Chapter 30

Cancer

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"Life well spent is long."
Leonardo da Vinci

CLINICAL IMPORTANCE

Cancer is among the most common causes of nonaccidental death of dogs and cats, often ranking first or second (Bonnett et al, 2005; Egenvall et al, 2005; Proschowsky et al, 2003; Moore et al, 2001). One study documented that 23% of 2,000 pets examined at necropsy died of cancer (Bronson, 1982). Additionally, in a more recent study of more than 350,000 insured dogs, cancer was the most common cause of death, accounting for 18% of deaths; cancer occurred more commonly in females than in males for most breeds (Egenvall et al, 2005).

In cats, cancer also commonly threatens life and quality of life. Cats have the largest number of different retroviruses of any companion animal and these are closely linked to feline leukemia virus infection (FeLV). The overall prevalence (number of diagnosed cases/year) of FeLV infection in the United States is between 1 and 3%; however, the prevalence may be as high as 30% in multi-cat households and 11.5% in sick cats (Macy, 1996). In addition, known carcinogens can affect animals as well as people. Recent studies have investigated the link between environmental tobacco smoke and the development of cancers such as lymphoma and squamous cell carcinoma (SCC) in cats, and respiratory tumors in dogs (Snyder et al, 2004; Bertone et al, 2002, 2003; Reif et al, 1998). Additional environmental risk factors for SCC in cats include consumption of canned food and tuna fish, and the use of flea collars. For dogs, the indoor use of kerosene or coal also increased the risk of sinonasal cancer. Furthermore, obesity and insecticide use have been linked to bladder cancer (Bukowksi et al, 1998; Glickman et al, 1989).

Often, cancer results in either rapid weight loss or an inability or unwillingness to eat that is difficult to circumvent. Nutritional options for cats with cancer are less well studied though equally important. Because of their size, cats may necessitate increased frequency of nutritional support. The overall prevalence of cancer in pets appears to be increasing (Macy, 1996) for a variety of reasons, including greater longevity, improved veterinary care and an increased awareness of veterinarians through specialty services and advanced diagnostics.

Cancer incidence continues to increase in the human population as well. Statistics show that approximately 38% of women and 45% of men will develop cancer in their lifetime (Jemal et al, 2007). An estimated 1.3 million people were projected to be newly diagnosed with cancer in 2006, and more than a half million people were projected to die (Jemal et al, 2007). Therefore, it is not unusual to realize that many pet owners have had a personal experience with cancer affecting themselves, family members, friends or acquaintances. Veterinarians and health care teams should approach pets with cancer, and their owners, in a positive, compassionate and knowledgeable manner. Many owners understand or are willing to be educated about the importance of nutrition and how proper feeding can enhance the quality and length of life for

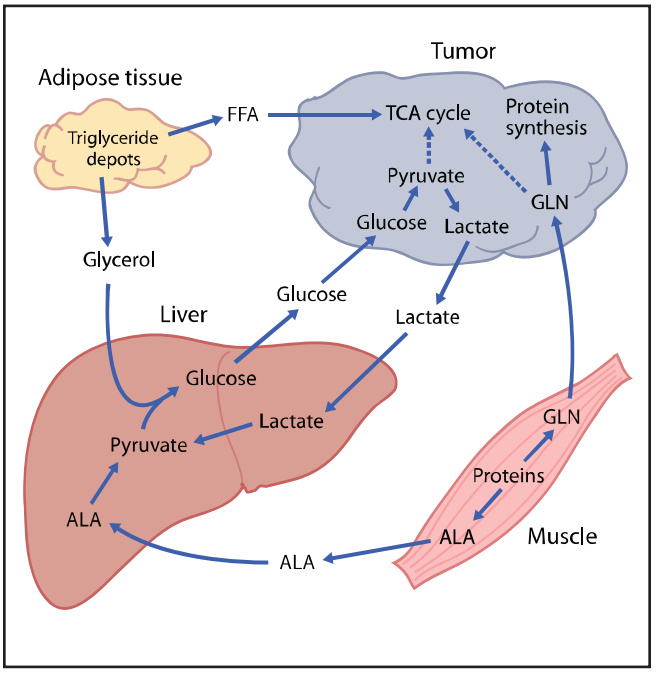

Figure 30-1. Metabolic relationships in cancer lead to increased proteolysis in the host's tissues, especially skeletal muscle. The Cori and glucose-alanine cycles undergo increased activity. High circulating concentrations of alanine (ALA) and glutamine (GLN) result, helping to feed the high glucose demand of the tumor.

pets with cancer.

Nutritional support can reduce or prevent toxicoses associated with cancer therapy and ameliorate the metabolic alterations induced by cancer in dogs and cats. Additionally, there is growing evidence that specific nutrients can be used to treat cancer directly or indirectly. This chapter focuses on the nutritional management of patients with cancer rather than on cancer prevention.

PATIENT ASSESSMENT

History and Physical Examination

The metabolic and clinical alterations in cancer patients have been described in four phases (**Table 30-1**) (Ogilvie and Vail, 1996, 1992, 1990; Ogilvie and Moore, 1995, 1995a; Shein et al, 1976; Theologides, 1979; Buzby and Steinberg, 1981; Landel et al, 1985; Bray and Campfield, 1975; Vail et al, 1990). The first phase is a preclinical "silent" phase in which patients do not exhibit overt clinical signs of disease, but subtle changes in behavior can often be observed. As the underlying malignancy progresses, owners often state that their pet seems to be "slowing down" or aging more rapidly, or is less active and less willing to engage in normal activities. Despite normal clinical appearances, patients in Phase 1 have quantifiable metabolic changes such as hyperlactatemia, hyperinsulinemia and alterations in blood amino acid profiles (**Figure 30-1**).

The second phase is a clinical phase in which patients begin to exhibit anorexia, lethargy and early evidence of weight loss. These patients are likely to exhibit side effects associated with chemotherapy, radiation therapy, immunotherapy and surgery that may alter nutrient intake and use, and thus the nutrition support plan.

The third phase (cancer cachexia) is characterized by marked debilitation, weakness and biochemical evidence of negative nitrogen balance such as hypoalbuminemia. In this phase, cancer patients begin to lose body protein and fat stores. Chronic vomiting, diarrhea, weakness, lethargy and weight loss are reported by owners of dogs and cats with endstage cancer.

A fourth phase (recovery or remission) occurs in those patients undergoing treatment with apparent elimination of their disease. Metabolic alterations persist in some patients despite elimination or control of the cancer via chemotherapy, radiation or surgery. Here again, the therapy itself may cause changes that affect the feeding plan. Animals may develop food aversions at any time because of treatment-induced alterations in taste and smell.

Clinical staging of cancer is performed by assessing tumor size, depth of tumor invasion, presence of tumor in regional lymph nodes and by identifying tumors in distant sites. This information is used to stage tumors by the TNM system: T (tumor size and/or invasion), N (nodal involvement) and M (distant metastasis). Tumor staging may correlate with clinical behavior in certain types of cancer and, in the future, may help determine whether a tumor will respond to nutritional management. To date, body condition scoring and body weight changes are the most practical tools for monitoring the overall nutritional effects of cancer and cancer treatment in dogs and cats (Chapter 1).

Laboratory and Other Clinical Information

Laboratory evaluation of total lymphocyte count, hematocrit, serum glucose, albumin, urea nitrogen concentrations and thyroid hormone levels can be helpful to further evaluate nutritional status. Toxic changes in neutrophils have been seen in cats with cachexia, and were significantly associated with longer hospitalization and higher treatment cost (Segev et al, 2006). Use of these parameters is somewhat limited because they may have causes unrelated to cancer. Albumin also has a relatively long half-life (eight days in normal dogs; the half-life of albumin in cats is unknown, but suspected to be between 5.7 and 8.2 days) and is slow to respond to changes in nutritional status. Plasma levels of triiodothyronine (T_3), reverse T_3, free thyroxine (T_4) and thyroid stimulating hormone (TSH) were severely altered in malnourished patients undergoing surgery for T_1 to T_4 carcinomas of the head and neck, as compared to well-fed cohorts. This study suggests, as starvation and overfeeding modulate thyroid hormone metabolism, thyroid hormone status can potentially be used to evaluate nutritional status of cancer patients (Siroen et al, 2006).

Body weight becomes an insensitive index in patients with severe intestinal malassimilation including marked hypoalbuminemia and ascites due to changes in total body water rather than lean body mass. Apart from this, body weight is a very sensitive long-term (weeks to months) indicator of decline or

recovery of animals. Dogs and cats in the pre-clinical or "silent" phase may appear clinically normal but may gradually lose weight despite a good appetite.

Plasma amino acid profiles and serum lactate concentrations, parameters associated with tumor cell progression in the canine cancer model, have not been used clinically to assess the nutritional status of veterinary cancer patients. Likewise, biomarkers associated with tumor growth and subsequent nutritional support such as serum creatine kinase (Fascetti et al, 1997); mitogen-activated protein kinase (MAPK) (Saker et al, 2002); serum mineral content including zinc, chromium, iron and total iron-binding capacity (Kazmierski et al, 2001) and the vascular endothelial growth factor (VEGF) system, including VEGF and the VEGF receptors, Flt-1and KDR (Millanta et al, 2006) have yet to be instituted clinically. Acute-phase reactant proteins, although not specific for cancer, can be measured in serum and can predict prognosis and response to therapy. The combination of certain acute-phase proteins can be more powerful than one assay (others include C-reactive protein and alpha-fetoprotein). Alpha 1-acid glycoprotein is an acute-phase protein that is increased in cats with cancer, and has been used to predict loss of remission for dogs (but not cats) with lymphoma (Selting et al, 2000; Correa et al, 2001; Hahn et al, 1999).

In certain tumors, grading the degree of malignancy histologically predicts biologic behavior. Although a direct relationship between tumor grade and nutritional status including cancer cachexia has not been established, it is thought that more aggressive cancers tend to cause more pronounced systemic effects on body condition. Conversely, even a benign tumor can significantly affect the nutritional status of a dog or cat if it interferes with intake or assimilation. Oral tumors such as SSC in cats may inhibit food intake, and intestinal tumors such as lymphomas can cause poor nutrient absorption, decreased appetite and diarrhea. Tumor grade may correlate with survival, metastatic rate, disease-free interval or with frequency or speed of local recurrence. Not only can a prognosis be determined based on tumor grade, but more aggressive nutritional therapies may be applied to higher grade tumors. Clearly, no single "gold standard" test exists for determining a cancer patient's nutritional status.

Table 30-1. Phases of clinical and metabolic alterations in cancer patients.

Phase	Clinical changes	Metabolic changes
1	Preclinical, silent phase No obvious clinical signs	Hyperlactatemia Hyperinsulinemia Altered blood amino acid profiles
2	Early clinical signs Anorexia Lethargy Mild weight loss More susceptible to side effects from chemotherapy, etc.	Similar metabolic changes
3	Cachexia Anorexia Lethargy More susceptible to side effects from chemotherapy, etc.	Similar changes but more profound
4	Recovery Remission	Metabolic changes may persist Changes secondary to surgery, chemotherapy or radiation therapy

Risk Factors

Numerous studies have outlined risk factors of certain nutrients and their relationship to development of cancer. For example, decreased fiber and increased fat have been most commonly incriminated as causal factors for the development of a wide variety of malignant conditions of the gastrointestinal (GI) tract, breast and urinary bladder in people.

Existing data are controversial regarding the cause and effect relationship between diet and cancer in pets. One group of investigators conducted a case-controlled study of nutritional factors and canine breast cancer (Sonnenschein et al, 1991). Neither a high-fat diet nor obesity one year before diagnosis increased the risk of breast cancer. However, the risk of breast cancer was significantly reduced among neutered dogs that had been thin at nine to 12 months of age. Among intact dogs, a thin body condition at nine to 12 months of age reduced the risk of breast cancer. Results of this study suggest that nutritional factors resulting in altered body composition early in life may be important in canine breast cancer. A case-control study evaluated the possible relationship between diet and dietary management in 86 healthy control dogs and 102 dogs with mammary gland tumors or mammary gland dysplasia (Perez-Alenza et al, 1998). Body composition, diet and reproductive history were reviewed. Nutritional status was evaluated from serum selenium and retinol values and adipose fatty acid profiles. Obesity at one year of age and an obese body condition score (BCS) one year before diagnosis are significantly related to a higher prevalence of mammary tumors and cell dysplasias in dogs. Additionally, intake of homemade meals vs. commercial foods is significantly related to a higher incidence of tumors and dysplasias; increased intake of red meat (beef, pork) strongly influences disease incidence. Results from this study indicated that obesity at one year of age was independently and significantly associated with risk of developing mammary tumors and dysplasia. A five-year retrospective study evaluated the distribution of BCS values for dogs with and without histologically and behaviorally malignant neoplasms (Weeth et al, 2007). A total of 14,760 dogs (1,777 with cancer; 12,893 controls) met the inclusion criteria. Dogs with cancer were further allocated into the general categories of sarcoma (n = 582), carcinoma (n = 428) or round cell tumor (n = 767) based on histologic classification of tumor cells. Using a 9-point BCS system, 21.6 and 14.8% of dogs were classified as overweight or obese, respectively. Overall, the mean BCS of all dogs with cancer was 5.4 ± 1.2 vs. 5.3 ± 1.2 for noncancer controls. Investigators reported a significantly lower prevalence of overweight and obese dogs with cancer compared to control dogs without cancer. The

study revealed a lower prevalence of overweight and obese dogs with sarcomas and carcinomas, but no difference in distribution of BCS in dogs with round cell tumors compared to controls.

Overweight or obese body condition in dogs may also influence the risk of bladder cancer. Investigators have evaluated the role of diet in preventing bladder cancer in Scottish terriers, a breed predisposed to the development of transitional cell carcinoma of the urinary bladder. This survey-based study evaluated each dog's diet for one year before diagnosis and compared data to that from non-neoplastic counterparts. Results were adjusted for age, sex and weight. There was a statistically significant decreased risk of developing transitional cell carcinoma in dogs fed green leafy and yellow-orange vegetables and for dogs fed vegetables at least three times per week. Although the risk of transitional cell carcinoma was lower in dogs fed cruciferous vegetables, the finding was insignificant. These results suggest diet may play a role in the prevention or management of bladder cancer (Raghavan et al, 2005).

Currently, there is no common thread or single measurable parameter that defines the population at risk for or experiencing cancer. Risk assessment for cachexia and nutritional support for cancer must be tailored to each patient with consideration for breed, age, tumor type and other factors.

Etiopathogenesis

There are three basic steps that ultimately lead to generation of a cancer cell from a normal cell: 1) initiation, 2) promotion and 3) progression (London and Vail, 1996). Initiating agents induce permanent and irreversible changes in the DNA of affected cells. Promoting agents cause reversible tissue and cellular changes up to development of the first autonomous tumor cell. Promoting action generally occurs over a long latency period and requires nearly continuous exposure to the promoting agent. Progressing agents convert initiated cells, or cells undergoing promotion, into cells that exhibit the malignant phenotype capable of developing into a mature neoplasm.

Multi-step carcinogenesis occurs through five basic pathways; more than one pathway may be involved in the generation of a particular tumor (London and Vail, 1996). The five carcinogenic pathways are: 1) heritable, 2) passive, 3) biologic, 4) chemical and 5) physical.

Although little is known about breed-specific genetic alterations that may predispose domestic pets to develop neoplastic disease, certain breeds of dogs have a higher incidence of cancer than others. Recent studies have examined breed-specific predispositions to certain types and subtypes of cancer, such as lymphoma (Modiano et al, 2005). Breeds commonly overrepresented in tumor-bearing cohorts include boxers, rottweilers, German shepherd dogs, Scottish terriers and golden retrievers. Siamese cats appear to be at more risk than other feline breeds. Perhaps the best characterized genetic mutation suspected to cause a specific cancer is found in German shepherd dogs with renal cystadenocarcinoma and nodular dermatofibrosis. The chromosomal region that overlaps the human Birt-Hogg-Dubé (BHD) locus responsible for a phenotypically similar syndrome in people, showed mutation of exon 7 of the canine BHD gene. Genetic analysis and pedigree evaluation support this mutation as causative for this cancer (Lingaas et al, 2003).

Point mutations, chromosomal translocations and gene amplification occur as spontaneous events in any dividing cell population. These changes accumulate over a lifetime, possibly explaining why many cancers arise in mature or aged individuals.

Carcinogens can be found in many different aspects of the environment. The most common biologic agents capable of inducing cancer are retroviruses, DNA tumor viruses and some parasites. Various chemical compounds, some naturally occurring and some synthetic, are capable of inducing malignant neoplasia. In most cases, chemical carcinogens require repeated administration or exposure to demonstrate an effect. Physical carcinogens include ultraviolet radiation, ionizing radiation and foreign materials (London and Vail, 1996).

Cancer Cachexia

Cancer cachexia is a complex paraneoplastic syndrome that adversely alters the functional status of the patient (**Figure 30-2**). It manifests as weight loss, reduced food intake and systemic inflammation as a consequence of the cancer disease process (Fearon et al, 2006). This syndrome differs from simple starvation in that both protein and fat stores are lost almost simultaneously in cachectic patients. Initially in simple starvation, fat stores are lost preferentially followed later by loss of protein stores. The time frame for onset of noticeable cachexia-induced weight loss in dogs and cats with cancer can vary. One survey-based study examined dogs as they were presented to the oncology service (Michel et al, 2004). Body weight before cancer diagnosis was available for 64 of 100 dogs. Twenty-three percent had lost more than 10% of their body weight before diagnosis. Body condition scoring, however, found only 4% of dogs with cachexia and 15% with clinically evident muscle wasting; 29% were markedly overweight (Michel et al, 2004). Although body condition scoring and changes in weight are good clinical measures of body condition, they do not consider the complexity of factors influencing the cachectic state such as the metabolic alterations that can occur even before any overt clinical signs associated with cancer cachexia are identified (Ogilvie and Vail, 1996, 1992; Ogilvie and Moore, 1995).

Cancer cachexia may be partly due to negative energy balance secondary to decreased energy intake or altered energy expenditure (Lawson et al, 1982; Dempsey et al, 1984). Investigators have found alterations in basal metabolic rate and resting energy requirement (RER) that were associated with altered carbohydrate, protein and lipid metabolism in human patients with cancer cachexia (Lawson et al, 1982; Dempsey et al, 1984). Additionally, resting energy expenditure and caloric requirements are increased in some tumor-bearing people and animals when compared to healthy individuals (Dempsey et al, 1986; Hansell et al, 1986; Fredrix et al, 1991; Zyliez et al, 1990; Delarue et al, 1990).

Several studies have evaluated energy expenditure in dogs with lymphoma and non-hematopoietic malignancies. Dogs with osteosarcoma have been compared to normal beagles to evaluate metabolic alterations using indirect calorimetry (rest-

ing energy expenditure and respiratory quotient), stable isotope tracers (protein synthesis and glucose flux) and dual x-ray absorptiometry scans (body composition). Dogs with osteosarcoma were described as being "weight-stable." These dogs had higher resting energy expenditure before and after surgery, decreased rates of protein synthesis, increased urinary nitrogen loss and increased glucose flux postoperatively (Mazzaferro et al, 2001).

Earlier studies evaluated energy expenditure in dogs with carcinomas and sarcomas (Ogilvie et al, 1997; Walters et al, 1993). These studies found no significant differences in energy expenditure (and presumably caloric requirements) in dogs with a wide range of malignancies compared to healthy, client-owned dogs. This finding suggested that, in general, dogs with cancer and no evidence of weight loss do not have energy requirements higher than those of apparently healthy dogs without cancer. Furthermore, these parameters did not change significantly in dogs with cancer when the tumor was removed surgically (Ogilvie et al, 1996).

Because the thyroid gland and its hormones are intimately involved in the control of energy homeostasis (Premachandra et al, 1981; Sestoft, 1980), investigators have speculated that perturbations in thyroid function or thyroid hormone concentrations play a role in altering energy states in tumor-bearing individuals. In one study, researchers compared thyroid hormone concentrations in dogs with cancer (with and without chronic weight loss) with those in nontumor-bearing dogs (with and without chronic weight loss) (Vail et al, 1994). Diminished serum concentrations of T_4, T_3 and free T_3 occurred in proportion to the degree of weight loss, regardless of tumor-bearing status. Apparently, these reductions in hormone concentrations are related to the abnormal nutritional state or severity of illness rather than to a tumor-related phenomenon. This has been termed "euthyroid sick syndrome." Taken together, these studies illustrate that daily energy requirement (DER) in animals with uncomplicated cancer are similar to those of normal animals, and there is a complexity of metabolic alterations that can occur in cancer patients even in the absence of clinically evident cachexia.

The endstage of cancer cachexia is weight loss that is due not only to primary effects of the tumor, such as compression or infiltration of the alimentary tract, but also to: 1) therapy (e.g., chemotherapy-induced anorexia, nausea or vomiting) or 2) alteration of metabolic pathways composing this paraneoplastic syndrome (**Figure 30-2**) (Ogilvie and Vail, 1996, 1992; Ogilvie and Moore, 1995). Many tumor-bearing animals have altered metabolism, which necessitates special methods for delivering nutrients and specific types of fluid and nutrient support (Ogilvie and Vail, 1996, 1992, 1990; Ogilvie and Moore, 1995, 1995a; Shein et al, 1976; Theologides, 1979; Buzby and Steinberg, 1981; Landel et al, 1985; Bray and Campfield, 1975; Vail et al, 1990, 1990a, 1990b; Ogilvie et al, 1992).

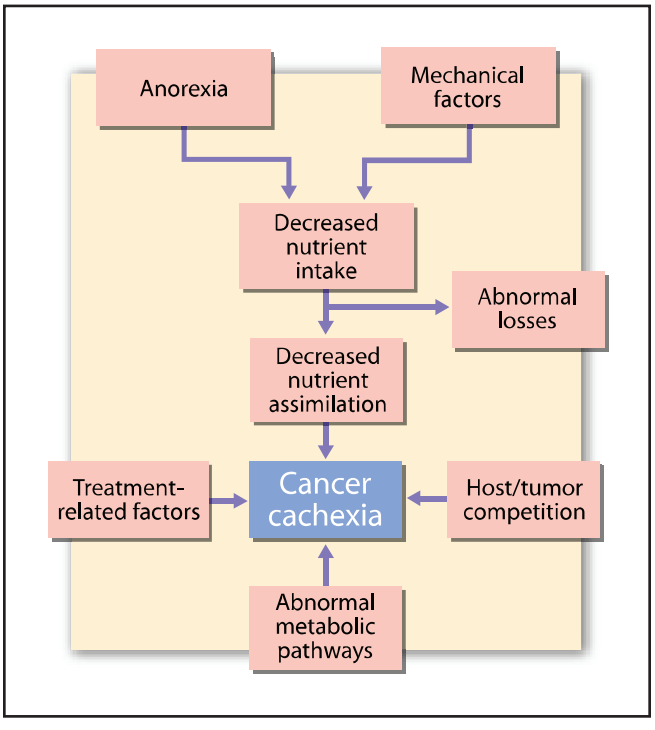

Figure 30-2. Mechanisms of cancer cachexia.

Nutritional Effects from Cancer Treatment

Besides the effects of cancer itself, various modalities used to treat cancer (radiation, chemotherapy and surgery) may adversely affect a patient's nutritional status. The malnutrition that results from treatment assumes even more importance given that many cancer patients are already debilitated from their disease. Anticancer therapy may produce only mild, transient disturbances, such as mucositis, or it may lead to severe, permanent problems, as in small bowel resection or disabilities of mastication and swallowing after head and neck surgery or radiation. Generally, nutritional problems should be anticipated, feeding tubes placed and patients fed earlier to lessen the adverse effects of treatment.

Surgery

Surgery is used in the treatment of cancer in an attempt to remove tumors or alleviate clinical signs (e.g., intestinal or urinary tract obstruction). Nutritional problems that may develop depend on the surgical location and type of procedure performed (**Table 30-2**). Preliminary studies in dogs suggest that metabolic alterations associated with cancer persist even after tumors are removed surgically (Ogilvie et al, 1997). In general, feeding tubes (esophagostomy, gastrostomy, jejunostomy) should be placed at the time of surgery to avoid additional anesthesia and to allow early feeding.

Radical head or neck surgery may lead to significant malnutrition by altering a patient's ability to eat. Although some of these changes are temporary, many patients have permanent difficulty with chewing and/or swallowing with subsequent risk of aspiration. Proactive placement of gastrostomy tubes (Chapter 25) during head and neck surgery will facilitate enteral feeding during the immediate postoperative period. These tubes may be used for long-term enteral feeding of some cancer patients (Chapter 25). In one retrospective study of cats

Table 30-2. Effects of surgery that may have nutritional implications for cancer patients.

Cancer sites	Surgical procedures	Possible nutritional problems
Head, neck, tongue	Mandibulectomy Maxillectomy Glossectomy	Difficulty prehending, chewing and swallowing food
Esophagus	Esophagectomy, with or without reconstruction	Dysphagia Regurgitation
Stomach	Gastrectomy, partial or complete	Altered gastric emptying Diarrhea
Small intestine	Resection	Malabsorption Diarrhea Intestinal obstruction
Large intestine	Colectomy, partial or complete	Fluid and electrolyte imbalances
Pancreas, liver	Pancreatectomy Cholecystectomy Cholecystoduodenostomy	Diabetes mellitus Maldigestion

Table 30-3. Effects of chemotherapy that may have nutritional implications for cancer patients.

Alterations in smell or taste
Constipation
Decreased appetite
Diarrhea
Food aversions
Nausea
Stomatitis, glossitis, pharyngitis
Vomiting

undergoing mandibulectomy for oral neoplasia, nearly half had an enteral feeding tube placed at the time of surgery, and tubes were used for a median of 74 days postoperatively. Tube placement was deemed an appropriate aspect of management for oral neoplasia as 72% of the cats experienced dysphagia postoperatively, and 12% never regained the ability to eat. Additionally, 83% of owners were satisfied with the outcome of treatment (Northrup et al, 2006).

The nutritional sequelae of gastric and intestinal resection are directly related to the site and extent of resection and to the individual functions of the various segments. The ability of various segments of the small intestine to increase absorptive capabilities over a period of several months prevents major clinical problems after small bowel resection unless the resection is massive. With massive resection, malabsorption (short bowel syndrome) becomes the primary nutritional problem (Chapter 59). In people, colon surgery is usually well tolerated. The large water and electrolyte losses in the early postoperative period decrease rapidly after surgery. Feeding frequency and nutrient composition of the diet should be closely managed to optimize nutritional support for patients with surgical treatment of GI cancers.

Chemotherapy

Chemotherapeutic agents may contribute to malnutrition through a variety of direct and indirect mechanisms (**Table 30-3**). These problems should be anticipated and feeding tubes placed before therapy because early feeding lessens the adverse effects of therapy. Chemotherapeutic agents affect normal and malignant cells but have the greatest effect on rapidly proliferating cells such as epithelial cells of the GI tract. The degree to which GI function is affected depends on the chemotherapeutic agent, drug dosage, duration of treatment, rate of metabolism and the individual animal's susceptibility.

Small bowel villous damage is a major side effect of some chemotherapeutic agents and may be greatly intensified when radiation therapy is given concurrently. The rapid renewal rate of the alimentary tract epithelium usually means that clinical problems from drug-induced mucositis are short-lived.

Nausea and vomiting commonly accompany the administration of many anticancer drugs. Alterations in smell and taste are reported to occur in people and may occur in animals. Side effects experienced during chemotherapy make it difficult for some patients to consume adequate amounts of food.

Corticosteroids such as prednisone are used in chemotherapeutic protocols for some cancers, most notably lymphoma. High doses or prolonged therapy with corticosteroids causes profound polydipsia and polyuria and increased loss of water-soluble vitamins.

It is important to consider the effects of nutritional manipulation and supplemental therapies on the pharmacokinetics and pharmacodynamics of standard cytotoxic chemotherapy. Clients often regard supplements as harmless and may not report their use to the treating clinician in both human and veterinary medicine. However, growing evidence suggests that certain supplements may have toxicity of their own, and may interact with other drugs, including chemotherapeutic agents. Herbal supplements may affect metabolizing enzymes, interfering with pharmacokinetics of some drugs. Antioxidants may squelch free radicals responsible for the anticancer effect.

Because omega-3 (n-3) fatty acids have been associated with improved survival and decreased side effects in dogs with lymphoma, and have many possible anticancer properties, the effect of these fatty acids on the handling of doxorubicin was recently examined. Dogs with lymphoma were enrolled prospectively and randomized to receive a food either high or low in omega-3 fatty acids. There was no significant difference between food groups in this study (Selting et al, 2006).

Fatty acids, vitamins and herbal remedies are readily available over the counter and it is important to understand the possible effects of these and other supplements, such as singular amino acids, antioxidants and flavonoids on cancer therapy.

Radiation

Veterinary patients receiving radiation therapy may have complications that affect food intake. The complications of radiation vary according to the region of the body radiated, dose, fractionation and associated antitumor therapy such as surgery or chemotherapy. Complications may develop acutely during radiation or become chronic and progress even after radiation therapy has been completed (**Table 30-4**).

Radiation to the head and neck affects the oral mucosa and salivary secretions. Saliva production decreases in conjunction with an increase in saliva viscosity, when the salivary glands are in the field of radiation. In addition to causing mouth dryness (xerostomia) and impairing swallowing, the decrease in salivation alters the oral bacterial flora, which in turn may promote dental disease and stomatitis. In people, the thick, scant secretions may also create a feeling of nausea (Ross, 1990).

The mucosa of the mouth and oropharynx is sensitive to radiation, which can produce a sore mouth or throat, painful ulcerations, bleeding or even chronic radiation ulcers. Radionecrosis of oral tissue may result from the combination of trauma and infection superimposed on highly radiated tissues. Radiation damage alters or suppresses taste and smell sensations and affects sensitivity to food texture and temperature. In people, taste returns gradually within two to four months after radiation therapy is completed, but may take up to one year (Sandow et al, 2006). Alterations in smell and taste undoubtedly occur in animals but have not been well documented. These changes create a potentially serious situation because patients are often already anorectic and undernourished.

Radiation to the thoracic area induces esophagitis and dysphagia. These lesions and signs usually disappear after cessation of therapy. Tumor necrosis, however, may produce delayed complications such as ulceration, fistula formation and obstruction from fibrosis and stricture.

Abdominal or pelvic radiation may alter intestinal function. Patients receiving upper abdominal radiation may experience nausea and vomiting whereas those receiving radiation to the lower abdomen often experience diarrhea due to intestinal mucosal damage, loss of villi and accompanying malabsorption. Acute radiation enteritis usually disappears after therapy is discontinued. However, late effects of abdominal radiation may occur months to years after completion of radiation therapy and are manifested as intestinal obstruction, fistula formation and chronic enteritis (Kokal, 1985).

Radiation therapy in animals is usually performed on five successive days per week with patients restrained by general anesthesia, which presents an opportunity to place a feeding tube (Chapter 25). This treatment schedule requires careful planning of the feeding method to ensure that patients consume their required amount of food each day.

Unless nutritional intervention is provided, many patients lose weight during radiation therapy. Assisted feeding is indicated if food intake is inadequate (Chapters 25 and 26).

Table 30-4. Effects of radiation therapy that may have nutritional implications for cancer patients.

Treatment areas	Acute effects	Chronic effects
Head and neck	Mucositis of mouth, tongue, esophagus	Dry mouth Dental disease Alterations in smell Alterations in taste
Thorax	Esophagitis	Esophageal fistula Esophageal stricture
Abdomen	Nausea, vomiting Enteritis, diarrhea Malabsorption	Intestinal obstruction Fistula formation Chronic enteritis

Table 30-5. Key nutritional factors for foods for canine and feline cancer patients.

Factors	Dietary recommendations
Digestible carbohydrate (NFE)*	Avoid excess digestible carbohydrate NFE = ≤25% DM or <20% of the food's ME
Fat	Provide a large proportion of energy from fat Fat = 25 to 40% of DM or 50 to 65% of the food's ME
Omega-3 fatty acids	Provide foods with increased levels of omega-3 fatty acids (>5% DM)
Omega-6: omega-3 fatty acid ratio	Provide foods with an omega-6:omega-3 ratio as close to 1:1 as possible
Protein	Avoid protein deficiency Provide protein in excess of adult requirements Dogs: protein = 30 to 45% of DM or 25 to 40% of the food's ME Cats: protein = 40 to 50% of DM or 35 to 45% of the food's ME (Taurine is always a necessary inclusion in feline diets)
Arginine	Provide foods with arginine DM levels >2%

*Key: NFE = nitrogen-free extract, DM = dry matter, ME = metabolizable energy.

Key Nutritional Factors

Alterations in carbohydrate, lipid and protein metabolism precede obvious clinical disease and cachexia in cancer patients. These metabolic alterations may persist in patients with clinical remission or apparent recovery from their cancer. Key nutritional factors in cancer patients include digestible (soluble) carbohydrate, fat, fatty acids and protein, including a few specific amino acids, notably arginine. Several other amino acids have been identified as potentially imparting benefits to cancer patients; however, evidence-based studies in companion animals are not yet available. The key nutritional factors for the dietary management of cancer and their recommended amounts are discussed below and listed in **Table 30-5**. Additional nutrients and nutritional factors that have been identified in human cancer nutrition research include polyphenols, flavonoids and specific vitamin and mineral antioxidants. Veterinary patient data are not currently available to recommend specific dietary levels of these other nutrients, but research is ongoing to clarify their benefit or potential harm in the dietary management of veterinary cancer patients.

Digestible Carbohydrate

The complex role of carbohydrates in mammalian tumor cell metabolism was identified more than 50 years ago by biochemist Otto Warburg (Ristow, 2006). Warburg noted that tumor cells have high rates of anaerobic glycolysis and impaired respiration. Others have since confirmed these metabolic alterations and numerous mechanisms have been proposed to explain oxidative metabolism in cancer cell growth. Recent studies indicate that neoplastic cells require not only ATP derived from glycolysis, but also biosynthetic precursors from

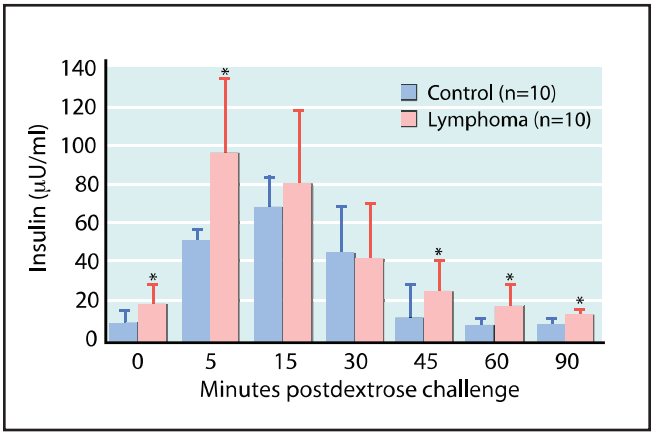

Figure 30-3. Serum insulin concentrations from dogs with and without lymphoma before and after intravenous administration of 500 mg glucose/kg body weight. Asterisks indicate values from dogs with lymphoma that differ significantly ($p < 0.001$) from control dog values obtained at the same time. (Adapted from Vail DM, Ogilvie GK, Wheeler SL, et al. Alterations in carbohydrate metabolism in canine lymphoma. Journal of Veterinary Internal Medicine 1990; 4: 307.)

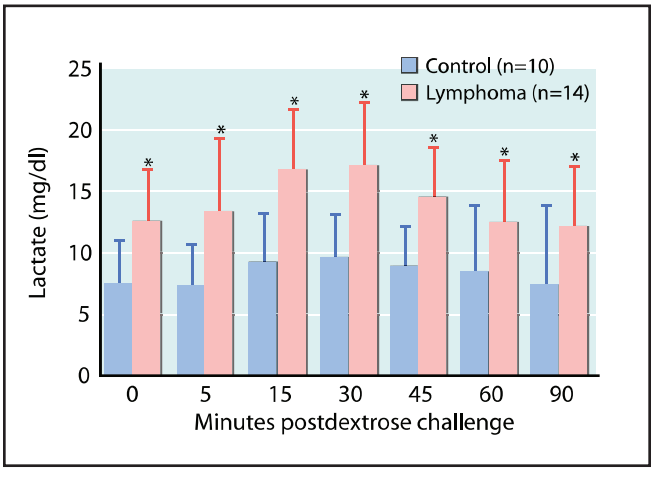

Figure 30-4. Serum lactate concentrations from dogs with and without lymphoma before and after intravenous administration of 500 mg glucose/kg body weight. Asterisks indicate values from dogs with lymphoma that differ significantly ($p < 0.001$) from control dog values taken at the same time. (Adapted from Vail DM, Ogilvie GK, Wheeler SL, et al. Alterations in carbohydrate metabolism in canine lymphoma. Journal of Veterinary Internal Medicine 1990; 4: 307.)

glycolytic intermediates in order to proliferate and invade (Chesney, 2006). One such intermediate, fructose-2,6-biphosphate, controls the overall rate of glycolysis in tumor cells. A second intermediate, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase, controls the intracellular concentration of glucose in tumor cells and is constitutively expressed by several leukemias and solid tumor cells (Chesney, 2006). The high glycolytic flux to pyruvate/lactate observed in tumors also alters intracellular pH, causing apoptosis in normal surrounding cells. Increased glucose transport (Birnbaum et al, 1987) and overexpression of oncogenes associated with glucose transport (Flier et al, 1987) have also been associated with tumors cells. Increased glycolysis in tumors may also be a consequence of hexokinase redistribution in subcellular and mitochondrial compartments, or the altered ability of mitochondria to metabolize substrates other than carbohydrates or their derivatives for energy (Ristow, 2006). Numerous mechanisms have been proposed and studied to clarify the altered mitochondrial metabolism in tumor cells.

Regardless of the exact mechanism(s) involved, increasing the rate of glycolysis in tumor cells promotes tumor cell growth in several species including dogs (Ogilvie and Vail, 1992; Heber et al, 1986), forming lactate as an end product. The host must then expend energy to convert lactate to glucose via the Cori cycle, resulting in a net energy gain by the tumor and a net energy loss by the host (Vail et al, 1990b; Heber et al, 1986; Bozzetti et al, 1980; Dempsey and Mullen, 1985). Abnormalities in dogs have been documented in peripheral glucose disposal, hepatic gluconeogenesis, insulin effects and whole body glucose oxidation and turnover (Vail et al, 1990a, 1990b; Ogilvie et al, 1992).

Following a 90-minute intravenous glucose tolerance test, serum lactate and insulin concentrations were significantly higher in dogs with lymphoma when compared with control values (**Figures 30-3** and **30-4**) (Vail et al, 1990). The noted hyperlactatemia and hyperinsulinemia did not improve when these dogs achieved remission with doxorubicin chemotherapy (Ogilvie et al, 1992). Additionally, a subset of dogs with non-hematopoietic malignancies (e.g., osteosarcoma, mammary adenocarcinoma and pulmonary bronchogenic adenocarcinoma) demonstrated hyperlactatemia and hyperinsulinemia, which did not improve when their tumors were completely excised (Ogilvie et al, 1997). The same metabolic alterations are suspected to occur in cats, but there are no published reports to date to verify this assumption.

The clinical significance of altered mitochondrial respiration and increased glycolysis resulting in altered carbohydrate metabolism is highlighted by hyperlactatemia and its sequelae. Foods high in carbohydrate also appear to increase the total amount of lactate produced when fed to dogs with lymphoma. Mean blood glucose, lactate and insulin concentrations obtained during food tolerance testing were often higher in dogs fed a high-carbohydrate, low-fat food (9% dry matter [DM] fat, 58% DM carbohydrate) compared to those fed a low-carbohydrate, high-fat food (37% DM fat, 14% DM carbohydrate) (Ogilvie et al, 1992). However, although there was a positive initial response to chemotherapy, there was no difference in the duration of remission between the two groups.

Blood lactate concentrations in dogs with lymphoma were significantly elevated compared to values in controls before, during and after lactated Ringer's solution was infused (4.125 ml/kg body weight/hr) (**Figure 30-5**). This lactated Ringer's-induced increase in lactate concentration may create an additional metabolic burden, requiring the host to convert lactate back to glucose, further exacerbating energy demands. This finding may be even more important for septic, critically ill cancer patients that require more intensive fluid therapy. It is also

important to consider that glucose-containing fluids delivered to septic, critically ill patients can exacerbate the septic state.

Because alterations in insulin and glucose metabolism occur in cancer patients, concerns about dietary carbohydrate (glucose) are further warranted from the perspective of oxidative metabolism of tumor cell growth and metabolic mechanisms of stress hyperglycemia (Mechanick, 2006). In acute and chronic cancer patients, as with all critically ill patients, the stress response leads to a plurality of organ-system derangements including glucose allostasis, immune-neuroendocrine axis activation and insulin receptor signal transduction (Mechanick and Brett, 2005). The concurrent inflammation, tissue catabolism and hyperglycemia should be evaluated when designing a feeding protocol. Manipulating the dietary fat, protein (amino acids) and digestible carbohydrate concentrations can potentially minimize physiologic sequelae resulting from the stress response and slow tumor progression. Digestible carbohydrates may be poorly used because of peripheral insulin resistance. Feeding high levels of digestible carbohydrate may lead to hyperglycemia, glucosuria, hyperosmolarity, hepatic dysfunction, respiratory insufficiency and hyperlactatemia. More specifically, until further information is known about the effects of hyperlactatemia on critically ill animals with cancer, glucose- and lactate-containing fluids should generally be avoided. Carbohydrate levels in foods for canine cancer patients should contain no more than 25% DM digestible carbohydrate.

The specific role of dietary carbohydrates has not been reported in feline cancer patients. Although carbohydrate metabolism in healthy cats differs from that of healthy dogs, it is suspected that tumors in cats use carbohydrates as an energy source. Redistribution of hexokinase and its influence on the rate of glycolysis in tumor cells may be of particular interest for managing the nutritional aspect of feline cancer patients. Based on guidelines discussed below for dietary fat of 25 to 40% DM and protein of 40 to 50% DM, the caloric contribution from digestible carbohydrate is limited to 25% DM or less.

Fat and Fatty Acids

In contrast to the ready use of carbohydrates and proteins by tumor cells, some tumor cells have difficulty using lipids as a fuel source. Theoretically, this preferential use of digestible carbohydrates and proteins leaves lipids available as an energy source for the host (Shein et al, 1986). This finding led to the hypothesis that foods relatively high in fat may benefit patients with cancer compared to foods relatively high in carbohydrates. Recent studies have identified alterations of lipid metabolism in canine cancer patients; this knowledge is paramount for developing feeding protocols. An overview of the current literature may help determine if the focus should be on total amount of fat, specific sources of fat or both for cancer patients.

Highly malignant tumors, in rodent models and in vitro cell cultures, can exhibit up to an 85% decrease in the rate of fatty acid usage. This decrease is linked to decreased activity of the key activating enzyme of β-oxidation, acyl thiokinase (Ristow, 2006). Conversely, well-differentiated tumors can retain the ability to metabolize fatty acids, especially under hypoxic conditions (Ristow, 2006; Swinnen et al, 2006; Menendez and Lupu, 2006). Although tumor type may influence fat usage, a high proportion of weight loss in cachectic cancer patients is attributed to loss of body fat. Not surprisingly, people and animals with cancer have marked abnormalities in lipid metabolism (Chlebowski and Heber, 1986; Dewys, 1982; McAndrew, 1986; Ogilvie et al, 1994; Shein et al, 1986; Tisdale et al, 1987; Daly et al, 1991).

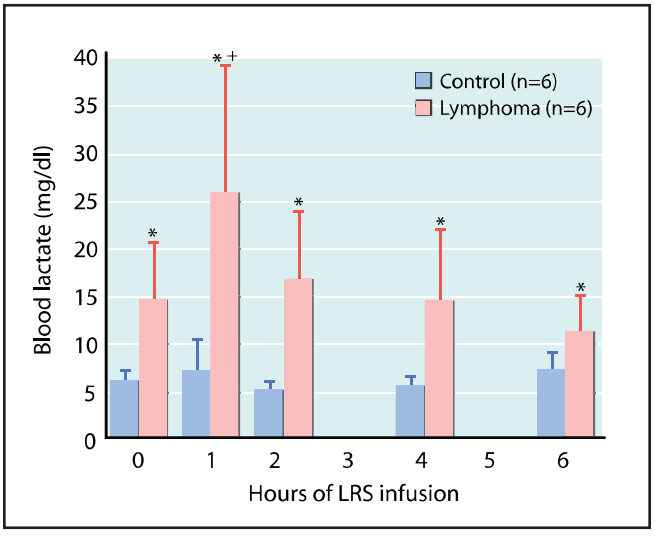

Figure 30-5. Blood lactate concentrations from dogs with and without lymphoma before and during intravenous infusion of lactated Ringer's solution (LRS). Asterisks indicate values from dogs with lymphoma that differ significantly ($p < 0.05$) from control dog values obtained at the same time. Plus signs indicate values that differ significantly ($p < 0.05$) from pre-infusion baseline values within the same test group. (Adapted from Vail DM, Ogilvie GK, Fettman MJ, et al. Exacerbation of hyperlactatemia by infusion of lactated Ringer's solution in dogs with lymphoma. Journal of Veterinary Internal Medicine 1990; 4: 228-232.)

The decreased lipogenesis and increased lipolysis observed in people and rodents with cancer cachexia alter the lipid profile dramatically. Changes include increased blood concentrations of free fatty acids, very low-density lipoproteins (VLDL), triglycerides (TG), plasma lipoproteins and hormone-dependent lipoprotein lipase activity and decreased concentrations of endothelial-derived lipoprotein lipase (McAndrew, 1986). Lipid profiles have been evaluated in dogs with lymphoma to determine if alterations similar to those reported in other species are present (Ogilvie et al, 1994). In contrast to healthy controls, dogs with lymphoma had significantly altered concentrations of cholesterol-associated VLDL, TG, VLDL-TG, low-density lipoprotein (LDL-TG) and high-density lipoprotein (HDL-TG). In dogs with lymphoma, HDL-TG and VLDL-TG concentrations were significantly increased above pretreatment values after remission was lost. Additionally, dogs developed overt signs of cancer cachexia. These abnormalities did not normalize when clinical remission was obtained. The clinical significance of the previously mentioned lipid parameters in dogs with lymphoma is unknown.

Epidemiologic studies and meta-analyses examining the

effects of dietary fat and cancer in people have produced conflicting results. Despite this lack of consensus regarding human data, murine and experimental studies have shown suppression of tumor growth by specific fatty acids, particularly in breast, colon and prostate cancers. Omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) generally have an inhibitory effect on tumor growth, whereas omega-6 (n-6) fatty acids (linoleic acid, γ-linolenic acid) enhance metastases. In vivo studies have shown that EPA has selective tumoricidal action without harming normal cells (Lowell et al, 1990; Ramesh et al, 1992; Dippenaar and Booyenes, 1982; Begin et al, 1986, 1985; Plumb et al, 1993; Mengeaud et al, 1992; Pascale et al, 1993; Jenski et al, 1993; Roush et al, 1991; Holian and Nelson, 1992).

Similar findings have been reported to occur in canine patients with lymphoma and non-hematopoietic malignancies (Ogilvie et al, 2000). Dogs receiving chemotherapy for lymphoma and fed a food supplemented with arginine and omega-3 fatty acids had elevated plasma arginine, EPA and DHA levels. Plasma levels of arginine and omega-3 fatty acids were positively correlated with survival time. Similarly, in dogs undergoing radiation therapy for nasal carcinomas, plasma levels of arginine, EPA and DHA were positively correlated with quality of life and negatively correlated with inflammatory mediators and mucositis in irradiated areas (Anderson et al, 1997).

Focus on nutritional support of feline cancer patients involves fatty acid influence on the mechanisms of tumor cell signaling. Human estrogen receptor insensitive breast tumor cells have nearly identical histology to feline malignant mammary tumor cells (Perez-Alenza et al, 2004). This provides a two-way model for mammary tumor research. Estrogen receptor insensitive breast tumor cell lines maintained in omega-3 enriched media exhibited significantly reduced activation of MAPK pathway intermediates (Ras, Raf, MEK and MAPK), increased apoptosis, decreased cell proliferation and decreased cyclooxygenase-2 (COX-2) pathway inflammatory eicosanoid expression compared to cells in omega-6 enriched media (Phipps et al, 2004; Saker et al, 2002, 2002a, 2004). Feline feeding studies associated with MAPK expression and dietary fatty acids are equally as compelling.

Healthy adult cats fed diets providing varying omega-6:omega-3 fatty acid ratios (5:1 to 0.4:1) exhibited a ratio dependent decrease in MAPK activation. In addition, omega-6 concentrations decreased and omega-3 concentrations increased in mammary adipose tissue and leukocytes (Saker et al, 2002). Furthermore, a threefold decrease in MAPK activity was detected along with stasis of tumor cell growth as measured by ultrasound and caliper readings in cats with either pancreatic masses or inflammatory mammary carcinomas when the fatty acid content of their food was changed from enriched omega-6 (16:1) to enriched omega-3 (<1:1). MAPK activity increased by 3.5-fold when the original food enriched with omega-6 fatty acids (16:1) was reintroduced. Taken together, these data support the value of enhanced omega-3 fatty acid diets as antitumorigenic and antiinflammatory (**Box 30-1**).

Fish oil may also affect colon cancer development, depending on dietary fiber source. The effect of either omega-3 or omega-6 fatty acids in combination with different fiber types in a rat model of carcinogen-induced colon cancer was reported. Dietary fish oil in combination with pectin was more protective against colon cancer than omega-3 fatty acids with cellulose or omega-6 fatty acids with any fiber type (Chang et al, 1998). The mechanism of enhanced protection appeared to be due to increased colonocyte apoptosis through simultaneously increased reactive oxygen species production and decreased antioxidant enzyme activity (Sanders et al, 2004).

Other potential benefits of omega-3 fatty acids focus on their reported anticachectic effect and association with decreased blood lactate levels. EPA decreases protein degradation without altering protein synthesis; the net effect is anticachectic (Beck et al, 1991; Jho et al, 2002). **Box 30-1** explores suggested mechanism(s) by which fatty acids influence tumor growth and cachexia.

Foods with high omega-3 fatty acid concentrations ameliorate endotoxin-induced lactic acidosis in guinea pigs (Pomposelli et al, 1989). This finding may be of clinical importance because hyperlactatemia occurs commonly in dogs with lymphoma.

Although studies have identified some of the mechanisms involved in lipid use by cancer patients, much more research is needed to match dietary fat levels and omega-6:omega-3 fatty acid ratios to specific tumor types and cancer stages in cats and dogs. Currently, recommendations for canine and feline cancer patients continue to be focused on foods with increased fat calories (25 to 40% DM fat); increased levels of dietary omega-3 fatty acids (>5.0% DM) and an omega-6:omega-3 fatty acid ratio approximating 1:1.

Protein and Arginine

Altered nitrogen balance is observed in human cancer patients, which appears to be a consequence of decreased body muscle mass and skeletal protein synthesis. Increased skeletal protein breakdown, liver protein synthesis and whole body protein synthesis apparently promote tumor growth because tumors often use amino acids for energy (Heber et al, 1986; Bozetti et al, 1980; Dempsey and Mullen, 1985; Chory and Mullen, 1986; Langstein and Norton, 1991; Kurzer and Meguid, 1986; Teyek et al, 1986; Oram-Smith and Stein, 1977). Tumor use of amino acids for energy becomes clinically significant when protein degradation exceeds protein intake. This imbalance can alter immune response, GI function and surgical wound healing (Langstein and Norton, 1991; Kurzer and Meguid, 1986).

In one study, cancer-bearing dogs had significantly lower plasma concentrations of threonine, glutamine, glycine, valine, cystine and arginine and significantly higher concentrations of isoleucine and phenylalanine than did normal control dogs (Ogilvie and Vail, 1990). The results were the same for different types of tumors, and observed alterations in plasma amino acid profiles did not normalize after tumors were surgically removed. This finding suggests that cancer induces

Box 30-1. Omega-3 Fatty Acids, Tumor Growth, Cachexia and Inflammation.

Polyunsaturated omega-6 (n-6) and omega-3 (n-3) fatty acids alter protein-lipid interactions and lipid-based signal transduction pathways in cells. The simultaneous generation of inositol phosphates and diacylglycerol, yielding the secondary release of intracellular calcium and activation of protein-kinase C (PKC) depend on phospholipase C, a lipid-comprised phosphatidylinositol. In addition, the specific lipid composition of the diacylglycerol (i.e., omega-6 vs. omega-3) results in a differing affect on the mitogen activated protein kinase (MAPK) signal transduction pathway. MAPK, one of several cell signal transduction pathways, is paramount in regulating tumor (mammary, uterine, prostate, lung) cell proliferation. Numerous human and murine studies have reported the value of omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) in inhibiting tumor growth and metastasis through alterations in expression of the pro-angiogenic vascular endothelial growth factor (VEGF) and down-regulation of the proinflammatory regulator cyclooxygenase 2 (COX-2). COX-2 enzyme activity promotes proinflammatory eicosanoid production, which stimulates VEGF and vascularization of tumor tissue. Fatty acids attenuate transcriptional activity of COX-2 and VEGF through anti-MAPK and -AP-1 mechanisms in breast cancer cell lines.

The anticachectic effect of EPA has been reported to influence cytokine release from tumor cells. Administration of omega-3 fatty acids reduced secretion of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-1α (IL-1α) and interleukin-2. This may be especially important because IL-1 and TNF are important mediators of cachexia and may act as tumor growth factors.

The onset and perpetuation of the anorectic state in cancer and critically ill patients can be influenced through omega-3 fatty acid supplementation. Studies have demonstrated that omega-3 fatty acids modulate changes in the concentrations and actions of several orexigenic and anorexigenic neuropeptides in the brain. These peptides include neuropeptide Y, α-melanocyte stimulating hormone, serotonin and dopamine. In patients with acute or chronic inflammatory conditions, as is thought to occur in many cancer patients, omega-3 fatty acid supplementation suppresses proinflammatory cytokine production and improves food intake by normalizing hypothalamic orexigenic peptides and neurotransmitters.

The Bibliography for **Box 30-1** can be found at www.markmorris.org.

long-lasting changes in protein metabolism.

The anorexia-cachexia syndrome prevalent in cancer patients is associated with profound metabolic perturbations including increased muscle proteolysis. Thus, decreased lean body mass and increased protein requirements in cancer patients are driven by amino acid redistribution for: 1) synthesis of hepatic acute-phase-reactant proteins, 2) support of the cellular immune response, 3) provision of gluconeogenic substrates and 4) direct oxidation for fuel.

To date, there appears to be less of a focus on protein metabolism in cancer patients compared to the focus on fat metabolism. Despite the unique protein requirements of cats, protein use studies in companion animals have been limited to canine cancer patients. Current recommendations for dietary protein are based on a limited number of companion animal cancer studies, well-founded knowledge of protein metabolism in critically ill patients and extrapolation from non-veterinary species.

Dietary protein levels in foods for cancer patients should exceed levels normally used for maintenance of adult animals, assuming renal and liver function is adequate to tolerate enhanced protein. If signs of intolerance are observed, titrate down to tolerable protein levels. Currently, recommended protein levels in foods for dogs with cancer are 30 to 45% DM. Based on dietary protein requirements for critically ill cats, suggested protein levels in foods for cats with cancer are 40 to 50% DM.

Arginine is an essential amino acid for cats and is considered to be a conditionally essential amino acid for dogs. Arginine is synthesized endogenously in the kidney from gut-derived citrulline and is converted by the enzyme arginase into ornithine and urea. Arginine has potent secretagogue effects on several endocrine and neuroendocrine glands. Intravenous administration of arginine induces secretion of growth hormone, prolactin, insulin, glucagon, insulin-like growth factor-1, pancreatic polypeptide, somatostatin and catecholamines (Barbul, 1986). Arginine, given in large doses, exerts numerous beneficial effects on the immune system, particularly on thymus-dependent and T-cell-dependent immune reactions. The exact mechanism whereby arginine stimulates T-cell function is unknown. In addition to its positive effects on immune function, arginine may also influence tumor growth, metastatic rate and survival time in patients with cancer.

Adding arginine to parenteral solutions decreases tumor growth and metastatic rate in rodent cancer models (Tachibana et al, 1985). Increased dietary arginine, in conjunction with increased dietary omega-3 fatty acid intake, influenced clinical signs, quality of life and survival time in dogs with lymphoma (Ogilvie et al, 2000) and enhanced quality of life for dogs undergoing radiation therapy for nasal carcinomas (Anderson et al, 1997). The minimum effective level of dietary arginine for cancer patients is unknown; however, based on work in other species, it is thought appropriate to provide more than 2% DM arginine in foods for dogs with cancer. There are no reports demonstrating efficacy of additional arginine in feline cancer patients. The minimum recommended allowance for queens in late gestation and peak lactation is 1.5% (DM) (NRC, 2006). Therefore, this same recommendation (>2%, DM) is probably minimally satisfactory for dietary arginine in feline cancer patients.

Other Nutritional Factors

Several amino acids, vitamins, minerals and novel foods and ingredients have received considerable attention in cancer prevention and therapy (**Boxes 30-2** through **30-5**).

Box 30-2. Amino Acids and Cancer.

GLUTAMINE

Glutamine may have specific therapeutic value. Glutamine is an essential precursor for nucleotide biosynthesis and is an important oxidative fuel for enterocytes. Supplementation of enteral preparations with glutamine has benefited several animal models of intestinal injury by improving intestinal morphometry, reducing bacterial translocation, enhancing local immunity and improving survival. Glutamine has only recently been recognized as a conditionally essential amino acid in certain pathophysiologic states including stress. Glutamine is added to most human enteral formulas, and has been evaluated in parenteral formulations for its potential to protect intestinal integrity in critically ill, anorectic patients. The parenteral studies have most consistently delivered a 2% solution of L-glutamine.

One study using a feline model of methotrexate-induced intestinal injury failed to demonstrate a beneficial role for glutamine supplementation to an amino acid-based purified food. A recent review indicated glutamine and glutamate metabolism appears to be intact in tumor mitochondria, suggesting that the mitochondrial activity of tumor cells can be restored by using supplemental glutamine as a fuel source. Contrary to these findings, dietary glutamine was reported to suppress mammary carcinogenesis in a 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast cancer animal model. Glutamine supplemented at 1 g/kg/day to tumor-induced rats for 11 weeks significantly decreased tumor glutathione (GSH) levels, altered tumor GSH/GSSG status and enhanced tumor apoptotic activity by Bax, caspase-3 and Bcl-2. Additional studies are needed to determine the potential mechanism(s) by which glutamine alters tumor cell growth, and if commercially available foods supplemented with glutamine improve intestinal integrity during cancer treatments.

BRANCHED-CHAIN AMINO ACIDS

Branched-chain amino acids (BCAA), notably leucine, isoleucine and valine, are neutral amino acids with clinically relevant metabolic effects. Their potential role as anti-anorexia and anticachectic agents has been reported. Numerous human clinical trials indicate anorexia is associated with deranged brain tryptophan/serotonin metabolism. Tryptophan crosses the blood-brain barrier via a specific transport mechanism shared with other neutral amino acids. Therefore, supplementation with competing neutral amino acids (BCAA) reduces tryptophan entry into the brain, thereby inhibiting hypothalamic serotonin synthesis and release with subsequent amelioration of anorexia. Supplemental oral BCAA given to cancer patients at a dose of 14.4 g/day for seven days significantly improved energy intake by Day 3.

The anticachectic value of BCAA, particularly leucine, was evaluated in experimental studies and human clinical trials. Tumor-bearing rats fed a leucine-enriched diet had a 1.4-fold higher rate of protein synthesis and decreased expression of the ubiquitin-proteosome system and chymotrypsin-like activity. Bed-rested, catabolic patients receiving 18 g BCAA/day for a month exhibited improved lean leg mass, strength and protein synthetic rate. The long-term benefit of BCAA administration was evaluated in patients with hepatocellular carcinoma. Those who received 11 g BCAA supplementation/day for one year had lower morbidity, higher serum albumin concentrations and a better quality of life compared to values in control group patients. These findings indicate BCAAs appear to have specific anticachectic effects.

BCAA appear to influence cell growth in canine tumor cell lines. Canine osteosarcoma, bronchoalveolar carcinoma and Madine-Darby kidney cells were cultured under the influence of 0 to 100 mM concentrations of leucine, isoleucine or valine to evaluate the anti-proliferative effects of these BCAAs. Study results were tumor-type dependent; leucine appeared to have the most significant effect in diminishing neoplastic cell growth at supraphysiologic concentrations. Additional studies are needed to establish relevancy in the management of veterinary cancer patients. Available human trial data suggest supplementation with 10 to 15 g/day of BCAA as leucine, isoleucine and valine may provide anti-anorexic and anticachectic benefits.

METHIONINE AND ASPARAGINE

Certain tumor cell lines require methionine for growth. Replacing methionine with its precursor, homocysteine locks these tumor cells into late S and G2 phases of the cell cycle. Because certain cancer chemotherapeutic agents are cell-cycle specific, the percentage of tumor cells sensitive to chemotherapy increases, improving the therapeutic index. Asparagine is essential for tumor cell growth in lymphoma. Treatment of dogs and cats with L-asparaginase has induced complete remissions in up to 80% of dogs and cats with lymphoma.

TYROSINE AND PHENYLALANINE

Tyrosine and phenylalanine restriction has been reported to suppress melanoma cell growth in tissue cultures and in rodent tumor models. Administration of tyrosine and phenylalanine increased the survival of melanoma tumor-bearing mice and increased the effectiveness of levodopa against melanoma.

GLYCINE

Some amino acids may decrease the toxicity associated with chemotherapy. For example, glycine reduces cisplatin-induced nephrotoxicity.

The Bibliography for **Box 30-2** can be found at www.markmorris.org.

FEEDING PLAN

Although cancer and traditional cancer treatments in dogs and cats result in a spectrum of metabolic/nutritional derangements, a number of these derangements are common to most types of cancer and provide the basis for development of a general feeding plan.

The previous sections discussed the clinical fundamentals of cancer from clinical importance to patient assessment and determination of key nutritional factors. This section describes how to feed patients with cancer. It continues the iterative process by developing these feeding plan topics: 1) assess and select the food, 2) assess and determine the feeding method and

Box 30-3. Vitamins and Cancer.

Retinoids, β-carotene, vitamin C and vitamin E all appear to influence the growth and metastasis of cancer cells by a variety of mechanisms. Some of these mechanisms include selected receptor-mediated anti-proliferative activities. These vitamins have been reported to bind their cytosolic receptors followed by translocation of the bound complex to the nucleus where the receptors mediate gene regulation. Other effects result from antioxidant, hormone-like and immunomodulator capabilities.

RETINOIDS

"Retinoids" refer to the entire group of naturally occurring and synthetic vitamin A derivatives, including retinol, retinal and retinoic acid. Retinoids appear to have the potential for regulating cancer cells either alone or in combination with other agents. Specific studies in human and veterinary medicine suggest that retinoids alone or with other agents can be effective for the treatment of certain types of malignancies. The synthetic retinoids, isotretinoin and etretinate, have been used successfully in some dogs with intracutaneous cornifying epitheliomas, other benign skin tumors, cutaneous lymphoma, solar-induced squamous cell carcinoma and associated preneoplastic lesions. The retinoids promote cellular differentiation and may enhance the susceptibility of neoplastic cells to chemotherapy and radiation therapy.

VITAMIN C

Vitamin C (ascorbic acid) has been reported to inhibit nitrosation reactions and prevent chemical induction of cancers of the esophagus and stomach. 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.

Ascorbic acid may be one therapeutic alternative for overcoming drug resistance in some cancer cells. Studies suggest that an ascorbic acid-sensitive mechanism may be involved in drug resistance to vincristine in certain cancer cell lines. Despite the extensive amount of vitamin C research, few direct data exist proving its efficacy in dogs and cats.

VITAMIN E

Vitamin E (α-tocopherol) can also inhibit nitrosation reactions. Vitamin E also has a broad capacity to inhibit mammary tumor and colon carcinogenesis in rodents. Research indicates that vitamin E influences a variety of cell functions including free-radical scavenging, which can prevent oxidative damage that leads to cell death.

In addition to its anticancer properties, vitamin E may potentially convey therapeutic efficacy against certain malignancies. Vitamin E has been reported to have anti-proliferative activity, which involves the binding of the vitamin to salicylic receptors, followed by translocation to the nucleus where DNA binds on the domains of receptors that mediate gene regulatory events. Recent evidence suggests that the two prominent vitamin E isoforms, vitamin E succinate (VES) and α-tocopherol acetate (α-TEA) have specific anticancer activity. Both isoforms increased apoptosis in human breast cancer cell lines, ovarian and cervical cancer cell lines, mesothelioma cells, lung cancer cells and gastric cells without affecting surrounding normal cells.

Retrovirus-induced tumorigenesis involves transformation of normal cells into tumor cells. Evidence suggests that vitamin E may normalize the immune system by interacting with macrophages and T lymphocytes to inhibit retroviral-induced infections.

The Bibliography for **Box 30-3** can be found at www.markmorris.org.

Box 30-4. Minerals and Cancer.

Minerals that have been suggested as being important in patients with cancer include selenium, iron and zinc. Optimal levels of specific minerals for cancer prevention and treatment have not been established for pet animals.

SELENIUM

Selenium has been one of the most heavily studied minerals associated with the development of cancer. Low serum selenium levels have been observed in human patients with gastrointestinal cancer. In rodents, dietary supplementation with selenium inhibits colon, mammary gland and stomach carcinogenesis.

IRON

Iron transferrin and ferritin have been linked to cancer risk and cancer cell growth. Lung, colon, bladder and esophageal cancer in people have been highly correlated with increased serum iron concentrations and increased transferrin saturation. Because many tumor cells require iron for growth, it has been suggested that the increased use of iron by the tumor depresses serum iron levels in human cancer patients. Mice with low levels of iron have slow tumor growth compared to those with normal iron levels.

ZINC

In people, low levels of zinc in blood and diseased tissue have been observed in esophageal, pancreatic and bronchial cancer. Zinc deficiency appears to enhance carcinogenesis in laboratory animals.

The Bibliography for **Box 30-4** can be found at www.markmorris.org.

3) reassess and modify the feeding plan, as necessary. The key nutritional factors identified in the previous section are used here as benchmarks for comparing selected foods marketed for the dietary management of cancer.

Nutritional support of cancer patients must be individualized. Nutritional therapy should be undertaken with the overall prognosis of the patient clearly in mind so that the aggressiveness of dietary intervention (e.g., supportive, adjunctive, defin-

Table 30-6. Selected commercial foods for canine cancer patients compared to recommended levels of key nutritional factors.*

Dry food	Energy density (kcal/cup)**	Carbohydrate (%)	Fat (%)	Omega-3 fatty acids (%)	Omega-6: omega-3 ratio	Protein (%)	Arginine (%)
Recommended levels	**-**	**≤25**	**25-40**	**>5**	**~1:1**	**30-45**	**>2**
Medi-Cal Development Formula	425	na	17.5	na	na	28.4	na
Moist foods	**Energy density (kcal/can)****	**Carbohydrate (%)**	**Fat (%)**	**Omega-3 fatty acids (%)**	**Omega-6: omega-3 ratio**	**Protein (%)**	**Arginine (%)**
Recommended levels	**-**	**≤25**	**25-40**	**>5**	**~1:1**	**30-45**	**>2**
Hill's Prescription Diet a/d Canine/Feline	180/5.5 oz.	15.4	30.4	2.62	2.3:1	44.2	2.37
Hill's Prescription Diet n/d Canine	569/12.7 oz.	19.9	33.2	7.29	0.3:1	38.0	2.95
Iams Veterinary Formula Maximum Calorie/Canine & Feline	333/6 oz.	12.2	37.2	na	na	41.8	na
Medi-Cal Development Formula	445/396 g	na	14.1	na	na	32.2	na
Medi-Cal Recovery Formula/ Canine & Feline	185/170 g	na	32.1	na	na	53.4	na
Purina Veterinary Diets DM Dietetic Management Feline Formula	194/5.5 oz.	8.1	23.8	0.88	3.8:1	56.9	na

Key: na = Information not available from manufacturer; values were obtained from manufacturers' published information, g = grams.
*Nutrients expressed on % dry matter basis, unless otherwise stated.
**As fed energy density is useful for determining amount to feed; cup = 8-oz. measuring cup; to convert to kJ, multiply by 4.184.

Table 30-7. Selected commercial foods for feline cancer patients compared to recommended levels of key nutritional factors.*

Dry foods	Energy density (kcal/cup)**	Carbohydrate (%)	Fat (%)	Omega-3 fatty acids (%)	Omega-6: omega-3 ratio	Protein (%)	Arginine (%)
Recommended levels	**-**	**≤25**	**25-40**	**>5**	**~1:1**	**40-50**	**>2**
Medi-Cal Development Formula	425	na	23.9	na	na	34.7	na
Purina Veterinary Diets DM Dietetic Management Feline Formula	592	15.0	17.9	0.39	5.6:1	57.8	3.57
Moist foods	**Energy density (kcal/can)****	**Carbohydrate (%)**	**Fat (%)**	**Omega-3 fatty acids (%)**	**Omega-6: omega-3 ratio**	**Protein (%)**	**Arginine (%)**
Recommended levels	**-**	**≤25**	**25-40**	**>5**	**~1:1**	**40-50**	**>2**
Hill's Prescription Diet a/d Canine/Feline	180/5.5 oz.	15.4	30.4	2.62	2.3:1	44.2	2.37
Iams Veterinary Formula Maximum Calorie/ Canine & Feline	333/6 oz.	12.2	37.2	na	na	41.8	na
Medi-Cal Development Formula	216/170 g	na	27.5	na	na	45.0	na
Medi-Cal Recovery Formula/Canine & Feline	185/170 g	na	32.1	na	na	53.4	na
Purina Veterinary Diets CV Cardiovascular Feline Formula	223/5.5 oz.	23.1	26.8	na	na	42.5	na
Purina Veterinary Diets DM Dietetic Management Feline Formula	194/5.5 oz.	8.1	23.8	0.88	3.8:1	56.9	na

Key: na = Information not available from manufacturer; values were obtained from manufacturers' published information, g = grams.
*Nutrients expressed on % dry matter basis, unless otherwise stated.
**As fed energy density is useful for determining amount to feed; cup = 8-oz. measuring cup; to convert to kJ, multiply by 4.184.

itive) can be adjusted appropriately. Owners of cancer patients should be educated about the integral role nutrition plays in the total management of their pet's disease, but at the same time should understand the limitations of the dietary management component of the overall treatment plan. The feeding plan depends on the extent of disease, anorexia, nausea, weight loss and consequences of treatment.

Assess and Select the Food

There is only one veterinary therapeutic commercial food[a] that has been specifically developed for canine cancer patients. This food has been shown to improve the longevity and quality of life of selected canine patients with cancer. However, other veterinary therapeutic foods provide certain key nutritional factors at near recommended levels. **Tables 30-6** (dogs) and **30-7** (cats) include the key nutritional factors from **Table 30-5** and compares them to the levels in selected commercial foods. The food selected should most closely fit the recommended levels for patients with cancer.

Another criterion for selecting a food that may become increasingly important in the future is evidence-based clinical nutrition. Practitioners should know how to determine risks and benefits of nutritional regimens and counsel pet owners accordingly. Currently, veterinary medical education and continuing education are not always based on rigorous assessment of evidence for or against particular management options. Still, studies have been published to establish the nutritional benefits of certain pet foods. Chapter 2 describes evidence-based clinical nutrition in detail and applies its concepts to various veterinary therapeutic foods. Evidence Grade 1 (the highest level) exists for at least one food used for canine cancer patients.[a] See Case 2-1.

Some owners feed debilitated or cachectic pets home-cooked foods to enhance palatability and food intake and as a means of bonding with their pet. Interest in homemade diets has peaked in recent years as a feeding alternative for healthy and ill pets. Numerous references are available that contain published recipes or provide computer-based recipes. Homemade diets must be nutritionally balanced. Adequate provision of protein and energy to maintain the cancer patient and consideration of key nutrient concerns should be the focus of home-cooked diet formulations. (See Chapter 10 for basic guidelines for formulating and evaluating homemade diets.) Research efforts to identify optimal foodstuffs and levels of nutrients for veterinary cancer patients are ongoing. As more experimental and clinical trial data become available, diet selection for cancer patients will expand and likely become tumor-type and disease-stage specific. **Tables 30-6** and **30-7** list commercially available diet choices; however, when selecting a diet, the overall goal of supplying daily water, protein and energy requirements to sustain an acceptable quality of life should not be overlooked. Patient assessment and owner constraints may affect diet selection.

Assess and Determine the Feeding Method

The feeding method includes the amount to feed as well as how often and by what route. Careful assessment of the feeding method is important to determine whether the patient is currently receiving its caloric requirement and if it is able to prehend, masticate, swallow and assimilate its food.

How Much to Feed

Calculation of the patient's energy requirement, determination of the energy density of the food, careful measurement of the amount of food eaten by the animal and body condition scoring will help establish whether cancer patients with weight loss are actually receiving sufficient calories and nutrients. Limitations to the accurate calculation of RER or DER in veterinary patients can offer a challenge to maintaining or improving the patient's body weight and condition. Again, routine assessment is paramount to fine-tuning the feeding protocol for each patient. The general "rule of thumb" is to feed ill, hospitalized patients at RER for their current body weight, and increase to DER for a more optimal body weight during "at home" feeding. As feeding for cancer patients is individualized, these guidelines do not hold true for all cases, but rather should be considered as starting points.

Hospitalized patients should eat enough food to at least meet their estimated RER. Calculations for determination of energy requirements can be reviewed in Chapters 1 and 5. Initiate an assisted-feeding protocol for hospitalized patients that fail to consume enough food to meet RER for three or more days. (See How to Feed below.)

Patients managed at home should eat enough food to meet their estimated DER, which takes into account increased activity and a less controlled environment. Determination of DER should start at current body weight using a species-specific factor that accounts for low activity. As the patient tolerates this intake, a gradual increase in daily calories can be attempted with a goal of feeding DER at a more optimal body weight. Based on individual assessment (including activity, attitude, age, prognosis, etc.) the DER factor typically ranges from low activity (1.1 to 1.3 x RER) to adult maintenance (1.4 x RER for cats and 1.6 x RER for dogs). Frequent recording of body weight and condition helps ascertain the appropriateness of the feeding plan.

Some underweight animals with cancer will stabilize at a less than optimal BCS (2/5 rather than 3/5). It may be difficult to achieve weight gain in these patients; therefore, the goal should change to maintaining this leaner body condition (Chapter 25, Accommodation).

How to Feed

Enteral feeding is the preferred route for providing nutritional support because it is less complicated and safer for patients fed at home. Additionally, enteral feeding is more physiologic because it improves intestinal mucosal thickness, stimulates gut trophic hormones and stimulates IgA production. Enhancing food palatability is the simplest means of increasing voluntary intake. A food can sometimes be made more palatable by heating to improve its aroma and mouth feel. Hand feeding critically ill, weak or depressed pets may enhance intake. Human companionship appears to increase the pet's interest in food. It

Box 30-5. Novel Foods, Ingredients and Cancer.

PROTEASE INHIBITORS

Much information suggests that soybean-derived Bowman-Birk inhibitor can inhibit or suppress carcinogenesis in vivo and in vitro. Extracts of the Bowman-Birk inhibitor suppress carcinogenesis in several animal model systems, including colon- and liver-induced carcinogenesis in mice, anthracene-induced cheek pouch carcinogenesis in hamsters, lung tumorigenesis in mice and esophageal carcinogenesis in rats. Bowman-Birk inhibitor concentration inhibits metastases and weight loss associated with radiation-induced thymic lymphoma in mice. Irradiated rodents treated with dietary Bowman-Birk inhibitor have fewer deaths, lower average grade of lymphoma and larger fat stores than controls. Various soy products produce dramatic protection against methotrexate (MTX)-induced enterotoxicity in rodent models.

One study was performed using a feline model of MTX-induced enteritis to determine the impact of purified foods containing intact protein sources (soybean protein or casein) or crystalline amino acids on intestinal structure and function. Cats receiving a commercially available (complex) food served as the control group. MTX administration was associated with severe enterotoxicity manifested by vomiting and diarrhea, especially in cats receiving crystalline amino acid and casein-based purified foods. Cats receiving the casein-based purified food had the largest decrease in total white blood cell (WBC) and platelet counts, the greatest villous atrophy (**Figure 1**) and the highest incidence of positive mesenteric lymph node and hepatic bacterial cultures (50 and 33%, respectively). Cats fed the soybean protein-based purified food had the least villous atrophy (**Figure 2**) and a significantly smaller magnitude of reduction in WBC counts compared with cats receiving the crystalline amino acid (**Figure 3**) and casein-based purified foods. Feeding complex (**Figure 4**) and soybean protein-based foods was also associated with the greatest secretagogue activity on plasma cholecystokinin (CCK) concentrations after ingestion of the respective meals, compared with concentrations in cats receiving the amino acid and casein-based purified foods. This study showed an association between feeding a soybean protein-based purified food and improved intestinal integrity. These findings might be associated with a greater secretogogue effect in stimulating trophic gut hormones such as CCK. In contrast, the casein-based purified food was associated with increased morbidity, villous atrophy, increased bacterial translocation and decreased secretogogue activity on CCK. Additional studies may determine the underlying mechanism of protection and the exact compound(s) responsible for soybean protein's protective effects.

POLYPHENOLIC COMPOUNDS AND FLAVONOIDS

Numerous health benefits result from consumption of diets rich in phytochemicals such as polyphenolic compounds. Polyphenolic compounds are potent dietary antioxidants and it is thought that

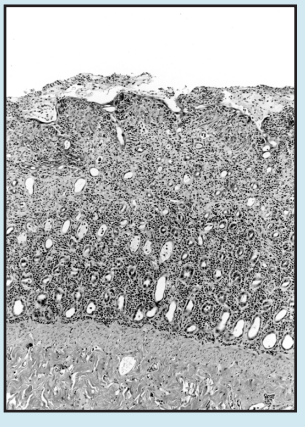

Figure 1.

Figure 2.

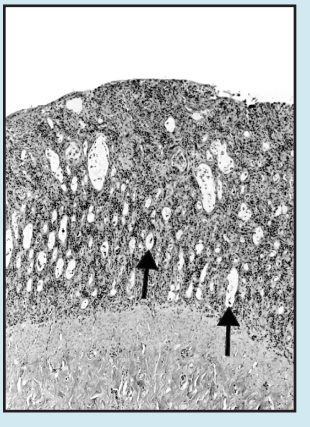

Figure 3.

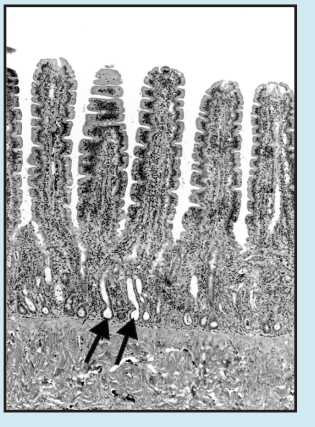

Figure 4.

Figure 1. Distal duodenal section obtained 72 hours postmethotrexate administration from a cat fed a casein-based purified diet. The villi are severely blunted and fused with multifocal ulceration. Crypt loss is marked and the remaining crypts are severely dilated.

Figure 2. Proximal duodenal section obtained 72 hours postmethotrexate administration from a cat fed a soybean protein-based purified diet. Villi have normal architecture and crypts are moderately dilated.

Figure 3. Proximal duodenal section obtained 72 hours postmethotrexate administration from a cat fed a purified diet containing free amino acids. Villi are completely effaced. The surface is covered with an intermittent layer of attenuated enterocytes. Crypts are severely dilated and distorted (arrows).

Figure 4. Distal duodenal section obtained 72 hours postmethotrexate administration from a cat fed a commercial food containing intact protein sources. Villi have normal architecture. Crypts in the lamina propria are moderately dilated (arrows).

(**Figures 1** to **4** adapted from: Marks SL. Dietary modulation of methotrexate-induced enteritis in cats. PhD Dissertation, University of California, Davis, 1996.)

Box 30-5 continued

the antioxidant properties of these compounds confer protection against certain chronic diseases such as cancer. Antioxidants may act directly by limiting oxidative stress and indirectly through preserving protective enzymatic pathways and modulation of signaling pathways. Flavonoids added to neoplastic cell lines have shown promising results. An interesting example is the phytochemical activity of pomegranate fruit. Pomegranate polyphenolic extracts inhibit growth in human leukemia cells, prostate cancer cell lines and suppress formation of chemically induced skin tumors and colon carcinogenesis in rodent models.

Supplementation of estrogen receptor sensitive and insensitive cells with a 1 or 5% commercial juice extract or fresh fruit extract inhibited in vitro cell proliferation by up to 90%. Although investigations to identify the mechanism(s) of action are ongoing, the potential for using natural food products to manage cancer patients is encouraging.

GARLIC

Epidemiologic studies have suggested a correlation between high garlic consumption and reduced risk of cancer. Garlic, garlic extracts and several thioalkyl compounds inhibit the activation of carcinogens and carcinogen-induced aberrations in the cell nucleus. Garlic extracts have an anti-promotion effect in animals exposed to carcinogens. Furthermore, garlic exerts direct cytolytic effects against cultured human breast cancer and melanoma cells. The concentrations of garlic used in these studies to arrest cancer cell growth had no effect on normal cells.

Pretreatment 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, dogs and cats.

The Bibliography for **Box 30-5** can be found at www.markmorris.org

has been suggested that critically ill patients often have a diminished will to live; their bodily energy and normal GI function including motility, digestion and absorption are likewise diminished. Building a patient's Zheng Qi, or bodily energy, has been addressed using herbs and herbal formulas. This approach to managing critically ill patients by enhancing use of enteral nutrition requires a substantial knowledge of herbs and drug interactions. References and individuals experienced in the area of veterinary botanical medicine are available for consultation by interested pet guardians. Acupuncture appears to have a cumulative "feel good" affect on pets following chemotherapy (Wurth, 2003). The better patients feel, the more likely they are to have interest in eating.

If necessary, drug therapy can be attempted before offering food. Administration of a benzodiazepine derivative (diazepam or oxazepam) or cyproheptadine increases appetite transiently; however, these drugs are unreliable for ensuring adequate caloric intake. Benzodiazepine derivatives are contraindicated in patients with severely reduced hepatic function, especially when signs of hepatic encephalopathy are present. In addition, the appetite-stimulating properties of these agents appear to wane with time when used in sick animals. Megestrol acetate causes weight gain and increases appetite in people with cancer. The clinical benefit of this drug in veterinary patients remains to be determined. Controlled studies with human cancer patients have revealed that cyproheptadine, corticosteroids and nandrolone decanoate have little to no impact on improving food intake, body weight and clinical outcome (Kardinal et al, 1990; Chlebowski et al, 1986; Willcox et al, 1984). A deficiency of B vitamins is associated with anorexia and may occur in some cancer patients fed unbalanced homemade foods or patients that have decreased food intake.

Assisted-feeding techniques should be considered if these appetite-stimulating efforts fail and/or the patient has not voluntarily eaten for three or more days. Enteral and/or parenteral techniques can be used for nutritional support while patients are hospitalized (Chapters 25 and 26). As noted in previous sections, before starting a treatment regimen (i.e., chemotherapy, radiation, surgery), an assisted-feeding device can be proactively placed to ensure adequate nutrition regardless of treatment side effects. Examples include placing a gastrostomy tube in patients with oral tumor resections or before radiation treatment to the nose, oral cavity or neck.

If feeding assistance is required at home, syringe or tube feeding (i.e., nasoesophageal, esophagostomy, gastrostomy tube) protocols can be established to allow the owner to successfully deliver nutritional support to the pet.

Parenteral nutrition (PN) is a more complex system in terms of formulation and delivery of the admixture, as well as patient monitoring (Chapter 26). PN is less physiologic with respect to gut health; however, evaluation of admixture supplementation with specific nutrients to promote gut integrity is ongoing (Burke et al, 1989; Sheng-Long et al, 1992), which may help promote the efficacy of PN for critically ill patients. Nevertheless, PN is generally reserved for patients that are unable to assimilate nutrients or those with intractable vomiting. An example is a patient with GI lymphoma that is stabilized with PN until remission is obtained with chemotherapy. Optimally, the next step would entail DER being met with a combination of PN and enteral nutrition. Eventually, as appetite and tolerance improve, the enteral route can be used exclusively. PN in human cancer patients is still controversial; some clinical trials have failed to demonstrate benefit, whereas others demonstrate a positive effect with respect to nutritional parameters, survival or tumor response (McGeer et al, 1990; Chlebowski, 1991). Large clinical trials have not been performed with veterinary cancer patients; however, one author (KES) has reported PN to be beneficial for managing individual canine and feline cancer patients. Benefits have been assessed by weight maintenance, enhanced immunocompetence and wound healing, improved attitude, maintenance of normoglycemia and hydration status and successful transition from the ICU to at home feeding.

REASSESSMENT

Reassessment of cancer patients should include monitoring the effects of: 1) cancer on the animal, 2) treatment and nutrition-

al management on the tumor and 3) treatment and nutritional support on the patient. The frequency of reassessment depends on each patient's treatment protocol, response to treatment, the complexity of the feeding plan and prognosis. Initially, reassessment may be required daily or multiple times per day. After the patient is discharged and managed at home, reassessment may be conducted weekly, monthly or quarterly until the patient's condition stabilizes.

Comparing the current body weight and BCS with previous assessments best assesses the overall effects of cancer, cancer treatment and nutritional management on the animal. The patient's appetite should be assessed and the daily caloric intake monitored closely. These parameters are most accurately assessed by frequent (daily) record keeping by the pet owner. The veterinarian can review these records and correlate them with recheck physical examination and diagnostic findings to ascertain the adequacy of the overall treatment and feeding plan. Additionally, nutrient status influences stabilization of organ function, protein status, leukocyte number, hydration, blood glucose and electrolyte status; these parameters are easily monitored through routine blood work and urinalysis. Additional markers of tumor growth and disease staging, which are currently more amendable to monitoring in a research setting, have been reviewed in previous sections. Appropriate modifications to the feeding plan should be made as the patient's status changes.

Food and feeding method changes may be part of the management plan. An important goal of assisted feeding is to transition the patient to voluntary intake. This can be facilitated by: 1) decreasing the amount of food administered and/or the feeding frequency and 2) offering an appropriate palatable form of food for voluntary consumption before, or in place of, the scheduled tube feeding. As the patient increases voluntary caloric intake, calories delivered via the assisted route should be decreased proportionately. After the patient is consuming 75% of DER calories voluntarily, assisted-feeding devices can be removed.

Patient management may require diet alternatives due to physiologic changes that result in food aversion or inability of the patient to consume a certain form of diet. In the case of suspected food aversion, first choose an alternate diet with novel protein sources. A second attempt might include increasing the fat and/or sodium content. If aversions persist with commercial diet options, consider a home-cooked diet.

Assess the patient's ability to adequately prehend and swallow the form of diet offered. Moist diets may be easier to consume in adequate amounts compared to dry kibble. Moistening dry food with warm water or a flavored broth may enhance intake.

ACKNOWLEDGMENTS

The authors and editors acknowledge the contributions of Drs. Gregory K. Ogilvie and Stanley L. Marks in the previous edition of Small Animal Clinical Nutrition.

ENDNOTE

a. Prescription Diet n/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

REFERENCES

The references for **Chapter 30** can be found at www.markmorris.org.

CASE 30-1

Diarrhea and Weight Loss in a Gordon Setter

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Patient Assessment

A seven-year-old, 23-kg, intact male Gordon setter was examined for anorexia, lethargy, diarrhea and weight loss of six weeks' duration. Physical examination revealed a depressed, cachectic dog (body condition score 1/5). The remainder of the physical examination was unremarkable except for mild dehydration (5%). Abnormal results of a complete blood count, serum biochemistry profile and urinalysis included hypoalbuminemia (2.1 g/dl, normal 2.8 to 3.5) and hypoglobulinemia (2.3 g/dl, normal 3.0 to 3.5). Thoracic and abdominal radiographs were normal. Intestinal lymphoma was confirmed based on histopathologic evaluation of biopsy specimens taken from the small intestine during flexible endoscopy of the upper gastrointestinal (GI) tract.

The cachexia was likely due to a combination of diminished caloric intake, malassimilation and altered metabolism secondary to malignancy (**Table 1**). The anorexia was probably associated with the intestinal lymphoma, secondary abdominal pain and hyperlactatemia. The dehydration and lethargy were probably secondary to the underlying problems causing cachexia.

Assess the Food and Feeding Method

The dog was normally fed one cup of a dry specialty brand food twice daily (810 kcal [3.39 MJ]) with occasional table foods. The food had the following nutrient profile (% dry matter basis):

Protein	29	Sodium	0.4
Crude fat	19	Phosphorus	1.3
Crude fiber	3.5	Potassium	0.6
Calcium	1.6	Magnesium	0.1
Chloride	0.5	NFE (carbohydrate)	44

Questions

1. What indices can be used to assess this dog's nutritional status in the face of severe cachexia?
2. What are the types and amounts of macronutrients that should be fed to this dog?
3. What is this patient's caloric requirement?
4. What food and feeding method should be used for this dog?

Answers and Discussion

1. Because anthropometric measurements are usually not performed in dogs and cats, nutritional status is determined by a thorough history and physical examination. Laboratory evaluation of total lymphocyte count, hematocrit and serum albumin and urea nitrogen concentrations can be helpful to further evaluate nutritional status. These parameters have limited usefulness because hypoalbuminemia and lymphopenia have many causes unrelated to nutritional status. Albumin also has a relatively long half-life (eight days in normal dogs) and is slow to respond to changes in nutritional status. In the face of severe intestinal malassimilation with marked hypoalbuminemia and ascites, body weight becomes an insensitive index. Body condition assessment is the best means of assessing nutritional status of patients with cancer.
2. Some tumor cells preferentially use carbohydrates and protein, but have difficulty using lipids. Host tissues can continue to oxidize lipids for energy. This phenomenon has led to the hypothesis that foods relatively high in fat benefit animals with cancer compared with foods high in easily digested carbohydrates. Dietary carbohydrates should be reduced to limit the tumor from metabolizing glucose for energy by anaerobic glycolysis with the formation of lactate as an end product. Fluid therapy to correct dehydration should avoid fluids containing lactate. High concentrations of carbohydrate may result in peripheral lactate production and energy loss by futile cycling through the Cori cycle. Other complications of excess dietary carbohydrate include hyperglycemia, hyperosmolar states, excess CO_2 production and hepatic steatosis. An appropriate formulation for supporting canine cancer patients contains 30 to 45% protein calories, 50 to 65% fat calories and fewer than 20% carbohydrate calories.
3. The estimated resting energy requirement (RER) for this dog at its current weight is RER = $70(BW_{kg})^{0.75}$ or 735 kcal (3.08 MJ). Daily energy requirement (DER) would be approximately 1,000 kcal (4.15 MJ) (1.35 x RER). This amount could be increased if activity level were higher or if weight gain was being promoted.
4. Although the cure for intestinal lymphoma remains elusive, it is clear that adequate, aggressive nutritional support is a key adjuvant to the treatment plan for cancer patients with chronic diarrhea. The enteral route is the preferred route of nutritional support because it is easier, less expensive and more physiologic than parenteral administration. However, some animals are temporarily unable to assimilate nutrients administered into the GI tract because of functional (severe malassimilation secondary to intestinal lymphoma), anatomic (short bowel syndrome) or mechanical (ileus or obstruction) reasons.

   Patients with intractable vomiting or diarrhea, severe malabsorption and severe pancreatitis may also benefit from parenteral nutrition (PN). PN is indicated in this dog because of the absence of available functional bowel to digest and absorb sufficient nutrients to promote recovery. It is well documented; however, that patients receiving long-term PN develop intestinal mucosal atrophy, bacterial translocation and reduced concentrations of secretory IgA.

   Beause enteral feeding improves mucosal thickness, stimulates gut trophic hormones and stimulates IgA production, partial enteral feeding via nasoesophageal intubation is recommended. PN can be used to supply the majority of the dog's energy and protein requirements, whereas enteral feeding can be used to help maintain intestinal mucosal integrity and limit bacterial translocation. Nasoesophageal tubes are an excellent first choice for the short-term (i.e., less than 10 days) enteral feeding of most critically ill dogs and cats. One disadvantage of nasoesophageal tubes is their small diameter (3- to 8-Fr. tubes), necessitating the use of a liquid enteral formula.

Treatment and Feeding Plan

PN was initiated on Day 2 of hospitalization at a rate of 20 ml/hr (50% of the estimated DER). The rate was increased to 40 ml/hr on Day 3 of hospitalization. The parenteral solution consisted of 8.5% crystalline amino acids, 20% lipid, 50% dextrose and B-complex vitamins. Body weight, attitude, rectal temperature and concentrations of serum total protein, glucose and electrolytes were monitored to allow for early recognition and management of complications. A multi-drug approach to treat lymphoma was started on Day 2 of hospitalization.

Nasoesophageal feeding was instituted on Day 3 using an energy-dense (1.3 kcal/ml, 5.44 kJ/ml) commercial enteral formula

(Prescription Diet a/d Canine/Feline[a]) that contains high levels of protein (44.2% dry matter [DM]), fat (30.4% DM), glutamine (5.2% DM), arginine (2.4% DM) and omega-3 fatty acids (2.6% DM). The enteral formula was tube-fed four times daily (50 ml per feeding) to supply 20% of the dog's estimated caloric requirement. Although low fat foods are better tolerated in a variety of GI disorders, the multiple small feedings and slow rate of administration were felt to abrogate this concern. The dog was receiving its DER on Day 4 of hospitalization through the combined use of enteral and parenteral routes. No complications were observed with the feeding regimen. The dog appeared brighter and had gained 1.1 kg of body weight.

The dog gained an additional 1.5 kg of body weight over the next four days of hospitalization and its attitude and diarrhea continued to improve. On Day 8 of hospitalization, the PN administration rate was decreased to 20 ml/hr (50% of estimated caloric requirement). In place of the nasoesophageal feedings, small frequent feedings of a moist commercial veterinary therapeutic food (Prescription Diet n/d Canine[a]) were given to meet 50% of the dog's caloric requirement. The dog was discharged 10 days after initial hospitalization following discontinuation of parenteral feeding. The moist veterinary therapeutic food was continued at home. DER was increased to 1,300 kcal (5.44 MJ).

The dog continued to do well throughout the rest of the induction period (six weeks), and was seen weekly for physical examinations, complete blood counts and chemotherapy administration. Apart from continued mild nonregenerative anemia, and mild neutropenia on Day 31, the dog maintained in complete remission and showed no adverse effects to chemotherapy. The dog had gained 6 kg of body weight at the end of the induction period (Day 45) and its body condition score had improved to 2/5. Reassessment on Day 180 revealed a bright, alert and responsive dog that appeared to be in complete remission.

Further Discussion

It is imperative that a cancer patient's response to dietary therapy be evaluated and modified if needed. The DER can vary by as much as 20% between different dogs with the same body weight and catabolic insult. Thus, the patient's caloric intake may need to be increased or decreased depending on body weight and condition. Long-term administration of chemotherapeutic agents such as prednisone or other immunosuppressive therapy could further worsen malnutrition and predispose patients to significant infective complications.

Endnote

a. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

Bibliography

Matus RE. Chemotherapy of lymphoma and leukemia. In: Kirk RW, ed. Current Veterinary Therapy X. Philadelphia, PA: WB Saunders Co, 1989; 482-488.

Table 1. Nutritional problems associated with gastrointestinal neoplasia.

Anorexia with progressive weight loss and dehydration
Taste changes causing reduced food intake
Alterations in fat, carbohydrate and protein metabolism
Intestinal malabsorption associated with:
Protein-losing enteropathy
Electrolyte and fluid loss

CASE 30-2

Chronic Vomiting in a Cat

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Patient Assessment

A 10-year-old, neutered female domestic shorthair cat was examined for persistent vomiting of 10 days' duration. The vomiting occurred most commonly after meals, was projectile at times and was becoming more frequent. Two months earlier, another veterinarian removed an "abscessed lymph node" found during an exploratory celiotomy that was performed to determine the cause of intermittent vomiting. Histopathology was not performed on the excised lymph node.

The cat appeared very depressed, slightly dehydrated and was breathing slowly (10 breaths/min.). Dried vomitus was adhered to its lower jaw and chest. Rectal temperature was 38.8°C (102°F). The pulse rate was 180/min. Mucous membranes were tacky and

pale pink. Body weight was 3 kg and the body condition score was 2/5.

A complete blood count, serum biochemistry profile, urinalysis, chest and abdominal radiographs and feline leukemia virus and feline immunodeficiency virus tests were performed. Results of these tests were negative or within normal limits except for the following values: hypoalbuminemia (2.1 g/dl, normal 2.8 to 3.5), hypochloremia (109 mEq/l, normal 118 to 125), hyponatremia (120 mEq/l, normal 147 to 156), hypokalemia (3.0 mEq/l, normal 4.0 to 4.5) and metabolic alkalosis (bicarbonate 39 mEq/l, normal 17 to 24). A dilated stomach and proximal duodenum were noted on radiographs. Very little abdominal fat was present. A tentative diagnosis of proximal gastrointestinal obstruction was made.

The metabolic problems were treated with intravenous fluids (0.9% NaCl with 40 mEq KCl/l) in anticipation of an exploratory celiotomy. A "napkin ring" stricture of the proximal duodenum was surgically resected. Intraoperative cytology and subsequent histopathology confirmed a diagnosis of intestinal lymphoma.

Assess the Food and Feeding Method

The cat was normally fed a commercial dry specialty brand cat food formulated for adult cats. The food was offered free choice.

Questions

1. Why is nutritional management important for recovery of this patient?
2. What short- and long-term feeding methods should be used for this patient?
3. Chemotherapy is indicated in this cat to control systemic disease. Can the adverse effects of chemotherapy be managed nutritionally?

Answers and Discussion

1. Hypoalbuminemia, reduced fat mass and less than ideal body condition indicate significant malnutrition in this patient. Cancer cachexia is associated with slow wound healing, decreased immune response, increased toxicity from chemotherapy and decreased survival. Nutritional support of cancer patients maximizes healing, decreases side effects of chemotherapy and prolongs the disease-free interval and survival.
2. Feeding tubes and enteral nutritional support should always be considered in cancer patients undergoing surgery. Placement of feeding tubes at the time of surgery is convenient and allows both short- and long-term nutritional management of patients. It is far easier to prevent development of cancer cachexia than to return a patient with cancer cachexia to a more normal state. Feeding tubes are also convenient to ensure that medications (e.g., antiemetics, antibiotics) are administered without the need for central venous access. Chemotherapy, radiation therapy and cachexia are associated with poor wound healing in cancer patients. Because of these factors, gastrostomy tubes may be associated with higher complication rates such as leakage and development of peritonitis. Esophagostomy tubes may be preferred in these types of patients for enteral nutritional support.
3. Well-controlled studies in human cancer patients show that adequate nutritional support is associated with decreased toxicity from chemotherapy. Although similar studies have not been performed using dogs and cats, it is likely that side effects of chemotherapy would also be minimized in animals receiving appropriate food in adequate amounts.

Progress Notes

Jejunostomy and esophagostomy tubes were placed during surgery. Within 24 hours after surgery, feeding was started with a commercial human liquid food (Osmolite HN[a]) supplemented with protein (Promod[a]). Chemotherapy was started for lymphoma even though no obvious disease was found outside the intestinal tract. The cat was treated initially with cyclophosphamide, vincristine, prednisone and doxorubicin at the time of suture removal.

As soon as vomiting subsided (one week after surgery), jejunostomy tube feeding was discontinued and feeding through the esophagostomy tube was initiated. Metoclopramide was given via the tubes as needed to control further vomiting. After four weeks, the cat had gained weight and was able to maintain improved body condition with voluntary oral feeding of a veterinary enteral product (Prescription Diet a/d Canine/Feline[b]). This food was fed for three months during chemotherapy. The original dry specialty food was fed when chemotherapy was discontinued. The cat has remained in clinical remission for three years.

Endnotes

a. Ross Laboratories, Columbus, OH, USA.
b. Hill's Pet Nutrition, Inc., Topeka, KS, USA.