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## **FROM TOP TO BOTTOM: CANINE GASTROINTESTINAL TUMORS**

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### **INTRODUCTION**

Tumors of the stomach, intestines, and perineum are common in dogs. Physical examination, ultrasonography, contrast radiography, endoscopy, CT, and surgical exploration all play vital roles for localization and diagnosis but it is beyond the scope of this lecture to discuss the benefits, and limitations of these tests. This lecture will focus on the common gastrointestinal tumors in dogs and how surgery, chemotherapy, radiation therapy, and combinational therapy, can be used to effectively manage tumors in these locations.

### **GASTRIC CANCER**

**Incidence and Signalment** – The most common tumor of the stomach is adenocarcinoma. Other gastric tumors include adenomas, leiomyomas, leiomyosarcoma, lymphoma, other sarcomas, carcinoids, mast cell tumors, and plasma cell tumors. Gastrointestinal stromal tumors (GISTs) have been described in the stomach, and were likely previously classified as leiomyosarcomas. GISTs express c-KIT, a tyrosine kinase receptor and mutations in c-KIT play a role in tumorigenesis of this cancer. Also, c-KIT immunohistochemistry may be helpful to distinguish this tumor from other gastrointestinal smooth muscle tumors. Most carcinomas occur in the lower two-thirds of the stomach, particularly the pylorus. Most affected dogs are older (median age = 10 years) and there is a male predominance (2-3:1). Chow Chows have a 40X risk of gastric carcinoma compared to the general population.

#### **Gastric Carcinoma**

*Biological Behavior* – Gastric adenocarcinomas often involve a large area of the stomach wall and surgical resection may be difficult. They arise in the mucosa, but most often extend to or through the serosal. Ulceration is common. The metastatic rate is high; >75% of dogs will have metastases to gastric lymph nodes, peritoneum, liver, and other viscera.

*Treatment and Prognosis* – Surgery: Advanced size at diagnosis, diffuse nature, and high metastatic rate usually lead to a poor outcome with surgery alone. Procedures such as side-to-side gastrojejunostomy, gastroduodenostomy (Billroth I), and even complete gastrectomy have been reported. Survival times are generally short – usually 2-4 months. Chemotherapy: Results of chemotherapy remain anecdotal. Protocols containing 5-fluorouracil, cyclophosphamide, doxorubicin or cisplatin are reasonable choices.

#### **Gastric Leiomyoma / Leiomyosarcoma**

*Biological Behavior* – Leiomyomas are usually discreet and solitary. Leiomyosarcomas are invasive and approximately 30% may metastasize. Paraneoplastic hypoglycemia has been reported.

*Treatment and Prognosis* – Surgery: Leiomyomas can be easily “shelled out” and dogs will be cured after complete excision. Due to their invasive behavior, the prognosis for leiomyosarcoma is guarded. Tumors can recur locally after incomplete excision or even after an apparent complete excision. Median survival after surgery might be approximately 1-year. Chemotherapy – Chemotherapy remains anecdotal. Reasonable choices include protocols containing doxorubicin, platinum agents, and ifosfamide.

### **Gastrointestinal Stromal Tumors (GIST)**

*Biological Behavior* – Approximately 30% of GISTs will metastasize.

*Treatment and Prognosis* – Surgery: Outcome after surgery is probably similar to that described for gastrointestinal leiomyosarcoma. Chemotherapy: In people, GISTs may respond to c-KIT inhibitors (eg. Gleevec). When safe and affordable c-KIT inhibitors become available, their role for treatment of canine GISTs will need to be evaluated.

## **SMALL INTESTINAL TUMORS**

**Incidence and Signalment** – Adenocarcinoma, leiomyosarcoma, and lymphoma are the most common canine intestinal tumors. Less common tumor types include leiomyoma, other sarcomas, GISTs, carcinoids, plasma cell tumors, and mast cell tumors. Intestinal tumors occur in older dogs (median age = 10 years). There might be a slight male predilection and collies and German shepherds might be overrepresented, especially for adenocarcinoma of the small intestines.

### **Intestinal Adenocarcinoma**

*Biological Behavior* – The metastatic rate for adenocarcinoma of the small intestines might be as high as 70%. Most common metastatic sites are mesenteric lymph nodes, liver, omentum, and lungs. Nearly half of small intestinal carcinomas express COX-2. Nonsteroidal inhibitors, such as piroxicam, might play a role in their treatment but no studies are available.

*Treatment and Prognosis* – Surgery: Surgical resection is the primary treatment. Without the presence of metastases, median survival is 10 months. When metastases are diagnosed during surgery, median survival is 3 months. Chemotherapy: Results of chemotherapy for intestinal adenocarcinoma have rarely been reported. Doxorubicin and cisplatin have anecdotal efficacy.

### **Small Intestinal and Cecal Leiomyosarcoma**

*Biological Behavior* – Approximately 30% of intestinal leiomyosarcomas will metastasize. The liver is the most common site for metastasis, but lymph nodes,

omentum, and lungs might also be involved. Paraneoplastic hypoglycemia has been reported in dogs with intestinal leiomyosarcomas as well as other syndromes including diabetes insipidus and erythrocytosis.

*Treatment and Prognosis – Surgery*: Surgical resection is the primary treatment. Without the presence of metastases, median survival is 12 months. The prognosis for leiomyosarcoma of the cecum may be shorter (8 months). When metastases are diagnosed during surgery, median survival is 3 months. *Chemotherapy* – Chemotherapy for intestinal leiomyosarcoma remains anecdotal (see gastric leiomyosarcoma).

**Gastrointestinal Stromal Tumors (GIST) - See above.**

## **LARGE INTESTINAL TUMORS**

**Incidence and Signalment** – Most large intestinal tumors occur in the rectum (colorectal). Approximately 10% may occur in the colon. Adenocarcinomas are the most common tumors of the large intestines. Leiomyosarcomas, leiomyomas, lymphoma, and plasmacytomas of the rectal wall occur less commonly. The median age at diagnosis is 11 years. There are no breed or gender predilections.

### **Colorectal Tumors**

*Biological Behavior* – There is a clear clinical and molecular progression from colorectal polyp, to adenoma, to carcinoma *in situ*, to invasive colorectal carcinoma. Colorectal carcinomas have a very low metastatic potential.

*Treatment and Prognosis – Surgery*: Due to possible progression to a malignant phenotype, adequate resection of colorectal polyps, adenomas, and carcinoma *in situ* is recommended. Cryotherapy and other techniques such as electrocoagulation and Nd:YAG laser have been described. Recurrence is uncommon unless polyps are multiple or diffuse. The prognosis for dogs with colorectal carcinoma is highly dependent on the extent of disease. Dogs with single, pedunculated colorectal carcinomas have an average survival of 32 months and local recurrence may occur in 50%. Dogs with multiple, cobblestone nodules have an average survival of 12 months. Dogs with annular tumors have average survival of 2 months. *Other treatment modalities* – Chemotherapy has a minimal role in the treatment of colorectal carcinoma since the disease is most often only localized. Radiation therapy is seldom used because of intestinal motility and toxicity, but can be considered for distal lesions. COX-2 may be a therapeutic target but there is only limited information available.

## **ADENOCARCINOMA OF THE ANAL SAC**

**Incidence and Signalment** – The average age of dogs with anal sac carcinomas is 10 years and there is no gender predilection. English cocker

spaniels, Springer spaniels, and Cavalier King Charles spaniels appear to be predisposed. 25-50% of dogs may have paraneoplastic hypercalcemia secondary to production of parathyroid hormone-related peptide (PTH-rp) by tumor cells. Owners might notice a rectal mass or tenesmus. Dogs with hypercalcemia might be PU/PD, inappetent or vomit. Importantly, in up to 60% of dogs, the tumor is found incidentally during a routine physical examination.

*Biological Behavior* - Primary tumors can be well-encapsulated and confined to the anal sac or large and infiltrative into perineal soft tissues. At diagnosis, approximately 50% of dogs will have metastases and ultimately, approximately 80% of dogs will develop metastatic disease. Metastases to the sublumbar and iliac nodes can occur early. Other frequent sites for metastases are liver and lungs. Less frequent sites are spleen, bones (lumbar vertebrae, other bones), and inguinal or popliteal nodes. A high index of suspicion for metastatic disease can be made by examining surgical biopsies for the presence of lymphatic invasion by tumor cells, although this association has not been confirmed.

*Treatment and Prognosis* – Surgery should be done to remove the primary mass. Palpation to distinguish noninvasive from invasive tumors may provide information about the potential success for surgery. Dogs with small (<2.5-cm), completely excised tumors and no metastases will have long survivals. In one study, the median survival was over 3 years. Dogs with larger (>2.5-cm) primary tumors can still be well-controlled with an adequate surgical excision; median survival is 2 years. The prognosis is likely worse for tumors that are incompletely excised or are very large at diagnosis. In one study, dogs with tumors >10-cm<sup>2</sup> had a median survival of 8 months. Adjuvant radiotherapy is indicated if surgical margins are incomplete. Dogs with metastases to only iliac lymph nodes might still be candidates for surgery. If metastatic lymph nodes are small (<4.5-cm) and the primary tumor is likely to be completely excised, the surgery should be considered for both sites. If the outcome of removal of the primary tumor is uncertain, then I usually “stage” the two procedures. In one study, dogs with small primary tumors and metastatic lymph nodes treated with aggressive surgery had a median survival of approximately 1.5 years. Due to metastatic disease, adjuvant chemotherapy is indicated and may further improve tumor control. Most response have been observed when platinum agents (cisplatin, carboplatin) have been used to treat dogs with anal sac carcinomas. Doxorubicin may also have efficacy. Adjuvant radiation therapy to an incompletely resected primary tumor bed and lymph node bed may also play a role. Additional tumor control when chemotherapy or radiation therapy are used in these multi-modality regimens is still unclear. The presence of large iliac lymph nodes or hypercalcemia is likely associated with a worse prognosis; median survival times are < 8 months. Finally, dogs with distant metastases have a very poor prognosis; survival times are usually 2-6 months. Chemotherapy can be considered as a sole modality in select cases. Additional therapies might be needed for dogs with hypercalcemia, either pre-operatively or if surgery is not an

option (eg. distant metastases). Corticosteroids or drugs that inhibit osteoclast activity (eg. pamidronate) might provide temporary resolution of hypercalcemia.