Cancer Evaluation: Beyond Bi-dimensional Measurements

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Case Presentation
36 F Nausea/Vomiting and Neck Pain, Stage IV Breast Ca

- Metastatic disease to liver
- Prior outside whole-brain radiation
- Mild rotatory nystagmus.
  - Otherwise normal physical examination
  - ROS noncontributory
  - P 113, BP 100/80, T 36.6°C
- T2 FLAIR
36 F Metastatic Brain Cancer Treated By Radiotherapy

- Initial MRI images (T2 and FLAIR)

- Post-radiotherapy images (Contrast and FLAIR):
36 F Radiotherapy to Brain, Enlarging Lesion, Ataxia

- Initial post-radiotherapy images (contrast and FLAIR):

- Eighteen months after 1400 cGy stereotactic boost
36 F Radiotherapy to Brain, Enlarging Lesion, Ataxia

- Initial FLAIR

- Later FLAIR
36 F Enlarging Lesion, Ataxia: Radiation Necrosis

- Initial FLAIR
- Low N-Acetyl-Aspartate
  - Depletion of normal neuronal peptide
- Elevated lactate
  - Tissue breakdown
- Normal FLAIR
  - No increased cell turnover
- All radiation necrosis without recurrent disease.
Historical Cancer Evaluation

- Detected clinically
  - Weight loss
  - Change in stool
  - Cough
  - Headache
  - Lump
- Staged by physical exam
  - Symptoms
  - Palpation (size and firmness)
  - Lymph nodes
  - Laboratory values
  - Laparoscopy
Current Cancer Imaging Evaluation

- Predominantly by Computed Tomography
- World Health Organization criteria 1981
  - Bi-dimensional measurements
- Response Evaluation Criteria In Solid Tumors (RECIST 2000)
  - Up to 5 lesions per organ, 10 lesions total
  - Officially, single longest dimension ≥10 mm
  - Sum all single longest dimensions
    - 30% decrease for partial response
    - 20% increase for progressive disease
- Minimum 6-8 week interval
- “Non-target” lesions are not measurable
Current Cancer Imaging
Nuclear Medicine

- Tissue specificity instead of size resolution
- Analogs of tissue substrates
  - Iodine
  - MDP - bone mineral
  - MIBG - neuroendocrine precursor
  - Pentatretotide - somatostatin receptor
  - FDG - glucose
- Unknown mechanism
  - Thallium, sesta-MIBI, and Gallium
- Antibody-mediated
  - Oncoscint and Prostascint
Why Not Just Use PET-CT For Everything?

- Combines resolution of CT & specificity of PET
- Allows characterization of size and activity
- No contraindications
  - NB Dosing can be tricky in diabetics
Why Not Just Use PET-CT For Everything?

• However…
  • FDG is taken up by inflammation
  • FDG is not taken up by many tumors
  • Specific Uptake Value depends on many factors
    • Patient weight
    • Insulin level
    • Activity of dose administered
    • Delay between injection and scan
    • Skeletal muscle activity
  • FDG-avid organs cannot be evaluated
  • FDG and CT resolutions are different
  • CT acquisition is suboptimal
    • Must optimize for PET coregistration
New Paradigms in Cancer Imaging

• PET-CT is still the workhorse for most staging, restaging, and follow-up.
• Initial therapy is often determined by local involvement, well below the resolution of FDG-PET, e.g. vascular or local invasion.
• We need a way to characterize tumor beyond anatomic size
  • Determine initial therapy aggressiveness
  • Choice of tumoricidal, tumorstatic, and anti-angiogenic therapies
  • Shorter-term follow-up
On the Horizon

• New MRI techniques, long utilized as research tools, are beginning to enter the clinical arena
• Spectroscopy for extracranial applications
  • The concentration of choline correlates strongly with cellular turnover, roughly tumor grade
• Diffusion-weighted imaging
  • Densely packed cells restrict free water motion
  • Therapy monitoring for necrosis or fibrosis
• Enhancement kinetics model blood flow
  • Capillary leakiness correlates with invasiveness
  • Anti-angiogenic therapy monitoring
Therapy Monitoring

- Currently, therapy efficacy is evaluated by a change in tumor size or laboratory values.
- A change in the standardized uptake value on FDG-PET can be seen after one or two treatments in eventual responders.
- Spectroscopy, diffusion, and enhancement kinetics have all shown similar promise in treatment monitoring.
  - Earlier failure detection would allow a change in therapy sooner.
  - However, the kind of change depends on both tumor histology and therapy type.
A Word About Renal Function and MRI

• Nephrogenic Systemic Fibrosis or Nephrogenic Sclerosing Dermopathy is a scleroderma-like syndrome closely correlated to prior exposure to gadolinium-containing (MRI) contrast in renal failure patients, especially those who have recently undergone a transplant or, to a lesser extent, other surgery.

• Although exceedingly rare, no other predictive factors have been identified.

• Currently, each institution formulates its own policy regarding MRI contrast for patients in renal failure.
Brain Tumors: The Model for Modeling

- The brain is a convenient organ in which to study new techniques
  - Does not move
  - Stereotyped location and morphology
  - Blood supply well characterized
  - Neoadjuvant therapy and reimaging
- Not always the best model
  - Blood-brain barrier unique – other organs have different blood supply dynamics
  - Brain tissue and CSF are quite unlike many other organs
Brain Tumors: Spectroscopy

• We have already seen how spectroscopy is useful for differentiating treated versus recurrent disease.
• Low-grade and mixed-grade tumor evaluation
  • Do not enhance if blood-brain barrier intact
  • Often little edema on FLAIR sequences
  • Alteration in chemical composition on MRS can more accurately predict extent of disease
• Uses the principle of nuclear magnetic resonance to separate resonance peaks of some common simple chemical constituents.
Diffusion-weighted imaging uses the vector-component of MRI to determine the degree to which free water motion is restricted.

Sensitive for the discrimination of tumors from benign entities.
- Epidermoid versus arachnoid cyst
- Abscess versus necrotic tumor

Because this is a vector, it can be quantified and used as a marker for therapeutic response.

This technique is being applied to other organs, including the prostate.
Breast Cancer: Dynamic Contrast Enhancement

• Mammography is sensitive for tumors in predominantly fatty breasts and for DCIS.
• Ultrasound can be sensitive in densely glandular breasts, but is user-dependent.
• MRI with contrast has been shown to have up to 100% sensitivity for breast tumors, with its specificity improved by modeling of enhancement curves.

• Multifocal (one duct system) vs. multicentric disease?
Breast Cancer: Dynamic Contrast Enhancement

- The American Cancer Society now recommends MRI screening for women at high risk of breast cancer.
  - BRCA-1 or BRCA-2 mutation
  - First-degree relative with BRCA-1/2 mutation
  - Lifetime risk ≥ 20% by standard assessment tools
  - Chest radiation between ages 10 and 20
  - Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or a first-degree relative with one of these syndromes
Breast Cancer: Dynamic Contrast Enhancement

- Currently, we use enhancement curves to characterize the level of suspicion only
  - Temporal resolution is sacrificed to improve spatial, and thus anatomic, characterization
- New techniques may allow us to share spatial and temporal information, effectively optimizing both
- Five papers have used MR to gauge therapy response
  - The change in $K_{\text{trans}}$ early on is predictive of response
  - Initial $K_{\text{trans}}$ may also be predictive
Pharmacokinetic Assumptions

• The general kinetic formula, \( k_{ep} = \frac{K^{\text{trans}}}{V_e} \) is based on the following model:

  Vascular Space (Input function) \( K^{\text{trans}} \) Extracellular Extravascular Space (EES) \( k_{ep} \)

• The above is the basis for many other complex models which take into account “lesion leakage space” and other parameters, e.g.:

\[
\frac{S_{CM}(t)}{S_0} = 1 + A \left[ \frac{k_{21}}{(k_{21} - k_{el})} \right] \left[ \exp(-k_{el}t) - \exp(-k_{21}t) \right]
\]

Where \( K21 \) is the rate of exchange from the tumor space back to plasma
Liver Cancer

- Gadolinium-contrast enhanced MRI is the most sensitive scan for hepatocellular cancer.
- A second contrast agent, Feridex, is nearly equally efficacious for improving detection of suspicious and benign lesions.
  - Basically “rust,” similar to sulfur colloid
  - Taken up by reticulendothelial system
  - Normal liver and some benign lesions (focal nodular hyperplasia) become darker
  - Must be slowly infused followed by a delay
  - Causes back pain, mechanism unknown
Liver Cancer Example
MR Lymphangiography

• Conventional lymphangiography is a lost art. It required cannulation of small lymphatics in the feet.
• Cross-sectional imaging allows easy identification, but not characterization, of lymph nodes.
• A contrast agent similar to Feridex is taken up by normal, but not pathologic, lymph nodes. Normal lymph nodes drop in signal on MRI.
  • Must be administered intravenously hours prior to scan
  • Not yet FDA-approved
Example: Prostate Cancer

- Case presentation
  - 72 M
  - PSA rising, now 8.2
  - Biopsies show Gleason 3+4=7 in 80% of tissue on the right
- Evaluate for surgical resectability
- Also, for our own uses, evaluate for localization of disease
Prostate MRI

- T2 Anatomic image
- Applied diffusion coefficient
- Spectra from the right
- Spectra from the left
Prostate MRI

- However, the capsular margins are preserved
Prostate Cancer

- Dynamic enhancement shows fair specificity but is not well characterized for PPV.
- Diffusion imaging has also shown promise. Prostate and whole-body diffusion imaging is being studied as a staging modality.
- Elastography has also been suggested as a promising technique.
- Although prostate spectroscopy correlates strongly with Gleason score, it is of limited utility in diagnosing all but gross seminal vesicle invasion or extracapsular extension.
- Conventional surgical resection is not often altered by imaging findings.
Prostate Cancer

- Dynamic Contrast
- MR Lymphangiography
New Prostate Cancer Therapies

- New technologies offer *in situ* therapy
- Localization of disease may become a necessity for these new therapies.

**Prostate Cancer's Prognosis**

*New therapies exist, but men still face a tough call: get treated now, or wait*

By Adam Voiland

By the time Jim Hurley, 54, learned last year that he had early-stage prostate cancer, the disease had already killed his father and struck two brothers. With that family history, the plaster artisan from Springfield, N.J., wasn't about to take chances. For two months, he pored over scientific studies, books, and websites about the cancer. He discussed his situation with doctors, his brothers, and other survivors. A surgeon recommended surgery. A radiation oncologist advocated a form of radiation therapy. But Hurley, concerned that either could leave him impotent or incontinent, settled on a novel technique that attacks cancer with sound waves. He had to drop $23,500 and fly to Toronto to get treated with high-intensity focused ultrasound, or HIFU. (Health officials in Canada and Mexico permit the procedure, but U.S. regulators haven't made a decision on it.) So far, he's pleased with the results.
Overall Research Goals

- Develop standardized, reproducible MR scanning techniques that can yield preliminary imaging biomarkers for apoptosis and angiogenesis imaging in the clinical environment. Timeline: 2-6 months.
- Validate imaging biomarkers against clinical endpoints and pathologic correlates across a range of tumor histologies for apoptosis and anti-angiogenesis. Timeline: 6-18 months (anatomic correlation) and 24-48 months (clinical validation) per tumor histology.
- Integrate MR imaging biomarkers into existing solid oncology research programs. Timeline indefinite.
Technical Development

- Currently, only prostate imaging is being investigated
  - Much like the brain, the prostate does not move during scanning
  - However, prostate cancer tends to be multifocal
  - Most cases get resected no imaging follow-up
- Dynamic contrast enhancement sequences are not very useful for anatomic characterization
  - Do not need anatomic resolution
  - Can acquire data sets and analyze using different packages
- Diffusion and spectroscopy are used clinically
  - Spectroscopy is useful as a problem solving tool
  - Diffusion has improved specificity and equal sensitivity for organ-confined, but not extrapsular, disease than traditional anatomic images
Technical Development

• The next step is to apply these same techniques (dynamic contrast enhancement and diffusion) to other organs
  • Liver
  • Pancreas
  • Lung
  • Kidney
  • Cervix/uterus
• The difficulty will be adapting to respiration
  • Short, breath-held sequences
  • Respiratory compensation
Validation

- Spectroscopic data has been shown to correlate significantly with the Gleason score of prostate cancer specimens
- The applied diffusion coefficient, a measure of free water restriction, does not clearly correlate with Gleason score
- DCE parameters have not been well characterized in the prostate yet
- Other histologies will be correlated as those scan types come online
- Eventually, will correlate with gene/protein array data
Thank you