REGIONAL CANCER THERAPY – THE 4TH PILLAR:
CAN WE IMPROVE LOCAL RESULTS?
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Non-resectable and metastatic tumors present a difficult challenge for veterinarians and pet owners. The relatively limited efficacy of intravenous chemotherapy for macroscopic disease, and the cost and morbidity associated with radiation therapy have stimulated the search for additional therapeutic options. Similar difficulties in human oncology have inspired various creative, image-guided, regional tumor therapies in the continuously developing subspecialty of interventional radiology (IR). IR involves the use of contemporary imaging techniques such as fluoroscopy and ultrasonography to selectively access vessels and other structures in order to deliver different materials for therapeutic reasons. In the past two decades, IR techniques have expanded considerably with both vascular and non-vascular procedures being performed routinely in humans. Specifically, IR techniques are being increasingly utilized to help palliate humans with cancer in which traditional therapies have failed or have been demonstrated to provide little benefit. These techniques are particularly useful in cases of regional disease in order to maximize local therapy and minimize systemic toxicity. While results have been variable, regional techniques such as percutaneous tumor ablation, intra-arterial chemotherapy, transcatheter arterial embolization/chemoembolization, and/or palliative stenting have been demonstrated to improve survival times, disease-free intervals, recurrence rates, or completeness of tumor necrosis (Additional references available from author upon request).

Traditional Therapies

Traditional treatment modalities still remain an important part of managing patients with metastatic or non-resectable cancers. Systemic chemotherapy typically demonstrates poor response rates for most bulky tumors or metastatic disease, however can occasionally shrink excessively large tumors enabling subsequent resection. Radiation therapy is routinely used for palliation of pain associated with bony tumors and is useful for carcinomas and oral tumors but internal tumors and sarcomas are more difficult to treat. Surgery can still play a major role in animals with advanced malignancies, even when tumor excision is not possible. De-bulking non-resectable tumors or closing ulcerated masses may occasionally be indicated, but is typically avoided as the patient’s quality of life is often not substantially improved in these situations, and surgical complications are not uncommon.

Palliative Stenting for Malignant Obstructions

Animals are routinely euthanized for local effects of a tumor rather than the systemic effects associated with a large cancer burden. For example, malignant obstructions of the urinary tract associated with transitional cell carcinomas or prostatic tumors can result in life-threatening signs associated with complete urinary tract obstruction. IR techniques involving the placement of intra-luminal stents to palliate similar malignant obstructions in humans have been described. Palliative stenting procedures in the urinary tract (Figure 1), respiratory tract, and upper and lower gastrointestinal tracts to relieve luminal obstructions due to neoplasia in animals as small as a ferret have recently been performed under...
fluoroscopic guidance. These IR techniques were rapid, safe, minimally-invasive, and effective, and complications were minor and uncommon.

**Intra-Arterial Chemotherapy Delivery**

Current therapies for bulky tumors not amenable to complete surgical include chemotherapy, radiation therapy, and surgical debulking, but none are able to consistently produce durable remissions. Research suggests that some of these tumors can respond more favorably to higher concentrations of chemotherapy, however significant deleterious side effects often result when dose escalations are attempted. Recent advancements in interventional radiology techniques now enable veterinarians to administer different drugs into the arteries feeding the actual tumors via minimally-invasive approaches in order to achieve very high regional drug concentrations within the tumor without the systemic side effects that would occur had these levels been administered intravenously. This basically provides a local dose escalation without the increased systemic toxicities. Studies confirm both higher achieved levels of chemotherapy within the targeted tissues as well as improved tumor remissions in laboratory animals. It is possible that we can demonstrate similar effects in our canine patients with naturally occurring tumors not amenable to currently available standard-of-care treatments.

**Arterial Embolization / Chemoembolization**

“Embolotherapy” involves the use of fluoroscopy to selectively access specific vascular structures in order to deliver particulate material to control hemorrhage, occlude vascular malformations, or reduce tumor growth. Arterial embolization techniques using polyvinyl alcohol particles or other materials have been performed in veterinary patients to control intractable epistaxis associated with nasal tumors, to reduce hemorrhage associated with non-resectable tumors, or to control pain and slow tumor growth of metastatic cancer. In some cases, subsequent surgical resection was possible following the embolization-induced tumor shrinkage (Additional references available from author upon request).

Chemoembolization involves super-selective intra-arterial chemotherapy delivery in conjunction with subsequent particle embolization. Intra-arterial chemotherapy has been shown to result in a 10- to 50-fold increase in intra-tumoral drug concentrations when compared to systemic intravenous chemotherapy administration. Subsequent particle embolization results in tumor cell necrosis and paralyzes tumor cell excretion of chemotherapy resulting in minimized systemic toxicity. This procedure is most commonly used in the treatment of diffuse hepatocellular carcinoma or metastatic liver disease in humans. Most hepatic tumors depend upon hepatic arterial blood supply (up to 95%) for growth in contrast to the normal liver parenchyma that receives the majority of its blood supply via the portal vein (only ~20% from the hepatic artery). Hepatic artery embolization should theoretically cause more ischemia to the liver tumor while the remaining normal hepatic parenchyma obtains sufficient oxygenation from the portal venous system. In addition, when used within the liver, the chemotherapy is often typically mixed with a carrier agent, Ethiodol (Savage Laboratories, Melville, NY). This oily substance supplies radiographic contrast to the chemotherapy as well as acting as a tumor localizer and embolic agent. Hepatic tumors lack Kupffer cells which are important for metabolizing oily substances (lipid) in normal hepatic parenchyma. Therefore, the
Ethiodol and accompanying chemotherapy are concentrated within the liver tumor rather than the surrounding healthy hepatic parenchyma. More recently, chemotherapy-eluting beads are being evaluated in veterinary patients with nonresectable liver tumors (Figure 2).

Reported complications in the human literature include hemorrhage at the vascular access site, non-target embolization complications (skin necrosis, damage to normal parenchyma), hepatic infarction/abscessation, acute renal failure (for liver tumors), and post-embolization syndrome, a collection of clinical signs characterized by malaise, fever, and pain.

Percutaneous Tumor Ablation

Percutaneous tumor ablation techniques (radiofrequency ablation as well as microwave ablation, laser thermal ablation, cryoablation (Figure 3), and percutaneous ethanol injection) tend to be most effective with a few (<3), small (<4 cm diameter) lesions. These circumstances are fairly uncommon in the author’s clinical experience, however with the routine use of more advanced imaging techniques in veterinary medicine, lesions of this size and number may become increasingly apparent during tumor re-staging procedures, making tumor ablation techniques a reasonable option in the future. More recently, advances in local ablation technology have provided the ability to more closely monitor the areas of ablation as well as to provide larger ablation areas. We are currently evaluating the use of some of these techniques for head and neck tumors, and other soft tissue tumors in areas not easily amenable to aggressive surgical excision.

References