The continuing quest for quantitative image analysis

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Overview

- Introduction: Medical imaging & Computer vision
- Breast cancer
  - Quantitative mammography + analytics, dose
  - Breast MRI
- Measuring therapy response
  - Colorectal cancer
- What cures cancer?
  - A cautionary tale: melanoma
  - Angiogenesis
- Another cautionary tale about quantitation
  - Shape and size of liver tumours

Medical Image Analysis ≠ Computer vision + clinical data

Medical image analysis addresses a specific medical problem:

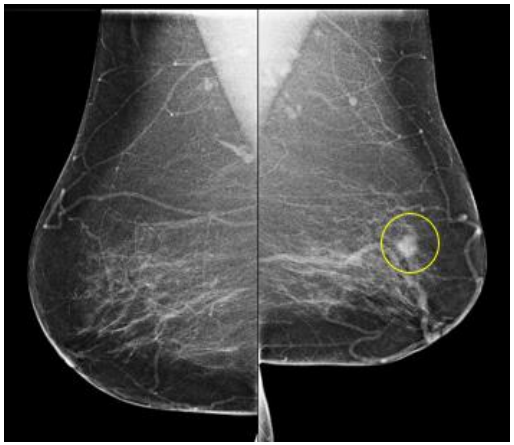
- Working with clinicians
- What clinicians need
- What clinicians use
- The fundamental roles of models

Working with clinicians

Doctors specify the problem

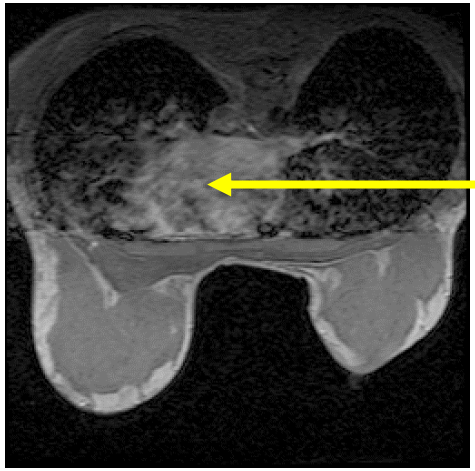
$$E^{\text{imp}}(\mathbf{x}) = \phi(V_t, \mathbf{x}) A_p t_s \int_0^{E_{\max}} N_0^{\text{rel}}(V_t, \varepsilon) G(\varepsilon) D(\varepsilon) \exp^{-\mu_{\text{lucite}}(\varepsilon) h_{\text{plate}}} \exp^{-h\mu(\varepsilon)} d\varepsilon$$

Doctors are unimpressed by mathematics, algorithm details, ….



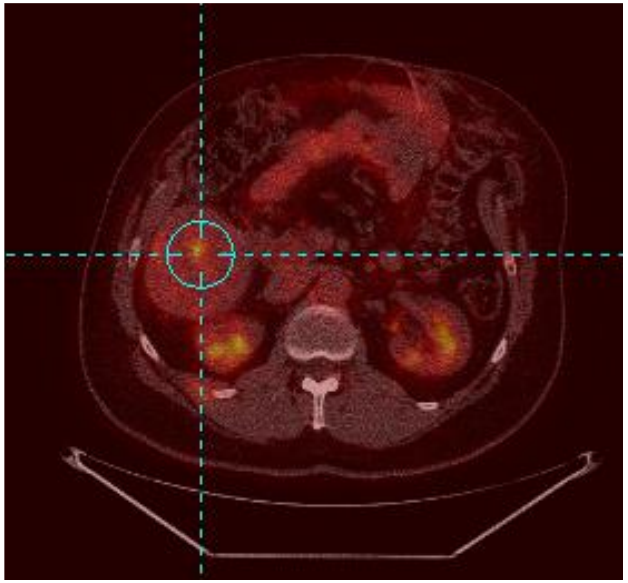
Doctors are impressed by results that enable them to work better

Confidence builds slowly, but can drop like a stone

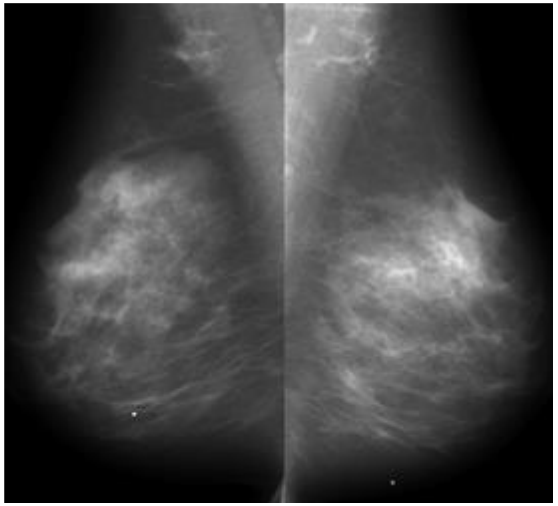


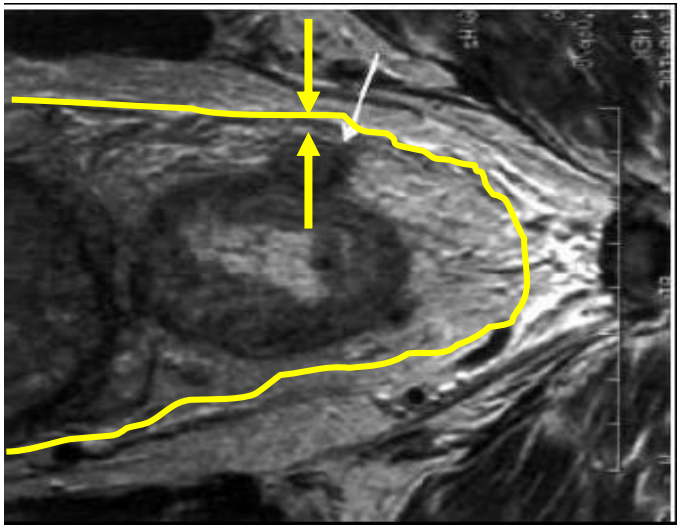
Algorithm: “this is a rapidly enhancing region, suggestive of cancer

What clinicians need



Focal enhancement of FDG in liver*





It is recommended that the circumferential resection margin be at least 1mm if surgery is to be an option

	Right	Left
Volume of Fibroglandular Tissue (cm³)	129.5	123.3
Volume of Breast (cm³)	631.7	645.5
Volumetric Breast Density (%)	20.5	19.1

1.5 mGy | 9.1 kPa | 19.8%

Tools they can trust & provide the information they need

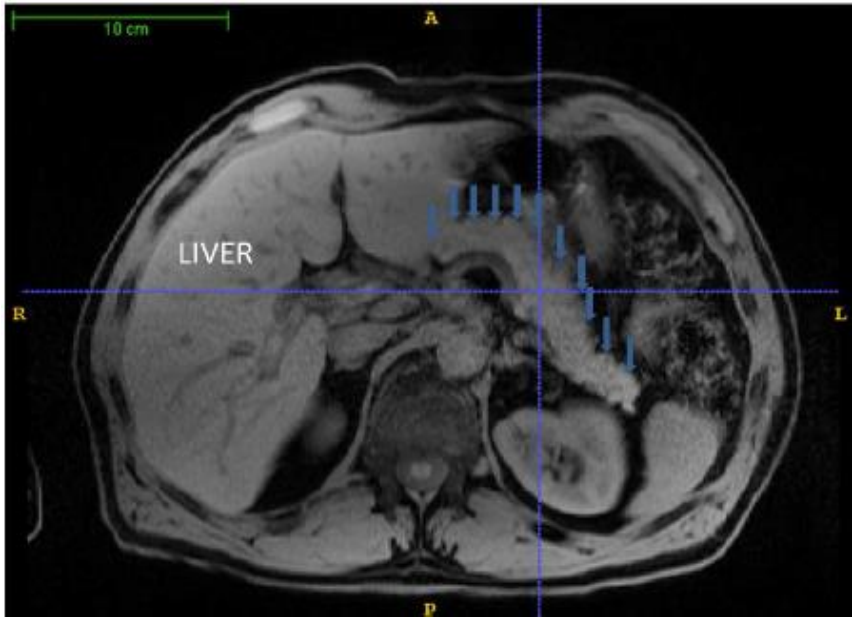
Numbers!!!

Accuracy

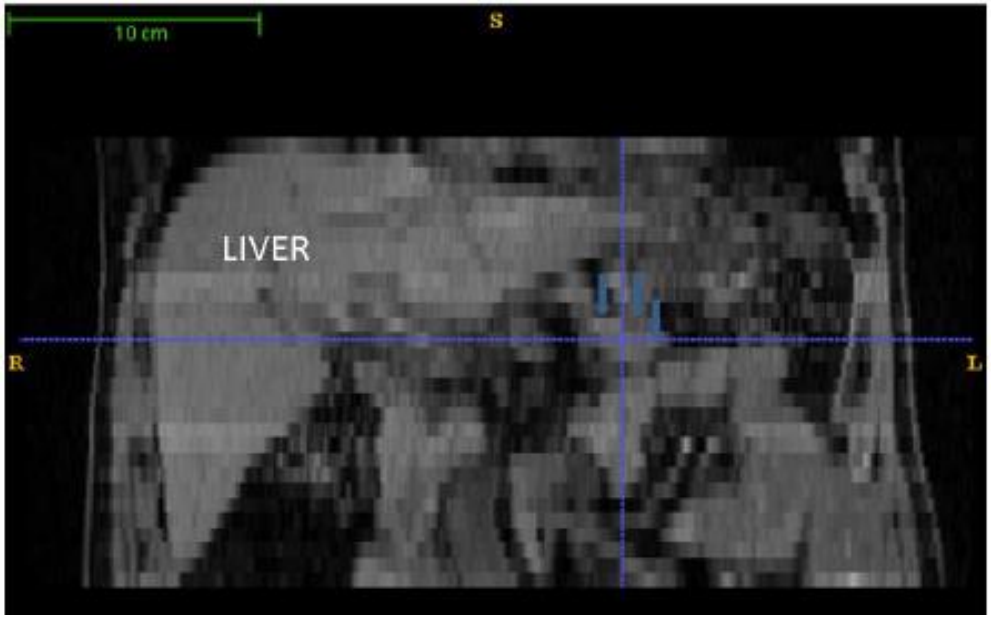
Response to therapy: If error in measurement m_i is ε_i, then error $(m_1 - m_2) = \varepsilon_1 + \varepsilon_2$

*XD3, Mirada Medical Ltd.

Image quality



Axial view of liver and pancreas (blue arrows)



Coronal view of the liver

Poor SNR compared to vision cameras, subject to artefact (e.g. bias field)

Poor sampling density:

- Partial volume effect
- Volume estimation and segmentation
- Interpolation? (Friday)
- Probability density function? (Friday)

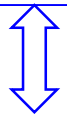
The need to deliver accurate results, 24/7, 99.9% of the time, with poor SNR and sampling, massive variations across the normal population … ➔ incorporate models

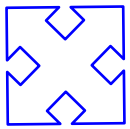
Clinical aspects of Cancer

- Breast cancer
  - Breast density
  - Microcalcifications
  - Stellate masses
- Colorectal cancer
  - circumferential resection margin
  - lymph node analysis
  - dceMRI & pharmacokinetic modeling
- Liver cancer
  - bias correction
  - breath hold
  - time to enhancement
  - morphology to aggressive mutation

Image analysis methods

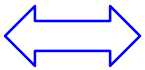
- Feature detection
  - Phase congruency
  - Monogenic signal
  - scale-saliency
- Deformable registration
  - Physiological constraints
- Probability density estimation
  - Non-Parametric Windows
- Level sets
  - Bhattacharya flow





Biological aspects of Cancer

- Angiogenesis
  - Compartment model
  - angiogenic switch
- Glycolysis
  - quiescence
  - pH control
- Hypoxia
  - vascularity
  - AKT/PTEN modulation of HIF
  - relation to PET imaging



Models of image formation

- (x-ray) Mammography
  - X-ray attenuation, Beer's law
  - Scatter
- MRI
  - T1 estimation
  - bias correction
  - contrast enhancement & pharmacokinetics
  - pharmacokinetic modelling
- PET/SPECT
  - radioligand
  - gated PET

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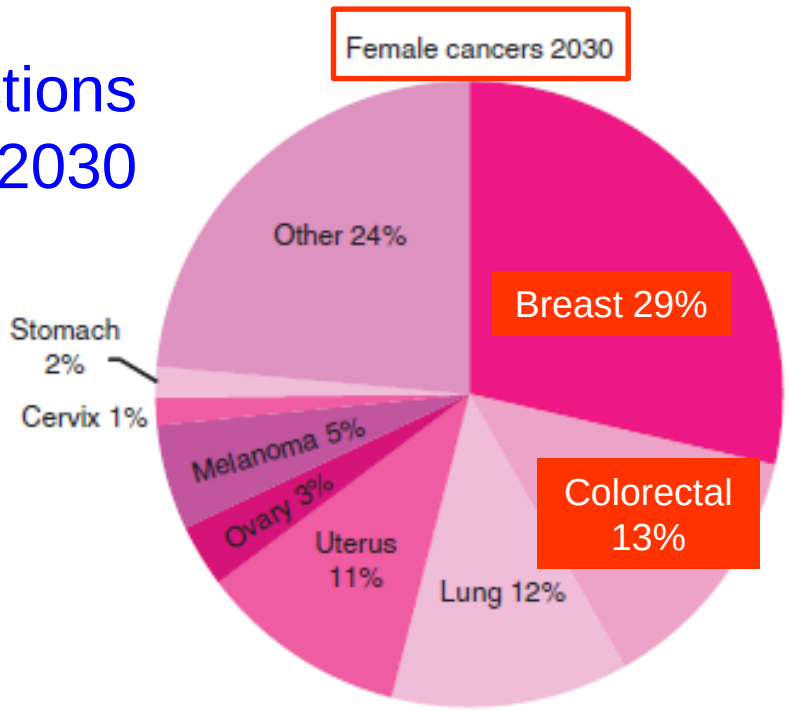
Cancer in Europe 2012

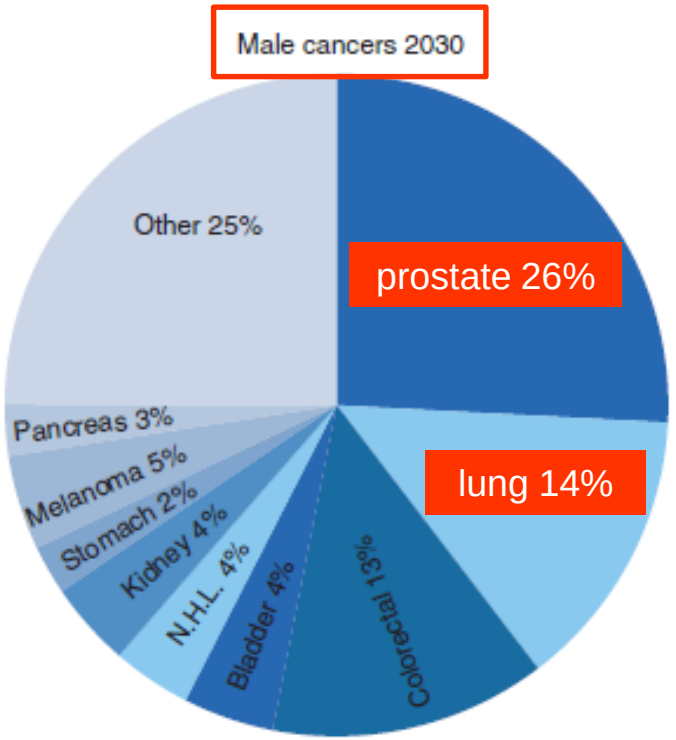
- New cases: 3.45M, deaths: 1.75M
- Cases
  - Breast : 474,000 (deaths: 131,000)
  - Colorectal: 447,000 (deaths: 215,000)
  - Lung: 411,000 (deaths: 353,000)

UK lifetime risk of getting cancer will be 47% by 2020 (44% in 2012)

By 2020, 38% will survive cancer to die of another cause (35% in 2012)

Projections 2030



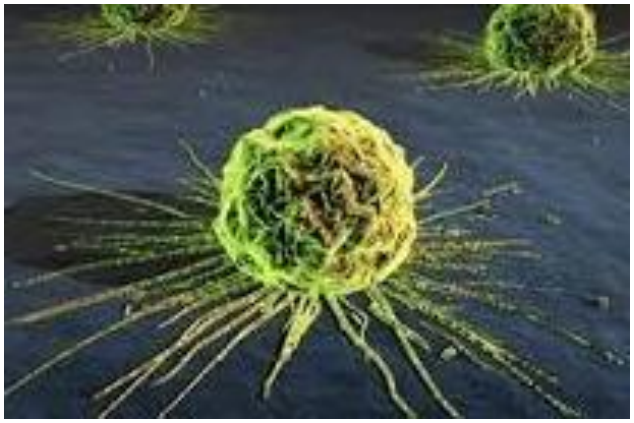


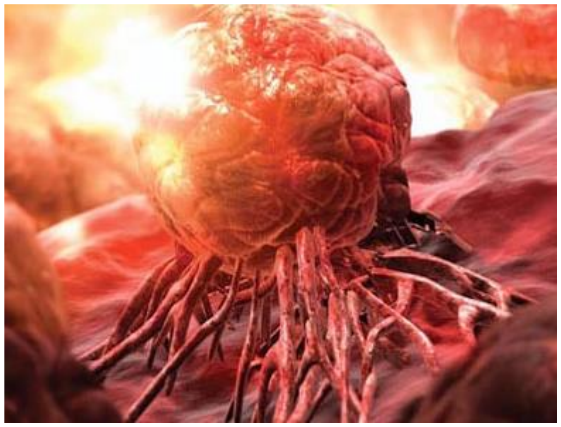
How many different kinds of cancer are there?

- Until 20th Century: 1
- 1990: over 100
- Today:

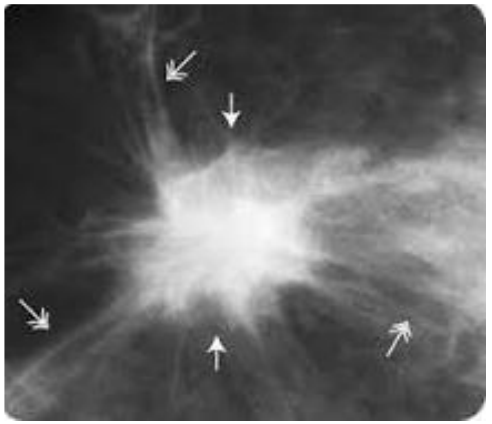
> **“**There are more than 200 different types of cancer. You can develop cancer in any body organ. There are over 60 different organs in the body where a cancer can develop. Each organ is made up of several different types of cells.”

The word “cancer” was apparently first coined by Hippocratus, 1500BCE, because of the resemblance of the shape to a crab..

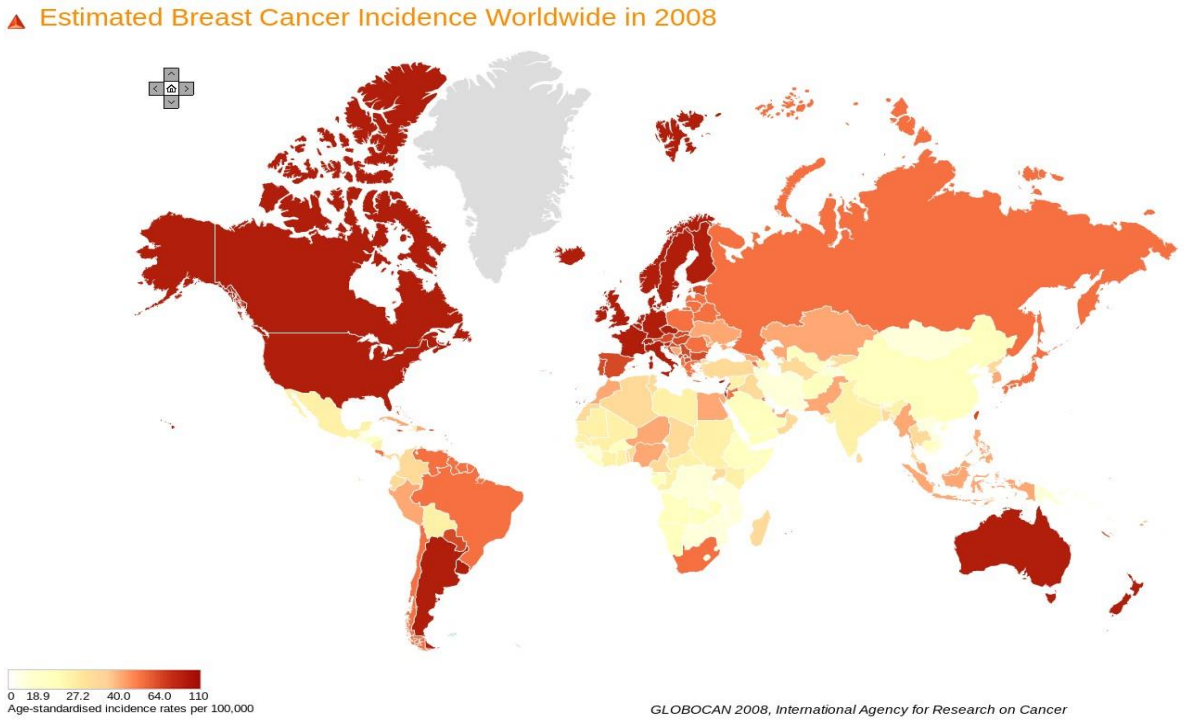




Mammogram spiculated mass



Breast cancer incidence



- In developed countries, 1 in 8 women will get breast cancer at some point
- 23% of all cancers in women – projected to rise to 29% by 2030
- Peak incidence is women over 60

- In developing countries, including BRIC, numbers are rising rapidly, already 500,000 cases in 2008
- Reasons: increasing urbanisation, changes in lifestyle
- Impacting particularly on younger women

Early detection + chemo/radio/conservative surgery + risk analysis is transforming morbidity

Personalised screening

Mammogram

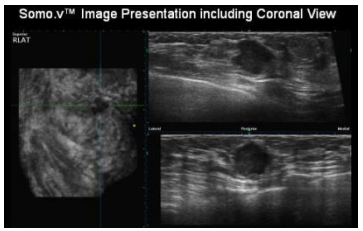
74M annually world wide
Compare to previous mammograms
Computer-aided detection

Measure breast density
(as a surrogate of risk)

Low density
= low risk

Await next screening
round (2-3 years)

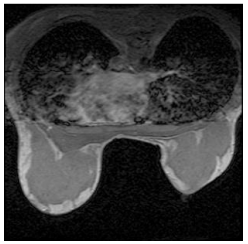
High density = high risk
➔ ***stratification***

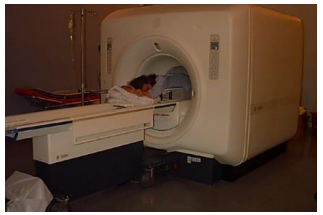


Weigh the evidence
scientifically

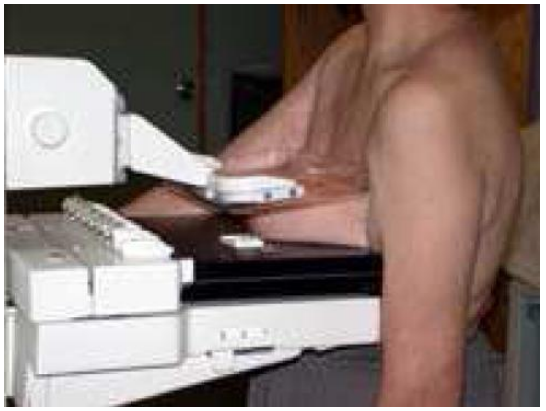
Breast
ultrasound

Breast
MRI





Mammogram




If Women controlled medicine
The Manogram


Yes I did have a Mammogram
Today ... Why do you Ask?

Breast density

- Mammography is only 48% effective in dense breasts, compared to 98% in fatty breasts
- 40% of women have dense breasts, postmenopausal, i.e. involution ineffective
- Breast density is a more significant risk factor than having a mother and sister with breast cancer
- Cancer recurrence is four times more likely in women with dense breasts
- Perfect storm …
- BIRADS: the result of years of discussion by the American College of Radiology

Current Breast Density Classifications

BI-RADS®: The American College of Radiology (ACR) has published a set of criteria which radiologist's use to categorize their opinion of the absence or likelihood of disease. Within that criteria is also a visually-assessed BI-RADS breast density category (an area-based breast density assessment method). Those categories are:

Category 1 — The breast is almost entirely fat (<25% glandular).

Category 2 — There are scattered fibroglandular densities (approximately 25-50% glandular).

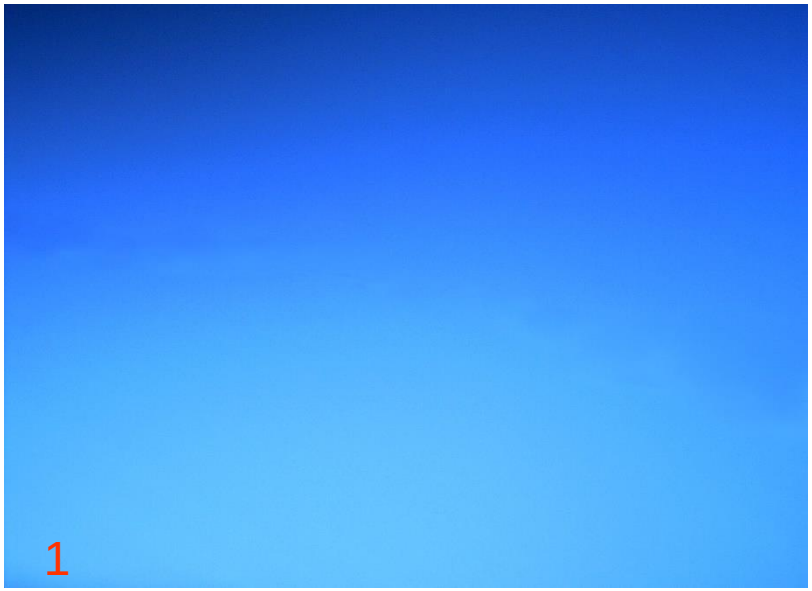
Category 3 — The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% – 75% glandular).

Category 4 — The breast tissue is extremely dense. This may lower the sensitivity of mammography (>76% glandular).

These are commonly called the BI-RADS breast composition categories. Radiologists in the US should record every woman's breast density using the BI-RADS scheme.

ACR® AMERICAN COLLEGE OF RADIOLOGY

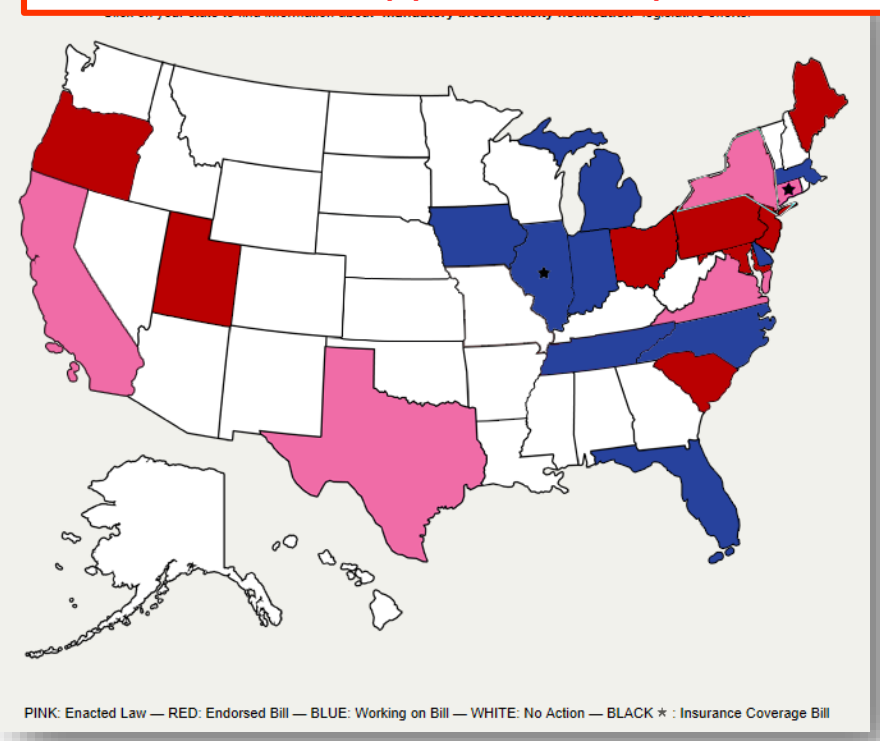
BIRADS = cloud classification



Surely, we can do better? Remember that we want numbers!

Breast Density Legislation

This is welcomed by women; but what are clinicians supposed to report??



PINK: Enacted Law — RED: Endorsed Bill — BLUE: Working on Bill — WHITE: No Action — BLACK ★ : Insurance Coverage Bill

AMENDED IN SENATE MARCH 27, 2012

SENATE BILL **No. 1538**

Introduced by Senator Simitian
(Principal coauthors: Senators Alquist and Runner)

A BILL

To require breast density reporting to physicians and patients by facilities that perform mammograms, and for other purposes.

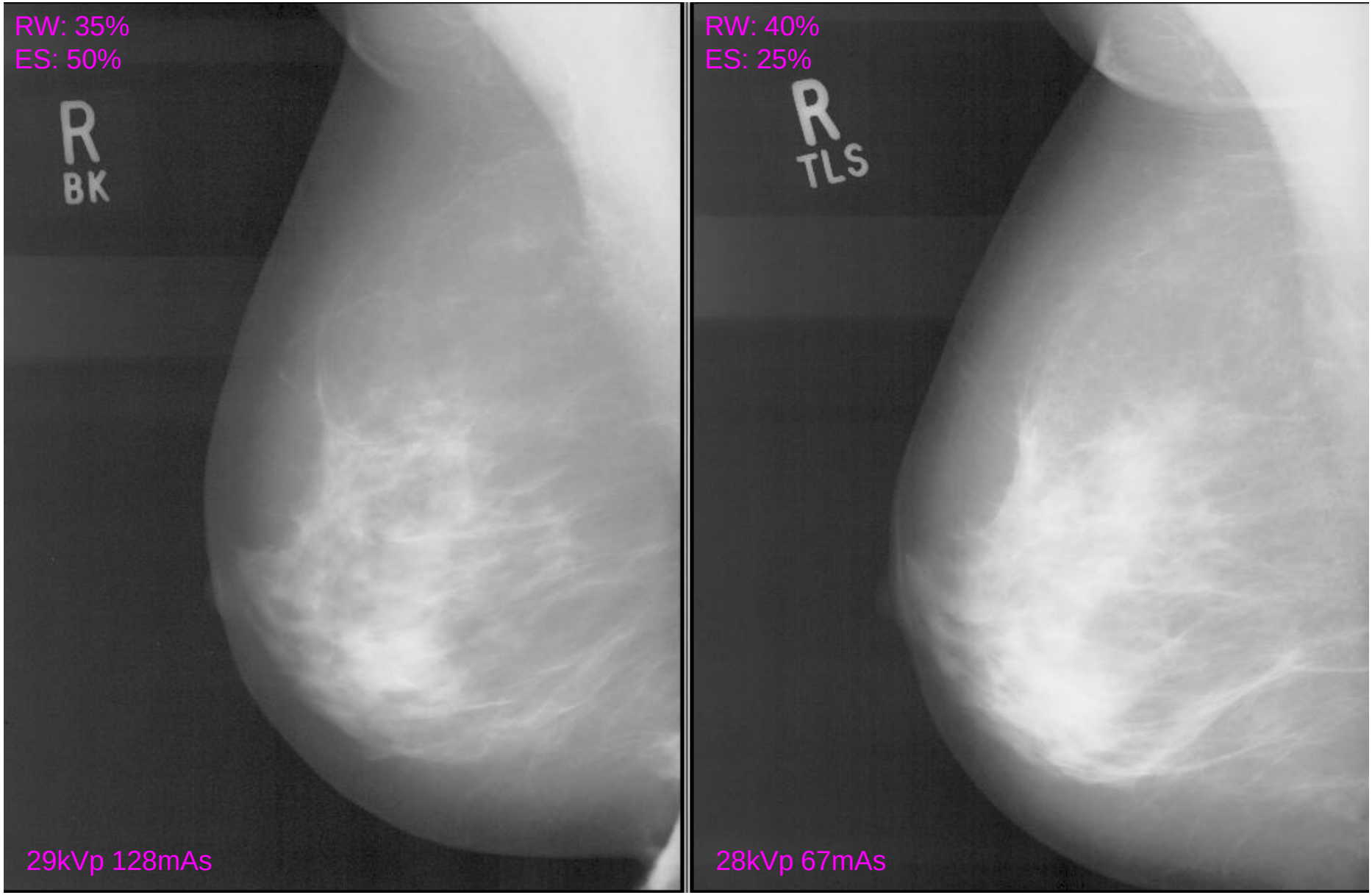
Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

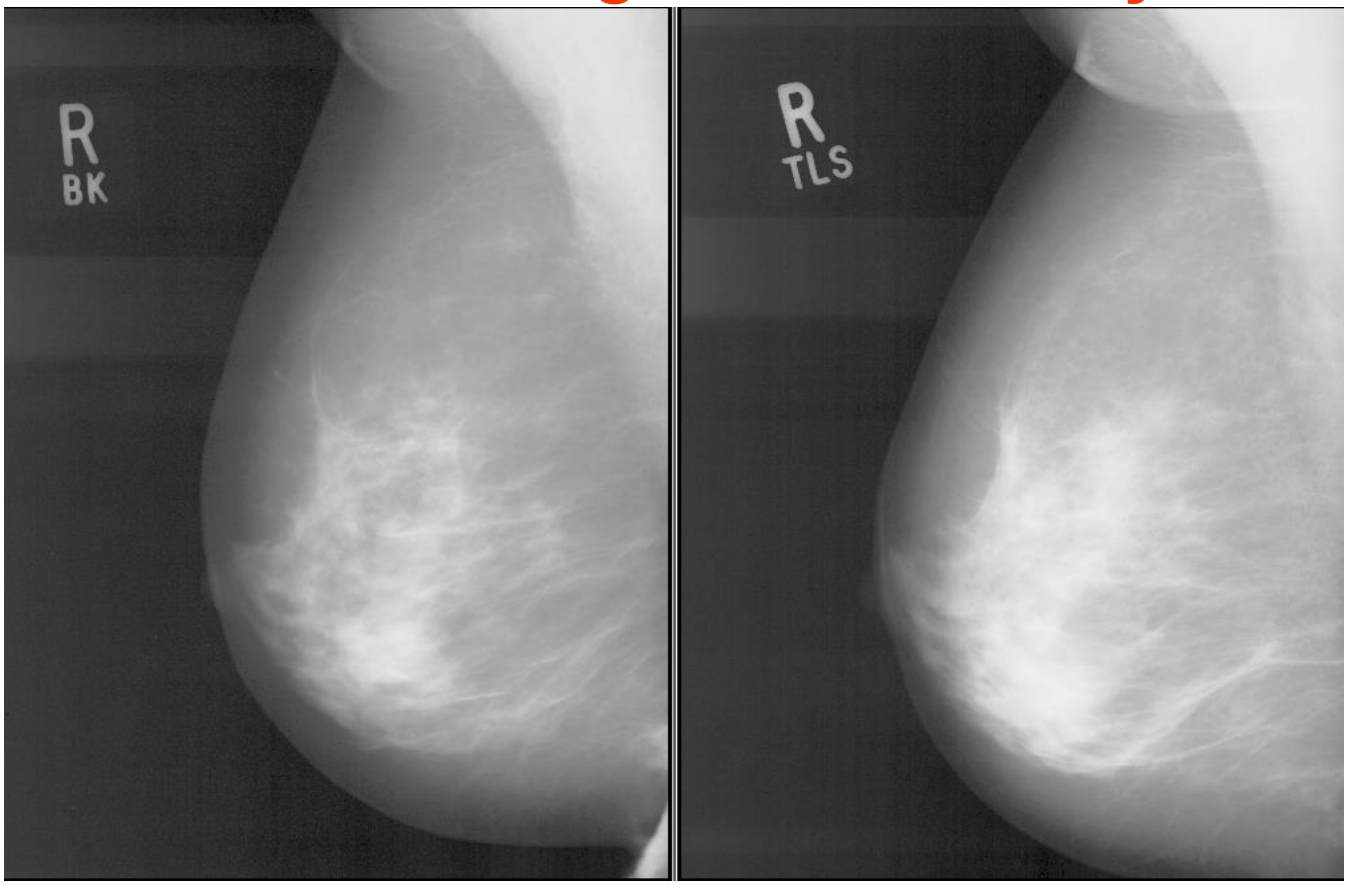
This Act may be cited as the "Breast Density and Mammography Reporting Act of 2014".

Are You DENSE?
ADVOCACY
because your life matters®

Mammography: Image Parameter Dependence



Estimating breast density

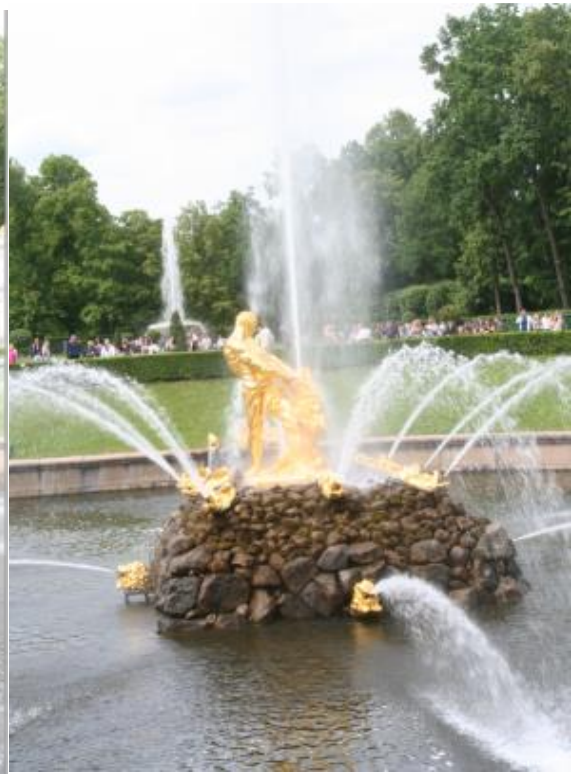


Two of the UK's most experienced breast radiologists each examined the two mammograms shown, to estimate the percentage of dense tissue.

BK estimated 25%; TLS estimated 40% …. but it is the same breast!!!

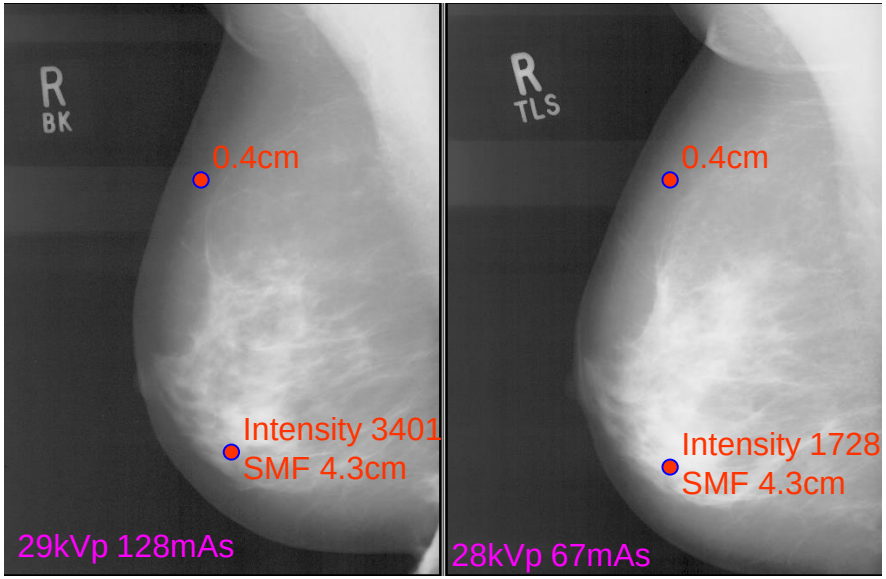
Why is that?

Answer: the left image was exposed to x-rays twice as much as the right



In photography, we exploit exposure time, F-stop, “film speed”, … to create a range of effects, and to highlight things that we are interested in…

First technological capability: need for quantitative analysis in mammography



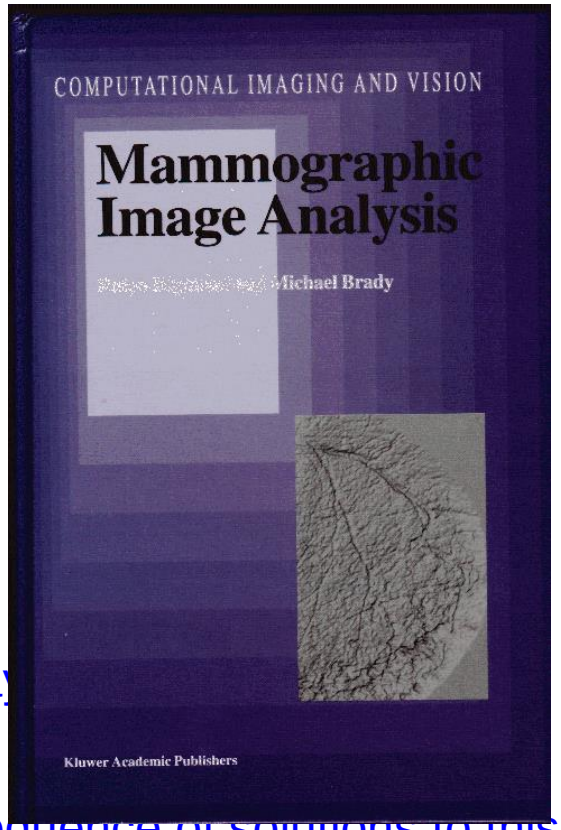


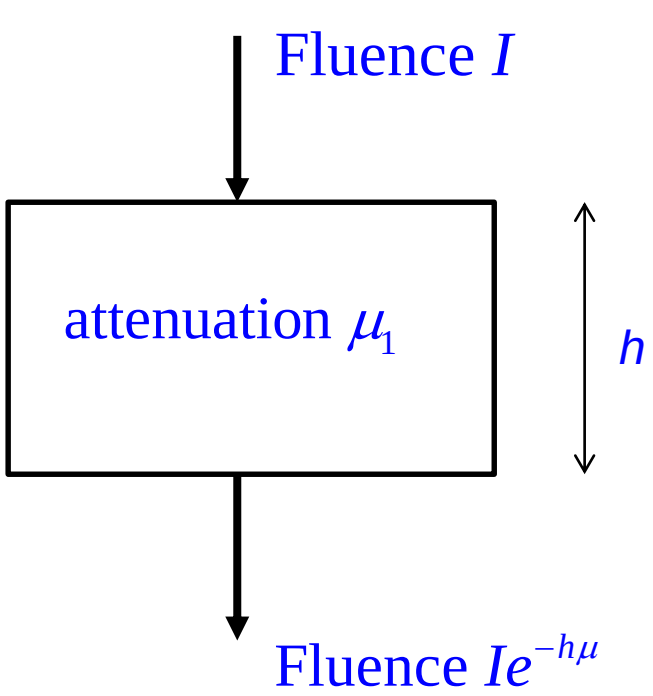
Image intensity relates to anatomy in a very complex way, making image analysis a hard problem.

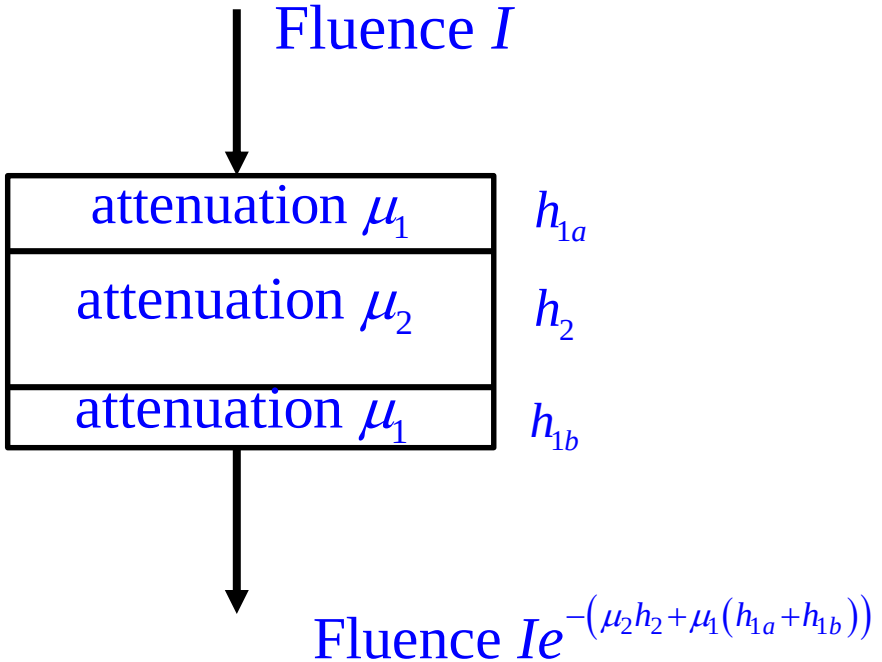
Starting 1994, with Ralph Highnam, I have invented a sequence of solutions to this problem:

- $h_{int}(x)$ – a ***quantitative*** representation of the image – assigning to each pixel x the ***amount of non-fat (interesting) tissue*** at that pixel location x;
- ***Volpara density*** – a fast, relative physics model developed by Matakina Ltd

* SMF = Standard Mammogram Form

First, a tiny bit of physics: Beer's Law

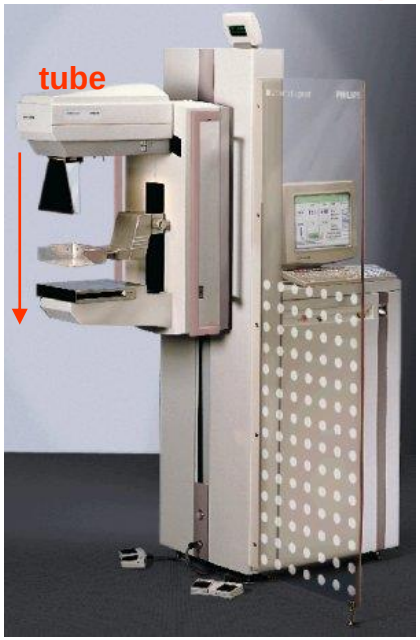




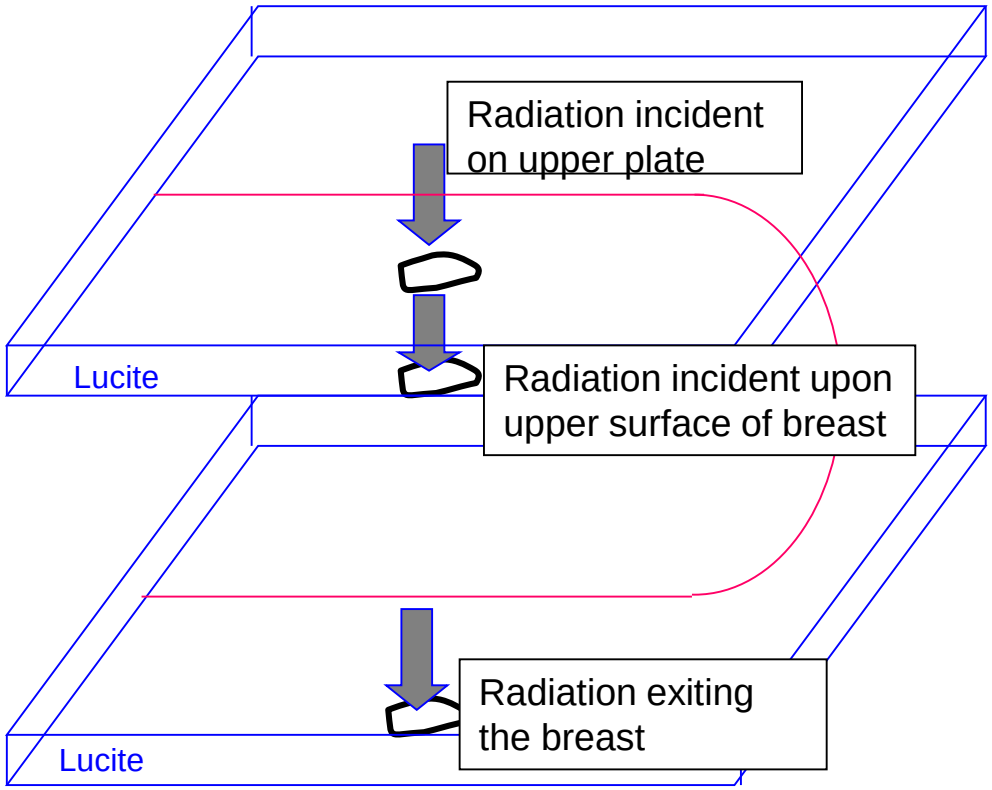
Note that the exiting fluence is the same irrespective of where, vertically, the block of attenuation μ_2 is.

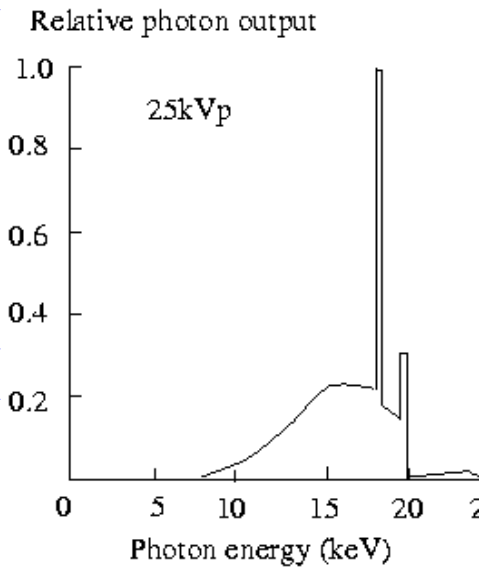
Mammography is fundamentally projective: though digital breast tomosynthesis is changing that…

A model of mammographic image formation



↓ indicates photon fluence





Output of a typical mammography x-ray tube

Device $\Longrightarrow$ X-ray photon fluence model

$\phi(V_t, \mathbf{x})$ = tube voltage

t_s = exposure time

A_p = pixel size

Energy that reaches the imaging sensor:

$$E^{\text{imp}}(\mathbf{x}) = \phi(V_t, \mathbf{x}) A_p t_s \int_0^{E_{\max}} T(\varepsilon) \exp^{-\mu_{\text{lucite}}(\varepsilon) h_{\text{plate}}} \exp^{-h\mu(\varepsilon)} d\varepsilon$$

where $T(\varepsilon)$ is the transfer function (spectrum energy, image gain, ...)

Highnam & Brady's h_{int} model

The literature tells us* that you cannot distinguish stromal tissue and tumours on the basis of their x-ray attenuations ➔ two kinds of tissue: ***fat*** & ***"interesting"***. If the compression between the plates is H cm, then at any given pixel **x**, we have $H = h_{\text{fat}}(\mathbf{x}) + h_{\text{int}}(\mathbf{x})$

Our job is to find $h_{\text{int}}(\mathbf{x})$ for every voxel **x.** We know *H* and the tube parameters.

What can we find from the equation of photon fluence?:

$$E^{\text{imp}}(\mathbf{x}) = \phi(V_t, \mathbf{x}) A_p t_s \int_0^{E_{\max}} T(\varepsilon) \exp^{-\mu_{\text{lucite}}(\varepsilon) h_{\text{plate}}} \exp^{-h\mu(\varepsilon)} d\varepsilon$$

We measure this

We know all this stuff

Compression plates – we know that too

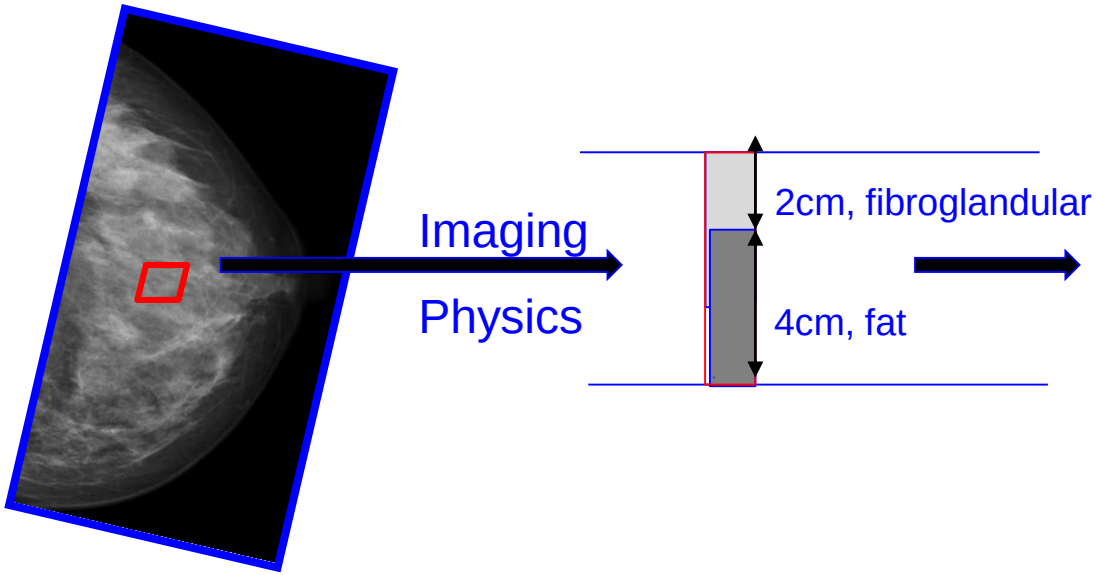
The bit we don't know!

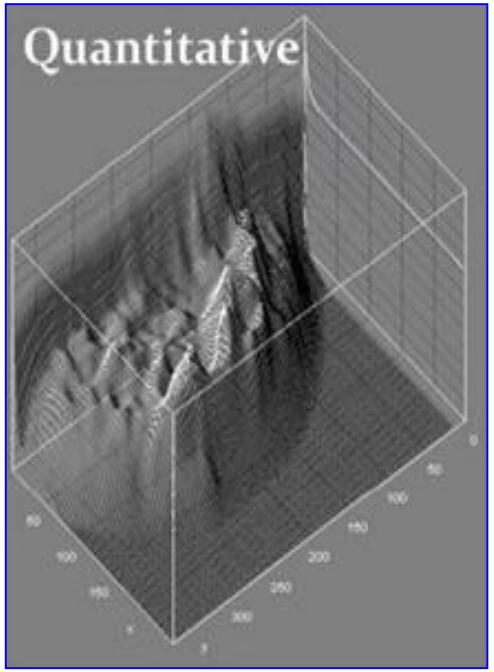
$$h\mu(\varepsilon) = h_{\text{int}}\mu_{\text{int}}(\varepsilon) + h_{\text{fat}}\mu_{\text{fat}}(\varepsilon)$$

$$= h_{\text{int}}(\mu_{\text{int}}(\varepsilon) - \mu_{\text{fat}}(\varepsilon)) + H\mu_{\text{fat}}(\varepsilon)$$

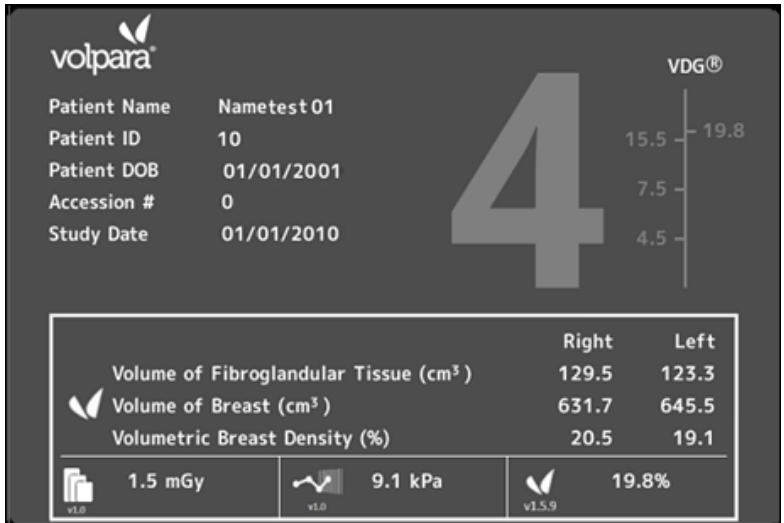
* It may be wrong ☺

Volume-based Density Measurement





$$\text{Volumetric Breast Density} = \frac{\text{Volume of "interesting" tissue}}{\text{Volume of the breast}}$$



“Relative physics”

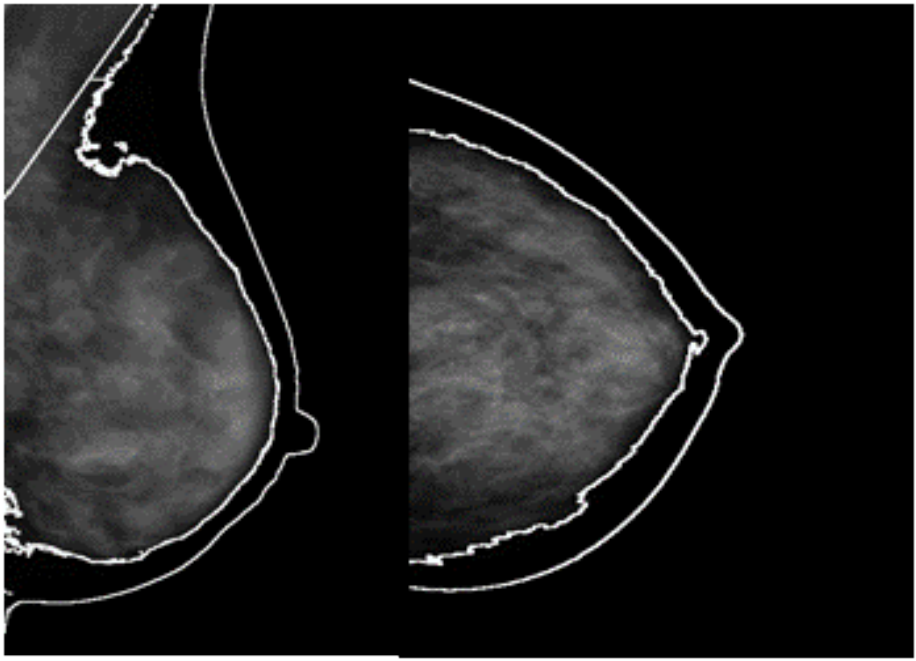
Highnam, Brady, Karssemeijer, and Yaffe

We have to know all those calibration parameters for Highnam and Brady’s method to work. We can guess at lots of them.. BUT

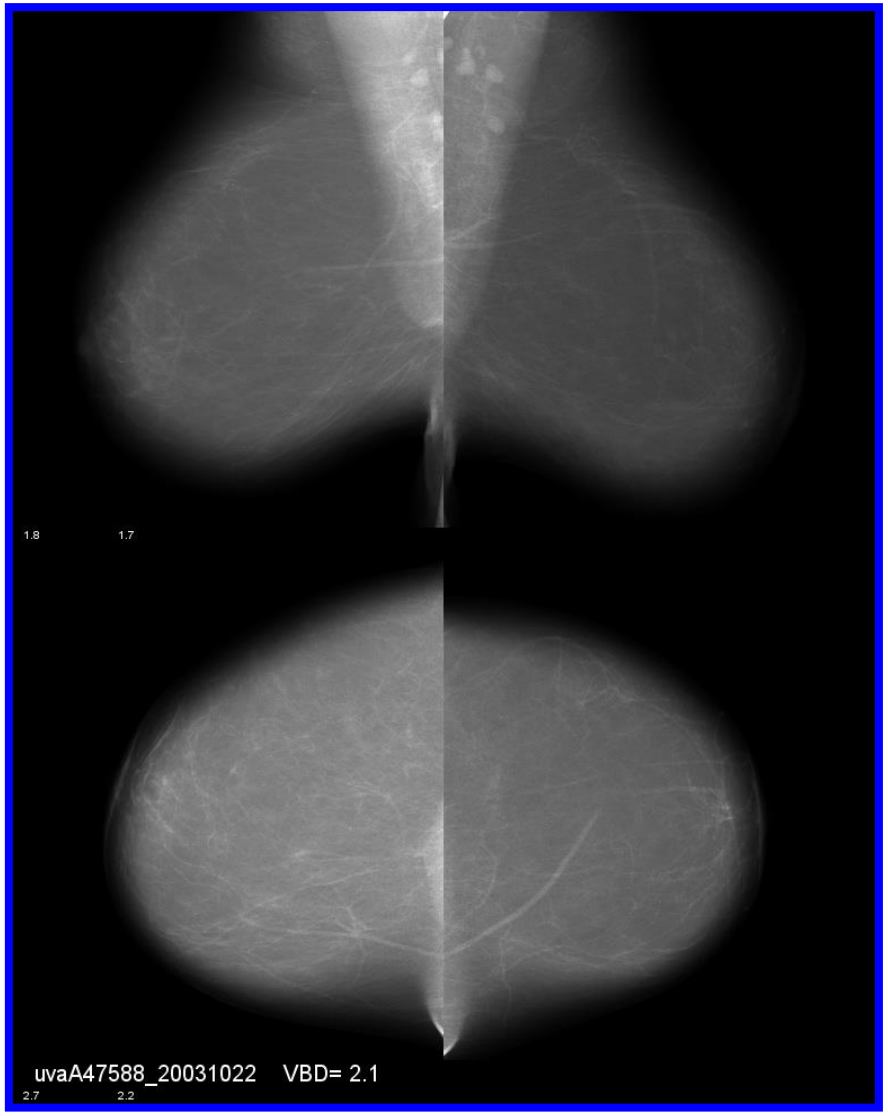
Suppose we knew a region of the breast that was ***entirely fat***... We could then use this as a “reference”

$$h_{\mathrm{d}}(\mathbf{x}) = \frac{\ln\left(I_{\mathrm{obs}}(\mathbf{x}) / I_{\mathrm{fat}}\right)}{\mu_{\mathrm{fat}} - \mu_{\mathrm{dense}}}$$

We need accurate breast inner/outer boundary segmentation .... We use phase congruency



Volume-based Methods for Density Measurement



Volpara v1.5.8
Breast Density Assessment

volpara™

Patient Name	ewbcHR075
Patient ID	075
Patient DOB	07/02/1941
Accession #	0001261930
Study Date	07/02/2009

1

15.5
7.5
4.5
3.9

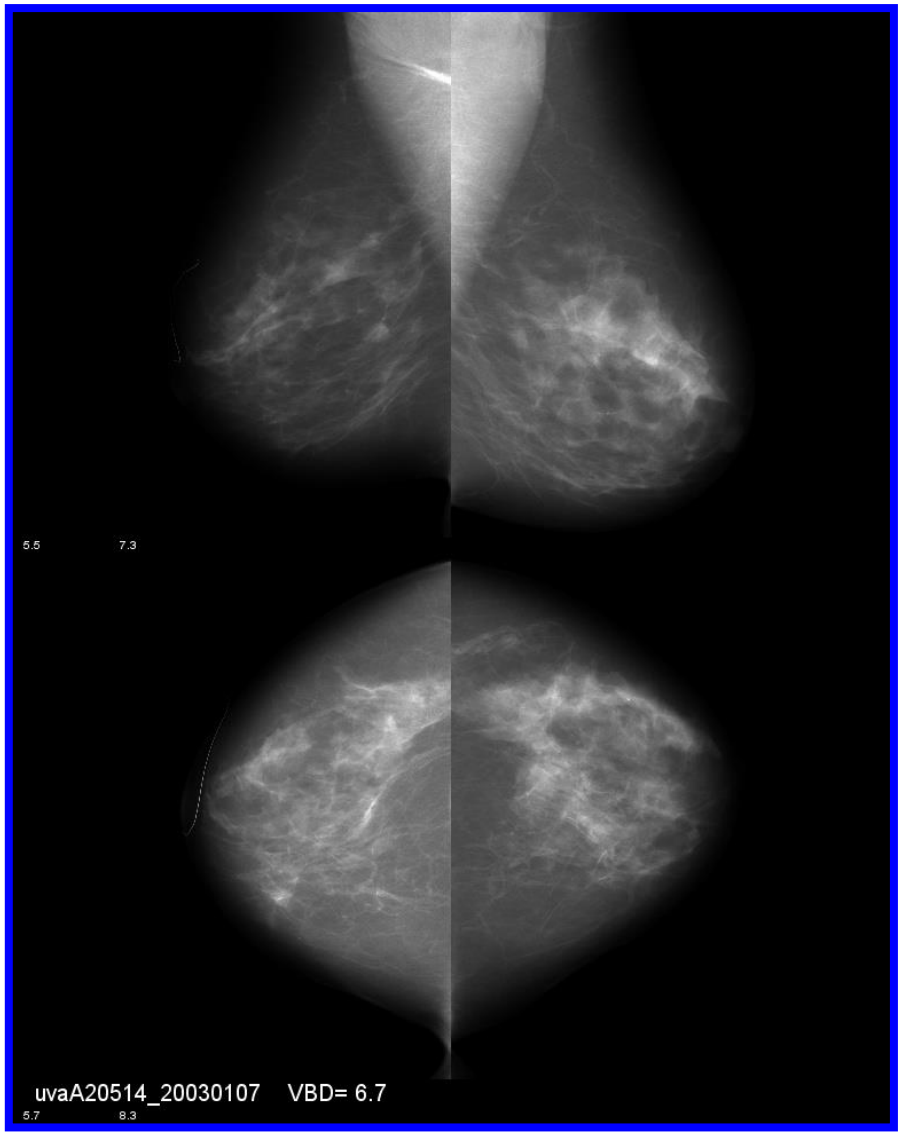
	Right	Left
Volume of Fibroglandular Tissue (cm^3)	37.0	39.8
Volume of Breast (cm^3)	933.9	1031.8
Volumetric Breast Density (%)	4.0	3.8
Volpara Density Grade®	1	

Sky analogy

Over 3,000,000 mammograms processed over past 12 months

volpara™

Volume-based Methods for Density Measurement



Volpara v1.5.8
Breast Density Assessment

volpara™

Patient Name	ewbcHR065
Patient ID	065
Patient DOB	06/23/1944
Accession #	0001260803
Study Date	06/23/2009

2

15.5
7.5
4.5
5.4

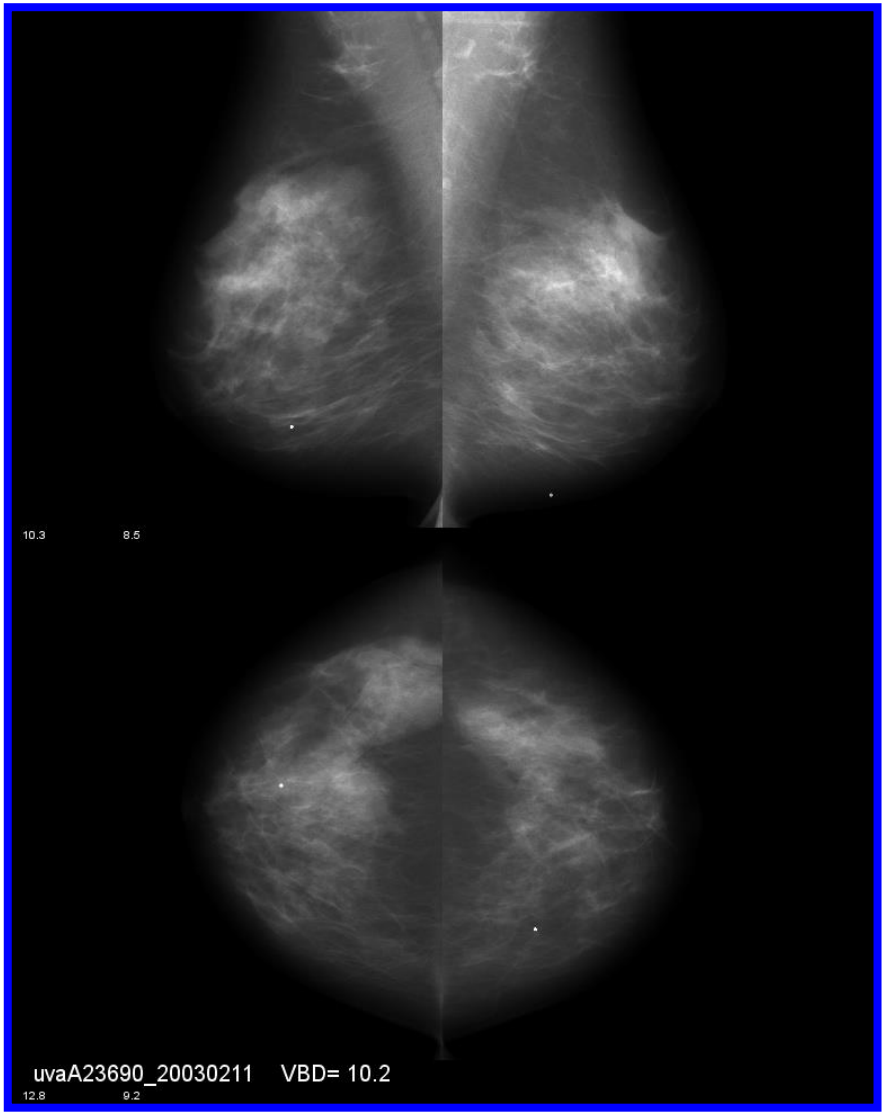
	Right	Left
Volume of Fibroglandular Tissue (cm^3)	83.9	75.7
Volume of Breast (cm^3)	1476.9	1504.6
Volumetric Breast Density (%)	5.7	5.1
Volpara Density Grade®	2	

Sky analogy

Over 3,000,000 mammograms processed over past 12 months

volpara™

Volume-based Methods for Density Measurement



Volpara v1.5.8
Breast Density Assessment

volpara™

Patient Name	ewbcHR003
Patient ID	003
Patient DOB	06/23/1960
Accession #	0001373639
Study Date	06/23/2010

3

15.5
12.8
7.5
4.5

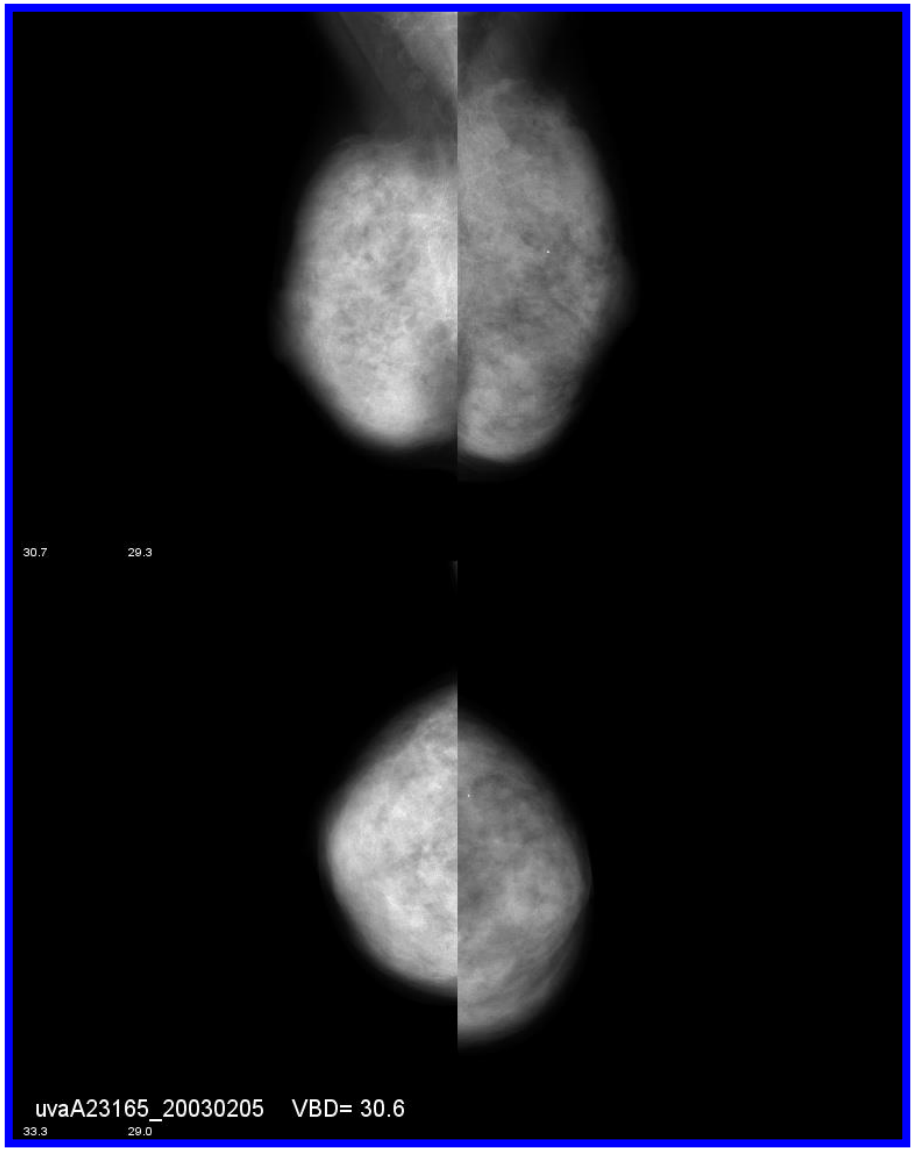
	Right	Left
Volume of Fibroglandular Tissue (cm^3)	52.7	52.3
Volume of Breast (cm^3)	390.3	430.2
Volumetric Breast Density (%)	13.5	12.1
Volpara Density Grade®	3	

Sky analogy

Over 3,000,000 mammograms processed over past 12 months

volpara™

Volume-based methods for density measurement



Volpara v1.5.8
Breast Density Assessment

volpara

Patient Name	ewbcHR008
Patient ID	008
Patient DOB	06/23/1945
Accession #	0001248610
Study Date	06/23/2009

4

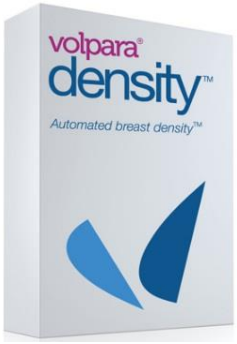
15.5 – 18.4
7.5
4.5

	Right	Left
Volume of Fibroglandular Tissue (cm^3)	29.0	49.3
Volume of Breast (cm^3)	209.3	216.3
Volumetric Breast Density (%)	13.9	22.9
Volpara Density Grade®	4	

Sky analogy

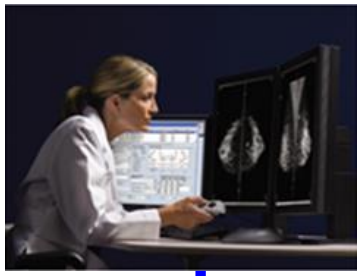
Over 3,000,000 mammograms processed over past 12 months

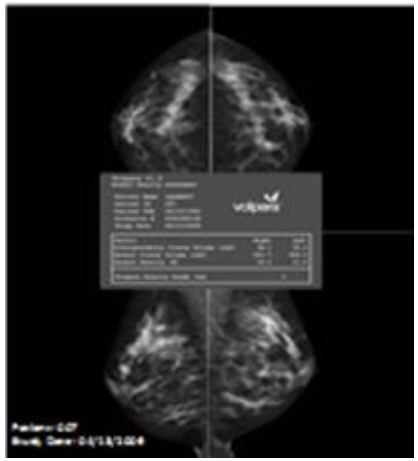
volpara



Patient stratification

Woman has a mammo

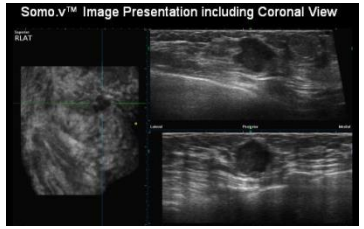


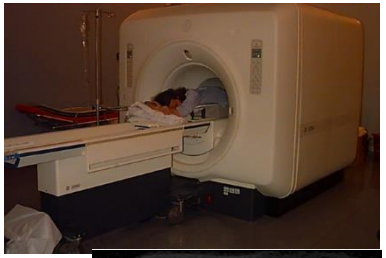


Volpara breast density score immediately available

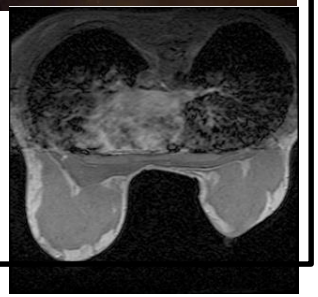
Woman can decide on supplementary screening before she leaves clinic.

Breast ultrasound



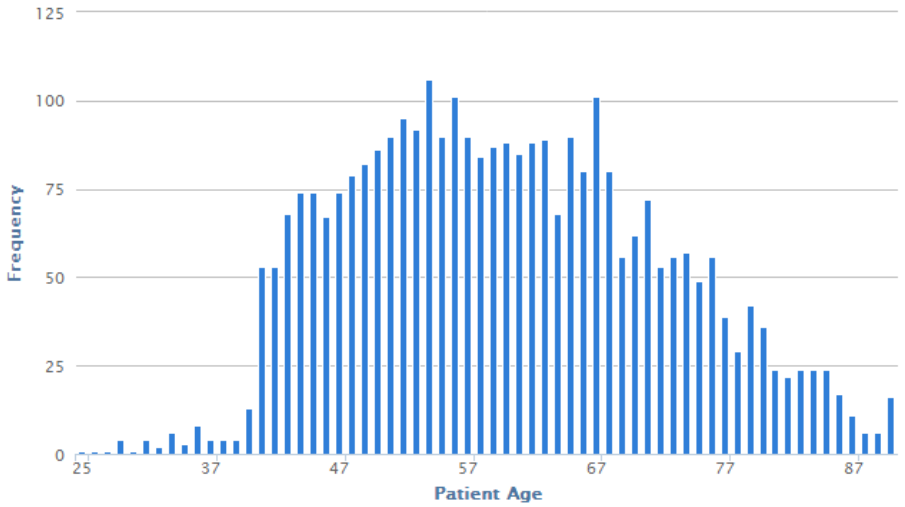


Breast MRI



Numbers provide statistical power

volpara analytics™ | Configure | Population Report | Comparative Report | Time Analysis | Alerts | matakina



Population Statistics

	All
Number of Images	12434
Number of Studies	3151
Number of Unique Patients	3150
Median Patient Age	59
Median Fibroglandular Tissue Volume (cm³)	53.9
Median Volumetric Breast Density (%)	7.1
Median Breast Volume (cm³)	781
VDG 1 (%)	21.5
VDG 2 (%)	31.9
VDG 3 (%)	32.7
VDG 4 (%)	13.9
Mean VDG	2.4

Remember:

- 74 million mammograms per year
- Density varies with population
- There may be genetic involvement beyond HER-2
- Analysis lends itself to cloud delivery

Management Information

volpara analytics™ | Configure | Population Report | Comparative Report | Time Analysis | ! Alerts | matakina

Date Range ▾ | Columns ▾ | Filter by Operator ▾ | Switch to Operator Report

Mammography Unit Report for All Operators

Date Range: 26 Sep 2013 - 11 Nov 2013

	Mammo1	Mammo2	Mammo3	Mammo4	All
Manufacturer ▾	GE	GE	Hologic	Hologic	
Number of Images ▾	2978	1971	4304	3181	12434
Number of Studies ▾	751	500	1095	805	3151
Number of Unique Patients ▾	751	499	1095	805	3150
Median Studies per Day ▾	29.0	15.0	34.0	25.0	25.0
⊞ Median Patient Age ▾	55	64	57	62	59
⊞ Median Fibroglandular Tissue Volume (cm³) ▾	51.4	47.0	59.4	54.8	53.9
⊞ Median Volumetric Breast Density (%) ▾	6.9	5.5	8.0	7.6	7.1
⊞ Median Breast Volume (cm³) ▾	793	821	754	752	781

Most large screening centres have multiple mammography units

- They vary by manufacturer, model, and vintage
- They may show variable results – but is this due to the population screened using that machine or due to the machine itself?

Quality control

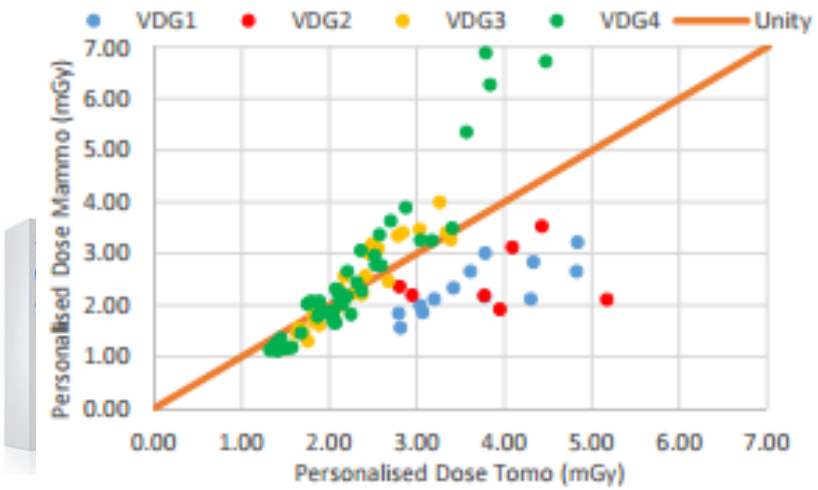
Automated quality control of mammography machines, radiographers, population usage … all this needs statistical power to be meaningful

	1	2	3	4	5	6	7	8	9	10	11	All
Number of Images	317	316	270	254	214	209	195	173	148	113	68	18364
Number of Studies	81	81	69	64	54	53	50	44	37	30	18	4680
Number of Unique Women	81	81	69	64	53	53	50	44	37	30	17	4656
Median Age	55	56	60	59	57	55	59	59	55	51	59	58
Median Volumetric Breast Density (%)	6.7	6.8	6.9	8.5	6.2	7.0	7.6	6.8	7.3	6.1	7.8	7.0
Median Fibroglandular Tissue Volume (cm^3)	55.0	52.7	53.2	52.3	51.1	53.5	53.9	53.4	62.2	45.1	58.5	54.0
Median Breast Volume (cm^3)	810	876	798	623	773	758	713	851	821	754	791	772
Median Breast Thickness (mm)	62	62	60	53	62	61	58	59	61	62	63	60
Median Compression Force (N)	75	98	66	98	73	79	83	108	73	70	58	80
Median Contact Area (mm^2)	9993	8570	7754	7515	9059	8103	7256	9064	7348	6652	7982	7993
Median Pressure Applied (kPa)	8.3	11.4	7.9	12.1	7.6	10.1	9.9	12.6	8.9	10.3	6.4	9.8

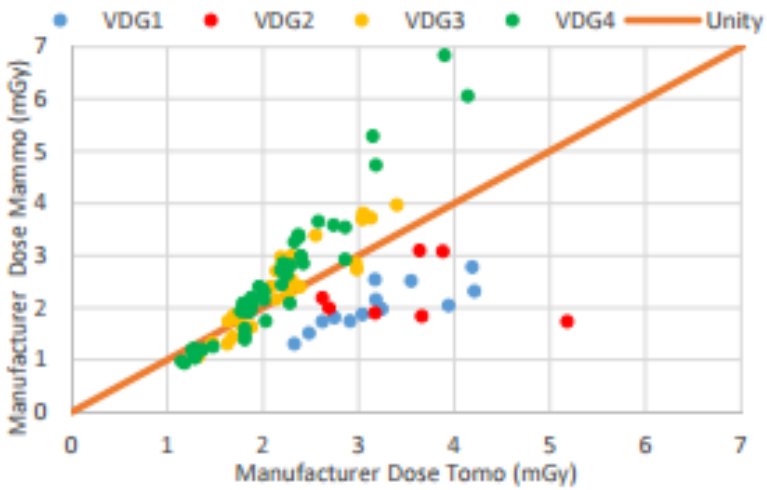
This provides usage statistics on individual radiographers (technologists in US parlance)

Operator 11 may need re-training….

Personalising x-ray dose calculation



VolparaDose™ Personalized MGD



As Reported – Hologic

- X-ray dose is low in mammography, but
  - Millions of women per year X minimal risk of excessive dose per woman = likelihood of x-ray induced cancer each year
- FDA MQSA requirements are that the mean glandular dose is under 3mGy for *specific phantoms*
  - Women are not phantoms!
- Each manufacturer shows mean glandular dose (MGD) for each image, but
  - Each manufacturer uses a different algorithm to estimate MGD
  - Comparison machine/machine and model/model is nigh impossible
  - Records of accumulated dose become highly suspect
- Calculate it using our mathematical model + DICOM header information

Personalised screening

Mammogram

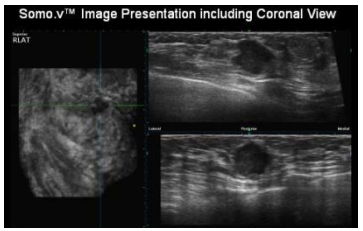
74M annually world wide
Compare to previous mammograms
Computer-aided detection

Measure breast density
(as a surrogate of risk)

Low density
= low risk

Await next screening
round (2-3 years)

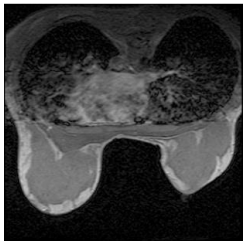
High density = high risk
➔ ***stratification***

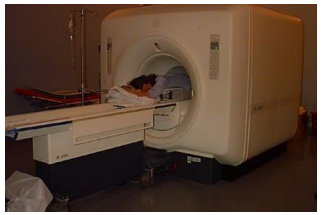


Weigh the evidence
scientifically

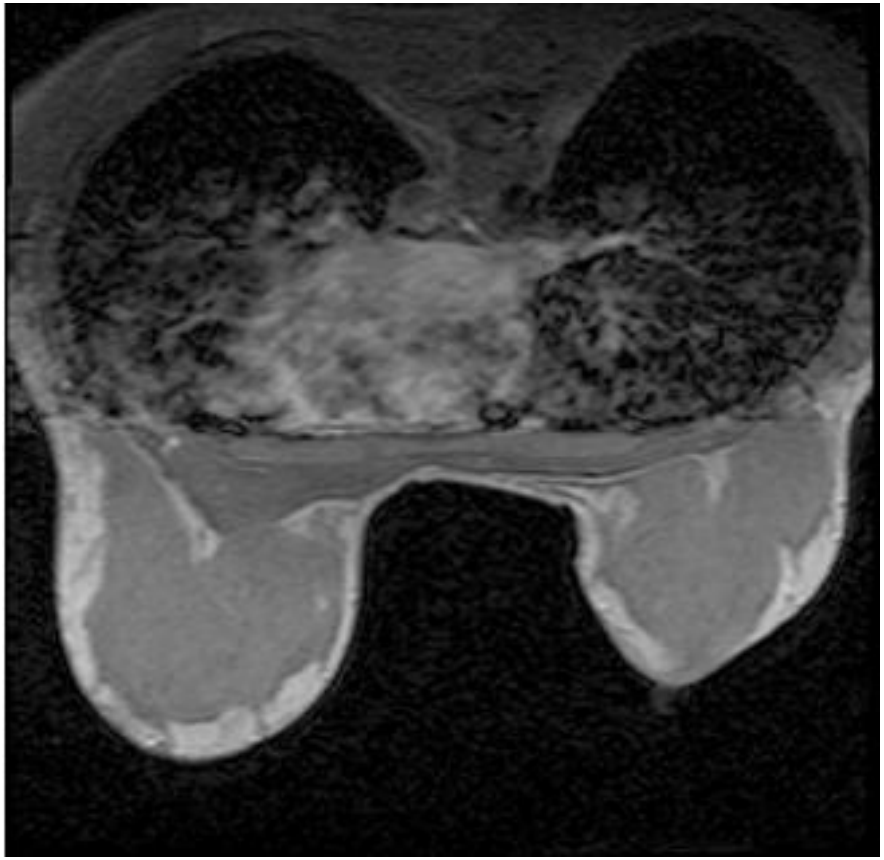
Breast
ultrasound

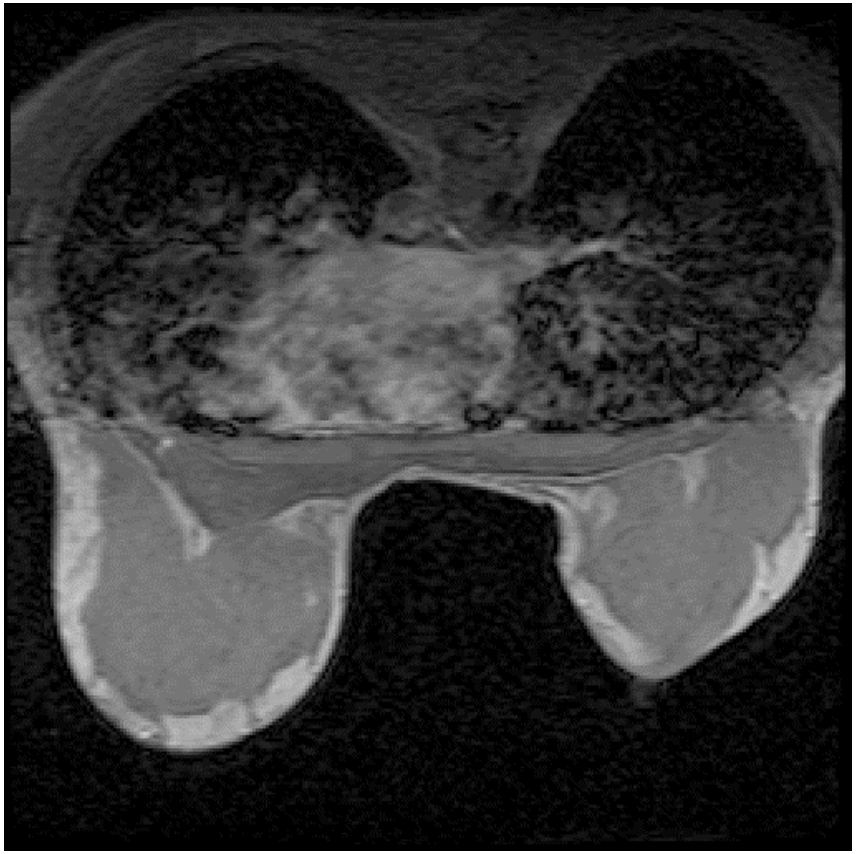
Breast
MRI





Breast MRI uses contrast agent

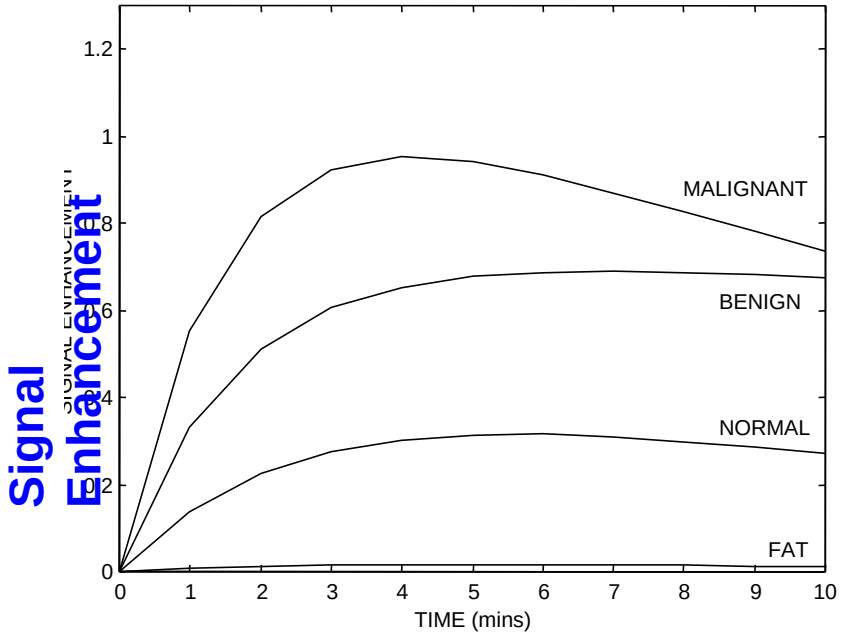


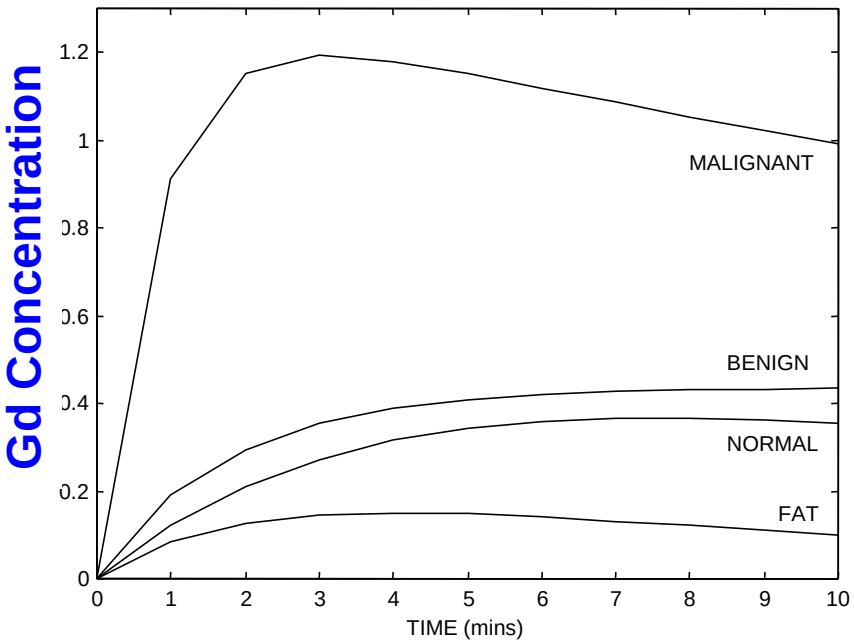


No abnormal tissue visible

Contrast Agent Uptake Profiles

- Malignant to benign distinction is improved using concentration based analysis.





Gd concentration is proportional to the change ΔT_1 so we need first to ***measure T_1***

Measuring T_1

For a MRI gradient echo pulse sequence, one can derive a signal model:

$$S = g\rho e^{-TE/T_2^*} \sin\alpha \frac{1-e^{-TR/T_1}}{1-\cos\alpha e^{-TR/T_1}}$$

Note that T_2^*, T_1 are of interest, fixed for any given voxel (but are not known);

g, ρ depend on the particular machine, and are also unknown

The only things we can vary are: α, TR, TE : in practice, vary α

Rearranging: $$\left[\frac{S}{\sin\alpha}\right] = e^{-TR/T_1}\left[\frac{S}{\tan\alpha}\right] + g\rho e^{-TE/T_2^*}\left(1-e^{-TR/T_1}\right)$$

$$y = mx + c$$

Fixing TR, TE and choosing a set $\{\alpha_i\}$, observing resulting $\{S_i\}$:

estimation of $m = e^{-TR/T_1} \Rightarrow \hat{T}_1$

Contrast agent

- Signal model

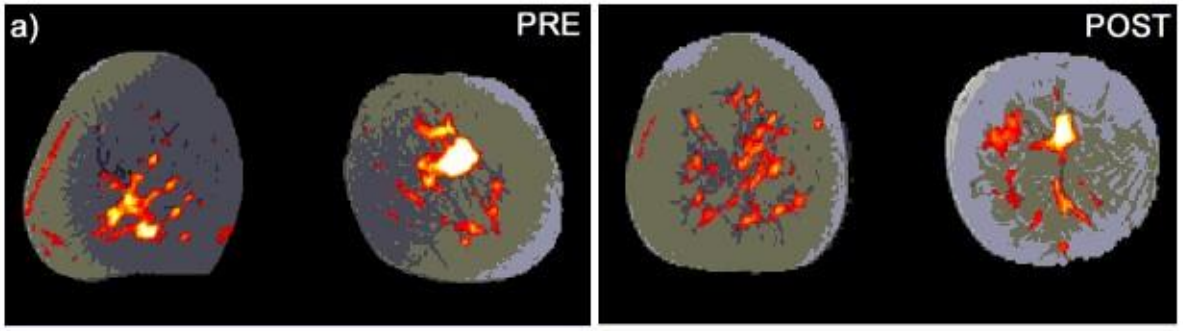
$$S = g\rho e^{-TE/T_2^*} \sin\alpha \frac{1 - e^{-TR/T_1}}{1 - \cos\alpha e^{-TR/T_1}}$$

- Add effects of contrast agent (T_1 & T_2 alteration).

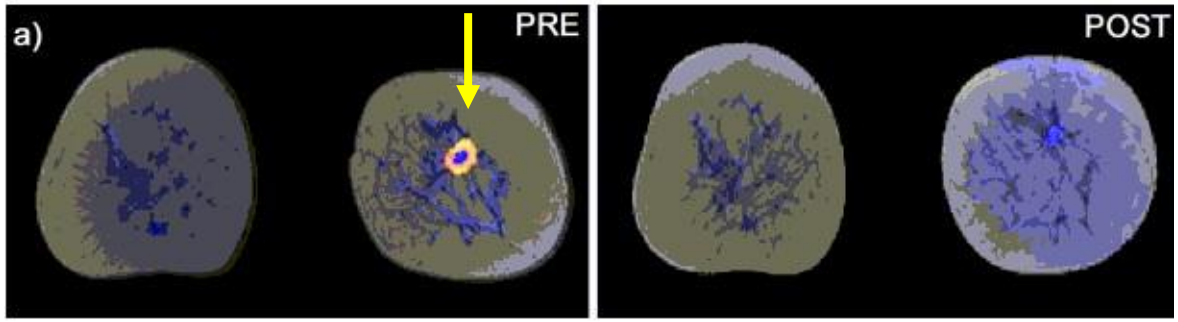
$$S(C_t) = g\rho e^{-TE\left(\frac{1}{T_2^*} + R_2 C_t\right)} \sin\alpha \frac{1 - e^{-TR\left(\frac{1}{T_1} + R_1 C_t\right)}}{1 - \cos\alpha e^{-TR\left(\frac{1}{T_1} + R_1 C_t\right)}}$$

… there are numerous other methods for estimating T_1 and there are models for all other MRI pulse sequences, such as spin echo, …

Measuring effect of chemotherapy



Pre- and post-chemotherapy
Percentage increase in intensity at right

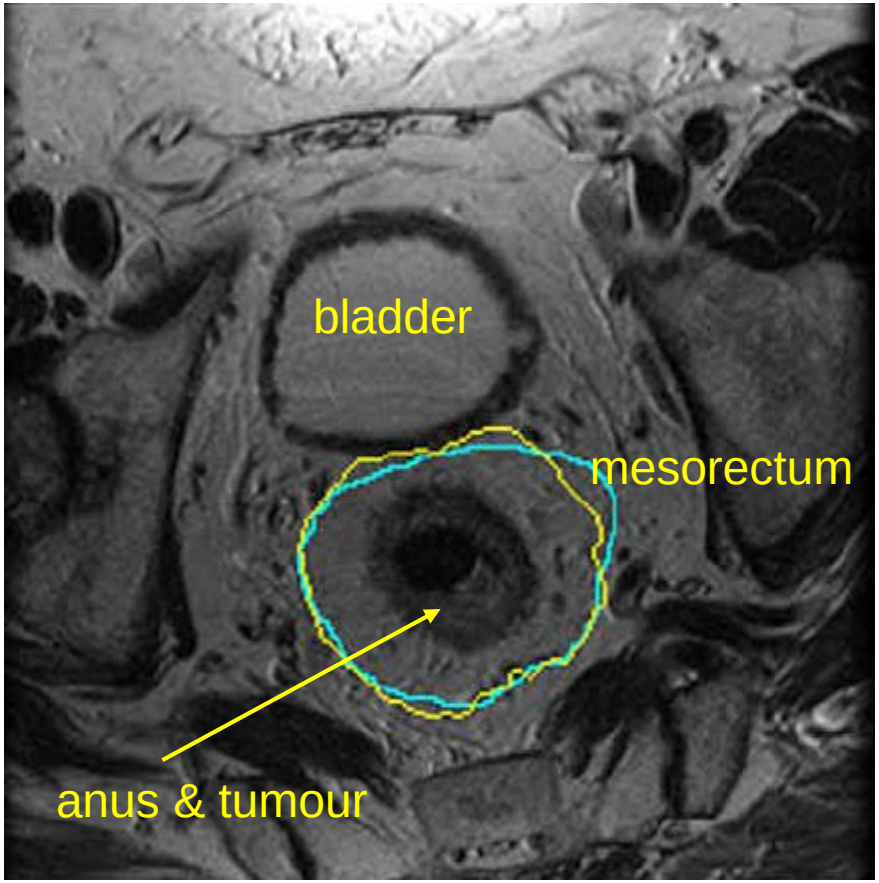


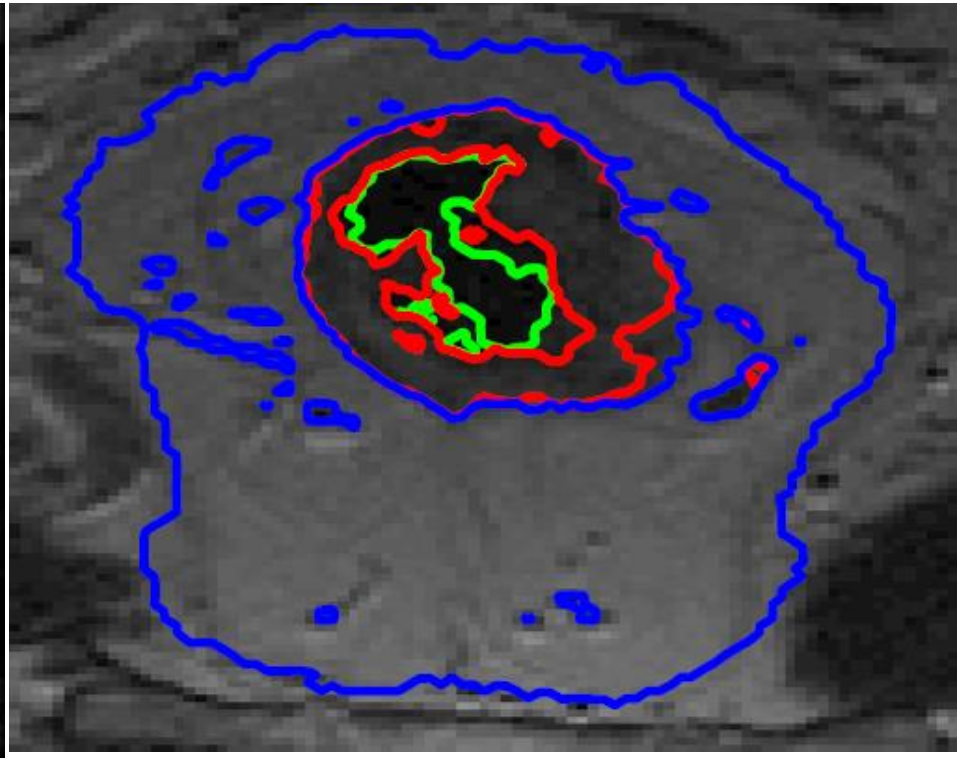
Pre- and post-chemotherapy ΔT_1 at left

(non-rigid) registration and pre- and post-chemotherapy, from $\Delta T1$

Armitage, Brady and Behrenbruch, Medical Image Analysis (2005)

Colorectal cancer: downstaging chemotherapy

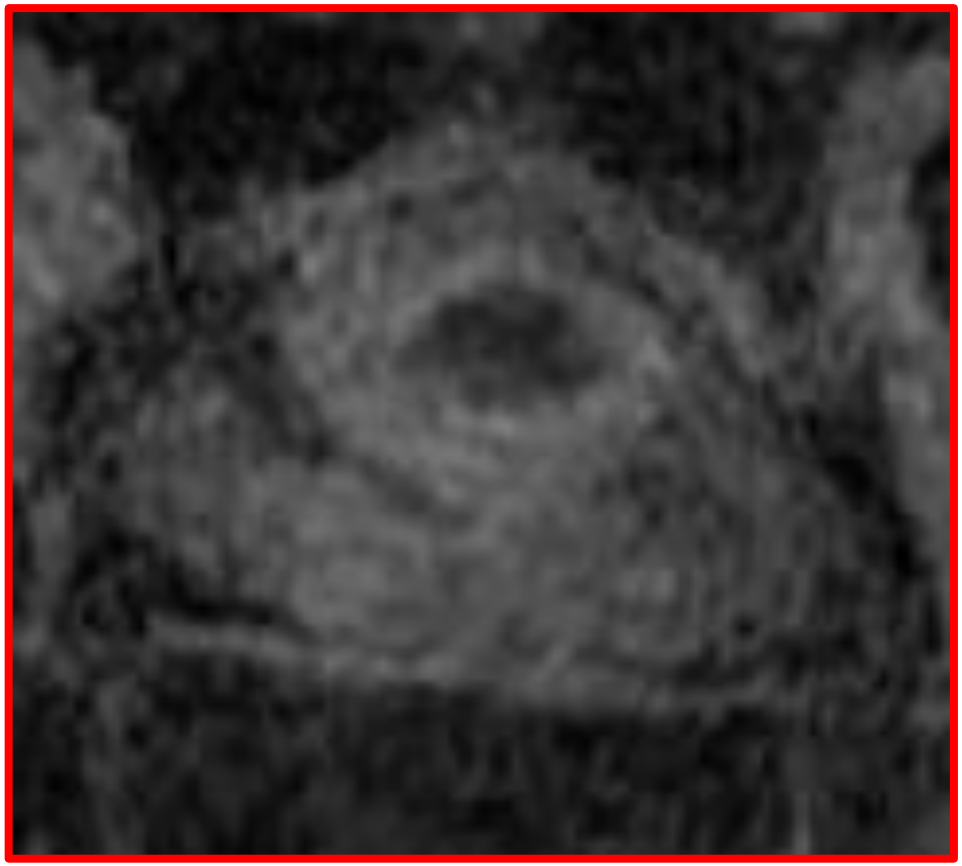




Segmentation of mesorectum (blue), rectum/lumen (red); and tumour (green)

Most patients get down-staging chemotherapy prior to surgery
10% of patients who have surgery turn out to be complete responders to the chemotherapy; but still have the surgery (and the substantially negative impact on quality of life afterwards)
Can we tell who are most likely to be complete responders??

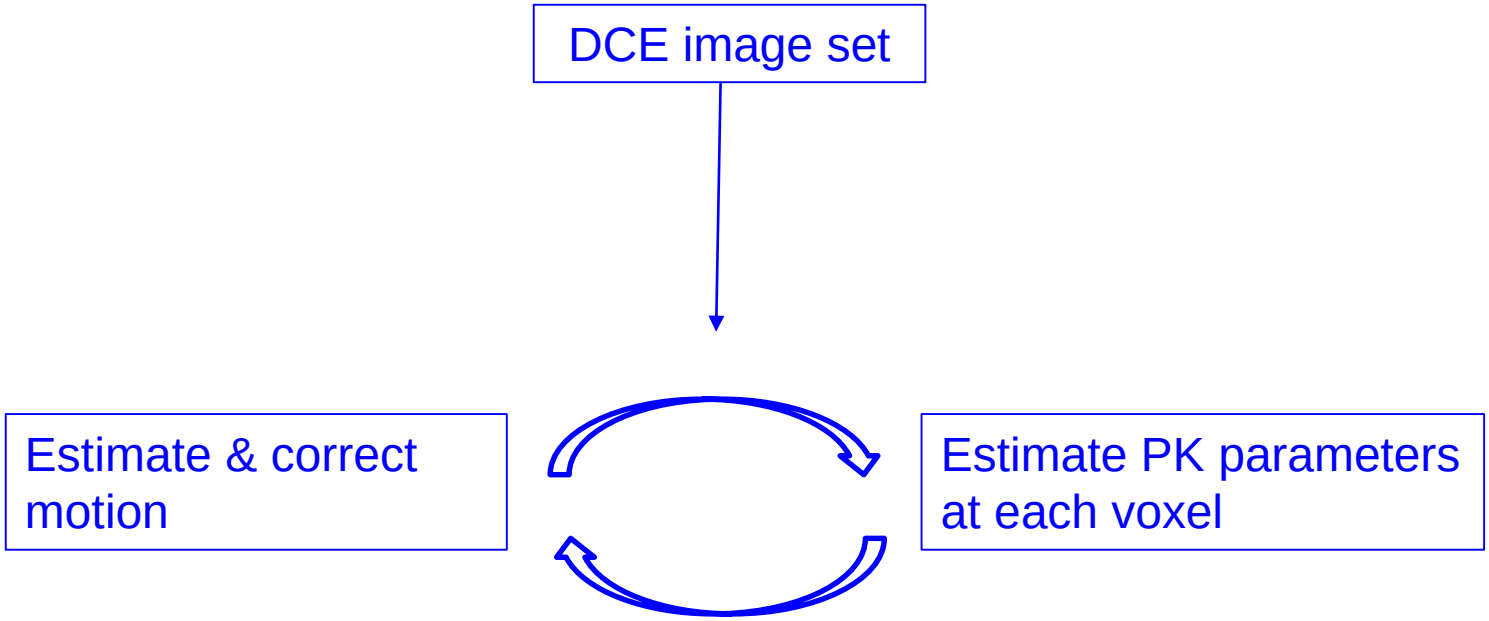
Colorectal cancer dceMRI : motion



Original data

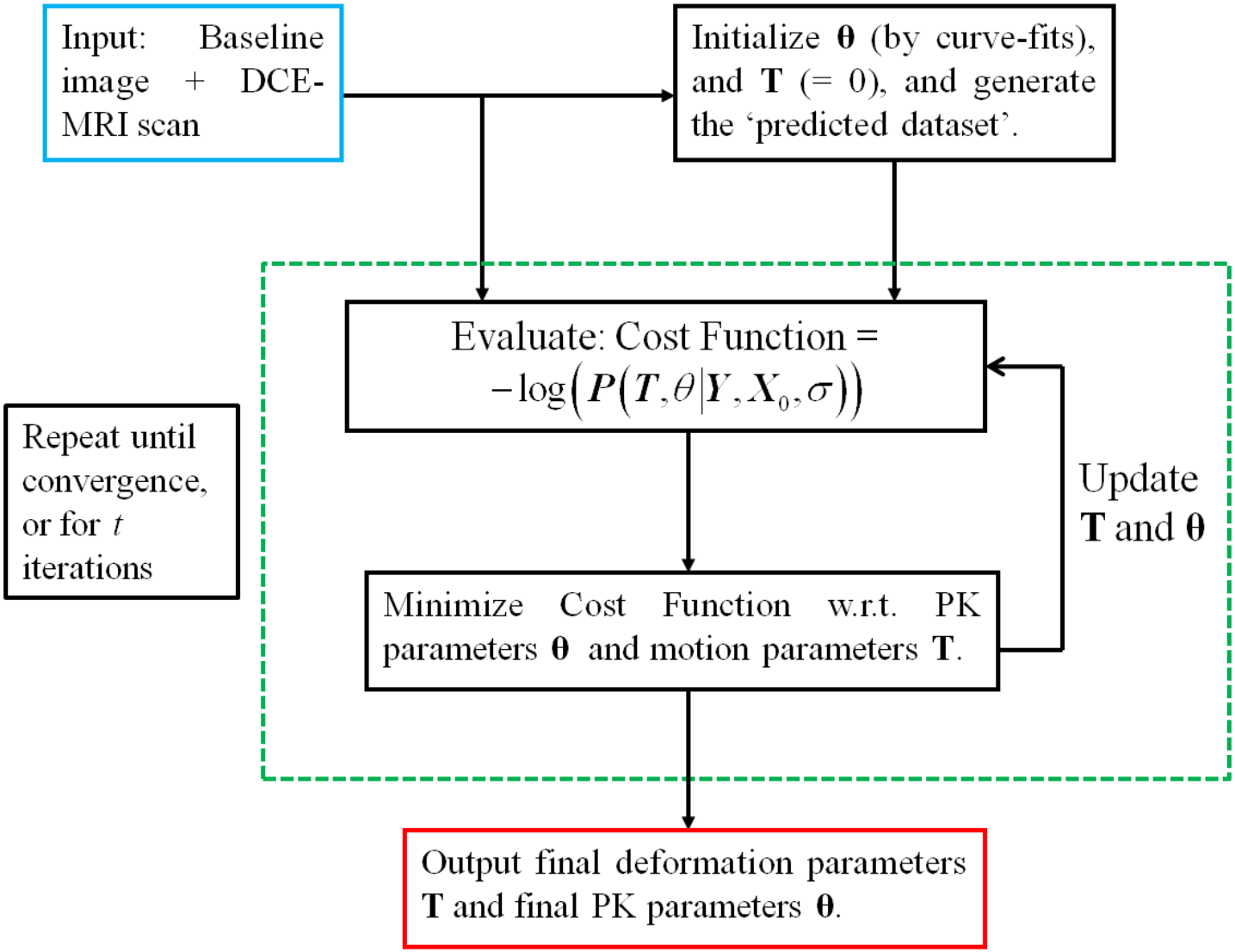
Dr. M. Bhushan, Profs. Schnabel, Jenkinson, Brady

Simultaneous estimation of motion parameters and PK parameters



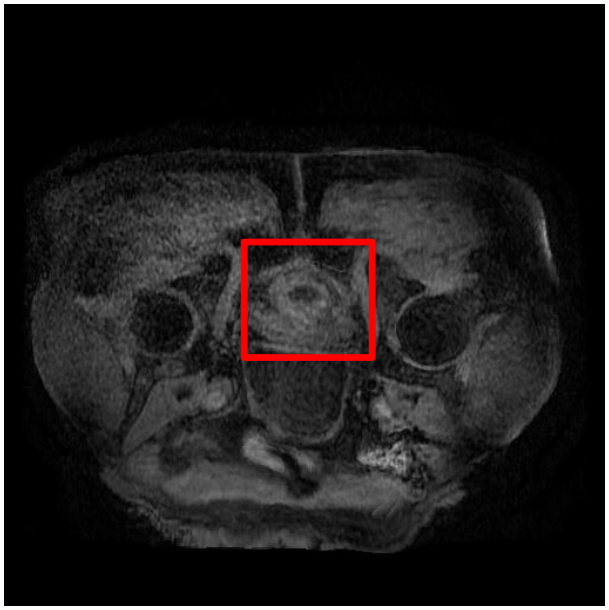
There are numerous ways in which this cycle can be developed mathematically and implemented in an efficient algorithm. The simplest is expectation-maximisation…though there are several others

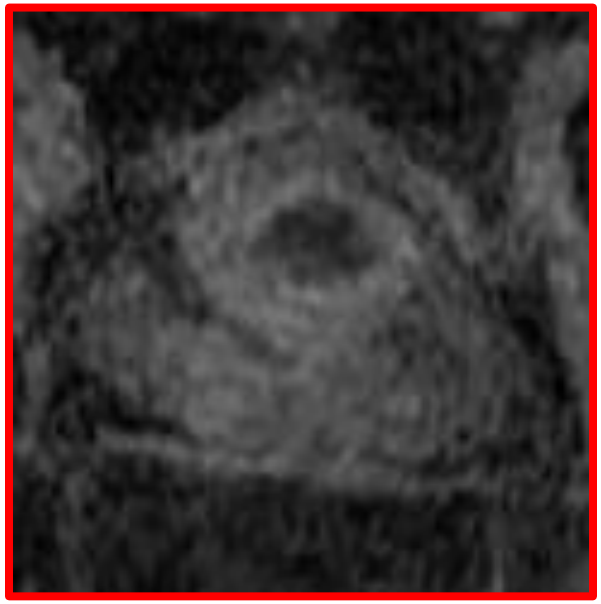
Model-based Registration and Parameter Estimation (MoRPE)

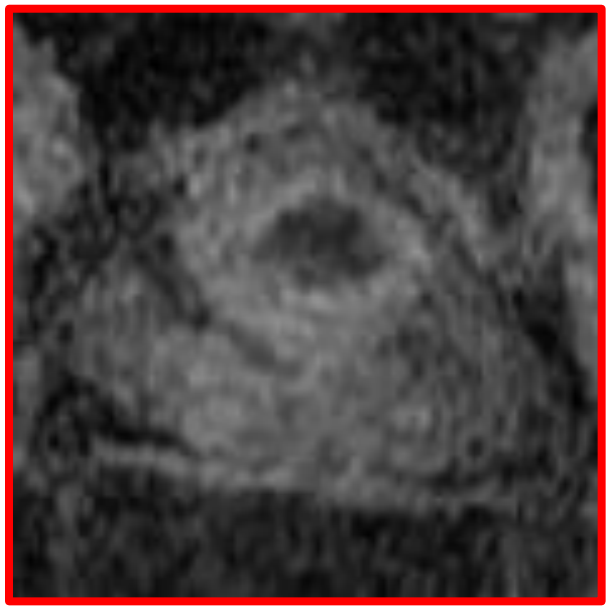


M Bhushan et al. MICCAI'11,ISMRM'12

Motion correction of dceMRI volumes for colorectal cancer



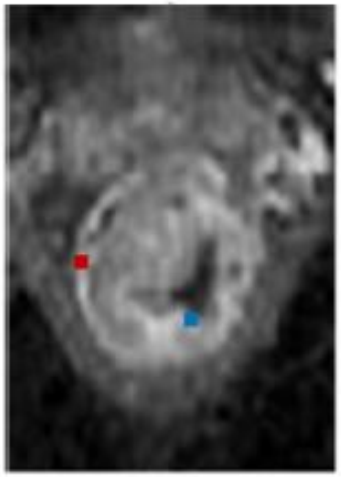


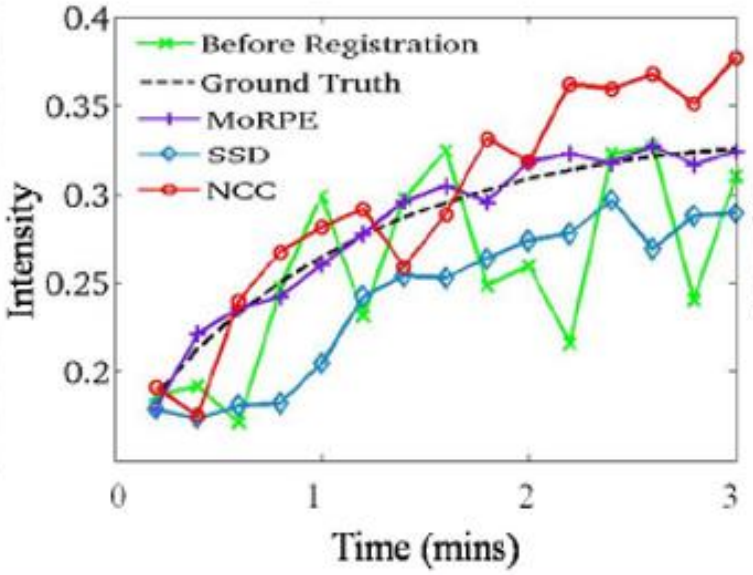


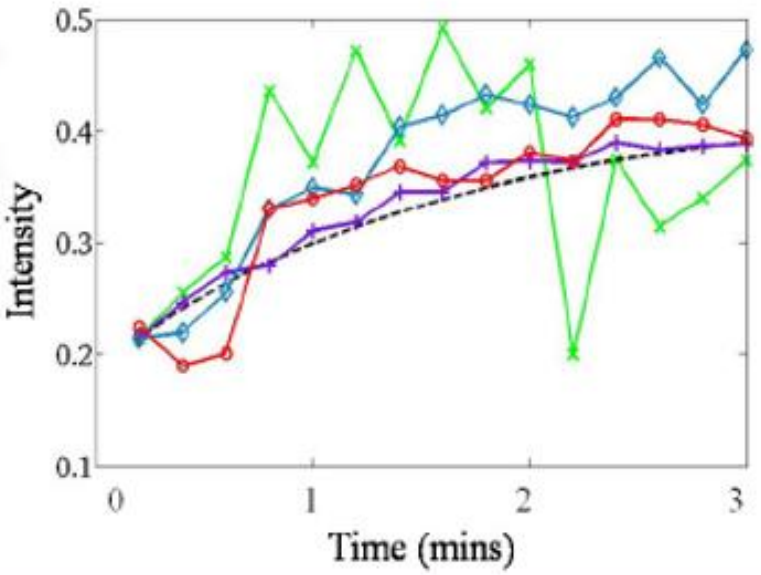
Original data

Motion corrected

Signal intensity curves





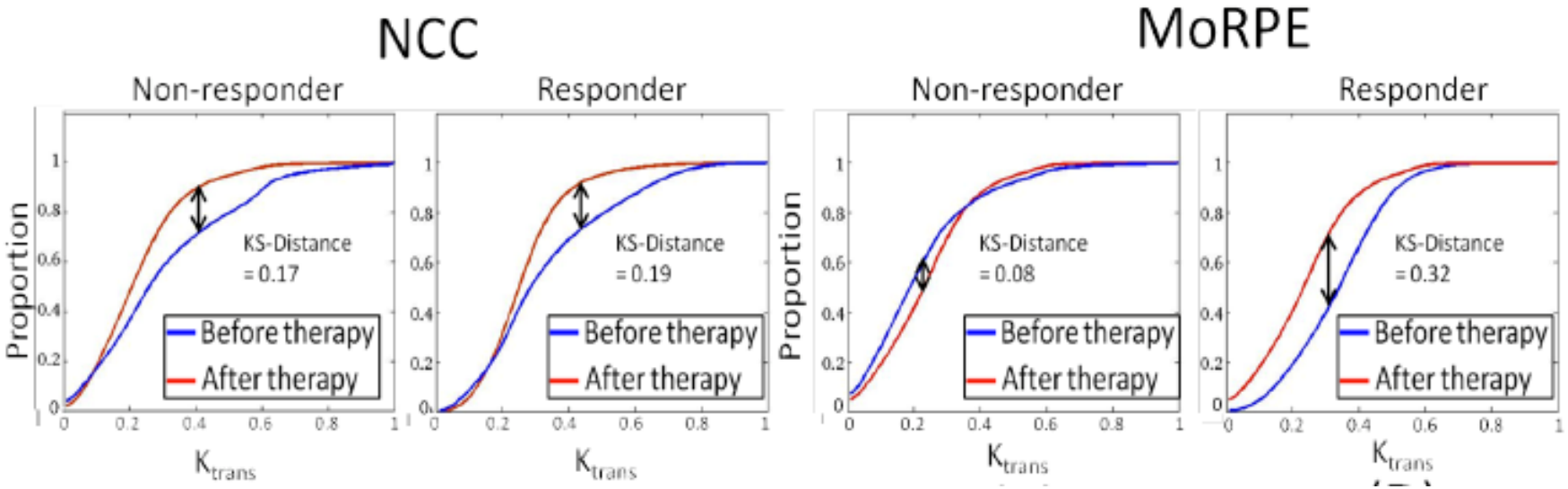


In this case, the signal change and motion were simulated. (-----)
The simultaneous algorithm:

Two standard similarity criteria for deformable registration:

M Bhushan et al. MICCAI'11,ISMRM'12

Measuring therapy response



No discrimination for non-responder/ responder case using conventional normalised cross-correlation (NCC) registration

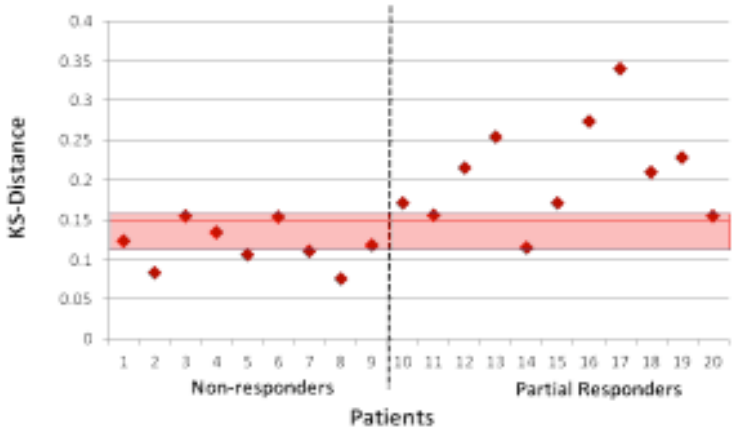
Increase in perfusion for responder vs no change in non-responder case using MoRPE (PK model-based registration)

Motion correction: Differences in K_{trans} distributions before & after therapy

M Bhushan et al. MICCAI'11,ISMRM'12

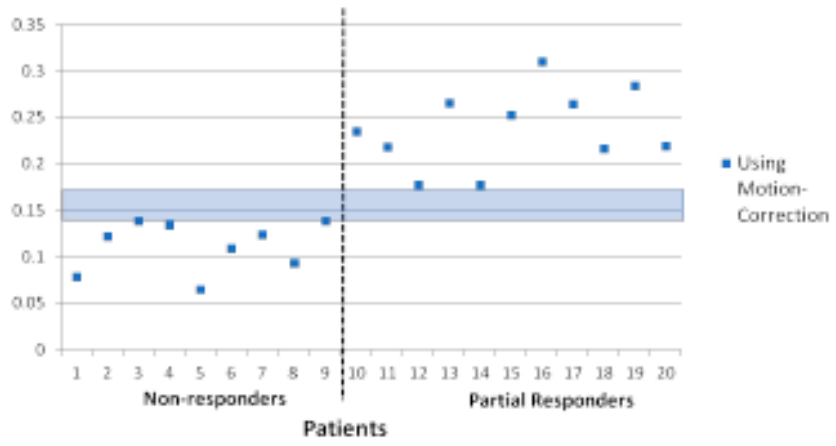
The importance of motion correction

Without Motion Correction



discrimination between responders & non-responders is not possible without motion correction

Motion correction using our algorithm



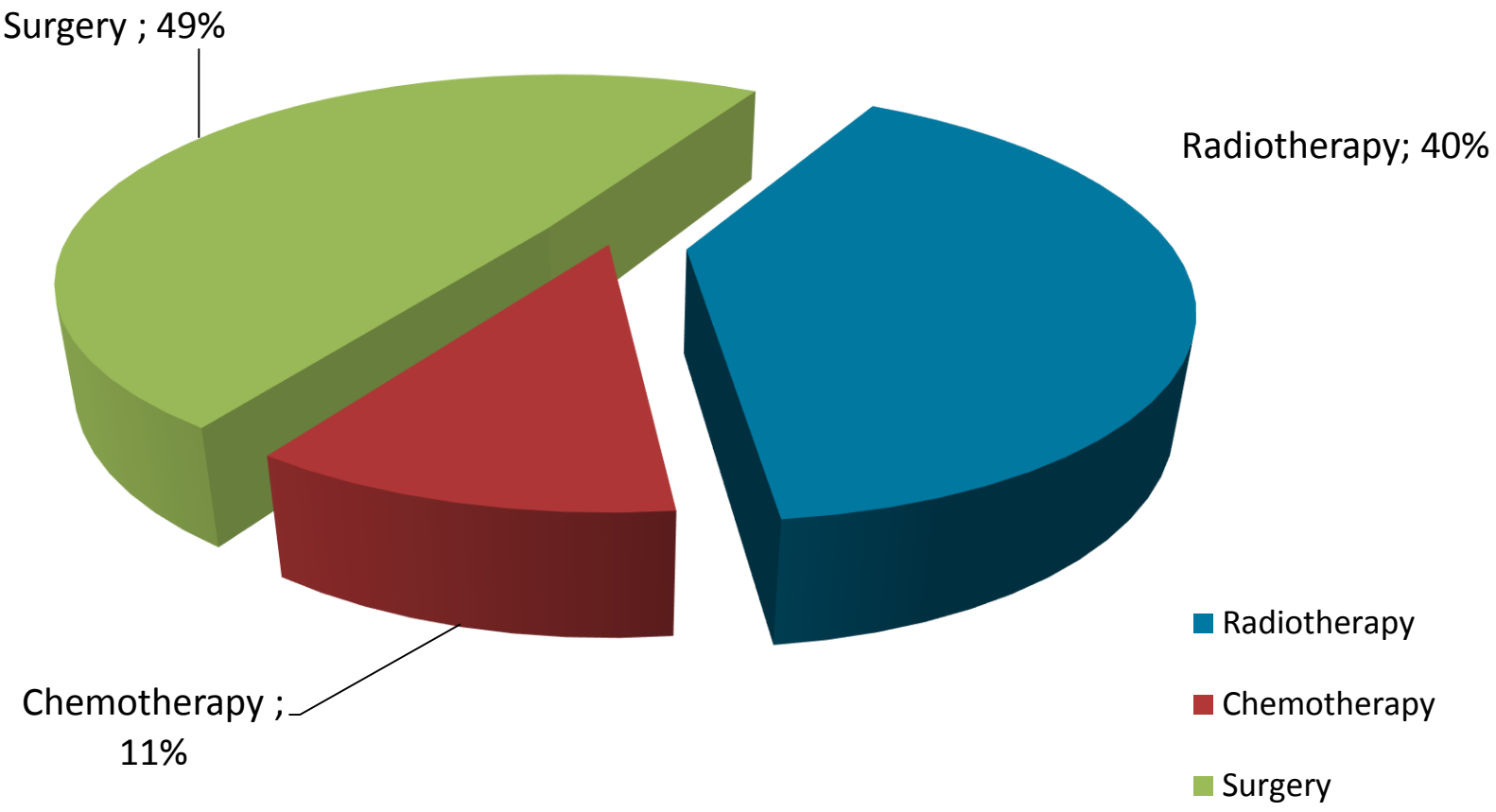
Statistically significant* discrimination between responders & non-responders

We use the Komogorov-Smirnov test, KS

M Bhushan et al. MICCAI'11,ISMRM'12

What can currently cure cancer?

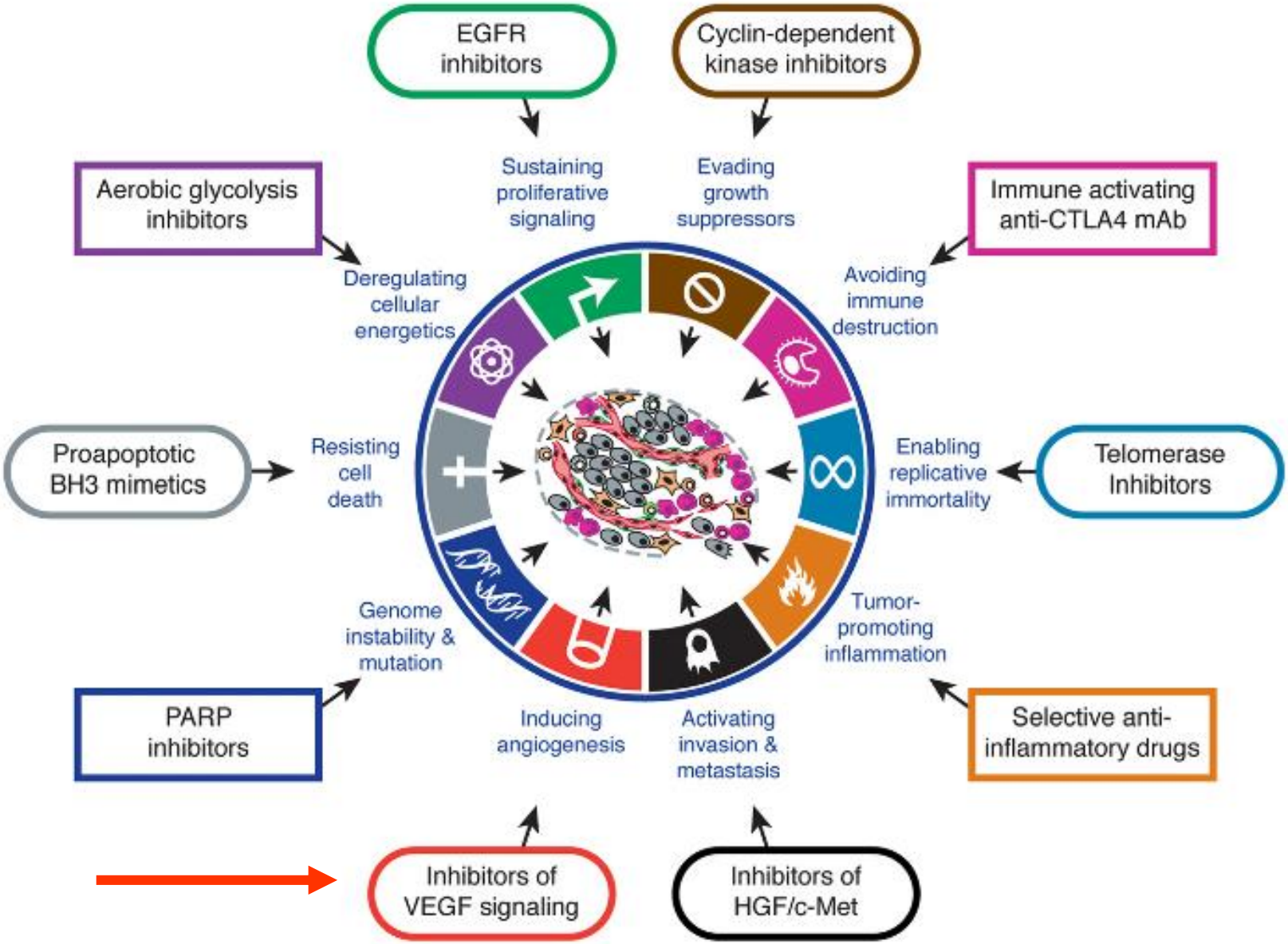
Professor Sir Mike Richards, NCRI 2011



Can we define biological processes that regulate or are markers of the responsiveness of tumours?

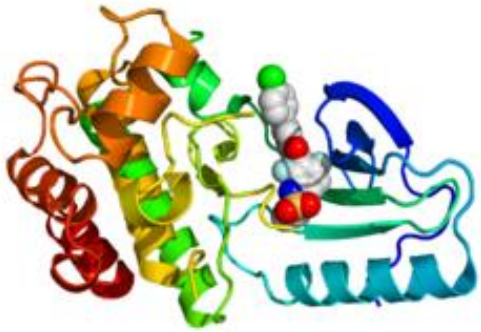
Can agents that target these processes be taken into the clinic to alter outcome?

Hanahan and Weinberg Hallmarks of Cancer

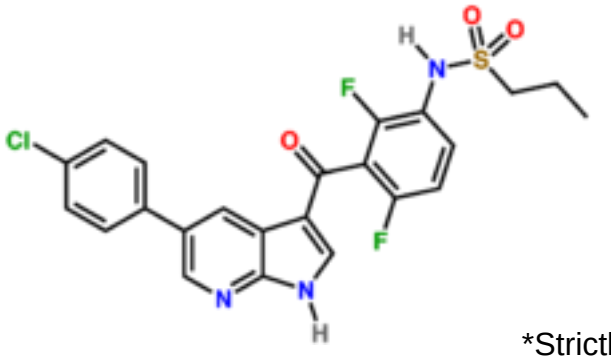


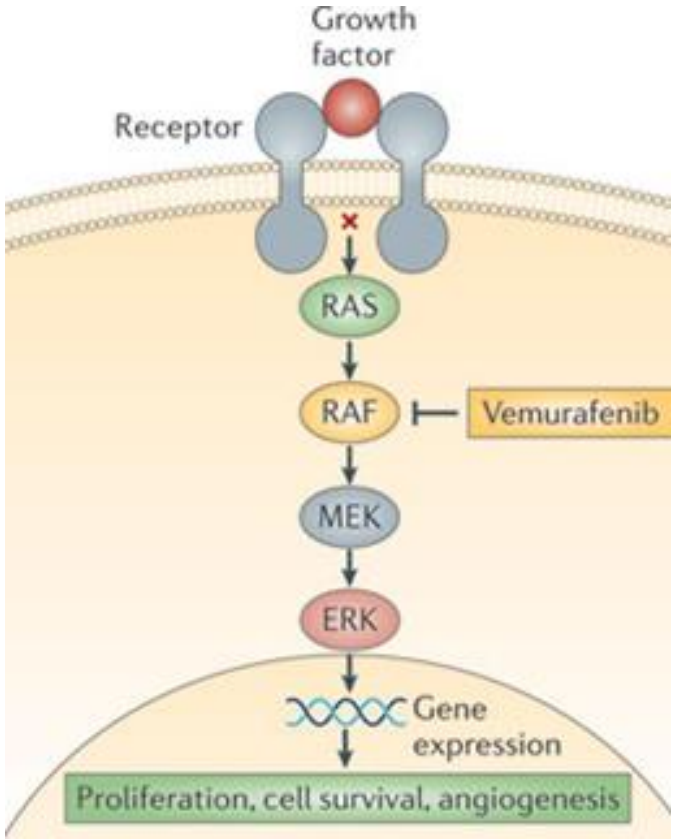
An early example: Melanoma*

40-60% of patients with melanoma have activating mutations of BRAF – a proto-oncogene that makes a protein B-RAF, which is involved in signalling in cells related to cell growth



PLX4032 (Vemurafenib) is an inhibitor of BRAF kinase

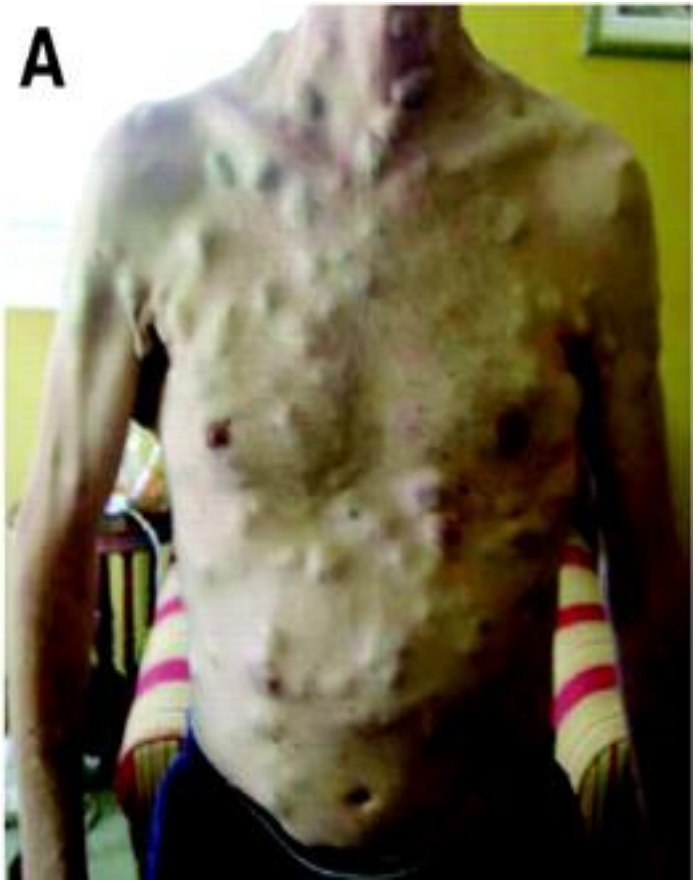




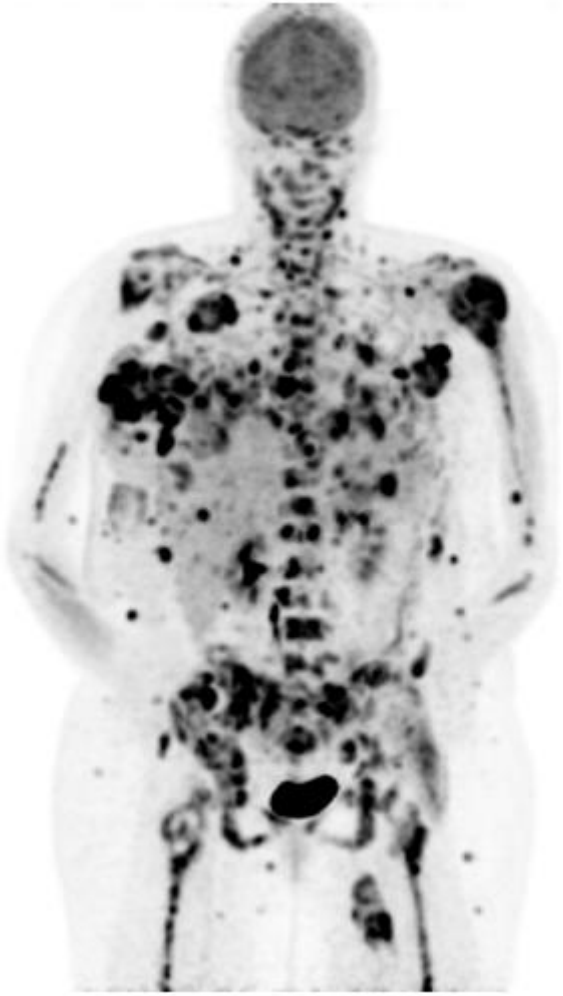
Vemurafenib targets the RAS-RAF1-MEK-ERK pathway

*Strictly: Chronic Mylogenous Leukaemia

Image of a BRAF-mutant melanoma

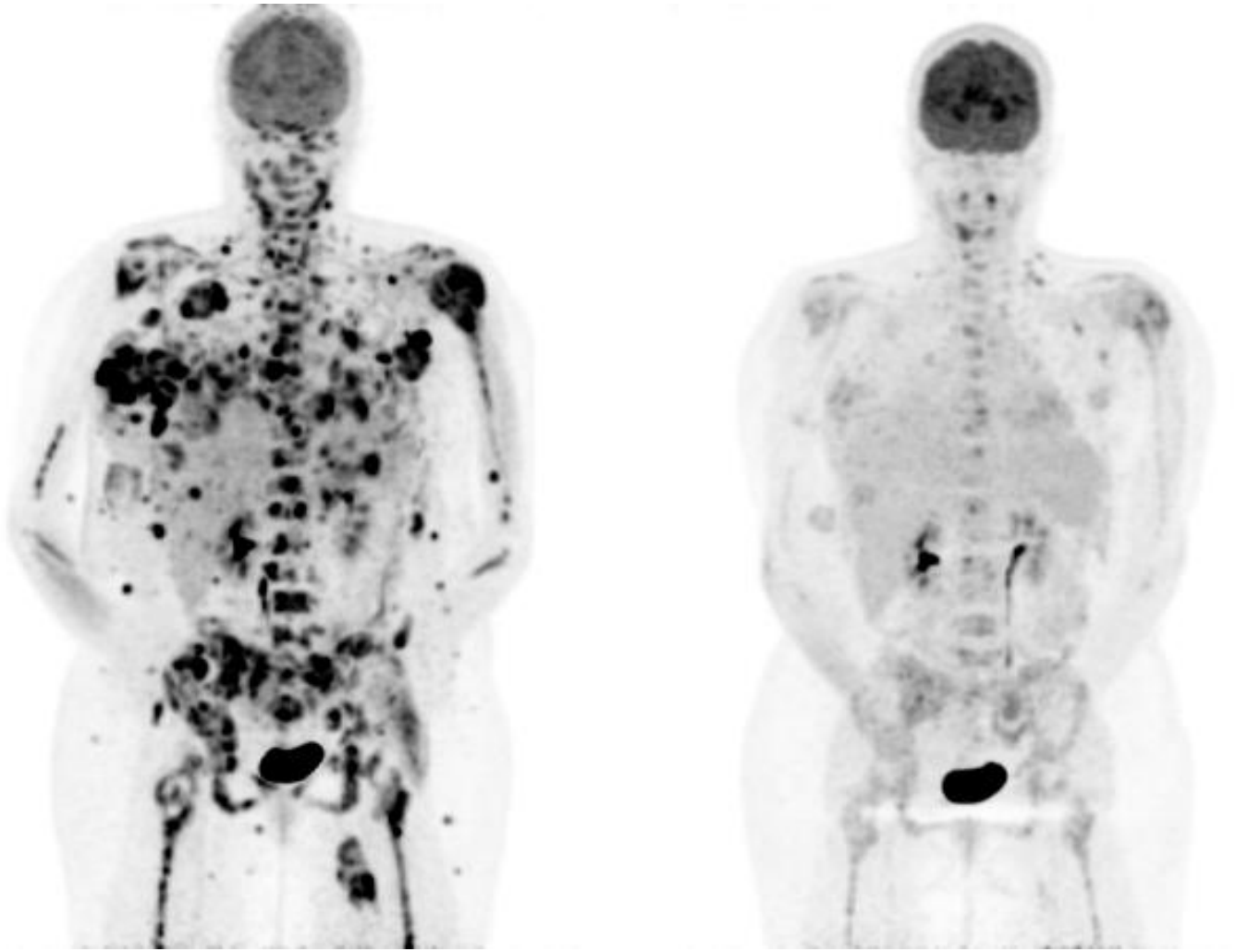


Man, 38 years old with a BRAF-mutant melanoma



PET fluorodeoxyglucose (FDG) image

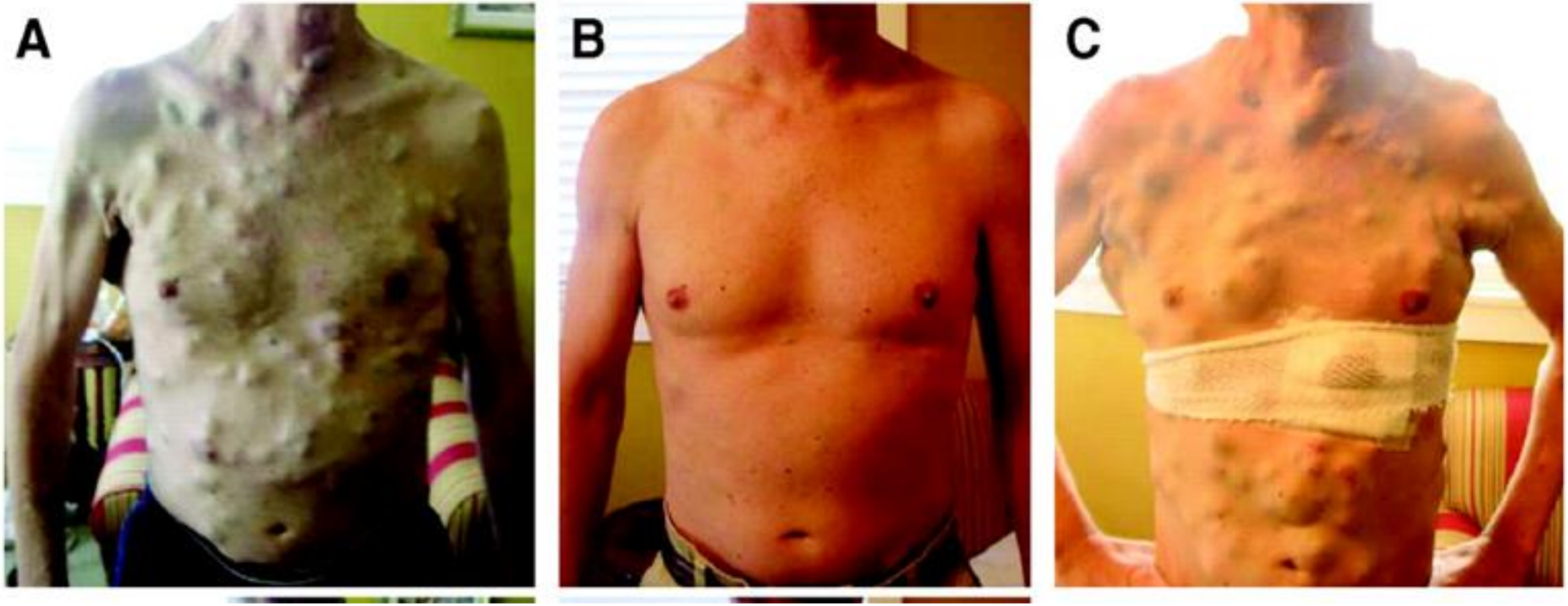
PET imaging shows the impact of Vemurafenib



Before and two weeks after initiating PLX4032

“This is one of the best examples I’ve ever seen of science triumphing over disease.” Brian Druker

…or so they thought



Before treatment | 15 weeks... | 23 weeks...

Conclusion

....cancer is agile.. It rapidly learns to mutate to accommodate a new therapy.....

This is a salutary lesson … but it is not all such bad news….

A bit of biology....

Cancers don't just develop as aberrant processes ***within*** a cell, rather by a complex series of interactions with the cells in their neighbourhood, that form the normal epithelia.

In normal tissue, these form the basement membrane

Tumour angiogenesis has many similarities to normal wound healing …

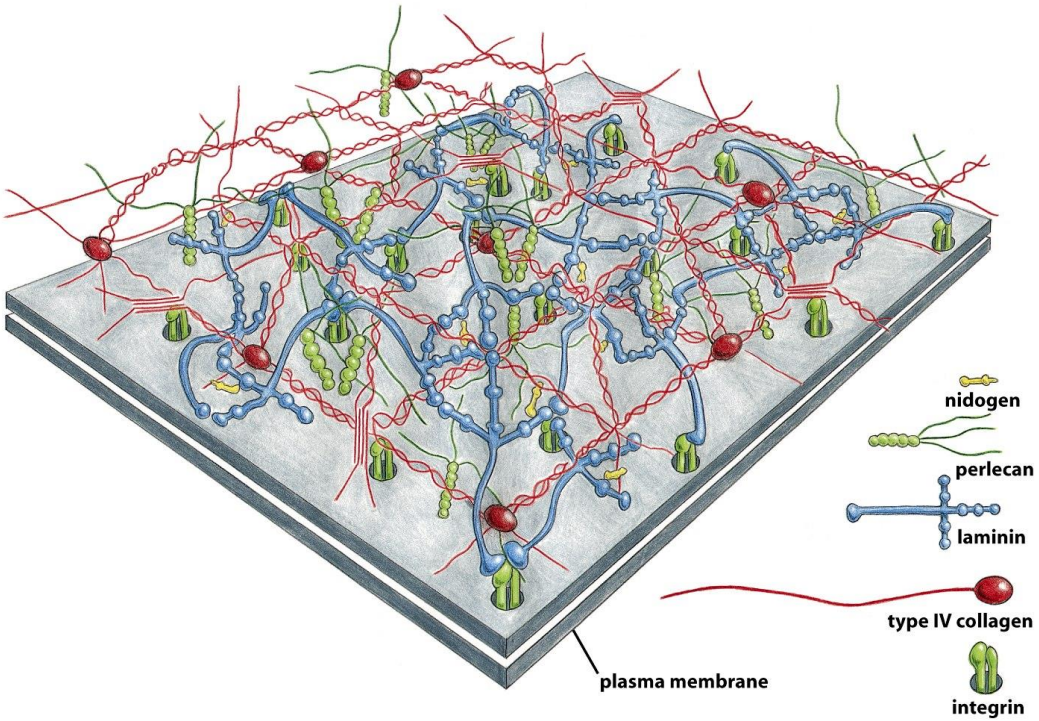
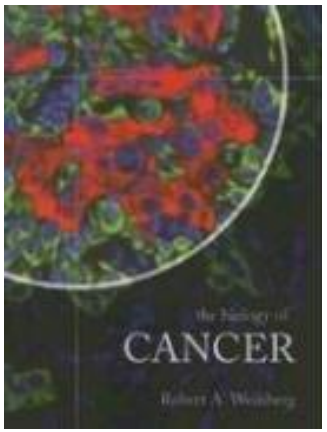


Figure 13-5b The Biology of Cancer (© Garland Science 2007)



A picture of wound healing....

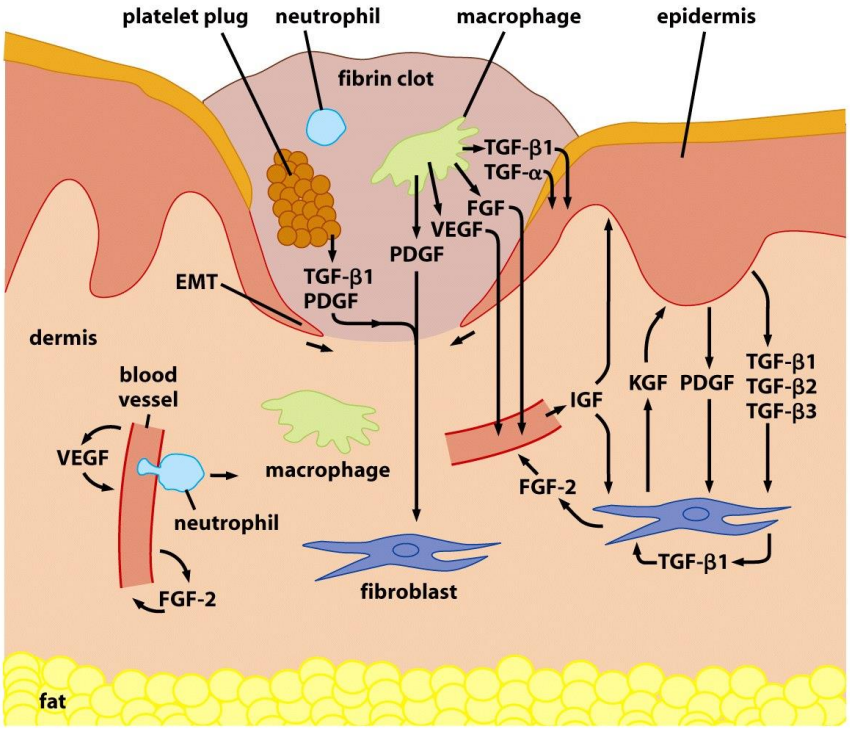


Figure 13-14 The Biology of Cancer (© Garland Science 2007)

Pathway model

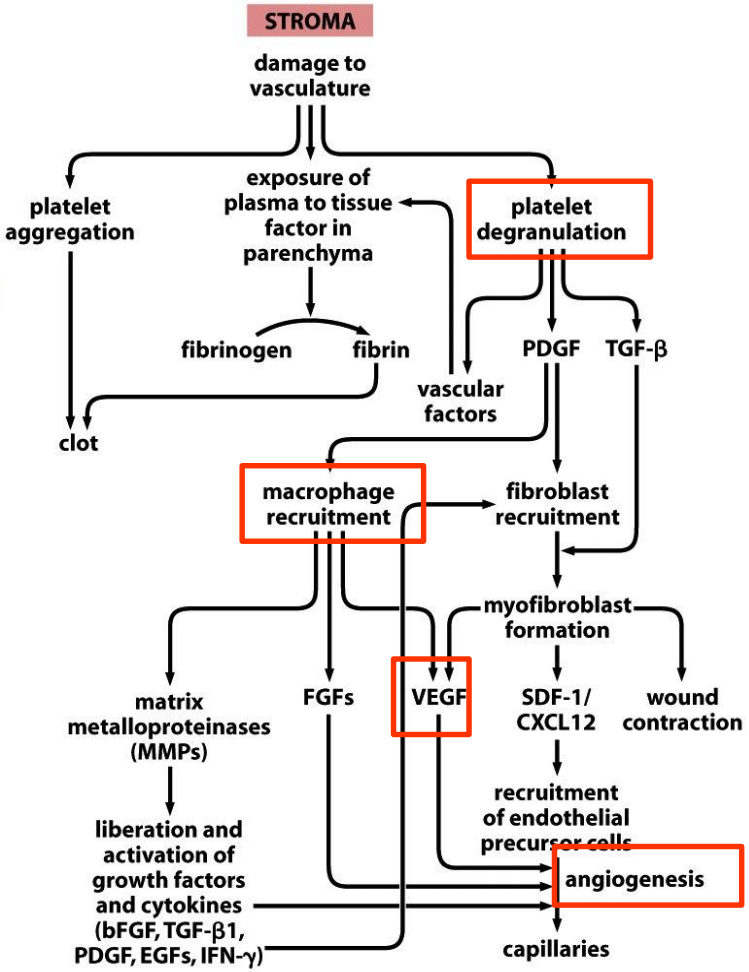
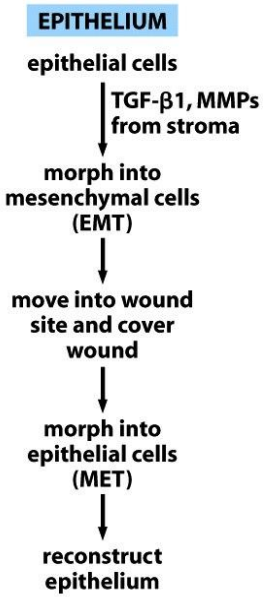


Figure 13-10 The Biology of Cancer (© Garland Science 2007)



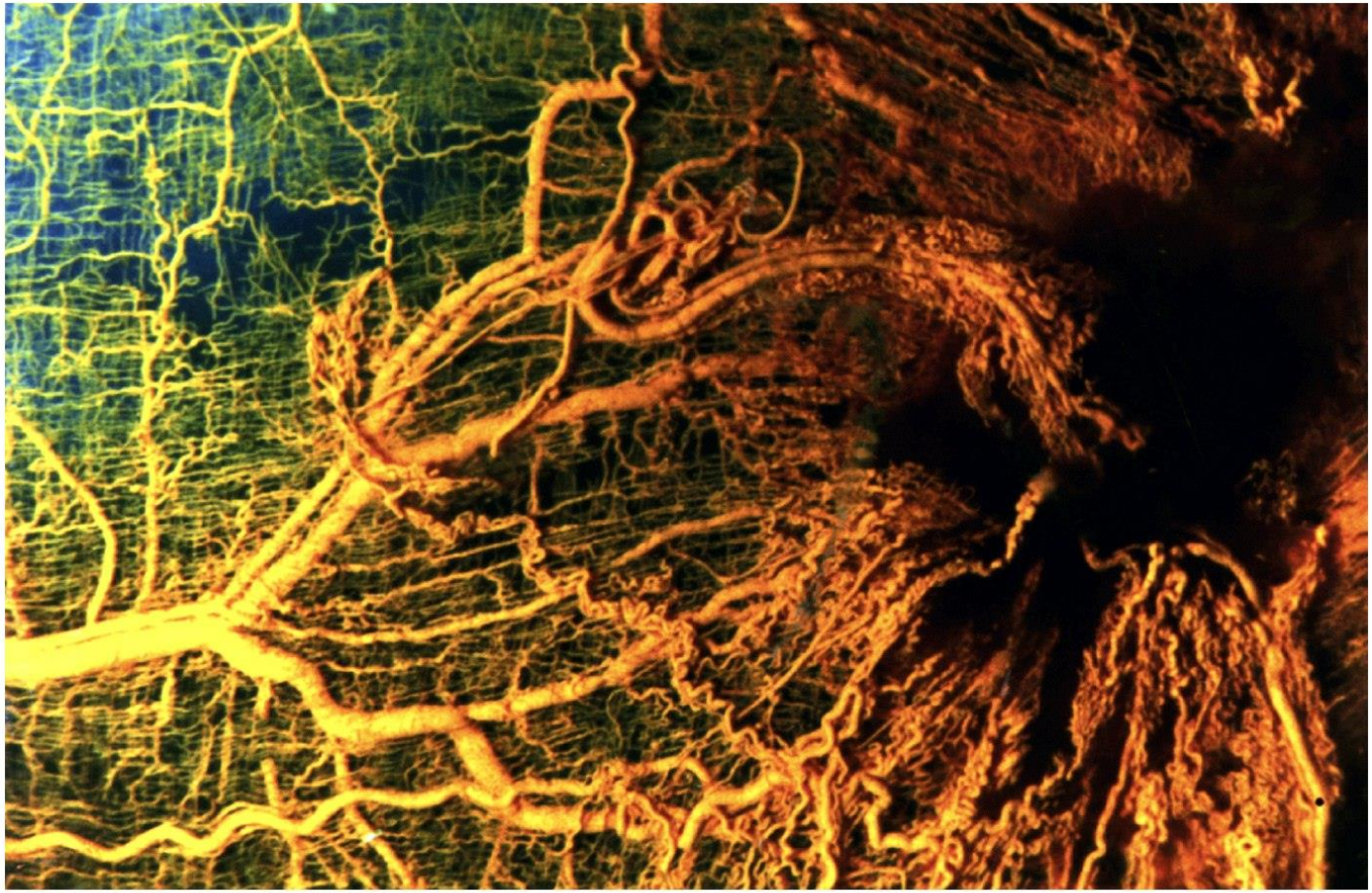
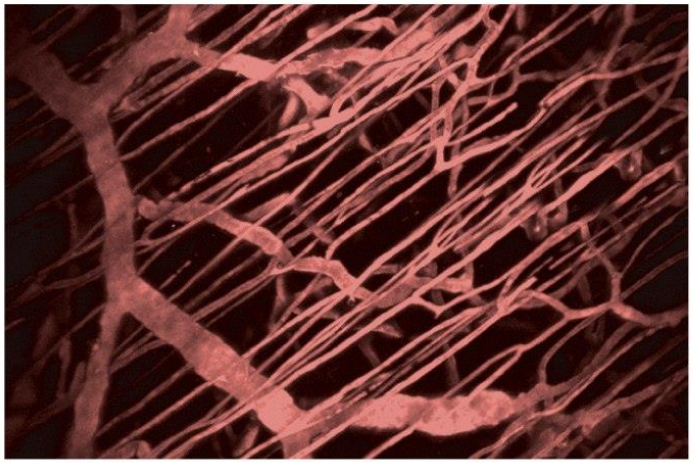


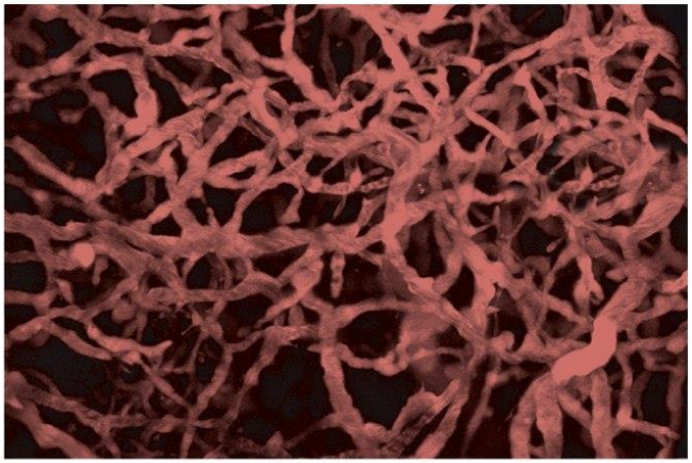
Figure 13-34a The Biology of Cancer (© Garland Science 2

Above, left: normal; right chaotic (tumour is black)

Another rendition of chaotic & leaky neovasculature

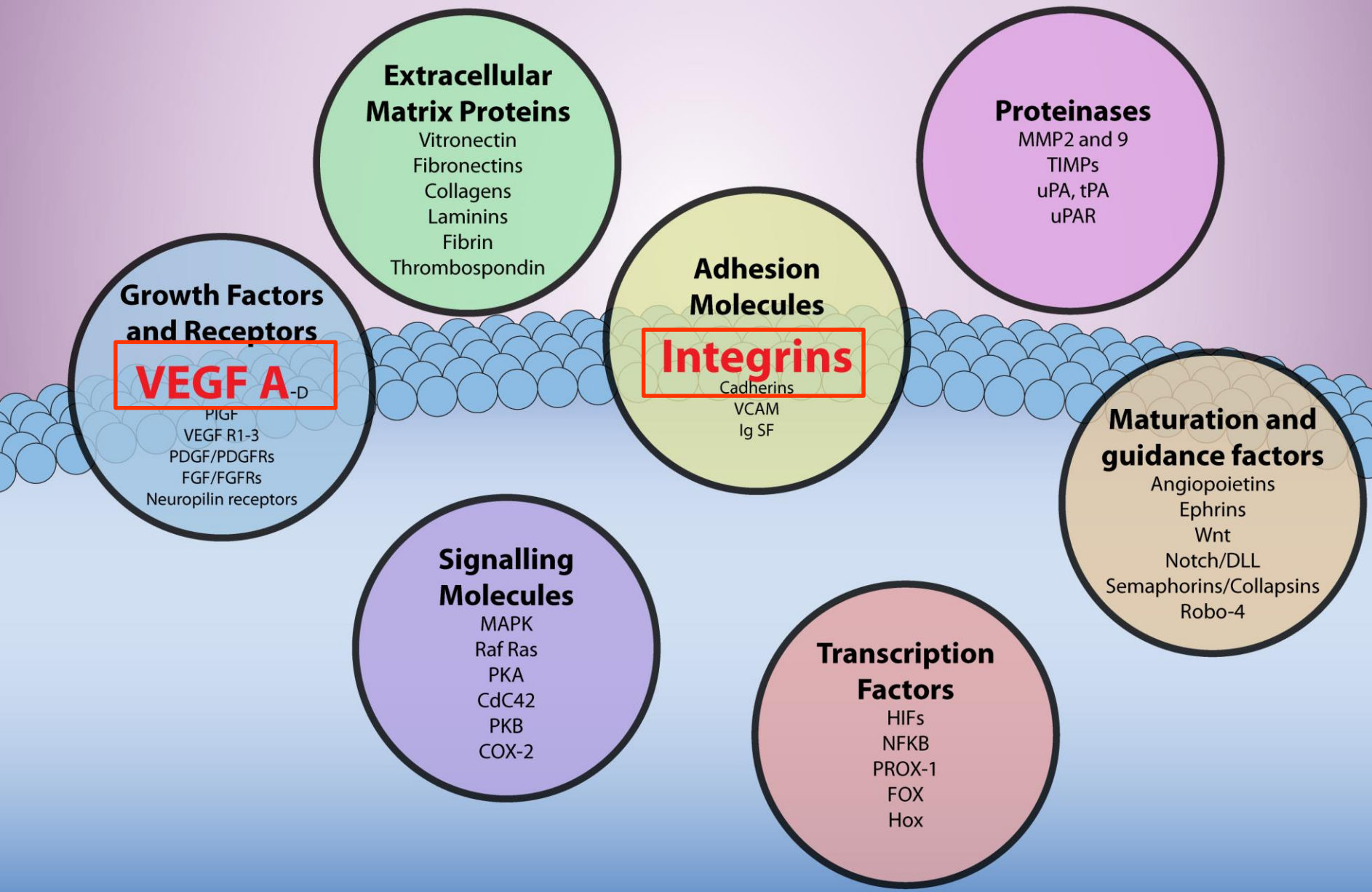


normal tissue



tumor

Imaging angiogenesis: many targets!

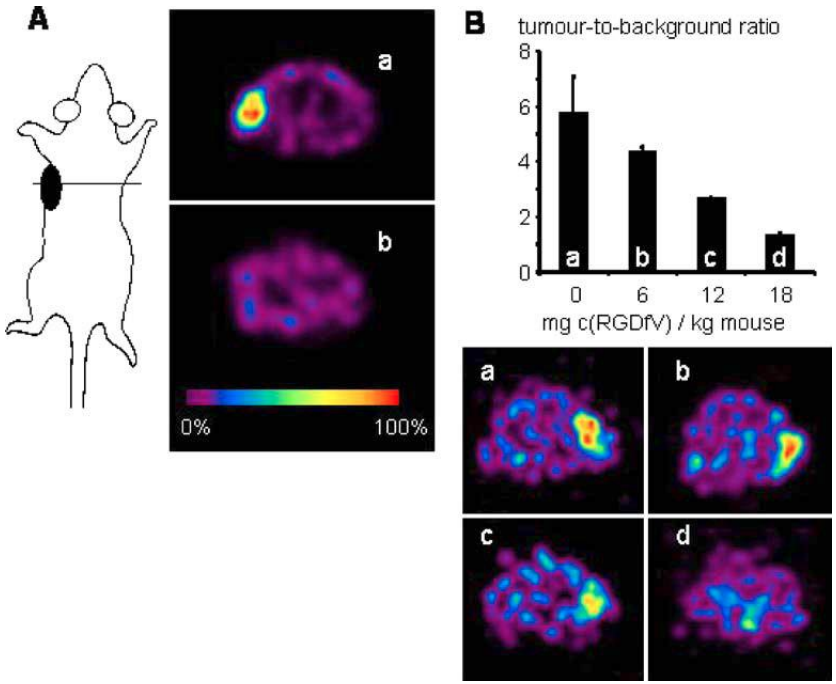


Courtesy Dr. Neel Patel, Oxford

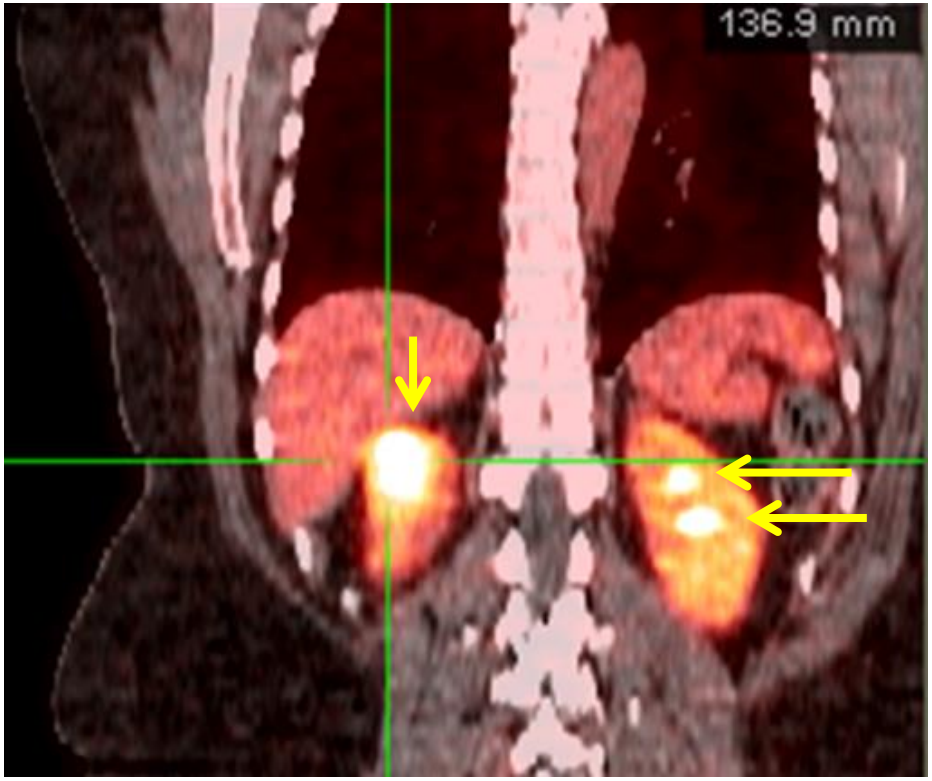
Integrin targeting for angiogenesis

Integrins 'integrate' signals from the extracellular matrix (ECM) to the intracellular cytoskeleton in focal adhesions.

In particular, the integrin αvβ3 mediates the migration of endothelial cells through the basement membrane during blood-vessel formation. It binds to peptides containing the amino-acid sequence RGD*



* Arginine-Glycine-Aspartic acid



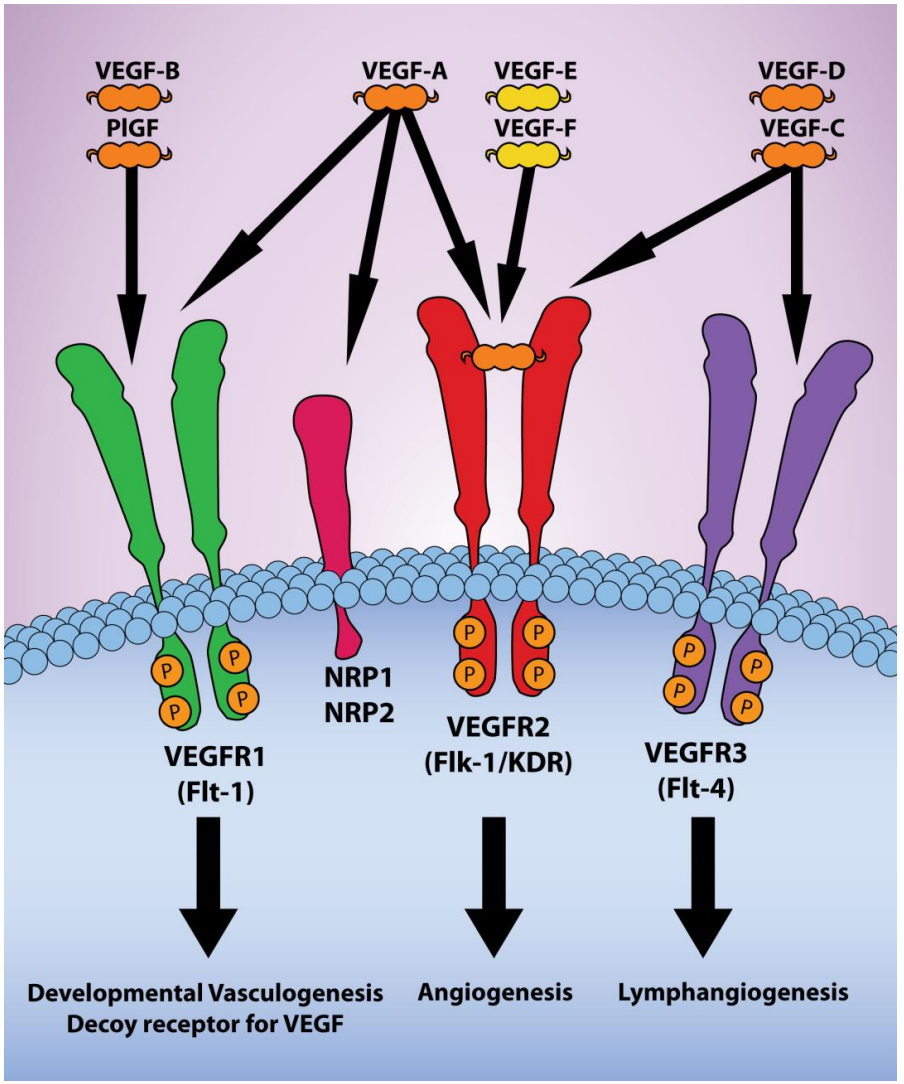
^{18}F-RGD PET-CT image of small renal tumours

Courtesy Dr. Neel Patel, Oxford

VEGF for inhibition of angiogenesis

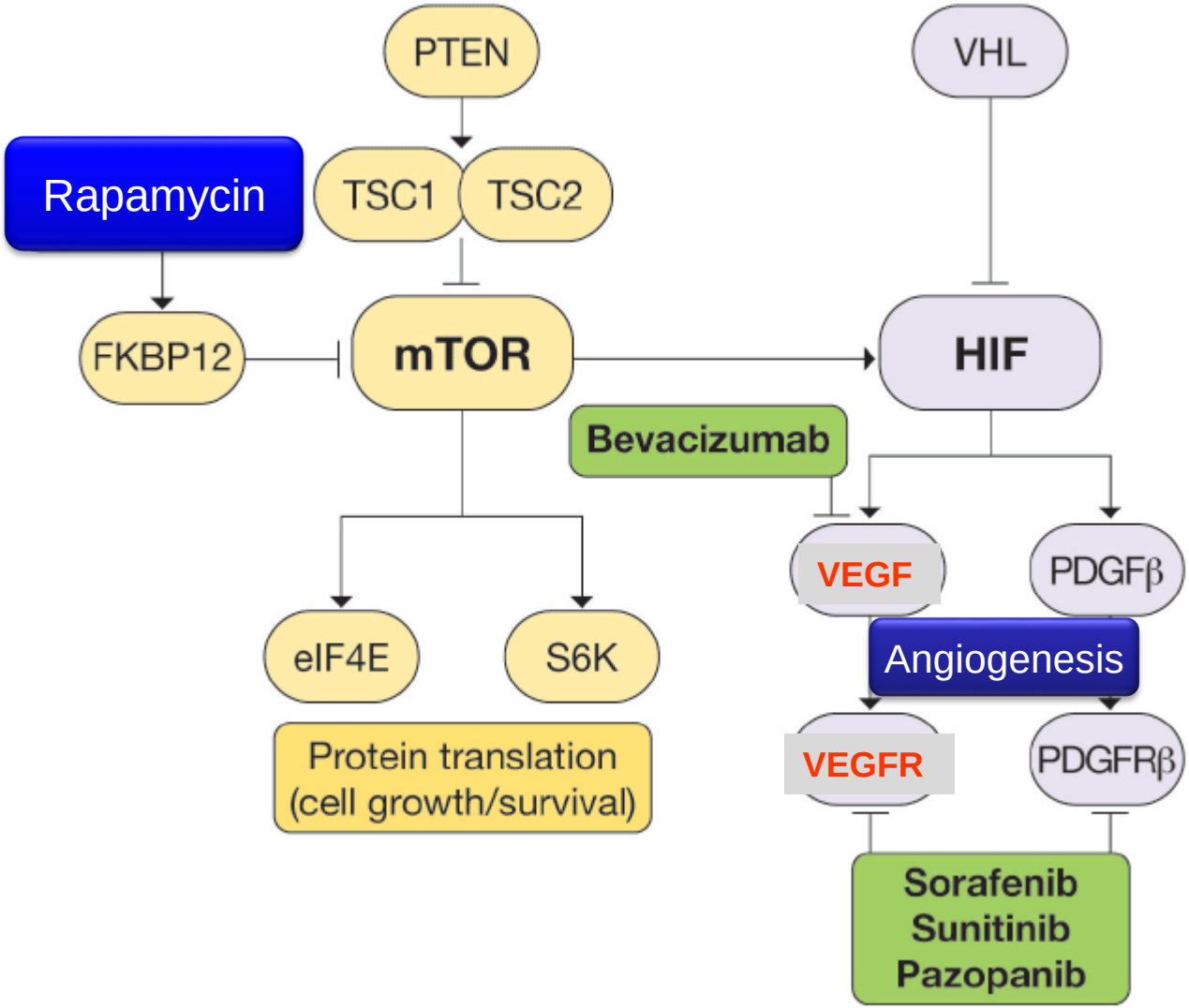
Vascular Endothelial Growth Factors
VEGF A-D are signalling proteins

Cellular response through the tyrosine kinase receptors (the VEGFR 1-3) on the cell surface

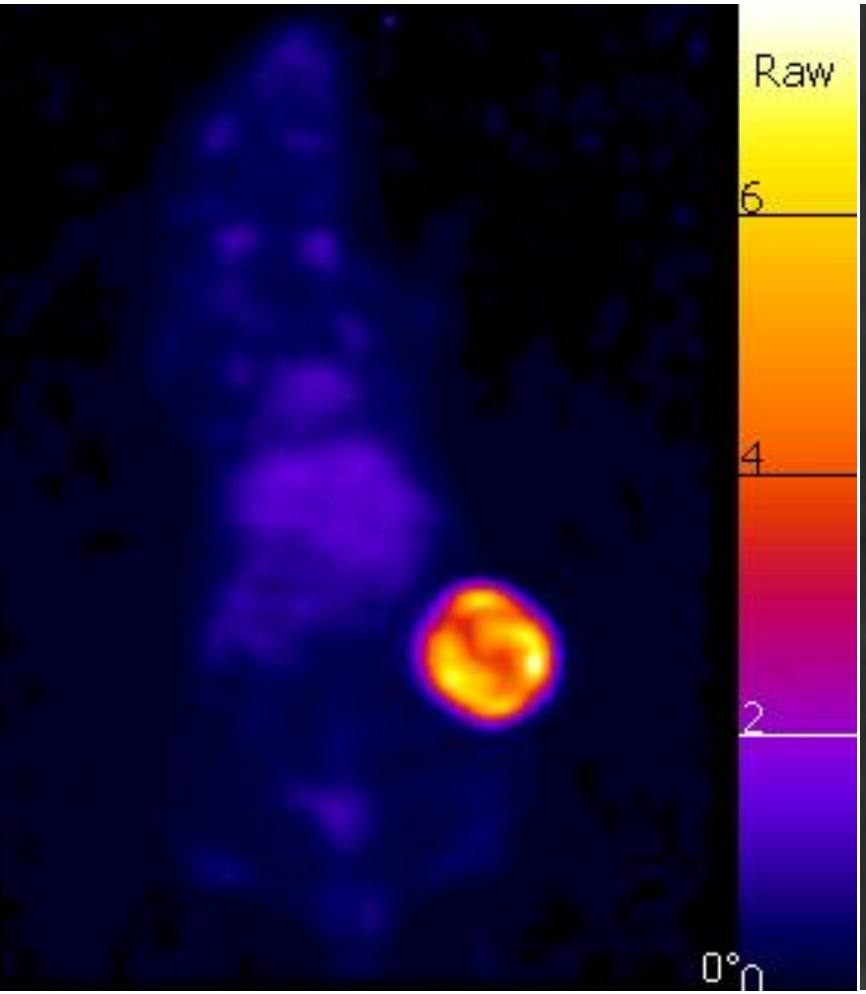


Courtesy Dr. Neel Patel, Oxford

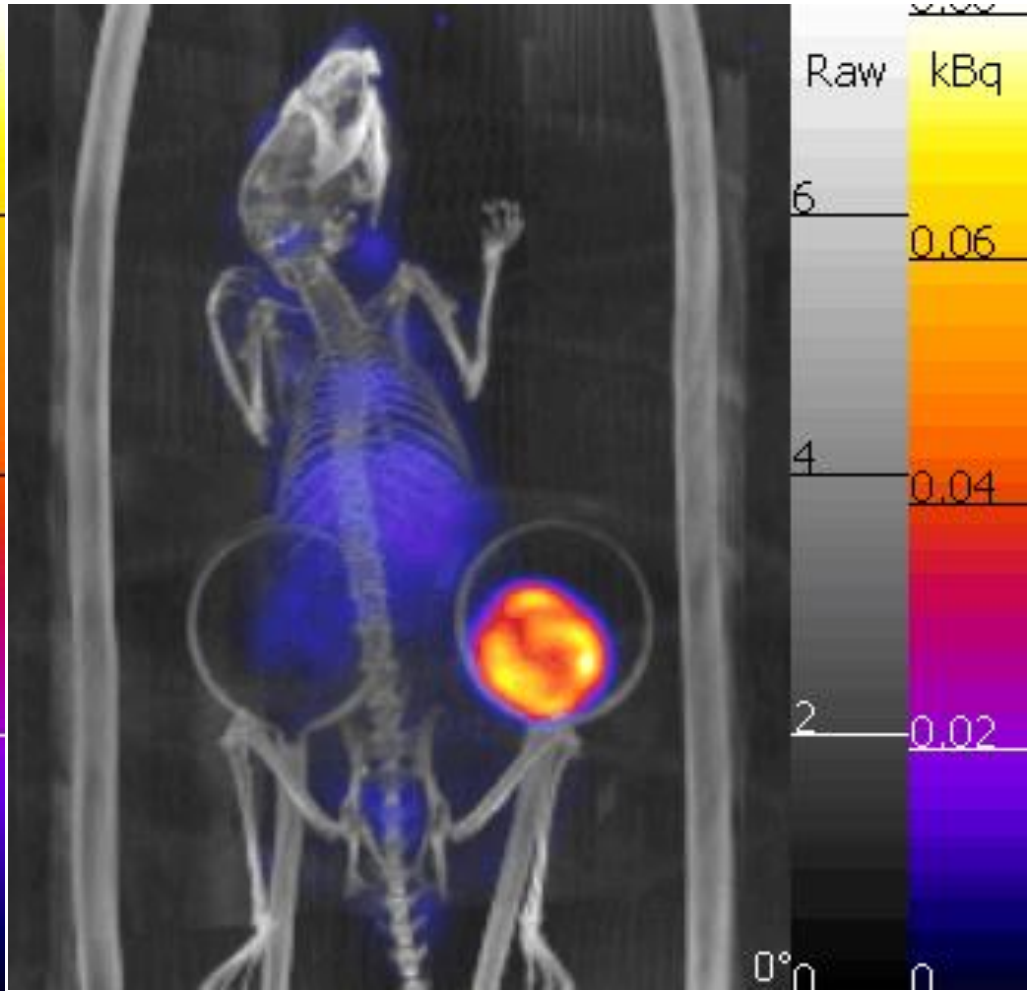
A range of related targets



Imaging Avastin bound to SPECT emitter ^{124}I

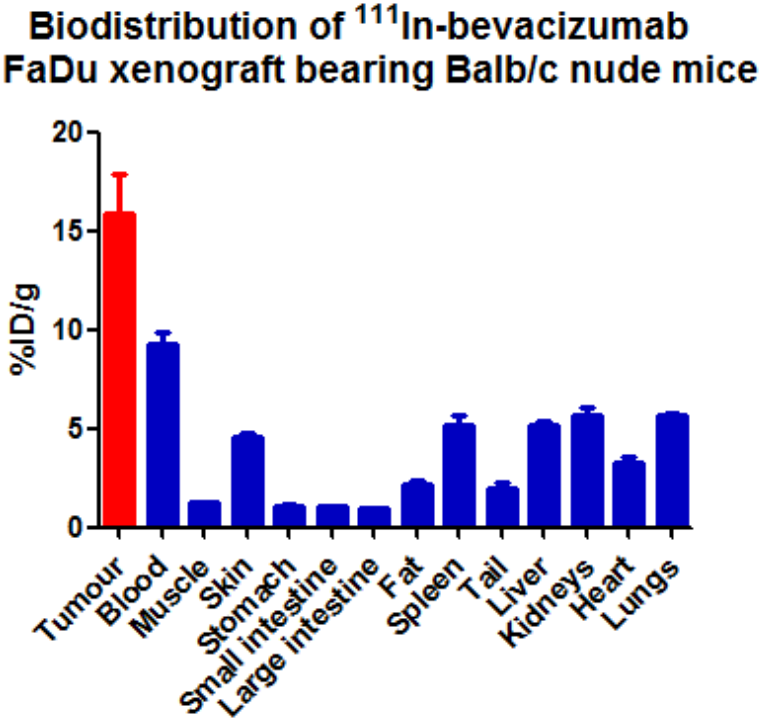


SPECT

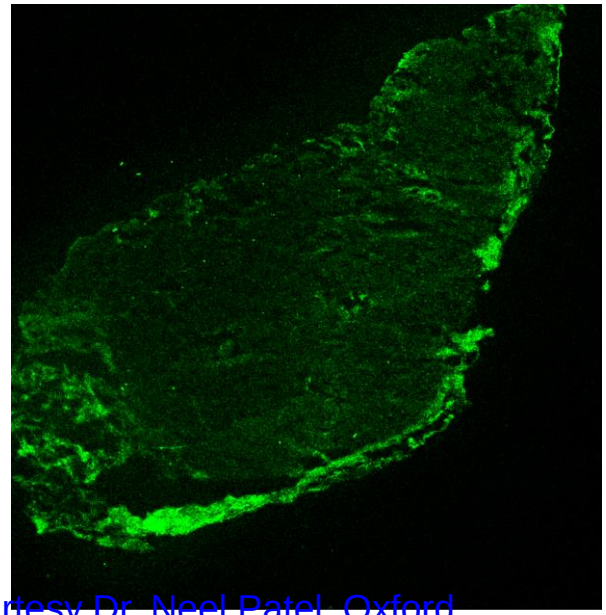


CT fused with SPECT

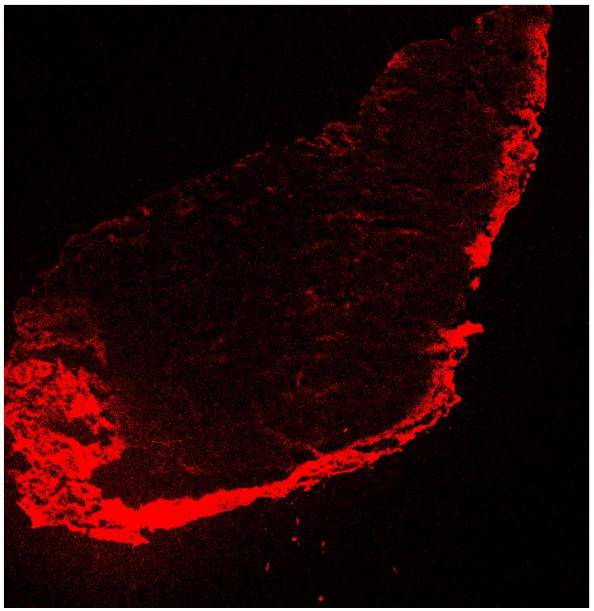
Biodistribution & immunohistochemistry



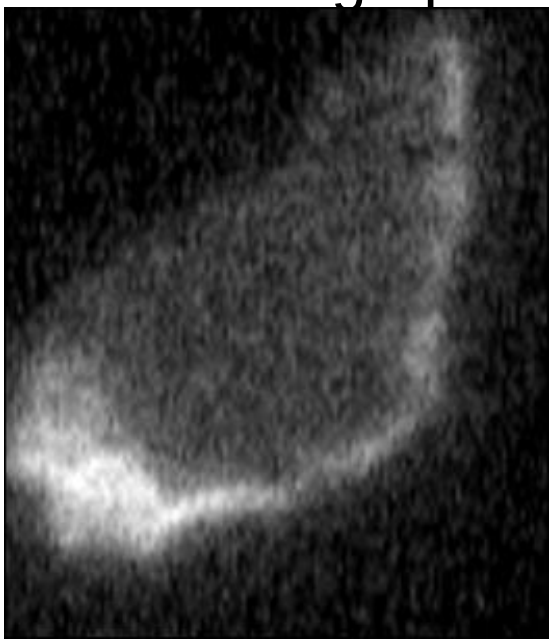
VEGF



Avastin



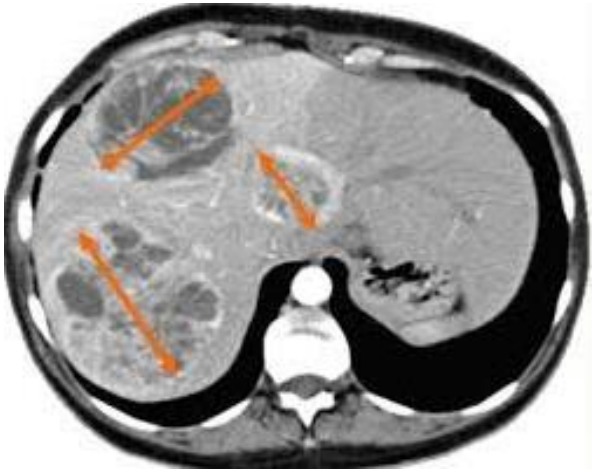
Autoradiograph



Courtesy Dr. Neel Patel, Oxford

Finally, a cautionary tale about quantitation

How are tumour progression/response measured?



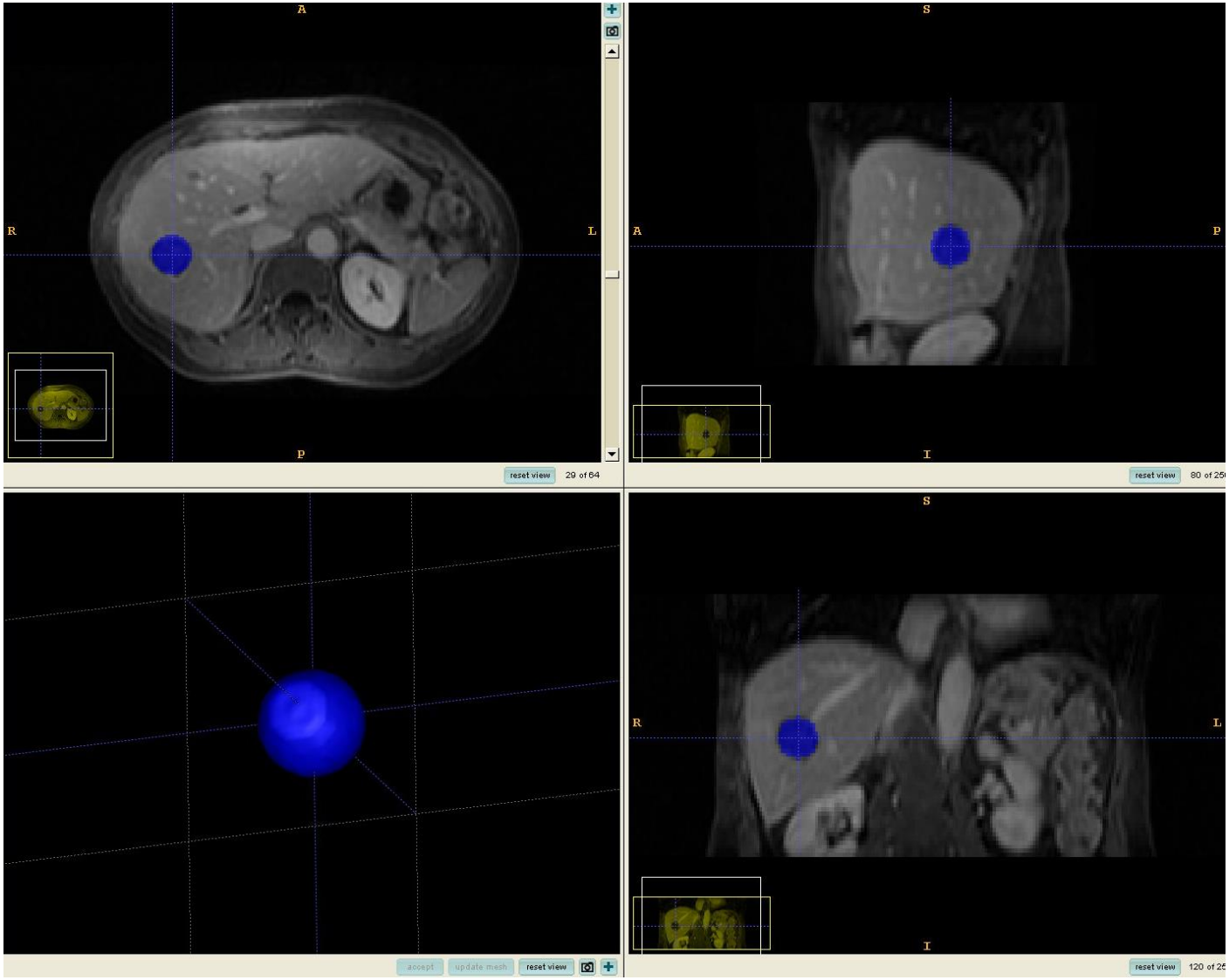
Response Evaluation Criteria in Solid Tumours (RECIST)

For target lesions

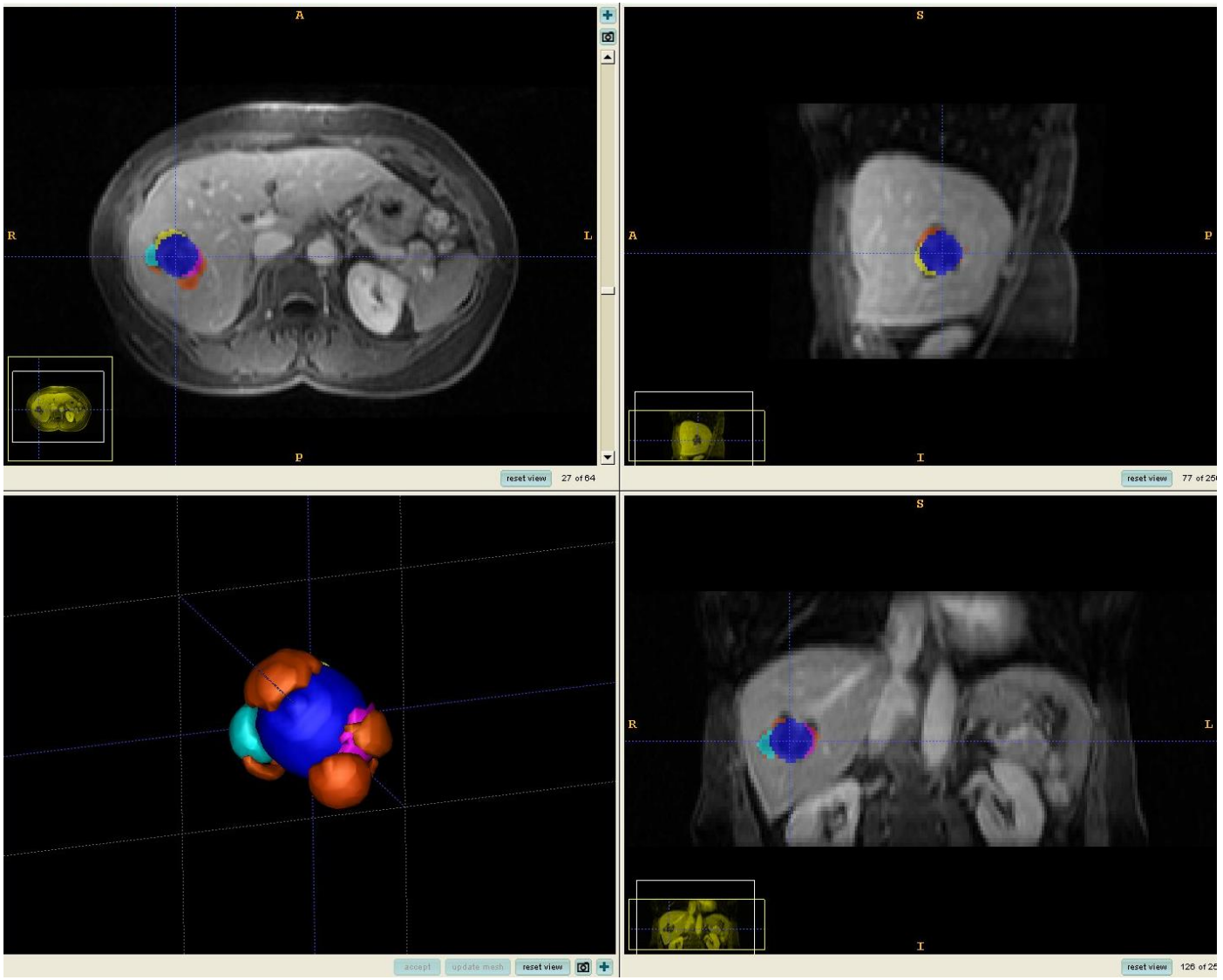
- Choose up to 5 lesions, up to 2 per organ
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the “sum of the longest diameters” (SLD)

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

(Liver) tumour shape pre-chemotherapy

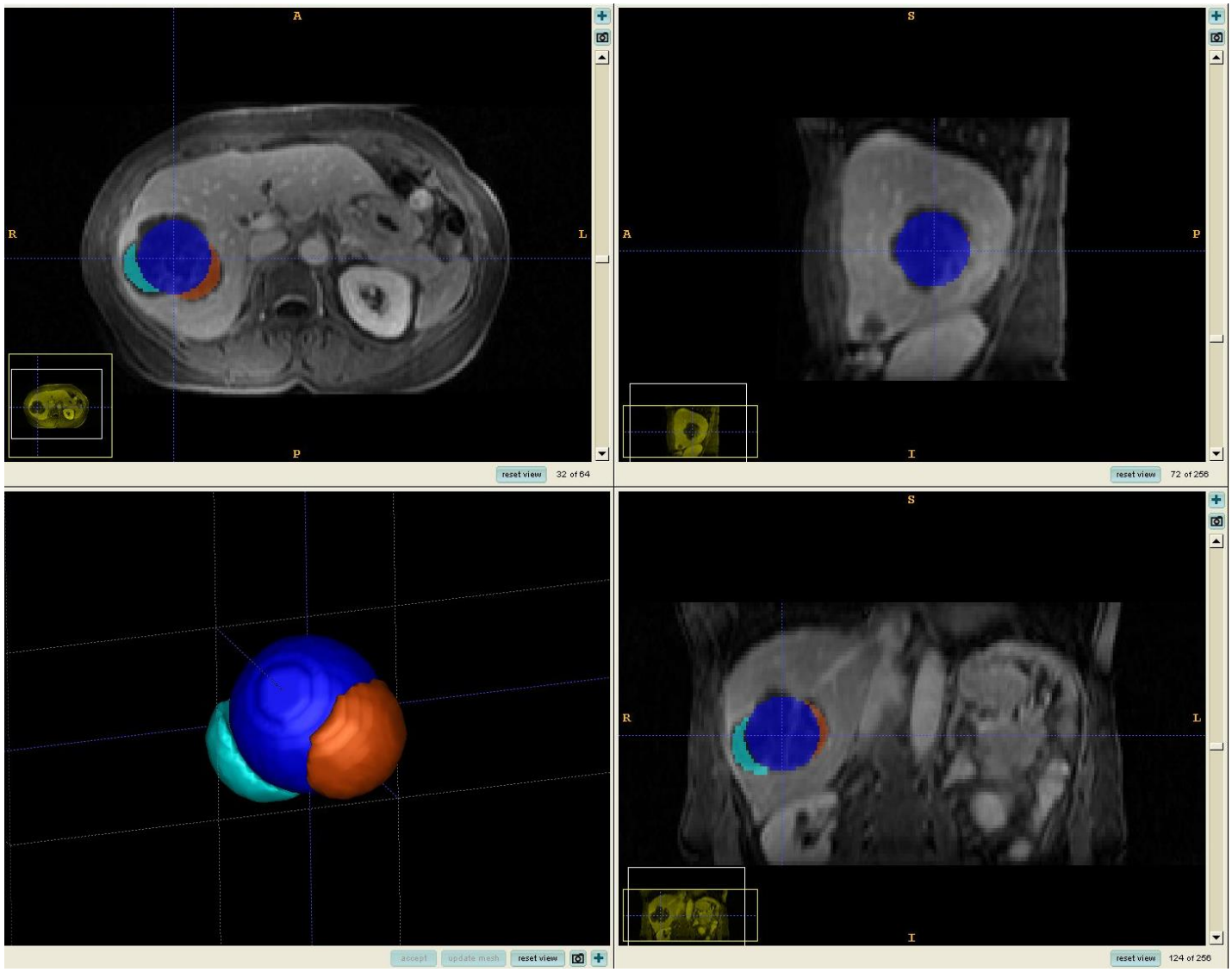


Liver tumour shape post-chemotherapy, 9 months later

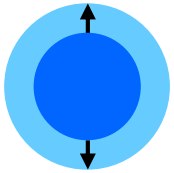


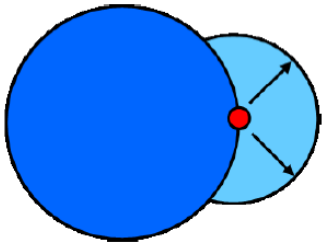
Eng Sci, Surgery, Radiology, Pathology, Clin Pharm, Mathematics, WIMM, GE Healthcare

pre-ablation, another 3 months later

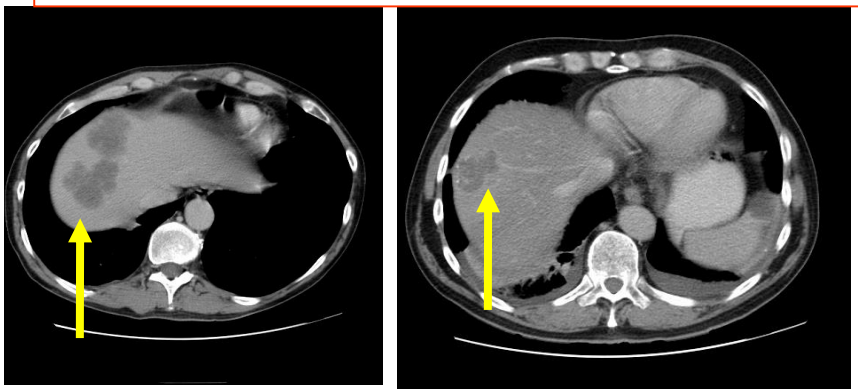


Tumour Growth Model

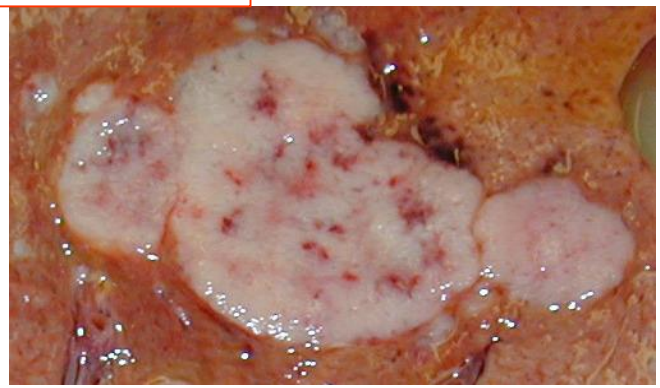




- Early tumour masses are often approximately spherical and grow as spheres. Mathematical models treat this case.
- They can sprout additional spheres (this corresponds, biologically, to clonal expansion)
- Heterogeneous tumours with multiple clonal centres may demonstrate variations in response to therapy (i.e. resistant clones)
- Can we relate morphological changes, determined from images, to underlying cancer growth processes?



recent examples from the Churchill



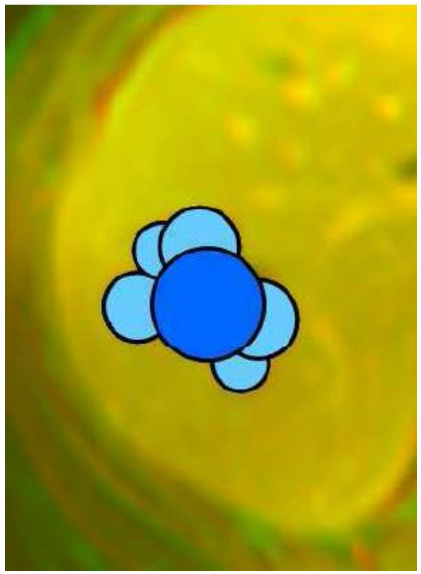
The shape of the resected specimen

We conjecture that shape and shape changes encode the evolution, mutations, and severity of a tumour

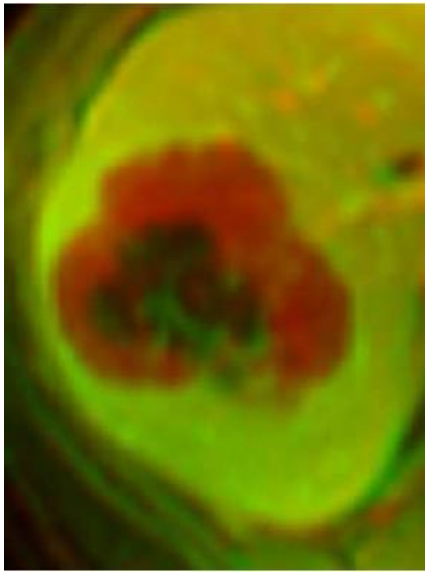
Olivier Noterdaeme, Dr. Matt Kelly, Mike Brady, and numerous clinicians

Tumour growth model

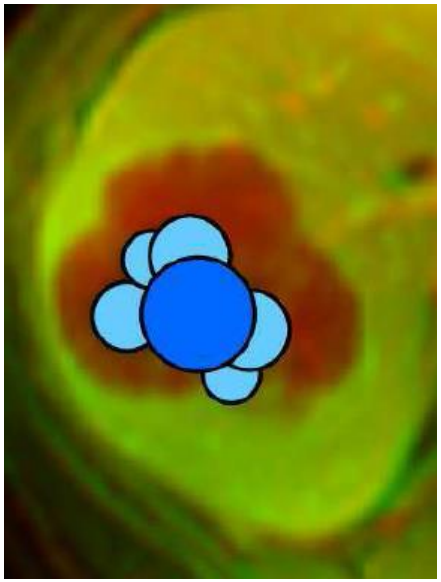
Clinical case from Churchill: growing metastatic colorectal (Dukes B) tumour



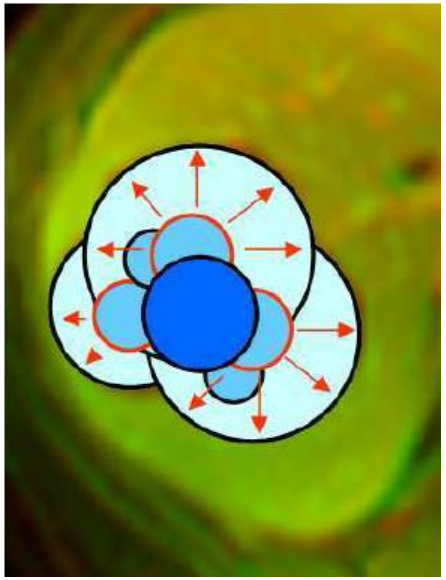
Spheroid fit after 9 months of chemotherapy



Tumour shape after 3 more months



9 month spheroids centred on 12 month shape

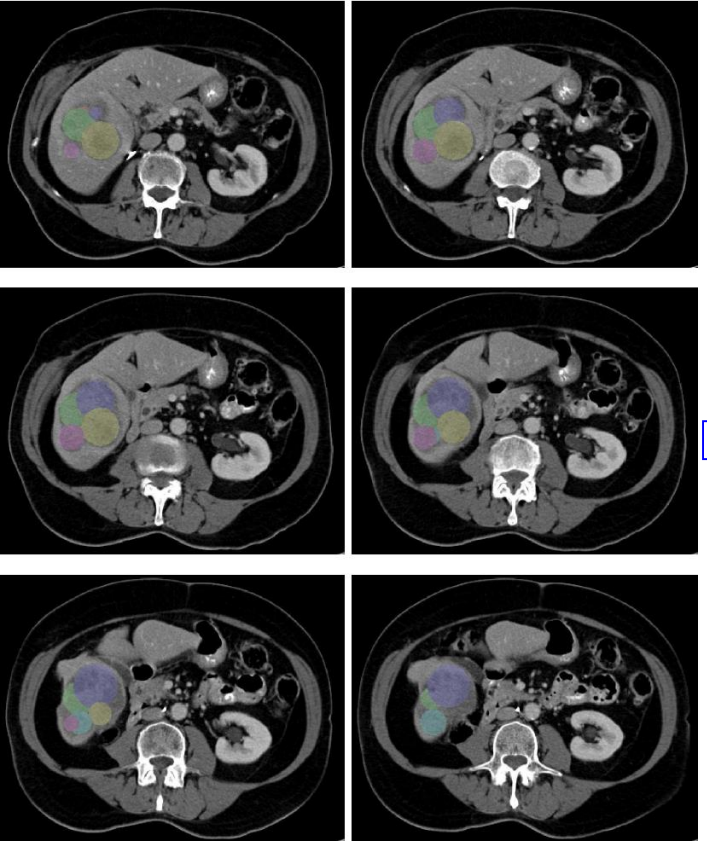


9 month spheroids grown (red) and static/shrunk (black)

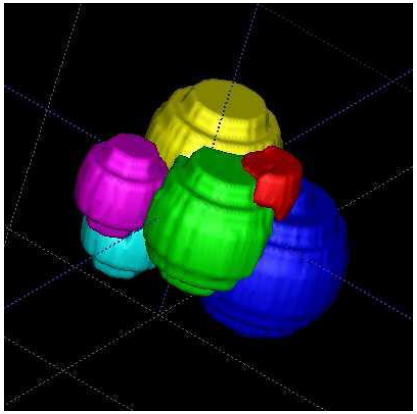
The tumour growth model gives a plausible account of tumour morphology; but the key question remains: do the successively sprouted clonal centres correspond to increasingly severe mutations of the original tumour DNA?

More precisely, we conjecture that the genomes of samples within a spheroid will show minor variation; but that the genomes of samples from different spheroids will have substantial variation.

Noterdaeme, Kelly & Brady 2008



Pre-resection CT (6 slices shown)

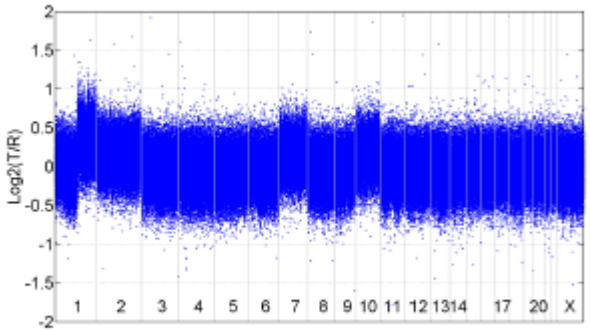


3D model of tumour

SampleID	spheroid	labelling yield [μg]
310	red	11.891
311	yellow	27.331
312	torquoise	13.113
313	torquoise	9.001
316Q	magenta	24.346
317	magenta	24.91
318	blue	10.27
319	blue	9.729

DNA extraction (proteinase K digestion & purification).

Nuffield Department of Clinical Laboratory Sciences



(b) 312

array Comparative Genomic Hybridization (aCGH),
NimbleGen, Iceland

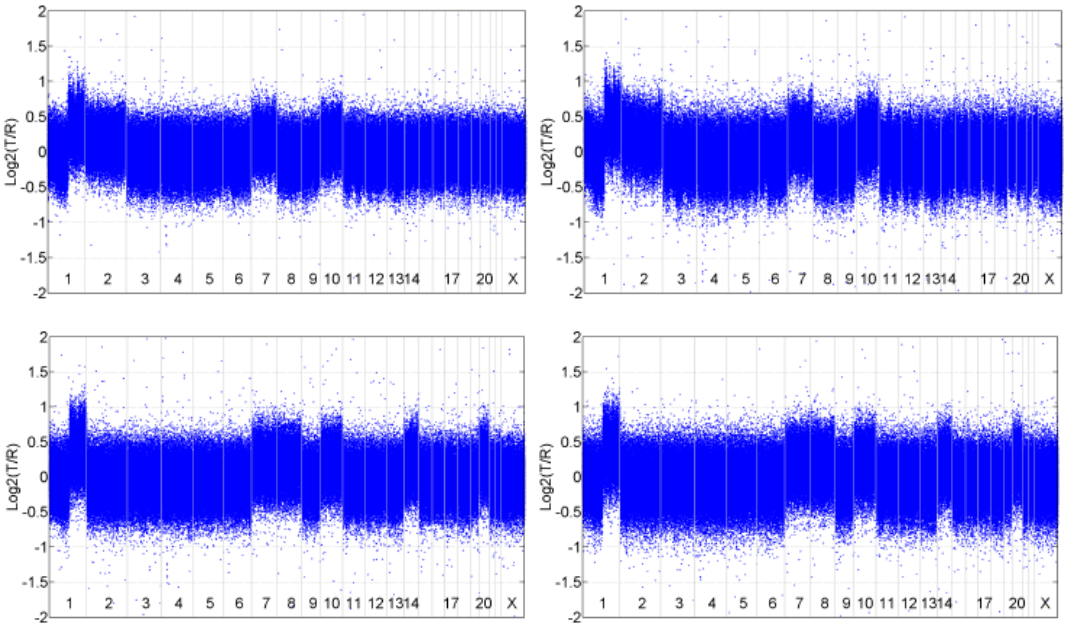
385,000 probes of a sample 17.4mm X 13mm ➔ 6270 base pairs analysed

This shows the amplification of each of the genes in each of the chromosomes of the particular DNA sample – in this case from the turquoise spheroid

Noterdaeme, Kelly & Brady 2008

Log2 intensity ratios as a function of chromosome position for 7 hybridisations.

Horizontal axis is chromosome number; vertical axis is log intensity ratio – higher values show amplification of a particular chromosome = significant changes of the DNA sequence in the genes that make up the chromosome.



(f) 318

(g) 319

312 and 313 are from the same spheroid, and show ***similar*** amplification of chromosomes 2, 7, 10

318, 319 are both from another spheroid and show ***similar*** amplification of chromosomes 7, 8, 10, 14, and 20

More importantly, note that the amplification pattern is ***different*** for the two spheroids – this finding is repeated for ***all distinct spheroids***.

We have linked developing tumour shape to increasing DNA mutations

So what?

Current clinical practice assesses tumour response to therapy using RECIST – *Response Evaluation Criteria in Solid Tumours.*

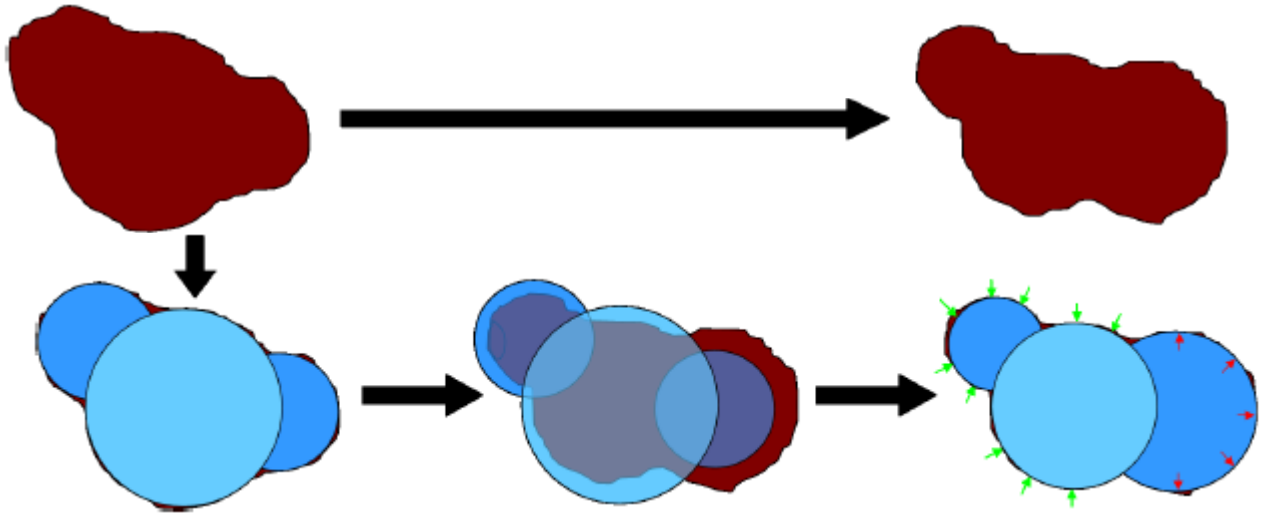
Disease ***progression*** ≡ increase by at least 20% in *longest linear dimension*

Disease ***response*** ≡ decrease by at least 30% in *longest linear dimension*

Otherwise, disease is considered to be ***stable***

9 month tumour shape

12 month tumour shape



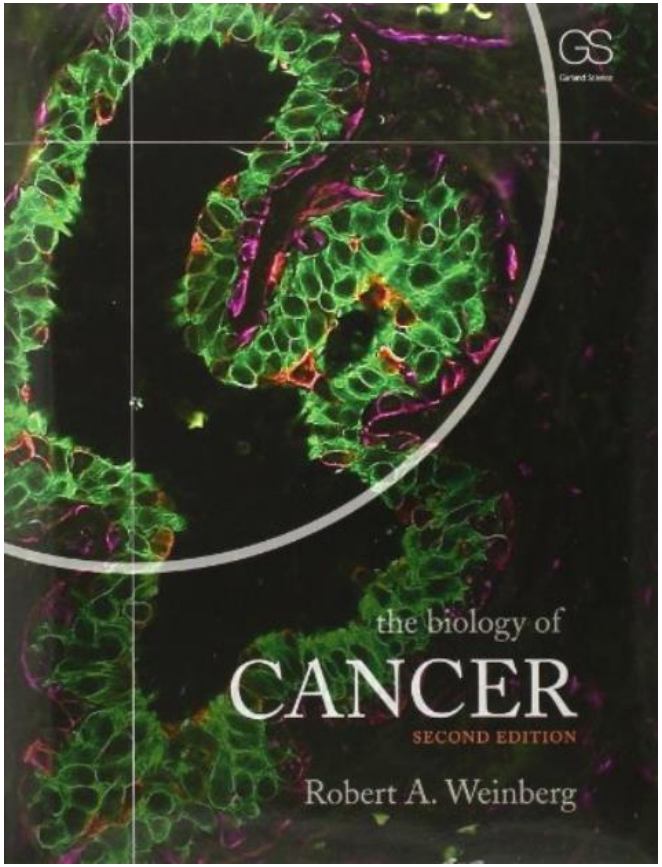
According to RECIST, stable disease

According to our model, the tumour has shown some response (green) ***but there is evidence of aggressive growth in a new spheroid***

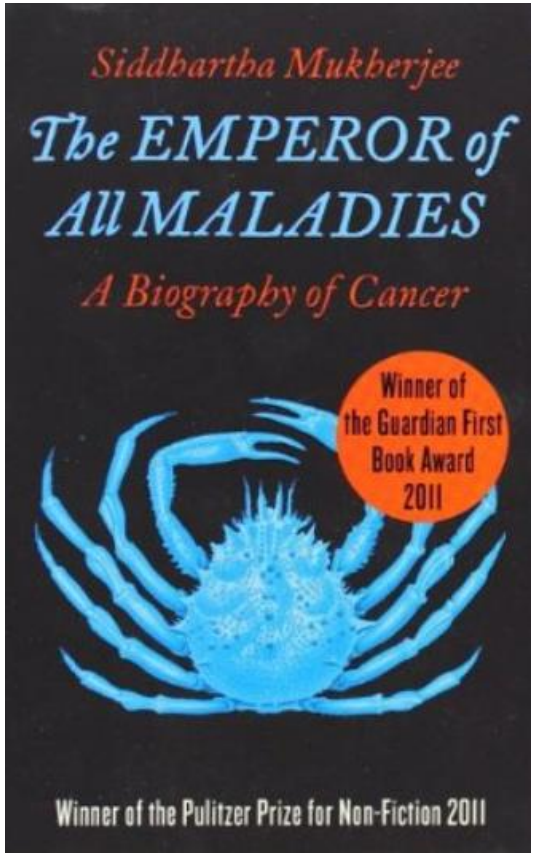
Conclusions

- Medical image analysis involves difficult image analysis challenges
- Doctors need numbers, error bars, results that enable them to do their jobs better
- Doctors couldn’t care less about mathematics or algorithms, just results
- Models enable measurements in mammography, breast MRI, colorectal MRI, angiogenesis, and clonal expansion of tumours
- Measurements can also be misleading

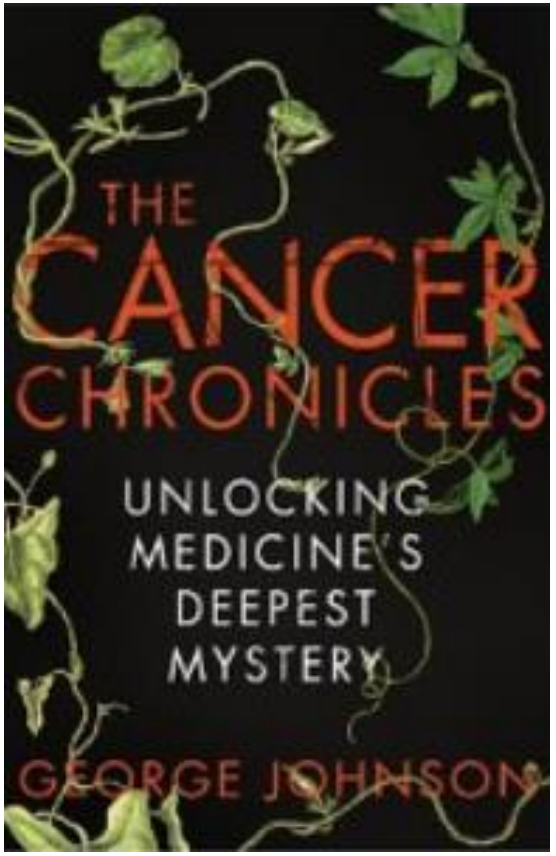
Books on Cancer



Great introduction to cancer biology. Updated in 2013.



Wonderful popular history of cancer. Well worth buying.



A recent book, very well written, intermediate between the other two.