

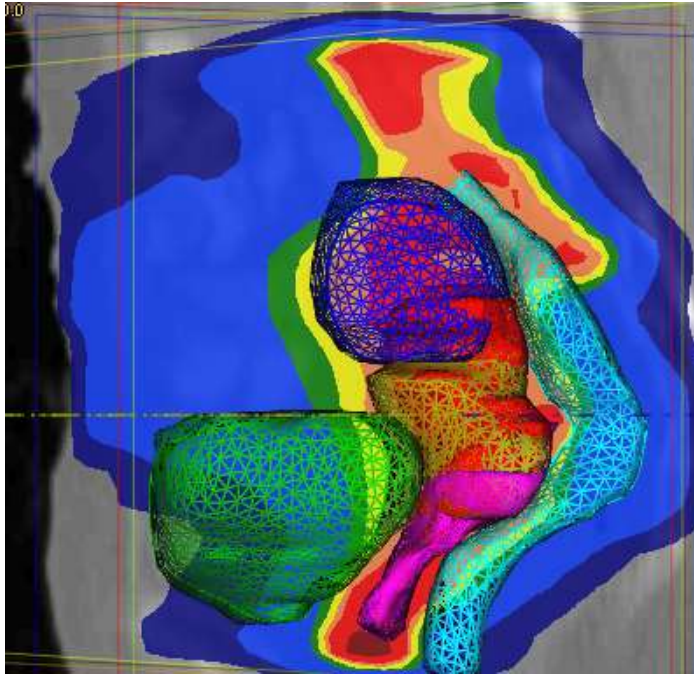


Uncertainties in Radiation Medicine: *An Oncologist's Perspective*

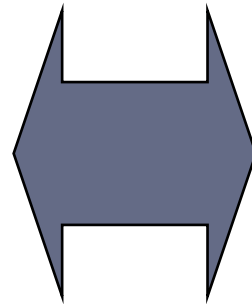
Michael Milosevic

Department of Radiation Oncology, University of Toronto
Radiation Medicine Program, Princess Margaret Cancer Centre
Toronto, Canada

Personalized Radiation Medicine



Anatomic targeting

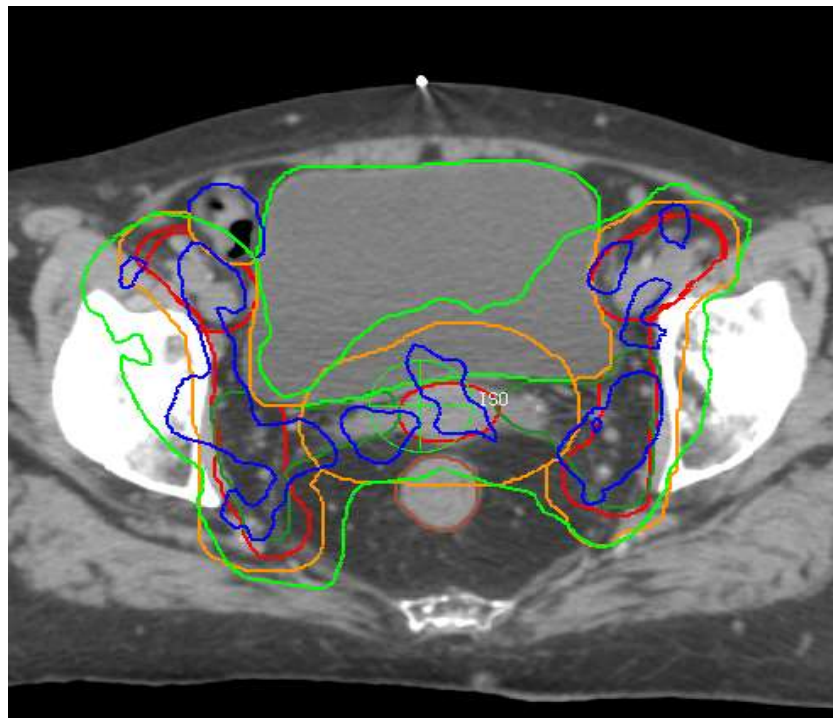


Molecular targeting

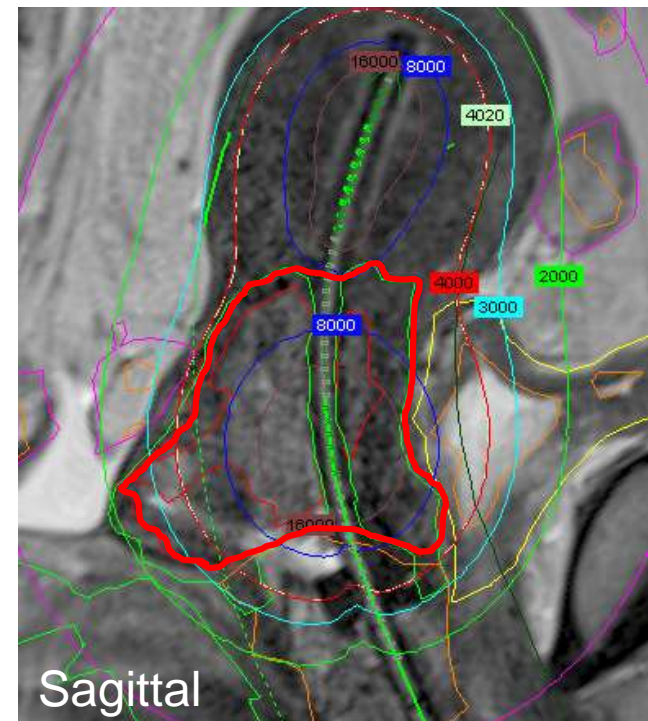
Complementary strategies to improve tumor control and reducing side effects

Uncertainty is Context-Specific

The clinical significance of uncertainties depends on patient, tumor and treatment related factors



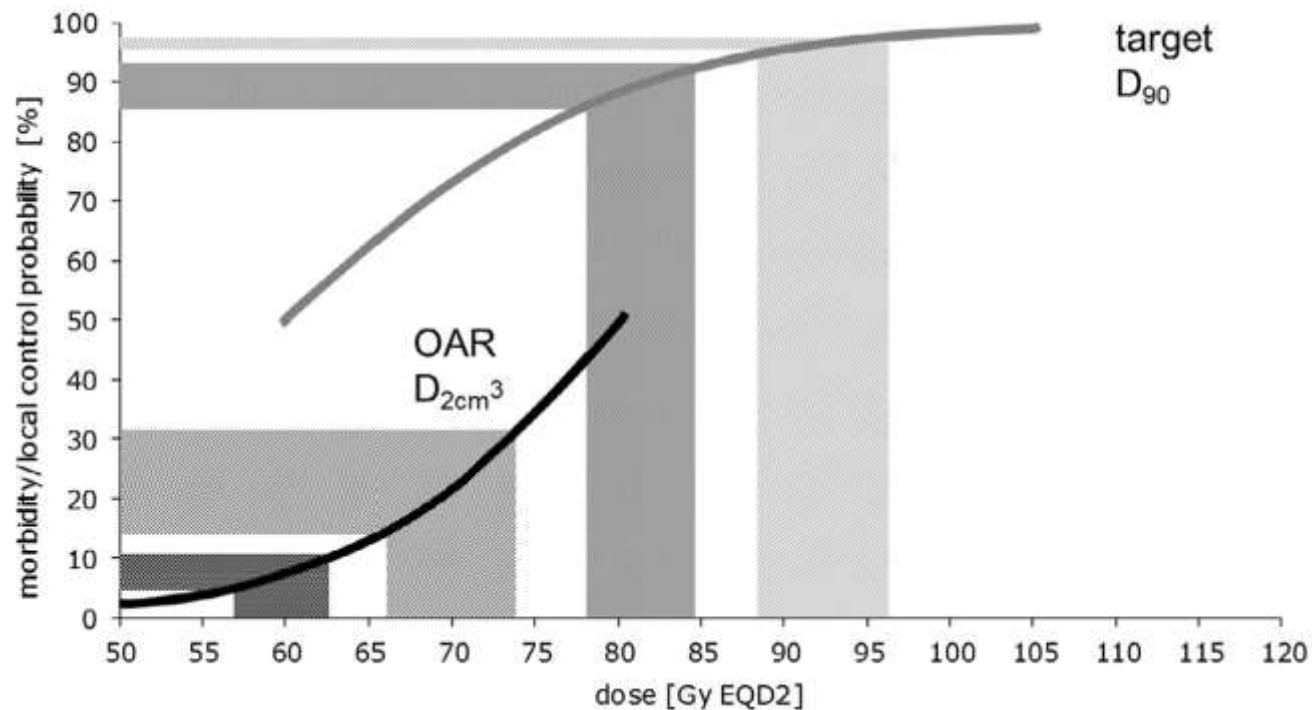
Pelvic IMRT for cervical cancer



MRgBT for cervical cancer

Uncertainties and Clinical Outcome

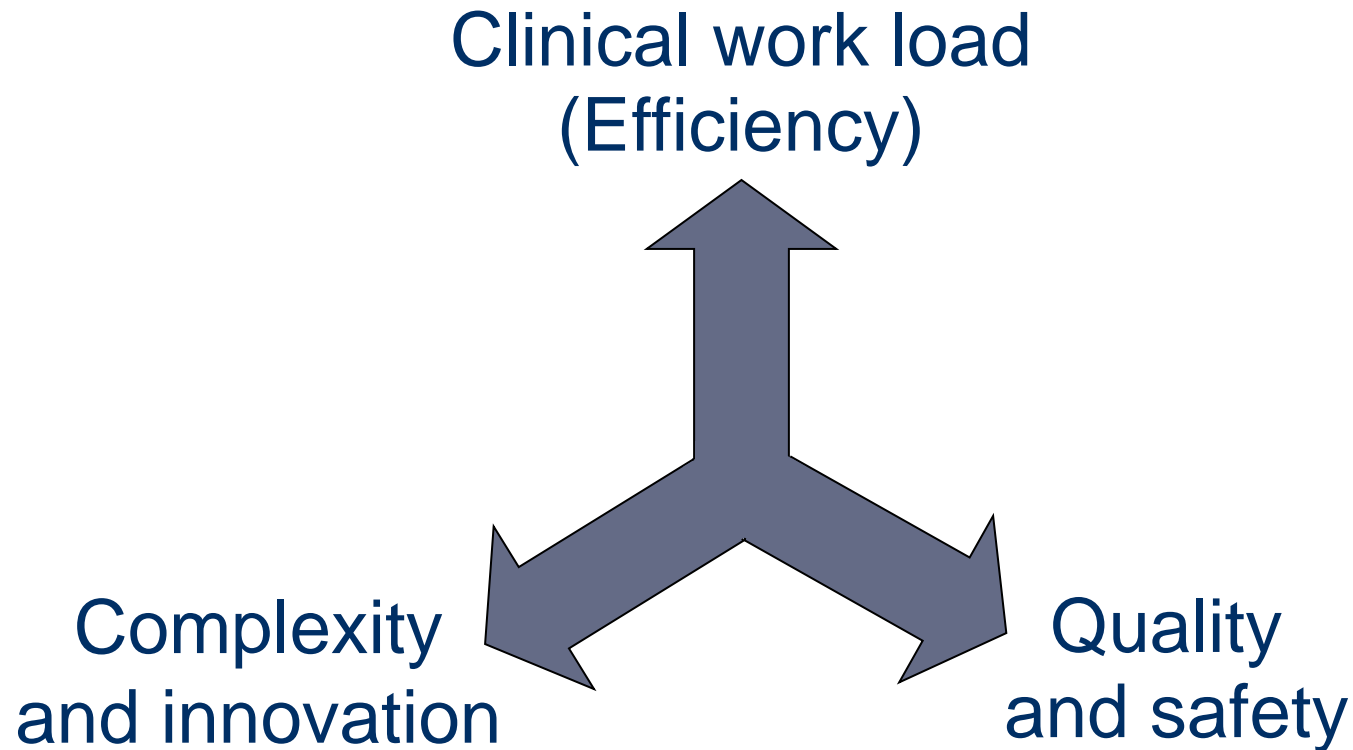
Implications of dosimetric uncertainties for tumor control and toxicity



Clinical Challenges

- Harmonizing care in the face of uncertainty
 - Target delineation
 - Internal target and OAR motion
 - Tumor regression and deformation
 - CTV margin for subclinical tumor
 - Clinical response to a shrinking tumor
- Measuring and reporting clinical outcomes
 - Harmonization of care improves our ability to demonstrate clinical benefit

Priorities in Radiation Medicine



Resource limitations (costs) impose constraints

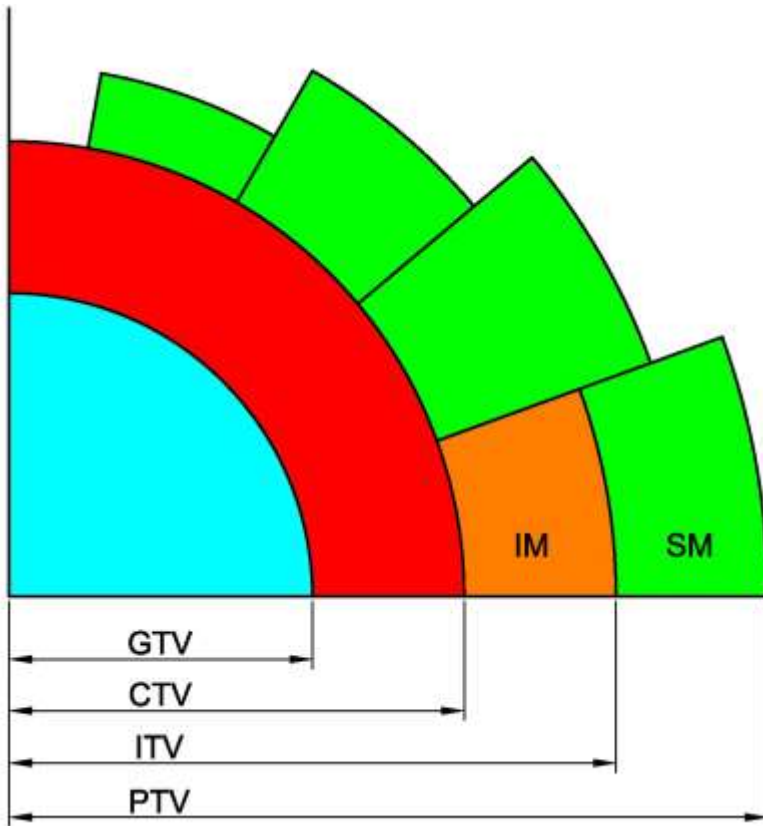
Harmonizing Clinical Care

Harmonizing care in the face of uncertainty

- Standardization
- Clinical practice guidelines
- Consensus statements
- Clinical trials
- Peer review
- Education and training

ICRU Target Definitions

ICRU 50 and 62



GTV: Gross tumor volume

- 'Visible' tumor

CTV: Clinical target volume

- Microscopic tumor

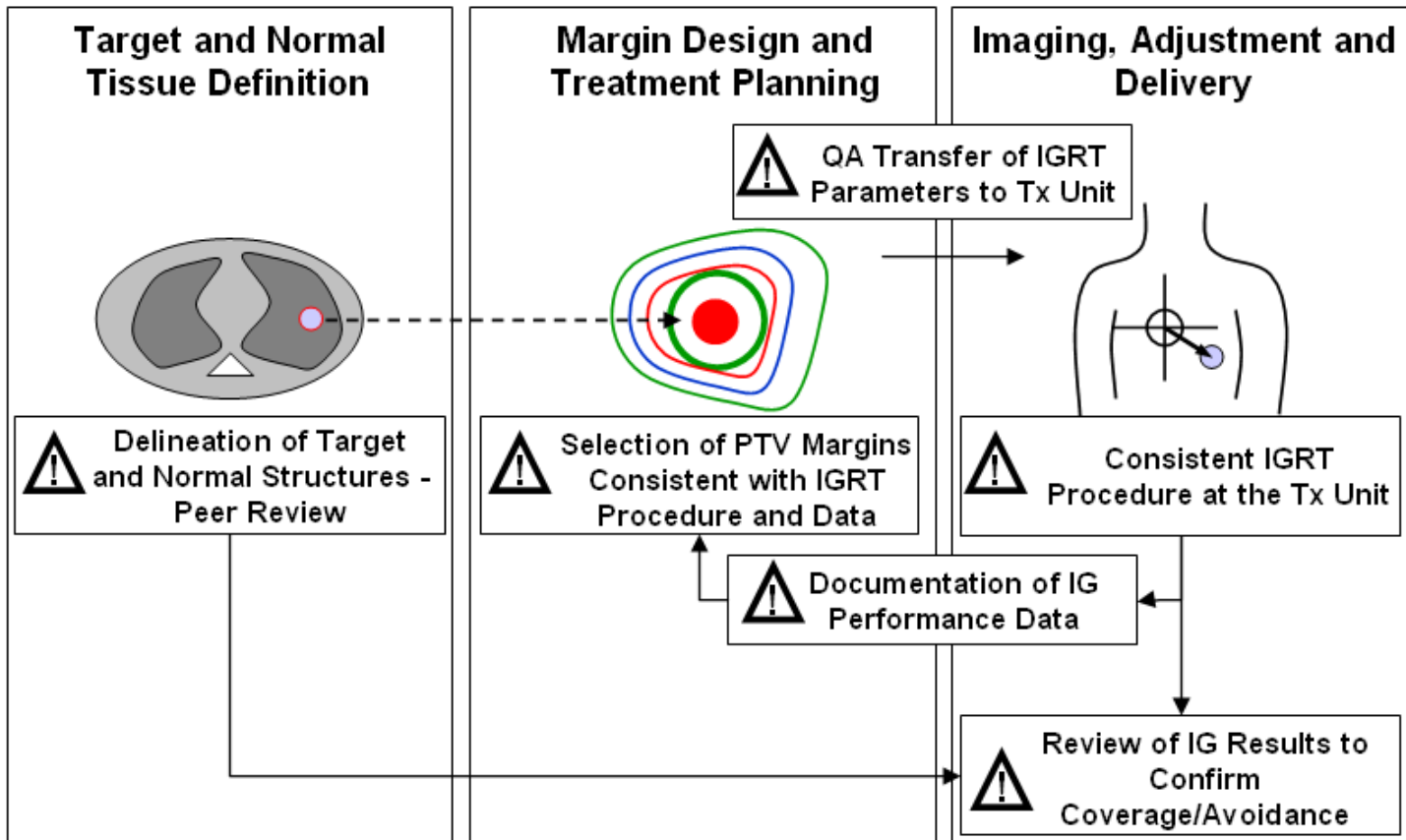
ITV: Internal target volume

- Target motion

PTV: Planning target volume

- Setup variability

IGRT Guidelines

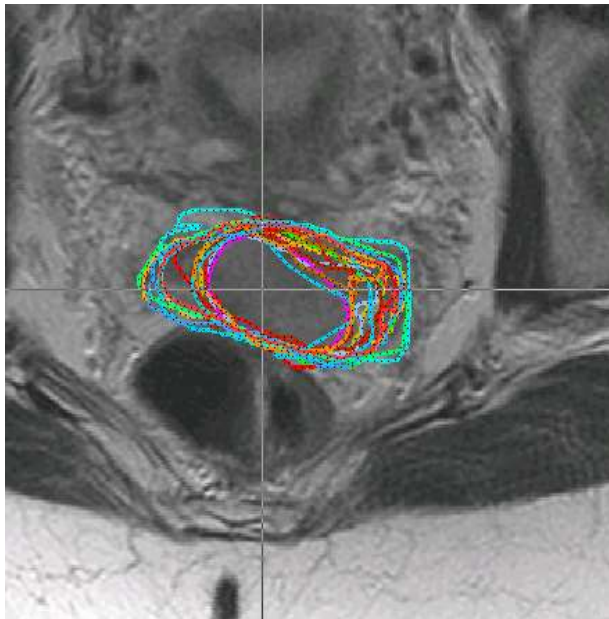


ASTRO White Paper on Quality and Safety in IGRT, 2013

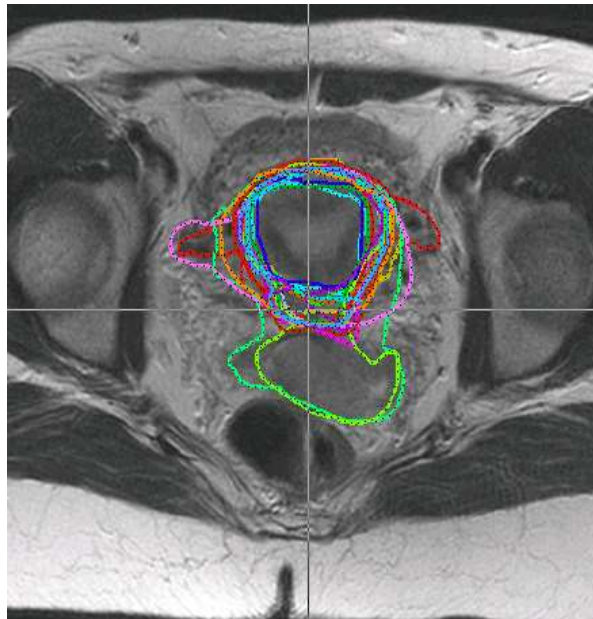
Target Delineation

... the weakest link in the search for accuracy
in radiotherapy

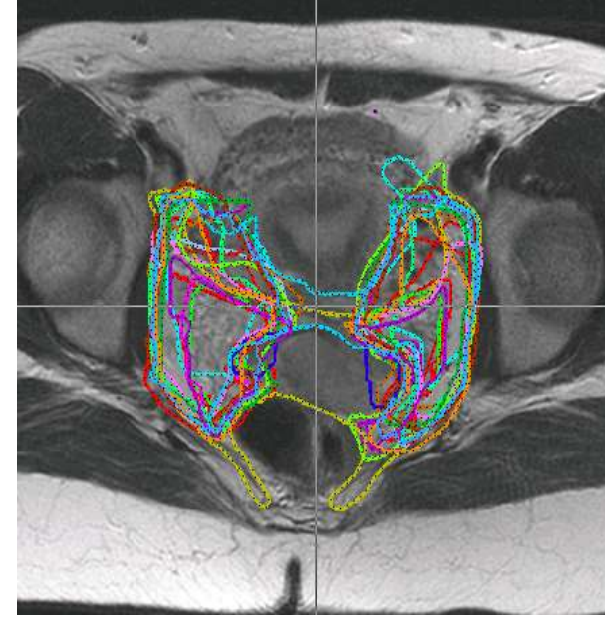
C.F. Njeh, J Med Phys, 2008



Cervix



Uterus



Parametria

19 international experts in GYNE radiation oncology

Lim, 2010

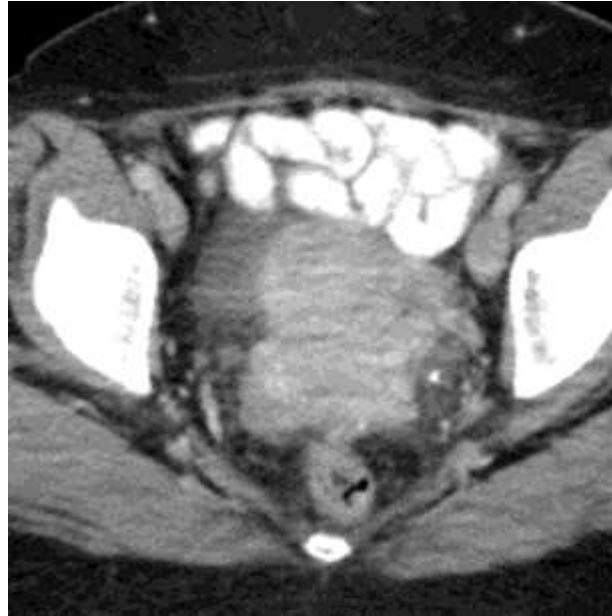
Improving Contour Agreement

- High quality imaging
 - Anatomic, metabolic, multi-parametric
- Contouring guidelines and atlases
- Simplification and automation
- Peer review
 - Radiation oncologists, other specialists
- Education and training

The Importance of Imaging



CBCT



Diagnostic CT



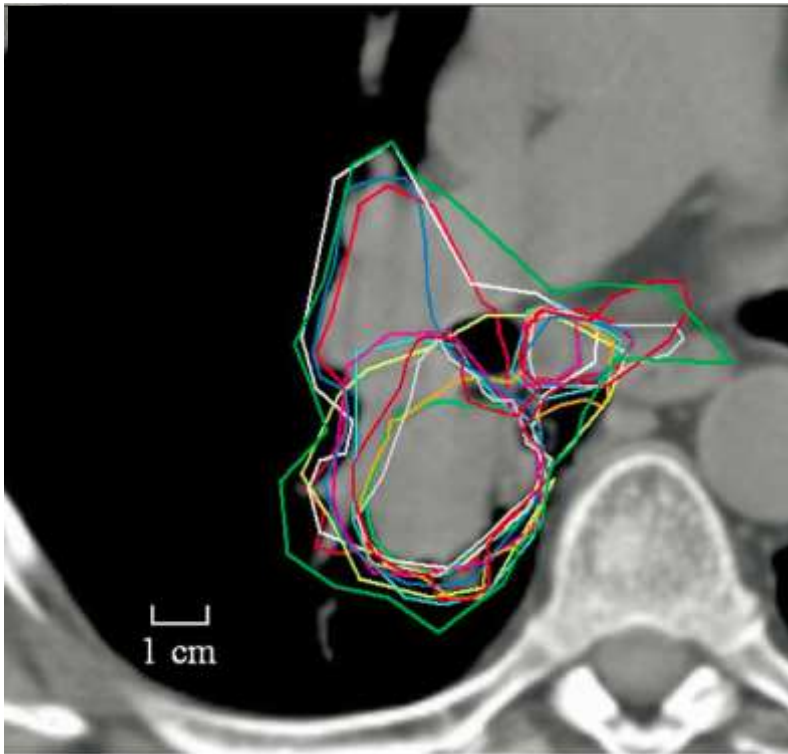
T2-MR

Cervical Cancer

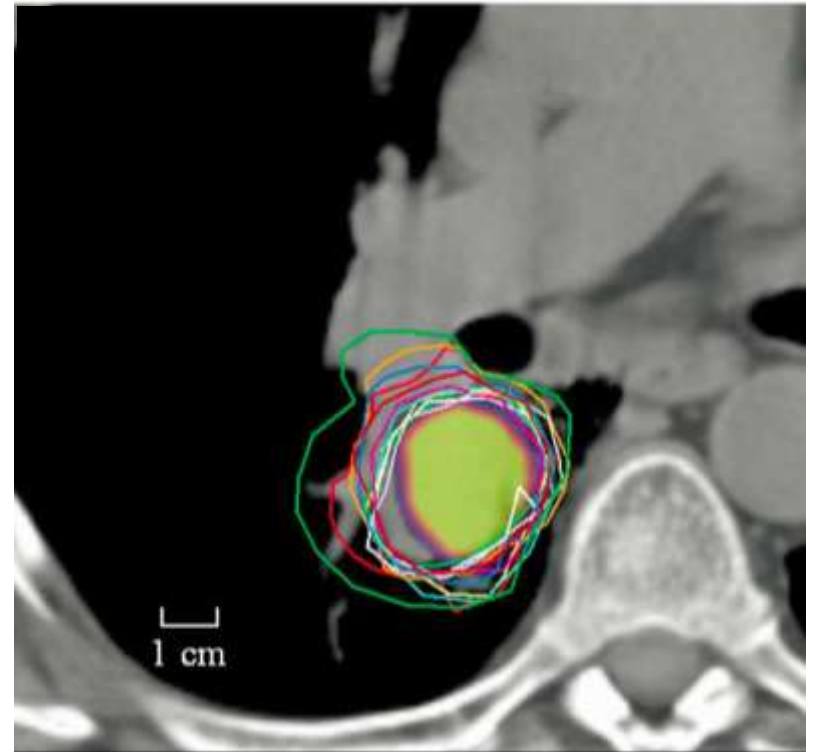
Increasing physician confidence

The Importance of Imaging

FDG PET imaging to guide contouring in lung cancer



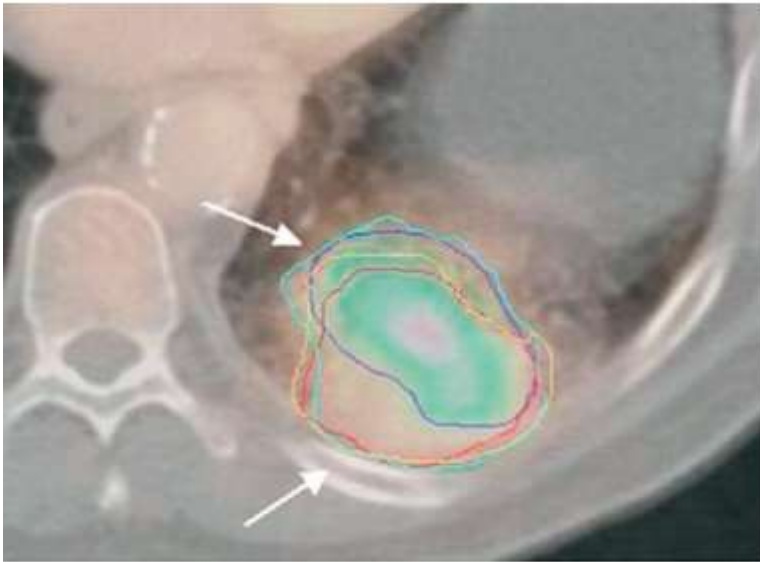
CT alone



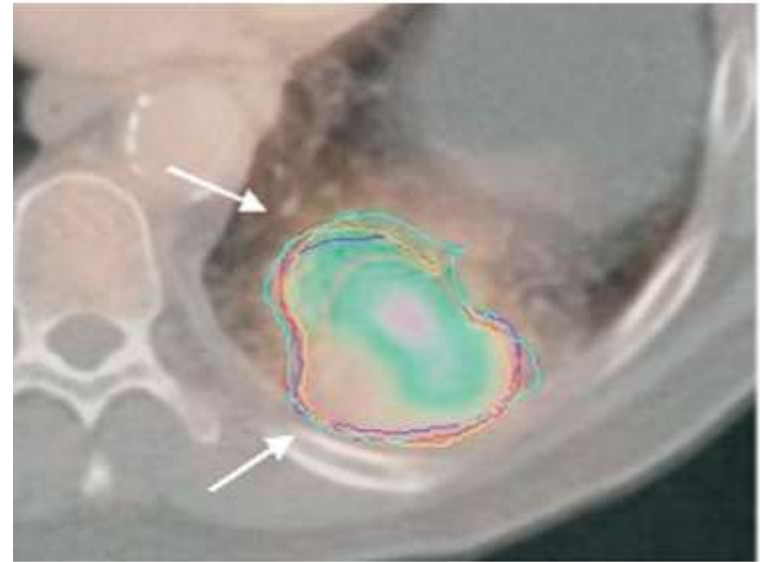
FDG PET CT

The Importance of Imaging

Automated delineation of FDG PET metabolic target volume in lung cancer



Manual contours



Automated contours
(40% of SUV_{Max})

Contouring Guidelines and Atlases

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

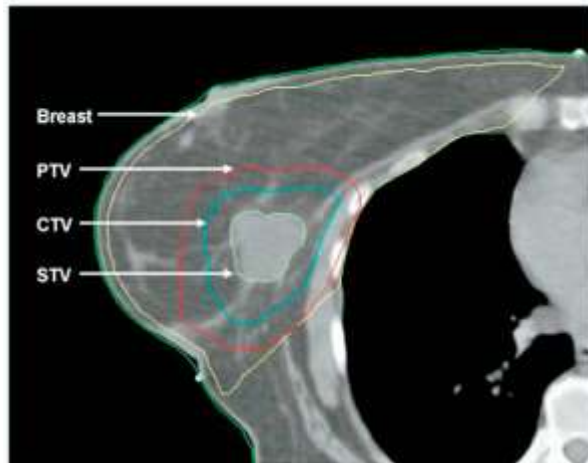
KAREN LIM, M.B.B.S.,* WILLIAM SMALL, JR., M.D.,[†] LORRAINE PORTELANCE, M.D.,[‡]
CARIEN CREUTZBERG, M.D., Ph.D.,[§] INA M. JÜRGENLIEMK-SCHULZ, M.D., Ph.D.,^{||} ARNO MUNDT, M.D.,[¶]
LOREN K. MELL, M.D.,[¶] NINA MAYR, M.D.,** AKILA VISWANATHAN, M.D.,^{††} ANUJA JHINGRAN, M.D.,^{‡‡}
BETH ERICKSON, M.D.,^{§§} JENNIFER DE LOS SANTOS, M.D.,^{|||} DAVID GAFFNEY, M.D., Ph.D.,^{¶¶}
CATHERYN YASHAR, M.D.,[¶] SUSHIL BERIWAL, M.D.,*** AARON WOLFSON, M.D.,^{†††}
ALEXANDRA TAYLOR, F.R.C.R.,^{†††} WALTER BOSCH, Ph.D.,^{§§§} ISSAM EL NAQA, Ph.D.,^{§§§}
AND ANTHONY FYLES, M.D. * FOR THE GYN IMRT CONSORTIUM.

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group[☆] (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder^{a,*}, Richard Pötter^b, Erik Van Limbergen^c, Edith Briot^a,
Marisol De Brabandere^c, Johannes Dimopoulos^b, Isabelle Dumas^a, Taran Paulsen Hellebust^d,
Christian Kirisits^b, Stefan Lang^b, Sabine Muschitz^b, Juliana Nevinson^e, An Nulens^c,
Peter Petrow^f, Natascha Wachter-Gerstner^b

Contouring Guidelines and Atlases

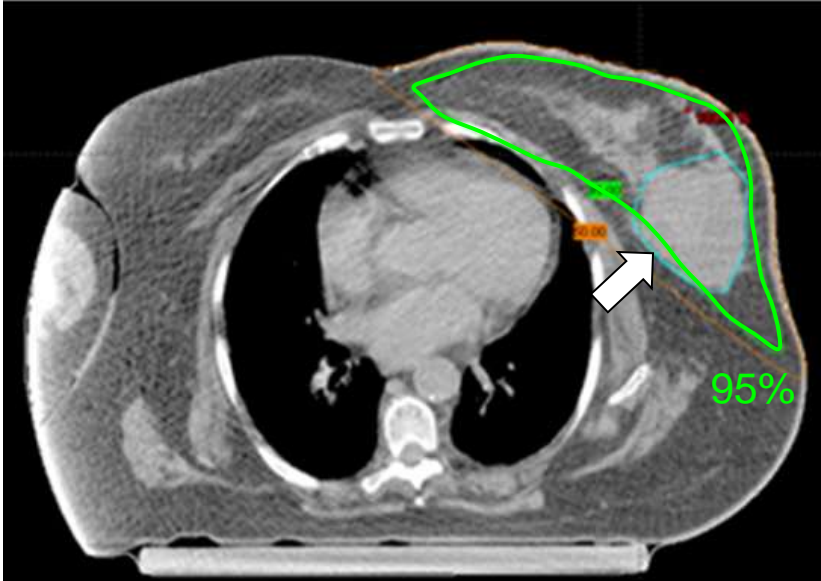
Seroma contouring guideline for partial breast RT



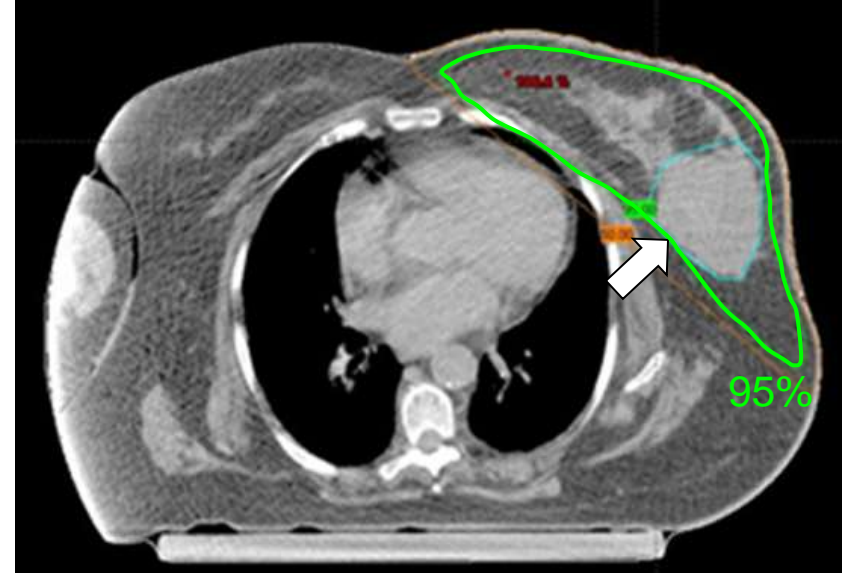
Greater contour agreement with training and adherence to guidelines

Case no.	Seroma target volume (cm ³)					
	Phase 1 Mean (SD)		<i>p</i>	Phase 2 Mean (SD)		<i>p</i>
	Trained	Untrained		Doubly trained	Newly trained	
1	187.4 (9.8)	207.4 (3.5)	0.008	68.6 (6.8)	69.4 (7.5)	0.87
2	74.8 (3.9)	100.2 (6.1)	0.0004	13.5 (4.4)	10.45 (2.1)	0.26
3	30.4 (2.2)	36.7 (2.8)	0.01	150.0 (5.3)	150.0 (14.4)	1.0
4	22.6 (4.9)	28.8 (3.8)	0.09	14.7 (1.0)	15.0 (2.8)	0.86
5	12.8 (5.6)	18.1 (4.8)	0.20	63.2 (16.9)	56.8 (16.2)	0.60

Peer Review of Treatment Plans



Original plan:
Inadequate target coverage



Revised plan
after peer review

Peer Review of Treatment Plans



CPQR
Canadian Partnership for
Quality Radiotherapy
PCQR
Partenariat canadien pour
la qualité en radiothérapie

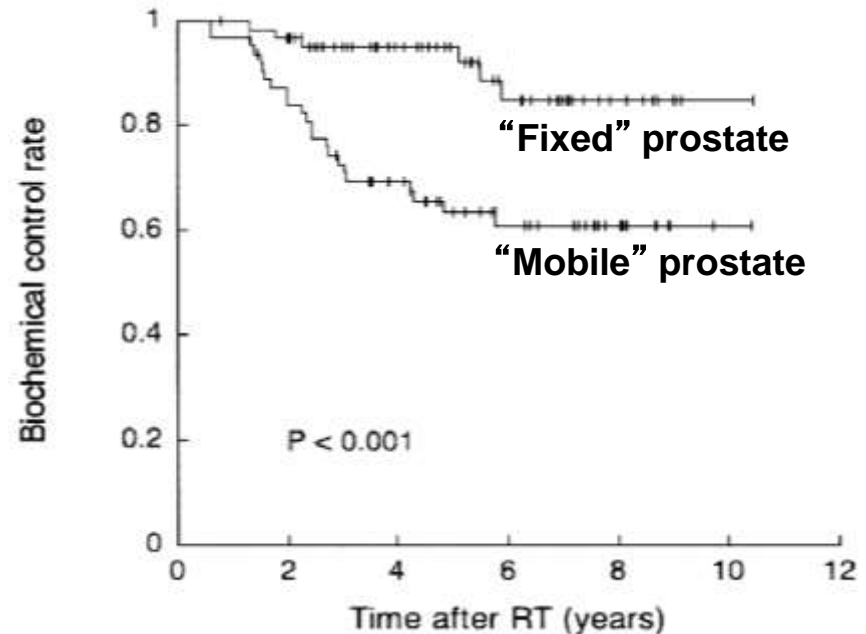
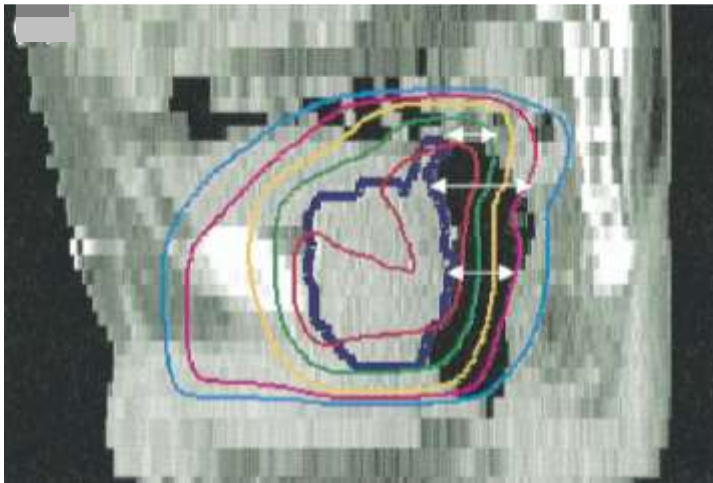
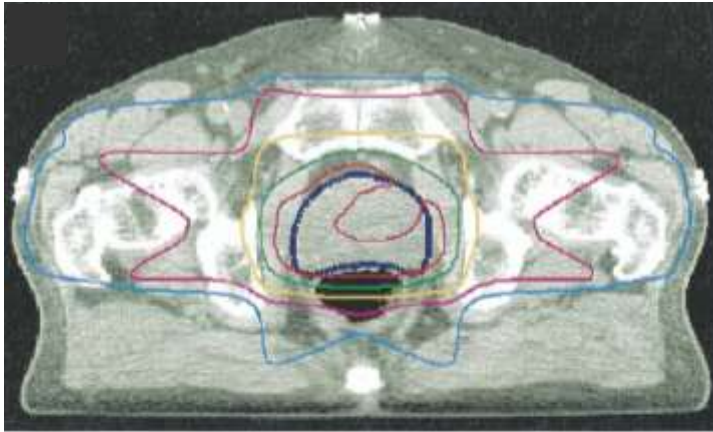
Programmatic Quality Assurance Guidance for Canadian Radiation Treatment Programs

www.cpqr.ca

6.10 Radiation Oncology Peer Review of Treatment Plans

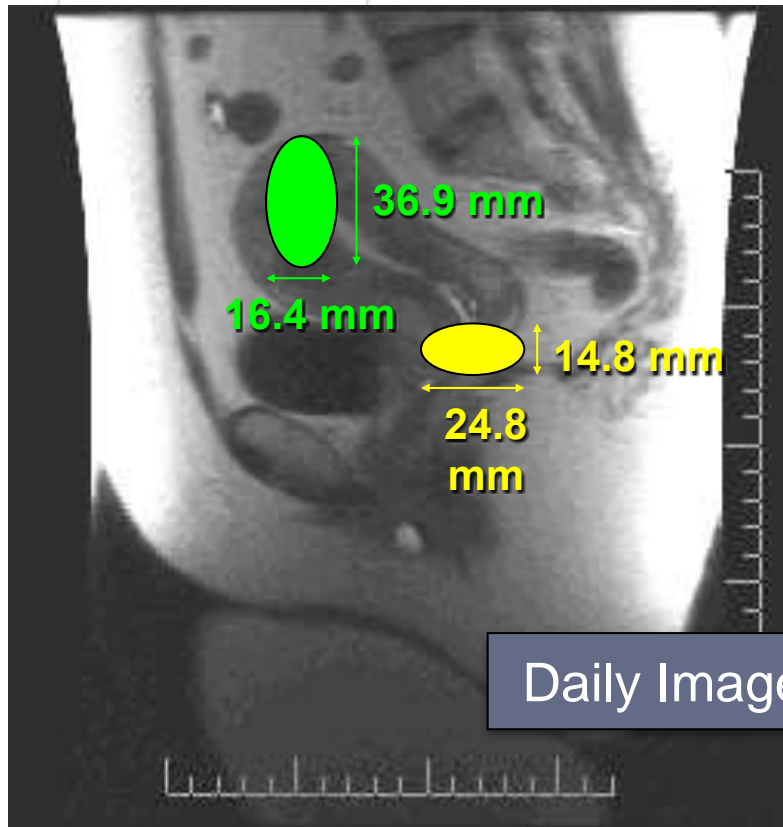
<i>Key Indicators</i>	<i>Indicator Range</i>
Percentage of adjuvant or curative radiotherapy treatment plans that undergo radiation oncology peer review at any time.	0-100%
Percentage of adjuvant or curative radiotherapy treatment plans that undergo radiation oncology peer review prior to the start of treatment.	0-100%
Percentage of adjuvant or curative radiotherapy treatment plans that undergo radiation oncology peer review after the start of treatment but before 25% of the prescribed dose has been administered.	0-100%

The Importance of Internal Motion

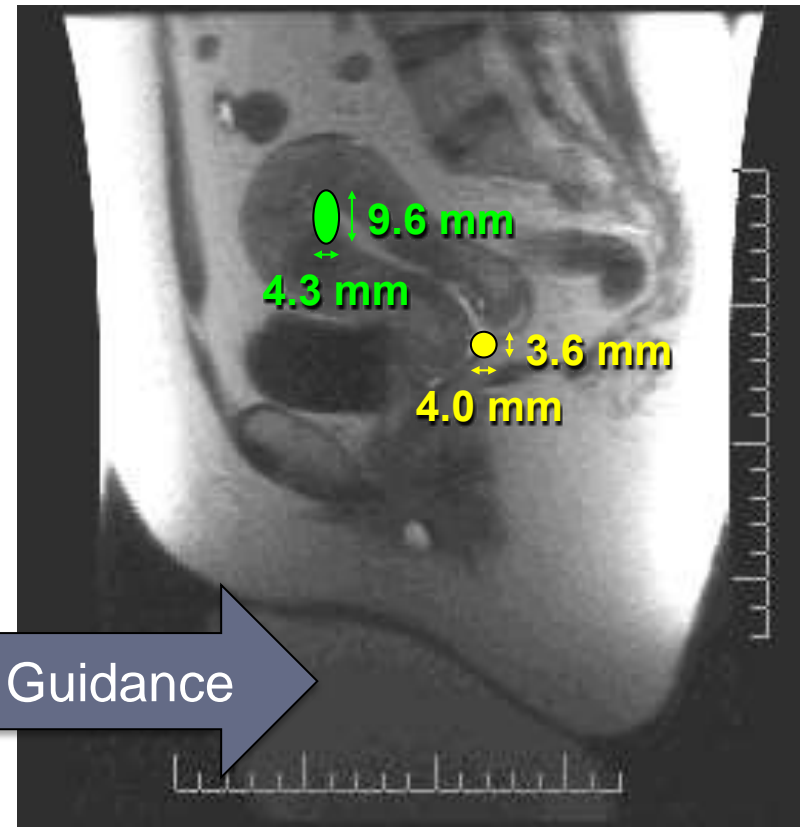


Failure to compensate for tumor and OAR motion can offset the benefits of dose escalation and increase side effects

Population PTV Margins



For Inter-Fraction Motion



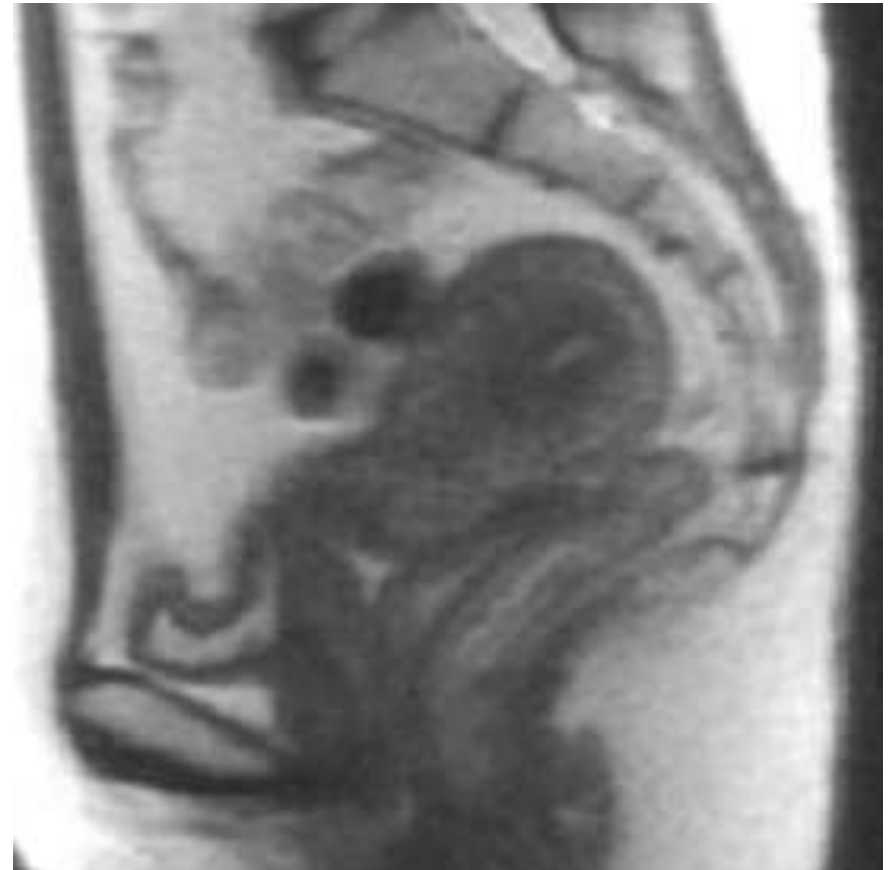
For Intra-Fraction Motion

Daily Image Guidance

Cervical Cancer Extreme Motion



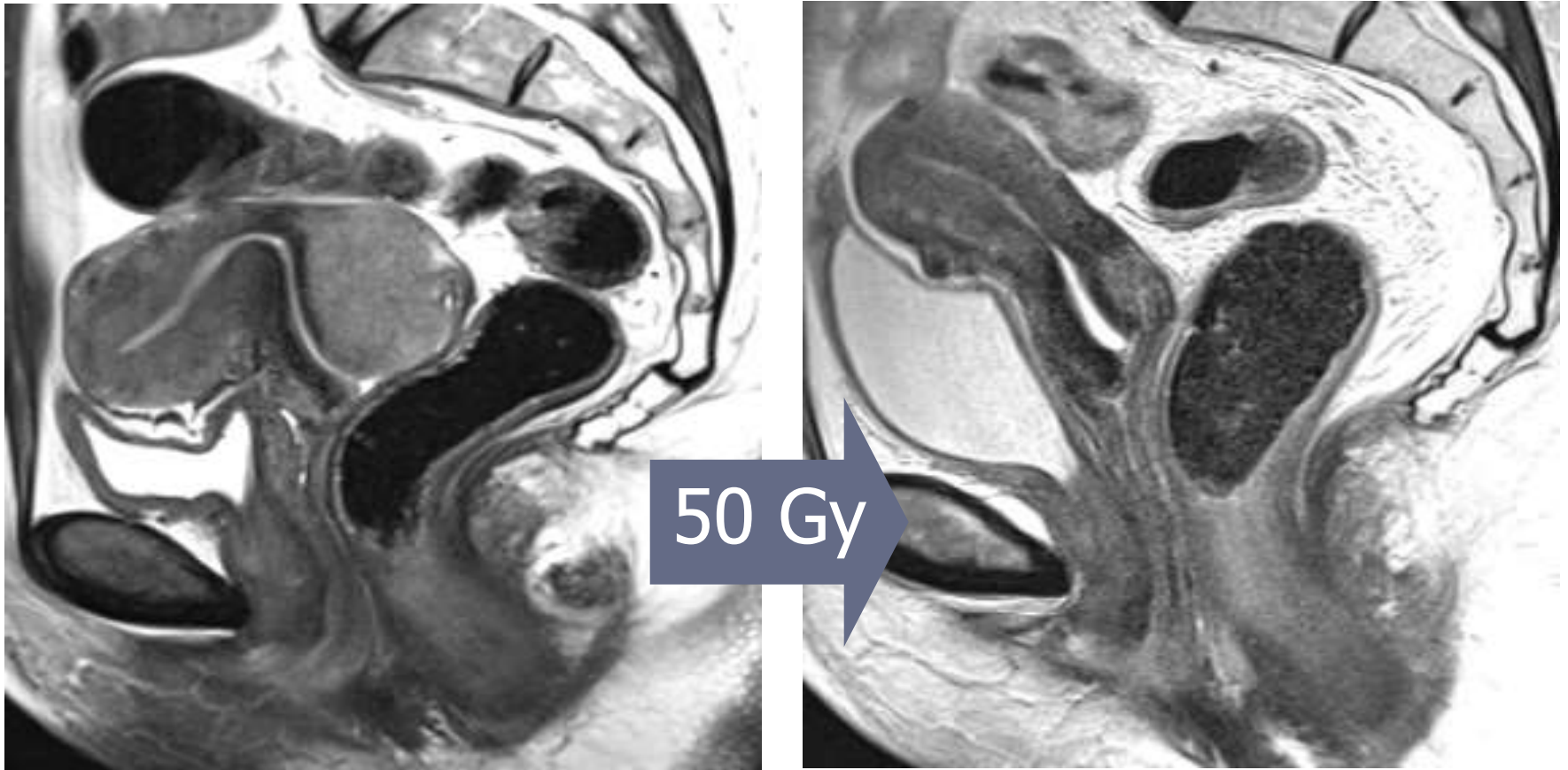
Cervix cancer (Week 1)



Cervix cancer (Week 3)

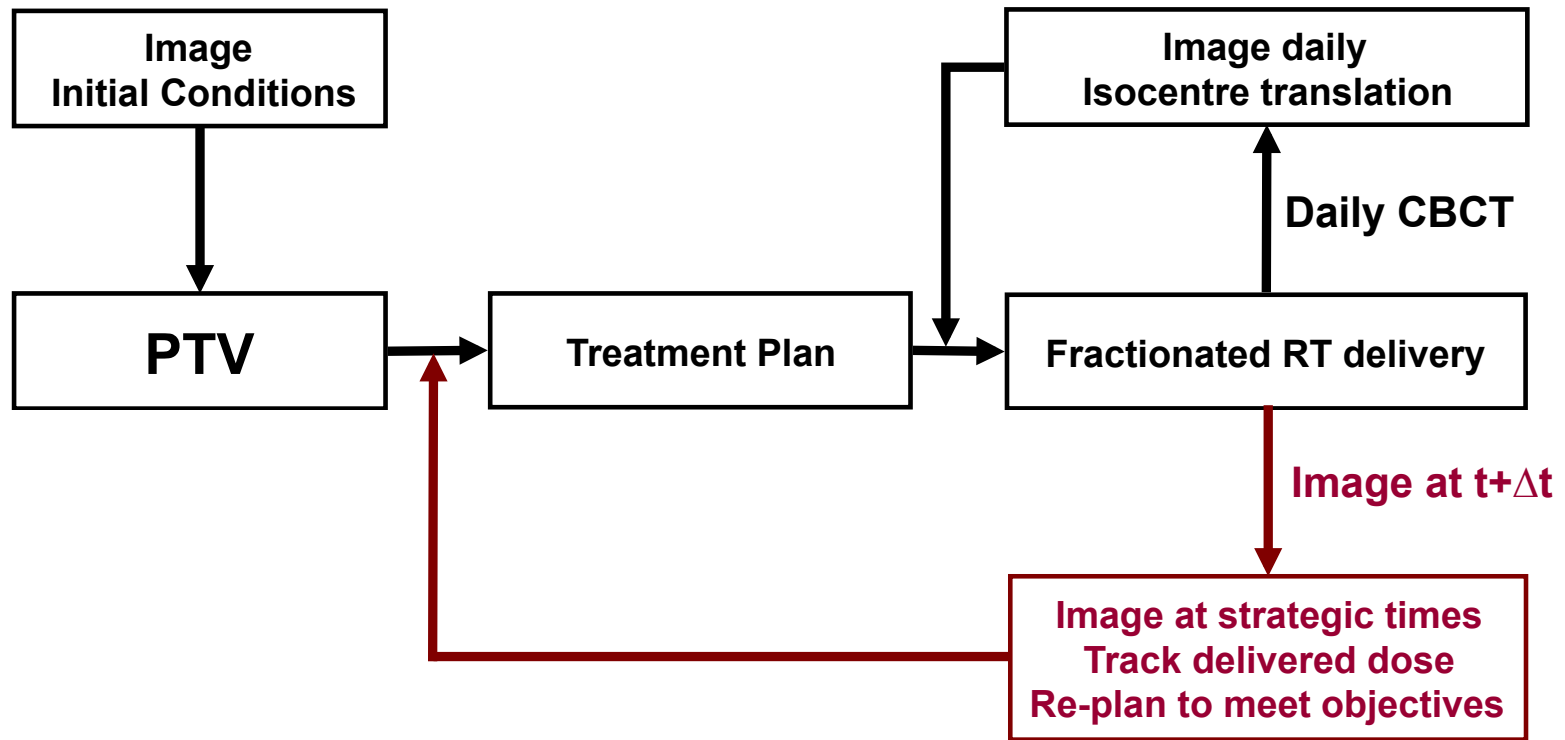
Extreme unpredictable motion

Cervical Cancer Regression



Tumor regression during treatment

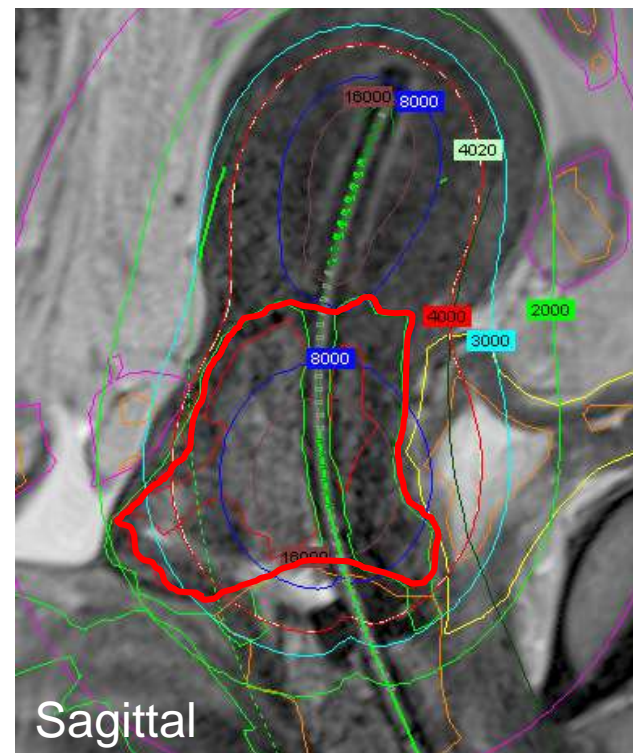
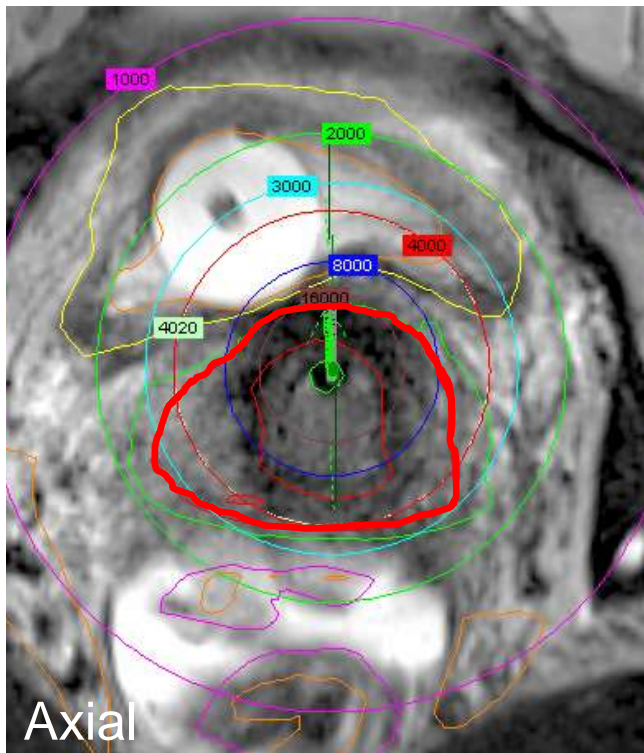
Adaptive Radiotherapy



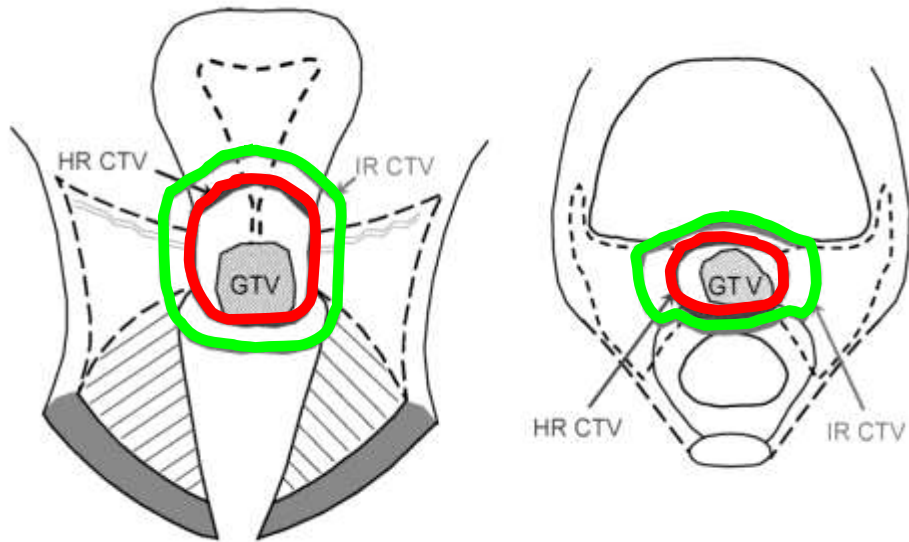
New uncertainties and challenges
to assure optimal, safe treatment

MRgBT for Cervical Cancer

MR-guided brachytherapy for cervical cancer:
Adapting to tumor regression during EBRT



GEC-ESTRO Cervix Guidelines



Planning constraints

- IR-CTV D_{90} $>60 \text{ Gy}_{10}$
- HR-CTV D_{90} $>85 \text{ Gy}_{10}$
- Sigmoid D_{2cc} $<75 \text{ Gy}_3$
- Rectum D_{2cc} $<75 \text{ Gy}_3$
- Bladder D_{2cc} $<90 \text{ Gy}_3$

IR-CTV: Tumor volume at diagnosis

HR-CTV: Tumor volume at brachytherapy

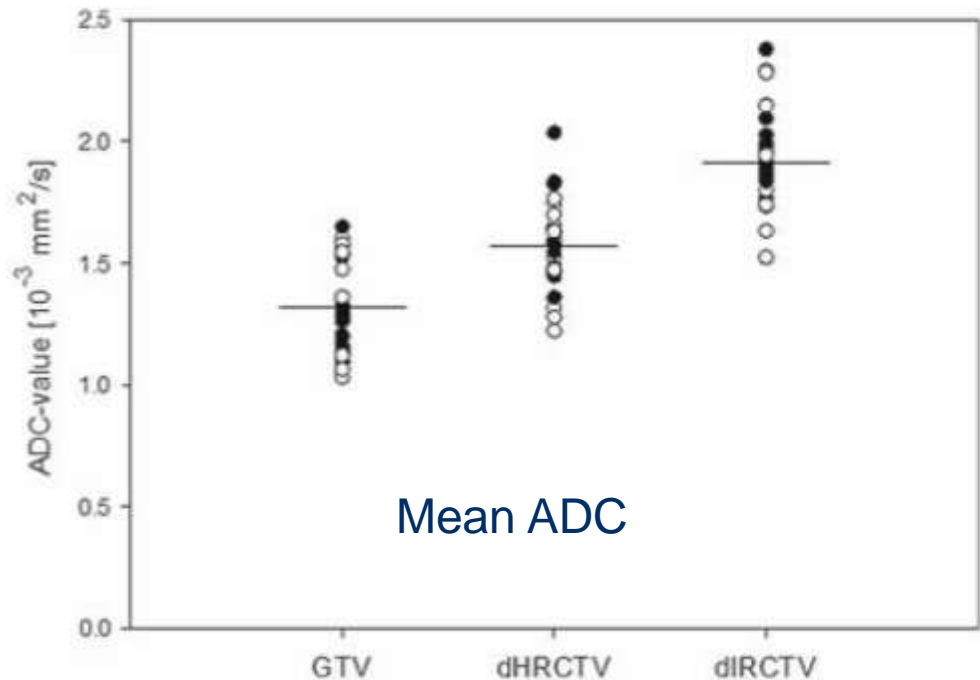
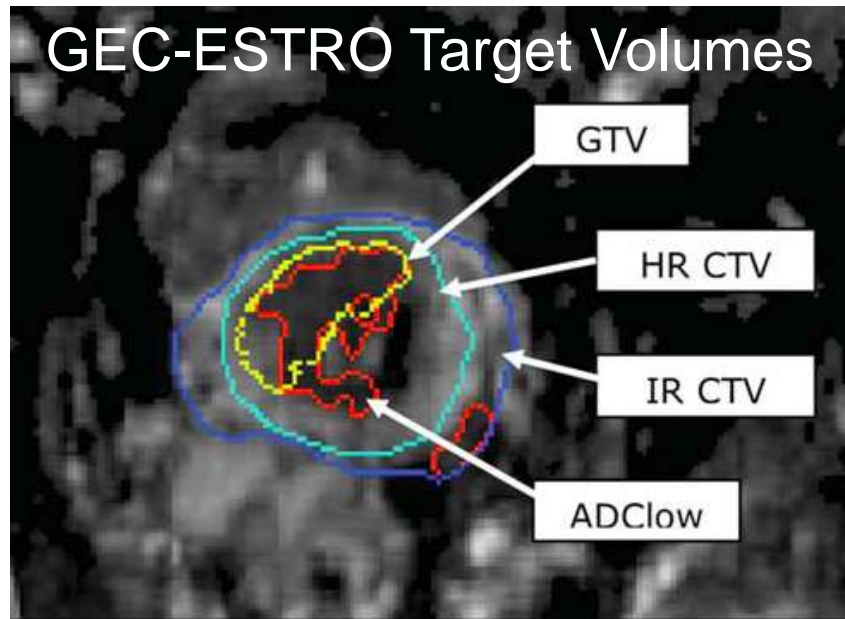
New ICRU Definitions

Revision of ICRU Report 38: *Prescribing, Recording, and Reporting Cervical Brachytherapy*

CTV-T	Primary tumor clinical target volume
CTV-N	Lymph node clinical target volume
iGTV	Initial gross tumor volume
rGTV	Residual gross tumor volume
aCTV	Adaptive clinical target volume

A vocabulary for adaptive radiotherapy

Shrinking Tumor Volume?



Restricted diffusion as a function of target volume:

GTV	37% low ADC $<1.2 \times 10^{-3} \text{ mm}^2/\text{s}$
HR CTV	22%
IR CTV	12%

MRgBT for Cervical Cancer

145 patients

T1b-3b

RT \pm CT

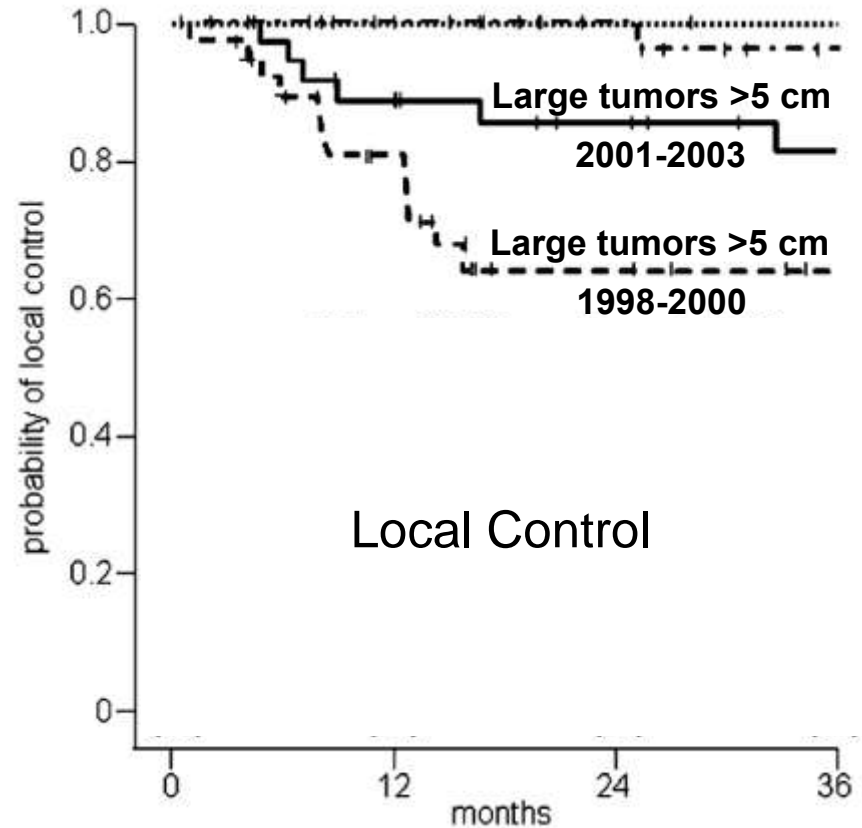
BED 80-85 Gy₁₀

Outcome at 3y

Local control 88%

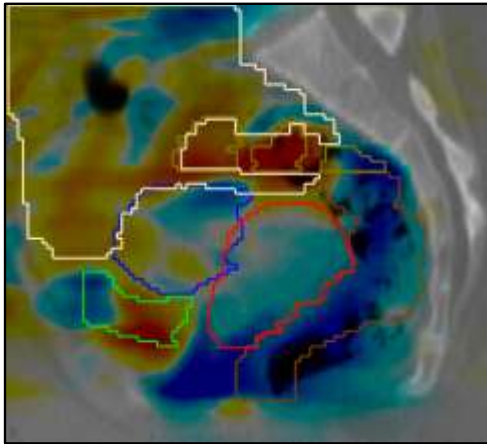
Overall survival 58%

Severe late toxicity 5%

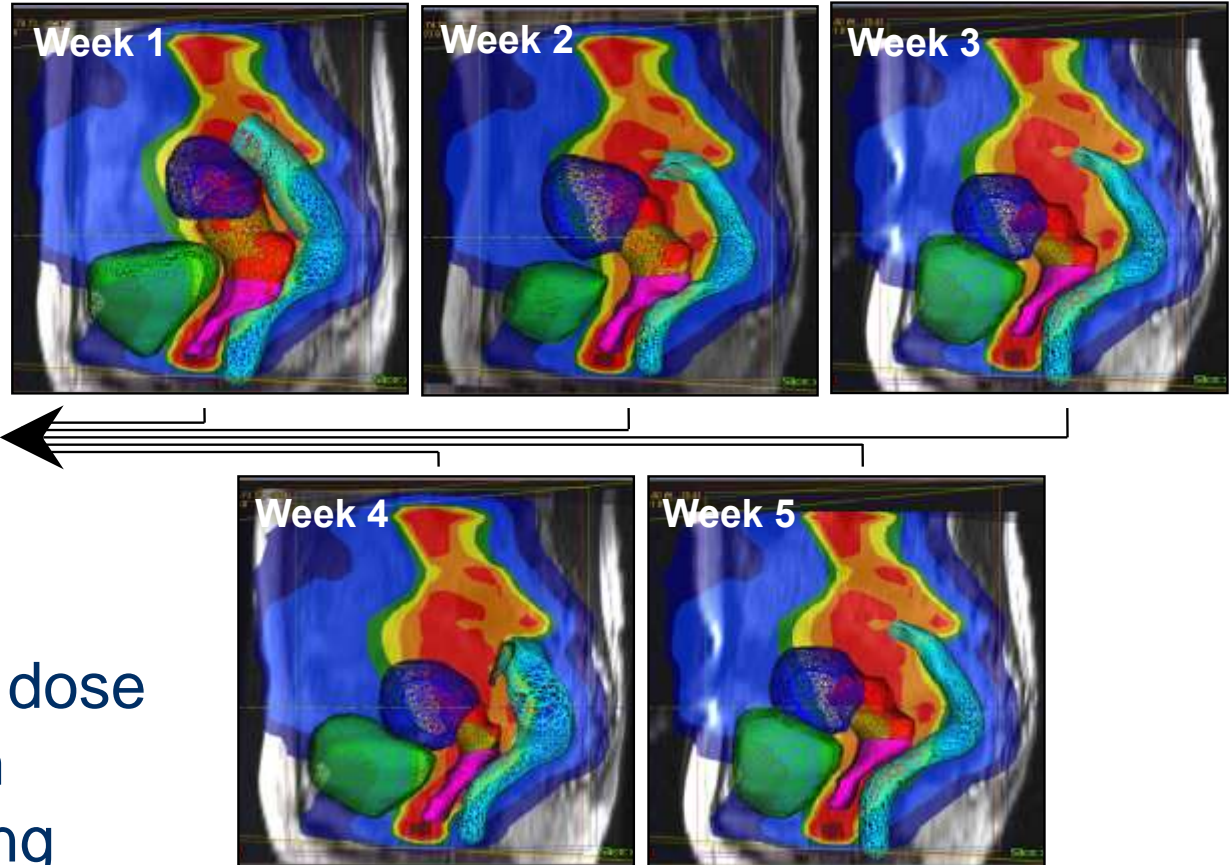


Adaptive EBRT for Cervical Cancer

Dose-Difference Map

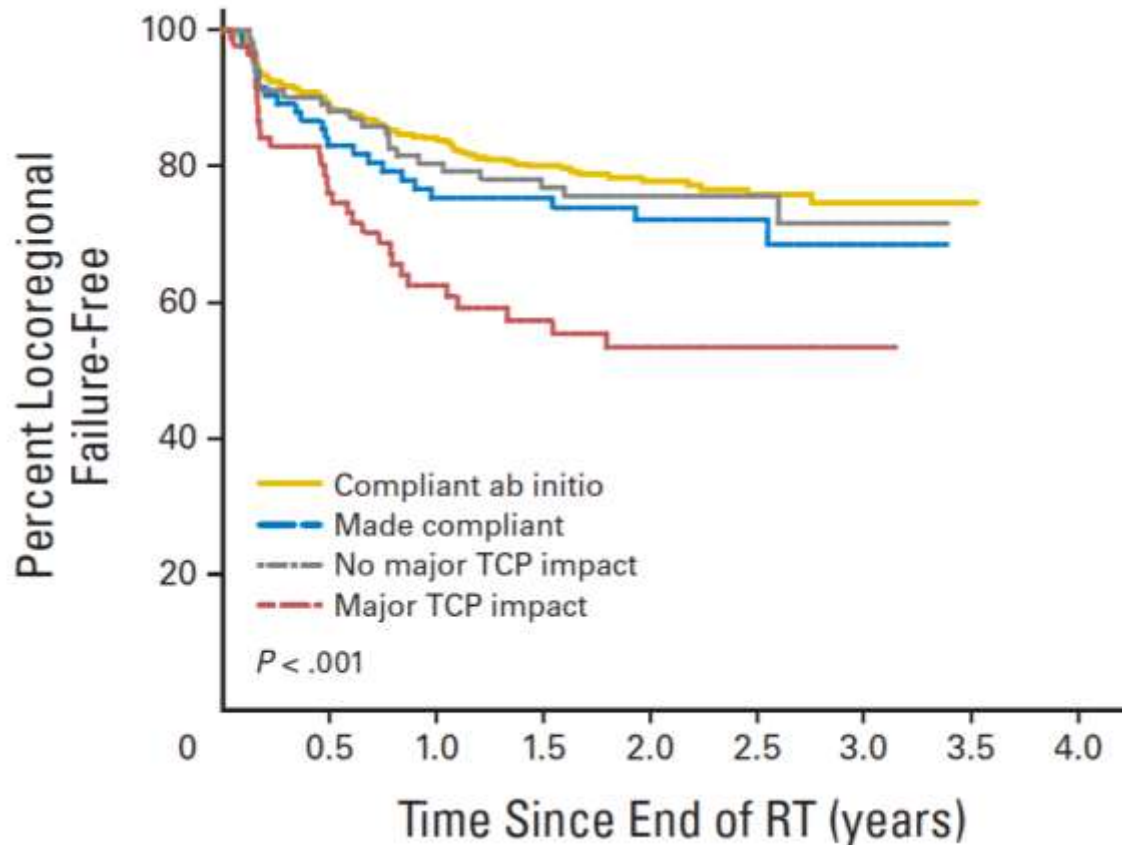


Weekly (or daily!) dose accumulation with adaptive replanning



Kristy Brock, James Stewart, Karen Lim

Harmonized Care Improves Outcome



Effect of protocol compliance in a HN cancer clinical trial

Summary

- The clinical significance of uncertainties depends on patient, tumor and treatment factors.
- Uncertainties about target volume, internal motion and response to a shrinking tumor currently limit further advances in tumor targeting (in some sites).
- Advances in biology and technology will enable more personalized radiation treatment, reduce some uncertainties and introduce new challenges.
- In the face of uncertainty, harmonization of clinical care based on expert consensus agreement can improve clinical outcome.