Medically Inoperable Endometrial Cancer

Adannia Ufondu, MS-4

Resident Mentor: Bailey Nelson, PGY-4

Faculty Advisor: Teresa Meier, MD

University of Cincinnati, Department of Radiation Oncology

Cincinnati, Ohio

Overview

- Case Presentation
- Epidemiology
- Work-up Pearls
- Staging
- Medical Management
- Radiotherapy Management
- Applicators for HDR Brachytherapy
- Dose Specification and Dosimetry
- Follow-up Recommendations
- Management of Recurrent Disease After Definitive Radiation

Case Presentation

HPI: 73-year-old woman presented to ED after falling in the shower. She reported vaginal bleeding for the last 4 months with passage are large blood clots. She had not seen a physician in many years.

Gynecologic History: menopause age 50, G1P1, used OCPs for 1 year, no hormone therapy replacement

PMHx: Obesity (BMI 40), HTN, venous stasis of bilateral lower extremities causing lymphedema

Surgical Hx: non-contributory

Medications: Norvasc, Colace, Ferrous sulfate

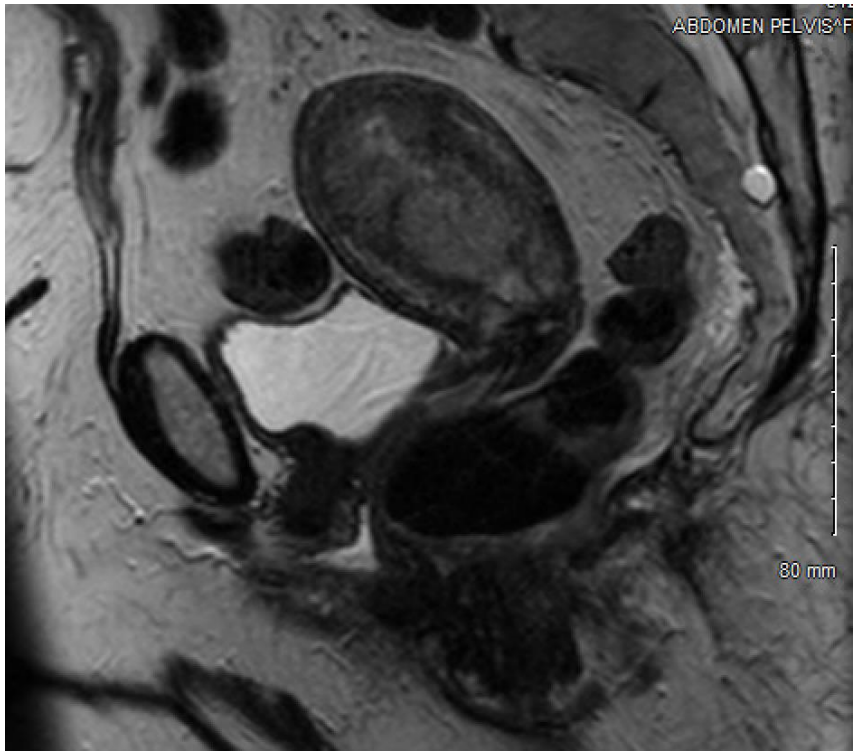
Social History: non-smoker

Case Presentation

- Transvaginal Ultrasound
  - Uterus measuring 9.4 x 5.5 x 6.7cm for a total volume of 181mL. Endometrial stripe thickness is ill defined with echogenicity extending into myometrium. Intramural fibroid in left lower uterine segment measuring 3.2 x 2.6cm
- Endometrial Biopsy (EMB)
  - Benign endocervical polyp with extensive squamous metaplasia.
- Dilation and Curettage (D&C) with hysteroscopy
  - Pathology: fragments of endometrioid adenocarcinoma, FIGO grade 3. Additional fragments of endometrium with hyperplasia and endometrial intraepithelial neoplasia
- Cervical biopsies
  - Negative for malignancy
- **Patient was deemed medically inoperable due to her morbid obesity**

Case Presentation

- MRI Pelvis
  - Central uterine neoplasm measuring 6.5 x 6 x 3.5 cm with deep myometrial invasion to within 5 mm of the uterine serosal surface without extrauterine invasion
  - No pelvic metastatic disease identified
- CT Chest
  - No intrathoracic disease



MRI Sagittal T2

Epidemiology

- Endometrial carcinoma is the most common gynecologic cancer in the United States
- It is estimated that there will be 66,570 new cases of endometrial cancer in 2021
- According to SEER data, ~3.1% of women will be diagnosed with uterine cancer at some point in their life

Medically Inoperable Patients

- Standard upfront treatment for endometrial adenocarcinoma is a TAH-BSO; however, some patients are unable to undergo surgery due to:
  - Medical comorbidities
    - Cardiovascular disease
    - Pulmonary disease
    - Venothromboembolic disease
    - Cerebrovascular accidents
    - Hemophilia
  - Morbid obesity
  - Performance status is a key factor in determining suitability for anesthesia

Work-up Pearls for Medically Inoperable Patients

- TVUS to evaluate endometrial thickness
- EMB or D&C if EMB is non-diagnostic
  - Pathology
    - Grade and histology are important factors
- MRI to assess the depth of myometrial invasion
  - Contrast-enhanced and T2 weighted MRI have been shown to have negative predictive values greater than 85% for identifying deep myometrial involvement
- CT Chest/Abdomen/Pelvis or PET-CT to assess nodal or distant disease

Staging for Medically Inoperable

- Clinical staging relies on pelvic examination
  - Sounding the uterus: assess size of cavity
  - Rectal/bimanual exams: evaluate parametria and adjacent organs

Clinical staging system for endometrial cancer

- Stage I—confined to the uterus
  - IA—Uterine cavity sounds to <8 cm
  - IB—Uterine cavity sounds to >8 cm
- Stage II—Involves the corpus and cervix
- Stage III—Parametrium, adnexa, or vagina but confined to true pelvis
- Stage IV
  - A—Involving local structures (rectum/bladder)
  - B—Metastatic

Medical Management

- When using hormonal therapy, imaging should show no evidence of cervical invasion, pelvic or aortic lymphadenopathy, or involvement of the ovaries
- Oral progestin
  - Ushijima et al. cites regression in 55% of patients with presumed early-stage disease.
  - Can be associated with recurrence rates of 25% or higher
- Levonorgestrel-releasing IUD
  - Used in precancerous and Grade 1 endometrial adenocarcinoma
  - Can be used in combination with oral progestin in morbidly obese patients as a bridge until sufficient weight loss for safe surgery is achieved

Management with Radiotherapy

- Stage I, Grade 1 or 2 endometrial cancer with minimal myometrial invasion
  - Brachytherapy alone
    - GTV = gross disease and endometrial lining (delineated on MRI)
      - EQD_2 of 80-90 Gy
    - CTV = whole uterus extending out to uterine serosa
      - D_{90} EQD_2 of 48-62.5 Gy

HDR total dose (Gy)	HDR dose fractionation	EQD_2 (Gy)
36	6 Gy × 6	48
38.4	6.4 Gy × 6	52.5
36.5	7.3 Gy × 5	52.6
34	8.5 Gy × 4	52.4
40–50	5 Gy × 9–10	50–62.5

Management with Radiotherapy

- Stage I endometrial cancer with deep myometrial invasion (>50% of myometrial depth)
  - EBRT 45-50 Gy (uterus + nodal areas at risk) + Brachytherapy
    - GTV = gross residual disease after EBRT + endometrial lining
      - EQD_2 80-90 Gy
    - CTV = whole uterus to serosal surface, including cervix and upper 1-2 cm of vagina
      - EQD_2 65-75 Gy

EBRT (Gy)	HDR total dose (Gy)	HDR dose fractionation	EQD_2 (Gy)
45	19.5	6.5 Gy × 3	71.1
45	18.9	6.3 Gy × 3	69.9
45	20.8	5.2 Gy × 4	70.6
45	25	5 Gy × 5	75
45	17	8.5 Gy × 2	70.5
50.4	12	6.0 Gy × 2	65.6
50.4	22.5	3.75 Gy × 6	75.3

Management with Radiotherapy

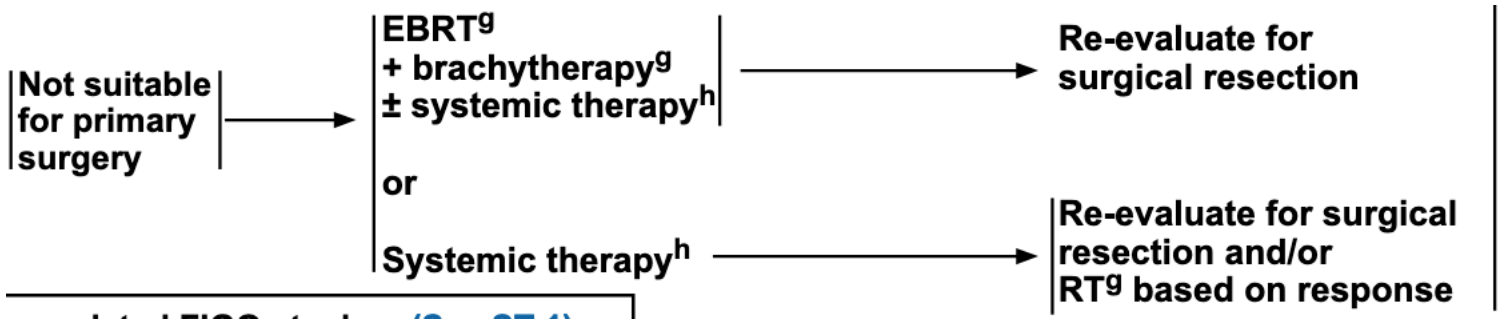
- Stage II endometrial cancer (involves cervix)
  - EBRT
    - Consider adding paracervical and pre-sacral LNs
  - Brachytherapy
    - Applicator should include ring or ovoids to deliver dose to cervix

Management with Radiotherapy

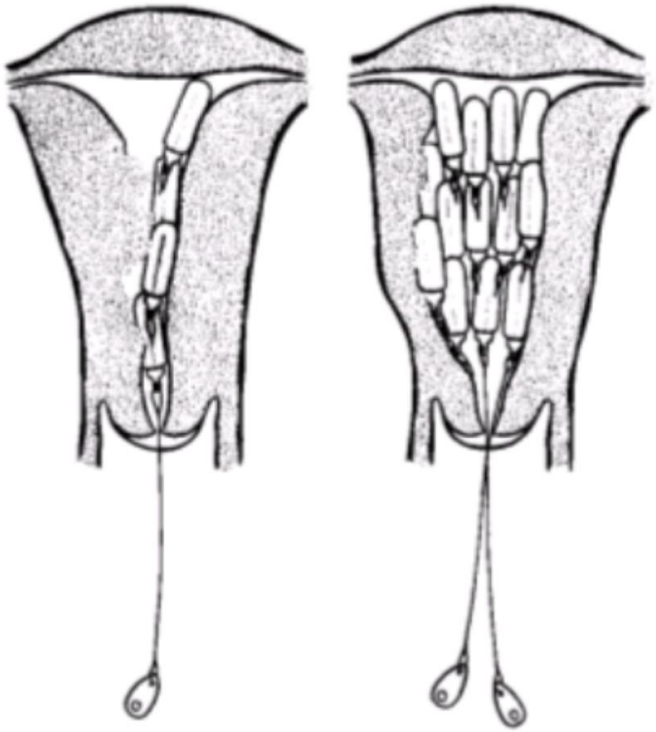
- Stage III endometrial cancer
  - EBRT + Brachytherapy
  - SIB with IMRT to treat enlarged lymph nodes
    - Or sequential boost to respect normal tissue tolerances (usually small bowel)
    - 55 Gy in 25 fractions

Medically Inoperable Endometrial Cancer: High-Risk Histologies

- Histology
  - Serous carcinoma
  - Clear cell carcinoma
  - Carcinosarcoma
  - Undifferentiated carcinoma
- Consider the addition of systemic therapy



Heyman Capsules



Y-Tandem

Triple Tandem

Brachytherapy Applicators

Brachytherapy Applicators

- There are several techniques available, including single applicator, dual (Y), and triple tandems. Choice of applicator should be specific to patient.
- Single tandem applicators may be less effective, especially for patients with larger uteri.
- Small Dosimetry study by S.B. Johnson et al. of dose planning for 3 patients with inoperable cancer and different uterine shapes, using single, dual, and triple tandems found:
  - Triple tandem applicator improved dose coverage to the uterus regardless of uterine shape for point-based planning and minimized dose to OARs for volumetric planning
  - Regardless of point or volumetric-based normalization, uterine size and shape and proximity of OAR are important considerations for tandem selection
  - Patient with closer OARs received more dose to OARs using single tandem applicator

Dose Specification and Dosimetry

- Volume-based planning preferred over point-based approach
- If MRI is not available or feasible, target-based planning is limited to the CTV (no GTV)
- Best data available for tolerable dose to OARs suggest
  - D_{2cc} Sigmoid and Rectum be limited to 70-75Gy
  - D_{2cc} Bladder to 80-100 Gy

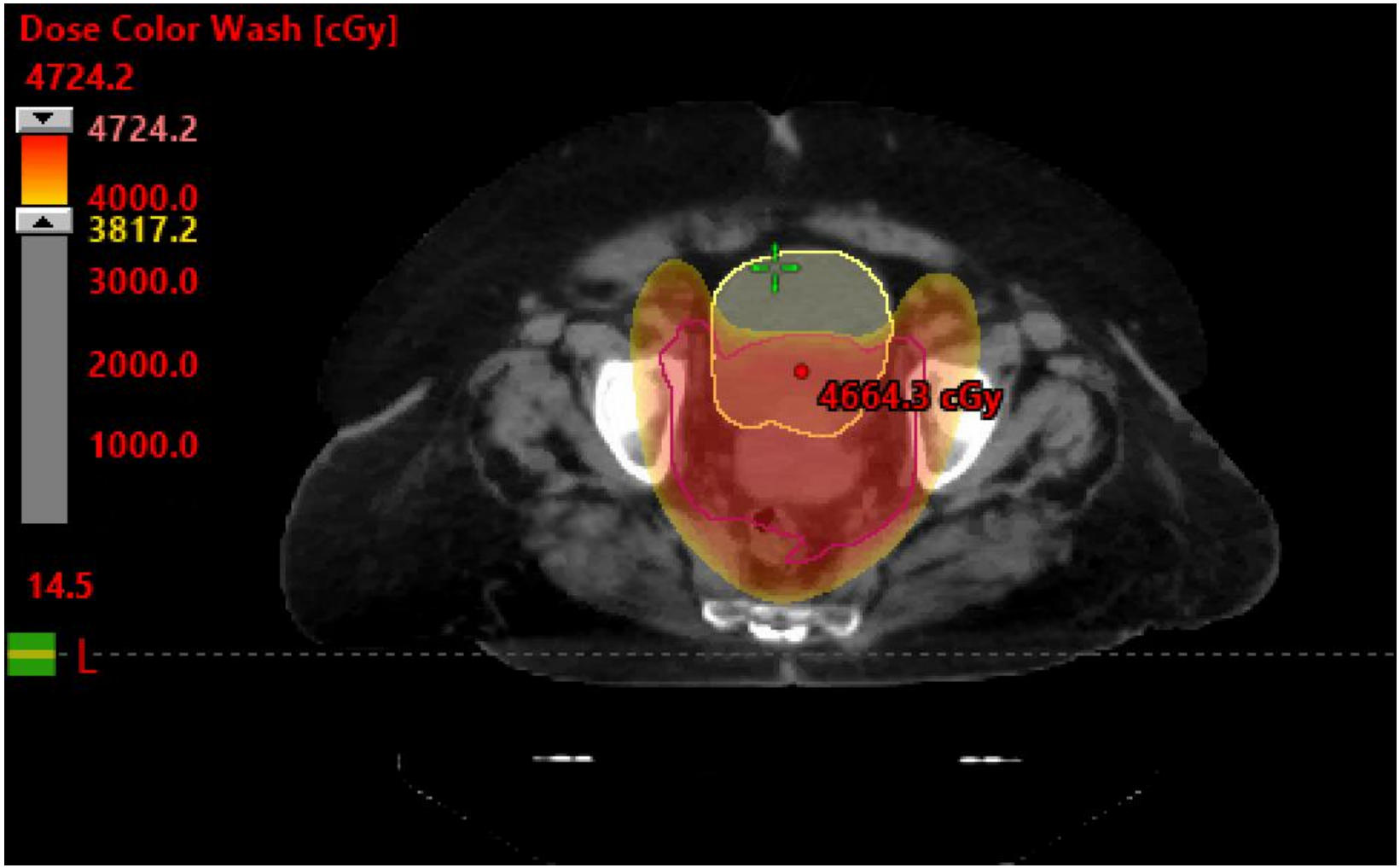
Potential Treatment Side Effects

- Acute complications
  - Procedural
    - Uterine perforation: 13.7% rate of uterine perforation detected with CT
  - Fatigue
  - Loose stool/diarrhea
  - Vaginal irritation/bleeding
  - Irritative urinary symptoms
- Late complications
  - Bowel injury
    - Proctitis
    - Sigmoid stricture
    - Bowel obstruction and fistula
  - Chronic urinary symptoms
  - Pelvic insufficiency fracture
  - Chronic diarrhea
  - Vaginal stenosis
  - Secondary malignancy

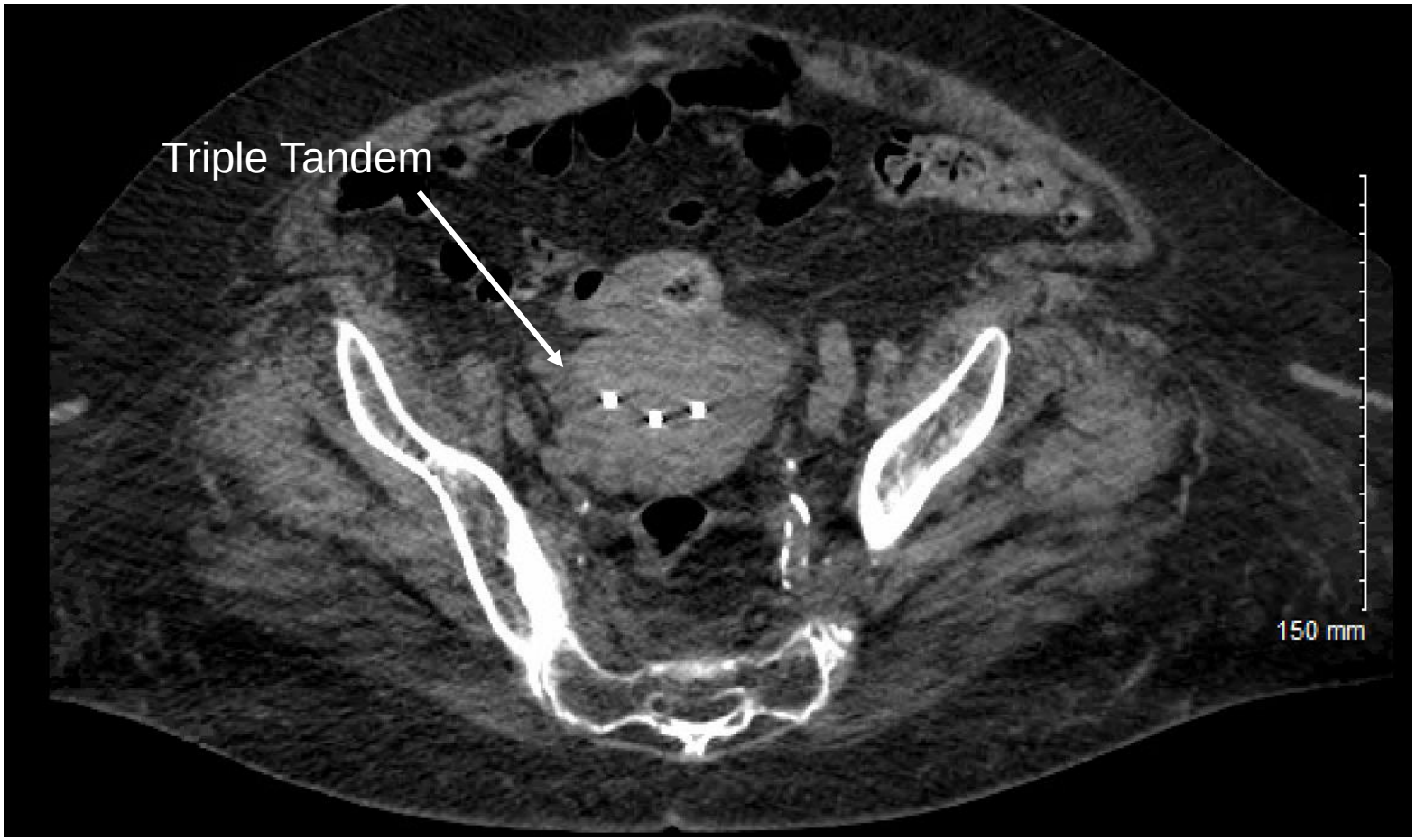
Case: Treatment

- Patient diagnosed with Stage I endometrioid adenocarcinoma with deep myometrial invasion
- Treated with combination of EBRT + Brachytherapy
  - EBRT 45 Gy in 25 fractions to the uterus and pelvic lymph nodes with TomoTherapy
  - HDR Brachytherapy with a triple tandem
    - Prescription: 6.5 Gy x 3 fractions
    - HR-CTV D_{90}: 77.3 Gy
    - GTV D_{90}: 83 Gy
    - Bladder D_{2cc}: 64.9 Gy
    - Sigmoid D_{2cc}: 65.8 Gy
    - Rectum D_{2cc}: 50.4 Gy

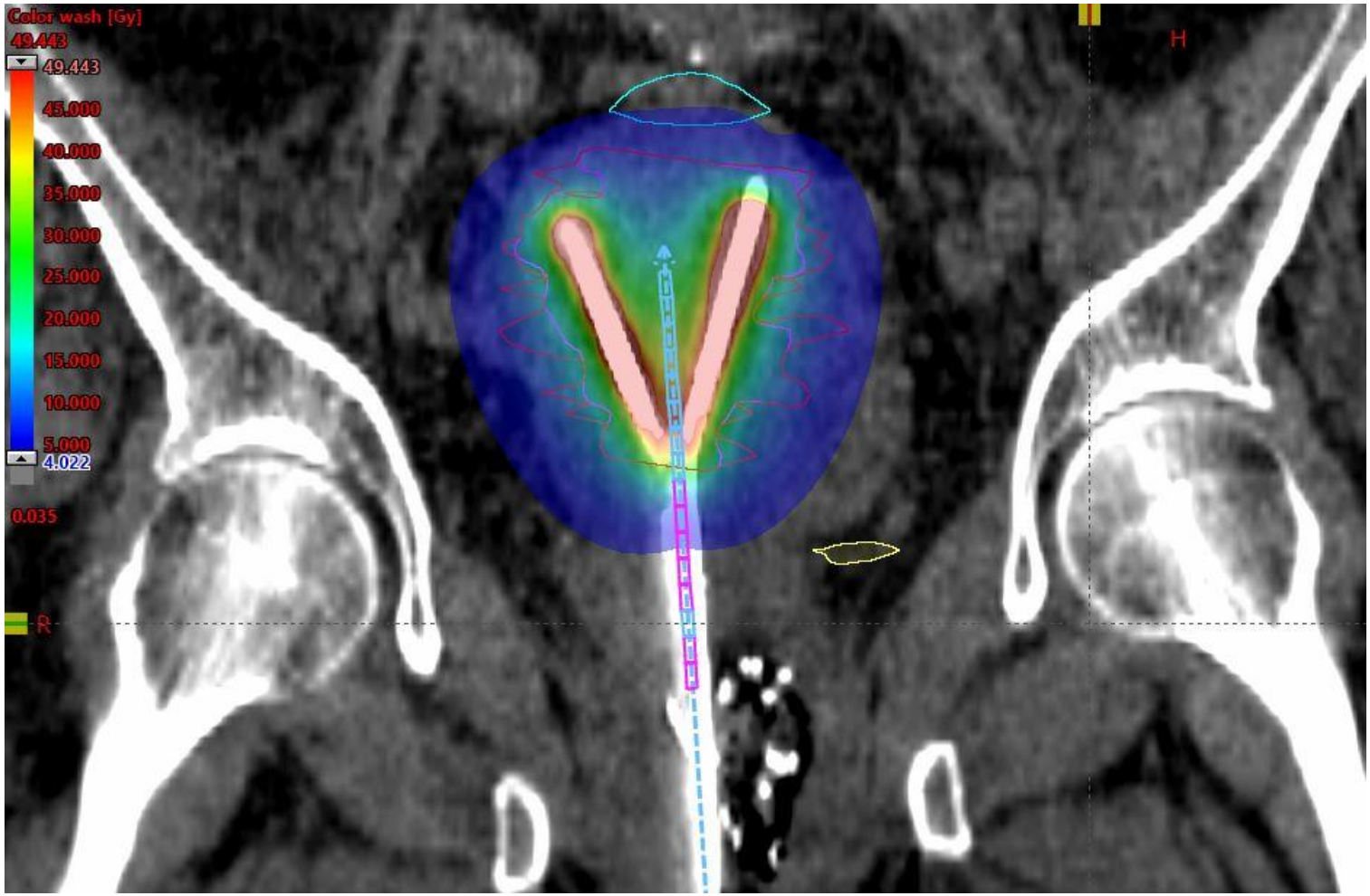
Treatment Plan: EBRT



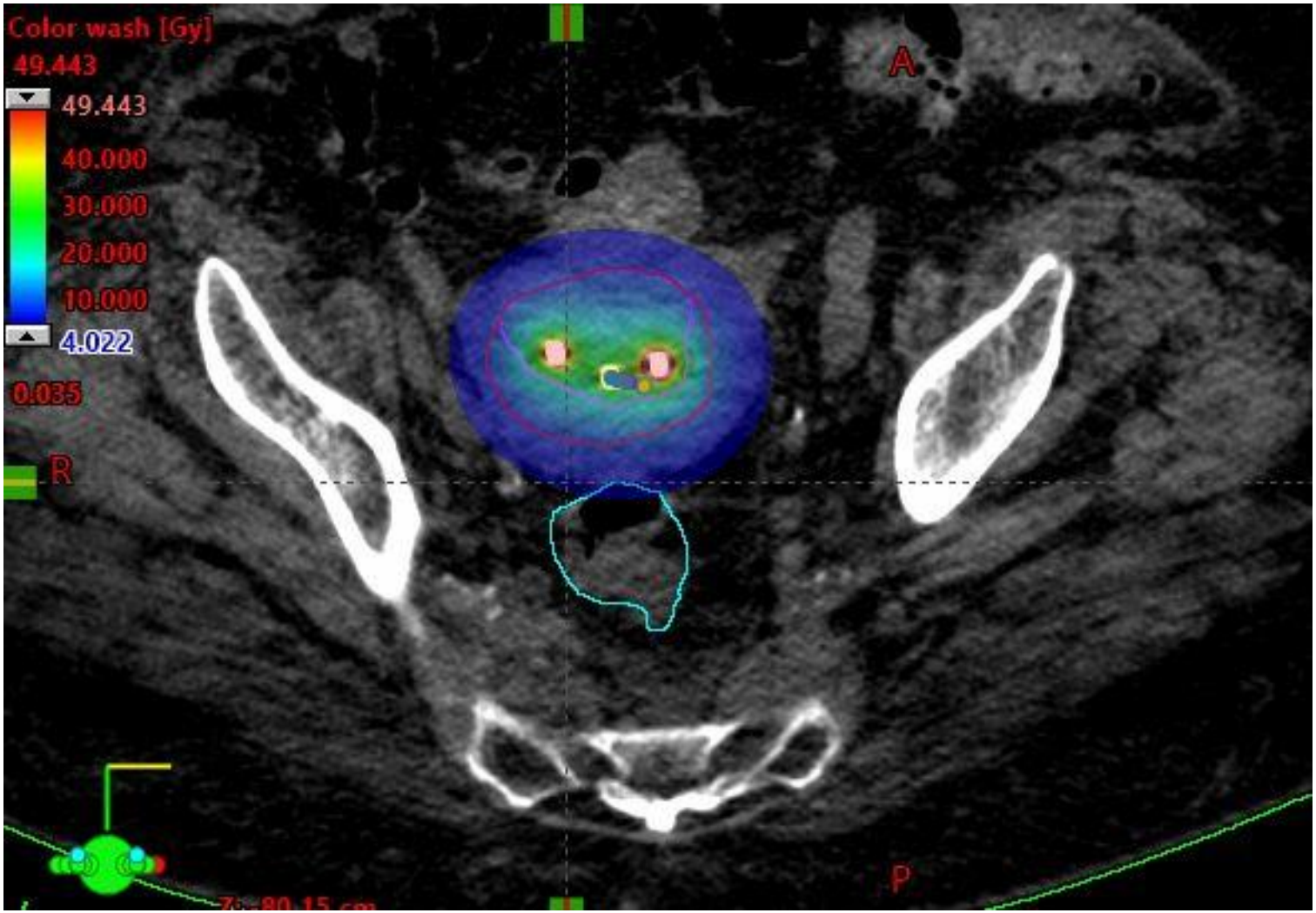
Treatment Plan: Brachytherapy



Treatment Plan: Brachytherapy



Treatment Plan: Brachytherapy



Follow-Up

- Relapses most often occur within the first 3 years after treatment with 70% of recurrences being symptomatic.
- Medically inoperable patients are more likely to succumb to their medical comorbidities.
- Recommended Surveillance
  - Pelvic and speculum exams every 3 to 6 months
  - After 5 years of recurrence-free follow-up, may consider returning to annual exams

Case: Follow-Up

- Patient reported resolution of bleeding, clots, and discharge 1 month following radiation therapy
- She had some intermittent diarrhea and constipation. She reported no pelvic pain.
- Post-treatment PET CT obtained 3 months after treatment
  - Focal mild FDG uptake in central uterus likely related to post-treatment inflammation
- CT Abdomen/Pelvis obtained 3 months before death (for other reasons) showed no residual disease

Management of Recurrent Disease After Definitive Radiation

- Suspected recurrence
  - Obtain imaging and biopsy
  - Review realistic salvage or palliation treatment options with the patient
    - For patients with symptomatic recurrence, the use of palliative radiation may be beneficial for severe bleeding or pain
    - If ER/PR+, hormonal therapy is first-line
    - Uterine artery embolization may be used for treatment of hemorrhage
    - Can consider surgery if medical status has improved

References

- Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007;25:2798e2803.
- Schwarz JK, Beriwal S, Esthappan J, Erickson B, Feltmate C, Fyles A, Gaffney D, Jones E, Klopp A, Small W Jr, Thomadsen B, Yashar C, Viswanathan A. Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer. Brachytherapy. 2015 Sep-Oct;14(5):587-99. doi: 10.1016/j.brachy.2015.06.002. Epub 2015 Jul 15. PMID: 26186975.
- Van Der Steen-Banasik, E.; Christiaens, M.; Shash, E.; Coens, C.; Casado, A.; Herrera, F.; Ottevanger, P. Systemic review: Radiation therapy alone in medical non-operable endometrial carcinoma. *Eur. J. Cancer* **2016**, *65*, 172–181
- Beddy, P., O'Neill, A. C., Yamamoto, A. K., Addley, H. C., Reinhold, C., & Sala, E. (2012). FIGO staging system for Endometrial Cancer: Added benefits of MR Imaging. *RadioGraphics*, *32*(1), 241–254. https://doi.org/10.1148/rg.321115045
- Johnson SB, Zhou J, Jolly S, Guo B, Young L, Prisciandaro JI. The dosimetric impact of single, dual, and triple tandem applicators in the treatment of intact uterine cancer. Brachytherapy. 2014 May-Jun;13(3):268-74. doi: 10.1016/j.brachy.2013.09.005. Epub 2013 Oct 23. PMID: 24269144.
- Knocke, T. H., Kucera, H., Weidinger, B., Höller, W., & Pötter, R. (1997). Primary treatment of endometrial carcinoma WITH high-dose-rate BRACHYTHERAPY: Results of 12 years of experience with 280 patients. *International Journal of Radiation Oncology*Biology*Physics*, *37*(2), 359–365. https://doi.org/10.1016/s0360-3016(96)00486-5
- J. Heyman, O. Reuterwall & S. Benner (1941) The Radiumhemmet Experience with Radiotherapy in Cancer of the Corpus of the Uterus, Acta Radiologica, 22:1-2, 11-98, DOI: 10.3109/00016924109171580
- Fung-Kee-Fung, M., Dodge, J., Elit, L., Lukka, H., Chambers, A., & Oliver, T. (2006). Follow-up after primary therapy for endometrial cancer: A systematic review. *Gynecologic Oncology*, *101*(3), 520–529. https://doi.org/10.1016/j.ygyno.2006.02.011
- Chao, C. K. S., Grigsby, P. W., Perez, C. A., Camel, H. M., Kao, M.-S., Galakatos, A. E., & Boyle, W. A. (1995). Brachytherapy-related complications for medically inoperable stage I endometrial carcinoma. *International Journal of Radiation Oncology*Biology*Physics*, *31*(1), 37–42. https://doi.org/10.1016/0360-3016(94)00399-6

Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com