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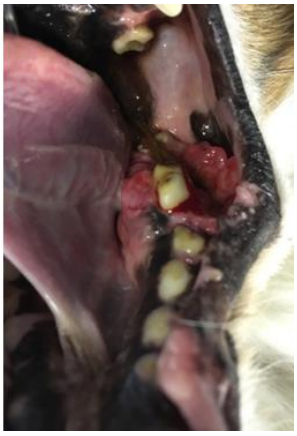
Treating aggressive sarcomas & carcinomas in Small Animal Practice Mini Series

Session Three: All about the approach….. to intranasal tumours, oral tumours, anal gland and urogenital tumours



Treating Aggressive Sarcomas and Carcinomas

Study Notes: Session 3

3a: Oral & Nasal Tumours

Oral tumours in dogs are characterised by locally-aggressive disease. Obtaining a good prognosis for your patient hinges around good local control of the primary tumour. Although the metastatic rate varies with the diagnosis (and in the case of melanoma the metastatic rate is very high), the possibility of metastasis is entirely academic if good local control cannot be effected; due to the pain of the primary tumour euthanasia will be necessary long before metastatic disease threatens the dog's life.

A finite list of differential diagnoses will cover the vast majority of canine oral tumours; melanoma is the commonest, followed by squamous cell carcinoma, followed by fibrosarcoma and acanthomatous ameloblastoma. Osteosarcomas and round cell tumours occur rarely. The diagnostic investigation is reasonably stereotyped, and involves haematology, serum biochemistry, urinalysis, imaging of the oral cavity and thorax, fine needle aspiration of the local lymph nodes (bilaterally) and biopsy of the mass. The use of 3-dimensional imaging like CT is very useful since conventional radiography will not detect osteolysis unless 60% of the bone cortex has been destroyed. 3-dimensional imaging also helps to plan local therapy. Here is a summary of the necessary margins and suggestion of sensitivity to different therapies:

Diagnosis	Surgical Response	RT Response	Chemo Response
Melanoma	+++ 2cm Margins	+++++	Poor
SCC	+++ 2cm Margins	+++	Poor
Fibrosarcoma	+++ 3cm Margins	+/-	Poor
Acanthomatous Epulis	+++ Just complete Excision	+++	Poor
(Osteosarcoma)	+++ 2cm Margins	+/-	Poor

Melanomas of the oral cavity in dogs are aggressive tumours, with a high rate of metastasis. Survival times for oral melanomas treated with surgery alone range from 5-17 months, with 1 year survival rates 21-35%. If the local disease in the mouth is adequately addressed, most dogs with oral melanomas are later euthanased because of metastatic disease.

As for all oral tumours, local therapy is the keystone in good management. Surgery is usually the first consideration but for locations which are not amenable to surgery then melanomas respond well (80% response rate) to hypofractionated radiation therapy; often responses are complete. Following surgery there are two main options for systemic management of potential metastatic disease in canine melanoma: immunotherapy (Merial Melanoma Vaccine) and systemic drug therapy.

Immunotherapy involves treating with the Merial melanoma vaccine (Oncept). This is a DNA vaccine consisting of xenogeneic (human) tyrosinase DNA in a bacterial plasmid vector. The aim of the vaccine is to trigger an immune response against canine tyrosinase (expressed in melanocytes but not in other cells) and thus it represents a specific therapy. This vaccine is administered intradermally every 2 weeks for 4 treatments and then every 6 months thereafter. It has to be imported from the USA on a named patient basis, and is only available to veterinary oncology or internal medicine specialists currently. The vaccine appears to be safe with minimal adverse effects. Occasional erythema (redness) can be seen at the vaccination site and momentary discomfort can be experienced during administration. Vitiligo (depigmentation) of the skin has been seen in a few patients. There are studies indicating potential benefit in increasing survival in melanoma patients. One study showed a significant benefit in survival in vaccinates compared to historical controls. The median survival for controls was 324 days and the median was not reached for vaccinates at the time of publication. The time beyond which 75% of the population was expected to survive was 156 days for historical controls and 464 days for vaccinates.

However there is some controversy over the tyrosinase vaccine's efficacy. In one recent independent randomised study, no survival benefit was seen in vaccinated dogs, and response to the vaccine in the majority of dogs, anecdotally, seems to be disappointing. Nonetheless there are definitely some dogs who respond very favourably to the vaccine and for these individuals the vaccine represents a highly-effective treatment.

In general, canine melanomas are poorly responsive to systemic drug therapy (as is the situation in human medicine), however the following treatments can be considered:

1) Cytotoxic chemotherapy (Carboplatin): This would entail intravenous injections every 21 days, for a total of 4 to 6 cycles. The response rate for dogs with oral melanoma (that have measurable tumour burdens) treated with carboplatin is 28%, with a median survival time of 165 days.

2) Metronomic chemotherapy: Although its use has not been investigated specifically for management of canine oral melanoma, it has been shown to have an anti-angiogenic and immunomodulatory effect. In view of the latter effect, metronomic chemotherapy could theoretically be beneficial used alongside the melanoma vaccine - however this has not been proven.

3) Targeted therapy (tyrosine kinase inhibitor e.g. toceranib). There is preliminary evidence of efficacy in some melanomas. One study looked at 3 dogs with melanoma given a TKI, and 2 had some tumour shrinkage.

Whichever therapy is chosen, monitoring would be performed by regular physical examination (particularly assessing the local tumour site and lymph nodes, as well as restaging with a CT scan or radiographs approximately every 3 months, to assess for the presence of any distant metastatic lesions.

Oral squamous cell carcinomas (SCCs) in dogs are usually very locally invasive, but the metastatic rate is in the order of 20-30%. When metastasis occurs, it is usually to the regional lymph nodes, or the lungs. Managing the local disease in the jaw can be difficult as surgical excision with adequate margins is extremely hard to achieve in the oral cavity. For this reason, surgery is often followed with radiation therapy, to try to sterilise the surgical margins. If surgery is not possible, radiation therapy can be used in the gross disease setting; many SCCs of the dental arcades will respond well to radiation however not perhaps to the same extent as melanomas, and a hyperfractionated protocol is required (with consequent greater expense).

In cases which involve metastasis, or where margins of surgical excision are incomplete and adjunctive radiation therapy is not possible, adjunctive chemotherapy is usually offered. Carboplatin is probably the best-evidenced drug to use in this setting, and the client should understand that it is still not as effective as adjunctive radiation therapy. Metronomic chemotherapy may also be a consideration for an older dog. In the gross disease setting then responses have been observed to toceranib (Palladia) but it should be remembered that providing it works this is an ongoing treatment (not a course).

Dogs receiving appropriate local control of a mandibular squamous cell carcinoma (effected by appropriate surgery with or without radiation therapy) have achieved a good quality of life for an extended period (in the region of 2 years or more).

Oral fibrosarcomas are the most invasive oral tumour. Up to a third of cases metastasize (to local lymph nodes or lungs) but local disease is nearly always the cause of euthanasia. Complete resection of such a tumour will necessitate a radical rostral maxillectomy or mandibulectomy procedure, involving removal of the tumour and at least 3cm of healthy “margins.” Early reports of recurrence after this surgery stated a 40-60% local recurrence rate, more recent reports are of 20-25% recurrence. For this reason, surgery is best followed by adjunctive radiation therapy, even in the cases that are resected with clean margins.

If surgery is not possible, there are no equally-effective alternatives. Oral fibrosarcomas are generally resistant to chemotherapy and only have a modest response to radiation therapy in the gross setting (although they are more responsive to radiation therapy when surgically “debulked” first).

Despite the disfiguring nature of the surgery, dogs tolerate it very well. They typically eat and drink without a problem (albeit more messily at first), and experience no residual pain after the surgical wound has healed. Many dogs have gone on to have an excellent quality of life for the long term afterwards. Because the lining of the nose is exposed however, permanently moist nasal discharge (which can cause dermatitis, inflammation of the surrounding skin) is common and frequent rhinitis (infection of the nose) is possible.

Feline oral tumours are even harder to treat than their canine counterparts, partly because of smaller jaws and more delicate anatomy makes complete surgical resection difficult in many cases, and partly because cats often tolerate oral surgery, particularly mandibulectomy procedures, poorly; maxillectomies are often much better tolerated than mandibulectomies. After oral surgeries, cats typically have to be fed by an oesophagostomy tube for a period of time, and in some cases, this is permanently. The diagnostic approach is very similar for cats as per dogs, and the list of differential diagnoses covering 99% of tumours is even smaller – most tumours are oral SCCs, with fibrosarcomas making up the remainder.

Oral SCCs in cats are usually fast growing and locally invasive, carrying a poor prognosis. Although they metastasize infrequently to regional lymph nodes, and rarely to distant sites, the morbidity associated with the local disease in the mouth often brings people to elect euthanasia on welfare grounds within months of diagnosis.

Managing the local disease is challenging because surgical excision with adequate margins cannot be achieved in the oral cavity. Thus, a combination of some or all of: surgery, radiation therapy, and chemotherapy are often employed, the precise treatment being tailored to the specific details of each individual case. These treatment options rarely effect adequate long term local control however. The one-year survival rate is generally less than 10%, with a median survival time of about three to six months for most treatment regimes.

The same principles apply as for the canine disease, with the exception that the feline oral SCC is typically very resistant to radiation therapy. If surgery and radiation therapy are not possible or declined, then chemotherapy can be used and carboplatin, toceranib, thalidomide and bleomycin are agents which are commonly considered. Chemosensitivity of these tumours is often very low (responses are rarely seen) so attention should focus on aggressive analgesia, treatment of secondary infection, and above all, counselling of the owner about the cat's welfare.

Oral fibrosarcomas in cats shares the radiation resistance of their canine counterparts, and of the feline oral SCC – oral tumours in cats are generally very radiation resistant. The oral fibrosarcoma is extremely invasive and so complete resection is hard to achieve, local recurrence is common, and despite having a low metastatic rate, the prognosis is guarded to poor. Chemotherapy is frequently used, often in the gross disease setting but most cases I have treated have experienced a survival in the order of 4-8 months. Doxorubicin and carboplatin, or metronomic chemotherapy are the most popular choices for chemotherapy but insufficient cases have been treated to establish the optimal medical treatment.

Canine nasal tumours Rare tumours and represent ~1% of all neoplasms in dogs. They are mostly diagnosed in older dogs (average age 10 years), but has been reported as young as 1 year; large and medium breeds are predisposed. Carcinomas represent nearly 2/3 and sarcomas nearly 1/3 of tumours and there are rare reports of various other tumours (lymphoma, HSA, neuroendocrine carcinoma, nerve sheet tumour, fibrous histiocytoma, rhabdomyosarcoma, leiomyosarcoma). Clinical signs include mucopurulent discharge, epistaxis, sneezing, dyspnoea, stertor, and facial deformity but

some cases will present with exopthalmus or depression of mentation. Differential diagnoses include fungal and inflammatory rhinitis, nasal foreign body and in cats nasopharyngeal stenosis.

Nasal tumours share a similar, quite steotyped approach with oral tumours. From a practical point of view, the diagnosis very often doesn't affect the treatment (radiation therapy) but it is important to ascertain the diagnosis before treatment proceeds to confirm the lesion is neoplastic and not one which is treated medically. Numerous techniques to obtain the diagnosis have been described, including nasal flush, rhinoscopy-guided, "needle core" using a urinary catheter or jamshidi needle, or fine needle aspiration of facial deformities.

In imaging a nasal tumour, radiography can be as sensitive as CT in detecting nasal cavity abnormalities, however CT provides improved anatomic detail, which allows accurate determination of extent of tumour, localisation of pathology-allowing tumour staging and important for treatment planning and helps define the involvement of the cribriform plate. Additionally, CT is important for computer planning of radiation treatments. No advantage of MRI over CT has been found. The Adam's modified staging system – has been shown to be prognostic, but this is by virtue of the stage 4 tumours (those involving the cribriform plate) have a significantly denuded survival time compared to lower-stage tumours.

Treatment of nasal tumours is Directed primarily at control of local disease. Curative surgery alone is of limited value due to morbidity and (almost certain) incomplete excision. Radiation therapy treatment of choice and achieves an average survival in the order of 18 months in most cases. Reirradiation of nasal tumours can then be performed, with a median duration of 9 months, and a less complete response than in the first treatment. If radiation is performed post surgical exenteration of the nasal cavity the survival time is doubled to approximately 3 years, however dogs have lasting effects of the procedure for example permanent nasal discharge and upper respiratory noise due to lack of turbinates.

Adverse effects of radiation therapy can be acute or chronic. Definitive (hyperfractionated) RT is associated with a higher risk of acute adverse effects (but much lower risk of late (chronic) effects, and is the treatment of choice of a nasal tumour. Palliative (hypofractionated) RT is associated with a higher risk of late adverse effects, but minimal acute effects. Acute adverse effects include KCS, blepharitis, conjunctivitis, mucositis and moist desquamation. Chronic adverse effects include cataracts, optic nerve axonal degeneration, fibrosis, bone necrosis and brain necrosis. These effects are nearly always permanent, incurable and often incompatible with life.

Chemotherapy is always the least-best option for nasal tumours, as it is for oral tumours, due to inherently insensitive tumours in a gross disease setting and above all a low metastatic rate; the need for a systemic therapy is low. If instituting chemotherapy for a nasal tumour I would consider carboplatin or doxorubicin with an NSAID since it has been shown to have a - 75% RR (6/8 dogs) and survival time of 7 months in these individuals. Failing that, metronomic chemotherapy could be considered.

Nasal tumour embolization or chemo-embolization is a relatively new technique which has yet to be evaluated in a large number of dogs, but it could be considered if radiation therapy is impossible or has been declined. Tying off carotid a carotid artery can also provide palliation from persistent epistaxis.

Feline nasal tumours are less common than canine nasal tumours, and consist mostly of nasal lymphoma and carcinomas. Diagnosis is often difficult due to overlapping of clinical and imaging findings with inflammatory disease of the nose, but features strongly predictive of neoplasia include displacement of midline structures, unilateral generalised soft tissue opacity/loss of turbinates and extension of disease into orbit/facial soft tissues (NB some fungal diseases present outside the UK can also cause such changes however).

The clinical signs and approach to feline nasal tumours is the same as for canines. Few reports of treatment for feline nasosinal tumours exist (owing to the relative rarity of the tumours) and case numbers small. However, nonlymphoproliferative neoplasms of the feline nasal cavity, treated with definitive RT achieved slightly shorter survival times to dogs with MST 12months and 44% surviving to 1 year and 16% surviving to 2 years.

For palliation of both canine and feline nasal tumours in the gross setting, intermittent nasal flushes can be considered.

3b: Anal Gland & Urinary Bladder Carcinomas

Apocrine gland adenocarcinomas of the anal sac have a high metastatic rate; 50-80% have metastasized at the time of diagnosis. Regional (sublumbar) lymph nodes are the most common site of metastasis (comprising the medial iliac, hypograstric and sacral lymph nodes) and distant metastatic sites include the lungs, liver, and spleen. Nevertheless, despite being highly metastatic (and therefore incurable), this cancer is typically slow to progress and so prolonged survival and excellent quality of life is often achieved, providing adequate local therapy is instituted. Paraneoplastic hypercalcemia, mediated by parathyroid hormone-related peptide secreted by the tumour, has been documented in 27% of cases.

Surgical excision is the most important step in managing an anal gland adenocarcinoma; carcinomas are usually poorly-sensitive to chemotherapy and radiation therapy is most effective on "minimal residual disease" (for example after surgery, to sterilise the "roots" of the cancer). Surgery carries the risk of faecal incontinence, but this risk is low (only 12% of surgeries experience complications and these complications are MINOR). Owing to the invasive nature of these tumours however, surgery rarely achieves a complete tumour excision, and further therapy, preferably radiation therapy needs to be considered to consolidate the local control. Metastatic sublumbar lymph nodes can be surgically excised concurrently in the majority of cases.

Radiation therapy is an effective means of treating the remaining cancer cells around the surgical site, and it can also be used to treat the local lymph nodes (preferably after incomplete-excision but RT will remain effective in the macroscopic disease state). Radiation therapy involves the delivery of multiple, small "fractions" of radiation to the target area; many protocols for this cancer will involve daily fractions for 3-5 days each week (for a period of several weeks). The necessity of multiple fractions greatly reduces the adverse effects of radiation therapy, and means that it is a well-tolerated treatment in dogs and cats. Possible adverse effects can include local discomfort, erythema and desquamation (skin rashes) of the skin, and colitis, but these signs are usually temporary and resolve within a couple of weeks after finishing radiation therapy, with supportive care. More serious late complications such as rectal strictures can occur uncommonly. The patient has to be anaesthetised for each fraction to make sure the dose is delivered safely and accurately.

If adjunctive radiation therapy is not possible, chemotherapy has been used to try to slow down local tumour recurrence. Chemotherapy is less effective than radiation therapy in this setting, but is still beneficial; one study using melphalan showed a median survival time of 20 months after diagnosis and surgery, if local metastases were present (and 29 months if no metastatic disease was present). The melphalan should be given in 3-week (21 day) cycles, with melphalan given daily for 5 consecutive days, followed by 16 days off. Haematology should be performed prior to each chemotherapy cycle initially, for the first 2 cycles. Depending on the results, it may be possible to extend the monitoring interval to every other cycle subsequently. Please note that neutropenia and thrombocytopenia can occur with melphalan. Thrombocytopenia can be delayed and prolonged. Mild gastrointestinal problems might also occur. These are usually mild and self-limiting; melphalan is generally well-tolerated.

A variety of other chemotherapy agents and protocols have been used in the treatment of this disease, including pulse-dose carboplatin or mitoxantrone injections, metronomic chemotherapy and tyrosine-kinase inhibitor therapy. The optimal drug regime, timing of adjuvant therapy and schedule has not been established. A combination of surgery, radiation and chemotherapy promises to give the longest reported survival time (median survival time in the order of 2.5 years - Turek et.al, 2003), but if both surgery and RT are possible, then the benefit of chemotherapy is likely to be relatively minor.

If an anal gland tumour is not surgically excised, getting a good prognosis for the dog will be much harder. In the gross-disease setting, most chemotherapy drugs have not been shown to produce a response however radiation therapy has been used as the primary treatment in anal sac adenocarcinomas for which surgery was not possible or declined; in a small number of dogs, a survival time of 447 days was achieved (Polton et.al, 2016). If surgery is not possible, then a combination of chemotherapy and radiation therapy (both on the primary tumour and the lymph node bed) would be prudent.

And if both surgery and RT are not possible, then the dog's prognosis will be significantly undermined. In the gross disease setting, carboplatin has shown a limited response rate, of approximately 33% (1 of only 3 dogs responded). Carboplatin treatment consists of an intravenous administration of the drug every 3 weeks, for 4-5 treatments, typically followed by oral maintenance therapy, with either oral melphalan treatment, or metronomic chemotherapy with a NSAID and low dose cyclophosphamide.

Tyrosine kinase inhibitors have recently shown promise in the treatment of anal sac adenocarcinomas and may be another consideration in the gross disease setting. A study evaluating the use of toceranib indicated clinical benefit in 28 of 32 apocrine gland adenocarcinomas (8 partial responses and 20 stable diseases). Toceranib is generally well tolerated, however adverse effects reported in dogs include gastro-intestinal toxicity (anorexia, vomiting, diahhroea or GI bleeding), mild neutropenia, muscle cramping, epistaxis, hypertension and protein-losing nephropathy.

Finally, metronomic chemotherapy (with cyclophosphamide in conjunction with a NSAID), has been used in the gross disease setting, aiming to achieve stable disease. For monitoring I recommend performing blood tests (haematology, urinalysis and renal biochemistry if USG<1.030) before the

beginning of the treatment, and repeating monthly for 3 months and then spreading the interval to 6-8 weeks if all has been well in the first 3 months. With this treatment, possible complications of gastrointestinal inflammation, and rarely ulceration may occur. Myelosuppression can occur secondary to the administration of cyclophosphamide / chlorambucil (although unlikely at the doses used) and this will be monitored on the blood work. Cyclophosphamide medication can occasionally cause sterile haemorrhagic cystitis (SHC) in approximately 15% dogs.

Since anal gland tumours are common, and stage is prognostic, these tumours are potentially curable by recognizing them early enough. There is a case to be made then, to perform routine rectal examinations on older dogs, especially Spaniel breeds. Anal gland tumours in cats are characterized by local invasion but less distant metastasis than in dogs. Owing to their rarity their metastatic potential or optimal treatment remains to be established.

Transitional cell carcinoma (TCC) is the most common bladder tumour in dogs. Diagnosis can be difficult in some cases because other diseases of bladder and urethra (for example papillomatous cystitis or granulomatous urethritis) can mimic the thickening of the urothelium or even cause a mass lesion. Histopathology is the best way to make this diagnosis but neoplastic cells will be found in urine cytology (please remember to submit an EDTA tube of urine!) in approximately 30% cases. If histopathology or cytology are non-diagnostic then a PCR test for the BRAF mutation (found in over 80% urothelial carcinomas) is commercially available via Sentinel Biomedical (USA) and is reported to be highly sensitive and specific for any urothelial carcinoma.

In treating a TCC of the bladder many of the same theoretical principles apply as for anal gland carcinomas; the prognosis is much poorer because local therapy techniques are often not possible. Surgical resection of a TCC is often inappropriate due to the tumour's proximity to the ureters and urethral sphincter, however where the tumour is distant from these structures a partial cystectomy will be very beneficial (such is the situation with many feline TCCs). Historically, radiation therapy did not provide demonstrable benefit however with more advanced planning radiation has now been shown to be a very effective local treatment, especially in cases with urethral obstruction or where further analgesia is required. The main problem with radiation therapy is that access to such advanced treatments is not readily-available in the UK currently. Chemotherapy is frequently used to treat TCCs, but when used alone this treatment is likely to achieve only a partial response or stable disease. Thus, the best treatment for most TCC cases would involve combining chemotherapy with radiation therapy if possible.

Options for standard chemotherapy that would be considered include carboplatin, mitoxantrone or vinblastine. Like all chemotherapy agents, these drugs can cause the adverse effects of gastrointesinal upsets or myelosuppression. Alongside chemotherapy, COX-1 and 2 inhibition (with an NSAID drug) has been shown to be very beneficial. Since a high proportion of TCC cases have a concurrent UTI, treatment of this is indicated, as well as comprehensive and pre-emptive analgesia. If a dog is to experience flare-ups of discomfort during TCC treatment then assessing for a urinary tract infection is indicated.

In choosing an appropriate TCC treatment I would recommend consideration of response rates before progression-free intervals or survival time. Common treatments are summarised here:

Therapy	ORR (%)	PFI (days)	MST (days)
Chlorambucil	67	119	221
Vinblastine	86	122	147
Mitox + Pir	81	194	291
Carbo + Pir	83	-	161
Deracoxib	88	133	323

Therapy	CR (%)	PR (%)	SD (%)
Chlorambucil	0	3	67
Vinblastine	0	36	50
Mitox + Pir	2	32	45
Carbo + Pir	0	38	45
Deracoxib	0	17	71

After one treatment fails, I would recommend use of another, and then another etc.. Ultimately most dogs with TCCs live between 5-10 months. Survival time is dependent on the tumour's stage at diagnosis (tumour size, regional lymph node status and presence of distant metastasis). Presence of complications for example hydronephrosis or urethral obstruction will also impact survival time, however since this isn't a directly-lethal disease, possibly the most important prognosticator is comfort levels, and how well comfort can be controlled. Dogs in acute and severe discomfort a few weeks after treatment starts are likely to live no more than a weeks to a few months. Conversely, dogs who have minimal clinical signs at diagnosis will often do well, and some may exceed 12 months' survival. Cases who have a partial cystectomy often live 12-18 months. Monitoring comfort levels is the most important part of treating a TCC and is more important than imaging findings.

If progression of a TCC blocks a ureter or urethra then radiation therapy is the best treatment, and can produce rapid regression of the intraluminal obstruction. Stenting is a second-best choice. Urethral stenting is associated with urinary incontinence and recurrent / chronic urinary tract infections in most cases. The average survival time is in the order of 2-3 months after the stent is placed.

TCCs in cats bear similarities to those in dogs, with the exception that a much higher proportion occur at the bladder apex and so are amenable to partial cystectomy.

Reference Books for this Course:

- Withrow, Vail, Page; "Withrow & Macewen's Small Animal Clinical Oncology;" 5th Edition; Elsevier.
- Raskin, Meyer; "Canine and Feline Cytology: A Color Atlas and Interpretation Guide;" 3rd Edition; Elsevier

Further Reading for Session 3:

- PJ Bergman, JD Wolchok; Of mice and men (and dogs): development of a xenogeneic DNA vaccine for canine oral malignant melanoma; Cancer Therapy Vol 6; 817-826; 2008
- Smedley et.al; Prognostic Markers for Canine Melanocytic Neoplasms: A Comparative Review of the Literature and Goals for Future Investigation; Veterinary Pathology 48(1); 54-72; 2011
- Polton, GA, Brearley MJ; Clinical Stage, Therapy, and Prognosis in Canine Anal Sac Gland Carcinoma; J Vet Intern Med 2007;21:274–280
- Mochizuki H, Shapiro SG, Breen M; Detection of BRAF Mutation in Urine DNA as a Molecular Diagnostic for Canine Urothelial and Prostatic Carcinoma; PLOS ONE | DOI:10.1371/journal.pone.0144170 December 9, 2015
- Bryan JN, Keeler MR, Henry CJ, Bryan ME, Hahn AW, Caldwell CW; A population study of neutering status as a risk factor for canine prostate cancer; Prostate. 2007 Aug 1;67(11):1174-81