Personalized Cancer Medicine: Precision Therapy Redux

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Disclosure

Presenter has a financial interest in some of the technology reported here and research collaborations with Elekta, Philips, IMRIS, Varian, and Raysearch.

Results from studies using investigational devices will be described in this presentation.

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RaySearch Laboratories

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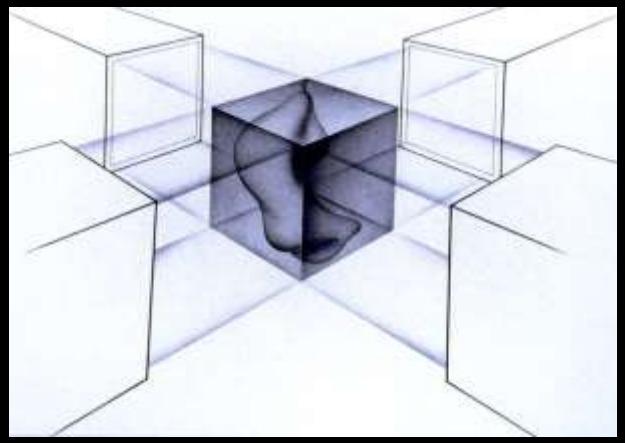
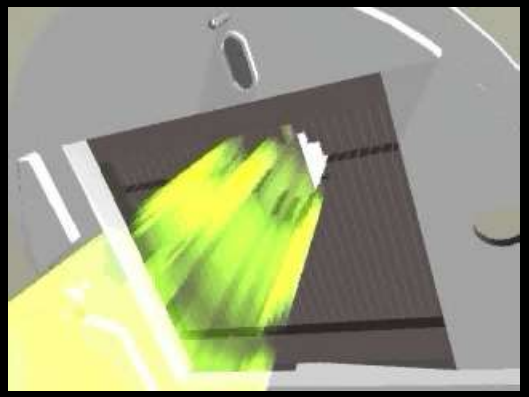
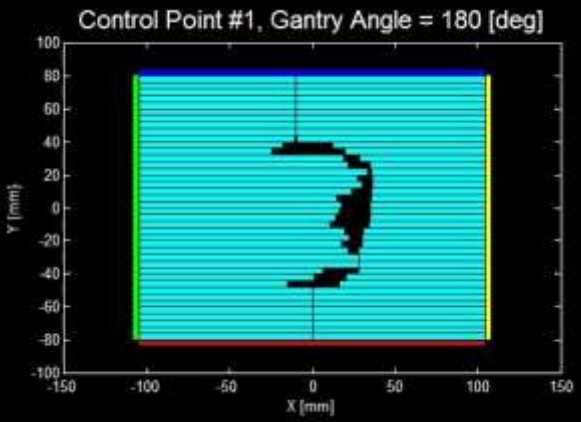
Fidani Chair in Radiation Physics

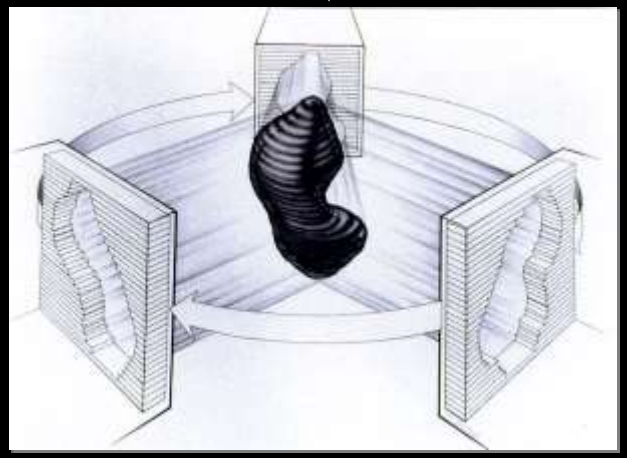
A single dream. A world of hope.
The Terry Fox Foundation

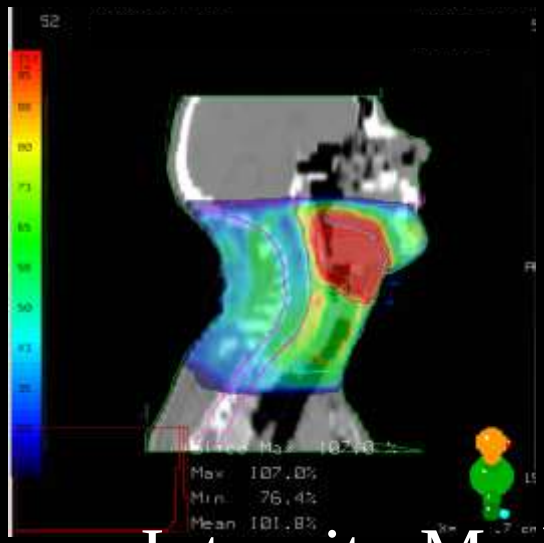
Over Three Decades of Personalizing Cancer Treatment











Conformal Radiation Therapy (CRT)

Intensity Modulation Radiation Therapy (IMRT)

Supervised Robotic Intensity-modulated, Image-guided Radiation Therapy

In a period of 10 years, Radiation Therapy has evolved from employing:

10 Mb to 1000 Mb of Data (100X)

10 to 1000 Digital Treatment Parameters (Robotic Control)

Supervised, Image-guided Operation

Estimate Error & Adjust If Error > Tolerance

Position Patient and Acquire Image

Align to Reference Images Used in Planning

CLINICAL INVESTIGATION Lung

INFLUENCE OF TECHNOLOGIC ADVANCES ON OUTCOMES IN PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER RECEIVING CONCOMITANT CHEMORADIOTHERAPY

ZHONGXING X. LIAO, M.D.,* RITSUKO R. KOMAKI, M.D.,* HOWARD D. THAMES, JR., PH.D.,§ HELEN H. LIU, PH.D.,† SUSAN L. TUCKER, PH.D.,‡ RADHE MOHAN, PH.D.,† MARY K. MARTEL, PH.D.,† XIONG WEI, M.D.,* KUNYU YANG, M.D.,* EDWARD S. KIM, M.D.,‖ GEORGE BLUMENSCHEIN, M.D.,‖ WAUN KI HONG, M.D.,‖ AND JAMES D. COX, M.D.*

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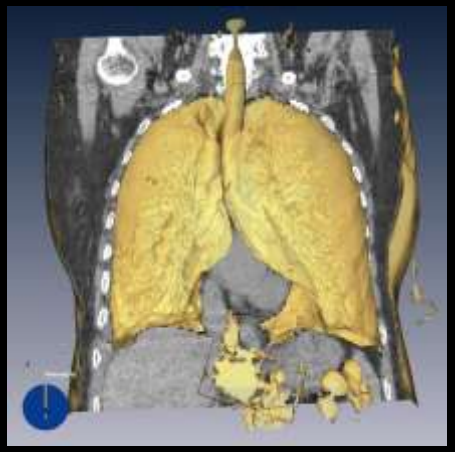
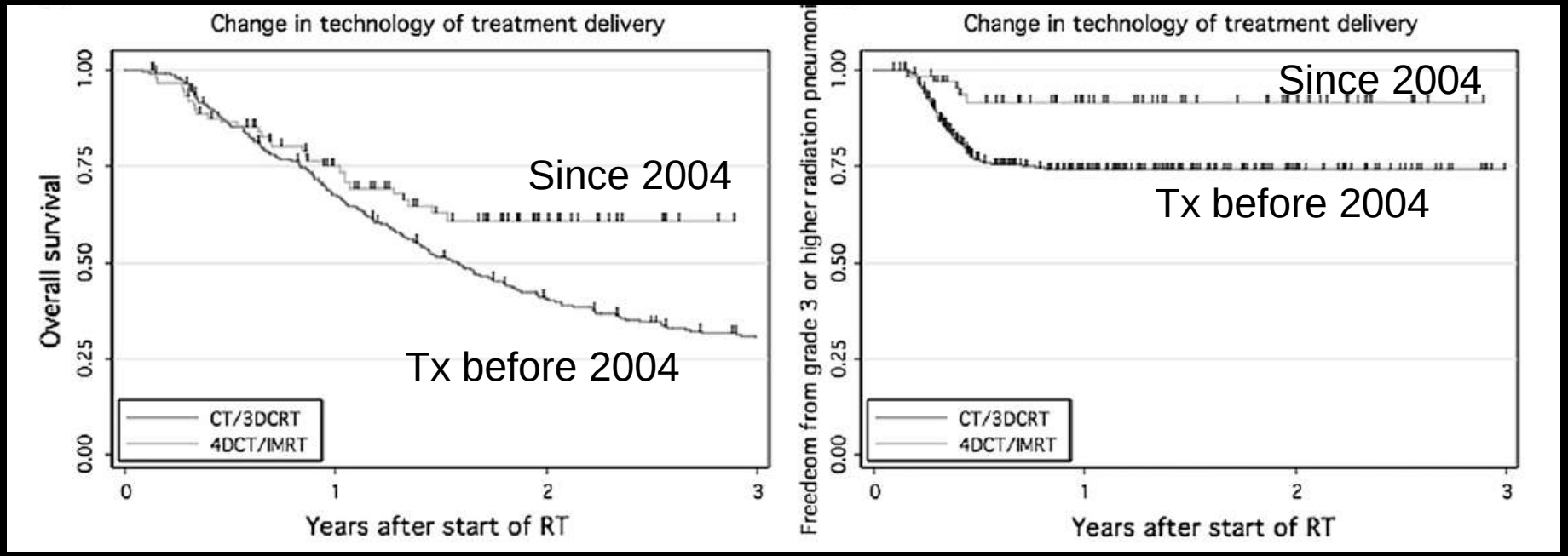




Accommodating the 4D nature of the lung and tailoring dose patterns to anatomy.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, pp. 775–781, 2010

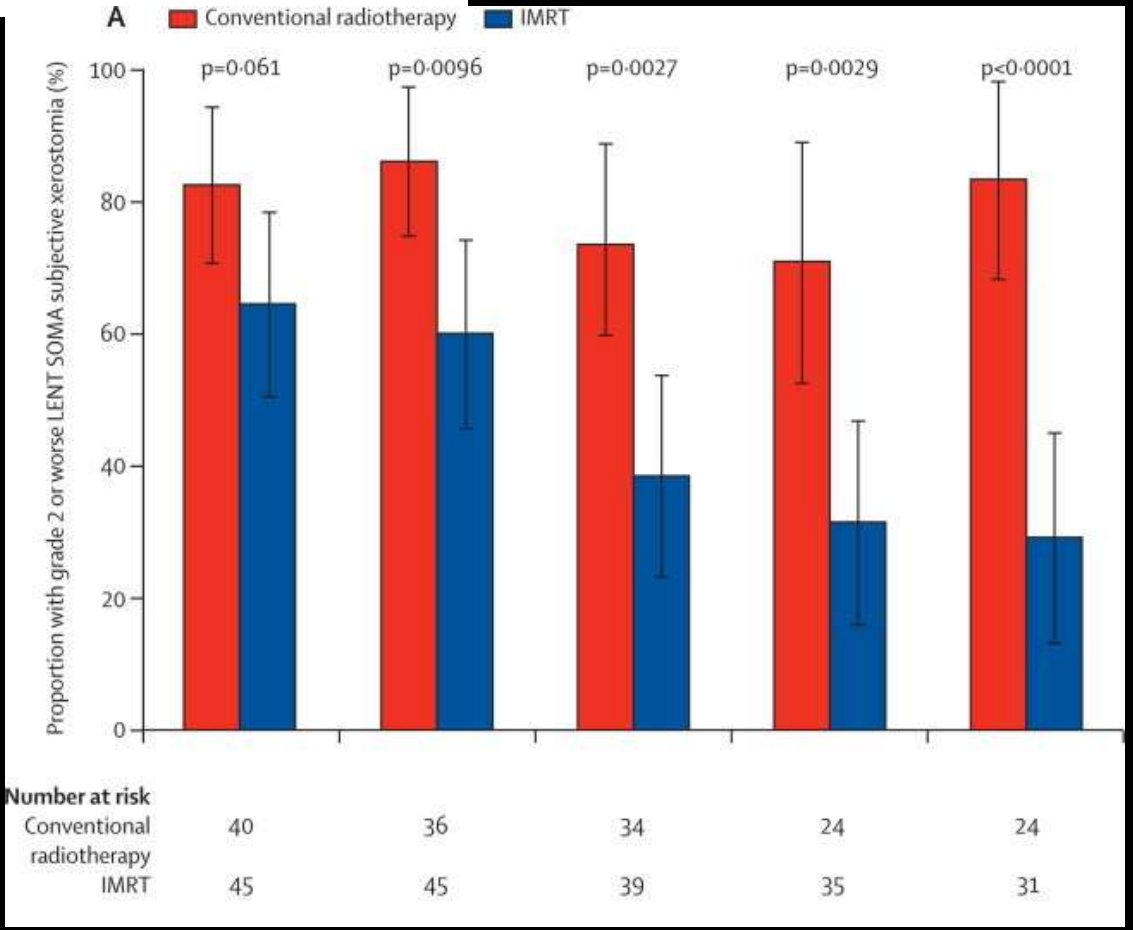
Published as: *Lancet Oncol.* 2011 February ; 12(2): 127–136.

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting[a,b,*], James P Morden[b], Kevin J Harrington[a,b], Teresa Guerrero Urbano[c], Shreerang A Bhide[a], Catharine Clark[d], Elizabeth A Miles[e], Aisha B Miah[a], Kate Newbold[a], MaryAnne Tanay[a], Fawzi Adab[f], Sarah J Jefferies[g], Christopher Scrase[h], Beng K Yap[i], Roger P A'Hern[b], Mark A Sydenham[b], Marie Emson[b], Emma Hall[b], and on behalf of the PARSPORT trial management group[†]

At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival.

47 patients were assigned to each treatment arm. Median follow-up was 44·0 months (IQR 30·0–59·7). At 12 months xerostomia side-effects were reported in 73 of 82 alive patients; grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional radiotherapy group.



Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

Michael J. Zelefsky, M.D.,* Marisa Kollmeier, M.D.,* Brett Cox, M.D.,* Anthony Fidaleo, B.A.,* Dahlia Sperling, B.A.,* Xin Pei, Ph.D.,* Brett Carver, M.D., Ph.D.,† Jonathan Coleman, M.D.,† Michael Lovelock and Margie Hunt, B.S.†

*Departments of Radiation Oncology, †Medical Physics, and ‡Surgery, Memorial Sloan-Kettering Canc NY

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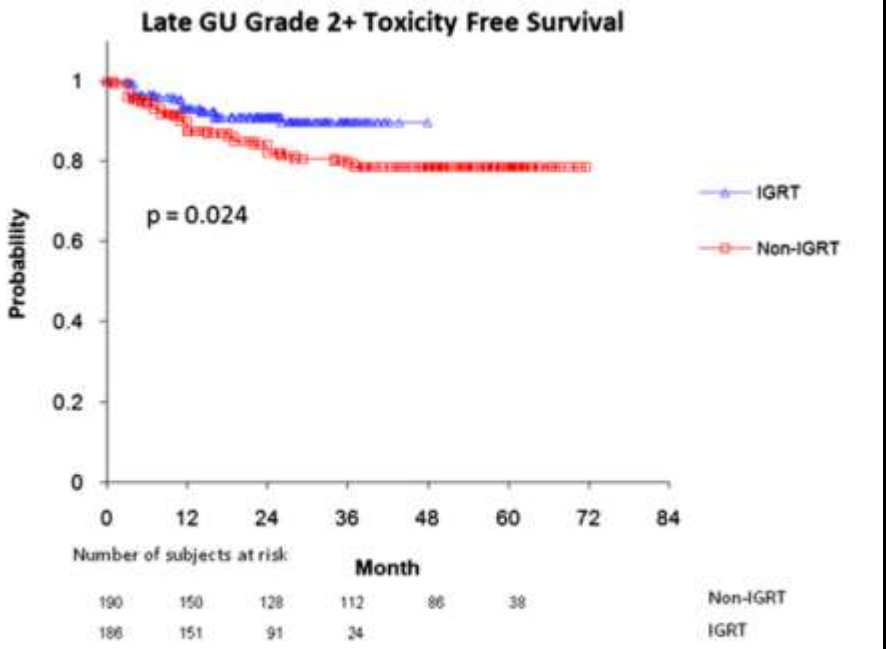
Int J Radiation Oncol Biol Phys, Vol. 84, No. 1, pp. 125–129, 2012

Adoption of daily IGRT with same PTV margins. Retrospective analysis of toxicity and biochemical control (N=186 vs N=190)



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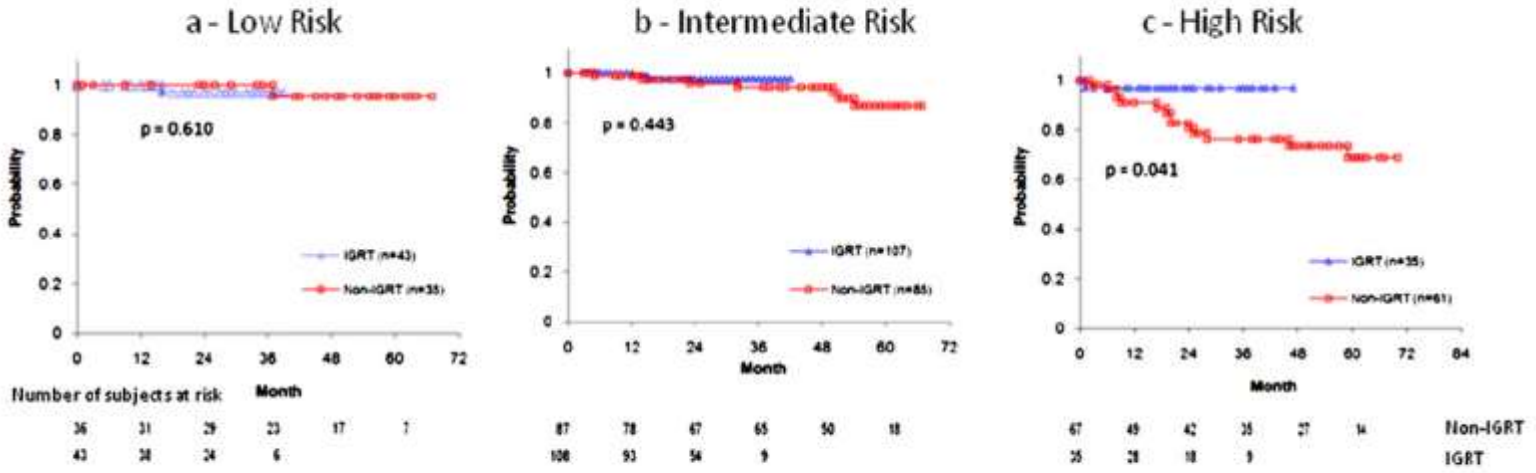
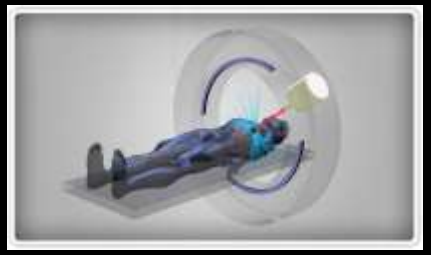


Fig. 2. Comparison of prostate specific antigen relapse-free survival outcomes between patients treated with image-guided radiotherapy (IGRT) to 86.4 Gy and those treated with intensity-modulated radiotherapy to the same dose level.

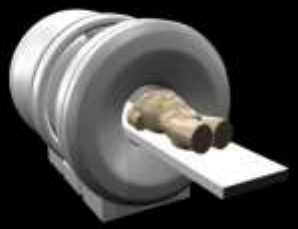
Next Gen RT Technologies: Better dose control through physics, imaging, computation, and robotics.



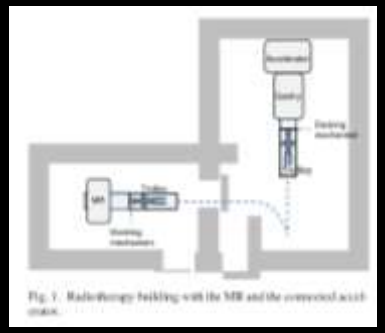
PET-guided RT

Edmonton Solution

Utrecht Solution

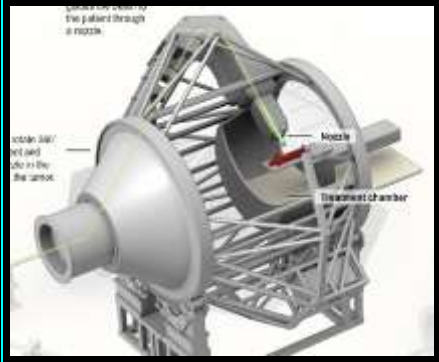


Viewray Solution



Adjacent Solutions

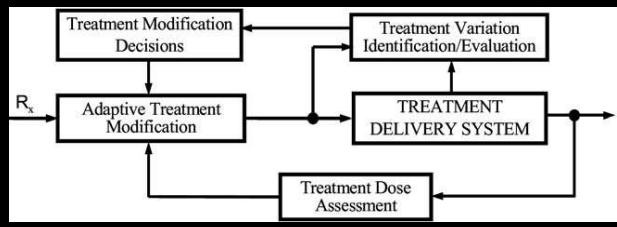
MR-Guided RT



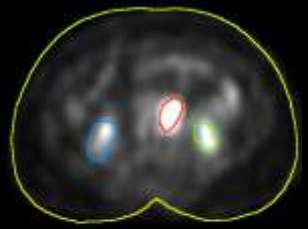
Protons+

Next Generation of Personalization

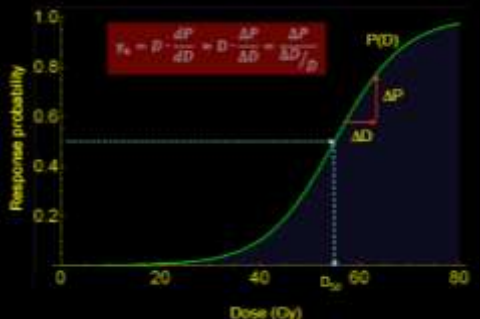
- Adaptive Radiation Therapy – geometric and functional



- Image-based Biological Targets - targets and normal tissues



- Patient-specific Radiation Sensitivity – decision-making and dose prescription.



Capacity to Integrate Molecular/Functional Imaging in RT

Database of Dose Targets and Tolerances

CT

CT/PET

MR

Contouring

$\Sigma;\Delta$

Optimization

Calc'n

IMRT Beam Patterns

Geometry Change

d

IGRT Adjustments

Specific Patient

Biology Change

From the ‘3D Hypothesis’ to the ‘4D Hypothesis’

- *4D Hypothesis:* Adapting to imaged changes in geometry or function during RT will improve the therapeutic ratio.
  - *A.k.a. ‘Adaptive Radiation Therapy’*

COMPUTED MEDICAL IMAGING

Nobel Lecture, 8 December, 1979

BY
GODFREY N. HOUNSFIELD
The Medical Systems Department of Central Research Laboratories EMI, London, England

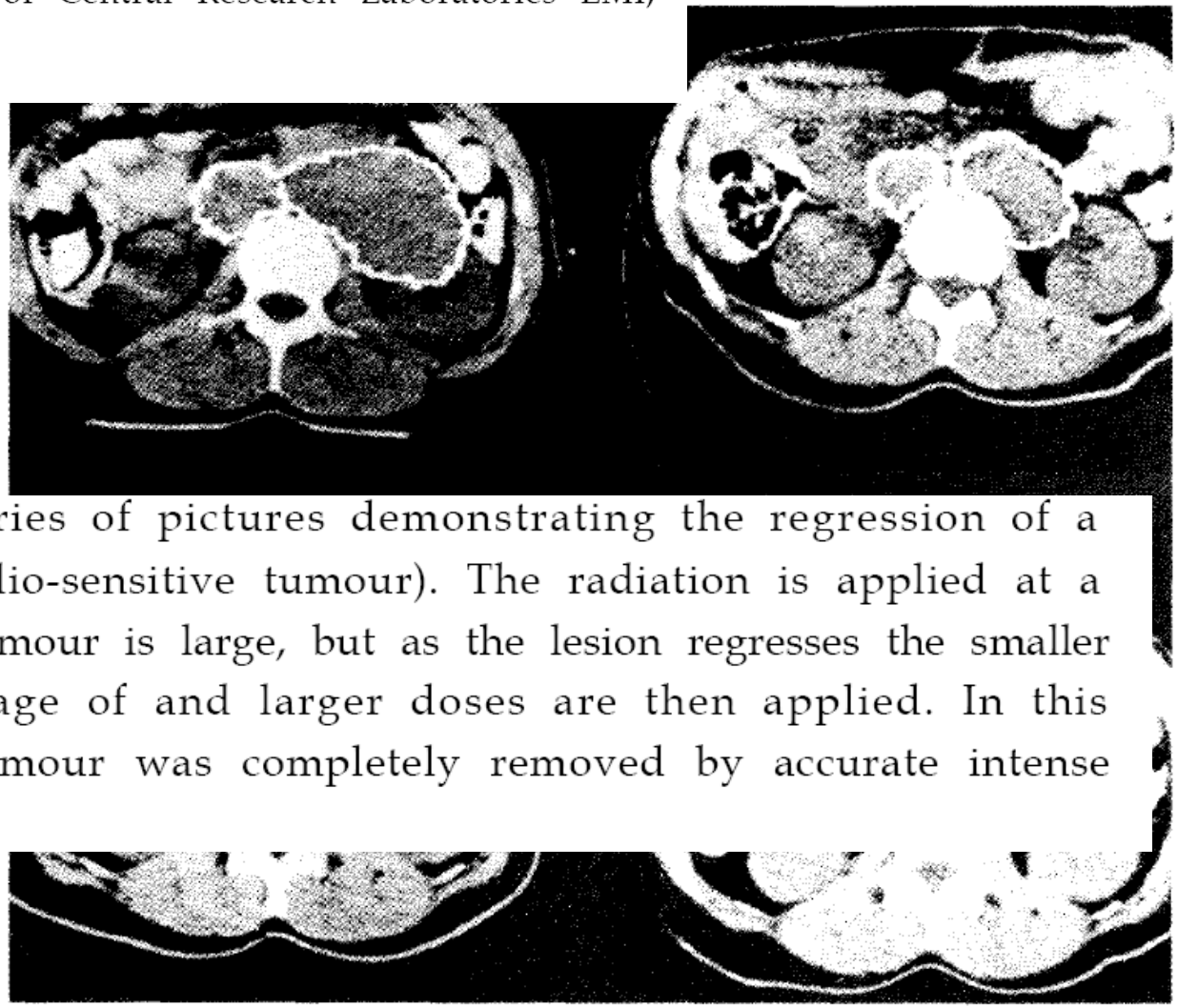
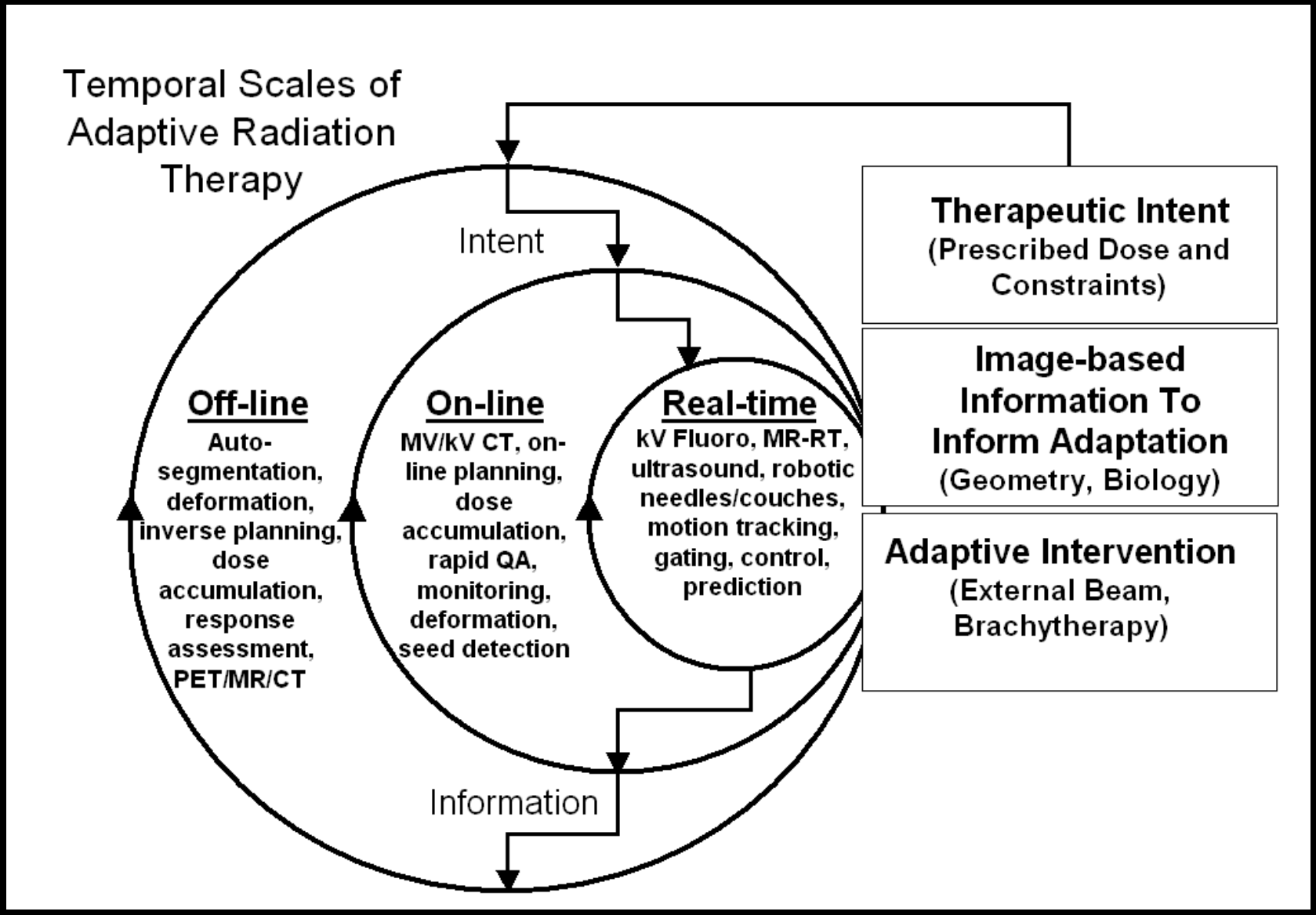


Fig. 13 shows a series of pictures demonstrating the regression of a seminoma (a very radio-sensitive tumour). The radiation is applied at a low level while the tumour is large, but as the lesion regresses the smaller area is taken advantage of and larger doses are then applied. In this particular case the tumour was completely removed by accurate intense radiation.

Fig. 13. Demonstrating the regression of a seminoma after four stages of therapy treatment.

Complex Machinery of Adaptive



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Seminars in
RADIATION
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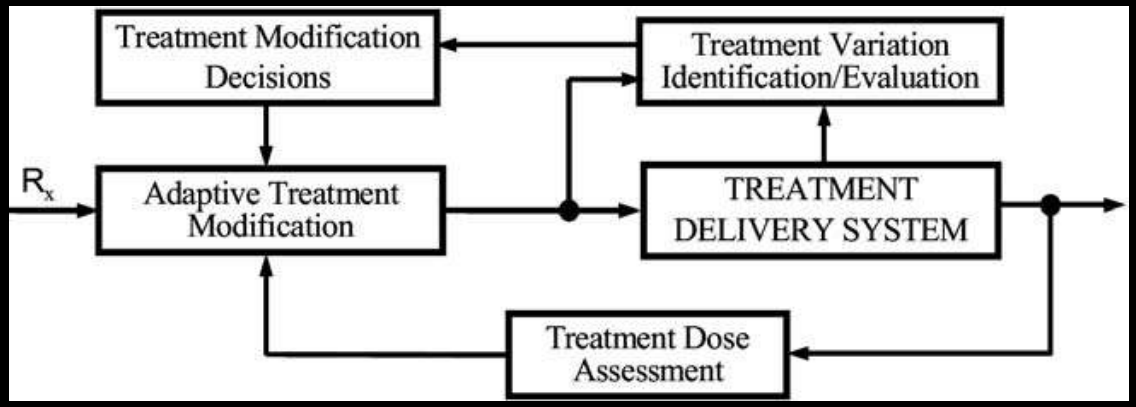
Volume 20, Number 2 April 2010

Adaptive Radiotherapy: Merging Principle Into Clinical Practice

"Adaptive radiotherapy has been introduced as a feedback control strategy to include patient-specific treatment variation explicitly in the control of treatment planning and delivering during the treatment course." D. Yan



WBH Adaptive Experience

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Seminars in RADIATION ONCOLOGY

Adaptive Radiation Therapy for Prostate Cancer

Michel Ghilezan, MD, PhD, Di Yan, DSc, and Alvaro Martinez, MD

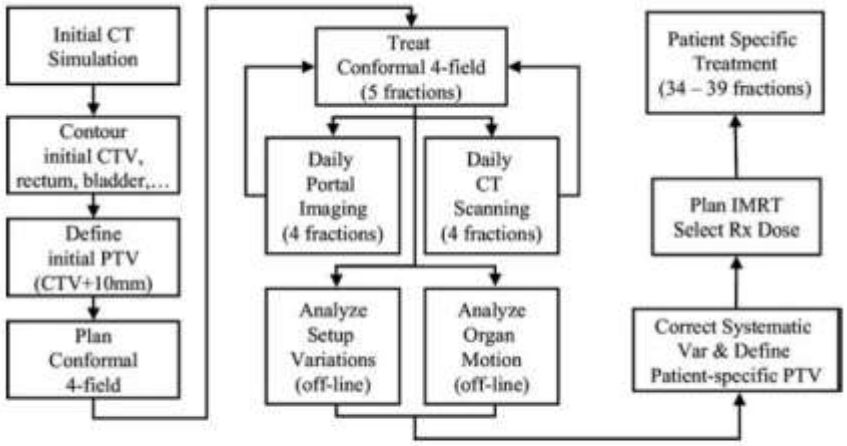

Figure 1 Flow chart depicting the off-line image guided adaptive radiation therapy process.

Table 3 Toxicity in 728 Patients Treated With Adaptive CRT/IMRT

	Adaptive CRT	Adaptive IMRT	*P*
Acute	Grade 2 + 3	Grades 2 + 3	
GU frequency/ urgency	34%	30%	.29
Dysuria	5%	2%	.15
GU incontinence	0.5%	2%	.04
Urinary retention	7%	2%	.03
Rectal	19%	5%	<.01
pain/tenesmus			
Diarrhea	10%	8%	.43
Chronic			
GU frequency/ urgency	12%	8%	.12
Urinary retention	3%	0.5%	.05
Hematuria	4%	5%	.43
Urethral stricture	1%	2%	.10
Rectal	1%	0%	.16
pain/tenesmus			
Diarrhea	3%	2%	.51
Rectal bleeding	16%	4%	<.01

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Seminars in
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ONCOLOGY

Adaptive Management of Cervical Cancer Radiotherapy

Kari Tanderup, PhD,* Dietmar Georg, DSc,† Richard Pötter, MD,† Christian Kirisits, DSc,†
Cai Grau, DMSc, MD,* and Jacob C. Lindegaard, DMSc, MD*

Since the breakthrough 10 years ago with concomitant radio-chemotherapy, substantial progress in the treatment of locally advanced cervical cancer has been lacking. Radiotherapy continues to be the cornerstone in the treatment of this disease and now shows much potential for progress, as image guidance of both external beam radiation therapy and brachytherapy, linked with strong tools for treatment planning and dose delivery, is be-

coming available. With these new techniques, it again seems possible to improve the therapeutic ratio as we begin to understand how the treatment for each patient can be individualized, not only in terms of volume (3-dimensional), but also during treatment (4-dimensional), as the tumor regresses and the topography of the target and organs at risk change significantly. New promising data with increased loco-regional control and de-

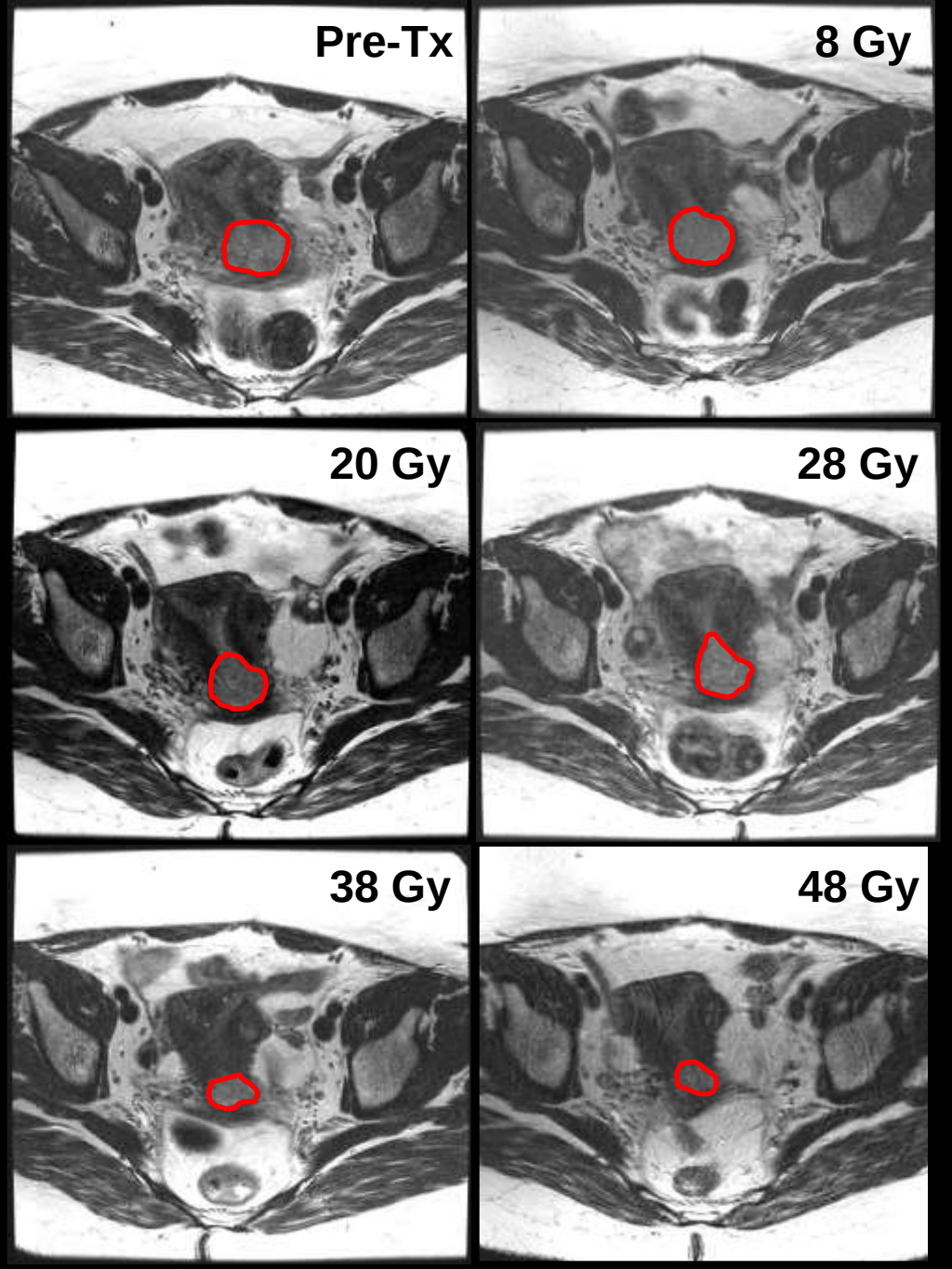
radiotherapy in the multimodal management of locally advanced cervical cancer.
Semin Radiat Oncol 20:121-129

Rationale and Potential

Today, the standard treatment of locally advanced cervical cancer is external beam radiotherapy (EBRT), concomitant

aging and point-based BT dose prescription. High rates of local control in the range 80%-95% can be achieved in small tumors, such as International Federation of Gynecology and Obstetrics stage IB1 and small stage IIB. However, the local

Ca Cervix: "Tumour" Shrinkage & Deformation During RT

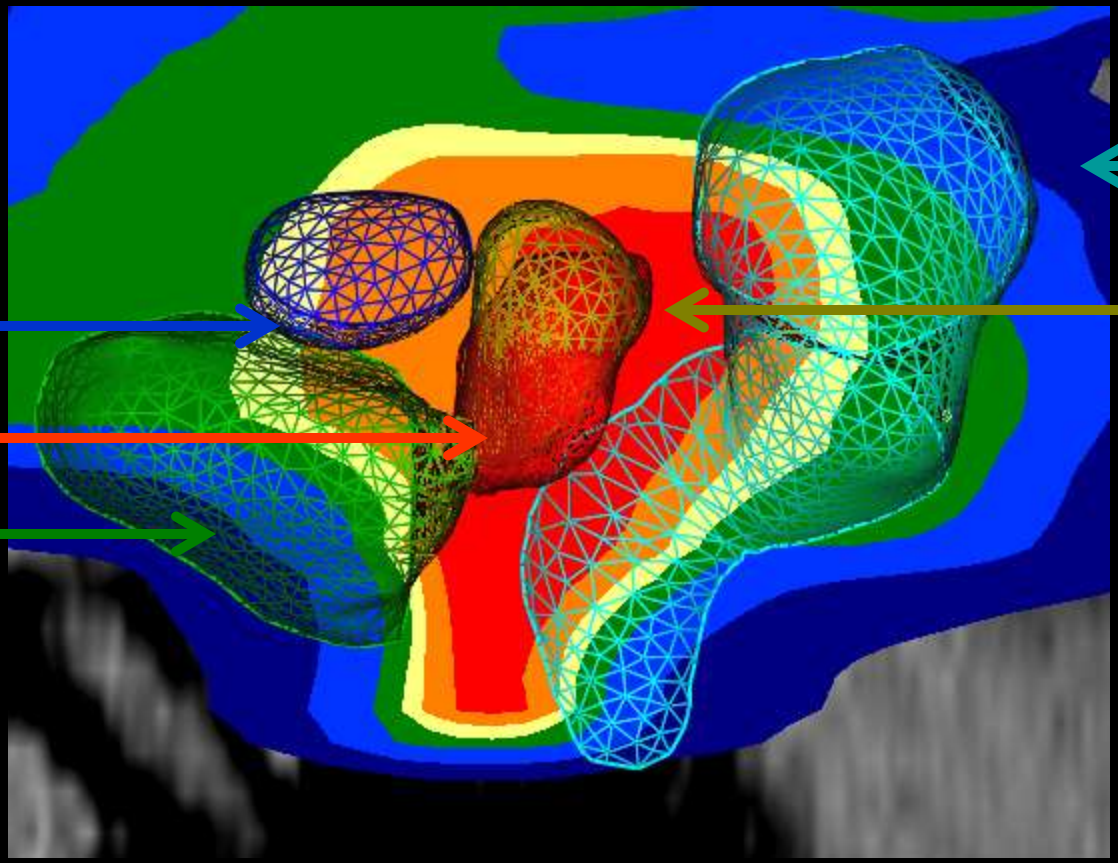


GTV - T2 Enhancement on MR

Gyne Site Group - PMH

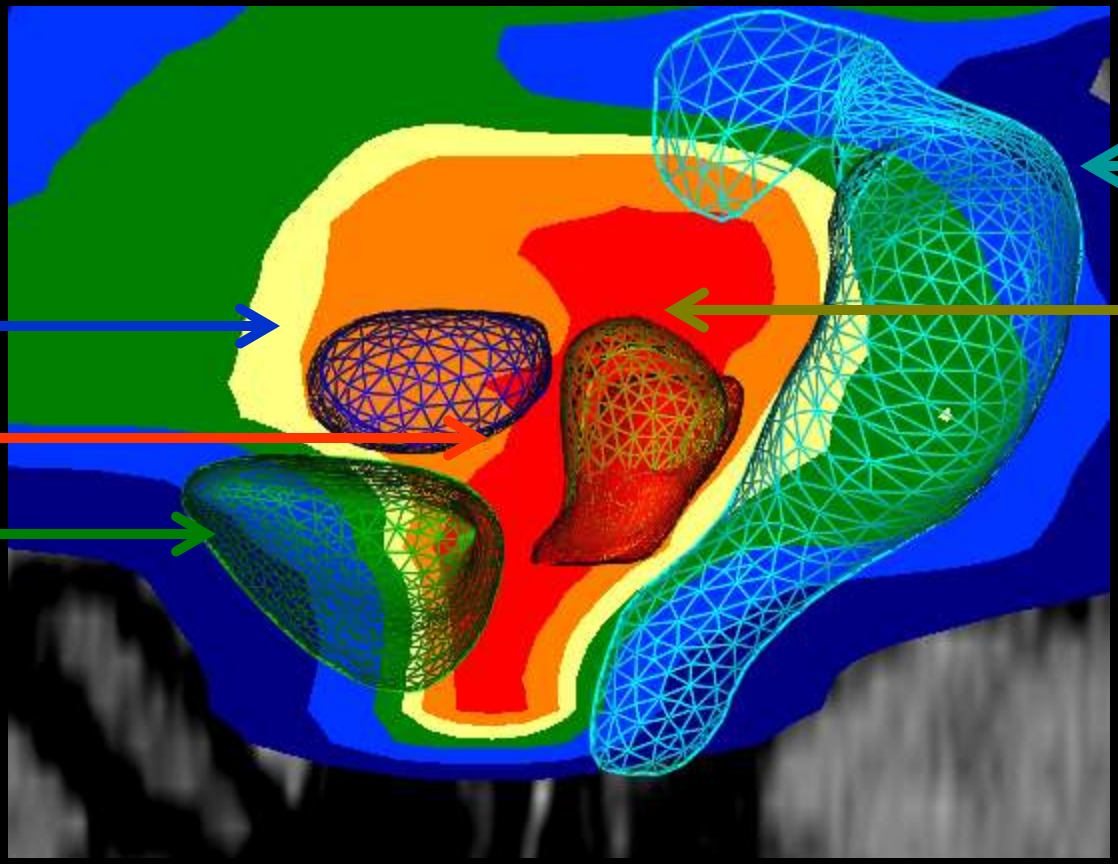
Ca Cervix – Interfraction Motion

Ca Cervix – Interfraction Motion



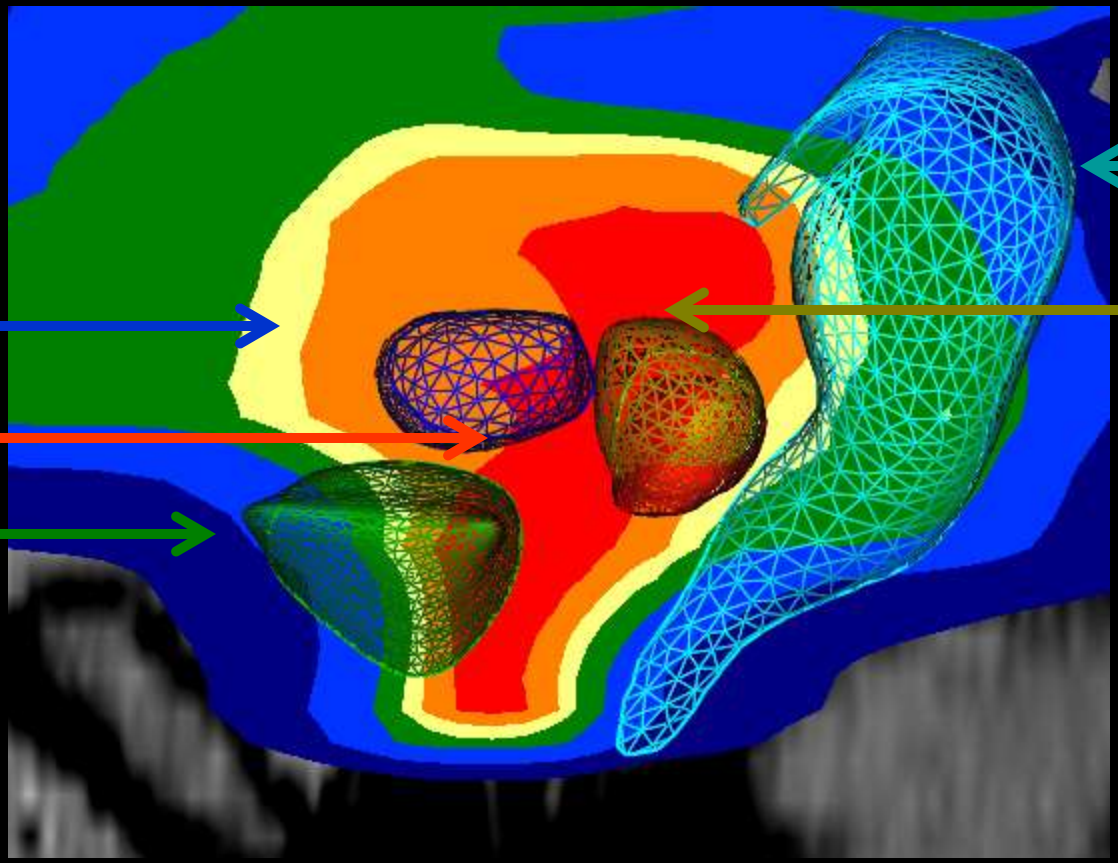
Week 1

Ca Cervix – Interfraction Motion



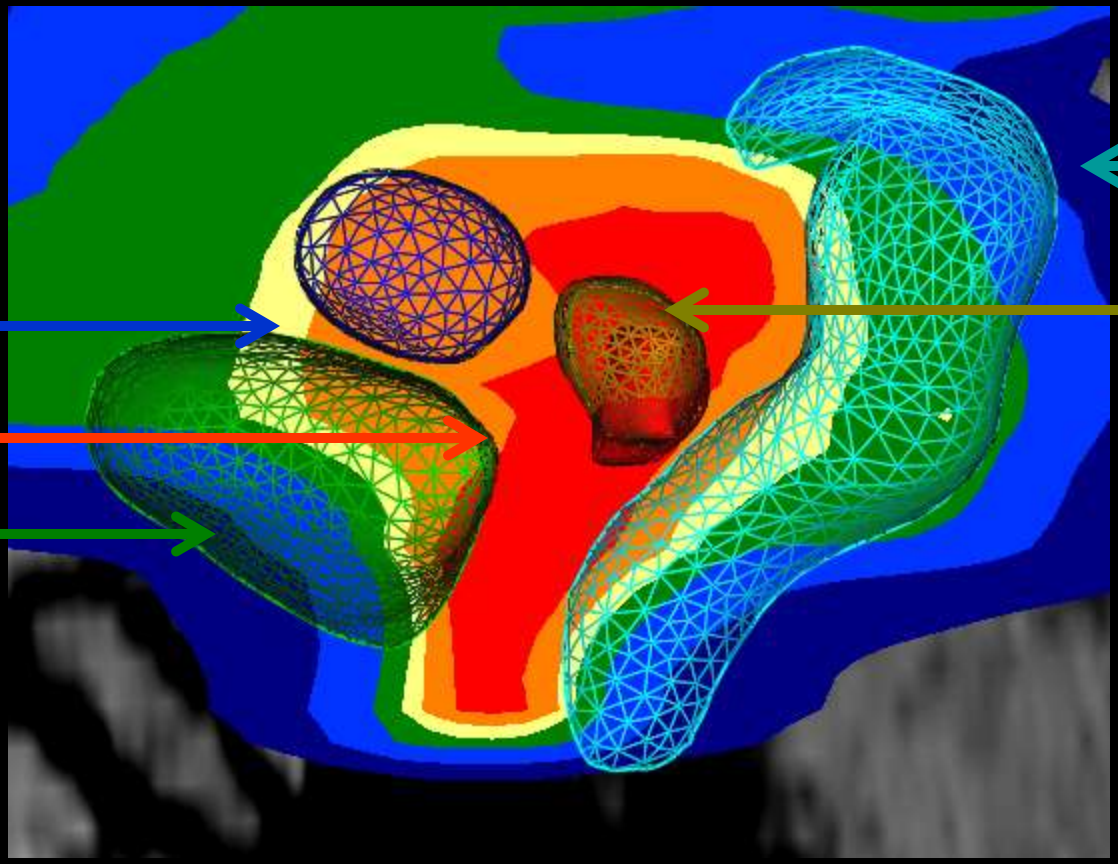
Week 2

Ca Cervix – Interfraction Motion



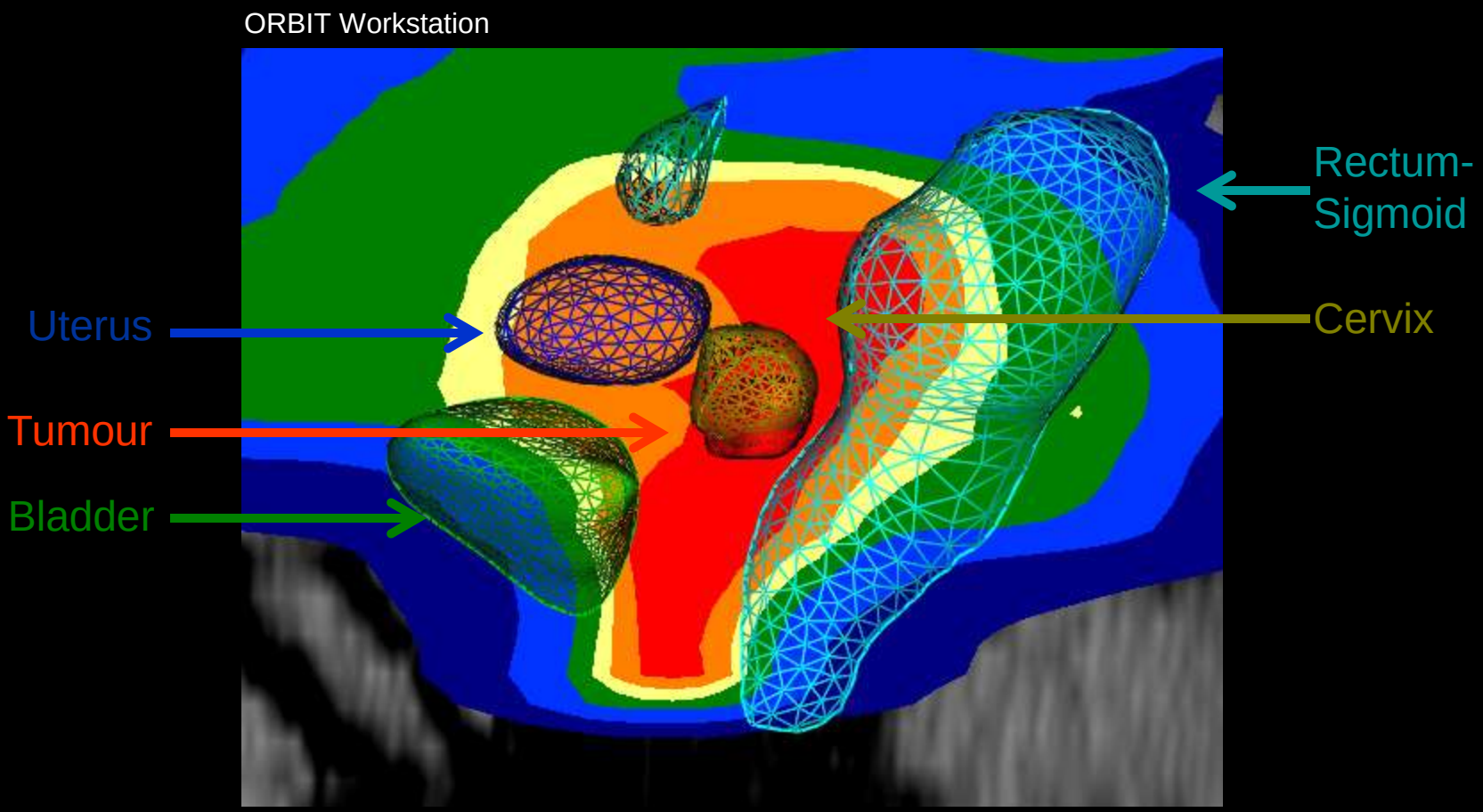
Week 3

Ca Cervix – Interfraction Motion



Week 4

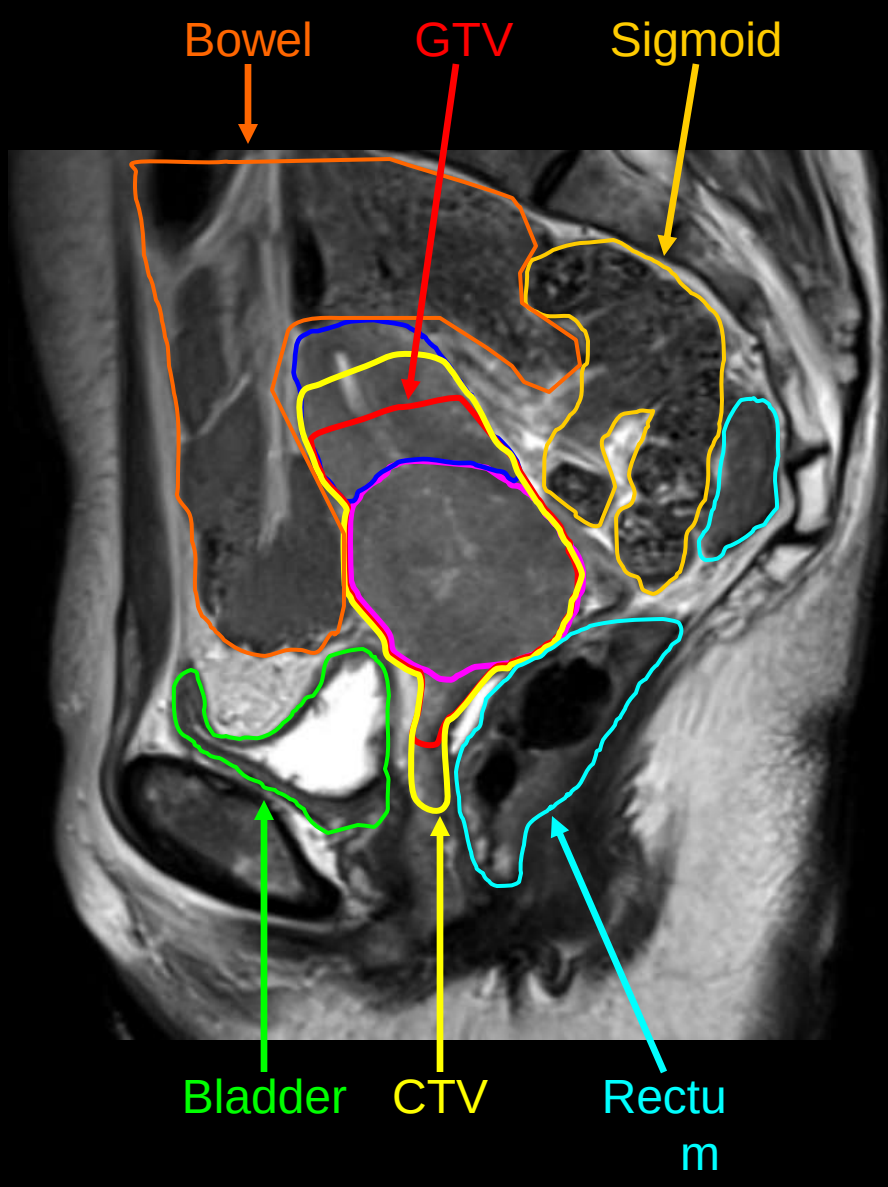
Ca Cervix – Interfraction Motion



Week 5

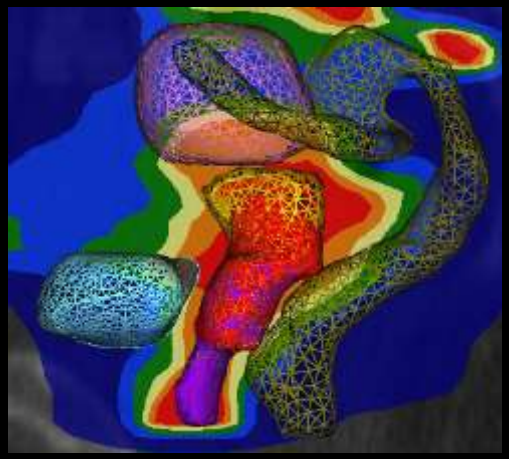
Methods

- 33 patients with stage IB-IVA cervix cancer
- Target volumes (GTV and CTV) and OARs (rectum, sigmoid, bladder, and bowel) contoured on fused MR-CT baseline image and subsequent weekly MR scans
- Primary CTV defined as union of:
  - GTV
  - Cervix
  - Parametria
  - 2 cm of uterus superior to GTV
  - 2 cm of upper vagina inferior to GTV

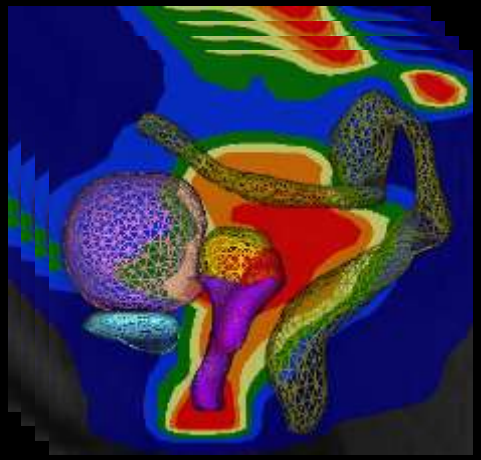


Methods – Dose Accumulation / ORBIT

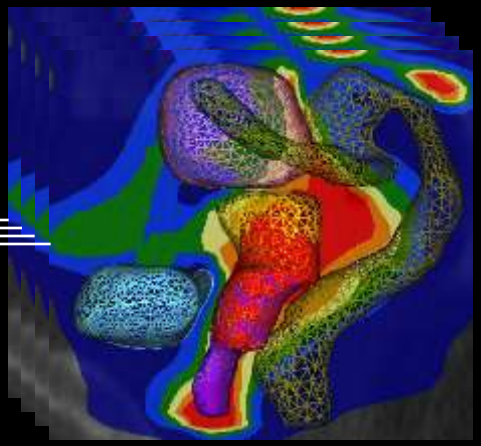
Planned Dose



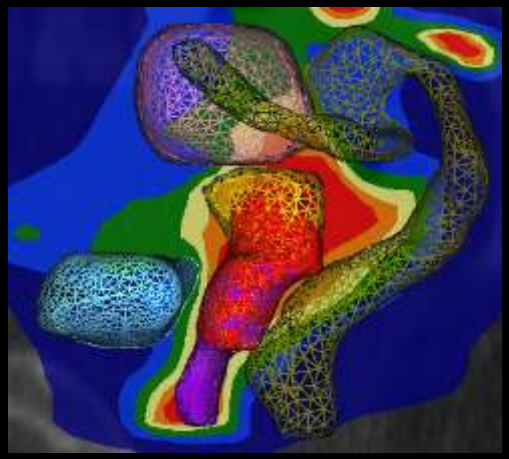
Apply planned dose at each fraction



Deform each fraction to planning geometry

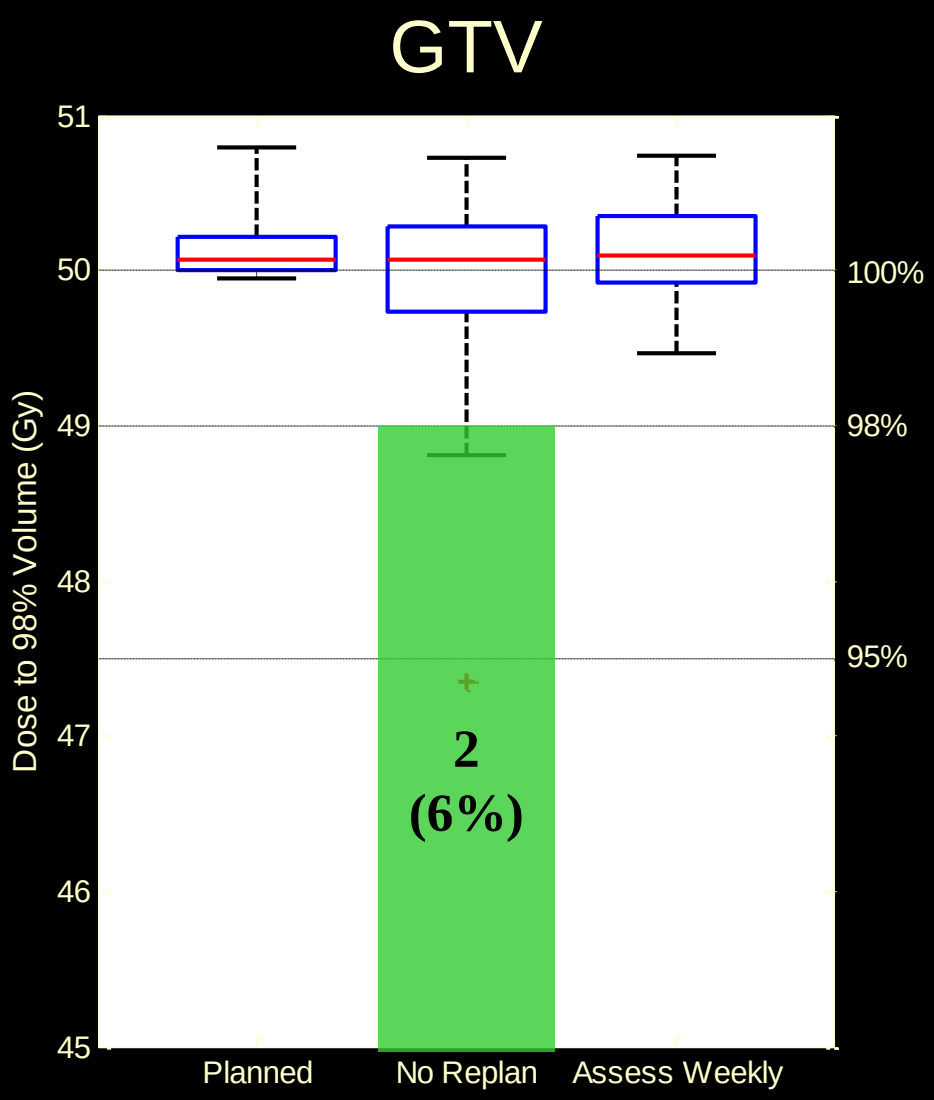


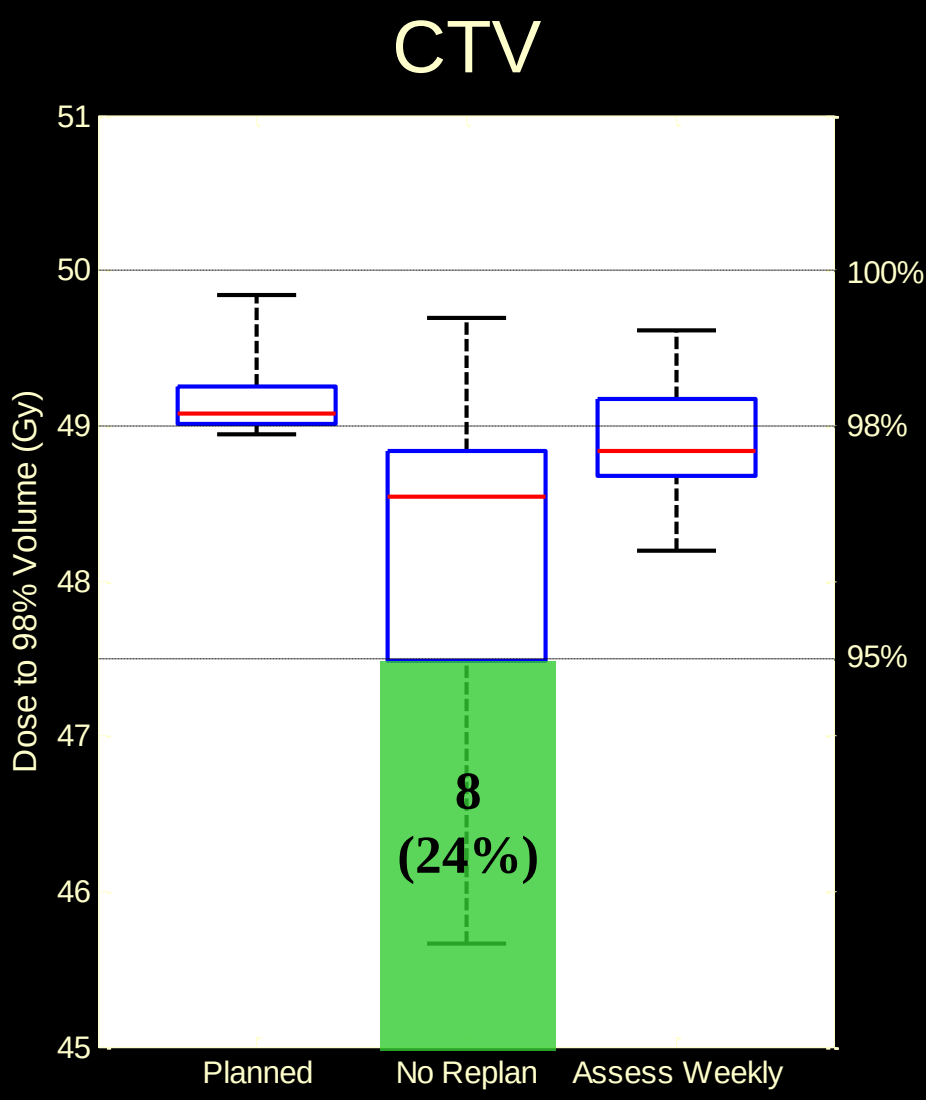
Accumulate across all fractions



Accumulated Dose

Results – Target Coverage

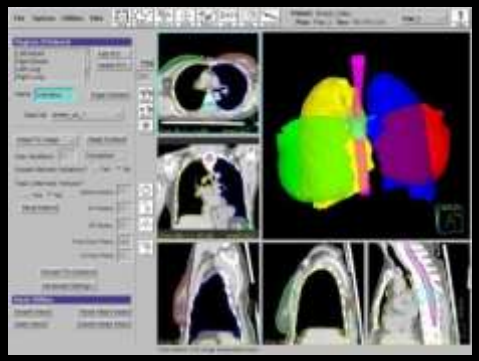


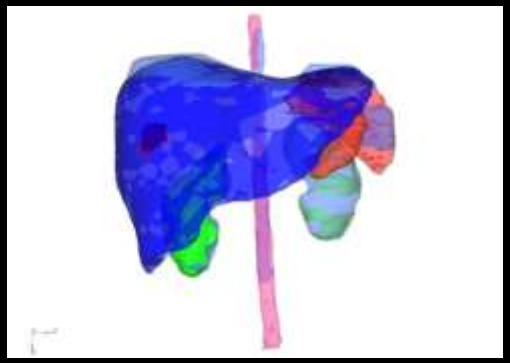


Message: A large fraction of patients would maintain coverage with a 3mm margin!

Computational Advances Needed for Testing the '4D' Hypothesis

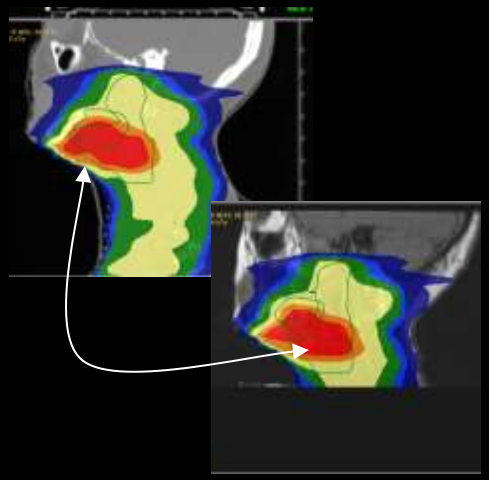
Auto-segmentation

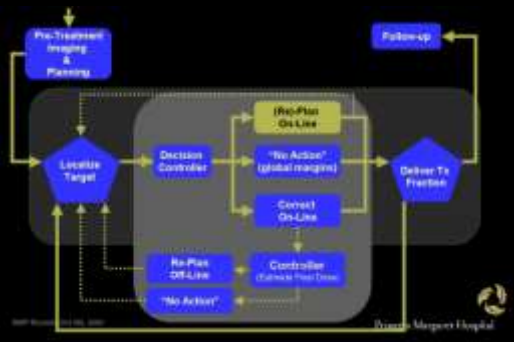




Deformable Registration

Dose Tracking





Re-planning

From the ‘3D Hypothesis’ to the ‘BTV Hypothess’

- *BTV Hypothesis:* Patterning radiation dose according to imaged functional or molecular distributions of the individual will increase the therapeutic ratio.
  - *A.K.A. ‘Biologically Targeted Radiation Therapy’*

Conceptual Framework for Integration of Functional/Molecular Imaging

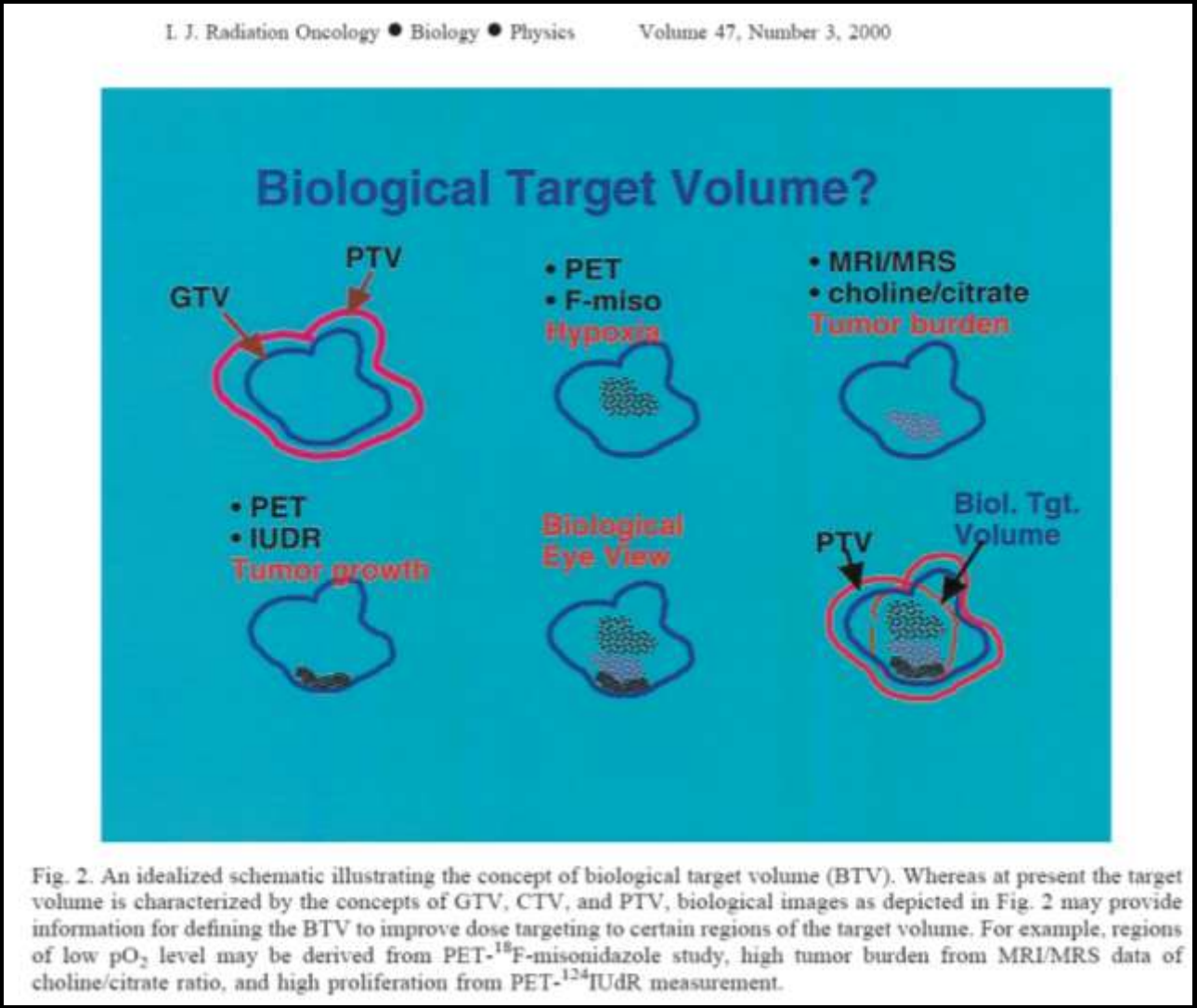


Fig. 2. An idealized schematic illustrating the concept of biological target volume (BTV). Whereas at present the target volume is characterized by the concepts of GTV, CTV, and PTV, biological images as depicted in Fig. 2 may provide information for defining the BTV to improve dose targeting to certain regions of the target volume. For example, regions of low pO_2 level may be derived from PET-^{18}F-misonidazole study, high tumor burden from MRI/MRS data of choline/citrate ratio, and high proliferation from PET-^{124}IUdR measurement.

"Incremental to the concept of gross, clinical, and planning target volumes (GTV, CTV, and PTV), we propose the concept of "biological target volume" (BTV) and hypothesize that BTV can be derived from biological images and that their use may incrementally improve target delineation and dose delivery." - Ling et al.

Ling et al., Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 551–560, 2000

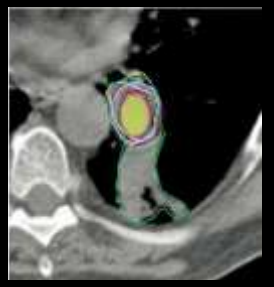
Functional and Molecular Imaging for RT

- Tumour burden, altered metabolism, and clonogen density (e.g. FDG, MRS)
- Tumour hypoxia (e.g. F-MISO, I/FAZA, CAIX, MR-BOLD, HX4)
- Tumour proliferation (e.g. FLT)
- New imaging targets (e.g. FACBC amino acid, EGFR for re-population)
- Functional imaging of crucial healthy tissues (e.g. SPECT/CT/MR derived lung perfusion)
- Vascular and physiological measures (DCE-MR/CT, MR DWI/ADC)

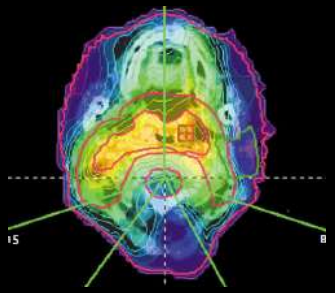
Adapted From 'Theragnostic imaging for radiation oncology: dose-painting by numbers' - S.M. Bentzen - Lancet Oncol 2005; 6: 112–17

Impact of Specific and Sensitive Imaging of Disease on Radiation Therapy

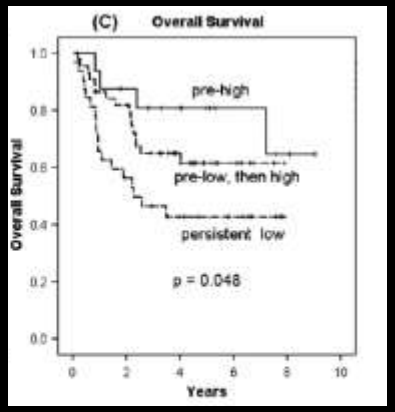
1. Reduce observer-dependent variation in the extent of gross and clinical targets.



2. Enable biologically-modulated targeting of the radiation dose.



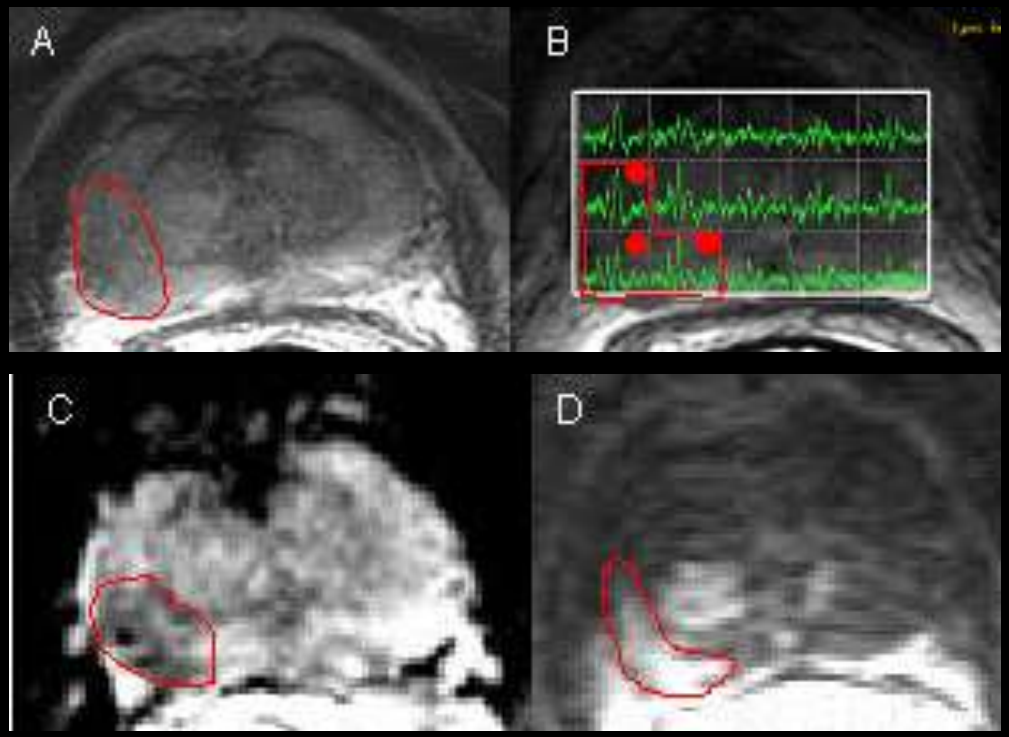
3. Enable prediction of response based upon pre- or intra-treatment changes in the image-based biomarkers.



See Steenbakers 2006, Bentzen 2005, Mayr 2010

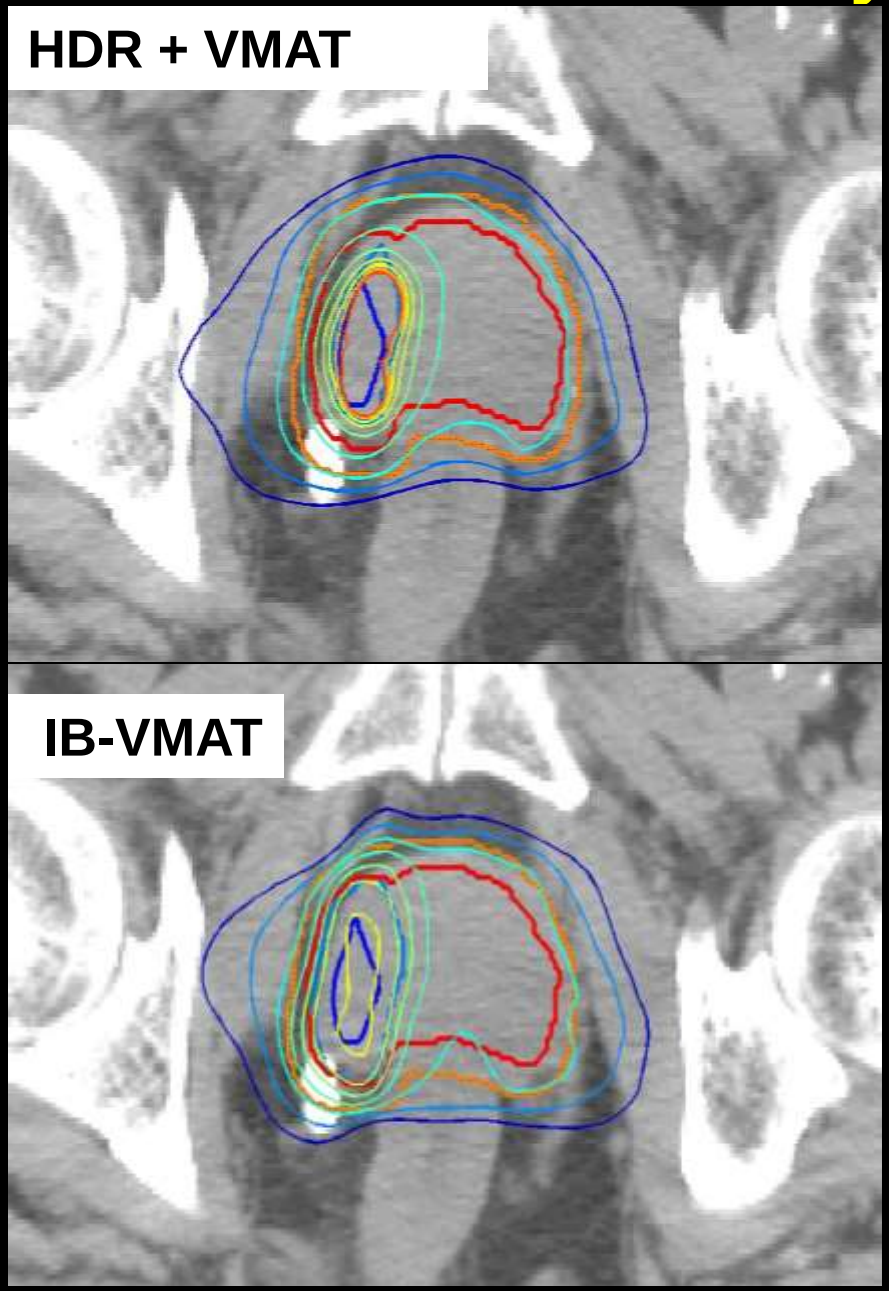
Magnetic Resonance Imaging: Burden of Disease in the Prostate

- ↓ T2
- Fast T1 contrast enhancement & washout
- ↓ Water diffusivity
- ↑ Choline/Citrate



Courtesy of C. Menard

Boost – Either HDR Brachytherapy or VMAT



Dose (EQD2 [Gy])

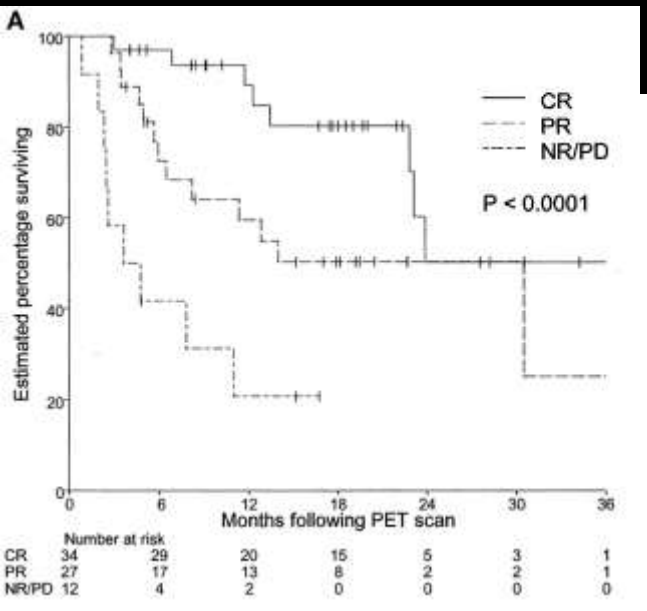
50
60
70
80
90
100
110
120
130

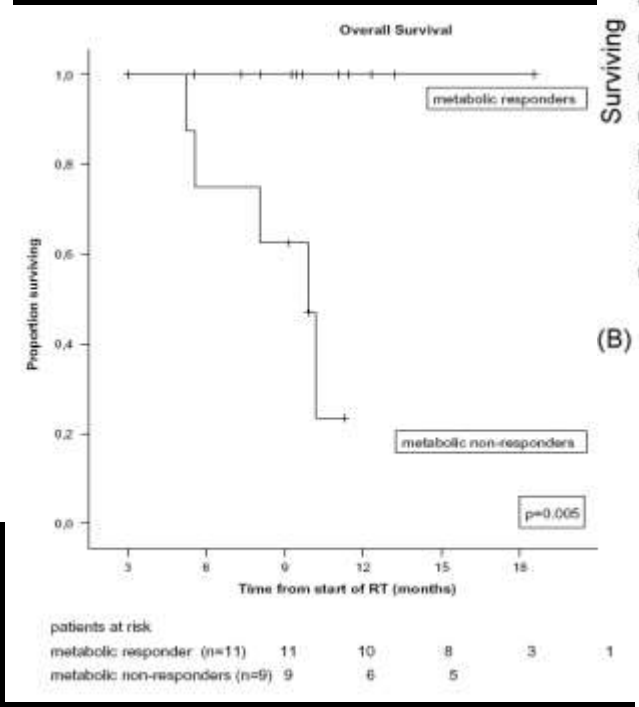
Structures

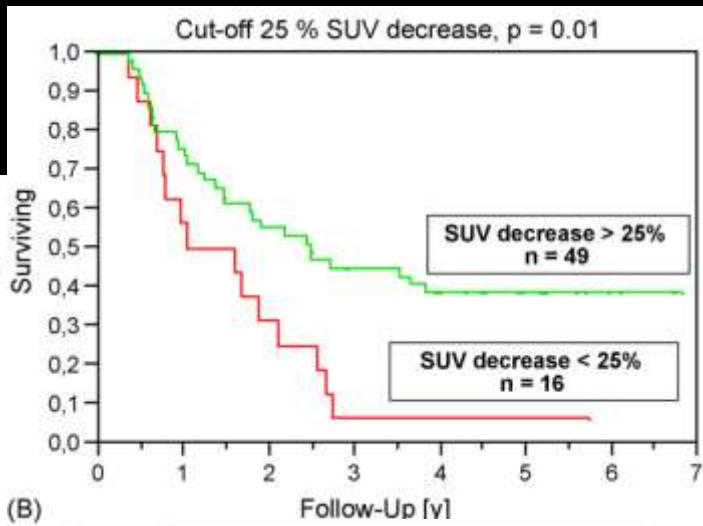
GTV
CTV
PTV(GTV)
PTV(CTV)

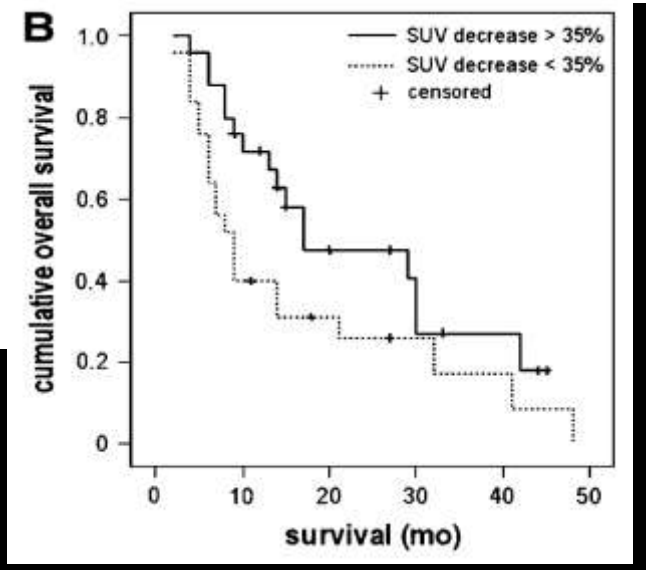
NCIC Funded Project - Menard/Craig - PMH

Lung Cancer - Survival of Metabolic Responders vs Non-responders



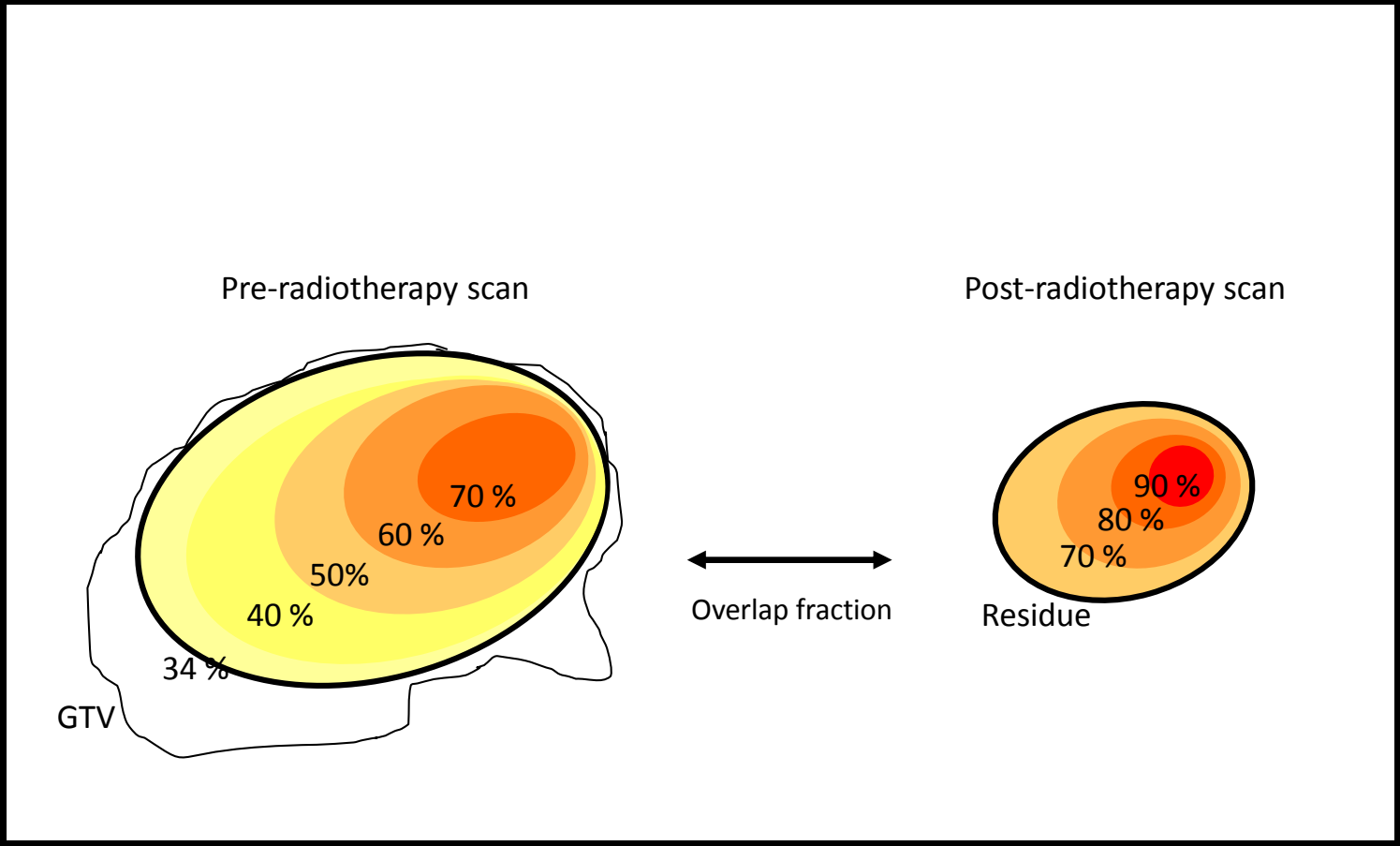






L: Mac Manus (Melbourne), JCO 2003;21(7):1285
M: van Baardwijk (MAASTRO), Radiother Oncol 2007;82(2):145
RT: Eschmann (Tuebingen), Lung Cancer 2006;55:165
RB: de Geus-Oei (Nijmegen), J Nucl Med 2007;48:1592

Residual Response Correlates with Site of Recurrence



Can we spend our IGRT-enable normal tissue dose savings on a well-placed concurrent boost?

A. Dekker - Maastricht

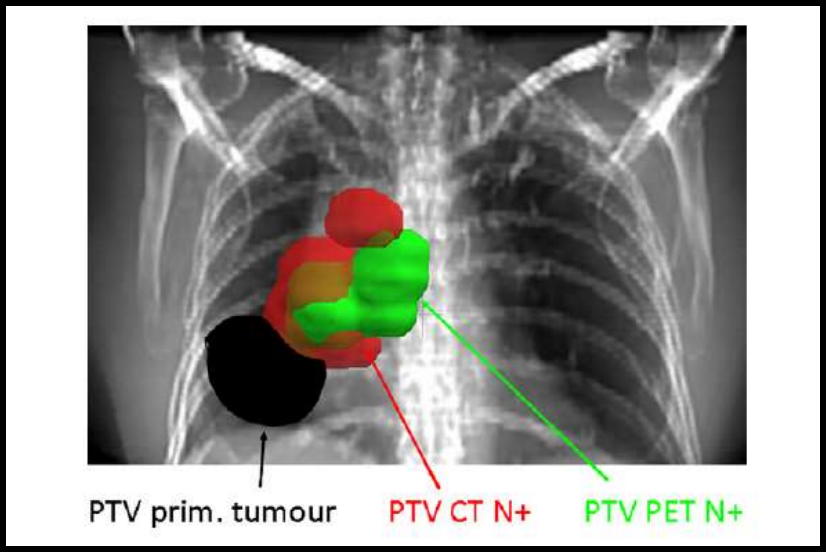
Lung cancer

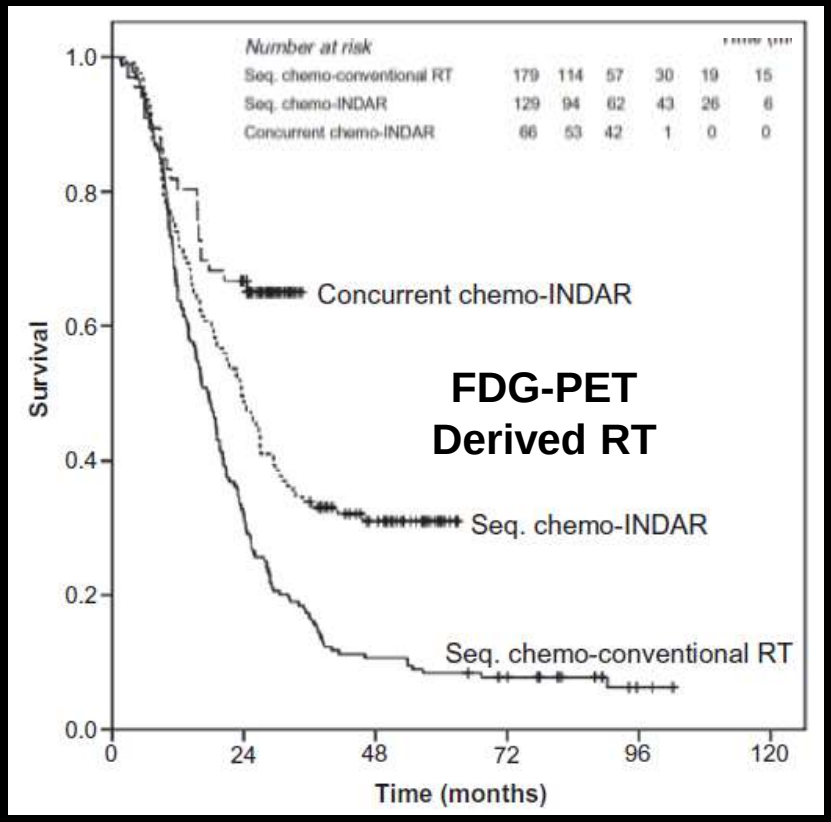
Individualised isotoxic accelerated radiotherapy and chemotherapy are associated with improved long-term survival of patients with stage III NSCLC: A prospective population-based study

Dirk De Ruysscher [a,*], Angela van Baardwijk [a], Jessie Steevens [b], Anita Botterweck [a], Geert Bosmans [a], Bart Reymen [a], Rinus Wanders [a], Jacques Borger [a], Anne-Marie C. Dingemans [c], Gerben Bootsma [d], Cordula Pitz [e], Ragnar Lunde [f], Wiel Geraedts [g], Michel Oellers [a], Andre Dekker [a], Philippe Lambin [a]

[a] Department of Radiation Oncology, Maastricht University Medical Centre; [b] Comprehensive Cancer Centre The Netherlands, Maastricht, The Netherlands; [c] Department of Pulmonology, Maastricht University Medical Centre; [d] Department of Pulmonology, Atrium Medical Centre, Heerlen; [e] Department of Pulmonology, Laurentius Hospital, Roermond; [f] Department of Pulmonology, St. Jansgasthuis, Weert; [g] Department of Pulmonology, Orbis Medical Centre, Sittard, The Netherlands

"INDAR" - Individualised iso-toxic accelerated radiotherapy (INDAR) to the primary tumour and the pre-Tx involved lymph nodes on FDG-PET-CT scan.





D. De Ruysscher et al. / Radiotherapy and Oncology 102 (2012) 228–233

*64.8 Gy given in 36 bi-daily fractions of 1.8 Gy

Patient-specific Radiation Sensitivity

Radiotherapy and Oncology, 17 (1990) 177–190
Elsevier

RADION 00659

The ESTRO Regaud Lecture*

Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response

Lester J. Peters

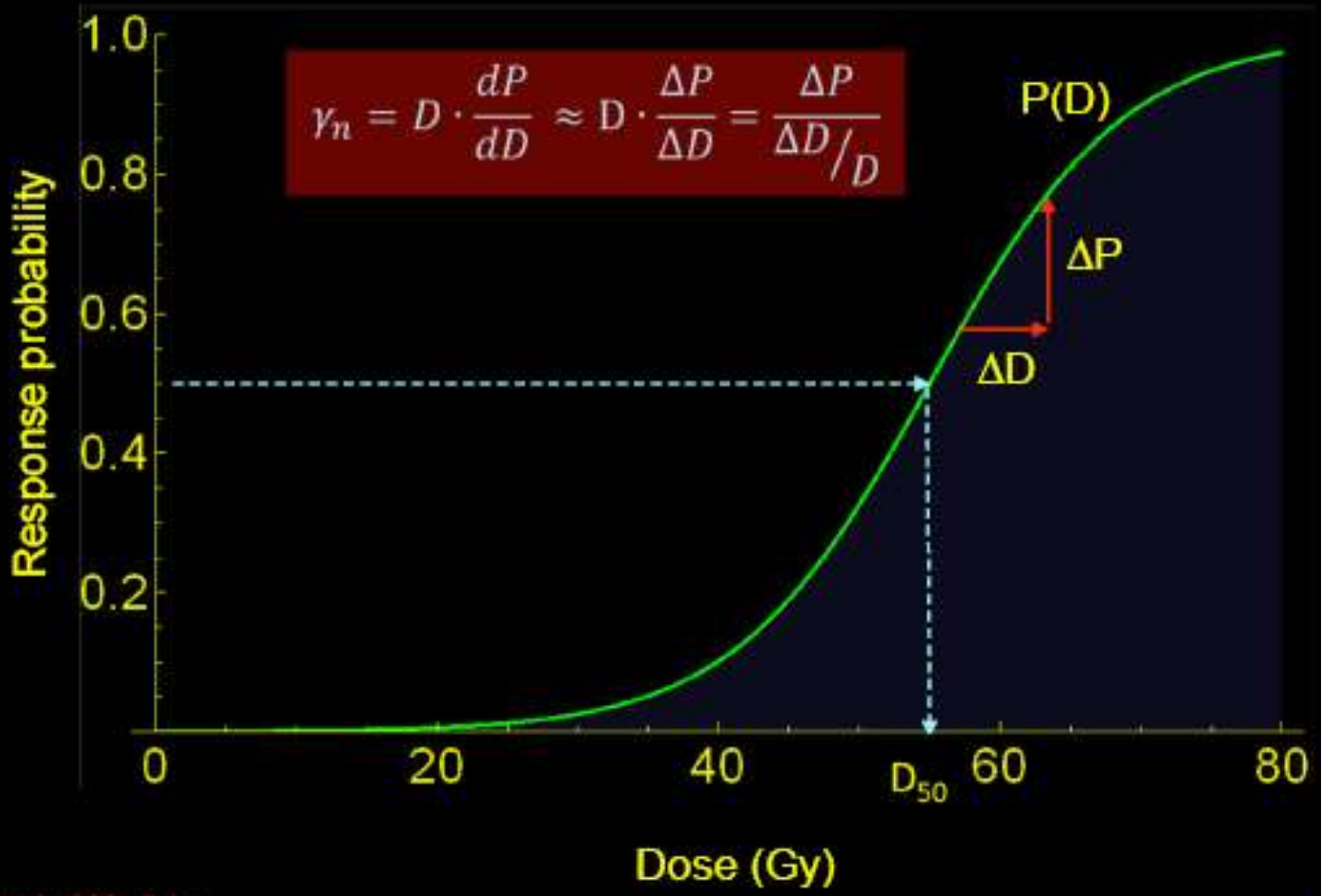
Division of Radiotherapy, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

(Received 23 July 1989, revision received 23 August 1989, accepted 23 August 1989)

Key words: Tumor c

In his introduction to this lecture, Dr. Fletcher characterizes prediction of the radiocurability of individual tumors as the "Holy Grail of Radiotherapy".

The normalized dose-response gradient

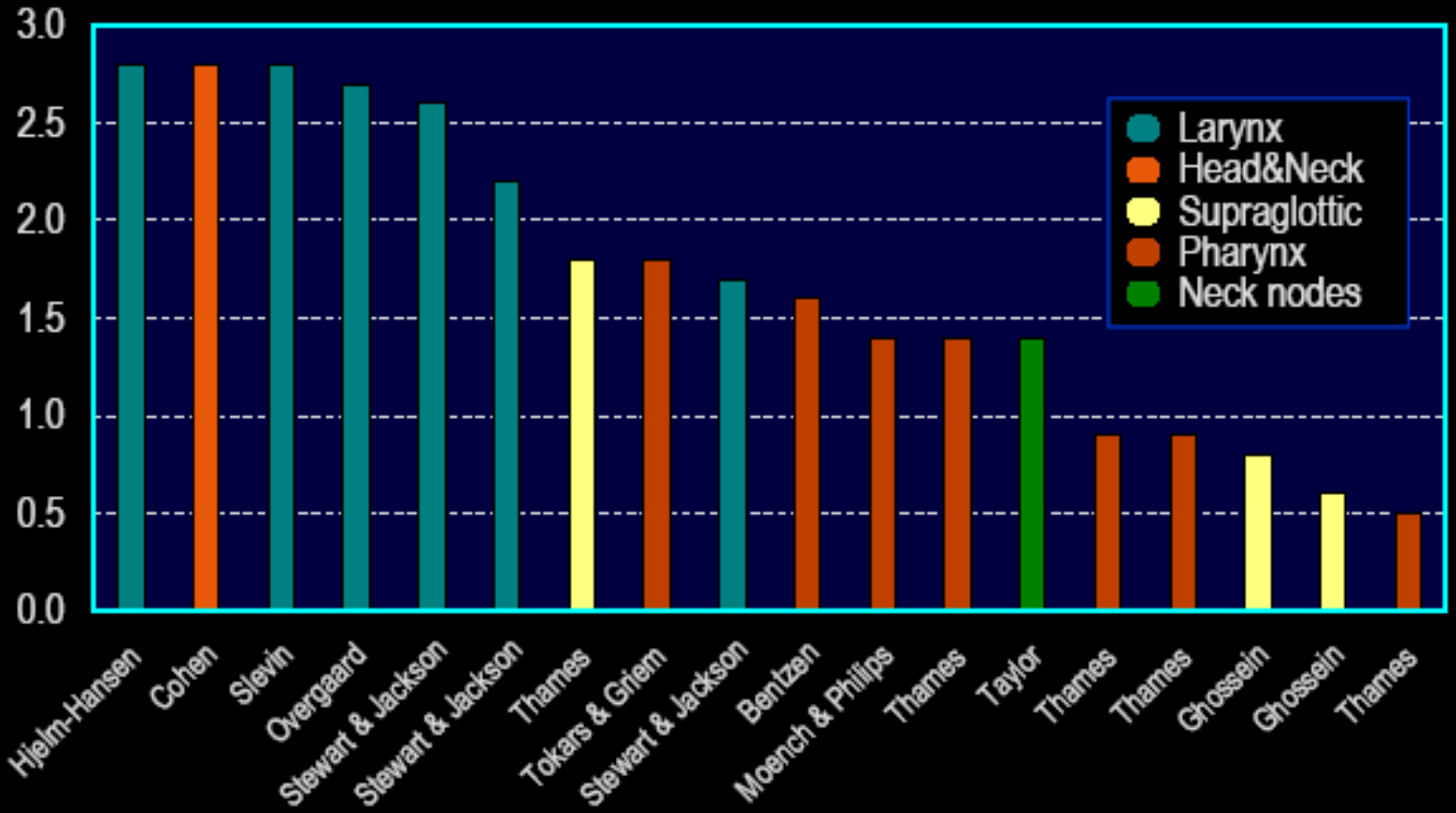


School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON

/SMB 09/11

Courtesy of S. Bentzen

Steepness of DR curves for HNSCC



School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

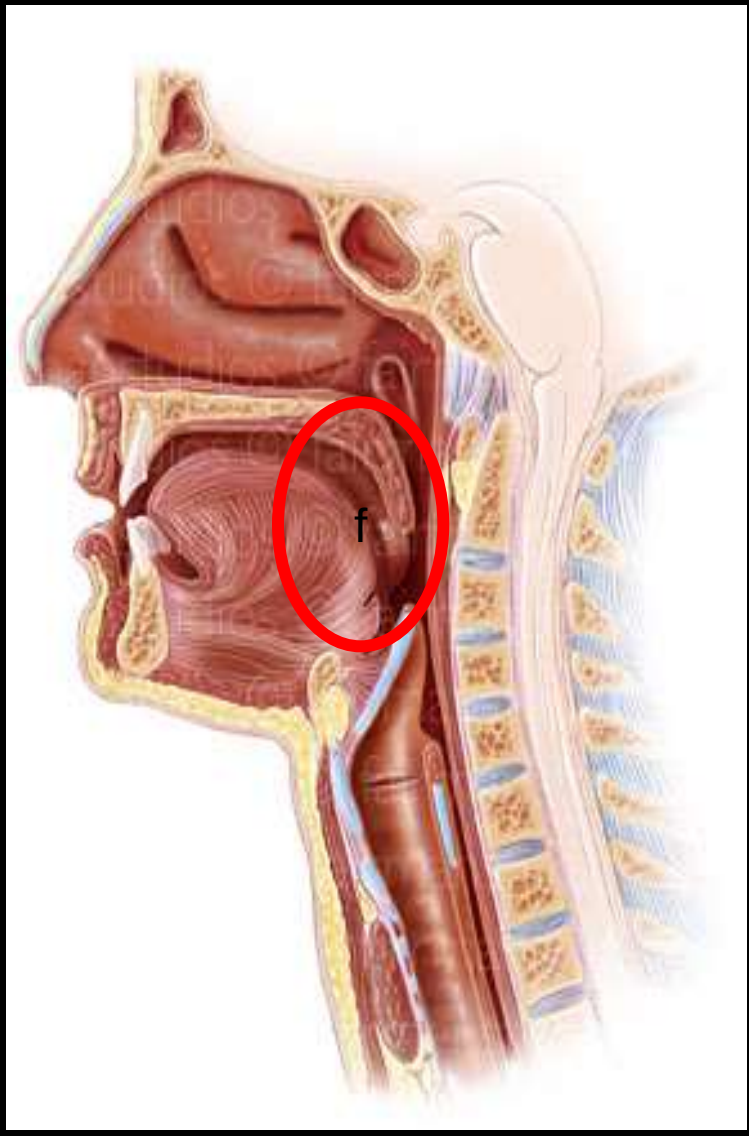
Bentzen *R&O* 32: 1 (1994)

/SMB

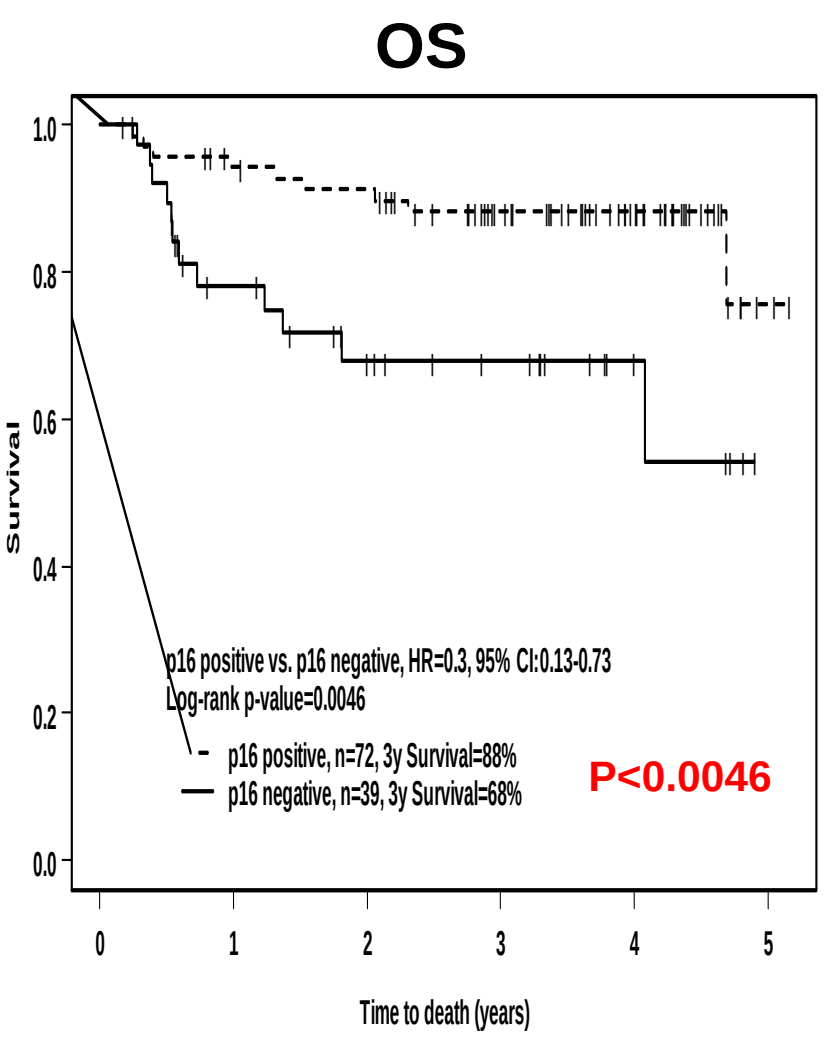
Courtesy of S. Bentzen

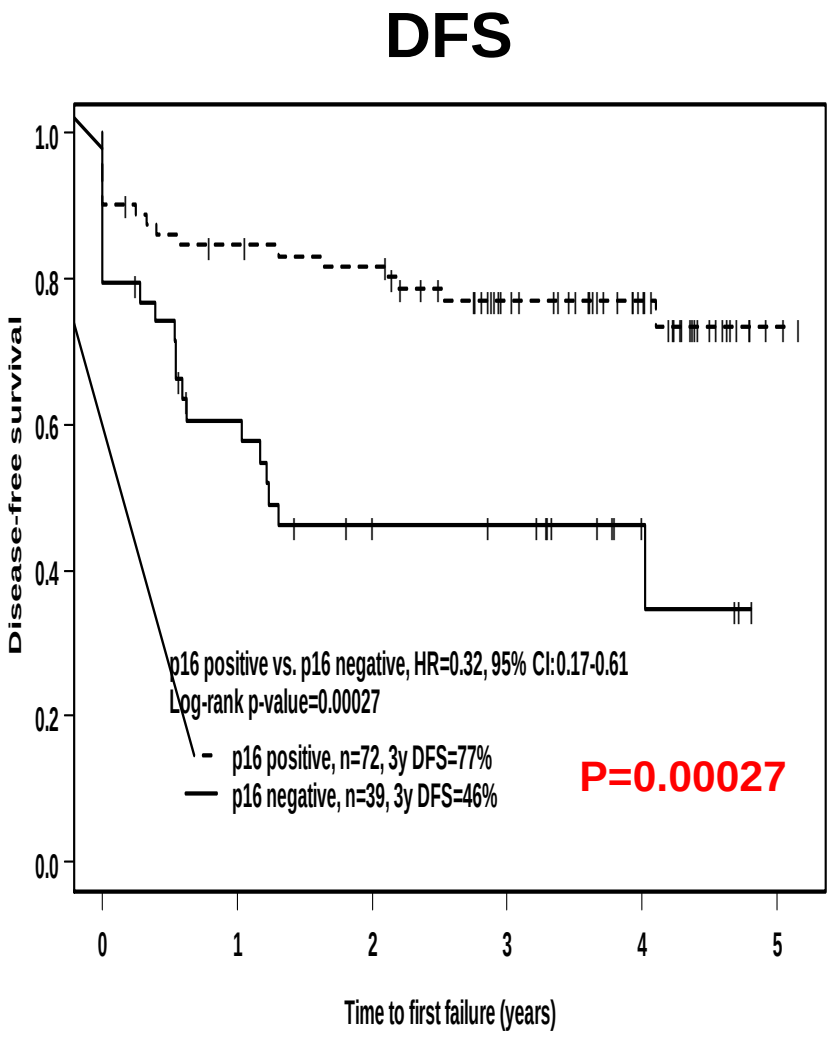
HNC – Oropharynx: Two Populations?

- Traditional risk factors for head & neck cancers (HNC) are cigarette smoking, and EtOH consumption
- Epidemiology has changed in recent decades
- HPV-related Disease versus Classical Disease



Separation of Patients by p16 Expression





Shi *et al*; *JCO* 27:6213, 2009

Radiotherapy and Oncology, 17 (1990) 177–190
Elsevier

RADION 00659

The ESTRO Regaud Lecture*

Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response

Lester J. Peters

Division of Radiotherapy, The

(Received 23 July 1

Key words: Tumor cell radiosens

In his introd
characterizes
individual tu
therapy".

TABLE I

Examples of empiric and radiobiologic prognostic factors.

	Empiric	Radiobiologic
Tumor	Site of origin	Clonogen number
	Histology	Radiosensitivity
	Size (stage)	intrinsic
	Morphology	environmental
		Proliferation kinetics
Patient	Performance status	Genetic determinants
	Age, sex	of radiosensitivity
	Host-response parameters	

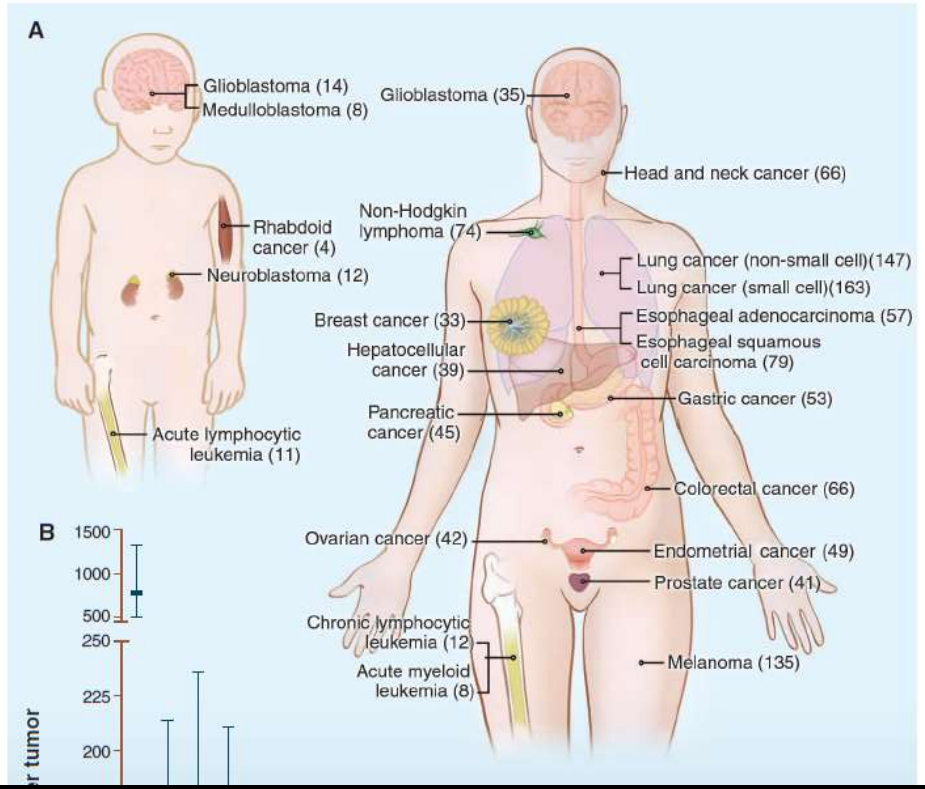
CANCERGENOMICS
www.sciencemag.org/special/cancergenomics

29 MARCH 2013 VOL 339 SCIENCE

REVIEW

Cancer Genome Landscapes

Bert Vogelstein, Nickolas Papadopoulos, Victor E. Velculescu, Shibin Zhou, Luis A. Diaz Jr., Kenneth W. Kinzler*



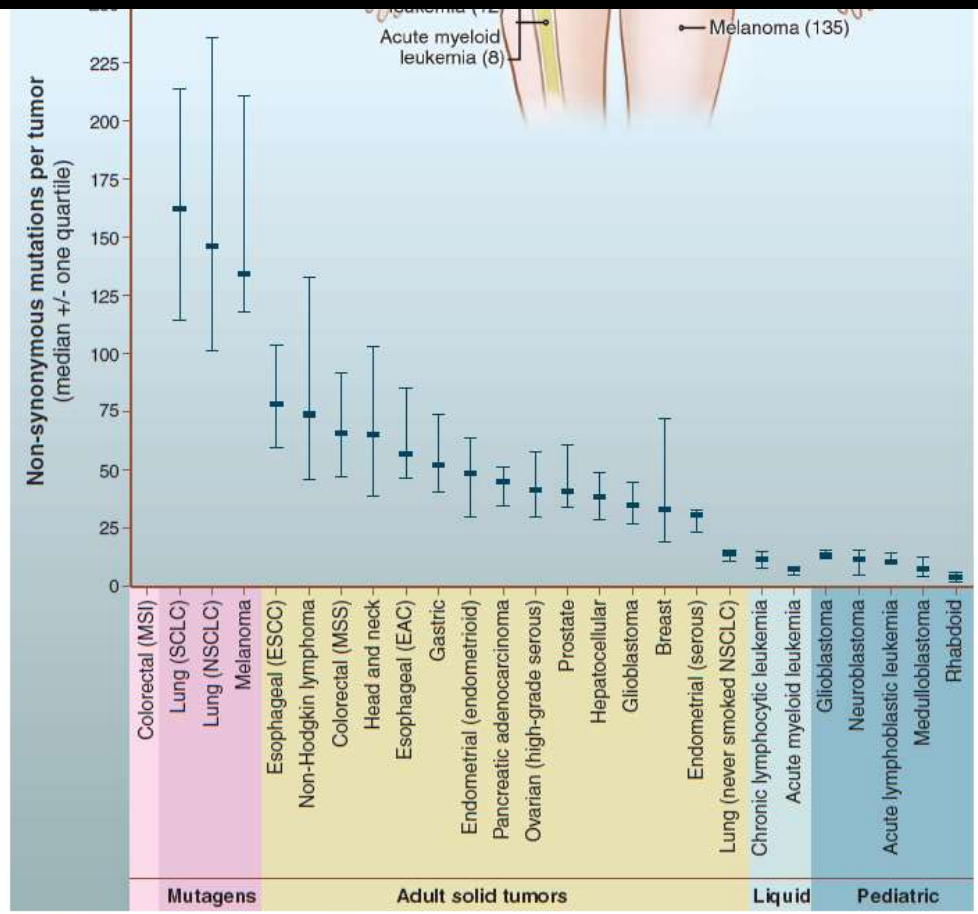


Fig. 1. Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies. (**A**) The genomes of a diverse group of adult (right) and pediatric (left) cancers have been analyzed. Numbers in parentheses indicate the median number of nonsynonymous mutations per tumor. (**B**) The median number of nonsynonymous mutations per tumor in a variety of tumor types. Horizontal bars indicate the 25 and 75% quartiles. MSI, microsatellite instability; SCLC, small cell lung cancers; NSCLC, non–small cell lung cancers; ESCC, esophageal squamous cell carcinomas; MSS, microsatellite stable; EAC, esophageal adenocarcinomas. The published data on which this figure is based are provided in table S1C.

Median number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies.

CANCERGENOMICS
www.sciencemag.org/special/cancergenomics

REVIEW

Cancer Genome Landscapes

Bert Vogelstein, Nickolas Papadopoulos, Victor E. Velculescu, Shibin Zhou, Luis A. Diaz Jr., Kenneth W. Kinzler*

Genetic heterogeneity in tumors – illustrated by a primary pancreatic tumor and its metastatic lesions.

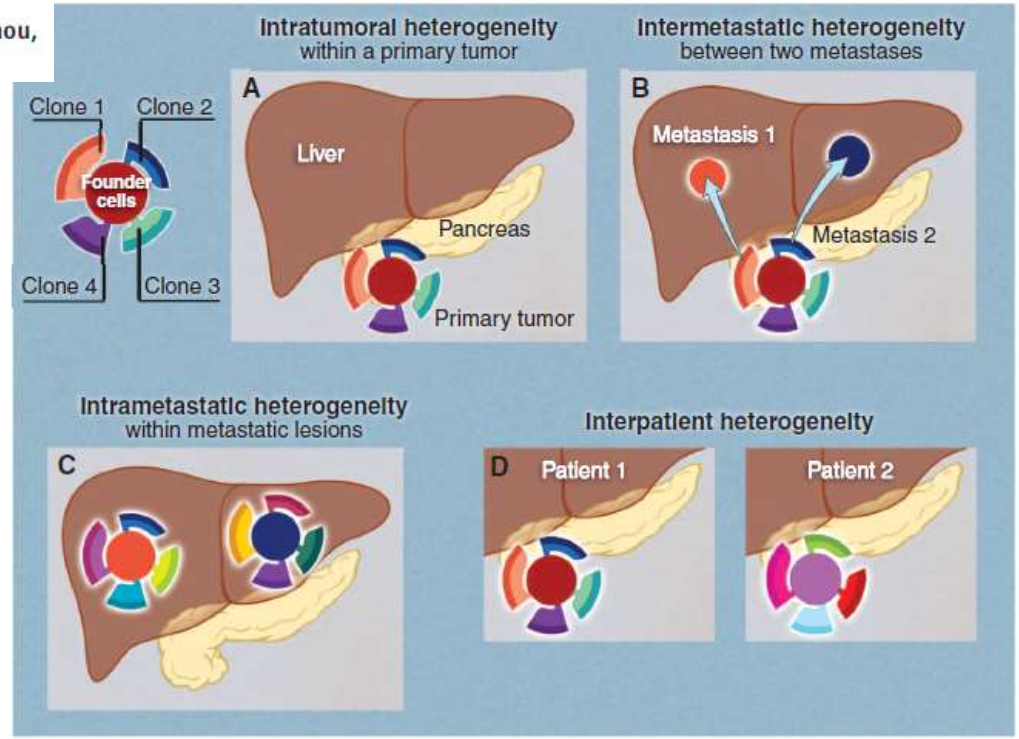


Fig. 6. Four types of genetic heterogeneity in tumors, illustrated by a primary tumor in the pancreas and its metastatic lesions in the liver. Mutations introduced during primary tumor cell growth result in clonal heterogeneity. At the top left, a typical tumor is represented by cells with a large fraction of the total mutations (founder cells) from which subclones are derived. The differently colored regions in the subclones represent stages of evolution within a subclone. (**A**) Intratumoral: heterogeneity among the cells of the primary tumor. (**B**) Intermetastatic: heterogeneity among different metastatic lesions in the same patient. In the case illustrated here, each metastasis was derived from a different subclone. (**C**) Intrametastatic: heterogeneity among the cells of each metastasis develops as the metastases grow. (**D**) Interpatient: heterogeneity among the tumors of different patients. The mutations in the founder cells of the tumors of these two patients are almost completely distinct (see text)

A molecular assay of tumor radiosensitivity: a roadmap towards biology-based personalized radiation therapy

Javier F Torres-Roca

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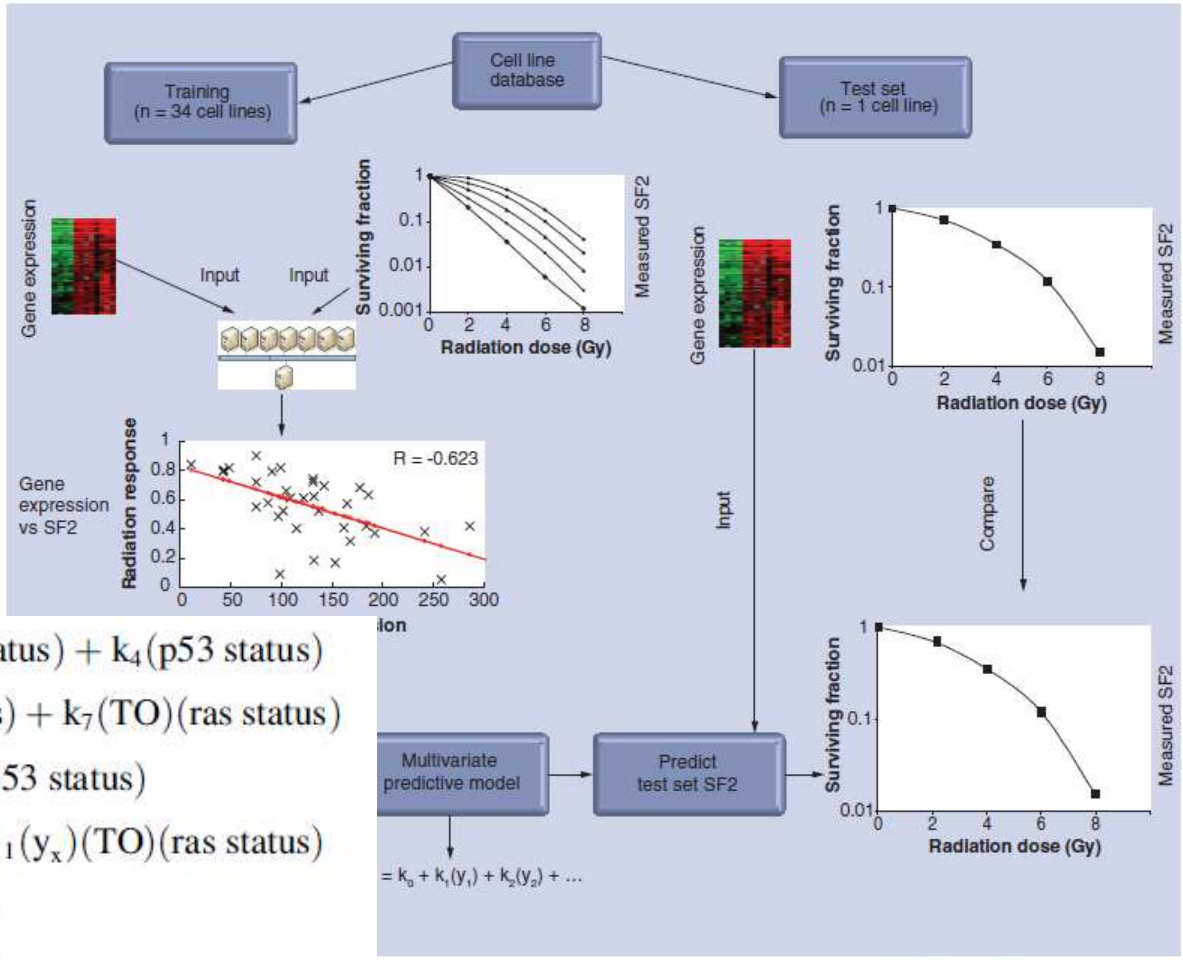
javier.torresroca@moffitt.org



$$SF2_X = k_0 + k_1(y_x) + k_2(TO) + k_3(\text{ras status}) + k_4(\text{p53 status}) + k_5(y_x)(TO) + k_6(y_x)(\text{ras status}) + k_7(TO)(\text{ras status}) + k_8(y_x)(\text{p53 status}) + k_9(TO)(\text{p53 status}) + k_{10}(\text{ras status})(\text{p53 status}) + k_{11}(y_x)(TO)(\text{ras status}) + k_{12}(y_x)(\text{ras status})(\text{p53 status}) + k_{13}(TO)(\text{ras status})(\text{p53 status}) + k_{14}(y_x)(TO)(\text{ras status})(\text{p53 status}) +$$

classifier. A leave-one-out cross-validation approach was utilized to develop and test the dentify radiation-specific biomarkers to build the classifier. The classifier was based on a linear pression for the selected genes and k_x are coefficients generated during the training process. ariable prediction (not binary; p = 0.002).

Data taken from [44].

Personalized Medicine (2012) **9**(5), 547–557

A molecular assay of tumor radiosensitivity: a roadmap towards biology-based personalized radiation therapy

Javier F Torres-Roca
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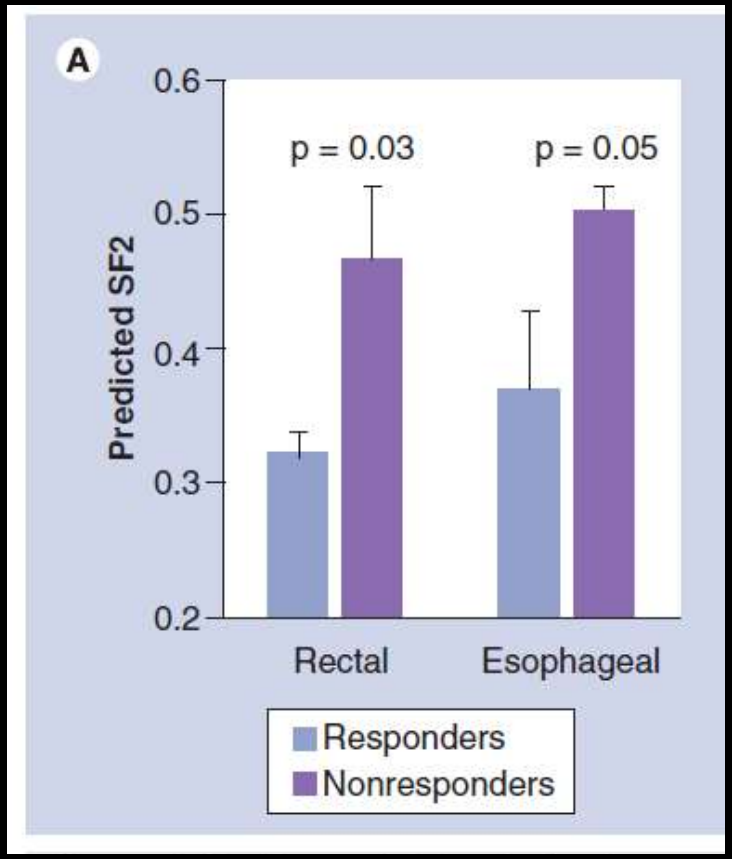


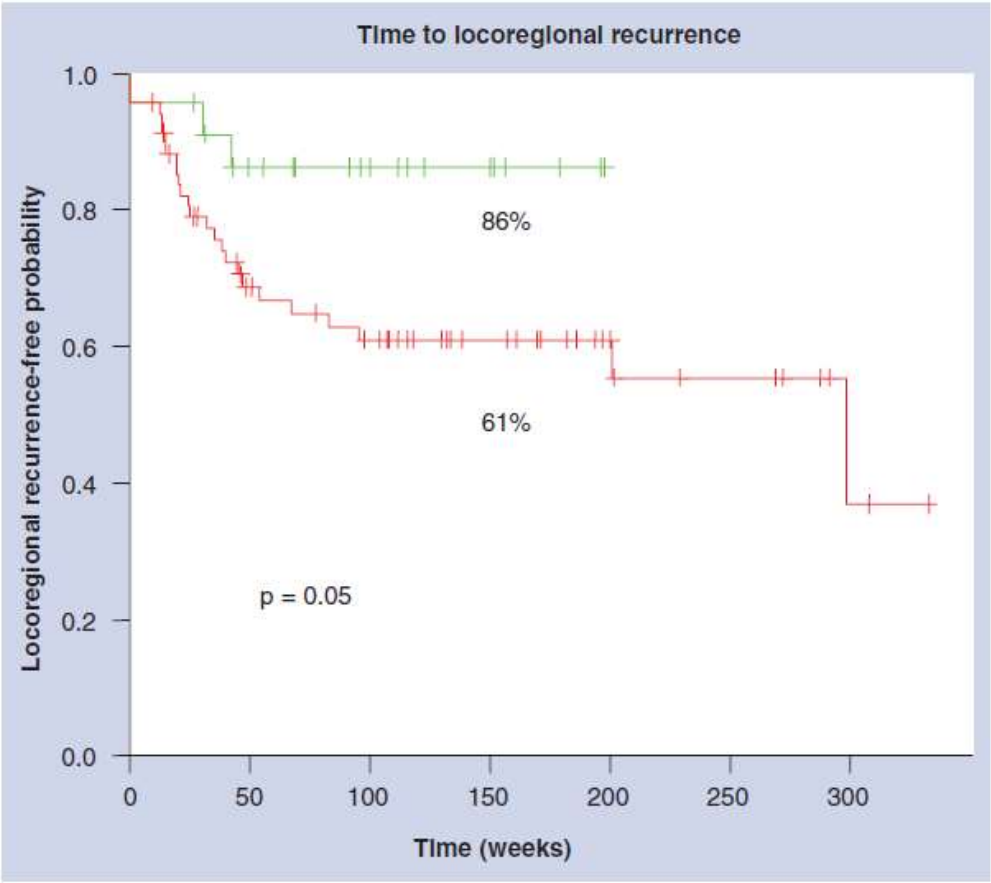


Figure 5. Radiosensitivity index distinguishes clinical populations with different disease-related outcomes in head and neck cancer. Radiosensitivity predictions were generated with the gene-expression model as described in 92 patients treated with definitive concurrent radiochemotherapy at The Netherlands Cancer Institute (Amsterdam, The Netherlands). Using the 25th percentile as the cutoff point, there is a superior 2-year locoregional control in the predicted radiosensitive group (green vs red, 86 vs 61%; p = 0.05) Reproduced with permission from [64] © Elsevier (2009).

Personalized Medicine (2012) **9**(5), 547–557

Clinical Oncology xxx (2013) 1–7

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Biomarkers of Radiation Exposure: Can They Predict Normal Tissue Radiosensitivity?

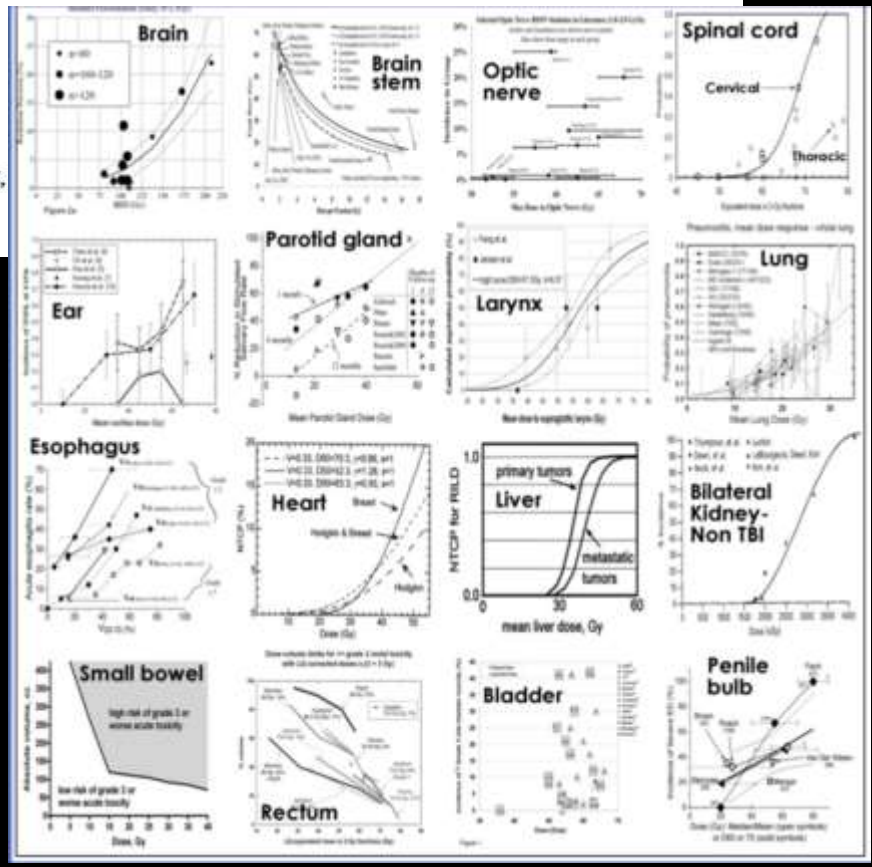
M.L.K. Chua *†, K. Rothkamm †

* University College London Cancer Institute, London, UK
† Public Health England, Centre for Radiation, Chemical and Environmental Hazards,

Received 28 February 2013; received in revised form 23 April 2013; accepted 26 June 2013

Radiogenomics and biomarkers:

- SNPs, CNV, GWAS Studies
- Radiogenomics Consortium – 2009
- What dose was actually delivered?



Quantec - IJORBP Vol. 76, No. 3, Supplement, 2010

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

RAPPER: The Radiogenomics of Radiation Toxicity

N.G. Burnet *, G.C. Barnett *†, R.M. Elliott §, D.P. Dearnaley §, P.D.P. Pharoah †, A.M. Dunning †, C.M.L. West ‡ on Behalf of the RAPPER Investigators[a]

* *University of Cambridge Department of Oncology, Oncology Centre, Addenbrooke's Hospital, Cambridge, UK*
† *University of Cambridge Department of Oncology, Strangeways Research Laboratory, Cambridge, UK*
‡ *Translational Radiobiology Group, University of Manchester, Christie Hospital, Manchester, UK*
§ *Institute of Cancer Research, Sutton, Surrey, UK*

Received 20 February 2013; accepted 26 February 2013

RAPPER (Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy)

"The ultimate goal of radiogenomics is to add an additional element of personalised medicine to the radiotherapy planning and prescription, to improve the outcome for the patient. Such individualisation, combined with the very best radiotherapy treatment planning and delivery techniques, will also allow for more imaginative combination with pharmaceutical agents and should achieve both lower toxicity and higher cure rates."

Clinical Oncology 25 (2013) 431-434

Identification of noninvasive imaging surrogates for brain tumor gene-expression modules

Maximilian Diehn*†, Christine Nardini*, David S. Wang*, Susan McGovern‡, Mahesh Jayaraman§, Yu Liang¶, Kenneth Aldape‡, Soonmee Cha‖, and Michael D. Kuo*,**††

*Department of Radiology and **Center for Translational Medical Systems, University of California San Diego Medical Center, San Diego, CA 92103; †Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305; ‡Department of Neuropathology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; §Department of Radiology, Brown University, Providence, RI 02912; ¶Department of Neurological Surgery, Brain Tumor Research Center, University of California San Francisco Medical Center, San Francisco, CA 94143; and ‖Department of Radiology, University of California San Francisco Medical Center, San Francisco, CA 94143

Communicated by Helen M. Ranney, University of California at San Diego, La Jolla, CA, February 9, 2008 (received for review October 16, 2007)

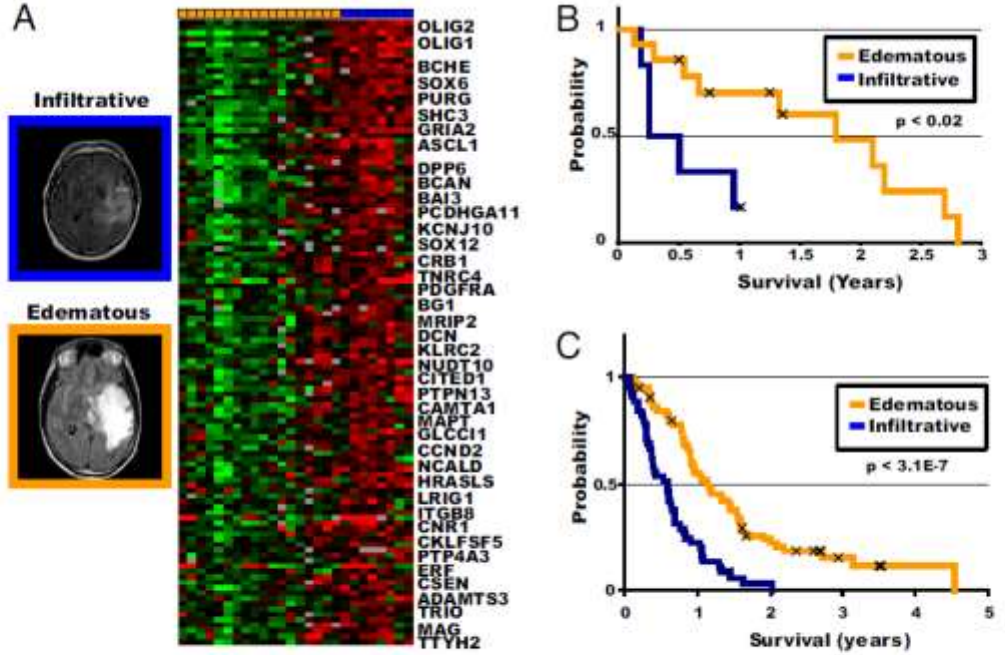
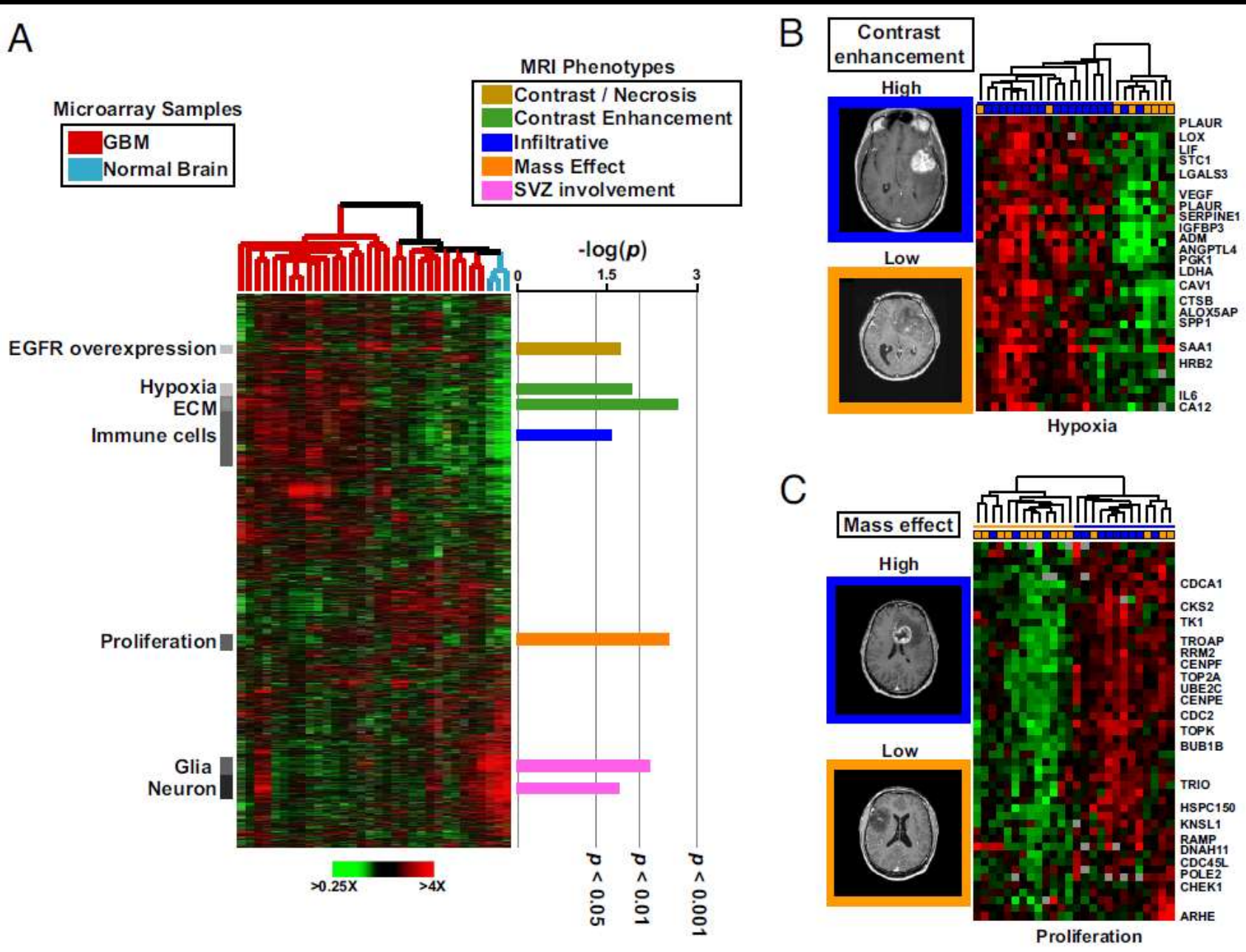


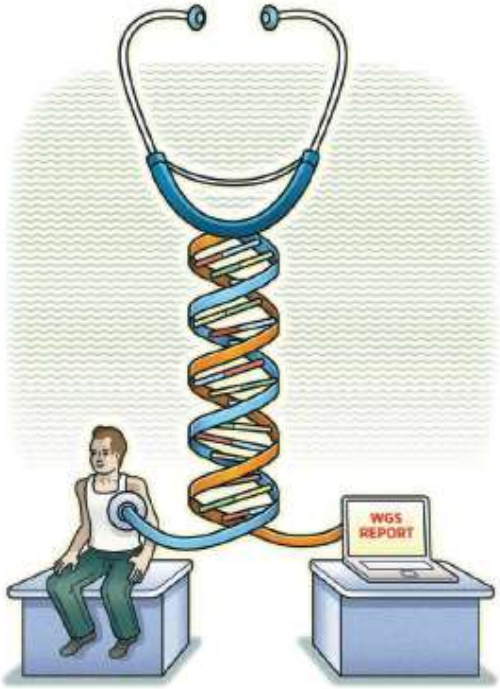
Fig. 4. The infiltrative/edematous radiophenotype predicts survival of GBM patients. (*A*) Expression of the infiltrative radiophenotype-associated genes in the initial set of GBMs. Data are displayed as in Fig. 1. (*B*) Kaplan–Meier analysis based on the infiltrative/edematous radiophenotype for the initial set of GBMs. (*C*) Kaplan–Meier analysis based on the infiltrative/edematous radiophenotype for an independent cohort of 110 GBM patients. Median overall survival was 390 days for edematous tumors and 216 days for infiltrative tumors ($P < 3.1 \times 10^{-7}$).


A
Microarray Samples
GBM
Normal Brain
MRI Phenotypes
Contrast / Necrosis
Contrast Enhancement
Infiltrative
Mass Effect
SVZ involvement
-log(p)
0
1.5
3
EGFR overexpression
Hypoxia
ECM
Immune cells
Proliferation
Glia
Neuron
>0.25X
>4X
p < 0.05
p < 0.01
p < 0.001
B
Contrast enhancement
High
Low
PLAUR
LOX
LIF
STC1
LGALS3
VEGF
PLAUR
SERPINE1
IGFBP3
ADM
ANGPTL4
PGK1
LDHA
CAV1
CTSB
ALOX5AP
SPP1
SAA1
HRB2
IL6
CA12
Hypoxia
C
Mass effect
High
Low
CDCA1
CKS2
TK1
TROAP
RRM2
CENPF
TOP2A
UBE2C
CENPE
CDC2
TOPK
BUB1B
TRIO
HSPC150
KNSL1
RAMP
DNAH11
CDC45L
POLE2
CHEK1
ARHE
Proliferation

Personalized Medicine: Temper Expectations

THE 1 JUNE POLICY FORUMS, "THE ULTIMATE GENETIC TEST" (R. DRMANAC, P. 1110) AND "Whole-genome sequencing: The new standard of care?" (L. R. Brunham and M. R. Hayden, p. 1112), discuss clinical breakthroughs that might be possible through whole-genome sequencing (WGS). We offer a cautionary note about the interpretation and expectations of personalized medicine and its subset, individualized drug therapy, specifically those that pertain to risk prediction in the individual patient.

As first shown in 1918 (*1*), a complex quantitative trait can be explained by Mendelian inheritance if multiple genes affect the trait. From this analysis, one can infer that accurate statistical predictions of a complex trait require identification of many small-effect variants which, in combination, can explain a large fraction of variance in the phenotype. For most complex traits, this is an unachievable goal. Although we can obtain WGS data from a large number of patients, effect sizes for the majority of small-effect variants are simply too miniscule to be detected, even with any practicably attainable sample size. The anticipation of personalized medicine and individualized drug therapy thus seems unrealistic. We might be able to obtain accurate genomic data from an individual patient, but our ability to tailor treatment will be limited to only a small fraction of variants that have relatively large ("identifiable") effect sizes.



Before 1990, a number of examples of pharmacogenetic traits, usually binary, were published [e.g., (*2*–*6*); reviewed in

24 AUGUST 2012 VOL 337 SCIENCE www.sciencemag.org

"We now realize that most examples of pharmacogenomic traits (adverse drug reactions, as well as drug efficacy) resemble complex diseases and other multi-factorial traits such as height or body mass index. These traits reflect contributions from innumerable low-effect genes."

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MEDICINE

(De)Personalized Medicine

Ralph I. Horwitz,[1] Mark R. Cullen,[2] Jill Abell,[3] Jennifer B. Christian[4]

Integration of clinical, social, and environmental data with genomic and molecular information is needed to develop a personalized approach to medicine.

Personalized medicine is often described as genomics-based knowledge that "promises the ability to approach each patient as the biological individual he or she is" (*1*). This is an appealing description, yet unless clinical, social, and environmental features that affect the outcomes of disease are also incorporated, the current approach

9.8% for those who received a placebo; the relative risk and relative risk reduction were 0.74 and 26%, respectively. Although these kinds of statistics are typically used to describe the results of therapeutic trials, the findings can also be described differently. In the case of the BHAT, the results could also be reported as the absolute difference in mortality between

"The failure to give suitable weight to clinical variation is not the fault of the statistical paradigm any more than it is the fault of the molecular orientation of contemporary medicine. The problem lies with the atrophy of clinical science. Physician investigators whose clinical knowledge equips them to create the needed clinical taxonomies have been distracted by quantitative models or reductionist science. What is needed to complement the power of genomics is an emphasis on personal attributes of patients and their environments, and to incorporate these features into an enriched approach to personalized medicine."

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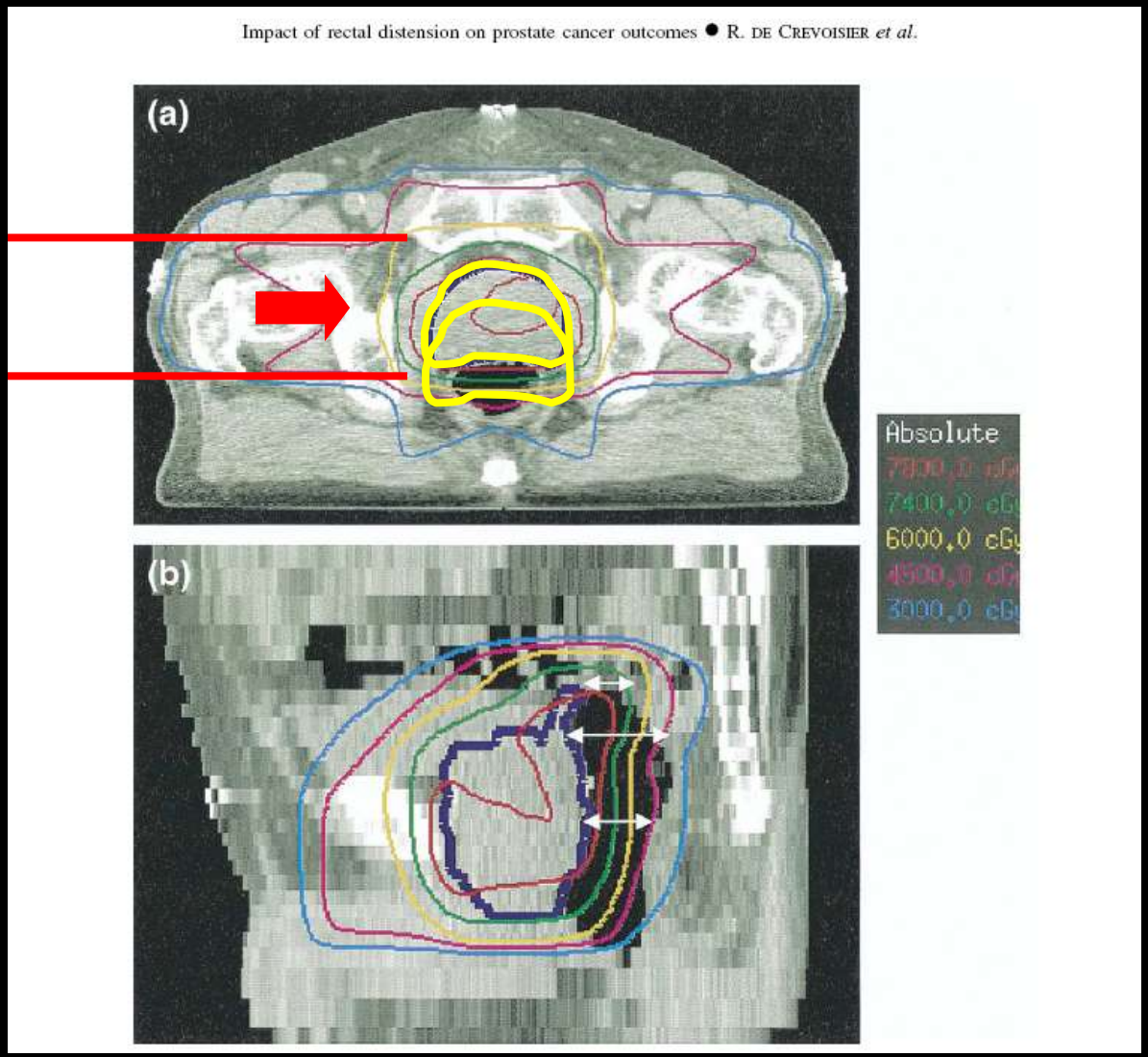
Is it possible for us to integrate these rich and varied data sources?

Can we draw this information together to assure precision and accuracy in treatment?

What else affects our Kaplan-Meier curves?

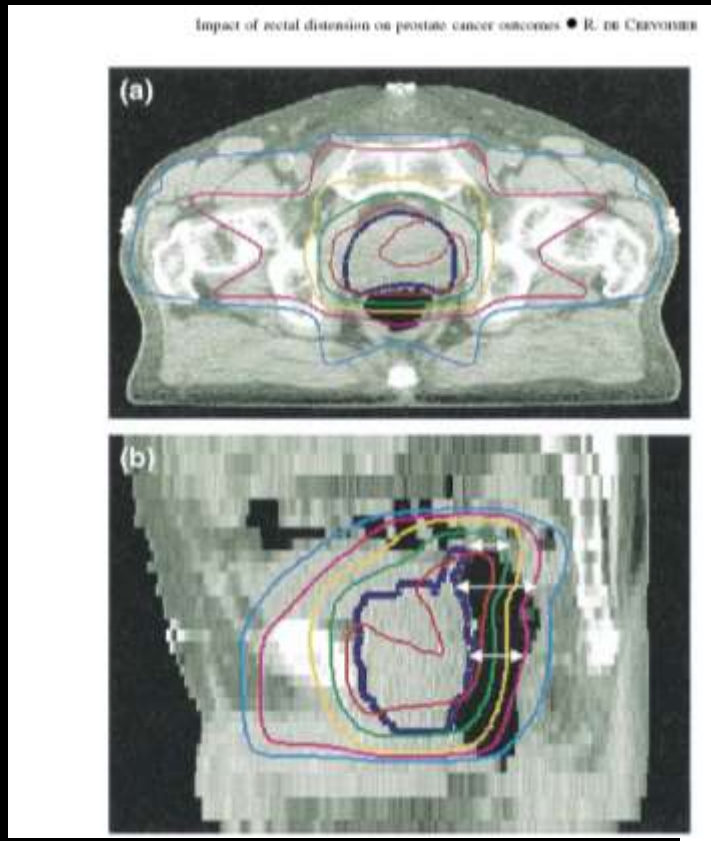
Methods:

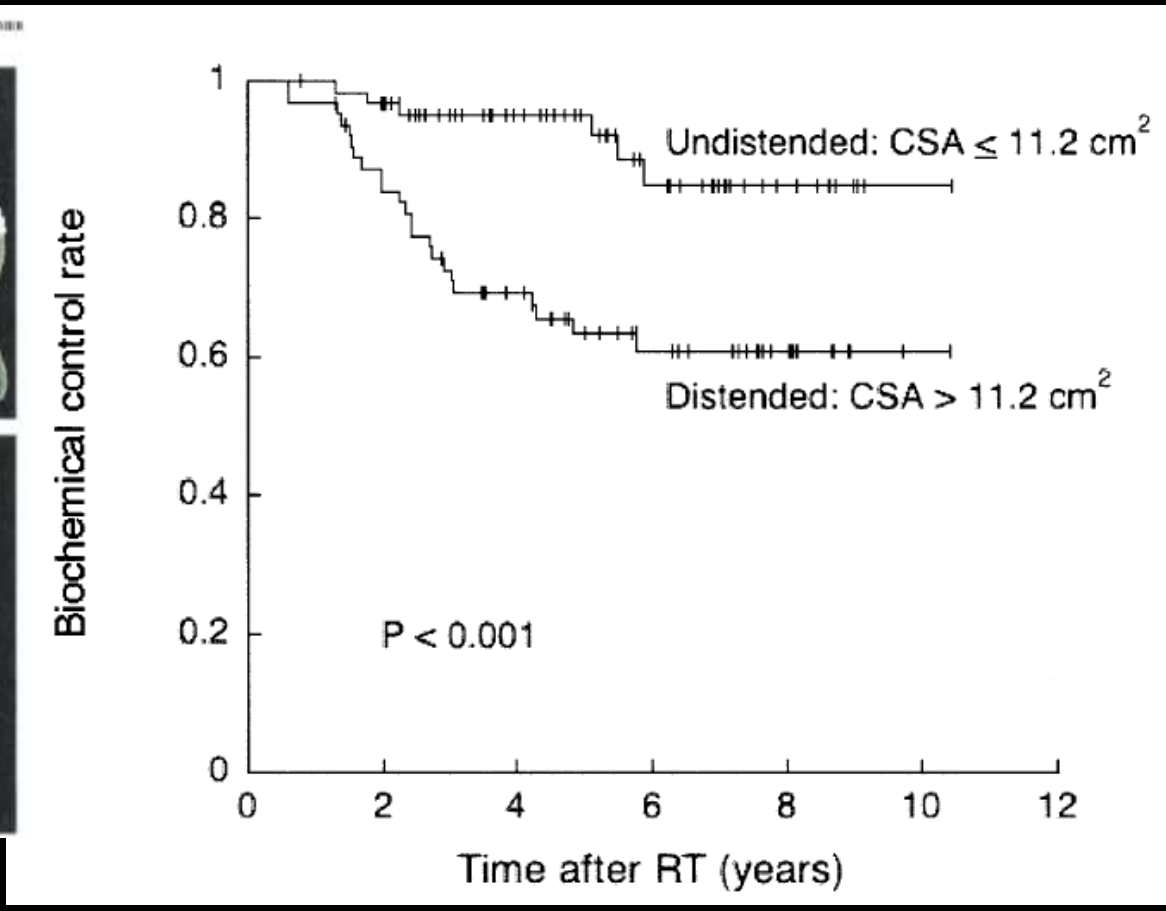
- **127 patients with definitive 3D-CRT for prostate cancer (78 Gy)**
- **Rectal distension assessed by calculation of the average cross-sectional rectal area (CSA; defined as the rectal volume divided by length) and measuring three rectal diameters on the planning CT.**
- **Test the impact of rectal distension on biochemical control, 2-year prostate biopsy results, and incidence of Grade 2 or greater late rectal bleeding was assessed.**



de Crevoisier et al., Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 965–973, 2005

The quality of the intervention is important for each patient, but also for advancing PCM





Median Cross-sectional Area (CSA) = 11.2 cm^2

de Crevoisier et al., Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 965–973, 2005

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ORIGINAL REPORT

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher, and Danny Rischin

TROG Trial #02.02 was designed to test the benefit of using a new drug (tirapazamine) in combination with chemo+RT. The outcomes were negative. Why?

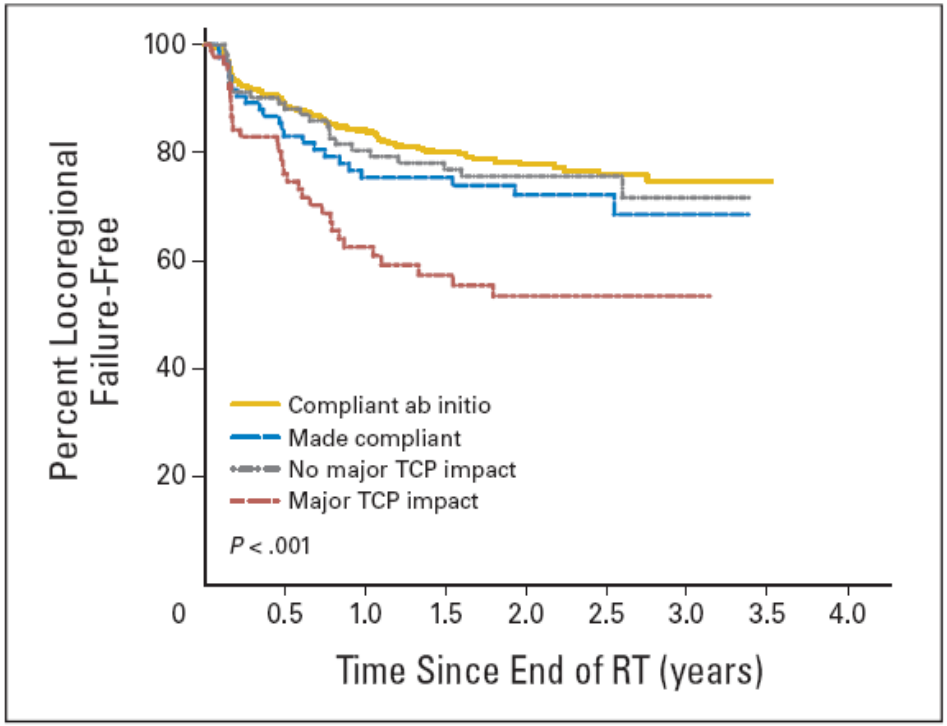
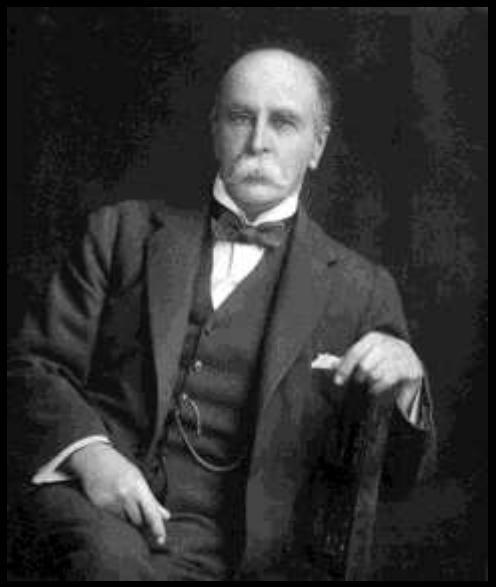


Fig 3. Time to locoregional failure by deviation status. The four cohorts are (1) compliant from the outset (n = 502), (2) made compliant following a review by the Quality Assurance Review Center (n = 86), (3) noncompliant but without predicted major adverse impact on tumor control (n = 105), and (4) noncompliant with predicted major adverse impact on tumor control (n = 87). Overall $P < .001$.

Peters et al. JCO 2010

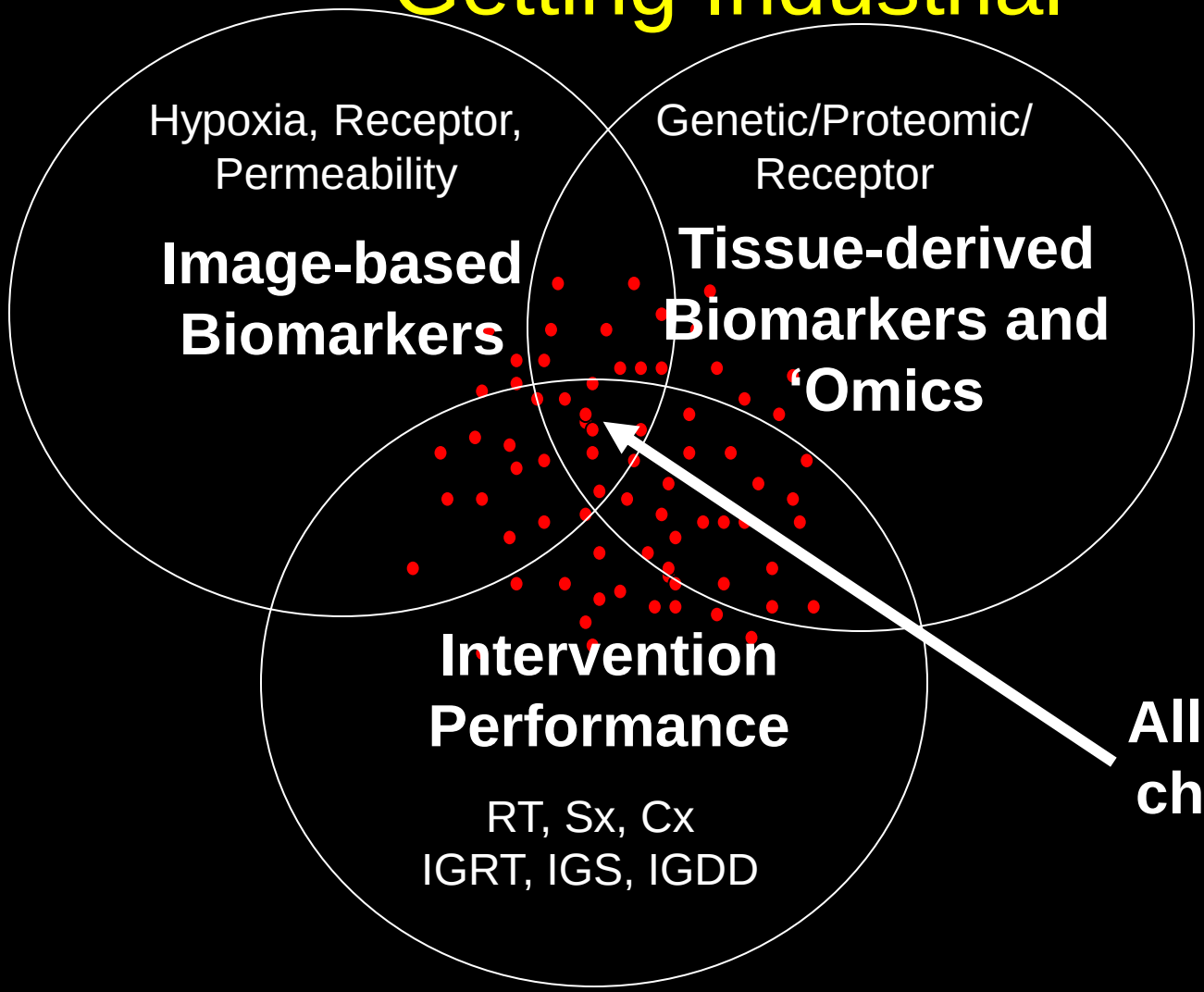
Patients or practitioners?



"If it were not for the great variability among individuals, medicine might as well be a science, not an art."

Sir William Osler, 1892

Paradoxically, Getting Personal Requires Getting Industrial



Understanding cancer, developing personalized cancer medicine strategies, and delivering high performance cancer therapy are highly dependent activities.

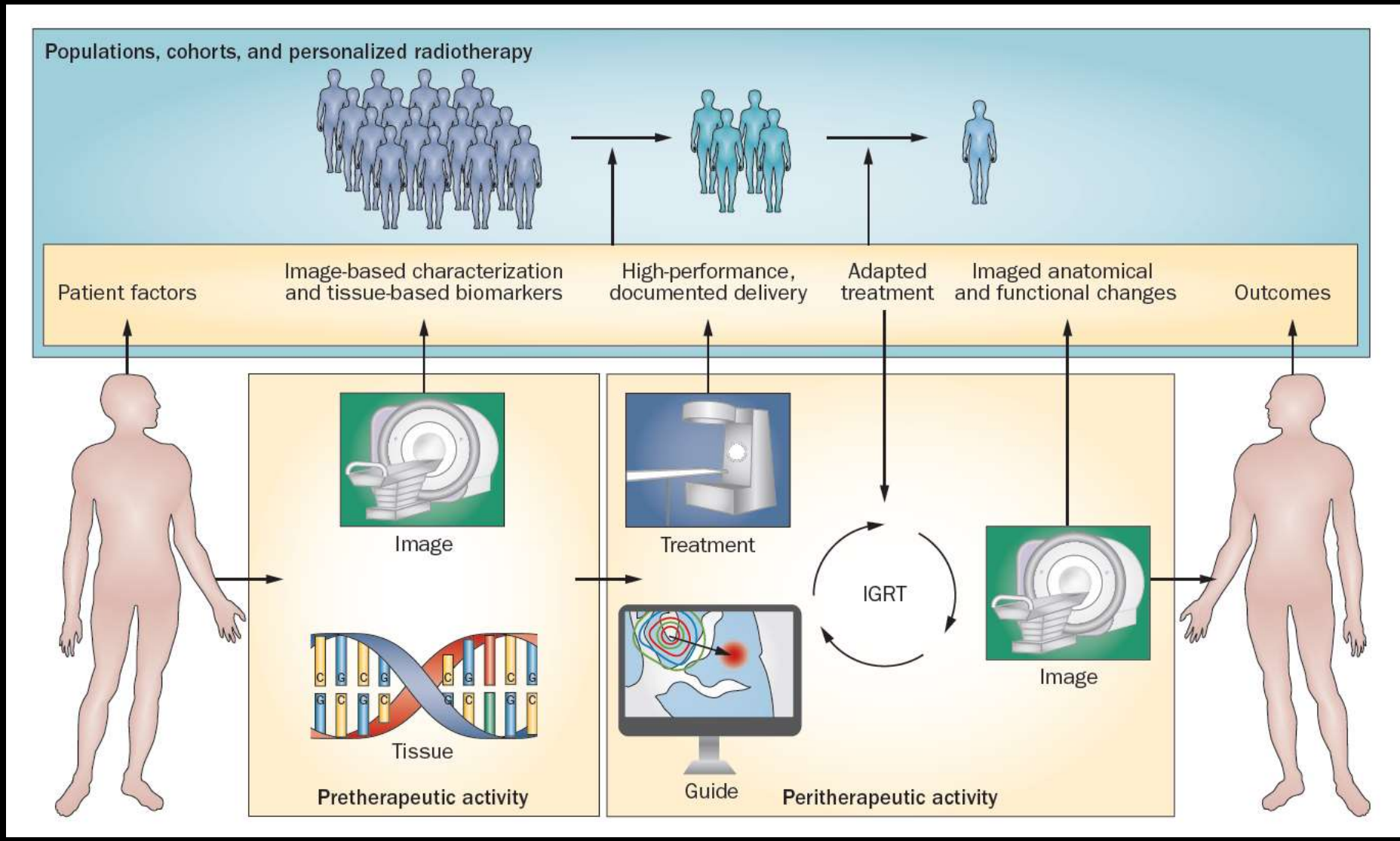
Medical Physicists have become very good at managing complexity.

- Over the past 20 years medical physicists have brought one the most complex technology in healthcare (IG-IMRT) alive with a remarkable track record.
- This is a powerful skill.
- Where do we go next?

Converting on the Promise of Personalized Cancer Medicine

- From delivering ‘state-of-the-art’ care to driving the next generation of care.
  - Medical physicists have always innovated practice, but this needs to be industrialized to accommodate the complexity of data collection, decision making, and delivery.
- Maximizing intervention performance (quality) to detect sub-populations and evaluate the value of new, more personalized therapies
- Building cancer informatics tools to enable analysis, exploration, and rapid evaluation of novel therapies or stratification.

RT: A Highly Personalized Cancer Medicine



Jaffray, D. A. *Nat. Rev. Clin. Oncol.* **9**, 688–699 (2012)

Summary

- Medical physicists have always been at the forefront in bringing greater precision to cancer treatment.
- We have established skills in the domains of computing, informatics, quality management, and clinical interaction that are of extreme relevance to the future of personalized medicine.
- The opportunity for further engagement in the domains of technology and processes, informatics and modeling, and from basic to clinical science are greater than ever.
- Few medical professions are better equipped to contribute.

More Complete H&N cancer BN