You Can Irradiate That??
New and Little Known Uses for Radiation

Ira Gordon, DVM
Diplomate American College Veterinary Radiology- Radiation Oncology
Overview

• Radiation Background
  • What is radiation
  • Types of radiation

• Radiation Innovations
  • What’s new

• Courses of Radiation
  • Full-course
  • Hypofractionated
  • Stereotactic

• Common Applications

• New and Novel Uses of Radiation
What is radiation?

- Electromagnetic (Photons; x-rays and gamma rays)
  - Properties of both particles and waves
  - Wavelength inversely proportional to frequency/energy
- Particles
  - Electron
  - Proton
  - Neutron
How do you make radiation?
What’s new in radiation therapy
What’s new in radiation therapy
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What’s new in radiation therapy
As of September 19, 2015, the ACVR membership includes 97 Diplomates in Radiation Oncology and 19 Residents-in-Training in Radiation Oncology.
What are common “courses” of radiation

- **Full-course Protocols**
  - Aka “Definitive” or “curative-intent”
  - ~15-20 fractions
  - Daily Mon-Fri
  - Approximately 3.5-4 weeks

- **Hypofractionated Protocols**
  - Aka “Short-course” or “palliative”
  - 2-6 fractions
  - Daily or weekly
Time, Dose, and Fractionation
# Full-Course Radiation

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<thead>
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**49.5 Gy Total**
# Hypofractionated Radiation

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<td>8 Gy</td>
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<td>8 Gy</td>
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32 Gy Total
### Accelerated Hypofractionated Radiation

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<tbody>
<tr>
<td>4 Gy</td>
<td>4 Gy</td>
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</table>

**20 Gy Total**
Stereotactic Radiation Therapy (SRT)

- Large dose / fraction in 1-5 fractions
- **Treatment planning:**
  - Assign maximum and minimum dose to tumor volume and normal structures
- Multileaf collimators or stereotactic cones “sculpt” radiation dose to tumor volume
- Goal to deliver outcomes that compare to full-course therapy in just a few treatments
Precision Conformal High-Dose Radiation (aka SRT/SRS)

Conventional radiation
• Relies on fractionation to minimize damage to surrounding normal tissues
• 12-20 doses for definitive-intent or ~4 larger doses given over time for palliative-intent
• Wide margins around gross tumors to account for invasive microscopic disease and setup/delivery uncertainties

Stereotactic radiation
• Relies on extreme accuracy and steep dose gradients to spare surrounding normal tissues
• Few large doses within one week for definitive-intent treatment course
• Narrow margins around gross tumors to account for invasive microscopic disease and setup/delivery uncertainties
## Stereotactic Radiation

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<td><strong>8-12 Gy</strong></td>
<td><strong>8-12 Gy</strong></td>
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</tr>
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</table>

**24-36 Gy Total**
Tumors “commonly” treated with radiation

- Soft Tissue Sarcomas
  - Microscopic – Full course
    - 95% 1 year control, 85% 3-5 year control
  - Macroscopic –
    - Full course – 50% 1 year
    - Hypofractionated – 50% 5 month
    - SRT- Not reported yet in dogs, 50% 8 months in cats
Tumors “commonly” treated with radiation

- Mast cell tumors
  - Microscopic – Full course – 90% 3-5 year control
    - Treat lymph node for high risk MCT – median DFI 3 years
  - Macroscopic – Full course, Hypofractionated +/- stereotactic
Tumors “commonly” treated with radiation

- Nasal tumors
  - Medical treatment – 2-5 month ST
  - Full course – 1-1.5 year ST
  - Hypofractionated- 5-10 month ST
  - SRT – 1+ year
Tumors “commonly” treated with radiation

- Oral tumors (Melanoma, SCC, FSA)
  - Stereotactic, Full course, hypofractionated
Tumors “commonly” treated with radiation

- Oral tumors (Melanoma)
  - Hypofractionated
    - 85% Response rate
    - 7-12 month ST
    - Consider PLNI
    - Adjuvant immunotherapy
Tumors “commonly” treated with radiation

- Invasive Thyroid tumors
  - Full course
    - Slow to respond (max 6-12+ months)
    - 50% PFS 2-3+ years
  - Hypofractionated
    - >1 year average tumor control
Tumors “commonly” treated with radiation

- **Brain Tumors**
  - Surgery vs radiation therapy, vs surgery + radiation therapy
    - Feline meningioma – Surgery often curative
    - Canine meningioma
      - Surgery may result in more rapid clinical improvement
      - Radiation may result in longer PFS
      - Unclear if surgery + radiation improves PFS
  - Canine glioma – Radiation often preferred over surgery
  - Pituitary tumors
    - Surgery is risky and performed at very few places
    - Radiation therapy associated with 2.5-3.5+ year MST
- **Full course versus stereotactic radiation – most recent studies**
  - SRT – 13 month median survival time (16 month Disease Specific Survival)
  - Full course conformal – 19 month median survival time (30 month Disease Specific Survival)
Tumors “commonly” treated with radiation

- Brain Tumors
  - Microscopic – Full course
  - Macroscopic – Stereotactic or full course
Tumors “commonly” treated with radiation

- Brain Tumors
  - Why do we fail?
    - Viable tumor cells outside of the target region (most likely with SRT)
    - Radiation resistant tumor cells within the target volume (most likely with fractionated radiation therapy)
  - What can we try?
    - Can we do both?
      - A full-course of radiation therapy with an integrated stereotactic boost
Is there anything that isn’t a candidate for radiation therapy?

- Systemically advanced/metastatic tumors
- Cardiac tumors
- Lung tumors?
- GI tumors
  - Intestinal
  - Pancreatic
  - Hepatic
Did You Know?

- Bone tumors (osteosarcoma) can be effectively treated without amputation?
  - Palliative radiation therapy
Canine OSA

“Palliative” Radiation Therapy
- Weekly x 4, daily x 2
- Well tolerated, outpatient, less expensive
- Good pain control in 75-90% of cases
- Median duration = 2-4 months
  - May be improved with chemo or bisphosphonates
- Can be repeated
Stereotactic Radiation Therapy: Preliminary Outcomes

- Median Survival Time = 300 days (n=50)
- Promising local tumor control
- Minimal, well-tolerated skin side effects
- Case selection reduces risk of fracture
  - Reported to be ~30%
Did you know?

- Epulides are effectively treated with radiation therapy
- Slow and/or incomplete regressions
- 80% 3-year PFS
Genitourinary tumors have improved outcomes with radiation therapy

- Full course IMRT for GU carcinomas
  - Overall survival – 22 months
  - Event free survival – 10 months
- SRT – an option for prostatic but not bladder tumors
- Hypofractionated RT
  - Can relieve urinary obstruction in most dogs
You can irradiate lipomas!

- **Infiltrative lipomas**
  - Rare variant characterized by aggressive local tissue invasion and frequent recurrence after surgical excision

- **Radiation therapy**
  - Effective post-operatively or as primary mode of therapy
  - 80% PFS at 3 years post-RT
Plasma cell tumors
Anal Sac Carcinomas

- Multimodal therapy results in best reported outcomes
- Surgical excision of primary mass alone
  - 6-10 months
- Excision of primary mass and SL LNs
  - 12-18 months
- Excision of primary mass plus chemo
  - 12-18 months
- Excision of mass plus RT and chemo
  - 30 months
  - Primary tumor and lymph nodes
Thymoma

- **Canine/Feline**
  - 75% response rate to RT for non-resectable thymoma
  - MST – dogs=8 months, cats=24 months

- **Rabbit**
  - >50% perioperative mortality with surgery
  - 10% peri-readiation mortality
  - MST ~2 years
Hemangiosarcoma

- Radiation therapy for non-splenic hemangiosarcoma
  - 70% response rate
  - MST 3 months (due to metastatic disease)
  - Usually treated with hypofractionated RT
Lymphoma!

- Radiation is the treatment of choice for solitary extra-nodal lymphoma
- Radiation is effective at palliating relapsed multicentric lymphoma sites but remissions are brief unless additional chemo is effective
- “Half-body” radiation in treatment of canine lymphoma improves long-term cure rates in several studies when included in induction treatment protocol
  - May improve outcomes in rescue setting if lymphoma can be driven into remission


**Sequential Low-Dose Rate Half-Body Irradiation and Chemotherapy for the Treatment of Canine Multicentric Lymphoma**

Lymphoma!

- GI lymphoma
  - >90% response rate in RESCUE setting
  - Median survival of 7 months post RT (12 months overall from diagnosis)


Dorothy L Parshley DVM, PhD1,2,3*, Susan M LaRue DVM, PhD, DACVS, DACVR (Radiation Oncology)4, Barbara Kitchell DVM, PhD, DACVIM (Oncology and Internal Medicine)1,2, David Heller DVM, DACVIM (Oncology)1,5, Ravinder S Dhaliwal DVM, MS, DACVIM, DACVP1,6
Other uncommon indications for radiation therapy

- Histiocytic sarcoma
  - Estimate >75-80% response rate
  - Variable duration, always consider chemotherapy

- Heart base tumors (chemodectoma)
  - High rates of response, frequently durable for >1 year
Tumors that were previously irradiated

- Response rates for second RT courses are similar to original response rate
  - 89% for nasal tumors
  - 75% for bone tumors
- Response rates usually shorter with second course
  - 9 versus 17 months for nasal tumors
  - 1-2 months versus 3-4 months for bone tumors and palliative RT
- Rule of thumb
  - Reasonable to expect a response of about 50% of initial response
Radiation Treats Benign Diseases
Radiation Treats Benign Diseases (Humans)

- Used extensively abroad (primarily in Germany)
  - >35,000 patients with benign disease per year treated with RT
    - 2/3 are inflammatory or degenerative osteoarticular diseases

- Reasons for lack of use domestically
  - Fear of radiation induced tumors
  - Fear of litigation
  - Lack of established/optimal protocols
Fear of radiation induced tumors

- Risk of carcinogenesis
  - Highly complex
  - Presumed risk is extrapolated from effects at high or moderate doses with calculations based on the most conservative assumptions
    - Atomic bomb explosions (Hiroshima and Nagasaki) and nuclear plant accidents (Chernobyl)
    - RT for ankylosing spondylitis, repeated fluoro for tuberculosis
  - Biggest risk factor is age
    - People < 30 years have highest risk and >60 year have lowest risk
Fear of radiation induced tumors

- Epidemiologic studies with low doses of radiation have overall not detected significant increases in cancer risk
  - May be too weak to appear statistically significant in studies to-date
- Populations with increased natural radiation exposure
  - In some cases, have decreased cancer risk and fewer cellular chromosomal aberrations
- Nuclear plant workers exposed to low-dose radiation
  - Inconsistent results may be due to lack of statistical power
What is the risk of carcinogenesis with low-dose radiation?

- Could be nonexistent
- Probably too weak to appear statistically significant
Anti-inflammatory effects of low-dose radiotherapy

- Low dose RT has a strong anti-inflammatory effect
- Demonstrated efficacy in people for
  - Degenerative bone and inflammatory disease
    - Osteoarthritis
    - Bone spurs
Mechanisms of Anti-inflammatory effects of low-dose radiotherapy

- Decreased adhesion of neutrophils to endothelial cells
- Induction of apoptosis of inflammatory cells
- Decreased expression of adhesion molecules
- Decreased nitric oxide and reactive oxygen species
- Increased expression of anti-inflammatory cytokines
- Decreased AKT expression in neutrophils
- Increased AP-1 activity
- Activation of NF-kappa B

<table>
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<tr>
<th>Tab. 1</th>
<th>Summary of radiobiological mechanisms of LD-RT</th>
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<tbody>
<tr>
<td>Mechanism</td>
<td>Dose tested</td>
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<tr>
<td>Immunoglobulin superfamily</td>
<td>No change in expression of ICAM-1 or VCAM-1 (dose 0.1–1 Gy) [21, 24, 25, 31]</td>
</tr>
<tr>
<td>Selectins</td>
<td>↓ expression L-selectin (minimum dose of 0.3 Gy), no change in E-selectin or P-selectin [31]</td>
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<td>↓ expression E-selectin (minimum dose of 0.7 Gy) [25, 53]</td>
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<td>↑ E-selectin (0.5 Gy) [21]</td>
</tr>
<tr>
<td>iNOS</td>
<td>↓ iNOS (≤1.25 Gy) [24, 26]</td>
</tr>
<tr>
<td>ROS</td>
<td>↓ ROS (0.3–0.6 Gy) [58]</td>
</tr>
<tr>
<td>NF-κB</td>
<td>↑ NF-κB (maximum of 0.5 Gy), ↓ 0.6 Gy 0.8 Gy and ↑ again at 1–3 Gy [54]</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>↑ TGF-β1 (maximum of 0.5 Gy) [54]</td>
</tr>
<tr>
<td>AP-1</td>
<td>↑ AP-1 (maximum of 0.3 Gy), ↓ 0.5–1 Gy and ↑ again at 3 Gy [52]</td>
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</table>

ICAM-1 Intercellular adhesion molecule 1, VCAM-1 vascular cellular adhesion molecule 1, iNOS inducible NO-synthetase enzyme, ROS reactive oxygen species, NF-κB nuclear factor kappa B, TGF-β1 transforming growth factor β1, AP-1 activator protein 1
<table>
<thead>
<tr>
<th>Author</th>
<th>Experimental model</th>
<th>RT dose/time</th>
<th>Results</th>
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<tr>
<td>Van Pannewitz</td>
<td>Rabbit knee arthritis (electrocoagulation)</td>
<td>1 Gy</td>
<td>↓ inflammation symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Different</td>
<td></td>
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<tr>
<td>Glenn</td>
<td>Healthy rabbit leg</td>
<td>0.1–10 Gy (90–400 KV)</td>
<td>↑ phagocytic index at 1 Gy</td>
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<td></td>
<td></td>
<td>24 h–2 weeks before study</td>
<td>↓ phagocytic index at doses &gt;1 Gy</td>
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<tr>
<td>Budras</td>
<td>Rabbit knee arthritis (intraarticular granugoenol</td>
<td>5 fractions of 1.5 Gy</td>
<td>↓ inflammation (↓ cellular proliferation at sinovial membrane; ↓ synovial fluid)</td>
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<td>injection)</td>
<td>Immediately, 6 or 12 weeks after injection</td>
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<tr>
<td>Trott</td>
<td>Rat knee arthritis (intraarticular <em>Mycobacterium</em> TBC</td>
<td>5 Gy</td>
<td>↓ inflammation (4 fractions of 1 Gy (↓ articular swelling, ↓ destruction of cartilage and bone)</td>
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<td></td>
<td>injection)</td>
<td>4 fractions of 1 Gy (daily)</td>
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<td>3 h after injection</td>
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<tr>
<td>Fischer</td>
<td>Rabbit knee arthritis (Intraarticular injection of</td>
<td>5 fractions of 1 Gy (daily)</td>
<td>↓ inflammation (also histological)</td>
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<tr>
<td></td>
<td>papain)</td>
<td>1 day post-injection</td>
<td>(↓ articular diameter, ↓ synovial membrane thickness, ↓ synovial membrane cells)</td>
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<td>Hildebrandt</td>
<td>Mice granulomatous disease</td>
<td>2 Gy day 2</td>
<td>↓ inflammation (also histological)</td>
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<td>2 Gy day 6</td>
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<td>5 fractions of 0.5 Gy from day 2 to day 6</td>
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<tr>
<td>Hildebrandt</td>
<td>Rat knee arthritis (<em>Mycobacterium</em> TBC)</td>
<td>5 fractions of 1 Gy</td>
<td>↓ inflammation (also histological)</td>
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<td></td>
<td>5 fractions of 0.5 Gy</td>
<td>↓ iNOS and ↑ HO-1</td>
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<td>15–19 days post-induction</td>
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<tr>
<td>Liebmann</td>
<td>Rat leg arthritis (<em>Mycobacterium</em> TBC)</td>
<td>5 fractions of 1 Gy</td>
<td>↓ inflammation (more effective 5 fractions of 1 Gy)</td>
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<td>5 fractions of 0.5 Gy</td>
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<td>10–26 days post-induction</td>
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<tr>
<td>Schaeue</td>
<td>Mice superficial dorsal air cell model</td>
<td>0–5 Gy</td>
<td>↓ iNOS, ↑ HSP-70 and ↑ HO-1</td>
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<tr>
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<td>6 h after induction</td>
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<td>Arenas</td>
<td>Mice systemic inflammation model with lipopolysaccharide</td>
<td>0.1, 0.3, 0.6 Gy</td>
<td>↓ leukocyte adhesion</td>
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<tr>
<td></td>
<td>(LPS)</td>
<td>5, 24, 48, 72 h</td>
<td>ICAM-1 not modified</td>
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<tr>
<td></td>
<td></td>
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<td>↑ TGF-β1</td>
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iNOS: inducible NO-synthetase enzyme, HO-1: hemoxygenase-1, HSP70: inducible heat shock protein 70.
But does it work?

Keller et al. Radiation Oncology 2013, 8:29
http://www.ro-journal.com/content/8/1/29

RESEARCH

Efficacy of low-dose radiotherapy in painful gonarthrosis: experiences from a retrospective East German bicenter study

Stephanie Keller¹, Klaus Müller², Rolf-Dieter Kortmann², Ulrich Wolf², Guido Hildebrandt³, André Liebmann², Oliver Micke⁴, Gert Flemming⁵ and Dieter Baaske⁶
### Table 2 Patient characteristics

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<thead>
<tr>
<th>Item</th>
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<tr>
<td><strong>Gender</strong></td>
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<td>Male</td>
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<td>30.5</td>
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<tr>
<td>Female</td>
<td>721/1037</td>
<td>69.5</td>
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<tr>
<td><strong>Age group</strong></td>
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<td>≤ 60 years</td>
<td>319/1037</td>
<td>30.8</td>
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<tr>
<td>&gt; 60 years</td>
<td>718/1037</td>
<td>69.2</td>
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<td><strong>Severity</strong></td>
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<td>Minimal</td>
<td>119/651</td>
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<td>Moderate</td>
<td>228/651</td>
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<tr>
<td>Severe</td>
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<td><strong>Duration of pain</strong></td>
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<td>&lt; 1 year</td>
<td>213/867</td>
<td>24.6</td>
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<tr>
<td>&gt; 3 years</td>
<td>439/867</td>
<td>50.6</td>
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### Figure 1 Overall response to radiotherapy

Pain, as it was subjectively graded by the patients immediately or up to two months after the completion of a series of radiotherapy.
Figure 4 Response to radiotherapy split by radiological severity of gonarthrosis. Pain, as it was subjectively graded by the patients immediately or up to two months after the completion of a series of radiotherapy. There was a significant difference in radiation-induced pain relief between minimal/ moderate and severe gonarthrosis (p = 0.036).
Figure 6: Response to radiotherapy according to the additional mail survey (106 evaluable questionnaires). Pain after the end of radiotherapy, as it was subjectively graded by the patients in a retrospective mail survey, which was effected in 2010, i.e., two to fourteen years after treatment.

Figure 8: Response to radiotherapy according to the additional mail survey. Duration of clinical improvement after radiotherapy, as it was subjectively reported by the patients in a retrospective mail survey, which was effected in 2010.
Anti-inflammatory Radiation (AIR) Therapy

- In dogs (personal communication, Carla Rohrer-Bley, DVM DAVCR)
  - 2 Gy x 3 fractions on consecutive or every other day
  - 80% response to initial course, >90% if repeat due to lack of improvement 2-3 weeks later
    - 60% at 3 months
    - 40% at 12 months
    - Can be repeated multiple times (>5 courses in some dogs)
  - No significant acute side effects/toxicity
  - Hair color change <5% of the time
AIR in cats

- Osteochondrodysplasia
  - Severe, progressive and debilitating disease causing lameness
  - Marked responses reported to radiation that can last for many years

Journal of Veterinary Internal Medicine

Case Report
J Vet Intern Med 2015

Efficacy and Complications of Palliative Irradiation in Three Scottish Fold Cats with Osteochondrodysplasia

A. Fujiwara-Igarashi, H. Igarashi, D. Hasegawa, and M. Fujita
AIR in cats

- Other arthritic diseases in cats
  - Treated several cats as alternative to chronic NSAID use with good initial results
Acral lick dermatitis

- Aka lick granuloma or canine neurodermatitis
  - Stereotypic behaviour resulting in self-mutilation
  - Reported to have an 80-90% response rate to radiation therapy
A newly designed radiation therapy protocol in combination with prednisolone as treatment for meningoencephalitis of unknown origin in dogs: a prospective pilot study introducing magnetic resonance spectroscopy as monitor tool

Katrin Beckmann\textsuperscript{1*}, Inés Carrera\textsuperscript{2,3}, Frank Steffen\textsuperscript{1}, Lorenzo Golini\textsuperscript{1}, Patrick R Kircher\textsuperscript{2}, Uwe Schneider\textsuperscript{4,5} and Carla Rohrer Bley\textsuperscript{4}
Granulomatous Meningoencephalitis (GME)

- All dogs had improvements to imaging
- All dogs responded/improved (half fully, half partially)
  - 1 dog only responded for a few weeks
  - 5 other dogs responded for >12 months
- Separate study showed MST of 400 vs 40 days with RT-steroids versus steroids alone
Anecdotal applications for benign disease

- Chronic rhinitis
  - Clinical improvement for 8-12 months with hypofractionated protocols
- Refractory feline stomatitis
  - N=1, marked clinical response in a cat with persistent stomatitis after full-mouth extractions and aggressive medical therapy
- Potential considerations (n=0)
  - Refractory IBD
  - Pancreatitis
  - Polyarthritis
Strontium Plesiotherapy
Strontium Plesiotherapy
Strontium indications

- >95% response rate, 80% non-recurrence rate

- >95% control rate
Strontium indications

- Avian uropygial gland tumors
- Equine eyelid and conjunctival tumors
- Canine/Feline small oral tumors
  - Plasmacytoma, SCC
- Canine/feline eyelid/eartip tumors
  - SCC
- Canine/feline small dermal tumors
Don’t Think Outside The Box
Think Like There Is NO BOX!