Imaging markers for prediction and assessment of response in head-neck cancer

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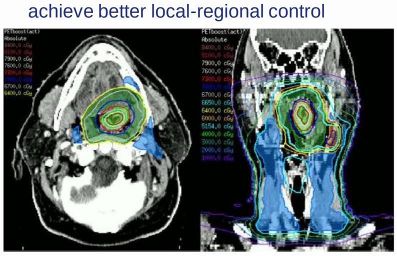
Dose Painting in Head & Neck Cancer

- additional dose to tumor regions resistant to treatment to achieve better local-regional control



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Heukelom et al. BMC Cancer 2013;13:84

Phase II randomized trials on dose painting

- FDG-PET
  - University Hospital Ghent
  - ArtForce, multi-center
- Hypoxia PET tracers
  - F-MISO PET: Tübingen University
- Perfusion/permeability
  - DCE-MRI: University of Michigan

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Phase II randomized trials on dose painting

- FDG-PET
  - University Hospital Ghent
  - ArtForce, multi-center
- Hypoxia PET tracers
  - F-MISO PET
- Perfusi
  - Michigan

What is a suitable imaging technique for dose painting?

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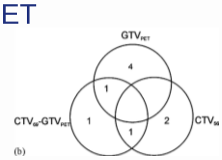
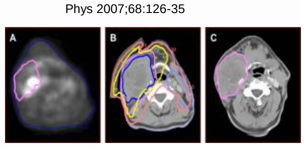
Evidence for dose painting based on FDG-PET

- Pre-clinical studies
- Patterns of failure
  - Recurrences overlap with pre-treatment FDG positive volume



Madani et al. Int J Radiat Oncol Biol Phys 2007;68:126-35



Soto et al. Radiother Oncol 2008;89:13-8

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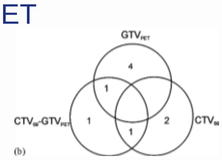
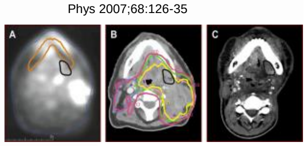
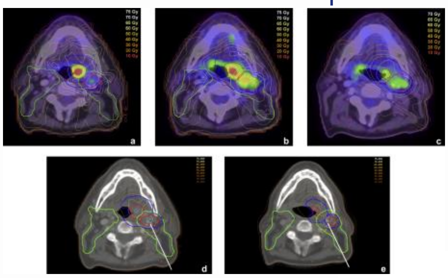


Madani et al. Int J Radiat Oncol Biol Phys 2007;68:126-35



Soto et al. Radiother Oncol 2008;89:13-8

Combining dose painting based on FDG-PET with adaptive RT



Dose planning for a) fractions 1-10, b) fractions 11-20; c) fractions 21-30

Berwouts et al. Radiother Oncol 2013;107:310-316

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	Standard	Dose redistribution
PTV-PET-Primary	70	77 mean dose (70-84)
PTV-Primary	70	67 mean dose (64-70)
PTV-Lymphnodes	70	70
PTV-elective	54.25	54.25

- Christie Hospital (Manchester)
- Vall d'Hebron (Barcelona)
- INSERM (Paris)
- Gustave Roussy CancerInstitute (Villejuif)
- Karolinska Institute (Stockholm)
- NKI-AVL (Amsterdam)
- Maastro (Maastricht)
- RaySearch (Maastricht)
- UMC Utrecht
- EMC Rotterdam

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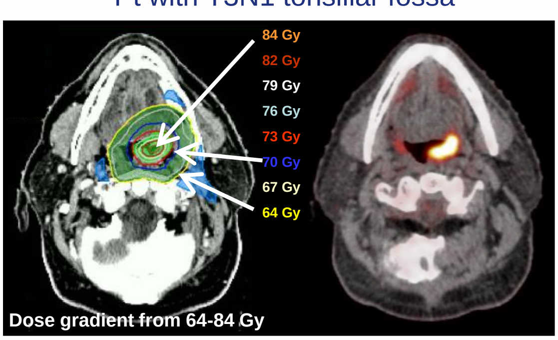
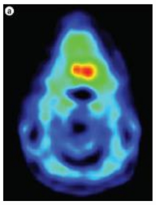
Artforce
Pt with T3N1 tonsillar fossa



PET hypoxia measurements

Accumulation of tracers in hypoxic regions

- FMISO, FAZA, HX4, .. (nitroimidazoles)
- Cu-ATSM, ..



Horsman et al. Nat Rev Clin Oncol. 2012;9:674–87

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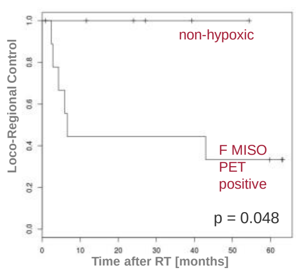
Baseline dyn. FMISO PET is prognostic for loco-regional control



LRC rates

F-MISO PET +: 32%
Non-hyp: 100%

Courtesy Daniela Thorwarth

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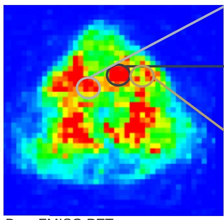
Hypoxia dose painting (HDP) in HNC: A randomized phase II trial in Tübingen

Aims	• Feasibility and toxicity of PET-based HDP • Prospective validation of a hypoxia TCP model
Imaging	• Planning CT + FDG PET/CT • Dynamic FMISO PET/CT in treatment position • Second dyn. FMISO PET/CT after approx. 2 weeks of RT
Therapy	• Randomization of hypoxic patients in 2 arms: - **Arm 1: Standard IMRT** - 70 Gy in 35 fx - **Arm 2: HDP** - homogeneous dose escalation of 10% in hypoxic tumor areas defined on dynamic FMISO PET/CT data

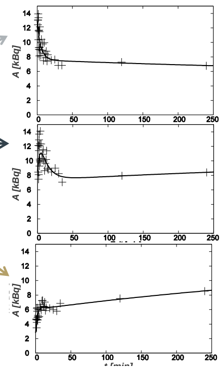
Courtesy Daniela Thorwarth

Dynamic FMISO PET:
Different Shapes of voxel-based Time Activity Curves

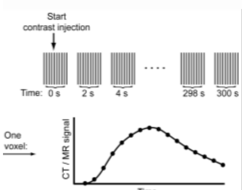


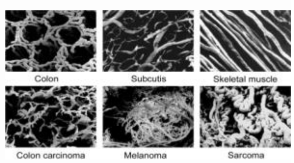
Dyn. FMISO PET
1 min pi

Thorwarth et al. Phys Med Biol 2005;50:2209-24

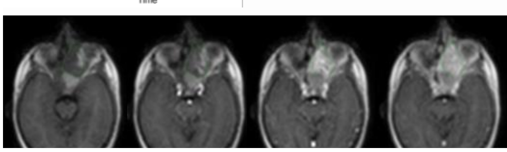


Dynamic Contrast-Enhanced (DCE) MRI/CT





Vaupel, 2004; Semin. Radiat. Oncol. 14:198-206



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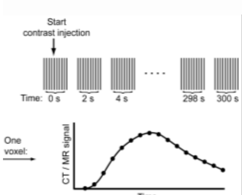
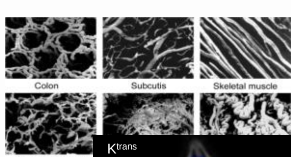
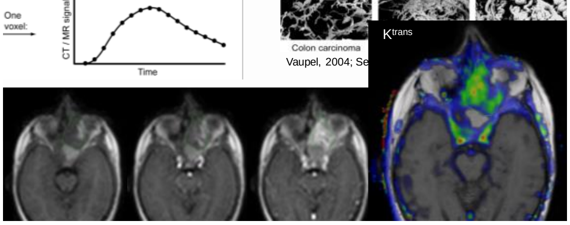


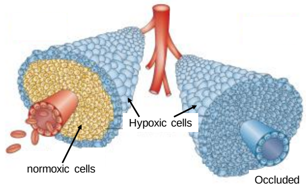


Vaupel, 2004; Se



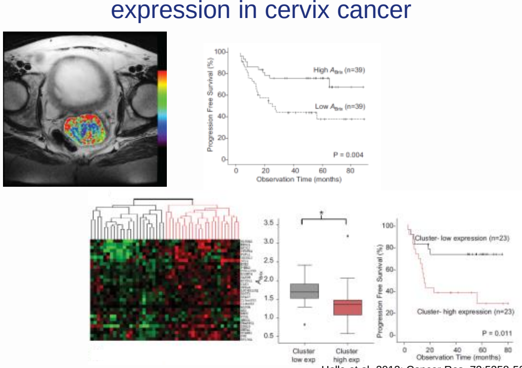
Hypoxia with MR

method	measures
DCE	micro-vasculature
R_2*	dHb
Relaxometry	pO_2
MRS	lactate



Horsman et al. Nat Rev Clin Oncol. 2012;9:674–87

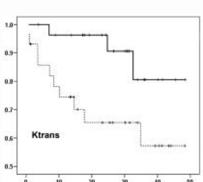
Correlate DCE-MRI with hypoxia gene expression in cervix cancer



Halle et al. 2012: Cancer Res. 72:5258-5295

Evidence for dose painting based on DCE-MRI

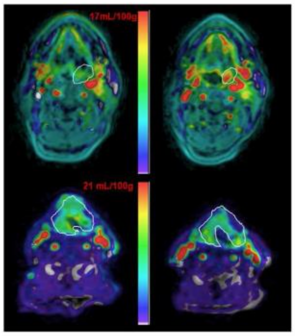
- Several (small) studies suggest that a high value of K^{trans} is associated with good response;



Patients with higher pretreatment K^{trans} values (solid line) demonstrate significantly prolonged disease-free survival compared with patients with lower K^{trans} values (dashed line, P = .029).

S. Chawla et al. AJNR Am J Neuroradiol 2011;32:778-784

Increase in BV predicts good response in head-neck cancer



- DCE-MRI pre-treatment and after 2 weeks of CRT
- Local control (top): increase in blood volume
- Local failure (bottom)
  Little change in blood volume

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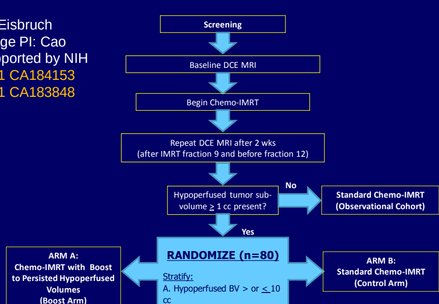
Cao et al. Int J Radiat Oncol Biol Phys. 2008;72:1287–90

UMCC 2013-062: Schema

University of Michigan Medical School

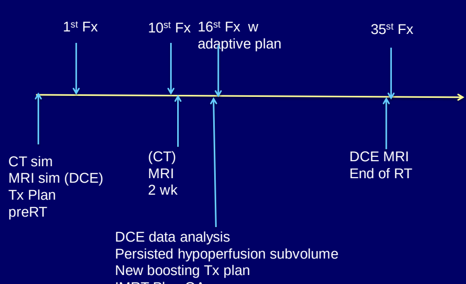
PI: Eisbruch
Image PI: Cao
Supported by NIH
RO1 CA184153
UO1 CA183848



Courtesy Yue Cao

Workflow

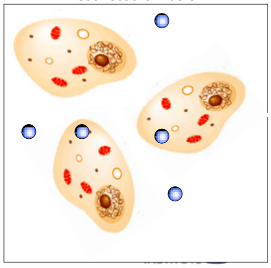
University of Michigan Medical School



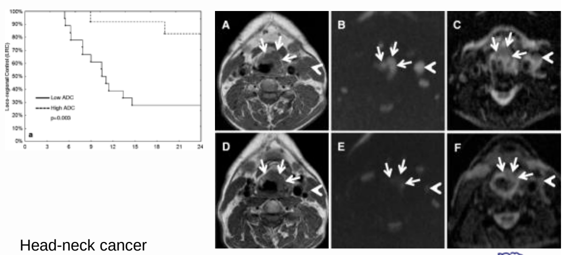
Courtesy Yue Cao

Diffusion-weighted MRI (DWI)

- Measures the freedom of water protons to move
- Reflects
  - micro-anatomy
  - Response to treatment



Diffusion-weighted MRI as early imaging marker for response to treatment



Head-neck cancer

- >25% increase in ADC after 2 weeks of chemoradiation is associated with good loco-regional control

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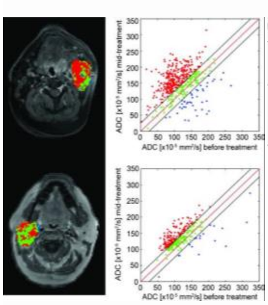
Vandecaveye et al. 2010; Eur. Radiol. 20:1703-14

Diffusion-weighted MRI in head-neck



Early Response of Volume and Tumor ADC Values at 3 Weeks after Treatment Initiation.

	Volume [cm³] (SEM)		ADC [x10⁻⁵ mm²/sec] (SEM)	
	Pretreatment	Midtreatment	Pretreatment	Midtreatment
Primary	**28.8 (9.5)**	**19.3 (7.2)**	145.8 (11.3)	163.3 (10.6)
Lymph nodes	**43.7 (9.9)**	**29.6 (10.2)**	**122.5 (5.0)**	**153.4 (5.1)**
CR	**30.6 (5.9)**	**18.2 (5.4)**	**133.5 (7.7)**	**162.9 (6.3)**
PR	**57.8 (22.3)**	**47.1 (19.7)**	132.7 (8.6)	141.5 (9.5)

- Possibly use DWI to identify the most resistant part of a tumor for boosting

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Galbán et al. Transl Oncol 2009;18:184-90

Many plausible imaging techniques for dose painting

- FDG-PET
- Hypoxia:
  - F-MISO and other PET tracers
  - DCE-MRI
- Response:
  - DWI

Many plausible imaging techniques for dose painting

- FDG-PET
- Hypoxia:
  - F-MISO and other PET tracers
  - DCE-MRI
- Response:
  - DWI

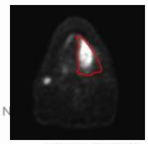
Do these techniques identify the same Biological Target Volume?

FDG-PET and diffusion-weighted MRI

- 19 radiotherapy HN patients
  - Oral cavity, oropharynx, nasopharynx, hypopharynx
- Planning CT, PET and MRI exam
  - Within 2 weeks
- GTV delineated by radiation oncologist according to local clinical guidelines
  - GTV volume: 3 ml - 120 ml

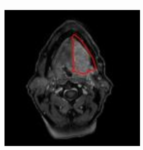
Imaging protocol: ^{18}FDG-PET

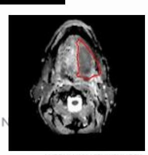
- Philips Gemini TF scanner
  - In RT mask
- CT
  - Attenuation correction
  - Registration to planning CT
- ^{18}FDG-PET scan
  - 3 minutes per bed position
  - 2 x 2 x 2 mm^3 voxels
  - Standardized uptake value (SUV_{max}) calculated



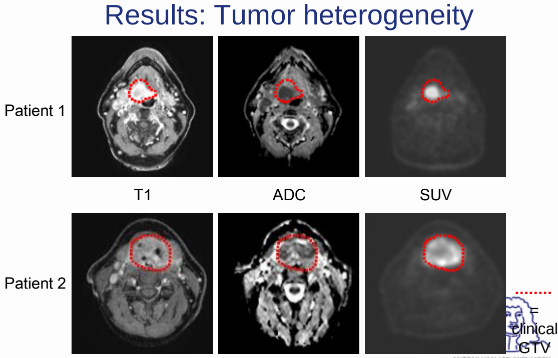
Imaging protocol: DWI

- Philips Achieva 3T scanner
  - Without RT mask
  - 16 element neurovascular coil
- T1-weighted scan
  - Registration to planning CT
- DWI scan
  - EPI imaging with SENSE factor of 2
  - 2.1 x 2.6 x 4 mm^3 voxels
  - b-values: 0 and 1000
  - Apparent diffusion coefficient (ADC) calculated on scanner



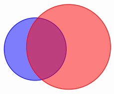


Results: Tumor heterogeneity



Houweling et al. Radiother Oncol. 2013;106:250-4

Results: Dice similarity coefficient



DSC < 1

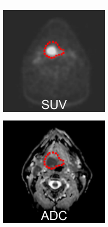
$$DSC = \frac{2(A \cap B)}{A + B}$$

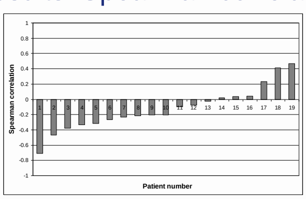
- A
- B
- A ∩ B

	Volume (ml)		Dice
	Median	Range	
$SUV_{40\%\ SUV_{max}}$	6.4	1.8 - 34.8	-
$ADC_{0.7 \cdot 10^{-3}\ mm^2/s}$	8.7	0.2 - 56.2	0.27
$ADC_{1.1 \cdot 10^{-3}\ mm^2/s}$	15.5	1.7 - 97.6	0.44
$ADC_{1.5 \cdot 10^{-3}\ mm^2/s}$	23.6	2.4 - 121.5	0.47

Houweling et al. Radiother Oncol. 2013;106:250-4

Results: Spearman correlation





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Houweling et al. Radiother Oncol. 2013;106:250-4

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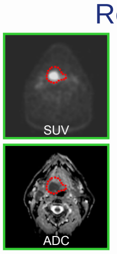

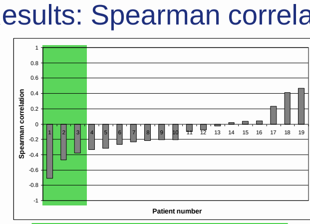

- Consistent information
  - High SUV correlates with low ADC

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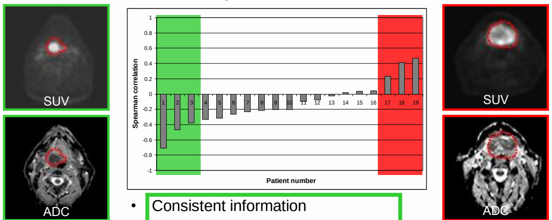
Results: Spearman correlation



- Consistent information
  - High SUV correlates with low ADC
- Conflicting information
  - High SUV correlates with high ADC
- Complementary information
  - Weak correlation

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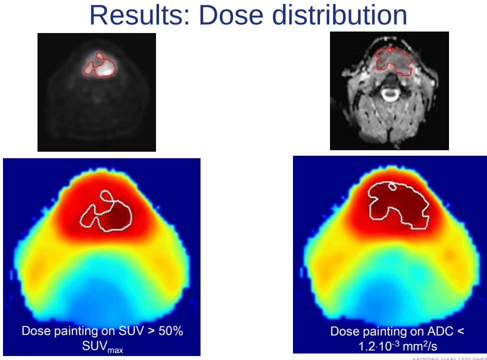
Results: Dose distribution



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Houweling et al. Radiother Oncol. 2013;106:250-4

Coverage of BTV based on FDG-PET or DWI

Table 3
Dose coverage of the different SUV- and ADC-targets.

	D_{mean} (Gy)	$D_{98\%}$ (Gy)	$D_{2\%}$ (Gy)
$SUV_{50\%max}$			
Average	81.3	76.9	84.3
Range	78.9–82.7	70.6–80.3	80.9–85.0
$SUV_{60\%max}$			
Average	81.9*	78.0*	84.3*
Range	79.5–82.9	70.6–81.0	81.0–85.4
$SUV_{40\%max}$			
Average	80.4*	75.0*	84.2*
Range	78.4–82.6	70.5–79.7	80.9–84.9
$ADC_{<mean}$			
Average	76.8*	83.7*	
Range	71.4–81.0	66.9–75.6	80.9–84.7
$ADC_{<mean-SD}$			
Average	76.4*	69.9*	83.1*
Range	71.5–80.0	66.6–74.7	80.3–85.0
$ADC_{>mean}$			
Average	75.4*	69.4*	83.1*
Range	72.7–80.7	66.4–74.9	79.0–84.3

Abbreviations: D_{mean} = mean dose; $D_{98\%}$ = near-minimum dose; $D_{2\%}$ = near-maximum dose.
* Significantly different from the $SUV_{50\%max}$ isocontour with $p < 0.001$.

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FDG-PET and DCE-MRI

- Which tumor regions are resistant to treatment?

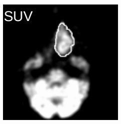
FDG-PET

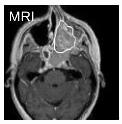
Loco-regional failure in high SUV areas

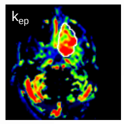
Jansen et al. 2012
Bisdas et al. 2010

DCE-MRI

Low K^{trans} related to poor treatment outcome







Aim: voxel-based comparison

Ref: Soto et al. 2008, Kim et al. 2010, Wang et al. 2012, Yoo et al. 2012, Chawla et al. 2013

Patient Inclusion

- 28 patients with head & neck cancer receiving radiotherapy
- FDG-PET/CT and DCE-MRI exam within one week
- All exams in radiotherapy mask

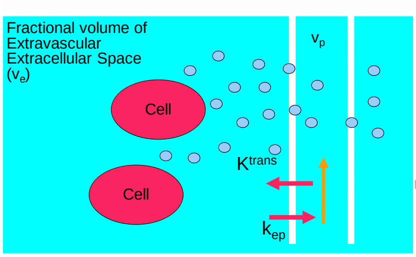
FDG-PET scan parameters
- Gemini TF Philips
- 190-240 MBq FDG
- Voxel size = 2*2*2 mm^3 (recon)
- 3 bed positions (FH 36 cm)
- Total scan time = 9 min

DCE-MRI scan parameters
- 1.5 T (Achieva Philips)
- TR/TE/α = 4.0/1.16/15
- FOV = 250*200*115
- Voxel size = 3*3*4 mm^3 (acq)
  1.4*1.4*4 (recon)
- 29 slices
- Dyn scan time = 2.5 s
- Total scan time = 3 min
- 15 mL dotarem 3 ml/s

Tracer kinetics modeling – Tofts Model

- Extended Tofts model:

$$C_{tiss}(t) = v_p \cdot C_a(t) + K^{trans} \cdot C_a(t) \otimes R(t)$$
with $R(t) = e^{(-Ktrans/ve) \cdot t}$



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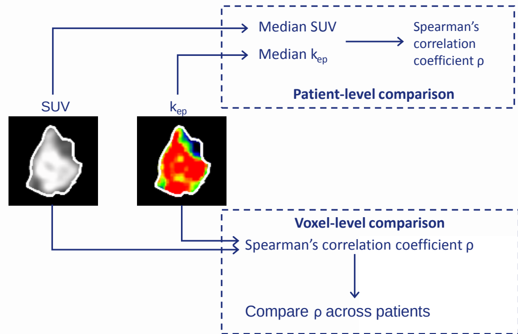
Comparison SUV and DCE maps

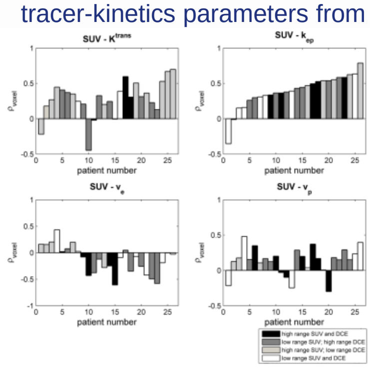


Correlation SUV and DCE parameters

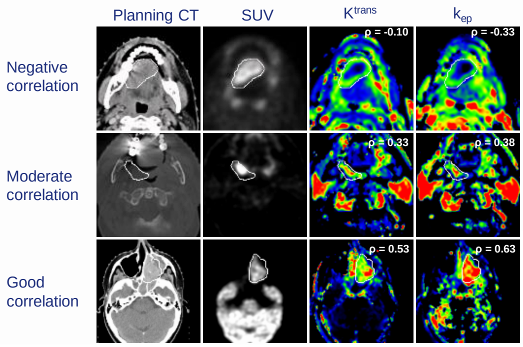
	ρ voxel-level	ρ patient-level
SUV vs. K^{trans}	0.25* (-0.35 – 0.55)	0.15
SUV vs. k_{ep}	0.36* (-0.33 – 0.64)	0.18
SUV vs. v_e	-0.11 (-0.56 – 0.33)	0.11
SUV vs. v_p	0.11 (-0.29 – 0.34)	0.03

* $p < 0.01$

Correlation coefficients between SUV and tracer-kinetics parameters from DCE-MRI



Examples



Observations

- Different imaging modalities are prognostic for response to (chemo-)radiotherapy
- Their predictive value is currently tested in dose painting trials of head and neck cancer
- Limited correlation between these imaging modalities reflects a high degree of tumor heterogeneity
- Correlations between FDG SUV and K^{trans} and k_{ep} were significant and higher at voxel-level
  - High FDG-PET uptake and low perfusion/permeability seem to identify different parts of the tumor

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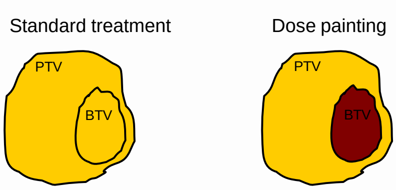
Dose escalation to BTV



- Probability of local control increases with dose escalation
- Normal tissue complication probability also increases with dose escalation

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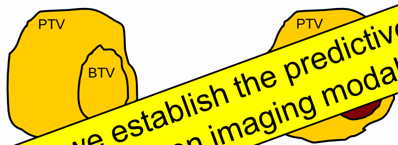
Dose escalation to BTV

Standard treatment | Dose painting



How do we establish the predictive value of our chosen imaging modality?

...trol increases with dose escalation
...complication probability also increases
...ose escalation

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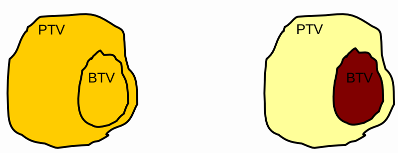
Dose redistribution between BTV and PTV

Standard treatment | Dose painting



- If integral dose to the PTV is the same between both arms, the TCP should not change, unless the imaging modality is predictive

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Strategy for dose painting trials

- Dose redistribution is more likely to test the benefit of dose painting than simple dose escalation
- Choose one imaging modality as the basis for dose painting
- Include as many other modalities as feasible in the pre-treatment imaging protocol
  - Analyze outcome using all imaging modalities
  - Use this to generate hypotheses for the next generation of clinical trials

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Conclusions

- Ongoing trials of dose painting in head-neck cancer use different imaging techniques to identify a biological target volume
- Limited correlation between these imaging modalities
- It is impractical to test all functional imaging modalities in clinical trials
- Dose redistribution is more likely to test the benefit of dose painting than simple dose escalation
- By adding multiple imaging modalities to a dose painting trial, we can possibly derive dose-effect relationships for more modalities within a single trial

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