Cervical Cancer: Definitive Chemoradiation

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Clinical Presentation

47 year old G2P2 female presented with abnormal vaginal discharge and several months of irregular bleeding. Unremarkable Pap smear. Abdominal ultrasound revealed a 5.5 x 3.7 x 4.6 cm mass involving cervix located in the endocervical canal

Gyn Hx: Still has regular menstrual cycles. No history of abnormal Pap smears (most recent Pap was 7 years ago)

PMHx: Noncontributory

PSHx: Noncontributory

FHx: Mother and father alive without cancer history. Daughter history of thyroid cancer, alive.

SHx: Married. No smoking or alcohol use.

Pelvic exam: Blood noted in the cervical os (patient was menstruating at time of exam) making it difficult to visualize the cervix.

Bimanual exam revealed expanded and full cervix with freely mobile parametria

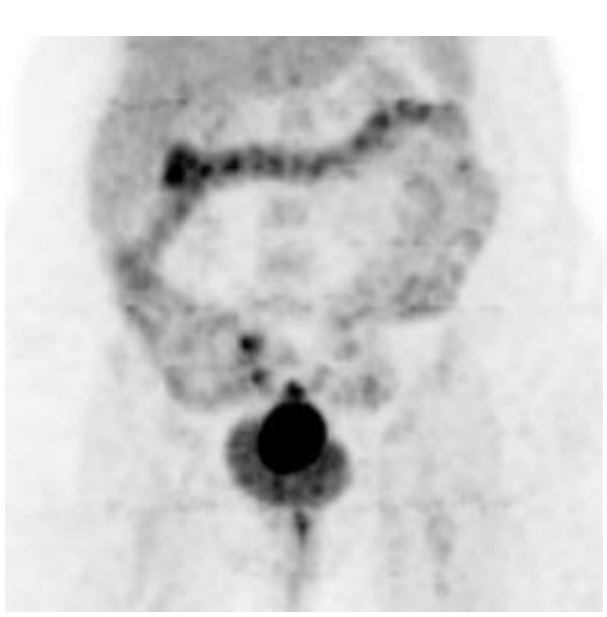
Rectovaginal exam revealed no discrete nodularity or masses, without obvious vaginal extension.

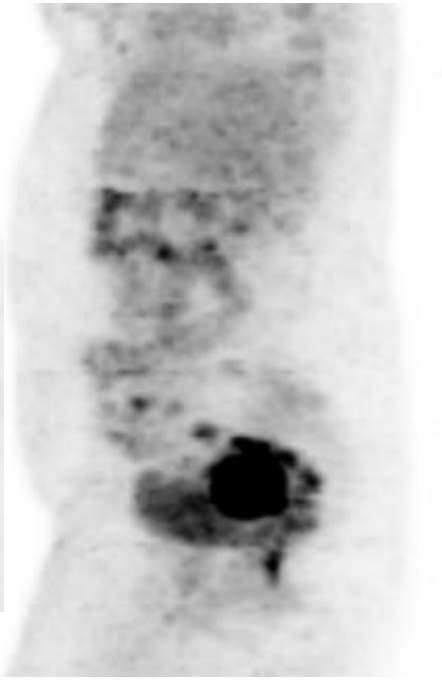
Next steps?

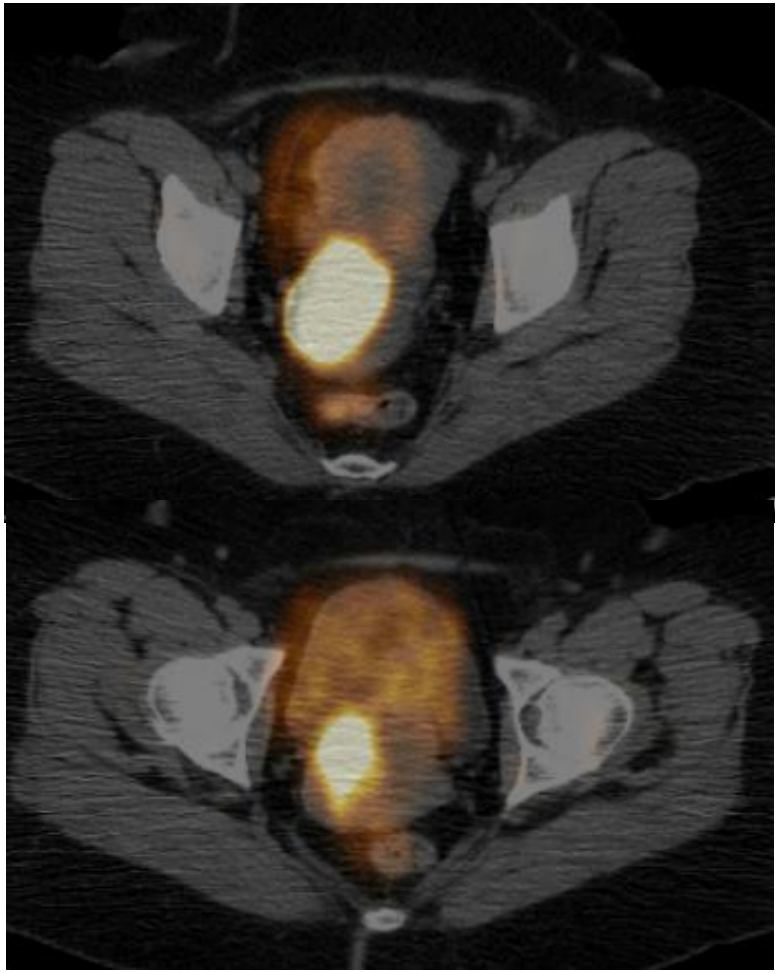
- Based on H&P and imaging, there is high suspicion for a malignant process
- What further work-up is necessary?
  - Cervical biopsy→ Revealed high grade carcinoma with squamous differentiation
  - Pelvic Imaging
    - MRI pelvis
    - Or CT Pelvis
  - Systemic Staging
    - PET/CT
    - Or Chest Xray or CT Chest, Abd
  - Labs: CBC, Electrolytes including Ca and Mg,LFTs, Renal Function
  - Consider cystoscopy, sigmoidoscopy for advanced cases
  - Stent or percutaneous nephrostomy if hydronephrosis

PET-CT Scan

- PET-CT: hypermetabolic uptake within primary cervical mass SUV 31. No abnormal uptake in pelvic LNs or distant metastases.

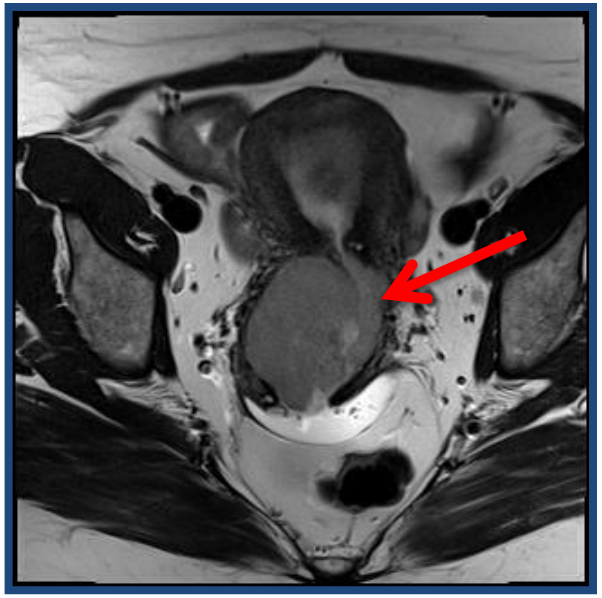




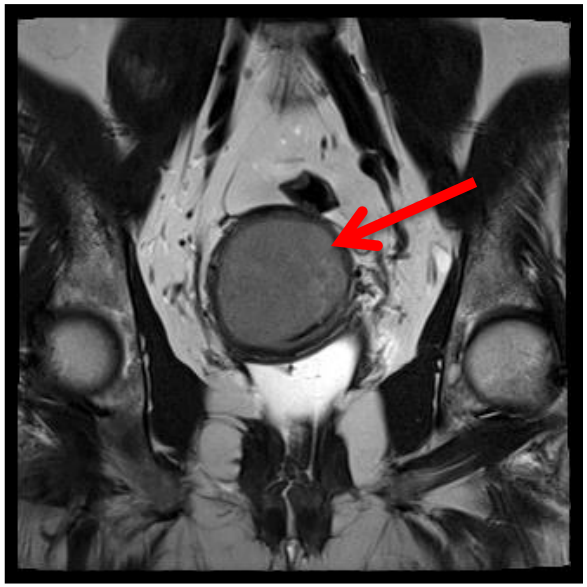


Pelvic MRI

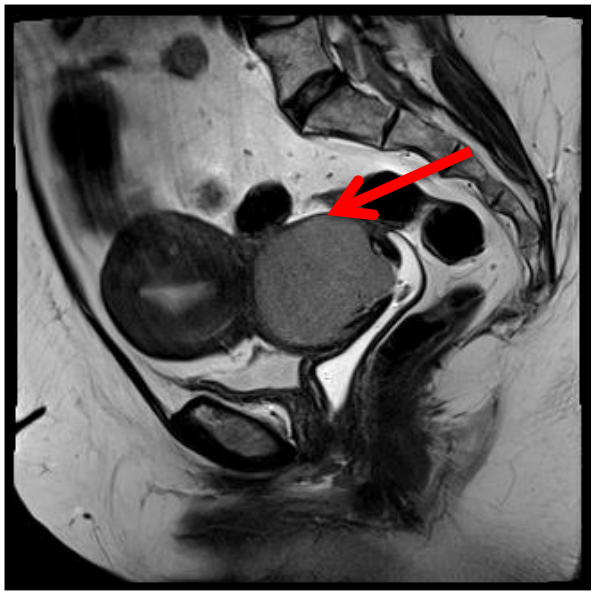
Axial



Coronal



Sagittal



Hyperintense, enhancing mass infiltrating the cervical stroma, predominantly located in the right lateral wall, causing extrinsic compression of the cervical canal and retention of endometrial secretions.

No parametrial spread visualized

Small right common iliac and left lateral pelvic lymph nodes (considered to be reactive).

FIGO Staging

How is cervical cancer staged?

- Stage I – tumor confined to cervix
  - Stage IA – microscopic disease only
    - IA1 – measured disease <7mm, invasion <3mm
    - IA2 – disease <7mm, invasion 3-5mm
  - Stage IB – clinically visible disease or preclinical larger that IA
    - IB1 – Smaller than 4cm
    - **IB2 – larger than 4cm**
- Stage II – Tumor beyond cervix, but not to side wall or lower 1/3 vagina
  - Stage IIA – no parametrial involvement
  - Stage IIB – obvious parametrial involvement
- Stage III – Extends to pelvis sidewall or lower 1/3 vagina
  - Stage IIIA – Extension to lower third of vagina
  - Stage IIIB – Extension to pelvic sidewall, includes all cases of hydronephrosis
- Stage IV – beyond pelvis or invasion of other pelvic organs
  - Stage IVA – Spread to adjacent organs (bladder or rectum)
  - Stage IVB – Distant spread

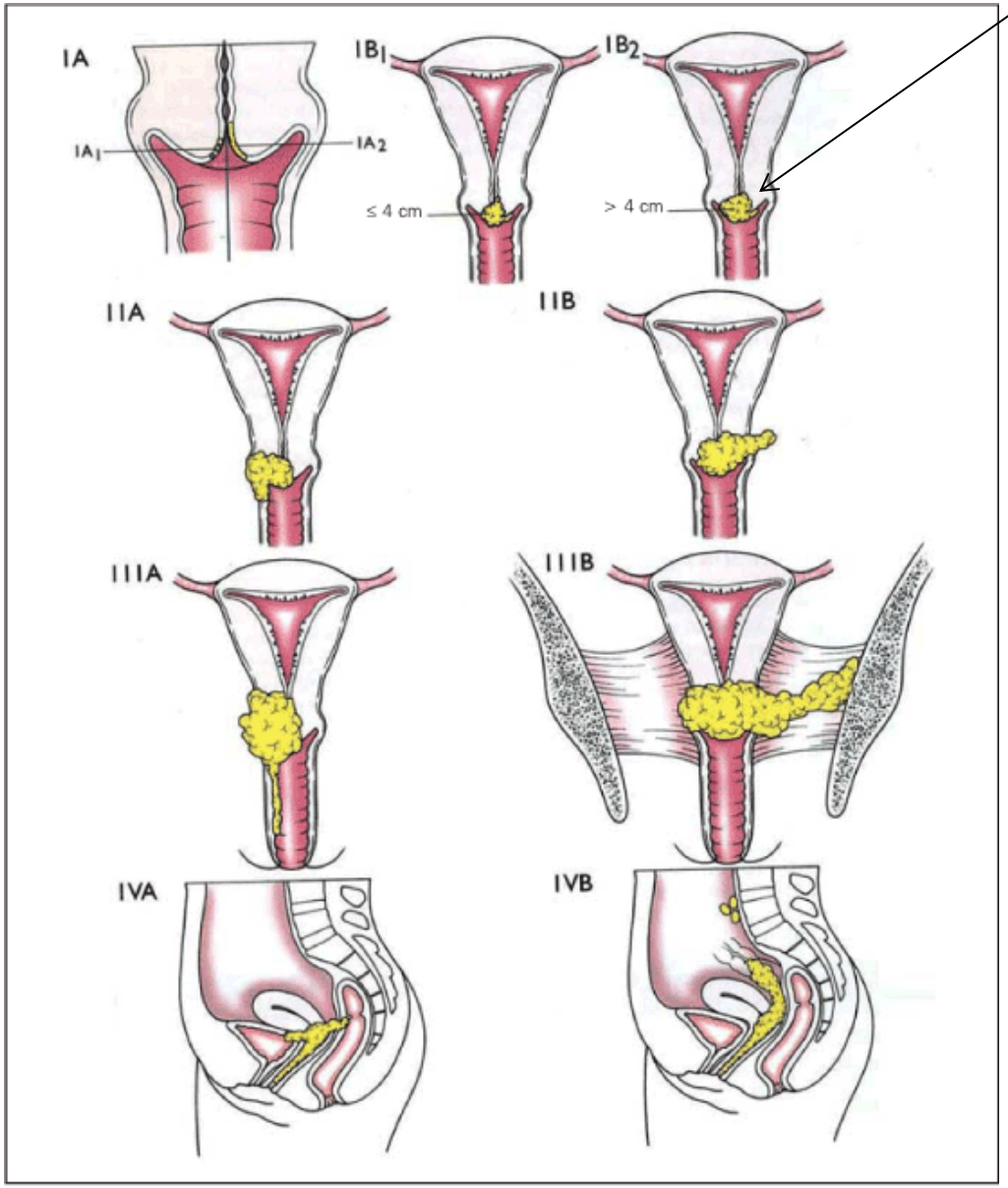


Figure 1. Staging of uterine cervix carcinoma according to FIGO[3].

> 4cm lesion confined to cervix without parametrial extension (Stage IB2)

Image adapted from:
http://www.scielo.br/img/revistas/rb/v40n3/e13f1.gif

Treatment Decision

- For IB2 cervical cancer, limiting the number of different treatment modalities is recommended to limit toxicity
- The preferred approach is definitive chemoradiation (NCCN v3.2013)
- A majority (50-80%) of patients with IB2 cervical cancer (i.e. >4 cm lesions) require post-operative radiation
- Therefore, were this patient to undergo surgery, she would likely require adjuvant radiation, which may increase lymphedema and bowel toxicity
  - (Landoni et al. 1997 Aug 23;350(9077):535-40)

*Teaching point- Indications for adjuvant RT or adjuvant ChemoRT ?

Sedlis Criteria (RT alone)
* At least 2.
+LVSI, Deep stromal invasion (>1/3), tumor >4 cm, Adenocarcinoma

Peters Criteria (Chemo and RT)
-" 3 p's"
+Positive Margins
+Parametria Involvement
+Positive Lymph Nodes

Treatment Summary

- 45 Gy delivered to the whole pelvis using 3D-CRT with concurrent, weekly, low-dose cisplatin (40 mg/m2) administered as a radiosensitizer
- 5 x 5.5 Gy HDR tandem ovoid (Fx 1-2) and tandem ring (Fx 3-5)
- Each HDR fraction was administered using MRI based brachytherapy using GEC ESTRO contouring guidelines

*Teaching point: Extending total treatment to >8 weeks will result in inferior outcomes due to accelerated repopulation

Alternative Regimen (per NCCN guidelines):
- HDR: 6 Gy x 5 HDR, Point A dose = 30 Gy
-Generally accepted to be equivalent to LDR Point A = 40 Gy

For additional information please see "GEC ESTRO" --> http://estro-education.org/publications/Documents/IA%2014%2001082002%20Cervix%20cancer%20print_procTW.pdf

EBRT Planning

- Simulation: Vaginal marker or fiducial (institutional preference), determine if prone versus supine position is needed, full bladder
- Targets
  - Cervix/uterus, LN (common iliac, external/internal iliac, presacral)

  **Consider inguinal coverage for IIIa disease with distal vaginal involvement

- Field design

  Contour targets to ensure inclusion when designing radiation fields

  **Traditional field borders less important than ensuring targets are covered

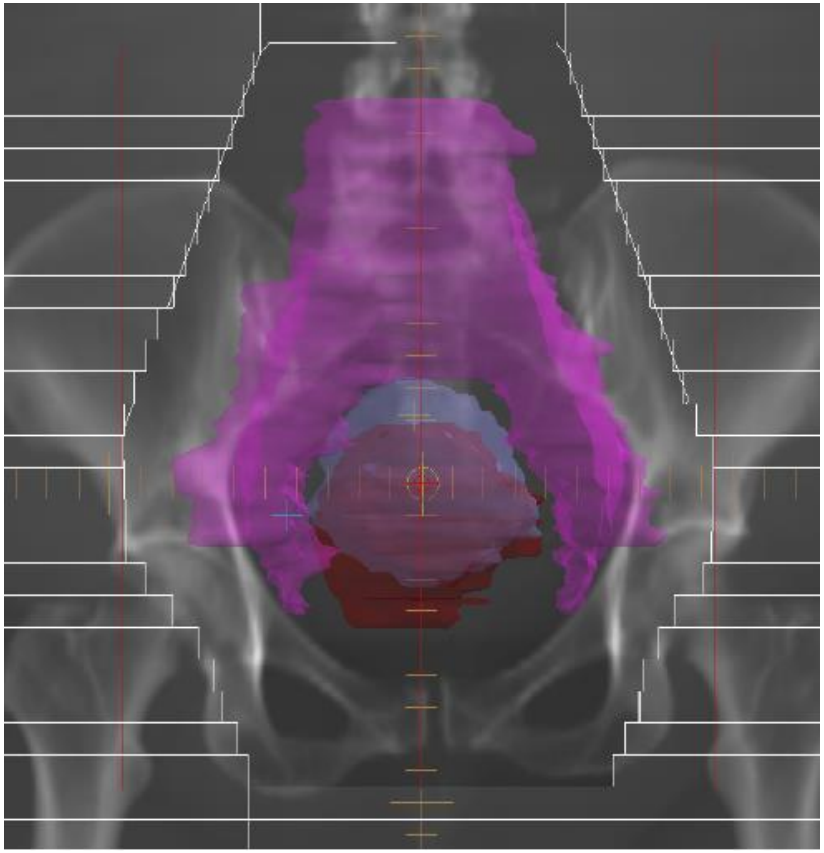
  <u>AP Fields</u>

  Superior border
  - Above common iliacs (approximately L4/5). Contour LN CTV to ensure inclusion

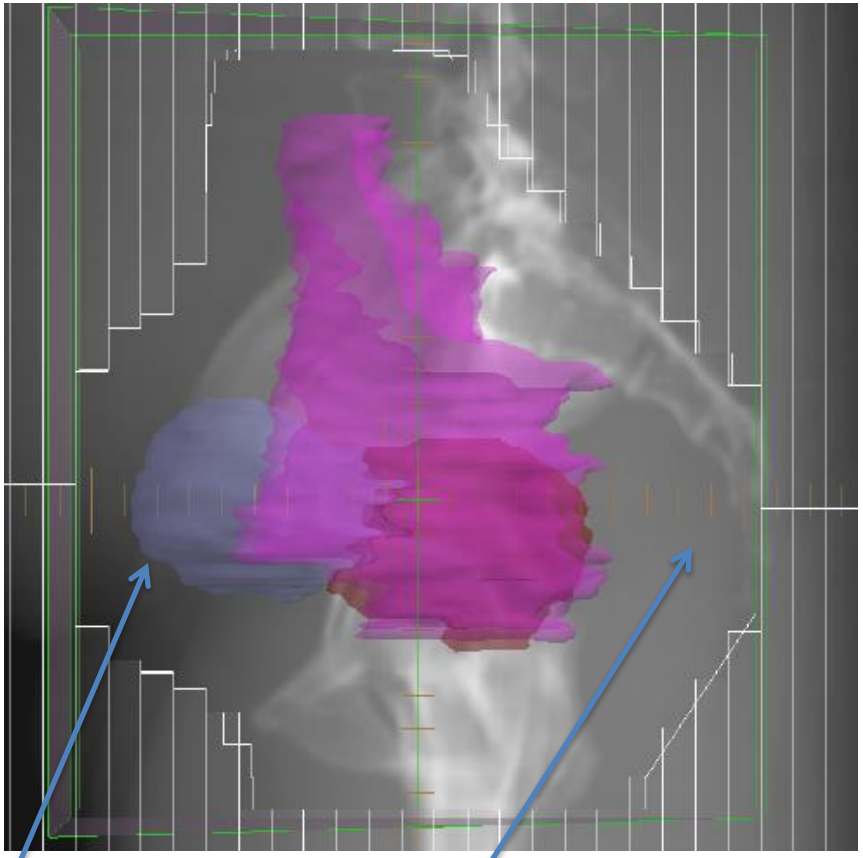
  Inferior border
  - 3 – 4 cm below most inferior extent of disease
  - 2 cm around bony pelvis laterally

  <u>Lateral fields</u>
  - Should include entire sacrum posteriorly to ensure coverage of presacral LN and uterosacral ligaments
  - Anteriorly ensure coverage of external iliac LN and uterine fundus

AP Field

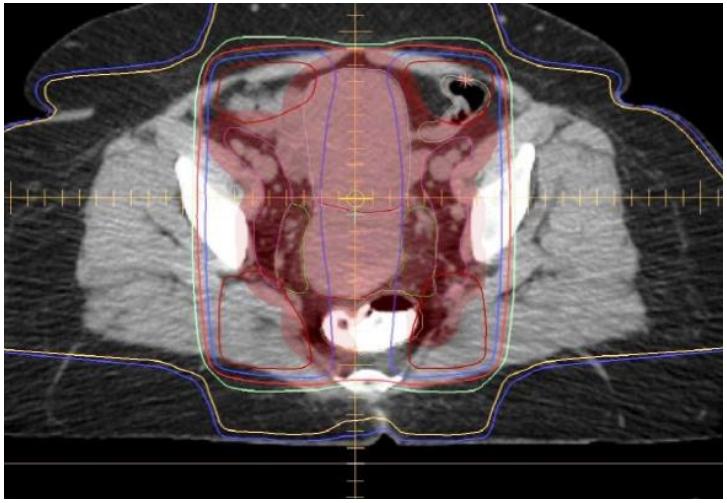


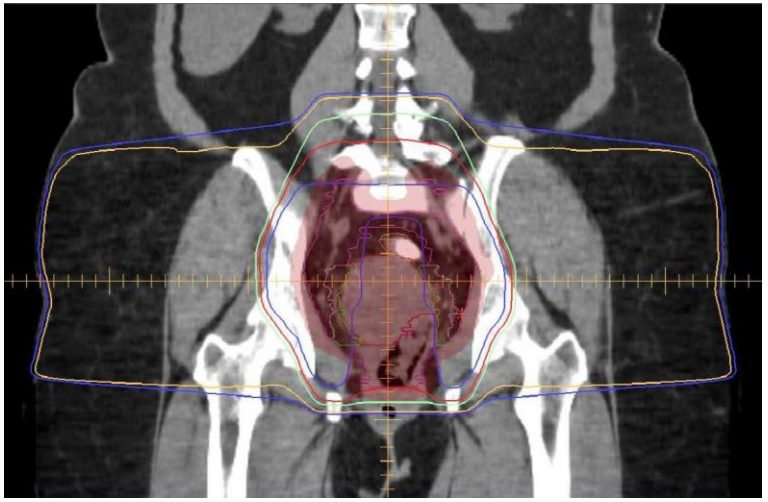
Lateral Field

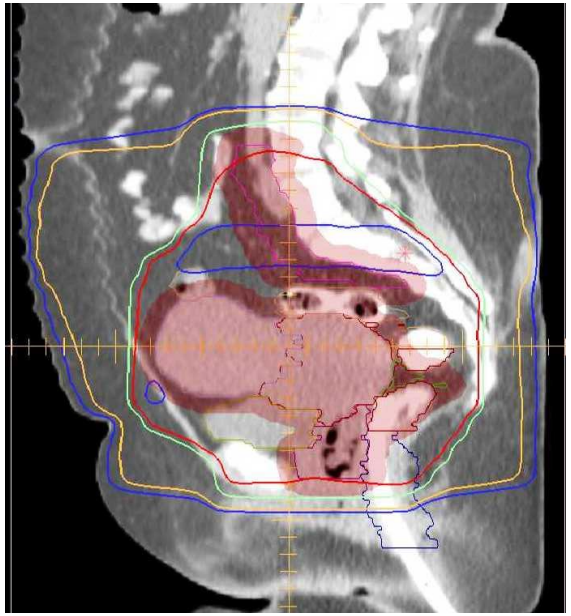


** Teaching Points:
-In the setting of an anteverted uterus,
ensure adequate margin anteriorly
-Ensure coverage of presacral LN posteriorly

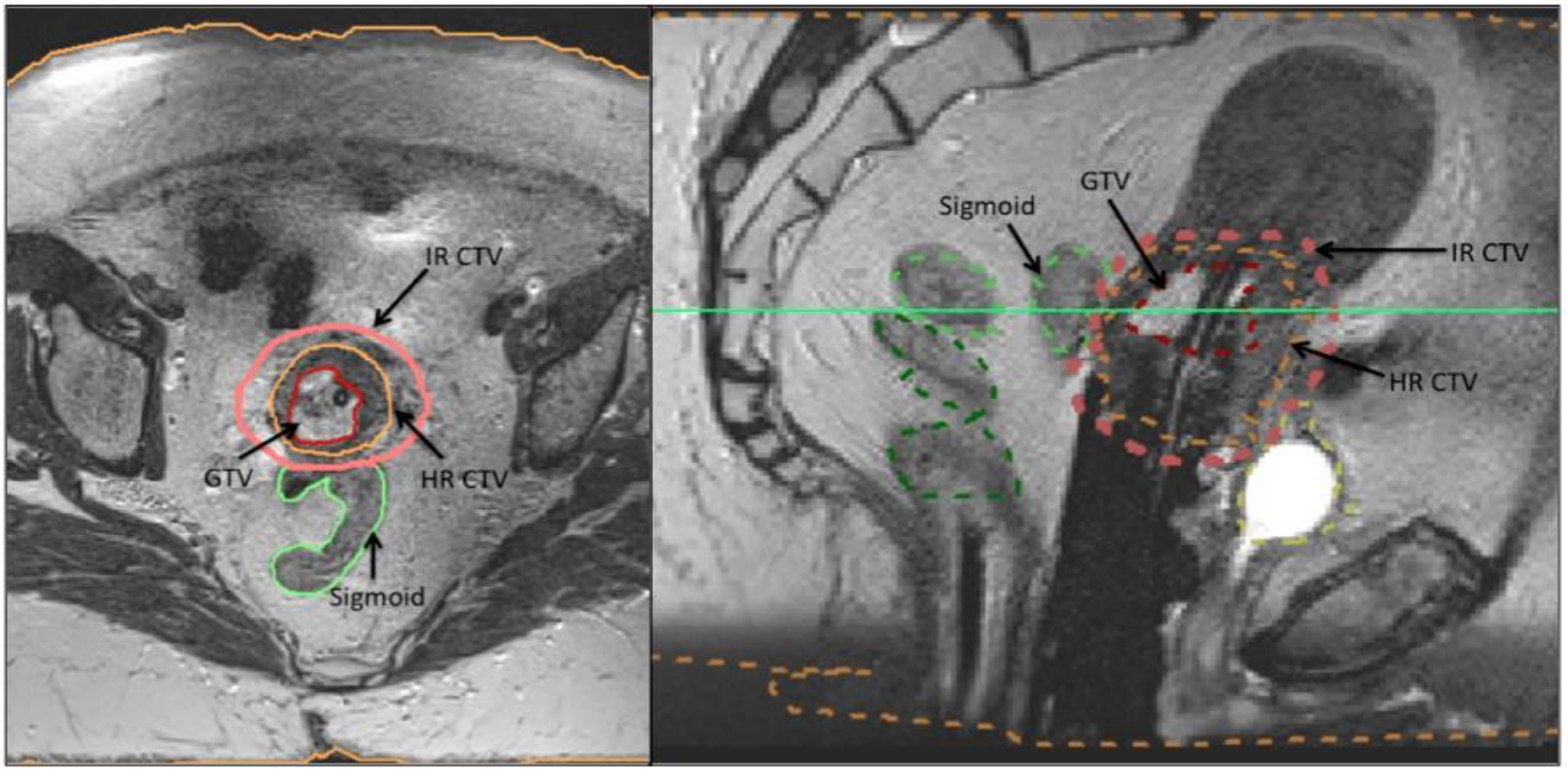
Dose distribution of EBRT







Brachytherapy: Tandem and Ovoid



Contours for the HR-CTV, GTV, and OAR according to the GEC-ESTRO guidelines using MRI Based-Adaptive Brachytherapy
HR-CTV= High Risk Clinical Target Volume, IR CTV= Intermediate Risk Volume, GTV= Gross Tumor Volume)

**** MRI allows for identification and dose calculation of tumor (GTV) , HR CTV, and organs at risk (bladder, rectum, sigmoid, small bowel)**

**** Use of CT planning at a minimum will allow for identification and dose calculation to organs at risk**

Constraints

Prescribed target dose to the HR CTV is D90 ≥ 80-90 Gy

Using an interactive spreadsheet*, the Biologically Equivalent Dose (EQD2) were used to calculate the total dose to HR-CTV and OAR

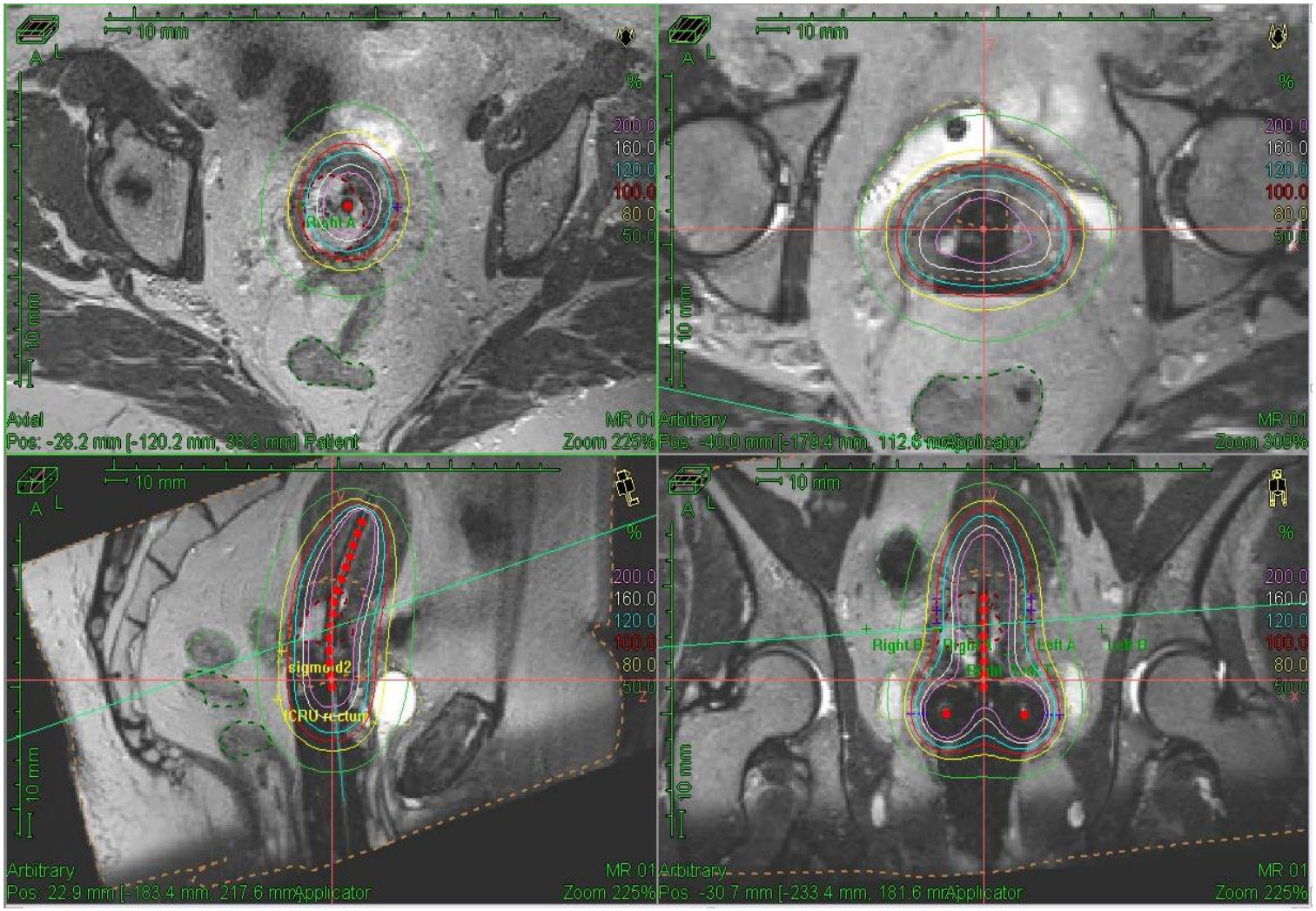
Dose distribution was modified to enhance coverage of the HR-CTV and to spare the OAR by altering dose specification distances around the tandem and the percentage of the point A dose around the ring/ovoids.

Organ at risk	D2cc
Rectum	<70-75 Gy
Sigmoid	<70-75 Gy
Bladder	<90 Gy

*Interactive Spreadsheet: http://www.americanbrachytherapy.org/guidelines/index.cfm

Isodose Distribution

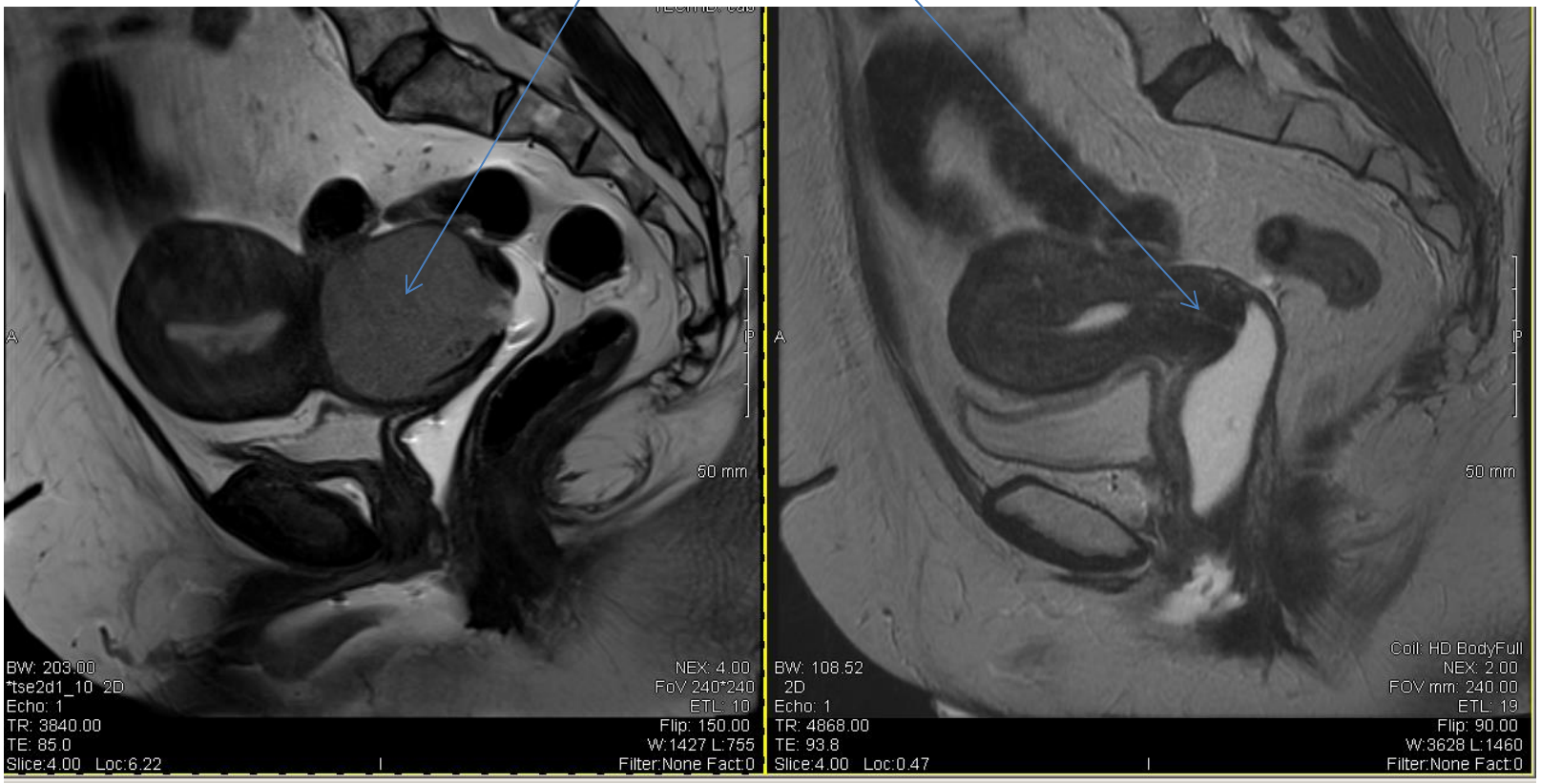
Tandem and Ovoid Fraction 1



Resolution of cervical mass

Pre-tx MRI

Post-tx MRI



Evidence for Chemo XRT

Several trials established concurrent chemoradiation as standard of care. show improved survival by ~ 15%

- **GOG 85**: 5-FU/Cisplatin XRT Versus Hydroxyurea XRT
- **RTOG 9001:** XRT alone to pelvis and paraortics vs ChemoXRT (cisplatin/5-FU)
- **GOG 120**: 1. XRT/ hydroxurea 2. XRT cisplatin/5-FU 3. XRT/cisplatin
- **NCIC Trial:** XRT vs cisplatin/XRT

- The NCI issued a clinical announcement endorsing chemoradiation as a standard result of these clinical trials
  - (http://www.nih.gov/news/pr/feb99/nci-22.htm)

-Concurrent cisplatin recommended (NCCN 3.2013)

-Addition of 5-FU may result in added GI toxicity without improved efficacy (GOG120)

Toxicities

What are some of the toxicities?

- Acute: GI, GU, skin, blood counts

OAR	Toxicity
Rectum	Bleeding, ulcer, fistula
Bladder	Bleeding, ulcer, fistula
Vagina	Stenosis, dryness, sexual dysfunction
Others	Ovarian failure, pelvic fractures

- Regular use of vaginal dilators following treatment is recommended to reduce the risk of vaginal stenosis.

Surveillance and Follow-up

- NCCN v 3.2013
  - Every 3-6 months for 2 years.
  - Every 6-12 months for years 2-5, then annually.
  - Consider cervical/vaginal annually. Utility of cytology following treatment is controversial.
  - Imaging and labs not routinely recommended as part of surveillance unless indicated by clinical symptoms.

References

- Dimopoulos JCA, Petrow P, Tanderup K, *et al.* Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. *Radiother. Oncol.* 2012;103:113–122.
- Pötter R, Georg P, Dimopoulos JCA, *et al.* Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced ce
- Pötter R, Haie-Meder C, Limbergen EV, *et al.* Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother. Oncol.* 2006;78:67–77.
- Haie-Meder C, Pötter R, Van Limbergen E, *et al.* Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.* 2005;74:235–245.
- NCI Statement on ChemoXRT: http://www.nih.gov/news/pr/feb99/nci-22.htm