Targeted Therapy for Hepatic Tumors: Assessing Response

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OBJECTIVES

- Discuss liver directed therapy- RF ablation (RFA), transarterial chemoembolization (TACE) and Y90 radioembolization
- Unique aspects of imaging interpretation related to liver directed therapy-limitations of size criteria; use of diffusion-weighted images
INTERPRETATION OF IMAGES AFTER IR TREATMENT

• Among the most difficult in radiology
• No one fights to read these cases
• No significant decrease in size or paradoxical increase in size is seen with ablative therapies such as RF ablation; TACE and Y90 radioembolization—result of hemorrhage and necrosis
• No uniform standard of interpretation
• Ring enhancement mistaken for tumor and may be post treatment changes including scar tissue or reactive edema
ANATOMIC IMAGING BIOMARKERS

• Traditional chemotherapeutic agents are cytotoxic and eliminate neoplastic cells

• As result, change in tumor size and disappearance of lesion
  – only widely accepted and validated radiological marker of treatment response
  – Unfortunately often does not apply for local therapy in HCC
TREATMENT OPTIONS

• Ablation-number of types-will focus on RFA
• TACE
• Yttrium
RADIOFREQUENCY ABLATION

- Destroys tumor by heating
- Generally treat when 4 or fewer lesions and <3-4 cm in long axis to ensure complete ablation
- Percutaneous RFA has emerged as a definitive therapy for small HCCs (<3 cm)
  - Lencioni RA et al. Radiology 2003
- Survival similar to surgery for HCC <5 cm (96%, 82%, 71%, and 68% at 1, 2, 3, and 4 yrs)

Lopez PM et al. Liver Trans 2006;12:1747-54

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Follow-up imaging can be difficult to interpret

- Image immediately after, 1 month and 3 months after ablation
- Immediate nonenhancement
  - Sharp interface
    - Margin > 0.5 cm
  - Involutes over months
  - Ringlike enhancement normal (benign periablational enhancement at treatment margin mimics tumor)

Pretreatment

Post: 1 month later-larger but necrotic

FOLLOW-UP IMAGING CAN BE DIFFICULT TO INTERPRET

- Image immediately after, 1 month and 3 months after ablation
- Immediate nonenhancement
  - Sharp interface
    - Margin > 0.5 cm
  - Involutes over months
  - Ringlike enhancement normal (benign periablational enhancement at treatment margin mimics tumor); typically gone by 6 mos.

Post: 4 month later lesion is smaller

FOLLOW-UP IMAGING CAN BE DIFFICULT TO INTERPRET

- Residual/recurrent disease often at periphery of ablated lesion
  - Often enhances
  - Peripheral recurrence may relate to lower energy deposition and reduced heating
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HCC PREABLATION

Venous Phase Post Contrast
POST RFA
2 MONTHS POST RFA
4 MONTHS POST RFA-CORONAL IMAGES HELPFUL
7 MONTHS POST RFA
7 MONTHS POST RFA
EMBOLIZATION - BACKGROUND

- Normal liver has hepatic arterial and portal venous blood supply
- Tumors especially HCC almost completely supplied by hepatic artery
- Tumors treated by directly injecting hepatic artery with embolic material, chemotherapy or radioembolization (Y90)
  - TACE-Goal is to cause obstruct the feeding artery causing ischemia and accumulation of the chemotherapeutic agent within the tumor
TACE

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IMAGING FOLLOW-UP

- MODALITY:
  - CT or MRI

- TIMING:
  - HAE/TACE
    - Immediately post-procedure—generally CT (lipiodol accumulation)
    - 4-6 weeks
    - q3-6 months
  - Y90
    - 1 month
    - q3-6 months
ASSESSMENT OF RESPONSE

• ANATOMIC
  – Decrease in \textit{tumor size} - classic approach for therapy
    • WHO, RECIST, Volume
  – \textit{Necrosis} - defined as a lack of enhancement of lesion
    • EASL

• FUNCTIONAL
  – Changes at diffusion-weighted MRI
  – Perfusion imaging
  – Metabolic activity at FDG PET-especially mets
  – Serum tumor marker reduction
CHALLENGES

• Different institutions report findings differently which affects transplantation and treatment assessment
  – size of lesion including necrotic part vs. just enhancing part (tumor)

• Type of treatment and imaging studies need be based on local expertise of your institution
HCC AND TACE: PRETHERAPY AND LIPIODOL POST THERAPY

Pretherapy

Post-RX CT
MAY BE DIFFICULT TO ASSESS ENHANCEMENT AFTER THERAPY

T1 FS Precontrast

Postcontrast
71 year old female w HCC treated w TACE
Yttrium-90 microsphere

- Local radiation therapy for unresectable liver tumors
- Mechanism: Tumors are more vascular than normal liver and supplied predominately from the hepatic artery, Y90 trapped in capillaries resulting in >3x radiation exposure of tumor relative to normal liver
- Allows tumors receive over 150 Gy

Courtesy Dr. Riad Salem
Response based on necrosis not just size
NODULE AFTER Y90

- May be residual enhancing nodule - residual tumor or slower treated tumor/post treatment changes
- Often does not metastasize or grow with Y90
- Different from RFA or TACE when typically is tumor and need treat early
Pre treatment

6 weeks post treatment

3 years post treatment
THIN RIM ENHANCEMENT AFTER TREATMENT

• Seen in 32% (25/76) lesions after treatment measuring < 5mm in thickness

• Thin rim compatible with inflammatory reaction and correlated well with histologic necrosis

Keppke A et al AJR 2007
PVT WITH TREATMENT RESPONSE

Pre tx

1m post tx

3m post tx

26m post tx
LIMITATIONS OF ANATOMIC ASSESSMENT

• Anatomic response lags behind functional changes
• Difficult to prospectively predict tumor response

Salem et al JVIR Dec 2005
FUNCTIONAL IMAGING: DIFFUSION

• Percentage enhancement on arterial and portal venous phases
  - Extracellular space
  - Tumor vascularity

• Detects altered water mobility
  - Cellularity
  - Integrity of the cell membrane
DIFFUSION: OVERSIMPLIFICATION

- Following therapy, tumors with restricted diffusion (dark on ADC maps) become less restricted diffusion (bright on ADC maps) – increase in ADC values
- Some of changes in ADC may precede changes in size of lesion
- Bright on diffusion images (dark ADC)-restricted diffusion-live tumor
- Dark on diffusion images-favorable response
- Successful treatment-dark on DWI and shows increase in ADC
HCC POST TREATMENT

Post contrast Post Treatment

Dark

DWI Post Treatment

Post Treatment

DWI Pretreatment
The Role of Functional MR Imaging in the Assessment of Tumor Response after Chemoembolization in Patients with Hepatocellular Carcinoma

Ihab R. Kamel, MD, PhD, David A. Bluemke, MD, PhD, John Eng, MD, Eleni Liapi, MD, Wells Messersmith, MD, Diane K. Reyes, RT, and Jean-Francois H. Geschwind, MD, PhD

- 38 HCC patients/Imaging 4-6 weeks post TACE
- Targeted tumors demonstrated:
  - targeted tumors DID NOT change significantly in size
  - mean decrease in arterial enhancement of 30%
  - mean decrease in venous enhancement of 47%
  - Less restricted diffusion (Tumor ADC value increased from 0.0015-0.0018 mm²/sec after treatment)
Intrahepatic Cholangiocarcinoma Treated with Local-Regional Therapy: Quantitative Volumetric Apparent Diffusion Coefficient Maps for Assessment of Tumor Response

- 29 cholangioca patients/Imaging 3-5 weeks post TACE
- Better response to therapy and improved overall survival:
  - Early decrease enhancement did not correlate with survival
  - Percentage volumetric increase in ADC of >45% and volumetric ADC over 1.6 x 10^-3 m2/s did correlate
68 YR CHOLANGIOCARCINOMA TREATED TACE

- Axial RECIST: 10.5 cm to 10.9 cm – stable disease
- Mean volumetric ADC increased from 1.63 to 2.55 × 10^{-3} mm²/sec
- Rightward shift in histogram - increase ADC
- Red- 92% of tumor volume had ADC above threshold - excellent response
  - Halappa et al John Hopkins Group
HCC POST SORAFENIB AND Y90

Pretherapy

T1 Post Gad Art Phase  b500  ADC

Posttherapy

T1 Post Gad Art Phase  b500  ADC

HCC POST SORAFENIB AND Y90

Pretherapy

T1 Post Gad Art Phase  | b500  | ADC Histogram

Posttherapy

T1 Post Gad Art Phase  | b500  | ADC Histogram

Venous Phase

Arterial Phase

DWI

ADC
FUTURE DIRECTIONS: PRIMARY INDEX LESION

- Patients with locoregional therapy have at least 1 dominant lesion: “Primary Index Lesion” targeted during initial session: alternative biomarker for response in HCC
- Do not need to follow all the lesions but only the dominant primary index lesion
- Response can be measured using WHO, RECIST and/or EASL
- Statistical significant correlation with disease progression and survival

LIMITATIONS OF DIFFUSION AND PERFUSION

- Limited data on reproducibility
- Vendor variations and potentially different values dependent on scanner and more time consuming
- Has not been universally adapted
CONCLUSIONS

• Tumor response assessment is challenging especially following Yttrium, TACE, or RFA
• Need to evaluate not just traditional size (RECIST, WHO) criteria but also necrosis
• Need use and develop functional techniques: DW and Perfusion weighted MR and PET scans to show response earlier
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