Physical Perspective on Radiation Response Modulation of Tumors with Gold Nanoparticles

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Prologue

Perfecting Radiation therapy ...

Variation of radiation quality → h, e-, n, p, …

Control of organ motion → Manipulation of radiation intensity / fluence

Image guidance / tumor tracking

Radiation Response Modulation of Tumor
Radiation Response Modulation of Tumors using high Z media

- Almost universally achievable in theory with enough accumulation (< ~ 10 wt. %)

- Efficacy varying dependent on the ability to control the two following parameters:
  - Amount of physical dose enhancement
  - Location of high Z materials: sites of interactions with radiation

Rationale for Use of GNPs

Why GNPs?
- Mediators for increased secondary electron production in tissue irradiated with hν, e-, p, etc.
  - Example: Interaction probability for photoelectric absorption ~ Z^4 to Z^4.8
    - Iodine (Z=53)
    - Gadolinium (Z=64)
    - Platinum (Z=78)
    - Gold (Z=79)

Adapted from Brigger et al, Adv. Drug Deliv. Rev. 54, 2002
Why GNPs?

• Possibility of achieving high tumor specificity of gold by conjugating GNPs with antibodies for tumor markers (e.g., EGFR) or angiogenesis markers (e.g., VEGFR) — “Active Targeting”

Why GNPs?

• Possibility of achieving significant cellular uptake of GNPs via active targeting — “Internalization”: high Z gold in close proximity to the cell nucleus and DNA, the main target for radiation damage

Why GNPs?

• Possibility to generate therapeutic dose of heat through photothermal effect / plasmon resonance

Why GNPs?

• Acceptable toxicity for high concentration (up to 3% of body weight) of gold in the body
  - potential toxicity of GNPs: inconclusive at this time and needs to be investigated further
  - possibility to perform in-vivo molecular imaging before/during/after the treatment through x-ray fluorescence imaging (e.g., XFCT)
GNP-mediated Physical Dose Enhancement

Physical Dose Enhancement around GNPs

Macroscopic Estimation of Dose Enhancement

- Average dose enhancement across tumor
- Applicable to passive targeting scenario or so-called contrast-enhanced radiation therapy
- Dose enhancement as a function of GNP concentration and photon beam quality
  - Uniform distribution of GNPs within the tumor
  - Uniform mixture of gold and tissue
  - MC calculations or Analysis of energy absorption coefficients
**MC Simulation Geometry:**
*External beam cases*

- Photon/x-ray beam
- SSD
- Tissue phantom (30 x 30 x 30 cm³)
- Tumor + GNPs

**Macroscopic Dose Enhancement Factor (MDEF)**
*External beam cases*

<table>
<thead>
<tr>
<th>Concentration (per gram of tumor)</th>
<th>140 kVp</th>
<th>6 MV FF</th>
<th>6 MV NFF</th>
<th>4 MV FF</th>
<th>4 MV NFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 mg Au</td>
<td>2.114</td>
<td>1.007</td>
<td>1.014</td>
<td>1.009</td>
<td>1.019</td>
</tr>
<tr>
<td>18 mg Au</td>
<td>3.811</td>
<td>1.015</td>
<td>1.032</td>
<td>1.019</td>
<td>1.044</td>
</tr>
<tr>
<td>30 mg Au</td>
<td>5.601</td>
<td>1.025</td>
<td>1.053</td>
<td>1.032</td>
<td>1.074</td>
</tr>
</tbody>
</table>

FF: flattening filter, NFF: no flattening filter

MDEF = average tumor dose with Au / average tumor dose without Au

**Macroscopic Dose Enhancement Factor (MDEF)**
*250 kVp in-vivo experiment*

**MC Simulation Geometry:**
*Brachytherapy cases*

- Brachytherapy source at the center
- Tumor + GNPs
- 30 cm radius tissue phantom
MDEF: Ir-192 & Yb-169

Secondary electron spectra
I-125 gamma ray irradiation

Secondary electron spectra
6 MV photon irradiation

MDEF: 50 kVp & I-125
Experimental Verification of Dose Enhancement

GNP-loaded Radio-sensitive Gels irradiated by 110 kVp

Microscopic Estimation of Dose Enhancement

• Dose enhancement around GNP on nanoscale
  • Applicable to active/passive targeting scenarios with heterogeneous distribution of GNPs
  • Basis for GNP-mediated DNA damage calculations

Computational Approaches
- Detailed history MC calc with hypothetical dimensionless GNPs
- Mixed history MC calc with various sizes of GNPs
- Semi-analytic calc using microscopic e- energy deposition kernel/pattern

Microscopic Estimation of Dose Enhancement

Dose point kernels

Microscopic Estimation of Dose Enhancement

Microscopic dose enhancement factor (mDEF)
Microscopic Estimation of Dose Enhancement
microscopic dose enhancement factor (mDEF)

alternative approach using mixed history MC simulations

250 kVp

21 MeV e

250 MeV p

6 MV

H\textsubscript{2}O d=20 nm

GNP d=20 nm

H\textsubscript{2}O d=20 nm

GNP d=20 nm
Correlation between physical model and biological outcome

Modeling of GNP-mediated Radiation Response Modulation

- Quantification of physical dose enhancement on micro-/nano-scale (cellular & DNA level estimation)
- Identification of GNP locations within tumor (cell)
- Identification of proper biological pathways (known & unknown)

Cellular & DNA level quantification of microscopic dose enhancement

- on the order of 10 μm

Microscopic dose enhancement in tissue

Microscopic dose enhancement in tissue

\(\text{GNP-mediated radiosensitization with 6 MV?}\)

- In-vitro setting: \(~20\%\) per cell survival assays

Predictable using calculated mDEF for 6 MV!
GNP-mediated radiosensitization with 6 MV?

- In-vivo setting: Inconclusive

Physically, no significant dose enhancement again, but the location of GNP is probably the key . . . .

Gold Nanoparticle-aided Radiation Therapy (GNRT)

- Dual action
  - tumor blood vessel disruption
  - enhanced cell-killing: increase in relative biological effectiveness (RBE) for radiation

- Further improvement of therapeutic ratio for radiotherapy

Biological Consequences of GNRT

Various GNRT scenarios
Radiation sources for GNRT

- Brachytherapy sources
  - Yb-169
  - 50 kVp miniature x-ray source
- External beam sources
  - low-energy enhanced MV beam
  - synchrotron/monochromatic or orthovoltage x-ray beams: tomotherapy/rotational delivery
  - electron and proton

Epilogue

- The concept appears to be applicable to human cancer treatment
- Physical model alone may not be adequate to explain all biological outcomes
- Even so, physical model based on realistic outlook may still play an important role for clinical translation

Thank you for your attention!