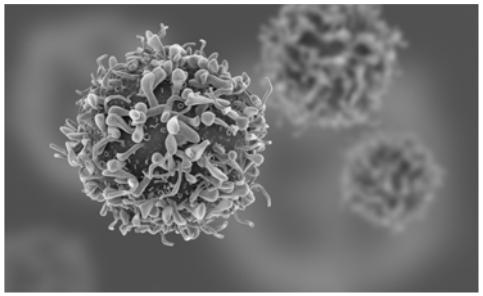

Advances in Cancer Therapy for Animals and Humans

Sue Armstrong MA VetMB VetMFHom CertIAVH MRCVS RsHom

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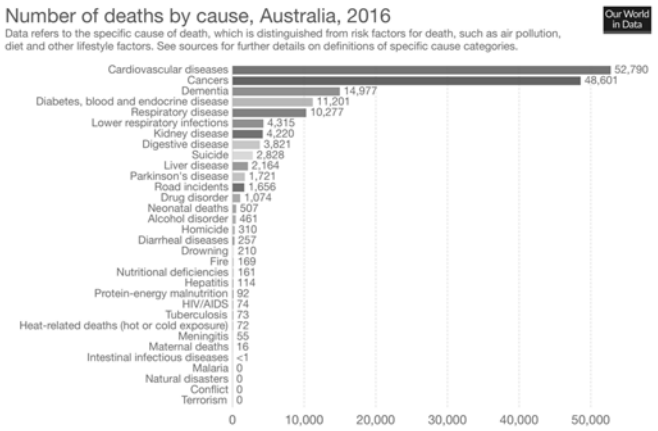
As communicable diseases and overt nutritional deficiencies decline as the major causes of death they are replaced by increased levels of diseases of the 'unexpended organism"

How long are we supposed to live?

2



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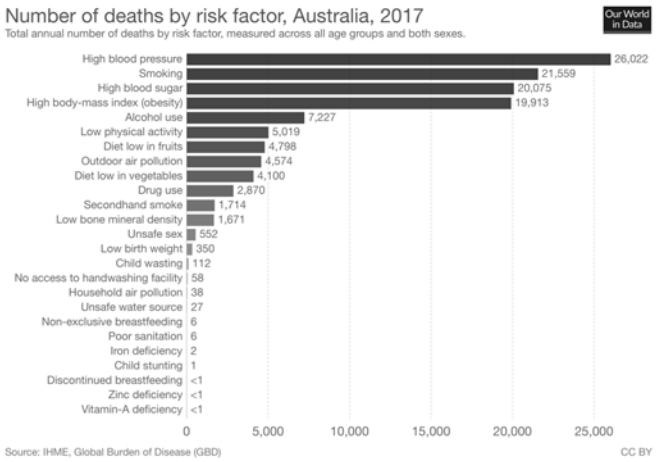

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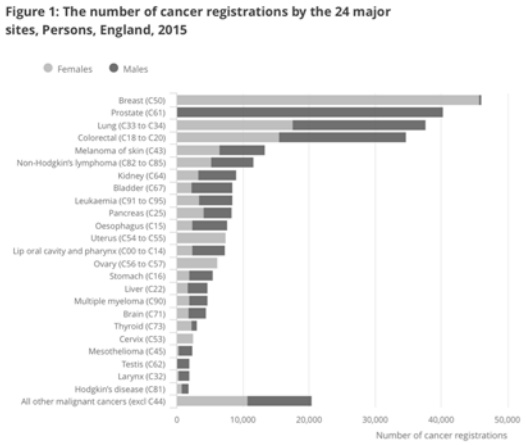

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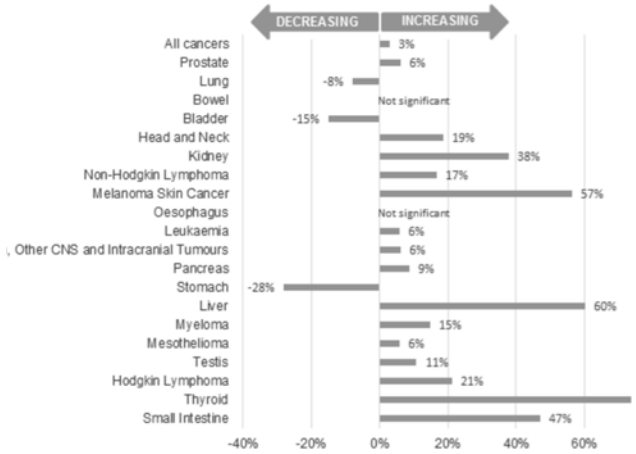

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Do we know these rates in dogs, cats and horses?

How many companion animals are diagnosed each year with cancer?

There are 65 million dogs and 32 million cats in the United States. Of these, roughly 6 million new cancer diagnoses are made in dogs and a similar number made in cats each year. See http://ccr.nci.nih.gov.

How does this figure compare with the human population?

According to the American Cancer Society, approximately 11,028,000 people are living with cancer in the United States. Over 1,000,000 new diagnoses are made each year. 1 in 2 men and 1 in 3 women will be diagnosed with cancer in the United States. See http://www.cancer.org.

How are pet cancers similar to human cancers?

Cancer in the pet population is a spontaneous disease often similar to cancer seen in humans; some examples include non-Hodgkin's lymphoma, prostate cancer, head and neck carcinoma, mammary carcinoma, melanoma, soft tissue sarcoma, and osteosarcoma.

In what ways is the companion animal model relevant to the study of human cancer?

The Canine Genome Sequencing Project at the Broad Institute successfully mapped the genome of a boxer named Tasha in 2005. The map of the genome has been used to confirm that many of the same genes involved in dog cancers are also involved in human cancers. See http://research.nhgri.nih.gov/dog_genome.

No mandatory databases
For recording animal death causality

Closest we come to a census is through Insurance data

7

Animal Cancer Foundation

COMPARATIVE ONCOLOGY
Uniting Pet and Human Research for a Cure™

RESEARCH ARTICLE | OPEN ACCESS

Estimating canine cancer incidence: findings from a population-based tumour registry in northwestern Italy

Elisa Baioni, Eugenio Scanziani, Maria Claudia Vincenti, Mauro Leschiera, Elena Bozzetta, Marzia Pezzolato, Rosanna Desiato, Silvia Bertolini, Cristiana Maurella and Giuseppe Ru

BMC Veterinary Research BMC series – open, inclusive and trusted 2017 **13**:203 | DOI: 10.1186/s12917-017-1126-0

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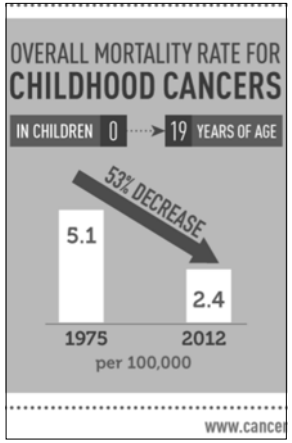


Is good always what it appears to be?

The perils of data

9

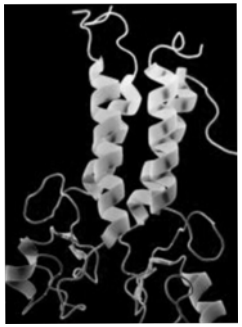
So what is cancer?

- Cancer is a **complex multigenic disease**
- **There is no such thing as a single gene for a specific cancer**
- A **series** of **genetic events** and **multiple mutations** are required for a cell to become a cancer cell
- Contrary to many models which suggest that mutations occur sequentially, evidence suggests that they are **random**

10

The Hallmarks of Cancer 1.

- Enabling Characteristics
  - **Genomic instability** and mutation
  - Tumour promoting **inflammation**
- Emerging Characteristics
  - **Deregulating cellular energetics**
  - **Aerobic Glycolysis**
  - **Avoiding immune destruction**



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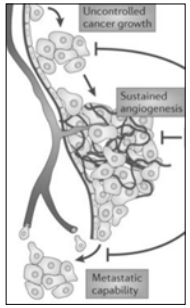
The Hallmarks of Cancer 2.

1. Self sufficiency in growth signals
2. Insensitivity to anti growth signals
3. The ability to evade **apoptosis**
4. Limitless reproductive potential
5. Sustained **angiogenesis**
6. The capacity to invade tissues and metastasise



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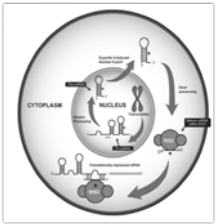
Cancer Genes

- **Two major classes of cancer genes:**
  - **Genes that directly affect cell growth**
    - Ability to control cell division (birth) or cell death (apoptosis)
    - **Positively = oncogenes** e.g. Ras, Myc
      - Normally tightly controlled – in cancer usually a single allele dominant mutation
    - **Negatively = tumour-suppressor genes** e.g. Rb, p53
      - Normally restrain cell growth – ability is lost in cancer
      - Both alleles must be inactivated – recessive mechanism
  - **Caretaker Genes**
    - Affect the ability of the cell to maintain its integrity
    - Cells with a deficiency of these genes have an increased rate of mutations including oncogenes and tumour suppressor genes.



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Conventional therapeutics for decades relied upon surgical removal and/or destroying the cancer cells slightly faster than the healthy cells of the body

CAM therapies in general have from the beginning recognised the concept of individuality and that the target of therapy are the immune and energy systems

These worlds are now beginning to converge

We have to be sure that what we have to offer is better or at least as good as the conventional pathway

We have to know how the conventional treatment will be affected by any intervention that we offer

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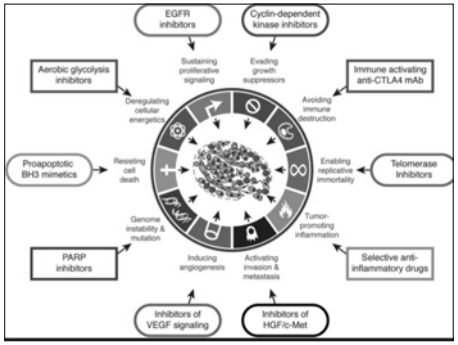
New Therapies Aimed at the Affected Genes



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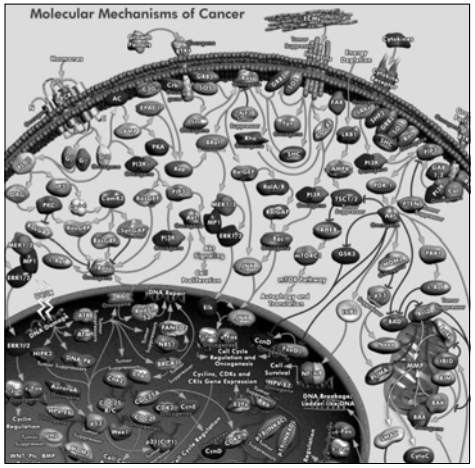

From:
Qiagen 2013

Nuclear DNA
vs.
mDNA
vs.
Microbial DNA
vs.
ECM signaling

16

DIAGNOSIS

17

Cancer Screening Programmes

- NHS Breast Screening
  - 50-70 year old women
  - Looking for radiographic changes
- NHS Cervical Screening
  - 25 - 64 year old women
  - Looking for cellular changes
- NHS Bowel Cancer Screening
  - people aged 60 - 74
  - Looking for blood in the stool

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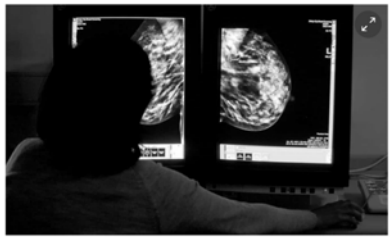
theguardian 2016

Study casts doubt on breast cancer testing

Researchers study original Swedish trial data, which provided evidence for UK's and other screening programmes, and claim benefits were vastly overestimated



A consultant studying a mammogram. The latest study is set to reignite the debate over breast cancer screening. Photograph: Rui Vieira/PA

The reduction in deaths is probably approx 10% in those screened versus those not

19

Blood Screening

- **Inflammatory markers** in the blood e.g. C-reactive protein
  - Not specific
- **PSA** - prostate
- **CA 15-3** - raised in mammary cancer, lung, colon, pancreas, liver, ovary, cervix and endometrium
  - Used to monitor recurrence
  - Used to monitor response to therapy
- **CA 19-9**
  - Pancreas and colorectal, liver stomach and biliary tree cancers

Tumour Biomarkers in Dogs

Mitotic index e.g. cell proliferation indicators AgNOR, PCNA, Ki67

C-kit mutation – cell survival/proliferation Tyrosine kinases (Masitinib, Toceranib)

P-53 mutations (immunohistochemistry detects Overexpression of mutate p53)

cLBT (canine lymphoma blood test) (2 acute phase proteins)

Hypercalcaemia

Neoplasia index – CRP + TK1 (thymidine kinase)

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Familial Cancer (Humans) - Inherited Faulty Genes

- Bowel cancer
- Breast cancer
- Kidney cancer
- Melanoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Retinoblastoma (eye cancer)
- Thyroid cancer
- Womb cancer

In Dogs more and more online labs are offering tests to pet owners we have to be aware of the implications of this

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Imaging Techniques

- **Positron emission tomography – PET**
  - Radioactive tag added to a molecule e.g. glucose that is rapidly taken up by the cancer cells
- **Magnetic Resonance Spectroscopy – MRS**
  - During MRI, pulsed radio waves bounce off different molecules in the body with different frequencies, that can then be interpreted using MRS analysis e.g. high levels of choline is often associated with cancer and can be detected in this way
- **Photo Acoustic Imaging – PAI**
  - Modified version of ultrasound combining light and sound.
  - Different molecules return different wavelengths of ultrasound providing contrast to the image and information related to the tumour e.g. seeing areas of active blood vessel development by tracking O2 carrying haemoglobin

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Treatment

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Just some of the chemotherapy protocols

7+3, also known as DA or DAC in case of daunorubicin, or IA or IAC in case of idarubicin use	7 days of Ara-C (cytarabine) plus 3 days of an anthracycline antibiotic, either daunorubicin (DA or DAC variant) or idarubicin (IA or IAC variant)	Acute myelogenous leukemia, excluding acute promyelocytic leukemia
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine	Hodgkin's lymphoma
AC	doxorubicin (Adriamycin), cyclophosphamide	breast cancer
BACOD	bleomycin, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), dexamethasone	Non-Hodgkin lymphomas
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone	Hodgkin's lymphoma
BEP	bleomycin, etoposide, platinum agent	testicular cancer, germ cell tumors
CA	cyclophosphamide, doxorubicin (Adriamycin) (same as AC)	breast cancer
CAF	cyclophosphamide, doxorubicin (Adriamycin), fluorouracil (5-FU)	breast cancer
CAPOX or XELOX	capecitabine and oxaliplatin	colorectal cancer
CAV	cyclophosphamide, doxorubicin (Adriamycin), vincristine	lung cancer
CBV	cyclophosphamide, BCNU (carmustine), VP-16 (etoposide)	lymphoma
CHOEP	cyclophosphamide, hydroxydaunorubicin (doxorubicin), etoposide, vincristine (Oncovin), prednisone	Non-Hodgkin lymphomas
CEPP	cyclophosphamide, etoposide, procarbazine, prednisone	Non-Hodgkin Lymphomas
ChVPP/EVA	chlorambucil, vincristine (Oncovin), procarbazine, prednisone, etoposide, vinblastine, doxorubicin (Adriamycin)	Hodgkin's lymphoma
CHOP	cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine (Oncovin), prednisone	non-Hodgkin lymphoma
CHOP-R or R-CHOP	CHOP + rituximab	B cell non-Hodgkin lymphoma
ClaPD	clarithromycin, pomalidomide, dexamethasone	multiple myeloma
CMF	cyclophosphamide, methotrexate, fluorouracil (5-FU)	breast cancer
CMV	cisplatin, methotrexate, vinblastine	transitional bladder carcinoma
COP or CVP	cyclophosphamide, Oncovin (vincristine), prednisone	non-Hodgkin lymphoma in patients with history of cardiovascular disease

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Molecular and Genetic Testing
are important for the diagnosis of cancer
and for predicting risk
but can become
even more critical
when it comes to therapy

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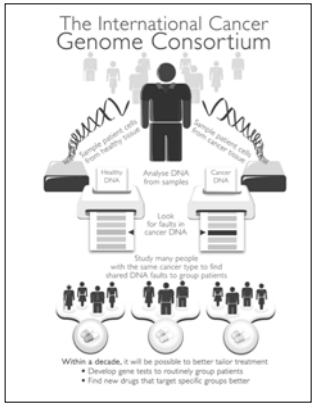

ICGC is mapping the genetic faults in 25,000 tumour samples from patients with 50 different types of cancer, including breast, bowel, ovarian, pancreatic and lung cancers. Cancer Research UK is leading the projects investigating prostate and oesophageal cancer.

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Molecular Diagnostic tests

Molecular diagnostics test a patient's cancer for particular genetic mutations

This can then help doctors work out the best course of treatment for that patient – be that a certain type of chemotherapy, or a **targeted drug** if available for the type of genetic mutation – giving the patient the best possible chance of a good outcome.

These tests can mean patients can **avoid side effects** from the drugs that will probably not work for them.

What are the tests?

For lung cancer, patients' tumour samples can be tested for faults in two genes: EGFR and ALK. EGFR faults mean they're likely to be sensitive to drugs like gefitinib and erlotinib. ALK faults suggest the drug crizotinib.

For bowel cancer, certain forms of the KRAS and NRAS genes suggest the patient may benefit from drugs like cetuximab.

For melanoma, patients with faulty forms of the BRAF gene can be offered drugs like vemurafenib and dabrafenib.

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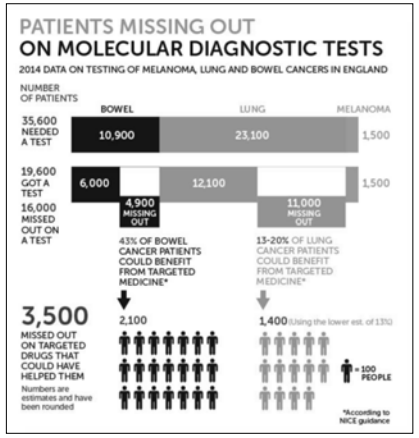
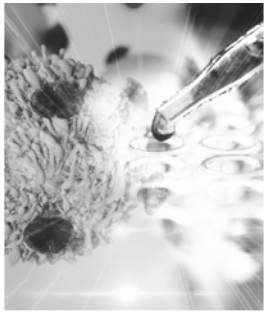


This situation will be many times worse in dogs due to cost
BUT
We have to be aware of the potential

28

Immunotherapy

- Treatments that harness the bodies own immune system to destroy tumours
- **Immune checkpoint inhibitors** - remove the brakes on normal immunological control e.g. Nivolumab - small lung cell cancer, melanoma
- **IMM-101 killed bacterium** to stimulate the immune system to reawaken when the cancer has switched it off
- **Monoclonal antibodies** e.g. Herceptin® (Trastuzumab) - HER2 positive breast cancer
- **Non-specific cancer immunotherapies and adjuvants** e.g. cytokines, interleukins, drugs e.g. Thalidomide in Multiple myeloma



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Cobemetinib

Elotuzamab

Daratumamab

We are now living in the world of '-mabs' and 'ibs'

The canine lymphoma blood test (cLBT) is commercially available. Studies demonstrate that this test is able to reliably detect recurrence of lymphoma up to 2 months prior to signs such as lymphadenopathy.

Osimertinib

Exazumib

Necitumumab

30

Some common cancers in which vaccines are being tested

Some of the more common types of cancer in which vaccines are now being studied include:

- Brain tumors (especially glioblastoma)
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Kidney cancer
- Lung cancer
- Lymphoma
- Melanoma
- Pancreas cancer
- Prostate cancer

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Advances in Radiotherapy

- **IMRT** - intensity modulated radiotherapy - varies the beam according to the shape of the target
- **IGRT** - image guided radiotherapy - external beam radiation with the position verified using imaging prior to each fraction
- **High Dose Brachytherapy** - hollow tubes inserted into the affected area e.g. prostate deliver high dose radiation directly to the tissue - ultrasound guided
- **CFRT** - High Dose Conformal Radiotherapy - 3D dose calculation using 3D anatomic and functional imaging

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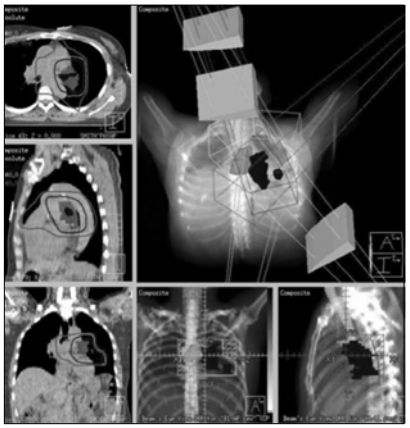

IGRT

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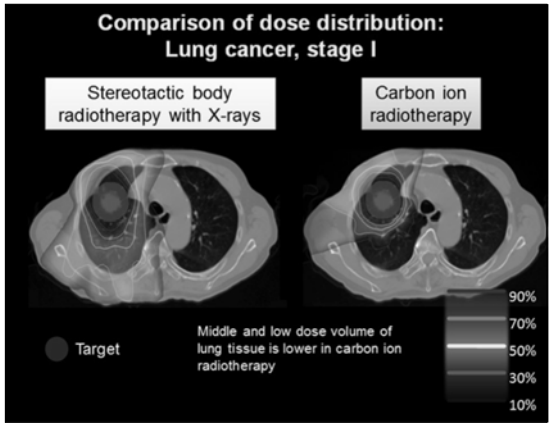

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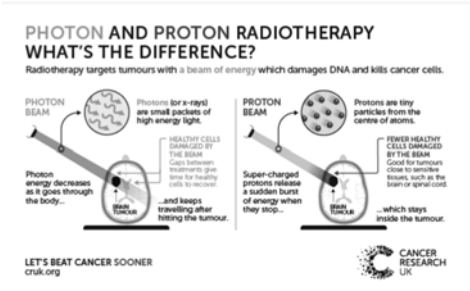
Proton Beam Therapy



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NHS
The Christie
NHS Foundation Trust

The Christie cyclotron has been built by Varian in Troisdorf, Germany - 2018. The cyclotron weighs the same as a Boeing 747 and is the size of a family car.

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What else is new in Dogs?

- There are advances both in the medical and surgical fields of veterinary cancer treatment
- The Veterinary Society of Surgical Oncology
  - Incorporates surgery and other treatment modalities
  - Exciting pioneering work at centres such as Fitzpatrick Referrals Animal Cancer Hospital
    - Limb sparing ops for dogs with osteosarcoma
    - Extensive lymph node removal in e.g. anal adenocarcinoma's, MCT's
    - More aggressive multimodal combined techniques
- And of course animals too are beginning to get more access to 'ib's' and 'mabs'

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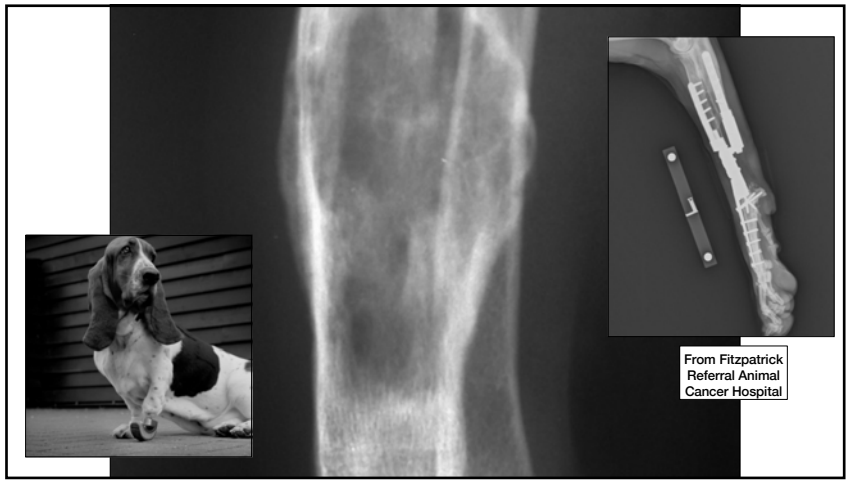

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