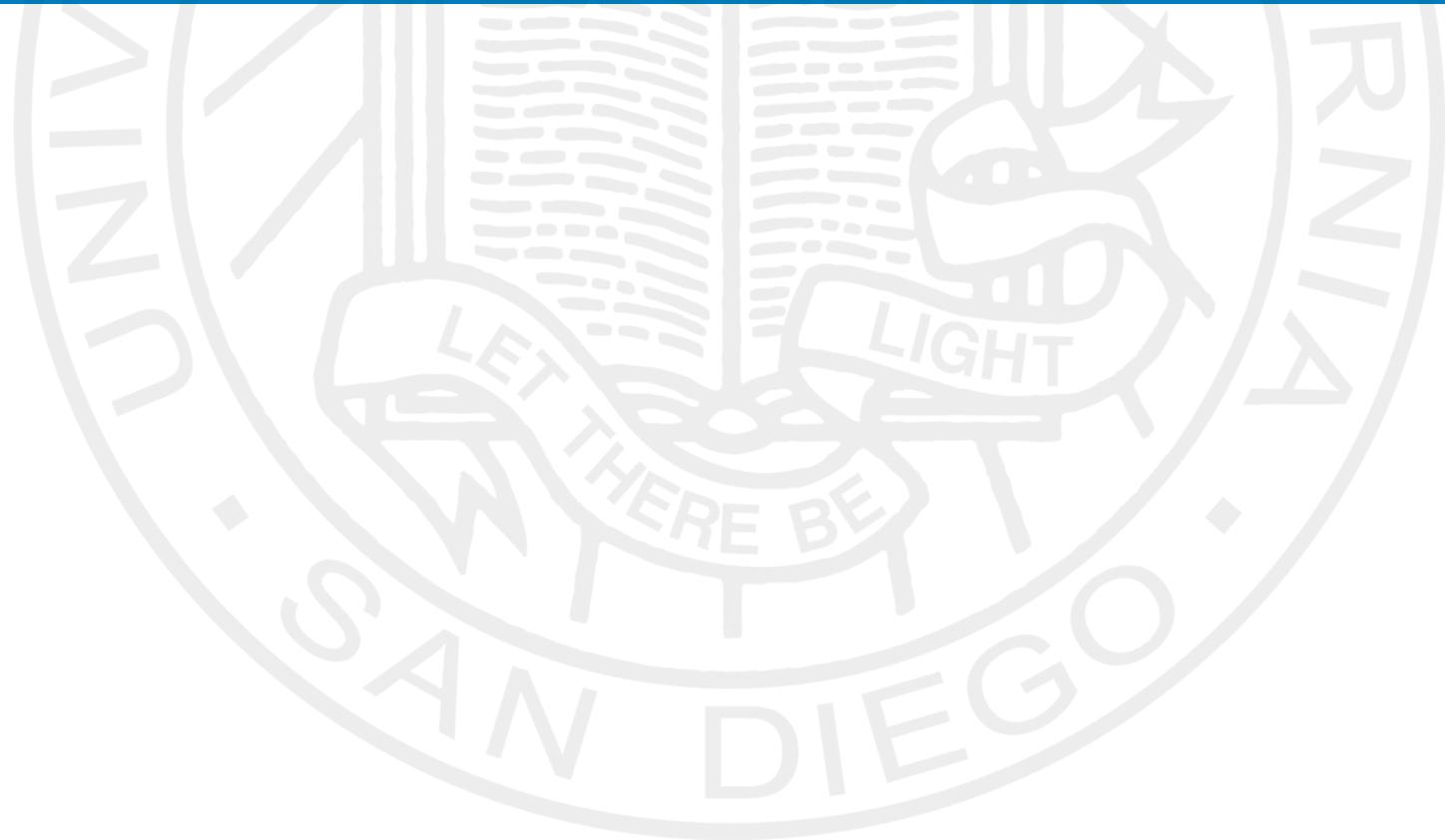


Radiation Advances for Gynecologic Malignancies

Dominique Rash, MD

Associate Professor

Radiation Medicine & Applied Sciences

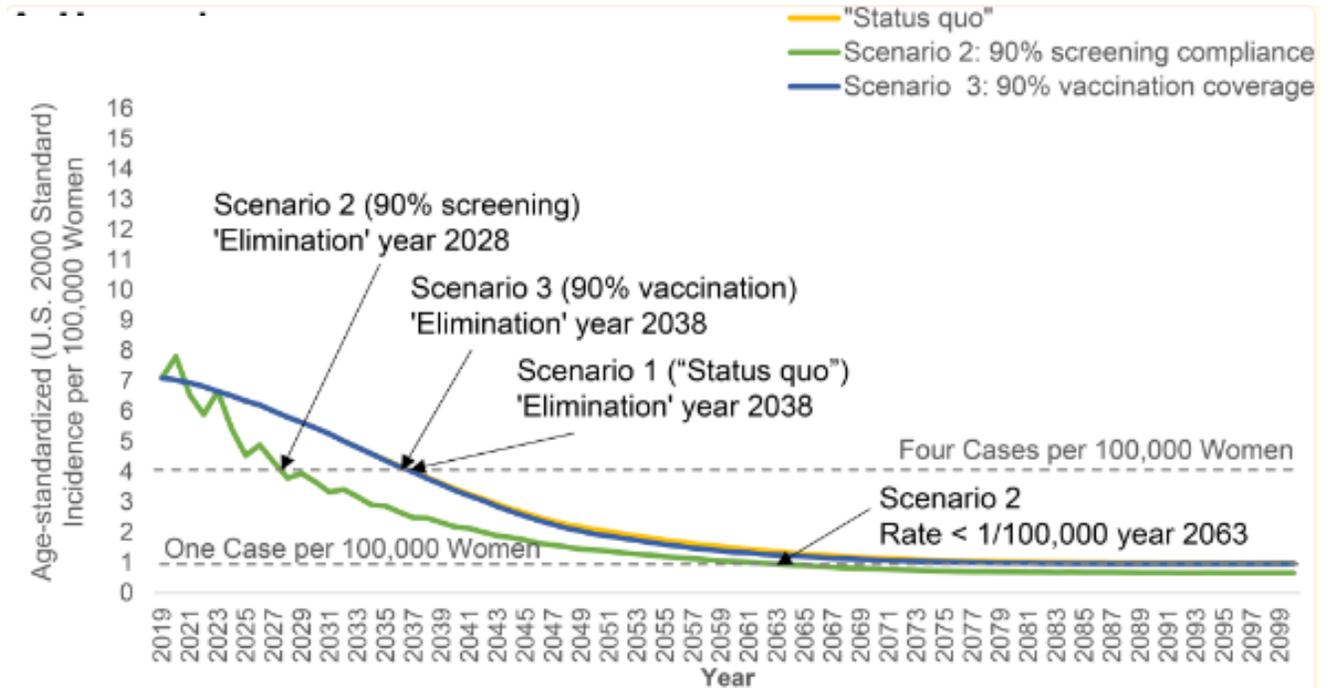


Present radiation challenges

- Reducing radiation treatment volumes
- Incorporating immunotherapy into treatment

Cervical Cancer: Ongoing Cancer Threat

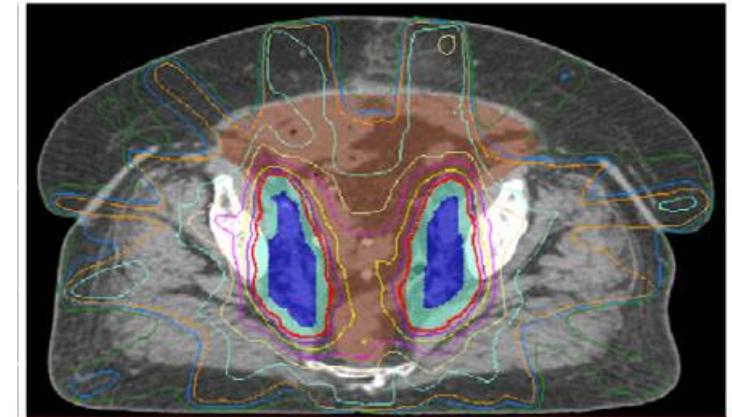
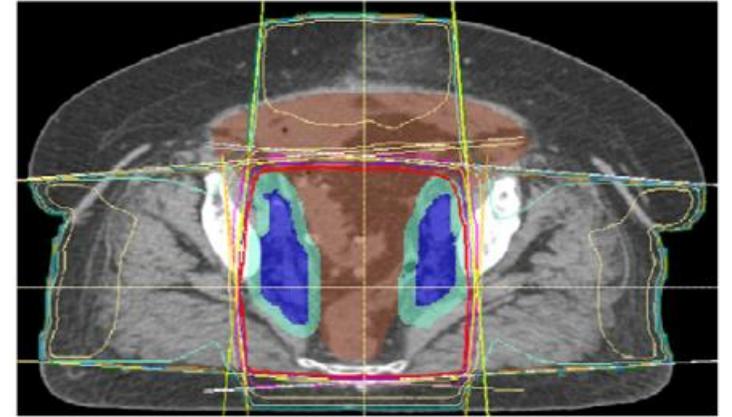
- 14,100 estimated new cases in 2022
- 7.3/100,000 women
- Overall survival 66%
- HPV vaccine: 61% compliance among US teens



Burger et al. Lancet Public Health 2020

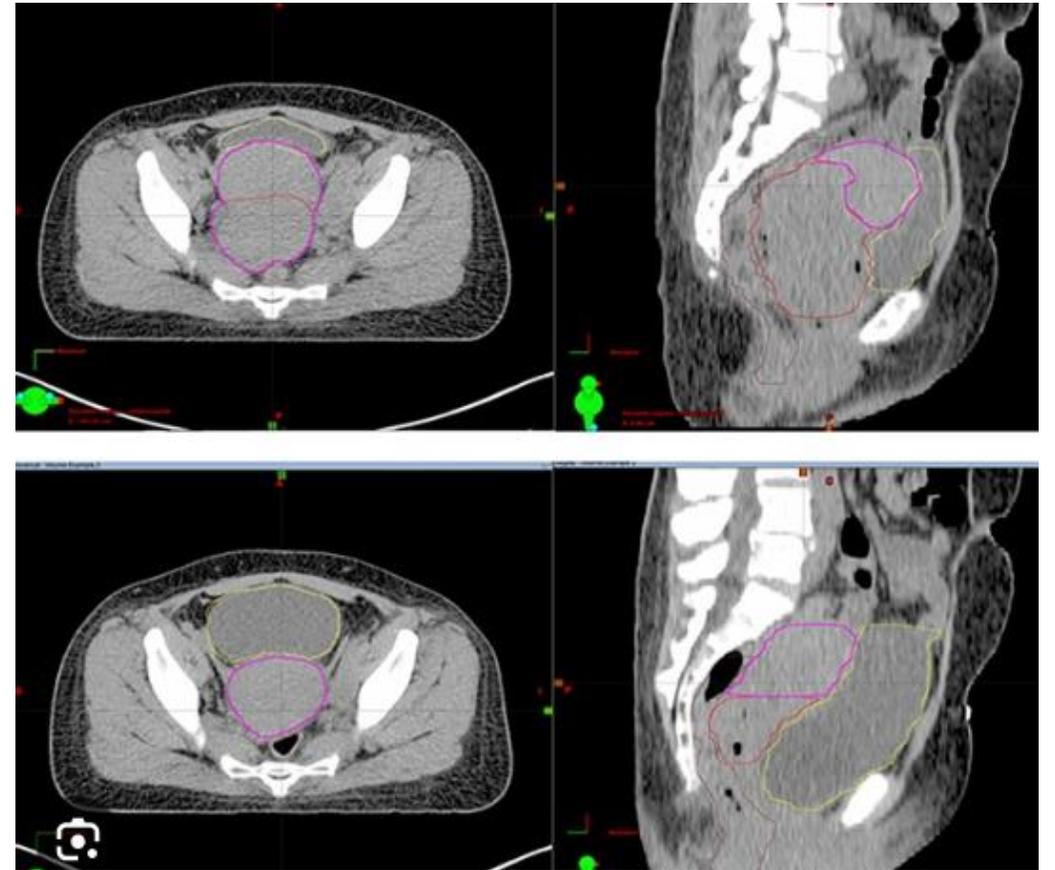
Reducing radiation treatment volumes

- 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



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

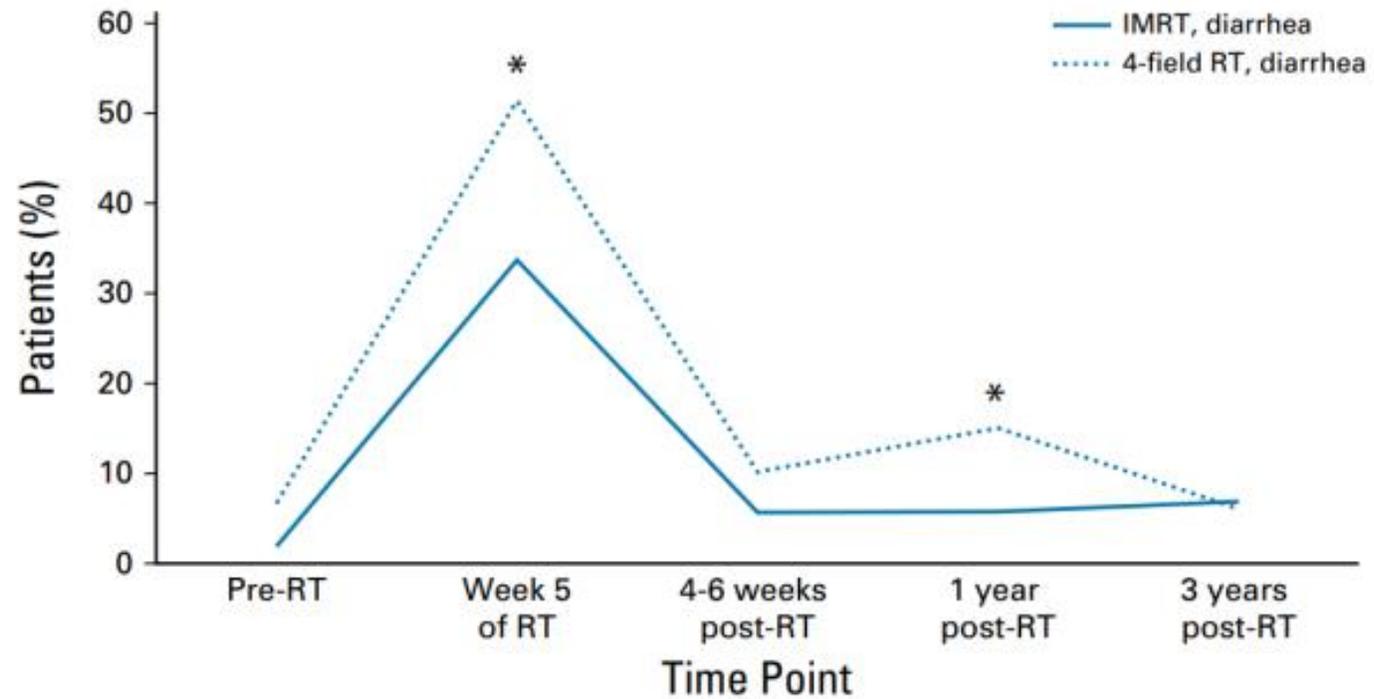


IMRT for Gynecologic Malignancies

- 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

IMRT for Gynecologic Malignancies



No. at risk:

IMRT	106	92	88	87	58
4-field RT	120	109	108	93	66

IMRT for Gynecologic Malignancies

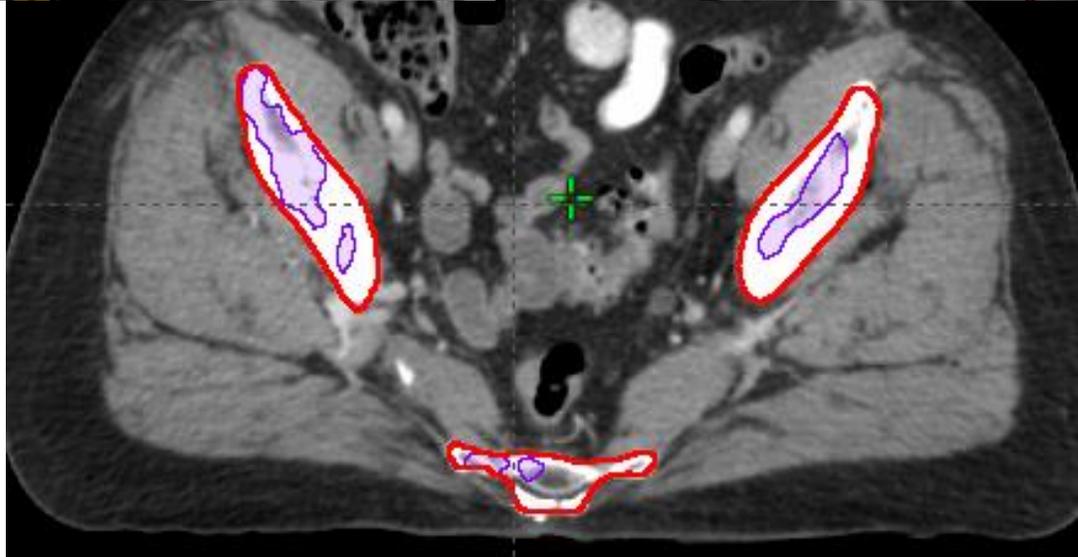
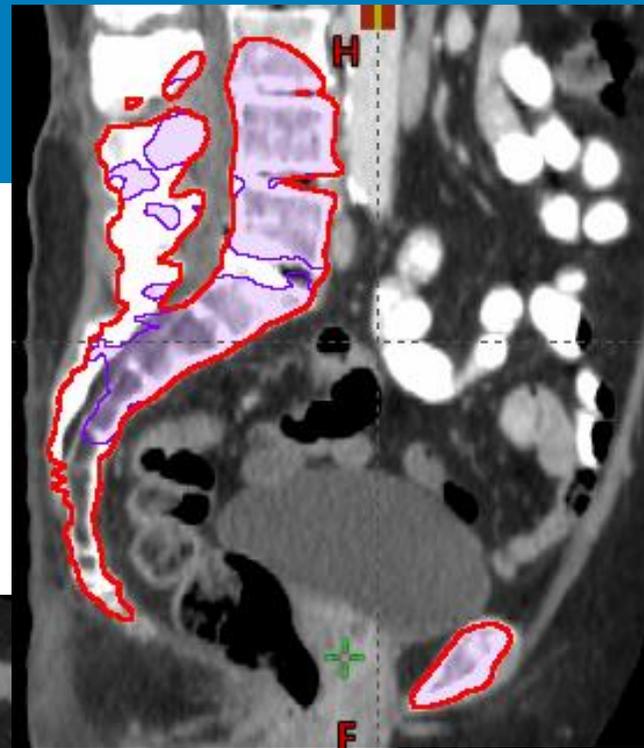
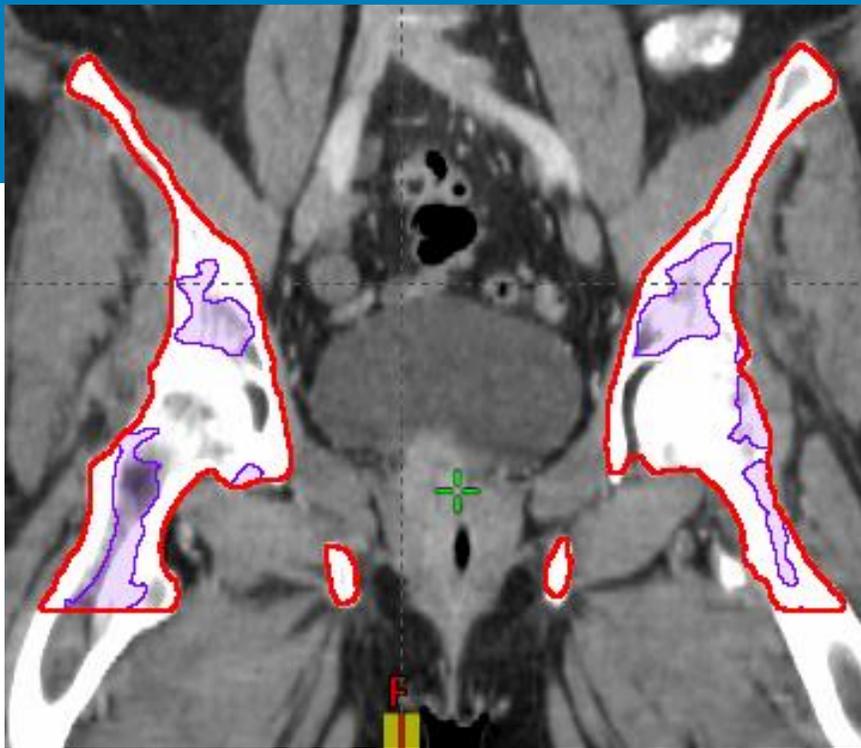
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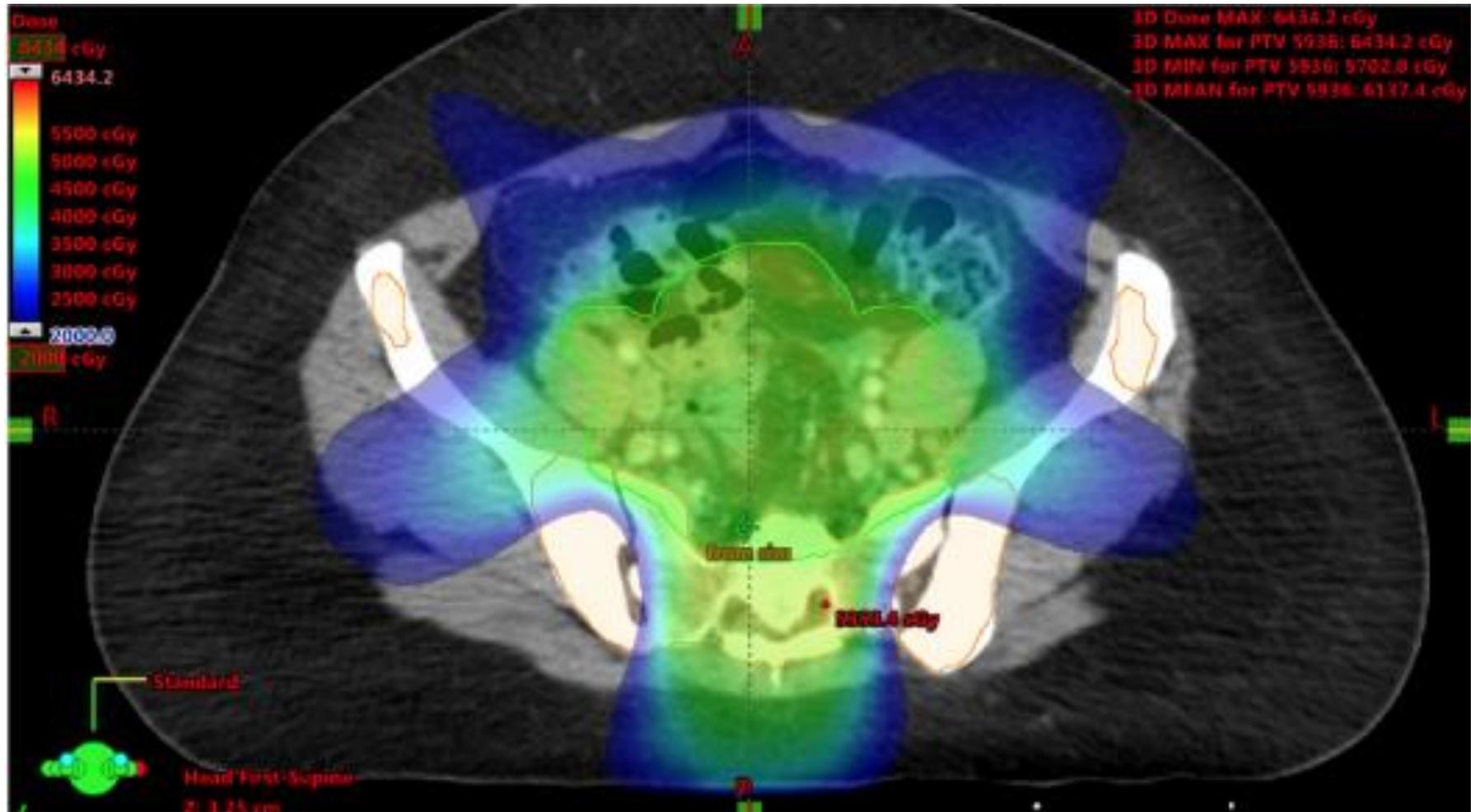
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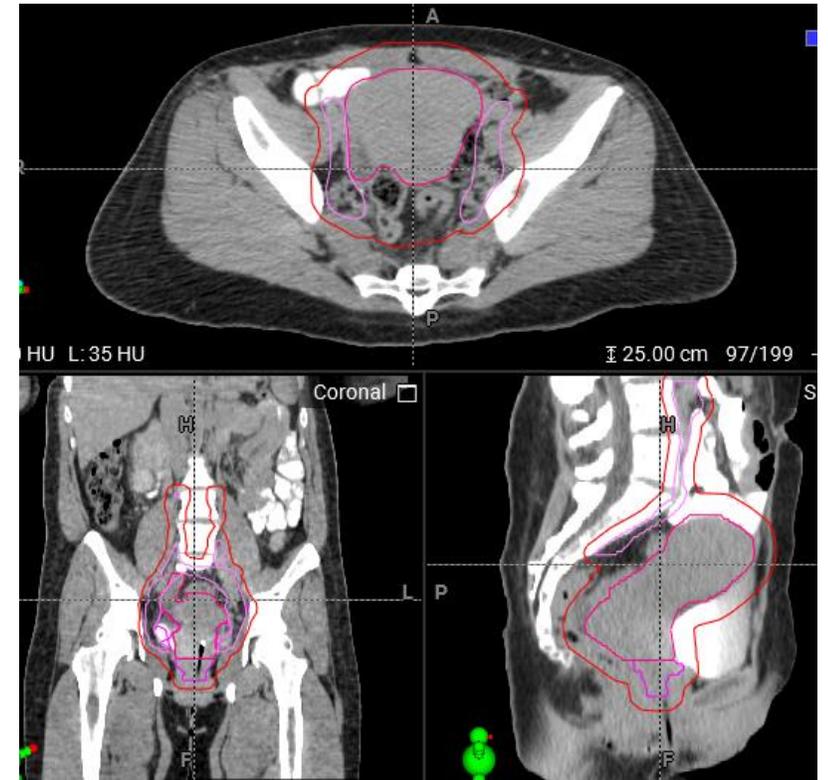


-  Bone Marrow
-  Active Bone Marrow defined by PET



Adaptive Radiotherapy

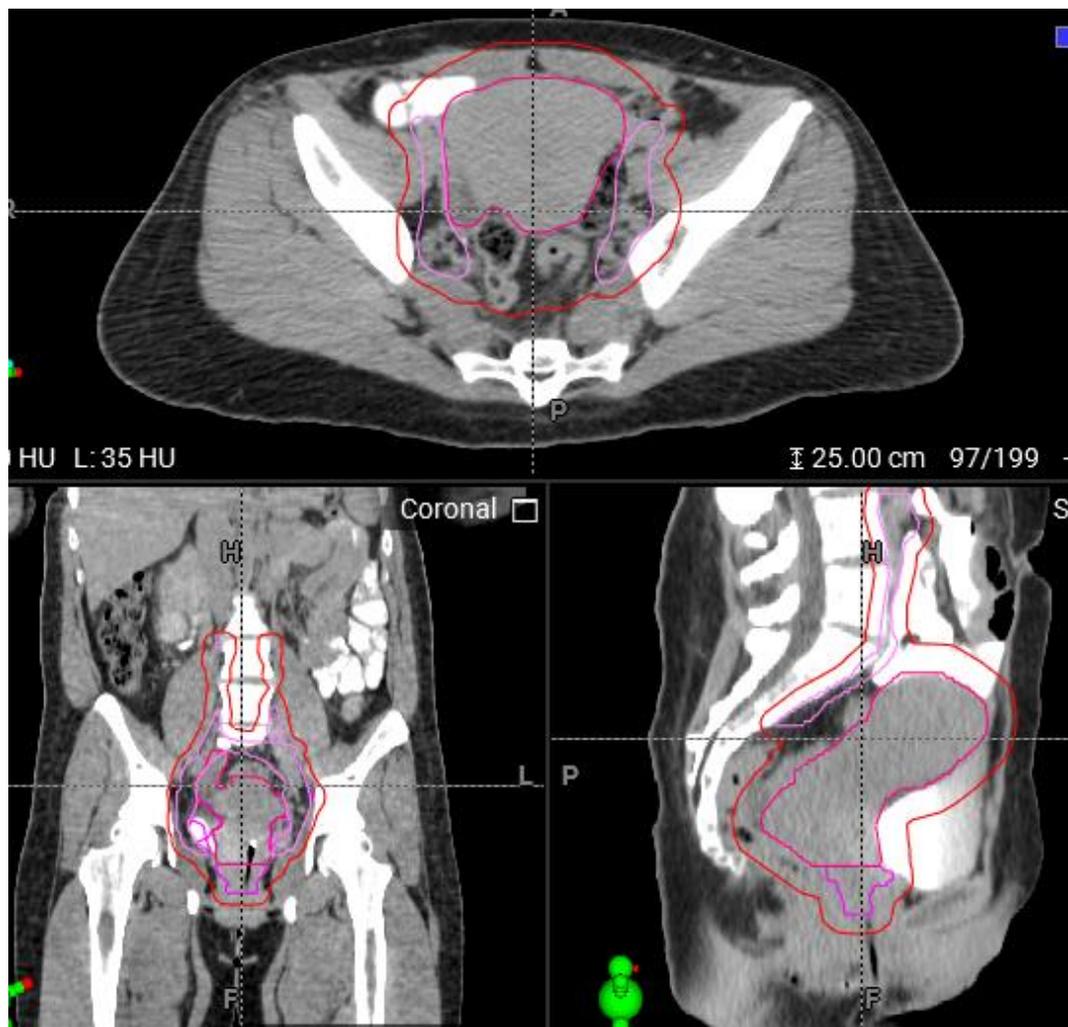
- IMRT requires margins that account for organ motion and daily image guidance
 - Uterus and cervix margin: 1.5 cm
 - Parametria and vagina margin: 1.0 cm
 - Lymph node margin: 0.7 cm



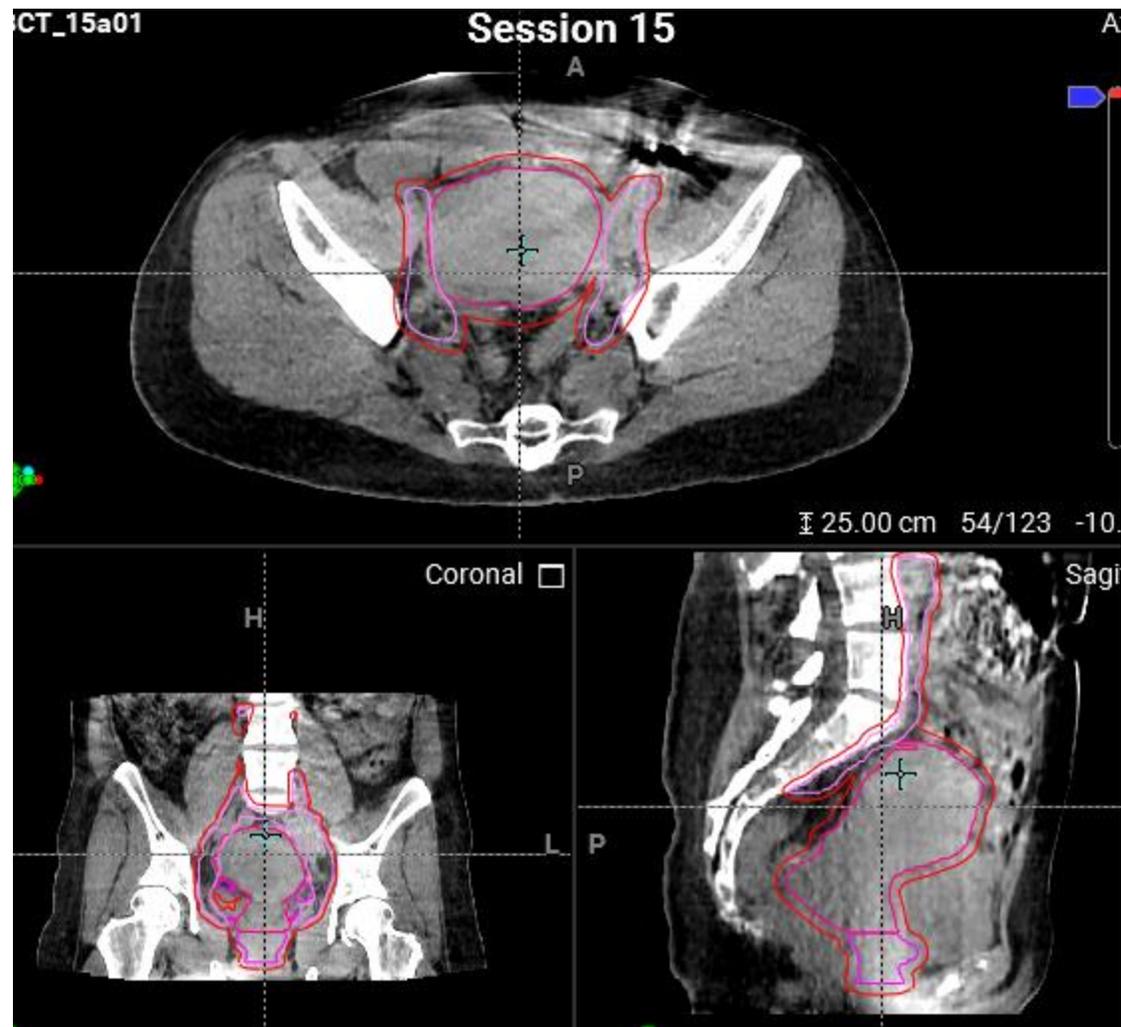
Adaptive Radiotherapy

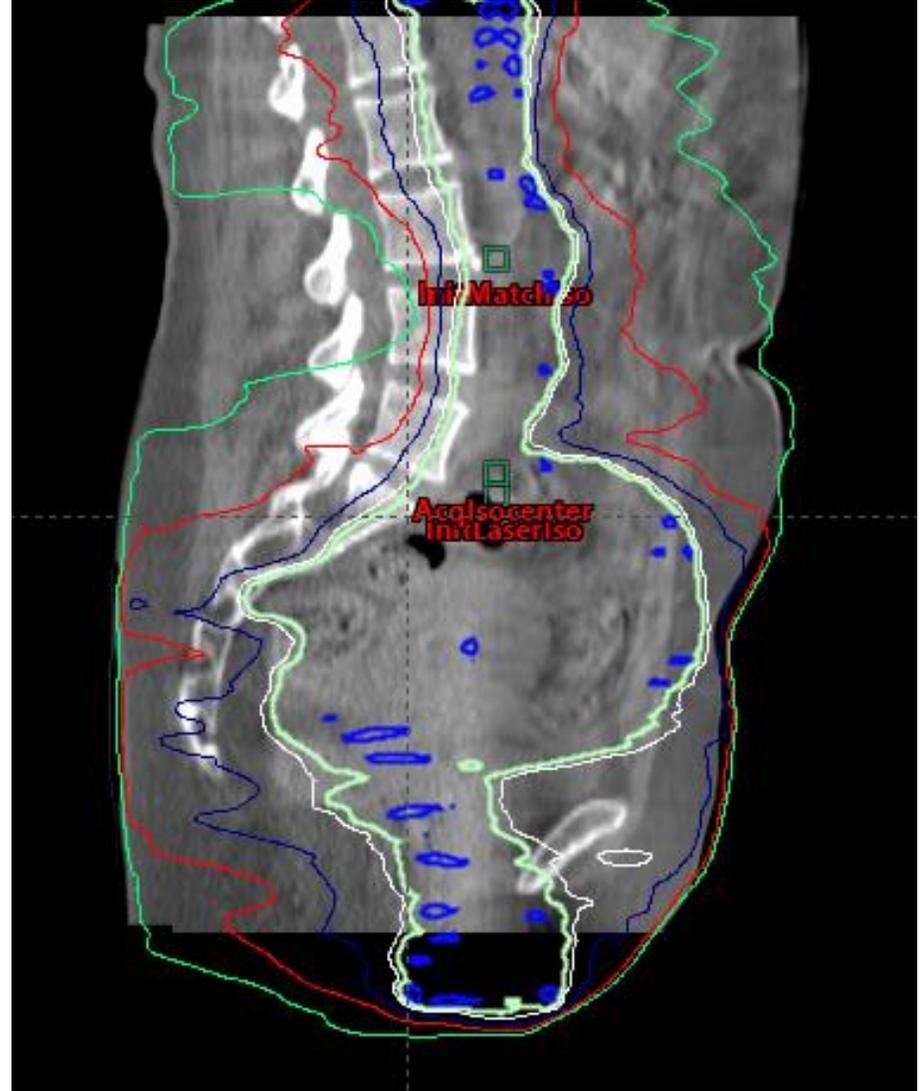
- Adaptive radiotherapy creates a new treatment plan for each daily fraction based on day of imaging
- Allow for tighter treatment margins

IMRT Treatment Margins



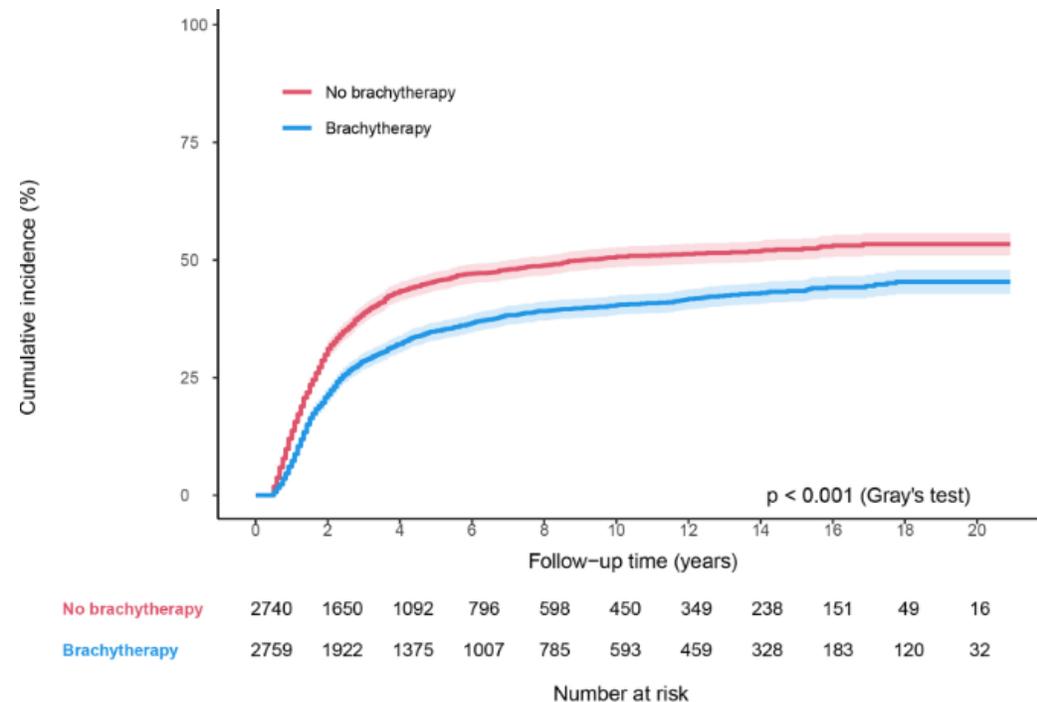
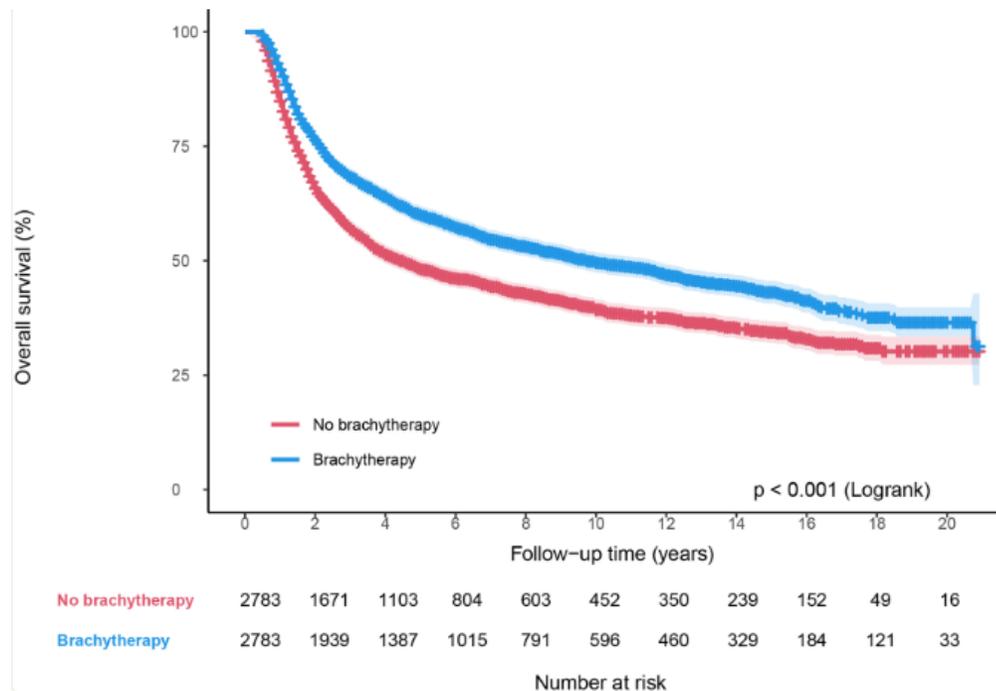
Adaptive Treatment Margins





Brachytherapy

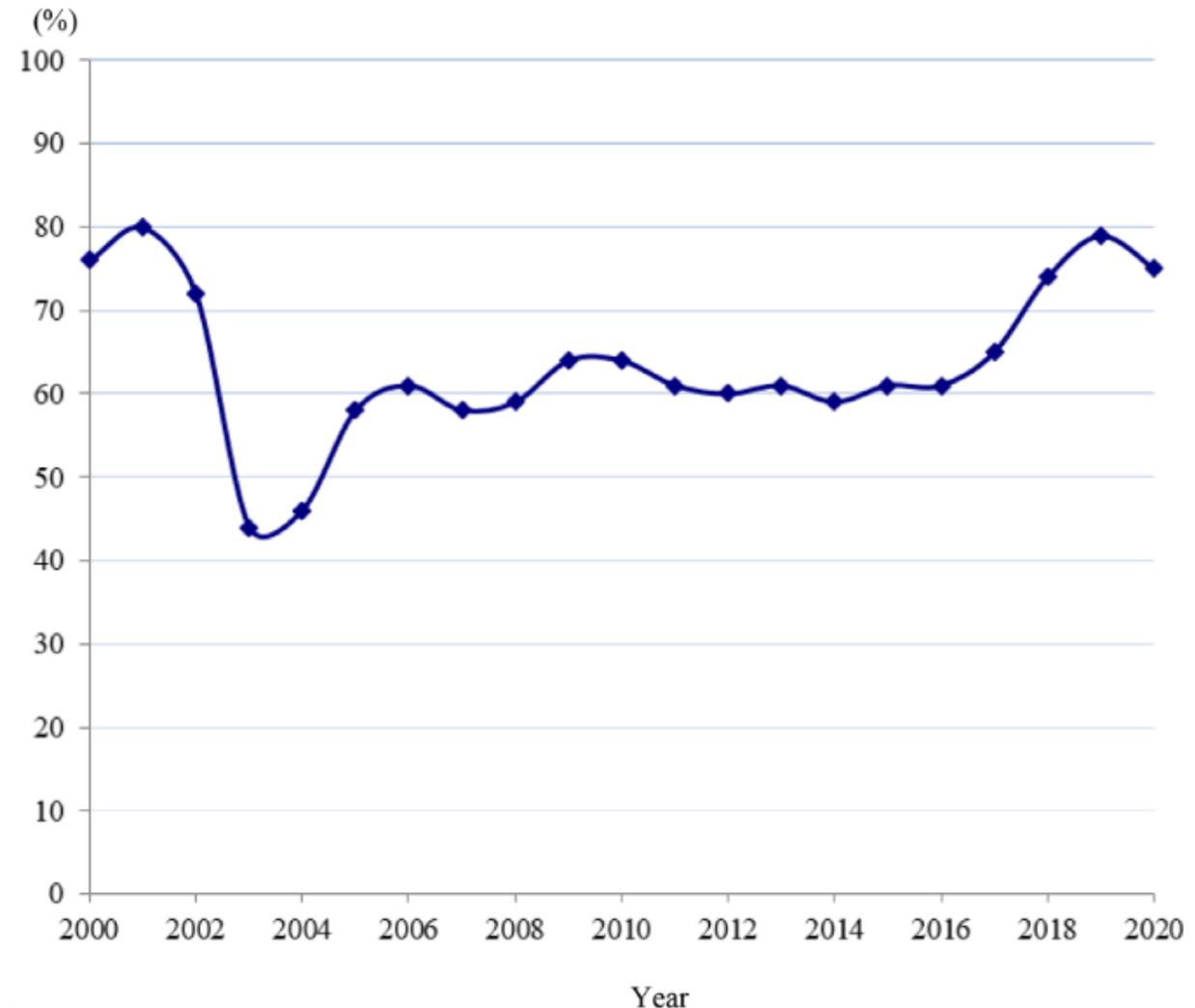
- Intracavitary brachytherapy improves cancer specific mortality and all-cause mortality



Brachytherapy

- Trend towards decreased brachytherapy utilization between 2005-2015
- Survival outcomes with IMRT or SBRT boosts are inferior to brachytherapy (Gill et al. IJROBP 2014)

Brachytherapy utilization SEER analysis



Hybrid Brachytherapy Implants

Standard intracavitary applicators

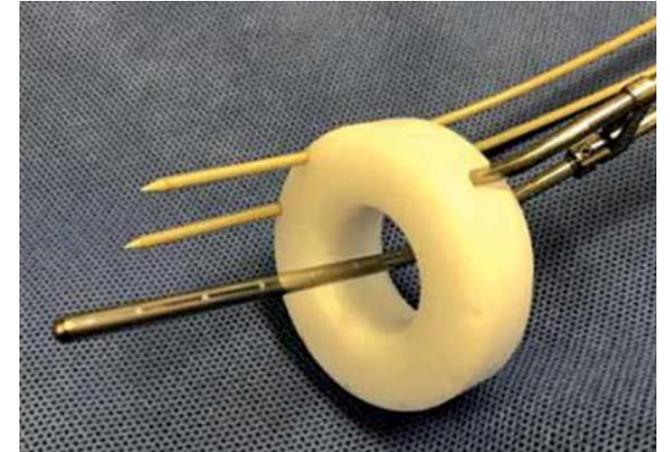
Tandem and ovoids



Tandem and ring

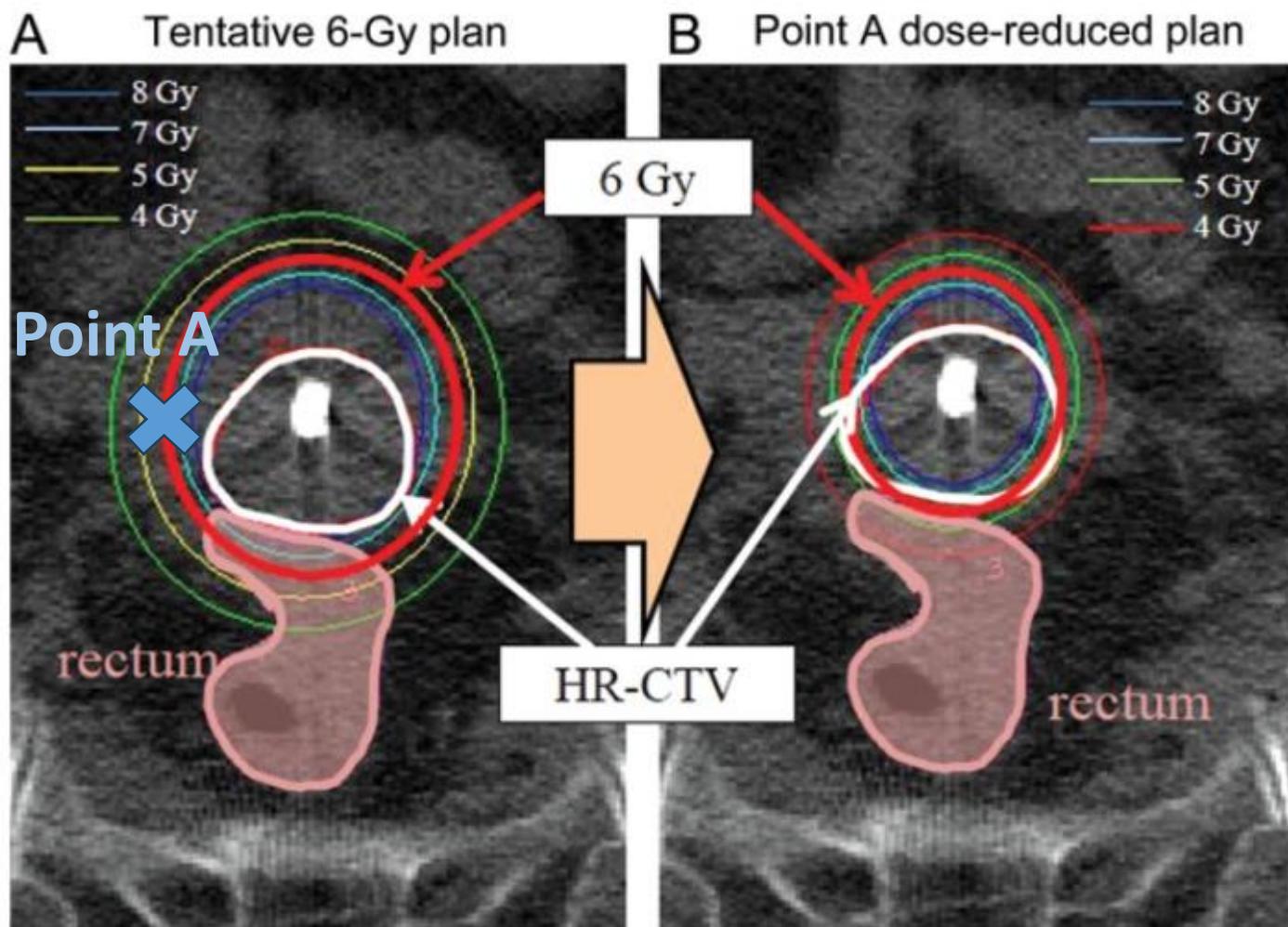


Hybrid Applicator

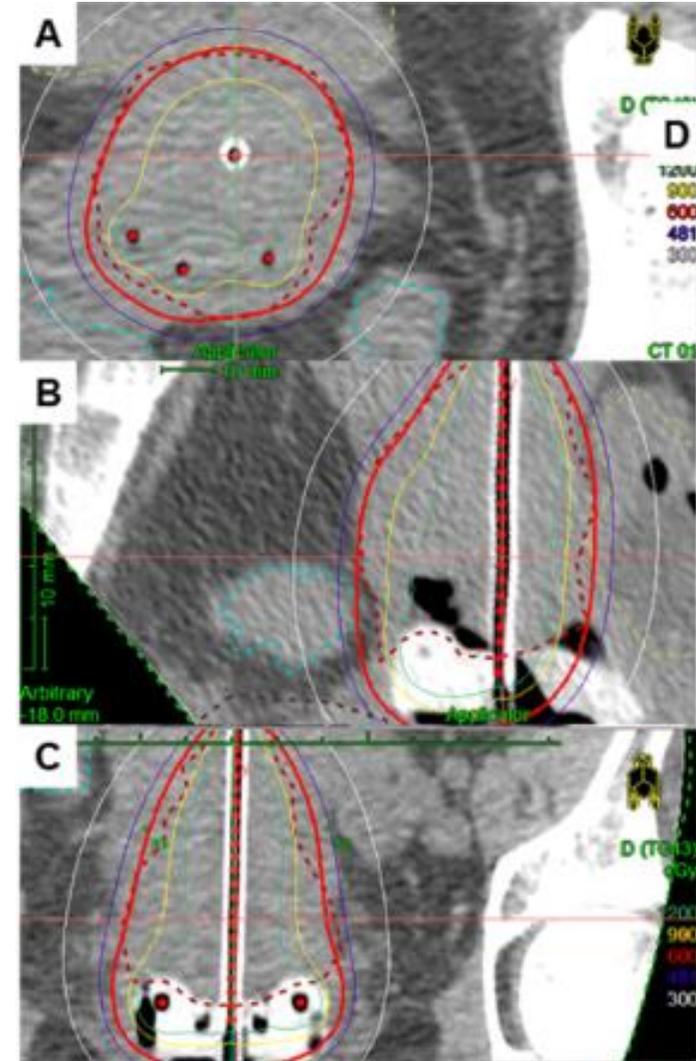


Intracavitary brachytherapy implants for cervical cancer can be enhanced with the addition of interstitial needles

Reducing brachytherapy volumes



Hybrid Brachytherapy Implants



Hybrid Brachytherapy Implants

- Advantages

- Improves coverage of the clinical target (tumor)
- Decreases dose to the surrounding organs at risk

- Disadvantages

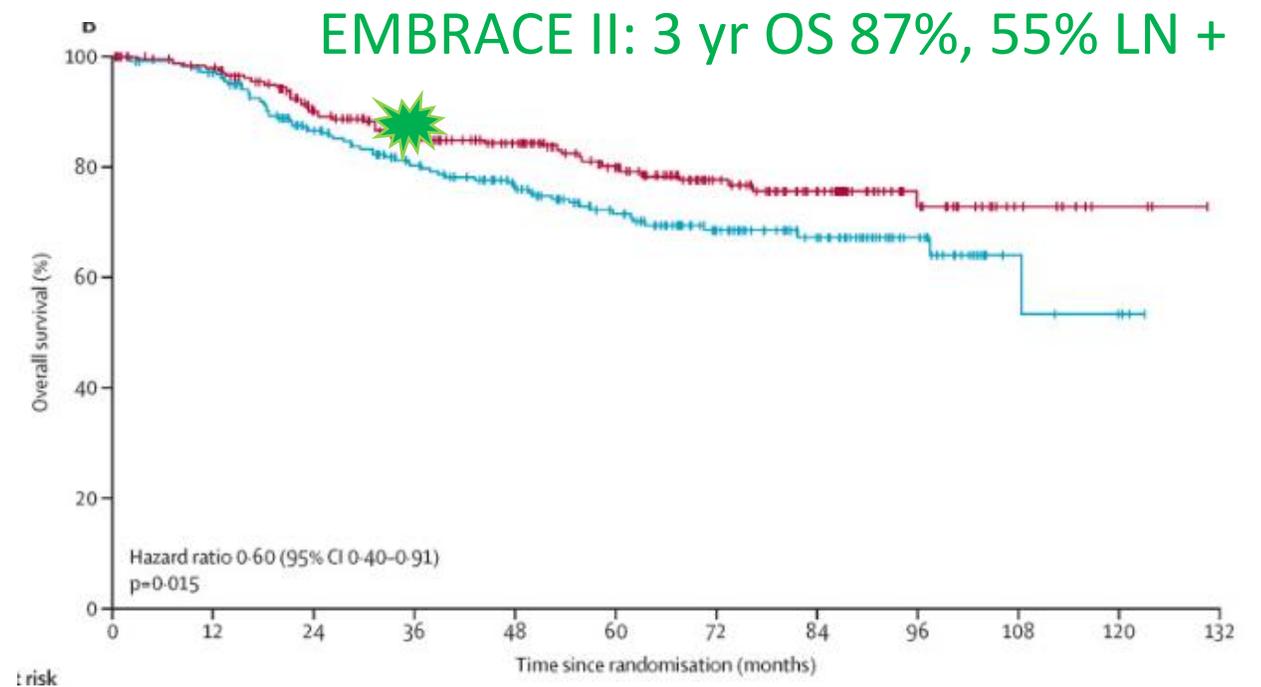
- Increases planning time
- Increased risk for bleeding with placement of interstitial needles
 - Transrectal or transabdominal US during needle placement

EMBRACE II ESTRO 2025

- Prospective, multicenter international trial
 - 1482 patients, 49 centers
- Multiple hypotheses: MRI/PET-CT staging, adaptive target definition, image guided techniques, elective PA nodal irradiation
- Modern techniques: 3 yr OS 87% (55% node positive pts)
 - 3 yr local control rates 93%; Late grade 3-5 morbidity 8.9% (Gr 4+ 1%)
 - Majority of pts completed treatment within 50 days
 - A dose of 5 Gy (CTVHR) is required to compensate an increase of OTT by one week (RetroEMBRACE 2016)

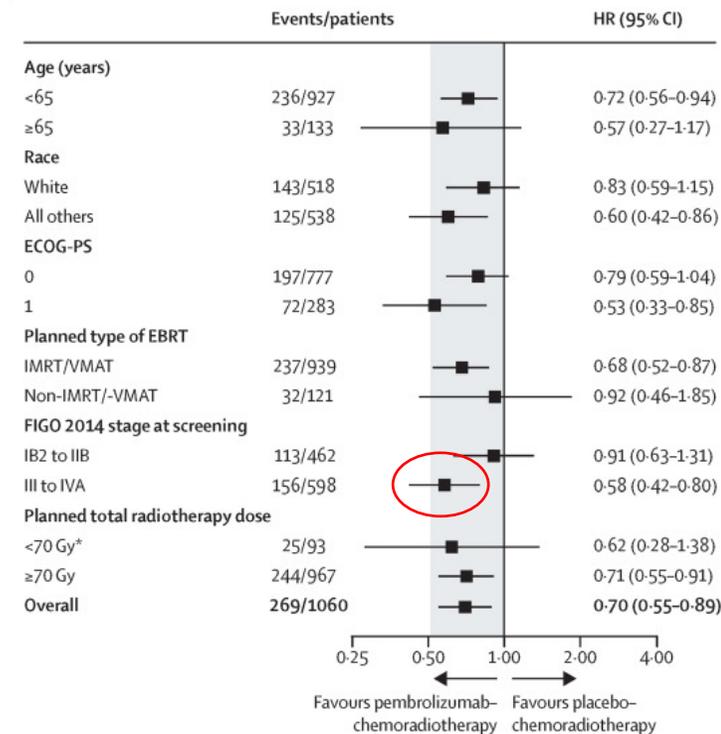
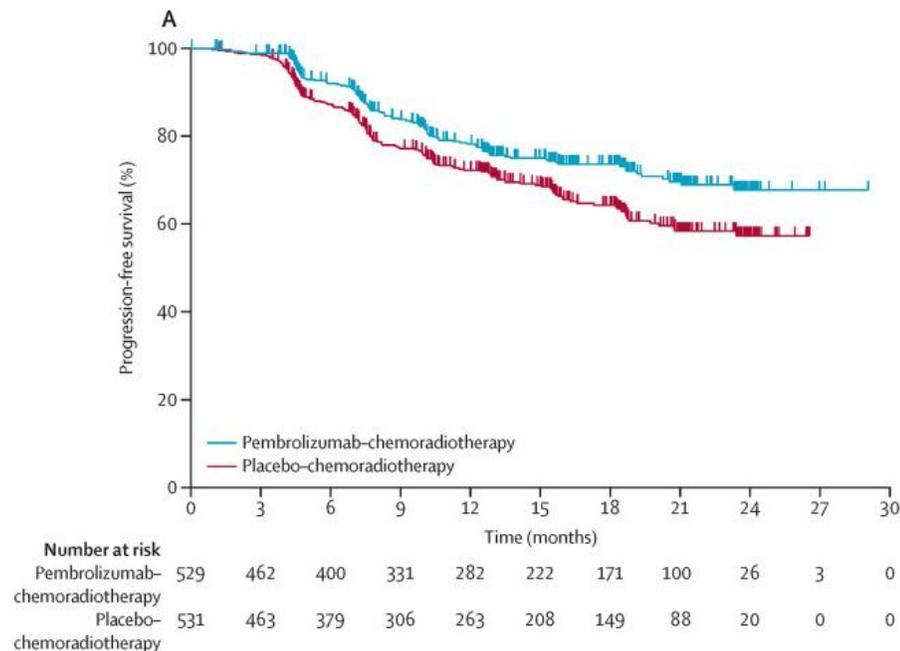
Treatment intensification?

- INTERLACE: Induction chemotherapy followed by definitive chemoradiation may improve progression-free survival and overall survival
 - Pts: FIGO 2009 stage IB2-IVA (except stage IIIA), and node positive stage IB1
 - 81% pts stage IIB-III B. 43% of pts LN+
 - Carbo/Taxol weekly x 6 followed by chemoradiation vs chemoradiation alone
 - ChemoRT started 1 week after induction chemotherapy
 - 5 yr OS 80% vs. 72% (HR 0.6 0.4-0.91)
 - Increased grade 3-4 heme events in induction arm (30% vs 13%)



Incorporating Immunotherapy

- KEYNOTE A18: The addition of concurrent and adjuvant pembrolizumab to definitive chemoradiation improves PFS and OS, regardless of PD-L1 status
 - Pts: FIGO 2014 stage IB2–IIB with node-positive disease or stage III–IVA regardless of nodal status



Ongoing Clinical Trials

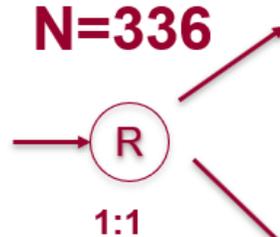
NRG GY037 Schema

Phase 3 RCT
(NCT07061977)

- Newly diagnosed histologically confirmed FIGO (2018) Stage IIIA(T3aN0), IIIB (T3bN0); Stage IIIC1 (T3aN1, T3bN1) IIIC2 (T3aN2, T3bN2); IVA
- Squamous cell, adenocarcinoma, adenosquamous cervical cancer

Stratification:
PALN + vs. -
Stage III vs. IVA

NRG
ONCOLOGY™



Power: 90%
Alpha: (one sided 5%)

Arm 1: SOC

Cisplatin 40 mg/m² QW for 5 cycles + EBRT followed by brachytherapy +
Pembrolizumab 200 mg Q3W for 5 cycles
Pembrolizumab 400mg Q6W for 15 cycles

Arm 2: Induction

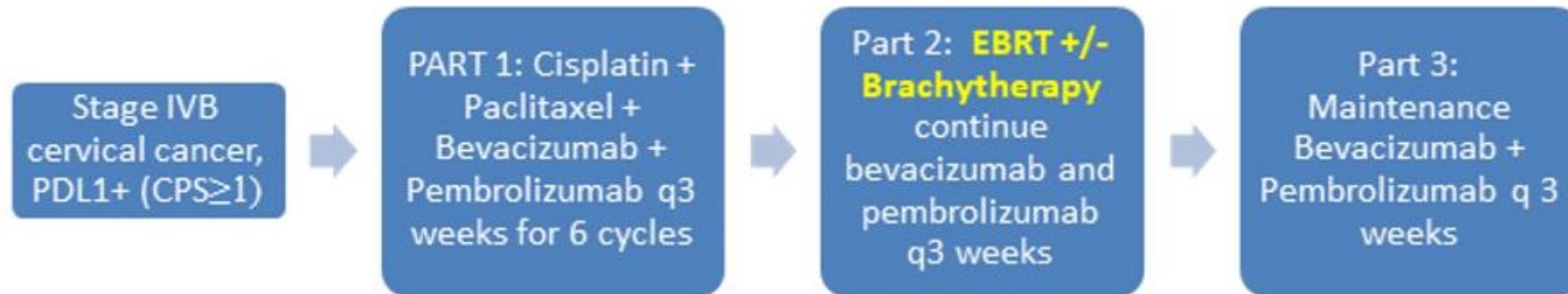
Induction chemotherapy with carboplatin/paclitaxel q wk. + pembrolizumab 200mg q 3wks 2 cycles (6 wks.)

RT to start ASAP: wk. 7↓

Cisplatin 40 mg/m² QW for 5 cycles + EBRT followed by brachytherapy +
Pembrolizumab 200 mg Q3W for 5 cycles
Pembrolizumab 400mg Q6W for 14 cycles

Ongoing Clinical Trials

A prospective cohort study of integrating radiotherapy into chemotherapy with pembrolizumab and bevacizumab in newly diagnosed Stage IVB cervical cancer



Currently open at ULCA, pending activation at UCSD, Emory, Uva, and U of Oklahoma

Summary

- Adaptive radiotherapy and hybrid interstitial brachytherapy are decreasing dose to organs at risk in the pelvis
- Hybrid intracavitary brachytherapy can improve local control and minimize the risk for severe grade 3-5 complications
- Careful selection of patients for immunotherapy can help optimize treatment outcomes