

# The Use and Mechanism of Action of High Intensity Focused Ultrasound for Adipose Tissue Removal and Non-Invasive Body Sculpting

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## PURPOSE

To document the feasibility of use and mechanism of action of High Intensity Focused Ultrasound (HIFU) for adipose tissue removal and body sculpting.

HIFU has been used extensively in the clinical setting to treat different types of tumors, however, there is no published literature on its use for adipose tissue removal.

## MATERIALS AND METHODS

### Pre-clinical study:

Transcutaneous HIFU\* was administered to subcutaneous abdominal adipose tissue in swine to establish safety.

### Clinical study:

Twenty-four patients underwent HIFU treatment to their lower abdominal adipose tissue followed by abdominoplasty at different time points.

The clinical study was performed between July, 2003 and February, 2004 at Hospital Santa Monica in Mexico City after Ethics Committee & Ministry of Health approval was obtained.

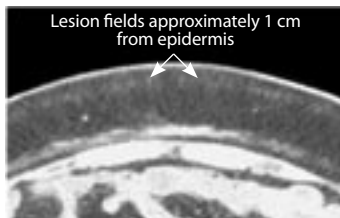
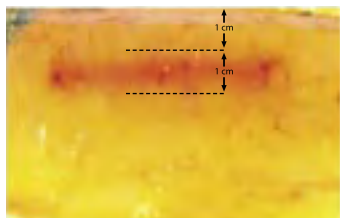
Lesion fields (swine & human) were examined for gross and histological HIFU induced pathophysiological changes at various times after therapy, from several hours to eight weeks.

## RESULTS

The depth from skin to lesion field, as well as the depth of the HIFU treatment site, was determined by the transducer focal length. (A)

Histology with computer-aided mapping of damaged adipocytes demonstrated control of therapy within the target area. (B)

Gross pathology and CT imaging revealed discrete lesion fields within the adipose tissue that did not extend into the dermis, the rectus muscle or fascia. (C, D)



C Abdominoplasty specimen

D

Peri-acute (hours) and acute (7 days) phase histology revealed a well demarcated zone of adipocyte disruption with minimal inflammatory response, consisting predominantly of macrophages. (E)

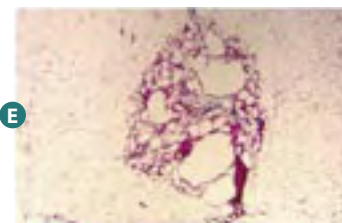
Four-week chronic histology revealed scavenger macrophages with abundant foamy cytoplasm within treatment zones. (F)

Eight-week chronic histology demonstrated 75% resolution of the treated adipose tissue with collapse of the surrounding fibrovascular stroma. (G)

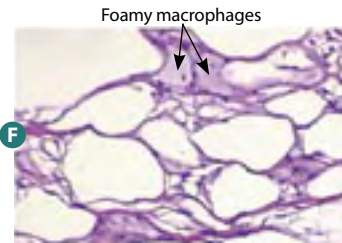
Eight-week gross pathology from both pre-clinical and clinical studies demonstrated excellent resorption of damaged adipose tissue. (H)

Lipid panels drawn from human patients throughout the trial did not reveal any new clinical changes from baseline.

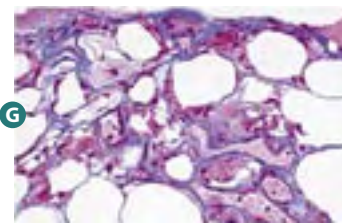
One-week and six-week full-body necropsy studies on swine revealed no fatty liver changes or other systemic abnormalities.



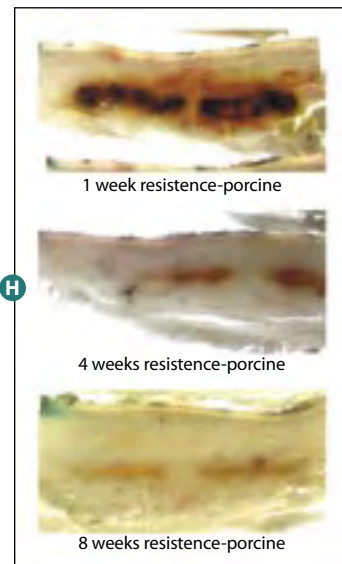
E



F



G



H

## CONCLUSIONS

*The use and mechanism of action of HIFU therapy for fat removal has been proven in both pre-clinical and human clinical trials and provides a non-invasive method for body sculpting.*

# Oncological image analysis:

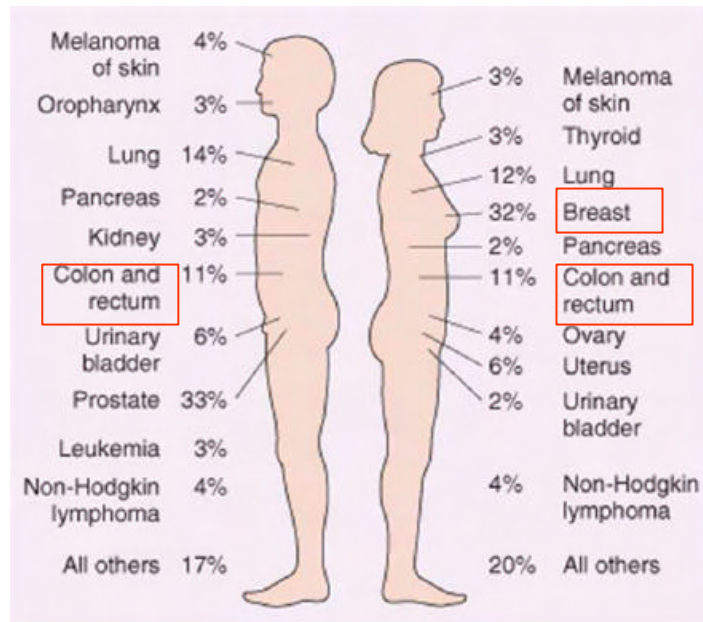
## Medical and molecular image analysis

Professor Sir Michael Brady FRS FREng  
Department of Engineering Science  
Oxford University

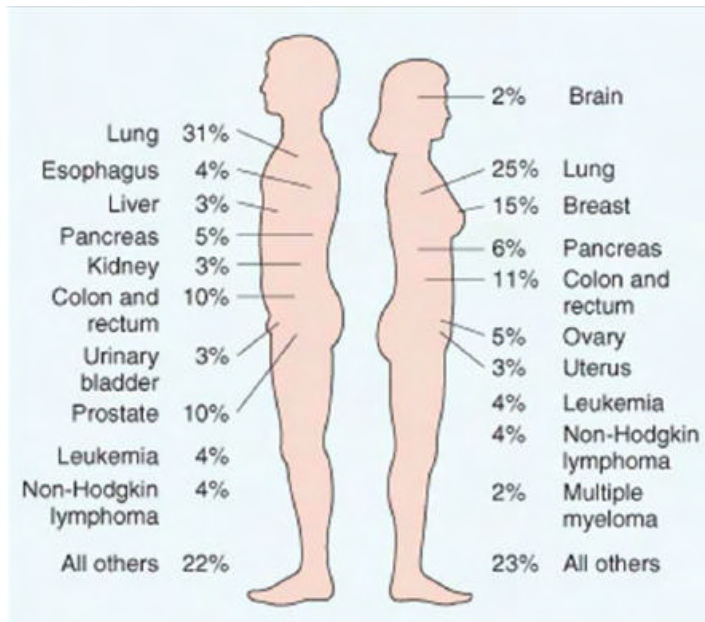


# Cancer statistics

- In developed countries, 1 in 3 will be diagnosed with cancer during their lifetime
- Incidence (new cases) is 10,000,000, and this will double over next 20 years
- 550,000 died of cancer in USA in 2002



Cancer incidence



Cancer deaths

# Treating cancer

- Early diagnosis massively improves prognosis
  - Breast screening programmes
  - BMJ 2006 “It is time to accept that, despite its limitations, [screening for breast cancer] does save lives”
  - Screening: 6 cancers/1000; 24% missed; 80% biopsies turn out to be unnecessary
- Improved drug treatments
  - Tamoxifen; (5FU); oxaliplatin; capecitabine; cetuximab; irinotecan; anti-VEGF; anti-EGFR; anti-HIF; ...
- Breast conserving surgery
  - Yet, Total Mesorectal Resection remains norm for colorectal
- Cancer treatment remains costly
  - Breast \$7Bn; colorectal \$6.5Bn (USA, 2001)



# Many roles of image analysis

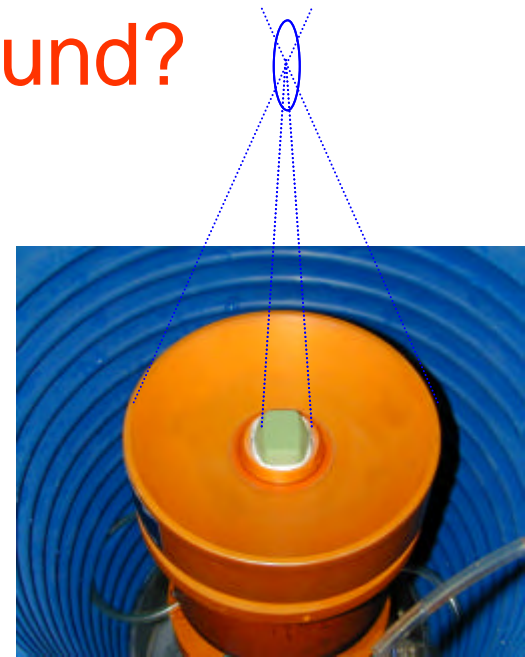
- (Early) detection of cancer - CAD
- Treatment evaluation
  - Pre- and post-resection
  - Pre- and post-chemoradio
- Monitoring
  - Longitudinal studies
- Metastatic spread
- Patient management & therapy selection
  - Resection, HIFU, chemoradiotherapy
  - Palliation
  - Decision support
- Teleradiology & Grid
- Drug development & evaluation
- Dose determination
- Basic science
  - Tumour growth, computational bioscience

# High Intensity Focused Ultrasound?

Plane transducer with  
integral aluminium lens  
(with different lengths)

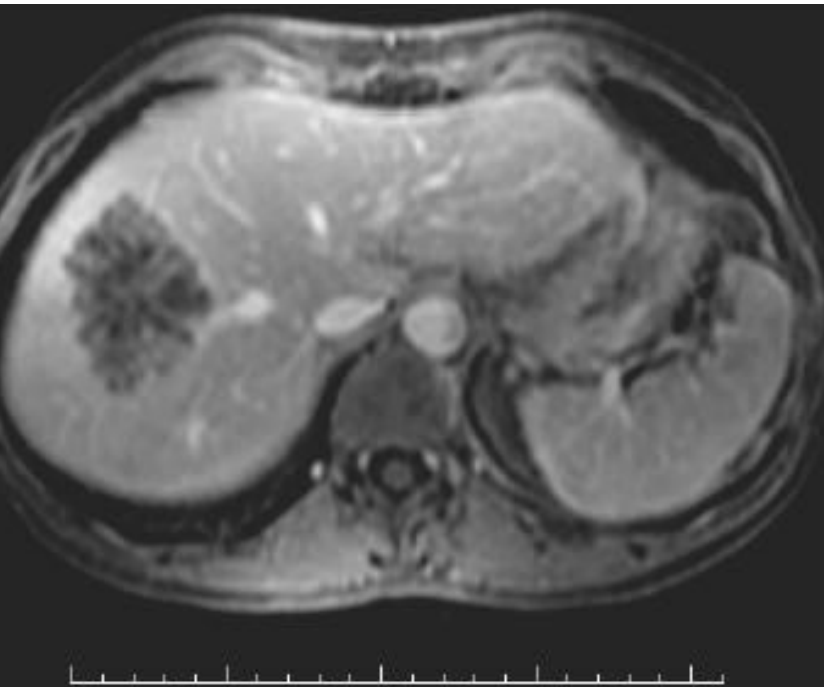
Imaging:

- Built-in coaxial 3.5 MHz diagnostic transducer
- Real-time imaging of treated area  
(using computer assisted analysis of grey-scale changes)



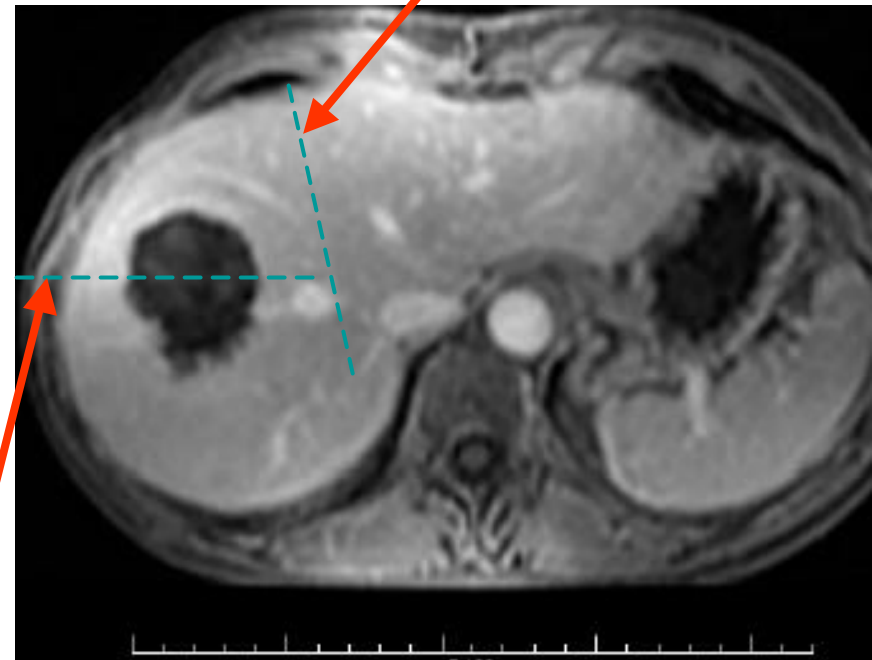
# Metastatic colorectal carcinoma

1 weighted images, 1 minute post IV contrast



2 days pre-HIFU

Plane of surgical resection



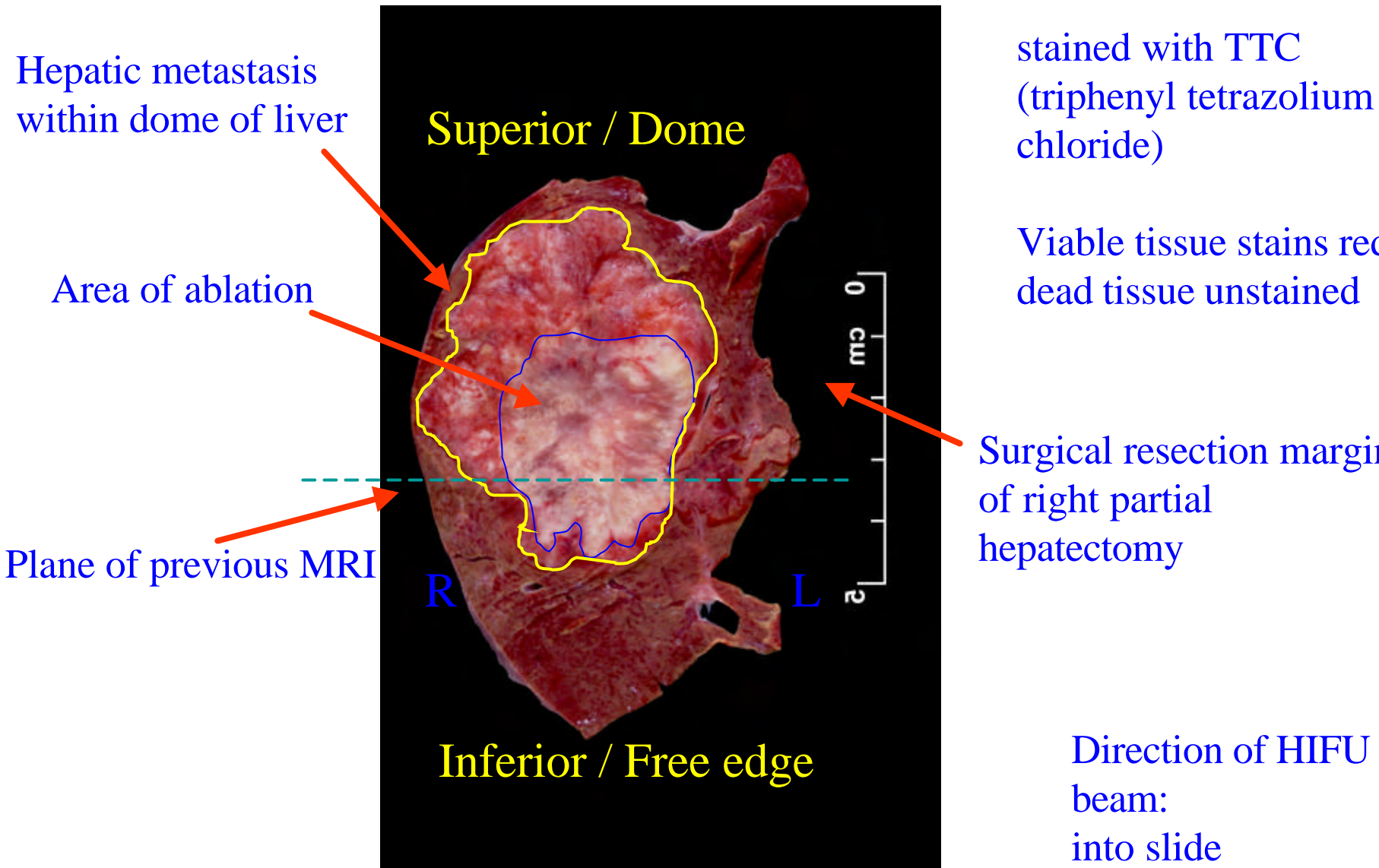
1 day post-HIFU

Plane of histological slice

# Radiological Report

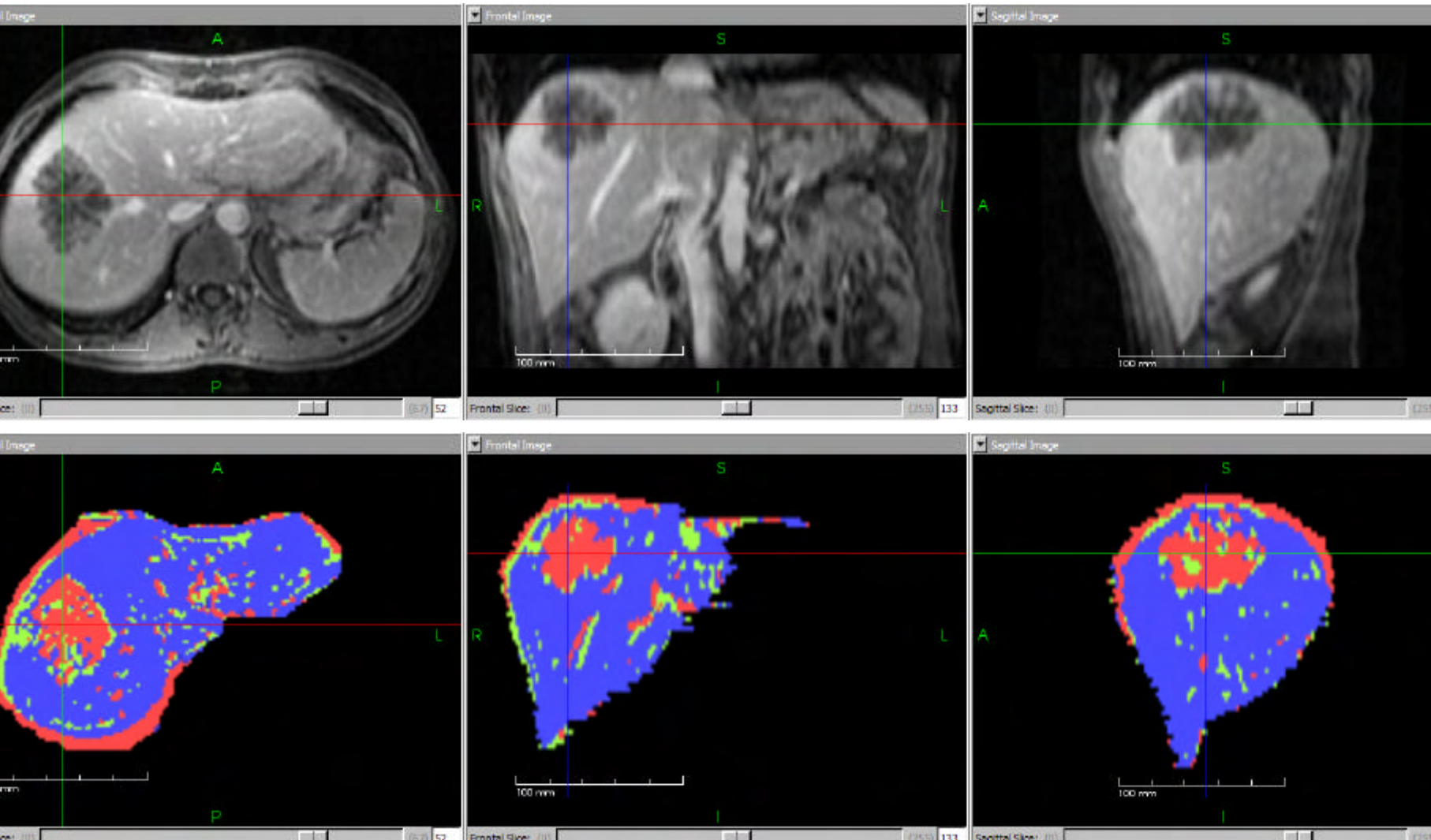
- pre-HIFU:
  - Solitary focal abnormality
  - Lobulated peripheral margin and internal mixed signal
  - Appearance consistent with central necrosis
- post-HIFU:
  - Mixed signal internally
  - Internal intralesion haemorrhage
  - FAME, significant interval signal change consistent with post ablative necrosis
  - Peripheral perilesional enhancement
  - Focal perfusion defect
  - Minor degree of overlying subcutaneous oedema at the site of HIFU treatment

# Gross histological specimen

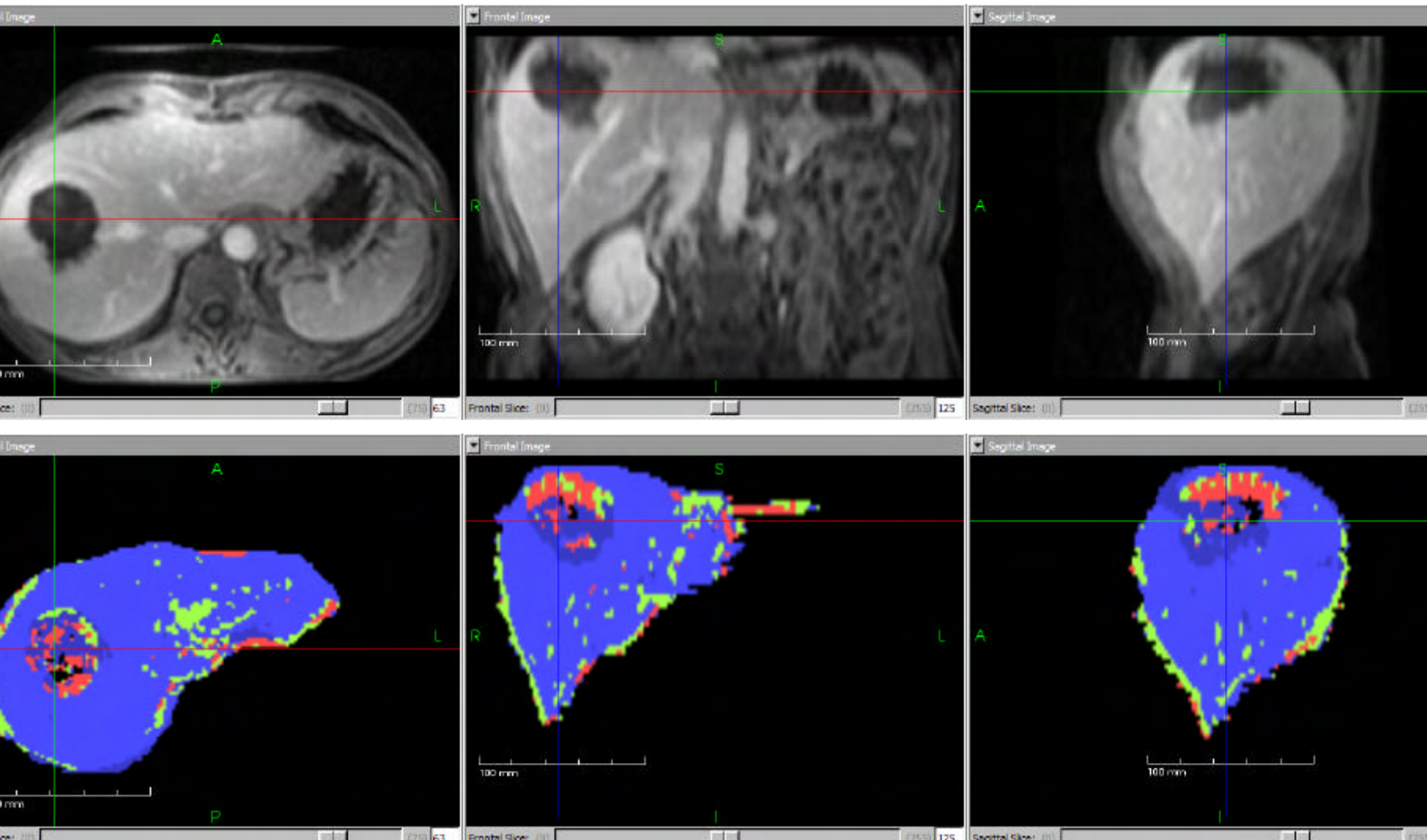




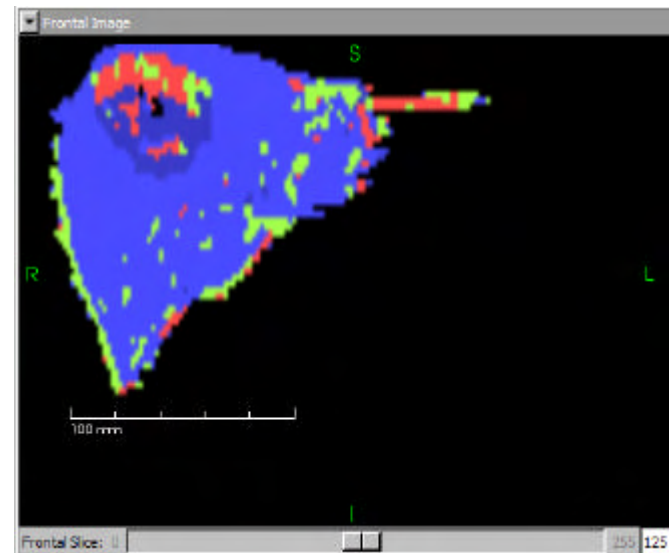
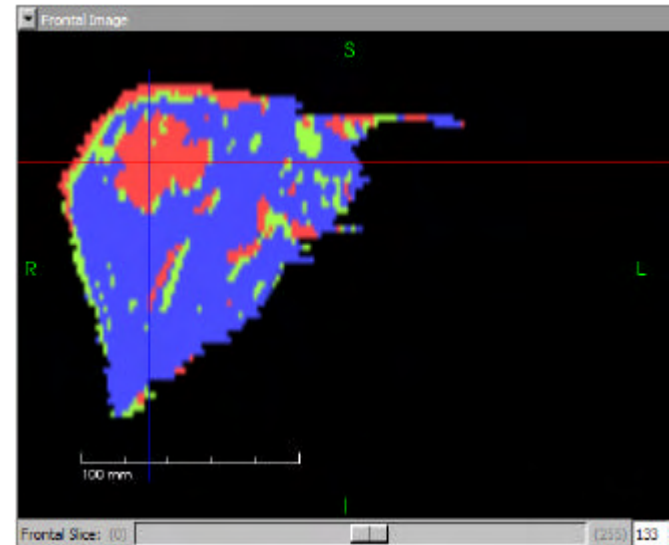
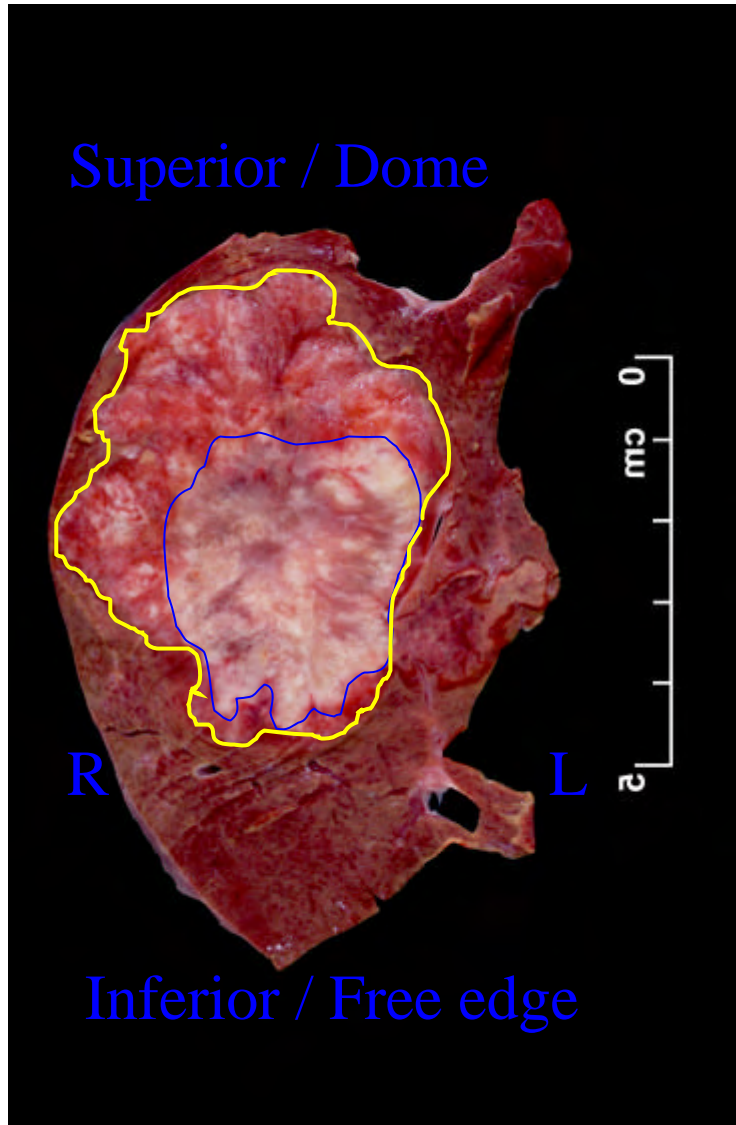
# DCE-MRI (pre HIFU)



# DCE-MRI (post HIFU)



# Correlation pre-/post HIFU and histology

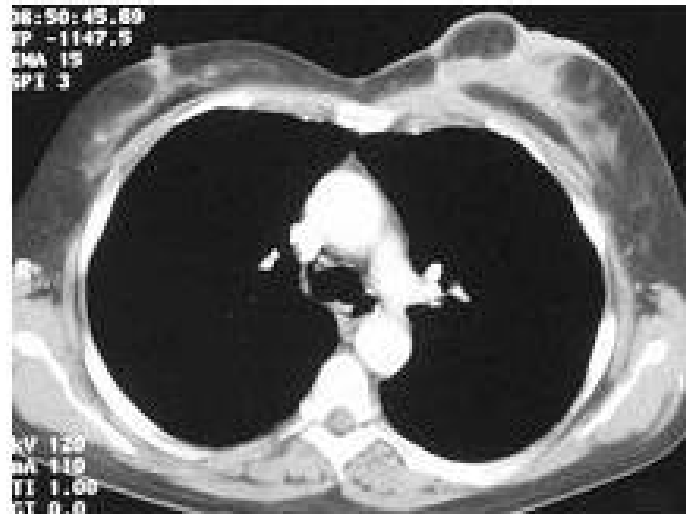
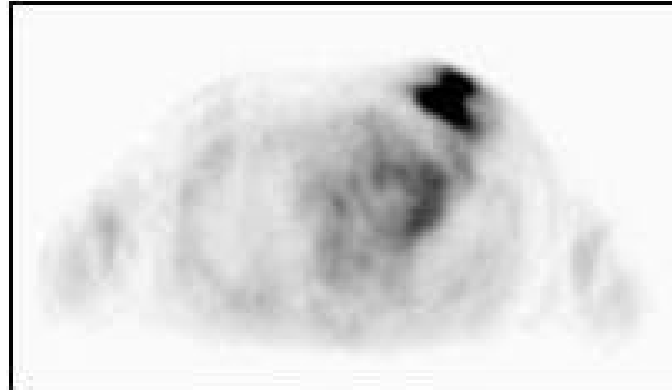


# Cancer has many facets

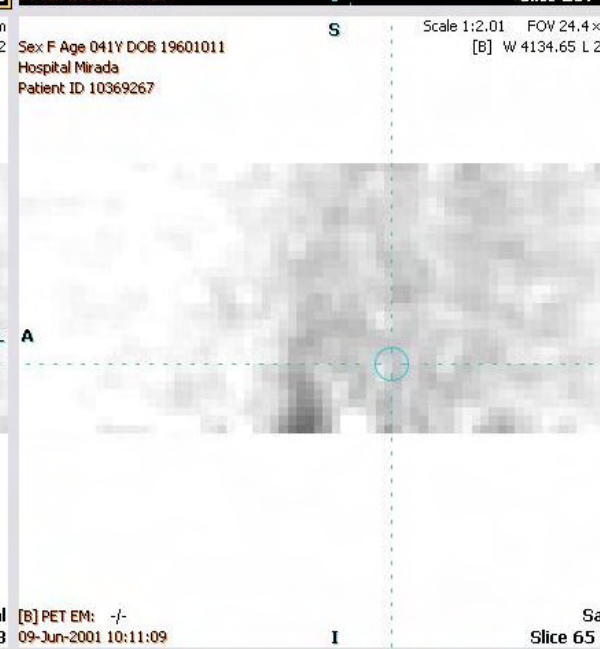
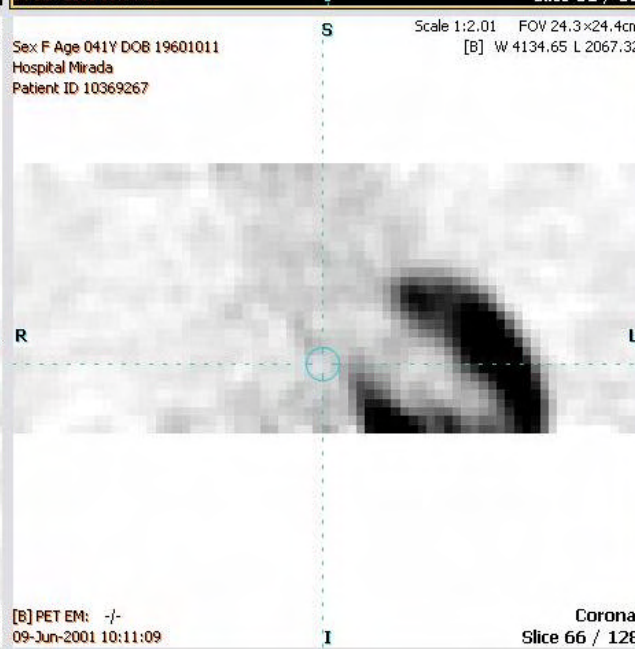
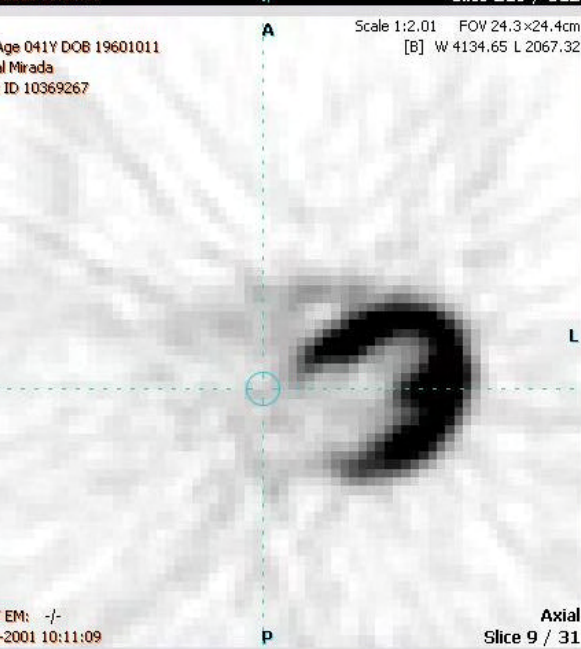
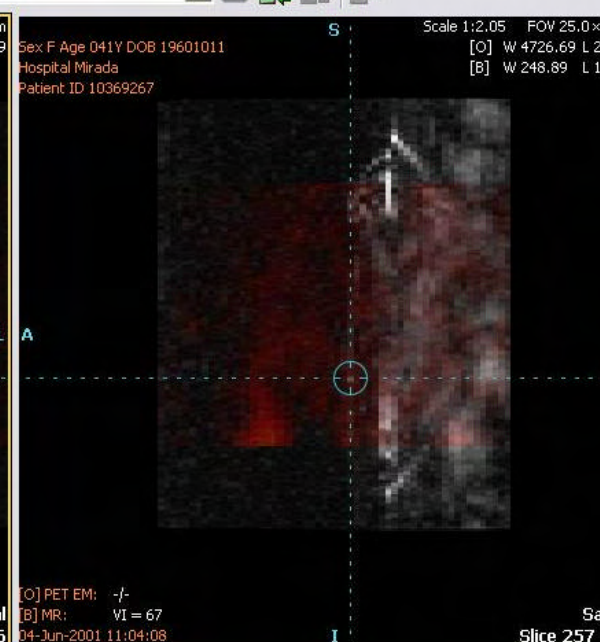
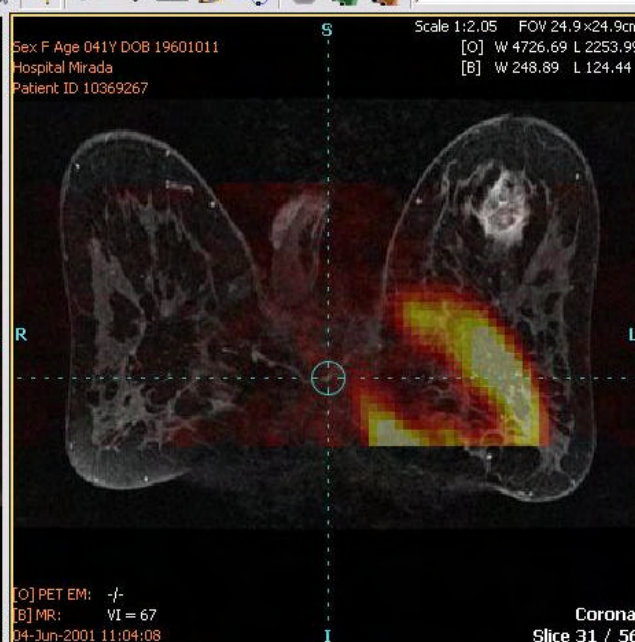
Cancer tissue is radiologically dense, microcalcifications	mammography
Cancer tissue is biomechanically dense	ultrasound
angiogenesis	ceMRI, more recently BOLD MRI
Cancers have massively elevated need for food, eg glucose	FDG-PET, SPECT
Cancer cells divide rapidly	FLT-PET
Cancers are most dangerous when they metastasise	Whole body PET
Cancers can control their local acidity (pH)	ce-MRI with pH-sensitive & pH-insensitive Gd-DTPA
Cancers grow hypoxically	PET + nitroimidazoles (FMISO, FAZA, FETNIM), Cu-ASTM, ...

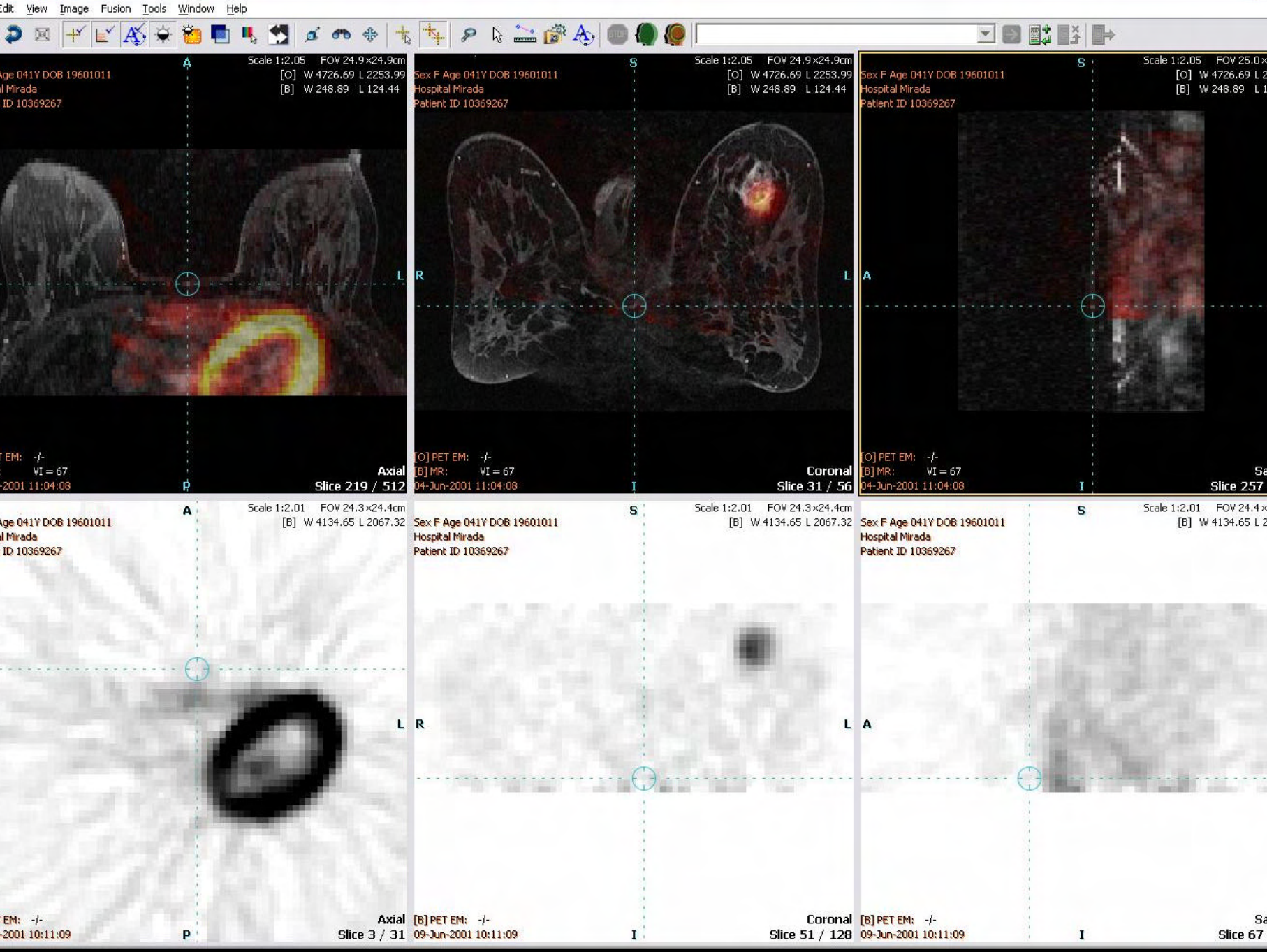
Image fusion is increasingly key to the clinical patient management of cancer

# PET & CT Breast cancer











# Need for models

To build systems that really work (24/7, 99%, few FP), we need to mobilise **knowledge** about – image formation, anatomy, physiology, disease processes, ...

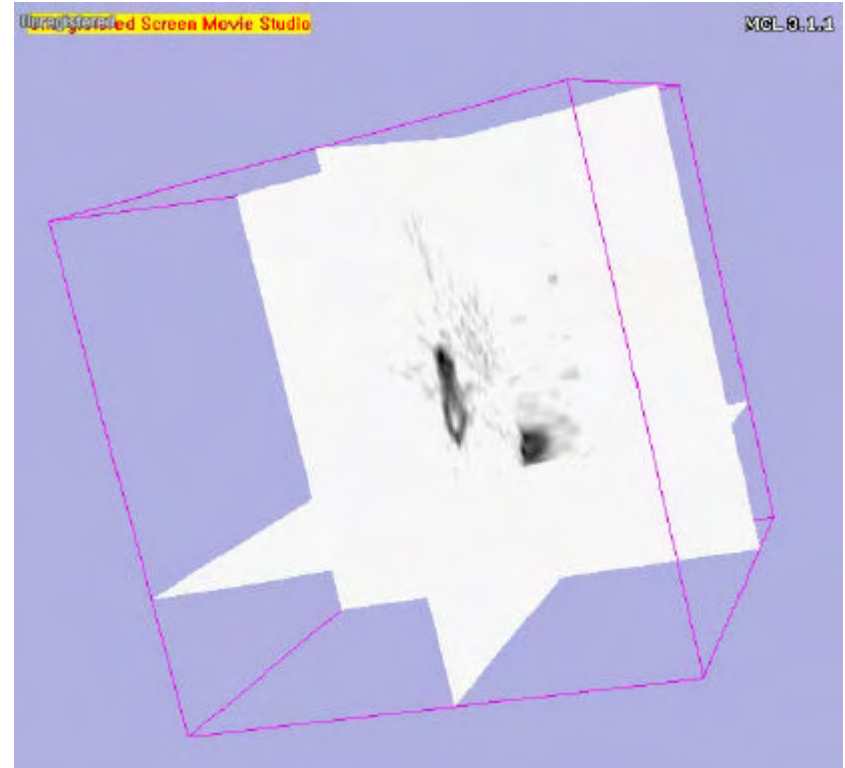
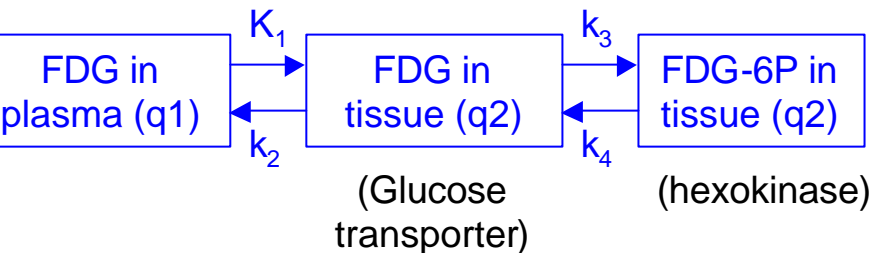
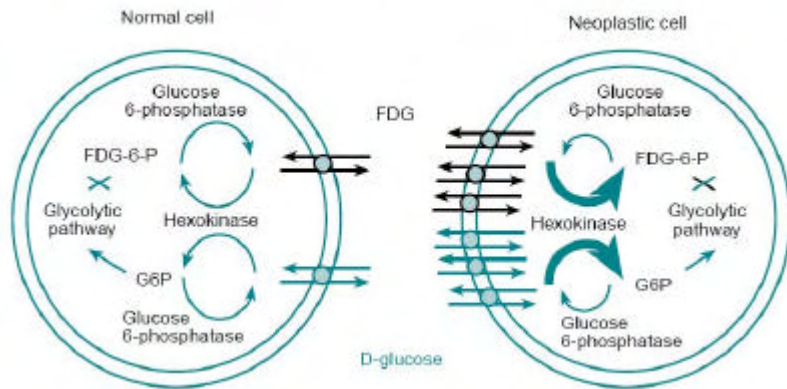
- ***Models of image formation:***
  - passage of x-rays through breast tissue
  - pharmacokinetic models for dynamic contrast enhanced MRI;
  - dynamic PET reconstruction and PK
- ***anatomy:***
  - Segment colorectum, find mesorectal fascia & lymph nodes
  - Liver segments
- ***physiology:***
  - tumour segmentation in dce MRI and FDG-PET
  - constrain non-rigid registration of pre- and post-chemotherapy images of the colorectum

# Model-based PET segmentation

PET image noise model (inside and outside tumour)

+

Pharmacokinetic model of  $^{18}\text{F}$ FDG take up



Level set method (optimisation to solve regularised differential equation)

# Breast cancer

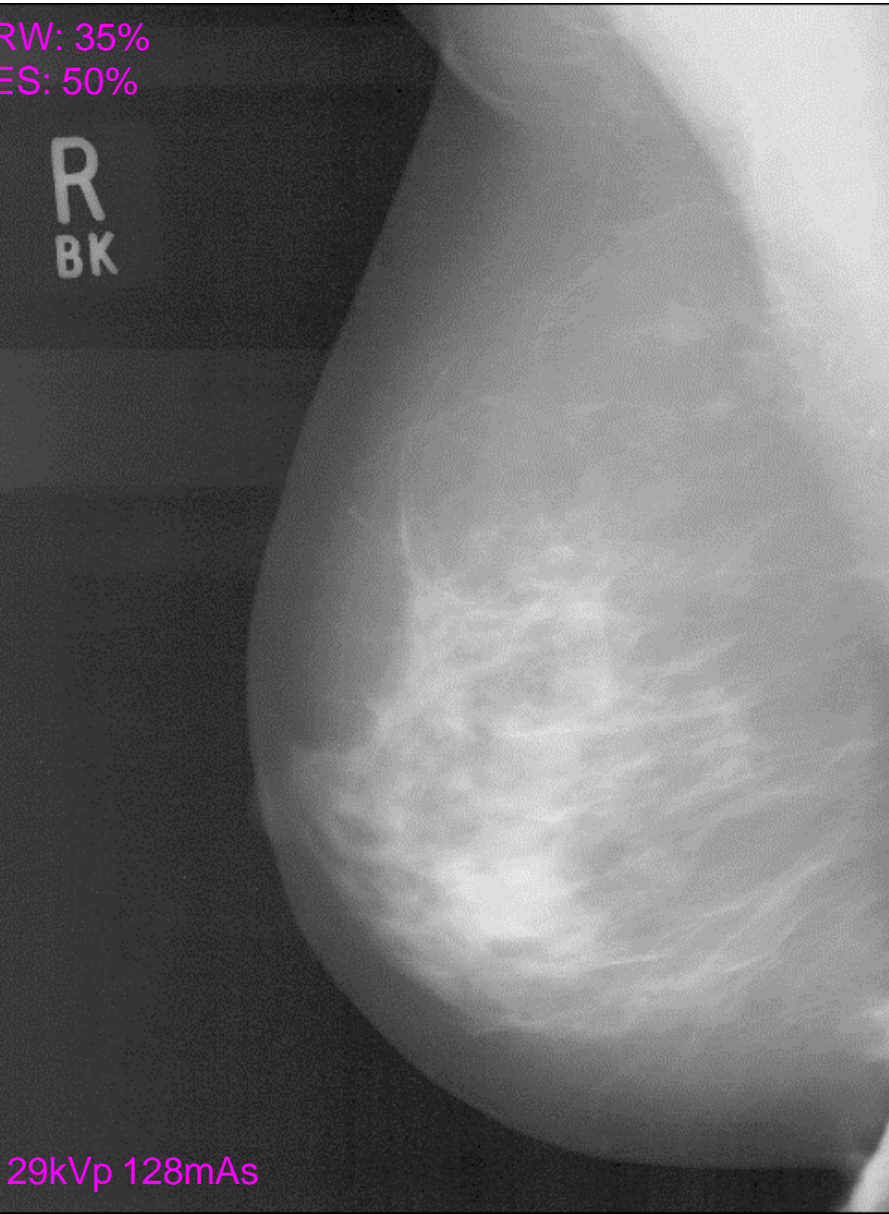
- Mammography
  - Imaging parameters → estimate attenuation
  - non-rigid temporal registration of mammograms
  - Texture analysis
  - estimating breast density and breast cancer risk
- dceMRI
  - Need to estimate T1
  - PK modelling
  - Motion compensation
  - simultaneous segmentation and registration
- Breast ultrasound: elastography
- Tomosynthesis
- (Fusion
  - Mammography & MRI)



# Image Parameter Dependence

RW: 35%  
ES: 50%

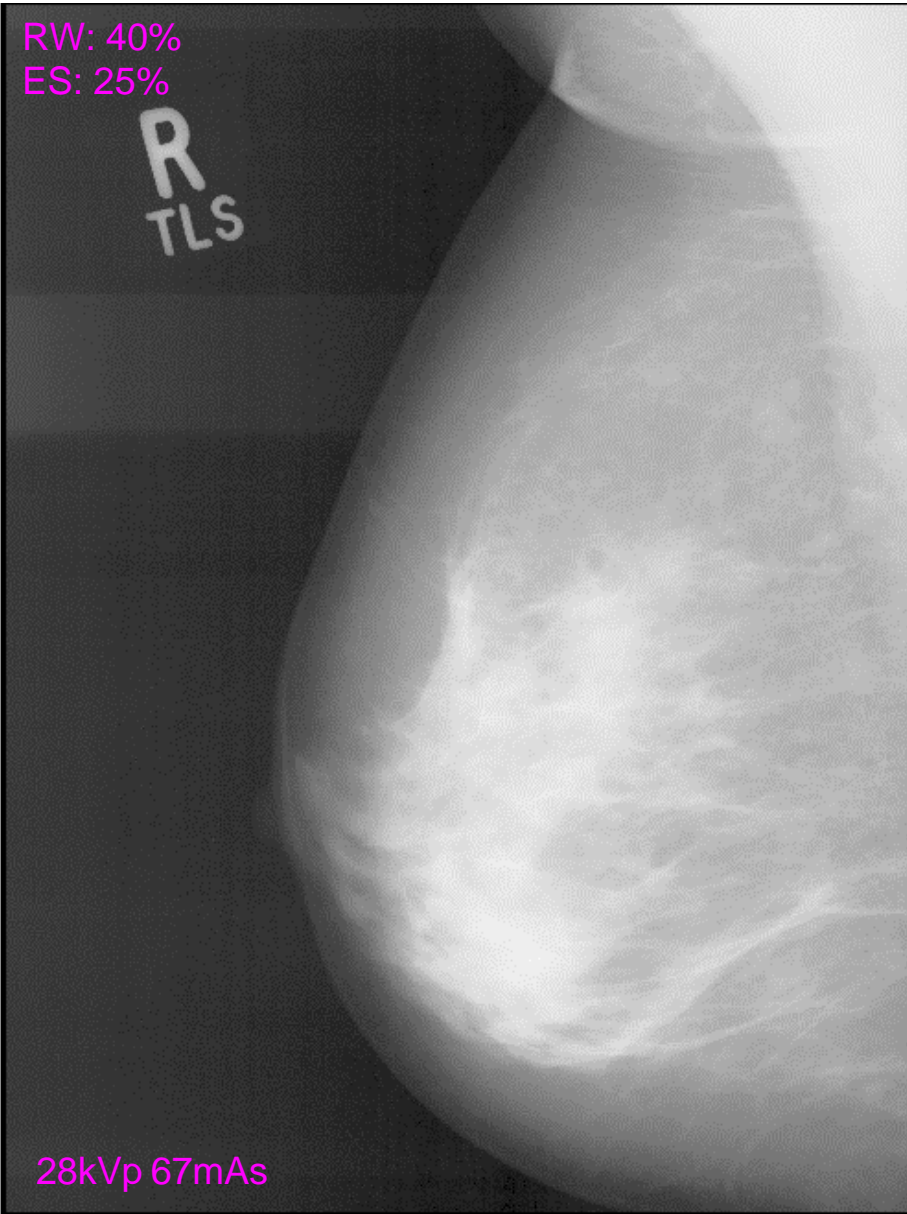
R  
BK



29kVp 128mAs

RW: 40%  
ES: 25%

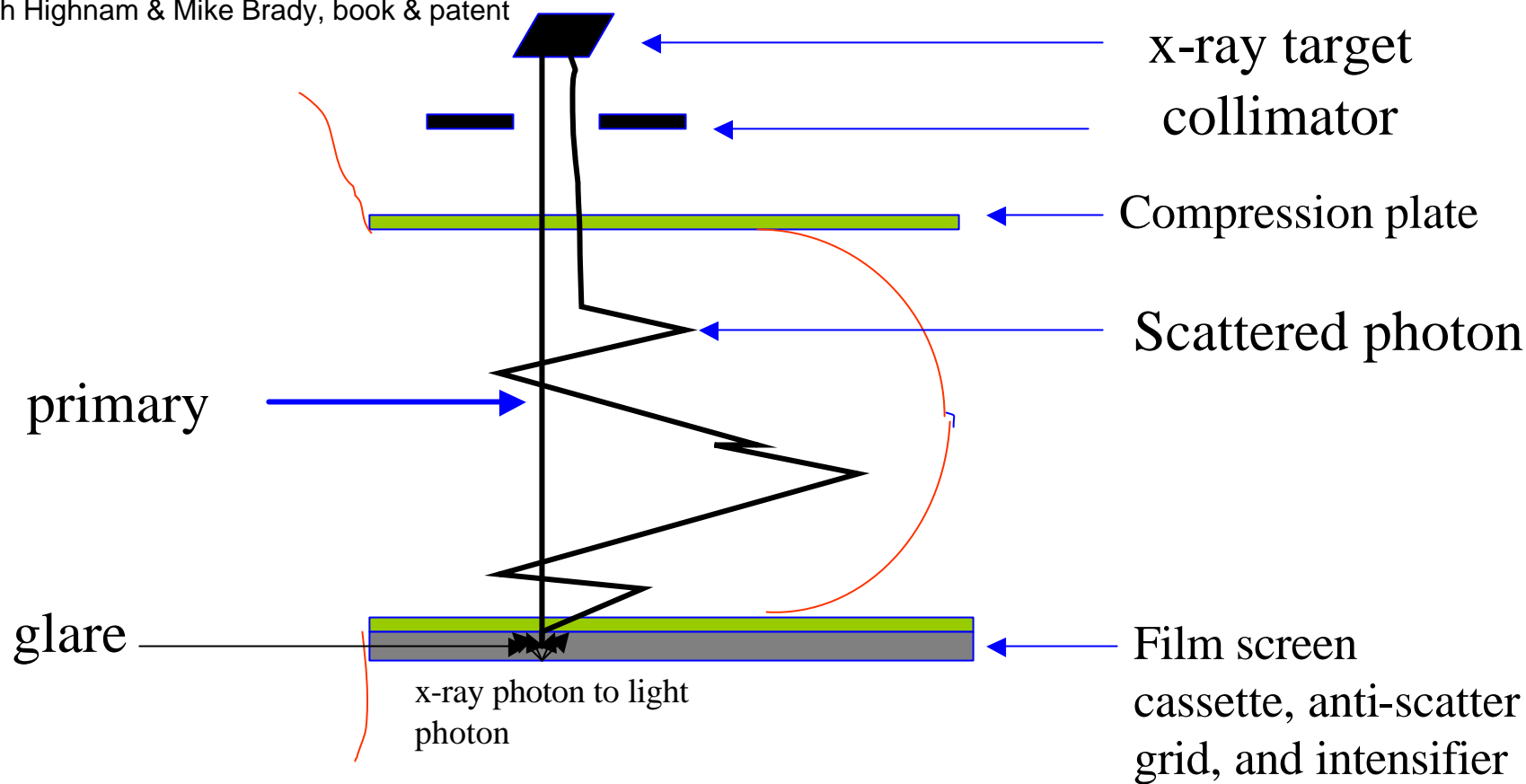
R  
TLS



28kVp 67mAs

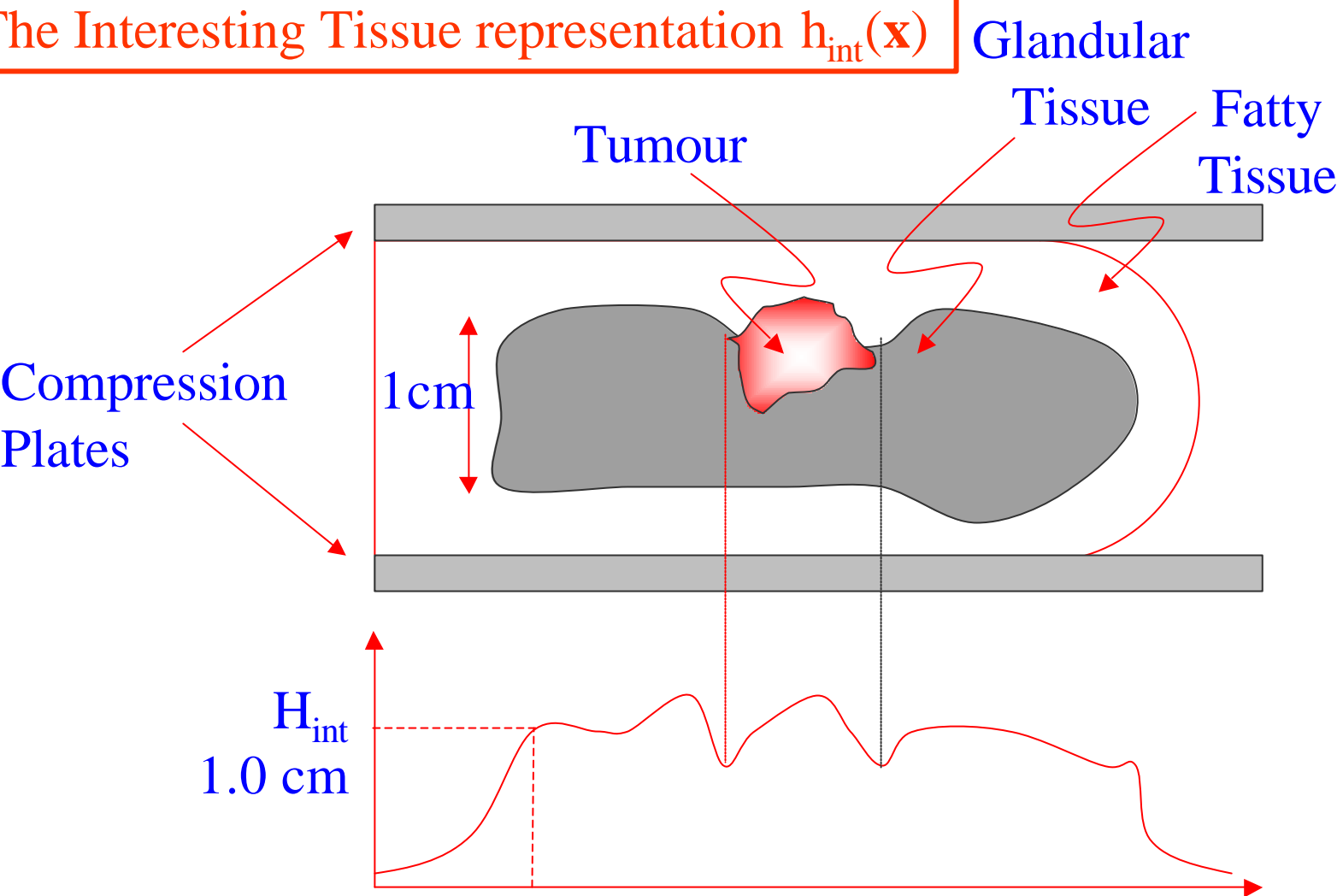
# The model: image formation

alph Highnam & Mike Brady, book & patent



Complicated by factors such as: extra focal radiation, anode heel effect, beam hardening, screen mammography (shown here) and full-field digital mammography, enabling successive images to be compared meaningfully.

The Interesting Tissue representation  $h_{\text{int}}(\mathbf{x})$



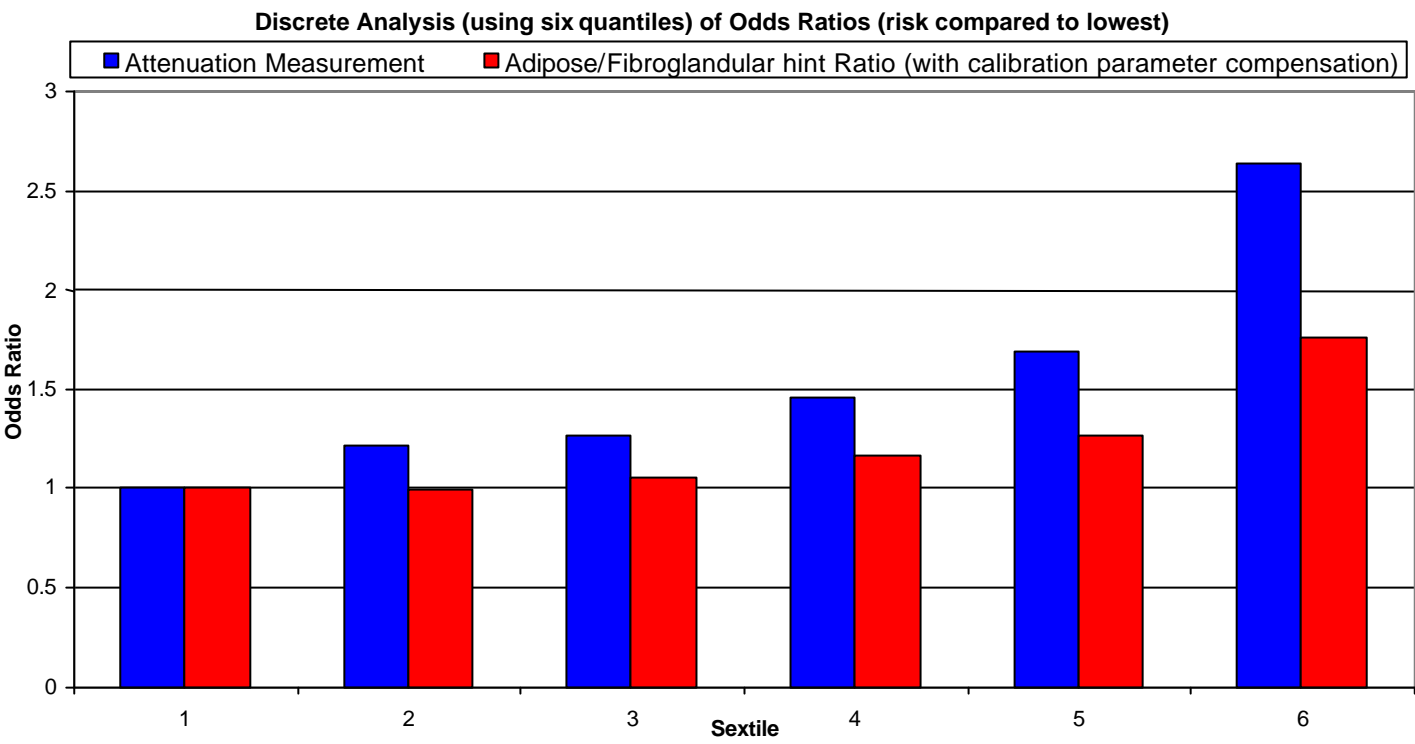
This is a quantitative representation of non-fat breast tissue. If we assume just two classes – fat vs “interesting” – microcalcifications violate a physical constraint

Tommy and I have recently completed a second version of the Highnam Brady model, and shown how to correlate average attenuation to breast cancer risk

# Performance Comparison

476 Cancers and 1815 Controls on digitised film with full acquisition details.

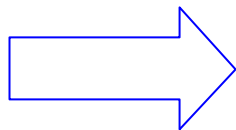
Technique	Odds Ratio Coefficient	Std. Err.	z	P>z	95% Conf. Interval	
%h <sub>int</sub> (GenerateSMF_v2.2)	1.116	0.0357	3.44	0.001	1.048	1.188
Attenuation Measure	1.309	0.0684	5.17	0	1.182	1.451



Two-tailed P-value from 't' test: 0.01

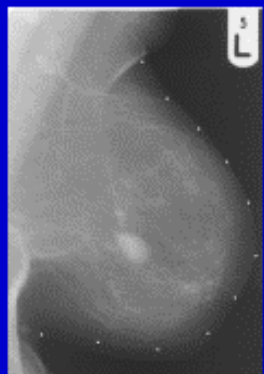


Mammogram fragment

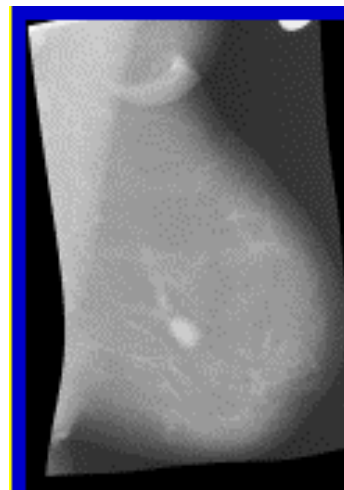
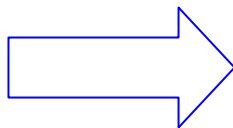
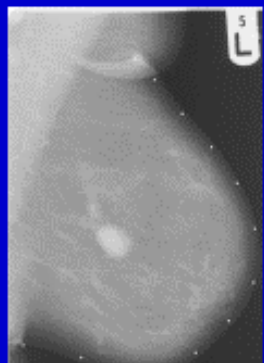


Detected microcalcifications

First visit



Second  
visit; two  
years later



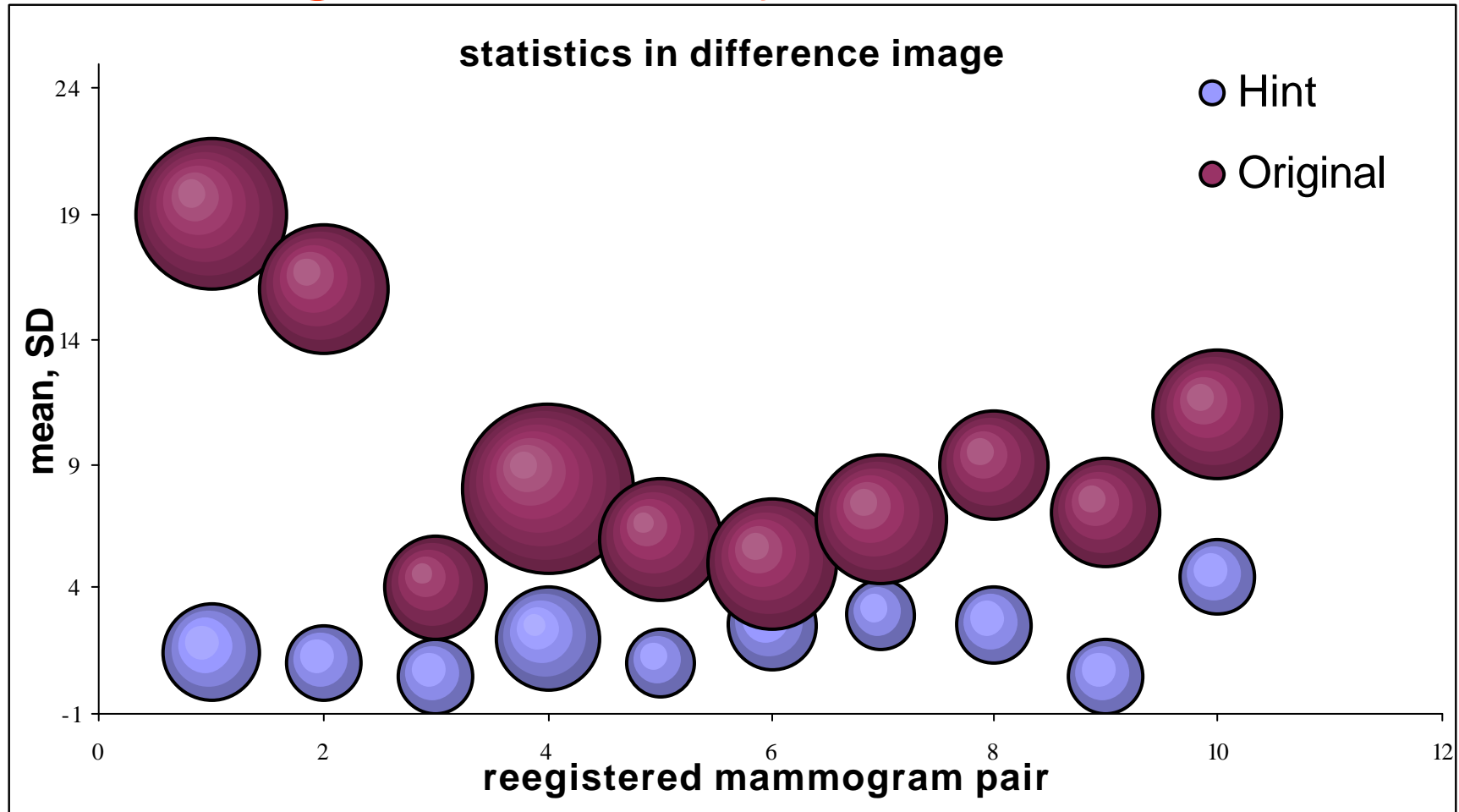
Second image  
registered to  
coordinates of  
first image



Difference image  
*after* registration  
quantitative  
assessment



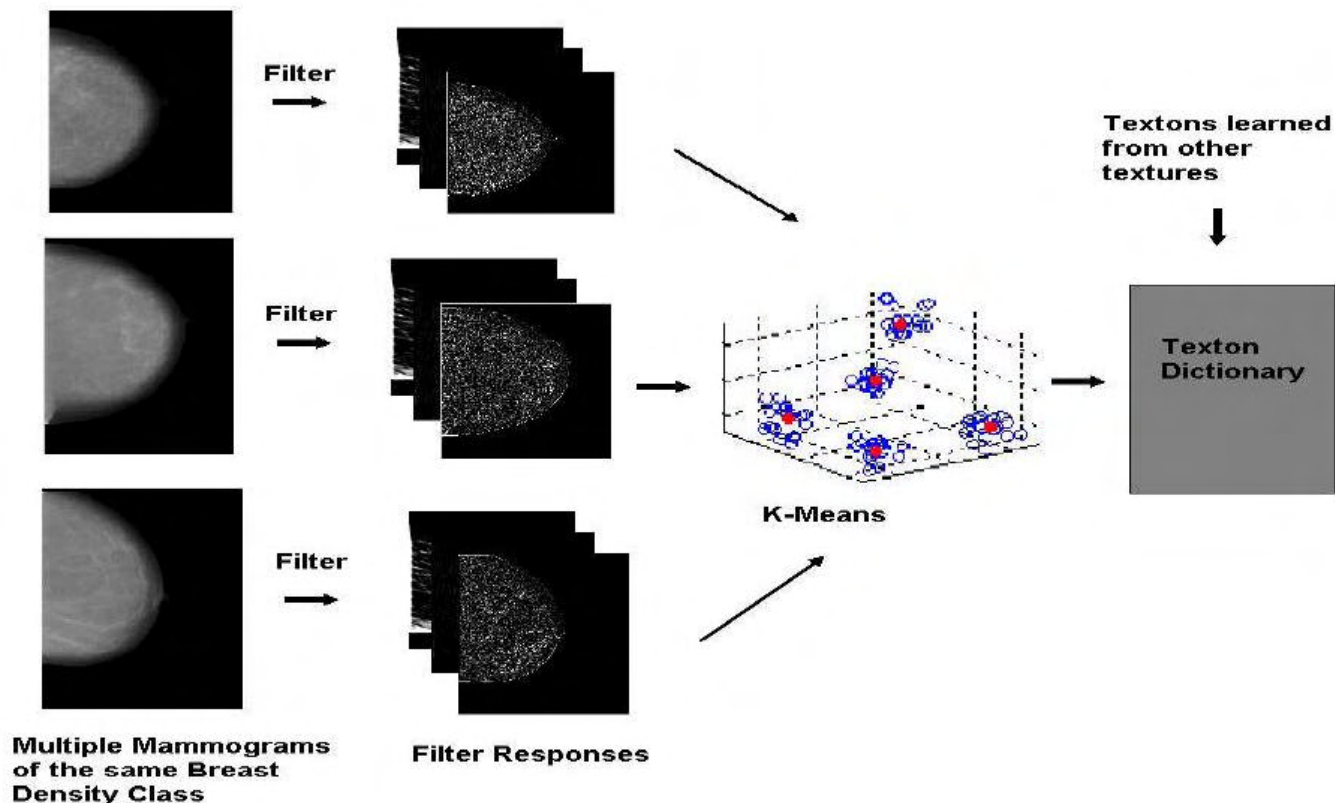
# improvement in temporal registration if you use SMF



Results for 10 pairs; SMF consistently lower mean, SD and variation in these

# Learning breast (texture) patterns

Regions of dense tissue are textured in characteristic ways. We seek to make the intuitive concept of “texture” mathematically & computationally precise. To do this, we **learn** texture descriptions for mammograms from each of a number of “classes”



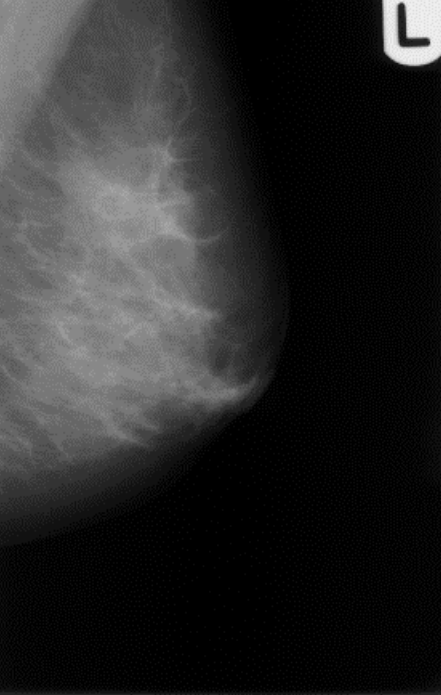
Multiple texton descriptions are learned for each trained class. We have replicated the results for: Wolfe, BIRADS, SCC.

# Classifier results

(single class to entire mammogram)

Accuracy %	N1	P1	P2	DY
Four density classes	91	64	70	78
N1&P1 vs P2&DY	94%		94%	

N = 132, two independent readers, both experienced screening radiologists



Segmentation  
of  
mammogram  
into textured  
regions  
according to  
textons (using  
a HMRF)



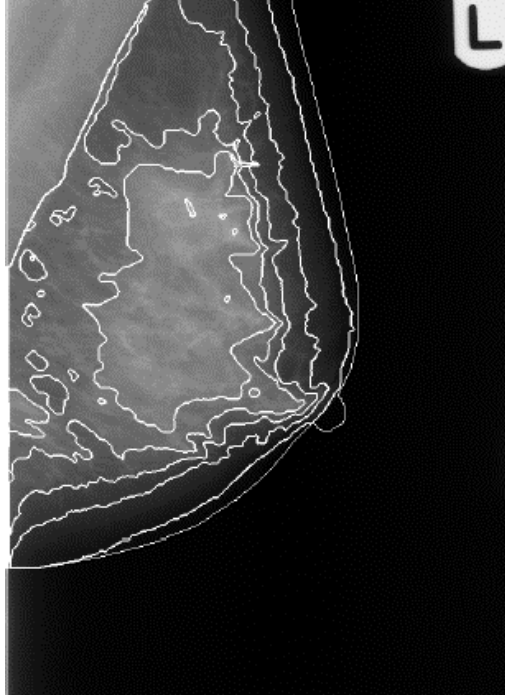
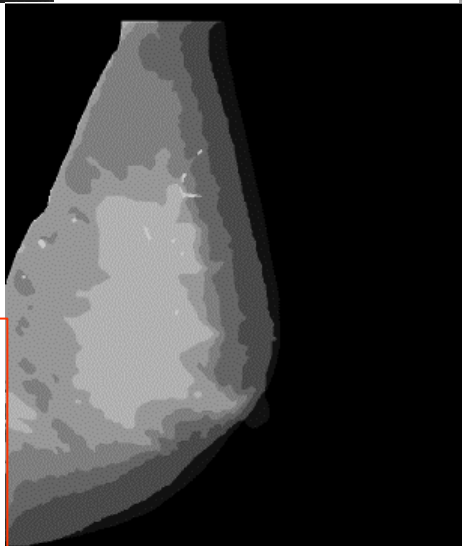
Original  
mammogram

Density accuracy:

Dense = 96.7%

Fatty = 93.8%

Edge = 92.8%



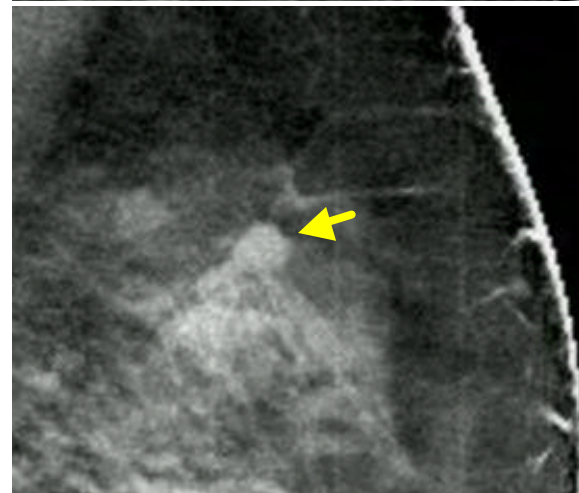
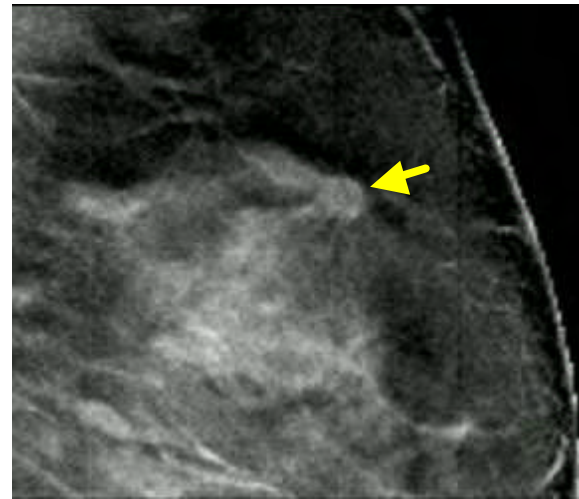
Texture regions  
sketched on  
mammogram by  
experienced  
radiologist (RW)



Texture regions  
superimposed on  
the original  
mammogram



# Digital mammo (left) vs Tomosynthesis (right)

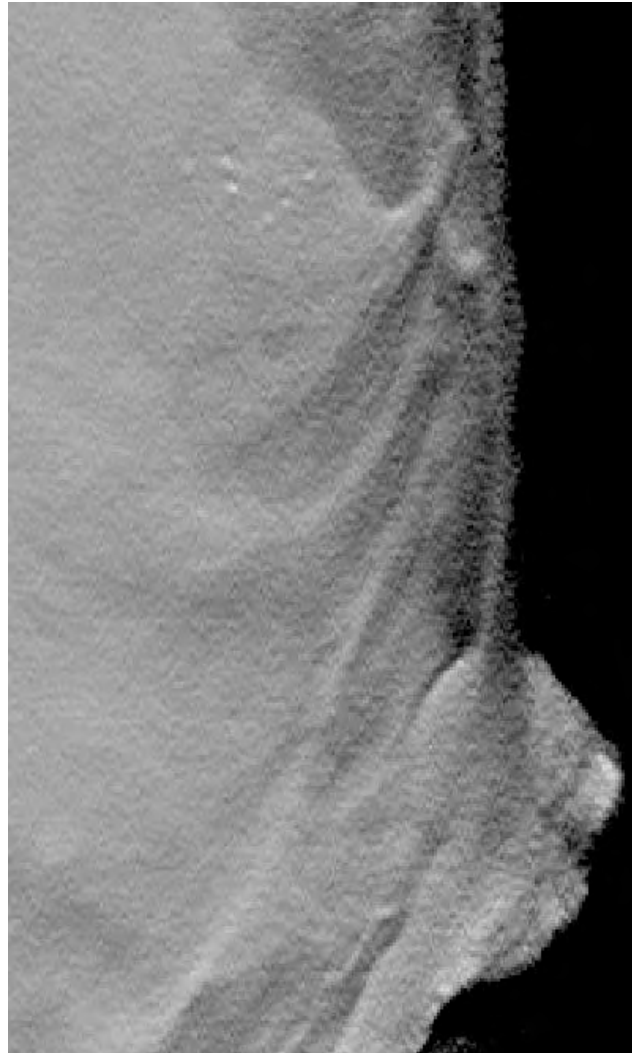


Imaging performed  
at MGH

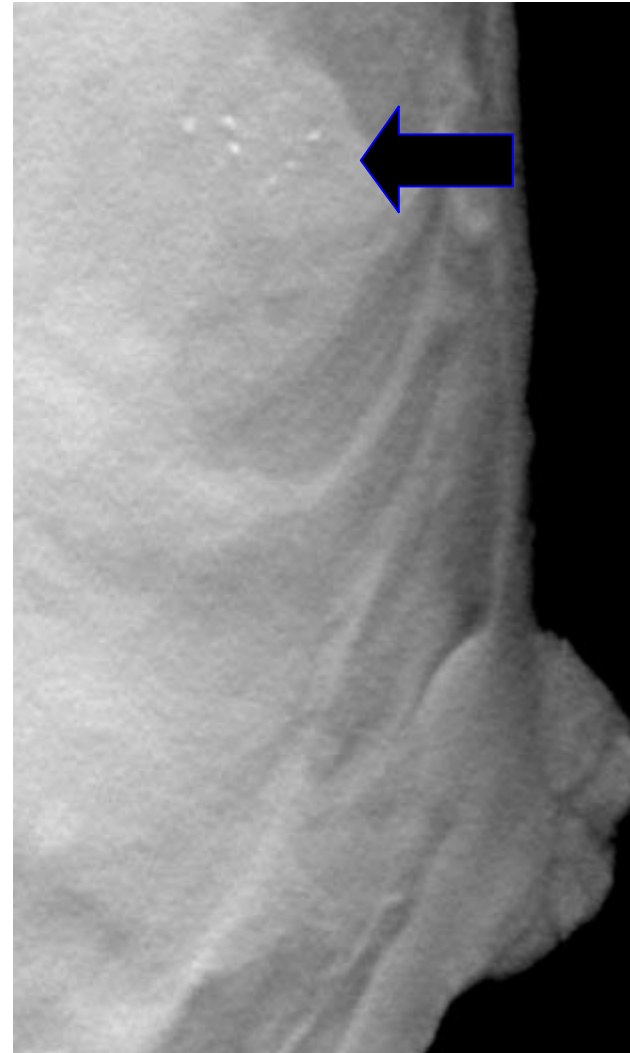
On the left is a standard 2D image which showed a single cancer. The two tomosynthesis images on the right show two different planes in the same breast. In the top right the first cancer is now more easily identified. In the bottom right a second cancer not seen in the 2D image is easily identified.

# 3D Reconstruction Methods

Dexela's high-speed iterative reconstruction methods can lead to substantial improvements over standard methods



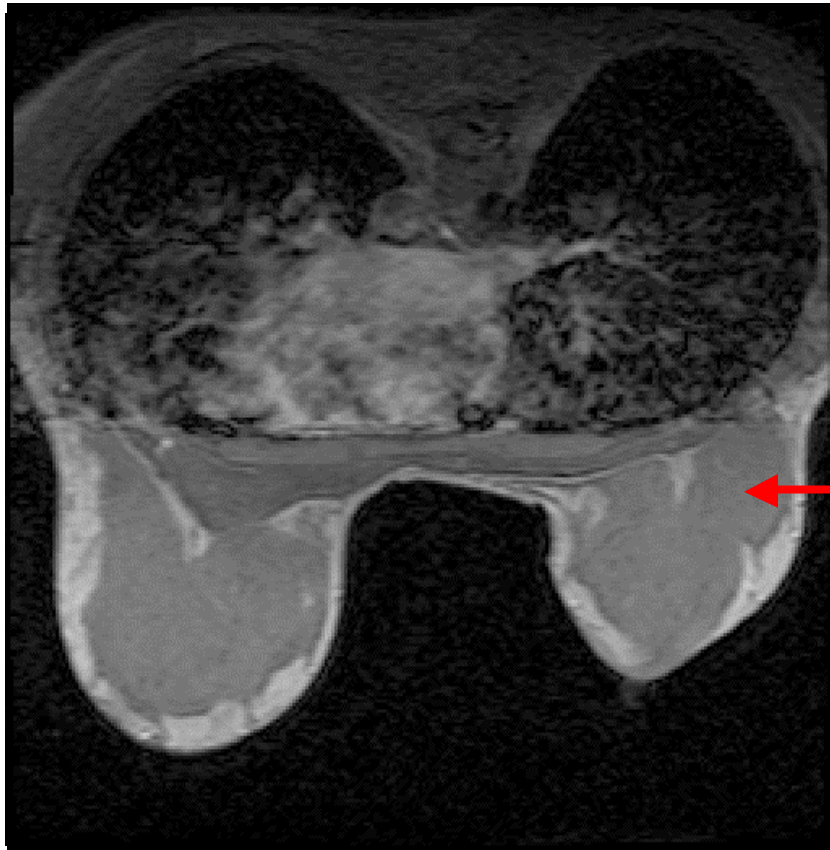
Filtered Back Projection (standard recon method)



Dexela's recon shows cluster of tiny calcification



# Limitation of anatomical imaging

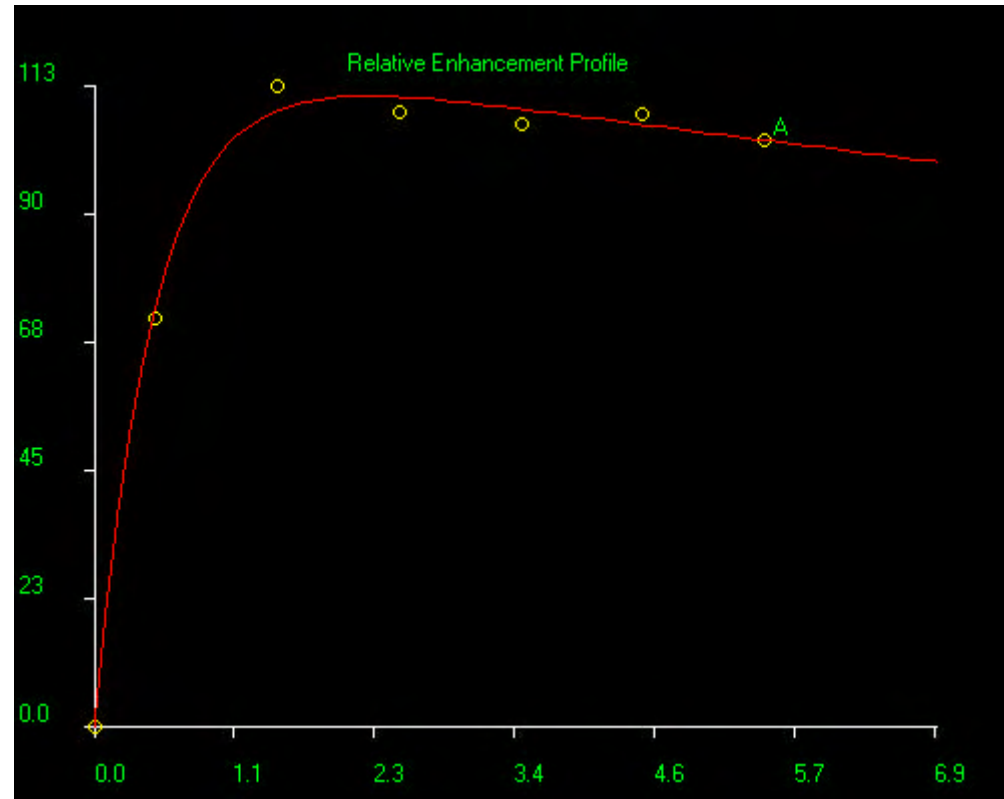
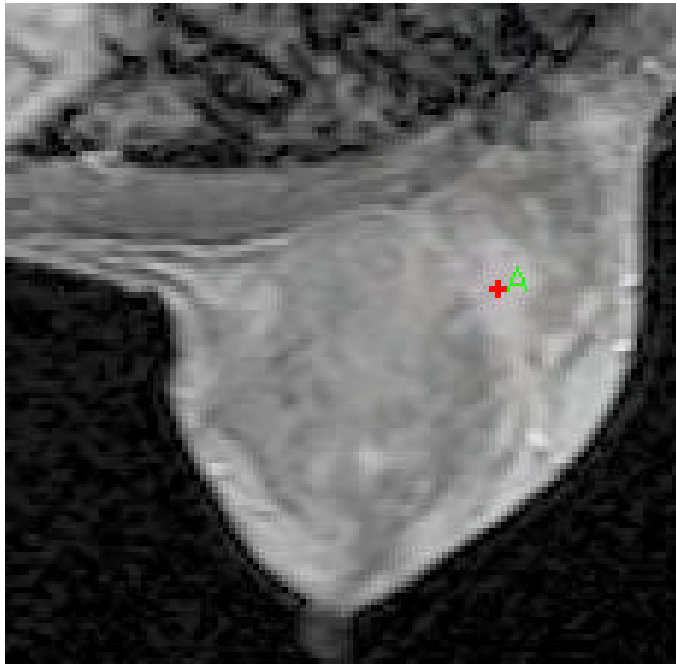


There is a massive adenocarcinoma just there – with secondary spread

The tumour cannot be differentiated by its  $T_1$ ; conventional MRI gives information about anatomy **not** physiology

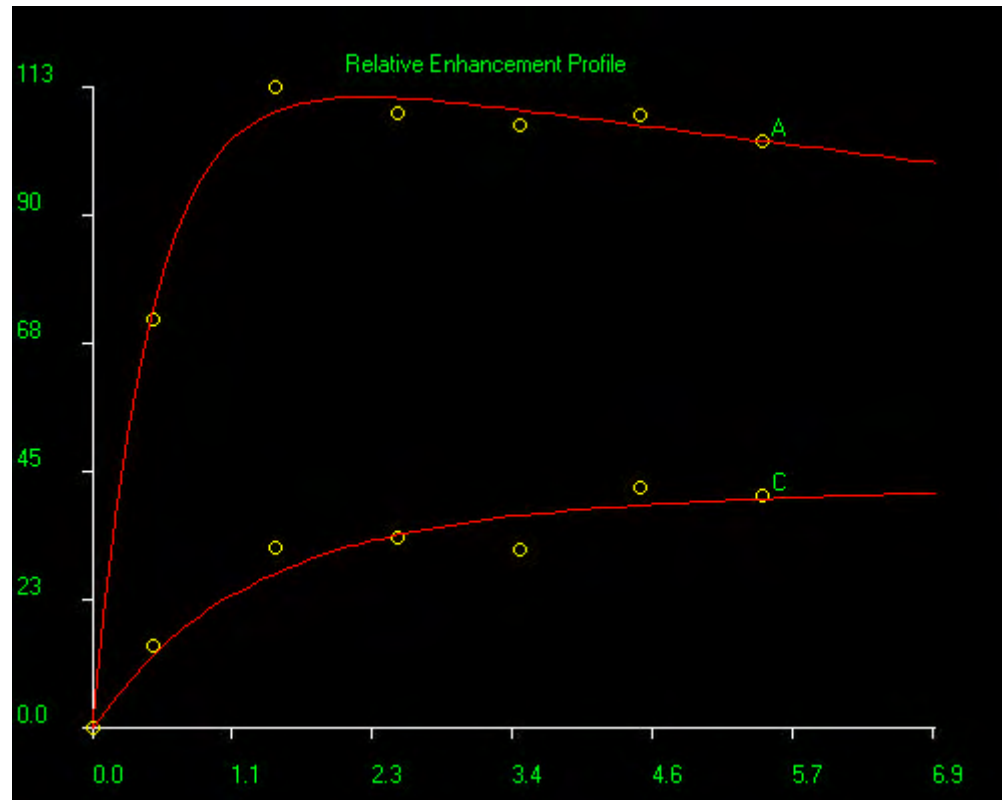
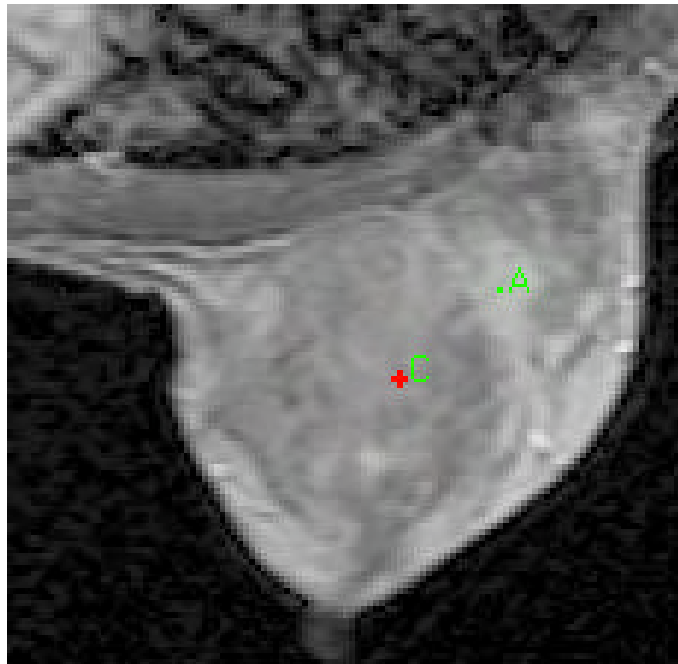
Solution is to use a contrast agent

# Contrast agent take-up



Inside the tumour, the enhancement is over 100%

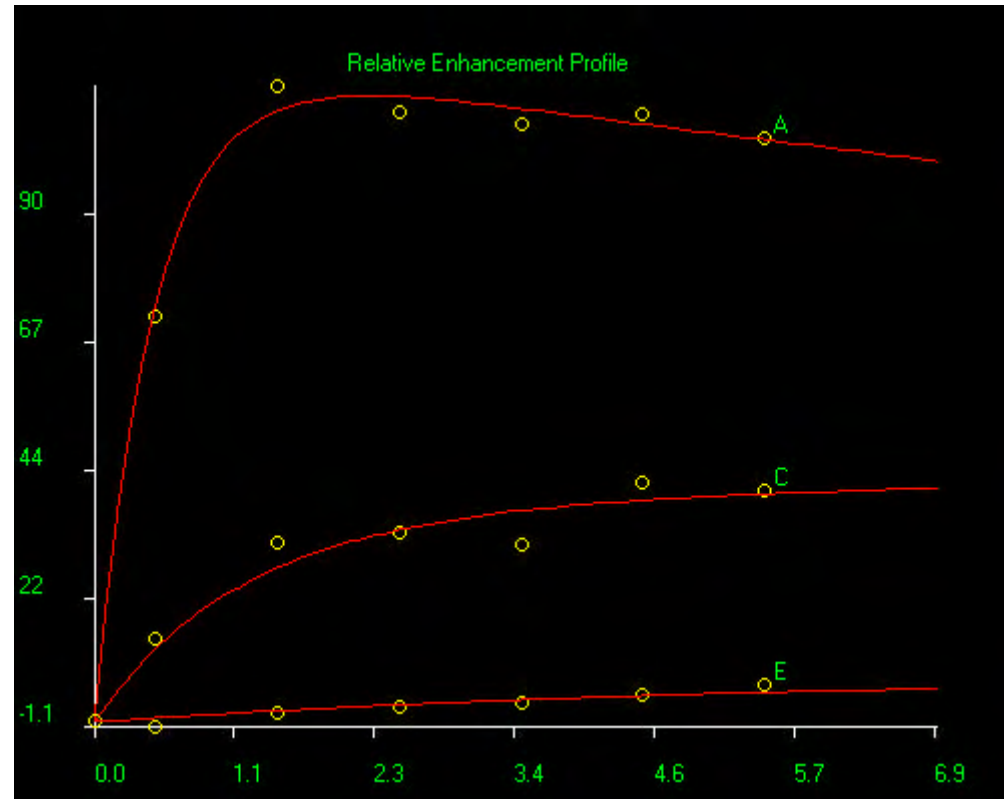
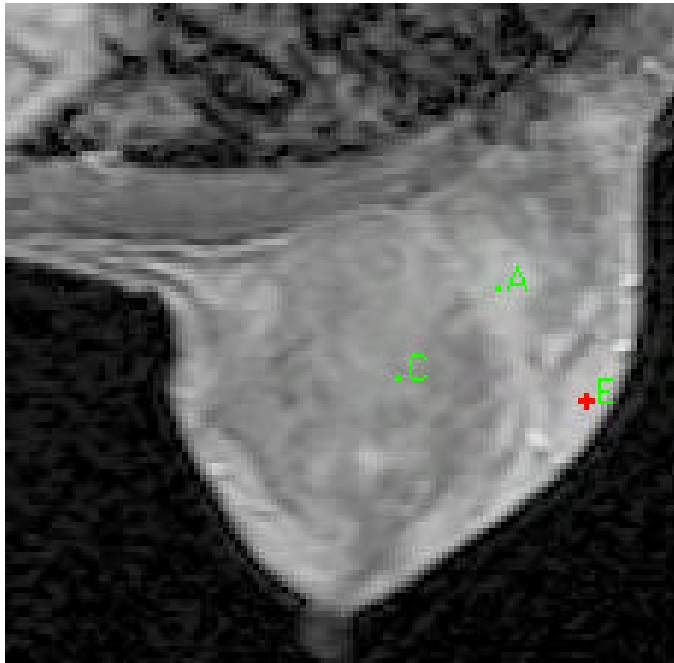
# Contrast agent take-up



.. Normal tissue enhances less

# Contrast agent take-up

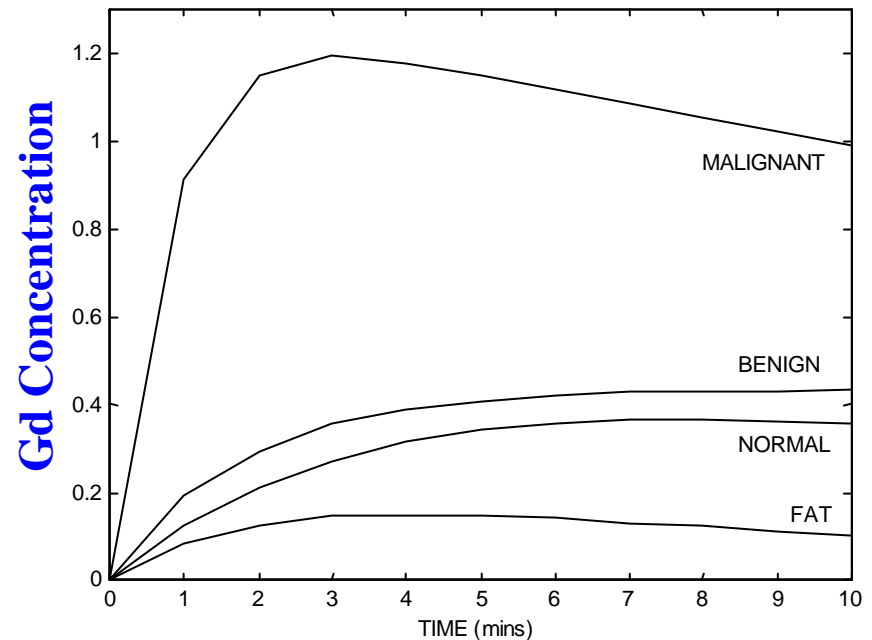
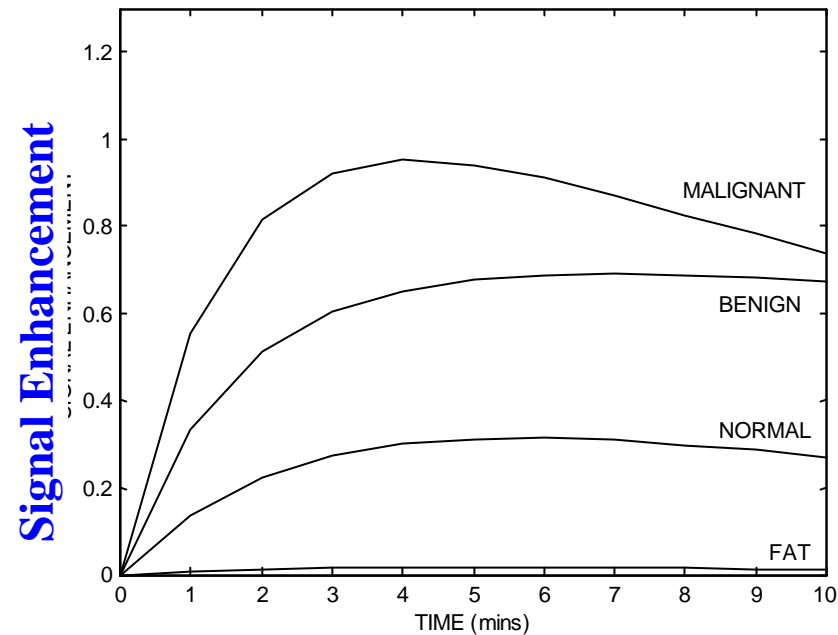
Unfortunately, some benign tissue can enhance more than malignant, and the amount of uptake is highly variable, making quantitative analysis difficult



Reason: contrast agent take-up is non-linearly related to intensity change

# Contrast Agent Uptake Profiles

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



Gd concentration is approximately proportional to change in T1  $\rightarrow$  estimate T1 and its temporal change. Use as basis for segmentation and PK modelling.

# Gradient Echo Signal Model

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

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

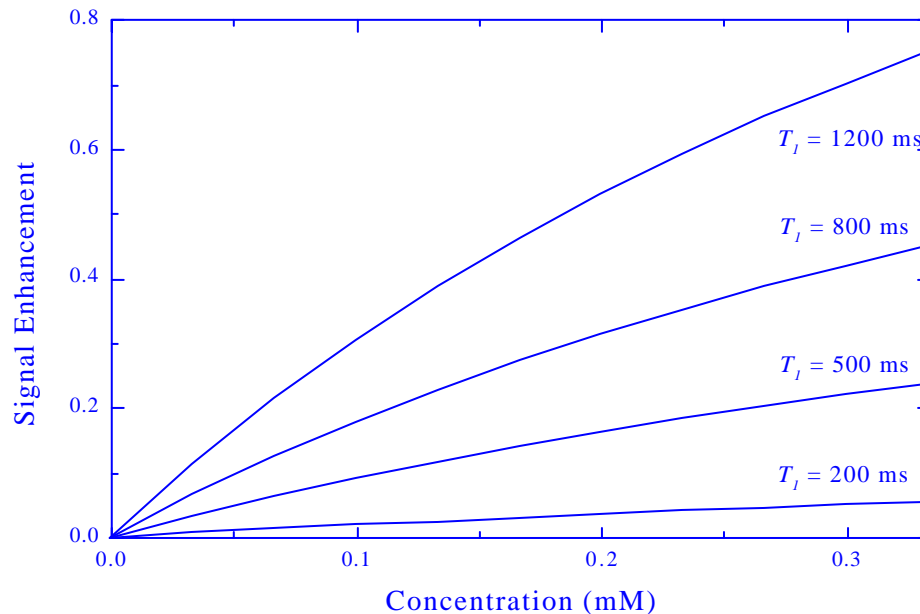
- Add effects of contrast agent ( $T_1$  &  $T_2$  alteration).

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

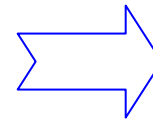


# Signal Enhancement vs. Concentration

$$E(C_t) = \frac{S(C_t)}{S(0)} = e^{-TER_2 C_t} \left( \frac{1 - e^{-TR\left(\frac{1}{T_1} + R_1 C_t\right)} - \cos \alpha \left( e^{-TR/T_1} - e^{-TR\left(\frac{2}{T_1} + R_1 C_t\right)} \right)}{1 - e^{-TR/T_1} - \cos \alpha \left( e^{-TR\left(\frac{1}{T_1} + R_1 C_t\right)} - e^{-TR\left(\frac{2}{T_1} + R_1 C_t\right)} \right)} \right)$$



Nonlinear variation  
with T<sub>1</sub>

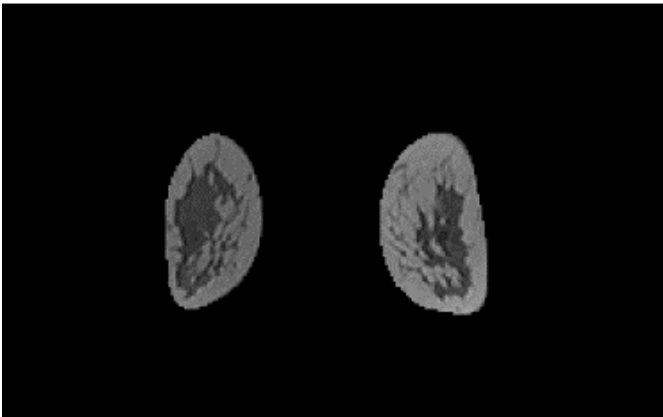


T<sub>1</sub> must be  
measured

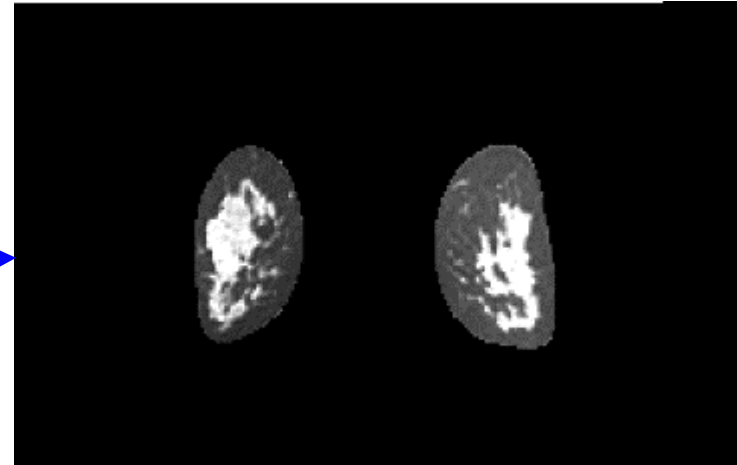
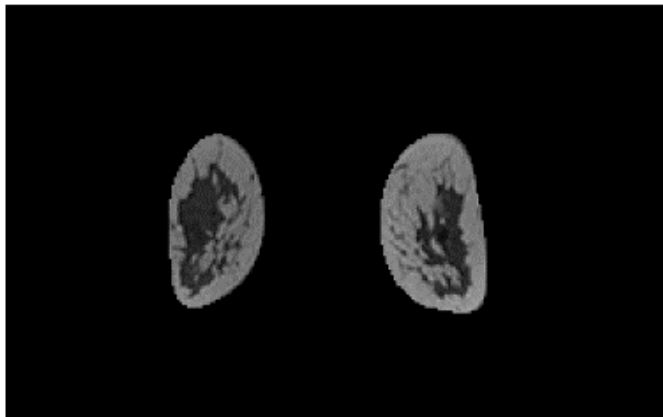
$\alpha = 3$



$\alpha = 10$



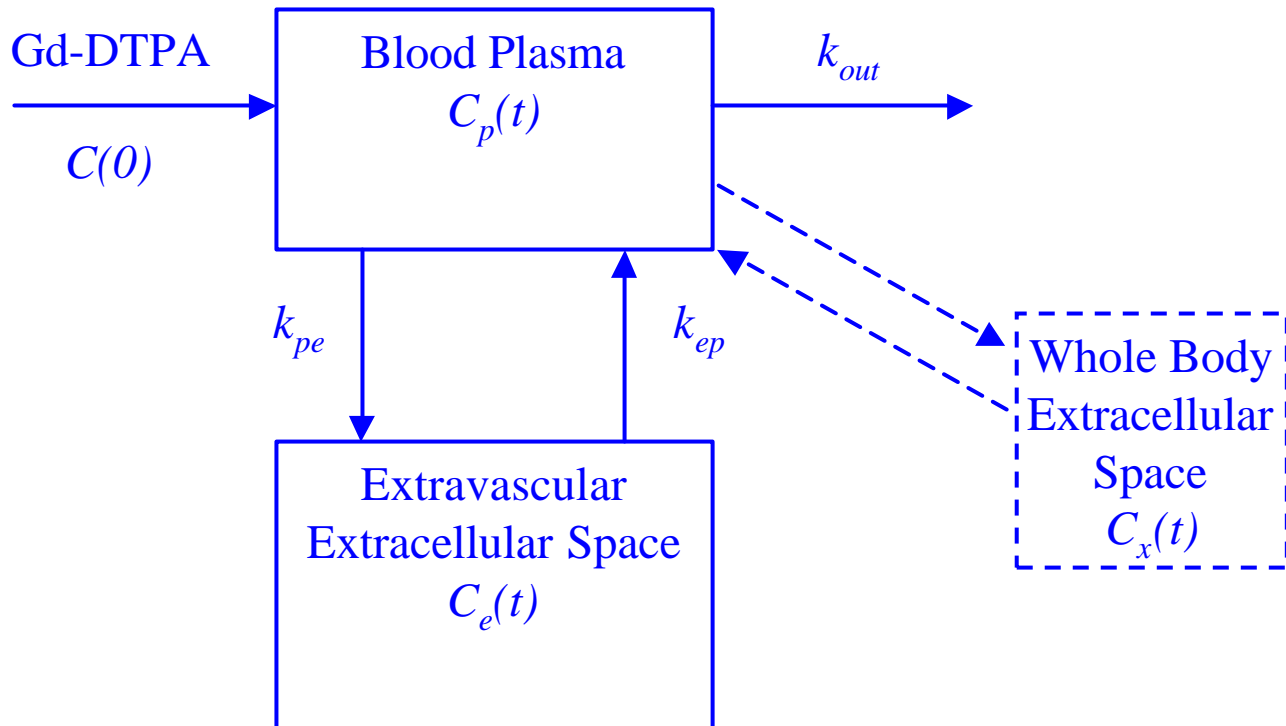
$\alpha = 17$



$T_{10}$  map estimated from three images at left by Ketsetzis and Brady (IEEE TMI) variant to the Armitage, Brady, Behrenbruch method

# Two-Compartment Pharmacokinetic Model

- Models interaction between a blood pool and lesion leakage space (EES).



# Differential Equations

- Conservation of mass leads to :

$$V_p \frac{dC_p}{dt} = k_{ep} V_e C_e - (k_{pe} + k_{out}) V_p C_p + M_{in}$$

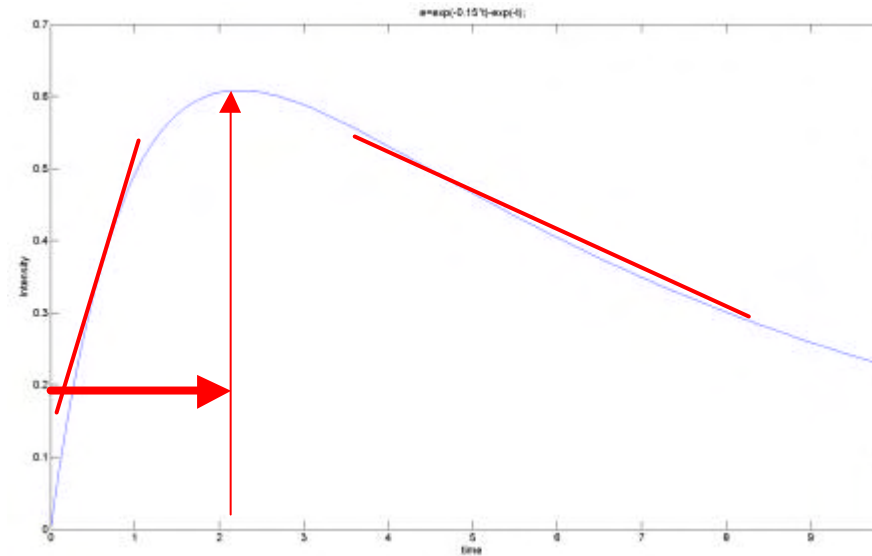
$$V_e \frac{dC_e}{dt} = k_{pe} V_p C_p - k_{ep} V_e C_e$$

- Solution gives the following:

$$C_e(t) = \frac{A}{a-b} \left( e^{-bt} - e^{-at} \right) = f(A, a, b)$$

# Numerical fitting

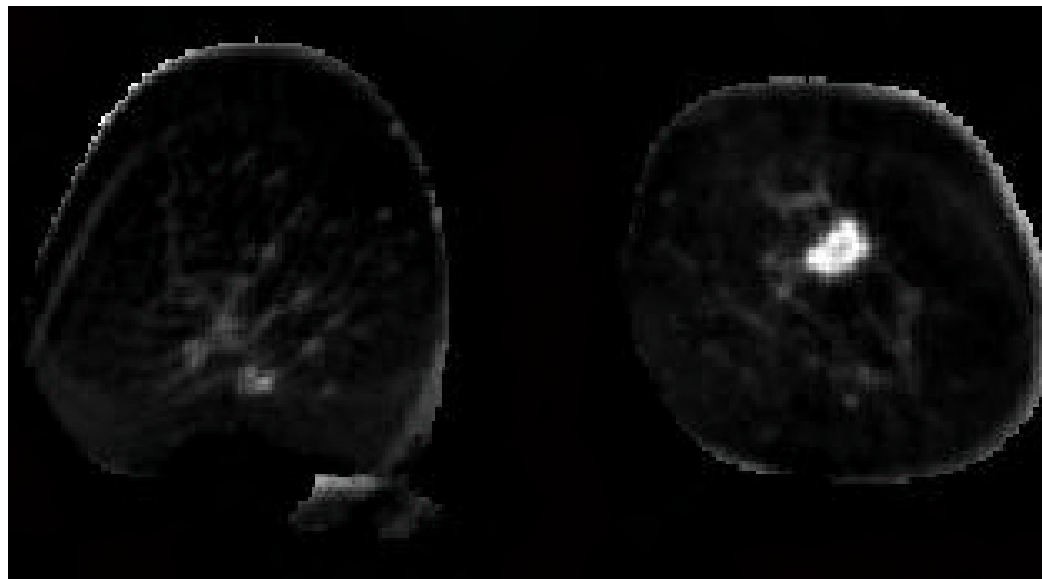
- Sparseness of data → **time to max** is the most appropriate parameter to look at (for the moment!)
- Possible parameters:
  - Uptake slope
  - Washout
  - Maximum % change in intensity
  - Time to max
- **Novel sequences** (Despot) will be implemented with the HD upgrade and allow full Volume acquisition every 5 seconds!
- **PK fitting** will be possible



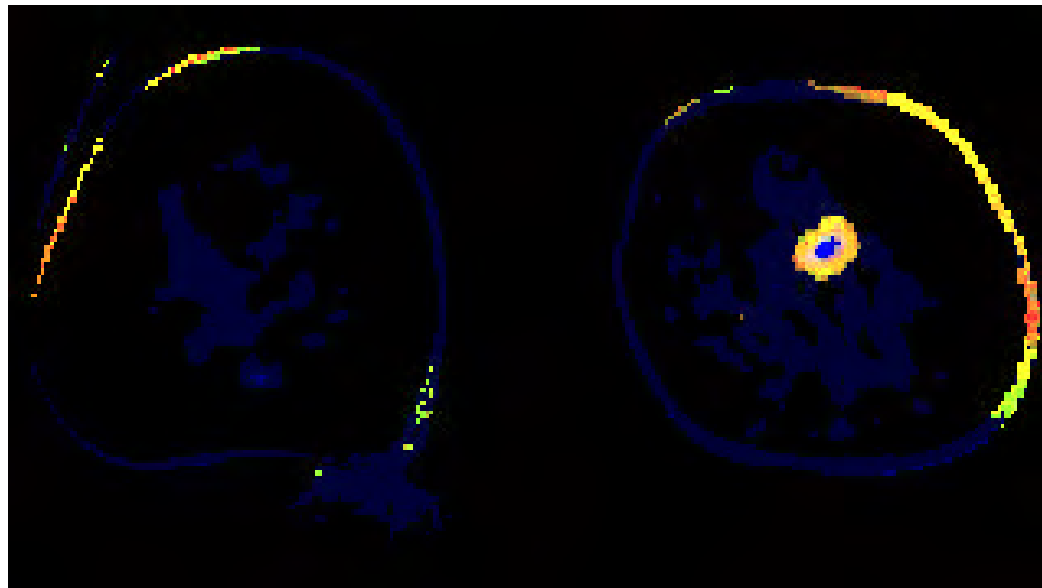


# Parametric $T_1$ mapping for analysing ce-MRI

Conventional analysis based on intensity change

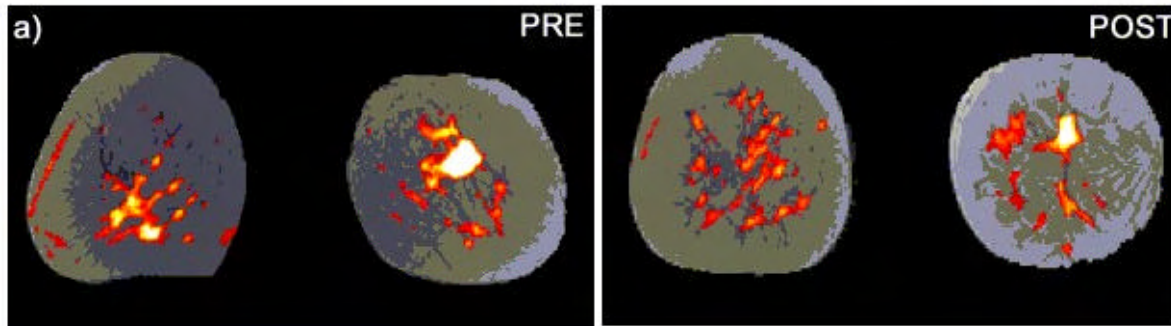


Estimating change in  $T_1$  and its visualisation



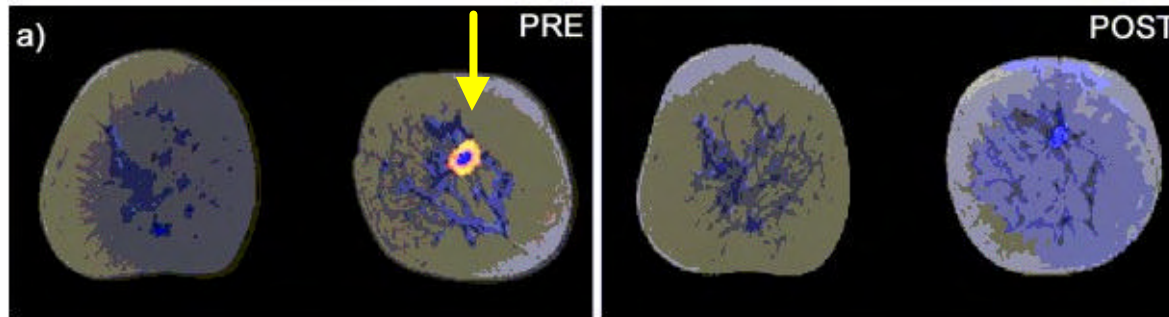
Multiple acquisitions prior to injection of Gd is well-known. We have developed a method that minimises the error in the estimation of  $T_1$

# Measuring effect of chemotherapy



Pre- and post-chemotherapy

Percentage increase in **intensity** at right

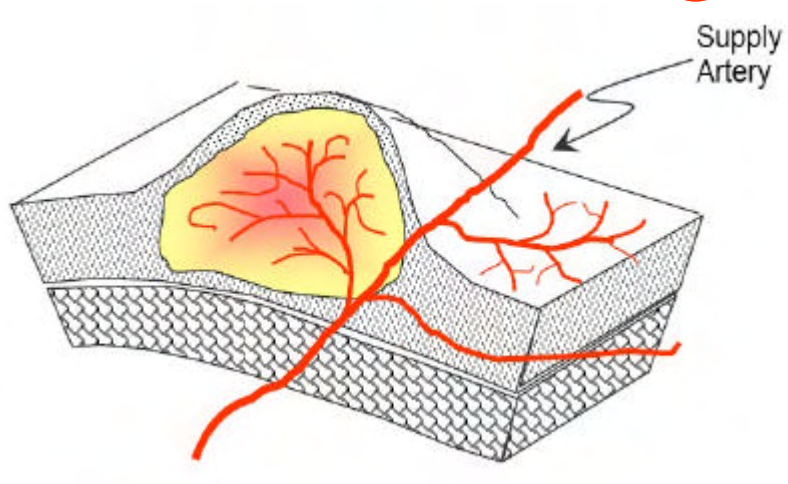


Pre- and post-chemotherapy ?  $T_1$  at left

(non-rigid) registration and pre- and post-chemotherapy, from ?  $T_1$



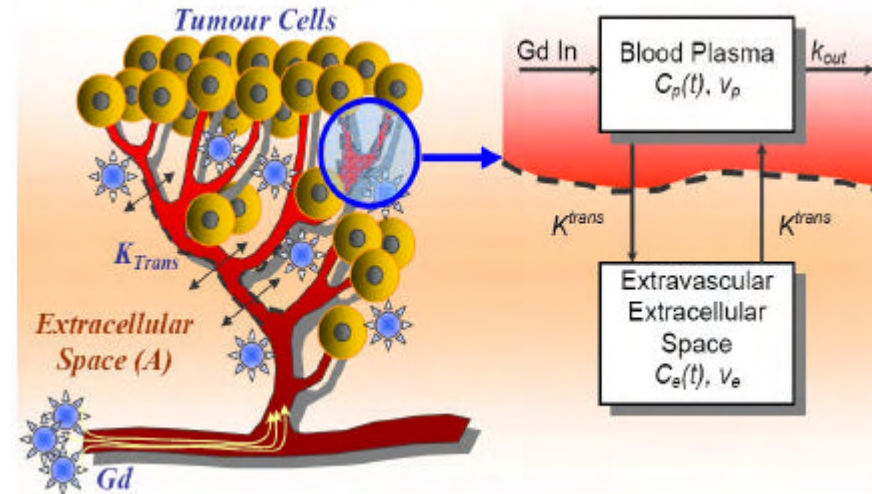
# Tumour vascularity & angiogenesis



Millions of micro blood vessels are grown – this new blood is angiogenesis

In order to fuel its growth, a tumour grows a network of millions of micro-vessels that tap in (like shunts) into supply arteries

The blood vessels are both small (microns) and leaky, so Gd molecules stick around the vicinity of a tumour



# The need for non-rigid registration.

In this case,  
relaxation of  
the pectoral  
muscles  
causes  
severely non-  
rigid motion...



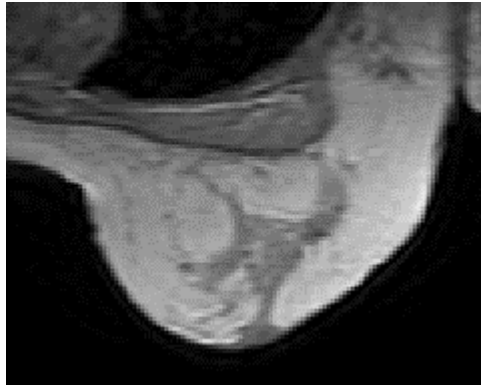
# Registration Results.

The computed  
non-rigid  
motion field.

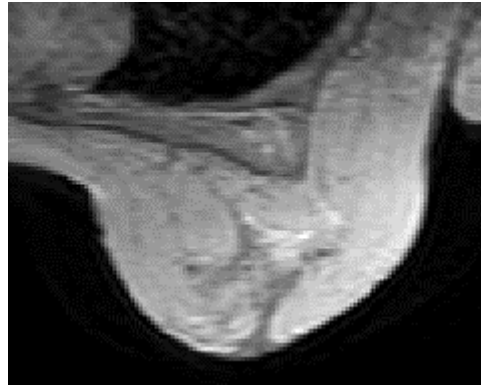




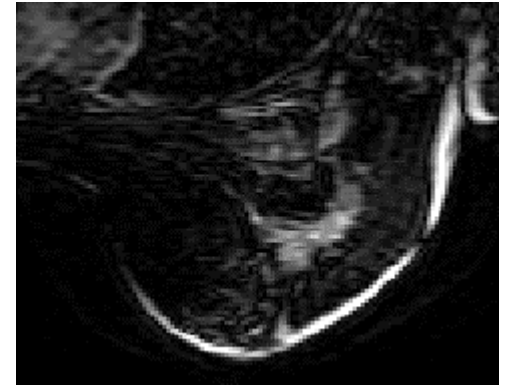
# registration and image re-sampling



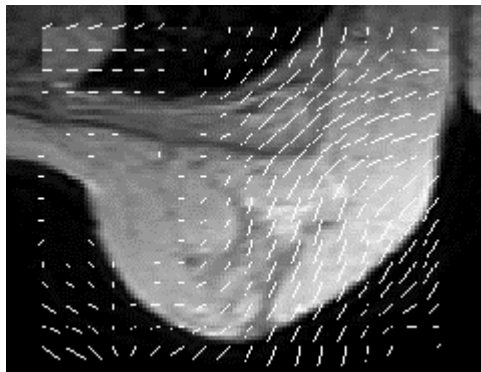
pre-contrast image



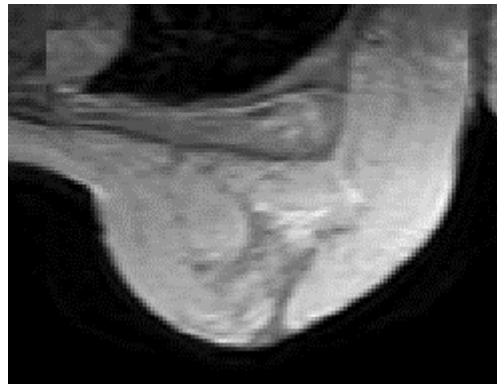
post-contrast image



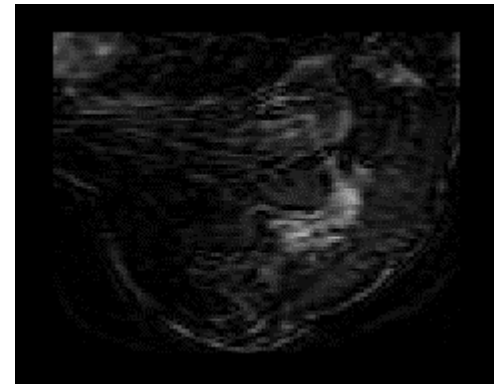
subtraction image



motion field



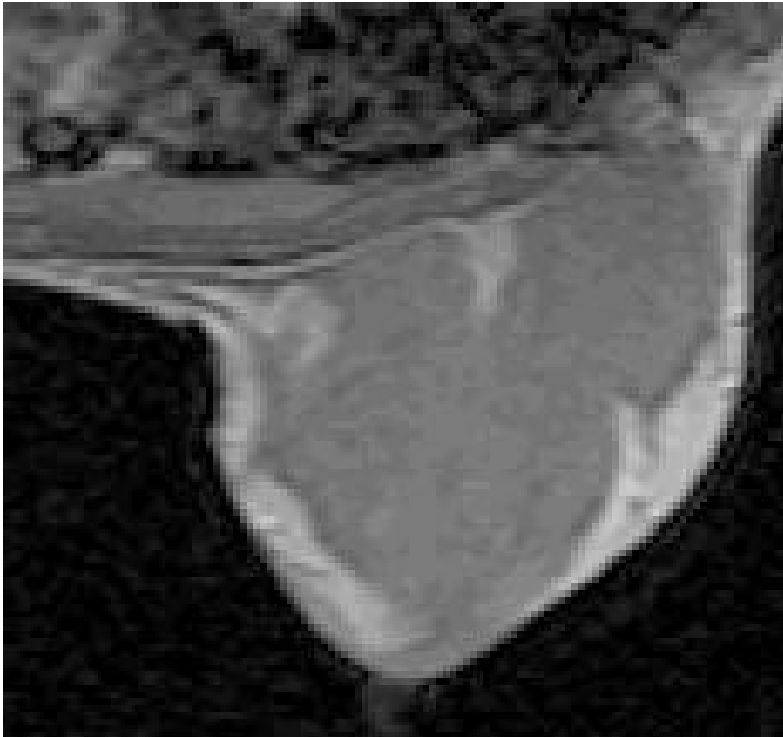
corrected post-contrast image



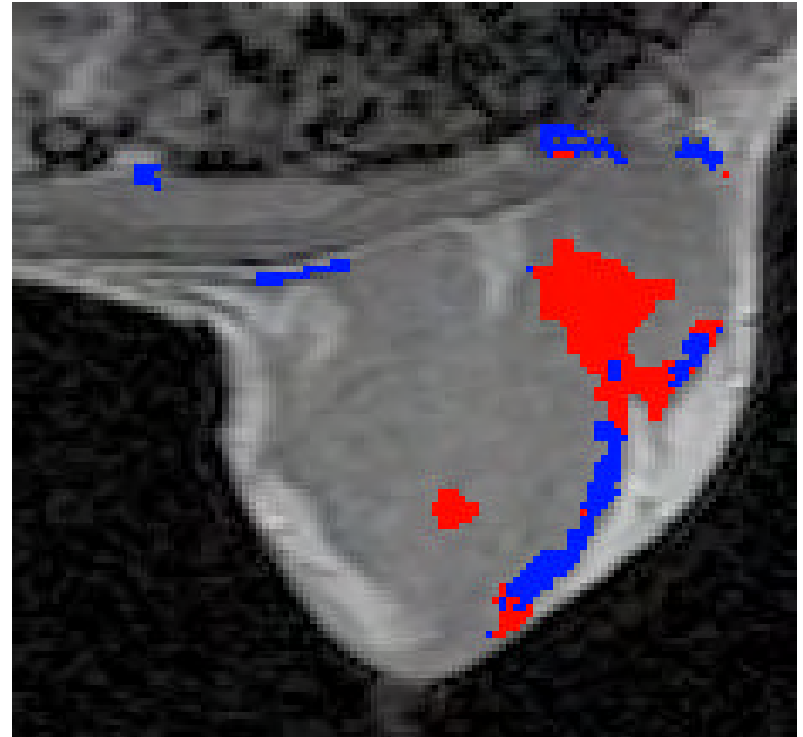
corrected subtraction

# Detecting Areas of Focal Enhancement.

Image Sequence



Detected Regions

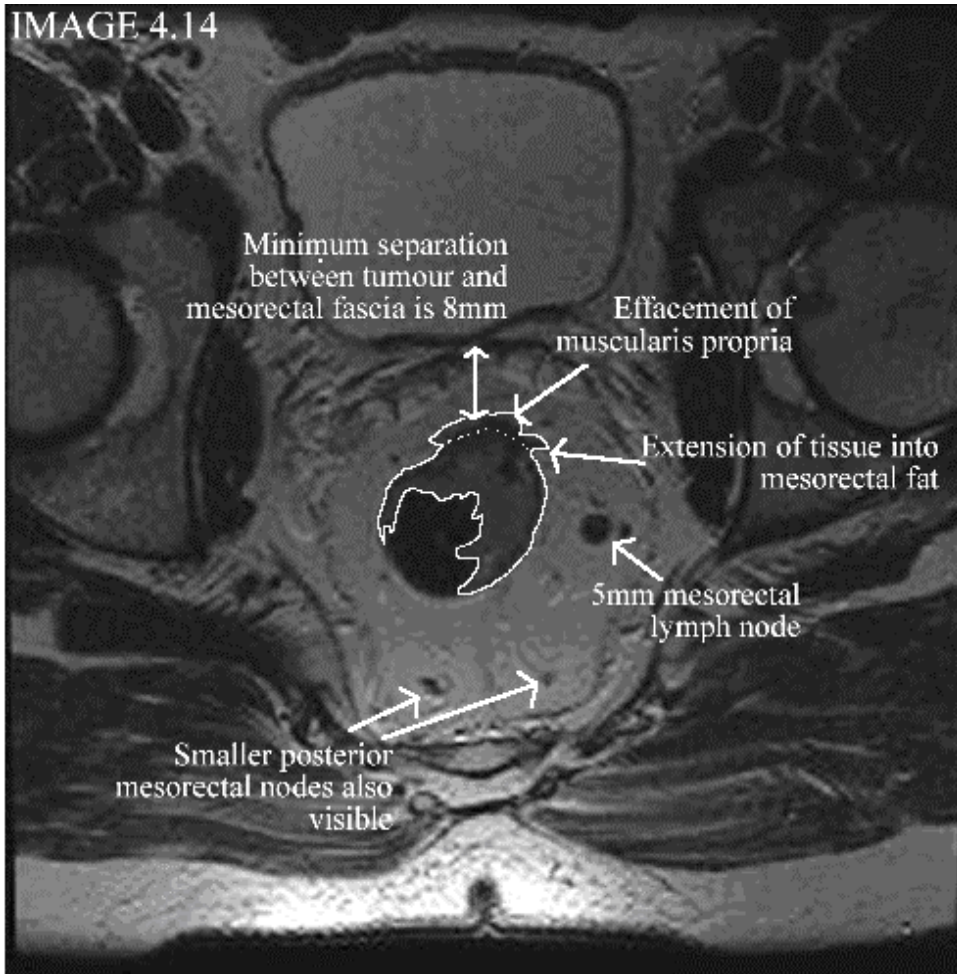


# Colorectal cancer

- disease of the developed world
- approximately 500,000 new cases annually
- Survival rate at 5 years is 50%
  - Principal metastases to liver, pelvis
- surgery is only curative therapy
  - Local excision surgery has been slow to take off
- chemotherapy use in 65%
- Primary metastases to liver and pelvis

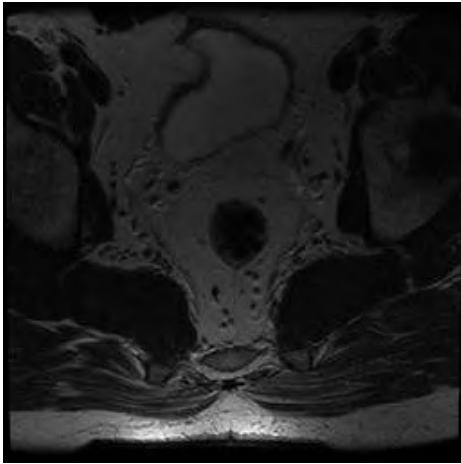
# Radiologist's Staging

IMAGE 4.14

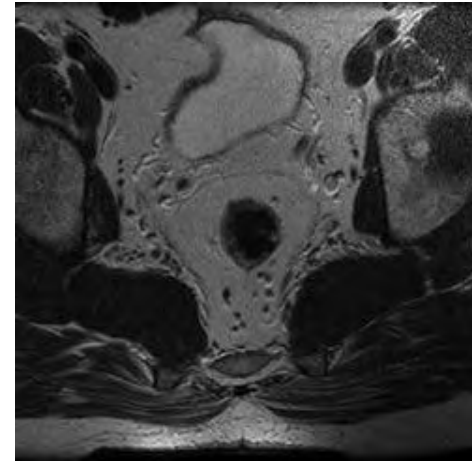


- *Eccentric mass present within the distal rectum extending from approximately 10 o'clock - 5 o'clock.*
- *Effacement of the muscularis propria from 12 o'clock - 2 o'clock and there is extension of tissue into the mesorectal fat anteriorly at 2 o'clock superiorly.*
- *The appearances suggest early T3 disease.*
- *The minimum separation between tumour and the mesorectal fascia is 8 mm superiorly.*
- *There is a 5 mm mesorectal lymph node laterally on the left and other smaller posteriorly placed mesorectal nodes. At this size they are indeterminate.*

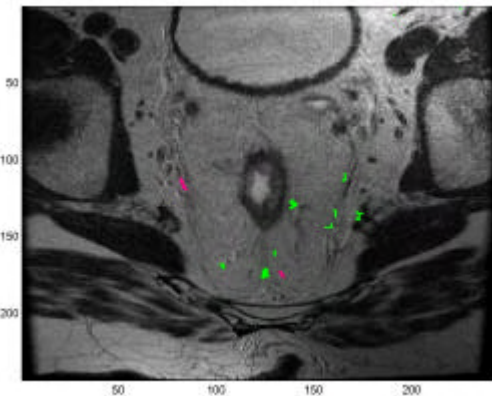
# Colorectal cancer



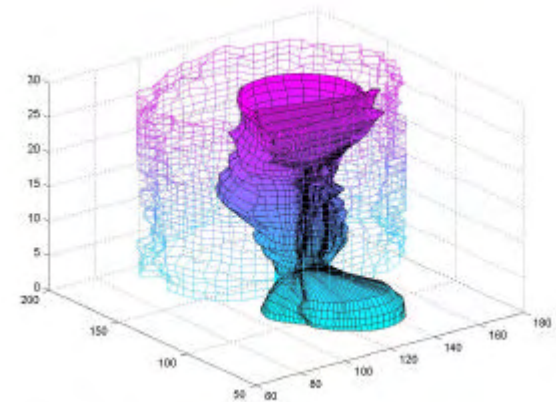
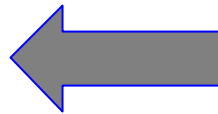
Original image for multidisciplinary team



After removal of "bias field"



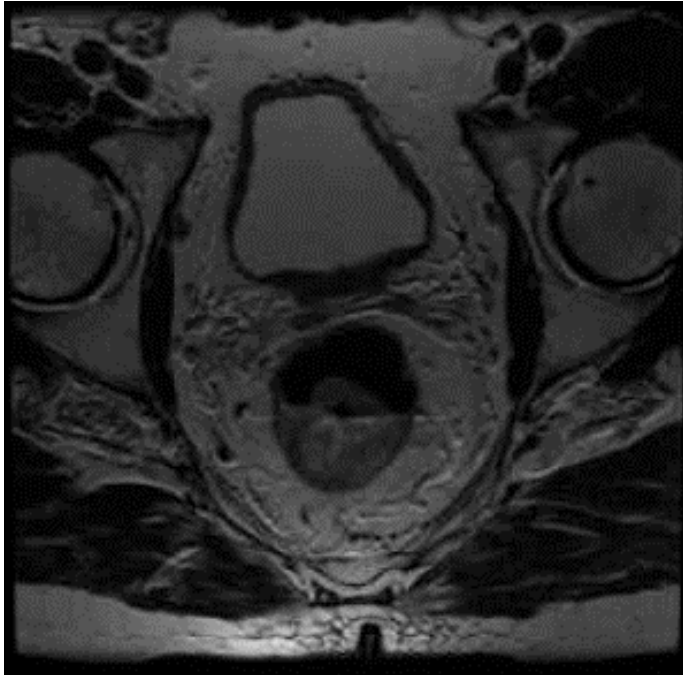
Detected nodes



3D reconstruction of colorectum and mesorectal region

# Aligning pre- and post-chemo

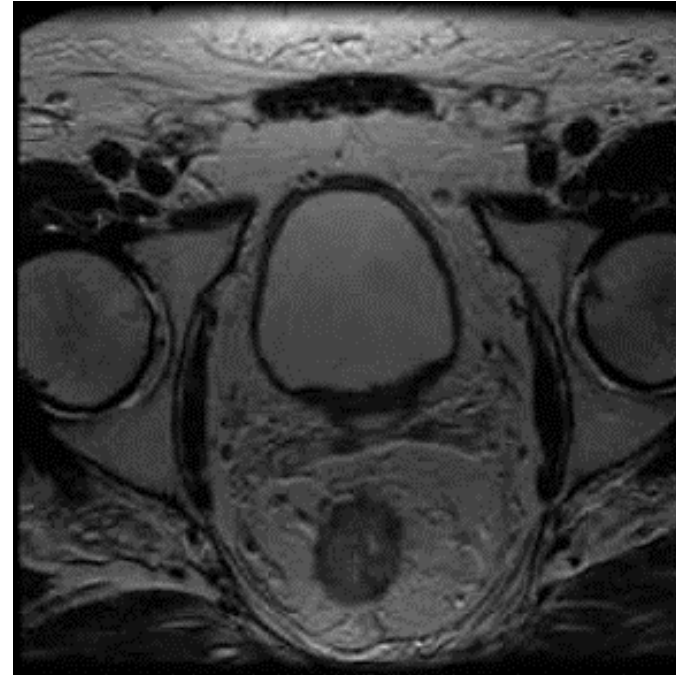
pre



Non-rigid  
deformation



post



Applied the six best-known algorithms from the research literature to a set of patient data.

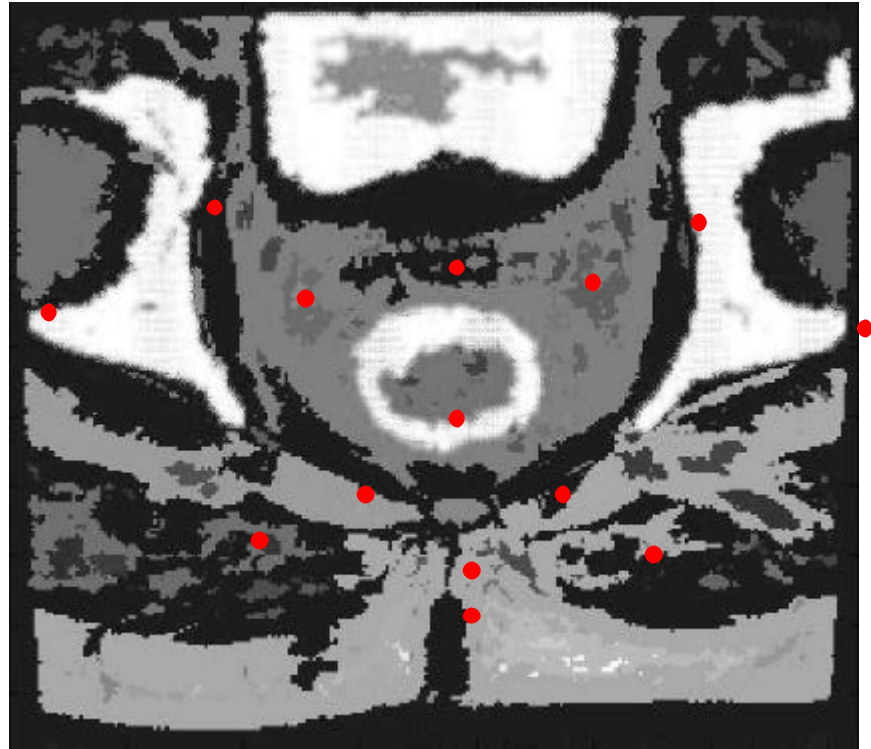
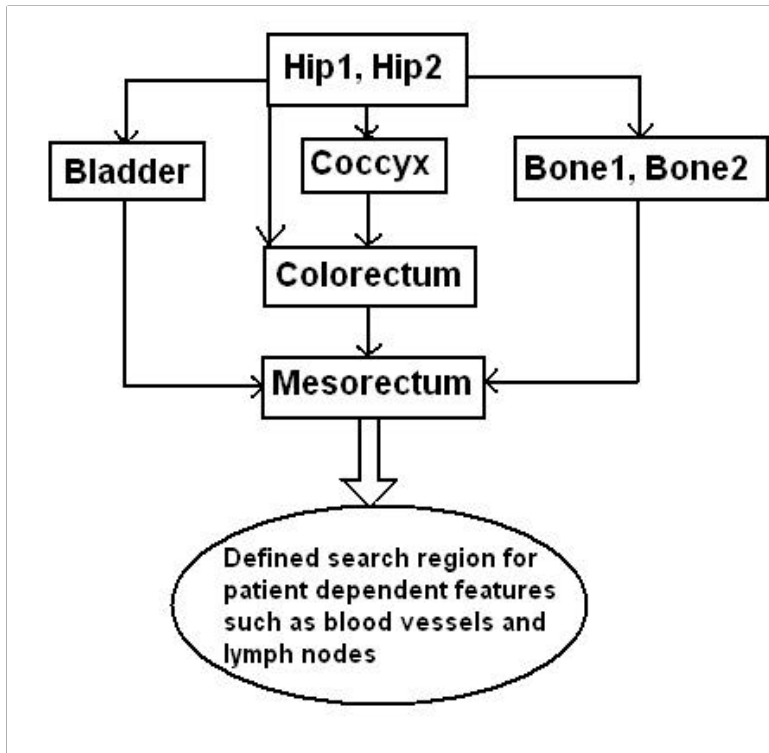
Typically fail 30% of the time. This is because the algorithms are completely general, so they do not embody knowledge of colorectal anatomy/physiology



# Alignment using current algorithms

Method	Average misalignment of lymph nodes
Rigid registration	21mm
B-splines & Mutual Information <i>(Rueckert et al. 1999)</i>	30mm
Mis-match measure <i>(Park et al. 2004)</i>	21mm
Fluid registration <i>(Crum et al. 2003)</i>	7mm
RevealMVS™ <i>(Mirada Solutions Ltd.)</i>	7mm
Insight ToolKit (ITK) <i>(<a href="http://www.itk.org">http://www.itk.org</a>)</i>	10mm

# Using an Anatomical Atlas

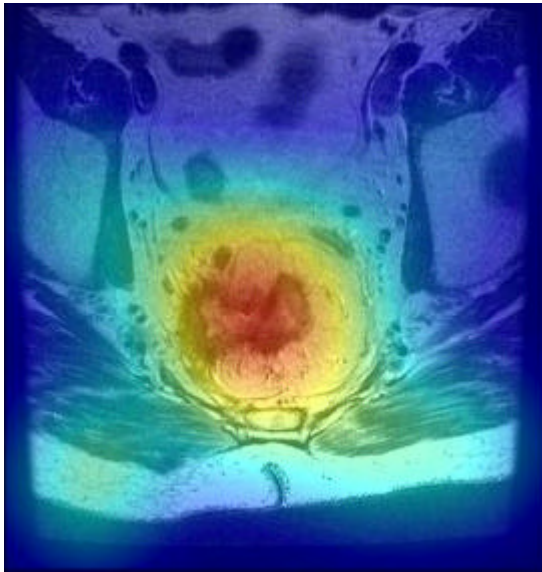


- Relational anatomical atlas guides non-rigid registration. Arrows show influence of constraints
- Automatically find the bone structures, as well as the bladder and colorectum in the images. From these, we can find meaningful landmarks.
- Incorporate expected physiological changes, eg reduction of adenosis

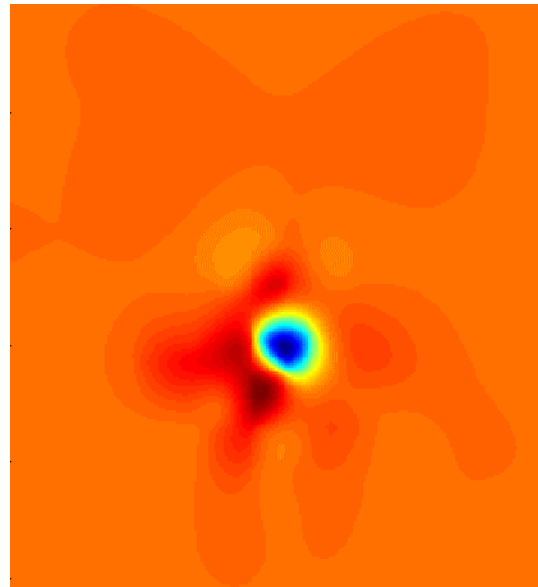
# Jacobian of the deformation as a regulariser

The Jacobian  $J$  is a scalar representation of the deformation (vector) field ( $F$ ).

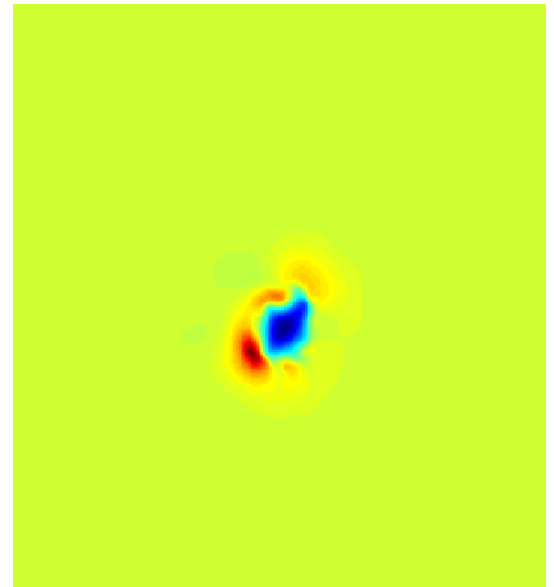
$$J = \det \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix}$$



Nature of the deformation field shows the central part of the image is shrinking



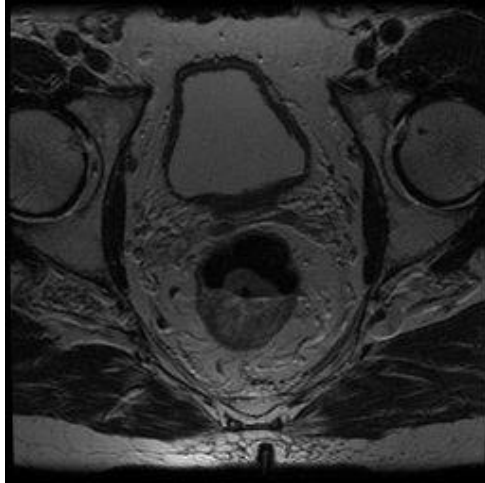
Jacobian of the actual deformation field.



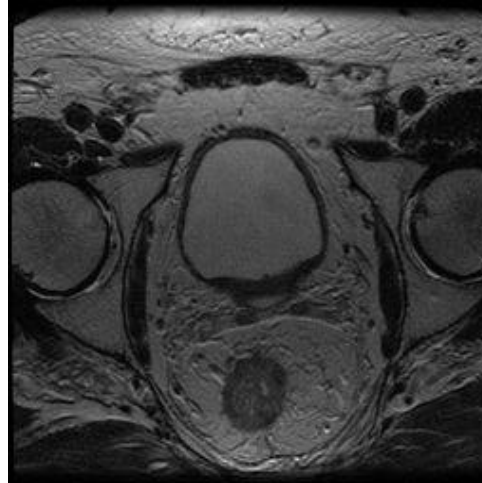
Jacobian estimated from the segmentation can be used as a regulariser.

# Registering with Shape Information

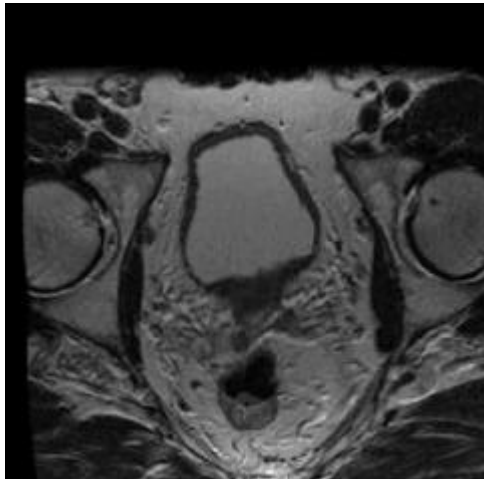
Before  
treatment



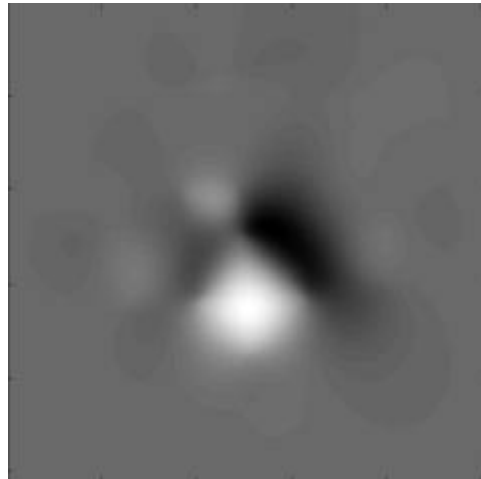
After  
treatment



Registered  
before to  
after using  
Thin Plate  
Splines

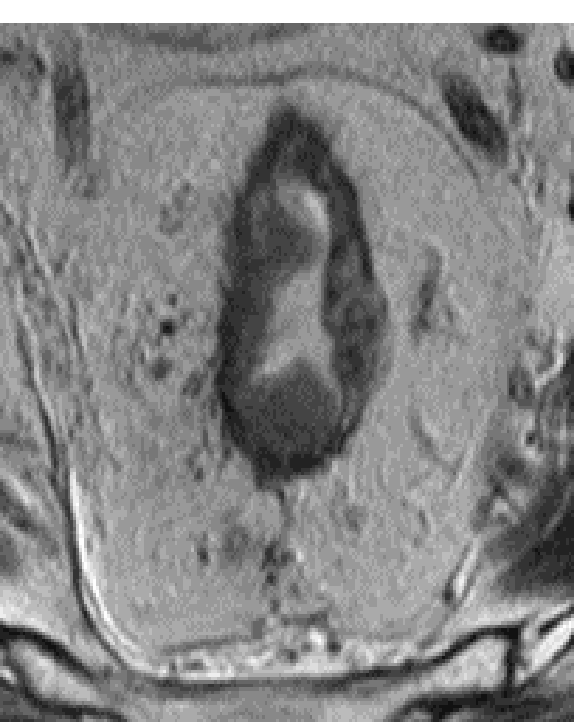


Jacobian of the  
transformation

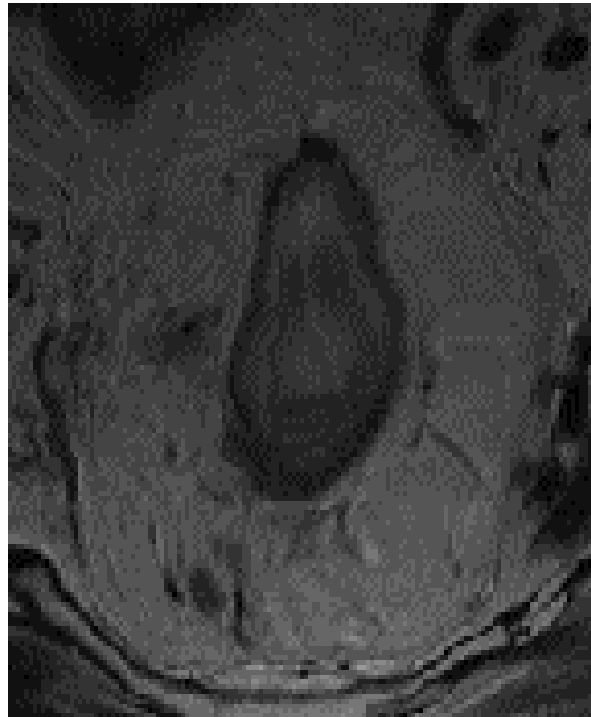


# Changes due to radiotherapy

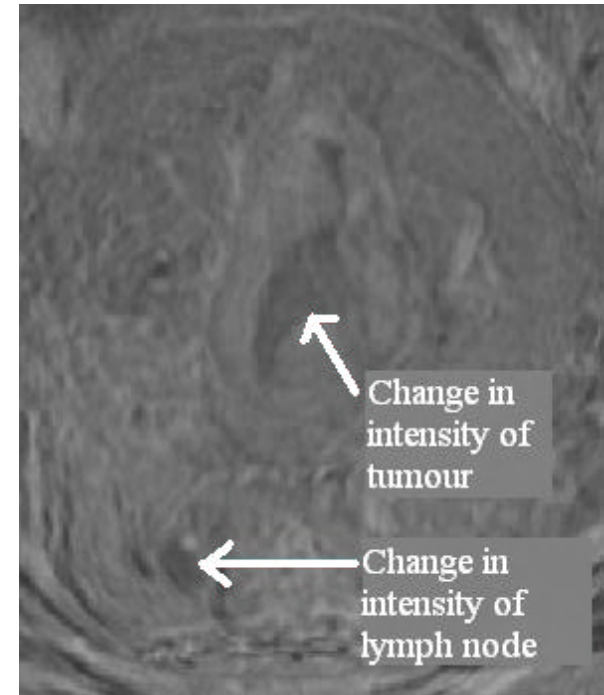
Example of how the registration of pre and post-treatment images can be used to assess the effects of treatment. Focussing in on the region of interest, the changes wrought by radiotherapy can be clearly analysed



Pre-treatment image



Warped post-treatment image

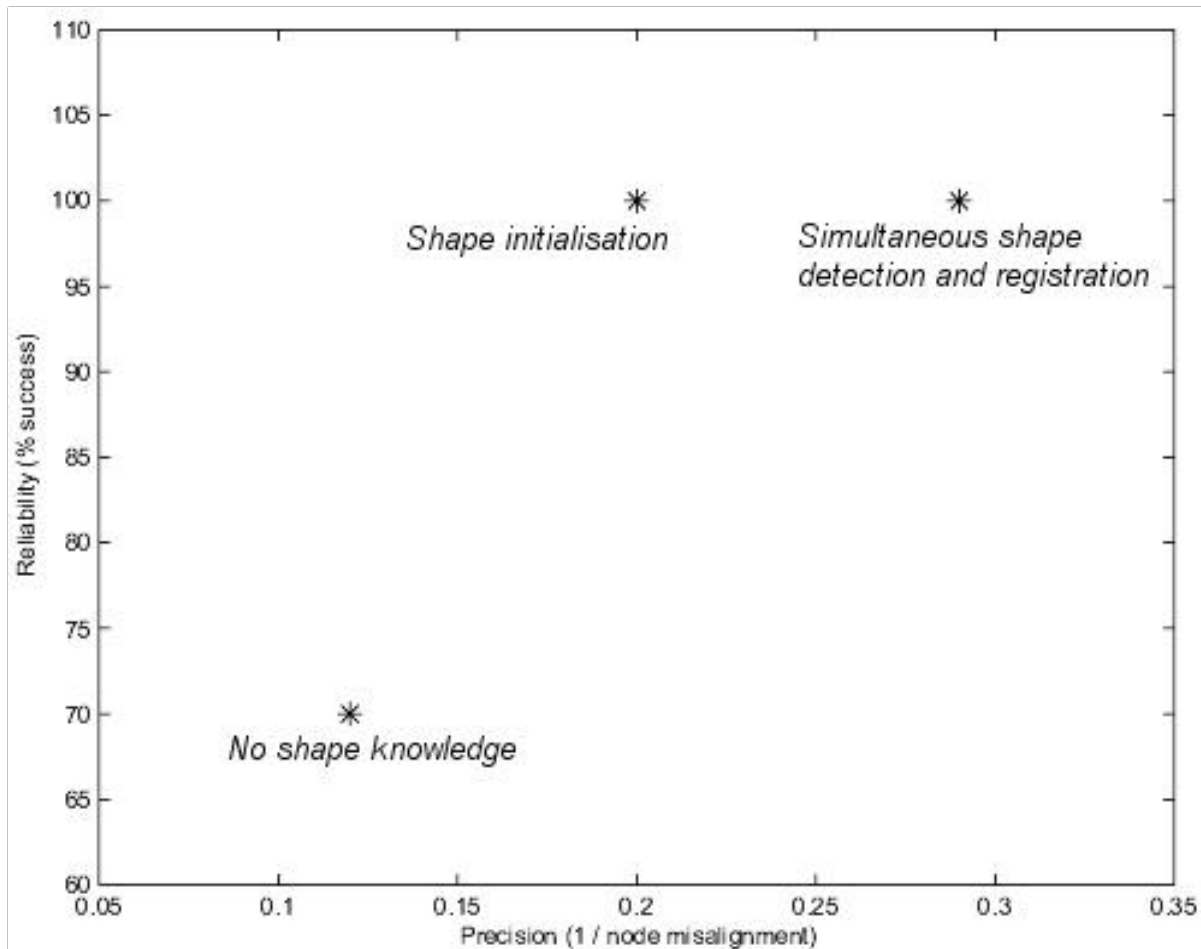


Difference image

# Results from Incorporating Shape Information

Method	Average misalignment of lymph nodes
Rigid registration	21mm
B-splines & Mutual Information <i>(Rueckert et al. 1999)</i>	8.3mm
Mis-match measure <i>(Park et al. 2004)</i>	5.0mm
Fluid registration <i>(Crum et al. 2003)</i>	5.9mm
RevealMVS™ <i>(Mirada Solutions Ltd.)</i>	4.6mm

# Robustness and Precision

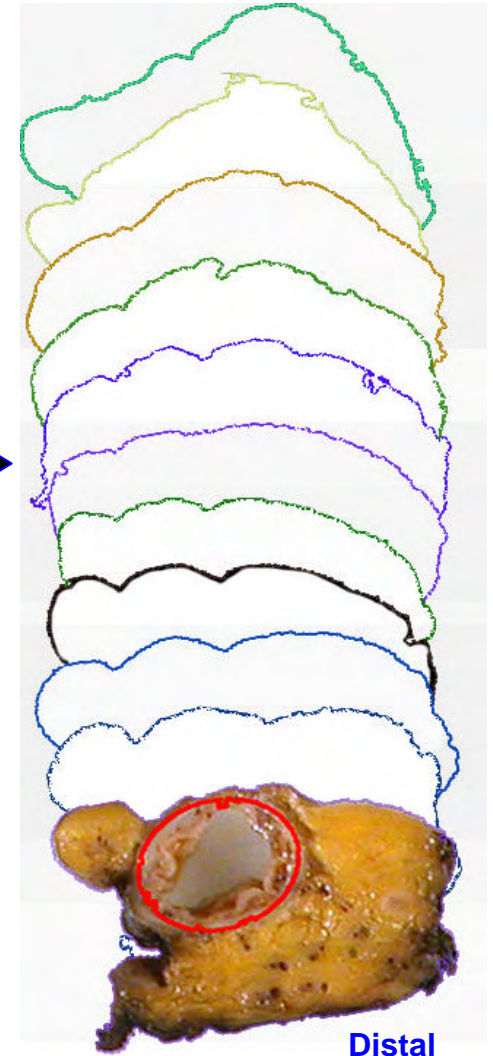




# Reconstruction From Macro Slices

Resected specimen

Distal



Distal

Distal

# Registration is Needed

- Animation of slices before registration



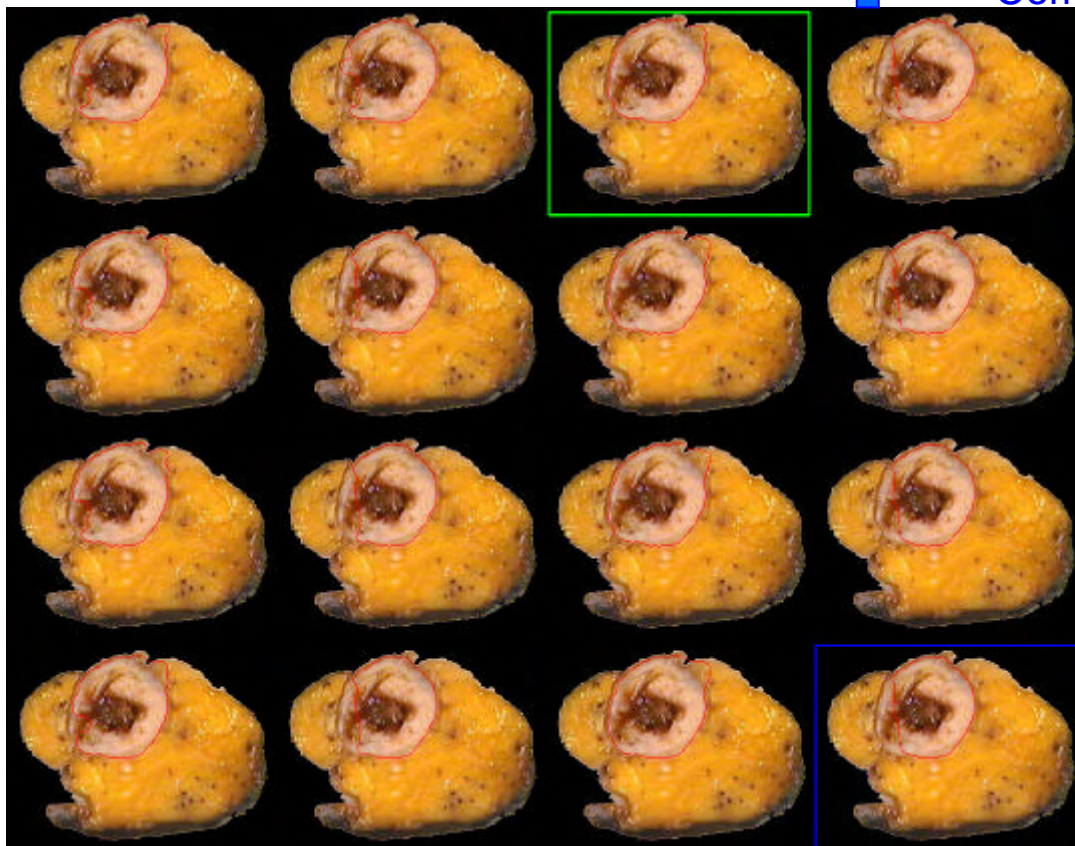


Initial segmentation



Final rectum contour

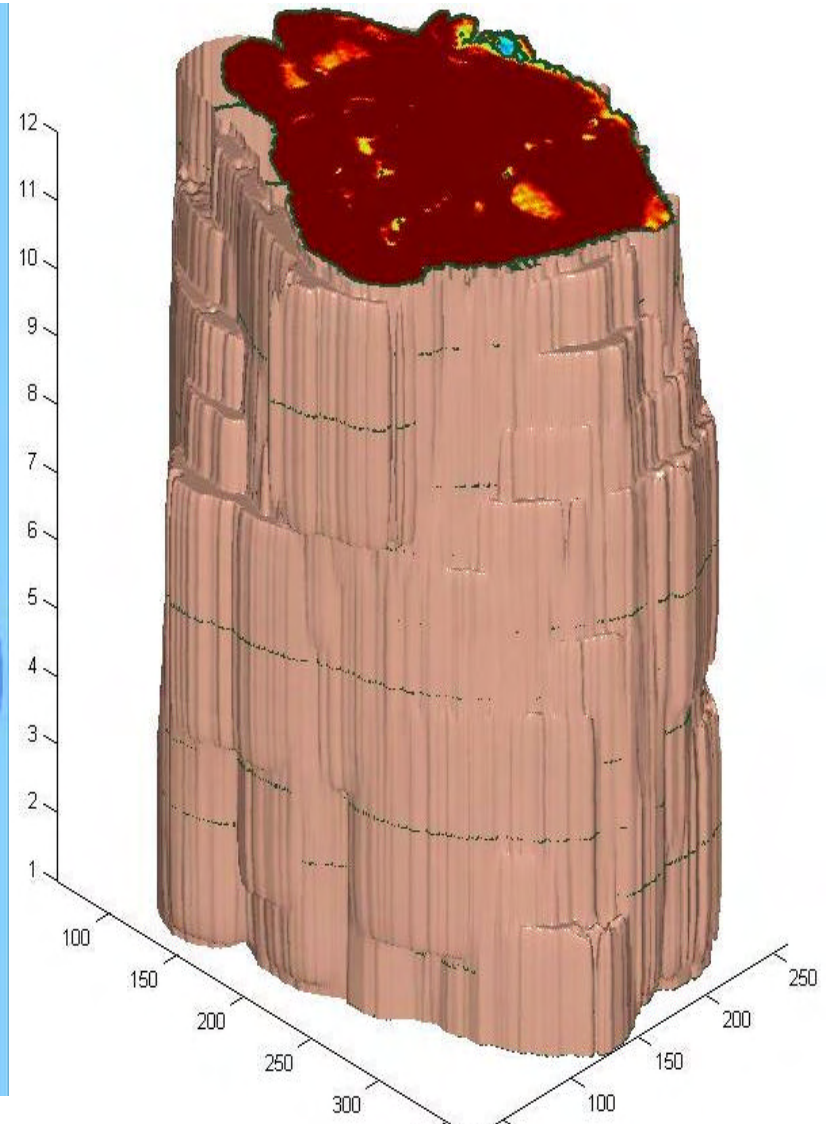
Morphological  
operations



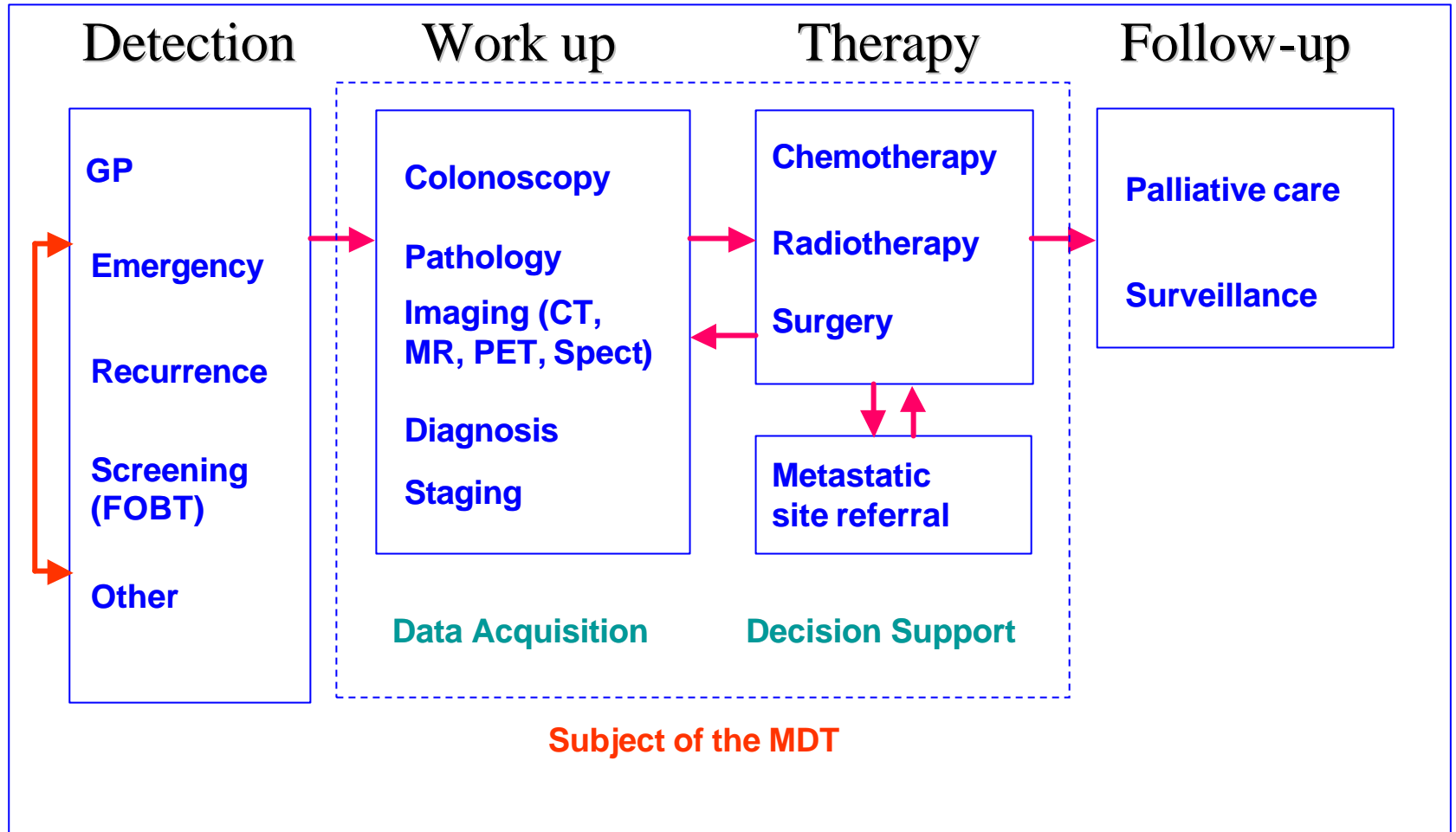
Combination



# Registration and reconstruction



# Patient Journeys in CRC



Each individual follows their personal “journey” through these options

# Weekly Multi-Disciplinary Team Meetings

- Each case on a pre-determined worklist receives the consideration of a team of clinicians with expertise in different aspects of cancer management (30/40 cases per hour)
- Aims to ensure all patients receive the same, high-standard of care
- Requires each member be presented with **all information** necessary for each decision
- The case load requires each patient is presented **efficiently**, via the display of **different modalities** of information (CT, pathology etc..)
- Cost of bringing together such expertise is high, therefore need to make process as efficient as possible to make best use of clinicians' time
- Core members of the multi-disciplinary team:
  - Histopathologist, Oncologist, Radiologist, Surgical specialist, Nurse specialist : *dialogue of the hard of hearing!*
  - Individual members liable to change with each successive discussion of an individual's cancer

# MDT Meetings – Current Situation

- Image display is rudimentary with no use of computer-based analysis (information is qualitative)
- Patient information reported and integrated **informally** into patient management decisions
- Decisions are recorded but contingencies mostly **implicit**
- **No explicit representation** of previous decisions and dependencies, or how the new information effects those contingencies – no “corporate memory”
- Clinicians’ memories relied upon to avoid **errors of omission**
- Clinicians struggle to keep up to date with an **exponentially growing** body of research in their field

Need for: conventional IT support and decision support

The Oxford GE project concentrates on the latter








# Decision Support




- Built on the *PROforma* engine (John Fox, CRUK & UCL)
- Decision recommendations made by summing up Arguments for and against each Candidate
- Doctors are uncomfortable with probabilities
- Decision support, final choice always made by clinicians
- Facilitates decision making for straightforward cases while supporting the art of medicine for more complex scenarios
- Arguments are backed up visibly by the salient data, reducing errors of omission


MDT Suite - Mozilla Firefox

File Edit View Go Bookmarks Tools Help




http://localhost:8080/mdtsuite/formReviewQueuedPatient.jsp?study\_id=107







Multi Disciplinary Team Review



John Smith (67M) T2N1M0

Patient De...Patient Hi...PathologyCTMRIGenomicsDecision

 Patient Data 

Age67

ForenameJohn

NHS Number1

Patient Date Of Birth14/09/1939



Patient No.1

PostCodeOX1 1JJ

SexMale

Consultant in ChargeProf Neil Mortensen

SurnameSmith

 Patient History 

Any Family Members with CRCNo

Past Medical History - Serious IllnessesProstate Cancer

Duration of Symptoms3 Months






SymptomsChange in Bowel Habits, Unexplained Weight Loss.

WHO Performance Status0




Applet MDTSuiteGUIApplet started


MDT Suite - Mozilla Firefox

File Edit View Go Bookmarks Tools Help




http://localhost:8080/mdtsuite/formReviewQueuedPatient.jsp?study\_id=107







Multi Disciplinary Team Review




John Smith (67M) T2N1M0


Patient De... Patient Hi... Pathology CT MRI Genomics Decision


Decision Options


☒ Neo Adjuvant Radiochemotherapy 





Guidelines suggest pre-op 5-FU/RT or Transabdominal excision for T3 or N1-2 rectal cancer

☐ Symptomatic Care 


☐ Further Imaging Required 

☐ Neo Adjuvant Chemotherapy 


☐ Surgery 



Guidelines suggest pre-op 5-FU/RT or Transabdominal excision for T3 or N1-2 rectal cancer



Tumour does not meet resectability criteria

☐ Follow Up 

There are no applicable arguments for that candidate.

Applet MDTSuiteGUIApplet started



## Multi Disciplinary Team Review



John Smith (67M) T2N1M0

Patient De... Patient Hi... Pathology CT MRI Genomics Decision

Mouse Manipulation

☐ WLAWV(All Images)

☒ WLAWV(Single)

Default WLAWV

Reverse

☐ Move

☐ Zoom

Reset Move/Zoom

☐ Loupe

Reset Angle

Rotate L

Rotate R

Flip RL

Flip UD

Cine Mode

<<

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ImageNo

1

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|||

>

LessFrame

MoreFrame

Patient Info.

none

Anonymized

none

none

Study Info.

none

Anonymized

1995-06-26

11:20:00

126/252

103


# MDT Suite Prototype

MDTSuite - Mozilla Firefox

File Edit View Go Bookmarks Tools Help

http://cadbox01:47068/mdtsuite/formReviewQueuedPatient.jsp?study\_id=101&decisionId=2

Entrez-PubMed NCBI Bookshelf Google Scholar Google News Slashdot PLoS Computational ... Test Insilico Digest Tool MDT Suite DMET TestDMET



Name: Charles Burns Return Home Age: 81

Summary Pathology ... CT Image S... Decis

**Decision Options**

☐ **Neo Adjuvant Radiochemotherapy** ✓  
+ Guidelines suggest 5FU/RT for T4 rectal cancer

☐ **Surgery** ✓  
+ Tumour is mobile  
- Lymphovascular of perineal invasion  
+ Margins clear

☐ **Follow Up**

☐ **Neo Adjuvant Chemotherapy**

☐ **Further Imaging Required**

☐ **Symptomatic Care**

☐ **Other**

Confirm

**The following information was not available:**

- Height From Anal Verge (cm)
- Circumference of bowel involved
- Maximum Tumour Diameter (cm)
- Distant Metastases Site

**Decision History**

**2006-02-15: Post Op Decision: Symptomatic Care**

**2006-02-08: Post Neo Adjuvant Decision: Surgery**

- + Tumour is mobile
- Lymphovascular of perineal invasion
- + Well or moderately differentiated
- + Margins clear
- + Neo adjuvant therapy was carried out with the goal of going to surgery
- + The tumour has been downstaged
- + Guidelines suggest pre-op 5-FU/RT or Transabdominal excision for T3 or N1-2 rectal cancer

**2006-02-01: Primary Treatment Decision: Neo Adjuvant Radiochemotherapy**

- + Guidelines suggest 5FU/RT for T4 rectal cancer

- “Smart UI” focuses on most relevant information
- Recognizes missing / incomplete data
- Captures decisions and rationales
- System maintains up-to-moment knowledge base
- Links to web for published articles supporting decisions

# Hannhan and Weinberg's six hallmarks of cancer

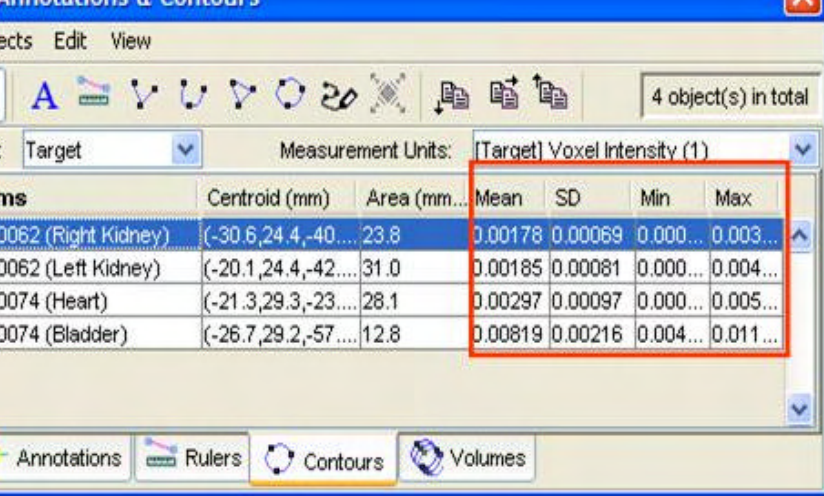
1. Growth signal autonomy
2. evasion of growth inhibitory signals
3. evasion of apoptosis
4. unlimited replicative potential
5. angiogenesis
6. invasion and metastasis

Increasingly, we are combining the insights from (medical) image analysis and molecular medicine: molecular imaging

# Molecular imaging

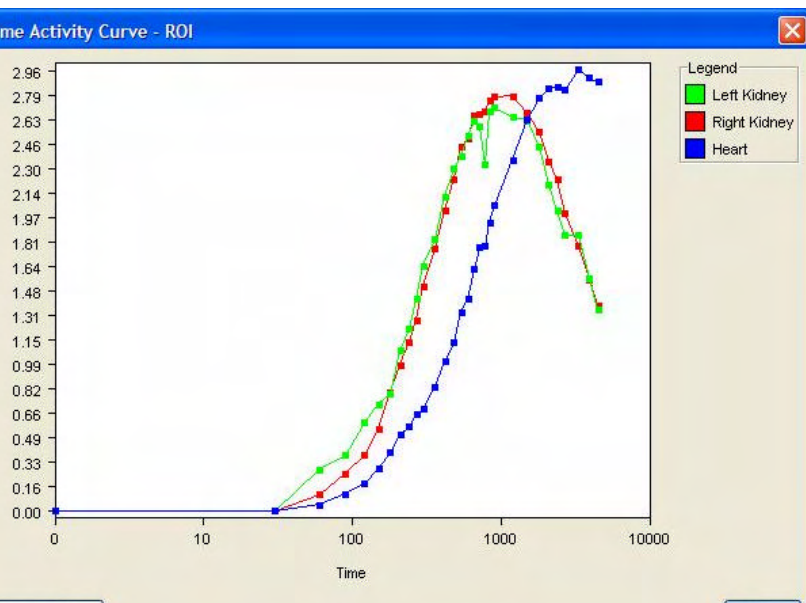
- Research centres on the visual representation, characterisation, and quantification of biological processes at the cellular and subcellular levels within intact living subjects.
- Whereas conventional imaging techniques rely on (non-specific) physical or physiological characteristics of tissues to obtain contrast.  
***Molecular imaging aims to exploit (specific) molecules as the source of image contrast.***





Segmentation tool

Time activity curves of drug concentration



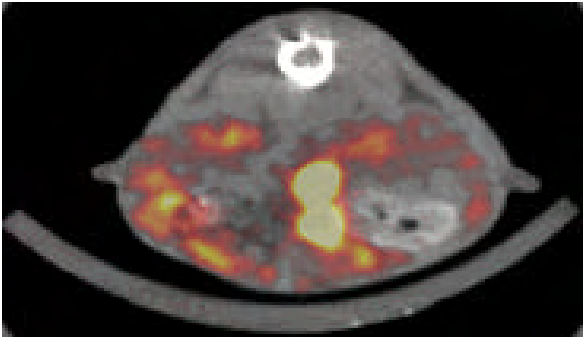
Modelling the take up of candidate drugs



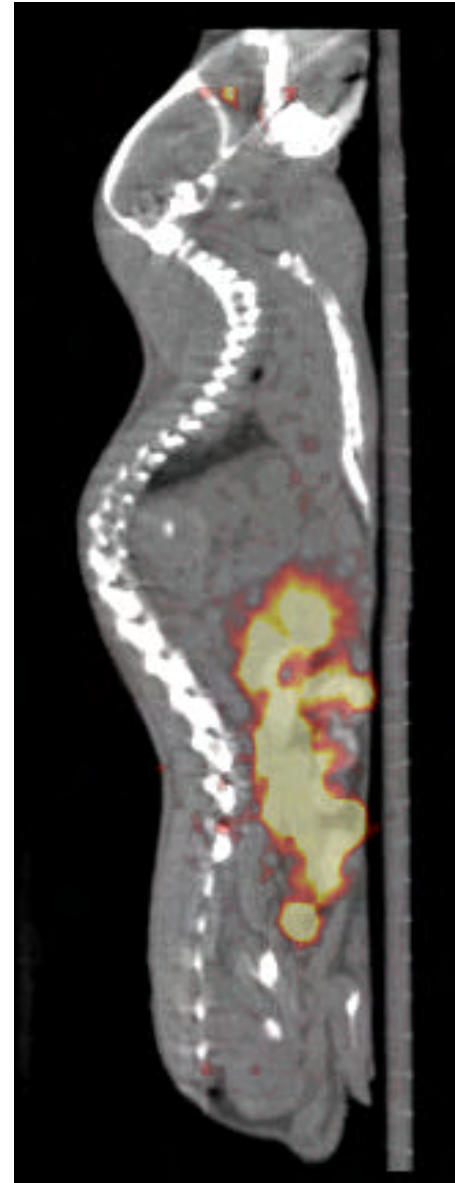
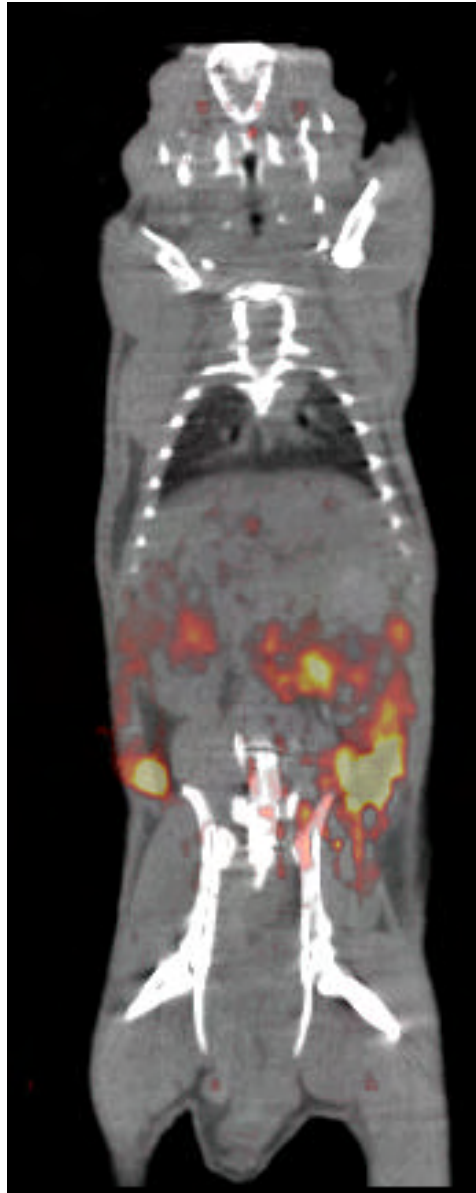
Organs of interest segmented

Mirada's *Research MVS*

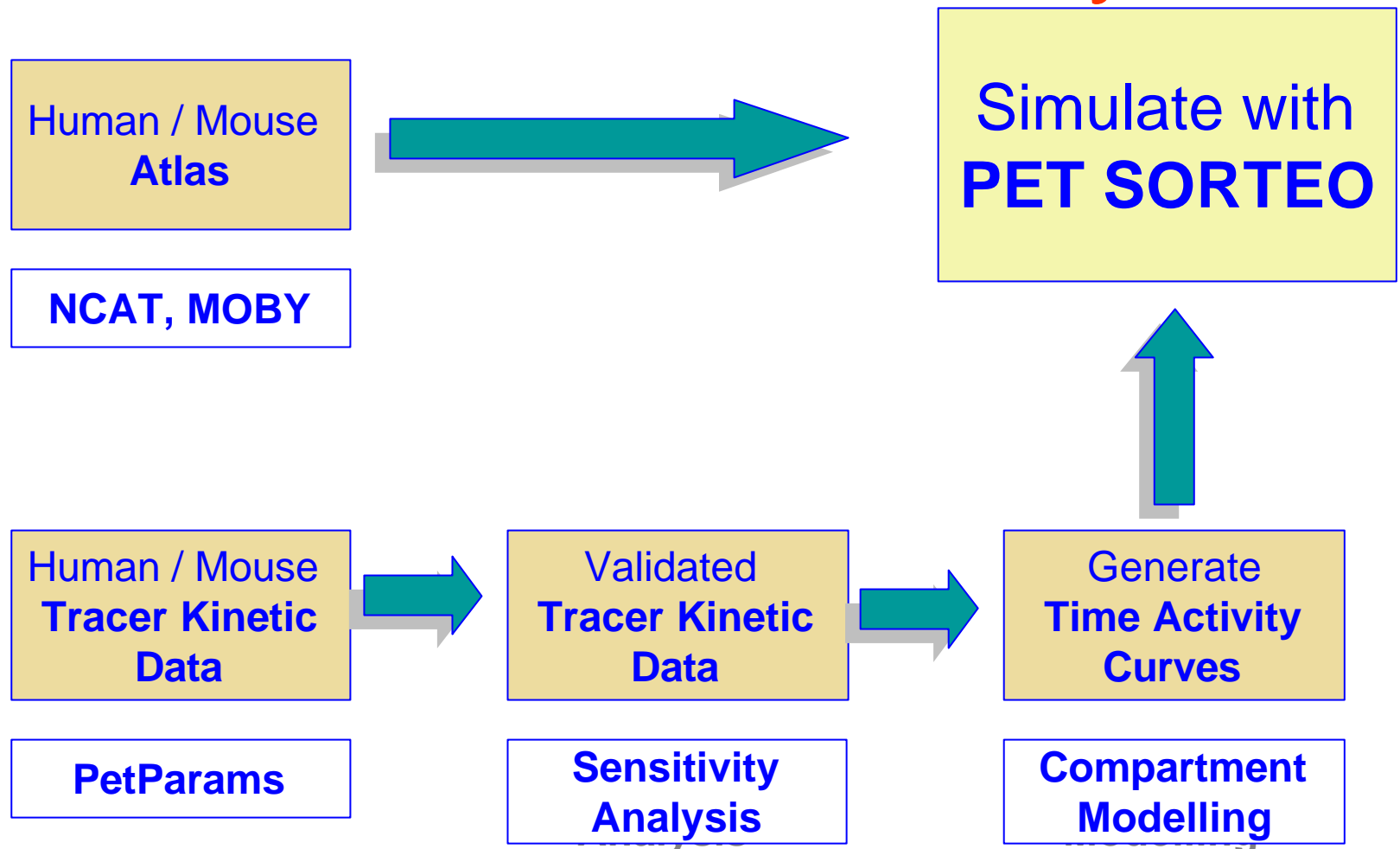
# Siemens Molecular Imaging (he Mirada) Research MVS software to work with MicroPET



We are beginning to image and model the dynamics of drug activity – and relate these to cellular and molecular processes



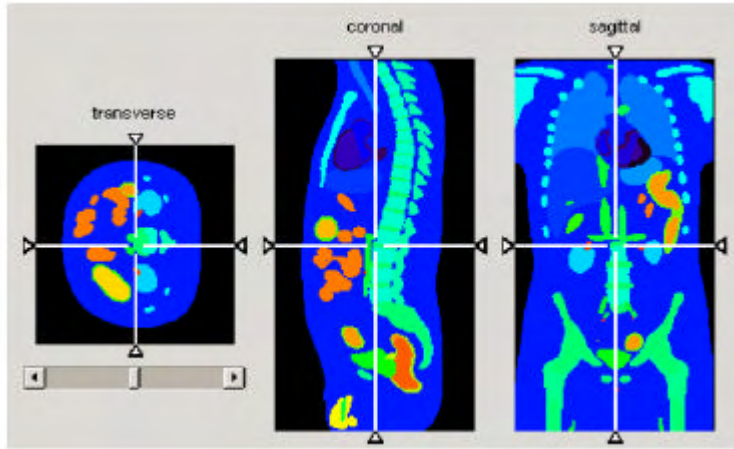
# Simulation Pathway



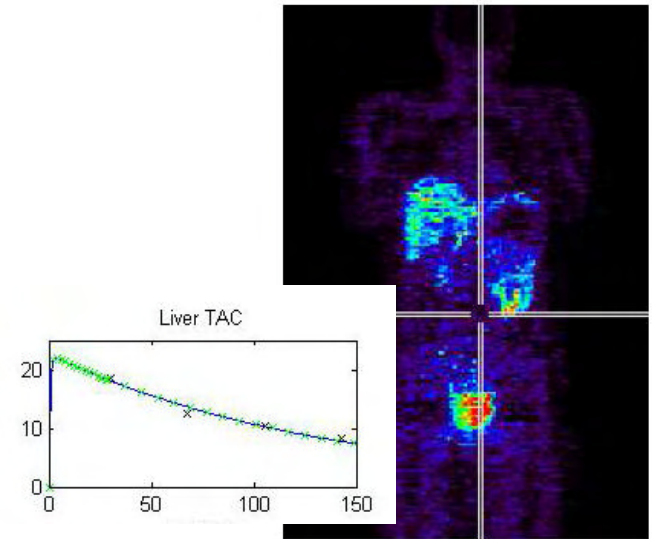
We have acquired a powerful 20 node computer cluster to reduce SORTEO simulations from a day to a few minutes

# PET Simulations

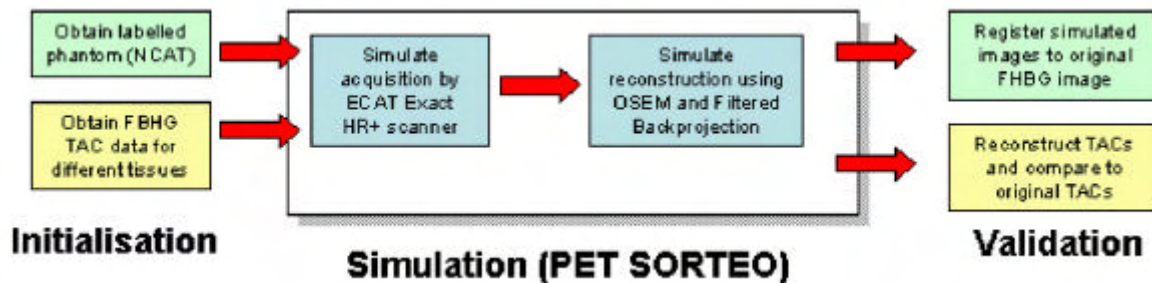
Real FHBG Patient PET Image



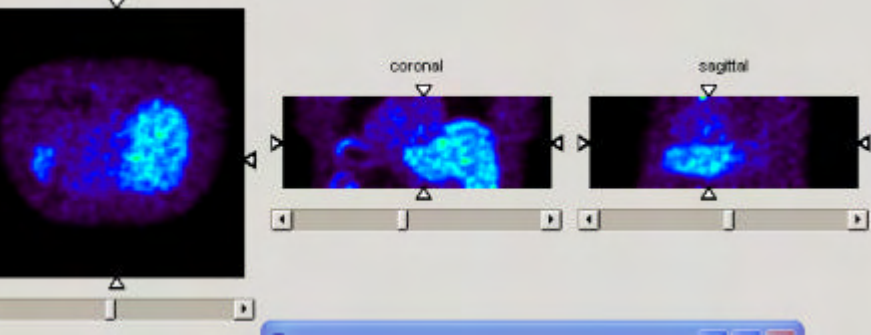
NCAT Human PET Phantom



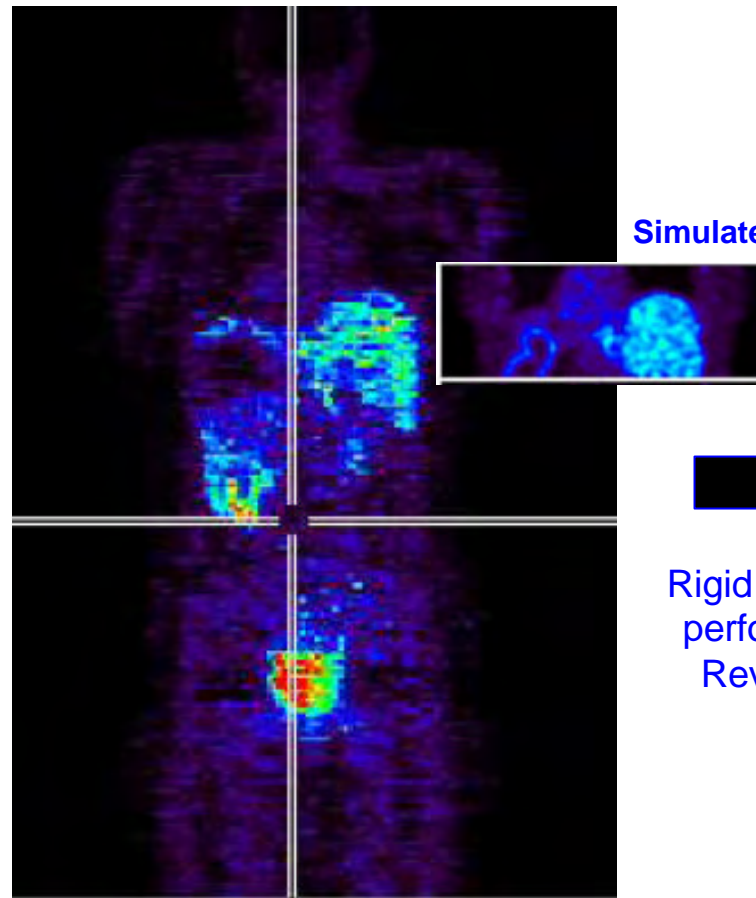
Experimental TAC  
From PET Images







# Simulation and Validation of data

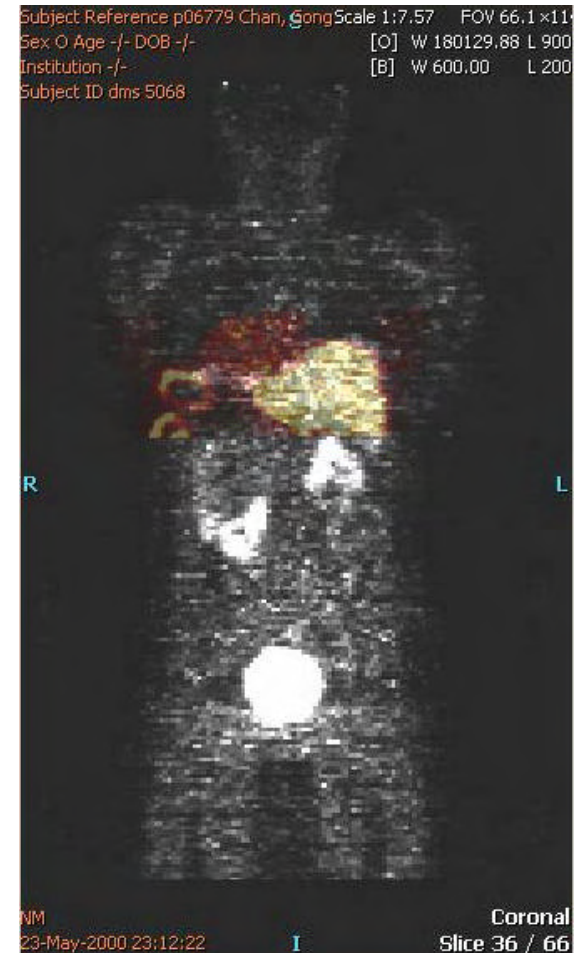


Simulated Data



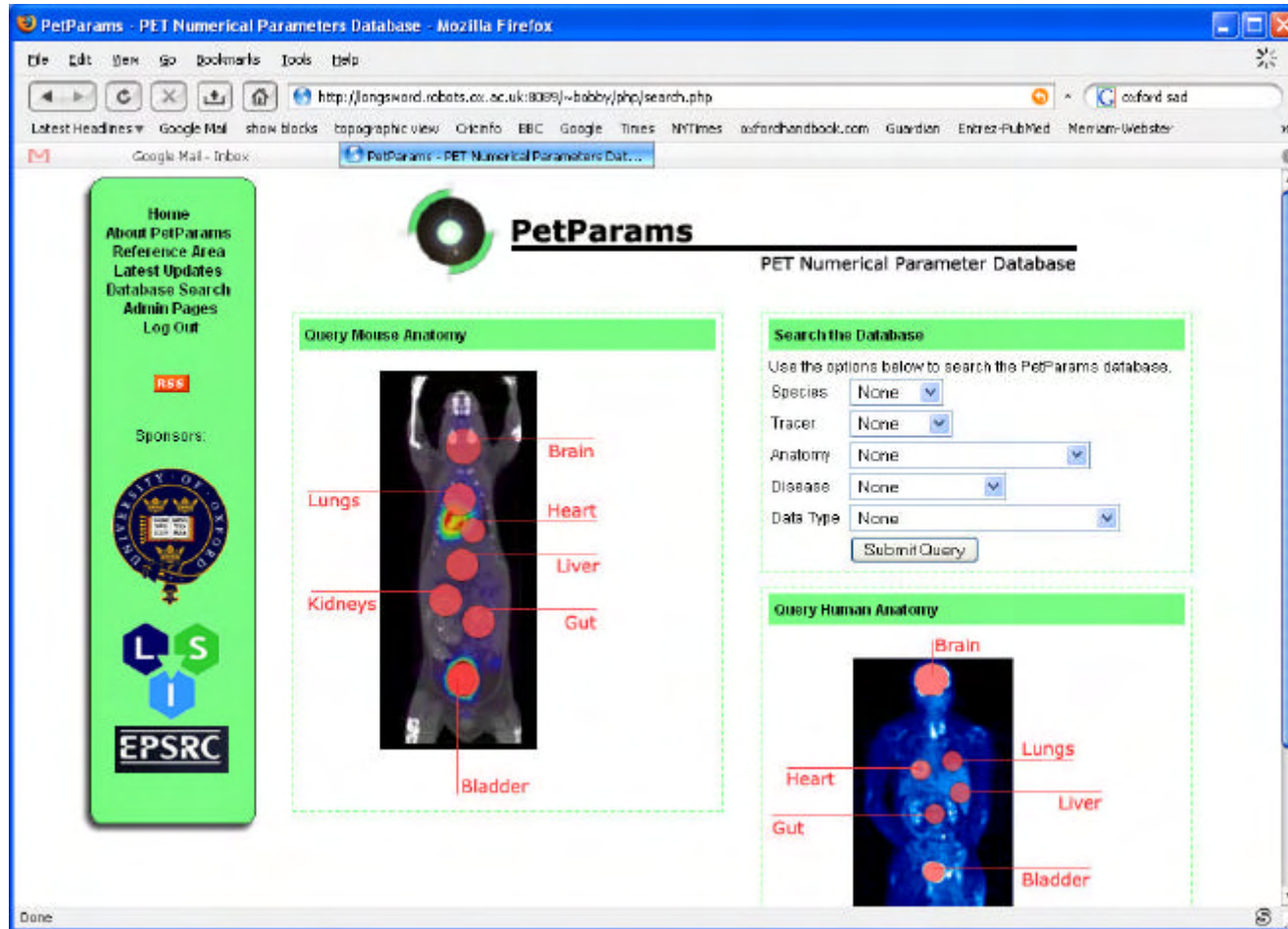
Rigid registration  
performed with  
RevealMVS<sup>1</sup>

Patient Data



Registered Composite Image

# Parameter Database



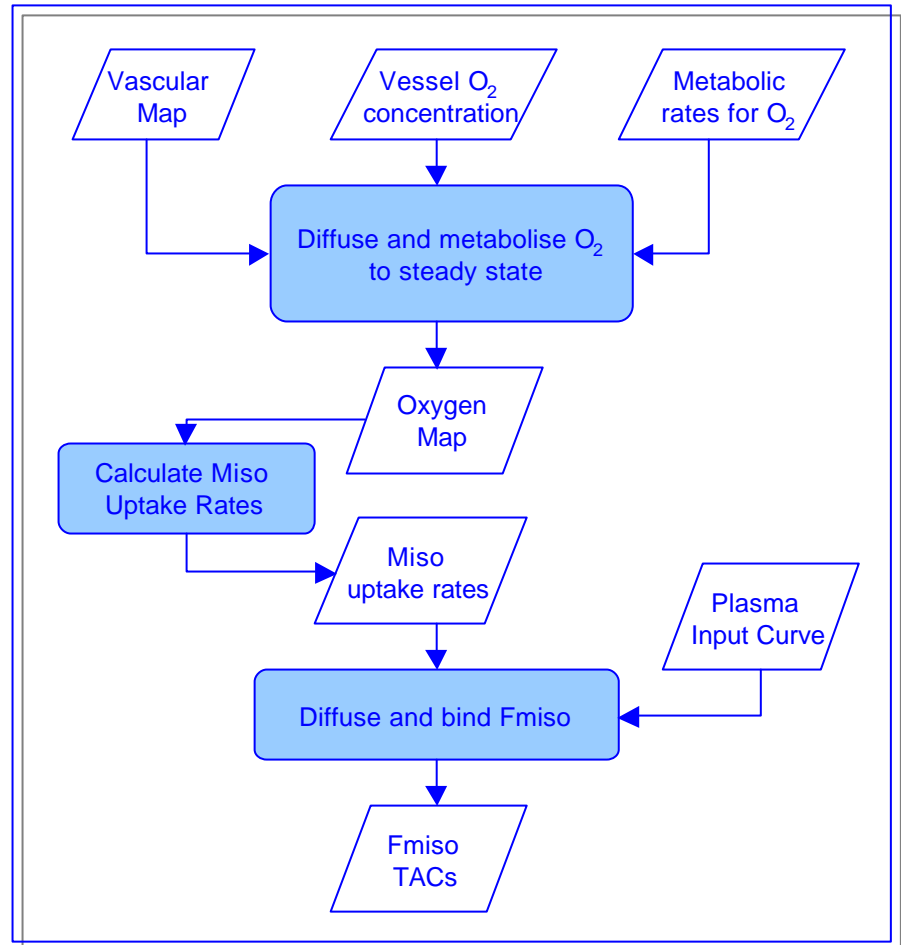
Repository of pharmacokinetic parameters used in published studies, with pubmed links for each.

# Modelling oxygen consumption

Calculates tumour  $pO_2$  at steady state

Calculates hypoxic parameters

Simulates administration of tracer



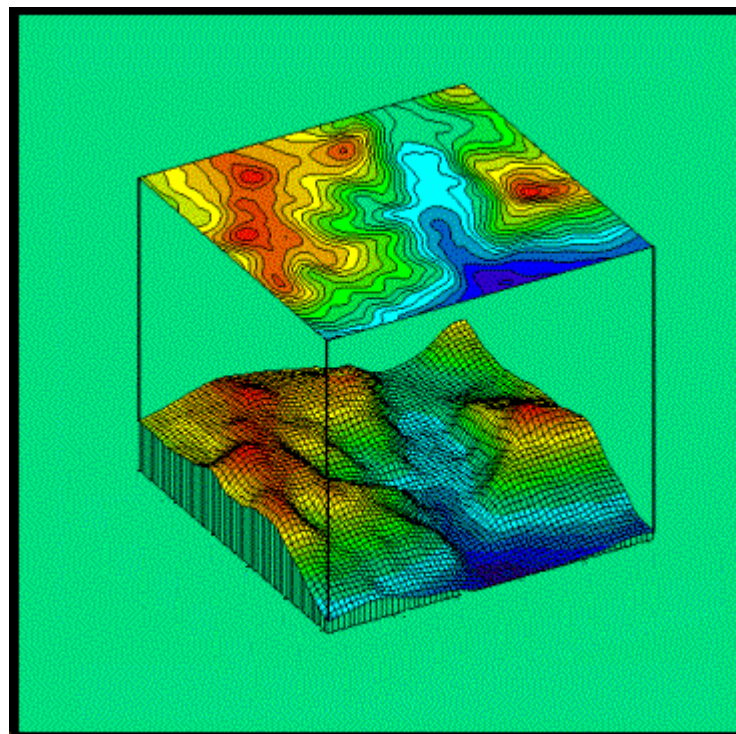


# Vascular Distribution

Explicit representation of microvasculature not ideal:

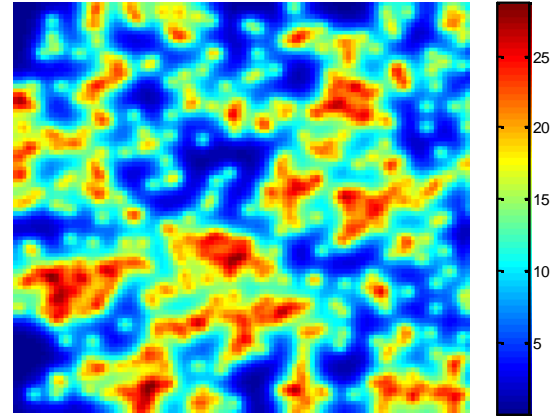
1. Resolution of PET is unable to identify individual vessels
2. For 2D simulations, the effects of out-of-plane vessels are usually not accounted for.

Model using smoothly varying local density function.



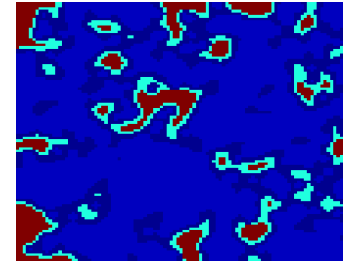
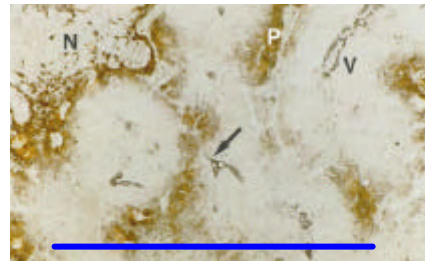
# Oxygen Maps

Oxygen map for  
1mm tumour. Scale  
in mmHg



Distribution of hypoxic regions  
corresponds well to empirical  
data.

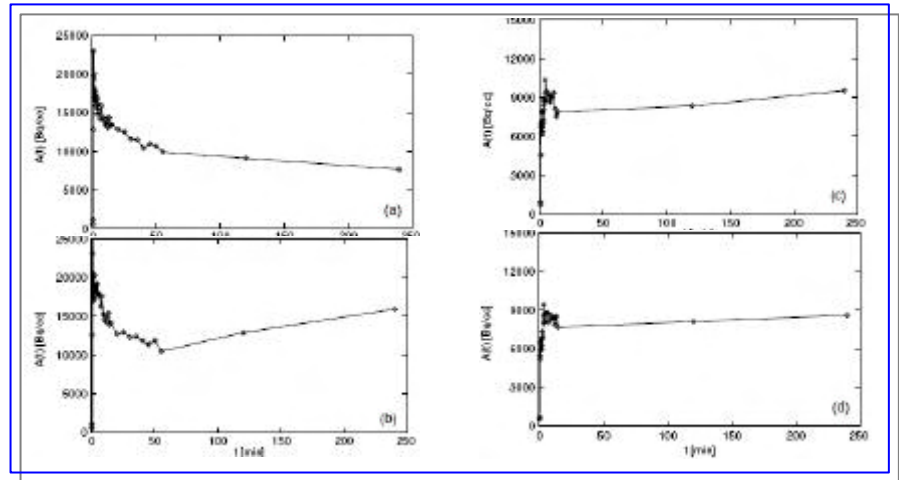
Note *similarity* of textures in  
figure to the right.



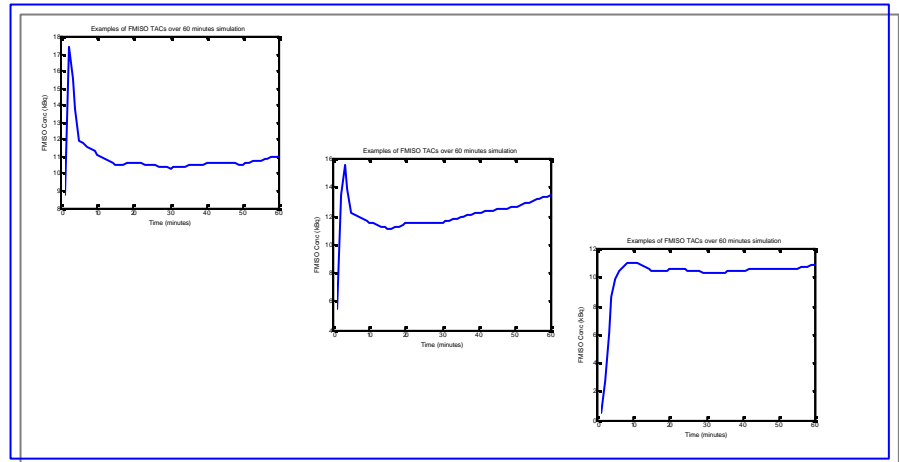
Left: Distribution of pimonidazole staining (provided by Dr. Karin Haustermans, Leuven). Right: Potential hypoxic regions (simulated). Black line represents 1mm

# Tissue Activity Curves

Patient plasma curves  
provided by Daniela  
Thorwarth of Tübingen  
University



Simulated TACs are realistic



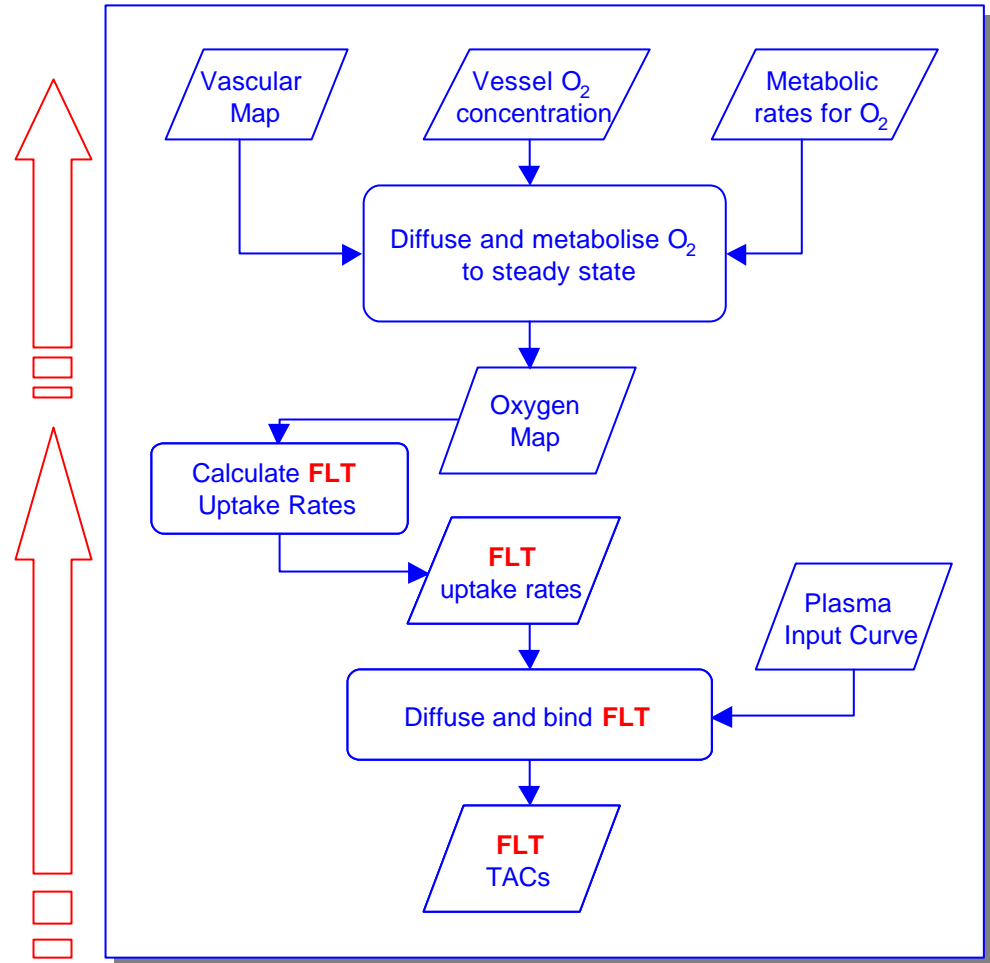
# Current Work

Consider the effects of other processes.

- pH
- Interstitial pressure.
- Lymphatic Drainage

Modify for different tracers (e.g. FDG, FETNIM, FLT, Cu-ATSM).

Invert the model to ascertain physiological causes for observed images

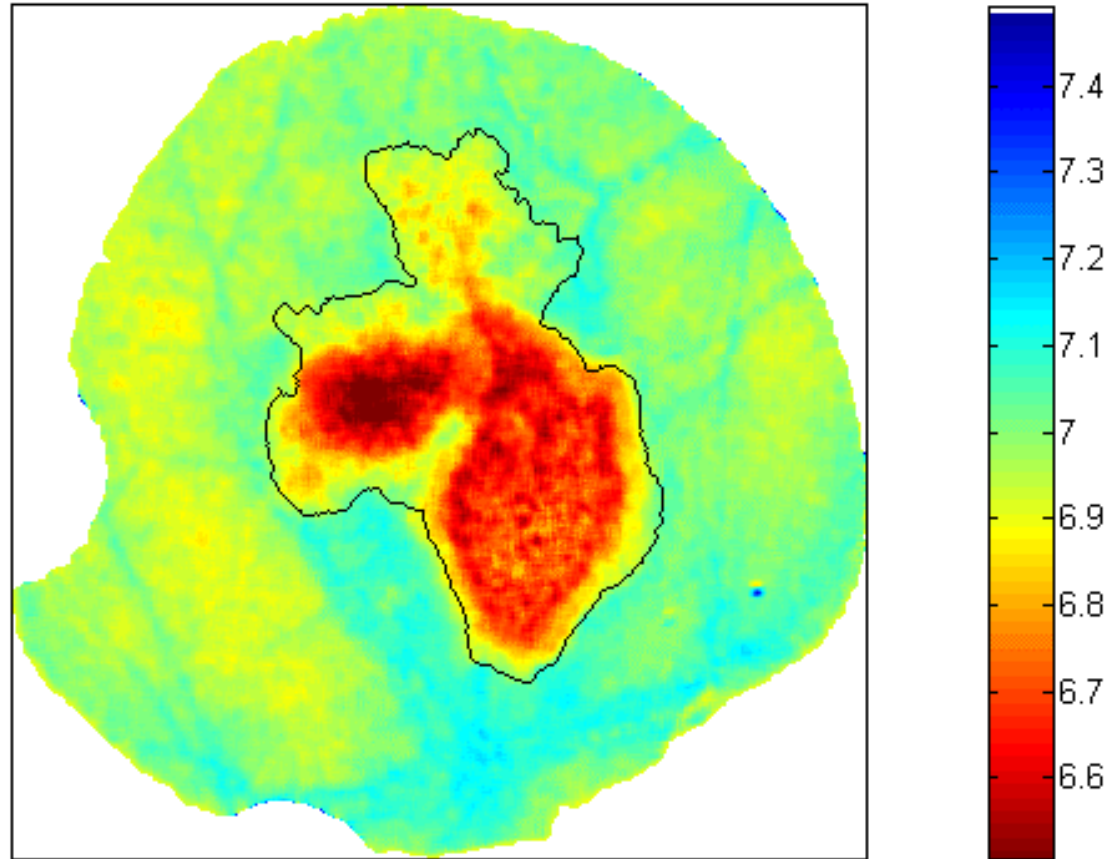


# Typical Tumour pH Profile

Image taken post injection of seminaphthorhodofluor-1 (SNARF-1) into tumour, which exhibits a spectral shift with changing pH

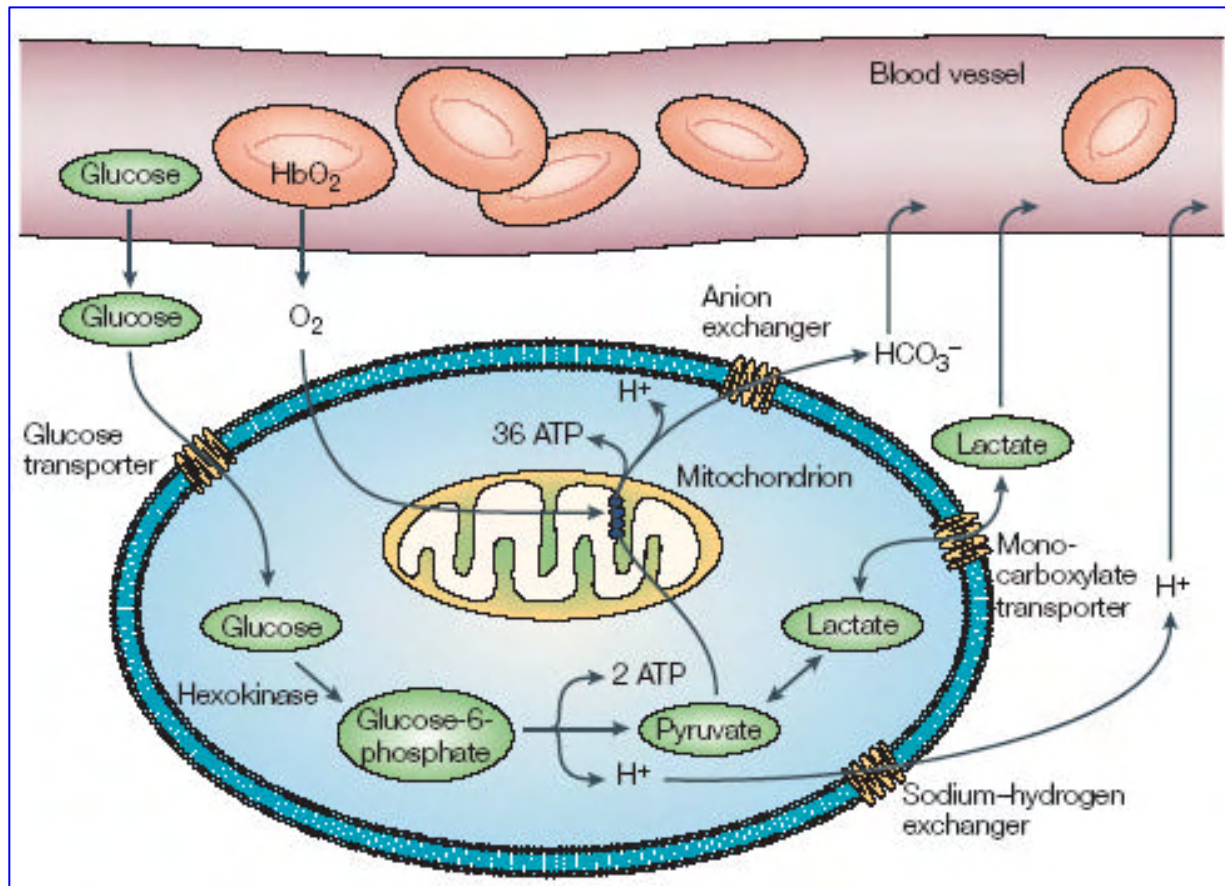
Consequences of significantly lowered pH:

- Resistance to therapy
- Increased:
  - Metastases
  - Invasion
  - Mutation



Courtesy B. Kaylor, University of Arizona

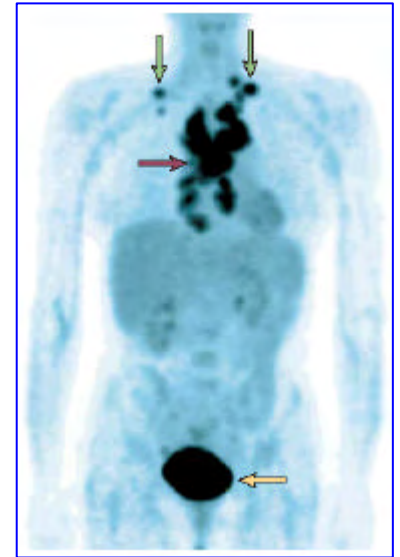
# Mammalian Glucose Metabolism



Acidosis modulation is fundamentally related to the glycolytic phenotype and to tumour hypoxia

# Glycolytic Phenotype

- Clinical use of FDG-PET has demonstrated the upregulation of aerobic glycolysis in most human cancers.
- Carcinogenesis:
  - selective pressures promote proliferation of phenotypes best-suited to their microenvironment...



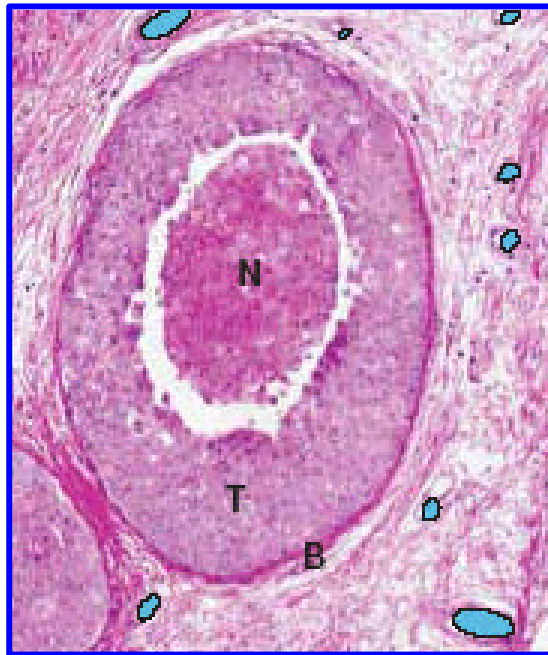
Normal cells  
Aerobic respiration  
36 ATP / glucose



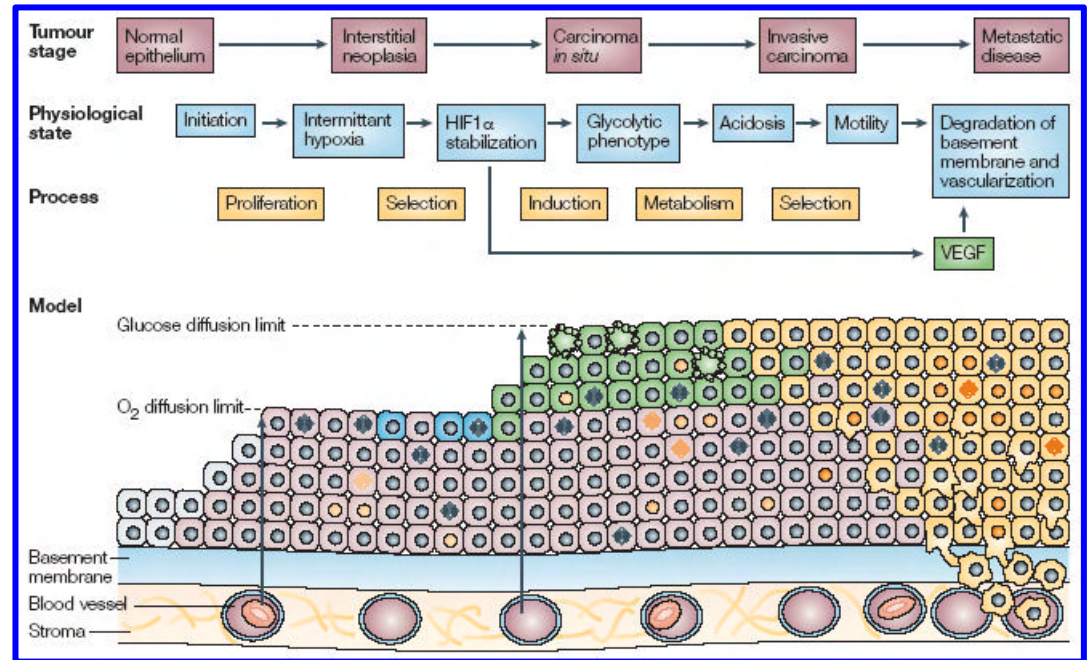
Cancer cells  
Anaerobic respiration  
2 ATP / glucose



# Carcinogenesis Model



DCIS

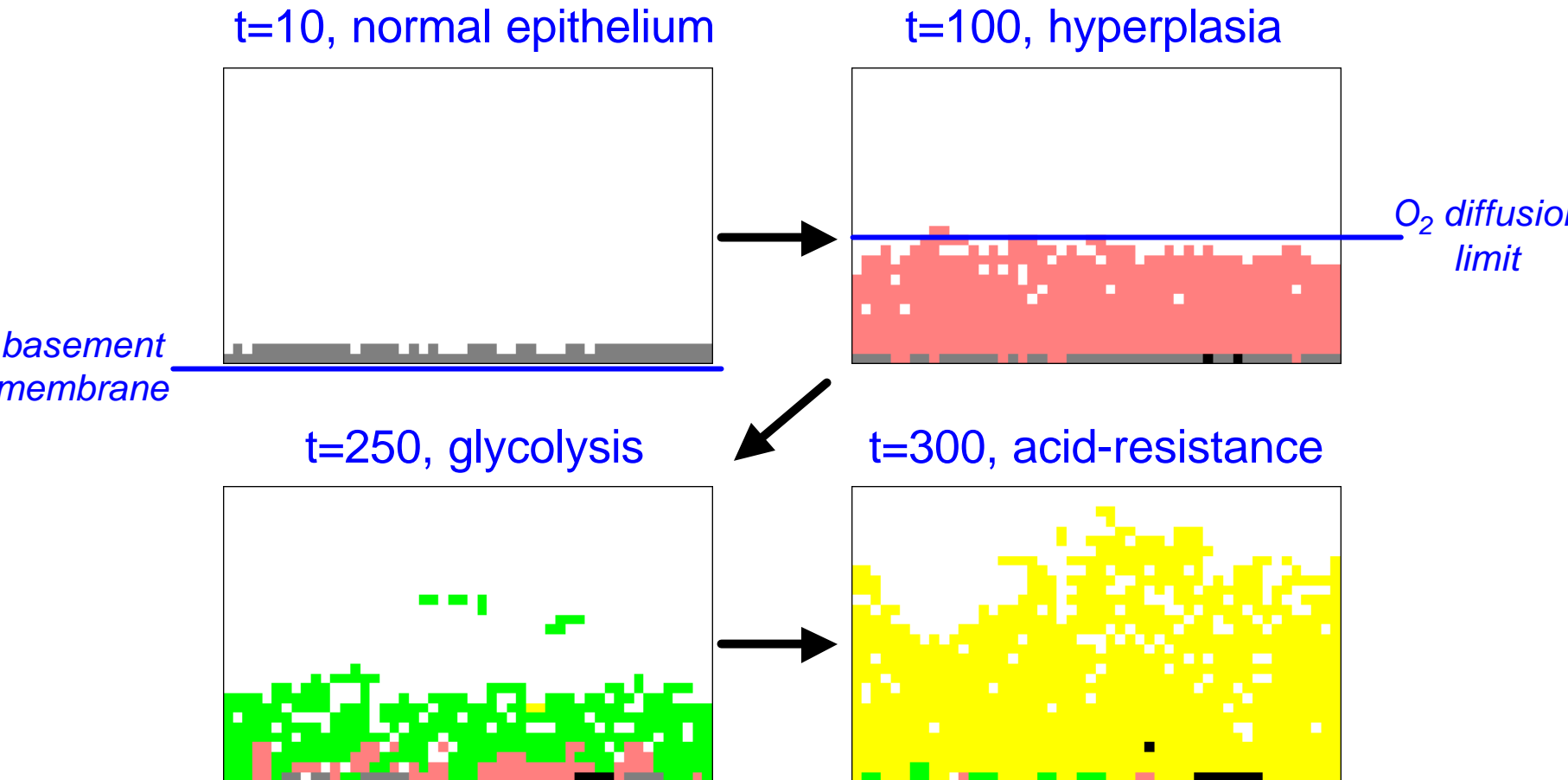


Model

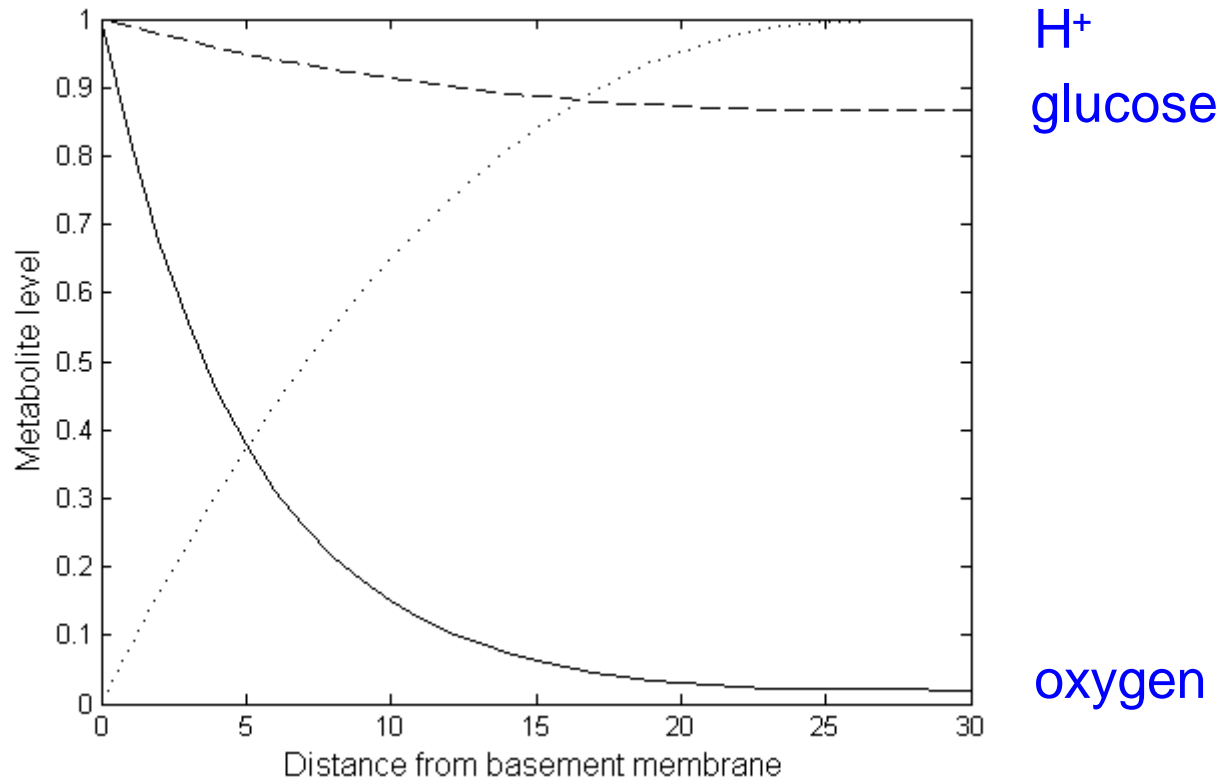
# Cellular Automaton Model Development

- Hybrid cellular automaton:
  - Cells as discrete individuals
    - Proliferation, death, adaptation
  - Oxygen, glucose,  $H^+$  as continuous fields
  - Calculate steady-state metabolite fields after each generation
- Heritable phenotypes:
  - Hyperplastic: growth away from basement membrane
  - Glycolytic: increased glucose uptake and utilisation
  - Acid-resistant: lower extracellular pH to induce toxicity

# Typical Automaton Evolution

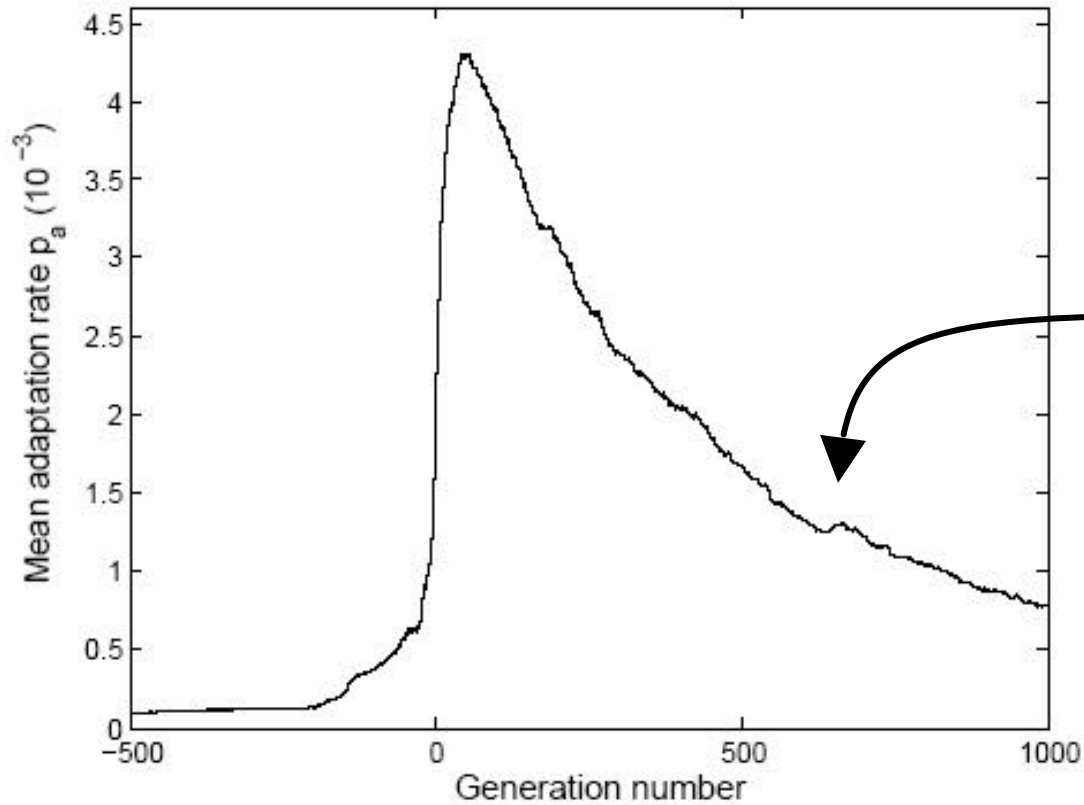


# Variation in Metabolite Concentrations



- Hypoxia common in premalignant lesions such as DCIS
- Glucose supply not a limiting factor over length-scale of carcinogenesis

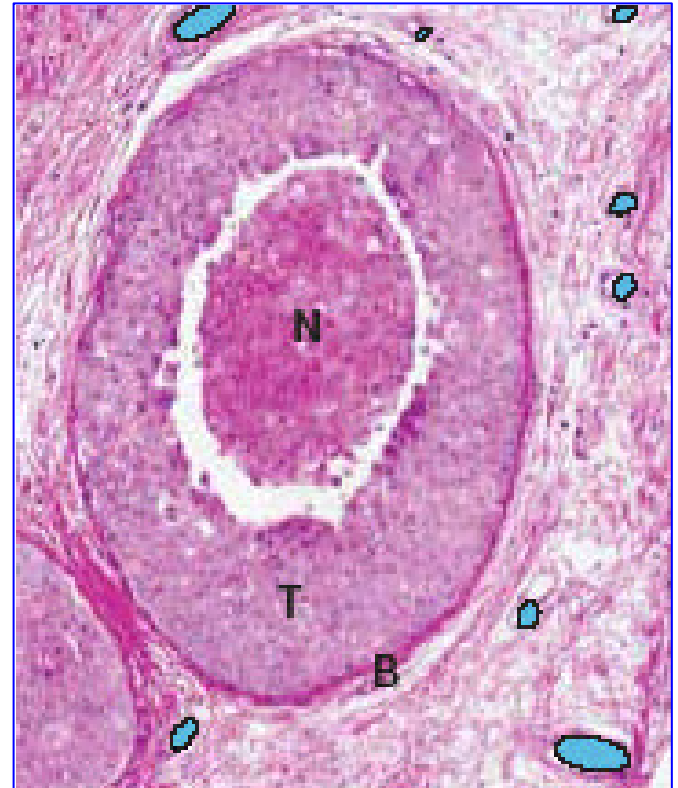
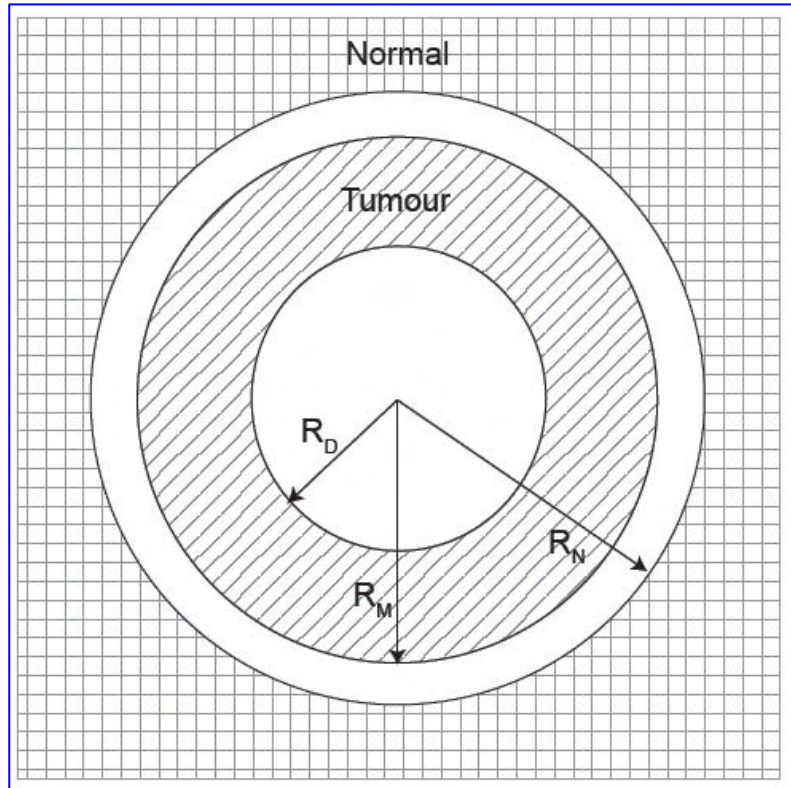
# Variable Adaptation Rate



Slow decrease  
after reaching  
“fittest” phenotype

Large increase following  
onset of invasive phenotype

# Acidity in Tumour Growth



Model tumour using spherical symmetry:  
Necrotic core, active tumour tissue, peritumoural normal tissue

# PDE Model

- Assumptions. Acid:

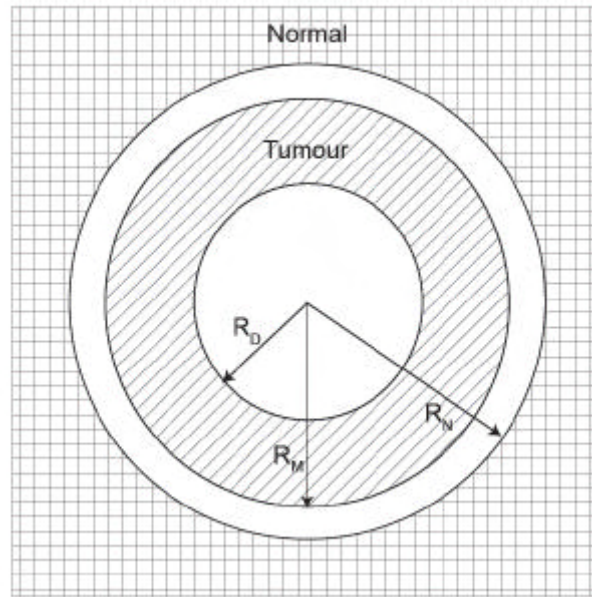
- causes tumour and normal cell death when  $H^+$  concentration above critical levels  $H_T$  and  $H_N$  respectively.  $H_T \gg H_N$  as tumour cells relatively resistant
- produced by active tumour tissue, not normal or necrotic tissue
- removed through blood vessels. Consider both vascular and avascular tumours

- Results. Two typical growth patterns:

- if the tumour is avascular, or  $h_T < 1$ , we see exponential growth followed by auto-toxicity, resulting in a benign tumour
- if the tumour is vascularised and  $h_T > 1$ , we see sustained growth, invading the whole normal tissue space.



# Mathematical model of tumour growth



$$r_H M - r_V V H + \frac{D_H}{R^2} \frac{d}{dR} \left( R^2 \frac{dH}{dR} \right) = 0$$

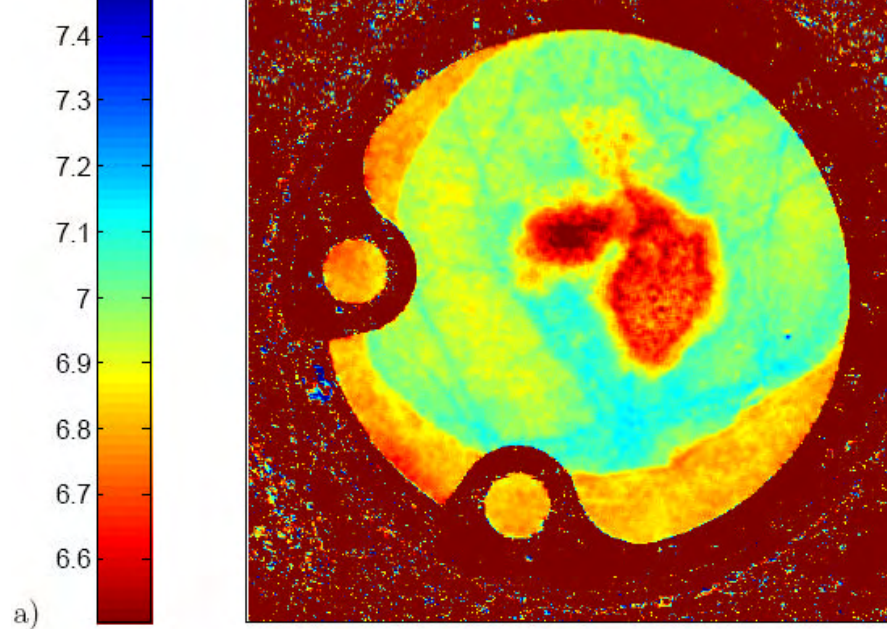
$M$  = tumour cell density

$D_H$  = acid diffusion

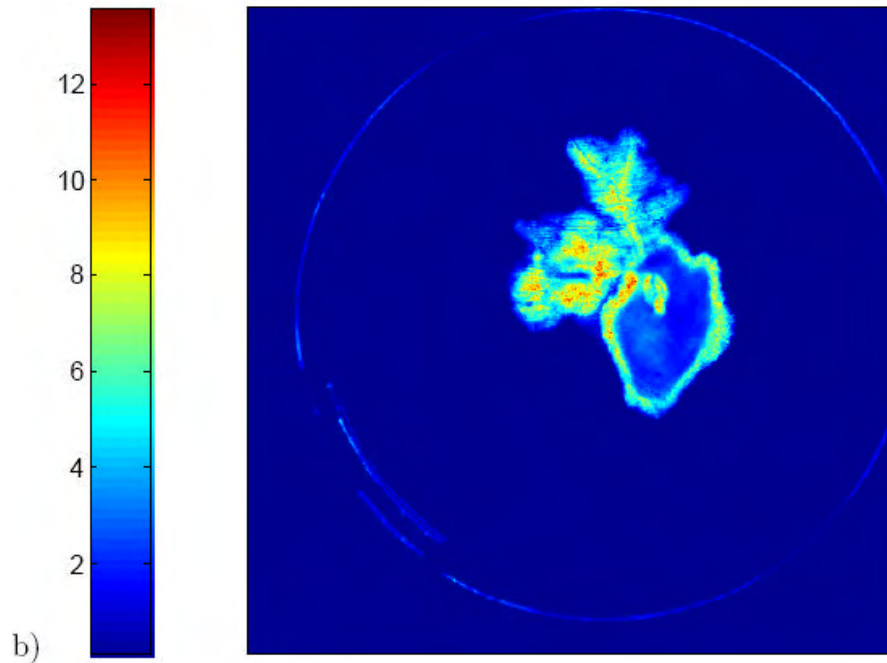
$H$  = extracellular concentration excess H ions

$V = 0, R < R_N; V_N$

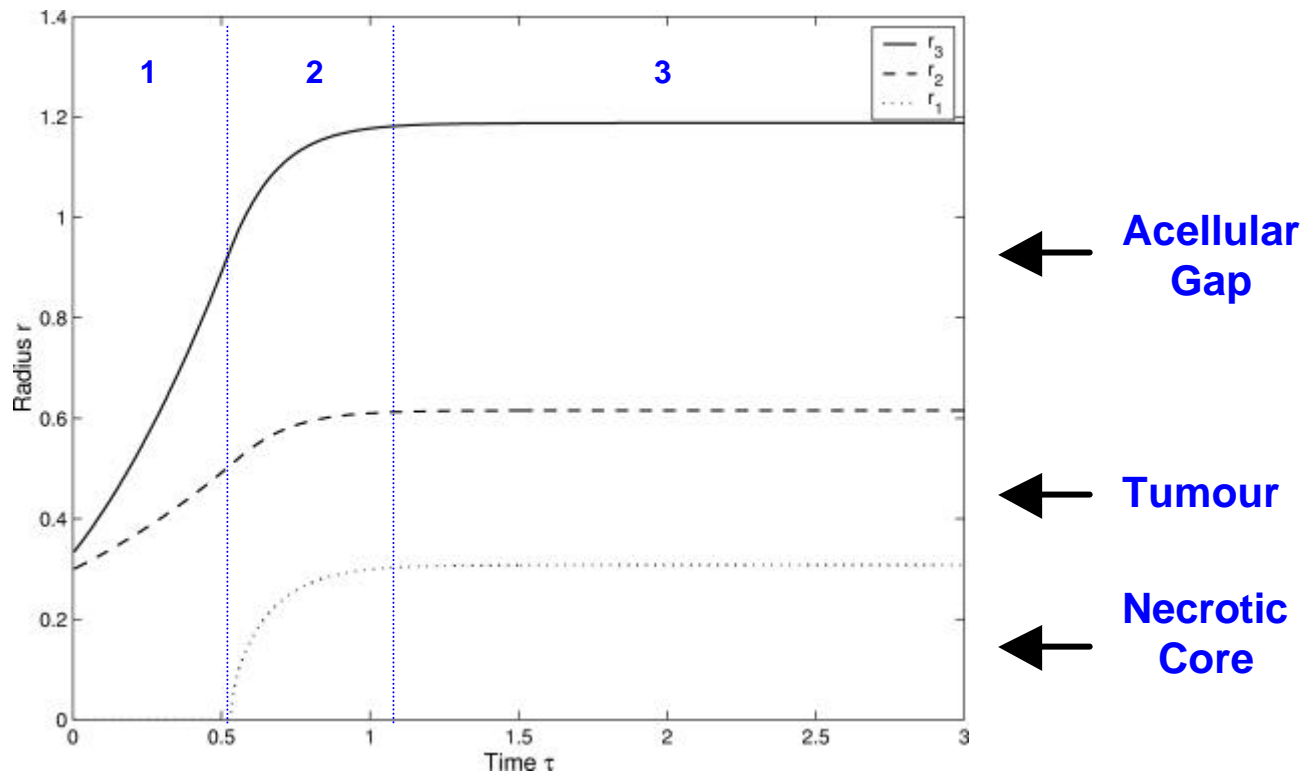
Image taken post injection of seminaphthorhodofluor-1 (SNARF-1) into tumour, which exhibits a spectral shift with changing pH

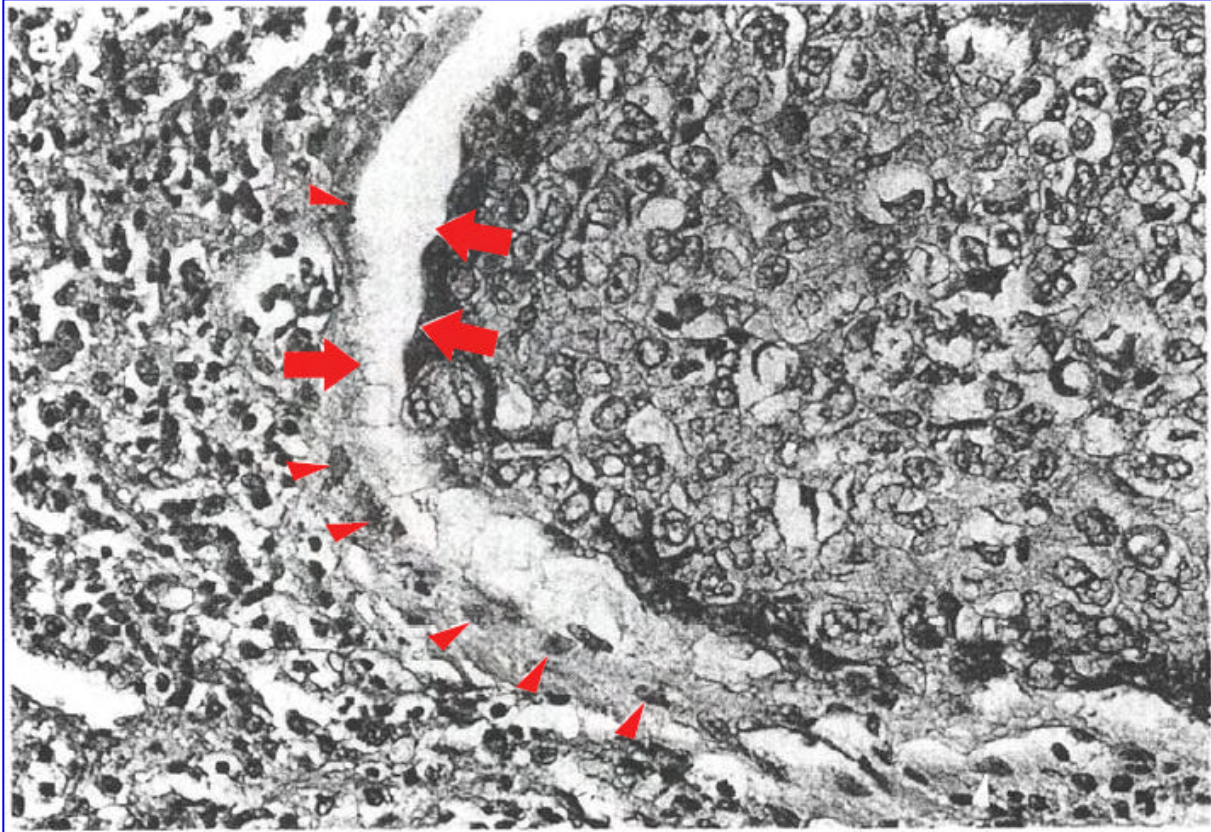


Green fluorescence protein image of the same tumour



- Typical “benign” three-phase growth pattern.



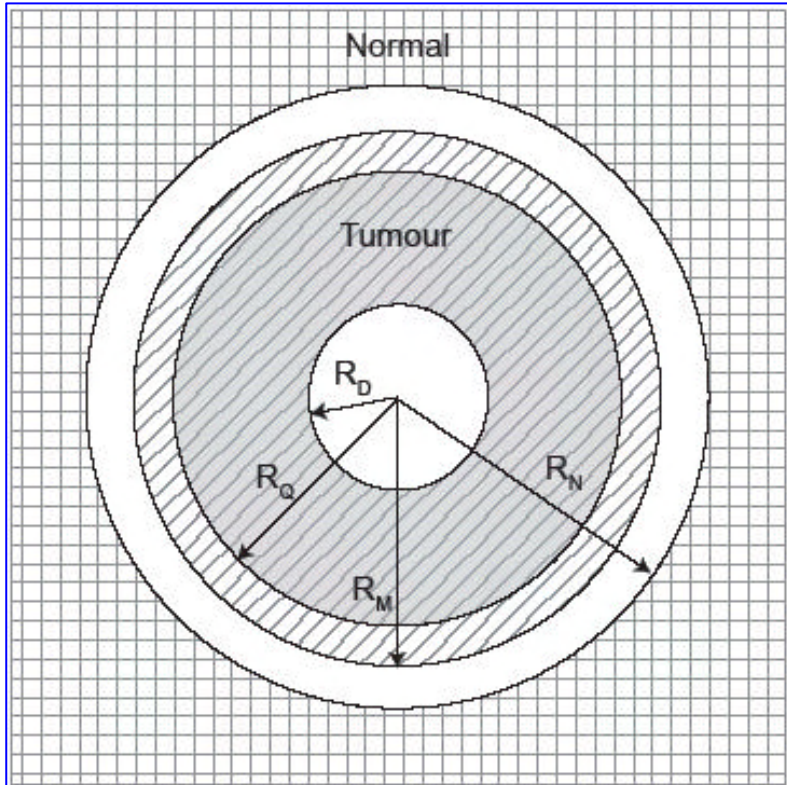


Acellular gap in human neck carcinoma

- Typically of size 100  $\mu\text{m}$



# Quiescent Cells

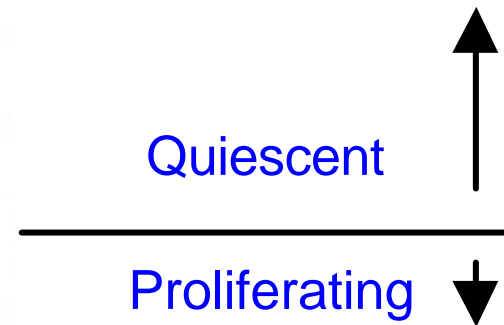
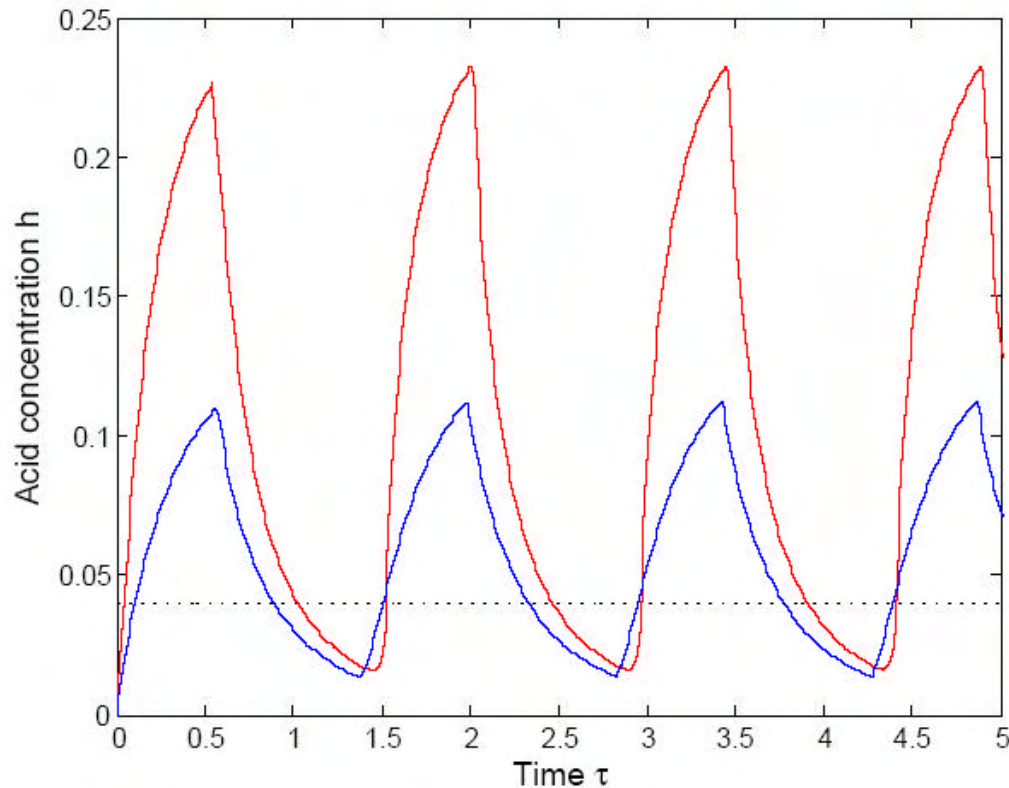


More accurate description of tumour geometry

- “Resting”, non-proliferating cells
- Induced by high acidity
- Produce significantly less acid than active counterparts

? Under this description, tumour radius  $\sim 10 \times$  gap size

# Cyclical Acidosis

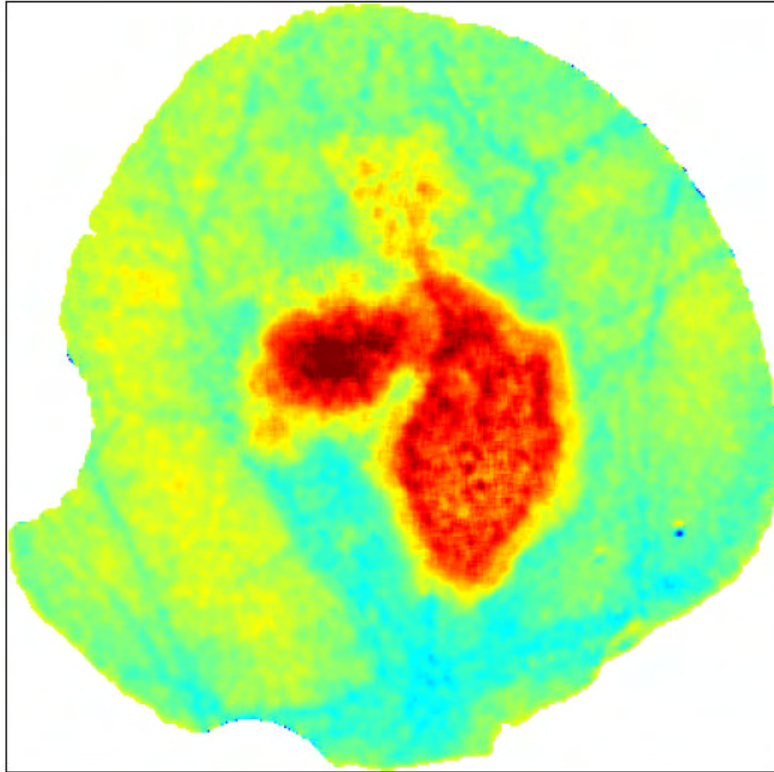


... at tumour centre (red) and tumour edge (blue)  
Cycle time  $\sim$  4 hours

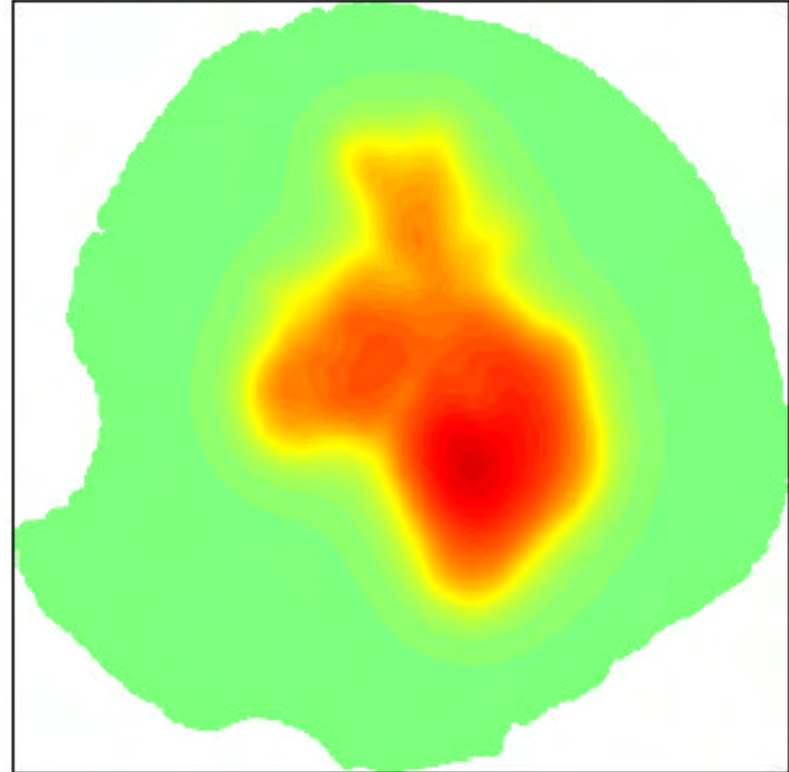


# pH Image Analysis

RMS 0.07 pH



Experimental pH image



Best-fit profile  
& 3 key parameters

available at [www.sciencedirect.com](http://www.sciencedirect.com)  
journal homepage: [www.europeanurology.com](http://www.europeanurology.com)



## Prostate Cancer

# Control of Prostate Cancer by Transrectal HIFU in 227 Patients

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### Abstract

**Purpose:** To evaluate the results of high-intensity focused ultrasound (HIFU) treatment of localized prostate cancer with reference to disease-related prognostic factors.

**Materials and methods:** Patients with T1–2 localized prostate cancers, prostate specific antigen (PSA)  $\leq 15$  ng/ml, Gleason score  $\leq 7$ , prostate volume  $\leq 40$  cc and no previous radical treatment for prostate cancer were treated with the Ablatherm HIFU device. Follow-up included PSA measurements, and prostate biopsies 3 months after HIFU and in cases of rising PSA. Failure was defined as any positive biopsy or a PSA  $> 1$  ng/ml with three consecutive rises.

**Results:** The study included 227 patients. Mean follow-up was  $27 \pm 20$  months (12–121 months). Eighty-six percent had negative control biopsies. Median nadir PSA was 0.10 ng/ml. The actuarial 5-year disease-free survival rate (DFS<sub>r</sub>), combining pathologic and biochemical outcomes, was 66%. DFS<sub>r</sub> showed a significant decrease when stratified according to initial PSA level: 90% with PSA  $\leq 4$  ng/ml versus 57% and 61% with PSA between 4.1 and 10, and between 10.1 and 15 ng/ml, respectively. Incontinence and bladder neck stricture decreased with the treatment procedure standardization from 28% and 31% to 9% and 6%, respectively.

**Conclusions:** HIFU for localized prostate cancer offered high control of local disease with low morbidity. The ability to repeat the HIFU treatment is of major interest.

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## 1. Introduction

Since 1989, in our department transrectal high-intensity focused ultrasound (HIFU) has been studied as a minimally invasive treatment for localized prostate cancer. The first pilot study demonstrated the feasibility of the treatment, and this result has been confirmed by additional short-term evaluations [1,2]. We now present comprehensive data from 227 consecutive patients who underwent this procedure between April 1994 and July 2003.

## 2. Materials and methods

### 2.1. The HIFU principle

HIFU produces ultrasound waves that are generated by a spherical transducer. The ultrasound energy is focused on a fixed point. The aim is to treat the entire gland by juxtaposition of elementary lesions. The device has a fixed focal ultrasound transducer and a motorized system for successive movements of the focal point. Contiguous shots (5 s on, 5 s off) are delivered repeatedly to obtain a complete treatment of the whole gland, while preserving the rectal wall and the surrounding tissues. The HIFU-induced necrosis phenomenon has been modeled by the National Institutes of Health and Medical Research (INSERM Unit 556, Lyon, France) [3].

### 2.2. Equipment

All patients were treated with the Ablatherm HIFU device (EDAP SA, Lyon, France). From 1993 to 1999, the patients were treated with prototype devices. In 1999, the device was granted the CE label and, after 2000, patients were treated with the commercially available device. The differences between the prototypes and the commercially available devices are described in Table 1.

### 2.3. Procedure

In parallel with technical progress, clinical procedures have evolved gradually to attain an efficient level of treatment. The HIFU treatment initially involved just one session for each prostate lobe (1993–1996), followed later by a single session to treat the whole gland. A safety margin of 6 mm was defined for treatment of the apex, taking into consideration heat accumulation and diffusion, to protect the external sphincter—and thus to control the risk of treatment-related

incontinence—while nevertheless treating the apical tissue. Similar logic is applied currently to obtain nerve-sparing procedures. The last issue was the risk of prolonged retention after treatment, caused by the sloughing of necrotic tissue, and possible secondary obstruction. This issue was solved by performing a transurethral resection of the prostate (TURP) immediately before the HIFU session and while the patient was under the same anesthesia. The catheter was removed on day 3 post-HIFU. This combined procedure dramatically simplified post-HIFU patient management and comfort. Since 2000, the patients were treated according to the standardized HIFU treatment procedure: hospitalization the day before treatment for rectal preparation, a single session treatment combining TURP and HIFU with a safety margin for treatment of the prostate apex and discharge from hospital at day 4 with no urinary catheter.

### 2.4. Patient selection and follow-up

For this study, patient selection was based on the following criteria: localized prostate cancer, clinical stage T1–T2, baseline prostate specific antigen (PSA)  $\leq 15$  ng/ml, prostate volume  $\leq 40$  cc, no previous radical treatment for prostate cancer and at least 1 year of follow-up.

All patients were assessed regularly on the following criteria: baseline PSA, post-HIFU PSA measurement at 1, 3, 6 and 12 months then every 6 months, and prostate sextant biopsies performed before inclusion and 3 months after HIFU treatment. Additional control biopsies were performed during follow-up in cases of rising PSA. All the patients satisfying these criteria were included. Assessment criteria included the nadir PSA, the posttreatment negative biopsy rate and the disease-free survival rate (DFSr). Failure was defined as any positive biopsy or a PSA  $> 1$  ng/ml with three consecutive rises. Kaplan-Meier product-limit methods and log-rank tests were used to evaluate the data. In case of positive prostate biopsy during follow-up without evidence of metastasis, HIFU retreatment was performed. For those retreated, the only considerations were the follow-up time and assessment after the last session.

The need for an adjuvant treatment after single or repeated HIFU was defined by general rules (i.e., a rising PSA level, with or without residual local cancer evidenced by biopsy). External radiation therapy, hormonal deprivation or a combination of both was administered in the light of the patient's general status and life expectancy. Patient status and treatment-related complications were followed up by periodic patient visits and by self-administered questionnaires. Stress incontinence was graduated into three grades. Grade one was

**Table 1 – Development of the device**

Dates	Device	Transducer frequency (MHz)	Shot duration (s)	Safety features	HIFU sessions	TURP
1993–1995	Prototype no. 1	2.5	4	No	1 per lobe	No
1996–1998	Prototype no. 2	3	4.5	Control of the distance rectal wall transducer	1 per lobe	No
1998–1999	Prototype no. 3	3	5	Rectal cooling	1 per prostate	No
2000–2003	Final device	3	5	Safety features	1 per prostate	Yes

defined as loss of urine during heavy exercises but using not more than 1 pad per day, grade two as loss of urine during light exercises but not at rest or during sleep, and grade three as a total loss of urine. Patients able to penetrate their partner without pharmacologic support were rated potent. The International Index of Erectile Function (IIEF) questionnaire (mailed) was used to accurately measure erection quality in patients treated by means of a nerve-sparing procedure. Contrast-enhanced, dynamic magnetic resonance imaging (MRI) examinations were performed in a study protocol. Twenty-one patients, who gave informed consent, were included in the MRI protocol [4]. They underwent pre- and postoperative (2–5 days after HIFU treatment) MRI examinations. The MRI findings were compared with the results of the transrectal biopsy examinations.

### 3. Results

#### 3.1. Patient characteristics

A total of 227 patients satisfied the inclusion criteria and were considered for analysis. The baseline characteristics are summarized in Table 2. The mean follow-up period for the whole population was  $27.5 \pm 20$  months, ranging from 12 to 107 months (median, 20.5 months), the follow-up being defined as the interval between the last HIFU session and the last PSA measurement. Between 1993 and 1999, 51 patients were treated with the prototypes, and between January 2000 and July 2003, 176 were treated with the commercially available device. In this subgroup, the HIFU session was combined with a TURP.

The mean number of HIFU sessions was  $1.4 \pm 0.6$  (1 session, 130 patients; 2 sessions, 87 patients; 3 sessions or more, 10 patients). On average,  $419 \pm 126$  shots per HIFU session were delivered (median, 415), corresponding to  $581 \pm 197$  shots per patient (median, 570). Compared with the mean gland volume in this cohort, on average, 111% of the volume was

treated after the first HIFU session and 156% after the subsequent HIFU sessions.

In total, 76 patients received neoadjuvant hormonal deprivation: Six patients with long-term hormonal ablation (mean duration, 24 months), who switched to a curative option, and 70 who received a short hormonal deprivation for gland reduction (mean duration, 4.7 months). Hormonal deprivation was used when the initial size of the gland was greater than 40 cc. Any hormonal therapy was discontinued at the time of the HIFU session.

#### 3.2. MRI findings and pathologic results

Fat-saturated gadolinium-enhanced MRI can demonstrate accurately the extent of tissue damage induced by HIFU. The treated area appears as a nonenhancing hypointense zone surrounded by a peripheral rim of enhancement 3 to 8 mm thick. These abnormalities correspond to a nucleus of coagulation necrosis surrounded by a peripheral zone of inflammation, consistent with the pathologic HIFU effect.

Treatment-induced MRI abnormalities usually disappear within 3–5 months in a centripetal way and MRI is not suitable for long-term monitoring.

After the HIFU treatment, prostate volume (assessed by transrectal ultrasound) decreased considerably from  $23.9 \pm 10.2$  cc (median, 25 cc) before to  $10.5 \pm 8.8$  cc (median, 9 cc) after. As the prostate volume was small after HIFU, sextant control biopsies usually were used to evaluate the local control of the cancer. Post-HIFU biopsies were negative in 196 patients (86%). Of the 31 (14%) patients presenting with residual cancer, 19 received an adjuvant treatment: external radiotherapy for 12 patients, hormone administration for three patients and combined treatment for four patients. Twelve (5%) patients with residual cancer did not receive any additional treatment but were closely monitored—that is, watchful waiting because of a low and slowly rising PSA level: Mean nadir PSA was  $0.38 \pm 0.50$  ng/ml, mean PSA at last follow-up was  $0.89 \pm 0.83$  ng/ml and mean PSA velocity was  $0.25 \pm 0.21$  ng/ml/yr. For these patients, an additional HIFU session was considered during follow-up on the basis of evolution in the PSA level.

#### 3.3. Biochemical results

The nadir PSA was observed within 6 months after HIFU in all patients (mean time for reaching nadir, 4.4 months). The mean nadir PSA was  $0.33 \pm 0.70$  ng/ml, with a median at 0.10 ng/ml. For the overall

**Table 2 – Patient baseline characteristics**

No. of patients	227
Mean ( $\pm$ SD) age (yr)	$68.8 \pm 5.82$
Mean ( $\pm$ SD) PSA (ng/ml)	$6.99 \pm 3.48$
Clinical stage	
T1A	6 (3%)
T1B	17 (7%)
T1C	99 (44%)
T2	105 (46%)
Gleason score	
2–6	152 (67%)
7	75 (33%)
Mean ( $\pm$ SD) prostate volume (cc)	$23.9 \pm 10.26$



population, 191 (84%) patients presented a nadir PSA  $\leq 0.5$  ng/ml, 17 (8%) patients presented a nadir PSA between 0.51 and 1 ng/ml, and 19 (8%) patients presented a nadir PSA  $> 1$  ng/ml.

### 3.4. Disease-free rates

The actuarial DFSR at 5 years, as judged from the combined pathologic and biochemical results, was 66% for the whole population (Fig. 1). No significant variations were observed when the calculation was stratified according to the T stage, initial Gleason score and neoadjuvant hormonal deprivation (Fig. 2 b–d). Significant variations in DFSR were observed when the calculation was stratified according to the initial PSA value: 90% with PSA  $\leq 4$  ng/ml versus 57% and 61% with PSA between 4.1 and 10, and between 10.1 and 15 ng/ml, respectively (Fig. 2a). The DFSR for the patients treated since 2000 with the commercially available device (with associated TURP) was 70%, which was greater than the DFSR (58%) obtained between 1993 and 1999 with the prototypes (without associated TURP), but the difference was not significant (Fig. 2e).

### 3.5. Clinical outcome

The Foley catheter was removed at a mean of 7 days after the treatment. According to the procedure used, catheter duration dramatically decreased from 12 days (HIFU session without associated TURP) to 5 days (HIFU session associated with TURP). The need for an adjuvant treatment for local disease control is described in section 3.2. In addition to local control, patients with negative biopsies but significantly rising PSA levels also received an adjuvant treatment. All patients presenting with a significantly rising PSA level received an adjuvant treatment, regardless of local control

and biopsy results: of the 28 (13%) patients who received an adjuvant treatment, nine had negative control biopsies but a rising PSA and 19 had residual cancer in the prostate. In total, 15 (7%) patients underwent external radiotherapy, 6 (3%) patients received an adjuvant hormone therapy, and 7 (3%) patients received a combined radiohormonal treatment. These results correspond to an actuarial adjuvant treatment-free rate at 5 years of 77% (Fig. 3). Hormonal deprivation was used in patients with poor general status, radiation therapy alone in patients with long life expectancy and combined treatment in patients with involvement of the prostate capsula identified by the control biopsies (patient under staged at the initial biopsies).

### 3.6. Outcome prognostic factors

We evaluated the prognostic value of the observed nadir PSA. For this purpose, three subgroups were defined according to the nadir PSA level: nadir PSA  $\leq 0.5$  ng/ml, nadir PSA between 0.51 and 1 ng/ml, and nadir PSA  $\geq 1.1$  ng/ml. In these three subgroups, the negative biopsy rates observed were 89%, 76% and 68%, respectively.

### 3.7. Treatment-related morbidity

Seven patients died during the follow-up, all from nonrelated diseases: cardiovascular disease for one patient (stroke), cancer in four (one myeloma, one primary lung cancer, one colon cancer, one bladder transitional cell carcinoma), one from natural causes and one from a car accident. The main treatment-related side effects are listed in Table 3. Only acute morbidity was observed after HIFU treatment; the latest possible adverse effect was bladder neck/urethra stricture that became symptomatic about 6 months after treatment and was resolved with a cold knife incision or TURP. Four patients needed complementary procedures for recurrent strictures.

The impact of the device and clinical procedure on treatment efficacy was difficult to establish because of the time effect, but it can be quantified easily in relation to the acute morbidity (Table 4). Better knowledge of heat diffusion, thanks to computer simulation, made it possible to define a safety margin for treating the prostate apex, which resulted in a sharp decrease in stress incontinence and even the disappearance of severe incontinence. Combined with TURP, this method led to a sharp decrease in prostate urethra or bladder neck stenosis (6% versus 31%). Valid data on potency were available from only 67 patients who answered

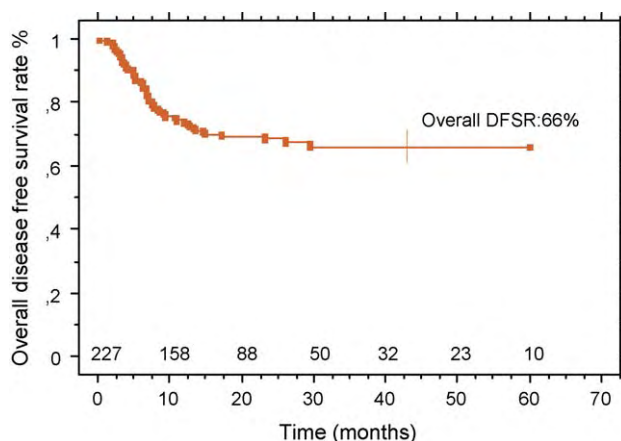


Fig. 1 – Overall disease-free survival rate.

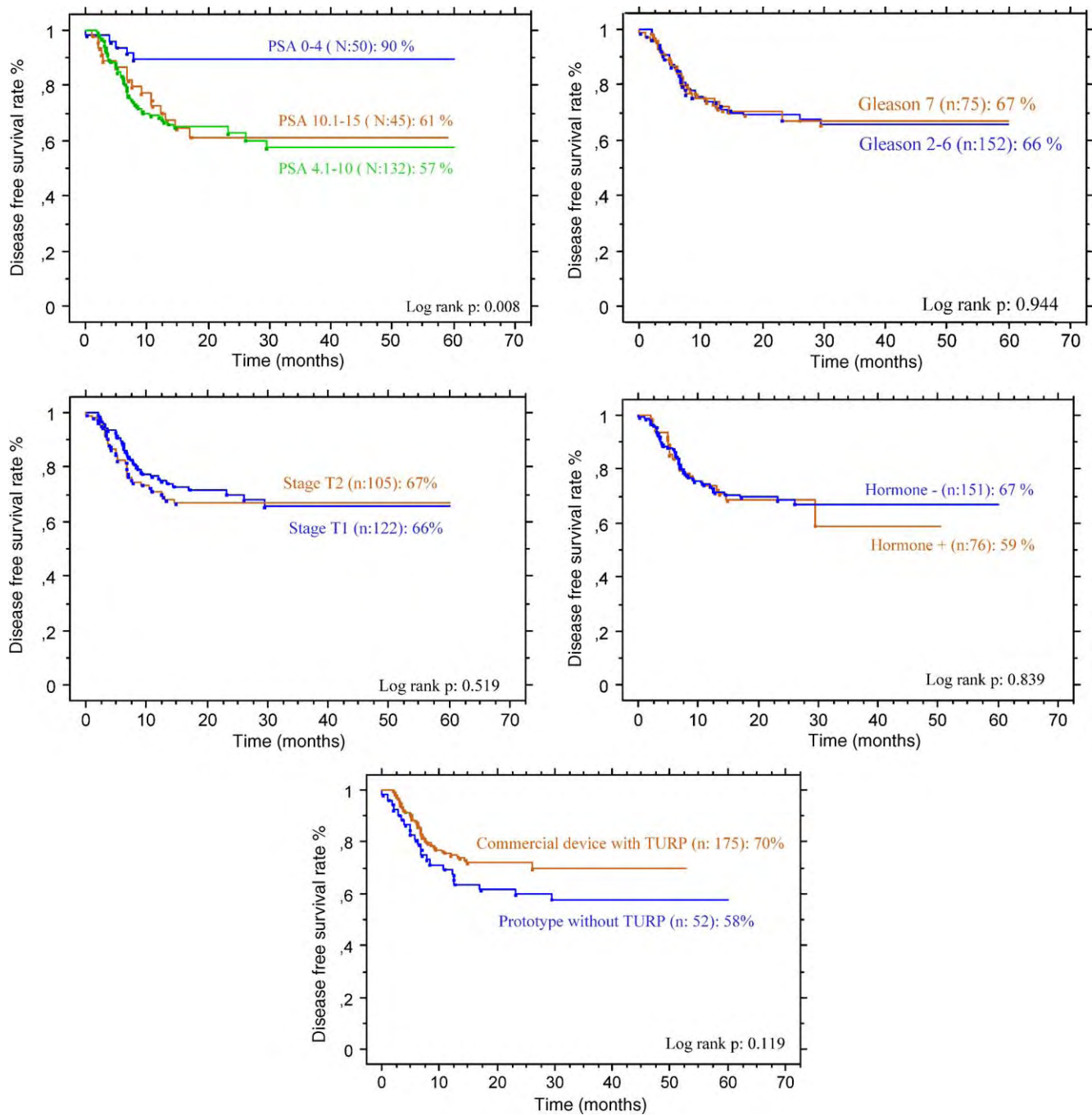


Fig. 2 – (a) Disease-free survival rate in relation to initial PSA level. (b) Disease-free survival rate in relation to Gleason score. (c) Disease-free survival rate in relation to clinical stage. (d) Disease-free survival rate in relation to neoadjuvant hormonal deprivation. (e) Disease-free survival rate depending on procedure.

questionnaires. A total loss of potency was observed in 16 of 41 (39%) previously potent patients treated without a nerve-sparing procedure. In 26 patients, nerve-sparing procedures were possible. Erections were preserved in 18 (69%) patients. The IIEF score was >16 in eight (31%) patients and between seven and 15 in 10 (38%) patients.

#### 4. Discussion

HIFU resulted in local control (negative biopsies) in 86% of our patients, which is similar to the results reported for the other options. Holmberg [4] reported a 20% risk of local progression verified by biopsy 8 years after radical surgery. After external beam



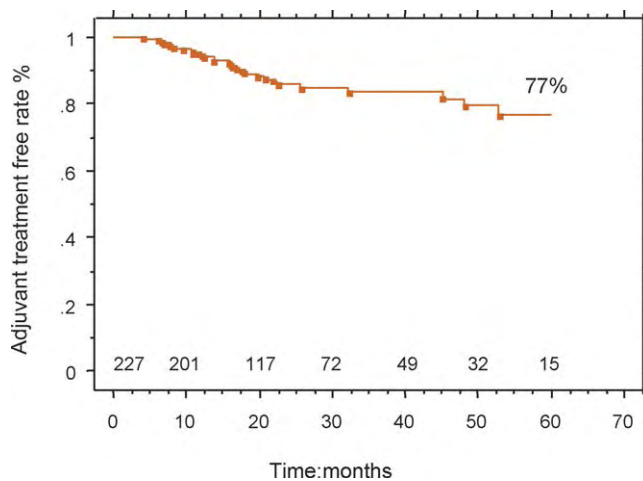


Fig. 3 – Overall actuarial adjuvant treatment-free rate.

radiation therapy (EBRT), high positive biopsy rates were reported, from 43% [5] to 62% [6]. After brachytherapy, two publications reported positive biopsy rates of 22% [7] and 26% [8]. The biochemical failure after EBRT was defined in 1997 by the American Society for Therapeutic Radiology and Oncology as three consecutive PSA increases, but without any valid end point or PSA threshold to define this biochemical failure. This definition implies at least a 3-month time interval between the successive PSA measurements.

The use of combined criteria (biopsies and PSA stability) is certainly the best adapted for evaluating the efficacy of HIFU treatment. Because of excessive cavitation, which induces the formation of macro-bubbles (boiling effect), coagulation necrosis is not totally homogeneous within the treated area. Persistent normal glandular foci explain why residual PSA secretion is observed commonly after HIFU. We chose a PSA threshold of 1 ng/ml. A similar PSA cutoff was used after EBRT [9].

No significant difference was observed in the DFSR with regard to the Gleason score. According to the temperature level reached in the prostate tissue [3], there is no reason to suppose that high-grade cells are less destroyed than low-grade cells.

Table 3 – Side effects

Adverse effects		
Side-effects	No. of patients	%
Incontinence	30	13
Stenosis	27	12
Sloughing	20	9
Urgency	12	5
Perineal pain	7	3
Acute UTI	4	2
Hematuria	1	0.5

No significant difference in the DFSR was observed in relation to previous hormonal deprivation: Hormonal deprivation was able to reduce the size of the gland, but no synergistic effect with the HIFU treatment was observed.

Blana et al. [10] recently reported a 5-year disease-free rate of 71% in a population similar to ours. In this trial the event occurrence was determined by strict criteria: any positive biopsy and/or PSA rise of >0.4 ng/ml. In this German study, 93.4% of the patients had negative control biopsies, and the median nadir PSA was 0.07 ng/ml. The treated volume was 146% of the prostate volume with considerable overlapping of the treated areas. The incidence of the main adverse effects did not increase despite the increased thermal dose. This study showed that it is possible to improve the efficacy of HIFU therapy by increasing the number of shots during the first HIFU session.

Only 28 of our patients required adjuvant therapy. Previous studies using data from CaPSURE have suggested that the need for a secondary treatment may be an appropriate surrogate end point for defining treatment failure [11]. The management of recurrence after HIFU is very different from that after radiation therapy, because there is no maximum dose and HIFU sessions can be repeated. Moreover, HIFU therapy is not a therapeutic impasse, and external radiation may be considered for salvage curative therapy after HIFU.

HIFU makes it possible to have early feedback on treatment efficacy, the nadir PSA usually being

Table 4 – Incontinence and stenosis depending on procedure

	1993–1999 51 patients	2000–2003 176 patients	Total 227 patients
Incontinence			
Grade 1	8 (16%)	13 (7%)	21 (9%)
Grade 2	3 (6%)	3 (2%)	6 (3%)
Grade 3	3 (6%)	0 (0%)	3 (1%)
Total	14 (27%)	16 (9%)	30 (13%)
Stenosis	16 (31%)	11 (6%)	27 (12%)

reached in the following 4 months. Because this nadir is attained soon after HIFU treatment, statistical analysis could be used in a patient cohort followed for over a year. This early biochemical response is a significant advantage for quickly identifying patients with residual cancer.

The incidence rate of side-effects significantly decreased with the development of the device and treatment procedure. Three cases of total incontinence were reported in patients treated with the prototype, and 27% complained of stress incontinence. A 6-mm safety margin from the apex has now been defined to preserve the external sphincter, thus avoiding these adverse effects. No grade 3 incontinence occurred after this modification, and only 9% of the patients reported mild or moderate stress incontinence, with no increase in apical residual cancer. The rate of urinary outlet obstruction observed after HIFU dramatically decreased after we combined the HIFU session with a TURP. The feasibility of this combined TURP and HIFU treatment was assessed first by Vallancien [12] who concluded that it significantly reduced the urinary catheter time, with early removal of the catheter after HIFU, and dramatically simplified post-HIFU patient management and comfort. The TURP defect does not affect the treatment, since it is collapsed to a virtual cavity by the intra-rectal inflated balloon. Chaussy and Thuroff [13] demonstrated that this combined procedure significantly decreased the International Prostate Symptom Score (IPSS). Moreover, there is less sloughing and bladder outlet obstruction because of improved clearance of necrotic tissue. Bladder neck and urethral stenosis are the only late side-effects seen after HIFU. The adverse events were managed with cold knife urethrotomy or bladder neck incision. The continence of the patients with bladder outlet obstruction was evaluated after treatment of the strictures. Total loss of potency occurred in more than 39% of the previously potent patients; this effect probably was induced by heat diffusion in the neurovascular bundles during treatment of the lateral part of the gland. It seems that it was possible to preserve the potency in 69% of previously potent patients by using a safety margin for one erectile nerve in those low-risk patients with unilateral positive biopsies.

## 5. Conclusion

Transrectal HIFU is a minimally invasive therapy that controled localized prostate cancer locally in 86% of the cases. This therapy provided disease control in 66% of the patients with clinically confined prostate

cancer. Early feedback on treatment efficacy was gained by using nadir PSA (obtained within 4 months) and random control biopsies.

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# Allocating Assets – Opportunistic Acquisitions\*

*Expanding product line, manufacturing and servicing capabilities, tactical benefits and technological prowess*

Year	Business	Strategic Purpose
1999	Focus Surgery	HIFU Technology/Multiple Applications
1999	Hearing Innovations	New Technology/Application
2000	Sonora Medical	Ultrasound Equipment Servicing
2000	CraMar Technologies	Ultrasound Equipment Servicing
2000	Sonic Technologies	Measurement and Testing Lab
2001	Fibra Sonics	Neurosurgery, Liposuction, Lithotripsy
2006	UKHIFU	Distribution for HIFU Products in Europe

\* Certain transactions were investments for less than 100% ownership

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# Benefits of Ultrasound for Medical Devices

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- Benefits to our patients:
  - Less invasive -- ultrasound therapy is the **ONLY** non-radiating technology that allows for treatment without puncturing the targeted organ
  - Patient-friendly
  - Non-toxic alternative to radiation therapy; Non-infectious
  - Reduced bleeding; Induces coagulation
  - Repeatable
- Benefits to our clinical customers:
  - Ease of use; Cleaner operating environment
  - Practice differentiating technology
  - Reduces procedure time
- Benefits to our shareholders:
  - Relatively low cost production
  - Traditionally high margins
  - New growth opportunities -- appeals to medical industry's desire for innovative and advanced practices; reduction in healthcare costs

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# New Products

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## Large Markets



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## European Distribution of the SB500 Technology from Focus Surgery

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- Presently 161 centers or sites in Europe (total HIFU players)
- Distributors in 9 countries
- Finishing a 5 site study – 1<sup>st</sup> done
- Newly diagnosed prostate cancer cases in Europe is approximately 250,000 per annum, which is about the same as the number in the U.S.
- Worldwide there are more than 3,500 patients that have been treated with the Sonablate 500



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# The Sonablate® 500 and Misonix in Europe

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- **UK study for Visually Directed HIFU – the latest technique for non-invasive treatment**
  - **Successfully treated 84% of patients as measured by PSA nadir levels dropping to 0.2ng/ml or less after treatment**
  - **Measurement not achieved by previous published HIFU techniques**
  - **PSA nadir levels with SB500 are similar to more invasive surgical approach**
- **Five site clinical study in Europe**
  - **We have not seen better results published for other HIFU products or modalities**
  - **PSA levels in 89% of men were below 0.5ng/ml, against a standard of 1.0ng/ml**
  - **Potency levels of 70% after the procedure, with 95% potency after use of a drug for erectile dysfunction**

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# Rights to Kidney, Liver & Breast Technology Worldwide

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- First ever 510(k) for laparoscopic HIFU clinicals
- Kidney clinicals at three sites in Europe
- Ongoing discussions with potential development partners outside of U.S.
- Liver and breast to be developed

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## High Intensity Focused Ultrasound Kidney Cancer

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- Installed base of kidney lithotriptors – 3,000
- Annual incidences of kidney cancer 200,000 worldwide
- Nephrectomies performed per year 45,000
- \$150 million market
- Do not have to clamp renal vessels; no need to puncture the organ
- Reduces bleeding
- Minimally invasive approach
- Safer than partial nephrectomy
- Received FDA Approval

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# High Intensity Focused Ultrasound Liver Cancer

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- Annual Incidences of primary liver tumor 630,000 worldwide
- Annual Incidences of secondary liver cancer 500,000 worldwide
- Present surgical resection has high mortality
- Market for RF ablation is \$700 million
- HIFU will not require puncturing the organ
- Less bleeding
- No extraction necessary
- Minimally invasive

# HIFU Growth Initiatives From Sonablate

## Liver, Kidney, Breast and Prostate Cancer

### *Market Size – Annual Incidences*

	<u>U.S.</u>	<u>World</u>	<u>Est. Market</u>
<b>Liver</b>	20,000	500,000	\$100 mil.
<b>Kidney</b>	32,000	200,000	\$150 mil.
<b>Breast</b>	184,000	1,050,346	\$600 mil.
<b>Prostate</b>	200,000	543,000	\$750 mil.

# Investor Fact Sheet

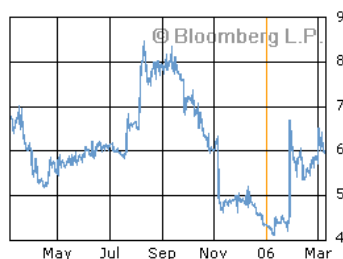
# MISONIX, INC.

March 2006  
Nasdaq: MSON



## PROFILE

Nasdaq Symbol	MSON
Market Cap.	\$43M
Price (3/05)	\$6.20
52-Week Range	\$4.07-\$8.85
Outstanding Shares	7.00M
Daily Volume	85,000
Net Sales (LFY)	\$46M
Sales Growth (LFY)	18%



## HIGHLIGHTS

- 4 Consecutive Years of Earnings
- Pure-play Medical Device Story Driven by Recent Corporate Initiatives
- Focus on Cancer Treatment Using Emerging HIFU (Ultrasound) Technology
- Robust Product Pipeline; Diversification Through Product Mix and Region
- Strong Balance Sheet

## ULTRASONIC PLATFORM OF MEDICAL DEVICES AND EQUIPMENT

Misonix, Inc. has been at the forefront of ultrasonic technology for over 50 years. The Company is a world leader in the design, development and manufacturing of ultrasonic medical devices, such as the Sonablate 500 (pictured at right) which focuses on the therapeutic treatment of cancer and benign tumors of the prostate. In addition, Misonix designs, develops, manufactures, and markets scientific and industrial ultrasonic equipment, laboratory safety equipment and air pollution control products.

Misonix's ultrasonic platform is the basis for several innovative medical technologies. These devices include High Intensity Focused Ultrasound (HIFU), which is a state-of-the-art technology utilizing the power of ultrasound to destroy deep-seated tissue without affecting surrounding healthy tissue. *Fortified by proprietary research and the benefits of HIFU, Misonix is positioned as the only US public company with a primary focus on the ultrasonic treatment of cancer.*

A strategic advantage for Misonix is a diversified platform of commercialized

products and services. Far beyond a developmental stage company, Misonix has demonstrated impressive top line growth in excess of industry growth estimates. With four consecutive years of earnings, Misonix



has been investing for future exponential growth. In particular, management has increased funding of R&D, expanded its sales and marketing efforts, and is upgrading to a digital ultrasonic platform.

## Existing Operations Gaining Traction

### Track Record of Execution – 5 Years of Progress

*Investing for the Future and to Enhance Shareholder Value*

	FY1999	FY2000*	FY2004	FY2005
SGA % of Sales	30%	30%	31.5%	32%
R&D % of Sales	4%	5%	7%	8%
Total Assets	\$29 million	\$31 million	\$34 million	\$38 million

\* First full year of management team

### Track Record of Execution – 5 Years of Progress

*"Smart Growth"*

	FY1999	FY2000*	FY2004	FY2005
Total Revenue	\$25 million	\$29 million	\$39 million	\$46 million
Medical Device Revenue	\$9 million	\$12 million	\$21 million	\$25 million
Commercial Medical Devices	1	5	9	9

\* First full year of management team



# Investor Fact Sheet

## March 2006



<i>Ultrasonic Platform (Partial List)</i>	<i>Strategic Partners</i>	<i>Market Size (Annual)</i>	<i>Stage</i>
Prostate cancer and benign tumor treatment	Licensed HIFU from Focus Surgery (18% diluted ownership by Misonix); direct distribution in Europe	\$750 million estimated	Commercial in Europe, Russia, Japan and South Africa; FDA trials in US
Breast cancer and benign tumor treatment	Misonix has HIFU rights for development and global commercialization	\$600 million estimated	Development
Liver cancer and benign tumor treatment	Misonix has HIFU rights for development and global commercialization	\$100 million estimated	Development
Kidney cancer and benign tumor treatment	Misonix has HIFU rights for development and global commercialization	\$100 million estimated	FDA 510(k); clinical studies being conducted
Wound debridement	Internally developed with plans for worldwide distribution	\$3 billion estimated	510(k) in US and approved in Canada in July 2005; planning product launch
Laparoscopic and open surgery tissue cutting and coagulation	Proprietary technology licensed to U.S. Surgical/Tyco Healthcare (NYSE: TYC)	\$120 million estimated	Commercial
Neurosurgery	Proprietary technology distributed in the US by Aesculap and directly to the rest of the world	\$80 million estimated	Commercial
Kidney and bladder stone removal	Proprietary technology distributed worldwide through agreement with ACM	\$10 million estimated	Commercial
Cosmetic surgery/Liposuction	Proprietary technology licensed for production and distribution to Mentor Corp. (NYSE: MNT)	\$40 million estimated	Commercial
Equipment testing/refurbishment	Sonora (90% owned by Misonix)	\$500 million	Commercial

### COMPANY INFO:

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631-694-9555  
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Michael McManus, Jr.  
President, CEO  
Richard Zaremba  
SVP, CFO

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## Future Growth Driven By Robust Product Pipeline Focused On Cancer

Finding a cure for cancer before it strikes remains illusive despite significant funding from public and private sectors for advanced research. Chemotherapy, radiation and new drug treatments for patients diagnosed with cancer have met with some success, but the side effects and long term impacts limit the desirability of these methods.

Across a broad spectrum of therapeutic and diagnostic applications, ultrasound devices - particularly those using HIFU - have proven to be minimally invasive, life enhancing, efficient, and patient-friendly. The SB-500 has been used successfully in more than 3,000 procedures. Its European distribution is growing and more prominent doctors recognize the value of

this treatment.

Leveraging its continued investment in R&D of ultrasonic technology, Misonix is laying the groundwork for years of profitable revenue growth with a diversified portfolio of medical devices, including those for wound debridement, bone cutting and a recent 510(k) on HIFU treatment of tissue, including breast, liver and kidney. Based on the strength and prospects for the Company's established businesses, Misonix has increased its R&D funding to nearly 8% of revenues.

Misonix has no net long term debt, a healthy working capital position, access to a \$6 million credit line, and potential proceeds from the sale of non-core businesses to fund future growth opportunities as a pure-play medical devices company.

This material is for informational purposes only. Forward-looking statements contained in this Fact Sheet are within the meaning provided by the Private Securities Litigation Reform Act of 1995 and involve risks and uncertainties that could cause actual results to differ materially from those expressed or implied herein. Please refer to Misonix's various Securities and Exchange Commission filings for a more detailed discussion of these risks. This Fact Sheet should not be construed as a recommendation to purchase or sell Misonix's common shares.

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# Investor Fact Sheet

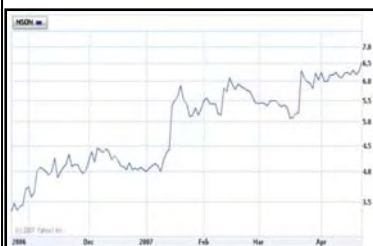
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April 2007  
Nasdaq: MSON



## PROFILE

Nasdaq Symbol	MSON
Market Cap.	\$46M
Price (4/23)	\$6.50
52-Week Range	\$3.25-\$7.29
Outstanding Shares	7.00M
Daily Volume	41,000
Net Sales (LQA)	\$42M
New Products for CFY	4



## HIGHLIGHTS

- Premier Platform of Ultrasonic Medical Devices
- Focus on Cancer Treatment Using Emerging HIFU (Ultrasound) Technology
- Impressive Distribution Network & High Barriers to Entry
- Robust Product Pipeline; Diversification Through Product Mix and Region
- Healthy Balance Sheet

## ULTRASONIC PLATFORM OF MEDICAL DEVICES AND EQUIPMENT

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Misonix's ultrasonic platform is the basis for several innovative medical technologies. These devices include High Intensity Focused Ultrasound (HIFU), which is a state-of-the-art technology utilizing the power of ultrasound to destroy deep-seated tissue without affecting surrounding healthy tissue. *Fortified by proprietary research and the benefits of HIFU, Misonix is positioned as the only US public company with a primary focus on the ultrasonic treatment of cancer.*

A strategic advantage for Misonix is a diversified platform of commercialized

products and services. Far beyond a developmental stage company, Misonix has demonstrated impressive revenues for existing medical devices and has completed the development of significant new products for introduction in 2007 and 2008.



Misonix has been investing for future exponential growth. In particular, management has increased funding of R&D, expanded its sales and marketing efforts, and is upgrading to a digital ultrasonic platform.

### Track Record of Execution

	FY 1999	FY 2006
Revenue	\$25 Million	\$39 Million
Medical Devices	1	11
R&D as % of Sales	4%	9%

### Focus on Key Growth Initiatives

- ✓ Grow European Distribution
- ✓ Support Launch of SonicOne® for Wound Care
- ✓ Launch Bone Shaver
- ✓ Distribution and Launch of Bone Cutter
- ✓ Sales of Sonatherm for Kidney Cancer



# Investor Fact Sheet

## April 2007



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Across a broad spectrum of therapeutic and diagnostic applications, ultrasound devices - particularly those using HIFU - have proven to be minimally invasive, life enhancing, efficient, and patient-friendly. The SB500 has been used successfully in more than 4,000 procedures. Its European distribution, most notably on a fee-per-use basis, is rapidly growing and prominent

doctors recognize the value of this treatment.

Leveraging its continued investment in R&D of ultrasonic technology, Misonix is laying the groundwork for years of profitable revenue growth with a diversified portfolio of medical devices, including those for wound debridement, bone cutting and a recent 510(k) on HIFU treatment of tissue, including breast, liver and kidney. Based on the strength and prospects for the Company's established businesses, Misonix has significantly increased funding of medical research and development.

Misonix has a healthy balance sheet and working capital position, access to an \$8 million credit line, and potential proceeds from asset sales to fund future growth opportunities as an ultrasound medical devices story with the greatest number of products in the market.

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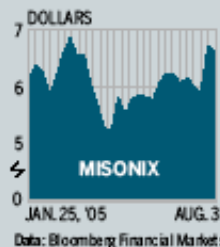
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AUGUST 15, 2005

INSIDE WALL STREET

# Misonix Zaps Prostate Cancer

HEADING  
BACK  
UP FAST



Misonix ([MSON](#)), a maker of medical and scientific gear, has investors interested in its new ultrasound device for prostate cancer. Shares of the little-known outfit have risen from 5.22 on Apr. 18 to 6.50 on Aug. 3. Its Sonablate 500 device is in Phase 2 and in three clinical trials in the U.S. -- and is already in the market in Britain, China, Italy, Japan, Mexico, and Russia, says CEO Michael McManus Jr. Over 3,000 treatments have been successfully done, he adds.

Sonablate, which uses high-intensity focused ultrasound, beams in intense heat that attacks prostate cancer cells. It targets the tissue, he says, without injuring adjacent flesh. (Usual treatment is removal of the prostate gland.) John Nobile of securities firm Taglich Brothers, which owns shares, expects earnings of 20 cents a share in 2005 on sales of \$44 million and 40 cents in 2006 on \$55 million. He rates it "speculative buy."

*Note: Unless otherwise noted, neither the sources cited in Inside Wall Street nor their firms hold positions in the stocks under discussion. Similarly, they have no investment banking or other financial relationships with them.*

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Xerox Color. It makes business sense.

## Major Milestones Announced for Sonablate 500 HIFU Treatment of Prostate Cancer at Annual American Urology Association Conference

Technology Upgrades Enable 48% Reduction in Procedure Time and Improved Efficacy

FARMINGDALE, N.Y.--(BUSINESS WIRE)--June 6, 2007--Misonix, Inc. (Nasdaq: MSON) today announced major milestones for the Sonablate(R) 500 ("SB500"), a medical device using high intensity focused ultrasound ("HIFU") for non-invasive treatment of prostate cancer, at the American Urological Association's Annual Conference, held from May 19-24 in Anaheim, CA. Medical experts in the field of urology from around the world attended the conference and celebrated the milestones achieved by the SB500 which has now been used in 6,000 treatments in over 100 clinics over the past six years.

The American Urological Association's (AUA) Annual Conference is the world's largest meeting of urologic professionals. With more than 10,000 urologists and health care professionals and 5,000 exhibitors in attendance and over 350 exhibitors showcasing their urological products or services, there is no better place to learn about the latest advances in urology, such as those introduced for the SB500.

The SB500 was developed by Focus Surgery, Inc. ([www.focus-surgery.com](http://www.focus-surgery.com)) and is manufactured by Misonix. Misonix also has the exclusive European distribution rights for the product. Misonix is an investor in privately-held Focus Surgery, one of the most prominent developers of HIFU technology in the world. Other investors in Focus include Takai Hospital Supply, Inc. ([www.thsinternational.com](http://www.thsinternational.com)), which has the exclusive distribution rights to market the SB500 in Asia, Australia, Japan and part of the Middle East, and US HIFU, LLC, the exclusive distributor in the Americas region and South Africa.

Focus Surgery and its international distribution partners showcased the SB500 at the annual AUA event to a groundswell of support. Momentum has been accelerating for the SB500, with adoption rates rapidly growing among urologists and other medical professionals. "We are seeing a shift among international as well as domestic physicians toward HIFU technology for the treatment of prostate cancer and other soft tissue cancers," said Michael A. McManus, Jr., President and Chief Executive Officer of Misonix. "As witnessed at the AUA conference this month and the annual European Association of Urology conference in March, medical professionals are signing up for training workshops, joining our information network and contemplating therapeutic applications with HIFU medical devices as part of their every day practices. These are clear indications that the global medical community is embracing HIFU technology -- and the SB500 in particular -- as one of the most significant scientific advances in years."

Urologists and other international users of the SB500 convened at the 7th Annual User Group Meeting on May 21, 2007, held simultaneously with the AUA conference. The user group meeting was chaired by Dr. Mark Emberton, a member of the Clinical Effectiveness Unit of the Royal College of Surgeons of England, London, UK, and Dr. T. Uchida, of Tokai University, Tokyo, Japan. Technological advancements in the software that powers the SB500 was the primary topic of discussion by Dr. Uchida, one of the world's most experienced users of the medical device. Results achieved by Dr. Uchida using the latest software, version 4.0 with enhanced 3-dimensional imaging capabilities, delivered improved efficacy and a success rate of 94% for the SB500, an increase of 50% as compared to earlier results with the prior software version. Dr. Uchida also stated that the technology upgrades enabled more efficient treatment cycles with procedure times reduced by an average of 48%. Treatments by Dr. Uchida, which based on his experience have been performed increasingly on



patients with higher risk profiles as determined by age of patient and size of prostate, among other factors, are now in a range of under an hour to approximately 1.5 hours, a substantial decrease from a range of approximately 1.5 hours to over 2.5 hours prior to using the latest software package.

The annual user group meetings are intended to encourage dialogue among medical professionals currently or considering treating patients with the SB500. The event was a success as urology experts from Australia, Japan, Canada, the United Kingdom and the Dominican Republic shared clinical data. Dr. Emberton, another leading user of the SB500 who performs treatments on patients with higher risk profiles, was among the speakers who noted the favorable results and highly reduced morbidity for patients enrolled in an ongoing hemiablation study using the SB500. The results to date for the study showed that the hemiablation procedures were successfully completed with positive ablation of cancerous tissue in the effected area of the prostate gland, and patients showed 100% continence and 100% potency in follow-up examinations. Unlike many of the traditional prostate cancer surgeries which treat or remove the entire gland, HIFU hemiablation using the SB500 involves ablation of cancer in patients who have had biopsy-proven prostate cancer limited to one side of the prostate. It has been noted that patients undergoing radical prostatectomy treatment of the prostate gland experience erectile dysfunction between 20%-90% of the time and incontinence between 20%-30% of the time. These treatment options presented significant shortcomings for patients, until the new HIFU hemiablation technique was introduced.

Medical professionals from four continents participated in discussions at the user group meeting. Among other featured speakers, noteworthy contribution was made by a respected Canadian-based professor and chief of urology, who emphasized low morbidity and excellent results achieved in studies recently undertaken using the SB500 in his clinic.

A final milestone for the SB500 announced at the AUA meeting was the inauguration of the first Medical Advisory Board for the Americas. The purpose of the Board is to provide expert opinion and guidance to assist with the growth and adoption of current and future technologies, versus the Medical Review Committee which was established to provide oversight of the HIFU procedures and to provide a basis for standardization of treatment methods.

"We are gratified by the growing global interest in and success of the Sonablate 500," continued Mr. McManus. "Between Focus Surgery, US HIFU, Takai and Misonix, we are combining the strengths of four companies to elevate what increasingly is being understood as the world's most important medical device using unique technology for the treatment of prostate cancer. Through our collective endeavors, we have seen the performance of the SB500 steadily improve. Some of our more recent accomplishments for prostate cancer treatment include what we believe to be the most efficacious HIFU results documented and a substantial reduction in procedure time resulting from our continued investment in research and development. In the six years that the SB500 has been available for use, we have worked with surgeons from around the world with various backgrounds and professional practices. We have culminated a myriad of protocols and have advanced from treating low risk patients to successfully handling more aggressive cases. We believe our efforts with the SB500 will result in further progression of the impressive results announced to date, including optimal patient outcomes, minimization of negative quality of life issues and reduced health care costs as compared with surgical and other treatment methods for prostate cancer."

About the American Urological Association:

Founded in 1902 and headquartered near Baltimore, Maryland, the American Urological Association ([www.auanet.org](http://www.auanet.org)) is the pre-eminent professional organization for urologists, with more than 15,000 members throughout the world. An educational nonprofit organization, the AUA pursues its mission of fostering the highest standards of urologic care by carrying out a wide variety of programs for members and their patients, including [UrologyHealth.org](http://UrologyHealth.org), an award-winning on-line patient education resource, and the American Urological Association Foundation, Inc., formerly AFUD.

#### About Misonix:

Misonix, Inc. (NASDAQ: MSON) designs, develops, manufactures, and markets medical, scientific, and industrial ultrasonic equipment, laboratory safety equipment, and air pollution control products. Misonix's ultrasonic platform is the basis for several innovative medical technologies. Misonix has a minority equity position in Focus Surgery, Inc. which uses high intensity focused ultrasound technology to destroy deep-seated cancerous tissues without affecting surrounding healthy tissue. Addressing a combined market estimated to be in excess of \$3 billion annually, Misonix's proprietary ultrasonic medical devices are used for wound debridement, cosmetic surgery, neurosurgery, laparoscopic surgery, and other surgical and medical applications. Additional information is available on the Company's Web site at [www.misonix.com](http://www.misonix.com).

With the exception of historical information contained in this press release, content herein may contain "forward looking statements" that are made pursuant to the Safe Harbor Provisions of the Private Securities Litigation Reform Act of 1995. These statements are based on management's current expectations and are subject to uncertainty and changes in circumstances. Investors are cautioned that forward-looking statements involve risks and uncertainties that could cause actual results to differ materially from the statements made. These factors include general economic conditions, delays and risks associated with the performance of contracts, uncertainties as a result of research and development, acceptable results from clinical studies, including publication of results and patient/procedure data with varying levels of statistical relevancy, potential acquisitions, consumer and industry acceptance, litigation and/or court proceedings, including the timing and monetary requirements of such activities, regulatory risks including approval of pending and/or contemplated 510(k) filings, the ability to achieve and maintain profitability in the Company's business lines, and other factors discussed in the Company's Annual Report on Form 10-K, subsequent Quarterly Reports on Form 10-Q and Current Reports on Form 8-K.

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SOURCE: Misonix, Inc.



## Misonix Announces FDA Clinical Trial Enrollment Acceleration for Sonablate 500 HIFU Treatment of Prostate Cancer

### Update on U.S. Clinical Trial Activities and Positive User/Patient Feedback

FARMINGDALE, N.Y.--(BUSINESS WIRE)--June 5, 2007--Misonix, Inc. (NASDAQ: MSON), a developer of ultrasonic medical device technology for the treatment of cancer and other chronic health conditions, today announced the acceleration of patient enrollment relating to the United States Food and Drug Administration ("FDA") clinical trials for the Sonablate(R) 500 ("SB500"), a medical device using high intensity focused ultrasound ("HIFU") for non-invasive treatment of prostate cancer. The Sonablate(R) 500 is approved by the FDA as an investigational device for clinical trials in the United States. The increased enrollment pace pertains to the ongoing FDA approved pivotal study for the treatment of prostate cancer. Over 16 patients in the pivotal study have been treated using the SB500 device at two clinical study sites. A third clinical study site will start treatments in June 2007.

The SB500 is a medical device developed by Focus Surgery, Inc. ([www.focus-surgery.com](http://www.focus-surgery.com)) and manufactured by Misonix. Misonix also has the exclusive European distribution rights for the product. Misonix is an investor in privately-held Focus Surgery, one of the most prominent developers of HIFU in the world. Other investors in Focus include Takai Hospital Supply, Inc. ([www.thsinternational.com](http://www.thsinternational.com)), which has the exclusive distribution rights to market the SB500 in Asia, Australia, Japan and part of the middle east, and US HIFU, LLC, the exclusive distributor in the Americas region and South Africa. US HIFU and Focus Surgery are leading the FDA clinical trials and approval process.

With the SB500 being used in 6,000 treatments in over 100 clinics in six years, interest in and usage of the HIFU medical device for prostate cancer treatment is gaining momentum. Drs. Michael Alabaster and Walter Rayford recently released preliminary data from the first U.S. clinical trials for the treatment of de novo localized prostate cancer using the SB500. Based on their positive results, the doctors report that interest in participating in the FDA clinical trials has been extremely heavy, with calls received from all over the country requesting patient entrance into the trials.

Dr. Alabaster, managing partner with Southeast Urology Network ("SUN") of Memphis, TN, had been performing HIFU procedures outside of the United States for approximately two years prior to his participation in the FDA clinical studies using the SB500. He stated that the demand for this procedure is great, with scores of American citizens going for HIFU treatment every month in Europe, Canada, Mexico, and the Dominican Republic where the SB500 is presently being used. HIFU treatment with the SB500 only became available in the U.S. as part of the next phase of FDA approval process which commenced in March 2007. With the approval of the trials by the FDA earlier this year, Dr. Alabaster stated, "I have been inundated with calls almost daily for three months."

Dr. Rayford, an Urologic Oncologist with SUN, stated that the PSA data for their patients following treatment with the SB500 has been "astounding at six weeks status post-surgery." He added, "These patients have probably not even reached their nadir yet, and at six weeks we are finding their PSAs typically almost undetectable...(Furthermore,) the side effect profile to date within our clinical trials, as well as previous offshore experience, definitely offers an advantage over the standard treatments presently approved in the United States."

"There is long-term data out there to support the technology as being as effective, if not more so, than many forms of treatment that presently are being deployed in the United States," noted Dr. Alabaster. "There is no doubt that this will be a heavily demanded procedure by patients, as they seek other treatments that are less invasive than presently available procedures and maintain a better quality of life."

The Memphis clinical study site is currently enrolling patients with prostate gland sizes 40 grams or less, Gleason scores of 6 or less, and PSAs scores of 10 or less. Meeting these criteria, Stuart Boyd, a professional pilot from Florida, enrolled for treatment in May. Immediately following the procedure, he stated, "I was feeling so good the next day, I went out to dinner that night. I found out about this technology from a fellow pilot who had gone to Canada for the same treatment. His result and quality of life was excellent and that led me to search the Internet. I found the trials being offered by Focus Surgery and SUN. I have returned to my normal baseline in several days and was using all bodily functions as they were designed to be used!"

Mr. Boyd offered Dr. Alabaster his thanks for performing the surgery and changing his life. Then, after a short pause, he added, "No, I mean thank you for NOT changing my life in terms of incontinence and impotence."

#### About Misonix:

Misonix, Inc. (NASDAQ: MSON) designs, develops, manufactures, and markets medical, scientific, and industrial ultrasonic equipment, laboratory safety equipment, and air pollution control products. Misonix's ultrasonic platform is the basis for several innovative medical technologies. Misonix has a minority equity position in Focus Surgery, Inc. which uses high intensity focused ultrasound technology to destroy deep-seated cancerous tissues without affecting surrounding healthy tissue. Addressing a combined market estimated to be in excess of \$3 billion annually, Misonix's proprietary ultrasonic medical devices are used for wound debridement, cosmetic surgery, neurosurgery, laparoscopic surgery, and other surgical and medical applications. Additional information is available on the Company's Web site at [www.misonix.com](http://www.misonix.com).

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FOCUS  
SURGERY

# *Sonablate*®

*The Choice for HIFU Worldwide*



The advanced High Intensity Focused Ultrasound (HIFU) technology resident in the Sonablate® 500 originated over 25 years ago at the Indiana University Medical Center, and has been developed at leading research centers across the United States, Europe and Japan for the treatment of prostate cancer.

HIFU is a state-of-the-art technology utilizing the power of ultrasound to destroy deep seated tissue without affecting the surrounding healthy tissue. The HIFU energy is focused sharply from the transducer surface to the targeted tissue in the prostate. Temperature is elevated in the targeted tissue up to 90°C within one second causing cell death. The treatment consists of placing HIFU lesions (each requiring only a few seconds to create) side-by-side until the entire desired volume is treated.

Now the urologist can plan the treatment under ultrasound image guidance, target the prostate and monitor the therapy, all using a single transducer and probe. This design provides maximum precision, flexibility, safety and control for the clinician.

*"Since we introduced the Sonablate technology on a wide scale across Australia we have seen some outstanding outcomes, still keeping patient complications low. The reliability of the hardware and the support we receive from FSI/TCS is excellent."*

*"We look forward to the continuing development of the technology."*

*-Michael Fehrmann  
Managing Director - Meditron  
Australia*

*"I feel fine, excellent in fact. The quality for HIFU should be commended. There was no knife involved and the treatment feeling like it was a breeze."*

*-Douglas, 73 years Old  
United Kingdom*

*"When I was diagnosed with prostate cancer in 2002, I honestly felt that my world was rapidly coming to an end. Fortunately, I discovered HIFU. My roommate at the Indiana University Hospital had undergone a standard prostatectomy two days before me... and was in considerable pain while I was up walking laps around the perimeter of the 6th floor within four hours of regaining consciousness. My progress has been steadily upward ever since. Thank you for giving me my life!"*

*-Norman, 64 years old  
United States of America*

# Focused on Quality

Sonablate® 500 HIFU  
across Australia we  
clinical results while  
ions to a minimum.  
is fantastic and the  
HIFU is outstanding.  
continued advancement of

Pty. Ltd.

*"For a prostate cancer therapy to be successful, it needs to be able to destroy the diseased tissue within the prostate and at the same time, preserve the vital structures around the gland that are involved in normal bladder emptying, preservation of continence and preservation of erectile function."*

*Now the urologist can plan the treatment under ultrasound image guidance, target the prostate and monitor the therapy, all using a single transducer and probe that is part of the Sonablate® 500 system. This design provides maximum precision, flexibility, safety and control for the clinician."*

*-Nick Stevens, Managing Director of UKHIFU  
United Kingdom*

fact. Anyone who can  
opt for that option. There  
and I woke up from the  
was a summer morning..."

*"I only hope more men will go for the HIFU procedure. My 1st PSA test came back as 0.11. My next PSA test will be at the end of May 2007, and I expect that one to be very low too. Also, I have very few side effects with the HIFU procedure."*

*-Ken, 63 years old  
Canada*

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*"When I heard that I had prostate cancer I was surprised and frightened. Because I was older, I couldn't have surgery. So when my doctor asked me if I was interested in the ultrasound therapy I said 'Yes, definitely. I want to have HIFU!'"*

*-M. Hasegawa, 83 years old  
Japan*

*"I can't say enough about it. I'm obviously a successful patient running around. I am feeling great about the procedure I went through."*

*-Jim, 67 years old  
United States of America*

# Quality of Life





### Probe

Bi-Plane, transrectal ultrasound probe with two focal lengths (3.0/4.0cm) provides imaging and HIFU therapy to treat the whole prostate without requiring TURP

### Sonachill™

Active cooling system for the rectum during therapy ensures patient comfort and safety (16-20°C)

### Console

Completely digital and modular control system with state-of-the-art software, computer and signal processing components, provides clear high definition targeting images and sharp HIFU therapy lesions in a mobile, lightweight and easy to use integrated unit



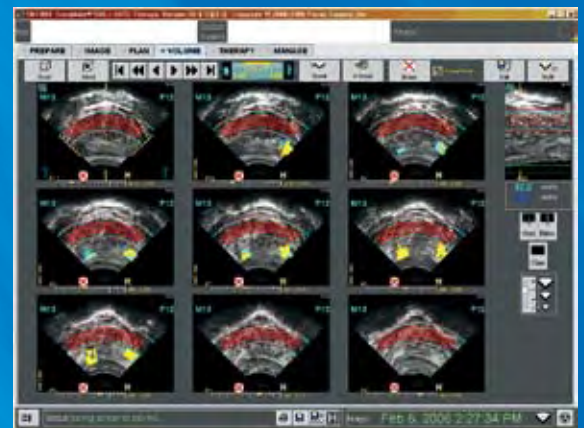
# So



The Neuro-Vascular Bundle detector function aids the physician in locating the blood vessels surrounding these critical structures and is seamlessly integrated into the Sonablate® imaging and treatment screens. Once the blood vessels have been detected, the physician is able to exclude that area from the treatment plan.

## 1 See it

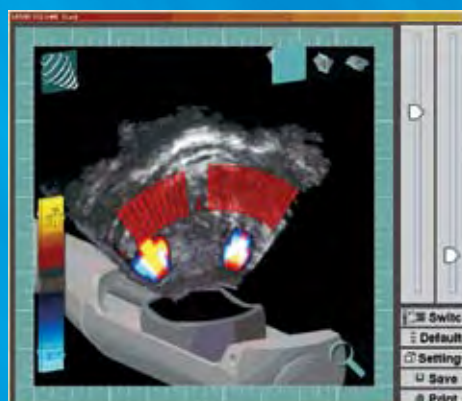
The Sonablate® 500's patented dual sided transducers - combining High Definition imaging and HIFU therapy - are used to treat prostate cancer precisely. The HD imaging allows the physician to simultaneously image both the transverse and sagittal planes of the prostate. This ultrasonic imaging system, along with cutting edge software, compiles multiple image slices to provide a high resolution 3D image of the patient's entire prostate gland.



## 2 Set it

Every patient is different which is why the Sonablate® has been designed to allow the physician to have complete control in creating patient specific treatment plans. The advanced Sonablate® interface and 2D/3D capabilities provide the physician with the tools to select multiple treatment zones as necessary for a user-directed, computer-controlled treatment.

Integrated 3D Volume Ultrasound Imaging for unprecedented display, review, modification, and interaction with the treatment plan and prostate images to define a thorough and safe treatment.



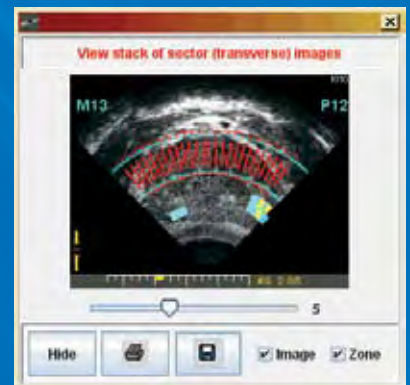
*Visually Directed HIFU™ for Tailored Treatment*

# Sonablate®

## Treat it

Physicians can treat and monitor the progress of the HIFU treatment in real time while the Sonablate® 500's integration of multiple focal length transducers in a single probe allow for faster treatment. At the same time important safety features such as the Reflexivity Index Measurement (RIM™) and rectal wall temperature and distance measurements, analyze real-time B-mode image and temperature data to maximize patient safety.

Refine the treatment plan at any time before or during the procedure utilizing the 2D Stack feature.



Reference color overlay of treatment plan allows physician to monitor therapy progress

High Frequency Sagittal and Longitudinal live and reference images displayed immediately after every HIFU exposure for complete therapy progress monitoring



Temperature monitoring at rectal wall for added safety

RIM™ Continuous reflectivity index measurement indicates tissue change at rectal wall for added safety

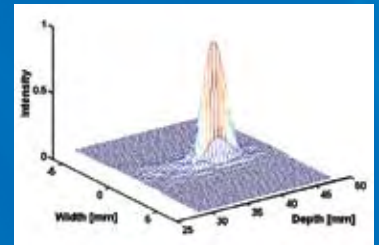
Real-time marker shows physician exact location of current HIFU treatment site in synchronized bi-plane images

Interactive power level controls and verification for total physician control

tment

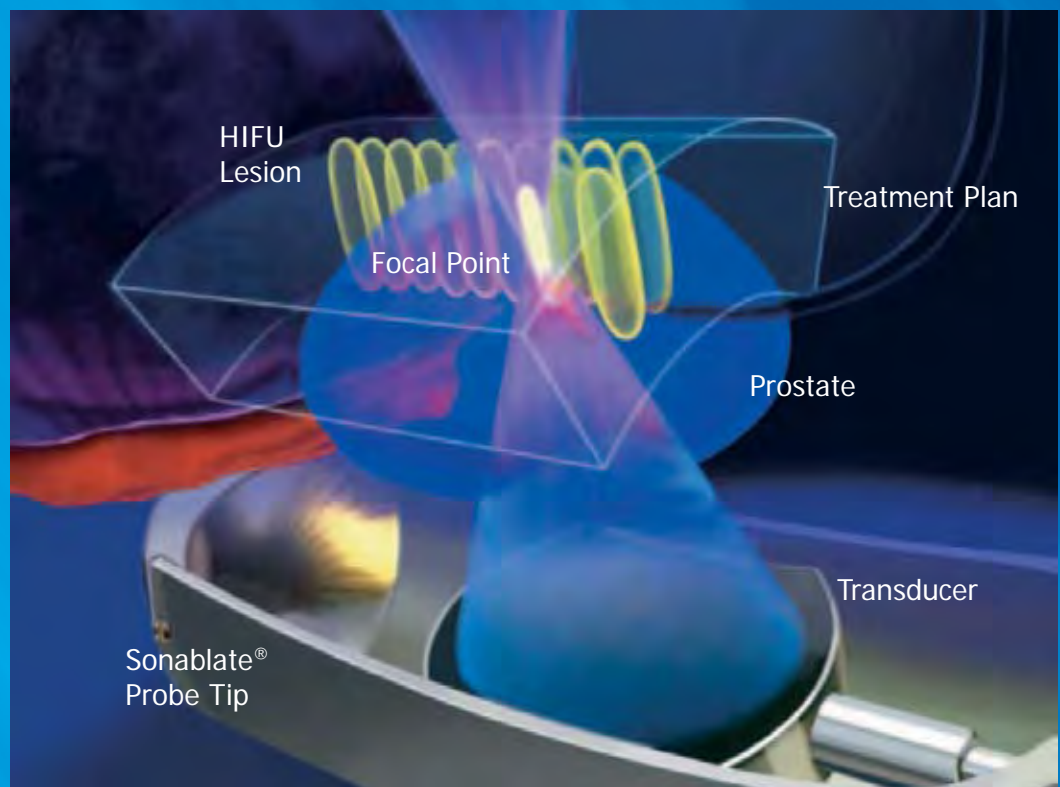


The Sonablate® 500 uses HIFU ablation therapy for the treatment of prostate cancer that is a safe, precise and clean energy that has no cumulative effect like radiation or scarring and blood loss like surgery. Sonablate® HIFU also offers an option for retreatment – or even treatment after another prostate therapy has failed to cure the cancer. Only local or spinal anesthesia is required, and a short hospital stay or outpatient procedure is common. Sonablate® HIFU has been proven in clinical studies and hospital use around the world to be safe and effective for the treatment of localized prostate cancer. The Sonablate® 500 is also the only true non-invasive prostate cancer treatment that does not require a transurethral resection of the prostate (TURP) prior to treatment in order to achieve effective results.

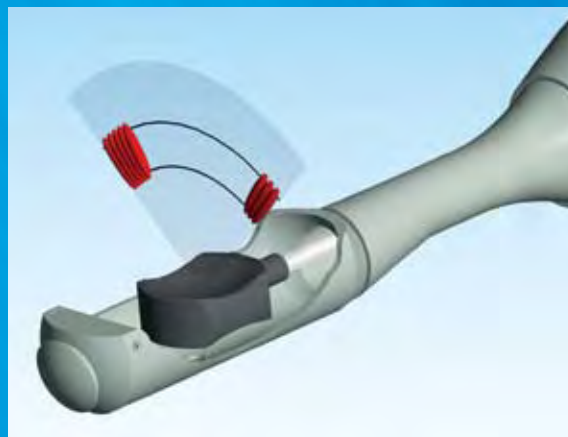


HIFU Intensity Profile: the highest intensities are located in the focal zone, allowing targeted tissue ablation while sparing intervening tissue.

HIFU energy is focused by a patented transducer which integrates ultrasound therapy and imaging in a single device. An overlapping pattern of HIFU lesions covers the entire treatment volume.



The Sonablate® Probe features a wide 90° treatment field; the next generation of probes feature the choice of longer focal length transducers.



Cutaway section showing the arrangement of the two different focal length transducers used for treating tissue at different depths.

## HIFU Ablation Therapy

is non-invasive thus does not require any incisions - there is no bleeding or need for transfusions.

Only local or spinal anesthesia is required, and a short hospital stay or outpatient procedure is common. Initial follow up indicates effective long term results.



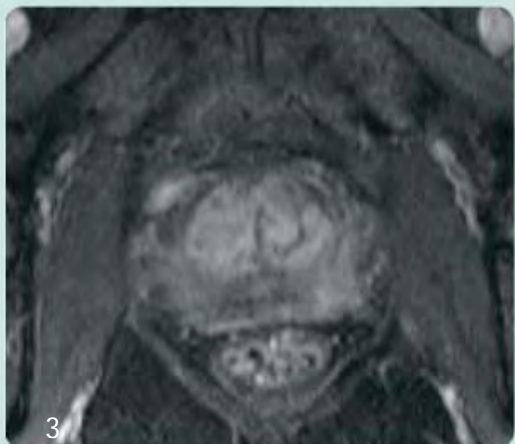
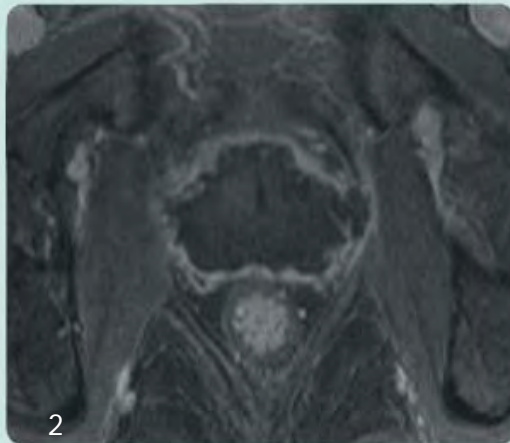
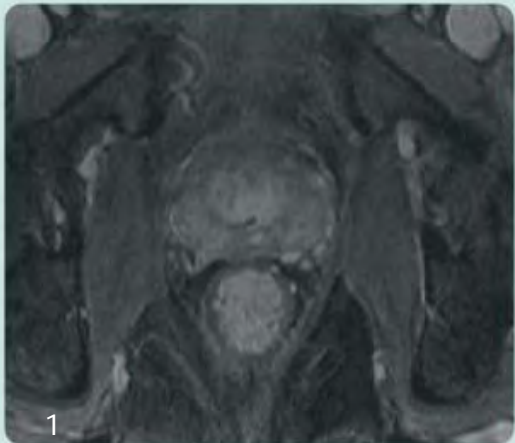
*"For many reasons, transrectal HIFU appears highly attractive as a minimally invasive treatment for localized prostate cancer. One of the most favorable advantages is that HIFU therapy can be repeated or added even though patients with local recurrence have already been treated with a radical prostatectomy, cryoablation of the prostate and radiation therapy including brachytherapy."*

*-Dr. Toyoaki Uchida, M.D., Ph.D.  
Professor - Department of Urology  
Tokai University Hachioji Hospital  
Tokyo, Japan*

*"I have been using the device for the treatment of prostate cancer since April. In my experience, the results have been found to be very effective."*

*-Dr. Abraham Sidi, M.D.  
Chairman - Department of Urology  
Wolfson Institute  
Tel Aviv, Israel*

# Focused on HIFU



**Image 1:** Pre-treatment image showing an enhancing region suspicious of cancer in the left peripheral zone.

**Image 2:** Two weeks after the Sonablate® HIFU treatment, lack of contrast uptake within the prostate consistent with coagulation necrosis throughout the entire prostate tissue.

**Image 3:** Pre-treatment gadolinium contrast enhanced MR Image of the prostate showing uptake throughout the gland.

**Image 4:** One week post Sonablate® HIFU Hemiblation gadolinium contrast enhanced MR Image of the prostate showing no uptake on the left side of prostate. This image demonstrates the selective targeting capability and resulting treatment time reduction of the Sonablate®.

MR Images provided courtesy of Dr. Mark Emberton, M.D., FRCS (Urol) and Dr. Rowland Illing, M.D., MRCS





*"The Sonablate® 500 appeals to the urological surgeon because it enables him or her to control the exact position (focal point) and, in addition, vary the intensity of the energy delivered to any single part of the prostate."*

*-Dr. Mark Emberton, M.D., FRCS (Urol)  
Consultant Urologist & Senior Lecturer in Oncological  
Urology Institute of Urology  
University College  
London, United Kingdom*

*ing the Sonablate® 500  
reatment of localized prostate  
il 2006.... Based on my  
Sonablate® 500 system has  
e safe and effective."*

*ji, M.D.  
ent of Urology*

*"As a busy urologic surgeon, faced with the morbidity associated with the radical surgery experienced by my patients, I wanted to find the least invasive, but equally cancer curing procedure around and make it available to my patients. The Sonablate® 500 answered that description."*

*-Dr. Jack Barkin, M.D., FICS, FAZC, FRCS, DABU  
Chief of Urology - Humber River Regional Hospital  
Director - The Male Health Centre-Toronto  
Director - Can-Am HIFU  
Assistant Professor - Department of Surgery, University of Toronto  
Toronto, Canada*

# Results

## CLINICAL STUDIES

### COMPLETED STUDIES

#### United States

- ◇ Spring 2007– completed FDA approved feasibility study at two clinical sites for "High-Intensity Focused Ultrasound in Treating Patients With Locally Recurrent Prostate Cancer" for patients who had PSA 0.5-10 ng/ml and a Gleason score of  $\leq 7$  [IDE #G000280]
- ◇ April 2005 - completed FDA approved Phase I clinical studies for "Ultrasound in Treating Patients With Prostate Cancer Confined to the Prostate" the treatment of localized prostate cancer for patients who had PSA < 10 ng/ml and Gleason score  $\leq 7$  [IDE #G00276]

#### Supporting Publication:

M. Koch, T. Gardner, L. Cheng, R. Fedewa, R. Seip, N. Sangvhi, "Phase I/II Trial of High Intensity Focused Ultrasound in the Treatment of Previously Untreated Localized Prostate Cancer", Journal of Urology, (in review).

#### Japan

- ◇ March 2004 (Last Treatment) or September, 2005 (results published)- Finished the Multi-Site MHLW Approval Study in Japan

#### Supporting Publication:

T. Uchida, et al. "Transrectal High Intensity Focused Ultrasound in the Treatment of Localized Prostate Cancer: A Multicenter Study," Acta Urology Japan, 2005.

### ONGOING STUDIES

#### United States

- ◇ August 2006 - Received FDA Approval for the Phase III Pivotal Study for "Ultrasound in Treating Patients With Prostate Cancer Confined to the Prostate" the treatment of localized prostate cancer for patients who had PSA < 10 ng/ml and a Gleason score  $\leq 7$  [IDE #G060129] - For details on the clinical studies visit <http://www.cancer.gov/clinicaltrials/search>

#### Europe

- ◇ "An Evaluation of Hemi-Ablation Therapy Using High Intensity Focused Ultrasound in the Treatment of Localized Adenocarcinoma of the Prostate." funded in part by UK Cancer Research and approved by the UK National Cancer Research Network (NCRN)



**FOCUS  
SURGERY**

[www.Focus-Surgery.com](http://www.Focus-Surgery.com)

Focus Surgery Incorporated  
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Indianapolis, Indiana 46226  
Tel: (317) 541-1580  
Fax: (317) 541-1581

Focus Surgery, Inc. is the worldwide leader in pioneering the development and commercialization of High Intensity Focused Ultrasound (HIFU) for the treatment of prostate disease including Prostate Cancer and Benign Prostate Hyperplasia (BPH).

Based in Indianapolis, Indiana, Focus Surgery designs, manufactures and distributes the Sonablate® system, an image-guided, non-invasive acoustic ablation device. Focus Surgery's advanced Sonablate® system is in use on six continents with hundreds of trained users and over 100 established clinical centers around the globe.

Thousands of patients have been treated with the Sonablate® – firmly establishing the Sonablate® as "The Choice for HIFU Worldwide".

***Our Mission:  
Preserving Potency, Continence  
and Improving Quality of Life***

**International Distribution Partners**



Misonix Incorporated  
Farmingdale, New York  
[www.Misonix.com](http://www.Misonix.com)



Takai Hospital Supply Incorporated  
Tokyo, Japan  
[www.Takai-hs.co.jp](http://www.Takai-hs.co.jp)

THS International Incorporated  
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[www.THSGlobal.com](http://www.THSGlobal.com)



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Charlotte, North Carolina  
[www.USHIFU.com](http://www.USHIFU.com)