Cancer Imaging 2010
Role of Magnetic Resonance Imaging

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Cancer Imaging 2010
Goals of this Presentation

• Review principles of functional MRI
• Update clinical utility in clinical trials in-
  – Predicting outcome
  – Predicting response to therapy
• Describe other emerging imaging tools
Cancer Imaging: Facts 2010

• Tumor shrinkage (RECIST/WHO) is still standard end point for response assessment
• Tumor dimensions lag behind biologic and molecular changes in responders
• Functional MRI offers more potential as predictor of therapy outcome and response
  – most use is still in clinical trials
Which MRI Studies are Functional?

• Functional studies
  – Measure physiology
  – Diffusion weighted imaging (DW-MRI)
  – Dynamic contrast-enhanced (DCE-MRI)

• Metabolism
  – MR spectroscopy--used more for tumor characterization, not response assessment
Dynamic Contrast Enhanced (DCE) MRI

- Imaging modality for measuring the physiology of tumor microcirculation, including hypoxia and angiogenesis

- Based on changes in signal intensity following injection of a contrast medium (Gadolinium)
Methodology DCE-MRI

• Contrast injected
• Sequential images obtained during wash-in & wash-out
• Imaging reflects microvascular changes in tumor
DCE-MRI: Quantitative Analysis

• Primary end points are:
  — Time vs. signal intensity curve (estimate of perfusion, semi-quantitative, non-physiological)
  — Volume transfer constant, $K_{trans}$
    (physiological, measure of exchange in plasma and extracellular extravascular space)

\[ K_{ep} = \frac{K_{trans}}{V_e} \]
- Cancer shows rapid & higher enhancement
- Cancers are leaky, have increased permeability (*K*<sub>trans</sub>)
Clinical Applications for DCE-MRI

• Detection of many types of tumors including breast, cervical, osteosarcoma, bladder, rectal
• Tumor staging
• Monitoring response to treatment
  – Conventional treatments (chemotherapy/RT)
  – Novel biological treatments specifically antiangiogenic/vascular targeting drugs
• Predicting outcome
DCE-MRI Predictor of Outcome
What do we know?

• In general, cancers with high baseline enhancement or permeability ($K_{trans}$) are associated with better tumor regression

• Attributed to better perfused tumors having less hypoxia-related radioresistance

• Used in cervical, rectal, hepatocellular cancers

Hayes et al. NMR Biomed 2002; 15:154
DCE-MRI: Predictor of Outcome
Is it reproducible and valid?

• In cervical cancer

• High enhancement levels predict response to radiation therapy (RT) (Cooper 2001)

• High enhancement levels predict response to radiotherapy and also correlate with intratumoral O₂ levels (Loncaster et al, Int J Radiat Oncol Biol Phys 2002)
Outcome Predictor: Cervical Cancer

- Kaplan-Meier plot: MR enhancement predicted outcome
- Relationship between flow amplitude & tumor O₂ levels

Outcome Predictor: Rectal Cancer Reproducibility and Validation

- Advanced cancers (T3/T4)
- *High baseline permeability* (Ktrans) correlates with response to CRT (Dzik- Jurasz Lancet 2002; George 2001 Br J Surg)
- And also correlates with reduction in microvessel blood flow (MVD) (Lussanet Rad Oncol 2005)
- MVD is anatomic index of tumor vessel density
Outcome: Rectal Cancer

- High permeability ($K_{\text{trans}}$) correlates with survival

Next: DCE-MRI Monitoring Treatment Response--Does it work?

- *Early decrease in signal intensity* (within one week) predicts response to chemotherapy in bladder cancer (Barentsz, Radiology 1998)
- *Early decrease in permeability/k-trans* predicts response to CRT in cervical and hepatocellular cancers (Yuh et al, Invest Radiol 2009; Zhu A JCO 2009)
DCE-MRI: Bladder Cancer

• Responders show early decrease in signal intensity and slope of curve

Barentz Radiol 1998; 207:791
Positive tumor response
96% drop in K-Trans before tumor shrinkage

Baseline, 14 days and 6 points during 1st 3 cycles of Sunitinib
Significant decrease in Ktrans with PR or SD compared with patients with PD (average decrease 38%)

Zhu A, Sahani D et al. JCO 2009
DCE-MRI: Monitoring Antiangiogenic Therapy

- Phase I study PTK/ZK (anti-VEGF inhibitor)
  - colorectal liver metastases (n=26)
  - responders showed reduced blood flow & k-trans in a dose-dependent manner early in therapy (26-33 hrs) (Morgan 2003, 2004)
  - DCE-MRI biomarker for angiogenesis inhibition

Morgan, JCO 2003; 21:3955
DCE-MRI Benefits

- Can determine tumor response to chemotherapy, radiation and anti-angiogenic therapies
- Can potentially predict if a patient will respond to a treatment
- Can predict response before tumor shrinkage
- Correlates with histological assessments of tumor neovascularization such as microvessel density and VEGF pathways
DCE-MRI Limitations

- Standardized acquisition pulse sequences and analysis techniques are absent
- There are only small studies assessing reproducibility (test/retest)
- Software not commercially available
The Competition--CT Perfusion (CTp)?

CONVENIENT

- Available technique
- High spatial resolution
- High inter-tester reproducibility ($r=0.90-0.94$)
- Software is commercially available

Miles KA. Acad Radiol 2000;7:840–50

Detection  Staging  Monitoring
Perfusion CT (CTp)

- Measure of tumor microcirculation
- Simple compartmental model. Shows arterial, $a(t)$, tissue, $c(t)$, and venous, $v(t)$, time enhancement curves
CTp Technique
Quantitative Parameters

- BF = Blood flow
- BV = Blood volume
- MTT = Mean transit time
- PS = Permeability surface

Parameters dependent on mathematic modeling
What do we know?

- Limited information
- Rectal cancers with high baseline flow and volume show good response (Bellomi Radiology 2007, Sahani 2005)
- Attributed to better perfused tumors having less hypoxia-related radioresistance (like MR)
Can CTp Predict Therapeutic Response?

• There are more data (clinical trials)
  – liver, lung, rectum, pancreas
• Early decrease in blood flow, volume and permeability/k-trans but increase in mean transit time values correlated with response to therapy
Lung Cancer Response to CRT

- Reduced blood volume correlates with response--precedes change in tumor size
CTp: Monitoring Antiangiogenic Response
Hepatocellular Carcinoma

Drop in Blood Flow
Drop in Blood Volume
Drop by 76%
Favorable Response

Zhu et al. The Oncologist 2008; 13: 120
Sarcoma: Antiangiogenic therapy

Reduction in blood volume and increase in mean transit time correlated with response

Pre-Avastin

Post-Avastin

BF

MTT

24.3 ml/100g/min

7.9 sec

13.9 ml/100g/min

13.9 sec
Monitoring Antiangiogenic (Avastin) Response in Rectal Cancer

Monitoring Antiangiogenic (Avastin) Response in Rectal Cancer: CTp changes

## CTp Validation and Reproducibility

<table>
<thead>
<tr>
<th>Clinical Application</th>
<th>Author (Journal/Year)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Ma et al (BMC Cancer, 2008)</td>
<td><em>BF, BV and PS</em> values of peripheral lung cancer correlated positively with MVD</td>
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<tr>
<td>Liver</td>
<td>Sahani et al (Radiology 2007)</td>
<td>Reproducibility of <em>BF, BV, PS and MTT</em> values with high correlation and variability of 4% in HCC</td>
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<tr>
<td>Pancreas</td>
<td>d'Assignies et al (Radiology 2008)</td>
<td><em>BF</em> values of pancreatic endocrine tumors correlated well with MVD</td>
</tr>
<tr>
<td>Colon &amp; Rectum</td>
<td>Goh et al (Am J Roentgenol 2006)</td>
<td><em>Quantitative perfusion</em> measurements are reproducible in colorectal cancer</td>
</tr>
</tbody>
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Chan NG et al. CTp JCAT 2009
CTp Challenges

- Limited sample volume (2-4 cm)
  - Choice of location for investigation critical
- Patient motion can impact perfusion values
# CTp vs. DCE-MRI

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CTp</th>
<th>MRI</th>
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<tbody>
<tr>
<td>Coverage</td>
<td>2-4 cm</td>
<td>Entire organ</td>
</tr>
<tr>
<td>Computation</td>
<td>Simpler (linear relationship)</td>
<td>Complex</td>
</tr>
<tr>
<td>Parameters</td>
<td>Flow, volume, transit, permeability</td>
<td>K trans (permeability)</td>
</tr>
<tr>
<td>Limitations</td>
<td>Motion Reproducibility</td>
<td>Motion Reproducibility</td>
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Functional MR Imaging
Diffusion-Weighted Imaging (DWI)

• Evaluates motion (diffusion) of water molecules
• Amount of diffusion is quantified by the apparent diffusion coefficient (ADC)
• Cancer tends to have more restricted diffusion than normal tissue (lower ADC)
• Does not require contrast
Restricted Diffusion in Cancer

- Increased cellularity and reduced extracellular space = restricted diffusion

Cancer  Normal tissue
Prostate Cancer-ADC Map

- DWI: Cancer brighter than normal
  - Reflects restricted water motion

![Image of Prostate Cancer-ADC Map]

Normal tissue
ADC 1.3 x 10^{-3} \text{ mm}^2/\text{s}

Tumor
ADC 0.75 x 10^{-3} \text{ mm}^2/\text{s}
Basis of DW MRI in Monitoring Response

• With successful treatment, changes in cell density resulting from necrosis or apoptotic processes lead to increases in tumor H$_2$O diffusion and increase in ADC
DWI-MRI as Outcome Predictor
Does it work?


• High pretreatment ADC values are seen in necrotic tumors which are frequently hypoxic, acidotic, poorly perfused with low sensitivity to chemotherapy or RT

• Rectal, hepatocellular cancer
Outcome Predictor: Rectal Cancer

- N=20, CRT
- Pretreatment ADC values inversely correlated with percent reduction tumor size (p<.005)

Pearson r = -0.73 (p = 0.008)

Change in tumor size as percentage of original size
Outcome Predictor: Liver Metastases in Colorectal Cancer

- Liver metastases ($n = 20$)-DW MRI pre chemotherapy
- High baseline ADCs predicted poor response to therapy

Can ADC Predict Response to Therapy?

- *Early increase in ADC value* after starting therapy (1-2 wks) was *surrogate biomarker of response*

- *Change in ADC occurs before change in size*
  - Kamel IR JVIR (2006) 17: 505

- *ADC correlates with necrosis in rabbit model*
Monitoring Therapeutic Response
Rectal Cancer

- Responders show higher pre-treatment & early increase in post-therapy ADC values (p<.005-0.0001)
  - (Thielmann 2004, Kamel 2006), Yankeelov 2007; Eccles 2009)
- Preceded changes in WHO/RECIST criteria
- Conclusion: ADC can predict responders
Liver Cancer (HCC, cholangioca, mets): Monitoring Response to Radiotherapy

- DW MRI at 1 and 2 weeks and 1 month (n=11)
- *Early increase in ADC correlates with tumor response, whereas RECIST did not (p<.005)*

Eccles Acta Oncologica 2009; 48:1034
DWI-MRI Limitations

• DWI-MRI processing technique to predict outcome and response, BUT
• Infection, abscess may have impaired diffusion
• Lack of standards for measurements
  – Best gradient (b value) unknown
What else is new?
MR Elastography (MRE)

- Noninvasive test that quantifies tissue stiffness
- Based on generation of mechanical vibrations in tissues and processing software to create images
- Currently used for detection & characterization
- Premise is that stiffness of cancer is greater than that of normal tissues or benign tumors
MRE: Obtaining the Image

• Mechanical driver device is placed on the patient’s body to generate shear waves (60Hz)

MRE: Resulting images are displayed as wave maps

- Short wave lengths

- Stiffness < 2.9 kPa

Taouli AJR 2009; 193; 14-27
MRE in Liver Tumors

- N=44 tumors
- Stiffness of malignant tumors > benign tumors, fibrotic liver, and normal liver ($p < 0.001$)
- MRE evaluates stiffness or shear forces

Venkatesh, AJR 2008;190:1534
MRE: Focal Liver Masses

Adenoma

stiffness value = 3.1 kPa
normal liver = 2.4 kPa

HCC

stiffness value = 10.8 kPa

Venkatesh, SK. et al. AJR. 2008;190:1534-1540
Alternative is US elastography

- Measures tissue response to stress & displays information as a color scan
- ‘Stiff’ structures (tumors) displayed in blue
- Soft tissues displayed in red, green
- Stiffness calculated
Soft liver parenchyma (red–green) contrasts with hard intercostal muscles (blue) (mean speed 105.31)

Hard liver parenchyma (blue) contrasts with surrounding soft tissues (red–green) (mean speed 227.26)

Alternative: US Elastography

Saftoiu AJR 2007 189:W232-233
Lymph Node

Endoscopic US elastography--malignant mediastinal node in a patient with esophageal carcinoma
Hard tissue (tumor) is blue. Normal soft tissue is red–green
Quantitative Analysis
Elastography coefficients

Strain index > 4 is predictor of thyroid cancer ($P < .001$)
Why is Functional MRI a Good Biomarker and also CT?

• Provides a precise (quantitative) indication of treatment response
• Noninvasive
• Can be used before or very early in treatment to predict disease response and outcome
• True validity will not be known until large, prospective trials are performed
Grazie per la Vostra Attenzione

PATHOPHYSIOLOGY

Blood Vessels

flow

diffusion

[Images of medical scans and diagrams related to blood vessels and flow/diffusion]