

# Reirradiation in Cervical Cancer

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# Conflicts of interest

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- None

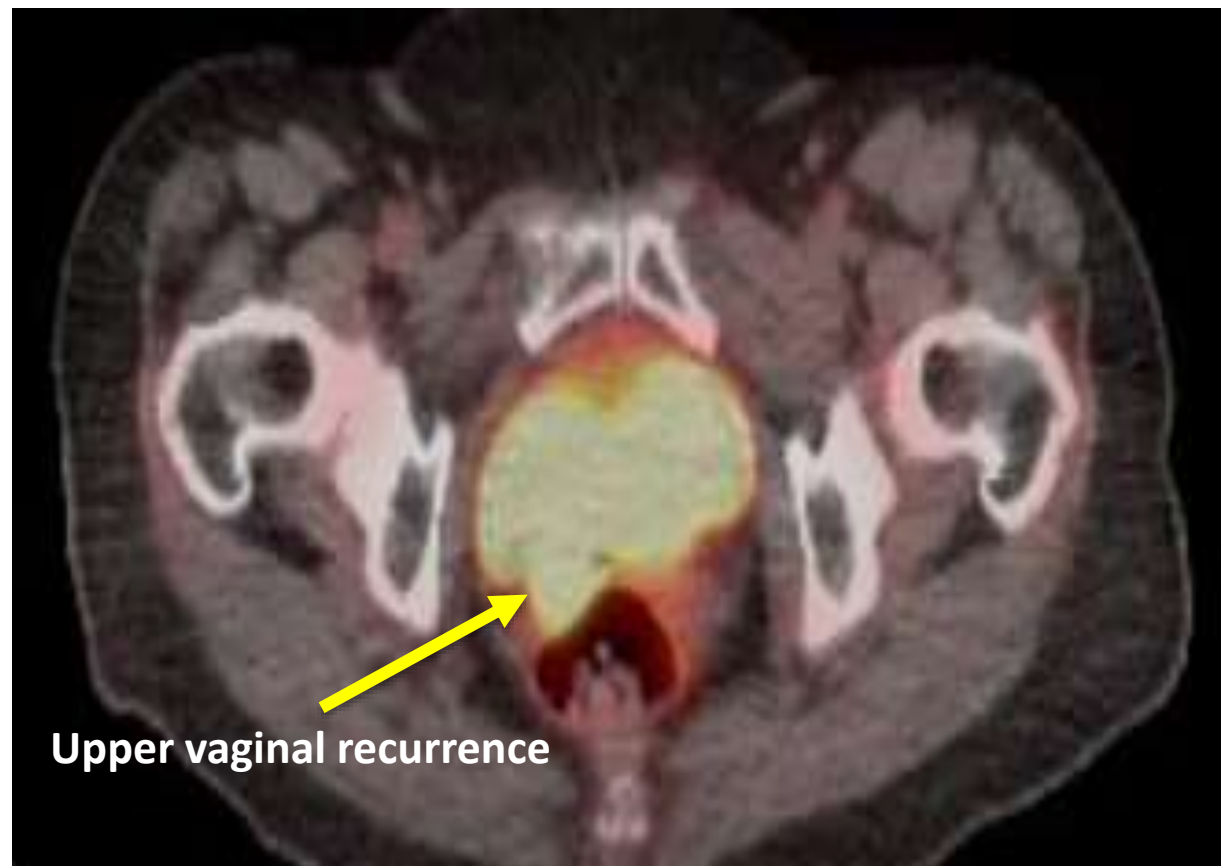
# Learning Objectives

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- Treatment options for cervical cancer central recurrences
- Clinical evidence for reirradiation with brachytherapy
- Dose/constraints/planning issues
- Future directions

## Clinical Case: Central recurrence of cervical cancer in previously irradiated field

- 69 yo, IB1G3 SCC of the cervix
- Robotic RH, Pelvic LND
- Pathology sig for 1 positive pelvic LN
- Adjuvant CRT, 45 Gy IMRT + cis
- 2 y later vaginal bleeding
- 1.5 cm right upper vaginal recurrence
- Biopsy + for recurrence
- PET/CT: no regional/distant disease



# What is the most appropriate treatment?

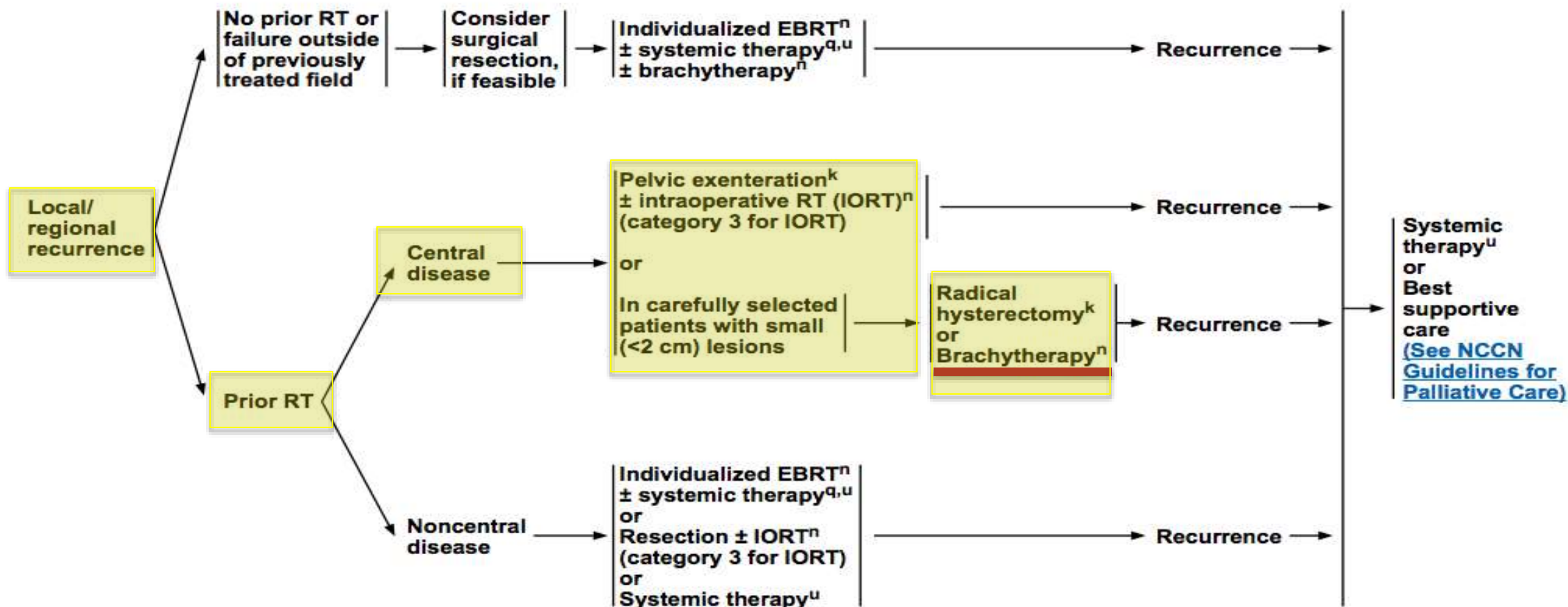


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## NCCN Guidelines Version 4.2019 Cervical Cancer

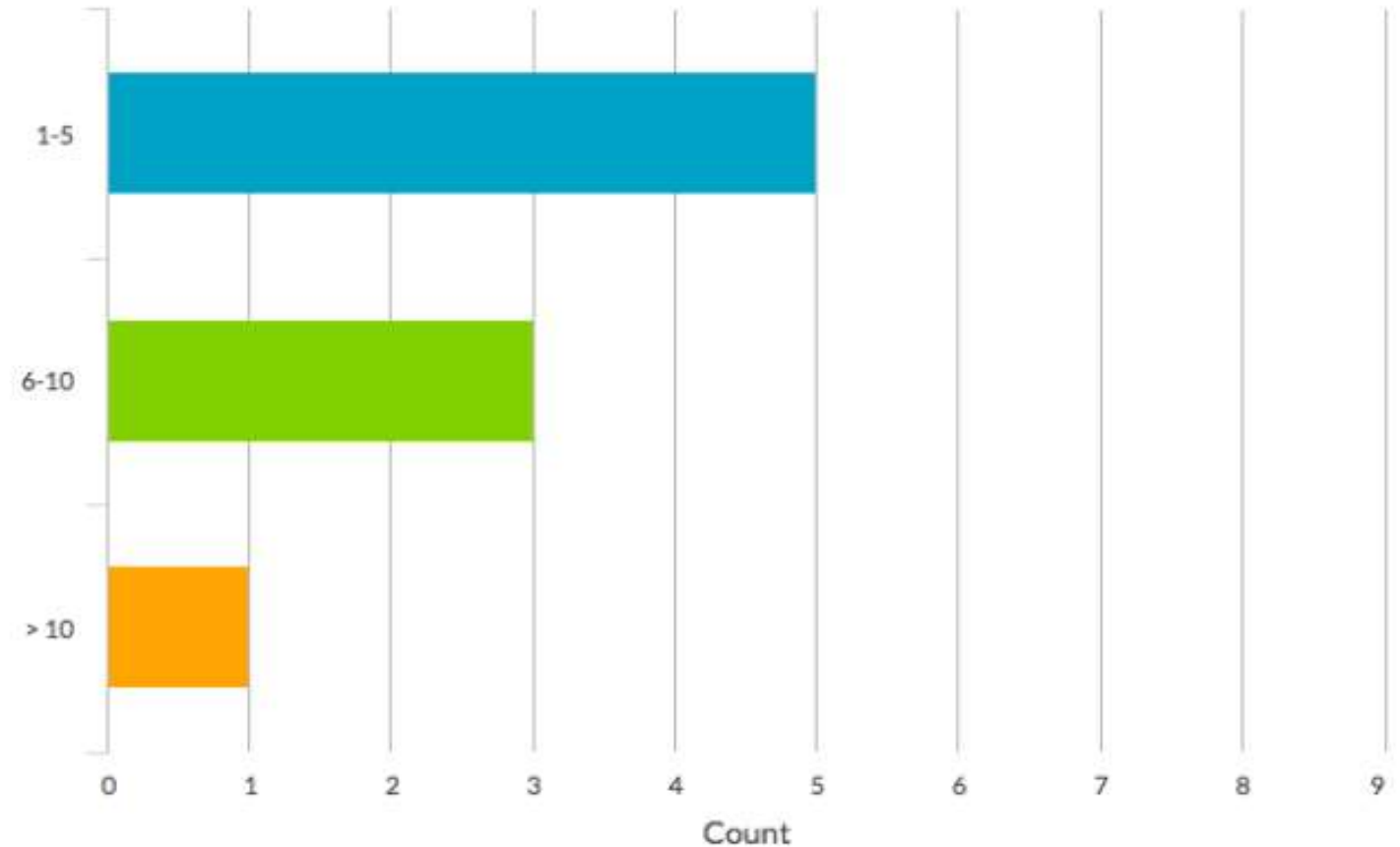
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### THERAPY FOR RELAPSE



# Reirradiation accounts for a small proportion of cases

20. How many gynecologic retreatment cases do you do a year?



- Gyn brachy reirradiation literature review
- Included 20 question survey of 9 rad oncs specializing in gyn

Sturdza A *et al.* Manuscript submitted.

# Cervical Cancer: Brachytherapy reirradiation series

Author	# of pts	Median F/U	Median Time b/w RT	Median ReRT Brachy dose (EQD2)	Outcomes	Toxicity	Comments
Mahantshetty U, 2014	30 (20 post-op)	25 m	25 m	42 Gy	2 y LC 50% 2 y DFS 42% 2 y OS 52%	G3 23%	
Umezawa R, 2018	18 (14 post-op)	18 m	15 m	D90 63 Gy	2 y LC 51% 2 y PFS 20% 2 y OS 61%	≥ G2 28%	Hgb, tumor size sig for LC
Mabuchi S, 2014	52 (35 post-op)	56 m	13 m	60 Gy	77% 2 m CR 5y OS 53%	G3/4 25%	DFI, tumor size sig for OS

Mahantshetty U *et al.* Brachytherapy. 2014.

Umezawa R *et al.* Brachytherapy. 2018.

Mabuchi S *et al.* Int J Gyn Cancer. 2014.

# Factors to consider for Re-irradiation

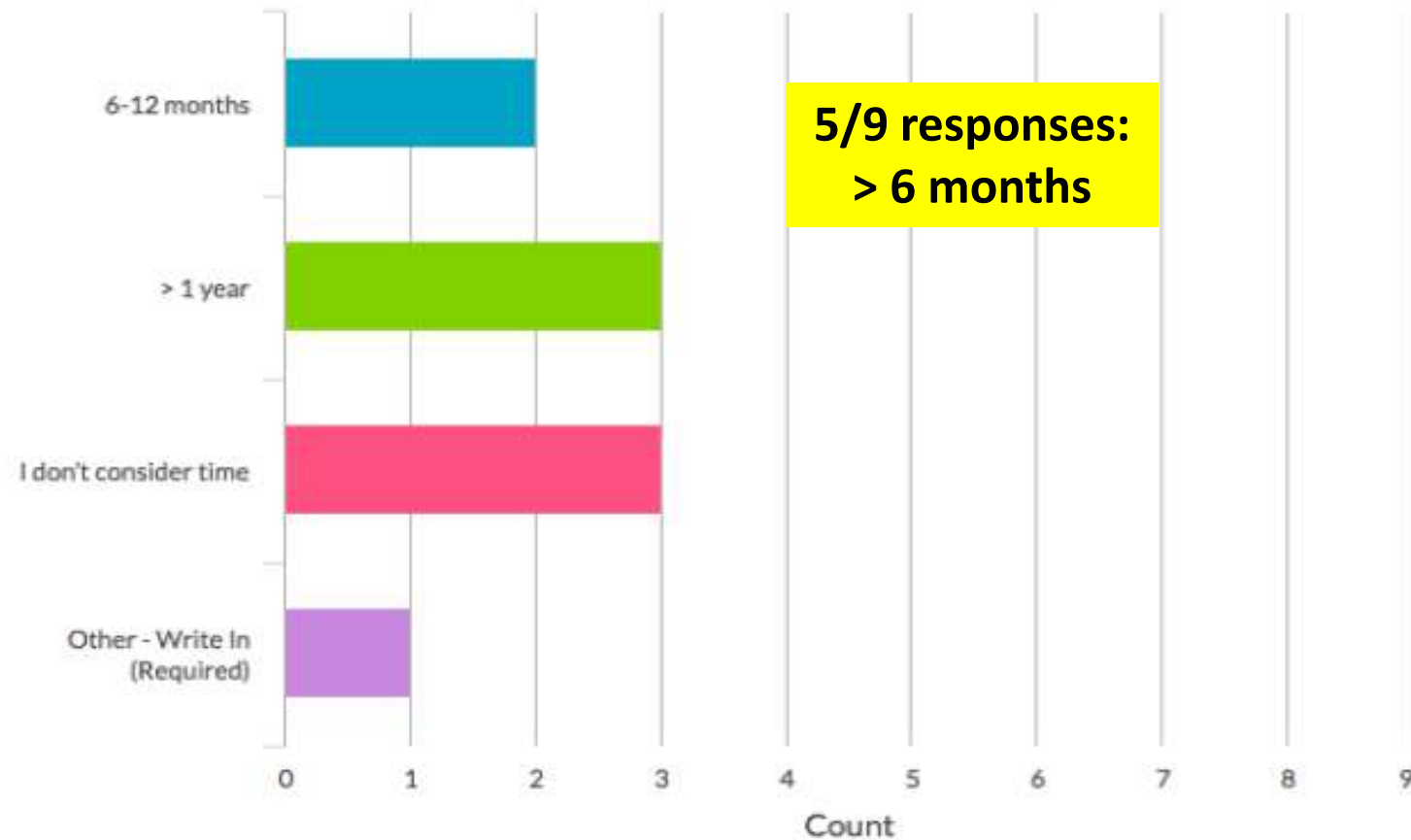
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- Performance status/Comorbidities
- Prior RT dose/field
- Time from prior RT
- Prior chemo
- Size of recurrence
- Histology (SCC vs adeno)
- Central/sidewall recurrence
- Isolated local failure vs part of regional/distant failure
- Treatment intent: palliative vs curative
- Institutional expertise to manage a complication



# Time between 1<sup>st</sup> and 2<sup>nd</sup> course of RT

14. Is there a minimum time that you require between a person's prior radiation and considering retreatment?



Sturdza A *et al.* Manuscript submitted.

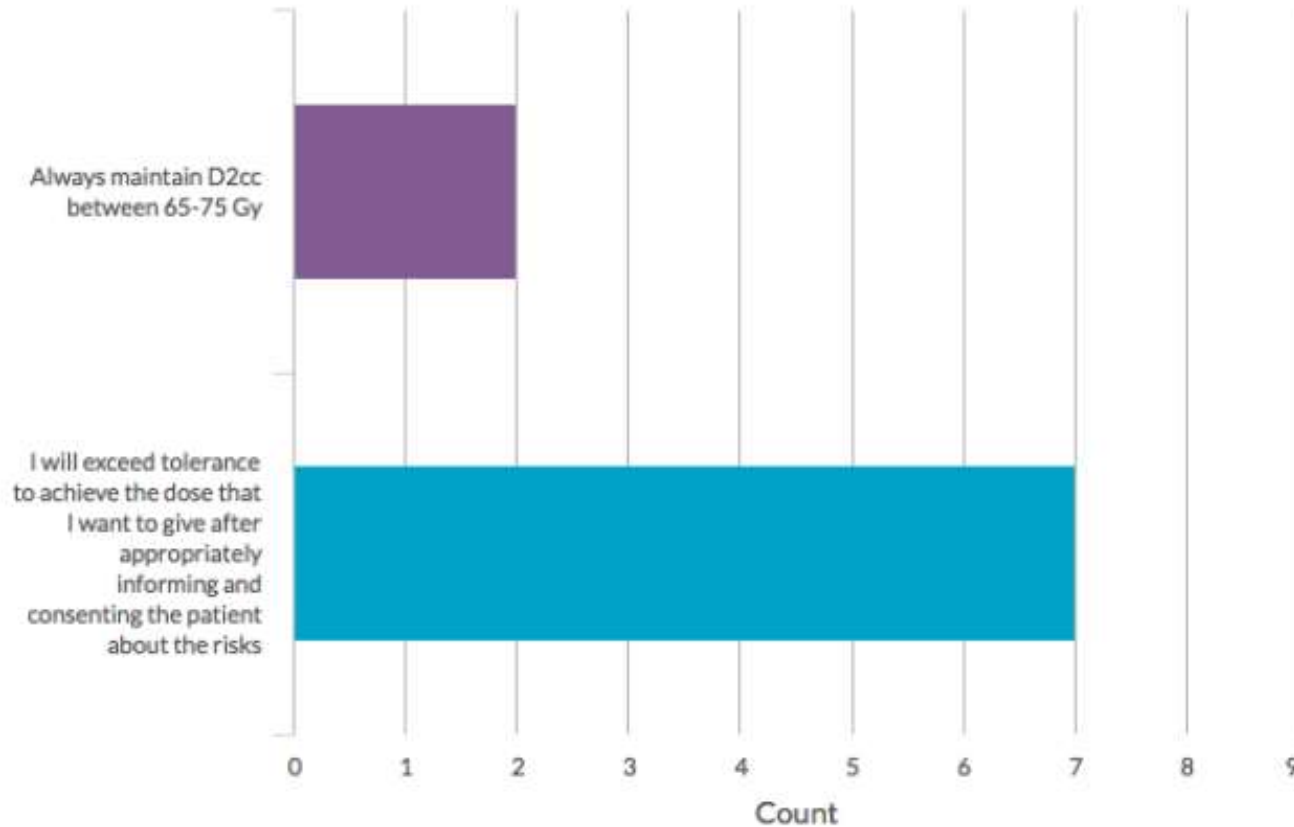
# Can you “forget” prior RT dose after a certain amount of time?

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- 5/9 responded NO
- 4 other responses:
  - 10% per year
  - 50%
  - 30% after 5 years and 50% after 10 years
  - Allow cumulative D2cc rectum to 75 Gy (rather than 65) and bladder to 90 Gy (rather than 80)

# Constraints – Rectum

16. For the rectum what dose constraint do you utilize in the retreatment setting?



If you exceed tolerance, do you have a hard stop cumulative dose for the rectum?

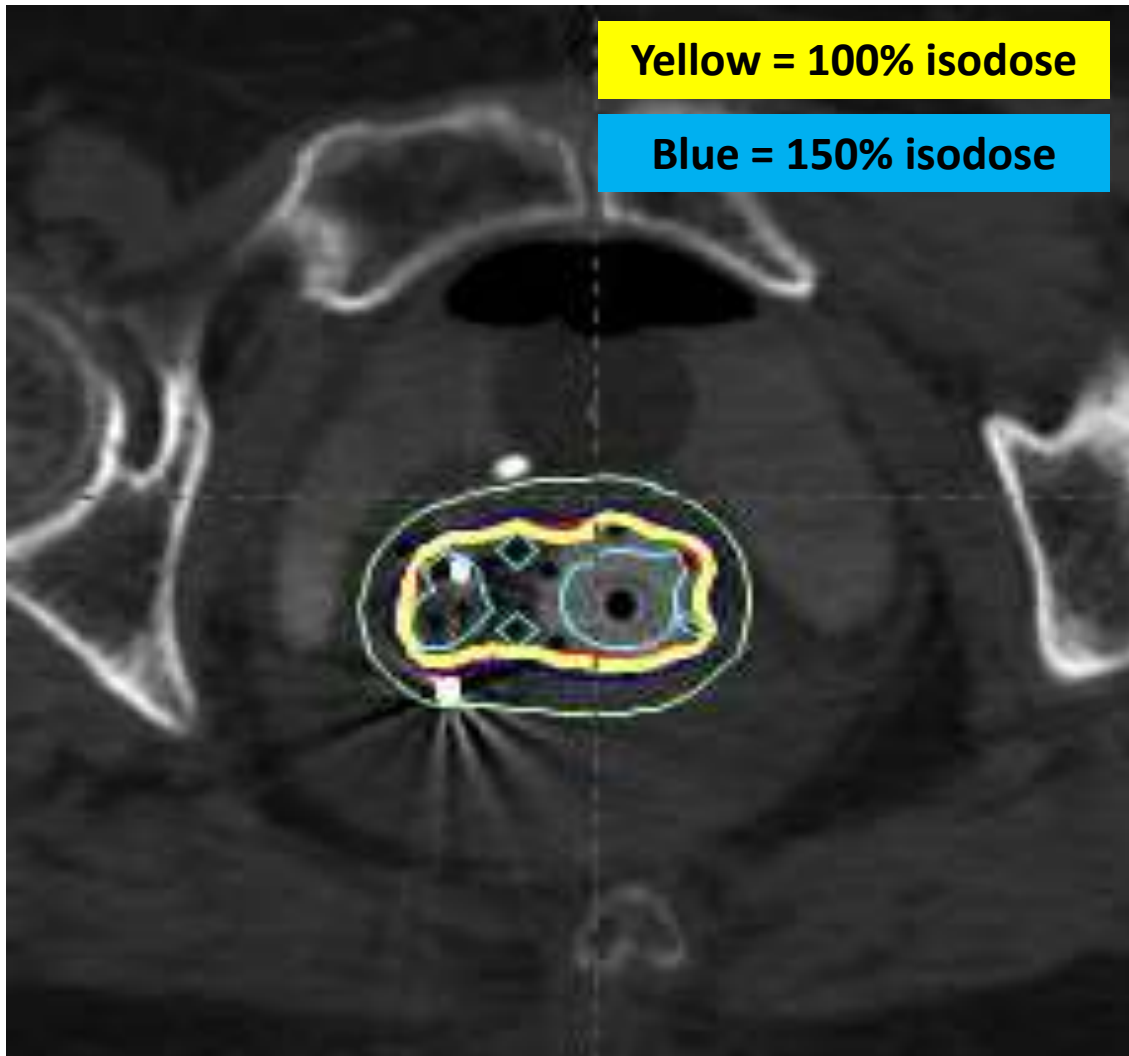
5 responses: D2cc < 80-85 Gy

2 responses: No clear upper limit

For bladder 6 responses: D2cc < 90-100 Gy

Sturdza A *et al.* Manuscript submitted.

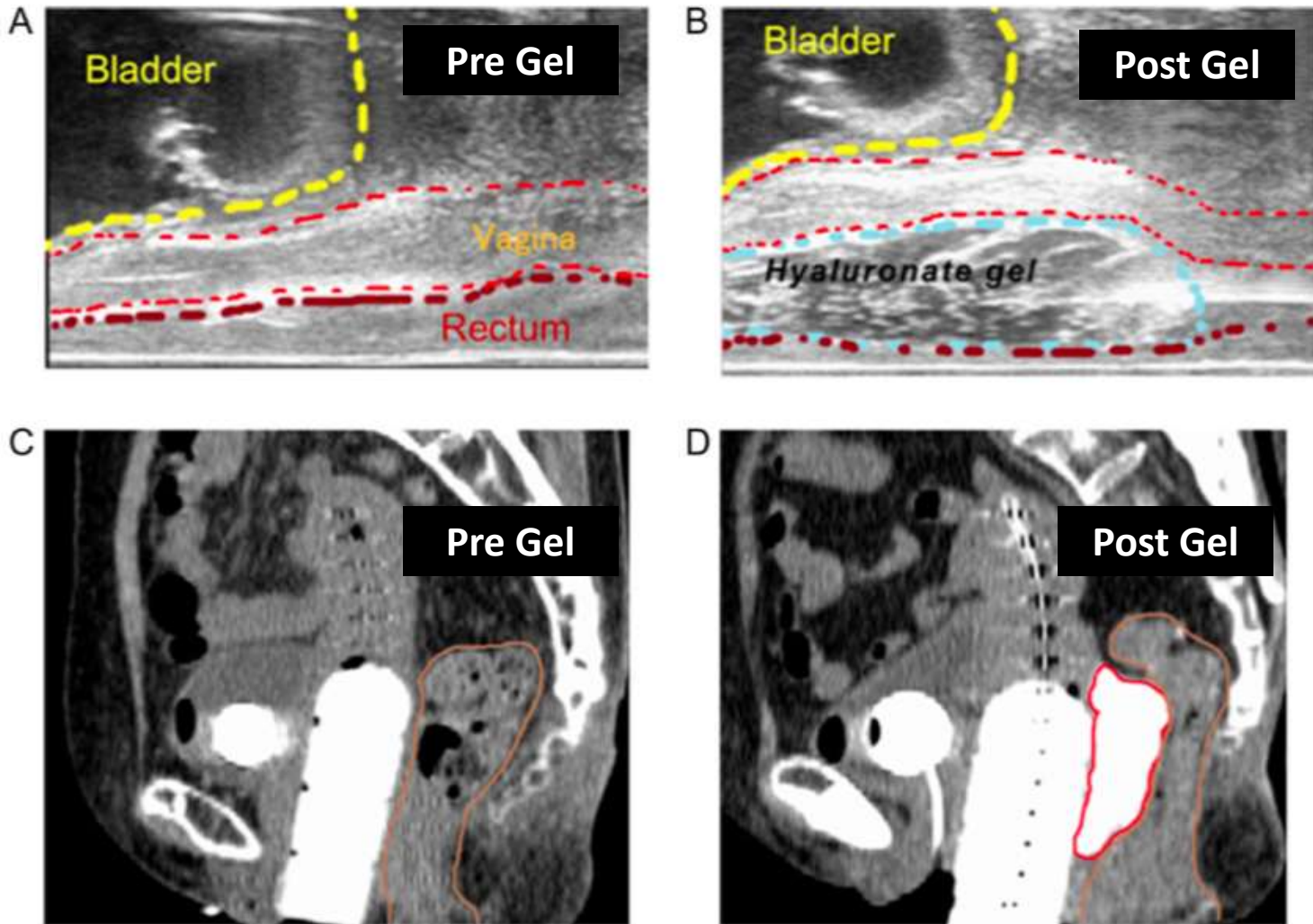
# Dose and Planning



- Dose
  - Goal was EQD2  $> 40$  Gy,  $< 50$  Gy
  - D2cc rectum/sigmoid  $< 75$  Gy<sup>1</sup>
  - D2cc bladder  $< 90$  Gy<sup>1</sup>
- Planning
  - Weighed tandem heavily to limit hot spots in vaginal mucosa

1. Ling D *et al.* Gyn Onc. 2019.

# Improving the therapeutic ratio: Normal tissues



- 36 Gyn patients
  - 30 definitive, 6 re-RT
- Mean 20 cc of hyaluronate gel
- No  $\geq$  G3 acute/late SE from gel at median 222 days

**Rectum D2cc pre vs post gel:  
4.8 vs 3.7 Gy ( $p < 0.001$ )**

# Improving the therapeutic ratio: Radiosensitizing tumor tissue, Pembro?

## Optimism?

- Pembrolizumab
  - FDA approved recurrent/metastatic cervical cancer
    - Keynote 158 (Chung H et al, JCO, 2019)
    - ORR ~12–14%
  - FDA approved for MSI-High and dMMR metastatic/unresectable tumors w/ no standard therapy options
    - Pooled data from 5 Keynote trials
    - ORR ~40%

## Caution?

### Dose-limiting Urinary Toxicity With Pembrolizumab Combined With Weekly Hypofractionated Radiation Therapy in Bladder Cancer

Alison Claire Tree, FRCR, MD(Res),<sup>\*,†</sup> Kelly Jones, MSc,<sup>\*</sup>  
Shaista Hafeez, FRCR, PhD,<sup>\*,†</sup> Mansour Taghavi Azar Sharabiani, PhD,<sup>\*</sup>  
Kevin Joseph Harrington, FRCR, PhD,<sup>\*,†</sup>  
Susan Lalondrelle, FRCR, MD(Res),<sup>\*,†</sup> Merina Ahmed, FRCR, MD(Res),<sup>\*,†</sup>  
and Robert Anthony Huddart, FRCR, PhD<sup>\*,†</sup>

- Trial stopped after 5 patients
  - 3 pts G3 GU, 1 pt G4 rectal perforation

Tree A et al. IJROBP. 2018.

# Improving the therapeutic ratio: Radiosensitizing tumor tissue, Bevacizumab?

- GOG 240 – chemo doublet + bev
  - 14.5% fistula rate (any grade)
  - All patients with fistula had prior RT

## **Increased Bowel Toxicity in Patients Treated With a Vascular Endothelial Growth Factor Inhibitor (VEGFI) After Stereotactic Body Radiation Therapy (SBRT)**

Brandon M. Barney, MD,\* Svetomir N. Markovic, MD, PhD,<sup>†</sup> Nadia N. Laack, MD,\* Robert C. Miller, MD,\* Jann N. Sarkaria, MD,\* O. Kenneth Macdonald, MD,<sup>†</sup> Heather J. Bauer, RN,\* and Kenneth R. Olivier, MD\*

**6 m estimate of SBI in 26  
pts getting VEGFI w/n 3 m  
of SBRT was 38%**



# Conclusions

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- Reirradiation with brachytherapy reasonable to consider in select cases
- Based on published data:
  - Expected 2 y local control ~50%
  - Expected  $\geq$  G3 toxicities ~25%
- With an individualized dose and tighter constraints may be able to maintain similar local control (~50%) but reduce toxicities
- Late toxicities happen late
- Even if you achieve local control these patients are still at high risk of elsewhere failures