

#### Comprehensive NCCN Guidelines Version 1.2016 Panel Members Vulvar Cancer (Squamous Cell Carcinoma)

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#### Comprehensive NCCN Guidelines Version 1.2016 Staging Vulvar Cancer (Squamous Cell Carcinoma)

Table 1 AJC Federation Staging Sys	C Tumo of Gyneo stems for	r-Node-Metastases (TNM) and International cology and Obstetrics (FIGO) Surgical r Carcinoma of the Vulva	Regional Ly TNM Categories	Regional Lymph Nodes (N) INM FIGO Categories Stages		
Primary Tur TNM Categories	nor (T) FIGO Stages		NX N0 N1		Regional lymph nodes cannot be assessed No regional lymph node metastasis One or two regional lymph nodes with the following features	
TX T0		Primary tumor cannot be assessed No evidence of primary tumor	N1a	IIIA	1 or 2 lymph node metastases each 5 mm or less	
Tis* T1a	А	Carcinoma in situ (preinvasive carcinoma) Lesions 2 cm or less in size, confined to the	N1b	IIIA	One lymph node metastasis 5 mm or greater	
		vulva or perineum and with stromal invasion 1.0 mm or less**	N2	IIIB	Regional lymph node metastasis with the following features	
T1b	IB	Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm,	N2a	IIIB	Three or more lymph node metastases each less than 5 mm	
T2***	п	confined to the vulva or perineum Tumor of any size with extension to adjacent	N2b	IIIB	Two or more lymph node metastases 5 mm or greater	
		perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)	N2c	IIIC	Lymph node metastasis with extra-capsular spread	
Т3****	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa,	N3	IVA	Fixed or ulcerated regional lymph node metastasis	
*Note: FIGO **Note: The d	no longer epth of inv	rectal mucosa, or fixed to pelvic bone includes Stage 0 (Tis). vasion is defined as the measurement of the	Distant Met TNM Categories	astasis (M FIGO Stages	D.	
tumor super ***FIGO uses ****FIGO uses	from the ficial derm the class s the class	epithelial–stromal junction of the adjacent most nal papilla to the deepest point of invasion. fification T2/T3. This is defined as T2 in TNM. sification T4. This is defined as T3 in TNM.	M0 M1	IVB	No distant metastasis Distant metastasis (including pelvic lymph node metastasis)	
Used with the per Seventh Edition (2 quotation of this n written permission For the original FI Int J Gynaecol Ob © National Compret	mission of th 2010) publisi naterial musi of Springer GO staging istet 2009;10 iensive Cance	ie American Joint Committee on Cancer (AJCO), Chicago, Illinois the bry Springer Senanes Business Media, LLC (SBM), (For comp the or software Senanes Business Media, LLC (SBM), (For comp SBM) on bahali the AJCC SBM) on bahali the AJCC stabiles see: Peocealli S. Revised FIGO staging for carcinoma of the 55 103-104, Copyright 2009.	The original and pri lete information and iis information herei e vulva, cervix and e is illustration may no	imary source fo data supportii n does not auti endometrium. F it be reproduce	or this information is the A-UCC Cancer Staging Manual, ing the staging tables, visit <u>www.springer.com</u> ) Any citation or forcize any reuse or further distribution without the expressed, FIGO Committee on Gynecologic Oncology. <b>ST-1</b> d in any form without the express written permission of NCCN®	































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# NCCN Guidelines for Vulvar Cancer – Underlying principles

#### Vulvar cancers are rare tumors

- Heterogeneous presentation and risk
- Only 2 randomized treatment trials 'completed'
- A handful of important prospective observational studies

# NCCN Guidelines for Vulvar Cancer – Underlying principles

Early stage disease – often cured by resection alone

- Evolution from 'Halstedian' approach to more limited, tailored surgery
- Sentinel lymph node evaluation
  - » GROINSS-VI (van der Zee, JCO 2008; Grootenhuis, Gynecol Oncol 2016)
    - Solution of the second state of the second
  - » GOG 173 (Levenback, JCO 2012)
    - False negative predictive value 3.7% (tumors 2-6 cm)
    - **False negative predictive value 2.0% for tumors < 4 cm**

# NCCN Guidelines for Vulvar Cancer – Underlying principles

- Site matters! primary site vs groins
- Often considered 'separately' in treatment planning
  - Metachronous groin failures occur early; rarely curable
  - Local vulvar failures occur later and are often cured with additional surgery (recurrence vs re -occurrence)
    - » Stehman, Am J Obstets Gynecol 1996
    - » Oonk, Cancer 2003
    - » Cormio, Eur J Cancer Care 2010
    - » Grootenhuis, Gynecol Oncol 2016
    - » ? Frey, Int J Gynecol Oncol 2016

# NCCN Guidelines for Vulvar Cancer – Underlying principles

For early stage tumors - adjuvant radiotherapy is an effective treatment modality that significantly decreases recurrence in surgically resected groins with positive LN(s), leading to improvements in RFS and OS

- Greatest independent predictor of groin relapse is groin node involvement at presentation
- Radiation to the vulva can lead to significant morbidity
- For locally advanced disease neoadjuvant radiotherapy (typically with chemotherapy) results in significant clinical and pathologic responses, allowing for reduced-scope/nonexenterative surgery

# NCCN Guidelines for Vulvar Cancer – Underlying principles

- Chemotherapy in addition to radiation (concurrent) may provide additional therapeutic benefit
  - Especially in advanced, 'unresectable' disease
  - May help address systemic risk in patients with multiple positive LNs





















#### Adjuvant therapy considerations for 1 groin LN+

Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study

Maaike H Oonk, Bettien M van Hemel, Harry Hollema, Joanne A de Hullu, Anca C Ansink, Ignace Vergote, René H Verheijen, Angelo Maggioni, Katja N Gaarenstroom, Peter J Baldwin, Eleonora B van Dorst, Jacobus van der Velden, Ralph H Hermans, Hans W van der Putten, Pierre Drouin, Ingo B Runnebaum, Wim J Sluiter, Ate G van der Zee

Interpretation Our data show that the risk of non-sentinel-node metastases increases with size of sentinel-node metastasis. No size cutoff seems to exist below which chances of non-sentinel-node metastases are close to zero. Therefore, all patients with sentinel-node metastases should have additional groin treatment. The prognosis for patients with sentinel-node metastases larger than 2 mm is poor, and novel treatment regimens should be explored for these patients.

Lancet Oncol 2010

#### Prophylactic Groin RT (no IFND) in vulvar cancer

 GOG 88 - Clinical N0/N1 vulvar cancer (RV) <u>randomized</u> to groin dissection vs RT (Stehman, Int J Radiat Oncol Biol Phys 1992)

Groin dissection - 5/25 pts with + nodes - all received post-op RT - no groin recurrence

Groin RT - 5/27 patients failed in-field

Concluded that groin radiation group had significantly decreased survival, PFI, and regional tumor control

Radiation patients received 50 Gy at 3 cm, 50% electrons









- Very few groin nodes lie within 3 cm of skin
   (Koh, IJROBP 1993; Eifel, Front Radiat Ther Oncol 1994)
- Clinical palpation of groins is unreliable
  - Subclinical disease ≠ microscopic disease
  - CT-based planning is necessary

# Proper radiation treatment planning allows good groin prophylaxis

- Petereit, IJROBP 1993
- Leiserowitz, Gynecol Oncol 1997
- Katz, IJROBP 2003





# 'Inadequacy' of RT to the undissected groin: Potential causes

Inadequate RT coverage – GOG 88

#### ?Tumor biology

- ?Residual tumor volume
- ?SLNB-induced changes to the groin microenvironment
  - » Tumor hypoxia, accelerated repopulation

#### Other reasons?

# Scope of RT for GN+ vulvar ca

#### Issues

- GOG 37 radiated bilateral groins and pelvis, regardless of nodal laterality
- Current emphasis on minimizing toxicity and reducing extent of therapy in early stage disease (risk of lymphedema with RT following GND)
- Adequacy of contralateral groin evaluation

#### Scope of RT for GN+ vulvar ca

Incidence of contralateral (undissected) groin +, when ipsilateral groin is +

- ~ 20% in GOG surgicopathologic study of 277 lateral vulvar cancers, especially if tumor thickness > 5mm (Holmesley, Gynecol Oncol 1993)
- ~ 18% in Mayo study of 163 lateral tumors, (tumor size > 2 cm, thickness > 5 mm, or > 2 ipsilat LN+) (Bosquet, Gynecol Oncol 2007)

#### Management of the pelvis

- 28% of patients with GN+ had pelvic LN+ on GOG 37 PND arm (Holmesley, Obstet Gynecol 1986)
- Mayo analysis 14/108 (13%) of GN+ had pelvic LN+, increasing to 40% if > 2 GN+ (Bosquet, Gynecol Oncol 2007)





# Adjuvant RT for vulvar ca - Primary site?

Predictors of vulvar relapse (Heaps, Gyn Oncol 1990)

- Tumor-free margin < 8mm (48% LF)</p>
  - » de Hullu, Cancer 2002; Chan, Gynecol Oncol 2007
  - » Viswanathan, Gynecol Oncol 2013 used 5 mm margin cutoff
- Tumor thickness, depth of invasion > 10mm
- 'Spray' pattern histology
- Vascular space invasion
- Toxicity of RT to vulvar tissues
- Majority of vulvar relapses salvageable



#### Adjuvant therapy for groin node + vulvar ca Concurrent chemotherapy?

- No phase III data
- GOG 37 (Holmesley, Obstets Gynecol 1986)
  - Groin node +, superior RT arm
    - » 2 year survival rate = 68%
  - Pelvic LN+

» 2 yr survival rate = 23%

- Extrapolated data of enhanced response rates and distant control with chemoRT in LN+ cancers (cervix, rectal)
- Elderly with medical comorbidities













(1	vioore 98, 1	viontana 2	000	, 1	RODP)	
Week	1	2	3	4	5	6
Chemo						
5FU	FFFF				FFFF	
Cisplatin	с				с	
RT	xxxxx	xxxxx			xxxxx	xxxx
	xxxx				xxxx	

# GOG 101 - Preop CRT for localregionally advanced vulvar ca

#### Primary tumors (Moore, IJROBP 98)

- 71 evaluable patients (non primary RV candidates)
- 2 unresectable, 1 exent, 2 colostomies
- All others underwent resection of tumor bed (or bx's if cCR)
- 34 cCR (48%), 22 pCR (31%)
- 55% A/NED, median 50 m f/u

#### Groin nodes (Montana, IJROBP 2000)

- 38/40 (95%) of groins rendered resectable
- 41% pCR
- 12 pts A/NED, median 78 m f/u

#### Locally advanced vulvar cancer – GOG 205 (Moore, Gynecol Oncol 2012)

- Evaluated primary tumor only (successor to GOG 101)
  - Increase RT dose to GTV to 57.6 Gy
  - Weekly CDDP @ 40 mg/m2/wk x 6-7 cycles (no 5FU)
  - Eliminate elective break
  - All patients undergo initial bilateral GND unless unresectable
    groin node RT is then tailored to groin pathology findings (GOG bias)
  - Endpoint analysis: 45% pCR (20% relative improvement over 31% pCR in GOG 101)
  - 58 evaluable patients (non primary RV candidates)

Locally advanced vulvar cancer GOG 101 vs 205 (Moore, Gyn Oncol 2012)					
	GOG 101	GOG 205			
Evaluable	71	58			
CCR	34 (48%)	37 (64%)			
PCR	22 (31%)	29 (50%)			
PCR/CCR	22/34 (65%)	29/37 (78%)			

# GOG 279 - successor trial to GOG 205: locally advanced vulvar cancer

- Cisplatin/gemcitabine/RT phase II study
  - Increase GTV dose to 64 Gy
  - IMRT incorporated to reduce toxicities
- **Primary endpoint goal**  $pCR \ge 65\%$ 
  - If pCR sufficiently high, especially in cCR cases, do all patients need post-chemoRT surgery?

# <section-header><figure>



# Vulvar cancer – locally advanced

**BUT...<u>Generous</u> RT coverage is needed** 

- Not analogous to early vulvar cancer with 'skin-bridge' preservation, 'triple incisions'
- May have significant altered/obstructed lymphatics









#### Locally advanced vulvar cancer

Initial ChemoRT to primary, groins, and pelvis

- Concurrent weekly cisplatin (30-40 mg/m2/wk)
- 45 Gy to at-risk, microscopic CTV
- 57.6 60 Gy to GTV (primary and nodes)
  - » Careful use of IMRT (generous volumes)
- Re-image and reevaluate at 6-8 weeks
  - » Resect/biopsy primary tumor site
  - » Limited groin resection of imageable residual
- In clearly node+ cases, I favor up-front chemoRT to avoid delay of primary therapy, groin wound breakdown prior to RT, etc

