

CANINE AND FELINE MELANOMA

THE GOOD, THE BAD AND THE UGLY

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CANINE MELANOCYTIC TUMORS

Melanocytic tumors (n = 1.652)			
Anatomical location		Histologic characterization	
Oral cavity	63%	Malignant	70%
Skin	27%	Benign	30%
Digit/Nail bed	9%		
Ocular	1%		

Gillard et al., 2013

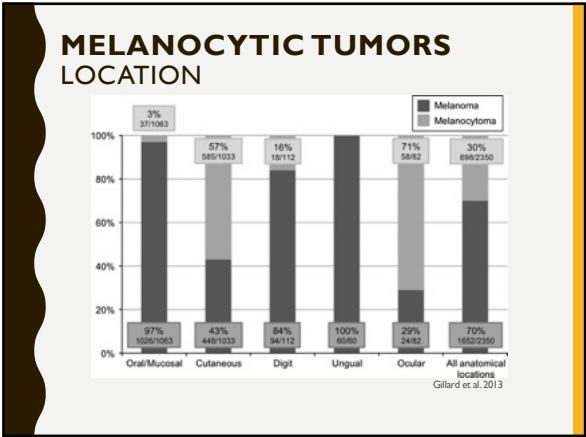


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MELANOCYTOMA VS MELANOMA

- Malignant (melanoma) vs Benign (melanocytoma)
- Grading only possible with histology, **not** cytology
 - May require “bleaching” of the biopsy
 - Ki67-index
- Nature of a melanocytic tumor can be “guesstimated” based on :
 - Species
 - Anatomical location
 - Morphology
 - Staging findings (presence of metastatic disease)

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MELANOCYTYC TUMORS ETIOLOGY

No consensus, but reported factors include:

Cutaneous and Oral:

- genetic
 - pure-breed > mixed breed
 - specific breeds
- trauma
- chemical agents
- hormones

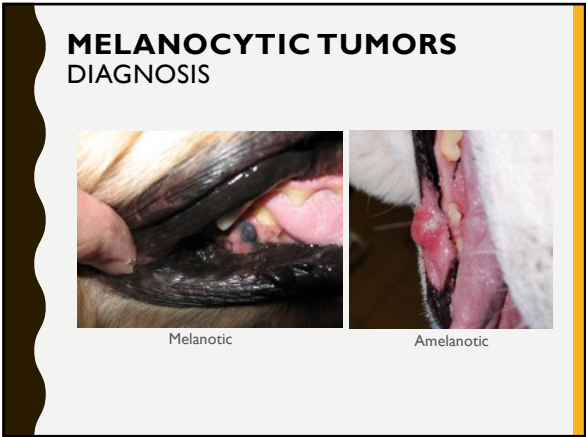
Cutaneous

- sunlight – more often in sun-exposed skin face and pinna

Oral:

- presence of pigmented cells
- buccal microflora?
- Inflammation?

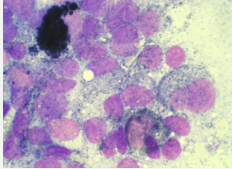
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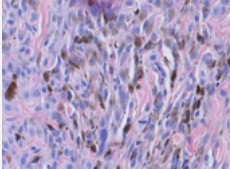
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MELANOCYTIC TUMORS

DIAGNOSIS



Variable morphology
Cytology does not distinguish between melanoma or melanocytoma

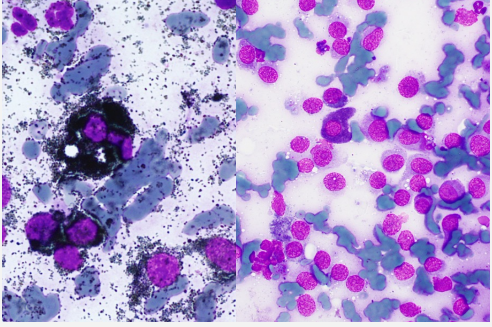


Different histological subtypes, but these are not prognostic

Immunohistochemistry
Melan-A, PNL-2, TRP-1, TRP-2, (vimentin, S-100, NSE)

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MELANOMACYTIC TUMORS

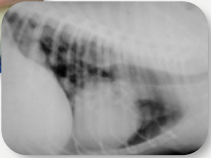


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MELANOCYTIC TUMORS

DIAGNOSTIC WORK-UP





Staging according to TNM-system

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MALIGNANT MELANOMA

STAGING – CUTANEOUS/ORAL

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3any	N0i	M0
IV	Any T	Any N	M1

Tumor (largest diameter)

T1 < 2 cm

T2 2-4 (5) cm

T3 > 4 (5) cm

Oral melanomas

a No bone involvement

b Bone involvement

N = regional lymph node

N0 No node involvement

Ni Node involvement

Ni Fixed nodes

M = distant metastases

M0 No metastases

M1 Metastases

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Melanocytic Tumors

Potential prognosticators (dog)

Location	Oral/Lip Melanocytic Neoplasms	Cutaneous/Digit Melanocytic Neoplasms
Distant metastasis	Poor prognosis	Poor prognosis
Lymphatic invasion	Poor prognosis	Poor prognosis*
	10 consecutive fields starting in area w/highest mitotic activity	10 random fields
Mitotic index	Avoid areas of ulceration for both methods	
	< 4/10 hpf	Favorable prognosis
	≥ 4/10 hpf	Poor prognosis
	% atypical nuclei in 200 cells counted	Subjective assessment
Nuclear atypia*	< 30%	Favorable prognosis
	≥ 30%	Poor prognosis
	Subjective assessment	
	% pigmented cells	Scale 0 (no pigment) to 3 (high pigment)
Degree of pigmentation	≥ 50%	Favorable prognosis
	< 50%	Uncertain prognosis
	0 to 1	
Presence of ulceration	No prognostic significance	Poor prognosis
Level of infiltration/invasion	Shallow w/in bone (yes)	Favorable prognosis
	Deep w/invisible bone (yes)	Poor prognosis
	Average number of positive nuclei per grid (5 hpf grid areas counted)	% of positive nuclei in 500 cells counted
Ki67 index	Avoid areas of ulceration and inflammation and assess highest staining areas for both methods	
	< 19.5	Favorable prognosis
	≥ 19.5	Poor prognosis

* Parameter was not specifically examined for neoplasms of the digit

* Parameter should be assessed in epithelioid predominant neoplasms and in spindle neoplasms with sufficiently observable nuclear detail.

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Ocular

Melanocytic Tumors

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MELANOCYTIC TUMOR PALPEBRAL



Nova Scotia duck tolling retriever
MN 4Y

Doberman Pinscher
MN 6Y

Eyelid melanocytoma
Dog - typically benign
Cat - rare

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MELANOCYTIC TUMOR CONJUNCTIVAL

Dog & Cat

- variable pigmentation
- potential for subconjunctival and orbital invasion
- potential for metastasis

Dog:

- retrievers, rottweilers, cocker spaniels
- Location: membrana nictitans

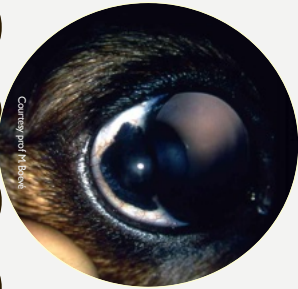
Cat:

- DSH
- Location: bulbar conjunctiva
- Highly malignant



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MELANOCYTIC TUMOR LIMBUS



Dog

- German Shepherd, retrievers predisposed
- Pigmented, fan-shaped, nodular, solitary sharp delineation, most commonly on dorsal limbus

Typically benign
Adjuvant treatment in case of incomplete resection

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MELANOCYTIC NEOPLASIA

IRIS - DOG

- Breed: Labrador retriever, Golden retriever, Bouvier de Flandres
- Age: 2M – 17Y (82% >7Y)
- Signs: intraocular mass, glaucoma, hyphema
- Benign : Malignant: 85 : 15
- Metastatic rate: ±5% (<3M!)
- Prognosis: M1 <2 vs >4

Suspect iris melanoma
2 shades of pigment,
dyscoria

Courtesy prof M. Boeve

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MELANOCYTIC NEOPLASIA

IRIS - DOG

Iris melanoma
Pigmented mass, dyscoria,
cells on lens capsule

Courtesy prof M. Boeve

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MELANOCYTIC NEOPLASIA

IRIS – ADDITIONAL DIAGNOSTICS

US (L) and CT-scan (R) of a large iris tumor (dog)
(note enlargement globe and thinning of the sclera due to secondary glaucoma)

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MELANOCYTIC NEOPLASIA IRIS - CAT

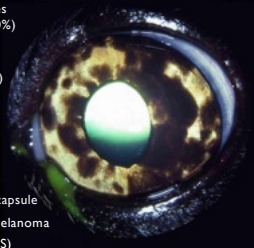
Diffuse iris melanoma

- Main differential: melanosis/iris freckles
- Most common intraocular tumor (±80%)
- Indolent, but malignant
- Age: >10Y
- Metastases: 60-70% (kidney, liver, lungs)

Clinical presentation

- progressive iris pigmentation
- raised lesion/mass effect
- iris thickening
- dyscoria
- cells in anterior chamber/ on lens capsule

Diffuse iris melanoma
(cat, OS)



Courtesy prof M. Boëvé

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FELINE DIFFUSE IRIS MELANOMA CRITERIA FOR MALIGNANCY?

Diffuse iris melanoma vs melanosis

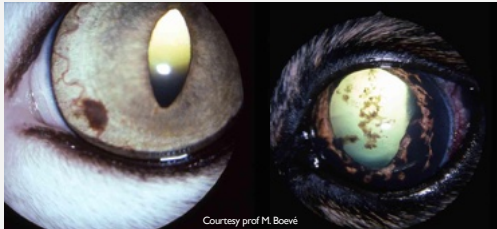
- Morphology (*extension, surface*)
- Degree of pigmentation?
- Cells in anterior chamber?
- Pupil shape (*mydriasis!*)
- Uni- of bilateral?
- Presence of metastatic disease?

Enucleation recommended:

- Iris contour changes
- Tumor cells extend into the iridocorneal angle
- Glaucoma
- Normotensive buphthalmia

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FELINE UVEAL MELANOCYTIC NEOPLASIA



Courtesy prof M. Boëvé

Suspect iris melanoma Recommend active monitoring	Typical diffuse iris melanoma Recommend enucleation following staging
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FELINE UVEAL MELANOCYTIC NEOPLASIA



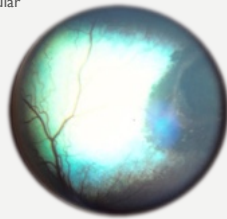
Typical diffuse iris melanoma

Dyscoria is sometimes best appreciated following pupil dilation using mydriatics (right)

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MELANOCYTIC NEOPLASIA Choroid

- Rare in dog and cat
 - typically benign in both species
- Can be locally infiltrative; potentially leading to:
 - retinal detachment and intraocular hemorrhage
 - secondary uveitis
 - glaucoma



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Cutaneous Melanocytic Tumors

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MELANOCYTIC TUMORS

Skin

	Melanocytoma	Malignant Melanoma
Frequency	60%	40%
Age	8.1 years	11.6 years
Morphology	solitary, small, pigmented, firm, not fixated to deeper structures	fast-growing tumors, often ulcerated, often pigmented (grey, brown, black), can be amelanotic
Location	face (near the eyelids), trunk, and extremities	head, ventral abdomen, scrotum, digit, nail bed



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MELANOCYTIC TUMORS

Breed Predilections

- Cutaneous
Schnauzers, Scottish terrier, Doberman Pinscher, Cocker Spaniel
- Digit
Irish and Gordon Setters, Schnauzer, Scottish terrier, Golden Retriever



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MELANOCYTIC TUMORS

SKIN

Variable	No. of case dogs	No. of control dogs	OR	95% CI	P value
Age					
2 wk-12 mo	5	277,747	0.02	0.01-0.05	< 0.001
> 1-2 y	5	131,810	0.05	0.02-0.12	< 0.001
> 2-4 y	14	189,027	0.10	0.05-0.16	< 0.001
> 4-7 y	105	214,004	0.70	0.53-0.90	0.010
> 7-10 y	252	162,203	3.08	2.65-3.59	< 0.001
> 10-15 y	326	127,844	6.21	5.36-7.18	< 0.001
> 15 y	26	10,885	3.50	2.33-5.27	< 0.001
Breed					
Visual	21	1,896	17.34	11.21-26.83	< 0.001
Miniature	83	18,624	7.53	5.99-9.47	< 0.001
Schnauzer					
Chesapeake Bay	12	3,172	5.84	3.30-10.35	< 0.001
Retriever					
Boxer	38	13,850	4.35	3.14-6.04	< 0.001
Airedale Terrier	10	4,517	3.41	1.82-6.36	< 0.001
Scottish Terrier	11	5,519	3.07	1.69-5.57	0.002
Doberman Pinscher	60	32,015	3.02	2.25-3.93	< 0.001
Golden Retriever	64	39,712	2.58	2.01-3.35	< 0.001
Irish Setter	23	15,962	2.23	1.47-3.38	0.002
Mixed	117	229,801	0.82	0.51-1.35	< 0.001
German Shepherd	22	69,430	0.47	0.31-0.71	0.005
Dog					
American Cocker	12	41,285	0.43	0.25-0.77	0.003
Spaniel					

There were 721 case dogs with cutaneous melanoma and 1,113,620 control dogs without a diagnosis of cutaneous neoplasia. The OR represents the odds of cutaneous melanoma in the age group or breed of interest, compared with the odds in all other dogs.

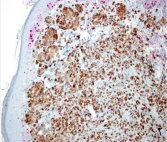
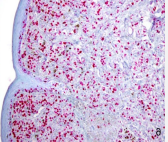
Older animals
M : F = 1.4

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MELANOCYTIC TUMORS

Good vs Bad

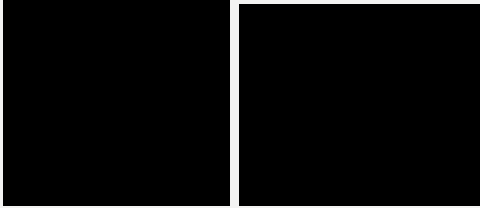
Skin	Melanocytoma	Malignant Melanoma
Frequency	60%	40%
M.I.	<3	≥3
Ki-67	<15%	≥15%
Nuclear atypia	<20%	≥20%



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MELANOCYTIC TUMORS

CUTANEOUS PROGNOSIS



pigmentation, ulceration, metastases, invasion, nuclear atypia, MI, Ki-67
size, junctional activity, necrosis, inflammation, DNA-ploidy
signalment, weight, histological type, deep location, expression markers

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MELANOCYTIC TUMORS

SURVIVAL

- Skin
 - Mostly benign (± 85%)
 - Melanocytoma / benign melanoma
 - no recurrence or metastases
 - median OST 1.463 days
 - Malignant melanoma
 - 36% recurrence
 - median OST 384 days
- Digit
 - Second most common digital tumor
 - Mostly malignant
 - Metastatic rate (@ presentation): 30-40%
 - 1-year survival ± 40%, 2-year survival ± 10%



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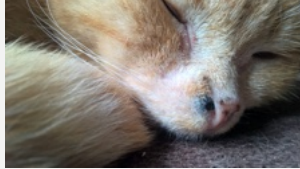
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Feline Cutaneous Melanocytic Tumors

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FELINE CUTANEOUS MELANOMA

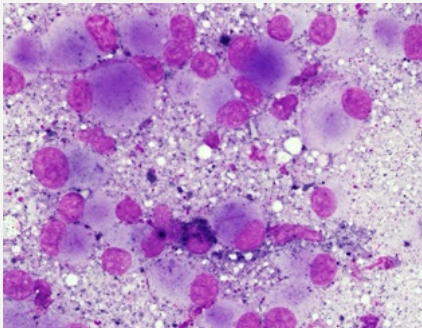
- Rare disease
 - NL 57/1.530 feline skin tumors (4%; 1991-95)
- Signalment
 - DSH
 - median age 11.5Y (2-20)
 - M=F
- Most common locations
 - Nose
 - Digit
 - Base ear/pinna



Dunn et al, 2000; Charrel et al, 2015

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FELINE CUTANEOUS MELANOMA



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FELINE CUTANEOUS MELANOMA

Prognostic

- Size (>0.6 cm malignant)
- Location (nail bed worse)
- Pigmentation (amelanotic worse)

Not prognostic

- Histological subtype
- Grade?

Outcome

- 40% local recurrence,
- ±30% distant metastases
- 80% died from PD @ mean 5M



Duna et al, 2000; Chamel et al, 2015

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FELINE CUTANEOUS MELANOMA

Grading feline non-ocular melanocytic tumors

A tumor is high grade if it is

- Located on nasal planum, lip, oral or nasal mucosa:
 - ≥4 mitotic figures in 10 high-power fields (HPF) and/or
 - Presence of intratumoral necrosis
- All other locations: both criteria present

Median survival time

- Low grade tumors: not reached
- High grade tumors: 90 dagen

Pittaway et al., 2019c

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Canine Oral Melanocytic Tumors

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CANINE ORAL MELANOMA

- Breeds
 - Oral: (miniature) poodle, dachshund
 - Lip: Irish setter, Chihuahua, Golden Retriever, Cocker Spaniel
 - Tongue: Chow Chow, Shar Pei
 - Reduced risk: German shepherd, Boxer?
- Older dogs (mean 11.4Y)
- ± ½ amelanotic melanomas
- Often (±60%) osteoinvasive



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CANINE ORAL MELANOMA STAGING

Often early metastases (>65%)

- regional lymph nodes (14 - 74%)
- lungs (14 - 92%)
- CNS!

What is the sentinel node?

Regional lymph nodes	Metastatic disease
– (sub)mandibular	6 / 11
– medial retropharyngeal	3 / 11
– parotid	2 / 11

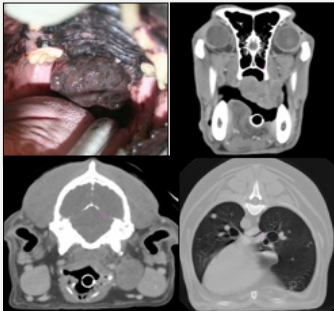
- Most non-enlarged nodes not palpable
- Poor correlation cytology/histology



Herring et al, 2002; Janet et al., 2017

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CANINE ORAL MELANOMA STAGING – CT-SCAN



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CANINE ORAL MELANOMA

THERAPY & PROGNOSIS

Therapy

- Good local tumour control possible with surgery and/or radiotherapy
- Poor distant tumour control
 - Chemotherapy: carboplatin little effect
 - Immunotherapy?
- 1-year survival rate after surgery ~25 %

Prognosis

- Survival rate negatively affected by:
 - Tumor size
 - mOST: 18 months < 2cm > 6 months
 - Tumor stage
 - Tumor grade
 - Tumor proliferation (M.I./Ki-67)

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CANINE ORAL MELANOMA

PROGNOSIS - GRADE

Mitotic index

Ki67

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CANINE ORAL MELANOMA

PROGNOSIS - RISK FACTORS

	N	Median
No risk factor	18	21 mo
1 risk factor	47	11 mo
2 risk factors	57	5 mo
3 risk factors	18	3 mo

1. Tumor sublocation (rostral > caudal)
2. Tumor volume (microscopic > macroscopic)
3. Presence of osteolysis (no > yes)

Proulx et al, 2003

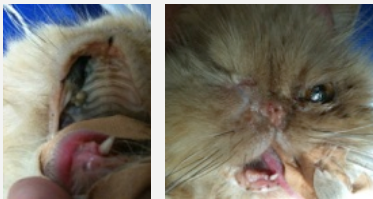
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Feline Oral Melanocytic Tumors

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ORAL MELANOMA CAT?

- Rare in cats, poor prognosis
- Therapy:
 - Surgery
 - Radiotherapy
 - Immunotherapy: Oncept® melanoma vaccine has been safely used; benefit?



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MELANOCYTIC TUMORS TREATMENT OPTIONS?

1. Surgery
2. Surgery!!
3. Surgery!!!!
4. Radiotherapy
5. Immunotherapy
6. Targeted therapy
7. Chemotherapy
(platinum drugs, alkylators)



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MELANOCYTIC TUMORS TREATMENT




Melanoma -
Wide (2 cm) excision

Melanocytoma -
Marginal excision

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CANINE MELANOMA OTHER TREATMENT OPTIONS?

- Chemotherapy
 - No proven benefit carboplatin, cisplatin, melphalan
 - Platinum drugs radiosensitizer?
- Radiotherapy
 - Effective for local control
- Immunotherapy
 - The future??

1284 Vol. 9, 1284-1290, April 2003 Clinical Cancer Research

Advances in Brief

Long-Term Survival of Dogs with Advanced Malignant Melanoma after DNA Vaccination with Xenogeneic Human Tyrosinase: A Phase I Trial¹

Philip J. Bergman,² Joanne McKnight,
Andrew Novmad,² Sarah Charney,⁴

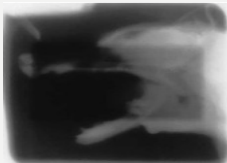
IV disease had long-term survival (>21 and 58+ days) in the face of significant bulky metastatic disease, and two other dogs with locally controlled stage I/III disease had

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CANINE MELANOMA RADIOTHERAPY

- Generally considered to be an intrinsically radioresistant tumor
- Dogs
 - 3x 10Gy
 - 4x 9Gy
 - 6x 6Gy
 - 12-19x 2-4Gy

No difference in outcome and toxicity between these protocols
Hypofractionated protocols favored



Treatment field:

- Surgical site/Tumor
- Regional lymph nodes

Sause et al, 1991; Proulx et al, 2003

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CANINE ORAL MELANOMA RADIOTHERAPY



>80% of cases significant to complete reduction in tumor volume
Typically within 2 to 3 weeks after start radiotherapy

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CANINE ORAL MELANOMA PROGNOSIS WITH RADIOTHERAPY

Stage	PFS time (months)		PFS-rate (%)	
	Mean	Median	1-year	3-year
Overall	18	8	36	20
T ₁	38	19	71	54
T ₂	12	6	28	12
T ₃	12	7	23	9

T₁ <2cm, T₂ 2-4cm, T₃ >4cm

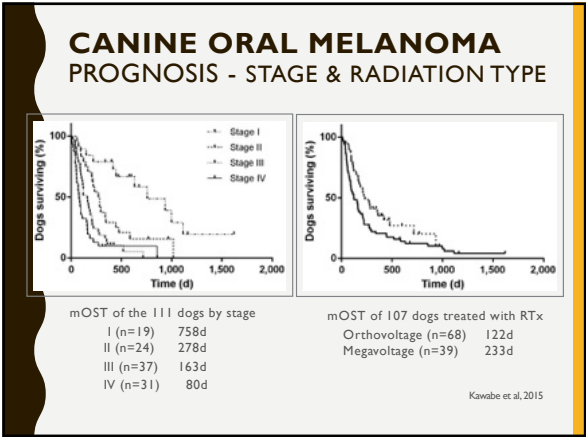
Théon et al, 1997

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CANINE ORAL MELANOMA RADIOTHERAPY – TOXICITY (6x 6Gy)



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CANINE MELANOMA IMMUNOTHERAPY

Immunostimulation

- Various approaches reported
 - Aspecific: BCG, levamisole: no effect
 - Specific: DNA-based, whole cell, dendritic cell, virolytic therapy
 - Checkpoint blockers: CTLA-4, PD1/PDL-1
- Note: Clear rationale for combining RTx with immunotherapy

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IMMUNOTHERAPY ONCEPT®- MELANOMA VACCIN

- 33 stage I-III loco-regionally controlled MM
- Median OST 569 days
- Anti-Tyrosinase Abs detected!

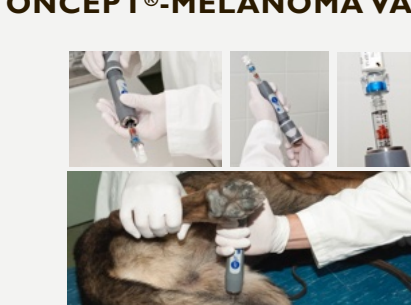
Proportion Surviving

Days

Bergman et al, Vaccine 2006

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ONCEPT®-MELANOMA VACCIN



The image displays three photographs related to the Oncept Melanoma Vaccine. The top left photo shows a hand holding a syringe with the vaccine. The top right photo shows a hand holding a syringe with the vaccine. The bottom photo shows a hand using a syringe to inject the vaccine into a dog's skin.

[illegible]

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MELANOMA VACCINE ADVERSE EVENTS?

- Little to no side-effects
- DNA microseeding well tolerated
 - no significant toxicity beyond local site irritation
 - sometimes mild (pain?) response to vaccination
- No signs of autoimmunity
- Rare cases of depigmentation

“Dino”, beagle, M, 6 Y
stage 2 oral melanoma,
After 5 cycles of vaccination



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IMMUNOTHERAPY

IMMUNE CHECKPOINT BLOCKADE

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IMMUNOTHERAPY

IMMUNE CHECKPOINT BLOCKADE

PD-1/PD-L1 are present in a variety of canine cancers including oral MM

PD-L1 antibody: clinical benefit in 1/7 dogs with oral MM

PD-1 antibody

- ±33% had clinical benefit
- mPFS 70 days, mOST 215 days

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TARGETED THERAPY

ONCOGENETIC PATHWAYS

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OTHER TREATMENT OPTIONS TARGETED THERAPY

Oncogenetic pathways

- Humans: mutations in BRAF, KIT, NRAS and PTEN common
- Dogs (n=95): no mutations in BRAF, KIT, NRAS 3/95 and PTEN 2/95
- BRAF-inhibitors have a role in human, but not canine melanoma
- Kit: possibly relevant in feline diffuse iris melanoma
- PI3K/Akt activation
 - Present in human and canine melanocytic neoplasia
 - Cell cultures sensitive to inhibitor (rapamycin)
- Dog: activation of ECM-receptor interaction, protein digestion and absorption, focal adhesion fibronectin type III domain, ADAMTS2

Shelly et al, 2005; Shin, et al, 2007; Muekawa et al, 2014; Bracheler et al, 2017

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MELANOMA CONCLUSIONS

- Know your enemy!
 - Location is key!!
- Check for metastases, especially in case of oral and ungual melanoma
- Therapy of choice:
 - Surgery: tumor (wide) incl. regional lymph nodes
 - No proven benefit of adjuvant chemotherapy
 - Oral melanoma: add hypofractionated RTx protocol
- Systemic treatment options necessary!!
 - Immunotherapy?

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