Image-Guided Interventional Cancer Therapy with Nanoparticle-Carried Radionuclides

Ande Bao, PhD
Department of Radiology & Department of Otolaryngology
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Outline

• Review of therapeutic radionuclides
• Radionuclide dosimetry
• Image-guided interventional delivery of cancer therapeutics
• Lipid nanoparticles (Liposomes) used in drug delivery
• Cancer radionuclide therapy with intratumoral administration
• Cancer radionuclide therapy with intraoperative radionuclide therapy
• Breast cancer brachytherapy
• Summary

Therapeutic Radionuclides

• \(\alpha\)-Emitter
• \(\beta\)-Emitter
• Auger Electron Emitter
• Low Energy Photon Emitter
α-Emitters


Table 1. Properties of the α-emitting radionuclides $^{213}$At and $^{212}$Bi.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Approximate tissue range (μm)</th>
<th>Mean particle energy (MeV)</th>
<th>α Particle yield per 1000 decays</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{212}$At</td>
<td>7.2 h</td>
<td>55</td>
<td>5.87</td>
<td>62</td>
</tr>
<tr>
<td>$^{212}$Bi</td>
<td>60.6 min</td>
<td>57</td>
<td>6.15</td>
<td>36</td>
</tr>
</tbody>
</table>

β-Emitters


Table 2. Low-energy β-emitting radionuclides. $\beta_{\text{ave}}$ and $\beta_{\text{max}}$ are the root mean square and maximum electron energies, respectively.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>$\beta_{\text{ave}}$ (MeV)</th>
<th>$\beta_{\text{max}}$ (MeV)</th>
<th>$\beta_{\text{ave}}$ (MeV)$^{2}$</th>
<th>$\beta_{\text{max}}$ (MeV)$^{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C</td>
<td>0.9</td>
<td>1.7</td>
<td>0.83</td>
<td>2.9</td>
</tr>
<tr>
<td>$^{11}$N</td>
<td>0.02</td>
<td>0.22</td>
<td>0.001</td>
<td>0.049</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>0.05</td>
<td>0.45</td>
<td>0.025</td>
<td>0.204</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>0.05</td>
<td>0.45</td>
<td>0.025</td>
<td>0.204</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>0.45</td>
<td>1.75</td>
<td>0.21</td>
<td>3.04</td>
</tr>
<tr>
<td>$^{36}$Cl</td>
<td>1.75</td>
<td>5.65</td>
<td>3.04</td>
<td>12.8</td>
</tr>
<tr>
<td>$^{38}$Cl</td>
<td>1.75</td>
<td>5.65</td>
<td>3.04</td>
<td>12.8</td>
</tr>
<tr>
<td>$^{39}$Ar</td>
<td>1.75</td>
<td>5.65</td>
<td>3.04</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Auger Electron Emitters


Table 6. Selected radionuclides that decay by electron capture or isomeric transition and emit low-energy electrons (Auger and Coster-Kronig electrons).

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life (days)</th>
<th>Emission yield per decay</th>
<th>$\beta_{\text{ave}}$ (MeV)$^{2}$</th>
<th>$\beta_{\text{max}}$ (MeV)$^{2}$</th>
<th>Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{10}$N</td>
<td>11.2</td>
<td>4.2</td>
<td>0.003</td>
<td>9.992</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{10}$B</td>
<td>27</td>
<td>2.0</td>
<td>0.020</td>
<td>9.996</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{10}$P</td>
<td>0.04</td>
<td>2.2</td>
<td>0.022</td>
<td>9.991</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{10}$B</td>
<td>0.6</td>
<td>4.4</td>
<td>0.118</td>
<td>9.015</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{10}$B</td>
<td>80</td>
<td>25</td>
<td>0.084</td>
<td>9.028</td>
<td>Reactor</td>
</tr>
<tr>
<td>$^{10}$B</td>
<td>3.7</td>
<td>2.4</td>
<td>0.064</td>
<td>9.013</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{10}$B</td>
<td>0.42</td>
<td>2.4</td>
<td>0.055</td>
<td>9.021</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{10}$P</td>
<td>4.1</td>
<td>20</td>
<td>0.075</td>
<td>9.097</td>
<td>Reactor or cyclotron</td>
</tr>
<tr>
<td>$^{10}$P</td>
<td>4.0</td>
<td>20</td>
<td>0.075</td>
<td>9.097</td>
<td>Reactor</td>
</tr>
</tbody>
</table>

* Total electron yield (Auger plus Coster-Kronig electrons)
### 186Re and 188Re

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>186Re</th>
<th>188Re</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{1/2} (h)</td>
<td>90.64</td>
<td>16.97</td>
</tr>
<tr>
<td>Decay Pattern</td>
<td>β -</td>
<td>β -</td>
</tr>
<tr>
<td>Average β-Energy (MeV)</td>
<td>0.362</td>
<td>0.764</td>
</tr>
<tr>
<td>Average β-Range (mm)</td>
<td>1.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Major γ-Ray</td>
<td>137 KeV (10%)</td>
<td>155 KeV (15.5%)</td>
</tr>
<tr>
<td>β / γ-Energy Ratio</td>
<td>16.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Production</td>
<td>186Re(n,γ)</td>
<td>187Re(n,γ)</td>
</tr>
<tr>
<td></td>
<td>186W(n,γ)(n,γ)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td>Similar to 99mTc</td>
<td></td>
</tr>
</tbody>
</table>

#### 186Re and 188Re

- T_{1/2} (188W): 69.4 d.
- Perrenate (ReO_{4}⁻) vs pertechnetate (TcO_{4}⁻)
- Can be reduced to lowed valent with stannous chloride.
- Form the same or similar coordinate structure with lower valent as 99mTc.
- Not bone avid.

### β-Spectrum

![β-Spectrum](image.png)
There is a challenge in obtaining high resolution in vivo radioactivity distribution. It is generally more practical to calculate average radiation absorbed dose in each major organ.

To calculate radiation absorbed dose in each organ, nuclear images can be used to obtain radioactivity in each organ at various time points to calculate cumulated radioactivity in each organ.
MIRD Method

• It is assumed that radioactivity distributes homogeneously in each organ.

• Fractions of radiation dose coming from the radioactivity in each organ are deposited in itself and also the other organs.

• Absorbed Fraction, \( \phi \)

Hereby, \( r_i \) refers to a source organ and \( r_k \) refers to a target organ; \( \phi \) is the Absorbed Fraction of the \( i \)th emission of the radionuclide.

• In specific human profile, \( \phi \) relates to the type of radiation and its energy.

MIRD Method

• Equilibrium Absorbed Dose Constant,

\[ \Delta_i = N_i E_i \]

• When the unit of the average energy is in MeV, to convert \( \Delta_i \) into SI unit of Gy.kg/(Bq.Sec), the following corrected equation needs to be used:

\[ \Delta_i = 1.602 \times 10^{-13} N_i E_i \]

MIRD Method

• Average Absorbed Dose by the target organ,

\[ D(r_i \leftarrow r_k) = \frac{\Delta_i}{m_i} \sum \phi_i(r_i \leftarrow r_k) \Delta_i \]

• Mean Dose per Cumulated Activity,

\[ S(r_i \leftarrow r_k) = \frac{1}{m_i} \sum \phi_i(r_i \leftarrow r_k) \Delta_i \]

\[ \bar{D}(r_i \leftarrow r_k) = \bar{\Delta} \times S(r_i \leftarrow r_k) \]
MIRD Method

• For the convenience of radiation absorbed dose calculation and to avoid the consideration on the variances of different subjects, MIRD method classifies human subjects into a few groups by using standard average human models.

• Thus, Mean Dose per Cumulated Activity, $S(\alpha \leftarrow \beta)$, is a constant respect to each human model and a specific radionuclide.

Approximate Calculation

• Radiation particles emitted from radionuclide decay can be classified into non-penetrable components ($\alpha$, $\beta$-particles, and Auger Electrons) and penetrable components ($\gamma$, and x-ray).

• Generally, most of non-penetrable (np) components is absorbed by the organ itself and this radiation absorbed dose contribute most of total dose in the organ-of-interest.

• Thus an approximated radiation absorbed dose in a specific organ may be calculated with:

$$D = \frac{A}{m} \left( \sum h_i \right)_{\text{np}}$$

Characteristics of Radionuclide Therapy

• The rule of thumb of thyroid cancer therapy with sodium $^{131}$I is 1 rad per 1 $\mu$Ci.

• Thus, 150 mCi $^{131}$I corresponds to 1,500 Gy average dose to thyroid cancer.

• The regular radiation therapy prescribes a total dose of only 70 Gy.

• The short path length of therapeutic radiation particles with radionuclides and the respective non-homogeneous radiation absorbed doses in tumor and normal organs provides challenges while also potential significant advantages than external beam radiation therapy.
Image-Guided Interventional Delivery of Cancer Therapeutics

Challenges in Intratumoral Drug Delivery

• Inefficient intratumoral drug delivery in solid cancer therapy.
• High interstitial pressure of solid cancer, which prevents the fast transfer of therapeutic agents into tumor interstitial space from circulation, while the clearance of therapeutic agents are more rapid.
• Tumor vasculature is leaky, which allows drug-carrying nanoparticles below a cutoff size accumulating in the tumor interstitial space; however, the accumulation procedure generally requires over tens of hours to reach a balance concentration.


Intravascular Interventional Radionuclide Therapy

• Localized radionuclide therapy with intravascular interventional administration has been used in primary and metastatic hepatocellular carcinoma therapy.
• This therapy uses $^{90}$Y-microspheres: SIR-Spheres™: 20 – 60 μm (35 ± 5 μm); Therasphere™: 20 – 30 μm (25 ± 10 μm) in diameter.
• Microspheres at these sizes can be trapped in the microvasculature of liver cancer thus a high local therapeutic retention of $^{90}$Y-microspheres is achieved.
• However, the application of this therapy technique strongly depends on the hypervasularity of liver cancer (Right Figure) and many other solid cancers do not have this well-formed tumor vasculature to hold these microspheres.
• Alternatively, intratumoral administration into tumor interstitial space for interventional radionuclide therapy may be broadly applied in the therapy of various kind of solid cancers.
Liposomes and the Use as Radionuclide Carriers

- Liposomes are lipid-based nanoparticles with available diameters from less than 100 nm to over 2 μm. The availability of a segregated inner aqueous space enclosed by lipid membrane enables it an ideal nanoparticle drug carrier system.

- Many liposome-based drugs are available for clinical use or are under development.

- In our lab, an inventive technique of a convenient and practical encapsulation of radionuclides, $^{99m}$Tc, $^{186}$Re and $^{188}$Re with high efficiency and great stability has been developed.


Liposome Drug Encapsulation
Active Post-Manufacture Entrapment

Chemical gradient steered high efficiency drug encapsulation

$^{99m}$Tc-BMEDA  $^{186/188}$Re-BMEDA
Encapsulation of Radionuclides into Liposomes (Mechanism I)

1. Liposomes encapsulating glutathione (GSH) were used for radiolabeling
2. M(V)O-BMEDA crosses the double membrane of liposomes
3. In the inner space of liposomes, $\text{M(V)O-BMEDA + GSH} \rightarrow \text{M(V)O-BMEDA/GSH}$
4. M(V)O-BMEDA/GSH are hydrophilic and can be trapped in the inner space of a liposome

Encapsulation of Radionuclides into Liposomes (Mechanism II)

1. Liposomes encapsulating Ammonium sulfate (pH gradient liposomes) were used for radiolabeling
2. The neutral complexes, M(V)O-$^\text{SNS/S}$, cross the double membrane of liposomes
3. In the inner space of liposomes, $\text{M(V)O-}^\text{SNS/S} + H^+ \rightarrow [\text{M(V)O-}^\text{SNS/S}]H^+$
4. [M(V)O-$^\text{SNS/S}$]H$^+$ is hydrophilic and can be trapped in the inner space of a liposome

Ammonium / pH Gradient Liposomes
Animal Model

- Head and neck squamous cell carcinoma (HNSCC) xenograft model in nude rats has been set up by subcutaneous administration of SCC-4 cells at the back of each animal at the level of neck.


Micro-SPECT/PET/CT Small Animal Imager
Radiology Department
University of Texas Health Science Center at San Antonio
Cancer Radionuclide Therapy with Intratumoral Administration

- In tumor therapy via intratumoral administration of $^{186}$Re-liposomes, $^{186}$Re-liposomes were administered into tumor interstitial space mediated by convection (tumor size: $1.25 \pm 0.14 \text{ cm}^3$; 8, 4.7, and 2.7 mCi/cm$^3$ tumor) ($n=3$ each).

Imaging on Distribution of Radiolabeled Liposomes


Imaging on Micro-distribution of Radiolabeled Liposomes

Convection-Mediated Delivery of Drug Carried Nanoparticles in Size Exclusion Gel

2.0 ml liposomal doxorubicin (Doxil™) (Left) and free doxorubicin (Right) (0.2 mg doxorubicin each) eluted through columns (2.5 ml bed volume). Sealed to keep wet when all of the buffer eluted out. No further elution.

Cancer Therapy with Intratumoral Administration

- Tumor growth curves with HNSCC xenografts following intratumoral infusion of 186Re-liposomes. The liposomes had the same lipid formulation as Doxil™ but did NOT contain doxorubicin. The radioactivity dose of 8 mCi/g tumor almost completely stopped the tumor growth over a 20 day period. Compared with control tumors, the radioactivity doses of 4.7 and 2.7 mCi/g tumor also greatly suppressed tumor growth. The 8 mCi/g dose was below the maximum tolerated dose.

Cancer Radionuclide Therapy with Intraoperative Radionuclide Therapy

- Most of tumor tissue was surgically removed and around 0.5-1.0 cm² tumor was intentionally remained in the surgical bed followed by the injection of 99mTc-liposomes / 186Re-liposomes into positive tumor margin and surgical cavity.
- Intraoperative retention and distribution study was performed with 99mTc-liposomes at various formulation and particle diameters from 100 nm to 2 μm.
- In intraoperative therapy, 186Re-liposomes were injected into positive tumor margin and surgical cavity (4.8±0.4 mCi for neutral liposomes and 3.9±0.2 mCi for cationic liposomes) (n=8 each). Tumor sizes were measured daily and toxicity was also monitored.
Intraoperative Therapy

- Local retention for the $^{186}$Re-neutral-liposome group ranged from 86.2 $\pm$ 1.0 %IA at baseline to 18.8 $\pm$ 5.3 %IA at 140 h. In comparison, the $^{186}$Re-cationic-liposome group showed a range of local retention from 81.6 $\pm$ 2.7 %IA at baseline to 28.7 $\pm$ 3.6 %IA at 140 h.

- The $^{186}$Re-cationic-liposome group received an average absorbed dose of 801.9 $\pm$ 184.9 Gy in tumor compared to 617.9 $\pm$ 187.0 Gy with $^{186}$Re-neutral-liposome group over the period of 140 h.

Breast Cancer Brachytherapy

Current status of early stage Breast Cancer Brachytherapy:
- Relatively high normal breast radiation absorbed dose.
- Difficult to modulate to irregular surgical cavity.
- No capability of simultaneous lymph node irradiation.

Nanoparticle-carried therapeutic radionuclides provide the potential of improving these limitation for breast cancer brachytherapy.

Supported by Susan G. Komen Breast Cancer Foundation, the research is in progress.

Intracavitary Administration of $^{99m}$Tc-Liposomes
Radioactivity Distribution Model

Breast Cancer Brachytherapy
Intracavitary Dose Distribution
Summary and Conclusion

• Image-guided cancer interventional therapy with liposome-carried \( \beta \)-emission radionuclides resulted in a high local retention of therapeutic radionuclides and an optimal intratumoral micro-distribution for the coverage of therapeutic dose to the whole tumor.
• The path range of a few mm of \( \beta \)-particles is optimal to balance both radiation dose coverage throughout a tumor and a low radiation dose in nearby normal tissues.

Summary and Conclusion (Cont.)

• Liposomes have the convenience of easy and convenient administration to various situations and may have the potential of simultaneous lymph node irradiation.
• Our animal cancer therapy studies have shown the optimism of cancer therapy and a low normal tissue toxicity.
• Human cancer interventional brachytherapy is emerging.

Acknowledgements

• William T. Phillips, MD
• Beth Goins, PhD
• Randal A. Otto, MD
• Gerald D. Dodd, III, MD
• Pamela M. Otto, MD
• Sean X. Wang, MD
• Xavier Garcia-Rojas, MD
• Anuradha Soundararajan
• Stephanie J. Herrera, MD
• Shihong Li, PhD
• Xia Nancy Zhao, PhD
• Cristina Santoyo, MS
• Ricardo Perez, III
• Marcela Saenz
• Geoffrey D. Clarke, PhD
• Gary D. Fullerton, PhD
• Brian A. Hrycushko
Grant Support

• NCI / NIH SPORE Grant
• San Antonio Area Foundation
• Susan G. Komen Foundation