THE USE OF HYPOXIA IMAGING FOR RADIOTHERAPY

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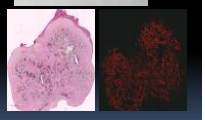
Why measure tumor hypoxia?

- 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.

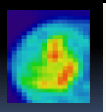
How can we measure tumor hypoxia?

- 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

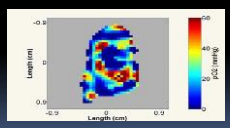


Methods to detect hypoxia by non-invasive imaging

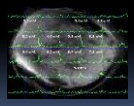
- Nuclear Medicine – inject hypoxia specific radiotracer
- Electron Spin Resonance – inject spin probe
- Magnetic Resonance – inject hypoxia probe, microenvironmental dependent metabolites



PET



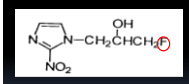
EPSR
Courtesy of Howard Halpern



MRS Lactate Image
Courtesy of Jason Koutcher

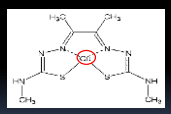
Tracer Selection for Hypoxia Imaging

^{18}F-FMISO
110 min



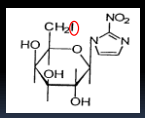
Short half-life of ^{18}F necessitates imaging within 3 hr

^{60}Cu/^{64}Cu-ATSM
24 min/12.6 hr



High signal at early times, but uptake hypoxia specificity questionable

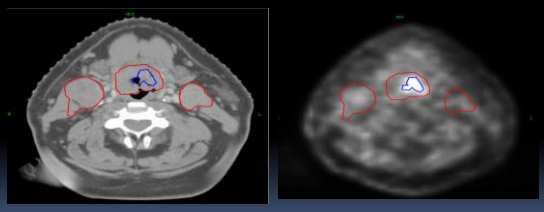
^{124}I-IAZGP
4.2 d



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

^{18}F-FMISO Scans of H&N Patients

The concept of a GTV_h



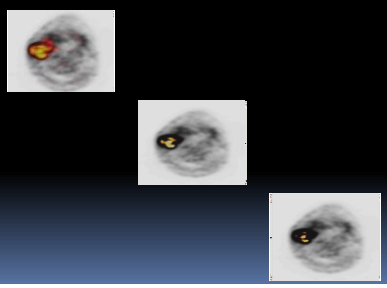
Lee et al, Int.J.Radiat.Onc.Biol.Phys. 2008 70:2-13.

Effect of segmentation threshold

FDG-FMISO
T/B > 1.0

FDG-FMISO
T/B > 1.2

FDG-FMISO
T/B > 1.4

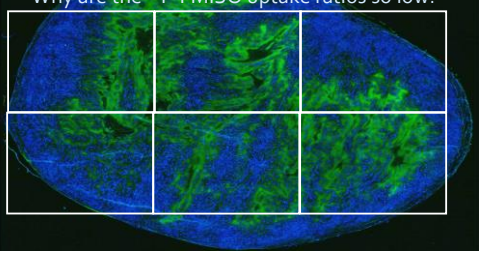


PET VOXELS overlaid on tumor histology

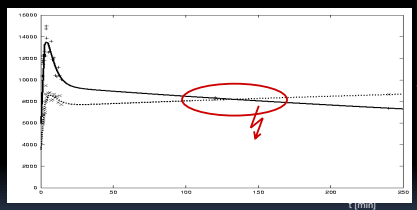
Why are the ^{18}F-FMISO uptake ratios so low?

Hoechst 33342 – perfused - BLUE

Pimonidazole – hypoxia - GREEN



Analysis of ^{18}F-FMISO Dynamic PET



Hypoxia criterion

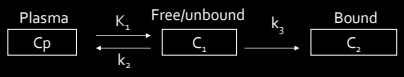
Tumor-Blood Ratio(T:B) ≥1.4

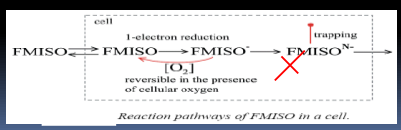
not reliable

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

Thorwarth et al, BMC Cancer. 2005 Dec 1;5:152.

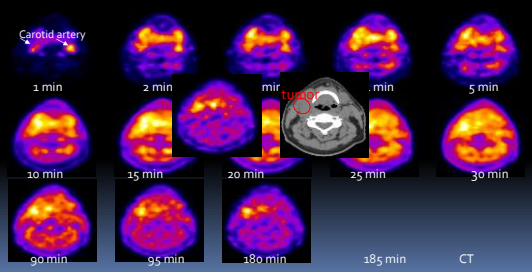
A compartmental model to mimic FMISO metabolism



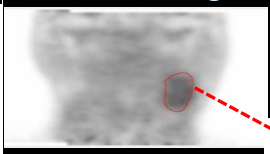


Reaction pathways of FMISO in a cell.

H&N Patient Dynamic PET Images



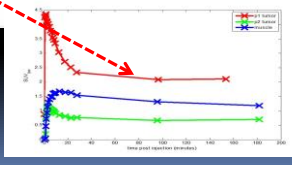
Late 3hr images in two patients



Patient 1

Well perfused tumor

With small hypoxic component

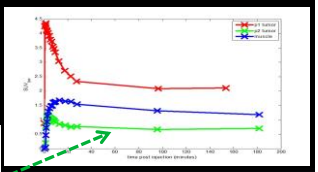


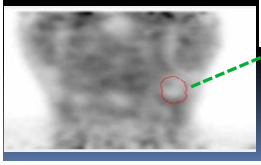
Late 3hr images in two patients

Patient 2

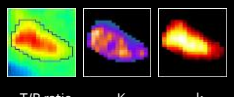
Poorly perfused tumor, perhaps large necrotic center

With small hypoxic component

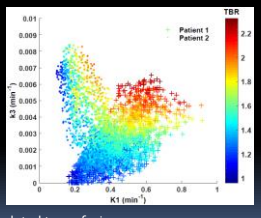




Parametric maps may differentiate between tumor phenotypes



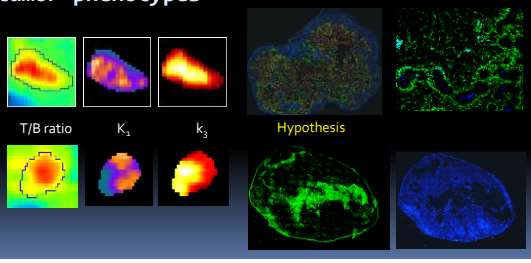
T/B ratio K_1 k_3



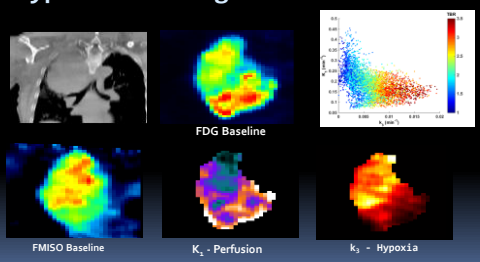
Patient #1 – FMISO trapping is linearly related to perfusion

Patient #2 – FMISO trapping is inversely related to perfusion

Parametric maps may differentiate between tumor phenotypes



Hypoxia in Lung Cancer

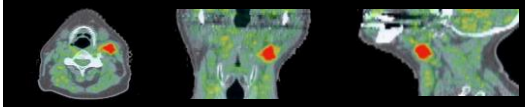


Support -NIH grant 1 U01 CA157442-01A1 *Quantitative Imaging for Evaluation of Responses to Cancer Therapies*

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?

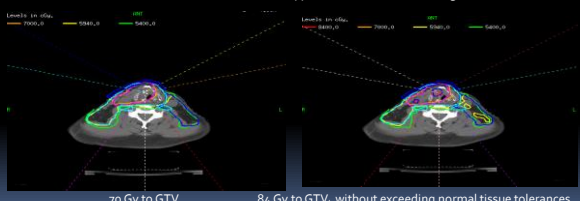
Paper just accepted by Nancy Lee entitled
"*A Strategy of Using Intra-treatment Hypoxia Imaging to Selectively and Safely Guide Radiation Dose De-escalation Concurrent with Chemotherapy for Loco-regionally Advanced Human Papillomavirus-Related Oropharyngeal Carcinoma*"

When hypoxia persists consider dose painting to the hypoxic regions.

IMRT plan for a loco-regionally advanced supraglottic carcinoma

Delivered Treatment Plan

Hypothetical Plan escalating dose to the GTV_h



70 Gy to GTV

84 Gy to GTV_h without exceeding normal tissue tolerances

Lin Z, Mechalakos J, et al.. Int J Radiat Oncol Biol Phys. 2008 Mar 15;70(4):1219-28.

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 be prognostically relevant.

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