Adaptive Radiotherapy
The Next Frontier in Radiation Medicine

Michael Milosevic

Radiation Medicine Program
Princess Margaret Hospital and
University of Toronto
Toronto, Canada

Radiation Oncology
UNIVERSITY OF TORONTO

Princess Margaret Hospital

Radiotherapy in the 21st Century: *Individualized Treatment*

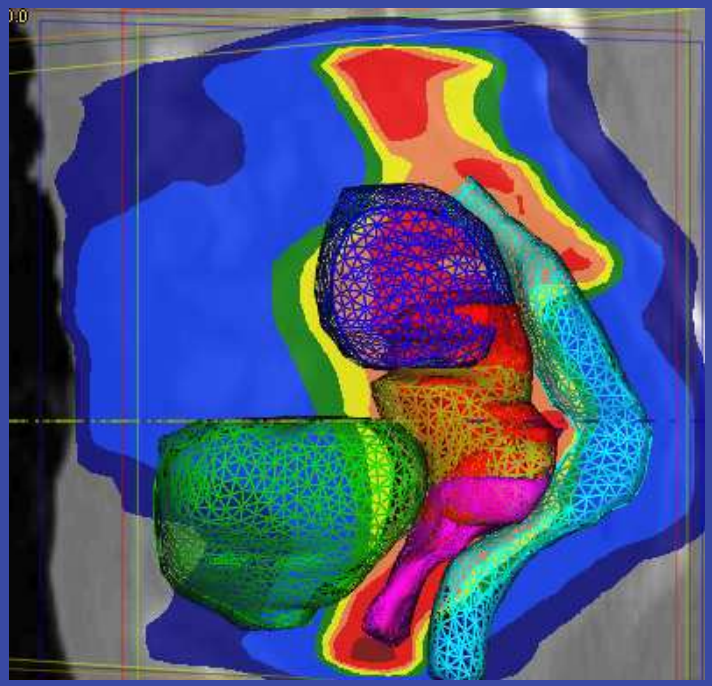


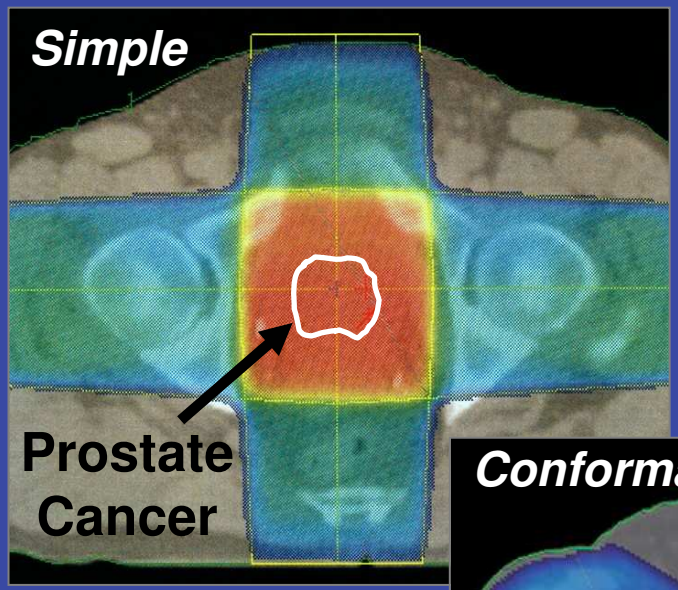
Image-guided adaptive RT

Biology and molecular targeting

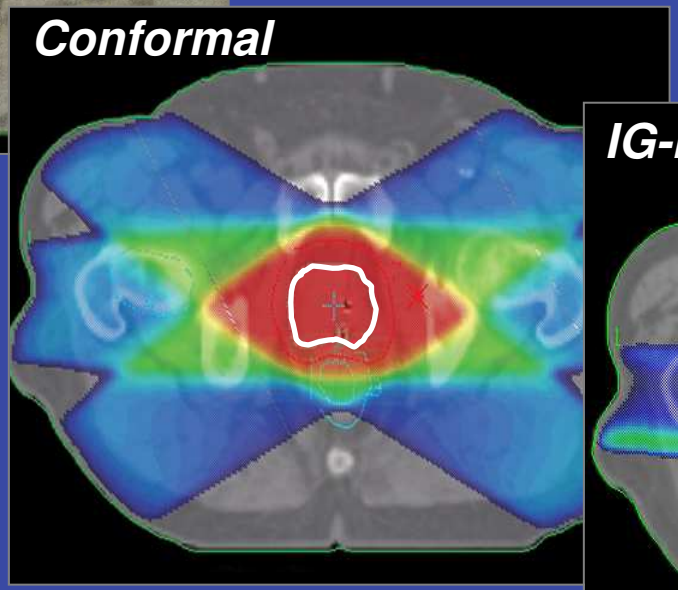
Synergistic strategies for improving tumor control and reducing side effects

M. Milosevic, 2010

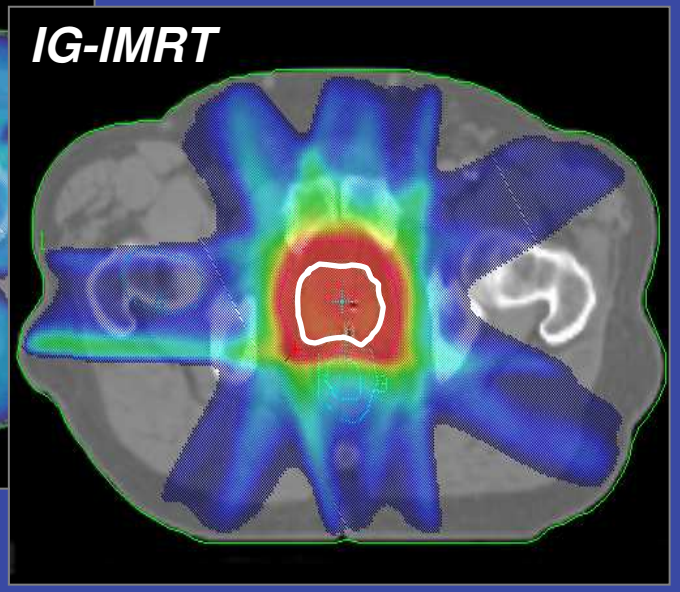
The Evolution of Radiotherapy for Cancer



1980's: 60 Gy



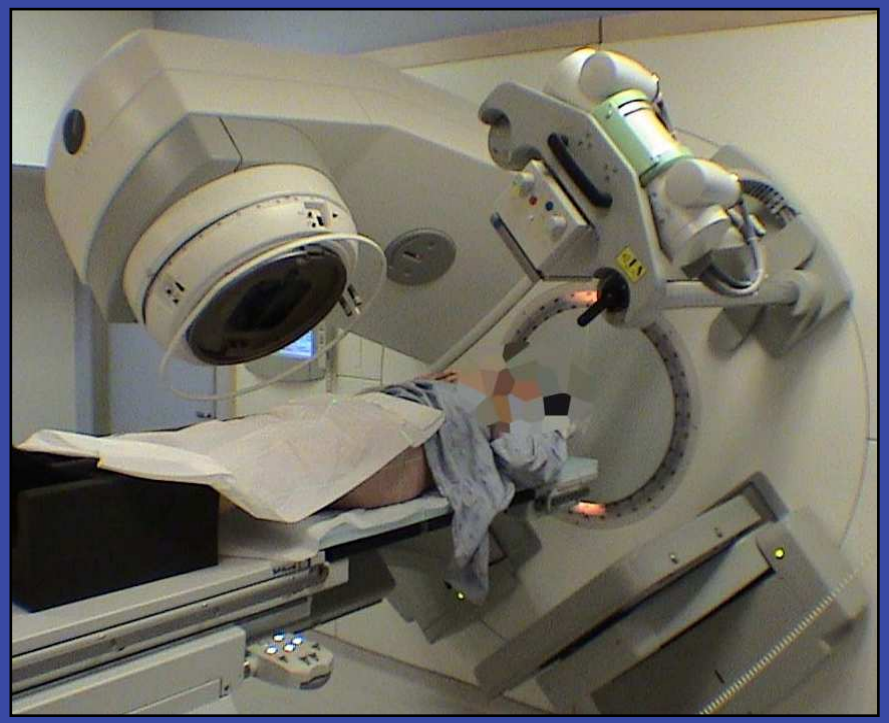
1990's: 70 Gy



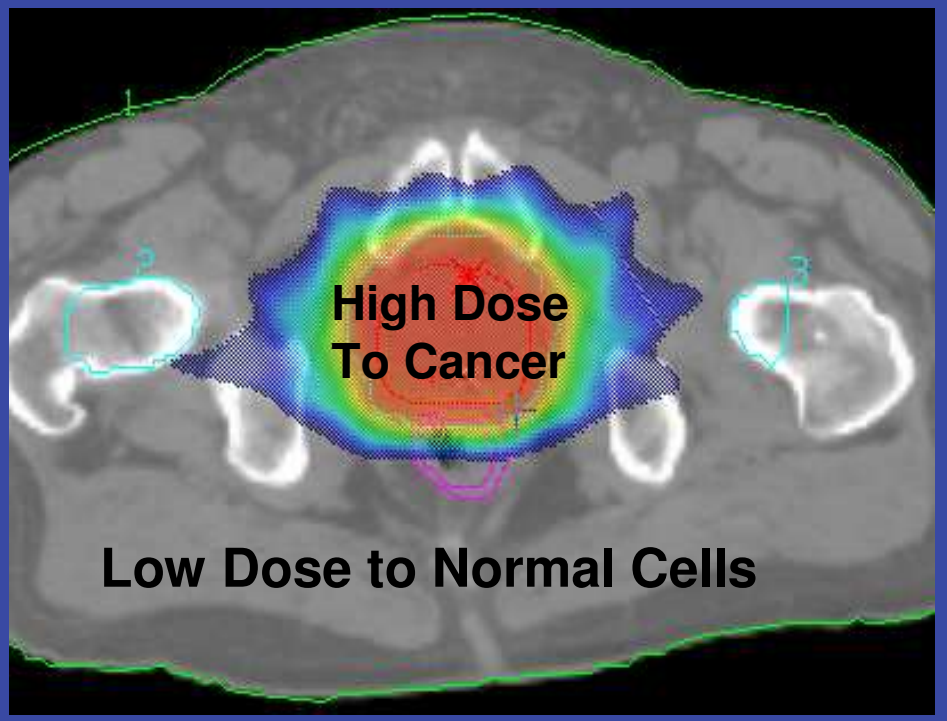
2000's: 80 Gy

M. Milosevic, 2010

High Precision Radiotherapy



Linear accelerator
with integrated CT imaging



Treat the tumor and
avoid normal organs

Image-guided IMRT to ↑ tumor control and/or ↓ toxicity

M. Milosevic, 2010

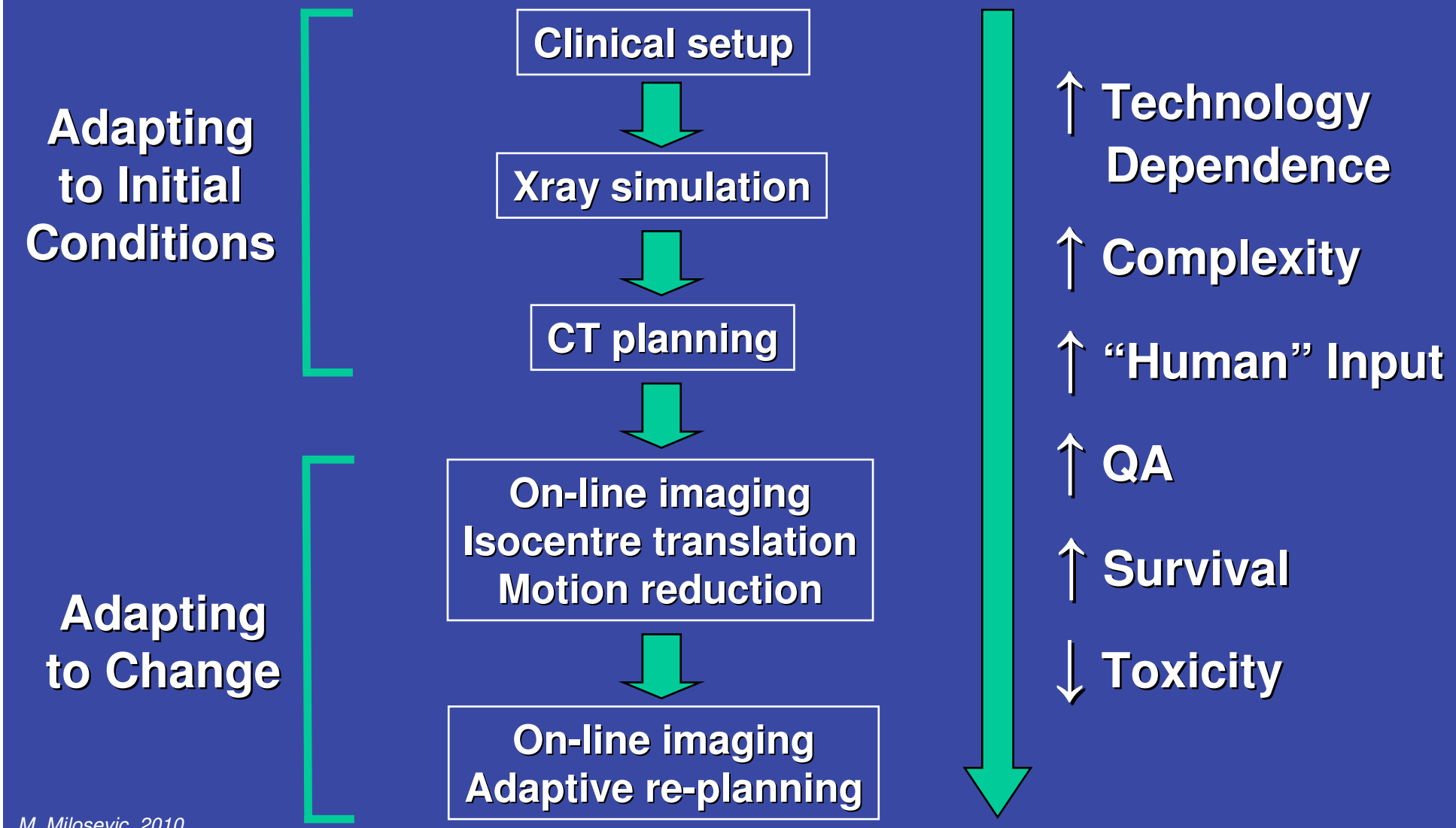
Tumors Change

- Tumors are spatially heterogeneous
- Tumors are unstable
- Position changes
  - Inter-fraction, Intra-fraction
- Size and shape changes
- Biology changes

Liver metastasis

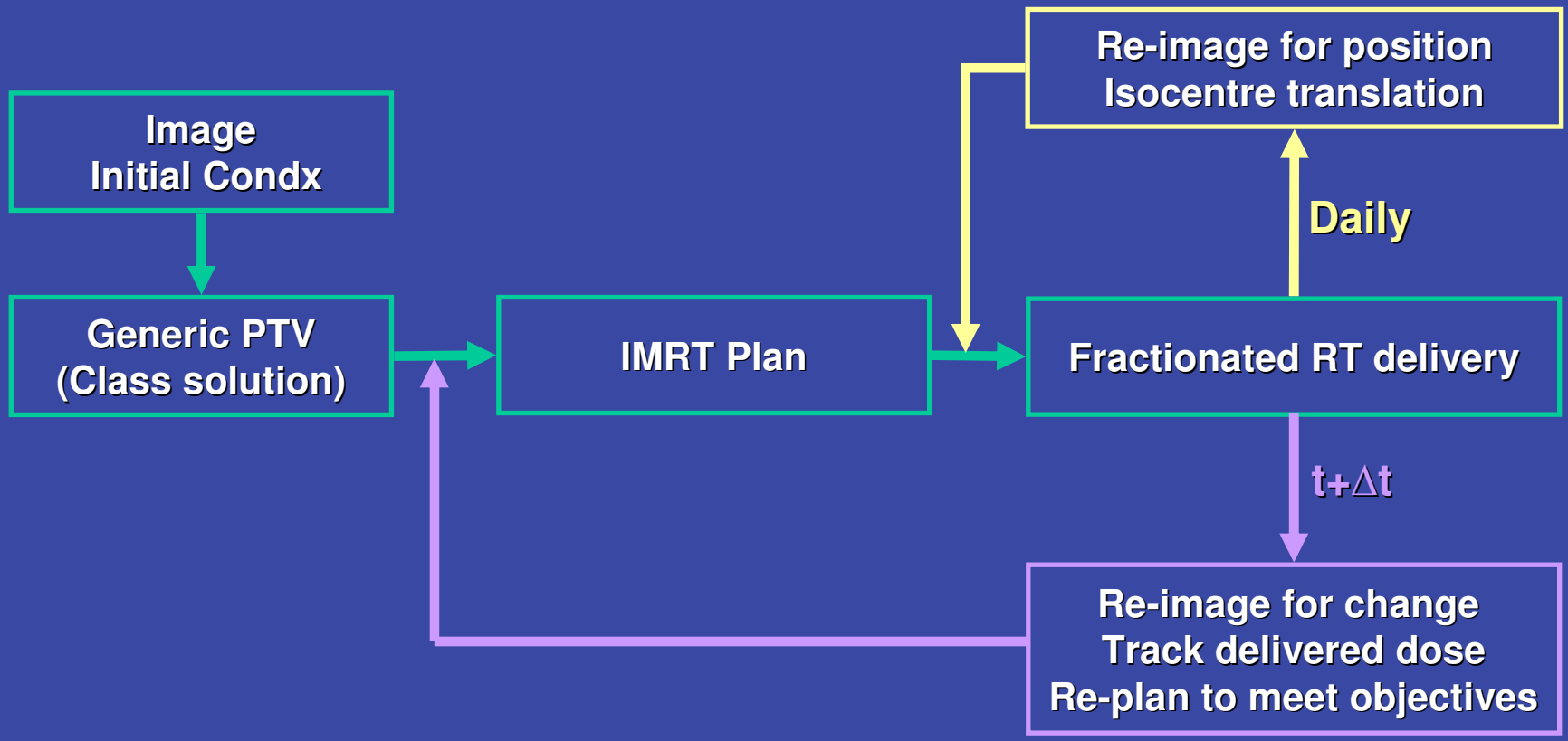
Courtesy of Laura Dawson

The Evolution of Adaptive RT



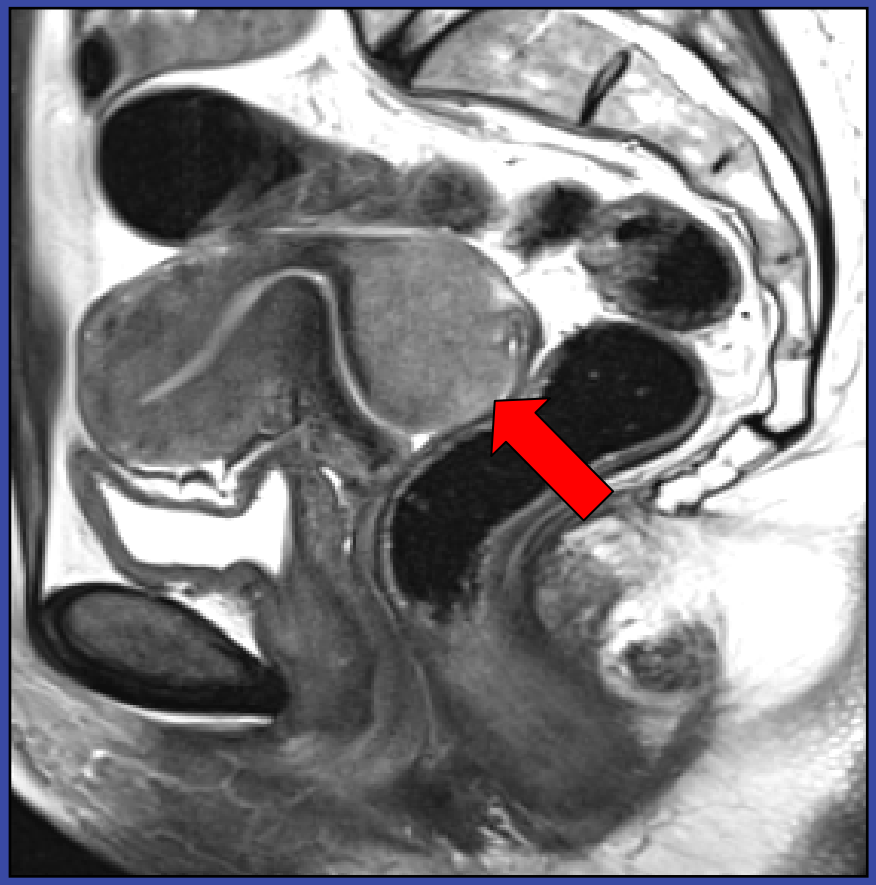
M. Milosevic, 2010

Adapt to Changing Conditions



M. Milosevic, 2010

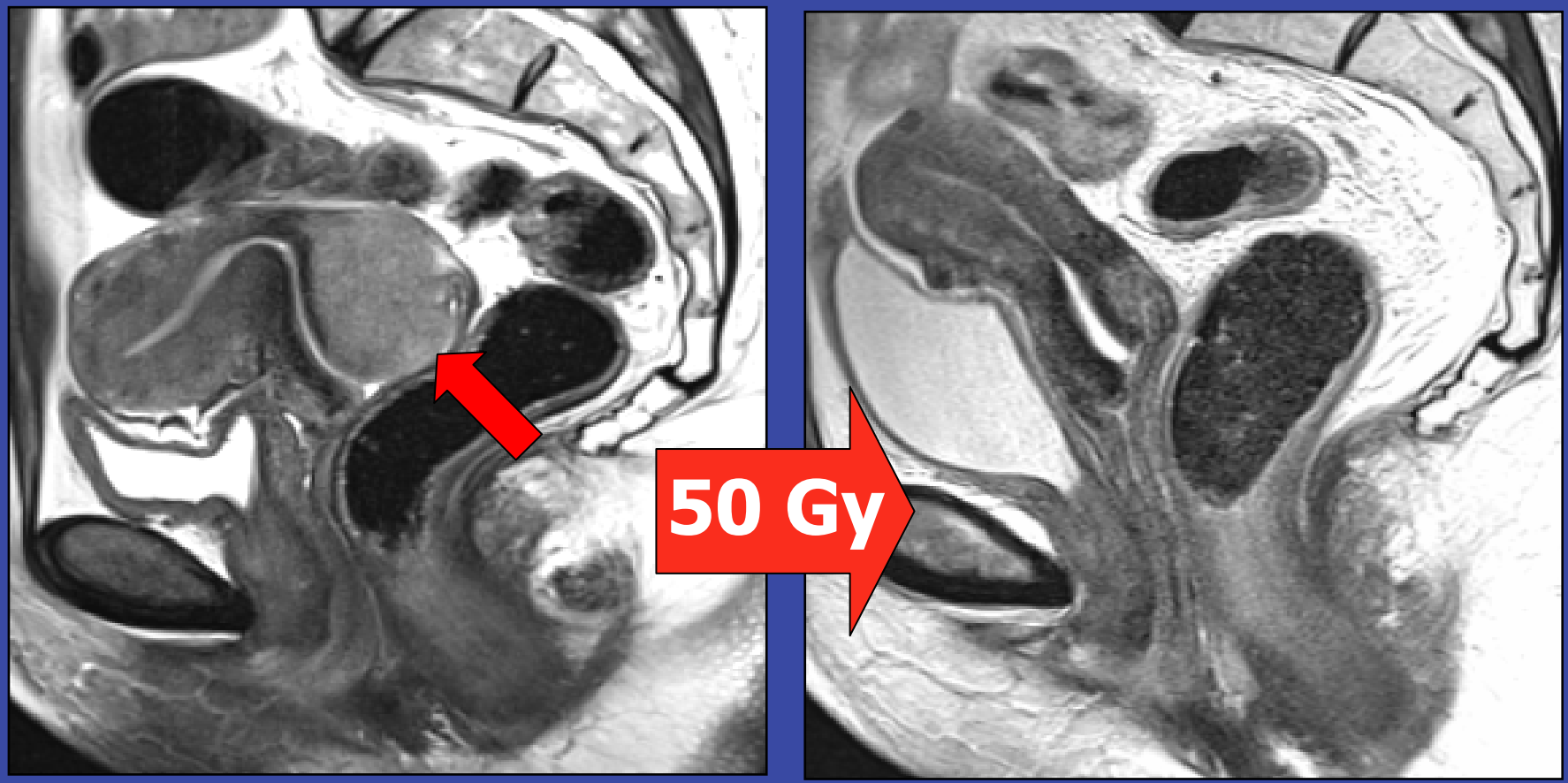
Cervix Cancer



Diagnosis

M. Milosevic, 2010

Cervix Cancer

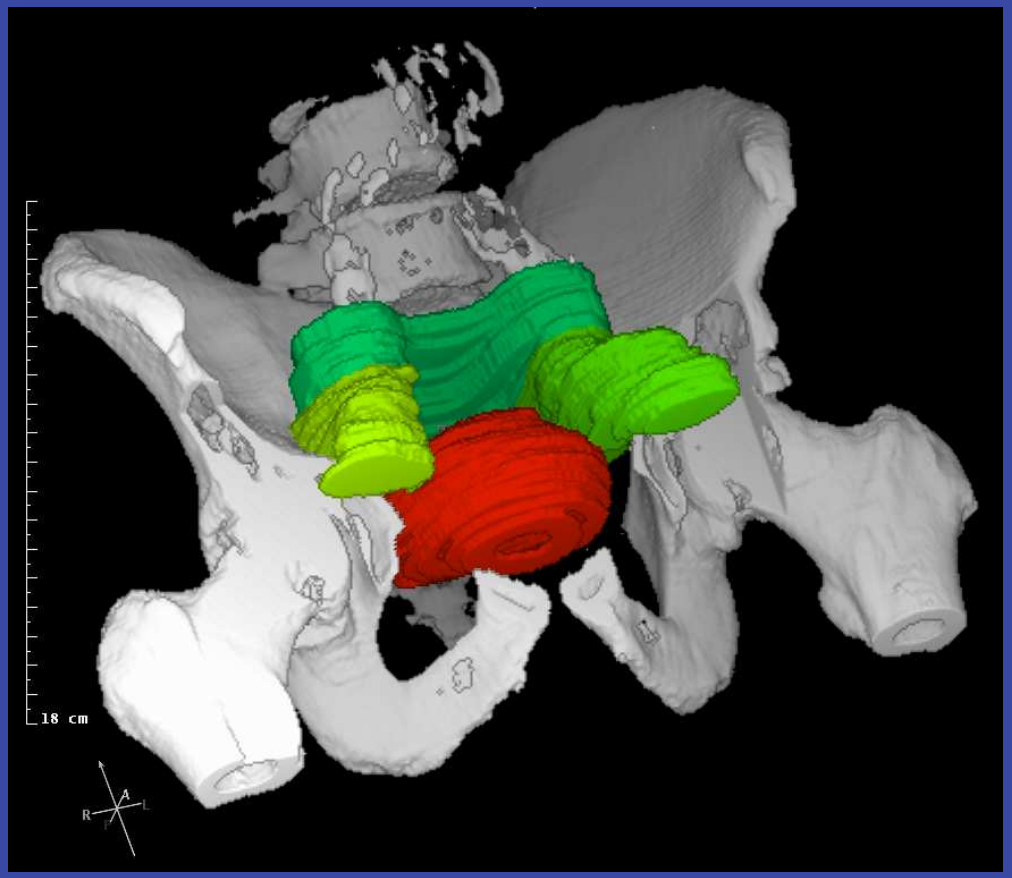


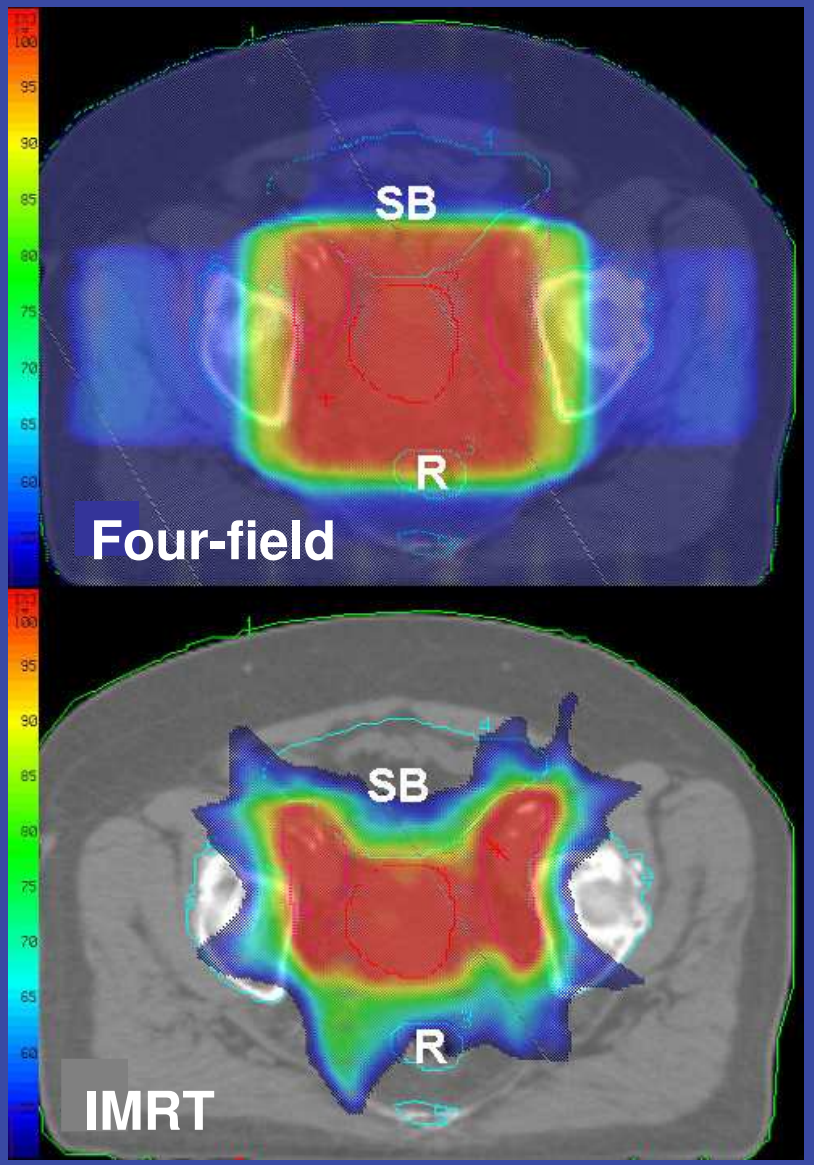
Diagnosis

Mid-treatment

M. Milosevic, 2010

IMRT for Cervix Cancer





M. Milosevic, 2010

IMRT for Cervix Cancer *Challenges*

- Tumor and LN identification
  - Gross, microscopic, observer agreement
- Complex target volumes
- Tumor and normal tissue motion
- Tumor regression and deformation
- Clinical response to a shrinking target
- Online daily image quality
- Workload (contouring, planning, quality)

M. Milosevic, 2010

Cervix Cancer
Motion, Regression, Deformation

INTER- AND INTRAFRACTIONAL TUMOR AND ORGAN MOVEMENT IN PATIENTS WITH CERVICAL CANCER UNDERGOING RADIOTHERAPY: A CINEMATIC-MRI POINT-OF-INTEREST STUDY

Philip Chan, M.B.B.S.,*†‡ Robert Dinniwell, M.D.,*†‡ Masoom A. Haider, M.D.,§¶ Young-Bin Cho, Ph.D.,*† David Jaffray, Ph.D.,*† Gina Lockwood, M.Math.,‖ Wilfred Levin, M.B.,*† Lee Manchul, M.D.,*† Anthony Fyles, M.D.,*†‡ and Michael Milosevic, M.D.*†‡

*Radiation Medicine Program, §Department of Medical Imaging, and ‖Clinical Study Coordination and Biostatistics, Princess Margaret Hospital/Ontario Cancer Institute, University Health Network, Toronto, ON, Canada; Departments of †Radiation Oncology and ¶Medical Imaging, and ‡Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada

CERVICAL CANCER REGRESSION MEASURED USING WEEKLY MAGNETIC RESONANCE IMAGING DURING FRACTIONATED RADIOTHERAPY: RADIOBIOLOGIC MODELING AND CORRELATION WITH TUMOR HYPOXIA

Karen Lim, M.B.B.S.,*† Philip Chan, M.B.B.S.,* Robert Dinniwell, M.D.,*† Anthony Fyles, M.D.,*† Masoom Haider, M.D.,‡§ Young-Bin Cho, Ph.D.,*‖ David Jaffray, Ph.D.,*† Lee Manchul, M.D.,*† Wilfred Levin, M.D.,*† Richard P. Hill, Ph.D.,†‖¶ and Michael Milosevic, M.D.*†

*Radiation Medicine Program, ‡Department of Medical Imaging, and ‖Division of Applied Molecular Oncology, Princess Margaret Hospital/Ontario Cancer Institute, University Health Network, Toronto, ON, Canada; Departments of †Radiation Oncology, §Medical Imaging, and ¶Medical Biophysics, University of Toronto, Toronto, ON, Canada

Motion and deformation of the target volumes during IMRT for cervical cancer: What margins do we need?

Linda van de Bunt[a,*], Ina M. Jürgenliemk-Schulz[a], Gérard A.P. de Kort[b], Judith M. Roesink[a], Robbert J.H.A. Tersteeg[a], Uulke A. van der Heide[a]

[a]*Department of Radiation Oncology, and* [b]*Department of Radiology, University Medical Center Utrecht, The Netherlands*

An assessment of interfractional uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancer☆

Alexandra Taylor*, Melanie E.B. Powell

Department of Radiotherapy, St. Bartholomew's Hospital, London, UK

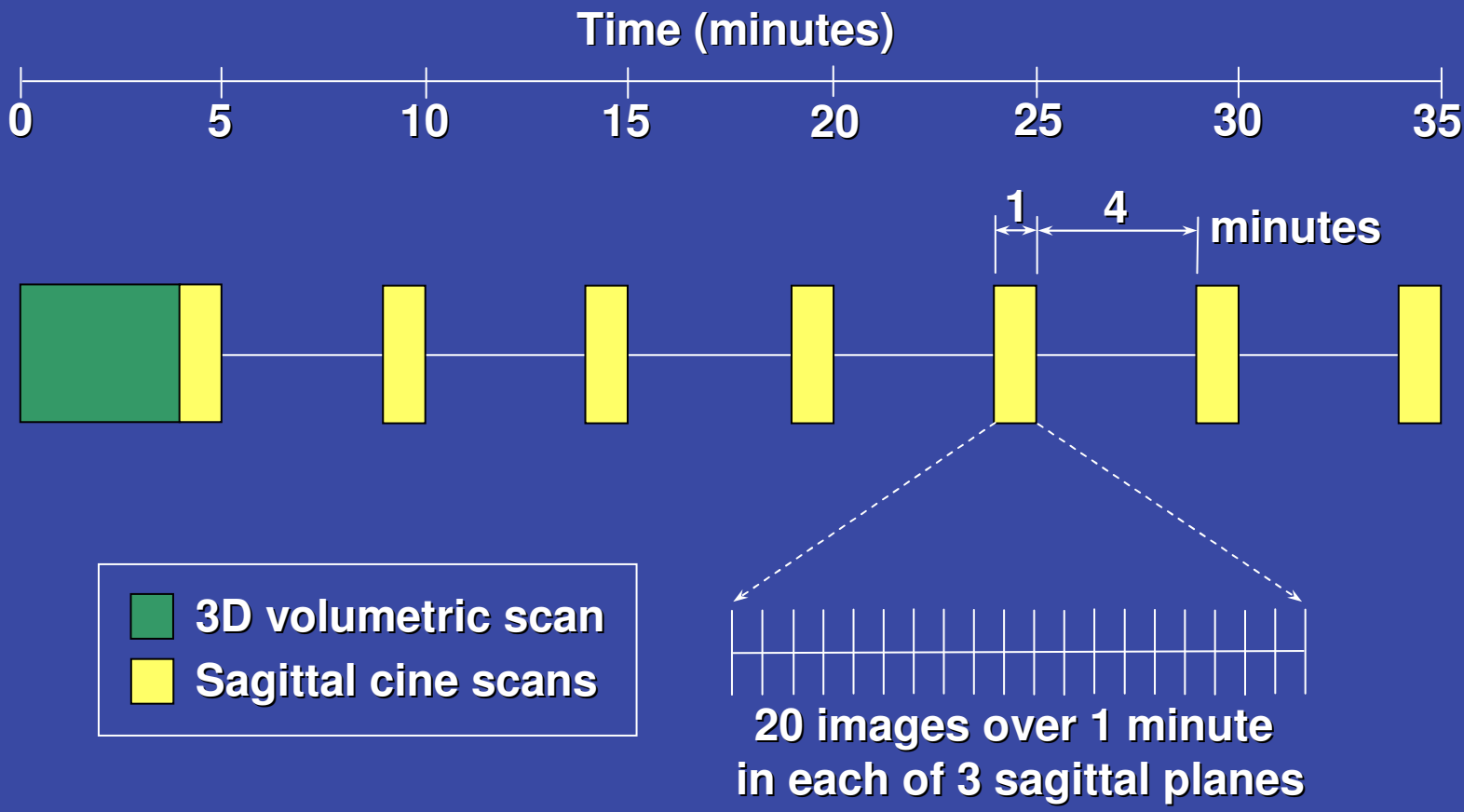
CERVIX REGRESSION AND MOTION DURING THE COURSE OF EXTERNAL BEAM CHEMORADIATION FOR CERVICAL CANCER

Beth M. Beadle, M.D., Ph.D.,* Anuja Jhingran, M.D.,* Mohammad Salehpour, Ph.D.,† Marianne Sam, B.S.,* Revathy B. Iyer, M.D.,‡ and Patricia J. Eifel, M.D.*

Departments of *Radiation Oncology, †Radiation Physics, and ‡Diagnostic Imaging, The University of Texas M. D. Anderson Cancer Center, Houston, TX

M. Milosevic, 2010

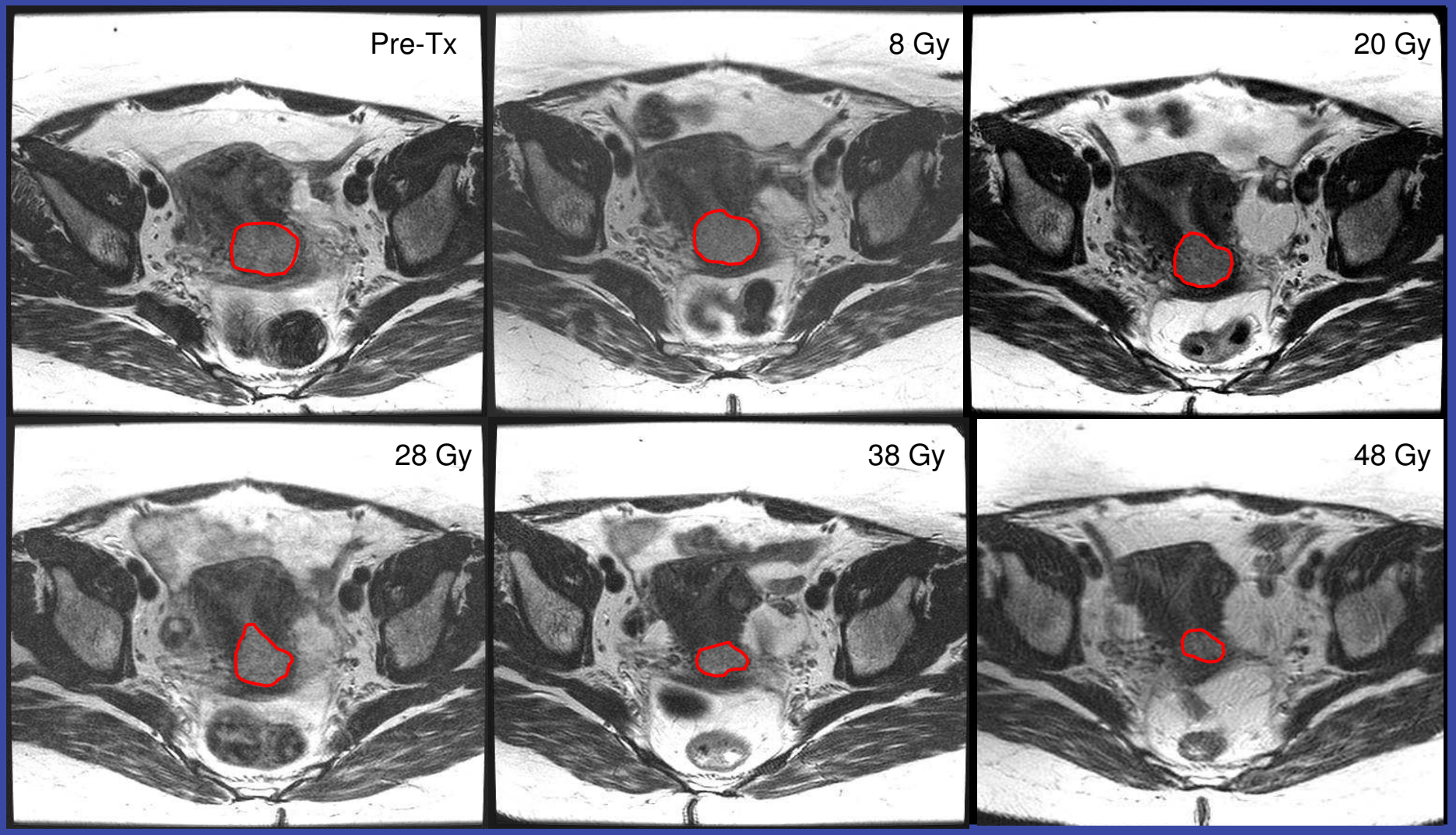
Cervix Cancer: Change During RT



Weekly MR imaging to track tumor movement

M. Milosevic, 2010

Tumor Regression During RT

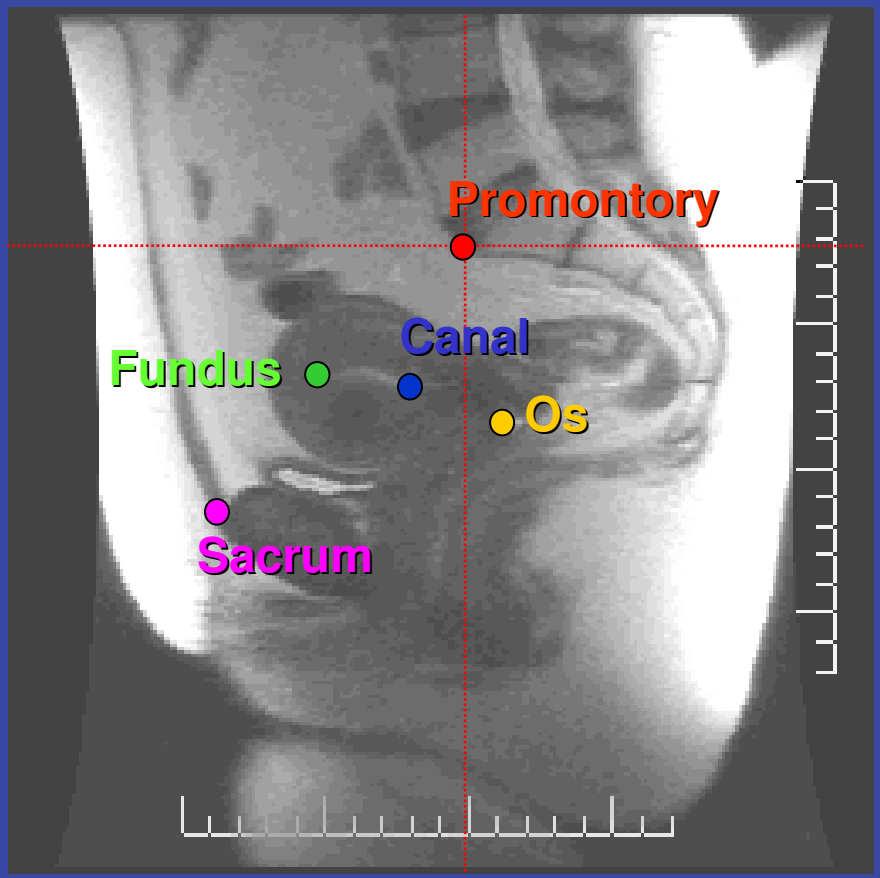


M. Milosevic, 2010

Karen Lim, 2008

Cervix Motion During RT

Cervix (Week 1)

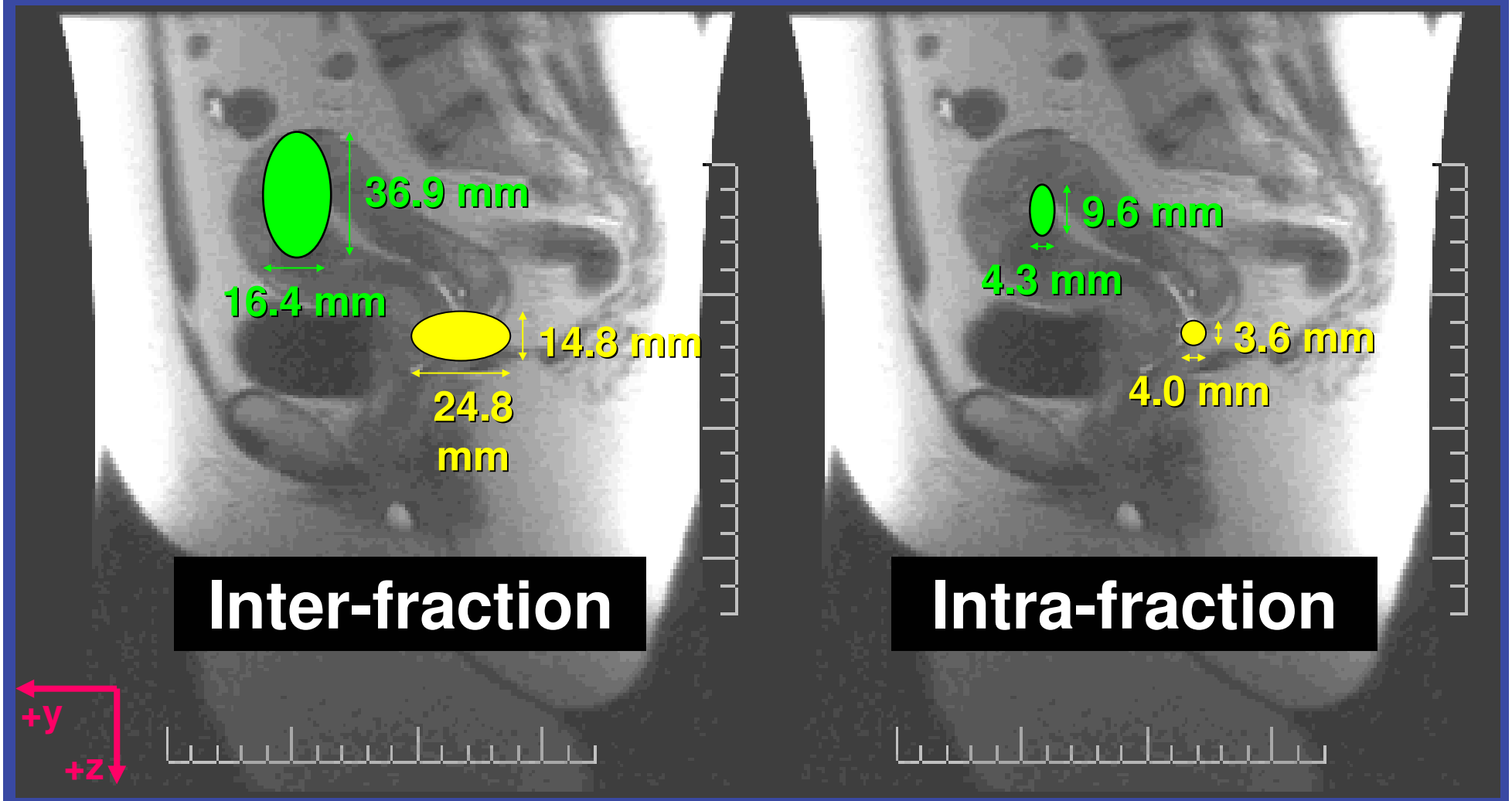


Point-of-Interest (POI) Analysis

Philip Chan, 2008

M. Milosevic, 2010

Uterine PTV Margins for IMRT



M. Milosevic, 2010

Philip Chan, 2008

Cervix Cancer Motion
Summary

- Complex, spatially-dependent motion
- Large inter-fraction tumor motion
- Small intra-fraction tumor motion
- Tumor regression and deformation

M. Milosevic, 2010

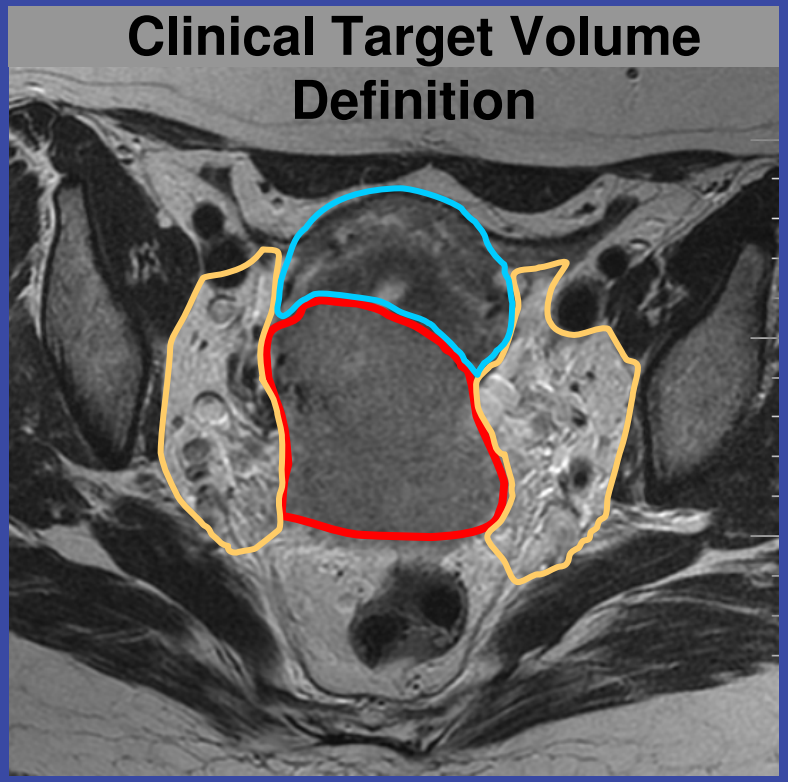
Cervix Cancer Motion
Summary

- Complex, spatially-dependent motion
- Large inter-fraction tumor motion
- Small intra-fraction tumor motion
- Tumor regression and deformation
- How do these changes during treatment influence the dose delivered to the tumor and critical normal tissues?

M. Milosevic, 2010

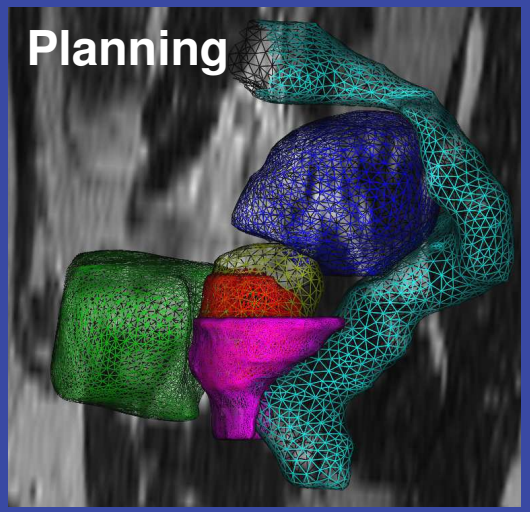
Cervix Cancer Motion
Dosimetric Impact of Margin Size

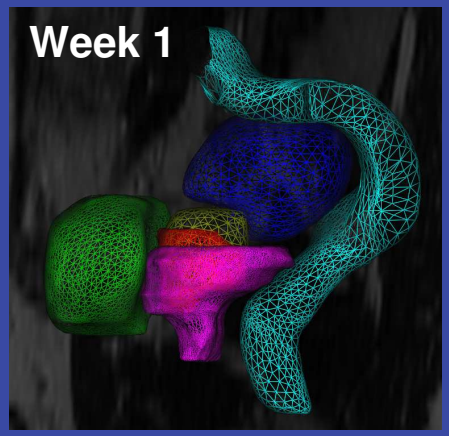
- 20 patients, weekly MR's
- 3 plans (50 Gy):
  (a) Conventional
  (b) 20 mm PTV
  (c) 5 mm PTV
- "Delivered" dose accumulation over the course of treatment

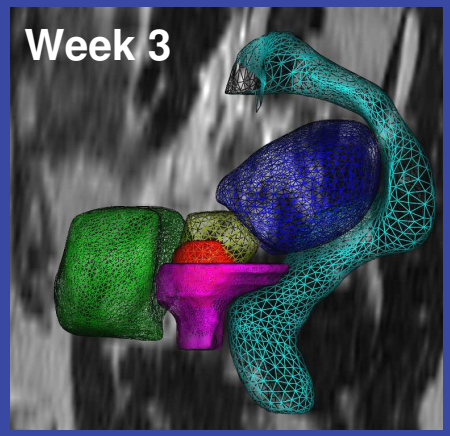


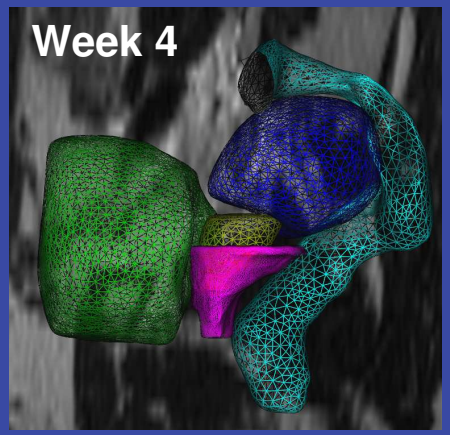
Courtesy of Karen Lim

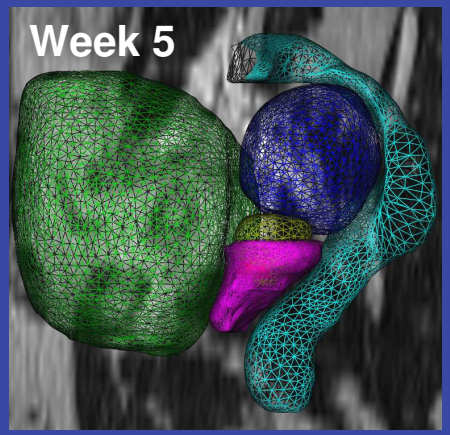
Deformable Soft Tissue Modeling









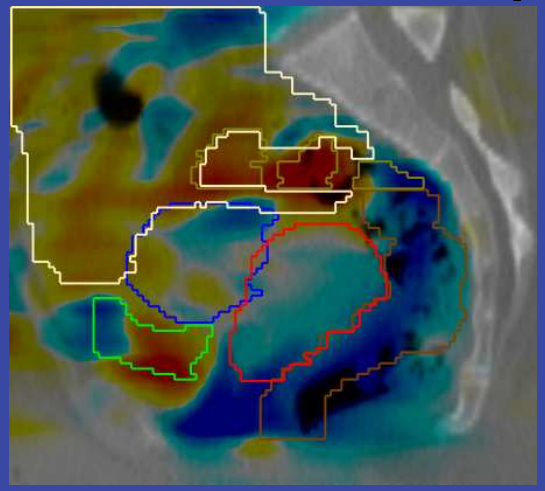


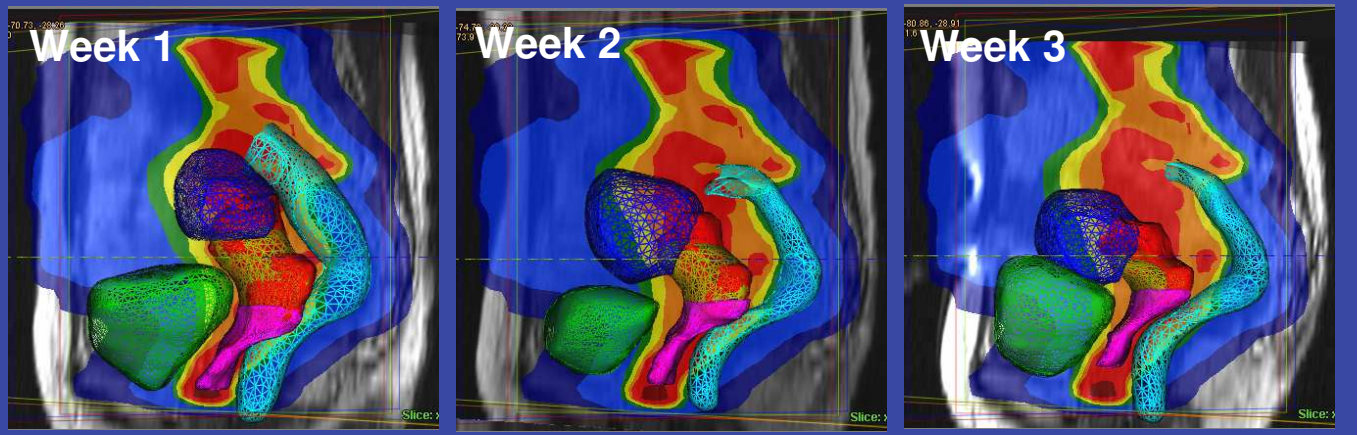
MORPHEUS:
Mapping of weekly anatomy to planning geometry

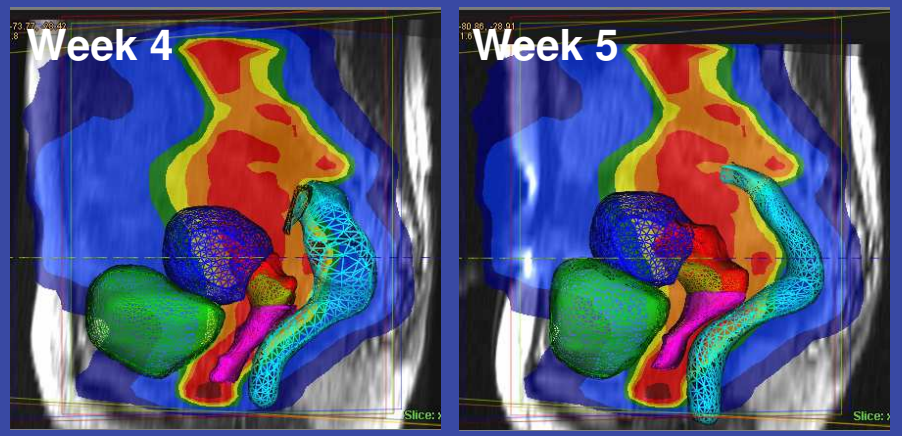
Courtesy of Kristy Brock and James Stewart

Delivered Dose Accumulation

Dose-Difference Map







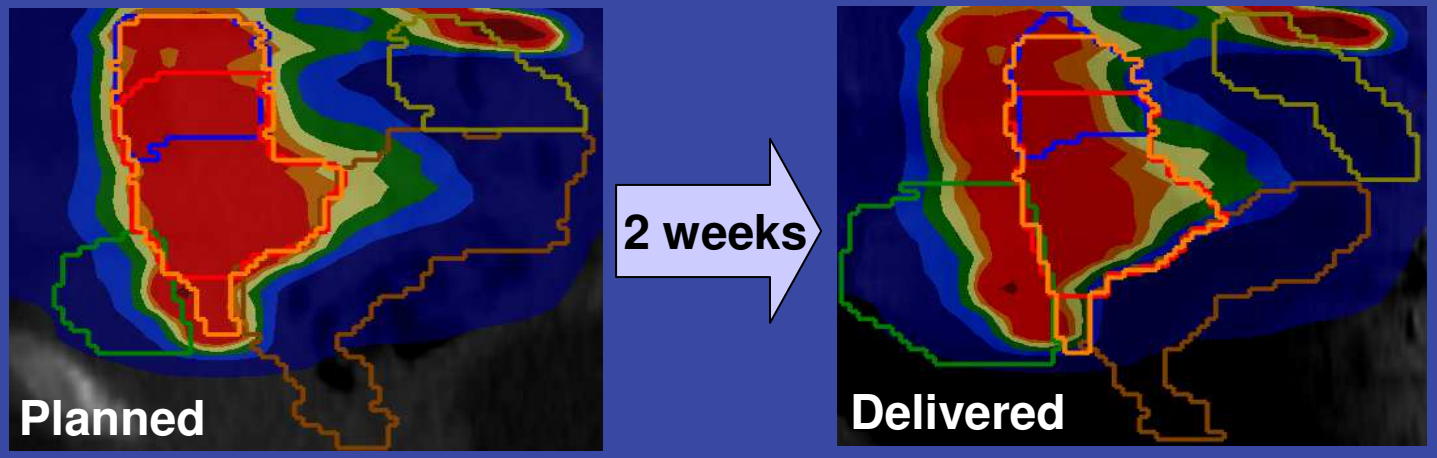
ORBIT: Mapping of delivered vs. planned dose to tumor and normal organs

M. Milosevic, 2010

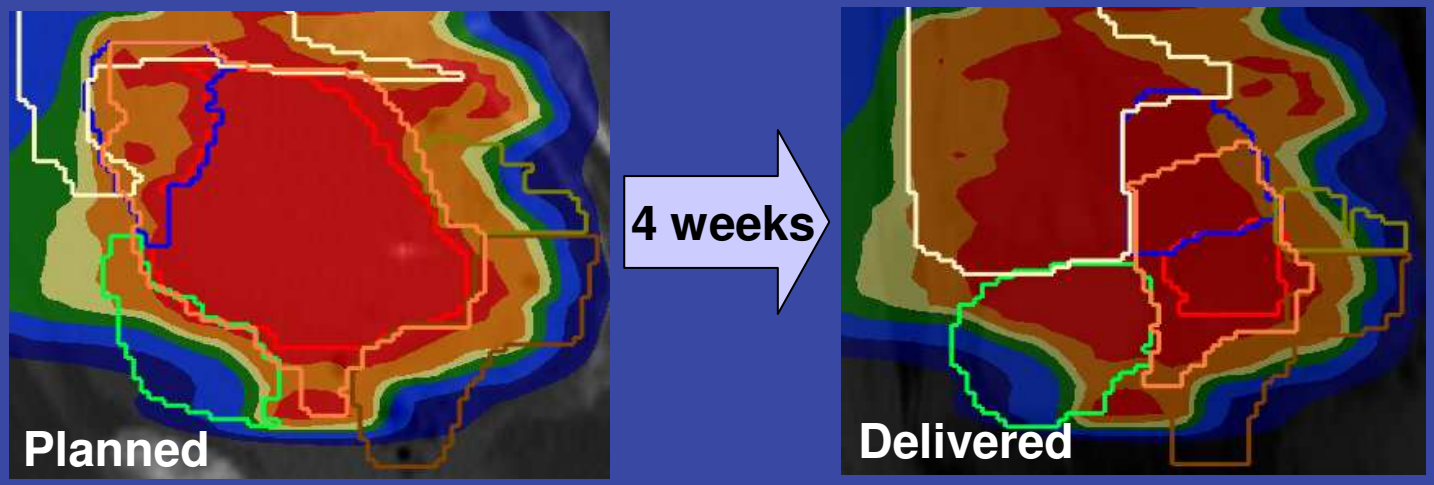
Courtesy of Karen Lim and Val Kelly

Cervix Cancer Motion and Dose

Case 1

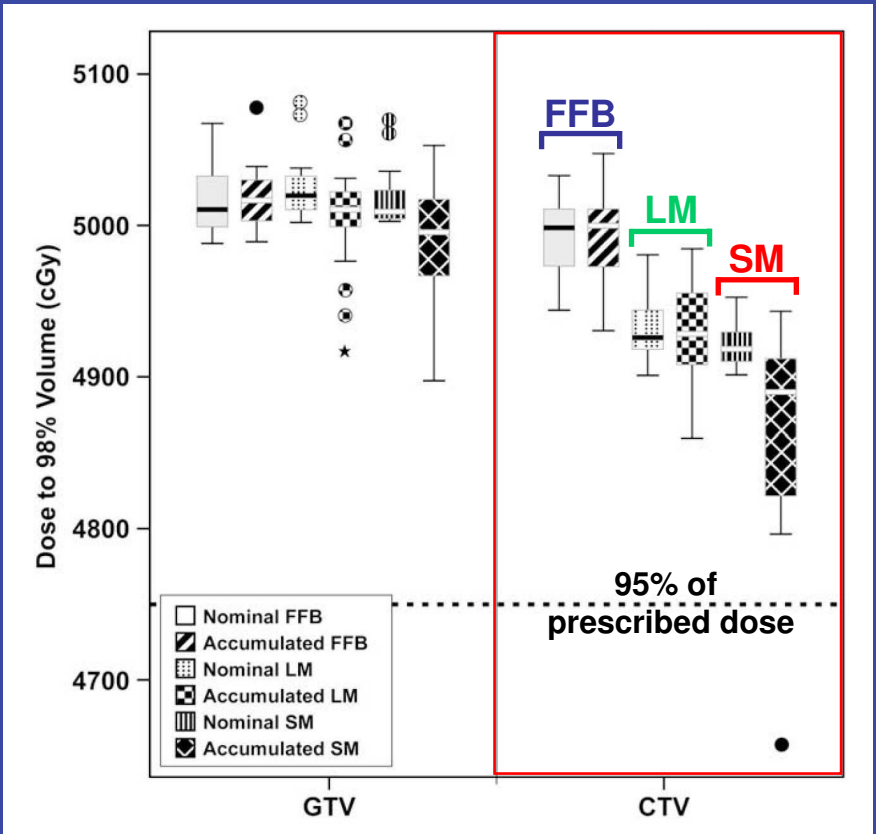


Case 2



Courtesy of Karen Lim and James Stewart

Cervix Cancer Motion
Dosimetric Impact of Margin Size

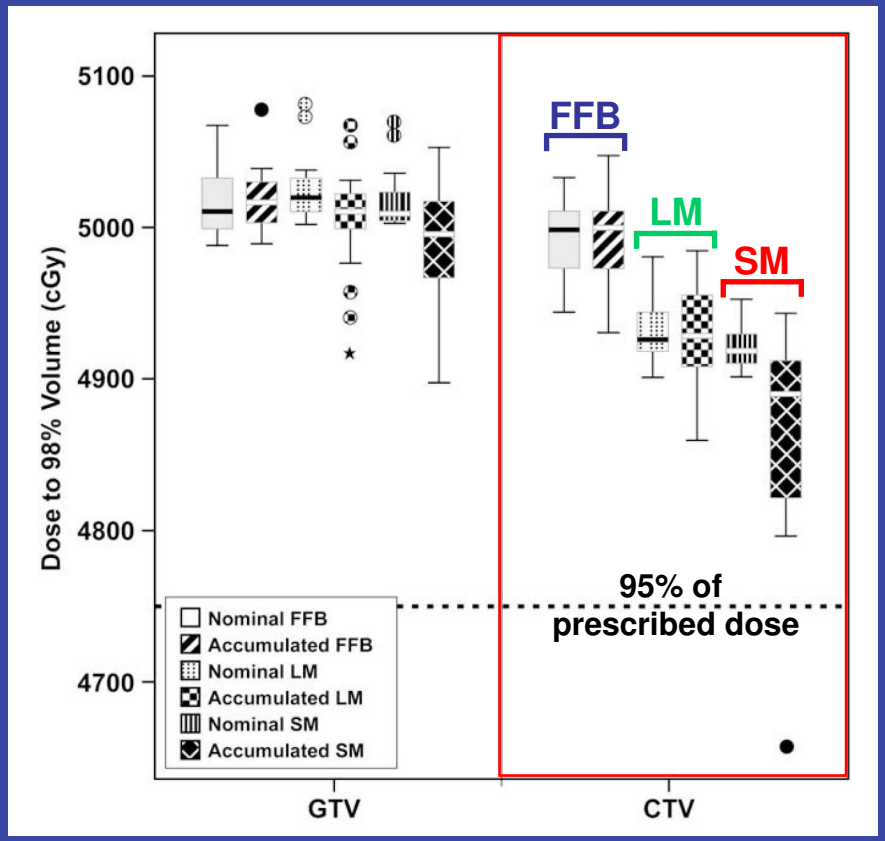


Tumor coverage

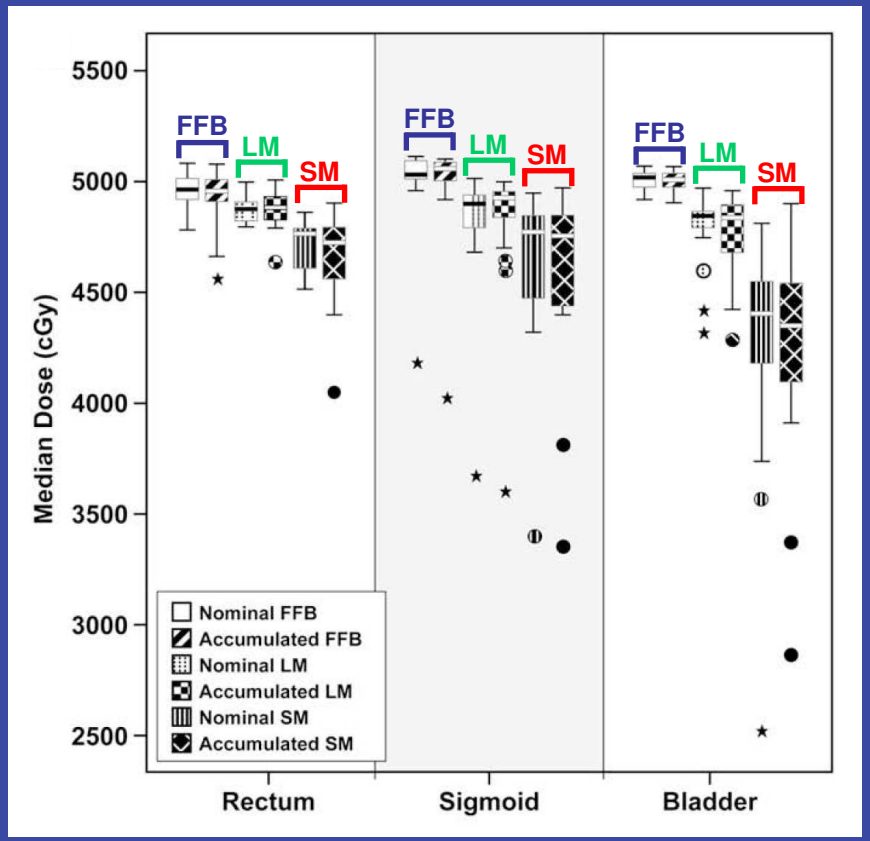
M. Milosevic, 2010

Karen Lim, 2009

Cervix Cancer Motion
Dosimetric Impact of Margin Size



Tumor coverage

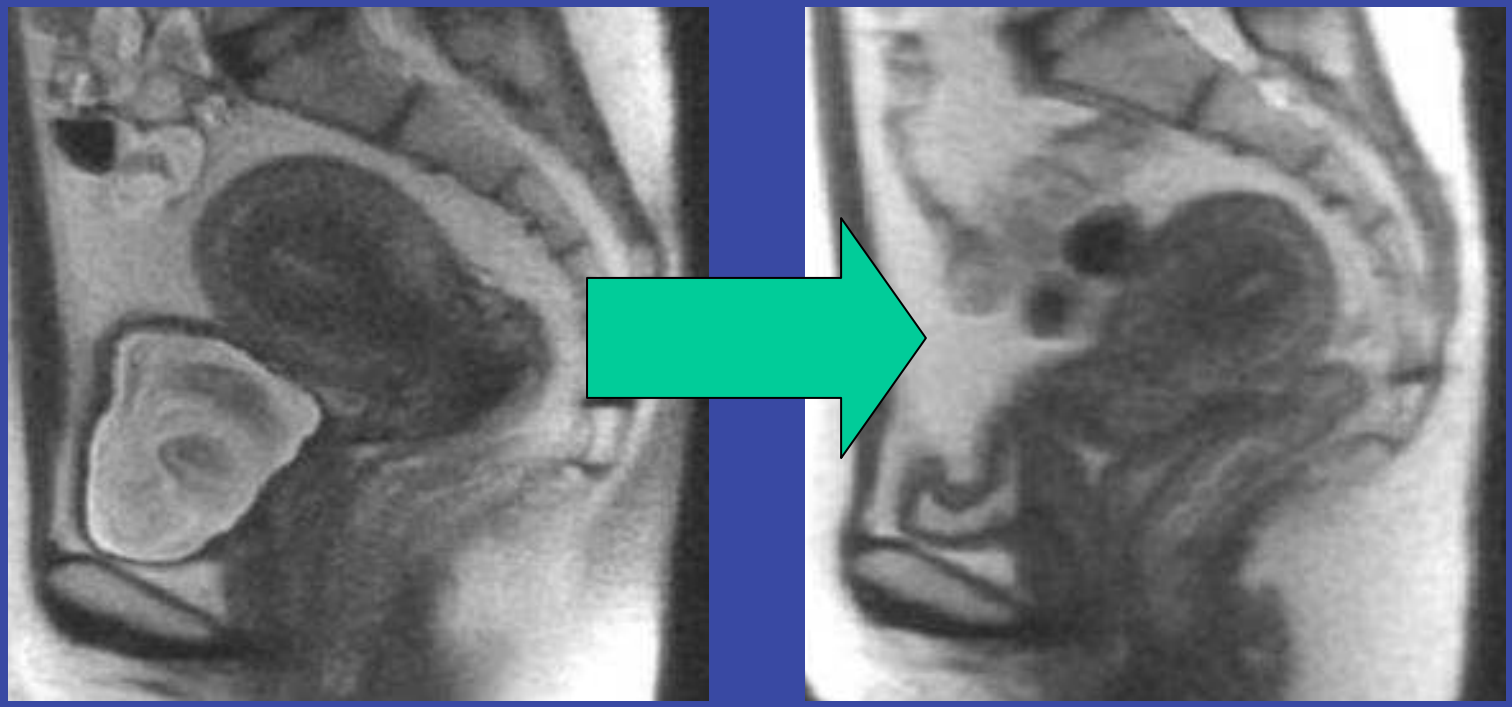


Normal organ sparing

Karen Lim, 2009

M. Milosevic, 2010

Cervix Cancer Motion



Extreme, complex and unpredictable motion implies the need for:

- Daily image guidance

- Daily “adaptive” re-planning

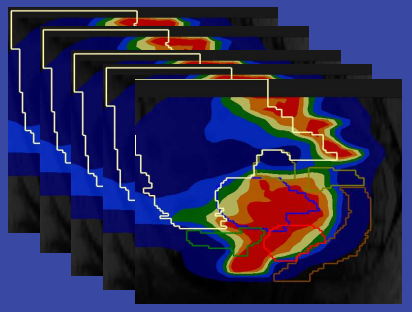
M. Milosevic, 2010

Cervix Cancer Adaptive RT

1) IMRT with uniform 3mm PTV margin, no replanning

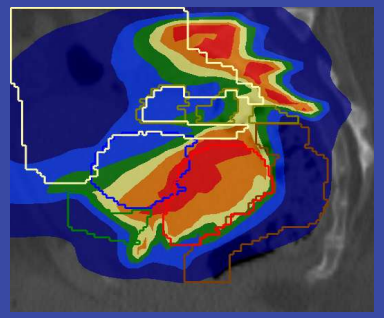
IMRT Plan Optimization Function

Planning



25 Fractions

Deliver



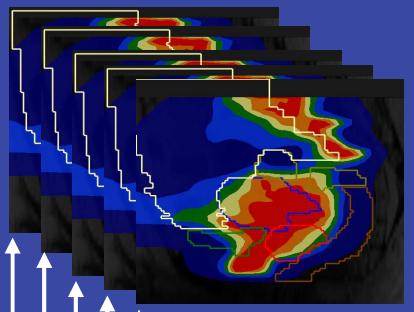
Criteria:

- D98% GTV > 50 Gy
- D98% CTV > 49 Gy
- D98% PTV > 47.5 Gy
- OARs subject to RTOG 0418 protocol

2) Automatic replan with pre-treatment optimization function

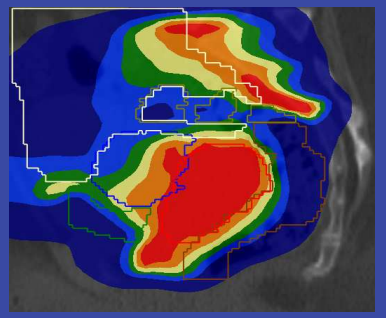
IMRT Plan Optimization Function

Planning



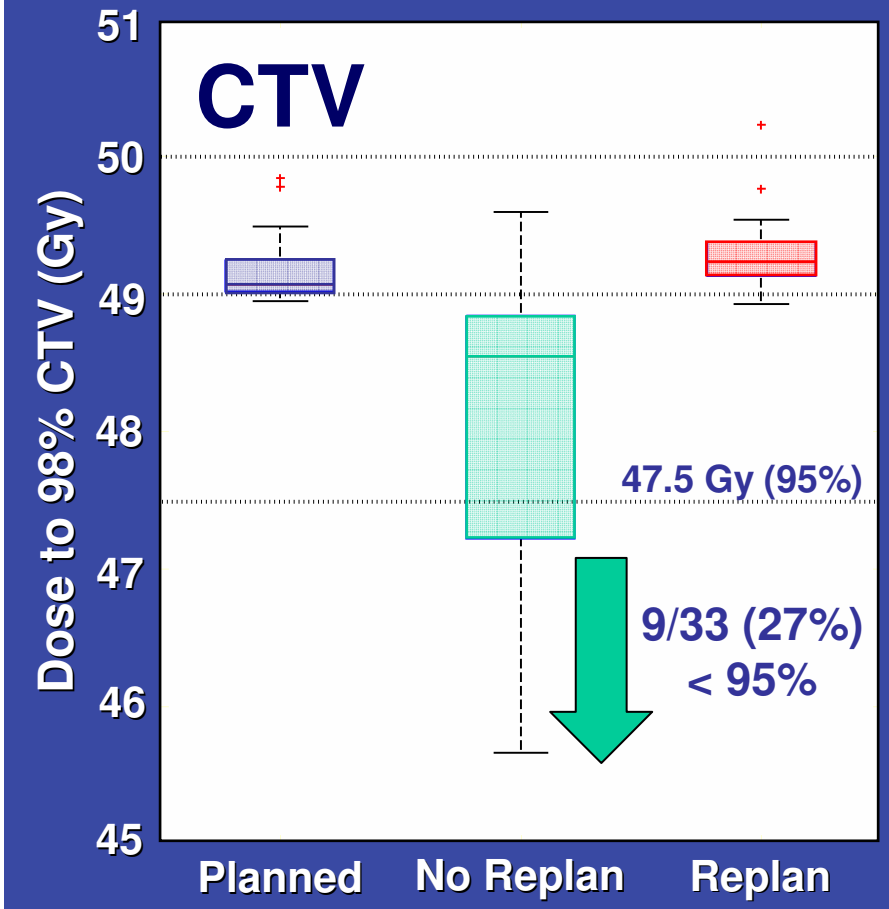
Automatic Weekly Replan

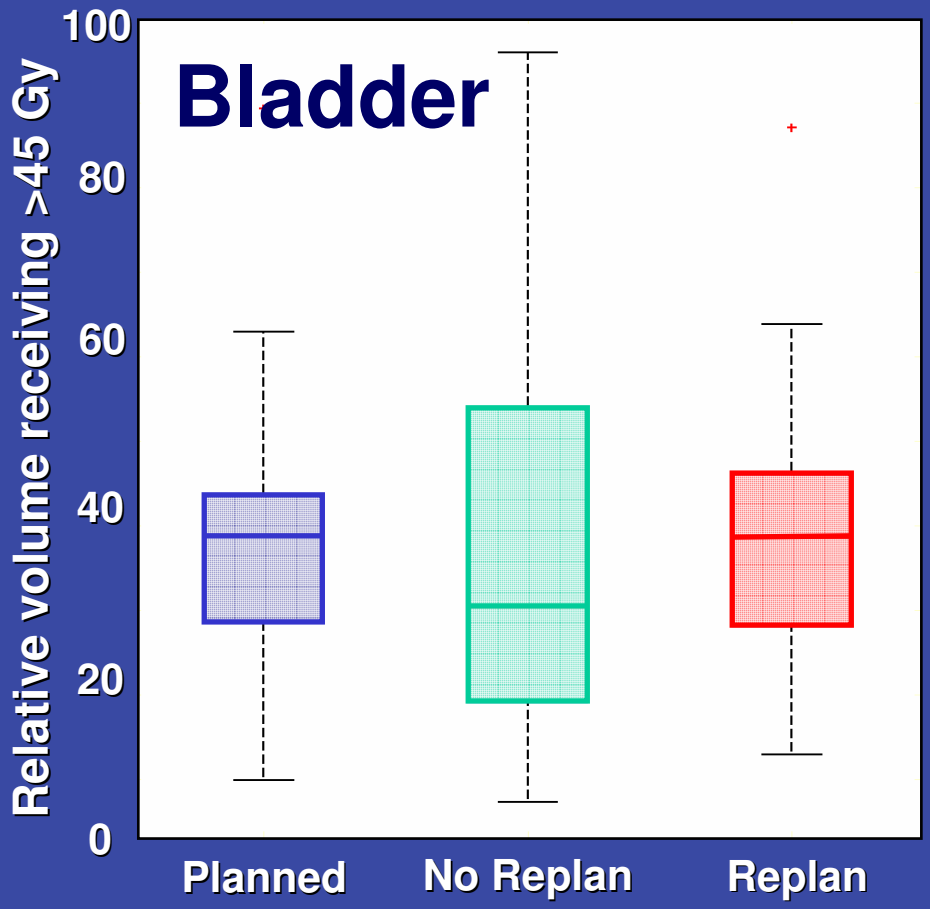
Deliver



M. Milosevic, 2010

Cervix Cancer Adaptive RT





M. Milosevic, 2010

Courtesy James Stewart

Summary

- Tumors move, shrink and change shape.
- Extreme, unpredictable anatomic changes can occur.
- Large safety margins are required to account for inter- and intra-fraction movement and avoid missing tumor.
- Smaller margins may be feasible with daily online imaging and adaptive replanning, allowing dose escalation and/or normal tissue sparing.
- Opportunities for research and development
  - Daily online image quality, automated contouring, automated re-planning, quality assurance, biologic adaptation

M. Milosevic, 2010

OCAIRO

Ontario Consortium for Adaptive Interventions in Radiation Oncology

- Alliance of 7 Ontario institutions
- Inter-disciplinary
- Funding from Ontario Research Fund
- Research Themes:
  - 3D/4D imaging for adaptive RT
  - Adaptive RT processes
  - Validation of imaging, deformation and dose accumulation techniques
  - Software development for clinical translation

M. Milosevic, 2010

Princess Margaret Hospital

Radiation Oncology: A. Fyles, W. Levin, L. Manchul, K. Lim, P. Chan
Medical Physics: Y-B Cho, K. Brock, D. Jaffray, J. Jezioranski, I. Yeung, T. Craig, J. Stewart, J. Moseley, M. Sharpe, J, Xie
Medical Imaging: M. Haider
Radiotherapy: V. Kelly, J. Paterson
Biostatistics: M. Pintilie, G. Lockwood

RaySearch Laboratories AB

A. Lundin, H. Rehbinder, J. Löf

Supported by:

Canadian Cancer Society
Terry Fox Foundation
Giovanni and Concetta Guglietti Family Trust

M. Milosevic, 2010