Hypoxia-guided adaptive radiation dose escalation in head and neck cancer

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ICTR-PHE
Feb. 2016

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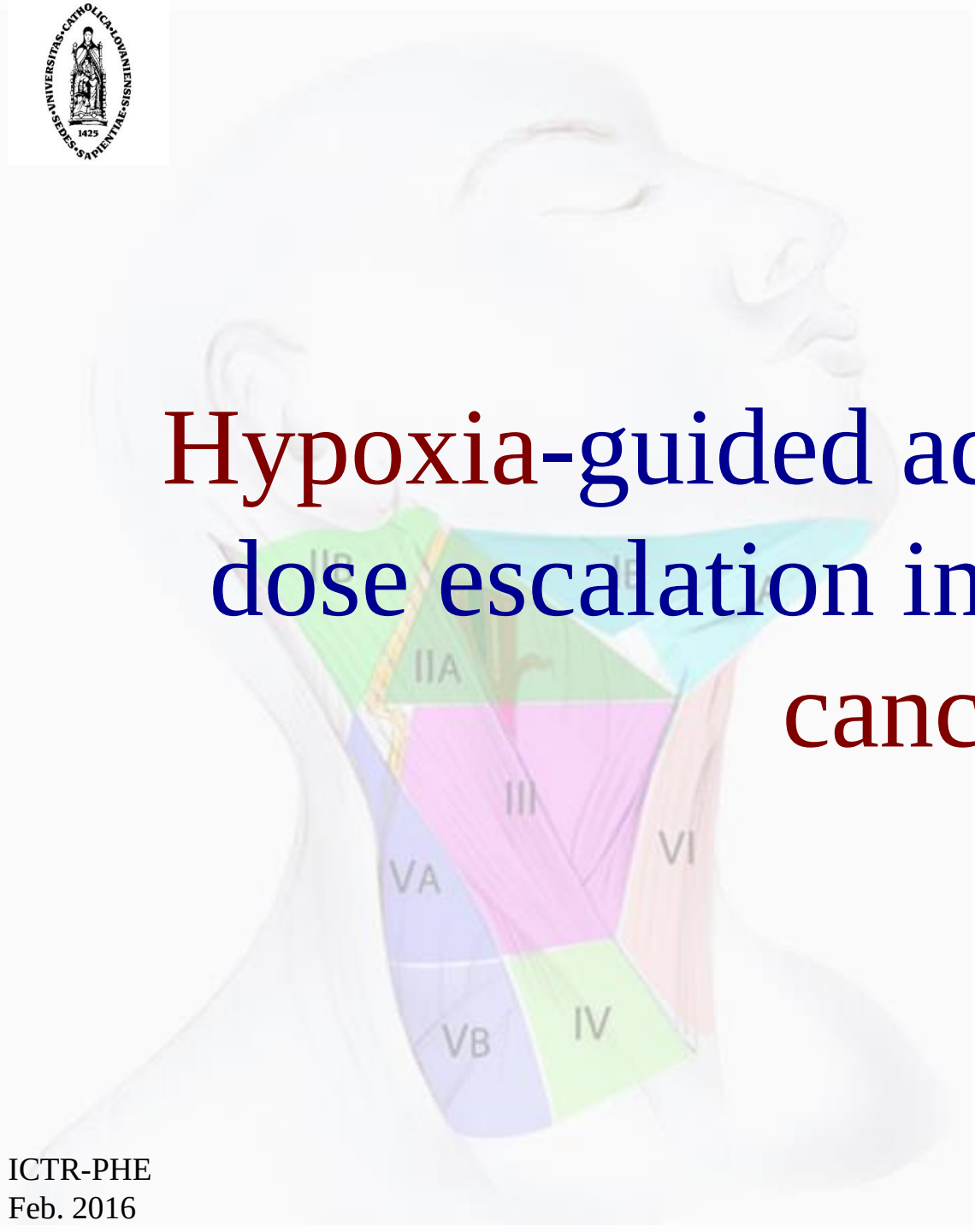

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Tumor hypoxia : clinical evidences

Tumor type	Median pO_2 (mm Hg)	fraction <10 mm Hg (%)
Breast C.	23-28	26-32
Cervical C.	2-21	21-46
Rectal C.	19-25	-
Lung C.	14	36
Soft tissue sarcomas	18-27	44
Glioblastomas	7	61
Head & Neck C.	19-26	33
H&N lymph nodes	9-25	14-54
Melanoma	10	49

From Vaupel et al., 1998

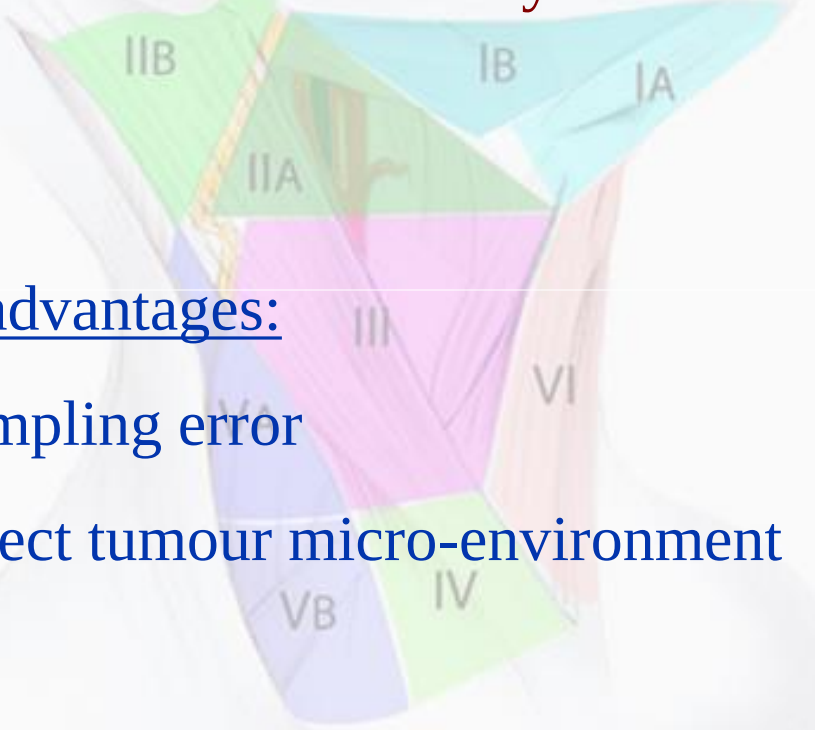
Measurements of tumor oxygenation

INVASIVE

- Eppendorf / OxyLite
- Immunohistochemistry

NON-INVASIVE

- MRI: dynamic and functional
- ^{19}F-MRS
- EPR
- PET/SPECT



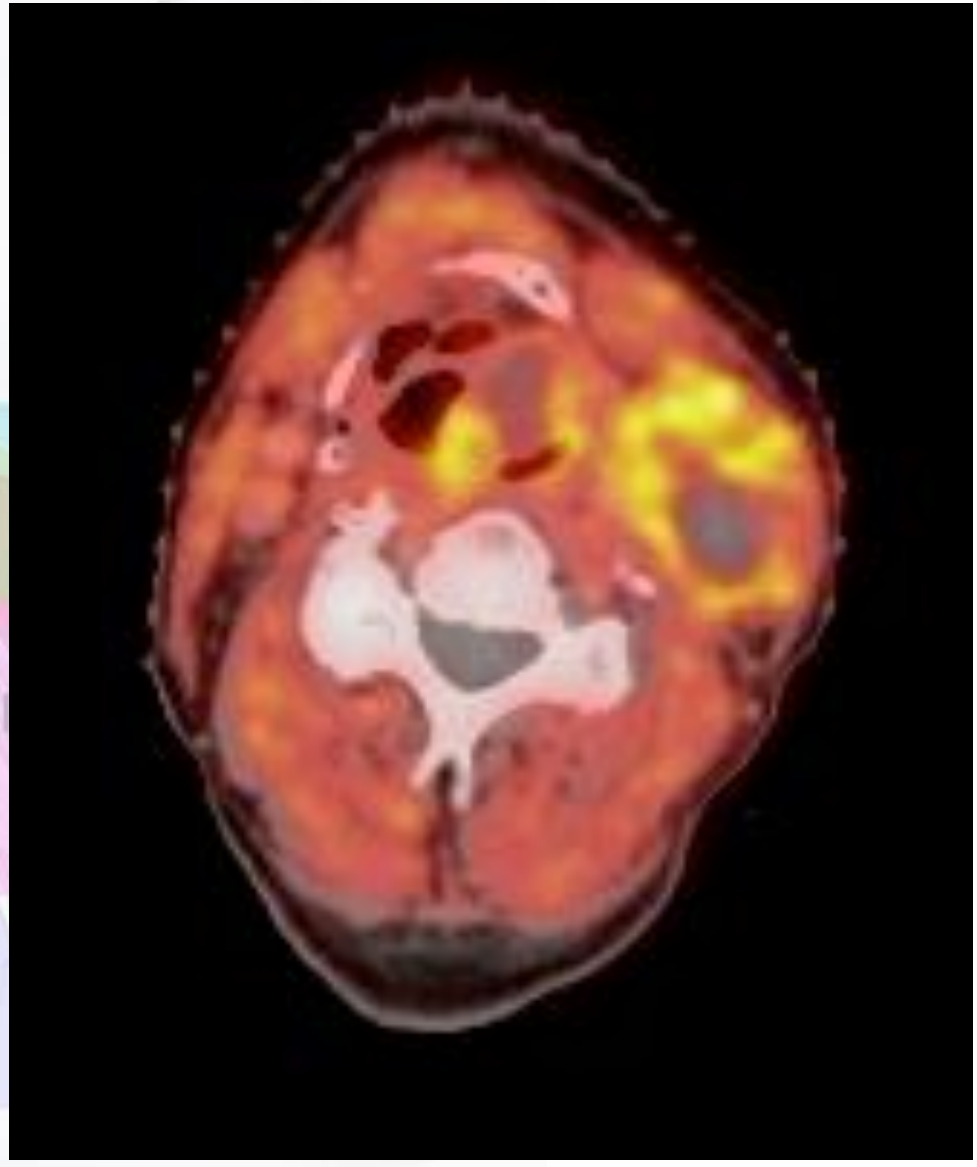
Disadvantages:

- sampling error
- affect tumour micro-environment

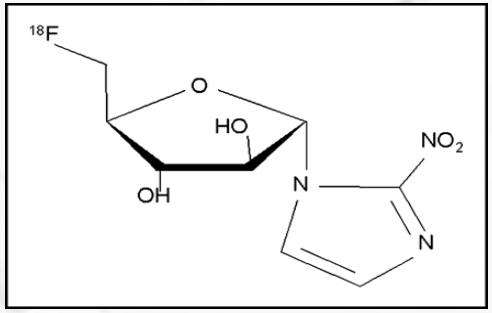
Advantages:

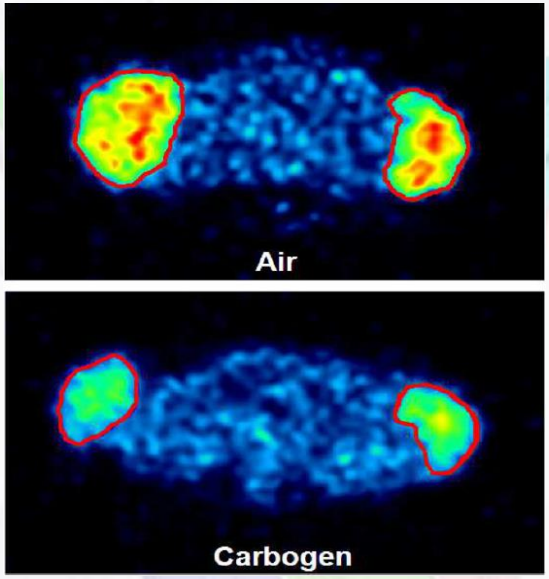
- preserves tumour micro-environment
- longitudinal measurements
- whole tumour

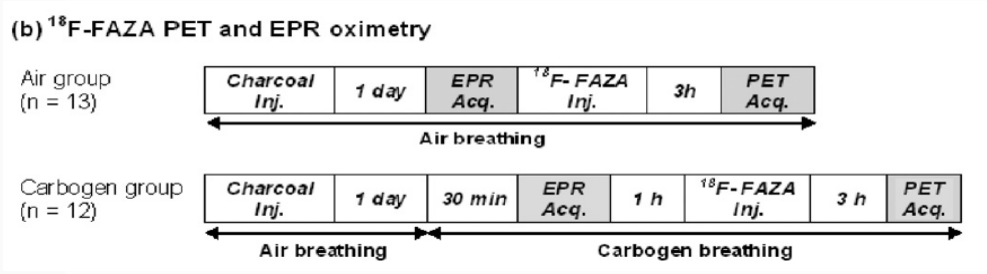
Hypoxic tracer ^{18}FAZA

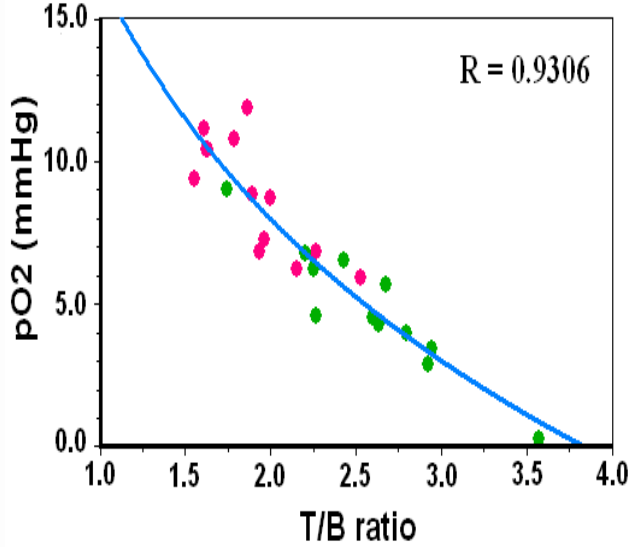


^{18}F-FAZA accumulation in tumors as a function of pO2
Qualification by EPR oximetry





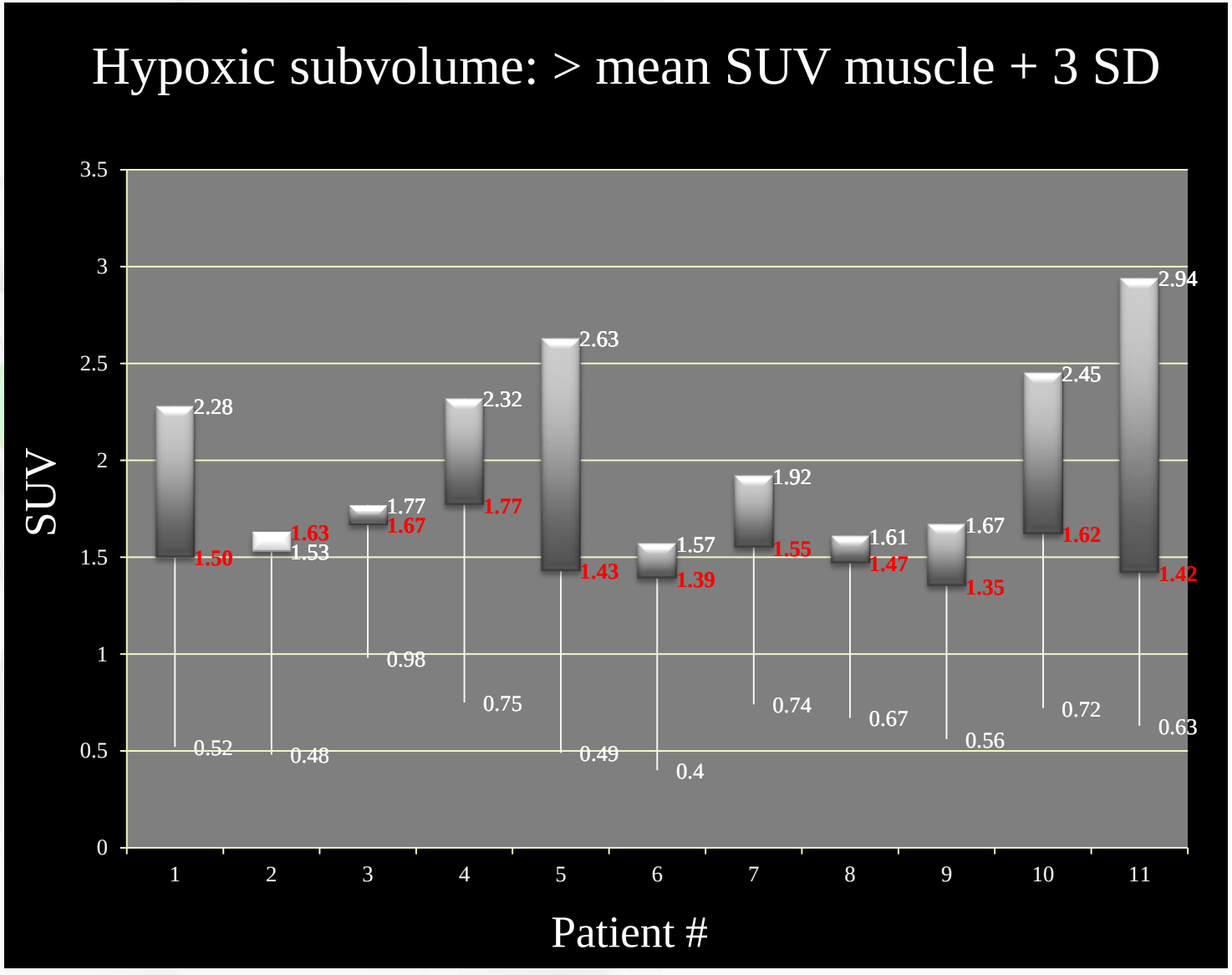




Accumulation increases under 10 mm Hg
(radiobiologically relevant hypoxia)

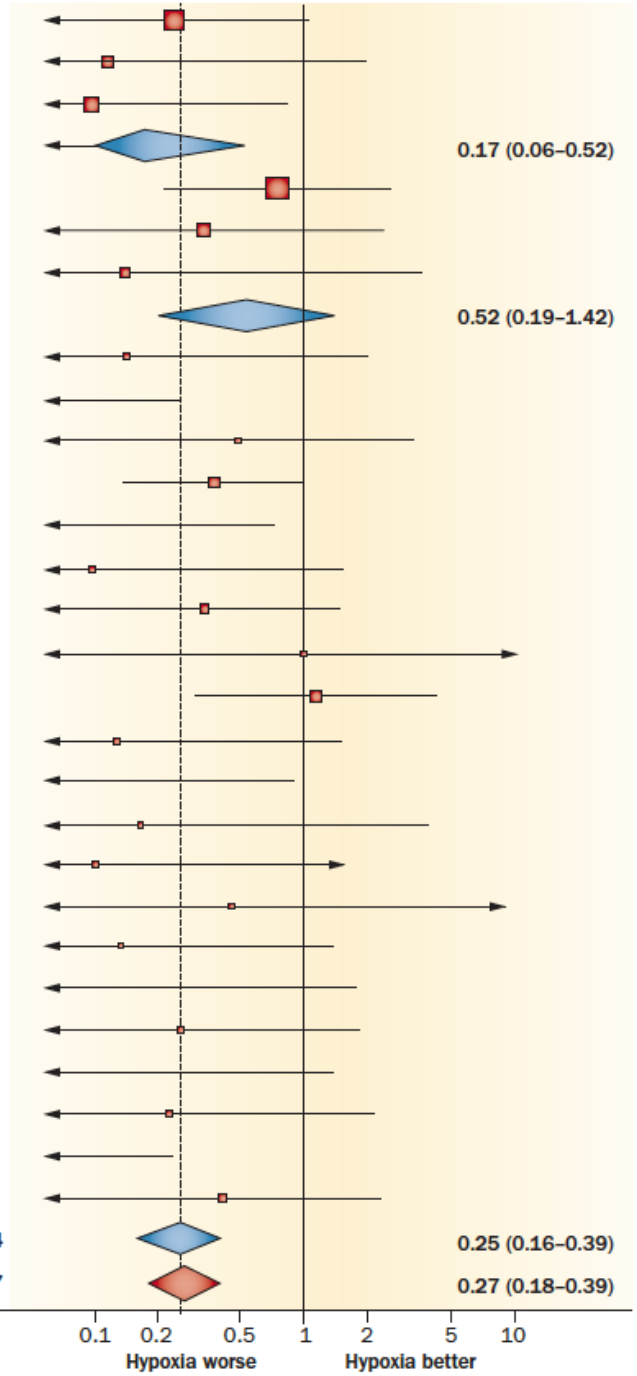
Tran et al, Radiother. Oncol. 2012, 67, 53

^{18}F-AZA image segmentation



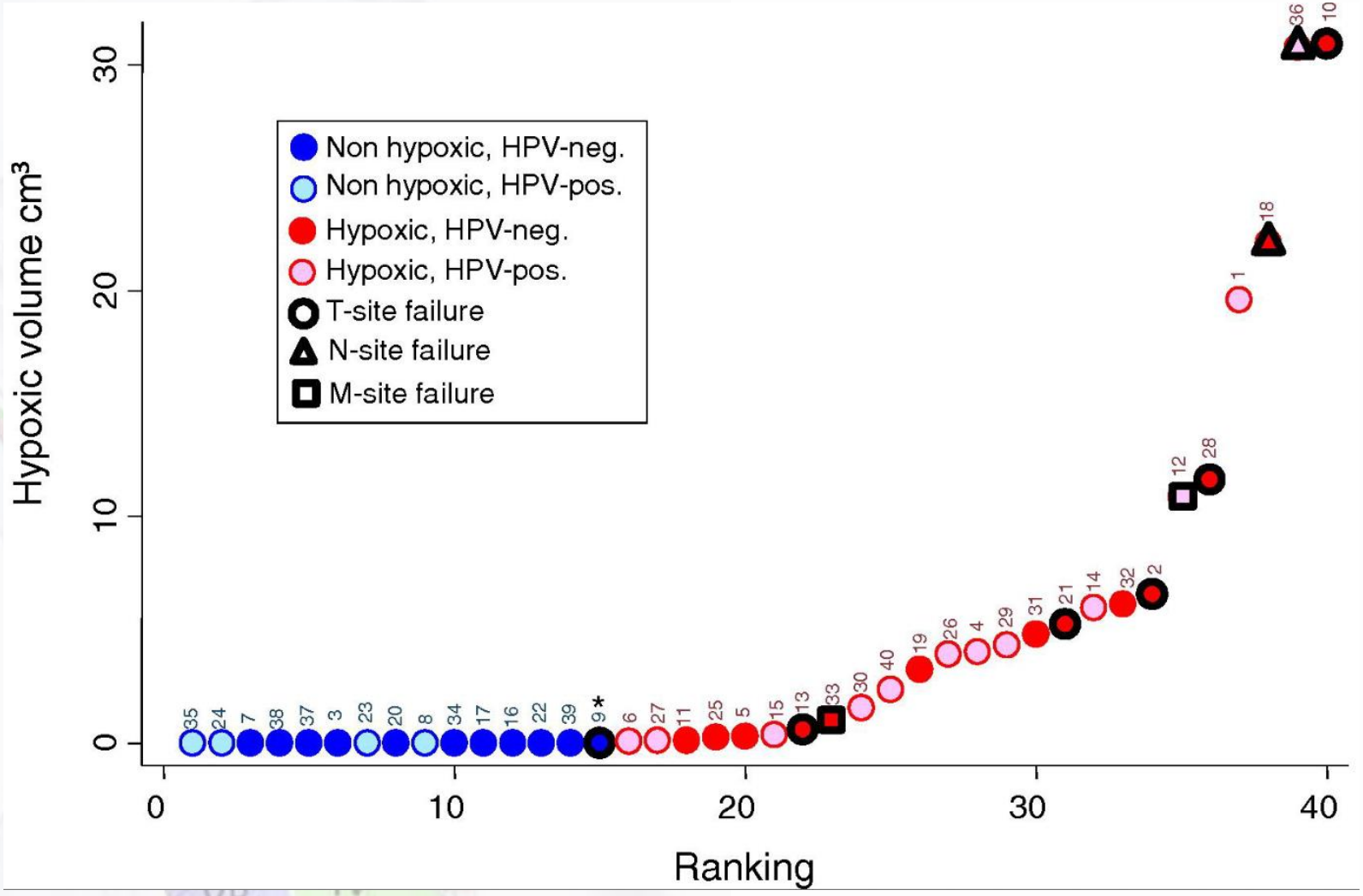
Prognostic value of tumor hypoxia

Study	Tumour	Tracer	Events/total No hypoxia	Events/total Hypoxia	Odds ratio (95% CI)
Loncaster (2002)[97]	Cervix	DCE MRI	3/25	9/25	
Mayr (2010)[98]	Cervix	DCE MRI	0/16	17/82	
Andersen (2012)[99]	Cervix	DCE MRI	1/41	8/40	
DCE MRI all			**4/82**	**34/147**	**0.17 (0.06–0.52)**
Hermans (1999)[87]	HNSCC	CTperf	9/21	10/20	
Bisdas (2009)[88]	HNSCC	CTperf	2/11	4/10	
Truong (2011)[89]	HNSCC	CTperf	0/6	2/6	
CT perfusion all			**11/38**	**16/36**	**0.52 (0.19–1.42)**
Urtasun (1996)[102]	HNSCC	IAZA	3/10	3/4	
Dehdashti (2003)[70]	Lung	CuATSM	0/8	6/6	
Lehtiö (2004)[52]	HNSCC	FETNIM	4/9	5/8	
Rajendran (2006)[53]	HNSCC	FMISO	10/37	18/36	
Rischin (2006)[28]	HNSCC	FMISO	1/10	8/13	
Thornwarth (2006)[54]	HNSCC	FMISO	1/6	4/6	
Li (2006)[104]	Lung	Tc-HL91	8/16	12/16	
Eschmann (2007)[55]	HNSCC	FMISO	2/4	4/8	
Dehdashti (2008)[71]	Cervix	CuATSM	9/22	6/16	
Dietz (2008)[72]	Rectal	CuATSM	1/9	4/8	
Khamly (2008)[56]	Sarcoma	FAZA	3/9	7/8	
Spence (2008)[57]	CNS	FMISO	9/11	11/11	
Dirix (2009)[58]	HNSCC	FMISO	2/6	5/6	
Lee (2009)[59]	HNSCC	FMISO	0/7	1/11	
Li (2010)[60]	Lung	FETNIM	8/13	12/13	
Schuetz (2010)[47]	Cervix	FAZA	0/10	2/5	
Kikuchi (2011)[61]	HNSCC	FMISO	3/10	5/8	
Minagawa (2011)[73]	HNSCC	CuATSM	0/5	6/10	
Mortensen (2012)[62]	HNSCC	FAZA	1/17	7/25	
Yue (2012)[63]	Oesophagus	FETNIM	1/14	11/14	
Zips (2012)[64]	HNSCC	FMISO	3/13	5/12	
PET/SPECT all			**69/244**	**142/244**	**0.25 (0.16–0.39)**
All studies			**84/364**	**192/427**	**0.27 (0.18–0.39)**



Horsman, Nat. Rev. Clin. Oncol.,

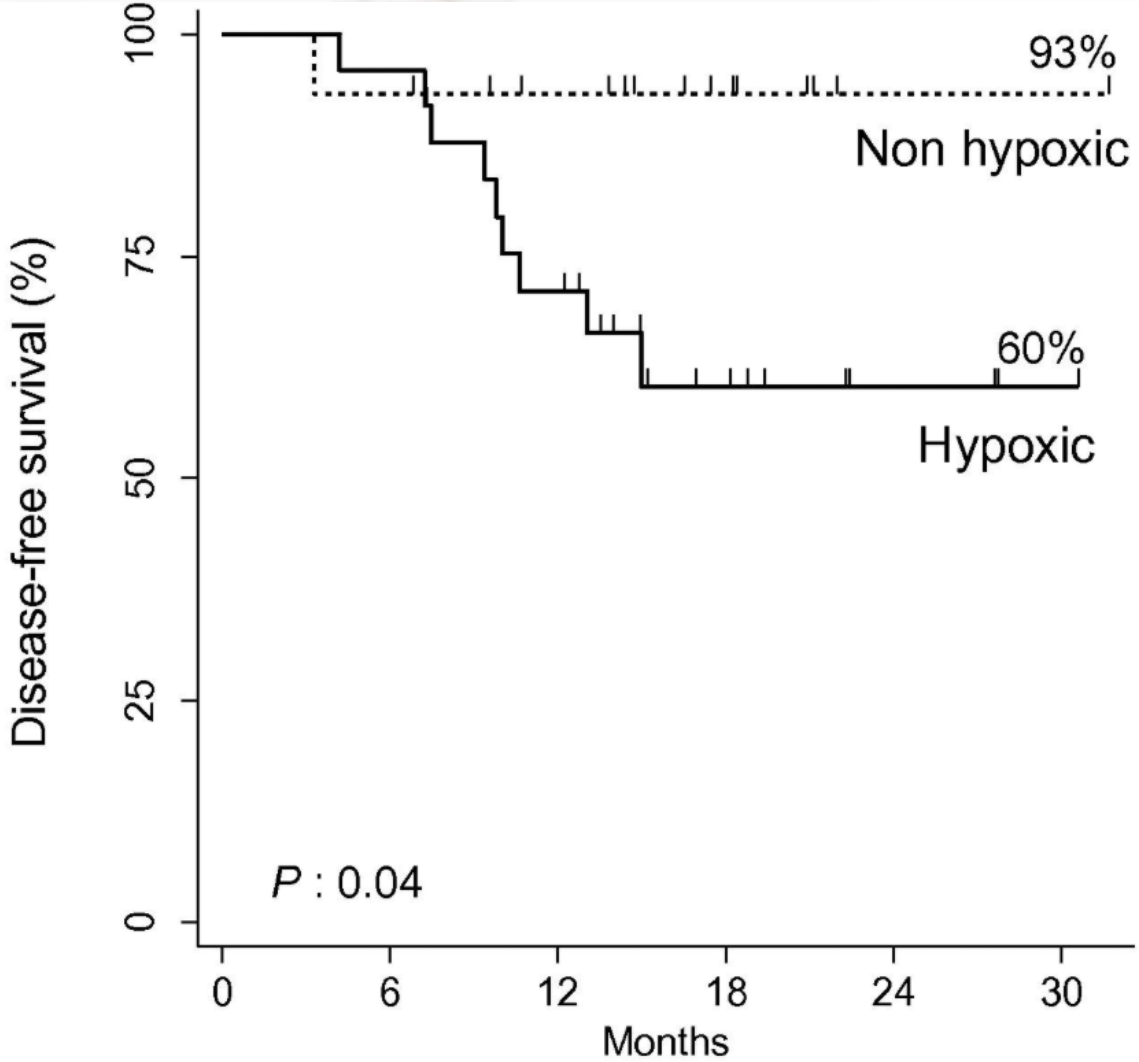
FAZA-PET as prognostic factor in HNSCC



- n= 40
- Hypoxic Volume: SUV > 1.4 in 66% of pts
- RT + nimoral ± weekly cddp (n=22)

Mortensen, R&O 2012

FAZA-PET as prognostic factor in HNSCC



Pts at risk:

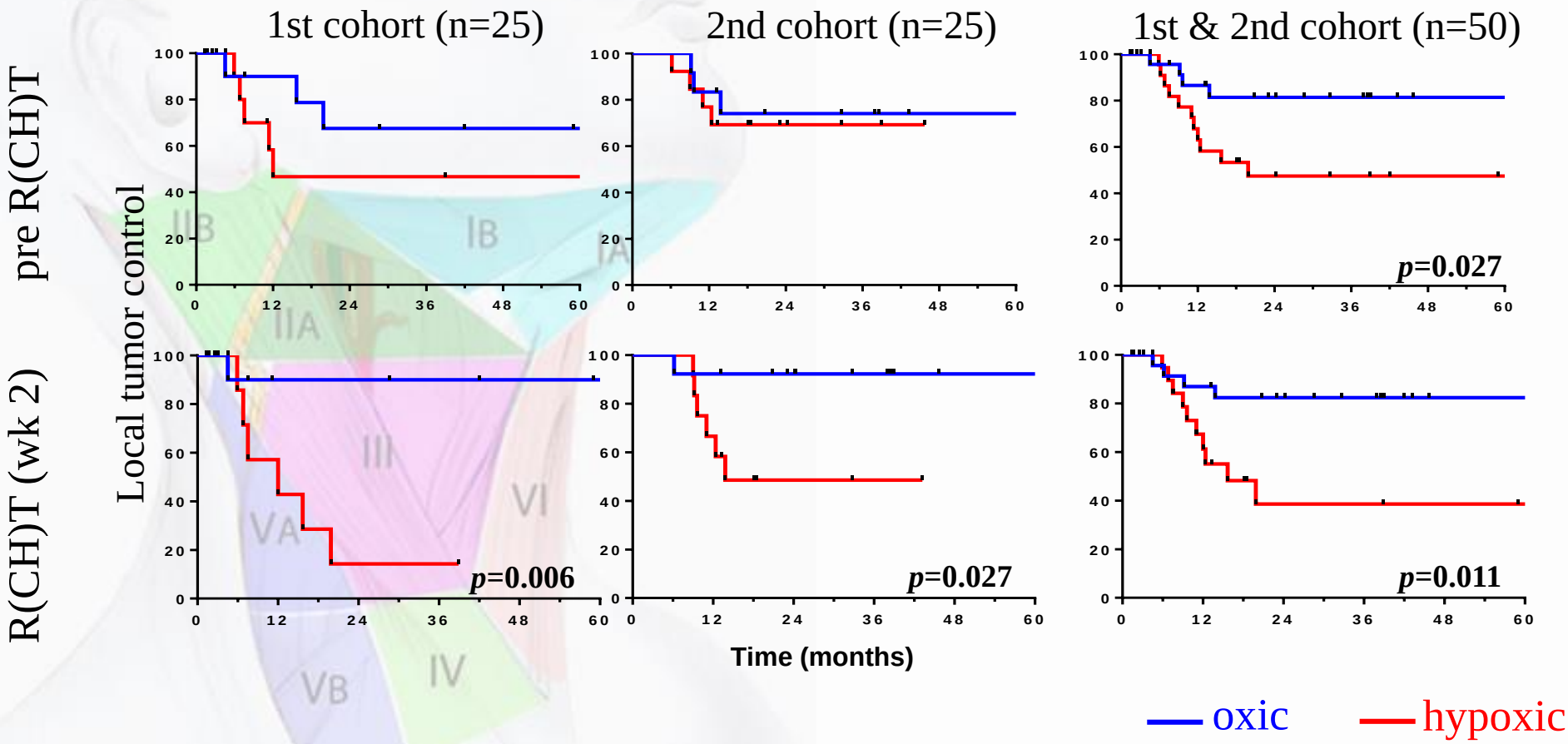
Non hypoxic:	15	14	11	6	1	1
Hypoxic:	25	24	17	8	3	1

- n= 40
- Hypoxic Volume: SUV > 1.4 in 33% of pts
- RT + nimoral ± weekly cddp (n=22)

Mortensen, R&O 2012

F-Miso PET and local tumor control

Tumor hypoxia: TBRatio > 1.6



Courtesy of Baumann and Troost, 2015

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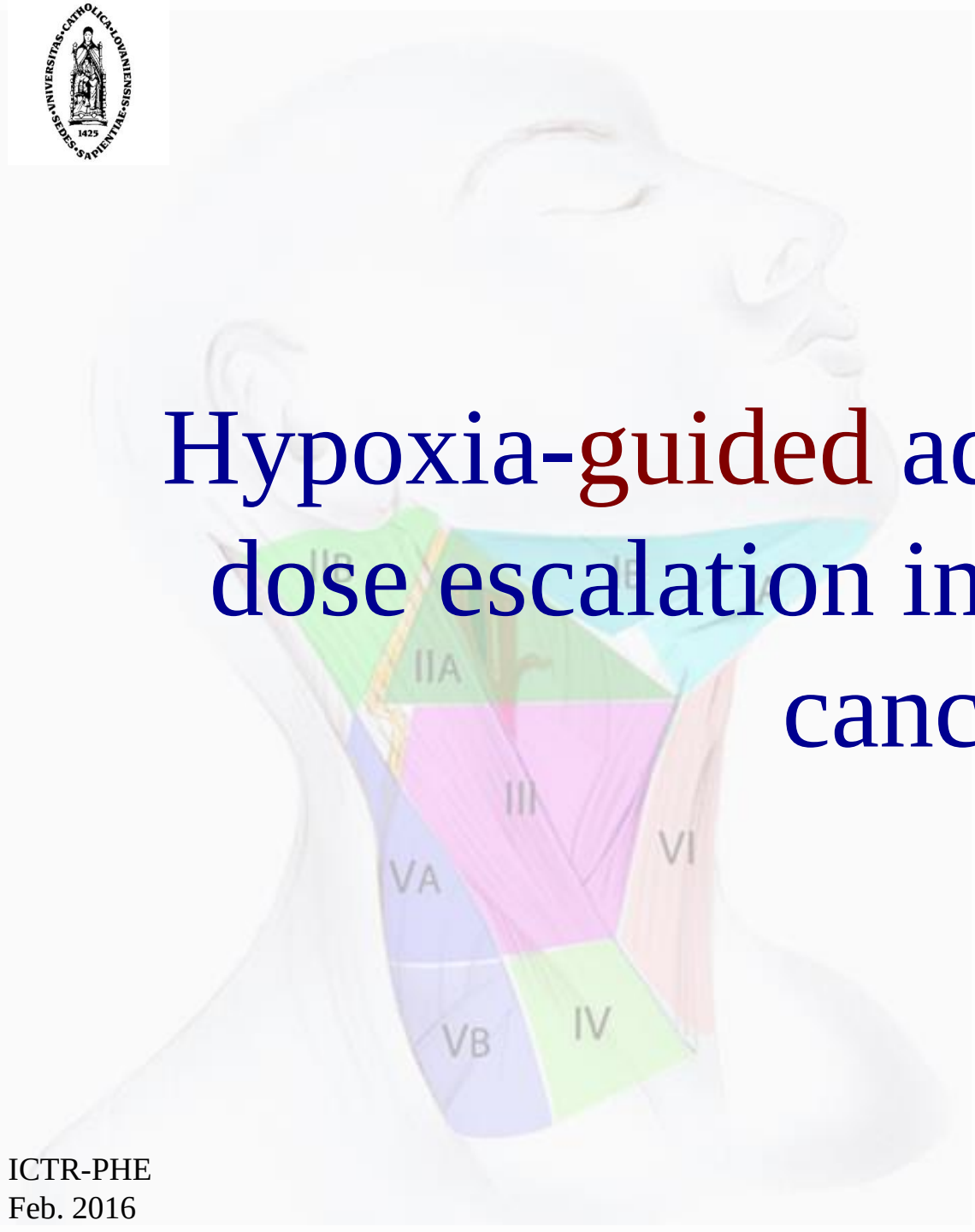

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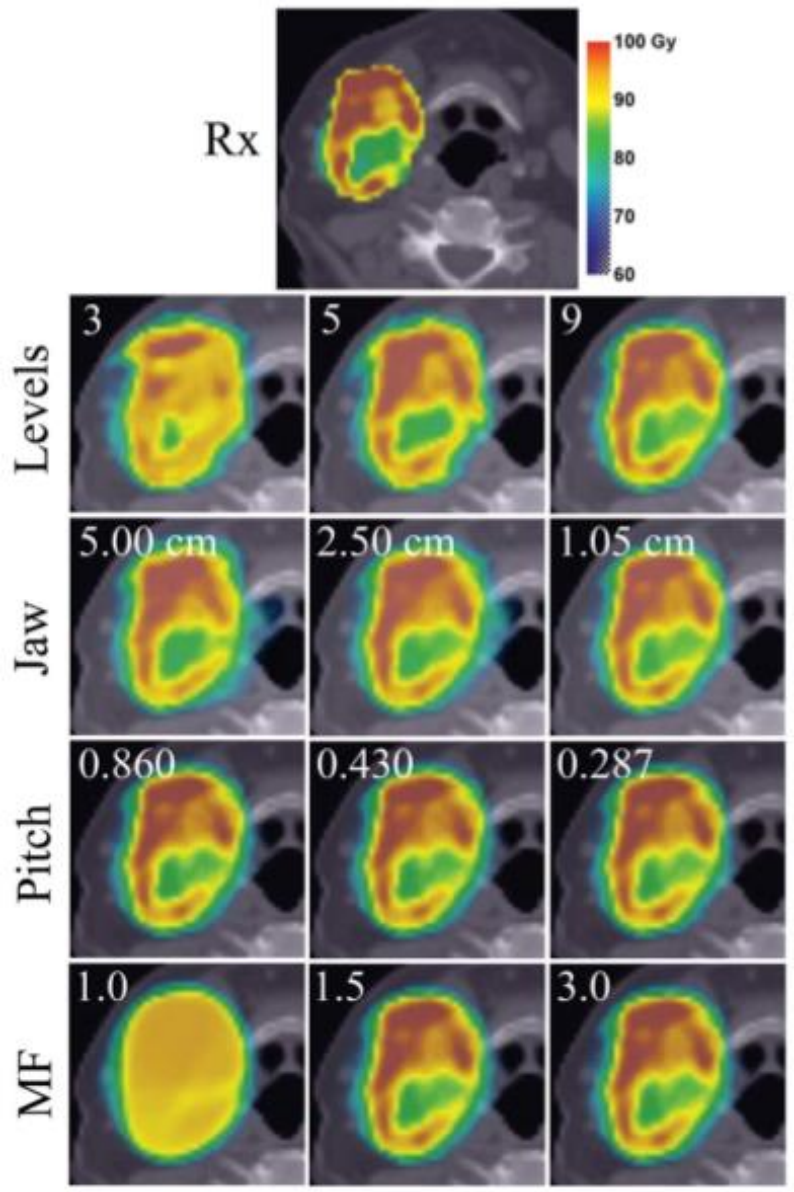
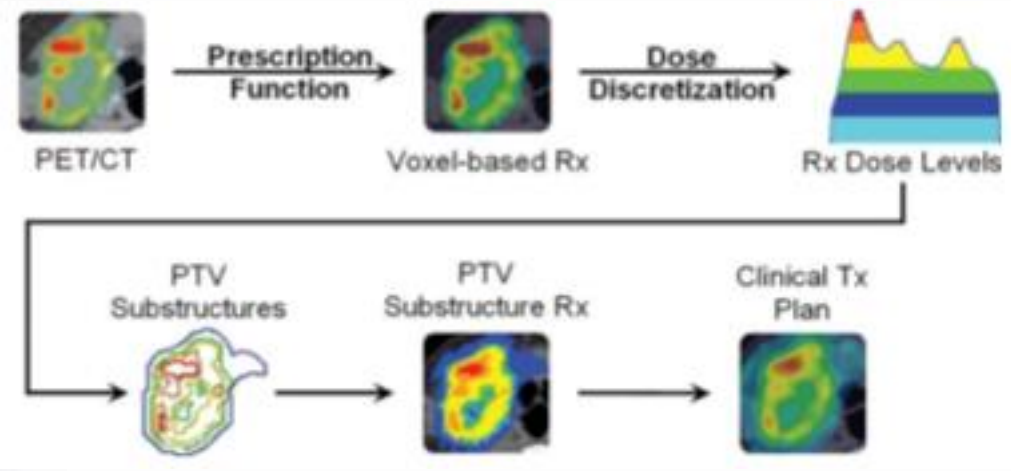
Molecular imaging dose painting by number



- Tomotherapy Hi-Art
- H&N SCC: T4N2bM0
- 60 Gy + SIB of 30 Gy
- Hypoxia (Cu-ATSM)



Deveau et al., 2010

Relevant issues for hypoxia dose painting in H&N SCC …

- Hypoxic tracer?
- Spatial resolution?
- Dose prescription function?
- Uncertainties in $GTV_{hypoxia}$ positioning?
- Clinical validation?

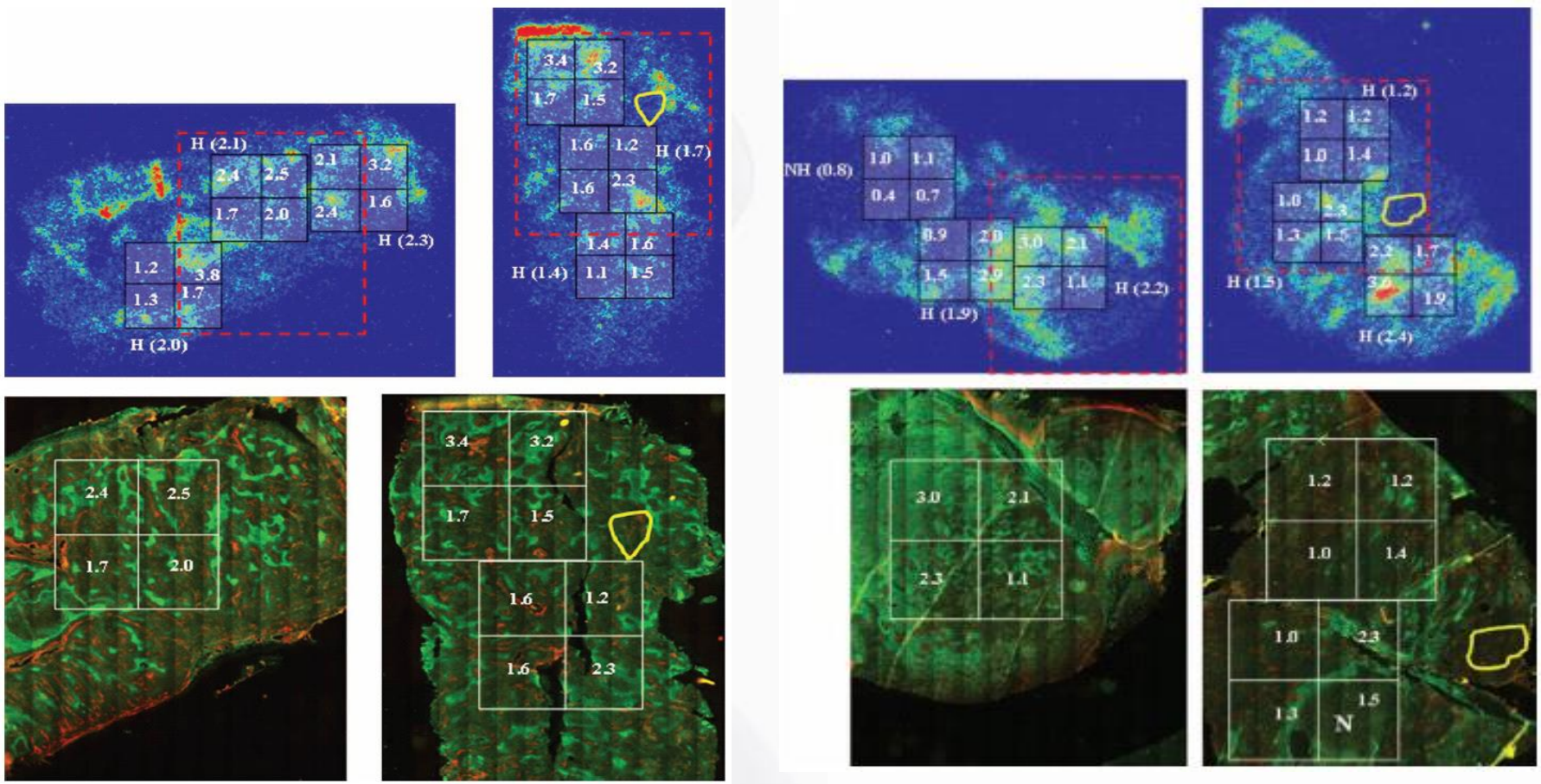
Hypoxic tracers: which one?

Comparison of various ^{18}F-labeled nitroimidazole tracers in rodent

	FETNIM	F-miso	EF1	EF3	EF5
Octanol/water	0.17	0.40	0.35	1.25	4.0
$T_{1/2}$ in blood (min)	98	108	n.a.	78 (mice!)	150
Early biodistribution	+	++	++	+++	++++
GI clearance	+	++	++	++	+++
Kidney clearance	+++	+++	+++	+++	++
Circulating metabolites (2h)	20%	50%	n.a.	20%	n.a.
Specific activity (Ci/mmol)	8,000	650	1.5	4	1
Tumor / muscle	1.4-6.0	1.7-8.3	1.0-3.0	2.1-6.1	1.5-3.0

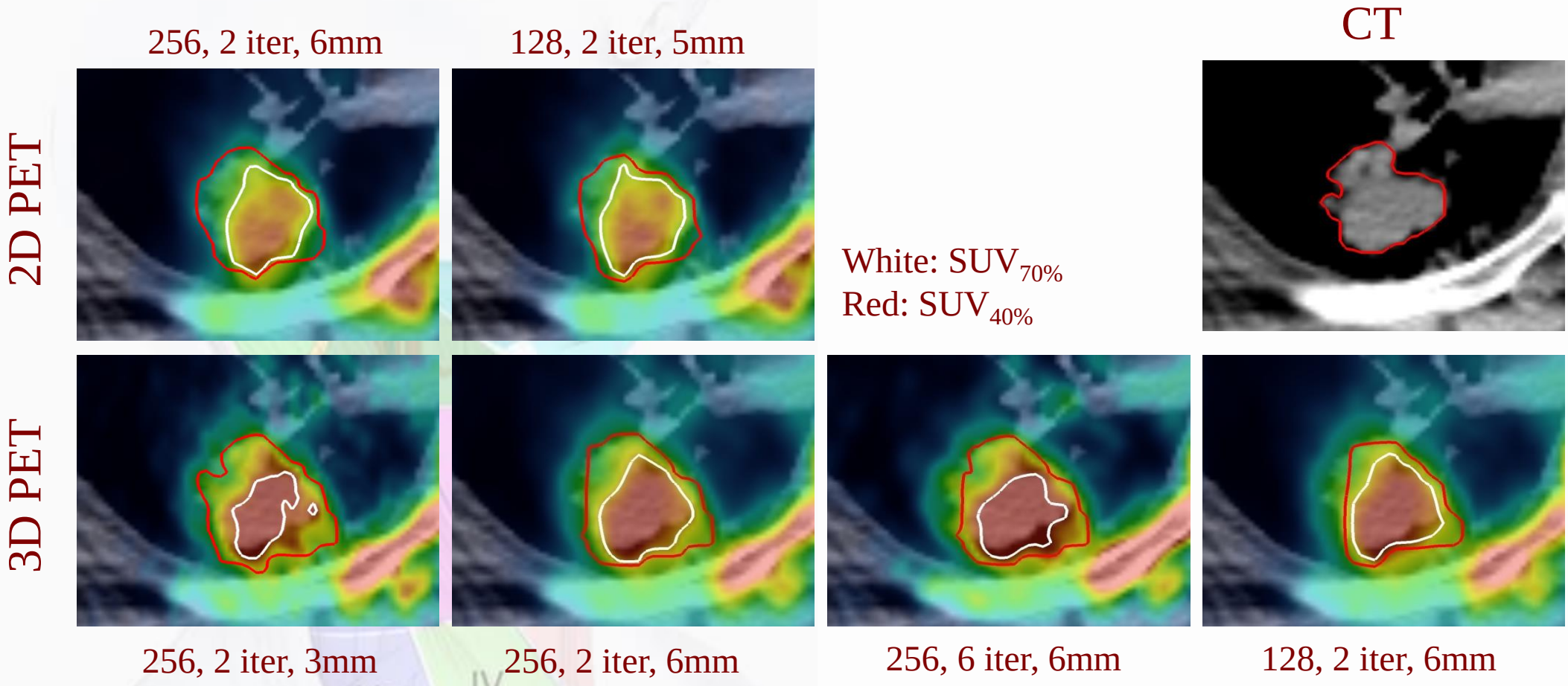
FAZA spatial resolution

Comparison between autoradiogram & pimonidazol



Busk et al Acta Oncol, 2008;47:1201-1210
Busk et al IJRBOP 2008;70:1202-12

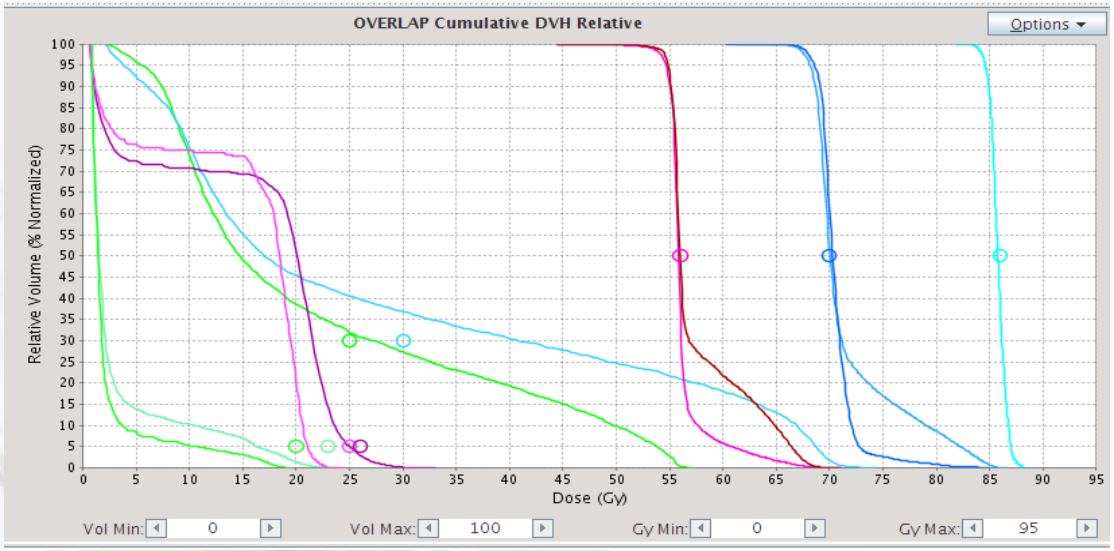
Same imaging acquisition … different reconstruction & segmentation …



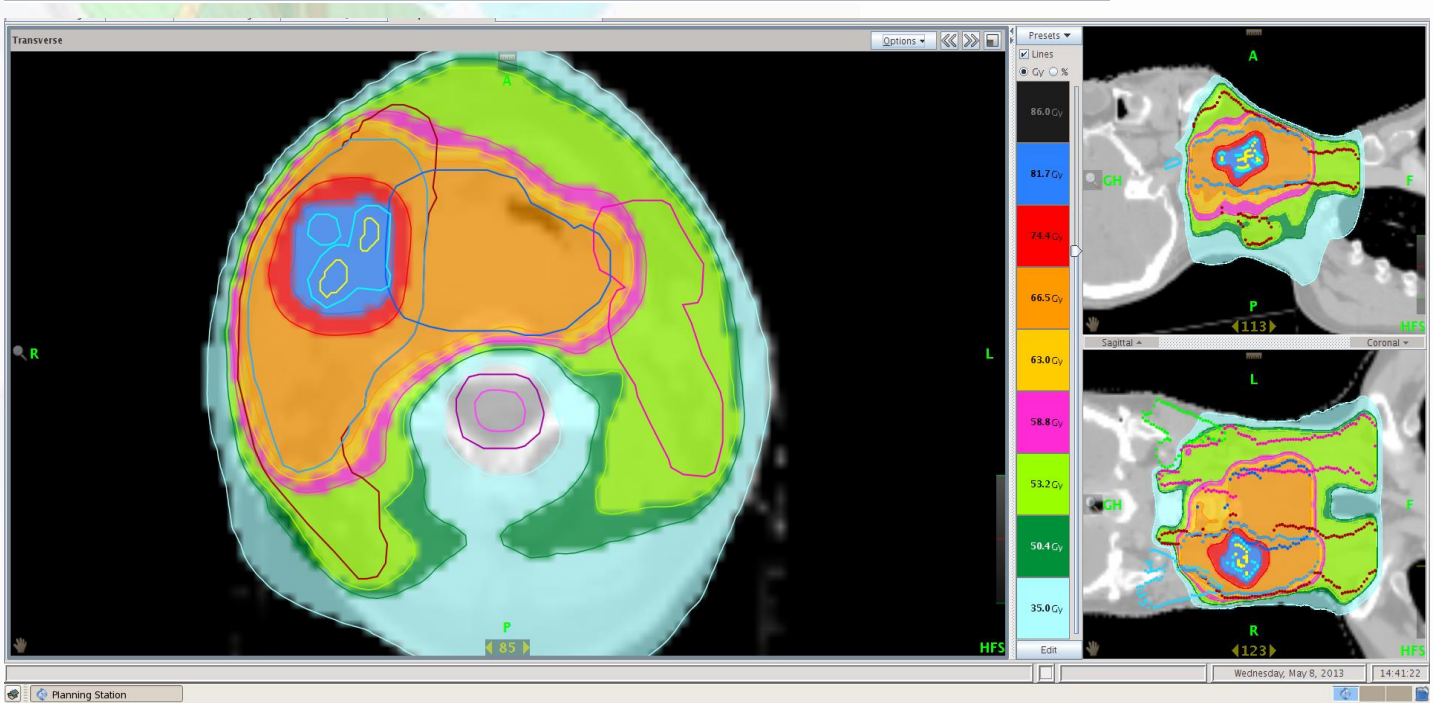
$SUV_{40\%}$: Volume [26-32 cm^3], SUV_{mean} [3.1-4.1]
$SUV_{70\%}$: Volume [4-11 cm^3], SUV_{mean} [3.8-5.3]

Courtesy of R. Jeraj

Hypoxia (^{18}F-AZA) dose painting



"Binary" dose esca-lation, e.g. from 70 to 86 Gy



S. Servagi, 2014

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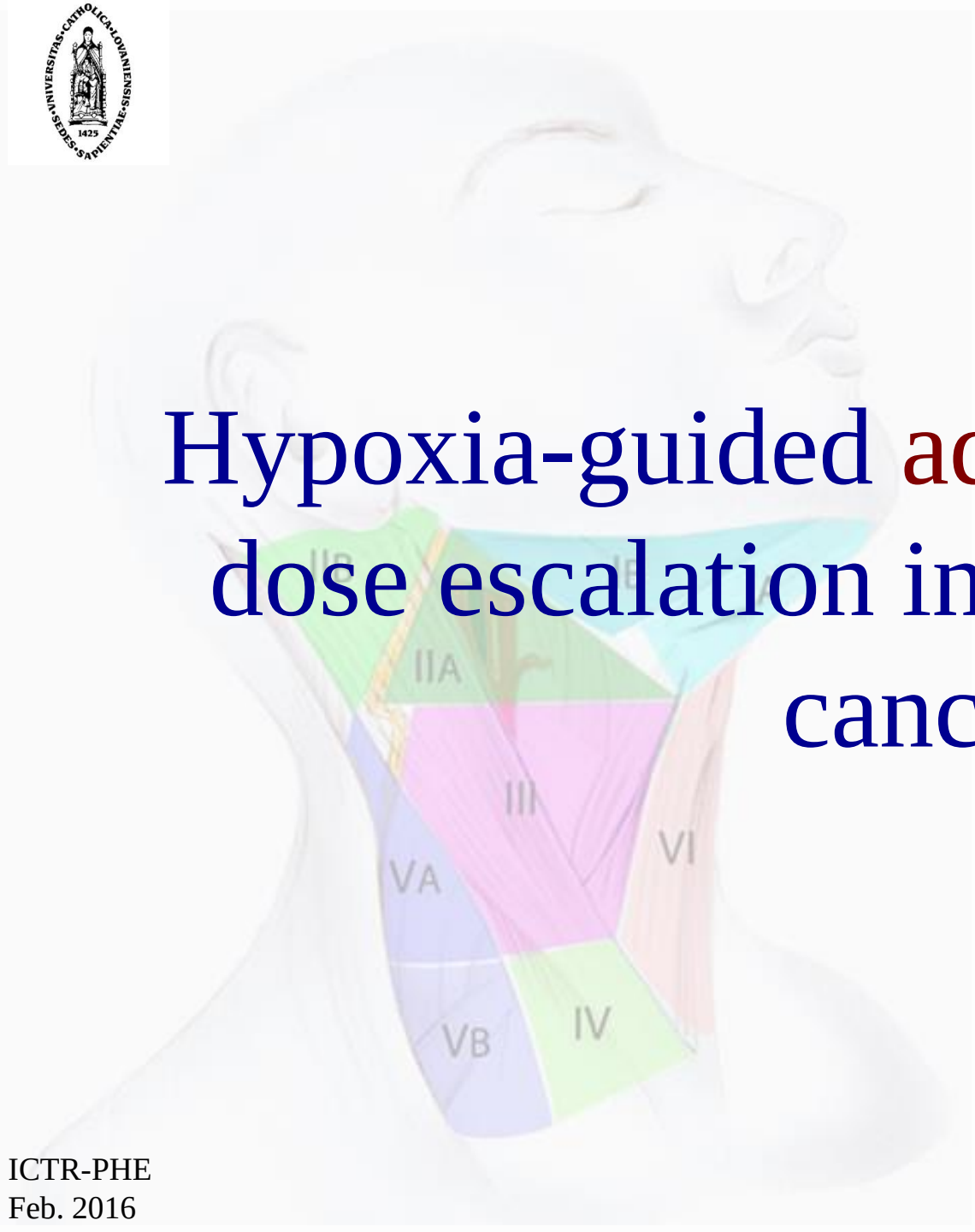

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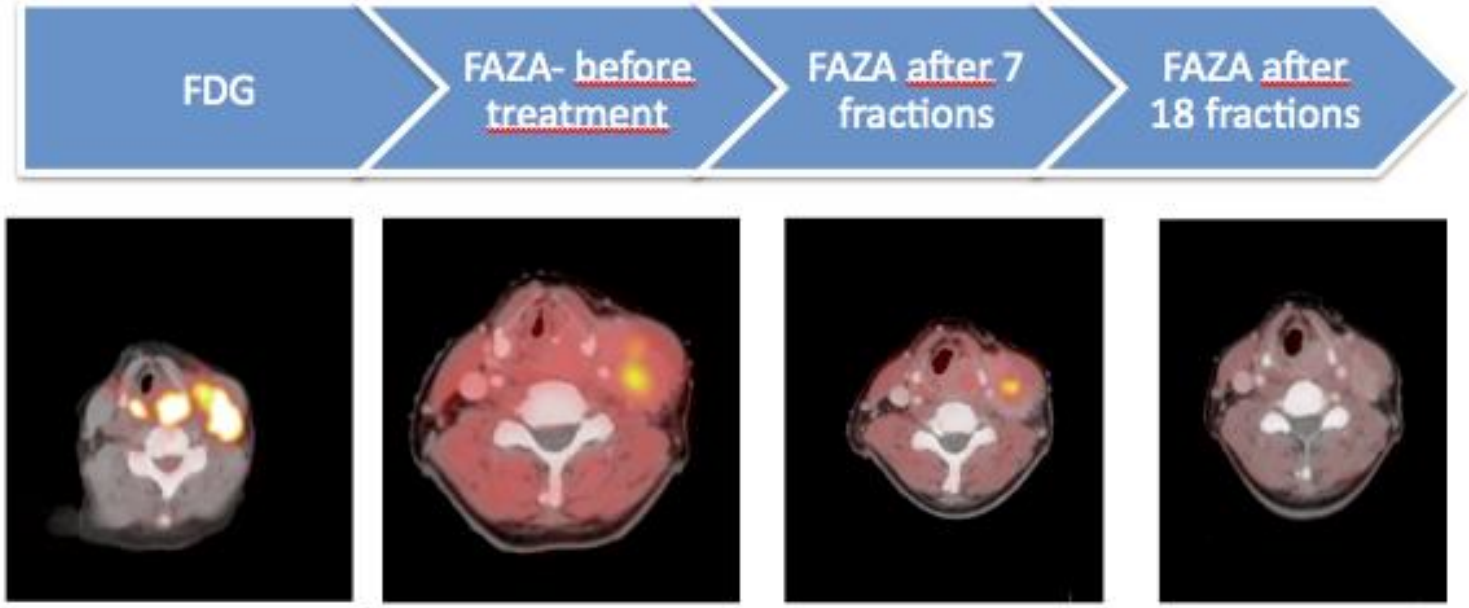
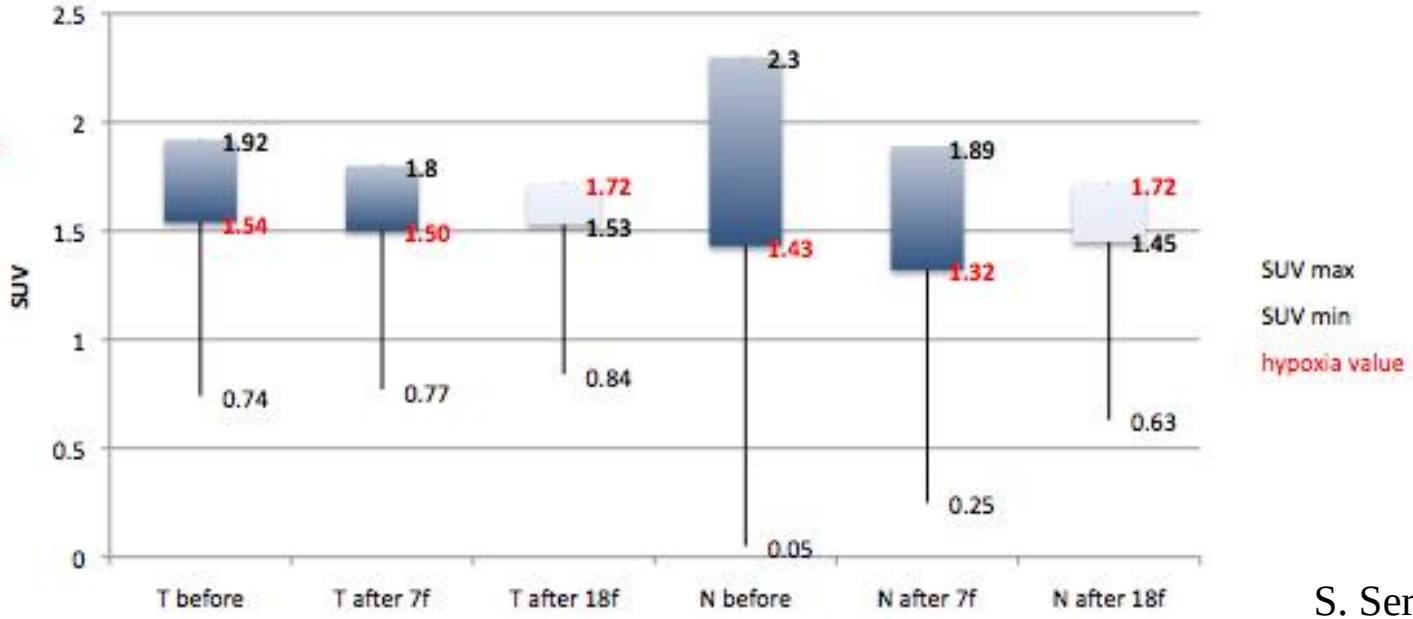
Variation of hypoxia during RT-CH

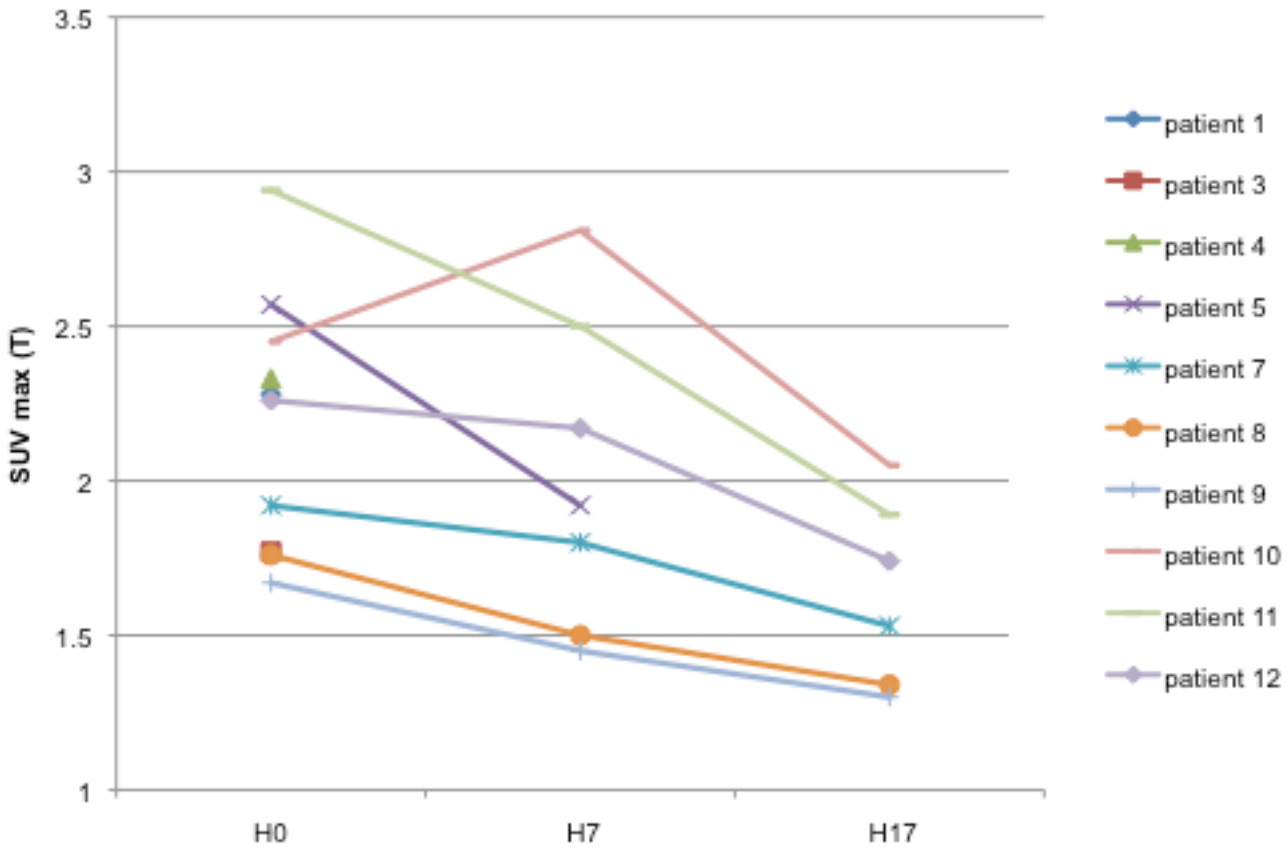


Hypopharynx
T3N2b



S. Servagi, 2014

Variation of hypoxia (^{18}F-AZA) during RT-CH



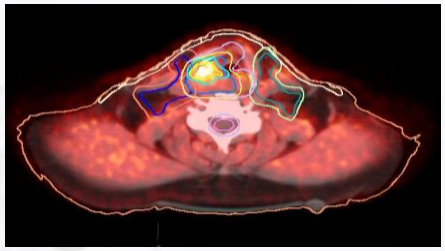
S. Servagi, 2014

Hypoxia (^{18}F-AZA) dose painting

Pre-treatment	Week1	Week2	Week3	Week4

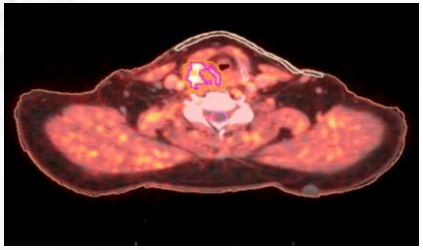
PET

PET $H_{n=0}$



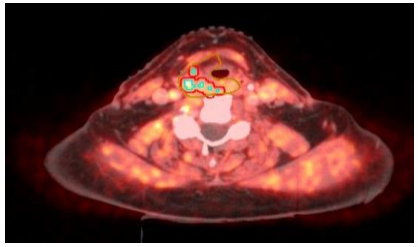
GTV $H_{n=0}$

PET $H_{n=7}$



GTV $H_{n=7}$ =
GTV $H_{n=7}$ - GTV $H_{n=0}$

PET $H_{n=17}$



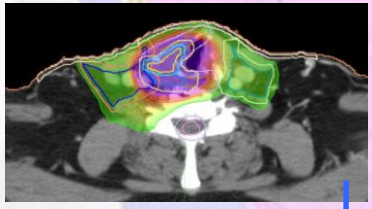
GTV $H_{n=17}$ =
GTV $H_{n=17}$ - GTV $H_{n=7}$ - GTV $H_{n=0}$

PTVs

PTVs = GTVs H + 2.5 mm

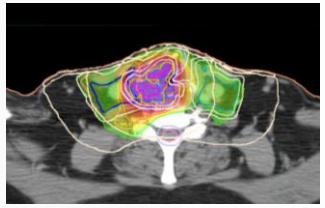
Dose planned

PTV $H_{n=0}$: 86 Gy
(2.46 Gy/f)



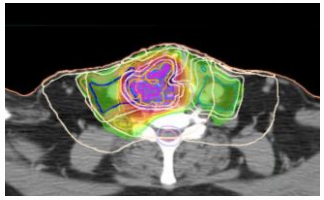
Fractions 1 – 7

PTV $H_{n=7}$: 89.95 Gy
(2.57 Gy/f)



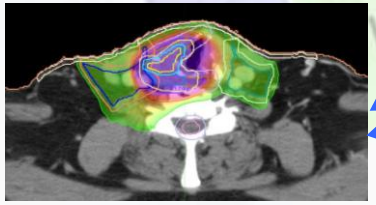
Fractions 8 - 17

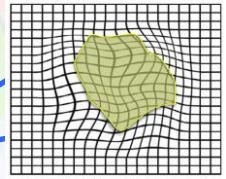
PTV $H_{n=17}$: 101.15 Gy
(2.89 Gy/f)



Fractions 18 - 35

Add dose





Anti-chronological dose summation

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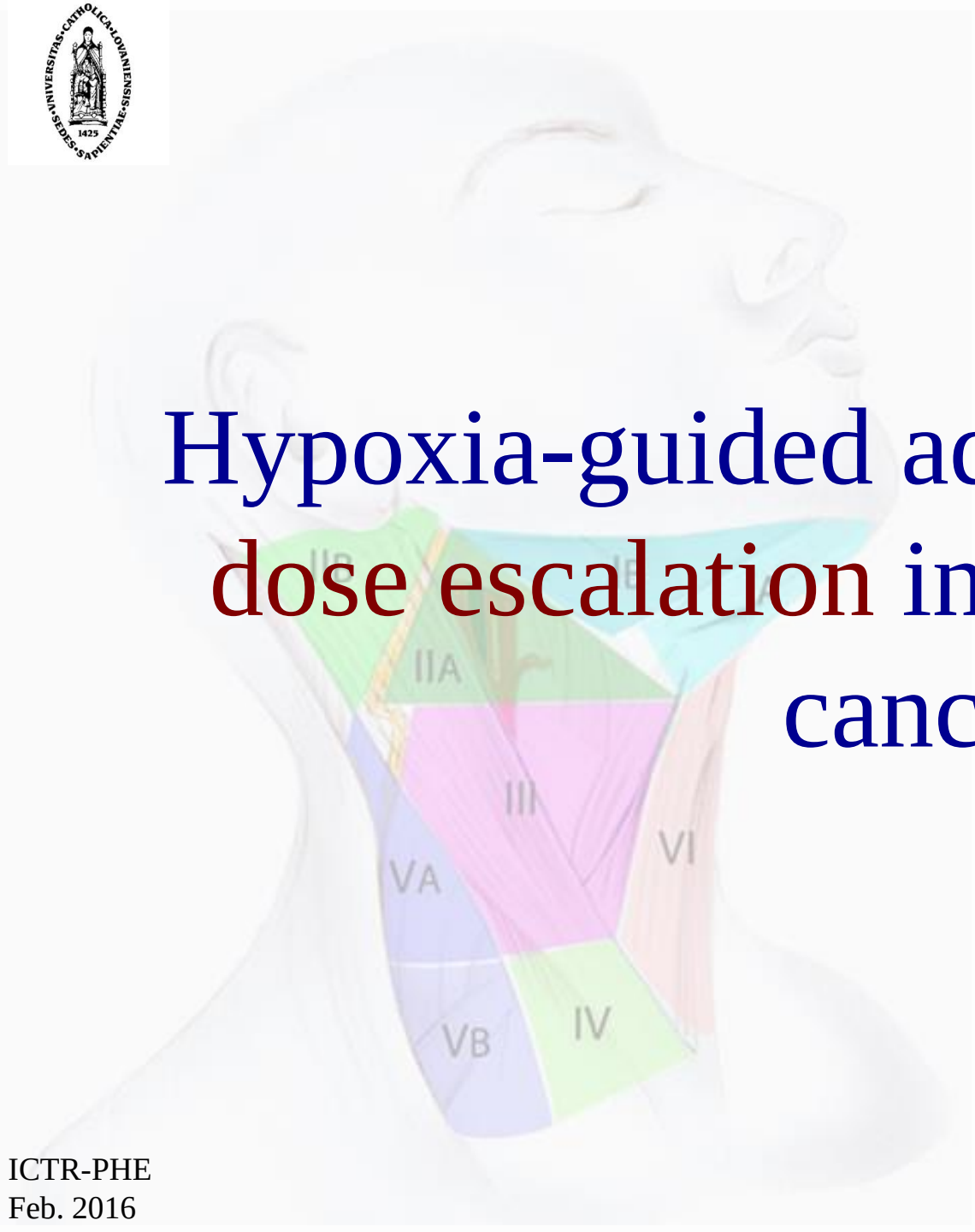

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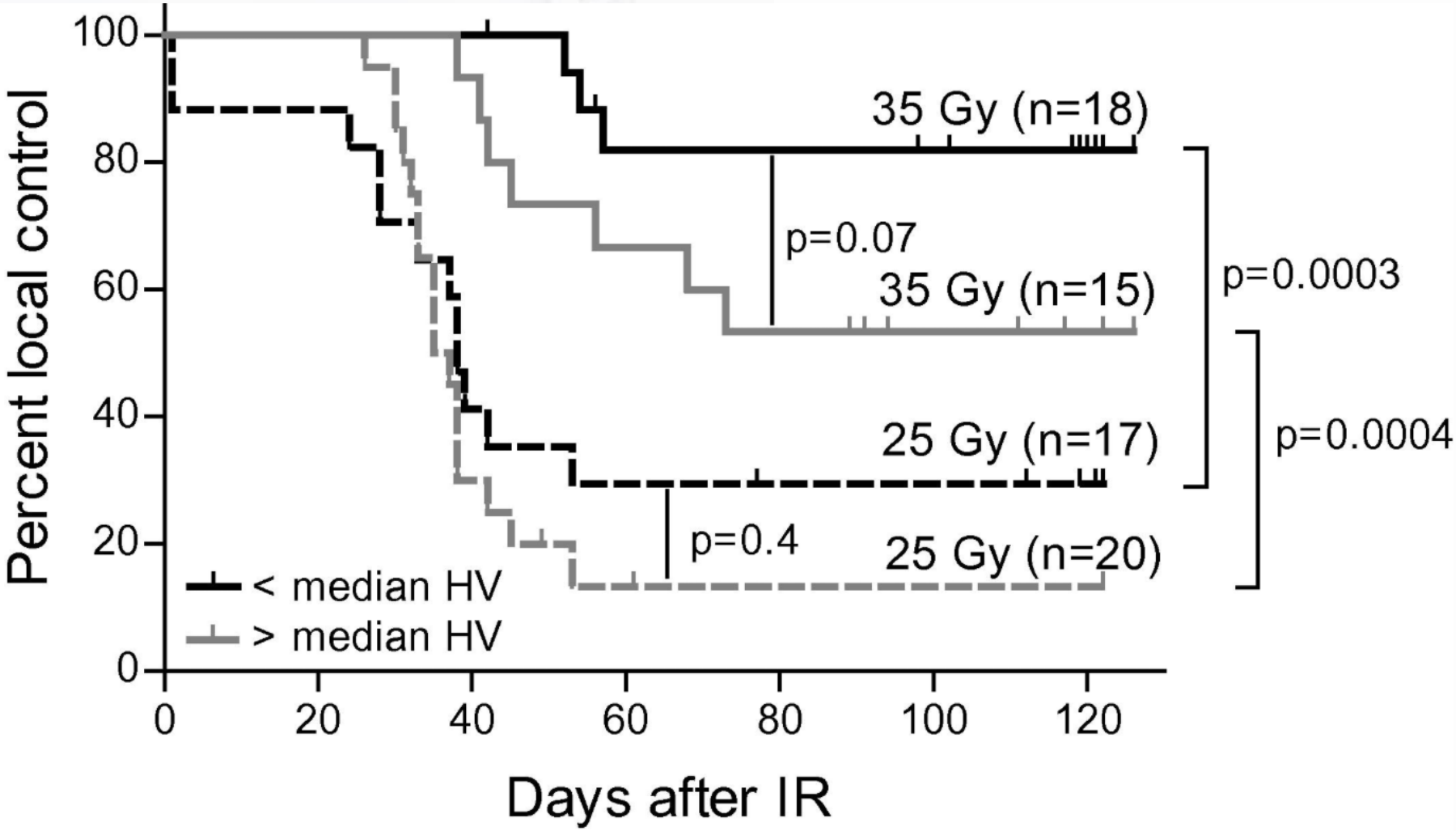
Dose escalation *in vivo*

Comparison between hypoxic and non-hypoxic tumor in FaDu tumors imaged with F-Miso PET



Schütze et al, R&O, 2014

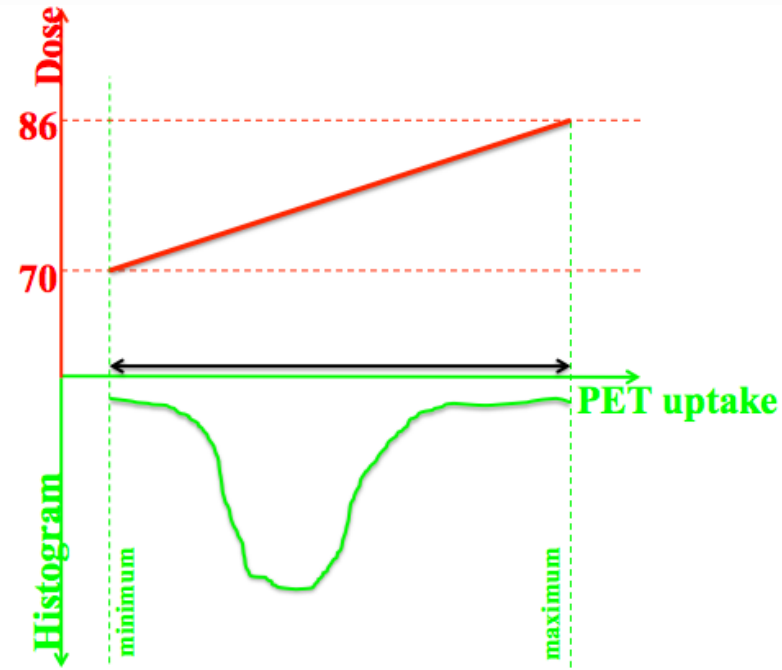
Dose painting: dose prescription function

"Radiosensitivity"

Dose Prescription for Dose Painting by Numbers

The simplest, reasonable, voxel-based prescription function is a linear interpolation between a minimum dose, D_{min}, and a maximum dose D_{max} when the voxel image intensity, I, varies between its lower and upper bound, I_{min} and I_{max} within the target volume[9,89]:

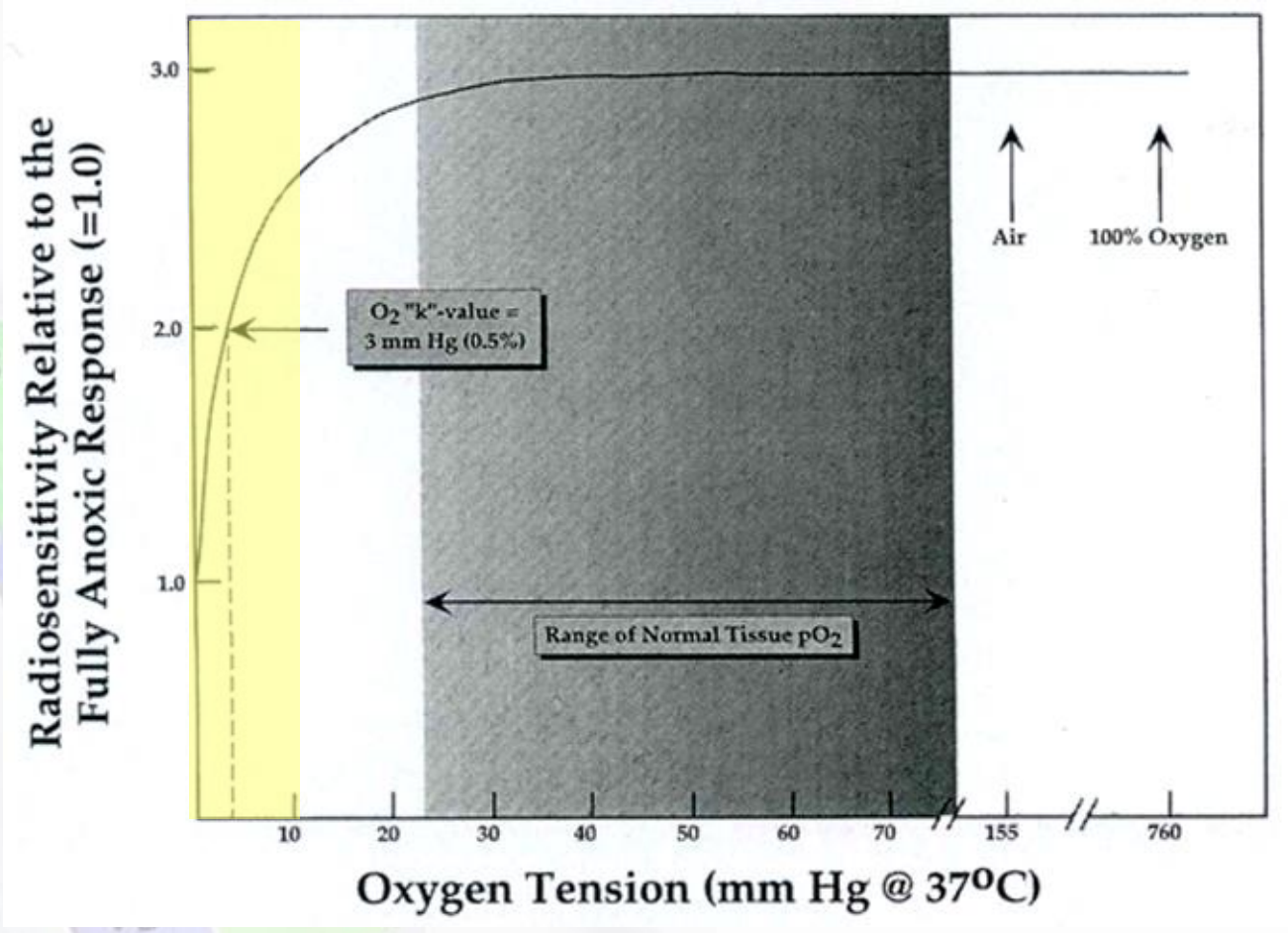
$$D(I) = D_{min} + \frac{I - I_{min}}{I_{max} - I_{min}} \cdot (D_{max} - D_{min})$$



Vanderstareten, 2006

Dose painting: dose prescription function

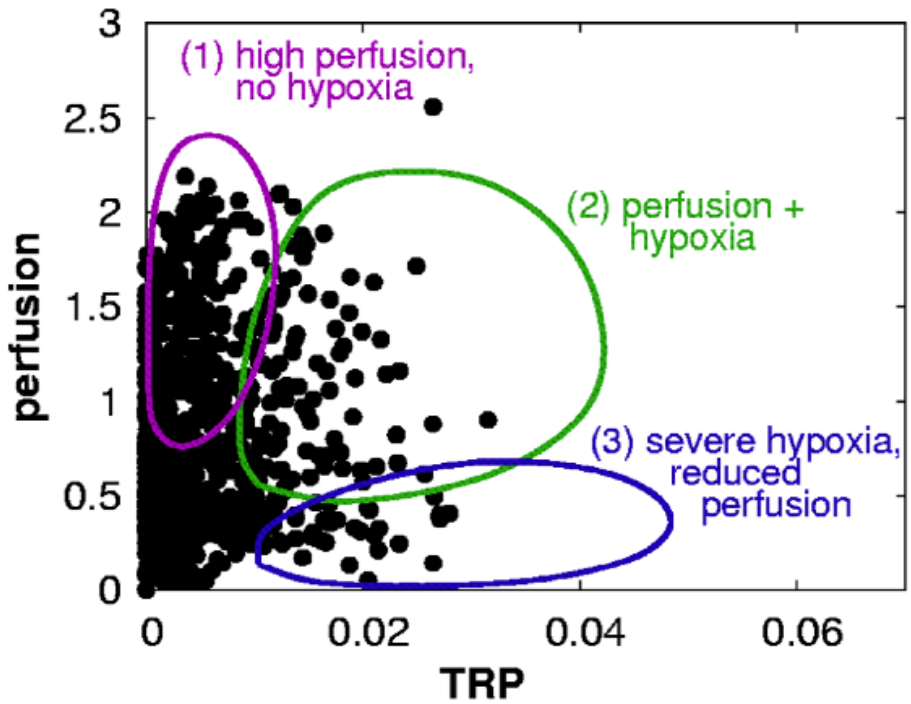
Hypoxia

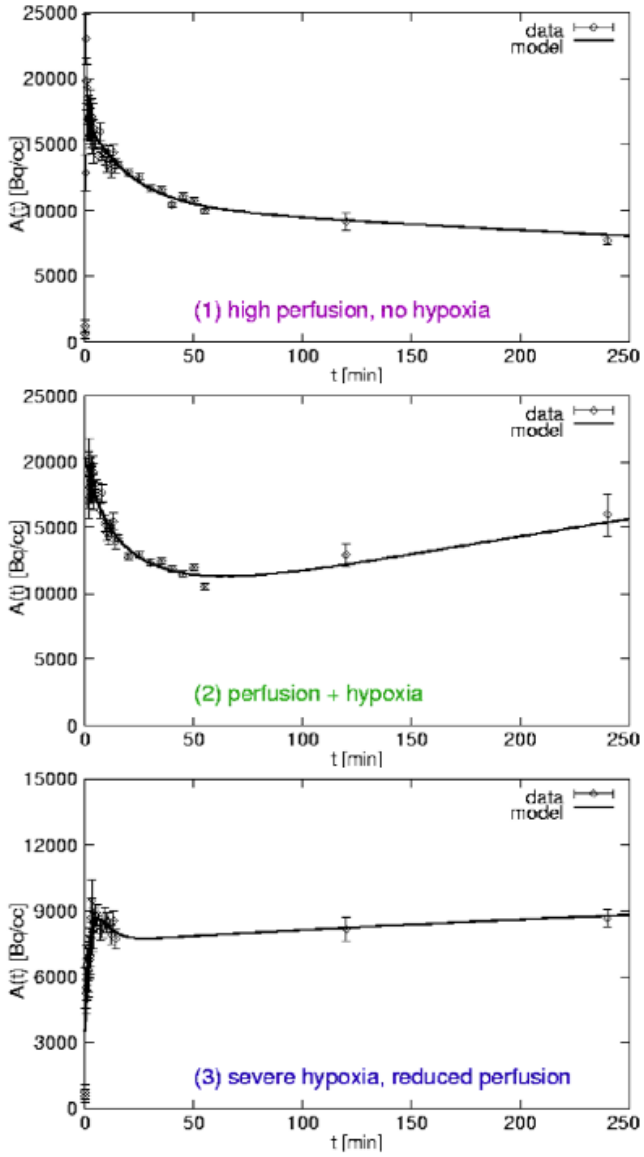


PET tracer range

From Zeman, 2000

Dose painting: dose prescription function

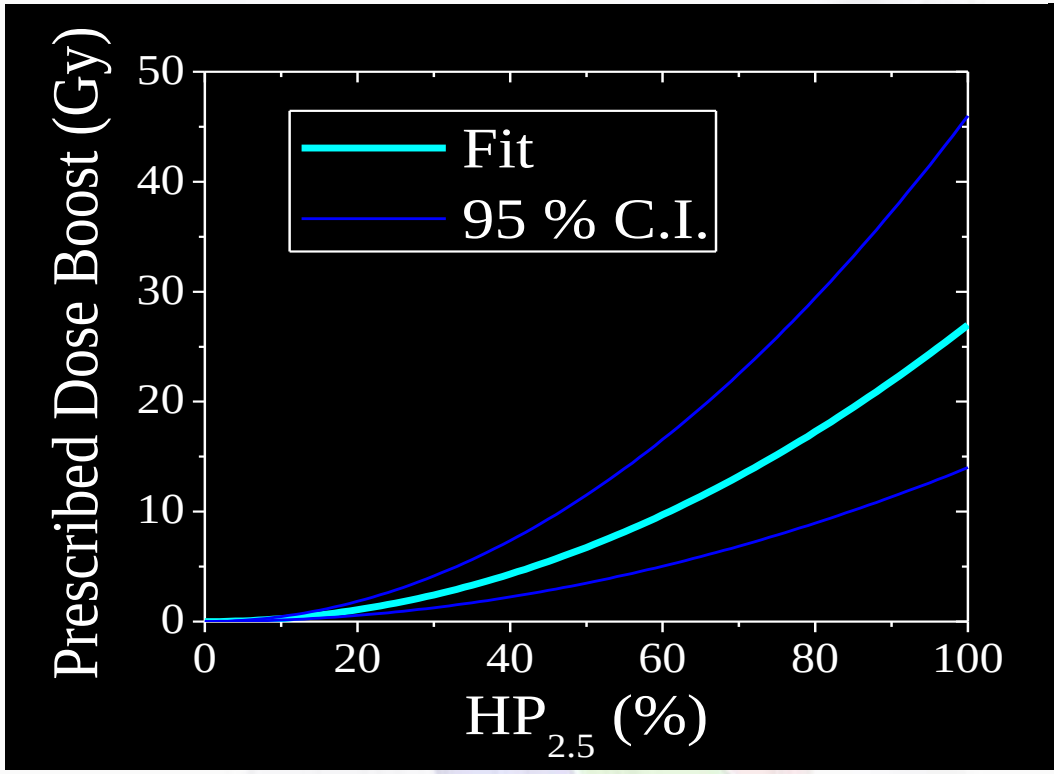


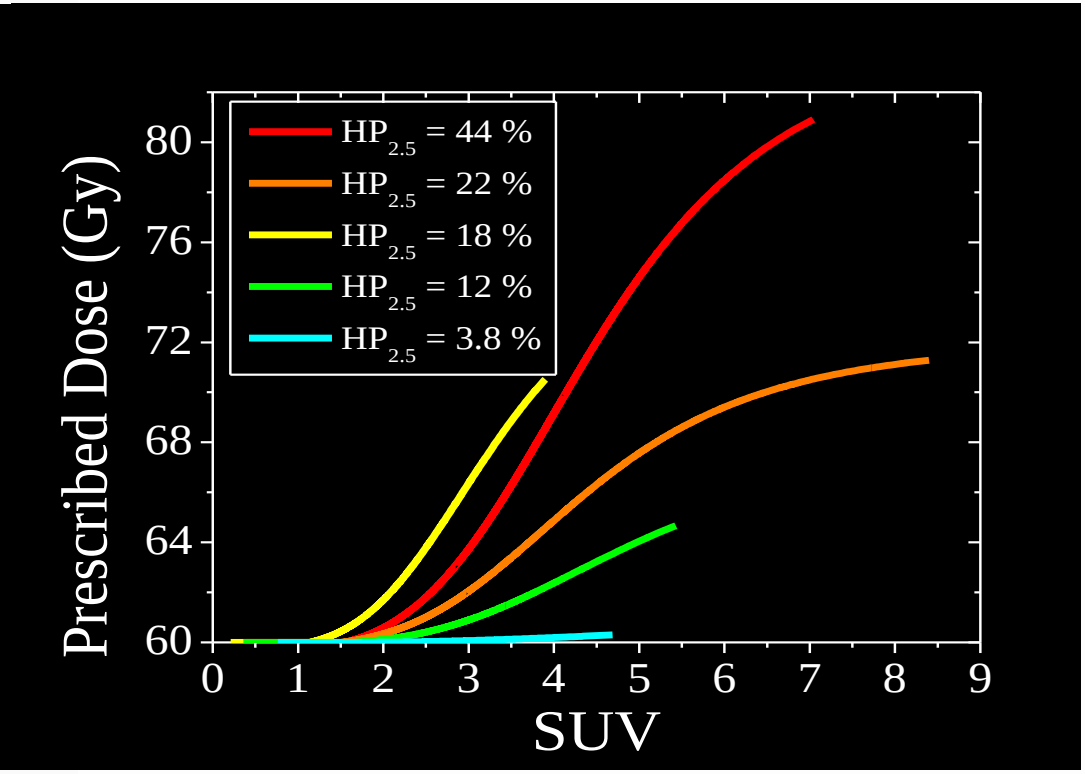


- 15 pts with stage IV HNSCC
- 70 Gy IMRT or 3D-CRT ± CH
- Dynamic F-Miso PET

Thorwarth et al, BMC Cancer, 2005

Molecular imaging dose prescription function (hypoxia)





R. Jeraj, submitted 2011

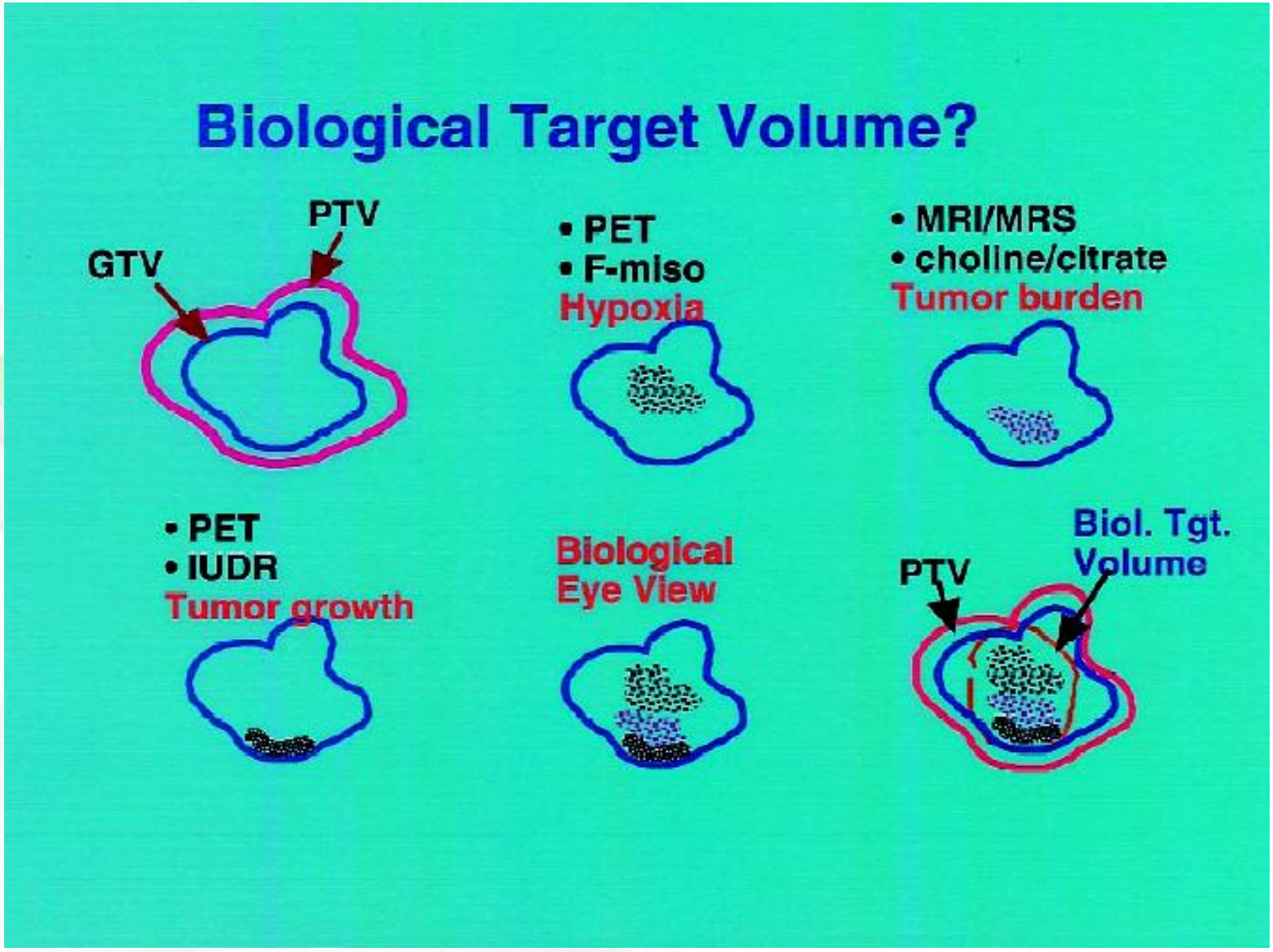
Randomized trials on dose painting / dose escalation in locally advanced HNSCC

Acronym	Stage	Molecular imaging	Design	Due date
De Neve*	II-IV	FDG-PET	Std IMRT >< dose escalation IMRT	Dec 2015?
Escalox (Munich)	III	F-Miso PET	70 Gy + CDDP (w1, w5) >< 80.6 Gy + CDDP (w1, w5)	> July 2015
Baumann* (Dresden)	III-IV?	F-Miso PET	Δ 10% between 2 arms	To start in 2016
Xuzhou Medical College, China	III-IV§	F-Miso PET and FDG-PET	RT-CH >< dose escalation on FDG >< dose escalation on F-Miso	June J015?

§ nasopharyngeal carcinoma
* randomized phase-II

ClinicalTrials.gov, February 2016

In 2000 …



C.C. Ling, 2000

And in 2015 … ?

Dose painting is like Teenage Sex …

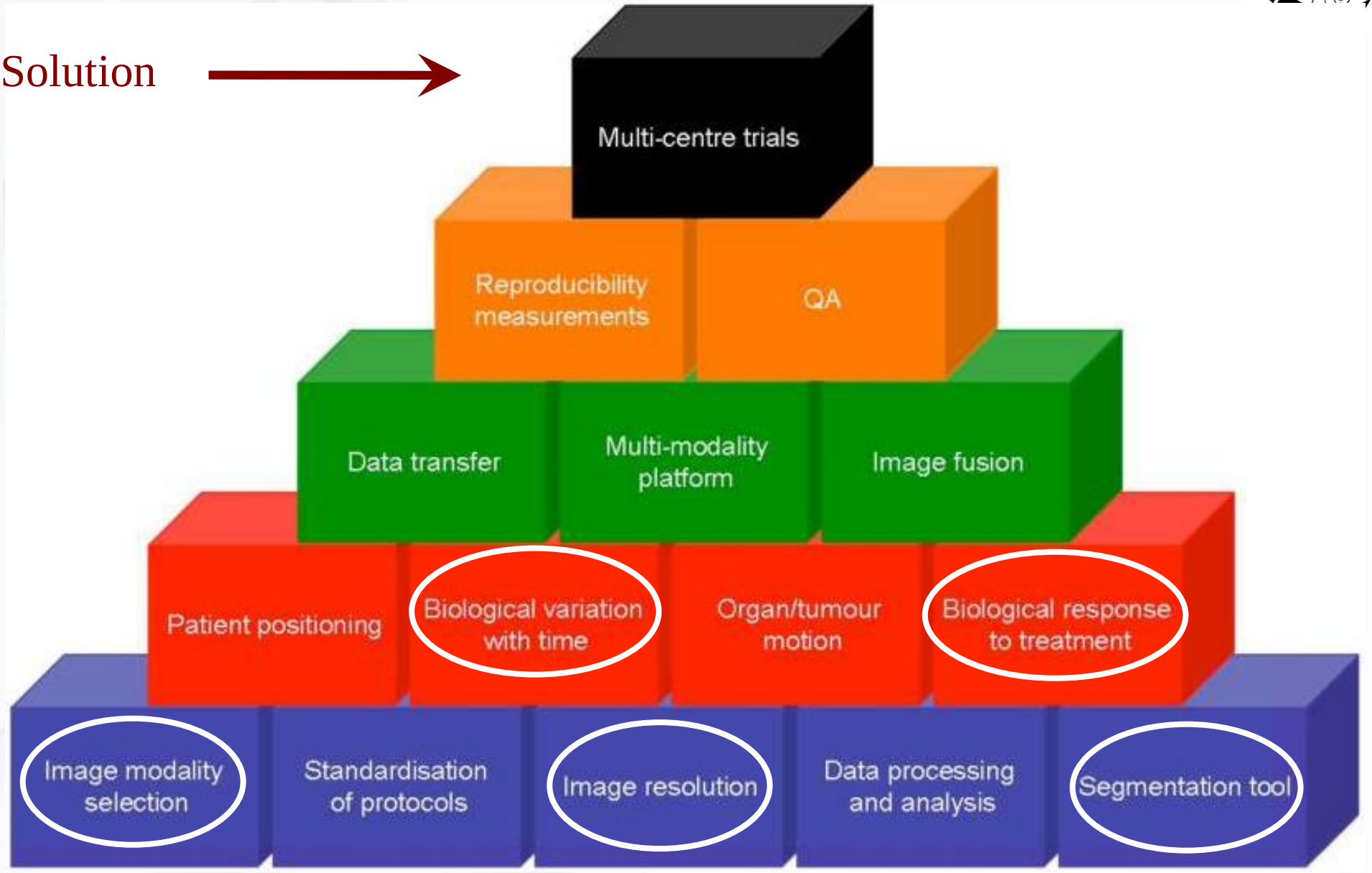
It is on everybody's mind all the time,
Everyone is talking about it all the time,
Everyone thinks everyone else is doing it,
Almost no one is really doing it,
The few who are doing it are doing it poorly,
Sure it will be better next time,
Not practicing it safely.

Joseph Ting, PhD
Emory Clinic

Molecular imaging in radiotherapy planning

Solution →

Challenges



Newbold, 2012