Radiation Advances for Cervical Cancer

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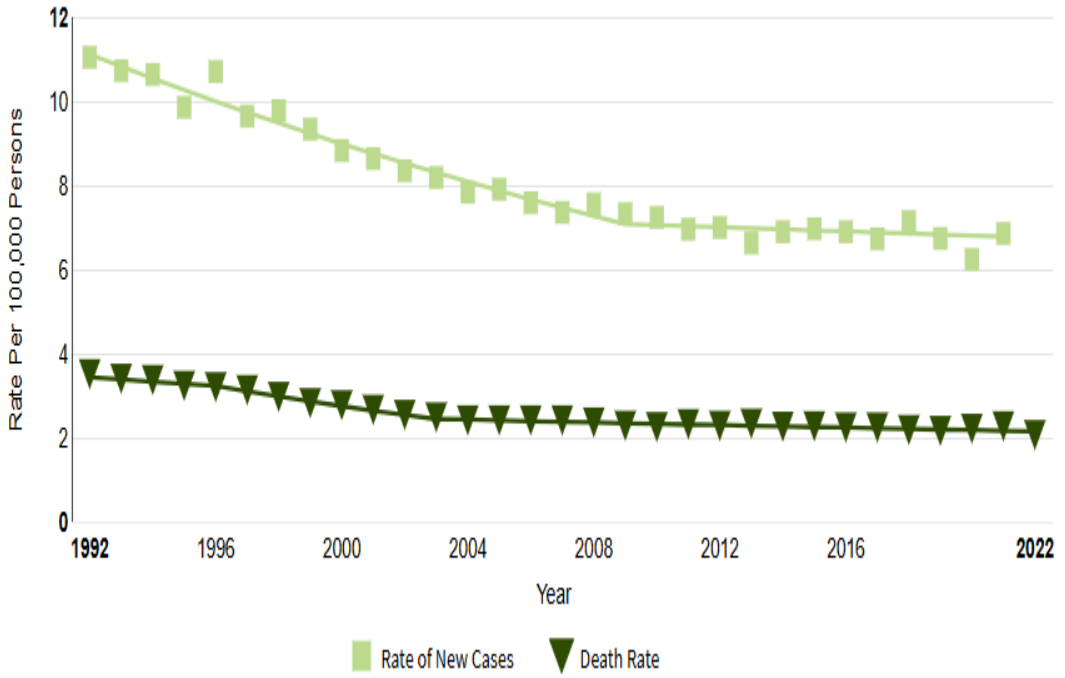
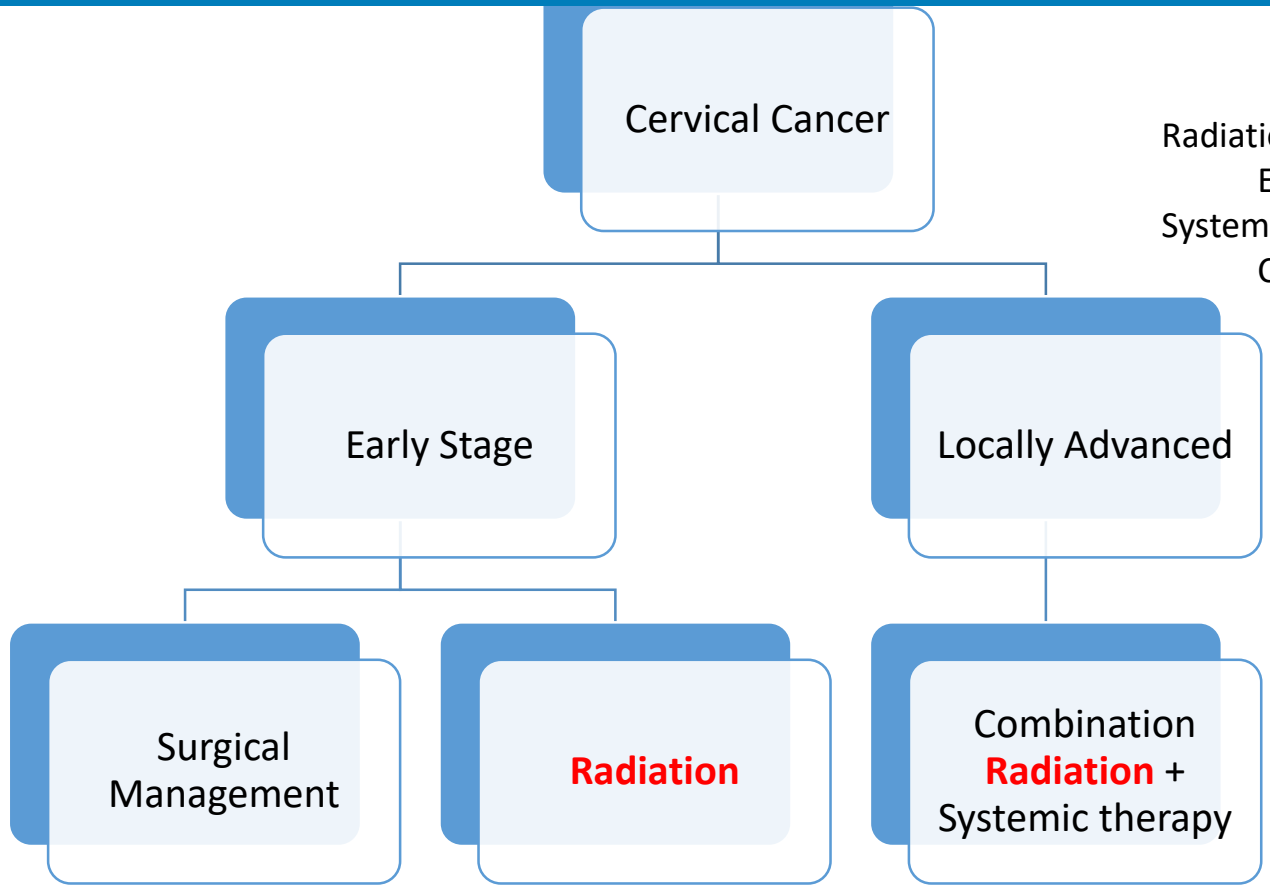
Cervical Cancer: Ongoing Cancer Threat

- 13820 estimated new cases in 2024
- 7.6/100,000 women
- 5yr Relative survival 67%
- HPV vaccine: 61% compliance among US teens



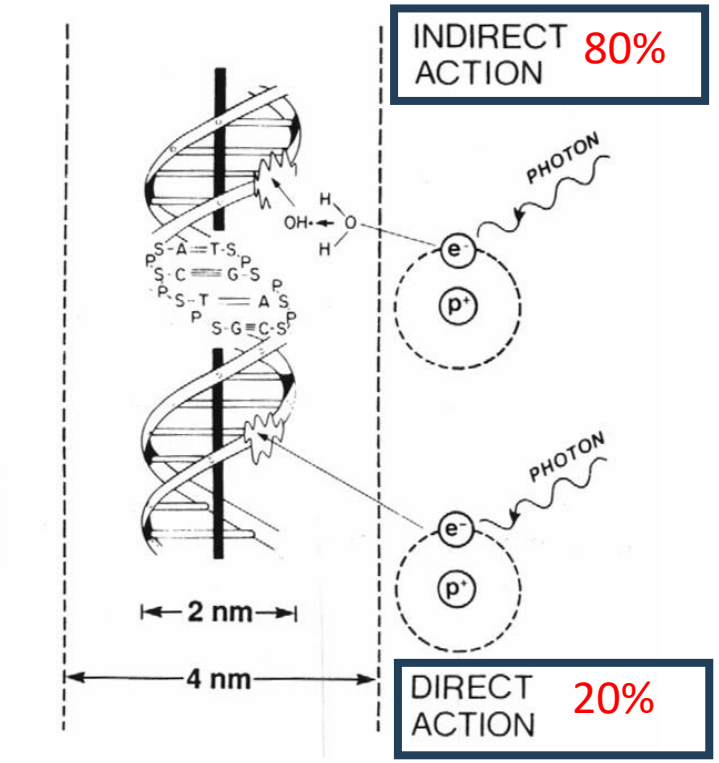
SEER 2004

General Management of Cervical Cancer



Radiation:
External Beam Radiation +/- Brachytherapy
Systemic therapy:
Chemo +/- Immunotherapy

How Radiation Therapy (RT) works



X-rays interact with **water**

↓

radiolysis

↓

free radicals

↓

bind to and damages **DNA**

↓

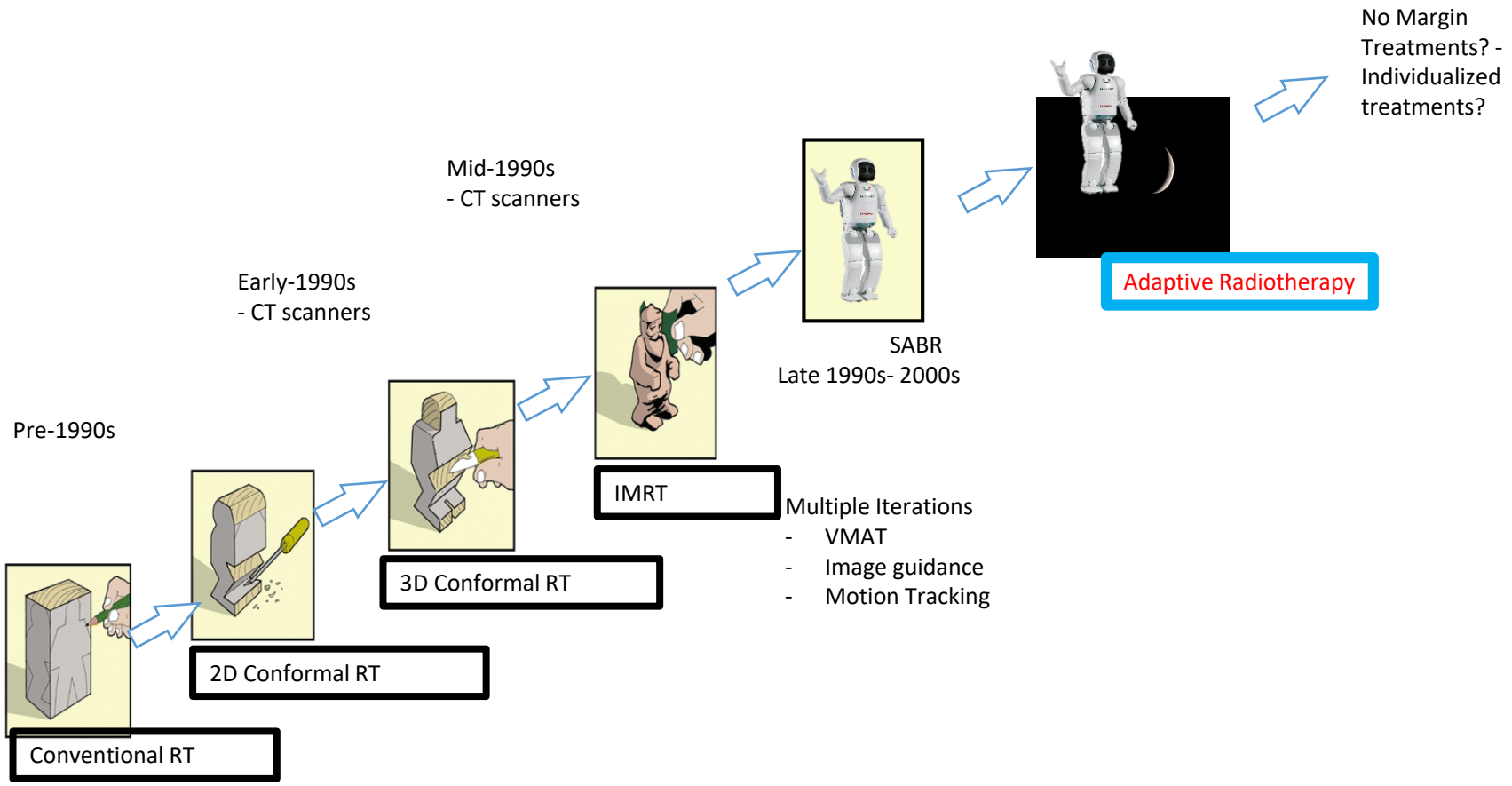
mitotic catastrophe

↓

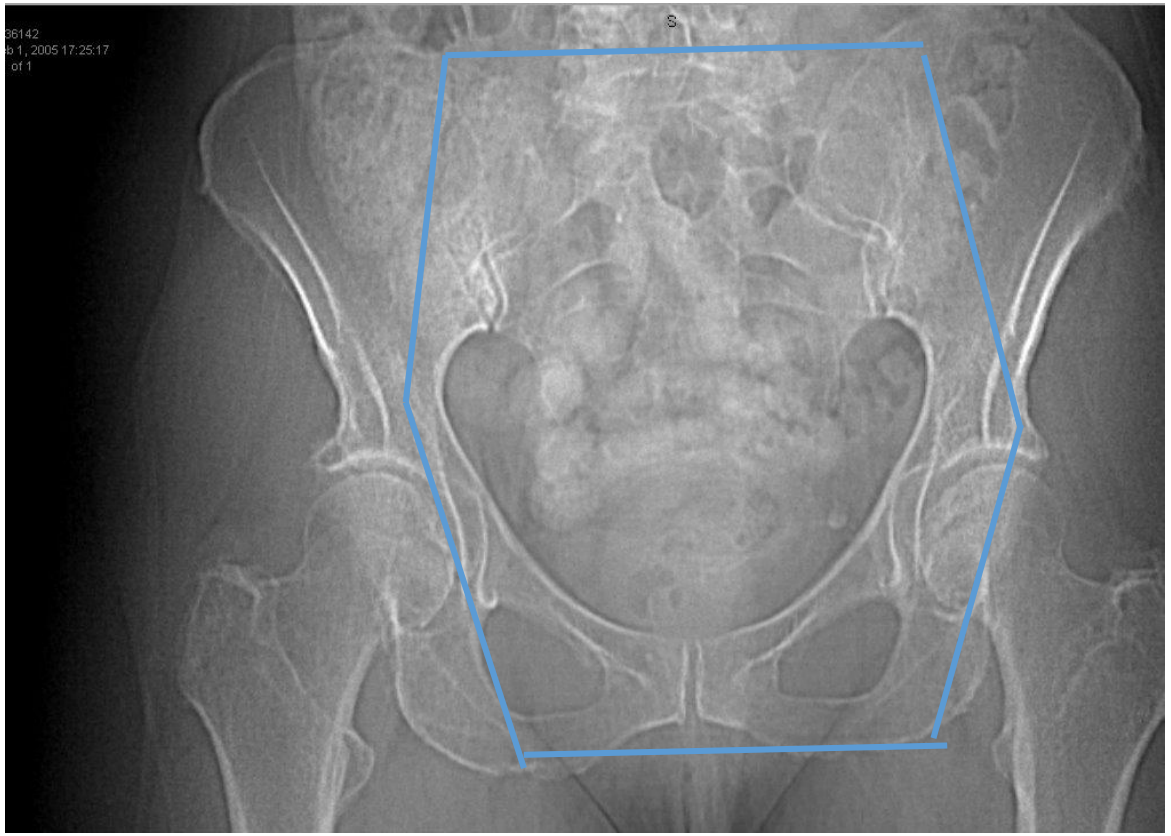
cell death

Cancer cells are more susceptible to RT due to impaired DNA repair pathways

Milestones in Radiotherapy

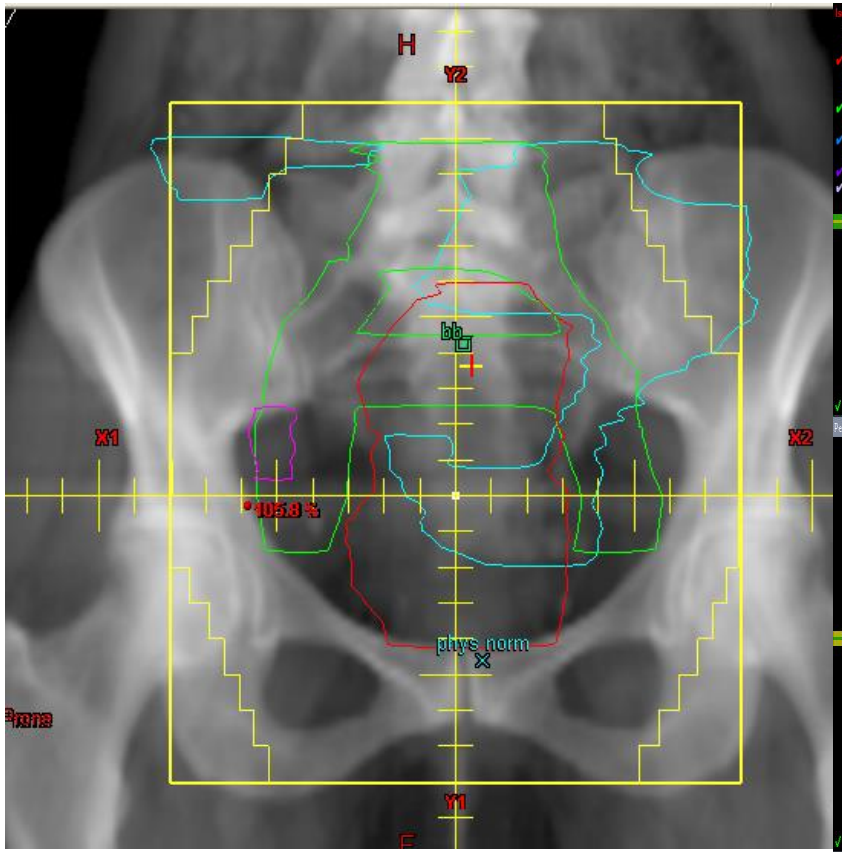


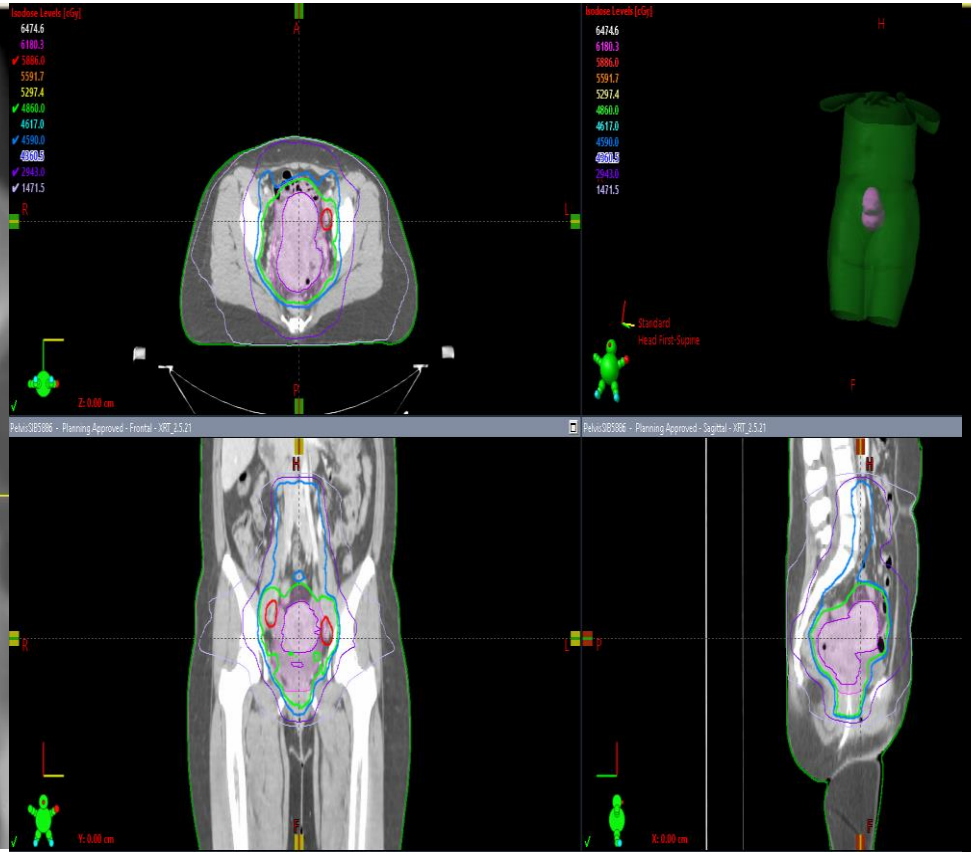
Management of Cervical Cancer in 19080s

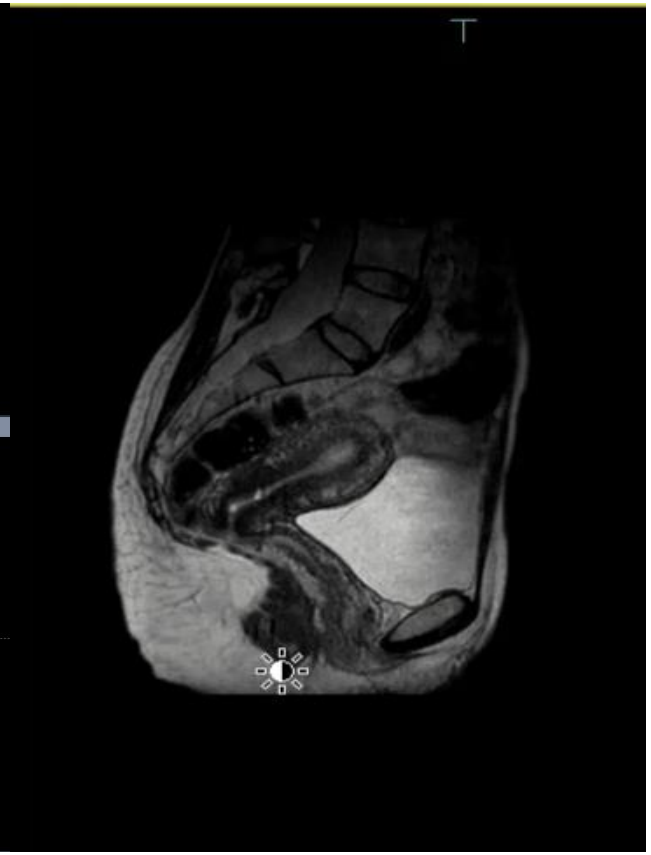


- Dosing: 45-50GY
- Fields : based on bony anatomy
- No routine of PET/CT or high quality imaging
- No Immunotherapy or targeted therapy

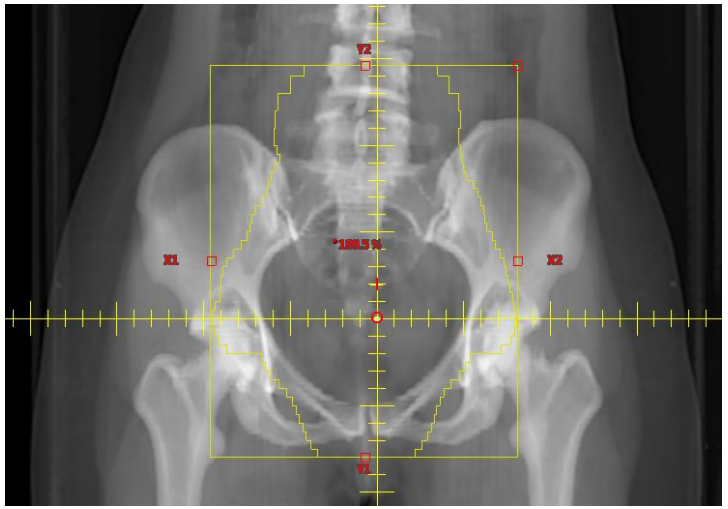
2D → 3D→ CT based planning --> MRI Imaging

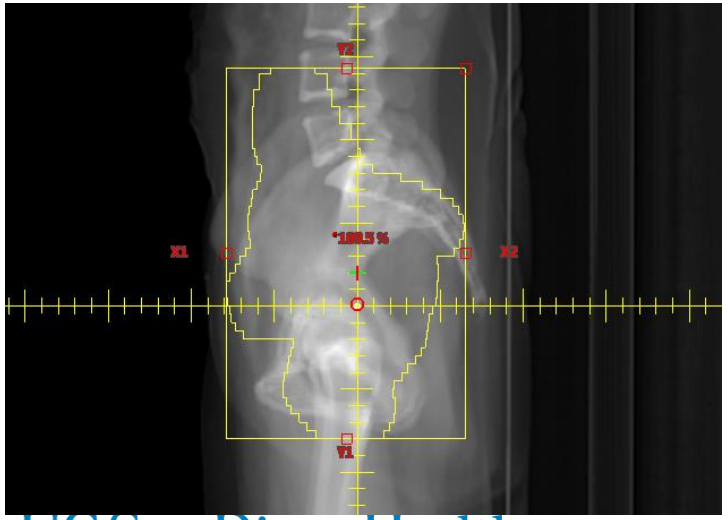






Evolution of External Beam Radiation Therapy

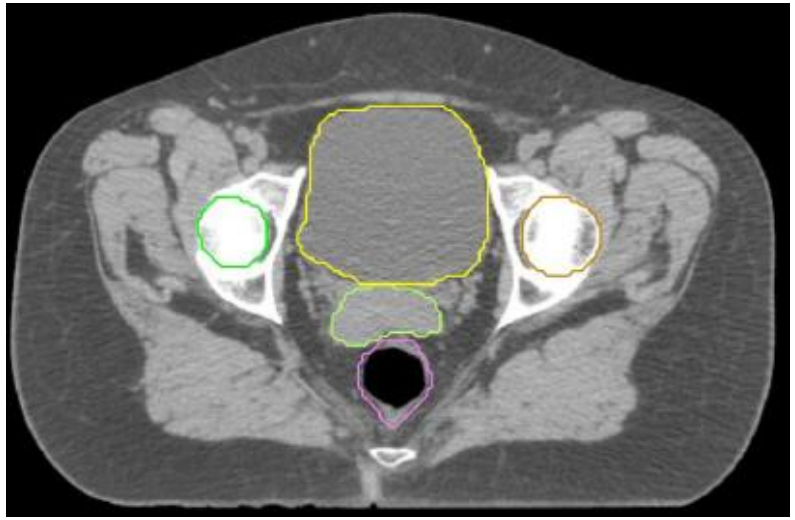


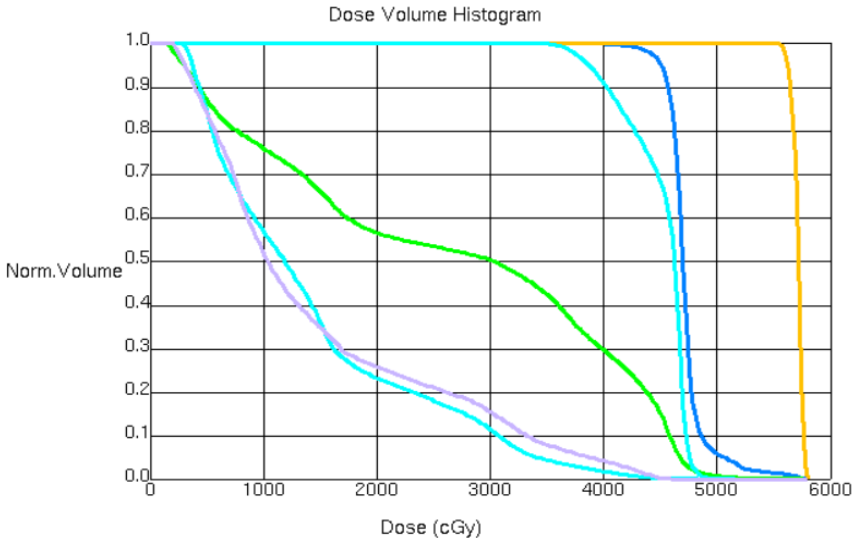


3-D treatment planning using CT scan enables:

1) More accurate delineation of target and normal structures

2) Accurate dose calculation to tumor and organs at risk of toxicity so the “quality” of the plan can be evaluated (i.e. probability of cure or toxicity)





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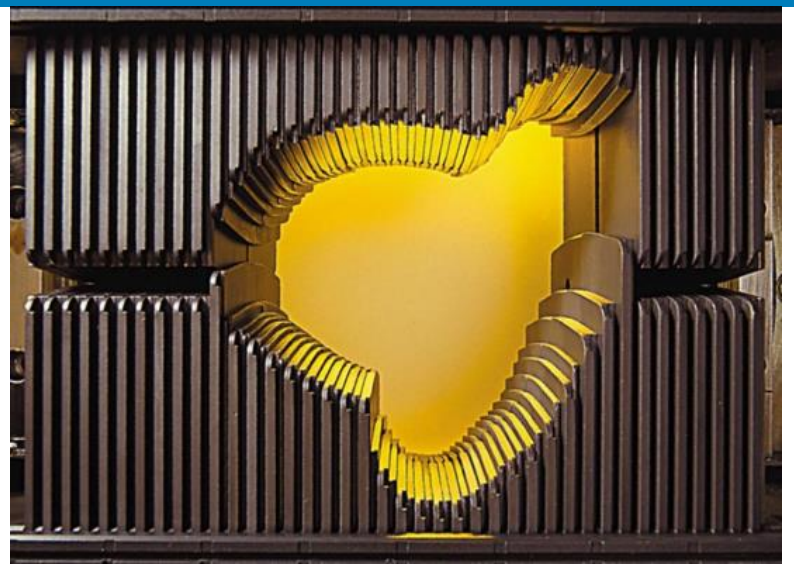
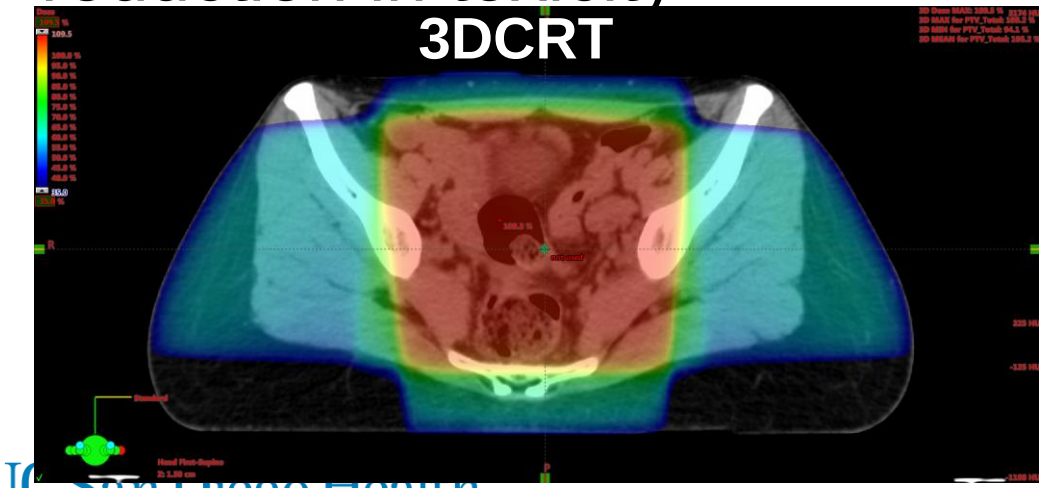
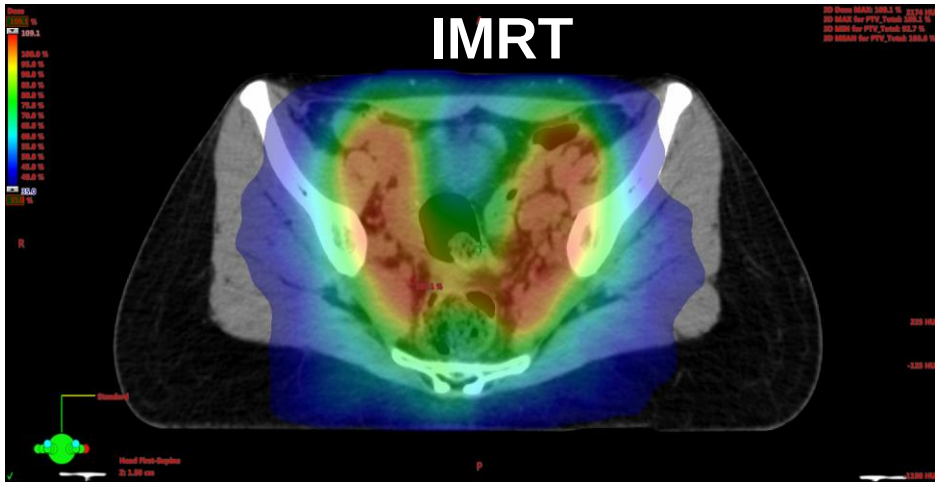
Evolution of External Beam Radiation Therapy

Use of dynamic MLCs to create irregular (non-uniform) radiation from each field and adjust the intensity around a curved target volume

Enables dose escalation or reduction in toxicity



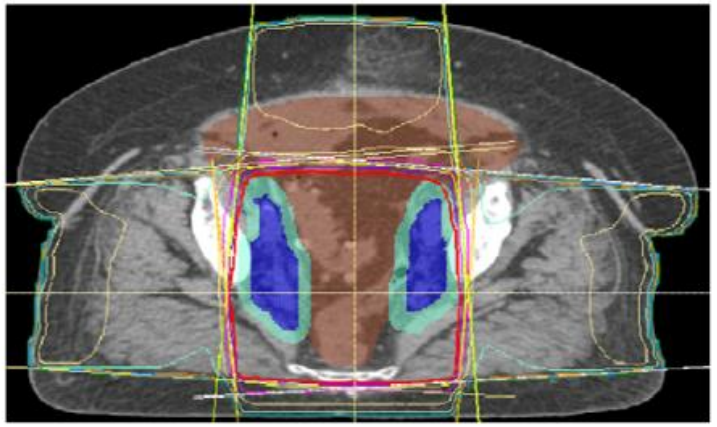


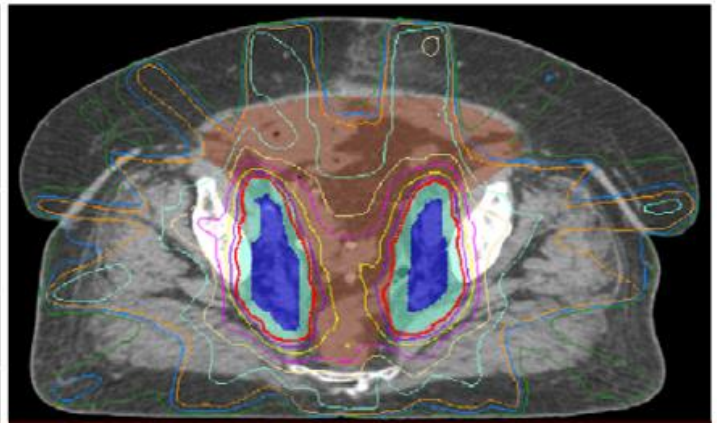


Klopp *et al*, 2018

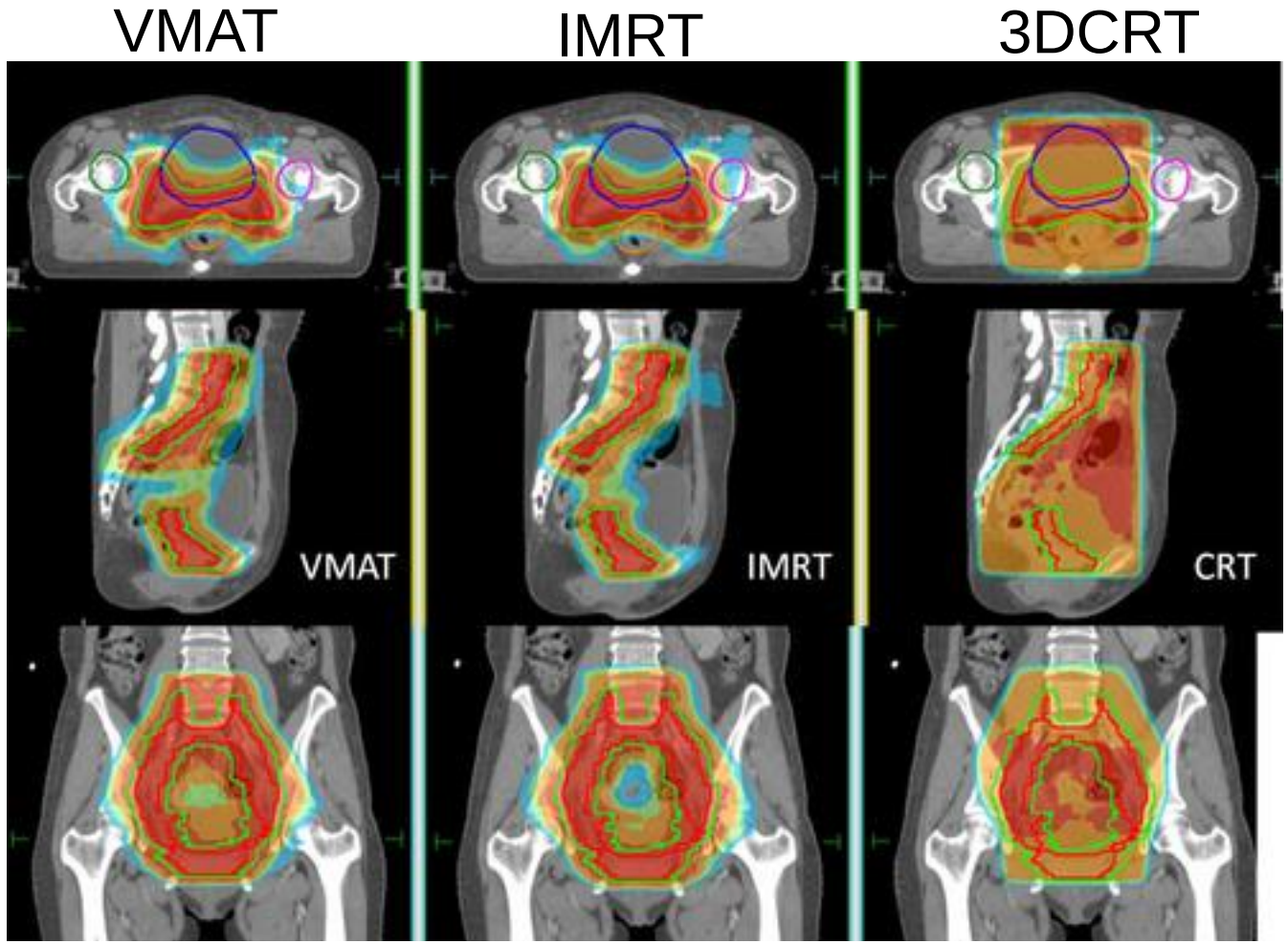
Reducing radiation treatment volumes

- Intensity modulated radiation therapy for cervical cancer
  - Dosimetric studies initially published 2000-2001
  - First clinical series published in 2001
  - By 2009, 18+ retrospective studies published suggesting improved toxicity with IMRT compared to 3DCRT

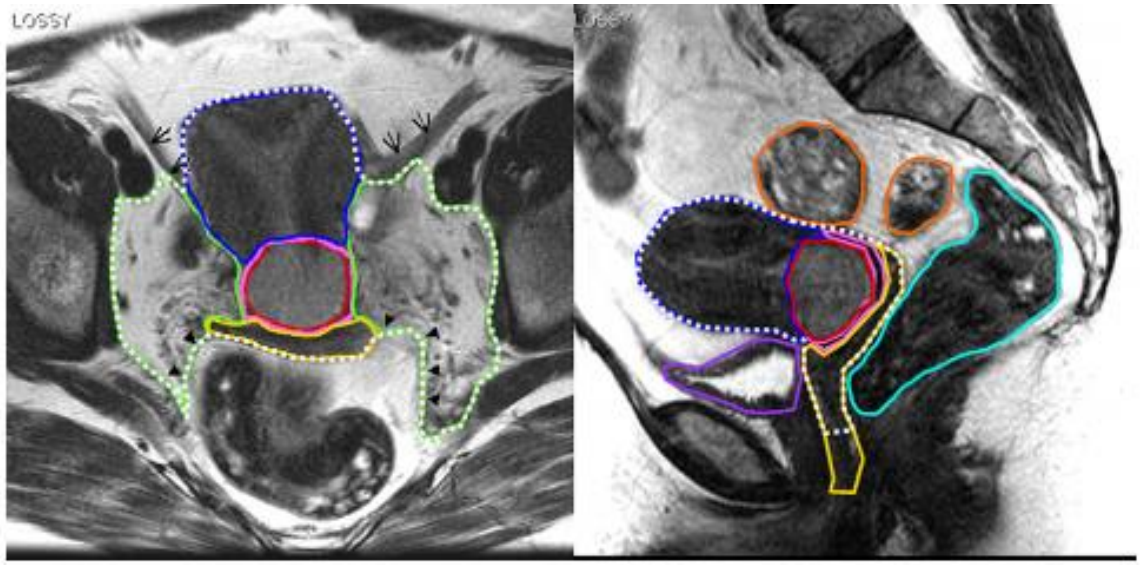




Standard of Care for Cervical Cancer



Deng et al Journal of Applied Clinical Medical Physics 2016



Lim et al 2011 IJROBP

IMRT for Gynecologic Malignancies

- IMRT decreases acute grade II diarrhea and late grade 2 anorexia, abdominal bloating, bowel obstruction
- Benefit greatest among pts receiving concurrent chemotherapy
- Image-guided bone marrow sparing IMRT can decrease acute grade III neutropenia: 19% with vs 54% without BM sparing

Chopra et al. PARCER *IJRO* 2020
Klopp et al. RTOG 1203/TIME-C *JCO* 2018
Williamson et al. INTERTECC *IJROBP* 2022

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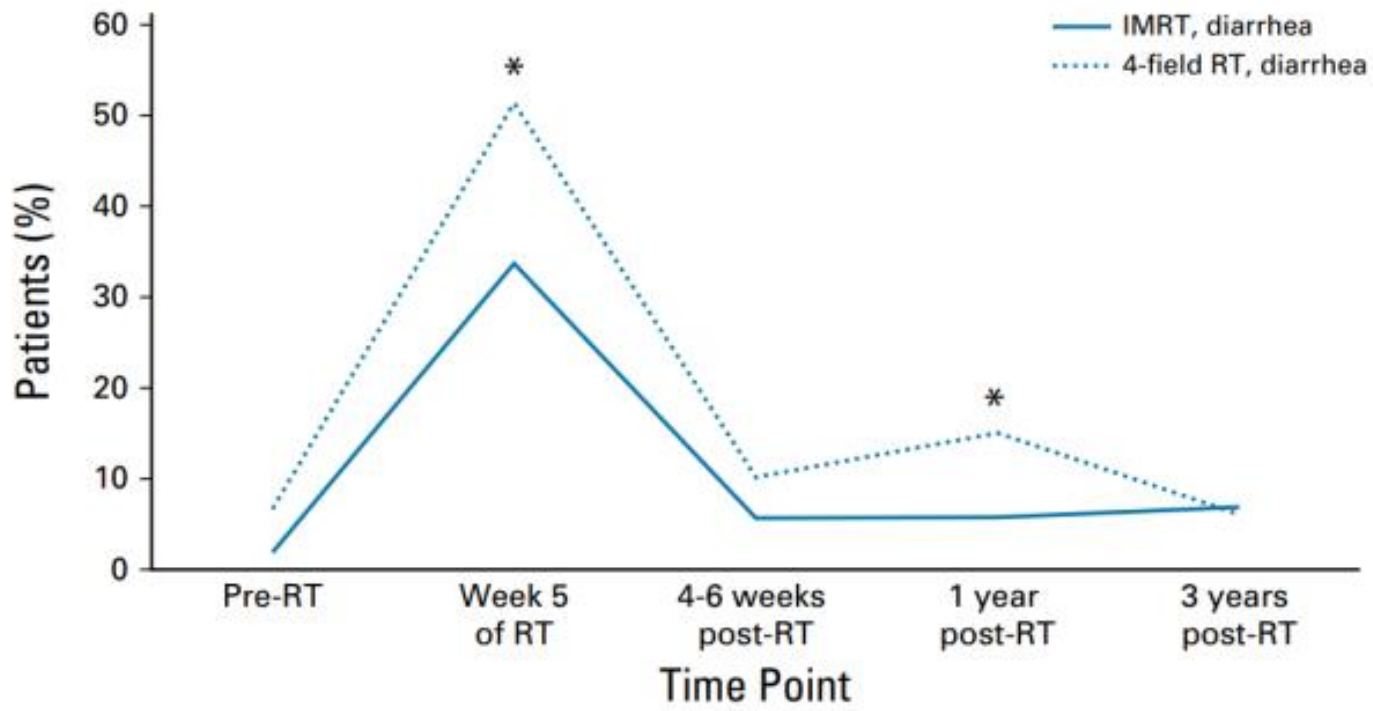

No. at risk:					
IMRT	106	92	88	87	58
4-field RT	120	109	108	93	66

Klopp et al. RTOG 1203/TIME-C *JCO* 2018

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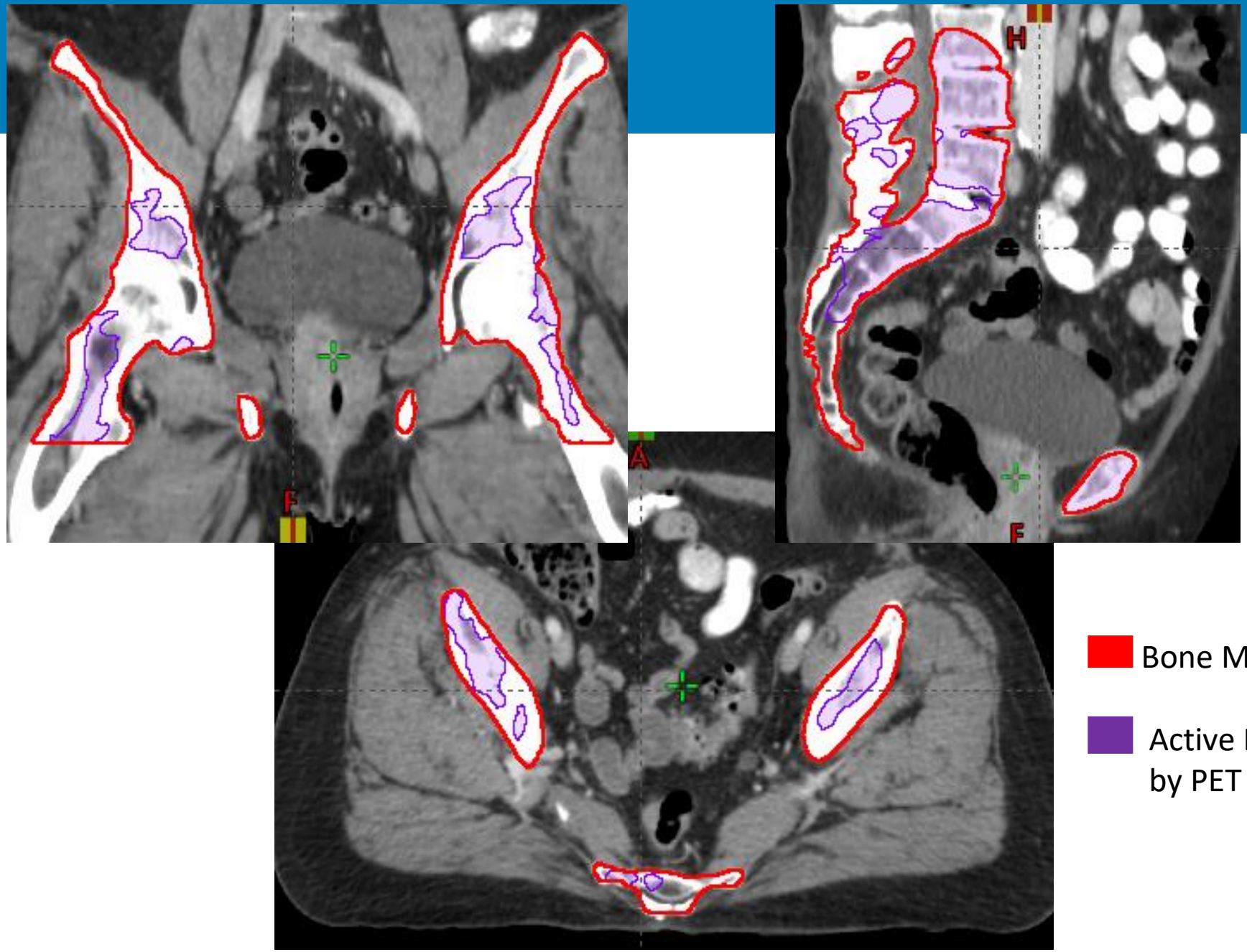

Bone Marrow

Active Bone Marrow defined by PET

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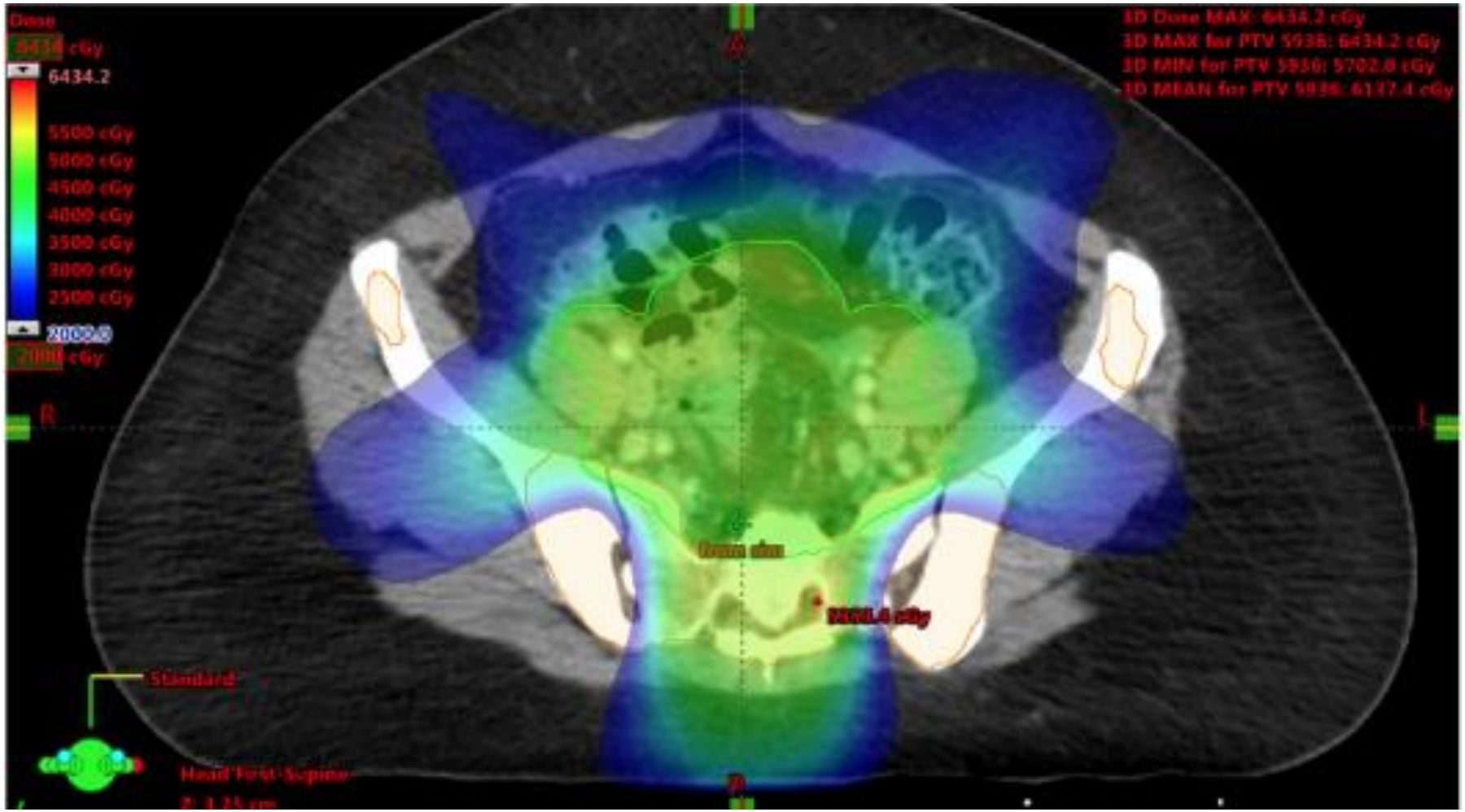

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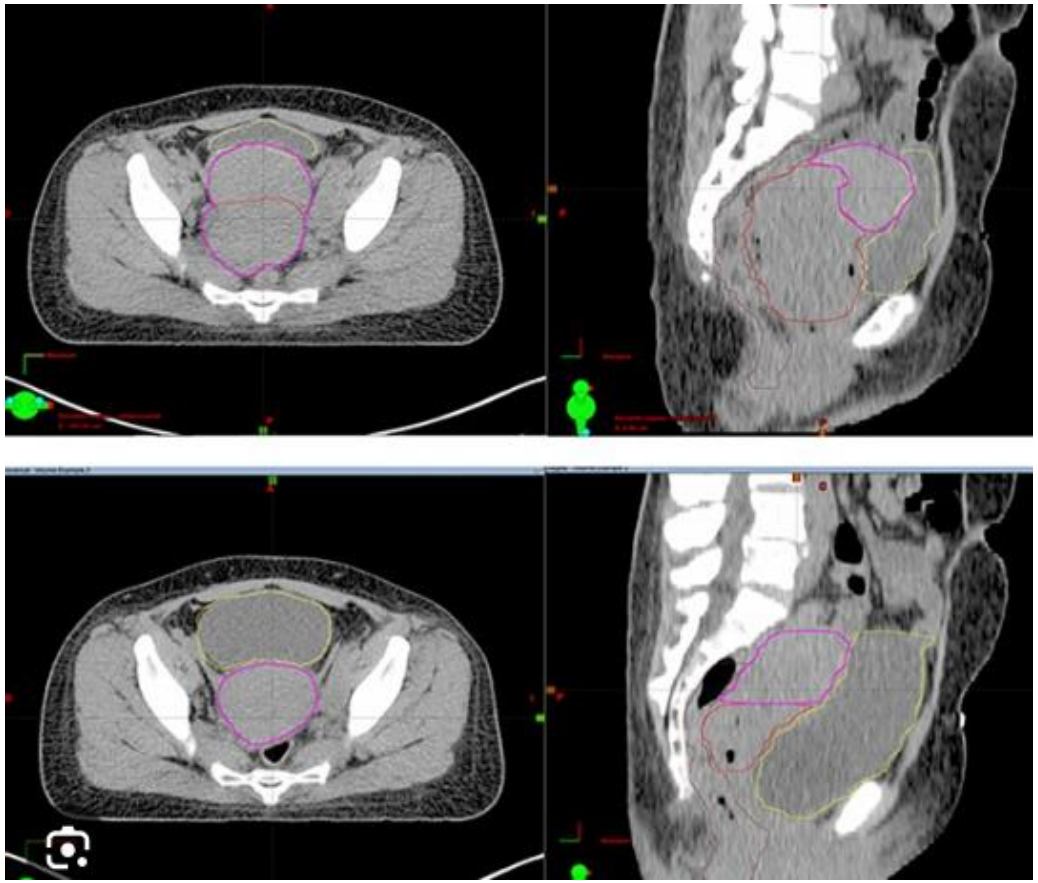
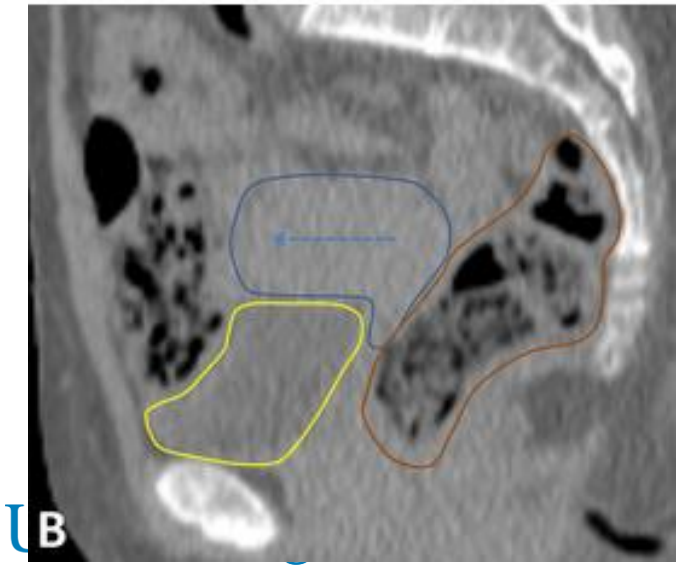
Reducing radiation treatment volumes

- Cervical cancer presents unique radiation challenge in that uterus and cervix are highly mobile structures
- Changes in target position may arise due to several reasons
  - Bladder filling
  - Rectal filling
  - Tumor shrinkage



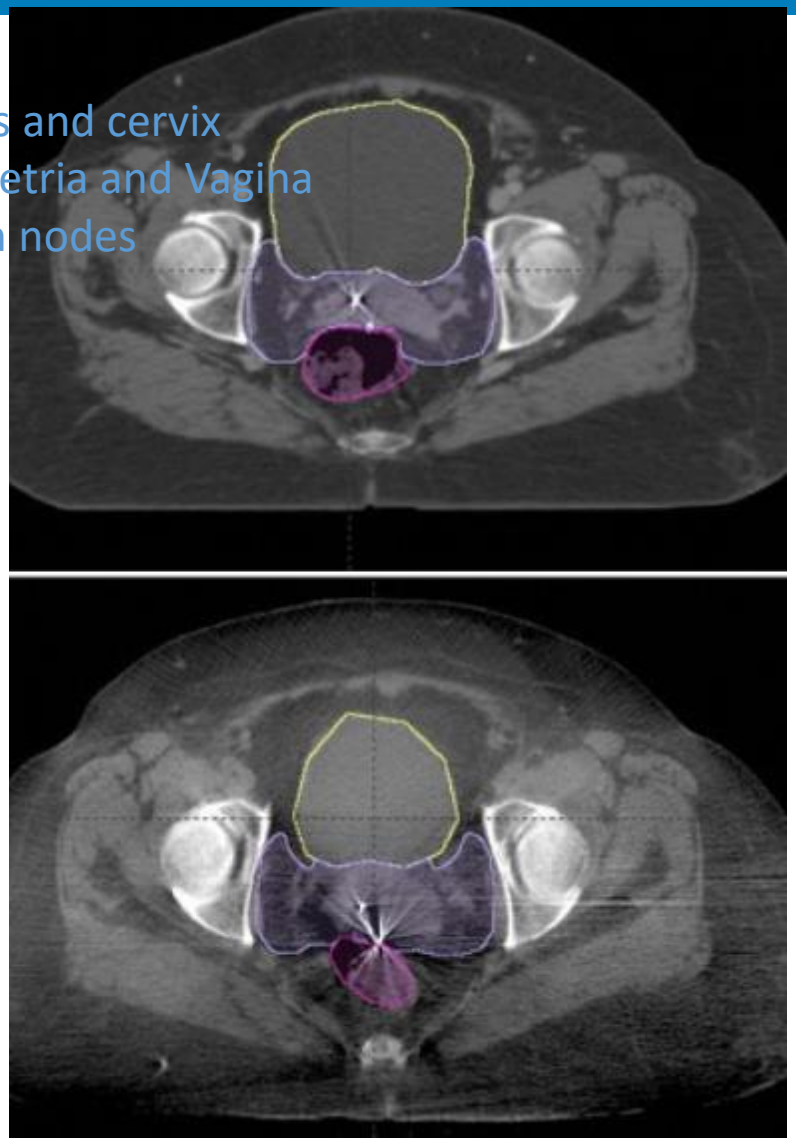
Internal Organ motion during simulation and treatment



Contour tumor position with empty and full bladder CTs, but treat with full bladder (to push bowel out of the way)

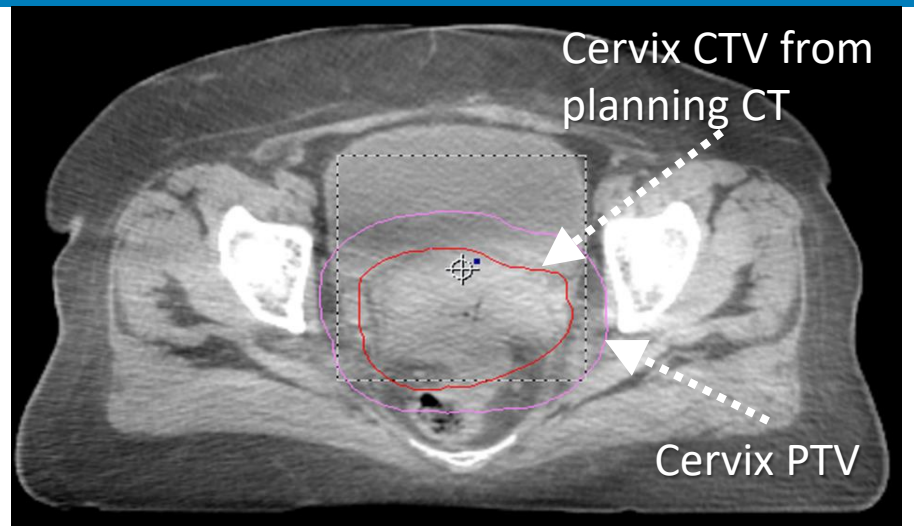
Daily image guidance (e.g. CBCT) to assess for shifts in soft tissue anatomy enables margin reduction around tumor

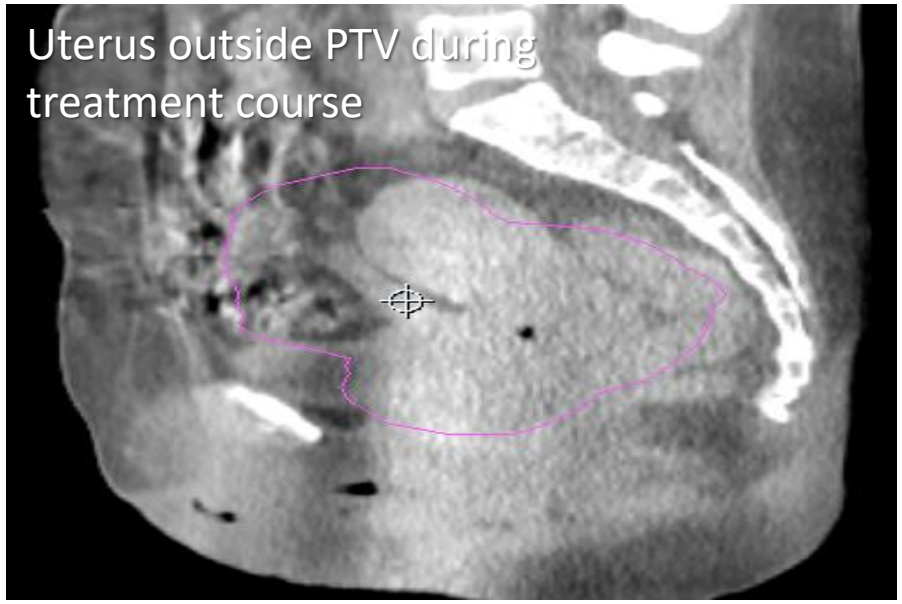
Margins:
1.5cm- uterus and cervix
1.0cm-Parametria and Vagina
0.7cm- lymph nodes



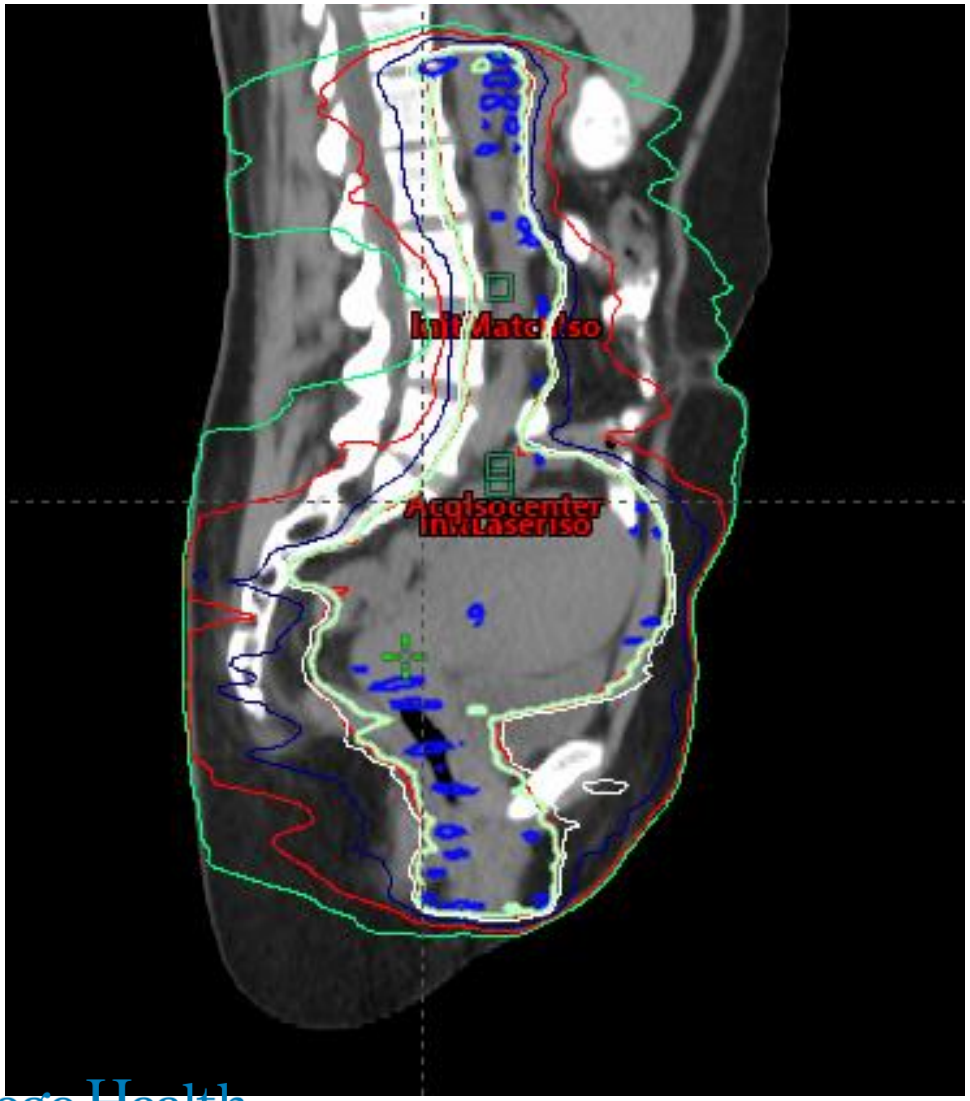
Planning CT is a snapshot of anatomy at beginning of treatment

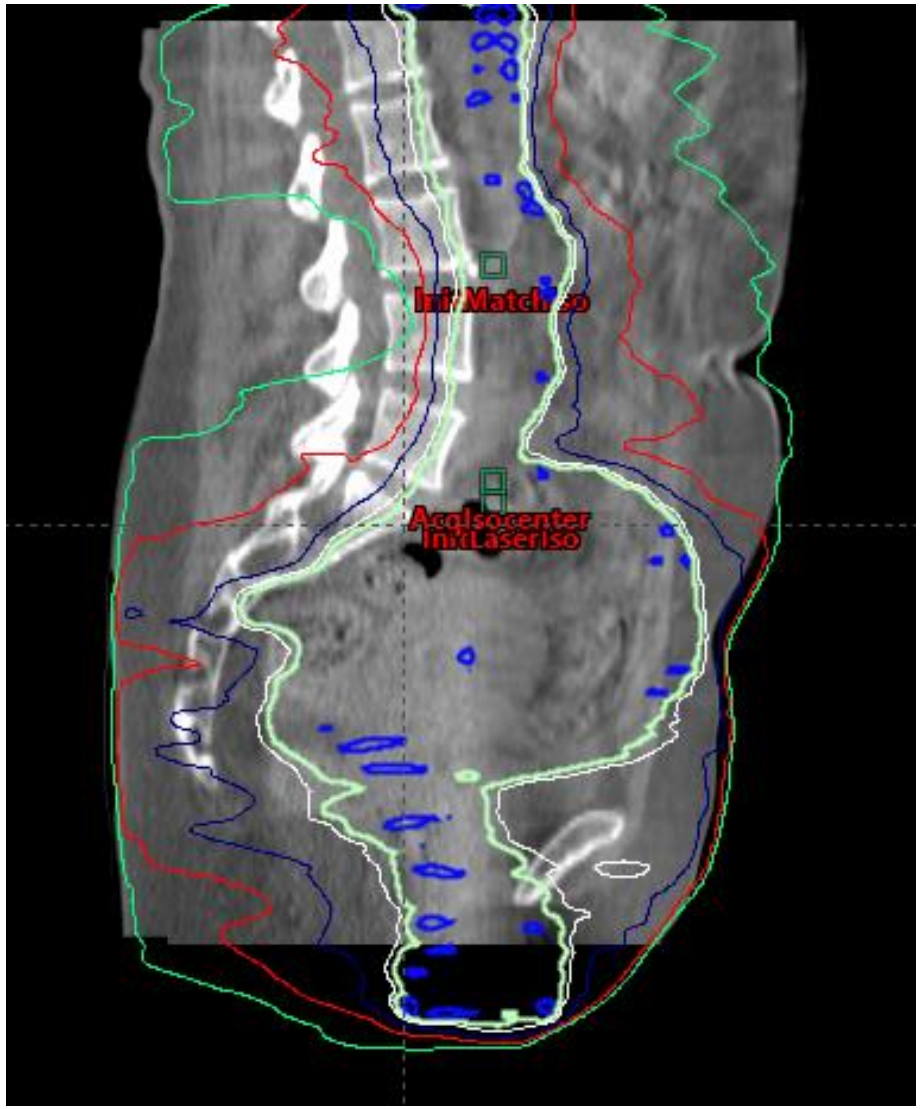
- Dramatic volume changes of bulky tumors during EBRT
  - Gradual change – infrequent adaptation ok
- Weight changes over treatment course
  - Gradual change – infrequent adaptation ok
- Large variability in day-to-day position of uterus, bladder, rectum (inter-fraction motion)
  - Daily adaptation can significantly reduce CTV-PTV margins and correct for changes from planning CT snapshot
- Changes in bladder filling-/rectal distention during treatment (intrafraction motion)
  - Primary driver of CTV-PTV margins with daily adaptation





Tumor Shrinkage during treatment





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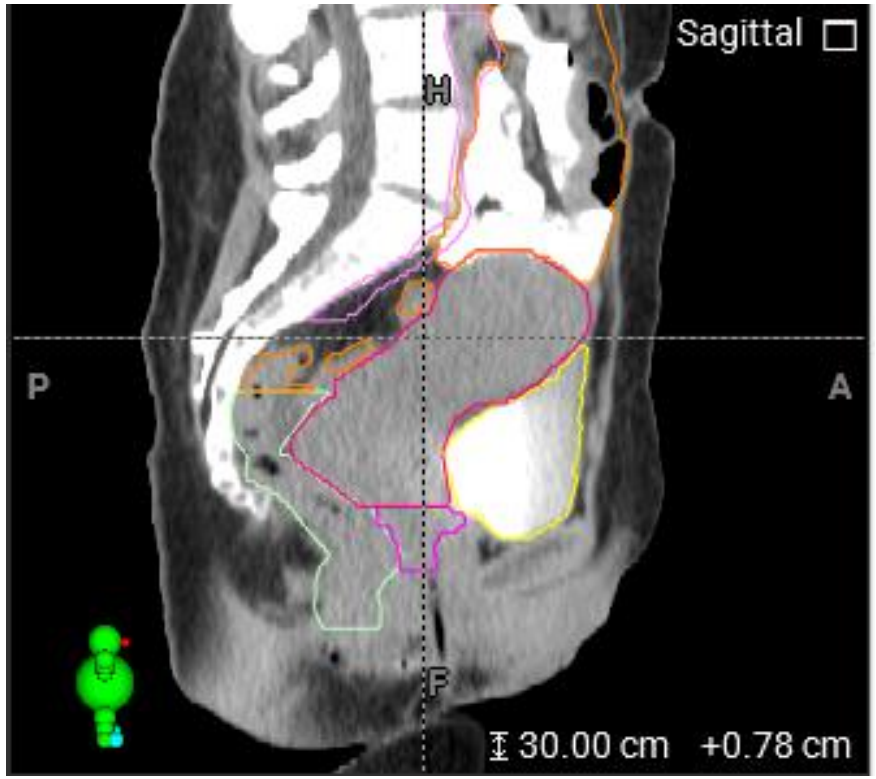
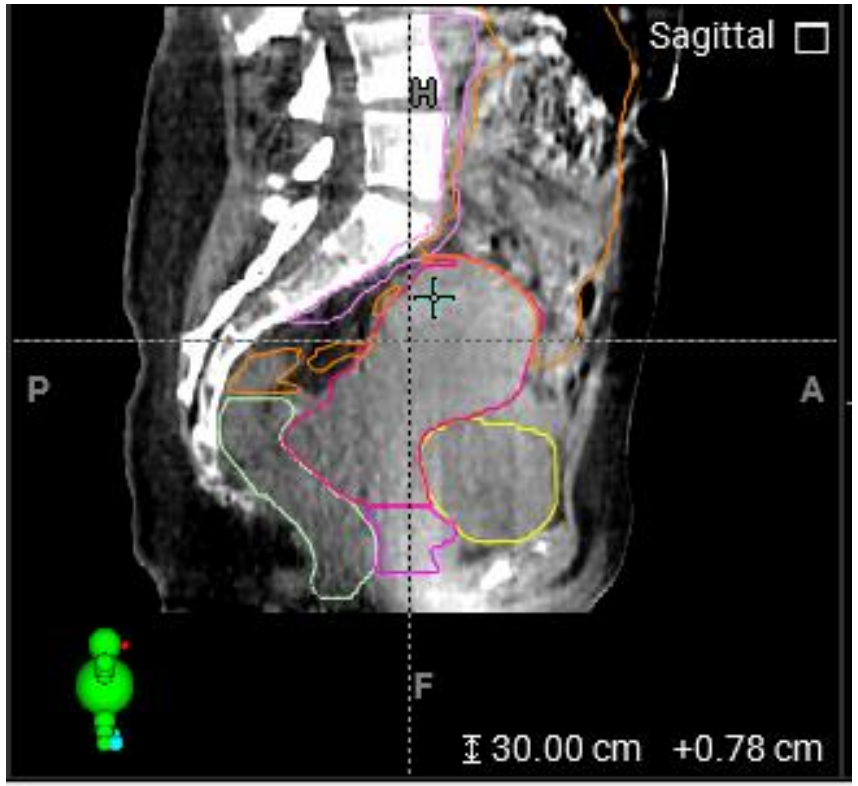
Adaptive Radiotherapy

- Adaptive radiotherapy creates a new treatment plan for each daily fraction based on day of imaging
- Allow for tighter treatment margins

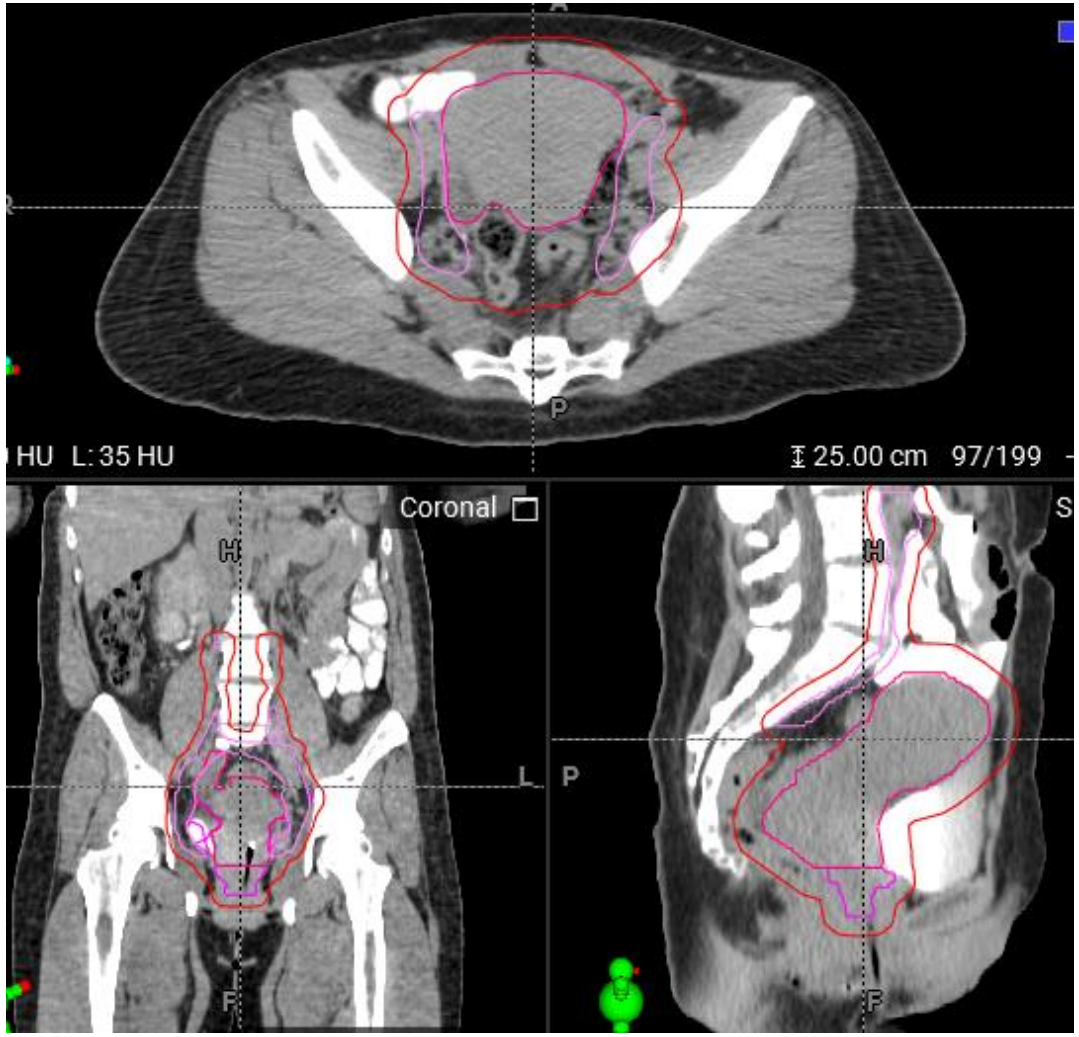
Adaptive Radiotherapy



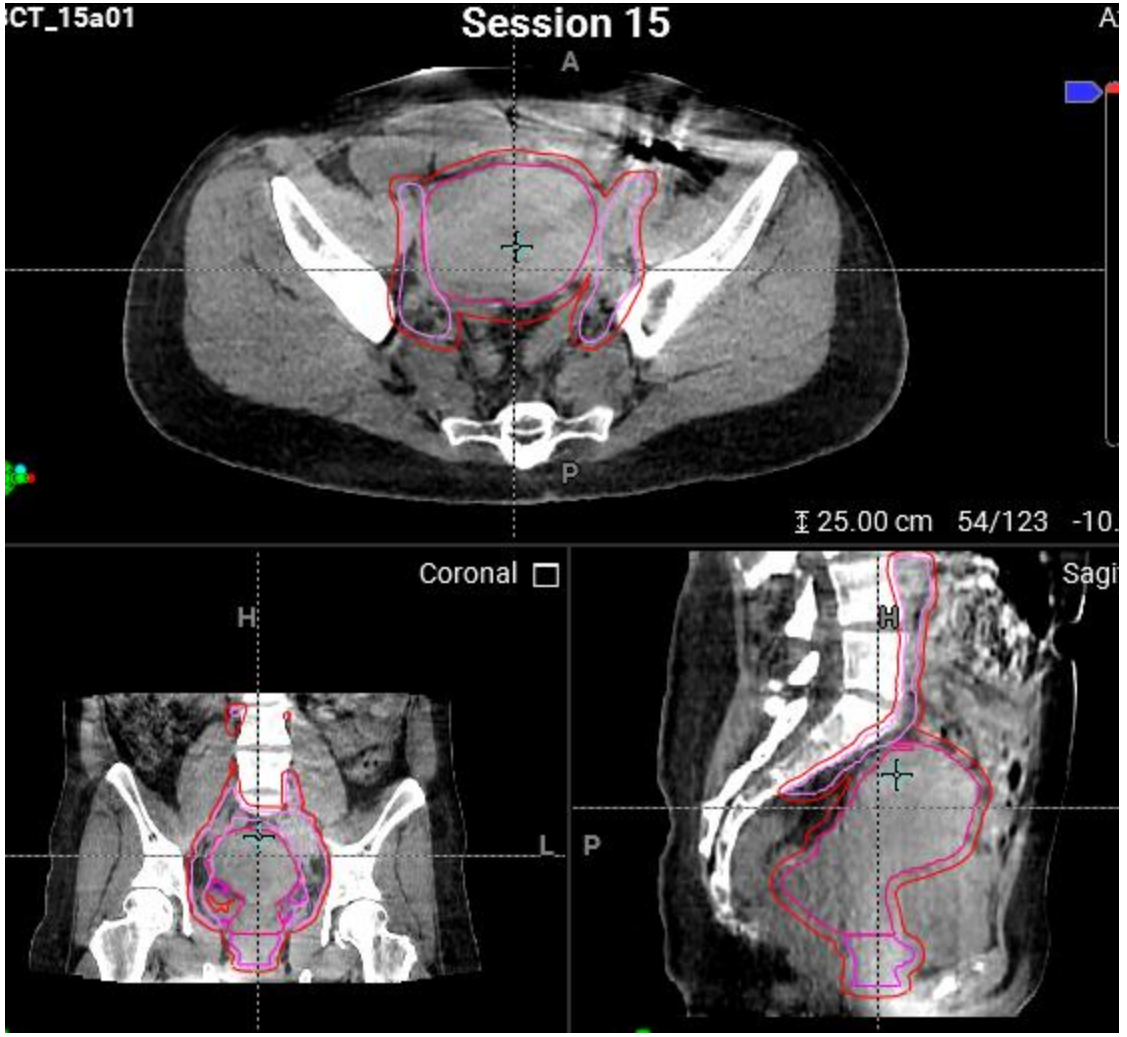


Adaptive Radiotherapy

IMRT Treatment Margins



Adaptive Treatment Margins



Adaptive Radiotherapy

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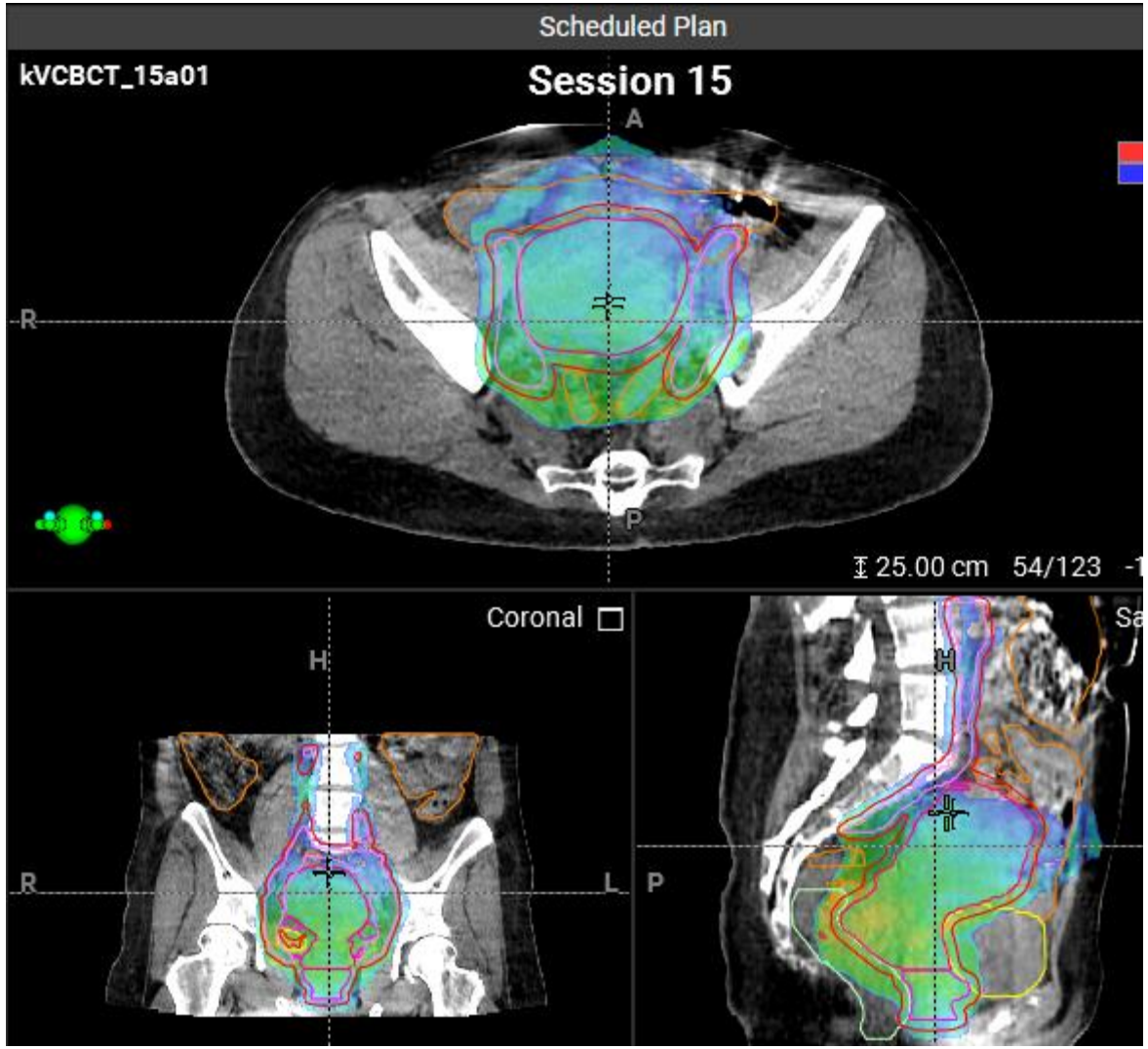

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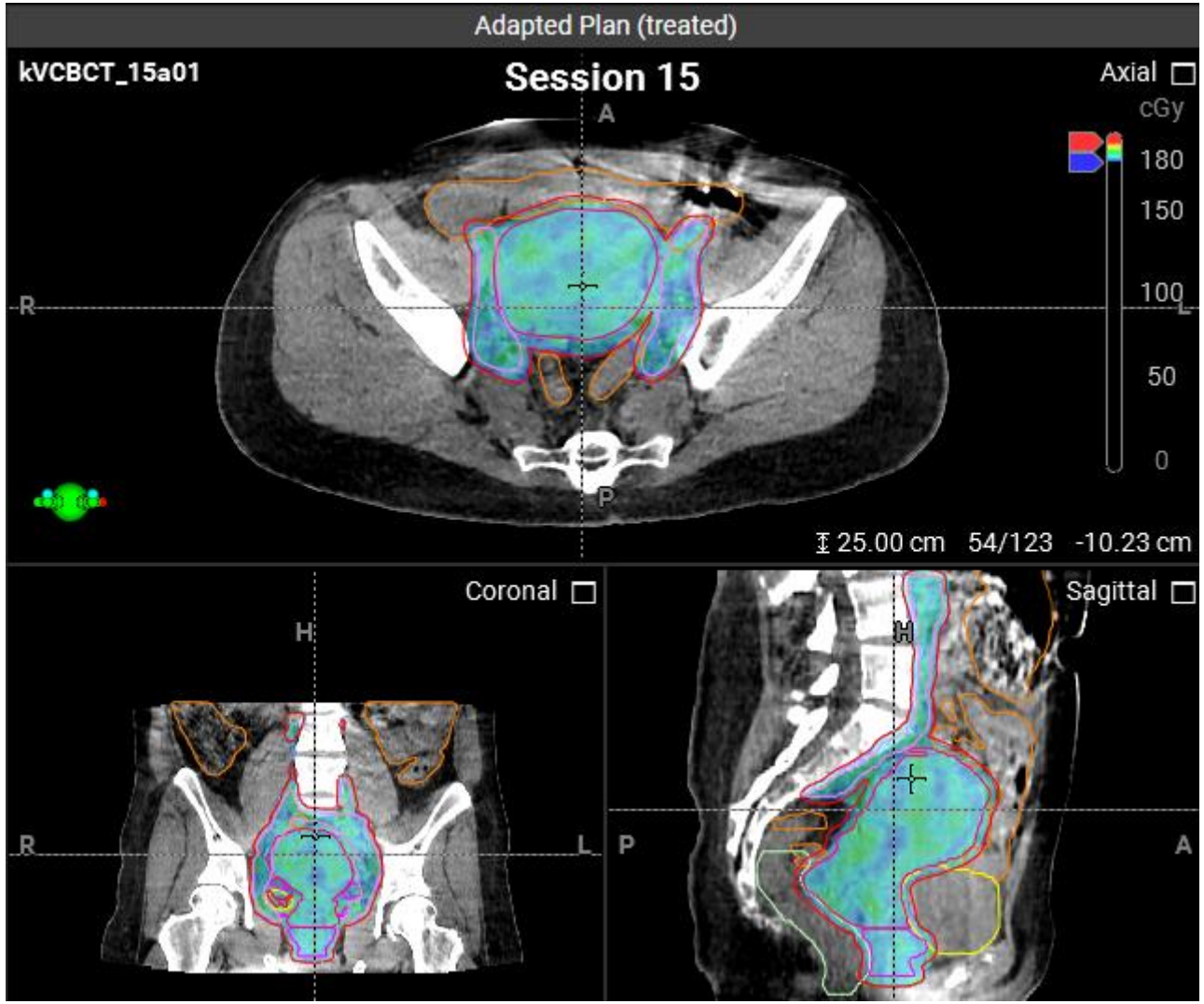


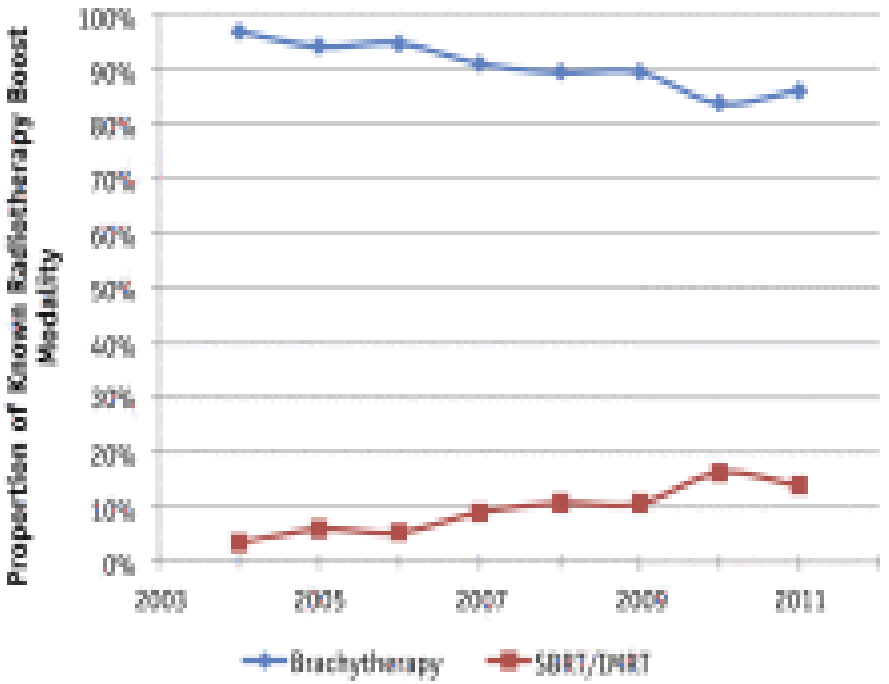
Use of Chemotherapy+/- Immunotherpy with Definitive RT

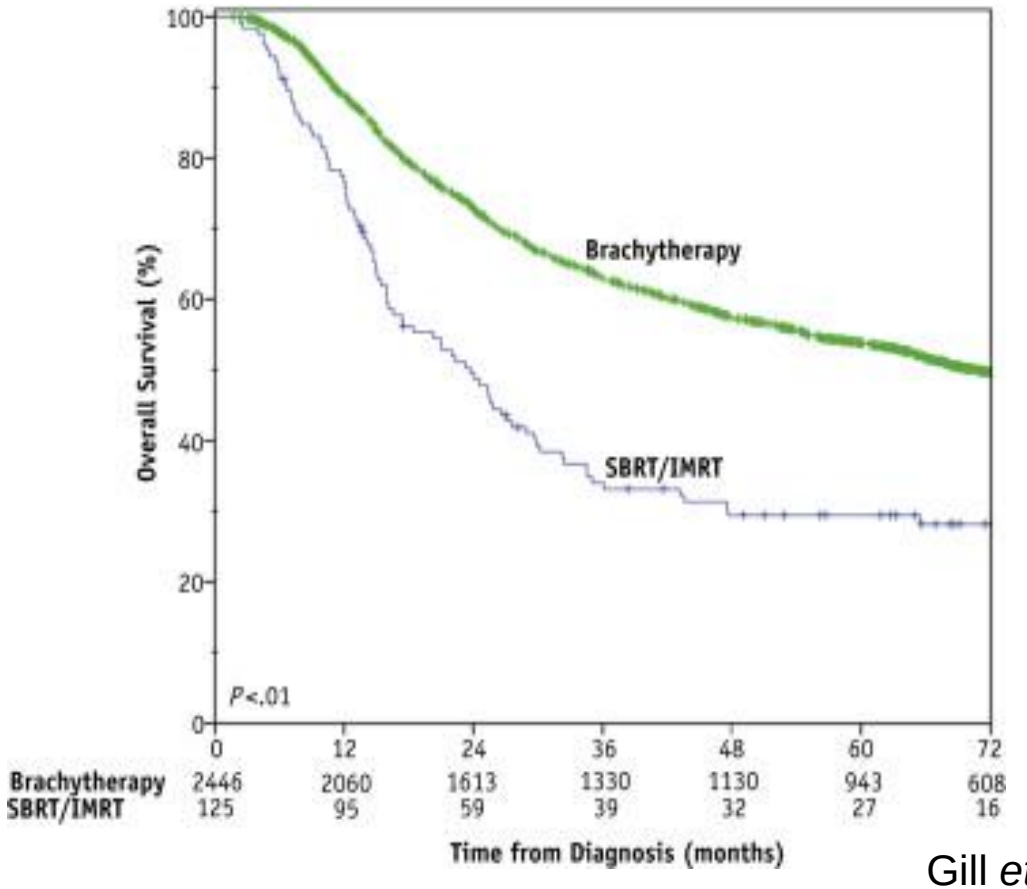
- Phase II study of NAC followed by ChemoRT- was feasible but without significant negative outcome[1]
- Induction chemotherapy followed by definitive ChemoRT improved PFS and OS – (GCIC Interlacce Trial)[2]
- Addition of concurrent and adjuvant pembrolizumanb to definitive chemoRT improves PFS and OS (83% vs 75%) (Keynote A18).[3]
- FDA Approved Pembro for FIGO 2014 Stage III and IV cervical cancer – but will likely be the new standard of care.

1. McCormack *et al*, 2013
2. McCormack et al (IGCS 2023)
3. Lorusso et al (Lancet 2024 and ESMO 2024)

Brachytherapy Is a Critical Part of Definitive Management of Cervical Cancer

- Declining utilization in recent years has correlated with reduced survival





Gill *et al*, 2014

Summary

- Adaptive radiotherapy are major advances in treatment of LACC allows us decreasing dose to organs at risk in the pelvis
- Major advances in clinical outcomes of locally advanced cervical cancer are on the horizon via immunotherapy