AAPM Annual Meeting in Nashville, TN
Molecular Imaging: From Cancer Screening to Clinical Trial
WE-J-KDBRB1-2, August 1, 2018

Molecular Imaging (MI) in Radiation Oncology

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Disclosure

- No conflict of interest.

- Chair of AAPM WGMIR
- The content of presentation was neither reviewed or approved by WGMIR.

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AAPM Working Group of Molecular Imaging in Radiation Oncology (WGMIR)

Charge: Education of medical physicists on molecular imaging through lectures and review articles.

- Established in 2005
- WG of Therapy Imaging Subcommittee (TISC).
- First educational review article in Medical Physics (2013).
- Currently 13 voting members.
- Two active task groups (TG211, TG294).
- More to come.

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Outline

1. Introduction
2. Current MI tools
3. Clinical applications
4. Challenges: shortcomings and Issues
5. Solutions
6. Future directions
7. Conclusions
8. Bibliography

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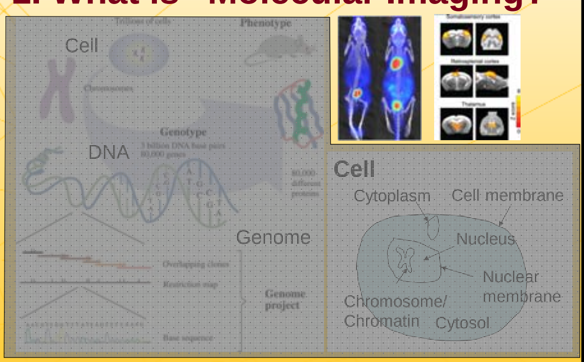
1. What is "Molecular Imaging?"



Weissleder R, Mahmood U Radiology 2001;219:316-333

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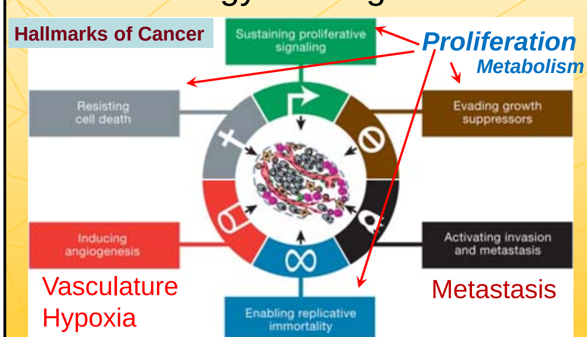
Which biology to image with MI?



Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

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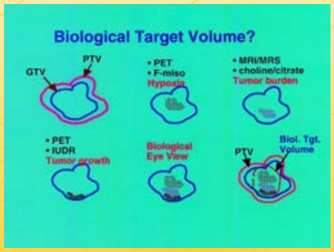
Biologically Guided Radiation Therapy

1. Hypoxia
2. Metabolism
3. Proliferation
4. Biochemical species



Ling, C.C., et al., IJROBP 2000. 47(3): p. 551-60.

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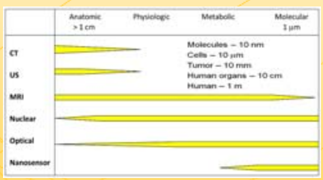
2. Current MI Tools

- CT (X-ray)
- Ultrasound (US)
- MRI
- Nuclear medicine (PET/SPECT)
- Optical Imaging



- <u>Spatial scale</u> – macroscopic, mesoscopic, microscopic
- <u>Functional</u> – anatomical, physiological, metabolic, molecular

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Molecular Imaging Techniques

Category	Biologic process	Modality	Technique (surrogate, tracer, biomarker)
Physiology	Metabolism	PET	FDG
		MRI	^{13}C hyperpolarization
Microenvironment	Hypoxia	PET	^{18}F-MISO, ^{63}CuATSM, FAZA, IAZA, FETNIM, ^{18}F-DCFPyL
		SPECT	^{99m}Tc-HL91, IAZA
	pH	MRI	acidoCEST
	Vascular density (angiogenesis)	PET	DCE
		MRI	DCE, BOLD
		US	MB
	Cellularity	MRI	DWI, DTI, MRE (elasticity)
Cellular	Cell proliferation	PET	FLT
		MRI	APTw-CEST
Molecular	Proteins/Ligands	MRI	MRSI
Nanoparticles	Proteins/Ligands	NP	PET, SPECT, MRI, XCT, US, OMI

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3. Radiotherapy Applications

1. **Tumor characterization**
   Diagnosis and staging
2. **Target delineation**
   Molecular signature determination
3. **Response monitoring**
   Assessment of treatment efficacy during the treatment course (for adaptive therapy) and after the treatment.

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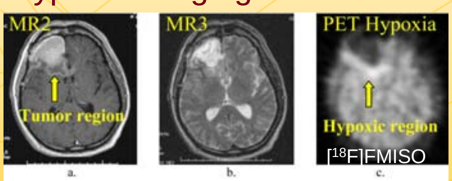
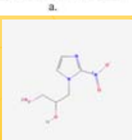
3.1. Tumor Characterization
Hypoxia imaging: FMISO-PET



a. T1w
b. T2w
c. PET



- *Misonidazole* is reduced under hypoxic conditions.
- In reduced form, it covalently ***binds to macromolecules in hypoxic cells***.
- *Misonidazole* is a nitroimidazole with radiosensitizing and antineoplastic properties.

Fluoromisonidazole (FMISO)

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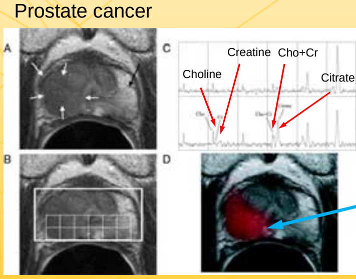
Tumor characterization: MRS

Prostate cancer



Prostate cancer = elevated choline and reduced citrate

Healthy tissue = low choline and high citrate

$$\frac{Choline + Creatine}{Citrate}$$

Kurhanewicz, J. et al. Neoplasia 2:166 (2000)

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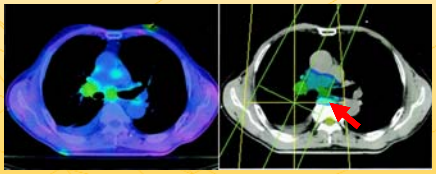
3.2. Target Delineation: PET/CT

(an example of geographic miss)



(Left) PET image coregistered with CT.
(Right) Treatment plan for the target drawn only using CT. Only 70% of $PTV_{PET/CT}$ receives at least 90% of prescribed dose.

Mah, K. et al., IJROBP 52:339 (2002)

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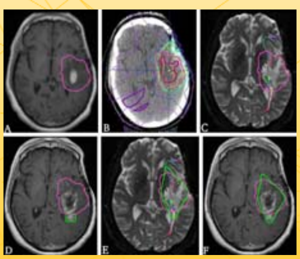
Target Delineation: DT-MRI

(another = example of geographic miss)



A. T1w image of the astrocytoma and treatment margin (pink: 90%isodose line).
B. CT image
C. Diffusion tensor image (DTI)
D. T1w image (3 month after A) showing recurring tumor (green box) at the same location as the major posterior bundle in (C).
E. New target (green) using DTI.
F. T1w image with old and new targets.

Krishnan, AP et al., IJROBP 71:1553 (2008)

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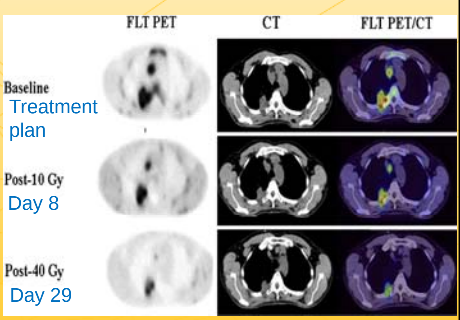
3.3 Response monitoring: FLT-PET

Method:
- NCSLC
- 5 patients
- RT: 2Gyx30
- 1 x FDGPET
- 2~3 x FLTPET

Results:
- Reduction of tumor/lymph nodes FLT uptake
- Reduction of bone marrow uptake.



Everitt S, et al., Int J Radiat Oncol Biol Phys. 2009. doi:S0360-3016

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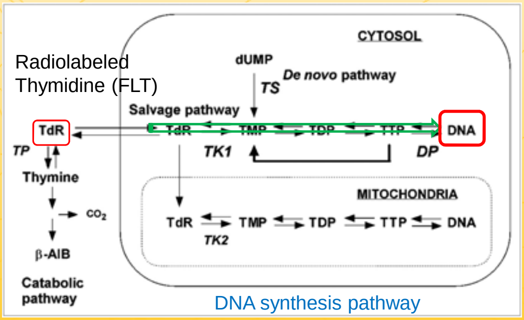
[^{18}F] Fluorothymidine (FLT)

FLT accumulates in dividing cells



Bading, J.R. and Shields, A.F., J Nucl Med 2008;49:64S-80S

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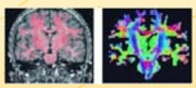
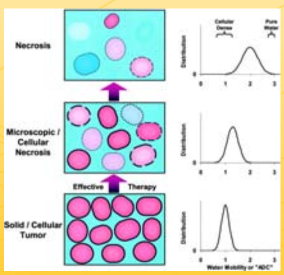
Diffusion weighted MRI (DWI)



- Images the relative mobility (or random Brownian motion) of water molecules.
- Diffusion is dependent upon fluid viscosity, intra- and extra-cellular permeability, active transport mechanisms and the microstructure of the local environment.

What is Apparent Diffusion Coefficient (ADC)?



Ross B D et al. Mol Cancer Ther 2003;2:581-587

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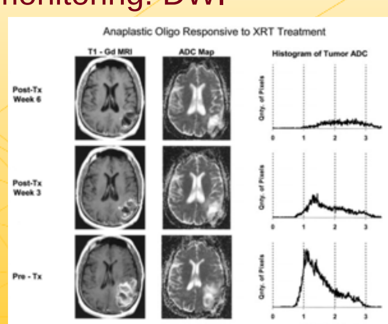
Response monitoring: DWI

Method:
- Oligodendroglioma
- 2 Gy x 35 = 70 Gy

Results:
- ADC indicates greater water mobility, implying necrosis.



Ross B D et al. Mol Cancer Ther 2003;2:581-587

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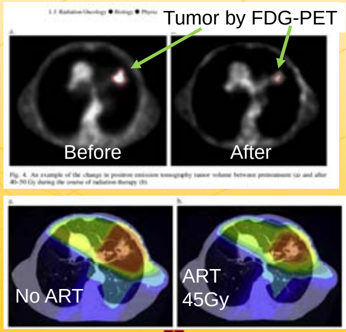
Adaptive Radiation Therapy (ART)

Method:
- 14 patients
- Stage I-III NSCLC
- 3DCRT, 60Gy
- 2x FDG-PET
- Re-plan with mid PET

Results:
- Metabolic activity significantly changed after 40-59Gy,
- ART allowed dose escalation by 58 Gy mean (30 – 102 Gy)



Feng, M. et al, IJROBP 2009, 73:1228

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4. Challenges of MI

1. ***Accuracy of image fusion/registration***

   Wide variation in spatial scale and information contents requires multiple images

2. ***Accuracy of biologic characterization and target delineation***

   Incorrect image interpretation for target delineation and treatment monitoring due to insufficient biologic data and understanding. Need of standardization.

3. ***Imaging time and cost***

   Frequent imaging for treatment monitoring

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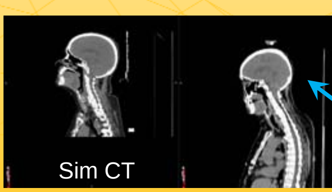
Difficulty of Image Registration

- CT-CT, CT-MRI, CT-PET, CT-MRI, MRI-PET, etc..
- Rigid image registration
- *Deformable image registration*

Must!!



CT of PET/CT

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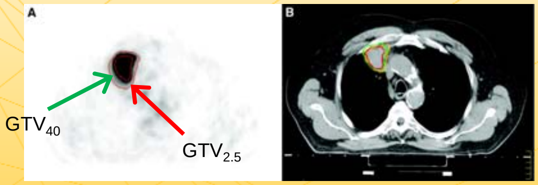
Uncertainty in Target Definition



PET
SUVmax=30

Planning CT
red GTV_{40}, green GTVbg, yellow GTVCT

"The different techniques of tumor contour definition by [18]F-FDG PET in radiotherapy planning lead to substantially different volumes, especially in patients with inhomogeneous tumors. "

Auto-segmentation

Nestle, U. et al. J. Nucl Med 46:1342 (2005)

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Economics of MI

- MRI/PET/CT ~ $1000 per scan (< $7000).
- The total number of scans is at least two (treatment planning and follow-up) during the course of RT.
- If used for adaptive treatment, the number increased to 5 or more.
- Currently, only two scans per treatment are covered by insurance (or Medicare).

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5.1. Solution: Standardization

Quantitative Imaging Biomarkers Alliance (QIBA), RSNA

- Mission: to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time.
- QIB or measurand: ratio variables or interval variables.
- QIBA Profiles: a standard document that includes Claim(s) and Specifications.

http://www.rsna.org/QIBA/

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5.2. Solution: Auto-segmentation

AAPM Task Group 211
"Classification, Advantages and Limitations of the Numerical Lesion Segmentation Approaches for PET"

TG group chair: A.Kirov, Ph.D.

Charge: To study the advantages, the limitation, and the applicability of proposed PET-Automatic Segmentation methods (PET-AS).

Report: Hatt, M., et al., "Classification and evaluation strategies of auto-segmentation approaches for PET: Report of AAPM task group No. 211," Med Phys. 2017 Jun;44(6):e1-e42.

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5.3. Solution: FDG-PET Quality

AAPM Task Group 174
"**Utilization of 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in Radiation Therapy**"

TG chair: Shiva Das, Ph.D.

Charge: To recommend guidelines/protocols for consistent imaging, treatment planning and treatment assessment using FDG-PET in radiotherapy. This report is envisioned as laying the foundation for standardizing the use of FDG-PET in radiotherapy.

Report: under review.

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5.4. Solution: Education of MRI

AAPM Task Group 294
"MR Biomarkers in Radiation Oncology"

TG chair: Kiaran P. McGee, Ph.D.

Charge: To collect and combine existing knowledge on MR biomarkers and to present this information in a coherent and summarized fashion.

Report: Due in 2019.

To provide an educational resource on MR imaging biomarkers and their use in radiation oncology.

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6. Future directions of MI in RT

- More innovative and quantitative MI tools
  Nanoparticles as biomarkers
- Multimodality MI
  PET-CT, PET-MRI, mpMRI, …
- MI with radiomics and AI/ML
  Radiomics: the poor man molecular imaging? (P.Lambin, 2017)
- Standardization for routine clinical applications and clinical trials

MI as a tool of precision medicine by individualization of prescription and treatment

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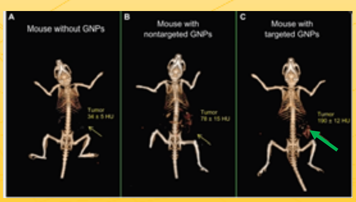
X-ray CT for MI

- Enhanced photon attenuation by gold
- *Anti-EGFR conjugated gold nanoparticles*



Reuveni, T. et al., International journal of nanomedicine **6**, 2859-2864 (2011).

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Radiomics and MI:

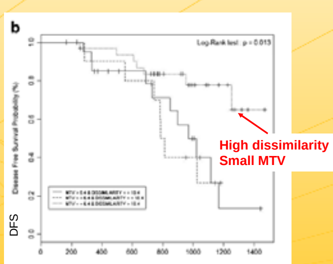
Radiomics can be used with molecular imaging tools.

Method:

- 63 patients w. NSCLC
- FDG-PET
- SBRT
- SUV-max, mean, metabolic tumor volume (MTV) etc.
- 13 textural features
- Uni-,multi-variate analysis
- Overall survival (OS), disease specific survival (DSS), disease-free survival (DFS).

Results:

- Textural feature "dissimilarity" is strongly associated with DSS/DFS.
- Small MTV and high dissimilarity lead to better DFS.



Lovinfosse P, et al. "FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy," EJNMMI. 2016;43(8):1453-60.

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Conclusions

- Molecular imaging (MI) is used to provide clinically valuable information on the biological state of the tumor.
- MI technology is evolving and more MI tools are on the way to our clinics.
  - ➢ *Medical physicists need good understanding of underling biological mechanisms to effectively utilize the MI tools in clinics.*

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Weissleder R, Ross BR, Rehemtulla A, Gambhir SS, editors. Molecular Imaging: Principles and Practice. Shelton, CT, USA: People's Medical Publishing house; 2010.

Pysz M A, Gambhir S S, and Willmann J K 2010 Molecular imaging: current status and emerging strategies *Clinical Radiology* 65 500-16.

Munley M.T., Kagadis G.C., McGee K.P., et al., 2013 *An introduction to molecular imaging in radiation oncology: A report by the AAPM Working Group on Molecular Imaging in Radiation Oncology (WGMIR)*, *Medical Physics* 40, 101501.

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Benfey, P.N., *Quickstart Molecular Biology: An Introductory Course for Mathematicians, Physicists, and Engineers*. 2014, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press. (160 pages)

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Acknowledgement:

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Thank you!
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