conjunction with an inability of the gastrointestinal tract to retain, digest and/or absorb adequate quantities to meet the animals nutritional needs. The benefit of long term TPN in cancer patients is questionable at best. While the theoretical gains of TPN are similar to those espoused for enteral support, few have been realized to date in the scientific literature. The authors recommend TPN in cancer patients when enteral feeding is not possible and when the facility and personnel are experienced in this methodology. In addition, TPN is indicated for those who have a high probability of recovering from their diseases. This includes post-operative gastrointestinal surgery patients, those with chemotherapy induced anorexia, and patients with tumors where remission or cure is likely.

Conclusions

1. What clinically significant alterations in metabolism occur in animals with cancer cachexia?

Dogs and cats with cancer have significant alterations in carbohydrate, lipid and protein metabolism that can result in cancer cachexia. These alterations in metabolism have the potential to decrease quality of life, reduce response to therapy and shorten survival times.

2. How can knowledge about the metabolic alterations in metabolism change the way you use nutrition to treat your cancer patients?

While the ideal anticancer diet is not known, research to date would suggest that any nutritional support is better than none. Normal feeding practices should begin early before evidence of cachexia are noted, and plans should be designed to support the patient when voluntary feeding is not optimum. In addition, the following guidelines may be considered early for each patient:

* Arm clients with appropriate information, dietary plans and appetite stimulants such as cyproheptadine and megestrol acetate from the very beginning. The goal is to prevent anorexia and weight loss from ever happening.

* Consider foods that are highly bioavailable, easily digested, and highly palatable with a good smell and taste

* Consider foods that are relatively low in simple carbohydrates, moderate amounts of good quality sources of proteins and soluble and insoluble fiber, and moderate amounts of fats; fats of the n-3 fatty acid series may be effective in reducing or eliminating some of the metabolic alterations associated with cancer cachexia. Antioxidants are essential whenever n-3 fatty acids are used. The only commercially available diet that meets this profile is Hill's Prescription Diet nd.

* Enhanced quantities of arginine, cystine and glutamine may be of value in maintaining a more normal immune, hematologic and gastrointestinal tract.

* Fiber, both soluble and insoluble, is essential to maintain normal bowel health. A diet with adequate amounts of fiber is essential to prevent or to treat various problems of the gastrointestinal tract.

3. Does surgery, chemotherapy or cancer increase or decrease the energy needs and the amount you should feed your patient?

Each patient should be assessed as an individual and the nutritional profile, including the amount to be fed should be prescribed for each animal on a daily basis based on reassessments. As a general rule, with the exception of septic animals, dogs and cats with cancer, critical care illnesses, or that are recovering from surgery do not have energy needs that exceed those of normal animals. A formula that approximates the need for many animals with cancer in a resting state is as follows: $1.1[30(\text{wt in kg}) + 70] = \text{kcal}$ s required per day.

4. Are there any data on the efficacy of the nutrients my clients constantly ask me about: vitamins, minerals, proteases, enzymes, garlic, tea and shark cartilage? What nutrients should you feed your cancer patient?

Data exist demonstrating that many antioxidants, minerals, proteases, garlic, enzymes, and tea all have some potential for reducing the risk of cancer, or the growth and metastases of established malignant diseases. Research must be done to establish ideal dosages, and optimum applications of these nutrients. The lay press and word of mouth can bypass the presence of any research data demonstrating efficacy as it has for shark cartilage. To date, little if any data exist demonstrating that shark cartilage is effective for treating spontaneously occurring cancer in an outbred species. Despite this lack of proof, the public does believe that shark cartilage does have some efficacy.

5. What are the indications for intervening aggressively with appetite stimulants, tube feeding or total parenteral feeding for your cancer patients?

For maximum benefit, intervention should begin early in the course of the disease. The owner must have a clear plan for dietary intervention beginning first with the choice of nutrients, followed by appetite stimulants, and then on to feeding tubes for those patients that cannot or will not support themselves.

6. When and how do I place these feeding tubes in my practice?

Think ahead! Place feeding tubes early at the time of initial therapy in high risk cancer patients. It is better to place feeding tubes early and to remove them without use than to not provide nutritional therapy because of the lack of a feeding tube. See details above concerning placement of various tubes. As a general rule, esophagostomy tubes are the "work horse" of all tube feeding methods. Jejunostomy tubes can be used whenever vomiting or complications occur in the upper gastrointestinal tract that would preclude the use of these nasogastric, esophagostomy or gastrostomy tubes.

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