Making Sense of Hepatic Tumor Post-therapy Imaging: Limitations of RECIST

Frank Miller, M.D.
Chief, Body Imaging Section and Fellowship
Medical Director, MR Imaging
Chief, GI Radiology
Professor of Radiology
Northwestern University, Feinberg School of Medicine, NMH
Chicago IL
OUTLINE

• Discuss liver directed therapy-TACE (transarterial chemoembolization) and Yttrium

• Unique aspects of imaging interpretation related to liver directed therapy-limitations of size criteria
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
Pre treatment

22 months

CHALLENGES WITH INTERPRETATION

Courtesy Dr. Riad Salem
TOWER OF BABEL / ALPHABET SOUP: NO UNIVERSAL LANGUAGE ESPECIALLY FOR HCC RX

- WHO
- RECIST 1.0 / RECIST 1.1
- EASL
- mRECIST
- CHOI
- RECICL
- PERCIST
COMPETING METHODS OF ASSESSING RESPONSE

1. Uni-dimensional
   - Response Evaluation Criteria in Solid Tumors (RECIST) - longest diameter of target lesions

2. Bi-dimensional
   - World Health Organization (WHO)

3. Volumetric measurements

4. European Association for the Study of the Liver (EASL)

5. Functional: Diffusion-Weighted (DW) MR Imaging (ADC), Perfusion weighted MR and PET Scans

Courtesy Dr. Robert Lewandowski
COMPETING METHODS OF ASSESSING RESPONSE

1. Uni-dimensional
   - Response Evaluation Criteria in Solid Tumors (RECIST)

2. Bi-dimensional
   - World Health Organization (WHO) - cross product of target lesions

3. Volumetric measurements

4. European Association for the Study of the Liver (EASL)

5. Functional: Diffusion-Weighted (DW) MR Imaging (ADC), Perfusion weighted MR and PET Scans

Courtesy Dr. Robert Lewandowski
COMPETING METHODS OF ASSESSING RESPONSE

1. Uni-dimensional
   - Response Evaluation Criteria in Solid Tumors (RECIST)
2. Bi-dimensional
   - World Health Organization (WHO)
3. Volumetric measurements
4. European Association for the Study of the Liver-necrosis as reduction in enhancement
5. Functional: Diffusion-Weighted (DW) MR Imaging (ADC), Perfusion weighted MR and PET Scans

Courtesy Dr. Robert Lewandowski
INTERPRETATION OF IMAGES AFTER IR TREATMENT

- Among the most difficult in radiology
- No one fights to read these cases
- 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
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

Pretreatment Trip

Post-treatment Trip
ASSESSMENT OF RESPONSE

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

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

• OTHERS
  – Angiographic response
  – Clinical improvement
NECROSIS: SIZE NOT CHANGED - FOCUS ON NECROSIS

Pre Tx

Post Tx
NECROSIS

Necrotic HCC

Live HCC
CHALLENGES

• Different institutions report findings differently which affects transplantation and treatment assessment
  – size of lesion including necrotic part vs. just enhancing part (tumor)
NECROSIS
HCC AND TACE: PRETHERAPY AND ETHIODOL POST THERAPY
MAY BE DIFFICULT TO ASSESS ENHANCEMENT AFTER THERAPY - SIZE UNCHANGED
POST TACE: SUBTRACTION IMAGES ARE HELPFUL
METABOLIC ACTIVITY AT FDG PET: NOT APPLICABLE FOR ALL HCC
TUMOR MARKER REDUCTION
Yttrium-90 microspheres

- Local radiation therapy for unresectable liver tumors
- Mechanism: Tumors are supplied predominately from the hepatic artery, Y90 trapped in capillaries resulting in >3x radiation exposure of tumor relative to normal liver
LESION SIZE MAY NOT REFLECT TREATMENT RESPONSE

MR - Pre tx  3.1x3cm  
CT - 1m post tx  7.5x4.6cm
<table>
<thead>
<tr>
<th>TREATMENT RESPONSE</th>
<th>WHO (size)</th>
<th>RECIST (size)</th>
<th>% NECROSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Disappearance of lesion</td>
<td>Disappearance of lesion</td>
<td>Total necrosis</td>
</tr>
<tr>
<td>Partial response</td>
<td>&gt;50% decrease</td>
<td>&gt;30% decrease</td>
<td>&gt;30-50% ?</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>&lt;50% decrease or &lt;25% increase</td>
<td>&lt;30% decrease or &lt;20% increase</td>
<td>&lt;% defined for partial</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>&gt;25% increase or appearance of new lesions</td>
<td>&gt;20% increase or appearance of new lesions</td>
<td></td>
</tr>
</tbody>
</table>
Imaging of Hepatocellular Carcinoma After Treatment with Yttrium-90 Microspheres

Ana L. Kepple\(^1\)
Riad Salem\(^1\)
Denise Reddy\(^1\)
Jie Huang\(^2\)
Jianhua Jin\(^2\)
Andrew C. Larson\(^1\)
Frank H. Miller\(^1\)

**OBJECTIVE.** Yttrium-90 radioembolization is an emerging therapy for unresectable hepatocellular carcinoma (HCC). Although therapeutic response based on size has been evaluated in numerous studies, necrosis has been used as a criterion of response in only a few studies. The purpose of our study was to describe the imaging features of HCC after \(^{90}\)Y treatment and to compare size criteria (World Health Organization [WHO] and Response Evaluation Criteria in Solid Tumors [RECIST]) with necrosis criteria and combined criteria (RECIST and necrosis) for assessment of response.

**MATERIALS AND METHODS.** CT images of 42 patients with 76 \(^{90}\)Y-treated HCC lesions were analyzed. We used four response criteria: WHO size, RECIST size, necrosis, and com-

- **Retrospective review of 42 pts, 52 lobes, 76 treated HCC’s, imaged w/ CT or MR**

<table>
<thead>
<tr>
<th>Treatment Response</th>
<th>WHO</th>
<th>RECIST</th>
<th>Necrosis</th>
<th>Combined criteria = RECIST + Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td>Disappearance</td>
<td>Disappearance</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>≥50% decrease</td>
<td>≥30% decrease</td>
<td>≥30%</td>
<td><strong>Greatest change determined response</strong></td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>&lt;50% decrease to &lt;25% increase</td>
<td>&lt;30% decrease to &lt;20% increase</td>
<td>&lt;30%</td>
<td></td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>≥25% increase or new lesions</td>
<td>≥20% increase or new lesions</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*AJR 2007; 188:768–775*
Treatment Response by Patient (n = 42):

<table>
<thead>
<tr>
<th>Treatment Response</th>
<th>WHO</th>
<th>RECIST</th>
<th>Necrosis</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>26%</td>
<td>23%</td>
<td>57%</td>
<td>59%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>78%</td>
<td>78%</td>
<td>NA</td>
<td>59%</td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22%</td>
<td>22%</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Keppke et al. (AJR 2007) Imaging of HCC after treatment with $^{90}$Y Microspheres
IMAGING OF HCC AFTER TREATMENT WITH $^{90}$Y Microspheres

- **Other Conclusions:**
  - **Time to response:**
    - WHO/RECIST criteria: 120 days (median) - TOO LONG
    - Necrosis: 30 days (median)

Keppke et al. (AJR 2007) Imaging of HCC after treatment with $^{90}$Y Microspheres
BRIDGE TO LIVER TRANSPLANTATION

- Partial response using necrosis not RECIST/WHO
  - Mural nodule of enhancement
- Completely necrotic at explant
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
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 applies for WHO, RECIST and/or EASL
- Statistical significant correlation with disease progression and survival

LIMITATIONS OF ANATOMIC ASSESSMENT

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

Salem et al JVIR Dec 2005
DIFFUSION MR

- Difficult to assess treatment following therapy [RF Ablation, transhepatic arterial chemoembolization (TACE) or Yttrium]
- Lesions often don’t change in size or may grow from hemorrhagic necrosis
- Diffusion MR can play role
FUNCTIONAL IMAGING-DIFFUSION

- Detects altered water mobility
  - cellularity
  - integrity of the cell membrane

- Percentage enhancement on arterial and portal venous phases
  - extracellular space
  - tumor vascularity

Anatomic

T1 post-gadolinium

Functional

Diffusion-weighted (DWI)
DIFFUSION: OVERSIMPLIFICATION

- Bright on DWI (dark ADC)-restricted diffusion-live tumor
- Dark on DWI-favorable response
- Successful treatment-dark on DWI and shows increase in ADC
HCC PRETREATMENT

Bright
HCC POST TREATMENT

Post contrast Post Treatment

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%
  - Tumor ADC value increased from 0.0015-0.0018 mm²/sec after treatment-LESS RESTRICTED DWI
DWI TUMOR RESPONSE

• 58 yo male
  - Y\(^90\) therasphere

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>1 mo post</th>
<th>3 mo post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>24 mm</td>
<td>22 mm</td>
<td>15 mm</td>
</tr>
<tr>
<td>ADC</td>
<td>0.9 x 10(^{-3}) mm(^2)/s</td>
<td>2.0 x 10(^{-3}) mm(^2)/s</td>
<td>1.6 x 10(^{-3}) mm(^2)/s</td>
</tr>
</tbody>
</table>
POST - $^{90}\text{Y}$ REACTIVE EDEMA

- DW-MRI may differentiate tumor from peripheral reactive edema after therapy related to Y90 or TACE
CONCLUSIONS

• Tumor response assessment is challenging especially following local therapy such as Yttrium, TACE, or RFA
• Need to evaluate not just traditional size (RECIST, WHO) criteria but also necrosis
• Consider functional techniques: DW and perfusion weighted MR and PET scans to show response earlier
ACKNOWLEDGEMENTS-HUGE THANKS

- Dr. Shawn Haji-Momenian
- Dr. Laura Kulik
- Dr. Andrew Larson
- Dr. Robert J Lewandowski
- Dr. Reed Omary
- Dr. Riad Salem
- Dr. Yi Wang
REFERENCES

REFERENCES