Imaging Biomarkers

Quantitative and Functional Imaging

BME 4420/7450

Fall 2022

Topics

- Biomarkers
- Imaging biomarkers
- Course summary
- Course evaluation
- Final exam

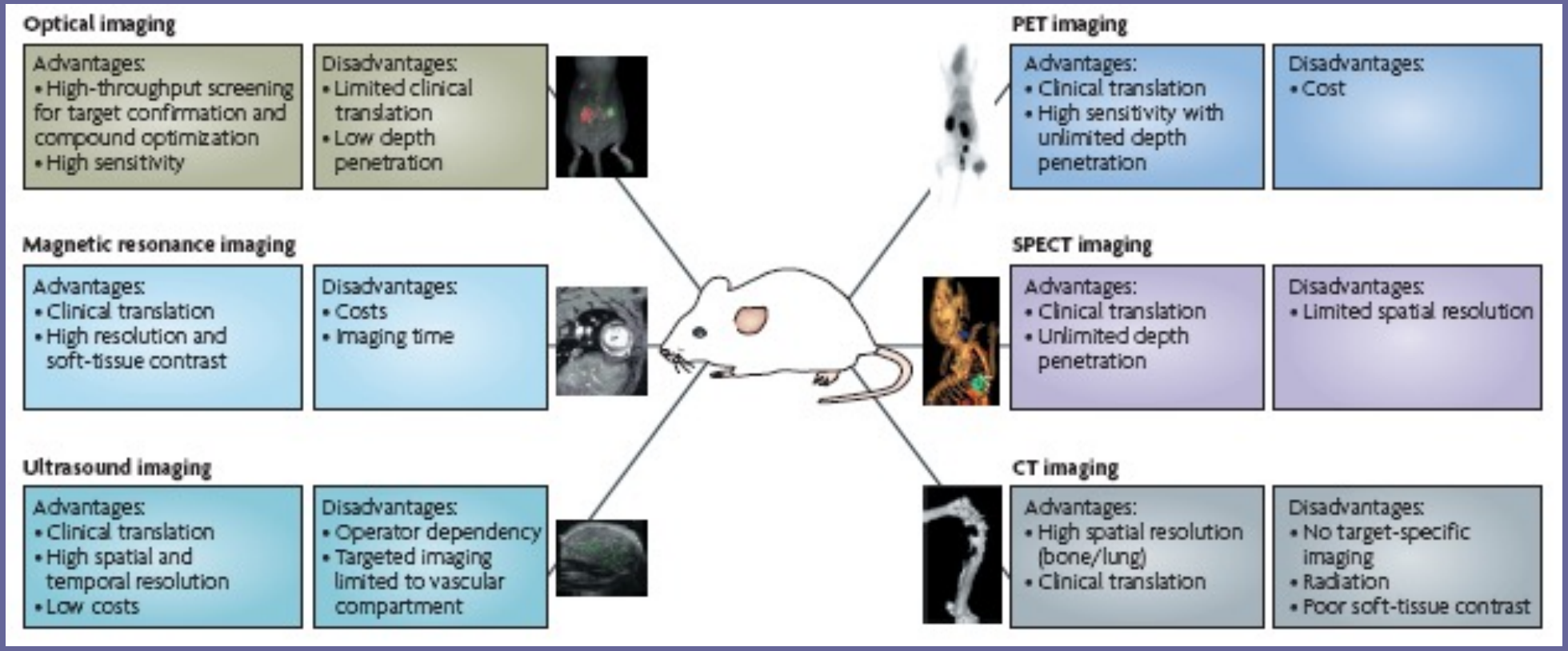
Biomarkers

- Any detectable biological parameter that can help establish the presence or severity of disease
  - Biochemical
  - Genetic
  - Histologic
  - Anatomic
  - Physical
  - Functional
  - Metabolic

Imaging biomarkers

- Any biomarker detectable through imaging
- A good biomarker
  - Is closely related to disease
  - Measurement is
    - Accurate
    - Reproducible (across time, imaging centers)
    - Feasible over time
- Imaging biomarkers can be more specific than standard clinical biomarkers
- Many of the same imaging biomarkers can be used in preclinical and clinical trials
  - Translational research

Imaging for preclinical testing



Willman (2008)

Preclinical and clinical imaging

TABLE 2.1
Summary of Current Imaging Modalities of Interest in Drug Research and Discovery

Technique	Clinical Imaging	Resolution	Animal Imaging	Resolution and Time Scale	Application
SPECT (low energy γ-rays)	Yes	6–8 mm; s	Yes	1–2 mm; min	Functional
PET (high energy γ-rays)	Yes	4 mm; s	Yes	1–2 mm; min	Metabolic, functional, molecular
CT	Yes	0.5 mm; s	Yes	50–100 μm; min	Anatomical, functional
Ultrasound	Yes	300–500 μm; s	Yes	50 μm; min	Anatomical, functional
MRI	Yes	1 mm; s to min	Yes	80–100 μm; s to h	Anatomical, functional, molecular
Bioluminescence	No	—	Yes	1–10 mm; s to min	Molecular
Near infrared fluorescence imaging	No	—	Yes	1–3 mm; s to min	Molecular

Beckmann (2006)

Imaging in clinical trials

- Safety and efficacy of treatment is tested in clinical trials
- Imaging may improve trial efficiency
  - Identify promising treatment earlier
  - Identify ineffective treatment sooner
  - Reduce number of patients required
    - Identify patients most likely to benefit
- Example: metastatic liver cancer
  - Traditional end point: 5 year survival
  - Surrogate end points
    - Tumor volume on CT
    - Biomarkers for angiogenesis (blood flow and volume) on MRI
  - Longitudinal study to test for effects of therapy

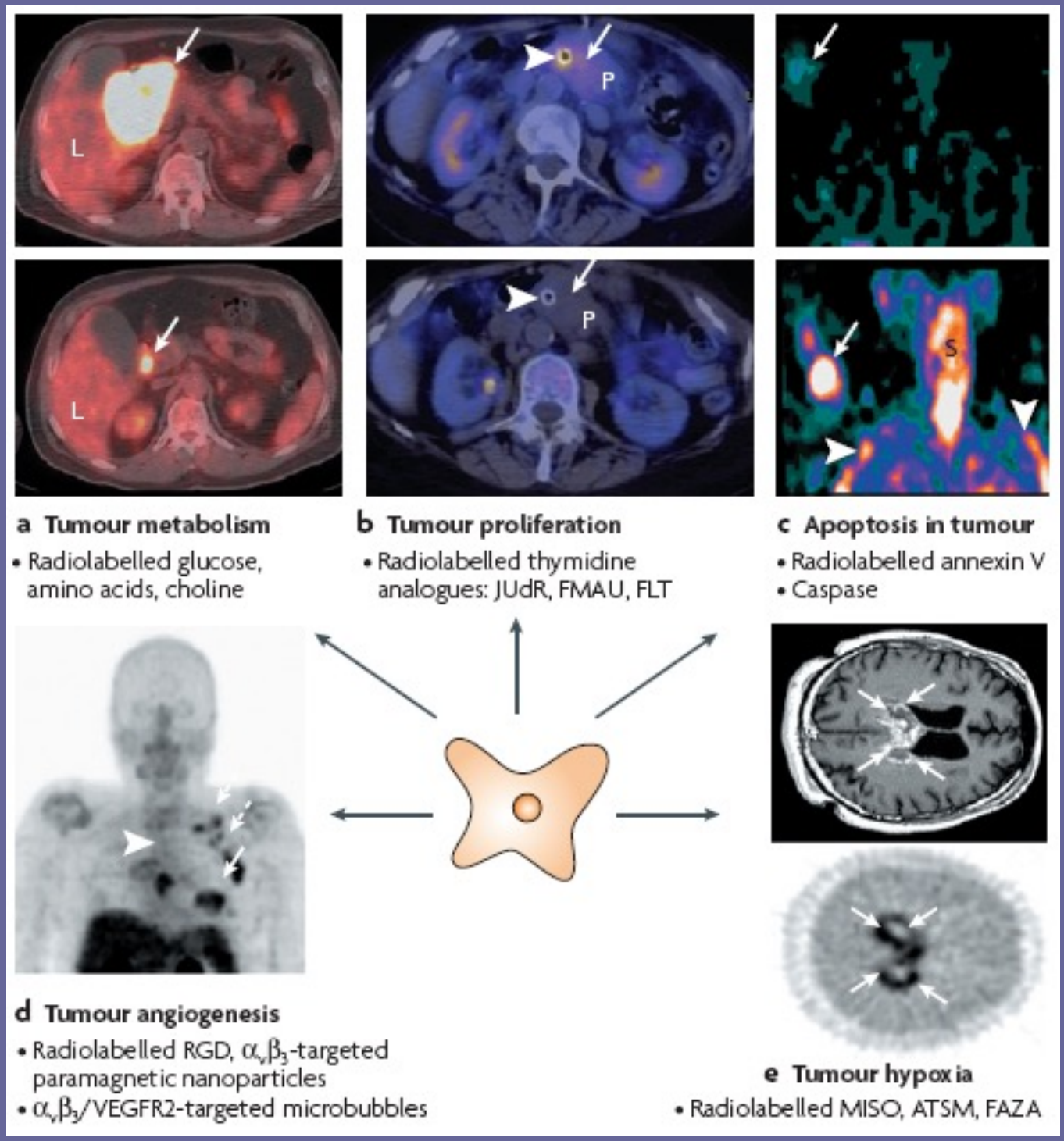
Field	Imaging biomarker	Imaging modality
Oncology	Tumour size and extent	MRI, CT, ultrasound
	Tumour metabolism/proliferation	PET, SPECT
	Tumour angiogenesis	PET, SPECT, MRI, ultrasound
Cardiology	Vulnerable atherosclerotic plaque	MRI, PET, ultrasound, CT
	Angiogenesis in ischaemia and infarction	PET, MRI, ultrasound
	Viability of myocardium	PET, MRI
	Cardiac contraction function	Ultrasound, MRI, CT
	Lumen diameter/volume	MRI, CT
	Carotid intima/plaque thickness	Ultrasound
	Carotid plaque composition	MRI, CT
	Coronary artery plaque	Ultrasound (intravascular)
	Coronary artery calcification	CT
Neurology	Brain infarction size and extent	MRI, CT
	Lesion size and activity in multiple sclerosis	MRI, PET, SPECT
	Structural atrophy in Alzheimer's disease	MRI
Rheumatology	Loss and chemical change of articular cartilage	MRI
	Inflammatory activity	MRI, PET
	Bone density	CT, plain radiography
	Bone fracture	CT, plain radiography, MRI
Pulmonology	Inflammatory activity	MRI, CT
	Perfusion and ventilation	SPECT, MRI

Willman (2008)

Imaging strategies using PET/SPECT

Drug	Technique	Measurements	Phase	Application
Positron-emission/single-photon-emission tomography				
Cisplatin	^{13}N-Cisplatin	Pharmacokinetics	Preclinical/clinical	Glioblastoma[138]
Fluorouracil	^{18}F-Fluorouracil	Pharmacokinetics	Clinical	Colorectal cancer[139]
Tamoxifen	^{18}F-Tamoxifen	Pharmacokinetics	Clinical	Breast tumour[140]
HuMV833	^{124}I-HuMV833	Pharmacokinetics	Clinical	Solid tumour[141]
Gefitinib	^{18}F-FDG	Tumour metabolism	Preclinical	Non-small-cell lung cancer and epithelial carcinoma[142]
Neoadjuvant chemotherapy	^{18}F-FDG and ^{15}O-water	Tumour metabolism and blood perfusion	Clinical	Locally advanced breast cancer[143]
Combretastatin A4 phosphate	^{15}O-water and ^{15}O-carbon monoxide	Tumour blood perfusion	Clinical	Solid tumours[144]
HSV-1 TK gene therapy	^{124}I–FIAU	Extent of HSV-1 TK gene expression	Clinical	Glioblastoma[145]
Various chemotherapeutic drugs	^{99m}Tc-Annexin V	Apoptosis	Clinical	Lung cancer, lymphoma, breast cancer[79]
Gefitinib	^{18}F-FAZA	Hypoxia	Preclinical	Squamous cell carcinoma[108]

Willman (2008)



Willman (2008)

Pharmacokinetics and microdosing studies

- Suboptimal pharmacokinetics can lead to up to 40% of drug failures by Phase I trials
- Microdose study (~1% of the estimated therapeutic dose)
- PET can measure drug
  - Absorption
  - Biodistribution
  - Metabolism
- Two approaches
  - Direct labeling of drug
  - Competitive binding
    - Measures occupancy with and without drug in system

Strategies using US

Drug	Technique	Measurements	Phase	Application
Ultrasound (US)				
Gemcitabine	Targeted microbubbles	Tumour angiogenesis	Preclinical	Pancreatic tumour[95]
SU5416* and endostatin	Contrast-enhanced Doppler US	Tumour blood perfusion	Preclinical	Prostate cancer and glioblastoma[156]
ZD6126‡	Doppler US	Tumour blood perfusion	Preclinical	Melanoma[157]
Soluble form of VEGFR2	Contrast-enhanced Doppler US	Tumour blood perfusion	Preclinical	Prostate cancer[158]
ZD6126‡ and DC101§	US with speckle variance flow processing	Tumour blood perfusion	Preclinical	Breast carcinoma[159]
Thalidomide	Contrast-enhanced US	Tumour blood perfusion	Clinical	Hepatocellular carcinoma[160]
Thalidomide	Power Doppler US	Tumour blood perfusion	Clinical	Hepatocellular carcinoma[161]
SU11248‖	Power Doppler US	Tumour blood perfusion	Preclinical	Lung carcinoma[162]
Interferon-γ	Power Doppler US	Tumour blood perfusion	Preclinical	Melanoma[163]
Paclitaxel	Paclitaxel-containing microbubbles	US-guided drug delivery	Preclinical	Improved drug delivery[164]
DC 101§	Contrast-enhanced Doppler US	Tumour blood perfusion	Preclinical	Squamous cell carcinoma[165]

Willman (2008)

Imaging strategies using MR

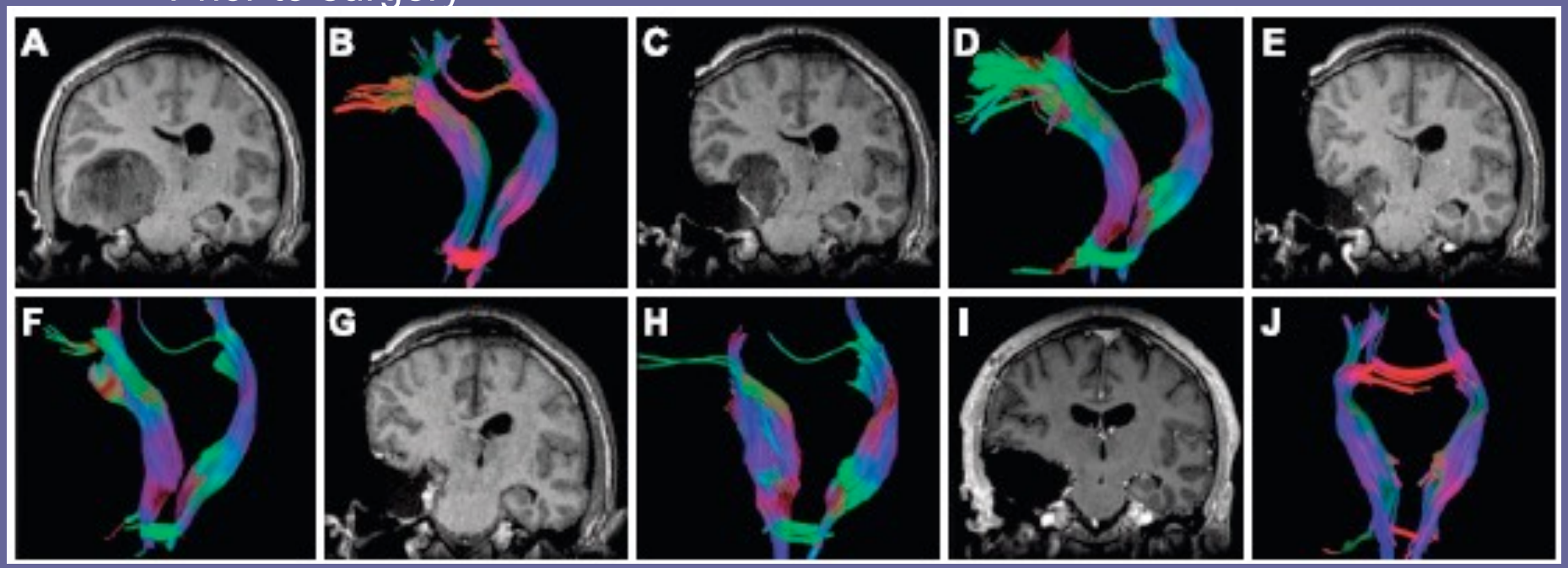
Magnetic resonance imaging (MRI)/spectroscopy				
AG013925*	Contrast-enhanced MRI	Tumour blood perfusion	Preclinical	Colon carcinoma[146]
Various chemotherapeutic drugs	Contrast-enhanced MRI	Tumour blood perfusion	Clinical	Urinary bladder cancer[147]
PTK787/ZK222584	Contrast-enhanced MRI	Tumour blood perfusion	Clinical	Colorectal cancer[148]
ZD6126‡	Contrast-enhanced MRI	Tumour blood perfusion	Preclinical	Rat GH3 prolactinoma and murine RIF-1 fibrosarcoma[148]
Combretastatin A4 phosphate	Contrast-enhanced MRI	Tumour blood perfusion	Clinical	Solid tumours[150]
Endostatin	Contrast-enhanced MRI	Tumour blood perfusion	Clinical	Solid tumours[151]
Combretastatin A4 phosphate	Contrast-enhanced MRI	Tumour blood perfusion	Preclinical/clinical	Rat P22 carcinosarcoma and human solid tumour[152]
Fluorouracil	^{18}F-Fluorouracil	Pharmacokinetics	Clinical	Breast, colorectal, and other tumours[153]
Gemcitabine	^{18}F-Gemcitabine	Pharmacokinetics	Preclinical	Colon carcinoma[154]
Ifosfamide	^{31}P-Ifosfamide	Pharmacokinetics	Preclinical	GH3 prolactinoma and breast tumours[155]

Willman (2008)

Diffusion MRI as a guide to therapy

- Relation of tumor to neighboring fiber tracks
- Example: pyramidal tract displaced by astrocytoma, viewed intra-operatively

Prior to surgery

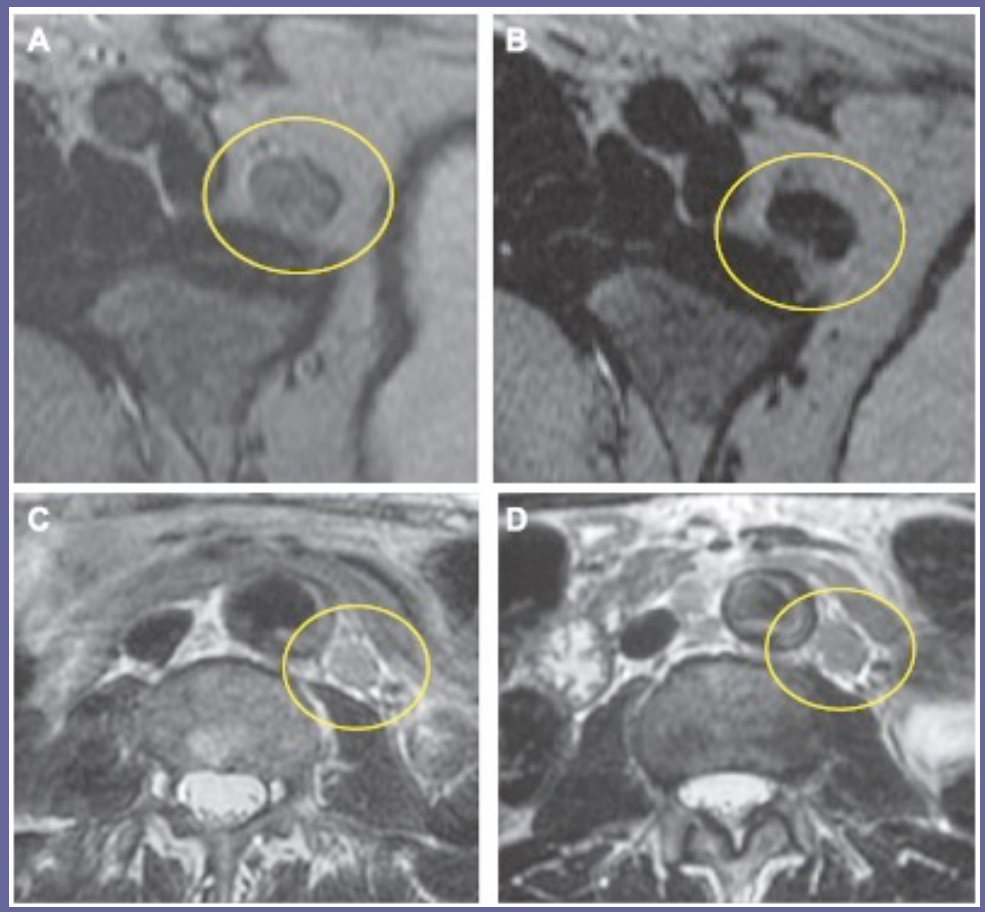


Sorensen (2006)

3 months post-surgery

Targeted contrast agents

- Iron-based T2 contrast agent (ferumoxtran-10)
  - taken up by healthy lymph nodes
- Distinguishes healthy (top) from malignant tumor (bottom)



Pre-injection Post-injection

Imaging in Clinical Trials and Imaging Biomarkers

- PET, US, and MRI can be used to evaluate drug distribution, efficacy
- Clinical trials are expensive, high-risk
- Imaging biomarkers can
  - Reduce costs
  - Improve the odds of identifying good treatments
  - Benefit pharmaceutical industry, physicians, and patients

Course Overview: What have we been talking about?

- Image information
  - Ways to quantify image quality
  - Sources of contrast
  - Data modeling
  - Limitations of imaging
- Image-based measurement of
  - Intrinsic tissue properties
  - Position
  - Volume and shape
  - Motion
    - Diffusion and tissue microstructure
    - Tissue perfusion
    - Blood flow
  - Metabolism
    - Oxygen use
  - Molecular receptor density

The Bigger Picture

https://www.athome.com/wall-frames/

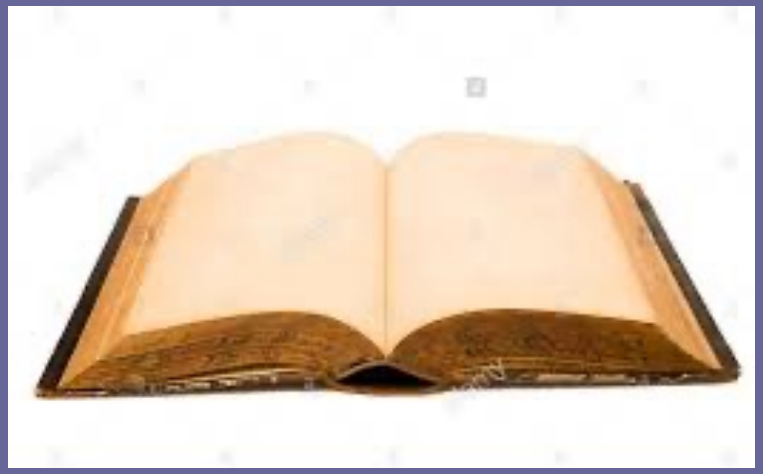
- Applications of quantitative imaging
  - Measure tissue structure and physiology
  - Characterize disease in an individual
  - Group studies to understand general features of diseases
  - Evaluate therapy
    - ‘Precision’ medicine
- How medical imaging technology is being used in
  - Medical centers
  - Pharmaceutical industry
  - Biomedical research institutes
- Developed skills for image research
  - Programming tools for image analysis
  - Modeling experience
  - Relation of image information to tissue properties

Course Evaluation

- Check your email for “course evaluation”
- Provide your feedback on the course:
  - What works well now?
  - What could work better?
  - What topics are missing?
  - Should we spend class time differently?
  - Any suggestions for making the course more interesting/valuable?
- It’s your gift to future QFI students!

Announcements

- Take-home final
  - Available on Brightspace (Sunday)
  - Open notes, books, internet (but not conversation)
  - Turn in by Tuesday (Dec. 13, 11:59pm)



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Sources

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- AG Sorensen, Magnetic resonance as a cancer imaging biomarker. *J Clin Oncol* 24: 3274-3281 (2006).
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