Models for Cancer Imaging

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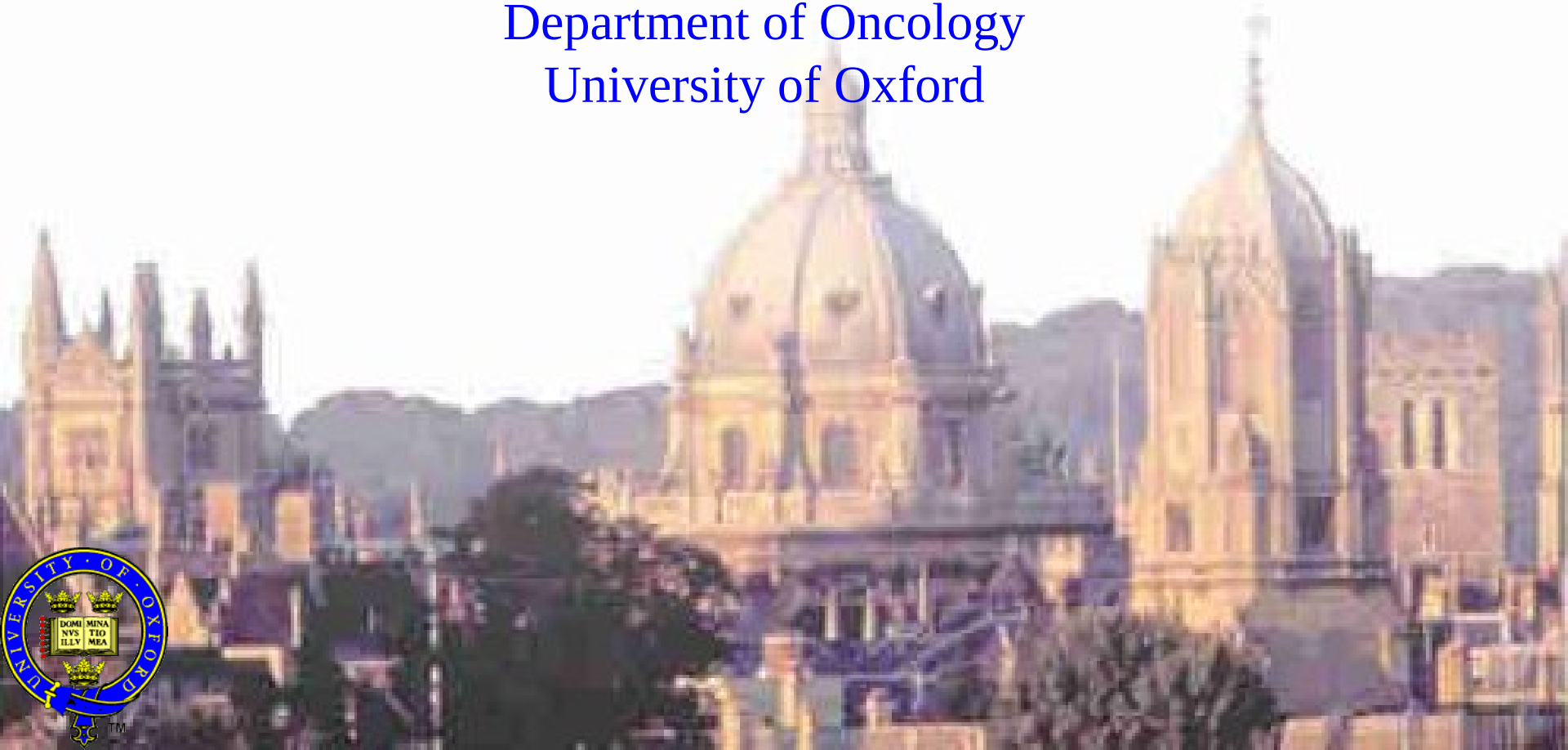


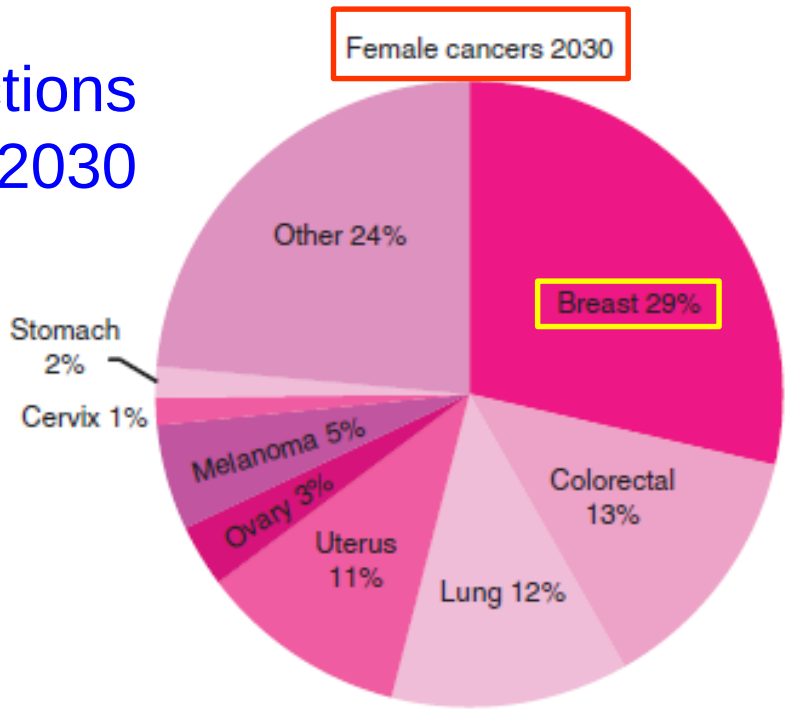
Cancer in Europe 2012

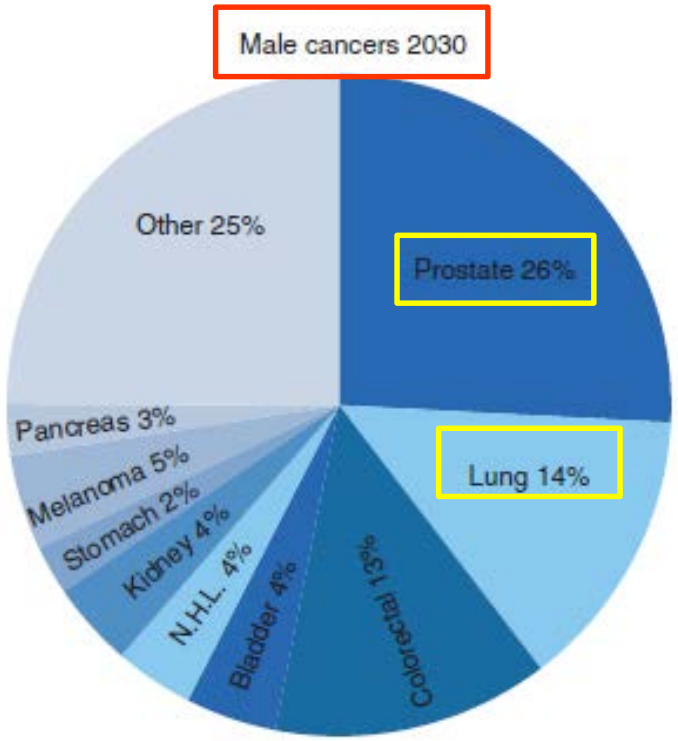
- New cases: 3.45M, deaths: 1.75M
- Cases
  - Breast : 474,000 (deaths: 131,000)
  - Colorectal: 447,000 (deaths: 215,000)
  - Lung: 411,000 (deaths: 353,000)

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

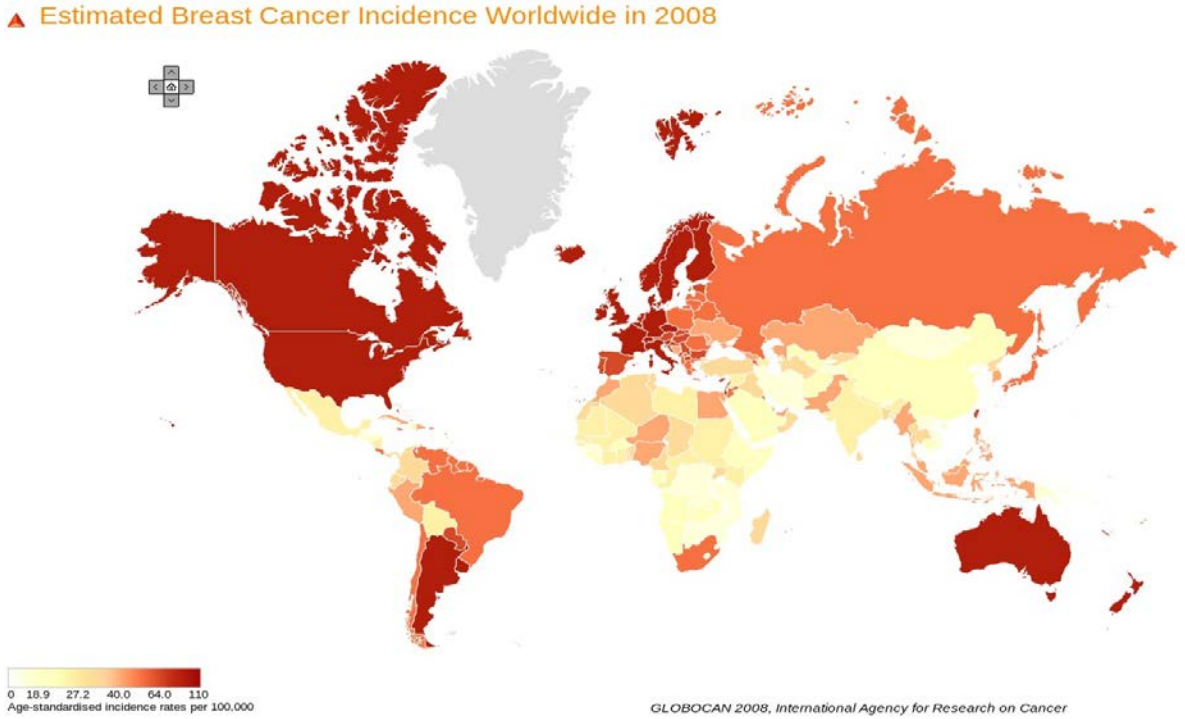
By 2020, 38% will survive cancer to die of another cause (35% in 2012)

Projections 2030





Breast cancer incidence

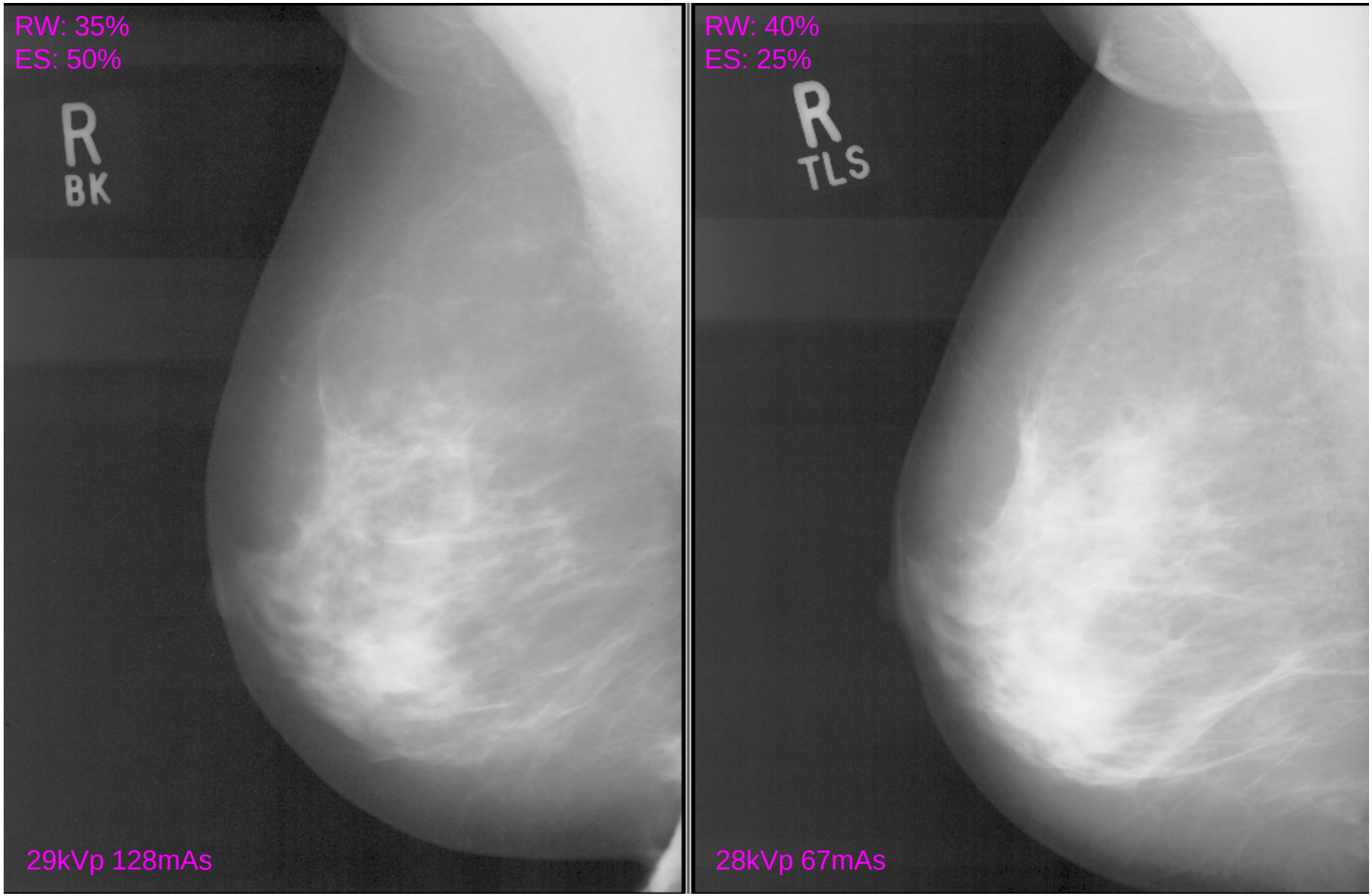


- In developed countries, 1 in 8 women will get breast cancer at some point
- 23% of all cancers in women – projected to rise to 29% by 2030
- Peak incidence is women over 60

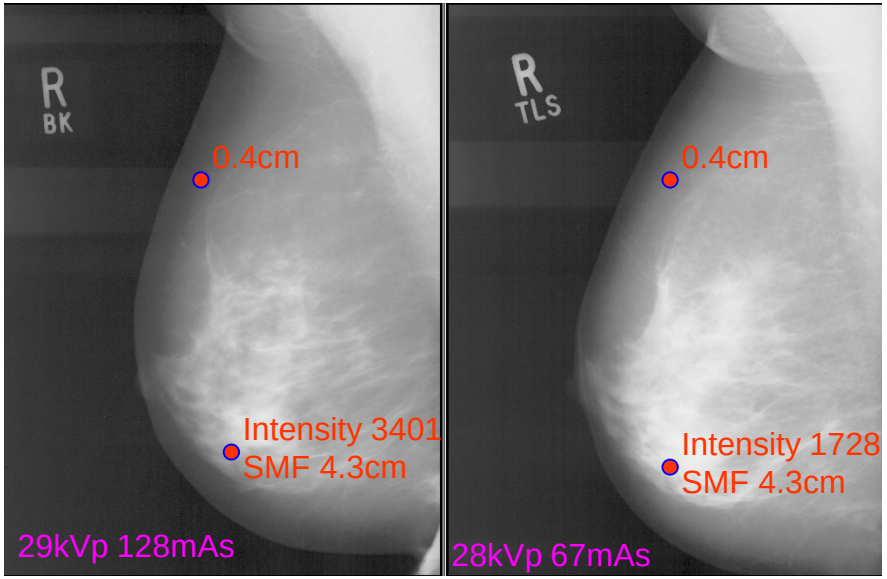
- In developing countries, including BRIC, numbers are rising rapidly, already 500,000 cases in 2008
- Reasons: increasing urbanisation, changes in lifestyle
- Impacting particularly on younger women

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

Mammography: Image Parameter Dependence



First technological capability: need for quantitative analysis in mammography



Two of the UK's most experienced breast radiologists each examined the two mammograms shown, to estimate the percer key risk factor

BK est ted 40%

But it i aged 2X right

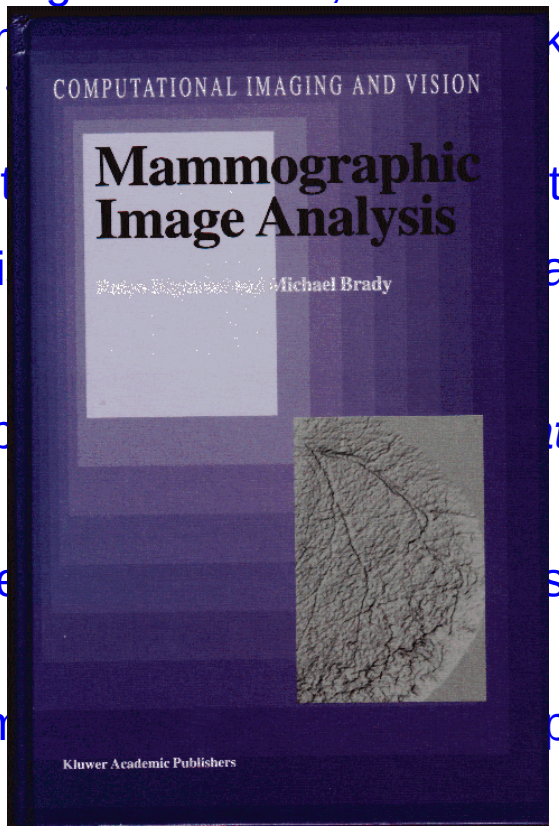


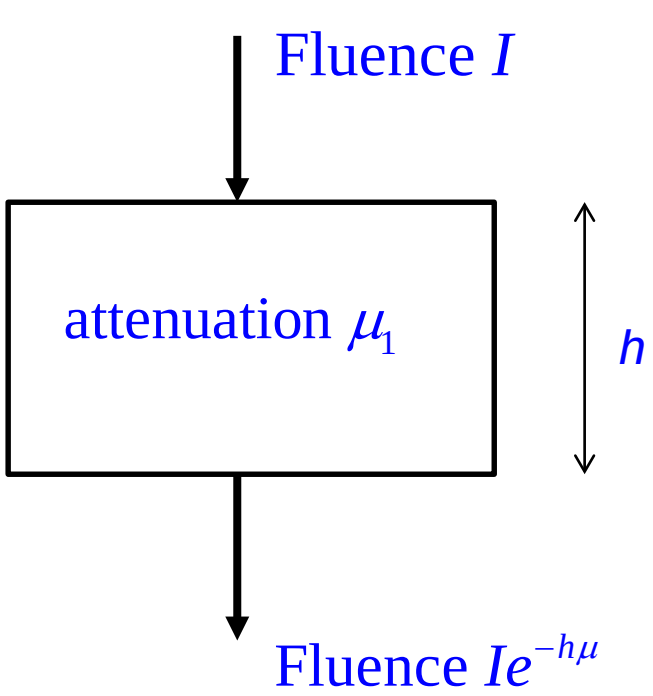
Image intensity relates to anatomy in a very comp ***tive*** image analysis a hard problem.

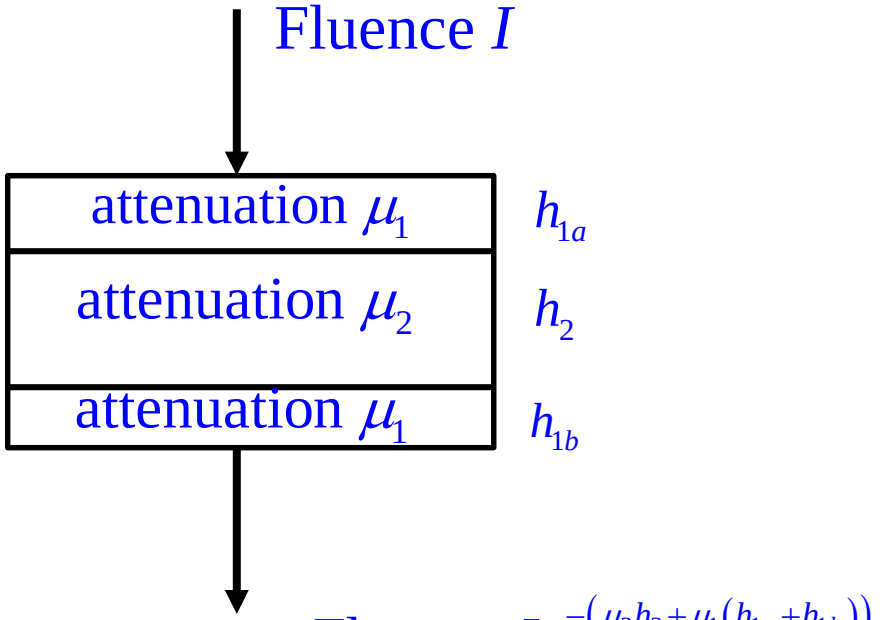
Starting 1994, with Ralph Highnam, I have invente s to this problem:

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

* SMF = Standard Mammogram Form

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



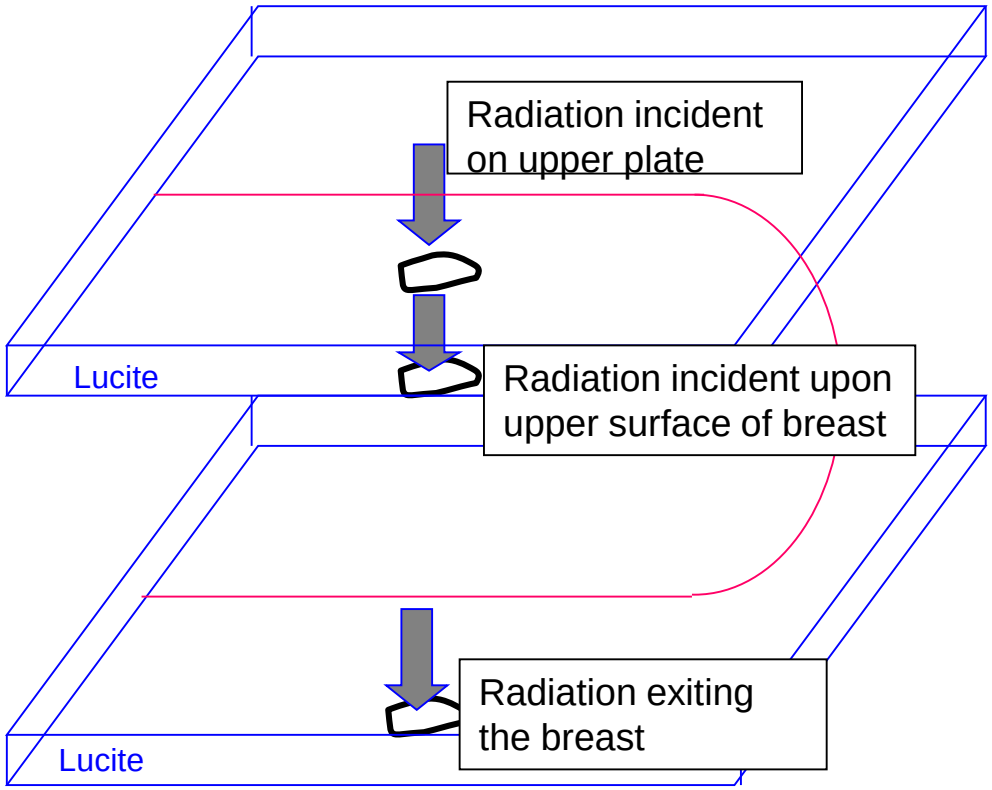


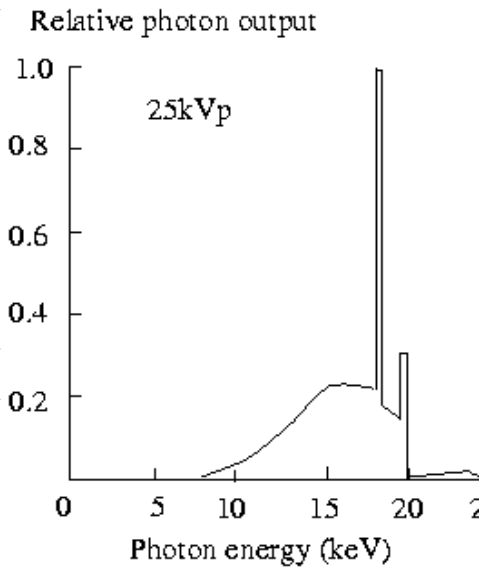
Note that the exiting fluence is the same irrespective of where, vertically, the block of attenuation μ_2 is.

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 ⟹ X-ray photon fluence model

Energy that reaches the imaging sensor:

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

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?:

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

We measure this

We know all this stuff

Compression plates – we know that too

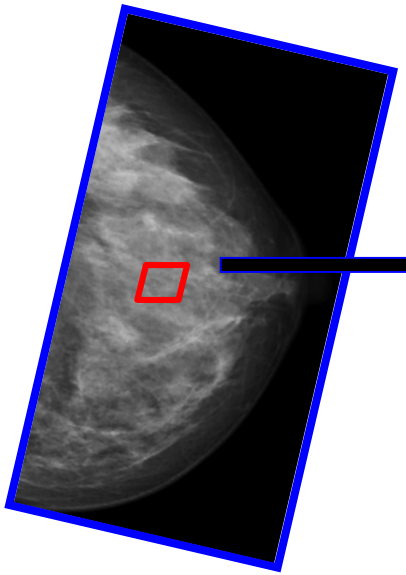
The bit we don't know!

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

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

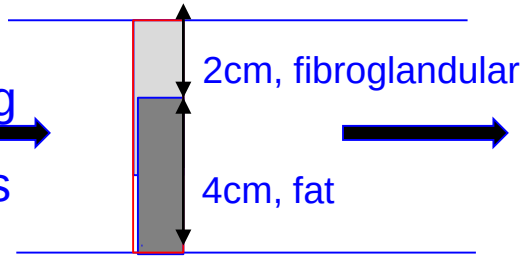
* It may be wrong ☺

Volume-based Density Measurement

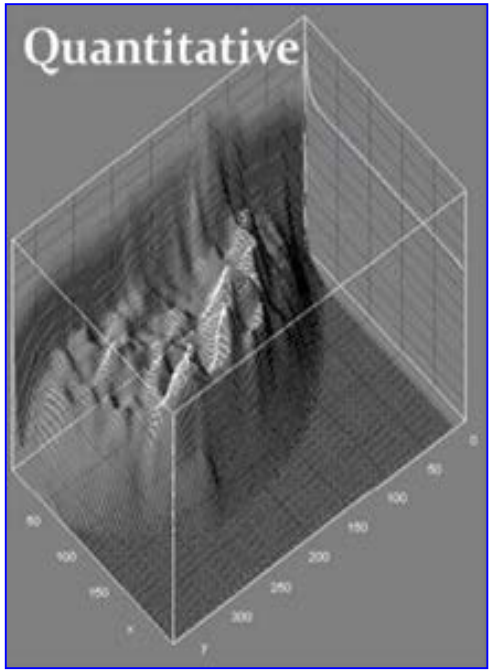


Imaging

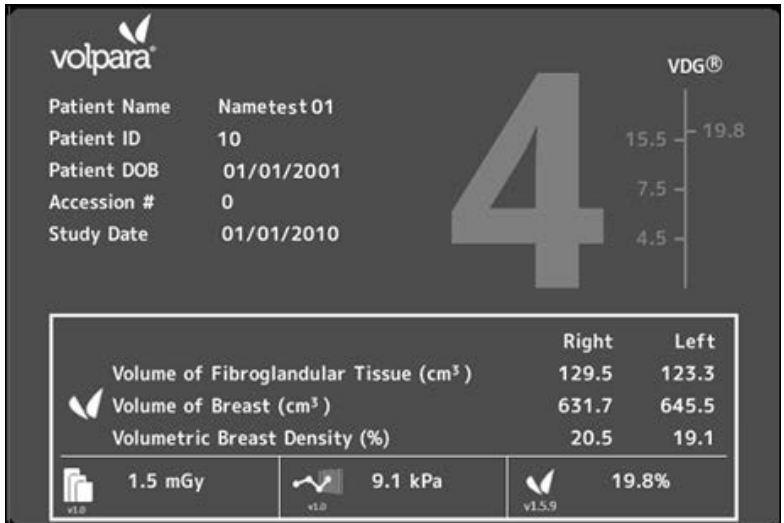
Physics



cm



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



“Relative physics”

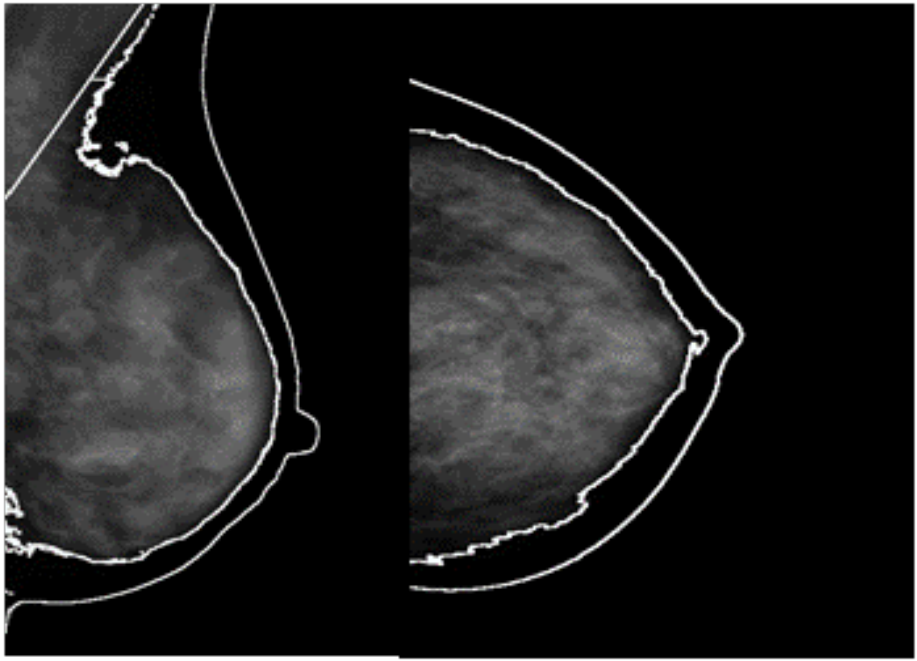
Highnam, Brady, Karssemeijer, and Yaffe

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



Why is Breast Density Important?

- 40% of women have dense breasts
- Mammography is only 48% effective in dense breasts, compared to 98% in fatty breasts
  - This is why mammography gets criticised
- Dense breasts are 4-6 more times to develop cancer than fatty breasts
- 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
- 35+ Years of research with very large number of published papers have documented the importance and difficulty associated with classification of breast density

volpara™

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).

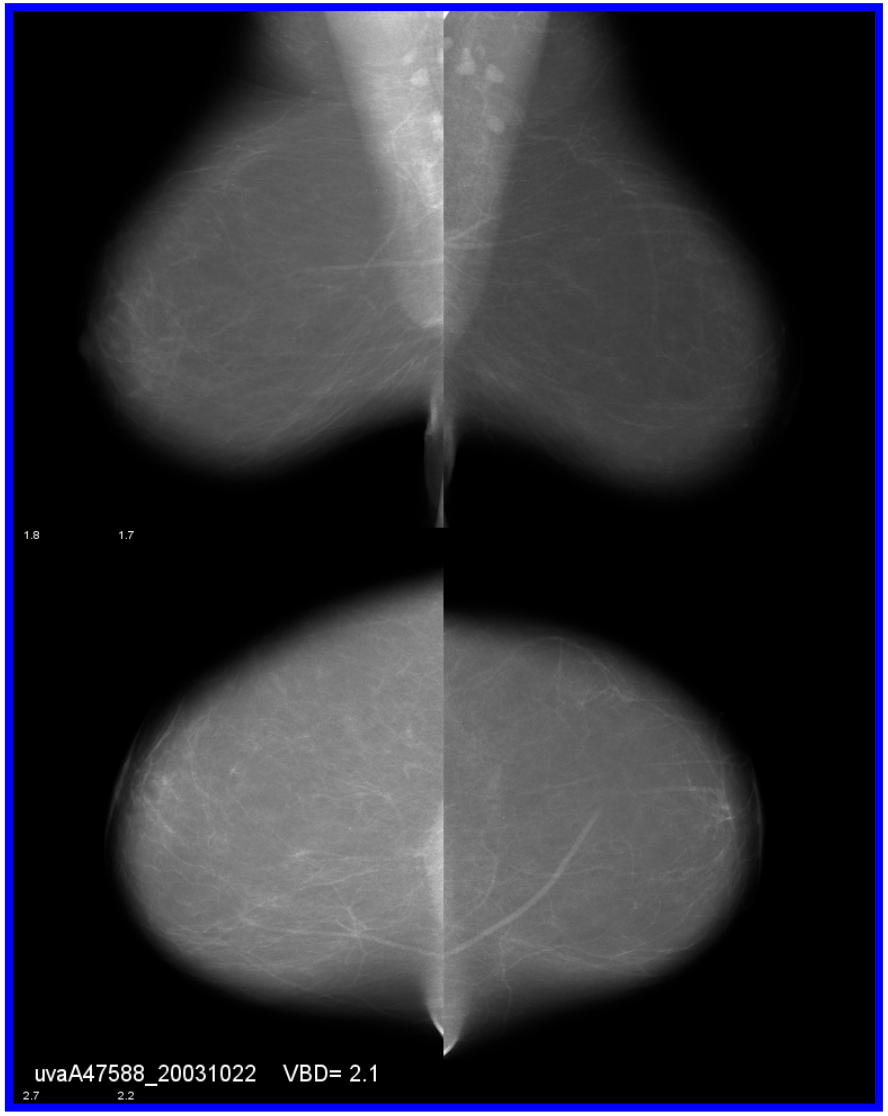
Category 3 — The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% – 75% glandular).

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

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

Approximately 2,000,000 mammograms processed over past 12 months

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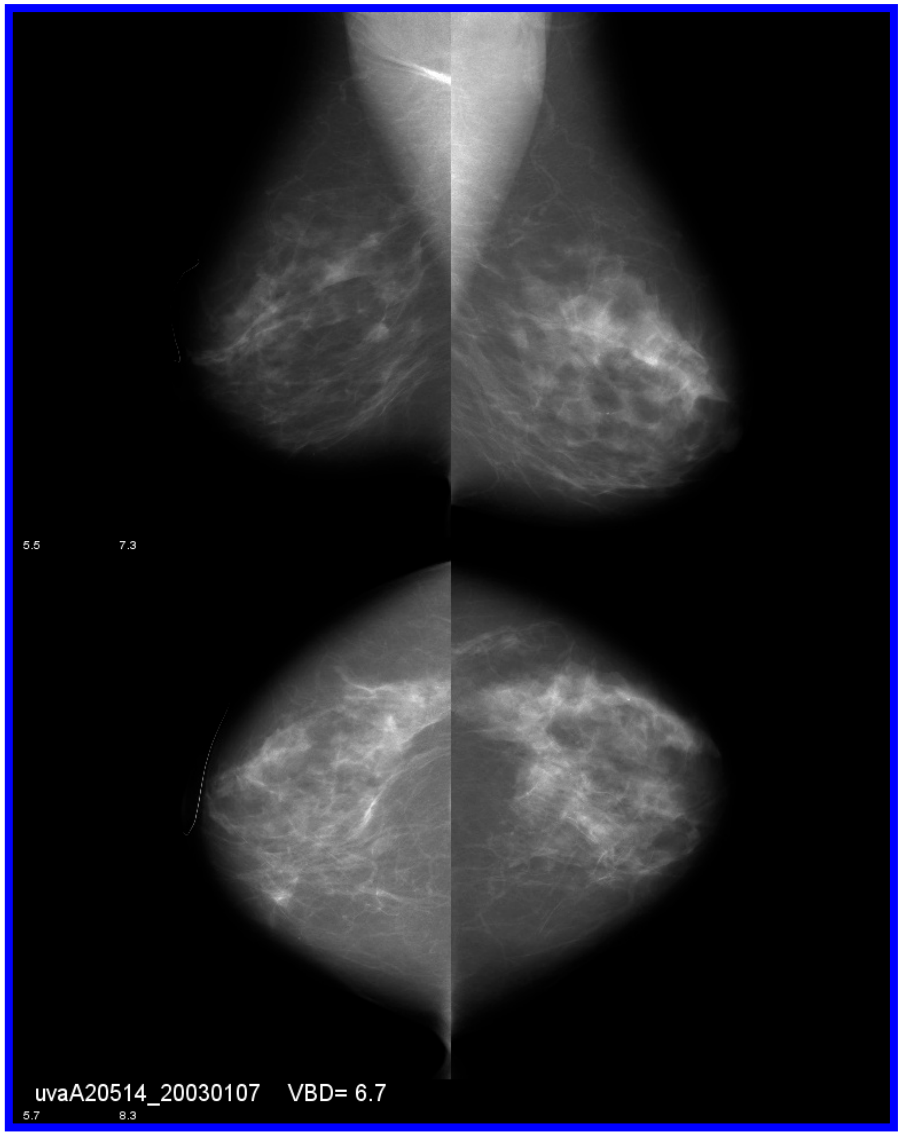
Volume-based Methods for Density Measurement



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

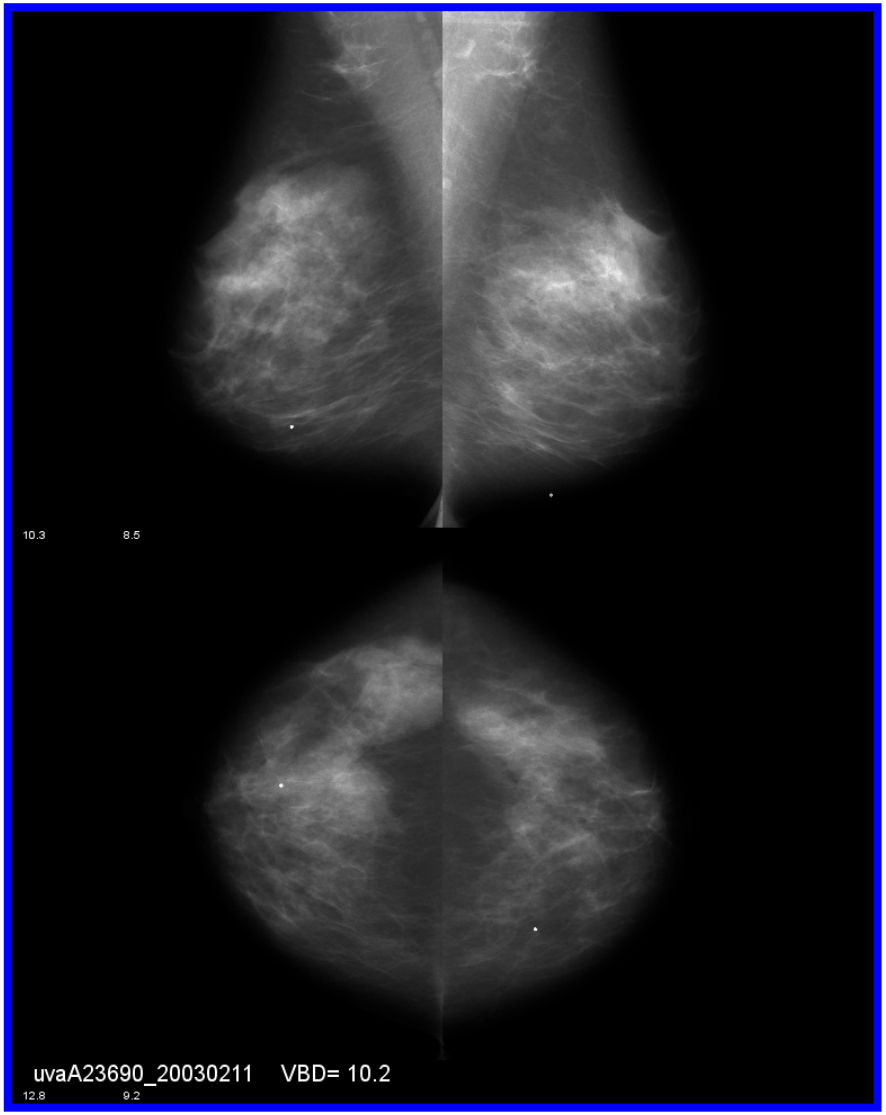
	Right	Left
Volume of Fibroglandular Tissue (cm^3)	83.9	75.7
Volume of Breast (cm^3)	1476.9	1504.6
Volumetric Breast Density (%)	5.7	5.1
Volpara Density Grade®	2	

Sky analogy

Approximately 2,000,000 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

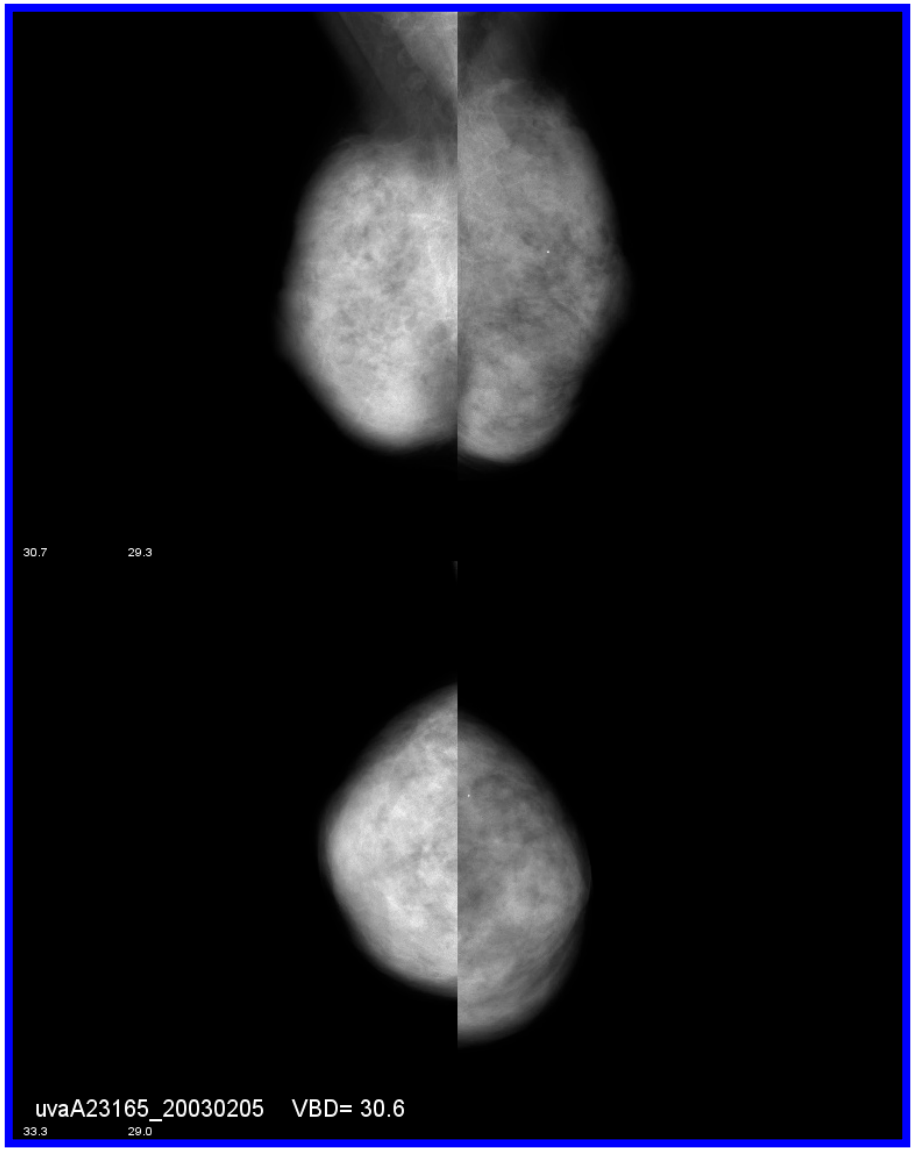
	Right	Left
Volume of Fibroglandular Tissue (cm^3)	52.7	52.3
Volume of Breast (cm^3)	390.3	430.2
Volumetric Breast Density (%)	13.5	12.1
Volpara Density Grade®	3	

Sky analogy

Approximately 2,000,000 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

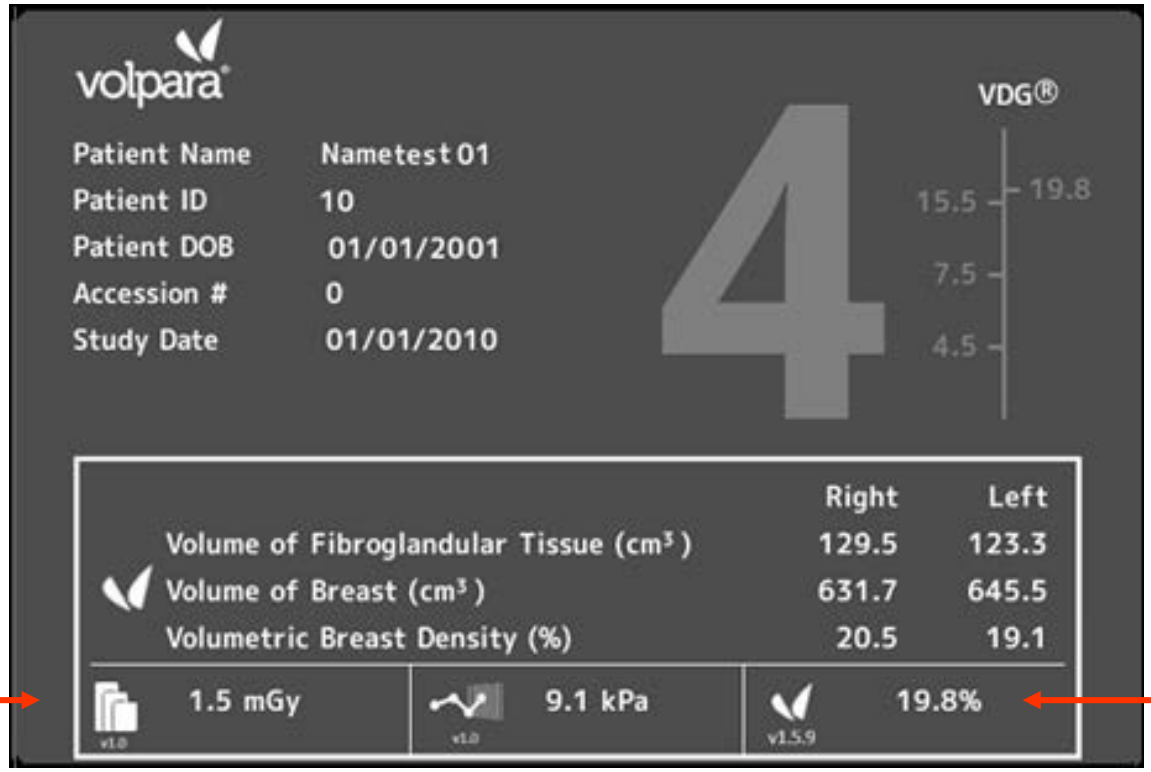
15.5 – 18.4
7.5
4.5

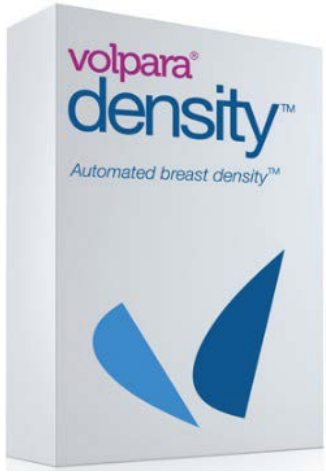
	Right	Left
Volume of Fibroglandular Tissue (cm^3)	29.0	49.3
Volume of Breast (cm^3)	209.3	216.3
Volumetric Breast Density (%)	13.9	22.9
Volpara Density Grade®	4	

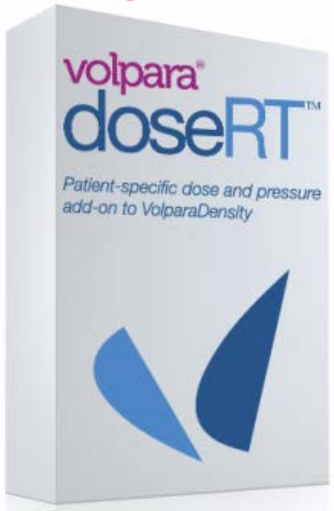
Sky analogy

Approximately 2,000,000 mammograms processed over past 12 months

volpara







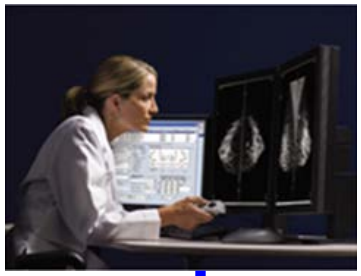
Population Report

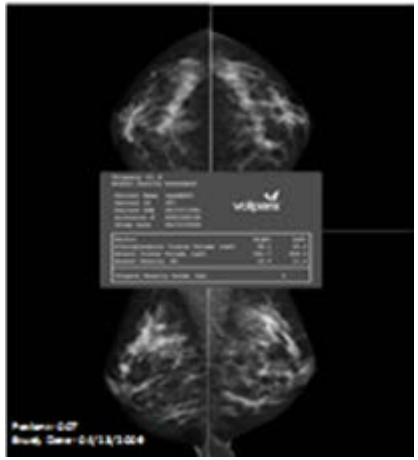
Patient Profile by Mammography Unit

Comparative Report

Patient stratification

Woman has a mammo

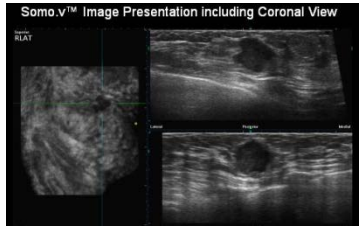


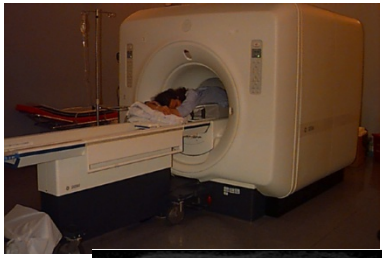


Volpara breast density score immediately available

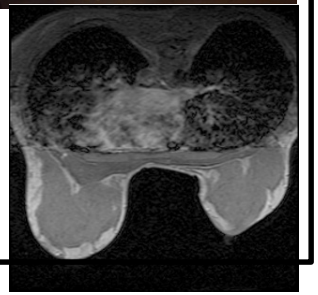
Woman can decide on supplementary screening before she leaves clinic.

Breast ultrasound

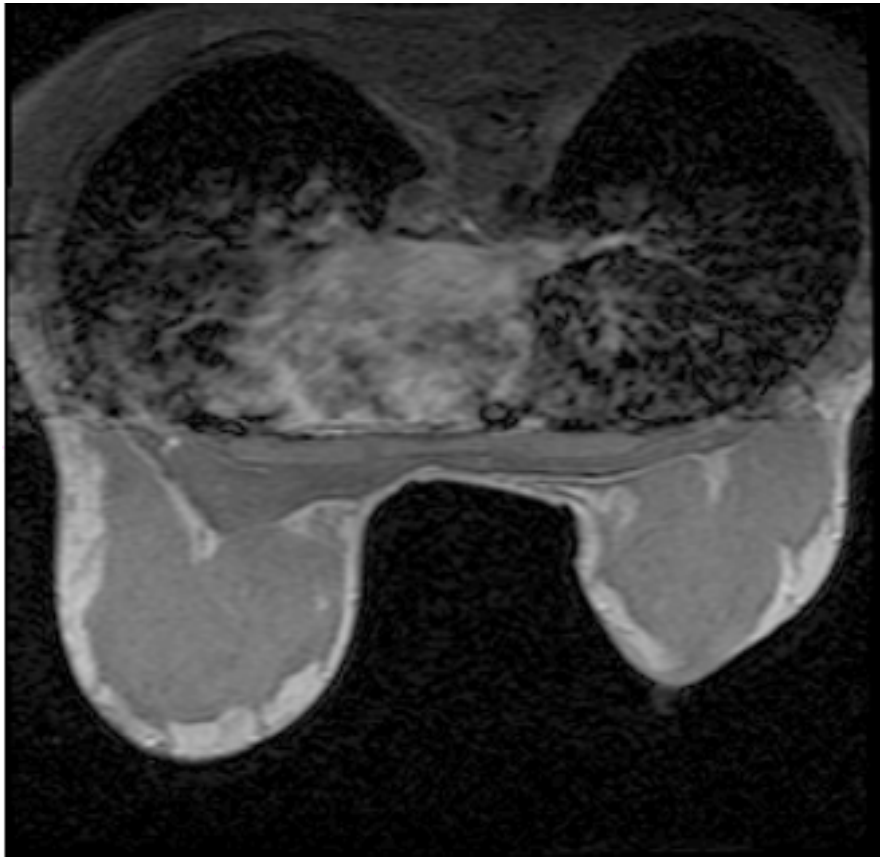


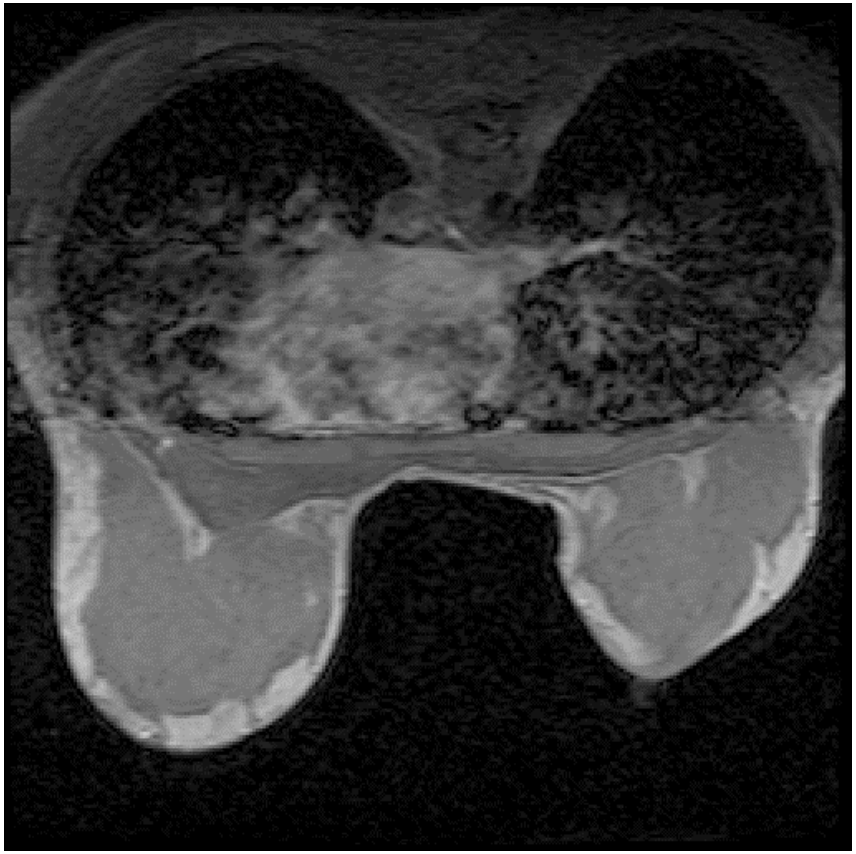


Breast MRI



Why do we need contrast agent?

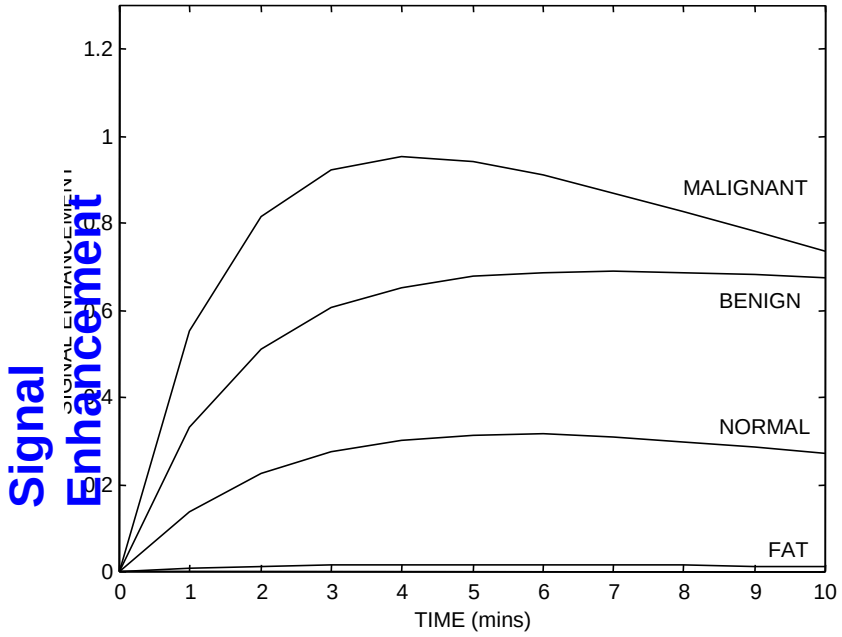


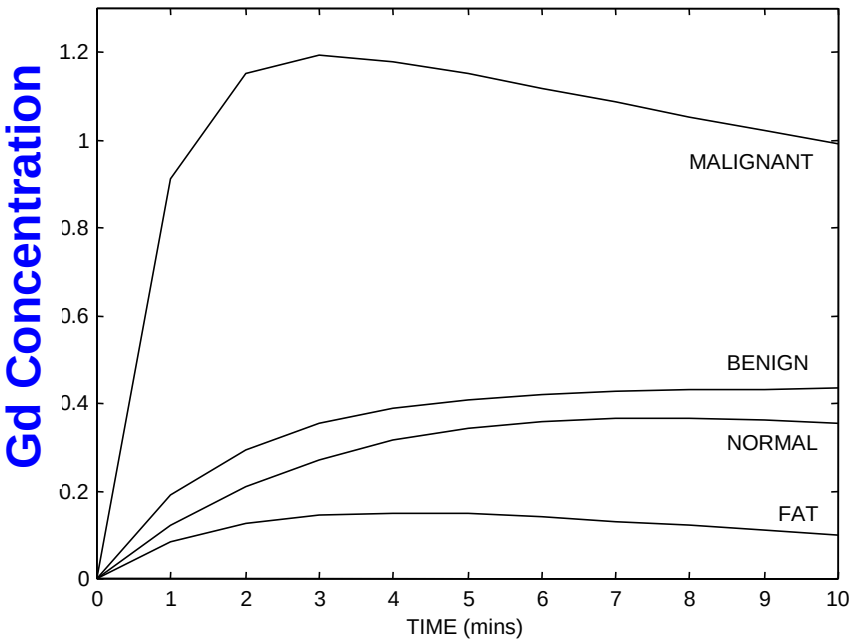


No abnormal tissue visible

Contrast Agent Uptake Profiles

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





Gradient Echo Signal Model

- Use Bloch equation to describe signal for a gradient echo pulse sequence (for example)

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

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

$$S(C_t) = g\rho e^{-TE\left(\frac{1}{T_2^*}+R_2C_t\right)} \sin\alpha \frac{1-e^{-TR\left(\frac{1}{T_1}+R_1C_t\right)}}{1-\cos\alpha e^{-TR\left(\frac{1}{T_1}+R_1C_t\right)}}$$

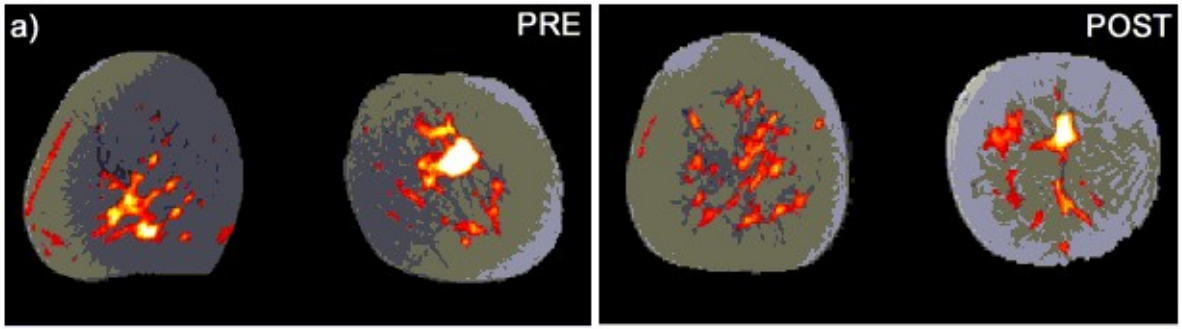
TE, T_2^*, T_1 are fixed for any given voxel;

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

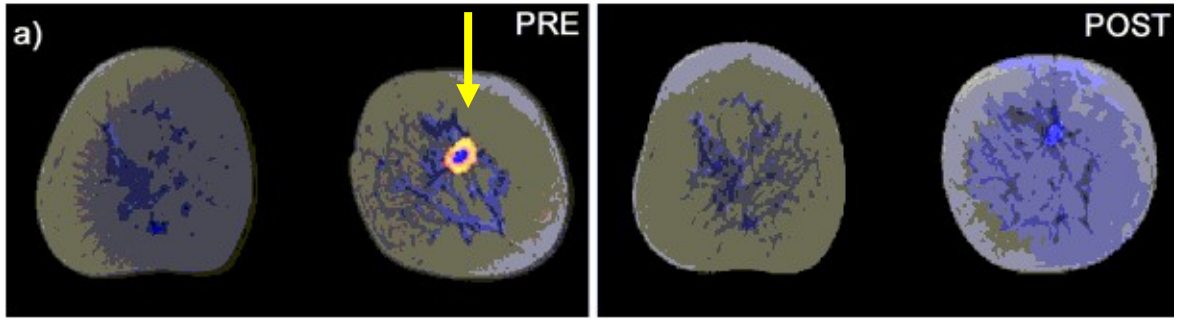
The only things we can vary are : α, TR

In practice, vary α

Measuring effect of chemotherapy



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

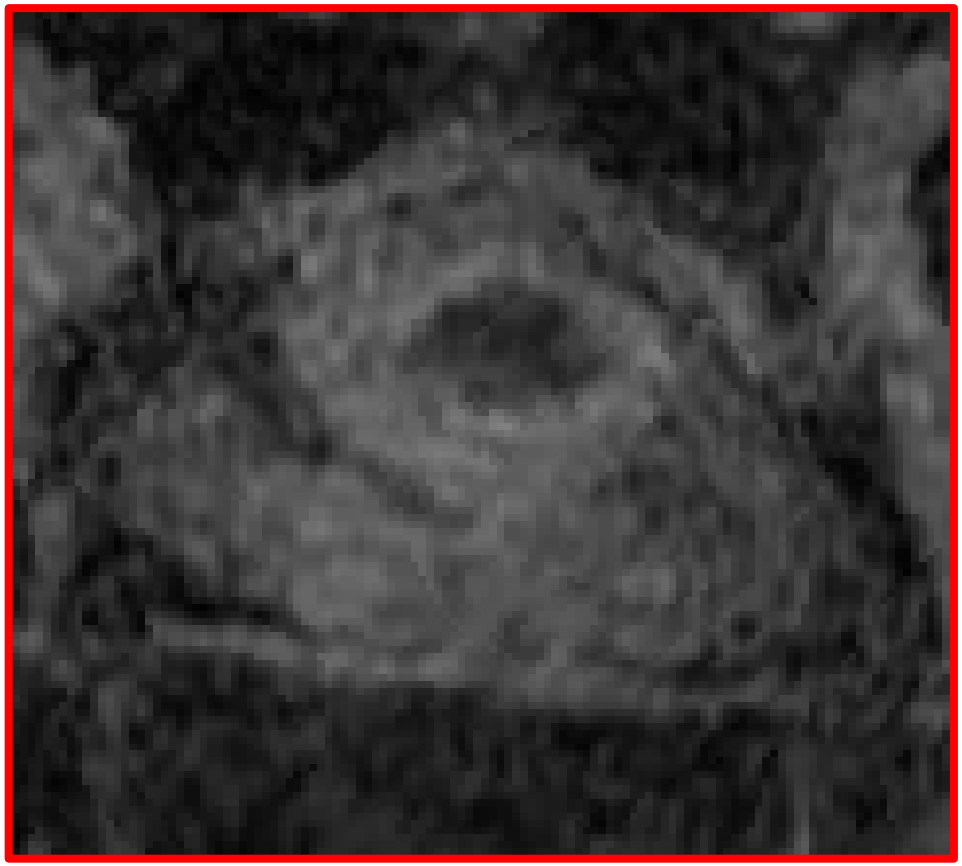


Pre- and post-chemotherapy ΔT_1 at left

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

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

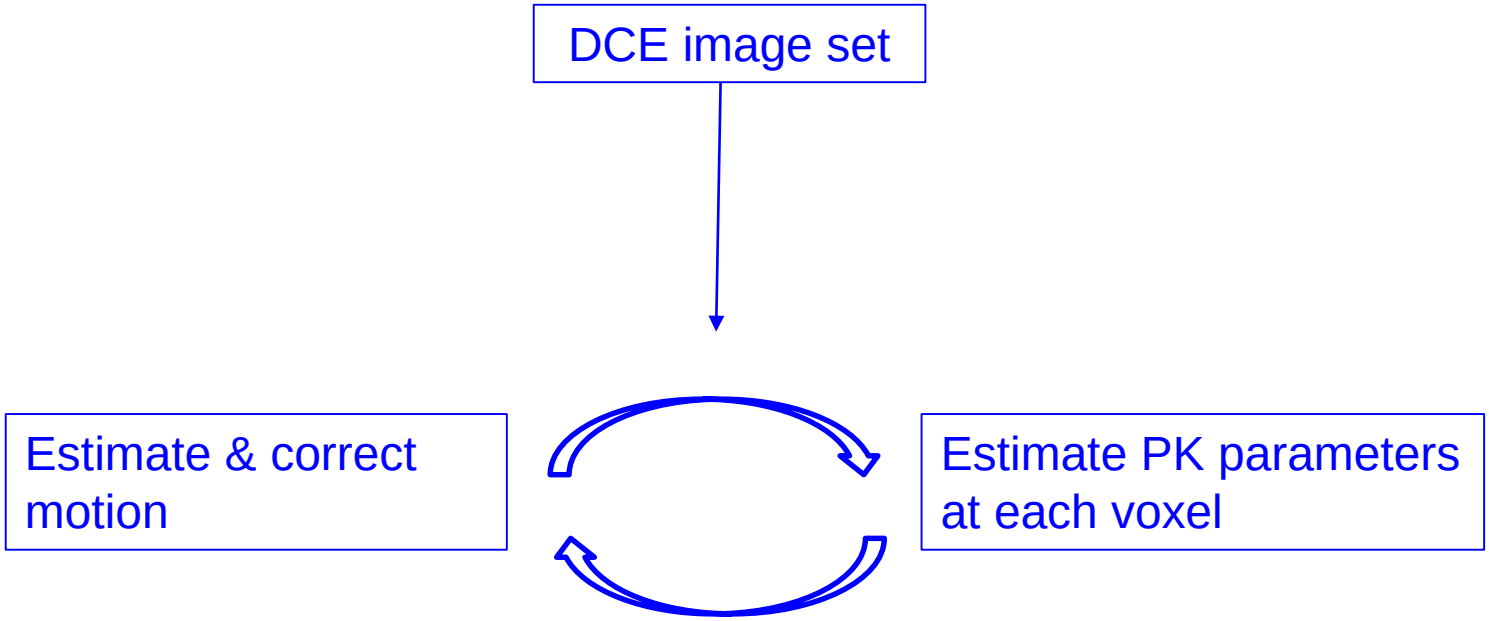
Colorectal cancer dceMRI : motion



Original data

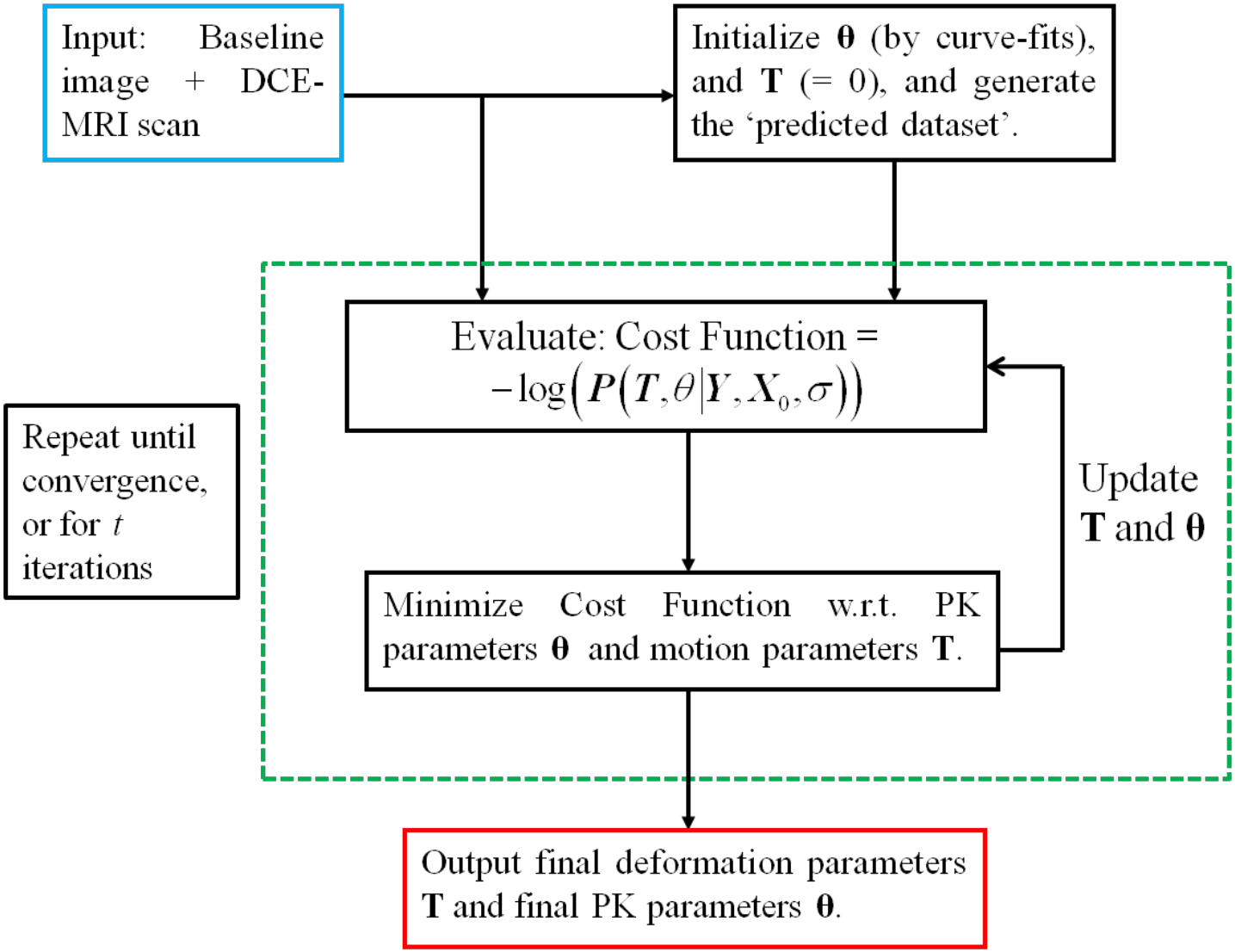
Dr. M. Bhushan, Profs. Schnabel, Jenkinson, Brady

Simultaneous estimation of motion parameters and PK parameters



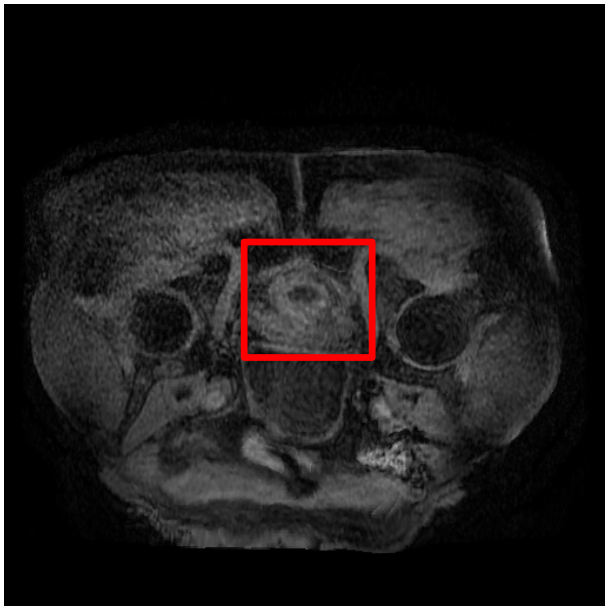
There are numerous ways in which this cycle can be developed mathematically and implemented in an efficient algorithm. The simplest is expectation-maximisation…though there are several others

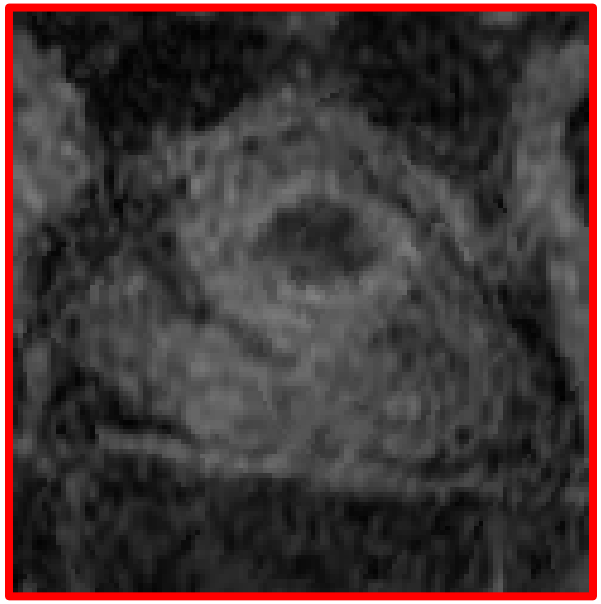
Model-based Registration and Parameter Estimation (MoRPE)

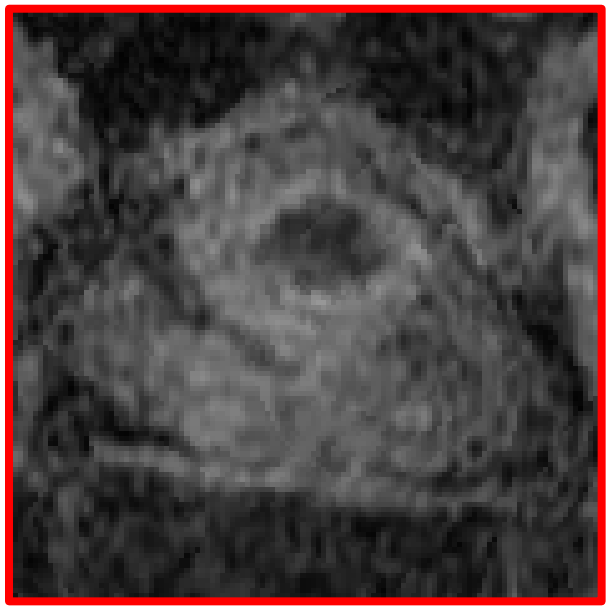


M Bhushan et al. MICCAI'11,ISMRM'12

Motion correction of dceMRI volumes for colorectal cancer



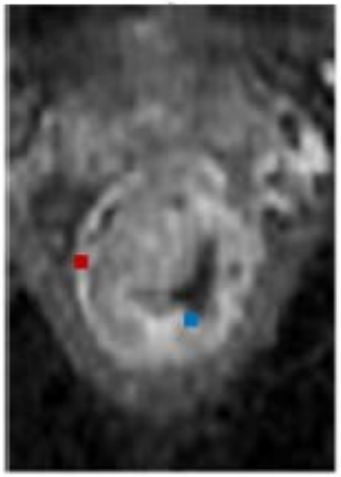


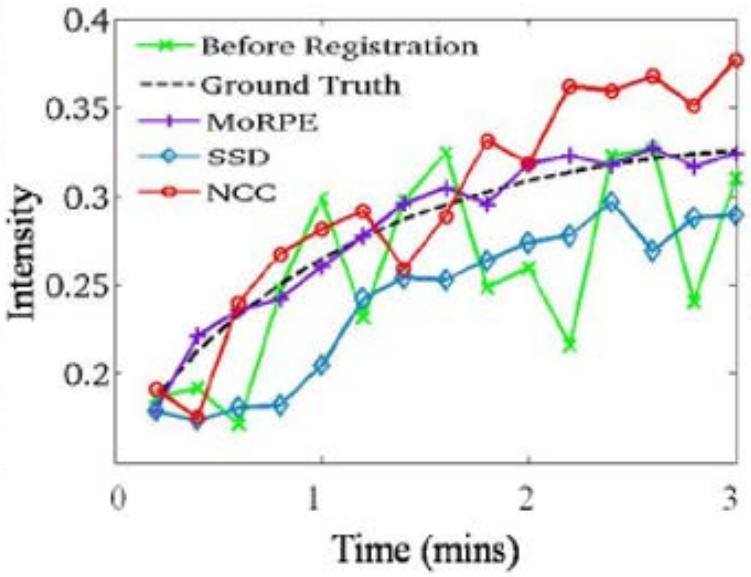


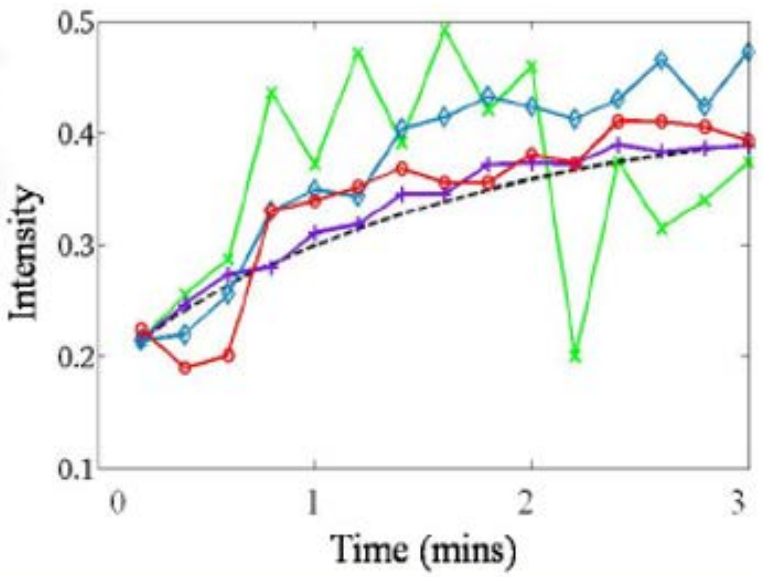
Original data

Motion corrected

Signal intensity curves





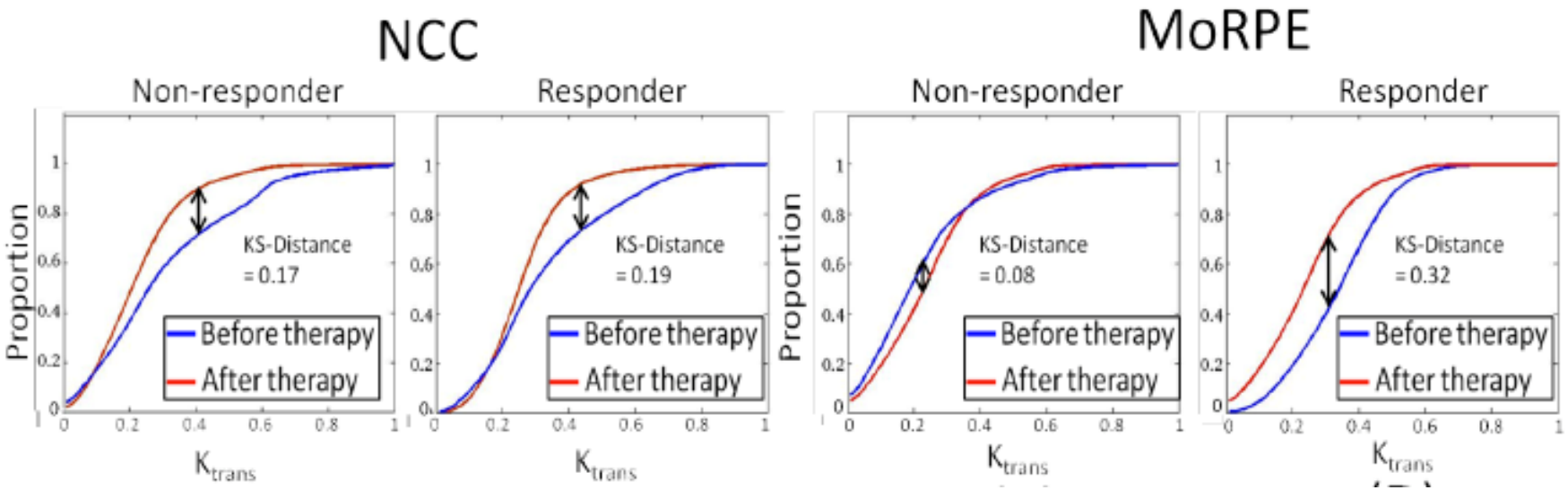


In this case, the signal change and motion were simulated. (-----)
The simultaneous algorithm:

Two standard similarity criteria for deformable registration:

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

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



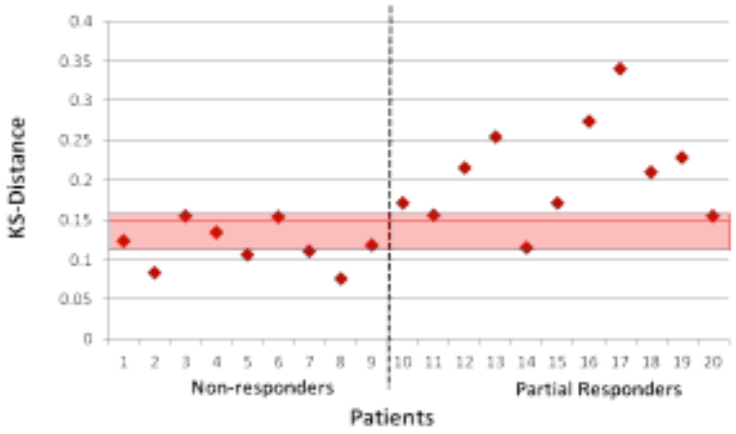
No discrimination for non-responder/ responder case using conventional normalised cross-correlation (NCC) registration

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

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

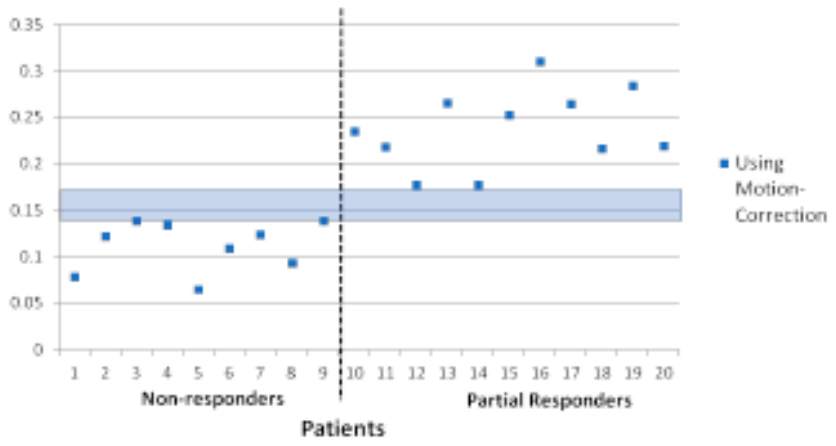
The importance of motion correction

Without Motion Correction



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

Motion correction using our algorithm



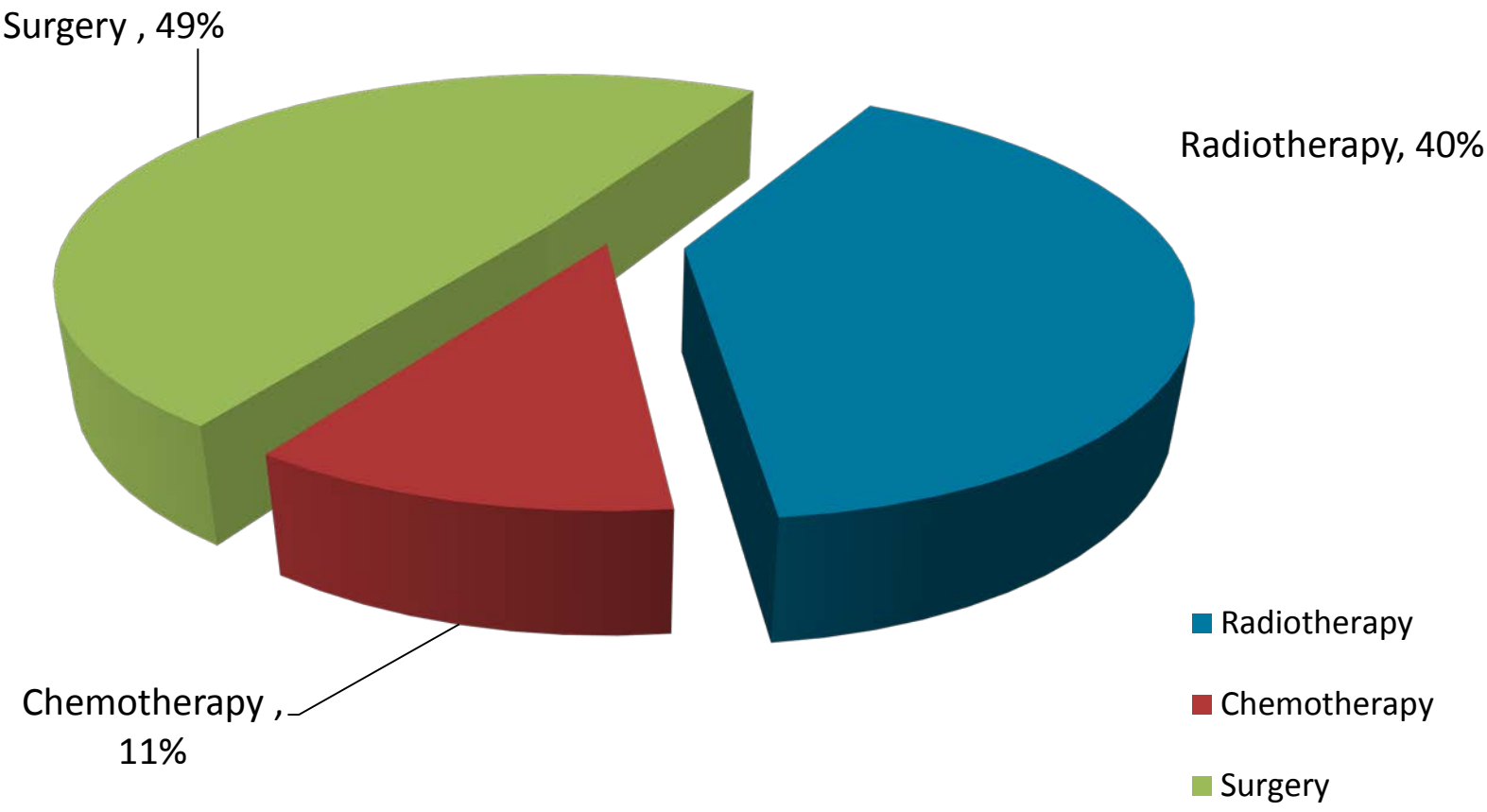
Statistically significant* discrimination between responders & non-responders

We use the Komogorov-Smirnov test, KS

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

What can currently cure cancer?

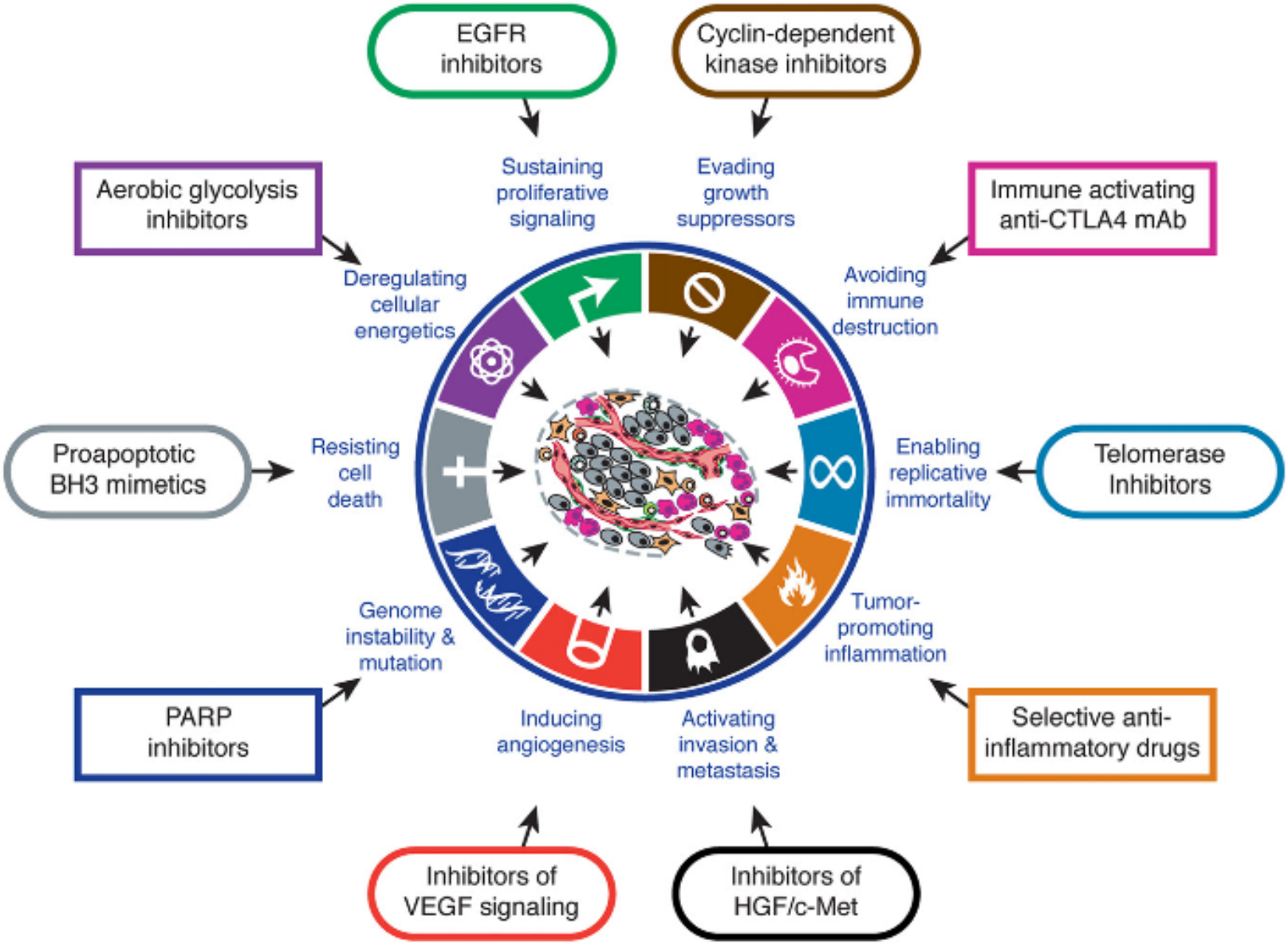
Professor Sir Mike Richards, NCRI 2011



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

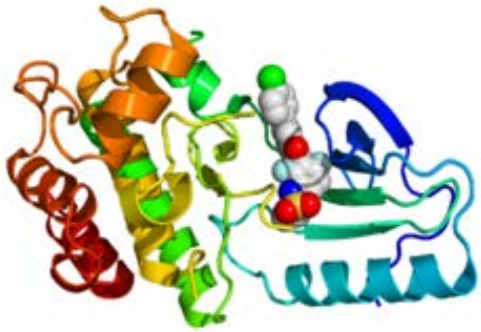
Can agents that target these processes be taken into the clinic to alter outcome?

Hanahan and Weinberg Hallmarks of Cancer

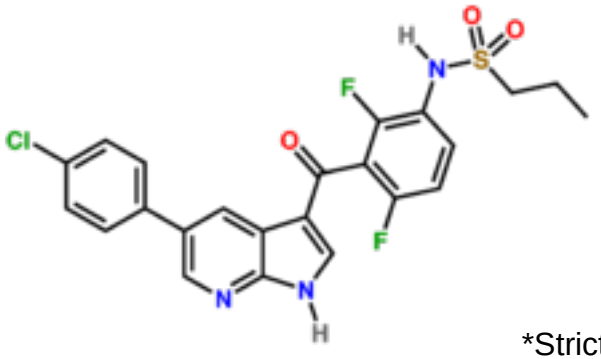


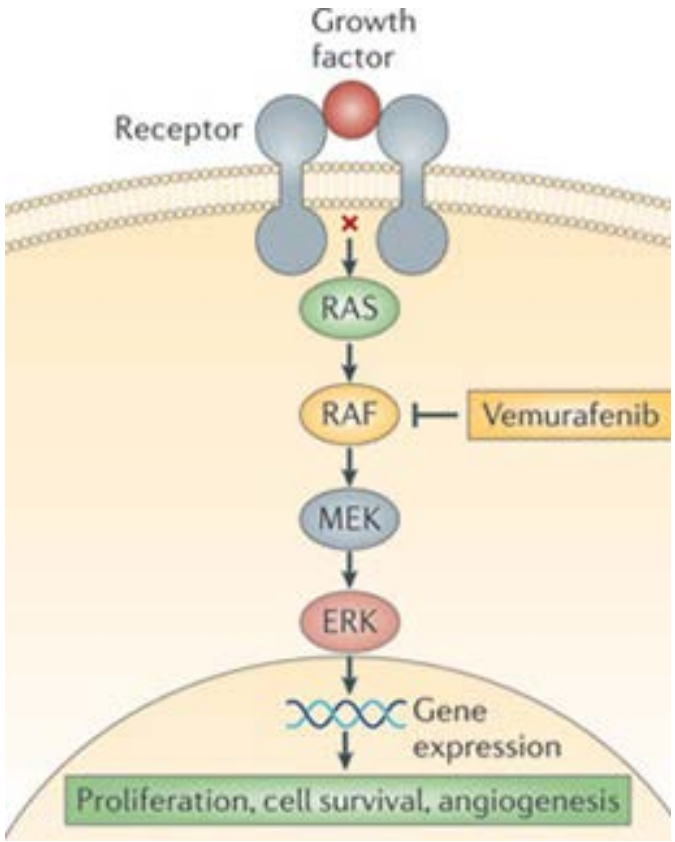
An early example: Melanoma*

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

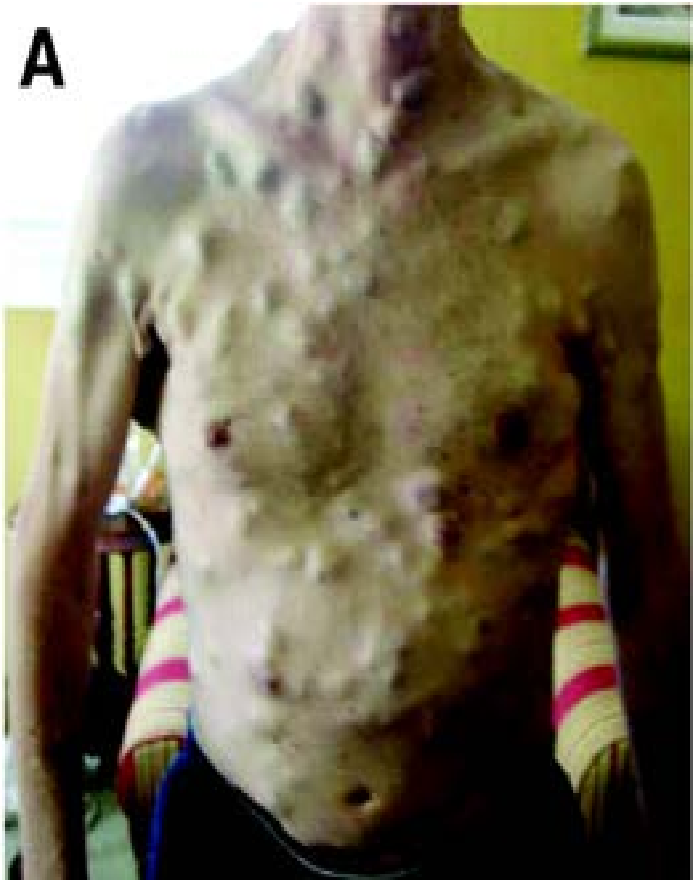




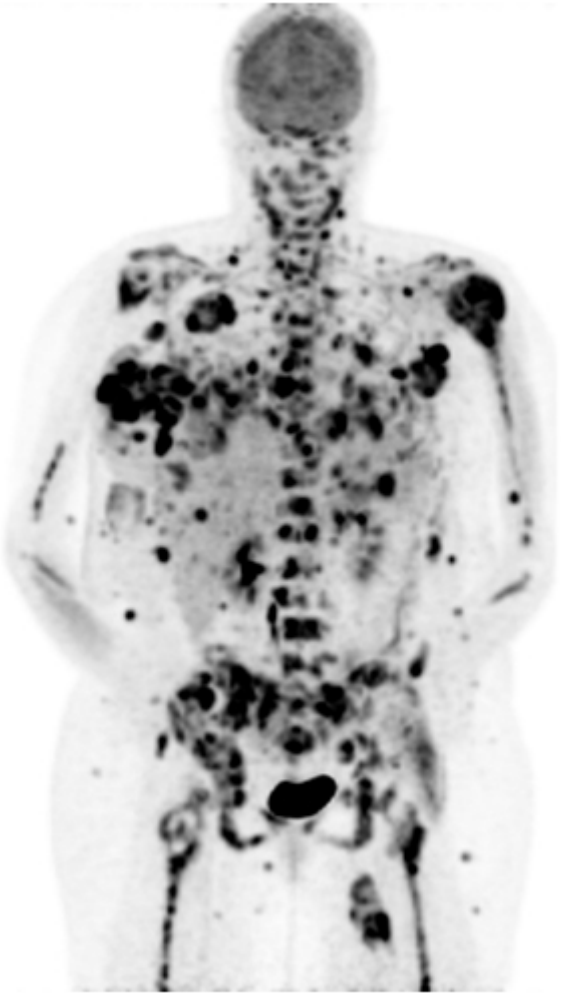
Vemurafenib targets the RAS-RAF1-MEK-ERK pathway

*Strictly: Chronic Mylogenous Leukaemia

Image of a BRAF-mutant melanoma

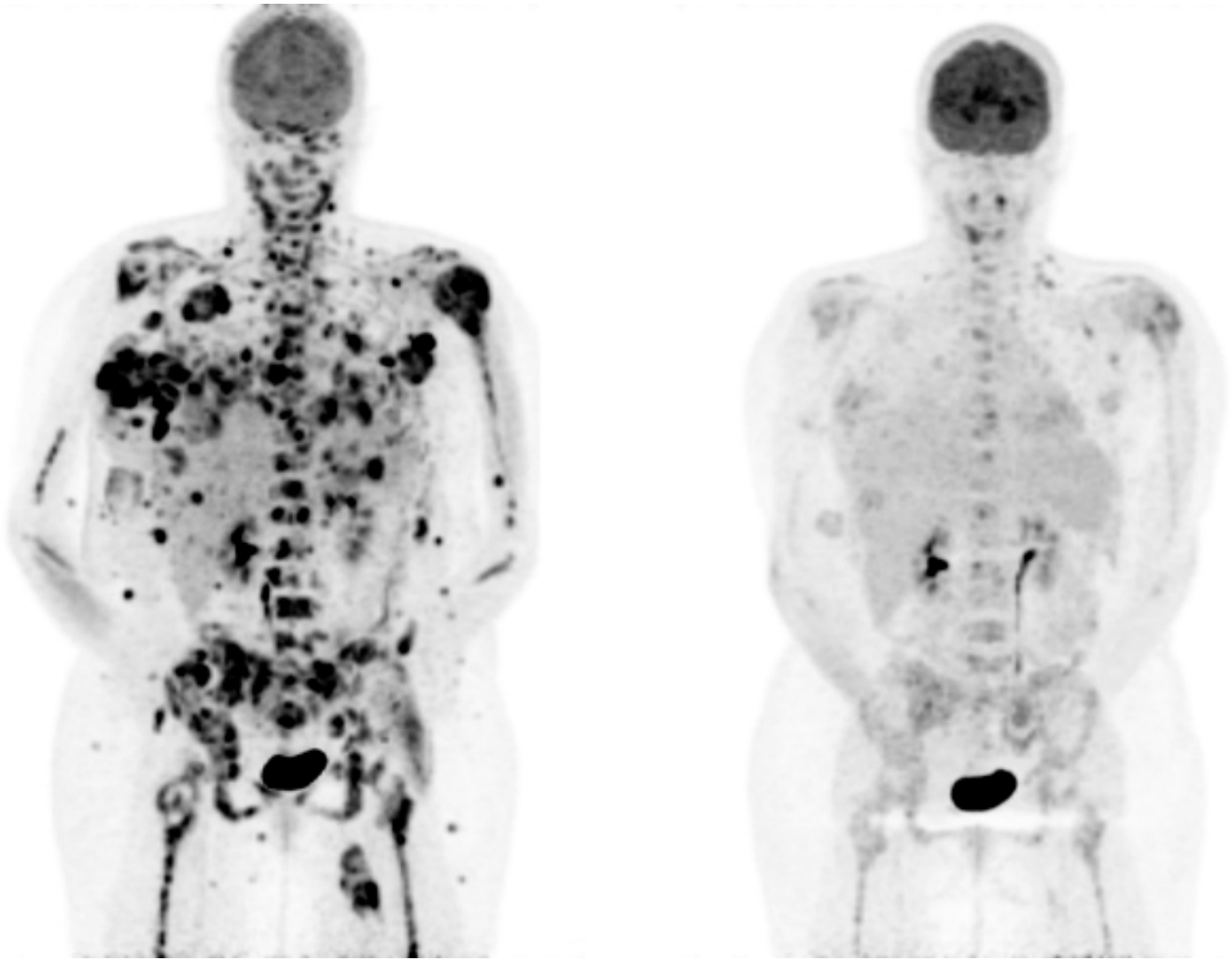


Man, 38 years old with a BRAF-mutant melanoma



PET fluorodeoxyglucose (FDG) image

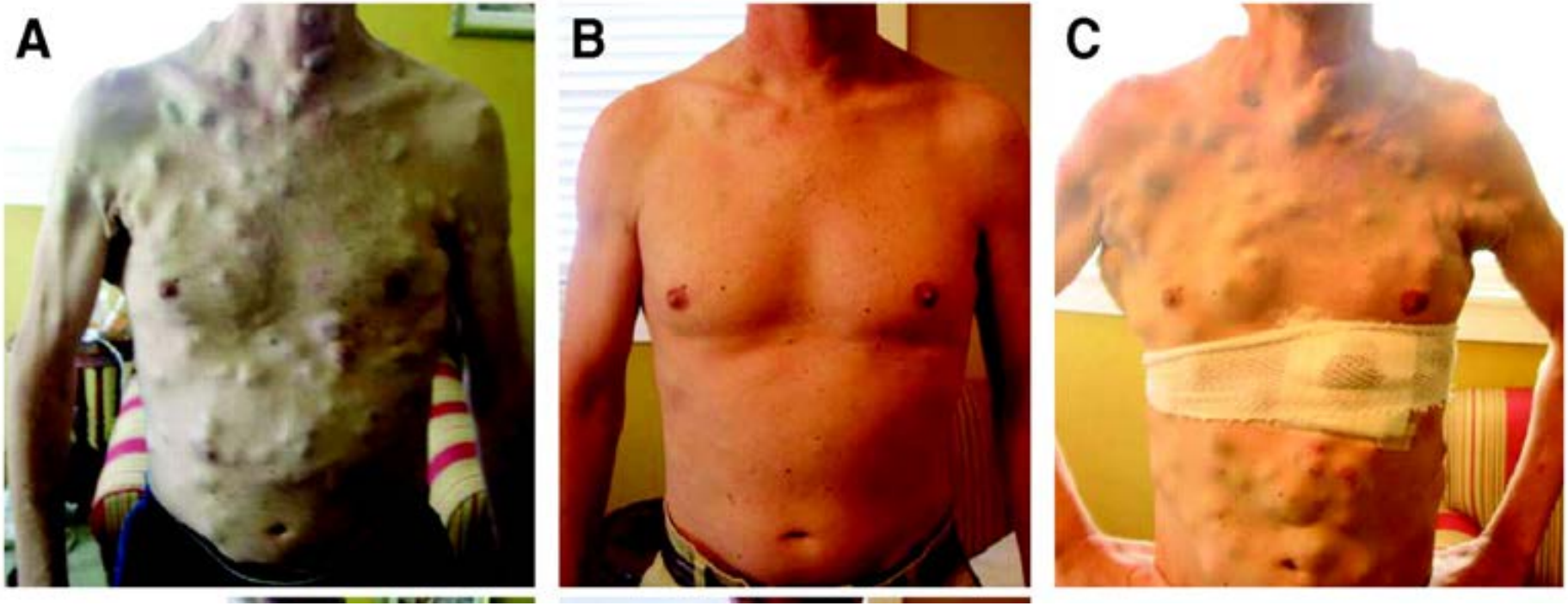
PET imaging shows the impact of Vemurafenib



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 …

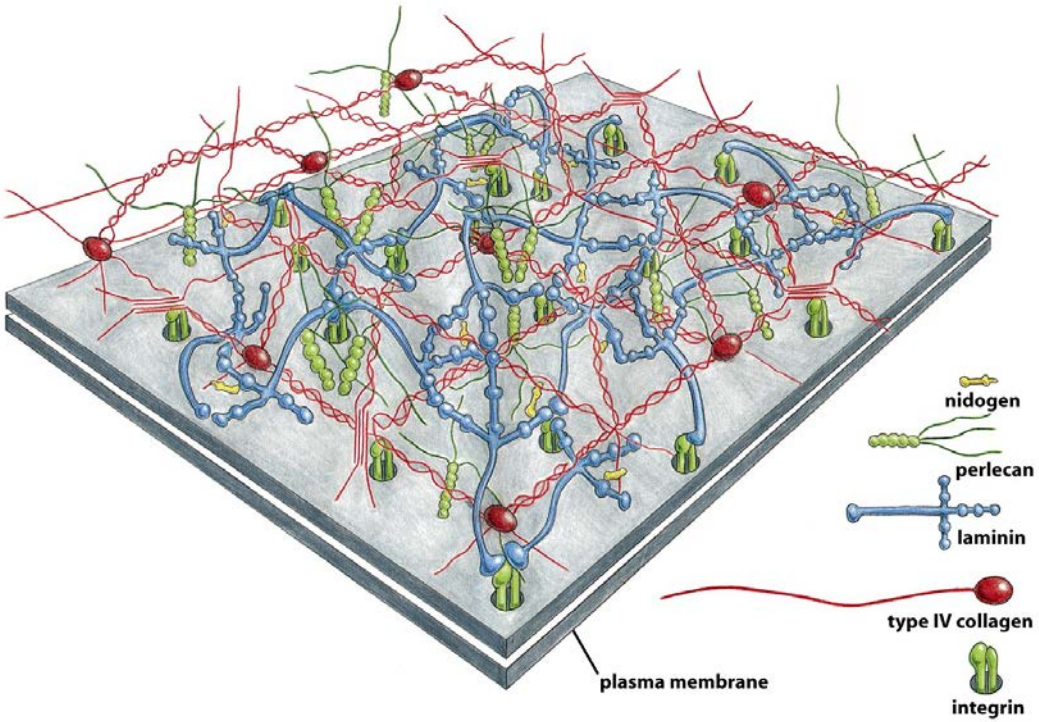
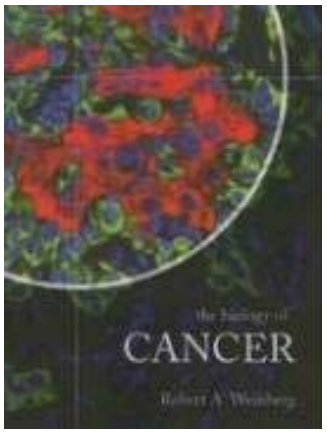


Figure 13-5b The Biology of Cancer (© Garland Science 2007)



A picture of wound healing....

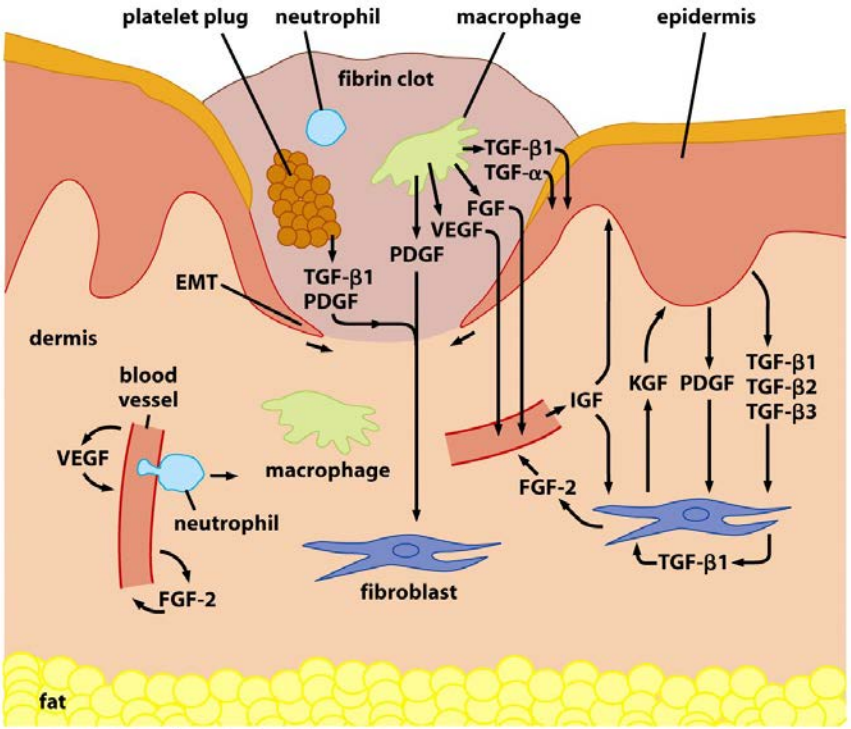
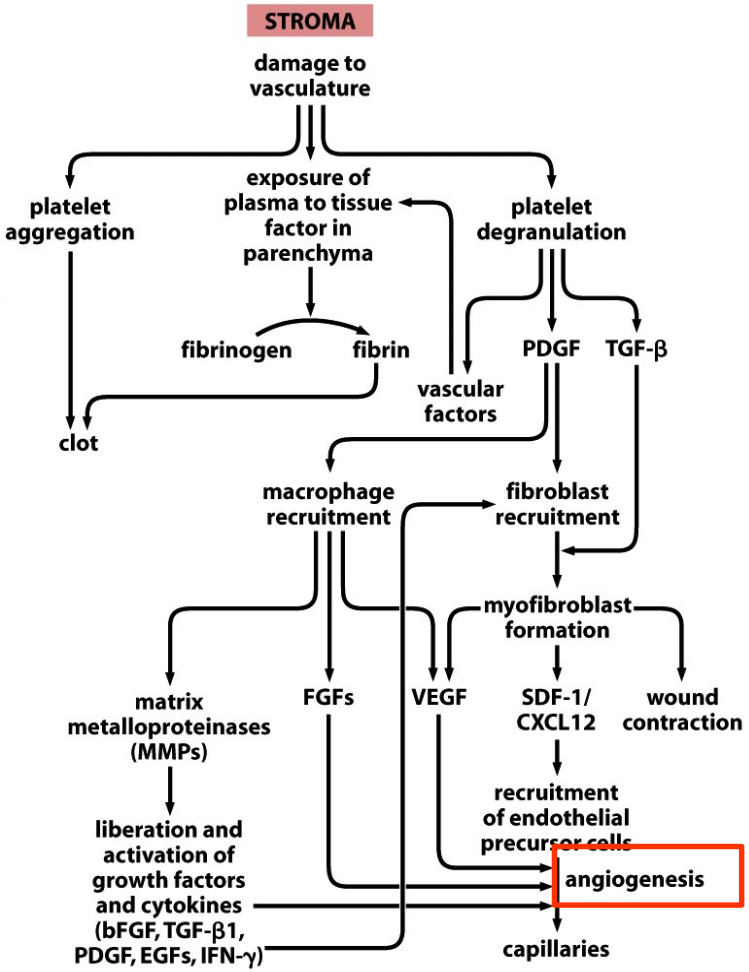


Figure 13-14 The Biology of Cancer (© Garland Science 2007)

Pathway model



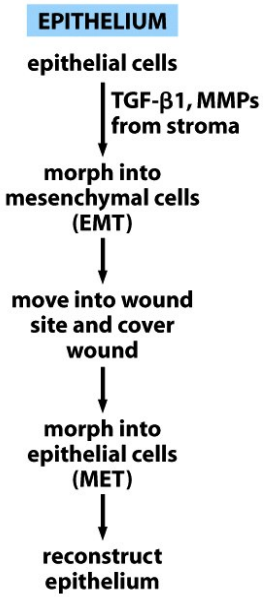


Figure 13-10 The Biology of Cancer (© Garland Science 2007)

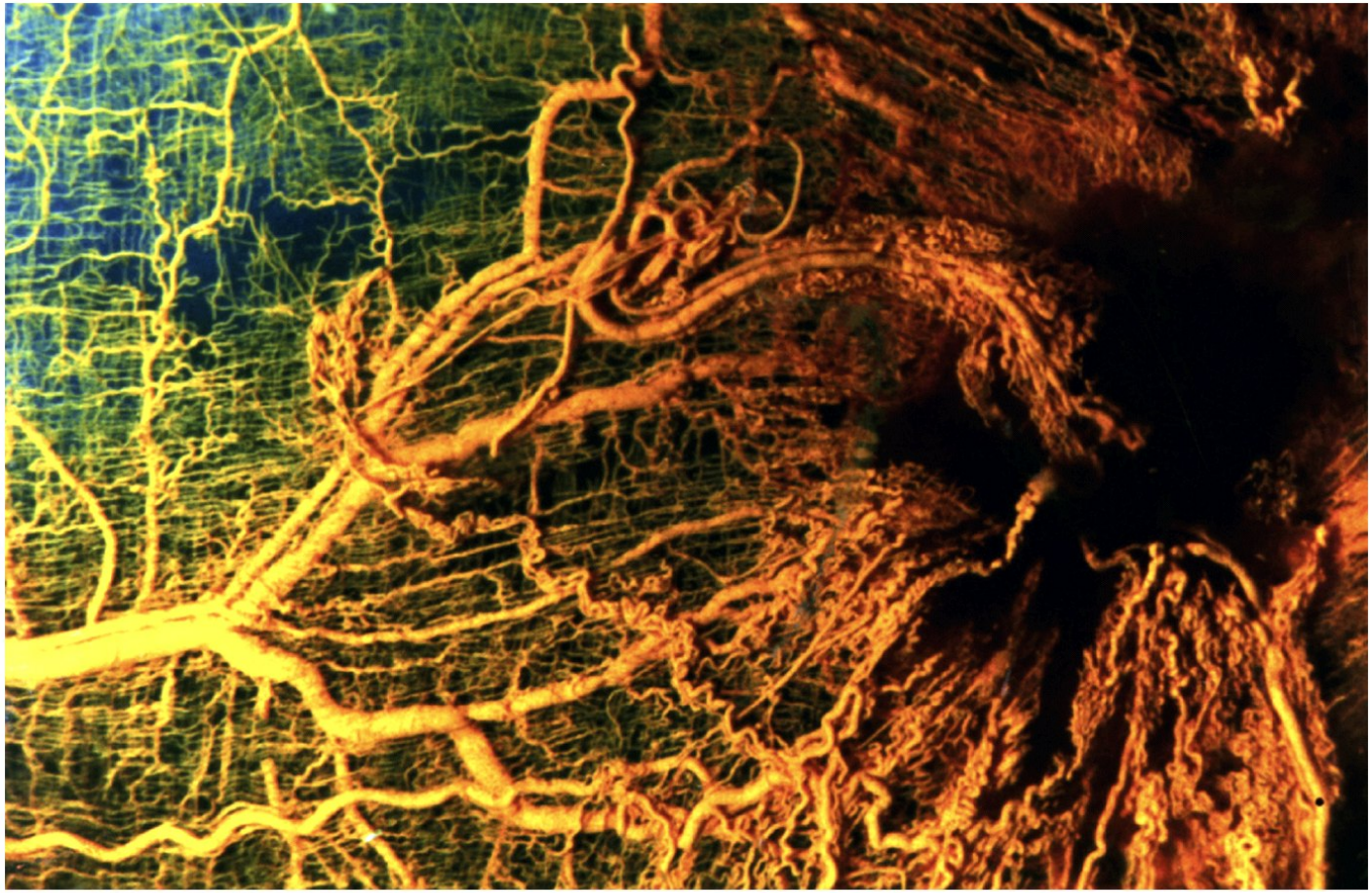
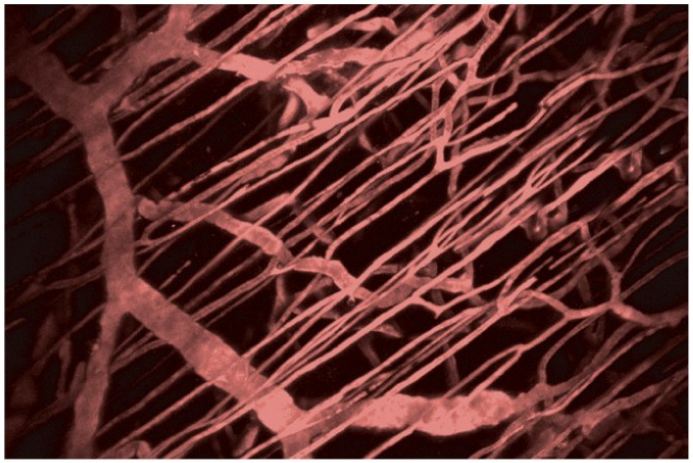


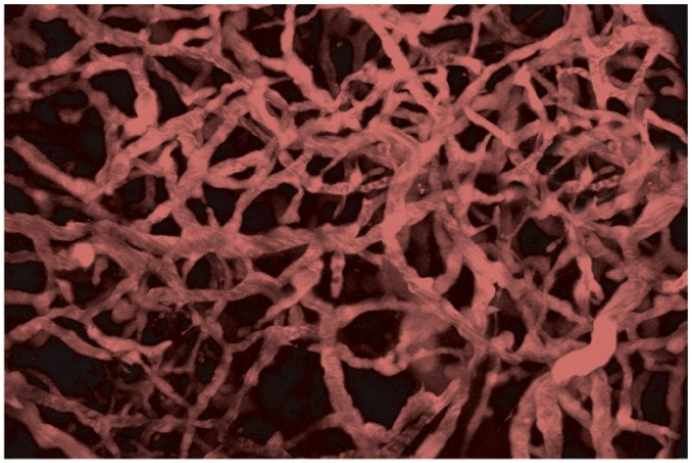
Figure 13-34a The Biology of Cancer (© Garland Science 2

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

Another rendition of chaotic & leaky neovasculature

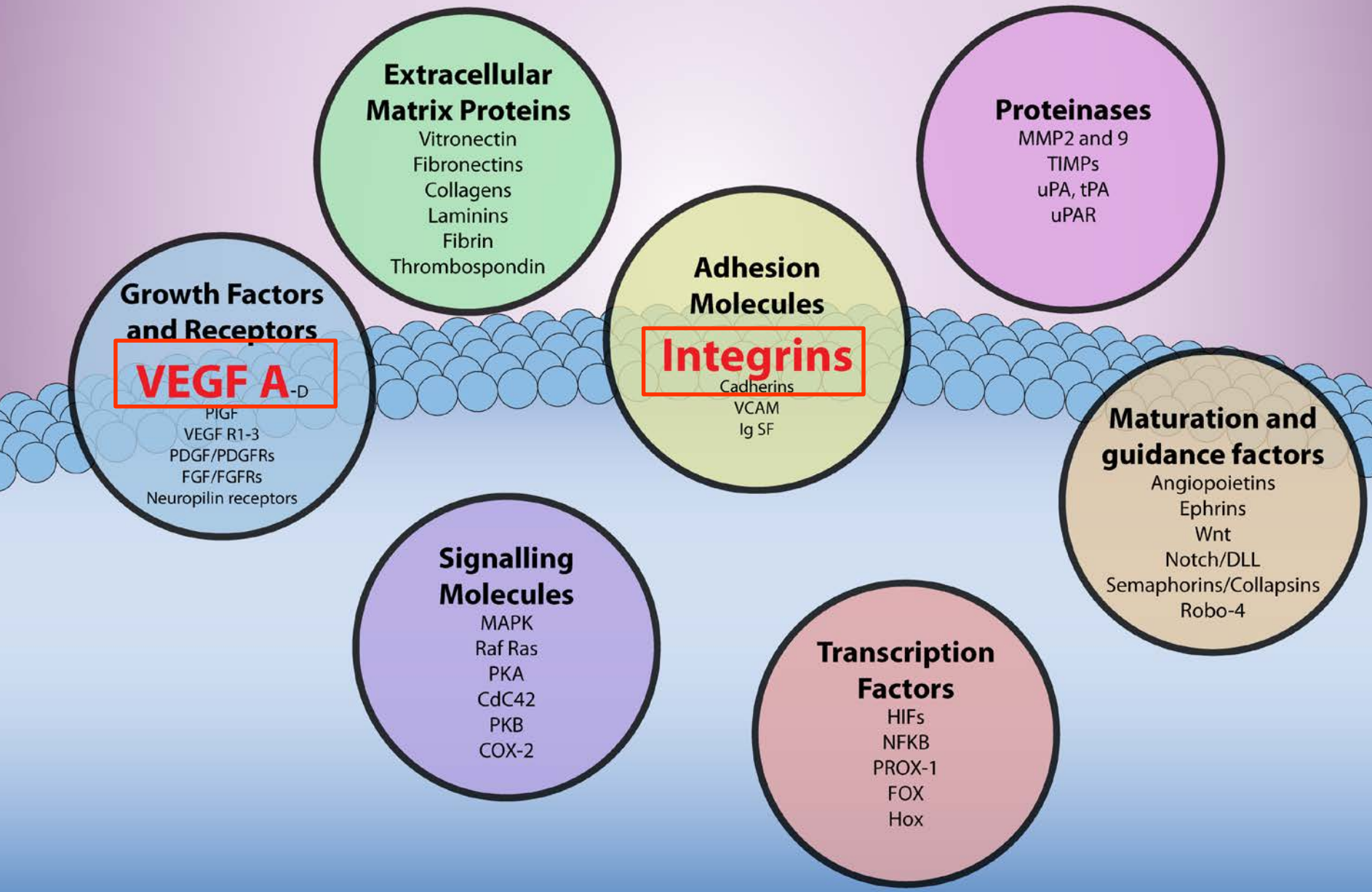


normal tissue



tumor

Imaging angiogenesis: many targets!

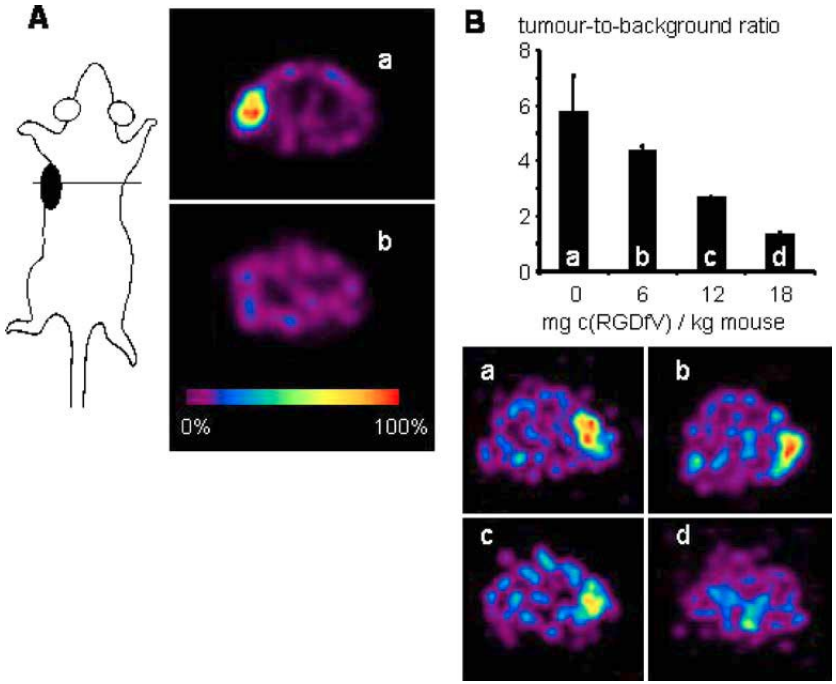


Courtesy Dr. Neel Patel, Oxford

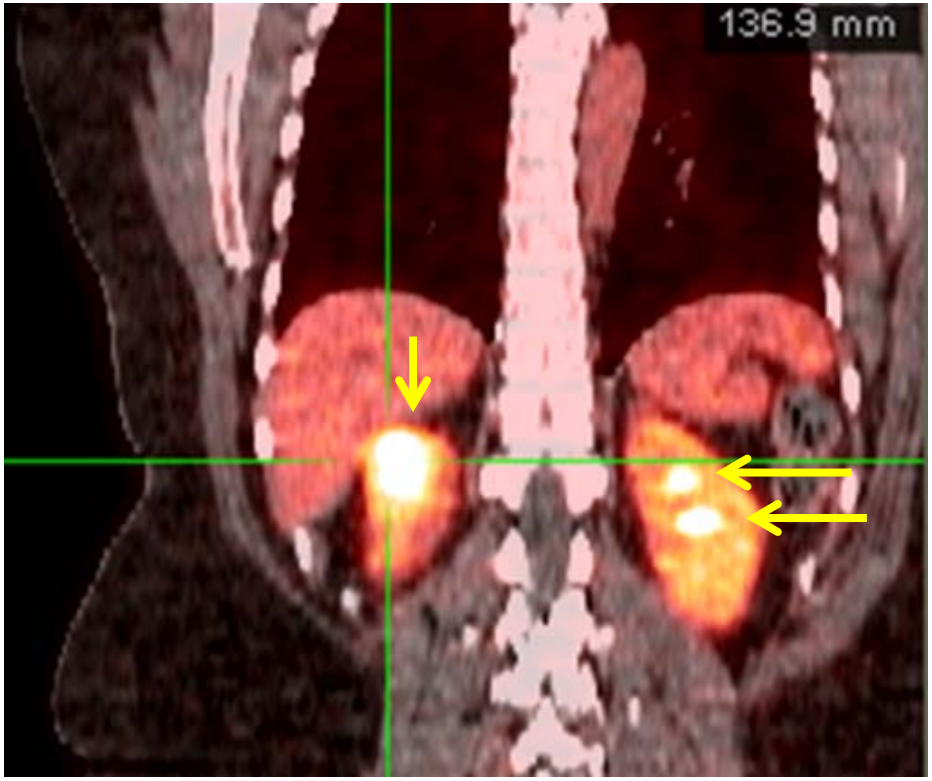
Integrin targeting for angiogenesis

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



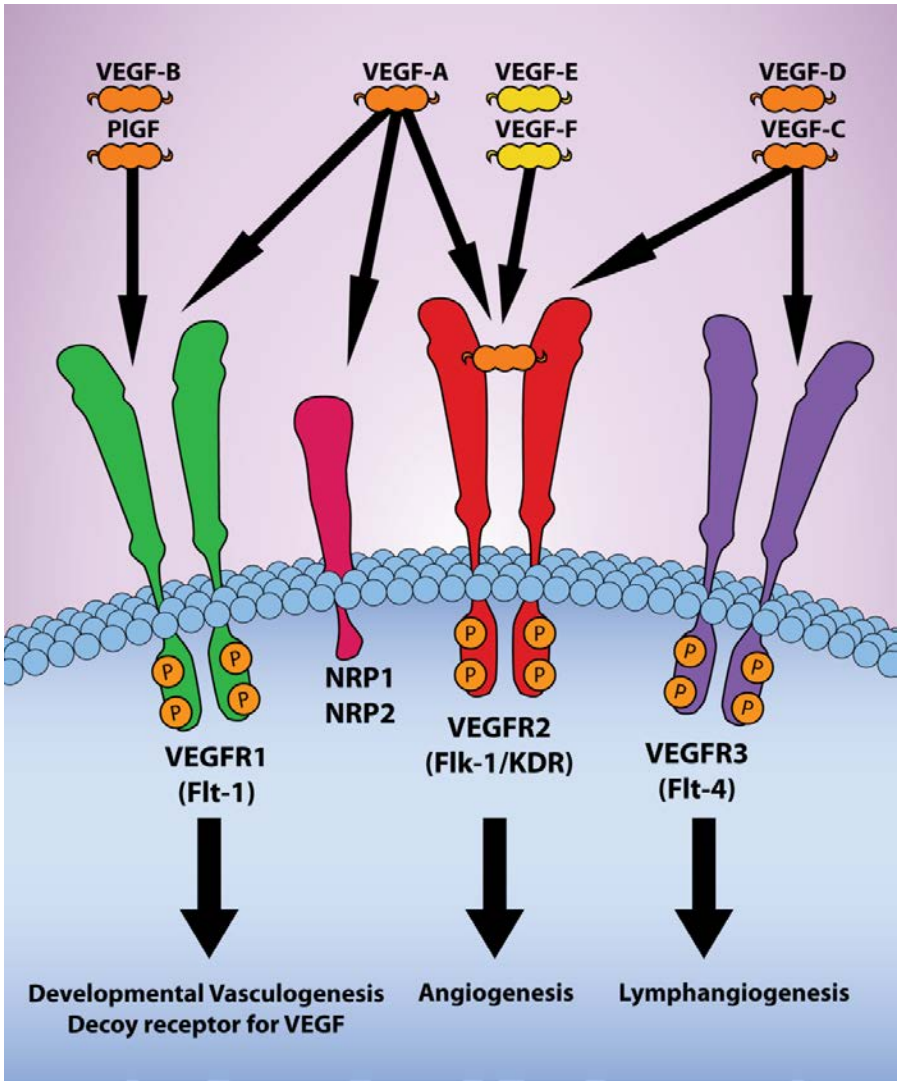
^{18}F-RGD PET-CT image of small renal tumours

Courtesy Dr. Neel Patel, Oxford

VEGF for inhibition of angiogenesis

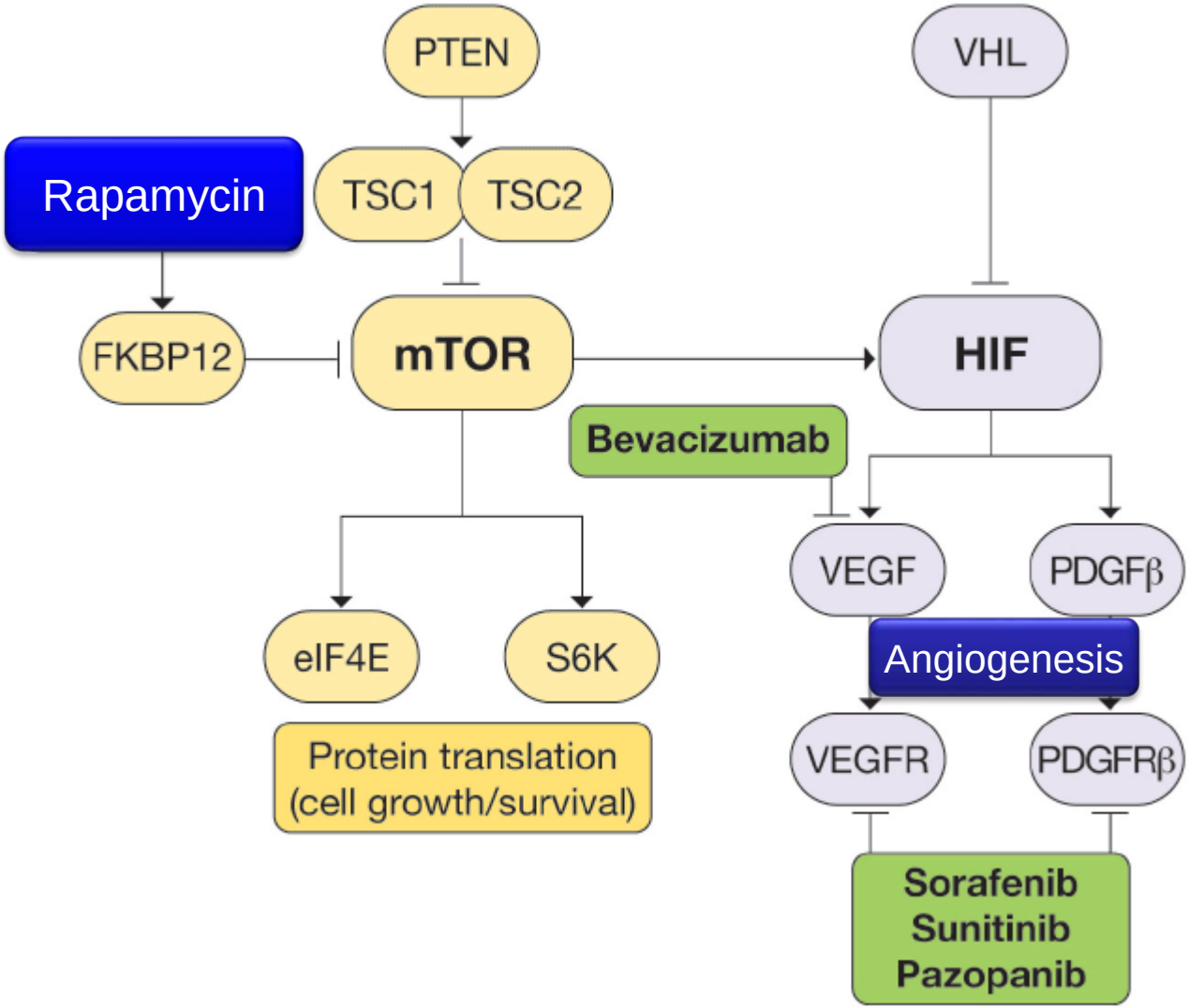
Vascular Endothelial Growth Factors
VEGF A-D are signalling proteins

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

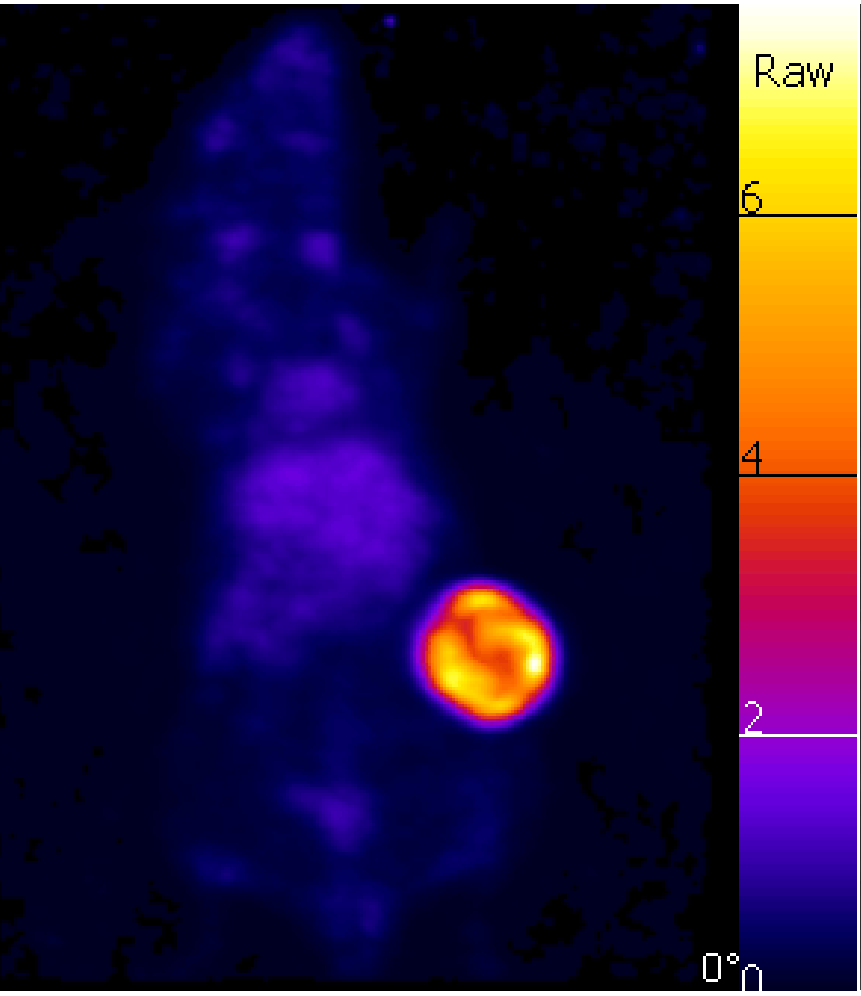


Courtesy Dr. Neel Patel, Oxford

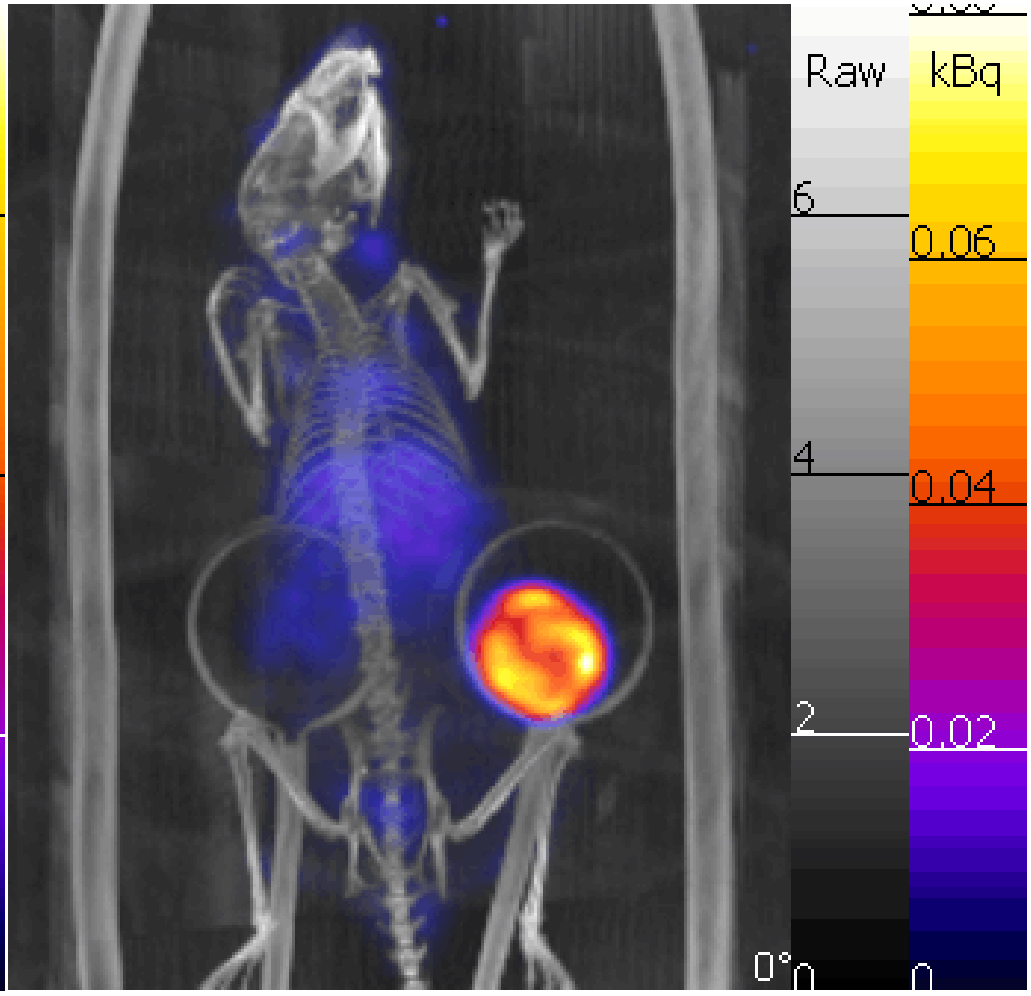
A range of related targets



Imaging Avastin bound to SPECT emitter ^{124}I

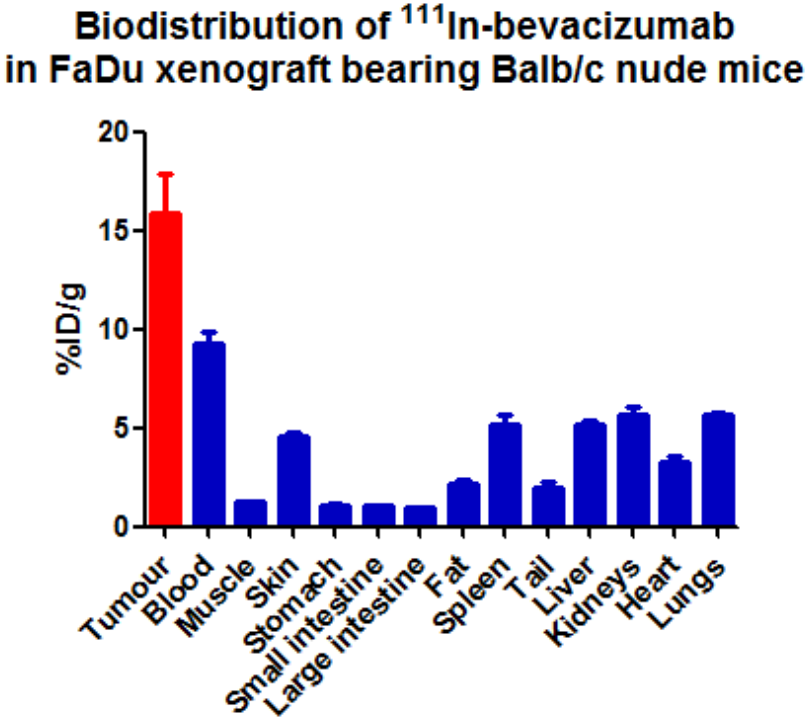


SPECT

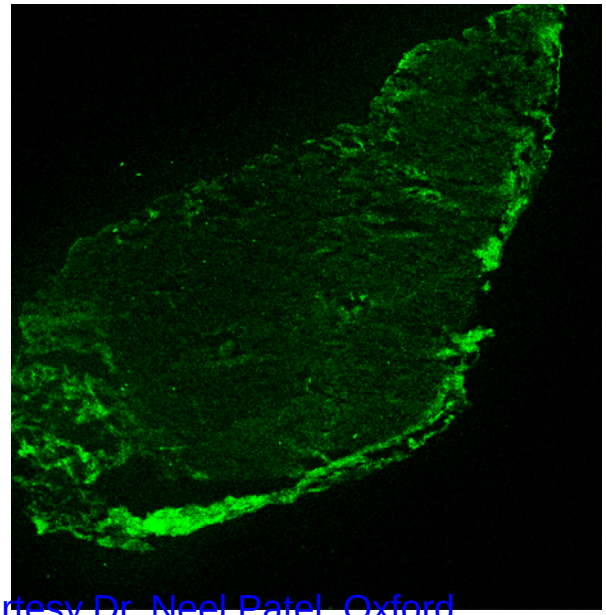


CT fused with SPECT

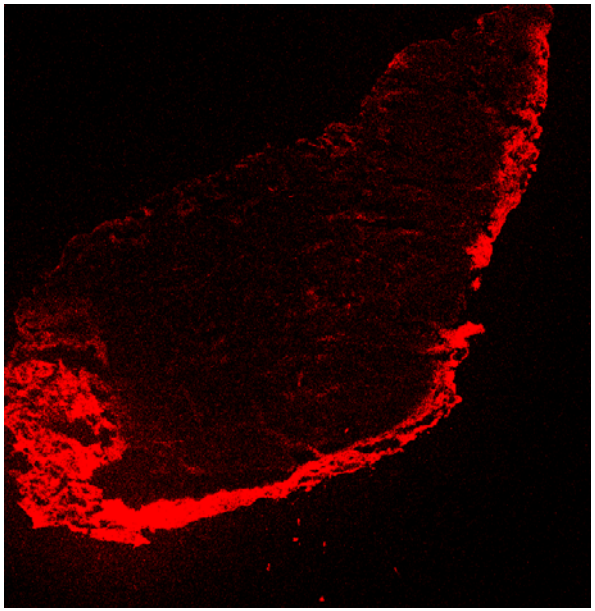
Biodistribution & immunohistochemistry



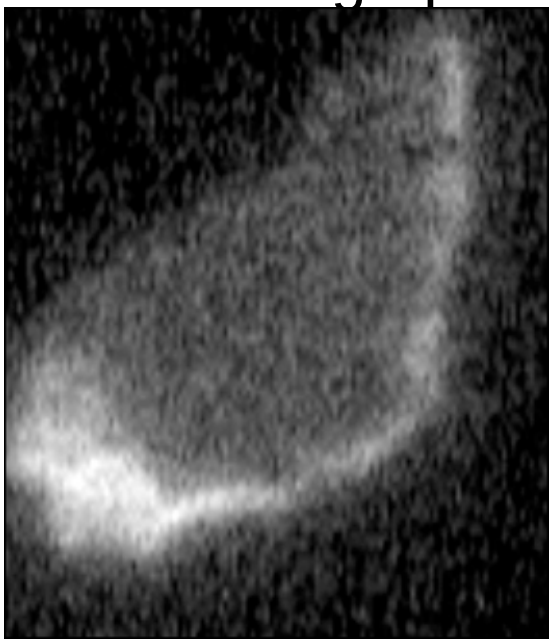
VEGF



Avastin

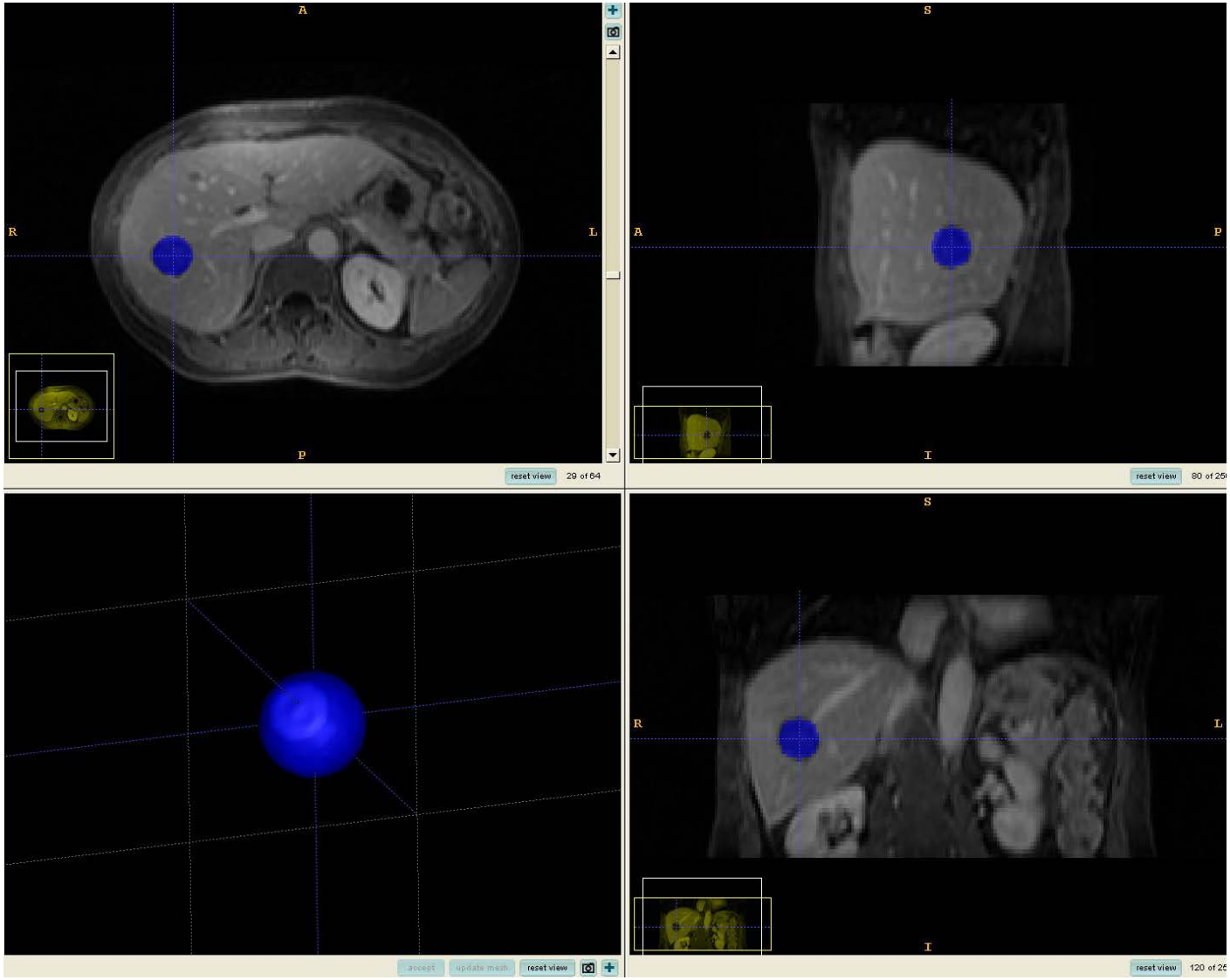


Autoradiograph

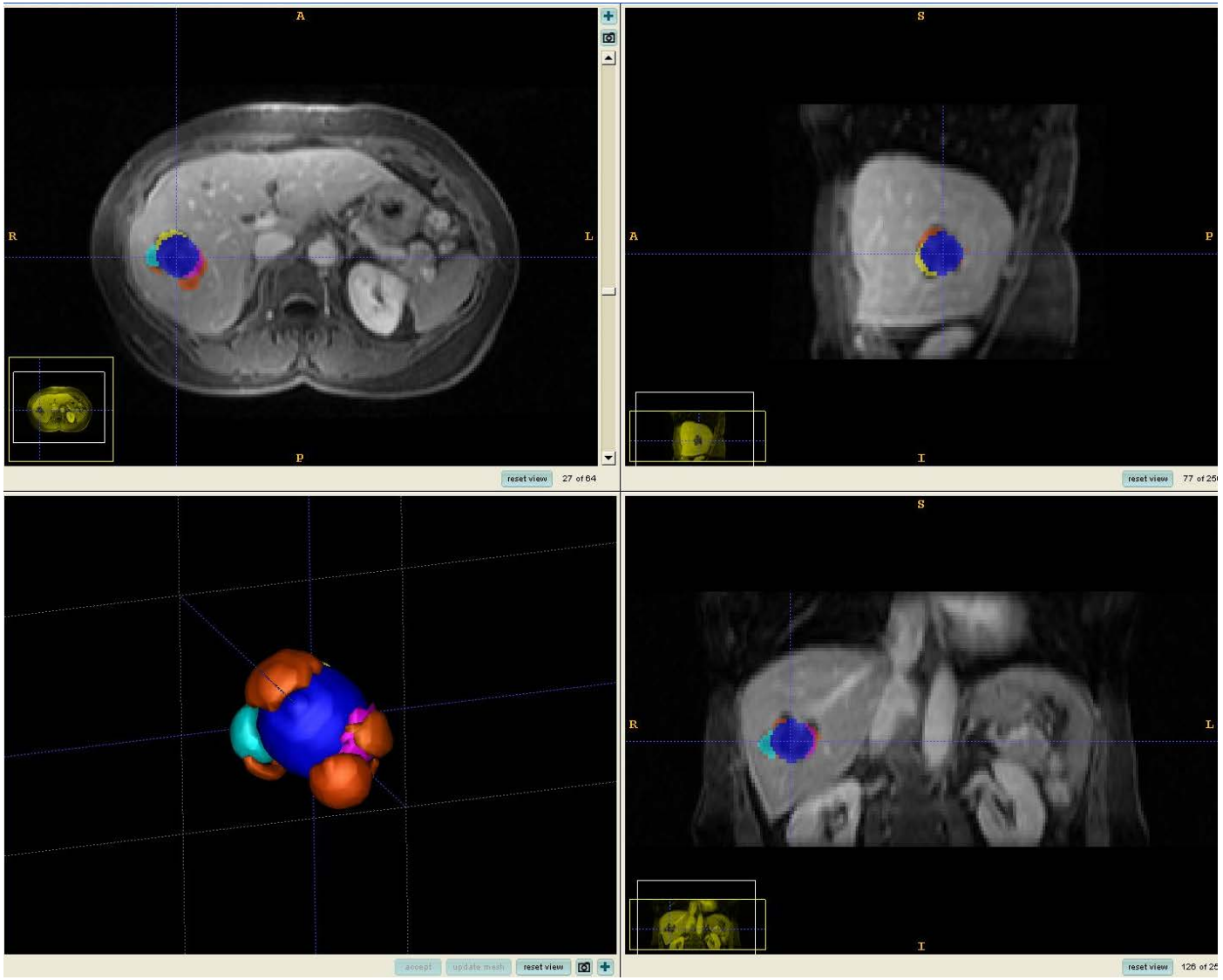


Courtesy Dr. Neel Patel, Oxford

(Liver) tumour shape pre-chemotherapy

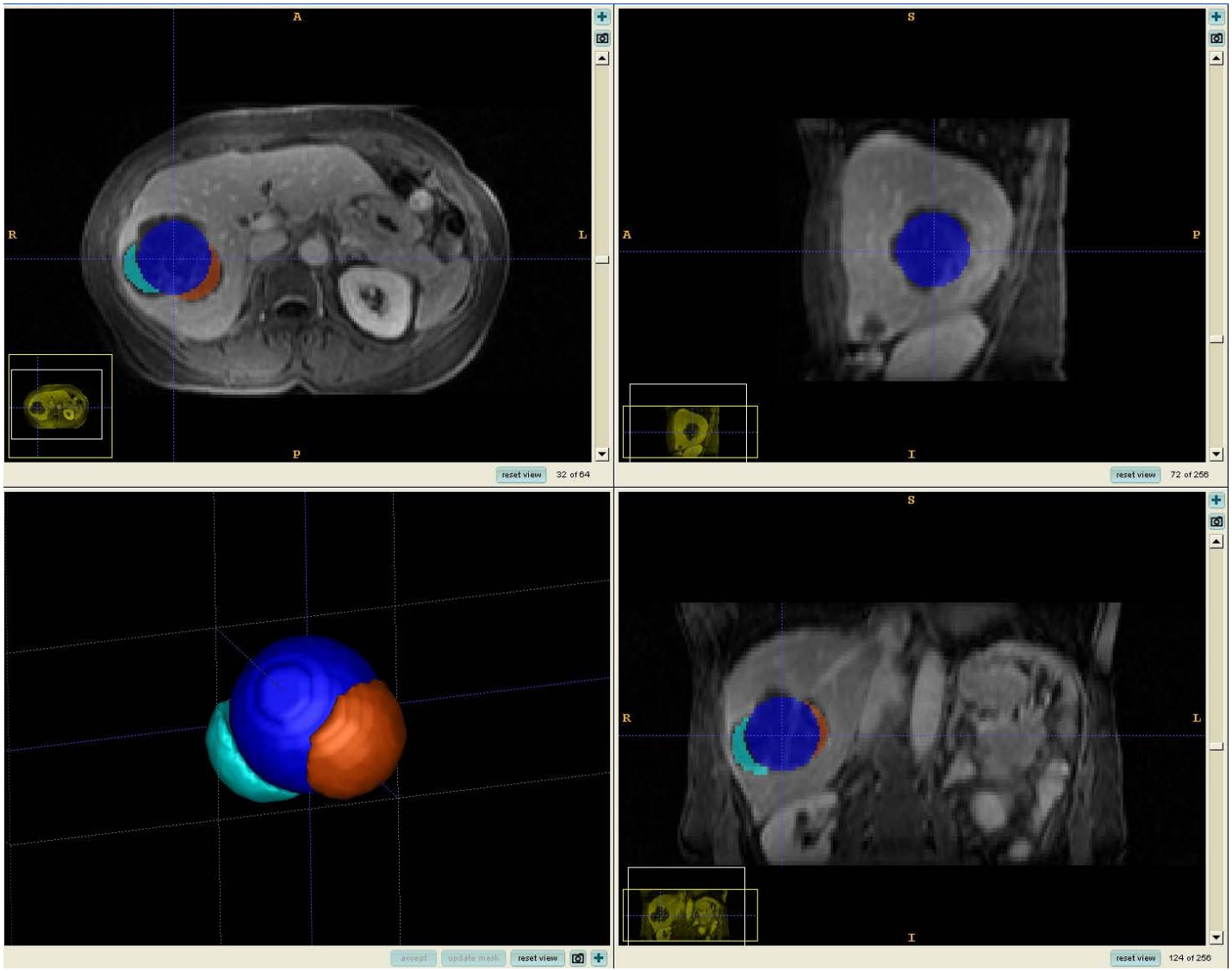


Liver tumour shape post-chemotherapy, 9 months later

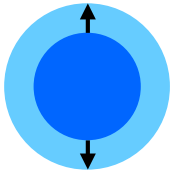


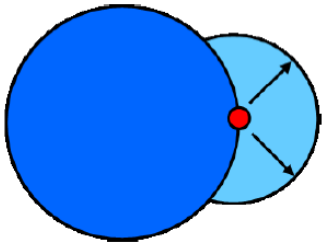
Eng Sci, Surgery, Radiology, Pathology, Clin Pharm, Mathematics, WIMM, GE Healthcare

pre-ablation, another 3 months later

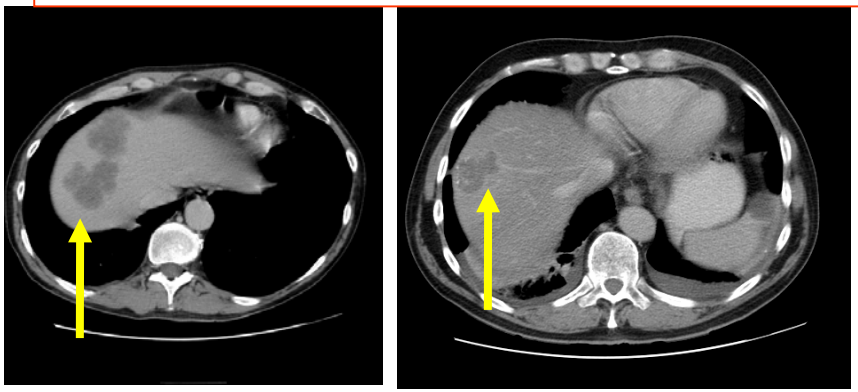


Tumour Growth Model

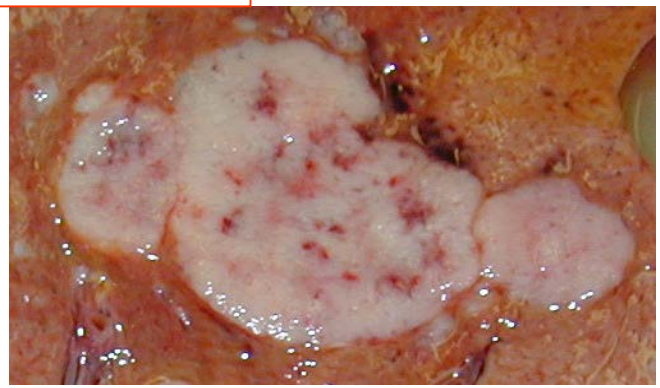




- Early tumour masses are often approximately spherical and grow as spheres. Mathematical models treat this case.
- They can sprout additional spheres (this corresponds, biologically, to clonal expansion)
- Heterogeneous tumours with multiple clonal centres may demonstrate variations in response to therapy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



recent examples from the Churchill



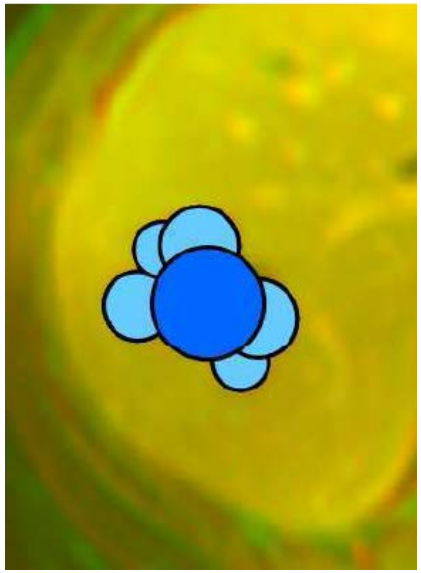
The shape of the resected specimen

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

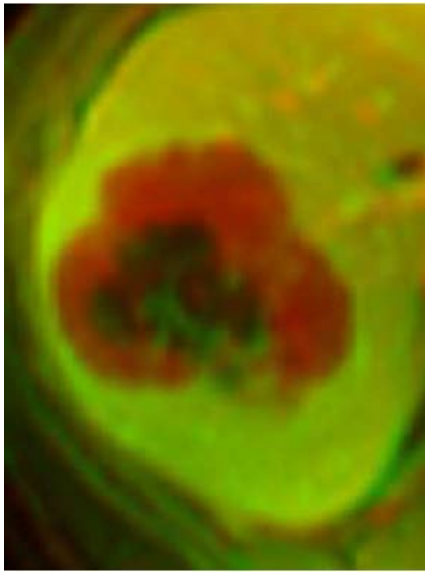
Olivier Noterdaeme, Dr. Matt Kelly, Mike Brady, and numerous clinicians

Tumour growth model

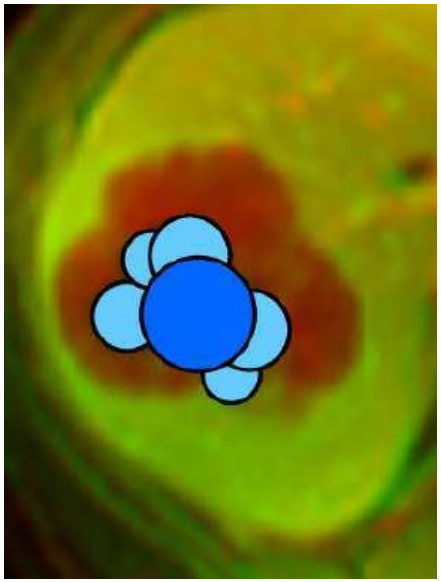
Clinical case from Churchill: growing metastatic colorectal (Dukes B) tumour



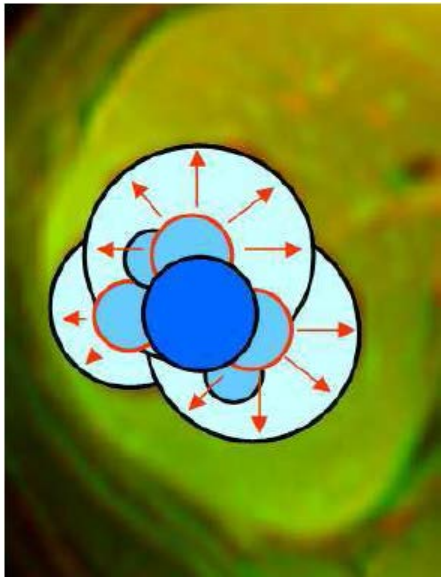
Spheroid fit after 9 months of chemotherapy



Tumour shape after 3 more months



9 month spheroids centred on 12 month shape

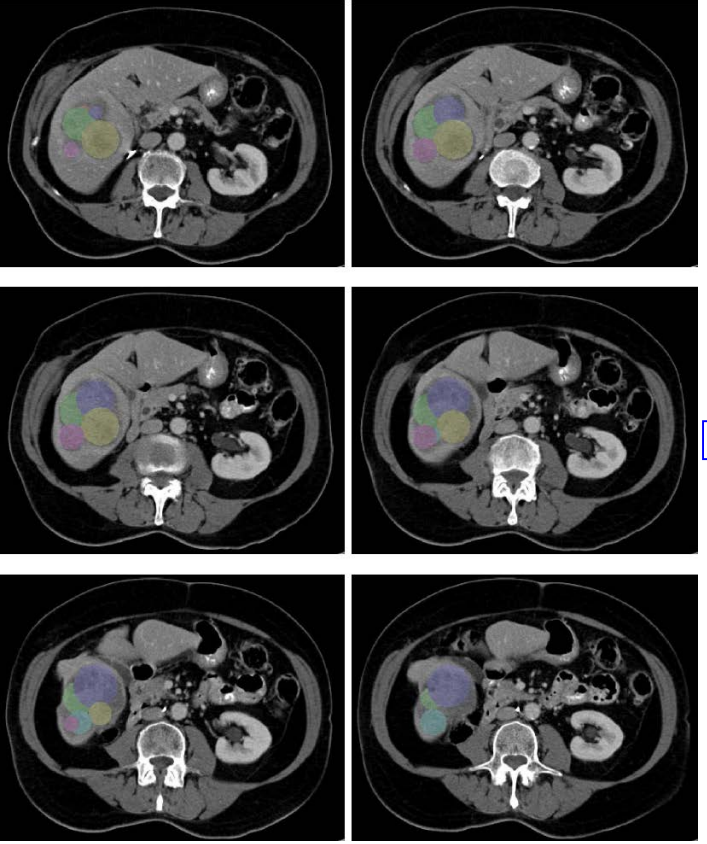


9 month spheroids grown (red) and static/shrunk (black)

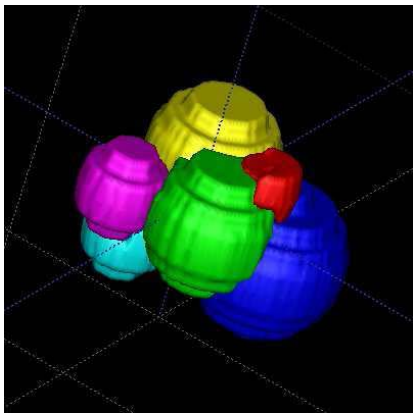
The tumour growth model gives a plausible account of tumour morphology; but the key question remains: do the successively sprouted clonal centres correspond to increasingly severe mutations of the original tumour DNA?

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)

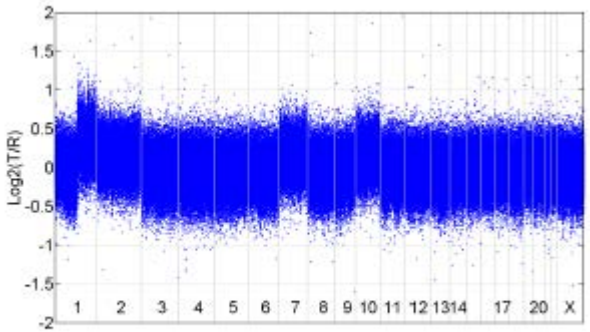


3D model of tumour

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

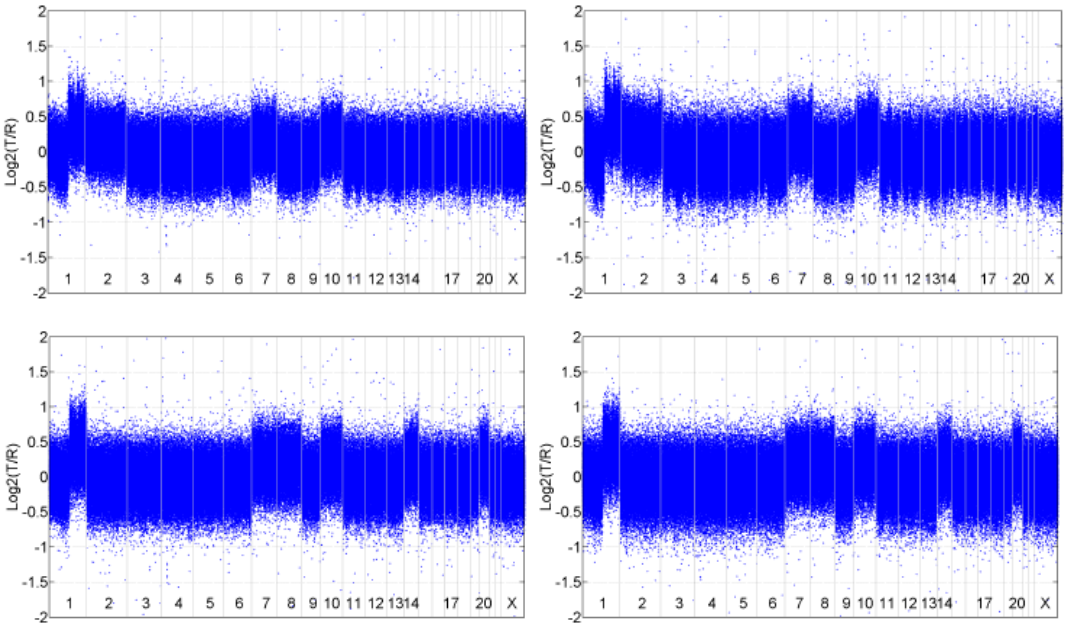
385,000 probes of a sample 17.4mm X 13mm ➔ 6270 base pairs analysed

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.*

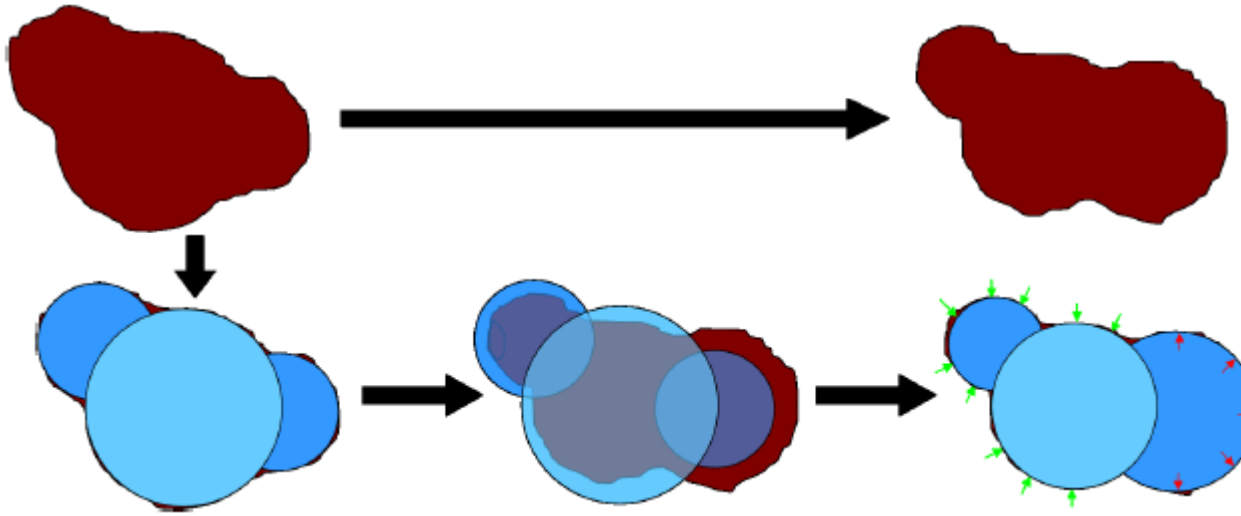
Disease ***progression*** ≡ increase by at least 20% in *longest linear dimension*

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***