Promise and challenges of PET for target definition and treatment response evaluation

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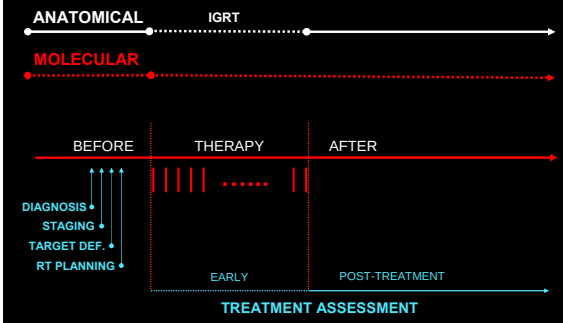
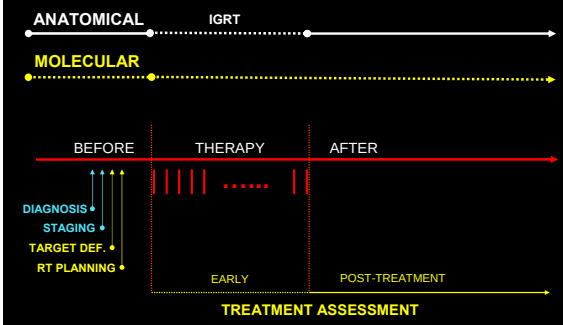
Role of imaging in oncology



Role of imaging in oncology



Qualitative and quantitative imaging

- Images are mostly used in diagnostic context – **diagnostic imaging (qualitative)**
- Imaging in therapeutic context is completely different – **therapeutic imaging (quantitative)**
- **Very limited experience** with imaging in treatment context, compared to diagnostic!
- **Very dangerous** to use diagnostic quality imaging in a therapeutic context **(qualitative ≠ qualitative)**

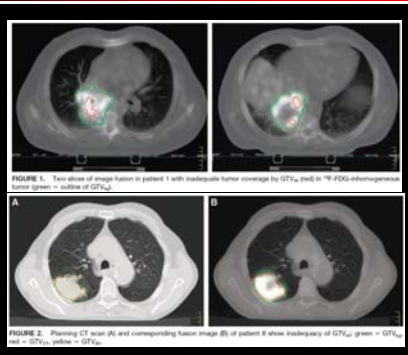
PET imaging uncertainties

- **Technical factors**
  - Relative calibration between PET scanner and dose calibrator (**10%**)
  - Residual activity in syringe (**5%**)
  - Incorrect synchronization of clocks (**10%**)
  - Injection vs calibration time (**10%**)
  - Quality of administration (**50%**)
- **Physical factors**
  - Scan acquisition parameters (**15%**)
  - Image reconstruction parameters (**30%**)
  - Use of contrast agents (**15%**)
  - ROI (**50%**)
- **Biologic factors**
  - Uptake period (**15%**)
  - Patient motion and breathing (**30%**)
  - Blood glucose levels (**15%**)

Boellaard et al 2009, J Nucl Med 50: 11S

Imaging for target definition

Target definition – a mess



Nestle et al 2005, J Nucl Med 46 (8): 1342.

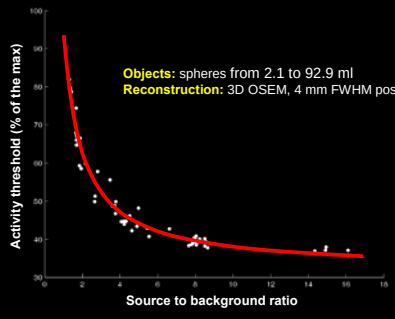
Close-up of the mess

	GTV_{ref}	GTV_{vis}	$GTV_{2.5}$	GTV_{50}	GTV_{iter}
Maximum	138	115 (+40%)	93 (+65%)	31 (-54%)	45 (-25%)
Minimum	22	12 (-55%)	8.8 (-60%)	1.7 (-92%)	2.3 (-90%)
Average	76	58 (-20%)	60 (-16%)	17 (-76%)	26 (-63%)
SD	42	33 (+30%)	30 (+34%)	10 (+13%)	13 (+20%)

All numbers in ml (% difference)

Greco et al 2008, Am J Clin Oncol 31: 439.

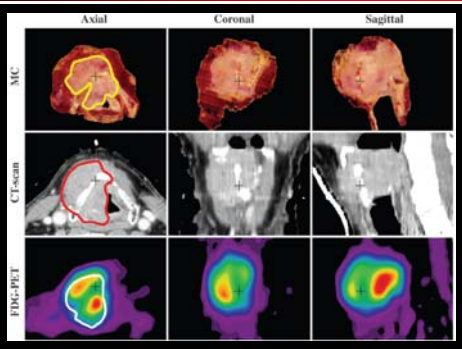
Why such a mess?



Objects: spheres from 2.1 to 92.9 ml
Reconstruction: 3D OSEM, 4 mm FWHM post filter

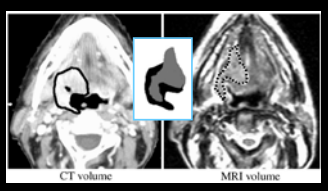
Geets et al 2007, Eur J Nucl Med Mol Imaging 34, 1427.

What is the real tumor extent?



Daisne et al 2004, Radiology 233, 93.

Different modalities – different answers



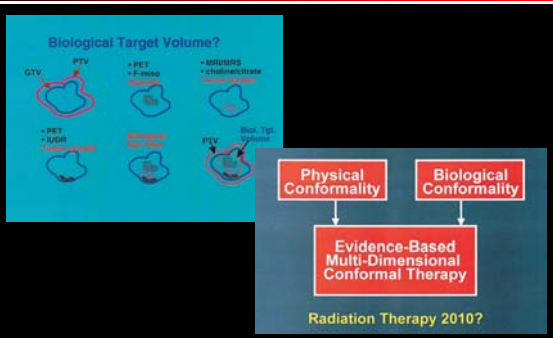
Average Mismatch of Laryngeal GTVs between Imaging Modalities and the Surgical Specimen

Pair	Mismatched Volume (%)
CT	
To MR imaging	26 (6.2/23.8)
To FDG PET	48 (7.8/16.3)
To specimen	81 (10.2/12.6)
MR imaging	
To CT	45 (9.3/20.8)
To FDG PET	67 (11.0/16.3)
To specimen	107 (13.4/12.6)
FDG PET	
To CT	17 (3.5/20.8)
To MR imaging	15 (3.6/23.8)
To specimen	46 (5.8/12.6)
Specimen	
To CT	10 (2.0/20.8)
To MR imaging	9 (2.2/23.8)
To FDG PET	13 (2.1/16.3)

Note.—Data in parentheses are the average mismatched volumes in cubic centimeters.

Daisne et al 2004, Radiology 233, 93.

Future – dose painting?

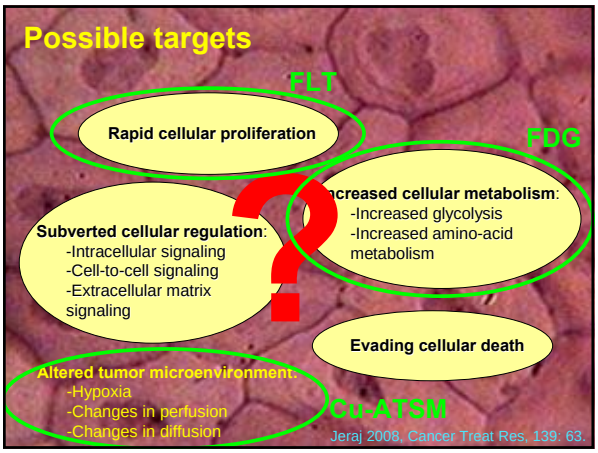


Ling et al 2000, Int J Rad Oncol Biol Phys, 47, 551

What targets to choose?

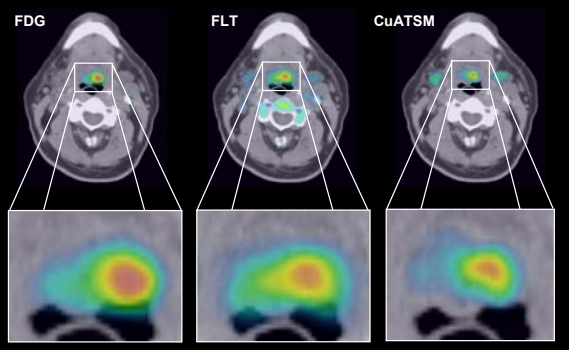
- **Hypoxia:**
  - Chao et al, Int J Radiat Oncol Biol Phys, 2001. 49(4): 1171-82.
  - Thorwarth et al, Int J Radiat Oncol Biol Phys, 2007. 68(1): 291-300.
  - Grosu et al, Int J Radiat Oncol Biol Phys, 2007. 69(2): p. 541-51.
  - Søvik et al, Phys Med Biol, 2007. 52(2): p. 499-513.
  - Rajendran et al,Eur J Nucl Med Mol Imaging, 2006. 33 Supp 1: 44-53.
  - Lee et al, Int J Radiat Oncol Biol Phys, 2008. 70(1): p. 2-13.
- **Metabolism:**
  - Gregoire et al, J Nucl Med, 2007. 48 Suppl 1: p. 68S-77S.
  - Madani et al, Int J Radiat Oncol Biol Phys, 2007. 68(1): p. 126-35.

Possible targets

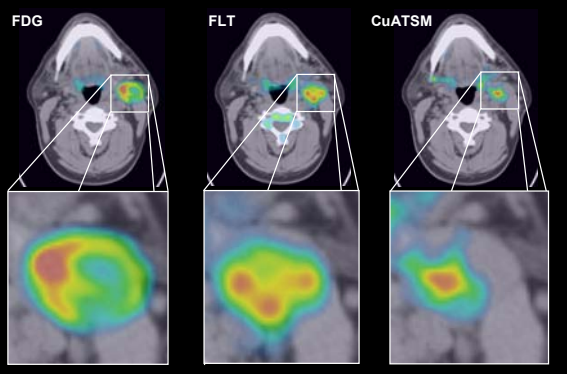


Jeraj 2008, Cancer Treat Res. 139: 63.

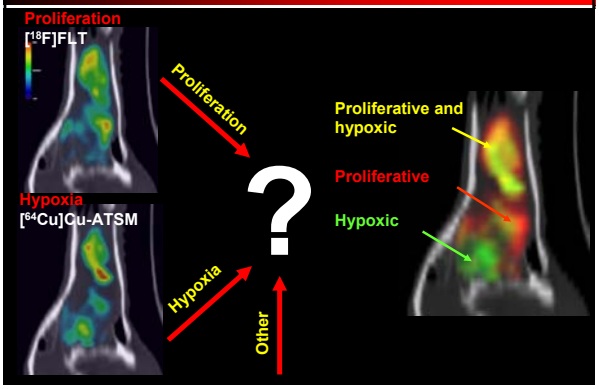
Spatially robust target



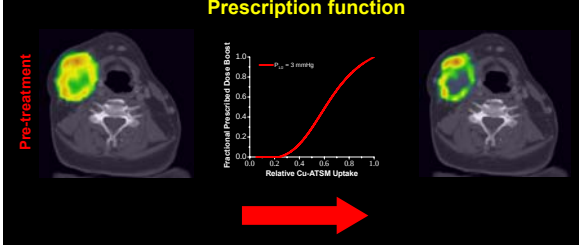
Spatially ambiguous target



What to do with this information?



Dose painting



Imaging for treatment assessment

Anatomic response criteria

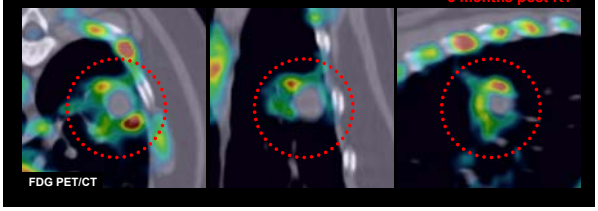
- **WHO (Miller, Cancer, 207, 1981):**
  - The size of a tumor should be estimated based on **two perpendicular diameters**
  - Positive tumor response to therapy defined as a reduction of **at least 50%** in the product of these two diameters
- **RECIST (Response Evaluation In Solid Tumors) (Therasse, JNCI, 205, 2000):**
  - The size of a tumor is estimated based on **unidimensional measurement**
  - Positive tumor response to therapy is defined as **at least 30%** decrease in the largest dimension of the tumor

EORTC response criteria

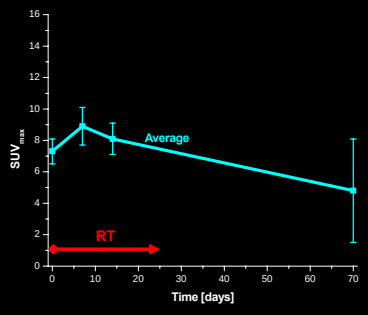
- **Complete Metabolic Response (CMR):** Complete resolution of FDG uptake within the tumor volume
- **Partial Metabolic Response (PMR):** A reduction of a **minimum of 15-25%** in tumor FDG SUV after one cycle of chemotherapy, and **greater than 25%** after more than one treatment cycle. **No recommendation for radiotherapy!**
- **Progressive Metabolic Disease (PMD):** Increase in FDG tumor SUV of **greater than 25%** within the tumor region, or increase of extend of FDG uptake (20% in the longest direction) or appearance of new lesions
- **Stable Metabolic Disease (SMD):** Increase of **less than 25%** or a decrease of **less than 15%** in tumor FDG SUV and no visible increase in extent (20% in the longest dimension)

Treatment assessment in RT

- Radiation induced inflammation is a known effect – temporal and spatial dependence
- Not known how much it is a confounding factor in treatment assessment
- FDG PET shows increased uptake post therapy

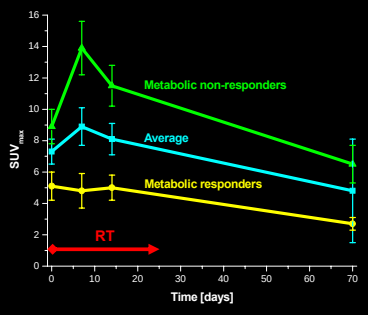


FDG PET and radiation therapy



Baardwijk et al 2007, Radiother Oncol, 82: 145.

FDG PET and radiation therapy



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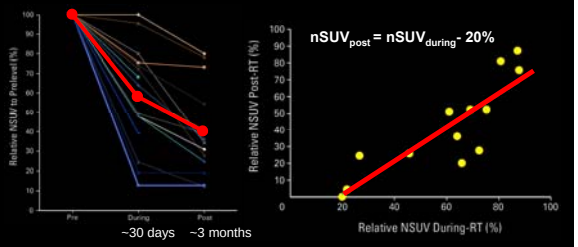
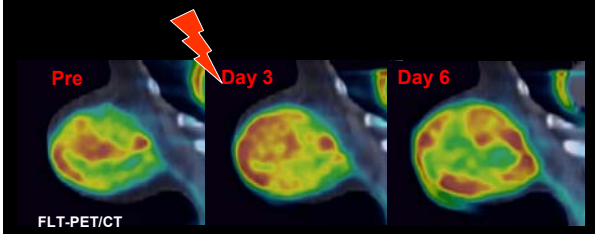
FDG PET and radiation therapy

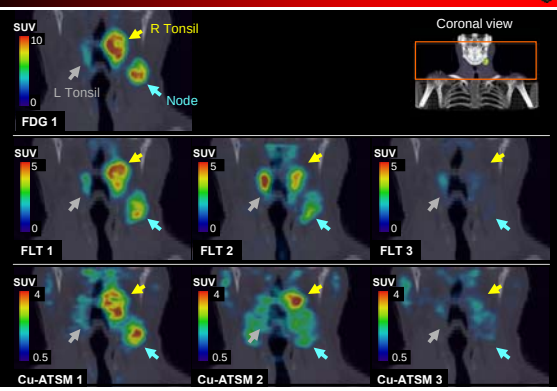


Kong et al 2007, J Clin Oncol, 25: 3116.

Temporal development



Multimodality longitudinal assessment



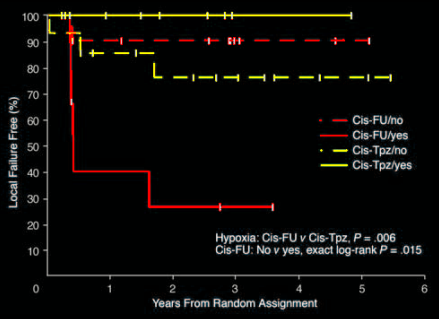
Predicting response

Hypoxia Status	Treatment: Chemoboost — No. of Locoregional Failures	Chemoboost — No. of Patients	TPZ/CIS — No. of Locoregional Failures	TPZ/CIS — No. of Patients
Nonhypoxic	1	10	2	3
Hypoxia in primary tumor and/or nodes	8	13	1	19
No residual hypoxia	4	9	0	14
Residual hypoxia in primary tumor and/or nodes	4	4	0	2

Abbreviation: TPZ/CIS, tirapazamine and cisplatin.

Rischin et al 2006, J Clin Oncol, 24: 2098.

Predicting response



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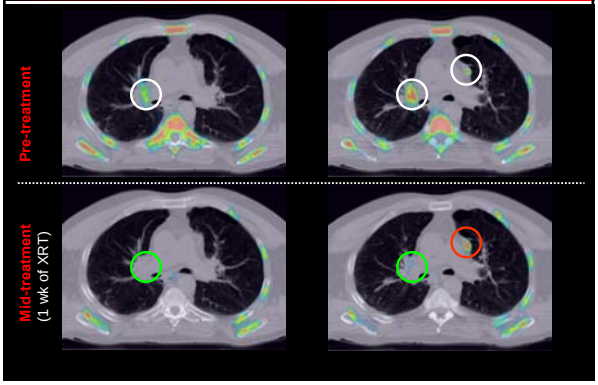
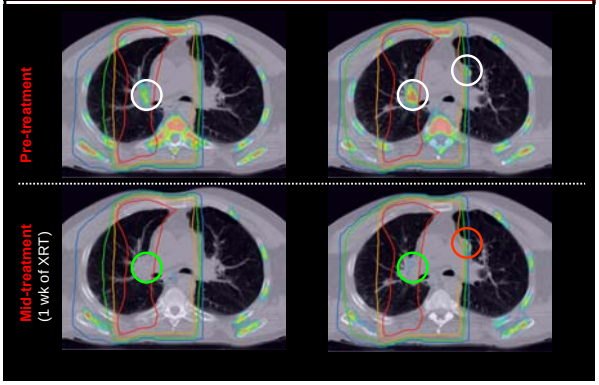
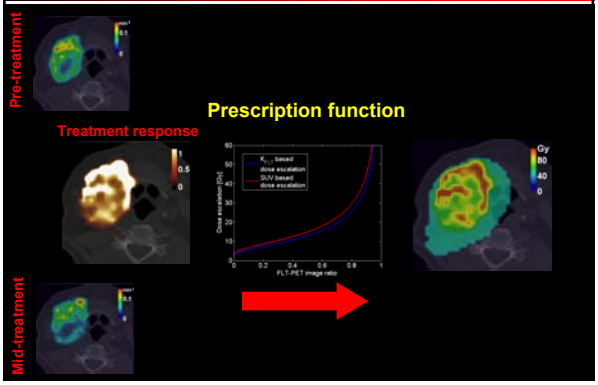
Adaptive radiotherapy



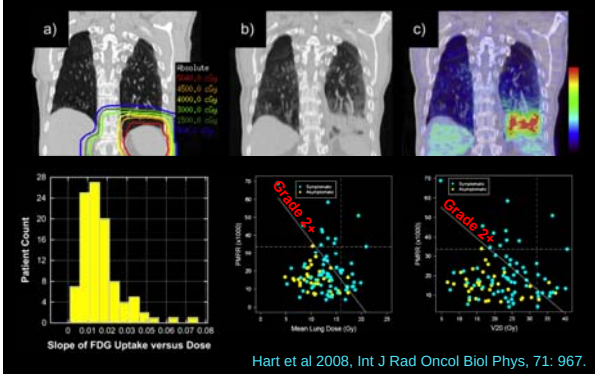
Adaptive radiotherapy



Treatment response prescription



Normal tissue response



Hart et al 2008, Int J Rad Oncol Biol Phys, 71: 967.

Conclusions

- **Molecular imaging for target definition**
  - Still in its infancy
  - Understanding limitations of molecular imaging
  - Many uncertainties remain (GTV-PTV)
  - Great potential for dose painting
- **Molecular imaging for treatment assessment**
  - Still in its infancy
  - Many applications for tumor assessment (adaptation, dose painting)
  - Normal tissue assessment

Thanks to:

- **Image-guided therapy group**
  - Vikram Adhikarla
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  - Dhanabalan Murali
  - Rock Mackie
- **Radiology**
  - **Scott Perlman**
  - Chris Jaskowiak
- **Veterinary School**
  - **Lisa Forrest**
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