THE USE OF HYPOXIA IMAGING FOR RADIOThERAPY

John L. Humm Ph.D.
Vice Chair of Research
Department of Medical Physics
MSKCC
1275 York Avenue
New York, NY 10065

Session TH-E-202-0
Thursday August 4th

Why measure tumor hypoxia?

- The oxygen enhancement ratio – more radiation dose is required for equivalent cell kill of hypoxic cells.
- Hypoxia leads to a more aggressive environment and increases the metastatic potential of tumor cells.
- Treatment efficacies are diminished when tumors are hypoxic.

How can we measure tumor hypoxia?

- Direct $pO_2$ probe measurement
  - Eppendorf polarographic electrode
  - OxyLite luminescence probe
- Immunohistochemistry
  - Endogenous markers e.g. HIF, Ca-9
  - Exogenous markers e.g. pimonidazole
- Non invasive imaging methods
Methods to detect hypoxia by non-invasive imaging

- Nuclear Medicine – inject hypoxia specific radiotracer
- Electron Spin Resonance – inject spin probe
- Magnetic Resonance – inject hypoxia probe, microenvironmental dependent metabolites

Tracer Selection for Hypoxia Imaging

- ¹⁸F-FMISO 110 min
  - Short half-life of ¹⁸F necessitates imaging within 3 hr
- ⁶⁰Cu⁶⁴Cu-ATSM 24 min/22.6 hr
  - High signal at early times, but optimal hypoxia specificity questionable
- ¹⁷⁷⁴⁴HIAZGP 4.2 d
  - Ability to measure several hours post injection, but signal too low for clinical imaging

¹⁸F-FMISO Scans of H&N Patients

- CT
- PET
- EPSR
- MRS Lactate Image

Courtesy of Howard Halpern
Courtesy of Jason Koutcher
The concept of a GTV<sub>h</sub>


Effect of segmentation threshold

FDG-FMISO T/B > 1.0

FDG-FMISO T/B > 1.2

FDG-FMISO T/B > 1.4

PET VOXELS overlaid on tumor histology

Hoechst 33342 – perfused - BLUE
Pimonidazole – hypoxia - GREEN

Why are the 18F-FMISO uptake ratios so low?
Analysis of 18F-FMISO Dynamic PET

Hypoxia criterion
Tumor-Blood Ratio (T:B) ≥ 1.4
not reliable

Kinetic analysis of Time-Activity Curves (TAC) is necessary

Thorwart et al. BMC Cancer. 2005 Dec 9;5:152

A compartmental model to mimic FMISO metabolism

Plasma
\[ \text{Free/unbound} \]
\[ k_2 \]
\[ \text{Bound} \]

FMISO \[ \rightarrow \] FMISO \[ \rightarrow \] FMISO \[ \rightarrow \] FMISO \[ \rightarrow \]

Cp

Bimolecular reaction pathways of FMISO in a cell.

H&N Patient Dynamic PET Images

Carotid artery

1 min 2 min 3 min 4 min 5 min 10 min 15 min 20 min 25 min 30 min

180 min 185 min CT
Late 3hr images in two patients

Patient 1
Well perfused tumor
With small hypoxic component

Patient 2
Poorly perfused tumor, perhaps large necrotic center
With small hypoxic component

Parametric maps may differentiate between tumor phenotypes

Patient #1 – FMISO trapping is linearly related to perfusion
Patient #2 – FMISO trapping is inversely related to perfusion
Parametric maps may differentiate between tumor phenotypes

Hypothesis

FMISO Baseline

K₁ - Perfusion

k₃ - Hypoxia

How might we use hypoxia images in radiation therapy?
Hypoxia response during XRT

PRE THERAPY (baseline)

MID THERAPY (after 5 x 2Gy)

Support - NIH grant 1 R01 CA157770-01A1 - Hypoxia Image-Guided Radiation Therapy

When there is no Hypoxia or Hypoxia goes away – Consider dose de-escalation?

Paper just accepted by Nancy Lee entitled

When hypoxia persists consider dose painting to the hypoxic regions.
Conclusions

- Ideally we would like to perform single time point imaging and directly derive radiobiological information for radiotherapy planning.
- Late images may not describe the intra-tumor hypoxia distribution work in all cases.
- Compartmental analysis is considerably more complex, but provides a more comprehensive understanding of radiotracer behavior.
- Hypoxia tracers are expected to be prognostically relevant.

ACKNOWLEDGEMENTS

Dept of Medical Physics
Milan Grkovski, Brad Shatlev, Joseph O’Donoghue, Sean Carlin, James Russell, Sadek Nahmeh, C. Clifton Ling

Cyclotron / Radiochemistry
Jason Lewis, Eva Burnai, Shangde Cai

Radiation Oncology
Nancie Lee