

THE USE OF HYPOXIA IMAGING FOR RADIOTHERAPY

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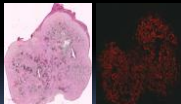
Session TH-E-202-0
Thursday August 4th

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.

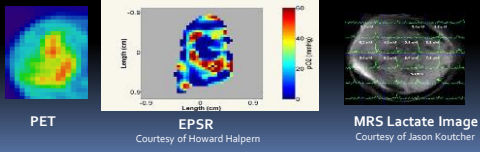
How can we measure tumor hypoxia?

- Direct pO₂ probe measurement
 - Eppendorf polarographic electrode
 - OxyLite luminescence probe
- Immunohistochemistry
 - Endogenous markers e.g. HIF, Ca-g
 - Exogenous markers e.g. pimonidazole
- Non invasive imaging methods



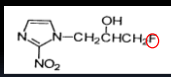
Methods to detect hypoxia by non-invasive imaging

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



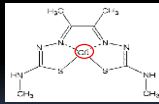
Tracer Selection for Hypoxia Imaging

¹⁸F-FMISO
110 min



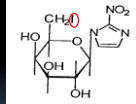
Short half-life of ¹⁸F necessitates imaging within 3 hr

⁶⁰Cu/⁶⁴Cu-ATSM
24 min/12.6 hr



High signal at early times, but uptake hypoxia specificity questionable

¹²⁴I-IAZGP
4, 2 d

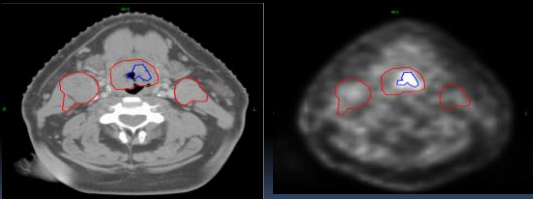


Ability to measure several hours post injection, but signal too low for clinical imaging

¹⁸F-FMISO Scans of H&N Patients



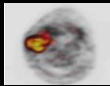
The concept of a GTV_h



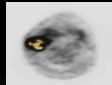
Lee et al, Int.J.Radiat.Onc.Biol.Phys. 2008 70:2-13.

Effect of segmentation threshold

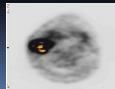
FDG-FMISO
T/B > 1.0



FDG-FMISO
T/B > 1.2



FDG-FMISO
T/B > 1.4

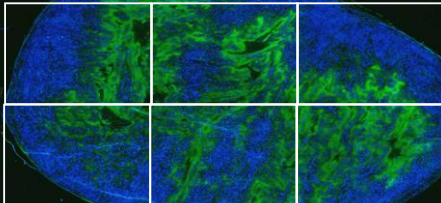


PET VOXELS overlaid on tumor histology

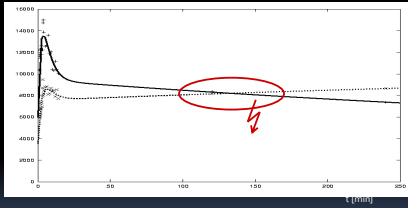
Hoechst 33342 – perfused - BLUE

Pimonidazole – hypoxia - GREEN

Why are the ¹⁸F-FMISO uptake ratios so low?



Analysis of ¹⁸F-FMISO Dynamic PET

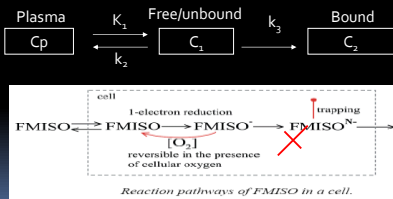


Hypoxia
criterion
Tumor-Blood
Ratio(T:B) ≥1.4
not reliable

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

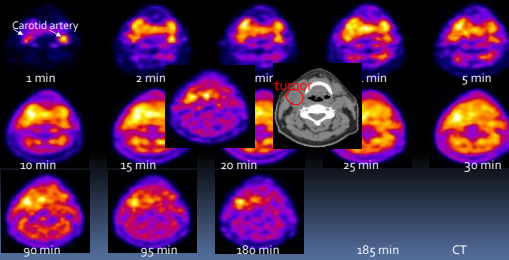
Thorwarth et al, BMC Cancer. 2005 Dec 4;5:152.

A compartmental model to mimic FMISO metabolism

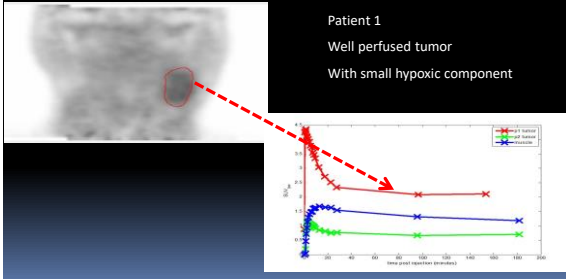


Reaction pathways of FMISO in a cell.

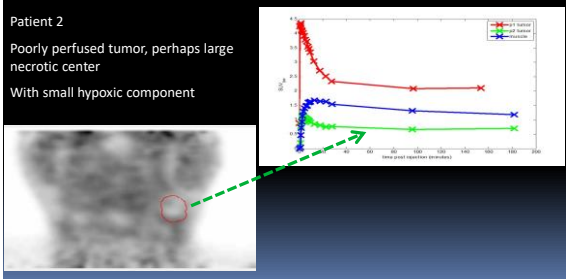
H&N Patient Dynamic PET Images



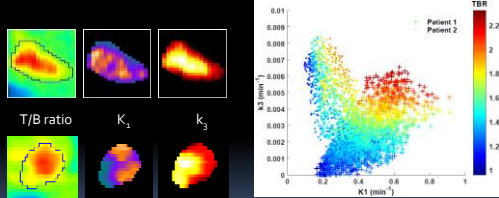
Late 3hr images in two patients



Late 3hr images in two patients

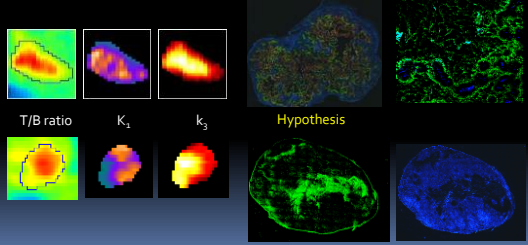


Parametric maps may differentiate between tumor phenotypes

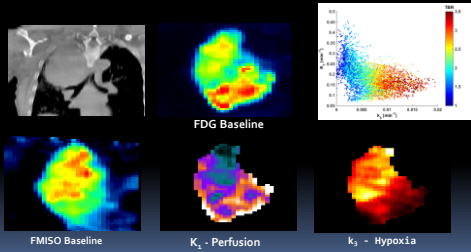


Patient #1 – FMISO trapping is linearly related to perfusion
Patient #2 – FMISO trapping is inversely related to perfusion

Parametric maps may differentiate between tumor phenotypes



Hypoxia in Lung Cancer

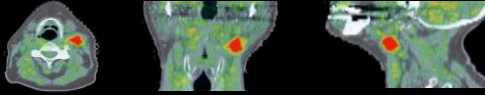


Support - NIH grant 1 U01 CA157442-01A1. Quantitative Imaging for Evaluation of Responses to Cancer Therapies

How might we use hypoxia images in radiation therapy?

Hypoxia response during XRT

PRE THERAPY (baseline)



MID THERAPY (after 5X 2Gy)

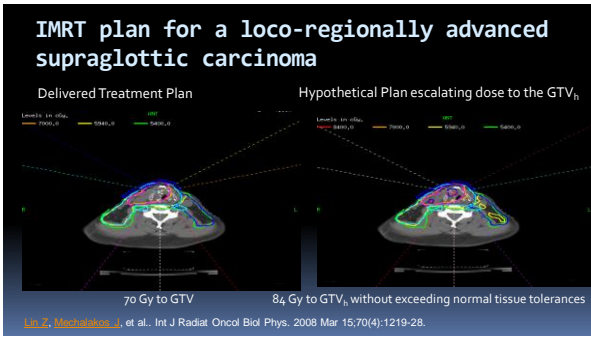


Support - NIH grant 1 R01 CA157770-01A1 Hypoxia Image-Guided Radiation Therapy

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

Paper just accepted by Nancy Lee entitled
"A Strategy of Using Intra-treatment Hypoxia Imaging to Selectively and Safely Guide Radiation Dose De-escalation Concurrent with Chemotherapy for Loco-regionally Advanced Human Papillomavirus-Related Oropharyngeal Carcinoma"

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 considerable 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 Beattie,
Joseph O'Donoghue,
Sean Carlin,
James Russell,
Sadek Nehmeh,
C. Clifton Ling

Cyclotron / Radiochemistry

Jason Lewis,
Eva Burnazi,
Shangde Cai

Radiation Oncology

Nancy Lee

Nuclear Medicine Service

Heiko Schöder
