ARRO CASE
Operable Vulvar Cancer

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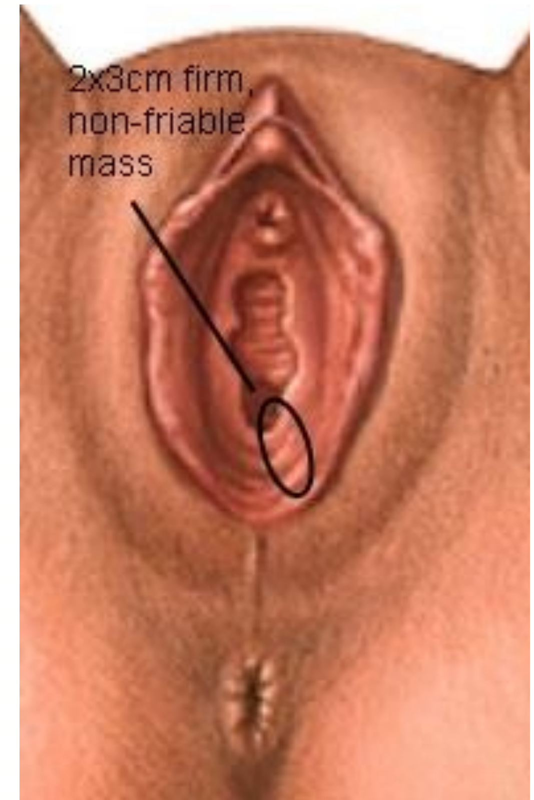
Case Presentation: History

- 62 yo female with HIV on HAART
- "Several week history of a growth in my groin"
- Denies change in size, pruritis, or bleeding from site
- PMH: HIV+ - on HAART, Hep C cirrhosis - no meds, HTN, Depression/Anxiety
- PSH: TAH
- Past Gyn History:
  - G1P1, SVD x 1, post-menopausal
  - Prior abnormal paps: many LGSIL paps with HPV+
  - Not currently sexually active
- SH: + smokes 1ppd x 49yrs, drinks beer on weekends, no current illegal drug use, past use of IV heroin 20-30 yrs ago

Physical Exam

- **General**: Alert and oriented, No acute distress.
- **Respiratory**: Lungs are clear to auscultation, Respirations are non-labored.
- **Cardiovascular**: Regular rate, Normal rhythm.
- **Gastrointestinal**: Soft, Non-tender.
- **Genitourinary**: Vagina: White, adherent lesion 2x 3cm at vaginal cuff & Mucosa is within normal limits
- **Lymphatics**: Inguinal: No lymphadenopathy.
- **Integumentary**: Warm, Dry.
- **Neurologic**: Alert, Oriented.
- **Psychiatric**: Cooperative, Appropriate Mood & affect



Case Presentation

Pathology

- **Colposcopy with biopsies**
- **Vaginal cuff, condylomatous lesion 10:00:** High-grade squamous intraepithelial lesion (VAIN II)
- **Vaginal cuff, epithelial scrapings 11:00:** Pronounced HPV cytopathic effect, low-grade squamous intraepithelial lesion (VAIN I)
- **Left vulva, necrotic lesion (specimen #3); punch biopsy:** Squamous cell carcinoma, moderately to well-differentiated

Laboratory Studies

- HIV viral load undetectable
- CD4 count 1200
- CBC and CMP within normal limits
  - Hgb 13.3

Vulvar Cancer [1]

- < 5% of all GYN cancer
  - – 4,850 cases/year and 1,030 deaths/year [2]
- Median age 70
- Most common presenting symptoms are pruritis, bleeding, pain or discharge
- 85% squamous cell carcinoma

Vulvar Carcinogenesis [1]

Keratinizing squamous

- 80% of cases
- Usually in older women with vulvar dystrophy, lichen sclerosis
- May have p53 mutation
- p16 rarely positive

Basaloid squamous

- 20% of cases
- Younger women
- Often times multifocal
- Associated more commonly with HPV infection
- p53 usually negative
- p16 more commonly positive

Vulvar Anatomy [1]

Primary

- Midline: within 1 cm of introitus
  - Mons Pubis
  - Prepuce (2.5%)
  - Clitoris (15%)
  - Vaginal vestibule
  - Posterior forchette /Perineal body (5%)
- Potentially "well-lateralized"
  - Labia Majora/Minora (70%)
  - Bartholin's glands (2.5%)

Lymph Nodes

- Pattern of spread: Superficial inguinofemoral -> Deep inguinofemoral -> External illiac
  - "Gateway to the pelvis" – **Cloquet's node**, most superior deep femoral lymph node
  - Lateralized lesions, rare to have contralateral groin involvement without positive ipsilateral groin
- Clitoris can spread directly to obtrurators and external illiacs

Vulvar Cancer Risk Factors [1]

- 16, 18, 33 HPV
- Vulvar Intraepithelial Neoplasia (VIN)
- Paget's disease
- Chronic irritant vaginitis
- Immunosuppression
- Bowen's disease
- Leukoplakia
- Smoking
- Work in laundry & cleaning industry
- Erythroplasia
- Lichen Sclerosis

Work-up [1]

- History and Physical
- Exam Under Anesthesia
- Biopsy of Primary
- FNA or excisional Biopsy of concerning inguinal nodes
- Pap Smear
- Cystoscopy, Sigmoidoscopy as indicated by clinical symptoms
- Consider Pelvic CT or MRI or PET/CT
  - **Not used in FIG0 staging
- CXR

Basic Treatment Overview Resectable Vulvar Cancer [1]

- **Surgery +/- Adjuvant Therapy**
  - Primary: Wide Local Excision
    - Surgery has evolved to become less extensive and less morbid
  - Nodes: Ipsilateral (or bilateral) inguinal dissection (or at least sentinal lymph node under the care of an experience Gyn Onc)
    - If depth of invasion < 1mm, may omit inguinal dissection as lymph node risk low

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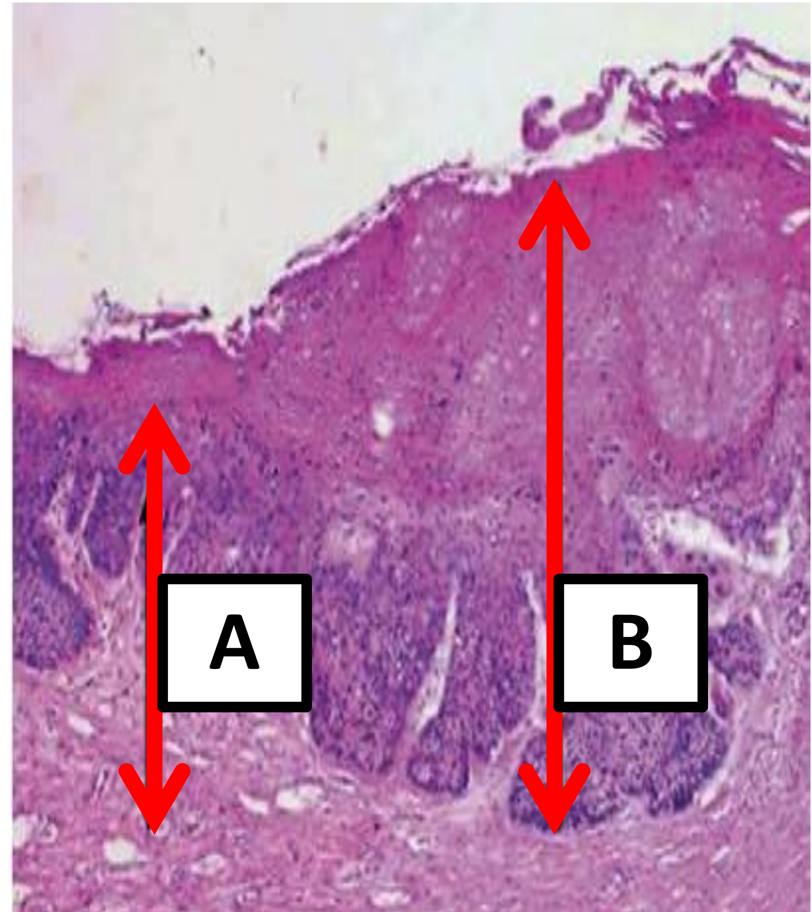
Case Presentation

- Surgical Resection
  - Exam under anesthesia, vaginal biopsy, laser CO2 ablation of the vagina and **radical vulvectomy**
  - **Pathology**
    - Invasive Squamous Cell Carcinoma, 2.2 cm in greatest dimension
    - Multifocal, moderately differentiated, keratinizing type
    - Associated VIN III, warty type
    - Depth of stromal invasion by carcinoma: **0.7 cm**
    - No lymphovascular or perineural invasion
    - Margins are **negative** for invasive carcinoma: **at least 0.8cm**
      - 12 o'clock to 6 o'clock vulvar skin margins are + VIN III

Important Pathologic Definitions [3]

- **A: Depth of invasion**
  - Epithelial-stromal junction of adjacent most superficial dermal papillae to deepest point of invasion
    - **Correlates with lymph node metastasis risk**
- **B: Tumor thickness**
  - Granular layer to deepest point of invasion



Risk of Inguinal Nodal Involvement[1]

- **Depth of Invasion (DOI)**
  - <1% for <1mm
  - 6.6% for 1-2mm
  - 8.2% for 2-3mm
  - 22% for 3-4mm
  - At least 25% for > 4 mm
- **Tumor Size**
  - 37.5% > 5 mm
  - 45.8% > 2 cm
  - 54.2% any extension beyond vulva

Clinical exam not sufficient to determine extent of inguinal disease as 11-43% of clinically node negative patients are pathologically node positive

Case Presentation

- Patient's vulvar lesion had a **depth of invasion > 1mm**
- **RECOMMENDATION**
  - Left inguinofemoral lymph node dissection followed by right inguinofemoral lymph node dissection if positive node identified

- **PATHOLOGIC FINDINGS**
  - **Left deep femoral lymph node:** Metastatic squamous cell carcinoma, involving two lymph nodes
    - Size of metastasis is 0.9 cm and no extracapsular extension present
  - No right lymph nodes positive
  - Total of 7 lymph nodes resected

Staging [1]

- AJCC, 7th edition: T Stage

AJCC T Stage	Definition	FIGO
Tis:	in-situ dz	N/A
T1a:	≤ 2cm, confined to vulva or perineum » Stromal invasion ≤ 1mm	IA
T1b:	**>2cm,** confined to vulva or perineum » **Stromal invasion > 1mm**	IB
T2:	Extension to adjacent perineal structures » Ex. Distal 1/3 urethra, distal 1/3 vagina, Anal involvement	II
T3:	FURTHER extension » Ex. Proximal 2/3 urethra, proximal 2/3 vagina, Bladder mucosa, Rectal mucosa, Pelvic bone fixation	IVA

Staging [1]

- <u>N Stage</u>
  - N1a: 1-2 LN met, ≤ 5mm
  - N1b: 1 LN met, >5mm
  - N2a: ≥ 3 LN mets, <5mm
  - **<u>N2b: ≥ 2 LN mets, ≥ 5mm</u>**
  - N2c: +ECE
  - N3: Fixed or ulcerated LN mets
- <u>M Stage</u>
  - M1: Distant mets
    - Including pelvic LN mets

<u>FIGO Staging</u>

N/M Stage	FIGO Staging
N1a, N1b	**III A**
N2a, N2b	**III B**
N2c	**III C**
N3	**IVA**
M1	**IV B**

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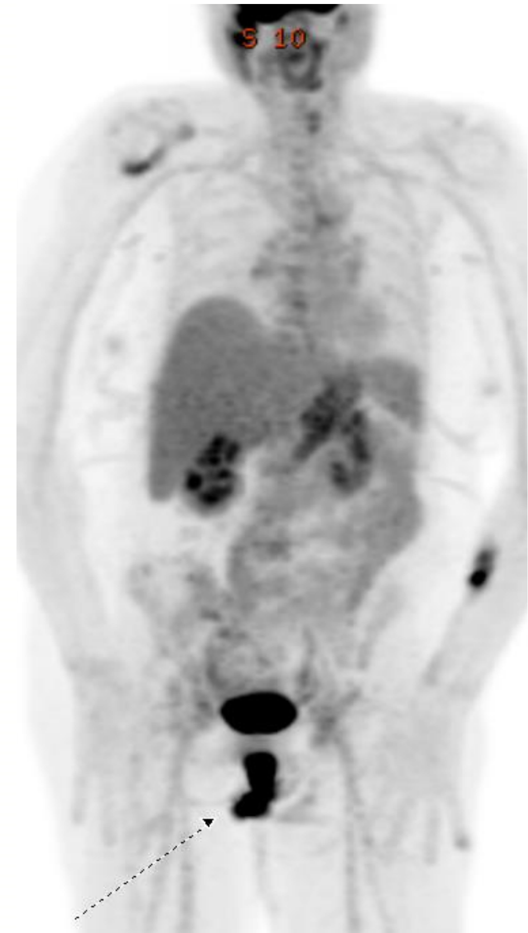
Imaging

- Post-operative PET scan
  - No definite evidence of distant metastatic disease
  - Increased metabolic uptake at primary site likely post-surgical change.



Case Summary

- 62-year-old female with well-controlled HIV has FIGO stage IIIB, pathologic T1b N2b M0 Sqcc of the vulva s/p radical vulvectomy and bilateral inguinofemoral dissections that is well-healed and without evidence of residual disease on post-operative exam.
  - Increased risk for locoregional recurrence due to **depth of invasion** and evidence of **deep positive lymph nodes**
- **Adjuvant Treatment Plan Recommendation: Radiation Therapy**
    - Delivered to the primary, bilateral groins and pelvis
    - 45 Gy in 1.8 Gy fractions
    - IMRT to minimize risk of side effects
  - Encouraged smoking cessation and Active Infectious Disease follow-up for HIV management
  - CT simulation scheduled 2 weeks post-operatively
  - Continue joint care with Gyn Onc

Overview of Adjuvant Therapy Indications

Local [3]

- Close or positive margins
- LVI
- Depth of invasion >5mm
- Consider if
  - Planning to treat regional nodes**Add reference to Dusenbery
  - Infiltrating histology
  - Tumor thickness > 1cm
  - High mitotic index
  - Increased keratin

Regional (Inguinal and Pelvis) [5]

- cN+
- ≥2 pN+
- ECE
  - **Consider concurrent chemotherapy for ≥3 pN+ and ECE

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Local Recurrence [3]

- Risk factors found to be signficant for local recurrence (LR) s/p radical vulvectomy in **Heaps** et al. surgical series 1990
- **Surgical margin < 8mm**
  - Most powerful predictor of local recurrence
  - ~50% risk of recurrence
  - 91 patients > 8mm margin and **none** had LR
- **LVSI**
  - ~40% w/LVSI developed LR
- **Depth of invasion >5mm**
- **Tumor thickness: <** 10mm
- **Infiltrating growth** pattern increase risk vs. pushing border growth pattern
- **Increasing keratin** and **> 10 mitoses per high power field**

Post-Operative Radiation [4]

- **Adjuvant radiation improves local control**
  - Retrospective review, Faul et al.
  - 62 patients with close (<8mm) or +margins were treated with XRT or observed
    - Referral for XRT at surgeon discretion
  - XRT: AP/PA, 4867 cGy for close margins and 5854 cGy for positive margins
    - Target: vulva, bilateral inguinals, and low pelvis
  - **58%** local recurrence without XRT vs. **16%** with XRT

Regional Radiation [5]

- GOG 37, Homesley et al.
  - 1977 -1984, 114 patients
  - Eligibility: Primary invasive squamous cell carcinoma of vulva found to have **positive inguinal lymph nodes**
  - **ALL** completed radical vulvectomy and bilateral inguinal lymph node dissection
  - Randomized: pelvic lymph node dissection vs. adjuvant radiation
    - Pelvic Dissection: Common, External and Internal Iliacs, and Obturator
    - XRT: 4500-5000 cGy to midplane and 2-3 cm depth at inguinal and femoral lymph nodes
      - XRT Target: Common, External, and Internal Iliacs, Obturator, Femoral and Inguinal Nodes, NO XRT to VULVA

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Regional Radiation [5]

- Overall Survival by Groin Nodal Stage

	Definition	2-yr OS
cN0 / N1	Negative or normal LN	78%
cN2	Suspicious LN	52%
cN3	Fixed, ulcerated LN	33%

- Positive inguinal nodes had 30% risk of pathologically positive pelvic nodes

Regional Radiation [5-6]

GOG 37, 1986 2 year outcomes	No XRT	XRT	Comment
Groin Recurrence	23.6%	5.1%	This benefit thought to be main contributor to OS improvement
Overall Survival	54%	68%	P=0.03, but subset analysis showed that benefit was limited to patient with > 1 LN positive and cLN+
GOG 37, 2009 6 year outcomes	**No XRT**	**XRT**	**Comment**
Groin Recurrence	48%	14%	Remained statistically significant
Overall Survival	41%	51%	No longer significant, but remained significant for > LN positive, ECE, and cLN+
Cancer Related Death	51%	29%	Many of late radiation deaths were not related to vulvar cancer

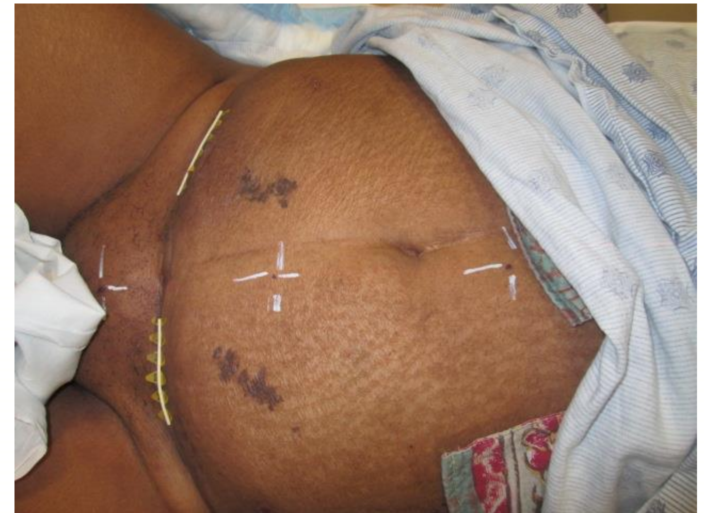
Local Recurrence after Regional XRT

- GOG 37 [5-6]
  - Coverage of vulva not required
  - 23% of recurrences were local in vulva
- Dusenbery et al. [7]
  - Reported vulvar recurrence rate of 48% in patients treated with midline block while receiving adjuvant nodal radiation
- **Recommend vulva local radiation, if treating regional lymph nodes**

Case Presentation

CT SIMULATION

- Supine in frog leg position
- Arms up on a wing board and in an immobilization device
- Wire on all scars
- Anal bb placed
- No bolus placed as IMRT utilized, but in vivo dosimetry with thermoluminescent dosimeters on day 1 (optional)
- Consider IV contrast
- Full bladder for CT simulation and daily treatment
- Consider ITV full and empty bladder
  - in order to compensate for variable bladder fill



Treatment Target [1]

- Classic field borders [1]
  - Wide AP and Narrow PA
    - Superior: Mid – Sacroiliac Joint
    - Inferior: Flash Vulva
    - AP: 2 cm lateral to pelvic brim and encompassing bilateral inguinal/femoral LN stations (~greater trochanter)
      - Supplement dose to inguinal region with two electron fields
    - PA: 2 cm lateral to pelvic brim
      - Blocking femoral heads

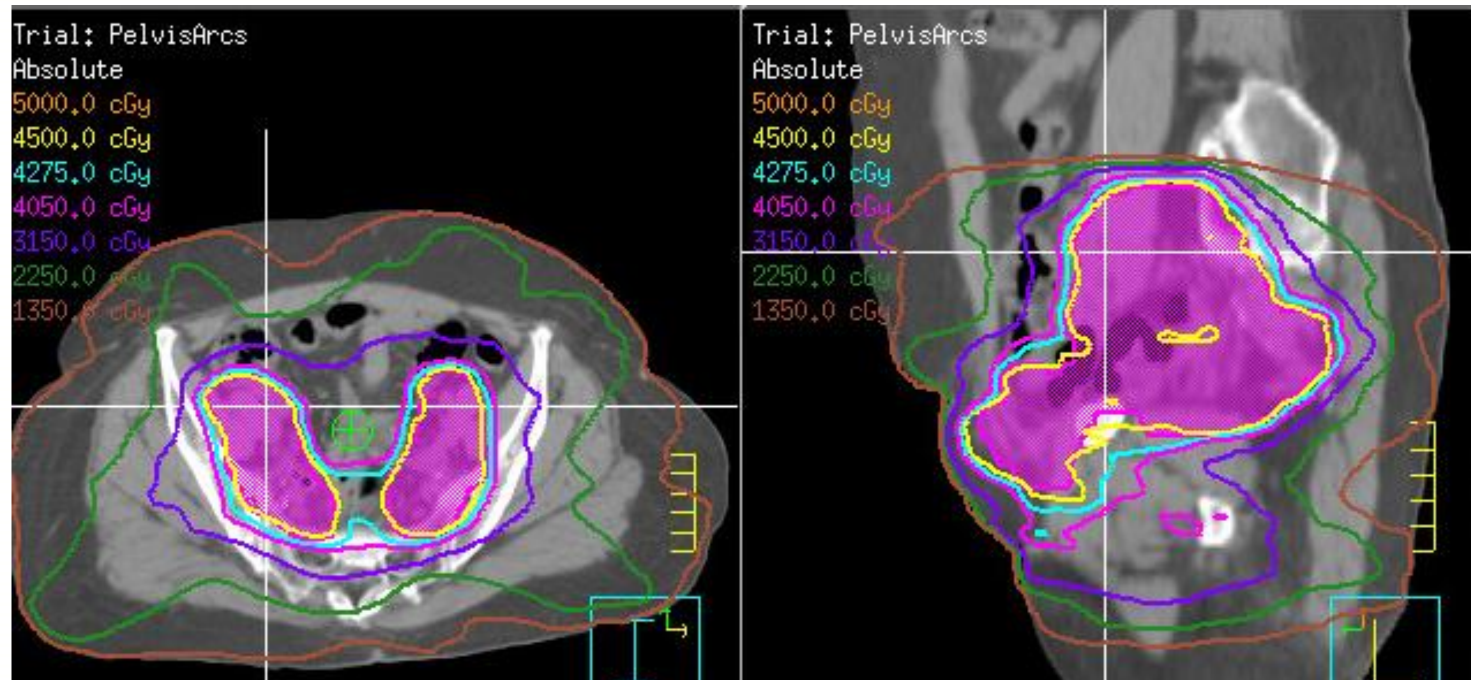
Treatment Planning[8-9]

- **IMRT** [8-9]
  - GTV (only for pre-op) defined by PET, clinical exam, wire markers
  - CTV primary includes entire vulva and surgical incisions
    - 7mm -2cm around bilateral external iliac, internal iliac, and inguinofemoral nodes
    - 1 cm around entire vulvar region including post-operative bed
      - Pre-sacral nodes included if vaginal involvment to S1-2
      - Peri-rectal nodes included if anal/rectal involvement
  - PTV=CTV + 7-10mm

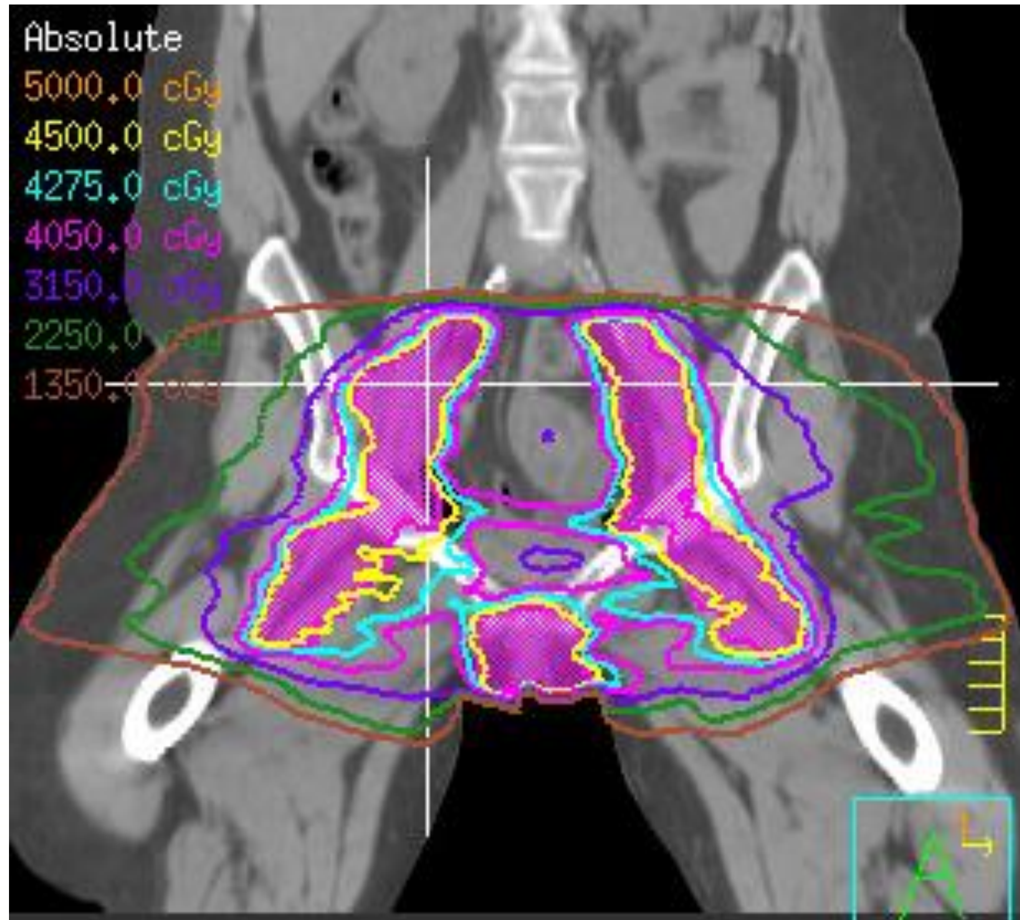
Case Presentation

Treatment Plan Summary:

- Adjuvant XRT utilizing IMRT with 2 arcs to 45 Gy in 25 fractions of 1.8 Gy with in-vivo dosimetry verification
- Target: Vulva, bilateral inguinal, external and internal Iliac lymph nodes to level of bifurcation of internal/external iliac



Case Presentation



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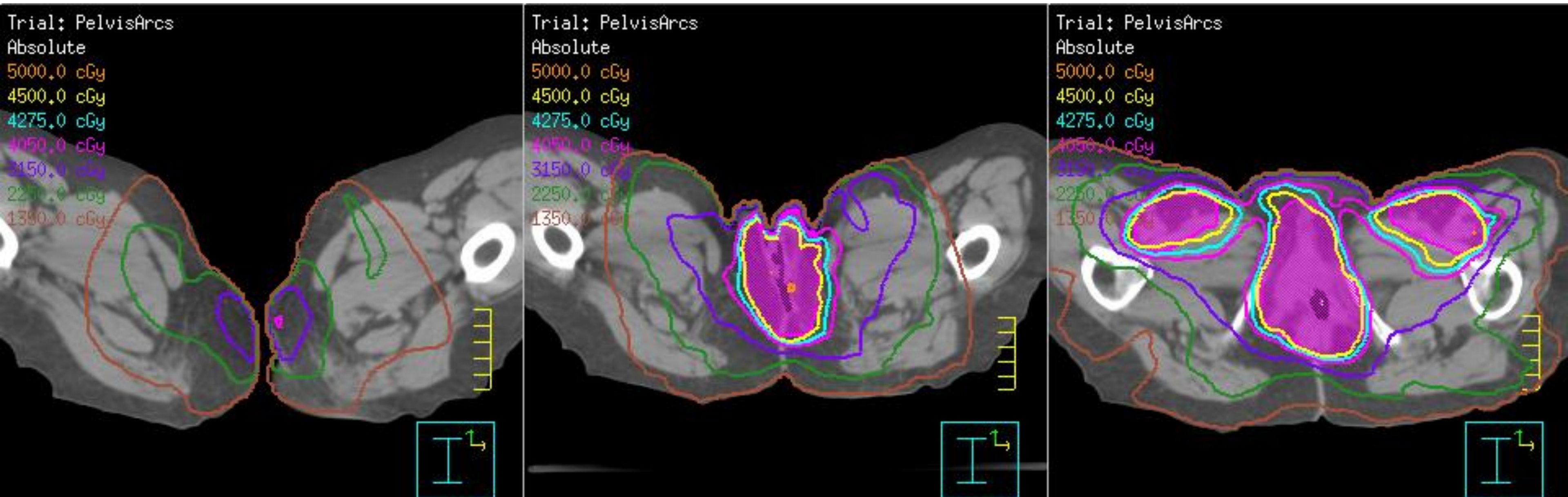

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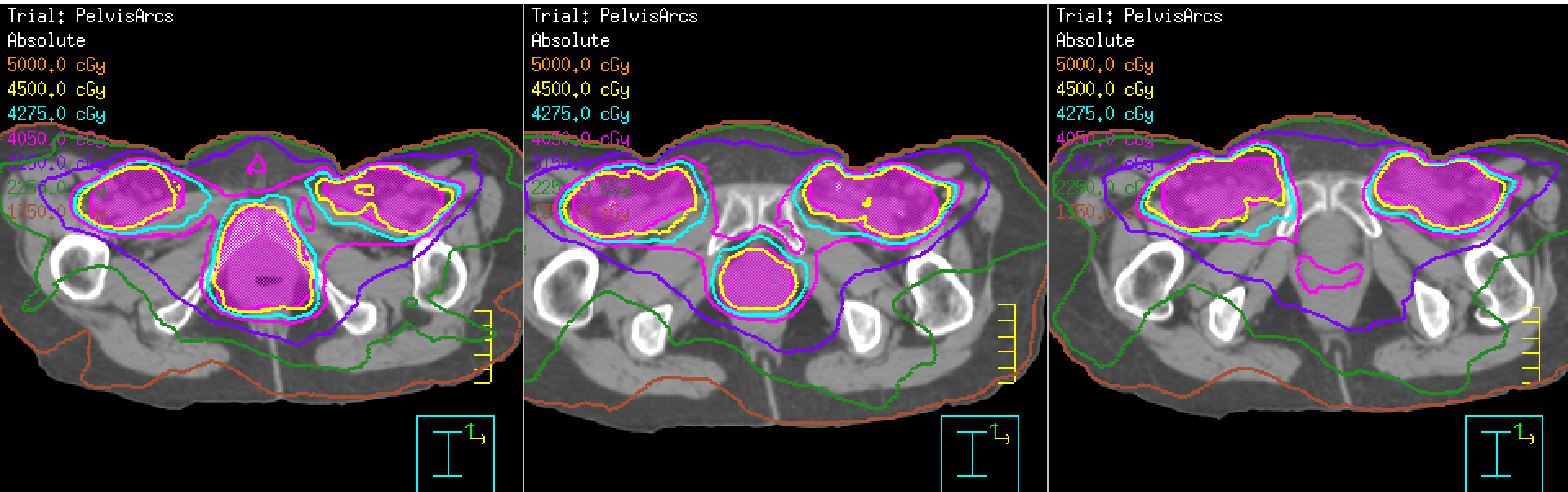

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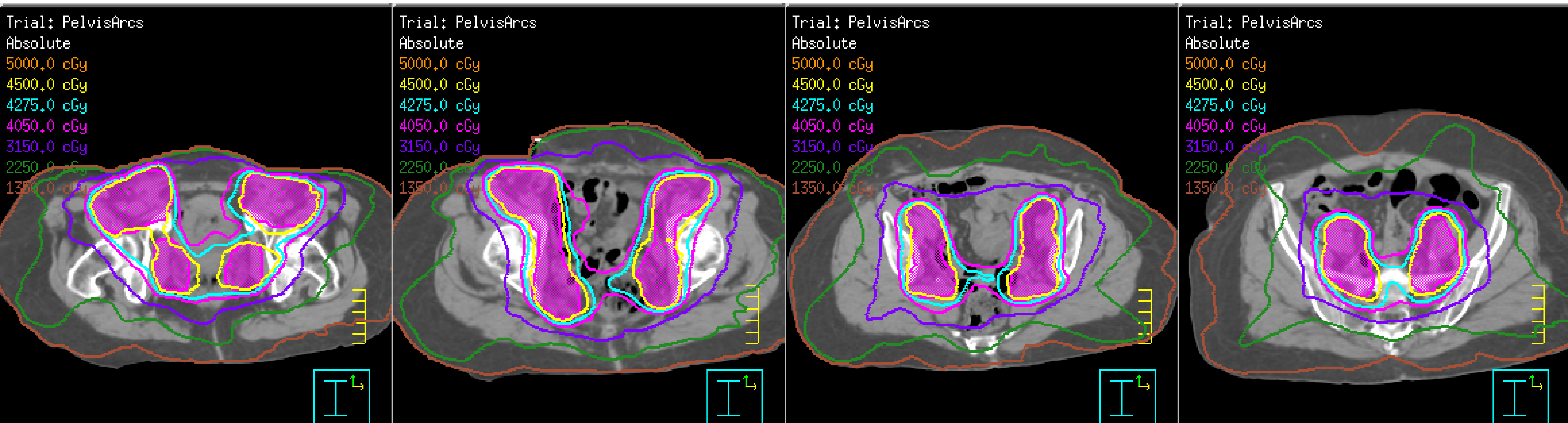


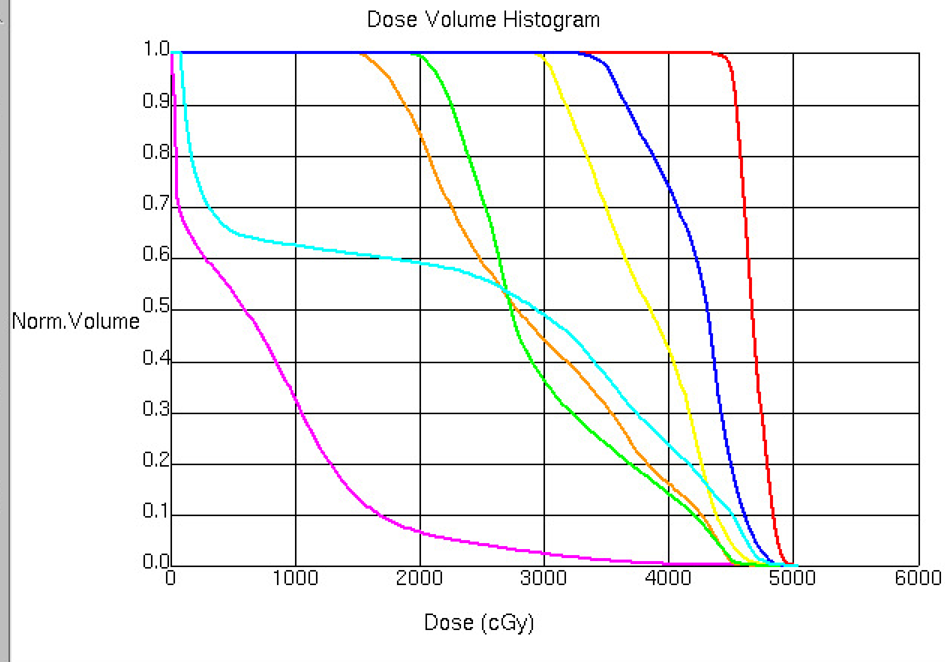
ROI | ROI Group

Trials

Display	Name	Line Type
✓	PelvisArcs	Medium Solid

ROIs

Display	Name	a
✓	PTVFInal	1
✓	Bladder	1
✓	Rectum	1
✓	SmallBowel	1
✓	Femur_L	1
✓	Femur_R	1
✓	3mmSkinRing	1
	External	1
	External1	1
	RtNodes	1
	LtNodes	1
	CTV_Vulva	1



DVH Calculation
- ◆ Cumulative
- ◇ Differential

Dose Axis Display
- ◇ Normalized Dose
- ◆ Absolute Dose

- ◆ Auto-Compute Max
- ◇ Specify Max Dose

Volume Axis Display
- ◆ Normalized Volume
- ◇ Absolute Volume

Tabular DVH...

DVH Tools | Reset

ROI Statistics | Compute

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max	Generalized EUD
magenta	3mmSkinRing	PelvisArcs	--	4757	742	782	0.00 %	0.00 %	--
yellow	Bladder	PelvisArcs	2920	4849	3814	457	0.00 %	0.00 %	--
orange	Femur_L	PelvisArcs	1484	4651	2928	869	0.00 %	0.00 %	--
green	Femur_R	PelvisArcs	1750	4703	2979	697	0.00 %	0.00 %	--
red	PTVFInal	PelvisArcs	3793	5008	4676	114	0.00 %	0.00 %	--
blue	Rectum	PelvisArcs	3148	4916	4210	349	0.00 %	0.00 %	--
cyan	SmallBowel	PelvisArcs	73	4932	2329	1773	0.00 %	0.00 %	--

Case Presentation – Dose Constraints

	Dose (Gy)	Goal %	Volume (cm3)	Total Volume	%Volume
PTVFinal	45	95	937.74	973.39	**96.3%**
Rt_Fem_Head	50	<5%	0.00	123.32	**0.0%**
Lt_Fem_Head	50	<5%	0.00	117.11	**0.0%**
Rectum	40	80	51.33	69.43	**73.9%**
Bladder	45	<35%	2.21	52.85	**4.2%**
SmallBowel	40	30	362.51	1533.9	**23.6%**
SmallBowel	45	<195cc	154.74cc	<195cc	
SmallBowel	56	<.03cc	0.00	1533.9	**0.0%**

Vulvar Dose[10]

Postop Vulva Doses in cGy at 180 cGy/fraction							
	Vulva		Groin nodes			Pelvic nodes	
Initial Fields	5040		5040			5040**	
Boosts, if needed	Neg margin	Pos margin	No ECE*	Early ECE*	Extensive ECE* or gross dz	Normal	Enlarged or positive
	5040 (no boost)	Focal: 5940 > Focal: 6480	5040 (no boost)	5940	6300-6480	5040** (no boost)	5940-6480
*ECE = Extracapsular extension of tumor ** Dose to pelvic nodes reduced to 4500 if patient is extremely frail							

Case Presentation - On Treatment Management

Day of Treatment

- Place TLDs at site of primary tumor& incision
  - **Under bolus
- Check positioning of legs
  - May need extra tattoos or set-up marks on legs to get correct angle
- Check bolus placement

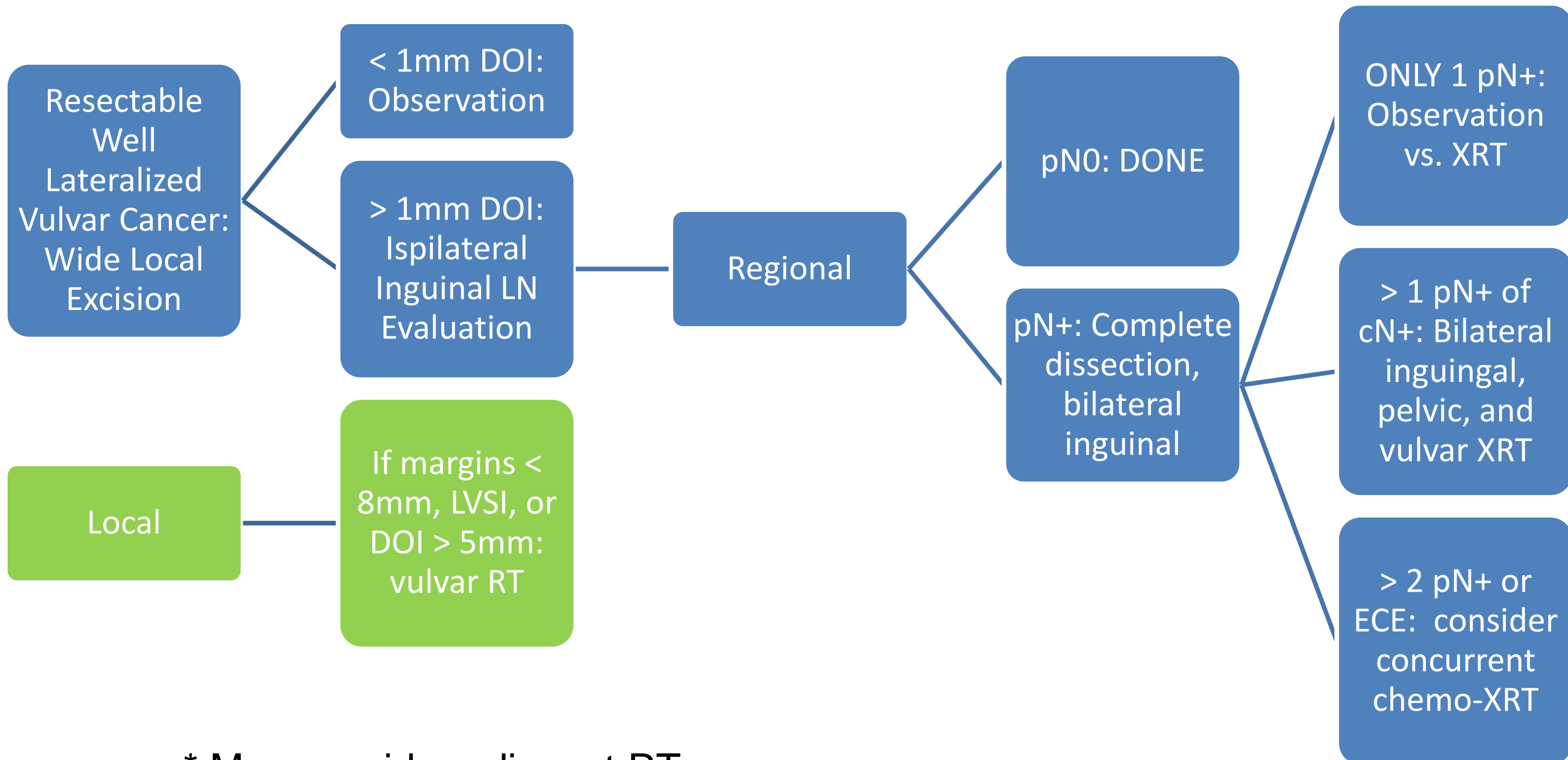
Weekly Visits

- Examine Skin
- Recommend sitz baths
- Silvadene
- Vagisil
- Imodium
- May need temporary catheter
  - **when treating definitive doses
- Vaginal dilator for late stenosis

Case Counseling [1]

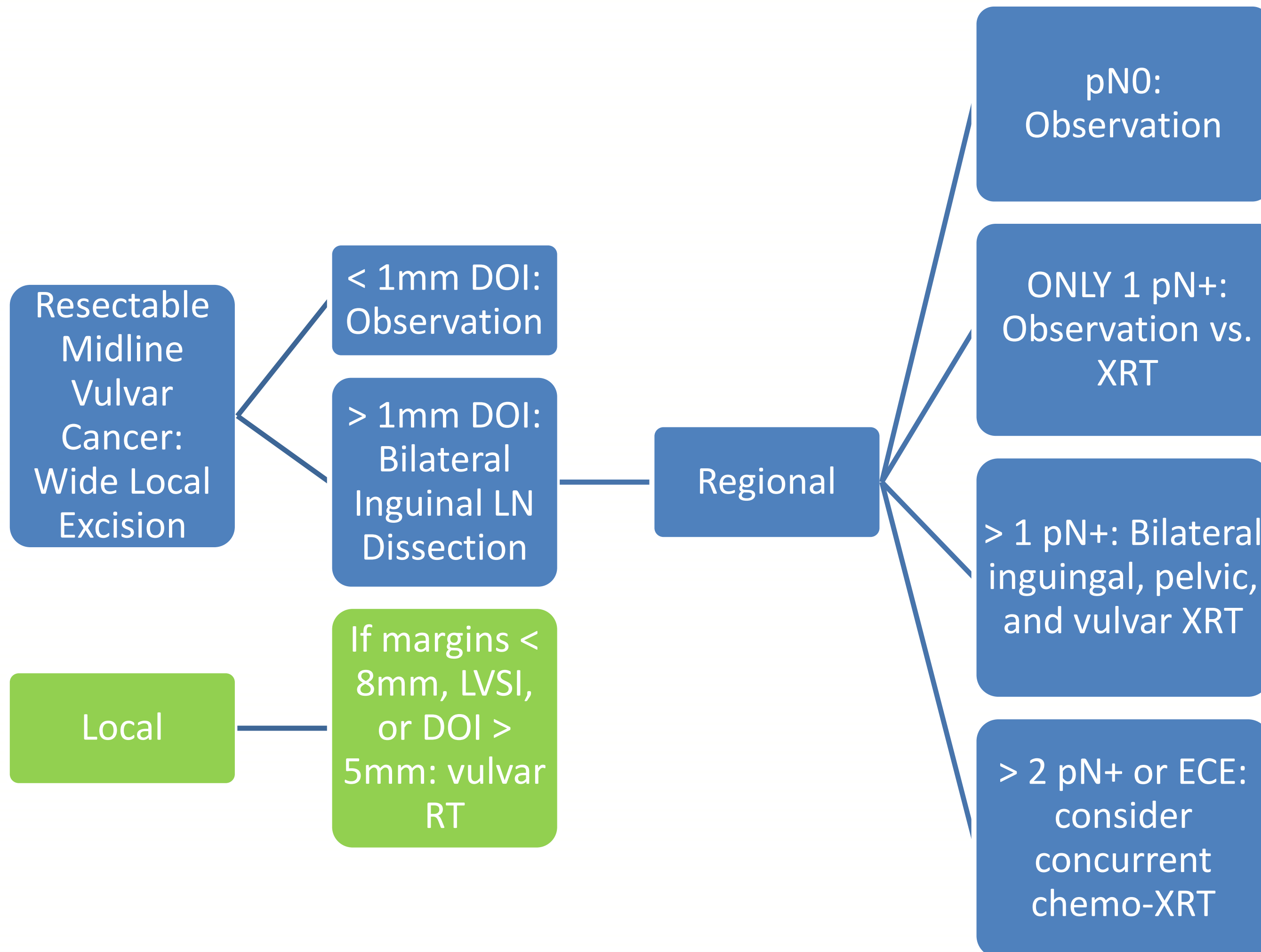
- Potential side effects of treatment
  - Radiation dermatitis
    - Increased with increasing BMI [6]
  - Fatigue
  - Cystitis
  - Proctopathy and Diarrhea
  - Vaginal Stenosis
  - Lymphedema
    - ~16% per GOG 37 [5-6]

Treatment Algorithm [1]



* May consider adjuvant RT

Treatment Algorithm [1]



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