Advances in models of quantitative imaging: validation, predictive power and clinical trials

Vitali Moiseenko, PhD, FCCPM

AAPM, Indianapolis, August 2013

Department of Radiation Medicine and Applied Sciences
University of California, San Diego
La Jolla, California

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OUTLINE

Can we image for biological properties? Validation?
- Hypoxia in tumours
- Cell Density

Do biological properties affect outcomes?
- Local control as a function of volume deemed hypoxic

Do not forget normal tissue

- Dose boost
- Change the property

Clinical evidence?
- One arm clinical trial vs. historical data
- Randomized trial

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Current state

- CT: e^- density + 3D data for planning, delineation of target volumes and organs at risk, DRRs for verification
- MRI: soft tissue contrast, leakage of blood
- PET: metabolic activity

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Validation

- Mechanistic explanation
  - FLT
- Independent measurement
  - Eppendorf probe
- Inferred, e.g., absence of X means presence of Y
  - Lack of perfusion equal hypoxia

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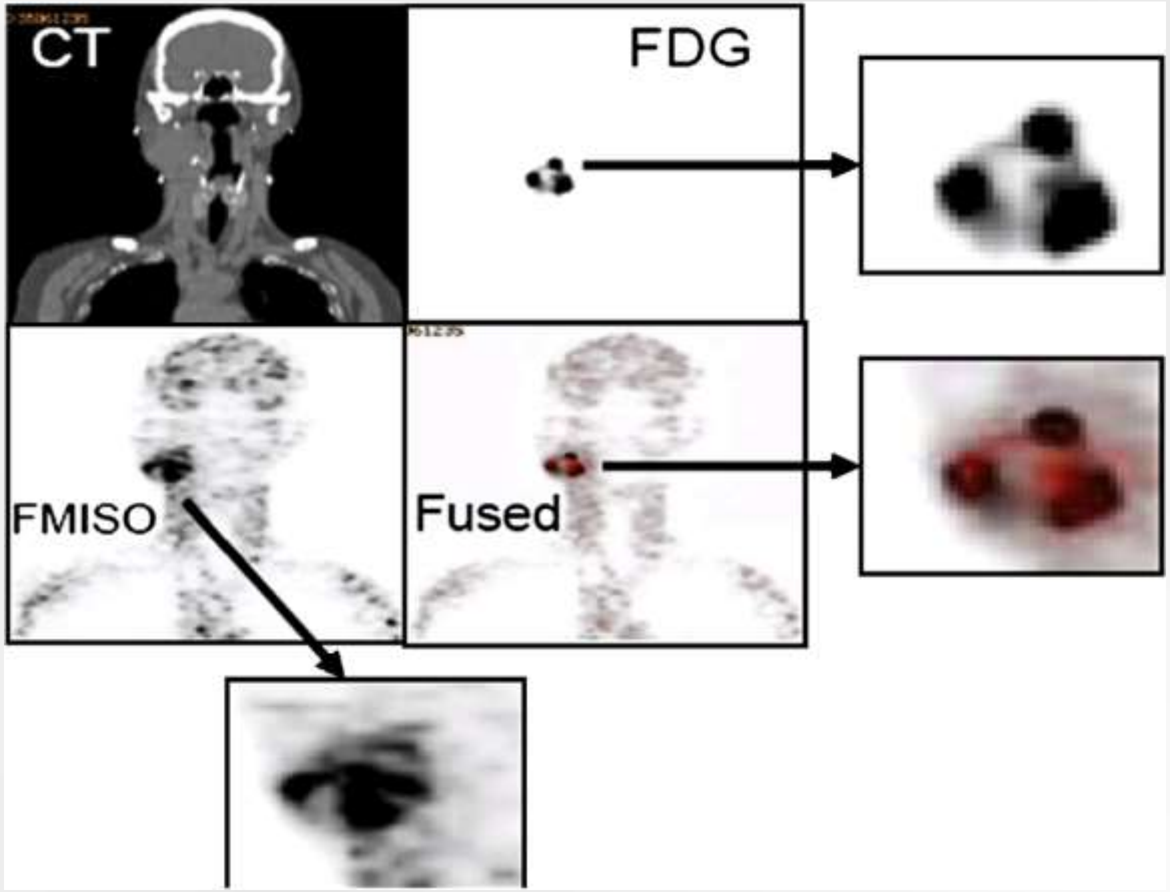
Imaging for hypoxia



Lee et al. 2008

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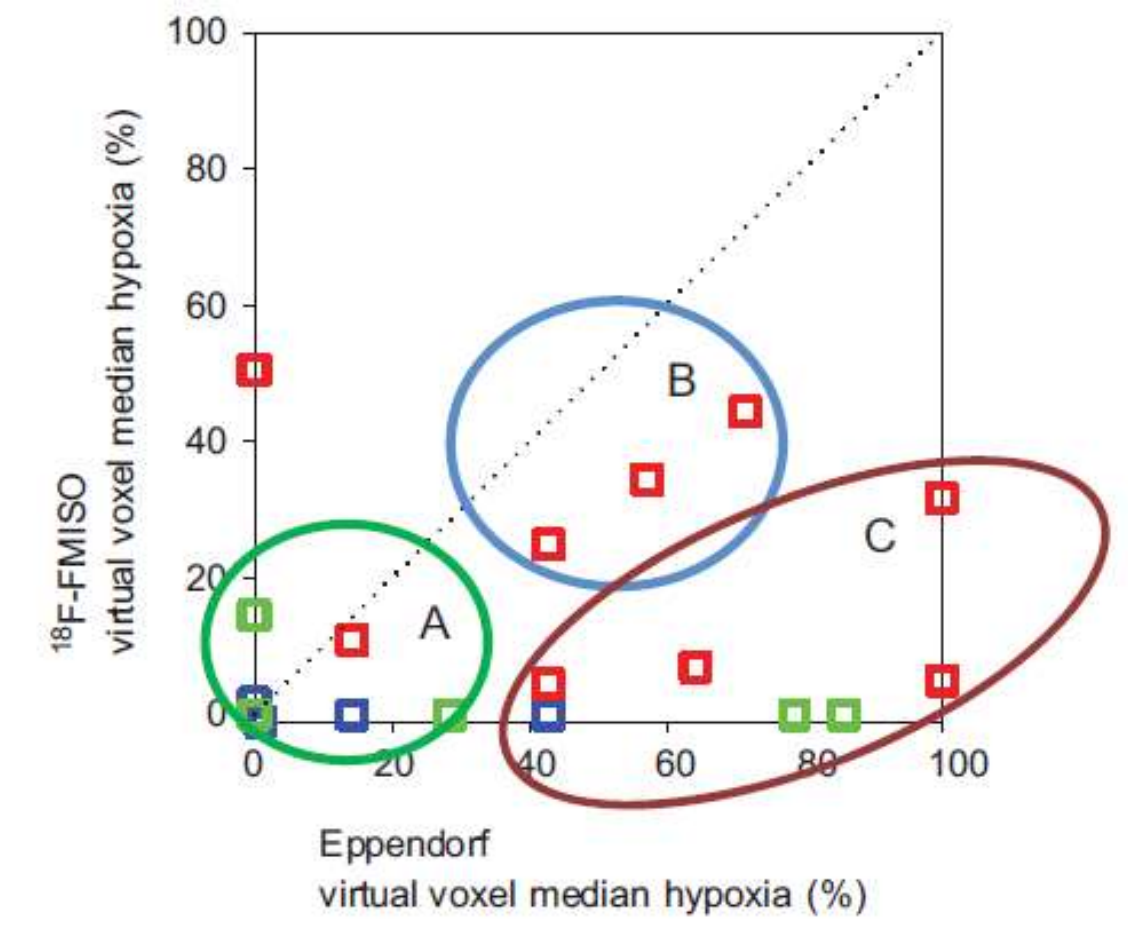
Imaging for hypoxia



- HNSCC
- Benign tumors
- Soft tissue tumors

Mortensen et al. 2010

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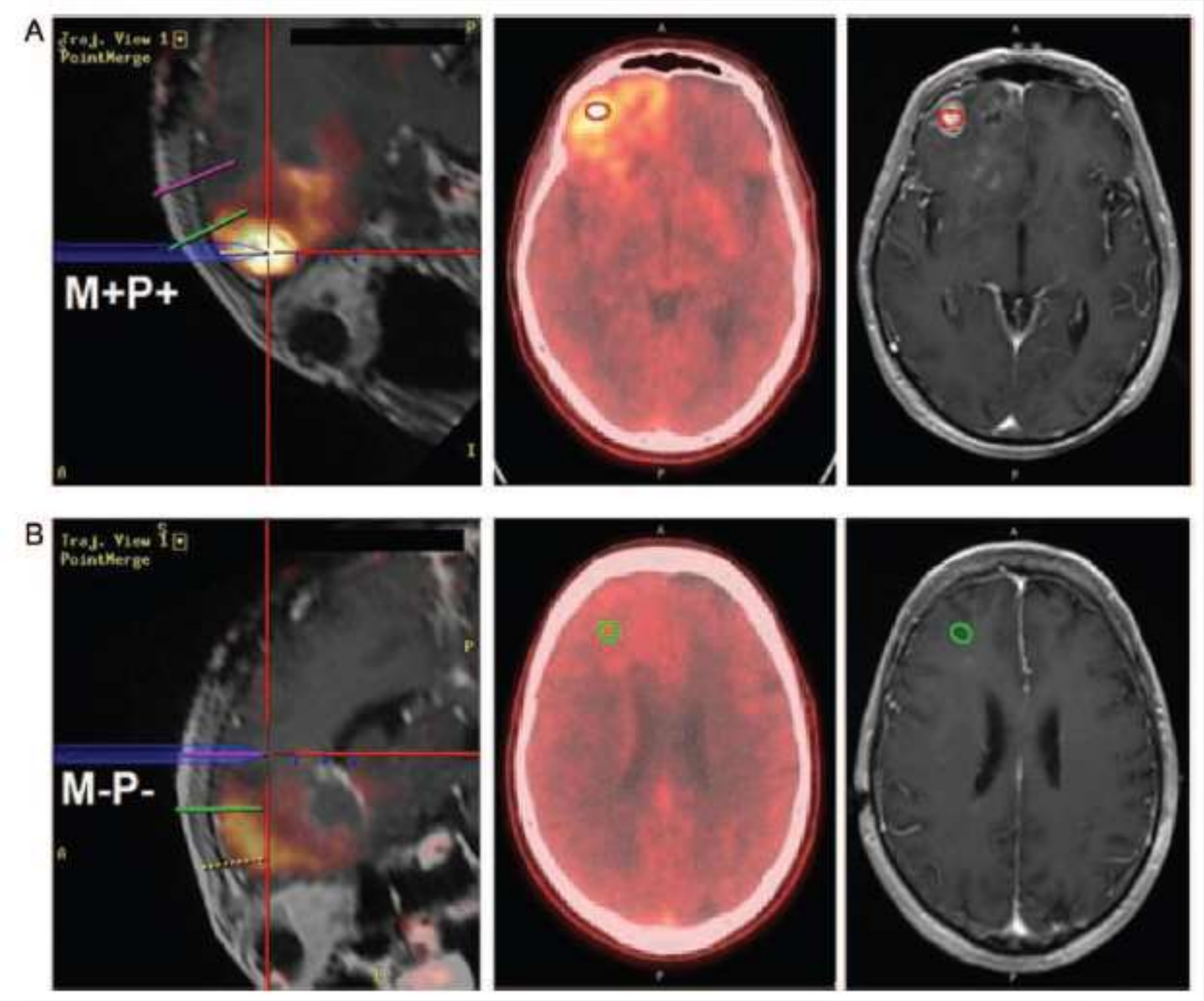
^{18}F-DOPA for glioma imaging



- M+/- T1 contrast enhancement/ no enhancement
- P+/- PET uptake/ no visible uptake

Pafundi et al. 2013

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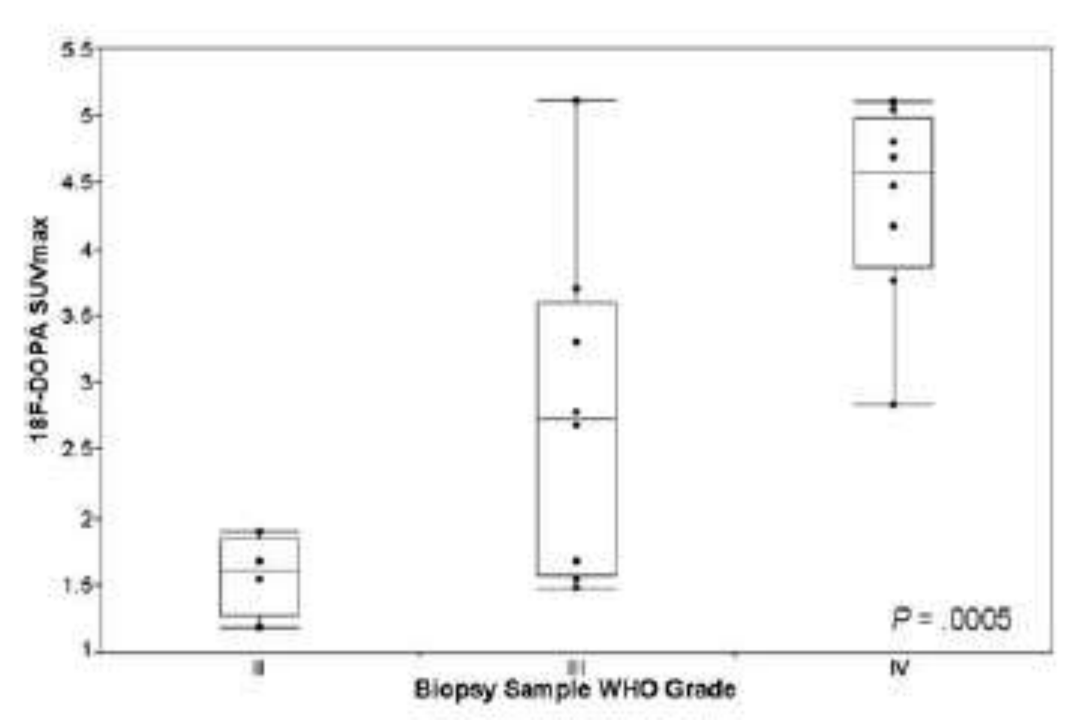
^{18}F-DOPA for glioma imaging



M+P+	IV	Astrocytoma (GBM)
M−P−	II	Astrocytoma
M−P+	IV	Astrocytoma (GBM)
M+P+	IV	Oligoastrocytoma
M−P+	II	Oligodendroglioma
M−P+	II	Oligodendroglioma
M−P−	No tumor	No tumor
M+P+INF	IV	Astrocytoma (GBM)
M+P+ANT	IV	Astrocytoma (GBM)
M+P+SUP	IV	Astrocytoma (GBM)
M−P−	II	Astrocytoma

Pafundi et al. 2013

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PET as predictor

Primary Tu… e (SUV_{max})
Measured … n Emission
Tomography … ue for Survival
in N… CLC)

A Systematic Re… European Lung
Cancer Workin… Staging Project

Thierry Ber… mans, MSc,‡
Claude Hoss… taigne, MD,¶
Arnaud Scherp… Moreau, MD,‡
*Martine Roelan… ert, MD, PhD,**
Edward F. Patz, Jr, M… ul Sculier, MD, PhD||||*

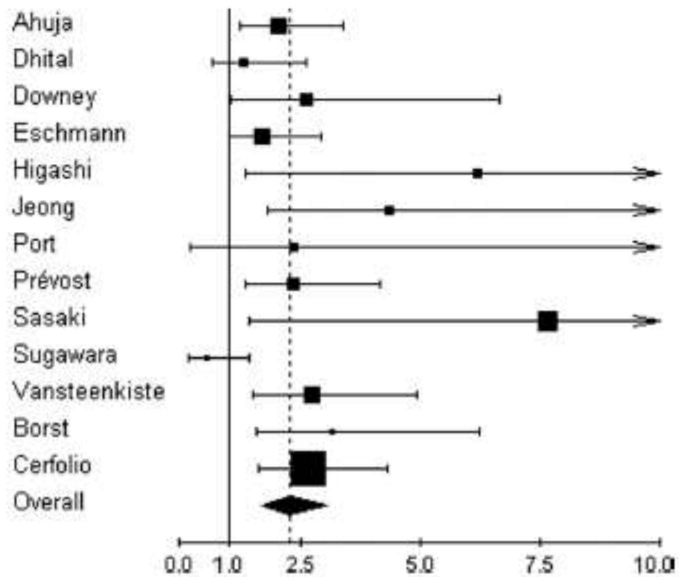

FIGURE 1. Graphical representation of the prognostic role of primary tumor SUV on survival in lung cancer. HR and 95% confidence interval (CI) for survival comparison in studies evaluating primary tumor SUV in lung cancer. HR >1 implied a survival benefit for reduced primary tumor SUVmax. The square size is proportional to the number of patients included in the study. The center of the diamond-shaped lozenge at the bottom of the figure gives the combined HR of the meta-analysis and its extremities the 95% CI HR = 2.27; 95% CI 1.70–3.02 (random-effect model). Total number of patients: 1474. SUV = standardized uptake value.

JTO, 2008

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PET as predictor

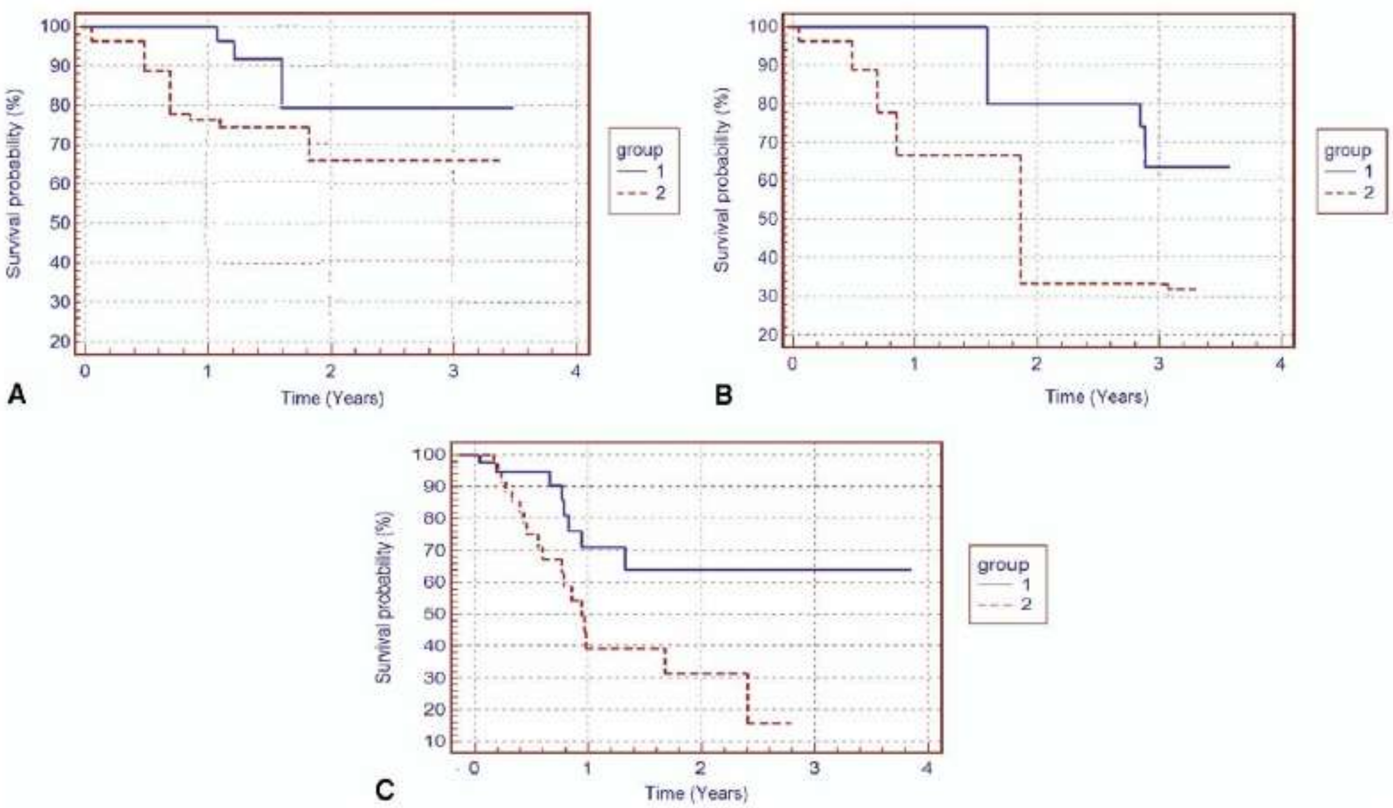

Figure 3. Kaplan-Meier curves depicting the actual survival for patients with a low maximum SUV compared with those with a high maximum SUV stratified by stage. *Group 1*, Patients with a maximum SUV lower than the median maximum SUV in that stage (low maximum SUV group). *Group 2*, Patients with a maximum SUV greater than or equal to the median maximum SUV in that stage (high maximum SUV group). A, Stage Ib NSCLC (*P* = .048); B, stage II NSCLC (*P* = .028); C, stage IIIA (*P* = .0120).

Cerfolio et al. 2005

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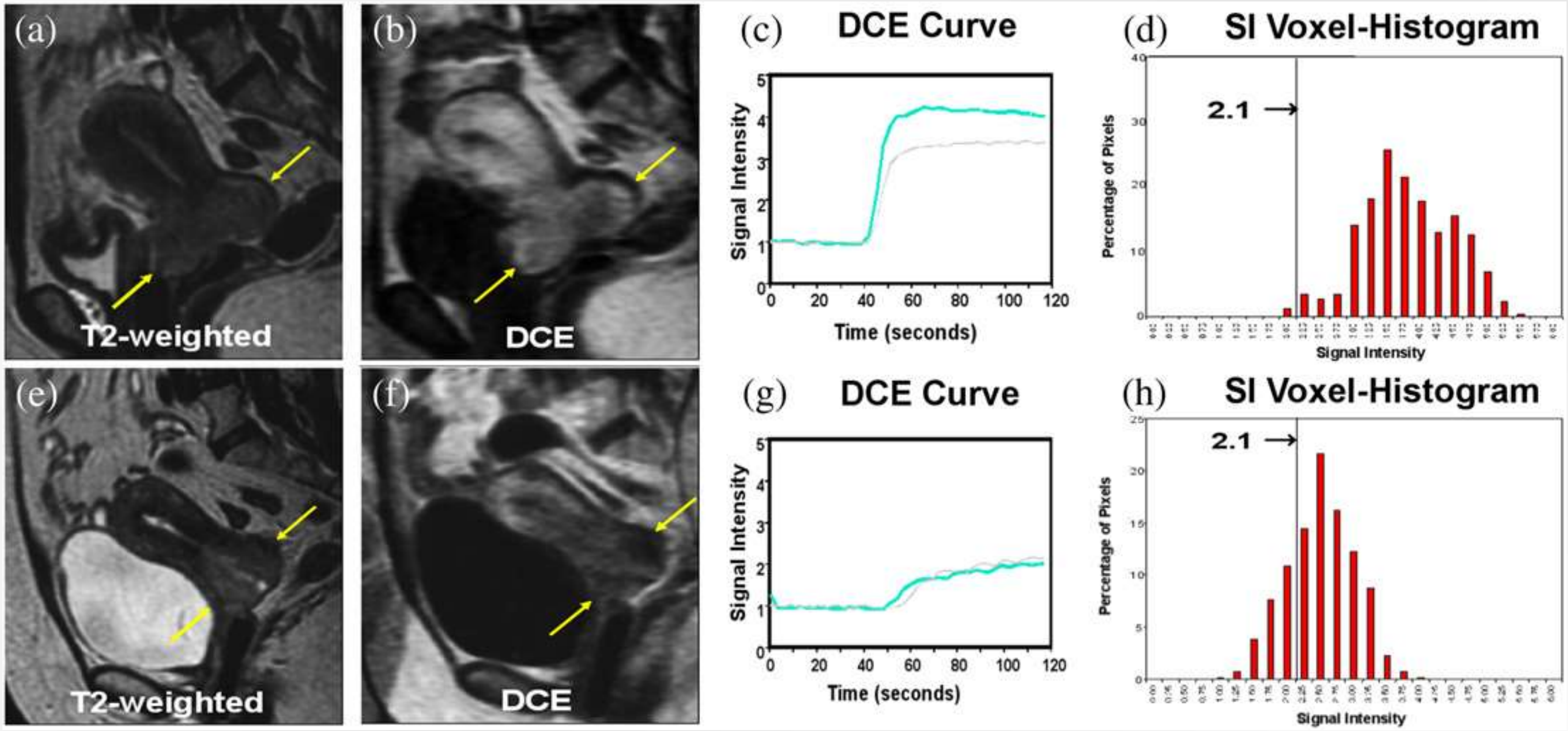
Imaging for hypoxia



Cervical cancer pts dynamic contrast-enhanced MRI, a-d: pt with voxels showing good perfusion after 2 weeks of RT; e-h poor perfusion. Grey lines (c, g) pre-RT, blue lines – 2 weeks into RT

Mayr et al. 2012

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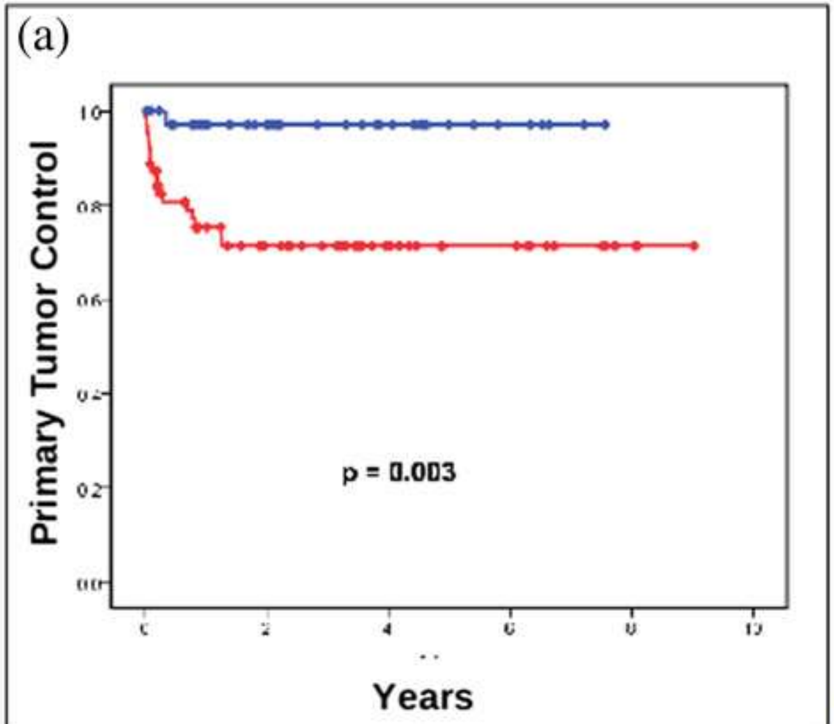
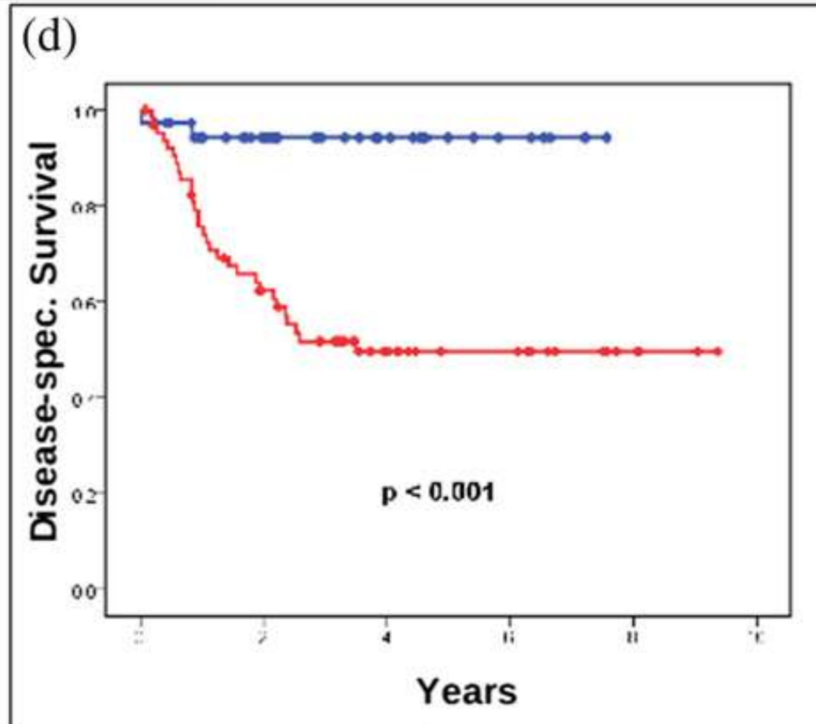
Does it matter?



FRV$_1$



DCE-MRI prior to RT

Mayr et al. 2012

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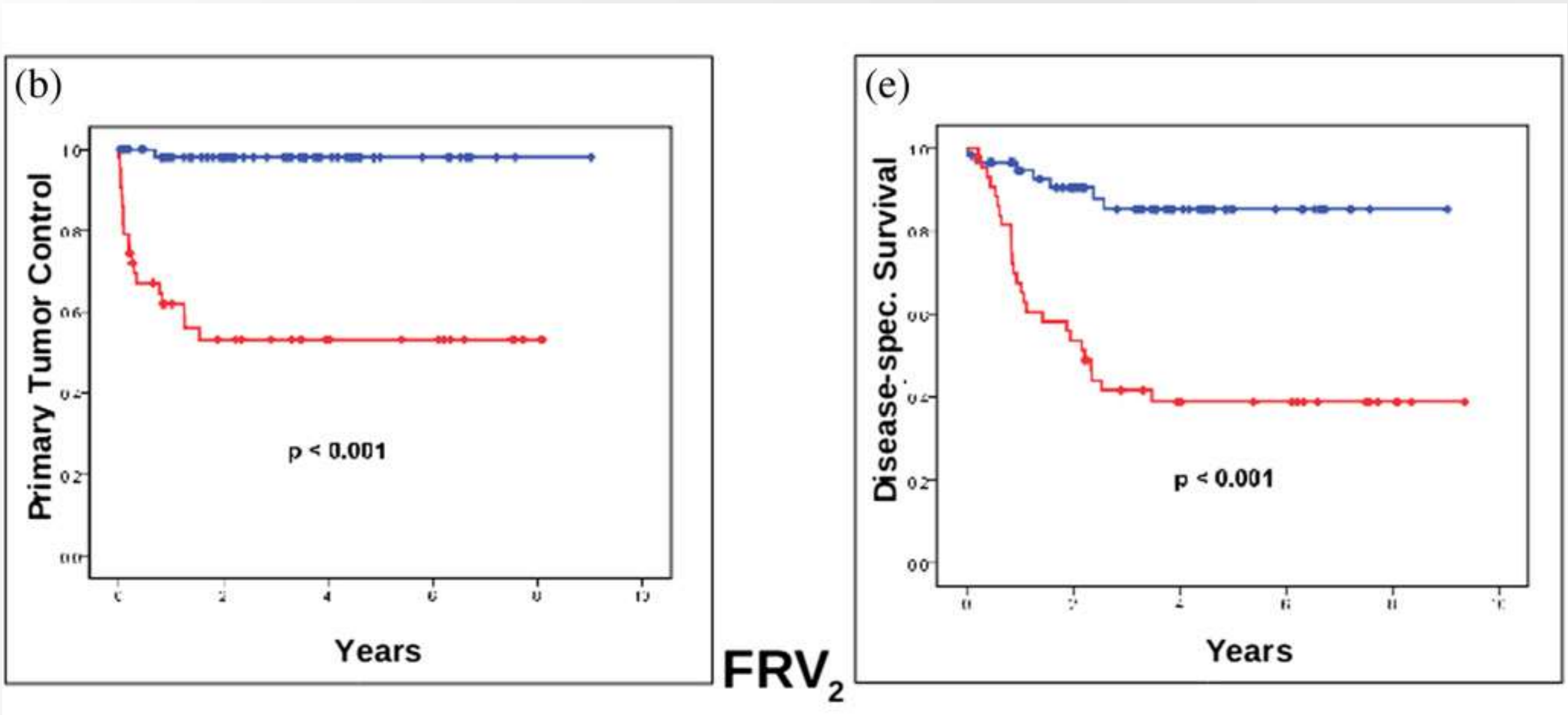
Does it matter?



DCE-MRI after 2 weeks of RT

Mayr et al. 2012

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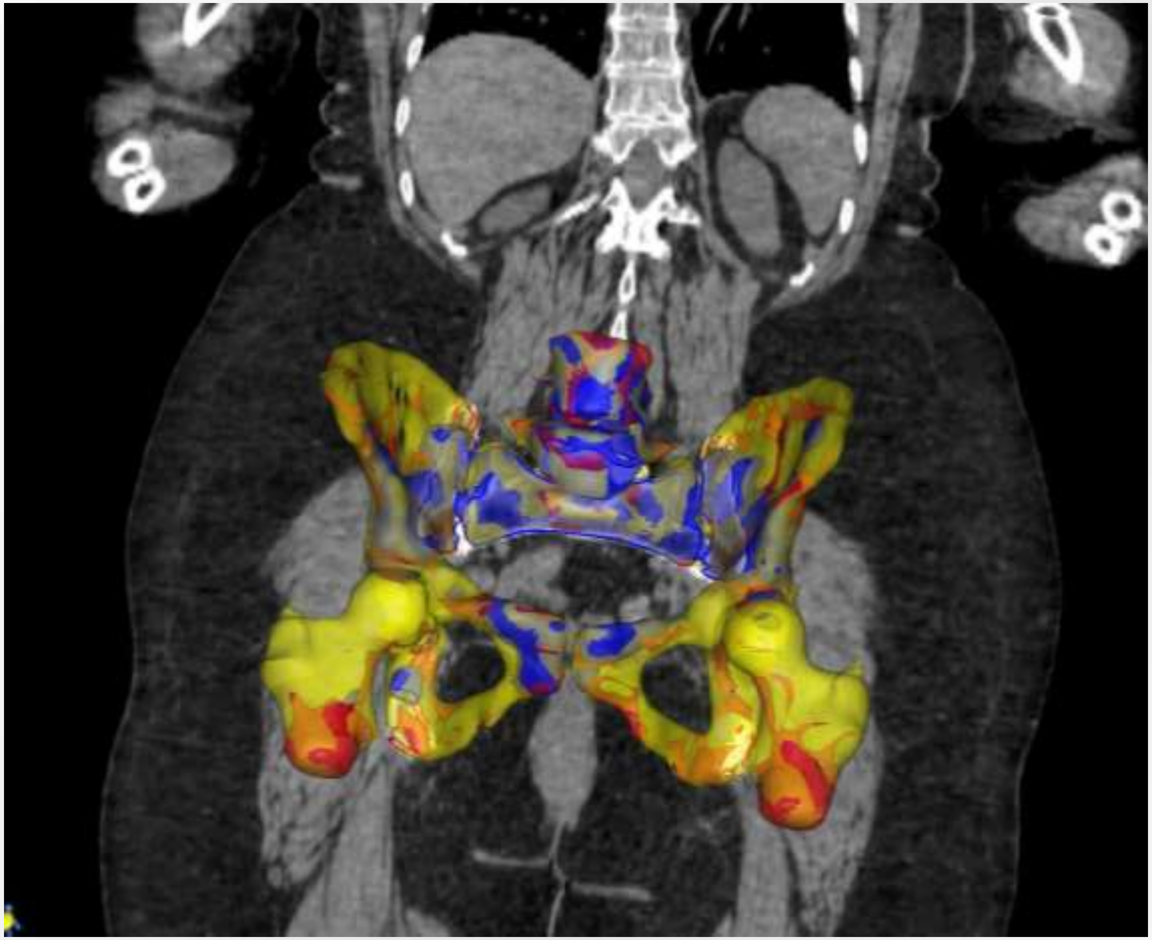
Do not forget normal tissue



- Active bone marrow (PET, >mean SUV)
- Low fat fraction (MR, <mean FF)
- Pelvis

Slide: Jakub Pritz

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What can we do?

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Accelerated Radiotherapy With Carbogen and Nicotinamide for Laryngeal Cancer: Results of a Phase III Randomized Trial

Geert O. Janssens, Saskia E. Rademakers, Chris H. Terhaard, Patricia A. Doornaert, Hendrik P. Bijl, Piet van den Ende, Alim Chin, Henri A. Marres, Remco de Bree, Albert J. van der Kogel, Ilse J. Hoogsteen, Johannes Bussink, Paul N. Span, and Johannes H. Kaanders

Therapeutic Advances in Urology *Review*

Carbogen gas and radiotherapy outcomes in prostate cancer

Kent Yip and Roberto Alonzi

Ther Adv Urol

(2013) 5(1) 25–34

DOI: 10.1177/ 1756287212452195

Prostate cancer RT: SIB for IPL

- Literature review: “prostate cancer SIB (IPL, DIL) radiotherapy”
- 19 papers identified

  9 RT planning
  - ✓ 4 nodes/seminal vesicles/prostate
  - ✓ 5 IPL

  8 radiotherapy experience/outcomes
  - ✓ 7 nodes/seminal vesicles/prostate
  - ✓ 1 IPL (Fonteyne et al. 2008, University of Ghent), modest escalation from 78 (median dose to PTV) to 82 Gy (median dose to IPL)

  2 other (TCP, MC)

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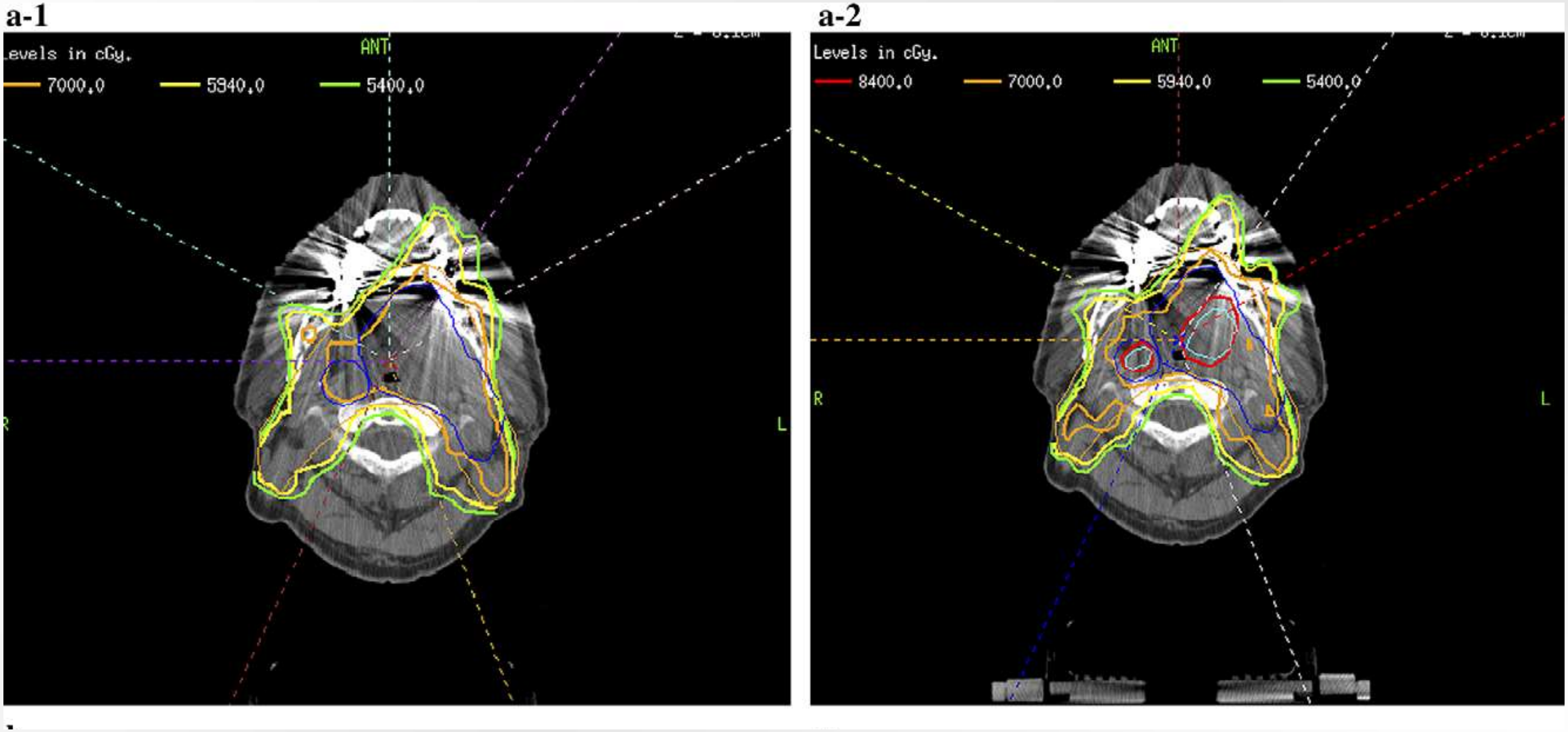
SIB planning (FMISO)



Lee et al. 2008

Ca oropharynx, regular IMRT (a-1) and FMISO-guided IMRT with boost (a-2), delineation based planning

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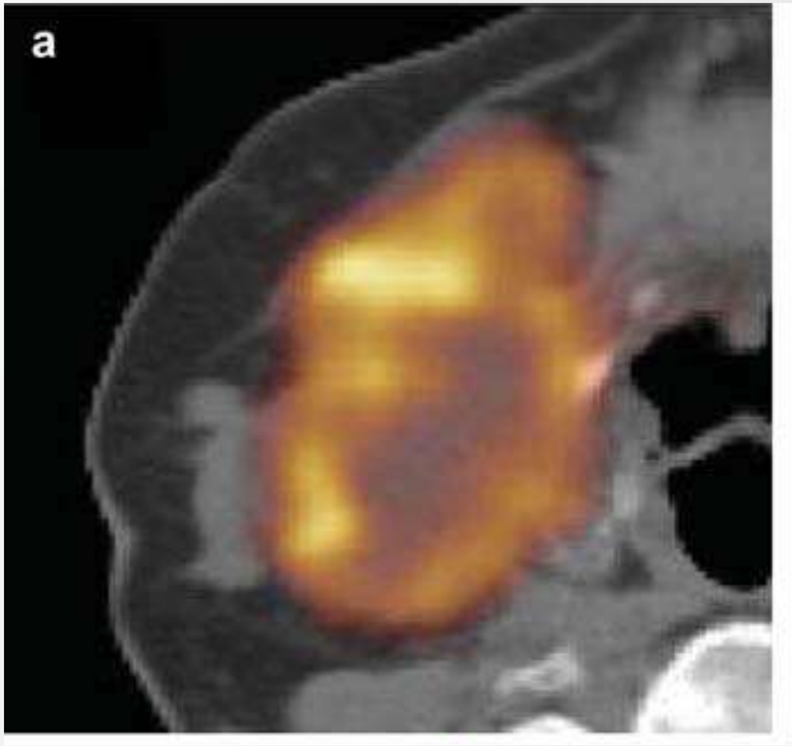
Intensity → biological property → dose



Base dose of 60 Gy
Mean dose of 90 Gy
^{61}Cu-ATSM PET-guided boost

$$D_i = 60Gy + 30Gy \times PET / < PET >$$

Korreman et al. 2010

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Clinical trials

- We need evidence that SIB (or sequential boost) to high risk volumes changes outcomes
  - Lung
  - Prostate
  - Brain
  - Head& Neck

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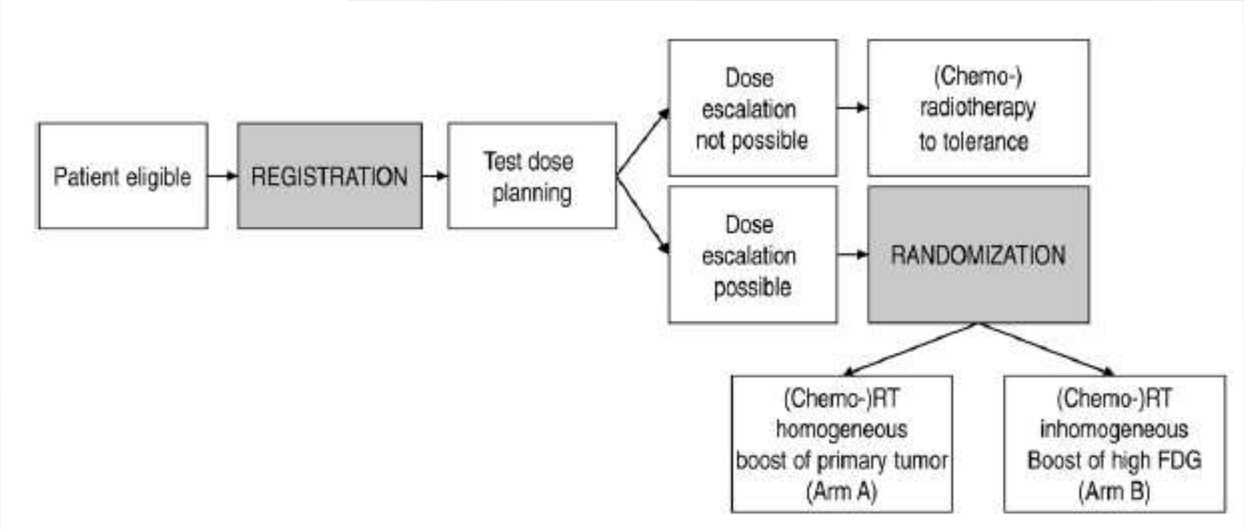
Clinical trials



- Arm A: 66Gy in 24 fractions of 2.75 Gy with an integrated boost to the primary tumor as a whole
- Arm B. 66Gy) in 24 fractions of 2.75Gy with an integrated boost to the 50% SUVmax area of the primary tumor (pre-treatment FDG-PET-CT)
- Boost to at least 72 Gy if can be accommodated without violating normal tissue constraints

Clinical trials

Radiotherapy and Oncology 104 (2012) 67–71

ELSEVIER

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

PET in lung cancer RT

The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer

Wouter van Elmpt [a,*], Dirk De Ruysscher [a], Anke van der Salm [a], Annemarie Lakeman [b], Judith van der Stoep [a], Daisy Emans [a], Eugène Damen [b], Michel Öllers [a], Jan-Jakob Sonke [b], José Belderbos [b]

[a] *Department of Radiation Oncology, Maastricht University Medical Centre, Maastricht;* [b] *Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

- Dose escalation was possible in 15 of the first 20 patients enrolled
- For the boost region dose level of 86.9±14.9Gy was reached

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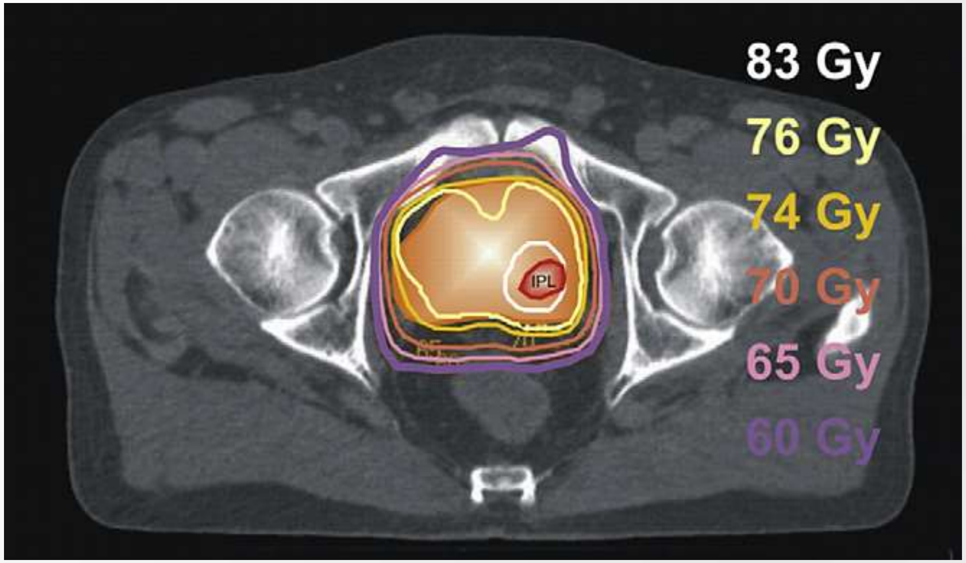
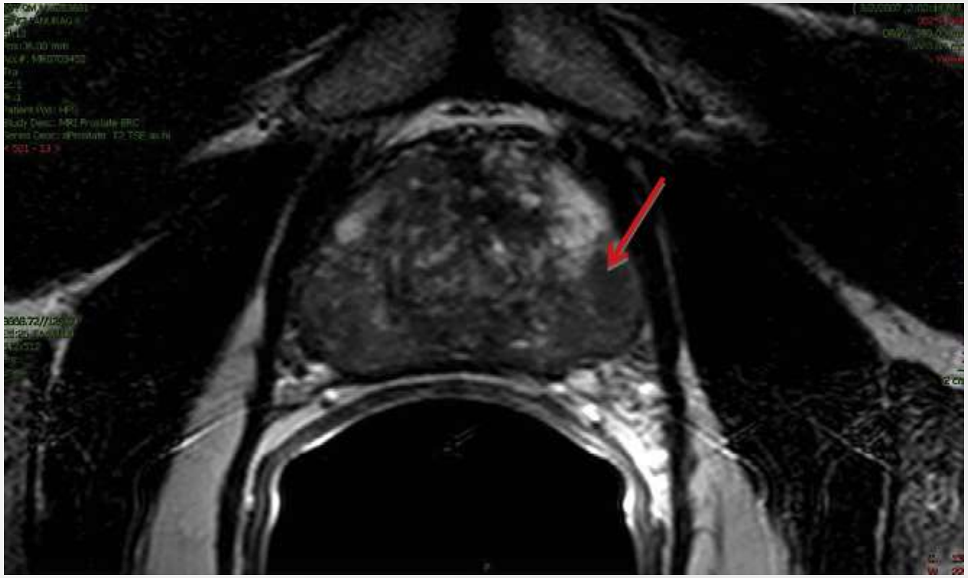
Prostate cancer RT: SIB for IPL



Fonteyne et al. 2008, MRI/MRS - defined IPL, boost to IPL using fixed gantry IMRT



Housri et al. 2011, MRI/MRS - defined IPL

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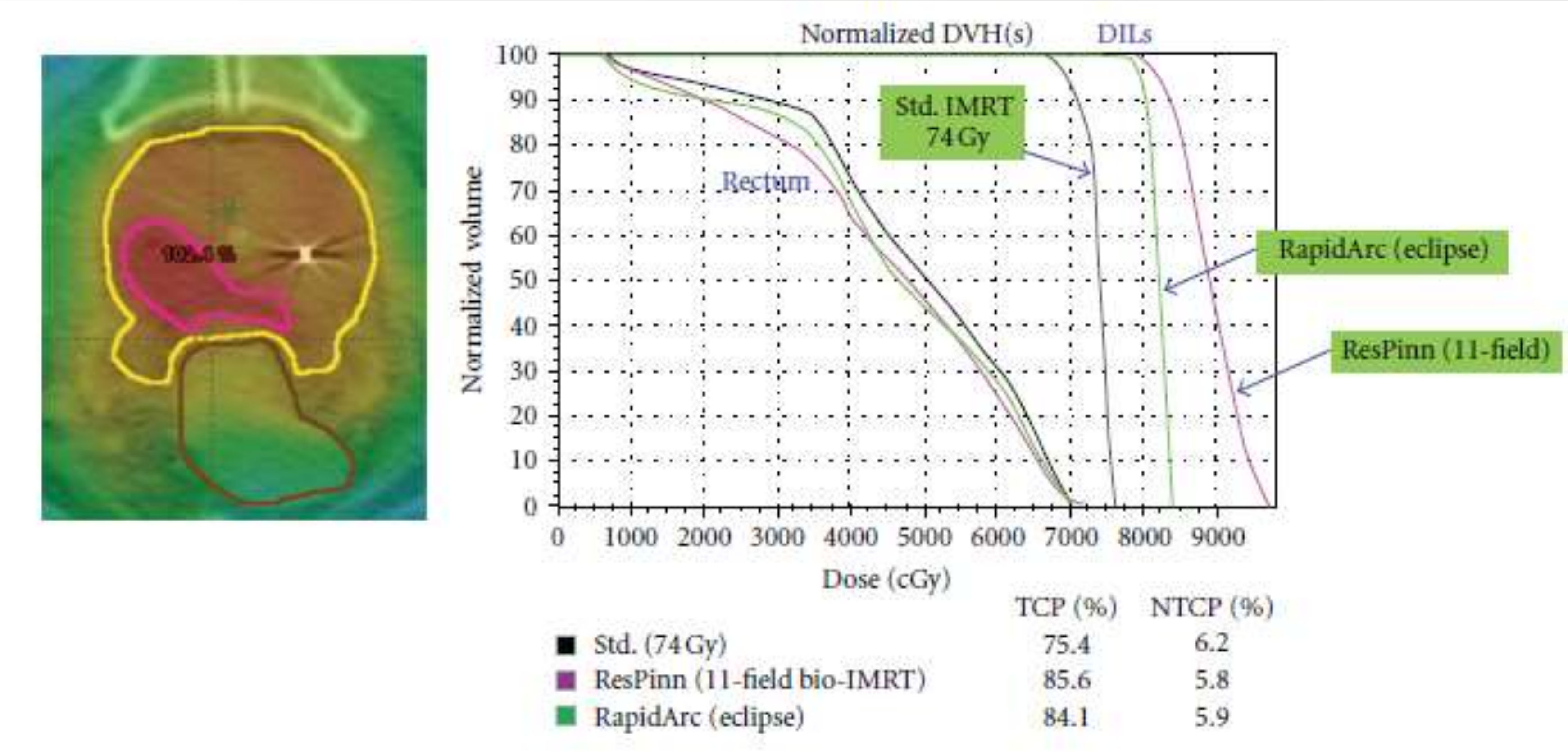
Prostate cancer RT: SIB for IPL



- 37 Fx
- NTCP (rectum) < 7%
- Max DIL control

Nahum and Uzan, 2012

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Phase II trial for glioma: SRS+60Gy/30

International Journal of
Radiation Oncology
biology • physics

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Clinical Investigation: Central Nervous System Tumor

Phase II Trial of Radiosurgery to Magnetic Resonance Spectroscopy—Defined High-Risk Tumor Volumes in Patients With Glioblastoma Multiforme

Douglas B. Einstein, M.D., Ph.D.,* Barry Wessels, Ph.D.,* Barbara Bangert, M.D.,† Pingfu Fu, Ph.D.,§ A. Dennis Nelson, Ph.D.,† Mark Cohen, M.D.,‖ Stephen Sagar, M.D.,‡ Jonathan Lewin, M.D.,† Andrew Sloan, M.D.,¶ Yiran Zheng, M.S.,* Jordonna Williams, R.N.,* Valdir Colussi, Ph.D.,* Robert Vinkler, R.T.T.,* and Robert Maciunas, M.D. M.P.H.¶

*Departments of *Radiation Oncology, †Radiology, ‡Neurology, §Biostatistics, ‖Pathology, and ¶Neurosurgery, Case Comprehensive Cancer Center, Case Western Reserve University Kettering, Ohio*

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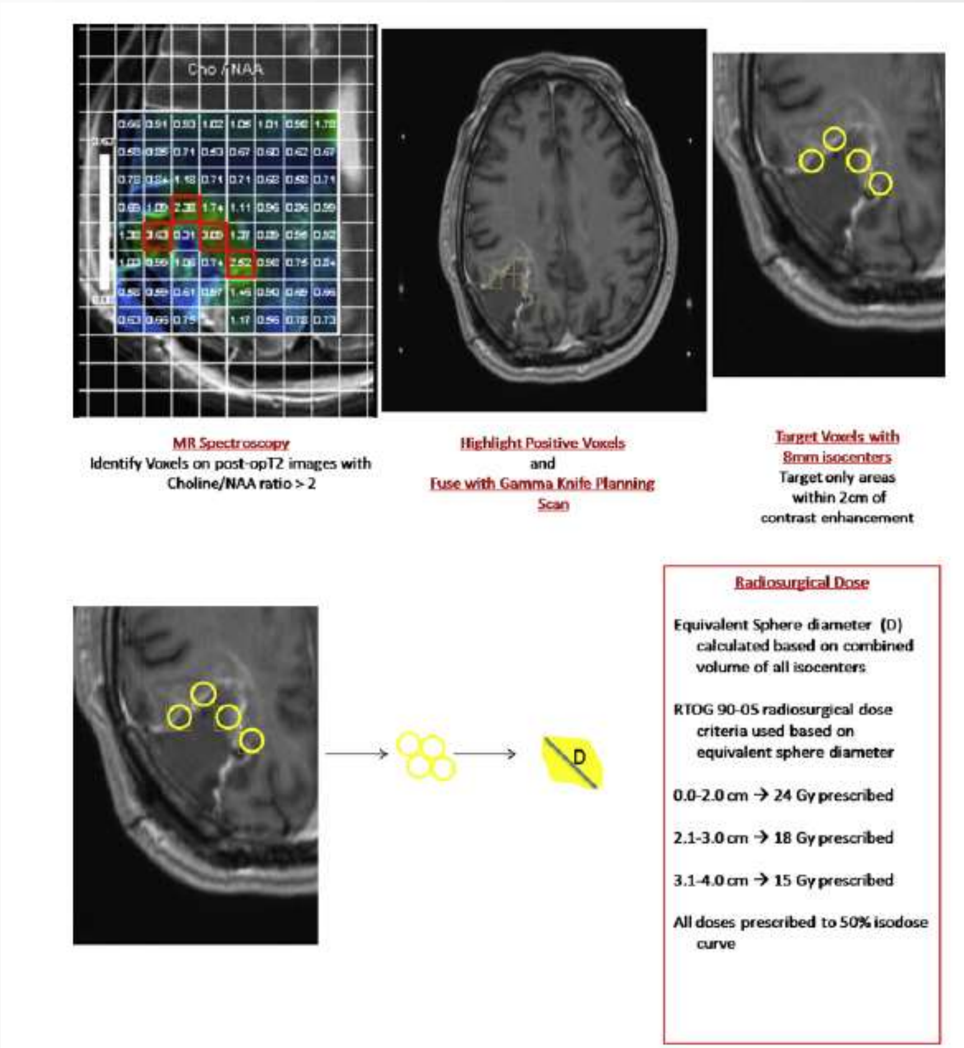
Phase II trial for glioma: SRS+60Gy/30



- Surgery (Day 0)
- MRS by day 35
- SRS by day 35
- CRT 60Gy/30 fx by day 49 (46Gy+14 Gy)

- 35 patients
  - Median age 62 y (21-84)
  - Median KPS 90 (60-100)
  - 29 pts RPA class 4 or 5
  - 16/35 concurrent chemo

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Phase II trial for glioma: SRS+60Gy/30

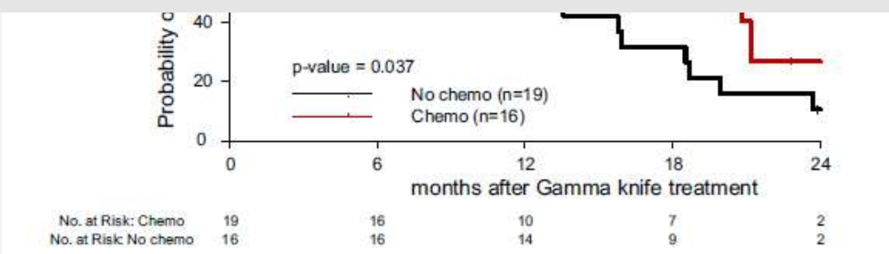
Table 4 Summary of patient survival time by prognostic classification

Classification	No. of patients	Survival time (mo)				
		GK MRS median survival	RTOG historical control, XRT alone	Survival difference of GK MRS patients vs. historical control	EORTC historical control, XRT + temodar	Survival difference of GK MRS patients vs. historical control
RTOG RPA Class 3	4	>22*	17.9	4.1†	21.4	0.6†
RTOG RPA Class 4	13	18.7	11.1	7.6†	16.3	2.4†
RTOG RPA Class 5	16	12.9	8.9	4.0†	10.3	2.6†
Concurrent temozolomide	16	20.8	NA	NA	14.6	6.2†

Abbreviations: GK = Gamma Knife; MRS = magnetic resonance spectroscopy; RTOG = Radiation Therapy Oncology Group; XRT = radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; NA = Not applicable. Other abbreviation as in Table 2.

* Median survival not yet reached at time of analysis.

† Statistically significant.



was available

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Conclusions

- Validation of FI needed
- Correlation with outcomes established
- Sufficient proof from planning studies that boost is feasible
- Need trials which are likely to provide conclusive evidence

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