Radiation Advances for Gynecologic Malignancies

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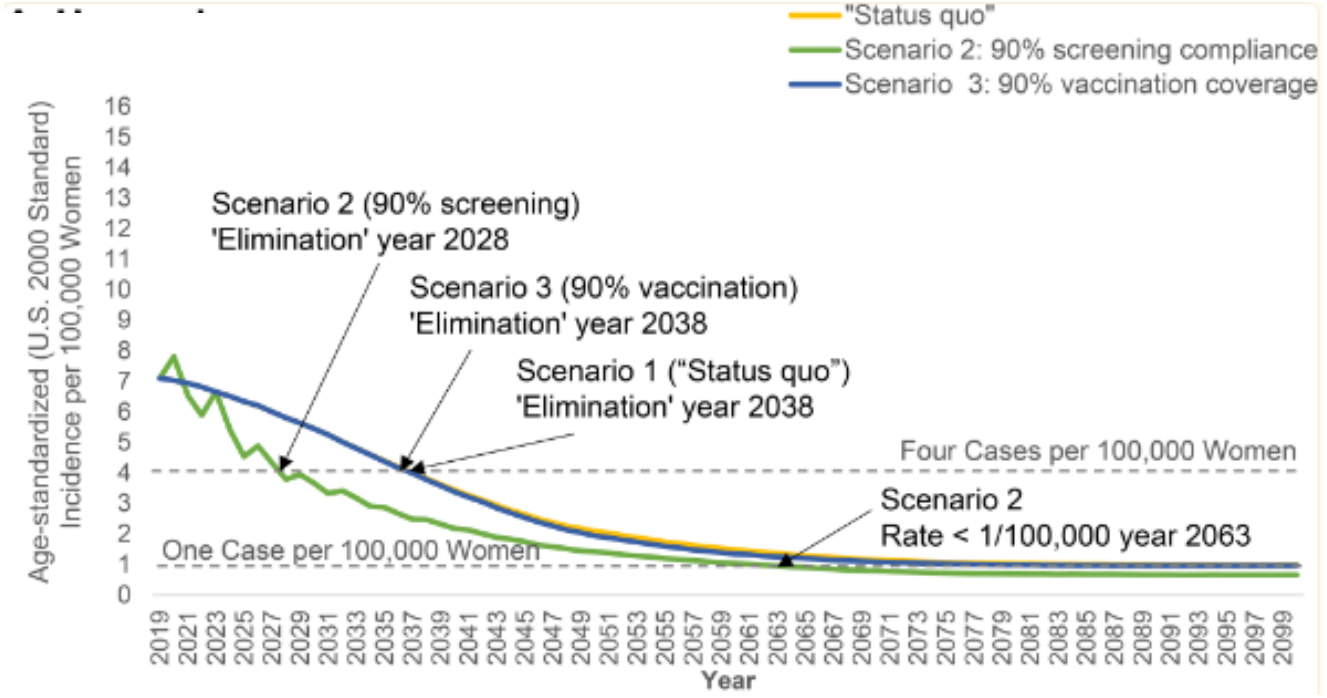
Present radiation challenges

- Reducing radiation treatment volumes
- Incorporating immunotherapy into treatment

Cervical Cancer: Ongoing Cancer Threat

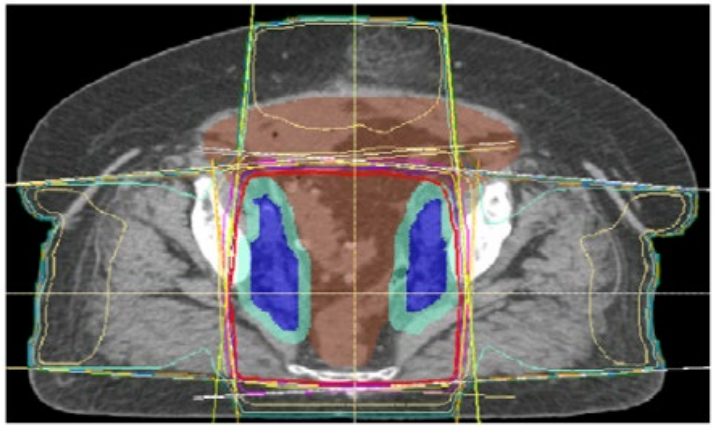
- 14,100 estimated new cases in 2022
- 7.3/100,000 women
- Overall survival 66%
- HPV vaccine: 61% compliance among US teens

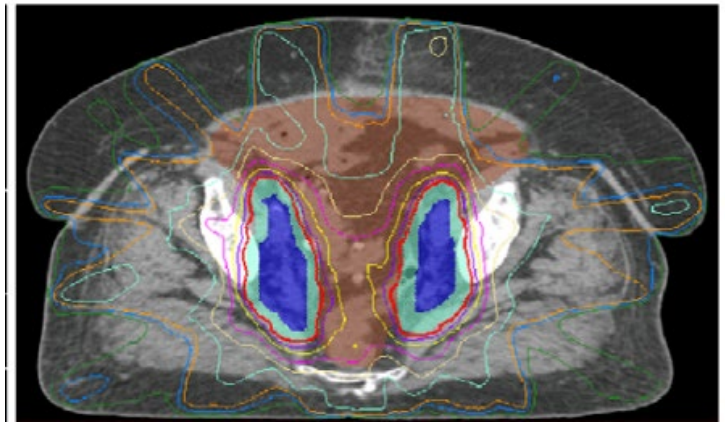


Burger et al. Lancet Public Health 2020

Reducing radiation treatment volumes

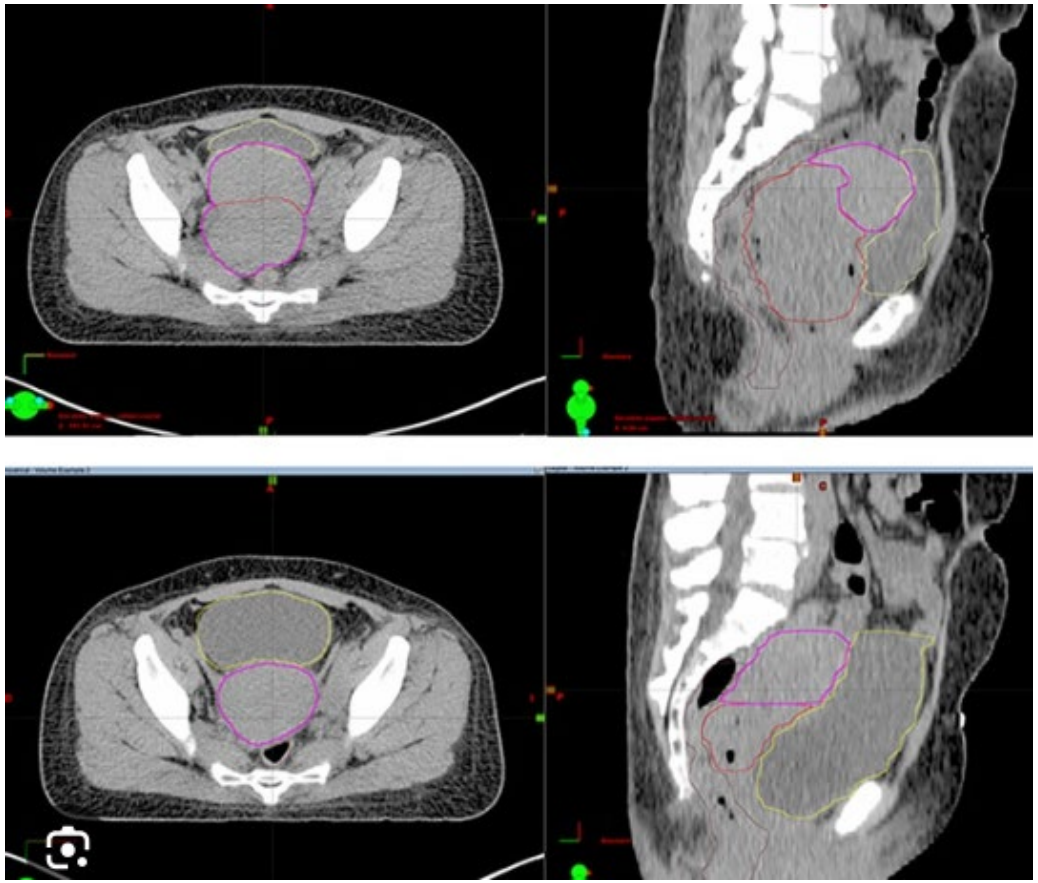
- Intensity modulated radiation therapy for cervical cancer
  - Dosimetric studies initially published 2000-2001
  - First clinical series published in 2001
  - By 2009, 18+ retrospective studies published suggesting improved toxicity with IMRT compared to 3DCRT





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

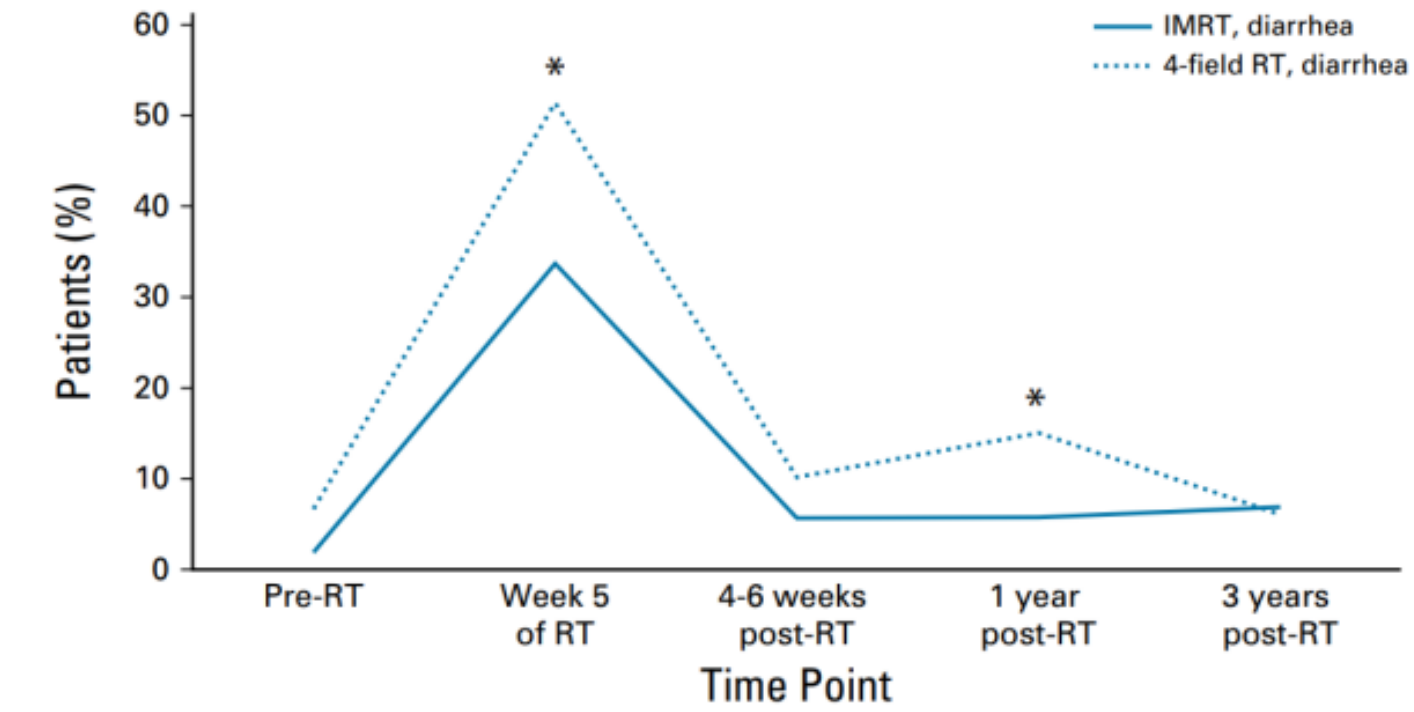


IMRT for Gynecologic Malignancies

- 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

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

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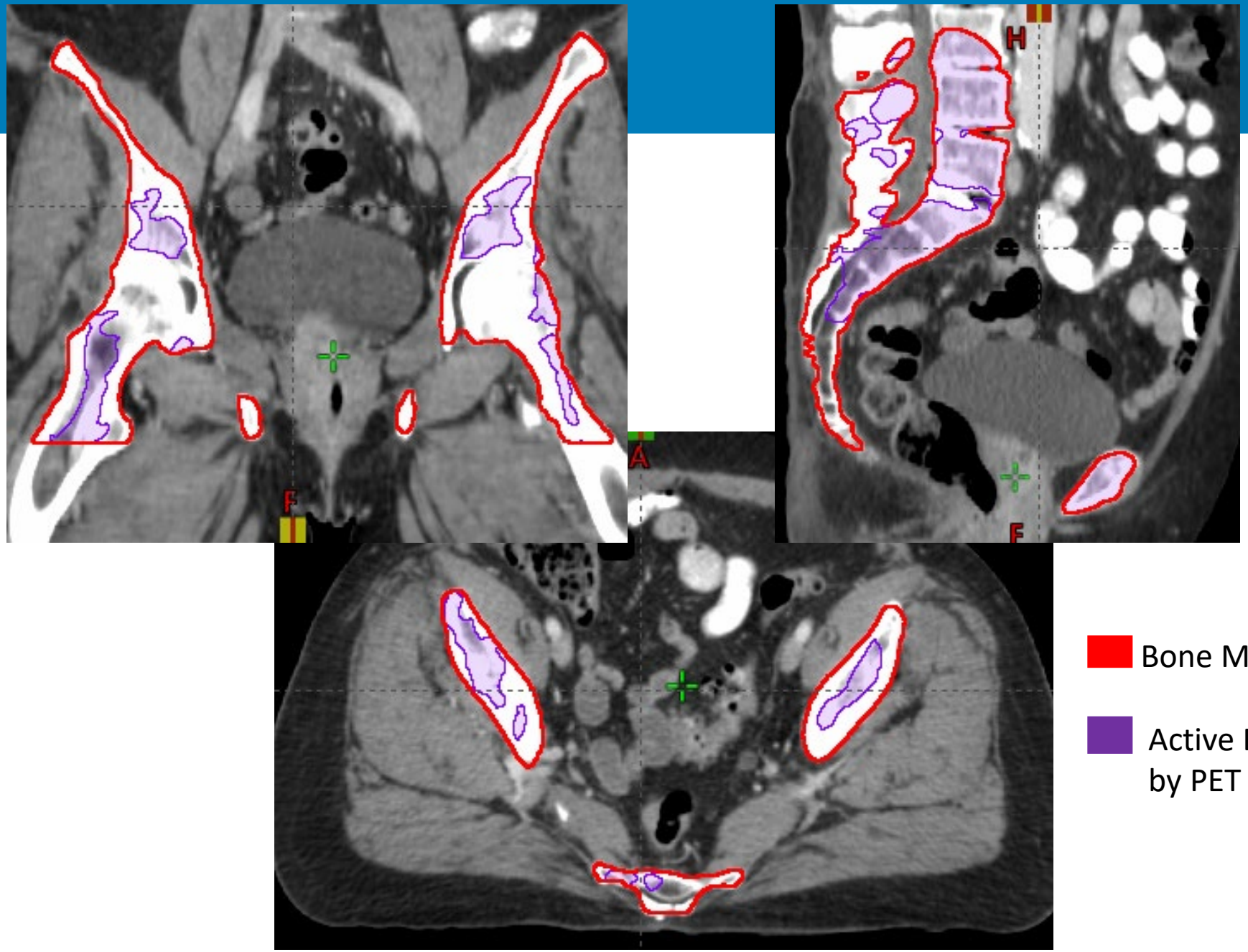

Bone Marrow

Active Bone Marrow defined by PET

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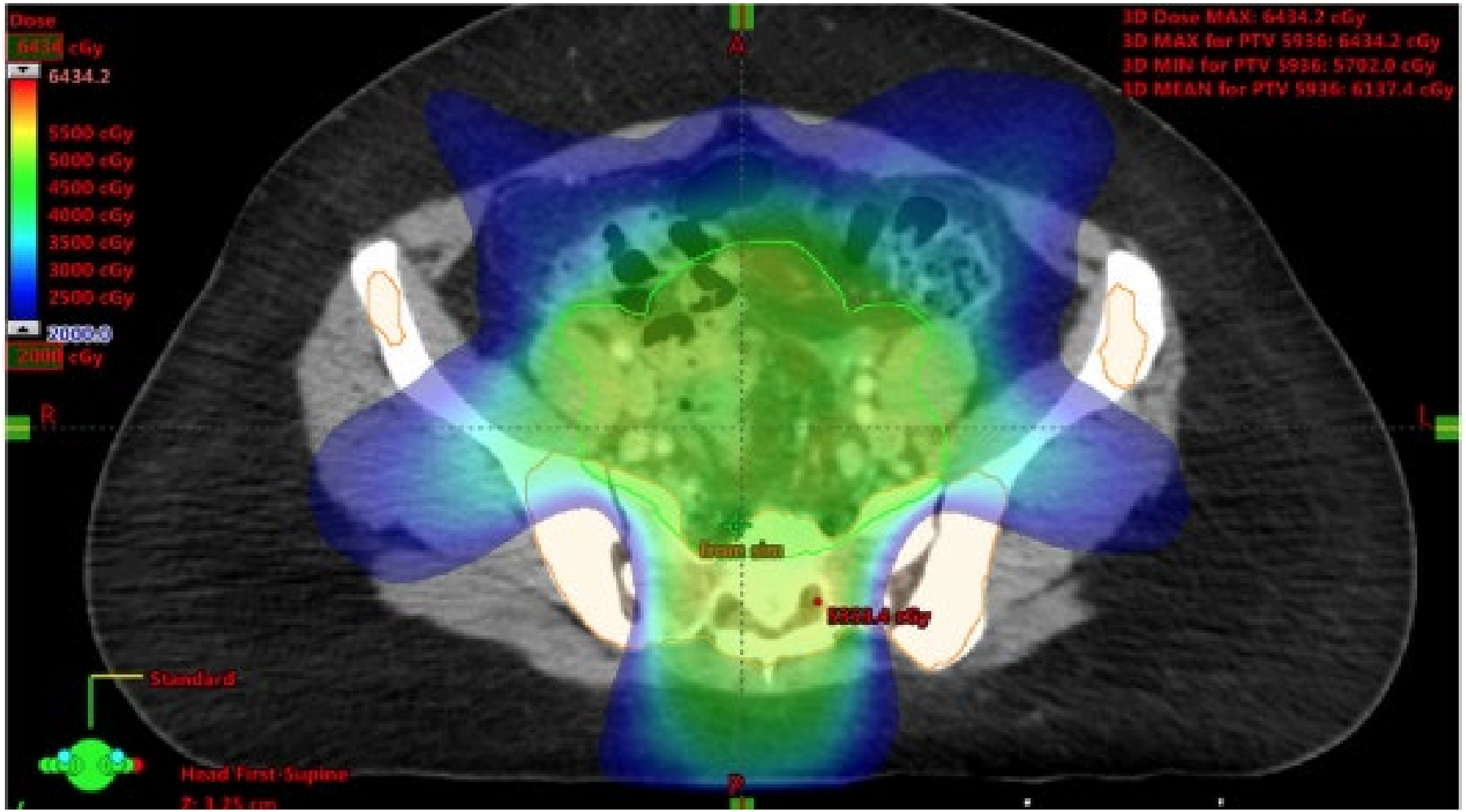

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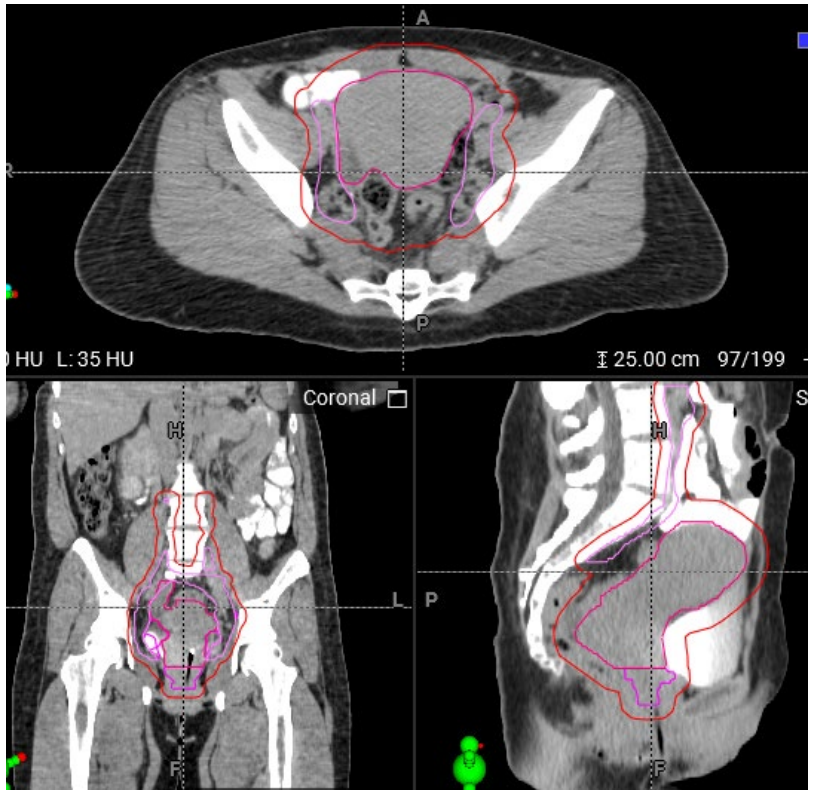
Adaptive Radiotherapy

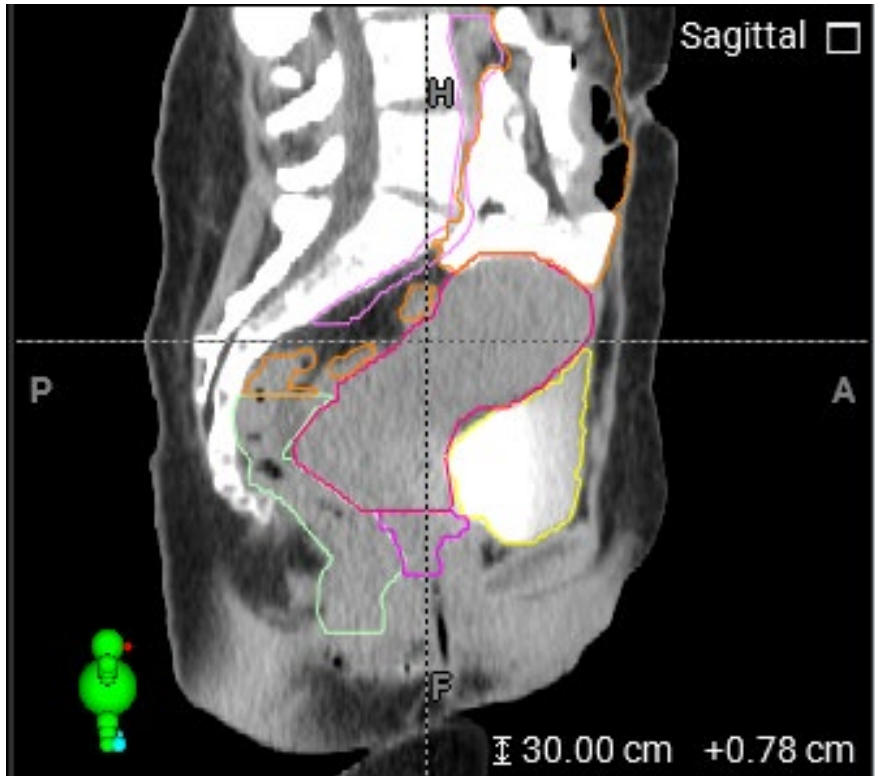
- IMRT requires margins that account for organ motion and daily image guidance
  - Uterus and cervix margin: 1.5 cm
  - Parametria and vagina margin: 1.0 cm
  - Lymph node margin: 0.7 cm

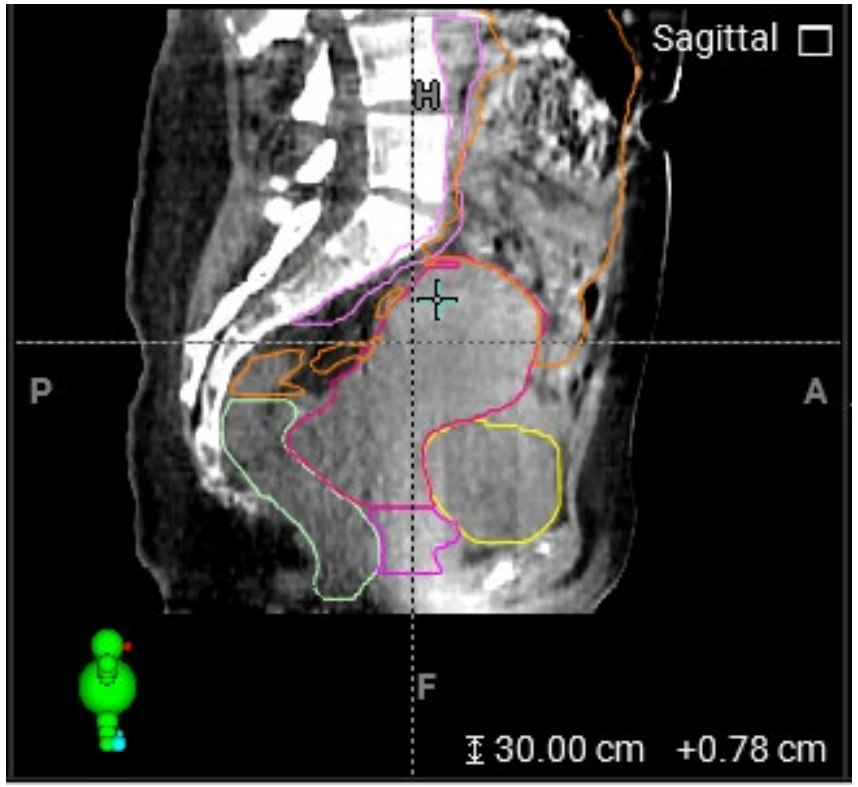


Adaptive Radiotherapy

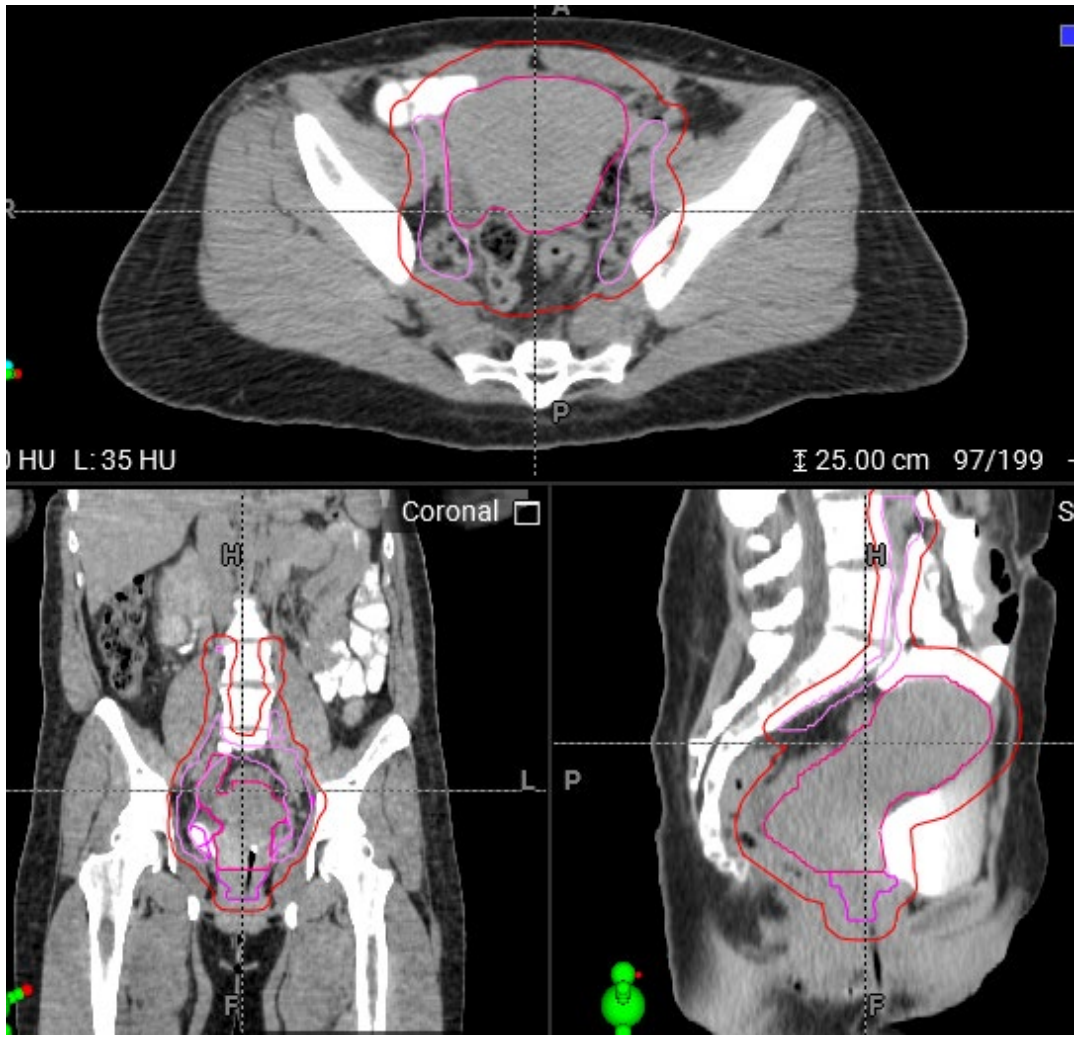
- Adaptive radiotherapy creates a new treatment plan for each daily fraction based on day of imaging
- Allow for tighter treatment margins

Adaptive Radiotherapy

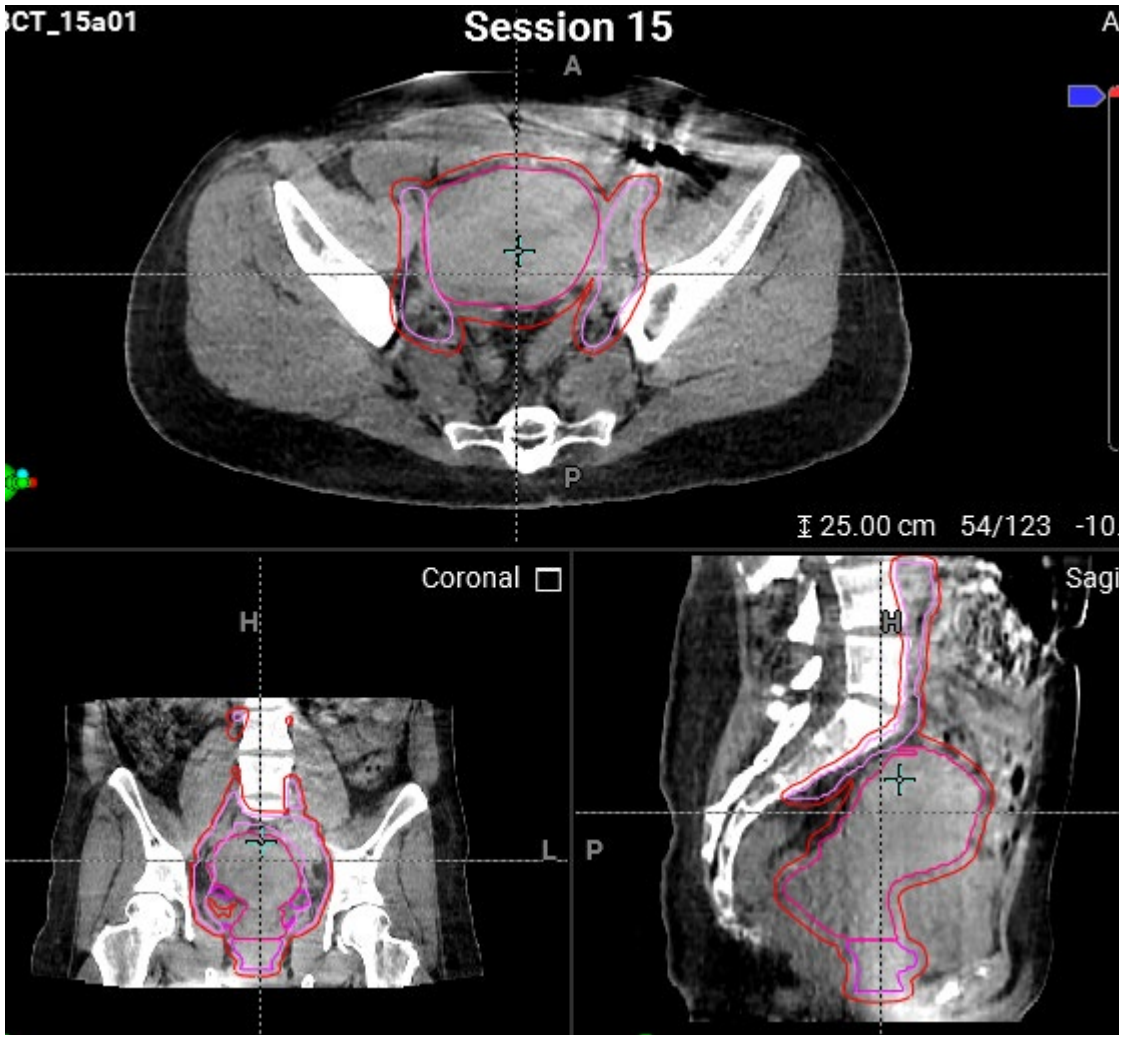




IMRT Treatment Margins



Adaptive Treatment Margins



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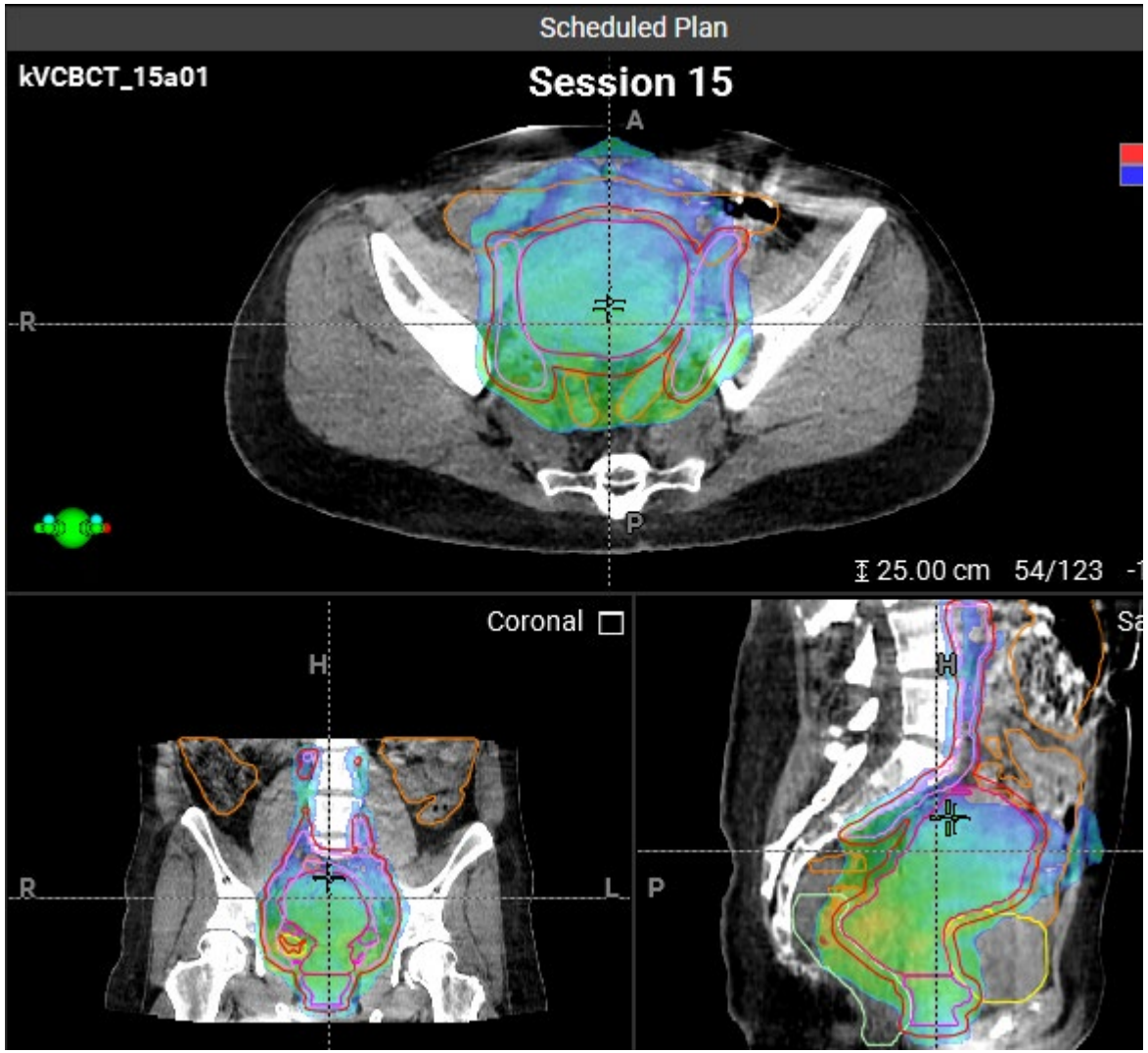
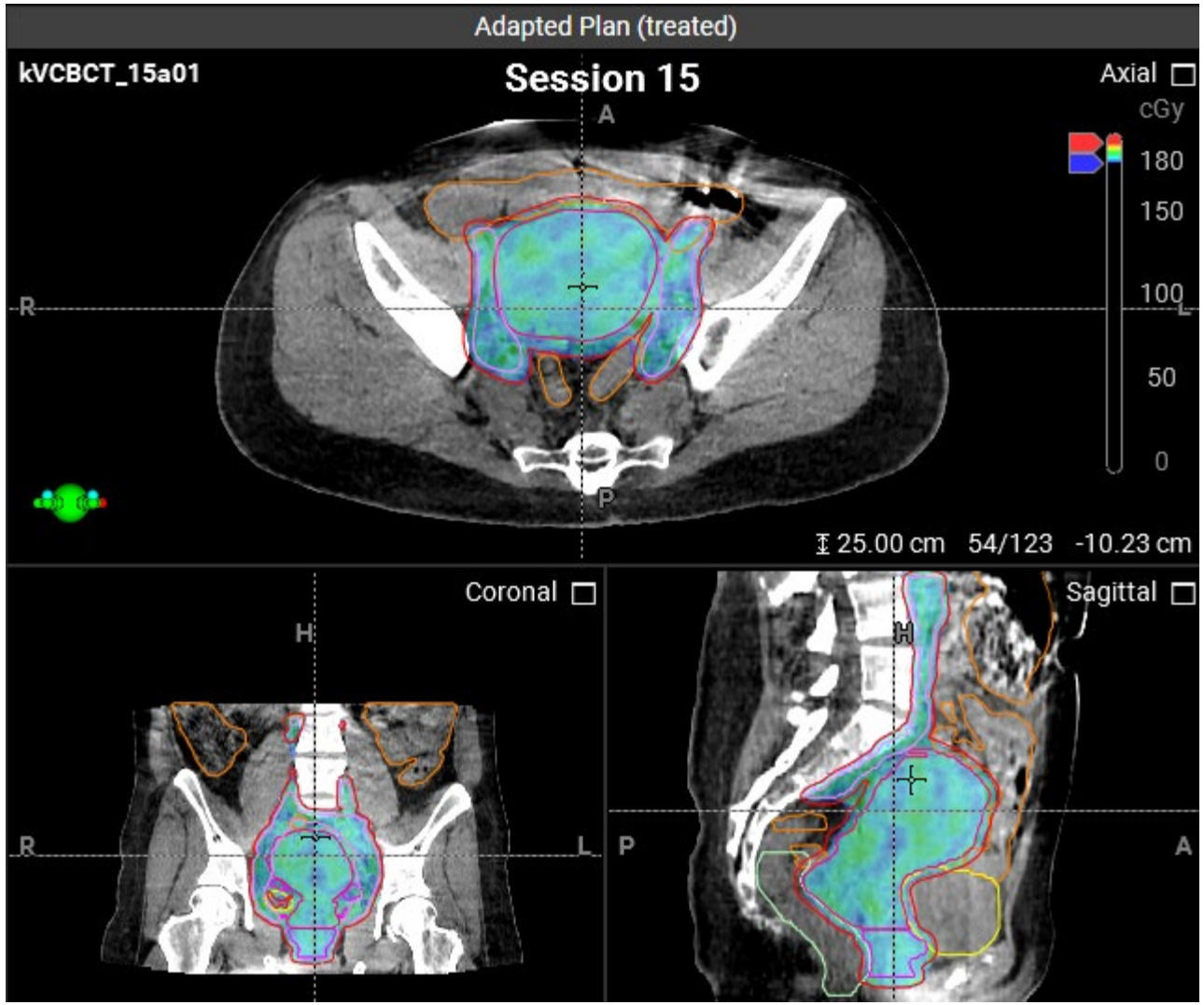




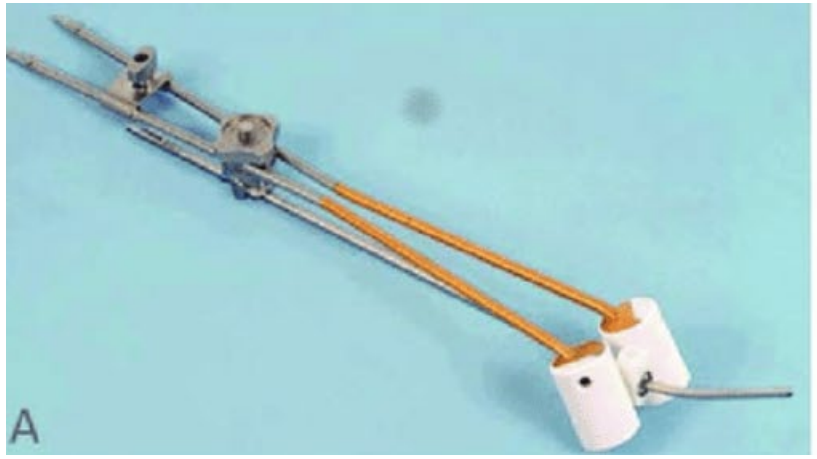
Hybrid Brachytherapy Implants

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

Hybrid Brachytherapy Implants

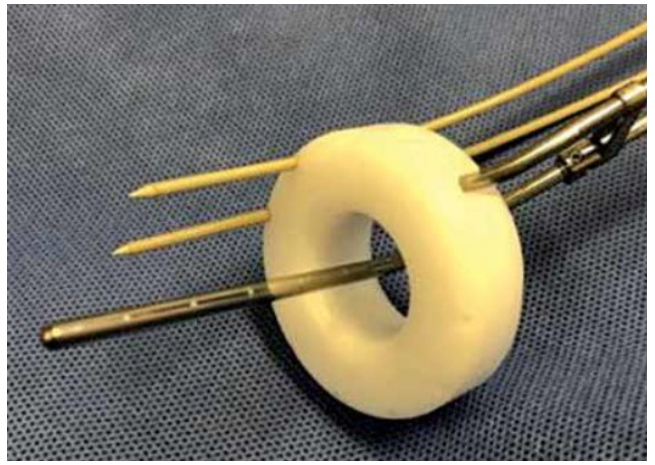
Standard intracavitary applicators

Tandem and ovoids

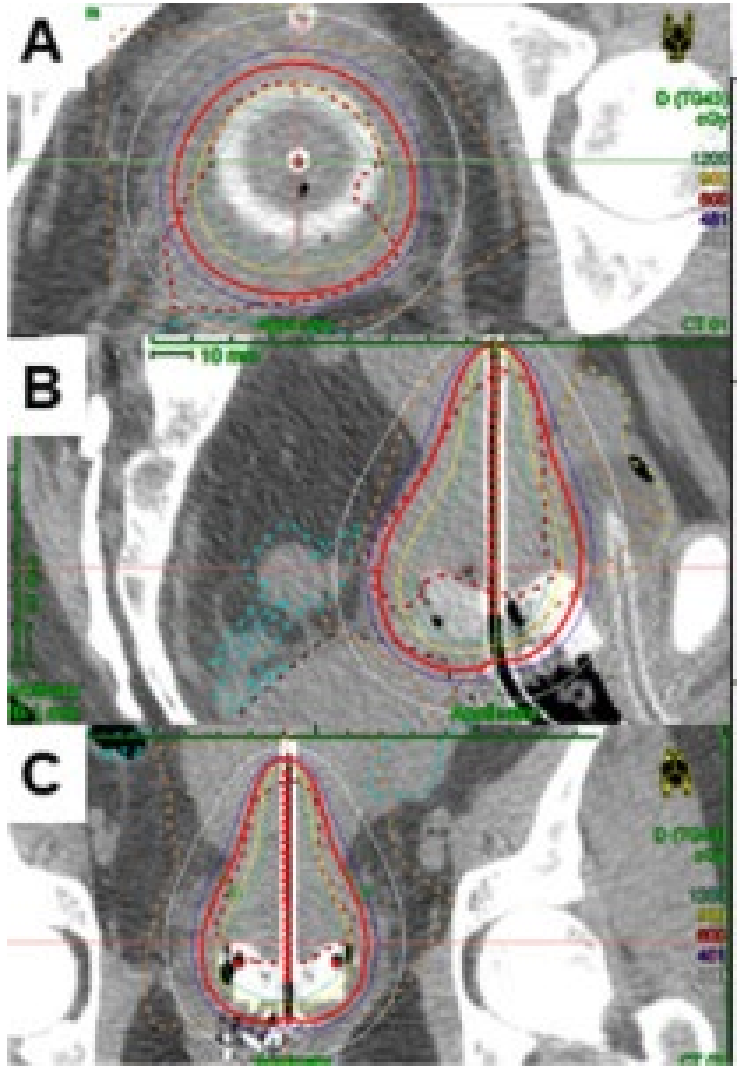


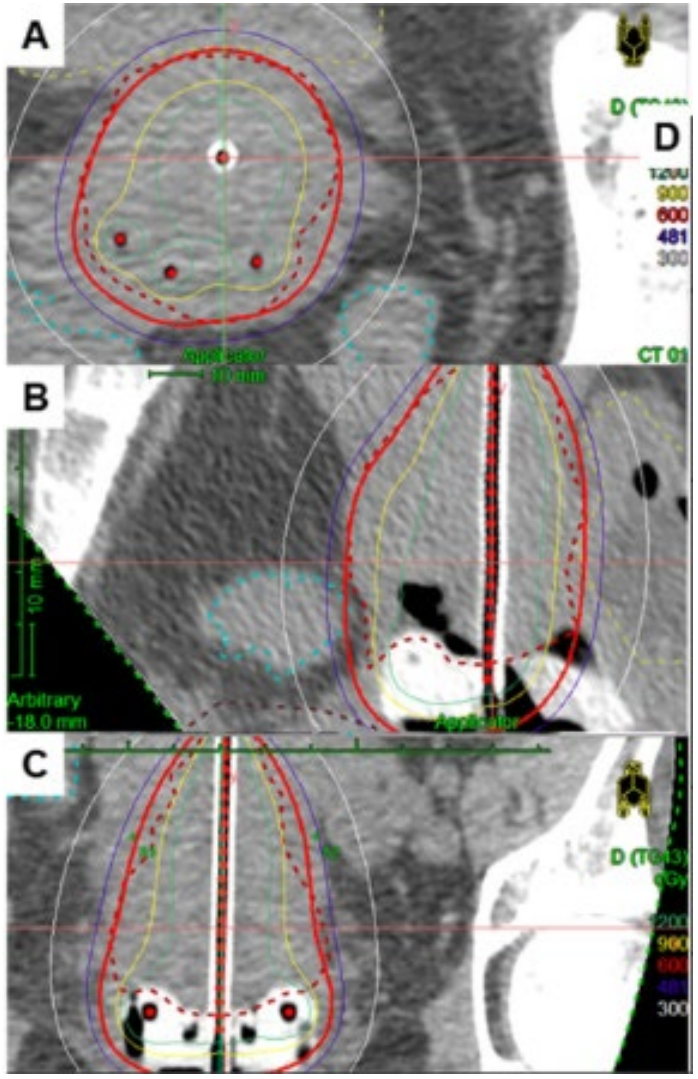
Tandem and ring

Hybrid Applicator



Hybrid Brachytherapy Implants





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Ladbury C, et al. A practical guide to hybrid interstitial/intracavitary brachytherapy for locally-advanced cervical cancer. Brachytherapy. 2023 Sep-Oct;22(5):640-648.

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

Endometrial Cancer: Ever Present Danger

- 66,000 estimated new cases in 2022
- Overall survival 84% at 5 yrs
- Surgery is the primary treatment for endometrial cancer
  - Postoperative radiation +/- chemotherapy depends on pathologic features
  - National guidelines are not entirely clear re:optimal treatment recommendations

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Endometrial Carcinoma

NCCN Guidelines Ir
Table of Cont
Discus

All staging in guideline is based on updated FIGO staging. (ST-1)

CLINICAL FINDINGS (Endometrioid Histology)[a]

HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]

Surgically staged: Stage I[e] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if ≥60 y and/or LVSI or Consider observation if age <60 y and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

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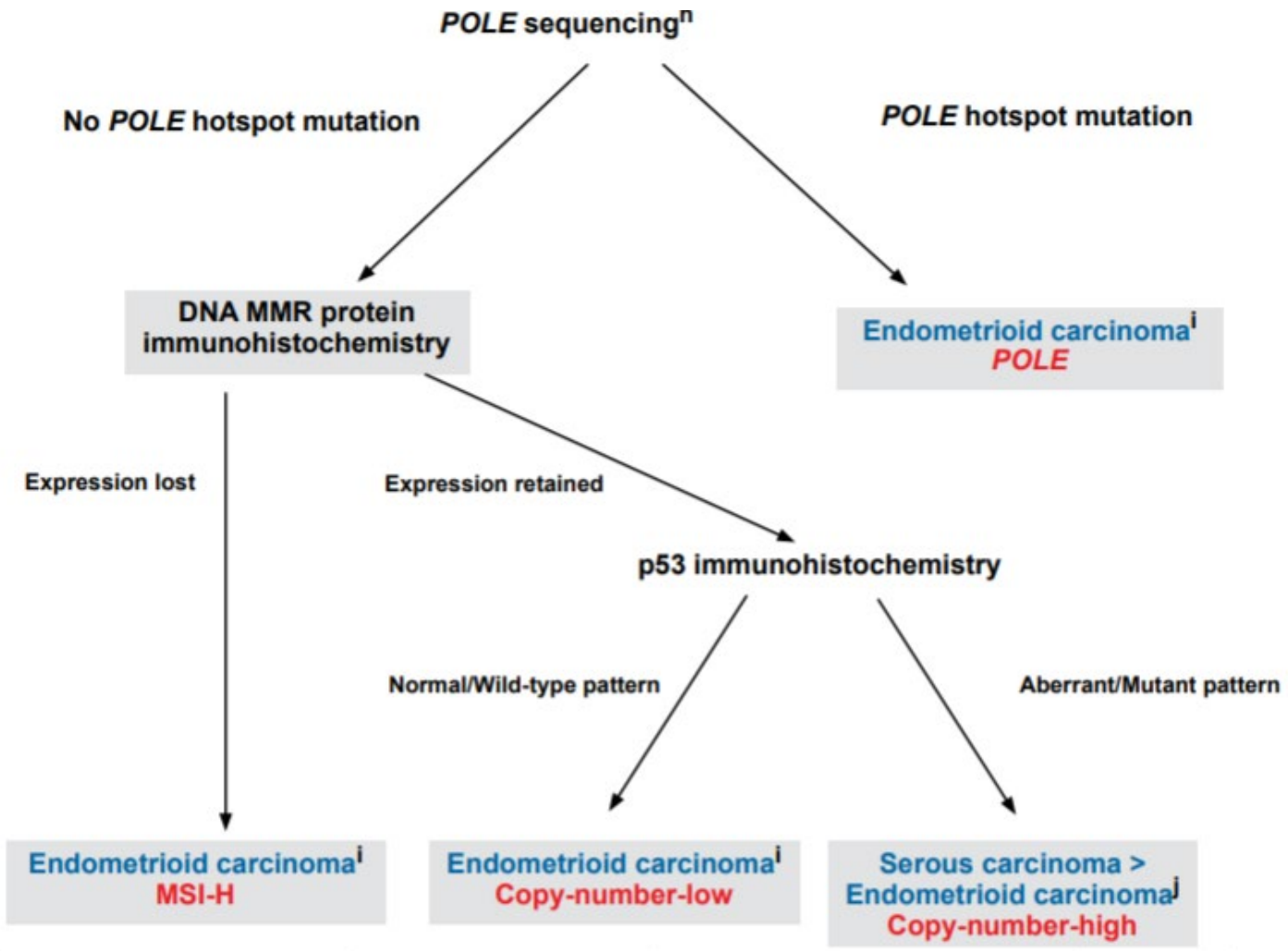
Mismatch Repair in Endometrial Cancer

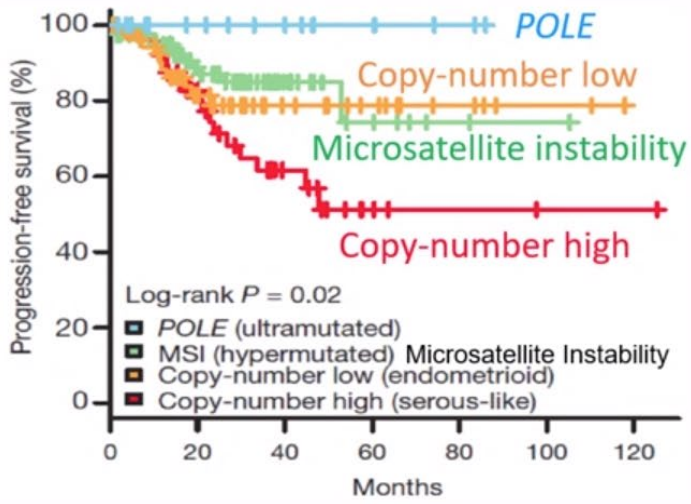
- Loss of DNA mismatch repair genes
- Germline mutations present in 4% of pts
- Somatic mutations present in 25% of pts
- dMMR is less likely to occur in non-endometrioid subtypes
- Testing: MSI testing or IHC staining for MLH1, PMS2, MSH2, MSH6
- Patients with dMMR have higher response rates to anti-PD1 tx

TCGA Sequencing



Molecular Subtypes of Endometrial Cancer

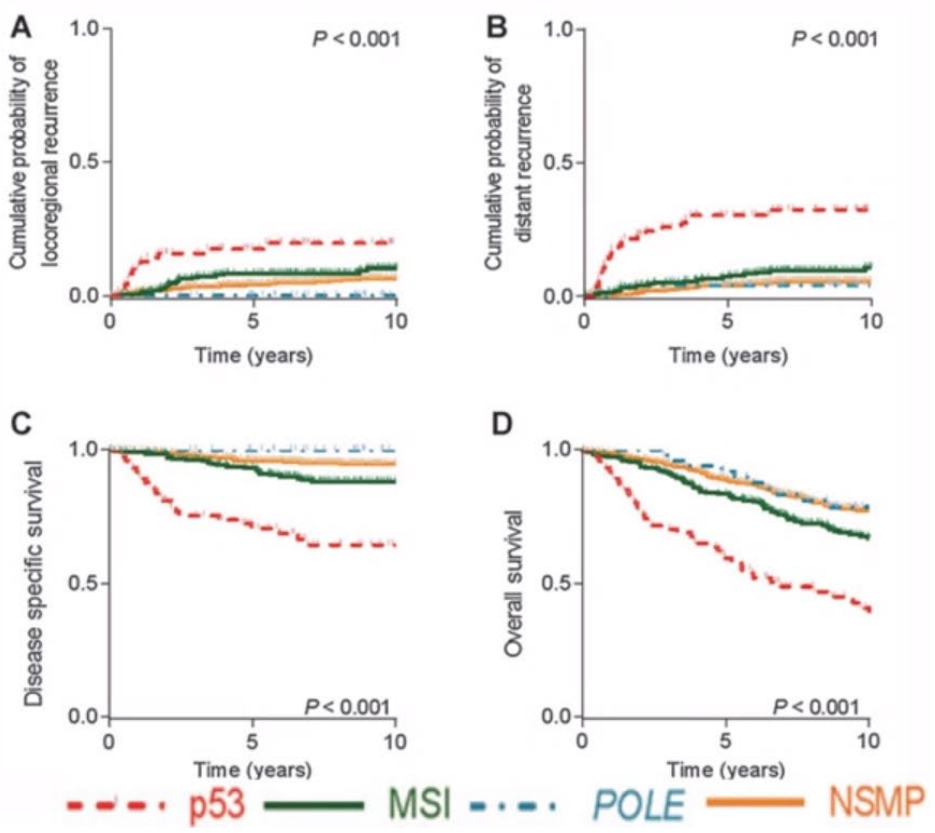
The Cancer Genome Atlas (TCGA)



Most favorable: *POLE*

Least favorable: Copy-number high (serous-like)
(25% of G3 endometrioid)

Pooled PORTEC-1 and 2 Analysis



TCGA Nature 2013

Stelico et al. Clin Cancer Res 2016

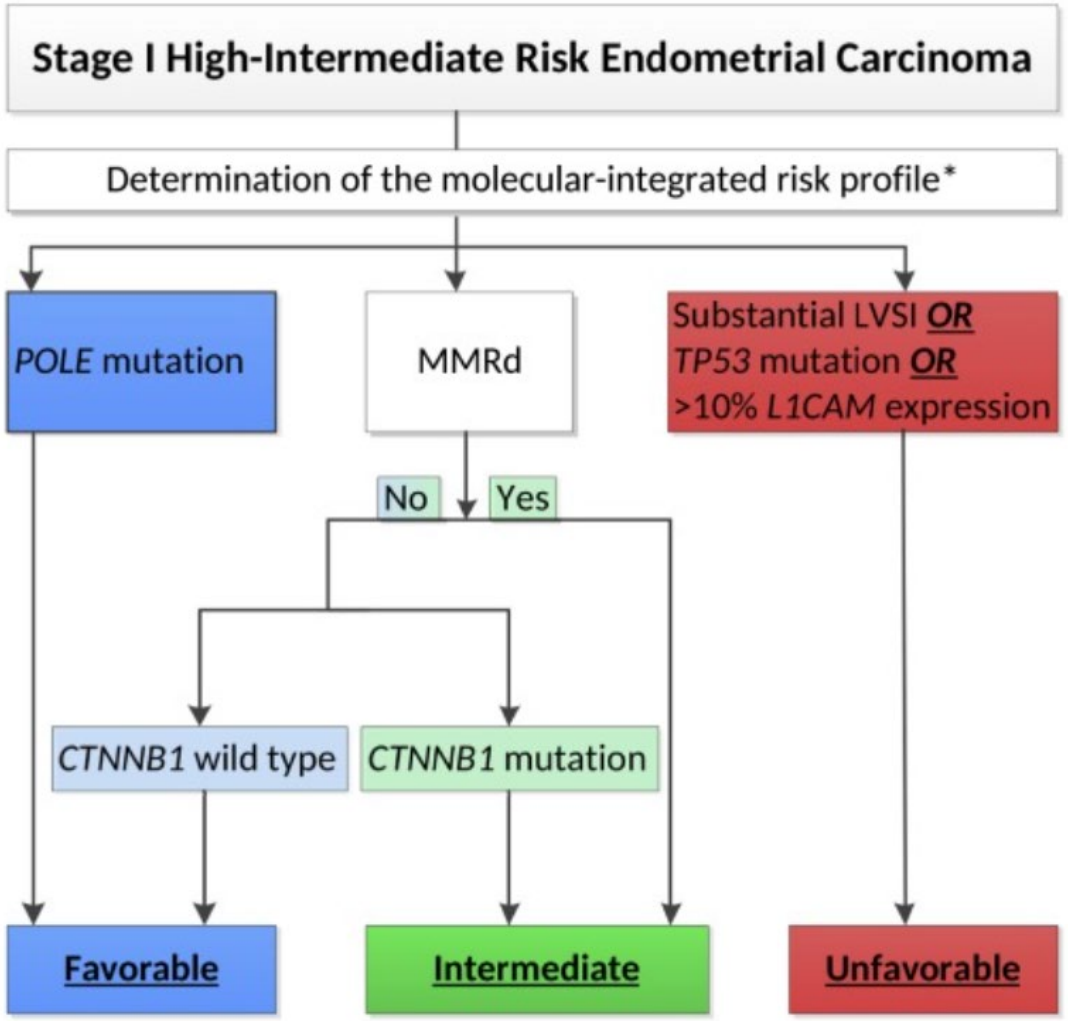
GOG 210 MMR testing

- Over 1,000 pts, all tumors assessed for MSI, MMR IHC and MLH1 methylation
- Four molecular classes identified:
  - 65% MMR normal (no MSI, no IHC defect)
    - Most commonly grade1
  - 26% epigenetic MMR defect (MSI+, MLH1 methylated)
    - Older, lower BMI, higher stage, higher grade, LVI
  - 10% probable genetic MMR mutation (MSI+ and/or IHC deficient without MLH1 methylation)
    - Higher grade, LVI
  - 2% MSI-low

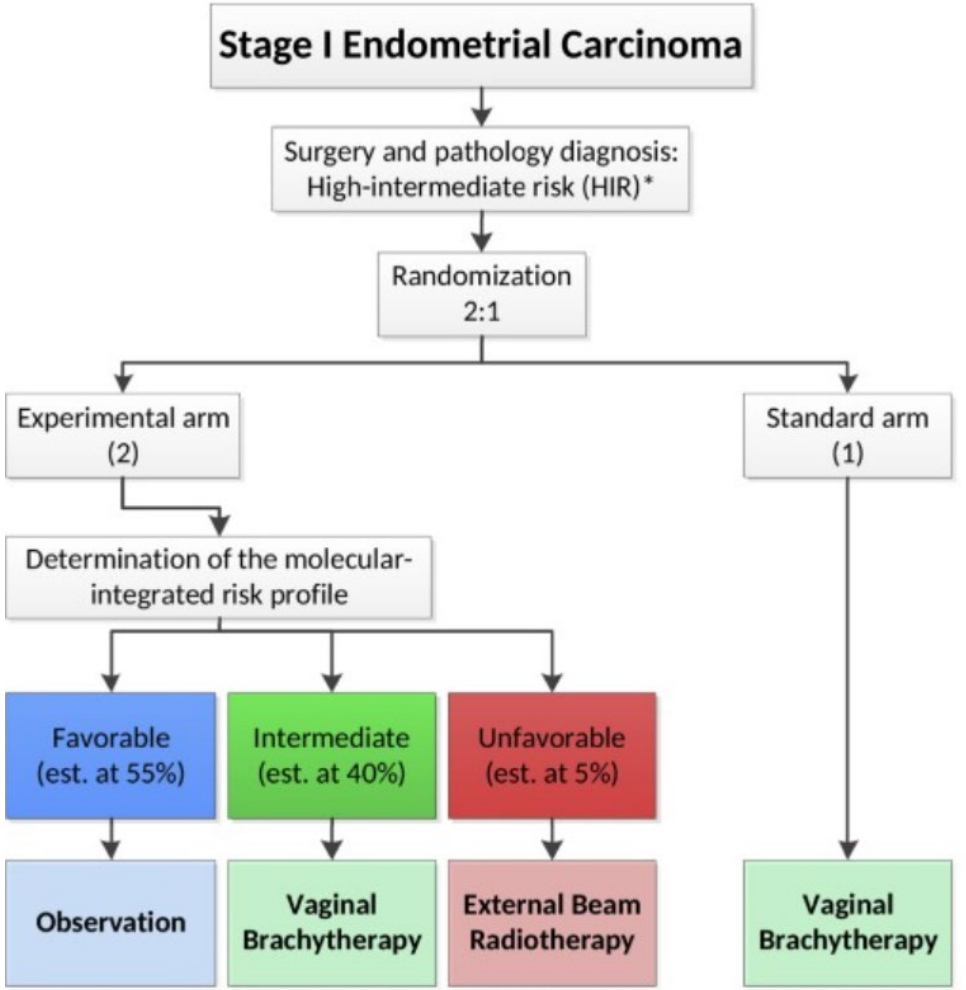
Mismatch Repair in Endometrial Cancer

- Additional data from OSU looking at pts classified as early stage high intermediate risk and found dMMR pts had a higher rate of recurrence, with notably higher distant metastases. (Backes et al. Cancer 2018)

PORTEC 4a



*Patients with multiple characteristics (double classifiers) were designated intermediate risk. MMRd = Mismatch repair-deficiency. For details, see text.



*High-intermediate risk (HIR) endometrial cancer: stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.

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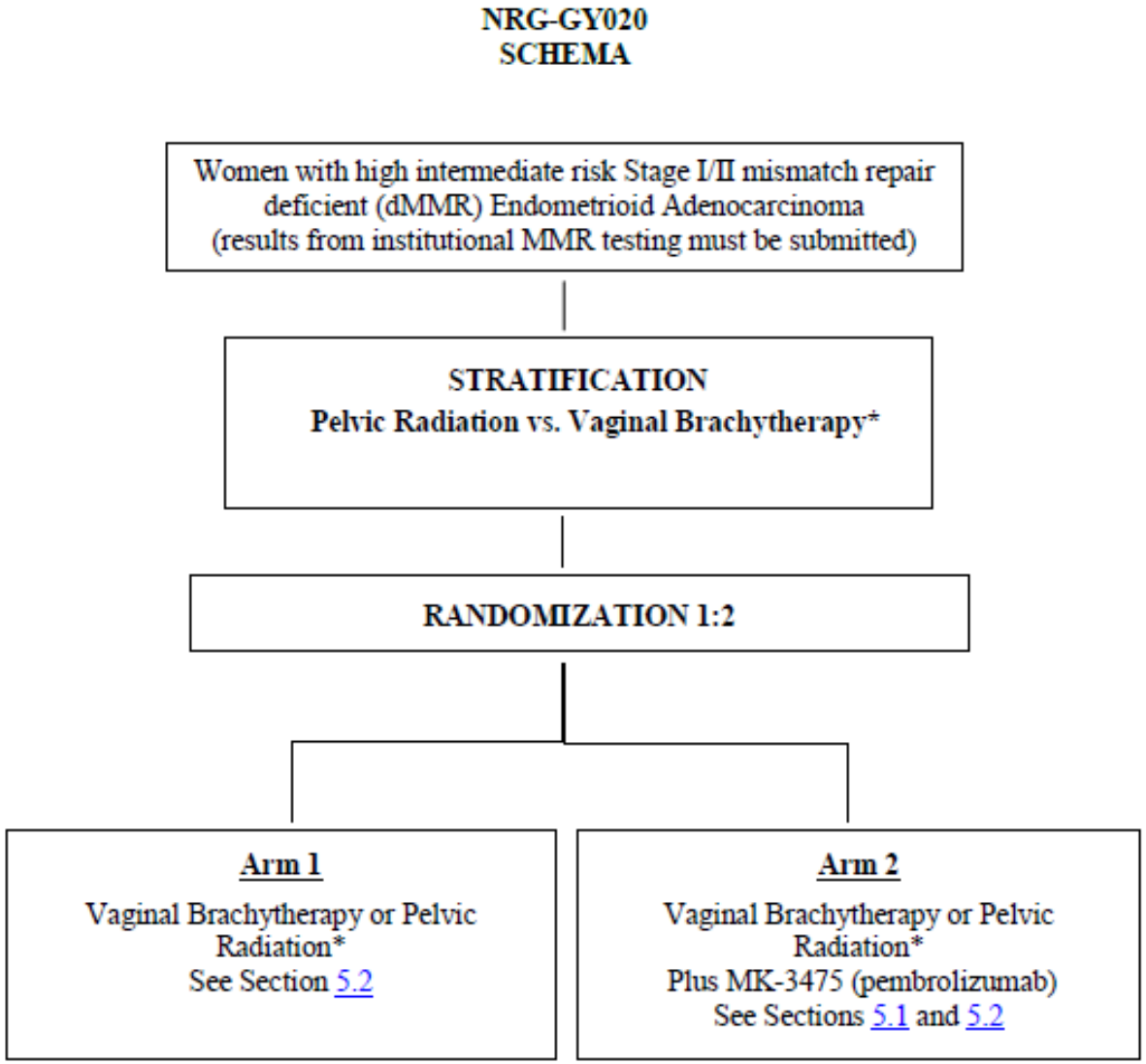
Immunotherapy for Endometrial Cancer

- GY020



Summary

- Adaptive radiotherapy and hybrid interstitial brachytherapy are decreasing dose to organs at risk in the pelvis
- Understanding of the genomics and tumor microenvironment for cervical cancer and endometrial cancer are rapidly evolving
- Major advances in clinical outcomes of locally advanced cervical cancer are on the horizon via immunotherapy
- Molecular profiling of endometrial cancer will enhance our ability to appropriate select patients for adjuvant therapy