Feline oral squamous cell carcinoma (FOSCC) is the most common oral tumor in cats, accounting for 70% to 80% of all oral tumors. Squamous cell carcinoma (SCC) arises from the normal squamous epithelium of the oral cavity.

**RISK FACTORS**
The underlying cause of carcinogenesis is unknown, but potential risk factors include:
- Feeding of canned foods, particularly canned tuna
- Use of flea collars
- Cigarette smoke exposure.

In a study evaluating these risk factors, cats that consumed canned food had a 3.6× increased risk for oral SCC, while those that consumed canned tuna had a 4.7× increased risk. The proposed mechanism for this association has been an increased rate of dental disease or differences in food content, but further studies are needed.

Use of flea collars was associated with a 5.3× increased risk for oral SCC, possibly due to oral carcinogen exposure during grooming.

A common genetic cause may be the loss or mutation of the p53 tumor suppressor gene, which helps regulate the cell cycle in the presence of DNA damage. Exposure to environmental tobacco smoke has been associated with a 4.5× increased risk for p53 mutation on FOSCC biopsy results.

Human papillomavirus is a risk factor for head and neck SCC in humans, but no association has been made with FOSCC.

**CLINICAL PRESENTATION**

**Clinical Signs**
Common clinical signs of FOSCC may include inappetence or dysphagia, halitosis, increased drool or oral discharge, or blood present in the food or water dish. Signs, such as weight loss, decreased grooming, or increased hiding, may be subtle and nonspecific.
Physical Examination

FOSCC can arise in the sublingual area, lips, maxilla, or mandible (Figures 1 to 3) and behaves in a locally aggressive fashion, with extensive tissue invasion, including invasion of adjacent bone.

Masses may be incidentally found during dental examination and cleaning (Figures 4 and 5). Underlying neoplasia should be suspected during dental evaluation when focal areas of extreme dental disease or tooth mobility are present or when nonhealing lesions remain after dental biopsy.5

Rostrally located tumors may be more readily noticed by an owner, leading to earlier detection and potentially more effective treatment. Tumors located within the caudal oral cavity may pose an increased risk for metastasis because of increased density of lymphatic and vascular channels.6
Metastasis is generally considered rare; however, a recent study of 49 cats assessed via 3-view thoracic radiography and mandibular lymph node aspiration found metastasis in 10% and 31% of patients, respectively. 

**DIAGNOSIS**

A cat with an oral mass or a suspected oral mass requires examination under sedation to:

- Obtain the best estimates of size and location of the mass
- Assess for bone invasion and possible extension into the lymphatics, including the tonsils.

**Biopsy**

A punch or wedge biopsy may be completed under the same sedation as the oral examination, although complications, including jaw fractures, delayed wound healing, or secondary infection, may result from the often friable and necrotic nature of this tumor. In addition, ideally the biopsy should be completed in such a way that the biopsy tract can be removed or treated with local therapy; for example, a biopsy should not be taken through the lip if that area is not otherwise involved.

Owners should be counseled about the risk for an increase in oral discharge or hemorrhage as a result of the biopsy procedure. Occasionally, fine-needle aspiration is sufficient for diagnosis and can be attempted before biopsy.

**Cytologic Assessment**

Cytologically, SCC typically appears as round to irregularly shaped squamous cells that occur individually or in small clusters (Figure 6). The

**Staging Feline Oral Squamous Cell Carcinoma**

Staging tests to evaluate for metastasis can be readily performed during biopsy of the primary mass and include:

- **Fine-needle aspiration** of the mandibular lymph nodes (ideally both ipsilateral and contralateral lymph nodes because lymphatic drainage for the oral cavity is not strictly one-sided)
- **Thoracic radiography.** Even if the lymph nodes appear normal on palpation or computed tomography (CT), aspirates should be obtained because studies of other head and neck cancers have shown discrepancies between lymph node size and presence of metastatic disease. 

In older patients, a minimum database for general health screening—complete blood count, serum biochemistry profile, and urinalysis—is advisable. Rarely, cats with FOSCC can present with hypercalcemia. 

Skull radiography can be performed but is limited by superimposition of tissues and the need for heavy sedation or anesthesia. CT proves more informative, if available, because it can show the extent of disease for treatment planning (surgery or radiation) (Figure 7). Including the thorax in the CT examination is recommended to evaluate for possible pulmonary metastatic disease. 

Most important, if radiation therapy is a treatment consideration, the CT scan should be obtained at the same facility where treatment will be administered because CT may be required for radiation planning and set-up.
cytoplasm is usually pale to deep blue, with a “ground glass” appearance.

Malignant squamous cells can be distinguished from normal squamous epithelium by the retention of nuclei and more pronounced anisocytosis and anisokaryosis.

Inflammatory cells may or may not be present. In the case of severe inflammation, normal squamous cells can undergo dysplastic changes that may mimic neoplastic changes, which is one of the reasons biopsy is recommended.

**SURGICAL THERAPY**

Surgery is considered first-line therapy for most local cancers, including FOSCC.

**Surgical Challenges**

Surgical management of FOSCC faces many challenges, including the commonly occurring sublingual location, invasion of bone, late detection, and advanced tumor stage. Surgical excision to achieve adequate surgical margins, or even to resect gross disease, is usually limited given the small stature and anatomy of the cat skull. Furthermore, unlike dogs, cats do not tend to tolerate aggressive oral surgery without significant morbidity.

**In the Literature**

A study evaluated 42 cats that underwent mandibulectomy for management of oral neoplasia, 21 of which were diagnosed with SCC:

- 72% experienced dysphagia or inappetence postoperatively
- 12% never regained the ability to eat
- 41% required placement of enteral (esophageal) feeding tubes.

The overall complication rate in the acute setting was 98%, while 78% of cats had long-term side effects; complications included tongue protrusion, ptysalism, mandibular drift, and difficulty grooming, in addition to the previously mentioned dysphagia and inappetence (Figures 8 and 9).

Despite these risks, 83% of owners were pleased with the outcome and stated that they would pursue mandibulectomy again. In this study, cats...
with FOSCC had a decreased median survival time compared with cats that had other tumor types (217 days versus median not reached in cats with fibrosarcoma or odontogenic tumors).

Other studies have reported similar outcomes and complication rates. Median survival in these reports has ranged from 1 to 10 months in cats treated with surgery alone. The longest reported survival, 14 months, occurred in a study evaluating the combination of surgery and definitive radiation therapy.¹¹

Postoperative Radiation Therapy

The role of postoperative radiation therapy is to sterilize or slow the growth of residual microscopic disease that often remains after surgical resection of even the smallest tumors. Unfortunately, FOSCC is often locally advanced at time of diagnosis; as a result, surgery is not a viable option for most affected cats.

Client Education

Owners should be adequately counseled about the risk for postoperative complications when surgery is being considered. CT and consultation with a soft tissue or oral surgeon are useful to help determine whether surgery is feasible in a particular patient.

RADIATION THERAPY

When surgery is not pursued due to anatomic limitations or owner preference, radiation therapy can usually be considered.

Definitive versus Palliative

In general, radiation therapy can be used to treat cancer with definitive (curative) or palliative intent:

• Definitive protocols involve daily radiation treatments for 2 to 4 weeks
• Palliative courses are shorter with less frequent treatments.

Palliative-intent radiation therapy has the primary goal of alleviating pain and clinical signs associated with the tumor rather than sterilizing a maximum number of cancer cells. Disease regression or extending patient survival is not necessarily expected, although alleviation of clinical signs and discomfort can inherently lead to increased survival times.

Side Effects

With definitive-intent radiotherapy, early radiation side effects, such as mucositis and moist desquamation, are more prevalent, while late side effects, such as fibrosis, bone necrosis (osteoradionecrosis), and cataracts, are rare.

With palliative-intent radiotherapy, the incidence of early side effects is low, which is in line with the palliative goal of the treatment. While the risk for late-term side effects may be increased in this setting, these complications are generally expected to occur beyond the anticipated survival of the patient.

Interestingly, in our clinical experience, cats generally appear to have a higher tolerance for radiation than dogs. Given similar radiation treatments, the risk for early or late effects in cats is lower than that in canine patients.

Definitive Therapy Results

Due to the combination of hypoxia and necrosis in most tumors, SCC is considered relatively radioresistant, with decreased responsiveness to radiation.⁷,¹⁶ In addition, rapid cell proliferation/regrowth has been noted between radiation treatments, contributing to poor long-term tumor control.

Various definitive protocols have been investigated, including accelerated radiation delivery; but despite attempts to optimize radiation schedules, definitive radiation has failed to achieve a significant survival benefit.¹⁶-²² Given the aggressive nature of FOSCC and poor responsiveness to definitive radiation, the focus of radiotherapy often centers on palliation in most cats.

Palliative Therapy Protocols

Several different palliative or hypofractionated radiation protocols have been evaluated in the veterinary literature. Most reports suggest a median survival time of 2 to 4 months, with approximately 50% of cats experiencing palliation.¹⁶-²¹

At our institution, the typical palliative protocol involves 4 fractions of 8 Gray given once weekly to a total radiation dose of 32 Gray. The 1-week interval between fractions allows the mucosal lining of the oral cavity and external skin to heal, minimizing early side effects.

In a study¹⁷ evaluating 54 cats treated with similar hypofractionated protocols, the overall median survival time was 113 days. The addition of chemotherapy did not improve clinical outcomes.¹⁶,¹⁹

Another palliative protocol of 5 fractions of 4 Gray given over the course of 1 week (Monday through Friday to a total of 20 Gray) has been evaluated, and cats with FOSCC had an overall response rate of 54.5%. The median progression-free survival time and median survival time were brief for this protocol (1.8 months and 3 months, respectively).²¹

In smaller, nonresectable SCC lesions (size < 2 cm), a more aggressive radiation protocol of 10
fractions of 4.8 Gray (48 Gray total) given Monday through Friday for 2 weeks has been associated with the best reported clinical outcome after radiotherapy.\textsuperscript{22} In a small study of 21 cats:\textsuperscript{22}

- The overall median survival time for this protocol was 174 days.
- Cats with T1 lesions (\(n = 4\)) had a favorable median survival time of 590 days.
- All cats experienced grade 2 oral mucositis secondary to radiation therapy (defined as patchy mucositis with patient seemingly pain free\textsuperscript{23}), which was effectively managed with oral antibiotics and pain medications.
- All patients prophylactically received esophageal feeding tubes for management of early radiation side effects.

For most cats with FOSCC, palliative radiotherapy is a logistically feasible treatment approach associated with minimal side effects. Unfortunately, clinical benefit is achieved in only about half of patients and is short-lived in most animals that respond favorably.

**CHEMOTHERAPY**

FOSCC is considered resistant to traditional cytotoxic chemotherapy agents. High levels of necrosis within these tumors limit chemotherapy delivery to cancer cells and lead to increased chemotherapy resistance.\textsuperscript{1} Because chemotherapy kills a fraction of actively dividing cancer cells with each dose, the presence of large, bulky tumors in most patients means that chemotherapy will likely have only minimal effect, if any.\textsuperscript{1} Various IV or locally administered chemotherapy agents, including bleomycin, carboplatin, doxorubicin, gemcitabine, and mitoxantrone, have been used, with minimal to no benefit.\textsuperscript{1,7}

**TYROSINE KINASE INHIBITOR**

Toceranib phosphate (Palladia, zoetisus.com) is a small-molecule inhibitor that targets receptor tyrosine kinases, including C-kit, vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and Flt-3. Tyrosine kinase receptors are transmembrane receptors that control downstream cellular functions, such as replication, growth, differentiation, and angiogenesis.

Although the drug was originally marketed and licensed for the treatment of canine mast cell tumors, activity against a variety of canine and feline solid tumors, including oral SCC, has been demonstrated with off-label use.\textsuperscript{24}

A study\textsuperscript{25} of cats with oral SCC compared toceranib phosphate treatment with no treatment:

- Those that received toceranib phosphate had a longer median survival time (145 days versus 45 days).
- Of those that responded to toceranib phosphate (with response defined as stable disease or better), median survival time was 201 days.
- Anorexia was the most common adverse event, occurring in 70% of cats. Most anorectic episodes were transient and mild, and no cats required medical intervention.
- Other reported adverse events included afebrile, low-grade neutropenia; elevation of liver enzymes; and progressive azotemia.

A major limitation and potential confounding factor of this study was the allowance of nonsteroidal anti-inflammatory drugs (NSAIDs) in both the treatment and control groups. Progressive azotemia was seen only in patients receiving concurrent toceranib phosphate and NSAIDs; therefore, the contribution of each medication is difficult to elucidate.

Overall, toceranib phosphate appears to be well tolerated in cats. Among various studies, reported adverse events have included anorexia, other gastrointestinal signs (such as vomiting and diarrhea), lethargy, anemia, and liver enzyme elevation; most of these side effects were considered mild.\textsuperscript{25-27}

Further studies are needed to determine whether toceranib phosphate, alone or in combination with chemotherapy or radiotherapy, has a role in the treatment of FOSCC.

**MEDICAL MANAGEMENT**

**NSAIDs**

Cyclooxygenase-1 and -2 (COX-1 and -2) have been demonstrated to be upregulated in FOSCC.\textsuperscript{28} In neoplasia, upregulation of COX can lead to increased cellular proliferation, growth, invasion, and angiogenesis. Therefore, use of COX-inhibiting anti-inflammatory medications may have several beneficial effects in cats with SCC, including:

- Pain relief
- Reduction of neoplasia-associated inflammation and edema
- Potentially, anticancer effects, such as disease response or stabilization.

No studies have assessed the response of FOSCC to NSAIDs alone, although in one study NSAID use was associated with a 2-fold reduction in the hazard ratio for death.\textsuperscript{29} Clinical experience suggests that, while NSAID use may have a short-lived palliative effect in some cats with FOSCC, significant tumor responses are not observed.
Currently, meloxicam is the only NSAID licensed for use in cats in the United States, and only as a 1-time injection for perioperative pain (0.5 mg/kg). A “black box” notice warns against repeated use of meloxicam given the risk for acute kidney injury. However, in Australia and Europe, low-dose meloxicam (0.01–0.03 mg/kg Q 24 H) has been evaluated for use in cats with osteoarthritis. This and many other studies have assessed the safety and efficacy of this dosing and have found no progression of azotemia, even in cats with pre-existing renal disease. Another study showed no increased risk for death in cats with pre-existing renal disease that received meloxicam versus those without pre-existing renal disease. In our opinion, cats with FOSCC are good candidates for meloxicam. As previously stated, using this medication has many potential benefits, especially increase in patient comfort. These patients are more likely to die of FOSCC progression than of renal disease. Of course, the risks and benefits of every medication should be assessed on an individual patient basis and thoroughly discussed with the pet owner.

Other Medications
Other oral medications can be used to increase patient comfort and control clinical signs of disease. The most commonly used and effective oral pain medication in cats is buprenorphine. This synthetic opioid acts as a partial mu agonist. It is especially beneficial in cats given its ability to be administered and fully absorbed across mucous membranes. Recommended dosing is 0.01 to 0.03 mg/kg Q 8 H.

Oral antibiotics may help treat infections of tumor tissue secondary to normal oral flora, which can cause increased clinical signs and often be mistaken for disease progression. In general, antibiotics that penetrate bone and/or have anaerobic spectrum activity, such as doxycycline, amoxicillin trihydrate/clavulanate potassium, and clindamycin, are recommended. Nutritional Support
As tumors progress and grow in size, cats may have progressive anorexia and dysphagia due to difficulty with prehension, discomfort, or both. As previously discussed, mucositis secondary to radiation therapy can also contribute to these side effects.

Feeding tubes are sometimes considered to support cats with FOSCC. A complete discussion of parenteral feeding options is beyond the scope of this text, but esophageal feeding tubes are generally the most commonly used given the relative ease of placement and client use.

In our opinion, feeding tubes should be considered only for transient use to manage treatment side effects. Difficulty eating due to the oral tumor itself indicates that the disease is negatively affecting the patient’s quality of life. Given the overall poor prognosis and the lack of effective treatment options, humane euthanasia should be considered at this point.

PROGNOSIS
Despite the availability of therapeutic options, including radiotherapy, chemotherapy, and toceranib phosphate, the prognosis for FOSCC remains poor. Most cats present with advanced (T2 or greater), nonresectable local disease, and treatment is generally ineffective or associated with a short-lived tumor response. Median survival times range from 2 to 5 months. Cats with small tumors, especially those located in the rostral mandible that are amenable to surgical resection, may have improved outcomes. Adjuvant definitive radiotherapy may delay tumor recurrence in that setting.

As new treatments become available, multimodal therapy, including combinations of local therapy, chemotherapy, and medical therapy, may prove beneficial for this uniformly aggressive disease and should be evaluated in future studies.

COX = cyclooxygenase; CT = computed tomography; FOSCC = feline oral squamous cell carcinoma; NSAID = nonsteroidal anti-inflammatory drug; SCC = squamous cell carcinoma

References
9. Skinner OT, Boston SE, Souza CH. Patterns of lymph node metastasis identified following bilateral mandibular and medial retropharyngeal lymphadenectomy in 31 dogs with malignancies
of the head. J Vet Comp Oncol May 2016 [epub ahead of print].
Learning Objectives
After reading this article, the practitioner should be able to recognize, diagnose, and stage feline oral squamous cell carcinoma; discuss treatment options and adverse events; and recommend specific treatment and management options to clients. The practitioner should also understand and be able to counsel pet owners regarding the prognosis.

Article Overview
Feline oral squamous cell carcinoma is the most common oral tumor in cats. This article presents a basic overview for the general practitioner, including diagnosis, treatment options, and prognosis.

1. Which of the following risk factors has NOT been associated with feline oral squamous cell carcinoma (FOSCC)?
   a. Use of flea collars
   b. Canned foods, specifically canned tuna
   c. Environmental tobacco smoke
   d. Papilloma viruses

2. Which of the following clinical presentations should increase suspicion for FOSCC?
   a. Cat with a visible oral mass and hypercalcemia
   b. Cat with oral discharge, halitosis, and weight loss
   c. Cat with a focal area of tooth laxity and gingivitis on dental examination
   d. All of these scenarios could represent FOSCC

3. Which of the following are the most appropriate staging tests for a cat with FOSCC?
   a. Blood analysis (complete blood count, serum biochemistry profile) and skull radiography
   b. Abdominal ultrasound and thoracic radiography
   c. Blood analysis (complete blood count, serum biochemistry profile), thoracic radiography, and aspiration of both mandibular lymph nodes
   d. Full-body computed tomography and aspiration of regional ipsilateral lymph nodes only if enlarged

4. Which of the following is the least ideal method to obtain a diagnosis of FOSCC?
   a. Fine-needle aspiration
   b. Biopsy of an oral mass through the external skin/lip
   c. Punch biopsy
   d. Wedge biopsy

5. Which of the following cats would be the best candidate for surgical resection of FOSCC?
   a. Cat with a sublingual tumor
   b. Cat with a small (< 2 cm) mandibular tumor and bilateral lymph node metastases
   c. Cat with a small (< 2 cm) rostrally located maxillary tumor
   d. Cat with a small (< 2 cm) rostrally located mandibular tumor

6. Which of the following is FALSE regarding complications of surgical resection of FOSCC?
   a. In one study, 12% of cats never regained the ability to eat on their own and 17 of 42 required esophagostomy tubes.
   b. It is uncommon to have incomplete margins when a tumor is resected.
   c. Common complications include mandibular drift, dysphagia, ptysmal, and difficulty grooming.
   d. Complications after surgery are common, with one study reporting an acute complication rate of 98%.
7. Which of the following is \textbf{TRUE} regarding radiation therapy?
   a. Definitive intent radiation therapy protocols are associated with a high risk for early side effects and a low risk for late side effects.
   b. Palliative-intent radiation therapy protocols for FOSCC have resulted in survival times of 300+ days.
   c. Prolonged survival can be achieved with a 10-fraction radiation protocol regardless of tumor size.
   d. Cats are more sensitive to early radiation side effects compared with dogs.

8. Which of the following is \textbf{TRUE} regarding chemotherapy for FOSCC?
   a. Chemotherapy is effective in FOSCC, with high response rates and improved survival.
   b. Toceranib phosphate should be used only for mast cell disease.
   c. A possible reason for FOSCC chemotherapy resistance is tumor necrosis leading to decreased chemotherapy delivery.
   d. Toceranib phosphate is not well tolerated in cats, with neutropenia reported as a common adverse event.

9. Which of the following is \textbf{FALSE} regarding the use of nonsteroidal anti-inflammatory drugs for FOSCC?
   a. Cyclooxygenase (COX)-1 and COX-2 are upregulated in FOSCC.
   b. Upregulation of COX receptors has been associated with increased cellular growth, proliferation, and angiogenesis.
   c. Low-dose meloxicam has been evaluated in Europe and is associated with a high risk for progression of renal disease.
   d. Standard-dose meloxicam is associated with a “black-box” warning due to risk for renal toxicity.

10. Which of the following is \textbf{TRUE}?
    a. Oral masses can frequently become secondarily infected, and treatment with antibiotics should be considered.
    b. All patients with FOSCC should have a feeding tube placed for nutritional support.
    c. Buprenorphine must be injected via SC or IV route to be effective in cats with FOSCC.
    d. Nasogastric tubes are considered the best feeding tube option for FOSCC given the ease of placement, ease of use, and permanence of placement.