Evolving Role of TheraSphere® in Liver Cancer Care in Asia – Hong Kong Experience

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Comprehensive Oncology Centre
Hong Kong Sanatorium and Hospital

APPLE meeting Hong Kong, 8 July 2016
HCC in Hong Kong (2013)

- No. 4 most frequent cancer overall
- No. 4 most frequent cancer in males and no. 9 in females
- Male to female ratio 4:1
- 1852 new cases, 6% of all cancers
- 1,542 deaths due to HCC
- 42.3 per 100,000 in male
- 11.5 per 100,000 in female
HCC Epidemiology

- HCC sixth most common form of cancer worldwide
  - 3rd most frequent cause of cancer-related death worldwide\(^1\)
  - In US, NCI estimate 30,640 new cases and 21,670 deaths in 2013\(^2\)

- Only about 20% of HCC patients are considered resectable\(^3\)
  - Contraindications
    - Significant portal hypertension
    - Poor liver function

\(^2\)National Cancer Institute [www.cancer.gov](http://www.cancer.gov)

Therefore, high demand for non-surgical treatment for unresectable Hepatocellular carcinoma
Current Treatment Approaches for Inoperable HCC

• Local Ablation (Localized tumour)
• Transarterial locoregional therapy (TARE, TACE) (Localized tumour)
• Systemic treatment (Metastatic disease)

HCC = hepatocellular carcinoma; TACE = transarterial chemoembolization; TARE = transarterial radioembolization
Asia-Pacific Association for Study of Liver Consensus on Treatment of HCC

Confined to the liver
Main portal vein patent

Solitary or multifocal tumor in noncirrhotic liver or Child A cirrhosis

Yes

Resection / RFA (for < 3 cm HCC)

No

Solitary tumor ≤ 5 cm
≤ 3 tumors ≤ 3 cm
No venous invasion

Child A

Local ablation

Child B

Transplantation

Child C

Extrahepatic metastasis
Main portal vein tumor thrombus

Child A / B

Sorafenib or systemic therapy trial

Tumor > 5 cm
> 3 tumors
Invasion of hepatic / portal vein branches

Child A / B

TACE

Child’s C

Supportive care

Omata et al. Hepatol Int 2010
Radioembolization (TARE)

- Intra-arterial (trans-arterial) administration of yttrium-90 microspheres (e.g. TheraSphere®) for the treatment of unresectable hepatocellular carcinoma
- 2 types commercially available in Hong Kong
  - TheraSphere® (BTG, UK)
  - SIR-Spheres® (SIRTEx, Australia)
What is $^{90}$Y?

- 100% pure beta emitter$^{1,2}$
- Decays to zirconium-$^{90}$$^{1,2}$
- Physical half-life of 64.1 hours (2.67 days)$^{1,2}$
- 94% of radiation delivered within 11 days$^1$
- Average energy of 0.9367 MeV$^{1,2}$

1. TheraSphere® [EU package insert]. Surrey, UK: Biocompatibles UK Ltd, a BTG International group company
2. EU reference manual

$^{90}$Y = yttrium-90
What Is TheraSphere®?

- $^{90}$Y glass microsphere therapy indicated for the treatment of hepatocellular carcinoma$^1$
- Radioactive $^{90}$Y is an integral component of glass$^{1,2}$
- Delivered to tumor vasculature through hepatic artery$^{1,2}$

Mean diameter of 20—30 μm$^1$
Activity per sphere at calibration is 2,500 Bq$^3$
1 GBq in tissue delivers 50 Gy/kg$^1$

$^{90}$Y = yttrium-90; HCC = hepatocellular carcinoma; PVT = portal vein thrombosis; TARE = transarterial radioembolization

(Components Not to Scale)

- 20 mL Syringe
- IV Bag
- Empty Vial
- Injected into Hepatic Artery
- Catheter Inserted into Femoral Artery
- TheraSphere® Dose Vial
- Priming Line
- Delivery Line

Liver
TheraSphere® Mechanism of Action

TheraSphere® glass microspheres:

- Are infused via transfemoral catheterization of hepatic artery\(^1,2\)
- Penetrate and lodge within the tumor arteriolar capillaries\(^1,2\)
- Emit beta radiation with an average tissue penetration range of 2.5 mm\(^1,2\)

Pre- and Post-Treatment Imaging*

**Pre-Treatment**: Contrast-enhanced MRI demonstrates a large right lobe HCC (14 x 8 cm)

**Post-Treatment**: 4-month follow-up CT demonstrates significant decrease (74% reduction) in tumor size (6.9 x 4.3 cm) and complete necrosis

CT=computed tomography; HCC=hepatocellular carcinoma; MRI=magnetic resonance imaging.

Pre- and Post-Treatment Imaging

**Pre-Treatment:** MRI demonstrates a large right lobe lesion (6.3 x 5.8 cm)

**Post-Treatment:** 14-Month follow-up CT demonstrates a decrease in lesion size (2.2 x 2.2 cm)

CT=computed tomography; MRI=magnetic resonance imaging.
Common Adverse Events (usually grade 1 – 2)

• Fatigue
  - Usually lasts 10–12 days

• Mild abdominal pain or discomfort
  - Bloating/nausea
  - Relieved by conservative measures

• Lower grade fever/Night sweats
  - Bulky disease
  - Cytokine release from tumor necrosis
  - Rule out other causes
  - Relieved by conservative measures
TheraSphere® Treatment for Inoperable Hepatocellular Carcinoma

- Hong Kong Experience in Hong Kong Sanatorium and Hospital
  - From 2014 - 2016
Selection Criteria for TheraSphere® Treatment

- Localized unresectable HCC
- Minimal extra-hepatic disease allowed
- Acceptable liver function
  - Albumin > 30
  - INR < 1.4
  - Total bilirubin < 3 x ULN
- Patent main portal vein
- Branched PVT thrombosis is allowed
Pre Treatment Investigations

- Liver function tests and clotting profile
- PET CT scan with dual isotopes (18-FDG and C11-acetate)
- Tumour and non tumour volumetrics
- Hepatic Angiogram plus injection of Technetium labeled macroaggregated albumin (Tc-MAA)
- SPECT CT scan after Tc-MAA to measure:
  - Lung shunting %
  - Tumour to normal liver uptake ratio
Pre-treatment Tc-MAA scan on Mar 20, 2015

MAA Lung Shunting Scintigraphy

Tc-99m MAA Statics [Processed Perfusion Series] 3/20/2015

Statistical Table
Perfusion
Anterior Chest
Posterior Lung

<table>
<thead>
<tr>
<th></th>
<th>Anterior Chest</th>
<th>Posterior Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Counts) Total</td>
<td>113K</td>
<td>087K</td>
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</tbody>
</table>

Liver Tomo [Series ROI And Curve] 3/20/2015

<table>
<thead>
<tr>
<th>Series: Liver Tomo [Corrected - AC]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frame / Image: 46 / 1</td>
</tr>
<tr>
<td>Tumor: 10061 cts.</td>
</tr>
<tr>
<td>Normal: 1433 cts.</td>
</tr>
<tr>
<td>T/N ratio: 7.4339</td>
</tr>
</tbody>
</table>

Geometric Mean Lung

<table>
<thead>
<tr>
<th></th>
<th>Anterior Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Counts) Total</td>
<td>098K</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Lung</th>
</tr>
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<tbody>
<tr>
<td>(% Ratios) Total</td>
<td>7.50</td>
</tr>
</tbody>
</table>
Treatment Procedures for TARE with Therasphere®

- Second hepatic angiogram and delivery of TheraSphere® under monitored anaesthetic control (MAC)
- Post treatment Bremstahlung SPECT scan and PET CT scan to be done on day 1 after treatment
- Discharge on day 1 after procedure
- Reassessment PET CT scan with dual isotopes 2 months after treatment to document response
Post treatment evaluations

- Bremsstahlung SPECT CT scan
- PET CT scan (without isotope)
- PET MRI scan (without isotope, since 2015)

Purposes:
1. Evaluate distribution of Y-90
2. Dosimetric estimation
3. Verification of Tc-MAA distribution
Post Therasphere® Bremsstrahlung scan
Post Therasphere® PET/CT scan
MRI PET: Fusion with Yttrium
Post Yttrium-90 scan

Spect CT

PET-CT

PET-MR
PET/CT on 27/10/2014

57.9 mm LD x 49.9 mm PD
ACT: SUVmax 16.4, delayed 14.7
2 months after TS: PET/CT on 19/01/2015
Radioembolization with Therasphere® in Hong Kong Sanatorium and Hospital (2014 – 2016)

<table>
<thead>
<tr>
<th>Total number of patients work up for Therasphere®</th>
<th>57</th>
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</thead>
<tbody>
<tr>
<td>HCC</td>
<td>51</td>
</tr>
<tr>
<td>Metastatic Liver Cancer</td>
<td>6</td>
</tr>
<tr>
<td>Male : Female</td>
<td>47 : 10</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>60 (32 – 83)</td>
</tr>
<tr>
<td>Total number of patients treated</td>
<td>51</td>
</tr>
<tr>
<td>HCC</td>
<td>45</td>
</tr>
<tr>
<td>Metastatic Liver Cancer</td>
<td>6</td>
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Radioembolization with Therasphere® in Hong Kong Sanatorium and Hospital (2014 – 2016)

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<td>HCC</td>
<td>45</td>
</tr>
<tr>
<td>Metastatic Liver Cancer</td>
<td>6</td>
</tr>
<tr>
<td>Median dose (range)</td>
<td>2.35 (1 – 3.9) GBq</td>
</tr>
</tbody>
</table>
Patients rejected for treatment

- Total 6 patients rejected after HAG + Tc-MAA
  - 2 patients with poor T/N ratio
  - 1 patient with high lung shunting
  - 2 patients with both poor T/N ratio and high lung shunting
  - 1 patient with rapid disease deterioration and liver failure
MAA Lung Shunting Scintigraphy

Tc-99m MAA Statics [Processed Perfusion Series] 10/26/2015

Statistical Table

<table>
<thead>
<tr>
<th>Perfusion</th>
<th>Counts</th>
<th>Post Chest Posterior Lung</th>
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<tbody>
<tr>
<td>Total</td>
<td>586K</td>
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<table>
<thead>
<tr>
<th></th>
<th>Counts</th>
<th>Anterior Lung Total 765K</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Counts</th>
<th>666K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T/N ratio calculation

Series: Liver Tomo [Corrected - AC]

Frame / Image: 36 / 1
Tumor: 10258 cts.
Normal: 2212 cts.

T/N ratio: 2.3935

Liver Tomo [Series ROI And Curve] 10/26/2015

<table>
<thead>
<tr>
<th></th>
<th>(Counts)</th>
<th>Geometric Mean Lung Total 666K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lung 40.36 100</td>
</tr>
</tbody>
</table>
Hong Kong Sanatorium and Hospital Experience

- 2 abstracts, both oral presentation, in the Society of Nuclear Medicine, San Diego 2016
Response prediction in HCC patients treated with $^{90}$Y glass microspheres based on metabolic parameters: post-radioembolization $^{90}$Y PET/CT tumor dose and pretreatment $^{11}$C-acetate & $^{18}$F-FDG PET/CT metabolic grading

Chen SR$^1$, Cheung SK$^1$, Leung WT$^2$, Leung YL$^1$, Cheng KC$^1$, Wong KN$^1$, Wong C$^1$, and Ho CL$^1$,*

1. Dept. of Nuclear Medicine & PET, 2. Comprehensive Oncology Center, Hong Kong Sanatorium & Hospital
Response prediction in HCC patients treated with $^{90}$Y glass microspheres based on metabolic parameters: post-radioembolization $^{90}$Y PET/CT tumor dose and pretreatment $^{11}$C-acetate & $^{18}$F-FDG PET/CT metabolic grading

- 28 patients: 23M, 5F, mean age: 60.0±14.7 y; 19 HBV, 1 HCV
- Pretreatment $^{18}$F-FDG and $^{11}$C-acetate PET/CT

**Pretreatment $^{11}$C-acetate and $^{18}$F-FDG PET/CT** → $^{90}$Y glass microspheres TARE → $^{90}$Y PET/CT → Post-treatment $^{11}$C-acetate and $^{18}$F-FDG PET/CT

1. $^{11}$C-acetate or $^{18}$F-FDG avidity: HCC grade/aggressiveness
2. Metabolic tumor burden

15-min/bed
“time-of-flight” reconstruction
Parameters to assess tumor burden and response

**Metabolic tumor burden (MTB)**
\[ \text{MTB} = \sum \text{lesion SUV}_{\text{mean}} \times \text{lesion volume of all HCC lesions on } ^{11}\text{C}-\text{acetate/}^{18}\text{F-FDG PET} \]

**Metabolic response**
\[ \text{Metabolic response} = 100\% \times (\text{posttreatment MTB} - \text{pretreatment MTB}) / \text{pretreatment MTB} \]

Based on PET Response Criteria in Solid Tumors (PERCIST): “a reduction of >50%” in metabolic response

Good responder
Results

<table>
<thead>
<tr>
<th>Tumor dose by $^{90}$Y PET/CT</th>
<th>Range: 73~363 Gy, mean: 196±82 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-mo good response rate</td>
<td>50.0% (14/28), 71.4% (5/7) for PVT patients</td>
</tr>
</tbody>
</table>

1.) Baseline tracer avidity and 2.) TD as 2 independent predictors associated with treatment response

<table>
<thead>
<tr>
<th>Original avidity</th>
<th>Good responder</th>
<th>Tumor volume</th>
<th>Injected activity (IA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C-acetate</td>
<td>76.9%</td>
<td>282±207 ml</td>
<td>2.45±0.91 GBq</td>
</tr>
<tr>
<td>$^{18}$F-FDG</td>
<td>26.7%</td>
<td>271±189 ml</td>
<td>2.37±0.76 GBq</td>
</tr>
</tbody>
</table>
Results

Tumor dose (TD) threshold to predict tumor response

- A threshold TD value of $154\text{Gy}$ predicted tumor response for all the 28 patients (sensitivity: 85.7%, accuracy: 78.6%, AUC: 0.791)

- For $^{18}\text{F-FDG}$-avid group, the cut-off TD value for good response was higher than that for $^{11}\text{C}$-acetate group ($242 \text{ vs } 150\text{Gy}$), indicating that a higher IA of $^{90}\text{Y}$ was needed for $^{18}\text{F-FDG}$-avid (high grade) HCC.

- By using 2 different cut-off TD values, the treatment response could be more accurately predicted than a single TD ($89.3 \text{ vs } 78.6\%$)
Results

Good response for $^{11}$C-acetate-avid HCC patient treated by $^{90}$Y microspheres

Baseline PET/CT

$^{11}$C-acetate

Follow-up PET/CT

$^{11}$C-acetate

$^{18}$F-FDG

Baseline HCC avidity: $^{11}$C-acetate

IA: 1.08 GBq
TD: $288 \text{ Gy} > 150 \text{ Gy}$

Good response?

Outcome

Treatment response: 100%
Survival: >24 mo
Poor response for $^{18}$F-FDG-avid HCC patient treated by $^{90}$Y microspheres

Baseline HCC avidity: $^{18}$F-FDG

- IA: 2.40 GBq
- TD: 182 Gy > 154 Gy but < 242 Gy

Poor response?

Outcome

Treatment response: 30%
Good reponse for $^{18}\text{F-FDG}$-avid HCC patient treated by increased IA of $^{90}\text{Y}$ microspheres

Baseline HCC avidity: $^{18}\text{F-FDG}$
- IA: 2.80 GBq
- TD: 254 Gy > 242 Gy

Good response?

Outcome
- Treatment response: 90%
- Survival: >24 mo
90Y PET/CT for dosimetry measurement and quantitative optimization in inoperable HCC patients treated by 90Y glass microspheres radioembolization

Chen SR¹, Leung WT², Cheung SK¹, Leung YL¹, Cheng KC¹, Wong KN¹, Wong C¹, and Ho CL¹,*

1. Dept. of Nuclear Medicine & PET, 2. Comprehensive Oncology Center, Hong Kong Sanatorium & Hospital
Methods

Patients: April 2014 ~ Oct 2015, N=34, 28M, 6F
age range: 34~82y, mean: 60.1±13.9y; 24 HBV, 1 HCV

Pre-treatment simulation by $^{99m}$Tc-MAA planar and SPECT/CT to estimate

- lung shunting (% of injected activity)
- tumor-to-non tumorous liver ratio (T/N ratio)

- To calculate biological absorbed dose with reduced injected activity
- To correlate pre-treatment Tc-MAA scan data with post treatment PET CT scan
Estimation of radiation dose

$^{90}$Y distributed to the liver, non-tumorous liver and lung

- actual PET-measured activities corrected for positron branching ratio ($3.186 \times 10^{-5}$) & time decay: $PA_{(GBq)}$

Volume of tissue containing $^{90}$Y

- CT volumetrics of lung
- PET volumetrics of tumor and non-tumorous liver

Biological absorbed dose when $^{90}$Y decay to infinity

$$D_{(Gy)} = PA_{(GBq)} \times 49.67 / W_{(kg)}$$

Bremsstrahlung SPECT/CT

$^{90}$Y PET/CT
Results

33/34 patients received reduced IA (2.45±1.11GBq) with ILD 40 ~ 100Gy (median: 60Gy), 50% of recommended

Biological absorbed dose

1. TD (30/34): 215±72Gy, range: 139~363Gy; 73~117Gy in 4 patients >120Gy!

2. NTD (34/34): 37±11Gy, range: 16~55Gy <70Gy of the limiting liver dose
Results

Lung shunting on $^{90}$Y PET/CT lower than that on $^{99m}$Tc-MAA planar for all patients

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{90}$Y PET/CT</td>
<td>1.8 ± 1.2%</td>
<td>0.4 ~ 14.6%</td>
</tr>
<tr>
<td>$^{99m}$Tc-MAA planar</td>
<td>6.8 ± 3.8%</td>
<td>2.9 ~ 15.4%</td>
</tr>
</tbody>
</table>

Accuracy of $^{90}$Y PET/CT for dosimetry measurement: comparing the summation of image-measured activity in tumor, liver and lung with injected activity

Recovery coefficient: 91.2~99.3%, median=96.4% of IA

$^{90}$Y PET/CT for dosimetry is feasible and accurate
Correlation between T/N ratios from posttreatment $^{90}$Y PET/CT and pretreatment $^{99}$Tc-MAA SPECT/CT

$TNR_{^{90}Y} = 1.044 \times TNR_{^{99}Tc-MAA} - 0.033$

$p << 0.05$

mean $= 5.6 \pm 3.6$ $^{90}$Y

mean $= 5.4 \pm 3.0$ $^{99}$Tc-MAA
Results

Reduced IA but high TD for patient with high TNR

6 cm

$^{11}$C-acetate PET/CT

$^{99m}$Tc-MAA planar & SPECT/CT
Lung shunting: 4.6%
TNR: 14.2

Recommended IA: 2.85 GBq
Injected activity: 40%

TD: 288 Gy >> 120 Gy
NTD: 19.2 Gy << 70 Gy
LD: 2.2 Gy
Recovery coefficient: 98.7%

Lung shunting: 4.4%
TNR: 15.0
Reduced IA with consideration of limiting NTD

99mTc-MAA planar & SPECT/CT
Lung shunting: 11.7%
TNR: 5.1

Recommended IA: 4.64 GBq
Injected activity: 60%

TD: 254 Gy >> 120 Gy
NTD: 53.6 Gy < 70 Gy
LD: 5.6 Gy
Recovery coefficient: 93.1%
Lung shunting: 4.6%
TNR: 4.7
Conclusion

- PET/CT post $^{90}$Y-radioembolization could provide accurate dosimetry measurement and confirmation of biodistribution in HCC patients, thus obviating the conventional use of Bremsstrahlung-SPECT.

- The TNR predicted by $^{99m}$Tc-MAA SPECT/CT is accurate but lung shunting is overestimated by $^{99m}$Tc-MAA planar imaging, therefore, the threshold limit might be given greater allowance.

- Quantitative optimization of IA of $^{90}$Y glass microspheres could be individualized and guided by target TD or limiting NTD instead of a routinely fixed ILD.
THANK YOU!